Molecular Cell Biology Strategic Academic Vision – Round Two

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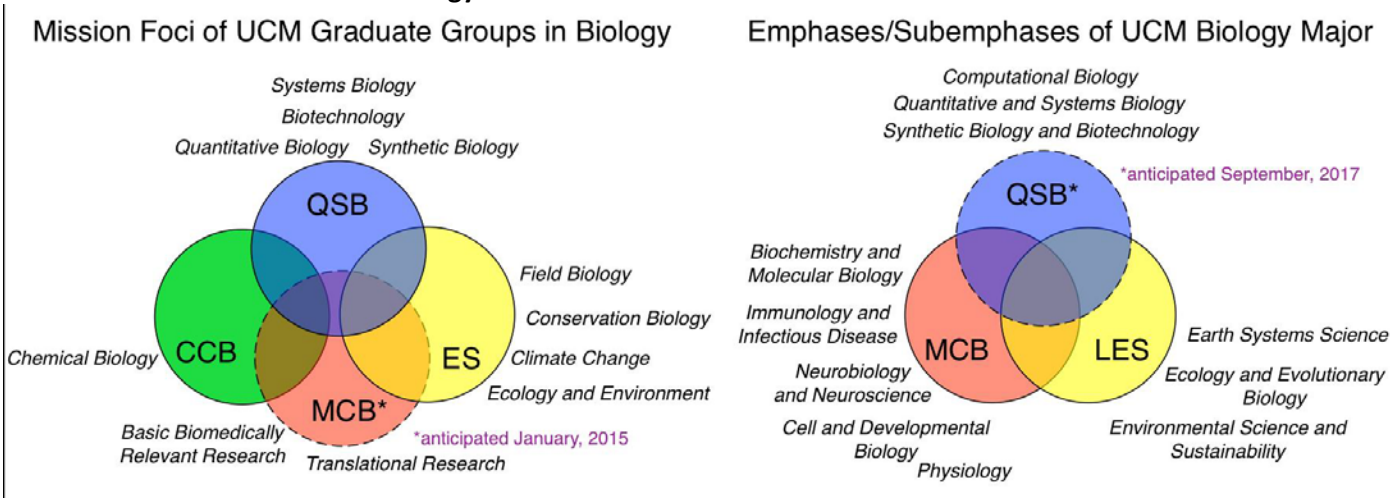
A. Executive Summary of Initiative

The Molecular and Cell Biology (MCB) Unit is currently comprised of 16 faculty members whose research is focused in 1) Biochemistry, Physiology and Molecular Biology, 2) Cell and Developmental Biology, 3) Microbiology and Immunology, and 4) Neurobiology. We currently serve 1084 undergraduate students in the Biological Sciences (BIO) major and 45 masters and doctoral students in the Quantitative and Systems Biology (QSB) Graduate Group. Our research focus is a natural fit to the 2014 proposed Strategic Vision themes of "Human Health," "Life Sciences", and the health component of "Environment Sustainability." As we progress forward to 2020, we envision that basic biological research in the core MCB disciplines will continue to foster these themes. Here, we present our vision and strategy to build the MCB Unit to achieve excellence in disciplinary and interdisciplinary research, and simultaneously improve the quality of the BIO undergraduate major by 2020. As part of this plan, we envision strong research partnerships with the proposed MCB graduate group (under review), QSB, HSRI, BEST, LES/ES/SNRI, and the emerging Public Health program.

