INSIDE PATHOLOGY

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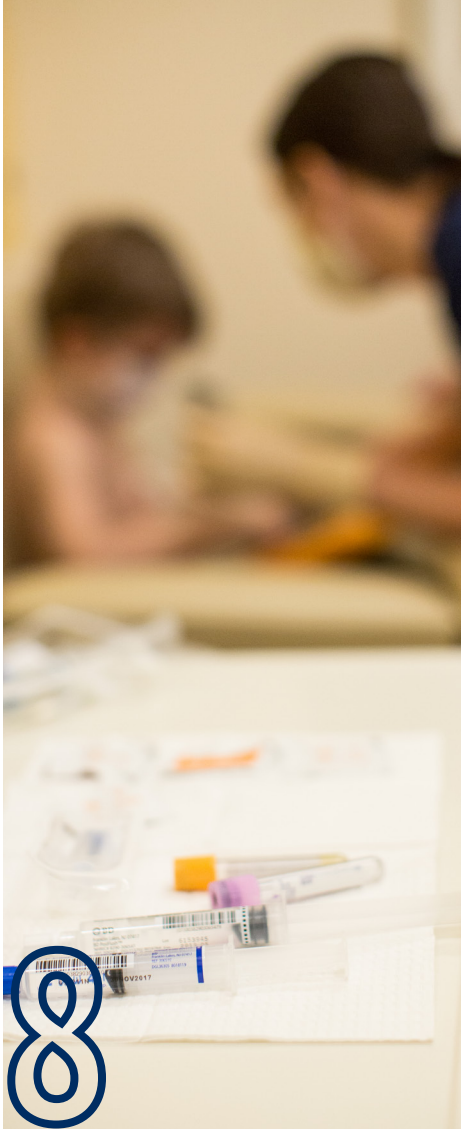
2017



M INSIDE PATHOLOGY

SPRING 2017

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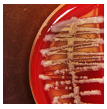

An Arms Race with a Superbug

Why the World Needs an Essential Diagnostics List

Pathology Informatics Goes 3D

www.pathology.med.umich.edu/**news**

On the Cover

Dr. Sriram Venneti, MD, PhD and Postdoctoral Fellow, Chan Chung, PhD investigate pediactric brain cancer. **Read More on pg 5.**
Photography by Dustin Johnston

Photo by **Dustin Johnston**

The Department of Pathology had an extraordinarily successful and busy 2016 - 2017. During this time, the University of Michigan Health System has been re-named Michigan Medicine to better reflect the three-part mission of patient care, education, and research.

There were many outstanding awards and accomplishments in the Department of Pathology on a national/regional level, including Dr. Sriram Venneti, who received the Kimmel Scholar Award for his contribution to brain tumor research, the Doris Duke Charitable Foundation Clinical Scientist Development Award, and the American Society for Clinical Investigation Council Young Physician-Scientist Award. The three awards are given to physician-scientists early in their careers. You can read more about his lab's work to better understand pediatric brain cancer in this issue.

In *Year in Photos* you'll learn more about the accomplishments of our faculty and staff and Dr. Laura Cooling, who received the American Society for Apheresis 2016 Lecturer Award. Dr. Cooling shares insights she gained from a personal experience with breast cancer in *Through the Looking Glass*.

The Smallest Among Us provides insight into the career of pediatric pathologist, Dr. Raja Rabah, who was born in the West Bank and raised in Morocco and Syria. Her career in medicine began when she opened a pathology department that was the first of its kind to serve Palestinians in the West Bank.

Phlebotomy staff in C.S. Mott Children's and Women's hospital participated in a research study to ease the anxieties associated with blood draws and other procedures. Read about what they learned would take the pain out of pokes in *More Than a Blood Draw*.

Also in this issue, Christine Baker, the Senior Project Manager for our Pathology Relocation and Renovation Project gives us another update on Pathology's move to the North Campus Research Center. Construction is underway and on track for completion at the end of 2017.

These are truly exciting times for Pathology at Michigan. I hope you enjoy reading this issue as much as I did.

Please send us feedback. We would be delighted to hear from you!

Charles A. Parkos, MD, PhD
Carl V. Weller Professor and Chair
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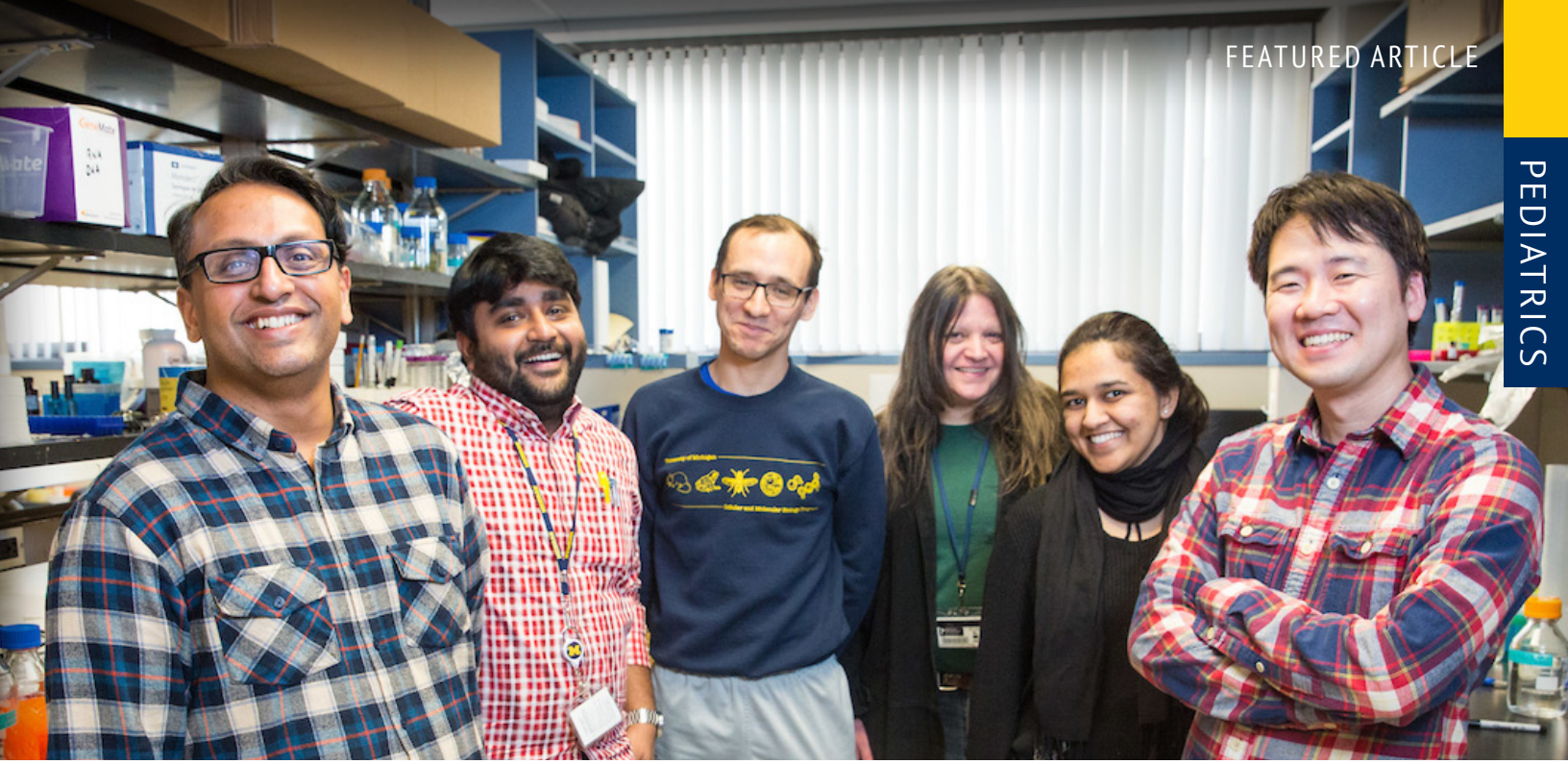


(Left to Right): Dr. Sriram Venneti, Abhijit Parolia, Adam Banda, Jill Bayliss, Pooja Panwalkar, Chan Chung.

