

MSK PATHOLOGY REVIEW

INITIATIVES
INNOVATIONS
ACCOMPLISHMENTS



Memorial Sloan Kettering
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COMMENTARY FROM THE DEPARTMENT CHAIRMAN

LOOKING FORWARD: DIAGNOSTIC PATHOLOGY IN THE TECHNOLOGICAL ERA

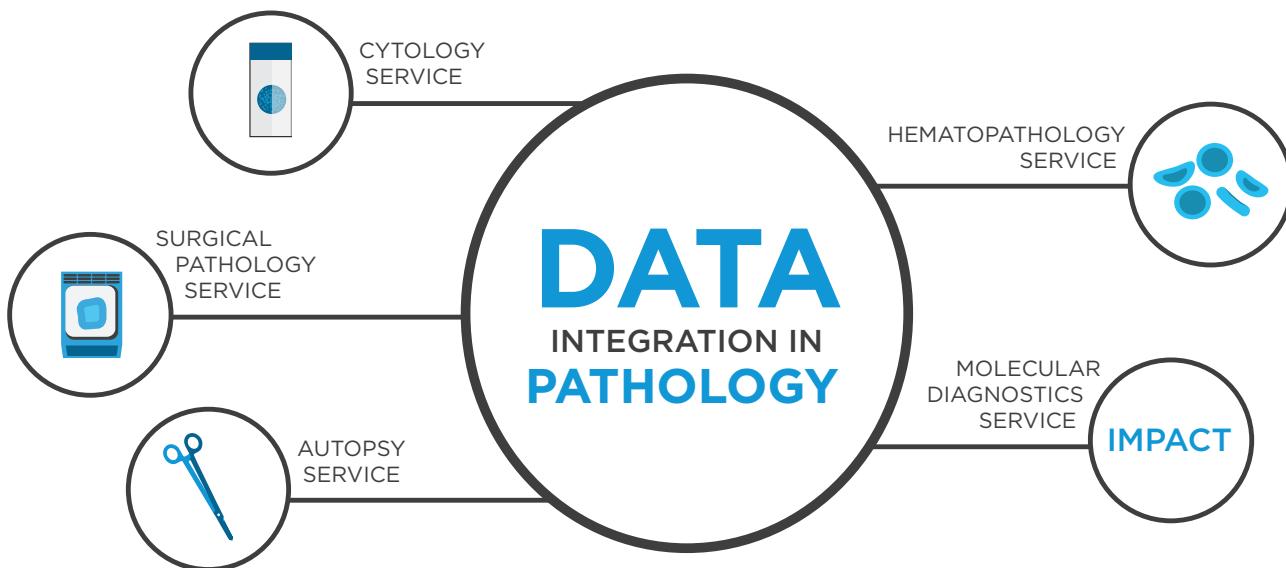
With the explosion of new technology entering the field of diagnostic pathology, questions often arise about how our discipline will evolve. The emergence of molecular diagnostics, proteomics, multiplexed immunomorphology assessment, computational pathology and other novel diagnostic modalities has made it apparent that some changes must occur in the practice of pathology. When will the light microscopic assessment of tissue, like histochemical staining and electron microscopy, cease to be the primary means of pathologic diagnosis and be relegated to secondary status behind newer techniques? Some might argue this has already occurred for certain diagnostic indications, given our reliance on immunohistochemistry. But of course, we continue to rely primarily on morphologic assessment as the basis for most of the diagnostic tasks we perform. What is occurring already is the change in focus of our reports. Rather than simply establishing the diagnosis of cancer and providing basic histopathologic descriptions, in hopes that accurate assessment of prognostic factors will serve to guide treatment, our analysis is increasingly focused on the identification of specific therapeutically relevant features – biomarkers that serve as very precise indicators of therapeutic sensitivity. When Juan Rosai published a book on the history of surgical pathology in the United States in 1997, he titled it “Guiding the Surgeon’s Hand”; today, a more accurate descriptor of our role in directing therapy would be “Guiding the Oncologist’s Hand” (meaning both medical and surgical oncologists). Many of the newer diagnostic tests seek to identify specific therapeutic biomarkers – molecular alterations that confer sensitivity to targeted agents – but additionally there are many biomarkers embedded within histologic data that, while perhaps not quite as specific as a targetable mutation, provide critical information about the potential for a particular treatment to succeed. As an example, the typical morphology of small cell carcinoma – whether in the lung or in an extrapulmonary location – provides one of the most reliable indications that platinum-based chemotherapy is likely to be effective. A search for the specific molecular mechanisms that confer platinum sensitivity is underway at MSK, with J.T. Poirier and Charles Rudin in thoracic oncology, collaborating with Natasha Rekhtman and others in thoracic pathology. But at present, morphology remains the main predictor of treatment response in this tumor system.

One key constant among most of the newer diagnostic technologies is the production of massive amounts of data. Dozens of antibodies are assessed already by immunohistochemistry and flow cytometry, and the multiplexed immunomorphology platforms being developed by Travis Hollmann superimpose the morphologic relationship of different cell types upon the distribution of antigen expression, yielding immense datasets beyond the ability of casual morphologic examination to interpret. MSK-IMPACT, under the direction of Marc Ladanyi, Maria Arcila, Ryma Benayed, and many others on the molecular diagnostics service, yields complex information about multiple types of genomic alterations, currently in 468 genes (soon to be augmented – again), which requires specific bioinformatic analysis by Mike Berger, Ahmet Zehir, and the clinical bioinformatics team to interpret. Proteomic profiling – being led by Michael Roehrl and Ahmet Dogan, can simultaneously examine over 10,000 proteins, quantitatively, and computational pathology being conducted in the Warren Alpert Center for Digital and Computational Pathology with Yukako Yagi and Thomas Fuchs harnesses the power of machine learning to perceive new types of morphologic correlates within tumor tissues. Pathology is rapidly facing the challenge of “big data” interpretation to make sense of the wealth of novel information we now derive from tissue samples. How to digest all of these data in a way that provides meaningful guidance to the treating clinician – that will be the challenge for diagnostic pathologists in the next decade.

At present, much of our focus is devoted to understanding how new techniques can be applied in the diagnostic setting. Each new assay requires its own workflow, with all the attendant operational challenges, and generates its own report. Herein lies one of our primary hurdles. Already we are populating the medical record with reams of diagnostic data. Standard surgical pathology reports often run to several pages, including details displayed in our synoptic reports to document every histologic facet of the patient’s disease. Molecular testing can generate several additional reports on the same tumor sample. In hematopathology, an individual bone marrow specimen can have routine histology, aspirate smear results, immunohistochemistry, flow cytometry, cytogenetics, and molecular diagnostics – each technique potentially generating a separate report sent to the treating clinicians. Unless these growing datasets can be collected, integrated, and interpreted, we risk creating a potentially confusing picture about the pathology of each tumor. And more importantly, we potentially turn over the task of generating an overall, integrated interpretation of all of the pathology data to our clinical colleagues. In order to maintain (and enhance) our position as the analysts of tissue-derived diagnostic information, it is critical that we develop the means to integrate the data we are producing, to distill it into a clinically relevant form that can guide patient management. This will require the development of informatics tools and, with all of our current super-specialization, continuous education to understand the relevance of new types of diagnostic information.

We are now aggressively taking steps to begin to integrate the data we produce. Ahmet Dogan in hematopathology has instituted integrated reporting of bone marrow biopsies, in which all of the data from the various laboratories are collected in a single report with a final summary comment providing the definitive interpretation of all important findings. Presently, this is a manual and time-consuming process, as the constraints of our laboratory information system do not easily allow automated data collection from multiple individual laboratory accessions. One solution involves the creation of an external database that collects the data from CoPath and then allows more creative organization and analysis. Already, Ahmet Zehir and the molecular diagnostics team have utilized this approach to extract data from MSK-IMPACT testing to generate fully annotated molecular reports with an easy-to-view format. Under the leadership of Victor Reuter, Joe Sirintrapun, and Ahmet Zehir, a team is now working with Evan Stamelos and our IT group to use similar tactics for data integration from multiple different accessions on the same patient specimen. For instance, integrated reports could include the information from surgical pathology, cytology, and molecular diagnostics reports and allow for an integrated comment to summarize the findings and explain how they interrelate. Progress is already being made, and we anticipate that 2018 will see at least the ability to combine multiple different molecular tests into a single final report. There are challenges to this approach, of course. Integrated reports potentially will contain information in a different format, or even additional information, compared to the “official” report that lives only in CoPath. Unstructured data, such as our morphologic diagnoses other than those in synoptic templates, are difficult to extract and restructure into an integrated report. And, critically, an integrated report is of maximal value only if a pathologist reviews the data and provides an integrated final diagnosis; otherwise, we would still be simply dumping partially digested data into a more convenient place for the clinicians to derive the final interpretation. But, given the landscape of data expansion facing us, I believe these challenges must be met. Pathologists are in a better place now than ever before to take the lead in recommending the best treatment for our patients. We must not let this opportunity slip through our fingers.

David S. Klimstra, MD



A FOCUS ON RARE RENAL CELL CARCINOMA

Ying-Bei Chen's research is improving molecular characterization of high-grade kidney cancers

By Hope Cristol

Ying-Bei Chen, MD, PhD

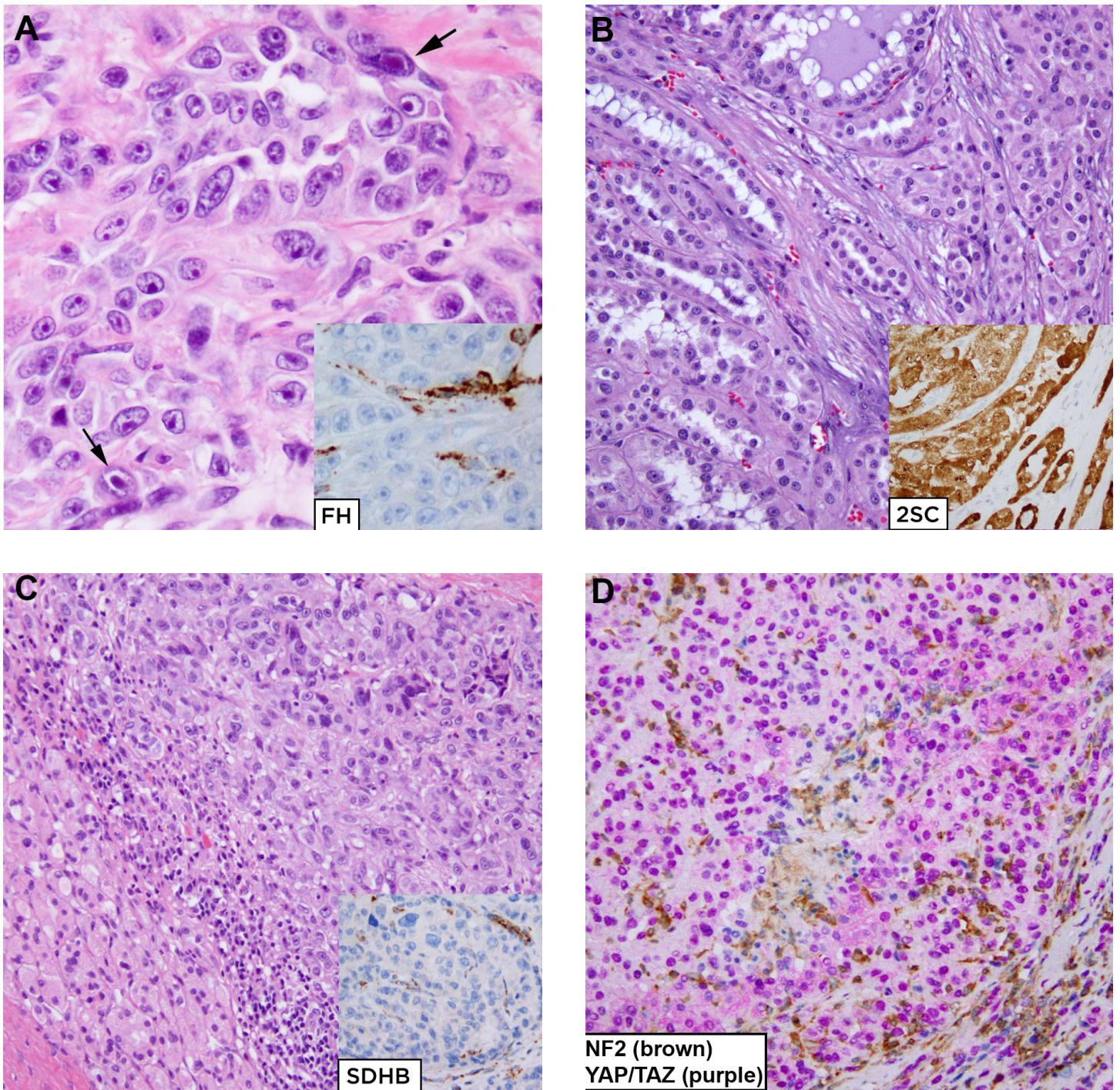
Ying-Bei Chen, MD, PhD, a pathologist on the genitourinary (GU) team, regularly handles complex prostate, bladder, kidney, testicular and adrenal cases. But as a researcher, she has focused her efforts on renal cell carcinomas that are tough to diagnose and to treat.

