Stories of hope: Patients in remission
Distiller able to fill his glass with a lifetime of experiences

Tennessee distiller Philip Prichard and his wife, Susan, plan to launch a new business venture and create a lifetime of fun memories. They are excited to move on because Philip is now in remission from metastatic renal cell carcinoma that doctors originally predicted would kill him in a matter of months. That was in the summer of 2012.

The diagnosis
For 18 years, Prichard worked as a traveling representative for his family’s business. Then, one day four years ago, he returned home from a trip more tired than usual and everything changed. “I came off the road on a Friday and just crashed for the entire weekend. My wife Stacy Moulder, MD, associate professor of Breast Medical Oncology, did not set out to become an expert in metaplastic breast cancer, a rare and aggressive malignancy that tends to produce chemorefractory tumors composed of multiple cell types. But today she stands at the forefront of critical clinical and molecular efforts that have significantly expanded understanding of the mechanisms driving this disease, and she has identified treatment regimens that have given numerous patients their lives back.

“Metaplastic tumors were initially thought to develop from two individual tumors in the breast, which was thought to be why they are so uncommon,” Moulder said. “It turns out to be one tumor with the same molecular aberrations that makes different cell types. We think that may be because the cell takes on stem-cell like behavior or the abnormality happens in a stem cell so that different cell types can be made.” As a result of their distinct cell phenotype heterogeneity, metaplastic tumors can be identified using light microscopy by the presence of

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was already worried about me and told me, ‘You’re going to the doctor,’” he recalled. That Monday, a physician examined Prichard and found a hard spot below his rib on the right side. A CT scan determined it to be an 8-inch, 3 ½-pound tumor. “I didn’t even know it was there,” said Prichard, who also experienced symptoms including sudden high blood pressure, minute amounts of blood in his urine, intermittent pain in his pelvic area, and a large and painful varicose vein that ran down the side of his right leg. His wife mentioned one more thing — her husband had been losing weight. They both had been trying to accomplish that through a dietary cleanse, which called for drinking a lot of water, eating more fruits and vegetables, and taking nutritional supplements. During the process, Prichard commented that he was proud of his weight loss, except for the “love handle” on his right side, which was later revealed to be the tumor. During surgery to remove that growth, doctors discovered another tumor on Prichard’s adrenal gland. He subsequently was treated for four months with the tyrosine kinase inhibitor pazopanib (Votrient), which had successfully reduced spots found on his lungs, followed by a second operation in which surgeons were unable to remove the adrenal tumor.

“That’s when they told me there was nothing else they could do for me,” recalled Prichard. He and his wife then researched hospitals and came to MD Anderson in February 2013. “We had heard it was one of the best cancer centers in the country and, at that point, my options were running out,” said Prichard, who at the time was 48.

A miracle option

Upon arrival, Prichard met Nizar Tannir, MD, professor of Genitourinary Medical Oncology, and his clinical research team. They offered him a place in the open-label, randomized Phase III CheckMate 025 Study in which he received the immunotherapy drug nivolumab (Opdivo) at 3 mg/kg every two weeks for three years. Prichard had a 50/50 chance of being selected for that therapy. Nivolumab works in some patients by targeting and boosting the immune system to destroy cancer cells. Researchers believe the drug is more effective than certain targeted agents at shrinking tumors, plus it has reduced side effects. “We are pleased with the promise and potential of immune checkpoint inhibitors to cure renal cell cancer. Going on this trial was the only option to get nivolumab for him,” said Tannir.

Prichard had some fever, pain, night sweats, weight loss, and anemia before he received his first infusion, but he had no side effects from nivolumab. Eight weeks and four infusions later, his biggest tumor had shrunk by more than 30%, Tannir said. That was in the spring of 2013. Two years later, his tumors were virtually undetectable. “Every time we came back to the hospital, there was good news. It gave me a little glimmer of hope,” Prichard said. On May 24, 2016, he received his last treatment and was able to go off the trial. Tannir said that no further systemic therapy is planned, however, “We are considering resection of a residual abnormality seen on CT scans in the area of the previous right nephrectomy bed.”

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Pouring themselves into a new venture

“After coming through this and being in the position I’m in right now, I have hope for the future. Before my diagnosis, Susan and I had thought about opening up our own business. But when I got sick we didn’t know what the future would hold. Now we believe we have a future, so we’re busy building what we want,” said the man who was diagnosed days before his second wedding anniversary. “We’re in the early planning stages of starting our own whiskey bar and we want to feature at least 300 whiskeys from around the world. We’d like to find commercial space close to Beale Street in Memphis,” Prichard said. His message to other people confronting a cancer diagnosis: Stay positive, be strong, and find the best doctors you can. “Hopefully, you’ll come out on the other end much better than you were going in.”
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The right combination in the right patient

both an epithelial and non-epithelial component, the latter of which may be a sarcoma-like, squamous, or osteoid cell type. Additionally, these tumors are commonly triple negative for estrogen receptor, progesterone receptor, and HER2/neu, but are enriched in epithelial-to-mesenchymal transition (EMT) characteristics and, importantly, PI3K pathway activation and mutations.

While triple negative breast cancers (TNBC) on the whole have an incidence of PI3K mutation ranging from 10–15%, Moulder noted that PI3K pathway mutations in metaplastic tumors are overwhelmingly more common, with incidence approaching 70%. “Most of these mutations are in the gene coding for PI3 kinase itself, some are loss of PTEN which is the brake for the system, and some are other genes or proteins that can activate the PI3K pathway,” she clarified. This molecular propensity inspired investigation of chemotherapeutic combinations containing the targeted agent temsirolimus, which interferes with activity of mTOR, a kinase that functions downstream of PI3K and propagates its activation signals.

A chance encounter with patient Laurie Dragon, who had been diagnosed with high-grade, triple negative, metastatic, sarcomatous breast cancer, revealed just how powerful this targeted agent could be in the right patient. Metastasis of Dragon’s primary disease pushed her to come to MD Anderson for treatment, where Moulder found her an open spot on a Phase I trial combining temsirolimus with the cytotoxic agent liposomal doxorubicin and the anti-angiogenic bevacizumab (all together known as DAT; see Breast and Ovarian Cancer Moon Shot story on page 11). After eight cycles of DAT therapy, two without bevacizumab due to toxicity, Dragon attained a complete response, and six years later remains disease-free, taking only the daily maintenance oral mTOR inhibitor everolimus. Today, she treasures each day spent with her grandchildren or indulging in hobbies such as traveling, camping, sewing, working in the yard, and relaxing by the pool, often looking back on her time at MD Anderson with Moulder as the experience that saved her life. “Dr. Stacy Moulder and clinical studies coordinator Thorunn Helgason were there with me every step of the way,” she said. “I couldn’t have done it without them, and I currently stay in touch with both of them. If it were not for the brilliant doctors and nurses at MD Anderson, I would not be here today. One of my greatest blessings is being able to speak with other cancer patients and their families sharing my knowledge of this disease and being able to give them hope and encouragement.”

Interestingly, instead of PI3K mutation, molecular analysis revealed loss of function mutation in NF2, which codes for a negative regulator of mTOR Complex 1 (mTORC1) in Dragon’s tumor. This protein complex is composed of mTOR and several other factors, which together regulate downstream cellular processes including growth, nucleotide biosynthesis, and autophagy. Inactivation of NF2 allows continued activation of mTORC1, leading to aberrant cell growth and proliferation. Ultimately, Dragon’s response in the context of her NF2-mutated tumor emphasizes the importance of blocking the PI3K pathway activation via inhibiting mTOR activity in metaplastic breast tumors.

In terms of future directions, Moulder noted that the next goal is to extend the impact of this promising therapy combination to the broader category of mesenchymal breast cancers, of which metaplastic cancers account for approximately one-third of cases. Mesenchymal subtype breast cancers, which in turn make up about one-third of TNBC cases, share the higher rate of PI3K aberrations observed in metaplastic cancers, suggesting that this broader group may also be amenable to mTOR inhibitor-based treatment. “What I’d like to see is a randomized clinical trial looking at DAE (everolimus instead of temsirolimus) versus chemotherapy alone to make sure that the targeted therapy does add benefit,” Moulder noted. She emphasized the crucial science generated in the laboratory of Gordon Mills, MD, PhD, chair of Systems Biology, and the leadership and collaboration of Filip Janku, MD, PhD, assistant professor of Investigative Cancer Therapeutics, and Reva Basho, MD, a 2016 graduate of the Medical Hematology/Medical Oncology Fellowship Program (see page 4), in carrying out and the original Phase I trials that have made recoveries like Laurie Dragon’s possible.

‘If it were not for the brilliant doctors and nurses at MD Anderson, I would not be here today. One of my greatest blessings is being able to speak with other cancer patients … to give them hope and encouragement,’ says Laurie Dragon, pictured with husband, Derek.

Photo courtesy of Laurie Dragon
Graduating fellows urged to live up to MD Anderson’s legacy

“The some fellowship programs pay lip service and say they’ll support you whatever your career goals are, but tonight I must say that MD Anderson does it for real. I can’t thank Hematology/Oncology Fellowship Program leaders enough for the opportunities I’ve had in this part of my training,” said Aaron Schueneman, MD, upon accepting his certificate of completion at a graduation ceremony held June 17. He will be practicing medical oncology in Blue Ridge, Ga., working in the foothills of the Appalachian Mountains to help build an oncology program there. Schueneman also thanked his wife, Rose, for her support and told the audience that this next move will be their 10th in 13 years of marriage.