Understanding Pediatric Brain Cancer

by **Sara Talpos** | *Photography by* **Dustin Johnston**

Sriram Venneti's lab explores the interface of metabolism, epigenetics, and brain development in order to better understand—and eventually treat—childhood cancer.

On a sunny afternoon in September, Tammi Carr stepped to the microphone to thank participants and sponsors of the 3rd annual RunTough for ChadTough race. The 5k and 1-mile fun runs received more than $80,000 in donations to help support pediatric brain cancer, a condition that has deeply affected the Carr family, which includes former U-M head football coach Lloyd Carr. The family has sought to draw attention to the experience of Chad Carr, Tammi's son and Lloyd's grandson. Chad died this past year of brain cancer. He would have turned 6 on the day of the race.

"We're going to be releasing balloons before we start," said Tammi. "It's important to us to do that this year, to celebrate Chad's birthday." She paused, holding back tears, before adding, "He loved balloons."

More than one thousand people were onsite for the run, including Sriram Venneti, MD, PhD, assistant professor of pathology and neuropathology, and members of his lab. "It was so important for my lab to see this," Venneti says, referring to Tammi's introduction and follow-up comments from Carr family members. "Because you can play with these cells and create these mouse models, but what impact does your work have? Why is it important to do this?"

In the United States in 2016, an estimated 4,630 kids, ages 0-14, were diagnosed with some type of pediatric brain cancer. Venneti's lab focuses on cancers that originate not in the brain's neurons, but in the gluey support cells surrounding the neurons. These cancers are called "gliomas," and for many patients, the prognosis is grim. Chad Carr, for example, had something called a diffuse pontine glioma (DIPG) that bears mutations in proteins called histones. According to Venneti, 90% of children die within one year of this diagnosis.

Brain cancers for children and adults are notoriously difficult to study because

Top: Dr. Venneti
Below: Research team with Tammi Carr at RunTough for ChadTough.

so many occur in regions of the brain that aren't easily accessible to biopsy. As a result, treatment lags behind those available for other childhood cancers, such as leukemia.

Before his death, Chad Carr underwent thirty rounds of radiation at U-M's C.S. Mott Children's Hospital. Most children diagnosed with brain cancer receive chemotherapy or radiation. But these treatments were developed for adults, whose tumors behave differently. Although Chad initially showed improvement, ultimately the treatment wasn't enough. Venneti's goal is to elucidate the mechanisms of normal brain development in order to better understand why and how cancer occurs.

Epigenetics
An Emerging Theme

Venneti has begun to make a name for himself by studying the interface of cancer metabolism, epigenetics, and brain development—an interface that ten years ago, scientists didn't even know existed.

Seven years ago, when Venneti was a neuropathology fellow, researchers discovered a mutant enzyme present in the majority of adult gliomas. The enzyme was functioning within the Krebs cycle, a series of chemical reactions that transform nutrients into energy. The cycle is central to human metabolism. "That's very surprising," thought Venneti. "What is an enzyme mutation doing there?" Venneti was intrigued by this link between cancer and metabolism.

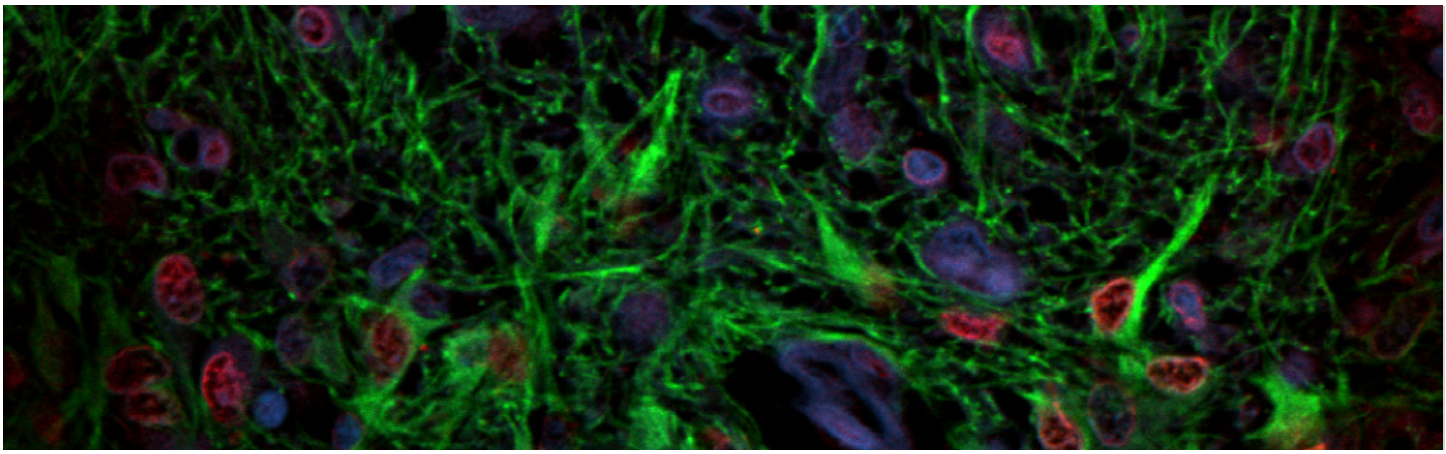
He decided to do his post-doc in New York City at Memorial Sloan Kettering Cancer Center, where he could pursue research to answer his question. "Life is full of serendipity," says Venneti, describing his experience with science.

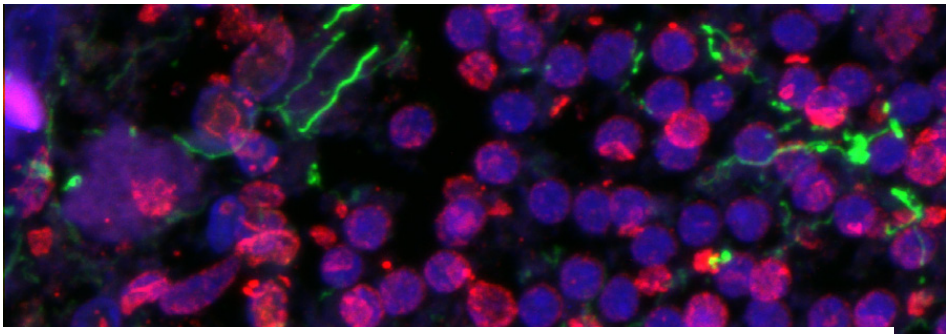
> "We're trying to find patterns in the noise."

"You find this weird thing and then you follow it up." While working in New York, Venneti discovered that childhood gliomas were quite different from adult gliomas. Specifically, childhood glial tumors exhibited different epigenetic markings.

Epigenetics is a relatively new, exciting, and sometimes contentious field that seeks to discover how various biological mechanisms can switch genes on and off. "We think that epigenetics is really important for brain development," says Venneti.

