# MSK PATHOLOGY REVIEW

INITIATIVES INNOVATIONS ACCOMPLISHMENTS





Memorial Sloan Kettering Cancer Center<sub>1</sub>,



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**Cover photo from left to right**- Oscar, Lin, MD, PhD, Chief, Cytology Service, Ahmet Dogan, MD, PhD, Chief, Hematopathology Service, Jorge S. Reis- Filho, MD, PhD, FRCPath, Chief, Experimental Pathology Service, David Klimstra, MD, Chair, Department of Pathology, Marc Ladanyi, MD, Chief, Molecular Diagnostic Service, Meera Hameed, MD, Chief, Surgical Pathology Service, Victor Reuter, MD, Vice Chair, Department of Pathology

## LETTER FROM THE DEPARTMENT CHAIRMAN



"With this inaugural issue of the MSK Pathology Review, we launch a new periodical designed to provide members of the department, alumni, and others in our academic community a snapshot of the activities ongoing in our department. The past decade has seen substantial growth in pathology - not only in the volume of specimens being reviewed and the corresponding staff required to diagnose them but also in the breadth of diagnostic and research activities. The advent of superspecialization more than 10 years ago required significant expansion of the diagnostic pathology faculty. Together with the Department of Laboratory Medicine, we created a new clinical service in hematopathology. The Molecular Diagnostics Service has grown exponentially in recent years as the emphasis has shifted from supporting anatomic diagnosis to identifying therapeutic targets, and the technology at hand to allow systematic and deep molecular characterization of tumors has become accessible for routine clinical use. An infusion of energy into novel research arenas has accompanied the growth in diagnostics. As a result, we have developed new disciplines within pathology, such as clinical bioinformatics, the research autopsy program, precision biobanking, digital and computational pathology, advanced immunomorphology, and proteomics, as well as growth and reorganization of the Experimental Pathology Division. I hope that the information and vignettes contained in this publication will help keep us abreast of these many developments, and we will select a few specific topics to be highlighted in each issue. Our discipline continues to evolve, and while we maintain the techniques that have remained the cornerstones of tumor diagnostics for much of our history, we are also excited about the many opportunities to expand the impact of the diagnostic information we provide. Now more than ever, pathology is at the center of the clinical management of patients with cancer, and our department will continue to lead the way in the development and assessment of novel tools to characterize this spectrum of human disease and to define the most effective therapies for our patients."

- David S. Klimstra, MD

## MSK-IMPACT LEADS THE WAY IN TUMOR SEQUENCING EFFORTS

To take advantage of the advances in the understanding of cancer genomics — and specifically the development of targeted therapies that exploit the molecular mutations that drive cancer — it is crucial to have an assay that can detect these mutations in an accurate and efficient way. This was the impetus behind the development of MSK-IMPACT, a powerful and ever-evolving tool for sequencing patient tumors.

Since 2014, pathologists in Memorial Sloan Kettering's Molecular Diagnostic Service have been using it to analyze the tumors of nearly every MSK patient diagnosed with an advanced cancer. The test allows doctors to detect mutations and other genetic changes that can help guide treatment decisions, including matching patients with clinical trials for experimental targeted agents.

The panel initially investigated 341 mutations known to be connected to cancer. It has since

been expanded several times and was recently updated from 410 to 468 mutations. "The genes that we recently added might be the focus of new trials in a few years," says Marc Ladanyi, Chief of MSK's Molecular Diagnostics Service. "We already had on the panel all the genes that are targets of trials today. We're being forward-looking to try to anticipate which mutations may be clinically essential several years from now."

Another new feature provides information about microsatellite instability within tumor cells, which can also guide treatment and aid in prognosis. "It's a continually evolving and improving assay that has become the centerpiece of the institution's precision oncology initiatives," he adds.

MSK-IMPACT relies on next-generation sequencing and an advanced bioinformatics effort. "We have a very sophisticated bioinformatics analysis group that processes the data in a







consistent and state-of-the-art fashion," Dr. Ladanyi says. Pathologists and bioinformaticians together review all the mutations that are detected in individual samples and issue a final report.

The MSK-IMPACT assay has led to the development of so-called basket trials — clinical studies that assign patients to receive targeted drugs based on the mutations in their tumors rather than the organ in which they arose in the body. It has also led to an improvement in diagnosing cancers that had previously been labeled cancers of unknown primary origin (CUP). Even in cases in which the primary site cannot be determined, sequencing results can provide guidance on the best course of treatment for patients with CUP.

In early 2016, the Pathology Department

passed the milestone of sequencing tumors from 10,000 patients. That number continues to grow and now stands at more than 8,000.

Results from MSK-IMPACT testing not only guide patient care, but they also are making an important impact on research. MSK's data contribution to AACR (American Association for Cancer Research) Project GENIE — a multicenter effort to aggregate tumor sequencing data and link it to patients' medical records — comes from results from MSK-IMPACT. Thanks to the assay, MSK leads the collaboration with the largest number of patients added to the AACR Project GENIE database.

MSK-IMPACT was developed in MSK's Department of Pathology. Dr. Ladanyi, along with genomics researcher Michael Berger, molecular pathologist Maria Arcila and bioinformatician Donavan Cheng, led the clinical validation and implementation of the test.

As patient tumor sequencing is not yet considered standard care, it is seldom covered by private insurance of the Centers for Medicare and Medicaid Services. MSK's Marie-Josée and Henry R. Kravis Center for Molecular Oncolongy, which coordinates many of MSK's molecular oncology efforts, provides philanthropic funding to cover the expenses.

- Julie Grisham

## DECODING THE GENETICS OF GYNECOLOGICAL CANCERS

Britta Weigelt leads a research team in Memorial Sloan Kettering's Department of Pathology and acts as the Director of the Gynecology Research Laboratory in the Department of Surgery. Her work focuses on the study of gynecologic cancers in particular ovarian and endometrial cancers. Βv combining pathology and stateof-the-art genomics methods, Dr. Weigelt's team is learning more about the genetic changes that bring about these cancers and may lead to more effective treatment, especially with targeted therapies.

"My background was in studying breast cancer, and I was surprised when I moved into the study of gynecologic diseases how little we know about the genetics of these tumors," she says. "Our research enables us to gain a much better understanding of gynecologic cancers."

The laboratory is focused on three areas of research.