He was among 13 graduates who became part of MD Anderson’s 75-year legacy of excellence in patient care and research, said Robert Wolff, MD, program director and deputy division head for clinical and educational affairs, “And I know that you all will fully accept the responsibility to excel in your fields and become thought leaders.” He shared impressions of the fellows as he presented their certificates and welcomed them to the podium to make remarks. Muhamed Baljevic, MD, who will be going to the University of Nebraska Medical Center in Omaha, was first. “We are all composites of great ideas, parents, friends, and teachers. If I have achieved something, the credit goes to all who have stood behind me. These experiences have molded me as a man, father, and physician,” he said. Wolff commented that John French, MD, was already in celebratory mode prior to accepting his certificate as he and his wife welcomed their second baby a few days prior to his graduation. Known among his fellow fellows as a “Southern Gentleman Physician,” French will return to his home state to work at the Northwest Georgia Oncology Center in Marietta. The program director said that supported her study of the impact of obesity in metastatic melanoma patients treated with dabrafenib and trametinib. In addition, this year, McQuade earned American Association for Cancer Research’s 2016 Women in Cancer Research Scholar Award for her work on a Phase II clinical trial that combined the MAGE-A3 vaccine with high-dose IL2 in patients with advanced melanoma. The combination produced a response rate of 25%, and three patients had very durable complete responses ongoing at two to four years. The complete responses all occurred while the patients were on MAGE-A3 vaccine maintenance therapy alone. Fellow Amishi Shah, MD, thanked institution faculty who worked as attendings and supervised their continuity clinics at Lyndon B. Johnson General Hospital. “Our faculty taught us that taking care of the patients is the best we can do for them. Sounds simple, but it is very complex. I also want to thank our patients, who showed grace and made our jobs worth doing,” Shah commented.
Fellows honor those who contributed to their training

The graduation program also allowed fellows and program leaders to acknowledge the contributions of particular graduates, faculty, and administrators. The fellows thanked the program’s administrative team — Catherine Butler-Gunn, JD, associate director; Crystal Franzese and Kary Garnica, program coordinators; and Camillia Moses, senior administrative assistant — for supporting them through regulatory challenges and for creating a family atmosphere in the office. The fellows acknowledged Michael Kroll, MD, professor of Benign Hematology and associate program director, for always giving them his full attention and providing them with plenty of research sources to help them better understand the hematologic challenges that patients face; Katherine Pisters, MD, professor of Thoracic/Head and Neck Medical Oncology, for not only teaching them how to manage lung cancer patients but also for demonstrating how to talk to them as well. “I know you’re returning to your native Canada soon, and I want to tell you that they will be lucky to have you. I hope you’ll always have fond memories of working with us,” said Zahi Mitri, MD, who will be moving to Portland to work at the Oregon Health and Science University. The fellows recognized Alyssa Rieber, MD, associate program director, program director at LBJ, and assistant professor of General Oncology, for simultaneously allowing autonomy and guidance. “You have so many responsibilities at LBJ, yet you’re always willing to drop everything to consult with us,” said Mitri, who presented Rieber with a custom sole for a pair of running shoes because she participates annually in the 39.3-mile Avon Breast Cancer Walk. Others acknowledged were Waun Ki Hong, MD, professor of Thoracic/Head and Neck Medical Oncology, founder and chair of the Advanced Scholar Program Oversight Committee, and former division head, whom the fellows hoped they had made proud; Patrick Hwu, MD, division head and professor of Melanoma Medical Oncology, whom they presented with a crystal bowl to store the carb-free nut treats that he enjoys; and Wolff, whom the fellows gifted with a small production of an “aged beverage” for him to enjoy. In addition, Andrew Livingston, MD, graduating fellow who will remain at MD Anderson in Sarcoma Medical Oncology, referred to Wolff as the group’s “fearless leader” and recited a personalized poem as a tribute. “Oh, the Things that Dr. Wolff Can Do” made references to his overseas travel, ad interim department chair positions, and administrative work as a deputy division head.

Celebrating success

In the Fellowship Awards program held June 14, several trainees in the division’s Hematology/Medical Oncology program were celebrated at DoCM Grand Rounds for their performance in the past year, and faculty were honored for their influence in the training program. Pavlos Msaouel, MD, PhD, accepted the Clifton D. Howe Award that recognizes an outstanding first-year fellow for leadership, work ethic, and reliability. “I’m truly honored to receive this award. I wake up every day and look forward to coming to work. How can you not give your all when you have patients who need you and mentors like Dr. Nizar Tannir to support you?” he posed. Wolflf (center) congratulates McQuade (left) and Goswami.

The Waun Ki Hong Achievement in Clinical Investigation Award was presented to Drs. Melmet Bilen and Zahi Mitri. The Waun Ki Hong Achievement in Basic Science Research Award was presented to Drs. Sangeeta Goswami and Jennifer McQuade. The Honorary Fellow Award, bestowed upon a faculty member who did not train at MD Anderson but has made a great contribution in the clinical, laboratory, or in education, was presented to Katherine Pisters, MD, professor of Thoracic/Head and Neck Medical Oncology. In recognition of the fellow who demonstrated exceptional collegiality and a human touch in relation to patient and colleagues, the Humanitas Award was presented to Mitri.

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Futreal (right) was named Mentor of the Year.

The fellows presented several awards as well. Among them was the Mentor of the Year, which went to Andrew Futreal, PhD, ad interim chair of Genomic Medicine. “This comes as a complete surprise to me because I just enjoy discussing data and ideas with these enthusiastic people who are often thrown in the deep end of a project without much help from me sometimes,” he said. The Teacher of the Year Award was conferred upon two people — Nishin Bhadkamkar, MD, assistant professor of General Oncology, and Cristhiam Rojas Hernandez, MD, assistant professor of Benign Hematology. General Oncology was dubbed Teaching Department of the Year.

Faculty awards presented by program leadership include the Vicente Valero LBJ Clinician Educator of the Year Award, which went to Bhadkamkar. “I’m humbled to have an award in Dr. Valero’s name as I consider him the consummate clinical caregiver. I want to thank Dr. Rieber for maintaining an environment at LBJ in which we can all thrive. I’m motivated to be the best educator I can because of you fellows and because our patients depend on us,” he said. Scott Kopetz, MD, PhD, associate professor of Gastrointestinal Medical Oncology, accepted the Distinguished Alumnus Award. “This fellowship has been a great foundation for a productive career. Like I am doing now, you’ll continue to communicate with the people you’ve met here throughout your career,” Kopetz said. Rieber accepted the Leadership in Education Award, saying that her work at LBJ is her passion and joy. She and Bhadkamkar presented awards to outstanding and second- and third-year fellows. Tina Cascone, MD, PhD, second year, was described as a triple threat who is so talented that she could excel as a clinician, researcher, and educator. “I also owe thanks to my LBJ attendings who take their time to teach us how to care for patients,” she said. John French, MD, accepted the honor for third-year trainees. “It’s been an amazing journey — 14 years of undergraduate school, medical school, residency, and fellowship. I know for sure that I have become a better clinician because of working with my fellow fellows,” he commented.

Where Are They Going?

Several graduating fellows will continue their careers at MD Anderson:

- Sangeeta Goswami, MD, PhD
  Advanced Scholar in Genitourinary Medical Oncology
- Andrew Livingston, MD
  Assistant Professor of Sarcoma Medical Oncology and Pediatrics
- Jennifer McQuade, MD
  Advanced Scholar in Melanoma Medical Oncology
- Aron Rosenstock, MD
  Assistant Professor of General Oncology
- Amishi Shah, MD
  Assistant Professor of Genitourinary Medical Oncology

Three graduates are headed to Georgia:

- Mehmet Bilen, MD
  Emory School of Medicine in Atlanta
- John French, MD
  Northwest Georgia Oncology Center in Marietta
- Aaron Schueneman, MD
  Georgia Cancer Specialists in Blue Ridge

Joining other programs are:

- Muhamed Baijevic, MD
  University of Nebraska Medical Center in Omaha
- Reva Basho, MD
  Cedars-Sinai Medical Center in Los Angeles
- Zahi Mitri, MD
  Oregon Health and Science University in Portland
- Maryam Nemati Shafae, MD
  Baylor College of Medicine in Houston
- Rachel Sanford, MD
  Memorial Sloan-Kettering Cancer Center in New York

Fellows honor those who contributed to their training

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Fellows honor those who contributed to their training
T32 trainees pursue diverse avenues in translational oncology

By Erica Di Pierro

Hematology/Medical Oncology fellows entering their second year in the program are eligible to participate in the T32 training program, a specialized educational track that allows two years of research-intensive training for fellows who seek careers in academic medicine. The program allows fellows to work one-on-one with clinical and laboratory faculty mentors as they develop the skills needed to become independent investigators. Currently, there are five second-year fellows and two third-year fellows taking part in this unique and enriching educational opportunity.

