# INSIDE PATHOLOGY

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

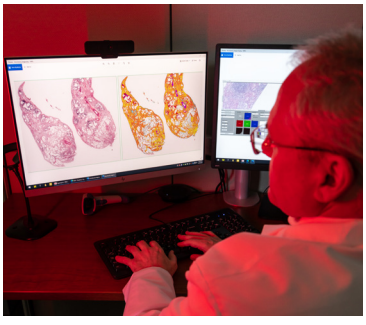
2022

# CONTENTS

INSIDE PATHOLOGY
2022 ISSUE



## On the Cover



*Photos:* Camren Clouthier
Dr. Pantanowitz demonstrates using machine learning in analyzing slides.

## Sections



**Department Chair**
Charles A. Parkos, MD, PhD

**Editorial**
Lynn McCain

**Photography**
Camren Clouthier

**Layout Design / Digital Artwork**
Brent Temple

**Find Us Online / Give Online**
*www.pathology.med.umich.edu*
If you have questions about philanthropy or establishing a gift to support the work of the Department of Pathology, please contact:

**Jason Keech**
jkeech@umich.edu
or 734-763-0866

**Stay in Touch**
To update your contact information, please e-mail Pathology Communications:
*path-communications@umich.edu*

There is a misconception regarding the breadth of career opportunities in the field of pathology. Many people, including many medical students, believe the field is limited to autopsy pathology. This has contributed to decreasing numbers of medical students applying for residency training in pathology. With a growing number of pathologists nearing retirement age, a serious national workforce shortage is looming. While the Michigan Medicine Department of Pathology is not immune from this challenge, we have the capacity and resources to train the best and brightest to be experts in more than 20 pathology subspecialties while supporting robust educational programs and research that offers a truly well-rounded academic experience. There are many fine academic pathology departments in the country, but ours is one of the very top programs. In addition to consistently being in the top 10 nationally in research, we offer outstanding educational opportunities for clinical training in many subspecialties, including pathology informatics.

The number of subspecialties in pathology is comparable to that in other fields of medicine. For those interested in clinical laboratory specialties, options include blood bank, chemistry, microbiology, toxicology, immunology, and molecular diagnostics, to name a few. Those interested in tissue-based pathology, termed anatomic pathology, can choose to focus on diseases of the skin, gastrointestinal tract, lung, breast, reproductive tract, blood system, forensics, and many others. To complement these subpecialized areas, there are innumerable opportunities in research, education, and information technology. There are even opportunities for those interested in direct hands-on patient care. Cytopathologists, for example, perform fine needle aspiration procedures targeting the thyroid, breast, and other tissues to aid in diagnoses of a variety of conditions. Abundant direct patient interactions also occur in apheresis and the blood bank. These are patient encounters that have gratifying aspects similar to those in family practice, for example, or being a clinical internist. Thus, pathology offers very broad and exciting career opportunities. A very underappreciated fact is that many of these specialties are significantly undersubscribed, providing immediate and excellent job opportunities.

At Michigan Medicine, there is a strong institutional commitment to the tripartite mission, including patient care, research, and education, and the

future remains very bright for pathology. The impact of genomic medicine on diagnostics, particularly in tumors and rare diseases is rapidly expanding as is pharmacogenomics, which shows promise for someday predicting the effectiveness of different drugs in individual patients. These areas will continue to grow and impact our specialty in a dramatic way.

Digital pathology is another opportunity with an exciting future that will grow over the next decade and impact many areas of pathology. Now FDA approved, pathology diagnoses can be rendered remotely. Digital pathology will surely enable the creation of centers of excellence offering highly specialized diagnostic/interpretive services. Given future workforce shortages, such centers of subspecialty expertise will provide remote access to expert care for patients regionally, nationally, and globally.

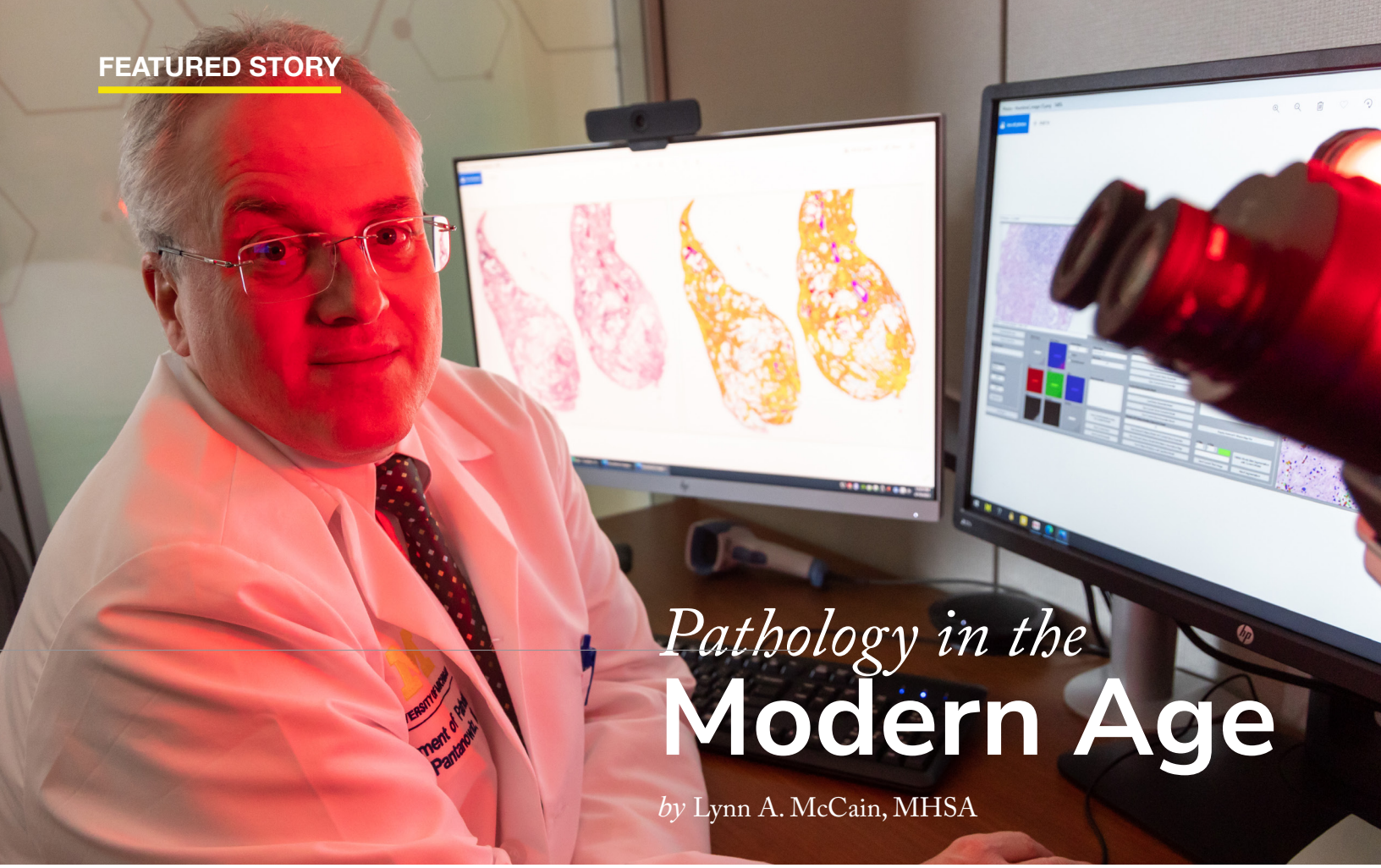
Equally exciting is the growth of pathology informatics. We are fortunate in this department to have a division of pathology informatics such that we can not only train informaticists in pathology, but partner with the health system informatics unit to offer laboratorian-based informatics expertise that not only spans intricacies of laboratory information systems but will be essential for integration of digital pathology and genomic pathology into pathology and health system workflows.

Outstanding scholarship opportunities also arise from our robust translational and basic science research program. This past year, more than 570 publications emanated from the department, and our grant funding success has continued to be extremely robust. We strongly support funding research projects for our residents and clinical faculty who spend a majority of their time in clinical service and training.

For individuals who may be considering a career in pathology, I encourage you to become fully informed and understand the specialty's many options. If you make the right choice, you have the opportunity to do what really excites you and experience an excellent work-life balance. There are endless translational or basic research opportunities that can be complemented by what you see under the microscope or in sophisticated assays of fluids/tissues derived from patients. Pathology has something for all academic interests. I welcome anyone to explore pathology as an exciting career pathway and learn about all the ways that our specialty makes a huge difference in people's lives every day.

**Charles A. Parkos, MD, PhD**
Carl V. Weller Professor and Chair
Department of Pathology
Michigan Medicine

FEATURED STORY



# *Pathology in the* Modern Age

*by* Lynn A. McCain, MHSA

The 1990s was a time of advancements toward a future of lasting change in the world. Grunge and hip hop were new, and cable tv came on the scene. The Hubble telescope was launched, and Dolly the sheep was the first mammal cloned from an adult somatic cell. The internet was booming as more businesses and households were purchasing personal computers, bringing in a new era of communication. And Pathology was stepping into a new frontier of what would become digital pathology. Dr. Ul Balis, Professor and Director of Pathology Informatics at Michigan Medicine, was at the forefront of this new field. Balis built a real-time telepathology linkage between the James A. Haley VA Hospital and the Bay Pines VA Hospital while in medical school, one of the first of its kind. With this, images viewed at one site could also be seen at the other, basically roboticizing a microscope. And the era of digital pathology was launched.

Throughout the 1990s, Balis continued to work in digital pathology, sitting on the College of American Pathology Informatics Committee and forming the Image Exchange Committee, which created the first Digital Imaging and Communications in Medicine (DICOM) standard for digital pathology, the visible light standard; ratified in 1999. In 2000, he began advising Aperio, the developer of the first whole-slide imaging scanner. Through his and others' efforts, this nascent field continued to grow and expand. On the other end of the spectrum, Dr. Liron Pantanowitz was serving as the Director of Pathology Informatics at Baystate Medical Center, one of the hospitals affiliated with Tufts University School of Medicine, when in 2005, he was asked to bring on an image analysis system for breast biomarkers. He discovered there were few resources and very limited knowledge on how to do this at the time. It required significant effort, but he successfully implemented such a system and then continued to work in the field, promoting the field of digital pathology, developing national guidelines, and engaging with organizations that educate about digital pathology.

