IRHRM Pilot Awards - Fall 2013

In July of this year, the IRHRM announced the availability of funding to conduct research and generate preliminary data to assist IRHRM members in competing for NIH or other grant funding (new or renewal applications) in reproductive health and regenerative medicine research. The awards are intended to foster collaboration among the IRHRM membership.

The IRHRM Executive Research Board received a number of outstanding applications for Pilot funding. Twelve awards were made, ranging from $5,000 to $10,000. Please join us in congratulating the following IRHRM members:

**Omar Aljitawi, MD** (KUMC-Internal Medicine); IRHRM Co-Investigator Jinxi Wang, “Investigating decellularized Wharton’s jelly matrix to accelerate bone healing in a murine calvarial bone defect model”

**Udayan Apte, PhD** (KUMC-Pharmacology); IRHRM Co-Investigator M.A. Karim Rumi, “Role of estrogen receptor-1 (ER-α) in regulation of hepatocyte proliferation”

**Jeremy Chien, PhD** (KUMC-Cancer Biology); IRHRM Co-Investigator Adam Krieg, “Post-transcriptional regulation of FoxM1 by TP53 in ovarian cancer”

**Yafeng Dong, PhD** (KUMC-ObGyn); IRHRM Co-PI Carl Weiner, “Cell free plasma RNA/miRNA and preterm birth prediction in early gestation”

**Joseph Fontes, PhD** (KUMC-Biochemistry): “Epigenetic regulation of inflammatory genes by the transcription factor ZXDC1 during monocyte differentiation”
Kathleen Gustafson, PhD (KUMC-Neurology); IRHRM Co-Investigators Holly Hull and John Colombo, “Developmental origins of fetal cardiac autonomic control: the effect of maternal BMI and gestational weight gain”

Adam Krieg, PhD (KUMC-ObGyn); IRHRM Co-Investigator Jeremy Chien, “Regulation of tumorigenic pathways by histone demethylases in ovarian cancer”

Ann Manzardo, PhD, MSCR (KUMC-Psychiatry); IRHRM Co-PI Merlin Butler, “Global DNA methylation in obesity-related conditions: an examination of highly methylated genes linked to obesity”

Nancy Muma, PhD (KU-Lawrence-Pharmacology); IRHRM Co-Investigator M.A. Karim Rumi, “Regulation of serotonin receptor signaling by estrogens: interrogating the roles of ERα and SUMOylation”

Peter Smith, PhD (KUMC-Physiology); IRHRM Co-Investigator Jay Vivian, “Epigenetic regulation of neuron regeneration”

Jay Vivian, PhD (KUMC-Pathology); IRHRM Co-PI Merlin Butler, “Development of a novel pluripotent stem cell reporter line to study the epigenetic control of imprinting in Prader Willi syndrome”

Jinxi Wang, MD, PhD (KUMC-Orthopedic Surgery); IRHRM Co-Investigator Jay Vivian, “Generation of bone sialoprotein (BSP) conditional knockout mice”

In the Spring of 2014, the awardees will present their pilot-funded results, as well as their plans for the external grant application submission, during the IRHRM monthly Chalk Talk sessions.

Visit us online for event updates, news highlights and more!

www.kumc.edu/irhrm

News to share? Questions, comments and/or suggestions? Contact

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Welcome New Members!

Please join us in welcoming our eleven new members who joined the IRHRM in 2013!

Justin Blumenstiel, PhD, Assistant Professor, Ecology and Evolutionary Biology, KU-Lawrence; *Genome evolution, transposable elements, RNA silencing, epigenetics, and molecular evolution*

Buddhadeb Dawn, MD, Maureen & Marvin Dunn Professor of Cardiovascular Diseases, Director, Division of Cardiovascular Diseases, Director, Cardiovascular Research Institute, Vice Chairman for Research, Department of Medicine, and Director, Midwest Stem Cell Therapy Center, KUMC; *Adult stem cell therapy for cardiac repair, organ protection during cardiopulmonary arrest, biology of adult stem cells, role of cytokines in cardiac remodeling, diabetes and cardiovascular injury*

Animesh Dhar, PhD, Associate Professor, Cancer Biology, KUMC; *Investigation of epigenetic events and alterations in chromatin structure with the development of cancer.*

Luciano DiTacchio, PhD, Assistant Professor, Pharmacology, Toxicology and Therapeutics, KUMC; *Genomic and environmental factors in the development of obesity, metabolic syndrome and Type 2 diabetes*

Leigh Eck, MD, Assistant Professor, Internal Medicine, Division of Metabolism, Endocrinology and Genetics, KUMC; *Vitamin D and its impact on premenopausal bone health, Vitamin D in end stage liver disease disease*

Joseph Fontes, PhD, Associate Professor, Biochemistry and Molecular Biology, KUMC; *How gene transcription is regulated during development and disease and how the mechanisms of regulation might be manipulated as a therapeutic strategy*
New IRHRM Members

Matthew Goering, PhD, HCLD, Director of Clinical Embryology, The Center for Advanced Reproductive Medicine, Obstetrics and Gynecology, KUMC; Identification of therapeutic targets or interventions that may preserve fertility and reduce the risk of pregnancy loss arising from aneuploidy

Jed Lampe, PhD, Assistant Professor, Pharmacology, Toxicology and Therapeutics, KUMC; Determining the mechanism of ligand binding and translocation in organic cationic drug transporters, designing novel bivalent inhibitors to target the anti-apoptotic protein Survivin

Joan Lewis-Wambi, PhD, Assistant Professor, Cancer Biology, KUMC; Identifying novel pathways of endocrine-resistance in breast cancer and using that knowledge to help develop alternative treatment options for patients with endocrine resistant and metastatic disease

Xiaogang Li, PhD, Associate Professor, Internal Medicine, Division of Nephrology and Hypertension, KUMC; To understand the molecular pathogenesis of autosomal dominant polycystic kidney diseases (ADPKD) and to translate these findings for ADPKD treatment

Dev Maulik, MD, PhD, FACOG, FRCOG, Professor and Chair of Obstetrics and Gynecology, TMC, Senior Associate Dean of Women’s Health, UMKC SOM, Professor of Basic Science, UMKC SOM, Chair, Maternal Fetal Medicine, CMH; Fetoplacental angiogenic mechanisms related to fetal growth restriction and preeclampsia, development of functional fetal echocardiography; novel Doppler ultrasound approaches for fetal hemodynamic assessment, novel Doppler ultrasound approaches for fetal hemodynamic assessment, development of electromyography of uterine activity, development of novel eicosanoids for tocolysis

Established in the Fall of 2010, IRHRM membership includes 76 researchers from 4 institutions, representing 26 academic departments.

