National Science Foundation – Science & Technology Center

ANNUAL REPORT
Center for Cellular Construction
Wallace Marshall, P.I.

GENERAL INFORMATION

1a.

Date submitted	5/20/2019
Reporting period	**10/01/18 – 9/30/19*** progress reported as of 5/20/19
Name of the Center	**Center for Cellular Construction**
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Participating Institutions: institutions, role, and name of contact person and other contact information, if changed since last reporting period.

No changes in institutions, roles or contact people.

Participating institutions

San Francisco State University

IBM Almaden Research Center

Exploratorium

Stanford University

UC Berkeley

1b. Biographical information for *new* faculty members *by institution*. Attach as *Appendix A*.

Biosketches are included for John Dueber, UCB and Robert McGinn, UCSF

1c. Primary person to contact with any questions regarding this report

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Annual Report 10/1/18 – 9/30/19
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Center for Cellular Construction

I.2. Context Statement

Overview of Vision and Goals

The Center for Cellular Construction is an NSF Science and Technology Center whose vision is to develop an engineering discipline that will allow us to design and build cells and tissue with specific three-dimensional structures. These structures will serve as living factories and building blocks for better and more sustainable products, materials, and devices to benefit humankind. The Center is comprised of participants from six institutions (UCSF 10 faculty, SFSU 8 faculty, IBM 1 faculty, Stanford 2 faculty, UC Berkeley 2 faculty, Exploratorium 1 faculty), for a total of 24 faculty engaged in research, education, diversity, and knowledge transfer research and education faculty.)

During this third reporting period, as activities and programs for the Center accelerate, we continue to forge our center into a unified, efficiently integrated group capable of executing our strategic goals. To this end we have supplemented our administrative and management team to bring in needed expertise and staffing, and further built relationships with administrative and management teams from our partner organizations to streamline overall communications and strengthen partnerships. We have focused on encouraging and strengthening collaborations among students, postdocs and researchers across labs and institutions to drive the Center's main research projects, and have worked out procedures for sharing key resources cross-institutionally, especially giving access to UCSF resources to faculty and students from SFSU, which has accelerated and augmented their research projects for the Center.

The activities of our center, to be described below in more detail, have been developed in the form of cross-institutional collaborations. Indeed, we have deliberately designed our projects to be inherently collaborative in nature, thus taking advantage of the diversity of interests and knowledge in the center, allowing us to accomplish tasks that the participating groups could not accomplish individually. During the first three years, we have launched 41 new collaborations among the twenty-four research and educational faculty at UCSF, SFSU, UC Berkeley, Stanford, IBM, and Exploratorium. All center faculty are involved in one or more collaborative projects. These collaborations have opened a path of communication between students and postdocs at the different participating institutions that we expect to lead to launching of new collaborative projects driven at the grassroots level.

The diagram below illustrates the current active collaborations, with each arc indicating an active collaboration in which joint research (black) or educational (red) projects are being carried out by center personnel in both groups.

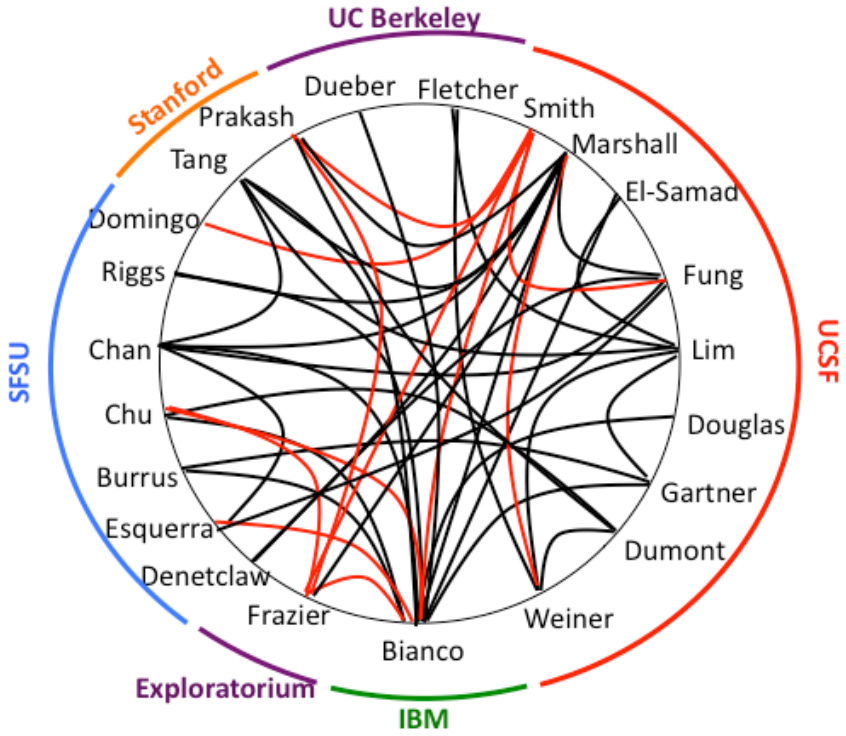


Figure I.1. Collaboration map showing research (black) and education/outreach (red) collaborations currently active in the center.

Integrative Research

In order to achieve our vision of engineering cells, we have organized our research activities around five Projects, three of which focus on enabling technologies for predictive specification of cell structure and interactions, and two of which focus on applications for cellular engineering. The first three projects (Project 1: Cellular Machine Shop; Project 2: CellCAD; and Project 3: Cellular Lego) are aimed at facilitating a design-build-test cycle for cells and cell collectives, using rational models as design tools. The final two projects (Project 4: Living Bioreactor and Project 5: Cell State Inference Engine / Cellular Sentinel) will pursue two broad classes of applications.

Project 1 – Cellular Machine Shop: We seek to create an efficient set of approaches and tools for controlling shape and interactions within cells at the organelle scale. The fundamental tools are those of standard cell biology, but in order to achieve the level of reproducibility necessary for an engineering design-build-test cycle, we are re-imagining every step of the build process, from how we barcode strains to how we communicate experimental protocols. Because of the inherent variability of biological systems, we envision high-throughput screening as an integral part of the fabrication cycle, such that a given design will be implemented not with a single construct, but with a constellation of many different construct variants, all of which are then tested by direct imaging of cell structure. For this reason, we have been invested substantial effort towards building robust computational tools for analyzing cellular structure, taking advantage of modern developments in deep learning and image analysis. Examples include new approaches for tracking chromosomes and spindles, locating the surface of organelles, and

deconvolving line-scan images from high throughput imaging platforms. All of these individual algorithm development projects have stemmed from collaborations among center labs, especially at SFSU and IBM.

Project 2 – CellCAD: Engineering is about building things, but so is tinkering, and part of what sets them apart is that engineering employs predictive models as design tools. To make cell biology into engineering, we seek to harness quantitative models of organelle and cell dynamics to build design software that will help guide decisions about genetic modifications, including gene knockouts and expression of interaction-driving constructs. The output will be a constellation of candidate molecular changes to be implemented using the tools of the Cellular Machine Shop. We envision two approaches: (1) A **model-driven strategy** in which we use coarse grained theoretical models for organelle dynamics to build design tools by applying control theory concepts to the organelle models, and (2) a **data-driven strategy** in which we use large datasets as the basis for empirical predictors built with machine learning methods. During year 3 we have focused the data-driven strategy by creating a linear vector-space formalism for describing cell state that allows us to ask fundamental questions about independent controllability and additivity of molecular perturbations. We find that perturbations affecting a given organelle typically affect other organelles as well, creating a significant problem for cellular design that can only be overcome with appropriate computational support, for which neural network-based strategies are now being developed. In parallel, we have found that when simple coarse-grained models for organelle size control are extended to the multiple-organelle case, the potential is high for undesirable outcomes, such as one organelle shrinks down to zero size while another organelle becomes larger than the whole cell. Again, this study argues that cellular design will require computational approaches to avoid such pathological cases. Both studies thus provide a concrete rationale for the need for CellCAD software going forward, something we had hypothesized in our proposal, but that we can now demonstrate.

Project 3 – Cellular Lego: Plant and animal tissues bring different cells together to accomplish new tasks. Why limit ourselves to those tissues that currently exist? We are working to build a standardized set of molecular interactions that can be used to link different cell types, including from different species or kingdoms, into larger structures, taking advantage of the natural self-organizing properties of cells. Our work in year 3 has focused on two directions for building artificial cell collectives: (A) a "tissue origami" approach in which DNA-mediated cell adhesion is used to attach contractile cells to a sheet of extracellular matrix in a pre-defined pattern, and (B) tissue self-organization using synthetic cell-cell interactions including the use of microfluidic approaches to test regenerative capacity of such self-assembled structures.

Project 4 – Living Bioreactor: The Living Bioreactor project builds on the concept of the cell as a chemical factory, and seeks to improve the production of useful chemical products by re-engineering the physical structure of the cell, for example by changing the volume and surface area of organelles that encapsulate key modules of biochemical pathways of interest. During year 3 our work on this project has focused on four main directions: (A) understanding how organelle size variation can change biochemical function, using the yeast vacuole as a test case, (B) development of the flagellar axoneme as a scaffold for docking fusion proteins at defined stoichiometries and quantities in a stable, easily purified nanoarray, (C) developing approaches to engineering peroxisomes as chemical factories, (D) implementing methyl halide production in yeast in order to test influence of vacuole geometry.

Project 5 – Cell State Inference Engine/Cellular Sentinel: The internal structure of cells is highly sensitive to their external environment. We are building automated tools for inferring extracellular conditions from cell images, suitable for deploying in the field to analyze environmental toxins or pollutants, or equally to be deployed in an industrial setting to track conditions in fermentation processes. We have continued to develop deep-learning based computational methods to analyze shape and behavior of ciliates found in ponds and reservoirs, combined with cheap, portable microscopes to be used as a front end. In parallel, we have implemented image analysis pipelines for reconstructing cellular state spaces and inferring cell state based on analysis of organelle morphology and cell movements. Development of yeast as a cellular sentinel has progressed by building strain collections and image analysis tools to quantitatively map the relation between genetic state and organelle morphology, initially using the vacuole as a model system.

Education

Our educational goals are focused on the mission of driving a new field of engineering based on building cells and building with cells. To do this we need to create awareness, in academia and in the public, of the cell as something that can be engineered, and also to train a new generation of engineers comfortable with using the cell as an engineering medium. Our educational programs encompass four target audiences: undergraduate students, graduate students, high school teachers and their students, and the general public.

Undergraduate

Our undergraduate educational program encompasses two aspects: developing new courses around center topics, and providing research experiences for undergraduate students in center labs. Drs. Ray Esquerra and Mark Chan at SFSU have developed two brand-new undergraduate courses on cellular engineering and microscopy, as detailed in section III. These are formal SFSU courses that will allow the courses and curriculum that we have developed in the center to be sustained beyond the lifespan of the Center.

Our undergraduate research experience component involves both round-the-year undergraduates, particularly at SFSU, as well as undergraduates from around the country who participate in the summer research training programs at center institutions, for which center investigators are serving as mentors. Year-round undergraduates attend the center Quarterly Meetings, and have presented their work in oral presentations at these meetings. Undergraduate participation is particularly emphasized at the Center Annual Retreat, where undergraduates present posters on their work alongside graduate students and postdocs. Overall, 46 undergraduates have taken part in research experiences in Center labs during the past year. Three center undergraduates were authors on center publications this past year, and undergraduates presented 22 posters at local and national meetings.

Graduate

At the graduate level, we have developed a brand new hands-on summer course on Cellular Engineering, inspired by the experience of Center faculty in teaching project-based courses at the Marine Biological Laboratory in Woods Hole. The CCC Summer Course will be offered for the first time this coming summer. It is targeted towards a mix of advanced undergraduates, masters, and Ph.D. students. The course will emphasize computational and microscopy techniques as well as the application of an engineering mindset to cell biology. The course will be run at

SFSU with the goal of eventually creating a formal summer course that can enroll students from around the country and provide dormitory housing, allowing the course to continue after the lifespan of the center has ended.

We continue to create new curricula by taking advantage of the "mini course" format at UCSF, in which faculty can organize 2-3 week long intensive courses on subjects of their choice. In year 3, we ran a third iteration of the graduate minicourse on cellular robotics that we had run in the first two years of the center. This cellular robotics course, in turn, has provided a basis for development of the high school teacher-student Cellular Construction Workshop.

One area of emphasis that spans graduate education and knowledge transfer is our internship program, whereby the center leverages our contacts with industrial partners to create new opportunities for internships for our students, both as a way to catalyze the exchange of ideas but also with an education goal of teaching the students about career pathways outside of the traditional academic route. CCC graduate students have done internships at IBM, Calico, Zymergen, and The Exploratorium. We are continuing to expand this program to include more students and an increased set of partner companies and institutions.

K-12

An important aspect of these overarching educational goals is that we believe cellular engineering provides a way to inject concepts of engineering into traditional biological curricula at all levels including K-12. To this end, we developed high school curricula based on an engineering view of cells. For the past two years, we have run a two week hands-on "Cellular Construction Workshop" course for high school science teachers and their students, in which LEGO mindstorms robotics was used to build robots to solve problems and challenges inspired by the challenges that living cells face. This course introduced students to the idea of a design-build-test cycle, as well as teaching programming. At the same time, students performed simple experiments in cell behavior, such as food-searching by *Physarum*, and hence students with pre-existing interest in engineering were exposed to the excitement of cell biology in a context that they could relate to. Evaluation and tracking during the past two years has shown that this course had a strong impact on the teachers who participated, and has changed the approach they are taking in their own classrooms. We are now transitioning this program to a free-standing format in which students and teachers pay to participate, and those who pay cover the costs of those who cannot afford to pay. Our approach is to gradually transition to this independent status during the next year, so that the summer workshop can continue to be offered at a vastly reduced expenditure of center resources, and can persist after the end of the center lifespan.

Public Education

Launching a new field requires awareness that the field exists, and to this end we are working to popularize the concept of engineering cells. The centerpiece of our public outreach effort is the development of new exhibits and demonstrations at the Exploratorium, one of the world's largest science museums with a long track record of hands-on science education. Center members at the Exploratorium are working to develop new presentations as part of the ongoing "Cells to Self" exhibit collection. In support of this development, the Exploratorium hosted a "CCC Faire" where center members presented demonstrations of their work to Exploratorium development staff as a way to brainstorm potential new exhibits or demonstrations.

Human Resources and Diversity

We believe that developing a new interdisciplinary field will require the maximum possible diversity of viewpoints and backgrounds. We are working to broaden participation and increase diversity primarily at three levels: graduate and postdoc training, mentorship, and strengthening research infrastructure resources for faculty training minority students. At the level of graduate and postdoctoral training, we are pooling our efforts to attract URM undergraduate students to join our graduate programs and, once in those programs, to encourage them to do their studies in center labs. Center Director Marshall has joined the SFSU MARC advisory panel as well as the diversity panels for the UCSF Tetrad and IPQB graduate programs. In this way, he is now in a position to help shape diversity policies in these programs, with a view to increasing the number of URM students admitted. He has also become a member of the UCSF Basic Science Faculty Diversity Committee, which is working to increase prioritization of diversity goals in the overall faculty hiring culture. We believe that by working actively to increase awareness of our center, and UCSF overall, as an environment that values diversity (and in fact sees diversity as core to its mission), we take at least a first step towards increasing diversity at all levels from student to faculty recruitment.

We believe that mentoring is important for broadening participation. Two of our center faculty, Professors Blake Riggs and Carmen Domingo, have participated in NRMN training (National Research Mentoring Network). At our annual retreat in 2018, we held a two-hour interactive training session on sexual harassment, mediated by Dr. Riggs. We are developing another interactive training session at our annual retreat scheduled for July 2019.

Within our center's four academic research institutions (UCSF, SFSU, Berkeley, and Stanford), SFSU has the most diverse faculty and students. SFSU has established a strong research track record and focus even though it has not, historically, received the same level of research infrastructure investment as the other research institutions in the center. Thus, a key element of our plan for broadening participation is to strengthen the research infrastructure at SFSU. We have negotiated access to all UCSF resources and core facilities for center members at SFSU. In this way, our center will strengthen the research capabilities at SFSU and in this way support the career success of those center faculty located there, while at the same time providing more access for SFSU students to the latest cutting edge technological resources available. The past year has continued to witness strong publications from SFSU center labs, as well as a steady increase in the number of diverse SFSU center students presenting work at national meetings. We believe these results confirm the effectiveness of our strategy.

A particularly dramatic example of the effectiveness of our partnership strategy was evident this year at the annual Minority Affairs Committee poster contest of the American Society of Cell Biology annual meeting. This is a poster contest for URM students and postdocs that is judged based on the research excellence of their work. Out of a total of 17 poster awards given, four of the prizes went to CCC trainees, including the undergraduate, graduate and postdoc categories. Given the large number of attendees at the ASCB meeting, the fact that the CCC was able to garner almost a third of the minority poster awards is highly significant and shows how our investment in research labs at SFSU is having an impact on the success of diverse trainees in our center.

We have found that diversity is lowest at the postdoctoral level, and we have spent the past year developing one approach to this problem. The UCSF IRACDA program is a postdoctoral training program that recruits and supports a diverse body of postdoctoral fellows who perform research at UCSF and teaching at SFSU. Our center has partnered with IRACDA to increase the number of host mentors at UCSF and to create a postdoctoral recruitment pipeline for applicants who apply to IRACDA, but cannot be accommodated by the limited number of slots available.

Knowledge Transfer

One key element of our knowledge transfer plan is disseminating information about the concept of cellular engineering to a wide audience. We began by setting up a temporary center website that has served two roles. First, it presents our face to the world and provides information about center members and activities. Second, through a secure sub-directory structure, the website is used to disseminate and collect internal information for the center members, to support annual reporting and coordination of activities. The site, available at *http://ccc.ucsf.edu*, is built on the Drupal platform to facilitate maintenance and cooperative editing of content. Our longer term goal is to produce a world-leading website for dissemination of scientific ideas from our center in a way that is accessible to the general public, while also providing user pathways that will allow scientific and industrial experts to delve deeper into the work of our center. *Anotherwise Company*, a web and graphic design firm based in San Francisco, has performed an extensive review of intended audiences, user flows, and desired outcomes, and has used this information to develop and implement a comprehensive web redesign which is now being populated with content. Additionally, we have contracted with Janet Iwasa (OneMicron Inc.) to develop custom computer animations for the site that will illustrate key concepts and ideas of the center as well as necessary scientific background in a visually accessible manner. The other side of our web dissemination strategy is harnessing social media. We have created a Twitter feed (@C3STC) which we are using to provide rapid updates on center activities. This format has been highly effective, with roughly one quarter of CCC tweets being retweeted by @NSF_bio.

The second key element of our knowledge transfer plan is industrial collaboration and partnership with existing companies. We have formalized a partnership with Serotiny, a San Francisco based startup that specializes in computational solutions for synthetic biology, providing a key element of the CellCAD project. We currently have 10 industrial collaborations underway as detailed in Section IV.

The third element of our knowledge transfer strategy is developing new IP. So far we have filed 9 invention disclosures. We have held meetings with local industry and startup experts, as well as members of our External Advisory Committee with experience in founding startups, to determine how best to use our resources to catalyze the launching of new companies. Based on these discussions over the past year, we have settled on a strategy of using our limited funds to seed research into new ideas developed in center labs for possible industrial solutions that could eventually either serve as the basis for new startups or be licensed to exiting companies. During year 3 we implemented an RFA mechanism for soliciting and evaluating ideas for seed level support. We will be issuing the first funds from this mechanism during summer 2019.

Management and Center Integration

It is challenging to put into place a management and leadership structure capable of supporting progress in all goal areas, and at the same time to integrate the six participating institutions into a cohesive unit working together on projects that no individual group could do separately. Managing collaborative programs and coordinating people requires developing relationships and assessing changing needs.

Changes to increase size of management team
To address acceleration of programs and dynamically changing needs among partner organizations, we have readjusted our budget to increase administrative core staffing and bring in expertise in events coordination and executive assistance. Details of our administrative team are included in the Management Section. The two most significant changes this past year were the recruitment of a former center student, William Chadwick, to serve as CCC student liaison and web content developer, and Dr. Kristin Dolan from the UCSF Research Development Office, to serve as CCC Program Manager. She has helped us to organize our strategic planning meeting this year and will be helping us track and plan center-wide progress in the lead-up to our renewal application.

External Advisory Committee
The CCC benefits from the advice of our ten-member External Advisory Committee, consisting of experts in cell biology, engineering, program management, education, and knowledge transfer, to provide external feedback on our activities. Dr. Radhika Nagpal (Harvard University) is the Chair of the EAC. A written EAC Charter has been distributed to all EAC members. This past year we added Dr. Tom Daniel to our EAC, with the specific goal of tapping into his expertise in program management of large NSF centers.

Coordination / Communications
We continue to use two primary approaches to maintain coordination among the participating institutions of the center: center-wide quarterly meetings and electronic communications. This year we have also increased face-to-face meetings among sub-groups on various projects and are communicating via regular phone conferences with faculty. Project leads have initiated meetings at UCSF, UCB, Stanford, SFSU, the Exploratorium and IBM. Joint subgroups are now held on a bi-monthly basis for the Living Bioreactor, Cell State Inference / Sentinel, and CellCAD projects. In addition to these project-focused team meetings, we have also formed Center-wide Working Groups based on the recognition that certain research projects cut across the five center projects. The two current working groups are Peroxisome engineering and Methyl Halide Production working groups. These working groups hold regular meetings and provide a catalyst for collaborations between the five different center project areas. We also have working groups for the new summer school course, workshops and other special initiatives.

We continue to hold Center-wide Quarterly meetings, the last two of which were held at UCSF and focused on research presentations, as a way to ensure that everyone in the center is fully up to speed on the overall center goals. Our Annual Retreat in July will be held again at a conference center run by SFSU in Tiburon, CA. In addition to research talks by students and faculty, we will again feature presentations on Responsible Innovation and on Mentoring Diversity. We have also added a monthly PI phone conference which provides a way for all center faculty to discuss upcoming plans and any emerging difficulties or opportunities.

CCC students have taken the lead in organizing their own get-togethers that take place at our quarterly meetings. After the main meeting, students get together to present a series of student-only research talks, and then socialize over pizza and a movie. This student meeting format is helping to give our students a sense of group identity and we plan to continue it at future quarterly meetings.

For electronic coordination, we have changed our mechanism for using email to distribute information – initially emails were sent to center faculty who were then expected to share information with their trainees. We have set up a center listserv that allows emails to be sent to everyone in the center. This has increased awareness of center activities among our students.

We are continuing to develop a customized version of the IBM Lab Book software, to negotiate with IT security mechanisms for sharing data, and to explore ways to integrate this platform with the CCC Slack channel.

Response to Review and Evaluation

We have made a number of changes this year in our center operations, influenced by internal assessment among our team, and by perceptive suggestions from our External Advisors, from the Site Visit review panel who visited in fall 2018, and from NSF program officials. In addition to those changes already noted above, the following changes were implemented.

A major recommendation of the site visit team was to add more formal program management expertise to our administrative structure. In order to accomplish this important goal within our existing budget constraints, we have done this by recruiting Dr. Kristin Dolan for professional Program Management, and by recruiting Dr. Tom Daniel to our EAC. The remaining Strategic Reserve in our budget does not allow the hire of a FT Research Program Manager, but we are prioritizing this in our renewal plans.

We have taken a concrete step towards ethics training and research by hiring Dr. Robert as an adjunct faculty member at UCSF, where he has implemented an ethics survey for center members (IRB approval currently in progress) and will be developing new curricula for CCC students based on the ethical considerations of synthetic biology. Our panel of advisors in bioethics is more correctly termed an ELSI Panel (Ethical, Legal, and Social Aspects or Implications); expertise and leadership among our advisors comprises social science aspects of cellular engineering ethics; policy and governance; empirical methods in the study of ethical questions in science, medicine, and health; and ethics education.

During the past year, on the advice of our site visit panel and NSF officials, we have scaled back our financial commitment to K-12 and public outreach in order to make more funds available for higher education. We have developed a strategy that allows our K12 and public programs to continue with reduced financial involvement from the Center. The funds freed by this realignment are being used to cover faculty release time for development of the two new undergraduate courses at SFSU and to run the CCC summer course discussed above. Funds from our Strategic Reserve have also allowed us to recruit John Dueber from UC Berkeley as a new center faculty member.

II. RESEARCH

1a. Research goals and objectives

The research mission of the Center for Cellular Construction is to launch a new engineering-based approach for understanding and designing cells through collaborative and interdisciplinary projects. Our vision for engineering cells revolves around developing engineering and design tools to facilitate a design-build-test cycle characteristic of engineering, rather than the hypothesize-test-refine cycle that characterizes scientific research. To make this happen, we require rational and predictive models to drive design – defining our approach as *engineering* as opposed to tinkering. We are building software to turn predictive models into design tools, and combining these design tools with powerful high-throughput strain construction and validation methods based on image analysis. A key aspect of our engineering focus is our vision that real-world applications will drive all research activities. Hence, all of our research projects (see section II.2) are either related to enabling the design-build-test cycle, or else relate to engineering cells with specific application goals in mind. We have designed our research projects specifically to be interdisciplinary, requiring participation by multiple research faculty and groups, as a way to ensure that collaboration is "baked in" to the design of our projects from the very beginning.

1b. Research performance and management indicators

During this past year, our primary management indicator has been to launch collaborative projects that are increasingly aligned with the primary research thrust areas, which we term "projects". We held a series of strategic planning meetings, culminating in a formal 2-day session in Feb 2019, to realign milestones in the strategic plan to accord with the evolving goals of our five project areas.

1c. Research problems

As with any large collaborative research project, the main challenge is aligning the effort of the individual researchers to focus on large-scale goals of the center. Direct engagement of center students and postdocs has helped to catalyze grassroots level collaborations and better understanding of center goals, with the result that research activities are showing improved alignment with center goals compared to the previous year.

2a. Research thrust areas

The research goal of the Center for Cellular Construction is to "turn cell biology into an engineering discipline." We are specifically focused on the engineering of structure — subcellular, cellular, and multicellular structure. Two engineering principles we incorporate into our efforts include: (i) the use of a "design, build, test" cycle for building cell/tissue structure, and (ii) research focused on potential downstream applications.

In order to achieve our vision of engineering cells and their structure, we have organized our research activities around five Projects; three of these projects focus on enabling technologies for predictive specification of cell structure and interactions (Cellular Machine Shop, CellCad, and Cell Legos), and two focus on applications for cellular engineering (Living Bioreactor, Cell State Inference Engine/Cellular Sentinels). However, we emphasize that all of these projects feedback directly into one another. For example, CellCad aims to develop the design principles necessary to engineer cell compartments, but experimental findings in the context of Living Bioreactor (using compartment for making useful products) motivates research in CellCad to better engineer compartments themselves.

Thus, all projects are inextricably linked. Moreover, for all five projects or thrust areas, we are currently exploring a range of possible approaches, with the goal of consolidating work around areas that are most promising as the work progresses. For example, over the last two years we have identified the peroxisome as a subcellular compartment with properties that are particularly amenable towards engineering. We have thus placed a lot of focus on this compartment in the last year.

Our five Projects, and their thrust areas, are as follows:

Project 1. **Cellular Machine Shop** (tools/instrumentation/infrastructure for measuring/building cell structures)
Project 2. **CellCad** (modeling tools for designing cell structures)
Project 3. **Cell Legos** (engineering multicellular structures)
Project 4. **Living Bioreactor** (engineering organelles, cells or multicellular structures for making useful products,
Project 5. **Cell State Inference Engine / Cellular Sentinel** (relating cell microenvironment and internal state to measurable cell structures)

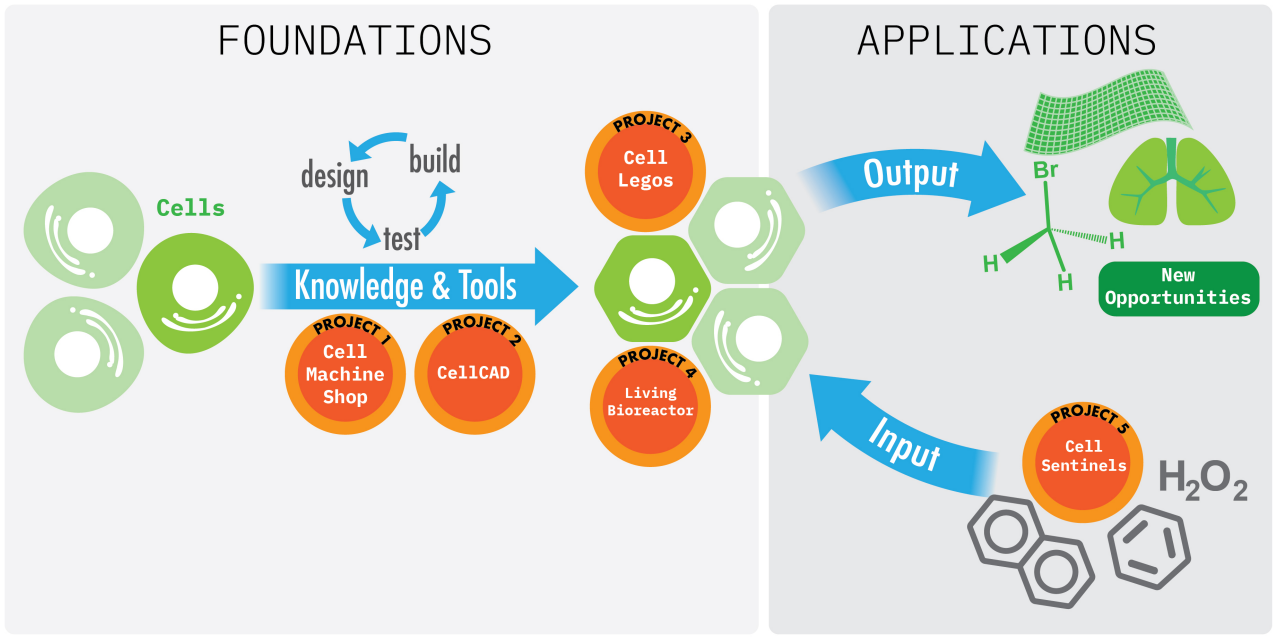


Diagram showing the flow of information between the five center Projects and the degree to which each Project focuses on fundamental knowledge, enabling tools, or real-world applications.

2b. Research Progress

The remainder of section II will describe our progress in each of the five main projects. We report on individual subprojects organized by theme, indicating center participation, collaboration, and synergies between Center research thrusts.

Project 1: Cellular Machine Shop

Cellular Machine Shop includes all projects aimed at developing tools useful for the other projects in the Center. Examples of research areas that would fit into the Cellular Machine Shop Project:

- Genetic tools for measuring cell structure
- New instrumentation for measuring cell structure
- Algorithms for measuring cell structure
- Infrastructure/methods for storing, sharing, comparing data
- Infrastructure/methods for automating, standardizing or prototyping
- New tools for manipulating cell structure

Major progress in the last year comes in four general areas.

First, we have made extraordinary strides in **incorporating machine learning approaches** into Center Research. Under the guidance of Simone Bianco and his team, innovations in the Machine Shop from the previous funding periods have now been transferred to every Project in the Center. Moreover, innovation continues in this area and we anticipate important new advances in the coming years.

Second, we continue to make important **advances in microscopy**. These include new tools for remote microscopy as well as new low-costs methods for fluorescence microscopy (some of these are discussed in Cell State Inference Engine/Cell Sentinels project due to the synergy between these two Projects). Given the central role of microscopy in measuring cell structure, these advances will be critical for the broader impacts of our efforts in the Center for Cellular Construction.

Third, we have made important advances in **molecule analysis at the single cell level** (e.g. MULTIseq) which will open the possibility in later years of directly correlating the molecular state of cells to their structure – key requirements for all other projects in the Center.

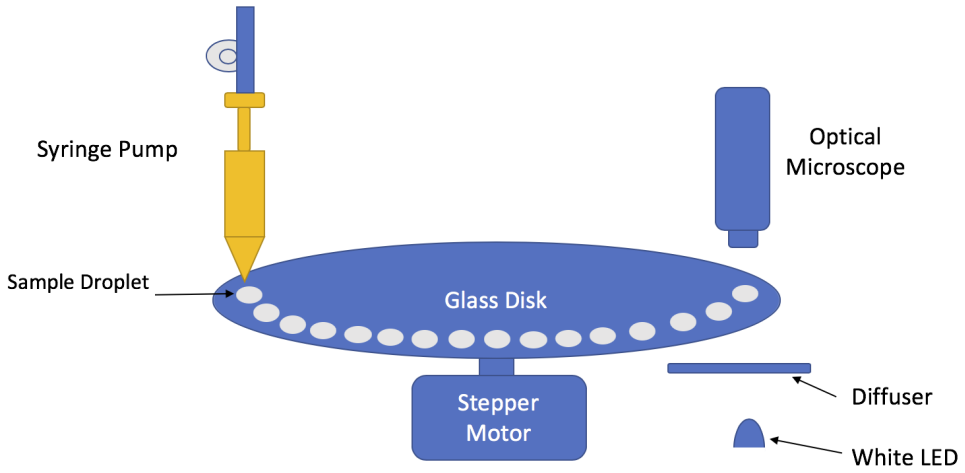
Fourth, we continue to advance strategies for **perturbing cell structure** (e.g. microneedles and optogenetics). These methods are also are beginning to impact other projects in the Center, for example, by providing entirely new strategies for releasing products from cells by controlled lysis.

Subprojects relating to this research thrust are summarized below.

Measuring Cellular Morphology and Dynamic of Stentor in a High Throughput Microscope
Primary Center Contributors: IBM Research (Bianco)

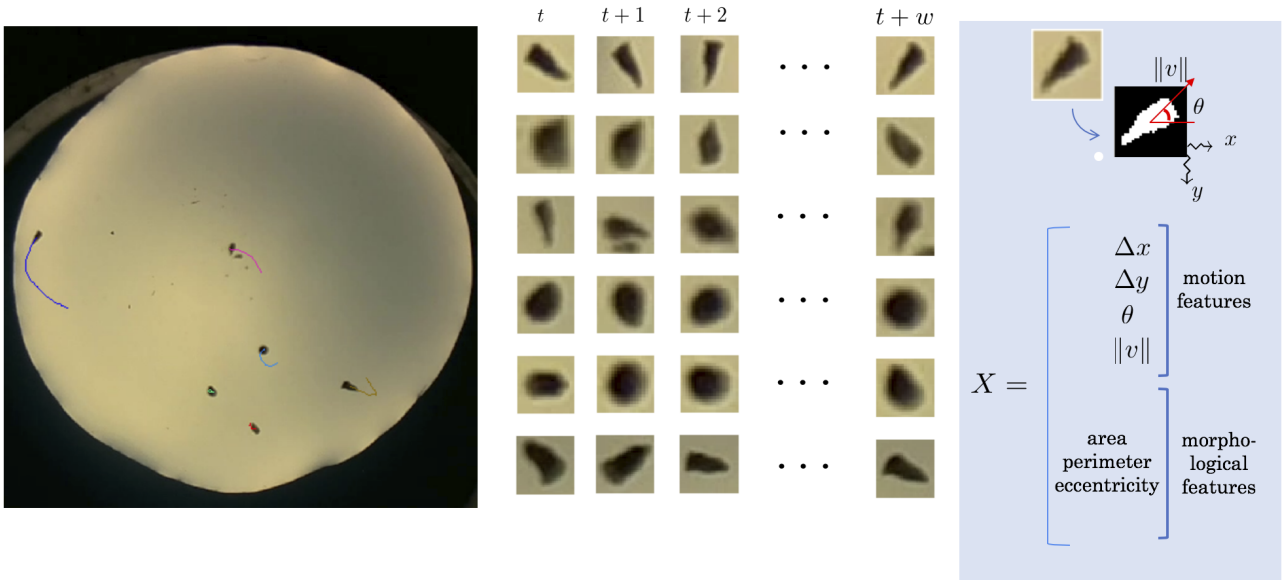
> **Description:** We have developed a background model-based tracking algorithms to follow stentors swimming in the aquatic medium. The idea has been to track the stentors before and after adding chemicals, and to study behavioral signatures (i.e., morphology and dynamic) that can help us detect the presence of the chemical added to the system. We have analyzed the swimming behavior of the stentors from the tracked trajectories, and trained a supervised machine learning algorithm to predict the changes in the stentor's swimming behavior when their natural habitat is altered.
> **Personnel:** Sujoy Biswas, Thomas Zimmerman, Vito Paolo Pastore, Lucrezia Maini, Cecelia Brown, Simone Bianco

Accomplishments: Paper accepted and published (High throughput analysis of plankton morphology and dynamic, SPIE Conference Proceeding, Biswas et al., Published: 4 March 2019, SPIE Conference). We are implementing a novel algorithm that tracks the swimming creatures through occlusion.
Anticipated changes: We are scaling up the tracking technologies for tracking a variety of creatures in their natural environment while measuring their response to various chemicals administered into the aquatic medium.
External Collaborators: Lucrezia Maini, an exchange student from EPFL, and Cecelia Brown, IBM intern from San Francisco State University, have worked on building the experimental setup and collected videos, under the supervision of Tom Zimmerman. Also, Aminat Adebiyi and her supervisor Luisa Bozano, both from IBM Research, Almaden, participated in data collection.
Benefit for other Center Research: The experimental protocol and the algorithm proposed will help study the cellular states and functions in response to various environmental stimuli. This project will help build the Cell State Inference Engine (Project 5) to use plankton as environmental bio-sentinels.



* Design and implementation: Thomas Zimmerman, IBM Research, Almaden, USA

Design of high throughput microscope that allows us capture videos of stentors swimming in the aquatic medium.

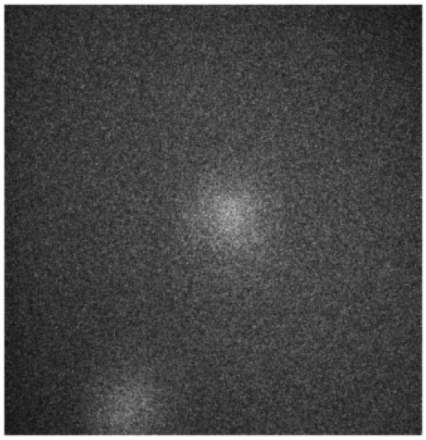


The proposed idea of morphology and dynamic feature extraction after tracking the Stentors individually: on left, the Stentors are shown with their immediate track history; in the middle each row illustrates an individual Stentor exhibiting various poses (t denotes frame number); on right we illustrate the morphological and dynamic features extracted from every Stentor

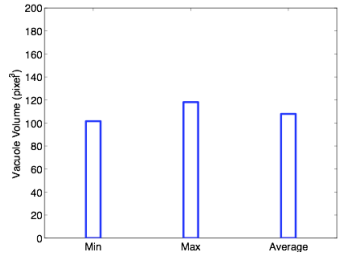
Vacuole Geometry Extraction in Budding Yeast Cells
Primary Center Contributors: IBM Research (Bianco), SFSU (Chan)

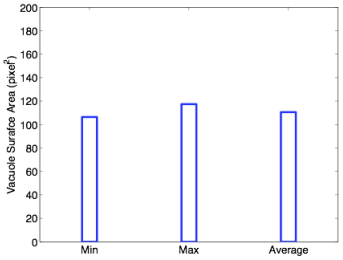
Description: Vacuole organelles in budding and fission yeast are morphologically complex organelles that perform a variety of biochemistries with potential for housing chemical synthesis pathways. This collaboration between SFSU (Chan) and IBM Research (Bianco), aims to implement machine learning algorithms to develop novel methods for detecting and measuring vacuole structure—i.e. volume, surface area, position, etc.—from fluorescence images, which contributes to the Cell Machine Shop. This tool will enable high-throughput analysis of data from the Living Bioreactor (vacuole size optimization for chemical synthesis) and Cellular Sentinel (vacuole structure responses to chemical and environmental perturbation).The objective of this study involves the following goals—(i) localization of the vacuoles in the budding yeast cells; (ii) computing their geometry, e.g., volume, surface area; and (iii) compute the distribution of these vacuoles with respect to the cell membrane. At present, the localization of the vacuoles is done manually and the process is tedious and labor intensive. Automation of this localization process reflects the overall goal of the Cellular Machine Shop to increase the efficiency of cellular image analysis using machine learning methods.
Personnel: Sujoy Biswas, Simone Bianco
Accomplishments: We have achieved early results of successful implementation of the following methodology: intensity based detection of CDCFDA illuminated vacuoles, and then inflating a 3D active contour model to extract their shapes and sizes. William Chadwick has used CDCFDA dye to illuminate the inner part of the vacuole which made the job of detecting them easier.

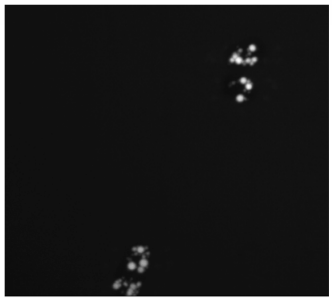
Plans: We are using the two image channels to derive various phenotypes like vacuole counts, their distribution in various parts of the cells, vacuole surface area and volumes. The two image channels include this – vacuole membrane and vacuole inner part (dyed with CDCFDA). We are working on such phenotypes to see how they change with respect to time. Also, studying them in mutant yeasts as compared to the control population is another direction in our research plan. By Summer 2019, we hope to complete a manuscript based on these results.
Center Collaborators: William Chadwick, Mark Chan, San Francisco State University
External Collaborators Fred Chang, UCSF; Sally Pasion, SFSU; and Kathy Gould, Vanderbilt (fission yeast experts)
Benefit from other Center Research: Some of the data was obtained within the Bioreactor project
Benefit for other Center Research: The experimental protocol and the algorithm proposed will help study the cellular states and functions in response to various environmental stimuli (for example the mutant variety as opposed to control population). This project will help build the cellular inference engine identify how mutation or time can influence the vacuole phenotypes in buddying yeast cells.



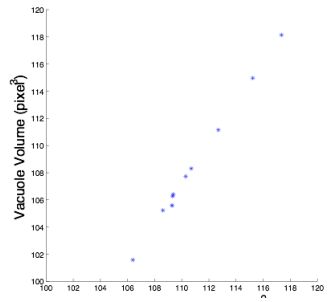
Too small vacuoles could not be reconstructed
Min Vacuole Volume: 101.57 px^2







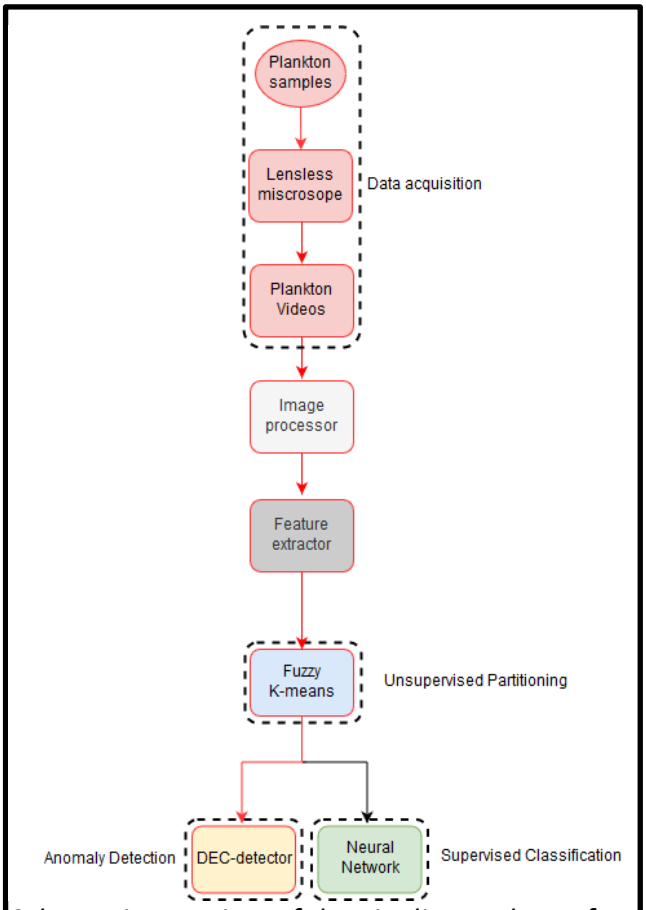
Max-Projection



Left: On top, vacuoles in budding yeast cells are shown, and at the bottom we see the inner part of the vacuoles highlighted with CDCFDA dye. Middle: the 3D reconstruction of the vacuole surfaces. Right: Top shows distribution of vacuole volume, the middle plot shows the same for vacuole surface area, and the bottom plot shows scatter plot between vacuole volume and surface area.

Unsupervised learning of plankton for classification and anomaly detection.
Primary Center Contributors: IBM Research (Bianco)

Description: We developed a novel set of algorithms to perform accurate detection and classification of plankton species with minimal supervision. We propose such a set of novel algorithms to reliably characterize and classify plankton data. Our method is based on an unsupervised approach to overcome the limits of supervised machine learning techniques. We developed our methodology having in mind a real-world application, where a collection system is continuously acquiring data which has to be classified on the fly. We named the developed unsupervised learning pipeline as Plankton Classifier. We applied the PC to a collection of videos of plankton containing ten fresh water species of plankton captured with a lensless microscope. Each video was ten seconds long and contains one or more species. As the method is unsupervised, no labels are provided to the pipeline during training. The plankton classifier we developed consists of four modules: an image processor, a feature extractor, an unsupervised partitioning module and a classification module. The image processor examines each frame of video and generates cropped images of each plankter. The feature extractor examines each plankter image and generates a collection of features. The unsupervised partitioning module clusters samples by features into classes. The classification module is composed by two alternative machine learning approaches to continuously classify plankton species based on the unsupervised partitioned classes inferred trough the clustering procedure. The first approach simply consists in training a standard state of the art classifier, such as a neural network. The second approach, which is alternative to the first one and represents our preferred classification method, is based on anomaly detection, and it extends the unsupervised learning a step further, potentially enabling the design of a continuous end to end monitoring pipeline of the aquatic environment. We also developed a novel neural-network based approach for anomaly detection. Such customized and novel architecture implementation, which we name Delta-Enhanced Class (DEC) detector, has a 2-neurons output, corresponding to a new organism either belonging or not to an existing class (i.e. anomaly). One DEC detector must be trained for each of the training species. For each observation, we train the neural network with the actual features vector and a delta-features vector obtained subtracting the actual observation and the extracted random set.



Schematic overview of the pipeline and set of algorithms used to detect and classify plankton species with minimal supervision. Our preferred embodiment is represented by the red lines.

Personnel: Vito Paolo Pastore, Thomas Zimmermann, Sujoy Biswas, Simone Bianco
Accomplishments: Paper submitted to *Nature Machine Intelligence,* currently under review. Two disclosures are also currently under review.
Plans: We will include more species into the training set and test the pipeline with the microscope in field.
Benefits from other Center projects: The engineered features and the unsupervised learning could be used for different kinds of data (not necessarily plankton).
Benefits for other Center projects: The ability to detect changes in plankton morphology can pave the way for using plankton as biosensors. This will further the research scope of Project 5, Cell State Inference Engine.

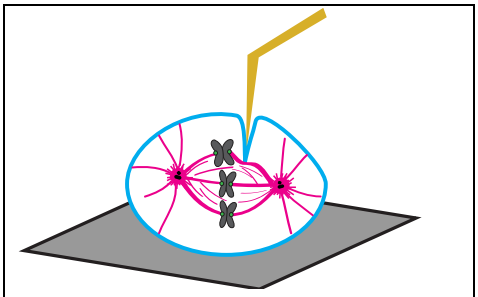
Optogenetic system for controlling organelle morphology in yeast.
Primary Center Contributors: SFSU (Chan), UCSF (Weiner)

Description: Vacuoles in budding and fission yeast are morphologically complex organelles that undergo dynamic changes in growth, fragmentation, fusion, and other events. As part of the overall goal of the Cellular Machine Shop to systematize methods for fabricating and verifying cells of defined structure, we aim to implement an opto-genetic system to allow triggered and predictable changes to vacuole structure.
Personnel: Mark Chan (SFSU), Brian Graziano, Orion Weiner (UCSF)
Accomplishments: This is a new project, and strain construction is ongoing.
CCC influenced or changed your research direction: The optogenetics was developed by the Weiner lab, and they are providing expertise in implementing and testing the system. A grant was also submitted with Chan and Weiner as collaborators.
Plans: We hope that the system will perform smoothly, in which case the ability to trigger changes in vacuole size will act as a tremendous tool. We expect to use it broadly in a number of existing and future projects.
Benefits from other Center projects and for other Center projects: These tools will be critical for the Living Bioreactor and possibly the Cell Legos projects. We will use them in both basic experiments linking vacuole structure to organelle and cellular function, as well as a way to engineer the organelle to optimizing yields.

Glass microneedles to manipulate internal cellular structures to probe their mechanical properties.
Primary Center Contributors: UCSF (Dumont), Stanford (Prakash)

Description: We use glass microneedles to move and deform cellular structures, and then computationally extract the structures' deformation map under force to infer their mechanical properties. We are currently using these tools to define the mechanical properties of the mammalian spindle in order to provide the Cellular Machine Shop with tools for mechanical manipulation and testing of cells.
Personnel: Pooja Suresh, Alexandra Long, Sophie Dumont
Accomplishments: We have successfully used these tools to analyze the mechanical properties of the mitotic spindle and are beginning to write up our results for publication.

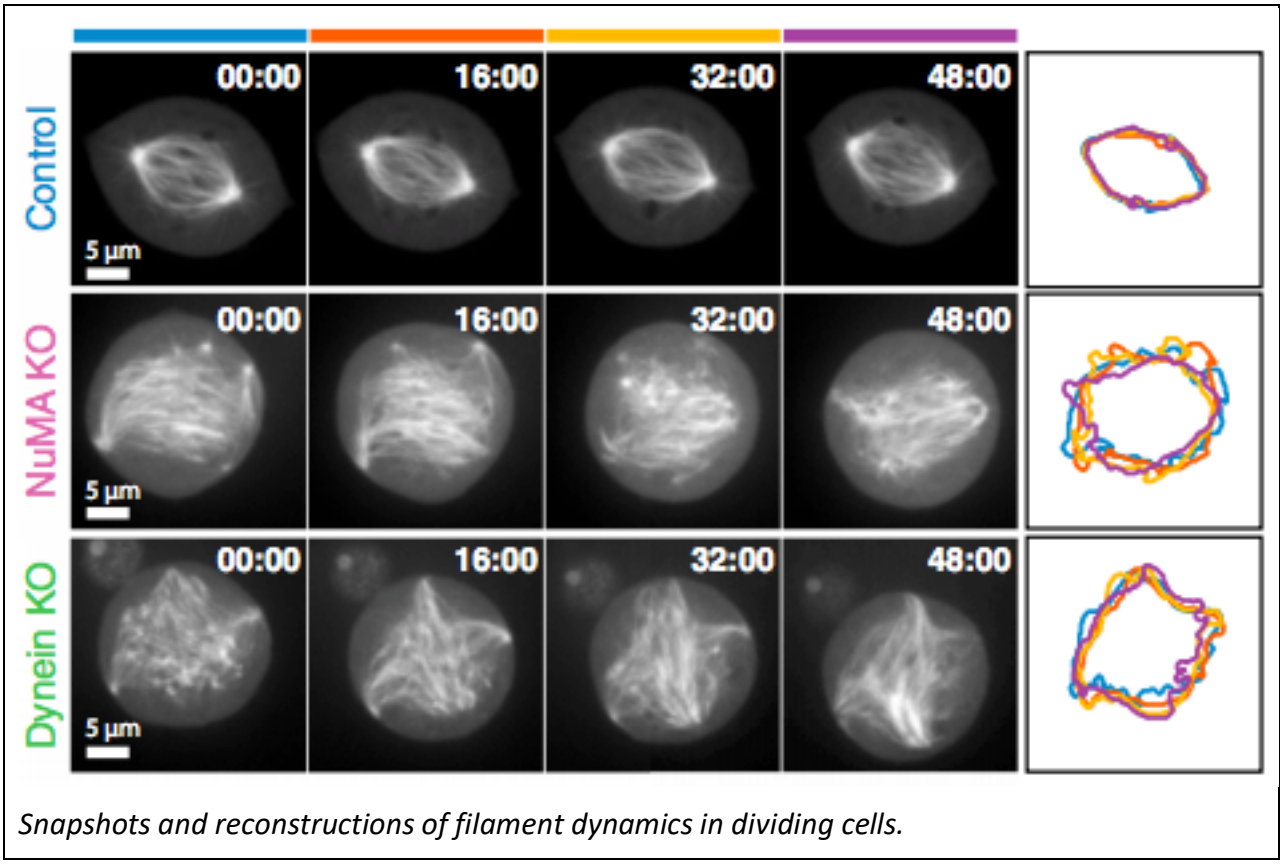
Center Influence on direction change: Being involved in the CCC provided ideas, inspiration and contacts for deciding how to best analyze data, and how to standardize the approach we are developing.
Plans: In the next year we hope to submit two manuscripts using the above approach.
Benefits from other Center projects: This project could benefit from CellCad (modeling tools for designing cell structures), though we have not used it yet.
Benefits for other Center projects: This project could help inform CellCad (modeling tools for designing cell structures), allowing us to experimentally test the mechanical properties of designed structures, moving towards the design of specific mechanical properties.



Probing spindle mechanical properties using microneedles

Tools for analyzing the dynamic organization of filamentous networks.
Primary Center Contributors: UCSF (Dumont), Stanford (Prakash)

Description: We have developed an experimental and computational approach to measure the dynamic organization of filament networks in cells, providing ways of defining cytoskeletal structures in cells. We used this tool to define the dynamic organizing of spindle microtubules, and to ultimately understand what organizational rule leads to steady-state vs. turbulent spindle structures.
Personnel: Christina Hueschen (graduated, now postdoc with Alex Dunn, Stanford), Lila Neahring, Sophie Dumont
Accomplishments: We successfully implemented the approach on the mitotic spindle.
Center Influence on Project: Being involved in the CCC gave us ideas, inspirations and contacts for thinking how to best analyze data, and how to standardize the approach we are developing.
Plans: We are currently trying to understand why cells would evolve a spindle structure where contractile and extensile activities simply appear to oppose each other. Understanding the purpose of this apparently futile opposition of contraction and extension may shed new light on the "building principles" used by cells.
External Collaborators: Rob Phillips, Caltech
Benefits from other Center projects: The use of optogenetics (Cellular Machine Shop/Cell Legos) for understanding the active matter properties of the spindle structure could be very powerful.



