Division of Hematology
AND
Hematologic Malignancies

Αἰὲν ἄριστεύειν - Ever To Excel

Bi-Annual Report 2013 - 2014
Department Chair Greeting
John Hoidal, Chair, Department of Internal Medicine

The Division of Hematology and Hematologic Malignancies, established by Maxwell Wintrobe in the 1940s, is a core clinical and research force in the Department of Internal Medicine. As medicine is undergoing a molecular genetic transformation, our Hematology Division is at the forefront of this development, with one of the largest extramural funding portfolios in the Department and high impact publications in key journals. Just like the Department of Internal Medicine, the Division is based on a culture of excellence paired with a deep sense of collegiality. Trainees will find this environment scientifically challenging, clinically rewarding and personally gratifying. Our Department is committed to support the Division in all its endeavors to help it maintain and expand its national reputation.

Huntsman Cancer Institute Greeting
Mary Beckerle, CEO & Director, Huntsman Cancer Institute

The Division of Hematology and Hematologic Malignancies is perfectly aligned with Huntsman Cancer Institute’s (HCI) core values: commitment to excellent patient care, rigorous high quality research and an atmosphere of mutual respect and collegiality. For decades, malignant hematology has driven scientific and clinical progress in oncology as a whole and the Division continues to make major contributions to the field. As the Director and CEO of HCI, I fully recognize the importance of hematology as a key discipline of cancer medicine and I am fully committed to support the Division’s ambition to remain at the forefront of translational research in malignant blood disorders, drawing on HCI’s unique resources and its strength in basic science.
are housed at Huntsman Cancer research, clinical service, education and administration, and believe dialogue. We are committed to excellence in all aspects of our work –

We welcome different opinions and enjoy the inspiration of a dialectic open discussion and free exchange of opinions is central to our success. A collegial working environment based on mutual respect that fosters transformed by the genetic revolution, we strive to be at the forefront of 

of heme and iron metabolism. As the practice of hematology is being 

greater emphasis on malignant hematology, while preserving our research 

scaope of hematology and academic medicine. /T_his has meant placing 

proud tradition as a tertiary referral center in the rapidly changing land-

scape of the Intermountain West. Close proximity of patient facilities, research 

labs and core facilities promotes rapid and seamless transfer of sam-

ples and ideas that facilitate the translation of new knowledge and 

discoveries from the bench to the bedside and back. Members of our 

Division have published manuscripts in first tier journals that impact 

thinking in their research communities and shape clinical practice. 

As malignant hematology is driving the personalization of oncology, we 

will continue to make key contributions to the field, train the next gen-

eration of clinical and lab-based hematologists and provide the best pos-

sible care to the patients in our growing catchment area. 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 and make a difference 

in a highly collaborative environment.

Our clinical services and research facilities are housed at Huntsman Cancer Institute (HCl), one of the most beautiful and technologically advanced cancer centers in the world and the only NCI-designated cancer center in the Intermountain West. Close proximity of patient facilities, research labs and core facilities promotes rapid and seamless transfer of samples and ideas that facilitate the translation of new knowledge and discoveries from the bench to the bedside and back. Members of our Division have published manuscripts in first tier journals that impact thinking in their research communities and shape clinical practice.

As malignant hematology is driving the personalization of oncology, we will continue to make key contributions to the 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. 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 and make a difference in a highly collaborative environment.

Why Come to Utah?
Michael Deininger MD PhD

Over the past two years we were fortunate to recruit eight outstanding clinicians, clinician/scientists and research faculty, from prime institutions in the US and Europe, soundly defying the notion that Utah is difficult to recruit to. How did this happen? The most common comment I hear from potential recruits once they have visited us is “I had no idea what was available out here.” In fact, Utah seems to be one of the best kept secrets in the nation. Our facilities at the Huntsman Cancer Institute are state of the art, and there is tremendous strength at the University of Utah in areas critical to hematology: human genetics, basic life sciences, drug discovery and development, and first rate hemato-pathology delivered by ARUP, a national reference lab affiliated with the University of Utah. But that’s not all: there is advanced imaging, nanotechnology and, importantly, the Utah population database, a nationally and internationally unrivalled research tool containing thousands of multi-member pedigrees ready to be mined for disease traits and novel disease genes. However, not everything that sets us apart from other places is easy to quantify; it’s the spirit of collegiality and collaboration that permeates the Medical School, the Huntsman Cancer Institute, and our Division that makes up for what we may not have in size or name recognition.

Coming from the outside myself, I found this place unique, but with time I got to know many others who had become hooked to this environment. And there is hardly a more beautiful place to live. Salt Lake City is becoming increasingly more diverse and has all the amenities one expects from a big city and yet it takes less than an hour to be on a ski slope or to find solitude in the middle of alpine meadows at 10,000 feet. If you are thinking about picking a place for your residency or fellowship or are looking for a great opportunity to advance your career in Hematology, think Utah. You won’t be disappointed.

Our combined Hematology/Oncology Fellowship Program strives to build the careers of future leaders in the fields of Hematology and Medical Oncology. We provide comprehensive education and training in the diagnosis and treatment of patients with cancer and hematologic disorders, and train young investigators in clinical and laboratory research to prepare them for a scientific career. Our three year program encompasses comprehensive clinical and research training, supported by a strong didactic curriculum.

Clinical training encompasses 18 months of intensive clinical rotations in a variety of in- and outpatient settings at the Huntsman Cancer Institute, University Hospital and Veterans Affairs Medical Center. Throughout their training, our fellows actively participate in out-patient continuity and subspecialty and research clinics, providing strong and continuous exposure to clinical realities. We take time to teach and take pride in training our fellows to become astute physicians who provide compassionate care to their patients. At the end of their training with us, our fellows are well prepared to take their exams, and more than 90% of our fellows pass their sub-specialty boards on the first attempt. Many have moved on to successful clinical careers in academia or private practice.

