Mentors for Medical Student Summer Program, 2017

1) Bhardwaj, Ratan
2) Burrell, Brian
3) Ehli, Erik
4) Foster, Gina
5) Francis, Kevin
6) Killian, Scott
7) Lee, Lance
8) Rezvani, Khosrow
9) Tao, Jianning
10) Travers, Henry
11) Weimer, Jill
12) Zhao, Haotian

The deadline for application is April 15.
Mentor Description Form

Mentor Contact Information
- Name: Ratan Bhardwaj, MD, PhD
- Title: Pediatric Neurosurgeon
- Phone: 602 920 2606
- E-mail: ratan.bhardwaj@gmail.com
- Lab web page: http://www.sanfordresearch.org/researchcenters/childrenshealth/bhardwajlab/

Location of Summer Research (Example: Sanford Medical Center, Sioux Falls):
Research center and or Children’s Hospital

Description of Your Research (<200 words)
Regenerative medicine holds great promise in the years ahead. Dr. Bhardwaj’s past research was focused on stem cell dynamics in adult human organs. The Bhardwaj Lab will focus efforts on studying the potential of cellular plasticity, by manipulating the epigenetic landscape and non-coding milieu. The team will investigate umbilical cord cells’ transdifferentiation potential under various biophysical and molecular manipulations.

Pediatric brain tumors represent a true challenge to children and their families. The Bhardwaj Lab has discovered novel molecular biological pathways in ATRT - a notoriously difficult tumor type to successfully treat. The team will use various compounds in current trials for other malignancies, to better treat and possibly cure this horrible cancer. Established industry collaborators partner in this work. Dr. Bhardwaj and his team will use combinations of cell lines, siRNA knock down, Western blots, immunoprecipitation, and flow cytometry to tackle this tumor type.

Description of Project(s) Available to Summer Students
We are currently very interested in following our work on curing malignant brain tumors with a new drug, currently in FDA phase 2 and 3 trials. We have elucidated a novel protein interaction and hope that our drug will be beneficial. We are also studying single cell transcriptomics with a novel RNA Seq platform and hope to better understand the transcriptional dynamics of the single cells that form the heterogeneous tumors that cause so much harm to our patients.
NAME
Ratan Dev Bhardwaj

POSITION TITLE
Associate Professor and Medical Director of Pediatric Neurosurgery

eRA COMMONS USER NAME
RBHARDWAJ

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

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<td>1993-1996</td>
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<td>Universite Paris IV, La Sorbonne</td>
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<td>Queen’s University, Kingston, Canada</td>
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<td>International Space University, Houston, USA</td>
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<td>University of Toronto, Toronto, Canada</td>
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<td>Neurosurgery</td>
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<tr>
<td>Medical Nobel Institute, Stockholm, Sweden</td>
<td>Ph.D.</td>
<td>2003-2007</td>
<td>Stem Cells</td>
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<tr>
<td>University of Toronto, Toronto, Canada</td>
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<td>2007-2009</td>
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<td>Rady Children’s Hospital, San Diego, USA</td>
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<tr>
<td>Sanford Burnham Institute, La Jolla, USA</td>
<td></td>
<td>2010-11</td>
<td>Cancer Stem Cells</td>
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A. Personal Statement

As a practicing clinician scientist in the field of pediatric neurosurgery, I have been greatly fascinated by the phenomenon of neuroplasticity within the clinical setting. My research interest lies within functional neurosurgery, as I became exceedingly intrigued by deep brain stimulation throughout my training in Toronto, with Dr. Andres Lozano. I have now successfully started a pediatric DBS program. I believe that we are currently at a very exciting intersection of many fascinating opportunities within DBS devices, animation suit movement detection, and white matter fiber tracking; all coming together at the same time. The ability to harness innovative, next generation DBS technology in the form of Activa PC+S, in our collaboration with Medtronic, will afford a wonderful opportunity to leverage novel technology into neuroscience discovery.

My PhD in molecular biology was devoted to better understanding human brain development in the setting of neurogenesis. The key discovery was that cortical neurons do not turnover, and that much of plasticity is likely related to white matter structural change over time. This background interest can now be applied towards understanding some aspects of how deep brain stimulation is able to affect a growing child’s clinical course of dystonia. This proposal will allow us to objectively observe facets of neuroplasticity within the brains of children, by way of direct neural recording, tracking MRI changes over time, and hopefully by correlating motor improvement as the neurostimulation adds therapeutic benefit.

B. Positions and Honors

Positions and Employment

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<tr>
<td>1996-2000</td>
<td>Medical Student at Queen’s University</td>
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<td>2000-2003</td>
<td>Neurosurgical Resident at University of Toronto</td>
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<tr>
<td>2003-2007</td>
<td>Ph.D. at the Medical Nobel Institute, Karolinska Institute, Stockholm, Sweden with Professor Frisen (human stem cell focus)</td>
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<tr>
<td>2007-2009</td>
<td>Completion of Neurosurgical Residency at University of Toronto</td>
</tr>
<tr>
<td>2010-2011</td>
<td>Combined Clinical Pediatric Neurosurgery and Stem Cell Basic Science Fellowships at Rady Children’s Hospital and Sanford Burnham Institute</td>
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2011-2015  Staff Pediatric Neurosurgeon at Barrow Neurological Institute at Phoenix Children’s Hospital
2015 onwards  Medical Director of Pediatric Neurosurgery and Staff Scientist at Sanford Children’s Hospital

Honors and Awards

1993  Offered University of Toronto’s Admission Scholarship to University College
1993  University of Western Ontario’s Elmer Avery Admission Scholarship
1995-1996  University of Western Ontario Scholarship
1993-1996  Canada Scholar awarded by the Canadian Prime Minister
1996  Rhodes Scholarship finalist from the University of Western Ontario
1997  Canadian Space Agency full scholarship to attend the International Space University (ISU) Summer Session in Houston, Texas
1998  J.D. Hatcher Award, Queen’s University Department of Physiology
1998  John F. Sparks Memorial Fund Scholarship, Queen’s University School of Medicine
2003-2005  Parkinson Society of Canada Basic Research Fellowship
2006  Heart and Stroke Foundation of Canada Research Fellowship
2006  CIHR-1A Recognition Prize in Research in Aging
2006  Canadian Institute of Health Research (CIHR) Fellowship
2007  Synthes Resident Craniofacial Award at the 75th American Association of Neurological Surgery in Washington, DC
2007  Krieg Cortical Kudos Prize from the Society for Neuroscience’s Cajal Club for most outstanding doctoral thesis
2009  K.G. McKenzie Memorial Prize for Clinical Research from the Canadian Neurological Sciences Federation
2014  Awarded Phoenix Business Journal’s Healthcare Hero Award for Medical Innovation
2014  Awarded a Certificate of Special Congressional Recognition based on biomedical work performed in Arizona, in 2014

C. Contribution to Science

1. I was instrumental in starting a clinical pediatric deep brain stimulation (DBS) program over the past year, and personally implanted ten children with DBS systems. This endeavor took leadership skill, passion, and determination in order to create a multidisciplinary team with the aim of helping children with movement disorders. These following papers demonstrate that I have been involved in innovative and novel clinical work in the field of pediatric functional neurosurgery, and emphasize how this positions me to optimally leverage the next generation DBS technology, explained within the scope of the grant:

2. During my PhD at the Nobel Medical Institute in Stockholm, Sweden, my thesis work directly looked at human cellular turnover in different organs in humans. My thesis work was able to devise a novel strategy using the carbon-14 isotope to retrospectively date various cellular populations from differing organs. A key aspect of this work allows one to see plasticity and stem cell dynamics in various organ systems. This work is instrumental to this project because neurogenesis has been implicated to mechanisms of DBS function, and cell turnover in the brain may be linked to the creation of new cells. Also, the DTI aspects which are
linked to cellular plasticity may also be occurring as a result of abnormal cell turnover. These papers demonstrate my prior contributions to this important field:


3. As a clinician scientist, I have demonstrated true passion in solving problems and attempting to help my patients. I had encountered a few children suffering from atypical teratoid rhabdoid tumors, which is a deadly form of infantile malignant brain tumors. The papers below show that I effectively challenged passion, curiosity, and novel technology into attempting to find better treatment paradigms for my patients. These works also show my commitment to research, to dedicating my efforts to focus on building a basic science laboratory, and finding tangible discoveries within novel research strategies:


4. I have also greatly enjoyed the opportunity to teach students during my PhD program as well as to medical students. This grant will allow me to interact with many experts in movement disorder, biophysics, imaging, and bioengineering. This will translate into many excellent learning and teaching opportunities for me to participate in during the course of this project.
Mentor Description Form

- **Mentor Contact Information**
  - Name: Brian Burrell
  - Title: Associate Professor
  - Phone: 605-658-6352
  - E-mail: bburrell@usd.edu
  - Lab web page: http://sites.usd.edu/brian-burrell/

- **Location of Summer Research** (Example: Sanford Medical Center, Sioux Falls): Lee Med Bldg., Vermillion

- **Description of Your Research (<200 words)**

Nociception (the perception of pain) is a critical function of the nervous system that protects us from additional injury or death. My laboratory is interested in the cellular mechanisms of how nociception is modulated and we are interested in a class of lipid neurotransmitters referred to as endocannabinoids. Specifically, we are examining how endocannabinoids can have both anti-nociceptive and pro-nociceptive effects. Our research suggests that these transmitters differentially modulated nociceptive and non-nociceptive synapses, depressing nociceptive synapses (an anti-nociceptive effect) and potentiating non-nociceptive synapses (a potentially pro-nociceptive effect). These studies utilize the medicinal leech, *Hirudo verbana*, as a model system because the nervous system in *Hirudo* is very well characterized in terms of the identity, functional role and synaptic connections of individual neurons. This makes it possible to carry out detailed analyses of pre– versus postsynaptic cellular mechanisms mediating synaptic plasticity and to link plasticity in individual neurons or synapses to changes at the behavioral level. The lab utilizes electrophysiological, behavioral, and molecular biology approaches to address these questions about endocannabinoids and nociception. This comparative approach can uncover fundamental mechanisms of nociception and endocannabinoid modulation that may also have applications for the treatment of chronic pain.

- **Description of Project(s) Available to Summer Students (<200 words/project)**

Behavioral studies to assess the role of habituation as a potential mechanism for reducing nociceptive signaling.

Cloning potential receptors and other intracellular signaling components associated with endocannabinoid signaling.
NAME: Brian Donald Burrell

eRA COMMS USER NAME (credential, e.g., agency login): BDBURRELL

POSITION TITLE: Associate Professor

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

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<tr>
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<td>Ph.D.</td>
<td>05/1995</td>
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<tr>
<td>Purdue University; West Lafayette, IN</td>
<td>Postdoc</td>
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<tr>
<td>Univ. of Miami Sch. of Medicine; Miami, FL</td>
<td>Postdoc</td>
<td>12/2000</td>
<td>Neuroscience</td>
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Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement
My research focuses the cellular mechanisms in the brain responsible for adaptive changes in behavior. I use *Hirudo verbana* (the medicinal leech) as a model system because it is possible to dissect changes at the neural circuit level that can be linked to specific forms of behavioral plasticity. Using both electrophysiological and behavioral approaches, I have studied the learning-induced neuromodulation, the effects of neuro-injury on learning, and, most recently, the role of endocannabinoids in modulating pain. This research has resulted in a number of new discoveries regarding the ability how endocannabinoids can have both pro- and anti-nociceptive effects and the role of Cl- gradients in regulating the “sign” of synaptic plasticity. This research has been supported by the NSF (2002-2006; 2011-2014) or by institutional bridge funds (2014-2016) and over the last seven years has resulted in 18 peer-reviews papers, several in prestigious journals such as the *Journal of Neuroscience*, *Neuroscience*, and *Journal of Neurophysiology*. In terms of graduate student training, I have begun to emphasize preparing students for multiple career paths given the current environment for academic research/faculty positions. I am happy to say that mentees have gone on to a variety of careers that include research at research at academic institutions, medicine, patent law, and private industry. My other professional objective is to enhance the environment for neuroscience research in South Dakota. Towards this goal, I serve as the Associate Director of the University of South Dakota (USD) Center for Brain and Behavior Research (CBBRe), an interdisciplinary, translational research program that draws from the strengths of faculty involved in both animal model- and human subject-based research.

B. Positions and Honors

**Positions**
2001 - 2004 Assistant Research Scientist, Department of Biological Sciences, Purdue University
2004 - 2010 Assistant Professor, Division of Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota
2010 - present Associate Professor, Division of Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota
2013 - present Associate Director, University of South Dakota Center for Brain & Behavior Research (CBBRe); Co-Director of the Summer Program for Undergraduate Research in Addiction (SPURA)

**Honors**
brains. activity community was convinced that invertebrate nervous systems were incapable of undergoing persistent, evolution

Physiology Journal of Neurobiology, Reviews in the Neurosciences, Nature Reviews Neurosciences, and this work was cited in a number of papers including reviews in studies were novel at the time in that they directly connected changes in excitability to learning and memory. These studies emphasized a role for modulation of intrinsic excitability at a time when synaptic plasticity was the sole focus of learning a

Effects of Neuro

C. Contribution to Science

Effects of Neuro-injury & Changes in Excitability during Learning and Memory: I was part of a study that examined how axotomy of a single interneuron in the medicinal leech (Hirudo verbana) could disrupt learning and that when the axon regenerated, learning could actually recover. This remains one of the only studies in which lesioning of a single neuron could disrupt learning so completely and was followed by studies examining how this single cell contributed to learning and memory. These studies emphasized a role for modulation of intrinsic excitability at a time when synaptic plasticity was the sole focus of learning and memory neurophysiology. In experiments where it was possible to monitor both electrophysiological and behavioral changes simultaneously, I observed decreases in excitability during habituation-type learning and increases in excitability associated with sensitization-type learning. Increased excitability during sensitization was mediated by serotonin which reduced the level of afterhyperpolarization, increasing the firing rate of this cell. These studies were novel at the time in that they directly connected changes in excitability to learning and memory and this work was cited in a number of papers including reviews in Current Biology, Trends in Neurosciences, Journal of Neurobiology, Reviews in the Neurosciences, Nature Reviews Neurosciences, and the Journal of Physiology. This work was funded, in part by, an award from NSF (IOS-0213458).