B. **Definition of Molecular and Cell Biology**



The 2009 Strategic Academic Vision included "Human Health" as a major research theme, with 3 objectives: 1) to establish the Health Sciences Research Institute (HSRI), which now exists, 2) establish a School of Medicine, and 3) evaluate the potential for a School of Public Health. Basic research in the biological sciences has been a primary driver for these initiatives at UC Merced. As we progress forward to 2020, we envision that the MCB Unit's research foci will continue to feed into the development of these objectives, through its research strengths in the core disciplines of biochemistry, cell and developmental biology, microbiology and immunology, molecular biology, neurobiology, and physiology. This focus is clearly distinguishable from the other Biology groups on campus, but does not prevent interaction with them (Figure 1, above). The MCB Unit research foci are clearly also part of the broader theme of "Life Sciences" that will serve as a primary initiating point as well as contribute to other biology SAF Initiatives such as "Health Sciences", "Quantitative and Systems Biology", and "Environmental Sciences". In addition, our research projects provide the data by which "Applied Mathematics" base mathematical models of biological systems, and can partner well with bioengineering research focused on tissue engineering and biomaterials. In this sense, we consider MCB not only to stand for Molecular and Cell Biology, but also for **Multidisciplinary and Collaborative Biology.**

C. Intellectual Components of the Strategic Initiative

The MCB Unit in the School of Natural Sciences is currently comprised of faculty whose research is focused in **four main interdisciplinary areas**: 1) Biochemistry, Physiology and Molecular Biology, 2) Cell and Developmental Biology, 3) Microbiology and Immunology and 4) Neurobiology.

There are several "grand challenge" research questions within these areas, which highlight their importance as an area of focused research.

- What are the mechanisms that control metabolism and how does dysregulation of these mechanisms contribute to metabolic derangements such as cardiovascular disease, diabetes and obesity?
- How can we identify and manipulate the genes that control stem cell differentiation to regenerate diseased tissues and organs?
- How do microbial communities develop, how do microbes within these communities talk to one another, and can we use this knowledge to prevent biofilm-based infections?
- What are the molecular and cellular mechanisms that control immune cell recognition and response to viral, bacterial and fungal pathogens, and do these mechanisms also initiate autoimmune disease?
- Can we predict the evolution of antibiotic and antiviral resistance and use this knowledge to design novel vaccines and chemical inhibitors to prevent and treat infection?
- How does the development and function of the brain go awry in disorders such as autism and addiction, and diseases such as dementia?

These grand challenge questions may be best answered using interdisciplinary approaches, contextualized in these broader questions: What are the evolutionary and systems-level causes of diseases like cancer, cell fate decision pathways, and other questions in the organization and dynamics of cells, molecular networks and cellular networks?

MCB faculty research to date has made significant impacts in their respective core disciplines (as demonstrated through our publications and research grants, which are key indicators of the development of a successful institutional program). The composition of the current MCB faculty provides unique and key opportunities for intellectual contributions by combining their personal expertise in the core disciplines and applying them to these grand challenge questions. In addition, we already have examples of interdisciplinary collaborations within the MCB Unit, as well as between the MCB Unit and other research groups (such as QSB, COGS). **Going forward, we aim to expand collaborative research in the following areas**:

1. **Stem Cell Biology and Regenerative Medicine**: This research focus falls under the themes of Developmental Biology, Neurobiology, and Immunology. Identification of mechanisms that control stem cell proliferation and differentiation has great potential for the use of embryonic, adult, tissue-specific and induced pluripotent stem cells to replace damaged or diseased tissues as part of regenerative medicine therapies. The MCB faculty has included strong stem cell biologists since its inception, including expertise in embryonic stem cells, hematopoietic stem cells, neural stem cells and adult stem cells. MCB stem cell research takes advantage of diverse model systems (flies, flatworms, mice, human cell lines) to identify the molecular and cellular basis of fundamental stem cell processes, including: cell survival, differentiation, interaction with support cells in niche environments, and interaction with the host immune response after transplantation. Some bioengineering faculty (McCloskey, Chin, Lu, Escobar) in the School of Engineering also study stem cell differentiation and potential interactions with novel biomaterials. Stem cell biology has been well-funded at UCM, as the laboratories of Drs. Cleary, Garcia-Ojeda, Manilay and Oviedo have been funded by several UC, CIRM, NSF and NIH research awards. Potential areas of expansion would leverage high-throughput technologies and modeling to discover novel mechanisms of stem cell self-renewal and differentiation, promote collaborations that compare the properties of different stem cell types (across tissues and organisms) and establish methodologies for the integration of stem cells and their derivatives into recipient tissues.