67 members - KUMC
3 members - Kansas State University
5 members - KU-Lawrence
1 member - UMKC/CMH
“Researchers find more evidence of estrogen’s role in female pain”
February 25, 2013
By C.J. Janovy

Scientists at the University of Kansas Medical Center continue to further our understanding of how estrogen — the hormone that most defines femininity — paradoxically contributes to female pain syndromes.

Researchers in the Women’s Pain Division of KU’s Institute for Neurological Discoveries have done pioneering work on how estrogen contributes to migraines. Now a group of researchers has published a paper in January’s Journal of Neuroscience that establishes a link between estrogen and pelvic pain.

“We’ve known for some time that estrogen can modulate pain,” says Peter Smith, Ph.D., professor in the Department of Molecular and Integrative Physiology and director of KU Medical Center’s Institute for Neurological Discoveries. “Some types of pain are associated with a drop in estrogen, as occurs on menopause, or an inability to respond to estrogen, which can happen to women in their teens and twenties.”

Smith says the study explores a new function for a protein called BMP4 is shedding new light on exactly how that happens.

“This particular molecule appears to be important in making sure you have the right number of pain-sensing nerves,” Smith says. Working with rodents, the researchers were able to show that when estrogen levels rise, BMP4 levels go down, resulting in fewer pain-sensing nerves. The fact that estrogen suppresses the ability to produce BMP4 wasn’t appreciated before, Smith says.

“We now have a mechanism that explains how, under normal conditions, peripheral sensory nerves - the pain-sensing terminals - go into a phase of rapid growth in female pelvic pain syndromes,” says Aritra Bhattacharjee, a doctoral student in Smith’s lab who is the paper’s lead author. “Sensory nerve growth can have significant implications in different pain syndromes — knee pain, joint pain, other inflammatory conditions, tendonitis, vulvar pain,” Bhattacharjee says. “Such inflammatory pain syndromes are highly prevalent with no effective cure.”

“We’re realizing now that there are a number of female pain syndromes out there, and certain types are quite
prevalent,” Smith says. “One of those is pelvic pain, so understanding what determines these pelvic pain syndromes is important.”

A decade ago, in a study of nearly 5,000 ethnically diverse women in Boston, Harvard researchers determined that 16 percent had histories of “chronic burning, knife-like pain, or pain on contact” that lasted at least three months. “Nearly 40 percent of women chose not to seek treatment, and of those who did, 60 percent saw three or more doctors, many of whom could not provide a diagnosis,” the researchers wrote. Their conclusion: “Chronic unexplained vulvar pain is a highly prevalent disorder that is often misdiagnosed.”

For women, estrogen levels rise and fall during the reproductive cycle, resulting in rising and falling numbers of nerves in the pelvic region — perhaps out of necessity. “When a pregnant woman is close to term,” Bhattacherjee points out, “estrogen levels shoot up, lowering the numbers of pain-sensing terminals in the reproductive tract, which may help in the delivery.”

What’s particularly exciting about this study, Bhattacherjee says, is that most studies of BMP4 in the adult nervous system come from injury-related models. But for the first time, KU Medical Center researchers studied a model that did not involve an induced injury.

“What’s novel is that we, for the first time, show a role for BMP4 in causing nerves to grow under normal conditions not induced by injury.”

Bhattacherjee, a Ph.D. student who is scheduled to defend his dissertation later this month, says he’s excited about the results of the research.

“It’s important to be able to contribute to this area,” he says. “In the bigger picture, this is really a gateway for us to understand nerve regeneration and nerve growth. It has broader implications for spinal cord injury, intellectual and developmental disabilities, and other developmental neurological disorders, because the BMP4 signaling pathway is involved in many other nervous system functions.”

Hinrich Staecker, M.D., Ph.D., a professor in the KU Medical Center’s Department of Otolaryngology, and M. A. Karim Rumi, M.B.B.S., Ph.D., a Research Associate Professor in the Department of Pathology and Laboratory Medicine, also contributed to the study.

This study was supported by the Eunice Kennedy Shriver National Institute Child Health and Human Development of the National Institutes of Health under award numbers HD049615 and HD002528.

Prenatal DHA reduces early preterm birth, low birth weight
Mon, 02/25/2013

LAWRENCE — University of Kansas researchers have found that the infants of mothers who were given 600 milligrams of the omega-3 fatty acid DHA during pregnancy weighed more at birth and were less likely to be very low birth weight and born before 34 weeks gestation than infants of mothers who were given a placebo. This result greatly strengthens the case for using the dietary supplement during pregnancy.

The results are from the first five years of a 10-year, double-blind randomized controlled trial to be published in the April issue of the American Journal of Clinical Nutrition. It is also available online. A followup of this sample of infants is ongoing to determine whether prenatal DHA nutritional supplementation will benefit children’s intelligence and school readiness.

“A reduction in early preterm and very low birth weight delivery could have clear clinical and public health significance,” said Susan Carlson, A.J. Rice Professor of Dietetics and Nutrition at the KU Medical Center, who directed the study with John Colombo, KU professor of psychology and director of the Life Span Institute.

