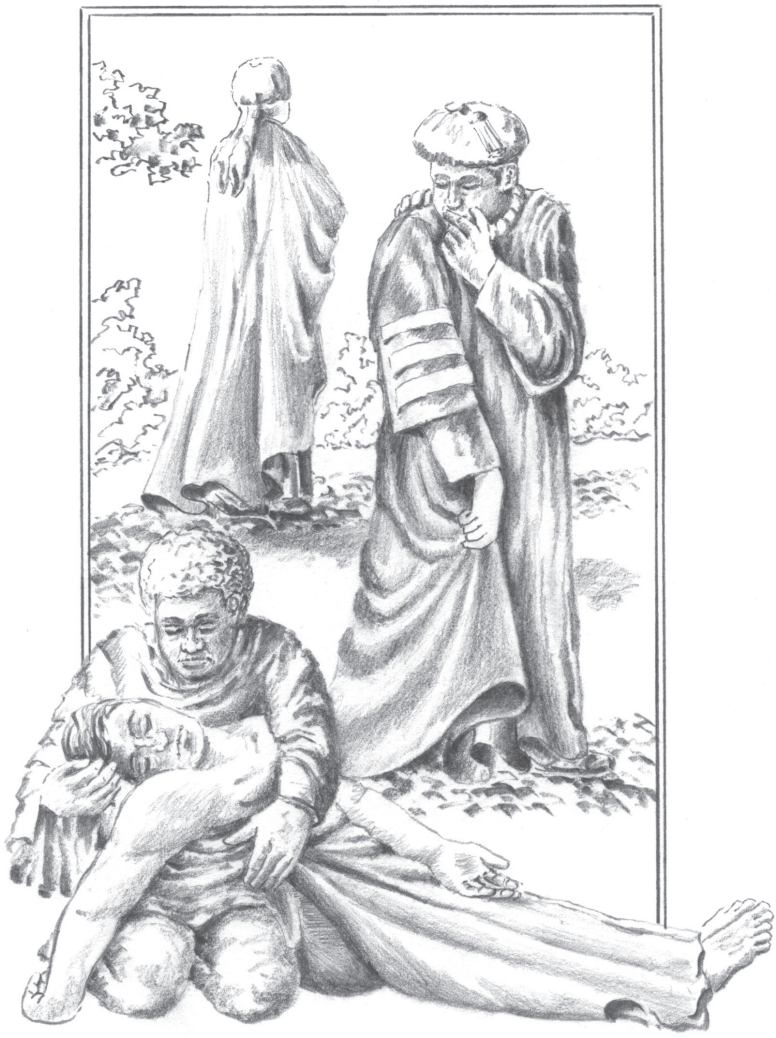

LOMA LINDA UNIVERSITY

School of Medicine

In Conjunction With

The Faculty of Graduate Studies

Graduate Consecration and Hooding Ceremony

Doctor of Philosophy and Master of Science Candidates

and

Faculty Recognition

Friday, May 28, 2021
3:00 p.m.
Randall Visitor Center Amphitheater

LOMA LINDA UNIVERSITY

School of Medicine

Graduate Consecration and Hooding Ceremony

May 28, 2021
Randall Visitor Center Amphitheater

WELCOME:	Richard Hart M.D., DrPH President, Loma Linda University
INVOCATION:	Dylis Brooks, M. Div. Associate Chaplain
SILVER CUP PRESENTATION:	Tamara Thomas, M.D. Dean, School of Medicine
R. BRUCE WILCOX MENTOR OF THE YEAR AWARD:	Penelope Duerksen-Hughes, Ph.D Associate Dean, Basic Science and Translational Research
	Tamara L. Thomas, M.D. Dean, School of Medicine
SPECIAL RECOGNITION:	Penelope Duerksen-Hughes, Ph.D.
	Hansel Fletcher, Ph.D. Assistant Dean, Graduate Student Affairs
SPECIAL MUSIC:	"Great is thy Faithfulness" Natasha Le, Ph.D. Student
INTRODUCTION OF SPEAKER:	Tamara L. Thomas, M.D.
MESSAGE:	Karl Haffner, Ph.D. Vice President, Student Experience, Loma Linda University
HOODING CEREMONY:	Penelope Duerksen-Hughes, Ph.D.
	Hansel Fletcher, Ph.D.
TRIBUTE TO FAMILY:	Graduating Class of 2021
SCIENTIST'S OATH:	Penelope Duerksen-Hughes, Ph.D.
PRAYER OF CONSECRATION:	Ronald Carter, Ph.D. Provost, Loma Linda University
UNIVERSITY MARSHALS:	Paul Herrmann, M.D. Professor
	Kevin Nick, Ph.D. Associate Professor
PIANIST:	Natasha Le

