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"I don't look like what I've been through"

Lymphoma survivor diagnosed while pregnant delivers healthy baby

– By Maxsane Mitchell

Westin coordinated care with Minix's obstetrician to ensure her son's health through treatment.

La Shunda Minix looks nothing like what she's been through in the past year, and she's proud of that.

At the beginning of October 2014, she was 33 years old, married, four months pregnant with her first baby, and an assistant principal at a middle school in Marshall, Texas. Things were going well. Then, she started experiencing shortness of breath that became so severe that even taking a shower exhausted her. Lying down was nearly impossible. "It was like my breath just cut off," she remembered. Minix said her doctor told her it was probably a sinus infection and he prescribed antibiotics. "But it didn't get better and I started swelling up," she said. When the at-home blood pressure monitor Minix used to keep an eye on her pre-existing hypertension revealed a dangerously high reading she went to the emergency room. Clinical staff gave her oxygen and partially propped her up for a chest CT scan that showed a mass covering half of her right and left lungs and her heart.

That mass, later identified as non-Hodgkin lymphoma (NHL), was causing superior vena cava syndrome in which the main vein that carries blood from the head, neck, chest and arms to the heart was blocked. "The doctors rushed me to intensive care, where they helped me with my breathing, and then to the oncology floor," Minix said. "The oncologist there told me that he was going to have me airlifted to MD Anderson." She immediately called her husband, Rod, and her mother and asked them to pack a bag for her and meet her in Houston. "And that's how my journey started," she said.

Minix landed at the institution on Oct. 14, 2014. Four days later, **Jason Westin, MD**, assistant professor of Lymphoma/Myeloma, told her that tests identified the specific type of NHL as diffuse large B cell lymphoma, with a primary mediastinal designation. NHL rarely presents during pregnancy, and this particular subtype only accounts for about 2.5% of patients with the disease. Her pregnancy meant that Minix would not be eligible for the preferred treatment, called R-EPOCH, a five-day regimen of rituximab with etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin. Instead, Westin recommended a similar treatment to be given once every three weeks—R-CHOP, a regimen of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone. Additionally, the MD Anderson team required the approval of Minix's obstetrician, Mildred Ramirez, MD, a fetal maternal specialist at Texas Children's Hospital who cares for pregnant cancer patients, prior to each infusion. "When Dr. Westin came in with the diagnosis, he had the paperwork in his hand for me to sign. We started that evening and finished the first round just after midnight," Minix said. Radiotherapy was scheduled for after the birth. "Ideally, we'd want to wait until the baby is born, but in Mrs. Minix's case, she presented with such an enormous mass that we had to treat her or she wouldn't have survived long. Her situation was going in the wrong direction in a hurry, and the baby wouldn't have survived either," Westin said.

Right before what would have been the sixth and final infusion, Ramirez found the baby's growth had slowed down, causing her to postpone chemotherapy so Minix's pregnancy could be induced. Little Denim Minix entered the world at 4 pounds and 3 ounces. He was healthy, and today at nearly nine months, he is hitting all the normal milestones and has three teeth. Denim has attended his first Dallas Cowboys game, goes on regular stroller-walks at the park, and gets hugs and kisses from all the people who prayed for him. "I want to do everything for him so he'll never know that I'm sick," said Minix. "A lady at church commented to me that I look nothing like what I've been through. I'm grateful for that because even though I've had my moments of sadness and crying, I never doubted God would bring me through this. I never believed I would lose my baby to chemo. Denim is a very busy little boy who keeps me going. Right now I feel like I did when Dr. Westin gave me the treatment papers to sign—let's go, let's go."

On Sept. 22, 2015, Dr. Westin informed Minix that follow-up tests found no evidence of disease.

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Inflammatory breast cancer

Making a way to see these patients faster

– By Maxsane Mitchell

October was Breast Cancer Awareness Month, but the faculty and staff who run the Morgan Welch Inflammatory Breast Cancer Research Program and Clinic, part of Breast Medical Oncology (BMO), didn't wait until the fall to launch a new effort to get these particular patients in faster. **Naoto Ueno, MD, PhD,** professor, said the Multi-Team Clinic started seeing patients in August. Similar to a multidisciplinary tumor board whose medical, surgical, and radiation oncologists convene to discuss cases and form treatment plan recommendations, the Multi-Team Clinic meets with patients each Wednesday to focus solely on this rare and aggressive form of breast cancer that represents 1% to 3% of all cases. "The department has been doing this multidisciplinary approach for a long time for breast cancers including IBC (inflammatory breast cancer). But our effort with IBC patients is in response to a growing, subspecialty need, to provide a one-day clinic visit with all specialties in the same room at the same time," Ueno said. IBC is unusual because it does not present with a single lump or tumor, but typically with swelling, skin that is reddened, discolored, or warmer than other areas, and sometimes thickened skin that feels pitted or dimpled like the surface of an orange. The affected breast may also be itchy and tender. The symptoms are the result of cancer cells blocking the lymph vessels in the skin. The affected breast may also have an inverted nipple. In fiscal year 2015, MD Anderson saw approximately 100 new cases of IBC.

Min Fu, MD, a BMO research data coordinator, helps to improve the speed in which IBC patients are seen by the Multi-Team Clinic by communicating with patient access specialists working at the Breast Center as they receive the first calls or online requests for appointments by patients or their referring physicians. BMO research data coordinator **LaKeisha DeBose, MS,** then reaches out to the schedulers of our medical oncologists, including Ueno and **Drs. Bora Lim** and **Vicente Valero,** to find the next available Wednesday appointment. Following insurance approvals and submission of diagnostic images and a pathology report, the patient's first encounter with the IBC Multi-Team is with a midlevel provider who then presents her case to faculty. "This gives us a good idea about what needs to be done, but then each doctor on our team does his own exam with the patient because we're all looking at different things," said Ueno. "Afterward, we'll talk among ourselves and then meet with the patient and her family to deliver the news about what we think needs to happen. This sort of rapid consensus could happen in 90 minutes."

Naoto Ueno, MD, PhD

A significant number of patients are local and choose to receive their entire treatment at MD Anderson, while others opt to go back home where they can have systemic therapy and then return to the institution for surgery and radiation that is performed by faculty and staff with expertise in IBC. Ueno said the team is open to communicating with a patient's local doctor, but cannot directly supervise. "A third category of patients come to us for a recommendation that they can bring home to their doctors and we don't see them again," commented Ueno, who added that the team decided early on to accept these one-time patients to reduce the number of misdiagnosed cases in the cancer community, reduce deviation from what should be standard care, and contribute to the education process of the physicians who refer them. "We want these women to obtain the right sequence of treatment in a timely manner because the outcome could be fatal if they don't." He acknowledged that many patients choose the second option because the commitment to stay close to Houston for six months of chemotherapy is too costly and logistically difficult for family members who want to be available to offer support. "Interestingly though, we have been able to retain some patients who originally intended to just come for a second opinion. We believe this is because once they meet with us and understand the level of subspecialized care that is available here, they find the financial means to stay with us," said Ueno. He and colleagues are developing what they believe will be the largest portfolio of clinical trials for this patient population. One of the active protocols is a randomized study of the anti-epidermal growth factor receptor (EGFR) antibody panitumumab combined

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Inflammatory breast cancer

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with chemotherapy. EGFR is overexpressed in triple negative and inflammatory breast cancers, and is a poor prognostic factor for long-term survival. Panitumumab with chemotherapy has been successful in reducing some tumors in colorectal cancer. "Previous studies at MD Anderson show the EGFR antibody with chemotherapy to achieve better results in IBC than what is found in general historical data," Ueno said.

Danielle Rasberry, MS, serves as program coordinator in the department. Her responsibilities include helping to promote the clinic by providing contact information for team members and their clinical support staff, materials about various support groups, newsletters published by the Morgan Welch Inflammatory Breast Cancer Clinic, and information about the program's Facebook and Twitter handles. Drs. Ueno and Lim have thousands of followers on Twitter. They post some fun personal items and also answer general questions about IBC and other breast cancers, provide links to journal articles about research developments, and encourage users to consider MD Anderson if they or loved ones have received a cancer diagnosis.

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MD Anderson launches male breast cancer support team

Breast cancer support groups for women are easily available, but what about for the less than 1% of cases nationwide in which men receive the diagnosis? MD Anderson, which treats about 20 of these patients a year, began addressing the issue this summer with the addition of the Male Breast Cancer Survivor Support Team, which is accessible via myCancerConnection@mdanderson.org or by calling 800-345-6324. **Drs. Debu Tripathy, Vicente Valero** and **Gabriel Hortobagyi** in the Department of Breast Medical Oncology, as well as Sharon Giordano, MD, MPH, chair of Health Services Research-Clinical, are supporting these efforts, with help from the Department of Volunteer Services, to pair newly diagnosed men with long-term survivors so they can feel comfortable talking to a peer about their special concerns. Survivor and volunteer Ronnie Pace has taken a big role in establishing the effort with Oliver Bogler, PhD, senior vice president of academic affairs and also a male breast cancer survivor. Faculty are available to answer medical questions about symptoms and treatment side effects. Among the most dominant risk factors for developing male breast cancer are growing older, just as with women, and having a strong family history of breast cancer or genetic alterations, such as abnormal BRCA1 or BRCA2 genes. Other factors include radiation therapy to the chest prior to the age of 30; and high estrogen levels, which can be due to certain medications and lifestyle factors.

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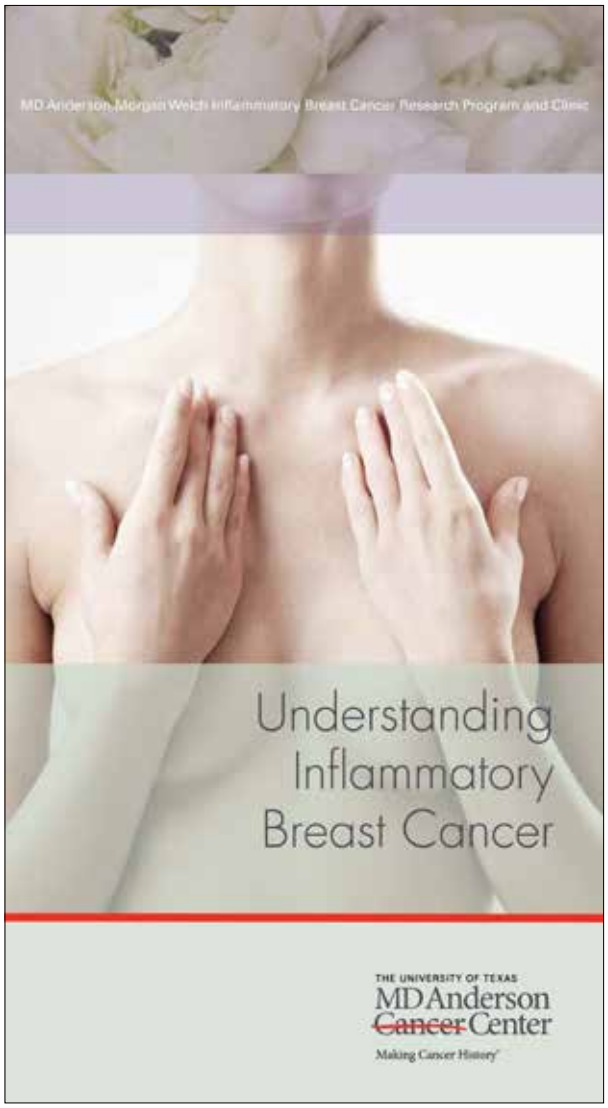
IBC brochure wins award

Patient Education's *Understanding Inflammatory Breast Cancer* brochure received a Bronze award in the 22nd annual National Health Information Awards. This program recognizes the nation's best consumer health information programs and materials. The awards program is coordinated by the Health Information Resource Center, a national clearinghouse for consumer health programs and materials. Recipients were:

- Lakeshia Brown, MPH, CHES, senior health education specialist, Patient Education
- **Danielle Rasberry, MS,** program coordinator, Breast Medical Oncology
- Gini Reed, BFA, senior communications designer, Creative Communications
- **Danielle Walsh, MBA,** scientific project director, Leukemia

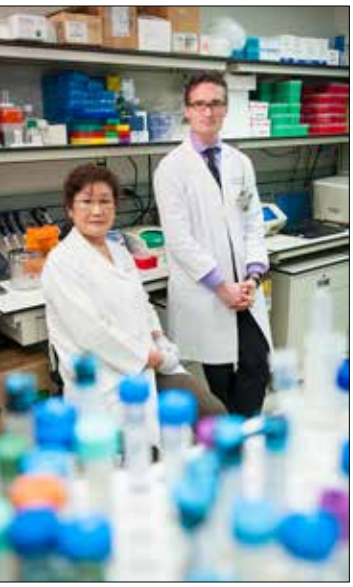


Up and Coming Investigator

Pioneering liquid biopsy

Janku taps into the bloodstream to observe tumor dynamics

– By Erica Di Pierro



Research scientist **Helen Huang, MD,** assists **Janku** in the lab to isolate cfDNA.