Snapshots and reconstructions of filament dynamics in dividing cells.

Controlling cellular structure in response to chemical stimuli.
Primary Center Contributors: SFSU (Esquerra, Chan)

Description: One important set of tools for the Cellular Machine Shop constitutes tools for sensing internal chemical state. We are pursuing the following aims: (i) To reveal how microviscosity is spatially distributed across a cell as a function of molecular structure; (ii) To develop chemical sensing tools for cells to selectively respond to chemical stimuli.
Personnel: Austin Murchison, Paulina Hernadez, Kloe Keeter, Donovan Ruiz, Juliet Gonzalez, Benazir Oluoch, Connie Kong, Sita Chandrasekaran
Accomplishments: We designed and validated a tool to measure microviscosity within a cell using a protein-based probe. This work was published.
Center Influence on Project: The microviscosity project is a direct result of interactions with members of the CCC and contributes to the goal of engineering cellular structure.
Plans: (i) measure how microviscosity depends on molecular size and shape; (ii) measure microviscosity in the vacuole and cytoplasm of yeast; and (iii) develop platforms to design, test and validate chemical biosensors.
External Collaborators: Eefei Chen and David Kliger, UCSC
Benefits from other Center projects: Executing this project relies on the ability to target expression and localization to specific organelles, using tools developed in other Machine Shop sub-projects.
Benefits for other Center projects The results would directly impact CellCad by providing inputs to the computational model. Also, the Living Bioreactor will be able to 1) understand how changes in microviscosity could be engineered into the design of more effective cellular

bioreactors, 2) develop tools to change cellular structure in response to external and internal changes in the chemical environment.

Genetic tools for perturbing and measuring vacuole structure.
Primary Center Contributors: UCSF (Fung, Marshall), SFSU (Chan)

Description: In order to develop a standardized set of mutations that alter vacuole morphology, we have been transforming the yeast deletion library with the fluorescent vacuole marker VPH1-GFP in order to create a library in which we can genetically manipulate vacuole morphology. This project fits into the research area of providing genetic tools for measuring and manipulating cell structure.
Personnel: Jennifer Fung, Wallace Marshall (UCSF), Mark Chan (SFSU)
Accomplishments: Library transformation initiated
Center Influence on Project: Previously we analyzed images using classical segmentation approaches suitable for low throughput analysis of cells. For all of our projects, involvement with the CCC has allowed us to develop the tools needed to do the high-throughput image analysis that is necessary to solve complex changes in cell morphology and to relate it to distinct biological pathways.
Plans: To facilitate our projects, we are developing an interface in which we can rapidly classify yeast organelle morphology. We are investigating if we can adapt publicly available Cell Profiler/Analyst algorithms to form our own specific pipeline for classification.
External Collaborators: Tracey Woodruff (UCSF), Josh Robinson (UCSF), Patrick Allard (UCLA)
Benefits from other Center projects: See **Influence** above.

Benefits for other Center projects: The library itself will benefit anyone interested in studying vacuole morphology, particularly for the Methyl Halide production project for the Living Bioreactor. The information gained in the vacuole morphological changes would benefit the Cellular State Inference Engine in order to interpret how chemical perturbations affect vacuole morphology and link them to biological pathways. In addition, the information obtained from how genetic changes affect morphology would feed into the information pipeline for CellCad to help develop modeling tools to develop cell/organelle structure. The high-throughput transformation protocol will help anybody interested in creating their fluorescently-tagged organelle markers in the yeast deletion library.

Tools for high content live cell imaging using the InCell 6000
Primary Center Contributors: UCSF (Fung, Marshall), SFSU (Chan)

Description: As part of improving the infrastructure for the Cellular Machine Shop, we have set up a data server for the InCell 6000 imager that allows 100 tb of data collection and image processing space. In addition, CO_2 incubation has been added to the InCell's capabilities.
Personnel: Daniel Elnatan, Ashwini Oke
Accomplishments: Completed data storage and incubation
Center Influence on Project: Previously, we acquired images using low throughput instrumentation. Involvement with the CCC has allowed us to acquire images to study cell morphology orders of magnitude more quickly.

Plans: To facilitate our projects, we are developing an interface in which we can rapidly classify yeast organelle morphology. We are investigating if we can adapt publicly available Cell Profiler/Analyst algorithms to form our own specific pipeline for classification.
External Collaborators: Tracey Woodruff (UCSF), Josh Robinson (UCSF), Patrick Allard (UCLA)
Benefits from other Center projects: See **Influence** above.
Benefits for other Center projects: The improvements to the InCell will allow more data to be collected more efficiently to increase the number of experiments per day that can occur. The CO_2 capability will allow live imaging of mammalian cells in the InCell; this was not possible before.

Segmentation tools for analyzing yeast imaged in multi-well plates.
Primary Center Contributors: UCSF (Fung, Marshall), SFSU (Chan)

Description: An important criterion for success in the cellular machine shop is not just analyzing a cellular structure, but doing so at a high enough throughput to select optimal outcomes from a constellation of cell designs. We have developed a segmentation algorithm to permit high-throughput analysis of yeast collected from multi-well plates. The purpose of the algorithm is to segment out fluorescently-tagged yeast cells from a monolayer of cells from a bright field image in preparation for downstream neural network based classification of organelle morphology. The segmentation pipeline consists of several steps: 1) creation of a training set, 2) image augmentation done in Keras using the Tensorflow backend, 3) employment of a U-Net step for convolutional networks based image segmentation 4) application of segmented cell to obtain corresponding 3-D fluorescence volume and 5) creation of a deconvolved, depth dependent color-coded 2-D representation of each cell's organelle morphology.
Personnel: Daniel Elnatan, Ashwini Oke
Accomplishments: established analytical framework.
Center Influence on Project: Previously, we segmented images using standard methods that resulted in low quality quantitative data. Bringing machine learning to bear on our data has been revolutionary and wouldn't have been considered without the input of the Center.
Plans: Build into current workflow for yeast organelle analysis
External Collaborators: Tracey Woodruff (UCSF), Josh Robinson (UCSF), Patrick Allard (UCLA)
Benefits from other Center projects: See **Influence** above.
Benefits for other Center projects: The In Cell project will be able to apply the segmentation algorithm to other types of cells. The same algorithm should be adaptable to organelle and mammalian cell segmentation.

Algorithms/tools for measuring cellular flows.
Primary Center Contributors: Stanford (Prakash), UCSF (Dumont)

Description: One of the reasons that engineering biology is so interesting, compared to existing engineering disciplines, is the highly dynamic nature of living systems. Most components of such systems are in constant motion. In order to analyze cellular structure and dynamics, we also require tools for analyzing the flows that occur within and around living

cells and tissues. We have developed Flow-Trace; an open source quantitative tool that enables visualization and characterization of flows generated in biological systems. We present a simple, intuitive algorithm for visualizing time-varying flow fields that can reveal complex flow structures with minimal user intervention. We apply this technique to a variety of biological systems, including the swimming currents of invertebrates and the collective motion of swarms of insects. We compare our results with more experimentally difficult and mathematically sophisticated techniques for identifying patterns in fluid flows, and suggest that our tool represents an essential 'middle ground' allowing experimentalists to easily determine whether a system exhibits interesting flow patterns and coherent structures without resorting to more computationally intensive techniques. In addition to being informative, the visualizations generated by our tool are often striking and elegant, illustrating coherent structures directly from videos without the need for computational overlays. Our tool is available as fully documented open-source code for MATLAB, Python or ImageJ at www.flowtrace.org. We have recently demonstrated that the same set of algorithms also perform very well for collective dynamics in multi-cellular systems all the way from multi-cellular swarming clusters to crawling ants.
Personnel: William Gilpin, Vivek Prakash, Manu Prakash
Accomplishments: 10 published papers already use the algorithms presented to publish new results.
Plans: We are now implementing this algorithm in real-time on GPU's to be able to project outputs in real time to enable robotic microscopes to make decisions on these algorithms.
External Collaborators: Chris Lowe, Stanford
Benefits for other Center projects: Motility provides a remarkable readout of cellular phenotypes. This year we will be implementing these algorithms to classify motile cellular behavior in natural conditions and under toxin screens. Thus, these tools will be very useful for Cell Sentinels, Cell Legos, and Living Bioreactor projects.

Methods of damaging cells to study organelle regeneration.
Primary Center Contributors: Stanford (Tang), UCSF (Marshall, Lim)

Description: One approach for manipulating cells in the Cellular Machine Shop is physical perturbation. We have developed two microfluidic device methods of experimentally damaging organelles: a microfluidic guillotine and a microfluidic squeezer. The microfluidic guillotine device can be used to create membrane wounds of a reproducible size and damaging the cell oral apparatus, while the microfluidic squeezer can be used for damaging the cilia and cytoskeleton. After damaging the cell, we study how these organelles can repair themselves. Such devices are important for understanding how the organelles repair, as well as how these organelles are formed in cells, which may lead to future engineering efforts to modify organelles for specific applications (Living Bioreactor).
Personnel: Lucas Blauch
Accomplishments: We determined that the microfluidic guillotine device is better than other device alternatives for creating controllable membrane wound sizes. We are in the process of quantifying wound size as a function of flowrate. We have also thoroughly characterized the microfluidic cell squeezer device and have observed its ability to damage cilia and the cytoskeleton. We filed a provisional patent, and are finishing converting it to a utility patent for the microfluidic guillotine device.
Obstacles /changed direction: We thought previously that the squeezer would be better for

creating membrane wound sizes, and spent a lot of time characterizing it. However, we realized our original guillotine device was better for this purpose.
Center Influence on Project: Cilia regeneration become of interest to us once we realized the squeezer could damage them and they regenerated. Using our devices to study how organelles regenerate and are formed.
Plans: We plan to publish one or more papers on each of these devices: specifically, the guillotine to control membrane wound size, and the squeezer to control cilia and cytoskeleton wounding. We also plan to use our devices to study wound repair in muscle cells, which could be used as an in vitro screening platform for muscular dystrophy drugs.
External Collaborators Juvena Therapeutics
Benefits from other Center projects: It would be exciting to expand this project by applying this to other cellular systems that are studied by CCC members.
Benefits for other Center projects: Could be used to study processes underlying membrane healing, cytoskeletal formation and repair, and cilia formation and repair, which could be used to engineer cells (living bioreactor). Already used to study synthetic organoid regeneration (Cell Lego), which has implications for the robustness of the biological pathways involved in creating the organoids. "Wounding" cells can also be used to insert molecules of interest into cells at a much higher efficiency than other methods, enabling for example genetic engineering of cells with high success rate.

Guillotine for serial bisection of tissue samples
Primary Center Contributors: Stanford (Tang)

Description: One set of tools that we have already implemented for the Cellular Machine Shop are microfluidic devices for cutting cells. In order to apply these tools to the goals of the Cellular Lego project, we are redesigning our original microfluidic guillotine device to work on tissue samples. By splitting tissue in a serial fashion into multiple ~100-200 μm fragments, we can study how the structure of the cells in the fragment contributes to the entire function of the fragment with actual tissue. As an example, how does the local structure of a bacterial biofilm lead to antibiotic resistance? As another example, how does the local structure of cancer contribute to chemotherapeutic resistance? This will inspire new synthetic engineered multicellular structures to make, and perhaps, lead to insights as to how and why cells structure themselves in particular ways in the body (Cell Lego). Additionally, insights gained into how structure of tissue fragments lead to function can lead to new models of how multicellular structure leads to function (CellCad).
Personnel: Lucas Blauch (Stanford)
Accomplishments: Obtained further funding for the project from Stanford. Lucas did an internship at ImpriMed working on the device. Redesigned device from observations during internship and will fabricate in coming months.
Center Influence on Project: Conversations with other members of the Center made us interested in how and why these natural biological structures form. We will understand this functionally through splitting the tissue into small fragments**.**
Plans: We found that our original microfluidic guillotine device was not sufficient to cut through stiff tissue. We are redesigning the device. We will continue our collaboration with ImpriMed, and start a new collaboration with Stanford Nanofabrication Facilities. We plan to have made a device by the end of the year that can cut through solid tissue and do a high-throughput test for chemo-drug resistance. We don't plan to link structure to drug resistance

this year.
External Collaborators: ImpriMed. Stanford Nanofabrication Facilities
Ethical, Legal and Social Implications (ELSI Issues)*[1]: Some of this work was done at ImpriMed, so we are working to address IP rights properly. We are openly communicating with both ImpriMed and the Stanford Office of Technology Licensing.
Benefits from other Center projects: There are several members engaged in imaging methods which will help study the tissue fragments. Additionally, they may give insight into why particular structures lead to function.
Benefits for other Center projects: By studying fragments of actual tissue we can gain new inspiration for the Cellular Lego and CellCad projects. There may also be implications in the Living Bioreactor project if we work with liver or kidney tissue, for example.

Optogenetic control of cell polarity and motility
Primary Center Contributors: UCSF (Weiner)

Description Cell polarity is a key element of cell morphology that dictates the arrangement of intracellular organelles. Learning how to re-engineer the cellular polarity axis is a key element in our overall goal of engineering cell structure. We developed tools to direct cell polarity and movement with light via optogenetic activation of PI3K signaling in neutrophils. This enables us to control the direction of cell movement and could be relevant for organizing the location and interaction of cells.
Personnel. Brian Graziano, Jason Town, Orion Weiner
Accomplishments: Implemented the system and demonstrated we could use it to control the direction of cell motility.
Plans Continue to develop infrastructure for automated analysis of cell shape and signaling for use in computer-controlled optogenetic experiments for significantly higher throughput and more sophisticated experiments. Existing work has been based on manual control of light patterns for optogenetic experiments. Next goal is automated control of light based on automated imaging feedback. Jason has been making good progress on this front and has succeeded in automated analysis of cell shape and movement and dynamically updating the spatial and temporal dynamics of optogenetic inputs based on this information.
Center Collaborators Zev Gartner's lab has interest in related optogenetic experiments around Ras/SOS signaling and discussions are in progress.
Benefits from other Center projects. CellCad may help with some of the modeling of cell signaling that will be useful for feedback control.
Benefits for other Center projects The optogenetic infrastructure for this project will be valuable for control of cell lysis and organelle size for the Living Bioreactor and Cell Legos.

Optogenetic control of T cell signaling
Primary Center Contributors: UCSF (Weiner)

Description: The Cellular Machine Shop seeks to develop new tools to control and analyze cell morphology and state. We developed an approach to control T cell activation using a light-activated ligand for a chimeric antigen receptor. We used this approach to demonstrate that T

[1] Ethical Legal & Social Implications issues noted here are derived from a 1st survey of all CCC faculty. An in-depth survey regarding issues emerging in center research projects is in process, led by R. McGinn.

cells use the lifetime of ligand binding rather than the occupancy of the receptor to trigger downstream responses. This is the first direct evidence of kinetic proofreading in T cell signaling in which the lifetime of ligand binding is the only variable being manipulated.
Personnel Doug Tischer, Derek Britain, Justin McLaurin, Orion Weiner
Accomplishments Paper submitted and under review at Elife
Plan This is a new use of optogenetics for us on several levels. First, we manipulate the timing (rather than the occupancy) of ligand binding to receptor. This will enable us to more broadly probe the role of single molecule timing in controlling cell signaling, which is thought the be relevant in a wide range of signaling cascades. Second, we use an extracellular handle on a cell surface receptor for this variant of optogenetics. The current approach should be relevant to any receptor that requires its ligand presented on a surface—such as cell-to-cell or cell-to-surface adhesion, notch-delta, and others.
External Collaborators Jay Groves (UC Berkeley)
Benefits from other Center projects: This project will benefit from the continued output of CellCad.

Regulation of cell volume for polarity/motility.
Primary Center Contributors: UCSF (Weiner, Dumont)

Description Cell size is a key factor in cell geometry, determining the packing of organelles and the available quantity of cytoplasm. Learning how to control cell volume is thus a key element in our efforts to construct cells of defined organization. Neutrophils increase their volume in response to chemoattractant stimulation, and artificially increasing/decreasing volume also increases/decreases directed cell movement. We are adapting a range of assays to accurately measure cell volume and have made some surprising findings of the pathways that regulate cell volume.
Personnel Tamas Nagy, Brian Graziano, Suvrajit Saha
Accomplishments Developed robust pipeline for measuring cell volume. Found volume increase upon chemoattractant stimulation is independent of actin cytoskeleton and does not appear to be driven by extracellular ion flux.
Plans The pharmacological approach we have used to change volume is non-ideal due to the fact that several of the drugs show general toxicity. Future plans will use CRISPR or shRNA pipeline for genetic interrogation instead.
External Collaborators Mathieu Piel
Benefits from other Center projects. Tools for organelle control in Living Bioreactor would benefit this project
Benefits for other Center projects Conversely, output of this work would also benefit the Living Bioreactor project.

Self-organizing of actin-based morphology.
Primary Center Contributors: UCSF (Weiner, Dumont)

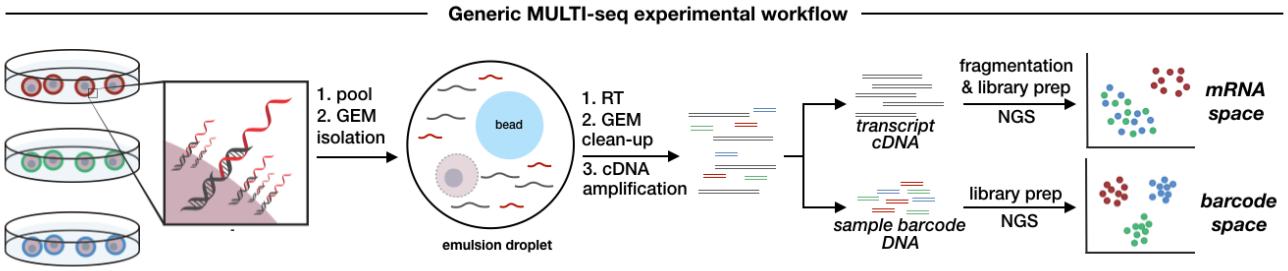
Description Learning how to gain engineering control over the cytoskeleton is critical for engineering overall cell geometry. The actin cytoskeleton is a key factor in positioning and dynamics of many organelles as well as overall cell shape. Different actin nucleators build

very different shaped protrusions, but we don't know how local protein interactions produce large scale control of cell shape.
Personnel Anne Pipathsouk, Rachel Brunetti, Brian Graziano, Suvrajit Saha, Jason Town
Accomplishments We discovered a nanoscale template for cell shape that could explain how an essential actin regulator (the WAVE complex) builds sheet-like protrusions through generating and sensing membrane curvature. We also developed tools to control nanoscale cell shape through nanopatterned surfaces and image cell shape at a variety of scales (super-resolution light microscopy, light-sheet microscopy, high-pressure freezing followed by tomography). The related actin regulator WASP may use a different set of rules to control membrane invaginations.
Plans Develop nanopatterned surfaces to directly test role of shape in behavior, use knockouts to test some possible shape sensors. It's been slow going getting the nanopatterns we need for this work and making new ones that are better suited to our questions, but we found a new collaborator that should be able to help us move this forward.
External Collaborators David Drubin (UC Berkeley), Julie Theriot (University of Washington), Bianxiao Cui (Stanford)
Benefits from other Center projects The microfluidic devices generated for other lab projects by Sindy Tang will be applicable to this project.
Benefits for other Center projects The output of this project will be relevant to both Cell Legos and Cell State Inference Engine.

MULTIseq: multiplexing tools for massively parallel single cell RNAseq.
Primary Center Contributors: UCSF (Gartner, Lim)

Description While the primary focus of the CCC is on cellular structure, we recognize and expect that alterations in structure will also gene expression patterns, and vice versa. We continue our efforts to develop tools to allow hundreds to thousands of individual samples to be analyzed in parallel using single cell RNA sequencing platforms like Dropseq, SeqWell, or 10X. This information is critical for measuring the internal chemical state of a cell – information that is necessary for building quantitative models for all center projects. We or collaborators have now demonstrated nearly one thousand unique samples can be analyzed in a single run and efficiently demultiplexed. The method decreases the costs of analyzing multiple samples by 10-100 fold while simultaneously improving data quality and removing common artifacts.
Personnel Chris McGinnis, Dave Patterson, Vasudha Srivastava, Jennifer Hu, Danny Conrad, Lyndsay Murrow
Accomplishments (i) paper accepted (ii) presented work at multiple conferences (iii) initiated numerous collaboration (iv) shipped reagents to over 50 labs and organizations for evaluation (v) submitted patent disclosure (vi) UCSF initiated negotiations with several companies for licensing reagents.
Center Influence on Project We are excited to apply this technology to Cell Cad and Cell Sentinels. Indeed, this project (and the Center in general) has led us to think more deeply about how we can merge single cell molecular information with morphological information (e.g. in Cell Sentinels project).
Plans We plan to scale up the technology and aim to bring down costs on both the cell library prep and sequencing steps. Our general goal is to democratize single cell sequencing

across the biological sciences. Our specific goal is to apply this technology to better understand how the molecular state of cells relates to their morphological state.
External Collaborators Zena Werb, Jonathan Weissman and others.
ELSI Issues Working with human and rodent tissues always involves ethical considerations. We've consulted with the UCSF IRB and IACUC offices where appropriate.
Benefited from other Center projects Progress in the Cellular Sentinels project will allow us to correlate gene expression patterns with cell structure – a long standing goal of the center.
Benefits for other Center projects We see this tool facilitating all projects in the center where the molecular programs that drive single cells structure and behaviors are important.



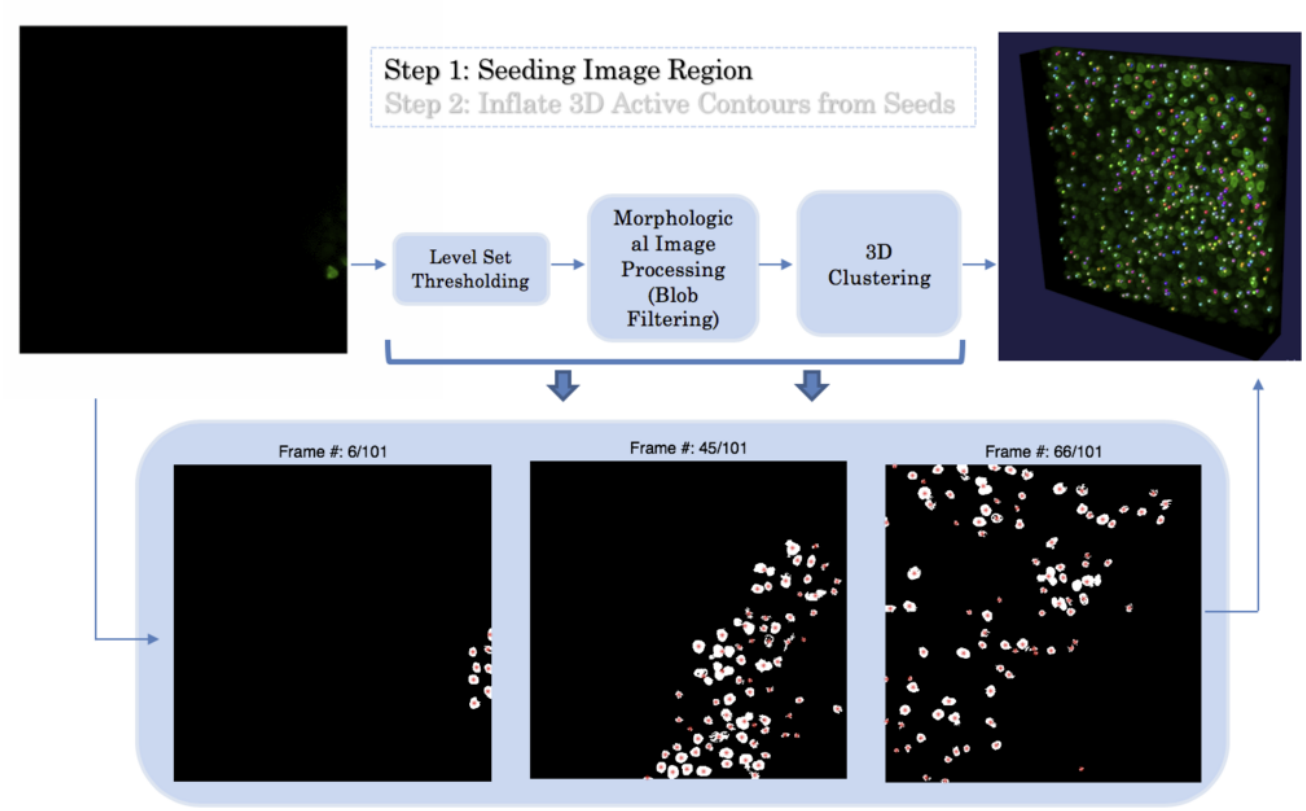
General MULTIseq workflow allowing multiplexing of multiple samples in one single cell RNA sequencing run. The workflow generates to data sets: a Cell x transcript_UMI matrix, and a Cell x Sample_UMI matrix.

Computational doublet detection in scRNAseq data.
Primary Center Contributors: UCSF (Gartner)

Description scRNA-seq data interpretation is confounded by technical artifacts known as doublets—single-cell transcriptome data representing more than one cell. Moreover, scRNA-seq cellular throughput is purposefully limited to minimize doublet formation rates. By identifying cells sharing expression features with simulated doublets, DoubletFinder detects many real doublets and mitigates these two limitations.
Personnel Chris McGinnis, Lyndsay Murrow
Accomplishments (i) paper accepted (ii) posted code to GitHub.
Plans This project is complete and is now available for others to use.
Benefit from other Center projects This project was motivated by the needs of the CellCad and Cell Legos projects.
Benefits for other Center projects This project grew out of the need to remove common artifacts from single cell sequencing data generated in the context of the Cell Legos project, as well as the need to provide "clean" molecular data for design and model generation in the CellCad project.

Nuclei Localization in Chicken Embryo Dataset.
Primary Center Contributors: IBM Research (Bianco), SFSU (Denetclaw)

Description Most of our image analysis efforts in the Cellular Machine Shop are directed at yeast and protists; however, if we can adapt these approaches to analyzing cellular structure inside multicellular organisms, it will increase the range of organisms that we can imagine engineering. As a test case, we are building a detector to detect nuclei in challenging 3D stack microscopic images of chicken embryo. The images have size 512 x 512, with approximately 30 to 40 slices.
Personnel Sujoy Biswas, Simone Bianco (IBM); Devan Shaw, Wilfred Denetclaw (SFSU)
Accomplishments Initial results show promise that we presented at the 2018 fall site visit.
Plans Variable image size can cause problems. Also, there was no annotation on this data set in the first place. We are resolving these problems and scaling up the detection process by generalizing from the limited annotation (with the help of data augmentation).
Benefit from other Center projects Some data was obtained from the Living Bioreactor project. Algorithms were adapted from existing ones in the Cell Machine Shop.
Benefits for other Center projects This project will help build the Cellular Inference Engine for several cellular lines. The experimental protocol and the algorithm proposed will help study the cellular states and functions in response to various environmental stimuli.



Top shows how we perform Otsu threshold based nuclei detection. Next using the detected nuclei as seed point we start inflating volume and surface area to extract the 3D shape of the nuclei.

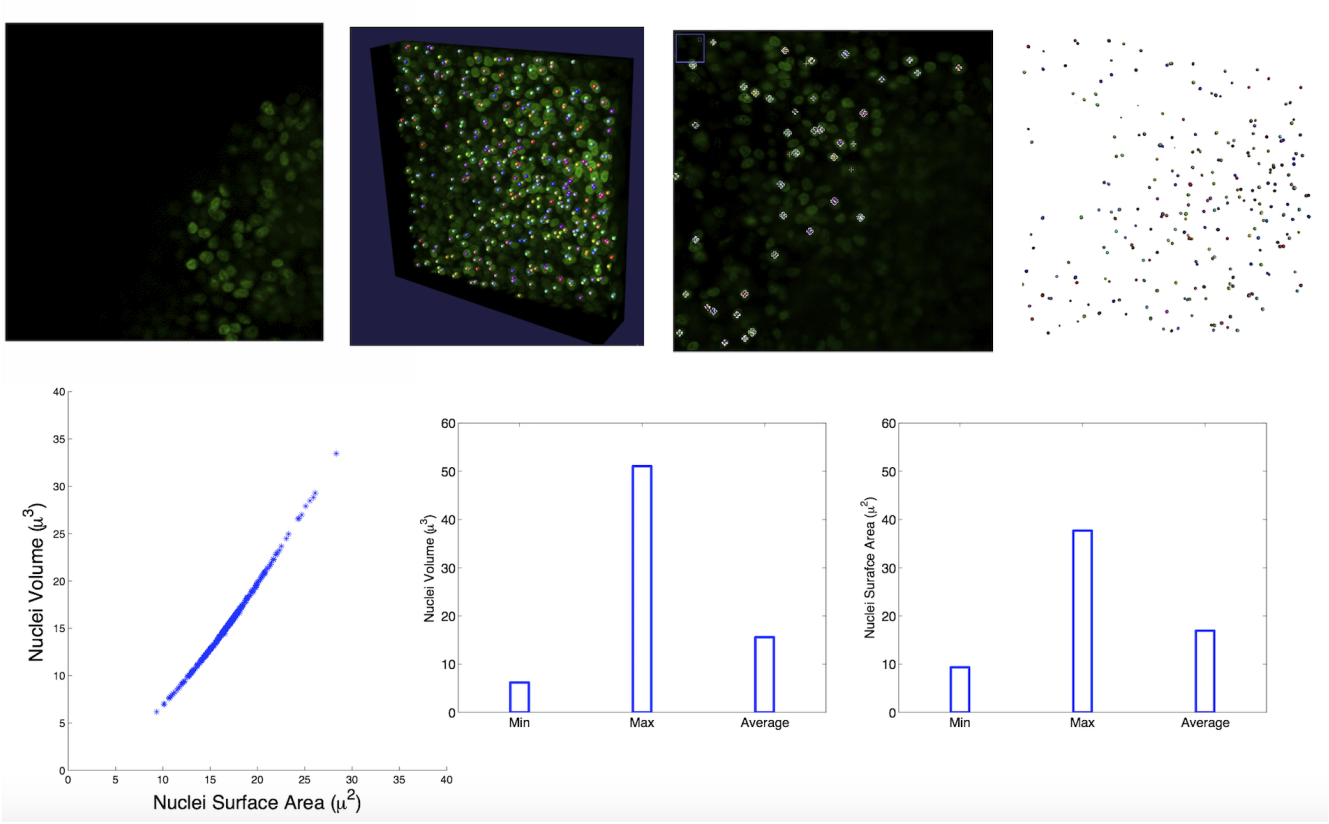


Illustration of nuclei volume and surface area distribution. On top we show the 3D reconstruction taking place. The bottom row shows (from left to right) scatter plot between volume and surface area, and the distribution of nuclei volume and surface area over various sizes.

Filopodia detection.
Primary Center Contributors: IBM Research (Bianco), SFSU (Burrus)

Description Filopodia are small cellular projections supporting cells movement and environmental sensing. Filopodia play fundamental roles in different biological processes and increases in filopodia number or size appear to be correlated with cancer. It is paramount, hence, a segmentation algorithm that allows for filopodia detection as well as features extraction. One possibility is a supervised approach, manually selecting each filopodia and using image manipulation software (e.g., imageJ) for further analysis. However, such an approach is difficult when analyzing the high volume of images that are necessary to consider physiological and pathological variability. A completely unsupervised approach, on the other hand, makes possible the analysis of a huge volume of images, but depends strongly on the characteristics of the image (e.g., resolution, illumination, noise, number of cells), and can easily mislead image segmentation. In the context of filopodia detection, we developed Filoanalyzer. It exploits a semi-supervised approach, which makes possible the analysis of huge volume of images, tuning the parameters of the algorithm to the specific typologies of image to analyze, providing the user a simple and intuitive Graphic User Interface (GUI). The toolbox is realized using OpenCV and python. Once the segmented image has been obtained, different statistics are extracted. The average number, length and width of filopodia per cell are extracted, indicated in dedicated text boxes, and can be easily saved for further analysis.

Finally, Filoanalyzer evaluates the orientation of the filopodia, considering radial of 15 degrees and computing the fraction of filopodia over the total number per cell, in each of these radial portions.

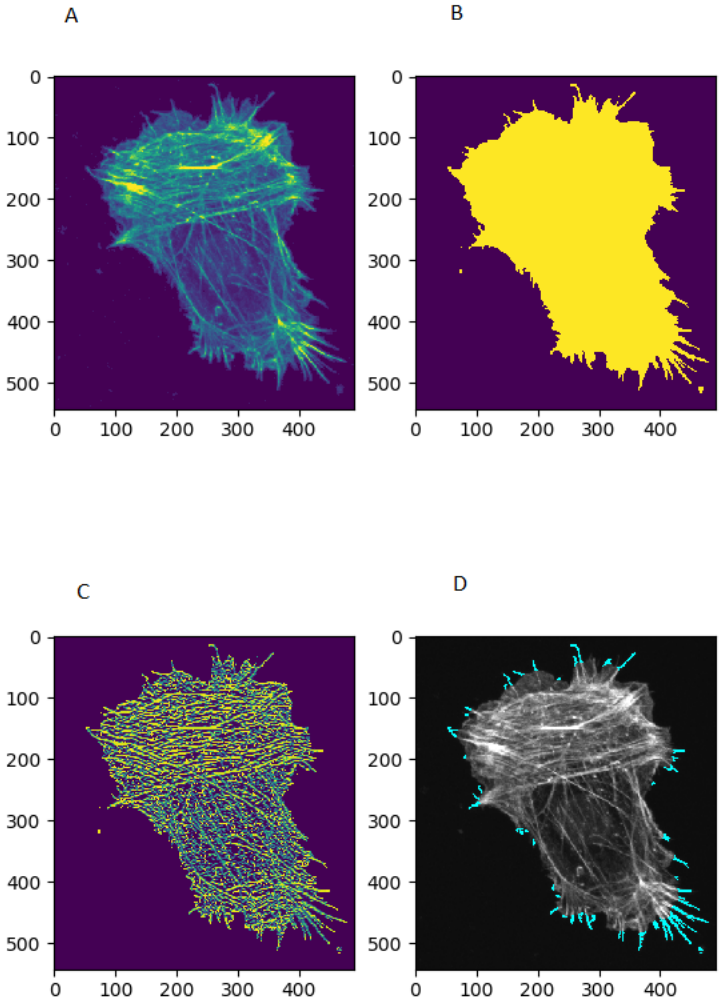
Personnel Vito Paolo Pastore, Simone Bianco (IBM Research); Lisa Galli, Fred Santana, Rocio Cisneros, Madu Nzerem, Destinee Lanns, Angela Lane, Laura Burrus (SFSU)

Center Influence on Project Laura Burrus's group provided the IBM group detail about how to build the tool so that it could provide important biological-related information.

Plans Releasing an initial version of the tool. Filopodia segmentation is a challenging problem, requiring dedicated research for solving the problem of noise reduction and image body segmentation. This is the focus of our ongoing efforts.

Benefit from other Center projects Some of the images used to create the algorithm derived from the Cellular Legos project.

Benefits for other Center projects The tool we developed can be used for filopodia detection and analysis from teams working on this topic (e.g., SFSU). This tool could benefit from integration with the CellCad idea and be part of a predictive platform for cellular structure and assembly.



Examples of results provided by FiloAnalyzer. (A) Original Image (B) cell body segmentaion (C) skeleton (D) filopodia detected

Publications relating to Cellular Machine Shop

Allard CAH, Decker F, **Weiner OD**, Toettcher JE, Graziano BR. 2018. A size-invariant bud-length timer enables robustness in yeast cell size control. *PLoS One* 13(12):e0209301

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Graziano BR, Town JP, Nagy TL, Fosnaric M, Penic C, Iglic A, Kralj-Iglic V, Gov N, Diaz-Munoz A, **Weiner OD**. 2019. Cell confinement reveals a branched-actin independent circuit for neutrophil polarity. *bioRxiv* https://doi.org/10.1101/457119

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Hueschen CL, Galstyan V, Amouzgar M, Phillips R, **Dumont S.** Microtubule end-clustering maintains a steady-state spindle shape. Current Biology 2019 Feb 18;29(4):700-708.

Gruber TD, Krishnamurthy C, Grimm JB, Tadross MR, Wysocki LM, **Gartner ZJ**, Lavis LD. 2018. Cell-specific chemical delivery using a selective nitroreductase-nitroaryl pair. *ACS Chem Biol*. doi: 10.1021/acschembio.8b00524

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Project 2: CellCad

CellCad projects represent modeling tools for designing subcellular, cellular, and tissue-level structure. The long term goal of this project is to build a set of CAD tools for designing/predicting cellular structure. We envision distinct strategies for CellCAD. The first is a model-driven strategy in which we employ coarse-grained mathematical models for organelle dynamics and use those models to predict parameter values that would achieve a particular cell morphology. The second strategy is a data-driven strategy in which we apply machine learning and data analytic methods to large datasets in which organelle morphology has been measured under many different molecular perturbations, and learn how to use this empirical data to predict molecular changes that can be combined to achieve a particular design goal.

Major progress in the last year comes in three general areas.

First, we are beginning to better understand the **"structure" of morphological space**. That is, it is increasingly clear that individual structures within the cells are tightly coupled, indicating that morphological space is highly non-linear. This understanding is going to be critical for refining our approach toward cell-structure design.

Second, we are rapidly advancing tools for **automated experimental design** for model refinement. These tools will allow us to rapidly triage models for CellCad, and refine the best models until they have real predictive ability.

Third, we continue to build new coarse-grained **models for important cellular structures**, with the goal of having a complete set of models applicable to every part of the cell.

Data driven modeling of cellular morphology.
Primary Center Contributors: IBM Research (Bianco), UCSF (Marshall), SFSU (Chan)

> **Description** A fundamental aim for cellular engineering is understanding the relationship between function and morphology in cells. To fulfill this aim, we analyzed mouse embryonic fibroblasts (MEFs) transfected with mutated H-ras, myc and a combination of the two mutagens, two weeks after conception. We segmented the images, used Opencv to extract 26 morphological features. We tried PCA analysis, as well as non-parametric test (Kruskal-Wallis test) to select features in which the differences between controls and the group single transformed-double transformed cells were statistically significant, but the features were not statistically different within the transformed group. Our aim was to build a data-driven model that could explain the combined effect of separate mutations starting from the images of singly mutated cells. Since the results were not accurate enough, we moved to non-linear classification. We trained a neural network using only controls and single transformed cells features. A test set of double transformed cells was classified as mutated by our neural network, suggesting that there is a non-linear relationship between single and double transformations. We are currently studying approaches to improve the interpretability of a neural network, in order to get the exact range of values for the features that change in a related way between single and double transformed, and that will help with building the data driven model. We implemented a RxREN approach, a recursive approach that allows to unbox the neural

network, providing the range of input values that is responsible of shifting the classifier toward one of its output.

Personnel Vito Paolo Pastore, Simone Bianco (IBM Research), Wallace Marshall (UCSF), Mark Chan (SFSU)

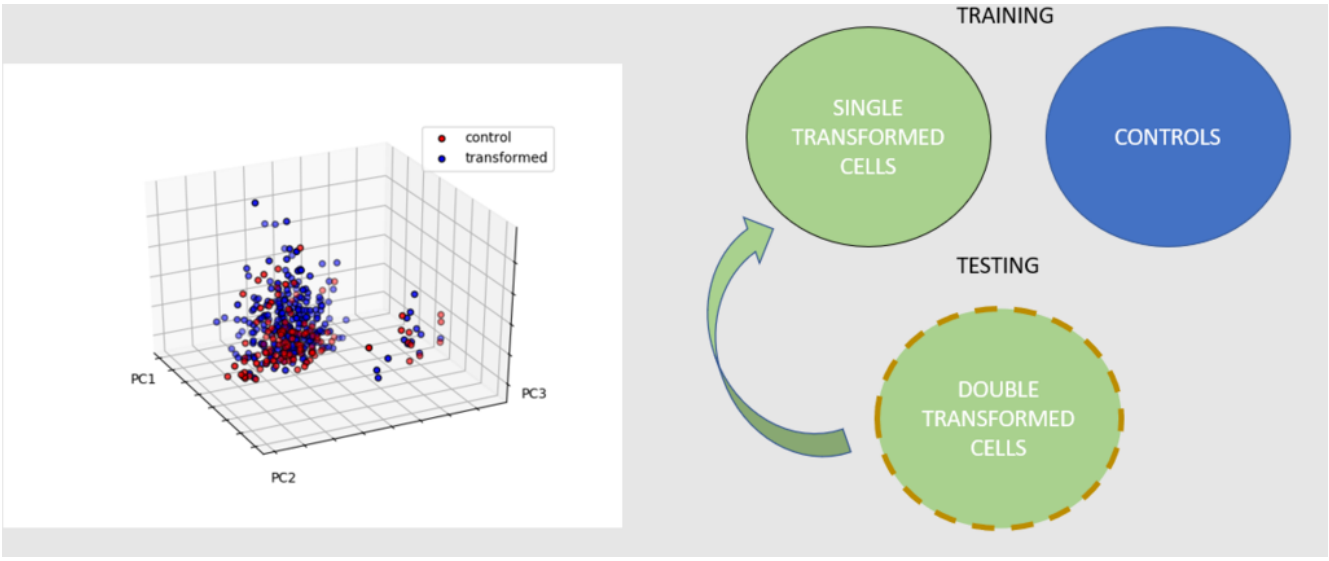
Accomplishments The project is still in a preliminary phase.

Center Influence on Project Meeting with the CCC members helped us in understanding the features to investigate, and the direction of research to follow.

Plans Using a linear approximation for modeling the interactions between the two different type of mutations was not accurate enough. We moved to a non-linear neural network-based approach. However, the neural network is a black box, so we had to focus on interpretability problems, developing a customized approach of reverse engineering providing an unboxing of the network, which is providing the range of input values that is responsible for shifting the classifier toward one of its output. We are currently building a mathematical model for the found relationships.

Benefits from other Center projects This project benefitted from Wallace Marshall's research on linearity of the mutation-morphology phase space.

Benefits for other Center projects The project could help provide a baseline of research for building data driven models.



Left. The PCA is not able to provide separation between control and transformed cells. Right. Scheme used for training and testing the neural network.

Modeling Dynamics of Viral Evolution.

Primary Center Contributors: IBM Research (Bianco), UCSF (Marshall)

Description We calculated the dynamics of a realistic model of virus mutation and evolution as they attack cells. We found evidence of the steady state phase transition at all stages of the dynamics. Viruses show differing strategies depending on their environment of temperature and cell immune response, including competition, collaboration, and a third very complex behavior involving continuous tradeoffs between the members of the viral quasi-species. At the values of

parameters associated with being right near the phase transition, the dynamics showed critical slowing down, “quakes”, “jamming”, and other evidence of glassy disordered behavior. As parameters are very near those of the phase transition, we can run for even 400,000 iterations before the system suddenly goes to the steady state values. (This is known as "quake" behavior.) We have presented this model to virus experts at conferences and at UCSF and have broad agreement that the model is very realistic, especially for human viruses. We are updating the model with suggestions, and in the process of preparing a manuscript.

Personnel Barbara Jones (IBM Research), Greyson Lewis, Wallace Marshall (UCSF)

Accomplishments We found three different strategies that the viruses use for survival, manifested in the dynamics. Also, in accomplishing a long-standing goal, we implemented two different infection mechanisms, one drawn from a distribution without replacement, and the other from a distribution with replacement. The latter was difficult numerically, because unlike the other, it was an iterative process and was difficult to converge numerically. We succeeded in getting phase diagrams for various physical properties of the system using both infection methods. A key question was whether the phase transition observed for the model with one version of infection would survive with an alternative method of infection, and it did: phase transitions, in different regions, were observed for both methods. The infection process involving viruses infecting host cells from a constant distribution was iterative, and for cases with many viruses, took a long time to run. For some months, we could not run the program for anything but a very few viruses. Greyson (see below) figured out a way to optimize the program and, as a result, phase diagrams have been produced for system sizes of up to 10,000 viruses. As the year progressed, we saw that we needed to interpret our data in new ways, including coming up with a workable model of the concept of “viral fitness”. We have bimodal distributions over a good part of phase space, and we realized we need to deal with the peaks separately (“speciation”) rather than just take averages. These changes occurred because Barbara and Greyson attended conferences in the field, attending talks which suggested these ideas, as well as receiving comments from experts on our talks. These conferences were both CCC and non-CCC.

Center Influence on Project This collaboration was initiated because the researchers met at CCC quarterly meetings, and guidance from center members at subsequent meetings has continued to shape the research direction.

Plans In the coming year we will conclude the calculations and write up and submit a paper.

External Collaborators Jamie Kaufman at IBM and Raul Andino at UCSF both contributed very helpful discussions. Neither will be authors on the paper, but will be in the acknowledgements.

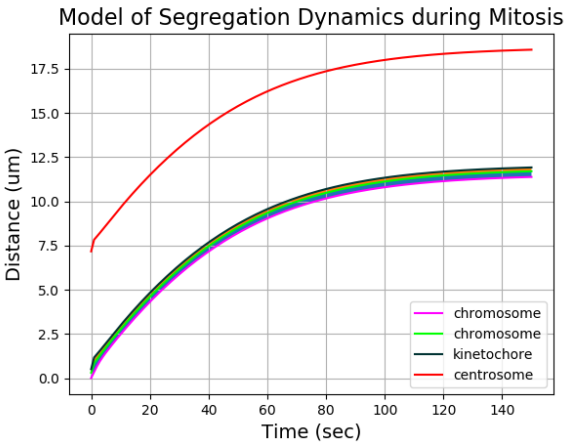
Benefit from other Center projects Any work that involves infection of cells, such as by bacteria, will be helpful in providing parallel perspectives that give insights to our work.

Benefits for other Center projects We envision that our results on infection, mutation, evolution, and immune response in cells will be of interest to anyone working with any infectious and/or evolving system.

Modeling anaphase chromosome segregation in *C. elegans*
Primary Center Contributors: IBM Research (Bianco), SFSU (Chu)

Description A key requirement for model-driven design in CellCAD is having predictive models for all cellular structures. One of the most complex and challenging structures is the spindle. Chromosome segregation during cell division is accomplished by all eukaryotic organisms largely with highly conserved fundamental components - chromosomes, microtubules, and motors - that generate forces that push, pull, and stabilize chromosome movement. However, different organisms and cell types balance the forces generated by these players in various ways to achieve daughter cells of distinct size, shape, and function. Thus, it is often difficult to apply knowledge gained from one system about these molecular players to another. Our study focuses on three cell division events in the same organism, *Caenorhabditis elegans*: mitosis, oocyte meiosis, and sperm meiosis. Our goal is to construct a simple modular model of chromosome segregation in *C. elegans* that can be applied not only to other cell types in *C. elegans*, but also different cell types in other organisms. *C. elegans* is ideal to construct this model because of the wealth of experimental *in vivo* imaging and genetic mutant analysis available that help to define the physical properties of molecular components and forces that drive chromosome segregation. Using these data, we derive a modular mathematical model that recapitulates chromosome movement and phenotypic changes during centrosome ablation in computer simulations. We are applying this model to then understand chromosome movement and define the balance of pulling, pushing, and stabilizing forces that separate chromosomes in different contexts - mitosis, oocyte meiosis, and sperm meiosis.
Personnel Simone Bianco, Barbara Jones, Elsa Rousseau (IBM), James Gerh (IBM/SFSU), Diana Chu (SFSU)
Accomplishments We updated our model of cell division, in which the critical components are masses, springs, and motors, using our physics background. We revised the values of the masses of the organelles using physical principles (volume and density), and likewise updated the spring constants (using a law of dependence of spring constant on rest length) and found improved biological agreement. Further, we devised a model of how the cell motors work based on physical principles, improved over other published models. We started with logistic functions for the motors, and then additionally implemented tanh functions. The logistic functions represent the active action of the motors, whereas the tanh functions represent the passive response of the motors to the external forces applied to them. We obtained biologically realistic behavior, showing that this more complex modeling of the motors is more accurate (Figure below). Additionally, we introduced polar microtubules into our model, which are microtubules attached from the centrosome to the cell wall, perpendicular to, and at an angle to, the main axis of chromosome segregation. We modeled these polar microtubules by approximating them by an average polar microtubule of angle θ, and implementing the effect of this average microtubule on the centrosome. We experienced some challenge to model the motors. As stated above, we started by modeling the action of the motors thanks to logistic functions. We found out that these functions were driving the segregation process, without any effect of external forces (from the other organelles involved in cell division) on the motors. Hence, after several rounds of discussions, we decided to add tanh functions to the motors to model the latter aspect. The two effects were at first difficult to work together and needed refinement of additional cutoffs added to the motors, as well as a modulation on the tanh.
Plans We will finish the last set of simulations needed after the implementation of tanh functions for the motors, fit to experimental data, and perform simulations in various contexts (mitosis, oocyte meiosis, and sperm meiosis). We will meet with external collaborator Moumita

Das to implement noise in the simulations. A paper is currently under preparation and will be completed to include the last updates.
External Collaborators Moumita Das (RIT), an expert on implementing realistic thermal effects and noise in models for cells.
Benefit from other Center projects The concepts of multicellular structure and design being explored in Cell Legos informs our approach. Our project benefits from the Cellular Machine Shop by utilizing data about cell division properties for use in our models.
Benefits for other Center projects Models of chromosome segregation will impact the design of new cells for the Living Bioreactor and Cell Legos projects. Models about chromosome segregation can benefit CCC members who are focused on building cells with distinct properties. This includes Sophie Dumont's group, which is also studying chromosome segregation dynamics. It will also provide data and models for how to alter properties of cells to alter cell size and shape.



Simulated organelles dynamics during cell division. The model simulates the dynamics of the chromosomes (one set of chromosomes is modeled as two distinct objects connected by a spring, to account for elasticity, in pink and green), the kinetochore (in black) and the centrosome (in red). Only one half of the cell is modeled as we assume symmetry.

Coarse grained modeling of the yeast peroxisome.
Primary Center Contributors: IBM Research (Bianco), UCB (Dueber), UCSF (Marshall), SFSU (Chan)

Description This project aims at establishing a pipeline to predictably modify peroxisome size and function through a combination of computational modeling, data analysis and experimental verification. Wet lab experiments by Jennifer Samson and Parbir Grewal (UCB) have been initiated, looking at altering expression level of predicted genes involved in peroxisome biogenesis and screening for increased protein cargo capacity. These data will be fed back to the computational researchers in Simone Bianco's laboratory in refine models of biogenesis.
Personnel Simone Bianco, Vito Paolo Pastore, Elsa Rousseau (IBM); John Dueber, Jennifer Samson, Parbir Grewal (UCB); Wallace Marshall (UCSF); Mark Chan (SFSU).
Accomplishments We are beginning to establish the framework for our approach.
Center Influence on Project This is a quintessential CCC project: We aim at demonstrating a whole cellular engineering pipeline around the organelle peroxisome
Plans We are at the very beginning of this project.
Benefit from other Center projects This project has been designed to tie together all the projects in the CCC, from Machine Shop to Inference Engine and cellular Lego. Orion Weiner's optogenetic bursting of the cell could be advantageous for providing a means to isolate larger, higher-capacity peroxisomes and their contents from the rest of the cell.
Benefits for other Center projects The results of this project will demonstrate a prototypical cellular engineering pipeline. Success in increasing protein cargo capacity will have clear connections with the Living Bioreactor projects.

Automated experimental design for biological systems.
Primary Center Contributors: UCSF (El Samad)

Description The goal of this project is to design an automated pipeline for modeling a biological system, analyzing its behavior, and devising perturbations that move its phenotype to a new desired one. When developing mechanistic models of biological networks, it is often the case that prior knowledge can be used to enumerate a finite set of plausible network topologies, which roughly correspond to specific biological hypotheses about the system of interest. Beginning with such a collection of alternate models, this pipeline automates the process of designing a series of maximally informative experiments to characterize the system of interest with the end goal of invalidating all "incorrect" models. The process alternates between a design phase, in which an experimental design with maximum expected payoff is selected, and an inference phase, in which parameter estimates are refined based off data collected in the previous experiment and invalid models are discarded. The pipeline is designed to support broad classes of models and experiment types, including those with complex time-varying inputs such as optogenetic signals.
Personnel Jared Lumpe
Accomplishments In the last year, we made headway in building an automated pipeline for building a model, estimating its parameters based on data, and using the parameter ensemble to extract salient features that explain the data. We can now use those ensembles to solve an optimization problem that allows us to design an experimental input that increases divergence between the model output for the different parameter ensembles, hence allowing us to possibly discriminate among a number of these models. An extension of this work along the same lines will allow for design.
Center Influence on Project This project has become a major focus of the goals for CellCad and will provide a means of generating models in constant feedback with experimental data.
Plans We will continue to develop this project in the next year
Center Collaborators We are in constant consultation with our colleagues working on CellCad.
Benefit from other Center projects Data types being generated by other Center projects can be used here.
Benefits for other Center projects If successful, this approach will be transformative for design efforts in Living Bioreactors and Cell Legos.

Inventing New Software Interfaces for Computer-Aided Design of Cells.
Primary Center Contributors: UCSF (Douglas, Marshall, Lim)

Description Our project focus is on inventing new software for multi-scale computer-aided design and modeling (CAD/CAM) of cells and related biological systems and tools. Our efforts will synergize with other center members who are currently developing predictive models using various computational techniques. To make those future models accessible and understandable to the broader community, they will need robust and intuitive user interfaces. We believe the invention of novel software tools represents a tremendous opportunity for the Center to accelerate the adoption of cellular systems as engineering platforms. While the models have

been under development by other Center members, we have focused on creating proof-of-concept tools to explore and understand well-characterized systems.

Personnel Shawn Douglas, Tural Aksel, Wallace Marshall, Wendell Lim

Accomplishments We launched the Gelbox website (http://douglaslab.org/gelbox/) and published a preprint in 2018.

