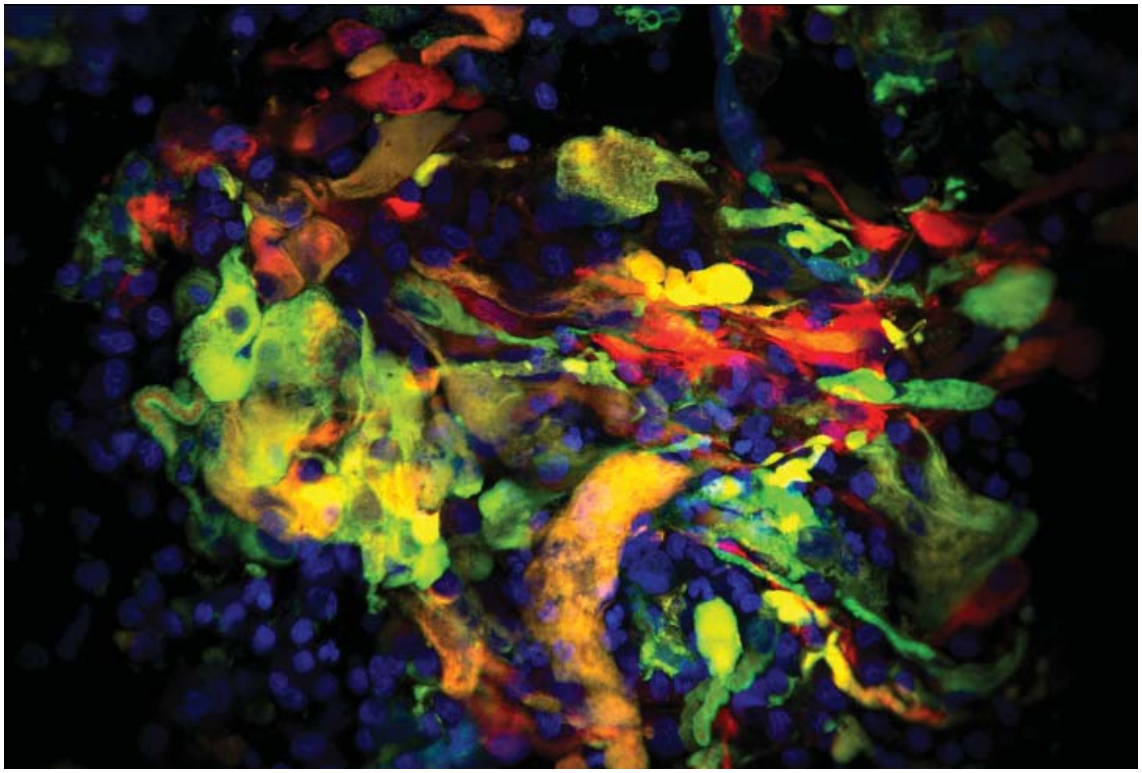
University of California Santa Barbara

Neuroscience Research Institute



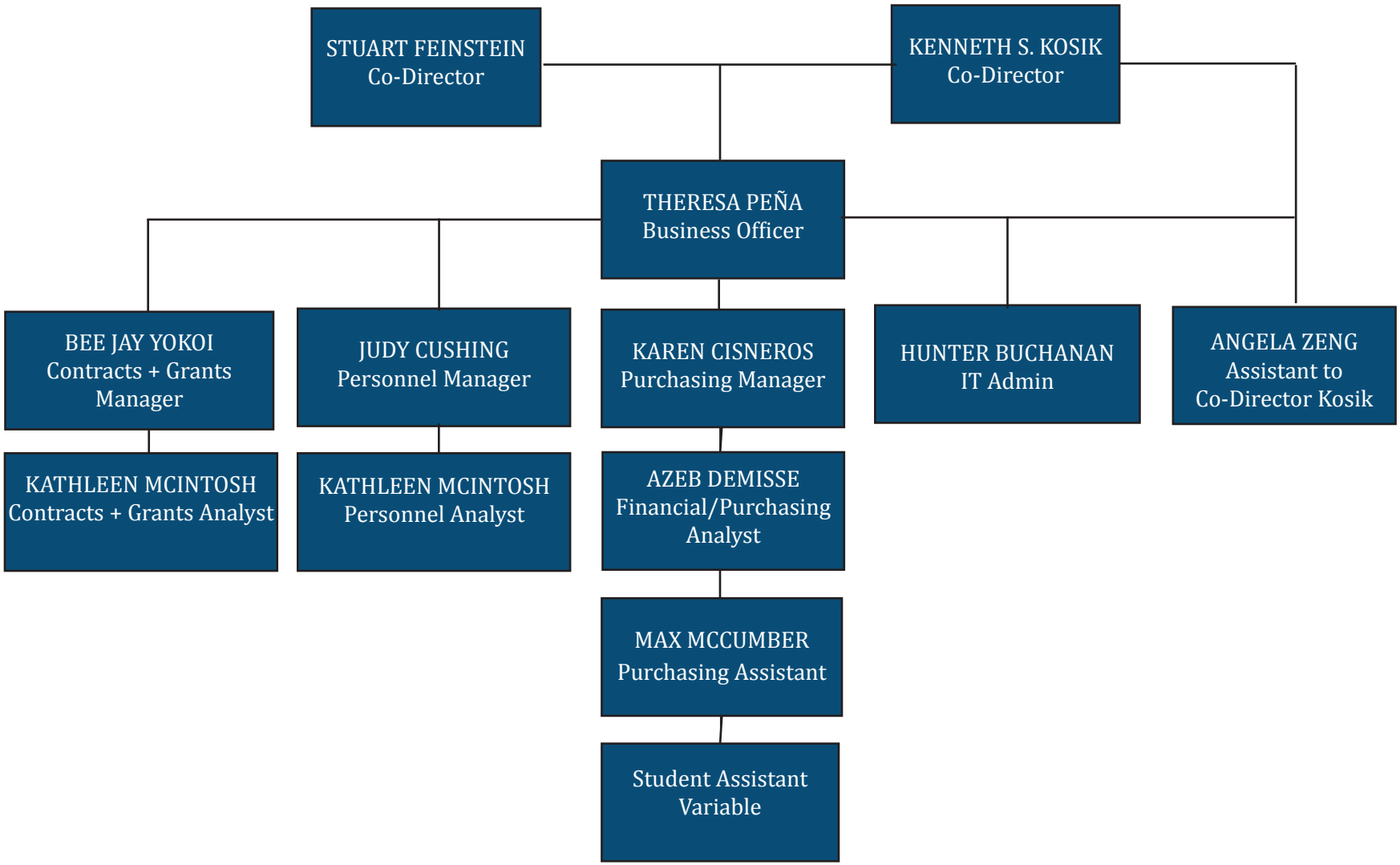
2014/15 Annual Report

Co-Director's
Stuart Feinstein and Kenneth Kosik

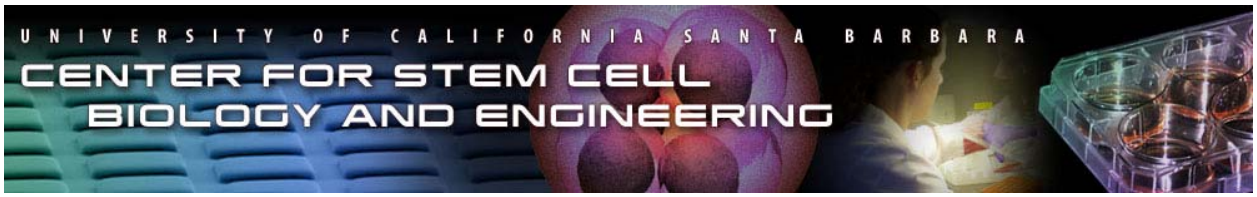
MISSION STATEMENT

The mission of the Neuroscience Research Institute is to foster knowledge and understanding of the nervous system by serving as a center for scientific research breakthroughs. The NRI is a group of investigators whose collective goal is to create an intellectual atmosphere conducive to exploration at the frontiers of human knowledge where disciplinary boundaries disappear. Investigators in the NRI recognize that the interests of neuroscience extend broadly from repair and prevention of human disease to the principles that underlie the earliest nervous systems, from the human mind to the single molecular building blocks of the brain.

Administrative Organization Chart



CENTER AND FACILITY REPORTS



UCSB Center for Stem Cell Biology and Engineering

Recent Activity

www.stemcell.ucsb.edu

Co-Directors and Holders of the Ruth Garland Endowed Chair:

James A. Thomson, Hyongsok "Tom" Soh

Executive Directors: Dennis O. Clegg, Peter J. Coffey

9-21-15

Research Highlights:

Significant progress was made in developing stem cell therapies for ocular disease, in understanding molecular mechanisms of stem cells, and in devising novel biotechnologies. News items are posted on our web site. Additional details are given below:

I. Age-related Macular Degeneration. UC Santa Barbara is involved in three large-scale efforts to develop cellular therapies for age-related macular degeneration (AMD).

A) Drs. Clegg and Coffey are part of **The California Project to Cure Blindness**, a collaborative effort between UCSB, USC, Caltech, City of Hope and University College London, funded by the California Institute for Regenerative Medicine. This group submitted an Investigational New Drug application to the FDA entitled "CPCB-RPE1 implant - Human Embryonic Stem Cell-Derived Retinal Pigment Epithelial (RPE) Cells Seeded on a Polymeric Substrate; A Phase I/IIa Open Label Single Center Study to Assess the Safety and Tolerability of CPCB-RPE1 in Patients with Age Related Macular Degeneration (AMD)". The application was cleared by the FDA on March 6, 2015, allowing initiation of the Phase I clinical trial for a stem cell based therapy targeting the "dry" form of AMD.

B) Dr. Coffey is also teaming with Pfizer in **The London Project to Cure Blindness**, targeting patients with the "wet" form of AMD who do not respond to drugs. This therapy also employs a human embryonic stem cell-derived RPE cells on a scaffold, but uses a different cell line, a different scaffold material, and targets a different patient population. Thus, the California and

London Projects are parallel synergistic efforts, rather than competitors. The first patient was treated in London in August 2015.