As medicine evolves, techniques to diagnosis, treat, and track disease are becoming less invasive and more targeted to minimize unnecessary pain and unintended side effects. Through efforts in the clinic and the laboratory, **Filip Janku, MD, PhD,** assistant professor of Investigational Cancer Therapeutics (ICT), hopes to improve cancer patient outcomes by refining how we obtain information about tumors over the course of disease. After completing medical and research education in his native Czech Republic, Janku transferred to Bon Secours Hospital in Ireland where he practiced oncology and put together a clinical trial unit. This experience affirmed his passion for organizing and conducting trials, which he pursued further during a clinical research fellowship here at MD Anderson. Originally intending to return to Ireland after this training, Janku found himself at home in this institution's diverse, ambitious environment, and earned an assistant professorship in 2011.

Janku's Phase I trial portfolio includes therapies targeting the PI3K pathway and IDH1/IDH2, genes commonly mutated in brain tumors, cholangiocarcinomas, and some sarcomas. In the laboratory, he focuses on the non-invasive liquid biopsy. This innovative method operates on the principle that cells, both malignant and normal, shed short fragments of DNA into the bloodstream that can be recovered from the serum fraction of whole blood. Known as cell-free DNA (cfDNA), these circulating fragments allow for convenient and minimally invasive retrieval of tumor DNA that can be sequenced to determine mutation profiles and real-time genetic changes that may correlate with various disease events including progression and therapy response. This concept is particularly useful in the Phase I clinical trial setting where there is a need for serial biopsy to track treatment responses and emergence of resistance. Indeed, clinical research is frequently limited by availability of high quality tissue specimens, the collection of which is also often associated with uncomfortable or even harmful complications for the patient.

Several major principles drive Janku's exploration into potential applications of this technique. First, to support wider use of liquid biopsy, a significant amount of work has shown strong concordance between liquid and tissue biopsy in mutation status for several commonly mutated genes including BRAF, KRAS, and PIK3CA in advanced cancers. Such results suggest that this method could be used in lieu of tissue, although Janku believes the new technology will instead add a new, more convenient dimension to monitoring cancer status. Additionally, mounting evidence shows that changes in cfDNA may correlate with response and resistance to therapy. For example, quantitative levels of circulating tumor DNA in the plasma have been shown to change after administration of therapy, indicating that this metric could be used as a biomarker for therapy response. Further, liquid biopsy may be able to identify mutations in cfDNA that drive therapy resistance, possibly allowing for pre-emptive intervention through treatment modification. "The only way for us to try to understand the mechanism causing therapy resistance in an individual patient is to do serial biopsy," Janku noted, a process made much easier by liquid biopsy. Levels of cfDNA may also predict prognosis in some cases; surprising recent findings from Janku's group have shown that patients with higher fractions of BRAF-, KRAS-, and EGFR-mutant DNA fare worse than patients with less, despite the fact that all three of these mutations have corresponding targeted therapies. In addition to blood, Janku has found that both urine and cerebral spinal fluid contain detectable amounts of cfDNA; he is also investigating the utility of genetic material-containing exosomes shed from tumor cells into plasma and other biological fluids.

Once a major rate-limiting step in the process, sequencing technologies have matured to a point where they are now central to the success of liquid biopsy. Janku employs multiple methods including droplet digital PCR, which partitions thousands of individual PCR reactions into water-oil emulsion droplets for high-throughput amplification within one tube. He also uses BEAMing (beads, emulsion, amplification, and magnetics), an exquisitely sensitive process that separates low levels of mutated DNA from abundant normal DNA using magnetic beads, then amplifies the mutant fraction. Janku also relies heavily on next-generation sequencing platforms to process large amounts of data. Among Janku's lab instrument arsenal is the Idylla, a fully automated, real-time PCR-based system that rapidly processes input DNA, spitting out a mutation profile panel in under an hour. In Janku's experience, mutation profiles from plasma DNA processed by Idylla demonstrate high concordance with profiles from biopsied tissue samples.

Key to establishing liquid biopsy as a go-to tool is to prove that information obtained from the procedure can improve patient outcomes. "We need to design clinical trials that will utilize the results of serial profiling of liquid biopsies. This way, we can test the question of if we act on what we see in these profiles, does it make a difference to the patient," Janku said. This will be the next major goal for the field.

1st Annual Hortobagyi Visiting Professor

Davidson making strides in hormone-resistant breast cancer research

– By Erica Di Pierro

Both **Hortobagy**i *(left)* and Davidson have earned an impressive array of awards.

Gabriel Hortobagyi, MD, is one of the most decorated physicians in the country, having received almost too many accolades to count, among them numerous citations as one of America's Top Doctors, the John Mendelsohn Lifetime Scientific Achievement Award, and the Charles A. LeMaistre Outstanding Achievement Award in Cancer. On Oct. 27, however, he received a truly special honor as he attended the first annual Gabriel Hortobagyi Visiting Professor Lectureship in Cancer Medicine, established to pay homage to his career as a luminary of cancer research. The body of knowledge generated and inspired by Hortobagyi over the last several decades has had decisive force in determining what we currently know about breast cancer and how to treat it. Perhaps his most crucial accomplishment is the transfer of his expertise to an expansive cohort of students over the years, many of whom continue to be impacted by his guidance and will carry it into the future of this field. The lectureship is sponsored by the Greenberg Foundation, represented by Paul Greenberg, MD, who spoke fondly of his former mentor, Hortobagyi, and expressed a desire for the series to "educate and inspire people to do great things."

Selected as the inaugural speaker, Nancy Davidson, MD, director of the University of Pittsburgh Cancer Institute, also with an expansive list of career awards, has contributed seminal findings about estrogen receptor (ER) signaling and led numerous standard-setting clinical trials that have determined best practices for treating breast cancer patients. Standing before the Division of Cancer Medicine Grand Rounds audience, she said, "It is a daunting task to come to MD Anderson and talk about anything related to breast cancer in front of Gabriel!" Mortality has declined significantly since the 1970s as researchers like Davidson and Hortobagyi have grasped some finer points of breast cancer biology, developed game-changing therapeutics especially for ER-positive breast cancers, and tweaked clinical regimens toward minimal amounts of targeted therapy. The next wave of research must seek to understand mechanisms of resistance to these therapies and alternative ways to destroy these tumors in the clinic.

Work in Davidson's group has demonstrated that some breast cancer cell lines and primary specimens that are phenotypically ER negative show repressive methylation modifications within the receptor coding sequence. Interestingly, ER expression could be restored upon inhibition of DNA methyltransferase (DNMT) and histone deacetylase (HDAC) enzymes. This finding suggests that agents like the HDAC inhibitor vorinostat could be used to resensitize hormone-resistant patients to endocrine therapies. While HDAC inhibitors do not have the cleanest side effect profiles, a window trial providing a short course of vorinostat before surgery in early breast cancer patients showed measurable biologic activity with no detectable toxicity. For late-stage metastatic breast cancer, Davidson's team devised a Phase II trial combining the DNMT inhibitor, 5-azacitidine with the HDAC inhibitor, entinostat, which produced partial responses in hormone-resistant patients. Importantly, the trial also confirmed acceptable toxicity for both agents and allowed for biopsy collection to better understand why some patients benefited and others didn't.

Davidson also discussed efforts to describe genetic differences between primary and metastatic breast cancer tumors, given that the genetic landscape of the latter is not well defined. A tissue bank study using matched normal, primary, and metastatic

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Davidson making strides in hormone-resistant breast cancer research

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patient samples revealed that numerous single nucleotide variants (SNVs) are gained in metastasis, sometimes in a tissue site-specific manner. Further, they identified structural variants including an ER-DAB2 gene fusion found in tissues of nodal recurrence that leads to a constitutively active, hormone-independent ER-DAB2 fusion protein. These studies emphasized the ability of genetic alterations acquired in the process of metastasis to negatively impact therapy response. Similarly, another tissue bank study revealed that ER mutations, often leading to a constitutively active and hormone-resistant receptor, are found predominantly in metastatic tumors and rarely in primary ones. Acquisition of these mutations can be tracked in the circulating DNA of patients, suggesting that liquid biopsy could be a useful proxy for tumor burden and therapy response. A prospective trial for ER-positive metastatic breast cancer that will correlate ER mutation status with clinical course is in the works.

Finally, Davidson spoke about new findings in lobular breast carcinoma, which, distinct from ductal carcinoma, originates in the milk-producing glands of the breast. Historically considered to be associated with favorable outcomes, some lobular tumors are actually more refractory to treatment than their ductal counterparts, showing elements of hormone resistance when treated with tamoxifen. Researchers in Davidson's group found two lobular breast cancer cell lines that express ER, and discovered that tamoxifen and other ER modulators could stimulate growth of these cells instead of eliminating them, as in prototypical ductal carcinoma cells. This growth was dependent on fibroblast growth factor receptor-1 (FGFR1) in a preclinical model, suggesting that a combination of tamoxifen and FGFR1 inhibitors could hold promise for treatment of invasive lobular carcinoma in patients. Only an ER-degrading agent was able to inhibit growth of these cells; accordingly, a window trial will test the relative efficacy of fulvestrant, which accelerates proteosomal degradation of the ER, over tamoxifen and an aromatase inhibitor in reducing tumor cell proliferation preceding operation.

Davidson closed with a wish for the future 20th annual Hortobagyi lecturer to present an even better view of breast cancer mortality as a consequence of the committed work of researchers and clinicians across the field and supporters like the Greenberg Foundation.

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John Mendelsohn Visiting Professor award

Jacks advances CRISPR-Cas9 use to study lung cancer

– By Erica Di Pierro

Jacks, *(left)* referred to **Mendelsohn** as a "true gentleman scientist."

The John Mendelsohn Visiting Professor award was established in 2007 to honor outstanding investigators who exemplify this momentous cancer physician-scientist and former MD Anderson president. During Mendelsohn's 15-year tenure as president, the institution more than doubled in size. Glittering new clinical and research facilities were erected, historic collaborations were forged, and productivity was unmatched. His personal research portfolio includes the pioneering seeds for anti-growth factor receptor therapy, upon which an entire treatment strategy and science have been built. This year, Tyler Jacks, PhD, director of the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology, was selected as the recipient of this prestigious award. A pioneer in his own right, Jacks has been a primary driver in the development of gene-targeting technologies to generate mouse models of cancer. He is a member of both the National Academy of Sciences and the National Academy of Medicine, a Howard Hughes Medical Institute investigator, chair of the National Cancer Institute's National Cancer Advisory Board, and the recipient of countless career accolades. He spoke fondly of Mendelsohn as a "true gentleman scientist" and "one of the great translational cancer researchers who built this institution into the clinical powerhouse that it is today."

Jacks spoke at the Division of Cancer Medicine Grand Rounds on Sept. 29, where he made a case for cancer as a disease that must be studied in context. Especially when metastasis occurs, countless cellular interactions can influence disease course and

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Jacks advances CRISPR-Cas9 use to study lung cancer

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pathogenesis. An understanding of this network of interactions and how to possibly exploit them for therapy in humans begins with mouse studies. To model non-small cell lung cancer (NSCLC), Jacks and his team created a mouse with mutations in KRAS and p53, the two most common genetic aberrations associated with this disease. They have used this model to address several major questions in cancer research, including an investigation into the genetic and molecular mechanisms that make one cancer cell different from another and account for considerable phenotypic heterogeneity at the tumor level.

