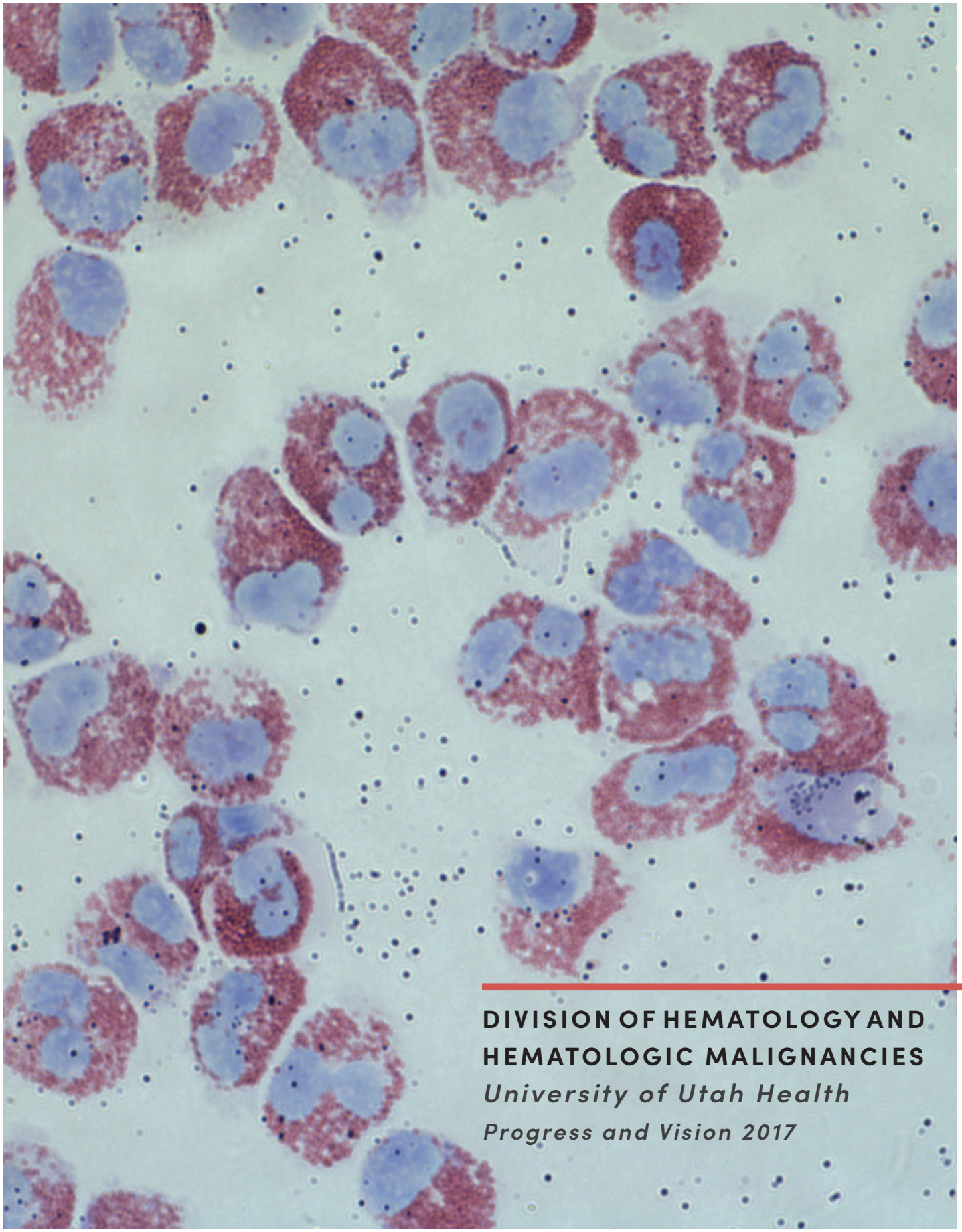
HEMATOLOGY



DIVISION OF HEMATOLOGY AND HEMATOLOGIC MALIGNANCIES

University of Utah Health

Progress and Vision 2017

HEALTH
UNIVERSITY OF UTAH

HUNTSMAN
CANCER INSTITUTE
UNIVERSITY OF UTAH

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OUR VISION

DIVISION CHIEF
MICHAEL DEININGER, MD, PhD

When people ask me why I decided to go into Hematology, I usually answer that I was fascinated by the beauty of blood cells seen under a microscope. No doubt everyone in our faculty will have a different story, but we are all united by a passion for blood disorders, malignant or benign, the mechanisms governing their deviation from the normal, and the desire to develop rational strategies to fix them when something goes wrong. Hematology has always been an intellectual feast. Led by giants like Maxwell Wintrobe and George Cartwright, our Division has played a central role in the University of Utah's development as the premier research institution in the Intermountain West. Today we continue this proud tradition in the rapidly changing landscape of Hematology and academic medicine.

With the overuse of fashionable terms, it's hard to state a vision that doesn't sound like everyone else's, so I will first explain why we are different and then how the defining features of our program allow us to make a difference. Foremost, our Division is a community of values. We aim for transparency, integrity, honesty, respect for each other, and a relentless commitment to excellence in all aspects of our professional life. We appreciate diversity and understand the fallacies of the human condition, qualities that translate into compassion for our patients. We believe that dialectic discussion is at the center of progress, and we welcome different opinions and new perspectives. As the practice of Hematology is being transformed by the molecular genetic revolution, we are at the forefront of discovery and translation of new information into clinical practice. Our ticket to success in this endeavor is scientific pursuit, driven by curiosity and the desire both to discover and advance the science of hematopoietic development and disease. We are committed to collaborating across specialties and to breaking down barriers that hinder progress. In the end, this is all about impact - changing lives for the better, contributing knowledge rather than only using it.

Our clinical services and research labs are housed at the Huntsman Cancer Institute, an NCI-designated Comprehensive Cancer Center, and the Eccles Institute for Human Genetics, architecturally inspiring and technologically advanced facilities that rival the best in the country. Close proximity of patient care, research and shared resources promote ease of transfer of samples and ideas. In this environment, it is no surprise that members of our faculty have published manuscripts in first-tier journals that impact thinking in their research communities and shape clinical practice. As Hematology has played a central role in building the foundation of modern medicine, we will continue to make key contributions to our field, train the next generation of clinical and lab-based hematologists, and provide the best possible care to the patients in our growing catchment area.

When I think about the future of Hematology research, the importance of integration across disciplines and utilization of diverse data sources tops everything else. Gone are the days when working in a vacuum you could have a major impact on the field - as a clinician doing clinical trials, a biologist or biochemist researching

Division of Hematology and Hematologic Malignancies Faculty

disease pathways, or an epidemiologist studying the population risk of blood disorders. These fields are all connected, and impact ensues when we facilitate information transfer, integrate data and translate the product of these combined efforts into clinically meaningful outcomes. Impact: for us this means making a difference in patients' lives, generating new knowledge, leaving our comfort zone to push the limits of technology. As an example, we are creating fully annotated clinical databases, using state-of-the-art natural language processing to convert amorphous data into searchable phenotype information. Our biobank holds more than 30,000 samples from more than 1,500 individual patients with hematologic disorders that are linked to clinical phenotype, diagnostic pathology and the Utah Population Database, the most extensive such database in the world. Data generated in our labs on samples from our biobank are being linked to complete the integration. This is an ambitious undertaking, but we have the expertise and dedication to do it, and once accomplished, we will make physiologic and pathophysiologic connections previously unrecognized.