C) Finally, the Clegg and Thomson labs are part of a team developing ocular therapies using induced pluripotent stem cells, funded by a Wynn-Gund Translational Research Acceleration Program Grant from the Foundation Fighting Blindness. This effort, still in the early phases of development, will combine IPSC-derived photoreceptors with RPE cells on a scaffold.

Our strategy is to combine efforts in collaborative, new directions, and many of our publications involve multiple Center faculty members. In the past year, we published new, clinically compatible methods to produce iPS cells as well as stem cell-derived retinal pigmented epithelium (RPE) – the key cell type needed for AMD therapies (Croze et al., 2014; Pennington et al., 2015; Silva et al., 2015). We found that inhibition of the TGF-beta pathway can improve the differentiation state of RPE (Radeke et al., 2015). In a high profile Cell Stem Cell paper, we showed that iPS-derived RPE are less immunogenic than other cell types (Zhao et al., 2015). We also showed that RPE can be converted to neuronal cells by bathing them in a membrane penetrating protein (Hu et al., 2014), and identified an important role for Wnt growth factors in the maturation of RPE (Leach et al., 2015). We developed a novel way to deliver RNAs to stem cells using gold nanoparticles (Huang et al., 2015). Increasingly we are using iPS cells reprogramed from patients to model ocular disease and investigate molecular mechanisms (Yvon et al, 2015; Forest et al., 2015; Schwarz et al., 2015). The Coffey, Soh and Thomson Labs collaborated to use microfluidic chips to identify aptamers (RNA molecules) that can bind to RPE and improve function (Cho et al., 2015).

II. *Diabetic retinopathy.*

Diabetic retinopathy (DR) is the leading cause of vision loss and blindness in the working-age population, affecting 75% of diabetic patients within 15 years of diagnosis (Cheung, Mitchell et al. 2010). Unfortunately, patients with DR are faced with limited effective treatment options; current DR therapeutic options depend on highly invasive surgery performed only at advanced stages of the disease and are ineffective in restoring visual acuity. The earliest and most specific sign of DR is a reduction in the number of pericytes in the retinal capillary. Pericytes are contractile cells that support vascular function throughout the body. Pericyte loss leads to vascular aberration and impairment of the inner blood-retina barrier resulting in macular edema, the leading cause of vision loss in diabetic patients.

As per our previous report, we continue to explore transcriptome profiles of retinal pericytes using single-cell technology and deriving pericytes from human embryonic stem cells.

In the past year, we also began exploring the best available animal model to study diabetic retinopathy. There were many factors to consider in choosing the animal disease

model that best reflects the human condition. The long duration of diabetes in human patients (approximately 10 to 20 years after diagnosis) was an important criterion in choosing the appropriate model to study. Models that reflect the longevity of the disease are limited, and so we chose to work with Arvicanthis Nilothicus, also known as the African grass rat or the Nile rat, as these rats can live with diabetes for one to two years without insulin treatment or other medical intervention.

Nile rats have a propensity to develop type 2 diabetes in captivity when fed regular laboratory rodent pellets without further genetic manipulation or chemical intervention however, a high fiber diet protects Nile rats against developing diabetes. This susceptibility to develop type 2 diabetes in captivity when fed rodent pellets is not unique to this species but rather is shared with at least one other species, the Psammomys Obesus. In summary, the development of type 2 diabetes in Nile rats has a polygenic component and a dietary component.

To the best of our knowledge, there is only one publication that looks at diabetic retinopathy in Nile rats. Noda et al. reported retinal vascular abnormalities consistent with known features of diabetic retinopathy (Noda, Nakao et al. 2014). Building on previous knowledge, we intend to investigate the progression of diabetic retinopathy in Nile rats using fundus fluorescein angiography and immunocytochemistry. Fundus fluorescein angiography allows us to track the progression of diabetic retinopathy in vivo by visualizing the retinal vascular network while immunocytochemistry allows us to pinpoint the involvement of distinct retinal cell types. These ground-breaking studies to establish this novel animal model for diabetic retinopathy will continue in the coming year.

III. Retinitis Pigmentosa (RP)

Steve Fisher's group has been instrumental in obtaining preclinical data in support of a cellular therapy for RP being developed at UC Irvine. Recently, the FDA cleared their IND application, and 4 patients were treated by injecting retinal progenitor cells into the eye. (see UCSB press release).

IV. Bioengineering real-time biosensors and feedback- control.

Homeostasis relies on biological control circuits that have evolved to regulate physiological processes in a closed-loop manner, resulting in the remarkable stability of human physiology even under extreme environmental conditions. Fundamentally, this regulation is achieved by controlling concentrations of biomolecules throughout the body. Technologies capable of mimicking this molecular control *in vivo* could enable precise, personalized treatment for a wide variety of medical conditions, especially for regenerative medicine. However, the transformative clinical potential of such closed-loop systems has not yet been

realized, because the vast majority of biomolecules cannot be measured in the body in real-time. The single exception is the "artificial pancreas," which regulates blood glucose levels in type I diabetes patients through continuous monitoring of blood glucose and feedback-controlled insulin infusion.

In the past year, the Soh lab developed a "universal" platform that generalizes the notion of closed-loop concentration control to a wide range of biomolecules in the body (See figure below). Using real-time biosensors and feedback control, our system can continuously maintain virtually any desired concentration profile in the body as a function of time, with minute-scale temporal response across different individuals and species. As an example, we directly controlled the circulating levels of the chemotherapy drug doxorubicin in live rabbits and rats, achieving optimal dosing in a personalized and adaptive manner.

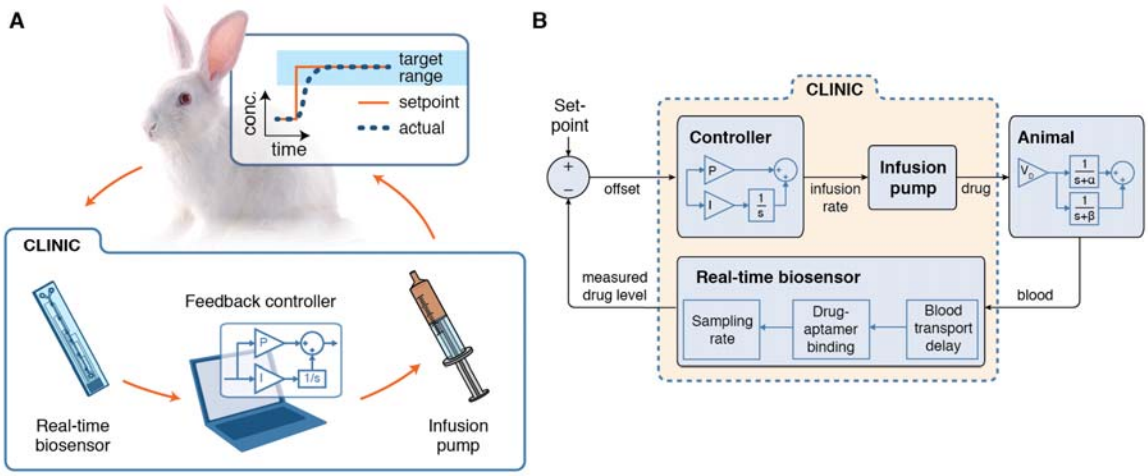


Fig. 1. Closed-loop control of *in vivo* drug levels with CLINIC. (**A**) As a programmable infusion pump injects drug into the animal, the bloodstream is sampled continuously by our real-time biosensor. The resulting electrochemical measurements of drug concentration are analyzed by our control algorithm, which calculates the infusion rate needed to maintain the desired circulating drug set-point at any given time, and automatically adjusts the infusion rate accordingly. (**B**) The feedback loop—comprising the controller, animal pharmacokinetics and real-time biosensor, along with systemic time delays and sampling rates—can be modeled as a linear time-invariant system. Simulations based on this model enable *in silico* controller tuning and optimization for control *in vivo*.

IV. Education and Outreach

An important activity within the Center is education and outreach to the public. To that end, we have developed two websites that describes our research: www.stemcell.ucsb.edu and http://garland.stemcell.ucsb.edu. We have also continued a series of seminars where outside experts can come and interact with researchers at UCSB (see website). Our labs were opened to

interns from high schools and undergraduate institutions over the summer as part of the CIRM Research Mentorship Program and the Institute for Creative Biotechnology Program (https://www.youtube.com/watch?v=QSeVhUls95k). In addition, Center faculty members traveled to outside universities and presented our research.

Two new courses in stem cell biology and ethics have been instituted thanks to funding from the CIRM Training Grants. Additional literature clubs, research roundtables and research symposia also feature stem cell research on campus.

Over the past year, the Center Faculty was also engaged in outreach via seminars to general audiences at various public venues. These included: Cate School Convocation, Carpintaria, CA (again this year); Foundation Fighting Blindness Symposium on Cell and Gene Therapy (Denver, CO); Foundation Fighting Blindness Fundraiser (Goleta, CA); Usher's Syndrome Family Conference (New Orleans, LA); Foundation Fighting Blindness Visions Meeting (Baltimore, MD); UC Santa Barbara Orientation (Santa Barbara, CA); Ground Breaking Research and Innovative Technology Talks, UC Santa Barbara (Santa Barbara, CA); Freshman Seminars, UC Santa Barbara (Santa Barbara, CA); Wilcox Family Chair in Biomedicine Investiture, UC Santa Barbara (Santa Barbara, CA); Lectures for 10th and 11th Grade Biology and Health Classes, San Marcos High School, (Santa Barbara, CA); Stem Cell Awareness Day, Camarillo High School (Camarillo, CA); Tech Savvy Event, GET WISE (Santa Barbara, CA); Stem Cell Awareness Day, Santa Barbara High School (Santa Barbara, CA); Family Ultimate Science Exploration Program (Santa Barbara, CA); Center for Science and Engineering Partnerships (Los Angeles, CA); California State University San Marcos (San Marcos, CA).

In addition, Dr. Soh's work was featured on PBS (http://www.pbs.org/wgbh/nova/next/tech/reengineering-pcs-phones-cheap-disease-detectors); and our publications have received attention in the press (see news items http://garland.stemcell.ucsb.edu).

