YOUNG INVESTIGATOR AWARDS 2023

The Children's Tumor Foundation is pleased to announce the 2023 Young Investigator Award recipients of this latest round of funding, an investment of nearly $1.2 million through the CTF Discovery Fund. These exciting new projects span all types of NF, including NF1, *NF2*-SWN, and SWN. The YIA is the Foundation's oldest grant-giving mechanism, given to early-career researchers. CTF's seeding of the NF field with new talent has been hailed as one of the key reasons for rapid advancements in NF research in recent years.

JADWIGA BILCHAK

University of Pennsylvania

Investigating the Link Between Sensory and Social Deficits in a Drosophila Model of Neurofibromatosis Type I

NF1 is characterized primarily by tumors of the nervous system, but in addition, up to 50% of patients experience learning and social communication deficits. The present study will investigate the molecular mechanisms in sensory neurons affected by *NF1* variants and how disrupted sensory messages are transformed in the brain to shape behavior. The results from this study will shed light on how *NF1* affects behavioral circuits in the brain and how this relates to differences in social interactions.

SRIRUPA BHATTACHARYA

Massachusetts General Hospital

To Understand the Role of Apelin-Mediated Angiogenesis in NF2-Associated Tumors

NF2-associated tumors have shown inconsistent response to treatment with the antiangiogenic drug bevacizumab (Avastin), which targets vascular endothelial growth factor (VEGF). Avastin can cause severe side effects like bleeding and high blood pressure. Previous work from the Ramesh lab showed increased expression of the angiogenic peptide apelin (APLN) in *NF2*-negative tumor cells. This study aims to understand the role of apelin in NF2 tumors and will explore if targeting apelin disrupts angiogenesis and tumor growth.

ROOPE KALLIONPÄÄ

University of Turku, Finland

Risk Factors and Characteristics of NF1-Associated Cancer

NF1 increases the risk for various cancers, such as MPNST and breast cancer, and such cancers are a major cause of premature deaths among individuals with NF1. The three main objectives of this study are determining the risk for multiple cancers in individuals with NF1, determining the role of family history in cancer risk in NF1 and correlating it with NF1 gene variants, and identifying breast cancer characteristics unique to NF1. The study will analyze a Finnish cohort of over 1800 NF1 patients, for whom data are also available through other comprehensive Finnish population and disease registers. Results from this analysis can lead to improved personalized care strategies for NF1 patients.

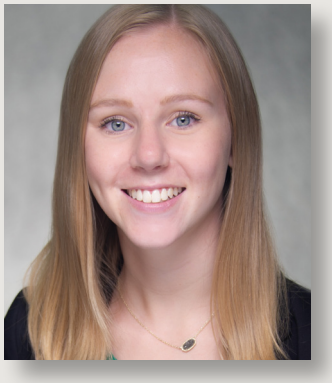
CLARA NOGUE I ANSON

IDIBELL Spain

Dissecting DGCR8 Syndrome and the Molecular Mechanisms Driving DGCR8-Associated Schwannomatosis

The Rivera group recently identified a variant in the *DGCR8* gene, also located on chromosome 22, responsible for a familial form of multinodular goiter that manifests together with peripheral schwannomas. This proposal will investigate the characteristics of *DGCR8*-mutated schwannomas and identify the mechanisms that lead to their formation. Given the global role of *DGCR8* in cellular processes, knowledge of key dysregulated events in *DGCR8*-schwannoma formation can also apply to other schwannomas with alterations on chromosome 22.

ALEXA SHEEHAN
The University of Iowa



Mechanisms of MPNST Metastasis

Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive tumors with high metastasis rate and poor clinical prognosis in NF1 patients. The present study will test newer formulations of Lox inhibitors, which are more specific and less toxic, to decrease MPNST metastasis. Since PRC2 loss also changes global gene expression in MPNSTs, this study will also test a second category of drugs called epigenetic modulators for their effect on metastasis. Overall, this study will determine if targeting Lox proteins induced by PRC2 loss is a viable treatment option for patients with metastatic MPNST.

ADITYA SHETH
Indiana University

CENPF as a Biomarker and Therapeutic Target for NF1-Associated MPNST

Preliminary data shows that the *CENPF* gene, which codes for the Centromere Protein F (CENPF), is activated when plexiform neurofibromas (PNFs) progress into MPNSTs. Higher levels of CENPF are detected in MPNSTs compared to PNFs, suggesting that this gene may promote the progression of PNFs into cancerous MPNSTs. This study will evaluate whether increased CENPF correlates with PNF progression and whether CENPF loss prevents MPNST formation.

JUN SUN
Weill Medical College of Cornell University

A Skeletal Stem Cell Basis and Novel Therapeutic Approaches for Fracture Healing Defects in NF1

Pseudarthroses or non-healing fractures are major skeletal manifestations of NF1 that contribute to overall pain and disability. MEK inhibitors, which are effective against NF1 tumors, are not clearly known to treat skeletal problems in NF1. This study will investigate the mechanism by which *NF1* loss in skeletal stem cells contributes to impaired fracture healing, MEKK2's role in this process, and the effect of MEKK2 inhibitors in reversing this effect. It will also develop a method to selectively deliver drugs to the non-healing fractures, avoiding unwanted side effects in other organs.

SARA VEIGA
Massachusetts General Hospital

Tumor: Macrophage Interactions in Schwannoma

Schwannomas are made of different cell types, including Schwann cells, axons (part of a nerve cell), blood vessels, immune cells, and an extracellular matrix. This complex microenvironment makes tumors very heterogeneous and is also suspected to contribute to the diverse clinical response of these tumors to drugs. Macrophages, a type of immune cells, are found in developing schwannomas and influence the presence or absence of pain. However, how these immune cells are recruited to the tumor is poorly understood. The goal of this proposal is to study how macrophages are recruited to schwannomas and to understand how they interact with schwannoma tumor cells to help the tumor grow. This understanding will be valuable for developing new therapies to fight tumor growth and alleviate symptoms such as pain.

ZHENZHEN YIN
Massachusetts General Hospital

Co-Targeting HMGB1 and EGF Signaling for the Treatment of NF2 and Associated Hearing Loss

Preliminary studies have shown that a protein called HMGB1, a potent inflammation initiator and amplifier is released by schwannomas and can cause inflammation in the ears, leading to hearing loss. The aim of this study is to test if blocking HMGB1 can prevent hearing loss in mice. Since the HMGB1 blockade activates epidermal growth factor (EGF) signaling, which may compensate for tumor growth, this study will also explore how combined HMGB1 and EGF receptor (EGFR) blockade can prevent hearing loss and delay tumor growth in mice with schwannomas. The study will help us understand how HMGB1 causes inflammation in the ears and how we can stop the tumors from growing, which can be useful in designing future treatments for patients with vestibular schwannoma.

YOUNG INVESTIGATOR AWARDS 2022

The Children's Tumor Foundation is pleased to announce the funding of nine Young Investigator Awards (YIA) for the 2022-2024 cycle.

SIMGE ACAR

Washington University

Global Protein Changes Associated with Chr8 Gain in MPNST

Malignant peripheral nerve sheath tumors (MPNST) are one of the common malignancies in individuals with NF1 and are associated with poor overall survival. Unlike plexiform neurofibromas, MPNSTs have an extra copy of chromosome 8 (Chr8q gain), which is hypothesized to induce genome-wide perturbations that specifically promote cancer progression. This study will analyze cells with Chr8q gain along MPNST samples from patients to test the above hypothesis and to characterize the molecular changes caused by this phenomenon.

