HIGHLIGHTS FROM THE DIRECTOR

With increasing worldwide trends in conceiving at later ages in life, there is a movement in research towards better understanding the link between age and spermatogenesis in older men. While it has long been known that women have risks and limits associated with conceiving at later ages, men traditionally thought they were immune from both the physiological and societal consequences of aging. However, recent research shows that advanced paternal aging (APA) can also affect reproductive success and in turn, offspring health.

As men age, their probability of producing an abnormal semen specimen increases. This is manifested in decreased sperm quality, motility, concentration, or sperm morphology. Ongoing repetitive cycles of spermatogenesis that occur throughout a man’s adult life may contribute to an increased likelihood of spontaneous, de novo mutations in the sperm; which in turn can lead to genetic mutations in their offspring, or even fetal loss due to abnormalities, malignancies, and other external causes. Mutations can result in conditions in offspring of older men, such as achondroplasia, cleft palate, neurofibromatosis, breast cancer, and autism. While detailed resources and guidance are available for women on maternal aging and conceiving, APA, has many questions and risks to be addressed. As society trends towards having children later in life, men must also be educated on the risk of genetic abnormalities, cancer, autism, psychiatric disorders, and other conditions passed on to their offspring due to APA.

Additionally, a better understanding of the link between APA and conceiving later will allow us to better care for the reproductive needs of older men, and offer them the appropriate counseling, testing, and knowledge they need in making a decision about conceiving later in life.

In closing, I need to share an important development in my own career with the Center for Reproductive Medicine (CRM) members. In a few months, I will be leaving Baylor College of Medicine after spending my entire academic career here—beginning as a post-doctoral fellow and rising through the academic ranks to my current position as Director of the CRM. I will move to a new position at Weill Cornell College of Medicine in New York. Despite this change in my career path and leadership in the CRM, I remain forever grateful for the opportunities afforded to me at Baylor and I am saddened to leave my Baylor Family.

DORRIE
Endometriosis is considered to be an estrogen-dependent inflammatory disease, but its etiology is unclear. Thus far, a mechanistic role for steroid receptor coactivators (SRCs) in the progression of endometriosis has not been elucidated. An SRC-1-null mouse model reveals that the mouse SRC-1 gene has an essential role in endometriosis progression. Notably, a previously unidentified 70-kDa SRC-1 proteolytic isoform is highly elevated both in the endometriotic tissue of mice with surgically induced endometriosis and in endometriotic stromal cells biopsied from patients with endometriosis, compared to normal endometrium.
Tnf−/− and Mmp9−/− mice with surgically induced endometriosis showed that activation of tumor necrosis factor α (TNF-α)-induced matrix metallopeptidase 9 (MMP9) activity mediates formation of the 70-kDa SRC-1 C-terminal isoform in endometriotic mouse tissue. In contrast to full-length SRC-1, the endometriotic 70-kDa SRC-1 C-terminal fragment prevents TNF-α-mediated apoptosis in human endometrial epithelial cells and causes the epithelial-mesenchymal transition and the invasion of human endometrial cells that are hallmarks of progressive endometriosis.

Participating in the inhibition of apoptosis by the SRC1-isoform is ERbeta nuclear receptor. ERbeta binds the SRC-isoform and together they substantiate the abrogation of apoptosis. Collectively, the newly identified ERbeta–SRC-1 isoform complex provides a functional axis that promotes the pathogenic progression of endometriosis.

**SPOTLIGHT: RHRD17 Keynote Speaker**

**AMY LYNN MCGUIRE, J.D., PH.D.**
Leon Jaworski Professor of Biomedical Ethics and Director, Center for Medical Ethics and Health Policy, Baylor College of Medicine

“Destiny’s Child: Reproduction in the Age of Genomics”

Dr. Amy McGuire explored the current state of genomic medicine and the ethical, social, and policy issues raised by prenatal and perinatal genomic sequencing and gene editing. She discussed concerns about return of results, impacts on the parent-child relationship, the challenges of living with uncertainty, and privacy and discrimination.