The first is to find rare subtypes of gynecologic cancer and to identify their genetic underpinnings. "We use a number of different sequencing technologies and molecular pathology techniques to

understand what drives them," Dr. Weigelt explains. "Much of what we do is whole exome sequencing, and to characterize some rare types we also do whole genome sequencing and RNA sequencing, which allows us to look for fusion genes and somatic genetic alterations affecting regulatory elements of cancer genes."

Another area of focus for the lab is intratumor heterogeneity. Some gynecologic tumors show morphologic heterogeneity under the microscope. For example, carcinosarcomas of the uterus are part sarcoma and part carcinoma: These





cancer phenotypes reflect two different cell lineages in the body. "This is a particularly aggressive type of disease, and although these tumors have been studied for a while, in the past they were analyzed as a whole," Dr. Weigelt says. "We're interested in studying the different areas and looking at their genetic alterations. We hope to eventually infer which came first: Did the carcinoma differentiate into a sarcoma, or was it the other way around? And we will compare these tumors with their counterparts in other anatomical sites."

The laboratory is also studying endometrial cancers that have two different morphologies under the microscope to determine if those differences are based on genetic variations in the cells. "At this point we're still learning about the biology," Dr. Weigelt explains. "Understanding the basis of the phenotypic diversity in these cancers will help us define the rules of genetic and phenotypic heterogeneity in endometrial cancers."

The third major area of study for the laboratory is the analysis of circulating cell-free DNA that originates from tumors. This line of work enables investigators to monitor how cancers develop, change, and become resistant to particular therapies by collecting a vial of blood rather than conducting biopsies, which are much more invasive.

Early efforts in this field have focused on ovarian cancer. "Resistance to chemotherapy is a big problem for ovarian cancer," Dr. Weigelt says. "Many of these tumors are sensitive to systemic chemotherapy agents in the beginning, but at some point they become resistant. We're hoping we can detect resistance earlier by monitoring DNA in the blood, because often when the disease comes back it's very hard to treat."

Unlike circulating tumor cells, which are whole cells that break off from the tumor and circulate through the bloodstream, cell-free DNA is free floating. However, inflammatory processes can also lead to freefloating DNA; thus not all cellfree genetic material comes from the tumor. Investigators are able to analyze the DNA to look for specific genetic alterations that are known to be cancerrelated.

Dr. Weigelt's lab has recently demonstrated the presence of BRCA1 and BRCA2 reversion mutations in patients treated with platinum-based chemotherapy. These mutations have been shown to constitute a mechanism of resistance to agents targeting a type of DNA repair that is defective in a substantial proportion of ovarian cancer patients. Her lab is now extending the study of cell-free DNA to include endometrial cancers as well. "We know much less about how this disease progresses than we do with many other cancers," she says, "In breast cancer we've shown that we can monitor a patient's response to therapy by detecting a drop in the percentage of the DNA in the blood that has cancer-related mutations, and that increases in the circulating tumor DNA in plasma predict relapses. We hope to extend this to other cancers as well."

- Julie Grisham

#### MEDICAL DONATION PROGRAM ADVANCES THE STUDY OF METASTASIS

Much of what we know about cancer genetics today comes from the study of patient tumors. But studying the genetics of metastasis has been difficult because those tumors are usually not removed or biopsied. Memorial Sloan Kettering's Medical Donation Program is advancing the understanding of the genetics of metastasis by studying all of patients' tumors after they die.

"There's a strong gene discovery aspect to this program," says Christine lacobuzio-Donahue, who was recruited to MSK in 2014 to head the program. "We sequence the primary tumors as well as the metastases and compare them. We've found a lot of genes that no one has ever found before, and this enables us to look for the cellular pathways that allow cells to metastasize."

Studies based on tissues collected as part of the program are already yielding important findings. In pancreatic cancer, which was the initial



focus, the researchers have found that pancreatic cancer does not always metastasize, and that complications from the primary tumor may be the cause of death. "That was a surprise, because it's not what everybody thought," Dr. lacobuzio-Donahue says. "The thing that correlated with this was the genetics of the original tumor."

Specifically, the investigators found that the gene responsible for this behavior was SMAD4. "The mutation is there in the beginning and drives the whole disease process," she adds. "This finding is starting to change the paradigm of how patients are treated. Depending on what



patient's cancer care team. It is so important for our patients to receive a timely, precise diagnosis to ensure they receive an appropriate treatment plan. At MSK, we are in a unique position to provide the most accurate diagnosis for our patients through our world-recognized subspecialty pathologists and our advanced diagnostic technologies.

### Q: What is most exciting about pathology right now?

I'm so thankful to work at an institution that fosters innovation and encourages us to always look for ways to do things better. We have invested in many new technologies in recent years and it is exciting to see recent innovations being incorporated into clinical practice, such as digital pathology, telepathology, and advanced diagnostic tests.

### Q: Why do you enjoy being apart of the MSKCC team?

The people! We have the best staff who truly go above and beyond every single day. I am

#### Administrator, Department of Pathology

### Q: Why is pathology such a vital piece of the cancer treatment process?

All of our staff in the Pathology Department are among the most important members of an MSK

mutations the tumors have, there may be a need for more intensive local therapy, such as an expanded role for radiation therapy."

The team has also found that neoplastic changes may exist in the pancreas for as long as two decades before growing or spreading, offering clues for early diagnosis and screening of the disease. "This shows us there's a long window for early detection of the disease, and has changed the view that it can't be caught in the early stage," Dr. lacobuzio-Donahue says. "Now we need to find out the best way to screen for it."

Since it was created, the Medical Donation Program has expanded to include other types of cancer, including myeloma, melanoma, and breast cancer. "So far our sample sizes have been very small, but we're already seeing that the genetic patterns by which these tumors grow, evolve, and spread is very different based on where the tumor originates," she explains.

One of the major goals of the program is to find alterations in cellular pathways that could be targeted with drugs. "We're also looking at the features of the microenvironment in the tumor that might give the cancer cells the tools to survive after they spread to secondary sites in the body," she adds.

Dr. lacobuzio-Donahue says that the program can provide comfort to patients who are dying of cancer, knowing that they will be able to make a contribution to the understanding of the disease. "It gives them the sense of leaving a legacy and contributing to something bigger than themselves," she notes. She adds that the program can also provide consolation to families of patients. MSK's pathologists make an effort to share the results of studies with patients' family members and often receive letters of gratitude.