Part of the challenge with renal cell carcinoma (RCC) is that the histological classification is still evolving. In fact, a significant portion of renal cell tumors still goes unclassified today. "It is clear that histologic subtyping has important

prognostic or management relevance. However, we also realize the limitations of the traditional morphologic criteria, and molecular alterations are increasingly being incorporated into the classification scheme," Dr. Chen says.

The lack of molecular understanding for many uncommon types of renal cancer contributes to the unfortunate reality of limited treatment options – and no standard therapy. But Dr. Chen's research could help change that.





Ancillary markers are playing an increasingly important role in the accurate diagnosis and classification of renal cell neoplasms. **(A-B)** Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome associated renal cancers diagnosed with the aid of two immunohistochemical markers, FH and 2-succinocysteine (2SC). Case **(A)** exhibited prominent viral inclusion-like nucleoli with perinucleolar halos (arrows) and showed a loss of FH staining (inset). Case **(B)** showed predominantly low-grade nuclear features (right) and entirely lacked the nuclear features highlighted in **(A)**. The diagnosis of this case was facilitated by a diffuse positivity for 2SC (inset) and genetic testing. **(C)** Succinate dehydrogenase (SDH)-deficient renal cancer displayed a loss of SDHB immunostaining (inset). **(D)** A subset of high-grade unclassified renal cell carcinoma is characterized by NF2-loss, dysregulated Hippo-YAP signaling, and aggressive clinical behavior. Immunohistochemical double-staining for NF2 (brown) and YAP/TAZ (purple) demonstrated a loss of NF2 staining (membranous and cytoplasmic) and an increased nuclear staining for YAP/TAZ.

UNDERSTANDING PATHWAYS OF UNCOMMON RENAL CANCER

Since joining MSK in 2010, Dr. Chen has been collaborating on research on a range of cancer types, including a SPORE in prostate cancer. But she says she's always been fascinated by kidney cancer. "At MSK, a world leader in treating renal cancer, I get to see a lot of unusual cases and learn from the experts on our team, and my interest continues to grow," says Dr. Chen.

Last year, Dr. Chen was lead author on a paper in *Nature Communications* that identified distinct subsets of aggressive renal cell carcinoma with unclassified histology. She and colleagues performed a molecular analysis of 62 high-grade renal cell carcinomas. They identified recurrent somatic mutations in 29 genes – some associated with better clinical outcome, others with worse survival. From carcinomas with NF2-loss, mTORC1 hyperactivity or DNA damage response defects to those with FH-deficiency or ALK translocation, distinct molecular subsets were found in 76% of this tumor cohort.

Now, those findings are being validated in a larger cohort of 79 cases with similar molecular alterations to confirm the findings they initially reported.

Together with her colleagues on the GU pathology team and other collaborators, Dr. Chen is also working on molecular characterization of other uncommon types of renal cell carcinoma with an aim to improve the current diagnostic criteria and develop biomarkers for diagnosis and therapy prediction. Other current projects include studies on hereditary leiomyomatosis and renal cell carcinoma (HLRCC), succinate dehydrogenase (SDH)-deficient RCC, renal medullary carcinoma and tuberous sclerosis complex (TSC)-associated RCC.

OVERCOMING TREATMENT CHALLENGES

Some of the molecular alterations in renal cell carcinoma appear to drive different clinical behaviors. That's an important piece of the puzzle for developing more tailored treatments – a goal for any type of cancer, and especially types that have no good treatment options, including high-grade, non-clear cell kidney cancer.

The tyrosine kinase inhibitors, for example, "are mainly developed for use in clear cell renal cell cancer," Dr. Chen says. "For many non-clear cell cancers, it often doesn't work."

Clear cell is by far the most common type of renal cell carcinoma. However, given the nature of MSK's cases, clinicians here tend to see a higher-than-normal presentation of rarer cancer types.

Dr. Chen hopes her research will "lead to more study on the pathways in non-clear cell renal cell cancer, and more study on whether any of our findings can be utilized for treatment – as a novel therapeutic target or as an approach to stratify patients for different therapeutic options."

A CALL FOR COLLABORATORS

Dr. Chen has a particular interest in developing better morphological diagnostic criteria and biomarkers for various types of renal cell cancer. "I would welcome any potential collaboration regarding any of the markers we are studying or any molecular aberrations we may identify – not only in kidney tumors, but also other types of tumors," she says.

CYCLE FOR SURVIVAL

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MSK TEAMS

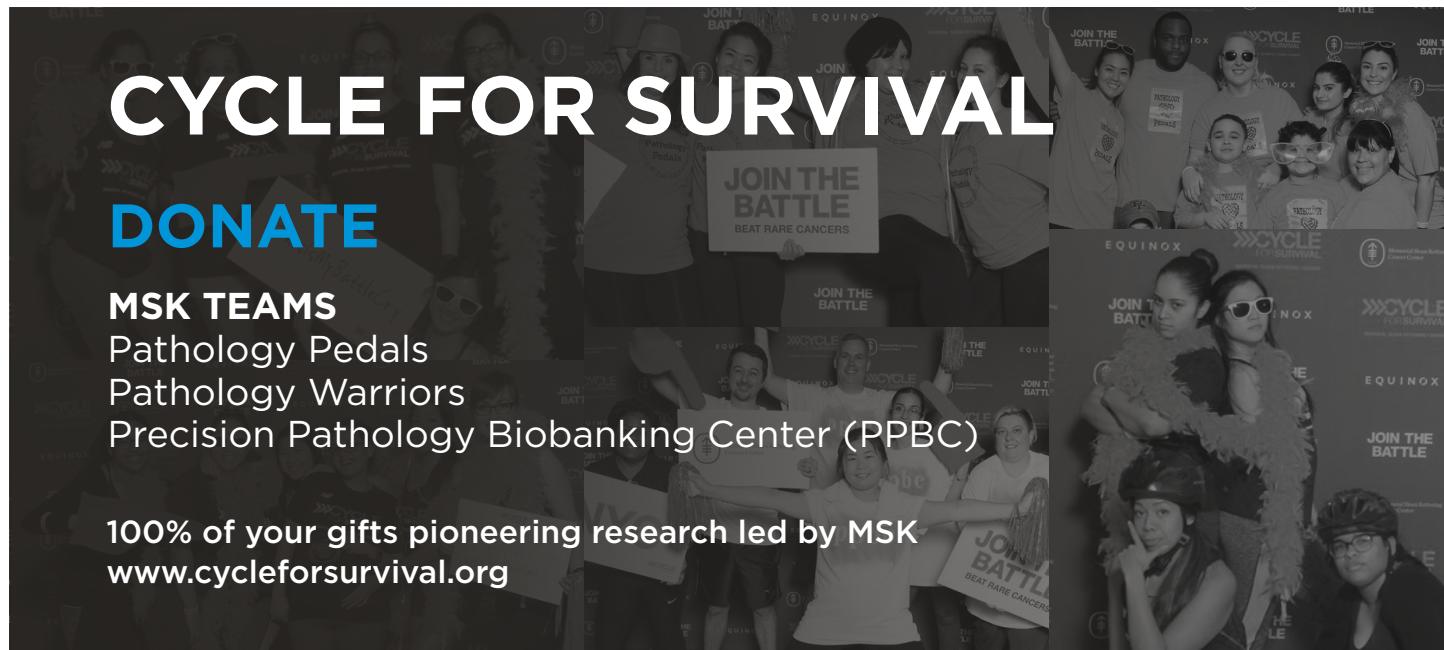
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5 KEY FACTS ABOUT GI PATHOLOGY AT MSK

Team leader Jinru Shia, MD,
shares the highlights

By Hope Cristol

You may have read about Jinru Shia, MD, in the last issue of *MSK Pathology Review*, which emphasized her research on microsatellite instability. Dr. Shia, who is Director of Gastrointestinal Pathology and Director of the Gastrointestinal Pathology Fellowship Program, is just as enthusiastic about her clinical and mentorship responsibilities. In fact, she uses the word passionate to describe how she feels about these responsibilities, and indeed about all aspects of GI pathology, including her colleagues and educating the next generation.



Bottom row: Jinru Shia, MD, Efsevia Vakiani, MD, PhD, Olca Basturk, MD, Jaclyn Hechtman, MD, Carlie Sigel, MD, Laura Tang, MD, PhD
Top row: David Klimstra, MD, Michael Roehrl, MD, PhD

5 KEY FACTS ABOUT THE NINE MEMBER GI TEAM

1

They're an all-star team handling one of the busiest subspecialties in the department

In 2016, GI pathologists reviewed more than 12,000 cases, encompassing a wide variety of common and rare GI neoplasms and allied diseases. "Our team possesses superb diagnostic skills, and we continuously strive to maintain such excellence," Dr. Shia says. "Our daily case review conference presided over by [GI pathologist and Pathology Chair] David Klimstra, MD, has served as one of the most effective forums to share experiences and achieve the best understanding of the nuances and variations of the various tumors."

They work hard to ensure accurate translation of pathological findings in patient care

As medicine advances and cancer treatment options expand, there is a continuous demand for precision pathology, whereby pertinent pathological information serves to guide specific management decisions. "The GI pathologists at MSK are at the forefront of ensuring that pathology reports include thorough, meaningful, clinically relevant parameters," Dr. Shia says. She adds that the GI team also prioritizes close, interdisciplinary interaction with clinical colleagues and active participation in patient care.

2

They're advancing precision oncology in the lab and in the clinic

GI team members conduct laboratory-based mechanistic studies to understand carcinogenesis (Iacobuzio-Donahue et al). Additionally, they are active participants in the development of some of the most important clinical tests tailored to precision oncology at MSK and beyond. "Most recently, our team helped validate the use of MSIsensor from MSK-IMPACT data to detect mismatch repair status across various cancers (Hechtman et al). This work carries important clinical implications," Dr. Shia says. Other recent and ongoing efforts on the biomarker front include immunohistochemistry-based tests for detecting alterations such as NTRK fusions, IDH mutation and PD-L1 expression in various tumors; and immune-proteomic based strategy to discover novel biomarkers (Roehrl et al).

They excel in the "gray areas"

Dr. Shia takes particular pride in sharing her team members' contributions to many "gray areas" in pathology - specifically, tumors that appear morphologically similar but may have distinct biological and clinical characteristics. "These pose significant challenges both diagnostically and in terms of clinical management. Work from our team has helped elucidate some of the ambiguities," Dr. Shia says.

She offers these examples:

High-grade, well-differentiated neuroendocrine tumor versus poorly differentiated neuroendocrine carcinoma (Tang et al.)

Colorectal adenocarcinoma with neuroendocrine differentiation versus true neuroendocrine carcinoma (Vakiani et al.)

Acinar cell carcinoma versus neuroendocrine tumor on cytology (Sigel et al.)

Pancreatic intraductal tubulopapillary neoplasm versus intraductal oncocytic papillary neoplasm versus intraductal papillary mucinous neoplasm (Basturk et al.)

They are passionate educators

Teaching fellows is a treasured role for GI pathologists. "After some years of doing pathology, when you've gathered some experience and learned some tricks, it really gives you pleasure to teach your trainees," Dr. Shia says. "When you realize that you are passing on that knowledge to your fellows as you review cases with them face-to-face, it's a rewarding experience." She adds that many of her colleagues share that sentiment - including Dr. Klimstra, who still signs out cases despite his many responsibilities as Pathology Chair.

Beyond everyday case review with fellows, the GI team also provides didactic conferences, GI subspecialty case review conferences, and interdepartmental tumor boards on a regular basis. In addition, as part of the Pathology Department's educational activity, the team offers a biennial GI tumor pathology course that is attended by pathologists from around the world.

4

RESEARCH PROFILES



Natasha Rekhtman, MD, PhD

ADVANCING LUNG CANCER RESEARCH

Learn about the high-impact work of Natasha Rekhtman, MD, PhD

By Hope Cristol

Thoracic pathologist and cytopathologist Natasha Rekhtman, MD, PhD, tells of a recent case she reviewed: a patient with stage IV lung cancer who first presented with brain metastasis 12 years ago. This was one of the first patients at MSK in whom molecular testing revealed an EGFR mutation. Since then, the patient's disease has been controlled with EGFR inhibitors and she has had good quality of life. It's an exceptional case, of course, but nevertheless a reflection of the progress made in lung carcinoma treatment thanks to targetable biomarkers.

The promise of tissue diagnostics in lung carcinoma was part of what drew her to thoracic pathology and cytopathology (an area that plays an essential role in lung cancer diagnosis and biomarker testing) during her training – first as a resident and fellow at Johns Hopkins, and then as a cytopathology fellow at MSK in 2007. When she joined MSK as a staff attending in 2008, "It was a peak area of transformation in lung cancer," Dr. Rekhtman says.

RESEARCH HIGHLIGHTS

Over the past 9 years, Dr. Rekhtman has helped advance lung cancer research at the molecular, immunohistochemical and basic histopathological level. Here are a few examples of her work in several areas:

PULMONARY LARGE CELL CARCINOMA

This is a morphologically-undifferentiated non-small cell carcinoma. Using combined genomic and immunohistochemical methods, she and her colleagues on the thoracic pathology and diagnostic molecular pathology teams demonstrated a relationship with other major lung cancer types in these tumors, which corresponded with clinical outcomes. The findings were published in *Modern Pathology* in 2014.