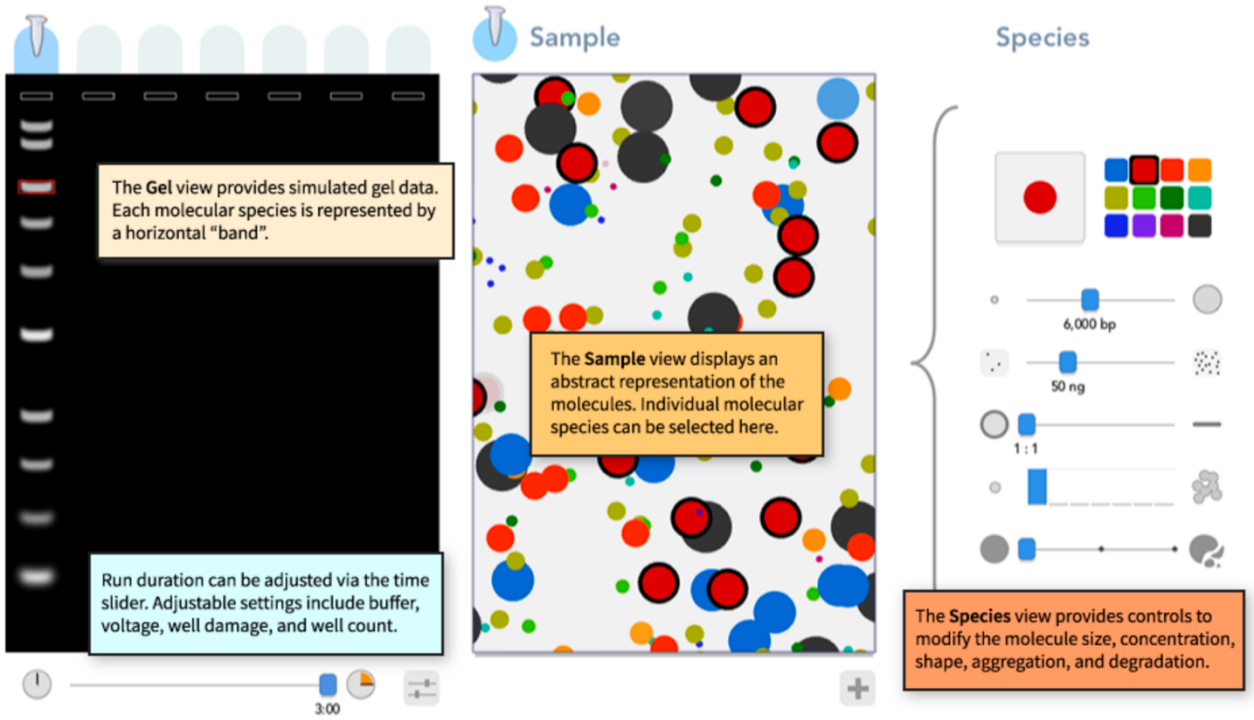
Center Influence on Project Prior to joining the Center, our focus has been primarily on method and tool development for molecular systems (DNA nanotechnology, proteins, electron microscopy). Center annual retreats and quarterly meetings have seeded many interactions with scientists outside our normal focus (i.e. cellular systems), and greatly broadened our horizons about what kinds of new tools are needed. The opportunity to work on the CellCad project has positively influenced our research direction, and reinforced our commitment to exploring creative and unique approaches to widespread software infrastructure issues, such as data sharing and management.

Plans We have identified key design principles in our work so far, including the value of building dynamic, interactive interfaces that give users immediate feedback during interaction, providing multiple linked representations that can be viewed simultaneously to highlight cause-and-effect relationships, and the importance of exposing model parameters for user editing, rather than creating "black box" systems. In the upcoming year, we plan to apply our knowledge to building new interfaces in collaboration with Center Collaborators.

External Collaborators Chaim Gingold (independent contractor, Oakland CA), Dynamicland (dynamicland.org, Oakland CA)

Benefit from other Center projects The next stage of this project (applying our knowledge toward implementing new CellCad interfaces) would not happen without the output of other Center Projects.

Benefits for other Center projects We hope that the next stage of this project will democratize Cellular Engineering tools within the center and to the broader community by providing powerful, intuitive, well-documented user interfaces to the underlying simulations and models.

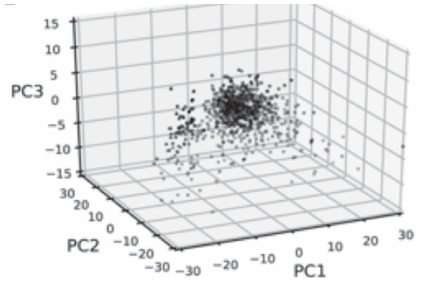


Summary of Gelbox interface used in this project

A morphological state-space formalism for data-driven cell design.
Primary Center Contributors: UCSF (Marshall), IBM Research (Bianco), SFSU (Chan)

Description A central requirement for CellCad is developing a representation for cell morphology that can be used to compare cells and to specify cell designs in formal terms. To this end, we have implemented a way to construct a morphological state space for cells by imaging large numbers of cells, extracting shape features, and using data dimensionality reduction methods to create a state space.
Personnel Amy Chang, Greyson Lewis, Wallace Marshall (UCSF), Vito Paolo Pastore, Simone Bianco (IBM Research), Mark Chan (SFSU)
Accomplishments We have performed cell state reconstruction using mouse embryonic fibroblasts. We find that all dimensions of the state space contain contributions from all organelles, suggesting that different organelles will not be independently addressable. Perturbations using drugs that target individual organelles affect other organelles, again confirming that organelles cannot be altered in isolation. To address whether the state space is linear, we compared position in morphology space for two single genetic perturbations as well as the combination of both perturbations. Results of this analysis clearly show that the perturbations do not combine linearly. By analyzing dynamics in morphology space we find that cell behavior can be predicted by using an equilibrium "energy landscape" formalism. We encountered several obstacles, including the fact that perturbations cannot target individual organelles in isolation, and do not combine linearly. – This has driven us now to focus on using nonlinear tools to prediction results of combinations of perturbations as a way to achieve a design goal.

Center Influence on Project This entire project was driven by the need for a morphology space representation in CellCad.
Plans During the next year we will explore nonlinear methods to solve the prediction problem for combining perturbations.
Benefit from other Center projects Data from the Cell State Inference / Sentinel project will be used to develop morphology state spaces for other cell types.
Benefit for other Center projects This morphological state space formalism will provide the basis for the development of design tools in CellCad.



Morphology space obtained by PCA analysis of over 200 morphological features measured in images of mouse embryonic fibroblasts.

Models for hydrodynamic cellular communication
Primary Center Contributors: Stanford (Prakash)

Description We have recently discovered a new mode of "hydrodynamic" communication amongst single cells – in the species. This is the first example of hydrodynamic communication that acts like a trigger wave – where a cell both generates a hydrodynamic signal and receives a hydrodynamic signal – much like a chain reaction. *We made this discovery in Spirostomum,* one of the largest single cell ciliate. Despite being a single cell, *Spirostomum* generates ultra-fast contractions that generate hydraulic waves in the medium which produce flows that can be characterized at medium Reynolds number flows with inertial components. Using experimental and mathematical models, we further show that *Spirostomum* can not only generate ultra-fast contractions leading to hydrodynamic packets of information propagating from the cell, but also read these packets and subsequently contract – leading to a contraction "soliton" that propagates in a population. Using mathematical models, we show that an extended shape of a cell enables this sensitive measurement. We further built a high-throughput single cell shearing apparatus using a hele-shaw geometry that can be used for a large number of organisms to collect quantitative data. This work has also led to a new technique for high-throughput mechanical perturbations.
Personnel Arnold Mathijessen, Manu Prakash
Accomplishments Paper submitted Mathijessen A et al., in review at *Nature*, 2018
Center Influence on Project Interactions with other Center members have led us to consider how hydrodynamic communication could be leveraged as a design principle for Cell Engineering.
Plans We will further develop the role of mechanosensitive ion channels in the sensitivity in readout of hydrodynamic strain. We have further developed a micro-injection technique for introducing drugs and constructs into these cells.
Benefits for other Center projects This project has revealed design principles of use to the Cell Legos project.

Connections between organelles during cell division
Primary Center Contributors: SFSU (Riggs), UCSF (Marshall), Stanford (Tang)

Description An important fundamental question in the CellCAD project is, to what extent can individual organelles be engineered independently of other organelles. We are using asymmetry of organelle inheritance in a novel strategy for testing organelle interactions, by asking which organelles show correlated segregation during division. We have examined localization, organization and dynamics of organelles during cell division in the early Drosophila embryo using timelapse confocal microscopy and lattice lightsheet microscopy.
Personnel Cecelia Brown, Jessica Bolivar, Alia Edington, Alma Aracey, Martinez Peraza, Bethany Morin, Matt DeCruz, Blake Riggs (SFSU); Ulises Diaz, Nicole Rodrigues, Wallace Marshall (UCSF); Luke Blauch, Sindy Tang (Stanford).
Center Influence on Project By interacting with the rest of the Center, we have been inspired to quantitate our imaging data and focus on physical measures of organelle movement.
Plans We struggled with storage issues from imaging data collected at the AIC, Janelia Farm. We collected over 60 TB of data but did not have access to a server or cloud based storage system for this data. Currently we are exploring storage with Amazon Web Service. Based on a recent publication, Ma and Mayr, Cell 2018, we are interested in investigating Tis11, a membraneless organelle that is juxtaposed to the Endoplasmic Reticulum (ER). We believe that Tis11 + organelles contains RNA binding proteins (Atx2) organizes polyribosomal transcripts necessary for cell programming. We are currently interested in examining the connection between the Tis11+ organelle and ER dynamics during cell division. This change in direction would represent a novel area in the CellCad. We are continuing to collaborate with Wallace Marshall and Sindy Tang to investigate the localization and changes in mitochondrial populations in Stentor based on cell stress and wound repair. Specifically, we will explore other dyes and labels for additional organelle distribution in Stentor after exposure to the microfluidic device for wounding. We are focusing our efforts in examining Tis11 during cell division and cell fate selection.
Benefit from other Center projects Imaging and quantitation tools in Cellular Machine Shop.
Benefits for other Center projects By exploring the connection between membraneless organelles, organelles and cell programming, our work would inform the predictive models that are being developed in other Center Projects.

Publications relating to CellCAD

Castillo U, Gnazzo MM, Turpin CGS, Nguyen KCQ, Semaya E, Lam Y, DeCruz M, Bembenek JN, Hall DH, **Riggs B,** Gelfand VL, Skop AR. 2019. Conserved role for Ataxin-2 in mediating ER dynamics. *Traffic*. doi: 10.1111/tra.12647

Gingold C and **SM Douglas**. Gelbox — An Interactive Simulation Tool for Gel Electrophoresis. 2018. bioRxiv https://www.biorxiv.org/content/10.1101/406132v1

Marshall WF, Fung JC. 2018. Modeling meiotic chromosome pairing: increased fidelity from a tug of war between telomere forces and a pairing-based Brownian ratchet. *Phys Biol. 2019 Apr 3. doi: 10.1088/1478-3975/ab15a7*

Condon A, Kirchner H, Lariviere D, **Marshall WF**, Noireaux V, Tlusty T, Fourmentin E. 2018. Will biologists become computer scientists? *EMBO Reports* 19, E46628.

Marshall WF. 2018. A dilution model for embryonic scaling. *Dev. Cell.* 46, 529-530.29.

Chang AY, **Marshall WF**. 2018. Dynamics of living cells in a cytomorphological state space. *Submitted.* Currently under revision at *PNAS. Preprint: bioRxiv*. 2019 doi: https://doi.org/10.1101/549246

Project 3: Cellular Lego (engineering multicellular structures)

This project aims to create the practical and theoretical tools necessary to build multiple cell types and organisms into multicellular structures capable of performing specific functional tasks. Examples of research areas that would fit into the Cell Legos project include:

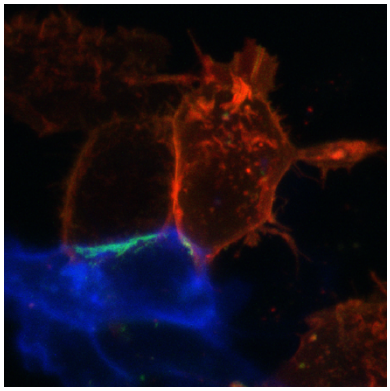
- Methods for controlling physical constraints of tissue growth
- Controlling tissue shape by engineering self-organization
- Efforts to reveal principles of self-organization that can be used for engineering applications
- Controlling cell number or tissue size through self-organization
- Engineering or understanding cell-cell communication
- Controlling collective cell behaviors or decision making

Major progress in the last years comes in two general areas.

First, we continue to elaborate the cell-cell communication tools we introduced last funding cycle. These include signaling filopodia, SynNotch-based tools, tight junctions and gap junctions.

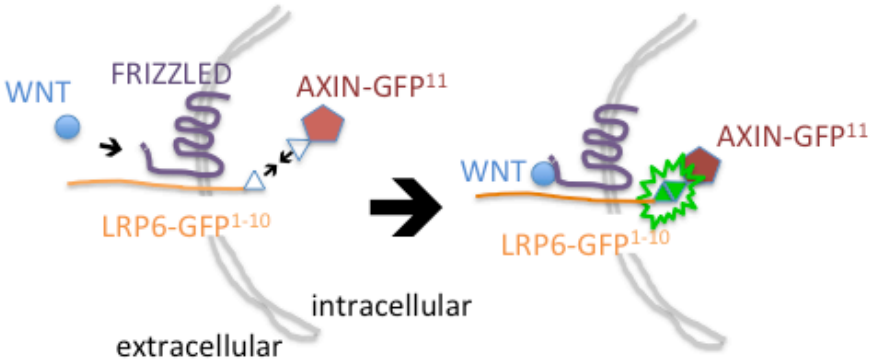
Second, we are quickly identifying design principles for multicellular structures from studying the fundamental properties of living systems. Important lessons learned include how to organize epithelia (Trichoplax, mammary gland); how to organize branching tissues (kidney); how to organize flows across tissues (lung, flatworms); how to organize differentiation (muscle). These findings are informing models developed in CellCad, motivating the development of new tools in the Machine Shop, suggesting chemical screens in the Cell State Inference Engine, and suggesting new roles for subcellular structures in the Living Bioreactor.

Cell-cell communication using filopodia.
Primary Center Contributors: SFSU (Burrus), UCSF (Gartner)



Description Filopodia are organelles that span the cell and tissue level and thus represent an important opportunity for achieving novel multicellular interactions by engineering a cellular organelle. We have evidence that overexpression of WNT1 and WLS induces new filopodia and increases Wnt signaling. While our data are consistent with an important role for filopodia in Wnt gradient formation, we have not yet obtained unequivocal proof. Madu Nzerem, an undergraduate, has shown that the machinery responsible for inducing new filopodia is associated with Wnt production and not reception. We have also been working to determine whether the contact of filopodia from a Wnt producing cell with a target cell activates signaling. To do this, we need to be able to visualize Wnt signaling in live cells. We are planning to leverage the split GFP system to detect the Wnt-induced association between two proteins. Before making specific constructs to detect Wnt signaling, we first used CD4-GFP$^{1-10}$ and CD4-GFP^{11}to validate that the split GFP system works in our hands. Indeed, we are able to visualize GFP at the site of contact between CD4-GFP$^{1-10}$ and CD4-GFP^{11} expressing cells (see Figure on the right – red cell is making CD4-GFP$^{1-10}$ and blue cell is making CD4-GFP^{11}. Though we have identified

several possible proteins to tag for these experiments, we have currently settled on LRP6 and Axin. LRP6 has been tagged on the C-terminus with GFP^{1-10} and Axin has been tagged on the N-terminus with GFP^{11} (as per figure below).
Personnel Lisa Galli, Fred Santana, Madu Nzerem, Rocio Cisneros
Accomplishments Validated split fluorescent protein system to report on cell-cell contact.
Center Influence on Project Learning that we could plate cells in specific positions has enabled to us to begin building a morphogen gradient in cultured cells.
Plans In the next year, we hope to nail down the role of filopodia in Wnt signaling. If filopodia are important, then we would expect cells with more filopodia to signal better than those with less. Rocio Cisneros, an undergraduate in the Burrus lab, is testing this theory. Specifically, she is overexpressing Myosin X to induce the outgrowth of new filopodia. The ability of WNT1 and WLS expressing control cells and Myosin X transfected cells to propagate Wnt signals is then being compared. Previous publications from other labs have shown that cdc42 is required for Wnt transport via filopodia in other model systems. We are now creating a dominant negative version of cdc42 that will be overexpressed along with WNT1 and WLS to test the requirement for cdc42 in filopodia induction and Wnt signaling. The finding that cdc42 is required for filopodia induction and Wnt signaling will provide key evidence that filopodia are critical for Wnt signaling.
Benefit from other Center projects This project will benefit from bringing Filoanalyzer (discussed under Cellular Machine Shop) online. The ability to quantify filopodia will be tremendously useful.
Benefits for other Center projects Images obtained for these experiments can be used for our Filoanalyzer project.

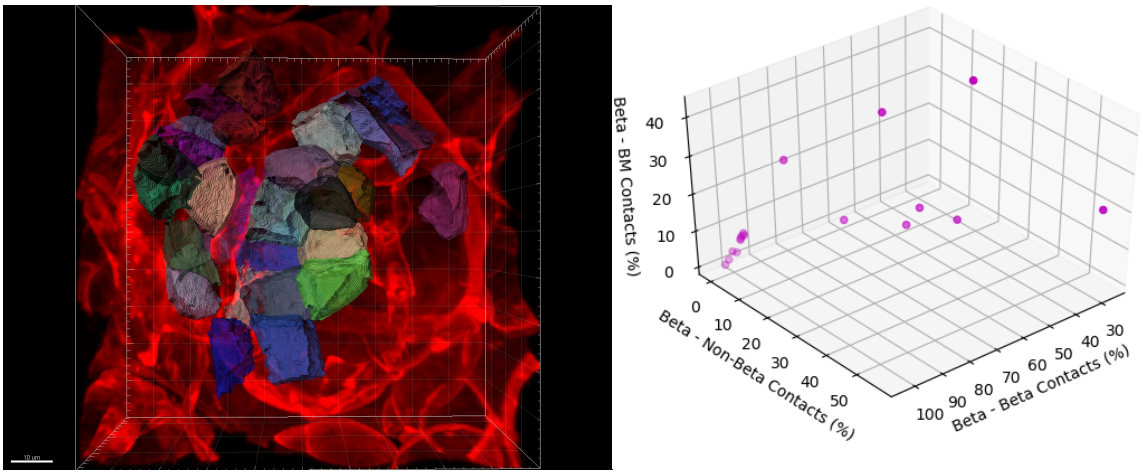


Cell-cell communication mediated by Wnt signals.

Measuring the structure of the pancreatic islet.
Primary Center Contributors: UCSF (Gartner, Fung), IBM Research (Bianco)

Description Before you can build a tissue, you need to know its structure. Remarkably, the structure of the pancreatic islet is unknown, despite it being one of the major targets for tissue engineers. We are measuring the structure and interfacial interactions of all cells in the islet using immunofluorescence staining and quantitative microscopy. Images are being segmented using machine learning algorithms and the three dimensional structure recreated using standard pipelines.

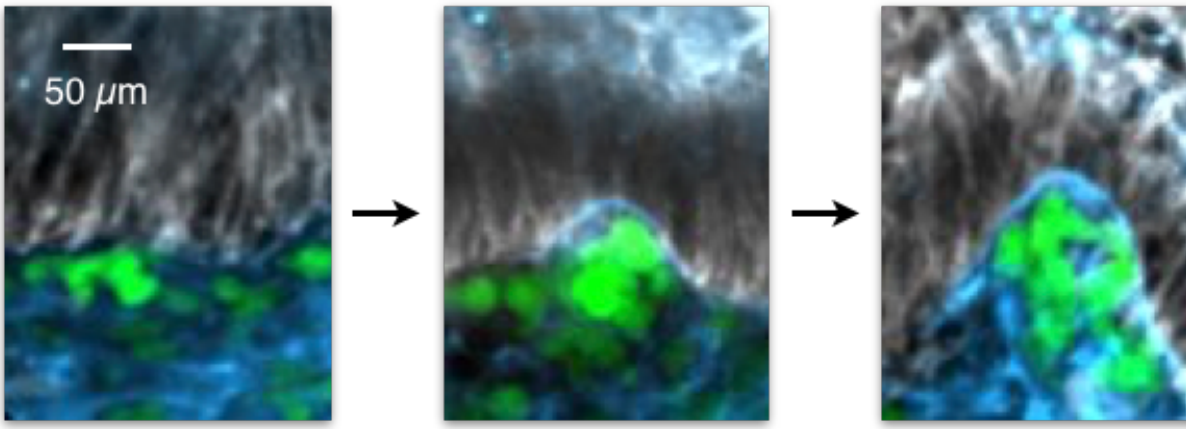
Personnel Olivia Creasey, Daniel Elnatan, Jennifer Fung, Zev Gartner (UCSF), Sujoy Biswas, Vito Paolo Pastore, Simone Bianco (IBM Research)
Accomplishments (i) identified conditions for clearing and staining of human and mouse pancreatic islets; (ii) collected data for numerous human and mouse islets; (iii) performed preliminary data analysis on islets identifying two unique types of Beta cells defined by their spatial neighborhoods; and (iv) began developing machine learning algorithm for unbiased image segregation in 3D.
Center Influence on Project Help with deconvolution from Jennifer Fung's lab has been critical. Working with Simone Bianco's group will become critical in the next year as we refine our analysis.
Plans Image segmentation remains challenging in 3D. We are working with Daniel Elnatan/Jennifer Fung to refine image deconvolution and Simone Bianco's group to improve our image analysis pipeline. Our major focus over the next year will be on image analysis. We are also attempting to focus our analysis on Beta and Alpha cells. We are currently using Ilastik to analyze our images. It works, but could perform better. We plan to work closely with Simone Bianco's group to develop a better segmentation pipeline. We will also work with Loic Royer's group to improve image resolution in 3D using some of his recent innovations.
External Collaborators Julie Sneddon (UCSF); Loic Royer (Biohub).
ELSI Issues Human pancreatic islets are sourced for donor cadavers. Mice are euthanized according to the Sneddon lab's animal protocol.
Benefit from other Center projects Image analysis will benefit hugely from tools developed in the Cellular Machine Shop.
Benefits for other Center projects The 3D image segmentation tools we will develop will become critical for other projects in Cell Legos.

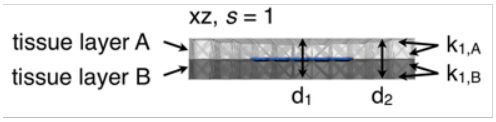


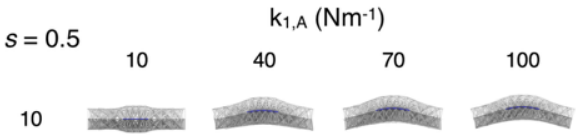
Left: 3D reconstruction of a mouse pancreatic islet showing vasculature (red) and segmented Beta cells (multiple colors). Right: Distribution of Beta cells based upon cell-cell and cell-basement membrane contact area. Note the cluster of cells in the lower left that only make contacts with other Beta cells.

Mechanical folding of the gut.
Primary Center Contributors: UCSF (Gartner)

Description We are investigating whether the villi of the mouse intestine fold according to a mechanism we identified in a previous CCC project. Specifically, we hypothesize that a mechanical compaction of the mesenchyme breaks the symmetry of the gut epithelium, setting the position of incipient curvature as the epithelium grows and folds. For this project, we are combining live cell imaging, physical measurements, single cell RNA sequencing, and mechanical modeling to identify the molecular and physical mechanisms of gut morphogenesis.
Personnel Chris McGinnis, Hikaru Miyazaki
Accomplishments (i) performed spatial and pseudotemporal single cell transcriptional analysis of villus morphogenesis; (ii) identified molecular markers consistent with a mechanical compaction of the mesenchyme. It remains challenging to image embryonic gut explants live. We continue working to improve our protocol.
Center Influence on Project Stimulating conversations with colleagues like Wallace Marshall, Simone Bianco, and Manu Prakash have advanced our thinking on this topic. Moreover, the excitement of other center members for our engineering-based approach has provided motivation for students and postdocs working on this project.
Plans We aim to refine a computational model for *in vivo* tissue folding that is a modified version of what we published previously (e.g. Hughes *et al*., *Dev. Cell* 2018). We also hope to measure the modulus of mesenchymal condensates in comparison to surrounding tissue so as to parameterize our model.
Center Collaborators Informal conversations have been influential.
External Collaborators Ophir Klein (UCSF)
ELSI Issues All studies involving mice as model organism have ethical questions. We aim to minimize the number of mice used in our studies.
Benefit from other Center projects Image analysis will benefit hugely from tools developed in the Cellular Machine Shop. Modeling tools are being refined as part of CellCad.
Benefits for other Center projects Folding is a ubiquitous phenomenon in biology. Thus, similar physical mechanisms likely contribute to the morphology of subcellular organelles such as the mitochondria and ER. This process also likely contributes to processes like branching morphogenesis, which is under investigation in the context of Cell Legos.





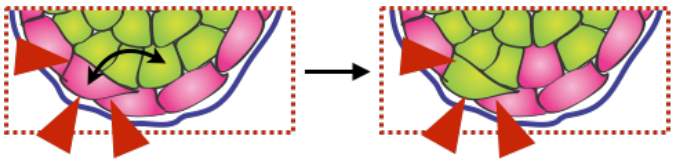


Top: Mesenchymal cells (green) condense into stiff aggregates at the interface between the epithelium (grey: E-Cadherin) and mesenchyme (blue: collagen I). Bottom: Mechanical model of condensate formation and tissue deformation showing how anisotropy of tissue stiffness can lead to placode formation or folding.

Building and breaking the mammary gland
Primary Center Contributors: UCSF (Gartner)

Description In order to engineer tissue, we need to understand the fundamental physical principles of tissue organization. We previously demonstrated that the steady state structure of the human mammary gland minimizes the total interfacial energy among cellular and ECM components of the tissue. We are currently working to understand the robustness of this self-organizing principle by analyzing the effects of genetic perturbations on tissue interfacial energies and cell dynamics. We have focused on perturbations predicted to disrupt tissue structure in the context of diseases like cancer. We have implemented a semi-quantitative computational model for structure formation and disruption and are currently validating the model in the lab using tissue reconstitution experiments.
Personnel Vasudha Srivastava, Jennifer Hu, Danny Conrad, Chris McGinnis, Lyndsay Murrow.
Accomplishments (i) identified PIK3CA as a genetic perturbation that changes tissue interfacial energies and disrupts tissue architecture in a manner predicted by our computational model (ii) identified a partial molecular mechanism downstream of PIK3CA activation that alters tissue interfacial energies and thereby alters tissue structure (iii) established an in vivo model to validate our findings (iv) began to explore the kinetics aspects of our model.
Center Influence on Project Working with colleagues focused on the physical mechanisms of structure formation in biology has been critical. Also, Wendell Lim's lab has become interested in cell sorting (the phenomenon we're studying here), which provides new colleagues for feedback.

Plans Our initial hypothesis that Rac1 was responsible for changes in cell-ECM interfacial energy downstream of PIK3CA was wrong. However, we identified Akt as a necessary kinase downstream of PIK3CA for the observed phenotypes. We are focusing on nailing down a molecular mechanism, validating our findings *in vivo*, and expanding the relevance of our findings by investigating cell plasticity in bipotent cells. In addition to the points listed above, we will work to refine our model so as to generate new testable hypotheses regarding the kinetics of tissue structure formation and breakdown.
External Collaborators Mark Labarge (City of Hope Medical Center), Andrei Goga, Thea Tlsty (UCSF)
ELSI questions All human samples are surgical discard material and are IRB exempt. However, all patients provide consent to have their tissue used.
Benefit from other Center projects Image analysis will benefit hugely from tools developed in the Cellular Machine Shop. Modeling efforts will continue to evolve with help from our colleagues working on CellCad. Our ability to synthesize lentivirus to perturb the structures was absolutely dependent on our collaboration with external partner Serotiny Inc.
Benefits for other Center projects The 3D image segmentation tools we will develop will become critical for other projects in Cell Legos.



$$W_{LEP\text{-}ECM} > \phi(W_{LEP\text{-}LEP} - W_{MEP\text{-}LEP}) + W_{MEP\text{-}ECM} + W_{MEP\text{-}MEP}$$

Top: the left image is the structure of the human mammary epithelium at the steady state. The image at the right represents a disrupted structure of the mammary gland where the internal cells (light green) are mispositioned in the basal layer (magenta). Red arrowheads indicate the cells that change positions on the left and right images. Bottom: A mathematical model describing how changes in interfacial energy (W) can lead to a tipping point in tissue structure stability. When this inequality is satisfied, the structure on the left is the most stable at the steady state.

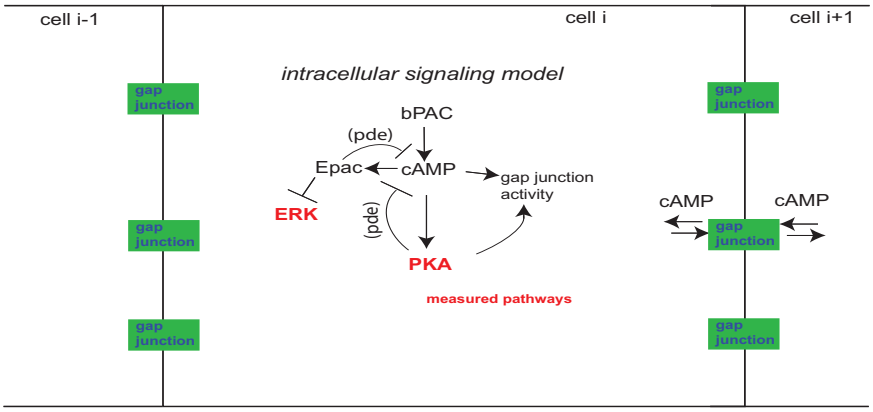
Cell shape and adhesion during muscle formation.
Primary Center Contributors: SFSU (Domingo)

Description The key concept of the Cellular Lego project is that by engineering the structure and properties of cells, we can control and tune the development of tissues. Cell adhesion is a perfect example of the interface between the cellular and tissue level of organization, and is one of the main intended targets for engineering in Cellular Legos. We are using pattern formation in the vertebrate embryo to examine the role that changes in cell adhesion play in coordinated cell movement and shape changes that underlie the formation of muscle.
Personnel Julio Ramirez, Katie Padilla, John Paul Bugay, Carmen Domingo
Plans We will continue to investigate the connection between cell adhesion, cell shape, and muscle differentiation.
External Collaborators Helen Willsey (UCSF), Richard Harland (UCB), Ilmi Yoon (SFSU)

Benefit from other Center projects Better understanding of the role of cell adhesion in building complex tissues.
Benefits for other Center projects Working with embryos provides a level of complexity that should complement the single cell work done by others.

Understanding the coupling of calcium and Erk signaling between cells.
Primary Center Contributors: UCSF (El Samad)

Description One of the motivations for building structures out of cells in the Cellular Lego project is that unlike the building blocks of inert materials, cells can actively communicate with each other and adjust their behavior according to their neighbors. How cells can couple their decision making remains a major mystery and one we must solve to program multicellular organisms. We are disentangling the mechanisms of regulation and propagation of the ERK/PKA/Ca2+ signals through the application of spatially localized cAMP inputs, and genetic and chemical perturbations. We are using the Madin-Darby Canine Kidney Epithelial cell line (MDCK) as our model system, specifically as a monolayer to allow for cell-cell coupling. We are also investigating the effects of intercellular communication in generating emergent transcriptional responses in response to spatially non-uniform cAMP perturbations.
Personnel Michael Chevalier, Joao Fonseca, Hana El Samad
Accomplishments We have made significant progress both experimentally and computationally. Specifically, we have focused on the coupling of cAMP from emitter cells, which contain optogenetically controlled adenalyl cyclase (bPAC), to receiver cells (no bPAC). We are interested in how this coupling affects the resulting ERK and PKA signals in each of these cell types and as a function of emitter cluster size. Experimentally, we have applied various chemical perturbations to inhibit different aspects of the system, including gap-junction inhibition, PKA inhibition, and PDE inhibition. In conjunction with the experiments, we have developed a multicellular computational model guided by the results from these experiments. This has allowed us to test different intracellular regulations and cell-cell coupling regulations for different configurations of emitter and receiver cells, and different combinations of genetic and chemical perturbations. Some of the significant results have driven us to develop new strains to further our understanding of the gap-junction regulation.
Center Influence on Project This project is motivated in part by our desire to fulfill a major goal of the Center – to understand, and then engineer, multicellular communication and decision making.
Plans We intend to drill down further into these findings in order to build further support for our model and elucidate the molecular mechanism. We hope to complete these studies and begin writing a paper describing our findings.
Center Collaborators Many informal discussions with our Center colleagues have shaped this project over the past three years.
Benefit from other Center projects Many informal conversations have helped focus our efforts, but more specifically, optogenetic tools from the Cellular Machine Shop have been critical for this project.
Benefits for other Center projects The transcriptional data we plan to generate will be informative for the Cellular Sentinels project.



Basic illustration of multi-cellular model where each cell has an intracellular circuit and couple to other cells through gap-junctions.

The origins of 3D tissue structure in Trichoplax.
Primary Center Contributors: UCSF (Dumont), Stanford (Prakash)

Description We are working to define the origins of tissue architecture in the simplest multicellular organism, *Trichoplax adhaerens*. Ultimately, understanding tissue architecture (a flat sheet of cells) in this organism will provide insight into the self-organization rules that pattern more complex tissue.
Personnel Lila Neahring, Sophie Dumont (UCSF), Manu Prakash (Stanford)
Accomplishments We have developed a robust protocol for immunofluorescence in this organism, and our initial data invalidates the only published model for how this organism forms a flat sheet of cells. Lila won the Popular Vote Best Poster Award at the UCSF DSCB 2018 retreat for this work. One major hurdle has been preserving organism architecture under fixation, and immunofluorescence. We are now collaborating with the Berkeley Electron Microscopy Lab to try flash-freeze and freeze-substitution.
Center Influence on Project Our collaboration with Manu Prakash has provided much expertise for working with Trichoplax, and conversations with other CCC faculty (e.g. Zev Gartner) have inspired our approach to study an animal with one of the simplest tissue architectures.
Plans We aim to quantitatively map cell shape, cell type abundance, and tissue-level strain under homeostatic conditions, and the tissue's response when we perturb the balance between dorsal and ventral layers – to test models for how flatness arises.
Benefit from other Center projects This project benefits from imaging and analysis tools developed in the cellular machine shop, as well as concepts being actively explored in the Cell Legos projects.
Benefits for other Center projects As the simplest multicellular organism, understanding tissue architecture in Trichoplax offers to reveal design principles that can become the basis of modeling efforts in CellCad and Cell Legos.

Building tight junctions between cells.
Primary Center Contributors: UCB (Fletcher), UCSF (Lim)

Description A key basic question in tissue organization, and one that presents opportunities for engineering tissues, is to understand how cells come together to form multicellular diffusion barriers that separate "inside" from "outside" and can be used to form large compartments. Epithelial tissues do this, but how cell-cell contacts are established to regulate diffusion of proteins and small molecules through cell monolayers is not well understood. We aim to understand fundamentals of cell-cell junctions and develop new tools that let us engineer cell-cell contact organization and transport.
Personnel Brian Belardi (postdoc); Tiama Hamkins-Indik (grad student); Lienna Chan (undergrad)
Center Influence on Project CCC has expanded our thinking about multicellular sheets and their functions. It has also formed new research connections (Wendell Lim) and brought us into contact with labs already thinking deeply about multicellular structures and working with exciting model systems with whom we would like to find a way to collaborate (Zev Gartner, Wallace Marshall).
Plans Over the next year, we aim to (1) identify the molecular "knobs" that will allow us to increase or decrease transport through epithelial monolayers and (2) advance our *in vitro* reconstitutions of cell-cell junctions to test the sufficiency of those molecular knobs. The larger goal is to be able to engineer transport barriers in multicellular structures.
Benefit from other Center projects This project benefits significantly from the Center's broad view of multicellular structures and multiple experimental systems, which is encouraging us to think about different contexts in which control of transport is necessary. This will help us connect with applications and other researchers where engineering transport through monolayers is important.
Benefits for other Center projects Once we better understand the molecular mechanisms and have developed the molecular tools that control transport between cells in a monolayer, those tools and design rules can contribute to both the Machine Shop and CellCad projects.

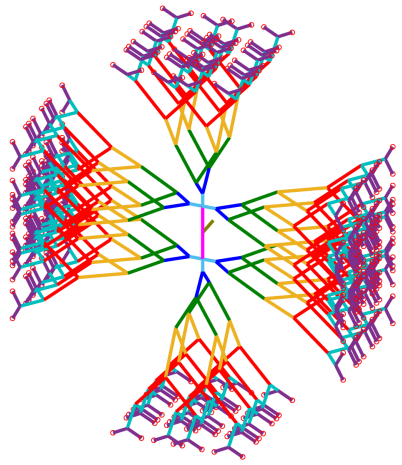
Programmed cell differentiation and self-organization through synthetic cell-cell interaction networks.
Primary Center Contributors: UCSF (Lim, Gartner), Stanford (Tang)

Description We have developed synthetic developmental programs that can be used to generate self-organizing multi-cellular tissues. We link synthetic cell-cell communication, via synNotch receptors, to the regulated expression of adhesion (cadherin) molecules, that drive cell association or segregation. Using circuits of this type, we can flexibly program a diverse set of multicellular structures that mimic key properties of developing tissues: autonomous formation of complex multi compartment structures, increases in cell types (differentiation), formation of asymmetric structure, and the ability to self-repair when damaged. This work shows how minimal networks that link cell communication and morphology can drive self-organization and lays the groundwork for programmed assembly of customized tissues.
Personnel Satoshi Toda, PhD postdoctoral scholar, Pilar Lopez, Junior Specialist, Jonathan Brunger, PhD postdoctoral scholar, Adam Stevens, PhD postdoctoral scholar, Wesley McKeithan, PhD postdoctoral scholar, Wendell Lim, Zev Gartner (UCSF), Luke Blauch, Sindy Tang (Stanford).

Accomplishments Reported findings in the journal *Science*.
Center Influence on Project Established key collaborations with Sindy Tang and Lucas Blauch (Stanford) and Zev Gartner (UCSF)
Benefit from other Center projects This project has benefited from tools generated in the Cellular Machine Shop (cell guillotines) and is increasingly benefiting from tools from CellCad (modeling morphogenesis).
Benefits for other Center projects SynNotch are critical tools for the entire Cellular Legos project.

Computational enumeration of tissue branching patterns.
Primary Center Contributors: UCSF (Marshall, Lim)

Description Most natural organs have an underlying branching morphology, and controlled branching of self-organized cell collectives is one of the ultimate goals of the Cellular Lego project. We are thus developing computational tools to understand branching morphogenesis, in particular to predict (and therefore design) how final 3D patterning results from local branching directions.
Personnel Wallace Marshall, Wei Yu, Wendell Lim (UCSF)
Accomplishments We have developed a formalism known as Branching Tissue Specification Language (BTSL), which can be used to specify any branching pattern. Using this scheme, we have implemented an enumeration program that can generate all possible branching patterns in the specific case of orthogonal bifurcation. We have used this software to compare the actual branching pattern seen in the kidney with the complete set of possible branching patterns. Last year, the results seemed to indicate that many different branching patterns were equally as good as the actual kidney pattern in term of placing endpoints on the surface of the tissue. However, a major accomplishment during the past year was that we identified a mistake in the way that the different branches were being indexed by our experimental collaborators, compared to the indexing scheme that our software uses. Once we corrected the indexing mismatch, we now find that the actual kidney branching pattern performs the best, compared to all other possible patterns. We believe this is a completely novel result that may explain why kidneys follow the developmental pattern that they do, and it represents an example of how an engineering approach, using generative models and figures of merit for design, can lead to new insights into basic biology.
Center Influence on Project This project was driven by the engineering design viewpoint for developing tissues as emphasized in the CCC. Collaboration between Marshall and Lim drove some of the spatial statistics tools used for the software.
Plans Future work will extend the modeling framework to allow a more general representation of branching patterns with subroutines, such as are seen in the lung
External Collaborators Keith Mostov (UCSF), Ross Metzger (Stanford)
Benefit from other Center projects Development of a more general version of modeling software and design languages for developing tissues will be strongly informed by the rest of the Cellular Lego project.
Benefits for other Center projects The computational framework developed for this project will be harnessed to help design novel branching tissues using methodologies in the rest of the Cellular Lego project.



An example of a computationally generated branching pattern

Long-range coordination of cilia-driven flows in epithelial sheets
Primary Center Contributors: UCSF (Marshall, Dumont), Stanford (Prakash)

Description An important challenge in Cellular Lego is programing long range order into self-organized tissues. Self-organization is known to occur in the biological context of multiciliated epithelia, where it appears that hydrodynamic interactions allow cilia to align to each other across distances much larger than a single cell. Mostly this has been studied in cell culture, but the degree of ordering achievable is usually much less than seen *in vivo*. We have developed methods to image ciliary flow in mouse tracheas, and are now using this method, combined with computational modeling, to understand how the sub-cellular and cellular scales of ordering affect the macroscopic ordering of long range mucus flows. Eventually, we hope to use what we learn to build artificial flow fields in multicellular assemblies.
Personnel Guillermina Ramirez-San Juan (UCSF/Stanford), Wallace Marshall, Lila Neahring, Sophie Dumont (UCSF), Arnold Mathijessen, Matthew Bull, Manu Prakash (Stanford)
Accomplishments The major research finding is that long-range flows show increased order compared to the ordering of the cilia that drive those flows. Computational modeling indicates that a certain level of local disorder is favorable for optimal long range flow. Dr. Ramirez-San Juan has presented this work at ASCB and in seminars at UC Berkeley, Harvard, and Brandeis. During the past year we have focused more on the mouse trachea and less on the flatworm, another model system for studying ciliated epithelia. Now that a paper is almost written on the trachea work, we will start going back to the flatworm system to harness its rapid RNAi capability.
Center Influence on Project This work would not have been possible without the collaboration with the Prakash lab, who were instrumental in developing the imaging methodology.
Plans The major focus for the next year is to use the flatworm system combined with RNAi to probe the effects of alteration in ciliary length and density on coordination of flow.
External Collaborators Lily Jan, UCSF
ELSI Issues Use of vertebrate model system always raises the ethical issue of animal

experimentation. We are conducting these studies after consultation and approval from the UCSF IACUC committee.

Benefit from other Center projects One future goal is to use micropatterning/microprinting methods employed by other Center labs to pattern ciliated cells in different spatial patterns, as a new way to explore flow coordination.

Benefits for other Center projects Eventually we hope this work will allow fluid flow to be added as an element of engineered tissue systems.

Publications relating to Cellular Lego

Hughes AJ, Miyazaki H, Coyle MC, Zhang J, Laurie MT, Chu D, Vavrusova Z, Schneider RA, Klein OD, **Gartner ZJ**. Engineered tissue folding by mechanical compaction of the mesenchyme. *Developmental Cell* (*2018*)

Martínez Vergara H. Ramirez J. Rosing T, Nave C., Blandino R., Saw D., Saraf P., Piexoto G., Coombes C., Adams M. and Domingo CR. 2018. miR-206 is required for changes in cell adhesion that drive muscle cell morphogenesis in Xenopus laevis. *Developmental Biology*. 438(2) 94-110. doi: 10.1016/j.ydbio.2018.03.021

Toda S, Blauch LR, **Tang SKY**, Morsut L, **Lim WA**. 2018. Programming self-organizing multicellular structures with synthetic cell-cell signaling. *Science* 2018 Jul 13;361(6398):156-162. doi: 10.1126/science.aat0271.

Toda S, Brunger JM, **Lim WA**. 2019. Synthetic development: learning to program multicellular self-organization *Curr. Opin. Systems Biol*. https://doi.org/10.1016/j.coisb.2019.02.008

Yu W, **Marshall WF**, Metzger RJ, Brakeman PR, Morsut L, **Lim WA**, Mostov KE. 2019. Design rules for kidney branching morphogenesis. *Submitted*. Under revision at *Cell Systems*.

Murrow LM, Weber RJ, Caruso J, McGinnis CS, Borowsky AD, Desai TA, Thomson M, Tlsty TD, **Gartner ZJ**. 2018. Mapping the complex paracrine response to hormones in the human breast at single-cell resolution. *bioRxiv* https://doi.org/10.1101/430611

Project 4: Living Bioreactor

This project aims to harness our ability to specify the organization of intracellular and multicellular structures to implement an entirely new approach to metabolic engineering or materials synthesis. Examples of research areas that would fit into the Living Bioreactor project include:

- Engineering organelle internal environment
- Engineering organelle structure/size/shape/number
- Engineering organelles to make a specific molecule/product
- engineering or understanding the relationship between organelle structure and internal environment
- Studying or engineering organelle dynamics and self-organization
- Engineering non-enveloped organelles
- Studying existing organelles to identify engineering principles that we can control
- High-throughput method for engineering/screening organelle structure/function

Major progress in the last years comes in four general areas.

First, we continue to make progress on **methyl halide production** in the vacuole.

Second, we are rapidly advancing tools for **automated experimental design** for model refinement. These tools will allow us to rapidly triage models for CellCad, and refine the best models until they have real predictive ability.

Third, we continue to develop **use interfaces for CellCad** that attempt to envision how future users to implement a cell structure design tool.

Fourth, we have identified the **peroxisome as an ideal subcellular structure** for engineering and applications. We have convened a highly productive cross-center and cross-project collaboration to model the peroxisome, perturb it and re-engineer its size and number, and apply the compartment to synthesize real-world products. Much of our effort here is discussed in the context of the CellCad project due to the close coupling between these projects.

Increased capacity for compartmentalizing a toxic, bottleneck enzyme in the BIA metabolic pathway.
Primary Center Contributors: UCB (Dueber), IBM (Simone)

Description The use of microbial cells as self-replicating factories often suffers from undesired interactions between the heterologously expressed proteins and native cellular factors. In many instances, the mechanism of resultant toxicity is not understood. One such example is the benzylisoquinoline alkaloid (BIA) pathway that comprises approximately 2,500 natural products with a broad range of bioactivities, including the analgesic opiates, potential anticancer therapeutics, antitussives, and anti-muscle spasm medications. Our previous efforts at engineering a BIA production pathway in *Saccharomyces cerevisiae* determined that the norcoclaurine synthase (NCS) enzymatic step is a bottleneck, rate-limiting step that severely limits titers. Accordingly, we have since isolated an engineered ortholog with considerably higher activity; however, this enzyme shows toxicity to the

yeast production host. We have not been able to determine the mechanism of this toxicity. This toxicity is alleviated through compartmentalization of NCS in the peroxisome, while the substrates and product can diffuse through the peroxisome membrane to allow production to continue. The current capacity of the peroxisome is limiting for production. Our aims in this project are to increase the peroxisome capacity for compartmentalization of enzyme cargo such as NCS.
Personnel Parbir Grewal, Dr. Jennifer Samson
Accomplishments We identified the first two genes candidates to screen combinatorial expression for increased protein cargo capacity. These two peroxisome biogenesis were chosen from genes induced upon oleic acid induction of peroxisome proliferation. Optimal expression levels of these two genes were determined and improved cargo capacity of a model enzyme model providing a visualization assay as well as NCS for improving the production rate of norcoclaurine.
Center influence on project We have initiated interaction with Simone Bianco's laboratory to predict other genes to include in a combinatorial expression library.
Plans We plan to further extend our approach with an increased number of candidate peroxisome biogenesis genes and develop a higher-throughput assay to screen these larger generated libraries.
ELSI Issues Improving flux through this upstream part of the BIA pathway can be combined with emerging improvements in downstream pathways for biosynthesis of increased titers of opiates. Illicit fermentation of opiates presents a clear dual-use scenario. In previous work, enabling flux from glucose through the BIA intermediate (S)-reticuline, we approached policy experts before publication, so that they could analyze and suggest policy approaches to minimize threats of illicit use, while not hindering research towards the promising beneficial applications of various pathway products.
Benefits from other Center projects The integration of computational predictions into our empirical screening for increased peroxisome capacity may provide non-intuitive combinations of gene expressions. Another promising synergy is the inducible cell lysis strategy from Orion Weiner's laboratory for aiding in the isolation of peroxisomes with compartmentalized cargo.

Can vacuole size be used to tune organelle and cytoplasmic pH?
Primary Center Contributors: SFSU (Chan, Esquerra), UCSF (Fung), UCB (Dueber), Stanford (Tang), IBM Research (Bianco)

Description We are investigating whether vacuole size/surface area are directly coupled to vacuole pH. In other words, do cells autonomously tune the pH of vacuoles together with their size/surface area.
Personnel Roberto Carlos Segura and Jamie Calma, (NIH Bridges to Baccalaureate summer student), Mark Chan, Ray Esquerra (SFSU); John Dueber (UCB); Jennifer Fung (UCSF); Sindy Tang (Stanford); Simone Bianco (IBM Research)
Accomplishments Our evidence suggests that vacuole size does not show a strong correlation with internal pH. However, there is evidence to suggest that vacuole size may impact the range of pH's internal to the organelle. Similar to previous years, there are technical difficulties (image quality, analysis throughput) which can be constraining. This project is wrapping up.
Center Influence on Project Due to the interactions with the CCC, emphasis has shifted a bit away from vacuole homeostasis towards engineering of vacuole structure (optogenetic, chemical, genetic) in predictable and dynamic ways.
External Collaborators Fred Chang (UCSF), Sally Pasion (SFSU) and Kathy Gould, Vanderbilt (fission yeast experts)
Benefit from other Center projects The direction of this project has been strongly shaped by discussions among students and faculty at Center quarterly meetings and retreats.

Benefits for other Center projects These projects are more the application of tools and ideas generated in other areas towards concrete applications. However, they are likely to reveal insights that will cross over into other areas, for example, in designing organelles for Cell Legos, or for predicting how organelle structure relates to the molecular state of the cell in Cell Sentinels.

Does vacuole size impact its ability to perform degradative and other chemistries?
Primary Center Contributors: SFSU (Chan, Esquerra), UCSF (Fung), UCB (Dueber), Stanford (Tang), IBM Research (Bianco)

Description We are investigating whether the size of the vacuole is directly linked to enzymatic activity in its lumen. In other words, do cells target unique enzymatic activities to large and small vacuoles.
Personnel Jasmine Sims, Mark Chan, Ray Esquerra (SFSU); John Dueber (UCB); Jennifer Fung (UCSF); Sindy Tang (Stanford); Simone Bianco (IBM Research)
Accomplishments We found a significant difference in vacuole size in M-phase, with the vacuole growing to larger volumes. This seems indicative of a cell-cycle dependence in vacuole fusion. Similar to previous years, there are technical difficulties (image quality, analysis throughput) which can be constraining, however these have consistently been overcome through center collaborations.
Center Influence on Project Due to the interactions with the CCC, emphasis in the lab has shifted a bit away from vacuole homeostasis towards engineering of vacuole structure (optogenetic, chemical, genetic) in predictable and dynamic ways.
External Collaborators Fred Chang, UCSF; Sally Pasion, SFSU; and Kathy Gould, Vanderbilt (fission yeast experts)
Benefits for other Center projects Future work in CellCAD is going to focus on modeling organelle biochemical function and how it is influenced by organelle geometry. The results of these experiments will provide the key experimental data on which to base such modeling efforts.

What is the impact of cell cycle on vacuole size?
Primary Center Contributors: SFSU (Chan, Esquerra), UCSF (Fung), UCB (Dueber), Stanford (Tang), IBM Research (Bianco)

Description We will measure whether yeast regulate the size of their vacuoles during the cell cycle.
Personnel Jasmine Sims, Mark Chan, Ray Esquerra (SFSU), John Dueber (UCB); Jennifer Fung (UCSF) Sindy Tang (Stanford) Simone Bianco (IBM Research)
Accomplishments We are still troubleshooting the experimental protocols, and hope to perform biochemical isolation of vacuoles and their contents for *in vitro* analysis (Western, chemical yield, etc.) Similar to previous years, there are technical difficulties (image quality, analysis throughput) which can be constraining.
Center Influence on Project Due to the interactions with the CCC, emphasis in the lab has shifted a bit away from vacuole homeostasis towards engineering of vacuole structure (optogenetic, chemical, genetic) in predictable and dynamic ways.

External Collaborators Fred Chang, UCSF; Sally Pasion, SFSU; and Kathy Gould, Vanderbilt (fission yeast experts)
Benefits for other Center projects The over-arching goal of the Cell State Inference / Cellular Sentinel project is to infer cell state by observing cell morphology. The results of this sub-project will provide an important test case for that strategy by asking whether cell cycle state can be inferred from vacuole morphology.

How does vacuole size depend on cell shape and division?
Primary Center Contributors: SFSU (Chan, Esquerra), UCSF (Fung), UCB (Dueber), Stanford (Tang), IBM Research (Bianco)

Description In this project we attempt to measure correlations between cell shape, nuclear status, and vacuole size.
Personnel Will Chadwick and Maura de Jesus, Mark Chan, Ray Esquerra (SFSU), John Dueber (UCB), Jennifer Fung (UCSF), Sindy Tang (Stanford), Simone Bianco (IBM Research)
Accomplishments We have found that vacuoles tend to cluster around the nucleus in fission yeast, and even "follow" the nucleus around in mutants where nuclear position is altered. William successfully defended his master's thesis at SFSU. Similar to previous years, there are technical difficulties (image quality, analysis throughput) which can be constraining.
Center Influence on Project Due to the interactions with the CCC emphasis in the lab has shifted a bit away from vacuole homeostasis towards engineering of vacuole structure (optogenetic, chemical, genetic) in predictable and dynamic ways.
Plans See above
External Collaborators Fred Chang, UCSF; Sally Pasion, SFSU; and Kathy Gould, Vanderbilt (fission yeast experts)
Benefit from other Center projects Great opportunities to receive feedback and develop collaborations.
Benefits for other Center projects These experiments will serve as a paradigm for efforts aimed at engineering peroxisome and other organelles. In addition, understanding the link between cell division and organelle dynamics will provide the basis for coarse grained modeling in CellCAD that takes cell division into account.

How is vacuole transferred asymmetrically between mother and bud?
Primary Center Contributors: SFSU (Chan, Esquerra), UCSF (Fung), UCB (Dueber), Stanford (Tang), IBM Research (Bianco)

Description In this project we are measuring how the vacuole is partitioned among mother and daughter cells.
Personnel Angeline Chemel (and Rachel Porter, NSF REU summer student), Mark Chan, Ray Esquerra (SFSU), John Dueber (UCB), Jennifer Fung (UCSF), Sindy Tang (Stanford), Simone Bianco (IBM Research)
Accomplishments We have found that individual cells may have different modes of inheritance, with some steadily transferring organelle from mother to bud, and others performing discrete transfer events only two or three times during budding. Similar to previous years, there are technical difficulties (image quality, analysis throughput) which can be constraining.