Tina Cascone, MD, PhD, is a second-year fellow in the Hematology/Medical Oncology fellowship program who completed her medical training in Italy, doctoral and postdoctoral studies with John Heymach, MD, PhD, and an internal medicine residency at Barnes-Jewish Hospital. Her overall research interests center on improving immunotherapies for lung cancer and evaluating the activity of targeted therapies on solid tumors in a Phase I setting. Cascone’s primary project as part of her ASCO Young Investigator Award involves targeting nonsense-mediated mRNA decay to enhance the immunogenicity of non-small cell lung cancer and augment the efficacy of immunotherapy. She is also studying how tumor-intrinsic glycolytic activity leads to immune resistance in lung cancer. Cascone has also received the Clifton D. Howe Award for Clinical Excellence, first place in the Second Annual Immunology YIA Investigators forum, and an ASCO Conquer Cancer Foundation Merit Award. Her mentors include Heymach, Michael Davies, MD, PhD, and Patrick Hwu, MD.

After pursuing a Fulbright fellowship in Shanghai, China and completing her medical education and training at Baylor Medical School then the Hospital of the University of Pennsylvania, Jennifer McCuade, MD, is now a third-year fellow in the Hematology/Medical Oncology fellowship. Her primary research interests lie in the effect of obesity on the clinical outcomes and biology of melanoma. She earned an ASCO Young Investigator Award in 2015, which she is currently fulfilling with a project on the impact of energy balance and the insulin/IGF axis on resistance to targeted therapy in melanoma. Her mentors include Michael Davies, MD, PhD, Peiying Yang, PhD, Lorenzo Cohen, MD, Patrick Hwu, MD, and Wen-Jen Hwu, MD, PhD. Most recently, she was awarded AACR’s 2016 Women in Cancer Research Scholar Award and an ASCO Conquer Cancer Foundation Merit Award.

Brittany Ragon, MD, a second-year Hematology/Medical Oncology fellow, fulfilled her medical training at the University of South Carolina and Vanderbilt University for internship and residency. She is particularly drawn to studying MDS and leukemia, as well as identifying novel therapeutic strategies and making use of large data sets. Specifically, Ragon is involved in numerous research and clinical efforts including proteomic profiling of MDS to identify therapeutic targets, a Phase I/II study of an IDH1 inhibitor in IDH1-mutated hematologic malignancies, a trial studying immune reconstitution after lymphodepletion in CLL patients, and evaluations of graft versus host disease. Her mentors include Steven Kornblau, MD, Naval Daver, MD, Naveen Pemmaraju, MD, Courtney Dinardo, MD, Gautam Borthakur, MBBS, and Richard Champlin, MD.

Following medical school at UCLA and internship/residency at Northwestern University, Sangeetha Reddy, MD, began her Hematology/Medical Oncology fellowship here at MD Anderson, where she is currently a second-year fellow. Working with mentors Debu Tripathy, MD, Naoto Ueno, MD, PhD, Jennifer Wargo, MD, Elizabeth Mittendorf, MD, PhD, and Funda Meric-Bernstam, MD, Reddy’s work focuses heavily on improving immunotherapy for patients with high-risk breast cancers. In the clinic, she has written or played a major role in multiple Phase II trials to improve response in patients with triple negative and inflammatory breast cancers. Her translational efforts include immune profiling of patients with inflammatory and hormone receptor positive breast cancers. She was recently awarded an ASCO Young Investigator award.

Second-year Hematology/Medical Oncology fellow Matthew Reilley, MD, has keen interests in gastrointestinal oncology, immunotherapy, and clinical trial development. His medical studies at Brown Medical School and internship/residency at the Hospital of the University of Pennsylvania prepared him to dive into clinical trial development as a fellow at MD Anderson. Working with mentors David Hong, MD, Michael Overman, MD, and Michael Curran, PhD, Reilley is involved with trials studying the effects of ipilimumab and a TLR9 agonist in advanced malignancies, combination of ipilimumab and imatinib, and is currently writing a trial to combine anti-CTLA4 with OX40 in colon cancer patients. His laboratory research involves studying the combination of intratumoral delivery of a TLR9 agonist and checkpoint blockade in mice. He was recently awarded an ASCO Conquer Cancer Foundation Merit Award.

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Byers: First R01 to explore mechanisms of response, resistance to PARP inhibition in SCLC

Lauren Byers, MD, assistant professor of Thoracic/Head and Neck Medical Oncology, recently received a fundable score on her R01 grant proposal entitled “Therapeutic strategies for targeting PARP1 in small cell lung cancer” that seeks to characterize the mechanisms of sensitivity and resistance to poly-ADP ribose polymerase (PARP) inhibitors in small cell lung cancer (SCLC) and explore novel therapeutic combinations to expand treatment options for the most aggressive form of lung cancer. This work is particularly critical given the abysmal nine-month average survival, and rapid development of therapy resistance and metastasis associated with this malignancy, paired with the absence of meaningful therapeutic advances in the last three decades.

Byers and her team are the first to make significant steps forward in the SCLC field since the 1980s. They recently discovered that PARP1, a polymerase that initiates single-strand DNA break repair, is overexpressed in SCLC cell lines and patient tumors, and that PARP inhibitors exhibit activity in both preclinical models and patients. In this grant, Byers outlines a strategy under three aims to build on and maximize understanding of these findings to benefit patients downstream.

Previous work implicated several cellular events including loss of the kinase ATM, overexpression of the putative helicase SLFN11, and the cytotoxic phenomenon known as PARP-trapping in promoting sensitivity of SCLC to PARP inhibitors. PARP-trapping occurs when this polymerase locks onto DNA and prevents its repair, replication, or transcription, leading to cell death. Byers’ first aim specifies preclinical models and patient specimens to determine the contribution of these factors to PARP inhibition, and to assess their utility in predicting response based on specimens collected from two clinical trials testing PARP inhibitors in relapsed SCLC. The second aim will detail the precise role of PARP1 in the DNA damage response (DDR) and regulation of important oncologic processes that underlie the aggressive nature of SCLC while also exploring possible mechanisms of resistance to PARP inhibitors. To achieve this, PARP knockdown and overexpression will be studied in human- and murine-derived cell lines and in vivo mice with concomitant expression level analysis for pathways relevant to SCLC, including factors involved in EMT, stem-cell and neuroendocrine phenotypes, and ETS transcription family members. Additionally, cell lines and mouse models with acquired resistance to PARP inhibitors will be molecularly and omically profiled to understand the mechanisms promoting resistance. Previous work strongly implicates activation of compensatory DDR pathways and loss of PARP1 expression, which may be overcome using PARP/DDR inhibitor combinations. Finally, Byers’ proposal will delve into PARP/DDR inhibitor combinations and that PARP inhibitors exhibit activity in both preclinical models and patients. In this grant, Byers outlines a strategy under three aims to build on and maximize understanding of these findings to benefit patients downstream.

Second-year fellow Michael Wagner, MD, pursued his medical training at Harvard Medical School and Mount Sinai Hospital, joining the Hematology/Medical Oncology fellowship in 2014. He is primarily interested in sarcoma, with a project focusing on the role of the MAPK signaling pathway as a driver of angiosarcoma and a retrospective review of Ewing sarcoma treatment using vincristine, actinomycin, and ifosfamide (known as VAI). He is also working to develop angiosarcoma cell lines, a VEGFR inhibitor-resistant model, and patient-derived cell lines and xenograft models. Wagner aims to continue down the physician-scientist path, developing clinical trials and identifying drug combinations that can improve outcomes for sarcoma patients. His mentors are Anil Sood, MD, Vinod Ravi, MD, Alexander Lazar, MD, PhD, and Patrick Hwu, MD.
combinations, exploring their activity in a wide array of cell lines and mouse models for future clinical application. This aim will look specifically at the PARP inhibitors olaparib, talazoparib, and veliparib in combination with CHK1, WEE1, ATR, and ATM inhibitors. To clarify the genomic and proteomic mechanisms of effective combinations, a custom barcoded siRNA screening library will be created to target key checkpoint kinases and cell death regulators in SCLC including CHK1, ATM, SLFN11, WEE1, cMYC, and others. This library will be transduced as a pool into SCLC cell lines, and drug response signatures for the various knocked-down factors will be determined for single agent and combination PARP/DDR inhibitor treatment.

Byers’ team has already delivered crucial knowledge that has revived a field in desperate need of new clinical directions. Completion of the work in this study will bring into sharp focus the mechanisms underlying activity of and resistance to PARP inhibitors in SCLC while also helping to identify the patient subsets most likely to benefit from this therapy as a single agent and in synergistic combination with other agents.

**Konopleva: Targeting the microenvironment to eliminate leukemic stem cells**

Marina Konopleva, MD, PhD, professor of Leukemia, recently received total funding of $506,879 for her new R01 entitled “Therapeutic targeting of glutamine metabolism in MDS.” Current standard-of-care treatment with the DNA methyltransferase (DNMT) inhibitor 5-azacytidine fails to eliminate myelodysplastic syndrome (MDS) stem cells that lurk in the bone marrow microenvironment to reinitiate disease in the future. This fact creates a need for novel therapeutic strategies specifically targeting these leukemic stem cells to prevent recurrence of this disease and downstream malignancy, acute myeloid leukemia (AML).