2. **Infectious Disease and Immunity**: This research area falls within the themes of Microbiology and Immunology and Biochemistry, Physiology and Molecular Biology. Infectious disease and Immunity is a basic research program to study infectious diseases and the immune system. Topics include emerging infections, zoonoses, and persistent and chronic infections, caused by viral, fungal, bacterial or protozoan pathogens, immune system development and function, inflammation, immune dysregulation, immune tolerance, and biochemical aspects related to infection, inflammation, and pathogenesis. This research area aligns with "genetic epidemiology" (genetic susceptibility to disease, including infectious diseases, in populations) proposed by HSRI. The program will be interdisciplinary and build on the research expertise of MCB faculty, the large multidisciplinary "immunity and infectious diseases" cluster in HSRI, and the health focus of the proposed Public Health graduate group at UC Merced. Strong collaborations with LES/ES/SNRI in environment sciences as it relates to studies of zoonoses, inflammation due to environmental contaminants, and other areas in environmental health are also envisioned. Infectious disease and immunity research has been well-supported by funding agencies; the laboratories of Drs. Barlow, Choi, Garcia-Ojeda, Hoyer, LiWang, Manilay, Nobile, and Ojcius have been funded by grants from UC, CIRM and NIH. UC Merced is uniquely positioned to develop a strong and interdisciplinary research program in this area, which also addresses health disparities in the region. We currently have strength in studying lymphocyte development, autoimmune disease, cellular and biochemical studies of inflammation, pathogenesis of chronic hepatitis C, novel treatments for HIV and its prevention, microbial pathogens such as Chlamydia, *Candida,* and Porphyromonas, the evolution of bacterial resistance, and biofilm development, which lay the foundation for programmatic growth in this area, intersecting basic science with translational research that can impact the local community as well as global health. Potential areas of expansion would be studies of pathogens to which the immune response is not well understood, such as the fungi that cause Valley Fever and the parasite that causes toxoplasmosis.

3. **Brain and Behavior** falls under the MCB research themes of Biochemistry, Physiology and Molecular Biology, Cell and Developmental Biology, Microbiology and Immunology and Neurobiology. Brain and Behavior is an interdisciplinary and

highly collaborative collection of research programs that study molecular mechanisms of brain health and disease, substances and environmental pollutants that trigger degenerative processes, how molecular signatures translate into behavioral and cognitive alterations, and the subsequent impact to our society. This theme will cover components from MCB (neurobiology and basic biomedical research), Public Health (behavioral/psychological phenotypes and public surveys), LES (environmental sustainability) and QSB (large data collection and bioinformatic-based analysis). In particular, UC Merced Neurobiology focuses on specific aspects of neurobiology that tightly link to our local underserved communities. Specific research areas include studying molecular mechanisms of alcohol addiction, mechanism of brain development, neuropsychiatric disorders, such as autism and eating disorders, and neurodegenerative diseases, such as Alzheimer's disease. Drs. Wolf Kitazawa, Saha, and Cleary are all currently funded by NIH in these areas. Socioeconomic disparities, poverty, substance abuse and its subsequent developmental complications, and agricultural/environmental toxicants/exposures that the Central Valley and other underserved communities commonly possess significantly increase the risk of substance abuse, developmental defects, and neuropsychiatric and neurodegenerative disorders. With multifactorial and interdisciplinary approaches, this theme aims to comprehensively understand healthy brain development and neurological conditions.