Center Facilities and Recent Faculty Recruitment:

- The MCDB Department hired Dr. Denise Montell, a leading stem cell biologist from Johns Hopkins University, who will occupy space in the new center.
- Dr. Adele Doyle, an expert on human embryonic stem cell differentiation, joined the Stem Cell Center faculty in July 2013.
- Core Facility – Funded by CIRM – ($800,000) The shared core facility – the Laboratory for Stem Cell Biology and Engineering, which has been operating since 2005.
- Center Laboratories: New Construction funded by CIRM and UCSB ($6.4M)– Renovation of 10,000 asf in Bio-2 for new stem cell research labs and facilities.

MICROSCOPY FACILITY

The NRI-MCDB Microscopy Facility, founded in 1990, is jointly maintained by the Neuroscience Research Institute and the Department of Molecular, Cellular and Developmental Biology at the University of California, Santa Barbara. The Facility's mission is to promote and facilitate research necessitating microscopy. To achieve this mission the Facility houses state-of the art instruments, supports expert full-time support staff, hosts outreach events and provides individual and workshop based training in microscopy.

The Facility is the primary light microscopy core on campus supporting researchers in more than 13 department/units including the Life Sciences, Physics, Chemistry, Materials and Engineering. The Facility has 80 registered Principal Investigators. In the past year, the Facility supported 145 users and more than 2500 reservations. The Facility users should acknowledge the Facility in their publications and report new publications supported by the Facility. A list of the research publications that have been reported to the Facility in 2014-2015 conclude this report.

This centrally located Facility is based within the Neuroscience Research Institute, in the Biological Sciences II Building. Presently, the Facility maintains multiple sophisticated instruments including a JEOL JEM-1230 transmission electron microscope, a new Olympus Fluoview 1000 Spectral Confocal Laser Scanning Microscope, an Olympus Fluoview 1000 Multiphoton Laser Scanning Microscope and an Olympus Spinning Disk Confocal. The Facility also hosts five Olympus compound microscopes configured with transmitted and fluorescent light-paths as well as a stereomicroscope configured with transmitted and reflected light. These microscopes are further equipped with research grade digital cameras and a high-end computer workstations for image acquisition, processing and analyses. The confocal and multiphoton microscopes are equipped with time-lapse software controls for automated long-term imaging and the Fluoview 1000 systems are equipped with a motorized X, Y stages for automated sampling of multiple locations. It also provides an Imaris 3D image processing and analysis workstation for the Facility users.

It should be noted that the conventional microscopes, computers, and cameras in the Facility are aging. Consideration to whether maintaining 5 conventional microscope workstations is a good use of resources. Given the advances in automated imaging, a single automated microscope would be more useful for research purposes. The mechanism to maintain the conventional microscope workstations for teaching purposes is unclear.

The Facility Director, Dr. Mary Raven is an experienced microscopist, scientist and manager. Dr. Raven is assisted by Dr. Geoff Lewis who oversees transmission electron microscopy and assists with confocal training as needed. Both Drs. Raven and Lewis have published numerous papers

employing conventional, transmission electron microscopy and confocal microscopy. Drs. Raven and Lewis provide training on a daily bases and regularly meet with individuals to provide advice and to address additional microscopy needs.

Director taught a graduate seminar MCDB 294MR and an undergraduate seminar on microscopy MCDB 194MR during the 2014-2015 academic year. The courses were fully enrolled and supported graduate students from EEMB, MCDB, BME, ChemE and ECE while the undergraduate seminar supported primarily MCDB undergraduate researchers. Dr. Raven also provided course support for MCDB 103L, MCDB 126BL and MCDB 133L.

Advanced Microscopy Workshop 2015

The Facility offers an advanced microscopy workshop each year in which students are trained in a variety of modern light microscopy principles and techniques. The most recent workshop was offered in Jan 2015 and focused on advanced microscopy and imaging live samples. The workshops are designed to advance graduate and post-doctoral development and generally more than half the participants are graduate or post-doctoral researchers. In the most recent workshop, 10 participants enrolled. Four of the workshop attendees were international visitors, three professors from Saudi Arabia and one graduate student from Sweden. Four other attendees traveled from national institutions and two participants were graduate students from the UCSB campus.

Funding

Olympus Corp of America: Advanced Microscopy Live 2015

The award paid the registration fees for four participants in the workshop. Scholarships were offered broadly and distributed to researchers from Miami University, Children's Hospital, University of MN and UCSC. One graduate student from the UCSB program was allowed to attend courtesy of the NRI-MCDB.

Gift from Applied Nanosolutions

In 2015, Applied Nanosolutions donated $2,000 to support outreach activities.

UC Work Group for Adaptive Optics in Biological Imaging

The UC Work Group for Adaptive Optics in Biological Imaging headed by Joel Kubby at UCSC was
selected for support by Multicampus Research Program. Dr. Mary Raven is serving as the UCSB campus lead.

Public Service and K-12 Outreach

The NRI-MCDB Microscopy Facility participates in campus-wide events as well as undergraduate and graduate student tours and orientations. In 2014-2015 the Facility participated in Parent and Family Weekend and the All Gaucho Reunion. The Facility also hosted tours for the INSET students from the Center for Science and Engineering Partnerships Summer Program, Brooks Institute scientific photography students, Chemistry 125L and BioEngineering 220B students.

Facility Supported Publications 2015

2015

Copp SM, Schultz DE, Swasey S, Gwinn EG. 2015. Atomically Precise Arrays of Fluorescent Silver Clusters: A Modular Approach for Metal Cluster Photonics on DNA Nanostructures. ACS nano.

M. Ramirez D, Oakley TH. 2015. Eye-independent, light-activated chromatophore expansion (LACE) and expression of phototransduction genes in the skin of Octopus bimaculoides. The Journal of Experimental Biology. 218:1513-1520.

Huang X, Hu Q, Braun GB, Pallaoro A, Morales DP, Zasadzinski J, Clegg DO, Reich NO. 2015. Light-activated RNA interference in human embryonic stem cells. Biomaterials.

Yan H, Catania C, Bazan GC. 2015. Membrane-Intercalating Conjugated Oligoelectrolytes: Impact on Bioelectrochemical Systems. Advanced Materials.

Seo S, Das S, Zalicki P, Mirshafian R, Eisenbach CD, Israelachvili JN, Waite JHerbert, B Ahn K. 2015. Micro-phase behavior and enhanced wet-cohesion of synthetic copolyampholytes inspired by a mussel foot protein. Journal of the American Chemical Society.

Taketa DA, Nydam ML, Langenbacher AD, Rodriguez D, Sanders E, De Tomaso AW. 2015. Molecular evolution and in vitro characterization of Botryllus histocompatibility factor.. Immunogenetics.

McNair HM, Brzezinski MA, Krause JW. 2015. Quantifying diatom silicification with the fluorescent dye, PDMPO. Limnology and Oceanography: Methods.

Levine ZA, Larini L, LaPointe NE, Feinstein SC, Shea J-E. 2015. Regulation and aggregation of intrinsically disordered peptides. Proceedings of the National Academy of Sciences.

DeMartini DG, Izumi M, Weaver AT, Pandolfi E, Morse DE. 2015. Structures, Organization and Function of Reflectin Proteins in Dynamically Tunable Reflective Cells.. Journal of Biological Chemistry. :jbc–M115.

Bailey JK, Fields AT, Cheng K, Lee A, Wagenaar E, Lagrois R, Schmidt B, Xia B, Ma D. 2015. WD

Repeat-Containing Protein 5 (WDR5) Localizes to the Midbody and Regulates Abscission. Journal of Biological Chemistry. :jbc–M114.

Di Maio A, Setar L, Tiozzo S, De Tomaso AW. 2015. Wnt affects symmetry and morphogenesis during post-embryonic development in colonial chordates. EvoDevo. 6:17.

2014

Chou C-S, Moore TI, Nie Q, Yi T-M. 2014. Alternative cell polarity behaviours arise from changes in G-protein spatial dynamics.

Rodriguez D, Sanders EN, Farell K, Langenbacher AD, Taketa DA, Hopper MRae, Kennedy M, Gracey A, De Tomaso AW. 2014. Analysis of the basal chordate Botryllus schlosseri reveals a set of genes associated with fertility. BMC genomics. 15:1183.

Barua S, Mitragotri S. 2014. Challenges associated with penetration of nanoparticles across cell and tissue barriers: A review of current status and future prospects. Nano Today.

Pang H-B, Braun GB, Friman T, Aza-Blanc P, Ruidiaz ME, Sugahara KN, Teesalu T, Ruoslahti E. 2014. An endocytosis pathway initiated through neuropilin-1 and regulated by nutrient availability. Nature communications. 5

Braun GB, Friman T, Pang H-B, Pallaoro A, de Mendoza THurtado, Willmore A-MA, Kotamraju VRamana, Mann AP, She Z-G, Sugahara KN et al.. 2014. Etchable plasmonic nanoparticle probes to image and quantify cellular internalization. Nature materials.

Rodriguez D, Langenbacher AD, Sanders E, De Tomaso A. 2014. Expression of vitellogenin and transforming growth factor β genes in follicle cells of the developing Botryllus schlosseri oocyte. Molecular reproduction and development.

Do TD, LaPointe NE, Sangwan S, Teplow DB, Feinstein SC, Sawaya MR, Eisenberg D, Bowers MThomas. 2014. Factors that Drive Peptide Assembly from Native to Amyloid Structures: Experimental and Theoretical Analysis of [Leu-5]-Enkephalin Mutants. The Journal of Physical Chemistry B.

Sivakumar K, Wang VBochuan, Chen X, Bazan GC, Kjelleberg S, Loo SChye Joach, Cao B. 2014. Membrane permeabilization underlies the enhancement of extracellular bioactivity in Shewanella oneidensis by a membrane-spanning conjugated oligoelectrolyte. Applied microbiology and biotechnology. 98:9021–9031.

Cook BM, Benbow SJ, Wozniak KM, Slusher BS, Littlefield BA, Wilson L, Feinstein SC, Jordan MAnn. 2014. Microtubule-targeting agents induce differential myelinated axon degeneration in a mouse model of peripheral neuropathy. Cancer Research. 74:5503–5503.

Huang X, Pallaoro A, Braun GB, Morales DP, Ogunyankin MO, Zasadzinski J, Reich NO. 2014. Modular plasmonic nanocarriers for efficient and targeted delivery of

cancer-therapeutic siRNA. Nano letters. 14:2046–2051.