At the genome level, lung cancer is extremely diverse, such that no two tumors seem to have the same mutational profile. Even different cells within the same tumor may be marked by radically different sets of mutations. At the patient level, this leads to tremendous variety in mutation profiles; at the research level, this creates an intractable amount of work to model and analyze the contribution of each single mutation to the lung cancer phenotype. Ingenious *in vivo* utilization of the transformative CRISPR-Cas9 methodology in their NSCLC mouse model has allowed Jacks and his research team to rapidly generate hundreds of mouse mutants with tumors that model this heterogeneity. In essence, a vector containing the inducible Cas9 endonuclease machinery and the sequence of a specified target gene is introduced directly into a live NSCLC mouse; when activated, Cas9 is guided to the target gene where it creates a double-strand DNA break. The cell's efforts to repair such breaks tend to introduce loss-of-function insertion or deletion mutations, and specific mutations can also be achieved via inclusion of a stretch of homologous DNA that can recombine in and replace the existing sequence. This system has so far allowed generation of hundreds of tumors with distinct genotypes, biology, and therapeutic targets at a fraction of the time and cost required with previous methodologies. Once established, the library of mutated mouse models can then become the focus of experiments to address how each mutation contributes to the disease. Recent work in the Jacks laboratory has centered on Keep1, the third most frequently mutated gene in human lung cancers. Keep1 inhibits another protein, Nrf2, which promotes cell survival during exposure to reactive oxygen species (ROS). Tumors select for mutation of Keep1 to ensure constitutive Nrf2 activity that will protect against damaging ROS. Separate mutation of Keep1 and Nrf2 in the NSCLC mouse model using the CRISPR-Cas9 system confirmed the inverse roles of these proteins in tumor development, the former as a tumor suppressor and the latter as an oncogene.

Aside from changes in the DNA sequence, epigenetic variation is also thought to generate a unique tumor cell fingerprint and contribute to disease. Jacks spoke about several epigenetically controlled transcription factors that drive tumorigenesis by determining tumor cell differentiation state. For example, Nkx2.1, which controls a lung-specific differentiation cascade, is expressed in early stages of tumor development but turns off in later stages. This occurs in trade-off with expression of Hmga2, an embryonic transcription factor that becomes upregulated in later disease stages. Transition of lung tumor cells to the Nkx2.1 negative-Hmga2 positive state brings about a tumorigenic, dedifferentiated cellular phenotype. The shift in expression is controlled by several layers of regulation, which can similarly be turned on and off. Since not all cells undergo these changes simultaneously, and they occur with considerable variability within a given cell, the result is a heterogeneous, patchwork tumor that gradually changes to an aggressive, poorly differentiated state as the expression profiles of its individual cells alter the biology of the whole.

Further, cell signaling programs, such as those controlling stemness, also seem to contribute to heterogeneity within a tumor. Work in Jacks' laboratory has demonstrated that one such cascade, the Wnt pathway, is active in a subset of lung tumor cells, and that these Wnt-positive cells come to populate most of the tumor, strongly implicating them as tumorigenic clones. This result was found by crossing the NSCLC mouse to a strain encoding an inducible fluorescent reporter that lights up Wnt-positive cells, and following the fate of these cells over several weeks. Novartis has produced an inhibitor of Wnt activation, which Jacks and team have shown can decrease tumor growth and prolong survival in their mouse model. Efforts are underway to demonstrate the same in a patient-derived xenograft model. Such a finding could represent an important new approach in the treatment of lung cancer, and potentially other cancers marked by Wnt activation. Jacks' innovative manipulation of lung cancer mouse models continues to enhance our understanding of the complex cell interaction networks governing this family of diseases.

Former DoCM division head **Waun Ki Hong, MD,** *(left)* and Jacks share a laugh after the lecture.

Acute myeloid leukemia/ Myelodysplastic syndromes

Blazing a trail for novel strategies

– By Erica Di Pierro

Principal Investigators: **Guillermo Garcia-Manero, MD,** professor of Leukemia, and **Hagop Kantarjian, MD,** chair of Leukemia *(left)*

Each year in the United States, approximately 13,000 people are diagnosed with myelodysplastic syndrome (MDS), a disorder marked by rapid expansion of immature myeloid progenitor cells in the bone marrow that interferes with production of normal blood cells. Approximately one third of patients with MDS progress to acute myeloid leukemia (AML) as these immature progenitor cells, called blasts, crowd out the bone marrow and cause various cytopenias. AML can arise independently from MDS, however, prognosis is particularly poor when it develops from MDS or after chemotherapy for another malignancy.

The primary goal of the AML/MDS Moon Shot is aligned with the overarching moon shot philosophy: to rapidly develop new compounds that can cure or change the course of AML/MDS disease. The past year has been very active for investigators contributing to this cause, as cell lines, mouse models, big data, and numerous clinical trials blaze a trail for novel therapeutic strategies and targets. **Guillermo Garcia-Manero, MD**, professor of Leukemia and co-leader of the AML/MDS Moon Shot, highlighted advances from the group's two flagship projects at institutional Grand Rounds on July 31. The moon shot has two major research flagships, the first focusing on overcoming resistance to hypomethylating agents (HMAs) and the second on development of cellular immunotherapies.

While a large fraction of AML patients respond to HMA treatment, the therapeutic effect of these agents is not durable. HMAs work by inhibiting DNA methylation, an epigenetic process that leads to gene silencing, aberrant expression patterns, and poor outcomes in MDS patients. Once treatment fails, patient survival drops dramatically, often limited to six months. The mechanisms behind this decline are one of the central focuses of the first flagship. Crucial to these efforts have been the development of MDS- and AML-like cell lines that have acquired resistance to HMAs following multiple years of exposure. Multilayered analysis of these cell lines including transcriptome, proteome, and methylome determination is already shedding light on molecular mechanisms that lead to resistance. Further, collaboration with the APOLLO platform aims to genomically annotate as many AML/MDS cases as possible to create molecular maps of these diseases that can help elucidate responses to treatment, development of resistance, and tendency to relapse. So far, this high-throughput investigation has analyzed about 4,000 samples. "Before Dr. DePinho and his team were here, we were really lagging behind in this type of ability. But now with the help of Andy Futreal and his team, we're systematically performing deep genomic analysis of all our patients who come through the clinic," Garcia-Manero said. He spoke highly of industry collaborations with Amgen and Bristol Myers Squibb, which are bringing rapid progress to anti-MDS monoclonal antibody development and immunotherapy clinical trials, respectively.

Beyond cell lines, researchers on the AML/MDS Moon Shot are also making use of several game-changing mouse models for these diseases to illuminate mechanisms of HMA resistance. **Irene Ganan-Gomez, PhD,** a postdoctoral fellow in Leukemia, discussed developments in two such models, the TertER/ER mouse and the Tet2-/- mouse. The TertER/ER strain was developed in the DePinho laboratory in 2011 and characterized in 2015 as a high-risk MDS model by **Simona Colla, PhD,** assistant professor of Leukemia *(above)*. Phenotypic manifestations seen in this model strongly parallel those observed in patients with an intermediate category of MDS known as refractory anemia with excess blasts. The Tet2-/- model is characterized by massive expansion of the hematopoietic stem cell (HSC) compartment with skewing toward the myeloid lineage, which resembles chronic myelomonocytic leukemia (CMML), a subset of MDS marked by high peripheral blood monocyte concentrations. When both mouse models were treated with the HMA azacitidine for one week, myeloid progenitor cell numbers dropped significantly, indicating that the drug is initially effective against the primary hematopoietic defect of the disease. With longer term treatment, however, myeloid progenitors recover in number and fail to respond to the drug. Additionally, upstream self-renewing HSC

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that give rise to the MDS-like myeloid progenitors are unaffected by azacitidine, suggesting that relapse is inevitable. The fact that these models recapitulate findings from the clinic affirm their importance for follow-up studies to understand why HSCs survive treatment, developing more effective combination therapies, and identifying molecular determinants of relapse and resistance.

In treatment of AML, bone marrow stem cell transplant remains a standard effective therapy for eligible patients. Transplants that induce midlevel graft vs. host response, part of which is directed against tumor cells, are associated with longer relapse-free survival. Dean Lee, MD, PhD, chief of Cell Therapy in the division of Pediatrics, discussed progress in the cellular immunotherapy flagship project focusing on the role of donor natural killer (NK) cells in mediating this graft vs. tumor response. A number of clinical trials have demonstrated the importance of NK cells in this process, particularly when donor and recipient cells express different numbers and phenotypes of cell surface KIR ligands. A 2005 trial led by **Richard Champlin, MD,** chair of Stem Cell Transplantation, *(left)* showed that providing two adoptive transfers of donor NK cells prior to transplant was associated with longer relapse-free survival in AML and MDS patients. However, this study was limited by the number of NK cells, which could only be collected via apheresis from donors in quantities large enough for a single infusion. Lee and team developed a method for artificially expanding a population of donor NK cells using IL21, ultimately allowing for infusion of up to 100 times as many NK cells starting from a simple blood draw. So far in the clinic, Lee and team await the results of a trial similar in design to Champlin's but delivering orders of magnitude higher doses of NK cells from KIR-matched and -mismatched donors. No dose-limiting infusion-related toxicities have yet been observed. A second trial has shown dramatic and durable reduction of a patient's AML blast counts after fludarabine/high-dose Ara-C/granulocyte colony-stimulation factor (FLAG) chemotherapy and multiple doses of cryopreserved NK cells. The precise mechanisms by which the NK cells mediate these effects remain to be characterized, but the crucial work already undertaken by this multi-disciplinary group will surely enable numerous future advances toward better treatments and outlooks for patients of AML and MDS.

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Breast and Ovarian Cancers

After FDA approves first PARP inhibitor for advanced ovarian cancer, progress continues

– By Maxsane Mitchell

Principal Investigators: Gordon Mills, MD, PhD, chair, Systems Biology; Anil Sood, MD, professor, Gynecological Oncology and Reproductive Medicine; Mien-Chie Hung, PhD, chair, Molecular and Cellular Oncology; and **Debu Tripathy, MD,** chair, Breast Medical Oncology *(left)*

"I have the opportunity to announce that the Food and Drug Administration (FDA) today granted accelerated approval of the first PARP inhibitor as a third-line therapy for advanced ovarian cancer," said Gordon Mills, MD, PhD, chair of Systems Biology and a co-principal investigator for the Breast and Ovarian Cancers Moon Shot, at an Institutional Grand Rounds held Dec. 19, 2014. As part of his moon shot overview, Mills said that the poly ADP-ribose polymerase (PARP) inhibitor olaparib, now marketed as Lynparza, is administered orally to women with mutated, defective BRCA1 or BRCA2 genes that can no longer repair damaged DNA and suppress tumor growth, which potentially leads to the development of high grade serous ovarian cancer (HGSOC). The agent, still under investigation in Flagship 1, was first introduced in trials nationwide in 2005 and moved quickly through Phase I and II after producing data showing distinctive success in BRCA-deficient and platinum-sensitive patients.