Center Influence on Project Due to the interactions with the CCC emphasis in the lab has shifted a bit away from vacuole homeostasis towards engineering of vacuole structure (optogenetic, chemical, genetic) in predictable and dynamic ways.
External Collaborators Fred Chang, UCSF; Sally Pasion, SFSU; and Kathy Gould, Vanderbilt (fission yeast experts)
Benefit from other Center projects Great opportunities to receive feedback and develop collaborations.
Benefits for other Center projects Understanding the interplay between organelle dynamics and inheritance will be essential for model-driven CellCAD.

Can vacuole size be manipulated as a way to accumulate and release product?
Primary Center Contributors: SFSU (Chan, Esquerra), UCSF (Fung), UCB (Dueber), Stanford (Tang), IBM Research (Bianco)

Description In this project we are testing the general idea that the vacuole can be used as a storage depot for metabolic intermediates or products, and that these can be "released" by directing changes to vacuole size.
Personnel Thanh Quach, Gabriela Alvarez-Azanedo, Mark Chan, Ray Esquerra (SFSU), John Dueber (UCB), Jennifer Fung (UCSF), Sindy Tang (Stanford), Simone Bianco (IBM Research)
Accomplishments We have been linking vacuole structure to environmental changes including temperature and chemical exposure (heavy metal, pesticide). We have also found that in classic Ade yeast mutants, the accumulation of a purine synthesis precursor may be dependent on vacuole size. A longer term goal is to use these results to optimize methyl halide synthesis. Similar to previous years, there are technical difficulties (image quality, analysis throughput) which can be constraining. Some new goals have been added.
Center Influence on Project Due to the interactions with the CCC emphasis in the lab has shifted a bit away from vacuole homeostasis towards engineering of vacuole structure (optogenetic, chemical, genetic) in predictable and dynamic ways.
External Collaborators Fred Chang, UCSF; Sally Pasion, SFSU; and Kathy Gould, Vanderbilt (fission yeast experts)
Benefit from other Center projects Great opportunities to receive feedback and develop collaborations.
Benefits for other Center projects These projects are more the application of tools and ideas generated in other areas towards concrete applications. However, they are likely to reveal insights that will cross over into other areas; e.g., in designing organelles for Cell Legos, or for predicting how organelle structure relates to the molecular state of the cell in Cell Sentinels.

How does vacuole structure relate with other organelles?
Primary Center Contributors: SFSU (Chan, Esquerra), UCSF (Fung), UCB (Dueber), Stanford (Tang), IBM Research (Bianco)

Description Here we are investigating whether vacuole structure can be specified/engineered independent of the structure of other organelles.
Personnel Adrian Barrera-Velasquez, Mark Chan, Ray Esquerra (SFSU), John Dueber (UCB), Jennifer Fung (UCSF), Sindy Tang (Stanford), Simone Bianco (IBM Research)

Accomplishments Strain construction is ongoing to create a library of strains with multiple organelle labels (vacuole, peroxisome, ER, golgi, mitochondria). Similar to previous years, there are technical difficulties (image quality, analysis throughput) which can be constraining. Some new goals have been added.
Center Influence on Project Due to the interactions with the CCC emphasis in the lab has shifted a bit away from vacuole homeostasis towards engineering of vacuole structure (optogenetic, chemical, genetic) in predictable and dynamic ways.
External Collaborators Fred Chang, UCSF; Sally Pasion, SFSU; and Kathy Gould, Vanderbilt (fission yeast experts)
Benefit from other Center projects As the Cellular Machine shop develops tools for quantifying various organelles, these will be used within this sub-project to speed up data analysis.
Benefits for other Center projects A major concern in the CellCAD project is the degree to which one organelle can be changed independently of the others. This sub-project will shed light on this key question and also provide a source of image data to be used for the data-driven approach to CellCAD.

Optimizing methyl halide production in yeast by modifying the yeast vacuole.
Primary Center Contributors: UCSF (Fung), SFSU (Chan, Esquerra)

Description We are testing the hypothesis that changing either the surface area or volume of the vacuole will increase methyl halide production in yeast that have been engineered with a salt marsh methyltransferase. This project encompasses the areas of 1) engineering organelles to make a specific product, and 2) high-throughput method for engineering/screening organelle structure/function. As part of this project, we have determined the actual linker sequence needed to target the methyltransferase enzyme to the vacuole and designed methods to prevents it degradation once it gets to the vacuole. As part of this project, we have been working on a high-throughput detection scheme of methyl halide transferase levels using fluorescence intensity. In addition, we have been working out a colorimetric scheme using 4-(4-Nitrobenzyl)pyridine as an alternative method to gas chromatography -mass spectrophotometry to detect methyl halide production.
Personnel Jennifer Fung, Daniel Elnatan (UCSF), Mark Chan, Ray Esquerra (SFSU)
Accomplishments Developed pipeline and software to rapidly segment yeast cells based on only brightfield images in order to evaluate vacuole morphology changes in the yeast knockout collection. We developed a high-throughput transformation protocol to incorporate VPH1-GFP into the yeast deletion collection. We were also able to produce a strain that generates methyl halide. The original paper upon which the vacuole targeted methyltransferase was based reported the wrong construct to target the methyltransferase. The yeast and plasmids sent from the lab were incorrect. We had to remake the plasmids and yeast strains using a different targeting sequence. Another obstacle was that the list of mutants that exhibit a certain type of morphology changed from Brenda Andrews' analysis (see below) is not completely classified properly. Although this is a launching point to analyze vacuole morphology mutants, we still need to verify her classifications with our own analysis of the mutants. We decided to start with a list of candidate mutations determined from Brenda Andrews' lab that alter vacuole morphology, since her lab has already queried the yeast deletion collection for morphology mutants.
Center Influence on Project This is an entirely new direction for all the labs involved..

Plans We are transforming yeast deletion strains with known changes in vacuole morphology with the methyltransferase construct to measure methyl halide production.
External Collaborators Brenda Andrews (University of Toronto)
ELSI Issues Methyl halide, although a useful intermediate in producing silicone, is also an increasingly banned pesticide.
Benefit from other Center projects Classification schemes from the Cellular Machine Shop may speed up the analysis of morphology changes.
Benefits for other Center projects The information gained by manipulating vacuole morphology in this sub-project will also be applicable to other sub-projects that involve vacuole engineering. The results of this work, and the methods developed here, should be broadly applicable to any project geared to making chemical products.

Optimized methods to measure production of methyl halide as a function of yeast strain and MHT construct.
Primary Center Contributors: SFSU (Esquerra, Chan), UCSF (Fung)

Description Methyl halide production will be measured using gas chromatography coupled to mass spectrometry (GC/MS). Results from this work will be used address the following specific aims: 1) Determine if the activity of methyl halide transferase is affected by adding our fluorescence tag. 2) Measure activity of methyl halide transferase as a function of yeast construct. 3) Test high-throughput methods for measuring methyl halide production. The long-term goal is to develop methods to rapidly screen strains for production. Our collaborators have developed two potential high- throughput methods to measure activity and this project will calibrate and test these methods using GC/MS. This work will lay the foundation for high-throughput screen and will eventually enable better design to optimize MHT activity to enhance methyl halide production.
Personnel Erin Kalbaugh, Aileen Hutrion, Kian Kolahdouzan, Ray Esquerra, Mark Chan (SFSU), Jennifer Fung (UCSF)
Plans This work is just getting under way.
Benefit from other Center projects This project grew out of previous work targeted for the Cellular Machine Shop.
Benefits for other Center projects Similar methods will become useful in the context of Cell Legos as the Center moves towards engineering cell consortia that interact to make useful chemical products.

Developing the Axoneme as a novel protein nanoarray / bioreactor.
Primary Center Contributors: UCSF (Marshall), Stanford (Tang)

Description The flagellar axoneme is a highly ordered structure that we hope to exploit as a scaffold for assembling proteins into dense arrays with highly uniform incorporation. This will serve as a platform for expressing hard to fold proteins and for assembling proteins into novel protein-based nanodevices.
Personnel Hiroaki Ishikawa, David Bauer, Nathan Hendel, Jeremy Moore, Karina Perlaza, Wallace Marshall (UCSF), Sindy Tang (Stanford)
Accomplishments The main accomplishments of the past year were showing proof of concept that we can express an enzyme (beta lactamase) targeted to the axoneme by fusion with

axonemal proteins, and that it still retains activity. We also demonstrated the ability to cleave axoneme targeted proteins away from the axoneme anchoring site using TEV protease, as well as the ability to encapsulate axonemes within droplets in an aqueous oil emulsion. Work was presented in a talk at Photonics West meeting.

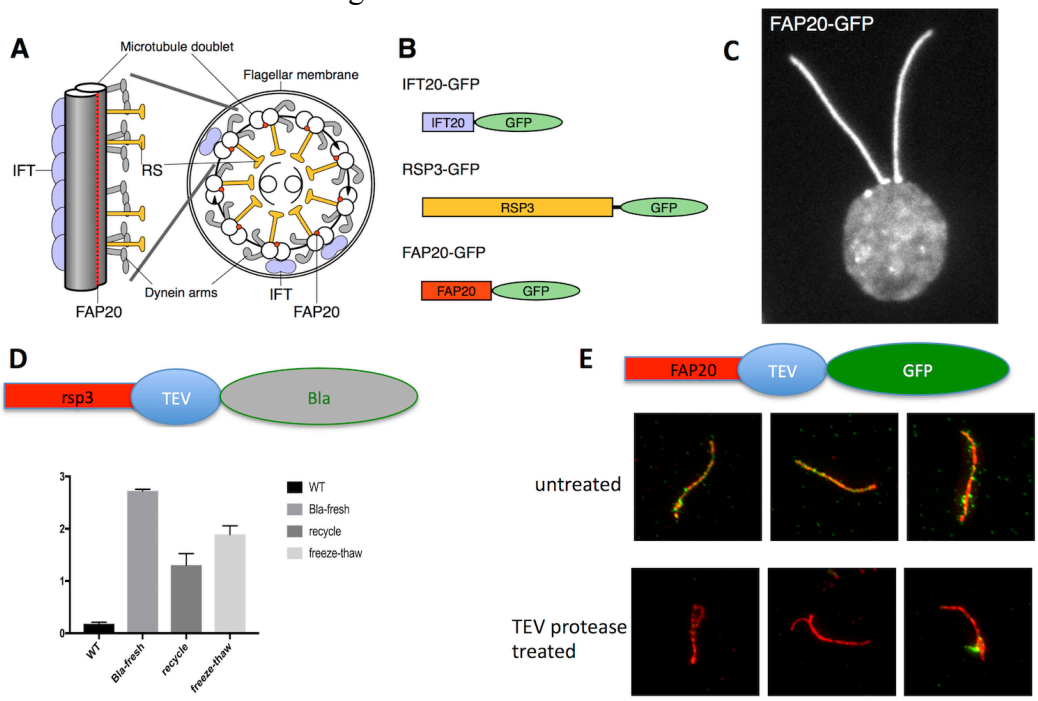
Center Influence on Project This whole project was triggered by the Living Bioreactor project and would not have been done otherwise**.**

Plans Focus on expanding the set of industrially relevant enzymes that can be targeted to the axoneme, and on testing incorporation of known hard-to-fold proteins. Also, we will start testing how alteration in axonemal length affects bioarray performance.

External Collaborators Dr. Hongmin Qin, Texas A&M

Benefits from other Center projects Cellular machine shop tools will help with combinatorial design of construct libraries. Collaboration with industrial partner Serotiny has already facilitated testing of multiple constructs in a short period of time.

Benefits for other Center projects We hope to use the axoneme as a platform for creating self-assembling living bioreactors, by targeting multiple enzymes into the compartment to achieve substrate channeling.



Engineering the flagellar axoneme as a protein expression system. (A) diagram of axoneme. (B) constructs tested for expression as fusion proteins. (C) FAP20 shows strong uniform incorporation into the axoneme. (D) FAP20 targets beta lactamase to the axoneme in an active form, confirming the system can be used to express enzymes. (E) axoneme-tethered protein domains can be released by TEV protease cleavage.

Microfluidic trapping of single cells.

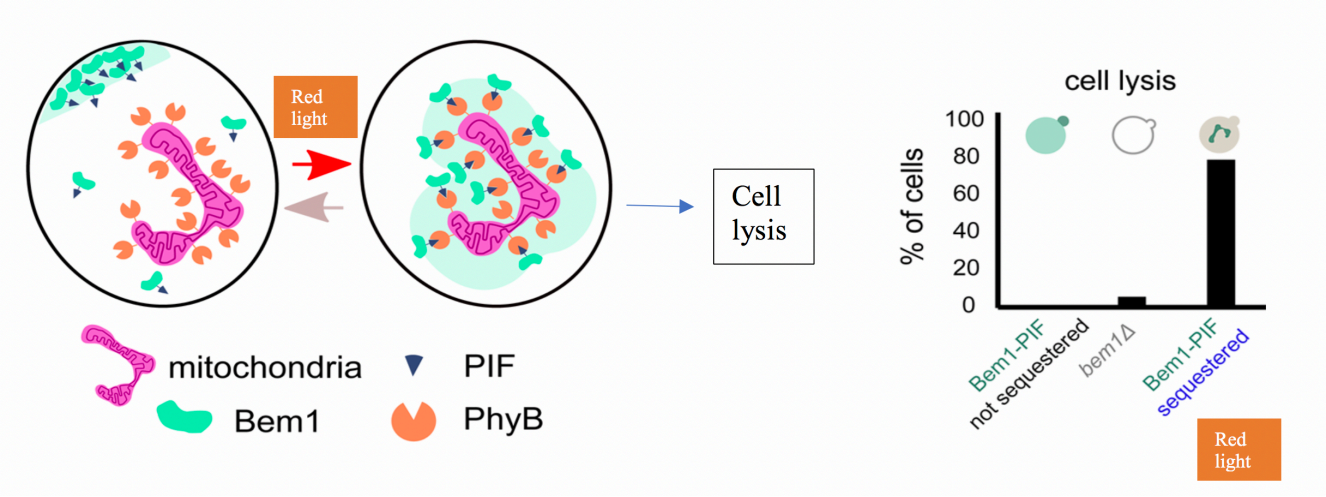
Primary Center Contributors: Stanford (Tang), SFSU (Chan), UCSF (Fung)

Description In order to assay chemical production from engineered cells within the Living Bioreactor project, we have prototyped microfluidic traps for long term incubation and monitoring of yeast and Stentor cells. This fits into Living Bioreactor because the traps are

important for characterization of bioreactor function. We have started using these traps to screen organelle structure and function, and cell behavior. We plan to continue testing these traps as a data collection tool. The traps will also allow studying of cell responses to the environment without the cells moving around (Cell sentinel).
Personnel Kevin Zhang, Seth Cordts, Sindy Tang (Stanford), Mark Chan (SFSU), Jennifer Fung (UCSF)
Accomplishments Fabricated several sets of test traps.
Center Influence on Project This project is the result of ongoing collaboration with other Center labs working on organelle structure and engineering.
Plans Previously we were trapping cells in droplets. We switched to traps because they can be made bigger and we can also flow in different reagents to monitor response. We plan to use the traps to study organelle structure and function.
Benefit from other Center projects This project has moved quickly due to progress engineering other microfluidic devices as part of the Cell Machine Shop.
Benefits for other Center projects Traps can be used for cell Sentinel and cell Lego projects, as well as study of any single cells.

Light-inducible cell lysis system for regulated disruption of budding yeast.
Primary Center Contributors: UCSF (Weiner)

Description Microbial cells such as yeast are increasingly being used as cheap renewable sources for high-value chemicals and biopharmaceuticals. However, only a subset of these biologically-based chemicals are secreted, and many important products such as fatty acids, biofuels, biopolymers, and many recombinant proteins require cell lysis for their isolation. Existing mechanical and enzymatic methods for yeast disruption are inefficient and costly and can represent a significant proportion of the overall production cost of these biologically-based chemicals. We recently developed a system for light-based disruption of yeast that is simple, inducible, non-invasive, and highly efficient.
Personnel Brian Graziano
Accomplishments We applied for a seed grant to further develop this technology as a general class of reagents that can be inducibly applied to our bioreactor project for cell disruption, shift to another step in metabolism, cell segregation to other locations within the bioreactor by flocculation/floating, etc.
Center Influence on Project Cell disruption had previously been viewed as a flaw in this experiment, but during discussions with the CCC it became apparent that in fact this flaw could be turned into a valuable strategy for cell lysis.
Plans Future work will focus on verifying that this mode of cell disruption is still compatible with relevant bioreactor products.
Benefit from other Center projects Would be useful to extend this idea for other projects in the Bioreactor regarding inducible control of cell behavior (disruption, metabolism, segregation) in a user-defined fashion
Benefits for other Center projects Analogous techniques may be useful for tissue fine-patterning in the Cellular Lego project. Could be used as an alternative to apoptosis.



Left: Diagram describing optogenetic yeast lysis. Right: Efficiency of yeast lysis upon red light illumination.

Publications relating to Living Bioreactor

Ishikawa H, Yu JE, Tian J, **Tang SKY**, Qin H, **Marshall WF**. 2019. Cell-based biosynthesis of linear protein nanoarrays. *Proc. SPIE* 108930F

Project 5: Cell State Inference Engine (aka Cellular Sentinels)

The scientific vision of this project is to create a software platform for converting images of cells into estimates of cell environment and signaling state. Examples of research areas that would fit into the Cell State Inference Engine project include:

- Efforts to relate measures of the micro-environment to cell/tissue structure
- Building devices to monitor cell structure remotely
- Building computational models that relate cell structure to specific micro-environments or cell states (e.g. proteomics, transcriptomics, metabolomics)
- Chemical genetic studies that aim to relate the effects of a molecule/drug to a measurable change in cell/tissue structure

Major progress in the last years comes in three general areas.

First, we have made significant advances in our ability to deploy and use **remote microscopic sensing techniques**. This moves us considerably closer to measuring the structure of microorganisms as "sentinels" of local microenvironment.

Second, we continue to make progress on developing **unsupervised image classification techniques** to recognize microorganism structure in images.

Third, we are deploying chemical libraries obtained in earlier years along with organelle tagged yeast to measure the **relationship between chemical microenvironment and cell structure**.

Establishing the baseline for using plankton as biosensor.
Primary Center Contributors: IBM Research (Bianco)

> **Description** Monitoring plankton is paramount to infer potential dangerous changes to the ecosystem. We used a collection of plankton species extracted from a large dataset of images from the Woods Hole Oceanographic Institute (WHOI) to establish a basic set of morphological features for supporting the use of plankton as a biosensor. Using a perturbation detection approach, we show that it is possible to detect deviation from the average space of features for each species of plankton microorganisms, that we propose could be related to environmental threat or perturbations. Such an approach can open the way for the development of an automatic Artificial Intelligence (AI) based system for using plankton as biosensor. For this purpose, a thorough characterization of the baseline of normal appearance or behavior needs to be carried out. We designed and implemented features divided into 4 characteristic classes, each of them describing different aspects of the image, embedding fundamental information for the purposes of classification and detection of perturbations: Geometric, moments-based, texture and contour-based features. We extracted a total of 128 morphological features describing different aspects of plankton images from the WHOI dataset. We defined a binary out of class detector based on the one-class SVM. The developed approach can reach a testing accuracy of about 94% on the collection of species extracted from the WHOI dataset. Such a result confirms the efficiency of the designed features in embedding the plankton morphological information and separating the different species. We also showed that the developed method could be used for detecting unseen species (i.e., not included into the

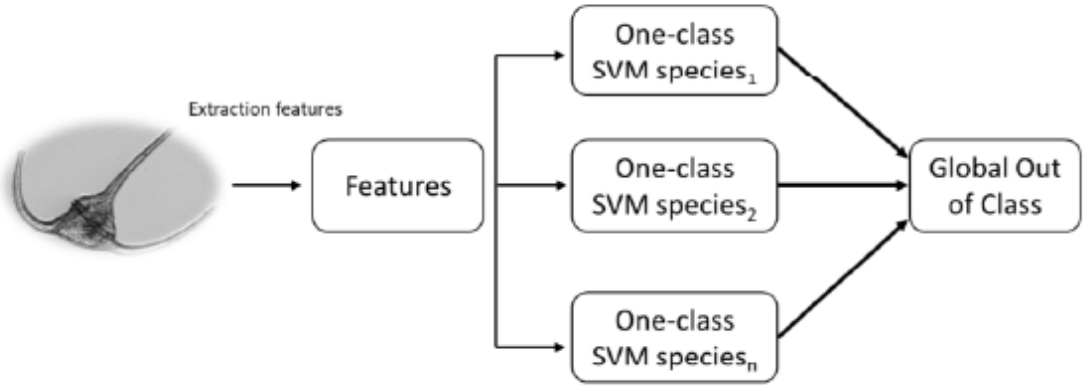
training set). In fact, removing two species from the dataset, they were recognized as anomaly with an accuracy higher than 95%, proving that the approach is not only valid in establishing a baseline for healthy plankton, but it can also be used for detecting unseen species (as well as modification due to environmental changes).

Personnel Vito Paolo Pastore, Thomas Zimmermann, Sujoy Biswas, Simone Bianco

Accomplishments Paper accepted and published (Establishing the baseline for using plankton as biosensor, SPIE Conference Proceeding, Pastore *et al*., Published: 4 March 2019, SPIE Conference)

Plans The features to be engineered have to be chosen carefully; we are making several analyses (e.g., decision trees) for understanding the correct features to be adopted for the algorithm. We will include behavior into the baseline for healthy plankton

Benefits for other Center projects The engineered features and the anomaly detector could be used for different kind of data (not necessarily plankton). The plankton change in morphology detected in this way can lead to the use of plankton as biosensor. This project will help build the cellular inference engine to use plankton as environmental bio-sentinels.



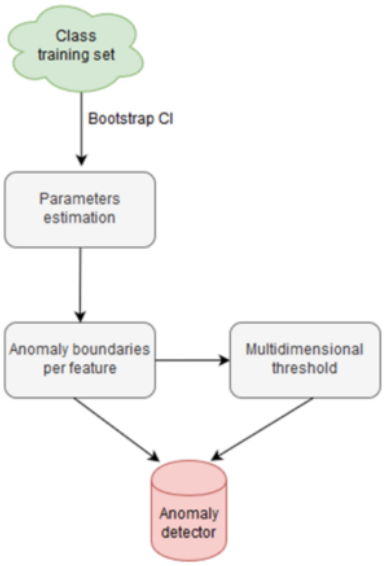
Schematic description of the pipeline designed for the testing our computational methodology.

Semi-supervised Classification of Microorganism.

Primary Center Contributors: IBM Research (Bianco)

Description We developed the Tail Detect (TDT) algorithm, an anomaly detection method able to learn the boundaries of each species of plankton in a space of engineered features. We proposed that an approach based on a parallel schematic of these algorithms could be used for detecting new species (i.e., species not included into the training set). We tested the approach using the 10 species of plankton acquired with our in house lensless microscope. In detail, we removed one species from the dataset and verified if it was considered as anomaly (and hence, it would be added as a new species) from the detectors built using the anomaly detection algorithm for all the other species. We repeated the procedure for all the species. We compared the results with a state-of-the-art approach of anomaly detection, based on one-class SVM. The TD algorithm outperforms the one-class SVM in both classification and anomaly detection, reaching an overall accuracy of 0.983 ± 0.014, a classification accuracy of 0.974 ± 0.03 and anomaly detection accuracy of 0.992 ± 0.08 (one-class SVM overall accuracy: 0.942 ± 0.004).

Personnel Vito Paolo Pastore, Simone Bianco
Accomplishments Paper in submission to *Plos Computational Biology* (An anomaly detection approach for classification of plankton microorganisms, Pastore et al.).
Plans The development of the algorithm is challenging because we only want to use in-class samples (no anomaly). The parameter definition is very important and has led us to a heuristic approach. We are testing the algorithm for other type of data.
External Collaborators Nimrod Megiddo, IBM Research, collaborated in supervising the design of the algorithm.
Benefits for other Center projects This project had provided a method that can be applied for detecting anomaly represented by unseen species, or morphological modification due to environmental changes, so in using plankton as biosensor.



For i **in** num_surrogates:

subset = *extract_with_replacement* (num_samples_per_subset)

For j **in** num_features:

μ_{ij}, σ_{ij} = *compute_parameters* (subset, j)

For j **in** num_features:

μ_j^*, σ_j^* = *compute_bootstrap_percentile* ($\mu_{:j}, \sigma_{:j}$)

n = *compute_with_indicated_confidence_training*(μ_j^*, σ_j^*, training_samples)

$\text{Anomaly\_boundaries}_j = \mu_j^* + n \cdot \sigma_j^*$

num_features_for_anomaly = *compute_thresh*(Anomaly_boundaries$_{:}$, training_samples)

Pseudo code and schematic representation of the TDT algorithm

Building computational models to relate cell structure to microenvironment.
Primary Center Contributors: IBM Research (Bianco)

Description With the detection and tracking framework established in the drop microscope [1] we aim in this project at tracking plankton in general in an unconstrained, natural setting. Using a raspberry-pi based lensless microscope (designed and invented by Thomas Zimmerman, IBM Research), we have collected more than 50 videos of plankton swimming in their natural environment. Tracking these creatures reliably and robustly require novel approach as most of them look very similar to each other. We have tested the idea of pose-based tracker and at present scaling up the algorithm to suit a wide variety of videos. Our hypothesis is that often the temporal cue of plankton dynamic alone can reveal a lot about the existing environmental condition, e.g., the presence of food nearby, the toxicity that repels the plankton, and similar environmental stimuli. However, inference of such environmental conditions necessitates fairly robust detection and tracking methodologies. Hence, we are in the process of evaluating and

benchmarking the state-of-the-art methodologies (along with the ones we developed) on our in-house dataset.
Personnel Sujoy Biswas, Thomas Zimmerman, Vito Paolo Pastore, Simone Bianco
Accomplishments The initial idea of this approach with promising results was reported in a paper listed below.
Plans Heavy occlusion, rapid change in direction, and similar appearance make the tracking very hard. We are implementing a novel algorithm that can track swimming creatures through occlusion by treating them as moving clusters. The trajectories can merge to form clusters, and the clusters can split into individual trajectories (or smaller clusters). The conception of clusters can help us manage trajectories which are close to each other during occlusion. We are scaling up the tracking technologies for tracking a variety of creatures in their natural environment while measuring their response to various chemicals administered into the aquatic medium.
Benefits for other Center projects This project will help build the cellular inference engine to use plankton as environmental bio-sentinels. The experimental protocol and the algorithm proposed will help study the cellular states and functions in response to various environmental stimuli.

The effect of chemicals on organelle morphology.
Primary Center Contributors: UCSF (Fung)

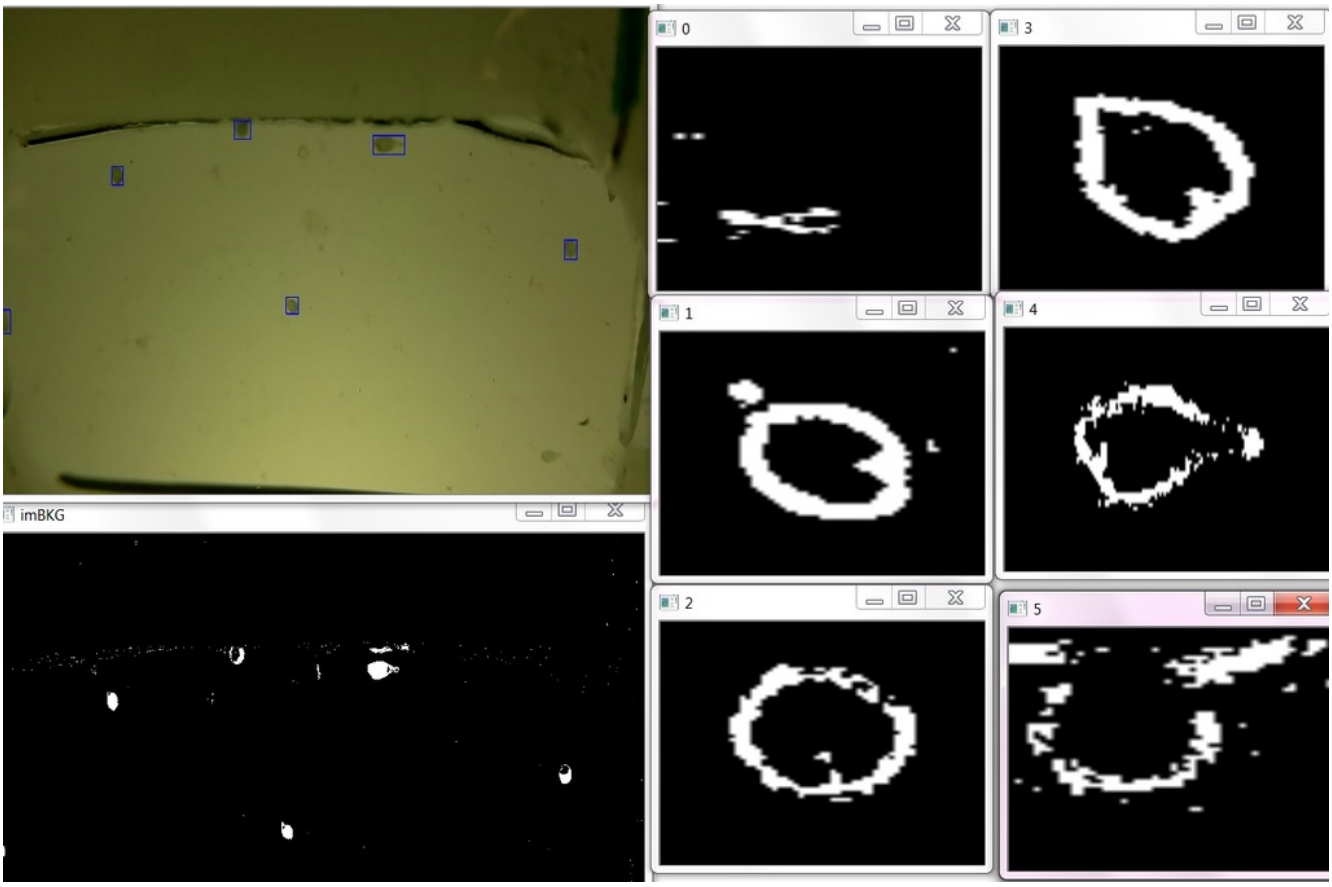
Description This project's goal is to evaluate the effect of chemicals on organelle morphology, with the ultimate goal of being able to infer environmental chemicals via microscopic analysis of organelle morphology. We created a chemical library that contains 150 chemicals identified by the EPA as being of high interest. We are testing them on vacuole structure in yeast.
Personnel Jennifer Fung, Ashwini Oke, Harry Bevir, Tatiana Gromova
Accomplishments Created a chemical library to test changes in yeast organelle morphology. Created a yeast chemical sensitive strain which we are now mating with the deletion collection to create a deletion collection with chemical sensitivity. Began testing the effects of chemical library on vacuole morphology
Center Influence on Project This is a core project for the Center and would not have been undertaken without Center Support.
Plans We remain in the testing phase of this project and will continue our efforts this year.
External Collaborators Tracey Woodruff (UCSF), Patrick Allard (UCLA), and Josh Robinson (UCSF)
Benefit from other Center projects This sub-project benefits from the expertise generated from all Center projects, but particularly the high content imaging instruments and workflows established in the Cellular Machine Shop.
Benefits for other Center projects We anticipate identifying compounds that have profound impacts on cellular morphology. RNA sequencing of these cells may reveal molecular changes that underlie these changes. These would then become the foundation for new engineering strategies for CellCad and Living Bioreactor.

Drop Microscope Improvements
Primary Center Contributors: IBM Research (Bianco), UCSF (Fung), Stanford (Tang)

Description A custom apparatus to monitor the response of plankton to chemicals consisting of a rotating disk of 80 wells underneath an optical microscope, a computer controlled syringe pump, and imaging system all controlled by a Raspberry Pi and Arduino microcontroller.
Personnel Tom Zimmerman, Vito Paolo Pastore, Sujoy Biswas, Simone Bianco (IBM Research), Jennifer Fung (UCSF), Sindy Tang (Stanford)
Accomplishments Improved drop microscope replacing unformatted glass disk with CAD machined 80 well plastic disk with gear driven stepper motor for greater rotational accuracy and stability. Servo controlled pipette was replaced by a syringe pump for greater control of plankton and chemical loading in wells. Collected videos of Stentor placed in wells and established baseline of Stentor activity when placed in well, defined as the ratio: ACTIVITY = # of moving frame / (t*frame_rate). where (t*frame_rate) is the total number of frame acquired at instant t of evaluation.
Plans Not all the wells are filled with one Stentor. Many are empty while others have multiple Stentor. Objectives have not changed. The availability of chemicals at UCSF and difficulty of working with toxic chemicals at IBM is motivating us to move the chemical testing to UCSF. We will be using electric field as a stimulus delivered by peristaltic pump instead of placing plankton in wells. Building a smaller apparatus that controls the number of plankton in the sensing chamber that can be moved to UCSF for chemical screening.
Benefit from other Center projects See Electric Stimulation Microscope
Benefits for other Center projects See Electric Stimulation Microscope

Electrical Stimulation Microscope
Primary Center Contributors: IBM Research (Bianco), Stanford (Tang)

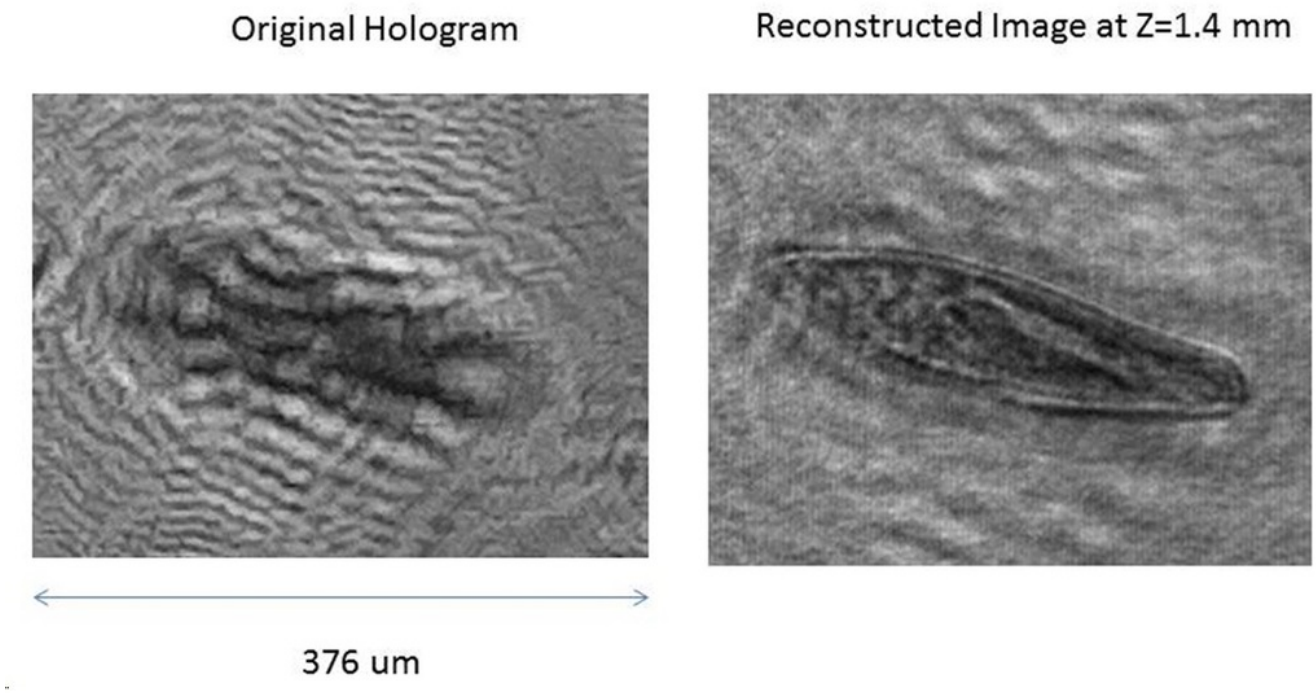
Description In support of the Cellular Sentinel project, we are innovating technologies to permit microscopic analysis of cells in environmental samples such as unicellular plankton in samples of water. A new microscope that automatically loads plankton (Stentor) into viewing chamber, applies controlled electric current, records plankton response, with option to inject chemical into viewing chamber. Can also be used to concentrate and select cells based on morphology.
Personnel Tom Zimmerman, Simone Bianco (IBM Research), Sindy Tang (Stanford)
Accomplishments Proof of concept constructed along with analysis code.
Changes Build out pumps and control circuitry. Improve image processing.
Benefit from other Center Research Microfluidic fabrication skills of Tang Lab (Stanford)
Benefit for other Center Research Marshall lab (UCSF) for concentrating and selecting plankton.



Electric stimulation of Stentor. (Top-left) The upper horizontal wire is the cathode (negative electrode) that attracts Stentor when energized. (Top-right images) Outlines of Stentor featuring the oral pouch (round circle on perimeter) that helps define

Stereo Hybrid Lensless Microscope
Primary Center Contributors: IBM Research (Bianco), UCSF (Fung)

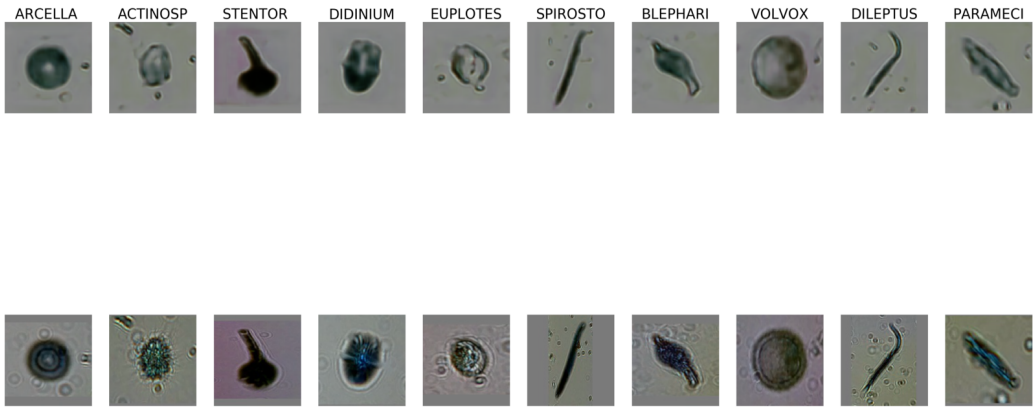
Description A new microscope has been developed that synergistically combines a stereo lensless microscope with a digital in-line holographic microscope, producing low-resolution color images and high-resolution monochromatic image of plankton along with the 3D location. This provides a way to obtain three dimensional images in environmental water samples to analyze the cells present in the sample, and their morphology.
Personnel Tom Zimmerman, Simone Bianco (IBM Research), Daniel Elnatan, Jennifer Fung (UCSF)
Accomplishments Developed working prototype. Presented paper at SPIE
External Collaborators Nick Antipa, Laura Waller (UC Berkeley)
Benefit for other Center Research Other center labs that's study Stentor will be able to use this method for more efficient imaging.



(Left image) Raw holographic image of paramecium captured by image sensor. (Right image) Mathematically reconstructed image of paramecium.

Supervised classification: Deep features extraction versus manually engineered features
Primary Center Contributors: IBM Research (Bianco)

Description The possibility of using plankton as a biosensor requires establishing a baseline of what healthy plankton look like. For this purpose, it is necessary to choose the correct and most meaningful features for the description of cell's images. In this preliminary work, we are comparing the manually engineered features (that have human interpretability, e.g., perimeter, area, color information, textures, etc.) with features extracted by means of deep neural networks. We explored several possibilities of neural networks, as well as autoencoder neural networks.
Personnel Vito Paolo Pastore, Simone Bianco (IBM Research)
Accomplishments We are currently writing a paper about the results
Plans Using the engineered features for other datasets.
Benefits for other Center projects The project will provide a standard for extracting features for different kind of cells images.



Example of reconstruction (top) of plankton images acquired using a lensless microscope (bottom) by means of a deep convolutional autoencoder. The code (i.e., the middle layer between encoder and decoder) can be used as features set for classification purposes.

Using the Chicken Embryo to validate new environmental toxins from Cellular Sentinel methods
Primary Center Contributors: SFSU (Denetclaw), UCSF (Fung, Marshall), IBM Research (Bianco)

Description One of the research threads in the Cellular Sentinel project is identifying compounds with previously unknown effects on cell biology using single cell based assays (including yeast and Stentor). A key knowledge transfer goal will be to convince toxicology researchers, and potentially regulatory agencies, that anything discovered in our cell-based assays is worth further epidemiological analysis. The key to doing so will be a way to move from unicellular to animal model systems, but we want to be able to do this quickly at high throughput, requiring an animal assay that is low cost, fast, and robust. Chick development within the egg is a perfect platform for testing chemical effects on development. As proof of concept, we have tested Round Up™ with glyphosate and heavy metal $CdCl_2$ in treatments *in ovo* to chicken embryos with results of severe decreases in overall embryo size and loss of somite formation, as well as smaller somites and myotome formation defects, including large myotome destruction. These chemicals have a common link in ability to generate reactive oxygen species (ROS) that can account for decreased cellular proliferation and to promotion of cellular death by apoptosis. We will pursue research utilizing the Machine Shop to aid us in constructing a ROS gene probe to transfect into chicken embryo finite cell line cultures to monitor and measure ROS formation and changes in cellular proliferation and cell death in this next grant year of funding.
Personnel Devan Shah, Omar Mendoza, Adrian Martin, Ashley Pereira, Genaro Lopez Morales and Amanda Johnson (SFSU); Jennifer Fung, Wallace Marshall (UCSF); Sujoy Biswas, Simone Bianco (IBM Research)
Center Influence on Project We have become more quantitative in our assessment of data utilizing novel CCC-developed computational tools, including an unsupervised algorithm for counting of nuclei in deep 3-dimensional confocal images. This work had previously been performed through manual image centroid and object edge detection for seeding and inflation

of image seeds to produce 3-D active contours for cell counting. This is then followed by IBM active learning for refining of automated segmentation, as well as, centroid and object detection. This algorithm assists our research in accelerated nuclei counts, as well as providing an automated cell counting tool in deep 3-D confocal images that will be useful both for our lab, and to other CCC labs..

Plans We are continuing to obtain more detailed data concerning Round Up™ and $CdCl_2$ while extending the project to include an increasing array of potentially toxic chemicals.

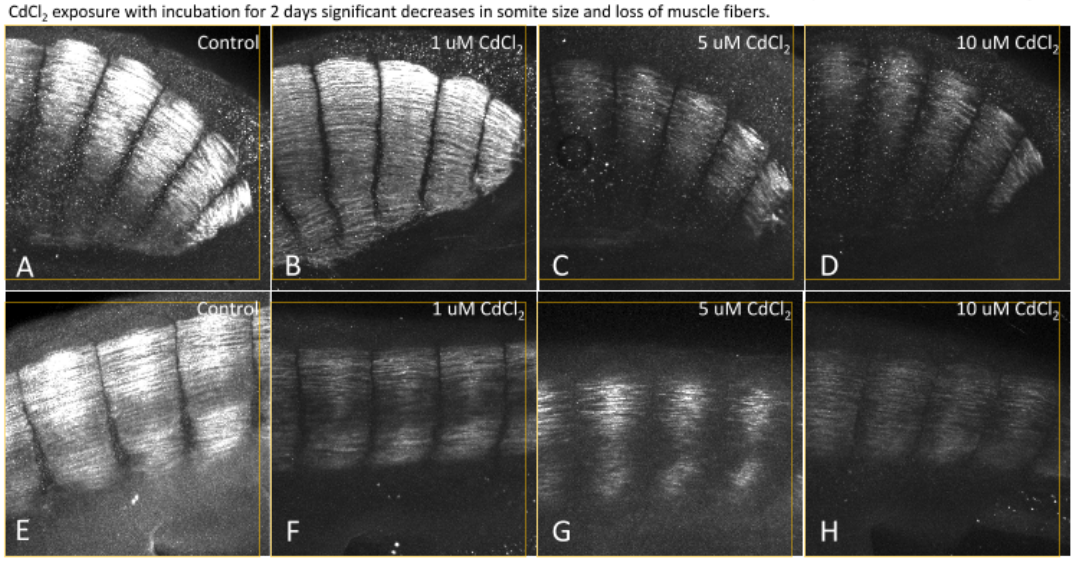
External Collaborators Dr. Takashi Mikawa, (UCSF)

Benefit from other Center projects Simone Bianco and Sujoy Biswas produced a novel unsupervised nuclei counting algorithm to use to determine cell numbers under treatment or absence of treatment with nitric oxide. Denetclaw group will now use this algorithm to determine cell proliferation changes under environmental chemicals in assessment of their hazardous effects. In addition, we plan cell morphology measurements under z-stacks files from confocal microscopy and would continue our work with them to develop a new unsupervised algorithm to monitor muscle cells (myotome and cardiomyocytes) in their natural 3-D morphologies in the embryo and under chemical stress treatment conditions.

Benefits for other Center projects The chick egg platform will benefit the rest of the Cellular Sentinel project by providing a bridge to animal system testing for any novel toxins that may be identified. This will provide the launching point for knowledge transfer of project results to the real world.

Heavy metal cadmium chloride ($CdCl_2$) decreases myotome differentiation and destroys myotome fibers

Cervical level somites (A-D) and thoracolumbar somites (E-H) in the chicken embryo labeled for myosin heavy chain show under increasing $CdCl_2$ exposure with incubation for 2 days significant decreases in somite size and loss of muscle fibers.



Inferring cell state from Cell Motility.
Primary Center Contributors: UCSF (Marshall), IBM Research (Bianco), Exploratorium (Frazier)

Description The overall idea of the cell state inference engine is to be able to infer the state of a cell, as influenced by its environment, by probing its internal structure. A key requirement is a way to determine what state a cell is in. We have explored two approaches. One method is to use cell motility as a state indicator. By tracking cells as they move across a dish and analyzing their trajectories, we compute a large set of numerical descriptors of trajectory shape, and then perform PCA to reduce the dimensionality of the behavioral state space. An alternative approach is to focus on cell geometry at the organelle level by imaging cells expressing fluorescent tags targeted to specific organelles. The images are then analyzed to produce a series of numerical descriptors of organelle size, shape, and distribution, and then these descriptors are used to generate a reduced dimensionality state space using PCA. We have applied these approaches to MEFs and to mouse muscle stem cells. In both cases, we find that the state space is continuous, not discrete, suggesting that the appropriate conceptual framework for understanding cell state would be the language of dynamical system theory. We also have used this approach to understand how cells change between states. Our results show that cell state transitions can be predicted by taking the gradient of an energy landscape inferred from state occupancy, meaning that even though cells are obviously non-equilibrium systems, their behavior in state space can be understood using an equilibrium framework. One challenge in our approach thus far has been the reliance on hand-crafted descriptors of cell motion or geometry. We have begun to move beyond this limit by using Deep Learning to infer classes of cell trajectories with distinctly different shapes. Two pieces of software, Heteromotility and Lanternfish, have been developed to support these approaches.
Personnel Jacob Kimmel (UCSF/IBM), Amy Chang, Matthew Johnson, Wallace Marshall (UCSF), Simone Bianco (IBM Research), Kristina Yu (Exploratorium)
Accomplishments During the past year, we completed development of a deep-learning based method for analyzing trajectories without relying on hand-selected features. This work was just accepted for publication (Kimmel et al., 2019).
Center Influence on Project The student driving the deep learning work, Jacob Kimmel, gained his knowledge of machine learning during a CCC internship at IBM**.**
Plans Our main goal now is to apply this approach to a range of cell types. In collaboration with the Exploratorium, we have begun analysis of trajectories in amoeba, a project inspired by a display at the Exploratorium as part of their Cells to Self exhibit.
Benefit from other Center projects Optogenetic methods from the Center will be useful for providing inputs to cells in order to probe input-output relationships.
Benefits for other Center projects The tools that we have developed can be used to study cell movement during programmed tissue development in the Cellular Lego project.

High-throughput microscopy.
Primary Center Contributors: Stanford (Prakash)

Description We have recently developed two low-cost automated platforms for high-throughput imaging: Modscope (modular microscopy) and Planktonscope capable of fluorescence, brightfield and spectral imaging. These high-throughput tools provide a new platform for field based microscopy. This capability will allow for teams developing “reporter

cells" to be probed in ecological conditions and data coming from these instruments analyzed in field conditions to provide a live monitoring platform at ecological scale.

Personnel Hongquan Li, Thibaut Pollina, Manu Prakash

Accomplishments We are now beginning to deploy several of these tools. We have already deployed our first flow-through microscope (Planktonscope) in Antarctica on a sailboat (Yvinec). The data is coming from this sailboat via a satellite link. The second modularScope is installed in Tribal village in Orissa, India. These deployments teach us methods to test robustness of these tools in field conditions.

Center Influence on Project This project was motivated in part by the goals of the Cellular Sentinels Project, but with the focus on sea-borne plankton rather than fresh water organisms.

Plans The goal this year is to deploy 30 microscopes around the world. Ensuring low cost of manufacturing will be a major goal moving forward; with a target price of $100 per instrument. Connectivity in deep regions of the ocean is limited; so sailors might need to send data once they arrive at a port. Next year, we aim to build a network of 30 sailors around the world continuously sending data via satellite links and our high-throughput flow-through microscopes.

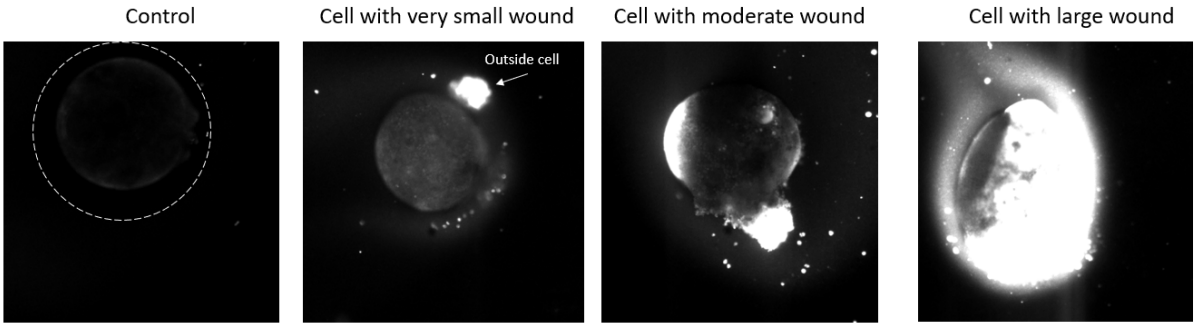
External Collaborators This work is in collaboration with "Plankton-Planet" (https://plankton-planet.org) team from France and US and the Tara expedition (https://oceans.taraexpeditions.org).

Benefit from other Center projects This project has benefited from concepts developed throughout Center projects, and is an example of how concepts from the Center are beginning to have an impact on outside collaborations that share the Center's general goals (here, the goals of the Cell Sentinels Project)

Benefits for other Center projects Given that microscopy is core to many Center goals, a set of inexpensive and automated microscopy tools is likely to have an effect on other projects as well as we find new and creative uses for these tools.

Environmental sensing based on cellular wounding in Stentor.
Primary Center Contributors: Stanford (Tang), UCSF (Marshall)

Description Cells can be wounded by toxins and pathogens in the environment. One way to quantify the toxicity of the environment would be to determine the degree of wounding on a cell, or conversely, the rate at which cells can heal wounds in different environments. We have shown that Stentor incubated in a media containing bacteria were wounded using our mechanical test for repair. The tubulin alignment of a Stentor may also change depending on its environment. We have worked on several methods for measuring the size of a membrane wound and measuring the time of wound repair. We have used a microfluidic mechanical test for wound repair, as well as developed a fixation method which doesn't wound the cells in order to use a fluorescent dye which can only enter the cells when they are wounded. We also worked on methods to quantify tubulin alignment, which gets damaged during wounding and repairs over time. These assays will be useful for the Cell state Inference Engine and Living Bioreactor projects.
Personnel Lucas Blauch, Kevin Zhang, Seth Cordts, Sindy Tang (Stanford), Wallace Marshall (UCSF)
Accomplishments We've developed a method of determining whether a cell has healed using a fluorescent dye on a fixed cell. We also utilized a mathematical algorithm to quantify tubulin alignment after wounding and during healing, and developed a protocol with the assistance of the Marshall lab to stain for tubulin in Stentor with an antibody. We presented on the mechanical test for wound repair at the CCC April quarterly meeting**.** As Stentor is a relatively unexplored model organism, a significant bottleneck has been the development of quantitative biological assays to image and probe cell state. It has been very difficult to see the size of wounds in the cells, as well as control wound size. We believe we have fixed these problems now.
Center Influence on Project This project grew out of interactions between the teams.
Plans We moved away from the mechanical test for wound repair because we were having several issues with it, and are focusing on the fluorescent method of wound detection in the next year. The current focus is on measuring how wound size changes the repair time of the plasma membrane.
Benefit from other Center projects Other methods for studying Stentor biology have been developed by the Marshall lab, such as RNAi in Stentor. They also helped develop the tubulin staining method.
Benefits for other Center projects Living bioreactor: Many cells make compounds which are not easily excreted from cells. To retrieve these compounds has previously required lysing the cells. However, another method of retrieving these compounds would be to create wounds to the plasma membrane through which the compound of interest can diffuse. By wounding the cells instead of lysing, cells will not have to be regrown after each harvest cycle. This is of particular importance for slow-growing cell types. To do this, we need to understand how cells heal wounds.



Fluorescence assay for wound-healing in Stentor based on uptake of DiBac

A Nanoscribe for nanoscale 3D printing of microfluidic knives
Primary Center Contributors: Stanford (Tang)

Description Building fluidic tools for probing cell state requires improved methods for rapid fabrication. The Nanoscribe is an incredible 3D printer at Stanford which can make structures at sub-micron resolution. Such a device has the potential to create microfluidic knives for cell wounding and other devices to benefit all projects in the CCC. We are working on methods to allow the Nanoscribe to be used to make microfluidic devices.
Personnel Lucas Blauch
Accomplishments Lucas got additional funding through Stanford to work on this project. He also developed a method of creating a secondary mold from the 3D printed structure, which he used to make hundreds of replicas of a microfluidic device.
Center Influence on Project Our work on cell and tissue wounding has dramatically accelerated due to Center interest and influence.
Plans We intend to characterize the Nanoscribe and write a methods paper on our results this year. We will also create training videos for other users of the Nanoscribe, as well as write up methods to be posted on Stanford's website.
External Collaborators Stanford Nanofabrication Facilities
Benefit from other Center projects Other activities at the CCC have motivated the use of the nanoscribe because of devices we can make with the Nanoscribe.
Benefits for other Center projects We can now make microfluidic devices with true 3D structures, which may benefit many projects. This could be used to make complex cell traps, a device to split tissue into small pieces for studies of structure to function, complex lenses for imaging, etc. It has already been used to create the mechanical test for wound repair for the cellular machine shop and cell state inference engine projects.