Research training begins in the first year with didactics on clinical trial design, statistical analysis and cancer biology. Fellows work with first year mentors to identify an area of scholarly interest. A unique strength of our program is the research track that offers protected time dedicated to scientific pursuits, a critical feature for fellows who aspire to careers in academic medicine. A full 18 months are dedicated
Fellowship Program Experience

Srinivas Tantravahi MD - 4th year fellow

My experience in the program has been exceptional, with strong clinical and research mentorship, and extensive exposure to a wide variety of clinical scenarios. Having the research institute in close quarters with the clinic and hospital provided me a seamless connection between bench and bedside. I enjoyed strong mentorship in lab-based research and clinical hematology by leukemia experts Drs. O’Hare and Deininger. This support helped me secure a highly competitive Research Training Award from the American Society of Hematology and an additional research year. My plan is to submit an application for a larger career development award and pursue a career in clinical-translational hematology. Living in Salt Lake City is easy and enjoyable. The cost of living is low and there is excellent public transportation and lots to do in a city that is becoming more diverse by the day. Annual Sundance Film Festival, the NBA’s Utah Jazz, and of course, the extremely close proximity to world-class skiing, mountain biking, road cycling, rock climbing, and (my favorite) thousands of hiking trails. This is the best place to live for me, by a large margin.

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2014-2015

Hematology/

Srinivas Tantravahi MD - 4th year fellow

hematology by leukemia experts Drs. O’Hare

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My experience in the program has been

department and vibrant research communities

in the School of Medicine. Clinical research is

supported by the Clinical Trials Office, tu-
ror tissue repositories and disease spe-
cific clinical databases, and the Utah
Population Database affords unique op-
portunities for fellows interested in pop-
ulation-based genetic research. We also
offer an Advanced Scholars program, provid-
ing one additional year of fellowship research
training to fellows with exceptional promise

in research and leadership. Approximately 50% of our fellows
pursue careers in academia.

The research and practice environment within
the University system prides itself on mentor-

fellow and junior faculty in developing
research ideas, identifying funding sources,
and assistance in grant writing. Trainees can
expect mentoring from each faculty member
in an open and prolific Division that assists
with publication of independent research,
editors, book chapters and case reviews.

Our Division has maintained an
NIH-funded T32 training program
in Hematology for 40 years.

Our training program provides financial support for an
interdisciplinary group of five postdoctoral fellows and
six predoctoral graduate students preparing for full-time
careers in hematology-related research. Trainees work on
projects relevant to the biology of blood cells and vascular
development and function. Twenty-nine principal investi-
gators participate in our program. Laboratory projects are
complemented by coursework, research seminars, journal
clubs, laboratory meetings, and attendance at national and
international meetings. Our goal is to facilitate the training
process to assure that trainees obtain the basic knowledge
and skills required to develop and maintain a successful in-
dependent career in a hematology-focused research field.

The Training Program is administered by the Division of
Hematology and Hematologic Malignancies and includes
researchers from both clinical and basic science back-
grounds who are focused on mechanism-oriented, labo-
atory-based projects. Participating faculty hold academic
appointments in the Departments of Medicine, Pathology,
Biochemistry, Neurobiology and Anatomy, Human Genetics,
and Oncological Sciences. The Program is co-directed by
Gerald Spangrude PhD and Elizabeth Leibold PhD. Trainees
receive funding to support stipends, medical insurance, travel,
and training-related expenses. We also host an annual retreat
that features prominent visiting speakers in addition to
trainee presentations and workshops.

Faculty associated with the Training Program direct
laboratories that actively conduct research in the
areas of blood cell development; acquired and
congenital disorders of red blood cells including
polycythemia and the myeloproliferative disor-
ders; murine models of hematopoietic stem cell
transplantation; the roles of macrophages and
microglial cells in tissue maintenance and
regeneration; the effects of HIV infection
and treatment on blood cell function; the
molecular biology of heme biosynthesis
and the metabolism, storage and transport
of iron; and the molecular regulation
of copper and zinc metabolism. The
research environment is outstanding
and includes robust Core Facilities
that provide training and services.
In addition, our program incorpo-
rates a strong Research Education,
Training, and Career Develop-
ment component that is funded
through a Clinical Translational
Science Award (CTSA), as well
as an institutionally supported
group of research training and
education modules.

TRAINING PROGRAM

T32

in Hematology

Betty Leibold PhD & Jerry Spangrude PhD,
Co-Principal Investigators, Jan Christian PhD,
Mentor and Professor of Medicine
Research is central to the Division’s mission, with the research programs of past Division Chiefs including Maxwell Wintroub, George Cartwright, Jack Athens and James Kushner laying a foundation of excellence. Our overarching goal is understanding the basic biology of malignant and non-malignant hematological disorders in order to develop therapeutics for improved clinical care of patients, and spans the entire spectrum from basic to clinical-translational research. We believe that multidisciplinary research is the most promising approach to make impactful contributions and train the next generation of basic, clinical and translational investigators.

Research within the Division of Hematology and Hematologic Malignancies is facilitated by the University of Utah’s exceptionally strong research base in human genetics and medical chemistry. Human genetics at the University has been leading the discovery of cancer susceptibility genes, such as ATM, p16, and BRCA1, to name a few. The Utah Population Database is one of the world’s richest sources of family pedigrees and is linked to cancer registries, thus providing an unparalleled resource for research into cancer predisposition. Another beacon of strength is the University’s Nano Institute of Utah, which pioneers the medical application of nano-biotechnology.