LUNG NEUROENDOCRINE NEOPLASMS

Her work in this area is funded in part by a two-year grant from the Fiona and Stanley Druckenmiller Center for Lung Cancer Research. Two recent studies – one in *Clinical Cancer Research* in 2016 and one in *Modern Pathology* in 2017 – involved molecular characterization of pulmonary large cell neuroendocrine carcinomas. Dr. Rekhtman and colleagues identified genomic subsets within these highly-aggressive tumors. Now they are working with oncologists to explore clinical significance of these findings. (She notes that her work in lung neuroendocrine tumors follows a long tradition of related research at MSK, including research by William Travis, MD, Director of Thoracic Pathology, and Pathology Chair David Klimstra, MD.)

SMALL THORACIC BIOPSY AND CYTOLOGY SPECIMENS

Specifically, practical issues related to their utilization for diagnosis and biomarker testing. This is a key area in lung cancer, given that lung biopsy specimens are some of the smallest of all body sites but the panels of diagnostic and predictive markers needed are some of the largest. In the last few years, Dr. Rekhtman worked with Oscar Lin, MD, PhD, Service Chief, Cytology, Darren Buonocore, MD, cytopathologist and thoracic pathologist, and other members of cytopathology to develop a new method of cell block preparation, which enables optimal preservation of cytologic material for ancillary studies. This method is now used by the Cytology Service.

In addition, Dr. Rekhtman was a senior investigator for several studies that will be presented by the thoracic pathology team at the upcoming United States & Canadian Academy of Pathology meeting. One study with thoracic research fellow Joseph Montecalvo, MD; thoracic pathologist and cytopathologist Jennifer Sauter, MD; and others addresses SMARCA4 (BRG1)-deficient tumors of the lung. Another study, with molecular pathology fellow Jason Chang, MD, addresses the genomic and clinicopathologic features of mucinous carcinomas of the lung.

EDUCATING OTHERS

These studies aren't the only form Dr. Rekhtman's non-clinical work takes. She regards teaching as a top priority, speaks regularly at pathology meetings and CME courses, contributed to several chapters of the recently-published WHO classification of thoracic tumors, and has been an author and editor of other recent books on pulmonary pathology.

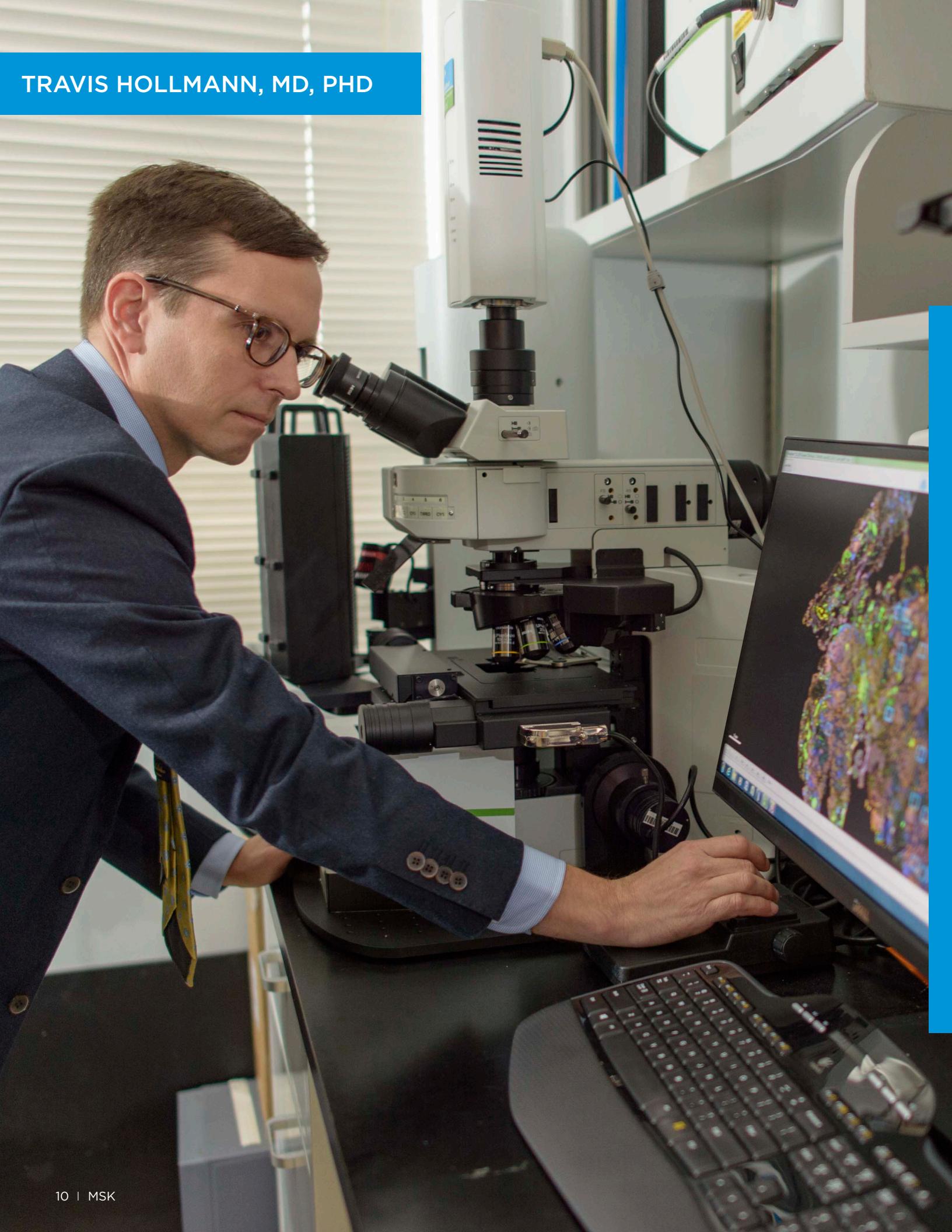
She is also the primary author and editor of the *Quick Reference Handbook for Surgical Pathologists*. Designed for pathologists in training, it includes at-a-glance information on immunohistochemistry, special stains, biomarkers and more. "It's tremendously gratifying to hear from our fellows that they find it helpful," Dr. Rekhtman says.

Dr. Rekhtman is taking primarily an editor role for the second edition, which is currently in progress.

A PROLIFIC RESEARCHER

These highlights represent a fraction of Dr. Rekhtman's pathology research. She also supports a large range of investigations with her clinical colleagues on the thoracic disease management team. Dr. Rekhtman has served as an author or co-author over 80 published studies. In 2017 alone, Dr. Rekhtman's research appeared in 18 publications.

TRAVIS HOLLMANN, MD, PHD



PIONEERING MULTIPLEX PLATFORMS

By Hope Cristol

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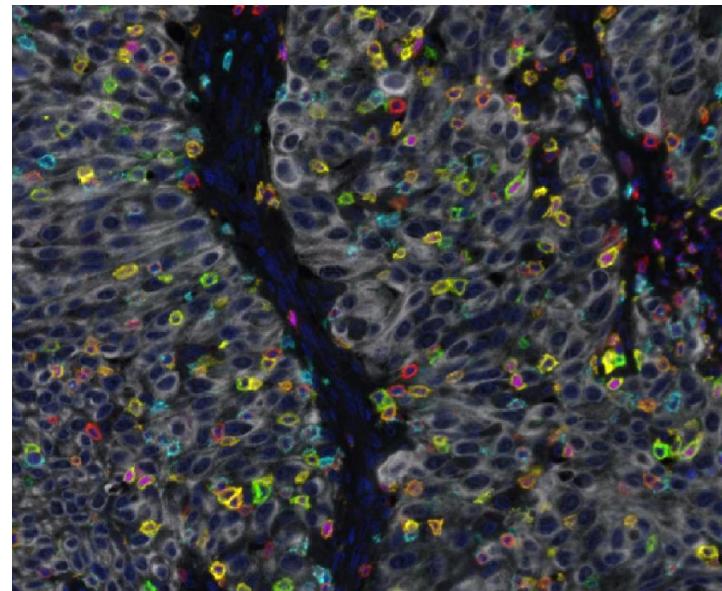
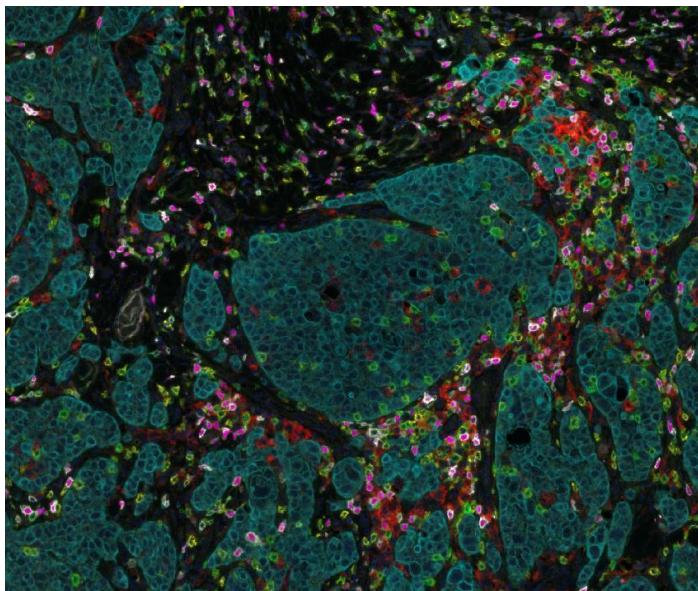
The next-generation tissue imaging platforms and analysis pipelines that we are working to develop and implement are part of the digital pathology revolution.”

Pathologist and immunologist Travis Hollmann, MD, PhD, leads a new immuno-oncology effort

Imagine being able to tell patients that their tumors have not one or two biomarkers that can be targeted with therapy, but several. It's a key goal of precision immuno-oncology, and pathologists are working toward it in numerous ways. Travis Hollmann, MD, PhD, Director of Advanced Immunomorphology Platforms, conducts research with novel staining and imaging technologies that can identify many more targetable antigens than the tools used in clinical practice can.

“In the clinical pathology lab we do over 100,000 immunostains per year with a chromogenic detection system, and we use two colors regularly: red and brown. The problem with that is that you can't easily detect co-localization in the same tissue compartment with standard light microscopy,” Dr. Hollmann says. “So, if CD8 and PD-1 proteins were expressed on the same cell membrane, you'd see overlapping brown and red, and it can be difficult to detect and quantify.” If there were three markers on the membrane, he adds, “it would be virtually impossible.”

The PerkinElmer Vectra is a high-throughput multiplexing system in Dr. Hollmann's lab that uses fluorescence-based detection to identify up to eight markers per tissue section. That's almost twice as many antigens as typical fluorescent microscopes can detect. Paired with slide scanning and a software platform that allows spectral unmixing of overlapping signals, it reports morphological



Fluorescent multiplex staining of pancreatic adenocarcinoma (left) with CD3 (green), FoxP3 (magenta), PD-L1 (red), ICOS (white), CD8 (yellow) and cytokeratin (aqua) and of lung adenocarcinoma (right) with CD3 (red), FoxP3 (magenta), GITR (green), ICOS (yellow), CD8 (aqua), cytokeratin (white) and DAPI (blue).

features, expression data, spatial relationships and other key information.

As impressive as the Vectra is, MSK will be one of a small number of U.S. institutions that will be operating a much more powerful beta instrument referred to as MIBI (multiplexed ion beam imaging). The MIBI platform will initially detect 40-50 biomarkers per tissue section with eventual expansion to 80-100 markers.

While much of Dr. Hollmann's work with these technologies will be in immuno-oncology research within the Parker Institute for Cancer Immunotherapy (PICI) pathology lab, which was established in December 2016, there are many other applications in tumor biology, immunity, cell signaling, tissue repair and development.

"There has been an explosion in the number of immunotherapy trials at MSK, but only a handful of those have a component of precision immuno-oncology," Dr. Hollmann says. "We have nearly 100 immunotherapy trials at MSK with limited knowledge of who would benefit from one trial versus another. We have less knowledge of which patients have a higher risk of adverse events."

The findings that PD-L1 expression in the tumor microenvironment can predict response to PD-1 pathway blocking antibodies is evidence that immune profiling can identify reversible, functional states of leukocytes near a tumor. The goal is to use these platforms to quantitatively profile the tumor microenvironment to reveal additional markers, combinations of markers and spatial relationships that can help stratify patients for trials and ultimately treatment.

A NEW TYPE OF PATHOLOGY LAB

In 2016, PICI leaders Jedd Wolchok, MD, PhD, and Marcel

R.M. van den Brink, MD, PhD, approached Dr. Hollmann about establishing an immuno-oncology-directed pathology lab. The idea was to bring in new technologies to support clinical trials, translational work and the basic science of the MSKCC-PICI investigators, Dr. Hollmann explains.

He's a natural fit to lead the effort. Among his many qualifications, he's both a pathologist – working in the MSK Surgical Pathology Service since August 2012 – and an immunologist. Prior to joining MSK, he worked in the immuno-oncology lab of prominent researcher Arlene Sharpe, MD, PhD, at Harvard Medical School. In addition, Dr. Hollmann has co-authored several studies on tumor response to immunotherapy drugs, and is a study pathologist for checkpoint inhibitor trials at MSK.

