Faculty Focus

Yale Pathology Recognition at USCAP 2017

Dr. Volkan Adsay (left), President of the USCAP and Peter Humphrey, MD, PhD, Professor of Pathology (right).

Dr. Volkan Adsay, President of the USCAP, presented the Maude Abbott Lecture plaque to Peter Humphrey, MD, PhD, Professor of Pathology and keynote speaker at the USCAP 2017 Annual Meeting, who delivered the Maude Abbott Lecture, “Prostate Cancer: Then and Now.”

John Sinard, MD, PhD, Professor of Pathology and of Ophthalmology and Visual Science; Vice Chair, Pathology; Director, Anatomic Pathology; Medical Director, Pathology Informatics, was awarded the F.K. Mostofi Distinguished Service Award for service to the USAP. His second 3-year term as Secretary of the USCAP starts this month. See page 10 for more USCAP news.

Chair’s Corner

Future Thoughts

Yale is embarking on a new capital campaign. In planning for this, the University has established an advisory committee, headed by Professor Scott Strobel, who is the Deputy Provost for Teaching and Learning and also Vice President for West Campus Planning and Program Development. Many of our faculty received his recent email soliciting assistance in developing a University-wide science strategy for the coming decade. We were encouraged to “dream big” and to identify ways our field can have a broad impact on the University to strengthen interdisciplinary connections. I know that many in the Department have discussed this with David Stern, who was charged with collecting some of your thoughts. How might we as pathologists and medical scientists respond?

While pondering this charge, I had the opportunity to attend Rom Celli’s excellent talk to the Department, in which he used network analysis to augment diagnostic evaluations in anatomic pathology. Rom is a graduate of our residency-training program, and will be joining the faculty in July after completion of his GI and Liver fellowship. His study (for which he received the Stowell-Orbison Research Award from the ASCAP) clearly demonstrated the power and promise that sophisticated computational analyses can bring to medical discovery and practice. That same day, Associate Professor Yuval Kluger, a member of our computational pathology program, came to discuss with me the opportunities to more thoroughly integrate deep-learning and data analysis of the clinical record with morphometric and genomic analysis of cancer tissues. “The pieces are all here,” he argued, “We only need a path and program to assemble them.”...And he is right. I would also note that our molecular diagnostics group (Nina Longtine, Jeff Sklar, Zenta Walter, Karin Finberg, Pei Hui, and David Rimm) has worked closely with Yale’s Cancer Center to bring genomic analysis into routine clinical practice. Genomic analyses of cancerous tissues

Celebrating Dr. Joseph Madri

Reported by Cynthia Ziehl

This June will mark the one-year anniversary of a significant event in the department: the tri-part celebration of the life and work of Dr. Joseph Madri on the occasion of his retirement; his and his wife Lucille’s endowment of the Joseph A. and Lucille K. Madri Professor of Experimental Pathology professorship; and the bestowal of that professorship on Gerald Shadel, PhD, Professor of Pathology and Director of the Yale Center for Research on Aging (Y-Age). With the upcoming symposium in honor of Joseph A. Madri, PhD, MD, Professor Emeritus of Pathology, we are publishing the following informative piece, along with our feature, “V.I.P.” (page 2), and together they cover some of Dr. Madri’s many achievements as well as his shared history with the department.

“New Endowed Professorship Established in Experimental Pathology”

Reprinted from Medicine@Yale, Jan./Feb. 2017.

In the 1980s, Joseph A. Madri, MD, PhD, Professor of Pathology and Leonard Bell, MD ‘84, then a postdoctoral fellow, enjoyed lingering in Madri’s lab after work and cooking up plans to launch a biotech company one day. “We had a folder on the Mac called ‘Fantasy,’” Madri recalls. Fantasy would become reality when Madri, Bell, and four colleagues met in 1991 at the Omni Hotel in New Haven, and set a course that would bring a startup called Alexion to life the following year. Today, Alexion is a global biopharmaceutical company that employs 3,000 people. It is a world leader

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Chair’s Corner
(article continued from page 1)

are no longer viewed as separate “tests” but are reported and integrated into our diagnostic tissue consultations and tumor boards, enhancing the precision of our diagnoses and guiding patient care in ways that were inconceivable just a decade ago. In other areas Kurt Schalper and David Rimm are leading investigators applying in novel ways quantitative histology, immunophenotyping, and image analysis to the evaluation of patient tissues, using tools such as mass spectroscopy and immunofluorescence. The expectation is that such studies will translate to the precise identification of patients suited for immune-blockade therapy. Hematopathology has already thoroughly integrated morphology, differentiation markers, flow cytometry, and genomics into a modern assessment that guides the therapy of lymphoid neoplasms. The same is now occurring with neuropathology. These ideas and practices are just glimpses of the future that will soon be upon us. Pathology is changing. Pathologists today are not only expert at the morphology of disease, but also consultants charged with bringing a wide array of scientific knowledge and techniques to their task. Positioned as we are at the boundary between medicine and science, our field offers a natural and impactful pathway for translation of science to medical practice. It is an important and pressing mission.

As Clayton Christensen, the Robert and Jane Eizik Professor of Business Administration the Harvard Business School, wrote in his influential book (The Innovator’s Prescription, 2009) “… technologies that enable precise diagnosis and, subsequently, predictively effective therapy are those that have the potential to transform health care through disruption.” Disruption is desperately needed. Our aging and growing population will soon create a healthcare and fiscal crisis that threatens the very foundations of our society. Notably, Institute of Medicine reports from 1999 (To Err is Human) and 2015 (Improving Diagnosis in Health Care) accurately reveal that errors in medical practice are the major drivers of medical costs and poor patient outcomes. Of these, diagnostic errors loom the largest. The entire promise of “precision medicine” relies on accurate prediction of the efficacy of a given therapy for a specific patient.

So in response to Professor Strobel’s query, my answer would propose that Yale’s strategic planning should seek to leapfrog conventional discipline boundaries, and build an infrastructure that will facilitate more robust models of science-based innovative diagnostic practice, diagnostic technologies, diagnostic decision support, and subsequent care pathways. A three-pronged approach might be envisioned, investing in i) diagnostic practice integration; ii) big-data informatics and deep-learning technologies; and iii) basic/translational science and engineering investments aimed toward enhancing innovative and more precise disease understanding and ultimately diagnostic practice. In addition to building its scientific infrastructure, Yale should establish a Center for Precision Diagnosis. Pathology, along with our partners in Laboratory Medicine and Diagnostic Imaging, could play an important role in such a Center as natural conduits for rapidly translating science and technology advances to clinical practice. Collectively, these three disciplines form the core of what might be called “Diagnostic Medicine.” Pathology and Laboratory Medicine alone have been noted by some authors to drive over 70% of critical medical decisions (and over 70% of healthcare expenditures) (e.g., Forsman, Clin. Chem. 42, 813 (1996). While the precise number can be debated, if Radiology is included, certainly these “diagnostic disciplines” are already hugely impactful. A center devoted to precision diagnosis would enhance the linkages between practice and science by bringing together medical specialists, scientists bridging multiple disciplines, biomedical engineers, and computational informaticists. Obvious scientific disciplines that would contribute would include genomics, epigenetics, metabolomics, microbiomes, proteomics, imaging science, cell biology, pharmacogenomics, and computer science. In our own Department, we have real strength in cancer biology, computational science; vascular biology, and mitochondrial genetics, and are building a broadly interactive program in aging research headed by Gerry Shadel. A precision diagnostics program would draw on the large and growing clinical database here for data mining and outcomes evaluation. The overall goal would be accurate, earlier, and evermore precise diagnosis for every malady. Regardless of whether Yale formally creates such a center, the concept is inevitable. The coming decade will be one of incredible advances in medicine. Pathology has an important role to play. Precision diagnosis based on multiple technologies will be the lynchpin of our future practice. I see it happening in our Department every day, and it is happening nationally. This is a tremendous opportunity for us. I urge all to embrace the challenges ahead with imagination and ingenuity, so we can deliver science-based precision diagnosis, followed by precision medicine, to every patient.

Jon S. Morrow MD, Ph.D. Raymond Yesner Professor and Chair Chief of Pathology, YNHH

• • • V.I.P. • • •

Very Important Pathologist: Dr. Joe Madri

A native of New York City, Joe Madri earned his BS and MS in Biology from St. Johns University, and then moved with his wife Lucille to join the MD-PhD program at Indiana University. Upon completion of his graduate work in chemistry and his medical degree, Joe and Lucille along with their young son Daniel moved to New Haven for residency training in Anatomic Pathology. Three years later, along with welcoming Jessica, their new daughter, Joe embarked on a fellowship in Experimental Pathology studying the extracellular matrix and endothelial cells under the tutelage of Professor Heinz Furthmayr. In 1980 Joe joined the Yale faculty as an Assistant Professor, and soon rose through the ranks to become a tenured Professor of Pathology.