HALEY HARDIN

University of Central Florida

Evaluation of BRD4 Inhibitors for Use in Combination with Kinase Inhibitors for NF2 Schwannomas

NF2 tumors respond to treatment with MEK inhibitors but eventually develop drug resistance. This study will evaluate a MEK-BRD4 inhibitor combination therapy for drug response in NF2 compared to MEK inhibitor monotherapy. Specifically, this study will investigate the drug resistance mechanism by examining the role of BRD4 in regulating the expression of resistance-mediating genes and will test various MEK-BRD4 inhibitor combinations to identify new drug combinations for NF2.

CHARLENE ILTIS

Memorial Sloan Kettering Cancer Center

Characterization of the Molecular Mechanisms Conferring Resistance to Treatment on NF1-associated MPNST

MPNSTs in the context of NF1 are often the result of malignant transformation of benign precursor lesions including plexiform neurofibromas. The proposed project will characterize a rare MPNST population with stem-cell like properties that is essential for tumor initiation and relapse, and elimination of which promotes tumor shrinkage and abolishes tumor relapse. This study can provide deeper insights into MPNST development and new therapies for targeting them.

TONCI IVANISEVIC

Vlaams Instituut voor Biotechnologie, Belgium

The Role of LZTR1 in Schwannomatosis Development and Progression

Pathogenic variants in the *LZTR1* gene account for up to 40% of the cases of familial schwannomatosis. However, the molecular mechanisms by which these variants predispose to schwannomas are still unknown. This project will perform multi-omic analyses of an *LZTR1*-deleted schwannoma model to identify the interactions between the RAS/MAPK and Hippo pathways during schwannoma development and progression. It will also develop clinically relevant 3D models of schwannomatosis to assess candidate drugs as monotherapy or in combination with Hippo pathway inhibitors.

PAUL JONES
Washington University

Early Detection and Model Development of NF1-MPNST Using Liquid Biopsy of cfDNA

MPNSTs are the leading cause of death in NF1 patients but current methods to detect them, especially the early-stage ones, and track their progression are insufficient. This project aims to develop an assay based on cell-free DNA analysis that will more sensitively detect early-stage MPNST formation. It will further apply this assay in mouse models to understand tumor evolution, treatment response, and resistance mechanisms.

ERICA LEIF
Alliant International University

The Impact of Self-Determination Theory on Increasing Health-Promoting Behaviors in Adults with NF1

NF1 is a complex health condition with multiple clinical manifestations including debilitating chronic pain. By applying the self-determination theory, which suggests autonomy, competence, and relatedness as main psychological needs for growth and change, this study will investigate NF1-associated pain and the contribution of a wide range of factors to successful self-management of pain.

NAMRATA RAUT
Cincinnati Children's Hospital Medical Center

The Role of Schwann Cells in the Onset of Pain due to NF1

The majority of NF1 patients experience moderate to severe neuropathic pain. However, the underlying mechanisms of pain development are not fully understood. The proposed study will examine the specific cell types and mechanisms involved in neuropathic pain development in NF1. Using preclinical mouse models, this study will test whether growth factors produced by Schwann cells together with select immune cell populations that infiltrate the affected peripheral nerves contribute to neuropathic pain-like behaviors.

NIPUNIKA SOMATILAKA
The University of Texas Southwestern Medical Center

From Cold to Hot: Reprogramming Tumor Microenvironment to Target NF1 Malignancies

MPNSTs associated with NF1 respond poorly to chemotherapy and radiotherapy. Immunotherapy drugs are also not effective against MPNSTs because these tumors are 'cold,' lacking T cells and other immune cells near or within the tumor. The present study aims to reprogram the MPNST microenvironment such that they are converted from non-T cell 'cold' tumors into T cell-rich 'hot' tumors. This will be achieved by activating the STING-IFN pathway using known small molecule agonists. This study will then test various combinations of STING agonists and immune checkpoint blockers to determine their efficacy in treating MPNST.

DEREK WONG
University Health Network, Canada

Integrated Analysis of Plasma Whole Genome Sequencing for the Early Detection of Malignant Tumours in Patients with NF1

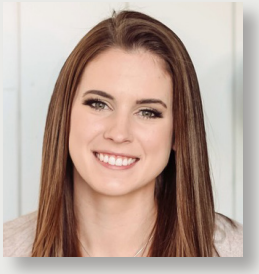
The clinical manifestations of NF1 are diverse and range in severity from mild (e.g., skin discoloration) to very serious (e.g., cancer). Clinicians need new ways to identify NF1 patients requiring heightened surveillance or treatment. The objective of this study is to develop an assay that utilizes cell-free DNA (cfDNA) to monitor NF1 disease severity and identify tumors with malignant potential. This assay will integrate two technologies that enable more thorough genetic and epigenetic profiling of cfDNA and will potentially allow physicians to deliver personalized, risk-adapted care to NF1 patients.

YOUNG INVESTIGATOR AWARDS 2021

The Children's Tumor Foundation is pleased to announce the funding of six Young Investigator Awards (YIA) for the 2021-2023 cycle.

JORDAN KOHLMEYER

The University of Iowa



Defining the RABL6A-YAP Axis in MPNST Pathogenesis and Therapy

NF1 patients are at increased risk of developing malignant peripheral nerve sheath tumors (MPNSTs) due to the possibility of neurofibroma transformation. This study aims to evaluate two powerful cancer pathways, RABL6A and the Hippo pathway, whose dysregulation promotes MPNST pathogenesis. We will investigate how RABL6A regulates the YAP protein to promote MPNST development, and will develop new combination therapies for MPNSTs that will have reduced toxicity and high efficacy.

LINDY ZHANG

Johns Hopkins University School of Medicine

The Effects of RAS Signaling Pathway Inhibitors on Tumor Cells and the Tumor Immune Microenvironment in MPNSTs

NF1-associated MPNSTs are resistant to MEK inhibition monotherapy because of activation of alternate cancer signaling pathways. This study will test combinations of MEK inhibitors, SHP2 inhibitors, and CDK inhibitors, which target different signaling pathways, to treat MPNSTs. Additionally, we will investigate the role of the tumor microenvironment and the impact of various inhibitors on immune cells to design trials of drugs.

SARA PARDEJ

University of Wisconsin-Milwaukee

Neural Underpinnings of Attention in Children with NF1

Attention difficulties are a common cognitive phenotype in children with NF1, yet very little is known about the underlying neural mechanisms. This research will test the feasibility of electroencephalography (EEG) approaches in children with NF1 to identify potential biomarkers of attention problems. By studying differences in neural functioning between children with NF1, their peers, and children with ADHD, we hope to find unique functioning patterns that can effectively track the impact of medical and psychosocial interventions affecting attention in NF1.

JAMIE GRIT

Van Andel Research Institute

Targeting inflammatory signaling in cutaneous neurofibromas

Cutaneous neurofibromas (CNF) are a major cause of morbidity in NF1 and clinically behave very differently than plexiform neurofibromas (PNF). Since CNFs rely more on inflammation than the strong MEK signaling that typifies PNFs, they may need different treatment approaches. This study will test diclofenac, an anti-inflammatory COX2 inhibitor ointment, on CNFs, and will determine patient experience and tumor response after treatment.

ISABELLE LOGAN

Oregon State University

Signaling Pathways Regulated by Nitrated Proteins as Novel Therapeutic Targets for NF2

Nitrated proteins are a novel category of NF2 tumor targets as they play a key role in schwannoma growth and are not present in normal cells. The goals of this project are to investigate the regulation of signaling pathways by nitration and to identify the specific nitrated protein(s) that support NF2 tumor cell survival. Besides NF2, these proteins could be new targets in conditions such as glioblastoma, breast cancer, and colon cancer, where protein nitration is involved in proliferation.

