UC RIVERSIDE | UNIVERSITY OF CALIFORNIA | School of Medicine

SUMMER 2017 EXTERNSHIP CLINICAL PROGRAM

Kaiser Permanente Medical Center (4 Positions)

Riverside Medical Clinic (2 Positions)

Riverside University Health Systems (6 Positions)

Summer Externship Clinical Program is a 6-week program consisting of one-week rotations in medicine, cardiology, general surgery, orthopedics, family medicine, neurology, pediatrics, and/or other services the student desire. This program acquaints the student with the private practice aspects of the various specialties in order to be in a better position to choose their eventual specialty.

Renuance Plastic Surgery Clinic (2 Positions)

The Renuance Cosmetic Surgery Center is located in Temecula, California. This one-site surgery center is nationally accredited through AAAASF, which is the highest level for outpatient surgery centers. They perform a broad range of cosmetic surgeries including breast augmentation, abdominoplasty, liposuction, facelifts and more. Dr. Brian Eichenberg, founder, is certified through the American Board of Plastic Surgery and specializing in areas of plastic surgery and aesthetic treatment. Facility has an on-site medical spa for multiple laser treatments.

Students will be acquainted with the clinical practice of plastic surgery and learn the basic surgery principles and practices. They will become familiar with multiple cosmetic surgery procedures as well as general operating room environment and will learn the underlying mechanisms for wound healing, flaps, suture techniques, Botox, filler and lasers.

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Summer 2017 Externship Research Program

SPONSOR: Dr. Ilana Bennett
CONTACT: ilana.bennett@ucr.edu
OPPORTUNITIES: 1 Position

We are all familiar with the notion that our memory gets worse as we get older. But, in fact, not all forms of memory decline with age. And it's not just about aging. Across the lifespan, some adults have worse memory than their peers. The Laboratory of Aging and Neurocognitive Imaging (LANI lab) focuses on cortical disconnection as a mechanism to explain these individual- and age-related differences in memory. According to this model, degradation of white matter is thought to account for cognitive declines associated with aging. White matter is a critical, yet relatively understudied, part of our brain. It provides the structural framework by which gray matter regions communicate and coordinate their processing.

The LANI lab uses a combination of neuropsychological, cognitive, and neuroimaging techniques to study various forms of learning and memory in younger and older adults. Both diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) are employed to characterize the neurobiological substrates underlying age-related differences in memory performance. Projects planned for this summer will allow students to be involved in developing and administering cognitive tasks, acquiring neuroimaging data and the newly constructed Neuroimaging Center, and analyzing existing or newly acquired structural (DTI) or functional (fMRI) neuroimaging data.

SPONSOR: Dr. Monica Carson
CONTACT: Monica.Carson@ucr.edu
OPPORTUNITIES: 2 Positions

Traumatic Brain Injury (Concussions) and Neurodevelopmental disorders

Project 1: 90% of TBIs are mild and difficult to detect with standard clinical imaging methods. As yet, there is no reliable method to predict which individuals will have poor outcome following single or repetitive injury. Here we are seeking to develop a blood panel defining risk and likelihood for poor progression in young athletes in the Inland Empire. Project involves both lab work and community outreach.

Project 2: Infancy and childhood are a time of first encounters with common infectious agents. Hence it is a time of frequent systemic immune challenges that for most of us does not lead to overt defects in cognition and/or brain function. However, infections during infancy and childhood do correlate with increased incidence of a wide spectrum of neurodevelopmental disorders ranging from autism spectrum disorders to epilepsy. Our lab uses murine models of systemic challenges to define which and how genetic, environmental and inflammatory factors interact to increase susceptibility to these neurologic disorders. Here, the project would involve the use quantitative analysis of behavior, gene expression, flow cytometry or confocal microscopy to quantify neuronal development and brain function in murine models of epilepsy and neurodevelopmental disorders.

Publication and Presentation Opportunities:
The medical student would work with post-doctoral fellows leading ongoing projects and have the opportunity to present their research at the annual SoCal symposium on Glia-Neuronal Interactions in Health and Disease, January 2017. Potential exists to help develop a critical review on TBI or neurodevelopmental disorders for publication.

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SPONSOR: Dr. Iryna Ethell
CONTACT: Iryna.Ethell@ucr.edu
OPPORTUNITIES: 2 Positions

Research in my lab focuses on understanding how neuronal networks are developed and maintained in the brain, with the goal of applying this knowledge to the development of therapeutics for neurodevelopmental and neurodegenerative diseases. We utilize new molecular and imaging approaches in neuroscience and mouse genetics to conduct research on the molecular basis of neurologic diseases. In particular, we are interested in molecular and cellular mechanisms that govern the synapse formation and plasticity in the brain areas that play a critical role in learning and memory.