Banu Arun, MD, professor of Breast Medical Oncology (BMO), *(left)* discussed more of the past year's progress in Flagship 1, which partly focuses on identifying and reducing the risk of developing or experiencing recurrence of triple negative breast cancer (TNBC) and HGSOC in families. "Currently, our genetic testing rate for TNBC and newly diagnosed HGSOC are greater than 90%, compared to the national averages of 35% and 14.5% respectively," she said. Investigators are using an innovative web-based tool to reach out to family members of TNBC and HGSOC patients to offer universal genetic

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Breast and Ovarian Cancers

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testing of BRCA1 and 2. The software makes risk calculations about which relatives to contact and then allows those family members to input their information. The module also asks questions about male breast cancer. When positive results occur, participants are given information and asked what they want to do—watch and wait, have risk-reductive surgeries, or receive educational materials. In highlighting the "right now" success of FP1A, Arun gave the example of an HGSOC patient who provided our investigators the names of kin on both sides of her family. It turns out that several people on the patient's paternal side had undergone genetic testing nearly a decade prior and that a number of them had been found positive for one of the mutations, but had never shared those details with anyone on the patient's maternal side. Years later, 10 people on the patient's maternal side were diagnosed. "That could have been 10 preventions had the others been told and given the option to have preventive surgeries including double mastectomies, hysterectomies, and/or oophorectomies," Arun said. The flagship also seeks to develop and implement a therapeutic platform based on synthetic lethal targeting of tumors that have defects in homologous recombination (HR) due to aberrant BRCA1 and 2 function and also various interactions with other critical pathways. Synthetic lethal targeting is designed to couple specific therapeutic agents with cellular deficiencies, together causing tumor cell death. **Jennifer Litton, MD,** associate professor of BMO, *(left)* and Shannon Westin, MD, assistant professor of Gynecologic Oncology and Reproductive Medicine, are significantly involved in this effort. Litton designed one of the first pilot neoadjuvant studies in the country for cancer patients with BRCA mutations. Patients are treated with the PARP inhibitor talazoparib for two months with baseline biopsies and ultrasounds followed by monitoring ultrasounds and a repeat biopsy at the end of treatment. Afterward, these patients will receive standard therapies—anthracyclines and taxanes—and undergo surgery. This study will look at DNA, RNA, and protein to evaluate why some people responded and why others did not. At press time, 47 patients were enrolled in a trial that is being run by Westin which combines two oral agents, the PI3K inhibitor BKM120 and the newly approved olaparib, for TNBC and HGSOC. This protocol is now in the dose escalation phase. Researchers continue to accept patients in a third trial, currently in Phase IB, for recurrent ovarian, breast, and endometrial cancers that combines olaparib with either the oral mTORC1/2 inhibitor AZD2014 or the oral AKT inhibitor AZD5363.

In Flagship Project 2, efforts continue to further identify adaptive resistance mechanisms and develop improved means of triaging patients to determine who should receive chemotherapy first and who should receive upfront surgery. Previous decisions had been based on standard clinical criteria such as CA125 values, disease distribution on CT scans, and physicians' opinion based on patient exams. The new method, called the Anderson Algorithm, is based on a scoring mechanism during diagnostic laparoscopy and agreed upon by two Gynecologic Oncology surgeons. Following this initiative, rates of complete gross resection have improved through cytoreductive surgery in both a primary and post-neoadjuvant chemotherapy setting. A pipeline of trials is planned for ovarian cancer patients who have tumors deemed by diagnostic laparoscopy to be unresectable, primarily with paclitaxel and carboplatin, MD Anderson's standard of care regimen, with the addition of a novel agent. Some trials include the anti-angiogenesis demcizumab, the anti-PD1 immunotherapy MK3475, and the platelet-lowering agent SPD535 to address highly elevated platelet levels that encourage tumor growth and reduce the survival of these patients. A molecular triaging approach is under investigation for patients with TNBC. Faculty in BMO have an umbrella trial in which patients can either be determined suitable for a Phase II combination study of doxorubicin, bevacizumab, and temsirolimus (DAT); a Phase II neoadjuvant study of enzalutamide with weekly paclitaxel for chemotherapy-insensitive androgen receptor positive disease; or Phase I/II study of neoadjuvant anti-PDL-1 therapy with nab-paclitaxel, which uses nanoparticle technology to deliver the agent in solutions that are less toxic than previous combinations. Investigators also want to expand some of these trials beyond the Texas Medical Center campus, so patients who receive care at the Houston-area locations and globally across our Sister Institutions will also be considered. To learn more about the mechanisms of treatment resistance, samples from pretreatment and those following therapy and surgery are being used to establish patient-derived xenograft (PDX) models and cell lines as another component of Flagship 2. The breast PDX models are being developed by Helen Piwnica-Worms, PhD, Vice Provost of Science, and **Funda Meric-Bernstam, MD,** chair of Investigational Cancer Therapeutics *(left)*. Jinsong Liu, MD, PhD, professor of Pathology Administration, leads the ovarian PDX model development. The PDX models will be used to characterize the different subsets of both cancers and investigators want to establish the first comprehensive catalog of breast and ovarian PDX models available to investigators worldwide.

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Melanoma Medical Oncology

Striving for individual and collective impact

– By Erica Di Pierro

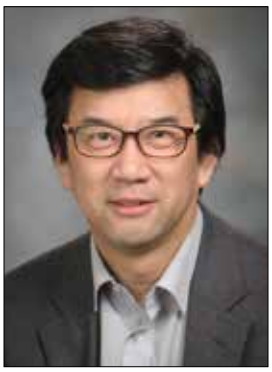
Research Retreats

Members of the Melanoma Medical Oncology (MMO) faculty convened on Oct. 3 to discuss recent research findings and define department goals. Division head and department chair **Patrick Hwu, MD,** proctored the meeting, starting the morning by declaring his pride in the transformative work being done across the group. Moving forward, he emphasized that faculty members should maximize the questions they are asking to make a unique impact individually and collectively, such that treatment options are always improving. Otherwise, "we aren't doing our job," he stated. Concerns were voiced about increases in patient load, identification of a new chair, the need for more mentoring and leadership, and for better cross-pollination between research and clinical teams. Following this was a series of chalk-talk style research updates from various faculty members under the umbrella topics of immunotherapy and central nervous system/uveal disease.

Immunotherapy updates

Jennifer Wargo, MD, associate professor of Surgical Oncology, and **Rodabe Amaria, MD,** assistant professor of MMO, *(left)* discussed their neoadjuvant studies, which seek to improve outcomes for late-stage melanoma patients by providing systemic therapy prior to surgery. Wargo's study combines BRAF and MEK inhibitors for patients with BRAF mutations, while Amaria's study will employ nivolumab singly and in combination with ipilimumab. Results so far from Wargo's study are promising, and she noted that the trial may be stopped early for a positive result. Insights gained from these trials could change the paradigm of how we treat stage III and IV melanoma patients, and will also provide a wealth of data on markers of therapy response through blood and tissue sampling.

Next, a conversation on intratumoral treatment approaches was led by **Willem Overwijk, PhD,** associate professor of MMO, and **Adi Diab, MD,** assistant professor of MMO. Intratumoral therapies are delivered directly into a tumor where they generate a systemic antitumor immune response to target and destroy local tumor cells and distant metastases. Such agents may work by priming the immune response, blocking immunosuppression, or ramping up innate inflammation, and can come in the form of oncolytic viral vectors, bacteria, and monoclonal antibodies. Overwijk recently started a preclinical study using mouse models with bioluminescent melanoma cells to explore use of immunotherapy for brain metastases. Overwijk also discussed extensive efforts to profile markers to therapy response and resistance, and development of peptide vaccines through collaboration with Immatics, a clinical-stage biopharmaceutical company focused on immunotherapy. Diab described application of several agents in the clinic, and the remarkable shrinkage of one patient's brain metastases after one dose of PD1 blockade combined with pro-inflammatory cytokine IL6.



Cassian Yee, MD, professor of MMO, *(left)* transitioned into ways to improve T cell therapy, noting the importance of long-term industry collaboration with companies like Immatics that are passionate about the biology behind therapies. He commented on personalized endogenous peptide therapy and T cell reactivity to non-primed antigens. Yee also highlighted the opportunity to take our influence beyond national borders, particularly in the case of uveal and mucosal melanomas, which have huge patient populations in Asia. **Chantale Bernatchez, PhD,** assistant professor of MMO, spoke about the tumor infiltrating lymphocyte (TIL) program, which infuses patients with expanded populations of T cells recovered from their tumors. Bernatchez discussed an effort to identify the most effective and anti-tumor reactive T cell clones within the TIL infusion population by cloning out and sequencing the T cell receptor in a collaboration with David Baltimore, PhD, of the California Institute of Technology.

Weiyi Peng, MD, PhD, instructor of MMO, discussed studies focusing on how PTEN loss promotes resistance to immunotherapy, a problem that may potentially be overcome by combining PI3K and VEGF inhibitors with immune checkpoint blockade agents.

Central nervous system/uveal disease updates

Michael Davies, MD, PhD, associate professor of MMO, spoke about the role of PTEN loss and PI3K activation in melanoma brain metastases, and the need for a representative animal model. He described the planned retrospective molecular and immunologic analysis of tissue from 1,700 patients diagnosed with melanoma brain metastases at MD Anderson. Further, intrathecal IL2 and TIL studies were mentioned.

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Melanoma Medical Oncology

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Next was a discussion on uveal melanoma led by **Sapna Patel, MD,** assistant professor of MMO, *(left)* and **Scott Woodman, MD, PhD,** assistant professor of MMO. Patel described a number of studies and collaborations, highlighting efforts to immune profile primary and metastatic melanoma samples at various time points during targeted therapy or immunotherapy treatment. She also spoke about intratumoral treatment of uveal melanoma, studying metastasis using circulating uveal melanoma tumor cells, and epigenetic therapies.

The retreat converged on a singular goal moving into the future: to have better treatments in five years than are currently available, and eventually to have enough effective treatment options that no patients are sent to hospice. Hwu emphasized that the exceptional faculty comprising the melanoma department are poised to make an enormous and unique impact toward eliminating this disease.

ET & ICT combine with IACS & ORBIT to foster collaborative efforts

– By Erica Di Pierro

The joint Experimental Therapeutics (ET), Investigational Cancer Therapeutics (ICT), Institute for Applied Cancer Science (IACS), and Oncology Research for Biologics and Immunotherapy Translation (ORBIT) research retreat took place Aug. 8 in the South Campus Research Building 4 conference room. In all, 44 participants attended the meeting. Hosted by **David Hong, MD,** associate professor of ICT, **Varsha Gandhi, PhD,** chair ad interim of ET, **Funda Meric-Bernstam, MD,** chair of ICT, and **William Plunkett, PhD,** professor of ET, the central goal for the symposium was to allow a medium for faculty to share their research in hopes of fostering productive collaborations among departments.

The morning began with a brief introduction from Gandhi. The first session focused on novel molecular targets, with a talk on nanocarriers from **Gabriel Lopez, MD,** professor of ET, *(left)* and on the ORBIT pipeline and partnerships from Michael Curran, PhD, assistant professor of Immunology. Following was a session on strategies to enhance therapeutic activity or overcome resistance mechanisms, which included a clinical trials overview from Meric-Bernstam; details of a Phase I/II study of AZD1775 and vorinostat in patients with head and neck cancer from **Siqing Fu, MD, PhD,** associate professor of ICT; a discussion on PI3K inhibition, resistance, and combination therapies from Gandhi; and reversal of resistance in cancers marked by wild-type p53 by **Zahid Siddik, PhD,** professor of ET. The third session shifted to establishing biomarkers for patient selection and resistance. During this late morning block, **Filip Janku, MD, PhD,** assistant professor of ICT, spoke about liquid biopsies; **Chang-Gong Liu, PhD,** professor of ET, gave a brief talk about the sequencing and non-coding RNA program; and **Geoffrey Bartholomeusz, PhD,** associate professor of ET, focused on target identification and validation care. The final module of the day was centered around translational study associated proof-of-principle trials, and was kicked off by **Vivek Subbiah, MD,** assistant professor of ICT, with a discussion about the search for the science behind exceptional responders. Within this session was a working lunch during which **Shuxing Zhang, PharmD, PhD,** associate professor of ET, delivered a talk on targeting ubiquitination for cancer therapy. The afternoon ended with two open discussions, the first led by Hong on molecules targeting cancer pathophysiology, and the second led by Plunkett on translation of mechanism-based therapy combinations.

In all, attendees were pleased with the retreat, but a post-event survey revealed the desire for more brainstorming and networking opportunities to clarify which agents to bring into clinic, which therapy combinations to test in preclinical studies, and how to introduce new diagnostics and technologies.

Gandhi *(standing)* chats with **Hong** *(left)* and **Meric-Bernstam** during a break.

New equipment builds peptides, splits DNA, and more

– By Claire Blondeau

Each fiscal year, faculty are given the opportunity to request capital equipment that can be shared with others throughout the institution. The goal is to obtain novel instruments that can be used by the most collaborators. After divisional requests are gathered by **Elizabeth Grimm, PhD,** deputy division head for research, they are discussed and evaluated jointly by representatives from each clinical department. The items are voted on and assigned a priority ranking, and the ranked list is submitted to Helen Piwnica-Worms, PhD, vice provost of science. (Laboratory-only departments send their requests directly to the vice provost.) An institutional-level committee then decides which items to fund. Following are details about the new equipment requested by DoCM faculty and approved for purchase in FY'16.