When we consider the future of patient care, the timeless beauty of a classical Greek sculpture comes to mind. It is perfection. You can neither add to it nor take away from it without creating something less. We use this concept in our approach to patient care - doing exactly what is needed to give our patients the best possible outcome, the best chance of a fulfilling life and the highest level of function. We aim for no unneeded tests, no mindless prescribing of drugs that causes more adverse events than beneficial effects, no mission-drifting from compassion to convenience. We are aware of the challenge this goal poses. We are launching multilayered efforts to form strong multidisciplinary care teams to leverage the combined experience of our faculty, advanced practice clinicians, and nurses. Some will call this "personalized medicine," but to hematologists, this all-encompassing approach to patient care is not new. We have treated leukemia and lymphoma based on cytogenetic markers decades before the term "personalized medicine" was coined, and we will continue to broaden the impact of molecular medicine while treating our patients with respect, empathy and compassion, always aware of the great privilege it is to be companions in their difficult journeys.

IMPACT: FOR US THIS MEANS MAKING A DIFFERENCE IN PATIENTS' LIVES, GENERATING NEW KNOWLEDGE, LEAVING OUR COMFORT ZONE TO PUSH THE LIMITS OF TECHNOLOGY.

What makes a good mentor? Someone you remember for all your professional life? The person who gets your career going? We have given this question a great deal of thought. In our Division, we are deeply committed to mentoring our fellows and junior faculty members. We have established scholarship committees that provide guidance and critical feedback for young clinicians and investigators starting their careers. We realize that despite all the rules and regulations, mentor-mentee relationships are still based on the old principles of apprenticeship that leave space for creativity and variation but are founded on mutual commitment to a common goal. These relationships are two-way streets of education and training. We expect dedication from both parties involved in a shared quest for clinical excellence and scholarly achievement: curiosity, tenacity, and a willingness to learn and to be challenged. The sky is the limit.

If you are a patient, we want you to experience the best care in the nation; if you are in training, we want you to join us to get the best education in the science and clinical practice of hematology; and if you are a researcher looking for a place to excel, we want you to join us so that you will have the support and collaborative opportunities you need to have an impact on your field of investigation.

HISTORY MEETS

Visionaries Dr. Maxwell Wintrobe, Chair of Internal Medicine, and Dr. George Cartwright, the first Division Chief (1950-1967), created the unique Hematology Training Program at the University of Utah that produced many of the early leaders in the field. Dr. Wintrobe is renowned for his textbook, Clinical Hematology. Remarkably, he wrote the first six editions single-handedly. The impact of Wintrobe's Clinical Hematology continues to the present, with work underway on publication of the 14th Edition. Dr. Cartwright began his research career while a houseofficer at Johns Hopkins under the aegis of Dr. Wintrobe, investigating the role of nutrients in hematopoiesis. Presciently, he also studied the effects of nitrogen mustard on lymphoma cells. When Dr. Wintrobe became the first Chairman of the Department of Medicine at the University of Utah, he recruited Dr. Cartwright to Salt Lake City where they continued their research collaboration, focusing on iron and copper metabolism. As a result of his groundbreaking work, Dr. Cartwright became internationally recognized as the foremost authority on the pathobiology, genetics and clinical characteristics of both Wilson's disease and hereditary hemochromatosis. Dr. John W. Athens, Division Chief from 1967 to 1991, made fundamental contributions to our understanding of blood cell physiology. He was the first to radiolabel blood cells, and in a series of classic papers, defined the kinetics of neutrophil production, life span, and distribution. Dr. James P. Kushner, Division Chief from 1991-2010, established a strong research program centered on the biochemistry of heme synthesis and disorders of heme metabolism, particularly the porphyrias. He made formative contributions to understanding the pathobiology of sporadic porphyria cutanea tarda and hereditary hemochromatosis. Under his leadership, the Division was twice recognized by the NIH through a Center of Excellence in Molecular Hematology Award. The Division subsequently became an NIH-funded Center of Excellence in Iron and Heme Disorders and is one of the six centers that formed the Porphyrias Consortium as part of the Rare Clinical Diseases Research Network, an initiative of the NIH's National Center for Advancing Translational Sciences. Dr. Michael Deininger, a renowned investigator whose research is aimed at elucidating the genetic and biochemical basis of myeloproliferative neoplasms and drug resistance in leukemia, became Division Chief in 2010 and established an intensive research focus on malignant hematology.

Why has the University of Utah played such an outsized role in discovering the genetic basis of human disease? It seems serendipity and visionary leadership combined in a fortuitous manner. It was the interest of members of the Church of Jesus Christ of Latter-day Saints (Mormons) in genealogy that preserved meticulous family records with detailed information on past generations. These genealogical records enabled investigators at the University to reconstruct large pedigrees that revealed disease inheritance patterns that would have been invisible without this unique resource. Visionary leadership allocated resources to the project, and the nation's first Department of Biomedical Informatics was founded at the University of Utah in 1964. In 1966, the Utah Cancer Registry began collecting population-based cancer data, soon including medical records, and in the 1970's, the Genealogical Society of Utah partnered with University of Utah scientists to link genealogies and registry data, which led to what is now known as the Utah Population Database (UPDB). The university made important contributions to the characterization of restriction fragment polymorphisms and polymorphic DNA markers to map the human genome. Discovery of some of the first genes that underlie familial cancers, including APC and BRCA1, followed. In the mid-1980s Mario Capecchi developed the technique of homologous recombination in mice as a method for investigating the role of specific genes in disease, a discovery that was honored with a Nobel Prize. Today, the UPDB contains genealogical, public health, and medical records of more than 8 million people, enabling discoveries that would not be possible otherwise. Members of our faculty rely on the UPDB as their key resource in studies aimed at identifying genetic predisposition both to multiple myeloma and to chronic lymphocytic leukemia.

FUTURE.

CLINICAL PROGRAMS

THE UNIVERSITY'S UNIQUE POSITION AS THE ONLY ACADEMIC MEDICAL CENTER IN THE INTERMOUNTAIN WEST ALLOWS OUR DIVISION TO SERVE PATIENTS WITH A WIDE VARIETY OF HEMATOLOGIC DISEASES.

The University's unique position as the only academic medical center in the Intermountain West allows our Division to serve patients with a wide variety of hematologic diseases. The catchment area, encompassing more than 10% of the continental U.S., includes Utah and large portions of Colorado, Idaho, Montana, Nevada, and Wyoming. To ensure convenient access for patients and referring providers, we have outreach clinics in Farmington, UT; South Jordan, UT; Rexburg, ID; Grand Junction, CO; and Reno, NV.

Patients served by the Division of Hematology and Hematologic Malignancies have full access to an array of investigator-initiated, national cooperative group and industry-sponsored clinical trials, including early, first-in-man studies. We carefully balance our portfolio with the goal that each patient referred to our clinics can be offered participation in a clinical trial. If the patient has a malignancy but does not require treatment at the time of referral, we offer observational trials such as studies of genetic predisposition to cancer. We also have tissue-banking protocols, allowing us to retrieve achieved samples for analysis should new information relevant to the patient arise.