FILIPP KULIKOV

Russian National Research Medical University

Exploiting Cytotoxic Role of Nuclear Rac1 to Develop Targeted Antitumor Therapy of NF2-Associated Tumor

There is no specific treatment for NF2 other than non-specific radiotherapy and surgery, which can sometimes be ineffective due to remote localization of tumor. This proposal will determine the mechanism by which statins and bisphosphonates induce Rac1 translocation into the nucleus, thereby causing cell death. We will also investigate the effectiveness of a statin-bisphosphonate combination therapy for NF2-associated tumors.

YOUNG INVESTIGATOR AWARDS 2020

The Children's Tumor Foundation is pleased to announce the funding of eight Young Investigator Awards (YIA) for the 2020-2022 cycle. Of the eight applications that were selected for funding, six were focused on NF1, one on NF2, and one on schwannomatosis.

NF1

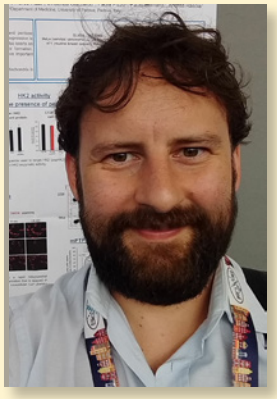
MATTHEW SALE

University of California, San Francisco

Unveiling the Molecular Mechanisms of Neurofibromin Regulation for Therapeutic Targeting in Neurofibromatosis Type 1

This proposal is based on the observation that neurofibromin is directly phosphorylated by ERK kinases. Matthew Sale will investigate if ERK-mediated phosphorylation negatively regulates neurofibromin function and if so, the mechanistic details of ERK-neurofibromin interaction and regulation.

NF1



FRANCESCO CISCATO

University of Padua, Italy

Hexokinase 2 Displacement from Mitochondria-Associated Membranes as a New Antineoplastic Approach in NF1-related tumors

Hexokinase 2 (HK2), a key metabolic enzyme overexpressed in cancers, displays antiapoptotic properties upon its binding to mitochondria. In this project, Francesco Ciscato aims to optimize and test in NF1 model systems a new chemotherapeutic peptide that would specifically displace HK2, thereby promoting tumor cell death.

NF1

KEVIN BRUEMMER

Stanford University

Mapping and Identifying the Roles of Protein Glycosylation in Neurofibromatosis Type 1

Glycosylation, which is the addition of sugar molecules to proteins, is an important post-translational modification that has not been studied in NF1 model systems. This proposal aims to create new chemical biology techniques to better characterize glycosylation using cell models derived from NF1 patients. Studying glycosylation may open up new avenues for therapeutic development by identifying new target pathways.

NF1

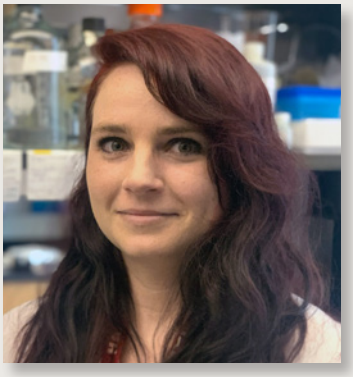
GAVIN MCGIVNEY

University of Iowa

Impact of PRC2 Loss on Glutamine Metabolism in MPNSTs

PRC2 mutations occur in 60% of MPNSTs and glutamine metabolism is an important pathway in MPNSTs with PRC2 loss. This study will examine the dysregulation of glutamine metabolism in PRC2-mutant MPNSTs and examine efficacy of the glutaminase inhibitor CB-839, which is currently in Phase II clinical trials for NF1-mutant tumors.

NF1



LAUREL BLACK
Medical University of South Carolina

Malignant Peripheral Nerve Sheath Tumors Achilles Heel: Combinatorial Targeting of ERBB3 and Calcium Signaling

ErbB3 and calmodulin (CaM) are necessary Ras-dependent and -independent signaling proteins required for MPNST survival. These pathways are dysregulated in MPNST cells but not in normal non-cancerous cells. Laurel Black will investigate the role that ErbB3 and calcium-mediated signaling pathways play in regulating cellular proliferation and survival in MPNSTs and the effect of simultaneously inhibiting them.

NF1

JENNIFER PATRITTI CRAM
Cincinnati Medical Center

Understanding the Role of Purinergic Signaling on Tumor Formation in a Mouse Model of Neurofibromatosis Type 1

P2RY14 is a purinergic receptor that is overexpressed in Schwann cell precursor-like tumor initiating cells. The objective of this study is to investigate the role of P2RY14 in driving neurofibroma growth and to use an NF1 mouse model to test if P2RY14 inhibitors can be used as a treatment for NF1 tumors.

NF2

LIYAM LARABA
University of Plymouth

The Use of Novel YAP/TEAD Hippo Pathway Inhibitors to Target Merlin Null Tumors

The Hippo signalling pathway is an important pathway in driving NF2 tumor development. Liyam Laraba, in collaboration with Vivace Therapeutics will investigate the effectiveness of a novel class of YAP-TEAD targeting compounds in animal models of NF2 meningioma and schwannoma. These compounds have already shown to be very effective at blocking non-NF2 tumor growth and with no visible side-effects, and thus hold promise for NF2-related tumors.

SCHWANNOMATOSIS

ARAM KO
Columbia University

Identification and Functional Characterization of the Substrates of LZTR1

LZTR1 is a substrate adaptor protein of the CUL3 ubiquitin ligase complex, which regulates protein turnover by attaching ubiquitin molecules to protein substrates. LZTR1 mutations are identified in a significant number of schwannomatosis patients. This proposal aims to identify and functionally characterize the substrates of the LZTR1 ubiquitin ligase complex and decipher how mechanistically LZTR1 operates to prevent tumor development in normal neural cells.

YOUR DONATIONS AT WORK

CTF awards more than 950K in the first half of 2019

YOUNG INVESTIGATOR AWARDS 2019

The Children's Tumor Foundation is pleased to announce the funding of two Young Investigator Awards (YIA) for 2019. Both awards are focused exclusively on malignant peripheral nerve sheath tumors (MPNSTs) and are funded by the NF Research Initiative, which is made possible by an anonymous donation to Boston Children's Hospital.

HARISH VASUDEVAN
University of California,
San Francisco

"Elucidating the clonal architecture and functional impact of genetic variants in MPNSTs using single cell genomics"

Malignant peripheral nerve sheath tumors (MPNSTs) are rare but aggressive tumors associated with NF1. There are currently no molecular biomarkers or targeted therapies available for MPNSTs due to the rarity of these tumors and incomplete understanding of their molecular composition. The overall aim of Dr. Vasudevan's proposed work is to use high throughput sequencing in single cells to characterize the molecular heterogeneity in MPNSTs at the DNA, RNA, and protein levels as well as evaluate the functional effect of these changes in primary Schwann cells. Given the heterogeneous nature of MPNSTs, single cell analyses will be critical to define clinically relevant tumor subpopulations, mutational co-occurrence, and rare genetic variants.