Two research projects are available in the lab as follows:

Project 1: To study the mechanisms underlying the pathophysiology of Fragile X Syndrome (FXS), a neurodevelopmental disorder associated with intellectual disability and autism; My lab discovered the role of MMP9 in pathophysiology of FXS and demonstrated beneficial effects of minocycline and MMP-9 deletion on synapse development and behavioral performance in an animal model of FXS (Bilousova et al., 2009; Dansie et al., 2013; Sidhu et al., 2014; Lovelace et al., 2016). These findings prompted several clinical trials that tested the effects of minocycline treatment in patients with FXS. Ongoing studies focus on the role of MMP9 and extracellular matrix in autistic behaviors associated with FXS, including the mechanisms of auditory hypersensitivity. In collaboration with Drs. Binder and Razak we are working to develop a preclinical model of auditory processing deficits in FXS. Our studies will determine the interactions between structural and functional changes in auditory circuits in Fragile X mice and will generate therapeutic ideas by targeting multiple pathways involved in the pathophysiology of FXS.

Project 2: To study glial control of synapse development and injury-induced synapse remodeling in the brain and its role in PTSD-related behaviors following traumatic brain injury (TBI). Our new studies also suggest that ephrin-B/EphB receptor signaling is involved in synapse remodeling triggered by TBI. While considerable efforts were devoted to the treatments that enhance neuron survival following brain injury, our understanding of the mechanisms that regulate injury-induced brain rewiring is limited. Brain injury can cause dramatic changes in synaptic connectivity in the brain may lead to cognitive and neuropsychological changes that persist for decades. In the ongoing studies, we investigate new mechanisms of astrocyte-mediated remodeling of synaptic connections in the brain that may aid the functional brain recovery after brain injury. The collaborative studies with Dr. Andre Obenaus's laboratory at the Loma Linda University we are investigating whether the regulation of ephrin-B levels in reactive astrocytes plays a protective or destructive role in the recovery after TBI using both genetic and pharmacologic approaches in a combination with biochemical, anatomical, electophysiological methods and non-invasive MRI imaging.

SPONSOR: Dr. Vagelis Hristidis
CONTACT: vagelis@cs.ucr.edu
OPPORTUNITIES: 1 Position

I have been working with two Computer Science PhD students and a Professor of Medicine from UCSD on a project to predict medical events in electronic medical records of patients using machine learning techniques.

The selected medical student will help with the evaluation of the methods, and is expected to become a co-author to the publication that we will submit.

Medicine 2.0 creates the need for applications that find similar patients based on a patient's electronic health record (EHR). We evaluate the hypothesis that we can leverage similar EHRs to predict possible future medical concepts (e.g. disorders) in a patient's EHR. We represent patients' EHRs using time-based prefixes and suffixes, where each prefix or suffix is a set of medical concepts from a medical ontology. We compare the prefixes of other patients in the collection with the state of the current patient using various inter-patient distance measures. The set of similar prefixes yields a set of suffixes, which we use to determine probable future concepts for the current patient's EHR. We evaluate our methods on the MIMIC II dataset of patients.

SPONSOR: Dr. Huinan Liu
CONTACT: huinanliu@engr.ucr.edu
OPPORTUNITIES: 1 Position

Dr. Liu's Biomaterials and Nanomedicine Lab research involves design, fabrication and evaluation of novel biomaterials for tissue regeneration, controlled drug delivery, and medical implant/device applications. Medical applications of nanomaterials and nanotechnology are actively explored through both fundamental studies and applied research. Materials studied in the lab include polymer, ceramic nanoparticles, polymer/ceramic nanocomposites and biodegradable metals. Students will be involved in developing novel materials and implants for neural repair, bone regeneration, etc. Students may acquire lab skills and gain experience in material synthesis, characterization, electron microscopy, x-ray spectroscopy, optical emission spectrometry, fluorescence microscopy, bacterial culture, mammalian cell culture studies, and performing surgeries for assessing novel orthopedic implants or neural implants in rat models. Previous outstanding student researchers in Liu lab have co-authored publications in scientific journals and/or presented their work at national/international scientific conferences. Specifically, for summer 2017, medical students will assist our collaborating surgeons in implanting bioresorbable metallic implants into rat models and assessing the implant performance in vivo.