The work proposed in grant aims to comprehensively describe the role of glutamine metabolism in MDS pathology and evaluate the therapeutic value of inhibiting glutaminase, the enzyme that performs the first step in glutamine breakdown. Konopleva and her team previously determined that glutaminase is overexpressed in AML patients with complex cytogenetics and those with high-risk MDS, and is associated with worse prognosis in MDS patients. Preliminary data also strongly suggest that the bone marrow microenvironment fosters metabolic reprogramming of leukemia cells toward increased dependence on glutamine metabolism. To move these findings to the next level, she has gained exclusive access to CB-839, a potent first-in-class glutaminase inhibitor with anti-proliferative activity in numerous MDS/leukemia cell lines and the ability to produce clinical response as a single agent in patients with advanced and/or treatment-refractory leukemias.

The first aim will detail the role of glutaminase in the growth and survival of MDS and AML cell lines and primary samples using either CB-839 or a knockdown shRNA construct to inhibit its activity. As part of this analysis, epigenetic profiling will be performed in conjunction with glutaminase inhibition to determine whether glutamine metabolism influences the methylation state of the genome via downstream production of oncometabolite 2-hydroxyglutarate. Additionally, a high-risk MDS mouse model and PDX mice will be used to ascertain the pre-clinical therapeutic potential of CB-839 alone and in combination with 5-azacytidine. The second aim will investigate the influence of the bone marrow stromal cell microenvironment on metabolic programming of MDS and AML cells toward increased dependence on glutaminolysis. This will involve metabolic profiling of both in vitro MDS/stromal cell co-culture experiments and MDS/stromal cells isolated from an in vivo MDS mouse model, with and without CB-839 treatment. Results from these experiments and from a novel in vivo extramedullary human bone/bone marrow model should reveal the mechanism of glutamine supply and uptake between stromal and MDS cells, respectively, as well as metabolic changes in TCA cycle intermediates and glutaminolysis as disease progresses from MDS to AML. The final aim will evaluate the tolerability and preliminary efficacy of CB-839 combined with 5-azacytidine in an investigator-initiated Phase I/II trial in patients with intermediate or high-risk MDS, with the hypothesis that this combination will prove more potent than 5-azacytidine alone. Marker analyses will evaluate glutaminase activity and downstream metabolite levels, and pre- and post-treatment MDS stem/progenitor cell mutational status, cytogenetics, expression of key regulators of glutamine metabolism, and methylomes; all markers will be correlated with therapy response. This trial will be the first study of a metabolic-targeting agent in combination with a DNMT inhibitor in cancer and has strong potential to translate to other tumor types.

**Shpall/Rezvani: Renewal continues efforts to optimize cord blood transplant engraftment**

Elizabeth Shpall, MD, (far left) and Katy Rezvani, MD, PhD, professors of Stem Cell Transplantation and Cellular Therapy (SCT/CT), were recently awarded total funding of $380,000 for renewal of their R01 “Hematopoietic Progenitor Cells-Cord Blood,”
Pathways to personalized therapy

Team identifies biomarker for proteasome inhibitor response in multiple myeloma patients

Work in the laboratory of Robert Orlowski, MD, PhD, ad interim chair of Lymphoma/Myeloma has recently culminated in an important article soon to be published in Cancer Cell that identifies a new potential biomarker for proteasome inhibitor (PI) response in patients with multiple myeloma.

While PIs like bortezomib and carfilzomib have been critical in advancing treatment outcomes for multiple myeloma, resistance to these agents has inevitably emerged and only a portion of patients treated have clinically meaningful responses. To address these issues, Orlowski and team resolved to identify biomarkers of response to inform optimal administration of PI-based therapy regimens in the clinic.

The gene encoding tight junction protein 1 (TJP1) was identified as a strong potential biomarker candidate based in part on its elevated expression in patients who responded to treatment with bortezomib across multiple completed clinical trials. In these trials, higher TJP1 expression was also associated with bortezomib across multiple completed clinical trials. In these trials, higher TJP1 expression was also associated with longer time-to-progression. Subsequent experiments using myeloma cell lines revealed that high TJP1 expression was associated with increased sensitivity of these cells to bortezomib and carfilzomib. Contrarily, knock-down of TJP1 expression preserved the viability of myeloma cells after exposure to both PIs, and it was consistently found to be down-regulated in bortezomib-resistant myeloma cells. When these phenotypes were investigated, TJP1 was shown to bind to and suppress signaling of the epidermal growth factor receptor (EGFR), ultimately leading to reduced downstream expression of LMP2 and LMP7, two catalytic subunits that contribute to proteasomal activity. The combination of these results emphasizes the crucial and selective role of TJP1 in modulating proteasome capacity and degradative activity; myeloma cells are significantly more sensitive to PIs and consequently more vulnerable to undergoing apoptosis when TJP1 is highly expressed, and more likely to exhibit resistance to PIs when TJP1 expression is decreased.

First author Xingding Zhang, PhD, noted that these findings are critical for multiple myeloma patients because they identify TJP1 as the first biomarker to distinguish patients who can reap the most benefit from PIs, which will help instruct therapy decisions in the clinic. Additionally, this research may shed new light on mechanisms of drug resistance to PIs, ultimately helping to refine available agents and even develop novel ones.

NIH Research Project Grants (R01s)

focusing on strategies to improve engraftment of cord blood (CB) transplants. Building on findings from their previous successful submission, Shpall and Rezvani have proposed a range of hypothesis-generating clinical trials and pre-clinical work with the goal of improving engraftment times in CB recipients to levels achieved with unrelated peripheral blood progenitor cell allografts. First, they will combine two techniques that have individually proven to decrease time to engraftment of neutrophils and platelets post-CB transplant: mesenchymal stromal cell-mediated CB cell expansion and CB cell fucosylation. An established trial will be modified to accommodate patient cohorts receiving this novel combination treatment as part of their transplant, accruing 25 patients. Following positive clinical results, mechanistic studies will help reveal the molecular underpinnings of improved hematopoietic recovery.

Another aim of the proposal will develop a method to ex vivo generate large numbers of specific CB megakaryocyte (MK) precursors, which have been implicated in shortening time to platelet recovery. This work will first identify phenotypic subsets of CB-MK cells supporting the most rapid platelet recovery in mice, then will optimize culture conditions to ensure maximal production of these subsets, and finally will evaluate the ex vivo expanded MK populations in CB transplant patients if pre-clinical results warrant such a trial.

In their third aim, Shpall and Rezvani will investigate the ability of systemic IL7 to improve immune reconstitution in CB transplant patients. Preliminary data from the blood of patients drawn at multiple time points post-transplant revealed that reconstitution of both CD4+ and CD8+ T cells was delayed up to one year, and that this delay was associated with both new viral infections and reactivations of prior infections. Cytokine IL7 enhances T cell survival and expansion in murine models of stem cell transplantation, and has been reported in other clinical trials to expand CD4+ and CD8+ T cell populations. A Phase I/II dose-escalation study is planned to determine maximum tolerated dose for IL7 administration and whether it enhances T cell recovery after CB transplant. Correlates of the trial will focus on identifying and characterizing the recovery of virus-specific T cells using immunophenotyping and high-throughput mass spectrometric analysis, and monitoring the impact of IL7 on T cell diversity via TCR sequencing.

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New approaches push toward personalized treatment in TNBC

Leaders: Debu Tripathy, MD, chair of Breast Medical Oncology; Gordon Mills, MD, PhD, chair of Systems Biology; Anil Sood, MD, professor of Gynecological Oncology and Reproductive Medicine; Mien-Chie Hung, PhD, chair of Molecular and Cellular Oncology

During Cancer Medicine Grand Rounds on Feb. 23, Debu Tripathy, MD, chair of Breast Medical Oncology (BMO), and Stacy Moulder, MD, associate professor of BMO, described the Breast and Ovarian Cancers Moon Shot efforts to molecularly describe disease over time, so real-time therapeutic decisions can be made based on a patient’s evolving tumor biology. Overall, the moon shot seeks to improve outcomes in breast and high grade serous ovarian cancers all along the cancer continuum from prevention to screening for inherited susceptibility to development of personalized therapies. Tripathy and Moulder focused on projects from Flagships 1 and 2 pertaining to triple negative breast cancer (TNBC), a highly proliferative and aggressive form of breast cancer characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression, leaving no approved options for targeted therapy. Currently, chemotherapy is the only known effective treatment for TNBC, and resistance is common. No biological therapies have yet to be approved, and while immunotherapy trials using anti-PD-L1 show some promise for generating durable responses, these efforts are still in infancy.

Recent findings have revealed that TNBC segregates into subtypes based on gene expression profiling, including mesenchymal and mesenchymal stem cell-like types that comprise 20–30% of all TNBC cases. Enriched for genes associated with the pro-metastatic epithelial-to-mesenchymal transition, angiogenesis, with frequent mutation of PIK3CA, and composed of a mixture of mesenchymal and epithelial components, tumors of this rare and challenging phenotype have come to be known as metaplastic breast cancer. Moulder spearheaded a recent Phase I trial conducted in conjunction with Investigational Cancer Therapeutics in which a combined chemotherapeutic/targeted therapy regimen employing liposomal doxorubicin, the angiogenesis inhibitor bevacizumab, and the mTOR inhibitor temsirolimus (all together known as DAT) was administered to patients with both metaplastic and non-metaplastic TNBC. Patients in the latter group achieved significantly better clinical outcomes with some durable responses exceeding five years; within the metaplastic group, those with PI3K aberrations showed higher response than those without.