JORDAN KOHLMEYER
University of Iowa

"The RABL6A-RB1 pathway in MPNST pathogenesis and therapy"

The overall objective of this study is to determine the role of RABL6A, a novel oncogenic GTPase, in regulating the retinoblastoma (RB1) tumor suppressor signaling. Preliminary work by Ms. Kohlmeyer support the hypothesis that RABL6A drives MPNST pathogenesis by RB1 inactivation, and therefore, the RABL6A-RB1 pathway can be an important, new therapeutic target. This study will determine the mechanisms and biological significance of RB1 pathway regulation by RABL6A in MPNSTs and the value of targeting this pathway to develop novel MPNST therapies.

2018

YOUNG INVESTIGATOR AWARDEES

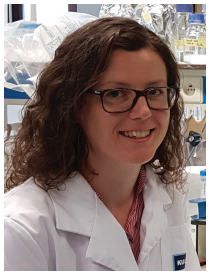
The Children's Tumor Foundation is pleased to announce the funding of five Young Investigator Awards (YIA) for 2018. The YIA is the Foundation's oldest research award program and serves to advance the understanding of the biology of NF1, NF2, and schwannomatosis. The NF Research Initiative (NFRI) and David Miller, MD, PhD, of Boston Children's Hospital are funding two of this year's YIA's in full. The NFRI is a newly established initiative that will focus exclusively on malignant peripheral nerve sheath tumors (MPNSTs).

MICHELLE WEGSCHEID

Washington University School of Medicine

"Employing human induced pluripotent stem cells (hiPSCs) to define brain developmental defects in NF1"

The overall objective of this project is to understand how germline *NF1* mutations affect the human brain. Ms. Wegscheid will employ stem cell cultures to characterize the cellular and tissue abnormalities in brain development due to different *NF1* gene mutations.



SARAH CATHERINE BORRIE, PhD

Katholieke Universiteit Leuven

"Deciphering and treating ASD-like social behavior deficits in mouse models for NF1"

NF1 patients frequently have cognitive and behavioral problems, with many having a diagnosis for autism spectrum disorder (ASD). This project will utilize *Nf1* and *Spred1* transgenic mouse models to further our understanding of mechanisms underlying autism spectrum disorder in patients with NF1, and will investigate possible treatment options.

EVAN O'LOUGHLIN

Harvard University

"Three-dimensional culture systems to assess the consequences of NF2/Merlin loss"

Merlin, a protein that is encoded by the *NF2* tumor suppressor gene, controls many of the cell's signaling pathways and behaviors. Furthermore, the way *NF2* deficiency leads to the formation of tumors is not fully understood. This project will use a three dimensional cell culture system to examine the signaling pathways controlled by merlin, and study how merlin loss impacts the behavior of cells. This study will advance our understanding of merlin deficiency, and will provide a framework for further examinations of the signaling pathways that may contribute to NF2 tumors.

FUNDED BY NFRI

JAMIE GRIT

Van Andel Research Institute

"Genetic and molecular mechanisms of targeted therapy resistance in NF1-associated MPNSTs"

Understanding how MPNSTs develop and progress in individuals with NF1 is key to understanding how to effectively treat these aggressive tumors. The goal of this proposal is to identify how RAS signaling is different between MPNSTs with mutations in *NF1*, compared to those with mutations in both *NF1* and *p53* genes. The most important result of this study will be the identification of a drug combination that blocks RAS signaling and stops MPNST growth even in *p53* mutant tumors.

DONG HYUK KI, PhD

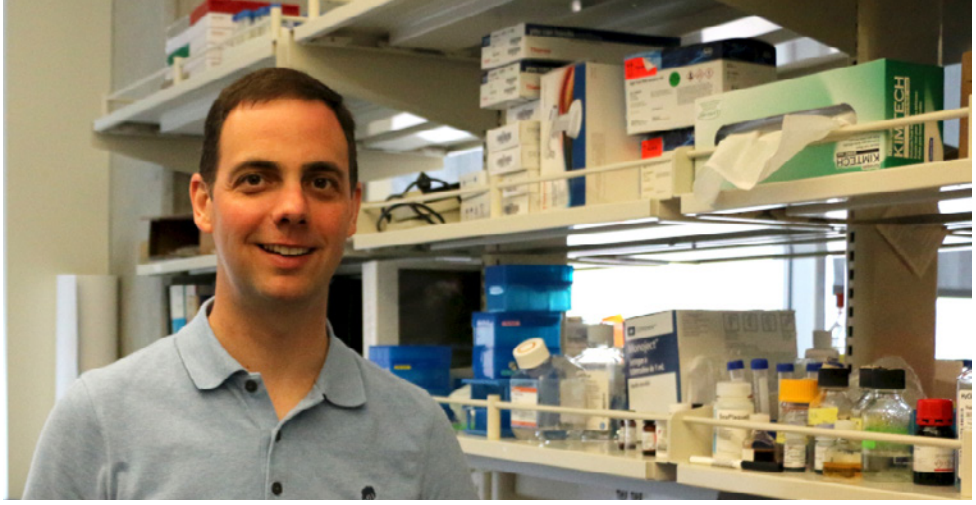
Dana Farber Cancer Institute

"The role of cap-dependent translation in NF1-assiciated MPNSTs"

The focus of this proposal is to test several drugs specific to the eIF4E pathway for antitumor activity and toxicity, and to also identify key proteins that depend on this pathway for expression. This study will clarify the mechanisms underlying the activity of mTOR inhibitors against NF1-associated MPNSTs, potentially leading to new and complimentary strategies to inhibit these pathways.

2017 Young Investigator Awardees

The NF Research Initiative (NFRI) and David Miller, MD, PhD, of Boston Children's Hospital are funding the 2017 Young Investigator Awards (YIAs) in full. The NFRI is a newly established initiative that will focus exclusively on malignant peripheral nerve sheath tumors (MPNSTs). Dr. Miller looked to CTF and its established YIA program as a resource that can readily identify young basic researchers through our outstanding peer-review process, and administrate the grants through our grant management systems.

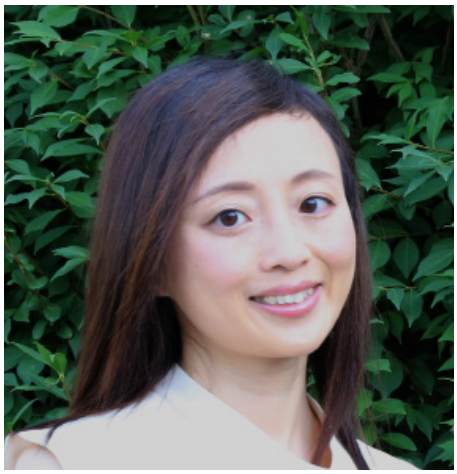


Kyle Brandon Williams, PhD, University of Minnesota
Exploiting Synthetic Lethality to Reveal Novel Vulnerabilities in NF1 Tumorigenesis
Award amount: $108,000

New technologies such as next-generation sequencing, gene knockout libraries, and proteomics profiling now allow researchers to apply great power to the study of human cells in culture and disease modeling.

Dr. Williams has a human cell line that is deficient for the NF1 gene, which is an outstanding research tool. He proposes to use these cells to look for drugs that could combine with the promising MEK inhibitors to preferentially kill the NF1-deficient cells. This could identify new, targeted combination therapies for potential clinical use. In addition to mutations in the NF1 gene, it has been established that other mutations are required for malignant tumors (such as MPNSTs) to develop in NF1 patients. Through this YIA, Dr. Williams will take their existing NF1-mutated cell models and engineer them to be more "MPNST-like" by incorporating some of those other mutations. Testing drugs in these cells will give additional confidence that these drugs will be effective against more aggressive and malignant tumors. This work will develop their NF1 drug discovery pipeline further and should allow identified drugs to more rapidly progress into clinical trials for people suffering from complications of NF1.