Phosphoproteomics of the wound healing process.
Primary Center Contributors: Stanford (Tang), UCSF (Marshall)

Description We aim to identify protein phosphorylation networks in *Stentor* that are involved in the wound healing process and how these networks are modulated both by wound size and over time.
Personnel Kevin Zhang, Seth Cordts, Lucas Blauch, Sindy Tang (Stanford), Rebecca McGillivary, Ulises Diaz, Wallace Marshall (UCSF)

Accomplishments We have resolved previous issues of chlorophyll saturation in phosphoproteomic experiments and have started collecting phosphoproteomic data of *Stentor* cells in various stages of wound healing.
Center Influence on Project Being involved in the CCC allowed us to see the opportunity to apply high throughput microfluidic devices to consistently and rapidly wound 1000's of cells to use in mass spectrometry and proteomics.
Plans Our preliminary data indicates lower sensitivity on the mass spectrometers than expected. We have been working closely with Stanford University Mass Spectrometry staff to develop a protocol that is compatible with both our wounding method and the facility's instruments in order to achieve the highest quality results. We will finalize our protocol with Mass Spectrometry staff which will yield high quality data. For the next year we plan to continue to collect phosphoproteomic data at different time points after wounding.
External Collaborators Stanford University Mass Spectrometry
Benefit from other Center projects Our phosphoproteomics data can be better interpreted if we can understand cell-level operations using Cellular Machine Shop projects to measure the dynamic cell structure during wound repair.
Benefits for other Center projects The phosphoproteomic data collected will answer key questions about how wound repair is initiated and modulated. Identification of crucial proteins involved in wound repair could help prioritize targets for Living Bioreactor projects. Phospho-proteomics data will also inform predictive models of cell state in Cell State Inference Engine projects.

Cilia flow field as a marker of regeneration state.
Primary Center Contributors: Stanford (Tang), UCSF (Marshall)

Description The flow field generated by the cilia of a *Stentor* cell can potentially hold rich higher-order information on the cell's health and state. We aim to develop a functional assay of cell behavior by correlating the evolution of a cell's flow field with the progression of wound repair.
Personnel Kevin Zhang, Lucas Blauch, Sindy Tang (Stanford), Wallace Marshall (UCSF)
Accomplishments We have started developing a functional assay using particle image velocimetry to measure the flow field generated by a *Stentor* cell. We have observed clear differences in the patterns of wounded and control cells.
Center Influence on Project This project emerged from our continued collaboration with the center, where we saw the opportunity to using cilia dynamics as a probe into internal cell state.
Plans We plan to continue testing the method in conjunction with cell motility and other readouts to relate function with wound repair.
Benefit from other Center projects The development of this assay can be expedited using Cellular Machine Shop (better ways to wound and assess wounds) and Cell State Inference Engine (better ways to calibrate wound and cell health) projects.
Benefits for other Center projects A higher order behavior metric of a cell contributes to a complete assessment of the cell across multiple scales and domains and would complement Cellular Machine Shop and Cell State Inference Engine projects.

Cell shape as a marker of regeneration state.
Primary Center Contributors: Stanford (Tang), UCSF (Marshall), IBM Research (Bianco)

Description The fundamental goal of Cell Inference is to be able to infer what state a cell is in based on its appearance. We aim to develop a machine learning model to correlate cell shape and structure to the progress of wound repair and regeneration. The model will be used as an efficient screening tool to assess how regeneration may be promoted or suppressed.
Personnel Kevin Zhang, Val Gonzalez, Luke Blauch, Sindy Tang (Stanford), Wallace Marshall (UCSF), Thomas Zimmerman, Sujoy Biswas, Vito Paolo Pastore, Simone Bianco (IBM)
Accomplishments We have made progress in developing a machine learning model to identify distinct stages of regeneration, as well as a model to distinguish between wounded and unwounded cells. Val Gonzalez gave a research talk on this project at the Stanford Summer Research Program (SSRP) Annual Research Symposium.
Center Influence on Project Among other things, being in the CCC afforded the opportunity to have informative discussions with experts in machine learning at IBM.
Plans The tendency of *Stentor* cells to spontaneously extend or contract poses a unique challenge in applying machine learning techniques to *Stentor*. To address this, we are exploring various strategies that have begun to show promise such as applying a temporal constraint. We will continue to refine the machine learning approach and develop better ways to collect richer data on individual cells over the next year.
Benefit from other Center projects Development of better imaging tools in the Cellular Machine Shop could enrich the dataset used in developing this project. For example, a general brightfield image of the cell could be enriched by fluorescent images showing localization of specific organelles or structures.
Benefits for other Center projects The ability to infer cell state across the timeline of wound repair will be useful for Cellular Lego, Living Bioreactor, and Cell State Inference Engine projects.

Publications relating to Cell State Inference / Cellular Sentinel

Biswas SK, Zimmerman T, Maini , Adebiyi A, Bozano, Brown C#, Pastore VP, **Bianco S**. 2019. High throughput analysis of plankton morphology and dynamic *Proc. SPIE* 1088109

Kimmel JC, Brack A, **Marshall WF**. 2018. Deep convolutional and recurrent neural networks for cell motility discrimination and prediction. *IEEE/ACM Trans. Comp.Biol. Bioinformatics.* In press. Preprint: *bioRxiv*. 2017 doi: https://doi.org/10.1101/159202

Zimmerman T, Antipa N, Elnatan D, Murru A, Biswas S, Pastore V, Bonani M, Waller L, **Fung J**, Fennu G, **Bianco S**. 2019. Stereo In-Line Holographic Digital Microscope. *Proc. SPIE* 1088315
Pastore VP, Zimmerman T, Biswas SK, **Bianco S**. 2019. Establishing the baseline for using plankton as biosensor *Proc. SPIE* 108810H

Pastore VP, Zimmerman TG, Biswas SK, **Bianco S**. 2019. Annotation-free learning of plankton for classification and anomaly detection. *Submitted.* Under review at *Nature Machine Learning*

III. EDUCATION

1a. OVERALL EDUCATION GOALS AND OBJECTIVES

The emerging field of Cellular Engineering, which is the focus of the Center for Cellular Construction, is an interdisciplinary field requiring not only knowledge and skills in the domain of cell and molecular biology, but also often physics (in order to test and understand how forces influence cellular structure and function across scales) and computational thinking (for harnessing the power of cells, to develop powerful predictive models of cellular structure and function, and to leverage machine learning to accelerate research progress).

Training center members and other students in this interdisciplinary approach is the overarching education goal of the CCC.

This interdisciplinary paradigm is well-aligned with the NSF's Big Idea, Growing Convergence Research, which stresses that one discipline alone will not solve the grand challenges facing our world. The NSF states that the nation must grow our capacity for Convergence Research if we are to successfully tackle these grand challenges. Developing a scientific workforce that is fluent across disciplines so that individuals can identify creative ways to model phenomena, test hypotheses, and design novel solutions to problems is seen as critical to our ability to solve these global problems. The Center for Cellular Construction is pioneering a model for educating students to conduct Convergence Research while simultaneously, through the research conducted in the Center, we are working to both Understand the Rules of Life, another of the NSF Big Ideas, and then apply our knowledge of these rules to develop innovative solutions to problems facing our world.

1b. PERFORMANCE AND MANAGEMENT INDICATORS

Our performance and management indicators are described in our revised Strategic Plan, to which we refer in the narrative below.

2a. INTERNAL EDUCATIONAL ACTIVITIES

Framework for Cellular Engineering Education

The development of a framework of concepts for cellular engineering education represents the foundation of our internal educational activities. Initial work on the education framework focuses on identifying the core ideas that define cellular engineering. As this framework will be used to inform Cellular Engineering Education across a wide range of levels – from work with the public, K-12 teachers and students, undergraduate, graduate students, and postdoctoral fellows. The framework will eventually describe ways of communicating these core ideas, and key concepts needed to understand these core ideas. Development of this framework is listed as Education Optimal Outcome 1 in our Strategic Plan.

Cell are Machines that Can be Engineered

A central tenet of the Center for Cellular Construction is that cells are biological machines that can be engineered to solve important problems facing the world. To fully unlock the power of cells as an engineering platform, researchers need to understand the Rules of Life that govern cellular structure and the assembly of multi-cellular structures. Similarly, research will further elucidate how the structure of cellular components impacts function.

Education work in the Center will:

- Build awareness of the Cell as an engineering platform;
- Develop trainees' fluency with the novel approaches and tools used to examine and manipulate cellular structure and function;
- Prepare trainees to use interdisciplinary approaches to design approaches to engineer new functionalities into cells.

An Engineering Approach to Biological Problems

Engineering is an inherently quantitative discipline, while traditionally biology relies on highly qualitative results. A large part of creating the discipline of cellular engineering will rely on creating more quantitative methods for use in biology. Those trained in biology must be taught to think like an engineer, and those trained as engineers must gain a deep understanding underlying biology so that they can properly utilize their problem-solving skillset. This necessitates that the Center develop novel approaches to preparing trainees.

Education work in the Center will:

- Work with trainees to develop an engineering mindset that shapes their approach to problems and that transcends the platform they are using;
- Build trainees comfort and fluency with Convergence Research;
- Prepare trainees to work effectively on interdisciplinary, inclusive teams;
- Prepare trainees to apply their knowledge and skills across disciplines to develop new tools and approaches for solving problems.

Engineering Complex Systems Requires Working Across Interfaces

Because biology is highly nonlinear, dynamic, and noisy, cellular engineers need to think differently about how to design biological machines, with an emphasis on ways to select from among many possible designs using high throughput methods and machine learning.

Education work in the Center will:

- Build trainees knowledge and skills in developing quantitative, predictive models of biological phenomena that can help inform approaches to problems;
- Prepare trainees to leverage approaches such as machine learning to facilitate using high throughput approaches in the engineering design cycle;
- Introduce trainees to control systems and other approaches to minimizing the variability inherent In biological systems.

New Graduate/Undergraduate Courses Developed as a Result of the CCC

Students at the Center and beyond are learning about Cellular Engineering in a variety of courses, described below. These courses include new courses developed directly as a result of NSF funding. These are now revised, updated and improved before implementation each year. In addition, faculty have integrated topics, problems and ways of thinking that have emerged from the CCC into the syllabi of courses that existed prior to the CCC, further increasing the number of students who learn cellular engineering approaches to solving biological problems. Development of these new courses is listed as Education Optimal Outcome 2 in our Strategic Plan.

In response to feedback from the 2018 Site Visit, the Center is launching a project-based summer course called the **Cellular Engineering Summer Workshop** in the Summer of 2019. Open to up to 40 students from any Center-affiliated institution, and serving students at the undergraduate and graduate level, the goal of this course is to bring together researchers from across CCC institutions to brainstorm

and implement research projects to understand and engineer cells. In the workshop, participants will expand their skills and push the boundaries of how we use cells to make useful things. Participants will learn how to work in interdisciplinary and inclusive teams to employ cell biology, programming, and engineering techniques to learn how cells work, and how cells can be used to build structures, solve biological problems, and produce useful compounds. The goal is to make observations, ask questions, design experiments to answer them, and work collaboratively to draw conclusions and improve designs. The course will also explore the ethical considerations of the research projects initiated in the course. The workshop will meet daily, 9 am-5 pm for two weeks in July 2019 and is using the structure of the Wood's Hole summer courses as a model. In addition to project time, daily sessions will include talks by Center members on their research, team-building activities, and discussions of ethics. While the full list of possible projects is still being developed, examples include:

- Engineering living cells to function as factories triggered with light (optogenetics) to produce biologically useful substances;
- Using microscopy and computational methods to determine how the slime mold Physarum solves complicated mazes;
- Applying microscopy and microfluidics to understand and manipulate cellular structures in living organisms.

By bringing together trainees and faculty from across all Center sites for this intensive, common experience, we expect to also strengthen participants' feeling of belonging to the Center. Development of the Summer Workshop is being led by Center Faculty Diana Chu, Mark Chan, and Wilfred Denetclaw, with support from Wallace Marshall and members of his lab, Rebecca Smith and Jessica Allen, Sindy Tang and lab member Lucas Blauch, Brian Graziano (Weiner Lab), and affiliate Sujoy Biswas. Michelle Phillips will evaluate the workshop to inform future iterations of the course.

Center faculty, Ray Esquerra and Mark Chan, have developed a course, **Introduction to Cellular Engineering** (SFSU BIOL877/CHEM877, 2 units). This course serves both advanced undergraduates and Master's level students and is open to students from SFSU and UCSF. This course will take a quantitative approach to understanding, predicting and engineering cellular behavior. Students learn how to describe complex biological systems with protein, RNA and DNA components using a mathematical framework. They will consider the cell as a compartmentalized reactor with many simultaneously ongoing chemical processes and build models for natural and engineered biological systems. Students will design new biological circuits and predict their behavior. The Introduction to Cellular Engineering course embraces the overall theme of all Center projects: engineering cells to improve functionality. The course introduces students to the fundamental engineering framework that biologists use to model and understand cells. Specifically, in its first offering (Spring 2019), the course discussed principles of designing living bioreactors and cell sentinels. The course will be offered annually in the Spring and will be expanded to three units in the Spring of 2020 so that additional topics in cellular engineering can be added. This course has been institutionalized at SFSU and will be offered annually.

Center faculty, Mark Chan, Ray Esquerra, and Affiliate Tom Zimmerman have collaboratively developed a new course that will be offered for the first time in the Fall of 2019, and will be taught annually thereafter. This course, **Introduction to Optical Engineering for the Biological Sciences** (SFSU BIOL 677/CHEM 677, 3 units), is intended for both advanced undergraduate and Master's level students. This course will provide a hands-on introduction to applying advances in low-cost computers and digital cameras to microscope design. Students will learn the fundamentals of optical engineering and image processing used in digital microscopy. Each student will build a low-cost lens-less microscope capable of capturing and processing images of plankton. Student will use their

microscope to conduct a research project, for example 1) determining the effect of environmental conditions on plankton and microbe motion, 2) extracting image features to classify microorganisms from a variety of sources, 3) building a more powerful microscope, or 3) a research project under the guidance of a faculty mentor. Students will learn essential skills in optical design, instrumentation and fabrication. Python and OpenCV will be used to capture and process images, and to develop algorithms that convert image information into scientific predictions. This course emerged from the achievements of the CCC and will build students' knowledge and skills to address projects in the Cellular Machine Shop as students develop their own microscopes and the Cellular Sentinel as students deploy these microscopes to collect information on cells. Twelve students are currently enrolled in the course, though this number is expected to grow over the summer. This course has been institutionalized at SFSU and will be offered annually.

Center faculty member Diana Chu developed the course, **Exploring and Practicing Science Communication** (SFSU BIOL719/SCI719) for advanced undergraduates and graduate students. In *Science Communication*, students are introduced to strategies to communicate their work to diverse audiences. They explore tools and settings to communicate their work and its goals and develop skills to engage audiences with a broad range of prior knowledge to understand the relevance and importance of research developments. The course includes discussions of ethics and the importance of engaging with the public to understand their questions and concerns about research directions. Each session of the course engages other Center members to share their research, model effective communication strategies, and to introduce students to the wide variety of tools and methods that can be effectively leveraged to communicate their work. This course, open to students from any Center institution, was first taught in Fall 2018. This course has been institutionalized at SFSU and will be offered annually, serving 20 students per year.

Center faculty, Jennifer Fung and Wallace Marshall, developed the course **Cellular Robotics** (UCSF Biochem210, 26 credit hours). First launched in Spring 2017, this course is offered annually for 14 students. The course relates to the overall center idea of the cell as a machine that can be engineered, and particularly to the Cellular Machine Shop in that students learn about control systems within cells that might represent new ways to alter cell behavior. Students also explore collective behaviors, which relates to the Cellular Lego project. By viewing cells as robots, controlled by computational circuitry made of genes and signaling molecules, it is possible to apply concepts from engineering and computer science to understand cellular behavior. In order to exploit such concepts, it is important to have a firm foundation in how robots are actually built and programmed. In this mini-course, participants explore robotics and computer science as paradigms for cellular behavior, in a hands-on project-based setting. Students read key literature on cell behavior in which ideas from computer science and electrical engineering are invoked. Then, they are given "challenges" – physical tasks for a robot to solve inspired by some of the things that living cells do. The students work in small groups to solve these challenges by building robots using the LEGO Mindstorms system – a robotics platform largely intended for children, but which is in fact built on a powerful LabView software system that allows concepts such as path planning and feedback to be rapidly prototyped. After solving a challenge, students discuss and compare their designs, with a particular view to asking whether the robot solved the challenge in a way that resembles how a cell would solve the same problem. In addition to these bio-inspired challenges, students also explore using Mindstorms to building laboratory automation. This, and all UCSF courses are open not only to UCSF students but also to SFSU students through the SF Consortium Intercampus Exchange Program, as well as any student from UC Berkeley.

Center Faculty Hana El-Samad and Wendell Lim, and UCSF faculty member Kole Roybal have developed a new graduate-level course, **Modularity in Biology: The Evolution of New Cellular**

Function (UCSF BP219)**.** The course aims to dissect the concept of modularity in biology with the purpose of identifying biological parts (e.g. protein domains, etc.) where new biological function can be designed and engineered in reliable and modular ways. The course connects to both the Cellular Machine Shop, CellCAD, and Cellular Lego projects through directed readings of the synthetic biology literature. Included in this course is a discussion of ethics of genome engineering, particularly as concerns the engineering of human cells. Serving 15-20 students each session, this course was offered for the first time in Spring 2019 and will be offered annually each Spring.

Existing Courses Updated to Include Cellular Engineering Topics

Center faculty members, Wilfred Denetclaw and Blake Riggs, have updated the San Francisco State course, **Experiments in Cell and Molecular Biology** (SFSU BIOL 351 GW, 4 units), to include Cellular Engineering topics, as a result of his participation in the Center for Cellular Construction. This senior-level course is designed as an introduction to research for undergraduates who have not had a prior research experience and teaches students methods and techniques used in biological research. Drs. Denetclaw and Riggs have designed new modules for this course that introduces students to the idea of using cells as biosensors (Cell State Inference Engine). Students investigate the impact of a variety of substances on cell growth and proliferation in chicken embryo cells. For example, students discovered that RoundUp™ had deleterious effects on the cells. Findings from the students' work in the course have been validated by members of Dr. Denetclaw's lab and will be submitted for publication. As part of this course, Dr. Denetclaw presented both a lecture on ethics (topics included: falsification of data and plagiarism, and also included case studies on ethics including readings and discussions on the David Baltimore and the Hwang Woo-Suk cases). In addition, students in the course give presentations on key ethical issues from the past that have shaped the formation of our ethical bylaws in research. In the future, the course directors have plans to include heavy metal and testing of other chemicals/small molecules from the EPA chemical hazards list that are appropriate for the course. This closely parallels work being done in Dr. Fung's lab. BIOL351 is offered in both the Fall and Spring semester and serves up to 25 students per section.

Center faculty member and Co-PI, Zev Gartner updated the UCSF Graduate Course, Systems Biology (Biophysics 205B) to introduce students to the idea that cells need to be measured at the single cell level – both molecularly and physically to understand how they self-organize and interact. This course is taught annually in the Winter quarter to approximately 12 first year graduate students.

Center faculty member Dan Fletcher plans to integrate topics and research projects inspired by the Center for Cellular Construction in the Woods Hole **Marine Biological Laboratory's Summer Physiology Course**, as he takes over as Course Director in Summer 2019. The Physiology Course is a seven-week long immersive experience for 28 graduate students representing 20 institutions from all over the world. Projects being planned for Summer 2019 include: using an engineering approach to reconstitute cellular processes and the manipulation of cell-cell interactions to engineer novel structures. Included in the plans for this summer's course are discussions of ethics as they relate to the engineering of cells.

Changing how we teach Cell Biology

As a byproduct of participation in the new courses produced by the CCC, we are finding that membership in the Center for Cellular Construction is affecting how Center faculty think and teach about cells, across Center institutions.

At San Francisco State University, faculty report that as a result of their experiences in the Center they are reframing how they teach about cells. They now emphasize the modularity of cellular structures

(organelles) and components (proteins). They introduce their students to the idea that by isolating and modifying these structures or components cells can be engineered, resulting in cells that have new functions. Additionally, they build students' understanding that the research questions probing cellular organization, communication, development and function can all be approached through an engineering lens. SFSU faculty also report that they now include engineering approaches in biology in both their biochemistry and biology classes now – and that this shift is a direct result of participation in the Center. Moreover, they state that being involved in the Center has shifted their own views of cell biology, and this shift is now reflected in their teaching, as they include more mechanistic example, and develop analogies to connect cellular function to everyday life.

Faculty at UCSF report that, as a result of their experiences in the Center, they are thinking more about the cell as a biological machine and are applying concepts from theoretical computer science to cell biology. A faculty member from Berkeley states that the CCC approach to a mechanistic understanding of cell biology has informed his approach to thinking and teaching about cells. Notably, he is leading the Woods Hole MBL Physiology Course in summer 2019, and this engineering approach, learned from his work in the Center, has shaped his plans for his team's projects this summer. Thus, the impact of the Center on training of future scientists extends beyond students formally affiliated with the Center.

Education in Ethics and Responsible Innovation

This year we recruited Dr. Robert McGinn (Professor Emeritus, Stanford University), to join the CCC and spearhead our education efforts in the ethics of cellular engineering. Dr. McGinn has been appointed as adjunct Professor at UCSF in order to give him access to all necessary resources, and during the next year he will be planning and implementing a graduate minicourse on the ethics of synthetic biology. As a concrete first step, he has developed a survey, to be distributed among all center participants, that probes the level of ethical thinking among members and asks about potential concerns or the lack thereof. This survey will provide the basis for planning the new course as well as for setting up discussions at future center-wide meetings.

We make ethics discussions a key element in all of our annual retreats. At the 2018 summer retreat, EAC member Brian von Herzen gave a presentation on his own experiences seeking engineering solutions to global challenges, including the relation between research and policy making.

2b. PARTICIPATION OF CENTER STUDENTS IN PROFESSIONAL DEVELOPMENT ACTIVITIES

Professional development activities from professional societies and organizations

SFSU has an active chapter of SACNAS. Center student Roberto Carlos Segura is the current president of the SFSU SACNAS chapter. Center students Angeline Chemel and Gabriela Alvarez-Azanedo are incoming co-presidents of this chapter. The SACNAS chapter holds regular workshops on student development, including work-life balance, finding research opportunities, and as well as providing other support for students.

SFSU students organized an SFSU-CCC Student Retreat. Held over three days in August, 2018, this event served to build community among the Center students at SFSU, was a leadership opportunity for retreat organizers, Devan Shah and Adrian Martin, and provided a space for all SFSU Center trainees to practice giving research talks in a supportive environment and learn new research techniques from

one another. Twenty students from SFSU participated (16 graduate students and four undergraduates) as well as two lab managers/technicians. Attendees appreciated the opportunity to better understand how their research projects connect to the work of the Center and probed ways to strengthen connections and collaborations between the Center institutions, labs, and members. Participating students indicated that in addition to wanting to further strengthen the relationships between Center institutions, they would also like there to be more Outreach events and opportunities to share the work of the Center with the public.

Center trainees also had the opportunity to participate in the QBI data analysis Hack-a-thon organized by CCC Image Analysis Expert Daniel El-Natan in Winter 2019, and in a Cell Modeling Hackathon organized by Wallace Marshall in February 2019. Four center students took part in these hackathons.

Center trainees were able to participate in professional development workshops led by scientific societies, or at conferences. Graduate student Athena Lin (Marshall Lab) attended the ASCB-KGI Biotechnology Course to learn about careers in biotechnology and the skills required to succeed in that sector. Center students Jasmine Sims and Athena Lin attended the 2018 NSF STC Professional Development Workshop Paths Afforded by the Research Enterprise, an NSF-sponsored professional development workshop for Ph.D. students.

Center trainees gained experience mentoring other students. Activities included graduate students, Lucas Blauch (Tang Lab) and Kevin Zhang (Tang Lab), serving as mentors for undergraduates in summer research program. Graduate students Lucas Blauch (Tang Lab) and Seth Cordts (Tang Lab) leading a panel for more junior graduate students in Mechanical Engineering at Stanford on preparing for Qualifying Exams. Lucas Blauch will also serve as a teaching assistant in this summer's inaugural Cellular Engineering Summer Workshop.

Mechanical engineering graduate student, Lucas Blauch, is part of a biotechnology fellowship. As part of this award, he participates in bi-weekly workshop to build fluency in biotechnology research topics among graduate students in engineering. Topics thus far have included: magnetic cell separation, single cell wound repair research, novel immunotherapies, neuron regeneration biomaterials, high-throughput and single cell methods of modeling disease, antibiotic resistance, among many others.

Center trainees Rebecca McGillivary, Nicole Rodrigues, Jessica Bolivar, and Alia Edington were invited to Janelia Farms to learn how to use their Lattice Lightsheet Microscope. Students stayed at Janelia for 12 days collecting data to further their Center research projects.

Center trainees, Katie Cabral and Olivia Creasey, attended the FRESH Bioprinting Workshop at Carnegie Mellon University. At this workshop, Katie learned how to assemble and operate an open-source 3D bioprinting platform and received in-depth technique training. Her attendance furthered the knowledge and capacity within the Center on 3D printing of BioMaterials.

Center trainee Olivia Creasey participated in a training on the Imaris 9 software. This package provides 3D and 4D visualization of cells and organelles, automates measurement of cellular structures, facilitates discovery of intracellular relationships, automates motion tracking, and allows data to be segmented in a variety of ways. Her knowledge of this research tool not only is of benefit to her research but she is now able to support others in their use of this tool.

Center trainee, Chris McGinnis, will participate in the upcoming NSF Simons Center for Multi-Scale Cell Fate Research, 2019 Workshop on Algorithms and Models for Single-Cell Genomics (UC Irvine,

June 2019). Participants at the workshop will share their expertise and learn how to integrate single cell technologies with mathematical and computational tools to address important biological questions.

Center trainee, Danny Conrad, participated in a two-day workshop, "Beyond the Cell Atlas" sponsored by the Chan-Zuckerberg Biohub. Participants at the workshop explored the application of new technologies to cell biological questions. Danny also participated in the Rockstars of Regenerative Engineering Conference held in January 2019 at UCSF.

Internships in Industry

A core feature of the CCC's education plan is the opportunity for Center trainees to have internships in both industry and informal science education. Industry internships build trainees' awareness of the variety of careers available to them once they complete their training while also 1) providing opportunities for them to apply what they have learned in their graduate training to concrete, product-driven projects in companies, and 2) learn new technologies, tools and skills that will help further their own research and that of the Center. During this reporting period, Center trainees held internships at IBM, Calico, ImpriMed during this reporting period. Leveraging industrial internships is described by Education Optimal Outcome 3 in our Strategic Plan.

Center graduate student, Cecilia Brown (Riggs Lab), held a three-month internship (June – August 2018) at **IBM** where she worked to develop an automated system to track the movement of Stentor in different environmental conditions. Through this project, Cecilia learned to conduct computational analysis and how to code in python. Her work was directly related to the Cell State Inference Engine project and the technology she developed helps move that project closer to its goals. In addition, this project resulted in a publication on cell tracking.

Center graduate student, Amanda Paulson (Gartner Lab), held a three month internship in the summer of 2018 at **IBM** where she worked to develop new tools for analyzing images using human in the loop machine learning. This project will be broadly applicable across the Center, supporting the Cell State Inference Engine, CellCAD, Cellular Machine Shop, and Cellular Legos projects. The project also supported Amanda's interest in helping her shift her career towards more computational work.

Center graduate student, David Bauer (Marshall Lab), held a three-month internship (September – December 2018) at **Calico** where he worked to develop a microfluidic platform for cell selection. Through this internship, David was able to strengthen ties between the Center and a major local company that focuses on quantitative cell biology while working on a project that directly supported the Cellular Machine Shop. The internship experience helped David see how he could apply his interests in fabrication and engineering to further his biological research goals while also gaining experience working in an industrial setting.

Center graduate student Lucas Blauch (Tang Lab) served as an intern at **ImpriMed** from September through December 2018. A mechanical engineering student, Luke's internship helped him to increase his knowledge of biological techniques while also gaining experience working in industry and as ImpriMed is a startup, he had the opportunity to learn about this type of environment generally and as well as many different aspects and roles of this small company. In his project, Luke developed new intellectual property related to microfluidic devices while applying this technology to a commercially important project – developing a device that can generate thousands of microtumors to provide material on which to test potential cancer drugs. As part of this project he also studied how cancer drugs change the microenvironment around cancer cells. This project supported the goals of the Cellular Machine Shop (Project 1), Cellular Legos (Project 3), and the Cell State Inference Engine

(Project 5).

Center graduate student Athena Lin (Marshall Lab) has an internship planned at **Zymergen** from May to September 2019. In her project, Athena will learn how to engineer strains using high throughput methods and will bring this state-of-the-art knowledge, critical to the progress of the Cellular Machine Shop, back to the Center. In addition, her placement will help strengthen connections between the Center and this local company with technologies that can support Center progress.

Science Communication Internships

Internships in informal science education and science communication provide trainees mentored opportunities to improve their science communication skills, introduce them to a wide variety of careers in both museum and science outreach organizations, and share their passion and enthusiasm for science with diverse audiences. These internships provide an opportunity for professional development, particularly for students intending to pursue an academic career that will involving teaching and science communication. These internships also provide a means whereby center members can serve as ambassadors to communicate science to the public, as described in Education Optimal Outcome 4 in our Strategic Plan.

Center postdoctoral fellow, Vasudha Srivastava (Gartner Lab) will return for a third summer to support the Cellular Construction Workshop. Through this internship, Vasudha has had extensive teaching experience, strengthened her communication skills, and learned to work with individuals from diverse backgrounds (wide range of scientific/educational backgrounds, socioeconomic status, race/ethnicity). In her second summer (2018), Vasudha took on a leadership role, revising some of the curricular materials based on assessment and evaluation data and feedback from the first year. She then led instruction using the revised materials. Summer 2019 will provide further opportunities for her professional growth. This summer she will help mentor a graduate student to take over this role as she will be on the job market in the fall of 2019. The CCW curriculum touches on several of the Center projects. Specifically, the course emphasizes structure function relationships and modeling (CellCAD – Project 2 and Living Bioreactor – Project 4), cellular behaviors and decision making (Cellular Lego – Project 3), self-assembly/self-organization (Cellular Lego – Project 3).

Center graduate student, Rebecca McGillivary (Marshall Lab), held an internship at the Exploratorium from October 2018 through February 2019. Through this internship, Rebecca gained experience in science communication while furthering the Center's goal of building awareness about cell biology and cellular engineering among members of the general public. Rebecca's work at the Exploratorium furthered the development of an interactive demonstration, called a "Cell-fie." This demonstration was designed to help visitors understand they are made of cells. At the Cell-fie station, visitors observe their own cheek cells and learn how cells organize into structures. This demonstration helps build the understanding of CCC projects 3 (Cellular Legos). In addition to her work on this project, Rebecca completed communication training, gave demonstrations for the public and the Exploratorium staff on her research with Stentor, leading to new ideas and scientific feedback to advance both the design of exhibits and demonstrations. Rebecca led her Cell-fie demonstration at an Exploratorium After Dark event, where approximately 200 people interacted with Rebecca and participated in the demonstration. This demonstration is now given several times a week on the Exploratorium floor.

Center undergraduate student, Ariana Yancy (Riggs Lab) is the most recent Exploratorium Intern (March -June 2019). As part of her work at the Exploratorium, Ariana has been identifying images of cells that will be projected as part of the "Cathedral of Slides" experience (see description in Optimal Outcome 5, below). In addition, she is sharing her scientific expertise with the *Cells to Self* team.

Ariana also helped organize a national workshop on visualization and modeling – learning new modeling software and approaches as well as being exposed to new scientific domains. Together, these projects further the goals of Center project 2 (Cell CAD), project 3 (Cellular Legos), and Project 5 (Living Bioreactor). Importantly, Ariana's experience at the Exploratorium helped improve her sense of belonging in science and strengthened her science identity while also exposing her to careers in science communication.

Center graduate student Andrew Bremer will hold an internship at the American Academy for the Advancement of Science (AAAS) in the Fall of 2019. In the internship he will explore science communication and outreach, the broader impacts of scientific research, and the ethical considerations of research, and this will help him explore careers in Science Policy.

Communications Training
Graduate students Athena Lin and Greyson Lewis attended the Student Program in Science Communications at the annual STC Directors Meeting at UC Berkeley in 2018.

Center graduate student Olivia Creasey had two opportunities for public speaking and communications training in 2018-19. As a finalist in the UCSF Grad Slam event, she received extensive coaching on preparing and delivering a short talk on her research. Olivia was one of ten finalists selected to present at the Grad Slam event held in February 2019. She was awarded second place for her 3-minute talk. She stated that "Grad Slam challenged her to talk about her research in a way that would appeal to someone "who hasn't had reason to think about cells since a high school biology class." Olivia also received communications and public speaking training as a part of her Discovery Fellows program.

Opportunities to Communicate their Work
Students from SFSU and UCSF each attended a number of meetings (including: ASCB, SACNAS, ABRCMS, Bay Area Worm Meeting, Bay Area Cytoskeleton Symposium), with many presenting posters and/or talks at these events. Posters and talks were listed in the Center-wide Outputs section of this report. Combined, Center trainees presented more than fifty posters and gave more than fourteen talks on their Center supported research at local, region, national, and international meetings.

Notably, Center trainees are frequently honored at the conferences at which they present for their poster and/or oral presentations. Four of the seventeen total poster award winners at the 2018 ASCB conference went to Center Trainees. In addition, Pooja Suresh (Dumont Lab) received the Best Poster Award at the EMBO Physics of Cells Conference. Finally, 23 Center Trainees presented their research at San Francisco State University's annual College of Science and Engineering's Student Project Showcase in May 2019.

2c. EXTERNAL EDUCATIONAL ACTIVITIES

Training High School Teachers and Students in Cellular Engineering

In order to ensure the development of Cellular Engineering as a field, it is important that high school students will become aware of and excited about the potential of building things and solving problems with cells, and move on to STEM majors in college and that high school teachers understand that cells are dynamic entities and are comfortable integrating big ideas of cellular engineering into their teaching. Training high school teachers, together with their students, in the concepts and approaches

of Cellular Engineering, is Education Optimal Outcome 6 from our Strategic Plan. Our primary vehicle to accomplish this goal has been the Cellular Construction Workshop. This workshop was originally funded entirely by CCC funds but starting this year, we are implementing a process whereby the workshop will transition to a fully independent self-sustaining format, allowing it to persist beyond the lifetime of the Center, while freeing up funds for the activities described above that focus more on higher education.

The CCW seeks to reframe how participants think and teach about cells. Throughout the workshop, participants engage in a variety of biological explorations designed to deepen their understanding of cells, cellular behavior, the relationship between cellular structure and function, and explore an analogy of cells as complex biological machines. Students and teachers alike begin to conceptualize DNA as the programming language of the cell. They learn how, by understanding the rules that govern cellular structure (e.g. organelle size) and processes (e.g. signaling and communication), scientists can engineer solutions to a wide range of real-world challenges. This framing of cell biology as a problem-based discipline and concurrent highlighting of the potential of cellular engineering to address global challenges helps students realize that science is a process of convergence and that scientific knowledge and discovery solve real-world problems.

In parallel, students and teachers work together to develop solutions to engineering design challenges, thus bringing together computational thinking, engineering design, and biology as they model cellular behaviors in Lego EV3 robots. Inspired and informed by the CCC's mini-course, Cellular Robotics, the CCW's engineering design challenges provide a project-based introduction to programming and computational thinking, engage participants deeply in the design-build-test engineering design cycle, and strengthen participants' understanding of the biological behaviors as they break these behaviors into steps to develop a robot model.

Since its inception, the CCW has served 16 high school teachers and 30 students in two sessions (summer 2017 and summer 2018), with another five teachers and fifteen students enrolled for this summer. Notably, demand for the workshop is increasing – this spring more than 80 students and 13 teachers applied for the available spaces in the workshop. Importantly, teachers are incorporating what they learn from the workshop into their classrooms, including implementing the engineering-design challenges into both biology and chemistry classes. Teachers comment on the workshop helping them understand the role of chemistry inside of cells, how dynamic cells are (and that teaching about cells this way is better aligned with the Next Generation Science Standards).

While the evaluation results will be presented in more detail, below, it is important to emphasize that, students report, both immediately following the CCW, **and up to 18 months after the workshop** that their participation in the CCW has influenced their interest in STEM fields and their desire to pursue a career in STEM post-college.

> *The workshop gave me a much better understanding of what it would actually take to pursue STEM, at least in a university. It took a scary concept, studying STEM, and gave grounding and context to it. (Student, immediately post-workshop)*
>
> *All the people that came in to talk about their careers was really helpful, especially since I hadn't heard of or thought of pursuing those careers before. (Student, immediately post-workshop)*
>
> *I have been interested in STEM since I was a little kid, and this workshop helped me explore this specific branch of STEM. Before I attended this workshop, I was unsure about pursuing a career in cellular engineering, but now I would like to know more about what I need to study in college in order to become an engineer. (Student, immediately post workshop)*

I was introduced to the STEM field in high school, but I never had a set idea of what it actually was and what careers were in this field. This workshop definitely opened so many options, ideas, and interests within STEM. Prior to this workshop, I had only taken a high school biology class that would be the closest thing to STEM, but now that I was able to explore engineering along with technology too, I definitely am now looking at this field tightly. In this workshop we were able to connect all aspects of STEM together, and I think that was what made this workshop special. (Student, immediately post-workshop)

The workshop allowed me to grow my interest in science and made me feel that I have a place in the STEM field. I also wrote about the workshop in one of my UC personal statements and I was able to get into all 7 of the UC schools I applied to. I will now be attending UCLA this fall! Again, thank you for hosting an inspirational workshop that left a lasting impact on my life. (*CCW 2017 Alumna, 1st Generation College Student*, 18 months post workshop)

Seven (of seven) CCW alumni from the first cohort (2017) who have finished high school have matriculated to college (CCW 2017). Two are at UC San Diego, one is a student at UC Berkeley (Chemical Engineering), one is at California State University Chico, and three are at City College of San Francisco. Another seven students from the 2017 CCW will finish high school this year (along with an additional seven students from the 2018 cohort). While it is still early to hear college decisions, those we have heard from will be attending: UC Berkeley (Mechanical Engineering – inspired by their participation in the CCW), UC Los Angeles, UC Irvine (Biology), UC Santa Cruz, and Clark University (BS/MS program in Biochemistry & Molecular Biology). In addition some students will attend their local community colleges. Program alumni will be asked to complete a longitudinal follow-up survey in May 2019 which will provide additional insight into the impact of the program on these students' trajectories.

Perceptions of the model

Evaluation of the two sessions (2017 and 2018) of the CCW offered thus far have been consistently positive and quantitative and qualitative results were presented in detail in last year's report.
In summary:

1) Both project staff experiences and evaluation data uncovered tremendous benefits for teachers and students. In the words of participating students and teachers:

   I like the fact that I was able to work with teachers because it boosted my confidence to see a teacher, someone who knows "everything" have the same struggles as me a student. (Student)

   I think having students work alongside of teachers is a great idea. I learned so much about technology from the students I worked with. (Teacher)

2) Evaluation of the CCW also uncovered that, given the novelty of the co-learner role, teachers have questions about their roles in the groups. While they naturally help facilitate learning by asking probing questions, the evaluation suggests we need to provide additional guidance about expectations for their roles in the group.

3) Teachers and students reported deepening their understanding of cells, engineering, and specifically cellular engineering, while also developing their programming skills. Students reported that the workshop strengthened their abilities to work in collaborative teams, and expanded their understanding of and interest in STEM careers.

   I liked how the challenge was connected to a hypothetical problem that could occur in real life. It gave us an idea of what some scientists have to deal with in the real world and created a cool challenge for us to work together on. (Student)

   The workshop gave me a much better understanding of what it would actually take to pursue STEM, at least in a university. It took a scary concept, studying STEM, and gave grounding and context to it.

(Student)

Implementing CCW Lessons in High School Classrooms

Teacher alumni of the CCW incorporated lessons from the workshop, including the engineering design challenges using robots, into their teaching – benefitting more than 250 additional students at multiple schools in the San Francisco Bay Area in the past two years. Evaluation of the CCW also investigated these students' experiences with the CCW in their teachers' classrooms. Like participants in the workshop itself, these students perceived the greatest gains in their team-work and collaboration skills. In addition, they responded very positively to the problem-based design of the challenges and appreciated the challenge's real-life relevance.

> *The most enjoyable part of this challenge was working together to create a robot that could accomplish a task. We worked in groups of four, each of us giving ideas on how to improve the efficiency and capabilities of our program and robot...Overall, the experience of working with others on so many different aspects of computing and robotics was most enjoyable. (Student)*

> *I liked how the challenge was connected to a hypothetical problem that could occur in real life. It gave us an idea of what some scientists have to deal with in the real world and created a cool challenge for us to work together on. (Student)*

Next Steps

When we began the Cellular Construction Workshop (CCW) we were unaware of other program that paired teachers and students as co-learners and viewed this structure as an experiment. Evaluation evidence has uncovered that it is a very promising model that benefits both teachers and students. A literature review this spring found only one published paper on teacher-student co-learning models. Like the CCW, the authors also found evidence that the model benefits both teacher and student learning – but did not dissect how and why this model works. We believe the teacher-student co-learner merits systematic study and so have just submitted an NSF STEM+C proposal to study the CCW. Thus, the intent is to spin the CCW out of the Center. This will allow current funding for the CCW to be reallocated for other education work (as the Review Panel has suggested) and will provide the support necessary to conduct a research study on the CCW and make the findings available to the broader science education community.

General Public Education through the Exploratorium

The *Exploratorium* is leading the Center's outreach work to members of the General Public through development of its *Cells to Self* exhibition. The *Cells to Self* exhibition will open October 2, 2019. This exhibition features exhibits, artworks, and ongoing demonstrations that foster public understanding of how organisms develop from a single cell to a "self." While the full exhibition contains sections on topics such as genetics (covered by other funding), there will be more than ten exhibits covering fundamental skills and concepts of cellular engineering. Incorporation of Cellular Engineering concepts into the Cells to Self exhibit represents Education Optimal Outcome 5 of our Strategic Plan. During this reporting period we will complete five new experiences for the *Cells to Self* area (including an ongoing public demonstration):

- **Cells to Scale.** This large-scale exhibit will contain seven bronze models of different cell types found throughout the exhibition, such as cheek cells, euglena, sea urchin, and E. coli all in "scale" or relative size to one another. The goal of this piece is to introduce visitors to the variety of cell shapes and sizes, and to provide an experience for sight-impaired visitors.
- **Cheek Cell Puzzle.** This exhibit is a large backlit table with translucent 3D printed cheek cells, which visitors can assemble into a higher order structure. The piece explores how cells form higher order structures, how cells adhere to one another, and how scientists use modeling software to study cells.

- **Cathedral of Slides.** Created in collaboration with CCC partner Dan Fletcher's lab at UC Berkeley, this installation allows visitors to explore different microscopic samples with the Fletcher lab's CellScope. A software application being developed for the phones that will be connected to the scopes uses image recognition software to identify different cell types and subcellular structures. This installation will aim to present content on the diversity of cell structures and highlight the role and function of image recognition in biological discovery.
- **Microscope Imaging Station: Zebrafish Heart.** This exhibit leverages the Microscope Imaging Station at the Exploratorium, a facility with research-grade Zeiss axiovert microscopes that can be controlled by visitors through an interface. This piece guides visitors through microscopic identification of cellular structures and uses image recognition software to foster observation and support inquiry. This exhibit is also part of a larger NSF-funded educational research study at the Exploratorium, Seeing Scientifically.
- **Cell-fie Demo.** A demonstration that happens multiple times a day in the exhibition space where visitors can have an image of their cheek cell (or "cell-fie") taken. Staff or CCC interns talk with visitors about what cells are, how cells form structures, and some organelles within cells. A media display with visitors' cheek cells will be continuously updated, showing how people of all different ages and backgrounds look the same at the cellular level. As described in the Optimal Outcome 4 section above, this demonstration was developed with the support of Center Intern Rebecca McGillivary.

These experiences focus on fundamental concepts and skills underpinning cellular engineering: cells are diverse shapes and sizes; cells form higher order structures; organisms are made of cells; microscopes allow us to observe cells and their structures; image recognition allows us to quickly identify cellular type and structures. This new batch of exhibits focused on humans to emphasize the "self" aspect of the *Cells to Self* show. Evaluations of the overall visitor experience of the initial prototype exhibition revealed that while visitors were gaining an understanding of cell biology, they were not connecting this understanding to themselves.

Impact of Center on Exploratorium's Work

Being part of the Center has added scientific vibrancy and resources to the Exploratorium's exhibit development process. There are many examples of how collaborations with the CCC have made new experiences possible: biology demonstrations by Spanish-speaking Center members at the Exploratorium's Latino Engineering Day; the development of the Cell-fie demo media capture (by CCC intern); development of the Cathedral of Slide exhibit with the Fletcher Lab; and a talk on Foldscopes and protists for museum staff by Center faculty member Manu Prakash. These collaborations are described further below, how being part of the Center has benefited development of the *Cells to Self* exhibit in several ways

- **Access to scientific expertise and samples.** The Exploratorium's connection with the network of CCC labs has given facilitated access to the scientific expertise and samples needed to create exhibits. When the exhibit team needs movies, images, or modeling software they reach out to the CCC. For example, stentor has been featured in a number of programs and on the Exploratorium's microscopes through affiliation with the Marshall lab.
- **New tools to adapt for public experiences.** Being part of the CCC gives the Exploratorium access to new tools, such as the Fletcher Lab's CellScope. This microscope can be attached to a cell phone for high resolution images. Affiliation with the Fletcher Lab has provided the technology, software, technical support, and ideas for content.
- **Embedded scientist interns.** CCC interns are an embedded and critical part of the exhibit team every Spring and Fall semester. These interns present their scientific projects (as part of

their communication training), post exhibit ideas and feedback on our project development site and bring their expertise and knowledge to all team meetings and other staff events. While Exploratorium staff have Ph.Ds in Cell Biology, having current practicing students adds more updated research to the museum's exhibitions.

- **Professional development on the latest discoveries, tools, and approaches.** Involvement with the CCC keeps Exploratorium team member's up to date on current research. This is a significant challenge for museums, where time must often be focused on exhibitions that will drive attendance. While exhibit developers intend to read research journals and go to conferences, the Center facilitates a connection, provides access to research talks, and enables exhibit developers to get research updates and see preprints in a more timely way than in the past. More importantly, members of the Exploratorium's exhibit team feel part of the CCC's dynamic and growing community.

External Collaborations that Arose as a Result of Participation in the Center
Work with the Center has fueled additional collaborations.

(1) Janet Iwasa, Professor of Biochemistry at University of Utah and expert in cell and molecular animation. Janet is a collaborator of PI Marshall's and asked the Exploratorium lead, Jennifer Frazier, to give a talk on her work visualizing scientific data (from the Cell Zoetrope exhibit in Phase 1 of Cells to Self) at the American Society for Cell Biology Meeting in 2017. This connection has led to Janet's involvement in an upcoming conference and public event the Exploratorium is hosting on scientific visualization, where Janet will be a speaker and share her movies of cellular processes with the public.

(2) Allen Institute for Cell Science. Allen Cell Science is creating a Cell Atlas and VR immersive cell experiences. They approached the Exploratorium to find out about potential collaborations on Cells to Self and were excited about the museum's role in the CCC. They are participating in a public event to share their molecular visualizations and VR experiences in the *Cells to Self* Area at an upcoming public event called "Designed by Data."

Challenges
There have been two notable challenges in the Exploratorium's work this year. First, challenges emerged bridging some of the research in Center Labs with the exhibition's need to focus on self. This new batch of exhibits (described above) focused more on humans to emphasize the "self" aspect of the *Cells to Self* show. Evaluations of the overall visitor experience of the initial prototype exhibition revealed that while visitors were gaining an understanding of cell biology, they were not connecting this understanding to themselves. To overcome this challenge, an important goal going into Year 4 is to add more engineering focused exhibits to the *Cells to Self* collection. While the grand opening is in October 2019, the current plan for Year 4 is to shift from "self" to creating experiences that focus on engineering skills and practices drawn from Center labs. Lab visits and preliminary research has already provided ideas for many exhibits on self-assembly, design-test-build cycles, and cell aggregation.

A second challenge has been finding ways to make visitors connect abstract representations of cells (and other biological features) to real phenomena. The exhibit team created a number of rough prototypes of cellular aggregation and assembly and found that visitors had a very hard time linking these models (often done with magnets or blocks) to biology. To address this challenge, as the focus shifts more on engineering, the project team will look to the educational research literature and other prior work for ideas on bridging the gap between models and real phenomena.

Next Steps

There are several next steps in the Exploratorium's work reaching the general public. As described above, after the opening of *Cells to Self* in October of 2019 the Exploratorium will shift conceptual focus from basic cell biology and microscopy to skills and concepts that are being pioneered by CCC labs as part of the new discipline of cellular engineering. These are being refined by a subcommittee within the Center, but examples being explored include concepts such as "Rules govern how cells form structures" and skills such as iterating on a design to solve a problem. Identifying concepts and skills for museums visitors to acquire is only one part of creating a compelling exhibit. To create an exhibit, we must find a compelling phenomenon, biological sample, or activity that conveys the concept or fosters a skill. Below are some of the next steps for exhibit and program development in Years 4 and 5 to add a new cluster of more engineering-oriented exhibits to the *Cells to Self* exhibition area:

Cellular Engineering Exhibit Cluster (Years 4 and 5)

- Refine concept map to identify concepts and skills being explored in the Center.
- Small convening with other educators who work in engineering education and biotechnology education to identifying unique attributes of cellular engineering.
- Identify samples, tools, phenomena by visiting Center labs and other research
- Prototype exhibits created and evaluated
- Final exhibit build
- Installation of final small collection (to be determined in added all at once or as made).

In addition to creating this next set of exhibits, the Exploratorium team will reach out to their Global Studios division and teacher groups to see which experiences might be adapted for larger scale dissemination.

IV. KNOWLEDGE TRANSFER

1a. Overall goals/objective - changes

Our goals for knowledge transfer are (A) to catalyze the transfer of center-developed ideas and results into the real world, so as to have a positive impact on the economy and society, and (B) to gain insights into methods, ideas, and approaches that could be useful for achieving our other center goals by drawing on expertise of partner institutions and companies. With regards to the second goal, we strongly believe that by involving potential knowledge transfer partners early in the development of our center, they can help us direct our research activities towards problems that are of actual relevance in industry, and also to help us train our students in a way that will prepare them to employ cellular engineering approaches in an industrial setting.

1b. Performance & management indicators

Our Strategic Plan lists several concrete metrics for knowledge transfer progress. During our first three years, our primary effort has been developing the knowledge that will ultimately be transferred; however we have already been able to make progress towards our knowledge transfer goals, in line with our overall strategy of trying to involve industrial partners in center activities not only as recipients of knowledge but also as sources of advice and ideas.

performance indicator: File invention disclosures reflecting center-developed knowledge

rationale: invention disclosures provide a direct way to track how many center ideas can at least in principle be commercializable, and also provide both a starting point for pursuing IP protection and a potential pathway to attract industrial partners for more extensive knowledge transfer activities.

goal: 2-5 disclosures written per year

status: We have written 3 new invention disclosures during the past year, as detailed in Center Wide Outputs, Section 4. These represent new disclosures on top of the six disclosures written during the previous two years. We thus continue to be on track with this goal.

performance indicator: Disseminate information about center activities to potential industrial partners

rationale: Before we can establish knowledge transfer relationships with companies, the companies need to be aware of what the Center is doing. By tracking the number of dialogues we establish with potential industrial partners, we can get an idea of our progress towards the early stages of setting up knowledge transfer interactions.

goal: Establish dialogues with 3-5 companies per year

status: During the past year, Center investigators from IBM and UCSF have presented non confidential work produced and inspired by CCC research to the following external interested parties:

- 10X Genomics
- Genentech/Roche

- Biolegend
- BioRad
- SystemOne
- Kallyope
- Provenance
- Amgen
- Wild Acres Farm, Bellingham WA

Past experience has shown that this type of initial interaction is effective in leading to real partnerships. For example, several interactions begun last year are now progressing; specifically the interaction with Nagase has progressed to the stage of a CDA, and the interaction with Evolva is progressing to that stage.

performance indicator: Establish active collaborations with industrial partners.
rationale: Once we have established dialogs with partners, the next step is to move to actual partnership. One approach is through licensing, but another is through direct scientific collaboration. The number of industrial collaborations provides an easily quantified metric for our progress in establishing meaningful interactions with the industrial world.

goal: To have three active collaborations in place by year 5

status: As an outcome of our efforts to disseminate information to industry (see above), we have, during the past three years, established a total of ten active collaborations with industrial partners. We have therefore completed this milestone ahead of schedule.
The following are the partner companies and institutions:
Nagase Inc, Tokyo Japan; ImpriMed, Inc, Palo Alto, CA; Juvena Therapeutics, Inc., Palo Alto, CA; Serotiny Inc., San Francisco, CA; Israel Water Works Association; Fabian Cousteau Ocean Learning Center; Monterey Bay Aquarium Research Institute, Moss Landing, CA; University of Genova, Italy; DynamicLand Inc., Oakland, CA; and Texas A&M University.
Details about these collaborations are provided in section 2a below.

performance indicator: Center trainees entering industrial workforce.

rationale: Since our goal is to help grow a new area of engineering, one measure of success is whether our trainees are in fact able to make use of the center-acquired skill base to take scientific leadership positions in industry.

goal: 10 center trainees will have entered the industrial workforce at the level of research scientist or above by year 5

status: This past year, almost all of the students who graduated from the Center have pursued further academic training. One trainee, Ph.D. student Jacob Kimmel, has been hired as a Computational Biologist at Calico Labs, South San Francisco, CA. This is a research scientist position. The purpose of our goal is not to discourage our students from pursuing academic careers, but to expose them to opportunities in the industrial sector as well. To this end, we are continuing with our industrial internship program – this year four students have engaged in internships arranged through the center, at IBM, Calico, Imprimed, and Zymergen.

performance indicator: CCC web site is the top ranked Google search result for term "cellular engineering"

rationale: One of the goals of the center is to increase awareness of the cell as an engineering medium, and we intend to use our center web site as one mode of spreading awareness. By tracking the search ranking of our center web site we can determine how well our center is being viewed as driving this field.

goal: To have our web site be the top search result for this search term

status: Currently, a Google search for "Cellular Engineering" links to several affiliates (IBM, UCSF SEP) before the Center website appears. However, if combined with the terms UCSF, IBM, or Exploratorium, it does appear in the first page of Google search results. Content and development of our upgraded web site is still in process; the site is close to being launched.