The team within Dr. Hollmann's lab is small; just him and the technical director, Yanyun Li, who worked in Dr. Wolchok's lab. They hired a third research assistant, Jason Zhang, to work with Dr. Li in late December, although Dr. Hollmann notes that scientists in other departments are also essential partners. "We've established the lab as a functional collaboration between oncology, pathology and computational biology," he says.

One of his most enthusiastic partners is Dana Pe'er, PhD, a leader in high-dimensional single cell technologies, who will work on downstream clinical correlations – though she has already been invaluable to the lab. Dr. Pe'er played a central role in acquiring the MIBI.

"I sort of envisioned all the different questions and computations and did an investigation in terms of what technologies are out there. My investigation showed that MIBI is a clear winner," Dr. Pe'er says. She also helped convince the Sloan Kettering Institute (SKI) that it was an intellectually valuable investment, as the platform will be a shared resource between Pathology and SKI's Single Cell

Research Initiative.

However, not anyone who wants the machine can have it. MIBI is so new that knowing how to interpret its data is a challenge, even for the company that builds it, Dr. Pe'er says. Just getting selected for the beta program was a feat.

"The combination of my skills as a computational biologist in a single cell domain and Travis's skills as a multiplexed pathologist and in optimizing staining protocols is why we were chosen to get the first machine outside of Stanford," Dr. Pe'er says. "We were chosen as a site to show what this technology could do and put it through its paces."

MULTIPLEX TECHNOLOGIES AT MSK

Dr. Hollmann compares the Vectra system to flow cytometry with spatial context. "If you have many antibodies bound to the same cell, each of those would be linked to a separate dye that has a different emission spectrum," he explains. A fluorescent microscope can detect these different colors – but that's not new to pathology.

"There are numerous fluorescent microscopes at MSK," Dr. Hollmann says. "The difference is that [what they detect] is usually limited to three or four markers on the same cell type. The Vectra uses a mathematical algorithm that corrects for spectral overlap, so you get almost double the usable markers." The Vectra is also a slide scanner designed to accommodate cohorts with automated staining using a Leica Bond RX and batch scanning on the Vectra, facilitated by a 200-slide capacity robotic loader.

Dr. Hollmann uses Indica Labs' HALO platform to help analyze and annotate slides. It reports morphological and multiplexed expression data and has sorting and filtering capabilities, so it's easy, for example, to find the location of the cell or cells with the highest biomarker intensity or to profile cells within any user-defined distance from the tumor.

These tools enable the lab to produce stacked digital images, with a layer for each biomarker, that are rich in spatial and expression information. Still, there's much room for both improvement in these platforms and customization of the output for the needs of the MSK PICI members.

Dr. Pe'er explains that the software requires a lot of manual effort when it comes to labeling, and it doesn't ask sophisticated questions, such as: Are there interesting patterns? Can we say that when you see a cluster of cells that look like cancer, are they likely to respond to a particular immunotherapy?

"To really understand the relationships and clinical implications, you need higher level analysis, and Travis is doing all of this by hand using the wonderful human mind. You can't scale that to large cohorts," Dr. Pe'er says.

Because HALO isn't open-source, MSK scientists can't build that functionality on top of it. To make the Vectra as useful as possible, Dr. Pe'er's team plans to build software that will enable high-level analytical capabilities.

In the meantime, Dr. Hollmann has already made solid progress in his short time focused on multiplexed imaging. His lab has optimized staining processes, validated over 70 individual immuno-oncology markers (including twelve multi-color panels) and processed a non-small cell lung

cancer cohort on Vectra, as well as cohorts of pancreatic adenocarcinoma and ovarian carcinoma.

In conjunction with MSK oncologist Ingo K. Mellinghoff, MD, Dr. Hollmann also co-directs the GE-MSKCC *in situ* single cell proteomics for cancer collaboration. As part of this important collaborative effort with GE Healthcare – and separate from the lab run by PICI – Drs. Mellinghoff and Hollmann have been optimizing another platform called Cell Dive, which extends fluorescent multiplexing to nearly 40 markers per slide.

Looking ahead, Dr. Hollmann and colleagues are eager to start working with the MIBI tool. Instead of using light emission spectra, it uses a mass spectrometer to detect antibodies bound to lanthanide metals.

"Just like fluorescence is analogous to flow cytometry with spatial contexture, MIBI is analogous to CyTOF [mass cytometry]," Dr. Hollmann says. "The MIBI uses secondary ion mass spectrometry so that wherever the antibody or DNA/RNA lanthanide metal conjugated probe is bound, a unique signal is detected."

Potential applications include checkpoint and immunomodulator expression, CAR T-cell functional characterization, vaccine target assessment, metabolic marker assessment, neoantigen expression and combinations thereof.

"The next-generation tissue imaging platforms and analysis pipelines that we are working to develop and implement at MSK are part of the digital pathology revolution," Dr. Hollmann says. "Quantification of multiplexed biomarker staining with new image analysis tools and deep learning techniques is important to guide precision medicine. This will eventually change the way we practice medicine."

TWO KEY BENEFITS

Advanced multiplexing platforms may still be nascent technologies, but they already show compelling advantages such as:

Efficient tissue utilization. Tools like the Vectra system enable pathologists to extract a wealth of information with a limited amount of tissue. That's especially promising for patients whose tumors are in a deep, difficult-to-access location, where only a small needle sampling can be obtained. It also enables more research to be conducted with less material than is often required.

Quantifiable single-cell expression with spatial relationships. "The tissue section is intact with all single-cell marker data embedded in the images," Dr. Hollmann says. "You can look at what is in the tumor microenvironment that may or may not be helping the patient fight the tumor." Several studies show that proximity of certain immune cells within tumors correlates with better outcomes.



Molecular testing of breast carcinoma is a major focus of scientific investigation at MSK, but most decisions regarding patient care still rest on the evaluation of classic histopathologic parameters and tumor receptor profile. Such evaluation has grown highly complex – especially compared to two or three decades ago, when a report might have simply read “invasive carcinoma.”

“There’s been a substantial increase in the number

of histologic parameters we need to evaluate and in the granularity of the information we provide,” says Edi Brogi, MD, PhD, Director of Breast Pathology. “For example, we routinely report the presence and extent of carcinoma transgressing the capsule of a metastatic lymph node. This detail is of fundamental importance to the radiation oncologist to decide whether to treat the axilla with an additional radiotherapy boost.”

As the boundaries of what constitutes routine assessment have expanded, so has case volume – making the breast team extremely busy. In fact, Dr. Brogi says it’s the busiest subspecialty, with more than 14,000 cases a year. About 8,000 of these are from biopsies and surgeries performed at MSK, while over 6,000 are second opinion cases.

As of the end of 2017, the breast pathology team at MSKCC consists of 10 staff pathologists. In addition to Dr. Brogi, the team includes Lee (Kiki) Tan, MD, Dilip Giri, MD, FACP, Christina Vallejo, MD, Melissa Murray, DO (Director of the Surgical Oncologic Pathology Fellowship), Marcia Edelweiss, MD (who is also part of the Cytology Service) and Dara Ross, MD (who is also part of the Molecular Diagnostics Service).

Hannah Wen, MD, Director of the Breast Pathology





INSIDE BREAST PATHOLOGY AT MSK

Director Edi Brogi, MD, PhD, talks cases, studies and more

By Hope Cristol

Fellowship, oversees the activities of the three breast pathology fellows. Amy Zhang, MD, PhD, and Timothy D'Alfonso, MD, just joined from MD Anderson and New York Presbyterian Weill Cornell, respectively. Fresia Pareja, MD, PhD, who also conducts laboratory research under the mentorship of Jorge Reis-Filho, MD, PhD, and Anne Grabenstetter, MD, actively involved in clinical sign out, are 2017-2018 breast instructors.

"Given the volume and complexity of our cases, we are all experts in the field," Dr. Brogi says of her team. "We also meet regularly around the microscope to share our most interesting or challenging cases, and we consult with one another as needed - which gives our team deep expertise, even for the rarest cases, and enables us to provide a timely turnaround of the diagnosis. All our breast pathologists together make our team truly unique and exceptional."

ONGOING STUDIES

Research, naturally, is also a priority for breast pathologists. One area of emphasis is tumor recurrence score (RS) for early stage invasive breast cancer. RS estimates the probability that a tumor will recur if it is treated with hormonal therapy and the possible added benefit of adjuvant



chemotherapy.

For early stage, lymph node-negative, estrogen receptor-positive and HER2-negative breast carcinoma, the RS is assessed based on a 21-gene expression assay. The MSK breast oncology service was among the first worldwide to adopt the 21-gene RS assay in a systematic manner,



From left to right (bottom): Edi Brogi, MD, PhD, Dara Ross, MD, Hannah Yong Wen, MD, PhD, Hong (Amy) Zhang, MD, PhD, Christina Vallejo, MD (top row): Fresia Pareja, MD, PhD, Lee (Kiki) Tan, MD, Dilip Giri, MD, FACP, Marcia Edelweiss, MD (not pictured: Melissa Murray, DO, Timothy D'Alfonso, MD, Anne Grabenstetter, MD)

generating a large body of data inclusive of clinical follow-up information. Recently, the breast pathology team has analyzed the data to assess the clinical utility and pitfalls of the 21-gene RS in specific clinical scenarios.

In one study, Hannah Wen, MD, PhD, evaluated the rate of distant metastases in a cohort of over 1400 patients with low RS (<18). Six patients (0.4%) developed distant metastases within five years of breast cancer diagnosis.

Interestingly, the rate of distant metastasis among patients younger than 40 years was 7.1%, compared to only 0.2% in women older than 40 years. This is a very important finding because patient age was said to not be significant in the study that validated the RS.

"Our results question the application of the RS in younger patients with breast cancer. Further information will probably emerge from the results of the prospective randomized TailoRx clinical trial," Dr. Brogi says.

MSK breast pathologists have conducted additional research on RS as well, including one study that found RS is significantly associated with the risk of locoregional recurrence, and raises the possibility that RS could be useful in identifying breast cancer patients who don't require radiotherapy.

Another line of research explores whether surgical

excision is warranted, as it was predicated in the past, if a high-risk breast lesion is identified by needle core biopsy. After producing seminal work on the management of lesions yielding classic lobular neoplasia (ALH and classic LCIS) at core biopsy, a research team led by Dr. Murray reported that surgical excision of benign vascular breast lesions identified by core needle biopsy is not warranted, as long as the radiologic-pathologic findings are concordant. Drs Edelweiss, Murray, Wen, and Brogi also collaborate closely with Dr Reis-Filho and his research team. In 2017, this joint effort has produced many publications, including novel and seminal work on the molecular alterations underpinning mammary fibroepithelial lesions.

In addition to clinical and research activities, the breast pathology team also plays an important role in education. In January 2018, Drs. Wen and Brogi will jointly teach a three-day, interactive microscopy course for the United States & Canadian Academy of Pathology (USCAP) called "A Practical Approach to Problematic Breast Lesions." Plus, a number of abstracts authored by fellows and team members will be presented at the upcoming USCAP meeting in Vancouver.

"The breast pathology team looks forward to 2018 being another exciting and productive year," Dr. Brogi says.

FDA AUTHORIZES MSK-IMPACT

Landmark validation of clinical relevance for genomic profiling of cancers

By Hope Cristol

In November, the U.S. Food and Drug Administration (FDA) announced the authorization of MSK-IMPACT, the flagship tumor sequencing test developed by our institution's genome scientists, bioinformaticians and molecular pathologists. It is the first test of its kind to receive this distinction. The FDA's authorization of MSK-IMPACT also advances a new policy framework that will allow for FDA third party review through the FDA's accreditation of New York State Department of Health (NYSDOH).

"It's cheaper, faster and more sensitive than other methods," says Michael F. Berger, PhD, Associate Director of the Marie-Josée and Henry R. Kravis Center for Molecular Oncology and an Assistant Attending Geneticist in the Department of Pathology. "MSK-IMPACT allows us to have, in one test, a comprehensive system for looking at any possible genetic mutation in any gene that's related to cancer."

The approval news comes after months of collaboration with MSK staff, the FDA and the New York State Department of Health (NYSDOH) – which approved the assay as a laboratory developed test in 2014 after a rigorous validation process. It has been further refined and optimized since then. Currently the assay tests for 468 genes, up from the original 341.