Protein Technologies Symphony X Multiplex Peptide Synthesizer

SymphonyX
(Photo courtesy of Protein Technologies, Inc.)

Researchers in the Center for Cancer Immunology Research (CCIR) are performing assays designed to better understand tumor-specific peptide antigens expressed on the surface of tumor cells that can be recognized and targeted by therapeutic cytotoxic and helper T lymphocytes. This recognition of specific peptide antigens constitutes the central focus of T cell-mediated immune responses that are the key to the recent successes of cancer immunotherapy. For the past two years, the labs of **Greg Lizee, PhD,** and **Patrick Hwu, MD**, have been working with David Hawke, PhD, in the Proteomics Facility to identify patient-specific tumor-associated peptides from fresh surgical samples using tandem mass spectrometry. After successfully identifying melanoma-associated peptides, they have begun identifying tumor-associated peptides expressed by ovarian, pancreatic, and colorectal cancers. Confirming the identity of the tumor-associated peptides requires synthesis of the same peptide and matching the fragmentation pattern against the peptide derived from the tumor. Until now, the group has outsourced peptide synthesis to commercial companies, paying up to $100 per peptide and waiting at least three weeks to receive the order. These costs and time constraints have hindered large-scale, cutting-edge immunological monitoring of cancer patients' antitumor immune responses. The latest high-impact immunology publications analyze several hundred peptides per patient in order to fully understand the breadth and complexity of immune responses, and until now researchers have been unable to compete at this level due to the cost restrictions of commercial peptide synthesis.

In collaboration with the Colon and Pancreatic Moon Shots in Year 1, Lizee and Hwu piloted mass spectrometry-based analysis of fresh patient tumor resections to identify tumor-associated peptides that can be used to develop personalized peptide vaccines and endogenous T cell-based therapies. As part of this effort, they analyzed approximately 20 pancreatic and colorectal patient samples but have been delayed from moving forward by the bottleneck with commercial peptide synthesis. Because both Moon Shot Programs will expand the numbers of patients analyzed in Year 2, delays were becoming a serious clinical issue. Having their own peptide synthesizer allows for timely confirmation of the tumor-associated peptide identities to get these patients treated much faster.

This equipment will be used by interdisciplinary teams including researchers from the departments of Sarcoma Medical Oncology, Stem Cell Transplantation and Cellular Therapy, Immunology, Lymphoma/Myeloma Systems Biology, and others. The peptide synthesizer will be located in South Campus Research Building 2 (2SCR3.3204) and will be available for use in early 2016. Contact Lizee for more information.

ProteinSimple Wes and Victor X3 Protein Plate Reader

The ProteinSimple Wes is an automated protein expression analyzer for western blotting. It can run up to 25 samples at a time and completes the entire analysis, including primary and secondary antibody incubations, in about three hours' time. A regular western blot takes 12 to 30 hours, depending on the antibody. The Wes is 10 times more sensitive than traditional western blot instruments and therefore uses less protein, which is invaluable when there is limited sample availability. It is automated and does not require monitoring during analysis, freeing up investigators' time. This equipment will be used to analyze proteins from patient samples or rare stem cells after fluorescence-activated cell sorting (FACS). Accompanying the Wes is a Victor X3 Plate Reader, which replaces an existing machine that has become dysfunctional. The plate reader measures protein concentrations in cell lines and clinical samples prior to analysis. There are many investigators who are looking forward to using this equipment in their research on targeted therapies for leukemia, breast cancer stem cells, myelodysplastic syndromes, and multiple myeloma. These items will be located in the Clinical Research Building (T6.3948) and are available for use as of Nov. 1. For more information, contact **Michael Andreeff, MD, PhD.**

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New equipment builds peptides, splits DNA, and more

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Seahorse XFe96 Extracellular Flux Analyzer

The Seahorse XFe 96 Extracellular Flux Analyzer profiles cellular metabolic functions using label-free, solid-state disposable optical sensors in a 96-well format. The XFe96 simultaneously measures mitochondrial respiration (oxidative phosphorylation) and glycolysis in the form of the oxygen consumption rate (OCR) and the extracellular acidification rate (ECAR), respectively. This analyzer metabolically stratifies cancer cell lines and tumor samples, which will facilitate patient stratification for testing novel metabolism-targeting agents for early clinical trials. It will also assist in advancing researchers' understanding of the molecular mechanisms of cancer metabolism, which could lead to the development of novel therapies and diagnostic/predictive markers. The XFe96 has integrated drug injection ports that automate the addition of up to four reagents. In addition to quantifying mitochondrial respiration and glycolytic activity, assay kits are available for measuring endogenous and exogenous fatty acid oxidation, substrate oxidation, and metabolic switching. Software is included for calculating these parameters. This equipment is applicable to several ongoing projects in melanoma and leukemia. It will be located in Life Science Plaza (LSP12.3018) and is expected to be available in December. Investigators interested in using this equipment can contact **Vash Yennu Nanda, MD, PhD.**

ZetaView Nanoparticle Tracking Analyzer

The Zeta View is a particle analyzer for assessing the properties of extracellular vesicles. Preliminary studies indicate that the expression of lymphoma apoptosis-regulating proteins are controlled by signals received in lymphoma cells when cocultured with mesenchymal stromal cells (MSCs), and researchers will use this equipment to examine extracellular communication between MSCs and lymphoma cells. Investigators also plan to define the signaling proteins and signaling nucleic acids carried in extracellular vesicles that affect mantle cell lymphoma stem cells. Additionally, investigators are developing a monoclonal antibody against a tumor derived exosome (TEX)-enriched isoform of HSP70. Current data using a polyclonal sera shows this approach blockades TEX signaling and intercellular transfer. This approach leads to the depletion of TEX numbers and reverses drug resistance to proteasome inhibitors. The measurement of TEX numbers and concentration is critical for this project to accurately quantitate the efficacy of this monoclonal antibody approach. The ZetaView will allow direct physical measurement of the TEX particles properties and their concentrations via Brownian motion, which is the most accurate way to measure the TEX. The device will be located in South Campus Research Building 1. Contact **Richard Jones, PhD,** for more information.

Diagenode Diagnostics Bioruptor Pico Sonication Device

The Bioruptor Pico is a hydro-sonicator that shears DNA for next-generation sequencing. It also shears chromatin and RNA, extracts protein from tissues and cells, and extracts DNA from formalin-fixed, paraffin-embedded (FFPE) samples. It incorporates a water-based cooling system to ensure precision temperature control resulting in higher quality samples. The Bioruptor is capable of simultaneous sonication of up to 12 samples. It is capable of shearing micro-volumes of 5µl to larger volumes up to 2ml of DNA, which is required for library preparation for a number of applications including whole exome sequencing, ChIP-sequencing and others.

It will be located in South Campus Research Building 4 (4SCR6.2080) and became available for use in December. There is a wide range of research that will benefit from the Bioruptor, including projects related to pancreatic ductal adenocarcinoma, glioblastoma multiforme, melanoma, and prostate cancer, as well as cancer biology, tissue transplantation, mouse models, checkpoint inhibitors, and immunotherapy. Contact **Kunal Rai, PhD,** for more information.

Agilent Technologies Bravo Automated Liquid Handling System

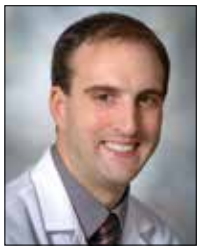
The Agilent Bravo Automated Liquid Handling Platform is a fast and versatile liquid handling system capable of a wide range of applications including high-throughput library preparation methods for next-generation sequencing applications such as single-cell RNA-sequencing and ChIP-sequencing, which are the major intended uses for this instrument. An additional use is for aliquoting small molecule inhibitor libraries. It is applicable in various projects involving high-throughput next-generation sequencing applications as well as some compound screens in different cancer systems.

The Bravo Platform uses high-accuracy pipette heads for dispensing from 100 nL to 200 µL in 96- and 384-well microplates with either disposable or fixed tips for specific applications. It will be located in South Campus Research Building 4 (4SCR6.2080) and available for use by May 1, 2016. Researchers will use this machine in their projects related to mouse models, tissue transplantation, checkpoint inhibitors, and immunotherapy, as well as pancreatic ductal adenocarcinoma, glioblastoma multiforme, melanoma, prostate cancer. Contact **Kunal Rai, PhD,** for more information.

Announcing our 2015 Advanced Scholars

– By Erica Di Pierro

The Advanced Scholars program provides physician-scientists in-training with an additional year of experience focused on honing their skills in academic research springboard into an academic career. This program is designed for those physicians who have excelled in both clinical and laboratory spheres, and seek to further develop their ability to translate basic science discoveries into meaningful and impactful therapies. This year, the division is proud to announce three Advanced Scholars.



Jonathan Brammer, MD

Brammer is utilizing his Advanced Scholar year to study T cell hematologic malignancies, with an emphasis on preventing disease relapse after allogeneic stem cell transplantation. He completed his first two years of hematology/oncology fellowship at the Oregon Health & Science University, and came to MD Anderson to specifically focus on stem cell transplantation under the mentorship of **Richard Champlin, MD,** chair of Stem Cell Transplantation and Cellular Therapy.

Brammer has designed and secured funding for a novel Phase I/II clinical trial utilizing the histone deacetylase inhibitor romidepsin in combination with chemotherapy before and after transplant in patients with T cell cancers. Romidepsin has been shown to possess direct anti-tumor effects against malignant T cells, and may favorably modulate graft vs. lymphoma effects while suppressing graft vs. host disease (GvHD). "This is the first prospective trial ever conducted that targets T cell malignancies specifically in individuals who are undergoing an allogeneic stem cell transplantation," Brammer said. Currently in the recruitment phase, this trial will afford Brammer the invaluable experience of conducting and interpreting clinical research while working alongside **Chitra Hosing, MD,** professor of Stem Cell Transplantation and Cellular Therapy and clinical medical director of the Apheresis Center.

In addition to this trial, he will also evaluate the immunologic effects of romidepsin post-transplantation by working in the laboratory of **Katy Rezvani, MD, PhD,** professor of Stem Cell Transplantation and Cellular Therapy, and develop his stem cell transplantation expertise working alongside Champlin.

Jennifer Goldstein, MD

Goldstein has found her calling in the field of cancer genomics, where she hopes to advance understanding of intratumoral heterogeneity and mechanisms behind therapy resistance. A 2015 graduate of MD Anderson's Hematology/Oncology Fellowship, she will continue to work during her year as an Advanced Scholar with mentor **Andrew Futreal, PhD,** chair *ad interim* of Genomic Medicine.

Experiences with cancer in her family motivated Goldstein along the oncology path, which she chose for the rewarding patient interactions it affords. "Sometimes we have to engage in difficult discussions about life and death, but I am up for the challenge of building trust with my patients while promoting the best possible outcomes," she said. During residency at UCLA, Goldstein pursued inhibitors of breast cancer cell division, working in the laboratory of Dennis Slamon, MD, who discovered trastuzumab.

Goldstein will continue a project initiated during her fellowship that utilizes a barcode system to uniquely tag individual tumor cells so that they may be tracked, identified and sequenced. She has used this system to understand the impact of temozolomide and radiation on the clonal architecture of glioblastoma tumors by quantifying individual cell barcodes in pre- and post-therapy tumors. This work earned her an American Society of Clinical Oncology Young Investigator Award and an American Association of Cancer Research Basic Cancer Research Fellowship. Ultimately, she also hopes to expand her studies into developing novel therapeutics for pancreatic cancer.

Jin Im, MD, PhD

Im seeks to understand the role of invariant natural killer (iNK) T cells from cord blood stem cell transplants in regulating GvHD. Her studies will be conducted under the guidance of **Jeffrey Molldrem, MD,** professor of Stem Cell Transplantation and Cellular Therapy, with whom she worked as a Hematology/Oncology Fellow from 2012 to 2015.