Joe’s career at Yale exemplifies all that could be asked of a professor. The NIH and the American Heart Association have continuously funded his laboratory for thirty-seven years. In 1999 he was awarded a 10-year NIH MERIT grant. His studies have made major contributions to our understanding of the role of the matrix on vascular biology, diabetes, angiogenesis, and most recently, the role of neutrophils in anti-tumor immunity. He has published 272 peer-reviewed articles and topical reviews describing this work, and has been invited to present his findings at nearly 200 national and international conferences and seminars. Joe has also excelled as an educator, one who has devoted considerable time and effort to teaching medical, graduate and undergraduate Yale College students. Over 100 post-doctoral fellows, MD-PhD, PhD, and undergraduate students studied in his laboratory. He served as director of Pathology education for almost two decades, and received the prestigious Chugai Award for Outstanding Mentorship and
and organ transplantation. Contributed to our better understanding of tissue growth led to breakthroughs in tissue transplantation. His work received the Borden Award in the Medical Sciences from the Association of American Medical Colleges. Dr. Greene served as Chair from 1950 until his death in 1969. In 1956, he moved to UC-SanDiego School of Medicine, where he was Professor and Chair of the Department of Pathology. As Chair or Dean at three institutions, he developed strong academic programs that excelled in the basic sciences as well as in the clinical disciplines. At Colorado, he created the Given Institute at Aspen, which was an outstanding summer learning program for almost two decades. Dr. Green was at the forefront of efforts to map, sequence, and of our discipline and to biomedical science. As Chair of Pathology at Columbia, Director of the Armed Forces Institute of Pathology, and Deputy Director of Research and Education at the National Library of Medicine. Throughout these many endeavors, Dr. King has been a consistent, strong and effective advocate of biomedical science and the central importance of merging basic science understandings with the practice of Pathology and Medicine. As Chair or Dean at three institutions, he developed strong academic programs that excelled in the basic sciences as well as in the clinical disciplines. At Colorado, he created the Given Institute at Aspen, which was devoted to providing fundamental science training to outstanding students and scholars. Beyond these many accomplishments, Dr. King has been an ardent student of history, mindful of the intellectual thread that begins with the early observations of the 19th century morphologists—Rokitansky, Ashof, Virchow—and extending through the more modern advances in cell biology, biochemistry, structural biology, and genetics that today collectively contribute to the basis of our discipline. More than a student, Dr. King has been a witness, participant, and catalyst of many of these advances. We at Yale are honored to count him as one our own (at least in part) and are thankful for his generous philanthropy that enables us to honor two additional colleagues who have contributed so significantly to the advancement of our discipline and to biomedical science.

Harry S. N. Greene (1904-1969)

Harry Sylvester Nutting Greene, MD, was the Anthony N. Brady Professor and Chair of the Department of Pathology at Yale School of Medicine, joining the faculty in 1943. He served as Chair from 1950 until his death in 1969. In 1956, he received the Borden Award in the Medical Sciences from the Association of American Medical Colleges. Dr. Greene was internationally renowned for his research in cancer that led to breakthroughs in tissue transplantation. His work contributed to our better understanding of tissue growth and organ transplantation.

Averill Abraham Liebow (1911-1978)

Averill Liebow, MD, born in Austria, was the leading expert and “founding father” of pulmonary pathology in the United States. He received his B.S. from the College of the City of New York in 1931 and his MD from Yale School of Medicine in 1935. From 1935-1968 he had a distinguished career in the Department of Pathology at Yale. In 1968, he moved to UC-SanDiego School of Medicine, where he was Professor and Chair of the Department of Pathology. He described many new pulmonary entities and authored the famous first classification of interstitial lung disease (1944).
Yale Scientists Study How Some Insulin-Producing Cells Survive in Type 1 Diabetes

February 9, 2017

This article is republished from Yale News.

Zongzhi Liu, PhD, Associate Research Scientist in Pathology, was part of a Yale-led research team that identified how insulin-producing cells that are typically destroyed in type 1 diabetes can change in order to survive immune attack. The finding may lead to strategies for recovering these cells in diabetic patients, said the researchers. The study was published on Feb. 9 in Cell Metabolism.

In patients with type 1 diabetes, an autoimmune disease, the immune system destroys beta cells — the cells that produce insulin in the pancreas. But some beta cells survive in diabetic patients even years after the onset of disease.

A team of researchers at Yale and the Broad Institute of MIT and Harvard studied the changes in beta cells that occur during immune attack that may lead to their persistence in both mouse models of type 1 diabetes and in human cells in culture.

The researchers identified a subpopulation of beta cells that resists immune attack. “During the development of diabetes, there are changes in beta cells so you end up with two populations of beta cells,” said professor of immunobiology and senior author Dr. Kevan Herold. “One population is killed by the immune response. The other population seems to acquire features that render it less susceptible to killing.” This subpopulation survives by using a “duck and cover” approach, Herold noted. The cells express molecules that inhibit the immune response. They also acquire “stemness,” or a stem-cell-like ability to revert to an earlier stage of development in which they can persist and proliferate despite immune attack.

The discovery will lead to further investigation of strategies that could benefit diabetic patients. “The next question is, can we recover these cells so that there is insulin production in someone in type 1 diabetes?” said Herold. He and his colleagues plan to test drugs to see if they can modify the beta cell subpopulation and turn it into insulin-producing cells.

Other authors are Jinxiu Rui, Songyan Deng, Arnon Arazi, and Ana Luisa Perdigoto.

The study was supported by National Institute of Health grants, grants from the Juvenile Diabetes Research Foundation and Yale CTSA, and a gift from the Howalt family.

Recent Grant Funding

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Unexpected Role for Epigenetic Enzymes in Cancer

January 3, 2017

This article is republished from Yale News.

To better understand how cancer initiates and spreads, Yale associate professor of pathology Qin Yan turned to the field of epigenetics, which examines changes in the expression of genes and proteins that do not affect the underlying genetic codes. In a Yale-led study, Yan and his co-authors focused on a family of enzymes — known as KDM5 — that had been shown in previous studies to be involved in cancer cell growth and spreading.

First author Lauren Blair, an associate research scientist, conducted biochemical studies with Baker’s yeast as the model system, and identified an unexpected role of these enzymes in the process by which genetic messages are interpreted by yeast cells. Further studies showed that the enzymes’ role as regulators of this process is also important for human tumor cells to grow and spread. The finding could lead to a therapy that inhibits the enzyme, and tumor growth, in cancer patients.

Read the full study in Science Advances.
PhD in Experimental Pathology

By Cynthia Ziehl

In his annual talk to Pathology faculty, Dean Robert Alpern likened the medical school to a chair with four legs, these legs representing the four crucial pillars of the school’s mission, namely research, clinical service, work climate, and education, and he discussed the pursuit of excellence in these areas. One component of our department’s multi-part, critically important teaching mission, namely graduate studies, is led by Themis Kyriakides, PhD, Professor of Pathology and Director of Graduate Studies. Themis pointed out early in our discussion that the graduate program is a “very active, successful program, which was headed by Gerry Shadel previously and prior to that David Stern, and it has been easy to carry on what they started.” Along with graduate studies, the department offers undergraduate courses, under the direction of Dr. David Hudnall; medical student teaching, directed by Dr. Robert Homer; the training/teaching of residents, led by Dr. Diane Kowalski, Residency Director; and Dr. Earl Glusac is Director of Physician Associate Studies.

Students in the graduate education program take courses; work in labs; design and conduct original research; teach; take oral, written and practical exams; and write a thesis to earn a PhD (Doctor of Philosophy) in Experimental Pathology. The students who are admitted have earned undergraduate degrees in the sciences, most typically a bachelor of science in biology. The program welcomes international as well as US students, and Yale has an arrangement for referring/recruiting students from Chinese universities, called the China Scholars Program.

Yale University has eight graduate training tracks; Pathology belongs to the Molecular Medicine, Pharmacology, and Physiology track, or MMPP. The three departments recruit and teach students together. Students spend the first year of training doing research rotations and taking classes. At the end of their first academic year, they join laboratories where they formulate their thesis work and at that time choose a department to join. Currently there are 9 first year graduate students in the MMPP track.

In their second year those students who have joined Experimental Pathology (ExPath) will be in a program that “emphasizes research on disease mechanisms, built upon a strong foundation of training in cell and molecular biology, biochemistry, genetics and bioinformatics.” There are currently 18 ExPath students, 2 of whom are MD-PhD students, and Themis anticipates that 3 students will be completing their PhDs this year and graduating. It takes on average 5 to 6 years to complete a PhD.

Students in MMPP and those who then join ExPath take specific classes, and Pathology faculty teach these as well as courses in the other departments. Themis explains, “We offer a number of courses that involve 14 to 15 of our faculty, and a majority of the faculty teaching courses for ExPath are Pathol-
Laura Stevens  
**Year:** 7  |  **Mentor:** Nguyen

Lung adenocarcinoma (ADC) is the most common subtype of lung cancer, and even when diagnosed at early stages, metastases can occur to distant organs. This propensity to metastasize suggests that a subpopulation of malignant cells with high metastatic potential may emerge in a subset of primary tumors. Cancer stem cells have been identified in the lung, but these cell populations are heterogeneous, and although they are all capable of propagating tumors, they display varying degrees of metastatic potential. Previous computational analysis from our lab has shown that genes associated with alveolar differentiation can stratify a cohort of primary lung ADCs into two distinct classes, a differentiated alveolar-like and a stem-cell like class. This stem-like signature classifies patients with poor survival, which indicates it may mark a de-differentiated cell type that has enhanced metastatic capabilities. My project will focus on identifying biomarkers that are differentially expressed in both the stem-like signature and in our experimental models to identify the origin of metastasis propagating cells in lung ADCs and determine their fate upon disseminating from the primary tumor. I will also determine the putative role of these biomarkers in mediating functional interactions between subpopulations of metastatic cancer stem cells and their microenvironment.