Huang X, Pallaoro A, Braun G, Morales D, Zasadzinski J, Reich N. 2014. Modular plasmonic nanocarriers for efficient delivery of siRNA with spatial and temporal control (749.2). The FASEB Journal. 28:749–2.

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Wei W, Tan Y, Rodriguez NRMartinez, Yu J, Israelachvili JN, J Waite H. 2014. A mussel-derived one component adhesive coacervate. Acta biomaterialia. 10:1663–1670.

Silva BFB, Majzoub RN, Chan C-L, Li Y, Olsson U, Safinya CR. 2014. PEGylated cationic liposome–DNA complexation in brine is pathway-dependent. Biochimica et Biophysica Acta (BBA)-Biomembranes. 1838:398–412.

Anselmo AC, Modery-Pawlowski CLynn, Menegatti S, Kumar S, Vogus DR, Tian LL, Chen M, Squires TM, Gupta ASen, Mitragotri S. 2014. Platelet-like Nanoparticles (PLNs): Engineering Shape, Flexibility and Surface Chemistry of Nanocarriers to Target Vascular Injuries. ACS nano.

Hu Q, Chen R, Teesalu T, Ruoslahti E, Clegg DO. 2014. Reprogramming Human Retinal Pigmented Epithelial Cells to Neurons Using Recombinant Proteins. Stem cells translational medicine. 3:1526–1534.

Morales D, Braun G, Pallaoro A, Chen R, Huang X, Zasadzinski J, Reich N. 2014. Spatiotemporally controlled delivery of biomolecules (1053.5). The FASEB Journal. 28:1053–5.

Thomas AW, Henson ZB, Du J, Vandenberg CA, Bazan GC. 2014. Synthesis, Characterization, and Biological Affinity of a Near-Infrared-Emitting Conjugated Oligoelectrolyte. Journal of the American Chemical Society. 136:3736–3739.

Chen M, Kumar S, Anselmo AC, Gupta V, Slee DH, Muraski JA, Mitragotri S. 2014. Topical delivery of Cyclosporine A into the skin using SPACE-peptide. Journal of Controlled Release.

Chen M, Gupta V, Anselmo AC, Muraski JA, Mitragotri S. 2014. Topical delivery of hyaluronic acid into skin using SPACE-peptide carriers. Journal of Controlled Release. 173:67–74.

Chen M, Zakrewsky M, Gupta V, Anselmo AC, Slee DH, Muraski JA, Mitragotri S. 2014. Topical delivery of siRNA into skin using SPACE-peptide carriers. Journal of Controlled Release. 179:33–41.

Li Y, Miller HP, Wilson L, Raviv U, Choi MChul, Safinya CR. 2014. Transformation of taxol-stabilized microtubules into inverted tubulin tubules triggered by a tubulin

conformation switch.

Ojeda-Lopez MA, Needleman DJ, Song C, Ginsburg A, Kohl PA, Li Y, Miller HP, Wilson L, Raviv U, Choi MChul et al.. 2014. Transformation of taxol-stabilized microtubules into inverted tubulin tubules triggered by a tubulin conformation switch. Nature materials.

Majzoub RN, Chan C-L, Ewert KK, Silva BFB, Liang KS, Jacovetty EL, Carragher B, Potter CS, Safinya CR. 2014. Uptake and transfection efficiency of PEGylated cationic liposome–DNA complexes with and without RGD-tagging. Biomaterials. 35:4996–5005.

Braden BP, Taketa DA, Pierce JD, Kassmer S, Lewis DD, De Tomaso AW. 2014. Vascular Regeneration in a Basal Chordate Is Due to the Presence of Immobile, Bi-Functional Cells. PloS one. 9:e95460.

Langenbacher AD, Rodriguez D, Maio A, Tomaso AW. 2014. Whole-mount fluorescent in situ hybridization staining of the colonial tunicate Botryllus schlosseri. genesis.

UNIVERSITY OF SOUTHERN CALIFORNIA
Dennis Clegg 8/1/2014-7/31/2015 $424,815
Phase 1 Safety Assessment of CPCB-RPE1, hESC-derived RPE Cell Coated Parylene Membrane Implants, in Patients with Advanced Dry Age Related Macular Degeneration

UCSB will develop a method for cryopreservation of CPCB-RPE1 – the final product being developed for treatment of age-related macular degeneration. The product consists of a mature monolayer of hESC-RPE grown on a vitronectin-coated parylene C membrane with ultrathin areas. Modern methods of cryopreservation and vitrification will be carried out, testing variety of parameters to optimize the method for maximal cell survival and function after thaw. We will explore various modifications of cell maturation protocol, cryopreservant, cryopreservation and vitrification methodology, transport, and protocols for thawing and recovery. Cells will be assayed after various times to determine shelf life. Assays of cells after thaw will include qPCR, ICC, ELISA measurement of growth factor secretion, and phagocytosis of photoreceptor outer segments. Cryopreseved CPCB-RPE1 will then tested in animal models of RPE dystrophy at USC to assess function in vivo.

UNIVERSITY OF WISCONSIN
Dennis Clegg 10/11/13-9/30/16 $255,000
Co-culture and analysis of neural retina and RPE derived from GMP super donor hiPSC lines
Generation of RPE cells from super donor iPS lines.

Development and analysis of planar scaffolds for iPS-RPE.
Development and analysis of PEG hydrogels for encapsulation of iPS-neural retinal cells.
Characterization of cell constructs in vitro and in vivo.

NRI RESEARCH FUNDS
Adele Doyle

NRI Start up funds: The Doyle group studies two interfaces linking physical forces with intracellular decision making circuits: the developmental of electrochemical signaling in differentiating neurons and the acquisition of mechanosensitivity in the vascular system. Initial efforts in the lab are executed via collaborations with the Theogarajan (shared graduate student: Sarah Grundeen), Kosik, Hansma, and Campas (shared graduate student: Adam Lucio) laboratories. Standalone efforts by students and visiting scientists in the Doyle group are using developing novel computational and high throughput data analysis methods to identify and simulate the molecular regulatory circuits necessary for electrical and mechanical force sensing in cells. Computational predictions will be tested in vitro as the projects progress.

CIRM CREATIVITY MENTOR AWARD
Adele Doyle

During Summer, 2015, four CIRM interns participated in research in the Doyle Group. Their efforts collectively: identified a suitable protocol for freezing primary neurons, a notoriously finicky cell type for cryopreservation; identified molecules participating in a genetic regulatory switch between GABA and Glutamatergic neuron specification; and enhanced an existing bioinformatics pipeline in the lab enabling rapid Gene Ontology-based data analysis to include human and zebrafish data. These funds also provided computer workstations in the lab that are currently being used to further these research projects.

CUREPSP

Stuart Feinstein	3/2/13-3/30/2015	$75,000
Tau Dimerization: A Mechanism of Tau Function and Dysfunction?		509-13

The protein tau is critical for the maintenance of the nervous system. It is also a key contributor to many neurodegenerative diseases, including PSP and CBD. While we understand many functions performed by tau, our understanding of how it actually performs these functions remains primitive. One half of tau, (the “C-terminal half”), can associate with microtubules and regulate their essential behaviors. However, the ability this region of tau to perform these critical functions drops dramatically without the other half of the protein (the “N-terminal half”), which lacks the ability to bind and regulate microtubules. Unfortunately, the mechanism(s) by which the N-terminal half exerts its potent influence(s) upon the C-terminal region remain completely enigmatic. The relevance of normal tau action to pathological tau action in PSP and CBD is that a fragment of tau, derived from the N-terminal half of the protein, has been shown to accumulate in PSP and CBD affected brains and to be neurotoxic, but the mechanism of its neurotoxicity is unknown.

However, we and our collaborators have recently reported biochemical and biophysical evidence indicating that the N-terminal region of tau promotes dimerization and that this dimerization is necessary for normal tau function. This leads to the hypothesis that tau mediated neuronal cell death and dementia in PSP and CBD is mediated by N-terminal tau fragment mediated inhibition of normal tau action, leading to a “loss-of-function” effect resulting in neuronal cell death and dementia. Our work supporting this dimerization hypothesis is based presently solely on in vitro data. The goal of this proposal is to test the hypothesis that tau dimerization mediated by the N-terminal region occurs in neurons and is required for tau action in neurons. By better understanding normal tau action, we will gain completely novel insights into pathological tau action in PSP and CBD.

AMERICAN SOCIETY FOR CELL BIOLOGY
Stuart Feinstein 2/1/2015-6/30/2015 $1,500
Chemotherapy Induced Peripheral Neuropathy Meeting

EISAI RESEARCH INSTITUTE
Stuart Feinstein 11/1/2014-10/31/2016 $630,772
Recovery from Chemotherapy-Induced Peripheral Neuropathy: Focus upon Neuronal Cell Biology and Biochemistry

The goal of the work described here is to acquire a detailed molecular characterization of key components of the recovery process from microtubule-targeted agent (MTA) induced CIPN. More specifically, we propose:

(i) to characterize the recovery from MTA-induced CIPN using molecular and morphological markers of neuronal cell death (i.e., apoptosis), inflammation and peripheral nerve regeneration;

(ii) to characterize the cellular recovery from MTA-induced CIPN with respect to microtubule biochemistry in neurons.

This work will integrate with work described in the accompanying proposal from Dr. Slusher and her colleagues at Johns Hopkins University. Together, we will develop an inter-disciplinary understanding of the differential abilities of animals to recover from MTA-induced CIPN, expanding upon and complementing our ongoing work examining the differential effects of different MTAs to induce CIPN.

