RESEARCH: Specific Goals, Performance Indicators and Progress to Date

Cellular Machine Shop

RESEARCH Optimal Outcome 1:

Instrumentation and reagents that allow "structure" to be a standardized and easily measured property of cell.

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
We have 10 genetically encoded fluorophore markers that can be used across species to perform standardized measurements of cell structure Standardized set of vectors for expression across species (as possible) Year 1 Contact: Mark Chan & Jennifer Fung	1) Identify candidate organelle markers from literature and existing collections, and test them in yeast cells. 2) Compile vectors required to express markers in yeast, mammalian cells, and industrially relevant microbes	Constructs validated for detecting budding yeast mitochondria (2 colors), vacuole membrane (2 colors), vacuole lumen, peroxisome, cell wall (cy5-concanavalinA), and nucleus. [Collaboration: Fung lab, UCSF; Marshall lab, UCSF; Chan lab, SFSU] Lentiviral construct validated for detecting mitochondria, chromatin, and microtubules simultaneously in mammalian cells using three genetically encoded fluorophore markers [Marshall lab, UCSF] Visualization of mitochondria in Stentor (key cell type for Cellular Sentinel project) [Riggs lab, SFSU; Marshall lab UCSF] Fluorescent tagged Wnt and Wingless, key signaling molecules involved in tissue organization [Burrus lab, SFSU]
Install high content imaging platform Train and set-up management system 6 months	Install high content imaging platform (searchable installation with GE) Set-up site training with Robert Moody Assign imaging liaison - SFSU – Annette Chan - UCSF – Jennifer Fung	COMPLETED Available high content imaging systems were evaluated. Decision made to purchase InCell 6000. System purchased and installed. Training and sign-up procedures put into place. [Fung lab UCSF]

Standard and scalable algorithms for detection of all key organelles in 3D 2 Years Simone Bianco		Software platform (Quantius) developed to facilitate crowd-sourced manual cell and organelle recognition tasks via the Amazon Mechanical Turk engine, and then use the results as training sets for deep learning algorithms. [Collaboration: Gartner lab, UCSF; Bianco group, IBM] Organelle segmentation and measurement pipelines have been developed for mitochondria, endosomes, nucleus, nucleolus, microtubule cytoskeleton, actin cytoskeleton, and filopodia. [Bianco IBM, Marshall, UCSF, Fung UCSF, Chan SFSU, Burrus SFSU, Riggs SFSU, Chu SFSU]
Software solutions exist to enhance reproducibility and communication of experimental methodologies. Year 3: Shawn Douglas	Graphical CAD system for planning protocols and designing experiments. Virtual reality platform for sharing experimental methods	Pre-release alpha version of Protocol Planner CAD system completed. [Douglas lab, UCSF] Implemented RealTalk operating system for integrating physical computing interface with virtual reality visualization of lab procedures. [Douglas lab, UCSF]
Develop tools to measure cytoplasm viscosity and dynamics Ray Esquerra Sophie Dumont	Develop polarization spectroscopic tools to measure microviscosity; implement tools in cells and specific parts of cells	Implemented microviscosity measurements as function of size and shape. Developed organelle specific tools. .
Ecosystem of high quality inexpensive lensed and lensless digital devices to detect and measure features of aquatic microorganisms. Simone Bianco	Development of portable lensless devices for laboratory use. Development of lensed high-throughput devices for laboratory use. Development of lensless portable devices for field use. Deployment of portable devices for environmental monitoring.	ONGOING Several microscopes already developed. Work is now needed to optimize the setup depending on the specific lab and field applications.

Tools to mechanically probe and describe cellular structures (e.g. mapping load-bearing connections) Sophie Dumont	Develop microneedle manipulation to deform (and displace) intra-cellular structures	We can now use microneedles to manipulate intracellular structures in mammalian cells -- at both mitosis and interphase. Currently, the microneedles are not force-calibrated and this remains a future goal.
Develop a microfluidic platform to perform cellular surgery (e.g., bisection, controlled wounding) and study repair/ regeneration/reorganization capability at the single cell or multi-cell level (e.g., organoids). Develop a microfluidic platform to measure the status of repair/regeneration/reorganization Sindy Tang	Develop a microfluidic tool bisect cells and organoids in a continuous flow manner. Develop a microfluidic tool to wound cells or organoids in a continuous flow manner. Develop a microfluidic tool to measure the repair or restoration of mechanical integrity of cell or organoid.	Demonstrated a microfluidic guillotine to bisect stentor cells and artificial organoids in a continuous flow manner. Demonstrated a microfluidic squeezer device to stretch and inflict wounds (both plasma membrane holes and mechanical integrity) on stentor cells. Demonstrated a confinement gradient device to measure the status of wound repair (sealing of membrane hole and mechanical integrity) based on the velocity of stentor cell in the device.

CellCAD
RESEARCH Optimal Outcome 2:

Computational tools can reliably predict the molecular perturbations necessary to produce cells of a desired organelle-scale structure

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
Establish a cell morphology space formalism for specifying organelle-scale structure Year 3 Contact: Wallace Marshall	1) Collect image datasets and perform dimensionality reduction to generate a morphology space 2) Determine the dimensionality of the space and the morphological features that contribute to each dimension 3) Develop algorithms to take a user-specified cell design and convert it to a position in morphological space 4) Develop tools to render images of cells based on position in morphological space	COMPLETED Morphological space reconstruction from 904 MEF cells, quantifying 205 morphological features based on imaging 3 organelles. ONGOING Construct morphological state space for budding yeast [Fung, Bianco] Graphical design tool to specify cell morphology and map onto design space [Douglass]
Implement a data-driven approach to realizing specific cell designs Year 5	1) Analyze how genetic and chemical perturbations alter morphological state using the morphology-space formalism by casting the effect of perturbations as displacement vectors in state space. 2) Test whether the feature displacements can be treated as a linear space (answer is probably no based on data we have so far but it would be nice to have more data). 3) To what degree can different organelles be independently addressed (i.e. can you change one without changing another --> are displacements targeting different organelles orthogonal to each other). 4) Assuming that the displacement vectors don't combine linearly, is there a way to use nonlinear methods such as machine learning to solve the design problem	COMPLETED Linear vector-space representation of cellular organization implemented and used to analyze independent control and addressability of distinct organelles relative to defined perturbations. [Collaboration: Marshall lab, UCSF; Chan lab, SFSU; Riggs lab, SFSU; Bianco group, IBM] Demonstrated that specific chemical modulators of individual organelles also affect other organelles, indicating that organelles are not individually addressable [Marshall lab] Development of neural net classifier strategy for predicting phenotypes of combined perturbations based on data analysis of individual perturbation experiments [Bianco group]

		ONGOING Implement prediction using manifold reconstruction methods [Bianco] Incorporate perturbation data from chemical and genetic high throughput screening as an additional source of displacements in feature space [Fung, Chan]
Implement a model-driven approach to realizing specific cell designs Year 5 Contact: Wallace Marshall	1) Build ODE-based (or other) models for all key organelles. 2) Create design software that will use the ODE models from this part to specify parameter sets that would target regions of morphology space as defined in part 1. 3) Learn how to link model parameters in ODE models with realizable biological perturbations (i.e. gene knockouts or promotor swap).	COMPLETED Model for spindle mechanics developed [Chu, Bianco, Dumont] Model reduction software designed for biochemical reaction networks [El Samad] Model-ensemble design tool using local parameter sensitivity and manifold gluing. [El Samad] ONGOING Model for peroxisome size and number dynamics [Bianco, Dueber, Marshall, Chan]
Establish a theoretical link between organelle scale morphology and biochemical function Year 5 Contact: Simone Bianco	1) Develop coarse grained models to relate biochemical function to organelle shape and size	Initiated collaboration with Vijay Rajagopal, University of Melbourne, Australia, who has developed biophysical models to predict the effect of organelle size and shape changes on organelle metabolic function.
Modeling framework/software for general organelle dynamics that will allow rapid modeling of new organelles in different contexts Year 4 Contact: Wallace Marshall	1) Identify function and structures for testing 2) Adapt existing pipeline	Coarse-grained organelle size control model for generalized organelle assuming linear dependencies. [Marshall] General nonlinear ODE modeling tool with interchangeable modules based on standardized representations of organelle dynamic processes (budding, fusion, etc). [Bianco, Marshall, Dueber, Chan]
Develop design tools for artificial tissues.	1) Track usage of computational engines and pipelines, to identify common shared computational	COMPLETED

Year 5 Contact: Zev Gartner	tasks that could benefit from automation. 2) Construct graphical user interfaces to simplify and facilitate common computational tasks in cell engineering.	Finite element modeling tool for tissue origami [Gartner] Branching tissue model predictor that enumerates branching patterns and analyzing end-point distributions [Marshall, Lim] Model for hydrodynamic interactions between motile cells [Prakash]

Cellular Legos

RESEARCH Optimal Outcome 3:

It is possible to direct the self-organization of multicellular structures that have properties or capabilities that single cells do not.