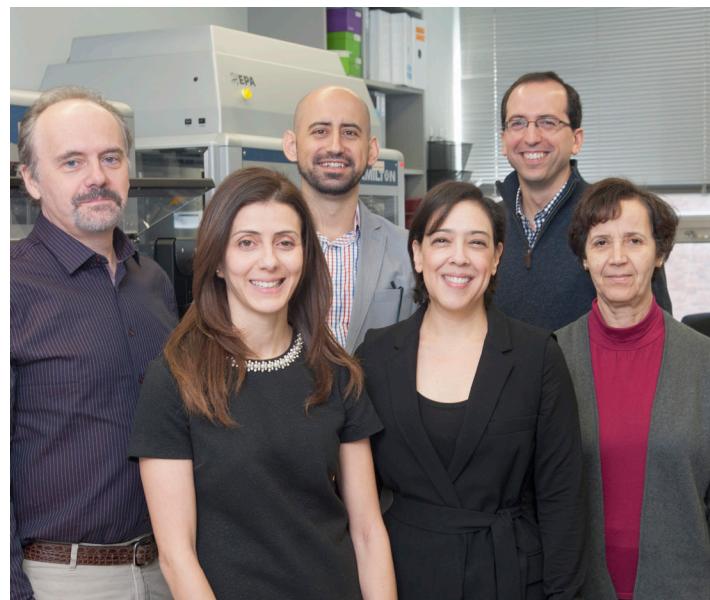
The authorization of MSK-IMPACT represents a major achievement from a large team in the Molecular Diagnostics Service, led by Marc Ladanyi, MD. In addition to assembling validation data and fielding numerous questions from the FDA, this team helped develop and refine the intended use statement, which dictates precisely how the test can be marketed – including what MSK can report and how it can be reported to clinicians.

While those at MSK emphasize the accomplishment is a team effort, they also point to the "heavy lifting" of one colleague in particular: Ahmet Zehir, PhD, Director of Clinical Bioinformatics. "My team is in charge of all the data analysis

for MSK-IMPACT, so I have been working with the FDA to provide them with the data points that they needed for the validation, as well as documentation on the software that my team has been developing," he says.

What could the FDA approval mean for the future? Dr. Berger is hopeful it could lead to broader insurance reimbursement. It may also help more patients get in to large clinical trials based on mutations in their tumors.

"What it doesn't mean is that we can sell the test to other labs," Dr. Berger adds. "It only pertains to the sequencing that we're doing at MSK. But this in itself is significant, as we have already tested more than 20,000 patients since 2014."



From left to right (bottom row): Ryma Benayed, MD, Maria Arcila, MD, Khedouja Nafa, PharmD, PhD (Top row): Marc Ladanyi, MD, Ahmet Zehir, PhD, Michael Berger, PhD

THE 2017 FRED W. STEWART AWARD

ANDREAS HELMUT ROBERT VON DEIMLING, MD

By Marc K. Rosenblum, MD

Dr. Andreas von Deimling is the 2017 recipient of the Fred Waldorf Stewart Award, bestowed annually by the Department of Pathology at Memorial Sloan Kettering Cancer Center on an individual who has made outstanding contributions to the characterization of human neoplastic disease. Honored for his efforts in the field of tumors involving the central nervous system (CNS) and its coverings, Dr. von Deimling currently serves as Chairman of the Department of Neuropathology at the University of Heidelberg, Germany (his home country) and as Founding Director of the Clinical Cooperation Unit (CCU) in Neuropathology under the auspices of the German Cancer Center (Deutsches Krebsforschungszentrum).

Dr. von Deimling completed his MD at the University of Freiburg, interrupting his studies there for two forays into laboratory-based research that bore early witness to his academic leaning. The first of these, in 1983, was to the famed Medical Research Centre Harwell (United Kingdom), an enterprise dedicated to the study of murine genetics and headed at the time by Mary Lyon (she of the Lyon hypothesis of X chromosome inactivation). Working under the direction of Dr. Jo Peters, Dr. von Deimling mapped the mouse biliverdin reductase gene. One year later, he travelled to the United States to work at the National Institutes of Health in the laboratory of Dr. Michael Potter, who had developed mouse models of plasmacytoma and who would win the Albert Lasker Basic Medical Research Award for fundamental investigations into immunoglobulin genetics that paved the road to hybridoma technology. It was there that Dr. von Deimling, under the tutelage of Dr. Konrad Huppi, had his first direct contact with molecular genetic methods.

In 1988, Dr. von Deimling commenced training as a resident in the Department of Neuropathology at the University of Zurich (Switzerland) under the distinguished Paul Kleihues. From those days date his earliest first-author efforts in the human brain tumor area, studies investigating



the histogenesis and differentiating potential of central neurocytomas. Unaware of the precise uses of such materials but realizing that assays of potential research interest such as Southern and Western blotting required non-fixed tissues, trainee von Deimling took it upon himself to begin systematically freezing CNS tumor samples coming from the operating rooms. This must figure among the earliest efforts in brain tumor banking and would pay high dividends in the years to come, but it was an exasperated Professor Kleihues who wondered at the diminishing size of formalin-fixed, paraffinized tumor sections crossing his microscope for diagnosis.

Dr. von Deimling's intellectual restlessness had him interrupting his residency and, in 1990, again making for the United States, this time to the laboratory of Dr. Bernd Seizinger in the Department of Neurosurgery and Molecular Neuro-Oncology at the Massachusetts General Hospital / Harvard Medical School. The experience determined the path of his subsequent career as an academic neuropathologist principally focused on the molecular genetics of primary brain tumors. In Boston, Andreas met and partnered with Dr. David Louis, embarking on large-scale loss of heterozygosity (LOH) studies that employed the brain tumor samples collected in Zurich. The pair and their co-workers, among many original observations, would implicate chromosome 19q in the pathogenesis of diffuse gliomas and demonstrate the consistent association of allelic losses involving this and chromosome 1p with tumors exhibiting the histology of

publications be provided, as if that number alone could stand guarantee of the subject's impress. Very well. We hover near 500 and, yes, these have regularly appeared in the most demanding and influential of periodicals. Dr. von Deimling's investigations have ranged over the spectrum of neuroepithelial, meningotheelial and mesenchymal neoplasms affecting children and adults, delineating genetic and epigenetic profiles that are now recognized as characteristic of diffuse gliomas, ependymomas, medulloblastomas and other embryonal tumors, choroid plexus tumors, meningiomas and neoplasms of peripheral nerve sheath origin. A close parsing of these contributions is beyond the confines of this sketch and so the writer has decided to invoke the spirit of Stewart himself and limn those works accomplished by von Deimling and his CCU Neuropathology that have come to bear specifically on the practice of surgical

“ THINKING is more interesting than KNOWING, but less interesting than LOOKING. ”

- Johann Wolfgang von Goethe

oligodendrogloma or oligoastrocytoma. Most readers will be aware that chromosome 1p/19q co-deletion is now a defining feature of “canonical” oligodendroglomas as codified in the 2016 World Health Organization (WHO) taxonomy of CNS neoplasms. Noteworthy as well from this period is a study so novel at the time that von Deimling and colleagues had great difficulty getting it published. It is hard to fathom the resistance they met now, as the work demonstrated that glioblastomas, recognized as heterogeneous in their clinical biology and histology, could be subdivided into molecular genetic subsets.

Following his sojourn in Boston, Andreas returned to Germany, completing his training as a resident in the Department of Neuropathology at Bonn where he was mentored by renowned Professor Otmar D. Wiestler and awarded the Hermann and Lilly Schilling Professorship. After several highly productive years as a consultant in that department, Dr. von Deimling went on to assume Directorship of the Department of Neuropathology, Charite, Berlin (1998–2006) before being recruited to his current Chair position at Heidelberg. The effort to create the interdisciplinary CCU Neuropathology was initiated when Andreas accepted the Heidelberg offer. He assumed personal responsibility for the recruitment of its members, who under his direction now constitute a team unrivaled in the defining of adult and pediatric brain tumors as molecular genetic entities and, of particular relevance to the award memorializing Fred Stewart, in the development of diagnostic tools for use by pathologists the world over.

Tradition demands of those composing academic encomia that the honoree's tally of peer-reviewed

neuropathology and that suggest the future course of this subspecialty.

Following the discovery of isocitrate dehydrogenase (IDH) mutations in a subset of glioblastomas, Dr. von Deimling and team demonstrated a high incidence of IDH1 codon 132 mutations in diffuse astrocytomas and oligodendroglomas (WHO grade II and III) as well as “secondary” glioblastomas arising in young individuals. These proved foreign to neuroepithelial neoplasms of other types and to reactive processes. In 2009, his group announced the development of a sensitive and specific antibody to IDH 1 R132H, the isoform accounting for approximately 90% of all mutant IDH species encountered in diffuse gliomas. The use of this commercially available reagent rapidly assumed standard-of-practice status in pathology laboratories the world over, as the immunohistochemical demonstration of IDH1 R132H labeling came to be accepted by both basic and clinical neuroscientists, neuro-oncologists included, as proof positive of this specific mutational event. The application of this single reagent to the analysis of neurosurgical material potentially allows even the unpracticed observer to identify a glial proliferation as neoplastic rather than hyperplastic, to assign the tumor thus identified to the diffuse glioma series, and to convey information of substantial prognostic and predictive import (IDH-mutant gliomas are considerably less aggressive than their wild-type counterparts and IDH inhibitors are in clinical trial for affected patients; in fact, von Deimling and crew have recently developed and characterized a novel pan-mutant IDH1 inhibitor that they have shown to be active against human IDH-mutant astrocytomas). The Heidelberg team subsequently challenged the legitimacy of traditional

histologic grading when divorced from an assessment of IDH status, showing that most IDH wild-type astrocytomas qualifying for WHO grade II designation actually have molecular genetic signatures associated with glioblastomas, generally behaving as such, and, in retrospective analyses, demonstrating that comparable outcomes attach to IDH-mutant astrocytomas classified as WHO grade II or III. This neuropathologist hasn't a colleague who does not employ the anti-mutant IDH1 antibody in a simple diagnostic algorithm (or some variant thereof) proposed by Dr. von Deimling and company for the subclassification of diffuse gliomas into molecularly distinct and clinically relevant entities.

The successes detailed above were repeated in 2011 when the von Deimling group announced the development of an antibody specifically identifying BRAF v600E, a mutant BRAF species encountered in a variety of extraneuronal tumors that prominently includes cutaneous melanomas, papillary carcinomas of the thyroid gland, Langerhans cell histiocytosis, Erdheim-Chester disease and, at lower frequency, borderline ovarian tumors and colorectal adenocarcinomas. Andreas and co-workers would go on to demonstrate BRAF v600E mutation in most pleomorphic xanthoastrocytomas and in a significant subset of gangliogliomas, the roster of potentially BRAF v600E-mutant brain tumors now including "epithelioid" glioblastomas, pilocytic astrocytomas, a variety of low-grade glial and glioneuronal neoplasms seen mainly in the young, and papillary craniopharyngiomas. This reagent has become a staple of practice across pathologic subspecialties for its obvious value in matters of tumor subclassification and in identifying candidates for BRAF inhibitor treatment. Andreas and colleagues have also demonstrated that meningeal hemangiopericytomas and solitary fibrous tumors constitute an entity unified by NAB2-STAT6 gene fusions, as displayed by their extraneuronal counterparts, and have proven the value of nuclear STAT6 overexpression as an immunohistochemical phenomenon reliably distancing such lesions from meningiomas and other neuraxial mimics.

Recent efforts by Dr. von Deimling and the Heidelberg team address epigenomic brain tumor profiling. Utilizing an expansive and carefully annotated collection of neoplasms, the group demonstrated that entities having established histologic features, genetic abnormalities and patterns of gene expression also have identifying signatures on CpG methylation array. Andreas and co-workers then developed a CpG methylation array-based algorithm for purposes of tumor classification that they offered to apply gratis to tumor samples sent to them by pathologists practicing anywhere in the world. This powerful technology has proved capable not only of accurately pigeon-holing many neoplasms of poorly differentiated or otherwise ambiguous morphology, but suffices to identify clinically relevant subtypes within tumor categories (e.g., Wnt or SHH-driven medulloblastomas, RELA-fused ependymomas and C19MC-altered embryonal tumors with multilayered rosettes). Methylation array profiling also played a major role in the recent identification of several novel entities hidden under the obscuring rubric of "primitive neuroectodermal tumor".

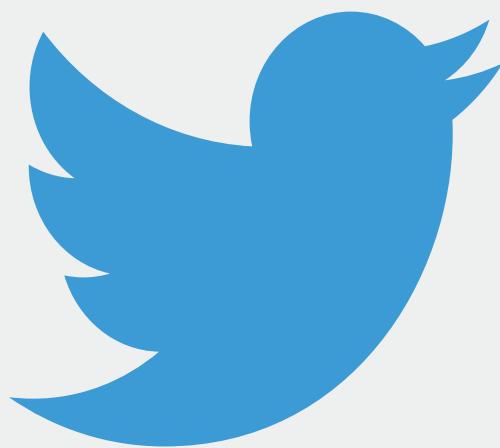
MSKCC is hardly first in recognizing Dr. von Deimling's



outsized role in brain tumor characterization and in shaping the careers of younger investigators in the field. An elected fellow of the European Academy of Cancer Sciences, he has delivered the A. Julio Martinez Lecture (created by the Department of Pathology at the University of Pittsburgh School of Medicine to memorialize the great Cuban-born neuropathologist), has won the Abhijit Guha Oration Award (bestowed by the Indian Society of Neuro-oncology in memory of the skilled neurosurgeon and investigator who figured prominently in the establishment of a National Neurosciences Centre in his native Kolkata), and is the recipient of the Dorothy S. Russell Medal (given by the British Neuropathological Society in celebration of the towering figure who co-authored Russell and Rubinstein's classic Pathology of Tumors of the Nervous System and who was the first woman to be appointed to a pathology chair in Western Europe). In 2016, Andreas collected the prestigious German Cancer Prize (Deutscher Krebspreis) in the translational research division. He was also recruited by the WHO as a senior advisor to the formulation of the revised 4th edition of the "blue book", WHO Classification of Tumours of the Central Nervous System (2016), a work that broke with a century of tradition by departing from the exclusively morphologic and building molecular genetic characteristics into the very definition of select entities.