“We believe that supplementing U.S. women with DHA could safely increase mean birth weight and gestational age to numbers that are closer to other developed countries such as Norway and Australia,” she said.

DHA (docosahexaenoic acid) occurs naturally in cell membranes with the highest levels in brain cells, but levels can be increased by diet or supplements. An infant obtains DHA from his or her mother in utero and postnatally from human milk, but the amount received depends upon the mother’s DHA status.

“U.S. women typically consume less DHA than women in most of the developed world,” said Carlson.

During the first five years of the study, children of women enrolled in the study received multiple developmental assessments at regular intervals throughout infancy and at 18 months of age. In the next phase of the study, the children will receive twice-yearly assessments until they are 6 years old. The researchers will measure developmental milestones that occur in later childhood and are linked to lifelong health and welfare.

Previous research has established the effects of postnatal feeding of DHA on infant cognitive and intellectual development, but DHA is accumulated most rapidly in the fetal brain during pregnancy, said Colombo. “That’s why we are so interested in the effects of DHA taken prenatally, because we will really be able to see how this nutrient affects development over the long term.”

The study is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Vitamin B3 holds promise for treating polycystic kidney disease, research suggests
June 17, 2013

By C.J. Janovy

Despite decades of research, treatments for polycystic kidney disease remain elusive. Now a new study by KU Medical Center researchers suggests that one mechanism for controlling the ravages of the disease might be found in vitamin B3.

Polycystic kidney disease is one of the most common life-threatening genetic diseases, affecting 600,000 Americans and 12.5 million people worldwide. People who inherit PKD develop kidney cysts that grow and multiply slowly over time — patients in their 20s might have few symptoms, but by the time they are into their 40s or 50s, normally fist-sized kidneys containing these fluid-filled sacs can grow to the size of a football, causing pain and destroying kidney function. With a research program dating back to the 1950s, KU Medical Center scientists are internationally recognized experts on the disease — and acutely aware that there is still no cure.

Recently, however, Xiaogang Li, Ph.D., an associate professor of Nephrology and Hypertension and a member of the KU Kidney Institute, found that vitamin B3 helped naturally inhibited the activity of a protein called Sirt1 that influences the formation and growth of cysts. Li and colleagues were able to show that vitamin B3 slowed the creation of cysts and restored kidney function in mice with PKD. The results were published in the June 17, 2013 Journal of Clinical Investigation (and earned a spot in the American Society of Nephrology’s June 25 “In the Loop” daily news briefing).

Li’s discovery is the second recent breakthrough from KU Medical Center scientists.

Xiaogang Li, PhD, and Xia Zhou, PhD

In November 2012, the New England Journal of Medicine reported that a clinical trial of 1,445 patients with PKD, conducted over three years at multiple international sites, showed that the drug tolvaptan slows the enlargement of cystic kidneys while also slowing the loss of kidney function. Tolvaptan was developed as a result of KU Medical Center research.

Because vitamin B3 is a commonly used supplement with little reported toxicity, Li hopes that efforts to test its effectiveness might bypass the early phase clinical trials that test toxicity in humans. “Promising therapies with vitamin B3 might rapidly be translated into human phase III clinical trials without years of normally required drug testing,” Li says.

Especially exciting, he says, is that after large-scale clinical trials confirm that vitamin B3 therapies are safe and effective for treating PKD, those therapies might also work for infants who are genetically at risk for developing the disease. “We may someday be able to safely treat mothers of fetuses with established genetic risks of developing PKD during their pregnancy to prevent the earliest stages of PKD development throughout fetal life,” he says. “We believe that administration of Vitamin B3 to a neonate, toddler or adolescent will effectively prevent or delay cyst formation and can be used for a lifetime.”

Li’s collaborators at the University of Kansas Medical Center are Xia Zhou, Ph.D., and Lucy X. Fan. William E. Sweeney, Jr. and Ellis D. Avner of the Medical College of Wisconsin and
John M. Denu of the University of Wisconsin also contributed to the study.

This study was supported by the National Institutes of Health (grant DK084097) and the PKD Foundation.


Unraveling the mysteries of the oocyte
June 18, 2013

By Donna Peck

David Albertini, Ph.D., has spent most of his career trying to understand one of life’s most mysterious cells: the oocyte, which eventually matures into an egg cell.

Albertini, who is a professor of molecular and integrative physiology and a member of the University of Kansas Medical Center’s Institute for Reproductive Health and Regenerative Medicine, is using the most advanced technology to shed new light on precisely what happens when an oocyte divides and how the oocyte receives support from other ovarian cells. Albertini’s research is contributing to scientists’ understanding of human embryo development and may guide future approaches for treating infertility and enhancing the use of stem cells in regenerative medicine.

Oocytes first arise in the fetal ovary and remain in an immature state for many years in most female mammals. They mature within a structure known as the ovarian follicle, which resides along the outer boundary, or cortex, of ovaries. During each reproductive cycle, several follicles begin to develop. In humans, only one oocyte per menstrual cycle will become a mature egg to be ovulated from its follicle.

Early on in a woman’s reproductive life, most oocytes have chromosomes in pristine condition, resulting in eggs that have the correct chromosomal complement. But as women age, the quality of their eggs deteriorates, and an increasing number carry chromosomal abnormalities, leading to increases in birth defects such as Down’s Syndrome.

“There is a very pronounced increase in the number of chromosomal defects in the oocytes of women by the time they reach their early thirties,” Albertini says.

For years, researchers have been puzzled about why chromosomes in aging oocytes begin to malfunction. Albertini says the technology allowing scientists to observe the behavior in live oocyte cells didn’t exist until recently.

“Before, we could study non-viable oocyte cells under a microscope, but that didn’t give us much insight into the cell division process of a live oocyte,” Albertini says. “But now we have special microscopes that allow us to see the molecules of live cells in detail and observe the flow of particles when a cell divides.”