4. **Redox Biology** is an interdisciplinary theme founded in strong basic research that examines the regulation of free radicals and reduction-oxidation reactions in basic cellular signaling and other processes that may be involved in health and disease and related basic biological questions, and falls under the MCB themes of Biochemistry, Physiology and Molecular Biology, and Microbiology and Immunology. Specific areas include redox signaling, homeostatic mechanisms regulating redox status (oxidant-antioxidant balance), redox-active and redox-dependent reactions in metabolism and immunity, and redox mechanisms of disease. Redox biology has been a common thread in diverse research programs at UC-Merced. Examples include oxidative stress in: insulin and AT1 signaling in the development of cardio-renal and metabolic diseases, signaling in the innate immune system, stimulation of inflammation in response to nanoparticles and bacterial pathogens, pathogenesis of chronic hepatitis C, and neurodegenerative diseases. This theme may transcend to other groups that have demonstrated interest in a related area in environmental and public health. Among the primary faculty contributing to this theme, Drs. Choi, Ojcius, and Ortiz have all secured NIH and other extramural funding to support their research directions in this area.

5. Systems Approaches to MCB includes integrative approaches to studying biology at the systems level. This approach focuses on understanding the organization and dynamics of living systems, and encompasses all of the MCB general themes. Key recent achievements in systems biology have shown that information processing and "learning" emerges from the collective behavior of multiple components: whether inside cells in protein and other macromolecular interaction networks, across cells in immune and neural networks, or between individuals in populations. Even in relatively simple biochemical systems, emergent phenomena such as cellular circadian rhythms have an essentially collective basis in molecular interactions. Advances in Next Generation Sequencing have laid bare microbial worlds within us and around us — worlds that matter greatly to health and the environment — about which truly nothing was known a decade ago. Innovations in single molecule and single cell analyses have revealed how noise and randomness actually generate order in biological systems. Drs. Nobile and Ardell are funded by NIH and NSF. The MCB research foci provide the raw data for quantitative and systems approaches to further understand biology at the molecular and cellular levels.

D. UC Merced's Role in the Promotion of Molecular and Cell Biology

Since 2005, the faculty recruited to the School of Natural Sciences have led to the formation of the nascent research groups listed above which have led to its **current strengths**. The MCB Unit (and UC Merced, as a whole) consists of a **group of collaborative individuals** that appreciate considering diverse approaches to their research problems

UCM has provided important **research infrastructure** to support some of these initiatives and that has attracted faculty recruits. For example, The California Institute for Regenerative Medicine (CIRM) major facilities funding for the Stem Cell Instrumentation Foundry (SCIF), which provides state-of-the-art flow cytometry, confocal microscopy and microfabrication facilities to the entire campus. The vivarium, run by the Department of Animal Research Services, is a

top-notch, accredited vivarium that surpasses the quality of other vivariums at UC campuses. DARS provides excellent controlled housing for rodents and frogs and could be expanded to house other model organisms such as Zebrafish. Most recently, the Chancellor provided funds dedicated to the purchase of next-generation sequencing equipment on campus for shared faculty research use.

In addition to these important research facilities, UCM has developed support of Early Stage Investigators, which have been especially helpful for MCB faculty to help them establish their laboratories and obtain preliminary data for their first independent grant proposals, and should continue to be supported. The Office of Research (OR) sponsors an annual Orientation for New Faculty, hosted by the Vice Chancellor for Research, with presentations by OR units including Research Compliance, Office of Technology Transfer, Office of Research Development Services, and the Office of Sponsored Projects Services. In addition, the Office of Research Development Services (RDS) conducts an annual two-day Grant Writing Institute geared primarily to junior faculty and open to all ladder rank faculty. Components of the Grant Writing Institute include sessions on institutional resources to support research, identifying research funding opportunities, research grantsmanship, the peer review process, writing skills, building scientific collaborations, and research development best practices.

The **Health Sciences Research Institute** is the only organized research unit on campus focused on health-related research, and many MCB faculty are members of the HSRI. HSRI aims to: 1) support the development of methodologically rigorous, multidisciplinary studies across the research continuum to advance understanding of health, health promotion, and disease prevention, 2) provide administrative research support to enable faculty to conduct world-class health research, 3) support and foster undergraduate and graduate students to pursue research in health-related fields, 4) support and mentor new and emerging faculty in conducting health research, 5) establish new and strengthen existing interdisciplinary research partnerships across all levels of the university and with community partners, and 6) facilitate rapid and effective transfer of knowledge into policy, practice, product, and measurable community impact.