She argued that the responsible integration of genomic sequencing and editing technologies will require an explicit shift away from genetic determinism towards genetic relativism.

**RHRD17 WINNERS**

Images: (top): 2017 t-shirt logo, designed by Marisol O’Neill, Graduate Student, Department of Molecular and Cellular Biology, Lab of Dr. Dolores Lamb; (middle): 2017 Abstract Winners (from left to right) Virginia Wotring, Ph.D., Nicholas Webster, Bryan Nikolai, Ph.D., Tiffany Katz, Ph.D., and Liesbeth Vossaert, Ph.D. (not pictured); (bottom) 2017 Poster Winners (from left to right) Shang Wang, Ph.D., Marisol O’Neill, Darius Devlin, Nasim Bekheirnia representing Alexandria Blackburn, Neil Chappell, M.D., and Jessica Rubin, M.D. (not pictured)
“A Population-based Assessment of Pediatric Cancer Risk in Children with Birth Defects”

One of the strongest risk factors for childhood cancer is being born with a congenital anomaly. Exploring the intersection of birth defects and childhood cancer is likely to provide valuable insights into what causes cancer, and may also provide information that can be translated into screening strategies for those children at the greatest risk of developing cancer. In spite of this, little is known about the risk of cancer among children with specific birth defects, including genitourinary anomalies. We are currently linking population-based birth defects and cancer registries to identify novel birth defect-childhood cancer patterns and enrolling families to determine the molecular underpinnings of these associations.

“Advancements in Oncofertility – the Tip of the Iceberg”

As the number of cancer survivors increases, awareness of cancer-related infertility and fertility preservation (FP) continues to grow. There has been improvement in the quantity and quality of fertility discussions with young people diagnosed with cancer and we have several viable options for FP. However, there are still many unmet needs that persist in this patient population. The field of oncofertility has generated more questions than answers, including those related to the ideal provision of services as well as reproductive and oncologic outcomes. As a result, it is fertile ground for investigatory inquiry; within the Texas Medical Center, research initiatives include the development of oncofertility databases, creation of a web-based FP decision aid, and investigation of ways to improve FP methods, such as ovarian tissue freezing. Ultimately, these results have the potential to improve the overall survivorship experience of young people diagnosed with cancer.
Since his undergraduate years, **JASON HEANEY, Ph.D.,** Assistant Professor of Molecular and Human Genetics, has been interested in the connection between stem cell biology and cancer genetics, and the idea of stem cells or precursor cells ceding cancer. As an undergrad, he focused on cancer research, and as a graduate student, worked on genome engineering in mouse embryonic stem cells. When the time came to identify a lab for his post-doc, he was looking for a way to bring together his interests in cancer, stem/progenitor cells, and genetic mouse models. This is where his interest in mouse models of testicular germ cell tumors (TGCTS) took off, and thus his research in testicular cancer.

**Q|** What sparked your interest in testicular cancer?

**A|** It was less of a cancer initiative, and more a developmental biology/progenitor cell interest because TGCTS initiate *in utero*. What’s intriguing is that the embryonic precursor cells that ultimately form sperm or eggs receive signals in the developing testis or ovary that tell them, “you are a male or female germ cell”—that is all they are supposed to do. They need these instructions because up to that point, they actually harbor characteristics of pluripotent cells, like embryonic stem (ES) cells, which have the capacity to form multiple cell lineages. In studying testicular cancer within the 129 inbred mouse model of TGCTS, this signal breaks down. It is either missed or not interpreted correctly. The pluripotent potential is still maintained, and the nascent germ cells lose track of what they are supposed to be. Instead they form pluripotent embryonal carcinoma cells which differentiate into a teratoma, a tumor containing bone, cartilage, hair, and so on. It is as if they are trying to form an embryo, but instead we have a “disorganized” mass. We can mimic this culture by taking ES cells and removing certain factors. It will start to randomly differentiate, and begin forming embryoid bodies. This is where my interest came from. Answering questions such as, *Why do these cells that have pluripotent potential lose it? What goes wrong? What is lost in that pathway that allows for this very peculiar type of cancer to develop?* As a post-doc, I started working on identifying genes that were involved in that process. I carried that work into my faculty position, where I became much more interested in not just what genes might be involved, but what developmental pathways (starting in embryogenesis) do these genes provoke to cause testicular cancer.