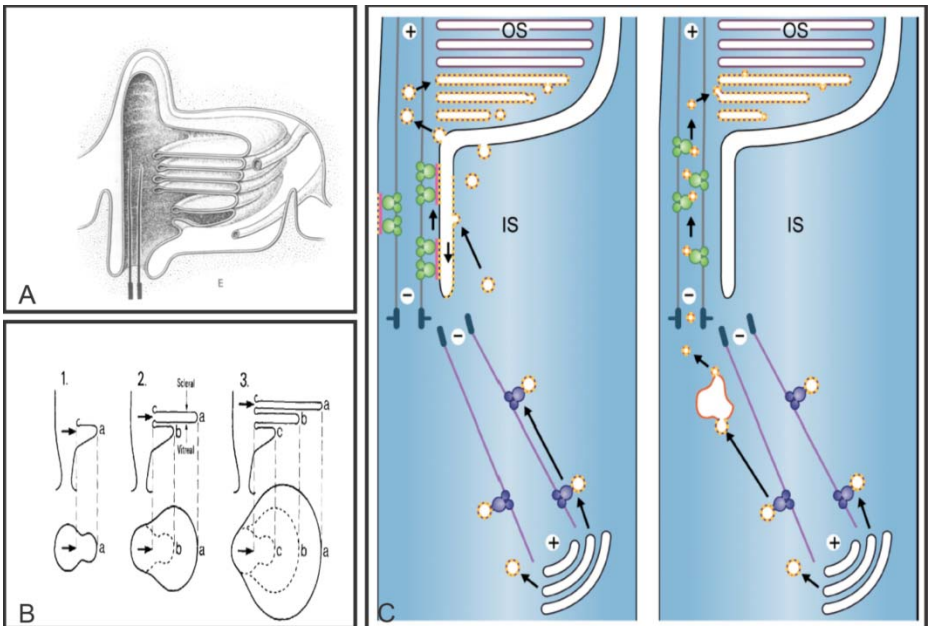
EISAI RESEARCH INSTITUTE
Stuart Feinstein 2/1/2015-6/30/2015 $3,700
Chemotheraphy-Induced Peripheral Neuropathy Symposium
Our goal through this symposium is to foster dialog between basic and clinical researchers within the field of CIPN so that the understanding of mechanistic causes can ultimately translate to CIPN treatment and management in patients. Reciprocally, the information gained in the clinic will benefit basic research by informing the prioritization of endeavors. Therefore the target audience includes basic science researchers as well as clinicians and medical professionals.

NIH National Eye Institute

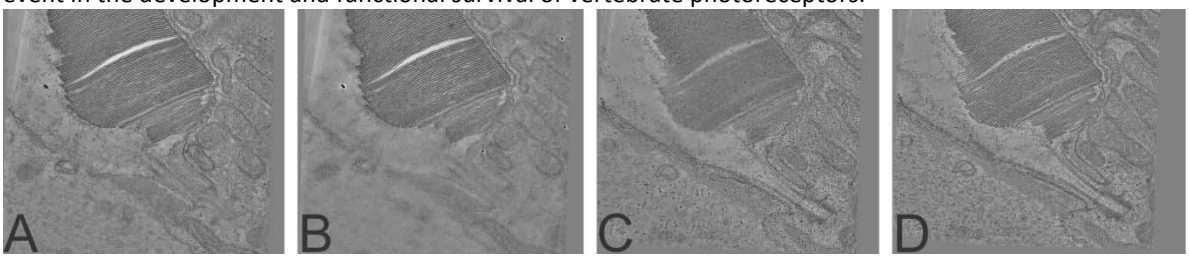
Steven Fisher 4/1/2015-3/31/2016 $384,375

Summary: NIH grant 1 R01-EY024667-01 “Photoreceptor Disk Membrane Morphogenesis”

The research will provide a fundamental mechanistic understanding of the way disk membranes of the photoreceptor outer segment are formed. It will apply novel 3-D image analyses to resolve nano-level structures of nascent disk membranes, and thus take the field of photoreceptor cell biology a major step forward. The research will include studies of mouse models retinal degeneration, specifically retinitis pigmentosa, cone-rod dystrophy, and macular degeneration, and thus will provide a basis for understanding the pathogenesis of these forms of blindness.



Drawings showing the proposed models of disk morphogenesis in vertebrate rod photoreceptors. The aim of this project is to determine at subcellular levels of resolution and in 3-dimensions the best-fit model for this critical event in the development and functional survival of vertebrate photoreceptors.



A figure showing data being collected for this project in collaboration with Dr. David Williams (co-investigator) at UCLA. The four panels show representative electron tomography images through a single rod photoreceptor outer segment. The images are from a “tilt series” of images taken from two sections, each 350 nm thick and then stitched together to form one continuous final tomogram. Each image (z-slice) in the tomogram is about 2.7 nm thick. The two dark parallel lines to the bottom right of C and D are the basal body that gives rise to the ciliary stalk that forms the light sensitive outer segment, the stack of parallel structures in the center of each panel. This data is used to create high-resolution 3D models of the outer segments at the critical point of new disk formation.

INTERNATIONAL RETINAL RESEARCH FOUNDATION, INC.

Steven Fisher 10/7/11-6/1/2014 $10,000

Creating Brainbow Astrocytes, A New Tool for Studying Retinal and Optic Nerve Astrocytes

The goal of this project was to create a transgenic mouse randomly expressing a set of 4 fluorescent protein genes in retinal astrocytes. Cottage Hospital's research program has on several occasions provided funds that lead to preliminary data used to submit a larger grant to a federal agency. To date, our lab has completed the design and construction of the brainbow plasmid, a critical part of the project. Using the funds provided by the Santa Barbara Cottage Hospital Research Program, we were able to clone 4 fluorescent proteins into a vector containing the human full-length glial fibrillary acidic protein promoter (GFAP). Subsequently this promoter was sequenced to verify that our design and engineered plasmid was correctly synthesized. Additionally, we were able to test this plasmid on cultured U-87 human glioblastoma cells, immortal mouse retinal astrocytes, and 293T kidney cells for cell-type specificity as well as transfection efficacy. We shipped our completed vector to UC Irvine's transgenic mouse facility in June for final purification and DNA microinjection on July 3rd, 2012. This mouse will allow us to view retinal astrocytes stained with a nearly 90 different fluorescent hues allowing us to study the attributes of individual cells and their reaction to injury.

SANTA BARBARA COTTAGE HOSPITAL

Claudia Gottstein 5/21/13-5/20/2015 $15,000

Discovery of specific antibodies against breast cancer stem cells

Our over arching goal is to develop targeted drugs against breast cancer, which improve outcome and prevent recurrence. There is increasing evidence that breast cancer stem cells (BCSC) play a critical role in tumor initiation, metastasis and recurrence, but they are relatively resistant to conventional therapies. A combination treatment of Antibody-drug-conjugates (ADCs) against BCSC with conventional therapy might significantly improve treatment outcome. However, there are currently no suitable antibodies available that could be incorporated into an anti-cancer stem cell ADC. We hypothesize that a new antibody phage display library format will require 1,000-10,000 fold less cells for successful selection of antibodies, compared with existing technology. This is based on lower library size, higher diversity and higher antibody affinity of the new design. If true, this would allow for the first time selection of antibodies against primary breast cancer stem cells from such libraries.

NIH NEUROLOGICAL DISORDERS & STROKE

Scott Grafton 9/1/13-8/31/15 $1,089,219

Spatial and Temporal Scales of Motor Sequence Learning

This project is a collaborative effort by a team of five motor systems laboratories seeking to probe the mechanisms that underlie the brain's capacity for learning a new motor skill. The common thread for all groups is to focus on changes that occur within motor circuits of the brain as a new sequential skill is acquired. The work is central to the problem of understanding the mechanisms where practice leads to reorganization of the human motor system in the face

of aging, neurodegeneration, stroke or brain injury. Understanding these mechanisms has an impact on the design of therapies directed at preserving function, developing compensatory movements and ultimately, developing novel motor capacity.

NATIONAL SCIENCE FOUNDATION
Michael Gurven 9/1/12-8/31/15 $22,746
Doctoral Dissertation Improvement: Maternal reproductive trade-offs and the duration of exclusive breastfeeding in a natural fertility population

Exclusive breastfeeding (EBF) for 6 months may significantly reduce risk of infant morbidity in non-industrialized populations, but is relatively rare. Early provisioning with non-milk solids and liquids may benefit mothers by reducing the time constraints and energetic costs of nursing, which in turn may lead to sustained positive energy balance and earlier resumption of menstruation. However, as early provisioning may negatively impact infant health, early provisioning reflects a trade-off in maternal reproductive interests. The proposed study will investigate how infant condition, maternal condition, number of existing young dependents, support from alloparents, perceptions of lactational performance, and beliefs about early feeding combine to influence EBF duration in a high-fertility population—the Tsimane of Bolivia. The study will examine if early non-milk provisioning by Tsimane mothers results in sustained positive energy balance and earlier resumption of menstruation, possible contributing to high fertility rates.

UC RIVERSIDE
Lincoln Johnson 7/1/2014-6/30/2016 $45,000
Development of low-molecular mass biomarkers of complement activation and testing in a macular degeneration model

C3d-binding compounds will be tested for their ability to mark sites of complement activation in Dr. Johnson's RPE-based *in vitro* system that mimics several aspects of AMD pathology including the formation of drusenoid basal deposits and the activation of complement by a subpopulation of these sub-RPE deposits on exposure to human serum as a complement source [1]. Complement activation is evidenced by deposit associated deposition of C5b-9 terminal complement complexes, monitored immunohistochemically. We have documented similar immunohistochemical evidence for complement activation associated with the RPE/choroid complex in AMD donor tissues [2]. These analytical approaches are routine in Dr. Johnson's laboratory. Initial studies will focus on the Mol 22, Mol 35 and Mol 50 (Fig 3), C3d-binding compounds with intrinsic fluorescence properties. Sections from RPE cultures exposed to human serum as previously described [1], as well as sections from RPE/choroid tissue from human donor eyes will be exposed to varying concentrations of the compounds over varying time periods. Binding patterns will be assessed by confocal microscopy; the excitation/emission properties of the compounds are compatible with our available confocal laser systems. To assess specificity, observed binding patterns will be compared with those for anti-C3d and anti-C5b9 antibodies in double-label assays. Additional specificity studies will assess the ability of anti-C3d antibodies to block the

binding of C3d-binding compounds and *vice versa*. Compounds with optimized C3dbinding and fluorescence properties developed during the course of the studies will be similarly analyzed. Candidate compounds for future testing in animal models will be selected based on their combined properties of high C3d affinity, robust fluorescence response and binding specificity in the RPE *in vitro* model and human AMD tissues.

