CLINICAL RESEARCH AWARDS

2021

FRANK BUONO, PhD

Yale University

The Development and Validation of the NF Pain Module (NFPM) within iCanCope-NF Clinical Trial

Dr. Buono's group will validate a mobile-app-based pain assessment tool for NF1. This grant is complementary to a Congressionally Directed Medical Research Program grant to develop a customized pain assessment tool specifically for NF1 that evaluates the pain comprehensively and can be used for clinical trials and treatment planning. The NF Pain Module (NFPM) will measure pain catastrophizing, tolerance, and threshold, along with more established measures such as pain severity and interference. It will provide a tool to facilitate differentiation in pain experience and tracking for adults with NF1. Additionally, the validation of this assessment may enable more individualized treatments for pain symptoms.

2020

DAVID LARGAESPADA, MD, PhD

University of Minnesota

A Nutraceutical/Dietary Intervention for Neurofibromatosis type 1

The concept of dietary interventions, or "nutraceuticals" as a way to slow or prevent the development of cutaneous and plexiform neurofibromas in NF1 has long been of interest. While very small-scale clinical trials of the "Mediterranean diet" have hinted at anti-tumor activity, there not yet been a thorough examination of the potential mechanism of action, safety, and effectiveness of key elements of this type of diet. Dr. Largaespada's group will test a purified, standardized combination of curcumin (the active ingredient in turmeric) and oleocanthanol (a bioactive component of extra-virgin olive oil) for its effects in cell culture and animal models and subsequently in human subjects who are unable to take MEK inhibitors such as selumetinib.

GEOFFREY MCCOWAGE, MD

Sydney Children's Hospitals Network, Australia

Towards improving MPNST molecular diagnosis for patients with neurofibromatosis type 1 through a liquid biopsy test

Accurate and timely diagnosis of malignant peripheral nerve sheath tumor (MPNST) in people with NF1 poses a challenge in current clinical settings. This study will explore whether detection of MPNST could be achieved by "liquid biopsy," a non-invasive method to detect the DNA biomarkers, or "signatures" of different types of tumors. The researchers will investigate whether methylation patterns, as well as somatic mutations, in SUZ12, EED, TP53, and CDKN2A/B genes can be identified in the blood of patients with NF1. Such findings could lead to earlier treatment and better outcomes for people at risk of MPNST.

VANESSA MERKER, PhD

Massachusetts General Hospital, Boston

Incorporating FDA Guidance on Patient-Focused Drug Development in NF: A Pilot Study of Qualitative Patient Interviews within NF Clinical Trials

This ancillary study will measure quality of life (QoL) in people with NF2 who are enrolled in the INTUITT-NF2 clinical trial. Dr. Merker's group will solicit patients' views on the symptoms and impacts that are relevant to and most important for their target tumor type. By embedding QoL measures within a treatment trial, the researchers can compare qualitative such as patients' self-reported symptoms, functioning, and quality of life to the INTUITT-NF2 trial's quantitative assessments of tumor volume, hearing, and adverse events. This study will be used to develop consensus guidelines on embedding qualitative interviews in NF clinical trials within the Response Evaluation in Neurofibromatrosis and Schwannomatosis (REiNS) collaboration. Such guidelines would be applicable to a wide variety of NF clinical trials in the future as the U.S. FDA moves towards requiring inclusion of more QoL information in clinical trial planning and the drug approval process.

BRUCE KORF, MD, PHD

University of Alabama at Birmingham

"Paired tissue biopsy for target inhibition and immune microenvironment changes in patients with NF1 and MPNST treated with MEK, bromodomain, and checkpoint inhibitors."

This grant is ancillary to a study funded by the Neurofibromatosis Clinical Trials Consortium in which NF1 patients with MPNST will receive selumetinib in combination with durvalumab (a bromodomain antibody). This Clinical Research Award will support tumor biopsies prior to treatment and while on treatment to better understand how these drugs act on tumor tissue**.**

Clinical Research Awards were not awarded in 2019.

2018

CLINICAL RESEARCH AWARDS

The Clinical Research Award program supports early stage pilot clinical trials of candidate therapeutics, or interventions for treatment of physical or psychosocial manifestations of NF1, NF2, and schwannomatosis.