SPONSOR: Dr. David Lo
CONTACT: David.Lo@ucr.edu
OPPORTUNITIES: 1 Position

Our lab is studying the mucosal barrier and immune surveillance at this barrier. We are focusing on one cell in the epithelial barrier called the M cell, which captures bacteria and viruses and transports them across the barrier and hands them off to cells in the immune system.

We recently found that in models of Inflammatory Bowel Disease, numerous M cells are newly generated in the colon. Since the colon has the highest concentration of microbes in the gut, we would like to know whether these M cells are helpful to immune surveillance or whether instead they enhance invasion of microbes into intestinal tissue, driving continued tissue inflammation.

In the small intestine, we also found that the toxin produced by the bacteria responsible for cholera (*Vibrio cholerae*; producing cholera toxin) also rapidly induces a different type of M cell in the distal ileum but not elsewhere in the gut. Again, we are interested in whether this phenomenon helps promote colonization by the bacteria or alternatively whether it is an attempt to boost local immune surveillance.

Projects in the lab will involve tissue imaging including Scanning Electron Microscopy to assess its potential as a novel diagnostic tool in endoscopic biopsies, as well as confocal and multiphoton imaging of immune surveillance mechanisms. Gene expression studies will also be done to identify key regulatory pathways in host epithelial responses. We will focus these studies on the question of whether M cell induction in these two models either (1) serves the host in increasing immune surveillance, or (2) serves the pathogens by enhancing their ability to invade and colonize, or (3) does something more complicated.

SPONSOR: Dr. Declan McCole
CONTACT: Declan.McCole@ucr.edu
OPPORTUNITIES: 1 Position

Our lab is focused on understanding the mechanisms involved in regulating epithelial barrier function. When the epithelial barrier in the intestine becomes "leaky" this can allow bacterial products to stimulate inappropriate immune responses and trigger inflammation. Increased permeability of the intestine is a very early event in many diseases including Crohn's disease, ulcerative colitis, celiac disease & diabetes. We use epithelial cell culture models, transgenic mice and intestinal biopsies from patients to study the role of a candidate gene (PTPN2) associated with all 4 of these diseases in regulating epithelial barrier function in health & disease. We also study how mutations in this gene contribute to barrier disruption in disease.

A summer research project in the McCole lab will focus on identifying signal transduction pathways that are increased in intestinal epithelial cells with deficient PTPN2 gene activity, and how these signaling pathways compromise intestinal barrier function. The project will involve learning some or all of the following approaches:

i) Epithelial cell culture techniques.
ii) Permeability assays to measure barrier function.
iii) Biochemical techniques to identify signaling pathways regulating the epithelial barrier (i.e. Western blotting).
iv) Fluorescence microscopy to identify changes in localization of key proteins in cultured cells and tissues.

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SPONSOR: Dr. Hyle Park
CONTACT: hylepark@ucr.edu
OPPORTUNITIES: 2 Positions

Project 1 - Label-free optical imaging of neural activity

Current methods for recording neural circuit activity fall into at least one of three categories: those using (arrays of) electrodes; methods based on indirect measures such as blood flow; or techniques that require introduction of a fluorescent label. The ideal method of detecting neural activity would: (1) be noninvasive; (2) be label-free; (3) directly reflect neural activity and not indirect characteristics such as blood flow; and (4) have high spatial and temporal resolution. We are developing methods for label-free optical imaging of neural activity with high spatial and temporal resolution. Neural activity in any tissue produces tiny physical change in the geometry and refractive index of neurons, which can be detected with interferometric methods that are the basis for optical coherence tomography (OCT). Unlike fluorescence methods, interference measurements do not require modification of the sample through direct or genetic introduction of an exogenous label. By utilizing both the intensity and the phase information obtained in OCT, we can, in principle, directly examine levels of activity over a millimeter-scale field of view and in single cells at sub-millisecond resolution. OCT has the added advantage over previous intrinsic optical imaging methods of being able to localize the sub-surface depth of these measures as well. We have previously demonstrated the ability of OCT to optically detect pathologic levels of activity in both in vivo and in vitro animal models, and validated these measurements with electrophysiology.