Fast forward 17 years and today there is a broad field entitled Computational Pathology that encompasses anything that has to do with computers in the field of pathology. Under this umbrella, there are whole-slide imaging systems, artificial intelligence, computer vision, as well as all the standard information systems, computer-aided laboratory equipment, and computational programs. Computer vision uses machine learning

and "deep learning" to translate digitized slide images into diagnostic images using heat maps and other features to identify the areas of the original image most likely to contain abnormal cells or structures. Machine learning occurs when algorithms learn from the data you input to classify that data in a specific way. Training is supervised or semi-supervised by a subject matter expert. Deep learning, on the other hand, utilizes artificial neural networks, often hundreds of layers deep, to perform analyses and to make decisions on its own. It works utilizing a completely unsupervised process, although the results are still reviewed by subject matter experts. "Deep learning requires large data sets of images, for example, and the algorithm itself decides what features distinguish classes of images and what those features are. It has the potential to extract novel classification and grading systems that pathologists don't currently use based on an entirely novel set of visual cues or features," explained Dr. Jerome Cheng, Associate Director of Pathology Informatics. "It is very powerful, but it is also potentially very dangerous in that it may be detecting artifacts. It has to be used with subject matter expertise as oversight." Balis expanded, "Deep learning is certainly the newest set of tools in our toolbox, but it should not be considered the only tool. It is one of many and it works in some cases and it doesn't work in others. It needs to be thoughtfully applied."

Deep learning has exciting potential applications, according to Pantanowitz. "What if we train the algorithm to do much more than a pathologist can do at the microscope? What if we want to predict who will respond to therapy and who will not? What if we wanted it to predict who will recur with a disease and who will not? Who will be alive in 5 years and who will not? Today, we use things like stage and grade in cancer to come up with some sort of a prediction. But deep learning has the capability of an artificial brain, and it is exciting that Jerome and Ul can write these algorithms for us to do so much more than pathologists can do at the microscope. That is why we are investing in the technology and that is why we want to bring it on in-house – to be able to do those kinds of things."

Deep learning is a "future state" application being developed in pathology, but in the present, the Department of Pathology continues to move forward with digital pathology applications. Digital pathology is the process of taking pathology assets, such as tissue slides, culture smears, etc. and converting them into digital images. "Then the pathologist remotely accesses and controls a computer, which in turn, controls a robotic microscope," explained Peter Ouillette, Digital Pathology Operations Manager. "This gives the pathologist the freedom to remotely manipulate the microscopic image, look at the tissue, and focus as they see fit." The department has used digital pathology, specifically whole-slide imaging, since 2006, primarily in education and research settings. "We have built up a public repository of whole-slide images for use by pathologists and trainees here at Michigan as well as around the world," said Ouillette. This has enabled faculty and trainees to become comfortable with the technology. In education, residents and fellows are able to view digital slides as part of their training from any location–whether they are at home, on service at the hospital or in the resident suite at the North Campus Research Complex. The large digital slide library enables researchers to access the assets they need for their research projects, publications, and presentations without ever leaving their office or lab.

Telepathology, which utilizes whole-slide images, robotic microscopy and/or real-time video streaming viewed remotely, has significantly expanded the ability of pathologists to support the clinical work of Michigan Medicine. A large proportion of the tumor boards now utilize this technology. Rather than having specialists from around the medical campus meet in a conference room to discuss cases, they view the cases remotely and meet virtually, which enables broader representation at tumor boards and improved patient care.

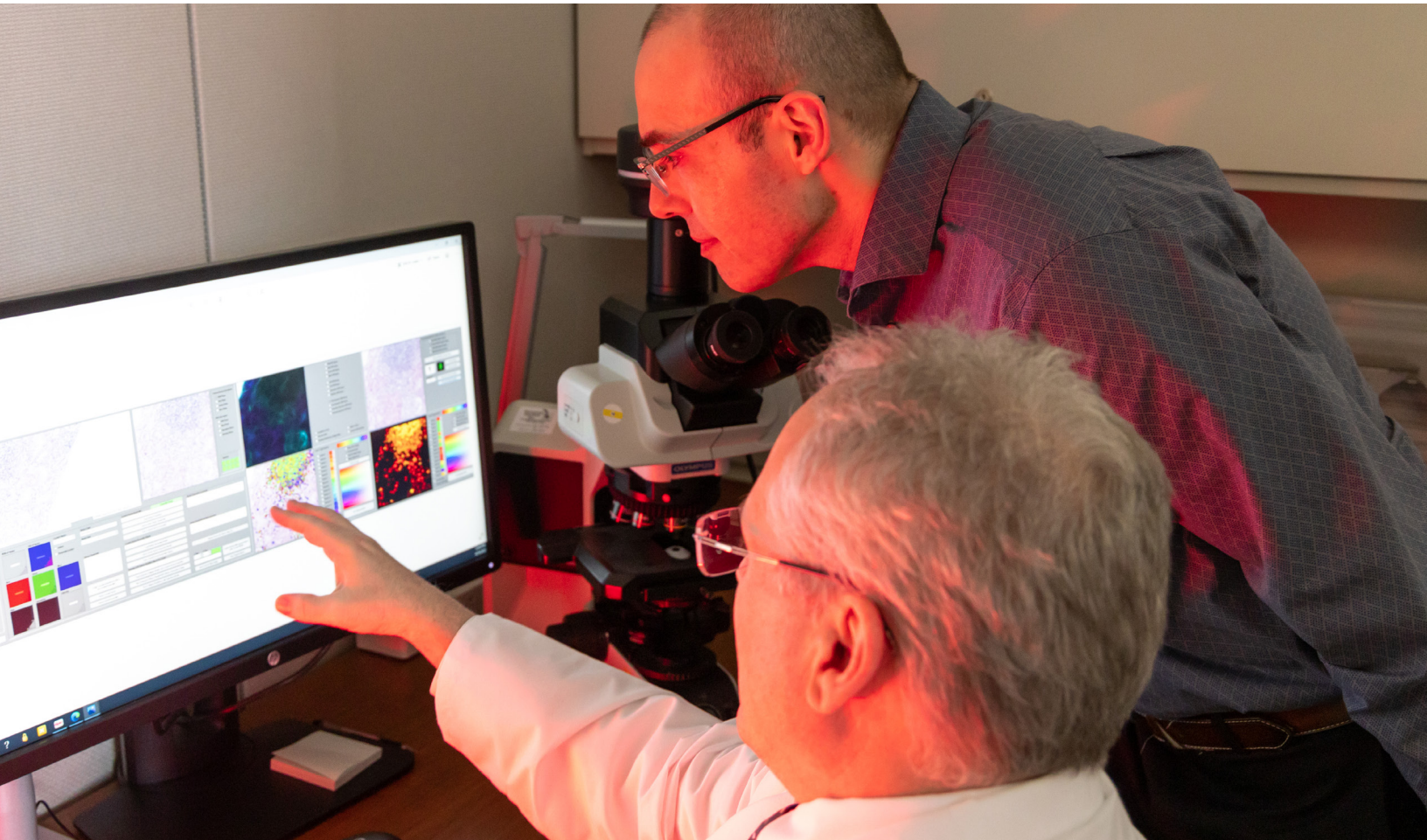
In addition to simply viewing digital images, the department is increasingly using image analysis, which uses algorithms to identify and quantify areas of interest. "In breast pathology, all our newly diagnosed breast carcinoma cases are analyzed using quantitative image analysis (QIA). Each of these cases have biomarker studies completed on them, ER, PR, and HER2/neu. QIA is also used to evaluate Ki67 (a proliferation marker) for neuroendocrine tumors. Using QIA, we now have a very standardized analysis and reporting mechanism, so it doesn't matter which pathologist is on service. They all use the same yardstick," explained Pantanowitz. "In fact, this is so reliable that we have outside hospitals send us their cases to report on."

"To date, our digital efforts have all been confirmatory analyses performed after the pathologists had reviewed the slides. As much

as we wanted to do so, we were unable to bring this technology to the general clinical setting for primary diagnostics due to regulatory constraints," explained Pantanowitz. "With the onset of the pandemic, however, many of these constraints were lifted, enabling pathologists to diagnose cases remotely." Over the course of the pandemic, the department moved from confirmatory analyses to limited primary diagnoses using digital pathology. Pathologists were having to quarantine, or they couldn't come to the clinic due to childcare issues or other pandemic-related issues. Processes were validated and regulatory requirements, some of which were under waiver, were met. The Pathology Informatics team then provided pathologists with the technology and training needed to perform remote diagnoses for patient cases. "While everyone is now back to work, some of our pathologists don't want to give up the convenience and flexibility of remotely utilizing digital pathology." Pantanowitz illustrated this point, "We have one faculty member who couldn't come to work for several weeks. He was able to continue signing out cases from home. Now that he is back to work, he doesn't want to give that up! He loves the convenience."

Balis added, "In addition to using digital pathology for primary diagnoses, this application is ideal for intraoperative consultations and rapid onsite evaluation in cytology to ensure specimen adequacy during biopsies and fine needle aspirations. The pathologists can ensure proper samples were procured without leaving their offices. They are virtually 'at the patient bedside' looking at what is coming back from CT-guided or other aspiration biopsies from multiple surgical suites at the same time." This means that patients undergoing biopsies spend less time in procedure rooms awaiting pathologist consultation completion. It can take 20-30 minutes for a pathologist to walk from the University Hospital to the Mott Children's and Women's Hospital to perform these frozen section tissue reviews. In addition to the hospital surgical suites, there are also several located at outpatient sites. It is not feasible to keep each site fully staffed with neuropathologists, frozen section support, cytopathologists, and other services on a daily basis. "This has allowed Michigan Medicine to open up endocrine clinics and still do thyroid FNAs with onsite evaluation in convenient facilities around Michigan Medicine," said Pantanowitz. "In the future, it may be easier for certain outside healthcare providers to send us their images for consultations than to mail us slides and blocks, which expands our reach and reduces turn-around times for consultations." In addition to the surgical reviews, the microbiology

**Below:** Dr. Pantanowitz (bottom) working along Operations Manager, Peter Ouillette.



laboratory has found digital pathology to be particularly useful. Whole-slide imaging of smears and stains of bacteria, parasites, and fungal organisms are viewed and diagnoses made quickly, which can allow patients to receive the appropriate antimicrobial therapy sooner, which leads to better patient outcomes.