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
Control cell-cell communication Contact: Wendell Lim	Identify and understand paracrine signaling pathways so that they can be engineered. Engineer paracrine signaling pathways so that they can impact cellular decision making. Couple cellular decision making to cellular behaviors through engineered paracrine signaling pathways	An extensive set of molecular tools based on the syn-notch system has been implemented for mammalian cells
Constrain boundary conditions - Having the technological infrastructure to do it - Knowing what the limits of how far the system can be perturbed or constrained before it can't put itself back together again (NOTE OF EXPLANATION: for all structures we are building, they rely on self-organization; there need to be constraints. In the context of the lab, we introduce different types of constraints.) Year 1-2 Contact: Zev Gartner	Implement methods to fabricate physical chambers/flow cells for growing or perturbing tissues Develop methods to position cells in tissues or in cell culture using top-down strategies Design methods to program the self-organization of boundary conditions (bottom-up)	Begun development of DNA-protein hybrid nanostructures to pattern cells on surface with nanoscale precision without requiring engineering of the cells themselves. [Collaboration: Douglas lab, UCSF; Gartner lab, UCSF] Developed microscopy procedures for simultaneous analysis of ciliary motility and mucus flow to probe long-range coordinate of cellular orientations by extracellular hydrodynamic forces. [Collaboration: Prakash lab, Stanford; Marshall lab, UCSF] Developed Micropatterning system for plating Wnt producing and receiving cells in a grid allowing us to probe spatial dependence of communication via filipodia in a developing tissue [Burrus lab SFSU] Developed methods for introducing tight junctions into giant unilamellar vesicles as a prelude to building multi-vesicle complexes [Fletcher lab, UCB]

Have established conditions for growing and modulating the shapes of epithelial and mesenchymal tissues Year 3-5 Contact: Zev Gartner and Wendell Lim	Develop systems to control the shape and morphogenesis of mesenchymal tissues Develop systems to control the shape and morphogenesis of epithelial tissues Implement multistep morphogenesis programs (i.e. the product of one step of morphogenesis is the input for a second)	Developed a two-parameter finite element model that predicts the trajectory of tissue folding from arbitrary patterns of condensates on slabs of collagen rich gels. [Gartner lab, UCSF] *In vitro* reconstitution of ERK/PKA/Ca2+ signal propagation between cells. [El-Samad lab, UCSF] Established a link between spindle orientation and cell differentiation in epithelial sheets [Riggs lab, SFSU] Tested a series of oncogenes for ability to disrupt luminal architecture in epithelial tubes and identified one candidate that can reliably break the default architecture, creating the possibility to engineer new tissue organizations. [Gartner lab, UCSF]
We have engineering control over cell number in a multicellular structure. Year 5+ Contact: Zev Gartner and Wendell Lim	Identify strategies for controlling the <u>proportions</u> of cells in consortia Identify strategies for controlling the steady state <u>number</u> of cells in consortia Implement multicellular feedback to make cell proportions and cell numbers a robust property of engineered tissues.	Implemented synthetic cell-cell communication protocol using SynNotch system, demonstrated capability to self-organize multi-layered structures, and found that these structures can repair themselves after physical disruption. [Lim lab, UCSF; collaboration with Tang lab, Stanford] Developed *in vitro* differentiation system showing top-heavy differentiation hierarchy [Gartner lab, UCSF]
We have engineered unique physical properties or functions to multicellular consortia	Control the buoyancy or affinity of large groups of cells	

Living Bioreactor

RESEARCH Optimal Outcome 4:

Engineering of cellular structure becomes a widely accepted standard approach for enabling academic and industrial processes and applications.

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
Correlate organelle structure to change in internal cellular chemical environment. Year 1 Contact: Mark Chan	1) Measure vacuole and other organelle size in conjunction with the effect on pH, redox potential, and other chemical environments that could affect biochemical output 2) Collaborate with Research Project 1 (to develop organelle markers) and Research Project 2 (to develop modeling and analysis tools)	Collected quantitative data on vacuolar pH as a function of vacuole surface area and volume, using wild-type and mutants that alter vacuole trafficking. [Chan lab, SFSU] Developed imaging and analysis methods to analyze shape, size, and pH in vacuoles of S. pombe [Chan lab, SFSU] Preliminary observations of altered peroxisome size in strains with increased peroxisomal protein import [Dueber lab, UCB]
Tune organelle structure to achieve desired biochemical function. Year 2 Contact: Mark Chan and Sindy Tang	1) Screen yeast knockout collection and combine with results of chemical screening in outcome 5 below to predictably alter vacuole percentage in yeast cells 2) Improve protein delivery to and capacity in peroxisomes (Dueber, Bianco)	Established high-throughput protocol for transformation of yeast KO collection with markers for vacuole. [Fung lab, UCSF; Chan lab, SFSU] Developed tools to control nanoscale cell shape through nanopatterned surfaces [Weiner lab, UCSF] Developed optogenetic control of cell size in yeast, allowing organelle scaling to be investigated and controlled [Weiner lab, UCSF] Hack-a-thon conducted to develop ideas/pathways for engineering peroxisome.

Correlate organelle morphology to chemical yield. Year 3 Contact: Jennifer Fung	1) Measure yield of methyl halide synthesis in identified yeast mutants or conditions	Strains have been constructed with MHT in vacuole morphology mutants for measuring synthetic yields.
Improve (2 fold) a chemical reaction's yield by tuning organelle structure in addition to metabolic pathways. Year 4. Contact: Mark Chan and Sindy Tang	1) Optimize run yields through a combination of organelle and metabolic engineering	Prelim testing of AIR production in ade- yeast to correlate with vacuole size [Chan]
Cellular structures can be used as living nanoarrays for recruiting industrially relevant proteins at high density and defined quantity. Year 5 Contact: Wallace Marshall	1) Develop flexible platform for docking fusion proteins onto one or more cellular array-like structures 2) Benchmark reproducibility and density using GFP fusions 3) Test increased efficacy in droplet fluidic assays using at least 5 different fusion protein constructs of potential industrial relevance	Tested two axonemal proteins, FAP20 and RSP3, to determine which gives more reliable recruitment, selected FAP20. [Marshall lab, UCSF. External collaboration with Dr. Hongmin Qin, Texas A&M] Confirmed enzymatic activity and ability to release constructs by proteolytic digestion [Marshall] Encapsulation of flagella inside droplets in aqueous oil emulsion [Tang]
Establish a standardized assay and prototype a platform technology to accelerate design-build-test cycle by interrogating 1000's cells structures and outputs. Years 1-5 Contact: Sindy Tang	1) Develop a yeast incubator compatible with chemical testing. Specifically, the device will allow the immobilization of yeast to provide access to introduced chemical moiety as well as having the ability to read off cellular changes. 2) Design, implement, and iterate a microfluidic device to: A. Test and measure methyl halide production using fluorescent reporter bacteria and validate with GC/MS measurements B. Select device materials compatible with reagents/chemicals to be used C. Design geometry, work flow compatible with high throughput screening	Designed and fabricated a gradient generate that can generate five different concentrations from a pair of inlets. [Tang lab, Stanford] Designed and fabricated a microfluidic yeast incubator combined with gradient generator that trap yeast cells in v-shaped wedge pairs and then exposes them to a flowing gradient generated from five inlets which, when coupled to the five outlets of the gradient generate, will allow five different concentrations to be tested in parallel while imaging the response of living yeast cells. [Tang lab, Stanford] Note this particular target spans two Research Projects: Project

		1 Cellular Machine Shop and Project 4 Living Bioreactor.
Cell and organelle structure can be engineered to improve recovery and harvesting of synthetic products	1) Develop ways to release cell content (Weiner) 2) Tune organelle size to store/release product to cytoplasm or cell exterior (Chan, Y4-5) Long term goal for years 5+ 3) (Cell Legos) Manipulate cell-cell interaction (flocculation?) to separate cells based on cell state/product accumulation	1. Optogenetic trigger of cell bursting [Weiner] 2. Methods in development to trigger changes to vacuole size [Chan]
New goal: Engineer synthetic pathways involving multiple organelles	1) Measure and describe structural interactions among organelles (Fung, Dueber, Chan) Y4-5 Long term years 5+ Engineer pathways to deliver molecules between organelles (ex. Peroxisome → Vacuole via autophagy	Constructed strains for high-throughput collection of structure data on multiple organelles Establish collaboration with Brenda Andrews (U Toronto) to share structure data

Cell State Inference / Cellular Sentinel

RESEARCH Optimal Outcome 5:

Analysis of cellular structure provides a reliable method for monitoring internal, natural and industrial environments.