Our clinical research efforts extend to the Veterans Health Administration (VHA), the largest integrated health care system in the U.S. Several members of our faculty have joint appointments at the George E Whalen VA Hospital in Salt Lake City. Members of our faculty closely collaborate with the Informatics Decision Enhancement and Surveillance (IDEAS) Center in Health Services Research, using state-of-the-art tools to reconstruct detailed phenotypes of patients with hematologic disorders, their disease characteristics, care processes, and associated outcomes. Availability of this data allows us both to study nationwide patterns of adoption of novel practices and to pursue comparative effectiveness studies of treatments in real-world settings.

UTAH BLOOD AND MARROW TRANSPLANT PROGRAM

The Utah Blood and Marrow Transplant (BMT) Program was established in 1991 and is physically housed at HCI. In 2016, we performed 130 transplants in adults, with 178 projected for 2017, in addition to pediatric transplants. Our center-specific outcomes have been recognized as among the best in the United States. The Utah BMT Program is fully accredited by the National Marrow Donor Program (NMDP) and Foundation for the Accreditation of Cellular Therapy (FACT) and is the only academic BMT program in the Intermountain West. We offer autologous and related and unrelated donor allogeneic transplantations, including the use of umbilical cord blood and haplo-identical-related donor cells. We are also the only BMT program in the Intermountain West to offer cutting-edge cellular-immune therapies, such as Chimeric Antigen Receptor (CAR) T cells, for the treatment of B cell leukemias and lymphomas.

Since 2015, the Utah BMT Program has welcomed the addition of several expert adult and pediatric BMT physicians. Dr. Daniel Couriel, Professor of Medicine, is a nationally recognized leader in the treatment of graft-versus-host-disease (GVHD) and serves as Program Director of the Utah BMT Program. Under his leadership, the Utah BMT Program is active in translational and clinical research of hematologic malignancies and GVHD, and we continue to participate actively in investigator-initiated trials, pharmaceutically sponsored trials, and cooperative group trials through the BMT Clinical Trials Network (BMT-CTN). Our faculty members, including Dr. Djordje Atanackovic, Dr. Mike Boyer, Dr. Dan Couriel, Dr. Catherine Lee, Dr. Tibor Kovacsovics, Dr. Vedran Radojcic, Dr. Doug Sborov, and Dr. Sri Tantravahi, are leaders or members of several national/international organizations.

The Utah BMT Program has recently started to bring cutting-edge BMT services to the community through satellite clinics, and in the near future, the program will use telemedicine to communicate with patients and referring physicians. This approach has fundamentally challenged the usual model of BMT care where the patient is expected to repeatedly return to the transplant center, which can be particularly difficult given the size of our catchment area. We now provide post-BMT care to patients living in Western Colorado and Northern Nevada. The University's outreach program will soon provide BMT care to residents of Boise, Idaho through telemedicine or virtual visits. We are committed to providing the highest quality transplant care to everyone, everywhere.

BENIGN HEMATOLOGY

Under the leadership of Dr. George Rodgers, our Benign Hematology Program provides inpatient and outpatient clinical hematology services for the University of Utah Hospital, the Huntsman Cancer Hospital, and the Veterans Administration Hospital. We train students, residents, and fellows in the clinical and research aspects of Hematology and run a large NIH-funded research enterprise. Our mission is to deliver coordinated, multi-specialty care for patients with nonmalignant hematologic disorders. Our inpatient Hematology service is primarily consultative, while our outpatient service provides care for patients with inherited and acquired anemias, other cytopenias, bleeding and thrombotic disorders, hemoglobinopathies and acquired non-malignant bone marrow failure disorders including aplastic anemia and paroxysmal nocturnal hemoglobinuria (PNH).

Inherited bleeding disorders, such as hemophilia, are frightening for patients and families. Patients may be at risk for bleeding after dental work, surgery, or trauma. They may also suffer internal bleeding, especially into joints, with no history of trauma. Management of these disorders requires a comprehensive approach involving physicians, nurses, pharmacists, physical therapists, and social workers. Today, due to advances in care at comprehensive treatment centers, patients with these disorders live far into adulthood. An Adult Hemophilia and Thrombosis Treatment Center was recently established at HCI to manage approximately 200 patients. The Center is a model for the comprehensive clinical management of patients with inherited bleeding disorders, as well as a vehicle for pursuing clinical and translational research.

A specific program, led by Dr. Charles Parker, is focused on abnormalities of heme metabolism (the porphyrias) and disorders of iron metabolism (primarily hemochromatosis). Dr. Parker also has a long-standing research interest in complement-mediated hematological disorders, particularly PNH, and provides comprehensive clinical care to patients with thalassemia, red blood cell membrane and enzyme defects, and congenital anemias. Dr. Paul Bray is an international authority on the genetic basis of arterial thrombosis and leads our clinical and research efforts in this rapidly evolving field that spans multiple disciplines.

MULTIPLE MYELOMA

Led by Dr. Djordje Atanackovic, our Myeloma Program serves as a tertiary referral center for myeloma patients in the Intermountain Region. It provides care for patients with multiple myeloma in all phases of the disease, including induction therapies, stem cell transplantation, maintenance therapy, and novel treatments for relapsed/refractory disease. Approximately 800 unique myeloma patients are seen annually at the Huntsman Cancer Institute Myeloma Clinic, including more than 200 patients per year with a newly diagnosed plasma cell dyscrasia. Both esprit de corps and a strong research effort characterize the Myeloma Program. Two new physicians, Douglas Sborov MD and Sabari Radhakrishnan MD, joined us in 2016 and 2017, respectively, and their presence has extended the program's clinical-translational research portfolio. The Myeloma Program is accredited by the Foundation for the Accreditation of Cellular Therapy (FACT).

Our Myeloma Program has a strong focus on translational research and aims at developing innovative therapeutic approaches, in particular immunotherapy strategies that include novel monoclonal antibodies, cancer vaccines, and the adoptive transfer of genetically modified T cells. The University of Utah and Huntsman Cancer Institute are in the process of establishing a platform for cellular immunotherapies. This platform will provide principal investigators with clinical-grade cellular products (CAR T cells, TCR-transduced T cells) for the treatment of multiple myeloma and other malignancies.

LYMPHOID MALIGNANCIES

The Lymphoid Malignancies Program, led by Dr. Martha Glenn, provides care for patients in our clinics at the Huntsman Cancer Hospital, the Veterans Administration Hospital and outreach locations. Our experienced team consisting of four hematologists, advanced practice clinicians, pharmacists, and specialized nursing staff, provide state-of-the-art care for patients and offer patients the opportunity to participate in clinical trials. Key to the lymphoma program is our close working relationship with colleagues in the Division of Hematopathology at the University of Utah. Additionally, our Cellular Therapy program, including the stem cell transplant group, collaborates closely with the lymphoma team in the care of patients requiring stem cell treatment.