Reception to Go

HOODING CEREMONY

Hannah Choi, Masters Candidate in Cancer, Developmental and Regenerative Biology
Hooded by: Dr. Hansel Fletcher

Hiel Rutanhira, Masters Candidate in Microbiology and Molecular Genetics
Hooded by: Dr. Hansel Fletcher

Karina Mayagoitia, PhD Candidate in Anatomy
Hooded by: Drs. Salvador Soriano and Geovany Siguenza

Mechanisms of Cognitive Loss Associated with Hypercholesterolemia

Alzheimer's disease (AD) affects more than 5 million Americans and has no cure. The etiology of AD is poorly understood, but cholesterol oxidation, particularly the accumulation of 27-hydroxycholesterol (27OHC), and inflammation are contributing factors. However, the mechanisms by which these two factors contribute to AD pathogenesis are unknown. To explore this question, I evaluated changes in brain inflammatory markers and cognitive status in mice in response to a high-cholesterol diet. I hypothesized that exposure to excess dietary cholesterol would alter inflammatory mediators, leading to cognitive loss. My findings showed that a high-cholesterol diet caused spatial memory loss and decreased brain interleukin-15 expression in mice. In addition, inhibiting the production of 27OHC with the 27OHC synthase inhibitor Anastrozole protected against memory loss induced by a high-cholesterol diet in mice. Together, my work provides evidence for pursuing 27OHC inhibitors as neuroprotective therapy against memory impairment caused by a high-cholesterol diet.

William Chen, PhD Candidate in Biochemistry
Hooded by: Drs. Danilo Boskovic and Hansel Fletcher

Keystone Periodontal Pathogen Porphyromonas gingivalis

Clinical studies suggests a link between periodontitis and increased risk for atherosclerosis, a major cause of death in the United States. The project objective was to characterize whole blood platelet and neutrophil responses to Porphyromonas gingivalis. Significant increases in platelet CD62P expression and platelet-neutrophil interactions were observed in whole blood preincubated with high level of P. gingivalis with or without subsequent addition of adenosine diphosphate (ADP). A 16-minute preincubation with P. gingivalis, followed by ADP addition, increased labeling of neutrophil associated DNA. Platelet plug formation was measured in response to varying P. gingivalis added concentrations and preincubation times. P. gingivalis reduced whole blood closure times in a concentration dependent manner. Increasing P. gingivalis concentration or preincubation times decreased closure times. This suggested prolonged P. gingivalis preincubation can compensate for reduced bacterial concentration, which enhances whole blood formation of platelet plug. Taken together, P. gingivalis can trigger whole blood platelet and neutrophil responses suggesting a role in the pathophysiology of thrombosis.

Janviere Kabagwira, PhD Candidate in Biochemistry
Hooded by: Drs. Nathan Wall and Danilo Boskovic

The Role of Survivin Splice Variants in Pancreatic Ductal Adenocarcinoma Chemoresistance

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer and is currently one of the most difficult diseases to treat. Its high mortality rates are attributable in part to increasing resistance to cancer therapy. Survivin, a member of the inhibitor of apoptosis (IAP) family has been linked to chemoresistance among several other hallmarks of cancer. Like many others, this gene undergoes alternative splicing which generates six splice isoforms. Although survivin has been linked to chemoresistance, the role of its splice isoforms has not been fully studied. It was my aim to determine whether survivin splice variants play a role in PDAC chemoresistance. Our results showed differential expression of survivin splice variants in both acquired and innate chemoresistance. Importantly, we found that knockdown of survivin splice variant 2β sensitized innate and acquired PDAC chemoresistant cell lines.

Meghri Katerji, PhD Candidate in Biochemistry
Hooded by: Drs. Duerksen-Hughes and Danilo Boskovic

Oxidative Stress and DNA damage as Promoting Factors of HPV Integration

Human papillomaviruses (HPVs) cause virtually all cervical cancers as well as many anogenital and oropharyngeal cancers. Integration of the HPV genome into the human genome is a key event in carcinogenesis, with DNA damage playing a crucial role in this critical process. DNA damage is primarily caused by overproduction of reactive oxygen species (ROS). We demonstrated remarkable variability in background ROS and subsequent DNA damage levels between different non-cancerous cervical samples, providing a possible explanation for why some but not most HPV-infected women develop cervical cancer. Another source of DNA damage is exposure to elevated doses of ionizing radiation. We demonstrated that ionizing radiation induces DNA damage in oral and cervical keratinocytes and promotes integration into the host genome, indicating that ionizing radiation puts exposed populations at higher risk for HPV malignancies. Overall, the insights gained from this work direct us toward strategies to prevent malignancies in HPV-infected individuals.