Our research capabilities are greatly enhanced by high quality core facilities, pilot funding opportunities and graduate training programs.
in the life sciences, all testimony to the University Administration’s commitment to scientific pursuit. Talented investigators, excellent technical personnel, a strong research infrastructure, an outstanding graduate training program, and an exceptionally supportive administration have facilitated discoveries whose impact by far outstrips the size of the University of Utah. However, this would not be possible without the highly collegial and collaborative atmosphere at our institution that provides a stimulating and enjoyable working environment.

RESEARCH FOCI

Dennis Wings PhD & Michael Deininger MD PhD

Research in our Division is broad-based. We have chosen to highlight four research areas in this issue:

MYELOPROLIFERATIVE NEOPLASMS

The O’Hare, Pechal and Deininger laboratories study the biology and therapy of myeloproliferative neoplasms (MPNs) including chronic myeloid leukemia (CML) and Philadelphia chromosome (Ph)-negative MPNs such as polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF) and chronic myelomonocytic leukemia (CMML). Constitutive activation of tyrosine kinases is common in MPNS. Examples include BCR-ABL1, a fusion kinase derived from the Philadelphia chromosome (Ph), which causes CML and the JAK2V617F allele, which is present in almost all patients with PV and some 50% of patients with MF. Tyrosine kinase inhibitors (TKIs) such as imatinib (Gleevec) are used to treat MPNs, with various degrees of success. The Deininger/O’Hare laboratory studies TKI resistance in MPNS, particularly the role of point mutations in the target kinases and the role of the microenvironment, with the overarching goal of developing strategies to restore clinical responses. This includes the discovery of novel inhibitors to target BCR-ABL1 and other key resistance mediators such as STAT3. More recently, their lab has started to identify new drug targets in CMML and acute myeloid leukemia, using conventional and functional genetic approaches.

Dr. Pchali’s group has identified the first acquired uniparental disomy in hematological malignancies that leads to homozygosity for JAK2V617F in PV, as well as a number of disease alleles that cooperate with the JAK2 V617F mutation in the pathogenesis of PV and has implicated epigenetic mechanisms as key players. They also study the role of hypoxia and oxygen sensing in polycythemic disorders and the mechanisms underlying physiological adaptation to life at high altitude. They have identified several key genes involved in pathologic as well as physiological circumstances, for example mutations in the von Hippel-Lindau (VHL) that cause Chuvash polycythemia and recently a mutation in the EGLN1 (encoding PHD2) gene that allows Tibetans to maintain normal hemoglobin despite low oxygen tension.

TUMOR & TRANSPLANT IMMUNOLOGY

It had long been known that autologous and allogeneic immune responses to cancer cells are powerful tools to achieve long-term disease control. However, recent breakthroughs in previously untreated cancers have galvanized the field and raised hopes that cancer immunotherapy will join chemotherapy, radiotherapy and surgery as the fourth pillar of cancer therapy. Our Division is playing an active role in developing novel approaches.

We believe that multidisciplinary research is the most promising approach to make impactful contributions and train the next generation of investigators.

Cancer/testis (CT) antigens are aberrantly activated and expressed in many human cancers. The laboratory of Drs. Atanackovic and Laertkens is developing strategies to harness autologous immune responses to CT antigens for immunotherapy in myeloma and other cancers. They have also identified novel myeloma-specific antigens as potential immunological targets for specific antibodies that elicit antibody-mediated cytotoxicity for chimeric antigen receptor (CAR) T cells derived from myeloma patients. Drs. Halwani and Deborah Stephens are developing early clinical trials to test new antibodies to target lymphoma or modulate the autologous immune system such that it recognizes and eliminates malignant cells.

Dr. Michael Boyer, Gerhard Hildebrandt and Pulsipher are investigating new approaches to better control the allogeneic immune response post transplantation, thereby enhancing graft-vs-leukemia effects while attenuating graft-vs-host disease (GVHD). Dr. Boyer has established novel protocols to use regulatory T cells (Tregs) to mitigate GVHD in the setting of haploidentical transplants. Dr. Hildebrandt is studying the role of neutrophils in GVHD. Dr. Pulsipher is exploring novel drug regimens to prevent GVHD while maintaining the graft-vs-leukemia effect of allogeneic transplants.

HEMATOPOIESIS

Blood cell development is regulated by an array of highly complex mechanisms, many of which are dysregulated in hematologic malignancies. Understanding the physiology of hematopoiesis provides a platform for understanding and treating blood cancer. Bone morphogenetic proteins (BMPs) are key signaling molecules in development and hematopoiesis. Dr. Jan Christian’s lab is elucidating how BMPs are processed to regulate their downstream targets and signaling pathways to inform hematopoietic stem cell (HSC) development. Dr. Gerald Spangrude has identified several intermediate stages in HSC maturation and developed protocols to track lymphoid cell development. He is also developing strategies to reconstitute brain microglial cells through transplantation of HSCs.

HEME, IRON AND MITOCHONDRIA

The regulation of iron metabolism in health and disease is a long-standing interest of our Division and spans a wide spectrum from basic biochemistry to clinical applications. Drs. John Phillips and Charles Parker are developing new therapeutic strategies for porphyria patients by attenuating the function of delta-aminolevulinate synthase through depletion of its cofactor pyridoxal phosphate. Dr. Betty Leibold is studying the role of iron regulatory proteins 1 and 2 in mammalian iron metabolism. Dr. Dennis Wings’ group is studying the pathway of heme trafficking in cells and the biogenesis of mitochondrial respiratory complexes. His group has identified a series of assembly factors that mediate the biogenesis of these complexes. Of particular interest is the succinate dehydrogenase (SDH) complex, as SDH deficiency is involved in the pathogenesis of many cancers.