Our faculty and staff contribute to an active research program, including clinical, translational, outcomes and genetic research. Dr. Deborah Stephens is focused on the development and therapeutic optimization of small molecule inhibitors in lymphoid malignancies, including ibrutinib and acalabrutinb. Dr. Ahmad Halwani explores the use of immunotherapy, especially monoclonal antibodies, including nivolumab and brentuximab vedotin, in treatment of lymphoid malignancies. Dr. Nicola Camp collaborates with Dr. Martha Glenn and other clinical colleagues to investigate the genetics of CLL. We are well represented in cooperative groups such as Alliance (SWOG), and contribute to four National Comprehensive Cancer Network expert panels (CLL, B cell NHL, T cell NHL and HL). Dr. John Sweetenham serves on the United Kingdom's Clinical Trials Committee of Leukemia and Lymphoma Research. Hematology/Oncology Fellow participation is woven into the lymphoid malignancies program, allowing trainees the opportunity to work with these experienced specialists, all of whom are committed to teaching and mentorship.

MYELOID MALIGNANCIES

Our Myeloid Malignancies Program has six committed and caring physicians – each with distinct interests and expertise in treating a bevy of rare and complex myeloid neoplasms. The current faculty members are nationally and internationally recognized experts in myeloid disorders and are contributors to advisory and consensus guidelines panels such as the National Cancer Center Network that define the standard of care in the field. Dr. Deininger has made key contributions to the development of kinase targeted therapies for chronic myeloid leukemia, including imatinib and ponatinib, which have changed the natural history of this previously fatal disorder. His research interests have expanded to include poor prognosis myeloid neoplasms, such as chronic myelomonocytic leukemia and aggressive systemic mastocytosis.

Dr. Prchal is a renowned physician and researcher in myeloproliferative neoplasms, particularly myelofibrosis and polycythemia vera, who brings to our center membership in the influential Myeloproliferative Disorders Research Consortium, an international multi-institutional group dedicated to basic and clinical research. Dr. Tsewang Tashi trained in our fellowship program and joined the Myeloid Malignancies Program in 2016. He collaborates with Dr. Prchal, investigating the genetics of myeloproliferative neoplasms.

Dr. Paul Shami and Dr. Tibor Kovacsovics lead our acute leukemia program, providing access to new therapies through an active early phase clinical trials program. Dr. Shami's lab is involved in drug development for AML, while Dr. Kovacsovics is spearheading the introduction of new diagnostic algorithms, collaborating closely with the Division of Hematopathology. The Myeloid Malignancies Team works in close affiliation with the University of Utah BMT program to coordinate care for acute myeloid leukemia and other conditions that are potentially curable with stem cell transplant.

ALL YOU NEED IS HERE

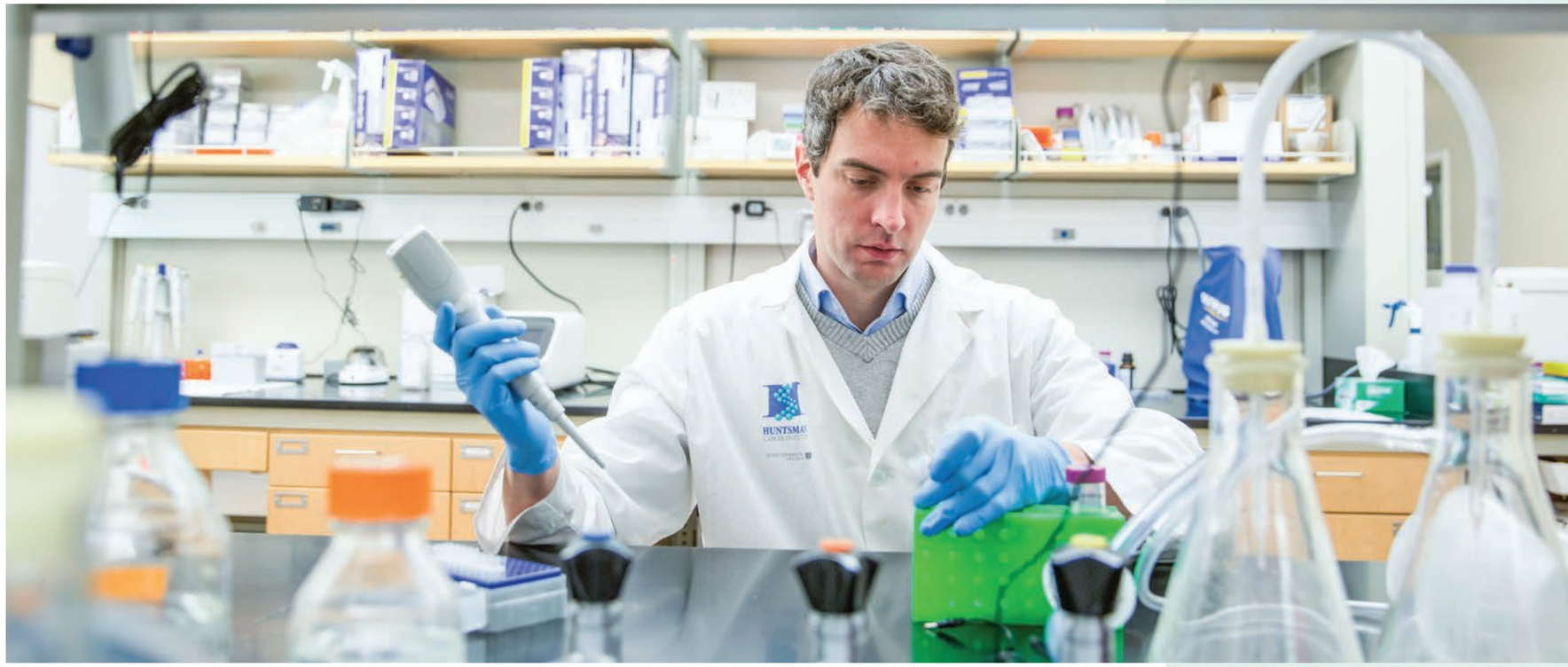
RESEARCH INFRASTRUCTURE

A tangible testimony to the commitment of the University of Utah to research excellence is the institution's support of an array of core facilities. "I had no idea what you've got out here" is a frequent comment from faculty candidates after their first visit to our institution. Huntsman Cancer Institute, the Department of Internal Medicine and the Division of Hematology and Hematologic Malignancies are playing central roles in establishing and maintaining this exceptional research infrastructure. The University Administration understands that successful research is dependent on access to advanced technologies at subsidized prices.

Core facilities. The University of Utah Health Sciences Center (HSC) operates a myriad of research core facilities (http://cores.utah.edu) with advanced technologies and equipment to empower research by faculty and students. Overseen by Division member Dr. John Phillips, these University-supported facilities ensure that cutting-edge technologies, including DNA sequencing, DNA/peptide synthesis, flow cytometry, mass spectrometry, metabolomics, metabolic phenotyping, genomics, mutation generation and detection, electron microscopy, drug discovery, bioinformatics and a centralized zebrafish facility, are available to research groups.