AARON SCHINDELER, MD

Children's Hospital at Westmead, Australia

L-Carnitine Safety and Effects on Muscle

Low muscle tone, muscle weakness, and high levels of fatigue are often concerns for individuals with NF1. Evidence suggests that an underlying change in metabolism may be a cause. Both human NF1 muscle biopsies and NF1 mouse models show a build-up of lipid (fat) droplets in muscle cells. In the mouse model, treatment with the nutritional supplement L-carnitine reduced muscle lipid and improved fatigue resistance, as reported by Aaron Schindeler, MD, of The Children's Hospital at Westmead, Australia, Based on these findings, CTF recently awarded Dr. Schindeler a $20,000 Clinical Research Award for a pilot study of L-carnitine supplementation to determine whether this intervention is safe and to explore whether it can improve quality of life and functional outcomes in children with NF1.

RAYMOND KIM

University of Toronto, Canada

Cell-free DNA as a biomarker in Neurofibromatosis 1

Neurofibromatosis type 1 (NF1) is a rare genetic condition that predisposes patients to many types of cancer. Because doctors cannot predict when or if patients will develop cancer, tumors are often discovered late and do not respond well to therapy. To improve care for NF1 patients, doctors need tests that can identify cancers earlier. In recent years, scientists have discovered that they can detect cancer using cell-free DNA (cfDNA). As tumors grow, cfDNA gets released into the blood stream and can be detected using special blood tests. Our team plans to determine whether 2 newly-developed cfDNA technologies can (a) detect early cancer in NF1 patients, (b) identify the tumor's location in the body, and (c) monitor disease severity. If successful, these tests will improve cancer care and health outcomes for those living with NF1.

2016 CLINICAL RESEARCH AWARDS

The Children's Tumor Foundation's Clinical Research Award (CRA) program supports early-stage pilot clinical trials of candidate therapeutics or interventions for the treatment of NF1, NF2, and schwannomatosis manifestations. These awards support innovative clinical trial–enabling studies.

A Phase II Trial on the Effect of Low-Dose versus High-Dose Vitamin D Supplementation on Bone Mass in Adults with Neurofibromatosis Type 1 (NF1)
David Viskochil, MD, PhD, University of Utah

Low bone density and vitamin D insufficiency occur frequently among people with NF1, but there are no proven preventive strategies in NF1 patients. This study is designed to assess the efficacy of oral vitamin D3 and calcium therapy to prevent abnormal loss of bone mass in adults with NF1. A two-year prospective double-blind trial of two different doses of daily vitamin D supplementation in adults with NF1, who are insufficient in serum 25(OH)-vitamin D [25(OH) D] at the time of enrollment, will be conducted. The CRA grant from CTF will supplement the investigators' Clinical Trial Award from the Department of Defense (DoD: #W18XWH-12-1-0487) . The grant amount is $146,267.

Reliability and Validity of Computerized Cognitive Outcome Tools in NF1
Karin Walsh, PsyD, Children's National Medical Center

Clinical trials targeting cognitive and learning impairments in children with NF1 have yielded mixed results to date, with methodological weaknesses thought to be partially responsible for these inconsistent outcomes. This CRA grant will support a proposal of the REiNS (Response Evaluation in Neurofibromatosis and Schwannomatosis) initiative's Neurocognitive Committee for the systematic review of current cognitive outcome measurement tools, and make recommendations for the most psychometrically sound (reliable, sensitive), feasible, and appropriate instruments for use in clinical trials. It will establish NF-specific normative data, test-retest reliability, and validity of several current, novel computerized cognitive test batteries (Cogstate and NIH Toolbox) to support recommendations for appropriate clinical-trial endpoints. The grant award amount is $150,000.

2015 CLINICAL RESEARCH AWARDS

The Children's Tumor Foundation's Clinical Research Award (CRA) program supports early stage pilot clinical trials of candidate therapeutics or interventions for the treatment of NF1, NF2, and schwannomatosis manifestations. These awards support innovative clinical trial enabling studies.