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
Correlate 500 common industrial chemicals with changes in cell/organelle structure Year 4 Contact: Jennifer Fung	1) High throughput yeast screen using Project 1 installation of the Incell system to screen chemicals for effects on organelle to cell structure. 2) Implement image classification software. 3) We will feed this information to Research Projects 1 (Cellular Machine Shop) and 2 (CellCAD) 4) Evaluate whether cellular wounding & healing as a sentinel for the environment 5) Exploring single cell transcriptomics to relate to chemical changes	InCell 6000 system installed, preliminary tests on yeast cells expressing tags for mitochondria and vacuoles, Required objective lenses determined and acquired. [Fung lab, UCSF] Assembly of a curated and validated chemical library of high interest industrial chemicals [Fung lab, UCSF] A robotic platform has been developed for presenting Stentor cells to the IBM on-chip microscope for screening purposes. [Collaboration: Marshall lab, UCSF; Bianco group, IBM] Automated cell and organelle classification methods implemented for yeast data [Collaboration Fung lab UCSF, Bianco group IBM] Begun construction of organelle-tagged knockout collection to allow us to map molecular pathway alterations onto quantitative variation in organelle size and shape. [Fung lab, UCSF] Barcoding strategy for single-cell analysis across thousands of conditions. [Gartner lab, UCSF]

		Algorithms for inferring cell state from cell motility patterns. [Marshall lab, UCSF] Built a tool to wound cells reproducibly and to measure if cells has been wounded or healed with higher sensitivity based on the swimming patterns of the cell. [Tang lab, Stanford; Marshall lab, UCSF] Leverage and integrate with Tom Zimmerman's microscopy setup for sampling of water [Tang lab, Stanford; Tom Zimmerman, IBM] Measure the sensitivity, specificity and other performance metrics by considering cellular wounding as sensor [Tang lab, Stanford; Tom Zimmerman, IBM; Fung lab, UCSF] .
Establish dynamic range / dose response of a cell / organelle to identified chemicals. Year 3	1) Use Incell and software developed by Project 2 to determine close response to identified chemicals to select best chemicals to monitor Year 3 Contact: Jennifer Fung 2) Test positives from yeast screens in chicken embryos, a human embryo animal model organism, in assessment of toxicity and cellular embryo growth/organogenesis developmental defects. Year 3 Contact: Wilfred Denetclaw SFSU 3) Inject positive from yeast screen into Drosophila embryos with fluorophores; dose response with organelle structural changes Year 4-5 Contact: Blake Riggs	Test of Stentor cell shape response to five chemical known to be present in effluents from landfill, including dose-response. Initial tests confirm a sensitivity equaling or exceeding that of Spirostomum in the "spirotox" assay. [Marshall lab, UCSF] Droplet microfluidic system for high-throughput analysis of Stentor morphology under thousands of conditions. [Tang lab, Stanford] Developed *ex ovo* chick embryo culture system, benchmarked with analysis of NO response. [Denetclaw lab, SFSU]

Prototype device that monitors chemical levels using cell sensors. Year 4-5 Contact: Ray Esquerra	1) Design a yeast specific system to incorporate the CooA chemically-regulated transcription factor system Year 4 Contact Ray Esquerra 2) Design a methyl halide detection system to monitor levels of methyl halide in the environment Year 4 Contact: Jennifer Fung 3) Develop prototype devices that monitors conditions in aquatic environments Year 4 Contact: Tom Zimmerman	Portable lensless microscope and analysis software invented at IBM for monitoring single celled organisms in water samples, and tested on Stentor as a model system for initial development. [Collaboration: Bianco group, IBM, and Marshall lab, UCSF] Design has begun on CooA constructs for expression in yeast [Collaboration: Esquerra lab and Chan lab, SFSU] Submersive immersive microscope for analyzing cell shape and behavior in open water. [Bianco group, IBM] Development of a high-throughput flow-through microscope for plankton analysis. [Prakash lab, Stanford]
Implement web/software infrastructure to integrate organelle classification and analysis with predictive models of morphological modification being developed as part of Outcome 2 Year 5 Contact: Simone Bianco	Cooperate with the CellCAD software development effort (Research Project 2) to adapt predictive models of organelle morphology with image classification framework	not yet started

EDUCATION- Specific Goals, Performance Indicators, and Progress to Date

EDUCATION Optimal Outcome 1:

Educators have mapped the knowledge, skills & processes used in the discipline cellular engineering and have developed a framework to guide teaching of cell biology through the lens of cellular engineering using an interdisciplinary, problem-based approach.

TARGETS / MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
1) Refined conceptual framework exists for cellular engineering education Year 5 Contact: Rebecca Smith	1a) Conduct a review of state of field in Cellular Engineering education. What courses, curriculum, outreach exist in Cellular Engineering and related fields (synthetic biology, bioengineering, etc)? Review should be framed by audience groups (e.g. graduate students, undergrads, high school, general public). 1b) Articulate how Cellular Engineering is different than other fields. Define/differentiate core ideas of Cellular Engineering vs. techniques used in this field (and others) 1c) Articulate 1) interdisciplinary nature of Cellular Engineering 2) the different strands of the field, and 3) the skills/habits of mind of researchers in this field. 1d) Develop concept map - unified conceptual framework. Steps to accomplish: 2a) Conversations with CCC members to identify big ideas/core concepts of cellular engineering. Understand current research in labs and what of these adapt well to education pieces. 2b) Continue to revise Framework to refine and update as discipline (and our understanding of how to best train Cellular Engineers) develops. Refinement process includes sharing framework within the Center to solicit feedback from a wide variety of Center members. 2c) Paper published in CBE-Life Science Education describing cellular engineering-based educational approaches by year 5.	1) A framework of key concepts has been collaboratively developed by Rebecca Smith and Jennifer Frazier and is informed by conversations with Center faculty, postdocs, and students, as well as through information obtained at research talks presented by Center members. This is presented in the 2019 Annual Report 2) Analysis of evaluation results from the 2018 summer workshop is underway and will form the basis of the planned publication.