Deborah Ayeni  
**Year:** 6  |  **Mentor:** Politi

Understanding the Effects of Loss of the Tumor Suppressor Gene, p53 on Mutant EGFR Lung Adenocarcinoma Initiation and Metastatic Progression.

Lung cancer continues to be the leading cause of cancer-related death in the US and worldwide. Studies have identified mutations in proto-oncogenes (like the Epidermal Growth Factor Receptor, EGFR) and in tumor suppressor genes (like p53) in lung adenocarcinomas, the most common of the four histological subtypes of lung cancer. In particular, mutations in the EGFR gene have been shown to play a role in tumor initiation and maintenance and we hypothesize that p53 mutations and/or loss contribute to tumor progression. Although more than fifty percent of patients with lung cancer have metastatic disease when they are diagnosed, factors that contribute to the spread of the primary lung adenocarcinoma to distant sites are yet to be well understood. Using mice with mutant EGFR transgenese and constitutive p53 deficiency, the goal of my project is to identify the genes and mechanisms that underlie metastatic spread.

Nicole Calabro  
**Year:** 6  |  **Mentor:** Kyriakides

The mechanisms behind TSP2’s regulation of angiogenesis and arteriogenesis.

Molly Gale  
**Year:** 5  |  **Mentor:** Yan

Epigenetic reprogramming of breast cancers in resistance to HER2-targeted therapies.

Resistance to anti-cancer drugs is a significant clinical problem. The goal of my thesis work is to identify strategies to combat the development of drug resistance by investigating epigenetic mechanisms. My work has two main aims. The first is to identify inhibitors of an epigenetic protein called KDM5A, which is known to be involved in anti-cancer drug resistance, as well as tumorigenesis and metastasis. Using a high-throughput screen, we identified and characterized a potent and specific inhibitor that was able to stop drug resistance to two different targeted therapies in two different types of cancer cells. The second aim is to identify epigenetic regulators of resistance to targeted therapies of HER2+ breast cancer. We are characterizing epigenetic changes that occur during the development of resistance as well as performing a functional short hairpin RNA (shRNA) screen to identify specific epigenetic proteins important in drug resistance. The goal is to identify new potential therapeutic targets or clinically useful biomarkers.

Britta Kunkemoeller  
**Year:** 5  |  **Mentor:** Kyriakides

The role of thrombospondin-2 in diabetic wound healing.

Impaired wound healing is a major complication of diabetes, and leads to the development of chronic wounds in millions of diabetes patients. Treatment strategies for these wounds are limited due to incomplete understanding of the underlying molecular mechanisms. Thrombospondin-2 (TSP2) is a matricellular protein expressed by fibroblasts during the proliferation and remodeling phases of wound healing. Its abnormal expression is associated with significant changes in dermal healing rate. Increased expression of TSP2, as observed in eNOS KO and aged mice, is associated with slow healing, while wounds in TSP2 KO mice heal more quickly than those of wild type mice. We have observed that TSP2 expression is increased in the wounds of diabetes patients, which suggests that TSP2 plays a role in wound healing in diabetes. My research focuses on exploring the mechanisms regulating TSP2 expression in diabetes and TSP2’s putative contribution to the delayed healing observed this disease.

Nathan Fons  
**Year:** 4  |  **Mentor:** Bindra

Targeting the biological and tumorigenic properties of PPM1D, H3F3A, and ACVR1 mutations in the context of DIPG and other pediatric high-grade gliomas.

Diffuse Intrinsic Pontine Gliomas (DIPGs) and other pediatric high-grade gliomas are devastating diseases, with no current effective therapies. My work focuses on modelling key genetic alterations which drive the proliferation of these tumors, and studying the complex biological interactions that ultimately result in glioma formation. Using insights gained from our ongoing studies, we hope to find novel therapeutics which specifically target these driving mutations and halt the development and progression of DIPGs and other terrible childhood brain tumors.

Xiaoni Liu  
**Year:** 4  |  **Mentor:** Bosenberg

Characterization of the role and regulation of intratumor heterogeneity in melanoma.
Sally Adua  
**Year: 3 | Mentor: Nguyen**  
Mechanisms of lung cancer metastasis and resistance to target therapies with an emphasis on the role of the tumor microenvironment.

Wesley Cai  
**Year: 3 | Mentor: Yan and Nguyen**  
Targetable epigenetic drivers of basal breast cancer and lung adenocarcinoma metastasis through in vivo screening.

Bomiao Hu  
**Year: 3 | Mentor: Politi**  
I am interested in cancer biology and signaling pathways in lung adenocarcinoma.

Alanna Kaplan  
**Year: 3 | Mentor: Peter Glazer**

Irina Krybaeva  
**Year: 3 | Mentor: Marcus Bosenberg**

Jade (Xiuqi) Li  
**Year: 3 | Mentor: Finberg**  
Metabolic Consequences of Iron Dysregulation  
Iron is a micronutrient that is essential for life. Altered iron homeostasis is associated with iron deficiency or iron overload. While iron deficiency impairs many processes in the body, including red blood cell production, iron overload can cause oxidative damage to organs such as the liver, heart, pancreas. For my thesis project, I will use genetic models to investigate the role of iron in various metabolic processes, and the negative health consequences when iron homeostasis is disrupted.

Emily Wingrove  
**Year: 3 | Mentor: Nguyen**  
Inhibiting epigenetic modifiers of the WNT pathway to suppress lung cancer metastasis  
Emily is a third year graduate student in the laboratory of Don Nguyen and is focusing on identifying the necessary modifiers of WNT signaling and epigenetic outputs that are required for orchestrating the plastic mechanisms of tumor progression with a focus on those modifiers that may be pharmacologically inhibited.

Jade (Xiuqi) Li  
**Year: 3 | Mentor: Finberg**  
Metabolic Consequences of Iron Dysregulation  
Iron is a micronutrient that is essential for life. Altered iron homeostasis is associated with iron deficiency or iron overload. While iron deficiency impairs many processes in the body, including red blood cell production, iron overload can cause oxidative damage to organs such as the liver, heart, pancreas. For my thesis project, I will use genetic models to investigate the role of iron in various metabolic processes, and the negative health consequences when iron homeostasis is disrupted.

Pok Fai Wong, MD  
**MD-PhD student Year: 2**  
Mentor: Rimm  
Gruber Science Fellow in Experimental Pathology

Yuting Liu  
**Year: 3 | Mentor: Rimm**  
The role of PD-L1 expression on immunocytes  
PD-L1 has been discovered as an escape mechanism of multiple tumors to avoid attack from our immune system, through binding to the PD-1 receptor. However, immunocytes, such as macrophages and NK cells, are also able to express PD-L1. Divergent hypothesis on the role of PD-L1 expression on immunocytes have been proposed. We will use detective methods to look into the possible roles of PD-L1.
Embryonic Stem Cell Research Threatened

January 27, 2017 — An article (reprinted below) entitled “Embryonic Stem Cell Research Threatened,” co-written by Drs. Diane Krause, Professor of Laboratory Medicine, of Cell Biology, and of Pathology, and Laura Grabel from Wesleyan, is published in The Hartford Courant.

More than any other scientific field, with the possible exception of climate change, embryonic stem cell research is subject to the ups and downs of politics and trouble may lie ahead for scientists in Connecticut and across the country.

Derived from early embryos, embryonic stem cells can become any cell in the body. Since the discovery of human embryonic stem cells in 1998, scientists have explored their potential use as therapies for diseases and injuries. Embryonic stem cell derivatives, for example, could replace the pancreatic cells lost in Type I Diabetes or the neurons lost in Parkinson’s Disease. But just as this approach begins to show promise, a new threat appears on the horizon.

U.S. Rep. Tom Price, R-Ga., Donald Trump’s nominee to head the Department of Health and Human Services with oversight over the National Institutes of Health, is on record opposing embryonic stem cell research. As stem cell researchers, we fear that this appointment would endanger human embryonic stem cell research in the United States and reverse the substantial progress made in recent years. There are promising clinical trials underway for macular degeneration, spinal cord injury and diabetes with more possible, including for Parkinson’s disease.

Connecticut has recognized the importance of human embryonic stem cell research and funded first the Connecticut Stem Cell Program, and now the Regenerative Medicine Research Fund. This brought Connecticut to the forefront of stem cell research. Continued support at the national level is also needed, however, if we wish to continue making progress toward effective cell-based therapies.

What makes this field of research so controversial is that an early stage human embryo (five days after fertilization) called a blastocyst is used to produce a human embryonic stem cell line. Federal funds may not be used to produce a new human embryonic stem cell line because the money cannot support research that directly uses human embryos. At this point, however, federal funds can be used to work on human embryonic stem cells. Despite this, a minority in the government strive to further limit federal funding so that it cannot be used even for studies on lines generated using alternative financial sources.

Many claim we can achieve our therapeutic goals using other stem cell sources, but as stem cell scientists we are keenly aware of the limitations of these alternatives.

