**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.

**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.

**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.

**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.

**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.
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.

JENNIFER PATRITTI
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.

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.

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.
**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.
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).

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.

**MICHELLE WEGSCHEID**
Washington University School of Medicine

“Employing human induced pluripotent stem cells (hiPSCs) to define brain developmental defects in 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 Spryed transgenic mouse models to further our understanding of mechanisms underlying autism spectrum disorder in patients with NF1, and will investigate possible treatment options.

**SARAH CATHERINE BORRIE, PhD**
Katholieke Universiteit Leuven

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

**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-associated MPNSTs”

The focus of this proposal is to test several drugs specific to the elF4E 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.
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.

Because of your gifts, young scientists are pursuing NF research. ctf.org/believe

Believe
WE CAN END NF
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

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.

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.

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.

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.

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.

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.

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## Children’s Tumor Foundation Partners with Alzheimer’s Drug Discovery Foundation

The Children’s Tumor Foundation has partnered with the Alzheimer’s Drug Discovery Foundation (ADDF) in the ADDF-Access program, a marketplace of contract research organizations (CRO) that provide services through all stages of drug discovery and development. The goal of this partnership is for CTF to help researchers accelerate the identification of effective treatments for NF. For more information: [http://alzdiscovery.org/research-and-grants/addf-access/](http://alzdiscovery.org/research-and-grants/addf-access/)

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## SYNODOS UPDATE

Experimental research in the labs began on May 1st and Sage Bionetworks has populated the Synodos Data Warehouse with pre-existing NF2 data, so work is well underway in this exciting new initiative. For more information please visit [www.ctf.org/synodos](http://www.ctf.org/synodos)
### 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 untreated 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 Nf1ox -/- mice and CNP: a new inducible pre-clinical model and a novel strategy to understand and treat NF1 tibial pseudoarthrosis.

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

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

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

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

**YIA Predoctoral Awardees**

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

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.

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

LOOKING FORWARD

09/15 – Little Rock, AR: Red Carpet for Research, Dancing with Our Stars
09/17 – Des Moines, IA: NF Walk
09/17 – Greenville, SC: NF Walk
09/23 – Atlanta, GA: Golf Tournament
09/24 – Fredericksburg, VA: NF Walk
10/01 – Lexington, KY: NF Walk
10/01 – Philadelphia, PA: NF Symposium
10/01 – Wilmington, NC: NF Walk
10/08 – St. Louis, MO: NF Walk
10/15 – Grand Forks, ND: Tea for NF
10/17 – Orlando, FL: Golf Tournament
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 adenyly 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.