Evolutionary conservation of mechanisms of synaptic plasticity: Starting in the early 90’s, the neuroscience community was convinced that invertebrate nervous systems were incapable of undergoing persistent, activity-dependent synaptic changes (e.g., LTP and LTD) utilizing the same mechanisms of found in vertebrate brains. David Glanzman’s lab was the first to discovered NMDAR-dependent LTP in an invertebrate, Aplysia.
My lab was the first to extend this discovery to Hirudo (an annelid). This initial discovery was published in *J. Neurosci* and reported in the *J. Exp Biol*’s “Outside JEB” section. Importantly, we found that, as in mammals, LTP required activation of postsynaptic PKA and CamKII signaling cascades while LTD required activation of postsynaptic protein phosphatases. We also carried out important work supporting the hypothesis that the balance of kinase vs. phosphatase activation played a key role in linking specific patterns of activity to potentiation vs. depression. Finally, we found that, as in the mammalian CNS, Hirudo synapses were capable of a diverse array of both NMDAR-dependent and independent forms of activity-dependent synaptic plasticity, including mGluR-mediated LTP and endocannabinoid-dependent LTD. This work was important because it demonstrated that invertebrates do possess the necessary cellular machinery to carry out activity-dependent forms of LTP and LTD comparable to what is observed in mammals and confirming the utility of invertebrates as model systems in studies of learning and memory, neurodevelopment, and sensory processing. This work was funded, in part by, an award from NSF (IOS-0432683).


**Burrell BD, Li Q (2008).** Co-induction of long-term potentiation and long-term depression at a central synapse in the leech. *Neurobiol Learn Mem* 90: 275-279. PMID 18182311


Li Q, **Burrell BD** (2011) Associative, bidirectional changes in neural signaling utilizing NMDA receptor- and endocannabinoid-dependent mechanisms. *Learning & Memory* 18: 545-553. PMID 21844187

*Principles of endocannabinoid-based modulation:* Endocannabinoids are known to mediate their effects via metabotropic cannabinoid receptors (CB1 & CB2), but they can also act on Transient Receptor Potential Vanillid (TRPV) channels. The *Hirudo* CNS possess the endocannabinoid transmitters, 2-arachidonoyl glycerol (2-AG) and anandamide, as well as TRPV channels, but lack CB1/CB2 orthologues (as do all protostomal invertebrates). This makes *Hirudo* a useful model system for examining the cellular mechanisms and functional significance of endocannabinoid/TRPV-based synaptic plasticity. The cellular mechanisms mediating endocannabinoid-dependent LTD (eCB-LTD) are largely conserved between mammals and *Hirudo*. Although these studies are relatively recent, they have been cited in four different review articles in a recent issue of the *Philosophical Transactions of the Royal Society*. Subsequent experiments made novel discoveries concerning the role of pre- and postsynaptic roles for transcriptional- and translational-dependent processes during eCB-LTD and that the endocannabinoid 2-AG was capable of activating TRPV (the latter has been recently confirmed in mammalian studies). We have also been investigating the capacity of endocannabinoid signaling to both depress nociceptive synapses and potentiate non-nociceptive synapses, the latter being the result of eCB-LTD of inhibitory inputs resulting in disinhibition. These effects are functionally relevant, with endocannabinoid reducing responses to nociceptive stimuli and enhancing responses to non-nociceptive stimuli. This research is highly relevant to understanding the potential clinical efficacy of cannabinoid-based approaches in treating pain, where conflicting results continue to be observed. Our findings suggest that endocannabinoid-based therapeutics are best applied to pain conditions dominated by hyperalgesic symptoms and should not be used in pain conditions involving allodynia. This work was funded by an award from NSF (IOS-1051734) and by institutional bridge funds.


Mentor Description Form

Mentor Contact Information
- Name: Erik A. Ehli
- Title: Scientific Director
- Phone: 605-322-5976
- E-mail: erik.ehli@avera.org
- Lab web page: http://www.avera.org/innovation-research/institute-for-human-genetics/

Location of Summer Research (Example: Sanford Medical Center, Sioux Falls):
Avera Institute for Human Genetics; Sioux Falls

Description of Your Research (<200 words)
Currently working as the Scientific Director at the Avera Institute for Human Genetics, I have a research interest in the molecular genetics of complex diseases. I am actively involved in leading genotyping projects on samples collected from children and adolescents through the Netherlands Twin Register. In addition, I have a deep interest in cancer genetics and am working on the molecular characterization of metastatic breast cancer and also have an interest in understanding the tumor genetics of gynecological cancer, specifically uterine sarcoma. I have extensive training in a diverse range of molecular genetics techniques, including high density SNP genotyping, methylation, next generation sequencing, and pharmacogenetic profiling.

Description of Project(s) Available to Summer Students (<200 words/project)
The Avera Institute for Human Genetics (AIHG) laboratory, Sioux Falls, South Dakota has established a formal partnership with one of the largest twin registers in the world (Netherlands Twins Register). Comparing data from monozygotic (MZ) and dizygotic (DZ) twin pairs makes it possible to discern genetic and shared environmental effects on complex traits and diseases. MZ twins are nearly always similar with respect to DNA sequence and are reared in the same family environment, while DZ twins share the same family environment but share on average only 50% of the segregating genes. In the classical twin design, the contribution of genetics and environment to complex traits and diseases is estimated by comparing MZ to DZ resemblance. By measuring genetic variants on twins through microarrays the location in the genome of genetic contributions to the trait can be elucidated. The AIHG has recently launched the first twin register in South Dakota. A project is available in our laboratory to investigate the similarities and differences of twins born in SD vs. the Netherlands in terms of allele frequency, methylation differences, and/or collected phenotypes.
A. Personal Statement

I am a molecular biologist and Scientific Director at the Avera Institute for Human Genetics. My research interest is the molecular genetic mechanisms of complex diseases. I am actively involved in leading genotyping projects on samples collected from children and adolescents through the Netherlands Twin Register (NTR). In addition, I also focus on next generation sequencing projects with several collaborative groups at the University of Texas MD Anderson Cancer Center and internal collaborations with physician scientists within our own health system (Avera Health). We utilize whole exome sequencing, RNA sequencing, and whole genome sequencing to discover somatic mutations through the use of a liquid biopsy sample. In addition, I lead next generation sequencing projects in collaboration with the MD Anderson Moon Shots program. I have extensive training in a diverse range of molecular genetics techniques; including DNA and RNA microarrays, Sanger and Next Generation Sequencing, and quantitative PCR. I have collaborated with researchers from the Netherlands Twin Register since 2008 and we have produced several manuscripts related to behavioral, neuropsychiatric, cognition, and several other complex traits.


B. Positions and Honors

Positions and Employment

2005-2006  Registered Nurse, Surgical Trauma Department, Avera McKennan Hospital & University Health Center, Sioux Falls, SD
2007-2009  Genetics Research Associate, Avera Institute for Human Genetics, Avera McKennan Hospital & University Health Center, Sioux Falls, SD
2009-2013  Project Coordinator, Avera Institute for Human Genetics, Avera McKennan Hospital & University Health Center, Sioux Falls, SD
2010-2013  Clinical Instructor, Department of Psychiatry, University of South Dakota, Sioux Falls, SD
2013-Present  Research Scientist, Avera Institute for Human Genetics, Avera McKennan Hospital & University Health Center, Sioux Falls, SD
2014-Present  Assistant Professor, Department of Psychiatry, University of South Dakota, Sioux Falls, SD
2016-Present  Scientific Director, Avera Institute for Human Genetics, Avera McKennan Hospital & University Health Center, Sioux Falls, SD

Honors

2014  Avera McKennan Emerging Leaders Class of 2014
2004  ARCH Scholarship (Avera McKennan Hospital & University Health Center)
2001  EPSCoR Research Fellowship
1996  Lipscomb Memorial Scholarship
1996  Scarborough (Regent’s) Scholarship
1995  CRC Outstanding Chemistry Student of the Year Award

Professional Memberships

2010-Present  American Society for Human Genetics (ASHG)
2014-Present  International Society for Twin Studies (ISTS)
2014-Present  Behavioral Genetics Association (BGA)
2015-Present  International Society of Psychiatric Genetics (ISPG)

C. Contribution to Science

1. Mapping major loci for complex disease genetics. I have provided molecular biology expertise to genome-wide association, candidate gene, and copy number variation studies to map genetic loci influencing complex traits, such as attention problems/attention deficit hyperactivity disorder, depression, aggression, cognition/intelligence, withdrawn behavior, internalizing problems, and educational attainment. I have generated high quality SNP and sequence data using DNA from several different biological sources including blood, saliva, buccal swabs, and formalin fixed paraffin embedded tissues. I have expertise in quality control of large scale genetic data.


2. Twin Genetics and Heritability. We have established a formal partnership and have collaborated with the Netherlands Twin Register on several projects since 2008. During this time, we have received most of the available biological materials on NTR participants in our laboratory including; DNA, RNA, PBMCs, buccal swabs, and fecal samples. I have been actively involved in leading the DNA extractions, biobanking, SNP genotyping, VNTR genotyping, and methylation typing on many of the samples received into the laboratory from the NTR. The genetic data has been utilized in downstream longitudinal and multivariate modeling of twin-family data using genetic association studies.


3. Custom Array Development. I have developed a useful panel of markers to determine twin zygosity in participants from the Netherlands Twin register (NTR) and the Vermont Family Study (VFS). The zygosity panel contains 30 markers in psychiatric informative candidate genes with a very high minor allele frequency. As a result, the resulting zygosity data has also been utilized for association testing. Recently, I have significantly contributed to the development of a custom Affymetrix Axiom array for the generation of high density SNPs which is currently utilized to genotype samples in the NTR for genome-wide association studies. The design features a custom backbone to provide optimal imputation when combining newly generated data within existing NTR-SNP datasets. Innovations and improvements consist of increased efficiency of X chromosome imputation, with 1200 markers evenly spaced on X. The design also incorporates a significant behavioral genetics focus by including the common variants from two large consortia (Psychiatric Genomics Consortium and Million Veterans Program). Over 60,000 markers are included from the UK BioBank array including known GWAS hits from the NHGRI GWAS catalog, with additional modules including apoE, HLA, cardiometabolic, and mitochondrial SNPs. Of are the approximate 8,000 custom SNPs selected to further projects within the NTR, with a large set of SNPs implicated in twinning.


4. Mechanisms of pAD1 plasmid stability in Enterococcus faecalis. The par locus of the Enterococcus faecalis plasmid pAD1 is required for the maintenance and stable inheritance of the pAD1 replicon. We have shown that par stabilizes plasmid replications by a post-segregational killing (PSK) mechanism. PSK systems stabilize their host plasmid in a population of bacterial cells by programming for death any cells that have lost the plasmid. par encodes two small RNAs. My work has shown that RNA I is relatively stable in vivo and encodes and open reading frame of 33 codons whose product is the par toxin. RNA II is the unstable antidote, which acts as an antisense RNA to prevent the translation of RNA I. Stability experiments have shown that RNA II is stabilized in the presence of RNA I. The results of these experiments resulted in a testable model for par function, for which experiments have been ongoing for several years.


Complete List of Published Works: https://goo.gl/SX5L1d
Mentor Description Form

Mentor Contact Information
- Name: Gina Forster, PhD
- Title: Professor
- Phone: 658-6349
- E-mail: gforster@usd.edu
- Lab web page: [http://www.usd.edu/faculty-and-staff/Gina-Forster](http://www.usd.edu/faculty-and-staff/Gina-Forster)

Location of Summer Research (Example: Sanford Medical Center, Sioux Falls):
Lee Medicine, Vermillion

Description of Your Research (<200 words)
Research in the Forster Laboratory aims to understand the neurobiology of anxiety states, and how factors such as early life stress, substance use, or traumatic brain injury affect brain function to produce anxiety states. These questions are addressed using molecular, neurochemical and behavioral assays in translational animal models, and also functional neuroimaging and hormone assays in human participants. Our research particularly focuses on neuromodulation within the limbic system and how stressors, injury or substance use modifies neurotransmission and activity of limbic system structures. The ultimate goal is to direct new and more effective treatment strategies for anxiety disorders.

Description of Project(s) Available to Summer Students (<200 words/project)
For the summer of 2017, projects will be available within two areas. The first relates to mild traumatic brain injury (mTBI) or concussive injury, which has been shown to be associated with increased incidence of anxiety disorders such as PTSD. Using a relevant rat model of mTBI, we have observed anxiety and PTSD-like symptoms, and disruption to limbic system structures in the brain. Recently we have noted sex differences in these outcomes. With brain tissue already collected from this model, potential projects include assaying neurotransmitter receptor levels/transporters and neuromodulator levels in the limbic system of male and female rats exposed to mTBI to determine underlying mechanisms (and potential therapeutic targets) that can explain how mTBI can lead to anxiety and why sex differences exist.