Adult stem cells, which have limited capacity for generating the high number of cells needed for human transplants and can only produce certain cell types, will likely work for some applications, but not others. Another type of stem cell, induced pluripotent stem cells, can be generated from adult cell types such as skin, without the need to start with a human embryo. These cells share many properties with embryonic stem cells, including the ability to become virtually any cell in the body. Work using these cells has exploded since their discovery 10 years ago. Induced pluripotent stem cells are useful for modeling human disease in a culture dish and for drug screening. For clinical application, however, these cells have several limitations. Virtually all the cell lines made to date are genetically modified, and this modification could potentially cause cancer, which precludes their use in humans. Most important, as described by many stem cell researchers, embryonic stem cells behave most consistently and therefore remain the gold standard against which other research is compared.

While this is not the place for a full discussion of the moral status of early human embryos, it is worth making some observations. The blastocyst forms 5 days after fertilization, prior to implantation in the uterus, and consists of a couple of hundred cells. All human embryonic stem cell lines that are approved for federally funded research are derived from blastocysts leftover from infertility treatment, with the informed consent of the donors. The alternative futures for these embryos are to be kept frozen indefinitely or to be destroyed. Given these options, many would agree that a future of producing a cell line that could eventually reduce suffering and save lives is a preferred fate.

The United States is a leader in embryonic stem cell research, from basic science to clinical application. This achievement has been fueled by successful collaborations between government-funded academic laboratories and the private sector. A skilled workforce and state-of-the-art infrastructure has been established. New restrictions could well lead to a brain drain and likely provide a serious roadblock to numerous cures.

Laura Grabel, PhD, is the Lauren B. Dachs Professor of Science and Society and a professor of Biology at Wesleyan University and president of the Connecticut Academy of Science and Engineering. Diane Krause, MD, PhD, is a professor at the Yale School of Medicine, associate director of the Yale Stem Cell Center, and director of the Clinical Stem Cell Processing Laboratory.

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Pyromaniacs and Polluters

A lesson from India

By Manju Prasad, MD


India is the home of many things. Today that list includes the city of burning lakes. The lakes of Bangalore, India’s Silicon Valley, are on fire due to the illegal dumping of waste and untreated sewage. Bangalore had 262 lakes in the sixties earning it the name ‘lake city’. That number has dwindled to 81, of which only 34 are considered living ecosystems now.

Several species of birds and animals, like kingfishers, parrots, parakeets, king cobras and monitor lizards are gone.

Unplanned urbanization, free market greed and lack of environmental protection have taken its toll on Bangalore’s flora and fauna and the humans are next — scientists believe that the city will be unlivable by 2025. Last month a fire started in the Bellandur lake, the third lake in Bangalore, the second in two years — the methane gas produced by the polluted lake had caught fire.

Another study shows that the air pollution in India rivals that of China and is causing 1.1 million premature deaths every year. How did we get here?

The explosion in personal car ownership and poor emission control is a major contributor to air pollution in India. Another is a love of fire in the majority Hindu population. We perform havans, a sacred fire ceremony, to seek God’s favor for auspicious beginnings, to express gratitude for stroke and heart disease.

Major contributors to air pollution are emissions from motor vehicles in the US and from industries in Asia. Satellite images have shown plumes of contaminated air, industrial fumes containing black carbon, mercury, sulfates, and nitrates being carried over by trans-pacific westerly winds from booming Asian economies over the Pacific Ocean reaching the West Coast of the US.

One of these pollutants, mercury, is neurotoxic and is strongly associated with Alzheimer’s and Parkinson’s disease. In pregnant women, it can cross the placenta and interfere with fetal brain development. Mercury is also released into the atmosphere after combustion of coal, and Trump wants to take America back to its coal-burning days. Trump is also considering relief for coal miners to dump waste in the streams of West Virginia. Ironically, unlike the people of Bangalore, Americans can dump waste legally. Our water and our air are precious. We cannot allow the repeal of the Clean Water Act and we need to ensure that there is still clean air to breathe for our children and grandchildren.

In 2012, the World Health Organization reported around 7 million deaths globally due to air pollution caused by high levels of ultrafine particulate pollutants.

These aerosolized particles enter the body through the lung, get absorbed into the blood and circulate causing severe respiratory problems, like asthma and pneumonia, and cardiovascular diseases like stroke and heart disease.

And now smog envelops major cities of India. And the children in Delhi, India’s capital, wear face masks to go to school, masks that filter particulate pollutants that I breathe when I visit my mother.

Another major cause of air pollution in Delhi is crop burning by farmers in Punjab, a neighboring state, as seen in images taken by NASA’s satellite Aqua. Crop-burning around Delhi is outlawed by India’s environmental courts. But who cares? In India, environmental regulations are weak, and there is no will to enforce those that are there, a state of affairs President Trump and the GOP might like to see in the United States after they cripple the Environmental Protection Agency with massive budget cuts and toxic leadership. No EPA, no regulations, no problem, except pollution.

Once upon a time, when members of Congress put their country before partisan politics, they enacted a series of Clean Air acts aimed to improve the quality of air Americans breathed.

In 1970, President Nixon signed the papers to establish the United States Environmental Protection Agency. And between 1970 and 2006, carbon monoxide emissions decreased by half, particulate emissions fell by 80 percent and lead emissions fell by more than 98 percent — irrefutable evidence that regulations work.

Now, the Trump administration has ordered a repeal of Clean Water Act protections for the nation’s wetlands and has already made it easier for coal miners to dump waste in the streams of West Virginia. Ironically, unlike the people of Bangalore, Americans can dump waste legally.

Regulations are of paramount importance to rein in the crop-burning farmers and the fire-loving Hindus of India, and to ebb the noxious emissions from gas-guzzling cars in the US and elsewhere, before it is too late.

President Trump, Scott Pruitt and the GOP leaders who are determined to cripple the EPA, only need to spend a week in Delhi or Beijing to remind them what major US cities would have been like without the will of previous lawmakers to ensure clean breathable air for all Americans. Trump environmental policies can certainly make America sick again.
Dr. John Sinard Announces Results of CAP Inspection

March 27, 2017 – The CAP inspection conducted the week of March 20 went very well for the department. It is always valuable to have an external review, which helps to identify areas for improvement. The inspection team was quite impressed with our operation and acknowledged that we have a high quality lab. Although the inspection itself is only a two-day process, it is the ongoing work of every member of the department day after day which is responsible for the quality of our lab. Your efforts and dedication to patient care are much appreciated.

In celebration of another successful inspection, the department hosted a lunch for all clinical services on Tuesday, March 28.

Recent Clinical Faculty Talks


Peter Humphrey and Angelique Levi: Yale Cancer Center Conference: The Evolving Role of Imaging in the Diagnosis and Treatment of Prostate Cancer. New Haven, CT. Mar 11. Case Reviews. (See article, page 11.)


Clinical News

Yale Pathology at the 2017 USCAP Annual Meeting

Reported by Cynthia Ziehl

Each year faculty, residents, and fellows from the department’s clinical services attend the United States and Canadian Association of Pathologists (USCAP) annual meeting. This year’s meeting, “Moving Information,” was the 106th and was held at the Henry B. Gonzalez Convention Center in San Antonio, Texas, from March 4-10. There were approximately 4,341 attendees from 82 countries around the world who participated in a variety of learning experiences that exposed them to contemporary information and translational research in a wide range of subspecialty “hot” topics.

The department hosted a cocktail reception for alumni, friends and guests on Monday evening, March 6. The photos on pages 12-13 (“USCAP 2017 Recap”) were provided by Dr. Marina Baine, Dr. Angelique Levi, and others, and Dr. John Sinard produced informative special editions of the “AP Newsletter” that cover the department’s extensive USCAP participation which included presentations, lectures, proffered papers, posters, and awards.

Highlights included the Maude Abbott Lecture, the keynote address of the meeting, presented by Dr. Peter Humphrey, Professor of Pathology, to an audience of thousands of pathologists from around the world, and a presentation to Dr. John Sinard, Professor of Pathology, of the F. K. Mostofi Distinguished Service Award for service to the USCAP (see page 1).

USCAP 2017 Recap

By John Sinard

This was another great year for the department at the 2017 USCAP annual meeting. Members of the department presented a total of 47 abstracts (as either posters or platforms), lectures, or microscopy sessions, including 17 by our current trainees.

The USCAP has links to access photo galleries and recap videos from the 2017 Annual Meeting, and there is a full meeting recap available on YouTube.

Next year’s meeting, the 107th, “Geared to Learn,” will be held March 17-23, 2018, in Vancouver, BC, Canada.
We look forward to supporting our faculty and marketing their talents and ex-
chures for some. It was a pleasure to tout our sub-specialized experts at this show!
playing publications and white papers of many, as well as specialized service bro-
tunity to proudly highlight several of our incredibly talented faculty, while dis-
The USCAP, unlike many of the other shows we attend, gave us a special oppor-
chures. Many took these resources upon visiting our booth.
We came back to CT with several leads to work with prospective clients around
we were excited to be able to share our new service-oriented sell sheets and new eye-catching Outreach bro-
We look forward to supporting our faculty and marketing their talents and ex-
pertise at future USCAP meetings.

Pathology Faculty Participate in SPORE and Prostate Cancer Conferences

Reported by Cynthia Ziehl

On Friday, March 10, Dr. Peter Humphrey, Professor of Pathology, and Dr. Angelique Levi, Assistant Professor of Pathology, participated in a multi-disciplinary research symposium at Yale’s West Campus hosted by the Yale School of Medicine Interdisciplinary Prostate Research group to explore present and future collaborations within the University that could support an application for a Specialized Programs of Research Excellence, or SPORE, grant. Drs. Jon Morrow and Qin Yan attended this informative conference, which was relevant to both research and clinical interests.