Beyond standard digital pathology is a newer application utilizing deep learning to provide image analysis on slides prior to pathologist review, which streamlines workloads for pathologists. Cheng is actively developing these applications for use in pathology. "The pathologist is actively directed to what needs to be reviewed, where the highest value locations are on the slide. This is more efficient, and pathologists are less likely to miss major findings because the slide has already been pre-screened. It is like having a digital resident or fellow."

While the promise of digital pathology is exciting, there are some very significant barriers slowing its adoption. First, training the algorithms used in deep learning applications is extremely time consuming and requires very large data sets. This is unreimbursed time, which is costly. In addition, the data storage and processing needs are intense and require large, high-powered computing clusters, either in-house or in cloud based servers, both of which can make any positive return on investment nearly impossible, especially since insurance coverage for digital pathology is minimal. These barriers need to be examined and overcome before digital pathology will live up to its promise. Other barriers include regulatory constraints. While the lab itself is not regulated by the FDA, some of the equipment is, which limits which equipment can be utilized.

In addition, the Clinical Laboratory Improvement Act (CLIA) stipulates lab operations must take place within a CLIA-certified facility. While this is currently waived for digital pathology, if the waiver is lifted, it will prevent digital pathology from reaching its potential. Finally, laboratory information systems often don't integrate well with digital pathology systems, which can make it challenging to implement. There are no pathology informatics interoperability standards, which need to be developed for digital pathology to reach its true potential.

In spite of these barriers, the field continues to advance. One exciting opportunity is use of 3-D images of organs for diagnostic purposes. 3-D imaging is already in use in other medical fields, such as radiology, and in very limited use in a few pathology settings. While this technology is not yet being utilized in pathology at Michigan Medicine, it is on the roadmap. 3-D imaging is an excellent option for Anatomic Pathology's gross examinations, where shape, color, and texture are used to determine disease state or cause of death in forensic applications. These images can be used for education, research, courtroom testimony, as well as in making diagnostic findings. The images can be viewed in 2-D, as on a computer screen, or in 3-D using virtual reality appIications. In addition, 3-D imaging can be used with 3-D printers to produce replicas that can be viewed and handled. These printers are now capable of creating life-like specimens using as many as 10 million colors for realistic representations. Transplant patients, in particular, appreciate the ability to view and handle explanted organs. Currently, "plasticized" organs can be used to educate patients. This is an expensive process, however, so patients are generally able to view only representative organs, not their own. The 3-D models allow for safe handling of otherwise biohazardous specimens and patients will be able to physically see accurate replicas of their own explanted organs.

Another advance is the use of light-sheet microscopy for slide-free, non-destructive ex-vivo microscopy (EVM). Light-sheet microscopy is a fluorescence microscopy technique with unparalleled ability to rapidly collect 3-D microscopic information from intact specimens. Open-top light sheet microscopic imaging is particularly well-suited for use in Pathology. The advantage of this method is that the tissue can be examined at multiple depths, which can provide a more complete diagnostic picture than a fixed slide image seen under a microscope, while maintaining a very similar look to the actual slide images.

Finally, "in vivo imaging" – imaging done in the patient without ever making a slide, is advancing. Dr. Sandra Camelo-Piragua, a neuropathologist in our department, has been working with neurosurgeons to image brain tissue during surgery. "They use magnetic resonance spectroscopy, and she helps them interpret the images in the patient. Right now, tissue is still being submitted for correlation, but this may eventually eliminate the need for tissue," explained Balis.

The field of pathology has come a long way since the 1990s, and more exciting advances are on the horizon. The Department of Pathology at Michigan Medicine has the expertise to continue to move the bar forward in both creation of new advances as well as in adoption of new applications. It is an exciting time in pathology. Stay tuned… there is more to come!


# From Red to Blue

*by* Lidija A. Fremeau & David Golden

When Nebraska plays U-M, Omaha native David Golden wears maize and blue. Though his Bachelor of Science in Biology, and his Master of Business Administration are from the University of Nebraska - Lincoln (UNL), he has been a faithful and respected employee of U-M since 1990. The chant of "Go Blue" struck David's ears as unusual at first, seemingly lacking a syllable after years of "Go Big Red." David feels that the Wolverines certainly deserve his loyalty now. He was originally hired to computerize zoological collections at the Museum of Zoology on main campus. In January 1994, he transitioned to Michigan Medicine's Department of Pathology.

David Golden is the Director of Finance in Pathology, while also filling in as the Department's Interim-Chief Department Administrator (CDA) following the unexpected death of Marty Lawlor in October 2021. David described Marty's leadership during a Zoom interview saying, "Marty was not somebody who micromanaged. He trusted the people around him and let us make decisions. We'd ask 'Are you okay with that?' And usually the answer was 'yes.' He understood pathology very well, and how to get things done." In contrast, David describes himself as more detail oriented. "Marty was a big picture guy. I'm more operationally focused. I'm a numbers person. This is how we differed. I'm not a micromanager, but I like to understand the details. I have to in order to do my job well." This has required a shift and how he approaches his job since becoming the interim CDA.

Regina Ferguson, Pathology Facilities Manager for Clinical & Research Pathology, fully appreciates David's efforts as he manages both roles. "We all knew Marty, we see visions of him passing in the hallway. When Marty got sick, we all jumped in together. What do we need to do?" In particular, she notes David's willingness to dive in. "It was needed; he just did it." And even with him pulling double duty, if she asks David for a moment, "He always makes time. He juggles it all."

Dr. Jeffrey Myers, Vice Chair for Clinical Affairs and Quality, adds, "David's calm, 'can-do' approach has not wavered despite the pressures that he inherited as interim CDA. He is serving during a time of unprecedented demand for a role already spread too thin, and in all of it maintains the same level of respect, kindness, and 'aw shucks' country boy modesty that is his brand. Truth is, David could and should serve as a role model for others who aspire to this role permanently."

With this additional level of responsibility, David definitely has more on his mind these days, and sleep is a little tougher to come by. With a cup of coffee in hand, David starts each morning reviewing his emails and planning what he wants to accomplish each day. David's day is spent meeting with a wide variety of individuals from across the Department and Michigan Medicine. His day can go any number of directions depending on what is needed to keep the department operations running. His added role has changed his language. He used to make statements such as "This is what I think is happening." Now, he says "This is what we're doing."

David is grateful to a long list of people who have helped him transition into a dual role executive. Both Kristina Martin and Christine Rigney, Directors of Operations, Division of Clinical/Anatomic Pathology respectively, who have helped fill in the gaps on the clinical side of things with which he hadn't much prior experience. Additionally, "I've relied heavily on my own staff: Kristina Andoni, John Harris, Christine Shaneyfelt, Sarah Dudley-Short, Nancy Parker, Jennifer Mattison, Rebecca Roberts, and Mike McVicker. They've reported to me, and I've shifted the work to them now."

He credits Regina Ferguson, Peggy Otto, and Yvonne Beadle with helping him to prioritize the many demands for his time. Support for David comes from many angles, including from Chair Dr. Charles Parkos, Vice Chairs Dr. Jeffrey Myers and Dr. Kathleen Cho, the department's Division Directors and the rest of the faculty. Matthew Comstock, Executive Director for Administration of U-M Medical School, Tony Denton, Senior Vice President and COO of UMHHS, and Scott Marquette, Associate COO for UM Health Operations and Safety Preparedness, have also reached out to ask how it's going, to inquire if David has any questions or needs any help.

This network is what keeps David inspired. "I spend a lot of time with these people, and they're family. I think that inspires me to support our faculty to the top of their level and provide them guidance and a pathway to success." Likewise, when asked what his proudest accomplishment has been, he thought for a moment and replied, "The team that I've built. Some people have been working for me nearly the whole time. They make my job a pleasure to come to everyday. I am most proud of the people I've hired and inherited."

The feeling is mutual. Christine Shaneyfelt, Senior Financial Analyst, who has reported to David for fourteen years, describes David as a "supportive, respectful, and appreciative leader. Working for David has been a pleasure as his approach is easy going and it makes the workplace feel a bit less stressful especially during the ever-changing environment. David is also compassionate. While dealing with a very tragic event a couple of years ago in my life, he would check in to see how things were going - if there was anything he could do or if I needed any help with work. This was very much appreciated and helped lessen the stress I was feeling at that time."

With a nearly thirty-year history in the Pathology department, it seems almost intuitive that David has stepped up to fill in as Interim CDA. He described a much smaller department when he first started. The job included billing in pathology. "We used to run our own billing office. Everything was centralized. We used to post payments. We don't do that anymore. Claims processing and payment posting have been centralized outside the Department." As the department has grown, and managers have left, he has progressively assumed roles and responsibilities. David has gone from managing a section of the finance office to the entirety of the department.


In his youth, David thought he wanted to be a medical doctor. In high school, a love of biology was born, and David had intended to study Ichthyology, the study of fish, in graduate school.

As an undergraduate student at UNL, he wrote and published "An Ichtyological Survey of Weeping Water Creek, Nebraska" in 1987 while studying in Dr. John D. Lynch's research laboratory. Ultimately, David chose to pursue an

MBA for graduate studies because "it would yield more opportunities and provide better financial security." Pursuing an MBA has served him quite well.

David and his wife Krista Golden, M.S. met at Cedar Point Biological Station, not to be confused with the amusement park 115 miles from North Campus. David spent five weeks at this Western Nebraska facility, taking classes to get to graduation a bit sooner. The young couple moved to Ann Arbor where the weather is not as extreme as Nebraska. They were well equipped to handle the moody Michigan seasons with ease. Though David used his blended interest in biology and numbers to end up in the Pathology department, Krista stuck with pure science and is currently a Research Laboratory Specialist for the Desch Lab researching blood disorders, specifically thrombosis and hemostasis.