EDUCATION OPTIMAL OUTCOME 2: **Center faculty have created innovative curricula/teaching materials that prepare *students (undergraduate through post-grad)* in knowledge, skills & habits of mind of cellular engineers.**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
Undergraduate		
Integration of key cellular engineering concepts into core undergraduate courses in biology and chemistry. Contact: Ray Esquerra	1) Review syllabi of current core courses in biology/chemistry at partner institutions. Identify "elegant fits" for introducing cellular engineering concepts into these courses. Year 4 2) Articulate process and timeline for the integration of these concepts into core courses. Year 4 3) Undergraduate core courses include cellular engineering concepts. Year 5	1) In progress 2) In progress 3) 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
Create 3 new undergraduate courses that build students' knowledge, skills, and habits of mind of cellular engineering. Contact: Ray Esquerra, Manu Prakash		COMPLETED: 1) "Principles of Cellular Engineering" which will focus on mathematical and computational modeling of cellular systems. SFSU BIOL 674 launched Spring 2019 (30 students/year) 2) "Frugal Science" a project-based course in which, students explore how tools from engineering and physics can be used to solve problems in the life sciences, with a particular focus on low-cost solutions that reduce barriers to entry. Stanford launched Fall 2018 (NOTE: serves undergraduate & graduate students) 3) New SFSU course in microscopy is continuing to be developed and will be offered for the first time in Fall 2019 (Esquerra, Chan, and Zimmerman)

Create new major/concentration in Cellular Engineering Contact: Ray Esquerra	1) Identify whether this is more appropriate as a major or concentration. 2) Submit proposal/course of study for approval. Long-term goal - Years 5+	The two new Cellular Engineering courses at SFSU will lay the foundation for this future development of a concentration or major, by testing the waters, establishing a track record of success, and developing approaches to curricula in this area.
Eighty percent of undergraduate students trained in center labs go on to further STEM training Year 1-5 Contact: Frank Bayliss	1) Leverage existing summer programs to recruit students to CCC labs by having CCC faculty take part in summer student selection and by giving recruiting presentations for the summer programs to URM undergraduate student groups at target partner institutions each year 2) Center leadership make hosting undergraduates an expectation of Center Members. 3) Undergraduates take part in center meetings and become part of the CCC scientific community.	Seven undergraduates graduated from Center institutions in year 3, two are going to medical school and the other 5 are all entering Ph.D. programs.
Graduate		
Two inter-disciplinary graduate level courses have been developed and assessed. Ongoing Contact: Jennifer Fung and Manu Prakash	Pilot one new course per year using the minicourse framework: 1) Three-week graduate minicourse using LEGO Mindstorms to explore robotics as an analogy for understanding cellular decision making has been piloted and assessed. 2) Pilot two-week mini-course “Self-organization” 3) Bioconjugation mini-Course 4) Computation by Cells mini-course 5) Modularity in Biological Regulation, Evolution, and Engineering:	COMPLETED 1) We have developed a Graduate Minicourse- Systems Biology: Cellular Robotics which has now run in three successive years. 2) Center PI Marshall piloted a two – week minicourse in Spring 2018 entitled “Self Organization” which combined guided readings of literature with computer simulation projects based on the papers discussed. 3) Center co-director Zev Gartner organized a minicourse on Bioconjugation that builds on the research expertise of his group. 4) Marshall also developed a third graduate minicourse “Computation by Cells” which ran in the spring semester 2018. 5) Center co-director Wendell Lim developed a minicourse entitled “*Modularity in Biological Regulation, Evolution, and Engineering:*

	Domains, Circuits, and Engineered Therapeutic Cells mini-course	*Domains, Circuits and Engineered Therapeutic Cells".* In this course students investigated the evolution and engineering of modular proteins and modular circuits in biology and how to harness modularity to engineer useful cells.
Center-wide		
Determine mechanisms for students from any center campus to participate in graduate courses at any other center campus Year 1. Contacts: Wallace Marshall and Diana Chu	Discussion with officials at participating institutions to determine what mechanisms can be leveraged.	Access for SFSU undergraduate and Masters students to take UCSF graduate courses for credit has officially been granted through the SF Consortium Intercampus Exchange program. Cross-campus access for courses between UCSF and UCB is officially permitted. In process: mechanisms for accessing Stanford courses.
Develop a center-wide project-based research course open to Center trainees from all member institutions Year 4 Contacts: Wallace Marshall & Diana Chu	Develop and launch (Summer 2019) a two-week long intensive research-based course open to all Center trainees. Course will build community across Center institutions, and provide intensive learning opportunity for trainees to engage in and tackle problems that are important to the Center.	In process. This course will launch Summer 2019. Curriculum has been designed, instructors and TAs have been assigned, students have been recruited, and we are currently in the process of placing orders for lab supplies for the course.

EDUCATION OPTIMAL OUTCOME 3: ***Center trainees*** **gain insight into careers in industry while developing new technologies that benefit the work of the Center through internships with industrial partners**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
Center graduate students and postdocs have gained experience in teaching and industrial workplace settings in order to expand their view of science career paths, to prepare them for future careers, and to build connections between center institutions as well as outside partners. Year 5	1) At least 2 IBM internships per year are arranged for students from Center labs in support of the centers Integrative Research project. Years 2-5 Contact: Simone Bianco 2) Leverage center industry collaborations and contacts to arrange student visits and 1-2 internships in companies outside the center per year for center students. Contact: Charly Craik 3) Interns from the center report back on their experiences during the annual retreat and quarterly meetings.	1) Four CCC students (two Ph.D. students and two Masters students) have done summer internships at IBM. 2) Four CCC students have done internships at other companies, namely at Calico, Imprimed, Zymergen, and The Longevity Fund. 3) Two students have done internships at The Exploratorium in order to learn Science Communication skills. 4) Reports from students about internship experiences were presented at the Spring 2018 quarterly meeting.

EDUCATION OPTIMAL OUTCOME 4:

All center members are prepared to act as ambassadors for the field by clearly communicating the importance of their work in a wide variety of settings, to help building awareness of the importance of cellular engineering and its potential to solve complex problems.

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
Offer scientific communications and outreach training to all Center members. This can include training on how to communicate with policy makers.	1) Organize Quarterly meeting focused on Scientific Communication, facilitated by recognized leader in the field such as COMPASS, AAAS or Alan Alda institute. 2) Track communications efforts by Center/Center members including: - social media analytics - "organic" outreach initiatives 3) Develop/utilize communication platform to share outreach opportunities, invite participation - e.g. Slack CCC Outreach channel	Twitter analytics is currently used to track science communication. CCC members who tweet their own tweets about the CCC include the @C3STC handle which then allows retweeting and tracking. CCC-wide Listserv is being used to disseminate information about science communication opportunities. New course in Science Communication developed by Diana Chu and offered at SFSU.
Center trainees have opportunity to intern in informal education settings to further learn different skills and strategies around scientific communication.	1) Exploratorium Internships: - Determine selection criteria for participation in Exploratorium internship program taking into account diversity goals and impact on training. - Write up description and schedule for internship projects. - Work with Exploratorium staff to set up infrastructure for CCC student interns. Contact: Jennifer Frazier 2) Center trainees have opportunity to intern at SEP to co-develop and teach in the high school level Cellular Construction Workshop, support development of Maker Faire and Science Festival Activities (N=1/year). Contact: Rebecca Smith	Two student interns, Jennifer Hu (2018) and Rebecca McGillivary (2019), both from UCSF, have worked at Exploratorium developing new exhibit concepts and demonstrations. 2) In 2017 one Center postdoc, Vasudha Srivastava, participated in a mentored teaching opporutnity in the In Summer 2018 she returned and was given more of a leadership role in the Workshop and developed a demonstration used at both the Workshop and in the Center's Science Festival booth.. Additional Center members led explorations of biological phenomena during the workshop. In 2017 & 2018, 15 students (7 from UCSF, 8 from SFSU) helped present an exhibit on cell behavior at Maker Faire Bay Area.

Center faculty have communicated about center activities at a variety of venues and to a variety of audiences. Year 5 Contact: Rebecca Smith	Venues include both sharing Center work at other institutions (academic & industry) as well as to the general public.	See annual report for full list of presentations given by Center Faculty
Center postdocs have the opportunity to gain experience teaching undergraduates in SFSU courses.	1-2 postdocs gaining teaching experience per year	New SFSU course, BIOL674 (*Principles of Cellular Engineering*), was developed collaboratively by Center Faculty Ray Esquerra and Postdoc Anum Glasgow. This collaboration provides a paradigm for involving CCC postdocs in course development for undergraduates.
Videos of Center members clearly articulate what Cellular Engineering is, are representative of the diversity of the Center, and present the exciting opportunities in terms of careers, problems to solve, and potential to invent new technologies through involvement in this field Ongoing through end of Award Contact: Diana Chu	2-3 videos per year, each highlighting a Center member (faculty, postdocs, graduate students) and their research	6 videos produced so far highlighting the CCC and its members

EDUCATION Optimal Outcome 5:

Members of the *general public* understand that cells are dynamic entities that respond to their environments. They recognize potential of using cells as an engineering platform to solve a wide variety of problems.