The program does not require that patients die at Memorial Hospital. Arrangements can be made in advance to collect the remains from home or a hospice facility. The tissues may be used in Dr. lacobuzio-Donahue's own research or — if patients consent — by investigators in other laboratories at MSK, or even beyond. Please contact Chelsea Michael, Clinical Coordinator at michaec1@mskcc.org for additional information.

- Julie Grisham

motivated to give 110% each day by feeding off the energy, hard work, and dedication that I see from all of our team members.

### Q: What exactly is an administrator responsible for?

An administrator is responsible for high level strategic planning for the department and partnering with our chair, Dr. Klimstra, and hospital administration to ensure that our department meets overall hospital goals and expectations. It's my job to argue for and justify any resource requests that we need to get our jobs done as efficiently as possible. I also need to be involved in all areas of our operations and finances from a high level. If we have any turn over in staff, it is my job to step in and step up to ensure our operations are continuous and not affected.

### Q: What advice would you give to a person seeking a career in pathology?

There are so many career options in our department that I had no idea about before working at MSK. As a student interested in

science, I had the incorrect assumption that you had to become a doctor or a nurse to enter the medical field. One of my goals for 2017 is to work on our outreach and education to high schools and colleges to make such bright, young minds aware of the opportunities that we have in all of our labs and in hospital administration. I love that some of our administrative staff are considering being trained in histology to make the transition to a laboratory based career by leveraging the resources we have in our department (exceptional managers and mentors) and MSK (tuition reimbursement).

#### Q: Why is MSK the place for you?

I believe that a job well done does not maintain the status quo. MSK can sometimes be a tough place to work but overall the organization is fair, supports its employees, and challenges each employee to work at a higher level. I have worked at MSK for 12 years now and I have had five very different job opportunities and never a boring day. I'm grateful to work in place with so many unique opportunities.

## THE 2016 FRED W. STEWART AWARDEE RALPH HRUBAN, MD



Dr. Ralph Hruban is the recipient of the 2016 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 our understanding of human neoplastic disease.

Dr. Hruban is a worldrenowned pancreatic cancer pathology expert who has devoted his academic career to the study of pancreatic neoplasms. He has made significant contributions to our understanding of all types of pancreas tumors – ductal, acinar and neuroendocrine. Importantly, his work on PanINs and IPMNs, the precursor lesions that give rise to invasive pancreas cancer, has had a particularly significant impact both in the field of pancreas research and with regard to how patients with this disease are prognosticated and managed.

Dr. Hruban obtained his undergraduate degree from the University of Chicago and his medical degree from the Johns Hopkins University School of Medicine. His pathology training consisted of residency in anatomic pathology at Johns Hopkins and fellowship in oncologic surgical pathology at Memorial Sloan Kettering Cancer Center. In 1990, upon completion of his fellowship, Dr. Hruban returned to Johns Hopkins to join the faculty and has remained there ever since. Quickly rising through the academic ranks to become professor of both Pathology and Oncology, Dr. Hruban has served multiple important roles over the years at Johns Hopkins and is currently Director of the Sol Goldman Pancreas Cancer Research Center. Director of the Division of Gastrointestinal and Liver Pathology, and Director of the Department of Pathology.

Dr. Hruban joined the quest to conquer pancreas cancer early on. In the 1990s, at a time when the world of biomedical research was in one of its more visible transformations from traditional analyses to newer and more complex technologies, and the focus on the origins of cancer was converging at the molecular level largely as a consequence of studies done with the newer technologies. Young Dr. Hruban and his colleagues took to techniques such as "mutant-enriched polymerase chain reaction analysis" in combination with "allele-specific oligonucleotide hybridization", and revealed that KRAS mutations (now known to represent one of the few big "mountains" in pancreas cancer's genomic landscape) were important events in pancreatic cancer. Dr. Hruban envisioned presciently that specific molecular alterations of this type would not only allow a better understanding of the genetic drivers for pancreas cancer development, but they would also have the potential to serve as markers for the detection of this deadly disease at an early stage during which intervention might still save lives. In the same spirit of applying innovative approaches to the study of cancer, and still in the early 90's. Dr. Hruban also co-founded the National Familial Pancreas Tumor Registry at Johns Hopkins, a patient registry that would later serve as an invaluable resource for the study of pancreas tumors.

During the 2 decades following these initial efforts, Dr. Hruban dove deeper into the field of pancreas neoplasia and maintained a focus on understanding the noninvasive precursor lesions from which invasive cancers develop (PanINs and IPMNs), the familial aggregation of some pancreatic cancers, and the pathologic ramifications of genetic alterations in the pancreas. At Hopkins and with multi-institutional collaborative groups mostly led by him, Dr. Hruban produced during this time meritorious scientific work that served both to advance pancreas cancer research, and to facilitate diagnosis, detection, prevention, prognosis, and treatment. As a testament to such achievements, Dr. Hruban has over 700 scientific papers and is credited by the "Essential Science Indicators" as the most cited pancreas cancer scientist in the world (for those who believe in the "H-index", Dr. Hruban's H-index is above 150!). Numerous awards have been bestowed on him in recognition of his achievements, including (but far from being limited to) the Arthur Purdy Stout Prize and the Ramzi Cotran Award from USCAP, the PanCAN Medical Visionary Award, the Ruth C. Brufsky Award of Excellence in Clinical Research for Pancreatic Cancer. and election to the German National Academy of Sciences Leopoldina. Most recently, riding on the wave of next generation sequencing, Dr. Hruban and a group of distinguished pancreas scientists including our own Drs. David S. Klimstra and Christine lacobuzio-Donahue discovered a new cancer pathway and new familial pancreatic cancer genes, defined the time course for the development of pancreatic neoplasia, and showed that each of the four cystic tumors of the pancreas has a unique mutational profile. Once again, these efforts have significantly improved our understanding of the fundamental genetic changes that characterize pancreatic neoplasms, and importantly, bear immediate clinical implications. It is only fitting that Dr. Hruban and his

colleagues were recognized for their efforts as recipients of the prestigious Team Science Award from the American Association for Cancer Research.