Center for Iron and Heme Disorders (CIHD). The NIH through NIDDK funds the Center for Iron and Heme Disorders (CIHD) within the Division of Hematology and Hematologic Malignancies. The CIHD also supports three scientific core facilities within the HSC: the Mutation Generation and Detection Core, Metabolomics, and the Iron and Heme Core. The Mutation Generation and Detection Core provides custom TALEN and Crispr-Cas9 DNA nucleases to induce mutations in a genomic region of interest, and this technology is used to perform reverse genetic studies in a variety of model organisms including zebrafish, Drosophia, C. elegans, mouse and mammalian cultured cells. The Metabolomic Core provides metabolite-profiling analyses, lipidomics and flux analysis. One innovative program spearheaded by the Metabolomic Core facility led by Dr. James Cox is to study hematologic disorders including porphyria cutanea tarda, erythropoietic protoporphyria, and polycythemia vera. Dr. Cox and his team developed a comprehensive platform that analyzes the entirety of the metabolome and lipidome of the erythrocyte. The CIHD also funds a Pilot and Feasibility Program to support three research projects per year at $25,000 each (http://cihd.cores.utah.edu). The goal is to promote new hematologic research by supporting collab-

THE UPDB IS THE ONLY DATABASE OF ITS KIND IN THE U.S. AND ONE OF THE FEW SUCH RESOURCES IN THE WORLD.



orative and interdisciplinary research initiatives. Pilot funding for hematologic research is also available through the Funding Incentive Seed Grant Program sponsored by the Vice President for Research's office *(http://research.utah.edu/grants/seed.php)*.

Cell Therapy and Regenerative Medicine Facility. The Cell Therapy and Regenerative Medicine (CTRM) program at the University of Utah is jointly governed by the Department of Internal Medicine and the Division of Hematology and Hematologic Malignancies. Under the leadership of Division Faculty members Dr. Jo-Anna Reems and Dr. John Phillips, the CTRM translates discoveries in cellular therapy, tissue engineering and regenerative medicine into clinical applications that extend and improve the quality of life of patients with debilitating diseases and injuries. Initially established in 1992 to support the Utah BMT Program, CTRM has evolved to facilitate the delivery of some of the world's most advanced human cell, tissue, and cellular-based products. The CTRM has delivered more than 2,500 blood and marrow products as either allogeneic or autologous transplants for the treatment of adult and pediatric patients, including those with leukemia, lymphoma, multiple myeloma, and aplastic anemia. The CTRM facility manufactures novel therapeutic cellular products under Good Manufacturing Practices (GMP) and Good Tissue Practices (GTP) in support of entrepreneurial and investigator-initiated clinical studies. CTRM is strategically positioned to support T-cell therapies, including CAR-T cell therapy, and facilitate research studies using these novel products. A major current focus of CTRM is clinical studies using proprietary birth tissue products for ocular GVHD, burn treatments, and management of complicated wounds. The CTRM facility has the expertise and infrastructure to address complex regulatory, financial and manufacturing challenges associated with delivering innovative cellular and tissue-based products. The CTRM facility is registered with the FDA, is certified by CLIA & CAP, and is accredited by the Foundation for the Accreditation of Cellular Therapy (FACT).

Utah Population Database. A unique resource is the Utah Cancer Registry that has recorded all cancers occurring in the state of Utah since 1966. The Utah Population Database (UPDB) encompasses genealogical data from 10 generations of Utahns. This large data set is linked to the HSC electronic data warehouse and state-based disease registries, creating an unmatched resource for population studies to analyze patterns of genetic inheritance and to identify new disease alleles. The UPDB is the only database of its kind in the U.S. and one of the few such resources in the world.

Hematology Tissue Bank. The Division, in conjunction with the Hematologic Malignancies Disease Oriented Team (DOT) at the Huntsman Cancer Institute and the Deininger lab, has established a biobank containing more than 30,000 samples from patients with hematologic disorders. These annotated samples are accessible to researchers within and outside the Division, providing a key resource for translational research in hematology.

UNIVERSITY OF UTAH RESEARCH COMMUNITY

The Division of Hematology and Hematologic Malignancies is tightly integrated into the research community at the University of Utah, promoting synergism and productive collaborations. Many of our faculty have adjunct appointments in other Departments at the University of Utah. Drs. Winge and Deininger bridge to biochemistry with front-line research in cancer metabolism, mitochondrial biology and structural biology. Drs. Prchal, Camp, Stephens and Bray are no strangers to the Departments of Human Genetics and Population Sciences, researching genetic predisposition in hematologic disease and clonal evolution of hematologic malignancies. Drs. Phillips and Leibold, associated with the Departments of Pathology and Oncological Sciences, respectively, are focused on iron and heme metabolism. Drs. Shami, Atanackovic and O'Hare collaborate with researchers in the Departments of Pharmaceutics and Pharmaceutical Chemistry and Medicinal Chemistry on novel drug delivery systems, therapeutic antibodies and T-cell targets, and cell-based therapies for metabolic diseases. Dr. Jan Christian studies hematopoiesis, holding a joint appointment in the Department of Anatomy and Neurobiology. Additionally, strong and productive collaborations connect multiple investigators in our Division with the Departments of Oncological Sciences and Pathology. Recent examples include collaborative work between the Deininger lab and Pathology Faculty member Dr. Ryan O'Connell, an immunologist studying the function of microRNAs in regulating physiological and pathological hematopoietic development in mammals. Their collaboration on the role of miR-155 in FLT3-ITD+ AML led to a high profile publication and opened the possibility of manipulating miR-155 to improve outcomes in AML.

RESEARCH HIGH-LIGHTS

DR. NICOLA CAMP, *PhD*
Identifying Genetic Variants in Hematologic Malignancies

Dr. Nicola J. Camp, who joined the University of Utah in 1998, is a genetic epidemiologist/statistical geneticist whose research focuses on the identification of inherited genetic mutations that increase cancer risk, specifically in hematological malignancies and breast cancer. Her research uses the 16 generations of genealogy in the Utah Population Database (UPDB) together with statewide cancer diagnoses from the Utah Cancer Registry to identify and study multi-generational cancer families. Her current research areas in hematological malignancy are chronic lymphocytic leukemia and multiple myeloma. In multi-disciplinary collaborations, she uses high-density SNP genotyping, whole exome, whole genome and whole transcriptome sequencing for her predisposition studies.

To understand the contribution of common genetic variations involved in genetic susceptibility to chronic lymphocytic leukemia (CLL), Dr. Camp and colleagues have conducted multiple collaborative genome-wide association studies (GWAS). To-date, these studies have identified 33 chromosomal regions harboring risk variants. Besides providing additional evidence for genetic susceptibility to CLL, characterization of these risk loci offer insights into the biological basis of CLL development. Many loci contain genes that participate in interconnecting cellular pathways central to B-cell development. Identification of risk variants and their biological consequences provide new opportunities for risk screening, disease prevention and development of novel therapies.

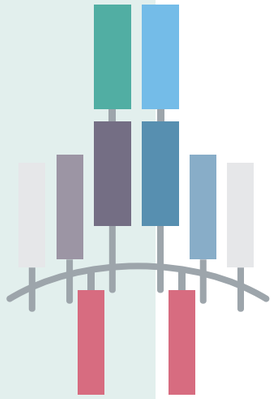
Within the International Multiple Myeloma (MM) Consortium, Dr. Camp and colleagues validated the role of family history and body mass index as risk factors for MM, and confirmed several low-risk loci in a multi-ethnic GWAS. They also identified a high-risk variant in the FOPNL gene that correlated with shorter survival. Dr. Camp and her collaborators pioneered the use of family sequencing studies. This novel approach led to the discovery of rare variants in the USP45 and ARID1A that segregate in high-risk families. Both genes are involved in DNA repair and chromatin remodeling.