An emerging body of research suggests that many childhood brain cancers are related to epigenetics. For example, some pediatric brain tumors have





Clock-wise from Top: Neuronal stem cells termed radial glia in the developing cerebellum; Neurons and supporting glial cells in the developed cerebellum; Stuffed dog that was given at ChadTough Run that the lab uses as their mascot.

mutations in the enzymes that modify histones, the proteins around which DNA is wound like a spool of thread. Other pediatric brain tumors have mutations in the histones themselves. And in other cases, the byproducts of cancer cell metabolism modify the tumor cell's DNA and histones.

Venneti and his team are working to understand how epigenetics drives pediatric gliomas, how metabolic byproducts influence epigenetics in these tumors, and how this relates with normal brain development. For his efforts, he has already been awarded four prestigious grants: a K08 award from the National Cancer Institute, a Sidney Kimmel Scholar Award, a Doris Duke Clinical Scientist Development Award, and a Matthew Larson Award.

Andrew Lieberman, MD, PhD, the Abrams Collegiate Professor of Pathology and director of Neuropatholoy, describes Venneti's work as "innovative," and likely to yield information that will help define prognosis and guide therapies.

Venneti is excited about the possibilities for his research, but it's the interactions with families like the Carrs that keep him motivated. "We're only as good as our hypotheses and nature is always much smarter than us," he says. "We're trying to find patterns in the noise. Science can be very depressing, so it's important to understand why we do it."

Most recently, Venneti was chatting with a couple, Lisa Carolin and Suzanne Murray, who were selling bread at the Ann Arbor Farmer's Market. Venneti learned that in 2010, Lisa's son had died of an aggressive glial brain tumor at the age of 15. The boy requested that his brain be donated for research. His guitar is now permanently installed in U-M's C.S. Mott Children's Hospital with a plaque dedicated to his memory.

"More than all the minutia of science," says Venneti, it's these human connections that matter to him: "That's what gets me out of bed in the morning."

—

www.venneti-lab.com

More Than a Blood Draw

Taking the pain out of pokes

by **Elizabeth Walker**
Photography by **Dustin Johnston**

A giant mural depicting a cheery forest of tree houses covers a wall in the C.S. Mott Children's and Women's Hospital (C&W) outpatient blood draw station. The artwork serves as a soothing distraction for waiting pediatric patients and their families.

Blood draws account for a significant component of the care provided at C&W. While the facilities are bright and comfortable, the Department of Pathology's Manger of Specimen Procurement, Harry Neusius, SM (ASCP) MBA explains that there's still a clinical air in the environment that can be significant for pediatric patients. "There is a need to calm the anxiety associated with needle-sticks," says Neusius. "It's not just a blood draw. There's more to it than getting access to a vein."

Phlebotomists are the face of the laboratory. They're on the front lines, having an opportunity to influence the patient experience with each poke. In an effort to ease anxieties on both sides of the experience, a two-year study was conducted to look at phlebotomists' self-reported knowledge, training, stress levels, and the techniques used with their patients during pediatric blood draws. The study also gathered feedback from the patients and their parents.

What resulted is a six-part care plan for pokes and procedures, known as the Poke Plan.

Part one focuses on gathering information from patients and their caregivers. "We wanted to give the child a voice, to ask how they want to have their blood drawn. Did they want to lie down? Be held by a parent?" explains Associate Supervisor of Inpatient Phlebotomy, Cindy Straub. In addition to positioning,

questions about helpful distractions, use of comfort measures, and whether or not the patient would like to watch are asked.

The answers are then shared with phlebotomists via an electronic version in the patient's chart and hard copies posted outside of patient rooms on the floors. Julie Piazza, MS, CCLS who was the primary investigator of the study and is a Child Life Specialist, says that families asked for a copy that they could keep. A version in the form of a paper passport was developed for patients. There are also plans to possibly develop an app for the future.

The second part of the plan involves using distraction to help children feel less anxious before their blood draw and to recover more quickly after. Piazza explains that pre-procedure interactions with the child and family are key. Building relationships starts with the phlebotomist introducing him or herself and then gravitating toward conversations that are common and comfortable.

Children may also benefit from counting, singing, blowing bubbles, reading a book, or using an iPad. Child Life Specialists are on call to bring toys and books as requested.

Patient positioning is the key to step three. Positions with some physical contact between parent and child allow each a sense of control.

While some parents may choose not to participate in the poke or procedure, those who do are encouraged to act as coaches before, during, and after a poke in step four. Parents should be aware of how their reaction to the situation may influence their child. Speaking in a calm, soothing matter and acknowledging that it's a difficult situation can be very helpful to a crying child.

Choosing the "best words" for the situation is step five. The rhetoric of the blood draw is an important component of the patient experience. Phlebotomists are encouraged to use "kid's speak" for medical terms. Referring to an alcohol prep pad as a "tiny washcloth", a tourniquet as "a tight hug for your arm", and veins as "tiny tunnels that run all through your body", can lessen a child's fear.

Finally, phlebotomists may use a topical numbing cream when accessing a patient's chest port or devices may be used to draw a child's attention away from the site of draw. A popular device is Buzzy®, which provides vibration in the form of a friendly looking bumblebee.

All of these steps allow phlebotomists to be successful in interacting with their patients and empower parents with inclusion in their children's treatment. "We found in this journey," says Piazza, "that the concern we have for their family member's comfort was key in patient satisfaction."

It's more than just a blood draw and the willingness of all stakeholders to participate in research improves safety, quality, and comfort outcomes.

Funding Great Causes

Our Mission

The Department of Pathology is advancing the future of health care through education, patient care, and research missions. We are committed to achieving the highest standard of service excellence to ensure an ideal experience for our patients and their families.

We ensure that our trainees have a strong foundation for their clinical practice by providing comprehensive training to our residents and clinical fellows and the next generation of research scientists through our Molecular and Cellular Pathology PhD program. Our robust research programs are making significant advances in basic science, translational pathology, drug discovery, and informatics. The department consistently ranks amongst the top ten Pathology departments in total funding from the National Institutes of Health. Many of our faculty members are recognized as international leaders in diagnostic pathology, education, and research.

Support Leaders & Best

In the pursuit of continued excellence in our educational training, clinical care and scientific discovery, the Department of Pathology has always been grateful for private support. Gifts from individuals, foundations, corporations and associations play a key role in medicine at Michigan.

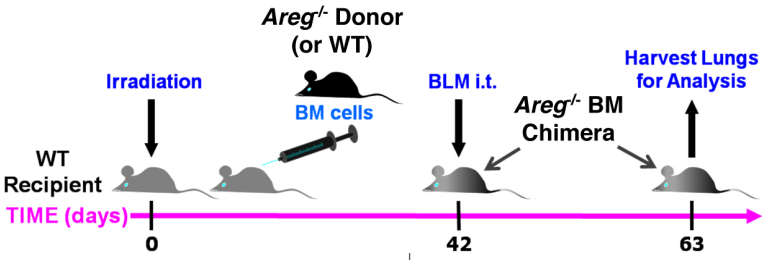
Available Funds

Pathology Faculty Research Fund
Established to support the research programs of faculty in the Department of Pathology

Pathology Resident Research Fund
Established to support research by Residents in our Anatomic and/or Clinical Pathology training programs

Pathology Fellowship Fund
Established to support Fellows in our clinical subspecialty fellowship programs

Research Highlights

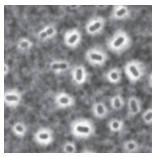


Chronic Lung Fibrosis

Research in the laboratory of **Sem Phan, MD, PhD**, is directed at understanding key mechanisms underlying chronic fibrotic lung diseases. First, the signaling and regulation of gene expression involved in myofibroblast differentiation is of interest since this activated mesenchymal cell is a key player in scar formation. Second, the significance of induction of telomerase in fibrosis appears to be cell type specific. These studies compare the effects of selectively depleting telomerase reverse transcriptase (TERT) in epithelial, mesenchymal or myeloid cells by crossing cell specific Cre expressing mice with floxed TERT mice. Inverse correlation between TERT expression and myofibroblast differentiation leads to studies of how TERT regulates Acta2 gene expression. Finally the bone marrow (BM) responds and contributes to lung injury and fibrosis. These studies indicate recruitment of hematopoietic progenitor cells to the injured lung, where they differentiate into CD11c+ cells. These cells secrete fibrogenic factors, such as amphiregulin, to induce fibroproliferation, myofibroblast differentiation and consequent propagation of fibrosis. These studies have the potential of identifying novel therapeutic targets for control of chronic fibrotic disease in the lung and other organs.