**Q|** How has your current work led to understanding these developmental pathways?

**A|** Our current work focuses on what signal is missing, or what signal is misinterpreted when these pluripotent germ cell precursors are supposed to become fixed to one fate, or unipotent—*What went wrong to begin with?* It seems that testicular cancer is driven by the lack of a response or an inappropriate response to male-specific sex differentiation signals in the developing testis.

Our research suggests that it is likely the later—a signal that is necessary for male germ cell development, when integrated inappropriately by germ cells, promotes their transformation. In other words, the internal programming of the germ cell is not setup to appropriately interpret signals from supporting cells in the developing testis. Instead of a normal male germ cell, they become cancer stem cells.

A second question we are starting to address is, *What is that last switch or commitment step to go from a pluripotent germ cell precursor to a pluripotent tumor stem cell?* It can’t go back once it hits the tumor stem cell—it forms the tumor.

**Q|** What makes testicular cancer different than other forms of cancer?

**A|** With testicular cancer, an individual complex, inherited genetic make-up causes a developmental disorder that disrupts normal male germ cell development; because of this developmental defect and the interesting pluripotent nature of germ cell precursors, cancer can occur.
Classifying it as cancer or a developmental defect is tough. The characteristic of how it progresses is a bit different than other cancers—this has always been an intriguing aspect to me. Most cancers are driven by either inherited single gene mutations (familial cancers) or accumulation of somatic mutations in a particular tissue. For testicular cancer, it’s not until the benign tumor precursors have already formed do genomic abnormalities seem to develop, further provoking tumor growth and tumor metastasis to occur. That’s why our research has taken a more developmental biology approach, because its origin is a developmental biology question.

In fact in the 129 inbred mouse model, we don’t see reoccurring mutations, chromosome-level alterations or either single gene mutations, in the testicular tumors. The tumors, once they form, have a normal karyotype and whole-exome sequencing, looking for individual gene-level mutations have not identified reoccurring mutations.

It’s the inherited variances in the genome of the 129 inbred mouse strain that are sufficient to disrupt normal male germ cell development and tumors to form.

Q| Are there different types of testicular cancer and treatments?
A| Testicular cancer is interesting in that it actually has three peaks. The first peak is Type 1 (pediatric teratoma), where infants are typically born with a fully developed tumor. The most common form of testicular cancer is Type 2 (second peak), and hits young men 25-35 years of age. This is where one’s germ cells develop abnormally in utero and tumor stem cells emerge during embryogenesis or are being provoked to form from abnormal germ cells during puberty (this is a topic of debate within the field). Both Type 1 and 2 are tied to defects during embryogenesis. The third peak is around the 70-year range and consist of spermatocytic seminomas derived from adult stem cells. These tumors are quite rare and understudied.

To detect testicular cancer, an ultrasound can be conducted and particular hormone levels associated with cancer development can be monitored. It’s one of those cancers that if you catch early, you have a 95% or higher survival rate.

As the cancer progresses and metastasizes, the rate goes down. On the flipside, there are approximately 10% of testicular cancer patients that are completely refractory to the one main line chemo therapy agents, all platinum-based chemo treatments, such as cisplatin. It is mainly used on young men (25-35 years old) with Type 2 testicular cancer. While cisplatin works really well, it’s harsh—its toxicities can cause infertility, and have long-term neurological effects on these young men. If we can find something that works equally as well, but is more targeted and less toxic, we can substantially improve the long-term quality of life of these individuals. This is the other way we try and look at our research. That’s why, from a human health standpoint, we think what we do is relevant.