EISAI COMPANIES (JAPAN)
Mary Ann Jordan 1/24/14-1/23/16 $601,767
Mechanisms of microtubule-targeted drug-induced neuropathy

Neuropathy induced by the clinical treatment of cancer with microtubule-targeted drugs such as taxanes, ixabepilone, and vinca alkaloids is a major and highly debilitating dose-limiting toxicity. The novel halichondrin, eribulin, shows significant clinical efficacy along with a reduced incidence of peripheral neuropathy as compared with that produced by other microtubule-targeted drugs. The molecular and cellular mechanism(s) underlying the reduced incidence of neuropathy are poorly understood. Neuropathy typically develops gradually and is cumulative over the course of drug treatment. Among the neuronal effects that accompany peripheral neuropathy are changes to axonal structure involving microtubule organization, as well as impaired mitochondrial activity. These effects can lead to neuronal oversensitization, axonopathy, and eventually neuronal cell death.

For the past 2 years, we have been collaborating with Dr. Barbara Slusher's group at Johns Hopkins University to examine cellular and molecular effects of eribulin, vincristine, paclitaxel and ixabepilone that occur coincident with peripheral neuropathy in mouse models. These experiments involved examining the sciatic nerves of mice treated for two weeks with the maximum tolerated dose of each drug. Using immunostaining/light microscopic strategies, the most important results of this work are (i) the discoveries that nerves from paclitaxel and eribulin-treated mice exhibit significant decreases in axon density and a marked disruption of normal myelin morphology, (ii) the discoveries that eribulin-treated mice exhibited increased expression of axonal tubulin, acetylated tubulin, tyrosinated tubulin and the microtubule (+) end binding protein EB1, and finally, (iii) the discovery that microtubule-based transport of mitochondria in neuronal cells is inhibited more strongly by paclitaxel, ixabepilone and vincristine than by eribulin, at their relevant chemotherapeutic concentrations.

Here, we propose to expand upon our initial molecular and cellular analyses of MT-targeted drug effects on peripheral neuropathy, driving toward more mechanistic investigations and continuing our collaboration with Dr. Slusher's lab at Johns Hopkins. other microtubule-targeted drugs. The molecular and cellular mechanism(s) underlying the reduced incidence of neuropathy are poorly understood. Neuropathy typically develops gradually and is cumulative over the course of drug treatment. Among the neuronal effects that accompany peripheral neuropathy are changes to axonal structure involving microtubule organization, as well as impaired mitochondrial activity. These effects can lead to neuronal oversensitization, axonopathy, and eventually neuronal cell death.

SANOFI-AVENTIS

Mary Ann Jordan 9/1/12-8/31/14 $969,158

Mechanism of Action of Cabazitaxel

Cabazitaxel is a semisynthetic dimethyloxy derivative of the modified taxane known as docetaxel. Cabazitaxel has undergone clinical development due to its poor affinity for P-gp, enabling efficacy against docetaxel-refractory prostate cancer. It is also superior to paclitaxel and docetaxel in its ability to cross the blood-brain barrier in animal models. It was approved by the U.S. Food and Drug Administration in 2010 as a new option for patients with prostate cancer, increasing the overall median survival benefit by 2.4 months for men with docetaxel-resistant metastatic castration resistant prostate cancer (CRPC). Its adverse side effects include neutropenia, diarrhea, and, rarely, neuropathy (Paller, Antonarakis, 2011, Drug Design, Development and Therapy 5:117-124). Since the drug is a taxane, it is believed to promote assembly of tubulin into microtubules and is hypothesized also to suppress microtubule dynamics, to arrest cells in mitosis, and to induce apoptosis. However, there appears to be little published data about its specific interactions with microtubules or its effects on microtubule polymerization or dynamics. Given the clinical efficacy of cabazitaxel and the interesting differences between the parent molecule docetaxel and cabazitaxel, it is essential to elucidate cabazitaxel's basic mode of action on microtubules, both with purified microtubules and in cancer cells, as compared with that of docetaxel.

CAL INSTITUTE FOR REGENERATIVE MEDICINE (CIRM)

Lina Kim 6/1/2012-12/1/2015 $61,580

Research Mentorship Program – Immersing High School Students in College Research

Entering its seventeenth year at the University of California, Santa Barbara (UCSB), the Research Mentorship Program (RMP) is a hands-on program for highly motivated high school students interested in participating in academic research in the arts, music, dance, social, life, physical sciences or engineering. During their six intensive weeks on campus, participants enroll in two credit bearing UCSB interdisciplinary courses – one a lecture course in which students learn to analyze papers and write their own, evaluate research presentations and present their own research in a culminating symposium, and a second course in which students engage in aspects of on-going research with a UCSB faculty or one of their research team members as a mentor. Depending on the nature of the project, lab hours may range from 30 to 40 hours a week, occasionally working into the night when needed. Students select their mentors after approximately 50 potential projects are presented to the class by UCSB researchers. From these, each student choses 8 preferred projects. One of these researchers will be assigned and act as the mentor while the pre-college students work on aspect(s) of the mentor's research for the rest of the program. Participants will work in the lab, library and/or in the field, and be guided in research techniques, learning how to collect and analyze data, how to write a research paper and how to present findings in a public research symposium.

UNIVERSITY OF ILLINOIS

Kenneth Kosik 9/19/12-8/31/15 $79,056

Dynamic regulation of translation by fragile X mental retardation protein FMRP

The Kosik lab will analyze samples of MOV10 immunoprecipitates to detect the associated mRNAs and small non-coding RNAs. This analysis will be performed on our SOLiD sequencer. A data analysis pipeline that includes BIoScope will be used to infer the results and follow up validation will be performed.

CAL H&W PUBLIC HEALTH, DEPARTMENT OF (CDPH)

Kenneth Kosik 7/1/13-6/30/16 $212,616

Detection of Genetic Factors which Modify the Age of Onset of Alzheimer's Disease

We will analyze the full genomes from members of a large Colombian family with familial Alzheimer's disease. Among the samples are patients that had the onset of dementia as early as age 39 and other patients with onset of dementia as late as age 67. From this genomic information we will search for genetic variants that are associated with outlier status in age at onset. These individuals have also contributed fibroblasts from which we can make neurons and use the neurons to identify the specific genes, which may be differentially expressed in neurons of the outliers. Finally we will determine whether any of the changes we observe in the DNA of these individuals corresponds to abnormal expression of the same gene in the neurons we are concurrently analyzing. This approach is a powerful means to discover genes that modify the age at onset of Alzheimer's disease and in some cases those genes may be suitable targets for treatment.

SANTA BARBARA COTTAGE HOSPITAL

Nichole LaPointe 11/1/13-10/31/15 $12,500

One of the two neuropathological hallmarks of Alzheimer's disease (AD) and several other neurodegenerative conditions are intracellular aggregates of tau protein. It has long been appreciated in the field that the spread of tau pathology through the brain follows disease-specific patterns. Only recently, however, have researchers discovered that the spread of tau pathology may be due to the direct passage of toxic tau from one neuron to another. This toxic trans-synaptic tau is an attractive potential therapeutic target, and so a major current goal of the field is to identify these toxic tau species. Using cultured neurons treated with toxic A□ as a model system, we aim to (i) biochemically identify the fragments and oligomers of tau generated following Aβ treatment of cultured neuronal cells (which also causes neuronal cell death), (ii) test the hypothesis that this complex mixture of tau species is neurotoxic, and (iii) assuming the mixture of fragments is cytotoxic (which is likely based on the literature but not a certainty, making this aspect of the proposal especially fitting for a seed grant program), use recombinant DNA procedures to generate individual tau fragments identified in Aim 1 and test the hypothesis that at least a subset of these tau fragments is individually neurotoxic and can form neurotoxic oligomers. If successful, this work will identify individual neurotoxic tau

species as candidates for subsequent work to elucidate molecular mechanisms of trans-synaptic tau mediated neuronal cell death, which leads to the progression of AD and related dementias.

SANTA BARBARA COTTAGE HOSPITAL
John Lew 5/21/13-5/20/15 $15,000
Development of p25 as a novel breast cancer therapeutic

CDK5/p25 is a neurotoxic protein that causes neuronal cell death. Our laboratory has shown that expression of p25 in all cells including tumor cells causes robust cell death, because while neurons specifically express p25, all cells express CDK5. The goal of this study is to develop a delivery system whereby p25 may be specifically targeted to breast cancer tumors, where its toxic action is anticipated to kill tumor cells. Our collaborator, Dr. Erkki Rouslahti, has developed a tumor homing system in which a small peptide sequence, iRGD (CRGDKGPDC), is capable of both homing specifically to tumor vasculature and internalizing bacteriophage particles or nanoparticles coated with this sequence. In this proposal, we will test if p25 fused to iRGD can be targeted to breast cancer tumors in tumor-bearing mice. The goal is to test the specificity of targeting and the ability of p25-iRGD to penetrate tumors and cause tumor cell death. This study will be the first to test the specific tumor targeting of p25 by iRGD, and will provide the proof of concept that p25 homing to tumors may be a novel and viable strategy for a new cancer therapy.

UC IRVINE
Geoffrey Lewis 1/1/13-12/31/16 $1,023,806
Retinal progenitor cells for treatment of retinitis pigmentosa

Over the last year, in collaboration with a group at UCI, we have completed the pre-clinical work required by the FDA for a CIRM funded project using human retinal progenitor cells for the treatment of retinitis pigmentosa. Specifically we demonstrated that the progenitor cells slowed the loss of photoreceptors without causing any adverse effects in the eyes of the RCS rat, an animal model for this disease. These studies, completed at the NRI, helped lead to clinical trials of this treatment method in patients with retinitis pigmentosa beginning in August of 2015. The desired outcome is that the progenitor cells will protect surviving photoreceptors at the time of treatment from the further damaging effects of the inherited disease.

ALLERGAN
Irvine, CA. "Effects of 3 experimental compounds on retinal pathology after experimental retinal detachment."

GALECTO BIOTECH
Copenhagen, Denmark. "An efficacy study of the anti-fibrotic potential of 2 compounds in a rabbit model of proliferative vitreoretinopathy (PVR)."
In 2 separate collaborations with private companies, we tested the ability of several compounds to reduce photoreceptor death and glial scarring in the retina, two events that we, and others,

have shown are common occurrences following experimental retinal detachment, for which there is currently no pharmacological treatment in patients.

