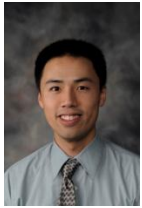


On this page we describe current and recent fellow research projects to highlight the variety of research opportunities (clinical, laboratory, quality improvement) in oncology, hematology and stem cell transplant/immunology.

The table presents a summary of research mentors and areas of research our fellows have participated in during the last 8 years.

Applicants to our fellowship program are encouraged to explore individual [UT Southwestern Faculty pages](#) for each of these faculty mentors for further information regarding their research activities and interests.

## Summary of Fellows' Research



### **Kenneth Chen, M.D. (2010-2013)**

Germ cell tumors (GCTs) are cancers of the testis, ovary, or extragonadal sites that occur in infants, children and adults. Cisplatin-based chemotherapy regimens have been successful in GCTs for decades, but they still fail to cure 20% of patients. Also, although GCTs in young children are biologically distinct from GCTs in adolescents and adults, currently there is no viable alternative to cisplatin-based therapy in young children, and there is little understanding of the biological and genetic differences that play a role in childhood GCTs. Currently, there are no known molecular markers to predict clinical behavior of GCTs. I will be conducting whole exome sequencing on frozen tumor samples along with matched germline DNA to look for point mutations and insertion/deletions which may drive GCT differentiation and pathogenesis. In addition, I will be interrogating a much larger number of GCTs which are housed as formalin-fixed, paraffin-embedded tissue samples using a molecular inversion probe microarray which can detect copy number variation and loss-of-heterozygosity events common to GCTs. In correlation with histology and clinical outcomes, this information may identify candidate genetic aberrations that could be used to refine risk stratification in future clinical studies.



### **Wilson File, M.D. (2010-2013)**

Communication is the foundation of a good therapeutic relationship between the patient and physician, and is considered a core competency by the American Council of Graduate Medical Education (ACGME) and American Board of Medical Specialties (ABMS). Effective communication has been clearly linked to patient/physician satisfaction, adjustment to illness and improved medical decision making. Despite the emphasis by governing boards and growing body of research to support its positive effects, few educational programs exist in post-graduate training programs to teach effective communication skills.

The primary aim of this project is the development of an educational curriculum for pediatric hematology/oncology fellows, to teach the skills necessary in effective communication with patients and their families. The curriculum will focus on the communication at the time of diagnosis, the enrollment of patients on clinical trials (including phase I studies) and the transition from curative therapy to palliative care. We believe that communication training will improve fellow confidence in the ability to lead these conversations and will improve patient care throughout all phases of the pediatric cancer experience.



**Kasey Leger, M.D. (2010-2013)**

The use of anthracycline chemotherapy in treating childhood cancer has led to dramatic improvements in cancer survival. Unfortunately, the cardiovascular complications of anthracyclines are far reaching, with cardiac events comprising the second most common cause of death in childhood cancer survivors. Currently we are unable to detect signs of cardiac remodeling and dysfunction early, prior to the onset of irreversible changes, thus our attempts at intervention are largely unsuccessful. My research is focused on exploring novel biomarkers useful for early detection of anthracycline-induced cardiac injury in children. My translational project, performed in collaboration with UT Southwestern cardiologists and the Cardiology Clinical Research Database (CCRD), will explore the role of regulators of gene expression and important cellular processes in the heart's response to stress. An enhanced understanding of these signals may herald sub-clinical cardiac injury, allow for early intervention, and reduce the burden of cardiotoxicity among childhood cancer survivors.



**Rachel Thienprayoon, M.D. (2010-2013)**

Pediatric palliative care is a comprehensive system of care aimed at preventing or relieving symptoms and suffering caused by a life-threatening illness. At the end of life, hospice is an important provider of palliative care. The goal of this study is to identify factors that are associated with hospice use in pediatric oncology, about which little is known. Although cure rates have dramatically increased in pediatric cancer, palliative care and hospice are an integral part of caring for the patients who do not survive. A better understanding of why parents and patients choose hospice can help improve the care of pediatric oncology patients at the end of life.



