2023 Drug Discovery Initiative (DDI) Awardees

The Children's Tumor Foundation is pleased to announce the 2023 Drug Discovery Initiative (DDI) award recipients, an investment of nearly $300,000 through the CTF Discovery Fund. The DDI stimulates NF drug discovery by funding researchers proposing to investigate novel or repurposed therapies for NF or to develop tools that support such research.

Sherif Ahmed
Massachusetts General Hospital

Development of Nanobody-decorated Bacterial Outer Membrane Vesicles for Schwannoma Immunotherapy

This research group recently showed that injecting attenuated *Salmonella typhimurium* alone or in combination with systemic checkpoint inhibitor directly into tumors in a schwannoma mouse model showed an anti-tumor effect. The present work, instead of using live bacteria, will utilize bacterial outer membrane vesicles (OMVs) for schwannoma therapy. OMVs are nanosized vesicles released by bacteria and possess the same immunostimulatory molecules, and preferentially accumulate in tumor tissues. Preliminary data showed that a single systemic injection of attenuated *S. typhimurium* OMVs, loaded with novel bispecific nanobody against CD74 and PDL-1 receptors, resulted in rapid tumor cell death and synergistic tumor regression in schwannoma mouse models, without any noticeable adverse effects. This study will further evaluate the effect of this novel therapy and investigate its long-term effects.

Dominique Lallemand
INSERM, France

Development of cell-penetrating peptides targeting the Yap/Tead complex in the context of NF 2

NF2-related schwannomatosis (*NF2*-SWN), characterized by the development of intracranial tumors, is caused by the inactivation of the *NF2* gene. The absence of merlin, the *NF2* gene product, inactivates the Hippo signaling pathway, resulting in the accumulation of YAP and TEAD proteins in the nucleus of affected cells. YAP and TEAD bind to each other and activate mechanisms that lead to tumor development. Thus, preventing the association of YAP with TEAD is a possible strategy to prevent tumor development. Previous work by the Lallemand group identified a candidate peptide that can enter cells and disrupt the binding of YAP to TEAD. The current study aims to improve this peptide to make it more stable and efficient at dissociating the YAP/TEAD complex. The study will also create new models of schwannomas that better replicate the proliferation of tumor cells and the growth of schwannomas.

Eduard Serra-Arenas
Health Sciences Research Institute of the Germans Trias i Pujol Foundation, Spain

Identification of Drugs Targeting Epigenetic Regulators in an iPSC-Based 3D MPNST Model

The Serra-Arenas group has developed a new cell-based model system for NF1 using induced pluripotent stem cells (iPSCs), cells that have the capacity to differentiate into any cell type. Using this system, they generated iPSCs with variants in multiple genes like in malignant peripheral nerve sheath tumors (MPNSTs). These cells can be grown in 3D spheres and exhibit the genetics and biological characteristics of MPNSTs. In this study, they propose to use this new 3D MPNST model system to rapidly screen ~600 compounds. Based on the results, a selected group of compounds will be tested further as single agents or in combination with other known drugs to identify new therapies for MPNST.

Lawrence Sherman
Oregon Health and Science University

Developing a Thrombopoietin Inhibitor to Treat NF2 Hearing Loss and Schwannoma Growth

Patients with *NF2*-SWN often suffer hearing loss, balance problems, and facial paralysis due to schwannomas on their acoustic nerves. The Sherman group previously found that a drug called losartan could prevent hearing loss in a mouse model of *NF2*-SWN. Although losartan is generally safe, it is unclear if it will be effective in *NF2*-SWN patients and sometimes has severe side effects. The proposed study will use a different drug, a thrombopoietin antisense oligonucleotide (TPO-ASO) that is being tested in clinical trials for other diseases and which also regulates platelets but does not have side effects linked to losartan. This study will test if TPO-ASO could be a drug candidate to protect or improve hearing and reduce tumor growth in *NF2*-SWN patients.

2022 Drug Discovery Inititative (DDI) **Awardees**

Four investigators were awarded a Children's Tumor Foundation Drug Discovery Initiative (DDI) Award for the 2022 grant cycle, a significant investment toward potential NF drug treatments.

Sylwia Ammoun, University of Plymouth

In vivo Testing of AXL inhibitor BGB324 and MERTK inhibitors UNC2025 and MRX2843 in the Postn-Cre; NF2flox/flox Mouse Model of Schwannoma

The protein receptors AXL and MERTK have been newly identified as potential therapeutic targets in *NF2*-related tumors. Inhibitors of these proteins successfully reduced the growth and survival of patient-derived schwannoma and meningioma tumor cells *in vitro*. The goal of the present study is to examine the efficacy of these inhibitors in mouse models of NF2 schwannomas. The data generated would enable the testing of these inhibitors in human clinical trials.