The Goldens have sent their two adult daughters out to the world. One is pursuing a screen writing career in Los Angeles. The other, a professional chef, has a catering and food truck business in the Lake of the Ozarks. These "kids" were front of mind when asked if David had a moment to spend with the twenty-year-old version of himself, what would he advise? "Things are going to turn out pretty good, really. Don't worry about the small stuff. Enjoy the time you have with your kids. It's so much work, and now I miss it. I have to call them instead of seeing them every day. There were so many activities around the kids: dance lessons, gymnastics, soccer, piano. I had so much fun doing that. I miss that stuff."

There is more to David than just finance and making decisions for the department. The empty nesters enjoy their evening walks with Lucy, the family's 13-year-old Whoodle: Wheaton Terrier and Standard Poodle mix. Golf is a biweekly pursuit for David at Radrick Farms Golf Course. Soon, perhaps another sailboat will enter the scene. David learned to sail when a friend needed a crew member for Wednesday night races on Lake Erie. He was quickly hooked. As a couple, the Goldens enjoy traveling and have adopted a Michigander's appreciation for "up north" and the west coast of the state.

David considers himself introverted and private. Spending nearly an hour talking about himself was likely not his favorite pastime. His energy shifted when he spoke of his family members and coworkers. He certainly preferred to talk about them more than himself. Regina Ferguson calls him a gem. "Talk about a down-to-earth individual who cares about the person. Family is important. And he and his wife care. That carries into the professional life." David has now lived in Ann Arbor for more years than he did in Nebraska. He has raised a family at home and cultivated a warm, trusting, and sincere atmosphere around himself at Michigan Medicine Pathology.

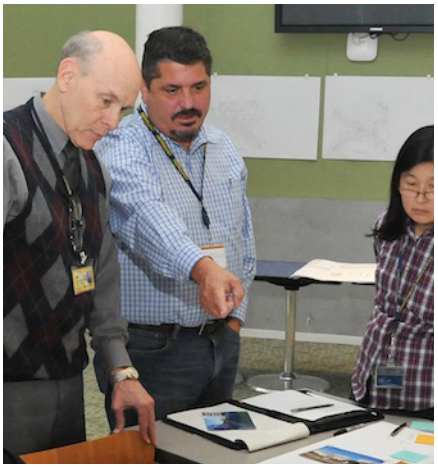
# Martin Lawlor

October 1964 – September 2021

*by* Lynn A. McCain, MHSA

Pathology's Chief Department Administrator, Martin "Marty" Lawlor passed away at the age of 56 on Friday, September 17, 2021, surrounded by his children, Maxwell, Sarah, and Brendan, his mother Sylvia Lawlor, and his partner Andrea Springsteen.

Marty joined the Department of Pathology in 2007 from the University of California – Los Angeles, where he served as the Chief Administrative Officer for Pathology and Laboratory Services. "Marty worked very closely with me in his capacity as the chief department administrator (CDA) since my arrival at the University of Michigan as Chair of Pathology seven years ago," reflected Dr. Charles Parkos. "During this time, Marty's commitment and loyalty to our department and Michigan Medicine were apparent in everything he did. Marty played a critical role in our pathology renovation and relocation project. He helped secure Regental approval in 2014 for the $160 million project to relocate and renovate our labs for future growth, and then helped oversee the project. Marty brought more than 100 staff, trainees, and faculty together in collaborative teams using LEAN facility design processes to create new clinical lab space and increase our footprint. This project involved renovating 145,000 SF of off-site space at the NCRC, about 2.5 miles from the main hospital complex, as well as a very complicated in situ renovation of 40,000 SF comprising our core stat laboratory at the University Hospital. Marty was also instrumental in helping us become the first hospital in Michigan to implement Professional Component Billing and obtaining strong hospital support through Part A agreements. He paved the way for explosive growth in our Forensic Pathology program, negotiating contracts with Washtenaw, Wayne, Monroe, and Livingston Counties that hugely expanded our forensic pathology services. Given his many contributions to the department and institution, it's no surprise that he received Michigan Medicine's Administrator of the Year award in 2014. Marty also had a very impressive regional and national service record. He served as Chair of the JVHL (Joint Venture Hospital Labs) Executive Committee which represents a group of 122 Hospitals in Michigan that work together to retain testing in hospital labs. Marty also served as the Chair of Pathology Department Administrators (PDAS) from 2015-2017, Immediate Past Chair from 2017-2019 and was a PDAS Council member for over a decade. Just this year, Marty was elected to the Board of Directors for the American Pathology Foundation."



"On a more personal note," Parkos continued, "I will truly miss Marty in ways that words can't describe. We would speak by phone at all hours of the day and night to discuss departmental and institutional business. Those calls would always start with 'hello boss' and often end with personal conversations about family and outside interests that commonly centered around travel, golfing, or fishing. We had many chuckles about things happening in the department on late Friday afternoons during the 4-6pm "witching hour." Marty was the consummate team player, always giving others credit even when he was primarily responsible for the outcome. He never forgot birthday and holiday cards or celebrations for the office. He was exceptionally committed to his family. I am so very grateful for his many contributions and his friendship and will miss him a lot."

# Creating the Opportunity

*by* Camren Clouthier

Highly trained medical laboratory professionals can be found all across Michigan Medicine's Department of Pathology. Whether they work in Specimen Processing, Hematology, or even Phlebotomy, these Allied Health staff members are key cogs within the daily success of the Department. These staff members do much of the behind-the-scenes work, such as analyzing human specimens, performing tests on a variety of samples, and operating complex medical instruments. Many Allied Health opportunities exist within the field of Pathology and Karen Barron MLS (ASCP), the Allied Health Education Program Manager, is eager to introduce this career pathway to others. In fact, her chief responsibility is to oversee the development of these staff members.

Karen Barron

Growing up in Sylvania, Ohio, Barron had been interested in science since her childhood. She officially got her start after completing a Medical Technology internship in Toledo. From there, she worked at ProMedica Health System and gained more experience in various roles in Infectious Disease, Microbiology, and Compliance and Quality, all while still in Ohio. Barron relocated to Michigan Medicine five years ago to take a job in Pathology, first in Point of Care testing. Later, the Department introduced a new role: the Allied Health Education Program Manager, into which Barron was promoted. She remarked that she chose Michigan Medicine because she was attracted to the strong culture in Ann Arbor. "I love the arts, the music, and the cultural opportunities. I've always enjoyed learning, working with people, and sharing science. The job in Allied Health practically had my name written all over it."

In her everyday role, Barron typically wears many different hats, with a variety of duties. In fact, Barron is Pathology's first full-time staff member who oversees the Allied Health Education services. Making connections is the name of the game. "I am building on work that was started by a lot of different people in Pathology," she notes. "Over the years, groups have worked to recruit, educate, and optimize the potential of our staff, so I am building on that, and every day is a little bit different." She is focused on developing a unique pipeline for

future laboratory professionals through community outreach, targeted engagement, and employee retention. One example of this is something that Barron does frequently: visit local high schools to educate students on what the field of Pathology is all about.

Barron, who also manages the Medical Laboratory Scientist (MLS) Internship program, adds that attracting more students to the laboratory setting is her specialty. "A baccalaureate degree is required to become a Medical Laboratory Scientist," she states. "Students typically complete a clinical practicum internship in Pathology during the final six months of their degree program." Moreover, the program is affiliated with a statewide network of public universities including Michigan State University, Eastern Michigan University, Ferris State University, and more. "The interns are granted the opportunity to work closely with both physicians and staff to gain real-world experience in a lab setting." Designated clinical educators from the involved labs work closely with the interns to develop their schedules, allot different tasks, and teach them about best laboratory practices. "They do patient work within four main rotations in the areas of Microbiology, Blood Bank, Chemistry and Hematology." Students also work in more specialized areas such as Molecular Diagnostics, HLA/Flow, Phlebotomy, Specimen Processing, or Cytogenetics. Barron says that providing this additional enrichment for students is crucial to their engagement. In the past, students interested in exploring different subspecialities were able to gain more knowledge about Autopsy/Forensic services, Cell Therapy, and even the Division of Quality and Health Improvement (DQHI). Because students can experience many of these different disciplines within Pathology, they can more easily determine where they want to work in the future. At the conclusion of their internship, students are often hired full-time to continue working at Michigan Medicine. "We have so much to offer," Barron expresses. "We have so many state-of-the-art labs doing all of this interesting work."

One major challenge that Barron often faces is grappling with the shortage of Allied Health staff employees. Expanding the capacity to take interns and retain current staff members is key. "We have to be creative to figure out how we can maximize the potential of our staff, bring in more interns and continue to reach out to the next generation of lab professionals." Barron has embraced the challenge, adding that it is an all-hands-on-deck effort. All members of the Allied Health program work in unison to ensure that employees are adequately supported and have the necessary resources to perform their jobs accurately.

Although she has only been in her role for a few months, Barron explains that the most rewarding part of her job is getting to work alongside such a diverse group of Allied Health staff, including Phlebotomy and the Point-of-Care team at the University Hospital. "When I go and talk to people, they are so passionate, dedicated, and excellent at what they do," she mentions. "I am proud to be a part of that." She enjoys helping her interns blossom into hardworking laboratory professionals. "To any prospective students, my advice would be to take the science courses, keep building up communication skills, and do not be afraid to be inquisitive." In the future, Barron hopes to continue focusing on making connections with staff members and positively impacting the Pathology culture. "We are a service industry and ultimately, it is all about being of service to our patients, physicians, and each other. Creating educational opportunities in science is the best way to serve." Barron concludes.

**Below:** Karen Barron educating a student at the 2022 Youth Summit.

## 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.

## 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 - 324557
*victors.us/pathologyfaculty*

Pathology Resident Research Fund - 324555
*victors.us/pathologyresident*

Pathology Fellowship Fund - 324556
*victors.us/pathologyfellowship*

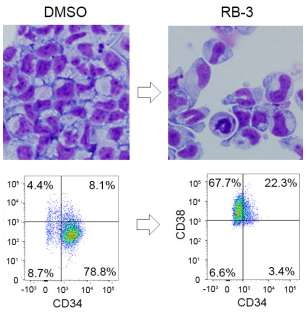
## Research Highlights

*www.pathology.med.umich.edu*

Our faculty were very productive this year, publishing over 450 manuscripts in peer-reviewed journals! These publications represent successful research efforts undertaken. Some of the key highlights of particularly impactful research of late have included the following studies:

### Development of first-in-class small molecule inhibitors

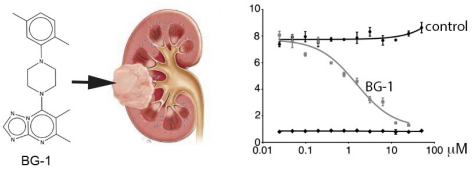
Most patients with acute myeloid leukemia (AML) die from the disease despite achieving initial remission upon treatment. Emerging evidence shows that recurrence of the disease results from the activity of leukemia stem cells (LSCs).