**Raven Cooksey, M.D. (2009-2012)**

Brain tumors are the second most common form of cancer during childhood. In the United States, an estimated 2200 children and adolescents are diagnosed with a brain tumor annually. With current five-year survival rates of 73.3% for children with brain tumors, the majority of these will become long-term survivors. Numerous treatment modalities are utilized in the care of children with brain tumors, namely surgery, chemotherapy, and radiation. Survivors may be at increased risk for specific late effects, including: neurocognitive deficits, endocrine deficiencies, growth failure, and stroke. These late effects can have dramatic effect on quality of life and life expectancy. A growing body of literature suggests that cranial radiation also portends an increased risk for early development of cardiovascular risk factors (dyslipidemia, central obesity, hypertension) and insulin resistance. This constellation of findings cluster into what is known as metabolic syndrome, and is associated with an increased risk for type II diabetes mellitus and atherosclerotic disease. Metabolic syndrome may represent the connection between childhood cancer survivorship and increased long-term risk of cardiovascular disease associated with significant morbidity and mortality, specifically in survivors treated with cranial radiation. My study will evaluate a cohort of brain tumor survivors treated with radiation for components of the metabolic syndrome. They will be compared to a group of survivors who did not receive cranial radiation. Our primary aim is to compare the frequency of metabolic syndrome between these two groups. Secondary aims include evaluating the individual components of metabolic syndrome, as well as investigation of novel biomarkers of insulin resistance and chronic inflammation in these two groups.



**Scott Furlan, M.D. (2009-2012)**

Pattern recognition receptors (PRRs) are proteins found in cells of the innate immune system that recognize pathogen-associated molecular patterns and initiate intracellular signals that upregulate transcription of genes responsible for an immediate immune response to infection. Preliminary work in our laboratory has shown that mice deficient in a critical signaling element of a subset of PRR family, the Toll-like receptors (TLRs), fail to expand their white blood cells normally in response to

infection. This observation lends itself to the notion that PRRs are not only able to recognize pathogens, but can also alter hematopoiesis.

- Determine the role of the PRRs in regulating hematopoiesis during viral and bacterial infections.
- Characterize PRR interaction between bone marrow stromal cells and hematopoietic precursors during acute infection.
- Evaluate the transcription of PRR-dependent cytokines and hematopoietic growth factors during acute infection.



**Carrie Laborde, M.D. (2009-2012)**

Lymphoblastic leukemia/lymphoma is the most common hematologic malignancy in children comprising 25% of all cancers in children. Central nervous system adverse events occur in 5-18% of all these patients excluding those with primary CNS disease. Events include methotrexate neurotoxicity, posterior reversible encephalopathy syndrome, hypertensive encephalopathy, ischemic or hemorrhagic stroke, and central sinovenous thrombosis.

It is hypothesized that all pediatric leukemia/lymphoma patients are at risk for an impaired neurocognitive function compared to the general population. Areas such as learning, working memory and concentration may be affected. Even so, it is not standard to routinely perform neurocognitive testing on all children after completion of therapy. Identified risk factors include younger age, female gender and certain therapies, like cranial radiation; however, little is known about the contribution of an acute CNS event during therapy on long-term neurocognitive outcome. Current research is ongoing to identify ways to adjust leukemia/lymphoma treatment to limit potential neurotoxicity without impairing survival. I aim to identify the long-term neurocognitive burden of acute CNS events with the goal of improving screening and interventions for these children. I hypothesize that children with CNS events during therapy will have a worse neurocognitive outcome compared to those that have not had events.

I will conduct a retrospective review of all leukemia/lymphoma patients in our institution over the past 10 years to determine the timing of CNS events, associated medications, presenting symptoms and current status. Patients identified with CNS events at least one year prior to enrollment and who have completed therapy will be asked to participate in this study and undergo testing of intellectual and adaptive functioning using the validated Adaptive Behavioral Assessment Evaluation and Wechsler Intelligence Test. Control groups will include leukemia/lymphoma patients without CNS events and patients without cancer but have had sinovenous thrombosis or stroke. By including a group of patients at risk for neurocognitive dysfunction, such as children with a history of stroke but not cancer, we may be able to generalize these results beyond lymphoma/leukemia patients in future studies.