Thomas DeRaedt, The Children's Hospital of Philadelphia

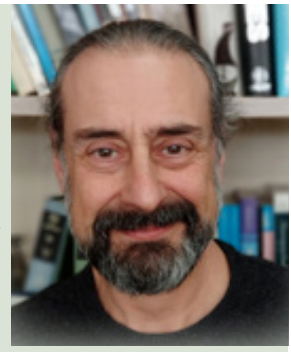
Combined Inhibition of MEK and BMI-1 for the Treatment of NF1-associated High-Grade Glioma

NF1-associated high-grade gliomas (HGG) are rare but aggressive brain tumors with no effective therapy. A combination of MEK and BMI1 inhibitors were recently identified to potently kill NF1-associated high-grade glioma cells. This study will evaluate if the combination of these drugs also extends the survival of NF1 mice with high-grade glioma. The study will test the MEK inhibitor Mirdametinib and the BMI1 inhibitor PTC596 in combination.

Lawrence Sherman, Oregon Health and Science University

A Screen for Novel Schwannomatosis Pain Therapies

Schwannomatosis patients suffer from chronic, untreatable pain and the degree or type of pain differs depending on mutation type (*SMARCB1* or *LZTR1*). Schwannomatosis tumor cells release proteins that influence the number of nerve cells that respond to pain signals. This study will use *SMARCB1*- and *LZTR1*-variant Schwann cells to test the ability of drugs targeting secretory proteins or pain-signaling proteins to relieve pain and any difference in their effects depending on the variant type.



Efthimios Skoulakis, Alexander Fleming Biomedical Sciences Research Center, Greece

Allele-specific Behavioral Pharmacogenetics of Novel NF1 Variants

NF1 patients present a variety of behavioral symptoms, including compromised learning, attention deficits, and activity and sleep disturbances, and the variability of these symptoms reflects the nature of the pathogenic variant. Drosophila modeling these human variants also present similar behavioral symptoms. This study will use variant Drosophila strains to test potential drugs against these deficits to develop personalized therapies for NF1 patients.

2021 Drug Discovery Inititative Registered Reports (DDI-RR) Awardees

Through a collaboration with top scientific journal *PLOS ONE*, in a process known as "Registered Reports," awardees are offered financial support from CTF and in-principle acceptance for publication by the journal. This model allows for more rigorous, reproducible, and transparent science, guaranteeing these awardees publication, regardless of study outcome.

Jonathan Chernoff, MD, PhD, Fox Chase Cancer Center

Evaluation of a PAK1-Selective PROTAC, Alone and With Hippo Inhibitors, as a Targeted Therapy in NF2

This project aims to test whether a newly characterized PROTAC version of NVS-PAK1-1, a Pak1-selective small-molecule inhibitor, impedes oncogenic signaling and cell survival in NF2. The drug will be tested in a panel of NF2-deficient schwannoma cells alone and in combination with a Hippo pathway inhibitor.

Wade Clapp, MD, Indiana University

Preclinical Therapeutic Evaluation of ALY101 in a Murine Model of Neurofibromatosis type 2

The aim of this project is to test a novel Pak1 inhibitor, ALY101, in a genetically engineered mouse model of NF2. ALY101 blocks RHOJ and CDC42 binding to Pak1, thereby inhibiting Pak1 while also avoiding off-target inhibition of Pak2 and other proteins. The investigator hypothesizes that ALY101 will successfully reduce tumor burden and hearing loss in the NF2 mouse model.

Brian Stansfield, MD, Augusta University

Targeting Endothelial Cell to Macrophage Communication in NF1 Tumors

This proposal will assess the efficacy of imipramine, an FDA-approved macrophage macropinocytosis inhibitor, in suppressing macrophage-mediated angiogenesis and tumor growth in NF1. The study will use NF1 mouse models to generate imipramine dose response curves to facilitate easier translation to phase 1 clinical trials.

Thomas DeRaedt, PhD, The Children's Hospital of Philadelphia

Targeting Combined MEK and HDAC Inhibition as an Effective Therapeutic Strategy for NF1 High Grade Glioma

This project is based on the observation that NF1-associated High Grade Glioma (HGG) cell lines are extremely sensitive to combined MEK-HDAC inhibition and will evaluate if this combination is also able to shrink NF1-associated HGG in mice and extend their survival.

Breakthrough Treatment for Kids with NF1 Muscle Weakness

We are happy to share an exciting breakthrough treatment from a research study co-led by CTF-funded researcher Aaron Schindeler, PhD of The Children's Hospital at Westmead, Australia. This treatment was successfully trialed in a study and has the potential to help children with NF1 who live with muscle weakness and fatigue. The researchers found that L-carnitine, a supplement used by athletes to prevent muscle fatigue, can considerably improve muscle function in children with NF1. The work was supported by the Children's Tumor Foundation.