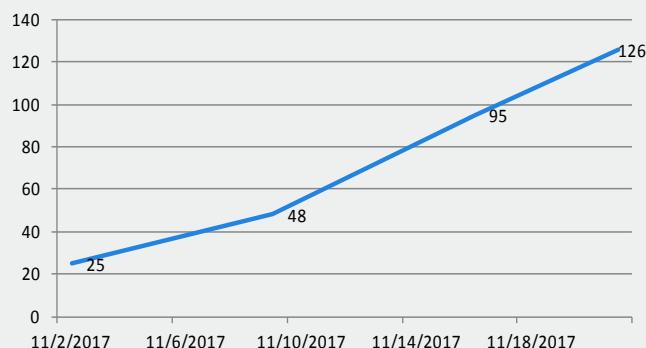
Dr. von Deimling must now make room in his trophy case for the Fred Waldorf Stewart Medal. That "the old man" approves is a surety. While rightly revered as a preternaturally gifted morphologist, Dr. Stewart, as dean of tumor pathologists, as James Ewing's successor to the Chair of Pathology at Memorial Hospital and Founding Editor of the journal Cancer, advocated throughout his career for the application of novel technical methods to the study of neoplastic disease. In this, he was propelled by that curiosity which has ever informed the creative and which was enunciated by one of Dr. von Deimling's great countrymen thus: "Thinking is more interesting than knowing, but less interesting than looking." - Goethe

To which we can only add — Keep looking, Andreas. Keep looking.



TWITTER USAGE STATS

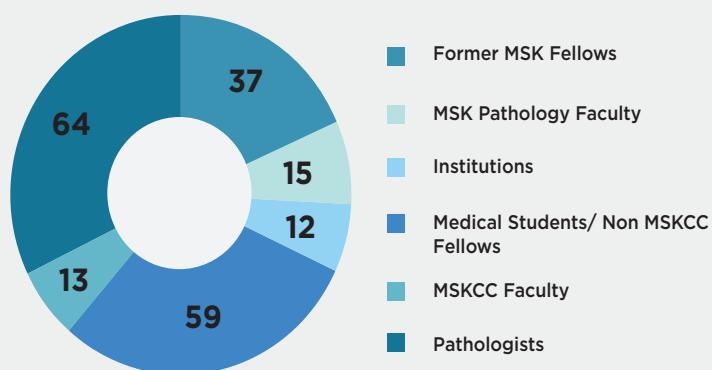
NUMBER OF FOLLOWERS



308 mentions regarding
#MSKImpact

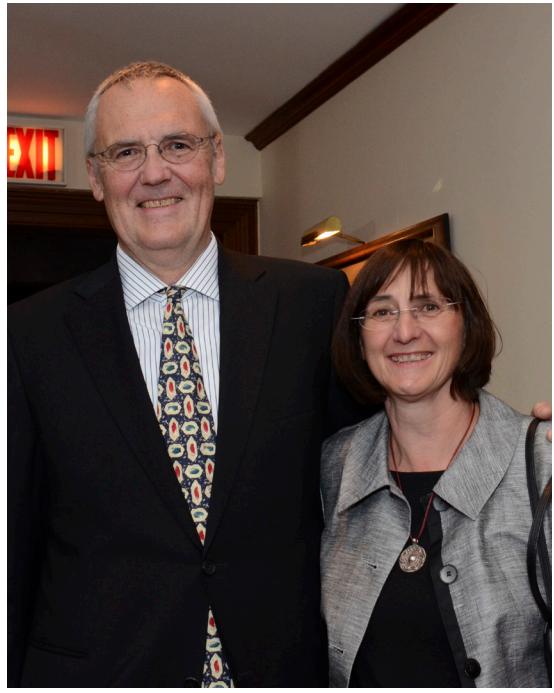
MD's WHO TWEET

- Hannah Wen @HannahYWen
- Natasha Rekhtman @NatashaRekhtman
- Olca Basturk @OlcaBasturk
- Ying-Bei Chen @Unclassified1
- Hikmat Al-Ahmadie @whynottwitgu
- Efsevia Vakiani @evakiani
- Edi Brogi @EdiBrogi
- Hong Amy Zhang @Hazhang9
- Jennifer Sauter @JL_Sauter
- Jaclyn Hechtman @JackieHechtman
- Samson Fine @rovingatuscap
- Marc Ladanyi @MLadanyi



2017 ALUMNI MEETING AND RECEPTION





NOVEL DISCOVERIES RARE EXPERTISE

Narasimhan Agaram's work on the bone and soft tissue team helps pathology and patients

By Hope Cristol

Like many pathologists at MSK, Narasimhan Agaram, MBBS, started as a fellow – but he didn't join the staff right away. Following his 2003-2004 fellowship in cytopathology, he pursued research for two years in the lab of Cristina Antonescu, MD, MSK's Director of Bone and Soft Tissue Pathology. Dr. Agaram then moved on, becoming an assistant professor of pathology at Indiana University School of Medicine.

His work in New York was not forgotten. When Dr. Agaram applied for a position at MSK a few years later, the Pathology Department was happy to bring him on board. "Memorial received a SPORE grant in soft tissue sarcoma, so this required one more pathologist to handle and share the clinical responsibilities," Dr. Agaram says.

He returned to MSK in 2011, this time working across two specialties: bone and soft tissue and Cytology. He notes that the bone and soft tissue team has made some important discoveries during his time here.

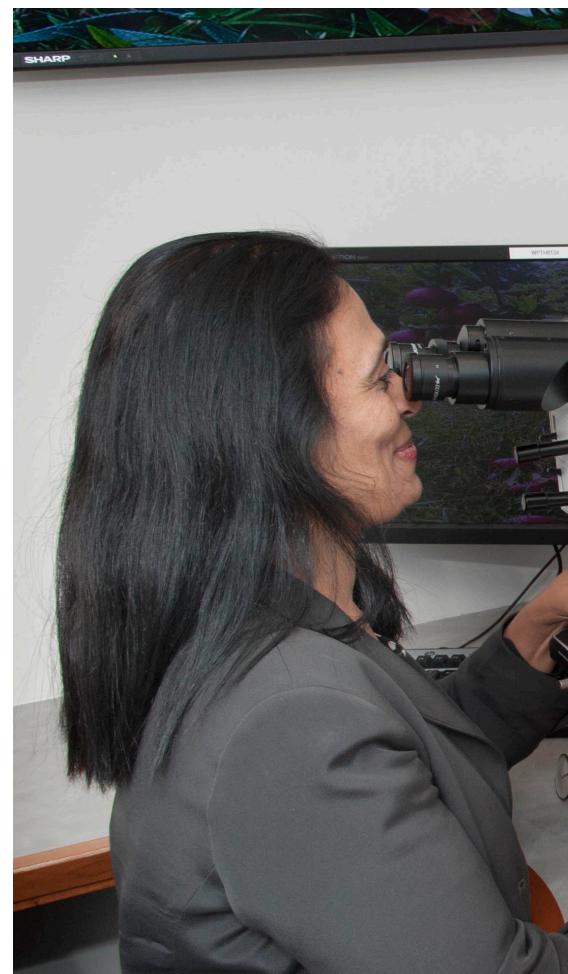
"We are subclassifying these lesions a lot better than we used to even a decade ago because we know a lot more about their genetic abnormalities," Dr. Agaram says. "What used to be commonly termed as one tumor, we may now split into different groups based on genetic abnormalities. Or, vice versa, what we thought of as different tumors before, we now

find they have the same genetic abnormalities."

RESEARCH: A TOP PRIORITY

Because bone and soft tissue tumors are relatively uncommon, the research aspect of this sub-specialty team including studies by Dr. Agaram in association with Dr. Antonescu, are especially important.

Dr. Agaram was the first author on a 2014 paper in *Genes, Chromosomes and Cancer* that suggests, among other things, MYOD1 mutations in pediatric rhabdomyosarcoma correlate with aggressive disease and high mortality.



The following year, in the *American Journal of Surgical Pathology*, Dr. Agaram was the first author on a paper that analyzed results of a comprehensive genetic analysis on perivascular epithelioid cell neoplasms (PEComa). These were located not only in soft tissue, but also organs including



Meera Hameed, MD, Narasimhan Agaram, MBBS, Cristina Antonescu, MD



NARASIMHAN AGARAM, MBBS

the uterus, kidney, liver and lung. The analysis found similar morphology and genetic alterations in TSC2-mutated, TFE3 fusion negative PEComas across the board – suggesting clinicians regard such tumors as a single group, rather than site-specific neoplasm.

And then there's the discovery of NTRK1 genetic abnormalities in a subset of spindle cell neoplasms. "When we identified the NTRK1 rearrangement it was unique. It was not known before that soft tissue tumors have NTRK1 rearrangements," Dr. Agaram says.

Previously, those genetic alterations were known to occur in other tumors, including gliomas, nevi and some colorectal tumors. Adding soft-tissue tumors to the list would, potentially, expand the indications for drugs that have been developed in the past few years to target the NTRK1 rearrangements.

SHARING RARE EXPERTISE

In addition to Dr. Agaram, the two

other senior pathologists on the bone and soft tissue sub-specialty team are Drs. Cristina Antonescu, team leader, and Meera Hameed, Chief of Surgical Pathology. All three share this rare expertise and their day-to-day cases include soft-tissue malignancies such as liposarcoma, leiomyosarcoma, undifferentiated sarcoma and other unique soft tissue tumors. Osteosarcoma and Ewing sarcoma, bone cancers that tend to strike young people and chondrosarcomas and chordomas which affect adult population are also routinely diagnosed.

There is a unique importance, and perhaps urgency, to their clinical work. "There is not much expertise out in the community for diagnosis and management of these tumors," Dr. Agaram says.

To ensure the most accurate diagnosis, and thus the best possible treatment outcome, educating and collaborating with MSK colleagues is crucial. In addition to working with surgeons and oncologists, "we work

very closely with musculoskeletal radiologists, especially for bone tumors," Dr. Agaram says. "Sometimes two different bone tumors can look similar under the microscope, but based on the imaging characteristics they may have very different connotations."

He also stresses the educational importance of weekly tumor boards, which include trainees in pathology, radiology and surgery and respective attendings.

"Through these conferences, we [pathologists] educate clinicians about any new genetic abnormality we've identified. If they know that a certain mutation may help determine whether one drug is more effective than another, they may decide to alter management," Dr. Agaram says. "That is one way we educate the clinicians about pathology and how genetic analysis of tumors may help better management of these patients."

GERMLINE TESTING

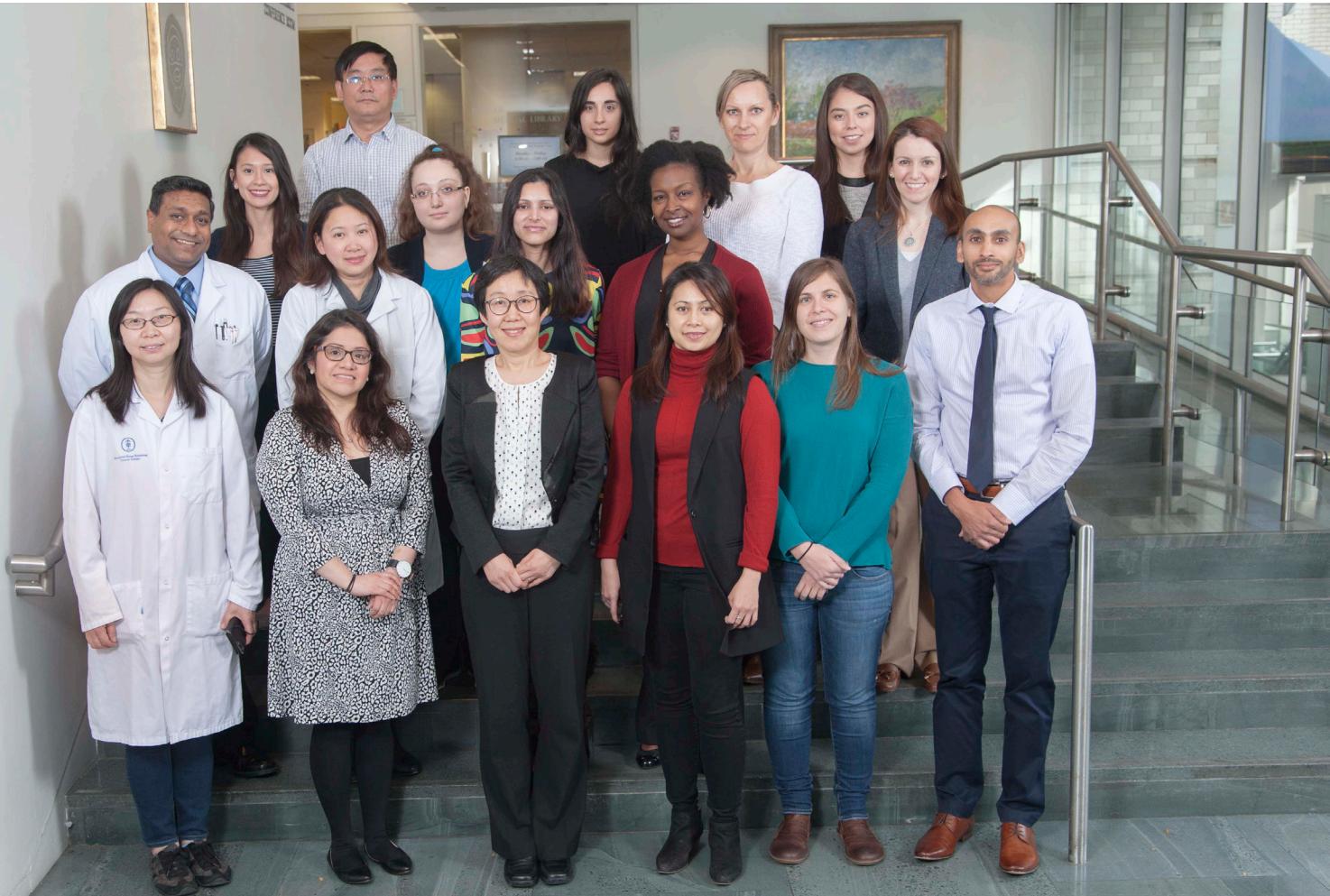
with MSK IMPACT

A conversation with two leaders in the assay's development and use

By Hope Cristol

MSK-IMPACT has been receiving well-deserved attention in the wake of its recent U.S. Food and Drug Administration (FDA) authorization as the first high-throughput tumor profiling assay for detection of somatic mutations. A separate assay, Germline MSK-IMPACT, tests for mutations that can indicate a hereditary predisposition to cancer. Although the germline genetic test was not submitted to the FDA for approval, it's a valuable tool for both clinical and research purposes at MSKCC.