**Ellen Plummer, M.D. (2009-2012)**

Iron deficiency anemia remains one of the leading mineral deficiencies worldwide, affecting nearly 700,000 toddlers and 7.8 million females of reproductive age in the United States. In addition to the symptoms associated with iron deficiency anemia such as fatigue and increased work demand on the heart, this condition has adverse effects on cognitive abilities with potentially lasting ramifications. While oral iron therapy is the initial treatment of choice, approximately 20% of patients fail to have an adequate response to this mode of iron delivery, primarily due to poor compliance and/or untoward side effects such as upset stomach and constipation. For those patients who are poorly responsive to oral iron therapy, investigation into alternative methods of iron delivery is needed to help correct the condition and prevent complications. Intravenous iron offers a potentially safe and effective alternative. Historically high molecular weight iron dextran has been avoided secondary to risk of anaphylaxis, however, newer preparations of intravenous iron exist. Based on studies in patients with chronic kidney disease, inflammatory bowel disease, and even pregnancy, these preparations appear both safe and effective in replacing iron stores, though they have not yet been well studied in otherwise healthy children. While there are various preparations available, low molecular

weight iron dextran, such as InFed, offers a comparable side effect profile to iron sucrose and iron gluconate with the added benefit of being able to infuse as a total dose infusion. In collaboration with Dr. Buchanan and Dr. Crary, I will perform a prospective descriptive study to demonstrate the safety and efficacy of low molecular weight iron dextran in children with iron deficiency anemia who have failed oral iron therapy.



**Mark Hatley, M.D., Ph.D. (2010)**

MicroRNAs (miRNAs) are evolutionarily conserved, endogenous, non-protein coding, approximately 22 nucleotide single-stranded RNAs that negatively regulate gene expression in a sequence-specific manner [1-3]. MiRNAs that bind with perfect complementarity to the protein encoding messenger RNA (mRNA) target the mRNA for destruction, and miRNAs that bind with imperfect complementarity to the 3' untranslated region (UTR) of the mRNA target repress mRNA translation.

MicroRNAs have been implicated in tumorigenesis. Specifically, the expression of miR-21 is increased in glioblastoma and many carcinomas including lung, breast, stomach, prostate, colon, hepatocellular and pancreatic [4-6]. Several tumor suppressors have been identified as putative targets for miR-21 including *PTEN*, *PDCD4*, *Maspin*, *RECK*, *TIMP3* and *TPM1* [6-10]. Increased expression of miR-21 is associated with poor survival and poor therapeutic outcome in colon adenocarcinoma and non-small cell lung cancer [11, 12]. More experiments are needed to determine if miR-21 has a direct function in tumorigenesis or tumor progression or is simply differentially modulated in these tumors. As well, it is tempting to speculate that miRNA expression signatures in pediatric tumors could have diagnostic and therapeutic implications. The specific aims of my research are as follows:

- To determine the sufficiency of miR-21 in tumorigenesis.
- To explore the necessity of miR-21 in tumorigenesis.
- To identify miRNAs regulated in Ewing's sarcoma.

These studies will provide insights into the microRNA regulatory mechanisms involved in tumorigenesis and will be an important step toward the possible therapeutic manipulation of microRNAs as an approach for tumor therapy.



**Amanda Blair, M.D. (2010)**

Hemochromatosis occurs as a result of iron overload and iron accumulation in vital organs.

Although hemochromatosis can be an inherited condition, most patients develop the clinical signs and symptoms related to iron overload as a consequence of chronic transfusion of packed red blood cells (PRBCs). It is well-known that children with thalassemia and sickle cell disease can suffer from the consequences of iron overload related to transfusions over a long period of time, often many years. We do not know if patients who receive multiple transfusions over a shorter period of time, such as occur in children receiving chemotherapy for cancer, share the same long-term toxicities. As the long-term survival rate for children treated for cancer continues to improve, it is possible that more children will be at risk for developing the clinical sequelae of iron overload. There currently are no published studies documenting transfusion patterns in children treated for cancer. Additionally, there is no documented or established threshold for transfusion volume that invariably puts children at risk for development of iron overload.

The objectives of my research project include (1) systematic investigation of transfusion practices in the pediatric oncology population at Children's Medical Center Dallas, (2) determination of high risk, heavily transfused patient groups, (3) examination of high risk patient groups for iron levels and organ toxicity and (4) determination of the transfusion volume threshold that puts children at risk for development of iron overload.