David F. Albertini, PhD
Albertini and Rong Li, Ph.D., a professor of molecular and integrative physiology at KU Medical Center and a researcher at the Stowers Institute for Medical Research, were able to see firsthand the molecular mechanisms that lead to oocyte maturation. Among other things, they observed that for an oocyte to mature into an egg, it needs the support of the cells around it. Their observations were published in the March 2013 issue of Nature.

“It requires a tremendous amount of energy to transform an oocyte into an egg,” Albertini says. “The machines within the oocyte that drive cell division need the help of cells around it to tell it what to do and how to do it.”

When an oocyte begins meiosis (the process by which the nucleus divides in all sexually reproducing organisms during the production of spores or gametes), homologous chromosomes, which have genes for the same traits in the same position, form pairs and exchange genetic material in the process known as recombination or crossing over. During the first meiotic division, one member of each pair of homologous chromosomes moves to each end of the cell, and the cell divides. Each of the two cells produced by the first division has just one set of 23 chromosomes. The two daughter cells then undergo the second meiotic division. In the human female, just one of those four daughter cells will become a functional egg.

This process of moving and extruding the chromosomes requires energy in the form of ATP (adenosine triphosphate) that the oocyte is unable to produce. Instead, the cells surrounding the oocyte make large amounts of energy during the process of ovulation and deliver these high energy products through channels that connect the ovarian cells directly to the oocyte. Albertini likens this to filling up the gas tank before taking a long trip. For the egg, the fuel acquired from these cells will be consumed in the process of making an embryo.

Albertini says it is only with the assistance of surrounding cells that the machines within the oocyte are able to push and pull the chromosomes apart during meiosis. He calls it “filling the oocyte’s gas tank.”

Albertini and Li suggest that as a woman ages, the cells around the oocytes that assist in meiosis also age. When the support cells are no longer able to help the oocytes through the cell division process, it can have a negative effect on chromosomes as they try to separate from one another at each division.

These new studies are helping identify the properties of a “good egg” - which is a key to the production of healthy embryos and babies. In fact, Albertini is an international leader in the rapidly growing field of fertility preservation, which is opening new doors for patients whose fertility may have been compromised due to treatments for cancer.

“Advances in the technology for freezing oocytes or ovarian tissues have reached a point where those patients unfortunate enough to have had their oocytes damaged as a result of radiotherapy or chemotherapy may soon be able to reproduce once their disease has been managed,” Albertini says.

Albertini says although there are differences in oocyte development in mice and humans, these latest discoveries are significant.

“I’m optimistic that these new insights into the molecular cell biology of oocytes from rodent models and humans will contribute to advances in the treatment of infertility and the field of regenerative medicine.”

KU obstetrician writes medications guide for women who are pregnant or breast-feeding
August 16, 2013

By David Martin

One of the most notorious prescription drug debacles in recent history involved the German-developed medication thalidomide. Doctors in Europe first prescribed thalidomide in the late 1950s to treat anxiety, insomnia and, in pregnant women, morning sickness. Thalidomide was withdrawn from the market in the early 1960s when doctors discovered that it caused devastating birth defects. About 10,000 children around the world were born with major malformations because their mothers had taken the drug during early pregnancy.

In the wake of the disaster, the U.S. Food and Drug Administration (FDA) created a “Pregnancy Risk Factor” grading system for medications. Drugs now receive one of five grades — A, B, C, D or X — based on what’s known about the risk they pose to a developing fetus. These grades are typically assigned when the drug is first released onto the market.

The system has limits. Two-thirds of all drugs sold in the United States are classified as Category C. The FDA says drugs in this category should be taken if the benefits outweigh the risk — a not particularly helpful recommendation.

In addition to carrying vague warnings, drugs can be slow to find their way into Category X, considered to be the most potentially harmful (thalidomide is Category X). For example, this past spring, the FDA advised that pregnant women should not take the anti-seizure medication valproic acid. But obstetricians have been warning of the dangers of valproic acid for years.

“We’ve known for decades that this drug causes birth defects,” says Carl Weiner, M.D., an obstetrician and expert in maternal-fetal medicine. “We know that there are other drugs that we can use in pregnancy that have a better safety profile from the standpoint of the fetus, but they might not be as effective in controlling the mother’s seizures.”

Weiner, professor and the Kermit E. Krantz Chair in Gynecology & Obstetrics at the University of Kansas School of Medicine, says the use of medication during pregnancy is a neglected area of research. Only a few drugs are tested on pregnant women. In fact, in 1977, the FDA excluded all women of childbearing age from early phases of clinical trials. The decision was overruled in 1993.
Still, much of the knowledge of a drug’s impact on pregnancy — and pregnancy’s impact on a drug — is derived from animal tests, epidemiological studies and registries of women who take medication and volunteer to provide information during and after their pregnancies.

“The art of medicine is based on relative risk, and it’s no different if we’re talking about a pregnant woman,” Weiner says. “Because this information has been hard to come by, because it was poorly distilled for use, physicians frequently tell women, ‘Stop all your medicine.’ But the truth is, many of those medicines were needed and stopping them posed a risk to the mother and the pregnancy.”

Weiner has worked to educate physicians about medication use pregnant and breastfeeding patients. He is the co-author of a textbook, “Drugs for Pregnant and Lactating Women,” about to enter its fourth edition.

Between updates, Weiner began to think about taking the material in the textbook and making it accessible to a wider audience. He found a professional lay medical writer, Kate Rope, who helped him translate the updated information into an affordable book for patients. The book, “The Complete Guide to Medications During Pregnancy and Breastfeeding,” was published this past April.

The A-to-Z directory starts with acarbose and ends with zolpidem. Each entry describes how the drug works, how it affects the mother and her baby, its safety while breastfeeding, any reasons for avoiding it, the potential interactions and a “bottom line” assessment. The guide, for instance, notes that acetaminophen is the “pain reliever of choice in the first trimester if one must be used.”