NIH GENERAL MEDICAL SCIENCES
Benjamin Lopez 8/1/13-7/31/14 $52,190
Determining How Tau and EB1 Affect Microtubule Structure & Kinesin Translocation

This project will determine how the presence of disease-linked microtubule associating proteins (MAPs) influence and regulate microtubule (MT) structure. In particular, we will investigate two important MAPs: tau and EB1. Normal tau binds to and regulates the growth and stability of MTs while certain tau mutations are known to cause neurological disease. EB1 binds to the growing plus-end of MTs, coordinates other end binding proteins and possibly changes the lattice structure of MTs. A wide array of cancer cells has been found to over express EB1. Using a custom-built multimodal microscope capable of simultaneous single-molecule fluorescence and optical trapping, this project will determine the effects of MAPs on MT stiffness and assess the ability of MAP-coated MTs to support kinesin-based transport. These investigations will first consider tau mutations known to cause frontotemporal dementia with parkinsonism-17, and progressive supranuclear palsy, devastating neurological disorders. The hypothesis that the GTP-rich EB1-coated plus end of a MT has differing stiffness and supports different rates of kinesin translocation compared to the rest of the MT will also be tested. These complimentary data sets will provide critical quantitative insight into the role of MT mechanics and structure in health and disease. In the short term, this project will answer fundamental biological questions about the role of MAPs in regulating the organization and function of the MT cytoskeleton. Ultimately, answers to these questions will contribute to improved medical diagnostics and/or treatments of diseases linked to MT and MAP dysfunction, including neuropathies, Alzheimer's disease and cancer.

SANTA BARBARA COTTAGE HOSPITAL
Dzwokai Ma 5/1/14-4/30/15 $15,000
Regulation of Cytokinesis by Histone Methyltransferase

UC CANCER RESEARCH COORDINATING COMMITTEE
Dzwokai Ma 7/1/14-6/30/15 $50,000
A novel role of histone methyltransferase subunits in cytokinesis

NIH GENERAL MEDICAL SCIENCES
Craig Montell 4/1/14-3/31/16 $307,000
TRPA1: A Polymodal Sensor for Aversive Stimuli 7R01GM085335-06

The long-term goal of the research is to use the fruit fly, Drosophila melanogaster, as an animal model to unravel the mechanisms through which insects respond to sensory cues, ranging from changes in temperature to insect repellents. These questions are of potential relevance to the control of insect pests, since mosquitoes that spread diseases are attracted to humans through thermosensory, visual and chemical cues. Aversive temperatures and chemical repellents deter

insects. Therefore, understanding the mechanisms underlying avoidance behavior may provide important insights into insect pest control. A key group of receptor proteins that sense environmental stimuli are Transient Receptor Potential (TRP) cation channels. Among the 13 Drosophila members, TRPA1 is of particular note as it is a detector for a wide array of noxious sensory inputs, including slightly warm or hot temperatures, insect repellents, and excessive light. Here, we propose to dissect the molecular, cellular and behavioral mechanisms through which TRPA1 allows larvae and adult flies to elude aversive stimuli. To accomplish our goals, we are employing a multidisciplinary approach, using a combination of molecular genetics, biochemistry, cell biology, electrophysiology and behavioral approaches.

NIH DEAFNESS & OTHER COMMUNICATION DISORDERS
Craig Montell 7/1/15-6/30/16 $322,926
Molecular Genetics of Contact Chemosensation 7R01DC007864-08

The long-term goal of this research project is to clarify the molecular mechanisms underlying the detection and discrimination of chemicals through contact chemosensation in the fruit fly, Drosophila melanogaster. Contact chemosensation allows flies to distinguish sweet from bitter molecules, as well as nonvolatile pheromones. Insect gustatory organs express a diversity of candidate molecular detectors. These include gustatory receptors (GRs), TRP channels, ionotropic receptors (IRs) and odorant binding proteins (OBPs), the latter of which promote the detection of chemicals by receptor proteins. However, the functions of most of these candidate gustatory receptors and binding proteins are unknown, or are understood poorly. This project is focusing on dissecting the mechanisms underlying contact chemosensation in flies using a multidisciplinary approach that includes electrophysiology, behavior, genetics, and cell biological approaches. During the last few years, the concept that GRs are required broadly for sensing sugars and bitter-tasting compounds has been confirmed. However, the biochemical functions of GRs are unclear. A long-term goal of this research is to apply the findings to the control of insect pests that spread disease.

NIH NATIONAL EYE INSTITUTE
Craig Montell 5/1/14-4/30/16 $376,075
Rhodopsins: from biosynthesis and degradation to unconventional functions

The goal of the research is to use the fruit fly, Drosophila melanogaster, as an animal model to unravel the molecular mechanisms underlying the biosynthesis, turnover and non-classical functions of rhodopsins. Rhodopsin is comprised of an opsin protein and a vitamin A-derived chromophore, which senses light. Among the most common forms of retinal degeneration are those that result from defects in the visual cycle (retinoid cycle)—an enzymatic pathway required for regeneration of the chromophore. Until recently it was thought that flies do not employ a visual cycle, since the chromophore does not normally release from photoactivated rhodopsin. However, some rhodopsin is internalized and the opsin gets degraded, thereby releasing the chromophore. We have recently made the discovery that flies use a visual cycle to regenerate the released chromophore. To accomplish our goals, we are employing a multidisciplinary approach using a combination of genetic, cell biological, electrophysiological,

molecular and biochemical techniques. The long-term goals of these studies are to 1) uncover mechanisms underlying the retinal degenerations that result from defects in the visual cycle with the ultimate goal of discovering new therapeutic approaches, and 2) uncover the roles of the enigmatic extra-retinal opsins.

Craig Montell 5/1/14-4/30/16 $376,075
Regulation of TRP channels and visual transduction

The long-term goal of this research project is to define the mechanisms through which the TRP channels in photoreceptor cells are activated and regulated in response to light. This project focuses on Drosophila phototransduction, which functions through a phospholipase C (PLC)-dependent signaling system, and culminates with Ca2+ and Na+ influx, via the TRP and TRPL channels. There exists a large family of mammalian TRPs, including channels in the intrinsically photosensitive retinal ganglion cells (ipRGCs) that are gated through a cascade that has notable parallels with fly phototransduction. The specific goals of this project are to answer major questions in Drosophila phototransduction concerning the mode of activation andregulation of the TRP channels. To accomplish our goals, we are employing a multidisciplinary approach, using a combination of molecular genetics, biochemistry, cell biology, and electrophysiology. The goal of aim 1 is to identify the molecule that directly gates the TRP and TRPL channels. Prior to activation of these channels, PLC causes hydrolysis of PIP2 to generate IP3, DAG and H+. However, despite the >20 years that have elapsed since the identification of the Drosophila TRP channels, the precise activation mechanism is not known. We recently identified a DAG metabolite that increased in concentration in a light-dependent manner.

We suggest that the studies that are the focus of this project are significant because they offer to resolve the mechanisms by which the TRP channels in photoreceptor cells are gated, localized and regulated. We also suggest that these studies will provide the framework for answering similar questions relevant to the channels in the ipRGCs, which contribute to light-induced circadian rhythms, sleep patterns and rudimentary image formation in the absence of rods and cones.

NIH GENERAL MEDICAL SCIENCES
Denise Montell 7/1/2014-6/30/2015 $499,864
Developmental Regulation of Collective Cell Migration

WASHINGTON UNIVERSITY
Stanley Parsons 6/18/2011-5/31/2016 $39,400
PET Probes For Imaging The Vesicular Acetylcholine Transporter

UC RIVERSIDE
Monte Radeke 7/1/13-6/30/15 $60,000
Drug Discovery for Macular Disease

OLYMPUS CORPORATION OF AMERICA
Mary Raven 1/12/2015-1/16/2015 $3,200
Advanced Microscopy Live 2015

The award paid the registration fees for four participants in the workshop. Scholarships were offered broadly and distributed to researchers from Miami University, Children's Hospital, University of MN and UCSC. One graduate student from the UCSB program was allowed to attend courtesy of the NRI-MCDB.

NIH NATIONAL EYE INSTITUTE
Benjamin Reese 1/1/14-12/31/15 $348,046
Development of Retinal Bipolar Cells R01 EY019968

This research program is identifying the molecular and genetic determinants controlling the natural variation in nerve cell number, examining the populations of synaptically connected photoreceptors, bipolar cells and amacrine cells in the retina. We are also determining how such variation in afferent and target cell number modulates the dendritic morphology of the post-receptoral cells. This program will, consequently, clarify the developmental events and their underlying mechanisms that produce the functional architecture and connectivity of the retina. These studies will contribute to our understanding of retinal development and degeneration, and will enlighten our approach in developing treatments for retinal disease, particularly where the latter seek to re-establish connectivity following cell replacement therapy.

NIH CHILD HEALTH & HUMAN DEVELOPMENT
Joel Rothman 6/1/13-5/31/15 $269,676
Specification and Differentiation of Endoderm in C. elegans R01 HD062922

We are continuing our studies on how cell division and growth are controlled by investigating the cellular components that switch dividing cells into non-dividing cells with specialized functions. These processes are critically important in the genesis of cancer and are uncontrolled in growing tumor cells. The project is providing training for graduate students and undergraduate researchers who are learning molecular genetic and cell biological experimental methods that effectively address these problems.

NIH CHILD HEALTH & HUMAN DEVELOPMENT
Joel Rothman 4/1/2015-1/31/2016 $310,483
Developmental reprogramming and transorganogenesis

NIH CHILD HEALTH & HUMAN DEVELOPMENT
Joel Rothman 4/1/2015-1/31/2016 $302,454
Plasticity in an embryonic gene regulatory network

NIH CHILD HEALTH & HUMAN DEVELOPMENT

William Smith 7/1/14-6/30/15 $316,851

Morphomic analysis of a simple chordate R01 HD059217

This proposed collaborative project will investigate fundamental processes driving chordate embryogenesis. The project will combine the skills and expertise of two research groups: one that works in the area of developmental biology, and the other in the area of image analysis and computer vision. The goal of the project is take a whole-embryo embryo approach to investigating morphogenesis in live embryos in all 4 dimensions (x,y, z and t). Specifically, we will collect and analyze confocal microscopy images to derive quantitative data on the division, shape, volume and movements of all cells in both selected developing organs and in whole embryos.