Dr. Camp received the Reed Gardner Award for Faculty Excellence, has been honored by the Leukemia and Lymphoma Society for her research, and is a recipient of a Presidential Early Career Award for Scientists and Engineers. She currently serves on the National Cancer Institute Board of Scientific Counselors and is a member of the American Society of Human Genetics, the American Association for Cancer Research, and the International Genetic Epidemiology Society.

Dr. Bray joined the faculty in the Division of Hematology and Hematologic Malignancies in 2016. Dr. Bray was a medical student at the University of Utah and worked under the aegis of Dr. George Cartwright. Prior to returning to Salt Lake, he was on the faculty of Jefferson Medical College where he served as Director of the Cardeza Foundation for Hematologic Research and Director of Hematology. Throughout his rich academic career, Dr. Bray has continued to care for patients with bleeding and clotting disorders. He is an internationally respected platelet biologist with a long-standing research interest in the genetic basis of arterial thrombosis. Dr. Bray has had 31 years of continuous funding from the National Institutes of Health (NIH) and currently is PI on three NIH R01 grants. He has published more than 160 peer-reviewed papers, book chapters and invited reviews. He has an extensive track record of educational successes, having trained more than 30 postdoctoral fellows, graduate students, hematology/oncology fellows and junior faculty.

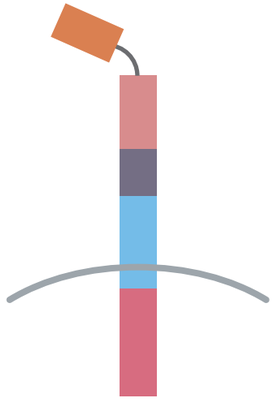
Dr. Bray cloned the genes for the major adhesive receptors on blood platelets and characterized their biosynthesis, function, and the mutations that caused inherited bleeding disorders. He also discovered the first platelet genetic variant associated with myocardial infarction. This work initiated a large effort by many investigators to identify other genetic risk factors involving platelets that were associated with heart attacks and strokes. He designed and conducted research studies that recruited subjects to identify genes and gene variants associated with human platelet activation. He discovered networks of platelet genes that were differentially expressed by age, gender and race, and developed a user-friendly web tool ("Plateletomics") to query the data. These tools are now facilitating discovery of novel mechanisms of regulation of platelet gene expression. In another seminal contribution, Dr. Bray's lab showed that platelets from women are "hyper-reactive" compared to platelets from men, and identified responsible mechanisms. This basic research work led to his recruitment as an investigator in the Women's Health Initiative, where, over the course of ten years, he helped identify demographic, genetic, and pharmacogenetic factors associated with cardiovascular morbidity and mortality in women. Recently, Dr. Bray's group discovered a platelet gene variant that accounts for the higher incidence and worse clinical outcomes after heart attacks occurring in African-Americans compared to whites. This finding may form the basis for selecting the most appropriate drugs to treat and prevent heart disease in African-American patients.

DR. PAUL BRAY, *MD*
Role of Platelets in Thrombosis and Hemostasis



T Cell Receptor

Monoclonal Antibody



Chimeric Antigen Receptor

TECHNOLOGY COMMERCIALIZATION

Since 1970, the University of Utah has spun out more than 230 companies based on technologies developed by faculty members. Over 130 of these companies are still operational. The University's spin-offs have collectively raised over $300 million in investment funding since 2011, secured over $70 million in grants, and have been involved in acquisitions totaling more than $5.7 billion. The Technology and Venture Commercialization (TVC) office at the University of Utah assists faculty in licensing their research inventions. The office acts as a bridge to coordinate efforts between industry, venture capitalists, and other funding sources to commercialize the University of Utah inventions. Dr. Paul Shami, a member of our Division, founded JSK Therapeutics to create a new class of cancer treatment drugs exploiting nitric oxide release to selectively kill AML and multiple myeloma cells. The company has exclusive licenses for the proprietary agents, their use in cancer treatment, and their formulation technology. They recently received a 2M dollar grant from the NIH to complete the pre-clinical development of their lead molecule. Dr. Djordje Atanackovic and Dr. Tim Lütkens are developing novel immunotherapies, including chimeric antigen receptor (CAR) T cells and monoclonal antibodies, for the treatment of hematologic malignancies and solid tumors, with a focus on multiple myeloma. CARs are artificial T cell receptors using single-chain antibody instead of T-cell receptor variable domains to recognize antigens on the surface of target cells. Early phase clinical trials have demonstrated high efficacy of CARs against different hematologic malignancies and led to the designation as a breakthrough therapy by the FDA. Together with the TVC office, the Atanackovic/Lütkens team has recently submitted a Patent Cooperation Treaty application for one of their novel CAR T cell products.

EDUCATION

HEMATOLOGY/ONCOLOGY FELLOWSHIP

The combined Hematology/Oncology fellowship program at the University of Utah is a 3-year training program designed to support the careers of the future leaders in our field. We provide comprehensive education in the

Hematology / Oncology Fellows

diagnosis and treatment of patients with cancer and hematologic disorders and train young investigators in clinical and laboratory research.

Training includes 18 months of clinical rotations in a variety of inpatient and outpatient settings at the Huntsman Cancer Hospital, the University Hospital, and the Veterans Administration Hospital. Weekly continuity outpatient clinics allow the fellows to provide long-term care and to understand the trajectory of their patients' diseases. At the end of their training, our fellows are well prepared to pass the sub-specialty boards and excel in their new positions. More than half of our fellows choose academic careers, reflecting our emphasis on how exploring the scientific basis of disease leads to discoveries that advance the field and ultimately improve patient outcomes.

Research training starts in the first year with didactic sessions on clinical trial design, statistical methods and cancer biology. Fellows begin exploring research opportunities in regular meetings with an assigned first-year mentor, during a series of informal scientific talks by potential mentors, and in individual meetings with researchers. All fellows are required to present a career development plan for their second and third year. Research opportunities are abundant, including clinical research in experimental therapeutics and phase I trials, quality improvement and outcomes studies, and of course, translational and basic laboratory research. Fellows who are serious about a career focused on investigation are encouraged to devote a full 18-24 months to their research efforts. Program leadership ensures that this time is protected by limiting clinical responsibilities. For exceptionally promising fellows, we offer an Advanced Scholars program that includes an additional year of research training. Fellows are encouraged to apply for research and career development awards, and the faculty is committed to guiding fellows through this process in order to maximize the quality of their training.

MENTORSHIP

In the Division of Hematology and Hematologic Malignancies, we consider mentorship of fellows and junior faculty a crucial component of education and career development. The Hematology/Oncology Fellowship program requires each fellow to have an advisory committee that serves as mentors and advisors to aid in the training and development of young investigators in clinical or laboratory research. Encouragement and guidance is provided for trainees in applying for mentored scientist development grants such as NIH K08 or similar types of awards from other sources such as the Leukemia and Lymphoma Society.