Im's path to the Advanced Scholar program wove through doctoral and post-doctoral research focused on the role of iNK T cells in autoimmune and infectious diseases, and subsequent medical education at the Albert Einstein College of Medicine that enlightened her to the blossoming field of immunotherapy within oncology. Of her experiences in medical school, Im said that "every day with patients on the wards validated my decision to become a physician-scientist."

A primary concern with any stem cell transplant is the possibility for GvHD. Cord blood stem cell transplants, however, are associated with reduced incidence of this problematic immunologic reaction. Im's fellowship research, funded through a New Investigator Award from the American Society of Blood and Marrow Transplantation, has shown this to be due in part to high numbers of iNK T cells in cord blood that produce regulatory as opposed to inflammatory cytokines, possibly quelling an immune response against host tissues.

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Message from the Division Head

Time spent now on Epic will pay off in long run

Patrick Hwu, MD

It's important that we learn as much as possible about Epic before OneConnect implementation in March. I'm convinced from attending training classes and demos that this will give us an improved system with greater ability to customize to better fit our needs across diverse services. What we can do is to learn as much as we can, and customize the order sets and the documentation per service and per individual provider. The implementation is forcing us to re-examine and make sure our workflows are logical and organized.

In the short run, we have to make sure that we are all trained so that we can find all of the windows and boxes that we need, and then customize them to be the way we anticipate using them. It's extremely important that we individualize within our own practice styles, as well as setting our own macros. If we can do that, then the Epic implementation should go smoothly. In the long run, there will be significant payoffs in terms of error-free and fast order entry, expedited and concise documentation, better monitoring of our patients through customized reports and overall improved quality of care.

For the Beacon chemotherapy module, orders are especially improved upon what we have today. Currently, we enter chemotherapy orders in and they get sent to the pharmacy and then the pharmacist puts them into a separate system by hand. That is a perfect setup for potential errors. With Epic, we put it in once and if we make a change it will change all of the medications downstream for cycles 2, 3, 4 and subsequent cycles. Beacon is far and above better than what we have today.

I'd like to commend James Yao, MD, chair of Gastrointestinal Medical Oncology, who gathering feedback from our colleagues at Dana Farber Cancer Institute who recently implemented Epic as well as heading up the treatment plan conversion advisory group. Sharing their experiences with us emphasized what we already knew – that training in advance and preparation are key to a smooth implementation. They were realistic about their experience, and the first month or so was a little rough for them, as it may be for us.

Epic is a flexible system and there are many ways to accomplish any given task, such as writing a prescription, which can lead to confusion. The best thing we can do is make sure we comply with the training plan for our role. The Epic operations team has been scheduling more training sessions as needed to make sure everyone gets the training they need in the correct sequence and in time for implementation.

Patient data are being transferred into Epic from ClinicStation using several automated methods as well as natural language processing. However, treatment plans must be entered manually, and before that can happen all structured data must be entered and validated. Including protocol patients, we have an estimated 5,000 to 15,000 patients with active chemo orders. This is a massive undertaking that requires medical oncology oversight, and our APNs, PAs, PharmDs and research nurses will be a vital part of getting this right. Providers have to complete their scheduled training before starting on treatment plan conversion. The DFCI providers emphasized that treatment conversion was the most important part of their training.

The impact on our time as care providers is substantial, and we all need to do what we can to keep our patients top priority while at the same time stay on top of our research mission. We're all in this together. Although we may feel some pain during the first quarter of 2015, our colleagues at DFCI reported being back on an even keel at about three months post go-live. A year post go-live, we all will be much more efficient and happy to be on Epic and saying, "We should've done this sooner!"

Regarding the recent announcement that the Epic system build is complete, think of it like building a house: We have walls and floors, but there are no utilities, flooring, or fixtures. That means the clinical content data flow still needs to take place.

Go-live strategy involves making decisions about increasing staffing vs. decreasing volume, and we must be sensitive to the downstream impacts with other departments. Wendy Austin, RN, MS, AOCN, NEA-BC, FACHE, in her new role as executive director of hospital and clinics, will help ensure that we're in sync with the other divisions.

Things we can do to alleviate potential impacts are to complete our required training by the end of January, minimize non-OneConnect activity in February and March, and schedule our long-term follow-up patients in January and February or a few months after go-live. In the end, we have to decide between what's perfect and what's functional, and err on the side of being functional. In an ideal world, everything would be 100% perfect, but we don't live in an ideal world. We have to think about getting the system functional. Also, we need to be involved in the decision-making process to ensure the best decisions are made regarding our practice. There is a lot of internal policy that needs to be made that will drive the go-live. We need to decide what's allowable.

In the long run, there are going to be a lot of efficiencies as well as an enhanced patient experience. With any large change, there are unknowns and uncertainty, but that's life! But in the long run, it's going to be absolutely fine. We'll have improved systems to help us provide the best care for our patients.

OneConnect

OneConnect: It takes a village to make it happen

– By Maxsane Mitchell

"Six months after everyone is using OneConnect, no one will want to go back to ClinicStation."

In an odd way, the proverb, "It takes a whole village to raise a child," adeptly applies to the small village of MD Anderson employees and faculty members that have been working together to raise the OneConnect system to become successful by March 4, 2016. That's the day it goes live throughout MD Anderson's entire clinical and research enterprise to replace ClinicStation, which was originally implemented in 2001. President Ron DePinho, MD, announced in 2012 that a new electronic medical record system was needed because despite the expense of $20 to $30 million dollars annually to upgrade ClinicStation, the older platform would not be able to keep pace with newer technology that can be adapted to expand in the years to come. Programmers and consultants with Epic Systems were selected in 2013 and have been working with institutional information technology employees to get the new system up and running. However, they need input from a cross-representation of people who will actually be using the system to care for patients, to input and retrieve laboratory/imaging results, and to enter data that can be used for research purposes. Hence, the Physician Builder Program was born to bring doctors, nurses, physician assistants, laboratory scientists, and many other specialty representatives together to give input on how the Epic suite, now referred to as OneConnect, can best serve all of its constituencies. When the call went out for volunteers, more than 1,800 people applied to become members of this elite group. Three of the 153 accepted to the program come from the Division of Cancer Medicine. They are **Megan Cornelison, MS, PA-C,** midlevel provider supervisor in Stem Cell Transplantation and Cellular Therapy; **Kimberly Koenig, MD,** clinical associate professor of Breast Medical Oncology; and **Vinod Ravi, MD,** associate professor of Sarcoma Medical Oncology. Cornelison is the only physician assistant at the entire institution to be selected. Their participation requires more involvement than that of super users.

Following a training session at Epic headquarters in Wisconsin, the trio began attending a series of sessions with programmers to communicate about customizing or building OneConnect to suit their needs, based on department-specific workflows. "The training was of great value to me to understand how the program was built, and what it's meant to do and not meant to do. It was helpful in explaining the possibilities and limitations to my colleagues," said Cornelison. "Without this working knowledge, we might have made 'build' choices that could have hindered us, but instead I think we made decisions that will facilitate our work by making creative tweaks that won't require us to overhaul our workflow."

She and Ravi agree that, despite an anticipated learning curve for everyone, OneConnect will be much better than the current system. "ClinicStation is at best a viewer of many types of data sources that stores patient information and allows limited data entry, reporting and search capabilities. It's a little like a web browser that allows us to view content from multiple servers. Data extraction and reporting capabilities are limited with ClinicStation at the end-user level. Ability to customize the way information is presented and viewed is also limited in ClinicStation. Epic enables content to be customized and displayed so providers are able to view information that is relevant to them, in a format that they can personalize. OneConnect will integrate patient information from multiple sources into one application that can be personalized," said Ravi. He commented that the system is expected to permit specialists to use data points to create charts or other visual aids to show patients their treatment progress.

It will allow for a greatly needed "clean-up" of oncologic histories. ClinicStation does not have a structured way of storing oncology history, which can cause some delays to read through the entire history of each patient before and after visits to determine next steps. "We're hoping Epic will enhance efficiency by letting us create structured data points that will allow filtering and search functions. Questions such as how many treatments a patient has had, and which ones worked the best during a period of time, will be easier to answer," Ravi said.

Our patient data system should incorporate more structured data if we want to get better at predicting outcomes on various treatments we use for our patients, he said. "For example, you can go to www.weather.com, and in a glance see what the conditions are right now, and what they're expected to be for your 5 p.m. drive home. This is made possible by a massive amount of data available for prediction modeling. If we want to get better at forecasting patient outcomes in the future, we should be thinking about laying the foundation for collecting more high-quality, structured clinical information at MD Anderson," Ravi added. Physician builders have a great role in facilitating this capability of OneConnect. It will take time, but if we can use technology to help our best experts predict outcomes and provide answers that patients can't get anywhere else, we should do it, he said. "Those are long-term plans, but in the immediate future, the enhanced clinical efficiency alone will justify the transition from ClinicStation to OneConnect. I think six months after everyone is using the new platform, no one will want to go back to ClinicStation," Ravi said.

Administration

New Division Administrator brings long history of institutional service

Martha Salas, MBA, MSW, returned to the Division of Cancer Medicine as division administrator on Oct. 1. A seasoned veteran of the MD Anderson Cancer Center with a proven track record of success, Salas began her career in 1998 as a social work counselor in MD Anderson's Genitourinary Care Center following completion of her master of social work degree at the University of Houston. In this role, she performed psychosocial assessments and provided treatment for about 100 cancer patients per month, trained and mentored graduate-level interns, helped to optimize patient care coordination, presented at numerous conferences, and coordinated multiple patient support efforts. Salas quickly learned to appreciate the impact of administrators in keeping the myriad parts of the health care system in motion, and pursued a master of business administration from the University of Houston after realizing that she wanted to contribute to this momentum. She then became a clinical business manager for the Gynecologic Oncology Center in 2003, where she administered a multimillion dollar budget, managed day-to-day business operations from revenue integrity to resource acquisition, and supervised the administrative support staff. After excelling in this position, Salas was promoted to department administrator of Genitourinary Medical Oncology in 2005. This role required her to wear many hats, directing human resource management for over 150 employees, controlling a multimillion dollar operating budget, and overseeing the David H. Koch Center for Applied Research of Genitourinary Cancers. She also developed high school and college summer internship programs, and expanded the department's communication reach by developing social media and Internet sites.

Salas assumed the position of division administrator for the Division of Cancer Prevention in 2012. During her three years in this role, Salas perfected the skills that will help her lead our division to continued growth and success. Her duties in Cancer Prevention included implementing the division's financial, human resource, patient care, research, and operational activities; managing more than 600 employees in five research and clinical departments; and overseeing the budget. For the DoCM, she is now responsible for more than 2,800 employees in 15 academic departments and 10 patient care centers. As Salas transitions into her new position, she is receiving continued support from her predecessor, Wendy Austin, RN, MS, AOCN, NEA-BC, FACHE, now the executive director of Hospital and Clinics.

Salas, a mother of three young children, adeptly balances work and home. In the end, she has never lost focus on her reason for being here—to serve the patients, a goal she can accomplish with lasting impact from her new position. "It's such a pleasure to join this group again and to be back home. I look forward to working alongside such amazing people and taking the reins from Wendy. She is feeding me with all the knowledge, background, and history so we can keep things moving forward," Salas said at a reception held in her honor on Oct. 16.

GIMO/General Oncology DA familiar with MD Anderson from prior role

Alicia Newton, MHA/MBA, FACHE, began her role as Department Administrator for Gastrointestinal Medical Oncology and General Oncology on August 24. Newton's professional background is rich in hospital/clinic operations, financial management and budgeting, customer service, and pharmacy operations experience, all of which have helped her step naturally into her new position at MD Anderson. Since 2008, she had been the administrator of three departments at Baylor College of Medicine, where she assumed financial, personnel, patient care, operational, and human resources responsibilities. Among some of her many noteworthy endeavors in these positions were preparation of annual department and division budgets that ranged in the multimillions of dollars, long-range projection and financial planning, participation in a transition to the Epic electronic medical record system, CLIA recertification for the Dermatology Department, and handling numerous operational and human resource activities from faculty hiring to off-boarding. Before this, Newton served as a project manager for the Methodist Hospital Physician Organization, a specialty physician group comprised of over 200 physicians and 900 total employees.