The goals of the conference were to demonstrate the current research strengths of YSM scientists and physicians; to identify collaborative translational research projects focused on the advancement of prostate cancer screening, prevention, diagnosis, and treatment; and to develop a roadmap for future research and SPORE application. Researchers across disciplines were invited to join for updates on current prostate research as well as to participate in interactive discussion of future directions and collaborations in prostate research at Yale.

At the conference Dr. Levi and Darryl T. Martin, PhD, Associate Research Scientist in Urology, were awarded a pilot grant for their research project, “MRI-Targeted Prostate Cancer Nanomarker” (see article below).

On the following day, Saturday, March 11, Drs. Peter Humphrey and Angelique Levi spoke at “The Evolving Role of Imaging in the Diagnosis and Treatment of Prostate Cancer,” a full-day CME conference/course for physicians featuring presentations by numerous YSM faculty experts in the fields of biomedical imaging, urology, therapeutic radiology, medical oncology, and pathology. Drs. Humphrey and Levi both gave presentations in “Prostate Pathology,” and provided data from their recent USCAP presentation correlating MRI PIRADS assessment categories with Gleason pattern in whole mount radical prostatectomy specimens from Yale’s MRI targeted biopsy program for prostate cancer detection using Artemis fusion technology. Additionally, they participated as panelists in case reviews, “Localized Prostate Cancer Panel and Discussion,” and “Advanced Prostate Cancer Panel and Discussion.”

Both conferences featured keynote speaker Daniel W. Lin, MD, Professor and Chief of Urologic Oncology; Vice Chair of Research; Pritt Family Endowed Chair for Prostate Cancer Research; and Director, Institute for Prostate Cancer Research, Department of Urology, University of Washington.

Dr. Angelique Levi Awarded Funds for Joint Research Project

A pilot study grant of $10,000 from the Department of Urology was awarded to Drs. Angelique Levi and Darryl T. Martin. Their collaborative project, judged by a multidisciplinary panel including the keynote presenter Dr. Lin, was selected as a winner among over 10 presentations given. Radiographically identifiable markers that can be placed at the time of targeted biopsy can more accurately localize MRI targets for better PIRADS and Gleason Score correlation on final pathology, and potentially be used for localized therapy. Dr. Levi explains, “Using Dr. Martin’s nanoparticle system in a mouse model, fluorophores can be encapsulated and potentially injected into target MRI lesions of the prostate at the time of Artemis biopsy. Dr. Martin describes it as “… creating a platform that will allow us to detect prostate cancer. We generated in vivo prostate cancer mouse models to study the prostate cancer environment. In collaboration with Dr. Tarek Fahmy (Department of Biomedical Engineering) and Dr. Gigi Galiana (Department of Radiology and Biomedical Imaging), we designed, fabricated, and tested functionalized nanoparticles co-encapsulating contrast agents and fluorophores for magnetic resonance imaging and for fluorescent in vivo imaging, respectively.” Dr. Levi further explains, “Nanmarkers can be developed for clinical use, and then used to validate PIRADS classification and more accurately localize MRI targeted lesions. This is significant because with a high degree of accuracy and confidence we will be able to correlate the MRI targeted biopsy Gleason Score (and percent high grade Gleason pattern), as well as PIRADS assessment categories to the pathology of the specific targeted tumor nodule, and the final pathology stage from correlation studies of nanomarked targets in follow up radical prostatectomy specimens. An exciting future possibility would be to use this nanoparticle platform to deliver localized treatment to focal prostate cancer lesions (that are reliably detected, scored, and graded) in men who aren’t candidates for prostatectomy or for those who choose a non-surgical, more conservative localized approach to therapy.”
Dr. David Rimm, Professor of Pathology and of Medicine (Medical Oncology); Director of Pathology Tissue Services; Director of Translational Pathology

Dr. Peter Humphrey, Professor of Pathology and keynote speaker, delivering the Maude Abbott Lecture, “Prostate Cancer: Then and Now”

Dr. Xinyu (Alan) Wu, PGY-2

Dr. Peter Humphrey, Professor of Pathology and keynote speaker, delivering the Maude Abbott Lecture, “Prostate Cancer: Then and Now”

Left to right: Drs. Jon Morrow, Angelique Levi and Peter Humphrey

Drs. Guoping Cai, Associate Professor of Pathology, and Marina Baine, PGY-2

Dr. Angelique Levi, Assistant Professor of Pathology, and Director, Pathology Outreach

Dr. Tao Zuo, Fellow, Breast/Gyn Service

Dr. Mohammadreza Shervinrad, PGY-2

Photos from USCAP 2017 provided by Drs. Marina Baine, Angelique Levi, and other attendees.

Drs. Marina Baine, PGY-2, and Robert Homer, Professor of Pathology, Director, Thoracic Pathology, Director of Medical Studies, Director, Medical Student Course Module

Poster displayed by Drs. Serena Wong, Assistant Professor of Pathology, and Natalia Buza, Associate Professor of Pathology and Associate Director of Gynecologic Pathology

Left to right: Drs. Pei Hui, Professor of Pathology, Director, Gynecologic Pathology, Clinical Director, Molecular Diagnostics Laboratory and Director, Gynecologic and Breast Pathology Fellowship Program; Tao Zuo, Fellow, Breast/Gyn; and Natalia Buza, Associate Professor of Pathology and Associate Director of Gynecologic Pathology.
USCAP 2017 Recap (continued)
(article continued from page 10)

The list that follows includes only scientific presentations. A number of our faculty also moderated sessions and served on committees, editorial boards, and as officers in subspecialty societies. Congratulations to all! – JS

Presentations
1. Parkash V: Pathologist Burnout and Disengagement: Trends in Pathology
2. Rimm D: Biomarker Analysis for Immunotherapy
3. Jain D: Cryptogenic Cirrhosis: Approach to the Diagnosis in the Era of Molecular Medicine
4. Parkash V: Rationale and Background for the iSGyP Endometrial Carcinoma Project

Proffered Papers
2. Parkash V, Sinard J: Using Root Cause and Human Factors Analysis to Investigate and Reduce Errors in Pathology – A Pilot Project

Posters
1. Chandler JB, Colunga M, Callender GG, Quinn CE, Prasad ML, and Adeniran A: Characteristic Cytopathology of Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NFTP): Implications for Patient Management in the Wake of a Nomenclature Change
4. Cheng L, Jain D, Kakar S, Torbenson M, Wu T, Yeh M: Hepatocellular Neoplasms Arising in Genetic Metabolic Disorders: Steatosis is a Common Finding in Both Tumor and Background Liver

(article continued on page 17)
Kidney Dialysis: Prolonging Life or Prolonging Death?

A doctor’s father considers whether the procedure is worth the risks and difficulties

Published January 5, 2017, PBS, http://www.nextavenue.org/kidney-dialysis/ (This article was provided by The OpEd Project.)

My father was dying. Thirty years of diabetes had destroyed his kidneys, nerves, blood vessels and eyes. He had anorexia, nausea and lethargy. His skin was streaked with angry itch marks. Proteins were draining out in his urine. Calcium was leaching from his bones. His toes were cold and blue and painless, without sensations. His deteriorating balance made even walking unsafe. He slept after every meal, the effort exhausting him.

Dad was 82 years old and had end-stage renal disease. One in seven Americans has some form of chronic kidney disease. According to the National Kidney Foundation, about 30 percent of patients with Type 1 diabetes and 10 to 40 percent of those with Type 2 diabetes eventually will suffer from kidney failure.

With each extra day my father lived, the risk of gangrene, blindness, falls and fractures increased.

The majority of those with chronic kidney disease won’t know it because the disease is asymptomatic in early stages. But some will progress to end-stage and will need renal replacement therapy, dialysis or a transplant to live.

Medicare spending for patients with chronic kidney disease exceeds $50 billion, representing 20 percent of Medicare spending, with an additional $31 billion spent on the more than 660,000 patients with end-stage renal disease.

Kidney Dialysis: ‘His Only Option’

Dad was too frail for a transplant. Dialysis was his only option, his doctor said.

Without doubt, dialysis extends life and is critical for patients waiting for a kidney transplant that may take several years. Patients who have no, or few, other diseases could get dialysis in a clinic or at home and go about their day as usual. My father needed dialysis three times a week, four hours each time. He would be tethered to a dialyzer for several hours for the remainder of his life.

Would dialysis prolong life or prolong dying? My father was confused.

Making the Case for Dialysis — Or Not

Dad was an engineer. He preferred data. As a professor at the Yale School of Medicine, I could analyze and summarize the medical literature for him, succinctly. I felt that I could help him make the most important decision of his life.

But studies on dialysis in octogenarians are scant, and the benefits controversial.

According to Dr. Manjula Kurella Tamura of the Stanford University School of Medicine, the majority of nursing home residents on dialysis suffered a substantial and sustained decline in functional status after its initiation. Dialysis could not guarantee improvements in symptoms or depression.