Lai Man (Natalie) Wu, PhD, Cincinnati Children's Hospital Medical Center
Molecular and Signaling Mechanisms of Malignant Transformation in Peripheral Nerve Sheath Tumors
Award amount: $108,000



Dr. Wu's initial study shows that a pathway, called Hippo, goes awry in MPNST tumors. Moreover, recent studies have reported nonsense mutations of LATS1, a Hippo-signaling molecule and a known tumor suppressor, in patients with nerve sheath tumors. This suggests that abnormal Hippo signaling activity may contribute to nerve sheath tumor growth. The goal of this study is to learn how Hippo pathway malfunction in Schwann cells causes MPNSTs, and to discover drug targets to treat these aggressive tumors.

Understanding how abnormal Hippo signaling drives Schwann cells to become cancer cells may aid the discovery of promising drug targets against MPNSTs. Dr. Wu will use a state-of-the art genome-wide target screen to identify molecules and pathways directly regulated by the Hippo pathway during tumor formation. She will further devise treatment strategies to modulate the activity of Hippo. In principle, this research emerges as a new paradigm in MPNST research and will have practical benefits that aid us in finding key therapeutic targets to effectively cure MPNST.

2016 YOUNG INVESTIGATOR AWARDEES

We are pleased to announce the 2016 Young Investigator Awardees, which include one pre-doctoral student and three post-doctoral individuals.

JOHN ELLIOTT ROBINSON, MD, PHD
California Institute of Technology
"Utilizing CLARITY, optogenetics, and novel viral vectors to deconstruct and reverse ADHD-like phenotypes associated with neurofibromatosis type 1"

This project will use technologically advanced methods for brain mapping to discover how abnormal development of circuits involved in decision-making and motivated behaviors produces cognitive symptoms in NF1, including learning disabilities, ADHD, etc., which affect up to 80% of individuals with NF1. Through the use of CLARITY on the whole brain (a tissue clearing method allowing individual neurons to be mapped across long distances), and optogenetics (a technique precisely controlling neuronal activity with pulses of blue light), the project will take important steps toward determining the NF1 connectome (a kind of "wiring diagram"), and fill in important gaps in understanding how abnormalities in specific brain circuits produce symptoms of NF1.

STEPHANIE BOULEY
Dartmouth University
"Targeting tumors with NF1 loss via modulation of autophagy"

Plexiform neurofibromas, a common NF1-specific tumor type, have the ability to develop into the more aggressive tumor type malignant peripheral nerve sheath tumors (MPNSTs), for which there are few treatment options. Loss of *NF1* has been shown to be important in the development of a number of cancer types, including MPNSTs, due to its role as a tumor suppressor. While the loss of tumor suppressing genes like *NF1* can help cancer cells survive, they can also introduce vulnerabilities into a cell. This lab has developed a novel way to identify the Achilles heel of cancer cells that have lost *NF1*, and has identified at least one drug that potentially can target tumors with *NF1* loss, such as MPNSTs. The focus of this proposal is to identify how this drug works in cancer cells with *NF1* loss and to determine if it could be a useful drug against tumors with *NF1* loss.

IONICA MASGRAS, PHD
University of Padua
"TRAPping the metabolic adaptations of NF1-associated tumors"

The overall focus of this research will be on an unexplored aspect of NF: the unprecedented possibility that NF1-associated tumors develop as a result of their metabolic changes. The goal is to shed light on a new mechanism by which loss of neurofibromin function in NF1 patients leads to cancer onset and on a possible therapeutic strategy involving the inhibition of molecules such as TRAP1, a protein that plays a key role in uncontrolled growth of cells, potentially reversing these tumor metabolic adaptations.

JEAN-PHILIPPE BROSSEAU, PHD
University of Texas Southwestern Medical Center
"Fibroblasts: the missing gap in NF"

This project plans to explain the contributions of fibroblasts, which are connective tissue cells required for tumor formation, to the development of neurofibromas. Anti-fibrosis and anti-cancer drugs that reduce the number of fibroblasts significantly enhance patient survival. This proposal intends to transfer this knowledge in the context of neurofibromas, opening the door to a wide array of clinically approved drugs already effectively targeting fibroblasts in classic organ fibrosis and cancer.

2015
Young Investigator Award Recipients

The Children's Tumor Foundation is pleased to announce the funding of six Young Investigator Awards (YIA) for 2015. The YIA is the Foundation's oldest research award program and serves to advance understanding of the biology of NF1, NF2, and schwannomatosis. Of the six awardees, three are pre-doctoral students and three are post-doctoral fellows. The title of the awardees' applicaton indicates the focus of the research that will be funded through this award.

LEI XING *is a fifth-year postdoctoral fellow at the University of North Carolina, School of Medicine.*

MAPK/ERK Hyperactivation on Neural Circuit Development in NF1

Dr. Xing will test the effect of layer V neuron activation in a genetic mouse model with upregulated ERK/MAPK signaling, which should mimic the effect of reduced neurofibromin activity. He hypothesizes that this may help us understand, and potentially be a marker for, the presence of NF1 features such as cognitive and psychomotor delays.

MARISA ANN FUSE *is a predoctoral student at the University of Central Florida.*

In Vivo Testing of FDA-Approved Drugs for NF2

The project leverages the work already being done in screening drug libraries, focusing on the potential PI3K and mTOR inhibitors that kill/suppress NF2-deficient schwannoma cells in vitro. This student will then test these drugs for effectiveness.

EBRAHIM TAAHEI SEYEDMOHAMMAD *is a predoctoral student at Vanderbilt University.*

The Inhibitory Role of Integrin beta3 in NF1 Impaired Osteogenesis

This student will use a tibial dysplasia mouse model to test whether the increased integrin beta3 that he found in NF1-deficient osteoprogenitor cells prevents them from differentiating into osteoblasts, leading to the failure of NF-related bone lesions to heal. He will subsequently test whether knocking down integrin beta3 production can lead to increased fracture healing.

VANESSA MERKER *is a predoctoral student at Massachusetts General Hospital.*

Coordinating Care for Patients with Schwannomatosis - Assessing the Field and Identifying Opportunities for Improvement

This student will investigate how schwannomatosis patients navigate the health care system with the long term goal of educating the medical community and patient population to improve patient access to appropriate medical care.

DIPAK N. PATIL *is a third-year postdoctoral fellow at the Scripps Research Institute.*

Understanding the G Protein Coupled Receptor (GPCR) Driven Interaction of NF1 with G Proteins

This project will perform experiments based on observations that activated GPCRs can inhibit neurofibromin's GAP activity by binding G protein subunits, which will lead to better understanding of the molecular mechanism involved in this important signaling regulation. This could lead to new targets for NF1 therapies.

AUBIN MOUTAL *is a second-year postdoctoral fellow at the University of Arizona (Tucson).*

Molecular Targeting of Migraine in the NF1 Population.

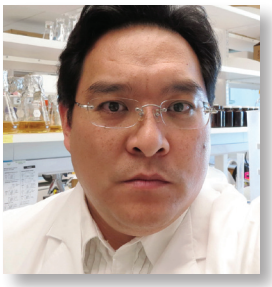
Dr. Moutal will study the interaction of the CRMP2 protein and neurofibromin, to determine whether its perturbation (by reduction of neurofibromin) could be related to migraine in patients with NF1. This work could lead to therapies specifically effective in NF1 or be of general use for migraine headache (or potentially be useful in understanding other NF1 features).