The second project relates to the observation that women are more likely to develop PTSD, and clear sex differences exist in animal models of PTSD. Using brain tissue collected from male and female rats (at different phases of the estrous cycle), a potential summer project would use immunohistological methods to determine sex differences in neurotransmitter receptors and neurotrophins within brain regions involved in fear learning and fear extinction. By doing so, it is anticipated that the biological basis in differences in fear conditioning would be clarified with implications for sex-specific treatment of PTSD.
NAME: Forster, Gina L

eRA COMMONS USER NAME (credential, e.g., agency login): gforster

POSITION TITLE: Professor and Director

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

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Positions:

1996-1997 Teaching and Research Assistant, Psychology Department, University of Otago, New Zealand
1997-1998 Research Fellow, Anatomy Department, University of Otago Medical School, New Zealand
1998-2000 Teaching and Research Assistant, Psychology Department, Macquarie University, Australia
2001-2001 Lecturer, Department of Biological Sciences, Macquarie University, Australia
2002-2004 Research Assistant Professor, Department of Biology, University of South Dakota
2005-2010 Assistant Professor (tenure-track), Division of Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota School
2010-2015 Associate Professor (tenured), Division of Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota School
2013-current Director, Center for Brain and Behavior Research, University of South Dakota
2015-current Professor (tenured), Division of Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota School

Honors/Awards:

1996 University of Otago Division of Sciences Award
1997 T.P.H. McKellar Award for top graduate, Honors I, Psychology, University of Otago
1997 University of Otago Division of Sciences Research Fellowship
1997-1998 Otago Medical Research Foundation Research Fellowship
1998-1999 New Zealand Neurological Society Student Award
1998-2001 Macquarie University Postgraduate Research Fellowship
1999 Australian Neuroscience Society Student Award
2000 International Society for Muscarinic Receptors Studentship
2001 Australian Neuroscience Society Neurochemistry Research Award
2003 Society for Integrative and Comparative Biology, Neuroendocrinology Travel Award
2005 University of South Dakota Research Office Faculty Travel Award
2009 South Dakota Young Investigator selected to represent South Dakota at the EPSCoR/IDEA meeting in Washington DC
2009 NIMH/NIDA Travel Award for the Axelrod Neuropharmacology Poster Session at the Society for Neuroscience Meeting, Chicago, IL
2009 President’s Award for Research Excellence (Early to Mid Career Investigators), University of South Dakota
2014 Chester McVay Award for Excellence in Teaching and Research, University of South Dakota Sanford School of Medicine
President's Award for Research Excellence (Established Investigator), University of South Dakota

**Professional Memberships:**
- 1998-current: Member of the Society for Neuroscience
- 2001-current: Member of the J.B. Johnston Club for Comparative Neuroscience
- 2002-current: Member of the Society for Behavioral Neuroendocrinology
- 2005-current: Member of the International Behavioral Neuroscience Society
- 2007-current: Full Member of Sigma-Xi
- 2009-current: Member of the “Faculty for Undergraduate Neuroscience”, a society for undergraduate neuroscience research and education

**Peer-Review Experience:**
- 2002-current: Reviewer for the journals *General and Comparative Endocrinology; Hormones and Behavior; Neuroscience; Brain Research; Neuroscience Letters; Progress in Neuropsychopharmacology and Biological Psychiatry; Pharmacology, Biochemistry and Behavior; Neuropsychopharmacology; Behavioural Brain Research; Neuroscience Research; Psychoneuroendocrinology, Neurobiology of Learning and Memory; Neuropharmacology; Synapse; Chinese Journal of Physiology; European Journal of Neuroscience, Cerebral Cortex, Journal of Neurochemistry; Journal of Neuroscience, Neuroimage, and Psychopharmacology.*
- 2005-2009: Ad Hoc grant reviewer for National Institutes of Health (NIH) MESH Study Section
- 2007: Grant Reviewer for the New Zealand Neurological Foundation
- 2007-current: Grant Reviewer for National Science Foundation (NSF)
- 2009: Member of the NIH Special Emphasis Review Panel (ZRG1 IFCN-L (52)) for AARA Area (R15) grants
- 2010: Member of the NIMH Special Emphasis Review Panel (ZMH1 ERB-L (2)) Identification and Characterization of Sensitive Periods for Neurodevelopment in Studies of Mental Illness
- 2010-current: Grant Reviewer for the Netherlands Organization for Scientific Research
- 2011: Member of the NIH Special Emphasis Review Panel MDCN-G (04): Molecular, Cellular and Developmental Neuroscience
- 2012-2016: Editorial Board Member, *Neuroscience*
- 2012-2016: Regular member of the National Institutes of Health (NIH) MESH Study Section
- 2013: Grant Reviewer, Medical Research Council (MRC), UK.
- 2013: Member of the NIH Special Emphasis Review Panel (ZAG1): Social Neuroscience and Neuroeconomics of Aging (SNNA)
- 2016: Member of the NIH/NIMH Special Emphasis Review Panel ZMH1 ERB-X (02): NRSA Institutional Research Training (T32) Grants

**Other Experience and Training:**
- 2000-2001: Organizer for Macquarie University Science Days
- 2000-2002: Research Mentor for promising undergraduate students in the “Advanced Biology Program”, Department of Biological Sciences, Macquarie University
- 2006-2011: Co-director of the USD Center for Biomedical Research Excellence (COBRE) Behavioral Core
- 2008-2009: Member of the LCME Research subcommittee, Sanford School of Medicine, USD
- 2008-2010: Chair of the Sanford School of Medicine Research Committee, USD
- 2007-current: Member of the Basic Biomedical Sciences Research Council, Sanford School of Medicine, USD
- 2008-2010: Member of the U Discover Committee (undergraduate summer research program), USD
- 2008-current: Member of the University of South Dakota Institutional Animal Care and Use Committee
- 2011: Member of the University of South Dakota Strategic Planning Council
- 2011: Visiting Fellow – Martinos Center Fellowship Program in Functional MRI, Massachusetts General Hospital, Boston

**Contribution to Science**

*Modulation of Dopamine Systems – Implications for Neurological and Psychiatric Disorders*: My very early career working with Dr. Charles Blaha was focused on determining the neuromodulators of dopamine systems involved
in movement and reward. The emphasis was on the cholinergic system ascending from the brainstem, important given this system directly innervates dopamine cell body regions, is implicated in arousal and salience, and exhibits cell loss in movement-related degenerative disorders. Therefore, understanding how the brainstem cholinergic system modulates forebrain dopamine has numerous implications for the underlying pathology and potential treatments of neurological disorders such as Parkinson’s disease, as well as schizophrenia and addiction-related disorders. Using in vivo electrochemical recording techniques and various behavioral assays, I found that the brainstem cholinergic system directly activates dopamine neurons to enhance dopamine release in the forebrain via a variety of receptor types, to increase dopamine-related behaviors. In collaboration with Dr. John Yeomans at the University of Toronto, we found a critical role for the muscarinic M5 receptor. The function of this receptor in the brain had been poorly characterized due to a lack of pharmacological tools. We used a mutant M5 mouse to show the M5 receptor functioned to prolong subcortical dopamine release, and demonstrated a link between this receptor’s function and schizophrenic symptoms, as well as responses to drugs of abuse. Overall, this work lead to the first identification of a role for the muscarinic M5 receptor in the brain with important treatment implications, and our publication in *Journal of Neuroscience* became one of the top ten cited for over a year. Furthermore, our characterization of the ability of the cholinergic brain stem to drive dopamine neurons opened up a new avenue of investigation that has been explored by numerous other investigators to better understanding the neurobiology underlying addiction.


*Corticotropin-Releasing Factor Type-2 Receptor as a Novel Target for Preventing Negative Effects of Early Life Stress*: In recent years, I have concentrated research efforts on determining the role of the corticotropin-releasing factor (CRF) type-2 receptor in normal neural function and how this is altered by early life stress. The CRF system had long been implicated in stress and anxiety, with the focus on the CRF1 receptor subtype. The role of the CRF2 receptor was more elusive, as it was characterized later and the pharmacological tools were not conductive to its study. Conflicting results from genetic vs. pharmacological manipulations left the role of this receptor unclear. Given its potential to modulate serotonin systems, I focused on elucidating the ability of this receptor to modulate serotonin in normal states, and in states of heightened anxiety as induced by early life social isolation of rats. My laboratory produced a body of work that definitively shows the CRF2 receptor expression is increased by early life stress, which increases serotonin activity, and this receptor can be blocked to reverse the anxiogenic effects of early life stress. This work was highlighted in a *Journal of Neuroscience Journal Club*, was profiled by the *Faculty of 1000 Medicine*, and identified in the “Science-Business eXchange” published by Nature Publishing Group as an important recent advance in potential pharmacotherapy.


A Systems Approach to Understanding How Serotonin Modulates Stress Responses – Implications for Drug Withdrawal: I have also dedicated time to the study of serotonin systems, and how serotonergic activity throughout a distributed system might produce adaptive and maladaptive stress responses. This is particularly important given that we know serotonin is strongly implicated in stress, mood and emotion and related disorders, but it is unclear where and how alterations to serotonin relate to symptoms of affective disorders. Using a systems neuroscience approach, I found that increased activity in regions such as the hippocampus and the medial prefrontal cortex reduce stress responses and anxiety, whereas serotonin in the amygdala enhances these states. This body of work points to a finely-balanced distributed serotonin system, that when disrupted, leads to symptoms of affective disorders. This work has been recognized as being important for our understanding of the neurobiology underlying disorders such as depression (e.g. “Rethink needed for the cause of depression”. New Scientist, July 24, 2010, pg 12-13). Furthermore, we have applied these concepts to the study of amphetamine withdrawal. Amphetamine misuse and abuse is rising, and a clear withdrawal syndrome emerges in over 80% of those with amphetamine dependence. Stress sensitivity and anxiety that develop during withdrawal are reported to promote craving and relapse. Therefore we conducted research that shows chronic amphetamine disrupts this balance of serotonin function in the limbic system, which directly results in heightened stress sensitivity and anxiety states. It is anticipate that these findings will help direct therapeutics for amphetamine withdrawal to prevent relapse.


Linking Mild Traumatic Brain Injury with PTSD-like Symptoms: Given the incidence of PTSD-like symptoms in soldiers who have received a mild traumatic brain injury, I sought to understand whether concussive head injury would alter the brain in a similar manner that is seen in PTSD – namely, reduced hippocampal function and increased amygdala function, thought to lead to symptoms of anxiety, hyperarousal and fear. I received a highly competitive Concept Award from the Department of Defense to develop a relevant animal model with which to study this question. Once the model had been developed and validated, we performed a series of studies that show mild traumatic brain injury results in increased cell death and reduced neurons in the hippocampus, with increased neuronal numbers in the amygdala, increased generalized anxiety, increased fear conditioning and impaired fear extinction. Our most recent research suggests an important role of the glucocorticoid receptor in mediating these effects. Overall, this most recent development in my laboratory demonstrated for the first time, a direct effect of concussive brain injury on the limbic system to produce PTSD-like symptoms and opens the way to now study the prevention and treatment of these debilitating outcomes.


Full list of publications: http://goo.gl/IAYOF8
Mentor Description Form

Mentor Contact Information
- Name: Kevin Francis
- Title: Assistant Scientist
- Phone: 605-312-6422
- E-mail: kevin.francis@sanfordhealth.org
- Lab web page: http://www.sanfordresearch.org/researchcenters/childrenshealth/francislab/

Location of Summer Research (Example: Sanford Medical Center, Sioux Falls):
Sanford Research Center, Sioux Falls

Description of Your Research (<200 words)
While a host of genetic conditions result in pediatric disease within the nervous system, the precise molecular mechanisms that underlie neurodevelopmental conditions are poorly understood. For example, perturbation of cholesterol homeostasis exerts dramatic effects on tissue development, function, and patient phenotypes, though both clinical and research findings are inconsistent and untreatable. My research projects utilize induced pluripotent stem cells and genetic mouse models to examine how cholesterol and lipids interact with developmentally critical signaling pathways to affect neural development, cellular function, and disease pathogenesis. One pathway of particular interest is Wnt/β-catenin signaling, an important regulator of early tissue development, brain function, and cancer progression. An array of experimental techniques is utilized, including iPS cell models and reprogramming methods, immunocytochemistry, whole genomic sequencing, high-throughput screening methods and standard molecular biology/biochemical assays, to identify causes and potential targets for patient therapy. These projects also explore basic biological questions regarding how lipid metabolism regulates normal mammalian development.

Description of Project(s) Available to Summer Students (<200 words/project)
My lab has multiple projects related to cholesterol metabolism and stem cell genetics that would be applicable for student projects. Work performed by students on these projects would significantly contribute to ongoing studies and expand upon preliminary data, leading to publications and authorship.