**Puja Gupta, M.D. (2010)**

Vascular endothelial growth factor A (VEGF) is a primary stimulant of angiogenesis in both normal and pathological settings. Solid tumor development and progression is dependent on angiogenesis, a process considered a hallmark required to sustain cancer. In the tumor

microenvironment, VEGF promotes endothelial survival, functions as a powerful permeability factor and modulates the recruitment and function of immune cells. Thus, inhibition of VEGF activity in tumors is a major focus of many academic and biotech research groups. The FDA has approved the use of therapies targeting the VEGF pathway, such as bevacizumab (Avastin). However, significant questions remain as to the most efficacious strategy to inhibit VEGF receptor activation in tumors. The development of the anti-VEGF antibody, r84, has opened a new avenue of research. r84 selectively blocks VEGF-induced VEGFR2 activation, but allows VEGF to signal through VEGFR1. My project focuses on the function and downstream signaling pathway of VEGFR1 in effort to better understand the efficacy and potential safety benefits of targeting the VEGF pathway with r84.

Platelet-derived growth factor receptor (PDGFR) plays a key role in the development and progression of lung cancer. Increased tumor PDGFR expression is associated with a more aggressive phenotype and worse clinical outcomes. A number of new targeted cancer therapies, including imatinib and sunitinib, inhibit PDGFR. However, these non-specific tyrosine kinase inhibitors block a number of signaling pathways. This lack of specificity makes it difficult to isolate the therapeutic effect of PDGFR inhibition. A novel PDGFR- human and mouse specific monoclonal antibodies will allow us to test the hypothesis that both anti-tumor and anti-stromal/vascular properties contribute to treatment effect on tumor xenografts models.



**Hanumantha "Chinni" Pokala, M.D. (2010)**

My research focuses on infectious complications in pediatric cancer patients. I am currently working on a project exploring rates of invasive fungal infections (IFIs) at Children's Medical Center of Dallas over the last 5 years. These infections are more severe than bacterial infections and harder to treat. There is significant morbidity and mortality due to the infections themselves, the toxicity of antifungal therapy, and the changes that are often made in the child's cancer therapy. An increase in the incidence of IFI has been noted at pediatric centers. In addition to known risk factors, there are reports of outbreaks of fungal disease during times of hospital construction. Children's Medical Center of Dallas has undergone construction for the past several years. During this time, there has been a perceived increase in cases of IFI.

I am performing a retrospective chart review of our patients with hematologic malignancies who started therapy in 2004-2008. These are the patients who were at the highest risk for developing an IFI. Each patient's chart will be reviewed for the known risk factors and when they occurred in the context of the hospital construction project. Additional information will be collected on patients who develop IFI. This will allow a more accurate assessment of any impact hospital construction may have had in the incidence and character of IFI at Children's Medical Center during this time. I hope this will help in the development of strategies for prophylaxis or preemptive therapies for children with cancer.



**Cristina Tarango, M.D. (2009)**

The antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPL Ab), increased risk for thrombosis, and pregnancy morbidity. Circulating aPL Ab are associated with deep venous thrombosis, pulmonary embolism, and stroke in children and adolescents as well as in adults. The mechanism(s) by which antiphospholipid antibodies cause such devastating disease is still unknown. *In vitro* studies indicate that the endothelium is a critical direct target of aPL Ab, which upregulate endothelial cell adhesion molecule expression and procoagulant activity. My project is investigating the molecular basis and disease implications of endothelial dysfunction caused by aPL Ab, using cell culture and mouse models to identify the necessary receptor(s) for aPL Ab actions on endothelium. It is anticipated that the new knowledge gained can then be effectively translated into novel prophylactic or therapeutic strategies to combat the devastating impact of APS on the health of the mother, the fetus, and the newborn.



**Martha Stegner, M.D. (2009)**

Pilocytic astrocytomas are the most common brain tumor diagnosed in children. While children diagnosed with these tumors have a very good survival rate, the treatment can often lead to significant long-term complications. We know very little about the molecular basis of this cancer.