CALIFORNIA BLUEPRINT FOR RESEARCH TO ADVANCE INNOVATIONS IN NEUROSCIENCE (CAL-BRAIN)

William Smith 6/1/2015-5/31/2016 $120,000

Whole brain imaging in a primitive chordate

The formation of organs and tissues in the developing embryo requires coordinated action of multiple cells. Cells are not uniform structures, but rather have distinct sides, a property we call polarity. For example, cells in an organ may adhere tightly to a substrate with one face, while actively secreting on another face. We use a simple model organism in which the organs are composed of only tens to hundreds of cells to investigate the cellular mechanisms by which cells sense directionality and coordinate polarity while they assemble into organs.

NIH DIABETES, DIGESTIVE & KIDNEY DISEASES

Thomas Weimbs 8/1/13-7/31/15 $184,607

A Novel Role of Syntaxin 3 as a Transcription Regulator R21 DK095248

SNARE proteins mediate membrane fusion events in virtually all cellular membrane trafficking pathways. We have discovered an unexpected, novel function of the SNARE protein syntaxin 3 (Stx3). Stx3 normally has a C-terminal trans-membrane anchor and is involved in trafficking to the apical plasma membrane domain of polarized epithelial cells. We found that Stx3 undergoes cleavage at an extremely conserved glutamine residue which removes its trans-membrane domain resulting in a soluble fragment, Stx3(1-225). Furthermore, a novel splice-isoform of Stx3 (Stx3E) lacks the trans-membrane anchor, and is expressed in human kidneys. Both, the cleavage fragment and Stx3E (collectively called “soluble Stx3”) bind to the nuclear import factor RanBP5, target to the nucleus and co-activate several transcription factors including ETV4. ETV4 is required for branching morphogenesis in kidney development, and associated with carcinogenesis and tumor metastasis. We found that kidneys from Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients express a small Stx3 fragment – consistent with soluble Stx3. We hypothesize that cleavage and transcriptional regulation in the nucleus is a novel function that may be a common feature of syntaxin members of SNARE proteins. This may be a novel signaling mechanism that transduces information from

cytoplasmic membrane trafficking events to the nucleus to affect changes in gene expression. If correct, this would introduce a new paradigm of SNARE function. More specifically, we hypothesize that soluble Stx3 plays a role in the regulation of renal epithelial morphogenesis, carcinogenesis and ADPKD.

EISAI RESEARCH INSTITUTE
Leslie Wilson 7/2/2013-7/07/2016 $773,782
Functional Interactions between Eribulin and Microtubule +TIPS

SPACE

Division	Department	Building Name	Space ID	Stations	Room Use	Function Code	Space Area (SF)
VCR - Research	NRII	Biological Sciences II	5103	6	210 -	RESRCH LAB - Research Lab	413
VCR - Research	NRII	Biological Sciences II	5106	4	210 -	RESRCH LAB - Research Lab	345
VCR - Research	NRII	Biological Sciences II	5107	2	225 -	RESRCH LAB - Research Lab	202
VCR - Research	NRII	Biological Sciences II	5111	0	225 -	EQUIPRM	203
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STATISTICAL SUMMARY FOR: (Neuroscience Research Institute)

	2014-2015
1. Academic personnel engaged in research:	
a. Faculty	30
b. Professional Researchers (including Visiting)	7
c. Project Scientists	11
d. Specialists	24
e Postdoctoral Scholars	24
f Postgraduate Researchers	
TOTAL	96
2. Graduate Students:	
a Employed on contracts and grants	27
b. Employed on other sources of funds	
c. Participating through assistantships	
d. Participating through traineeships	4
e Other (specify)	
TOTAL	31
3. Undergraduate Students:	
a. Employed on contracts and grants	26
b. Employed on other funds	
c. Number of volunteers, & unpaid interns	21
TOTAL	47
4. Participation from outside UCSB: (optional)	
a. Academics (without Salary Academic Visitors)	8
b. Other (local high school students/CIRM Creativity Program)	10
5. Staff (Univ. & Non-Univ. Funds):	
a. Technical	12
b. Administrative/Clerical	17
6. Seminars, symposia, workshops sponsored	5
7. Proposals submitted	48
8. Number of different awarding agencies dealt with*	19
9. Number of extramural awards administered	109
10. Dollar value of extramural awards administered during year**	28,943,026
11. Number of Principal Investigators***	46
12. Dollar value of other project awards ****	6,502,452
13. Number of other projects administered	53
14. Total base budget for the year (as of June 30, 2015)	323,042
15. Dollar value of intramural support	260,410
16. Total assigned square footage in ORU	14,584
17. Dollar value of awards for year (08 Total)	5,328,066

* Count each agency only once (include agencies to which proposals have been submitted).

** If the award was open during the year, even if for only one month, please include in total.

*** Number of PIs, Co-PIs and Proposed PIs (count each person only once.)

**** Other projects - such as donation, presidential awards, fellowships, anything that isn't core budget, extramural, or intramural.

ADVISORY COMMITTEE / ADMINISTRATIVE STAFF / TECHNICAL STAFF

2014-15 NRI Advisory Committee

Mark Brzezinski, EEM Biology
Dennis Clegg, MCDB
Peter Coffey, NRI
Steve Fisher, NRI
Scott Grafton, Psychology
Thomas Harriman, Community Member
Richard Lehman, Community Member
Craig Montell, MCDB
Denise Montell, Chair, MCDB
Art Rosenblatt, Community Member
Janice Taylor, Development
Ty Vernon, Gevirtz Graduate School of Education

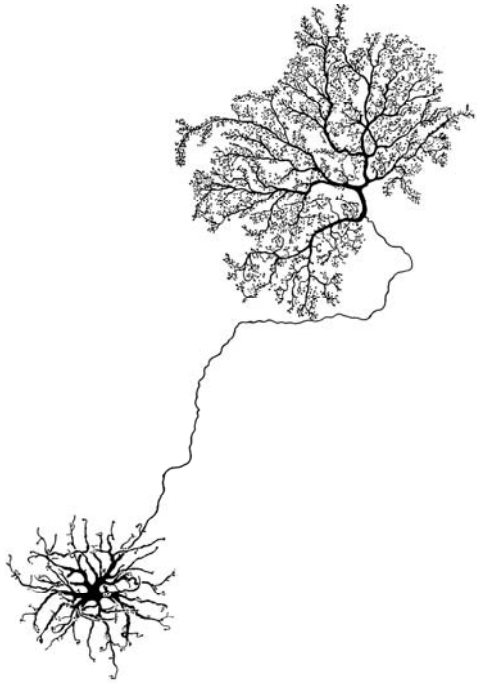
Ex-Officio Members:
Stuart Feinstein, Co-Director, NRI
Kenneth Kosik, Co-Director, NRI
Theresa Peña, Business Officer, NRI

NRI Administrative Staff

Judy Cushing, Personnel Manager
Karen Cisneros, Purchasing Manager
Azeb Demisse, Financial Analyst
Max McCumber, Purchasing Assistant
Kathleen McIntosh, Personnel/Contracts & Grants Analyst
Theresa Peña, Business Officer
Bee Jay Yokoi, Contracts and Grants Manager
Angela Zeng, Assistant to Kenneth Kosik

Technical Staff

Elmer Guzman, Sequencing Facility Assistant Director
Hunter Buchanan, Computer Support
Geoffrey Lewis, Microscopy Support
Mary Raven, Microscopy Director



PRINCIPAL INVESTIGATORS

Gregory Ashby	Researcher	Psychological + Brain Sciences
Aaron Blackwell	Assistant Professor	Anthropology
Sarah Benbow	Graduate Student	MCDB, NRI
Dennis O. Clegg	Professor, Executive Director	MCDB, Stem Cell Center
Peter Coffey	Researcher, Executive Director	NRI, Stem Cell Center
Adele Doyle	Assistant Researcher	NRI
Francis Doyle	Professor	Chemical Engineering
Stuart C. Feinstein	Co-Director, Professor	NRI, MCDB
Steven K. Fisher	Professor	MCDB
Michael Gazzaniga	Professor	Psychological + Brain Sciences
Claudia Gottstein	Adjunct Assistant Professor	MCDB
Scott Grafton	Professor	Psychological + Brain Sciences
Michael Gurven	Professor	Anthropology
Roger Ingham	Professor	Speech + Hearing Sciences
Lincoln V. Johnson	Research Scientist	NRI
Mary Ann Jordan	Research Scientist	NRI
Kenneth S. Kosik	Co-Director, Harriman Professor	NRI, MCDB
Tonya Kydland	Project Scientist	NRI
Nichole LaPointe	Assistant Research Scientist	NRI
John Lew	Associate Professor	MCDB
Geoff Lewis	Research Scientist	NRI
Chao Liu	Postdoctoral Fellow	NRI
Yanli Y. Liu	Postdoctoral Fellow	Chemical Engineering
Benjamin B Lopez	Postdoctoral Fellow	MECE
Dzwokai “Zach” Ma	Assistant Professor	MCDB
Michael Mahan	Professor	MCDB

B. Manjunath	Professor	Electrical and Computer Engineering
Melanie Martin	Graduate Student	Anthropology
Craig Montell	Professor	MCDB
Denise Montell	Professor	MCDB
Stanley M. Parsons	Professor	Chemistry + Biochemistry
Monte Radeke	Assistant Research Scientist	NRI
Mary Raven	Director	NRI Microscopy
Benjamin E. Reese	Professor	Psychological + Brain Sciences
Joel Rothman	Professor	MCDB
Tal Sharf	Postdoctoral Fellow	NRI
William Smith	Professor	MCDB
Jennifer A Smith	Postdoc	NRI
H. Tom Soh	Co-Director	Stem Cell Center
James Thomson	Professor, Co-Director	MCDB, Stem Cell Center
Megan T. Valentine	Assistant Professor	Mechanical Engineering
Carol Vandenberg	Professor	MCDB
Thomas Weimbs	Associate Professor	MCDB
Leslie Wilson	Professor	MCDB
Yali Zhang	Postdoctoral Fellow	MCDB