TARGETS /MILESTONES	ACTIVITIES/ACTIONS	PROGRESS
Exploratorium has developed 8 new exhibits and demonstrations for their new collection, *Cells to Self* Year 5 Contact: Jennifer Frazier	1) Define concepts and skills appropriate in informal learning contexts (based on work on Outcome 1 Year 3 2) Create 4 exhibits and/or demonstrations for the "Cells to Self" exhibit opening December 2017 Year 1 3) Create two more exhibits or demos for Cells to Self Phase Two, employing two interns (Center Trainees) Year 2 4) Create final four exhibits/demonstrations, building on lessons learned from the first four projects and considering concepts or skills that remain to be addressed Year 4 5) Develop plan for dissemination of completed exhibits and future traveling shows. Year 3	1) This is in process (see develop framework for Cellular Engineering Education, above). 2) The *Cells to Self* Exhibit opened December 2017. Two CCC exhibits are included in this initial opening, with others being added later so that they can be more closely tied to the research of the Center. These two include: ● Cell Zoetrope ● Cell Structures 3) Two interns (both Center trainees), Jennifer Hsu and Rebecca McGillivary have interned at the Exploratorium (a third will start Summer 2019) Interns each developed demonstrations
Exploratorium will provide opportunities for Center members to share their work and cross-fertilize ideas with staff from across the Exploratorium	1) Hold a "CCC Cell Faire" at Exploratorium to cross-fertilize ideas for exhibits and demonstrations based on center related themes. Year 2	COMPLETED Eight booths representing different Center groups presented their work/ideas for demonstrations to 200 museum professionals.
Five CCC faculty have presented public lectures/demonstrations at the Exploratorium	1) Develop database of faculty research and its potential relevance to the public Year 1	1) not yet started

Year 5 Contact: Jennifer Frazier	2) Arrange for at least 1-2 CCC faculty per year to present at existing Exploratorium programs (After Dark, Pairings, etc), of which 30% of faculty are from underrepresented groups. Ongoing: years 1-5	2) Center Faculty member, Manu Prakash presented • Wallace Marshall and his lab have helped inspire a new demonstration "Cell SuperHeroes," being developed for the museum floor. • The public program "Pairings" hosted an evening for the public that was derived from development of the Cell Structures exhibit. This session used the popular drink Kombucha and the multi-cellular (and multi-organism) biofilm (a "scoby") that plays an important role in creating the drink to explore multicellularity and the structures cells can build.

EDUCATION Optimal Outcome 6:

High school students **are aware of, and excited about, the potential of building things and solving problems with cells, and move on to STEM majors.** ***High school teachers*** **understand that cells are dynamic entities and are comfortable integrating big ideas of cellular engineering into their teaching.**

TARGETS /MILESTONES	ACTIVITIES/ACTIONS	PROGRESS
A network of science educators interested in learning to teach cell biology using an engineering-based approach to cell biology has been established. Network will represent the diversity of schools, educators, and students in the region. 18 months. Contact: Rebecca Smith	a) Identify target districts, schools, teachers to include within the network. Reach out to colleagues in informal science education who work with teachers from around the region. b) Send letter of introduction about center and opportunities to teachers within the network.	a&b) Target districts have been identified. We continue to work with contacts in those districts and in informal science education to continue developing this network and sharing information about Center opportunities. A network of teachers who participated in our summer cellular engineering workshops has now been established and continues to grow. We will continue to develop and expand this network in the coming years.
10-15 high school students per year have taken part in the summer bootcamp, the Cellular Construction Workshop program Years 1 forward	Two-week summer bootcamp for high school students and teachers offered annually.	First summer bootcamp was held July 24-Aug 4, 2017. Ten teachers and fourteen students participated in 2017. The second summer bootcamp ran from June 18-29, 2018, twenty-one high school

Contact: Rebecca Smith		students and teachers participated in Summer 2018. The workshop will begin transition to self-sustaining status starting summer 2019 when we implement a version of the course in which teachers and students who can afford to do so will pay to take the course.
85% of high school students trained through program pursue STEM majors in college Timeframe: ongoing through year 10. Contact: Rebecca Smith	Track high school participants through various means including: SFUSD Linkedin interface, National Student Clearinghouse, and surveys of program alumni	Tracking of CCW alumni, who have completed high school is underway using surveys, interviews, and the National Student Clearinghouse. Seven students from the first year of the CCW graduated from HS in 2018. 100% currently enrolled in college (one is unknown): 2 at UCSD, 1 at UC Berkeley, 3 at CCSF, 1 at CSU - Chico. SFSU has given recruitment presentations to all high school students in UCSF's summer programs.
Participating high school teachers incorporate lessons from the Cellular Construction Workshop into their teaching during the school year.	Conduct follow-up questionnaires and observations in participating teachers' classrooms to identify how the workshop lessons are being adapted to the classroom and obstacles teachers encounter.	Video produced to highlight an example of a teacher who is now making extensive use of our curriculum in her own classroom.

BROADENING PARTICIPATION

BROADENING PARTICIPATION Optimal Outcome 1: **The Center for Cellular Construction is a model for creating a diverse STEM workforce that is emulated by other institutions**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
All center participants have been trained in best practices for mentoring diverse populations and apply this training to all center activities Year 1. Blake Riggs & Carmen Domingo	Diversity mentoring events are held at all annual retreats, during which faculty who have participated in NRMN and other formal training can educate other center members, from students to faculty, in data-informed best practices.	Dr. Riggs presented two-hour workshop at the annual retreats in 2017 and 2018, focusing on mentoring diversity (2017) and sexual harassment (2018)
Broadening participation goals are woven into all center activities including research, education, and knowledge transfer Year 1. Frank Bayliss	Implement a procedure for tracking and reporting diversity of participation, and steps taken to broaden participation, linked to all individual center activities, which will allow for identification of activity areas that might require additional work in this area.	Data on diversity of participation have been collected in Table VIII and are now being linked with specific activities of the center. All SFSU CCC students attended at least one national research conference (ASCB, SACNAS, ABRCMS)
Partner institutions begin to emulate CCC approaches for collaboration between minority serving institutions and research-intensive institutions. Year 3. Wallace Marshall & Frank Bayliss	Establish an expanded network with select partner institutions that increases minority recruitment into our center while, at the same time, sharing knowledge with the partner institutions about ways to promote cooperation between institutions in broadening participation.	We have established contacts with UC Santa Cruz and UC Davis to spread the word about our center activities to minority undergraduates at these institutions. The director presented information about our efforts to increase diversity at the annual STC directors meeting in 2017. Dr. Bayliss presented a seminar on CCC diversity goals to the BioE department at UC Berkeley. One SFSU URM student was admitted to the BioE PhD program in fall 2018 and 3 SFSU URM students are currently being interviewed for fall 2019 admission.

BROADENING PARTICIPATION Optimal Outcome 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.**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
K-12 and informal science outreach activities of the Center have led to an increase in the number of URM students entering STEM degree programs Year 5 Rebecca Smith	1) Longitudinal tracking of high school student education and career outcomes following participation in summer bootcamp program. 2) Assess impact of Exploratorium and Maker Faire exposure on interest of URM student attendees in pursuing further education in STEM areas.	We have hired a professional evaluator to track student outcomes from summer bootcamp as well as public events such as Maker Faire. Exploratorium has their own evaluation team constantly tracking outcomes from their exhibits.
80% of undergraduate URM students who participated in Center summer research will be admitted into STEM graduate programs Year 4 Hana El-Samad	1) Provide mentoring to all faculty and student/postdoc mentors in summer research labs on best practices for mentoring diverse students prior to the start of each summer session. 2) Track outcomes for summer undergraduate students and assess their experience during the summer research experience. 3) Center faculty will actively recruit URM undergraduate students to participate in center-affiliated summer research programs by visiting minority serving institutions and undergraduate student research conferences to spread the word about the Center as a major research effort that welcomes diversity.	Tracking of summer undergraduate students will be conducted by the SRTP program. We are currently obtaining data for summer 2019 Center faculty participated at ASCB, SACNAS and ABRCMS each year. We also visited a number of minority serving institutions and student groups, for example in 2016 Dr. Marshall presented a talk to the SACNAS and LSAMP student chapters at CSU-Fresno, aimed at recruiting students to our summer program and to do graduate training in center labs. Dr Bayliss presented a talk at Arizona State U in March 2018.
90% of masters students in the Center ultimately join the STEM workforce, and of those who pursue doctoral-level training, 90% will complete their training successfully. Year 5 Frank Bayliss	1) Masters students are fully integrated into center research, education, and knowledge transfer activities and treated as equal partners, preparing them to compete successfully at the next level. 2) Masters students are given the same opportunity as PhD students, to participate in internship programs with center partner companies.	Of the 24 center MS students (86% URM) graduating during the first 3 funding years, 13 are now enrolled in Ph.D. programs, eight are employed in research-related positions (biotech industry, research scientist positions). Thus, 96% meet the stated goal, showing that we have been exceeding our target for this key metric.