The Children's Tumor Foundation is pleased to announce the funding of eight Young Investigator Awards (YIA) for 2014. YIA recipients focus on using animal models and cell and tissue cultures to advance understanding of the biology of NF1, NF2, and schwannomatosis, which is the first step toward better treatments for neurofibromatosis.

2014 Young Investigator Award Recipients

Chung-Ping Liao, PhD, University of Texas Southwestern

Tumor Microenvironment and Stem Cell Factor Contributions in Neurofibroma Development



Dr. Liao is a postdoctoral fellow in the laboratory of Dr. Lu Le at the University of Texas Southwestern. Dr. Le studied with Dr. Luis Parada there, and has now established his own independent research lab. His project will use NF1 mouse models to better understand the cell microenvironment conducive to neurofibroma development, including the role of a growth factor called stem cell factor. Better knowledge about the influences in the tissue surrounding neurofibroma cells may lead to new therapeutic targets and strategies.

Manuel López Aranda, PhD, University of California, Los Angeles

The Possible Role of Immune Activation in Autism Phenotypes in NF1

Dr. López Aranda is a postdoctoral fellow with Dr. Alcino Silva, at the University of California, Los Angeles. Dr. Silva is an established neuroscience investigator who performs basic and clinical research in NF1-related learning. In this project, to test a new hypothesis, the role of the immune system will be examined in NF1 patients who also have features of autism. If they find a link, it opens a line of research to consider therapies that modulate the immune system, as a potential intervention in children with NF1 that are on the autism spectrum.

Clare Malone, Brigham & Women's Hospital

Identifying Novel Drug Combinations that Target Cancer Cell Vulnerabilities in Malignant Peripheral Nerve Sheath Tumors

Clare Malone is a graduate student with Dr. Karen Cichowski, a well-established NF1 investigator at the Brigham and Women's Hospital in Boston. Ms. Malone's thesis project is focused on finding drug combinations that can best kill MPNST cells, based on understanding of altered pathways in these tumors. Her work will involve study of cell lines as well as testing in mouse models. Since single agents are not proving very effective for NF1 patients with MPNST, effective combinations need to be investigated.

Mariska van Lier, Netherlands Institute for Neuroscience

Altered Critical Period for Ocular Dominance Plasticity in Heterozygous NF1 Mutant Mice

Mariska van Lier is a graduate student in the laboratory of Dr. Christiaan Levelt, at the Netherlands Institute for Neuroscience in Amsterdam (and new to the NF field). Ms. van Lier's project will study the critical period of neuronal plasticity in mutant NF1 using synapse development in the visual cortex as a model. The hypothesis is that the critical period in NF1 mice closes too soon compared to wild type mice. If true, they will investigate environmental and pharmaceutical interventions that could modulate this period, and this will also lead to investigations of this phenomenon in children with NF1.

Krishna Chinthalapudi, PhD, Scripps Research Institute

Lipid-Directed Control of Merlin Tumor Suppressor Functions

Krishna Chinthalapudi, PhD is a postdoctoral fellow in the laboratory of Dr. Tina Izard, a researcher at the Scripps Research Institute. Dr. Izard is relatively new to the NF2 field, bringing her expertise in cell biology in merlin-related pathways. This project will examine the role of lipids in controlling merlin's functions, which may shed light on possible new therapeutic targets and approaches for NF2.

2014 Young Investigator Award Recipients (continued)

Robert J. Allaway, Geisel School of Medicine at Dartmouth College

Characterizing Novel Therapeutics that Exhibit Synthetic Lethality with NF1-Associated Tumors

Robert J. Allaway is a graduate student in the laboratory of Dr. Yolanda Sanchez, a relatively new NF investigator, at the Geisel School of Medicine at Dartmouth College. His thesis project used a system called a synthetic lethal screen, that his lab developed with Dr. Nancy Ratner, to identify compounds that will only kill neurofibromin-deficient cells. His preliminary work in NF1 tumor cells identified several lead pathways/compounds. His YIA work will further investigate the effectiveness of these compounds in mouse models, as well as dissect the mechanisms involved in the cell death (e.g. autophagy and oxidative stress).

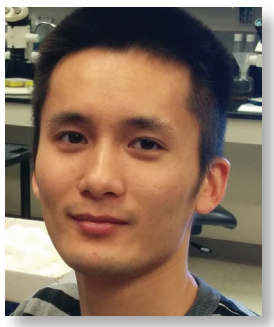
Susana Moleirinho, PhD, Scripps Research Institute

Identification of Novel Therapeutic Targets for the Treatment of NF2

Susana Moleirinho, PhD is a postdoctoral fellow in the laboratory of Dr. Joseph Kissil, a well-known NF2 scientist at the Scripps Research Institute in Florida. Dr. Moleirinho's research is a translational study to identify new drugable targets in NF2 tumors. She will focus on three kinase proteins whose expression is altered in merlin-null cells, likely promoting their uncontrolled division. She will test the effectiveness of drugs known to inhibit these kinases on tumor formation in NF2 mouse models.

Jiajie Xu, University of Chicago

Investigating Functional Interactions Between Merlin, Apical Polarity Proteins and Their Regulation of the Hippo Signaling Pathway



Jiajie Xu is a graduate student in the laboratory of Dr. Rick Fehon, an established NF2 investigator at the University of Chicago. The project will utilize the power of the Drosophila (fruit fly) genetically-malleable system to gain new information about the function of the merlin protein in growth. The study will focus on merlin's role in responding to signals from proteins that orient the cell, and transmitting those signals through the Hippo pathway to affect gene expression. Understanding more details about merlin's functional partners will fuel development of novel tumor therapies.

2013 YOUNG INVESTIGATOR AWARD RECIPIENTS

The Children's Tumor Foundation is pleased to announce the funding of nine Young Investigator Awards (YIA) for 2013. YIA recipients focus on using animal models and cell and tissue cultures to advance understanding of the biology of NF1, NF2, and schwannomatosis, which is the first step toward better treatments for neurofibromatosis.The 2013 YIA recipients include seven post-doctoral and two pre-doctoral awardees.

2013 Postdoctoral Awardees

Lu Zhou, Peninsula School of Medicine and Dentistry, UK
KSR1 as a Potential Therapeutic Target for Both NF1 and NF2

NF1 patients can develop plexiform neurofibromas (benign tumors that grow along nerves) which can become malignant peripheral nerve sheath tumors (MPNST) in 10% of cases. NF2 patients are likely to develop tumors of the Schwann cells called schwannomas, which lead to significant medical problems. Currently, there is no approved drug therapy for these complications of NF1 and NF2. This project will use cell cultures to explore the tumor-suppressing activity of Kinase Suppressor of Ras 1 (KSR1) as a new approach for the treatment of both NF1 and NF2.

Kairong Li, University of Alabama
Characterizing Novel NF1 Mouse Models and Developing New Therapeutic Interventions

The approach of using drugs that interact with a mutated gene or its gene product, with the goal of restoring gene function, has proved feasible in genetic disorders such as cystic fibrosis and Duchenne muscular dystrophy. This project will develop new mouse models mimicking human NF1 mutations to enable preclinical testing of such gene or protein-targeted NF1 therapeutics. It will focus on mice with mutations like those in NF1 patients in which there is a premature "stop signal." This type of mutation occurs in approximately 20% of people with NF1. The researchers will study mice with premature stop mutations, and test the ability of a group of drugs called "nonsense suppressors" to allow normal protein to be produced in these mice.