The New England Journal of Medicine reported that six months after starting dialysis, one in three octogenarians had died and only 28 percent remained independent. In Canada, 60 percent of the elderly on hemodialysis (a type of renal replacement therapy) regretted their decision after six months as the symptoms persisted or worsened. The burden of symptoms in older adults on dialysis rivaled that of cancer. One in three octogenarians ultimately discontinued dialysis, rejecting an unacceptable quality of life.

Costs Significant

Older people generally have multiple chronic conditions and are prone to infections and other complications requiring additional hospitalization. The annual cost of hemodialysis in people older than 67 is significant: $115,000 per person. With each extra day my father lived, the risk of gangrene, blindness, falls and fractures increased, and the survival time gained might be spent in the hospital.

Dad likened going for dialysis thrice weekly to going back to work, “without pay, like volunteering.”

If they chose that option, my mother would go with him despite her crippling arthritis. For her, too, it would also be like going to work, at 75 years of age. My sister would drive them. They would all spend less time with my sister’s little girl, the light of their life.

Home dialysis was considered. My mother would need to learn to connect him to bags of dialysate (a fluid used in dialysis) through a permanently-placed tube in his abdomen.

“Wouldn’t that cause infections? With the dogs around?” Dad wondered. It could. They had two Pekingese.

Unanswered Questions

“My doctor didn’t explain it to me,” Dad said, frustrated. “Not like this. He said dialysis was the only option since I am too frail for a transplant. He said I could even live for 20 years. I don’t want to live like this!”

Dad made his decision — no dialysis — the option his doctor hadn’t mentioned.

Shared decision making requires taking into consideration the patient’s quality of life, his wishes and goals and sometimes, helping him choose one option over the other. It requires of the physician good nonjudgmental listening and complete honesty. Violating the dignity of an incurable patient, using science to stop the inexorable march towards death, interfering with a “necessary end” should not be acceptable in any society, however advanced or civilized.

My father died seven months later, at home amidst his loved ones who had bravely struggled to let him live, or die, as he wished.
“Precision Medicine” and Dr. Janina Longtine in the News

Dr. Janina Longtine, Professor of Pathology; Vice Chair, Pathology and Laboratory Medicine; Director, Molecular and Genomic Diagnostics; and Director, Tumor Profiling Laboratory, Smilow Cancer Hospital, was quoted in an article published March 25, 2107, in The Day, entitled “Precision Medicine’ Now Being Used in Treatment of Local Cancer Patients.”

In a section entitled “Rapid Advancements,” the article’s author, Judy Benson, writes the following:

“At the Tumor Profiling Laboratory at Yale New Haven Hospital, Dr. Janina Longtine, who is Professor of Pathology, Vice Chair, Pathology and Laboratory Medicine, Director, Molecular and Genomic Diagnostics, and Director, Tumor Profiling Laboratory, Smilow, said that across the Yale New Haven Network, which extends from Greenwich to Westerly, all patients with stage 2 or higher melanoma, lung or colon cancer — the fifth, second and fourth most common types, according to the National Institutes of Health — are having 50-gene panel tests done to find target mutations. Next month, that is slated to increase to a 148-gene panel test, according to Kanowitz.

Longtine said the use of genomic testing in cancer care has advanced rapidly over the 14 years since the human genome was first sequenced. The first tests offered would look for just one or two genes prone to cancerous mutations, she said, but now advances in technology and understanding of tumors has expanded the numbers of genes routinely being sequenced, she said.

“Now, with one test, we can look at 50 genes for hot spots,” said Longtine. For patients with more advanced disease, she added, 400-gene panel testing is offered. In all, the lab is conducting about 90 of these tests per month, with each test taking three to four days.

One of the factors contributing to the rapid expansion of genomic testing for cancer is the development of new cancer drugs that target specific mutations, according to Dr. Longtine. In some cases, those drugs are replacing older chemotherapy drugs that would target all fast-growing cells and cause the telltale hair loss, nausea and other side effects long associated with cancer treatment.”

The article includes photos of medical technicians Rong Cong, Nadene El-Eid, and Jen Thomas from the Tumor Profiling Lab at Smilow, and goes on to quote Dr. Longtine on the costs of the tests and other challenges: “...cancer remains a tricky disease to cure completely. Cancers are smart, and sometimes they develop additional mutations that can escape treatment... Sometimes you have to have a second round of the tests to find a new therapy.”

To read the full article, go to: http://theday.com/article/20170325/NWS01/170329500.

Pathology Goes Red for Women’s Heart Health

By Rachael Leftridge

February was “Heart Health Month” and “Go Red for Women.” To show our support of women’s heart health and Yale’s Working Women Network, on February 3 we wore red, took a group photo, and enjoyed a heart-healthy snack.

But it didn’t stop there! To encourage physical activity, there was a friendly “step competition” for the month of February. Congratulations goes to Margaret Davitt, who finished the month with 269,113 steps! Way to go, Margaret!

“Bite-Size Heart-Healthy Muffins”

Recipe shared by Lori Charette.

[2 Weight Watcher smart points = approximately 100 calories per muffin]

1 cup unsweetened applesauce
1 lg. egg
¾ cup whole wheat flour
1 cup steel cut oats
1/3 cup sugar or sugar substitute
1 tsp baking powder
½ tsp baking soda
1 tsp cinnamon
¾ tsp salt
1 tsp vanilla
½ cup unsweetened almond milk or milk of choice
½ cup dried cranberries, blueberries, raisins—I mixed them up.
4 Tbsp coconut oil or whatever you prefer

Preheat oven to 350°. Mix all ingredients together. Bake at 350° for 20-25 minutes. Look for golden brown color; if not golden brown after 20-25 minutes, go about 5 minutes longer. I made this recipe bite-size by using a tart pan. You can make it a loaf or muffin size and adjust the baking times. You can add dark chocolate chips and/or nuts.

ENJOY!!!!!!
**Staff News**

**Accesioning Staff Member Recognized for YNHH Patient Safety “Great Catch”**

By Dr. John Sinard

Katina Stowers, one of our surgical pathology accessioners, was recognized by Yale New Haven Hospital as the recipient of the February Great Catch Award. The Great Catch Award is made monthly to honor employees who make a safety catch that prevents harm to an individual patient or produces a system change that benefits a greater patient population. Katina was recognized for “practicing a questioning attitude while processing a specimen for a maternity patient.”

While accessioning a specimen, she noticed that a specimen with the same patient’s name had been submitted the day before, and she escalated her concern to the nurse manager and clinical team. On investigation, it was discovered that the specimen had been mislabeled and actually belonged to a different patient.

Of course, this is just one example of the many patient safety catches made each day by many of our employees, and Katina’s recognition is representative of the great work and attention to detail by all of our staff, who are integrally involved in making our department great. We don’t do this for the recognition. Nonetheless, it is nice to be recognized! Congratulations, Katina.

**In Memoriam**

By Lori Charlette

Laura Ann Johnson, age 51, passed away on March 8, 2017 at Yale New Haven Hospital.

Laura was a long-time employee of Yale University. She worked in the Sterling Memorial Library for 20 years. After a short time in the layoff pool Laura came on board in Developmental Histology where she coordinated slide and block collections for investigators and other lab related duties.

Laura loved cats, not only her cat, Oliver, but also Grumpy Cat. She enjoyed reading light mystery books, watching British television programs, and drinking iced tea. Laura loved arts and crafts. She made beautiful necklaces and wore them proudly.

She was a kind, sweet person who smiled and laughed. Her laugh was contagious; you could hear it all the way down the hall. She will be missed dearly.

**Spotlight on Staff**

Meet Karen D’Angelo,
Pathology Graduate Program Registrar

By Cynthia Ziehl

We are fortunate in this department to have not only outstanding faculty and students but also highly skilled and responsive administrative support professionals, one of whom is Karen D’Angelo, the department’s Graduate Program Registrar, Grants 2nd chair, and teaching program and faculty support assistant. If this sounds like a lot of “hats” to wear, it is, and Karen manages them all energetically, with a helpful, cooperative attitude and exceptional competence.

Karen worked as a Registered Nurse prior to coming to Yale. She started her nursing career at Hartford Hospital where she worked in the ER for 2 years and 15 years in inpatient oncology. She then took a job as an out-patient oncology nurse but re-evaluated this career choice after 5 years and “too many funerals,” deciding to make the change to internal medicine, which ultimately she decided was not a good career fit. Karen commented that, “The nursing profession has changed a lot over the years. There’s a lot more paperwork, less patient contact and care, and the physical risks of the job have increased dramatically, in part because of the growing body weight of the average patient. I have friends who are nurses who’ve been seriously injured on the job from lifting patients.” (If you know Karen, you know that she’s petite!) This combination of physical and emotional demands left her wondering about other careers that would challenge her mind and engage her heart the way oncology nursing had but without the element of tragedy.

Karen came to Yale initially, over 13 years ago, as a fellowship coordinator for Pulmonary and Critical Care Medicine. This welcome move to involvement with both clinical and research aspects of medicine was her first introduction to the realm of academic medical research, and she has never looked back. In Pathology, where Karen has been for the past 3 years, she has seen the basic research side of medical advances, and, after so many years of working with the clinical trial aspect, it was exciting for her to see the circle completed that starts with the discovery of treatment modalities and ends in clinical trials. In addition to PCCM, Karen has also worked in the departments of Internal Medicine, Faculty Affairs, and Neurology, and her experience in these areas of the medical school has been helpful in her roles in Pathology.