CTF has contributed to both the preclinical and clinical studies that led to this incredible and very promising result, most recently in the Drug Discovery Registered Reports program, and the CTF-funded preclinical study. The CTF Clinical Research Award scheme partially funded the clinical study back in 2018 which led to a publication in the *American Journal of Medical Genetics*.

Read more about the impact this new treatment has had on the participants in the 12-week trial who live with NF1-related muscle weakness at **ctf.org/news**.

2020 **DRUG DISCOVERY INITIATIVE REGISTERED REPORTS** (DDI-RR) AWARDEES

Through a collaboration with top scientific journal *PLOS ONE*, in a process known as "Registered Reports," awardees are offered financial support from CTF and in-principle acceptance for publication by the journal. This model allows for more rigorous, reproducible, and transparent science, guaranteeing its awardees publication, regardless of study outcome.

ANDREA RASOLA, PHD
University of Padua

TRAPping Neurofibromas: Inhibition of the Mitochondrial Chaperone TRAP1 as an Anti-neoplastic Strategy for NF1-associated Tumors

The aim of this project is to investigate whether TRAP1 inhibitors can inhibit the growth of neurofibroma cells, both benign and malignant, in animal models. Moreover, they will be tested on a mouse model that is genetically prone to the formation of malignant NF1-related tumors, in order to study whether TRAP1-targeting molecules can cause the regression of these malignancies.

LEI XU, MD, PHD
Massachusetts General Hospital

Targeting the NRG-1/ErbB Signaling Axes for the Treatment of Schwannomatosis and Associated Pain

The project proposes to determine if schwannomatosis tumor cells, by expressing elevated levels of NRG-1, activate tumor-associated macrophages to produce inflammatory cytokines and induce pain response. The successful completion of this study will shed light on the mechanisms of schwannomatosis-induced pain and provide valuable information for the development of novel, efficacious therapies to treat this debilitating pain.

D. WADE CLAPP, MD
Indiana University

Experimental Therapeutic Evaluation of PSC5-6 using a Pre-clinical Mouse Model of Neurofibromatosis Type 1

In this study, the researchers will test whether the RAS inhibitor PSC5-6 (a drug candidate) can halt and/or prevent the progression of plexiform neurofibromas in a genetically engineered mouse model of NF1. The proposed experiments will generate preclinical data needed to advance PSC5-6 toward a clinical trial in human NF1 patients with plexiform neurofibroma who do not respond to currently available drug therapies.

JEREMIE VITTE, PHD
University of California, Los Angeles

Exploiting Macropinocytosis for Therapeutic Delivery to NF2-Deficient Schwannoma Cells

The goal of this proposal is to demonstrate that macropinocytosis, a mechanism by which cells access nutrients and other survival factors from external sources, is a specific mechanism in NF2-deficient tumors. The project will validate results obtained on cells in an NF2 mouse model.

2019 DRUG DISCOVERY INITIATIVE REGISTERED REPORTS AWARDEES

Two Drug Discovery Initiative Registered Reports Awards were granted for work on therapy resistance in NF2 and DNA damage in malignant peripheral nerve sheath tumors (MPNST).

KEILA E. TORRES, MD, PHD
MD Anderson Cancer Center
"Targeting DNA damage signaling and epigenetic deregulation as a combination therapy for malignant peripheral nerve sheath tumors"

People with neurofibromatosis 1 (NF1) are at risk of developing malignant peripheral nerve sheath tumors (MPNSTs) over the course of their lifetime. MPNSTs are aggressive tumors for which the only effective treatment is surgery. Often, though, the tumors grow back in the same location; thus, surgery to remove the MPNST may not always be an effective long-term treatment. The goal of this study is to address the lack of non-surgical treatments for MPNST by developing a therapy that combines two anti-cancer drugs to target pathways in the cell that are altered in MPNSTs. This research will measure how effective these anti-cancer drugs are when used together and will provide the preliminary results to help researchers decide whether this combination works well enough to be tested in people with MPNST.

CHUNLING YI, PHD
Georgetown University
"Evaluate Novel Hippo-Yap/Taz Inhibitors in Overcoming Therapy Resistance in NF2"

Hippo-Yap/Taz signaling pathway was identified as a major mechanism showed that NF2 tumor cells might be eradicated by combining a novel class of direct Hippo-Yap/Taz inhibitors with MEK inhibitors. Moreover, several other classes of drugs (including drugs that are FDA-approved and/or in clinical trials for NF2) synergize with Yap/Taz blockade in selective killing of NF2 schwannoma cells. This project will perform high throughput combination studies of four classes of drugs predicted by preliminary studies to be synergistic with clinical Hippo-Yap/Taz inhibitors developed by industry partner Vivace Therapeutics, and select the most efficacious combinations for testing in mice.