Such cells are capable of self-renewal, proliferation and differentiation into malignant blasts. LSCs are much more resistant to chemotherapy when compared to progenitors or blasts and development of new pharmacologic agents to selectively target LSCs would have strong clinical implications and represents a new challenge for drug discovery. PRC1 plays an essential role in maintaining the self-renewing capacity of leukemic stem cells. Core of PRC1 is composed of polycomb group proteins, including BMI1 and RING1B, which play crucial role in ubiquitinating histone H2A leading to repression many genes involved in cellular differentiation. To develop PRC1 inhibitors, the team led by Drs. Tomasz Cierpicki and Jolanta Grebecka performed screening of fragment-like small molecule compounds using a technique called NMR spectroscopy. They then performed extensive medicinal chemistry work and developed a compound called RB-3, which binds to the RING1B-BMI1 complex and inhibits activity of PRC1. This compound was extensively evaluated in various leukemia cells and treatment decreased ubiquitylation of histone H2A and induced differentiation. Importantly, BR-3 strongly reduced stem cell markers suggesting that it targets LSC properties. This was further confirmed in primary samples from AML patients and RB-3 induced differentiation of such samples without affecting normal human hematopoietic blood cells. Work from the Cierpicki and Grembecka labs demonstrates that directly targeting the activity of PRC1 with small molecules is feasible, and could lay the groundwork for the development of new pharmaceutical agents for leukemia and possibly other cancers.

*/grembecka-cierpicki-lab*

### Identification of Pax protein inhibitors that suppress target gene expression and cancer cell proliferation




During embryonic development, many genes and pathways drive rapid cell proliferation, promote cell migration, or control the specialization of cells into unique cell types. Such genes are often silenced in adults where cell proliferation and cell movement is limited. Yet such regulatory genes can be reactivated in cancer and other abnormal conditions in which uncontrolled cell proliferation is destructive. For example, the Pax family of developmental regulatory genes are common to all vertebrates, are essential for development of specific organs, but are also highly expressed in cancers. In the report by Bradford et al., we searched for small molecule compounds that could inhibit the activity of Pax2 and the related gene Pax8. These two genes are expressed in kidney cancer cells and in the abnormally proliferating kidney epithelial cells present in polycystic kidney disease, the most frequent single gene genetic disorder in the population. Using a cell-based activation assay developed in the Dressler lab, we identified small molecules that could inhibit Pax2 and Pax8 target

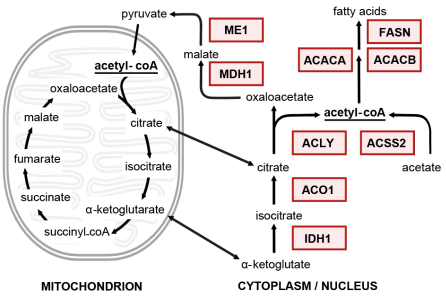
gene activation. Such molecules were shown to slow proliferation of Pax2 positive cancer cells, but not unrelated Pax negative cancer cells. Furthermore, targets of Pax2 activation were studied to determine the mechanisms of action of these small compounds. While the compounds did not impede Pax binding to DNA at potential target sites, the compounds prevented assembly of a larger protein complex needed to imprint positive epigenetic marks at the Pax target gene promoter or enhancer sequences. These studies represent a proof of principle that nuclear proteins can be effectively targeted by small molecule compounds. Since such nuclear regulatory proteins are often expressed only in specific cell or tissue types, compounds that inhibit such proteins may have less deleterious effects on the whole body if developed and utilized as anti-cancer agents.

—

*Cell Chem. Biol. 29, 412–422*

## New Clues to Control of Aging in A Long-Lived Mutant Mouse

Samuel J. Endicott and Richard Miller, both UM Pathology faculty members, have just published a new paper hinting at one way in which mutations can regulate aging, lifespan, and many age-related diseases. They used a mutant mouse, called GHRKO, which has poor responses to growth hormone. This mutation is known to increase mouse lifespan by about 40%, and to slow most of the diseases and disabilities that afflict aging mice and people. Endicott is an expert on a process ("Chaperone Mediated Autophagy," aka CMA) by which some proteins are picked out of the cell and chopped up in a specialized digestive organ called the lysosome. He had already discovered that this CMA digestive process was higher in cells of the long-lived mutant mice than in their normal siblings. The new study, just published in Autophagy, was focused on discovering just which proteins were regulated by this CMA process. Endicott, together with four UM students who worked with him on the project, discovered that of the 366 proteins that were lower in the liver cells of GHRKO mice, just 91 were lower because of the heightened CMA in these mice. The CMA-modulated proteins were not random: 16 of them were components of the ribosome, the organelle that translates messenger RNA into proteins, and another 4 were key controllers of ribosome action. Several of the 91 CMA-modulated proteins (red boxes in the illustration) play major roles in the production of fat molecules, by stealing building blocks from mitochondria, the powerplant of the cell. Since these data suggest a major role for high CMA in control of protein and fat metabolism, Endicott and his students are now working out the ways in which these changes postpone aging and disease, and exploring a set of drugs they have found which can augment CMA in normal mice. They hope that these CMA-stimulating drugs may someday have a role to play in delaying aging and its many ill effects in people.

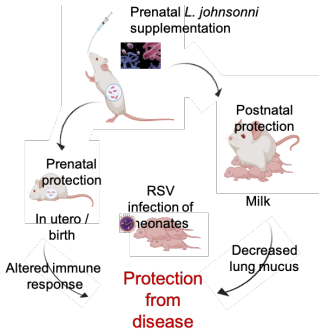



—

*Autophagy*

## Maternal microbiome impacts anti-viral immunity in neonates

It is becoming clear that the microbiome that colonizes the infant gut during early life is critical for modulating immune responses later in childhood. Early studies looking at children raised on farms or with pets have shown that these children are significantly less likely to develop allergies or asthma compared to children in urban areas. In fact, the microbiome at one month old is a strong predictor of allergy development later in life. Previous studies have found that dust collected from houses with dogs was able to protect mice from the development of allergic disease, in part due to a more diverse microbiome, including an enrichment with the probiotic Lactobacillus johnsonii. However, these studies were performed in adult mice. Because the protective effect in humans is seen so early in life, before infants are eating solid food, we asked whether the maternal microbiome has any impact on early-life microbial colonization and immune development. In this study, using a murine model, we found that altering the maternal microbiome by supplementing female mice with L. johnsonii resulted in changes in the neonatal immune development. We found that this development is impacted by the maternal supplementation in two ways. First, some aspects of the offspring immune development are altered by metabolites that are made by maternal gut microbes, to which offspring are exposed both in utero and during delivery. Other neonatal immune responses are altered by metabolites that are passed through the milk that the offspring consume prior to weaning. We also found that neonates born to females supplemented with L. johnsonii have a more diverse microbiome early in life. Thus, we were able to show that a diverse maternal microbiome impacts the development of the neonatal microbiome and immune response in early life.



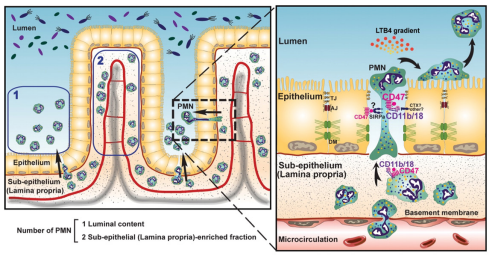

—

*J Exp Med. 2021 Nov 1; 218(11)*

*Continues on next page...*

## COVID-19 often causes serious skin issues

Neutrophils (PMN) are essential for host defense against invading pathogens and restoration of tissue homeostasis. However, excessive PMN migration across epithelial surfaces (TEpM) is a hallmark of multiple chronic inflammatory conditions including ulcerative colitis and Crohn's disease. Despite the close association between disease symptoms and TEpM, mechanisms defining this process remain poorly understood. Previous in vitro studies using blocking antibodies in transwell-based transmigration models led to the discovery of key mediators of PMN TEpM, including ubiquitously expressed CD47 and the leukocyte-

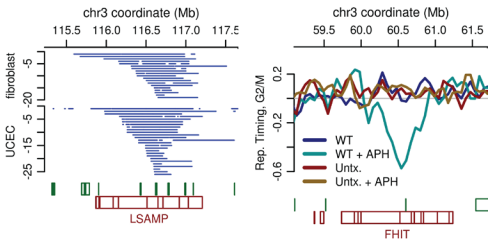



specific integrin CD11b/CD18. In some in vivo models of inflammation, mice with global loss of CD47 have reduced PMN migration into tissues. However, the relative contribution(s) of leukocyte-expressed CD47 has been hampered by the inability to create bone marrow chimeras and the lack of tissue-specific CD47 knockout mice. In this study, we created the first CD47 transgenic mouse model with selective deletion of CD47 in PMN. We used this new in vivo tool to gain insight into understanding CD47 contributions to PMN function. With these mice, we employed intestinal loop TEpM assays to demonstrate that CD47 expressed on PMN, but not on IECs, plays a major role in regulating PMN TEpM in vivo. Previous works reported CD47 to physically associate in cis with some integrins to regulate integrin function. In this study, we demonstrate that CD47 physically associates with CD11b/CD18 in the plasma membrane of PMN, and loss of CD47 results in impaired activation of CD11b/CD18 to a high affinity ligand binding state. Complementary in vitro and in vivo studies with function blocking antibodies further support a role of CD47 in regulating CD11b-dependent PMN TEpM and chemotaxis. In summary, these findings provide new insights into regulatory mechanisms controlling some of the many steps underlying the process PMN TEpM. Our results support a model where physical association of CD47 with CD11b/CD18 in PMN regulates integrin activation and adhesive function. Therefore, selective inhibition of CD47-CD11b interactions may offer potential therapeutic approaches to reduce dysregulated PMN trafficking in the gut during disease.