Available projects are attempting to answer the following questions:
1. How does cholesterol homeostasis affect stem cell and progenitor pools in the brain? Through the identification of altered Wnt signaling related to cholesterol defects, open questions persist regarding the functional consequences of this interaction on stem and progenitor cells within various brain regions. Primarily through use of fluorescent microscopy, molecular biology, and transgenic mouse models, we want to determine the specificity and extent of stem cell defects related to cholesterol homeostasis across brain regions in young versus aged animals.
2. How do cholesterol and other sterols regulate stem cell differentiation and functionality? Studies analyzing cholesterol metabolism demonstrate vastly different activity for cholesterol synthetic enzymes across species and between cell types, resulting in varied responses to changes in cholesterol homeostasis. However, how cholesterol metabolism affects human stem cell function and differentiation is unclear. Using in vitro stem cell culture methods, gene expression, and bioluminescent assays, we will define how levels of cholesterol and close metabolites regulate human stem cell function, metabolism, and differentiation.
3. How does altered cholesterol and sterol homeostasis affect hormone levels and associated signaling? A well-established function of cholesterol is to serve as a precursor for the generation of sterol-derived hormones critical for neurodevelopment and function. However, it's unclear how subtle alterations in cholesterol synthesis through accumulation of cholesterol precursors affect hormone levels and distribution. We are utilizing molecular biology techniques, such as ELISAs and qPCR, and cellular assays to explore how mutational events in cholesterol synthesis enzymes affect the generation of critical hormones such as estrogen and progesterone, while discerning how downstream events are affected.
4. Can we develop and utilize human iPS cell reporter cell lines using CRISPR/Cas9 gene editing? The development of precise gene editing techniques, such as the CRISPR/Cas9 system, allows researchers to create specific mutational or insertion events. Using this system, we are developing human stem cell lines carrying fluorescent reporters, allowing us to examine patterns of differentiation in neurologically affected patient populations and develop assays to optimize differentiation toward specific lineages. These projects utilize techniques encompassing molecular, cellular, and biochemical techniques.
A. Personal Statement

My research focuses on understanding the biological mechanisms underlying disorders of neurodevelopment using induced pluripotent stem (iPS) cells derived from rare patient populations. Using iPS technology and disease modeling, I’m studying the differentiation, neural function, and signaling pathways underlying neurological syndromes, including Smith-Lemli-Opitz syndrome (SLOS). We are utilizing various in-vitro assays to determine the effects of these disorders on pluripotent, progenitor and neuronal cell types. My work has been recognized for numerous awards and invited presentations during my training. My current laboratory at Sanford Research will continue these efforts with an expanded focus on the use of genome editing methods in therapeutic screening methods. I will also continue to mentor and train young scientists within my own research laboratory. While training at the NIH, I was the direct supervisor for six post baccalaureate trainees, two of which received NIH-wide awards for their research and four of which are authors on primary research articles. All six were accepted to prestigious medical and graduate training programs, including UCSF, Georgetown University, and Penn. Each student not only received extensive research experience, but also developed their skills in presenting their data in oral and poster formats, data management, and record keeping. I was also responsible for supervising numerous summer students and research interns during my postdoctoral and predoctoral training. I am very excited to continue to train the next generation of young scientists in my new position at Sanford Research and the University of South Dakota School of Medicine.

B. Positions and Honors

Positions and Employment

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<td>Graduate student</td>
<td>University of Georgia</td>
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<td>2004-2009</td>
<td>Doctoral candidate</td>
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<td>2009-2015</td>
<td>Postdoctoral fellow</td>
<td>National Institute of Child Health and Human Development</td>
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<td>2015-</td>
<td>Associate Scientist</td>
<td>Children’s Health Research Center, Sanford Research</td>
</tr>
<tr>
<td>2015-</td>
<td>Assistant Professor</td>
<td>Department of Pediatrics, University of South Dakota School of Medicine</td>
</tr>
<tr>
<td>2015-</td>
<td>Adjunct Assistant Professor</td>
<td>Department of Chemistry and Biochemistry, South Dakota State University</td>
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Other Experience and Professional Memberships

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<tr>
<td>2005-</td>
<td>Member, The Society for Neuroscience</td>
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2010- Member, The International Society for Stem Cell Research
2011-12 Monthly contributor to NICHD Newsletter, “The Connection”
2011-12 NIH Fellows Committee representative for NICHD
2011 NICHD Fellows Steering Committee chair

Honors
2004 American Association for the Advancement of Science award
2004 Graduate Assistance in Areas of National Need (GAANN) award
2005 MUSC Student Research Day Poster winner
2007-08 Training Grant in Environmental Stress Signaling – Dept. of Pharmaceutical Sci
2008 MUSC Graduate Studies Travel Award
2008 Annual Meeting of the Southeastern Pharmacology Society Poster winner
2011 Speaker – NICHD Fellows Retreat
2011 Speaker – NIH Center for Regenerative Medicine Research Symposium
2012 Speaker – 5th Annual Maryland Stem Cell Research Symposium
2013 Travel award – The International Society for Stem Cell Research Annual Meeting
2013 Best Poster Award – NIH Center for Regenerative Medicine Research Symposium
2015 Speaker – Perlman School of Medicine at the University of Pennsylvania CAROT Center
2015 Travel award – The Society for Inherited Metabolic Disorders Annual Meeting
2015 Speaker – The Society for Inherited Metabolic Disorders Annual Meeting
2015 Neil Buist Founder’s Award – The Society for Inherited Metabolic Disorders
2015 Speaker – American College of Medical Genetics and Genomics Annual Meeting
2015 Speaker – Pathways of Neurodevelopmental Disorders – Keystone Symposia
2015 Speaker – American Society of Human Genetics Annual Meeting
2015 Speaker – Sanford Health – SDSU Biomedical Research Symposium
2016 Speaker – Sanford PROMISE Community Lecture Series
2016 Speaker – Northern State University, Department of Biology
2016 Speaker – University of North Dakota School of Medicine Building Better Brains Symposium

Complete List of Published Works in MyNCBI/Bibliography

C. Contribution to Science

1. My most recent research focus has been the development and study of human iPS cells for rare neurological disorders. Using reprogramming methods, various biochemical and molecular assays, and CRISPR/Cas9 genomic editing, I’ve uncovered a novel interaction between cholesterol, cholesterol precursors, and Wnt/β-catenin signaling regulating pluripotency and neural development. This work has uncovered very specific effects of cholesterol versus cholesterol precursors on human development, as well as identifying key developmental differences between different disorders of cholesterol synthesis. Targeting Wnt signaling now has therapeutic potential for this currently untreatable class of disorders.


2. To address how hypoxic conditions affect stem cell function and neurodevelopment, I have studied how hypoxia affects the differentiation of human and mouse stem cell models, as well as cell replacement therapies using in vivo rodent models. This work provided novel findings regarding how brief periods of hypoxic conditioning promote cell survival and enhanced differentiation of excitatory neurons through anti-apoptotic signaling mechanisms. This work has important implications for cell transplantation therapies using stem cell models.


3. I have studied the development of functional neurons from embryonic stem cells to help understand the biological processes regulating neurodevelopment. These efforts spanned multiple research projects using both mouse and human model systems, identifying specific effects of the Src family of tyrosine kinases and voltage-gated ion channel function in the specification of excitatory neurons. This work also has significant implications for optimizing cell-based therapies in regenerative applications for the treatment of neurological disorders.


Mentor Description Form

Mentor Contact Information
- Name: Scott Killian, PhD, MPH
- Title: Assistant Professor
- Phone: (605) 658-6387
- E-mail: scott.killian@usd.edu
- Lab web page: https://sites.google.com/a/usd.edu/killian-lab/

Location of Summer Research:
- Dr. Killian’s laboratory is located in the Lee Medical Building in Vermillion but there will be ample opportunity to work remotely.

Description of Your Research (<200 words)
My research is focused on studies of the human immune response to viral infections. Emphasized in the laboratory are human immunodeficiency virus-1 (HIV-1), hepatitis C virus (HCV), zika virus (ZKV) infections. Our primary question is ‘Why do some individuals become infected and/or develop disease following infection, while others do not?’ We believe that host genetic differences influence the functionality of a subset of blood cells known as CD8+ T cells and are thereby responsible for the observed differences in viral pathogenesis.

Description of Project(s) Available to Summer Students (<200 words/project)
Elite Controllers of HIV-1 Infection. Elite controllers (EC) are rare HIV-1-infected individuals who are able to naturally control HIV infection without antiretroviral therapy. They maintain undetectable viral loads and have a very favorable clinical prognosis. The biologic explanation for EC status is unknown. Identification of the primary determinants of EC status will provide much needed insight for the development of a vaccine and new therapies for HIV infection. This project will investigate the immunologic and genetic features of elite controllers.

Participation in this project will:
1. Prepare the incoming medical student for the immunology block of Pillar 1,
2. Result in the submission of a manuscript for publication by the final week of the summer research program, and most importantly
3. It will be a fun summer research experience!
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Killian, M. Scott
ERA COMMONS USER NAME (credential, e.g., agency login): skillian
POSITION TITLE: Assistant Professor

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

A. Personal Statement

Dr. Killian is Assistant Professor in the Sanford School of Medicine at the University of South Dakota. He has over 20 years of immunology research experience ranging from the molecular characterization of T cell receptor repertoires in SCID-hu mice to the development of broadly neutralizing antibodies against novel HIV-1 envelope proteins. Dr. Killian received formal training in epidemiology under the mentorship of Dr. Roger Detels, PI of the Multicenter AIDS Cohort Study, and acquired skills necessary for study of complex human diseases. He conducted his doctoral research studies at UCLA in the laboratory of the late Dr. Janis Giorgi who is widely recognized for her contributions to the areas of adaptive immunity, flow cytometry and immune activation. Dr. Killian completed postdoctoral studies in Dr. Jay Levy's laboratory at UCSF, focusing on the immunologic, virologic, and genetic characterizations of elite controllers and other long-term survivors of HIV-1 infection. Dr. Levy is a co-discoverer of HIV and his research group made the seminal observation that CD8+ T cells inhibit HIV replication. As a Research Immunologist at UCSF, Dr. Killian made the discovery that CD8+ T cells secrete type 1 interferons (IFN1) at levels that inhibit HIV-1 replication in vitro and that neutralization of IFN1 eliminates nearly all of the soluble anti-HIV activity attributable to CD8+ T cells. Thus, his work revealed the identity of the long-sought CD8+ T cell anti-HIV factor (CAF). The recent gap in Dr. Killian’s publication record reflects his time spent as Director of Research at Therabiol Inc. where he developed and patented (lead author of WO 2014134547 A1) an immunogen and novel antibodies specific for conformational determinants of HIV envelope proteins. This research experience is particularly relevant to the present application and uniquely qualifies Dr. Killian to carry out the proposed project.

B. Positions and Honors

Positions and Employment
1995  Intern, Special Pathogens Branch, Centers for Disease Control, Atlanta, GA
2007-2012 Assistant Research Immunologist, Hem/Onc, UCSF Department of Medicine
2012-2014 Director of Research, Therabiol Inc., San Francisco, CA
2014-  Assistant Professor, Basic Biomedical Sciences, USD Sanford School of Medicine
Other Experience and Professional Memberships
2014- Editorial Board, Biologicals
2014- Editorial Board, Medicine: HIV/AIDS

Honors
2004    International AIDS Society Award
2004   NIH Scholarship Award
2007    NIH Scholarship Award

C. Contribution to Science

1. One contribution of Dr. Killian’s research is the characterization of the innate and adaptive immune responses to HIV-1 infection. He developed novel quantitative approaches for combining flow cytometry and transcriptional profiling to characterize the diversity of the T cell repertoire in healthy and diseased individuals. These methods are particularly useful for characterizing the breadth of the immune response in terms of the number of unique T cell clones responding to a particular antigen or pathogen. Dr. Killian’s research has detailed functional and translational aspects of plasmacytoid dendritic cells, autophagy, and soluble factors produced by T lymphocytes. Highlighting this focus on both innate and adaptive immunity is the identification that CD8+ T cells secrete interferon alpha as part of their antiviral functionality.


3. In addition to the research described above, Dr. Killian has developed a novel approach to deriving antibodies that target complex regions of macromolecular structures. This approach has been previously applied to HIV-1 and will be extended to ZIKV in the proposed studies.


Complete List of Published Work in MyBibliography:  https://goo.gl/hMWvm4
**Mentor Description Form**

**Mentor Contact Information**
- Name: Lance Lee, PhD
- Title: Assistant Professor, Department of Pediatrics
- Phone: 605-312-6410
- E-mail: lance.lee@sanfordhealth.org

**Location of Summer Research** (Example: Sanford Medical Center, Sioux Falls):
Sanford Research, Sioux Falls

**Description of Your Research (<200 words)**
The Lee Lab is devoted to understanding the genetic and molecular causes of the pediatric disorder primary ciliary dyskinesia (PCD). PCD affects approximately 1 in 16,000 newborn children worldwide and is commonly characterized by chronic respiratory infection, male infertility, and situs inversus, with hydrocephalus and female infertility also associated in some individuals. This syndrome results from dysfunction of motile cilia and flagella. Motile cilia are required for clearance of fluid and particles over the cell surface, and the structurally related sperm flagella are required for sperm motility. While the importance of cilia and flagella in human health is clear, the molecular mechanisms underlying ciliary function are still under investigation. In the lab, we use traditional and emerging genetic approaches to identify the underlying causes of PCD and its associated disorders in mouse models. We are also using a variety of biochemical and cell biological approaches to better understand the molecular mechanisms that regulate ciliary function. Identifying the genetic and molecular causes of PCD will ultimately lead to improved methods of diagnosis and treatment of this syndrome and its associated disorders.