2018

DRUG DISCOVERY INITIATIVE REGISTERED REPORTS (DDI-RR) AWARDEES

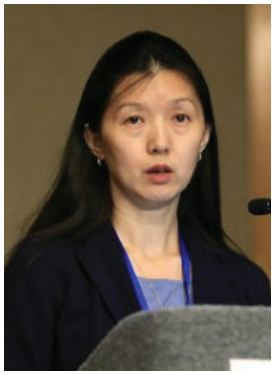
In 2017, CTF introduced a rigorous new way of reviewing and funding projects. Through a collaboration with top scientific journal PLOS ONE, in a new process known as "Registered Reports," awardees are offered financial support by CTF and in-principle acceptance for publication by the journal. This model will allow for more rigorous, reproducible, and transparent science, guaranteeing its awardees publication, regardless of study outcome.

ANDREA MCCLATCHEY, PhD

Massachusetts General Hospital

Exploiting macropinocytosis for the development of exosome-mediated drug delivery in NF2 mutant tumors

Merlin, the protein encoded by the *NF2* gene, is unique among tumor suppressors because it controls cell reproduction. Merlin controls how growth receptors respond to changes in the mechanical and physical properties of the cellular environment. We have recently discovered that merlin regulates how cells take up fluids and nutrients from the environment, through a process called macropinocytosis. In the absence of merlin, cells take in more fluids and nutrients. This project will seek to take advantage of this feature of NF2-mutant cells by utilizing this pathway for the delivery of drugs for the treatment of NF2 tumors. These studies will provide a foundation for the testing of this kind of treatment delivery for this and other therapies for NF2 patients.



LEI XU, MD, PhD

Massachusetts General Hospital

Reprogramming the Tumor Microenvironment to Enhance Anti-Tumor Immunity in NF2 Vestibular Schwannomas

The hallmark symptom of NF2 is benign bilateral vestibular schwannomas (VS). Over time, these tumors grow and may cause progressive hearing loss, which may lead to social impairment and increased clinical depression. In patients with progressive VS, a thickening of the connective tissue, called fibrosis, correlates with hearing loss. Fibrosis results in high collagen content. Recently, we found that NF2 patients with VS demonstrate elevated collagen content and fibrogenic signaling, and are plagued by hypoxia and immunosuppression. Based on these, we propose to target the fibrogenic signaling pathway to improve hearing and enhance immunotherapy efficacy. Our research will generate important and translatable results for new combination therapy paradigms that are desperately needed for this dreadful disease.

AARON SCHINDELER, PhD

The University of Sydney, Australia

Dietary Intervention for NF1 Muscle Weakness

NF1 is associated with a high tumor burden in adulthood, but for many children it most profoundly impacts their school experiences through learning disabilities, muscle weakness, poor coordination, and fatigue. Recent clinical studies indicate that muscle strength is reduced by 30-50% on average in children with NF1. Our breakthrough research has not only revealed that this weakness is linked to problems in fat metabolism in muscle, but also that dietary changes and supplements can overcome this weakness. We propose to complete a final series of preclinical studies with different diets and supplements to fine-tune our design for a dietary intervention trial in children, scheduled to start in 2018.

Drug Discovery Initiative 2017 Awardees

CTF is proud to have recently funded four Drug Discovery Initiative (DDI) awards. We are enthusiastic about these exciting projects!

Jeffrey Field, PhD, University of Pennsylvania, Perelman School of Medicine

MPNST Profiling and Screening: Extension for Exome Sequencing of the Cell Lines Screened

Award amount: $25,000

In a prior DDI award, Dr. Field developed a course for students to do drug screening for 130 relevant NF drugs against 9 NF1 cancer cell lines and two NF2 cell lines. They also screened thousands of drugs against representative NF1 and NF2 cell lines. Further funding will allow Dr. Field and these students to find the mutations for each cell line to more closely correlate the sensitivity to drugs tested, and to identify new drugs to test. Additionally, the data from this project will be made public.

Verena Staedtke, MD, PhD, Johns Hopkins University, School of Medicine

Evaluation of Mebendazole as Chemoprevention in a Neurofibromatosis 1 Transgenic Mouse Model

Award amount: $85,000

This project will explore using chemoprevention, the use of drugs to reduce the risk of cancer development, by repurposing a particular drug for the prevention of MPNST development. The drug, Mebendazole (MBZ), has shown benefits in colorectal cancer syndromes previously, and will be tested in a MPNST mouse model. If successful, the results will have an immediate impact on patient care; the highest death rate among NF1 patients is due to MPNST, and this project hopes to reduce this cancer frequency among NF1 patients.

Andrea Rasola, PhD, University of Padova, Department of Biomedical Sciences

Targeting the Mitochondrial Chaperone TRAP1 to Inhibit Plexiform Neurofibroma Growth

Award amount: $40,000

Changes in cell metabolism constitute a driving force for the growth of many tumor types. Dr. Rasola and his group have also found that TRAP1, a protein that has a crucial function in the control of the energy metabolism of tumor cells, is mandatory for neurofibroma growth. The aim of this project is the identification of molecules that inhibit TRAP1, which might block neurofibroma progression. It is hoped that these new compounds will be the first step in the development of selective and effective anti-neoplastic drugs for NF1 patients.