Dr. Janet Iwasa (OneMicron Inc), a world leader in computer animation of cell and molecular biology, is working on new computer animations and illustrations for the center web site.

We recognize that web sites are just one approach to creating awareness about the center among scientific colleagues, potential collaborators and trainees, as well as the general public. The other key element is social media. The Center for Cellular Construction maintains an active presence on Twitter (@C3STC). The account is managed by Center faculty member Diana Chu, who both regularly publishes original tweets about Center activities while also amplifying tweets published by Center members and affiliates that build awareness Center's work – in research, education and outreach programs, position announcements, awards received by center members, and it's efforts both within the Center and more broadly to support broadening participation in science. The Center's Twitter account currently as 464 followers, and its tweets in this project period generated nearly 43,000 impressions, with more than 2,400 "likes" in this period. Note that these analytics numbers are only for the @C3STC account and do not include the impressions generated by Center Faculty, affiliates, and trainees through their individual accounts. At the Center's Fall Quarterly Meeting, Center affiliate Jennifer Frazier (Exploratorium) provided a brief social media training that with the goal of helping to standardize the Center's brand identity in social media posts. Training included a discussion of effective use of hashtags and the appropriate hashtags to use when citing either the Center or the NSF.

1c. Problems.

No significant problems have yet been encountered.

2a. Knowledge Transfer Activities – Organizations Involved (TABLE 2.a)

Microfluidic device for cutting tumor biopsy samples		
Led by Sindy Tang		
Organizations Involved		
	Name	Address
1	**ImpriMed, Inc.**	Palo Alto, CA

ImpriMed, Inc. Lucas Blauch did an internship at ImpriMed, a startup based in Palo Alto, based on his work on the microfluidic guillotine The goal of the internship was to use the microfluidic guillotine developed in the Center to cut tumor biopsy samples into many small pieces for *ex vivo* drug testing and prediction of the best chemotherapy for a patient. Prior to doing the internship, we filed a provisional patent on his device. The full patent will be filed by June 2019.

Lucas secured further funding in March of 2019 to continue developing the guillotine at Stanford, which may result in a joint patent application between ImpriMed and Stanford.

Microfluidic device for wound-healing in muscle cells		
Led by Sindy Tang		
Organizations Involved		
	Name	Address
1	**Juvena Therapeutics**	Palo Alto, CA

Narrative: The Tang group and Juvena have a material transfer agreement to test the microfluidic guillotine on muscle cells. The goal is to create an *in vivo* test for wound repair efficacy, which could be used to screen or test therapeutics for muscular dystrophy and other diseases.

Quantifying organelle structure in industrial strains of Streptomyces		
Led by Simone Bianco		
Organizations Involved		
	Name	Address
1	**Nagase Inc**	Tokyo, JP

Narrative: The Bianco lab at IBM has established a confidential collaboration with Nagase, Inc. on studying the relationship between the structure of streptomyces cells and colonies. The aim is to use artificial intelligence algorithms developed at IBM to infer growth conditions related to useful industrial products, and understand potential morphological modifications which may be related to increased or decreased production. The collaboration is at the level of a pilot at the moment, with the possibility of establishing a contract.

Building a database of molecular parts for cellular engineering		
Led by Zev Gartner		
Organizations Involved		
	Name	Address
1	**Serotiny, Inc**.	San Francisco, CA

Narrative: We have formalized a partnership with Serotiny, a San Francisco based startup that specializes in computational solutions for synthetic biology, thus providing a key element of the CellCAD project. Serotiny maintains a database of molecular "parts" along with formal descriptions of interactions between these parts and algorithms to design multi-part constructs in a combinatorial manner. Seroniny's partnership with our center gives us access to Serotiny's computational tools, thus supporting our own CellCAD and Machine Shop projects, and low cost access to Serotiny's gene synthesis contracting service, which has already supported development of molecular tools for the Living Bioreactor project. At the same time, the partnership gives Serotiny access to our growing collection of molecular components and markers being developed through the Cellular Machine Shop, thus helping them to grow their database while helping us to disseminate our results into the industrial sector.
This year Serotiny has been focusing on 3 projects:

Engineered Switch (Cellular Sentinel Research project): Fletcher subgroup
Light-Sensitive Receptor (Cellular Legos) – Gartner subgroup
Localized Enyzmes (Bioreactor)- Marshall subgroup

Serotiny has made its protein design software available for use to all CCC members at https://ccc.serotiny.bio. Serotiny has helped fulfill multiple orders for 3 different projects, producing 32

novel protein products, utilizing >40 different protein components. All of the ordered DNA has been delivered to the labs, and is currently under evaluation.

Use of a lensless microscope for the detection of impurities in lake waters		
Led by Simone Bianco		
Organizations Involved (add rows as necessary)		
	Name	Address
1	**Israel Water Works Association**	Israel

Narrative: The Bianco lab at IBM has established a potential collaboration with the Israel Water Works Association. The aim of the collaboration is to use plankton morphology as a potential source of information of water quality. This ties directly into our Cellular Sentinel project. The collaboration is at the preliminary level and no confidential collaboration has been exchanged.

Survey of deep sea plankton		
Led by Simone Bianco		
Organizations Involved (add rows as necessary)		
	Name	Address
1	**Monterey Bay Aquarium Research Institute**	Moss Landing, CA

Narrative: The Bianco lab at IBM has started a collaboration with Thom Maughan at the Monterey Bay Aquarium Research Institute to develop a lensless microscope for both surface and deep sea plankton survey. We are working on an ultra-low power version of the lensless microscope we have invented which may be equipped on a surface glider, as well as a deep water instrument. Using an unsupervised classification method and a newly designed machine learning algorithm, we plan to help MBARI uncover new species of deep water plankton. The collaboration is non-confidential, and no confidential information is expected to be exchanged.

Survey of deep sea plankton		
Led by Simone Bianco		
Organizations Involved (add rows as necessary)		
	Name	Address
1	**Fabian Cousteau Ocean Learning Center**	Rhode Island

Narrative: Similarly to the previous opportunity, the Bianco lab at IBM has started a collaboration with Fabian Cousteau, CEO of the FC Ocean Learning Center to develop a lensless microscope for deep sea plankton survey on the new underwater learning center being built by the organization. The collaboration is non-confidential, and no confidential information is expected to be exchanged.

End-to-end monitoring system for sea water		
Led by Simone Bianco		
Organizations Involved (add rows as necessary)		
	Name	Address
1	**University of Genova, Italy**	Genova, Italy

Narrative: The Bianco lab at IBM has started a collaboration with the groups of Massimo Maresca and Pierpaolo Baglietto at the University of Genova. Drs. Maresca and Baglietto have designed a cloud based system to help the Italian Government monitor the water quality of the

Italian National Parks of Cinque Terre and Portofino. The collaboration aims at augmenting the existing platform with an AI powered monitoring system based on the IBM lensless microscope, to classify plankton and use its shape and behavior as an indicator of water quality. The collaboration is in its initial stage. The collaboration is non-confidential, and no confidential information is expected to be exchanged.

Realtalk molecular biology laboratory workflow		
Led by Shawn Douglass		
Organizations Involved (add rows as necessary)		
	Name	Address
1	**DynamicLand, Inc.**	Oakland, CA

Narrative: We have established a collaboration with DynamicLand (Oakland, CA) to implement their Realtalk computing platform within the CCC, and to customize the platform for use in the framework of molecular biology laboratory workflow.

Living Bioreactor for Stoichiometric Protein Production		
Led by Wallace Marshall		
Organizations Involved (add rows as necessary)		
	Name	Address
1	**Texas A&M**	College Station, TX

Narrative: The Marshall group at UCSF has established a collaboration with Dr. Hongmin Qin at Texas A&M to develop methods for using one organelle, the axoneme of the cilium, as a platform for assembling protein arrays of defined stoichiometry. An invention disclosure was written for this concept (see Center wide Outputs) and collaborative experimental work has now begun between the two labs. This collaborative project is now viewed as an important approach for our research project 4 – Living Bioreactor. The main outcome of this activity thus far has been filing of an invention disclosure. This project was also the starting point for our ultimately successful bid to add an engineering track to the UCSF Catalyst funding program (see below).

2b. Outcomes/impacts of the activities

Apart from the activities listed above, there has been tremendous cross-fertilization of ideas between IBM Almaden Research Center and the rest of the CCC labs. This exchange has completely redirected the emphasis of the Bianco group at IBM towards cell biology, and at the same time has redirected the research efforts of virtually all academic labs in the CCC to make greater use of machine learning methods in their cell biological research. We believe that this is a highly successful example of how industry and academia can work in a true partnership where knowledge transfer is not only an outcome in itself, but also an important driver of new research and educational work.

A second major impact of our knowledge transfer has been the introduction of a new engineering track within the UCSF Catalyst program. Catalyst provides seed funding for commercialization of new ideas along with the opportunity for investigators to receive mentorship and guidance from local experts in industry and venture capital. In the past year, Catalyst has funded a large number of projects relating to medicine, such as drug development and digital health. Proposals are sorted into several medical categories prior to evaluation. In the past none of these categories were appropriate for the engineering, non-medical focus of our Center. However, during this

past year, starting with the submission of a proposal to Catalyst from the Marshall lab, the Center Knowledge Transfer Coordinator, Charles Craik, was able to negotiate with Catalyst leadership, as a result of which the Catalyst program formally added a Biological Engineering track. In this way, the CCC has been able to effect a meaningful change in policy of an important local funder of early stage commercialization of research.

2c. Progress regarding indicators/metrics listed above.

Indicators are reported above. We are meeting or exceeding our goals of filing disclosures, establishing dialogs with industry, with industrial internships, and, most importantly, our goal of establishing meaningful collaborations with industrial partners. The only metric where we are lagging behind our goals has been in the number of center trainees entering the industrial workforce, which is explained entirely by the fact that most of our trainees are moving on to the next level of academic training. This particular metric will be best assessed after more time has elapsed to allow the Ph.D students and postdocs to seek their first independent position either in an academic institution, or in industry.

2d. Plans for next period

We will continue with our existing knowledge transfer approaches and contacts. Our center Strategic Plan currently specified that we would begin launching companies during the third year of the center, once enough scientific progress has been accomplished that new IP can be created. During the past year, in an effort to launch this new phase, we have extensively researched how best to catalyze the transfer of center knowledge and ideas into the startup space. In particular we have held detailed discussions with our EAC panel members who are involved in startups, and as a result of this intensive discussion we are formulating a revised plan that will place greater emphasis on seeding early stage of development within center labs, so as to better leverage the existing infrastructure, and then only moving to the startup stage, as needs dictate, when ideas have reached a more mature stage of development and reduction to practice. CCC Knowledge Transfer Coordinator Charles Craik, together with center leadership, has held a series of meetings with experts including our two CCC startup advisors on our EAC, Dan Widmaier and Kinkead Reiling, as well as Cathy Tralau-Stewart, the Associate Director of the Catalyst Program and Director of CTSI T1 Translational Research. All of these discussions led to the conclusion that our knowledge transfer budget could have a larger impact if we placed greater emphasis on developing technological innovations at an earlier stage within center labs rather than immediately launching startups with the attendant costs and IP issues.

To this end, we have set aside money in our budget for internal seed funding within the center, and sent out an RFA the winter of 2019, soliciting proposals from center faculty for seed projects, with funding on the order of $25K, that would allow labs to perform the one key "burning white hot" experiment that could determine whether a given idea has enough potential to be worth further efforts at development for commercial purposes. Five proposals were submitted within the center, and all were then evaluated by Dr. Charles Hart, Director of the UCSF Catalyst program, who generously volunteered his time to read each proposal, provide critical feedback to the investigators, and evaluate the proposals for commercializable potential. His written report was received end of April 2019. Our Center Knowledge Transfer Coordinator, Charlie Craik, is leading the final assessment process, consulting with a subset of the Center's external advisors, with the aim for a decision for funding in June 2019.

V. EXTERNAL PARTNERSHIPS

1a. Goals for developing external partnerships

The Center for Cellular Construction has adopted a strategy of seeking out external partnerships with researchers and educators who are interested in the idea of engineering cells. Our main goal for external partnerships is to raise awareness about the Center within the scientific community, in support of the longer term goals of attracting future collaborators and funding opportunities.

1b. Performance & management indicators to assess progress

Because of our policy of establishing external partnerships that relate to specific strategic goals of the center, we will track performance of these partnerships as part of our overall tracking of progress on center strategic goals.

1c. Problems

None to report. Thus far we have had strong enthusiastic reactions from the research and educational communities, and we expect that as we continue to spread the word about our center, we will continue to find new opportunities for partnerships.

2a. Activities conducted as part of partnerships

Presentations
Presentations by Center faculty and affiliates also help build awareness of the Center and its activities. Center faculty and students gave more than 44 oral presentations and 69 poster presentation. While listed in full in the Center-wide outputs section, these presentations are mentioned again here as they serve to build awareness of the Center and Center activities.

Outreach to the Scientific Community through Conference Organization
In addition to the presentations, described above and in the Center-wide output section of this report, efforts have been made to build awareness of the Center within the scientific community. One of our primary approaches to outreach has been through organizing conferences and workshops at which we can promote CCC-relevant ideas by bringing together participants with interests that are related to our center. Although these conferences are primarily aimed at promoting scientific interactions among the participants, they have also provided an excellent means for informing relevant members of the broader scientific community about our work. Our thre main conference organizing activities for the past year have been Gordon Research Conferences, an IDEAS lab, and the upcoming qBio 2019 summer conference.

Two center faculty members, Wallace Marshall and Orion Weiner, served as Chairs for Gordon Research Conferences this past year. Dr. Marshall chaired the GRC on Stochastic Physics in Biology (January 2019, Ventura CA) and Dr. Weiner chaired the GRC on Directed Cell Motility

(January 2019, Galveston TX). The process of selecting invited speakers was influenced by concepts and ideas from the CCC, and both chairs used the opportunity of the conference to inform attendees about the CCC goals and activities.

An emerging research area of great interest to the CCC is the effort to create entirely synthetic or artificial cells. Center PI Wallace Marshall served as Director of the NSF-funded Synthetic Cells Ideas Lab held in Warrenton, VA (late February 2019) with the Center administrative team responsible for organizing travel and logistics for participants. Dr. Marshall's role at this event increased visibility for the Center among members of the growing synthetic cell research community while helping the Center to learn more about this important new area.

One of the longest running conferences in quantitative biology is the annual qBio summer conference. Originally based at Los Alamos National Lab, the qBio conference has become a community organized event that takes place at a different location each year. qBio is an annual meeting held in the summer that focuses on quantitative biology, with an emphasis on information processing by cells. This year, the CCC was selected to serve as the local host organization, responsible for logistics, including housing, travel, and scheduling. As meeting hosts, we have set up a web site for the meeting that includes information about the CCC, and we will introduce the CCC to the whole audience during our Introductory Remarks. CCC and NSF logos will feature prominently on the web site and program booklet. The two CCC Directors will speak at the conference, Zev Gartner and Wallace Marshall. In addition, center faculty Mark Chan and Hana El-Samad are serving on the program committee, and many other Center members are part of the local organizing committee, with Mark Chan serving as overall chair. This year's qBio summer conference has already attracted more than 200 registered attendees from all around the U.S., and will present a unique opportunity to highlight the work of the Center to this group of researchers in the field of quantitative biology and attend the conference at UCSF in late July 2019.

2b. Other outcomes/impacts

none to report

2c. Progress

As word about our center spreads, an increasing set of opportunities has arisen for partnerships with professional societies and meeting organizations. This has allows us to greatly expand our outreach within the scientific community. Already, we are organizing much larger conferences, with a more global reach, than we did in the first two years.

2d. Plans for partnership activities

We plan to continue our existing partnerships, while continuing to explore new potential partnerships. We plan to ask the project leads for research and education to identify areas in which external partnerships might prove useful, and in such cases we will make an effort to identify and reach out to potential individuals or groups.

VI. DIVERSITY

1a. Overall goals for increasing diversity at the Center

Our goals for increasing diversity and broadening participation are structured to achieve the following four strategic outcomes:

1. The Center for Cellular Construction is a model for creating a diverse STEM workforce that is emulated by other institutions.

2. Advancement and retention of students, postdocs, and faculty towards STEM careers has been realized at all levels of participation, from K-12 to faculty.

3. Postdoctoral training has become a key element in promoting diversity and broadening participation.

4. Infrastructure and partnerships between SFSU and other CCC institutions increase opportunities for diverse faculty to succeed in their research.

1b. Performance and Management Indicators

As detailed in our Strategic Plan, we have formulated several criteria as indicators of progress in our efforts to broaden participation.

Metric: *90% Percentage of center URM Masters students entering the STEM workforce*
Progress

Year 3: Of the 10 center MS students (80% URM) graduating in year 3, 6 are now enrolled in Biomedical PhD degree programs, 2 are Research Associates at UCSF, one is in Biotechnology and one has a position in industry, thus, 90% meet the stated goal, showing that we have been meeting our target for this key metric.

Metric: *All center participants have been trained in best practices for mentoring diverse populations and apply this training to all center activities.*
Progress years 2 & 3: At our 2nd annual retreat in July 2018, Carmen Domingo and Blake Riggs developed a 2-hour interactive workshop in which all attendees participated actively (including the entire center leadership team as well as faculty, staff, students, and postdocs).

We will repeat and expand the mentoring training based on the National Research Mentoring Network (NRMN) training program for all Center participants including those newly added to the Center in 2019. The workshop is scheduled to take place during the second day of our annual retreat on July 8 & 9, 2019.

Metric: *Proportion of URM postdoctoral fellows increases at least 10% over non-center labs*
Progress: There are currently 7 postdocs supported by the Center, of whom 2 are URM.

This represents 28% URM among our postdocs. For comparison, a recent analysis of diversity among postdoctoral fellows (Meyers *et al*., 2018 Life Science Education https://doi.org/10.1371/journal.pone.0190606), based on data from the NSF Survey of Doctorate Recipients, estimates that approximately 11% of postdocs who earned Ph.D. degrees in the U.S. are URM. We are thus doing well in comparison to this nation-wide average. Nevertheless, we recognize that postdoctoral diversity is a key area in which we need to improve further, especially given its importance in eventually addressing diversity at the faculty level nationwide. Our focus going forward is to ensure diversity in additional new hires as they occur. Plans for doing so are discussed in section 2d below.

Metric: *50% increase in publications, presentations, and grants by diverse SFSU faculty*
Progress: As detailed in the Centerwide Outputs section of this report, we have seen a significant and sustained increase in the number of publications and presentations from SFSU faculty and students since joining the Center, with almost all of this increase involving authorship and presentation by URM students. We believe these numbers strongly confirm our concept of making SFSU a bona fide research partner in the center, rather than simply a pipeline for a small number of students to work at other institutions.

Publications:
Year 1 One publication from SFSU faculty.
Year 2 Eleven publications from SFSU faculty published or submitted. Seven of these were co- authored by URM undergraduate or masters students.
Year 3. Six publications from SFSU faculty published or submitted
The number of publications continues to vastly exceed our initial goal of a 50% increase for this metric.

Presentations at National Meetings (oral and poster)
Year 1. 8 presentations by SFSU faculty or students at national meetings
Year 2. 23 presentations by SFSU faculty or students at national meetings
Year 3. 37 presentations by SFSU faculty or students at national meetings
Note that these numbers do not include an additional large number of presentations held at local and state-wide conferences. Even considering just national meetings, the number of presentations has increased by almost 300%; thus, we have greatly exceeded our target goal for this metric.

Grants Submitted
Year 1: 0
Year 2: 2 (ESTEEMED, NSF-MRI)
Year 3: 2 (Genentech Foundation, NSF-MRI)

Genentech Foundation: Proposal to support earlier stage students in research training at SFSU

NSF MRI: Acquisition of a Super-Resolution Confocal Microscope to Advance Research and Research Training Opportunities at San Francisco State University PI Blake Riggs (Chu?) Center faculty Laura Burrus, Mark Chan, Diana Chu, Wilfred Denetclaw, Carmen Domingo served as co-PIs on the grant, and support letters were provided by other center faculty including Wallace Marshall. Although no new grants have yet been awarded based on center work, at least we do see an increase between the

first two years. As more publications are generated, these will serve to seed new grant applications in future years.

1c. Problems Encountered

At the graduate level, we need to do a better job of recruiting URM PhD students who join graduate programs at participating institutions into Center labs. This will require a concerted effort to increase the visibility of the center among incoming students, which we will accomplish by taking a major role in the graduate recruiting and admissions processes, so that students are aware of the center and its faculty before they even begin their graduate work.

At the postdoctoral level, we face a different problem, namely that any given center faculty member typically only is contacted by a small number of potential postdoc applicants in any given year, and with such small numbers it can easily happen that none of the applicants are URM students. We believe we can solve this problem by pooling our applicants by hosting center-wide postdoc interviews. Our idea is that when a URM candidate applies to do postdoctoral training in any center lab, they are invited out to interview with the whole center, being given a list of center faculty and asked to consider interviewing with any others that might be of interest. Interview costs will be paid by the center. In this way, the total number of URM postdoctoral candidates exposed to each faculty member is greatly increased, increasing the likelihood of identifying a good fit between candidate and mentor.

2a. Center activities contributing to human resource development in science and engineering in the U.S. – postdoctoral, graduate, undergraduate, and pre-college levels

Activity: Partnership with NSF INCLUDES "SF CALL"

Narrative: Center faculty at SFSU have been instrumental in setting up the SFSU NSF INCLUDES "SF CALL", which focuses on developing computer literacy in the San Francisco Unified School District (SFUSD) will attract large numbers of URM students to SFSU. Students entering SFSU from the SFUSD as freshmen will be targeted to the Promoting INclusivity in Computing (PINC) program focused on women and minorities to participate in a 5-course sequence for computing in the life sciences. The overall goal of the proposed activities is to increase the number of women that gain training in the field of computer science. We have designed a series of courses and structured mentoring activities that will lower the barriers that women experience in entering the computing science discipline. Specifically, we have designed a program for biology majors which consists of 15 units of computer science course work that will allow the students to earn a minor with "Emphasis in Computer Science". The program consists of five courses of 3 units each. The first three courses (CS 306, 307, and 220) will expose students to basic computing topics such as web design, mobile app development, data structures, and algorithms. More importantly, from the very beginning, the core concepts and tools will be applied to biological problems thus, providing the students an opportunity to connect what they are learning in biology with their new skill sets in computer science. To hone their skills, the last two courses will consist of a group project on a biology related research topic (CSc 690 Special Topics). Here, students will be able to apply their new CS skills to a particular Biology topic of their interest. This four-semester program will provide a strong foundation

in computer science that will broaden the career paths of its participants. The PINC program was officially designated as a minor in 2018 and the first class of 21 was graduated in May 2018. Two participants in the PINC program were selected as summer interns at IBM in summer 2018. One PINC participant (Nicole Rodrigues) has been working in the Marshall lab at UCSF to expand her computational and cell biological skills prior to applying to Ph.D programs in the fall.

Activity: ABRCMS recruiting

Narrative: Dr. Bayliss also attended and recruited at the national ABRCMS meeting in Indianapolis, Indiana in November 14-17, 2018 and similarly worked from the UCSF booth to recruit students and inform faculty from a large number of institutions with significant URM enrollments of the opportunity for their students to apply to SFSU or UCSF for advanced STEM training.

Activity: Mentoring center undergraduate and MS students at meetings

Narrative: Dr. Riggs, who is a member of the ASCB Minority Affairs Committee, attended the ASCB meeting December 8-12, 2018 to supervise 16 current SFSU CCC students presenting and applying for admission into PhD programs. He also promoted the CCC to several groups and to faculty at other institutions with significant URM enrollments.

Activity: Faculty visits to URM student groups at other academic institutions

Narrative: Dr. Bayliss visited UC Davis on Saturday, April 4, 2019 to present a panel discussion to faculty and students on successful approaches to recruiting and training URM students in STEM. Visits such as this one have strengthened the partnership between UC Davis and SFSU/UCSF and will likely result in increased application and admission of students from across California.

Activity: Implement a procedure for tracking and reporting diversity of participation

Narrative: All participants have been identified along with demographic information (Table VIII.5.) and have been recorded in the CCC Tracking database. By linking this information to all individual center activities, we can now track diversity of participation in all activity areas, which will allow for identification of activity areas that might require additional work in this area.

Activity: Partnership with UCSF SRTP, URI, and SFSU to increase diversity of summer undergraduates

Narrative: Although UCSF is a medical school, it does have a robust undergraduate summer research program known as SRTP (Science Research Training Partnership) which attracts students from around the country. An additional undergraduate program known as URI (Undergraduate Research Internship) is run through the department of OB/Gyn at UCSF and has a similarly strong track record of URM participation. Center Director Wallace Marshall is one of two members of the SRTP Diversity committee, in which capacity he personally reads all applications from URM students without any prior triages based on arbitrary criteria such as grades. This puts him in a position to identify students whose interests and experience make them a good fit for the summer program, and then to advocate for them in the program admissions process. He has also strongly encouraged center faculty at UCSF to mentor SRTP summer students. During the past three funding years, center faculty at UCSF have hosted 7 students from the SRTP and URI programs, three of whom were URM. This summer CCC faculty will host two additional SRTP summer students, both URM. In the long term we hope that by continuing in this direction we will increase the number of URM students who apply to graduate programs at UCSF relevant to the Center, putting us in a stronger position to recruit them into center labs once they join the programs.

At SFSU, there are 5 pre-existing summer research training programs for URM students each summer, NIH MARC, NIH RISE, NIH Bridge, NIH BUILD and NSF REU that collectively support in excess 60 students (approximately 30 of whom do their research in CCC labs each summer). All participants conduct research 32+ hours/week, participate in the Doctoral Preparation and GRE workshops 4 hours each/week and present an oral and poster summary of their research at the end of the summer (all 5 groups together). All students are made aware of the CCC and opportunities for them to participate. Four SFSU undergraduates who participated in the SFSU summer programs (MARC) have been admitted into UCSF PhD programs in 2017 and 2018.

Activity: Strengthen research infrastructure and partnerships for diverse faculty at SFSU

Narrative: The highly diverse faculty of SFSU have, historically, faced challenges caused by reduced infrastructure support compared to the other institutions in the center. Our Center aims to correct this imbalance by opening access to all core facilities and resources at UCSF to all center faculty at SFSU, which we have done by budgeting core funds specifically for this purpose and negotiating access policies. Thanks to center-led negotiations, SFSU center faculty and their students now have full access to the entire range of core facilities that center faculty from UCSF have. At the same time, UCSF students have been granted access to the SFSU microscopy facility, further promoting collaboration between the two campuses. In addition, seven active collaborations have been established between one or more SFSU faculty and one or more faculty at other institutions, including UCSF, Stanford, and IBM Almaden Research Center.

Activity: Expand the successful model developed between SFSU and UCSF for partnerships between R1 institutions and Minority Serving Institutions to other members of the Center for Cellular Constructions.

Narrative: Based on a discussion initiated between Frank Bayliss and Dan Fletcher during the CCC annual retreat in summer 2017, Dr. Bayliss was invited to present a seminar to the UC Berkeley Department of Bioengineering on October 23, 2017. The seminar "Enhancing the Recruitment, Training and Diversity of STEM Students" was successful and one of the current SFSU URM MS students has been accepted into the UCB/UCSF joint PhD program in Bioengineering to start fall 2018. Two SFSU students (one BS and one MS) were offered admission to the joint UC Berkeley/UC San Francisco Bio-Engineering PhD program for fall 2019. One student accepted and the other chose to attend Harvard U.

2b. Impact of these activities on enhancing diversity at the Center

The most immediate impact of our center's diversity activities has been the establishment of a highly diverse graduate student body at the Masters level, many of whom have already graduated and progressed now to Ph.D. training. We have hired two URM MS graduates as Research Associates in the Lim and Marshall labs in 2017 and this summer a new entering SFSU URM MS student will conduct her MS thesis research in the Lim Lab at UCSF (she is entering a PhD at Harvard in fall 2019). Because of the success at this specific level, we are focusing most of our additional activities at earlier and later career stages, especially at the undergraduate to graduate transition and at the postdoc recruiting level.

Year 3: As the direct result of placing a SFSU URM MS student in the Lim lab, 3 new SFSU URM MS students have started their MS thesis research in the LIM lab.

2c. Progress with respect to the indicators/metrics listed above

With respect to the indicators listed above (see section 1b), we have met two of our specified goals. We exceeded our goal of having 90% of URM Masters students continue in the STEM workforce, and we have met our goal of having the entire center membership in attendance at the retreat take part in diversity mentorship training. We have also, thus far, met our goal of having at least a 10% greater proportion of URM postdocs compared to non-center labs (under the assumption that non-center labs are following the national average), and we will be paying careful attention to ensure that this trend continues with future postdoc hires. We are continuing to achieve our metric of increased publications and grants by SFSU faculty as a result of center-mediated access to core research facilities..

Year 3: Of the 36 CCC MS students supported as participants in year 3, 61% were URM and 88.9% ethnic minorities. Of the 39 undergraduates trained in CCC labs in year 3, 13% were URM and 51% were ethnic minorities. Of the 21 Center research faculty, 10% were URM and 14% were ethnic minorities. Of the 7 Center post-docs, two were URM and 29% were ethnic minorities. The totals for all participants (faculty, post-docs, MS, and BS students), 9% are URM and 29% were ethnic minorities. With respect to gender, 54% of center undergraduate students, 46% of center graduate students, 42% of center post-docs and 28% of center faculty are female.

Table 2c.

CCC MS Graduates to PhD & Continuing MS Students

Yrs 1&2	Name	Eth/Race	Mentor	MS	Post Master's
1	Gaytan, Norma	HA	Riggs	C&MB	PhD Baylor U - 2017
2	Jimenez, Monet	HA	Chu	C&MB	PhD U Washington - 2017
3	Lowe, Troy	SEA	Esquerra	Biochem	PhD UC Los Angeles - 2017
4	Monroy, Marco	HA	Chu	C&MB	PhD UT Southwestern - 2017
5	Ollison, Gerid	AA	Riggs	C&MB	PhD U So. California - 2017
6	Gutierrez, Joshua	HA	Esquerra	Biochem	PhD New York Univ. - 2017
7	Christopher Pineda	HA	Domingo	C&MB	PhD U Michigan - 2018
8	Cecelia Brown	AA	Riggs	C&MB	PhD Stanford U - 2018
9	Sam Goodfellow	W	Burrus	C&MB	PhD U New Mexico - 2018
10	Lopez-Pazmino, P	HA	Domingo	C&MB	Research Associate UCSF - 2017
11	Jacques, Torey	AA	Riggs	C&MB	Coord. SFSU NIH BUILD - 2017
12	Elizarraras, Edward	HA	Burrus	C&MB	Visiting Scholar UCSF - 2018
13	Lopez, Alejandro	HA	Esquerra	C&MB	Research Genentech - 2018
14	Chadwick, Will	W	Chan	C&MB	Research Associate SFSU - 2018
15	Corpuz, Crizsel	PI	Chu	C&MB	Current Second Year MS
16	Shah, Devan	A	Denetclaw	C&MB	Current Second Year MS
17	Sims, Jasmine	AA	M Chan	C&MB	Current Second Year MS
18	Murchison, Austin	AA	Esquerra	C&MB	Current Second Year MS
19	Gehr, James	A	Chu	C&MB	Current Second Year MS
20	Bolivar-McPeek, Jessica	HA	Riggs	C&MB	Current Second Year MS
21	Hopp, Kellen	W	Domingo	C&MB	Current Second Year MS
22	Lanns, Destinee	AA	Burrus	C&MB	Current Second Year MS
23	Black, Chris	W	Chu	C&MB	Current Second Year MS
24	Garcia, Vivian	HA	W. Lim	C&MB	Current Second Year MS
25	Meisnner, Brett	W	Chu	C&MB	Current Second Year MS
26	Swinson, Wayne	AA	Chu	C&MB	Current Second Year MS
27	Law, Ashley	W	Esquerra	Biochem	Current Second Year MS
28	Najibia, Sayeeda	A	Esquerra	Biochem	Current Second Year MS
29	Santana, Frederick	HA	Burrus	C&MB	Current Second Year MS
30	Lopez, Alejandro	HA	Esquerra	C&MB	Current Second Year MS
31	Edington, Alia	AA	Riggs	C&MB	Current Second Year MS
32	Ortega, Jose	HA	Riggs	C&MB	Current Second Year MS
	CCC New MS Graduate Students 2018				
Yr 2	**Name**	**Eth/Race**	**Mentor**	**MS**	
33	Chang, Catherine	A	Esquerra	Biochem	Current First Year MS
34	Refuerzo, Russell	PI	Esquerra	Biochem	Current First Year MS
35	Kalbaugh, Erin	NA	Esquerra	Biochem	Current First Year MS
36	Pereira, Ashley	HA	Denetclaw	C&MB	Current First Year MS
37	Mendoza, Omar	HA	Denetclaw	C&MB	Current First Year MS
38	Huang, Wesley	A	Chu	C&MB	Current First Year MS
39	Villegas-Parra, A	HA	Chu	C&MB	Current First Year MS
40	Kseniya, Konova	W	Chu	C&MB	Current First Year MS
41	Kinney, Christian	W	Chu	C&MB	Current First Year MS

42	Esin, Jeremy	W	Chan	C&MB	Current First Year MS
43	Buenafe, Marick	PI	Esquerra	C&MB	Current First Year MS
44	Coombes, Coohleen	PI	Domingo	C&MB	Current First Year MS
45	Rodrigues, Nicole	A	Riggs	C&MB	Current First Year MS
46	Sun, Steven	SEA	Roy	C&MB	Current First Year MS
47	Chemel, Angeline	SEA	Chan	C&MB	Current First Year MS
48	Piaz, Jesus	HA	Chu	C&MB	Current First Year MS
49	Martin, Adrian	SEA	Denetclaw	C&MB	Current First Year MS
50	Azanedo, Gabriela	HA	Chan	C&MB	Current First Year MS
	Funded by CCC				

	CCC BS Graduates to PhD				
Yr 1&2	**Name**	**Eth/Race**	**Mentor**	**BS**	**Post Bachelor's**
1	Gabriel Fraley	AA/NA	Burrus	C&MB	PhD UC Davis - 2017
2	Talia Hart	HA	Domingo	C&MB	PhD Harvard U-2017
3	Dana Kennedy	HA	Esquerra	Biochem	PhD UC San Francisco - 2017
4	Ulises Diaz	HA	Riggs	C&MB	PhD UC San Francisco - 2017
5	Campit, Scott	PI	Esquerra	Biochem	University of Michigan -2017
6	Garcia, Jason	HA	Domingo	C&MB	PhD UC San Francisco - 2018
7	Campos, Jean Luke	PI	Chan	C&MB	PhD UC San Francisco - 2018

2019

CCC 2017-18 Continuing MS Students

	Name	**Eth/Race**	**Mentor**	**MS Degree**		**Post Master's**
1	Corpuz, Crizsel	PI	Chu	C&MB	Current Second Year MS	Continuing
2	Shah, Devan	A	Denetclaw	C&MB	Current Second Year MS	RA UCSF June 2019
3	Sims, Jasmine	AA	M Chan	C&MB	Current Second Year MS	PhD UC San Francisco
4	Murchison, Austin	AA	Esquerra	C&MB	Current Second Year MS	PhD Stanford U
5	Gehr, James	A	Chu	C&MB	Current Second Year MS	Continuing
6	Bolivar-McPeek,	HA	Riggs	C&MB	Current Second Year MS	PhD UC Davis
7	Black, Chris	W	Chu	C&MB	Current Second Year MS	Biotechnology
8	Garcia, Vivian	HA	Lim	C&MB	Current Second Year MS	PhD Harvard U
9	Meisnner, Brett	W	Chu	C&MB	Current Second Year MS	Continuing
10	Swinson, Wayne	AA	Chu	C&MB	Current Second Year MS	Continuing
11	Law, Ashley	W	Esquerra	Biochemistry	Current Second Year MS	Continuing
12	Najibia, Sayeeda	A	Esquerra	Biochemistry	Current Second Year MS	Continuing

13	Edington, Alia	AA	Riggs	C&MB	Current Second Year MS	PhD UT Southwestern
14	Ortega, Jose	HA	Riggs	C&MB	Current Second Year MS	Third year MS
15	Lanns, Destinee	AA	Burrus	C&MB	Current Second Year MS	Biotechnology
16	Chadwick, William	W	Chan	C&MB	Current Second Year MS	RA UCSF April 2019

CCC Continuing 2018-19 MS Students

1	Chang, Catherine	A	Esquerra	Biochemistry	Current First Year MS	Second Year MS
2	Refuerzo, Russell	PI	Esquerra	Biochemistry	Current First Year MS	Second Year MS
3	Kalbaugh, Erin	NA	Esquerra	Biochemistry	Current First Year MS	Second Year MS
4	Pereira, Ashley	HA	Denetclaw	C&MB	Current First Year MS	Second Year MS
5	Mendoza, Omar	HA	Denetclaw	C&MB	Current First Year MS	Second Year MS
6	Huang, Wesley	A	Chu	C&MB	Current First Year MS	Second Year MS
7	Villegas-Parra, A	HA	Chu	C&MB	Current First Year MS	Second Year MS
8	Kseniya, Konova	W	Chu	C&MB	Current First Year MS	Second Year MS
9	Kinney, Christian	W	Chu	C&MB	Current First Year MS	Second Year MS
10	Esin, Jeremy	W	Chan	C&MB	Current First Year MS	Second Year MS
11	Chemel, Angeline	SEA	Chan	C&MB	Current First Year MS	Second Year MS
12	Piaz, Jesus	HA	Chu	C&MB	Current First Year MS	Second Year MS
13	Martin, Adrian	SEA	Denetclaw	C&MB	Current First Year MS	Second Year MS
14	Azanedo, Gabriela	HA	Chan	C&MB	Current First Year MS	Second Year MS
15	Buenafe, Marick	PI	Esquerra	C&MB	Current First Year MS	Second Year MS
16	Chemel, Angeline	SEA	Chan	C&MB	Current First Year MS	Second Year MS
17	Coombes, Coohleen	PI	Domingo	C&MB	Current First Year MS	Second Year MS
18	Sun, Steven	SEA	Roy	C&MB	Current First Year MS	Second Year MS
19	Nik Mendoza	HA	Lim	C&MB	Current First Year MS	Second Year MS
20	Kong, Connie	A	Esquerra	Biochemistry	Current First Year MS	Second Year MS

CCC Undergraduates Graduating 2019

Name		Eth	Race	Major	Mentor	Current Status
Bugay	John Paul		PI	Biology	Domingo	PhD U Michigan
Chandrasekaran	Sita		A	Chem&Biochem	Esquerra	PhD UCB/UCSF BioE
Gonzalez	Juiliet	HA	NA	Chem&Biochem	Esquerra	PhD City of Hope
Segura	Carlos	HA	W	Biology	Chan	PhD U Washington
Nzerem	Madu		AA	Biology	Burrus	MS SF State
Odessa	Garay		A	Biology	Chu	MS SF State
Tam	Cynnie		A	Biology	Riggs	MS SF State
Yang	Johnson		A	Biology	Domingo	MS Stanford
Kolahdouzan	Kian		W	Chem&Biochem	Esquerra	Apply to Dental School
Nyznyk	Andrew		W	Biology	Domingo	Apply to Medical School
Johnson	Amanda		W	Biology	Denetclaw	Apply to MS SF State
Morales	Genaro	HA	W	Biology	Denetclaw	Apply to MS SF State
Yancey	Ariana		AA	Biology	Riggs	CCC Intern Exploratorium
Ramirez	Aura	HA	W	Biology	Domingo	Applying Biotech Positions
Clendenny	Melissa	HA	W	Biology	Domingo	RA UCSF

CCC Undergraduates Continuing 2019

Name		Eth	Race	Major	Mentor	Current Status
Keeter	Kloe	HA	PI	Chem&Biochem	Esquerra	Continuing
Aleman	Johana	HA	A	Biology	Chu	Continuing
Barrera-Velasquez	Adrian	HA	W	Biology	Chan	Continuing
Cetina-Antonio	Miriam	HA	W	Biology	Chu	Continuing
Cisneros	Rocio	HA	W	Biology	Burrus	Continuing
de Jesus	Maura	HA	W	Biology	Chan	Continuing
Hernadez	Paulina	HA	W	Chem&Biochem	Esquerra	Continuing
Huitron	Aileen	HA	W	Chem&Biochem	Esquerra	Continuing
Oluoch	Benazir		AA	Chem&Biochem	Esquerra	Continuing
Pablo	Michelle		A	Biology	Chu	Continuing
Quach	Thanh		A	Biology	Chan	Continuing
Ricardo	Solis	HA	W	Biology	Riggs	Continuing
Rodriguez	Ramon	HA	W	Biology	Chan	Continuing
Rozhin	Lak		W	Biology	Riggs	Continuing
Sanchez	Austin	HA	W	Chem&Biochem	Esquerra	Continuing
Tserendavaa	Mendsaikhan		W	Biology	Riggs	Continuing
Young	Dana		A	Biology	Chu	Continuing

Of the 32 active undergraduates in the SFSU CCC labs, 15 graduated and 17 are continuing. Four of the BS graduates have entered PhD programs, six have or will enter MS programs, one is applying to MD programs and another is applying to Dental Schools. One student who graduates has been selected to be a CCC intern at the Exploratorium, one is working as a Research Assistant at UCSF and another is applying for positions in the Biotechnology industry.

Although not captured in the tables above, of the 66 URM participants, 39 reported on three socioeconomic status questions. 79.5% are or will be the first in their family to complete a collegiate degree, 92% have been eligible for financial aid, while only 63% have been eligible for a Pell grant.

2d. Plans to enhance diversity for the next reporting period

Activity: Facilitating participation of underrepresented students at an earlier stage

Narrative: SFSU, in partnership with SEP and the CCC, submitted a proposal to the NIH NIBIB ESTEEMED PAR-17-221 to support a summer bridge before freshmen matriculation focused on math and chemistry preparation as well as workshops on transitioning to college and then a Freshmen and Sophomore Honors program to prepare URM STEM majors for research careers in science. Under this proposal, these students would receive significant personal funding ($1,000/month) for the first 2-years and then enter one of our 3 NIH funded upper-division Honors programs (NIH MARC, NIH RISE and NIH BUILD). The SF ESTEEMED program was envisioned to work closely with the SEP HIP and CCC programs that support 55 high school rising seniors to conduct summer research at UCSF. The proposal stipulates that Professors Bayliss and Marshall would meet with these students each summer to stimulate and encourage them to apply for the 12 SF ESTEEMED summer bridge and freshmen/sophomore year program positions. Drs. Esquerra and Bayliss are the NIH MARC Honors program directors and Drs. Domingo and Bayliss are the NIH RISE Honors program directors, thus ensuring the SF ESTEEMED students entering upper-division would continue to receive comparable financial and academic support in preparation to enter high quality PhD programs and science careers. These training activities were intended to have a direct impact on the CCC because all the SF ESTEEMED participants would conduct summer research in CCC labs after the sophomore year and would continue in the same labs during their junior and senior years. This proposal was not funded, but we are continuing to look for alternative funding sources to implement this program in the future. Drs. Bayliss and Domingo have been approached by a private foundation to submit a formal proposal in June 2019 to fund the above described program and to also include junior/senior honors and additional MS students to start in fall 2019.

Activity: Increasing diversity of center students at undergraduate and graduate levels
Narrative: We will work closely with undergraduate and graduate admissions at SFSU and graduate admissions at UCSF to identify and admit strong applicants. SFSU faculty trained in mentoring a diverse population provided a workshop for all CCC faculty, students, post-docs and staff at our annual Retreat in summer 2017 and will do so again at the upcoming 2018 annual retreat. Center director Wallace Marshall is a member of the UCSF Tetrad Graduate Program Diversity Committee as well of the iPQB Graduate Program Diversity Committee. Tetrad is the main molecular biology graduate program, while iPQB (Integrated Program in Quantitative Biology) is the primary program for computational biology, bioinformatics, and biophysics. In this capacity he personally reads all applications from URM students, discusses the applications during the overall admissions committee meetings, and thus has the opportunity to directly influence both the Tetrad and iPQB graduate programs to carefully consider a larger pool of diverse applicants. Center co-directors Gartner and Lim, as well as faculty members Fung, El- Samad, Weiner, and Dumont, are members of the admissions committees for either Tetrad or iPQB where they are thus able to support the same goal of admitting a more diverse student body. Gartner is Co-Chair of the joint UCB/UCSF Bioengineering PhD program. All center faculty will be expected to participate in annual fall retreats for these two programs, where they will meet with the incoming students each year, tell them about the center, and encourage them to perform rotations in center labs. This will enable

the center to recruit URM students from among the incoming student body.

The link between CCC labs at SFSU and UCSF has already resulted in an increase in URM Ph.D. students at UCSF. So far, 2 SFSU URM BS students entered UCSF PhD programs in 2017, one of whom (Ulises Diaz) has joined a CCC lab (Wallace Marshall). Another 2 SFSU URM BS students were admitted into UCSF PhD programs in 2018. In addition, 3 SFSU MS students entered PhD programs at UCSF and one SFSU URM MS student is performing her MS thesis research in a CCC lab at UCSF (Wendell Lim).

In 2019 one SFSU BS graduate has been admitted the joint UC Berkeley/UC San Francisco Bioengineering PhD program and three SFSU MS students have been admitted into UCSF PhD programs and one SFSU MS students has been admitted to Stanford U for a total of 5 new admits into CCC partner PhD institutions. Four new MS students started their MS thesis research in a CCC lab (Wendell Lim) in 2019 and a 2019 MS graduate has been hired to work as a research assistant by Dr. Lim starting June 2019.

Activity: Leverage IRACDA program to increase postdoctoral diversity

Narrative: Plans are in process for the center to engage more fully with the joint UCSF-SFSU IRACDA program http://iracda.ucsf.edu/ucsf-sfsu-mentors to broaden diversity in the postdoctoral community of the center and to further the professional development for those from varying backgrounds.

The UCSF IRACDA program provides financial support and mentoring for postdocs from under- represented groups in science, as well as professional development and training for teaching.
IRACDA scholars in turn mentor and teach SFSU undergraduates, masters and graduate students and provide outreach through SFSU's NIH BUILD, RISE, MARC, Bridges, and SRTP program to underrepresented groups in the community.

Raymond Esquerra, one of our center SFSU faculty members, is Co-Director of the IRACDA program. He is also Director of SFSU's NIH-funded MARC Program and serves on the Advisory Committees for SFSU's RISE and Bridges programs, two programs that aim to increase diversity in the pipeline in biomedical sciences. He has created on-line teaching modules for UCSF postdoctoral researchers to develop their teaching skills and has mentored an SFSU-UCSF postdoctoral scholar, Benjamin Sandler, who is currently an Associate Professor at Ashford University. These experiences make him the ideal liaison between the center and the IRACDA program, and put the center in a strong position to leverage the strength of this program in promoting diversity at the postdoctoral level. Center faculty Laura Burrus, Diana Chu, Wilfred Denetclaw, Carmen Domingo and Blake Riggs are all teaching mentors for the IRACDA program at SFSU.

During year 2, we held a series of discussions with Ray Esquerra and Holly Ingraham (UCSF), the IRACDA Program Directors, to steer IRACDA Scholar applicants to consider center faculty laboratories for their postdoctoral work and visit and interview with center faculty.

Progress: This year was the planning period for this activity and we developed an implementable plan of action for the upcoming funding cycle. The UCSF-SFSU IRACDA program is a highly effective program for providing excellent training for academic careers to

its fellows, but also, very importantly, plays a major role in diversifying the postdoctoral population at UCSF. The UCSF CCC seeks to interface with the UCSF-SFSU IRACDA program to 1) coordinate recruitment efforts to assure a diverse pool of CCC postdoctoral fellows, 2) work with the IRACDA program to design an "IRACDA-like" program specifically for the needs of CCC fellows, and 3) coordinate efforts on integrating CCC research and focus into new and exciting courses at SFSU.

Recruitment efforts will be focused on direct-marketing methods (SACNAS, ABRCMS, discipline specific meetings, webpage, Facebook, etc.). In addition, more active personalized recruitment will be used: reaching out to the extensive network of SFSU alumni, connections resulting from URM pipeline training success, and the UCSF-SFSU IRACDA program. The UCSF-IRACDA program will send candidate information of candidates not selected for IRACDA to the CCC for possible placement. The IRACDA program and CCC will refer interested candidates to apply to the IRACDA or a CCC lab. The CCC will invite URM postdoc applicants to any center lab to interview with multiple center labs to increase likelihood of being part of the center.

To help assure that the CCC is an environment that nurtures success in all its postdoctoral fellows, all center postdocs, regardless of their own minority status, are trained in broadening participation issues. This training will be part of the annual retreat and part of other UCSF Training Opportunities (SEP).

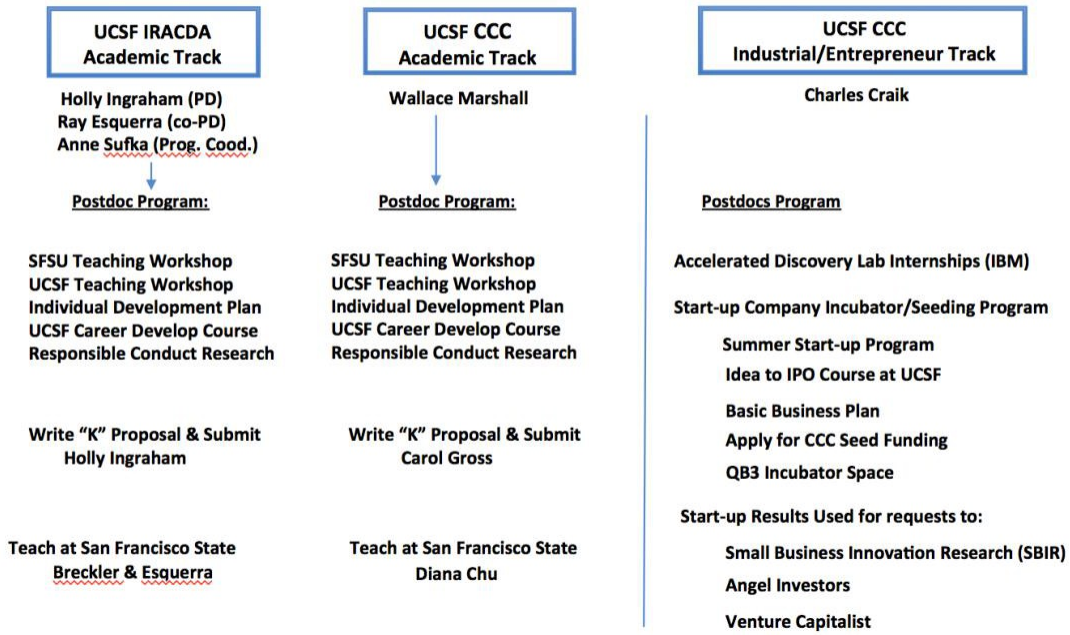
The figure below shows the design for the CCC postdoctoral "IRACDA-like" training. Unlike the IRACDA this program has two-paths, the academic and industrial. During the next year the CCC postdocs will join the IRACDA fellows in the teaching workshops, with the longer-term goal of implementing a workshop specifically for CCC post-doctoral fellows the following year. The academic component is modeled after the IRACDA directly, whereas the industrial pathway implements some best-practices learned from the IRACDA program.

The CCC-postdoc teaching experience and professional development activities are designed not to impact research productivity following UCSF-SFSU IRACDA program model. Although the CCC-fellows will be involved thru all aspects of the course, they will only teach ~25% of the course under a mentorship of experienced SFSU faculty.

In the Spring of 2019, IRACDA postdoctoral fellow, Anum Glasgow (teaching mentor: Dr. Ray Esquerra) will develop a new course entitled the "Principles of Cellular Engineering." In addition, Dr. Ray Esquerra and Dr. Tom Zimmerman (IBM) will develop an undergraduate microscopy and imaging course. In the future, we expect CCC fellows to develop teaching skills by evolving and improving on these courses.

Starting in summer of 2019, CCC postdoc Guillermina Ramirez-San Juan will be joining the UCSF IRACDA program. This represents the first tangible output of our discussions with that organization.

CCC Post-doctoral Training



VII. Management

1a. Organizational Strategy

During the first three years of this grant the two major areas of emphasis in our management development work has been to put into place a management and leadership structure capable of supporting all center programs, and of integrating the six participating institutions into a cohesive unit working collectively on projects that no individual group could do separately. Regarding the second goal, we have allocated resources among the participants and institutions according to our original plan with each participating group allocated a fixed quantity of funds, with further funds set aside for shared core resources, educational activities, and knowledge transfer activities. An important change that we made this past year was to establish a Strategic Reserve of funds to allow us to respond flexibly to unanticipated needs and to exploit new opportunities that may arise. The Strategic Reserve was created by re-allocating some of the funds originally designated for a 3D printing core (no longer necessary given the prevalence of this technology at all participating institutions), as well as funds freed up by eliminating direct financial support of public outreach activities other than at the Exploratorium, and by reducing our level of financial support for high school teacher and student training, as that program transitions to self-sustaining funding.

Our organizational strategy involves several layers of management and interaction. The **Executive Committee**, comprised of Wallace Marshall, Director, and Zev Gartner, -Co-Director, and Managing Director, Debra Singer (Ex Officio), share in the decision making process, but Dr. Marshall is Executive Director. Dr. Wendell Lim has stepped down as a co-director in order to be able to devote more time to running a new Institute that he directs, but he will continue to play a special role as leadership mentor for Drs. Marshall and Gartner, drawing on his experience in running other large centers. The formal request for this change is in process.

The Executive Committee has standing meetings every two weeks. We have added two center members from our Internal Advisory Committee to executive discussions this year – Simone Bianco, and Rebecca Smith, Education Coordinator. Olivia Viloria, Center finance manager, also attends management meetings, and we have added a former SFSU student, Will Chadwick, as an administrative assistant and liaison with management. Our plan going forward is to continue this process of rotating members of the Internal Advisory Committee through the Executive Committee, as a way to give them experience in the operations of the Center.