*Mucosal Immunol. 2021*

## Transcribing Large Genes Interferes with Replication to Create Fragile Sites in the Human Genome

Most human genes occupy tens of kilobases of genomic DNA. However, an exceptional set of a few dozen genes is nearly 100 times larger at more than a megabase. It has been known for many years that such large genes comprise fragile sites in the genome because they show breaks and gaps when chromosomes are visualized during mitosis after partial inhibition of DNA replication. More recently, the research team led by Drs. Thomas Glover and Thomas Wilson has shown that fragile sites are also hotspots for chromosomal rearrangement following replication stress. However, the relationship between these processes has been enigmatic. In a 2021 study, graduate student Irene Park and lab members Samreen Ahmed, Pam Bennett-Baker, and others provided key evidence that large genes must be actively transcribed for genomic instability to be observed at fragile sites. When they are transcribed, anything that perturbs




replication progression to even a small extent causes extreme replication delays such that unreplicated DNA persists into mitosis, where it must be dealt with by less accurate processes to avoid catastrophic consequences during cell division. The mechanism behind this transcription-replication interaction is almost certainly that transcription suppresses local replication origin firing and not that it creates RNA:DNA hybrids as had been previously proposed. These findings are important for human cancer, where cells with DNA repair deficiencies relevant in mitosis are known to accumulate mutations like those in the experimental system used in these studies. Follow-up studies will further address mutations that arise during brain development, when these large, often nerve-specific genes are first turned on in rapidly dividing neural progenitor cells.

*Nucleic Acids Res. 2021 Jul 21; 49(13)*

# Breaking Through Obstacles

*by* Christine Baker

If we get through this, we can do anything," I remember saying to a colleague as we looked again (and again) at the phasing plan for executing the PRR UH Renovation project.

By "this," I meant the first three phases of the Renovation effort. The unimaginable challenge of creating new laboratory space while keeping 24x7 laboratories operational—sometimes immediately on the other side of a thin construction barrier—seemed insurmountable.

Until we did it.

The first phasing plan for the UH Renovation had 19 individual phases and was going to take 6 years to complete. When that construction timeline was deemed not only too expensive but too risky to clinical operations, the design team came up with 6—and then 5—phases and reduced the duration to 4 years. This change, while deemed necessary for many reasons, also meant that Specimen Processing would be divided into two parts for one phase, and chemistry would be part of the first three phases. Chemistry was divided and separated such that it required staff to sneak around slanted walls and tight openings to access various points of their lab. We also had to relocate the Apheresis Patient Care Unit (APU) to Med Inn to clear space for the new Blood Bank to be built. We were pinched into temporary offices, and had to move some of our faculty, trainees, and staff to Med Sci 1 to allow for enough space for everyone to do their work.

During the past year, these obstacles and challenges were overcome again and again by the Pathology team at UH. Specimen Processing survived being separated into two sections and were reunited in their new space within the Clinical Core lab. Chemistry saw the building, validation, and integration of the new Chemistry Automation line, and then the removal of the old automation line and upgrade and completion of their lab space. The APU continued to thrive in their new location in Med Inn, allowing the new Blood Bank space to finish construction and move towards the activation of the new lab. The entire UH team saw hallways closed, endured power outages, and lived in close proximity to the sounds, interruptions, and dust that major construction projects bring.

And now, at long last, we have completed the entire Clinical Core lab, and are turning our attention towards not only the activation of the new Blood Bank, but also the completion of the new Cell Therapy Lab, the new Phlebotomy space and eventually the new APU.

**Below:** Medical Technologist Specialist, Destaw Addis, working in the Clinical Core Lab.


# 30 Years of Research
## at Michigan Medicine

*by* Lynn A. McCain, MHSA

The Centers for Disease Control (CDC) reports that Crohn's Disease and ulcerative colitis, collectively referred to as Inflammatory Bowel Disease, or IBD, affect approximately 3 million US adults and 80,000 US children, and these numbers are growing. IBD severely impacts the abilities of affected patients to live normal, active lifestyles. The Crohn's and Colitis Foundation reports that more than 160 genes have been identified that are associated with IBD and that "the gut microbiota (the bacteria and viruses that inhabit the gut) is a key link between genetic susceptibility and IBD onset/progression." By identifying the microbes that play a role in IBD, it is anticipated that researchers can create medications that specifically address triggers of the disease. One of the world's foremost researchers in this area is Dr. Gabriel Núñez, the Paul de Kruif Endowed Professor of Experimental Pathology in the Department of Pathology at Michigan Medicine.

In the late 1990s, Núñez's laboratory discovered Nod-Like Receptors (NLRs) and found that a member of this family, NOD2, is linked to the development of Crohn's disease. He subsequently found that certain molecular structures in bacteria are recognized by several members of the NLR family in mice including NOD1, NOD2, NLRP3, NLRC4. Núñez and his collaborators found that NOD2 was mutated in patients with Crohn's disease and activation of NOD2, which senses muramyl dipeptide, a fragment of the bacterial cell wall, was impaired in patients with IBD. His findings were the impetus for other researchers who then expanded upon his discoveries, leading to the more than 160 genes identified as playing a role in IBD.

However, Núñez did not begin his career with a focus on IBD and NLRs. As the oldest of ten children growing up in Seville, Spain, he loved to play soccer and to watch Avant Garde films. A particularly influential high school teacher who was passionate about filmmaking introduced him to these films. He took a course on the history and techniques of filmmaking, "and I loved it! I went to London for a camera and started making my own movies," recalls Núñez. "I didn't have the money for actors or anything, so I started out making silent movies and thought my career would be in filmmaking. I was also interested in medical research, though. I don't remember exactly how I became interested in this. I didn't have any family members who were scientists or physicians. I was just interested in biology and medicine as a teenager. I do remember one night, during my senior year in high school, going to see my parents in their bedroom to tell them I had decided to go to medical school."

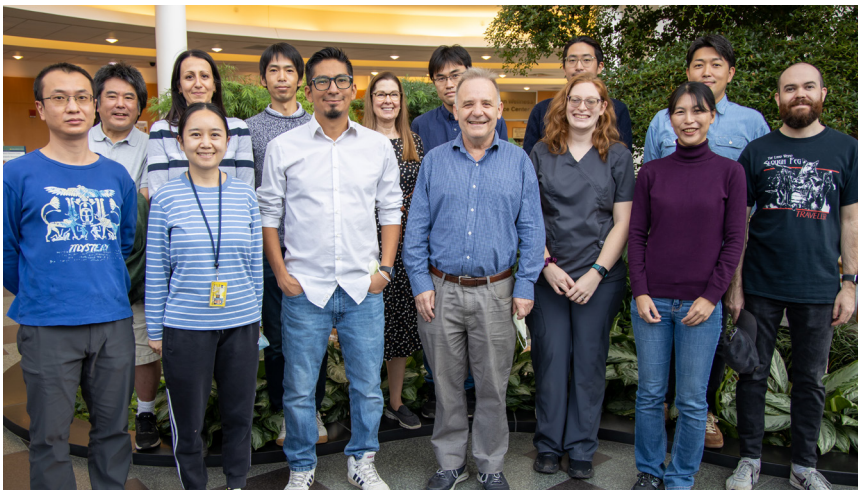
In medical school in Seville, Núñez worked in a transplantation immunology laboratory, conducting research. He met a young woman from Ann Arbor, Michigan who was also studying at Seville. It was this friendship that led to him coming to UM as a visiting medical student. He stayed with her family for a month while he completed his rotation at the old UM hospital. As he was nearing the end of medical school, he met Dr. Peter Stastny at a conference in Rome. Stastny invited him to complete a postdoctoral fellowship in his lab at the University of Texas Health Science Center in Dallas. His postdoctoral research focused on B cells and monoclonal antibodies in transplantation immunology as well as the relationship of the human immune response region (HLA-D) and susceptibility to immune-mediated disease.

A few years later, Núñez moved to Washington University School of Medicine to complete a pathology residency program and to continue his postdoctoral fellowship with Dr. Stanley Korsmeyer. In the Korsmeyer laboratory, he focused on the molecular biology of follicular lymphoma. This led him to Bcl-2 research and the role of apoptosis (cell death) in lymphoma and lymphoid development. During this time, he discovered that Bcl-2 inhibited apoptosis and maintains B-cell memory.

Then, on January 4, 1991, Núñez arrived in Ann Arbor, Michigan once again, this time as an Assistant Professor of Pathology. He had caught the eye of Dr. Peter Ward, former chair of Pathology, who also studied apoptosis. Ward

actively recruited Núñez to join the research faculty of the department. "I recruited Gabriel with expectations that he would become a world expert in the area of proteins that allow cells to recognize potentially harmful factors in bacteria, malignant tumors, etc. These studies would have the ability to revolutionize the field of microbiology linked to infectious bacterial diseases," recalls Ward.

Núñez now had two, very attractive competing offers. He fondly recalled Ann Arbor from his medical student rotation and decided to join the faculty at UM. He soon made many important discoveries related to the Bcl-2 family and their role in apoptosis and cancers. Then in 1998, he discovered NOD1, the first member of the NLR family. A year later, he discovered NOD2 and began to investigate the NLR family's role in host defense against microbes and their relationship to genetic susceptibility to inflammatory diseases, publishing for the first time on NOD2's association with susceptibility to Crohn's disease.



**Above:** Dr. Núñez (center-right) with members of his lab in 2021.

As a result of this discovery, the Núñez lab decided to continue to pursue this avenue of research and changed focus from cell death to host-microbial interactions and inflammatory disease. "This is the area of immunology that is involved in the detection of microbes and fighting against pathogens," explained Núñez. "In 1998, I wrote three R01 grants at once and I hit a home run; I was awarded all three. By 2000, I was able to make the research focus transition and work full-time on this topic." More recently, the Núñez laboratory was able to develop a mouse line that had a disease that mimics Crohn's Disease in humans. He has identified the bacterium in these mice that triggers Crohn's-like disease. "We just need to identify the same trigger in humans." For individuals who do not have the genetic mutations that make them susceptible to Crohn's Disease, the bacterium doesn't affect them. But for those with mutations, the same bacterium triggers the disease. However, the number of potential microbes and the variety of genetic mutations make the task of identifying the combinations difficult. "It is like finding a needle in a haystack," says Núñez.