The number of Ph.D. students from under-represented groups entering graduate programs with which the Center faculty are affiliated has increased by 20% Year 3	1) Center faculty will volunteer to join admissions committees for graduate programs at their respective institutions, where they can encourage the careful consideration of URM candidates. Contact: Wallace Marshall	1) Drs. Marshall, Weiner, and Fung are now members of graduate admissions committees at UCSF. Dr. Marshall is a member of the graduate admissions diversity committees for the two main graduate programs, TETRAD and iPQB, from which the center will draw its Ph.D. students.
	2) Center faculty will join diversity committees if such exist. If diversity committees do not exist for a given program, center faculty will volunteer to form such a committee. Contact: Wallace Marshall	2) Dr. Marshall has joined the UCSF faculty diversity committee for basic science. 3) Center faculty participated in ASCB, SACNAS and ABRCMS in 2016, 2017 & 2018 and also visited a number of minority serving institutions and student groups, for example in 2017 Dr. Marshall presented a talk to the SACNAS and LSAMP student chapters at CSU-San Jose, aimed at recruiting students to our summer program and to do graduate training in center labs.
	3) Center faculty will actively recruit undergraduate students into the respective graduate programs by visiting undergraduate serving institutions and attending SACNAS/ABRCMS conferences Contact: Frank Bayliss	
	4) Identify barriers that prevent URM students from persisting through the Ph.D., at each participating institution, so that these can be reduced or eliminated. Contact: Frank Bayliss	4) URM Ph.D. student participants currently in center labs have been identified, allowing us to track outcomes. Outcomes: Five SFSU students were admitted into UCSF, 2 into UC Berkeley and 2 into Stanford PhD programs in fall 2018

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BROADENING PARTICIPATION Optimal Outcome 3: **Postdoctoral training has become a key element in promoting diversity and broadening participation.**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
The number of postdoctoral fellows from underrepresented groups in Center labs increases by 10% relative to non-center labs Year 4 Contact: Wallace Marshall	1) URM postdoc applicants to any center lab will be invited to interview with multiple center labs to increase likelihood of being accepted into a center lab. 2) Postdocs are recruited from diverse pools of students 3) new: Integrate recruitment efforts with UCSF wide efforts to increase diversity. Participate in newly established Path-to-Postdoc UR postdoc recruitment program.	1) We have put into place a policy of joint interviews for all diverse postdoc applicants. 2) There are currently 7 postdocs supports 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. Our focus going forward is to ensure diversity in additional new hires as they occur.
Develop postdoc training program specifically designed for postdoctoral fellows interested in 1) academic careers or 2) industry careers.	For 1) provide teaching pedagogical workshops and opportunities to mentor undergraduates; provide opportunities to teach in SFSU courses and provide specialized workshops to undergraduates For 2, provide training in biotechnological business and entrepreneurship.	1) the first postdoctoral fellow will participate in a teaching workshop this SP. One center postdoctoral fellow will run a 20 person workshop on cloning and yeast cell culture. 2) One center postdoc has joined the UCSF IRACDA program
All center postdocs, regardless of their own minority status, are trained in broadening participation issues Year 2 Contact: Wallace Marshall	Postdocs participate in mentorship training.	Drs. Riggs & Domingo conducted training at the 2018 and 2019 annual retreats, which were attended by all center postdocs.

BROADENING PARTICIPATION Optimal Outcome 4: **Infrastructure and partnerships between SFSU and other CCC institutions increase opportunities for diverse faculty to succeed in their research**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
50% increase in presentations, publications, and grant awards by SFSU faculty after joining the Center Year 3	1) Establish at least one research collaboration between each SFSU CCC faculty and at least one other CCC faculty member. Year 1 Frank Bayliss 2) Establish core facility access at all CCC institutions for SFSU faculty members. 3) Center faculty from research intensive institutions work to get SFSU faculty invitations to present their work at national meetings Ongoing Frank Bayliss & Wallace Marshall	1) Seven active collaborations between SFSU faculty and faculty at other Center institutions have been established 2) Completed – all SFSU faculty have access to all core facilities at UCSF. 3) The importance of creating opportunities for SFSU faculty at national meetings will be conveyed to all faculty at the annual retreat. 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. Year 3. 33 Student presentations at National Scientific meetings.

KNOWLEDGE TRANSFER - Specific Goals, Performance Indicators, and Progress to Date

KNOWLEDGE TRANSFER Optimal Outcome 1: **The Center is known as a place that is generating ideas in cellular engineering that can be translated into products**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
At least five op-ed articles will be published by the Center to define cellular engineering according to our center mission. Year 4 Hana El-Samad	Write op-ed articles designed for electrical and chemical engineering audiences, and submit to IEEE Spectrum and Chemical & Engineering News, then write variations on these articles to target other engineering audiences	Marshall has written one piece on the cell as a computer. Bianco and Marshall currently writing a piece on cellular engineering for Nature Machine Intelligence.
Center Website and Social Media convey center goals, ideas, and results to a broad range of stakeholders, potential collaborators, and the general public. Year 3 Diana Chu, Debra Singer,	Construct a well-designed professional website Content is updated on a monthly basis and aggressively promoted through SEO techniques Design a compelling center logo that conveys our identity Create a “Cellular Engineering” Wikipedia page Develop a social media presence for the Center	Center twitter feed (@C3STC) currently has 473 followers and has issued 1174 tweets to date. Anotherwise Inc., a local web developer, has designed a new CCC web site and logo. The new site is currently being populated with content migrated from the old site. Contract in place with Dr. Janet Iwasa (U. of Utah and OneMicron.com) to provide custom computer animations making center concepts accessible to a wide audience
Center has established active collaborations with least three companies to explore possibilities of applying cellular engineering approaches in actual industrial processes. Year 4 Charly Craik	1) Assemble a center “slide deck” that any center member can use to introduce the center concept and activities 2) Establish dialogues with 3-5 companies per year working on biotechnology, fermentation processes, and materials production to explore potential collaborations or licensing agreements.	Center investigators have presented non confidential work produced and inspired by CCC research to companies of potential interest CCC has established ten active collaborations with industrial partners. Several examples are as follows: (1) We have also established a confidential collaboration with **Nagase, Inc**. to analyze cell and colony structure of an industrial strain of streptomyces. The project

		aims at analyzing cellular structures from images and videos to infer interesting and important genetic variants associated to increased yield and efficient production. (2) 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. (3) We 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'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 also gives Serotiny access to our growing collection of molecular components and markers, helping them to grow their database while helping us to disseminate our results into the industrial sector. 4) The Bianco lab at IBM and the Marshall lab at UCSF have partnered with Wild Acres Farm, an aquaponics company, to use cellular sensors and our AI powered microscopes to monitor the production cycle of fish and vegetables in an aquaponics company. This is an example of a direct translation of the research performed in the Cellular Sentinel project to a real world application. As a part of this project, we aim at collecting data which will constitute the baseline information to engineer ad hoc cellular sensors for this specific industrial application.