Weiner hopes that women will use guide as a springboard for a discussion with their health care providers. “A book is frozen in time,” he says. “New information comes out all the time. But they could use what we are providing them as a starting point to question whether a particular drug was safe for them.”

One challenge for Weiner and other obstetricians is that women of childbearing age are more likely to be taking medication than they were in the past. “We live in a far more medicated society than we did 20, 30 years ago,” Weiner says.

For instance, one in 10 Americans now takes an antidepressant medication. Drugs that target the neurotransmitters related to mood have been associated with birth defects and behavioral abnormalities. But untreated depression poses risks, as well. “A woman who cannot function because of the depth of her depression needs medication,” Weiner says. “She’s not going to help her fetus if she’s sick.”

In fact, very few medications are considered perfectly safe. Less than 1 percent fall into Category A (“possibility of fetal harm appears remote”). With the rest, women and their health care providers need to work to find a balance between the perceived risk and benefit.

Weiner acknowledges the ambiguity can be frustrating. “We have a tendency to think in black and white terms,” he says. “At least in my profession, black and white is the rarity. We have a lot of gray.”

One sure way to improve the outcomes of pregnancies is to plan for them. Weiner wishes that more women made a conscious decision to get pregnant. With an unplanned pregnancy, the fetus is more likely to be exposed to drugs and environmental toxins that have adverse effects.
An unplanned pregnancy is also a missed opportunity for preconception care, which has been shown to improve a woman’s chances having a having a healthy baby. Weiner would be happy if he met more new patients before the pregnancy has begun.

“If we were proactive, we could really change a lot,” he says.

Dr. Weiner discussed breast-feeding with other guests on the KCUR-FM program “Central Standard” on Aug. 15.


KU medical scientist patents method for better osteoarthritis treatment
April 03, 2013
By David Martin

Osteoarthritis — the most common form of arthritis — affects an estimated 27 million Americans. Often called wear-and-tear arthritis, osteoarthritis breaks down cartilage, the tough but flexible tissue that cushions joint surfaces. When joint pain is described as “bone on bone,” osteoarthritis is usually at fault. The disease typically occurs in individuals who are 45 and older, is more common in women than in men, and usually affects joints in the hands, neck, lower back, knees and hips. Doctors currently treat the symptoms of osteoarthritis by prescribing rest, physical therapy, pain medicine or joint injections of corticosteroid or other medications. Joint replacement surgery is also an option for patients with late-stage osteoarthritis.

Now a medical scientist at the University of Kansas Medical Center has identified a link between a protein and osteoarthritis. The protein forms the basis of a patent for a potential new method of preventing and treating the disease.

“Pain medicines may bring relief for the short term,” Jinxi Wang, M.D., Ph.D, says of current treatments, “but it’s not going to cure the disease.”

Wang is the Mary Alice and Paul R. Harrington Distinguished Professor of Orthopedics and the director of the Harrington Laboratory for Molecular Orthopedics at KU Medical Center. The two main research programs in his lab are bone repair and osteoarthritis.

Wang says there are several reasons why it has been difficult to make progress in the fight against osteoarthritis. For one thing, scientists are unsure what causes it. Joint injury or abnormal alignment might predispose an individual to osteoarthritis, though some forms of it appear to be hereditary. Hormones also appear to play a role.

Jinxi Wang, MD, PhD
In any case, the molecular and cellular mechanisms of osteoarthritis remain unclear. Previous studies have suggested that some enzymes and inflammatory proteins may cause cartilage breakdown. However, no anti-osteoarthritis drug candidate targeting a single inflammatory protein or degrading enzyme have proven effective in clinical trials.

**Establishing metabolic balance**

Wang and his team in the Harrington lab have looked for answers in metabolism, the sum of the chemical processes by which cells produce the materials and energy necessary for life. “To cure or prevent disease, you need to know molecular medicine,” he says. Individuals with osteoarthritis have an imbalance in the metabolism of their joint cartilage and surrounding tissues. There is too much catabolism, or tearing down, and not enough anabolism for repair, or building up.

“We want to find a good metabolic balance in joint tissues,” Wang says.

Wang and his collaborators have identified a protein that may play a role in maintaining the balance. His research group discovered that mice lacking the Nfat1 protein displayed changes in major weight-bearing joints — hip, knee, shoulder — including the loss of cartilage and bone changes such as the formation of bone spurs. The changes looked very similar to the osteoarthritis changes seen in humans.

For Wang, the next step is to determine the extent to which Nfat1 deficiency is associated with osteoarthritis in humans. Using blood and joint tissue surgeons have removed, he has determined that a substantial percentage of osteoarthritis patients have decreased Nfat1.

Wang says the mice and human studies suggest that Nfat1 may be a key factor for maintaining a healthy metabolic balance in the joint cartilage that covers the ends of bones. As a result, Nfat1 holds promise as a target for predicting, preventing and treating osteoarthritis at the early stage. For example, individuals with blood tests that show decreased levels of Nfat1 could be at risk for osteoarthritis. If further exams confirm the existence of early-stage osteoarthritis, an Nfat1 stimulator could be used to stop the progression of the disease. If osteoarthritis does not yet exist, an Nfat1 stimulator could be used for prevention of Nfat1 deficiency-related osteoarthritis.

Because Nfat1 may suppress the expression of multiple catabolic factors in joint tissues, Nfat1 could be a more effective anti-osteoarthritis target than previously tested drug candidates that only inhibit a single catabolic molecule.

In 2009, Wang filed a patent describing the role of Nfat1 deficiency in osteoarthritis and the various ways the protein could be used against the disease. The United States Patent and Trademark Office granted the patent last fall.

The Nfat1 patent is assigned to the University of Kansas. Wang worked with an office in Lawrence, the Center for Technology and Commercialization, which helps faculty members determine if their ideas need protection through a patent, trademark or copyright.