To allow more precise control of the stimulation site and intensity, the proposed summer project will entail local stimulation of a defined synaptic pathway in the hippocampal slice combined with OCT-based detection and MEA recordings. Stimulation of the Schaffer collateral pathway from CA3 to CA1 will be performed by (1) electrical stimulation and (2) optogenetic stimulation to trigger MUA in CA1 that will be then detected by MEA and correlated to the changes in the optical signal detected by OCT. An advantage of this approach is that stimulation is limited to a well-defined synaptic pathway and involves a small group of neurons. The size of the actived population of neurons will be varied by changing intensity of stimulation. Simultaneous MEA and OCT recording will be analyzed and cross-correlated. These experiments will define, for the first time, the ability of OCT to detect local synaptic activation in the hippocampus.

Project 2 - **Hyperspectral OCT imaging of retinal metabolism** *(collaborative project with Keck/USC)*

Ischemia and hypoxia play critical roles in the pathophysiology of vascular diseases such as diabetic retinopathy (DR) and retinal vein occlusions (RVO). However, current diagnosis and treatment regimens are based on relatively late-stage vision loss from macular edema, macular ischemia and neovascularization. While indirect clinical evidence suggests that retinal hypoxia has a causal role in DR and RVO, there are no direct clinical measures of capillary hypoxia in humans. Current research-based

oximetry methods only resolve large retinal vessels which are not the location of preclinical vascular changes. Since there is no direct clinical measure for capillary hypoxia and only infrequent assessments of ischemia (using fluorescein angiography (FA)) current treatments for DR and RVO assume a direct and static relationship between hypoxia and ischemia which is unlikely to be correct. OCT angiography and histological studies confirm that FA provides a limited assessment of capillary perfusion. This lack of fundamental knowledge about disease pathophysiology in humans underlies limitations in current treatments and our inability to develop novel rationale therapies to treat the early manifestation of these diseases. For example, the clinical course of DR occurs over 10-20 years but current methods cannot detect the disease until significant structural changes have occurred. The CVOS study illustrated that prophylactic pan-retinal photocoagulation does not prevent neovascularization in ischemic central RVO even when large amounts of non-perfusion are evident on FA. Moreover, a significant fraction of ischemic CRVO cases show improvements in visual function (20-30%) and a significant fraction of non-ischemic CRVO cases show deterioration in visual function (~50%) that is not well explained. Current treatments (intravitreal anti-VEGF, steroids and laser) may result in significant visual improvement but only in ~50-60% of subjects. These observations show that the correlations between retinal ischemia, hypoxia and sequelae of retinal vascular diseases are incompletely understood.

We hypothesize that a decrease in retinal capillary oxygen content (hypoxia) in human subjects with DR and RVO is an early biomarker of ischemic disease progression. Current multispectral and hyperspectral oximetry methods can only resolve large retinal vessels because of limitations in spatial-spectral range, resolution, image registration and scattered light. In addition, the variability and late changes in large vessel oxygen suggests that it is not an ideal biomarker of early disease. Therefore, there is a need for non-invasive and clinically feasible methods to detect retinal capillary hypoxia both for earlier disease detection as well as a better understanding of the fundamental pathophysiology.

Optical coherence tomography (OCT) provides excellent spatial resolution, is clinically feasible and is completely non-invasive. Current OCT systems measure structural tissue changes based on the reflectance intensity profile of the target tissue using interferometry over a single wavelength range. We expect to have completed construction and basic characterization of a broadband hyperspectral OCT (HS-OCT) system combining a standard structural OCT (sOCT) and a novel hyperspectral OCT (hOCT). This will allow spatially co-registered spectroscopy and structural imaging of retinal tissue *in vivo* with the resolution of current spectral domain OCT systems. This device will allow us measure *in vivo* human retinal capillary oxygen content based on the spatially resolved spectroscopic signatures of oxy- and deoxyhemoglobin. The scope of the proposed summer project entails late-stage system characterization in model eyes with simulated changes in blood oxygenation and early stage use in patients.

SPONSOR: Dr. Frances Sladek
CONTACT: Frances.Sladek@ucr.edu
OPPORTUNITIES: 1 Position

We have an on-going diet-induced obesity project in the lab that is focused on evaluating effects of various vegetable oils at the transcriptomic, metabolic and micro biome levels, particularly in relation to development of metabolic syndrome and inflammatory bowed disease (IBD). Interested students will be able to learn/perform procedures such as nuclear extract preparation, western blotting, frozen sectioning tissues and doing histological staining with hematoxylin-eosin as well as with Oil-Red-O and ALT assays. In addition, they will also be involved in data analysis and interpretation. This project is important as there is an increasing realization that long held dogma about certain aspects of our diet, such as potential health risks of saturated versus unsaturated fats, are actually not based in sound scientific evidence and could benefit from new analysis using the gamut of modern omics tools.