Dr. Hruban is also a superb surgical pathologist and an ardent educator. He has dedicated time and effort to the teaching of pathology, particularly GI and pancreas pathology, to trainees and practicing pathologists as well as patients worldwide. He disseminates knowledge through lectures, courses, books, and digital media. Dr. Hruban has written more than 150 book chapters and reviews and authored or coauthored 6 books, including the AFIP Fascicle on Tumors of the Pancreas and the World Health Organization "blue book" on tumors of the digestive tract. With a deep appreciation of visual arts, Dr. Hruban frequently utilizes creative images for the teaching of pathology and has developed unique iPad and iPhone applications that are valuable resources for medical professionals and patients alike. An award-winning iPad application created by him has taught pancreas pathology to many; another patient-oriented iPad and iPhone app that he created and is free to all has served as a valuable educational guide for patients and caregivers facing a diagnosis of pancreatic cancer.

It should come as no surprise that Dr. Hruban's achievements also extend into other realms. In addition to his many accomplishments in scientific research, patient care, and medical education, Dr. Hruban has also made his mark in additional fields. His inspirational biographies of

influential historical figures are but one example; history buffs - and I am very certain nonhistorian enthusiasts, too - will find Dr. Hruban's award-winning documentary on William Stewart Halsted, M.D. (http:// HalstedTheDocumentary.org) and a series of "Osler Minutes" on the philosophy of William Osler, M.D. (http://pathology. jhu.edu /department/ about/ history/osler-minutes.cfm) most enjoyable, and, like his other scientific works, intriguingly insightful.

Today, as we celebrate the memory of Dr. Fred Waldorf Stewart, a man who made significant contributions to the care of cancer patients through the practice of conventional pathology, it is most fitting that the medal in his name be bestowed on an individual who extended Stewart's tradition through innovative integration of conventional pathology with cutting-edge molecular and digital technologies. We congratulate Dr. Hruban on this well-deserved Stewart Award.

- Jinru Shia, MD

#### RECENT FRED W. STEWART AWARD RECIPIENTS

JUAN ROSAI, M.D., 2006 PETER C. BURGER, M.D., 2007 PAUL PETER ROSEN, M.D., 2008 ROBERT J. KURMAN, M.D., 2009 JULIA A. BRIDGE, M.D., 2010 STANLEY R. HAMILTON, M.D., 2011 E. LEON BARNES, M.D., 2012 RICHARD KEMPSON, M.D., 2013 THOMAS M. ULBRIGHT, M.D., 2014 ROBERT H. YOUNG, M.D., 2015



The Genitourinary team within Memorial Sloan Kettering's Department of Pathology focuses on a number of cancers of the genitourinary tract, including those arising in the prostate, kidney, urinary bladder and testis.

Members of this group examine thousands of biopsies and resections from patients' tumors every year in order to establish the correct diagnosis and determine the extent of these tumors. Members of the team are also involved in research on the molecular and genetic abnormalities of these tumors to identify markers that can help with diagnosis and prognosis and may also ultimately lead to new treatment strategies with targeted therapies.

One particular area of study is certain rare but aggressive subtypes of bladder cancer. Pathologist Hikmat Al-Ahmadie is studying many of these tumors. "Bladder cancer didn't get much attention for a long time, so there haven't been many advances in our understanding of it until very recently," Dr. Al-Ahmadie explains. "But in the past few years, we've learned a lot about the genetic drivers of these cancers."

One type of cancer that Dr. Al-Ahmadie has studied extensively is plasmacytoid carcinoma, urothelial an aggressive form of bladder cancer that rarely responds to chemotherapy and develops resistance to those drugs even if it does initially respond. Based on the genomic analysis of patients' tumor samples, Dr. Al-Ahmadie's team was able to identify a unique genetic event that is responsible for the vast majority of these tumors and thereby establish a molecular definition for this type of cancer. Specifically, they found that a

loss-of-function mutation in the CDH1 gene is pathognomonic for this subtype.

Another area of Dr. Al-Ahmadie's work is focused on exceptional responders (also called extraordinary responders). These are patients whose cancers respond especially well to treatment with targeted therapies even while the majority of patients with seeminaly similar tumors do not respond at all. Genomic analysis of tumors from these exceptional responders can reveal genetic abnormalities that illustrate how these patients are different. Once these abnormalities are identified, additional patients with the same abnormalities can be identified for clinical trials known as basket trials. This enriches the population of patients who are most likely to benefit from a particular treatment.

Dr. Al-Ahmadie is also studying the molecular events that lead to heterogeneity in bladder tumors. "Bladder cancer is very heterogeneous, and these varied regions may be associated with the failure to respond to a particular treatment or with a worse prognosis," he says. "A major part of my work is to identify the molecular basis for this heterogeneity and to find specific genetic abnormalities that may explain the morphologic differences that are seen in different parts of the tumor."

To do this, his group performs whole exome sequencing as well as targeted sequencing in different areas of the same tumor. "We are finding that these different areas have shared alterations, but each morphologically distinct region also has its own set of alterations that are different from the other regions," he adds.

On a wider scale, Dr. Al-Ahmadie has also been involved in the bladder cancer studies that are part of The Cancer Genome Atlas (TCGA), a government-funded, multicenter initiative that collects, processes, and characterizes the largest set of tumor samples to date using state-of-the-art genomic and

molecular techniques.

Along with members of the Bladder Cancer Oncogenome team, he is also beginning to focus on the study of cell-free DNA in patients with bladder cancer.

"The immediate effect of all of these different areas of research is that we can better understand genitourinary cancers," Dr. Al-Ahmadie says. "In the longer term, we hope to characterize more molecular changes that may be targets for treatment as well as identify additional genetic events that may be diagnostically and prognostically important for patients."

- Julie Grisham

# PATHOLOGY AT MSK

NUMBER OF CASES SEEN IN 2016 41,982 Surgical and biopsy cases 25,584 Submitted slide cases 4,565 Personal consult cases 32,530 Cytology cases 10,132 Frozen cases 8,621 Hematopathology cases 41,491 Molecular cases



APPROXIMATELY 5% OF CASES ARE

PERSONAL

CONSULTS

NUMBER Of 2016

74 ATTENDINGS across 5 services & 10 subspecialty teams

NUMBER OF TESTS AVAILABLE 22 Approved assays in Cytogenetics 56 Approved assays in Molecular Diagnostics 286 Approved assays in IHC



#### HEMATOPATHOLOGY SERVICE ADDRESSES GROWING NEEDS AT MSK

Every patient diagnosed with a blood cancer at Memorial Sloan Kettering has his or her specimens analyzed by the expert team in MSK's Hematopathology Service. Since it was established more than three years ago as a stand-alone service, the group has launched several initiatives to enhance patient care and advance research under the leadership of Service Chief Ahmet Dogan. The service encompasses both diagnostic and academic activities within the departments of Pathology and Laboratory Medicine.