Wang’s research into Nfat1 deficiency and osteoarthritis receives funding from the National Institutes of Health and the U.S. Department of Defense.

http://www.kumc.edu/news-listing-page/method-for-better-osteoarthritis-treatment-.html
Hypoxia researcher contributes to study describing potential diabetes treatment

September 16, 2013

Adam Krieg, Ph.D., assistant professor of obstetrics and gynecology, is a co-author of a new study describing a potential new treatment for type 2 diabetes.

Researchers at the University of Stanford School of Medicine are the lead and senior authors of two papers published online Sept. 15 in Nature Medicine. Krieg was a postdoctoral researcher at Stanford from 2003 to 2010. In a news release, Stanford said the studies “identified a molecular pathway — a series of interactions among proteins — involved in the development of diabetes. Furthermore, they have found that a drug already approved for use in humans can regulate the pathway.

“The studies, done in mice, identify a previously unexpected link between a low-oxygen condition called hypoxia and the ability of cells in the liver to respond to insulin. The drug, aflibercept (marketed as Eylea or Zaltrap), is used to treat metastatic colorectal cancer and a form of macular degeneration. Aflibercept is a member of a family of proteins that inhibit the vascular endothelial growth factor, or VEGF, pathway.”

Krieg, a member of the IRHRM, contributed to a study that identified a protein, PhD3, involved in the “cross-talk” between hypoxia and insulin signaling.

http://www.kumc.edu/school-of-medicine/about-the-school/inside-the-school-of-medicine.html

Dr. Gregory S. Kopf accepts new position

Dr. Greg Kopf has resigned, effective November 25, 2013, from his roles as executive director of the Research Institute and Associate Vice Chancellor of Research Administration at KU Medical Center. Greg was a valued member of the IRHRM’s Internal Advisory Board. He has taken a position as R&D Director of the Women’s Health Division for FHI 360, a global nonprofit headquartered in the Research Triangle in Durham, N.C. Please join us in wishing him well in his new venture.

Dr. H. Edward (Ed) Grotjan, Jr., passed away in March

Harvey Edward Grotjan, Jr. entered into rest, after his battle with Glioblastoma Multiforme (GBM), at Lake Saint Louis, Missouri, Tuesday, March 19, 2013.

Ed was a well-respected and highly versatile scientist with expertise in biotechnology, physiology, biochemistry, genetics and business development concentrated in the areas of endocrinology, reproductive health, genetics and gastroenterology. He earned his Ph.D. in Physiology/Endocrinology in 1975 from the University of Kansas School of Medicine, Kansas City, Kansas where he trained with Donald C. Johnson, Ph.D.

Ed had a very successful career. Most recently he worked for Shire Pharmaceuticals, Inc., as a Senior Medical Science Liaison from 2009-2012.
New Grant Awards

FACULTY GRANTS


“Dissecting the Functional Role of miRNAs in Decidualization”, Principal Investigator, Warren Nothnick, April 1, 2013 through March 31, 2014.

National Institutes of Health, “Progression of DCIS to invasive breast cancer through CCR2 chemokine signaling”, 1R01CA172764-01A1, Principal Investigator, Fariba Behbod, September 1, 2013 through August 31, 2018.


### New Grant Awards

**KUMC Research Institute Lied Basic Science Award**, “Role of iron metabolism in the pathogenesis of diabetes”, Principal Investigator, **Hao Zhu**, February 2013 through February 2014.

**NIH T32 Kansas Training Program in Neurological and Rehabilitation Sciences**, Fellowship to Matt Stroh, Mentor **Hao Zhu**, July 2013 through June 2014.


**The Danish Council for Strategic Research Program Commission on Individuals, Disease and Society “Fifty-Year Follow-up to the Danish Longitudinal Study on Alcoholism and Phenotypes in Alcohol Use Disorders: A Multidisciplinary Approach to Improved Diagnosis and Treatment of Patients with Alcohol Use Disorders”, Grant 12-129576, Principal Investigator, Ulrik Becker, Co-Investigator, **Merlin Butler**, $45,000, 2013 through 2018.


**KUMC NextGen Sequencing Pilot Award**, “RNA Sequencing in Individuals with Obesity or Alstrom Syndrome”, Principal Investigator, **Merlin Butler**, $5,075, 2013.

**KUMC NextGen Sequencing Pilot Award**, “Examination of RNA Sequencing in Alcoholism”, Co-Investigator, **Merlin Butler**, $5,075, 2013.

**Prader-Willi Syndrome Association (USA)** “RDCRN Fellowship Support to Study Rare Diseases Including Prader-Willi Syndrome”, Principal Investigator, **Merlin Butler**, $25,000, 2013. This competitive support arises from the NIH Rare Disease Grant (U54RR019478).

**KSU-CVM Success-FYI (Success for Young Investigators Award)**, “Transforming growth factor beta (TGFβ) signaling in male excurrent system epithelia in vivo”, Principal Investigator, **Fernando Pierucci-Alves**, $15,000, 2013 through 2014.