Molecular geneticist Liying Zhang, MD, PhD, Director of the Diagnostic Molecular Genetics Laboratory, and pathologist Diana Mandelker, MD, PhD, Associate Director of the Molecular Genetic Pathology Fellowship Program, are two leaders on the germline team. They recently spoke with *MSK Pathology Review* about the assay's evolution and potential role in cancer care.



From left to right (bottom row): Ciyu Yang, Sandy Naupari, Liying Zhang, MD, PhD, Marie Chamian, Ester Borras Flores, PhD, Tamim Malbari (2nd row): Josh Somar, Donna Wong, Sowmya Jairam, Samantha Phillip (3rd row): Andrea Rosado, Zarina Yelskaya, Edyta Brzostowski, Ozge Birsoy, PhD (Top row): Yirong Li, Silvana Ostafi, Stephanie Argueta (not pictured: Diana Mandelker, PhD)

Pathology Review: Why did you decide to create a separate germline assay?

Dr. Mandelker: In January 2014, we set up a protocol where mostly advanced cancer patients can have their tumor sequenced looking for somatic alterations. We had each patient submit a tumor as well as a blood specimen, and the blood specimen gave us the opportunity to detect germline mutations that confer hereditary predisposition to cancer. In 2015, we officially launched the germline assay, so patients who were undergoing tumor sequencing to look for somatic alterations could also consent to germline analysis to find out if they had a hereditary predisposition to developing cancer.

Pathology Review: Are there certain cancers the germline assay might be more relevant for than others?

Dr. Zhang: Yes, absolutely. We carefully selected the genes that would go on a 76-gene panel (recently expanded to 88 genes). The genes pretty much cover all cancer predisposition syndromes and can particularly detect hereditary breast, ovarian, colorectal, gastric and pancreatic cancers.

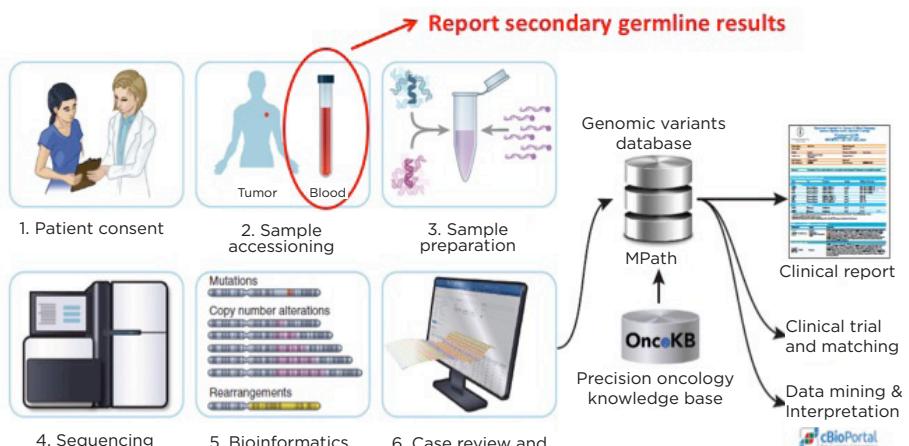
Pathology Review: Is it typical to test for so many cancer predisposition genes?

Dr. Zhang: The current genetic testing is driven by the NCCN [National Comprehensive Cancer Network] guidelines. Our research found that about half of the actionable mutations will be missed if we follow those guidelines, so this is an important contribution of our work to the field of cancer genetics.

Pathology Review: Why would a patient want germline testing, when somatic alterations tend to make the best drug targets?

Dr. Mandelker: A hereditary predisposition to cancer can be actionable in several ways. For example,

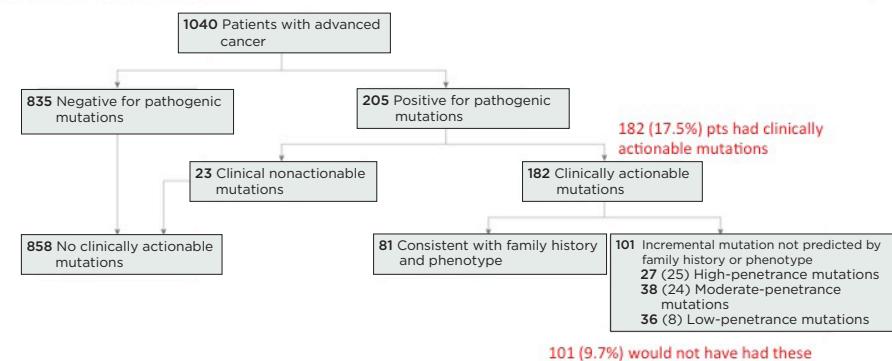
Overview of the MSK-IMPACT clinical workflow



Nature Medicine 2017 Jun;23(6):703-713

Major Findings in the JAMA Paper

Figure. Clinical Actionability, Concordance With Family History and Phenotype, Penetrance, and Founder Mutations in 1040 Patients Undergoing Sequencing of Germline and Tumor DNA

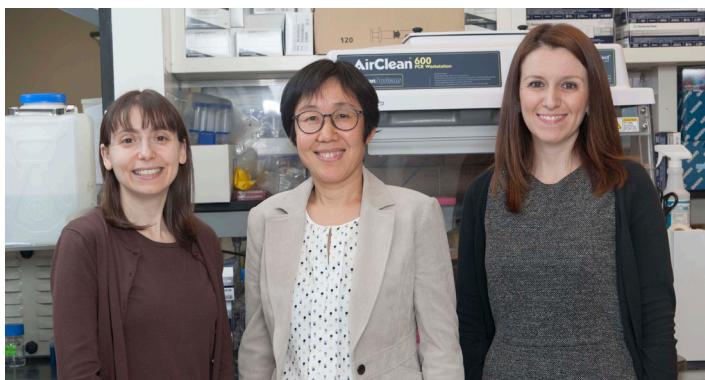


JAMA. 2017 Sep 5;318(9):825-835

patients with BRCA1 and BRCA2 pathogenic variants are candidates for a treatment called a PARP inhibitor. In addition, once we identify our patients with a hereditary predisposition to cancer, we then test their family members to determine which of them carry this same genetic mutation. For those family members at high risk, we can enact preventive measures such as earlier screenings. In some cases, such as in the BRCA1 and BRCA2 example, family members may choose to have prophylactic mastectomies or oophorectomies.

Pathology Review: After getting test results, how do patients know what to do next?

Dr. Mandelker: We are extremely fortunate here at Memorial Sloan Kettering Cancer Center that all patients who have germline pathogenic mutations are offered counseling by our Clinical Genetic Service so that they can themselves be counseled, and at-



Diana Mendelker, PhD, Liying Zhang, MD, PhD, Ozge Birsoy, PhD

risk family members can be identified and tested as well.

Pathology Review: What's the next stage of evolution for the germline assay?

Dr. Zhang: We expanded the panel to 88 genes and already received NYSDOH's approval to offer the assay under a research protocol. On the other side, we are going to break this large panel into smaller panels so they are more cancer specific – breast, colorectal, prostate, gynecologic, renal, etc. Another thing I want to mention is we currently test advanced cancer patients, but we have plans to offer the

Q & A WITH JENNIFER SAMBOY



Senior Project Manager for Pathology Initiatives and Strategic Planning

Q: You've been at MSK for 10 years. How has your career here evolved?

I started in the Radiology Department as an Administrative Coordinator in 2007, supervising the administrative staff who supported the radiologists and managing the interventional radiology (IR) clinic. I reported directly to the Department Administrator, Patricia Soto, who afforded me the opportunity to work on larger projects, such as space planning and IT initiatives to gain project management experience. In April 2011, I became the Administrative Manager in the Pathology Department, overseeing the day-to-day operations and managing the non-technical staff. I learned a great deal in my five years in the role. I am currently the Senior Project Manager for the Warren Alpert Foundation Center for Digital and Computational Pathology. I'm now responsible for the department's digital and computational pathology workflows and department-wide initiatives that require major workflow changes.

Q: What is one of the main responsibilities of your new role?

As manager for the Warren Alpert Center, I work collaboratively with the Center's directors to help move our digital and computational pathology initiatives forward. We are currently evaluating different technology and partnering with vendors to help improve the technology that's already out there. Hopefully we will influence the technology of tomorrow so that it has practical utility in a busy clinical setting like ours. My goal is to help make digital

test to early stage cancer patients and even their family members.

Dr. Mandelker: We're constantly on the lookout for new discoveries linking genes to a hereditary predisposition for cancer. We will add those genes to our panel to help provide the most comprehensive genetic testing that we can for our cancer patients. We are also monitoring clinical outcomes to see whether we are able to prevent cancer in relatives, and whether our patients respond to the therapies they receive as a result of the mutations we detect.

pathology exciting for our pathologists, our department and MSK!

Q: What else are you doing at MSK?

Other than the work that I do for the Warren Alpert Center, I also have other ongoing projects within the Pathology Department that I manage in my new role as Senior Project Manager. This year and next, we'll continue working toward electronic orders for specimen collection and a tracking system for our pathology material. I also help with space management in our department, which means finding space for new technologies and initiatives that we have going on. I also work on larger space planning initiatives such as the opening of the MSK David H. Koch Center for Cancer Care in 2018.

Q: What are some of your career highlights here?

I would say I'm known for space and operations management and have gained a lot of experience in IT project management. In the Pathology Department, I helped with the opening of Josie Robertson Surgery Center in 2016 and MSK Monmouth in 2017 – our first outpatient surgery facilities. It forced us to think outside the box about how to manage and support outpatient surgery centers that require pathology support, without the space to duplicate our processes at each of these sites. We're still finding new and creative ways of better managing and supporting via the use of telepathology and teleytology.

I also helped move Pathology from nonbarcoded labels to barcoded labels back in 2011 and 2012. That has facilitated the tracking of cases throughout the workflow in our laboratory information system. It also helped set the framework for everything that we're doing today in digital and computational pathology.