**Description of Project(s) Available to Summer Students (<200 words/project)**
The lab is currently focused on identifying the molecular and cellular mechanisms that regulate ciliary motility. Potential summer projects could involve investigating how ciliary defects affect ciliary protein localization and transport using live imaging techniques, identifying and validating novel ciliary protein-protein interactions, or investigating the molecular feedback mechanisms resulting from ciliary dysfunction.
A. Personal Statement

The goal of the proposed research is to identify the function of the mammalian ciliary central microtubule pair apparatus. The central pair apparatus (CPA) plays a critical role in regulation of motile cilia and flagella, but the mechanisms by which it regulates ciliary function remain unknown. We have demonstrated that loss of CA proteins CFAP221/PCDP1 (Lee et al., 2008), SPEF2 (Sironen et al., 2011), and CFAP54 (McKenzie et al., 2015) in mice result in primary ciliary dyskinesia (PCD) with structural or functional ciliary defects. Homozygous mutant mice have hydrocephalus, male infertility, and respiratory abnormalities associated with ciliary and flagellar dysfunction. These studies will apply a battery of cell biological and biochemical approaches to these genetic models to identify the role of the CPA and fundamentally advance the current understanding of the formation and function of mammalian motile cilia.

My background and experience in manipulation of mouse genetic models, gene identification, and analysis of ciliary function have given me the expertise to lead this research. This study will utilize three models of PCD, which we have published in papers that demonstrate expertise in manipulation of genetic models, molecular genetic techniques, and analysis of ciliary structure and function. In addition, this proposal includes a substantial amount of preliminary data showing proficiency in cell biological and biochemical techniques, including culture and manipulation of mouse tracheal epithelial cells and analysis of protein-protein interaction. We have also identified appropriate collaborators and consultants for this study. Dr. Todd Wyatt (University of Nebraska Medical Center, Omaha, NE), with whom we have collaborated in the past (Lee et al., 2008; Sironen et al., 2011; McKenzie et al., 2015), will perform biochemical analyses of the cAMP pathway in our models. He is a leader in the field with over twenty years of documented experience with the proposed techniques. Dr. Joseph Sisson (University of Nebraska Medical Center, Omaha, NE), with whom we have also collaborated (Lee et al., 2008; Sironen et al., 2011; McKenzie et al., 2015), will serve as a consultant for these experiments, as he too is a leader in the field with over twenty years of documented experience. Dr. Jennifer Panizzi (Auburn University, Auburn, AL) will perform gene knockdown and transgenic rescue experiments in zebrafish to demonstrate the biological relevance of identified protein interactors, as she has documented expertise in genetic manipulation and characterization of ciliary phenotypes in zebrafish. Dr. Steven Brody (Washington University School of Medicine, St. Louis, MO) will serve as a consultant for manipulation of mouse tracheal epithelial cells (mTECs), as he is a leader in the field with over ten years of documented experience with culturing and manipulation of MTECs. Within Sanford Research, Dr. Indra Chandrasekar will serve as a consultant for the high-resolution, live confocal imaging techniques that she has developed for analysis of primary cilia defects, and Dr. Kyle Roux,
who developed the BioID approach for identifying protein-protein interactions, will serve as a consultant for our application of this technique. The proposed studies combine my expertise, the expertise of my collaborators, unique mouse models, and innovative applications of powerful experimental approaches to identify the mechanisms by which the CPA regulates mammalian motile cilia.

Relevant Publications:


3. Rozzy Finn, Claire C. Evans, **Lance Lee**. (2014) Strain-dependent brain defects in mouse models of primary ciliary dyskinesia with mutations in Pcdp1 and Spef2. *Neuroscience*, 277: 552-567. (PMID: 25073043)


B. Positions and Honors

**Professional Positions and Employment**

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<tr>
<td>1997-1998</td>
<td>Research Technician</td>
<td>Department of Medicine, Division of Infectious Diseases, University of Connecticut Health Center, Farmington, CT</td>
</tr>
<tr>
<td>2010-</td>
<td>Associate Scientist</td>
<td>Sanford Children’s Health Research Center, Sanford Research, Sioux Falls, SD</td>
</tr>
<tr>
<td>2010-</td>
<td>Assistant Professor</td>
<td>Department of Pediatrics, Sanford School of Medicine of the University of South Dakota, Sioux Falls, SD</td>
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**Professional Societies**

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<td>2010-</td>
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**Honors**

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C. Contribution to Science

**I. Composition and role of the mammalian ciliary central pair apparatus**

The motile cilium is a highly complex organelle, and although numerous proteins have been identified that are required for proper ciliary function, how these proteins interact and function to regulate ciliary assembly and motility remains largely unknown. The ciliary central pair apparatus (CPA) plays a critical role in regulating ciliary motility, but how it regulates ciliary function is not well understood. Previous mechanistic studies were largely performed in *C. reinhardtii* due to a lack of existing tools for studying mammalian cilia, but there are distinct differences in the structure and function of mammalian cilia and *C. reinhardtii* flagella. Therefore, a more tractable system is required to truly understand the role of mammalian motile cilia. To begin to overcome the current barriers, we have shown that several proteins that localize to the CPA are required for proper ciliary function in mouse models of PCD. Using genetic approaches, we identified *Cfap221*, also known as *Pcdp1*, a novel gene
deleted in the spontaneous PCD model *nm1054* (Lee et al., 2008). We also demonstrated the requirement for SPEF2, which had previously been identified but whose function was largely unknown, in ciliary motility in the PCD model *big giant head (bgh)* (Sironen et al., 2011). Recent work demonstrated that CFAP54, which was identified in *C. reinhardtii*, is required for proper mammalian CPA assembly and ciliary motility in a gene-trapped mouse line (McKenzie et al., 2015). These genetic studies make a significant contribution to the current understanding of the components and their role in the mammalian central pair. Identifying CFAP221 enabled subsequent studies in *C. reinhardtii* demonstrating that the homolog forms a complex with four other proteins, including CFAP54, and regulates flagellar motility in a calcium-dependent manner. Those studies in turn enabled us to generate the gene-trapped allele of *Cfap54* and determine its requirement for CPA assembly and function in mammals. Ultimately, understanding the mechanisms by which the CPA regulates ciliary motility will facilitate development of pharmacological therapies for PCD and its associated disorders. The current proposal includes additional preliminary data indicating that CFAP221 and SPEF2 both influence cAMP-dependent regulation of ciliary motility, and novel SPEF2 interactors have been identified. The proposed studies will utilize novel applications of powerful biochemical and cell biological techniques to further understand the mechanisms by which the CPA regulates mammalian ciliary formation and function. My role in the past and current work has been designing and leading these studies, initially as a postdoctoral fellow at Boston Children’s Hospital from 2004-2010 (for identification of CFAP221) and as the principal investigator of my laboratory at Sanford Research from 2010 to the present.

**II. Genetic modifiers of PCD-associated hydrocephalus**

Congenital hydrocephalus is a devastating condition caused by accumulation of cerebrospinal fluid (CSF) in the ventricles of the brain, but the underlying genetic causes are not well understood, and treatment is limited to problematic surgical procedures. Ependymal cilia are believed to facilitate CSF flow, but hydrocephalus is common in mouse models of PCD, it is only sporadically associated with human cases. We have shown that mice lacking CFAP221 (Lee et al., 2008), SPEF2 (Sironen et al., 2011), or CFAP54 (McKenzie et al., 2015) have a more severe hydrocephalic phenotype on the C57BL/6J (B6) background than 129S6/SvEvTac (129), suggesting that there are genetic modifiers segregating in certain inbred strains. In addition, there is a severe defect in cilia-driven CSF flow in mice lacking CFAP221 or SPEF2 on both genetic backgrounds, suggesting that the modifiers may act independently of ciliary function (Finn et al., 2014). These findings indicate why ependymal ciliary dysfunction alone may not result in severe hydrocephalus and why syndromic hydrocephalus may be more sporadic in the outbred human population. In addition, the majority of existing PCD models are on the B6 background, and these findings have enabled investigators to backcross those models to 129 so that the respiratory and reproductive phenotypes can be more readily studied and modulated. Identifying the hydrocephalus modifier genes and the pathways influenced by those genes will potentially enable development of pharmacological treatments for congenital hydrocephalus. My role has been designing and leading these studies, initially as a postdoctoral fellow at Boston Children’s Hospital from 2004-2010 (for identification of CFAP221) and as the principal investigator of my laboratory at Sanford Research from 2010 to the present.

Published Work:  https://goo.gl/wC5ilf
Mentor Description Form

■ Mentor Contact Information
  ➢ Name: Khosrow Rezvani
  ➢ Title: Associate professor
  ➢ Phone: 605-658-6383
  ➢ E-mail: Khosrow.rezvani@usd.edu
  ➢ Lab web page:

■ Location of Summer Research (Example: Sanford Medical Center, Sioux Falls):
  Vermillion

■ Description of Your Research (<200 words)
  Treatment of patients with colorectal cancer (CRC) is commonly impeded by intolerable side effects or resistance to chemotherapy drugs (Black and Rezvani, 2016). These side effects of drug resistance create a limitation for the successful therapeutic management of CRC. Therefore, there is an urgent necessity for the development of a new generation of therapeutic agents that can selectively target cancer cells while leaving normal cells intact. It has been well accepted that overexpression of oncoproteins is a major factor for most failed treatments with current chemotherapeutic drugs. Convincing evidence in the current literature indicate that drug-induced degradation of oncoproteins is feasible and it can improve clinical outcome in both hematologic and solid cancers (Ablain, 2011; Reinstein, 2000 and Ray, 2015 #2995). My lab focuses on a dominant oncoprotein in human CRC called Mortalin-2.

■ Description of Project(s) Available to Summer Students (<200 words/project)
  The objective of this research is to study the biological significance of mortalin-2 degradation by a ubiquitin-like protein called UBXN2A (Sane et al., 2014, Abdullah et al., 2015). Our current publications indicate that UBXN2A binds and inhibits mortalin-2 functions. It still remains to show whether UBXN2A induces mot-2 degradation. Completion of this proposal will validate our central hypothesis: UBXN2A targets oncoprotein mot-2 for degradation in cancer cells and antagonizes cancer progression. We used a combination of basic and advanced biological techniques to examine our hypothesis. Ultimately, this study may introduce a new target for therapies for colon cancers by using UBXN2A protein against mot-2 oncoprotein in cancer cells.

BIOGRAPHICAL SKETCH
Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Khosrow Rezvani

eRA COMMONS USER NAME (credential, e.g., agency login): KHOSROWREZVANI

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)
A. Personal Statement

During the past six years of my professional career as an assistant and then associate professor in the Division of Basic Biomedical Sciences, I have established a productive research program focused on elucidating the biological and clinical significance of a novel ubiquitin-like protein, UBXN2A, in colorectal cancer (CRC). We have generated a unique mouse model for investigating the underlying mechanism of UBXN2A as a novel tumor suppressor protein in CRC. By utilizing this comprehensive tool that mimics human CRC, we were the first group to show that UBXN2A functions as a key tumor suppressor protein in murine and human intestinal cancer. Completing our *in vivo* experiments along with our drug testing will provide key preclinical data for advancing to early clinical trials. Our evolving understanding of the function of UBXN2A and its impact on tumor migration and invasion will certainly contribute to a novel paradigm in the treatment of patients with colorectal cancer.

I am collaborating with several local (Sanford Research) and out-of-state NIH-funded faculty experts in cancer biology, including Dr. Jennifer Black, Director of the Gastrointestinal Cancer Research Program at the University of Nebraska Medical Center. These mutual collaborations have led to ten publications in the past six years plus unique sharing experiences. In addition, I have significantly contributed to graduate education for the past six years. I have mentored one predoctoral trainee, one postdoctoral trainee, two medical fellows, two MS trainees, and ten undergraduate students since I joined the University of South Dakota. The above efforts, plus my background as a clinician, give me a sound foundation in both the theoretical and technical areas directly related to the subject of this grant proposal. In summary, based on my training and my achievements, I have become an expert in this area, and I am therefore uniquely qualified to carry out this proposed research plan with a realistic timeline and budget.

B. Positions and Honors

**Positions and Employment:**
1993-1994: Medical internship, Kashan University of Medical Sciences, Iran
1994-1996: General practitioner, Department of Ophthalmology and ENT, Fallahi Hospital, Iran
1996-1998: General practitioner, Department of Cardiology and emergency unit, Kosar Hospital, Iran
2002-2010: Postdoctoral fellow, Baylor College of Medicine, Houston, TX
2010-2016: Assistant Professor, Sanford School of Medicine, University of South Dakota, SD.
2016 to present: Associate Professor, Sanford School of Medicine, University of South Dakota, SD.
Contribution to Science

1. **Proteasomal degradation of metabotropic receptors through Homer-3 protein represents a novel mechanism of receptor regulation by the ubiquitin-proteasome pathway.** My PhD project, completed under the supervision of Professor John R. Mayer, led to the discovery of a new regulatory protein called Homer-3. My results introduced the Homer-3 protein as a novel shuttle protein that can target metabotropic receptors to the 26S proteasome complex for protein degradation. This discovery was important because I was able to identify a novel regulatory function for the S8 ATPase (Rpt6) subunit of the 26S proteasome complex as the receptor for the Homer-3 protein. In addition, my study revealed for the first time a complex relationship between a selective member of the Homer family protein and the 26S proteasome complex. Our three publications related to this discovery contributed to a new direction in the receptor trafficking field and their regulation by a coordinated strategy between the 26S proteasome complex and the adaptor protein in both temporal and spatial manners. This finding may have widely varied clinical implications including patients with schizophrenia.


2. **Nicotine molecule, a novel inhibitor of the 26S proteasome degradation machinery.** My postdoctoral fellowship was completed at the Baylor College of Medicine (Houston, Texas) where I continued my work on the role of the ubiquitin-proteasome pathway in protein trafficking under the supervision of Professor Mariella De Biasi (current address: School of Medicine, University of Pennsylvania). My project first focused on the nicotine molecule, which is one of the main components in cigarettes. My studies led to a publication in *The Journal of Neuroscience* in which we showed for the first time the ability of the nicotine molecule to suppress 26S proteasome catalytic activities. This discovery was very important because it enabled us for the first time to explain several functions of nicotine at the cellular level and in *in vivo* models that had remained obscure.