I am currently doing research to better understand the molecular mechanisms that lead to the growth and progression of these tumors. In order to accomplish this, I am using pilocytic astrocytoma tumor samples from the UT Southwestern pediatric tumor bank. Each of these samples is clinically annotated, thus allowing us to identify molecular alterations that influence the clinical behavior of these tumors. I am using a technique called array Comparative Genomic Hybridization (aCGH) to find gains and deletions of genes in the tumor DNA. I have identified several genes with recurrent alterations in these tumors. Along with colleagues in my laboratory, I am studying the oncogenic potential of the most promising of these genes, using astrocytes in cell culture and mouse models. The overall goal of this research is to discover new oncogenes and tumor suppressor genes that could potentially be targets of novel therapies for pilocytic astrocytomas and other cancers.



**Tim McCavit, M.D. (2009)**

I am interested in quality of care and outcomes research in pediatric hematology and oncology.

Currently, I am studying quality of care outcomes in sickle cell disease. Sickle cell disease is a common disorder of hemoglobin, the oxygen-carrying protein of red blood cells. Children affected by sickle cell disease suffer from a variety of health problems of which severe, recurrent, and episodic pain is the most common. Hospitalization for pain and other sickle-cell-related problems occurs frequently in sickle cell disease. We are currently studying a variety of quality of care related outcomes for these hospitalizations. Additionally, 10% of children with sickle cell anemia, the most common form of sickle cell disease, have a stroke by age 18. We are studying the impact of a stroke prevention program introduced in the late 1990's on the rate of hospitalization for stroke in the United States. My long term research interests include the development of useful clinical practice guidelines, the development of more effective models of care delivery for children with sickle cell disease, and studying the epidemiology of sickle cell disease.

**Research Opportunities**

<b>Fellow (graduation year)</b>	<b>Research mentor (Department)</b>	<b>General area of Research</b>
Nicholas Fustino (2011)	James Amatruda	Germ Cell Tumors
Amy Fowler (2011)	Naomi Winick	TPMT and ALL
Carrye Cost (2011)	Patrick Leavey	Febrile Neutropenia
Puja Gupta (2010)	Rolf Brekken	VEGF signaling
Amanda Blair (2010)	Janna Journeycake	Iron Overload
Hanumantha Pokala (2010)	Naomi Winick	Fungal infections in neutropenic patients
Mark Hatley (2009)	Eric Olson	Vasculogenesis
Cristina Tarango (2009)	Phil Shaul	Endothelial Cells
Martha Stegner (2009)	Elizabeth Maher	Neuro-Oncology
Tim McCavit (2009)	Charles Quinn	Sickle Cell Disease
Allyson Niece (2008)	Maite de la Morena (Pediatric Immunology)	Histiocytosis
Jason Litten (2008)	Gail Tomlinson (Pediatrics)	Epidemiology, Cancer genetics
Laura Klesse (2008)	Louis Parada (Cell Biology)	Neurofibromatosis
Tamra Slone (2007)	Naomi Winick (Pediatrics)	ALL
Jennifer Wright (2007)	Naomi Winick (Pediatrics)	Late effects – cardiac toxicity
Cindy Neunert (2007)	George Buchanan (Pediatrics)	Clinical hematology
Jon Wickiser (2006)	Gail Tomlinson (Pediatrics)	Cancer genetics
Shelley Crary (2006)	Janna Journeycake (Pediatrics)	Thrombosis
Brian Cauff (2005)	Matthew Porteus (Pediatrics)	Gene Therapy
Lajuan Jones (2005)	George Buchanan (Pediatrics)	Sickle Cell Disease
Jennifer Cox (2005)	Robert Ilaria (Int. Med., Simmons Cancer Center)	Mouse models for sarcoma tumorigenesis studies

## Pediatric Hematology/Oncology- Fellows' Research

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Anderson Collier (2004)	Gail Tomlinson (Pediatrics, Simmons Cancer Center)	Wilms tumor and tumor polymorphisms
Winston Huh (2004)	Louis Parada (Cell Biology), George Buchanan (Pediatrics)	Neurofibromatosis Sickle Cell Disease
Rebecca Olvera (2003)	Scott Cameron (Pediatrics)	Apoptosis
Chatchawin Assanasen (2003)	Philip Shaul (Pediatrics)	Nitric Oxide and Sickle Cell Disease
Meaghan Granger (2002)	Jerry Shay (Molecular Biology)	Telomerase
Douglas Scothorn (02)	Philip Thorpe (Simmons Cancer Center)	Angiogenesis