One major initiative since it was created has been to enhance the organization of the service. Hematologic pathology encompasses a number of technologies, including immunohistochemistry, flow cytometry, proteomics, and a variety of different genetic testing methods.

Members of the service support diverse efforts at MSK, including clinical trials. As more patients are being treated with targeted therapies, accurate



and efficient analysis is an increasingly important component of patient care. Since many patients with cancer are living longer and treatment of cancer is as a chronic disease is becoming more common, disease monitoring and management are imperative. The service also maintains MSK's tissue bank for hematologic patient samples.

Staff development and recruitment has been



The Hematopathology service extensively uses multiparameter flow cytometric immunophenotyping for diagnosis and monitoring of hematological neoplasms. Here is an example of a peripheral blood sample involved by T-large granular lymphocyte leukemia. The blue dots represent abnormal T-cells whereas red and green dots represent normal CD4 positive and CD8 positive T-cells, respectively.



B-cell maturation antigen (BCMA) is a new therapeutic target in myeloma and B-cell lymphomas. There are a number of clinical trials in progress targeting BCMA either using antibody-drug conjugates or chimeric antigen receptor T-cells. BCMA is strongly expressed in myeloma but also in a subset of B-cell lymphomas. In myeloma cells the expression has both a membranous and golgi pattern. The images show a case of myeloma with strong BCMA expression. (Image courtesy of Dr P Khattar, Hematopathology fellow).

an important priority. The service now includes ten board-certified hematopathologists with a wide variety of clinical and scientific expertise, 20 technologists and ten administrative staff members.

Education is also an important component, and the service oversees four clinical fellows, including three in the Accreditation Council for Graduate Medical Education-accredited Hematopathology Fellowship Training Program and one advanced fellowship. Fellows gain exposure to a wide range of hematologic neoplastic diseases, such as lymphomas, leukemias, myelodysplasia, and plasma cell myelomas/amyloidoses. They are also exposed to a variety of non-neoplastic hematologic diseases, including anemias, hemoglobinopathies, hemolytic syndromes, hemostasis and thrombosis and general hematologic conditions. In addition to fellows, the faculty educates other pathologists and oncologists in national and international forums.

Another area of focus since Dr. Dogan arrived has been the development of more infrastructure within the service. The service reviews approximately 20,000 hematological specimens every year and provides comprehensive diagnostic reports that integrate complex information from morphological assessment, immunohistochemical and flow cytometric analysis, and cytogenetic and molecular genetic studies. The service laboratories are internationally recognized for their innovation in clinical test development, in particular for development of assays to detect minimal residual disease and comprehensive proteomic and genomic analysis.

With the increased emphasis on research within the service, members are focused on new ways to follow patients. In the age of targeted therapy, hematopathologists have had to develop new ways to monitor for drug effectiveness and resistance. For example, if an antibody or small molecule is being used to treat a patient, changes in the tumor characteristics that result may indicate that the marker that was previously used will no longer prove effective.

In addition, flow cytometry enables the team to do multiparameter phenotyping through analysis of up to ten markers in every cell.

As immunotherapy increasingly has become a significant element of patient care for many types of cancer, immune monitoring has also developed into a key part of hematopathology's role. Flow cytometry enables analysis of immune cells in the tissue, which is much more difficult to do with solid tumors.

"There are endless collaborative research opportunities for members of the Hematopathology Service," Dr. Dogan concludes.

- Julie Grisham

### 2016-2017 USCAP PATHOLOGY PRESENTATIONS

#### **LECTURES**

(Endocrine Pathology Society): *The Role of Ki67 in Pulmonary Neuroendocrine Tumors* – William Travis, MD

(International Society of Urological Pathology): *Updates in TNM Staging of Prostate Cancer* – Samson Fine, MD

(Arthur Purdy Stout Society of Surgical Pathologists): *There Are No Magic Bullets: When Immunostains Can Get You into Trouble: Neuroendocrine Tumors* – David Klimstra, MD

(International Society of Bone and Soft Tissue Pathology): *Tumor Syndromes Predisposing to Osteosarcoma* – Meera Hameed, MD

(International Society of Breast Pathology): *Circulating DNA and NGS Technology* – Jorge Reis-Filho, MD, PhD, FRCPath

(International Society of Breast Pathology): *Breast Pathology: What is Trending Now* – Edi Brogi, MD

(American Society for Cytopathology): *Morphology and Molecular Testing in Non-Small Cell Carcinoma of Lung* – William Travis, MD

Prostate Pathology: Practical Issues: Neuroendocrine Tumors of the Prostate -- Samson Fine, MD

Short Course #60: Surgical Pathology and Cytopathology of the Pancreas and Ampulla (O. Basturk, MD, V. Adsay, MD, M. Dian Reid, MD)

Peculiar Polyps: Diagnostics of Less Common Colorectal Lesions and Awareness of Their Clinical Associations – Jaclyn Hechtman, MD

Short Course #21: Practical Molecular Diagnostics for the Practicing Surgical Pathologist—Maria Arcila, MD, PhD

(Pediatric GIST with an Inherited SDH mutation): *Case 4* - Christina Antonescu, MD, PhD

(Evening Specialty Conference – Breast Pathology): *Case Presentation* – Hannah Wen, MD, PhD

(Lower Genital Tract Carcinomas in the Post-HPV Vaccination Era): *Case 1: Gastric-Type Endocervical Adenocarcinoma* – Kay Park, MD

#### **PLATFORMS**

Pulmonary Ciliated Muconodular Papillary Tumor (CMPT) with Classic and Non-Classic Morphology: Expanded Morphologic and Molecular Spectrum of Bilayered Lesions with Bronchiolar-Type Differentiation (J. Chang, MD, J. Montecalvo, MD, M. Ladanyi, MD, W. Travis, MD, N. Rekhtman, MD PhD)