Q| Is testicular cancer solely a genetic cancer?
A| It is one of the most inheritable forms of cancer—40 to 60% of one’s risk is going to be genetics, the rest is environment. Testicular cancer incidents have more than doubled in the last 25 years. Our genes have not involved that quickly. This means there is an important environmental component to testicular cancer risk. Currently, it’s poorly understood, and very little is being done on the forefront of trying to understand what those environmental factors are.

Since, Type 1 and 2 testicular cancer start in embryogenesis, we are likely dealing with in utero exposure—what the mother was exposed to while she was pregnant. However, for Type 2 testicular cancer, which develops in young adults and may involve transformation at the time of puberty of germ cells that developed abnormally in utero, we may also be looking at environmental factors that provoke these abnormal germ cells around puberty. More than likely, environmental factors can’t do it alone, you need the genetic factors. In terms of our research, once we get a better idea of the genetics, we can start asking how and which environmental factors are interacting—\"IF WE CAN FIND SOMETHING THAT WORKS EQUALLY AS WELL, BUT IS MORE TARGETED AND LESS TOXIC, WE CAN SUBSTANTIALLY IMPROVE THE LONG-TERM QUALITY OF LIFE OF THESE INDIVIDUALS. THIS IS THE OTHER WAY WE TRY AND LOOK AT OUR RESEARCH. THAT’S WHY, FROM A HUMAN HEALTH STANDPOINT, WE THINK WHAT WE DO IS RELEVANT.\"—Dr. Heaney on treatments for testicular cancer
—with the genetics to cause this doubling incidence in testicular cancer to occur.

**Q| Why is it an area of research that should be emphasized upon?**

**A|** Testicular cancer is one of the most inheritable forms of cancer in humans. In the last five years, there have been Genome Wide Association Studies (GWAS) looking at variances in human populations (in particular white Caucasian men, who have the highest risk) that predispose individuals to developing testicular cancer. If your family already has these variances, then you are more likely to inherit these combinations that increase your risk. GWAS identifies genomic regions that harbor sequence variants and their associated genes that increase testicular cancer risk. Basically, *What genetic differences are in those regions that increase or decrease one’s chances of having testicular cancer?*

In the last five to six years, there have been over 50 loci (regions) of the genome that have been linked—meaning, if you have one version, you are more likely to get testicular cancer, or if you have another version of it, you are less likely to get it. This is because within those regions there are a series of genetic differences. The question now becomes, *Which gene is it, and which variant is it that either changes the amount of gene that is expressed (how much protein is made), or alters the protein in such a way that causes the function of that protein to go up or down?* To be able to develop screening paradigms and targeted treatment therapies, and identify at-risk individuals you need to have that information. *What is the risk-gene, and risk-variant? That’s where we get into genome editing.*

**Q| What role does genome editing, including CRISPR/Cas9, play in your research of testicular cancer within the mouse model?**

**A|** We have over 50 loci in humans, most of which harbor many genes—getting up to potentially 100 plus candidate risk promoting genes and thousands of potential risk promoting genetic variants. To find out the risk-gene and risk-variant, we have to model this. *How do we test if that particular gene or variant associated with that genome is actually causing the cancer risk?* The problem is that GWAS is really asking, *Who is at-risk of cancer initiating/happening, not really who is at-risk of cancer metastasizing?* To answer this, we need to do genetic manipulation to determine what changes a normal cell to a tumor cell.

The 129 inbred mouse model that we work on is the only inbred strain of mice that develops spontaneous testicular cancer. It’s a complex genetic trait in which a lot of genes or variances in the genome allow the cancer to form. Because 129 mice already get testicular cancer, we can add additional mutations on top and see if that provokes or suppresses incidence, meaning does it cause tumors to happen more or less often.