Hospital-Acquired Infections

Dr. Michael Bachman studies the bacteria *Klebsiella pneumoniae*, a common cause of hospital-acquired infections. *K. pneumoniae* can live in a patient's gut without symptoms, a process known as colonization, but then go on to cause urinary tract infections, bloodstream infections, and pneumonia. *K. pneumoniae* is increasingly antibiotic-resistant, and the Centers for Disease Control have declared it part of a group of "nightmare bacteria" because of high mortality. To help address this public health risk, the Bachman laboratory is using a combination of medical chart review, genetic analysis of *K. pneumoniae* isolated from patients, and



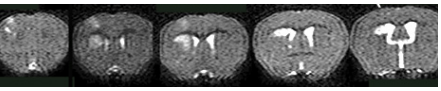
experimental infection models to define the risk factors for infection. They hope to develop new prognostic tests that could identify patients at risk of infection and guide medical interventions to prevent them.

Blood Brain Barrier

The key interface between blood and the central nervous system in health and disease.

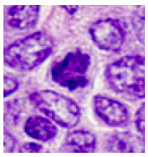
Dr. Anuska Andjelkovic-Zochowski's research focuses on the investigation of the role of the blood brain barrier in the pathogenesis and treatment of neurological disorders. Brain endothelial cells form a highly selective and restrictive barrier due to

complex structures – the tight junctions. Tight junctions are frequently disrupted, resulting in the improper movement of fluid and cells and fueling inflammation and tissue injury. Dr Andjelkovic-Zochowski is investigating protein-protein interactions and multi-protein assemblies within the brain endothelial tight junction and barrier formation. She is particularly interested in how tight junctions are affected and impaired in strokes, cerebral small vessel diseases and diabetes with the goal of developing novel means to correct barrier function and restore health. Recently Dr Andjelkovic-Zochowski's laboratory identified that the signaling molecule PDCD10/CCM3 regulates stability and organization of tight junctions. PDCD10/CCM3 mutation causes cerebral cavernous malformation,



and hemorrhagic stroke in young adults. By dissecting CCM3 downstream signaling pathways, Dr. Andjelkovic-Zochowski hopes to identify potential candidates for pharmacological treatment of CCM3 lesions.

Deregulated Epigenetics as a Driving Force of Acute Myeloid Leukemia

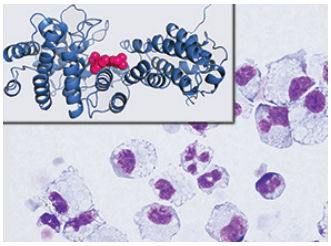


Acute myeloid leukemia (AML) is a cancer of the hematopoietic system caused by acquisition of genetic mutations. It is estimated that over 70% of AML patients harbor mutations in genes coding for epigenetic regulatory proteins, which function to alter gene expression through the chemical modification of chromatin. **Andrew Muntean, PhD** and his lab

aim to understand the epigenetic mechanisms driving AML for translation into more personalized therapies. One area of focus in the Muntean lab is on an epigenetic protein complex, termed the Polymerase Associated Factor complex (PAFc), which functions as a docking platform at gene promoters for several epigenetic proteins of biomedical importance. One such interaction occurs with MLL1, a histone methyltransferase involved in chromosomal translocations in AML. They identified a pro-leukemic gene program controlled by the PAFc-MLL1 complex that is necessary for AML but dispensable for normal hematopoietic stem cells, revealing an attractive therapeutic target for the treatment of AML.

Mixed Lineage Leukemia

Dr. Jolanta Grembecka's research has been focused on the development of new targeted therapies for cancer, with a particular focus on acute leukemias. Recent work from Dr. Grembecka's laboratory has been dedicated to the development of small molecules targeting the protein-protein interaction between menin and MLL fusion proteins as a new therapeutic strategy for acute leukemia patients with translocations of the MLL gene. Her laboratory has developed the first small molecule inhibitors of the menin-MLL interaction that demonstrate strong effect and specific mechanism of action in mice models of MLL leukemia. These compounds have also shown strong efficacy in solid tumors, including metastatic prostate cancer. Current efforts in Dr. Grembecka's laboratory are focused on advancing these compounds to clinical studies in MLL leukemia patients. Her



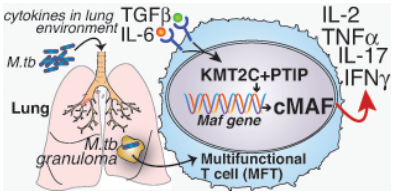
laboratory is also developing targeted therapies for hematologic and solid cancers by blocking novel epigenetic protein targets, including histone methyltransferases.

Multifunctional T Cells May Provide Key to Treating Tuberculosis

Mycobacterium tuberculosis (*M. tb*) has caused a pandemic affecting 2 billion people, thus making this pathogen the most successful organism in the world. Treatment involves a lengthy regimen of antibiotics, often giving rise to resistant strains of *M. tb.* An incomplete understanding of the host immune response has stymied the

development of an effective vaccine or immuno-therapeutic options. The **Steve Kunkel, PhD** and

Matt Schaller, PhD labortories are studying the induction of T cell immunity, a requirement for limiting mycobacterial growth. Traditional BCG skin vaccination strategies fail to elicit a robust T cell immune response. This vaccination method may be suboptimal compared to a lung-associated vaccination strategy. The local lung cytokine environment generates a specific protective T cell immune response that controls pulmonary mycobacterium growth. Their studies reveal that IL-6 and TGFβ, plus antigen, induce a



multifunctional T cell (MFT), expressing the transcription factor cMAF, which controls the down-stream cytokines IFNγ, IL-17, IL-2 and TNFα. This T cell uses an epigenetic mechanism where histone methyltransferase (KMT2C) and an adapter protein, (PTIP) facilitate the binding of KMT2C to chromatin. Their data demonstrate that cMAF expression is reduced in CD4+ T cells deficient in PTIP, ultimately resulting in failure of these cells to differentiate to the MFT phenotype and thus permitting increased microbial growth. Remarkably, the transfer of MFTs into an infected host is able to limit mycobacterial growth. The exquisite specificity of this MFT lung immune response provides the basis to potentially prevent and treat chronic pulmonary *M. tb* infection. The factors required for MFT differentiation may be useful in developing a clinically relevant *ex vivo* T cell based immunotherapy.

Clinical Pathology Symposium
April 24, 2017

Two-day educational event for Pathology medical laboratory scientists and staff geared towards a variety of lab topics. CE credits are applied to the Certification of Maintenance Program (CMP).