Other areas of active research are the antiangiogenic properties of ADAMTS13, the protein deficient in thrombotic thrombocytopenic purpura (Dr. George Rodgers’ lab), development of nitric oxide (NO) donors to treat acute myeloid leukemia (Dr. Shami’s lab) and the genetic predisposition to chronic lymphocytic leukemia (Dr. Martha Glenn).

RECENT RESEARCH GRANTS

Extramural competitive research funding in the Division exceeded $6.4 million in 2014 and is expected to increase to $7.4 million in 2015. Dedicated administrative staff from the University of Utah Office of Sponsored Projects, Division or HCI guide submission of research grants by our faculty and provide grants management support. Our success in securing extramural grants is based on our strong research faculty and our ability to provide scientifically rigorous feedback in a collegial and collaborative atmosphere. This has led to several new awards in 2014:

• Dr. Dennis Winge received a new NIH R01 to investigate the biogenesis of succinate dehydrogenase (SDH) and its role in disease. SDH is deficient in a range of cancers.

• Drs. Thomas O’Hare and Michael Deininger received a large, new, principal investigator NIH/NCI R01 to study ponatinib resistance in chronic myeloid leukemia.

• Drs. Dijorde Atanackovic and Tim Laertkens along with Drs. Michael Deininger and Tom O’Hare received an award from the Myeloproliferative Neoplasms Foundation to develop T cells expressing chimeric antigen receptors against calreticulin to treat myelofibrosis.
• Dr. John Phillips received NIH funding to study genetic modifiers of iron disorders in conjunction with the University of California Irvine and the Porphyria Clinical Research Consortium led by investigators at Mount Sinai Hospital.

• Drs. Thomas O’Hare and Michael Deininger received a V Foundation award to study CMML genetics and clonal evolution.

• Dr. Michael Pulsipher is a Co-PI on a new R01. In collaboration with St. Jude’s Children’s Hospital, they study the role of killer cell immunoglobulin-like receptors haplotypes in hematopoietic cell transplantation for acute myeloid leukemia.

• Dr. Jo-Anna Reems received an award from the Utah Cluster Acceleration Program for the Cell Therapy and Regenerative Medicine facility. This facility provides hematopoietic stem and progenitor cells to support the Division’s blood and marrow transplantation service.

KEY PEER-REVIEWED PUBLICATIONS

Recent high impact publications with key roles of Division investigators include:

• Dr. Jan Christian reported that bone morphogenetic protein 4 (BMP4), a protein essential to organ development, is synthesized as a precursor and requires proteolytic processing for activation [Tilak et al. (2014) “Simultaneous rather than ordered cleavage of two sites within the BMP4 prodomain leads to loss of ligand in mice” , Development 141, 3062-71].

• Dr. Gerhard Hildebrandt showed that recruitment of neutrophils to sites of GVHD is dependent on microbial flora and that depletion of neutrophils reduced GVHD-related mortality in mice [Schwab et al. (2014) “Neutrophil granulocytes recruited upon translocation of intestinal bacteria enhance graft-versus-host disease via tissue damage”, Nat. Med. 20, 648-54].

• Dr. Michael Deininger reported the results of the successful phase I study of ponatinib in CML patients with resistance to multiple TKIs [Cortes et al. (2012) “Ponatinib compound mutations in combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemias”, Cancer Cell 8, 428-42].

• Drs. Thomas O’Hare and Michael Deininger discovered that compound mutations in BCR-ABL1 confer resistance to all approved TKIs, including ponatinib. This work has major clinical/translational implications for the management of patients with advanced CML [Zabriskie et al. (2014) “BCR-ABL1 compound mutations in combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemia”, Cancer Cell 8, 428-42].

• Dr. John Phillips showed that acute hepatic porphyria can be mitigated by a single injection of an siRNA targeting 5-aminolevulinic acid synthase, thereby attenuating the level of neurotoxic porphyrins [Yasuda et al. (2014) “RNAi-mediated silencing of hepatic Alas1 effectively prevents and treats the induced acute attacks in acute intermittent porphyria mice”, Proc. Natl. Acad. Sci. USA 27, 777-82].

• Drs. Josef Prchal and Sabina Swierczek revealed in a seminal paper the genetic mechanism of high altitude adaptation of Tibetans, following his previous identification of three genetic determinants associated with the decreased hemoglobin levels in this population group [Lorenzo et al. (2014) “A genetic mechanism for Tibetan high-altitude adaptation”, Nat. Genet. 46, 951-6].

• Dr. Michael Pulsipher published results of a phase III COG trial on the role of mTOR inhibitors used during bone marrow transplantation for acute lymphoblastic leukemia (ALL) [Pulsipher et al. (2014) “The addition of sirolimus to tacrolimus/methotrexate GVHD prophylaxis in children with ALL: a phase 3 Children’s Oncology Group/Pediatric Blood and Marrow Transplant Consortium trial”. Blood 123, 2017-25].