These current strengths and infrastructure can only support our vision to expand in the strategic research areas of Stem Cell Biology and Regenerative Medicine, Infectious Disease and Immunity, Brain and Behavior, Redox Biology, and Systems Approaches to MCB, as described in Section C.

Medical practitioners in the Central Valley are motivated and interested in contributing to research that investigates the causes and predicts disease progression within our community, which has been understudied. **The MCB Unit is poised to take advantage of this community interest** and is already providing lay seminars on our research and collaborating with local physicians to research medical issues within the community to foster this additional unique source of partnerships. To provide an example, one health research focus of local interest is Valley Fever. Several new projects have begun to explore the immune components of Valley Fever infections, ways to measure local levels of the fungus in our environment, genetic risk factors associated with this infection, economic impact of the infections, and patient psychological responses to their disease. MCB laboratories are collaborating with groups from Bioengineering, LES, SSHA and HSRI at UC Merced, and with clinicians at Children's Hospital, Fresno on these projects. Already a new seminar series has begun, allowing researchers on campus and throughout our community to meet routinely and exchange ideas for making substantive progress in understanding this local infectious disease.

Continued and new investments in these areas will make our multidisciplinary and collaborative MCB program distinctive as we envision that these interdisciplinary studies will not only help to solve these questions, but also contribute to the scholarly development of our faculty, and ultimately, to imbed this intellectual desire into our graduate and undergraduate trainees, as well as into our undergraduate curriculum. MCB faculty have secured extramural funding to enhance the training of undergraduate scholars in biomedical and agriculture-related sciences to help fortify our training environment. We currently serve the majority of undergraduate and graduate students in the School of Natural Sciences: an estimated 1084 undergraduate students in the Biological Sciences (BIO) major in these emphasis tracks: Human Biology, Developmental Biology, Microbiology/Immunology, and Molecular and Cell Biology; and 45 masters and doctoral students in the Quantitative and Systems (QSB) Graduate Group, and we have proposed a

new Molecular and Cell Biology Graduate Group (under review). We anticipate that the BIO major will continue to be popular, but we require additional faculty and graduate students to achieve our research goals for 2020.

Extramural funds are absolutely required to support our research. Financial support for MCB faculty research comes from federal and state organizations (such as the National Institutes of Health, the National Science Foundation, California Institute for Regenerative Medicine), nonprofit and private sponsors (UC Cancer Research Coordinating Committee, American Heart Association, American Diabetes Association, National Kidney Foundation, Autism Speaks, Simons Foundation, American Cancer Society, Gates Foundation), local community research grants, industry partnerships, and philanthropists. One of our faculty members is exploring "crowd funding" as an additional funding mechanism. Interdisciplinary collaborations, both on and off campus, will play an important role in the continued success of the MCB program, especially if economic drivers of funding agencies are pushed to support a move from basic to translational research questions.

E. Faculty Participation

There are numerous opportunities for collaboration, including mathematical modeling, metabolic modeling, exploring microbial interactions with the immune system, exploring how cellular communities evolve, comparative studies across model organisms, structure-function analyses, environmental microbiology, ecology of infectious disease, and study of environmental health. This rich resource of colleagues gives us an advantage over other institutions, as we have the ability to more rapidly incorporate "higher-order" types of data analysis into our thinking and research plans. We will continue to foster existing collaborations with graduate groups such as QSB, BEST, ES, Applied Math and Public Health.