Current Topics in Blood Banking
May 2017

Educational program for medical lab scientists, residents, fellows and faculty, designed to discuss topics related to blood banking, hemostasis, quality and management. CE credits offered for medical lab scientists.

Advances in Forensic Medicine and Pathology
May 11-12, 2017

Two-day symposium, held yearly, designed to meet the needs of practicing pathologists, medical examiners, law enforcement personnel, coroners, health care professionals and district attorneys. A distinguished and diverse group of forensic pathology specialists serve as faculty. CME and MColes credits offered.

New Frontiers in Pathology
October 19-21, 2017

Annual two and a half day state of-the-art conference, designed to meet the educational needs of pathologists, residents and fellows. AMA PRA Category 1 CME and SAMs credits offered. U-M Pathologists lead lectures and breakouts with several acclaimed speakers giving plenary and keynote presentations. Attendees are encouraged to bring cases for consultation.

16th Annual Pathology Research Symposium
November 10, 2017

This Molecular and Cellular Pathology graduate student event showcases research within the department by faculty, postdoctoral fellows and Ph.D. students. Platform talks and posters are given and the day is highlighted with an invited keynote presentation.

CHAMPS Research Symposium
February 2018

One-day event showcasing scientific presentations by department clinical faculty and trainees with open discussions for applying lessons learned to attendee areas of interest.

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Find More Events

Visit our website to find more upcoming events and symposiums: *pathology.med.umich.edu/calendar*

Designing for the Future

PRR UPDATE

From **Christine Baker**, Senior Project Manager

Pathology Relocation and Renovation Project

Over the past 5 years, the Department of Pathology's clinical needs have grown at a rate of 7.8% annually, demanding a larger footprint and more efficient space. The multi-year, multi-phase Pathology Relocation and Renovation Project (PRR) will bring much of Pathology together at the North Campus Research Complex (NCRC) and new laboratories at University Hospital (UH) will transform the patient experience, producing better outcomes.

NCRC

The design has been completed. Demolition and construction is underway and on track for completion at the end of 2017.

Duane Newton, PhD, Associate Director of the Division of Clinical Pathology, has been named Clinical Activation Director and is working to coordinate the time frames for equipment moves, how the work is phased, and to manage any clinical implications of the move.

Move Captains from each team meet monthly and a methodology is being put into place to plan and track activation activities. Teams have started choosing furniture for the new space and a group is focusing on communications between NCRC and UH to ensure there are no gaps in clinical care due to the move.

UH Renovation

A comprehensive review of the current state of the labs, including analysis and mapping of key process flows was completed in early 2016. In June, 80 faculty and staff gathered for two days to begin high-level design of the space.

Using "paper dolls", participants laid out the adjacencies and alignment of the space with pieces of paper. The group developed multiple models of how the space could be laid out, and architects/engineers reviewed and analyzed the models. Starting in November, selected spaces will be mocked up in off-site warehouses, giving staff a feel for the spaces and allowing them to make edits based on ideal process flow.

Cancer Cytogenomic Array

by **Lina Shao, PhD**

The Clinical Cytogenetics Laboratory offers comprehensive cytogenetic testing, including standard chromosome (karyotyping), fluorescence in situ hybridization (FISH), and cancer cytogenomic array (CCA) assays. Cytogenetic studies encompass inherited or constitutional disorders such as birth defects, abnormal sexual development and infertility, as well as neoplasia which are mostly hematologic malignancies, but also some solid tumors.

The CCA assay detects DNA copy number gains and losses as well as regions of loss of heterozygosity. It enables detection of genomic lesions as small as several kilo-base pairs, resulting in almost a 100-fold increase in detection resolution when compared with conventional cytogenetic analysis where aberrations need to be greater than several mega-base pairs to be visible under microscopic analysis. It is particularly useful for malignant conditions with a low mitotic index or when limited material is available for cell culture for karyotypes.

The CCA assay in the Clinical Cytogenetics Laboratory uses the Affymetrix CytoScan HD platform (*photo on right*) which has approximately 2.7 million markers, with an average spacing of 550 bp in cancer genes and 1100 bp across the genome. Once a fresh or fresh-frozen sample is received in the laboratory, genomic DNA is extracted and 250 ng of quality-tested DNA will undergo amplification, fragmentation, labeling, and hybridization. The DNA chip will be washed and scanned to read the signal intensity at each marker and compared with an in silico reference to get copy number difference and allelic data.

The CCA assay has been used to improve prognostication in acute lymphoblastic leukemia (1), myelodysplastic syndrome, and acute myeloid leukemia.

Affymetrix CytoScan HD platform

It also detects genetic lesions that assist in differentiation and provide better prognostication in pediatric solid tumors, including tumors of the central nervous system. For example, pediatric gliomas can be challenging to diagnose by histology alone, especially when tissue sampling is limited. A central histology review of high grade glioma revealed a significant number of cases as discordant, the majority of differences resulting from inclusion of low-grade tumors. Pilocytic astrocytoma is a low-grade glioma (WHO grade I) which often has a good clinical outcome and only needs complete surgical resection. However, some features in limited samples may mimic a pediatric malignant high-grade glioma, triggering chemo- and/or radiotherapy. Approximately 70% of pilocytic astrocytomas harbor *KIAA1549-BRAF* fusion, but this is almost never seen in high grade diffuse infiltrating gliomas; therefore, the detection of a tandem duplication associated with *KIAA1549-BRAF* fusion will support the diagnosis of pilocytic astrocytoma. A previously diagnosed pediatric high-grade glioma from a small stereotactic biopsy did not respond to multi-agent chemotherapy after multiple cycles of induction and maintenance therapy. Re-biopsy was subsequently performed and the pathology was more consistent with pilocytic astrocytoma, WHO grade I. The CCA assay detected a duplication of 1.93 Mb at 7q34, consistent with the *KIAA1549-BRAF* fusion and a diagnosis of pilocytic astrocytoma. Given the new diagnosis, no further therapy was given and the patient was in stable condition two years after the second biopsy.

Reference

1. Wang Y, Miller S, Roulston D, Bixby D, Shao L. Genome-Wide Single-Nucleotide Polymorphism Array Analysis Improves Prognostication of Acute Lymphoblastic Leukemia/Lymphoma. J Mol Diagn 2016;18(4):595-603.

Through the Looking Glass

by **Laura Cooling, MD** | *Photography by* **Dustin Johnston**

During medical school and residency, our teachers share many clinical 'pearls' and stories as a routine part of our training. One such tale is the medical school dean who wished a serious medical illness to each medical student class. His strange benediction was a reminder that personal experience is also a great teacher and brings a unique perspective and understanding of the challenges that patients and their families face in dealing with a serious diagnosis. After 20+ years of practice, I considered myself a good and empathetic doctor. I have always been grateful for what patients have taught me about medicine, especially the subtle aspects of disease on daily living and the family. But as the old medical school dean implied, some things can only be truly understood through personal experience. I write this as a doctor and now, a cancer survivor.