Ana-Maria Vranceanu, PhD, a Clinical Research Award (CRA) recipient in 2013 and 2014, has been awarded a third CRA to adapt a psychosocial support method so that it can be offered to people with NF2. This population can experience significant social isolation as well as anxiety and depression, unemployment, or divorce or separation from significant others. The Relaxation Response Resiliency Program (3RP) has been found effective for improving Quality of Life (QoL) in NF1 and schwannomatosis populations in Dr. Vranceanu's previous CTF-funded research. With the new grant, Dr. Vranceanu's team will test 3RP delivered via Skype and using Communication Access Realtime Translation (CART). If effective, she plans to implement this approach for the broader population of NF2 patients. Dr. Vranceanu is an Associate Professor in Psychology working at Massachusetts General Hospital and at Harvard Medical School. The grant award amount is $149,836.

Gena Heidary, MD, PhD, a neuro-oncologist at Boston Children's Hospital, received a CRA to conduct a study of visual field outcomes in NF1-related optic pathway glioma (OPG). Her project builds on a multicenter study of NF1-OPG outcomes, funded jointly by CTF and the Gilbert Family Neurofibromatosis Institute. Dr. Heidary's work will examine whether visual field testing, which measures peripheral vision, is a valuable addition to conventional visual acuity testing for measuring visual outcomes in children with OPG. The grant amount is $150,000.

CLINICAL RESEARCH AWARD WINNERS ANNOUNCED

Resiliency Training for Adolescents with NF1 and NF2 via Skype

A Clinical Research Award of $148,000 was granted to **Ana-Maria Vranceanu, PhD,** a clinical psychologist at Massachusetts General Hospital. Dr. Vranceanu will test the ability of a Relation Response Resiliency Program (3RP) to improve quality of life for adolescents ages 12-18. The program teaches coping skills that have already been shown to improve quality of life and ability to deal with stress and symptoms in various other medical conditions. People with NF may experience depression, anxiety, stress, lower self-esteem, and pain. Psychological approaches such as relaxation exercises and cognitive therapies are potentially very helpful for these problems, but not everyone has convenient access to therapists trained in these mind-body techniques. For this reason, Dr. Vranceanu and colleagues are testing delivering these services via Skype. Her current CRA builds on a CTF Clinical Research Award to study 3RP with adults with NF1 or NF2. In the new study, Dr. Vranceanu's group will adapt the method for adolescents. If the program shows a greater benefit than a comparison group, Dr. Vranceanu plans to extend the program and to develop similar services for children and for deaf patients.

Phase 1 Trial of Combined MEK and mTOR Inhibition in MPNSTs

AeRang Kim, PhD, a pediatric oncology researcher at the Children's Research Institute in Washington, DC, was awarded a $150,000 Clinical Research Award to investigate a combination of drugs for treatment of malignant peripheral nerve sheath tumors (MPNSTs). These aggressive tumors can occur in NF1 and are difficult to treat successfully. Dr. Kim and her colleagues will use this award to test the safety in humans of a combination therapy that has shown promise in an animal model of NF1 MPNSTs. Both drugs target the RAS pathway, which is over-activated in NF1. One is temsirolimus (Torisel®) a type of mTOR inhibitor. The other is selumetinib (AZD6244), a MEK inhibitor. The study will test the ability of this combination to shrink MPNST tumors, and try to identify the optimal dose to use in future studies.

A Study of INFUSE Bone Graft in the Treatment of Tibial Pseudoarthrosis in NF1

Bruce Korf, MD, of the University of Alabama at Birmingham, a leading NF researcher, received a $200,000 Clinical Research Award to fund a study of a potential treatment for tibial pseudoarthrosis. This condition occurs in 2-5% of people with NF1 and can lead to multiple surgeries or amputation due to poor bone healing. The study will test the ability of a device called the INFUSE Bone Graft to improve bone healing when applied at the time of surgery. The device has a collagen base that contains the compound bone morphogenic protein-2 (BMP-2) and has previously shown to aid healing of complex tibial fractures in non-NF1 patients. The study will compare the results of INFUSE BMP-2 at the time of tibial repair surgery in children with NF1 to a control group of patients treated surgically without BMP2.