Karen says, “I love my job, all the different parts of it! I love the variety of tasks I have now. It’s always engaging. I like reading the grants as I’m working on them.”

Karen goes on to say that it’s not just the work she enjoys here. “I’m excited when I come to work. I think of the grad students as my kids; they’re younger than my own children! I love that if there’s a problem, they come to me, and I fix it; I’ve had two kids, they’ve grown up, gone to college, moved on, and I miss that. And it’s great to see the grad students grow into these amazing future leaders in science, research and education; we’re producing the ‘well-rounded package’ here—they’ll be able to communicate to laypeople and make them understand. When they talk about their work, it’s exciting.”

As well as enjoying the students, Karen enjoys working with the faculty. “It’s inspiring to see how well the PIs interact with their students; they’re patient, they’re mentors, guiding them along in their work. It’s fun when the grad students from the Yan, Nguyen, Stern, Wajapeyee, and Finberg Labs all come together for lunch on the third floor and collaborate.” Karen points out that her job combines two things she loves, namely engaging people and interesting science, and says, “I enjoy seeing the intersections.”

(article continued on page 20)
The “Cart Food” Corner

By Nicole Calabro, Cart Food Connoisseur (and 6th year ExPath grad student)

As graduate students, we are always on the lookout for great food, but unfortunately, don’t have a lot money to spend, or free time away from lab. Because of this, we have become cart food connoisseurs, running out to our beloved carts, grabbing one of their signature options, and dashing back to the lab. We have heated discussions about which cart is the best, and wax poetic about how we will miss our favorite dishes when we leave Yale. Since enjoying cart food plays such a central role in our day, we have decided to dedicate a column to a different cart each publication, allowing us to better know the master chefs behind our lunches. – NEC

The first article of “Cart Food Corner” highlights my preferred cart, Peking Edo III, run by Jackie Wei. Jackie, 56, is a friendly little spitfire of a woman who will enthusiastically serve your food with a smile. As her cuisine has a traditional Taiwanese focus, many dishes may be unfamiliar to individuals who frequent the classic “American-idea” of Chinese and other Asian restaurants. One of the best things about Jackie is that she will encourage you to try these “unfamiliar” dishes, giving you samples of what you are interested in and explaining what they are. Because of this, I have tried so many delicious things I would have never dreamed of tasting. As a huge noodle fan, I can never go wrong with any of the five choices in my rotation. If you’re looking for a spicy soup with perfectly tender meat, mala beef noodle soup is the way to go. If you’re looking for a mild soup with great flavor, check out the meatball mushroom noodle soup. For non-soup meals, Shanghai noodles or rice noodles are great choices. My personal favorite (along with it being Jackie’s favorite too) is crispy pork with noodles. These selections are only a fraction of what Jackie offers.

Since coming to the US in 1978, Jackie has worked in the restaurant industry, gaining exposure and experience in cooking all varieties of Asian food. This talent allows her to cook essentially anything you could ask for, with the most enjoyable part of her job being meeting new people and exposing them to new flavors. Jackie’s knowledge goes beyond food; she also serves as a bartender in the restaurant industry. Everyone simply assumed because she was the youngest person in the lab. We have heated discussions about which cart is the best, and wax poetic about how we will miss our favorite dishes when we leave Yale. Since enjoying cart food plays such a central role in our day, we have decided to dedicate a column to a different cart each publication, allowing us to better know the master chefs behind our lunches. – NEC

USCAP 2017 Recap (continued)
(article continued from page 13)


18. Sadare O, Quick CM, Owin K, Parkash V: The Expression of PD-L1, PD-1, and DNA Mismatch Repair Proteins in Clear Cell Carcinoma of the Ovary; A Pilot Assessment of Frequency, Clinicopathologic Significance and Potential Correlations


20. Hu J, Roma A, Parkash V, Sadare O: Metastatic Tumors Involving the Ovary; Pathologic Features Associated with Patterns of Clinical Presentation in 68 Case


22. Vyas M, Celi R, Zhang X: Tumor Buds and Micropapillae in Colorectal Carcinoma Demonstrate Similarities in Biological Behavior and May Represent Two Ends of the Same Spectrum


28. Ozerdem U, Tavassoli FA: Comparison of Oncotype DX and Magee Recurrence Scores in 60 Infiltrating Breast Carcinomas

29. Ozerdem U, Tavassoli FA: Oncotype DX Recurrence Score of Special Subtypes of Breast Carcinoma


32. Beech C, Rimm D, Neumeister V, Cai G: Assessment of PD-1 Status by Immunohistochemistry in Cytological Specimens of Non-Small Cell Lung Cancers: Correlation with the Results of Concurrent Surgical Specimens

33. Wu X, Celi R, Jain D, Zhang X: Gastrointestinal Histopathologic Manifestations in Patients with Common Variable Immunodeficiency (CVID)

34. Baine MK, Hui P, Buza N: PAX8, SOX10 and GATA3 Immunostains: Friend or Foe in the Diagnosis of Vulvar Paget Disease?


Special Course

Rimm D: PD-L1 IHC Assays: What is the Difference and What is Next?

Interactive Microscopy Sessions

1. Robert M: Morphology vs Molecular Markers in GI Biopsy Diagnosis: How Not to Get Tripped Up When Integrating Results

2. Buza N: Challenging Gestational Trophoblastic Lesions – Morphology and Beyond

Long Course

Humphrey, PA: Prostate Pathology: Unusual Variants of Acinar Prostate Cancer Mimicking Benign Conditions

Short Course

Bossuyt V, Provenzano E, Symmans WF: The Pathologists Role in Guiding Breast Cancer Treatment in the Era of Neoadjuvant Therapy
PhD in Experimental Pathology (continued)
(article continued from page 5)

Students meet as a group on average 4 times per year with Themis, in his role as DGS, to discuss graduate student issues, concerns, give feedback on academic and research experiences, and to talk about work climate, suggestions for changes, improvements, and other related matters. “As a result of graduate student feedback, for example, we just revised the format for the qualifying exam. For the first time, students are working on inviting a Grand Rounds speaker they will host for next year, so the students will have input into Departmental activities. Additionally, students participate in the departmental retreat, giving talks and poster presentations.”

The role of the Registrar, Karen D’Angelo (see “Spotlight on Staff,” page 16), is to ensure that all students take qualifying exams, form thesis committees, and have all necessary documents completed and requirements met. Another of Karen’s important jobs is to maintain records of students’ careers post-graduation. So what is a common path for ExPath graduates?

A majority go on to postdoctoral training in pursuit of an academic or pharmaceutical industry career. Some might go into other types of industry and some become consultants, although these paths are not as common directly out of graduate school. In the case of MD-PhD students, most go on to residency. In the recent survey of graduate students, 6 went on to postdoctoral associate positions, 1 is pursuing a second PhD at a Chinese university, 1 is working for a consulting firm, and 2 joined pharmaceutical firms.

Graduate students apply for fellowships and grants, and according to Themis, “Our students do very well in earning awards: from NIH, NSF (National Science Foundation), school-based fellowships, and others.” Later in their training, they apply for fellowships that are more specific to their areas of research, such as the American Heart Association and cancer research foundations. Costs for the first year of the graduate program are covered by the university; years 2 and 3 are covered by Yale Combined Program in the Biological and Biomedical Sciences (BBS), a Yale-wide program that oversees aids. Those who don’t have fellowships are placed on training grants; for years 4 and up they are supported by their respective PI’s lab funding. Fellowships provide support for students’ expenses and tuition but do not support research expenses, while a grant can be both stipend and research support. Grants for graduate students are the exception, however, as it is difficult for most to make a strong case for their specific experiments this early in their careers.

The graduate students also participate in teaching which is a requirement of the graduate program, but there are also opportunities for them to continue teaching on their own if they’re interested in doing so. One example of a student pursuing her interest in teaching is covered in the article, “Developing the fundamental basis of human disease” (see page 5).

If you would like to know more about the graduate studies program, go to http://medicine.yale.edu/pathology/education/graduateprogram/index.aspx. To learn about some of the department’s current graduate students, see page 6-7.

Very Important Pathologist: Dr. Joe Madri (continued)
(article continued from page 2)

Scholarship from the American Society for Investigative Pathology.

As if the above were not enough, Joe has been an outstanding citizen of Yale and the greater scientific and clinical community. He has served on multiple NIH study sections and study sections for the American Heart Association. He served as assistant and associate editor for the American Journal of Pathology, Laboratory Investigation, the FASEB Journal, and the Journal of Cellular Physiology and Angiogenesis. He advised as a member of the scientific advisory boards of The Shriners Research Institute and Genzyme Tissue Repair, Inc. He was a co-founder and Director of Alexion Pharmaceuticals, Inc. Throughout this, he has remained clinically active as a member of the medical staff of Yale New Haven Hospital. Finally, Joe and Lucille have been generous philanthropists, with major donations given to his Alma Mater and the City of New Haven; last year they established the endowed Joseph and Lucille Madri Professorship at Yale.

Beyond his academic efforts, Joe has for three decades been a student of the martial arts. He holds a 4th degree Black belt and is an International Instructor in Tae Kwon Do. Joe and Lucille are also avid bicyclists, and enjoy exploring the back roads of Connecticut. Now as emeritus, Joe is enjoying “being a post-doc again,” working in his laboratory on innate immunity and cancer, and spending more time with his family and friends.