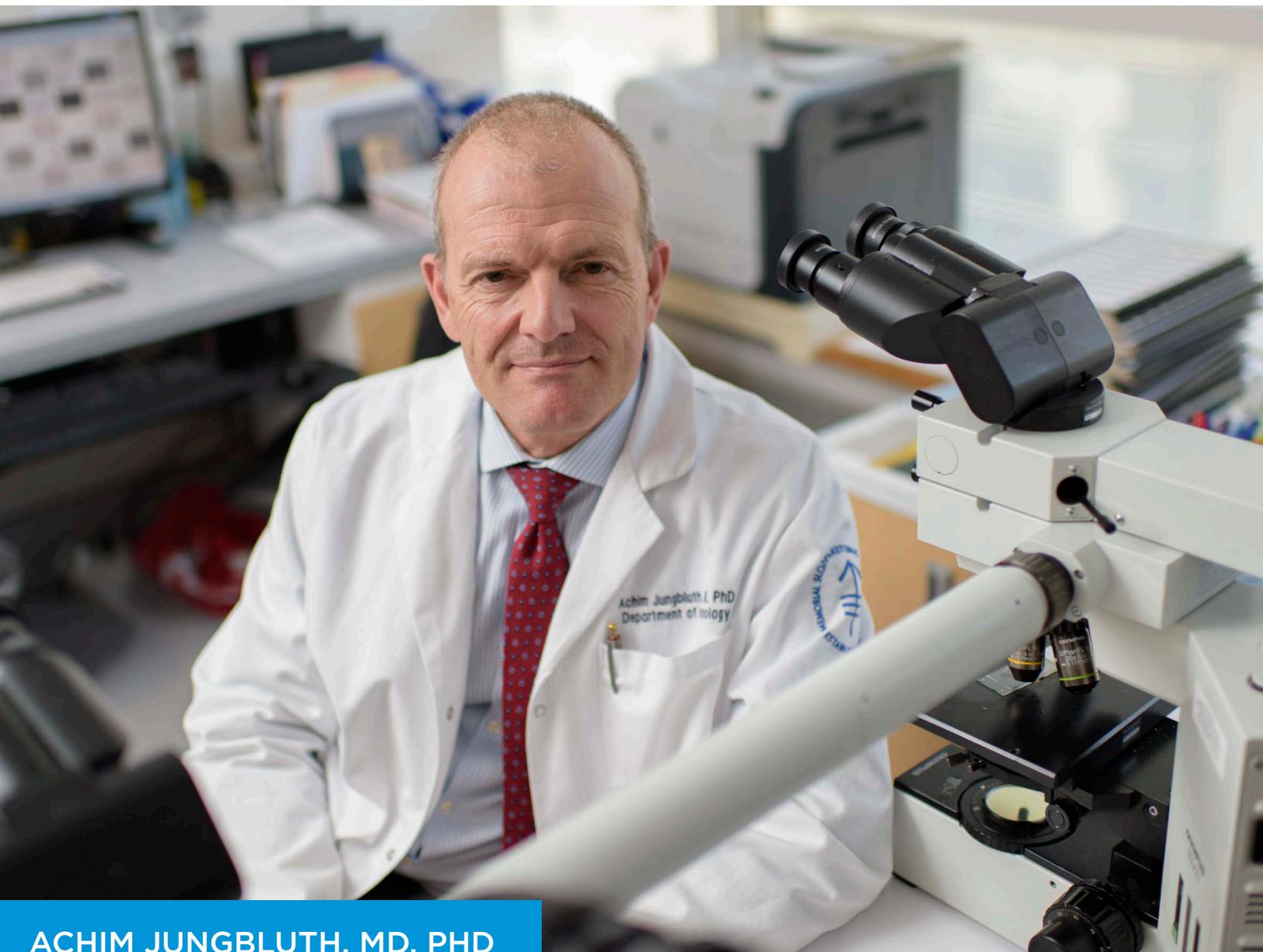
Q: Any facts about you that might surprise your colleagues?

I am shy! If you leave me alone in the corner to work, I'd be the happiest girl. I don't enjoy being the center of attention and public speaking does not come easy to me. I've been told that I'm good at it, but I would honestly prefer not to have to do it. Just recently I tried bribing Dr. Klimstra into giving a talk for me on department updates. Needless to say, that didn't work!

Improving, Standardizing and Harmonizing **IMMUNOHISTOCHEMISTRY**

Director of the Development IHC Laboratory Achim Jungbluth, MD, PhD, supports labs across the Pathology Department

By Hope Cristol



ACHIM JUNGBLUTH, MD, PHD

Immunohistochemistry (IHC) is a major component in surgical pathology, contributing to accurate diagnostic assessments of histological as well as cytological specimens. Yet as new molecular methods emerged, many people predicted the utility of IHC would sharply decline. Director of the Development IHC Laboratory Achim Jungbluth, MD, PhD, is pleased to say the opposite has happened.

"IHC has not only remained, it has gained even more importance," Dr. Jungbluth says. "New insights into the biology of cancer almost instantly extrapolate into new tests to categorize tumors or to predict eligibility for certain treatments. Consequently, there is an ever-increasing need to establish new protocols to type for new molecules and targets."

An important addition to the already existing IHC labs was the setup of a development IHC lab five years ago. Dr. Jungbluth says the lab is the Department of Pathology's answer to the rapid advancements in diagnostics and treatment: Its main purpose is the development of new IHC protocols to identify various molecules in a standard, formalin-fixed, paraffin embedded pathological specimens.

His lab has also broadened the panel of antibodies it uses and streamlined the setup of protocols. In addition, Dr. Jungbluth develops tools to help support consistency of IHC in individual labs – what he calls harmonizing IHC.

ESTABLISHING A CELL CULTURE LAB

One of Dr. Jungbluth's recent initiatives is establishing a cell culture lab to expand and optimize reliable controls for both immunohistochemistry and *in situ* hybridization (another method his lab uses).

Cell cultures can be a much more efficient and reliable source of controls than human tissue samples. This is especially true for cytological specimens. Since cytological material is processed in a different manner than tissue samples, not all IHC protocols will work equally for both applications.

"It is very important to screen in the early phase of developing a novel IHC protocol if it will work in cytological material," Dr. Jungbluth says. "Cell line preparations are ideal."

Furthermore, he explains that certain cell lines are widely used because they express certain antigens, which makes them very good controls. He uses HeLa cells as an example: "They contain Human Papilloma Virus (HPV). We consistently test for HPV in gynecologic and head and neck cancers, because a lot of them are HPV-induced."

Dr. Jungbluth adds that HeLa cells can also be used for cytokeratin staining, demonstrating the potency of cell line preparations for multiple applications.

A NEW KIND OF MULTI-TISSUE SAMPLE

Another effort to optimize controls is with multi-tissue samples. In collaboration with his senior technician Denise Frosina, he recently developed a new method that employs a carrier tissue, which he refers to as a Carrier-Based Multi-Tissue Block (CBMTB).

"The carrier is a normal tissue, for example spleen, in which a panel of other normal or tumorous tissues is inserted and re-embedded. The carrier serves as scaffold, holding the other tissues in an exact and defined position," Dr. Jungbluth says. Although multi-tissue blocks have been in use for decades, the carrier approach is so novel that MSK's Office of Technology Development decided to file for a patent on it.

Why this approach? Most of the molecules in IHC that play a role in tumors are also expressed in normal tissue. For example, certain molecules in melanomas are also present in normal melanocytes. So, he first tests all the new antibodies that come to the lab in a standard, carrier-based, normal multi-tissue block. In order to be used as an everyday tool and as standard controls, the assembly of CBMTBs has been perfected by Miriam Fayad, another technician in Dr. Jungbluth's lab.

Once the antibody is validated, the tissue panel can be used as a standard control in future testing. "With this approach, we have streamlined the whole process and cut it down into fewer steps," Dr. Jungbluth says.

"Yet another idea is to use CBMTBs as standardized controls in the clinical IHC lab. Once you do that, you can digitize the image and create software that reads it," Dr. Jungbluth says.

Instead of a technician deciding whether staining is adequate, a software program would make that determination. "It's something I'm trying to move towards, together with our IT and AI experts Dr. Joe Sirintrapun and Dr. Thomas Fuchs."

THE ADVANCEMENT OF DIGITAL AND COMPUTATIONAL PATHOLOGY

AT THE WARREN ALPERT CENTER

The Pathology Department has taken critical steps toward implementing a digital pathology workflow, building a high-performance compute (HPC) infrastructure, and making partners in industry to become a national leader in the development, integration, and advancement of digital and computational pathology. The Warren Alpert Center for Digital and Computational Pathology at MSK has invested in the expansion of MSK's compute cluster and HPC infrastructure for pathology data and image management, launching the world's most powerful deep learning cluster for pathology in November 2017. Deep learning is the basis for most clinical and research applications in computational pathology. The DGX-1 compute nodes with 8 Volta GPUs each are specifically tailored for deep learning imaging applications. With 6 DGX-1s and 6 petaflops of GPU processing power this system provides the foundation for large-scale machine learning and establishes MSK as a leader in deep learning for pathology.

Under the leadership of The Warren Alpert Center, the department will capitalize on MSK's extensive pathologic and genetic data to pioneer computer-aided cancer diagnosis and to lead the transition of pathology from a qualitative to a quantitative discipline, with the support of our computer science expertise.





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FELLOWS' FEATURE

We are pleased to announce the appointment of Melissa Murray, DO, as the Training Program Director of the Oncologic Surgical Pathology Fellowship Program. Dr. Murray has served as the Associate Training Program Director for the past 2 years and has shown great dedication to our trainees and to the support and advancement of the fellowship. Taking over as Associate Program Director is Nora Katabi, MD. Dr. Katabi has worked closely with the fellows throughout her career and her experience and leadership will contribute to the outstanding educational experience for our trainees. We look forward to their insights and direction as we strive to train excellent pathologists who will become leaders in the field of pathology. Dr. Kay Park will remain as the Director of Education for the Pathology Department and has also recently been appointed as the Vice Chair of the Graduate Medical Education Committee (GMEC) at MSK; she will continue to be involved with pathology fellowship education as well as focusing on broader educational initiatives within the Department of Pathology.



Melissa Murray, DO



Kay Park, MD



Nora Katabi, MD



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2017 NEW FACULTY



TIMOTHY D'ALFONSO, MD

Associate Attending Pathologist, Breast Service

Dr. D'Alfonso did his undergraduate training at Villanova University, where he obtained a BS in biology in 2003. He then received an MS degree in applied physiology in 2004 from Franklin University/Chicago Medical School in 2004, followed by an MD from the same institution in 2008. He completed residency training in Anatomic Pathology at New York Presbyterian Hospital/Weill Cornell Medical College in 2011, and he also completed a breast pathology fellowship there in 2012, working with Drs. Sandra Shin and Syed Hoda. Following fellowship, Dr. D'Alfonso joined the faculty at WCMC as an Instructor in Pathology and Laboratory Medicine, and he was promoted to Assistant Professor in 2013. He has established himself as an outstanding diagnostician, working closely with the clinicians and forging productive clinical and research relationships within his institution. His collaborations with Dr. Tracy Moo, who recently joined the breast surgery service at MSK, helped motivate his interest in moving to our institution, so that ongoing research could continue. His diagnostic skills are also invaluable to our breast pathology team as they have had occasion to interact with him directly.

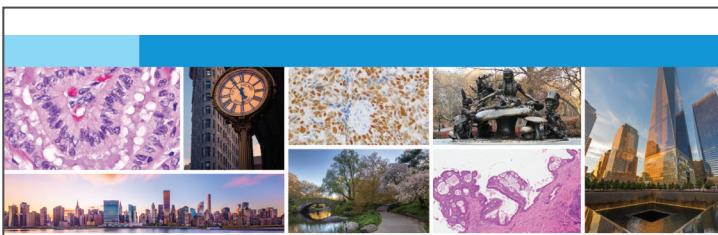


UMUT AYPAR, PHD, FACMG

Assistant Attending Cytogeneticist

Dr. Aypar received a BA, cum laude in Genetics and Microbiology at Ohio Wesleyan University in 2005. He then received his PhD, summa cum laude in Human Genetics and Genomic Medicine at the University of Maryland in 2011. After graduation he completed his fellowship training in Clinical Cytogenetics (2011-2013) and Clinical Molecular Genetics (2014-2014) at the Mayo Clinic. He received ABMGG Board certifications in Clinical Cytogenetics in 2013 and Clinical Molecular Genetics in 2015. He was the Co-Director of the Genomics Laboratory in the Department of Laboratory Medicine and Pathology and Assistant Professor of Laboratory Medicine and Pathology at the Mayo Clinic. He holds New York State Certificates of Qualification (CoQ) in cytogenetics, genetic testing, and oncology molecular and cellular tumor markers; thus, he already has all of the State regulatory requirements to sign reports from our molecular diagnostics laboratories. He is also particularly interested in further developing our array based diagnostics, which is an important service priority. Dr. Aypar joined MSK on September 1st.

UPCOMING COURSES

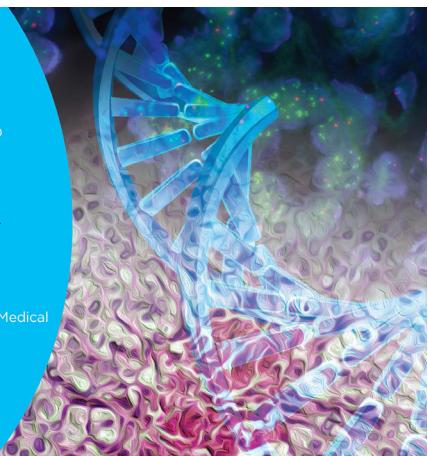


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Memorial Sloan Kettering Cancer Center

If you are interested in attending, please register through our CME website at www.mskcc.org/neoplasticdiseases

Featured Sub-Specialties: Head & Neck Pathology, Breast Pathology, and Gynecological Pathology



Third Annual Symposium in
Translational Research in Pathology
in honor of William Gerald MD PhD

March 29, 2018
Memorial Sloan Kettering Cancer Center
Zuckerman Research Center
New York, New York

Gerald Award Lecturer
A. John Iafrate, MD, PhD.
Professor of Pathology, Harvard Medical School
Pathologist, Massachusetts General Hospital

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If you are interested in attending, please contact Sarah Virgo at cooks@mskcc.org

1ST QUARTER 2018

Research Profile: Jorge Reis Filho, MD PhD

Research Profile: Cristina Antonescu, MD

Cytology Service

Neuropathology Team

Integrated Reports Initiative with Drs. Reuter & Zehir

Consult Portal Initiative with Dr. Sirintrapun

Mass Spectrometry Diagnostics with Drs. Dogan and Roehrl