The Division stipulates that each junior faculty member shall designate a Principal Mentor and a Secondary Mentor as part of their mentoring teams. A document outlining the expectations of the mentoring relationship is signed by both parties and submitted to the Division Chief. The Principal Mentor assists the junior faculty member in crafting a career development plan and, to facilitate the process, offers advice on selection of the mentoring team. The Principal Mentor guides junior faculty toward the goal of developing an independent research program and provides essential resources, including laboratory space and research funds, to support the mentee's work. The Secondary Mentor may be a faculty member who adds specialized expertise in methodology and scholarly breadth to the working group. Advisors may be included in mentoring teams to provide guidance on specific issues on an ad hoc or continuous basis. Each junior faculty member presents his or her work annually at the Faculty Research Conference, and mentoring committee meetings are held at least twice per year. For junior faculty in the Clinician-Scholar pathway in the Tenure Track, the mentoring team has broad academic advisory responsibilities similar to those for mentoring teams for junior faculty in the Scientist-Scholar track. The focus is on

WE CONSIDER MENTORSHIP OF FELLOWS AND JUNIOR FACULTY A CRUCIAL COMPONENT OF EDUCATION AND CAREER DEVELOPMENT.

guiding and supporting the mentee's scholarly and creative interests.

An explicit charge for mentors and mentoring teams for research-based junior faculty is to review and critique both research development plans and grant applications prior to submission. It is the mentee's responsibility to draft the application with a timeline that allows for detailed assessment and to arrange review by the mentoring team. Planning discussions on preliminary data and provisional aims are followed by a chalk talk presentation. We ascertain that this review proceeds with sufficient lead-time for the mentee to make deliberate and meaningful amendments (that are inevitably required) to the application. The Research Administration Offices within the Department of Internal Medicine and HCI provide support both for proposal preparation and for fulfillment of post-award obligations, which includes progress reports and management and accounting of expenditures.

Mentoring activities are a critical criterion in the formal yearly review of Division faculty and play a significant role in promotion, retention, and tenure reviews of associate and full professors in the Department of Internal Medicine.

An additional level of mentoring is available through the University of Utah's Vice President's Clinical & Translational (VPCAT) Research Scholars Program, which supports junior faculty committed to careers in clinical or translational research. VPCAT Research Scholars are selected through a competitive application process each fall. Accepted scholars participate in a two-year program designed to provide leadership competencies and develop the essential research knowledge and practical skills to be an effective clinical or translational investigator.

T32 TRAINING PROGRAM IN HEMATOLOGY

Research in Hematology at the University of Utah is supported by a T32 training grant from the NIH/NIDDK, directed by Division Faculty members Dr. Betty Leibold and Dr. Joseph Prchal. This training program has been ongoing since 1943 and supports both pre-doctoral (PhD and MD/PhD candidates) and post-doctoral researchers (pediatric hematologists, adult hematology fellows and PhD postdoctoral scholars) working in the areas of heme biosynthesis, iron metabolism, developmental hematopoiesis, stem cell biology and blood cell function in health and disease. Another T32 focused on translational research training in hematologic malignancies is currently under review at NCI.

AWARDS

Two of our fellows have received prestigious awards. Dr. Sabari Radhakrishnan was awarded a two-year American Association for Cancer Research-Pfizer Immuno-Oncology Fellowship. This fellowship provides funding to promising young investigators who have high potential to become productive and successful independent cancer research scientists. Dr. Radhakrishnan's research focuses on chimeric antigen receptor (CAR) T cell therapy for multiple myeloma. He has generated multiple CAR T cell clones targeting a multiple myeloma surface antigen and is testing the efficacy of his CAR T cells in a mouse multiple myeloma model. Dr. Ami Patel was selected for an ASH training scholarship by the Study Section of the American Society of Hematology's Research Training Award for Fellows (RTAF). This highly competitive award supports fellows with a strong commitment to translational research who have shown exceptional promise. Dr. Patel is interested in the mechanisms underlying the persistence of leukemia initiating cells in patients with FLT3 ITD-positive AML treated with tyrosine kinase inhibitors. Her preliminary data have implicated STAT family transcription factors as key mediators of resistance, and she has developed model systems to interrogate the contribution of these oncogenic proteins to the resistance process.

Junior faculty members Dr. Deborah Stephens, Dr. Ahmad Halwani, Dr. Douglas Sborov, and Dr. Catherine Lee were selected for the VPCAT Research Scholars Program. VPCAT is a two-year mentored program for junior faculty to enhance their effectiveness in clinical and translational research. Through the VPCAT program, these young investigators have access to training, research facilities and infrastructure to aid in generating rigorous data that will make them competitive for extramural grant funding. In recognition of her contributions to clinical research at HCI, Dr. Stephens was recently selected to become a member of the Society of Huntsman Translational Scholars. The high success rate of our junior faculty in getting selected for prestigious research and training awards speaks to our emphasis on scholarship and commitment to mentoring.

A LIFE FOR HEMATOLOGY RESEARCH

Dr. Josef Prchal was awarded the 2017 Henry M. Stratton Medal in the Basic Science Category for his seminal contributions to fundamental Hematology research. The Stratton Award is among the most prestigious awards in Hematology. Dr. Prchal has made original and lasting scientific contributions to the study of a broad range of red cell disorders. In particular, he is highly regarded for his research on disorders of increased red cell mass, including primary erythrocytosis/polycythemia, inherited and acquired forms of secondary erythrocytosis and acquired and familial polycythemia vera. His research has contributed substantially to the fundamental understanding of the genetic basis of both primary and secondary polycythemias. His laboratory described the VHL mutation that underlies Chuvash familial polycythemia and elaborated on the pathobiology of EPOR mutations in autosomal dominant familial polycythemia. More recently, he and his collaborators showed that Tibetans are protected from polycythemia as a result of a high altitude genetic adaptation due to variants of the EGLN1 gene and the EPAS1 haplotype.

THE FOCUS IS ON GUIDING AND SUPPORTING THE MENTEE'S SCHOLARLY AND CREATIVE INTERESTS.

DIVISION ACTIVITIES

MOLECULAR HEMATOLOGY TUMOR BOARD

The Molecular Hematology Tumor Board meets monthly and is organized jointly by the Divisions of Hematology and Hematologic Malignancies and Hematopathology and includes participation by the Pediatric Hematology/Oncology Faculty. This conference has emerged as a key component of comprehensive diagnosis of hematologic disorders. The broad scope of the Molecular Hematology Tumor Board covers not only the results of molecular diagnostic studies from conventional cytogenetics to next generation sequencing, but also discussion of available targeted treatment options and clinical trials, thereby assuring that patients receive state of the art treatment. Additionally, the meeting covers diagnostic and monitoring algorithms (in particular the integration into of measurable residual disease in management), and the agenda often includes review of recent papers presented in a journal club format. The frequently controversial discussion of challenging cases leaves attendees, particularly trainees, stimulated and enriched.

HEMATOLOGY FACULTY CONFERENCE

The weekly Hematology Faculty Conference is the primary research conference sponsored by the Division of Hematology and Hematologic Malignancies. The main purpose of this one-hour meeting is to provide a forum for faculty and trainees to present their original research. All trainees supported by our T32 training grant, and third and fourth year Hematology/Oncology Fellows engaged in hematology research are required to present their work at the conference. Additionally, both intramural and extramural speakers whose research is related to hematology are invited to speak, and faculty recruits introduce their research to Division members through this forum. The format of this conference is designed to encourage interaction between the speaker and the audience and spark lively scientific discourse.