F. Special Programmatic Needs for MCB

We are **currently in a deficit in terms of wet lab space** for experimentalists in MCB, and even with the opening of the new Science and Engineering-2 Building, all wet lab space will be full until an additional new building is constructed. The lab spaces for current MCB faculty do not allow for adequate growth for the addition of appropriate numbers of graduate students (our target graduate student to faculty ratio is 3:1), postdoctoral trainees and research staff. New wet laboratories will require temperature and air control, gas and vacuum lines, tissue culture rooms, and common work areas for chemical handling, shared equipment, glassware and consumable storage, and electrical capabilities to handle power -20C and -80C freezers, refrigerators, centrifuges, incubators and microscopes. **Shared computing resources are currently constrained** and MCB faculty will need access to central planning for computational resources, including server room space, time and staff support for research computing, and infrastructure to support servers, cloud computing, and sharing large data sets, and specialized computing (such as structural biology). It is envisioned that MCB will participate in the proposed Center for Theory and Computation (CTC) to fulfill some of these needs. To facilitate interdisciplinary collaborations, these labs would be co-housed in a building that is connected or in close proximity to faculty within the QSB program, which includes faculty researchers in biophysics, mathematical biology, and systems biologists.

To move forward, new **shared core research facilities are required.** UCM currently has an excellent vivarium, facilities for flow cytometry, confocal microscopy and genomics. However, additional core facilities, some with specialized space needs, are required. These cores need to be sustained and be located within close proximity to the faculty research labs that utilize them. Future core facilities should include:

- **Protein engineering/biochemical analysis core** comprised of one room for a mass spectrometer and another room for equipment for N-terminal sequencing, amino acid analysis, and for making new antibodies; space for proteomic and metabolomic analyses
- **Bioinformatics core** to include space for a core of 3-5 bioinformaticians and biostatisticians (staff, not to be confused with the tenure-track faculty) dedicated to assisting faculty with experimental planning and data processing (especially for large RNA-sequencing);

- **Histology core** including space for cryostat/microtome, large sink and fume hood for histological analysis of tissue specimens, and possibly a **human tissue repository** to store human tissue samples from healthy and diseased individuals.
- **Machine shop** for creating custom equipment.
- **Transgenic mouse facility** to be housed in the vivarium, including space for equipment of microinjection of cells and mouse embryos to create transgenic, knockin and knockout mice, collection of gametes and their cryopreservation
- **Animal behavior core** to carry out cognitive tests, assess locomotor activity, and motor performance tests
- **Extended imaging facility** including a laser microdissection microscope, stereology, and real-time, *in vivo* functional imagery for bioluminescence detection
- **Expanded genomics core** to house current DNA sequencing and genomics core, and add **oligonucleotide synthesis service** and next-generation Illumina sequencing equipment (with significantly greater data-generating capacity / sample-processing power than the current UCM next-generation sequencing machine) that is open to the entire UCM campus
- **Standalone BSL2+ to BSL3 facilities** for the study of pathogens that could cause severe or lethal human disease. Such facilities are usually confined to a specific area of a building with appropriate positive air pressure controls, ventilation, equipment for decontamination and biological safety cabinets.
- **Enhance NMR Facility** with a state-of-the-art 800 MHz NMR spectrometer equipped with a cryoprobe to tackle biochemically complex but fundamentally important systems
- **Robotics core** consisting of useful equipment for high throughput experiments, such as genetic and small molecule screens. Some examples of equipment in this core could be liquid handling robots like the Beckmann Fx, cell analyzers, plate readers, bulk liquid dispensers, plate washers and dispensers like the Biotek EL406, and colony plating robots to support the genomics and proteomics core.
- **Computational servers** to support management, archiving and storage of data generated via bioinformatics, imaging, flow cytometry, and similar approaches.
- **Common physical spaces that promote interactions and collaborations**, such as a dedicated large amphitheater/lecture hall for the seminars for the School of Natural Sciences outside of the main buildings that house the faculty labs. Reorganization and renovation of existing labs to shared spaces between faculty to promote efficiency through the use of shared equipment and facilities, as well as promote close interaction among collaborating labs, and laboratory safety.

Finally, **we must increase graduate student recruitment.** Currently, most of the graduate students in MCB faculty labs are recruited within the QSB Graduate Group. We proposed the formation of a new additional MCB graduate group (currently under review) that we anticipate will permit for the growth and strengthening of graduate education at UCM. **We aim to reach a goal of 3 graduate students to each faculty member by 2020**.