• Dr. Dennis Winge reported the discovery of a novel assembly factor for succinate dehydrogenase. SDHAF3 collaborates with a related factor SDHAF1 in the maturation of the iron-sulfur subunit of SDH. In the absence of these two factors, succinate dehydrogenase biogenesis is impaired and the assembly pathway is hypersensitive to endogenous oxidants [Na et al. (2014) “The LYR factors SDHAF1 and SDHAF3 mediate maturation of the iron-sulfur subunit of succinate dehydrogenase”, Cell Metab. 20, 253-66].
Thomas J. O’Hare, Ph.D., is an Associate Professor of Medicine (Research) in the Division of Hematology and Hematologic Malignancies. The bedrock of Dr. O’Hare’s training is bioorganic chemistry and mechanism-based inhibitor design, providing an excellent opportunity for team science with his close clinical and scientific collaborator, HCI Investigator, Dr. Michael Deininger. Together, they are designing patient-tailored therapeutic strategies for blood cancers and beyond. The team’s research program centers on target discovery and inhibitor development for leukemia, mechanism-based targeting of leukemic cells, including leukemic stem cells, and design and validation of function-first profiling technologies for new therapeutic targets. They have a longstanding interest in tyrosine kinase inhibitor (TKI) resistance in Philadelphia chromosome-positive (Ph+) leukemia, including resistance to the most advanced TKI, ponatinib. Two recent projects focusing on clinically problematic resistance mechanisms in Ph+ leukemia highlight the O’Hare/Deininger team science approach.  

(1) In patients with Ph+ leukemia, control of TKI resistance due to BCR-ABL1 single mutants is now achievable, but the ability of approved TKIs to target BCR-ABL1 compound mutants, defined as two mutations in the same BCR-ABL1 molecule, has yet to be investigated. Their 2014 study revealed that BCR-ABL1 compound mutations impart various levels of TKI resistance, underscoring the need for definitive sequencing screens to distinguish these from polyclonal mutations and suggesting that optimal therapy selection for patients harboring compound mutations will improve disease control in Ph+ leukemia. This resistance mechanism is operative in other clinical resistance scenarios such as FLT3-driven acute myeloid leukemia and EGFR or ALK mutation-driven non-small-cell lung cancer.

(2) Some CML patients relapse despite continued suppression of BCR-ABL1 kinase activity. They identified activation of STAT3 as an essential feature of BCR-ABL1 kinase-independent TKI resistance. By combining synthetic chemistry, in vitro reporter assays, molecular dynamics-guided rational inhibitor design and high-throughput screening, they discovered BP-5-087, a potent and selective STAT3 SH2 domain inhibitor that reduces STAT3 phosphorylation and nuclear transactivation. Mass spectrometry/deuterium exchange experiments established direct engagement of STAT3 by BP-5-087 and provided a high-resolution view of the STAT3 SH2 domain/BP-5-087 interface. In primary cells from CML patients with BCR-ABL1 kinase-independent TKI resistance, BP-5-087 restored TKI sensitivity. These findings implicate STAT3 as a critical signaling node in BCR-ABL1 kinase-independent TKI resistance and suggest that BP-5-087 has clinical utility for treating a range of malignancies characterized by STAT3 activation.


2. Eiring et al., Combined STAT3 and BCR-ABL1 Inhibition Induces Synthetic Lethality in Therapy-Resistant Chronic Myeloid Leukemia, Leukemia. 2014 Aug 19. [Epub ahead of print]
The Health Sciences Center (HSC) of the University of Utah operates 16 core facilities (http://www.cores.utah.edu/) administered through a central office in the School of Medicine. These facilities offer both advanced technologies and equipment beyond that found in individual laboratories. The goal of the Cores is to make technology and expertise available to all faculty members and students. The institutional view is that support for core facilities is the single best way that institutional funds can be used to promote the University’s research mission. Each Core has a faculty advisory committee to determine the feasibility of the current Cores and considers establishment of new Cores. Each Core has a faculty advisory committee to provide guidance on equipment maintenance, service contracts, services offered, new equipment needs and staff support. An annual survey provides information to the administrative bodies to align services offered, pricing and equipment availability with the needs of the users. The central administration of the Cores provides a consistent method for payment. Researchers set up an account with the central office, and all services and equipment use are billed directly through the central office, making it easy and efficient to track the use of facilities by PIs, and their laboratory personnel.

for Health Sciences, with additional funds through the Vice President for Research to support service contracts. A dedicated oversight committee determines the feasibility of the current Cores and considers establishment of new Cores. Each Core has a faculty advisory committee to provide guidance on equipment maintenance, service contracts, services offered, new equipment needs and staff support. An annual survey provides information to the administrative bodies to align services offered, pricing and equipment availability with the needs of the users. The central administration of the Cores provides a consistent method for payment. Researchers set up an account with the central office, and all services and equipment use are billed directly through the central office, making it easy and efficient to track the use of facilities by PIs, and their laboratory personnel.

Our Division currently has approximately 20 active therapeutic trials in hematologic malignancies. The trials cover diverse entities such as acute and chronic leukemias, myelodysplastic syndromes, myeloproliferative disorders, lymphoid disorders such as CLL, non-Hodgkin and Hodgkin lymphoma, and bone marrow transplantation. Our studies encompass early phase and randomized phase III trials, investigator-initiated studies (ISTS), and industry-sponsored and intergroup studies. The emphasis is on early phase trials using novel targeted agents and ISTs. For instance, we currently run phase I/II trials with antibodies against CD38 in multiple myeloma and against CD33 in AML, and with novel inhibitors against JAK2 in MPNs. The current trial list is available at healthcare.utah.edu/huntsmancancerinstitute/clinical-trials. Trials selected by individual investigators are discussed within disease groups and presented on a monthly basis to the Hematology Multidisciplinary Group. Studies are prioritized on the basis of multiple criteria, including scientific and academic merit, and the originality of therapeutic agents or combinations of agents. The priority is given to ISTs and to early-phase clinical trials with a translational component. The studies then undergo institutional review at the Huntsman Cancer Institute and the University. Clinical research is supported through the Clinical Trials Office of the Huntsman Cancer Institute, which provides regulatory and contractual support as well as dedicated research coordinators, nurses and data managers.