We primarily focus on asking which gene it is by disrupting gene function and testing for effects on tumor risk and the developmental defects that contribute to tumor initiation.

This helps human researchers because once we know which gene in a particular region of the genome is associated with risk, we can go back to the possibly hundreds of variants in that region and make better predictions about which is affecting the expression or function of that gene in humans. One reason for doing this in the mouse model is that these tumors develop during embryogenesis. Due to this, there are two options of studying tumor initiation and the developmental processes involved. We’re either dealing with fetal tissue, or we move to an animal model where dealing with fetal tissue is not a problem anymore. Additionally, modeling the complex interactions between embryonic germ cells and the several types of cells in the testis that supporting their development, would be extremely difficult using cell culture.

CRISPR/Cas9 genome editing technology takes what used to be a year-long or more process to make a genetically engineered mouse, down to two months—at a fraction of the cost. Now that we have a good existing mouse model of the cancer, and we want to start adding additional genetic changes to that model, we can very easily and quickly do it.

For my own testicular research, doing therapeutic genome editing is not how we are using the CRISPR tool. It’s more along the lines of building models that look for other therapeutics. For testicular cancer, the chances of CRISPR being used as a treatment paradigm are not very high.

**Q| How does your research translate to patient care?**

**A|** From a patient way of looking at it, once we know what the risk variants and associated genes are, we can ask, *Does an individual inherit them and how many of them?* If so, we can predict how likely of a chance that individual has to developing testicular cancer, and perhaps whether or not they should be screened more. There is indication that some of these genes identified by GWAS and risk-populations might also be associated with resistance to chemo therapy. Therefore, there is a possibility that some of the models that we are building could help benefit research into pre-clinical models of chemo resistance. Once we know the genes that are involved we can ask, *Are any of them targetable?* That’s another way of how we look at gene discovery, and where it can go. Developing efficient screening and targeted treatments are the selling points we try to get to.
AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE (ASRM)

73rd Annual Meeting
OCTOBER 28 - NOVEMBER 4, 2017
SAN ANTONIO, TX

Advancing Reproductive Medicine to Build Healthy Families

8900 Scientists, Physicians, Fellows, and Trainees Attended

91 Countries Represented

10 CRM Members Presented Oral Abstracts and Posters:

Sara Arian, M.D., Neil Chappell, M.D., Taylor Kohn, Derek O’Neill, Ph.D.,
Alexander Pastuszak, M.D., Ph.D.,
Jessica Rubin, M.D., Robert Rydze, M.D., Maria Szwarc, Ph.D., Terri
Woodard, M.D., Liubin Yang, M.D.

3 CRM Members Directed:

Interactive Case Presentation
Stump the Audience: Interesting and Unusual Cases in Pediatric and Adolescent Gynecology

Pre-program Congress – Course
Approach to Comprehensively Manage Your Male Clients’ Needs: From Sexual Dysfunction and Poor Semen Quality to Genetic, Psychological, and Aging Issues Developed in Cooperation with SMRU, SRS, SRBT, and MHPG
Dolores J. Lamb, Ph.D.

Expert Encounters
Difficult Management Cases in Male Infertility: From the Laboratory to the Bedside
Dolores J. Lamb, Ph.D. and Larry I. Lipshultz, M.D.

SEXUAL MEDICINE SOCIETY OF NORTH AMERICA

OCTOBER 26 - 29, 2017 | SAN ANTONIO, TX

The 18th Annual Sexual Medicine Society of North America (SMSNA) fall scientific meeting provided an innovative forum for the exchange of ideas, and the latest research in the field of sexual medicine and men’s health. The meeting featured lectures by the world’s most recognized experts in sexual medicine, including up-and-coming young physician and scientist research, an international symposia, didactics and cadaver labs, and the most advanced scientific research in sexual medicine. CRM members participated throughout the meeting as abstract and poster presenters, symposium leaders, and course directors, on topics such as Peyronie’s Disease, androgens, erectile and sexual dysfunction, prostate cancer, testosterone, and hypogonadism.