The Executive Committee interacts with the Management Team (see below) to execute center operations.

To manage individual activity areas, we have appointed project leads with responsibility for setting strategy and tracking progress on individual project areas. Education sub-groups have Project Leads, coordinating new initiatives, such as our new undergraduate /graduate course for July 2019 (organized by Diana Chu & Mark Chan, with Rebecca Smith & Jessica Allen, of UCSF SEP)

Zev Gartner, Co-Director, serves as overall **Research Coordinator**, in consultation this year with Kristin Dolan, of UCSF's Research Development Office (described below).

Each of the five core research projects has an appointed Project Lead responsible for organizing collaborations around each project.

Our working group leads to coordinate individual research areas are:
Project 1) Cellular Machine Shop – Simone Bianco
Project 2) CellCAD –Wallace Marshall
Project 3) Cellular Lego – Zev Gartner
Project 4) Living Bioreactor – Mark Chan
Project 5) Cell State Inference Engine/Cellular Sentinel – Jennifer Fung

Additional faculty members serve as **Diversity Coordinator** (Frank Bayliss);
Knowledge Transfer Coordinator (Charles Craik);
Education Coordinator (Rebecca Smith), and **Data Management Coordinator** (Jennifer Fung).

This past year we hired Dr. Robert McGinn to serve as **Lead Ethics Investigator and Coordinator** for the center, to oversee ethics training for the center, and strengthen our approach to ethical, legal, and societal implications of the CCC's research. (His role and activities are described below, in the Context Statement, and the in Education sections, and his NSF Biosketch is appended at the end of the report.)

Although management is centered at UCSF, each partner institution is represented by an Institutional CCC Coordinator (Mark Chan – SFSU, with Frank Bayliss; Sindy Tang – Stanford; Dan Fletcher – UC Berkeley; Simone Bianco – IBM; Jennifer Frazier – Exploratorium).

Our approach for Program Management is based around our Strategic Plan, in which we assigned 1-2 center faculty to oversee progress towards each specific milestone. These individuals report on progress to the leadership team, who then review center-wide progress on a quarterly basis. Feedback concerning plans and activities is provided by the external advisory committee as well as a professional evaluator hired specifically to provide formative evaluations of center activities.

We have organized CCC faculty and others in an Internal Advisory Committee (described below) to take on some of the routine activities previously handled entirely by the Leadership and Management teams in the first two years.

1b. Management Team

Our management team consists of four components: Center Management, Program Management, Evaluation, and Internal Advisory Committee.

Center Management
The Center Managing Director, Debra Singer, serves as primary liaison with the two CCC Directors, and oversees overall center operations, budget processes, evaluation, reporting, events, and participates in strategic planning and logistics for new directives and initiatives.

Ms. Singer is one of the most experienced project managers at UCSF, with over two decades of experience in project management, consulting, and coordinating large multi-PI grants. Ms. Singer plays a significant role in center communications, communicating with the federal agency and leads at our partner organizations. She works closely with our education, diversity, research and knowledge transfer coordinators, as well as faculty and others involved in CCC initiatives.

Center Management is supported by an Administrative Core. Our financial analyst, Ms. Olivia Viloria, works with Ms. Singer on overall budget, accounting and subcontract administration. A Center Administrative Assistant (Mr. William Chadwick) helps with organization and administrative tasks, especially meeting logistics and web site maintenance. Administrative needs are supplemented by shared administrative support from the PIs' departments UCSF Biochemistry, Cellular & Molecular Pharmacology, and Pharmaceutical Chemistry) and in coordination with administrative staff at our center's partner institutions and divisions. After reviewing needs for administration of the SFSU component, in the fall of 2018 we augmented funds for SFSU to allow for partial support of a program assistant at the Student Enrichment Office, directed by Center Diversity Director, Frank Bayliss.

Program Management
This past year our Management Team has been augmented by Dr. Kristin Dolan from the UCSF Research Development Office, who is acting as Program Manager for the center. She attends all Center meetings, works closely with Ms. Singer, and she took the lead as facilitator for our 2-day Strategic Planning meeting in February 2019. She brings a wealth of experience in program management for large grants and centers, and is working with our center to prepare us for submitting our renewal application this fall.

Evaluation
Our center has a formal contract with Phillips & Associates, a professional evaluation firm, to carry out evaluation of center activities. Michelle Phillips has extensive experience working with NSF-funded projects including several large Center grants including the NSF's National Center for Engineering and Technology Education (NCETE). Current scope of evaluation includes the experience of trainees in the various center activities; documenting the integration of the Center's various institutions and the value added from bringing these institutions together in the Center; and providing formative evaluation to help the Center continuously improve its culture, communication, collaboration, and education programs. Ms. Phillips has attended all center meetings, and has played a direct role in developing internal evaluation instruments in the form of online surveys for center participants, in order to identify challenges and possible ways to improve center operations and activities. She takes part in all PI-only meetings, so that she can pass along her insights to the rest of the faculty. Phillips & Associates provide their results to Rebecca Smith, our Education Coordinator, and Debra Singer, Center Managing Director.

Internal Advisory Committee
Our Internal Advisory Committee is made up of leaders spanning the center institutions and activity areas. The purpose of this committee is to have pre-designated individuals who will provide guidance to the center leadership on specific areas of expertise. The IAC is grouped around five decision task areas, three concerning routine decision tasks and two concerning special circumstances.

Routine:
Resources/IP/Data management (data sharing, resources, knowledge transfer)

Meetings (quarterly meetings, annual retreat)
Education and Dissemination (coherence, participation)

Special circumstances:
Conflict management (harassment, ethical violations, IP or personal conflicts)
Participation/ personnel (sunsetting, affiliates, replacements, succession)

Current IAC membership consists of the following seven members: Diana Chu (SFSU), Orion Weiner (UCSF), Shawn Douglas (UCSF), Rebecca Smith (UCSF/SEP), Jennifer Fung (UCSF), Sindy Tang (Stanford), Simone Bianco (IBM), Jennifer Frazier (Exploratorium).

The IAC members are assigned specific areas of primary responsibility within the "routine" category, as follows: Resources/IP/Data management (Fung, Bianco, Douglas); Meetings (Chu, Tang); Education and Dissemination (Smith, Frazier, Weiner). IAC members are currently consulted on an as-needed basis to handle specific decision-making tasks, for example in deciding on agendas for the annual retreat or planning new courses. Decision tasks in the "special circumstances" category were not assigned to specific individuals; rather, if those circumstances arise the whole IAC will convene as a group to discuss problems and solutions.

As on example of an active working group organized from the IAC, this year Diana Chu and Rebecca Smith took charge of organizing our new 2-week summer course, for undergraduates and graduates. They recruited Mark Chan to serve as course co-director with Diana Chu, and tasked Jessica Allen of UCSF SEP to help with logistics. They then sought out advice on curriculum from faculty members Orion Weiner and Wallace Marshall, who both had experience with project-based courses at the Marine Biological Laboratory in Woods Hole, as well as from Robert McGinn for advice about ethics components for the curriculum. They recruited TAs from among center postdocs and advanced students, and worked with Olivia Viloria and Debra Singer on the course budget.

Another working group was tasked with setting up our Centerwide Ethics Survey on Responsible Research and Innovation. IAC member Rebecca Smith worked with Ethics Coordinator Robert McGinn on navigating the UCSF IRB process for the survey developed by Dr. McGinn, while Debra Singer and William Chadwick worked on implementation of the survey in an online format.

These two examples illustrate our approach for distributing decision making among center faculty by drawing on members of the IAC to take the lead on organizing specific center activities. By delegating these decisions to working groups, the Executive Committee is able to focus energy on overall center vision and progress while ensuring that arrangements are made for specific activities.

Two specific "special circumstances," namely succession of the leadership team and sunsetting of center faculty who are failing to participate, are currently governed by written policies that are provided to the IAC, who will present a recommendation reached by majority vote to the Executive Committee, who will then make the final decision.

2a. Center-wide communications

Communications within the center currently entails four mechanisms: center-wide quarterly meetings, project group meetings, and monthly PI phone conferences.

The cornerstone of our approach for center communications and coordination is face-to-face meetings of center participants, in which ideas can be shared and problems discussed in an open and interactive manner. We believe that especially in the early stages of a large collaborative project, face-to-face in-person meetings can build a sense of trust and cooperation that simply cannot be achieved any other way. This approach is possible for our center because of the tight geographic distribution of participating institutions in the SF Bay Area, all are in easy driving distance of each other.

We hold regular **quarterly center-wide meetings** open to all center participants, including undergraduate research students. Quarterly meetings rotate among participating institutions, with transportation provided for those who cannot drive themselves. Parking permits are arranged for all attendees, and meals are provided, so that there is no cost to attending. Each quarterly meeting starts with an update on the center from the Director, update on planned activities from the Managing Director, and includes a one-hour faculty breakout session that provides an opportunity to discuss concerns, ideas, and future plans among all center faculty members. The bulk of each quarterly meeting is research presentations by center faculty and students, which serve as a way to catalyze new collaborative projects. Quarterly meetings end with a student social activity while the PIs have their faculty breakout session.

Our **annual retreats** are two-day long events held at a conference center in Tiburon. The annual retreats include research talks and posters from students and postdocs, special lectures from guest lecturers, and workshops focused on mentoring, increasing diversity, and on ethical, legal and societal implications of research and ethics training. Participation in the retreat is high and includes participants from all six institutions of the Center. Members from the EAC attend these annual retreats, giving them the chance to interact with center students.

In order to coordinate research activities, we have established quarterly **project group meetings** for the Living Bioreactor, Cell State Inference Engine/Cellular Sentinel, and CellCAD project groups. These meetings bring together faculty and students working on the different center project areas to update each other on progress and discuss new collaborative directions. These meetings rotate locations between UCSF, UCB, SFSU, Stanford, and IBM. Center members at the Exploratorium host meetings on prototypes for microscopes and projects demonstrating cellular engineering concepts.

Every month we hold a brief **PI phone conference** which takes place the same time each month so that all center faculty can hold that time open. This is an opportunity to discuss any matters arising, update faculty on future plans, and have an opportunity for center faculty to discuss ideas and concerns.

2b. Electronic Communications Systems

As a supplement to our face-to-face meetings, we are harnessing technological solutions that allow day-to-day coordination of activities, access to data, and easy access to materials such as planning documents. Each of these tasks has a different technical solution.

For day-to-day coordination of activities, such as announcement of meetings and seminars, answering questions about resource availability, and so on, we have set up a center-wide Listserv that allows anyone in the center to provide notification to the whole center membership. For

even more rapid interactions, we also employ a Slack channel dedicated to the CCC students, postdocs, and faculty. Slack gives us rapid, mobile interactivity across all center labs and activities.

For data sharing, we are implementing an electronic data sharing system so that center participants at all institutions can not only access each other's data and models, but more fundamentally find out what data and models currently exist. Our system uses IBM Lab Book as intermediary between the data and computer servers that store information, and the multiple lab notebook and project tracking systems currently in use in different center labs (for example, Jupyter Notebook or Slack). In order to provide data access across institutions, we have negotiated access to the UCSF Box data sharing system, which has the technical capacity to interface with IBM Lab Book, for all center participants. This involved a full IT security risk assessment that was performed internally at UCSF and is now completed. Lab Book is now installed on UCSF servers. A major challenge has been negotiating access permission to these servers by users off-campus, due to the concerns about patient data security. With the assistance of the UCSF administration, we have been working with the IT director to achieve this access permission, but the system is still unwieldy. We are currently exploring the option of using Lab Book in coordination with Slack to allow sharing of ideas and results and then use UCSF Box to actually share data, since Box is specifically designed to handle access permissions.

For access to shared materials, we are using our Center Website, which currently has a password protected sub-site with access restricted to center members. Center documents and center-specific announcements are uploaded to this site.

2c. Problems of communications

Communicating with and organizing a dynamic group of people from various institutions– faculty, staff, students, postdocs – is a challenge. We are learning best methods to reach individual center faculty and post and deliver important information in a few places, as the volume of email most of our team receives exponentially increases. We have recognized two dominant problem areas in communications, both of which stem from a reliance on communication via email. We have put in place new approaches designed to solve these problems.

The **main communication problem** is simply that faculty and management are inundated with emails, making it difficult to capture the attention of all faculty members on a routine basis. We have researched several technical communication interfaces –but the solution is clear – we need a way to capture the complete attention of center faculty, for specific periods of time, on specific topics that need timely responses. To this end, we have taken two concrete steps to better communicate with our group of academically active, productive and highly committed faculty. First, the faculty breakout session at each quarterly meeting provides a block of un-interrupted face to face time for the leadership team to discuss plans and center vision with center faculty, request information for reporting, and answer any questions that faculty may have. This has proven highly effective in helping faculty align their work with center goals, and has proven invaluable in gathering more complete information for reporting purposes. We also believe that these sessions help faculty feel informed about future plans in the center. Second, the monthly

faculty phone conferences, held on the first Tuesday of every month, have proven highly effective in promoting open discussion and engagement.

The **second main communication problem** has been that students were sometimes left out of communications about the center, leading to reduced awareness of center goals and plans, and a lack of center identity among some of the students. One source of this problem was that our primary method for disseminating information about center activities was via email to center faculty, who were then expected to share information with their lab members. This approach proved unreliable, and for this reason we have now set up a center-wide listserv and Slack channel, that allow information to be exchanged directly among all center members. A second source of the problem was that students had not been involved in center planning and, therefore, did not always understand how their work fit in with center goals. To overcome this problem, we now invite students to present their work at every quarterly meeting. After these meetings, project directors provide feedback to the students concerning how their work fits in with the center goals. We are finding that as students take part in more quarterly meetings, they gain a clear picture of the center as a whole and how their work fits in.

In the last year, we also recruited William Chadwick, an MS student from SFSU, to work for the Center as a special administrative liaison communicating with all CCC students & postdocs. Mr. Chadwick contributed to the bioreactor, sentinel and other projects in Mark Chan's lab, and graduated in the fall of 2018. Since then, he has helped with program management and strategic planning by providing a student-focused perspective. In April 2019, he organized a separate student-led talk session the evening of our day long quarterly meeting. He was able to engage ~20 undergraduates, graduates and postdocs to meet for informal presentations; those giving talks received mentoring in their projects from their peers. As of May 2019, Will has joined the Fung lab at UCSF as an Assistant Specialist working on the sentinel and bioreactor projects primarily, but he continues to provide support for the CCC website, as a liaison with the management team, and in engaging with center students and postdocs.

3. Names and Affiliations of the Center's External Advisors

The External Advisory Committee for our center was set up in the first year of the center, based on the goal of assembling a group of academic and industrial sector scientific leaders who were chosen because their fields of expertise complement the key areas of interest for the center:

Radhika Nagpal (Dept. of Computer Science, Harvard University)
Dr. Nagpal is designated as the **EAC Chair**.

Jennifer Lippincott-Schwartz (HHMI, Janelia Farm Campus)
Neda Bagheri (Dept. of Chemical and Biological Engineering, Northwestern University)
Wenying Shou (Fred Hutchinson Cancer Research Center)
Erin Dolan (Dept. of Biochemistry and Molecular Biology, University of Georgia)
Carlos Gutierrez (Dept. Chemistry and Biochemistry, CSU Los Angeles)
Brian von Herzen (CEO, Rapid Prototypes; Director, The Climate Foundation)
Kinkead Reiling (Co-founder, Amyris)
Dan Widmaier (CEO, Bolt Threads)
Tom Daniel (Dept. Biology, University of Washington)

After the last site visit in October 2018, we recruited Dr. Tom Daniel, Dept. of Biology University of Washington, to our EAC. Dr. Daniel has extensive experience in leadership of NSF centers, having served initially as Deputy Director, and then Director, of the NSF Center for Sensorimotor Neural Engineering, an NSF ERC center based at UW. He has also served on the Scientific Advisory Board of the NSF Mathematical Biosciences Institute, as well as on the Board of Directors of the Allen Institute of Brain Science (AIBS). We believe that his wealth of experience in running and advising NSF centers will be invaluable in guiding the future development of our center.

Appropriate NDAs have been executed with all advisors, and all have been provided with copies of our Strategic Plan. **An EAC Charter has been written and provided to all EAC members**. In year 2, four members of the EAC attended our Annual Center Retreat, after which we held a half-day EAC meeting in a separate room with additional EAC members connecting via Skype.

This summer we are holding a series of focused meeting with sub-groups of our external advisors, for internal assessment and renewal planning. Reports from advisors are a part of this process.

Ethics and Responsible Research and Innovation
Because our plans to engineer new types of cells raise bioethical concerns, we have also constituted a panel of advisors, consisting of the following ethics experts.

> ***Robert McGinn*** (Center for Work, Technology & Organization, Department of Management Science & Engineering, School of Engineering, Stanford University – 1978-2019) * Adjunct Professor, UCSF. (Hire effective 4/1/19).
> *Megan Palmer* (Center for International Security and Cooperation, Stanford University)
> *Barbara Koenig* (Director, UCSF Program in Bioethics)

We recognize that the issues confronting our center, as well as the expertise on our panel, comprise specialties in ethics, governance, professional development and social science aspects of cellular engineering ethics; consequently, after our Strategic Planning Meeting, we have renamed our Ethics Panel the **ELSI (Ethical, Legal, and Social Implications) Panel**.

We recruited Dr. McGinn, a renowned expert in professional development of engineering ethics. as Adjunct Professor at UCSF in April 2019, after his retirement from Stanford. He is Lead Ethics Investigator and Advisor for the Center, and Chair of this panel. Application of funds from our Strategic Reserve allowed our Center to hire him at 20% to serve as **Ethics Coordinator** for the entire Center. (A biosketch for Dr. McGinn is included in the Appendix.)

Dr. McGinn is primary advisor for the center, helping faculty design ethics training for cellular engineering courses in development, and working with lead project researchers on issues as they emerge. Center ethics training comprises discussion of the complexities emerging in the field of cellular engineering; policy and governance analysis, leadership training and discussion of moral responsibilities needed as the pace of technologies supersede existing governance structures. Workshops and a mini-course are in development.

Dr. Koenig is an anthropologist who brings a wealth of social science expertise to the teaching of bioethics, for which she is highly respected. Dr. Koenig is Director of UCSF's Bioethics Program, within the Institute for Human Genetics- working in the inter-disciplinary field of

bioethics. She founded and led Biomedical Ethics Research Programs at Stanford and Mayo Clinic. Dr. Koenig pioneered the use of empirical methods in the study of ethical questions in science, medicine, and health. Her interests include characterizations of race in a genomics age, emerging genomic technologies, including biobanking, return of research results to participants, and using deliberative democracy to engage communities about research governance. She is an active participant in policy development both at a federal level and through her role as fellow of the Hastings Center.

Dr. Palmer is a highly recognized expert in social risk and policy of synthetic biology, having previously served as the Deputy Director of Policy and Practices at the NSF-funded SYNBERC. Within SYNBERC, she led and contributed to projects in safety and security, property rights, and community organization and governance. As Senior Research Scholar at Stanford's Center for International Security and Cooperation (CISAC), she leads a research and practice program on risk governance in emerging technology development, with a focus on how security is conceived and managed as biotechnology becomes increasing accessible. Her current projects focus on assessing strategies for governing dual use research, analyzing the international diffusion of safety norms and practices, and the understanding the security implications of alternative technology design decisions.

4. Changes to the Center's Strategic Plan

The Center Strategic Plan was initially drafted at a meeting held in January 2017 when the center had only been in existence for a couple of months. At that point, the Center Directors had ideas about what the center would be doing, but many of the faculty had not been heavily involved and so their ideas had not yet fully taken shape. Perhaps more importantly, the opportunity to set up new collaborations had not yet been available. As center activities progressed during the first two years, and new collaborative ideas began to take root, several inadequacies become apparent in our strategic plan. First, it was clear that our approaches and goals had deviated from those initially written down. This was not a case of mission drift, but rather the natural evolution of science. For example, the emergence of deep learning as a core technology for handling cell biological data was not something we could have anticipated at the time that our plan was initially drafted. Furthermore, as new collaborations matured, goals were developed that superseded some of the initial goals. Consequently, it was becoming increasingly difficult to track our progress relative to the outdated goals of the initial plan.

To address these concerns, we held a second Strategic Planning meeting Feb 11-12, 2019. The organization of this meeting and the planning for it was orchestrated by Debra Singer and our Program Manager, Dr. Kristin Dolan; the meeting was supervised by Dr. Dolan. Prior to this meeting, individual project area teams met to discuss strategic goals for their projects. In addition to these project meetings, we also held two meetings of the IAC to discuss the overall strategic plan and the process for revising it. During the Strategic Planning meeting itself, individual groups presented their proposed revisions to the whole center team, resulting in refinement of some of the goals. Time was also set aside for discussing how the individual projects fit together, including the preparation of an interaction matrix under the direction of Dr. Dolan. This meeting was attended by NSF Program Officer Charlie Cunningham. Following the meeting, project leads went through a series of iterative drafts of the final revised plan to capture the ideas discussed and ensure that everyone is in agreement. The revised plan does not entail any major alterations in strategic goals, but does focus the milestones on the actual plans of the center faculty.

VIII. Center Wide Outputs and Issues

1.a. Publications (look back to June 2018)

Peer Reviewed Publications supported by center funds

bold *indicates center faculty*
underline indicates undergraduates
 # denotes URM

1. Allard CAH, Decker F, **Weiner OD**, Toettcher JE, Graziano BR. 2018. A size-invariant bud-length timer enables robustness in yeast cell size control. *PLoS One* 13(12):e0209301

2. Arter M, Hurtado-Nieves V, Oke A, Zhuge T, Wettstein R, **Fung JC**, Blanco MG and Matos J. 2018. Regulated crossing-over requires inactivation of Yen1/GEN1 resolvase during meiotic prophase I. *Developmental Cell* Dev Cell. 2018 Jun 18;45(6):785-800.e6. doi: 10.1016/j.devcel.2018.05.020.

3. Bergman Z, Diaz U#, Johnson B, **Marshall WF, Riggs B**. 2019. Microtubules are necessary for proper Reticulon localization during mitosis. 2019, Submitted to *Plos One*. Currently in revision.

4. Biswas SK, Zimmerman T, Maini , Adebiyi A, Bozano, Brown C#, Pastore VP, **Bianco S**. 2019. High throughput analysis of plankton morphology and dynamic *Proc. SPIE* 1088109

5. Castillo U, Gnazzo MM, Turpin CGS, Nguyen KCQ, Semaya E, Lam Y, DeCruz M, Bembenek JN, Hall DH, **Riggs B,** Gelfand VL, Skop AR. 2019. Conserved role for Ataxin-2 in mediating ER dynamics. *Traffic*. doi: 10.1111/tra.12647

6. Chang AY, **Marshall WF**. 2018. Dynamics of living cells in a cytomorphological state space. *Submitted.* Currently under revision at *PNAS. Preprint: bioRxiv*. 2019 doi: https://doi.org/10.1101/549246

7. Chen E, **Esquerra RM**, Melendez PA, Chandrasekaran SS, Kliger DS. 2018. Microviscosity in *E. coli* cells from time-resolved linear dichroism measurements. J Phys Chem B. 2018 Aug 29. doi: 10.1021/acs.jpcb.8b07362.

8. Condon A, Kirchner H, Lariviere D, **Marshall WF**, Noireaux V, Tlusty T, Fourmentin E. 2018. Will biologists become computer scientists? *EMBO Reports* 19, E46628.

9. Coyle SM, Flaum E#, Li H, Krishnamurthy D, **Prakash M**. 2018. Coupled active systems encode emergent behavioral dynamics of the unicellular predator Lacrymaria olor. *bioRxiv* https://doi.org/10.1101/406595

10. Elting MW, Suresh P, **Dumont S**. 2018. The spindle: Integrating architecture and mechanics across scales. *Trends in Cell Biology* 2018 Nov;28(11):896-910. doi: 10.1016/j.tcb.2018.07.003. Epub 2018 Aug 6.

11. Galli LM, Santana F#, Apollon C, Szabo LA, Ngo K, **Burrus LW**. 2018. Direct visualization of the Wntless-induced redistribution of WNT1 in developing chick embryos. Dev. Biol. 438, 53-64.

12. Gingold C and **SM Douglas**. Gelbox — An Interactive Simulation Tool for Gel Electrophoresis. 2018. bioRxiv https://www.biorxiv.org/content/10.1101/406132v1

13. Graziano BR, Town JP, Nagy TL, Fosnaric M, Penic C, Iglic A, Kralj-Iglic V, Gov N, Diaz-Munoz A, **Weiner OD**. 2019. Cell confinement reveals a branched-actin independent circuit for neutrophil polarity. *bioRxiv* https://doi.org/10.1101/457119

14. Gruber TD, Krishnamurthy C, Grimm JB, Tadross MR, Wysocki LM, **Gartner ZJ**, Lavis LD. 2018. Cell-specific chemical delivery using a selective nitroreductase-nitroaryl pair. *ACS Chem Biol*. doi: 10.1021/acschembio.8b00524

15. Hueschen CL, Galstyan V, Amouzgar M, Phillips R, **Dumont S.** Microtubule end-clustering maintains a steady-state spindle shape. Current Biology 2019 Feb 18;29(4):700-708.

16. Ishikawa H, Yu JE, Tian J, **Tang SKY**, Qin H, **Marshall WF**. 2019. Cell-based biosynthesis of linear protein nanoarrays. *Proc. SPIE* 108930F DOI: https://doi.org/10.1117/12.2510226

17. Kimmel JC, Brack A, **Marshall WF**. 2018. Deep convolutional neural networks allow analysis of cell motility during stem cell differentiation and neoplastic transformation. *Submitted*. Preprint: *bioRxiv*. 2017 doi: https://doi.org/10.1101/159202

18. Kuhn J, **Dumont S**. Mammalian kinetochores count attached microtubules in a sensitive and switch-like manner to control cell cycle progression. Biorxiv 2018: https://doi.org/10.1101/463471. Preprint

19. Liu F, Blauch LR, **Tang SKY**. 2018. Quantifying Phenotypes in Single Cells using Droplet Microfluidics. Methods Cell Biol. 2018;148:133-159. doi: 10.1016/bs.mcb.2018.09.006.

20. **Marshall WF.** 2018. A dilution model for embryonic scaling. *Dev. Cell.* 46, 529-530.29.

21. **Marshall WF, Fung JC.** 2018. Modeling meiotic chromosome pairing: increased fidelity from a tug of war between telomere forces and a pairing-based Brownian ratchet. *Phys Biol. 2019 Apr 3. doi: 10.1088/1478-3975/ab15a7*

22. Mathijssen A, Culver J, Bhamla MS, **Prakash M**. 2018. Collective intercellular communication through ultra-fast hydrodynamic trigger waves. *bioRxiv* https://doi.org/10.1101/428573

23. McGinnis CS, Murrow LM, **Gartner ZJ**. 2018. Doublet Finder: Doublet detection in single-cell RNA sequencing data using artificial nearest neighbors. *Cell Systems* 8,P329-337

24. McGinnis CS, Patterson DM, Winkler J, Hein MY, Srivastava V, Murrow LM, Weissman JS, Werb Z, Chow ED, **Gartner ZJ**. 2018. MULTI-seq: Scalable sample multiplexing for single-cell RNA sequencing using lipid-tagged indices. *bioRxiv* https://doi.org/10.1101/387241

25. Mclaurin J#, **Weiner OD**. 2018. Multiple sources of signal amplification within the B cell Ras/MAPK pathway. bioRxiv https://doi.org/10.1101/415737
39.

26. Murrow LM, Weber RJ, Caruso J, McGinnis CS, Borowsky AD, Desai TA, Thomson M, Tlsty TD, **Gartner ZJ**. 2018. Mapping the complex paracrine response to hormones in the human breast at single-cell resolution. bioRxiv https://doi.org/10.1101/430611

27. Pastore VP, Zimmerman T, Biswas SK, **Bianco S**. 2019. Establishing the baseline for using plankton as biosensor *Proc. SPIE* 108810H

28. Pastore VP, Zimmerman TG, Biswas SK, Bianco S. 2019. Annotation-free learning of plankton for classification and anomaly detection. *Submitted*. Under review at *Nature Machine Learning*.

29. Rath KA, Peterfreund A, **Bayliss F**. 2018. Programmatic Mentoring: Providing Mentoring as a Community, Going Beyond Mentor/Protégé Pairs. *Understanding Interventions* 9, 2

30. **Riggs B**. 2018. Mutually Beneficial Research Partnerships for Equity and Innovation in Science. *ASCB Newsletter* Dec 2018 issue. p 35-38.

31. **Tang SKY**, **Marshall WF**. Cell learning. *Curr Biol.* 2018 Oct 22;28(20):R1180-R1184. doi: 10.1016/j.cub.2018.09.015.

32. Tischer DK, **Weiner OD**. 2019. Light-based tuning of ligand half-life supports kinetic proofreading model of T cell signaling. *Elife* 8, e42498

33. Toda S, Blauch LR, **Tang SKY**, Morsut L, **Lim WA**. 2018. Programming self-organizing multicellular structures with synthetic cell-cell signaling. *Science* 2018 Jul 13;361(6398):156-162. doi: 10.1126/science.aat0271.

34. Toda S, Brunger JM, **Lim WA**. 2019. Synthetic development: learning to program multicellular self-organization *Curr. Opin. Systems Biol*. https://doi.org/10.1016/j.coisb.2019.02.008

35. Yoon I, Kulkarni A, Okada K, Pennings P, **Domingo C**. 2018. Promoting Inclusivity in Computing (PINC) via Computing Application Minor. American Society for Engineering Education. ASEE 2018 CoNECD - The Collaborative Network for Engineering and Computing Diversity Conference,
Crystal City, Virginia, April 29, 2018, Page Count: 11. Permanent URL: https://peer.asee.org/29566

36. Yu W, **Marshall WF**, Metzger RJ, Brakeman PR, Morsut L, **Lim WA**, Mostov KE. 2019. Design rules for kidney branching morphogenesis. *Submitted*. Under review at *Cell Systems*.

37. Zimmerman T, Antipa N, Elnatan D, Murru A, Biswas S, Pastore V, Bonani M, Waller L, **Fung J**, Fennu G, **Bianco S**. 2019. Stereo In-Line Holographic Digital Microscope. *Proc. SPIE* 1088315

Books and Book Chapters

Eroy-Reveles, A. A., Hsu, E., Rath, K. A., Peterfreund, A. R., & **Bayliss, F**. History and Evolution of STEM Supplemental Instruction at San Francisco State University, a Large, Urban, Minority-Serving Institution. February 2019, "*Diversity in Higher Education*" series by Emerald Publishing, Chapter 10, 28 Feb 2019
ISBN: 9781787569089.

1.b. Conference Presentations

1. 6/4/18 J. Gerh, E. Rousseau, B. Jones, N. Munoz#, S. Bianco, D.S. Chu Bay Area Cytoskeleton Symposium (selected talk), San Francisco, CA Mathematical model of segregation dynamics

2. 6/4/18 Christine Hueschen (Dumont lab). Spindle turbulence and mitotic cell motility in the absence of microtubule end-clustering. Bay Area Cytoskeleton Meeting, San Francisco, CA

3. 6/16/18 Zev Gartner Hacking Cell Biology to understand human tissue. World Ophthalmology Conference. Barcelona, Spain

4. 6/20/18 Zev Gartner Programming Tissue Self-Organization. Gordon Research Conference on Biointerface Science, Il Ciocco, Italy

5. 6/8/2018 Douglas S; Invited Panelist, InterPlanetary Festival, Santa Fe Institute, New Mexico

6. 6/17/2018 Douglas S; Keynote Speaker, ACM Symposium on Computational Fabrication, MIT Cambridge MA

7. 6/22/2018 Douglas S; Invited Speaker, Engineering Biomolecules Mini Symposium, University of Oregon

8. 7/19/18 J. Gerh, E. Rousseau, B. Jones, N. Munoz3, S. Bianco, D.S. Chu Center for Cellular Construction Annual Retreat, Mathematical model of segregation dynamics

9. 7/20 – 7/24/18 Shah D, Denetclaw W. Endoderm nitric oxide focally elevated 'hotspots' at the heart forming regions (HFRs) signals in early cardiogenesis in chicken embryos. Society for Developmental Biology 77th Annual Meeting, Marriot Downtown Waterfront Portland, Portland, Oregon

10. 7/24/18 Zev Gartner. Building tissues to understand how tissues build themselves. Gordon Research Conference on Signal Transduction by Engineered Extracellular Matrices

11. 7/31/18 Wallace Marshall The flagellar length control system. Physical Biology of the Cell summer course, Marine Biological Laboratory, Woods Hole MA.

12. 8/14/18 Zev Gartner. Building tissues to understand how tissues build themselves. Santa Cruz Developmental Biology conference. Santa Cruz, CA.

13. 8/21/18 Jennifer Frazier Seeing the unseen: Engaging the public in new areas of research through visualizations. NSF STC Annual Directors Meeting on Engaging Diverse Audiences: Broadening Participation Through Science Communication. Berkeley, CA

14. 9/13/18 Rebecca McGillivary. Nuclear dynamics in Stentor. UCSF Tetrad Program Retreat, Granlibakken CA.

15. 10/11/18 Shah D, Denetclaw, W. NOing the heart: endoderm nitric oxide focally elevated "hotspots" at the heart fields signal in early cardiogenesis in chicken embryos. SACNAS 2018 Annual Meeting, San Antonio, TX.

16. 11/14/18 Riggs B Annual Biomedical Research Conference for Minority Students (ABRCMS). Indianapolis, IN.

17. 12/4/18 Zev Gartner. Building tissues to understand how tissues build themselves. Harvard Mathematical Biology Workshop on Morphogenesis. Cambridge MA.

18. 12/8/18 Wendell Lim. Synthetic Notch circuits to direct multicellular organization, ASCB Annual Meeting, San Diego, CA

19. 12/8/18 Greyson Lewis (Marshall lab) The morphology space of yeast mitochondrial networks. ASCB Annual Meeting, San Diego, CA

20. 12/8/18 Jacob Kimmel (Marshall lab) Inferring cell state dynamics with machine learning methods. ASCB Annual Meeting, San Diego, CA

21. 12/9/18 Athena Lin (Marshall lab) Aurora kinases may control regeneration checkpoints in Stentor. ASCB Annual Meeting, San Diego, CA

22. 12/10/18 Rebecca McGillivary (Marshall lab) Macronuclear shape and positioning in the giant ciliate, Stentor coeruleus. ASCB Annual Meeting, San Diego, CA

23. 12/9/18 Jonathan Kuhn. Individual mammalian kinetochores count attached microtubules in a switch-like, highly sensitive manner to control cell cycle progression. ASCB Annual Meeting, San Diego, CA

24. 12/12/18 Jasmine Sims#. Effect of the cell cycle on vacuole size in S. cerevisiae Yeast. American Society for Biochemistry and Molecular Biology, Annual Meeting, Indianapolis, IN

25. 1/3/18 Zev Gartner. Building tissues to understand how tissues build themselves. BMES Cell and Molecular Engineering Conference. San Diego, CA.

26. 1/8/19 Barbara Jones. Dynamics of Viral Mutation and Evolution. Gordon Research Conference on Stochastic Physics in Biology, Ventura, CA.

27. 1/23/19 Brian Graziano. Cell-extrinsic mechanical forces induce neutrophil polarization in the absence of leading edge actin assembly pathways. Gordon Research Conference on Directed Cell Motility.

28. 1/30/19 Nat Hendel (Marshall lab) Diffusion as a ruler. Cell Modeling Hackathon, Half Moon Bay, CA.

29. 1/30/19 Greyson Lewis (Marshall lab) Building Mitochondrial Morphology Space. Cell Modeling Hackathon, Half Moon Bay, CA.

30. 1/31/19 Hana El-Samad. The Engineer's Journey: Untangling Feedback Loops to Design Smart Cells. UCSF Byers Award Lecture in Basic Science, San Francisco CA.

31. 2/4/19 Wallace Marshall Cell-based biosynthesis of linear protein nanoarrays
SPIE Photonics West, San Francisco, CA.

32. 2/4/19 Sujoy Biswas (IBM). High throughput analysis of plankton morphology and dynamic
SPIE Photonics West, San Francisco, CA.

33. 2/4/19 Vito Pastore (IBM). Establishing the baseline for using plankton as biosensor
SPIE Photonics West, San Francisco, CA.

34. 2/4/19 Zev Gartner. The Physical and Chemical Contributions to the Self-Organization (and Disorganization) of the Human Mammary Gland. Gordon Research Conference on Salivary Glands and Exocrine Biology. Galveston, TX.

35. 2/7/19 Thomas Zimmerman (IBM). Stereo In-Line Holographic Digital Microscope.
SPIE Photonics West, San Francisco, CA.

36. 2/5/19 Ramos Morin B K# South bay Drosophila meeting. SJSU.

37. 2/22/19 Martin A, Denetclaw W Nitric oxide synthase activated by mechanical stretch for ectoderm nitric oxide formation. CSU Research Competition, SFSU Campus.

38. 2/22/19 Pereira A#, Denetclaw W Nitric oxide role in early signaling events directing cardiac laterality. CSU Research Competition, SFSU Campus.

39. 3/8/2019 Domingo, C. The role of differential cell adhesion during embryonic muscle formation. Southwest Regional Developmental Biology Meeting, Denver, CO.

40. 3/17/19 Wendell Lim, Programming the formation of synthetic tissues. Synthetic Morphogenesis: From Gene Circuits to Tissue Architecture, Heidelberg, Germany.

41. 3/18/19 Wallace Marshall. The Flagellar Length Control System. Royal Society Conference on Unity and Diversity in Cilia. Chicheley Hall, UK.

42. 3/20/19 Zev Gartner. Building tissues to understand how tissues build themselves. Synthetic Morphogenesis: From Gene Circuits to Tissue Architecture, Heidelberg, Germany.

43. 3/27/19 Bolivar J#, Brown C# South bay Drosophila meeting. UC Santa Cruz.

44. 4/7/19 Zev Gartner. Building tissues to understand how tissues build themselves. FASEB Experimental Biology, Orlando FL.

45. 4/19/19 Wallace Marshall. The flagellar length control system. Chicago Cytoskeleton Meeting, Chicago, IL.

46. 4/29/19 Zev Gartner. Chemical tools for multiplexed single cell transcriptional analysis. Chemical Tools for Complex Biological Systems II (HHMI/Janelia)

47. 5/2/19 Wallace Marshall. Pattern formation and regeneration in a single cell. Exploring Frontiers Morphogenesis Symposium, Allen Institute, Seattle WA

48. 5/3/19 Wendell Lim, "Programming the formation of synthetic tissues," Exploring Frontiers Morphogenesis Symposium, Allen Institute, Seattle WA

49. 5/9/19 Riggs B, Keynote Speaker. Stanford Postdoc Symposium. *Changing the culture and practice of science: a 387.2 mile journey*. Stanford University.

50. 6/28/19 Riggs B Keynote Speaker. Bay Area Cytoskeleton Meeting. UC Berkeley.

51. 8/14/19 Denetclaw W Society for Redox Biology and Medicine SfRBM 2019 Regional Redox Symposium and 10th LPI International Conference, Oregon State University, Corvallis, OR, August 14-16, 2019

Poster Presentations

^Undergraduate, #Underrepresented Minority

1. 7/17/18 Martin A, Pereira A#, Denetclaw W. Models on ectoderm no generation through mecho-physical stretch or primary cilium toggling in chicken embryo. NSF-STC-CCC Annual Retreat, RTC Campus.

2. 7/20/18 Burrus L. Regulation of β-dystroglycan by miR-206 in early muscle development in Xenopus laevis". Society for Developmental Biology 77th Annual Meeting, Portland OR

3. 7/20/18 Shah D, Denetclaw W. Endoderm nitric oxide focally elevated 'hotspots' at the heart forming regions (HFRs) signals in early cardiogenesis in chicken embryos. Society for Developmental Biology 77th Annual Meeting, Portland OR

4. 8/12/18 #J. Garcia, #J. Ramirez, #C. Domingo. "Determining Target Genes Regulated by miR-206 and miR-1 during Early Skeletal Muscle Development in Xenopus laevis". 17th Intl Xenopus Conference, Seattle OR

5. 8/12/18 #Johnson Yang, #J. Ramirez, #C. Domingo. "Muscle development in the frog, Xenopus tropicalis". 17th Intl Xenopus Conference, Seattle OR

6. 8/18 S. Chandrasekaran, B. Olouch#, D. Ruiz#, R. Esquerra, The Molecular Mechanism of Intermolecular Signal Transduction in Cystathionine β-Synthase (CBS). Beckman Symposium, Irvine, CA

7. 8/18 D. Ruiz#, S. Chandrasekaran, W. Hartono, D. Kennedy, R. Esquerra "The Effects of a Heme Prosthetic Group on Cystathionine β-Synthase Product Formation." May 2018. Howard Hughes Medical Institute's Annual Research Symposium (HHMI-EXROP)

8. 8/22/18 Jasmine Sims# "Effects of the Cell cycle on vacuole size in S. cerevisiae" Yeast Genetics Meeting, Stanford CA

9. 8/22/18 Angeline Chemel "Inheritance and Biogenesis in S. cerevisiae" Yeast Genetics Meeting, Stanford CA

10. 9/14/18 Sophie Dumont. Mechanics of Cell Division. UCSF Tetrad Graduate Program Retreat, Granlibakken,Tahoe City, CA

11. 9/14/18 Tanya Gromova. A new role for telomerase in promoting meiotichomolog fidelity via telomere-led chromosome motion. UCSF Tetrad Graduate Program Retreat, Granlibakken,Tahoe City, CA

12. 10/18 Destinee Lanns#, Jayden Dalton, Lisa M Galli, and Laura W Burrus Characterizing the role of Filopodia in Triple Negative Breast Cancer (TNBC) SACNAS. San Antonio, TX.

13. 10/18 B. Oluoch, S. Chandrasekaran, R. Esquerra, Exploring the molecular mechanism of heme domain regulation of human Cystathionine beta-synthase (hCBS) activity. ACS student research symposium.

14. 10/11/18 Mendoza O#, Denetclaw W Nitric oxide signaling regulates primary myotome differentiation in chicken embryos. SACNAS 2018 Annual Meeting, San Antonio, TX.

15. 11/14/18 John Paul Bugay#, Julio Ramirez#, Carmen Domingo#. "Analyzing the Function of Muscle Specific MicroRNAs in Xenopus laevis". ABCRMS.

16. 11/14/18 Rocio Cisneros#, Lisa M Galli, Laura W. Burrus The Role of Filopodia in Wnt Cell to Cell Communication. Annual Biomedical Research Conference for Minority Students (ABRCMS), Indianapolis, IN

17. 11/14/18 Maduabuchukwu C Nzerem#, Lisa M Galli, Laura W Burrus The Role of Wnt and Wntless in Filopodia Production. Annual Biomedical Research Conference for Minority Students (ABRCMS), Indianapolis, IN

18. 11/14/18 B. Oluoch, S. Chandrasekaran, R. Esquerra, Purification and Mutagenesis of Human Cystathionine-β-synthase (hCBS). Annual Biomedical Research Conference for Minority Students (ABRCMS), Indianapolis, IN

19. 11/14/18 Sita Chandrasekaran. The Molecular Mechanism of Intermolecular Signal Transduction in Cystathionine β-Synthase (CBS). Annual Biomedical Research Conference for Minority Students (ABRCMS), Indianapolis, IN

20. 11/14/18 Austin Murchison#. Engineering Living Biosensors Using the Hemeprotein Transcription Factor CooA. Annual Biomedical Research Conference for Minority Students (ABRCMS), Indianapolis, IN

21. 12/9/18 James Gerh. A predictive model of dynamic segregation machinery. ASCB Annual Meeting, San Diego,CA.

22. 12/9/18 Jasmine Sims#. Quantifying changes in vacuolar morphology to predict degradative function in S. cerevisiae. ASCB Annual Meeting, San Diego,CA.

23. 12/9/18 Carlos Segura. Single cell analysis of vacuolar pH and size using confocal microscopy. ASCB Annual Meeting, San Diego,CA.

24. 12/9/18 Devan Shah. Endoderm nitric oxide signals to regulate development of cardiac progenitors in early cardiogenesis of chicken embryos . ASCB Annual Meeting, San Diego,CA.

25. 12/9/18 Angeline Chemel. Vacuole inheritance and biogenesis in S. cerevisiae. ASCB Annual Meeting, San Diego, CA.

26. 12/9/18 Frederick Santana#. Evidence for the involvement of filopodia in Wnt signaling in cultured cell lines and chick embryos. ASCB Annual Meeting, San Diego, CA.

27. 12/9/18 Greyson Lewis. Constructing the morphology space of mitochondrial networks in budding yeast. ASCB Annual Meeting, San Diego, CA.

28. 12/10/18 Jessica Bolivar-McPeek#. Investigating spindle rotation during mid blastula transition of Drosophila melanogaster development. ASCB Annual Meeting, San Diego, CA.

29. 12/10/18 Scott Coyle. Emergent hunting behaviors of the unicellular predator Lacrymaria encoded in coordination of its active molecular systems. ASCB Annual Meeting, San Diego, CA.

30. 12/10/18 Guillermina Ramirez-San Juan#. Efficient mucus clearance requires multi-scale integration of ciliary spatial organization and kinematics. ASCB Annual Meeting, San Diego, CA.

31. 12/10/18 Nicole Rodrigues#. A look into the mitochondrial morphology of Stentor. ASCB Annual Meeting, San Diego, CA.

32. 12/11/18 William Chadwick. Size and localization of vacuoles in fission yeast. ASCB Annual Meeting, San Diego, CA.

33. 12/11/18 Alia Edington#. Characterizing the segregation of organelles during asymmetric divisions of proneural cells during Drosophila embryogenesis. ASCB Annual Meeting, San Diego, CA.

34. 12/11/18 Jonathan Kuhn. Individual mammalian kinetochores count attached microtubules in a switch-like, highly sensitive manner to control cell cycle progression. ASCB Annual Meeting, San Diego, CA.

35. 12/11/18 Lyndsay Murrow. Single-cell RNA sequencing maps the cellular response to cycling estrogen and progesterone in the human breast. ASCB Annual Meeting, San Diego, CA.

36. 12/11/18 Nathan Hendel. Diffusion as a ruler: modeling kinesin diffusion as a length sensor for intraflagellar transport. ASCB Annual Meeting, San Diego, CA.

37. 1/4/19 Frank Bayliss. STEM Supplemental Instruction at San Francisco State University, a Large, Urban, Hispanic-Serving Institution. International Education Conference, Honolulu, Hawaii

38. 1/7/19 Nathan Hendel. Diffusion as a ruler: modeling kinesin diffusion as a length sensor for intraflagellar transport. Gordon Research Conference on Stochastic Physics in Biology, Ventura, CA.

39. 1/9/19 Greyson Lewis. Morphological Dynamics of Yeast Mitochondrial Networks. Gordon Research Conference on Stochastic Physics in Biology, Ventura, CA.

40. 3/18/19 Satoshi Toda. Programming self-organizing multicellular structures with synthetic cell-cell signaling. Synthetic Morphogenesis: From Gene Circuits to Tissue Architecture, Heidelberg, Germany.

41. 3/21 – 3/24/19 #Julio Ramirez, Johnson Yang, Coohleen Combes #Carmen Domingo. A Comparison of Embryonic Muscle Development between Xenopus laevis and Xenopus tropicalis. West Coast Regional Developmental Biology Conference, Cambria CA.

42. 4/6/19 A. Sanchez#, R. Refuerzo#, * R. Esquerra, Calmodulin Induced Changes in the Active Site of Nitric Oxide Synthase. American Society for Biochemistry and Molecular Biology (ASBMB), Orlando FL

43. 4/6/19 S. Chandrasekaran*, D. Ruiz#, W. Hartono, D. Kennedy, R. Esquerra, The Molecular Mechanism of Intermolecular Signal Transduction in Cystathionine β-Synthase (CBS) American Society for Biochemistry and Molecular Biology (ASBMB), Orlando FL

44. 4/6/19 Austin Murchison# & Raymond Esquerra "Engineering Living Biosensors Using the Hemeprotein Transcription Factor CooA" American Society for Biochemistry and Molecular Biology (ASBMB), Orlando FL

45. 4/6/19 D. Ruiz#, S. Chadrasekaran, W. Hartono, D. Kennedy, R. Esquerra "Elucidating the Heme Domain's Regulatory Role on Human Cystathionine β-Synthase (hCBS) Product Formation" American Society for Biochemistry and Molecular Biology (ASBMB), Orlando FL

46. 4/19/19 S. Chandrasekaran, R. Esquerra, Measuring Intracellular Microviscosity. CSU Student Research Competition.

47. 5/3/19 Adrian Barrera-Velasquez# "Cell Landscapes: Relating Organelle Size, Localization, and Morphologies to Cell State" SFSU College of Science and Engineering Student Showcase

48. 5/3/19 Gabriela Alvarez Azanedo# "Yeast as bioreactors: Understanding the role of vacuolar size in biochemicals concentration" SFSU College of Science and Engineering Student Showcase

49. 5/3/19 Roberto Carlos Segura# "Single Cell Analysis of Vacuolar Size and pH Using Confocal Microscopy" SFSU College of Science and Engineering Student Showcase

50. 5/3/19 Sita Srinivasan Chandrasekaran "Measuring the effect of size and shape on microviscosity from time resolved linear dichroism" SFSU College of Science and Engineering Student Showcase

51. 5/3/19 Angeline Chemel "The pattern of vacuole inheritance and biogenesis in S. cerevisiae" SFSU College of Science and Engineering Student Showcase

52. 5/3/19 Rocio Cisneros# "The Role of Filopodia in Wnt Cell to Cell Communication" SFSU College of Science and Engineering Student Showcase

53. 5/3/19 Alia Edington# "Labcademy: An Interactive Lab Discussion Platform" SFSU College of Science and Engineering Student Showcase

54. 5/3/19 Wesley Huang "Features of histone H2A variant HIS-35 incorporation before and after fertilization" SFSU College of Science and Engineering Student Showcase

55. 5/3/19 Kloe Keeter# "Exploring the molecular mechanism and structural characteristics of heme protein CooA (CO oxidation Activator protein) regulation and activity" SFSU College of Science and Engineering Student Showcase

56. 5/3/19 Connie Kong "Effect of Size and Shape on Microviscosity in E. Coli cells from Time-Resolved Linear Dichroism Measurements" SFSU College of Science and Engineering Student Showcase

57. 5/3/19 Adrian Martin "Stretch Activates Mechanically-Gated Calcium Channels for NO Formation in the Ectoderm of Chicken Embryos" SFSU College of Science and Engineering Student Showcase

58. 5/3/19 Omar Mendoza# "Environmental Chemical Hazards (Roundup and Cadmium Chloride) Disrupt Embryonic Muscle (Myotome) Formation and Alter Morphologies in Somites and Chicken Embryos" SFSU College of Science and Engineering Student Showcase

59. 5/3/19 Bethany Kristi Morin# "Investigating Rab5 distribution during mitosis in Drosophila neuroblast" SFSU College of Science and Engineering Student Showcase

60. 5/3/19 Destinee Nashai Lanns# "Characterizing the role of Filopodia in Triple Negative Breast Cancer (TNBC)" SFSU College of Science and Engineering Student Showcase

61. 5/3/19 Andrew Nyznyk "Determining Target Genes Regulated by miR-206 during Early Muscle Development in Xenopus laevis" SFSU College of Science and Engineering Student Showcase

62. 5/3/19 Jose Ortega# "Truncation of BubR1, a mitotic checkpoint complex protein, causes aberrant ER morphology in Drosophila melanogaster neuroblast cells" SFSU College of Science and Engineering Student Showcase

63. 5/3/19 Katie Padilla# "Origins of the Dermomyotome in Xenopus laevis" SFSU College of Science and Engineering Student Showcase

64. 5/3/19 Jesus Hinojosa Paiz# "Illuminating Chromatin Localization and Gene Regulatory Roles of the Sperm Specific HTAS-1 Histone Variant" SFSU College of Science and Engineering Student Showcase

65. 5/3/19 John Paul Bugay# "Analyzing the Function of Muscle Specific MicroRNAs in Xenopus laevis" SFSU College of Science and Engineering Student Showcase

66. 5/3/19 Ashley Pereira# "Calcium Signals in Chicken Embryo Sidedness and Includes Formation of Nitric Oxide in Regulation of Heart Loop Morphology" SFSU College of Science and Engineering Student Showcase

67. 5/3/19 Ashley Pereira# "Round Up Decreases Proliferation in Embryonic Cell Culture" SFSU College of Science and Engineering Student Showcase

68. 5/3/19 Vivian Priscilla Garcia# "Engineering synNotch T cells with AND-Gate Circuits Targeting non-Membrane Antigens" SFSU College of Science and Engineering Student Showcase

69. 5/3/19 Frederick R. Santana# "Development of a Split-GFP Reporter to Visualize Filopodia-Mediated Wnt1 Signaling Activation" SFSU College of Science and Engineering Student Showcase

1.c. Other Dissemination Activities

Departmental seminars on topics relevant to the Center

2/5/19 Carmen Domingo. Role of differential cell adhesion during embryonic muscle formation. Universidad de Puerto Rico, Humacao.

2/7/19 Wallace Marshall. The Cell as an Organism. Hopkins Marine Station, Monterey CA.

2/22/19 Blake Riggs. Department of Molecular, Cell, and Developmental Biology (MCD). Seminar Speaker. UC Santa Cruz.

3/1/19 Blake Riggs. Department of Biology, Seminar Speaker. Humboldt State University.

3/27/19 Blake Riggs. Department of Biomedical Sciences Seminar Speaker. University of Minnesota Medical School Duluth.

4/24/19 Blake Riggs. Department of Biological Science. Seminar Speaker. CSU Fullerton.

4/24/19 Wallace Marshall. Program in Physical Chemistry, University of Illinois Urbana Champagne.

5/15/19 Blake Riggs. MCD Department. Seminar Speaker. UC Davis.

Outreach Activities:

6/11/18 Tom Zimmerman. National Science Foundation (NSF) held the Community College Innovation Challenge (CCIC) Boot Camp, June 11–14, 2018, in Alexandria, Virginia

5/14/18 CCC produced video, for 2018 NSF STEM for All Video Showcase "Transforming the Educational Landscape: Center student Criszel Corpuz, with the SEP, made a video about the Center's Cellular Construction Workshop (the Center's summer program for high school students and teachers). http://videohall.com/p/1151

9/6/18 Hana El-Samad. *What would you like to see most in bioscience?* https://www.youtube.com/watch?v=D75VTX2jYJg

9/30/18 Guillermina Ramirez-San Juan# (Marshall lab postdoc), Latino Engineering Day at Exploratorium

10/6/18 Nashville Mini Maker Faire, Nashville, TN.