Su Ting, University of Chicago
Dissecting Merlin-mediated Regulation of the Hippo Growth Control Pathway Using FRET-based Biosensors

Loss of the NF2 tumor suppressor protein Merlin leads to tumor formation in humans and mice, and tissue overgrowth in Drosophila (fruitflies). Merlin is thought to regulate the activity of the Hippo growth control pathway that controls organ size and tissue stability. Due to a lack of laboratory methods for studying Hippo pathway kinase activity, we do not know exactly how Merlin regulates the Hippo pathway. The researchers plan to develop optical biosensors that measure the activity of Hippo pathway kinases with high resolution. They will use these to explore the role of Merlin in regulating the Hippo pathway during normal development, and in suppressing tumor formation in humans.

Christine Chiasson MacKenzie, Harvard University, Massachusetts General Hospital
Mechanical Organization of the Cell Cortex by the Tumor Suppressor NF2/Merlin

This researcher's group has recently discovered that the protein that is missing in NF2, Merlin, helps to organize the physical properties of the cell by restricting the function of the ERM family of proteins. Based on these findings, the researcher proposes a novel and unifying hypothesis: that the multiple features of NF2 are related to a failure of cells to appropriately respond to mechanical stimuli. She will use innovative bioengineering approaches to manipulate the mechanical environment experienced by cells and investigate how mechanical stimuli impact the activity of known Merlin-regulated signaling pathways in the presence or absence of Merlin. These studies will set the stage for future efforts to match the appropriate therapeutic strategy to a specific tumor type.

William Guerrant, The Scripps Research Institute, Florida
Small Molecule Inhibition of the Hippo-YAP Pathway as a Therapeutic Strategy in NF2

Currently, treatment options for NF2 are scarce. There is a pressing need for NF2 drugs. The Hippo-YAP pathway is involved in NF2 and has recently been shown to interact with many other important pathways that can cause cancer. It has therefore become an important new target for cancer researchers. The project will screen a 640,000 plus "library" of chemical compounds to identify inhibitors of the pro-growth signaling Hippo-YAP pathway and test the most promising inhibitors of human NF2 tumors in mouse models, with the goal of developing validated drugs for NF2 treatment.

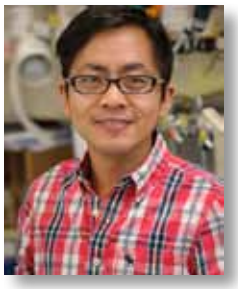
Shuning He, Harvard University, Dana-Farber Cancer Institute
In Vivo Analysis of the NF1 Tumor Suppressor in Neurofibromatosis

It is known that part of the NF1 protein down-regulates the function of another protein, called RAS, which can promote tumor formation when it is expressed at high levels. However, the functions of other regions of the NF1 protein have yet to be discovered. This project will study new functions of NF1 and how NF1 is involved in neurofibromatosis formation using a zebrafish model. When the functions of NF1 proteins are inhibited in zebrafish, they develop abnormally with defects that mirror the human disorder. The zebrafish model promises to be meaningful for the study of NF1 in humans and the development of improved therapies for patients with NF1.

2013 Predoctoral Awardees

Matthew Karolak, Vanderbilt University
FGFR1 and Neurofibromin Interactions During Endochondral Bone Formation

Approximately 30% of NF1 patients will have some type of abnormality related to skeletal development, bone remodeling, and bone fracture repair. Following fracture, these NF1 patients typically have healing abnormalities. In some cases, they are required to undergo multiple surgeries to achieve fracture healing. Frequently these attempts are still unsuccessful, may require limb amputation, and are associated with high morbidity. The molecular mechanisms underlying many of the skeletal aspects of NF1 remain unknown, and largely untreatable with drugs. This project will test the hypothesis that FGF Receptor 1 signaling in chondrocytes (the bone cells contributing to bone elongation during growth and the first steps of bone repair following fracture) is under the control of neurofibromin (the protein mutated in NF1 patients). If correct, this will identify a novel target against which pharmacological drugs targeting FGFR1 could be used to promote proper fracture healing in NF1 patients. In this study, tissue culture experiments will examine which FGFR1 signaling events are regulated by neurofibromin. A second part of this study will test whether inhibiting FGFR1 in a mouse model promotes bone healing. It will use a newly developed method to deliver an FGFR1 inhibitor at the fracture site in a controlled (slow release) and local manner. Overall, this study will determine the feasibility of the approach of blocking FGFR1 during the early phases of bone healing in NF1 patients in order to promote proper fracture healing and stable bone union following fracture.



Wei Mo, University of Texas Southwestern Medical Center
MPNST, a Disease of the Stem Cell?

Recently, the concept of cancer stem cells has arisen in multiple professional journals in the biomedical field and has been widely discussed as an important topic of public health. The traditional tumor growth model holds that every cancer cell has unlimited dividing and metastasis potential. However, it is difficult to explain tumor relapse after classical anti-tumor treatments such as chemo- and radiotherapies because the majority of the highly proliferative cancer cells are killed upon treatment. The cancer stem cell hypothesis can better explain tumor recurrence following treatment. Cancer stem cells (CSCs) represent a small population in cancers with self-renewal capability and maintain tumor heterogeneity. Malignant peripheral nerve sheath tumors (MPNSTs) are highly aggressive and lethal tumors that develop in 2-5% of NF1 patients. There is now opportunity to develop innovative and novel therapies for these tumors, if the CSC model is applicable to MPNST growth. The identification of CSCs in MPNSTs would suggest that a more aggressive treatment plan targeting the CSCs would be effective, and could lead to improved treatments for NF1 patients who develop MPNSTs.

Christine Kivlin, University of Texas, MD Anderson Cancer Center
PARP Inhibitors for the Treatment of NF1-associated MPNST

A malignant peripheral nerve sheath tumor (MPNST) is the most aggressive consequence of NF1. Currently, the only treatment for MPNST is surgery, if feasible. Additionally, about 50% of the patients develop metastases, which have a poor survival rate (20-50% five-year survival rate). This project will evaluate the use of Poly ADP Ribose Polymerases, or PARP, inhibitors to treat MPNSTs. PARP inhibitors are proteins that play an essential role in the repair of DNA damage. Recent evidence suggests that cancers have specific defects in DNA repair pathways that may predispose for sensitivity to various classes of cytotoxic agents, such as PARP inhibitors. Preliminary data from this laboratory strongly suggest that an MPNST is sensitive to the effects of AZD2281, a PARP inhibitor. The goal of this project is to further evaluate the effects of PARP inhibition on MPNSTs in cell lines and animal models. It also aims to identify why MPNST cells are sensitive to PARP inhibition. Understanding the mechanisms responsible for sensitivity would enhance our ability to identify MPNST patients that will most benefit from treatment with PARP inhibitors.

Children's Tumor Foundation Invests $884,000 in Neurofibromatosis Research and Development

The Children's Tumor Foundation is delighted to announce the funding of 11 Young Investigator Awardees (YIA) for the 2012 round. YIA research focuses on basic and translational biology of NF1, NF2, and schwannomatosis.

The 2012 YIA recipients include six postdoctoral and five predoctoral awardees.

YIA Postdoctoral Awardees

Jean De La Croix Ndong
Vanderbilt University
The Nf1osx -/- mice and CNP: a new inducible pre-clinical model and a novel strategy to understand and treat NF1 tibial pseudoarthrosis.