In the fall of 2014, I was diagnosed with bilateral multifocal breast cancer. I had discovered a mass and was fully aware that I would require a biopsy, but was not overly concerned since I had a negative biopsy in the past and there was no family history of cancer. My patient experience began when I was called back for a second set of mammograms. One downside of working in healthcare is fluency in our nonverbal communications— the poker face and guarded conversation that indicates an abnormal finding. It was difficult to sit in the waiting room as other women had their mammograms and were released, while I was repeatedly called back for more films, followed by a long diagnostic ultrasound. I thought I was emotionally braced for the bad news but burst into tears when the radiologists told me not to wait for the biopsies: I needed to find a surgeon in the next 1-2 days. I was luckier than most patients. Because I was a doctor, the radiologist offered to perform the fine needle and CT-guided biopsies that day. I am very grateful that I only had to wait for 4 days

"One of the biggest surprises from surgery was the physical toll in terms of fatigue and recovery time—"

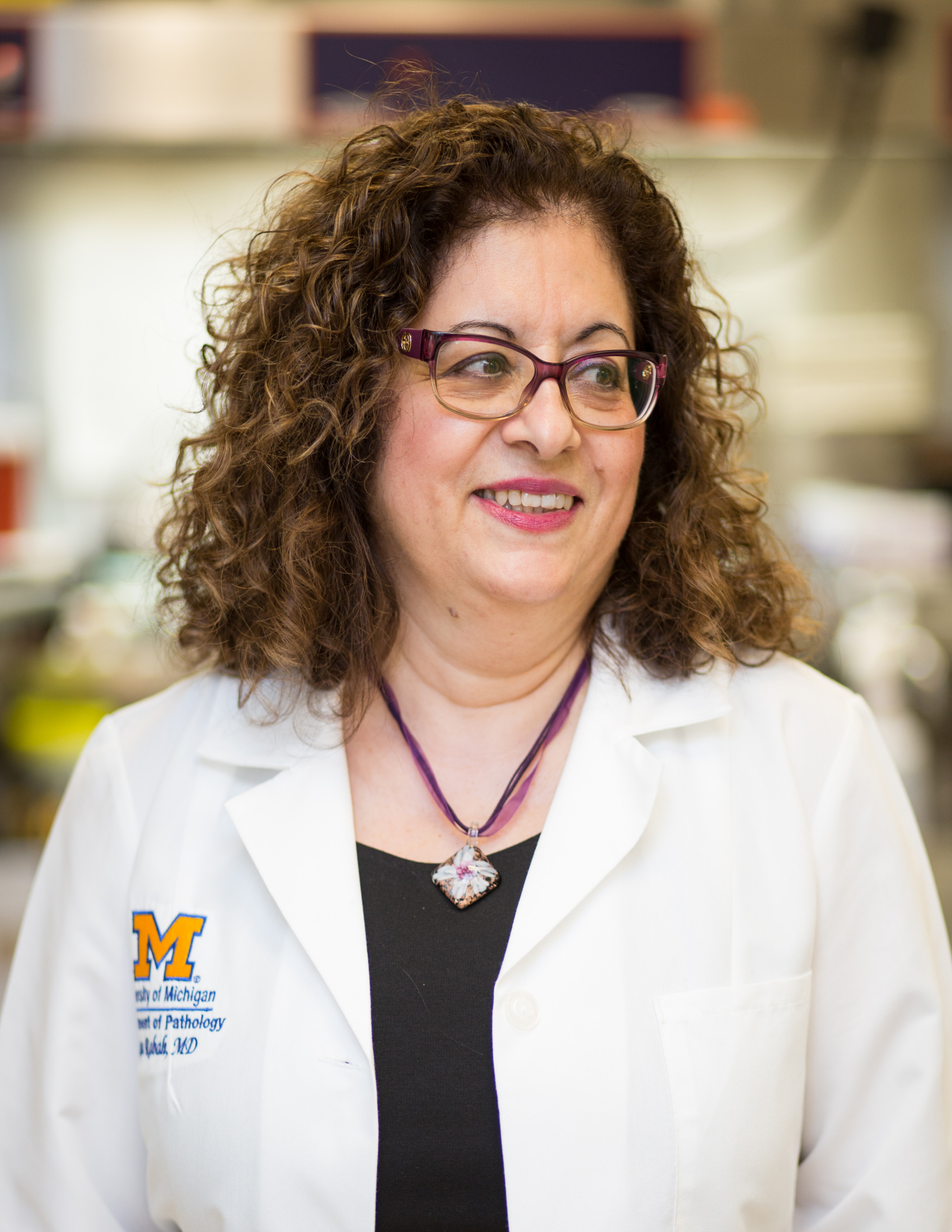
for an answer—I did not have to endure the weeks of doctor appointments, procedures and uncertainty before I had an answer. I have had many patients tell me that the limbo of uncertainty is as stressful as the diagnosis.

They instruct us in medical school that when giving a patient the diagnosis of cancer, the patient will only absorb about 10% of the subsequent conversation. With each visit, the patient will process a little more information as they acclimate to the diagnosis. I experienced that sense of numbness as I read my biopsy report, which I was able to access directly before my physician could contact me. It took me a week to be able to read the full report. Even now, I find it difficult to read my pathology reports and have never asked to see my slides. I am still overwhelmed by the findings and how lucky I was to get diagnosed at stage IIb.

Once given the diagnosis, I was very impatient to make a plan, start treatment and gain some control of the situation. I found myself spending hours online, trying to learn about mastectomies and breast reconstruction surgery. I now appreciate the frustration of trying to see and coordinate care between several specialists and every delay seems like a setback. One of the biggest surprises from surgery was the physical toll in terms of fatigue and recovery time—something I clearly underappreciated over all these years of practice. It took nearly 5 weeks before I could get through the day without at least one nap.

Another highly unpleasant surprise was news that I had positive lymph nodes, which upended my nice, neat time table for returning to work and a normal life. As an academic physician, I felt strongly that I should participate in clinical trials and enrolled in a randomized trial for women with breast cancer and 1-3 lymph nodes. I was hoping to be assigned to the experimental arm (tamoxifen only) which would allow me to return to work and skip chemotherapy, which is the standard of care. I was, however, assigned to chemotherapy and spent New Years Eve in the cancer center infusion clinic. Chemotherapy was unpleasant and difficult, both physically and emotionally. It is hard to keep a positive self-image when you see Gollum in the mirror every morning, but I tried to have fun with an array of very stylish hats. Radiation was not as difficult but did exacerbate and add to the fatigue and exhaustion from chemotherapy. I now really understand medical fatigue and the "wall", where you develop sudden overwhelming exhaustion that can require days of rest to recover. Even 15 months later, I still occasionally hit that "wall" but the episodes are fewer and I can recover over a weekend.

I don't ever want to repeat the experience but it did make me a better doctor, just as the old medical dean predicted. I also learned a few useful tricks, which I have passed on to my stem cell patients and my trainees. It made me appreciate all the good things in my life-my husband, friends and my 'Michigan family'. The support I received from our staff, colleagues and department was wonderful. If I have any advice, it is to send notes, cards and emails to combat the sense of isolation during a serious illness. I treasured and kept every card and note that I received.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The [Smallest] Among Us

by **Leslie Stainton** | *Photography by* **Dustin Johnston**

It was the detective work that first drew her to pathology—the chance to solve the riddles that underlie death and disease.

But it's the humanity of her work that keeps Raja Rabah going: The child who fails to respond to conventional chemotherapy. The mother who doesn't know why her infant died, or whether it's safe to risk another pregnancy. The father who worries that his daughter is genetically predisposed to the same cancer that killed his wife.

It's the families who spent four hours ferrying their dead children to East Jerusalem so that, during the seven years she ran a pathology department in the city's Al-Makassed Hospital, Rabah could diagnose the cause of death, and the families could begin to achieve some sense of closure.