3. **Regulation of receptor fate by a UBX domain-containing protein.** Following my initial discovery regarding the inhibitory role of the nicotine molecule on the proteasome complex, I decided to look for novel regulatory proteins that contribute to the trafficking of nicotinic receptors. This later study led to the discovery of hUBXD4 (UBXN2A) protein, a novel UBX domain-containing protein with unknown function, in 2009. Our results were published in *The Journal of Neuroscience* in 2009, where I explained for the first time the role of a ubiquitin-like protein in the trafficking of nicotinic receptors. We further found UBXN2A negatively regulate endoplasmic reticulum-associated degradation (ERAD) by binding to the CHIP E3 ubiquitin ligase. Collectively, Projects 2 and 3 completed during my postdoc training opened up a new aspect of 26S proteasome regulation mediated by small molecules or adaptor proteins with ubiquitin-like domains.


4. **UBXN2A is a novel tumor suppressor of colorectal tumors.** I started my faculty position in the Division of Basic Biomedical Sciences at the University of South Dakota in 2010. I joined a team of experts in protein quality control and degradation. Hence, my ubiquitin-proteasome background plus a full collaboration with other faculty members in the division and at other universities enabled me to start a new line of productive projects in my laboratory as an independent scientist. Following my initial proteomic experiments, I discovered that the UBXN2A protein has a significant anti-cancer function during tumor growth. This finding was unique because it highlighted the important role and druggability of a ubiquitin-like protein in various cancers. Based on the initial discovery, my recent project focuses on the underlying mechanisms, regulatory elements, and substrates that contribute to the UBXN2A pathway. Understanding the underlying mechanisms has already encouraged us to look for UBXN2A inducers and generate a conditional UBXN2A mouse model, which ultimately could turn into a new generation of targeted therapy alongside standard chemotherapy in patients with colon cancer.


5. **Development of a new high-resolution quantitative three-dimensional (3D) ultrasound imaging technology for colorectal cancer studies.** Mouse models of colorectal cancer have been widely used to understand tumorigenic pathways and to develop new generations of therapeutic drugs. We decided to develop a noninvasive but accurate technique to longitudinally study the formation and development of colorectal tumors in our mouse model of colon cancer. We developed usage of a three-dimensional (3D) ultrasound system combined with microbubbles. The combination of our 3-D ultrasound and microbubbles
allow us to monitor tumor growth and blood perfusion in live animals. Our 3D ultrasound shows great ability in accurately depicting the volume, shape, and location of tumors.


Complete List of Published Work in My Bibliography:  https://goo.gl/uBwhTi
Mentor Description Form

Mentor Contact Information
- Name: Jianning Tao
- Title: Assistant Professor, Sanford School of Medicine of the University of South Dakota
- Phone: 605-312-6419
- E-mail: Jianning.Tao@SanfordHealth.org
- Lab web page: http://www.sanfordresearch.org/researchcenters/childrenshealth/taolab/

Location of Summer Research (Example: Sanford Medical Center, Sioux Falls):
Sanford Research Center, Sioux Falls

Description of Your Research (<200 words)
The Tao Lab investigates the role of skeletal signaling pathways in the maintenance of osteosarcoma cancer stem cells and metastasis. Osteosarcoma (OS) is the most common form of bone cancer, usually affecting adolescents and young adults. We employ genetically engineered animal models that recapitulate the development of human OS to address two fundamental questions: 1) how do the genetic pathways such as Notch initiate and promote tumor formation?; and 2) what are the molecular mechanisms that maintain bone cancer stem cells and promote metastasis? Mouse tumors and primary cell lines derived from these models will be studied and expression profiling, sequencing, and proteomic analyses will be applied. Our long-term goal is to better understand requirement for critical genetic factors and pathways in tumorigenesis, to advance our knowledge of cancer stem cell, and to provide novel diagnostic biomarkers and more effective targeted therapies against childhood cancer.

Description of Project(s) Available to Summer Students (<200 words/project)
The survival rate for OS patients has not improved substantially over the past four decades. Molecular therapies for this disease are urgently needed. Tao lab has several short-term projects, which are designed to help students to not only gain “research experience”, but also gain an (co-)author on publication(s). For example, using primary cell lines from two subtypes of OS tumors (osteoblastic OS and fibroblastic OS), we found that those OS cancer cells present sustained PI3K/mTOR activity, indicating that inhibition of mTOR pathway may have therapeutic benefit. We propose in this project that treatment of OS cells with mTOR inhibitor (Rapamycin) to impede OS growth and metastasis. We will investigate efficacy of inhibitors in vitro by treating cells with alone and in combination with cisplatin, a DNA-damaging chemotherapeutic drug frequently used in OS patients. Viability, apoptosis and cell cycle will be evaluated to characterize the effects of the treatments. Biochemical analyses will be used to evaluate RNA and protein expression. The data obtained from this study may have clinical relevance for novel therapeutic strategies for the treatment of OS.
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

NAME:  Tao, Jianning

eRA COMMONS USER NAME (credential, e.g., agency login):  janningtao

POSITION TITLE:  Assistant Scientist/Assistant Professor

EDUCATION/TRAINING

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>DATE</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
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<tr>
<td>Sichuan University, Chengdu, China</td>
<td>B.S.</td>
<td>1991</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>West China University of Medical Science, Chengdu, China</td>
<td>M.S.</td>
<td>1996</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>University of Tennessee HSC, Memphis, TN</td>
<td>Ph.D.</td>
<td>2004</td>
<td>Biochemistry/Development Biology</td>
</tr>
<tr>
<td>Baylor College of Medicine, Houston, TX</td>
<td>Postdoc</td>
<td>2011</td>
<td>Human &amp; Molecular Genetics</td>
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</table>

A. Personal Statement

As a postdoc trainee, I began to seriously consider a career in childhood cancer research in 2008 when I observed a bone tumor later identified as osteosarcoma for the first time growing in a transgenic mouse I had been studying for its skeletal phenotypes. Since then, I have gradually devoted myself to studying animal models of osteosarcoma and have also collaborated with many pediatric oncology researchers such as Drs. Lawrence Donehower, Lisa Wang, and Jason T Yustein. Now, as a cancer biologist, my dream for curing cancer consistently pushes my projects into the next level. My overall research focuses on understanding molecular mechanisms of skeletal genetic pathways in bone tumorigenesis. As a principle investigator (PI) or collaborating scientist on previously funded NIH studies, I have established a foundation of success for the proposed research that includes establishment of novel osteosarcoma mouse models and conducted essential in vivo characterizations of those genetic animal models. Through a series of mouse genetic and global next-generation sequencing profiling studies, I have also identified a number of genes and pathways that are candidates for regulating tumor initiation, progression, and metastasis of osteosarcoma, a primary bone cancer in children. As a PI and associate scientist at Sanford Research, my lab is now actively pursuing individual genes and/or pathways and their interactions to determine their roles in osteosarcoma stem cells. In addition, I have demonstrated successful administration of collaborative projects and have developed a realistic sense of constructing feasible research plans, timelines, and budgets.

As a faculty member at Sanford Research, my projects aim to understand the genetic and molecular mechanisms of signaling pathways involved in skeletal health and disease including the childhood cancer, osteosarcoma. For example, mutations in components of Notch signaling pathway have increasingly been associated with birth defects and pediatric cancer including leukemia and sarcomas. Specifically, our studies in this proposal on treatments of tumor cells and nude mice with transplanted tumor will be closely associated with the research of another PI at Sanford Research, Dr. Keith Miskimins, who is Director of Sanford Cancer Biology Research Center and a NCI R01 awardee on a project entitled “molecular mechanisms by which the diabetic drug Metformin kills cancer cell”. In addition, since my lab heavily uses imaging and protein BioID techniques, I will intensively interact with Drs. Jill Weimer and Kyle Roux, who are directors of the image core and BioID protein biochemistry core, respectively.

B. Positions and Honors

Positions and Employment (Citizenship: U.S.A.)

2015-present  Assistant Scientist, Children’s Health Research Center, Sanford Research, Sioux Falls, SD
2015-present  Assistant Professor, Department of Pediatrics, Basic Biomedical Science’s program, Sanford School of Medicine of the University of South Dakota, Sioux Falls, SD.
2015-present  Adjunct Assistant Professor, Department of Chemistry/Biochemistry, South Dakota State University, Brookings, SD 57007
2011-2015  Assistant Professor, Molecular & Human Genetics, Baylor College of Medicine, Houston, TX
**Honors and Awards**

2014  Bones and Teeth Gordon Research Conference, Winner of 2nd prize of Poster Presentation, Galveston, TX, January, 2014

2013  John Haddad Young Investigator Award from Advances in Mineral Metabolism and American Society and Bone and Mineral Research (AIMM-ASBMR)

2011  Young Investigator Award from American Society for Bone and Mineral Research, 2011

2011  Rolanette and Berdon Lawrence Research Grant Award from Bone Disease Program of Texas, Houston, TX, 2011

2010  American Society for Bone and Mineral Research ASBMR Young Investigator Travel Grant Award, invitation for short oral presentation at the 32st Annual Meeting of ASBMR, Toronto, Canada, October, 2000

2008-2011  NIH Ruth L. Kirschstein National Research Service Awards (Kirschstein-NRSA awards)

1998-2004  University of Tennessee Health Science Center Graduate Research Fellowship

1993-1996  West China University of Medical Science Graduate Research Fellowship

1990  Sichuan University Summer Undergraduate Research Award

**Professional Memberships**

2008-present  Member, American Society for Bone and Mineral Research (ASBMR)

2002-present  Member, Society for Developmental Biology (SDB)

**Journal Reviewer**

Ad Hoc Journal Reviewer for Blood, Cell Biochemistry and Biophysics, Molecular and Cellular Biochemistry journal, Molecular Biology Reports journal, Scientific Reports journal, PLOS ONE.

**C. Contribution to Science**

C.1. My recent paper has addressed a critical role for notch signaling in the formation of osteogenic sarcoma (OS). There are few animal models of osteosarcoma since “driver” mutations have been poorly characterized pediatric patients. My work shows that Notch oncogene in vivo can act as a driver for a mesenchymal derived cancer. My studies demonstrate that Notch oncogenic activation is sufficient to cause OS in genetically engineered mice when expressing in a committed osteoblast lineage cell as well as the Rbpj-dependent or canonical Notch pathway is solely responsible for initiating downstream events of OS development. I have also shown how Notch gain of function interacts with the established role of p53 loss of function in murine OS. I found that Notch gain of function can synergistically accelerate tumor growth with p53; however, loss of Notch function is dispensable for tumor development in the context of p53-loss. Hence, these data suggest that Notch and p53 are independent tumor initiators for OS and can act synergistically. However, p53-driven tumorigenesis is not dependent on Notch canonical signaling. This suggests that Notch inhibition as a targeted therapy for cancer should be devised for different subtypes of OS initiated by deferent driver mutations. On other hand, by applying p53-driven OS model, I found that OS initiated by Notch shares the similar expression signature and pathways with p53-loss-induced OS. I also found osteoblasts as potential cells of OS origin. Together, these are the first studies to elucidate a causative role of Notch in vivo in a mesenchymal derived tumor such as OS. I intellectually steered these projects either as a postdoctoral fellow or later as an independent principle investigator for a NIH small grant. In addition, I have significantly participated in designing and interpretation of results of a study of RECQL4 mutations in skeletal defects in collaboration with Dr. Lisa Wang in Texas Children’s hospital. Using Recql4 tissue-specific knock-out mouse models, we found that deletion of Recql4 in early mesenchyme results in skeletal abnormalities that closely mimic the skeletal defects seen in humans with Rothmund-Thomson syndrome and other RECQL4-associated disorders. I recently authored a review article proposing a “three driver” model to recapitulate latency of pediatric osteosarcoma (OS) since most of currently available models have longer latencies similar to adult OS.


C.2. Beyond bone cancer, I have contributed to understanding bone development and diseases. I have studied skeletal signaling pathways including Notch canonical and non-canonical pathways in bone development, homeostasis, and bone diseases including osteosclerosis and chondrodysplasia. Among them, we found clear genetic evidence that osteosclerosis due to Notch Gain of Function depends on the canonical Rbpj-dependent pathway and the non-canonical pathway is dispensable in this pathological context. We also found a novel aspect of Notch regulation on chondrogenesis / chondrodysplasia in axial skeleton, in which cis-element for Sox9 regulation by Notch provides a mechanisms model of how Notch-mediated suppression occurs. I intellectually steered these two projects as a sub-group leader when I was a postdoctoral fellow and junior faculty. Furthermore, I have participated in a study of regulation of Notch pathway by the microRNA 34c (miR-34c). In this study, we have identified miR-34c as a key regulator of Notch signaling during bone development in a post-transcriptional manner. We found that osteoblast-specific gain of miR-34c mice shows an age-dependent osteoporotic phenotype due to the defect of osteoblast differentiation and the elevated osteoclastogenesis in non-cell-autonomous fashion.