MULTI-DISCIPLINARY TREATMENT PLANNING CONFERENCE

Our multi-disciplinary treatment planning conference is a weekly one-hour meeting attended by faculty and fellows from adult and pediatric Hematology/Oncology, Hematopathology, Radiology, and Radiation Oncology, as well as advanced practice clinicians and clinical research staff. Difficult or interesting cases are comprehensively reviewed, including clinical presentation, histopathology, molecular genetics and imaging. We believe that combining our knowledge and experience improves the care of our patients. We aim to reach a consensus on diagnosis and management, but controversial discussions are common, providing an excellent learning opportunity for fellows and faculty alike. Many research projects have originated from this conference, testimony to the power of discussions across disciplines.

DISEASE-ORIENTED RESEARCH TEAMS (DOTS)

The DOTs at Huntsman Cancer Institute, overseen by Dr. Deininger in his role as Senior Director for Transdisciplinary Research, are formed by clinical, translational and population-based researchers interested in a specific type of cancer. The mission of the DOT's is to promote scientific collaboration across disciplines, enhance competitiveness for multi-investigator grants, and build research infrastructure such as biobanks and clinical databases. Beyond their role as an integral part of the translational research culture at the Huntsman Cancer Institute, the DOTs are also tasked to engage the community, increase disease awareness, and promote philanthropic support.

AMYLOIDOSIS PROGRAM

Initiated by faculty from the Divisions of Cardiology, Nephrology and Hematology/Hematologic Malignancies, the University of Utah Amyloidosis program has grown into a national destination program that attracts patients with all types of amyloidosis. Patients are seen in a multidisciplinary clinic housed at Huntsman Cancer Institute and provided comprehensive diagnostic and therapeutic services. Fellows from the various disciplines have an uncommon opportunity to become familiar with a rare, complex, and clinically challenging disease.

FELLOW SUCCESS STORY:

SABARINATH "SABARI" RADHAKRISHNAN, MD

I joined the University of Utah Hematology/Oncology fellowship program in July 2013 and never looked back. I knew I would be a doctor early on, coming from a family with a long tradition of pursuing careers in medicine. I identified Hematology/Oncology as a career focus early in medical school, motivated by a sense that oncology care lacked sophistication in my home country of India and that I could make a contribution to improving the situation.

Like many of my compatriots, I applied to Internal Medicine residency programs in the US to obtain the best possible training and the opportunity to be on the frontier of biomedical research. I was fortunate to match in the LSU program at Shreveport. One day I went to Grand Rounds and heard the Director of Bone Marrow Transplantation, Dr. Gerhard Hildebrandt speak about graft vs. host disease following stem cell transplantation. Although I didn't understand many of the concepts discussed, I became fascinated with BMT and joined Dr. Hildebrandt's research group. I started as a complete novice, but I eventually became an integral member of the research group, managing to continue my research project while working full-time as a medicine resident.

I joined the Hematology/Oncology fellowship program at the University of Utah in 2012 and pursued additional laboratory training in the development of immunotherapy for malignancy, working with Drs. Lütkens and Atanackovic. Additionally I spent a 3-month rotation with Dr. Catherine Bollard at Children's National Hospital in Washington, DC. I was fortunate to be selected for an Advanced Research fellowship year in the Division, the key to a successful application for a two-year AACR/Pfizer career development award in Immuno-oncology. I joined the Faculty of the Division of Hematology and Hematologic Malignancies in July 2017 as an Instructor in Medicine, with protected time to continue my research on developing CAR T cells targeting multiple myeloma surface antigens for future use in multiple myeloma patients.

THE TARGET AUDIENCE FOR THESE CONFERENCES IS BROAD: HEMATOLOGISTS, ADVANCED PRACTICE CLINICIANS, NURSES, PHARMACISTS AND TRAINEES.

EDUCATION OUTREACH

Our Division organizes several educational conferences during the academic year. The target audience for these conferences is broad: hematologists, advanced practice clinicians, nurses, pharmacists and trainees. We currently organize the following events:

- *Huntsman Cancer Institute Annual Hematology Review* In 2011, our Division started a one-day conference held annually in February to provide physicians, advanced practice clinicians, pharmacists and other health care providers with a comprehensive update on developments in the management of malignant and benign hematologic diseases. Topics covered include the entire spectrum of clinical hematology. Talks are given by expert faculty from the Division and invited speakers. Keynote speakers in past years included Drs. Thomas Kipps, Peter Greenberg, Elihu Estey, Martin Tallman, James Armitage, and Jerald Radich. This conference has become one of the key educational events at the Huntsman Cancer Institute. Attendance to has steadily grown over the years, with more than 150 attendees from the Intermountain West region and beyond in 2017.

- *Multiple Myeloma Symposium* This one-day conference provides an update on all aspects of the management of multiple myeloma, including diagnosis, immunotherapy, targeted therapies, transplant, and psychosocial aspects of multiple myeloma management. The mission is to give attendees an overview of recent developments in all aspects of a disease whose management is rapidly evolving. Talks are given by expert faculty from the Division's myeloma program as well as invited national leaders in the field. Invited speakers have included Drs. Kenneth Anderson, Adam Cohen, and Yi Lin.

- *Amyloidosis Symposium* This symposium is an extension of the University of Utah Amyloidosis Program. It provides a comprehensive overview of the diagnosis and management of this group of rare and challenging diseases. Talks are given by expert members of the Amyloidosis Program as well as national experts in the field. Invited speakers have included Drs. Raymond Comenzo and Daniel Nelihan. Topics cover diagnosis, treatment, and management of amyloidosis-related organ damage, including cardiac, renal, and neurologic complications.

LIFE IN UTAH

Utah is an amazing place to live. We experience four seasons and Salt Lake City's proximity to the Wasatch Mountains provides opportunity for year-round, diverse recreational activities. Utah is world famous among outdoor enthusiasts who appreciate the variety of adventures offered by the State's mountains, deserts and five national parks (along with 42 state parks). Some of us like to boast that Utah has the greatest snow on earth. One only has to experience the fluffy powder on a "Blue-Bird Day" at one of 7 world-class ski resorts within 30 minutes of downtown to appreciate the uniqueness of the area. In addition to the great outdoors, Salt Lake City has a nationally recognized symphony, dance companies, theater, NBA basketball and Major League Soccer. The internationally renowned Sundance Film Festival is an annual fixture in nearby Park City that attracts visitors from around the world. Ethnic cuisine flourishes in Salt Lake City, and the city is a clean, safe place to raise children, with excellent public and private schools.

A SIDE NOTE FROM THE CHIEF—THE RESOURCE OF TIME

When I first came to work in the US someone showed me a cartoon with the title: "Meetings – the practical alternative to real work". In our Division we are cognizant that time is our most valuable resource and recognize that all meetings must prove their value. An example is our Friday morning research conference. Organized by Dr. Chuck Parker, this has become a magnificent forum to broaden our horizons, look over the fence into unknown territory, and get inspired – and challenged. This is my personal Happy Hour of the week, and the benchmark for time well-spent. I strongly believe we must approach all meetings as a value proposition. In the end feet will follow quality, no?

University of Utah Hospital

Huntsman Cancer Institute

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