A Palestinian born in the West Bank and raised in Morocco and Syria, Rabah opened a pathology department at Al-Makassed in 1987—not long after receiving her MD from Damascus University Medical School and completing her residency at New York University, followed by a fellowship in pediatric pathology at the University of Pittsburgh School of Medicine. The department was the first of its kind to serve Palestinians in the West Bank.

"It was extremely important for me to go and serve people there," says Rabah, today a professor and director of pediatric pathology at U-M. "Because I knew they had nothing. I felt like I had to pay back."

She knew she was filling a deep need—so deep that although she set out to serve only patients inside the hospital itself, soon people were coming from all over the West Bank to seek her expertise. Soon she was receiving weekly deliveries of tissue specimens from Gaza. "Thursday was my Gaza day," she remembers.

The need was so deep that Rabah stayed on at Al-Makassed Hospital through the First Palestinian Intifada and the First Gulf War. She stayed on through curfews, shootings, suicide bombers. She stayed on despite seeing children killed before her eyes, despite having her car stoned by protesters three separate times while she was driving.

By 1994 the situation was so difficult that Rabah and her husband, physician Adnan Hammad, felt they had no choice but to leave. They were living in Ramallah, in the West Bank, with their two young sons. The drive to East Jerusalem was only twenty minutes, but the checkpoint between the West Bank and Jerusalem closed so often they found themselves routinely trapped on one side of the border or the other. Rabah would get a call from the day care center in Ramallah asking her to pick up her children, but she couldn't get there. Or, like many physicians, she'd get stuck at the checkpoint, unable to reach her job.

Reluctantly, she and Adnan decided to "explore other chances." Through a colleague at Pittsburgh, Rabah learned of a job at Wayne State University, and in 1994 she and her family moved to southeast Michigan. Adnan eventually became director of the Community Health and Research Center at the Arab Community Center for Economic and Social Services (ACCESS) in Dearborn. The couple received U.S. citizenship. For Rabah, it

was the first time she'd had a passport that said "this is your nationality." The West Bank is not a nation, she explains, and although she grew up in Morocco and Syria, she'd never been a citizen of either country.

Rabah stayed at Wayne State for 15 years and then joined the pathology faculty at U-M. In Ann Arbor, as in East Jerusalem, she draws inspiration from the human connections that define her field. To pinpoint the cause of a child's illness or uncover a genetic disposition, she says, to help clinicians outline a course of treatment—"that motivates me. Each child I help, even if it's a simple problem, that's satisfaction."

She's keenly aware that to many people, pathologists are "inhuman," and she's working to change that perception. With a multidisciplinary team at C.S. Mott Hospital, she's developing ways to make autopsy reports more accessible to families, to revise processes and procedures to be more family-friendly. She's long welcomed the chance to meet with families in person and help them understand autopsy reports and diagnoses and their implications—for siblings, for future pregnancies, for the family at large.

"I know people think this is really not human, to do autopsies, especially in children," she admits. "But I think of it as a medical procedure, and my findings are extremely important in many things regarding the grief process for the family." Her reports help parents understand what went wrong and help show clinicians how to care for the next patient with a similar condition. "Knowing that I contributed to the knowledge—and to, I think, the closure of the family—that's an important process overall," Rabah says.

Her small office on the 11th floor of Mott is a vibrant reminder that pathologists are indeed human. Rabah's bookshelves are crowded with mementos from the Middle East and photographs of her grown children. On the wall opposite her desk, she has hung a portrait of the Medieval Arabic physician Ibn al-Nafis, who helped lay the foundations of modern medicine. The painting shows him treating a child. It's a reminder that, as Mahatma Ghandi said, "a nation's greatness is measured by how it treats its weakest members."

While she grieves for her homeland in the Middle East, and the bloodshed that grips the region, Rabah thrives on the knowledge that wherever she lives and works, she is helping to heal the smallest, most vulnerable of human beings—children, some of them just hours old. Under the microscope, she says, "a tumor in a Palestinian child looks exactly the same as a tumor in a child in the U.S." We are bound by our humanity.

LIFE AS A PEDIATRIC PATHOLOGY FELLOW

Interview of Pediatric Fellow Nathan Shaller, MD

by **Elizabeth Walker**

The pediatric pathology fellowship at Michigan Medicine allows trainees a comprehensive educational experience. Based in C.S. Mott Children's and Von Voigtlander Women's Hospitals, fellows have access to over 5,000 pediatric surgical pathology specimens over the course of their year-long program. Additionally, the 212 perinatal and pediatric autopsies and fetal examinations performed yearly prepare trainees to practice general pediatric pathology in an academic or community setting.

Nathan Shaller, our 2016 – 2017 pediatric pathology fellow, graduated with high honors from Ross University School of Medicine, Dominica, in 2012. After graduating, he performed drug-abuse research at Harvard before beginning his residency in pathology at Michigan Medical School.

Q: Why did you choose a career in pediatric pathology?

A: I never wanted to specialize to begin with! I pursued a career in pathology because it casts the widest possible net of patients and disease. Pediatric pathology appealed to me because it's the logical continuation of that philosophy. I could do an autopsy in the morning, and in the afternoon get a stack of surgical cases with skin, liver, bone, head and neck, with maybe a bone marrow thrown in. This is a marvelously complex field that can also be very emotionally uplifting, as every day I work as part of a team of absolute warriors who fight tooth-nail against any process that dares harm a child.

Q: What are the key challenges of a career in pediatric pathology?

A: Pediatric pathology requires dedication to life-long learning. This field is extremely challenging due to its exhaustive breadth of developmental, neoplastic, infectious, and genetic illnesses. It is ludicrous to expect total competency after one year of pediatric pathology subspecialty training. For myself, the biggest challenge has been to keep faith that I eventually will get to a point where I can be persistently confident in my abilities and trust myself.

Q: What's your favorite part of the work you do?

A: I love the wide variety of interdepartmental educational and clinical conferences. Our clinical colleagues in pediatric cardiology, surgery, radiology, oncology, and neonatology are passionate educators and it's a pleasure to be a part of the Mott team.

Q: What are your passions outside of work?

A: I live at home with my mini-pig, Kilo. He's my best friend, and we share the same passions: Sleep, bananas, and belly-rubs.

Q: Where do you see yourself in 10 years?

A: I would like to pursue a career in medical education in addition to pediatric and perinatal pathology, start a family, and raise a whole hockey team.

#7 / 176
NIH National Pathology ranking

18
Endowed Professorships inside the Department of Pathology

509
Number of articles published in FY 2015-16 by Pathology faculty

121
Number of Grants totaling **$31,568,098**

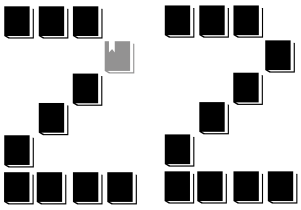
5.4M
Total Clinical lab tests performed

Residency graduates who ***continue their training*** in Michigan

Residents who go on to ***complete fellowships*** in our Department of Pathology

Fellowship graduates who ***practice in Michigan***

Resident Authors



Total number *of residents as authors. Most are first time authors.*

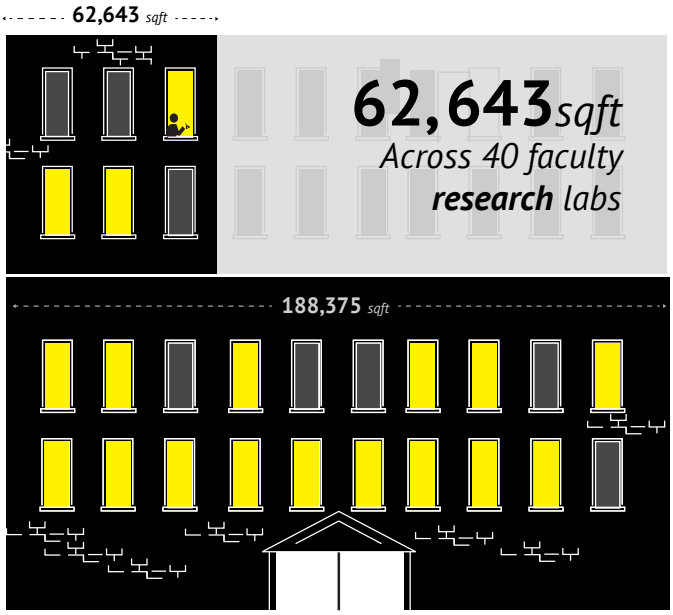
Applications

Number of Applicants for Residency and Fellowships ...