Dr. Marco Giovannini, MD, PhD, University of California, Los Angeles

Preclinical Safety and Efficacy Eevaluation of Long-Term Anti-VEGFA Treatment Administration in a GEM Model of NF2-Related Schwannoma

Award amount: $84,999

Case reports and clinical trials have reported that bevacizumab (Avastin), can induce both tumor regression and hearing improvement in patients with NF2-associated vestibular schwannomas. Dr. Giovannini will test Avastin in an NF2 mouse schwannoma model to analyze its efficacy in terms of tumor shrinkage and hearing performance. Setting the Avastin response baseline in mice will allow prioritization of new drugs by comparing their efficacy, and will therefore aid the choice of new drug candidates for clinical trials in NF2 patients.

NEW FUNDER-PUBLISHER PARTNERSHIP

PLOS ONE

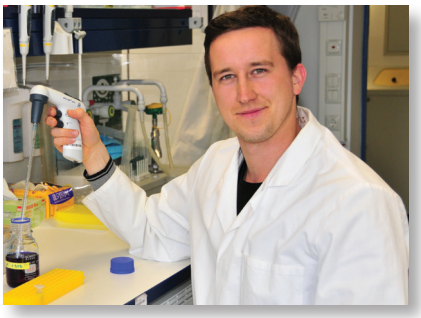
The Children's Tumor Foundation and the scientific journal PLOS ONE are collaborating on a new funding program in the area of neurofibromatosis research. The new initiative, called the Drug Discovery Initiative Registered Report (DDIRR) Awards, is a funder-publisher partnership to integrate the Registered Reports model in the grant application process.

Registered Reports pre-determine the research question, methodology, and design of a study to be carried out, and are designed to enhance the rigor, reproducibility, and transparency of the science produced. Upon thorough review of the study design at the time of grant application, awardees are guaranteed an in-principle acceptance to publication in the journal PLOS ONE. Provided the study is conducted according to the plan, acceptance in principle is honored regardless of study outcome—as such the Registered Report model contributes to eliminate publication bias. This new award will serve as a pilot and will evolve from the Foundation's classic Drug Discovery Initiative Award program.

The Request for Applications for the 2017 DDIRR Awards is now open. Learn more at **ctf.org/research**.

2015 **DRUG DISCOVERY INITIATIVE AWARDEES:**

CTF awarded five Drug Discovery Initiative (DDI) awards in its first of two calls for applications in 2015. Two of the awards will target novel therapies for NF1-related tumors, specifically malignant peripheral nerve sheath tumors (MPNSTs), and three for NF2-related tumor therapies. We are enthused to be able to fund these exciting projects!



Alexander Schulz, MD, PhD, ***of Leibniz Institute for Age Research, Germany,*** received an $85,000 *in vivo* award for his proposed study, ***"Establishing a protein replacement therapy for the treatment of Schwann cell-derived nerve sheath tumors."*** This proposal aims to establish an innovative approach using recombinant proteins to prevent schwannoma development by altering the interaction of Schwann cells and axons (long nerve cell protrusions).

Andrea McClatchey, PhD, ***of Massachusetts General Hospital/Harvard University,*** received a $40,000 award allowing her to continue to work on her 2014 project, ***"Expanded testing of centrosome-unclustering drugs in NF2-mutant tumors."*** Centrosomes are so-called cellular organelles that are essential for normal cell division, and their overduplication is a feature in tumor cells. The goal in this expanded study is to investigate the sensitivity of other NF2-mutant tumor cells, particularly meningioma, to centrosome targeting drugs and to test an expanded panel of these drugs that act in different ways on all NF2 tumor types.

Lei Xu, MD, PhD, ***of Massachusetts General Hospital,*** received an $85,000 award for her proposed study ***"Combining immunotherapy and antiangiogenic therapy in an NF2 schwannoma model."*** The use of bevacizumab, a so-called antiangiogenic drug, in the treatment of NF2 vestibular schwannomas has shown an ability to improve hearing in some patients. The proposed study will combine the use of bevacizumab with immunotherapy, and if the results are superior to either treatment alone, Dr. Scott Plotkin of MGH will use the results to design a clinical trial for NF2 patients.

Jeffrey Field, PhD, ***of University of Pennsylvania,*** received a $40,000 *in vitro* award for his proposal ***"MPNST profiling and screening: an experiment in research-based education."*** This project will create the first ever college course in drug screening, and will specifically screen for drugs for NF1 MPNSTs. Students will screen drugs, both known and novel, against NF tumor cell models, primarily cancer models. The known drugs will serve as a starting point for comparison with other screening efforts.