Victor Camberos, PhD Candidate in Physiology
Hooded by: Drs. Mary Kearns-Jonker and John Zhang

The Hippo/YAP Signaling Pathway in Cardiovascular Repair

Following cardiovascular injury, adult hearts are unable to replace damaged cardiomyocytes leading to scar tissue formation and increased risk of heart failure. Cell-based therapies for cardiac regeneration are currently being evaluated however, conditioning cells prior to application may be necessary for improved results. The Hippo pathway, specifically the expression of Yap1, is a major regulator of regeneration and is differentially activated in adults and neonates. Using adult and neonatal cardiovascular progenitor cells (CPCs) we confirmed elevated expression of Yap1 in the regenerative neonatal cells compared to those isolated from adults. To condition adult cells towards enhanced regenerative potential, we explored Yap1 induction through approaches such as spaceflight, simulated microgravity, and drug therapy. Our findings support the feasibility of inducing Yap1 in CPCs derived from adults and raise the possibility that conditioning adult progenitors prior to cell-based repair may improve outcomes of stem cell-based treatments outside of the neonatal window.

Katherine Knox-Concepcion, PhD Candidate in Physiology
Hooded by: Drs. Lubo Zhang and John Zhang

Effect of Glucocorticoid Receptor on Hypoxic-Ischemic Encephalopathy in the Neonatal Rat

Hypoxic-ischemic encephalopathy (HIE) resulting from asphyxia in the peripartum period is the most common cause of neonatal brain damage and can result in significant neurologic sequelae including cerebral palsy. Currently therapeutic hypothermia is the only accepted treatment in addition to supportive care for infants with HIE, however, many additional neuroprotective therapies have been investigated. Our study aims to elucidate the role of glucocorticoids and the glucocorticoid receptor in hypoxic-ischemic (HI) injury. In our first study, we investigated dexamethasone and hydrocortisone treatment given after hypoxic-ischemic (HI) insult in neonatal rats via intracerebroventricular (ICV) injection and intranasal administration. In this study, we demonstrated that dexamethasone significantly reduced rat brain infarction size when given after HI treatment via ICV injection; however it did not demonstrate any neuroprotective effects when given intranasally. Hydrocortisone after HI insult also significantly reduced brain infarction size when given via ICV injection; and the intranasal administration showed protective of brain injury in male rats at a dose of 300 μg. LPS sensitization did significantly increase the brain infarction size compared to controls, and hydrocortisone treatment after LPS sensitization showed a significant decrease in brain infarction size when given via ICV injection as well as intranasal administration in both genders at a dose of 300 μg. In our second study, we developed a model of the GR knock-down before HI injury to investigate the role of endogenous brain GR in HI injury in P9 pups. A mild HI treatment of P9 rat pups with ligation of the right common carotid artery In this study, we demonstrated that knockdown of brain endogenous GRs significantly increased brain infarct size after HI injury in male, but not female, rat pups. Moreover, GR repression resulted in a significant increase in inflammatory cytokines TNF-α and IL-10 at 6 hours after HI injury in male pups. Male pups treated with GR siRNAs showed significantly worsened reflex response and exhibited significant gait disturbances. These findings provide insight into the neuroprotective effects of glucocorticoids, even in the setting of sepsis. It further demonstrates that brain endogenous GRs play an important role in protecting the neonatal brain from HI induced injury in a sex-dependent manner in male pups, and suggests a potential role of glucocorticoids in sex differential treatment of HIE in the neonate.

Jeong Bin Lee, PhD Candidate in Physiology
Hooded by: Drs. Andre Obenaus and John Zhang

Development and Maturation of the Brain Following Pediatric mTBI

Pediatric mild traumatic brain injury (mTBI) is a major public health concern with the potential to produce long-lasting cognitive, adaptive, and socio-behavioral outcomes. However, our understanding of how TBI pathophysiology evolves in the developing brain is lacking. Our central hypothesis was that pediatric mTBI results in evolving microstructural dysregulation that leads to functional and structural deficits late in life. To test this hypothesis, we first sought to assess the influence of pediatric mTBI on white matter (WM) dysregulation in early adulthood. To accomplish this, we investigated the effects of single and repeated pediatric mTBI on white matter, focusing on the anterior commissure (AC), a white matter structure distant from the injury site. We demonstrated that mTBI leads to myelin-related diffusion changes in white matter and abnormal oligodendrocyte (OL) development in the AC which are accompanied by behavioral deficits two months after the initial injury. Second, we sought to examine the lifespan evolution of pediatric mTBI. To accomplish this, we investigated the long-term effects of pediatric mTBI at postnatal day 17 and mapped the temporal evolution of the long-term behavioral and associated structural deficits up to late adulthood (18 m) using clinically relevant in-vivo diffusion tensor imaging (DTI) in mice. We demonstrated that a single exposure to a pediatric mTBI in childhood can result in early temporally evolving structural deficits detectable through early diffusion neuroimaging and are correlated to spatial learning and memory impairments late in life. Our results suggest that early in life mTBIs elicit long-term behavioral alterations and OL-associated white matter dysregulation in the developing brain and that such early injuries have the potential to elicit temporally-evolving behavioral and structural deficits late in life. This dissertation provides new insights into how post-pediatric mTBI deficits are manifested both in early adulthood and later in life and describe how such injury evolves over a lifespan resulting in modified tissue characteristics and behavioral profile following pediatric mTBI. Such information will not only provide a deeper understanding of the complex pediatric mTBI pathophysiological development but can serve as the basis for long-term outcome prediction in pediatric mTBI.