UPCOMING **RESEARCH & GRANT DEADLINES:**

Drug Discovery Initiative (DDI)
Monday April 15, 2015
To apply please visit:
www.ctf.org/Research/Funding/

UPCOMING EVENTS

NF FORUM
Friday, April 17 - Sunday, April 19
Register at *www.ctf.org/nfforum*

NF CONFERENCE
Saturday, June 6 - Tuesday, June 9
Register at *www.ctf.org/NFConference*

2013 CTF CLINICAL RESEARCH AWARDS

KARIN WALSH, PSYD, CHILDREN'S RESEARCH INSTITUTE

The Impact of Ras/MAPK signaling pathway-targeted therapies on neurocognitive functioning in youth with NF1

We will use a brief, computerized battery of neurocognitive tasks (CogState) to evaluate change in functioning in a cohort of participants with NF1 enrolled on a clinical trial targeting the Ras/ERK pathway (MEK or BRAF inhibitors). This study design is innovative in that it addresses ongoing challenges in neurocognitive research by utilizing novel technology and reducing barriers that have plagued prior research (financial, personnel, and time). We will leverage the opportunity provided by known upcoming multi-site therapeutic trials to evaluate a large, diverse sample of individuals affected by NF1. This design incorporates collaborative sites with a history of expertise and success in clinical trials and neurocognitive research (NIH/NCI, Children's Hospital Boston, Children's Hospital of Philadelphia). Each site is highly qualified to carry out the proposed research efficiently and effectively. Primary Objective: To evaluate and characterize changes in neurocognitive functioning (measured by CogState), in children and adolescents (age 4 to 18 years) with NF1 who are enrolled on a clinical trial targeting the Ras/MAPK signaling pathway (e.g., MEK, BRAF Inhibitors) for treatment of glioma or plexiform neurofibroma (PN) in the following neurocognitive domains: learning/memory, working memory, attention, and processing speed.

ANA-MARIA VRANCEANU, PHD, MASSACHUSETTS GENERAL HOSPITAL

Resiliency training for patients with Neurofibromatosis via videoconferencing with Skype

The objective of the study is to test the acceptability, feasibility and preliminary efficacy of the 3RP (focused on teaching mind body coping skills) vs an attention placebo control (focused on providing general information on NF without teaching skills) in improving QoL and resiliency in patients with NFs. Delivery of both intervention and control will be via groups through Skype. The primary hypothesis is that patients in the 3RP group will show a bigger improvement in QoL and resiliency compared to patients in the control group. The study design is the best method of testing our hypotheses as it allows us to determine the effect of the 3RP beyond the effects due to nonspecific influences like therapist attention or positive expectations. We bring together experts in NF, mind body medicine, and excellent infrastructure making us the best, and to our knowledge the only group able to conduct this study at the present moment. We have already conducted preliminary data on treatment targets, and have shown acceptability, feasibility of the intervention within a face-to-face format, and are thus ready to pursue testing the intervention via videoconferencing with Skype. Impact: Findings from this study will support or refute the acceptability, feasibility and efficacy of the 3RP for NF patients delivered via videoconferencing with Skype. The results will also inform our understanding of the 3RP program in improving QoL and resiliency, and will provide insight into mechanisms of improvement in QoL in this population. Positive results from this study could serve as a basis for further research on cost effectiveness of the videoconference 3RP and serve as preliminary data for a large scale RCT in this population via an R01 NIH application.

The Children's Tumor Foundation Funds Three Clinical Research Awards

The Children's Tumor Foundation Clinical Research Awards fund small-scale clinical trials as part of an ambitious initiative to accelerate identification of NF drug therapies. In response to feedback from the research and clinical communities, the Foundation expanded the scope of the program so that Clinical Research Awards also fund adjunct studies to improve the design and implementation of clinical trials, making them faster and more meaningful.

Below are the three most recent Clinical Research Awards funded by the Children's Tumor Foundation:

Kathryn North, *The Children's Hospital at Westmead*
A Phase II Randomized Placebo-Controlled Double-Blind Cross-Over Trial of Methylphenidate in Children with Neurofibromatosis Type 1

Dr. North's research group in Australia will study whether children with NF1 and attention deficit hyperactivity disorder (ADHD) benefit from the use of methylphenidate (Ritalin, Concerta). It will try to determine the characteristics of those children most likely to be helped by this medication.