Steven Lewis Carroll, MD, PhD, ***of the Medical University of South Carolina,*** received an $85,000 *in vivo* award for his proposed study ***"Combinatorial therapy with receptor tyrosine kinase inhibitors for MPNST."*** This study will identify three drugs (all currently in clinical use or clinical trials for other cancer types) that effectively inhibit MPNST proliferation. These drugs will be tested in various combinations in hopes of generating sufficient data to attract follow-on funding from the NIH or DOD to expand testing of RTK therapies for the difficult-to-treat MPNSTs.

2015 DRUG DISCOVERY INITIATIVE AWARDEES

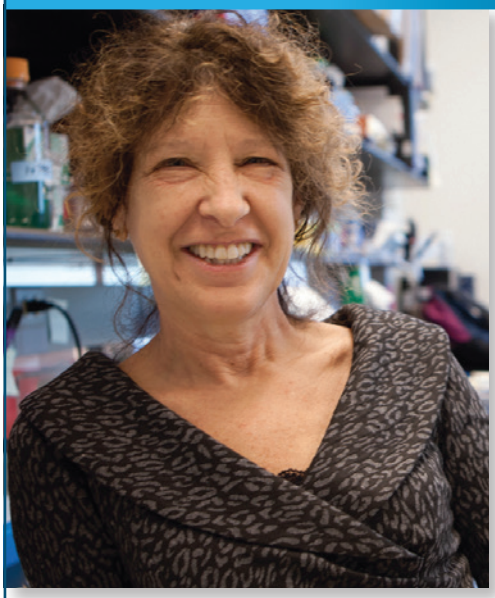
CTF awarded three additional Drug Discovery Initiative (DDI) Awards in its second of two calls for applications in 2015. The DDI Award program supports early stage testing of candidate drug therapies for the treatment of NF1, NF2, and schwannomatosis. These awards fuel the drug pipeline with promising leads.

A. THOMAS LOOK, MD,
of the Dana-Farber Cancer Institute, was granted an *in vivo* DDI Award for his proposal, ***"Drug discovery for NF1-associated malignant peripheral nerve sheath tumors using the zebrafish model."***

NF1-related MPNSTs are very aggressive tumors with poor prognoses for the patients who are diagnosed with it. Surgery to remove MPNSTs is not effective because they often recur and metastasize. Chemotherapy regimens are not only ineffective, but toxic to the patient. Dr. Look and his team have developed a zebrafish model, through which they will rapidly screen drugs that are already in use in humans, obliviating the need to perform expensive and time-consuming toxicology studies. They predict that they will be able to identify one or more already-FDA-approved drugs, which have been developed for other diseases, that will show activity against MPNSTs. These drugs could potentially be "repurposed" to more effectively treat this small subset of NF1 patients.

JOSEPH KISSIL, PhD,
of the Scripps Research Institute, was granted an *in vivo* DDI Award for his project, ***"Assessing the anti-tumor activity of crizotinib in NF2-deficient meningioma."***

Dr. Kissil and his team have identified an already-FDA-approved drug, known as crizotinib, as having anti-tumor activity against NF2-related schwannomas. This drug is already in use in patients with lung cancer and has demonstrated few side effects, and is therefore safe. A clinical trial is currently being initiated to test crizotinib against schwannoma in NF2 patients. The group will now assess whether crizotinib can also be useful against another NF2-related tumor, meningioma, by testing this drug in cell and animal models. Should this show a desirable effect, it would indicate that the trial being initiated should be expanded to include meningioma in addition to schwannoma.



NANCY RATNER, PhD,
of Cincinnati Children's Hospital, was granted an *in vitro* DDI Award for her study, ***"Mechanisms of resistance to MEK inhibition in neurofibroma."***

This study aims to find drugs that reduce neurofibroma size and are potentially curative. We already know that drugs that target MEK proteins shrink most neurofibromas. In patients with NF1, the mutated gene, neurofibromin, can no longer do its proper function of turning off a protein called Ras. When Ras is on, downstream pathways (that include MEK) are also active, contributing to neurofibroma formation. By using a drug to inhibit MEK, the over-active pathway is turned off, which can shrink neurofibromas. However, both in humans and in preclinical trials in mice, inhibiting MEK doesn't always work and some neurofibromas show resistance to MEK inhibition. Dr. Ratner and her team will work to determine what else is being turned on during MEK inhibition so that it can also be targeted, prevent drug resistance, and identify an increasingly successful treatment for patients with NF1.

2014 **DRUG DISCOVERY INITIATIVE AWARDS:** *Round 1 Recipients*

The Drug Discovery Initiative (DDI) awards program is focused on seed funding preclinical drug testing studies on neurofibromatosis in cell or animal models, and is one of the most successful Children's Tumor Foundation programs to date. The Foundation is pleased to announce the most recent recipients of this important grant.