*Microsatellite Unstable (MSI-H) Prostate Cancer (PCA): Correlation of Morphology, Mismatch Repair Immunohistochemistry* (MMR-IHC) and Next Generation Sequencing (NGS) (A. Gopalan, MD, J. Sirintrapun, MD, Y. Chen, MD, PhD, H. Al-Ahmadie, MD, S. Fine, MD, S. Tickoo, MD, M. Berger, PhD, J. Shia, MD, V. Reuter, MD)

Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups - Robert Soslow, MD

Histologic Patterns of Lung Cancers Associated with MET Exon 14 Splice Site Alterations (MESSA): A Study of 58 Cases (J. Montecalvo, MD, D. Alex, MBBS, MS, PhD, M. Arcila, MD, M. Ladanyi, MD, N. Rekhtman, MD, PhD, W. Travis, MD)

MET Exon 14 Splicing Mutations and Intragenic Deletions in Non-Small Cell Lung Cancer: A Study of Co-Occurring Genomic Mutations and Copy Number Alterations (Alex, MBBS, MS, PhD, J. Montecalvo, MD, W. Travis, MD, M. Arcila, MD, M. Ladanyi, MD)

Cytologic Evaluation of p16 Staining in Head and Neck Squamous Cell Carcinoma in Cytolyt vs Formalin-Fixed Material (D. Buonocore, MD, J. Cohen, MD)

**BCOR Is a Robust Diagnostic Immunohistochemical Marker of YWHAE-Rearranged High-Grade Endometrial Stromal Sarcoma** (S. Chiang, MD, C. Antonescu, MD, R. Soslow, MD)

SMARCA4/BRG1 Loss Occurs in Mediastinal and Pleural Tumors with Rhabdoid Morphology and Aggressive Behavior - Jennifer Sauter, MD

*Identifying Oncogenic Pathways in Renal Cell Carcinoma with Unclassified Histology (uRCC): A Validation Study of 59 Patients* (Y. Chen, MD, PhD, H. Al-Ahmadie, MD, S. Fine, MD, A. Gopalan, MD, J. Sirintrapun, MD, M. Arcila, MD, S. Tickoo, MD, V. Reuter, MD)

SMARCB1 (INI-1)-Deficient Sinonasal Carcinoma: A Series of 33 Cases Expanding the Morphological and Clinicopathological Spectrum of a Recently Described

#### Entity - Cristina Antonescu, MD

*Molecular Characterization of Tubulocystic Carcinoma of the Kidney* (Sarungbam, H. Al-Ahmadie, MD, A. Gopalan, MD, J. Sirintrapun, MD, S. Fine, MD, V. Reuter, MD, Y. Chen, MD S. Tickoo, MD)

*Primary Thyroid Carcinoma with Low-Risk Histology and Distant Metastases: Clinico-Pathologic and Molecular Characteristics* (Xu, MD, R. Ghossein, MD)

Pathologic Reporting of Tall Call Variant of Papillary Thyroid Cancer: Have We Reached Consensus? – Ronald Ghossein, MD

*The Genomic Landscape of PALB2-Associated Breast Cancers* (B. Weigelt, PhD, H. Wen, MD, PhD, F. Pareja, MD, PhD, J. Reis-Filho, MD, PhD)

Should Subcentimeter Non-Invasive Encapsulated, Follicular Variant of Papillary Thyroid Carcinoma (NI-EFV PTC) Be Diagnosed as Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)? (N. Farhat, MBBS, MA, MPH, Xu, MD, N. Katabi, MD, R. Ghossein, MD)

Genomic Landscape of Phyllodes Tumors with and without Fibroadenoma-Like Areas (F. Pareja, MD, PhD, M. Edelweiss, MD, M. Murray, DO, E. Brogi, MD, PhD, B. Weigelt, PhD, J. Reis-Filho, MD PhD)

International Endocervical Adenocarcinoma Criteria and Classification (IECC) (K. Park, MD, R. Soslow, MD)

*Recurrent SRF-RELA Fusions Define a Novel Subset of Cellular Myofibroblastic Neoplasms in the Spectrum of Cellular Myofibroma/Myopericytoma: A Potential* 

#### *Diagnostic Pitfall with Sarcomas with Myogenic Differentiation* (C. Antonescu, MD, N. Agaram, MBBS)

Comparison of Genomic Alterations in Urothelial Carcinoma (UC) with and without TERT Promoter Mutation Using a Next-Generation Sequencing (NGS) Assay (H. Al-Ahmadie, MD, A. Gopalan, MD, Y. Chen, MD, PhD, J. Sirintrapun, MD, S. Fine, MD, S. Tickoo, MD, V. Reuter, MD, M. Berger, PhD)

#### Genomic Alterations in Primary Bladder

Adenocarcinoma and Urachal Adenocarcinoma (A. Toubaji, MD, A. Gopalan, MD, Y. Chen, MD, S. Fine, MD, J. Sirintrapun, MD, S. Tickoo, MD, M. Berger, PhD, V. Reuter, MD, H. Al-Ahmadie, MD)

ETV Transcriptional Upregulation Is a More Reliable Diagnostic Tool in SBRCT with CIC Complex Abnormalities Compared to FISH and RNAseq Methods - Cristina Antonescu, MD

*Pan-TRK IHC Is an Efficient and Reliable Screening Assay for Targetable NTRK Fusions* (J. Hechtman, MD, S. Dogan, MD, PhD, M. Arcila, MD, M. Ladanyi, MD, A. Jungbluth, MD, PhD)

Genomic Landscape and Clinical Features of Carcinomas with ERBB2 S310 Extracellular Domain Mutations (P. Desmeules, MD, M. Arcila, MD, M. Ladanyi, MD)

A Recurrent Kinase Domain Mutation p.D463H in PRKCA Defines Chordoid Glioma of the Third Ventricle -M. Rosenblum, MD



### POSTERS

Expression of PD-L1 in Colorectal Carcinoma (CRC) Primarily Occurs in Stromal/immune Cells at Tumor-Stroma Interface (TSI), and Is Associated with High Tumor-Infiltrating Lymphocytes (TILs) Irrespective of the Microsatellite Instability (MSI) Status or the Molecular Mechanism of MSI (Liu, MD, J. Hechtman, MD, D. Rao, MD, E. Vakiani, MD, PhD, D. Klimstra, MD, J. Shia, MD)