Newton is also familiar with MD Anderson from her previous work as an office manager for the MD Anderson Radiation Treatment Center at Bellaire, the pilot location for the program that evolved into the Regional Care Centers. This role involved operational oversight, business development duties, budget planning and administration, staff training, and assisting with establishing and opening the Bay Area Radiation Treatment Center.

Newton earned a Bachelor of Science in psychology from Sam Houston State. She continued her education at the University of Houston-Clear Lake, earning her joint Master of Health Care Administration/Master of Business Administration (MHA/MBA) degrees in 2004, and participating in the Baylor Scott and White Health Executive Education Program in Austin, Texas, in 2014. Newton is a Fellow of the American College of Healthcare Executives (FACHE), a member of the Medical Group Management Association (MGMA), and a member of the Healthcare Financial Management Association (HFMA).

Since Newton's start date in late August, James Yao, MD, chair of Gastrointestinal Medical Oncology, has received numerous espousals of her adaptable, efficient, and grace-under-fire character from former colleagues as she begins her next professional chapter. Newton was officially welcomed at a reception held on Sept. 11.

Cancer Medicine Prominent at Faculty Honors Convocation

Logothetis Accepts LeMaistre Award; Andersson, Gandhi Receive Faculty Achievement Awards

– By Maxsane Mitchell

Christopher Logothetis, MD, chair of Genitourinary Medical Oncology, *(above)* was presented the Charles LeMaistre, MD, Outstanding Achievement Award in Cancer at the Faculty Honors Convocation, held Oct. 12, 2015. The award, presented since 1980, recognizes far-reaching contributions made by a physician and/or scientist to markedly enhance the reputation of The University of Texas MD Anderson Cancer Center. Logothetis enumerated impactful changes that have occurred in the field since he first joined the institution as a medical oncology fellow in 1977. "I've seen remarkable advances afforded to us because of CT scans, MRIs, minimally invasive surgeries, anti-emetics, growth factors, new chemotherapy agents, tyrosine kinase inhibitors, and the emergence of immunotherapy from the shadows to become a real, credible therapy option. Only those of us who have lived this transition understand the magnitude of change, and how it has impacted the daily care of our patients," Logothetis said. He also talked about the development of PCR, the sequencing of the human genome, and the transfer of "the centuries-old hold" that anatomists had on the taxonomy of cancer to cancer biologists. "And now, we look at a horizon with the promise of gene-editing enabled by CRISPR/caspase-9 that is unbelievable," Logethetis said. But even with all of those resources, he expressed concern that regulations and requests for reports "sets in motion a cascade of events leading to proportionally less experimentation that tends to be incremental and more cautious. I worry this will take us from being agents of change to champions of the status quo," he cautioned. "These challenges must be addressed if we are to achieve our aspirations."

Nominators referred to Logothetis as a transformative figure in the field of prostate cancer care and research. "He is best known for his discoveries on the use of combinations of chemotherapy and hormonal therapies, his pioneering research on the interaction of prostate cancer with the microenvironment in the bone marrow, and his exceptional skill at coordinating optimal care involving surgery, radiation, and chemo/hormonal therapy," wrote one colleague. Regarding his work in bone marrow microenvironment, another nominator expanded that Logothetis's early studies were instrumental to scientists' understanding of epithelial-stromal interactions between prostate tumor and bone, and that his early bone marrow samples were the basis of an impressive registry for the international research community. Logothetis currently is co-director of the David H. Koch Center for Applied Research of Genitourinary Cancers, co-leader for MD Anderson's Prostate Cancer Moon Shot, and principal investigator for grants from the National Institutes of Health, Department of Defense, and the Prostate Cancer Research Foundation. In February 2015, he was awarded the inaugural Finnerman Family Endowment in Translational Research, a $50,000 cash award to honor leading faculty members who conduct translational cancer research. Logothetis accepted the John Mendelsohn Lifetime Achievement Award in 2012, and is a frequently invited speaker who has published over 400 articles, abstracts, and book chapters. He's also credited with leading recruitment efforts to bring research superstars to MD Anderson—among them, renowned immunologist James Allison, PhD; **Peter Friedl, MD, PhD,** professor of Genitourinary Medical Oncology, an immunologist and an expert in the use of microscopy, which allows researchers to actually see cancer cells moving in mouse studies; and prostate cancer researcher **Timothy Thompson, PhD,** professor of Genitourinary Medical Oncology. "The generosity of taxpayers has furnished us with unprecedented resources, and what they ask from us in return is a cancer-free future. I believe our faculty and staff will remain good stewards of the trust placed in them as we commit as a community to execute on an operational vision that matches our scientific vision," Logothetis said. "So, thank you for affording me the privilege of membership in this exclusive fraternity that is engaged in a noble crusade."

Borje Andersson, MD, PhD, professor of Stem Cell Transplantation and Cellular Therapy, received the Pearl L. Walters Faculty Achievement Award in Clinical Research. He is credited with establishing a new standard of care for conditioning therapy prior to transplantation. Nominators say Andersson was the lead developer of the intravenous formulation of the alkylating agent busulfan as a preconditioning treatment for stem cell transplantation. His method set a new standard and demonstrated an unprecedented safety record for pre-transplant chemotherapy. Nominators credited him with pioneering additional combinations of analogs with histone deacetylase inhibitors, tyrosine kinase inhibitors, demythylating agents, and

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Cancer Medicine Prominent at Faculty Honors Convocation

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Andersson is credited with establishing a new standard of care for conditioning therapy prior to transplantation.

designing and executing over 15 MDACC trials, whose results doubled the three-year survival of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), as well as increasing event-free survival in AML by over 25%. Andersson has had similar success in high-risk hemoglobinapathies. Utilizing the institution's Global Academic Programs to decrease the gap in knowledge of these high risk diseases, he and his team worked with sister institution collaborators in Thailand to develop pre-transplant immune suppression methodologies (PTIS), improve transplants for identical donors and mismatched donors, and make possible the potential that every child with severe thalassemia could become a transplant candidate. Said one nominator, "Borje's body of work is an example of 'Making Cancer History,' and further expansion of scientific knowledge for the benefit of all patients."

Varsha Gandhi, PhD, *ad interim* chair of Experimental Therapeutics, accepted the William Randolph Heart Foundation's Faculty Achievement Award in Education. Nominators described her as someone with "an unbridled passion for education at all levels." When she realized a lack of formal training for young scientists to fully explore the abundance of career opportunities in translational therapeutics, she initiated the "Mechanisms of Cancer Therapeutics" course at The University of Texas Graduate School of Biomedical Sciences (GSBS) in 2003. Because of the continued interest in the subject, Gandhi was inspired to establish a PhD program that addressed the entire discipline of experimental therapeutics at GSBS in 2010. So far, 15 students have graduated with this concentration and now work in various science-driven careers. Additionally, Gandhi developed a new program that pairs junior faculty with senior mentors to provide work and career advice. She has previously said, "I educate the next generation of scientists by teaching them the fundamentals of cancer therapeutics and by supervising them as they test agents in the lab and apply them in the clinic. I strive to provide students the tools to test their hypotheses and the critical thinking skills to generate others so they can become optimistic that they will ably tackle the disease and cure it."

Gandhi accepts award from Oliver Bogler, PhD, senior vice president of Academic Affairs.

Division faculty receive $3.5 million in CPRIT research funding

Of the $22.2 million awarded to MD Anderson in November from the Cancer Prevention and Research Institute of Texas (CPRIT), four Cancer Medicine faculty racked up over $3.5 million in Individual Investigator Awards.

- **Michael Davies, MD, PhD,** associate professor of Melanoma Medical Oncology: Exploiting molecular and metabolic dependencies to optimize personalized therapeutic approaches for melanomas, $900,000
- **Giulio Draetta, MD, PhD,** professor of Genomic Medicine: Identifying new epigenetic vulnerabilities in pancreatic cancer, $900,000
- **Simrit Parmar, MD,** associate professor of Stem Cell Transplantation and Cellular Therapy: Clinical safety and efficacy of third party, fucosylated, cord blood derived regulatory T cells to prevent graft versus host disease, $900,000
- **Michael Wang, MD,** professor of Lymphoma/Myeloma: An adaptive personalized clinical trial using a patient-derived xenograft strategy to overcome ibrutinib resistance in mantle cell lymphoma, $841,606

OneConnect featured at lectures

– By Erica Di Pierro

Implementation of the new Epic electronic health record (EHR) system, known as OneConnect, will be the single largest transition in MD Anderson's history. As we approach the March 4, 2016, go-live date, training sessions are in full swing, the system build is well underway, and clinical content is being validated.

Mansfield reviews nuts and bolts of go-live

On Aug. 11, Paul Mansfield, MD, vice president of Acute Care Services, stressed that while it will come with peaks and valleys, the institution will benefit in countless ways as we collectively adjust to the new system. In terms of a strategy for training 15,000 employees, he said, "We're going to ask you to fly the plane. We need to teach you how to take off and land and then as you get more comfortable, you'll learn how to do loop-de-loops." Users will first master the basics of operating the system, and with time they will learn how to personalize and optimize their OneConnect experience to best fit their day-to-day needs. Training sessions will occur in five four-hour blocks including simulation and personalization labs, culminating in a test on which users must achieve an 85% score. Crucial to the success of the EHR are super users, a group of about 1,000 leaders who will be go-to resources for troubleshooting during the transition and beyond. Construction and testing of modules for ambulatory care, ER, pharmacy, oncology (known as Beacon), operating room, and others have been ongoing since last fall, and 2015 upgrades were recently worked into the system. Data cutover and conversion will be automated for many structured data elements, while other parameters including treatment plans and schedule procedures will need to be manually converted. However, once patient data is uploaded to OneConnect, it stays there forever and is easily accessible. Mansfield encouraged users in the division to attend integrated workflow walkthroughs, EHR Grand Rounds, and consult with EHR officers for OneConnect toolkits.

Dana Farber colleagues relate experiences

On Oct. 13, five representatives from the Dana Farber Cancer Institute traveled from Boston to offer advice from their recent Epic go-live experience. The discussion was led by Andrew Wagner, MD, PhD, medical director of ambulatory oncology, and leader of the Dana Farber Epic build and implementation. A supporting panel included Jennifer Chan, MD, assistant professor of medicine; Hillary Prescott, PharmD, clinical pharmacist; Janet Bagley, MS, RN, AOCNS, director of nursing and clinical services; Katie Keavany, director of disease center and ambulatory care operations; and Pat Stahl, MEd from volunteer services and programs. Dana Farber is part of the 24-institution Partners Healthcare network, which is undergoing phased Epic implementation through 2017. The ultimate goal of this transition is to create one record per patient and to have all information relating to that patient available across the entire network. Wagner mentioned numerous improvements associated with the system, including smooth transition between outpatient and inpatient status, easy and rapid tracking of lab or pathology results, and electronic medication administration to ensure the right patient gets the right medication. With these bright points, however, come the frustrations of using an unfamiliar interface that requires significant experience to become a proficient user. He stressed that, "Epic is what you make of it," and that it should be embraced as a totally new experience, not as a one-to-one replacement of the current system. The panel offered several pieces of advice, including that it's important to have a supportive environment going through the transition, to help others learn as you learn and keep up strong, proactive communication, especially with the support team. The most crucial point, Wagner said, is to remember that, "you know how to do your job," how to take care of the patient, regardless of the healthcare system being used.

Experts discuss current state of leukemia treatments

Have we cured CML?