As the laboratory focused on the NLR family, they investigated the role of another member of this family, Cryopyrin, also known as NLRP3. The lab discovered that Cryopyrin forms a multi-protein complex called "the inflammasome", which contains several proteins, including caspase-1. Cryopryin activates caspase-1, which begins a series of immune responses including the production of interleukin-1β, an essential component in infection resistance, when the body encounters bacterial RNA.

In 2008, the laboratory found that Nod1 and Nod2 are important for immune cells to recognize microbial infections and, together with Toll-like receptors, can trigger the body's defense signaling pathways against infection. Toll-like receptors recognize patterns, such as specific structures in a pathogenic bacterium, and are important for helping the body to recognize pathogens and get the immune response started quickly.

As he continued to pursue this avenue of research, he discovered that mice raised in a germ-free environment responded differently to pathogenic infections than did mice raised in a traditional environment. Those raised traditionally had normal amounts and varieties of microbes in their gastrointestinal system, but those raised germ-free did not. When exposed to a bacterium, *Citrobacter rodentium*, mice with normal guts were able to outcompete this bacterium, but those in a germ-free environment were not able to do so.

He also observed that neonates are much more susceptible to infections than adults. "By colonizing adult germ-free mice with the cecal contents of neonatal and adult mice, we showed that the neonatal microbiota is unable to prevent colonization by two bacterial pathogens that cause mortality in neonates. The lack of colonization resistance occurred when *Clostridiales* were absent in the neonatal microbiota." This added more information to his body of knowledge on the importance of specific bacteria essential for keeping the gut healthy and preventing inflammatory processes from occurring.

Recently, the lab explored the mechanism by which the gut microbiota protect us from infection by enteric pathogens. This study discovered that the microbiota consume dietary amino acids limiting

their availability to the pathogen *C. rodentium* early in the infection process. This finding may help to identify prevention and treatment modalities for enteric pathogens in humans, such as pathogenic *E. coli*, which functions similarly in people.

In addition to conducting research, Núñez is an excellent role model and mentor in the laboratory. He is very proud of his trainees' achievements and success in academia. His former trainees include: one department chair, two vice-chairs, 15 professors, and 18 associate professors. "An important aspect of leadership is to foster the development of future leaders at academic institutions," he reflected. "During my tenure at the University of Michigan, I have trained more than 65 postdoctoral fellows. Most of them are independent investigators at academic institutions in the United States and around the world." Dr. Roberta Caruso joined his laboratory as a postdoctoral fellow in 2013 and was promoted to Research Investigator in 2018. She commented, "Dr. Núñez has been an excellent mentor, and a great inspiration for me. He has inspired me to pursue my goals with hard work and dedication. Dr. Núñez has shown me the value of honesty, sincerity, and trust in research. The knowledge and wisdom he has imparted to me has been a great help and support throughout my career."

Dr. Peter Lucas, Professor and Vice Chair, Department of Pathology at the University of Pittsburgh School of Medicine, joined the Núñez lab as a research fellow in 1999. Lucas expressed his appreciation, "Gabriel is the kind of mentor that everyone dreams of having–incredibly insightful; brimming with ideas, enthusiasm, and passion; endlessly energetic; joyful and kind. He pushes you to reach your highest potential while giving you freedom, resources, support, and encouragement along the way." Lucas really appreciated Núñez's "open door" policy as a trainee. He made himself readily available to his trainees and was always willing to drop whatever he was doing to talk science. "Of all the things I am grateful for from my years in the Núñez lab, I am most indebted to Gabriel for his support and generosity in helping me launch an independent career. Gabriel was incredibly gracious and supportive in allowing me to take a research topic that we developed together in his lab and make it my own." Lucas has spent the past 20 years developing that topic, focused on chronic inflammation and the development of vascular, metabolic, and neoplastic diseases. Lucas concluded, "Gabriel stands as a shining example of how one can direct the most meaningful and rigorous scientific program while at the same time fostering and building the next generation of scientists who will carry on the mission." Ward is pleased with Núñez's success, "Gabriel exceeded all of our expectations and now has world-wide recognition for his ground-breaking discoveries at the University of Michigan."

**Above:** Dr. Núñez preparing paella.

Núñez' son is now in medical school, and he reports that his textbooks describe his father's research when covering the unit on IBD, a fact about which he brags to his classmates. "There are a lot of people working on this problem now," deflected the elder Núñez. With more researchers focused on finding the solution, the future may be bright for patients suffering from IBD. This drives researchers to dedicate their energies toward finding the answer. "I am driven by scientific discoveries and the excitement of getting new knowledge. Like other scientists, I love to try to solve the mysteries of life by doing experiments in the lab or in the field." However, Núñez also emphasized the need for a balanced life if one wishes to be successful in research. "You need to have other interests. Your entire life cannot be about research. I love the symphony, world history, and the arts in general. I love to cook and host paella parties frequently, bringing people from different walks of life together over paella, getting to know each other, and learning from one another. I also often cook for charities to help groups raise money." This essential work-life balance has allowed Núñez to sustain his 30+ years of research and keeps him energized for the coming years.

# Spotlight on Diversity, Equity & Inclusion

*by* Camren Clouthier

Diversity, Equity and Inclusion (DEI) at Michigan Medicine is among the highest priority core values for the health system. In collaboration with the Office of Health, Equity and Inclusion (OHEI), DEI refers to the idea of using employees' identities in order to understand, navigate, and accept all members within the workplace, no matter their differences. But what exactly does this mean in the context of Pathology?

Dr. Angela Wu, Associate Professor and Assistant Chair for Diversity, Equity and Inclusion in the Department of Pathology, describes DEI in three main parts. "Diversity has to do with identity. It is how you best define yourself, which can be so complex and different for each individual." It can be related to one's cultural background, how or where they grew up, their societal roles, political beliefs, what their families are like, and much more. "Ultimately, it is how you see yourself," Wu says. Diversity is also essential because it allows for more large-scale success in the organization. "Having different opinions and backgrounds is one of the most fundamental keys to success," Wu explains. "It challenges us in ways that cause us to develop new and innovative ideas."

Equity is the fair treatment of everyone, regardless of their race, religion, gender, creed, sexual orientation, or personal beliefs. Feeling like an employee's individual contributions are making a difference is also a key piece of the puzzle. "Everyone deserves the same opportunities to succeed, and they deserve to be valued," Wu describes. This goes hand-in-hand with inclusion, too. Despite the challenges that may arise, she remarks that workforces can be educated on how to improve as a community through a variety of trainings. "We all have unintentional biases and prejudices but being able to mitigate these things is the best way to promote equality."

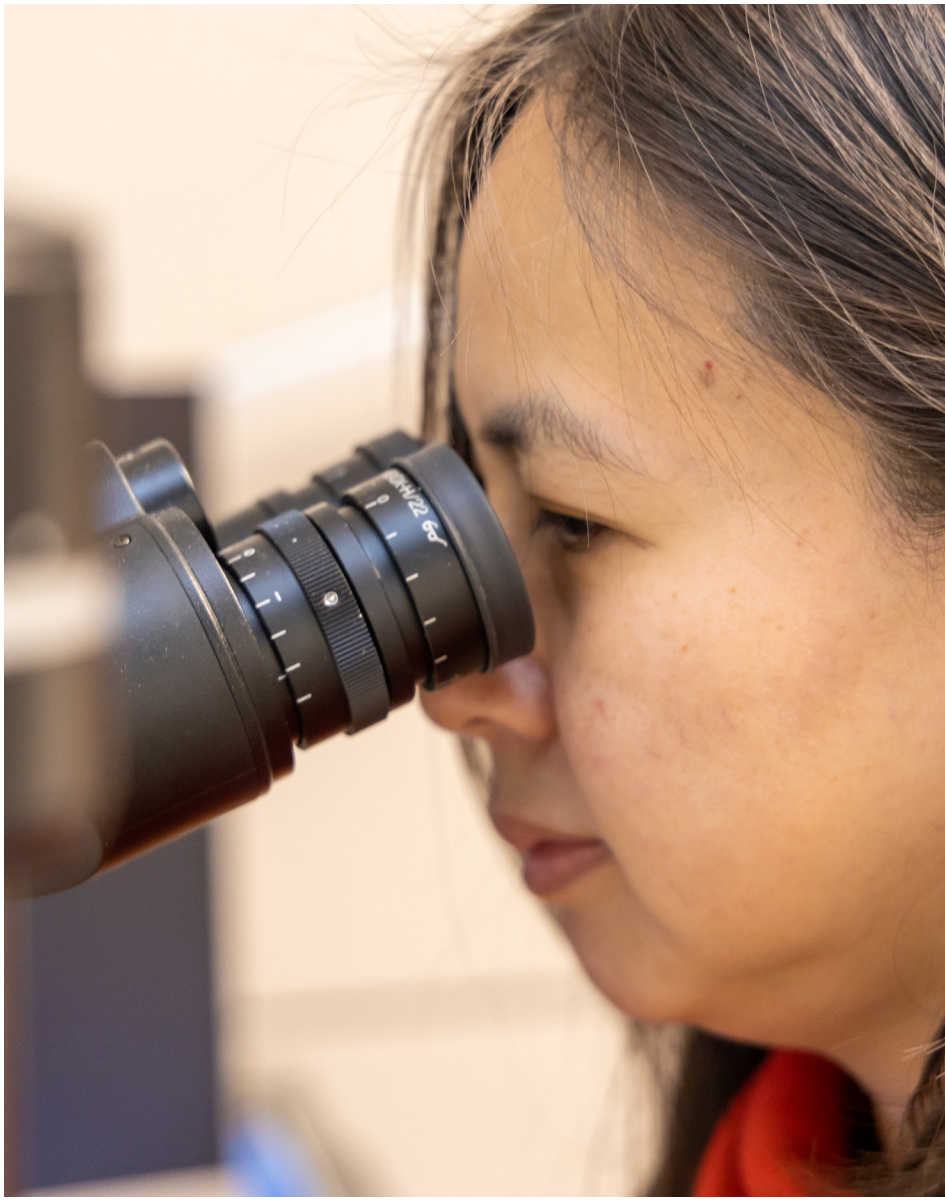
After initially completing Medical School at Northwestern University in Chicago, Wu attended the University of Michigan for her residency program in anatomic and clinical pathology, followed by fellowships in surgical and genitourinary pathology. "I knew it was a very highly-rated residency program," she says. "The reputation is unrivaled in terms of clinical care and research; it has truly become a second family." However, while progressing through her own residency program several years back, Wu

admits that diversity was never something that was acknowledged as heavily as it should have been, so it has motivated her to spearhead these efforts in her current role at Michigan Medicine. Because of her continued interest in DEI over the years, Wu was selected for the newly-created position of Assistant Chair for DEI, in addition to maintaining her status as a faculty member within the Department of Pathology.