CRM MEMBER AWARDS CONGRATULATIONS!

PEGGY SMITH, PH.D.
Director of the Baylor Teen Health Clinic, Professor of OB/GYN
Dr. Smith was honored with a Congressional Proclamation recognizing her positive impact on Houston teens and young adults as longtime Director of the Baylor Teen Health Clinic. Dr. Smith was presented the proclamation by Representative Sheila Jackson Lee on October 17 at the annual Foundation for Teen Health Clinic Luncheon, which raised money for the Clinic’s Project Bootstrap, which assists young parents with healthcare, education, and employment.

NANNAN THIRUMAVALAVAN, M.D.
Clinical Postdoctoral Fellow, Department of Urology
Dr. Thirumavalavan (middle) received Second Prize in the Basic Science Thesis Competition during the October 2017 SMSNA meeting.
“Regulation of the Spermatogonial Stem Cell Niche”

The interplay between male germ line stem cells and their niche microenvironment is crucial for sperm production, and dysregulation of this process will lead to sterility. We have discovered that two niche factors, glial-cell line derived neurotropic factor (GDNF) and the retinoic acid-degrading enzyme CYP26B1 are simultaneously downregulated by NOTCH signaling in Sertoli cells at stage VII-VIII of the seminiferous epithelium. Activated NOTCH signaling in Sertoli cells might therefore favor the differentiation of Aaligned spermatogonia into differentiating A1-A4 spermatogonia, which are committed to meiosis. Our recent data indicate that Aaligned spermatogonia activate NOTCH signaling in Sertoli cells through the NOTCH ligand JAG1, and we are presently studying the epigenetic regulation of these events at the promoters of NOTCH target genes.

“Maternal Nutrition and the Control of Female Meiotic Progression”

In human females, oocytes complete meiosis I at birth, and enter a long period of meiotic II arrest until onset of meiotic maturation at puberty. At the end of meiosis I, oocytes are packed with maternal RNAs, which, upon fertilization of the mature oocyte, are necessary for early embryonic development. Mechanisms that coordinate the generation and protection of maternal RNA during oogenesis with their timely degradation in the embryo are critical for understanding the molecular basis of infertility and birth defects. Our research works to unravel these mechanisms using *C. elegans* meiosis I as our model system, where we find that maternal nutrition engages the RAS/ERK signaling pathway which regulate Dicer to coordinate small RNA dynamics during meiosis I and oocyte to embryo reprogramming.
Known as a scientific innovator and a valued mentor, **ANTHONY ROSS MEANS, PH.D.**, Professor of Molecular and Cellular Biology, arrived to Baylor, along with Bert O’Malley, M.D., Chairman and Professor, Department of Molecular and Cellular Biology, in January 1972, where he rose to the rank of Professor and Vice Chairman of Cell Biology (now known as Molecular and Cellular Biology or MCB). In 1991, he was recruited to Duke University as Chair of Pharmacology and Cancer Biology and spent 20 years in that role. Upon his retirement from Duke in 2011, Dr. Means circled back to Baylor where he continues to serve part time as Professor of MCB. Dr. Means has received many honors, including election to the American Academy of Arts and Sciences, President of the Endocrine Society, and recipient of the Fred Conrad Koch Lifetime Achievement Award from the Endocrine Society. Since returning to Baylor in 2016, Dr. Means received the Outstanding Leadership in Endocrinology Award from the Endocrine Society and was appointed as a Distinguished Service Professor at Baylor. His return to Baylor has allowed him to work with some of his most esteemed former colleagues, and form a new research collaboration with Dr. Brian York, Associate Professor of MCB, in order to continue the calmodulin-related research he has been passionate about since his first appointment at Baylor. Here, Dr. Means takes us through his early research career at Baylor, how it’s evolved, and what it was like to be at the forefront of a department-building success story.