**FACULTY HONORS & AWARDS**

**Katherine F. Roby**  
Member, Scientific Advisory Panel, Endocrine Disruptor Panel, EPA, May 2013

Member, NIH, Special Emphasis Panel, Fellowships: Oncological Sciences. June 2013

Member, Scientific Advisory Panel, US Environmental Protection Agency. 2013

Chair, Department of Defense, Congressionally Directed Medical Research Programs, Ovarian Cancer Research Program Review Panel Clinical and Experimental Therapeutics October 2013

**Warren Nothnick**  
Appointed Scientific Director of Lab Animal Resources (LAR), February 2013

**Michael Wolfe**  
Appointed KUMC Research Integrity Officer, February 2013

**Jinxi Wang**  
NIH Study Section: Skeletal Biology Development and Disease (SBDD), February 2013

**Warren Nothnick**  
Faculty Investigator Research Award, Faculty Research Day, Oct. 8, 2013

**David Albertini**  
Section Editor “Gametes and Embryos” in 4th Edition Knobil and Neill’s Physiology of Reproduction, Editors-in-Chief Tony M. Plant and Anthony J. Zeleznik

2013 Beacon Award, Frontiers of Reproduction, MBL

**Fariba Behbod**  
Scientific Review Panel Member; NIH/NCI/ZCA1 GRB-I, 2013  
Fariba Behbod, Scientific Review Panel Member; Department of Defense Breakthrough Awards

**Merlin Butler**  
Selected as a Charter Member for “Peer Reviewed Physicians”, 2013

Selected by “Consumers’ Research Council of America, Guide to America’s Top Physicians”, 2013


**Michael J. Soares**  
Appointed to the Society for the Study of Reproduction (SSR) Board of Directors, 2013

**John Colombo**  
Elected to the external advisory committee of the High Risk Baby Siblings Research Consortium (consortium between Autism Speaks and NIH)

**Sacha Krieg**  
Board Certified in Reproductive Endocrinology and Infertility, April 2013
New Honors/Awards

TRAINEE HONORS & AWARDS

Lei Qiu, MS (mentor-Adam Krieg):
Podium Presentation, 2013 The Tumor Microenvironment: Hypoxia, Angiogenesis and Vasculature, 13th International Workshop

2013 Student Travel Scholarship (Amount of $500), Academic Affairs in the Graduate Studies Department, KUMC

IRHRM AWARDS - 2013 RESIDENT, POSTDOC AND FELLOW RESEARCH DAY

The IRHRM awarded 2 postdoctoral fellow presentation awards (certificate/plaque and travel award) at the 2013 RPF Day, one from the Center for Epigenetics and Stem Cell Biology, and one from the Center for Reproductive Sciences.

Aritra Bhattacherjee, PhD, (mentor-Peter Smith) CESCB; “Epigenetic Regulation of Peripheral Sensory Nerve Growth: Role of MeCP2 in Nociceptive Neurons”

Stephen Renaud, PhD (mentor-Michael Soares) CRS; “OVO-like 1 Regulates Human Trophoblast Differentiation” - Stephen also received 1st place from the Student Research Forum for his presentation

IRHRM AWARDS - 2013 STUDENT RESEARCH FORUM

Again this year, the IRHRM awarded 3 graduate student presentation awards (certificate/plaque and travel award) for the oral presentations in reproduction and regenerative medicine (one from each Center).

Lei Qiu (mentor-Adam Krieg)
CRS; “The Histone Demethylase JMJD2B Contributes to Ovarian Cancer Proliferation and Metastasis in Different Oxygen Levels”

Zhen Zhang (mentor-Chad Slawson)
CESCB; “O-GlcNAcylation Regulates Gamma-Globin Transcription”

Marlies Ozias (mentor-Susan Carlson)
CDOHAD; “Leptin and Resistin are Influenced by Increased Body Fat Measurements in Pregnant Women”
Some Recent Publications


The 10th Annual Gilbert S. Greenwald Symposium on Reproduction and Regenerative Medicine

The 10th Annual Gilbert S. Greenwald Symposium on Reproduction and Regenerative Medicine was held October 17-18, 2013. This annual event is hosted in honor and as a memorial to the life of Gilbert S. Greenwald, PhD, a former KUMC Distinguished Professor and pioneer in reproductive biology research at KUMC and at the national level.

Approximately 90 faculty, trainees and staff from across the regional participated in this day-and-a-half event.
Event Highlights: Greenwald Symposium

Martin M. Matzuk, MD, PhD, Stuart A. Wallace Chair and Professor of Pathology and Immunology at Baylor College of Medicine, kicked off the event on Thursday, Oct. 17 with a lecture in the School of Nursing auditorium titled “Genetic Manipulation of the Mouse for Translational Studies in Reproductive Medicine”.

After Dr. Matzuk’s lecture, everyone migrated across the street to the Beller Conference Center for the Greenwald Reception and Poster Session. Trainees and faculty presented 27 posters and took advantage of the wonderful opportunity to interact with our speakers and learn more about the research being conducted on reproduction and regenerative medicine.

Friday’s events were held at the Kansas City Public Library in downtown Kansas City, where plenary lecturers included Drs. Louis Muglia, University of Cincinnati, Frederick vom Saal, University of Missouri-Columbia, Shoukhrat Mitalipov, Oregon Health and Science University, Mary Hunzicker-Dunn, Washington State University, and Derek Boerboom, University of Montreal.

Four trainees were selected for oral presentation and did an outstanding job. Selected oral trainee presenters included Penghua Yang, PhD, Postdoctoral Fellow, University of Missouri-Columbia (mentor-R. Michael Roberts), Lei Qiu, MS, Graduate Student, KUMC (mentor-Adam Krieg), Stephen Renaud, PhD, Postdoctoral Fellow, KUMC (mentor-Michael J. Soares), and Adam Summers, PhD, Postdoctoral Fellow, University of Nebraska-Lincoln (mentor-Andrea Cupp).

At the conclusion of Friday’s symposium, four poster awards were presented to trainees for outstanding poster presentation. Congratulations once again to:

Prabuddha Chakraborty, MS, Graduate Student, University of Nebraska Medical Center (mentor-Shyamal K. Roy)

Susmita Jasti, PhD, Postdoctoral Fellow, KUMC (mentor-Margaret Petroff)

Damayanti Chakraborty, PhD, Postdoctoral Fellow, KUMC (mentor-Michael J. Soares)

Wei-Ting Hung, MS, Graduate Student, KUMC (mentor-Lane Christenson)

A special “thank you” to all the 2013 trainee hosts and trainee volunteers, and to all of our sponsors. Your contributions have once again helped make the event a success.