The 2nd Annual King Lecture (continued)
(article continued from page 3)

and understand eukaryotic genomes. His work included significant, start-to-finish involvement in the Human Genome Project. These efforts eventually blossomed into a highly productive program in comparative genomics that provided important insights about genome structure, function, and evolution. His laboratory also identified and characterized several human disease genes, including those implicated in certain forms of hereditary deafness, vascular disease, and inherited peripheral neuropathy.

As Director of NHGRI, Dr. Green is responsible for providing overall leadership of the Institute’s research portfolio and other initiatives. In 2011, he led NHGRI to the completion of a strategic planning process that yielded a new vision for the future of genomics research, entitled Charting a course for genomic medicine from base pairs to bedside (Nature 470:204-213, 2011). Since that time, Dr. Green has led the Institute in broadening its research mission; this has included designing and launching a number of major programs to accelerate the application of genomics to medical care. With the rapidly expanding scope of genomics, his leadership efforts have also involved significant coordination with multiple components of the NIH, as well as other agencies and organizations.

Beyond NHGRI-specific programs, Dr. Green has played an instrumental leadership role in the development of a number of high-profile efforts relevant to genomics, including the Smithsonian-NHGRI exhibition Genome: Unlocking Life’s Code, the NIH Big Data to Knowledge (BD2K) program, the NIH Genomic Data Sharing Policy, and the U.S. Precision Medicine Initiative.
Celebrating Dr. Joseph Madri (continued)
(article continued from page 1)

in developing life-extending therapies for people with rare, devastating, and potentially fatal diseases of the blood and bone.
The success of the company he helped to found has inspired Madri and his wife Lucille to endow a new professorship at the School of Medicine — the Joseph A. and Lucille K. Madri Professor of Experimental Pathology. Madri says he owes many professional achievements to the faculty, postdocs, and students in his lab and the medical school’s Department of Pathology, who have informed and inspired his work.
“We felt strongly that we should give back now that we have the ability,” Madri says. “I am a strong proponent of doing that through research that benefits the Department’s research enterprise, so we came up with a professorship for an experimental pathologist.”
The professorship’s first occupant is Gerald S. Shadel, PhD, who also is Professor of Pathology and of Genetics, and Director of the Yale Center for Research on Aging (Y-Age).
“Gerry Shadel is an ideal person to be the inaugural Madri professor, an outstanding scientist who is committed to understanding the cellular and molecular mechanisms of aging,” says Robert J. Alpern, MD, dean and Ensign Professor of Medicine. Shadel, who became a member of the faculty in 2004, researches the role of mitochondria — energy generators within cells — in disease, aging, and the immune system. Shadel’s laboratory has contributed crucial knowledge to the understanding of mitochondrial gene regulation and metabolic stress signaling pathways. The lab’s ground-breaking aging studies have shown that mitochondrial respiration and reactive oxygen species signaling are key components of conserved longevity pathways.
Madri notes that in making his gift, he had a particular desire to support a mid-career researcher, and he is confident Shadel is the right choice. “He is an outstanding investigator,” says Madri. “He has a true and abiding interest in developing the Department, its research, and its educational mission.” Madri also continues to pursue his own abiding goal — to help people worldwide whose health needs are often forgotten. The company he launched has worked hard to achieve that vision. Alexion Pharmaceuticals extends the lives of people who are afflicted with two rare blood diseases: atypical hemolytic-uremic syndrome and paroxysmal nocturnal hemoglobinuria. “We treat people who have paroxysmal nocturnal hemoglobinuria in 50 countries, and now they have a life expectancy that parallels the average person in their particular country, and they are productive members of society,” says Madri.
The company makes therapies that also treat the bone-softening disease hypophosphatasia, as well as lysosomal acid lipase deficiency, a condition in which uncontrolled accumulation of cholesterol and triglycerides leads to organ damage and early death.
“If I do nothing else in science, having helped thousands of people live a long, productive life is more than enough reward for me,” he says.
The Madris have spent their entire professional lives at Yale. Joseph Madri arrived as a postdoc in 1975. Lucille Madri held administrative roles at the University for 25 years.
It is rare for a faculty member to endow a professorship, but Madri says Yale and the Department of Pathology deserve such a special gift. “Yale is a unique place and the postdocs and students who’ve cycled through the lab have been outstanding,” he says.

Pathology Faculty and Student Create New Course (continued)
(article continued from page 5)

understandable, throw in humor. One of the most successful courses was when we had peer review groups, where students reviewed and discussed each others’ grants. It taught them how to be reviewers and also how to take constructive criticism.”
The course consists of 12 class sessions, two hours each, which Nicole describes as “intense.” Course content progresses from the basics of scientific writing, which assumes the student starts with no knowledge and experience, all the way to completion by each student of a ready to submit F31 grant at the end. Nicole explains, “We had an assignment due, some piece, every week, so students couldn’t put it off, they had to hand in something. Britta (Kunempooler) was our Teaching Assistant, and she also reviewed the work, so we had 3 reviewers for all the submissions. We had structure, outlines, detailed examples of specific language, a kind of formula, for these grants.” Students who took the course described it as one of the most demanding they’d ever taken at Yale but totally worthwhile, and some commented that it was one of the most useful courses they’d ever had.
Nicole is proud that Tony Koleske, PhD, BBS Director, intends to eventually expand the course BBS-wide. The goal would be for every graduate student to take the course in his or her second or third year. “The fall was our first iteration of the course; Katie is planning on teaching it again this coming fall. Since Katie and I did it, the course was obviously piloted in Pathology.” Some student grants from the course will be submitted for the April 2017 deadline. Nicole graduates this year and is still deciding her future, although she knows she’ll do “something at the university level, teaching or working for a science-related non-profit.” She says that teaching this course was fun and was “one of the best experiences in grad school. I love teaching and mentoring, and I know I will come back to that eventually.”

Dr. Madri, Dr. Shadel, and Lucille Madri at the official announcement of the newly endowed chair and its first recipient (June, 2016). Dr. Morrow, Chair, made the announcement.
Meet Karen D’Angelo (continued)
(article continued from page 16)

In discussing setting up the Anatomy Labs for the first and second year Medical Students, she says, “I’ve read about these things, I’ve seen them on x-rays, I’ve seen what effect they have on living patients, and it’s interesting to take these organs out in autopsy and to see it in the end stage. It brings a different reality.”

Karen is particularly excited about a new module in the graduate student curriculum. Graduate students in the Cancer Cell Biology Training Program now have both a clinical mentor and a research mentor, and they’ll be doing research here in the Department in their labs, but will also be shadowing their clinical mentor at the outpatient and inpatient areas of the Hospital for the next two years. This new program, organized by Drs. David Stern, Professor of Pathology, and Peter Glazer, Professor of Therapeutic Radiology and of Genetics, under a T32 training grant, will be utilized by 5 post-doctoral associates and 4 pre-doctoral students, and all areas in the department that are conducting cancer research will be offering clinical shadowing.

Karen’s son and daughter-in-law are expecting their second child any day now, making her a happy grandma again!

Greater New Haven Heart Walk team in honor of Laura Johnson

Lori Charette has created a team for the Greater New Haven Heart Walk event and is the team captain of team “Laura’s League.” This is an event to raise money for the American Heart Association (AHA). Laura had a cardiomyopathy heart condition. The team is doing well with donations to the AHA and is up to $225. To join or for more information, please call Lori at (203) 737-4198 or email lori.charette@yale.edu.

“Tracy’s Run,” a 5k Race to be Held in Memory of Tracy Reynolds

Tracy was a graduate student who earned her PhD in Experimental Pathology and worked in the labs of Drs. Robeck and Rose. RIP, Tracy.

Tracy’s Run: Running Through The Rain

When: Saturday, May 6, 2017 - 10:00 a.m.
Where: Platt Regional Tech School - 600 Orange Avenue, Milford, CT

What: A 5k race to help support individuals who struggle with mental health issues. Running was an outlet for this special woman, Tracy, who loved running through the rain. Sadly, she took her life. As a result of this tragedy, Milford Road Runners and Yale New Haven Psychiatric Hospital have partnered to create this event. Together, and with the support of our community, we hope to bridge the gap from illness to wellness highlighting there is hope for everyone. All proceeds will directly benefit patients at Yale New Haven Psychiatric Hospital.

Schedule: 8:30 a.m. Race Registration Begins (Ends 9:45 a.m.)
11:00 a.m. Awards Ceremony Begins

Please Welcome...

Serena DelBasso, Department of Pathology Operations Manager, and husband Ryan Wolfe welcomed their son Oliver Losi Wolfe, 6 lbs. 7 ozs., on January 6, 2017, at 1:15 am. Congratulations!

Dr. Olivia Snir with husband Yehuda and big sister Julia welcomed son Eli David, weighing 10 lbs., 4 ozs., on February 22, 2017, in plenty of time for St. Paddy’s Day!

On February 8, 2017, dad Dr. Rom Celli and mom Monica Colunga Calderon welcomed their daughter Simone Dinorah Celli Colunga shown at left with big sister Francesca. Congratulations!

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“OOOPS!”

We try to be as thorough, accurate, and complete as possible in our reporting of news from the Department. If we have missed something or need to print a correction or clarification, please let us know, and we’ll be sure to include it in the next issue.