Miriam Smith, PhD
University of Manchester

Treatment of Neurofibromatosis Type 2 (NF2) by Exon Skipping

Neurofibromatosis type 2 (NF2) is a neurogenetic disorder that predisposes patients to develop tumors of the nervous system. It is known that NF2 disease is caused by mutation of the NF2 gene. Dr. Smith will use the DDI award to develop a cutting-edge method to 'rescue' mutations in coding regions of NF2, where 98-99% of small mutations are found.

David Largaespada, PhD
University of Wisconsin-Madison

Targeting Hyaluronic Acid for NF1-associated Tumors

Malignant peripheral nerve sheath tumors (MPNST) remain the leading cause of death for NF1 patients and most therapies have failed to demonstrate effectiveness against plexiform neurofibromas and MPNSTs. Recently, Dr. Largaespada and colleagues showed that a combination of two drugs, RAD001 and PD-901, were effective at treating mice that develop Schwann cell tumors. To improve drug delivery to the tumors, Largaespada will combine these drugs with PEGPH20, which has been shown to safely and effectively improve drug delivery and efficacy of chemotherapy in patients.

Gregory Riggins, MD PhD
Johns Hopkins University

Testing Combinations of FDA-approved Agents with and without Radiation Therapy in an NF2 Schwannoma Murine Model

Dr. Riggins will use the DDI award to examine the safety and efficacy of radiation combined with compounds that effect NF2 tumor growth through multiple pathways, including kinase inhibtors and mTOR inhibitors. He will first test the toxicity and efficacy of each compound alone and then will test their effect together with and without radiation therapy.

Andrea McClatchey, PhD
Harvard Medical School

Preclinical Investigation of Centrosome Unclustering Drugs in NF2-mutant Schwannoma

Excess numbers of centrosomes, a part of the cell that is essential for normal cell division, occurs in many different tumor types and is a feature of tumors that differentiate them from normal cells. Merlin has a key role in controlling the number of centrosomes within cells. Dr. McClatchey will use the DDI award to test if NF2 tumors are more sensitive to drugs that target excess centrosomes.

For more information, please visit www.ctf.org/ddi.

More Children's Tumor Foundation Resources Available in Spanish

This fall, CTF is introducing two new features for the Spanish-speaking members of our community. People whose first language is Spanish will now be able to go to www.nfregistry.org and access the surveys in Spanish. In addition, our popular Newly Diagnosed with NF1 booklet is now available in Spanish. For copies, or a link to this publication on our website, please email info@ctf.org.

2014 **DRUG DISCOVERY INITIATIVE AWARDS:** *Round 2 Recipient*

The Drug Discovery Initiative (DDI) awards program is focused on seed funding preclinical drug testing studies on neurofibromatosis in cell or animal models, and is one of the most successful Children's Tumor Foundation programs to date. The Foundation is pleased to announce the most recent recipient of this important grant.

Florent Elefteriou, PhD
Vanderbilt University

A Dual Trametinib-BMP2 Treatment to Promote Bone Union in NF1

Children with neurofibromatosis type I (NF1) can present with skeletal dysplasia, including bowing of the tibia that often leads to fracture and does not heal (pseudarthrosis). This condition requires repeated and invasive surgeries, and is associated with extreme morbidity. Dr. Elefteriou has recently shown that combined MEK inhibition with BMP2 stimulation promotes bone healing in models of NF1 pseudarthrosis. This DDI award will allow Dr. Elefteriou to collect crucial preclinical data to support the use of Trametinib and BMP2 to promote bone repair in children with NF1 pseudathrosis, which may lead to a clinical trial.

2013 DRUG DISCOVERY INITIATIVE FUNDING AWARDED

The Drug Discovery Initiative (DDI) awards program was designed to provide a critical early-stage doorway to the NF preclinical pipeline. These small scale awards, with a quick application and turn-around process, allow the Foundation to fuel the therapeutic pipeline for a relatively small investment. This year, the DDI program funded four proposals in the first round and CTF is in the process of evaluating with reviewers the second round of applications.

The first four funded labs are:

Jean Nakamura, MD
University of California San Francisco
Identification of Novel Targets in NF1 Cancers by Drug Sensitivity Profiling

TEST DIFFERENTLY MUTATED SUBTYPES OF NF1 TUMORS FOR DRUG SENSITIVITY TO DEFINE SPECIFIC SIGNALING PROFILE SIGNATURES AND EFFECTIVE DRUGS FOR CLINICAL APPLICATION

The Neurofibromatosis Syndrome, characterized by loss of the NF1 gene, confers increased risk of cancer development. The investigators have developed a unique mouse model of cancers caused by NF1 loss. One of the goals of this study is to analyze these tumors to define how mutations in the NF1 gene lead to cancer, and how these processes can be stopped. The project uses a 94-compound drug library of established chemotherapeutic agents, representing multiple cancer signaling pathways, against the tumors generated to identify critical biological processes that work with NF1 to cause cancer. This information will help classify subtypes of NF1 tumors by characteristic mechanisms of cancer formation helping direct patients to appropriate and effective therapies.

