UT Southwestern Medical Center

Pediatric Hematology-Oncology Fellows' Research

Below are the current and recent fellow research projects highlighting the variety of research opportunities (clinical, laboratory, and 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 ten years. Applicants to our fellowship program are encouraged to explore the individual faculty pages for each of these mentors to learn more about their research activities and interests.

Summary of Current Fellows' Research

Third Year Fellows (2017-2020)

Rida Hasan, M.D.

PI: Andrew Y. Koh, M.D.
SOC Members: Drs. Nandini Channabasappa, Ayesha Zia and Martha Pacheco

Children with intestinal failure (IF) require long-term parenteral nutrition with central line placement and catheter-associated thrombosis is a major source of morbidity and mortality. While the central line itself is a predisposing factor, other host factors that promote thrombosis in this patient population are poorly understood. The majority of IF patients with thromboses had evidence of thrombophilia, as well as a concomitant decrease in levels of proteins C, S, AT III and elevated levels of factor VIII. Prior studies in gut microbiota of short bowel syndrome (SBS) patients, a large subset of IF patients, have shown evidence of gut microbiota dysbiosis with expansion of proinflammatory gram negative *Enterobacteraceae* (ENTERO) to 23% in SBS patients compared to less than 5% in healthy controls. I will be investigating if children with intestinal failure who develop thromboses will have a higher abundance of pro-inflammatory gut microbiota resulting in decreased intestinal barrier function, increased bacterial LPS translocation into the systemic circulation, and resultant hypercoagulability. I hope to develop a gut microbiota biomarker signature in IF patients, that will ultimately be applicable to a wide array of pediatric thrombotic events.

Kendra Johnston, M.D.

PI: Tanya Watt, M.D.
SOC Members: Drs. Patrick Leavey, Kenneth Chen and Ralph DeBerardinis

Neuroblastoma is the most common extra-cranial solid tumor in children. These tumors are classified as high risk or low risk based on the age of the patient and characteristics of the tumor. The outcomes of these children depend upon which risk group the tumors fall into. Despite treating with chemotherapy, surgery, radiation, and stem cell transplantation, high risk neuroblastoma is very difficult to cure and has a poor prognosis with only a 50% 5-year event free survival. On the other hand, low risk neuroblastoma has a 90% 5-year event free survival rate even though these tumors are treated with significantly less chemotherapy. To improve our treatment of high-risk disease, we need to discover new therapies. The way in which we plan to look for new potential targets for therapies is by studying the way these tumors process sugar to help them grow. Prior research has shown that tumor cells process sugar differently when compared to nor-mal healthy tissues. We plan to study high risk and low risk neuroblastoma samples in order to determine whether high risk neuroblastoma tumors use different processing pathways that may explain why they respond to chemotherapy in different ways. By identifying these differences, we hope to determine areas in these pathways that we can then target with medications to stop the tumor from growing. By doing this, we hope to improve the outcomes of our children with high risk neuroblastoma.

Michael Mitchell, D.O.

PI: Maralice Conacci-Sorrell, M.D.
SOC Members: Drs. Tanya Watt, Theodore Laetsch and Kenneth Chen

The MYC family of proto-oncogenes are the most frequently deregulated genes in human cancers. In neuroblastoma, amplification of the N-MYC gene is known to confer a poor prognosis and aggressive phenotype. I will be investigating the effect of both N-MYC and C-MYC expression on tryptophan metabolism in high-risk neuroblastoma. We plan to achieve this by mining existing datasets to identify signatures of genes involved in the kynurenine pathway of tryptophan metabolism and their correlation with MYC expression. By modulating MYC expression in neuroblastoma cell lines, we will validate MYC as a driver of tryptophan-dependent cellular proliferation. Early experimental observations in mouse models suggest that tryptophan depletion may curtail tumor progression in MYC-driven liver and colon cancer. Similar experiments in a neuroblastoma mouse model will be performed to assess the potential utility of targeted tryptophan depletion as a therapy for neuroblastoma.

Second Year Fellows (2018-2021)

Ashley Bui, M.D.

PI: Srinivas Malladi, M.D.
SOC Members: Drs. Kenneth Chen, Samuel John and Rolf Brekken

Renal cell carcinoma (RCC) comprises 85-90% of primary renal tumors in adults and 5-8% in children. Distant metastasis may be present at initial diagnosis or occur as isolated recurrence several years after treatment of the primary tumor. In these cases, most patients are considered incurable. My research will center on the mechanisms of delayed metastasis in RCC. I will study latency competent cancer (LCC) cells, which are the cells that have hematogenous spread to distant organs and can remain dormant until they later manifest as aggressive disease. Research on breast and lung cancers in our lab revealed that Sox2 and Sox9, key transcription factors in stem cell development, enable LCC cells to enter a dormant state and proliferate slowly. Additionally, inhibition of the WNT pathway via the DKK1 gene was found to contribute to LCC cells' ability to remain dormant and escape destruction by natural killer cells. In a similar manner, I will identify relevant genes in RCC LCC cells and examine their role in cell survival and metastatic potential. These results could lead to earlier detection of LCC cells in order to prevent or treat metastasis more effectively and improve overall survival.

Maria Hanna, M.D.