10/13/18 Wallace Marshall, *Robots, Human Evolution, and Reprogramming*. Hands-on research demonstration at the Saturday Night Science event, UCSF Mission Bay campus
Cells.

10/13/18 Zev Gartner & Shawn Douglas. Hands-on research demonstration at the Saturday Night Science event, UCSF Mission Bay campus

10/18/18 Wallace Marshall, public lecture "Xtreme Cell Biology", Café Scientifique, Palo Alto CA.

10/24/18 CCC video- What is Cellular Engineering?
https://www.youtube.com/watch?v=yMqTTwzWBQ4

11/14/18 Frank Bayliss attended the national ABRCMS conference in Indianapolis, Indiana to recruit URM STEM Students into UCSF PhD and Post-doctoral positions at UCSF.

1/22/19 Cellular engineering with DNA origami
https://www.youtube.com/watch?v=nJUk2OSRyqk

2/26/19 Rebecca McGillivary (Marshall lab graduate student). Seeing double: hands-on demonstration activity at The Exploratorium

4/6/19 Tang Lab CCC video – Cellular Guillotine
https://www.youtube.com/watch?v=efgajN0bgcg

4/6/2019 Frank Bayliss, Panel, UC Davis Graduate Division. "How to plan for a post-BS Gap Year(s)"

4/9/19 Wallace Marshall guest lecturer for undergraduate research class IDST 484 University of Richmond

2. Awards and Honors

7/20/18 Wilfred Denetclaw. CSUPERB Faculty Travel Grant Award to attend Society for Developmental Biology 77th Annual Meeting, Portland, Oregon

8/22/18 Angeline Chemel (Chan lab undergraduate). Poster award, Yeast Genetics Conference, Stanford, CA

9/13/18 Greyson Lewis (Marshall Lab graduate student): UCSF Discovery Fellow award.

10/2018 Omar Mendoza# (Denetclaw Lab): Conference travel award and poster, Society for Advancement of Chicanos and Native Americans in Science (SACNAS), San Antonio, TX

10/2018 Frederick Santana# (Burrus lab): ASCB MAC travel award to attend the ASCB meeting December 2018.

10/02/18 Lyndsay Murrow (Gartner lab postdoc). Third place, UCSF Postdoc Slam competition.

10/10/18 Carmen Domingo inducted into California Academy of Sciences

11/14/18 Erik Navarro# (Marshall lab graduate student). Carl Storm Underrepresented Minority (CSURM) Fellowship

2018 Shawn Douglas: Excellence in Teaching Award, UCSF Haile T. Debas Academy of Medical Educators

2018 Sophie Dumont: WICB Junior Award for Excellence in Research from American Society for Cell Biology

2018 Sophie Dumont: Outstanding Faculty Mentorship Award, UCSF Graduate Division.

12/9/18 Guillermina Ramirez-San Juan# (Marshall lab postdoc) First place, ASCB MAC poster award, postdoc category

12/9/18 Nicole Rodrigues# (Marshall lab undergraduate). Second place, ASCB MAC poster award, undergraduate category.

12/9/18 Roberto Carlos Segura# (Chan lab undergraduate). ASCB MAC poster award, undergraduate special recognition

12/9/18 Frederic Santana# (Burrus lab graduate student). ASCB MAC poster award, graduate special recognition

12/10/18 Sophie Dumont. ASCB Women in Cell Biology Junior Award for Excellence in Research

12/19/18 Jacob Kimmel (Marshall lab graduate student). PLoS Computational Biology Editors Picks for Cell Biology.

2018 Wallace Marshall: Chan Zuckerberg BioHub Investigator

2019 Blake Riggs: Nominated for American Society for Cell Biology Council.

2019 Blake Riggs: Don Catalano Distinguished Alumni Award. Oakes College, UC Santa Cruz.

2019 Hana El-Samad: Endowed Professorship – Kuo Family Endowed Chair

1/31/19 Hana El-Samad. UCSF Byers Award in Basic Science.

1/2019 Blake Riggs: Visit to Advanced Imaging Center (AIC), Janelia Research Campus, Ashburn, VA. Used Lattice Lightsheet Microscope to image ER partitioning during gastrulation.

3/2019 Blake Riggs: Session Co-Chair. Cell Biology: Cytoskeleton, Organelles, Trafficking. 60th Annual Drosophila Research Conference. Dallas, TX.

4/2019 Jennifer Frazier: UCSF Distinguished Alumni Award

5/2019 Wallace Marshall. Outstanding Faculty Mentorship Award, UCSF Graduate Division

Career Promotions for CCC Faculty

2018 Zev Gartner: Promoted to Full Professor

2018 Sindy Tang: Promoted to Associate Professor

2019 Carmen Domingo: Appointed Dean, SFSU College of Science and Engineering

3. Students who graduated (undergrad, MS and PhD) during this reporting period-

Last, First	Category	Institutional Affiliation	Lab	Departure date	Why Departed Center	Current/Projected Job Title	Company/University Name
Avalos Perez, Antonio	A	UC Berkeley	Fung	June 30 2019	graduation	med student	Applying Med School
Bolivar, Jessica	B	SFSU	Riggs	Jul-19	graduation	PhD student	UC Davis
Brown, Cecilia	B	SFSU	Riggs	Jun-18	graduated	PhD student	Stanford University
Brunger, Jonathan	F	UCSF	Lim	8/30/19	New Job	Postdoctoral Scholar	Assistant Professor, Biomedical Engineering, Vanderbilt
Chadwick, Will	B	SFSU	Chan	Spring 2019	New job	Technician	UCSF (Jennifer Fung)
Chandrasekaran , Sita	A	SFSU	Esquerra	Jun-19	graduation	PhD Candidate	UC Berkeley
Chang, Amy	B	UCSF	Marshall	Fall 2018	graduation	Postdoctoral researcher	UCSF
Edington , Alia	B	SFSU	Riggs	Jul-19	graduation	PhD student	UT Southwestern
Gonzalez, Valeria	A	Stanford	Tang	Sep-18	Summer Program	Undergraduate	UC San Diego
Gonzalez, Juiliet	A	SFSU	Esquerra	Jun-19	graduation	PhD Candidate	City of Hope
Hueschen, Christina	B	UCSF	Dumont	Dec-19	graduation	Postdoc	Stanford University (Alex Dunn lab)
Kimmel, Jacob	B	UCSF	Marshall	Apr-18	graduation - PhD awarded	Computational biologist	Calico, Inc
Lanns, Destinee	B	SFSU	Burrus	Summer, 2019	graduation	Will be applying to med school	
Mclaurin, Justin	B	UCSF	Weiner	Sep-18	graduation	associate consultant	ZS Associates
Murchison, Austin	B	SFSU	Esquerra	Jun-19	graduation	PhD Candidate	Stanford University
Pineda, Christopher	E	UCSF	Marshall	Fall 2018	Left to start graduate school	PhD Student	University of Michigan
Rodrigues, Nicole	E	UCSF	Marshall	Jun-18	graduated	Post-bac researcher, Marshall lab	UCSF
Santana, Frederick	B	SFSU	Burrus	Summer, 2019	graduation	PhD student	UCSF
Segura, Roberto Carlos	A	SFSU	Chan	Summer 2019	graduation	PhD Student	U Washington
Shah, Devan	B	SFSU	Denetcla w	31-May-19	graduation	visiting scholar	UCSF
Sims, Jasmine	B	SFSU	Chan	Summer 2019	graduation	PhD Student	UCSF
Tischer, Doug	B	UCSF		Feb-19	graduation	postdoc	David Baker lab, UW Seattle
Toda, Satoshi	F	UCSF	Lim	8/30/19	New Job	Postdoctoral Scholar	Jr. PI, Nano Life Science Institute, Kanazawa University
Verduzco, Rafael	A	UC Berkeley	Fung	June 30 2019	graduation	med student	Applying to med school

See Diversity Section for Table re: undergrad and MS students.

4. Outputs of Knowledge Transfer Activities

Fy03: Invention disclosures on work related to and funded by the Center for Cellular Construction
note: only new disclosures filed during the past year are included here

Invention Disclosure: *3D Microscope Using Front Surface Mirror*
Description: The present invention determines the 3D location of objects uses a conventional microscope. Objects (e.g. plankton in water) are placed on a front surface mirror, creating a pair of images for each object, specifically the object and its reflection in the mirror. The distance between the pair indicates the height (Z) of the object above the mirror.
Personnel: Tom Zimmerman (IBM Research)
Accomplishments: Developed working prototype. Submitted disclosure to IBM IP system.

Invention Disclosure: *Monitoring Environment Health with Networked AI Microscopes*
Description: The invention comprises a method to enable monitoring and classification of plankton morphology and behavior to predict the health of the environment with minimum human-intervention, using a network of AI Microscopes that implement distributed learning. Each microscope individually sample plankton and the collection of microscopes collectively learn new species and morphological and behavior perturbations of species. The invention performs unsupervised classification, assigning plankton samples into classes. The classes are then defined (labeled) by human expert, after which future samples are automatically classified as members of said defined classes or as anomalies, i.e. not belonging to any of the defined classes.
Personnel: Tom Zimmerman, Simone Bianco, Vito Pastore (IBM Research)

Invention Disclosure: *Stereo In-Line Holographic Digital Microscope*
Description: The invention teaches a method to provide a low-resolution color and high-resolution monochromatic image of objects and their 3D location using a lensless microscope. By detecting the 3D location of each object, holographic reconstruction is applied only to the volume occupied by each object, dramatically reducing reconstruction computation
Personnel: Tom Zimmerman
Center Collaborators: Daniel El Natan (UCSF, Fung Lab)
External Collaborators: Nick Antipa (UC Berkeley, Waller Lab)

Patents in progress
Filed:
none

Search concluded, preparing to file:
4/25/17 P201701399 – Generating 3D Models of Microscopic Subject from a Sequence of Images, Thomas G. Zimmerman, Simone Bianco, IBM Research; Rebecca McGillivary, Wallace Marshall, UC San Francisco. Search concluded. To be filed.

Search in progress:
5/2/17 P201701636 – Immersive Submerged Stereo Microscope, Thomas G. Zimmerman, IBM Research. Status: Search in progress.

4/25/17 P201701401 – Autonomous Plankton Sampler, Thomas G. Zimmerman, IBM Research. Search in progress.

7/9/17 P201703701 – Drop Microscope For High Throughput Viewing and Analysis of Specimens, Thomas G. Zimmerman, IBM Research. Search in progress.

7/9/19 P201703703 – 3D Microscope Using Front Surface Mirror, Thomas G. Zimmerman, IBM Research. Search in progress.

5. Participant table with demographic information – **Table VIII.5**

Table is appended at the end of this section.

Fy03 total participants186; affiliates 42

6. Summary list of all Center's research, education, knowledge transfer & other institutional partners

EXTERNAL PARTNERSHIPS

Organization Name	**Organization Type***	**Contact Name and Address**	**Nature of Partner****	**Nature of Partner's contribution – In Kind or Monetary-Leveraged Contribution*****	**160 hours or more? Y/N)**
UCSF Catalyst	Internal granting organization to support commercialization of research ideas	Nathaniel Porok, Catalyst Coordinator nathaniel.prorok@ucsf.edu	Funding	Monetary ($30,000) as well as opportunity to meet with industry experts and get advice about ways to commercialize center research	N
Nagase Inc	Company	Tokyo, Japan	Research, Knowledge Transfer	Confidential collaboration to study the relationship between the structure of streptomyces cells and colonies using artificial intelligence	N
Texas A&M University	Academic Institution	Hongmin Qin, Dept of Biology, TAMU College Station, TX 77843	Research	Scientific collaboration	N
University of California, San Francisco	Academic Institution	Robert Blelloch	Research	Collaboration to count exosomes formed in InCell. We developed their analysis package.	N
Biochemistry, University of Utah	Academic Institution	Prof. Janet Iwasa, expert in cell and molecular animation	Knowledge Transfer, education	Collaboration in Exploratorium Conference on scientific visualization May 9, 2019. Dr. Iwasa was a speaker and shared her movies of cellular processes with the public.	N

Allen Institute for Cell Science	Academic Institution	Seattle, WA	Knowledge Transfer	Collaboration with Exploratorium – Plan to present molecular visualizations and VR experiences in the Cells to Self Area at an upcoming public event called "Designed by Data."	N
California Science Project	Other	Maria Simani, UC Riverside	Funding Agency	Monetary – Leveraged Contribution $56,000. Collaboration with SEP, UCSF.	N
ImpriMed, Inc	Company	Sungwon Lim 2627 Hanover St, Palo Alto, CA 94304	Research	Lucas Blauch (Tang lab, Stanford) did internship based on microfluidic guillotine technology (~$30,000 in pay and research expenses). Continuing research partnership after internship, including use of research facilities and providing specimens for study	Y
Juvena Therapeutics, Inc	Company	Hanadie Yousef 2627 Hanover St, Palo Alto, CA 94304	Research	Providing muscle cells to Tang lab to test with microfluidic guillotine	N
University of Genova, Italy	Academic Institution	Massimo Maresca and Pierpaolo Baglietto, University of Genova, Italy	Knowledge Transfer	Collaboration to augment an existing cloud-based water monitoring platform with an AI powered monitoring system based on the IBM lensless microscope	N
Monterey Bay Aquarium Research Institute	NGO	Thom Maughan, MBARI, Moss Landing, CA	Knowledge Transfer	Collaboration to develop a lensless microscope for both surface and deep sea plankton survey	N
Fabian Cousteau Ocean Learning Center	NGO	Fabian Cousteau, CEO	Knowledge Transfer	Collaboration to develop a lensless microscope for deep sea plankton survey on the new underwater learning center being built by the organization.	N

*For organization type, please indicate whether the partner organization is a company, national laboratory, Federal government, state/local government, NGO, or other

**For type of partner, please indicate whether the partner organization is a research, education, knowledge transfer, diversity, or other partner. You may list more than one type, if applicable.

External Partners:

7. Summary table for NSF Reporting

For internal NSF reporting purposes, provide a Summary Table with the following information:

1	**NUMBER OF PARTICIPATING INSTITUTIONS** (all academic institutions that participate in activities at the Center) this value should match the number of institutions listed in Section I, Item 1 of the report plus other additional academic institutions that participate in Center activities as listed in the table above.	**4**
2	**NUMBER OF INSTITUTIONAL PARTNERS** (total number of non-academic participants, including industry, states, and other federal agencies, at the Center) this value should match the number of partners listed in the table in Section VIII, Item 6 (above)	**2**
3	**TOTAL LEVERAGED SUPPORT FOR THE CURRENT YEAR** (sum of funding for the Center from all sources *other* than NSF- STC) [Leveraged funding should include both cash and in- kind support that are related to Center activities, but not funds awarded to individual PIs.] this value should match the total of funds in Section X, Item 4 of "Total" minus "NSF-STC" for cash and in-kind support	**$290,000**
4	**NUMBER OF PARTICIPANTS** (total number of people who utilize center facilities; not just persons directly supported by NSF) . Please EXCLUDE affiliates this value should match the total number of participants listed in Section VIII, Item 5 (above)	**186**

8. Media Publicity Received

Press Releases

7/31/18 IBM press release:
Teaching AI to learn from non-experts
https://www.ibm.com/blogs/research/2018/07/ai-learn-non-experts/

8/1/18 UCSF press release:
New Tool Crowdsources Human Intelligence for Biological Research
https://www.ucsf.edu/news/2018/08/411386/new-tool-crowdsources-human-intelligence-biological-research

12/31/18 IBM Press release
A Year of big thinking: 10 ideas that mattered in 2018 – featuring 5-in-5 including CCC-funded work to deploy AI-driven microscopes to infer ocean water quality from cellular imaging
https://www.ibm.com/thought-leadership/best-of/2018/

Media Coverage

1/5/18 Kurzweil AI New article on tissue origami
http://www.kurzweilai.net/researchers-hack-cell-biology-to-create-the-complex-shapes-that-form-living-tissue

6/12/18 UCSF Magazine article
Startup Science: How the Idea for Synthetic Cells Took Silicon Valley By Storm
https://www.ucsf.edu/news/2018/06/410626/startup-science-how-wendell-lims-idea-synthetic-cells-took-silicon-valley-storm

6/28/18 BYU radio interview with IBM Jeff Welser about "5 in 5" including Bianco group CCC research
http://www.byuradio.org/episode/d0cbffbc-2be5-4ed9-ac5b-5f7836dd27d1?playhead=1356&autoplay=true

8/1/18 Teaching AI to learn from non-experts. Phys.org magazine.
http://ct.moreover.com/?a=34691710535&p=1pl&v=1&x=L6EtNC_kr4yT5PgCn8hjDg

8/6/18 Bizjournal article
UCSF, IBM team up to crowdsource biomedical research
https://www.bizjournals.com/sanfrancisco/news/2018/08/06/ucsf-ibm-crowdsource-biomedical-research-quantius.html

12/2018 Fung Lab featured in CNN media coverage of CCC chemical screening library,
(filmed Dec 2018, to air ~ May-June 2019)

Table VIII.V. All Center Participants

- Category:
  (a) undergraduate students, (b) graduate students, (c) faculty, (d) visiting faculty, (e) other research scientists, (f) postdoctorates, (g) pre-college student (h) teachers, (i) educators and (j) other participants
- Institutional Affiliation: the primary institution at which an individual is employed or affiliated with (e.g. for a faculty member, this would be their home university).
- Department: if participant is associated with a University, please list the academic department with which they are affiliated, if applicable.
- Gender: Female, Male.
- Disability: (select one or more) Hearing Impairment, Visual Impairment, Mobility/ Orthopedic Impairment, Other, None.
- Ethnicity: (choose one) Hispanic or Latino, Not Hispanic or Latino.
- Race: (select one or more) American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White.
- Citizenship: (choose one) U.S. Citizen, Permanent Resident, Other non-U.S. Citizen

Table VIII.5 Demographic Information – Center for Cellular Construction Participants

First, Last	*Category	Institutional Affiliation	Department / Lab	Gender	Disability Status	Ethnicity	Race	Visa/ Citizenship
Aksel, Tural	F	UCSF	CMP / Douglas	M	None	Not Hispanic/Latino	White	Decline to State
Aleman, Johana	A	SFSU	Biology / Chu	F	None	Hispanic/Latino	Asian	Decline to State
Allen, Jessica	J	UCSF	Biochemistry, SEP / SEP	F	None	Not Hispanic/Latino	White	Decline to State
Ascencio, Gerson	A	SFSU	Biology / Riggs	M	Decline to State	Decline to State	Decline to State	Decline to State
Avalos Perez, Antonio	A	UC Berkeley	Ob/Gyn / Fung	M	None	Hispanic/Latino	white	Decline to State
Azanedo, Gabriela	B	SFSU	Biology / Chan	F	None	Hispanic/Latino	Decline to State	Decline to State
Barrera-Velasquez, Adrian	A	SFSU	Biology / Chan	M	None	Hispanic/Latino	Decline to State	Decline to State
Bauer, David	B	UCSF	Biochem / Marshall	M	None	Not Hispanic/Latino	White	Decline to State
Bayliss, Frank	C	SFSU	Biology /	M	none	Not Hispanic/Latino	White	Decline to State
Belardi, Brian	F	UC Berkeley	Bioengineering / Fletcher	M	None	Not Hispanic/Latino	White	Decline to State
Bevir, Harry	E	UCSF	Ob/Gyn / Fung	M	None	Not Hispanic/Latino	White	Decline to State
Bianco, Simone	E	IBM	ADLab / Bianco	M	Decline to State	Decline to State	Decline to State	Decline to State
Biswas, Sujoy Kumar	F	IBM	ADLab / Bianco	M	Decline to State	Decline to State	Decline to State	Decline to State
Blauch, Lucas	B	Stanford	MechEng / Tang	M	None	Not Hispanic/Latino	White	Decline to State
Bolivar, Jessica	B	SFSU	Biology / Riggs	F	None	Hispanic/Latino	Asian	Decline to State
Bremer, Andrew	B	UCSF/UCB	Pharmaceutical Chemistry / Gartner	M	Decline to State	Not Hispanic/Latino	White	Decline to State
Briones, Jessica	B	SFSU	Biology / Lim	F	None	Not Hispanic/Latino	A/PI	Decline to State
Britain, Derek	B	UCSF	CVRI / Weiner	M	None	Not Hispanic/Latino	White	Decline to State
Brown, Cecilia	B	SFSU	Biology / Riggs	F	None	Not Hispanic/Latino	Black / African American	Decline to State
Brunetti, Rachel	B	UCSF	CVRI / Weiner	F	None	Not Hispanic/Latino	White	Decline to State

Bugay, John Paul	A	SFSU	Biology / Domingo	M	None	Not Hispanic/Latino	Pacific Islander	Decline to State
Burrus, Laura	C	SFSU	Biology / Burrus	M	None	Not Hispanic/Latino	White	Decline to State
Cabral, Katie	B	UCSF	Pharmaceutical Chemistry / Gartner	F	Decline to State	Not Hispanic/Latino	White	Decline to State
Cadiz, Brenda	F	U of PR, Humacao	Biology / Domingo	F	None	Hispanic/Latino	White	Decline to State
Castillo, Sonia	J	Exploratorium	Exploratorium / Exploratorium	F	None	Hispanic/Latino	White	Decline to State
Castro, Alonso	A	SFSU	Biology / Riggs	M	Decline to State	Decline to State	Decline to State	Decline to State
Cecelia, Brown	B	IBM	ADLab / Bianco	F	Decline to State	Decline to State	Decline to State	Decline to State
Cetina-Antonio, Miriam	A	SFSU	Biology / Chu	F	None	Hispanic/Latino	Other	Decline to State
Chadwick, William	E	UCSF	Ob/Gyn / Fung	M	None	Not Hispanic/Latino	White	Decline to State
Chan, Lienna	A	UC Berkeley	Bioengineering / Fletcher	F	None	Not Hispanic/Latino	Asian	Decline to State
Chan, Mark	C	SFSU	Biology / Chan	M	None	Not Hispanic/Latino	Asian	Decline to State
Chandrasekaran, Sita	A	SFSU	Chem&Biochem / Esquerra	F	None	Not Hispanic/Latino	Asian	Decline to State
Chang, Amy	B	UCSF	Biochem / Marshall	F	None	Not Hispanic/Latino	Asian	Decline to State
Chemel, Angeline	B	SFSU	Biology / Chan	F	None	Not Hispanic/Latino	Asian /White	Decline to State
Chevalier, Michael	E	UCSF	Biochem / El-Samad	M	None	Not Hispanic/Latino	White	Decline to State
Chu, Diana	C	SFSU	Biology / Chu	F	None	Not Hispanic/Latino	Asian	Decline to State
Cisneros, Rocio	A	SFSU	Biology / Burrus	F	None	Hispanic/Latino	White	Decline to State
Clendenny, Melissa	A	SFSU	Biology / Domingo	F	none	Hispanic/Latino	White	Decline to State
Conrad, Danny	B	UCSF	Pharmaceutical Chemistry / Gartner	M	Decline to State	Not Hispanic/Latino	White	Decline to State
Coombes, Coohleen	A	SFSU	Biology / Domingo	F	None	Not Hispanic/Latino	Pacific Islander	Decline to State
Cordts, Seth	B	Stanford	MechEng / Tang	M	None	Not Hispanic/Latino	White	Decline to State
Coyle, Scott	F	Stanford	Bioengineering / Prakash	M	None	Not Hispanic/Latino	White	Decline to State
Craik, Charles	C	UCSF	Pharm Chem / Marshall	M	None	Not Hispanic/Latino	White	Decline to State

Creasey, Olivia	B	UCSF	Pharmaceutical Chemistry / Gartner	F	Decline to State	Not Hispanic/Latino	White	Decline to State
Cynnie, Tam	A	SFSU	Biology / Riggs	F	None	Not Hispanic/Latino	Asian	Decline to State
de Jesus, Maura	A	SFSU	Biology / Chan	F	None	Hispanic/Latino	Decline to State	Decline to State
DeCruz, Matthew	E	SFSU	Biology / Riggs	M	None	Not Hispanic/Latino	White	Decline to State
Denetclaw, Wilfred	C	SFSU	Biology / Denetclaw	M	None	Not Hispanic/Latino	American Indan	Decline to State
Diaz, Ulises	B	UCSF	Biochem / Marshall	M	None	Hispanic/Latino	White	Decline to State
Domingo, Carmen	C	SFSU	Biology / Domingo	F	None	Hispanic/Latino	White	Decline to State
Douglas, Shawn	C	UCSF	CMP / Douglas	M	None	Hispanic/Latino	White	Decline to State
Dueber, John	C	UC Berkeley	Bioengineering / Dueber	M	None	Not Hispanic/Latino	White	Decline to State
Dumont, Sophie	C	UCSF	Cell & Tissue Biology / Dumont	F	None	Not Hispanic/Latino	White	Decline to State
Edington , Alia	B	SFSU	Biology / Riggs	F	None	Not Hispanic/Latino	Black / African American	Decline to State
El-Samad, Hana	C	UCSF	Biochem / El-Samad	F	None	Not Hispanic/Latino	White	Decline to State
Elnatan, Daniel	E	UCSF	Ob/Gyn / Fung	M	None	Not Hispanic/Latino	asian	Decline to State
Esquerra, Raymond	C	SFSU	Chem&Biochem / Esquerra	M	None	Hispanic/Latino	White	Decline to State
Flaum, Ellie Marie	B	Stanford	Bioengineering / Prakash	F	None	Hispanic/Latino	White	Decline to State
Fletcher, Daniel	C	UC Berkeley	Bioengineering / Fletcher	M	None	Not Hispanic/Latino	White	Decline to State
Frazier, Jennifer	E	Exploratorium	Exploratorium / Exploratorium	F	None	Not Hispanic/Latino	White	Decline to State
Fung, Jennifer	C	UCSF	Ob/Gyn / Fung	F	None	Not Hispanic/Latino	asian	Decline to State
Galli, Lisa	E	SFSU	Biology / Burrus	F	none	Not Hispanic/Latino	White	Decline to State
Garcia, Jason	B	UCSF	Biochem / Marshall	M	None	Hispanic/Latino	White	Decline to State
Garcia, Vivian	B	SFSU/UCSF	Biology / Lim	F	None	Hispanic/Latino	White	Decline to State
Gartner, Zev	C	UCSF	Pharmaceutical Chemistry / Gartner	M	Decline to State	Not Hispanic/Latino	White	Decline to State
Gehr, James	B	SFSU	Biology / Chu	M	None	Not Hispanic/Latino	White	Decline to State
Gomez Lopez, Maurico	A	Cal State Fullerton	Ob/Gyn / Fung	M	None	Hispanic/Latino	white	Decline to State

Gonzalez, Juiliet	A	SFSU	Chem&Biochem / Esquerra	F	Other	Hispanic/Latino	Native American	Decline to State
Graziano, Brian	F	UCSF	CVRI / Weiner	M	None	Not Hispanic/Latino	White	Decline to State
Grewal, Parbir	B	UCSF	Bioengineering / Dueber	M	None	Not Hispanic/Latino	Asian	Decline to State
Gromova, Tatiana	E	UCSF	Ob/Gyn / Fung	F	None	Not Hispanic/Latino	White	Decline to State
Hamkins-Indik, Tiama	B	UC Berkeley	Bioengineering / Fletcher	F	None	Not Hispanic/Latino	White	Decline to State
Hendel, Nat	B	UCSF	Biochem / Marshall	M	None	Not Hispanic/Latino	White	Decline to State
Hernadez, Paulina	A	SFSU	Chem&Biochem / Esquerra	F	None	Hispanic/Latino	White	Decline to State
Hu, Jennifer	B	UCSF	Pharmaceutical Chemistry / Gartner	F	Decline to State	Not Hispanic/Latino	Asian	Decline to State
Huang, Wesley	B	SFSU	Biology / Chu	M	None	Not Hispanic/Latino	White	Decline to State
Hueschen, Christina	B	UCSF	Cell & Tissue Biology / Dumont	F	Decline to State	Decline to State	Decline to State	Decline to State
Huitron, Aileen	A	SFSU	Chem&Biochem / Esquerra	F	None	Hispanic/Latino	White	Decline to State
James, Gerh	B	IBM	ADLab / Bianco	M	Decline to State	Decline to State	Decline to State	Decline to State
Joao, Fonseca	E	UCSF	Biochem / El-Samad	M	None	Not Hispanic/Latino	White	Decline to State
Johnson, Amanda	A	SFSU	Biology / Denetclaw	F	None	Not Hispanic/Latino	White	Decline to State
Jones, Barbara	E	IBM	ADLab / Bianco	F	Decline to State	Decline to State	Decline to State	Decline to State
Kalbuagh, Erin	B	SFSU	Chem&Biochem / Esquerra	F	None	Decline to State	Decline to State	Decline to State
Keeter, Kloe	A	SFSU	Chem&Biochem / Esquerra	F	None	Hispanic/Latino	Pacific Islander	Decline to State
Kimmel, Jacob	B	UCSF	Biochem / Marshall	M	Decline to State	Decline to State	Decline to State	Decline to State
King, Denise	J	Exploratorium	Exploratorium / Exploratorium	F	None	Hispanic/Latino	White	Decline to State
Kinney, Christen	B	SFSU	Biology / Chu	F	None	Not Hispanic/Latino	Asian	Decline to State
Kolahdouzan, Kian	A	SFSU	Chem&Biochem / Esquerra	M	None	Not Hispanic/Latino	White	Decline to State

Kong, Connie	B	SFSU	Chem&Biochem / Esquerra	F	None	Not Hispanic/Latino	Asian	Decline to State
Konova, Kseniya	B	SFSU	Biology / Chu	F	None	Not Hispanic/Latino	Asian	Decline to State
Kuhn, Jonathan	B	UCSF	Cell & Tissue Biology / Dumont	M	None	Not Hispanic/Latino	White	Decline to State
Lai, Celine	A	UCLA	Biology / Domingo	F	None	Not Hispanic/Latino	Asian	Decline to State
Lane, Angela	B	SFSU	Biology / Burrus	F	None	Not Hispanic/Latino	Black / African American	Decline to State
Lanns, Destinee	B	SFSU	Biology / Burrus	F	None	Not Hispanic/Latino	Black / African American	Decline to State
Lewis, Greyson	B	UCSF	Biochem / Marshall	M	None	Not Hispanic/Latino	White	Decline to State
Lim, Wendell	C	UCSF	Cellular and Molecular Pharmacology / Lim	M	None	Not Hispanic/Latino	Asian	Decline to State
Lindsey, Osimiri	B	UCSF/UCB	Bionegineering program / El-Samad	F	None	Not Hispanic/Latino	Black / African American	Decline to State
Lomba, Charles	A	UCSF	Biochem / Marshall	M	None	Hispanic/Latino	White	Decline to State
Long, Alexandra	B	UCSF	Cell & Tissue Biology / Dumont	F	None	Not Hispanic/Latino	White	Decline to State
Lopez, Pilar	E	UCSF	Cellular and Molecular Pharmacology / Lim	F	None	Hispanic/Latino	White	Decline to State
Marshall, Wallace	C	UCSF	Biochem / Marshall	M	Decline to State	Decline to State	Decline to State	Decline to State
Martin, Adrian	B	SFSU	Biology / Denetclaw	M	None	Not Hispanic/Latino	Asian	Decline to State
Mathijssen, Arnold	F	Stanford	Bioengineering / Prakash	M	None	Not Hispanic/Latino	White	Decline to State
McGinn, Robert	C	UCSF	Biochem / Marshall	M	None	Not Hispanic/Latino	White	Decline to State
McGinnis, Chris	B	UCSF	Pharmaceutical Chemistry / Gartner	M	Decline to State	Not Hispanic/Latino	White	Decline to State
Mclaurin, Justin	B	UCSF	CVRI / Weiner	M	Decline to State	Decline to State	Decline to State	Decline to State
Meisnner, Brett	B	SFSU	Biology / Chu	M	None	Not Hispanic/Latino	White	Decline to State
Mendoza, Omar	B	SFSU	Biology / Denetclaw	M	None	Hispanic/Latino	White	Decline to State
Mendoza, Nik	B	SFSU/UCSF	Biology / Lim	M	None	Hispanic/Latino	NA/PI	Decline to State
Miyazaki, Hikaru	B	UCSF	Pharmaceutical Chemistry / Gartner	F	Decline to State	Not Hispanic/Latino	Asian	Decline to State

Moore, Jeremy	A	UCSF	Biochem / Marshall	M	None	Not Hispanic/Latino	White/Asian	Decline to State
Morales, Genaro	A	SFSU	Biology / Denetclaw	M	None	Hispanic/Latino	White	Decline to State
Murchison, Austin	B	SFSU	Chem&Biochem / Esquerra	M	None	Not Hispanic/Latino	Black / African American	Decline to State
Murrow, Lyndsay	B	UCSF	Pharmaceutical Chemistry / Gartner	F	Decline to State	Not Hispanic/Latino	White	Decline to State
Nagy, Tamas	B	UCSF	CVRI / Weiner	M	None	Not Hispanic/Latino	White	Decline to State
Navarro, Erik	B	UCSF	Biochem / Marshall	M	None	Hispanic/Latino	White	Decline to State
Neahring, Lila	B	UCSF	Cell & Tissue Biology / Dumont	F	None	Not Hispanic/Latino	White	Decline to State
Nyznyk, Andrew	A	SFSU	Biology / Domingo	M	None	Not Hispanic/Latino	White	Decline to State
Nzerem, Madu	A	SFSU	Biology / Burrus	M	None	Not Hispanic/Latino	Black / African American	Decline to State
Odessa, Garay	A	SFSU	Biology / Chu	F	None	Not Hispanic/Latino	Asian	Decline to State
Oke, Ashwini	E	UCSF	Ob/Gyn / Fung	F	None	Not Hispanic/Latino	asian	Decline to State
Oluoch, Benazir	A	SFSU	Chem&Biochem / Esquerra	F	Decline to State	Not Hispanic/Latino	Black / African American	Decline to State
Orellana, Walter	B	SFSU	Biology / Burrus	M	None	Hispanic/Latino	White	Decline to State
Ortega, Jose	B	SFSU	Biology / Riggs	M	None	Hispanic/Latino	White	Decline to State
Pablo, Michelle	A	SFSU	Biology / Chu	F	None	Not Hispanic/Latino	Asian	Decline to State
Padilla, Katie	B	SFSU	Biology / Domingo	F	None	Hispanic/Latino	White	Decline to State
Paiz Hinojosa, Jesus	B	SFSU	Biology / Chu	M	None	Hispanic/Latino	Other	Decline to State
Pastore, Vito Paolo	F	IBM	ADLab / Bianco	M	Decline to State	Decline to State	Decline to State	Decline to State
Patterson, David	B	UCSF	Pharmaceutical Chemistry / Gartner	M	Decline to State	Not Hispanic/Latino	White	Decline to State
Paulson, Amanda	B	UCSF	Pharmaceutical Chemistry / Gartner	F	Decline to State	Not Hispanic/Latino	White	Decline to State
Peraza , Alma Aracely	B	SFSU	Biology / Riggs	F	None	Hispanic/Latino	White	Decline to State
Pereira, Ashley	B	SFSU	Biology / Denetclaw	F	None	Hispanic/Latino	White	Decline to State
Perlaza, Karina	B	UCSF	Biochem / Marshall	F	None	Hispanic/Latino	White	Decline to State

Phong, Kiet	B	UCSF	Pharmaceutical Chemistry / Gartner	M	Decline to State	Not Hispanic/Latino	Asian	Decline to State
Pineda, Christopher	E	UCSF	Biochem / Marshall	M	None	Hispanic/Latino	Decline to State	Decline to State
Pipathsouk, Anne	B	UCSF	CVRI / Weiner	F	None	Not Hispanic/Latino	Asian	Decline to State
Prakash, Manu	C	Stanford	Bioengineering / Prakash	M	None	Not Hispanic/Latino	Asian	Decline to State
Quach, Thanh	A	SFSU	Biology / Chan	M	None	Not Hispanic/Latino	Asian	Decline to State
Ramirez, Diana	A	East LACC	Biology / Domingo	F	None	Hispanic/Latino	White	Decline to State
Ramirez, Aura	A	SFSU	Biology / Domingo	F	None	Hispanic/Latino	White	Decline to State
Ramirez, Sergio	B	SFSU	Biology / Lim	M	None	Hispanic/Latino	White	Decline to State
Ramirez, Julio	E	SFSU	Biology / Domingo	M	None	Hispanic/Latino	AI/White	Decline to State
Ramirez-San Juan, Guillermina	F	UCSF	Biochem / Marshall	F	None	Hispanic/Latino	White	Decline to State
Ramos-Morin, Bethany	B	SFSU	Biology / Riggs	F	None	Hispanic/Latino	Asian	Decline to State
Reyes, Efren	B	UCSF	Pharmaceutical Chemistry / Gartner	M	Decline to State	Hispanic/Latino	Other	Decline to State
Richter, Manuela	B	UCSF	Cell & Tissue Biology / Dumont	F	None	Hispanic/Latino	Decline to State	Decline to State
Riggs, Blake	C	SFSU	Biology / Riggs	M	None	Not Hispanic/Latino	Black / African American	Decline to State
Rodrigues, Nicole	A	UCSF/SFSU	Biochem / Marshall	F	None	Hispanic/Latino	White/Asian	Decline to State
Rodriguez, Ramon	A	SFSU	Biology / Chan	M	None	Hispanic/Latino	Decline to State	Decline to State
Rousseau, Elsa	F	IBM	ADLab / Bianco	F	Decline to State	Decline to State	Decline to State	Decline to State
Rozhin, Lak	A	SFSU	Biology / Riggs	F	None	Not Hispanic/Latino	White	Decline to State
Ruiz, Donovan	A	SFSU	Chem&Biochem / Esquerra	M	None	Hispanic/Latino	White	Decline to State
Samson, Jennifer	F	UCSF	Bioengineering / Dueber	F	None	Not Hispanic/Latino	White	Decline to State
Santana, Frederick	B	SFSU	Biology / Burrus	M	None	Hispanic/Latino	White	Decline to State
Segura, Roberto Carlos	A	SFSU	Biology / Chan	M	None	Hispanic/Latino	Decline to State	Decline to State
Shah, Devan	E	UCSF	Cell Design / Lim	M	None	Not Hispanic/Latino	Asian	Decline to State

Shavey, Gavin	B	SFSU/UCSF	Biology / Lim	M	None	Not Hispanic/Latino	White	Decline to State
Sims, Jasmine	B	SFSU	Biology / Chan	F	None	Not Hispanic/Latino	Black / African American	Decline to State
Singer, Debra	J	UCSF	Biochem / Marshall	F	None	Not Hispanic/Latino	White	Decline to State
Smith, Rebecca	J	UCSF	Biochemistry, SEP / SEP	F	None	Not Hispanic/Latino	White	Decline to State
Solis, Ricardo	A	SFSU	Biology / Riggs	M	None	Hispanic/Latino	White	Decline to State
Soto-Montoya, Hazel	J	Stanford	Bioengineering / Prakash	F	None	Hispanic/Latino	White	Decline to State
Srivastava, Vasudha	B	UCSF	Pharmaceutical Chemistry / Gartner	F	Decline to State	Not Hispanic/Latino	Asian	Decline to State
Suresh, Pooja	B	UCSF	Cell & Tissue Biology / Dumont	F	None	Not Hispanic/Latino	Asian	Decline to State
Susan, Chen	B	UCSF	Biochem / El-Samad	F	None	Not Hispanic/Latino	asian	Decline to State
Tang, Sindy	C	Stanford	MechEng / Tang	F	None	Not Hispanic/Latino	Asian	Decline to State
Terrizzano, Ignacio	E	IBM	ADLab / Bianco	M	Decline to State	Decline to State	Decline to State	Decline to State
Tischer, Doug	B	UCSF	CVRI / Weiner	M	Decline to State	Decline to State	Decline to State	Decline to State
Toda, Satoshi	F	UCSF	Cellular and Molecular Pharmacology / Lim	M	None	Not Hispanic/Latino	Asian	Decline to State
Town, Jason	B	UCSF	CVRI / Weiner	M	None	Not Hispanic/Latino	White	Decline to State
Trocker, Matthew	J	Exploratorium	Exploratorium / Exploratorium	M	None	Not Hispanic/Latino	White	Decline to State
Tserendavaa, Mendsaikhan	A	SFSU	Biology / Riggs	M	none	Not Hispanic/Latino	Asian	Decline to State
Verduzco, Rafael	A	UC Berkeley	Ob/Gyn / Fung	M	None	Hispanic/Latino	white	Decline to State
Viloria, Olivia	J	UCSF	Biochem / Marshall	F	None	Not Hispanic/Latino	White	Decline to State
Vyas, Pranav	B	Stanford	Bioengineering / Prakash	M	None	Not Hispanic/Latino	Asian	Decline to State
Weiner, Orion	C	UCSF	CVRI / Weiner	M	None	Not Hispanic/Latino	White	Decline to State
Yancey, Ariana	A	SFSU	Biology / Riggs	F	None	Not Hispanic/Latino	Black / African American	Decline to State
Yang, Johnson	A	SFSU	Biology / Domingo	M	None	Not Hispanic/Latino	Asian	Decline to State
Young, Dana	A	SFSU	Biology / Chu	F	None	Not Hispanic/Latino	Asian	Decline to State

Zhang, Kevin	B	Stanford	MechEng / Tang	M	None	Not Hispanic/Latino	Asian	Decline to State
Zhang, Jesse	B	UCSF	Pharmaceutical Chemistry / Gartner	M	Decline to State	Not Hispanic/Latino	Asian	Decline to State
Zimmerman, Thomas	E	IBM	ADLab / Bianco	M	Decline to State	Decline to State	Decline to State	Decline to State

X. INDIRECT / OTHER IMPACTS

1. Center Engagement in international Activities

Activity: Research collaborations with international groups
Organization/people involved:

- Jennifer Fung (CCC) with Brenda Andrews (University of Toronto, Canada)
- Orion Weiner (CCC) with Mathieu Piel (Institute Curie, Paris)
- Wallace Marshall (CCC) with Vijay Rajagopal (University of Melbourne Australia)
- Wallace Marshall (CCC) with Nan Tang (NIBS, Beijing China)

Narrative: We have established, and will continue to seek out, collaborations with outside investigators whose expertise complements ours, and who can help us reach our goals by contributing their unique perspectives and knowledge. Among our external collaborations are the above listed international collaborations, which have the added effect of allowing our center work to impact research abroad.

Activity: International deployment of Modular Microscopes
Organization/people involved: "Plankton-Planet" (https://plankton-planet.org) team from France and the Tara expedition (https://oceans.taraexpeditions.org) also from France.
Narrative: The Prakash group (CCC) has developed two low-cost automated platforms for high-throughput imaging: Modscope (modular microscopy) and Planktonscope capable of fluorescence, brightfield and spectral imaging. These high-throughput tools provide a new platform for field based microscopy. We have already deployed our first flow-through microscope (Planktonscope) in Antarctica on a sailboat (Yvinec). The data is coming from this sailboat via a satellite link. The second modular Scope is installed in Tribal village in Orissa, India. These deployments teach us methods to test robustness of these tools in field conditions.

Activity: Translating BIOMOD textbook from Japanese to English.
Organization/people involved: Co-authors of the BIOMED Textbook include Satoshi Murata, Shin-ichiro M. Nomura, Ken Sugawara (Tohoku University), Shogo Hamada (Cornell University), Kei Fujiwara (Keio University), Hisashi Tadakuma (Kyoto University).
Narrative: Shawn Douglas continues to work with Japanese professors to translate and edit an English-language version of the BIOMOD textbook. Here is a link for a free copy of the book: https://leanpub.com/biomod/c/n1BEoT11tHzJ (BIOMOD Foundation takes all proceeds from sales to recoup the translation costs from the original Japanese version of this book). Shawn is planning for a "cellular engineering" chapter co-authored by CCC members. Last year, translation of the first six chapters, out of a total of eight, was completed and made available online.

2. Other Outputs

None

Appendix A

New Biosketches:

John Dueber
Robert McGinn

NSF BIOGRAPHICAL SKETCH

NAME: John Dueber

NSF ID: 000238396

POSITION TITLE & INSTITUTION: Associate Professor of Bioengineering, U.C. Berkeley

PROFESSIONAL ADDRESS: 512D EBB, Berkeley, CA 94704

PROFESSIONAL TELEPHONE, E-MAIL AND/OR WEB PAGE: jdueber@berkeley.edu

A. PROFESSIONAL PREPARATION

INSTITUTION	LOCATION	MAJOR/AREA OF STUDY	DEGREE (if applicable)	YEAR YYYY
University of California, Berkeley		Chemical Engineering	Postdoc	2005-2009
University of California, San Francisco		Biochemistry	Ph.D.	1999-2005
University of Delaware		Biochemistry	B.S.	1995-1999

B. APPOINTMENTS

2017 - present Individual Membership Committee, Engineering Biology Research Consortium
2017 - present Council, Engineering Biology Research Consortium
2017 - present Chair of Executive Committee of Bioengineering Graduate Group, UCB/UCSF
2016 - present Associate Professor, Bioengineering Department, University of California at Berkeley
2016 - present Adjunct Faculty, Biosciences Division, Lawrence Berkeley National Laboratory
2016 - present PI, Engineering Biology Research Center, Engineering Biology Research Consortium
2015 - present Vice-Chair, Bioengineering PhD Program, University of California at Berkeley
2015 - 2017 Co-Chair of Executive Committee of Bioengineering Graduate Group, UCB/UCSF
2011 - present Faculty, Synthetic Biology Institute
2010 - present Member, Chemical Biology Graduate Group, University of California at Berkeley
2010- present Member, Bioengineering Graduate Group, UCSF/UC Berkeley
2010- present Member, Biophysics Graduate Group, UC Berkeley
2010-16 Affiliate PI, Synthetic Biology Engineering Research Center (SynBERC)
2010-16 Adjunct Faculty, Lawrence Berkeley National Laboratory, Physical Biosciences Division
2010-16 Assistant Professor, Bioengineering Department, University of California at Berkeley

C. PRODUCTS

Products Most Closely Related to the Proposed Project

1. Halperin, S. O., Tou, C. J., Wong, E. B., Modavi, C., Schaffer, D. V., & Dueber, J. CRISPR-guided DNA polymerases enable diversification of all nucleotides in a tunable window. Nature, 560(7717), 248–252. (2018).
2. Deloache, W. C., Russ, Z. N., & Dueber, J. E.* Towards repurposing the yeast peroxisome for compartmentalizing heterologous metabolic pathways. Nature Communications, 7, 11152. (2016).
3. Deloache, W. C., Russ, Z. N., Narcross, L., Gonzales, A. M., Martin, V. J. J., & Dueber, J. E.* An enzyme-coupled biosensor enables (S)-reticuline production in yeast from glucose. Nature Chemical Biology. 11(7), 465–471. (2015).
4. Lee, M.E., DeLoache, W.C., Cervantes, B., Dueber, J.E.* A Highly-characterized Yeast Toolkit for Modular, Multi-part Assembly. *ACS Synthetic Biology*. 4(9):975-86. (2015).
5. Lee, M. E., Aswani, A., Han, A. S., Tomlin, C. J., & Dueber, J. E.* Expression-level optimization of a multi-

enzyme pathway in the absence of a high-throughput assay. *Nucleic Acids Research*. 41(22), 10668–10678. (2013).

Other Significant Products, Whether or Not Related to the Proposed Project

1. Hsu, T. M., Welner, D. H., Russ, Z. N., Cervantes, B., Prathuri, R. L., Adams, P. D., & Dueber, J. Employing a biochemical protecting group for a sustainable indigo dyeing strategy. Nature Chemical Biology, 89, 44. http://doi.org/10.1038/nchembio.2552. (2018).
2. Chen, R. Rishi, H.S., Potapov, V., Yamada, M.R., Yeh, V.J., Chow, T., Cheung, C.L., Jones, A.T., Johnson, T.D., Keating, A.E., DeLoache, W.C., Dueber, J.E.* A Barcoding Strategy Enabling Higher-Throughput Library Screening by Microscopy. ACS Synthetic Biology. 4(11):1205-16. (2015).
3. Latimer, L.N, Lee, M.E., Medina-Cleghorn, D., Kohnz, R.A., Nomura, D.K., Dueber, J.E.* Employing a combinatorial expression approach to characterize xylose utilization in *Saccharomyces cerevisiae*. *Metabolic Engineering.* 25C, 20–29. (2014).
4. Ryan, O. W., Skerker, J. M., Maurer, M. J., Li, X., Tsai, J. C., Poddar, S., Lee, M.E., DeLoache, W.C., Dueber, J.E., Arkin, A.P., Cate, J.H.D.* Selection of chromosomal DNA libraries using a multiplex CRISPR system. eLife, 3. http://doi.org/10.7554/eLife.03703. (2014).
5. Dueber, J.E.*, Wu, G.C, Malmirchegini, G.R., Moon, T.S., Petzold C.J., Ullal, A.V., Prather, K.L.J., Keasling, J.D. "Synthetic protein scaffolds provide modular control over flux through an engineered metabolic pathway." *Nature Biotechnology*. 27(8), 753–759. (2009).

D. SYNERGISTIC ACTIVITIES

1. Vice-Chair of UC Berkeley Bioengineering PhD Program: I am responsible for all matters concerning the Bioengineering PhD program at U.C. Berkeley. Relatedly, I am the Chair of the joint graduate program in Bioengineering between U.C. Berkeley and U.C. San Francisco.

2. Faculty member of Engineering Biology Research Center (EBRC): research center, formerly called SynBERC, providing contacts for efficiently implementing outreach activities and rich research environment with two conferences annually for postdoctoral fellows and students to present and interact with peers and other faculty.

3. Special Projects in Synthetic Biology: I advise a group of five to seven students of diverse backgrounds year-round in a cutting-edge research project. This project is devised to include students of under-represented backgrounds and be composed of both underclassmen and seniors as well as from diverse majors. The project provides ample peer and graduate school mentorship in addition to advising from myself.

4. Summer internship of community college transfer hopefuls: I provide a summer project for one to two community college transfer hopefuls each summer to provide both research experience as well as a laboratory support structure for increased confidence that they can make this substantial jump to a four-year research university such as Berkeley.

5. Faculty member of the Synthetic Biology Institute: Institute in UC Berkeley stimulating collaborations between UC Berkeley faculty and assisting interaction with industry.

NSF Biographical Sketch

Robert E. McGinn

Name:	Robert E. McGinn
Job Title:	Adjunct Professor
Professional Address:	c/o Dept. of Biochemistry and Biophysics, UCSF, Mission Bay Campus Genentech Hall 600 16th Street, San Francisco, CA 94158
Tel.:	1-650-646-1427
Email:	Robert.McGinn@ucsf.edu

(a) Professional Preparation

Institution	*Location*	*Major*	*Degree and Year*
Stevens Institute of Technology	Hoboken, NJ	Unified Science and Engineering	B.S. 1963
Stanford University	Stanford, CA	Mathematics	M.S. 1965
Stanford University	Stanford, CA	Philosophy and Humanities	Ph.D. 1969

(b) Appointments

Institution	*Year*	*Position*
UCSF	2019-	Adjunct Professor of Biochemistry & Biophysics
Stanford University	1979-2019	Professor (Teaching) of Management Science and Engineering (MS&E), and of Science, Technology, and Society (STS)
Bell Telephone Laboratories	1978-79	Group Supervisor, Science and Society
Stanford University	1971-78	Assistant Professor of Values, Technology, and Society
Barnard College, Columbia U.	1968-71	Assistant Professor of Philosophy

(c) Products

Related to Project:

1. THE ETHICAL ENGINEER: CONTEMPORARY CONCEPTS AND CASES (Princeton University Press, 2018).

2. "Discernment and Denial: Nanotechnology Researchers' Recognition of Ethical

Responsibilities Related to Their Work," *Nanoethics*, Vol. 7, No. 2, August, 2013, pp. 93-105.

3. "Ethics and Nanotechnology: Views of Nanotech Researchers," *Nanoethics*, Vol. 2, No. 2, 2008, pp. 101-131.

4. "'Mind the Gaps': An Empirical Approach to Engineering Ethics, 1997-2001," *Science and Engineering Ethics,* Vol. 9, No. 3, October 2003, pp. 1-26.

5. "What Is Different, Ethically, About Nanotechnology? Foundational Questions and Answers," *Nanoethics*, Vol. 4, No. 2, August 2010, 115-128.

Unrelated to Project:

1. "The Anatomy of Modern Technology," *Daedalus*, Vol. 109, Winter, 1980, pp. 25-54. Issue Topic: "Modern Technology: Problem or Opportunity" (with N. Bruce Hannay).

2. "The Art of the Invisible: Achievements, Social Benefits, and Challenges of Nanotechnology," *Frontiers of Knowledge* (Fundación BBVA: Madrid, 2008), pp. 93-101 (with Sandip Tiwari).

3. "Technology, Demography, and the Anachronism of Traditional Rights," *Journal of Applied Philosophy*, Vol. 11, No. 1, Spring, 1994, pp. 57-70.

4. SCIENCE, TECHNOLOGY, AND SOCIETY (Prentice-Hall, 1990; Foundations of Sociology Series).

5. "Optimization, Option Disclosure, and Problem Redefinition: Derivative Moral Obligations of Engineers and the Case of the Composite-Material Bicycle," *Professional Ethics*, Vol. 6, No. 1, 1997, pp. 5-25. Reprinted in J. R. Rowen and S. Zinaich, eds., ETHICS FOR THE PROFESSIONS (Harcourt, 2001).

(d) Synergistic Activities

1. Director, Co-Director, and Associate Director, Science, Technology, and Society (STS) Program, Stanford University, 1981-2011.

2. Coordinator, "Technology in Society Requirement," Stanford School of Engineering, 2000-2019.

3. Ethics Investigator, National Nanotechnology Infrastructure Network (NNIN), 2004-2015.

4. Member and School of Engineering Representative, Center for Ethics Steering Committee, Stanford University, 2002-2007.

5. Organizer, convener, and participant, international conference: "Issues of Risk and Responsibility in Contemporary Engineering and Science: French and U.S Perspectives," France-Stanford Center for Interdisciplinary Studies, Stanford, California, April 7-8, 2003.