C.3. In my Ph.D. dissertation study, I have first identified and characterized homologues of *Drosophila* transcription factor Grainyhead (Grh) in *Xenopus* early embryogenesis and mouse skin development. These vertebrate orthologues of Grh had not been previously studied and have tissue-specifically function in epidermal speciation and differentiation. In addition to my work on Grh1 and Grh3, I also found that Grh2 is specifically expressed in the neural crest cells, which generate a variety of cell types, such as bone and cartilage cells of head and neck; peripheral neurons and pigmented cells; and epinephrine-producing cells of the adrenal gland. I had intellectually driven these projects as a Ph.D. student researcher although I have obtained guidance from my mentor Dr. John Cunningham (a pediatric physician) and my collaborator Dr. Paul Mead. In my first postdoctoral period, I have also worked on a “pig-skin” phenotype caused by FATP4 gene mutation in mice. This resembles cornified manifestations of autosomal-recessive congenital ichthyosis in humans. In my second postdoctoral period, I have applied *Xenopus* model system to identify a novel mechanism for regulating TGFβ by ESL1, which has critical function during osteoblastogenesis and chondrogenesis in mice.


C.4. It is largely unknown for the roles and mechanisms of signaling pathways in bone cells to regulate the niche of metastatic cancer stem cell (MSCS) since bone is one of the most common locations for metastasis, particularly from breast, prostate, and lung cancers. I have recently collaborated with Dr. Xiang Zhang’s laboratory to study on bone niche of metastatic breast cancer cells. We found that bone micrometastases predominantly reside in a niche that exhibits features of osteogenesis. We also found and mTOR pathway associated with adherens junctions drives the progression from single cells to micrometastases. Our findings provide potential therapeutic targets to block progression toward osteolytic metastases.


C.5. Bone regeneration repairing bone defects caused by tumor resection, trauma, infection, and congenital malformation remains a significant clinical challenge. Biomaterial-mediated bone formation is an alternative approach for repairing bone defects. I recently have teamed up with Dr. Hongli Sun from University of South Dakota to use innovative biomimetic biomaterials to improve our understanding of repairing bone defects and cancer metastasis to bone. Our in vivo experiments using a critical-sized mouse cranial bone defect model showed significant bone growth in most of the gelatin nanofibrous (GF)- Desferoxamine (DFO) scaffolds comparing to very little bone growth in the GF scaffolds. These data suggest that it is a promising strategy to promote endogenous bone formation by using a hypoxia-mimicking nanofibrous scaffold.

Mentor Description Form

Mentor Contact Information
- Name: Henry Travers, MD, FACP, FCAP
- Title: Clinical Professor of Pathology
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- E-mail: henry.travers@usd.edu; sdobwan@icloud.com
- Lab web page:

Location of Summer Research (Example: Sanford Medical Center, Sioux Falls):
Wegner Library, Sioux Falls

Description of Your Research (<200 words)
Research is in the general area of historical scholarship, primarily related to medicine in South Dakota, but not limited to the state. Areas of inquiry include disease prevalence; variations in disease recognition and treatment; biographical studies of physicians and other health professionals; evolution of sociopolitical, economic and public health ideas, trends and movements; and bibliographical methods. Repositories of historical documents (for example, the Archives of the State of South Dakota in Pierre; the Center for Western Studies at Augustana; the Journey Museum in Rapid City), cemetery records, world-wide-web resources and medical and general libraries are the dominant sources of information. Scanning, optical character recognition, and other modern document-processing technologies are integral to the research. Publications derived from the research concentrate on placing information in historical context, rather than simply recording facts.

Description of Project(s) Available to Summer Students (<200 words/project)
INFECTIOUS DISEASE PREVALENCE IN SIOUX FALLS FROM 1880 TO 1940. Data are derived from internment records from Sioux Falls' oldest cemetery and are compared with a database from the Centers for Disease Control through Project Tychos at the University of Pittsburgh. Disease incidence and prevalence for typhoid, scarlet fever, and other disorders is examined in the context of prevailing public health practices and medical treatments of the times.

HISTORICAL STUDY OF THE EVOLUTION OF USD TO A FOUR-YEAR MEDICAL SCHOOL. This project involves selecting and digitally archiving previously identified documents, video and audio materials; and researching newspapers and other periodicals. The research is based on the premise that legislative bias and cost concerns were the dominant force in the resistance to extending the school for 4 years.
A native of South Carolina, Dr. Henry (Pete) Travers has retired from an active practice in pathology at Physicians Laboratory, Ltd., Sioux Falls, South Dakota in 2013. He remains clinical professor of pathology at the University of South Dakota Sanford School of Medicine, serves as the historian for the South Dakota State Medical Association and is Secretary-Treasurer of the World Pathology Foundation.

Dr. Travers received his undergraduate degree in chemistry from Eckerd College in St. Petersburg, Florida where he did research work on tris(ethylenediamine) cobalt compounds under the direction of Professor Richard Neithamer. He received his MD degree from the Pennsylvania State University College of Medicine in Hershey, Pennsylvania in 1971. He served a rotating internship (major medicine) followed by residency in pathology at the Naval Regional Medical Center in Portsmouth, Virginia. Thereafter he was the chief of the Clinical Pathology Branch of the Naval Regional Medical Center for 3 years.

Dr. Travers taught at the Eastern Virginia Medical School and the University of Kansas where he was professor and chairman of the Department of Pathology at the Wichita Campus. While in Kansas, he was president of the Kansas Society of Pathologists and the Group for Research in Pathology Education. His research interests have included placental disorders, human papillomavirus epidemiology in cervical cancer and mysteries in medical history.

Dr. Travers served in the Middle East as Laboratory Director for Fleet Hospital Six during the Desert Shield/Storm conflict. He has been a governor of the College of American Pathologists and served on numerous committees for the College. He received the Frank Hartmann award from the College. He chaired committees on Medical Practice and Education for the South Dakota State Medical Association. Internationally, he has been a director, Secretary-Treasurer and President of the World Association of Societies of Pathology and Laboratory Medicine. He is the recipient of the Gold Headed Cane award from that organization. He served on the Board of COLA, a laboratory accrediting organization, for five years. Dr. Travers is currently the secretary-treasurer of the World Pathology Foundation which provides Gordon Signy Fellowships to young pathologists around the world for further study abroad. He is an emeritus fellow of the American College of Physicians, an emeritus fellow of the College of American Pathologists, President of the South Dakota Society of Pathologists, and an emeritus member of the American Medical Association. In 2015, he was elected to membership in the American Osler Society.

Since retiring, Dr. Travers has written a number of articles about historic events as well as articles focused on the humanities in medicine. Dr. Travers and his wife, Sally, make their home in Sioux Falls and together have six children, five grown sons and one grown daughter.
Mentor Description Form

Mentor Contact Information
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- E-mail: jill.weimer@sanfordhealth.org
- Lab web page: http://www.sanfordresearch.org/researchcenters/childrenshealth/weimerlab/

Location of Summer Research (Example: Sanford Medical Center, Sioux Falls):
Sanford Research Center, Sioux Falls

Description of Your Research (<200 words)
Research in the Weimer Lab is focused on understanding the mechanisms underlying the mammalian central nervous system development and how perturbations in these processes lead to various neuropediatric disorders. Dr. Weimer and her team hope to gain a better understanding of the mechanism required for the polarized spatial restriction, advancing our knowledge of neural stem cell biology and aiding in the future treatment of neural developmental disorders and neurodegenerative diseases.

Description of Project(s) Available to Summer Students (<200 words/project)
Our lab studies rare genetic pediatric diseases that result in cognitive impairment. Currently, ongoing studies focus on Batten disease, neurofibromatosis and cortical malformation disorders. Our team takes a multi-facet approach to understand how various mutations result in cellular changes, how can we develop effective therapeutics once we understand more about the biology of these genes, and how can we efficiently and effectively screen these drugs in pre-clinical animal models. Summer interns have the opportunity to work with the Weimer team to identify a research project within this scope that fits their interest. One particular project that is at the forefront of our lab focuses on understanding the mechanism of how CLN6, a gene mutated in Batten disease, influence normal cortical development. Mechanisms that orchestrate differentiations of neurons as well as their axonal outgrowth and guidance of these axons to their target cells remain at the forefront of our study of neural development and axonal regeneration. CRMP2 is crucial for axon-dendritic specification and axonal extension in the developing brain and contributes to regeneration/degeneration in the mature brain. Many of the activities of CRMP2 are mediated through its ability to promote microtubule assembly via physical interaction with tubulin heterodimers and the Sra-1/WAVE1–actin complex. CRMP2-mediated axonal growth is facilitated through an interaction with Numb, allowing endocytosis of specific molecules such as the neuronal adhesion molecule L1 at the growth cone. Furthermore, CRMP-2’s ability to specify axon/dendrite fate and regulate cargo transport during axonal growth/regeneration has been shown to be facilitated and/or antagonized through a complex network of alternative protein-protein interactions, including CLN6. In this study, we focus on this novel interaction with CLN6, exploring how it may provide a unique mechanism for localized CRMP-2 signaling and how disruption in this interaction could facilitate a loss in many CRMP-2-dependent processes. Additionally, we explore how targeting of this complex with various drug compounds in Batten disease animal models may help delay the onset of this devastating neurodegenerative disease.
A. Personal Statement
As a developmental neuroscientist, the primary focus of my research is to understand the mechanisms regulating the proliferation, migration and differentiation of neurons in the developing cerebral cortex and how disruptions in these mechanisms lead to neuropediatric disorders. I use a collaborative team approach, drawing on expertise in cell and molecular biology, genetics and behavioral neuroscience, to test hypotheses that bridge from basic mechanisms of various signaling complex to determining whether these complexes may serve as druggable targets for treatment in translational animal models of disease. As the PI and Co-I on several NIH-funded research grants, I have extensive expertise in designing and executing collaborative projects, publishing peer-reviewed manuscripts, and presenting my work at national and international meetings. I am very actively involved in high school, undergraduate and graduate science education, having mentored 6 high school students, 13 undergraduates, 3 medical students, 5 MS, PhD or MD/PhD students and 3 postdoctoral fellows on research projects in my laboratory as well as serving on the thesis committees of 3 additional students. I have taught and developed a number of undergraduate and graduate level courses and feel that my extensive experience as an educational mentor would be well suited for direct this NIH T35 Training Program.

B. Positions and Honors

Positions and Employment
1997-2000  Laboratory Associate, Center for Aging & Dev. Bio., University of Rochester, Rochester, NY
2009-2014  Associate Scientist, Sanford Children’s Health Research, Sanford Research, Sioux Falls, SD
2009-2015  Assistant Professor, Department of Pediatrics, University of South Dakota, Sioux Falls, SD
2014-      Scientist and Director, Sanford Children’s Health Research, Sanford Research, Sioux Falls, SD
2015-      Associate Professor, Department of Pediatrics, University of South Dakota, Sioux Falls, SD

Other Experience and Professional Memberships
2001-      Member, Society for Neuroscience
2009-      Member, Graduate Women in Science, Founding Member, Past President, SD Chapter
2013-      Member, Faculty for Undergraduate Neuroscience (FUN) Research

Honors
2000      The Merritt and Marjorie Cleveland Graduate Fellowship awarded to an outstanding graduate student with interest in developing a neuroscience-related career
2003-2005  Multidisciplinary Training in Developmental Neuroscience from NIH/NIMH (T32 MH065181)
2008      Postdoctoral Scholars Award for Research Excellence, UNC - Chapel Hill
2011-2013  NIH-NINDS LRP entitled MARCKS-associated signaling complexes regulate cell polarity during progenitor proliferation and cellular differentiation
C. Contribution to Science
1. I was one of the first scientists to fully characterize several animal models of Juvenile and variant Late Infantile Neuronal Ceroid Lipofuscinosis (or Batten disease). Many of the findings that I first described both pathological and behaviorally, have become phenotypic hallmarks used throughout this disease field in preclinical drug screens. Over the years, I have intellectually steered these projects first as a graduate student and more recently as independent principal investigator. More recently this work has laid the foundation for a number of collaborative basic research projects as well as pre-clinical studies aimed at identifying effective therapeutic treatments for various forms of Batten disease. This collaborative spirit is highlighted in a recently submitted review articles with team members on this program grant Pearce, Kielian, and Hastings.


2. I have studied factors that regulate the proliferation and placement of neuroprogenitors in the developing cerebral cortex. While a postdoc I contributed to a series of studies demonstrating that reactivation of ErbB2 in the mature cerebral cortex could revert cells to a neurogenic state and how perturbation in this receptor complex leads to deficits in social behavior. Moreover, I demonstrated that MARCKS, the most prominent cellular substrate of PKC, serves as an anchor within cortical progenitors to localize signaling complexes to the apical surfaces of the cells.


3. In collaboration with Dr. Brian Kaspar’s team at Nationwide Children’s Hospital, I have recently developed and tested the intracranial delivery of self-complementing adeno-associated virus serotype 9 expressing human CLN6 (scAAV9-hCLN6) in a mouse model of CLN6-Batten Disease. This scAAV9-hCLN6 is the first viral studies to provide widespread rescue of a transmembrane organelle associated protein throughout the central nervous system. Additionally, the scAAV9-hCLN6 is able to rescue early indicators of disease pathogenesis, including glia activation and accumulation of autofluorescent storage material. We combined this pre-clinical mouse work with escalating toxicology data in mice and safety studies in non-human primates performed in the Kaspar lab to receive both NIH Recombinant Advisory Committee (RAC) and FDA Investigational New Drug (IND) approval allowing us to launch a first-of-its-kind human clinical trial for CLN6-Batten Disease patients in March 2016.