Nicole Ullrich, *Boston Children's Hospital*
Effect of Creating Visual Illness Narratives on Quality of Life in Children with Neurofibromatosis Type 1: A Pilot Intervention Study

Children and adolescents with NF1 will be guided in creating their own videos about their experiences. The aim is both to teach their clinicians what they need to know about living with NF1, and to empower these young patients by having them share their stories and articulate what they think and feel to an audience that is eager to listen and understand.

Lei Xu, *Massachusetts General Hospital*
Effect of Anti-VEGF and Radiation on NF2 Vestibular Schwannoma

Radiation therapy is standard for NF2 vestibular schwannomas, but is associated with hearing loss in 50% of patients. Bevacizumab is a drug treatment that shows promise as an alternative to radiation, but is not as effective as could be desired. This project will test whether a combination of radiation and bevacizumab might improve effectiveness and lessen unwanted effects.

Recent Research Awards Funded by the Children's Tumor Foundation

FOUNDATION SCHWANNOMATOSIS AWARDS — 2011

Over the past five years CTF has convened a series of Schwannomatosis Workshops to identify priorities for advancing and funding schwannomatosis research. Below are the latest recipients from the Schwannomatosis Awards program.

Betty Tyler, M.D., *Johns Hopkins University* – **$73,043**
Creating preclinical models of surgery for spinal schwannomas

Scott Plotkin, M.D., Ph.D., *Massachusetts General Hospital* – **$75,000**
Neurotrophin levels in schwannomas and schwannomatosis patients: Is there a relationship to chronic pain?

Laura Papi, M.D., Ph.D., *House Research Institute* – **$75,000**
Exome sequencing of schwannomatosis genomes

Larry Sherman, Ph.D., *Oregon Health & Science University* – **$75,000**
Regulation of TRPV1 in sensory neurons by SNF5—null Schwann cells

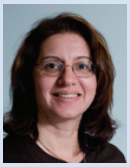
Marco Giovannini, MD, Ph.D., *House Research Institute* – **$75,000**
Development of a screening platform for schwannomatosis therapeutic agents

2011 FUNDED CLINICAL TRIAL AWARDS

Clinical Research Awards fund early stage pilot clinical trials of candidate therapeutics for the treatment of tumors and other manifestations of NF1, NF2 and schwannomatosis. We are pleased to announce the recent awardees from this program.

Computerized cognitive training for children with Neurofibromatosis type 1
Maria Acosta, M.D., *Children's National Medical Center*

Phase I trial of AZD6244 on plexiform neurofibromas
Michael Fisher, M.D., *The Children's Hospital of Philadelphia*



NF1-associated Gliomas Multicenter Consortium – Initiative for tumor stratification and the identification of prognostic indicators and treatable targets
Anat Stemmer-Rachamimov, M.D., *Massachusetts General Hospital*

LOOKING FORWARD

Here are a few events that may be of interest. For a complete listing or more information, please see www.ctf.org/calendar

05/12 - Washington, D.C.
Family Information Meeting on Neurofibromatosis Type 1

05/16 - Portland, OR
NF/schwannomatosis Group Meeting

05/19 - East Bountiful, UT
NF Women's Day Gathering

05/19 - Miami, FL
Miami Children's Hospital Medical Symposium

06/02 - Amesbury, MA
Molly's Spring for a Cure

08/11 - Lowell, MA
Dylan's Family Fun Day

NEW YORK CITY POKER TOURNAMENT

MAY 17, 2012
RADISSON MARTINIQUE ON BROADWAY

GRAND PRIZE:
Entry ticket to the World Series of Poker in Las Vegas, NV
(valued at $10,000)

For more information, please contact
Athina Moustakis
(212) 344-6633 ext. 228

CTF Funds Four New Clinical Research Awards

The Foundation's recent initiatives to accelerate the identification of NF drug therapies have included a Clinical Trial Awards program to fund small scale clinical trials. Through that program, last year we were delighted to announce the funding of two trials: lapatinib for NF2 vestibular schwannoma, with $125,000 awarded to Dr. Jaishri Blakeley at Johns Hopkins University in collaboration with GlaxoSmithKline; and sorafenib for NF1 plexiform neurofibroma, with $125,000 awarded to Dr. Bruce Korf at the University of Alabama to expand on a National Cancer Institute trial headed by Dr. Brigitte Widemann and Dr. Aerang Kim of NCI.