### Clinical Trials

**Division of Hematology**

**Tibor Kovacsiovics MD, Director of Clinical Research**

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RESEARCH HIGHLIGHT

Immunotherapy for Multiple Myeloma

Dr. Djojde Atanackovic is Director of the Myeloma Program & Cancer Immunology at Huntsman Cancer Institute. His research group is focused on multiple myeloma (MM), which is the second most common hematologic malignancy, causing more than 10,000 deaths per year in the U.S. alone. Significant responses can be induced in most myeloma patients during the initial phases of therapy. However, MM is still considered incurable and most patients will eventually suffer a fatal relapse. This is due to the persistence of chemotherapy-resistant precursor cells in the bone marrow even after destruction of the bulk of tumor. Dr. Atanackovic’s group is pursuing immunotherapeutic approaches to destroy the tumor bulk as well, as MM-promoting precursors and eventually achieve cures.

One approach involves the adoptive transfer of chimeric antigen receptor T cells (CARs). CARs are a new class of artificial T cell receptors utilizing a single-chain variable fragment for antigen recognition on the surface of target cells. Early phase clinical trials have demonstrated a high efficacy of CARs against different hematologic malignancies. Dr. Atanackovic’s group developed CAR constructs targeting a variety of molecules expressed on tumor cells by primary T cells transduced with these constructs. In addition, they are developing an MM-based CAR T cell library for the rapid development of novel CAR scaffolds. They also developed an efficient system for the cloning and transduction of antigen-specific TCR genes into autologous human T cells and the knockdown of native TCR genes using TAL effector nucleases. Currently, they are working on identifying clinically relevant T cell responses against a variety of myeloma-related antigens in order to determine the most promising TCR for the transduction and adoptive transfer into patients with MM.

Finally, Dr. Atanackovic’s group recently demonstrated that IL-16 is an important growth-promoting factor for MM and that targeting IL-16 inhibits the growth of MM cells and their precursors, defining IL-16 as a highly attractive therapeutic target in MM. They are developing a fully human monoclonal antibody against IL-16 to neutralize IL-16 in vivo. This is the first time that IL-16 has been targeted in a human cancer and their newly developed monoclonal antibody directed against this cytokine has the potential to improve therapies for MM and possibly also other types of cancer.


BENIGN HEMATOLOGY

Our mission is to deliver coordinated, multispecialty care, for patients with non-malignant hematologic disorders...

Hematology has been a premier Division of the University of Utah School of Medicine since its inception. The internationally acknowledged accomplishments and mentorships of current and past Hematology faculty members are an asset for hematologic training. Past Division Chiefs, Max Wintrobe, George Cartwright, Jack Athens, and James Kushner, were all internationally recognized leaders in Hematology. Especially noteworthy is the pioneering work done in Utah on the role of iron in health and disease, and the first description of the compartments and kinetics of neutrophils (Athens). The current faculty continues to be active and highly accomplished in iron research from bench (Drs. Elizabeth Leibold and John Phillips) to bedside (Drs. Josef Prchal, Charles Parker and George Rodgers III). Dr. Parker’s pioneering work laid the ground to our understanding of paroxysmal nocturnal hemoglobinuria pathophysiology. Dr. George Rodgers is nationally acknowledged for his contributions to the clinical and laboratory aspects of bleeding and thrombotic disorders. He is highly accomplished as an educator and highly respected as a consultant. Dr. Prchal’s translational research in erythrocyte enzymes, and cytoskeleton, iron metabolism, and congenital polycythemia was inspired by his patient’s phenotypes. His work on the molecular basis of congenital polycythemias has been extended from identification of dominantly inherited polycythemia with low erythropoietin due to gain-of-function erythropoietin receptor mutations to the evolutionary adaptation of Tibetans and other highlanders to hypoxia. He enjoys interacting with fellows as evidenced by recognition as the director of NIH awarded T32 training grants at University of Alabama Birmingham and Baylor College of Medicine in the past. Danielle Nance is a new faculty member, bringing with her expertise in rare bleeding disorders, specifically the biology of FVII deficiency, and the changing landscape of the care of bleeding and clotting disorders.

Our mission is to deliver coordinated, multispecialty care for patients with non-malignant hematologic disorders including patients with hemophilia, other inherited or acquired bleeding and thrombotic disorders, and red cell disorders. We foster close relationships with our patients within the entire Intermountain West. Given the broad geographic area, we actively collaborate with providers throughout the region. Compassionate patient care is central to the core mission of the Benign Hematology group, and faculty members actively participate in the Institution’s commitment to patient safety and practice improvement programs.

HEMATOLOGY

RESEARCH HIGHLIGHT

Immunotherapy for Multiple Myeloma

Dr. Djojde Atanackovic is Director of the Myeloma Program & Cancer Immunology at Huntsman Cancer Institute. His research group is focused on multiple myeloma (MM), which is the second most common hematologic malignancy, causing more than 10,000 deaths per year in the U.S. alone. Significant responses can be induced in most myeloma patients during the initial phases of therapy. However, MM is still considered incurable and most patients will eventually suffer a fatal relapse. This is due to the persistence of chemotherapy-resistant precursor cells in the bone marrow even after destruction of the bulk of the tumor. Dr. Atanackovic’s group is pursuing immunotherapeutic approaches to destroy the tumor bulk as well, as MM-promoting precursors and eventually achieve cures.