KNOWLEDGE TRANSFER Optimal Outcome 2: **We have created a broad community of researchers who are informed about how to take research and transform ideas into products**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
Each year a diverse group of center students, postdocs, and faculty will receive training in entrepreneurship and startups Year 2 and thereafter Contact: Charly Craik	1) Fund entrepreneurship educational programs in cooperation with QB3 2) Develop mechanism to select students and postdocs who will participate in training programs 3) Present talks about entrepreneurship at center quarterly meetings	Discussions have been held with QB3 and Catalyst members to plan how best to leverage center funding to support entrepreneurship education CCC students have taken the ASCB-Keck Biotech course Spring 2018 quarterly meeting focused on entrepreneurship and included talks from industry visitors

KNOWLEDGE TRANSFER Optimal Outcome 3: **We have generated companies, IP, and tangible products that grow the economy and create jobs around cellular engineering**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
The Center has launched four startup companies and supported them long enough to have a strong chance of securing VC investment. Year 5 Charly Craik	1) Create access to Bay Area early-stage seed funding for commercializable ideas. 2) Develop mechanism for selecting center member ideas to be supported by internal seed funding 3) Leverage center funds and contacts to identify opportunities for further startup support through alternative RFAs, VC, existing companies, and private foundations	Negotiations with UCSF Catalyst have successfully convinced Catalyst to add an engineering track to their early-stage seed funding category, allowing the CCC to apply for support for commercializable ideas. One CCC lab has already successfully obtained Catalyst funding for a project within the Living Bioreactor. The CCC has implemented a seed funding plan for incubating potentially commercializable ideas in-lab at an early stage, with the goal of bringing the work to the point that it can secure Catalyst funding.
The center has generated intellectual property in the form of 5 patents. Year 5 Charly Craik	1) Develop procedures for selecting proposals for center discoveries with sufficient potential value to justify pursuing IP protection 2) File 2-5 disclosures per year 3) File 3-5 patents by year 5 4) Develop approaches for disseminating information about center patents and discoveries to potential industrial partners, with the view towards establishing licensing agreements	IP management plan is in place among participating center institutions. Nine disclosures have been filed so far. Four patents searches are in progress, one has been completed and a filing is being prepared

KNOWLEDGE TRANSFER Optimal Outcome 4: **Cellular engineers trained in the center carry center concepts and approaches into the industrial workforce**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
Center trainees have entered the industrial workforce at the level of research scientist or above End of Year 5 Charly Craik, Frank Bayliss, & Rebecca Smith	1) Center students and postdocs will take part in the internship activities being organized within the Education component of the center 2) After internships are completed, the Center will maintain contact with host companies to explore possible collaborations, giving students a way to stay connected.	4 center students have been hired as interns at IBM, giving them their first experience of working in an industrial setting. One of these interns, Jacob Kimmel, (Ph.D. April 2018), has been hired as a Computational Biologist at Calico Labs, South San Francisco, CA. Another one of these interns, Amanda Paulson, will be a research scientist at UCSF, supported by an IBM award to Zev Gartner (February 2018). CCC students have done internships at Calico, Imprimed, and Zymergen

ETHICS - Specific Goals, Performance Indicators, and Progress to Date

ETHICS Optimal Outcome 1:

We have produced an academic and industrial cell engineering workforce that is aware of the ethical implications of engineering cells and trained in how to think about risk

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
100% of center participants have been trained in responsible conduct of research at their home institutions Year 1 and each year thereafter Contact: Frank Bayliss & Ray Esquerra	1) Implement a system for tracking progress of training across center institutions.	All new hires have been instructed to obtain RCR training at their participating institutions.
All graduate students and postdoctoral trainers in Center labs have been trained in ethical questions related to Cellular Construction End of Year 2 Contact: Orion Weiner	1) Develop polished materials to initiate students and faculty to the ethical implications of the discipline 2) Ethics discussion at each annual retreat	ELSI panel constituted. Robert McGinn recruited as Center Ethics Director January 2018 quarterly meeting was entirely devoted to the subject of Ethics. Presentation on Responsible Innovation was featured at the 2018 annual retreat
High school students and teachers are introduced to 1) the field of ethics broadly and 2) the role of ethics in the practice of science Year 1 (and ongoing) Contact: Rebecca Smith	1) Leverage existing materials in use in SEP programs to teach ethics in the context of science to high school students & translate these materials to a cellular engineering context. 2) Design an Asilomar-style conference simulation focused on cellular engineering questions, appropriate for high school students, which will be integrated into the 2-week summer bootcamp for high school students and teachers.	Completed The Summer Cellular Construction Workshop run by the SEP included a two hour module on ethics in science and cellular engineering

Center research projects provide case studies for ethics training Year 4 Contact: Robert McGinn	1) Ethical concerns arising from CCC research are identified via an ethics survey of center members 2) Case studies are developed around concerns identified in survey	An Ethics Survey has been developed and is awaiting IRB approval

ETHICS Optimal Outcome 2:

Center exploits state of the art technology to monitor and contain potential spread of industrially relevant cellular systems

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
Bar-coding of strains is implemented for all strain construction by the center Year 5 Contact: Zev Gartner.	A bar code scheme is developed along with a database to store information on strains as they are generated	Bar-coding methods have been implemented for studies of cellular function by the Gartner lab and these strategies will now be adapted center-wide.
Best practices for biosafety are established for center activities Year 1 Contact: Wallace Marshall	1) Consult with ethics advisory panel and institutional safety officers to determine potential laboratory hazards entailed by center engineering activities 2) Harness existing standard operating procedures and training to mitigate the specific types of risk that arise during center work.	The CCC Ethics Survey developed by Dr. McGinn will include questions about attitude towards safety and about potential risks in the lab that the center may need to be made aware of.
Genetic containment strategies are implemented for key industrially relevant microbes Year 3 Contact: Wallace Marshall	Research existing options for containment, such as engineered dependency and kill switches, and invest research resources if these prove inadequate	Group discussion of containment strategies, and the problems posed by lateral gene transfer in evading such strategies, was a topic of the center-wide bioethics discussion at the 2018 Winter Quarterly meeting.

ETHICS Optimal Outcome 3:

Stakeholders and general public are engaged in and aware of the center's commitment to ethics and safety

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
Center web site has a section discussing ethical implications to demonstrate our engagement with this issue. Year 4 Contact: Robert McGinn	1) Discuss with ethics panel to determine what aspects of center activity might generate ethical concerns among the public and stakeholders 2) Develop web site content that sets forth the center's approach to mitigating risk, while discussing the balance between risk and reward	Our current web site has a section on Ethics and Responsible Innovation as part of the "what we do" tab. As we generate more content pertaining to ELSI considerations, we will further populate this section.
Ethical considerations are addressed whenever the center engages with broader audiences Year 2 Contact: Jennifer Frazier	1) Speakers from the center presenting talks to the general public include a section in the talk addressing ethical concerns 2) Center publications aimed at the public and the larger engineering community address ethical issues	Discussing and engaging in questions of ethics is included in our training of personnel for outreach activities in Maker Faire.

LEADERSHIP AND MANAGEMENT

Optimal Outcome 1:

The center is an integrated community that lowers barriers for collaboration and creates new connections between participants at all levels

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
Mechanisms exist to foster and support collaboration and interaction among center members Year 1 Contact: Wallace Marshall & Zev Gartner	1) Establish a quarterly all-hands meetings at which two members will discuss their activities, with location rotating among all participating institutions 2) Establish an annual center-wide retreat that will focus on overall progress and team integration activities 3) Establish monthly group meetings for each of the main research project groups, as well as for education, broadening participation, and knowledge transfer 4) Center-wide working groups combine multiple project areas by focusing on specific highly collaborative goals that span center project areas 5) Implement center-wide electronic communication platforms to facilitate collaboration	1) COMPLETED: Quarterly meetings are now fully established. 2) COMPLETED: Our first 2-day retreat was held 8/16 – 8/17/17, and had 95 attendees. Our second retreat was held July 17-18, 2018, and had 110 attendees.. 3) A. Project working groups have been established for the CellCAD, Living Bioreactor, and Cell Stater Inference projects. B. The Internal Advisory Committee has been assembled consisting of working groups for Research, Education, Knowledge Transfer, and Diversity. 3) Two Center-wide working groups have been established, one for Methyl Halide production (spanning Living Bioreactor, Cell State Inference, and Cellular Machine Shop), and one for Peroxisome Engineering (spanning CellCAD, Living Bioreactor, and Cellular Machine Shop) 4) A Center-wide Slack channel is now in routine use by center members. Protocols are in place for granting access to the UCSF Box data sharing system for members at all Center institutions. LabBook has been deployed at UCSF and linked to UC Box.