Jorge Cortes, MD, professor of Leukemia, provided a comprehensive look at the state of chronic myeloid leukemia (CML) therapy and what the future is likely the bring for this malignancy on Sept. 1. Currently, there are three frontline tyrosine kinase inhibitors (TKIs) approved for CML chronic phase treatment: imatinib, nilotinib, and dasatinib, with imatinib at 400 mg daily being the standard of care. While imatinib 400 is an effective therapy, parallel studies have shown that treatment with nilotinib, dasatinib, and higher-dose imatinib results in a deeper molecular response that occurs faster and is more durable. In the long term, these alternative modalities do improve failure-free survival, with any divergence from complete cytogenetic response (CCyR) considered a failure, but do not yet seem to significantly improve overall survival over imatinib 400. Nevertheless, these agents may prove to be good options for future refining of CML standard-of-care therapy. A CCyR is the gold standard for therapy response, occurring when cytogenetic testing shows no evidence of cells containing the translocated Philadelphia chromosome that defines the disease;

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this response level correlates with excellent survival. Beyond cytogenetic responses are molecular responses, which evaluate the quantity of BCR-Abl fusion transcript being produced from the Philadelphia chromosome and are graded based on level of transcript detected. Achieving a deep molecular response on top of a CCyR can increase therapy response duration and reduce likelihood of failure. Although current treatments for CML keep the disease at bay, therapy must be continued indefinitely. Research is underway to determine the feasibility of stopping treatment in patients with sustained deep molecular responses. Treatment with nilotinib and dasatinib appears to lower chances of relapse and increase likelihood of achieving complete molecular response, but more time is required to solidify these associations. While effective at managing CML, these TKIs can produce side effects including vascular anomalies, fatigue, and renal dysfunction, which must be monitored closely. In terms of future avenues for CML, Cortes emphasized the importance of eliminating leukemic stem cells, which none of the current therapies are capable of doing, but JAK2 inhibitors hold promise.

CLL: The old and the new

Susan O'Brien, MD, associate director for Clinical Science for the Chao Family Comprehensive Cancer Center at the University of California Irvine and former MD Anderson faculty member, is one of the world's foremost experts on chronic lymphocytic leukemia (CLL). On Nov. 17, she presented a clinical history of CLL therapies, emphasizing that for certain patients, the field should not be too quick to cast aside standard-of-care chemotherapy in the wake of newer TKIs. The current standard is fludarabine-cyclophosphamide-rituximab (FCR), a combination of two chemotherapeutic agents (FC) and an anti-CD20 antibody (R). This regimen has proven overall response and complete remission rates, O'Brien said, but its myelosuppressive effects can be difficult to tolerate, and several subtypes of CLL are known not to respond well. Enter ibrutinib and idelalisib, targeted agents that block activity of Bruton's tyrosine kinase and PI3 kinase-delta, respectively, two kinases that are crucial to B cell receptor activation. Both agents significantly increase overall survival, rapidly reduce lymphadenopathy, and ibrutinib improves progression free survival in patients with FCR-refractory 17p deletion, all without myelosuppression. Despite side effects ranging from severe diarrhea to atrial fibrillation, the dramatic gains in overall and progression free survival achieved by these novel TKIs begs the question of doing away with FCR entirely. O'Brien argued that certain patients treated with FCR appear to be cured 10-14 years later, and that reserving FCR for this group is a promising idea. Such individuals may be identified on the basis of being negative for minimum residual disease and possessing a mutated IgVH gene. In the end, O'Brien said that B cell receptor inhibitors are "changing the landscape" of CLL therapy, but chemotherapy still has its place, especially for those who may become disease free thanks to FCR.

Getting personal: Drug development, screening and the microbiome

Realizing the true potential of personalized medicine

At the Sept. 22 Grand Rounds, **Giulio Draetta, MD, PhD,** professor of Genomic Medicine and director of the Institute for Applied Cancer Science (IACS), advocated on behalf of patients, who he said should be the sole motivators behind drug development efforts at MD Anderson. An extensive background in both academic and industry research environments has shown him the inefficiencies, miscommunications, and too-numerous transition points between these two arenas that hamper rapid approval of new drugs for cancer patients. He emphasized that we must only advance the most meritorious compounds—for example, those agents that have proven favorable pharmacokinetic and safety profiles, reach their known target in the body, and for which we can start to predict resistance mechanisms—and let go of the "let's just try it" mentality if evidence isn't strong enough to support moving forward. Draetta spoke highly of the progressive, game-changing platform and moon shot infrastructure that MD Anderson has put in place to accelerate availability of effective, optimized treatments. Some of these endeavors involve industry partnerships, which may be critical to get the ball rolling. However, Draetta said that we must always ensure that we remain in the driver's seat so that we can determine the fate of a project and prioritize what is best for our patients. He also gave a brief overview of several platforms, including IACS, a small molecule discovery group under Draetta's direction that has churned out IACS10759, an OXPHOS inhibitor that is turning out to be the poster child for the process of bottom-up, informed drug development. This compound was identified in a cell-based assay for hypoxia inhibitors, and subsequently its target, mechanism, suppressor mutations, safety profile, and pharmacokinetics were determined. Following promising pre-clinical studies, it will soon be advanced to the clinic for a phase I trial in acute myeloid leukemia. The best part about this compound and others to be developed through IACS, Draetta said, is that they belong to and are entirely controlled by MD Anderson, which will ultimately speed up the process of getting them to patients.

Cancer screening: The clash between science and intuition

National cancer screening campaigns have become increasingly common over the last century, but have these efforts reduced cancer-related deaths? Barnett Kramer, MD, MPH, director of the Division of Cancer Prevention at the National Cancer Institute, on Oct. 6 discussed the challenges and risks associated with mass screening programs and their impacts on the population. At its core, screening aims to identify indicators of cancer onset early enough to delay or prevent disease and extend life expectancy as a result. In reality, Kramer said, most screening protocols have costs that put large numbers of healthy individuals at risk and can wind up doing more harm than good on a population

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level. He presented data demonstrating that almost none of the currently available cancer screening tests have been shown to improve all-cause mortality, instead swallowing billions of healthcare dollars per year in false positives and unnecessary, sometimes invasive treatments resulting from overdiagnosis. In some cases, Kramer argued, this is the result of implementing protocols in which health outcome benefits do not outweigh harms, and numerous biases that trick researchers into believing a screening program has succeeded at achieving this benefit. Several vignettes were mentioned, including the occurrence of a dramatic spike in prostate cancer incidence in 1973, the same year that prostate specific antigen screening was introduced. Mortality rates, instead, did not change, suggesting that this spike resulted from overdiagnosis associated with the new screening method. One intervention that has proven to reduce mortality risk for lung cancer, Kramer emphasized, is use of low-dose CT scan instead of traditional chest x-ray to screen heavy and former smokers. Similarly, pap smears used to screen for cervical cancer have brought about a major reduction in deaths, likely because target tissue is easily accessible and can be directly analyzed by the pathologist. In the end, Kramer maintains that, currently, all cancer screening programs do some harm, and few do more good than harm at a reasonable cost.

Harnessing the microbiome to improve patient care

Samuel Shelburne, MD, PhD, associate professor of Infectious Diseases, visited DoCM Grand Rounds Nov. 3 to provide a broad overview of the exciting field of human microbiome studies and its complex interface with cancer. The most critical advance of the last 10 years in this field is the understanding that the vast collections of microbes that we carry in and on our bodies are not passive entities, but instead actively interact with and influence our health and disease states. Historically, the primary driving force behind microbiome studies has been the Human Microbiome Project, an international effort to understand as much as possible about how our microbial passengers impact health and disease. The first phase of the project was completed in 2012 and established solid data sets for what is a "normal" microbiome; important findings from this phase have shown that specific body sites are associated with specific sets of microbial organisms, and that while each person has a unique microbiome population, the organisms present at each site seem to be working toward the same ends in different patients based on which genes are expressed. MD Anderson hopes to contribute to the in-progress second phase, which will focus on the microbiome's relationship to numerous disease states, including cancer. With funding from the Moon Shot Knowledge Gap, Shelburne and others at MD Anderson are studying the microbiomes of patients with acute myelogenous leukemia as they undergo induction therapy prior to stem cell transplant. During this stage, patients frequently experience infectious complications and fever. Results so far suggest that patients who start out with lower diversity microbiomes and continue to lose diversity over the course of treatment are more likely to experience these complications. This data raises the possibility of using baseline microbiome measurements to risk stratify patients, so that physicians can intervene when leukemia patients exhibit particularly poor diversity. Shelburne's hope is that microbiome analysis will become as commonplace as complete blood counts, and that it will help us to optimize treatment outcomes, predict antimicrobial resistance, and resolve infections.

Epigenomics of melanoma progression

Kunal Rai, PhD, assistant professor of Genomic Medicine, studies the mechanisms by which the epigenome contributes to cancer progression, and how it changes as cells undergo malignant transformation. This set of heritable genomic marks includes chemical modifications to the DNA and histone proteins that affect chromatin stability and architecture. Histones are modified on flexible tail regions by a range of processes including methylation, acetylation, and ubiquitination, which occur in various combinations that dictate the transcriptional nature of neighboring DNA. Rai's research seeks to define the global histone modification changes that occur as a cell transitions from a benign nevus into a malignant phenotype, and eventually metastasizes. Making use of normal and malignant isogenic cell lines, he performed chromatin immunoprecipitation sequencing for 35 different epigenetic marks across the genome. This resulted in a genome-wide map in tumor and non-tumor cells lines illuminating where these specific marks are enriched and how chromatin state is affected. Globally, melanoma tumor cells appear to lose acetylation at promoter and enhancer regions, which affects downstream expression of genes involved in the cell cycle, DNA replication, regulation of apoptosis, and cell signaling. Lower levels of acetylation may tighten the grip of DNA around the nucleosome, promoting transition to a transcriptionally repressed heterochromatin state. Rai has also employed an in vivo RNAi screen to identify epigenetic regulators that play a role in malignant transformation. Pools of constructs designed to knock down 95 epigenetic enzymes were injected into mice to determine if suppression of any of these regulators accelerated tumorigenesis. Ultimately, six histone modifying enzymes were identified as hits in the screen. Knock-down of one of these genes, acetyltransferase Taf1, in non-tumor cells recapitulated acetylation changes observed in tumor cells and also made these cells more sensitive to treatment with a histone deacetylase (HDAC) inhibitor. Rai plans to follow up these studies by investigating the utility of Taf1 as a biomarker for response to HDAC inhibitors in melanoma. He will also address questions in the immunotherapy arena, seeking connections between chromatin state and epigenetic regulators in dictating response to immune checkpoint blockade agents.

DoCMessages

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

A peek into the Zayed Building

The Sept. 10 open house for our Sheikh Ahmed Bin Zayed Al Nahyan Center for Pancreatic Cancer Research showcased the new research building's bright and airy interior filled with colorful modern furnishings and spacious laboratory areas. Construction on the 12-story building began in November 2011, and about 60 people with the Ahmed Center took occupancy in February 2015. Pictured *(from left)* are **Bettina Marble, MPA,** the center's director of research planning and development; **Robert Wolff, MD,** deputy division head of Cancer Medicine, who was instrumental in securing the $150 million grant that funds the center; Anirban Maitra, MBBS, professor of Pathology, center scientific director; **Matonia Figgers,** the center's senior administrative assistant; and Jason Fleming, MD, professor of Surgical Oncology, center clinical director.

Upcoming Grand Rounds

January 5
Richard Schilsky, MD, FACP, FASCO
Chief Medical Officer, American Society of Clinical Oncology
Professor Emeritus, University of Chicago
"ASCO Initiatives in Personalized Medicine"

January 12
Wolfgang Wick, MD, Professor of Neurology/Neuro-Oncology
National Center for Tumor Diseases,
University of Heidelberg, Germany
"Understanding and Targeting Resistance in Glioblastoma"

January 26
Antoni Ribas, MD, PhD, Professor, Department of Medicine
Director, JCCC Tumor Immunology Program Area
UCLA Jonsson Comprehensive Cancer Center
"Treating Melanoma with the Immune System"

February 2
Richard Champlin, MD, Chair, Stem Cell Transplantation and Cellular Therapy
Michael Wang, MD, Professor, Lymphoma/Myeloma
"B Cell Lymphoma Moon Shot"

February 9
Ahmed Kaseb, MD, Associate Professor, GI Medical Oncology
"Personalized Hepatocellular Carcinoma Management: Recent Advances and Future Outlook"

February 16
Camilla Zimmermann, MD, PhD, FRCPC
Head, Palliative Care Program, University Health Network
Associate Professor, Department of Medicine,
University of Toronto
Rose Family Chair in Supportive Care, Faculty of Medicine,
University of Toronto

February 23
Debu Tripathy, MD, Chair, Breast Medical Oncology
"Breast and Ovarian Cancer Moon Shot"

DoCMessages is a publication of MD Anderson's Division of Cancer Medicine.

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