One approach involves the adoptive transfer of chimeric antigen receptor T cells (CARs). CARs are a new class of artificial T cell receptors utilizing a single-chain variable fragment for antigen recognition on the surface of target cells. Early phase clinical trials have demonstrated a high efficacy of CARs against different hematologic malignancies. Dr. Atanackovic’s group developed CAR constructs targeting a variety of molecules expressed on tumor cells by primary T cells transduced with these constructs. In addition, they are developing an MM-based CAR T cell library for the rapid development of novel CAR scaffolds using phage display. One of the central problems of CAR T cells is on-target and off-tissue reactivity leading to cross-reactivity with healthy tissues expressing the same antigen. They are in the process of developing strategies to prevent auto-reactivity in the framework of CAR T cell therapy. A second approach being taken is an adoptive transfer of T cells expressing transgenic tumor-specific TCRs. Naturally occurring T cell responses against tumors rely on recognition of intracellular antigens presented on the tumor surface as small peptides in the HLA context by an endogenous T cell receptor (TCR). The transduction of tumor-specific TCR into primary patient-derived T cells enables them to generate large numbers of functionally superior and cancer-reactive T cells for adoptive transfer. They developed an efficient system for the cloning and transduction of antigen-specific TCR genes into autologous human T cells and the knockdown of native TCR genes using TAL effector nucleases. Currently, they are working on identifying clinically relevant T cell responses against a variety of myeloma-related antigens in order to determine the most promising TCR for the transduction and adoptive transfer into patients with MM.

Finally, Dr. Atanackovic’s group recently demonstrated that IL-16 is an important growth-promoting factor for MM and that targeting IL-16 inhibits the growth of MM cells and their precursors, defining IL-16 as a highly attractive therapeutic target in MM. They are developing a fully human monoclonal antibody against IL-16 to neutralize IL-16 in vivo. This is the first time that IL-16 has been targeted in a human cancer and their newly developed monoclonal antibody directed against this cytokine has the potential to improve therapies for MM and possibly also other types of cancer.


HEMATOLOGY

Dr. George Rodgers III, Danielle Nance, Charles Parker & Josef Prchal

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The Utah Blood and Marrow Transplant Program is a combined adult and pediatric hematopoietic cell transplant (HCT) program, and was established in 1991.

The program has been FACT (Foundation for the Accreditation of Cellular Therapy) certified since 1998. It is the only university-based HCT program in the Intermountain West region, primarily serving Utah, Nevada, Idaho, Wyoming, Western Colorado and Montana.

There are currently seven faculty members in the transplant program, including BMT specialists and leukemia experts. Other team members include experienced Advanced Practice Clinicians, HCT pharmacists, transplant coordinators, nurse coordinators, a specially trained nursing team and support staff to focus on the unique needs of our patients.

Fellows in the Hematology/Oncology fellowship program are exposed to clinical HCT both inpatient and outpatient, supported by a structured lecture curriculum and weekly educational conferences.

In 2014, we performed more than 140 autologous and allogeneic transplants. Donors include matched related donors, mismatched unrelated donors and alternative donor sources such as cord blood and haploidentical transplants. The program is active in clinical trials, both investigator-initiated trials and as part of the BMT Clinical Trials Network (BMT CTN). Our faculty members participate in several national/international organizations, such as NCCN panels CIBMTR, NIH Chronic GVHD Interest Group and German/Swiss/Austrian GVHD Interest Group, and are active in both clinical and translational research. Results have been published in top peer-reviewed journals, including Blood and Nature Medicine.

To date, the program has performed more than 2200 transplants.

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Josef Prchal is Professor of Medicine in the Division of Hematology and Hematologic Malignancies. His research is focused on mutations associated with polycythemia disorders. Polycythemia can be caused by altered oxygen sensing, which can enhance erythropoietin production. Dr. Prchal discovered that mutations in the von Hippel-Lindau gene within the Chuvash Russian population lead to polycythemia. Recently, he turned his attention to Tibetans, who thrive in the thin air of the Tibetan Plateau. He and his colleagues identified a novel mutation in the EGLN1 gene that contributes to the Tibetans’ ability to live in low oxygen conditions without the complications of erythrocytosis. This study published in Nature Genetics reveals that this mutation happened approximately 8,000 years ago. Despite this relatively short time period on the scale of human history, 88% of Tibetans carry this variation, while it is virtually absent from closely related lowland Asians. The variation’s rapid rise in a selective population indicates it endows its carriers with an advantage for living in high altitude.

Dr. Prchal collaborated with experts throughout the world, including Peppi Koivunen from Biocenter Oulu in Finland, to uncover the Tibetan advantage. In those without the adaptation, low oxygen causes their blood to become thick with oxygen-carrying red blood cells, which can cause long-term complications such as heart failure. The researchers found that the newly identified genetic variation protects Tibetans by decreasing an over-response to low oxygen. The EGLN1 variation likely causes other changes to the body that have yet to be understood. Plus, it is one of a constellation of as of yet unidentified variations that collectively support life at high altitudes.

Prchal says the implications of the research extend beyond human evolution. Because oxygen plays a central role in human physiology and disease, a deep understanding of how high altitude adaptations work may lead to novel treatments for various diseases, including cancer. “There is much more that needs to be done, and this is just the beginning,” he said.

The Cell Therapy and Regenerative Medicine (CTRM) Program at the University of Utah was originally established to support the Utah Blood and Marrow Transplant Program. We are facilitating the delivery of some of the world’s most advanced cellular therapies for treating patients with a variety of neoplastic and degenerative diseases.

In addition to providing stem cell products to treat adult and pediatric patients diagnosed with leukemia, lymphoma, aplastic anemia or other types of blood disorders, the CTRM is working with academic and industrial partners to deliver new treatments for degenerative disc disease, chronic myocardial ischemia, advanced renal carcinoma, stroke, Lou Gehrig’s disease and Crohn’s disease.