**Re-Evaluation of 31 "Unclassified" Eosinophilic Renal Cell Carcinomas in Young Patients** – Victor Reuter, MD

Morphologic, Clinical and Molecular Features of Large Cell Neuroendocrine Carcinoma (LCNEC) of the Bladder (L. Mirsadraei, MD, Hao, MD, K. Huang, MDCM, PhD, Y. Chen, MD, PhD, A. Gopalan, MD, J. Sirintrapun, MD, S. Fine, MD, S. Tickoo, MD, V. Reuter, MD, H. Al-Ahmadie, MD)

Evaluation of Histological Changes in Radical Prostatectomy (RP) After Neoadjuvant Androgen Deprivation Therapy (NeoADT): Comparison Between Conventional and Newer Therapy Regimens (K. Huang, MDCM, PhD, L. Mirsadraei, MD, Y. Chen, MD, PhD, J. Sirintrapun, MD, H. Al-Ahmadie, MD, S. Fine, MD, S. Tickoo, MD, V. Reuter, MD, A. Gopalan, MD)

Intraductal Tubulopapillary Neoplasm of the Pancreas: A Clinicopathologic and Immunohistochemical Analysis of 33 Cases (C. Sigel, MD, D. Klimstra, MD, O. Basturk, MD)

*Molecular Characteristics of Intraductal Oncocytic Papillary Neoplasms of the Bile Ducts* (D. Rao, MD, D. Klimstra, MD, O. Basturk, MD) Genome-Wide DNA Methylation Profiling in the Diagnosis of Pediatric Ewing Sarcoma, Osteosarcoma, and Synovial Sarcoma - Marc Ladanyi, MD

*Intra-Tumor Genetic Heterogeneity in Metaplastic Breast Carcinomas* (E. Brogi, MD, PhD, H. Wen, MD, J. Reis-Filho, MD, PhD, B. Weigelt, PhD)

*Estrogen Receptor-Positive and -Negative Adenomyoepitheliomas of the Breast Are Underpinned by Distinct Genetic Alterations* (F. Pareja, MD, M. Edelweiss, MD, H. Wen, MD, PhD, A. Jungbluth, MD, PhD, B. Weigelt, PhD, J. Reis-Filho, MD, PhD)

Analysis of CDH1 in Invasive Lobular Carcinoma (ILC): Comparison of Morphology, Immunohistochemistry (IHC) and Mutation Profile Detected by Hybrid Capture-Based Next Generation Sequencing (NGS) (A. Grabenstetter, MD, K. Tan, MD, D. Ross, MD)

*Is Re-Excision of Benign and Borderline Phyllodes Tumors with Positive Margins Necessary?* (C. Cristando, MD, F. Pareja, MD, E. Brogi, MD, PhD, M. Murray, DO)

Validation of the Singapore Nomogram for Outcome Prediction in a US-Based Population of Women with Breast Phyllodes Tumors (PT) (C. Cristando, MD, E. Brogi, MD, PhD, M. Murray, DO)

Massively Parallel Sequencing Analysis of Myxoid Fibroadenomas Reveals a Genomic Landscape Distinct from That of Conventional Fibroadenomas (F. Pareja, MD, M. Murray, DO, E. Brogi, MD, PhD, B. Weigelt, PhD, J. Reis-Filho, MD, PhD)

*Outcome of Large Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)* (Xu, R. Ghossein, MD)



Small Cell Carcinoma of the Bladder (SCCB): Role of Multimodality Management and Genomic Predictors of Response (C. Hao, MD, A. Gopalan, MD, Y. Chen, MD, S. Fine, MD, J. Sirintrapun, MD, M. Berger, PhD, S. Tickoo, MD, V. Reuter, MD, H. Al-Ahmadie, MD)

Pathologic Features and Long Term Clinical Follow Up of Treatment-Naïve Non Invasive Papillary Urothelial Neoplasms of the Urinary Bladder (Sarungbam, H. Al-Ahmadie, MD, Y. Chen, MD, PhD, S. Fine, MD, J. Sirintrapun, MD, A. Gopalan, MD, S. Tickoo, MD, V. Reuter, MD)

A Synoptic Electronic Order Set for Placental Pathology: A Framework Extensible to Non-Neoplastic Pathology -- Sahussapont Joseph Sirintrapun, MD

A Subset of Malignant Mesotheliomas in Young Adults Are Associated with Recurrent EWSR1-ATF1 Fusions (P. Desmeules, MD, H. Al-Ahmadie, MD, D. Delair, MD, N. Rekhtman, MD, PhD, M. Ladanyi, MD, W. Travis, MD, C. Antonescu, MD)

A Recurrent Kinase Domain Mutation p.D463H in PRKCA Defines Chordoid Glioma of the Third Ventricle - Marc Rosenblum, MD

A Novel CRTC1-SS18 Gene Fusion in an Undifferentiated Round Cell Sarcoma- Ewing- Like Sarcoma or Poorly Differentiated Synovial Sarcoma- A Diagnostic Dilemma—Cristina Antonescu, MD

Different Patterns of PD-1 and PD-L1 Expression in Histologic Subtypes of Renal Cell Carcinoma (RCC) - Analysis of Data from the Cancer Genome Atlas (TCGA) Kidney Projects (Y. Sun, MD, H. Al-Ahmadie, MD, A. Gopalan, MD, S. Fine, MD, J. Sirintrapun, MD, S. Tickoo, MD, V. Reuter, MD, Y. Chen, MD, PhD) Frequency of Succinate Dehydrogenase and Fumarate Hydratase-Deficient Renal Cell Carcinoma Based on Immunohistochemical Screening with SDHA/SDHB and FH/2SC - Yingbei Chen, MD, PhD

*Pancreatic Neuroendocrine Tumors Expressing Proinsulin: A Clinicopathologic Analysis* - Laura Tang, MD, PhD

Luminal Androgen Receptor and Androgen Receptor-High Triple-Negative Breast Cancers Are Genetically Similar to Luminal B Breast Cancers (B. Weigelt, PhD, J. Reis-Filho, MD, PhD)

Patterns of Clonal Evolution in Colorectal Adenocarcinomas Characterized by Whole Exome Sequencing (E. Vakiani, MD, PhD, J. Shia, MD, C. Iacobuzio-Donahue, MD, PhD)