**Q**: How did your early research at Baylor provide the “springboard” for success in your later research endeavors?

**A**: From the time I was a graduate student, I have worked on reproductive hormones. As a Ph.D. student in the mid-1960s, I worked on the mechanism of action of estrogen in the uterus and identified a very early effect on nuclear RNA synthesis. I went on to do a postdoctoral training period in Australia, where I began to work on follicle-stimulating hormones (FSH) in the male, because at that time there were no known molecular effects of FSH in the male. Upon coming back to the U.S., I continued to work on FSH, and when recruited by Dr. O’Malley to Vanderbilt reprised my work on estrogen. He and I worked together on estrogen action in the oviduct, while I continued to work on FSH action in the testis during the Vanderbilt years as well as after, when I accompanied Dr. O’Malley to Baylor as a faculty member of Cell Biology. While a postdoctoral student with Peter Hall, I discovered that the actions of FSH in the male were in the testis.

After establishing my own independent laboratory at Vanderbilt and then Baylor, we defined the Sertoli cells as the FSH target cell and discovered the membrane-associated receptor for FSH. That led us to elucidate the sequence of intracellular events that occur following FSH binding to its receptor that result in induction of the mRNA for a specific protein, called androgen-binding protein (ABP) as well as the synthesis and secretion of ABP.

While working on FSH action, we found that it to be unusual for a protein hormone because it not only worked through the second messenger cyclic AMP, but it also elicited changes in intracellular calcium. In following the calcium connection, we discovered a calcium-binding protein that was mandatory for the FSH effects in Sertoli cells.
That calcium-binding protein, which we called Calcium-Dependent Regulatory protein (CDR), was later renamed calmodulin (CaM).

Our discovery of CaM in the testes, which occurred about the same time several other groups across the world were finding it in other tissues, was a seminal event for the new field dealing with calcium as another second messenger. It was also seminal for me in that after the discovery of CaM we have continued to work on it and the binding proteins that it regulates until today!

Q| What do you think are some of your most impactful research findings in reproductive biology while at Baylor?
A| We recognized that CaM is a protein essential for survival of all eukaryotic cells. Inhibition or deletion of CaM results in cell death, so it was impossible to question how a cell functions in the absence of CaM. Thus, we turned our attention to the study of calmodulin-binding proteins. We now know that CaM regulates over 120 different proteins and enzymes, but the ones we focused on were its target protein kinases. We began with myosin light chain kinase, which is the rate limiting enzyme required for smooth muscle contraction, followed by an enzyme discovered in brain called CaMKII. We were the first to produce synthetic versions of each of these enzymes and discover how CaM regulated their activities.

Our continuing studies in testis led to the discovery of a previously unknown kinase that was christened CaMKIV and is essential for spermatogenesis. Because a partial inhibition of CaM resulted in stalling of cell cycle progression, we began to use a genetically tractable fungus called Aspergillus. This led to an understanding of the roles of CaM in the cell cycle and the importance of a series of CaM kinases essential for various stages of the cell cycle.

Examination of how one of these kinases regulated mitosis pointed to a target kinase called NIMA and further analysis of how the CaM kinase regulated NIMA led to the discovery of a NIMA interacting protein called PIN1.

As it turned out, NIMA is not present in mammalian cells but PIN1 is. We found it to be essential for reproduction, because it is required for regulation of primordial germ cell division. In mice null for PIN1 there is a reduced number of primordial germ cell divisions. This results in infertility of both female and male mice due to a marked deficit of ova in the female and sperm in the male. That was another reproductive biology offshoot of our CaM efforts that took us in a completely different research direction.