Given the predictions that the emerging field of regenerative medicine will revolutionize the practice of medicine, the CTRM facility is working to bridge the efforts of basic researchers, bioengineers and the medical sciences to launch new therapeutic products. The CTRM facility has assembled the expertise and infrastructure to address complex regulatory, financial and manufacturing challenges associated with delivering innovative cell and tissue-based products. As a result of these efforts, in 2014 CTRM staff facilitated the opening of a clinical trial to treat patients with high risk hematologic malignancies with modulated haploidentical transplants. In the next several months we will launch two new tissue based products to treat wounds and joint ailments. Recognizing the value of regenerative medicine and the efforts that have already been put into the CTRM program, the program was recently award funds from

Administration
Amy Tanner MPH, MHA
Associate Director, Division of Hematology and Hematologic Malignancies

Our administrative staff is committed to providing support to Division faculty in all of their various functions starting at the moment of application to a faculty position and throughout the faculty member’s career. Every faculty member is provided secretarial support to assist with document preparation, scheduling, travel planning, mail, course material preparation, retention, promotion and tenure material preparation, IT assistance, reimbursements, etc. Research support is available for both pre and post award management. Clinical support includes assistance with credentialing and renewal applications, reviews of billing, transcription service, white coat cleaning, and clinic schedule assistance.

Huntsman Cancer Institute medical assistants, nurses, and advanced practice clinicians assist our faculty in their clinical practice. The administrative team is led by Amy Tanner, Associate Director, who is responsible for oversight of day-to-day operations, budgeting, human resources, recruitment, and issues related to any of the clinical, education, or research missions. Other team members are Jenny Ottley (Administrative Officer), Abby Rooney (Program Coordinator), Janet Hood (Research Administrator), and Heidi Andrew (Accounting Specialist).

Facilities
Amy Tanner MPH, MHA
Associate Director, Division of Hematology and Hematologic Malignancies

Clinical care is delivered mainly at the Huntsman Cancer Institute, which provides 100,000 highly specialized cancer treatments each year. The cancer hospital at Huntsman Cancer Institute has 101 private rooms (including 16 intensive care rooms and 25 bone marrow transplant rooms), 40 outpatient exam rooms, and 36 infusion bays. The hospital offers beautiful views overlooking Salt Lake Valley and the surrounding mountains to provide care to cancer patients in the most pleasant environment possible. Clinical facilities are within 2-3 minutes walking distance of research facilities, enabling seamless transfer of samples and information from the clinic to the lab and vice versa. Division research laboratories are housed in state-of-the-art research space in the School of Medicine or the Huntsman Cancer Institute. HCI is one of 25 National Comprehensive Cancer Network member institutions and offers the only phase I program in the Intermountain region. The Institute is housed in a beautiful and highly functional 673,000 square foot building. An expansion doubling the facility’s research space is currently underway. When completed, it will accommodate 35 new research teams and bring together the entire Hematology faculty in one location.
As one considers the compelling list of reasons for coming to Utah for training or academic advancement, one needs not look far to find an other unique feature—lifestyle.

The University of Utah, located in Salt Lake City and the flagship academic institution of the state, sits on the western foothills of the Wasatch Front, with a backdrop of towering mountains and captivating views of the Salt Lake Valley. Our 1,500 acre campus, with over 25,000 students representing all 50 states and many foreign countries, provides career opportunities to more than 2,000 clinical, adjunct, research, and visiting faculty.

A beautiful, safe, and vibrant city, Salt Lake combines the amenities of a major metropolitan area with the friendliness of a small city. Salt Lake City is frequently listed by national magazines and websites among the "best places to live" due to its outstanding recreational value, excellent business environment, pleasant climate and low crime rate. Major businesses have moved into Salt Lake City and the Valley, attracting an increasingly diverse populace. The Salt Lake International Airport is just minutes from downtown and is connected with University Hospital and Huntsman Cancer Institute by the city's ever-expanding light rail transit system.

Recreational opportunities abound with several professional sports teams (NBA's Utah Jazz, Real Salt Lake soccer, and baseball's Triple A Salt Lake Bees), lively entertainment and night life, diverse dining options, shopping, and a rich cultural scene featuring a symphony, opera, ballet, theater, and museums.

At an elevation of 4,330 feet above sea level, Salt Lake is the gateway to Utah's famous landscapes and outdoor recreational areas. As an internationally renowned ski destination, the city hosted the 2002 Olympic Winter Games, and skiers continue to flock to Utah to enjoy the "greatest snow on earth." In addition to its 14 ski resorts—a majority of which are located within 30 minutes to an hour of Salt Lake—Utah boasts five scenic national parks—Arches, Zion, Bryce, Canyonlands and Capitol Reef, all well known for their pristine environment and wonders in red sand stone.

Utah also has a variety of golf courses allowing for year-round play, hundreds of miles of hiking and biking trails, picturesque Lake Powell, and numerous other outdoor activities. For a quick getaway, the historic mining town of Park City is just a 30-minute drive from Salt Lake.

It's no wonder that those who experience what it's like to stay here for any length of time, keep coming back or make it their permanent home.
VISIT US

We Invite You to visit us at the Division of Hematology and Hematologic Malignancies and the University of Utah and see first hand our thriving community and rich medical heritage. Contact our office at (801) 585-3229 and we’ll be pleased to assist you in arranging a visit, and provide you with any additional information you are seeking.

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Living in Salt Lake City is easy and enjoyable. The cost of living is low, there is excellent public transportation, and lots to do in a city that is becoming more diverse by the day.