Watch for the 11th Annual Greenwald Symposium dates – coming soon!
Upcoming Events (December 2013 - March 2014)

December 2013

2  CRS Chalk Talk, Noon, 3070 HLSIC, Alison Ting, PhD, Oregon Primate Research Center, *Ovarian tissue cryopreservation for fertility preservation and primordial follicle activation in the rhesus macaque*

5  Seminar, 8:30-9:30 am, Lied Aud., Alexander Yu Nikitin, MD, PhD, Cornell University, *Transitional Zones, Stem Cells and Cancer*

11  CDOHAD Chalk Talk, Noon, 3070 HLSIC, Gene Lee, MD, *Title TBD*

12  Seminar, 8:30-9:30 am, Lied Aud., Dieter Egli, PhD, New York Stem Cell Foundation, *Genome Transfer in Human Oocytes*

18  CDOHAD Chalk Talk, Noon, 3070 HLSIC, Adam Krieg, PhD, *Regulation of metastatic mechanisms in ovarian cancer by a histone demethylase*

January 2014

16  CRS Chalk Talk, Noon, 3070 HLSIC, Kaz Imakawa, PhD, *Title TBD*

23  Seminar, 8:30-9:30 am, Lied Aud., Xiaoyong Yang, PhD, Yale University, *Nutritional and Circadian Control of Metabolism in Health and Disease*

29  CESCB Chalk Talk, Noon, 3070 HLSIC, Stuart McDonald, *Title TBD*

February 2014

5  CRS Chalk Talk, Noon, 3070 HLSIC, Jeremy Chien, PhD, *Title TBD*

February 2014 (continued)

12  CESCB Chalk Talk, Noon, 3070 HLSIC, Omar Aljitawi, MD, *Title TBD*

13  Seminar, 8:30 - 9:30 am, Lied Aud., Didier Stainier, PhD, University of California, San Francisco, *Imaging Organ Formation and Function in Zebrafish*

19  CESCB Chalk Talk, Noon, 3070 HLSIC, Jinxi Wang, MD, PhD, *Title TBD*

20  Seminar, 8:30 - 9:30 am, Lied Aud., Mana M. Parast, MD, PhD, University of California, San Diego, *Modeling Human Placental Development using Pluripotent Stem Cells*

27  James L. Voogt Lecture in Neuroendocrinology, 8:30 - 9:30 am, Lied Aud., Andrea C. Gore, PhD, University of Texas, Austin, *Are Environmental Endocrine Disruptors Impairing Reproduction, Brain and Behavior?*

March 2014

5  CRS Chalk Talk, Noon, 3070 HLSIC, Nancy Muma, PhD, *Title TBD*

12  CRS Chalk Talk, Noon, 3070 HLSIC, Peter Smith, PhD, *Title TBD*

13  Seminar, 8:30 - 9:30 am, Lied Aud., Clodia Osipo, PhD, Loyola University, *Regulation of Notch Signaling in HER2 + Breast Cancer: Therapeutic Implications*

19  CESCB Chalk Talk, Noon, 3070 HLSIC, Animesh Dhar, PhD, *Title TBD*

Sculpture: “Stemmer No. 7”, by David Fried, 2005
### Spring 2014 Schedule

**8:30-9:30 a.m. Lied Auditorium, KUMC Campus**

To request a meeting with our speakers, contact lshriver@kumc.edu

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<td>1-23-14</td>
<td>Xiaoyong Yang, PhD, Yale University</td>
<td>Nutritional and Circadian Control of Metabolism in Health and Disease</td>
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<td>Host: Chad Slawson, PhD</td>
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<td>2-13-14</td>
<td>Didier Stainier, PhD, University of California, San Francisco</td>
<td>Imaging Organ Formation and Function in Zebrafish</td>
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<td>2-20-14</td>
<td>Mana M. Parast, MD, PhD, University of California, San Diego</td>
<td>Modeling Human Placental Development Using Pluripotent Stem Cells</td>
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<td>2-27-14</td>
<td>Andrea C. Gore, PhD, University of Texas, Austin</td>
<td>Are Environmental Endocrine Disruptors Impairing Reproduction, Brain, and Behavior? -James L. Voogt Lecture in Neuroendocrinology</td>
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<td>3-13-14</td>
<td>Clodia Osipo, PhD, Loyola University</td>
<td>Regulation of Notch Signaling in HER2+ Breast Cancer: Therapeutic Implications</td>
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<td>Host: Joan Lewis-Wambi, PhD</td>
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<td>3-27-14</td>
<td>Peter Andrews, PhD, The University of Sheffield</td>
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<td>Host: Ivan Damjanov, MD, PhD</td>
<td>-Inaugural Ivan Damjanov, MD, PhD Lecture in Stem Cell Research</td>
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<td>4-3-14</td>
<td>Richard L. Stouffer, PhD, Oregon Health &amp; Science University</td>
<td>The Primate Ovary as a Model for Understanding and Treating Infertility -Donald C. Johnson Lecture in Reproduction</td>
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<td>Host: Michael J. Soares, PhD</td>
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<td>4-17-14</td>
<td>Julie Kim, PhD, Northwestern University</td>
<td>Influence of AKT on Progesterone Receptor Function</td>
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<td>Host: Warren B. Nothnick, PhD, HCLD</td>
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<td>4-24-14</td>
<td>Yang Shi, PhD, Children’s Hospital Boston</td>
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<td>Host: Adam J. Krieg, PhD</td>
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<td>5-8-14</td>
<td>Tracy L. Bale, PhD, University of Pennsylvania</td>
<td>Stressed Parents: Maternal and Paternal Epigenetic Reprogramming of the Developing Brain</td>
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<td>5-15-14</td>
<td>Frank McKeon, PhD, The Jackson Laboratory</td>
<td>TBD</td>
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<td>Host: Fariba Behbod, PharmD, PhD</td>
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