Q| Could you describe your experience here at Baylor, and some of your noteworthy moments?
A| We moved to Baylor because Dr. Michael DeBakey successfully recruited Dr. O’Malley to become Chairman of a basic science department then called Anatomy. Dr. O’Malley recruited a number of faculty members, including me, from Vanderbilt and changed the department’s name to Cell Biology. Initially, we inherited only a handful of faculty members of the old Anatomy department but, by the time I left for Duke in 1991, our highly successful recruiting campaign had grown the department to over 40 full time faculty members. One of the incentives for coming to Baylor was that we had complete freedom to grow the new department, and mold it to fit our dreams and aspirations. This was a unique opportunity for us, and I was delighted to play an enduring role in developing the Cell Biology department at Baylor into one of the best of its kind in the U.S.A. As you know, this trend continued after my move to Duke as MCB became the best-funded and best-known department of its kind in the country, and continues to be so to this day.

When we were at Vanderbilt, we applied for and received the first ever National Institute of Child Health and Human Development (NICHD) reproductive biology center. In considering our move to Baylor, NICHD initially told us we would be allowed to move the Center with us. However, once we got here, this was not to be so; we were required to apply for a new NICHD Center grant, which was also funded. Thus, not only did we obtain the first NICHD Center grant with Dr. O’Malley as Principal Investigator, but we were also awarded the second such Center, and I was the Associate Director of the Baylor one for all the years that I was at Baylor. Another thing that we accomplished was submitting and receiving a training grant in reproductive biology—I played a major role in that, as well. We also applied for and received a training grant in Molecular and Cellular Biology, which still exists today and I helped to write that grant. Thus, while at Baylor I played a major role in the growth of research and training in reproductive biology outside of my own laboratory efforts.

Q| Can you describe one or two fond memories you had from your time here at Baylor?
A| My fondest memory at Baylor was participating in the growth of the institution. Not just the department, but also Baylor College of Medicine itself, as it is now recognized as a national research powerhouse (it was not when we first came).
We were involved on the “ground floor” of this process and participated in the hiring of so many faculty members. Dr. O’Malley became and after 50 years remains one of my very best friends and I have nothing but fond memories at Baylor. My years at Baylor helped shaped me as a scientist, administrator, and a person. There are countless people here who have remained my friends for all these many years. One of the things that made me so happy to come back part-time is that so many of my friends from the 70s and 80s are still here. This made moving back to my beloved Texas truly like “coming home.” It is often remarked, “you can’t come back home,” but I am living proof that this statement is false! Walking the same halls, interacting with old and new friends, and ending up with an office and lab on the same floor where I was located when we first moved into the DeBakey Building after it was built—it’s almost surreal.

Q: What advice do you have for a starting scientist or medical professional?
A: I think that if you are going to do biomedical research these days, you first of all must have dedication and passion for the challenge it brings as a career path. It’s no longer just an occupation—it must be a passion. Can you still do it, and make a role for yourself in the world? Of course you can, but you have to be willing to work really hard, take chances and risks, and press on.

Identify problems that you feel haven’t been completely evaluated, and make it your goal to instill yourself as a leader in that particular discipline.

The second important thing is to establish lasting and meaningful connections—make friends and acquaintances, and keep them as such throughout your career. They need not work on the same thing or even in the same field that you do; in fact, it’s better in many instances if they don’t. If I look back at my lasting friends in biomedical sciences, most are working in many different areas of science, and in many diverse departments at different institutions, in many different countries. I think that this is a critical component of the formula that leads to success and self-fulfillment.

UPCOMING EVENTS

CRM and MCB R&D Workshop Series

“Meiosis and Chromosome Segregation in Mammals: Why Younger Isn’t Always Better”

Francesca Cole, Ph.D.
Assistant Professor, CPRIT Scholar in Cancer Research, R. Lee Clark Fellow, Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center

Thursday, January 11, 2018
12 – 1 p.m.
DeBakey Building, Room M616

Mark your calendars for our remaining winter/spring 2018 seminars taking place at Noon in DeBakey M616: February 8, March 8, April 12

CRM New Year’s Membership Meeting and Reception

Thursday, January 11, 2018
4 - 6 p.m. (reception begins at 5 p.m.)
Alkek Building, Room N317

Kindly RSVP to jyotip@bcm.edu.