Breast cancer is frequently treated with neoadjuvant chemotherapy such as DAT to minimize tumor burden prior to surgical resection. In TNBC, markers for identifying patients who maintain residual disease after neoadjuvant chemotherapy are still lacking. These patients have an 80% risk for developing metastatic disease within two years and could benefit significantly from tailored targeted agents. However, patients diagnosed with TNBC often do not want to participate in clinical trials because of a several week delay in treatment while waiting to determine if their tumor is chemosensitive. To address this concern, Moulder and colleagues designed a trial on which patients immediately begin four cycles of standard-of-care doxorubicin/cyclophosphamide neoadjuvant chemotherapy while their pretreatment biopsy and blood are molecularly analyzed. Based on the results, patients are assigned to either continue standard-of-care therapy if their tumor is chemosensitive or to move onto targeted therapy based on their molecular profile if their disease is resistant. Tissue samples collected pre-, mid-, and posttreatment are used to establish PDX mouse models to provide critical insights into how disease evolves over time at a cellular level, help identify drivers of chemoresistance, and potentially reveal new actionable biomarkers. The second phase of this project involves independent, non-randomized Phase II trials of various targeted agents including PDL1-, EGFR-, PARP-, and mTOR-inhibitors combined with chemotherapy, with the goal of improving pathologic complete response in chemoresistant patients from 5–20% using targeted therapy. The trials are designed to facilitate rapid “go/no-go” decisions. Agents showing promise will be considered for testing in larger randomized trials. Currently, two trials are open, one involving DAT and the other employing PDL1 blockade and chemotherapy. Drivers of chemoresistance identified through the PDX studies may reveal known druggable targets, providing direction for the next round of Phase II trials. The goal is to enroll 100–120 patients per year for the next three years.

Researchers aim to overcome multiple obstacles in pancreatic cancer

Leaders: Robert Wolff, MD, professor of Gastrointestinal Medical Oncology and deputy division head for clinical and educational affairs; Jason Fleming, MD, professor of Surgical Oncology; Anirban Maitra, MBBS, professor of Pathology

Pancreatic cancer remains one of the most challenging malignancies to manage in all aspects of disease, from detection to treatment. On Dec. 1, 2015, members of the Pancreatic Cancer Moon Shot provided a glimpse of the breadth of basic and clinical research ongoing in the program to address these dire needs in the field. Robert Wolff, MD, professor of Gastrointestinal Medical Oncology (GIMO), deputy division head for clinical and educational affairs and co-leader of the moon shot, explained the major obstacles to effective management of pancreatic cancer: lack of detection strategies for those at risk...
Researchers aim to overcome multiple obstacles in pancreatic cancer

and with early-stage disease, inadequate systemic cytotoxic therapy, and minimally impactful molecular therapies. This collective of researchers spanning disciplines from across the institution hopes to change the course of this lethal disease, predicted to be the second leading cause of cancer death in the United States by 2030.

Gauri Varadhachary, MBBS, MD, professor of GIMO and executive medical director of the Gastrointestinal Cancer Center, provided an overview of the pancreatic pre-operative program and its intersection with several ongoing trials. The pre-operative program aims to deliver therapy to all patients with potentially resectable disease and also incorporates leverage of tissues from this patient population to address questions of clinical mechanism. For example, Phase 0 studies have revealed critical information about tumor heterogeneity and have shown that intraoperative gemcitabine can be successfully delivered to the tumor in some patients, despite previous findings to the contrary. Additionally, this program is also diving into immunology; Jennifer Goldstein, MD, instructor of GIMO, and Daniel Halperin, MD, assistant professor of GIMO, have shown that while pancreatic tumors have minimal immune infiltrate compared with melanoma, patients with higher concentrations of CD4 and CD8 cells show better survival. Varadhachary is involved with a trial in resectable patients combining pembrolizumab (anti-PD1) with chemo-radiation therapy exploring impacts on immune biomarkers and tumor-infiltrating lymphocyte (TIL) concentration. Several other small window trials are in the works to produce mechanistic data that will shed light on drug delivery. Varadhachary also spoke about the DNA damage repair deficiency phenotype and using family history of BRCA-associated cancers in pancreatic patients who are themselves BRCA negative to determine likelihood of response to platinum agents, as well as a trial showing promising results for combining ACP196, a “better ibrutinib,” with pembrolizumab.

Anirban Maitra, MBBS, professor of Pathology and co-leader of the moon shot, discussed how genetic material contained in exosomes, which are shed abundantly from pancreatic tumors proportionately with disease stage, can help track therapy response, predict disease recurrence, and reveal expressed neoantigens. Obtainable from any body fluid, these exosomes contain high-quality RNA and double-stranded DNA perfectly suited for serial omics analyses, which accurately reflect the changing omics of the tumor over time without having to sample tissue. Importantly, these studies can identify neoantigens expressed by the tumor that can then be used to design directed T cell therapy. Additionally, real-time detection of the mutant KRAS allelic fraction contained within pancreatic exosomes can predict disease recurrence before the common pancreatic biochemical marker CA19-9 increases in expression. Maitra stressed that the liquid biopsy platform allows for acquisition of the same information provided by a tissue biopsy but circumvents the need for direct tumor sampling.

Working on the early detection front, Florencia McAllister, MD, assistant professor of Clinical Cancer Prevention, is trying to develop imaging and biomarker techniques to detect pre-neoplastic pancreatic lesions, known as PaNINs. Late-stage PaNINs often progress to pancreatic ductal adenocarcinoma and therefore are an optimal surrogate marker for early detection. McAllister is working on developing an imaging/biomarker-based method to detect PaNINs and differentiate them from chronic pancreatitis. She is also contributing to development of a clinic for assessing pancreatic cancer risk and screening/early detection for those at high risk. Assessment will consider factors including family history, presence of susceptibility genes like BRCA2 and Stk11/Lkb1, and environmental influences including smoking, alcohol use, and elevated BMI. High-risk individuals will be involved in studies for validating biomarkers and testing novel molecular imaging methods to detect PaNINs, and will continue with annual followups.

Finally, Greg Lizee, PhD, associate professor of Melanoma Medical Oncology, is hoping to improve therapy options by generating CD8 T cells that will recognize and attack overexpressed pancreatic tumor-specific antigens. Specifically, he is working in conjunction with Cassian Yee, MD, professor of Melanoma Medical Oncology, to develop a personalized immunotherapy pipeline in which highly expressed mutated peptides eluted from a patient’s resected pancreatic tumor are identified by mass spectrometry and T cells are generated in the lab or in vivo via administration of a peptide vaccine to react against the tumor. Optimal target peptide candidates are selected based on their predicted binding to the patient’s own HLA molecules as determined by an algorithm for this purpose. Tumor antigen-specific T cells are usually present in the peripheral blood at extremely low frequency but can be identified, enriched, and expanded outside of the patient and given back within approximately one month. Currently, Lizee’s and Yee’s groups are participating in both the Pancreatic and Colorectal Moon Shots, with 10 patients in each program. Lizee described the process from peptide identification through to adoptive T cell transfer for a pancreatic cancer patient expressing a novel antigen from gene vestigial-like 1 (VGLL1), which is possibly a marker of dividing cells. Additionally, the FDA has recently approved a personalized peptide vaccine protocol led by Michael Overman, MD, associate professor of GIMO, for treatment of pancreatic and colon cancer patients with up to 10 personalized mutated or non-mutated peptides. Pancreatic cancer poses a daunting challenge to researchers, but this team of investigators is committed to attacking it from every possible angle.

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Prostate flagships explore signaling, immunotherapy, and the epigenome

Leaders: Christopher Logothetis, MD, chair of Genitourinary Medical Oncology; Timothy Thompson, PhD, professor of Genitourinary Medical Oncology; Filippo Giancotti, MD, PhD, professor ad interim, Cancer Biology

In 2016, upward of 180,000 new cases of prostate cancer will be diagnosed in the United States, leading to more than 26,000 deaths. As with numerous other cancer types, it remains a primary objective of the field to distinguish patients with low-risk disease who may never need treatment from those with aggressive, rapidly progressing disease that requires immediate intervention. For those with castration-resistant prostate cancer, which fails to respond to androgen ablation, prognostic and predictive biomarkers to match patients to the best available therapies and new targeted agents and combination approaches are needed.