Complete List of Published Work in MyBibliography: https://goo.gl/4B0bjW
Mentor Description Form

■ Mentor Contact Information
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  ➢ Title: Assistant Professor
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■ Location of Summer Research (Example: Sanford Medical Center, Sioux Falls): Sioux Falls

■ Description of Your Research (<200 words)

Brain cancers are the most common solid tumors in children and the most frequent cause of death from childhood cancers. Little progress has been made in the past 2 decades for the management of pediatric brain cancers, for which standard treatment regimens leave survivors with life-long, devastating side effects. We are better equipped now than ever before with our understanding of the biology, the processes that drive these diseases. We are going to use this information to develop new treatments for childhood brain cancers in the hopes of improving the outcome for patients.

■ Description of Project(s) Available to Summer Students (<200 words/project)

Our laboratory is focused on the study of childhood brain tumors. The goals of our research are to identify biomarkers, understand mechanisms of tumorigenesis, develop innovative diagnostic strategies, and discover therapeutic targets in pediatric brain cancers for the development of safer and more effective therapies. The laboratory has expertise in different aspects of cancer biology, including cellular and genetic approaches to the study of childhood brain tumors. We developed multiple preclinical models with genetically engineered animals to understand the biology of pediatric brain tumors and to identify safer and more effective therapies.

- The choroid plexus (CP) in each brain ventricle is comprised of a fibro-vascular core lined by epithelial cells and responsible for the production of cerebrospinal fluid. Malignant CP tumors occur predominantly in childhood, they are poorly understood and highly lethal with few available treatments. Despite its dire consequence, knowledge of the molecular and cellular basis of malignant CP tumors is limited. We identified molecular defects in CP carcinoma that may represent therapeutic vulnerability in these aggressive tumors.

- Medulloblastoma (MB) is the most common malignant pediatric brain tumor that arises from the cerebellum. Leptomeningeal metastasis, frequently present at diagnosis and recurrence of MB, occurs when tumor cells spread to the leptomeninges along the surface of the brain and spinal cord. Recurrence/metastasis are serious complications with substantial morbidity and mortality. Our laboratory created a platform for understanding the molecular mechanisms of metastasis and evaluating potential diagnostics and therapeutics.
BIOGRAPHICAL SKETCH
Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FIVE PAGES.
NAME: Haotian Zhao
eRA COMMONS USER NAME (credential, e.g., agency login): Zhaohaotian

POSITION TITLE: Assistant Scientist

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

A. Personal Statement
Brain cancers are the most common solid tumors in children and the most frequent cause of death from childhood cancers. Little progress has been made in the past 3 decades for the management of pediatric brain cancers, for which standard treatment regimens leave survivors with life-long, deleterious side effects. We are better equipped now than ever before with our understanding of the biology and the processes that drive these diseases. Greater insight into how proliferation of brain cells is regulated, and how its disruption contributes to brain cancers in children will help to develop new therapies that specifically target tumor growth without damaging the developing brain.

As a research scientist dedicated to the study of childhood brain tumors, my career goal is to use this information to develop new treatments for pediatric brain cancers in the hopes of improving the outcome for patients. I pursued my post-graduate training as a developmental biologist at The Ohio State University where I received extensive training in molecular, cellular, and developmental biology under the guidance of Dr. Michael Robinson, publishing multiple papers on lens and kidney development. In 2004, I joined St. Jude Children’s Research Hospital as a postdoctoral research associate, and made significant progress as an ABTA fellow in the lab of Dr. Martine Roussel. This experience provided me with an opportunity to expand my expertise to many aspects of cancer biology, including cellular and genetic approaches to the study of pediatric brain tumors. My training in developmental biology and experience in mouse genetics prepared me to develop accurate preclinical models using genetically engineered mouse strains to understand the biology of childhood brain cancers and to identify potential therapeutic strategies.

B. Positions and Honors
June 2004-January 2010 Postdoctoral Research Associate, Department of Genetics and Tumor Cell Biology, St. Jude Children’s Research Hospital, Memphis, Tennessee
April 2010-Present Assistant Scientist, Sanford Children’s Health Research Center, Cancer Biology Research Center, Sanford Research, Sioux Falls, South Dakota
June 2010-Present Assistant Professor, Department of Pediatrics, Sanford School of Medicine, University of South Dakota, Sioux Falls, South Dakota

Academic Awards
April 2002 Award for research presentation, Columbus Children’s Hospital Annual Research Conference
April 2003  Travel Award for Research Presentation, The 2nd Annual Graduate and Post-Graduate Research Day, The Ohio State University Medical Center
May 2003   Award for research presentation, Columbus Children’s Hospital Annual Research Conference
April 2008 American Brain Tumor Association Basic Research Fellowship
November 2014 Pediatric Basic Research Award, The 19th Annual Scientific Meeting of the Society for Neuro-Oncology
November 2014 Young Investigator Basic/Translational Research Award, The 19th Annual Scientific Meeting of the Society for Neuro-Oncology

Memberships
2008-Present  Society for Neuro-oncology
2008-Present  American Association for Cancer Research

Invited Talks/Lectures
2. The 21st Annual Scientific Meeting of the Society for Neuro-Oncology. November 17-20, 2016, Scottsdale, Arizona, Targeted therapy for leptomeningeal metastasis of medulloblastoma
3. 2015 Pediatric Neuro-Oncology Basic and Translational Research Conference, May 7-8, 2015, San Diego, CA, Notch and Shh signaling pathways converge on the primary cilium to promote choroid plexus tumor initiation from epithelial progenitors
6. Department of Pharmacology, College of Pharmacy, South Dakota State University, October 3, 2014, Brookings, SD. Sonic Hedgehog signaling: a thread that links common and rare forms of pediatric brain tumors
7. USD-Sanford Health Biomedical Research Symposium, May 19, 2014, Vermillion, SD. Sonic Hedgehog signaling: a thread that links common and rare forms of pediatric brain tumors
9. Depart of Biology, Concordia College, October 2012, Moorhead, Minnesota. Calculating a Cure for Pediatric Brain Tumor by MATH1-ematical Analysis
10. Sanford Children’s Health Research Center Scientific Symposium, Sanford-Burnham Medical Research Institute, October, 2011, La Jolla, California. Generation and analysis of a murine model of metastatic medulloblastoma
12. Joint Meeting of the Society for Neuro-Oncology and the AANS/CNS Section on Tumors, 2009, New Orleans, Louisiana. Atoh1 collaborates with Gli1 to induce medulloblastoma by regulating Hes family members
15. Annual Meeting of Foundation for Advanced Cancer Studies, August, 2007, San Diego, California. BMP antagonizes Shh-dependent proliferation of neuronal progenitors during mouse development and in CNS cancers
16. American Society of Nephrology Annual Meeting, October, 2004, St. Louis, Missouri. Role of fibroblast growth factor receptors 1 and 2 in the developing kidney

C. Contribution to Science
**Study of the molecular mechanisms of lens fiber cell differentiation**

The vertebrate lens consists of a monolayer of epithelial cells that overlie its anterior face and a core of elongated, crystallin-rich fiber cells that are responsible for the refractive properties of the organ. The epithelial cells at the posterior of lens vesicle elongate and differentiate into primary fiber cells during embryogenesis; further growth of the lens results from the proliferation of epithelial cells and their subsequent differentiation into secondary fiber cells at the equatorial region of the lens. Epithelial-to-fiber differentiation is characterized by significant cell elongation, re-organization and upregulation of fiber-specific proteins. Environmental or genetic factors that perturb either process cause vision-destructing cataracts and/or microphthalmia. Knowledge of the underlying mechanisms that regulate the differentiation of lens fiber cells is important for identifying therapeutic strategies for these devastating diseases. Early observations indicate that the fate of lens cells is dependent on gradients of diffusible factors in the ocular environment. Over 20 years of cumulative evidence from different vertebrate species suggests that fibroblast growth factors (FGFs) and/or fibroblast growth factor receptors (FGFRs) are critical determinants of the polarity of lens development. However, the physiological role of FGF in this process remained unclear. To address this question, I studied the role of FGFR signaling in lens development using conditional knockout approach. To delete FGFRs in the lens, I generated transgenic mouse strains in which the αA-crystallin promoter drives the expression of the Cre recombinase specifically in lens epithelial and/or fiber cells. Using these transgenic lines, I demonstrated that Fgfr1 is not required for lens development, whereas signaling through Fgfr2 contributes to cell cycle exit and cell survival in lens epithelium. Importantly, I showed for the first time that different Fgfrs function redundantly to provide the essential signal for lens fiber differentiation. My studies provided the most conclusive evidence that FGFR signaling plays a vital role in lens fiber cell differentiation. In addition, the Cre transgenic lines I generated have become important tools to address important questions in lens biology; investigators around the world have used these transgenic mice extensively to delete genes of interest in the developing lens to examine their functions.


**Study of the molecular mechanisms regulating kidney development**

The metanephric kidney arises primarily from two tissues, the nephrogenic cord and the Wolffian (nephric) duct, which in turn give rise to the metanephric mesenchyme (MM) and ureteric bud (UB), respectively. At embryonic day 10.5 (day E10.5) in the mouse and week 5 of gestation in humans, the MM induces the UB to grow out from the Wolffian duct into the MM. Stromal mesenchyme between the Wolffian duct and the MM restricts the UB to its proper position and prevents ectopic budding. Ongoing signaling from the MM stimulates the UB to elongate and repeatedly branch, leading to formation of the collecting ducts, pelvis, and ureter. Shortly after making contact with the UB, the MM divides into a nephrogenic lineage lying adjacent to the bud, and a surrounding renal cortical stromal lineage. Each terminal tip of the UB induces local areas of nephrogenic mesenchyme to differentiate into nephron epithelia, progressing from renal vesicles, to comma-shaped bodies, to S-shaped bodies, and then to immature nephrons. Earlier studies suggested that FGF signaling plays an important role in kidney development. However, it was unclear which Fgfrs are required for the process. In addition, the effects of FGF signaling on MM and UB lineages were incompletely defined. To address these issues, I took genetic approach to determine which Fgfrs are critical for normal kidney morphogenesis. I used conditional knockout approach to specifically delete Fgfrs in the MM. I played a crucial role in proposing and planning the studies, identifying appropriate Cre transgenic strains to be used for gene targeting in MM. My study showed that Fgfr1 and Fgfr2 signaling (together) in the MM are critical for formation of the MM and early development of the UB. To determine which Fgfrs are critical for ureteric morphogenesis, I generated and characterized Hoxb7-cre-EGFP transgenic mice (expressing cre recombinase and a green fluorescent protein in the nephric duct and the UB), which were used to achieve ureteric deletion of the Fgfrs. I showed that UB-specific deletion of Fgfr2 leads to decreased proliferation and survival of UB cells, indicating that Fgfr2 is the major FGF receptor family member driving ureteric morphogenesis. These studies provide important evidence to support the crucial role of Fgfr signaling in patterning of virtually all renal lineages at early and later stages of development. In addition, the Hoxb7-cre-EGFP transgenic line that I generated has become an important tool to address important question in renal biology; investigators around the world have used these mice extensively to delete genes of interest to study their functions in ureteric morphogenesis.

**Study of the molecular and cellular mechanisms of medulloblastoma metastasis and therapies**

Medulloblastoma (MB) is the most common pediatric malignant brain tumors. MBs originate from the cerebellum and tend to disseminate through the cerebrospinal fluid (CSF) to the leptomeninges which cover the brain and spinal cord. Leptomeningeal dissemination (LMD) is a frequent finding (~30%) at the time of diagnosis in MB patients. Due to the risk of metastatic dissemination and associated poor prognosis, MB treatment requires craniospinal radiation and chemotherapy, which invariably causes debilitating cognitive and neuroendocrine sequelae. Despite marked improvement in the survival of MB patients, relapse occurs in a 20-30% of patients and carries substantial morbidity and mortality. Recurrent MBs can develop locally or as leptomeningeal metastasis. Understanding the molecular and cellular mechanisms of MB metastatic dissemination and recurrence is important for therapeutic development. Through careful experimentation, I demonstrated that Bone Morphogenetic Proteins (BMPs) and transcription factor Atonal Homolog 1 (Atoh1) comprise an important signaling axis in MB driven by aberrant Shh/Ptch signaling. I showed that Atoh1 plays an important role in Shh MB initiation, maintenance, and progression. Recurrent or metastatic diseases derived from Shh MBs are characterized by similar molecular signature, including persistent Atoh1 expression. To examine the role of Atoh1 in leptomeningeal metastasis of MB, we generated several conditional transgenic mouse strains expressing Atoh1 transgene which were subsequently bred to Ptch1+/− mice that exhibit increased Shh signaling. Approximately 25% of Ptch1+/− animals develop non-metastatic MBs; however, Ptch1+/− animals with conditional Atoh1 expression develop MBs at high penetrance (majority of lines at 100%), at a young age, and with extensive LMD and metastasis, indicating our innovative animal models of metastatic MB faithfully recapitulate properties of its human counterpart. A manuscript based on these novel results is under revision with Nature Communications.


In the past few years, I have made significant progress in understanding the molecular and cellular mechanisms of the CP tumors. In 2013 and 2015, I was invited to give oral presentations on this work at the “Pediatric Neuro-Oncology Basic and Translational Research” Conferences. As evidence of the innovation and significance of these projects, I won the Pediatric Basic Research Award for my work on CP tumor, and the Young Investigator Award for Basic/Translational Research for my work on MB metastasis in the 19th Annual Meeting of the Society of Neuro-Oncology in 2014, where I gave two oral presentations on my research. The following are the award-winning abstracts published in Neuro-Oncology.


Complete List of Published Work in MyBibliography*: https://goo.gl/5aNCdU