Dane Sorensen, PhD Candidate in Physiology
Hooded by: Drs. William Pearce and John Zhang

Hypoxic and Age-Dependent Functional Compartmentalization of Vascular MLCK

Changes in vascular structure and reactivity are amongst the most important that occur during the transition from fetal to newborn life, and are guided by the principle of ensuring adequate coupling of blood flow to metabolism. Of clinical importance, a consequence of maladaptive fetal vascular adaptation to hypoxia is an increased probability for loss of cerebral autoregulation, increased risk for neonatal encephalopathy, and hypoxic-ischemic cerebral injury. MLCK is a very specific calcium-calmodulin dependent enzyme, with its only known substrate being 20 kDa myosin light chain, and is essential in coupling of blood flow to metabolism. Several studies have demonstrated that despites low abundance of MLCK in immature arteries, rates of MLC20 phosphorylation are high, suggesting age-dependent changes in MLCK catalytic activity. Another key determination in the generation of contractile force is the organization and distribution of contractile proteins, such as MLCK, MLC20 and αActin. Our first study explored the hypothesis that subcellular changes in MLCK distribution contribute to hypoxic modulation of fetal artery contractility. As compared to normoxic term fetal lambs (FN), carotid arteries from fetal lambs maintained at high altitude (FH) displayed diminished contractility, with no parallel changes in MLCK protein or mRNA. Through integration of confocal analysis and total MLCK mass, we developed a model to calculate subcellular fractions of MLCK in VSMCs. These studies demonstrate that dynamic translocation of contractile MLCK mass accounts for a significant component of diminished contractility in response to hypoxia. The second study explored the hypothesis that the greater apparent catalytic activity of MLCK in fetal arteries is due to age-dependent changes in intracellular distribution of MLCK and MLC20. Optimization experiments yielded similar estimates of MLCK maximal velocity and substrate affinity in fetal and adult artery homogenates. A custom-designed, computer-controlled apparatus allowed electrical stimulation of paired adjacent segments for measurement of rates of MLC20 phosphorylation in intact arteries and confocal imaging of arteries immunostained for MLCK and pMLC20. These experiments revealed that fractional activation of MLCK is greater in the fetus than the adult and that MLCK activation is faster in peri-luminal than peri-adventitial region of VSMCs of both fetal and adult arteries.

Hanmin Wang, PhD Candidate in Physiology
Hooded by: Drs. Julia Unternaehrer and John Zhang

The role of the Snail/let-7 axis in stemness induction in distinct subtypes of ovarian cancer: the search for cancer stem cell targeting strategies

Epithelial ovarian cancer (EOC) has the one of the lowest survival rates, partly due to modern therapy's failure to consider the heterogeneity of EOC and the failure to effectively target cancer stem cells (CSC). The central hypothesis for this study is that SNAI1 directly represses let-7, leading to increased stemness in cancer cells; and that targeting SNAI1 in EOC subtypes will yield a significant improvement in terms of stemness and tumorigenicity. The long-term objective is to develop effective treatment strategies for targeting cancer stem cells. The short-term goal is to utilize SNAI1 as a potential target to prevent ovarian cancer tumor growth in a xenograft model. In conclusion, the SNAI1/let-7 axis is an important component of stemness pathways in cancer cells, and this study provides a rationale for future work examining this axis as a potential target for cancer stem cell-specific therapies.

THE SCIENTIST'S OATH

Before God these things I do promise:
In the acceptance of my sacred calling,
I will dedicate my life to the furtherance of Jesus Christ's
healing and teaching ministry.
As a member of the community of scholars,
I promise to uphold the values of this body
and all that it stands for:
I will give to my teachers the respect and gratitude which is their due.
I will impart to those who follow me,
the knowledge and experience that I have gained.
I will extend the boundaries of scientific knowledge with my
scholarship, teaching, research and publications.
I will deal fairly and justly with my fellow scientists, and will
practice scientific integrity in the handling, acquisition and
interpretation of all data.
I will never misuse my research for personal or financial gain,
or for the intentional harm of my fellow human beings.
I will respect the confidences entrusted to me by my
research subjects, fellow scientists and the general public.
May I always strive so as to preserve
the finest traditions of this community.

May God's kingdom,
His healing power and glory be experienced by me,
as I am faithful to this Oath.