The Prostate Cancer Moon Shot is comprised of faculty from across the institution working to develop novel, multi-disciplinary approaches. Speaking at Institutional Grand Rounds on April 29, Christopher Logothetis, MD, chair of Genitourinary Medical Oncology (GUMO), shared progress from flagship 1, which focuses androgen receptor signaling. A trial was designed to determine whether differences between early and late prostate cancer can be exploited for therapeutic benefit, on which patients were randomized to receive either one or two androgen-depleting agents before having their prostate removed for analysis. Results showed that more complete androgen depletion with two agents versus one led to significantly greater reduction in tumor volume and density. Importantly, fuller androgen ablation at early stages did not lead to activation of pathways associated with more aggressive disease, suggesting that this treatment modality could effectively prevent development of more serious disease. The only exception to this finding was increased expression of the glucocorticoid receptor, which was found to be an important early driver of tumor cell survival and androgen-depletion resistance. Logothetis also spoke about several trials that proved persistent androgen signaling is associated with progression in castration-resistant prostate cancer, and these patients can benefit from therapy with androgen biosynthesis inhibitors and depletion of androgen receptor. These findings overturned a long-held belief in the field and encouraged an immediate study to combine these treatment modalities.

Representing flagship 2, Sumit Subudhi, MD, PhD, assistant professor of GUMO, focused on efforts to optimize response to immunotherapy, including a trial that identifies tumor neoantigens from resected prostate cancer samples, administers four doses of ipilimumab (anti-CTLA4), and analyzes T cell responses along the way. So far, mutational load seems to correlate with efficacy to ipilimumab but specific neoantigens are still in the process of being identified. Additionally, a pre-surgical trial on which patients with localized prostate cancer received androgen depletion therapy followed by two doses of ipilimumab and radical prostatectomy revealed viable tumor tissue despite the presence of activated, licensed-to-kill CD8 T cells in the tumor microenvironment. Gene expression analyses revealed that immuno-suppressive PD1 and VISTA were upregulated on post-treatment tumor and immune cells; to address this, the flagship will run a trial concurrently targeting CTLA4 and PD1/PDL1 pathways. Finally, Subudhi discussed creation of a mouse model that recapitulates the relative lack of T cells found inside prostate tumors that have metastasized to the bone, and the ultimate goal is to use this model in co-clinical immunotherapy trials.

Kunal Rai, PhD, assistant professor of Genomic Medicine, spoke about his project in flagship 3 to understand the epigenomic changes that associate with treatment resistance in prostate cancer. Techniques in his lab allow for generation of maps that reveal the locations of various epigenetic marks across the tumor cell genome. A recent analysis compared epigenetic marks between untreated, resected versus aggressive, resistant prostate cancer samples. Results showed that the former group had activating epigenetic marks at loci for immune pathway-related factors including interferon-gamma and IL6, while the latter had activation marks at the androgen receptor and other related networks. In fact, androgen receptor expression in resistant samples appeared to be affected by a super-enhancer boost in expression. Rai noted that numerous co-occurring activating and repressive epigenetic marks often determine the regulatory state of a particular gene. A transition from silenced heterochromatin to a poised promoter/enhancer state on developmental genes including HOX, SOX, and ZNF genes appeared to accompany the transition from untreated to therapy resistant tumors.

Kurie awarded $5.9 million CPRIT grant

Congratulations to Jonathan Kurie, MD, professor of Thoracic/Head and Neck Medical Oncology for his recent Multi-Investigator Research Award (MIRA) from the Cancer Prevention & Research Institute of Texas CPRIT in the amount of $5,981,040 for research titled “Defining and Defeating Mechanistic Subtypes of KRAS-Mutant Lung Cancers.” Ignacio Wistuba, chair of Translational Molecular Pathology, also was awarded a $4,606,275 MIRA to study “Pathogenesis and Early Progression of Lung Cancer.” Both grants originate from MD Anderson’s Lung Cancer Moon Shot. The awards, announced in May with several others, bring CPRIT just over the halfway point for its funding authority. To date, the institute has awarded 1,033 grants totaling more than $1.57 billion. The agency was launched in 2009 after Texas voters approved a 2007 bond issue committing $3 billion to the fight to end cancer.
Eduardo Bruera, MD, chair of Palliative Rehabilitation and Integrative Medicine (PRIM), has been standing at the front of his department’s Patient Home Visits (PHV), formerly called Texas Bus Rounds, for 15 years. On average, the two-day workshops for physicians, medical residents, nurses, social workers, and chaplains is conducted nine times annually. They offer didactic sessions on best practice approaches for the most common issues addressed in hospice care and an opportunity for “rounds,” in which the group travels on a bus to inpatient facilities and private homes of all socioeconomic levels to see real-life examples of that care is delivered to patients facing end of life when curative or life-prolonging therapy is no longer indicated, and the focus turns to comfort rather than cure.

Bruera runs the largest supportive care and palliative oncology program in the United States, and is internationally renowned for developing the Edmonton Symptom Assessment System (ESAS), which uses a zero to 10 symptom-assessment scale for common symptoms that patients experience. Additionally, the 2015 John Mendelsohn Lifetime Achievement Award winner also is known for groundbreaking research that changed clinical practice to include use of methadone and opioid rotation for pain control, neuroleptics for delirium, among other aids for patients.

On Feb. 27, Bruera provided real-time instruction to 20 participants who traveled to Houston from all parts of the U.S., Canada, Spain, Colombia, Japan, and Germany to learn as much as they could about how bus rounds works in order to help their colleagues establish similar programs in their own communities. The PRIM team had contacted a local hospice nurse who pre-selected patients for the rounds and gained their permission to release their health information and to photograph them. Prior to departure, passengers received headsets equipped with microphones and Bruera advised participants to include this technology in their future programs because the mid-range devices allow everyone to hear clearly on the bus and during patient encounters — especially when it’s not possible to fit everyone into the room with a patient or the patient’s voice is faint. The microphone attached to the nurse will help everyone hear well. Bruera advised everyone onboard to give brief professional biographies of themselves so everyone could appreciate the unique perspective of their peers.

Themes addressed in home visits
- Pain
- Care for cognitive impairment and delirium
- Psychosocial distress: depression, anxiety
- Constipation, nausea, vomiting
- Spirituality
- Communication

Bruera provided some moments of levity on the bus when coaching the group about paying attention to even the smallest of details when it comes to planning rounds. The first he said was that the facilitator should keep the stops in close proximity to each other and arrange them in such a way that a hospice care facility is somewhere in the middle in order to give passengers an opportunity to use public restrooms, rather than inappropriately asking a patient or client’s family to use their private bathrooms. Also, Bruera gave an example of how important it is to try to provide the best possible transportation for the group. He recalled when he worked in Canada and had acquired a yellow school bus to take a group of doctors on rounds. He thought it was a reasonable accommodation, but his passengers did not, and they told him that although the PHVs were informative, that no one else would travel with him again unless he replaced the brightly colored, non-air conditioned bus with something that did not remind them of their days as schoolchildren! Lesson learned.
Two faculty earn high honors from ASCO

ASCOS-ACS Lecture and Award

Ethan Dmitrovsky, MD, provost and executive vice president at MD Anderson and professor of Thoracic/Head & Neck Medical Oncology, accepted one of the American Society of Clinical Oncology’s (ASCO’s) highest distinctions on June 6. He was presented the ASCO-American Cancer Society (ACS) Lecture and Award for his efforts in cancer prevention and control. “I am humbled and honored to receive this recognition,” said Dmitrovsky. “It is a privilege to serve the oncology community and our patients, whether as an oncologist, physician-researcher, or mentor or leader.”

Dmitrovsky’s examination of the mechanisms of the tumor-suppressing effects of natural and synthetic derivatives of vitamin A, known as retinoids, is groundbreaking. He and his team helped to establish use of all-trans-retinoic acid (ATRA) differentiation therapy for acute promyelocytic leukemia (APL), turning a highly fatal disease into a highly curable one. A vital component in combination treatment, ATRA leads to complete remission and a five-year survival rate in over 90% of patients. Further, Dmitrovsky’s team developed and patented a genetic test that is often used to diagnose APL and monitor treatment. His group also found a novel protein destruction mechanism that causes degradation of the dominant—negative translocation product found in this leukemia, PML/RARa. A mechanism responsible for diverse retinoid clinical effects was found to occur through a pathway that caused G1 cell cycle arrest, permitting a differentiation program to ignite or genomic damage to be repaired, depending on the cell context. This mechanism activated proteasomal degradation of G1 cyclins and caused cell cycle arrest. Dmitrovsky now focuses on lung cancer, building on his work with APL. His team engineered transgenic mice that target expression in the lung of wild-type or degradation-resistant cyclin E proteins. These mice recapitulate frequent features of human lung carcinogenesis, especially when degradation-resistant cyclin E species were present. Transplantable transgenic lung cancer models were developed from these mice — which are very useful in studying lung cancer biology to identify new means to combat the disease by treating or preventing this most common cause of cancer death for both men and women. The team completed proof of principle clinical trials and discovered that the same degradation pathways identified in the laboratory were activated in cancers of patients.

Dmitrovsky earned his undergraduate degree at Harvard University and medical degree from Cornell University Medical College. He trained in internal medicine at New York Hospital-Memorial Sloan Kettering Cancer Center and in oncology at the National Cancer Institute (NCI). Dmitrovsky spent more than a decade on Memorial Sloan Kettering’s faculty before moving to Dartmouth Medical School in 1998 as department chair of Pharmacology and Toxicology, a role he held for 12 years. He also was ad interim dean for Dartmouth Medical School. Dmitrovsky was senior advisor for science and technology to Dartmouth’s president. He is an American Cancer Society Professor, a member of the American Society for Clinical Investigation (ASCI) and the Association of American Physicians (AAP), and a fellow of the American Association for the Advancement of Science (AAAS). He chaired the NCI Board of Scientific Counselors for Clinical Sciences and Epidemiology and now chairs the NCI PREVENT Cancer external steering panel. Dmitrovsky testified before the President’s Cancer Panel about overcoming barriers to translational research and served on many scientific advisory and editorial boards.