432

To occupy **6** *positions*

Number of Labs / Square Footage



188,375*sqft* | *Total Square Footage*

107,715

Anatomic Pathology ***surgical specimens in FY 2016***

1 | Dr. Richard Lieberman received the Outstanding Consultant Award by Michigan Medicine Ob/Gyn Residents.

2 | Dr. Allecia Wilson became the Director of the Anatomic and Clinical Pathology Residency Program.

3 | Pathology Imaging Specialist, Mark Deming *(left)* seen here with Eugene Napolitan, retired in June after 37 years with the department.

4 | Jiaqi Shi, MD, PhD, joined the faculty as a Gastrointestinal Pathologist.

5 | The University awarded Dr. Henry Appelman with the prestigious Lifetime Achievement Award in Medical Education.

6 | Lauren Smith, MD, was named one of the Michigan Medicine Hospital Ethicist.

7 | Dr. Diane Roulston retired from cytogenetics.

8 | Dr. Julia Dahl was recruited as the Associate Director of MLabs.

9 | Hemamalina Ketha, PhD joined us as Director of Toxicology and Drug Analysis and Associate Director of the Clinical Chemistry Laboratory.

10 | Dr. Laura Lamps became the new Director of Gastrointestinal Pathology, replacing Joel Greenson. She's also Michigan Medicine's first Administrative Director of Patient Safety.

2016 Pathology Resident, Fellow and PhD Graduates

We are proud of all our trainees and look forward to future interactions with them. Listed here are their accreditations, areas of interest and where they are presently located.

Residents

Kristina Davis, MD
Transfusion Medicine Fellowship
Mayo Clinic

Andrew Hanosh, MD
Forensic Pathology Fellowship
Medical Examiner's Office in Denver, Colorado

Sandhya John, MD
Cytopathology Fellowship
Beth Israel Deaconess Medical Center

Carlos Murga, MD
Hematopathology Fellowship
University of Michigan

Nathan Shaller, MD
Pediatric Pathology Fellowship
University of Michigan

Reena Singh, MD
Gynecologic Pathology Fellowship
University of Michigan

Fellows

Ahmed Alomari, MD
Dermatopathologist
Indiana University School of Medicine

Ruth Asirvatham, MD
Surgical Pathologist
University of Florida

Jason Brazelton, MD
Hematopathologist
Private Practice, Bend, Oregon

Bronwyn Bryant, MD
Surgical Pathology Fellowship
University of Michigan

Karen Choi, MD
Gatrointestional Pathologist
University of Michigan

Amanda Fisher-Hubbard, MD
Forensic Pathologist
Western Michigan University

Elizabeth Gutmark, MD
Dermatopathologist
Private Practice - DTLA Derm

Charles Harmon, MD
Blood Bank Fellowship
University of Michigan

Vivian Hathuc, DO
Hematopathology Fellowship
University of Michigan

Carolyn Haus, MD
Surgical Pathologist
Genesys Regional Medical Center

Jennifer Hipp, MD, PhD
Surgical Pathologist
University of Toledo Medical Center

Martin Ishikawa, MD
Forensic Pathology Fellowship
University of Michigan

Sean Li, MD, PhD
Blood Bank and Chemical Pathologist
University of Michigan

James Lozano, MD
Forensic Pathologist
Charlotte, North Carolina ME Office

Andrew McDaniel, MD, PhD
Surgical Pathologist
Private Practice - Ameripath, Indianapolis, IN

David Moons, MD, PhD
Forensic Pathologist
Wayne County ME Office

Pawel Mroz, MD, PhD
Molecular Genetics Pathologist
University of Michigan

David Seward, MD, PhD
Molecular Genetic Pathologist
Vermont Medical Center

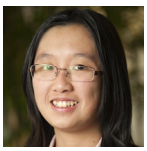
Hongliu (Daisy) Sun, MD, PhD
Cytopathologist and Surgical Pathologist
University of Toledo Medical Center

Aaron Udager, MD, PhD
Surgical Pathology Fellowship & Faculty
University of Michigan

Nilam Virani, MD
Cytopathologist
McLaren Health Care

Molecular & Cellular Pathology - PhD

Amy Han, PhD
University of Michigan

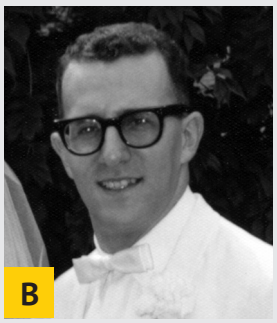


Shirley Lee, PhD
Cayman Chemical, LLC

Jonathan Pollock, PhD
Vividion Therapeutics

FLASH FROM THE PAST

Can you guess who these individuals are? They were all experts in their fields and are current Emeritus members of the department.



A. Constance D'Amato; **B.** Eugene Napolitan; **C.** Bernard Naylor

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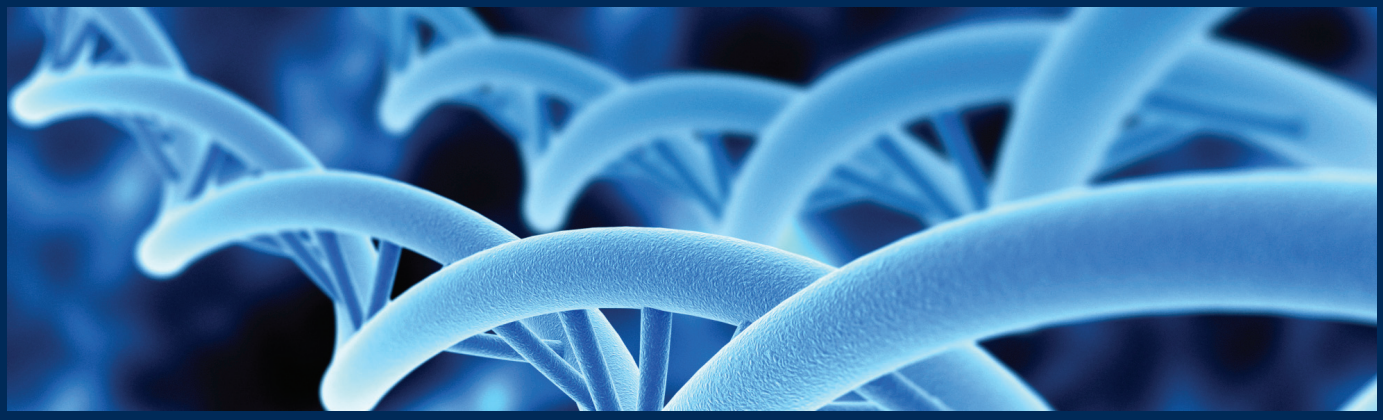

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