Tao Sun
Washington University in St Louis, School of Medicine, Department of Pediatrics
Sex differences in cyclic AMP signaling impact NF1-associated gliomagenesis

Yuan Wang
University of Michigan
Therapeutic intervention of NF1-asscociated cognitive deficits and optic nerve gliomas during early postnatal stages

Pamela Vanderzalm
The University of Chicago
Dissecting merlin function at the membrane

Rebecca Dodd
Duke University Medical Center
Investigating tumor biology in a novel mouse model of inducible NF1-driven soft-tissue sarcoma

Rebecca Lock
Brigham and Women's Hospital, Inc.
Developing novel therapies for malignant peripheral nerve sheath tumors

YIA Predoctoral Awardees

Richard Hugh Frost Bender
Washington University in St. Louis
Neurofibromin ras-molecule specific regulation of neural stem cells.

Amish Patel
UT Southwestern Medical Center
Epigenetic mechanisms underlie malignant peripheral nerve sheath tumor development

Jeff Gehlhausen
Indiana University
Generation of a novel, accurate murine model of neurofibromatosis type 2 and the genetic validation of a therapeutic target for schwannoma development

Gerald Sun
Johns Hopkins University
Neurofibromin I and regulation of neural stem cell fate choice

Alexander Schulz
Fritz Lipmann Institute, Jena, Germany
Axonal merlin regulates Schwann cell behavior via neuregulin signalling

Children's Tumor Foundation Invests $500,000 in New Neurofibromatosis Research

The Children's Tumor Foundation is delighted to announce the funding of SIX Young Investigator Awardees for the 2011 round. The recipients include three postdoctoral awardees and three graduate students; three focused on aspects of NF1 including tumors, bone dysplasia and learning disabilities; and three focused on NF2 or schwannomatosis. Four awardees are US-based and two are international.

Young Investigator Awards provide the recipient with two years of salary support plus a $5,000 travel stipend to attend the NF Conference and other meetings. The 2011 Awardees represent an investment for the Children's Tumor Foundation of just under $500,000.

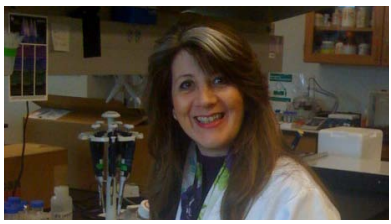
POSTDOCTORAL AWARDEES

Miriam Smith, Ph.D.
University of Manchester, United Kingdom
Project: Identification of novel genes predisposing to schwannomas and meningiomas by exome

Jonathan Payne, Ph.D.
University of Sydney, Australia
Project: The Neural Basis and Treatment of Reading Disability in Children with NF1

Jianzhong Yu, Ph.D.
Johns Hopkins University
Project: Molecular genetic characterization of the Merlin tumor suppressor protein complex

PREDOCTORAL AWARDEES



Alejandra Petrilli Guinart
University of Central Florida
Project: LIM kinase – a potential therapeutic target for NF2

Steven Rhodes
Indiana University School of Medicine
Project: Targeting the hematopoietic bone microenvironment in the treatment of NF1 pseudarthrosis

Adrienne Watson
University of Minnesota
Project: Understanding the Role of Wnt Signaling in Malignant Peripheral Nerve Sheath Tumors

2010 Young Investigator Awards

From NF2 Models in L.A. to Learning Disabilities in The Netherlands

The Young Investigator Award (YIA) highlights the Children's Tumor Foundation's enduring commitment to bringing new scientists into NF research. Six young individuals have been selected as YIAs. The award provides two years of salary funding plus a travel allowance to support attendance at NF-related research meetings such as the annual NF Conference. The six 2010 YIA projects are summarized below:

Nicolas-Xavier Bonne, M.D.
House Ear Institute
Use of radiosurgery and radiotherapy for NF2 management is highly controversial, with some physicians utilizing this and others not. There are differences of opinion as to whether observation, microsurgery or radiosurgery is more effective in hearing preservation, and whether this treatment may induce malignancy. Dr. Bonne will use NF2 mouse models to endeavor to address these important questions, treating the mice with radiotherapy and evaluating the short- and long-term outcomes.

Thomas DeRaedt, Ph.D.
Harvard Medical School/Brigham and Women's Hospital
Malignant Peripheral Nerve Sheath Tumors (MPNSTs) are a rare but devastating and lethal tumor that can develop in NF1 from plexiform neurofibromas. Building on the established finding that Rapamycin will have some effect on inhibiting NF1 tumor growth, Dr. DeRaedt uses mouse models of MPNSTs to test new combination drug treatment approaches for these difficult to manage tumors.

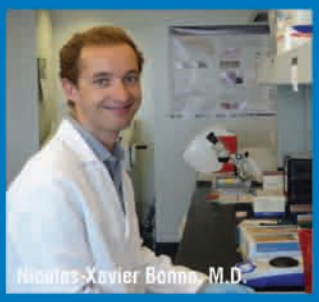
Jean Gouzi, Ph.D.
Harvard Medical School/Massachusetts General Hospital
Dr. Gouzi takes new approaches to understanding NF1-related learning disabilities by using the fruit fly to look at novel genetic regions that have been identified and may have a role in regulating NF1 gene function. Fruit flies make terrific models for studying learning behavior as have well established genetic homology (parallels) with humans allowing for the translation of results from flies to humans; and they can be assigned tasks and responses measured. As a result, by using flies with different genetic mutations or after they have received a drug treatment, new genes may be identified that are contributing to the learning defect and therefore represent future candidate drug targets.

Azar Omrani, Ph.D.
Erasmus Medical Center, The Netherlands
Dr. Omrani seeks to better understand learning disabilities in NF1 with an eye on developing clinical interventions (the primary focus of the laboratory in which she will be doing this research). She will focus on a special modified version of NF1 protein which is generated by a specific NF1 genetic element called exon9a and which plays an important role in regulating neuronal function in the normal brain. Mice lacking exon9a have learning deficits and Dr. Omrani will focus on whether understanding this can be harnessed to develop treatments for persons with NF1 learning disabilities.

Maryam Jahanshahi *(pre-doctoral awardee)*
Mount Sinai School of Medicine, New York
Study will utilize fly models of NF2 to examine the potential roles of new NF2 gene regulators in causing cell growth, with the goal of identifying new drug targets for NF2 treatment. Of particular interest Ms. Jahanshahi will endeavor to identify genes that are expressed at different levels in different individuals and may help explain why NF2 can affect persons with different levels of severity.

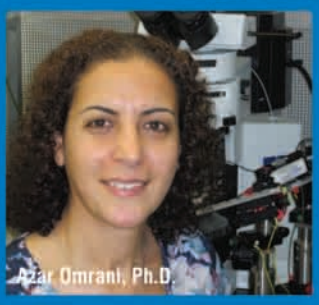
Sherry Phillips *(pre-doctoral awardee)*
Indiana University
Ms. Phillips focuses on an important but understudied aspect of NF1, which is to understand the fundamental causes of why individuals with NF1 can experience enhanced pain. This study focuses on cell signaling elements adenylyl cyclase (AC) and cAMP, and the underpinnings of their role in NF1 pain. The goal is to determine why there are enhanced pain sensations in NF1 and help elucidate future clinical management approaches.

YIA Awardees

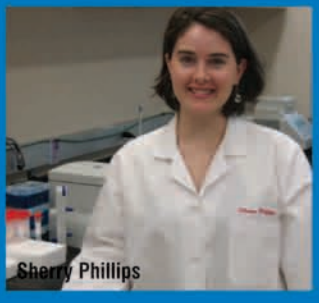

Nicolas-Xavier Bonne, M.D.


Thomas DeRaedt, Ph.D.


Jean Gouzi, Ph.D.


Azar Omrani, Ph.D.


Maryam Jahanshahi


Sherry Phillips