The Department has a variety of ongoing goals for creating a larger sense of belonging within the workplace. This includes participating in Michigan Medicine's Diversity in Medicine Conference, inaugural Youth Summit, hosting the annual Equality Walk for Juneteenth, and working closely with the Office of Health, Equity and Inclusion (OHEI) to strengthen the core values of the organization. Equally important, Wu notes, is involving trainees in DEI efforts. This has been accomplished through the creation of a resident-exclusive DEI committee, through which the residents sent out a survey focused on addressing some of the biases that may be present within the workplace. They also created more standardized recruitment tools, which have allowed them to target and appeal to larger groups of potential trainees across the country.

"Perhaps the most significant milestone is the development of the Pathology Anti-Racism Taskforce," Wu says. "This opens the door for new initiatives like Lunch and Learn educational film sessions, a book and movie club where folks can learn more about anti-racism as it is portrayed in media, expansion of the Equality Walk, and potentially even a new diversity-focused podcast," she describes. While it can sometimes be challenging to generate interest in DEI-related projects, the events are a great way to attract more people, including faculty, staff, and leadership. "Dr. David Gordon has been instrumental in the process," Wu explains. Gordon, who was named the Director of Faculty Programs with OHEI early in 2022, has a wealth of experience and knowledge as it relates to diversity, equity and inclusion within the health system. Likewise, Dr. Allecia Wilson, Director of Autopsy and Forensics, has done a great deal for DEI. In fact, Dr. Wilson has spoken to high school students and at local events to inspire folks to learn more about Pathology. Furthermore, Wu adds that support from the Office of the Chair, including Chair Dr. Charles Parkos and Vice Chairs Drs. Kathleen Cho and Jeffrey Myers have been key to setting these ideas into motion. "Despite being very busy, they continue to devote their time and effort to support this cause, which is what makes it so meaningful."

Looking ahead to the future, Wu remarks that DEI efforts never truly end. Because the Department of Pathology is so team-oriented, it is uniquely equipped to branch out in so many different aspects. "You are always striving and working towards improvement," she mentions. "To see that we are inspiring people, even the residents, is remarkable. I think that we have come a long way, but constantly wanting to do better is what DEI is all about," she concludes.



# Hello!

I'm Jason Keech, fund and friend-raiser for the Department of Pathology. I've been supporting the department since 2017 and have had the good fortune to meet so many of our incredible faculty, staff, alumni, and donors during this time. For this edition of Inside Pathology, I'd like to share a few thoughts about the art and science of development work.

In the Michigan Medicine Office of Development, we think of development as a process for creating and enhancing relationships with past, present, and (hopefully) future donors to support our clinical, research, and educational mission. To inspire people to give, we have to know them well enough to know what's important to them. People may give because they want to help advance our mission, or to honor the career accomplishments of a mentor, or because of a personal medical experience that motivates them to create better outcomes for future patients and families. In the context of our department's vast scope of work, this has translated to new gifts for faculty research, named lectureships and professorships, and resident education funds.

Once a donor decides to give, those donations arrive in many forms, from checks and online gifts, to major gifts of transferred stocks, to substantial gifts to the department designated in the donor's estate plans. When considering a major gift, it's wise to consult your financial adviser about tax-advantageous ways of supporting the organizations you care about.

After a gift is given, it's important to stay in touch with the donor to let them know how their gift is making a difference - what we refer to as stewardship. When we successfully create and maintain relationships with donors, they get to see the impact of their philanthropy and are more likely to give again in the future—that's "Development."

If you are thinking about making a gift, including the department in your estate plans, or just have questions about philanthropy at the University of Michigan, let's talk!

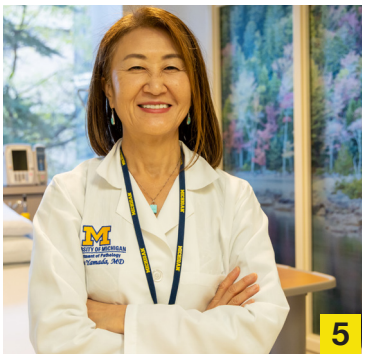
**Jason Keech**
Associate Director of Development
jkeech@umich.edu
734-763-0866


1


2


3


4


5


6


7

**[1]** Kristina Martin and Christine Rigney pose at the annual Pathology Fall Picnic at Wiard's Orchard in Ypsilanti, Michigan.

**[2]** As part of Phase 2.2 of the PRR, construction teams performed the removal of the barriers separating the new Chemistry lab from the Core Lab and Hematology space at UH.

**[3]** Eric Vasbinder leads Department leadership through a tour of the remodeled lab spaces at UH, including a view of the new automation line.

**[4]** Dr. Anuska Andjelkovic-Zochowski poses at BSRB.

**[5]** Dr. Chisa Yamada strikes a pose in the Apheresis unit at the University Hospital.

**[6]** Dr. Jeffrey Myers kneels to honor the legacy of George Floyd at the 2022 Pathology Equality Walk.

**[7]** DQHI Manager Brian Tolle leads a team meeting at NCRC.

## Clinical Instructors

Beena Ahsan, MD
GI Fellowship
*University of Chicago*
*Chicago, IL*

Aaron Belknap, MD
VA Hospital
*Ann Arbor, MI*

Rachael Fels Elliot, MD, PhD
Assistant Professor
*University of Kansas*
*Kansas City, KS*

Chaehwa Kim, MD
Thoracic Fellowship
*Michigan Medicine*

Emily McMullen, MD
Pathologist
*Spectrum Health*
*Grand Rapids, MI*

Abid Rahman, MD
Pathologist

Shula Schechter, MD
Assistant Professor
*University of Pittsburg Medical Center*
*Pittsburg, PA*

Chelsea Styles, MD
GI Fellowship
*Michigan Medicine*

Michella Whisman, MD
Assistant Professor
*University of Arkansas for Medical Sciences*
*Little Rock, AR*

Mustafa Yousif, MD
Assistant Professor
*Vanderbilt University*
*Nashville, TN*

## ACGME Fellows

Jacob Abel, MD
Physician, Molecular Pathology
*PSJH Molecular Genomics Laboratory*
*Portland, OR*

Yelena Fudym, MD
Neuropathologist
*Akron Children's Hospital*
*Akron, OH*

Audrey Jajosky, MD, PhD
Assistant Professor
*University of Rochester*
*West Henrietta, NY*

Tyler Menge, MD
Staff Dermatopathologist/Dermatologist
*CTA Pathology/VA*
*Ann Arbor, MI*

Ariane Robison, MD
Deputy Chief Medical Examiner
*Mississippi State ME Office*
*Pearl, MS*

Anna Shestakova, MD, PhD
MGP Fellowship
*University of Utah*
*Salt Lake City, UT*

Steven (Burke) Van Norman, MD
MGP Fellowship
*University of New Mexico*
*Albuquerque, NM*

Lin Zhang, MD, PhD
Pathologist
*Clinical Pathology Associates*
*Phoenix, AZ*

Nicholas Zoumberos, MD
Assistant Professor
*University of Arkansas for Medical Sciences*
*Little Rock, AR*

## Residents

Ashley Bradt, DO
Surgical Oathology Fellowship
*Michigan Medicine*

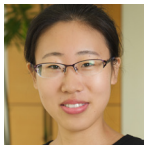
Laurie Griesinger, MD
Gynpathology Fellowship
*University of Virginia*
*Charlottesville, VA*

Cisley Hines, MD
Surgical Pathology Fellowship
*Michigan Medicine*

Ania Owczarczyk, MD, PhD
Hematopathology Fellowship
*Michigan Medicine*

Alex Taylor, MD
GU Fellowship
*Michigan Medicine*

## Molecular & Cellular Pathology - PhD



Xiaofang Shi, PhD
Defended / February 23, 2022
Mentor / Dr. Richard Miller
Position / Immunogenicity Scientist
*Amgen*

## FLASH FROM THE PAST

Can you guess who these individuals are? Two are faculty members, and the other an active emeritus professor in the department.




**A.** David Keren; **B.** Lee Schroeder; **C.** Peter Ward

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN
Department of Pathology and Clinical Laboratories
2800 Plymouth Rd, Bldg. 35
Ann Arbor, MI 48109-2800

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN
LABORATORIES

**19** SUBSPECIALTIES

**24-48** HOUR TURNAROUND*

**60** EXPERT CONSULTANTS

**15k** REFERRALS ANNUALLY

PHOTO FEATURING
**JULIA DAHL, M.D.**
*Assistant Professor, Placental, Gastrointestinal and Hepatobiliary Pathology*
*Associate Director, MLabs*

mlabs.umich.edu
800.862.7284

## We've got your subspecialty covered:

- Bone and Soft Tissue Pathology
- Breast Pathology
- Cardiovascular Pathology
- Cytopathology
- Dermatopathology
- Endocrine Pathology
- Forensic Pathology
- Gastrointestinal/Hepatic Pathology
- General Surgical Pathology
- Genitourinary Pathology
- Gynecologic Pathology
- Head and Neck Pathology
- Hematopathology
- Neuropathology
- Ophthalmic Pathology
- Pediatric and Perinatal Pathology
- Placental Pathology
- Pulmonary Pathology
- Renal Pathology