PI: Ayesha. Zia, M.D.
SOC Members: Drs. Stephen Skapek, Ralph DeBerardinis and Jimin Ren

The functional limitations caused by the post venous thromboembolism syndromes in children have not been well studied. More than 50% of previously active children experience decreased exercise tolerance as much as 6 months following diagnosis of acute DVT and PE. The exact mechanisms of decreased exercise tolerance have not been entirely clear. Possible mechanisms include venous hypertension causing swelling and reduced oxygen delivery to exercising skeletal muscle secondary to reduced venous outflow; and intrinsic skeletal muscle energy utilization abnormalities. We hypothesize that a defect in skeletal muscle energy metabolism after 1st episode of DVT is predictive of increased exercise intolerance. Moreover, we expect that there will be an even stronger relationship between exercise intolerance and the absence of robust venous collateral formation and/or impaired lymphatic outflow. Additionally, we hypothesize that the degree of thrombo-inflammation at DVT diagnosis will also be associated with severity of exercise intolerance.

Our aim will be to characterize alterations in skeletal muscle metabolism at rest and during progressive exercise performed to fatigue in children with exercise intolerance following acute DVT, as well as examine the relationship between collateral venous formations/lymphatic flow abnormalities following acute DVT with skeletal muscle metabolism alterations. We will also aim to delineate the effect of the hemostatic balance and inflammatory state at DVT diagnosis on exercise induced skeletal muscle metabolism abnormalities and their effect on exercise intolerance. To achieve our aims, we plan to leverage the VTE Outcomes Clinical Program at Children's Health as well as utilize magnetic resonance spectroscopy at the Advanced Imaging Research Center at UT Southwestern.

Peter Schoettler, M.D.

PI: Kenneth Chen, M.D.
SOC Members: Drs. Joshua Mendell and Jonathan Wickiser

Anaplastic Sarcoma of the Kidney (ASK) is a rare and poorly understood pediatric neoplasm first reported in 2007. The only genetic report on this cancer that has been published to date was testing for *DICER1* and *TP53* in 9 tumor samples. The finding of *DICER1* mutations in 8 of the 9 samples linked ASK to *DICER1* Syndrome, a cancer predisposition disorder caused by microRNA dysregulation. My research aim is to comprehensively characterize the clinical and genomic nature of ASK. This information can then be compared to that of other tumors within *DICER1* Syndrome to identify potential drug targets.

Summary of Former Fellows' Research

Former Fellows (by graduation year)	Research Mentor	General Area of Research
2019		
Kavita Desai	James Amatruda, M.D., Ph.D.	Wilms Tumor/microRNA
Shyamli Singla	Andrew Koh, M.D.	Hematopoietic Stem Cell Transplant
2018		
Erin Butler	Stephen Skapek, M.D.	MYOD1 gene/Rhabdomyosarcoma
Neethu Menon	Ayesha Zia, M.D.	Thrombin Generation/ Sickle Cell Anemia
2017		
Julia Meade	David Boothman, Ph.D.	Atypical Teratoid/ Rhabdoid Tumor
Samuel John	Alec Zhang, Ph.D.	CAR-T cells/treatment pediatric AML
Kathryn Dickerson	Jian Xu, Ph.D.	Polycomb repressive complex 2
2016		
Erin Lampson	Alice Holland, Ph.D.	Acute lymphoblastic leukemia (ALL)
Erika Lopez Bertiery	Sandi Pruitt, Ph.D.	Oncology
Gauri Sunkersett	Andrew Koh, M.D.	Gut microbiota
2015		
Shannon Cohn	James Brugarolas, M.D., Ph.D.	mTOR inhibitors
Jacquelyn Powers	George Buchanan, M.D. Timothy McCavit, M.D.	Iron deficiency anemia
Natalie Pounds	R. Potts, Ph.D.	Mage proteins /oncogenesis
Kathleen (Wiertel) Ludwig	Rolf Brekken, Ph.D.	Axl as a target for cancer therapy

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2014		
Ajla Wasti	Ralph DeBerardinis, M.D., Ph.D.	Ewing sarcoma
Priya Mahajan	Patrick Leavey, M.D.	PAX genes in childhood cancer
Sara Helmig	Stephen Skapek, M.D.	Rhabdomyosarcoma
2013		
Kenneth Chen	James Amatruda, M.D., Ph.D.	Germ cell tumors
Rachel Thienprayoon	Naomi Winick, M.D.	Pediatric palliative care
Kasey Leger	Naomi Winick, M.D.	Anthracycycline chemotherapy
Wilson File	Patrick Leavey, M.D.	Oncology
2012		
Scott Furlan	Chandrashekhar Pasare, Ph.D.	IgG1/ enhancement of anti-tumor immunity
Raven Cooksey	Naomi Winick, M.D.	Metabolic syndrome in brain tumor survivors
Carrie Laborde	Janna Journeycake, M.D.	Leukemia and CNS adverse events
Ellen Plummer	George Buchanan, M.D. Naomi Winick, M.D.	Iron deficiency anemia
2011		
Nicholas Fustino	James Amatruda, M.D., Ph.D.	Germ cell tumors
Amy Fowler	Naomi Winick, M.D.	TPMT and ALL
Carrye Cost	Patrick Leavey, M.D.	Febrile Neutropenia
2010		
Amanda Blair	Janna Journeycake, M.D.	Iron Overload
Puja Gupta	Rolf Brekken, Ph.D.	VEGF signaling
Chinni Pokala	Naomi Winick, M.D.	Fungal infection in neutropenic patient