ASCO Special Recognition Award

Waun Ki Hong, MD, professor of Thoracic/Head & Neck Medical Oncology and former head of Cancer Medicine, accepted one of ASCO’s highest distinctions at the President’s Dinner on June 3. The Special Recognition Award honors the major impact his work has had on the field and his longstanding commitment to the organization.

Accomplishments include Hong’s groundbreaking Veteran’s Administration Cooperative induction chemotherapy and radiotherapy trial for laryngeal preservation, which showed that patients could fare just as well with chemotherapy and radiation as those who underwent surgery that ultimately resulted in them losing their voice box and ability to speak. This work changed the way some diseases are managed and serves as a model for continued on page 16
Cohen elected vice chair of Integrative Medicine Consortium

Lorenzo Cohen, PhD, professor of Integrative Medicine, was elected vice-chair for the Academic Consortium for Integrative Medicine & Health. The mission of the consortium is to advance integrative medicine and health through academic institutions and health systems. Consortium membership includes over 60 academic medical centers and affiliate institutions, and represents thousands of scientists, educators, clinicians, and other health professionals. The consortium defines this evolving field in this way: “Integrative medicine and health reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic and lifestyle approaches, healthcare professionals, and disciplines to achieve optimal health and healing.” The group works to advance principles and practices of integrative healthcare within academic institutions by supporting and mentoring academic leaders, faculty and students, and by disseminating research and informing healthcare policy. Cohen, who is also a founding member and past president of the International Society for Integrative Oncology, co-authored with a consortium colleague a 2014 monograph for the Journal of the National Cancer Institute entitled “Advancing the Science of Integrative Oncology to Inform Patient-Centered Care for Cancer Survivors.” Cohen directs the Integrative Medicine Program within the Department of Palliative, Rehabilitation, and Integrative Medicine and conducts NIH-funded research of complementary practices and lifestyle changes aimed at reducing cancer treatment side effects and improving clinical outcomes.

ASCO Special Recognition Award

organ conservation in other cancers, including anal and breast. His studies were among the first to prove that cancer can be prevented or delayed in human beings. He led research that demonstrated that high-dose retinoic acid could reverse oral premalignant lesions and prevent the development of second primary tumors. Additionally, Hong was the architect for the first Biomarker-Based Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial that used molecularly targeted approaches to reduce morbidity and mortality in patients with lung, head and neck cancers. His most recent project, Profiling of Resistance Patterns and Oncogenic Signaling Pathways in Evaluation of Cancers of the Thorax and Therapeutic Target Identification (PROSPECT) has identified molecular targets and pathways in cell lines that predict drug sensitivity and resistance.

He has mentored hundreds of clinical and research oncologists, authored over 650 scientific publications, edited 11 books, served on editorial boards of 19 scientific journals, and participated on the National Cancer Advisory Board, as appointed by President George W. Bush. Hong, who recently was elected to the National Academy of Medicine, served as president of the American Association for Cancer Research (AACR), and accepted prestigious honors from the organization, including the Joseph A. Burchenal and Rosenthal memorial awards. Additionally, Hong served on ASCO’s board of directors and accepted some of the group’s most illustrious accolades, including the David Karnofsky Award and the ASCO-American Cancer Society Award. He is honored to receive ASCO’s Special Recognition Award for his research. “I thank the wonderful colleagues and trainees who have been part of our MD Anderson team. It is vital that we always work collaboratively to advance our knowledge, and never lose sight of our patients who rely on us,” he said.

A native of South Korea, Hong earned his medical degree from the Yonsei University of Medicine in Seoul, Korea. He served as Chief of Medical Oncology at the Boston VA Medical Center and was a faculty member at both the Boston University School of Medicine and the Tufts University School of Medicine before joining MD Anderson in 1984. At that time, he started out as chief of the Section of Head and Neck Medical Oncology, became the chair of Thoracic/Head & Neck Medical Oncology in 1993, and took on the responsibilities of head of MD Anderson’s largest clinical division, Cancer Medicine, in 2001. Hong retired in 2014 but continues to serve as a special advisor to the Cancer Medicine Advanced Scholar and Hematology/Medical Oncology Fellowship programs.
Accolades

Advocacy for women in science earns Grimm President’s Leadership Award

The Division of Cancer Medicine is proud to congratulate Elizabeth Grimm, PhD, deputy division head for research affairs, Waun Ki Hong Distinguished Chair in Translational Oncology, and professor of Melanoma Medical Oncology, as the 2016 recipient of this President’s Leadership Award for Advancing Women Faculty. This prestigious award was established by President Ron DePinho in 2013 to recognize MD Anderson faculty who have contributed to the career advancement of women faculty at the institution. Recipients of this award have demonstrated a consistent commitment to removing roadblocks and advocating for women faculty, allowing them to rise in the leadership ranks and foster an environment of inclusivity and diversity at MD Anderson.

In a heartfelt introduction at the award reception, DePinho lauded Grimm’s range of skills and accomplishments, stating that her “breadth, depth, execution capability, and scientific prowess,” have made her indispensable in the success of many institution-wide efforts, including the moon shots program and SPORE initiatives. He emphasized her steadfast commitment to helping other women advance from early on in her own career, serving as a mentor to many trainees and junior faculty, and founding the DoCM Women Faculty and Fellows Advisory Council. In 2014, she received the Provost’s Distinguished Faculty Mentor Award.

Grimm began her career at MD Anderson in 1986, focusing her research on improving mechanisms of immunotherapy, then in its infancy. She quickly became involved in numerous efforts to expand research and training opportunities, initiating and leading the institutional T32 training grant in Cancer Biology and earning the first SPORE for Melanoma Medical Oncology in 2004, which she continues to lead. When the Moon Shots Program was launched, Grimm served as the inaugural chief scientific officer.

Grimm expressed gratitude to DePinho for initiating the award and for his fervent support for women faculty. She also thanked Patrick Hwu, MD, head of Cancer Medicine and one of her nominators, acknowledging their “seamless ability to work together” based on many shared professional experiences. Further, she praised the institution as a melting pot of individuals that help make MD Anderson one of the best cancer care facilities in the world. “Women have arrived here from different cultures and with different views on how to work together. We can gain a lot from this,” she said. Grimm noted that earlier in her career, one’s scientific success was defined by individual achievement and fierce competition for grants and papers. While still common, she emphasized that this mentality is no longer conducive to approaching the intricate questions of science and medicine today. “I remain hopeful that we will continue to see advances in the inclusiveness of women and people of all cultures into teams, and that these teams are successful in solving the many complex problems of translating new knowledge about cancer for the benefit of our patients,” she concluded.

Clara D. Bloomfield, MD, professor of cancer research at The Ohio State University, was honored in the same ceremony with the prestigious 2016 Margaret L. Kripke Legend award for promotion of women in cancer medicine and cancer science. Bloomfield is an internationally renowned clinician and researcher whose work has helped shape standard-of-care treatments for leukemia and lymphoma, and who has devoted herself to the advancement and recognition of women faculty.

Cortes selected for inaugural Provost Protégé Program

Grooming executive leadership talent from within and enhancing the diversity of our faculty leaders are the chief goals of MD Anderson’s Provost Protégé Program, a partnership between the new office of Women and Minority Faculty Inclusion and the office of Ethan Dmitrovsky, MD, provost and executive vice president. Jorge Cortes, MD, professor of Leukemia and deputy division head for Global Oncology, is one of four faculty members selected for the program, which begins this summer. Participants will have six months at a time to shadow Dmitrovsky and Elizabeth Travis, PhD, associate vice president of Women and Minority Faculty Inclusion, as well as their division heads and Faculty Senate leaders, to gain exposure to the highest levels of academic leadership. Protégés will spend 20% of their time in the program and will identify and complete a project within 12 to 18 months. Candidates were identified by division heads after completing MD Anderson’s Faculty Leadership Academy or another development program, and selected by Dmitrovsky, who is also a professor in Thoracic/Head and Neck Medical Oncology.