All center members understand how their work fits in with the center and existing collaborations Year 1 Contact: Zev Gartner	1) Develop mechanism for onboarding of new center members (students and postdocs) which involves specific discussion of benefits and responsibility. 2) Director addresses benefits and responsibilities at the annual retreat each year 3) Benefits and responsibilities are specifically stated in the center's internal web site	This was discussed at the first annual retreat.
Center has developed a cohort of 10-20 collaborators outside the center involved with research, education. knowledge transfer, or broadening participation activities Year 5 Contact: Wallace Marshall & Zev Gartner	1) Center faculty and research working groups seek outside collaborators. 2) Implement a Center Affiliate program to identify potential collaborators and involve them in center meetings and seminars.	The CCC has established ten active collaborations with industrial partners outside the center so far., and ~ 40 academic collaborations. Center Affiliate: Last year we brought in our first Center Faculty Affiliate, Dr. John Dueber, from UC Berkeley. During that year he presented research at a quarterly meeting, his lab attended the annual retreat, and he became part of a collaborative project for Peroxisome Engineering that includes three other Center labs. Based on these contributions, he was brought into the center as a new funded faculty member starting in 2019.

LEADERSHIP AND MANAGEMENT Optimal Outcome 2: **Center decision-making is transparent and ensures that all voices are heard**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
Center members are aware of the process by which decisions are reached, the status of center goals and progress, and any potential problems or hurdles the center is facing Year 1 Contact: Wallace Marshall Zev Gartner	1) Implement an internal web site where members can go to read the center's strategic plan and updates from the leadership team 2) Reports from the leadership team at all regular meetings to keep members updated. 3) Center-wide Listserv to communicate upcoming events and decisions to all center participants	The current web site for the center has been configured to have an internal account-access area, which will then become the primary internal web site for sharing updates and plans Presentation of a leadership summary by the director is now a standard element of every quarterly meeting and retreat. A center-wide listserv is now a primary channel for notifying center members about upcoming events and opportunities within the center. The CCC Slack channel provides a mechanism for interactive discussion and exchange of ideas.
All center faculty have the opportunity to provide input into the activities of the center Year 2 Contact: Zev Gartner	1) Establish a monthly center PI phone conference for exchanging ideas and concerns 2) Conduct a center-wide brainstorming session at each annual retreat 3) Establish a Center Internal Advisory Committee to allow more faculty to have a voice in center planning	A monthly scheduled Zoom teleconference has been taking place for the past year Brainstorming session was held at the first annual retreat, and a second brainstorming session, focused specifically on techniques and methods, was presented at the second. An Internal Advisory Committee, consisting of Working Groups for Research, Education, Diversity, and Knowledge Transfer, has been established. These working groups are consulted by the Executive Committee on an as needed basis. Yr3: A new internal lead ethics investigator and advisor is consulted by working groups.

Students are included in decision making and organization Year 2 Contact: Debra Singer	1) Student-organized events at quarterly meetings and annual retreats 2) Student representation at the PI meetings held during the quarterly meetings	Students organized a session at the year 2 annual retreat. A student representative was appointed in year 2 and has attended all PI meetings at each quarterly meeting as well as the 2019 strategic planning meeting and PI meetings

LEADERSHIP AND MANAGEMENT Optimal Outcome 3: **Center leadership tracks progress in all goal areas and shifts resources as necessary to maintain progress**		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
Progress in research, education, broadening participation, and knowledge transfer is tracked relative to strategic goals Year 1 Contact: Debra Singer	1) Quarterly requests for status updates will be sent to all center PIs 2) Annual re-evaluation of center progress will be performed in conjunction with preparation of the center annual report	We have implemented a system of quarterly reporting, with a template being sent out to all faculty ahead of each quarterly meeting, and then a one hour faculty-subgroup meeting taking place at the end of each quarterly meeting where faculty sit down together and finish their quarterly reporting.
Center decision making is coordinated among the leadership and management team Year 2 Contact: Wallace Marshall	1) Weekly meetings of the Executive Committee, with financial analyst included as needed 2) Monthly long-range planning discussions between the Center Director and Co-Director	A standing meeting, lasting one hour, is scheduled every week between the center Director, Co-Director, and Managing Director. Drs. Marshall and Gartner meet in person to discuss long range goals for the center
Center progress tracking and planning is augmented by personnel with Program Management Expertise Year 3 Contact: Debra Singer	1) Professional Program Manager helps the center manage ongoing and planned future activities 2) EAC includes expertise in NSF Center Program Management	Dr. Kristin Dolan, an expert Program Manager, is working with the CCC for one year in preparation for the renewal Dr. Tom Daniel, University of Washington and past Director of NSF Center for Sensorimotor Neural Engineering has joined our EAC
Underperforming members are given the opportunity and whatever support they may need to become more actively engaged Year 2 Contact: Wallace Marshall, Zev Gartner	1) Underperforming members as identified in the annual review of progress will meet with center leadership team in order to determine whether the problem is lack of interest or because of external pressures 2) In the case of lack of interest, members will have the choice to become more engaged, or to withdraw from the center 3) In the case of low productivity due to external pressures, center leadership team will provide	A written policy for evaluation and sunsetting has been developed and is in place.

	mentorship and explore ways to support the member	
A strategic reserve fund allows the center to exploit new opportunities and to continue operations if funding gaps arise	1) Strategic Reserve is available to explore new directions related to center goals 2) If additional funding gaps from NSF occur, such as the unfunded gap in 2018, strategic reserve can be used to maintain key personnel until funding resumes	As part of the re-alignment of funds originally designated for high school education and public outreach, as well as by re-evaluating needs for shared core resources based on actual use, a strategic reserve fund has now been created

SUCCESSION PLANNING OPTIMAL OUTCOME:

The Center is able to continue its mission even if members of the leadership team leave the center

TARGETS/ MILESTONES	ACTIVITIES / ACTIONS	PROGRESS
A formal plan is in place to handle succession in the event that the current director is no longer able to act in that role Year 1 Wallace Marshall, Zev Gartner	1) The leadership team will review the existing succession plan that was developed during the first site visit	A formal written succession plan is now in place.
All leadership team members have designated successors who are kept updated to the corresponding component of center activity Year 1 Wallace Marshall, Zev Gartner	1) The co-directors will assign a designated successor for each leadership team member, and update this individual on the nature of the responsibility involved. 2) Each leadership team member will meet with their designated successor at the time that the annual report is prepared, in order to update them on progress and challenges that might have taken place.	The Internal Advisory Committee Working Groups have been put in place to help distribute decision in part to ensure that more faculty members gain experience in the plans and operations of the center.
A mechanism is in place to replace any center members who withdraw from the center Year 1 Wallace Marshall, Zev Gartner	1) If any center members withdraw from the center, the leadership team will evaluate possible replacements from among the cohort of Center Affiliates	Our Faculty Affiliate program now provides a route for replacement. Affiliates would be promoted to full members to replace any who withdraw.

SUSTAINABILITY OPTIMAL OUTCOME: Successful Center Activities continue to operate after NSF funding for the CCC has ended		
TARGETS/ MILESTONES	**ACTIVITIES / ACTIONS**	**PROGRESS**
The Center leverages its NSF-supported research to seek additional sources of funding for research, education, and knowledge transfer Year 5 Zev Gartner	1) Center faculty prepare grants for research and other activities that extend currently funded CCC research projects in novel directions or contexts beyond the scope of current funding 2) A mechanism exists for CCC knowledge transfer activities to be supported by the UCSF Catalyst program	Three proposals have been submitted based on preliminary results from Center research. UCSF Catalyst has added an engineering track to their proposal evaluation process and is currently supporting one project from the CCC.
Center Education activities become self-sustaining Year 5 Rebecca Smith	1) The Summer High School Teacher/Student workshop now has a mechanism for paid access by students and teachers with the resources to do so 2) The Cellular Engineering Summer Course for undergraduate and graduate students will become a formally listed SFSU course, allowing it to be supported by student tuition after the CCC funding ends 3) Courses for undergraduates and graduate students are formal courses at SFSU and UCSF so that they will keep running after CCC funding ends	The Internal Advisory Committee Working Groups have been put in place to help distribute decision in part to ensure that more faculty members gain experience in the plans and operations of the center.