Lei Xu, MD, PhD
Harvard Medical School, Massachusetts General Hospital
Effect of TGF-beta Blockade in Recurrent NF2 Vestibular Schwannoma

TEST OF NOVEL DRUG IN COMBO WITH RADIATION THERAPY FOR VESTIBULAR SCHWANNOMA

The hallmark of NF2 is bilateral vestibular schwannomas (VS). Ionizing radiation has become a standard treatment for VS. Despite the initial response to radiation, most patients with NF2 ultimately relapse and develop resistance to further radiation therapy. This project will focus on the effect of TGF-β, a particular cell signaling pathway, as the most potent inducer of fibrosis in general and fibrosis correlated with hearing loss in VS using an established VS model that mimics human disease by progressing after radiation. The data generated in this proposal will provide insights into the potential use of TGF-β blockade as a new adjunct to radiation therapy.

Cristina Fernandez-Valle, PhD
University of Central Florida
Creation of Human Merlin-Null Schwann Cells for NF2 Studies

FIRST ATTEMPT TO EMPLOY HUMAN SCHWANN CELL LINES FOR DRUG SCREENING - NOW MOST RESEARCHERS USE MOUSE LINES

A major roadblock to developing drug therapies for NF2 is the lack of human Schwann cell lines with reduced or no expression of the merlin tumor suppressor. The investigators of this proposal are both Schwann cell biologists with combined expertise in NF2 and the cultivation of human Schwann cells. Together they propose to create a set of human Schwann cells having reduced levels of merlin protein using two different strategies. The cell lines will be characterized and their response to a panel of compounds that have known anti-proliferative effects on mouse merlin-deficient Schwann cell lines will be carried out. The end result should be creation of human Schwann cell lines lacking merlin that can be used in larger drug screens.

Charles W. Yates, MD
Indiana University School of Medicine
Testing Periostin-Cre NF2 Conditional Knockout Mouse for Potential Treatment Compounds Useful for NF2

NEW NF2 ANIMAL MODEL GENERATION: FIRST NF2 ANIMAL THAT DEVELOPS VS AND BECOMES DEAF, NEED FOR VALIDATION AS PRECLINICAL MODEL – USE EXISTING EFFECTIVE DRUGS THAT WERE TESTED IN THE CLINIC AND SEE IF THE MODEL PREDICTS CORRECTLY

This group developed a genetically engineered mouse (a mouse with changes to the DNA similar to the genetic changes seen in people with the disease) by causing the gene, merlin, which is responsible for development of NF2, to have mutations early in development. Changes in the gene in this mouse led to some of the tumors similar to those most commonly seen in humans (vestibular schwannomas, which are otherwise known as acoustic neuromas). Using this mouse as a model would be helpful because testing compounds developed to treat NF2-related tumors could also test some of the specific endpoints similar to what is seen in people. To determine if this is a useful model, the group proposed testing AR42, a specific class of medication called an HDAC inhibitor and a compound that in lab studies of cells and other mouse models may potentially be useful in people with NF2 because it reduces or shrinks the size of vestibular schwannomas. The project will examine if the treated mice will respond with preservation of hearing and decrease in tumor size over a three month period of treatment.

Children's Tumor Foundation Funds Six Drug Discovery Initiatives

The Children's Tumor Foundation Drug Discovery Initiative (DDI) program, launched in 2006, provides a drug screening mechanism for researchers with a concept that may advance therapies for the manifestations of NF. DDI awards invest relatively small amounts of funding into projects that could provide exponential return in follow-on funds from government and industry sources.

Below are the six most recent DDIs funded by the Children's Tumor Foundation:


Chris Maxwell, ***University of British Columbia*** and **Conxi Lazaro,** ***Catalan Institute of Oncology-IDIBELL***: Targeting NF1 Associated MPNST with Aurora Kinase Inhibitors

Filippo Giancotti, ***Memorial Sloan-Kettering Cancer Center***: Preclinical Efficacy of the Neddylation Inhibitor MLN4924 in Neurofibromatosis Type 2

Nancy Ratner, ***Cincinnati Children's Hospital Medical Center***: In Vivo Testing of Anti-Oxidants in NF1 CNS

Andrea McClatchey, ***Massachusetts General Hospital***: Heterogeneity of Drug Response in NF2-deficient Schwannomas

Rajesh Khanna, ***Indiana University***: Assessment of Peptide-based Disruptors of the Neurofibromin and CRMP-2 Interaction as Novel Analgesics for NF1

Michael Brownstien, ***Pisces Therapeutics, LLC***: Small Molecule Ras Inhibitor for the Treatment of Neurofibromatosis Type 1