In fall 2010, responding to inquiries from the research and clinical communities we expanded the scope of this program to Clinical Research Awards. These can still be used to fund small scale clinical trials, but can also be used for adjunct clinical studies to identify 'biomarkers'. Biomarkers are clinical indicators that can be used to determine if NF is progressing or if a drug is working to slow progression. Biomarkers will ultimately be used to improve the design and implementation of clinical trials making them faster and more meaningful.

Four Clinical Research Awards have been funded: one clinical trial, and three adjunct biomarker studies. These are described below. Following an enthusiastic response to this program, CTF hopes to announce the next deadline for Clinical Research Award applications in spring 2011.

> Phase II Trial of Rapamycin – NF2 Tumors

Matthias Karajannis, New York University Langone Medical Center
Industry Collaborator: Novartis

In the past couple of years, clinical trials for candidate NF2 drugs have commenced, driven in part by CTF's commitment to advancing this area through hosting expert consensus advisory meetings, and also by funding some of the first NF2 clinical trials. This is the second NF2 clinical trial that CTF has funded; the first, a Phase Zero (presurgery) trial of lapatinib, is near conclusion and has been a collaboration between Dr. Jaishri Blakelely (Johns Hopkins University) and Dr. Matthias Karajannis (New York University Langone Medical Center). In this newly funded NF2 clinical trial, RAD001 (rapamycin) is assessed as a candidate drug therapy for NF2 by its effects on the growth and/or shrinkage of the characteristic NF2 tumors vestibular schwannoma, meningioma and ependymoma. RAD001 has been widely tested in patients and is known to be safe; indeed it was one of the first drugs to enter large scale clinical trials for NF1 plexiform tumors. This trial asks whether there is any potential efficacy of RAD001 in NF2. If there are promising results, this trial will pave the way for future combination therapy drug trials, since animal studies have suggested that RAD001 might be additive if combined with other drugs such as Bevacizumab or Laptinib, also being tested as candidate NF2 drug therapies.

Novartis is providing the drug and additional support for this trial, leveraging CTF's investment.

The following three studies, while independent of one another, are all being done as adjunct studies to the Congressionally Directed Medical Research Program's Phase II Clinical Trials Consortium. By funding studies in conjunction with larger government or industry funded studies, the Foundation maximizes the support of our donors.

> New Metrics for Optic Pathway Glioma Trials

Rob Avery, Children's National Medical Center

As NF clinical trials move ahead, it is becoming apparent that there is a need to develop more sensitive approaches for determining as early as possible if a drug is effective. This will mean that the timeline of clinical trials can be shortened, and that a greater number of patients can benefit more rapidly from promising drugs. In this study, Dr. Avery is utilizing a new technology termed Spectral-Domain Optical Coherence Tomography that can be used to detect changes in the optic pathway that will predict as early as possible whether trials to assess drugs for NF1-related optic pathway glioma are looking promising or not. By establishing a reliable quantitative biomarker, the results of this study will make a significant contribution to the advancement of drug treatment for NF1 optic pathway glioma. It should also improve ongoing ophthalmologic care for children with NF1 by acquiring much needed knowledge about the pathophysiology and natural history of NF1-related optic pathway gliomas. This new technology will be an essential biomarker component of future optic pathway glioma therapeutic clinical trials.

By funding studies in conjunction with larger government or industry funded studies, the Foundation maximizes the support of our donors.

> Blood Predictors of NF1 severity

Cynthia Hingtgen, Indiana University

Vascular disease is a manifestation of NF1 that is frequently overlooked, but individuals with NF1, particularly younger patients, are at a significantly elevated risk of vascular disease. Researchers are learning progressively more about the genetics and molecular signaling events that underlie this manifestation. This study aims to take this learning a step further and develop diagnostics to determine how severe vascular disease is likely to be by identifying a blood-borne marker that is