*Telecytology and Hands-Free Digital Voice Communication for High Volume Rapid On-Site Evaluation: A Workflow Optimization* (O. Lin, MD, PhD, J. Sirintrapun, MD) HER2/ ERBB2 Amplification in Colorectal Carcinoma Is Associated with KRAS Wild Type Status, Microsatellite Stability, and Left Sided Tumors (P. Cotzia, MD, D. Alex, MBBS, MS, PhD, J. Hechtman, MD, C.Liu, MD, D. Rao, MD, E. Vakiani, MD, PhD, D. Klimstra, MD, J. Shia, MD)

*Craniofacial Osteosarcoma: A Clinicopathological Study* (C. Lu, MD, L. Wang, MD, PhD, M. Hameed, MD)

*Immunohistochemical Evaluation of Chromatin Regulatory Gene Surrogates in Chordoma* (Ramirez, L. Wang, MD, PhD, K. Nafa, PharmD, PhD, M. Hameed, MD)

*EWSR1 Fusions with CREB Family Transcription Factors Define a Novel Myxoid Mesenchymal Tumor with Predilection for Intracranial Location* (M. Rosenblum, MD, C. Antonescu, MD)

Breast Carcinoma with Recurrence Score Lower Than 18: Rate of Locoregional Recurrence in a Large Series with Clinical Follow-Up (G. Turashvili, MD, PhD, E. Brogi, MD, PhD, H. Wen, MD, PhD)

*The 21-Gene Recurrence Score in Special Histologic Subtypes of Breast Cancer with Favorable Prognosis* (G. Turashvili, MD, PhD, E. Brogi, MD, PhD, H. Wen, MD, PhD)

Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP): Cytomorphologic and Molecular Correlates (C. Sebastiano, MD, Xu, R. Ghossein, MD, O. Lin, MD, PhD, J. Cohen, MD)

*In-Situ Protein Expression of Melanocyte Differentiation Antigen Tyrosinase-Related Protein-1* (TRP1) (A. Jungbluth, MD, PhD, T. Hollmann, MD, PhD, K. Busam, MD)

*Calretinin Positivity in Poorly Differentiated Colorectal Carcinoma: A Diagnostic Pitfall* (C. Liu, MD, D. Rao, MD, J. Hechtman, MD, E. Vakiani, MD, PhD, D. Klimstra, MD, J. Shia, MD)

*International Endocervical Criteria and Classification: Mucinous Endocervical Adenocarcinomas* (MEA) (K. Park, MD, R. Soslow, MD)

## **FELLOWS' FEATURE**

We had representation by our fellows at the USCAP 2017 Annual meeting in San Antonio, Texas. In total, 17 fellows presented their research and 3 fellows (pictured below) gave platform presentations. Congratulations to all!





**DEEPU ALEX** Surgical Pathology Fellow

Presented: MET Exon 14 Splicing Mutations and Intragenic Deletions in Non-Small Cell Lung Cancer: A Study of Co-Occurring Genomic Mutations and Copy Number Alterations. Alex D., Montecalvo J., Travis W., Arcila M., and M. Ladanyi.



NADA FARHAT Surgical Pathology Fellow

Presented: Should Subcentimeter Non-Invasive Encapsulated, Follicular Variant of Papillary Thyroid Carcinoma (NI-EFV PTC) Be Diagnosed as Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP)? Farhat, Xu, Katabi, Ghossein.



PATRICE DESMEULES Molecular Pathology Fellow

Presented: Genomic Landscape and Clinical Features of Carcinomas with ERBB2 S310 Extracellular Domain Mutations. Desmeules P., Arcila M., M. Ladanyi.

-Melissa Murray, DO

## 2016-2017 CLINICAL FELLOWS

#### **ONCOLOGIC PATHOLOGY FELLOWS**



NATASHA LEWIS











SABINA HAJIYEVA





CHENGBAO LIU







JAVIER ARIAS-STELLA



CHUANYONG LU



JAD SAAB



NADA FARHAT

YUE SUN



LONG YANG

**EVAN FOWLE** 

Cytopathology



RONALD ARANETA

HAMID ZIA

#### SPECIALTY FELLOWS



CAMILLA CRISTANDO HILLIGES Breast Pathology



MARY LE Dermatopathology

ALEX CHAN

GUO ZHU

Molecular Diagnostics

Hematopathology



SHABNAM MOMTAHEN Dermatopathology



PALLAVI KHATTAR Hematopathology



PATRICE DESMEULES Thoracic Molecular



**GULISA TURASHVILI** 

Breast Pathology



JENNIFER MAERKI Hematopathology



MOISES VELEZ Thoracic Pathology



JAMAL BENHAMIDA Molecular Diagnostics



CHRISTOPHER **SEBASTIANO** Cytopathology



LEILI MIRSADRAEI



CHRISTINE MOUNG Molecular Diagnostics



**KSENIYA** PETROVA-DRUS Molecular Diagnostics

19









DANIEL FIX GYN Pathology





PATHOLOGY REVIEW

### PROMOTIONS



DR. HIKMAT AL-AHMADIE Associate Attending Pathologist on Nov 2, 2016



DR. MARIA ARCILA Associate Attending Pathologist on Jan 29, 2016



DR. DARREN BUONOCORE Assistant Attending Pathologist on Jun 24, 2016



DR. ANURADHA GOPALAN Associate Attending Pathologist on Dec 14, 2016



**DR. NORA KATABI** Associate Attending Pathologist on Dec 14, 2016



DR. MELISSA MURRAY Associate Attending Pathologist on Dec 14, 2016



DR. LAURA TANG Attending Pathologist on Jul 28, 2016



**DR. LU WANG** Associate Attending Cytogeneticist on May 20, 2016



## **3RD QUARTER 2017**

WARREN ALPERT FOUNDATION CENTER FOR DIGITAL AND COMPUTATIONAL PATHOLOGY

Thomas Fuchs, PhD & Yukako Yagi, PhD

**PRECISION PATHOLOGY BIOBANKING CENTER** Michael, Roehrl, MD PhD

PATHOLOGY AT THE JOSIE ROBERTSON SURGERY CENTER

FINE NEEDLE ASPIRATION BIOPSY CLINIC Jean-Marc Cohen, MD

**RESEARCH PROFILE** Jinru Shia, MD