During a May 17 panel to introduce the program, Cortes attributed much of his success to goals his father set for him and his seven siblings. “My father grew up on a ranch in Mexico in a house that had a dirt floor. As he got older, my grandfather told him that if he wanted to continue his studies, he could — but that he’d first have to work to help feed the family,” Cortes remembered. “Later, when my dad started his own family, he told us, ‘You’re going to learn English and you’re going to go to school.’ And because of that vision, I am here.”
Beyond the transcriptome
Drivers of tumor plasticity and metastasis

Visiting from the University of British Columbia, Poul Sorensen, MD, PhD, spoke on May 3 about the role of several factors involved in the process of translational selectivity and cell plasticity in helping sarcoma cells handle the stresses associated with metastasis. First, the pathology professor and researcher of childhood cancer detailed work on protein YB1, which has a demonstrated role in promoting metastasis of Ewing’s sarcoma cells. He and his group found that YB1 influences the translation of numerous mRNA messages, ultimately affecting cell state and plasticity. For instance, YB1 binds to the 5’ untranslated region of HIF1α mRNA, allowing translation machinery better access to the message and thus increasing its translation. Sorensen also determined a compelling role for YB1 in formation of stress granules, protein, and RNA aggregates that form in cells undergoing stress. Stress granules appear to be required for sarcoma cell invasion and metastasis through a mechanism that relies on local translational activation of factor G3BP1 by YB1 within granules. The group has since determined that HDAC inhibitors potently inhibit stress granule formation, possibly via increasing the acetylation state of YB1. Sorensen and team hypothesize that YB1-mediated stress granule formation may allow cells to reduce and tolerate the various stresses associated with metastasis, including oxidative stress. The precise role of HIF1α in this process remains to be determined. Taken together, his work has implicated YB1 as a general cell plasticity factor that triages mRNA messages into or out of stress granules, thereby limiting or enhancing their translation, respectively. This allows the cell to respond to queues from its microenvironment, including tolerating higher levels of stress necessary for invasion and metastasis.

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Palliative care at every stage
Clinical trials show benefits of earlier intervention

A pioneer of early palliative care research and implementation, Camilla Zimmerman, MD, PhD, FRCP, director of the Palliative Care Program at Princess Margaret Cancer Centre in Toronto, provided an overview of the field including trials exploring benefits of early interventions, and barriers and approaches to integration of this specialized care. Once viewed as an exclusively end-of-life specialty, palliative care is shifting toward a model where it plays a role in each stage of treatment from diagnosis on. On Feb. 16, Zimmerman discussed a number of randomized controlled trials, several of which she led, that quantified the benefit of earlier palliative care intervention using metrics including quality of life, symptom control, mood, and satisfaction with care. Collective results of these trials found evidence for improved quality of life, patient satisfaction, survival outcomes, and lowered depression when palliative care intervention occurred early and regularly through a specialized or outpatient palliative care clinic. Additionally, qualitative chart reviews and interviews with palliative care providers suggested that these specialists provide a critical link between oncologist and patient, emphasizing psychosocial elements including emotional engagement, dealing with and understanding symptoms, interpreting difficult concepts in the care plan, and overall helping patients cope with their diagnosis and treatment. Despite these positive findings, there remains a short supply of trained palliative care specialists and the field is still largely perceived as needed only when death is imminent. A major factor in this perception seems to be tied to connotations evoked by the name “palliative.” A portion of surveyed patients, caregivers, and physicians were shown to be in favor of rebranding the specialty to the more positive moniker “supportive care.” Zimmerman also addressed models of palliative care, lauding the integrated care model conceived by Eduardo Bruera, MD, and David Hui, MD, chair and assistant professor, respectively, of Palliative, Integrative and Rehabilitation Medicine, in which the palliative care team works in close collaboration with the oncologist throughout treatment to manage patient symptoms and distress. She emphasized that the presence of a devoted outpatient clinic, symptom screening, early referral, and education by all oncologists are indicators of a well-integrated palliative care system.

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Epic solutions and updates

OneConnect optimization will be an ongoing process

The March 29 Grand Rounds focused on the successes and challenges that accompanied the monumental OneConnect transition. As the first speaker in the lineup, Paul Mansfield, MD, vice president of Acute Care Services, emphasized that no large changes proceed perfectly and that the institution will continue to optimize our experience with the OneConnect system for years to come. He applauded the collective spirit of coming together to solve problems and focusing on finding solutions while also appreciating how understanding patients have been of extended wait times. Further, he noted that we must transition away from ClinicStation tendencies while using OneConnect, saying that, “It would be like me giving you a motorcycle and you saying ‘How do you expect me to pedal this thing?’” Next, Pier Tansey, MS, PA-C, manager of Clinical Pharmacy Services, briefly walked through the process of medication reconciliation for new admissions, transfers, and discharges.

Division faculty connect with patients and colleagues at OneConnect forums

Division of Cancer Medicine faculty have played instrumental roles in the successful implementation of OneConnect from the earliest planning stages through continued monitoring and troubleshooting required today as the institution and our patients adjust and adapt through the first months in the new system. Through this process, division faculty members have been able to interface with patients, clinicians, and other faculty to address concerns, field questions, and offer strategies for improving efficiency.

Once a month, myCancerConnection from the Department of Volunteer Services and Merchandising hosts patients and caregivers at an educational survivorship forum known as Partners in Knowledge, News in Cancer (PIKNIC). On March 15, Neeta Somaiah, MBBS, assistant professor of Sarcoma Medical Oncology, shared her experiences with the institution’s recent transition to OneConnect and provided expert advice for patients’ concerns and questions.

Over the course of her career, Somaiah has experienced numerous electronic health records systems, but she noted that each system has its own workflow that requires some unavoidable growing pains. “Once we become adept at managing the flow, your clinic wait times will get much better,” she said.

With a few clicks, a doctor can send test results to patients who do not live in Houston and need to share this information with their local providers. Somaiah encouraged patients to log on to their myMDAnderson accounts to ensure accuracy of history and medications listed, and make the staff aware of any errors. Somaiah also fielded questions and concerns from several patients in the audience on topics including issues with the mobile application for myMDAnderson and setting up appointments on the website. Above all, she empathized deeply with patients, thanking them for their understanding and patience during this transition and acknowledging that it may be a scary time for them. “Know that it will get better,” she assured patients. “There’s one portal of communication now. Communicating information well is key to making sure we decrease errors as we move forward.”

Additionally, Vinod Ravi, MD, associate professor of Sarcoma Medical Oncology, led EHR Grand Rounds on June 29, where he touted the ability of OneConnect to encourage problem-based medical record keeping that allows for better patient care. Ravi noted the inefficiency of previous recordkeeping methods that bundle patient information into distinct categories and rely on separate provider notes as a primary method of communication within care teams when numerous providers are looking after the same patient. He referenced the ideas of Dr. Lawrence Weed as the foundation of problem-based record keeping, which involves asking providers to make a prioritized list of known problems for each patient reporting observations, treatment plans, and work up designs in an organized fashion. This approach, Ravi noted, is designed to condense records into the most crucial pieces of information to encourage efficient progression of treatment for each patient and account for the multiplicity of problems encountered in large volume clinics. As problems are resolved or change or new ones arise, this list must be updated accordingly; accurate tracking of changing and converging symptoms can help develop diagnoses. He demonstrated how to access and manipulate the problem list on the OneConnect interface, showing how the system allows collaborative, efficient review of a patient’s oncology history in a minimum number of clicks.

Informatics, spoke about InBasket as a clinical communication tool for patient safety that is undergoing various refinements to improve providers’ and patients’ experiences. She reviewed the various types of messages that providers may receive in their Epic email inbox while also clarifying the routing that occurs from patient to provider and the difference between an open chart and open encounter. James Yao, MD, chair of Gastrointestinal Medical Oncology, who has been leading OneConnect efforts for the division, and Dina Patel, RPh, manager of Clinical Pharmacy Services, spoke about the so-called “blue light” process for validating chemotherapy order sets being transferred from Clinic Station to become Beacon protocols in the OneConnect system. Teams of representatives from clinical pharmacy and research came together to validate close to 3,000 protocols. Yao lauded the collective “reactive to proactive” attitude and executive command center that helped manage long delays and issues in the ATC, and also emphasized the encounter-centric nature of Beacon versus the drug-centric nature of ClinicStation. Lastly, Allison Gulbis, RPh, manager of Clinical Pharmacy Services, briefly walked through the process of medication reconciliation for new admissions, transfers, and discharges.

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Validating Beacon protocols has involved a multi-pronged team that meets at least weekly. Crucial assistance has been provided by many members of the Pharmacy team, including Ryan Roux, PharmD, MS, RPH, director of Pharmacy Operations (seated); and several managers of Clinical Pharmacy Services, including (from left) Dina Patel, PharmD, RPH, Laura Michaud, PhD, PharmD, RPH, Deborah McCue, PharmD, RPH, and Alison Gulbis, RPH (seated).

Participants get creative with team names to raise money for SCOPE race

By Maxsane Mitchell

Bottoms Up, Erinn’s Team WRECKtum, and Kim’s Colonistas — were just some of creatively named teams that formed to participate in the SCOPE Race on March 12. They laced up their sneakers to honor loved ones who have died of colorectal cancer or survivors who are still confronting the disease. More than 1,400 people signed up for the 11th Annual Sprint for Colorectal Oncology Prevention and Education event. Cathy Eng, MD, professor of Gastrointestinal Medical Oncology, is a founding co-organizer. She said colorectal cancer is one of the top causes of cancer deaths, and it is one of the most preventable in many cases. This year, the American Cancer Society estimates 95,270 people will be diagnosed with colon cancer and 39,220 people with rectal cancer. The organization estimates more than 49,100 people will die of the combined malignancies this year. Some lifestyle risk factors are linked to the disease, such as having a diet high in red meats, processed meats, and low in vegetables, fruits, and whole grains. Physical inactivity, obesity, and smoking also increase a person’s chance of developing polyps or a malignancy. Non-lifestyle risks include age, personal history of polyps or colorectal cancer, or a personal history of inflammatory bowel disease. The race raised over $30,000 dollars!