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.

Clinics accepted into the NF Clinic Network

The Children’s Tumor Foundation is happy to announce that two more clinics have been accepted into the NF Clinic Network. All applications for the clinic network are reviewed by the CTF Clinical Care Advisory Board, and accepted or declined based on several factors, including NF expertise, clinic volume, multidisciplinary approach, research efforts, and involvement with CTF.

Lucile Packard Children's Hospital, Stanford
Palo Alto, California

Clinic Directors: Cynthia Campen, MD and David Stevenson, MD
Clinic Coordinator: Samantha Ingerick, NP

Dr. Campen is a board-certified child neurologist and pediatric neuro-oncologist with particular expertise in treating optic pathway glioma and other brain tumors, as well as general expertise in the neurologic complications of NF. Dr. Stevenson is a board-certified geneticist previously at the University of Utah who specializes in the musculoskeletal manifestations of NF1 and related conditions.

The clinic primarily follows pediatric patients, but collaborates closely with adult-care providers.

Moffitt Cancer Center
Tampa, Florida

Clinic Directors: Xia Wang, MD, PhD and Sepideh Mokhtari, MD
Clinic Coordinator: Ruth Alipio

Dr. Wang is board-certified in Clinical Genetics and Internal Medicine. Her research efforts have focused on breast cancer and other cancers in NF1. Dr. Mokhtari is board-certified in Neurology and Psychiatry, and is the Director of Neurologic Services at Moffitt Cancer Center. The clinic primarily follows adult NF patients.

For more information about the new clinics, or if you are looking for an NF clinic or doctor, please visit the “Find a Doctor” section of the Children’s Tumor Foundation website at www.ctf.org. This site includes providers that are part of the clinic network, as well as a separate listing of other NF specialists. To suggest a new provider, please visit ctf.org/nfspecialists.
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.

MORE CLINICS ACCEPTED INTO THE NF CLINIC NETWORK

Three additional NF clinics have been accepted into the NF Clinic Network (NFCN) bringing the total to 50 NFCN Affiliate Clinics in the United States. As our network continues to expand, the Children’s Tumor Foundation is making every effort to increase access to and improve the quality of NF care throughout the country.

Congratulations to the most recent clinics accepted into NFCN:

- **Children’s Hospital of Orange County** in Orange, CA
  with Clinic Director Neda Zadeh, MD, and Clinic Coordinator Narda Hernandez.

- **Connecticut Children’s Medical Center** in Farmington, CT
  with Clinic Director Francis DiMario, MD, and Clinic Coordinator Alyssa White, RN, BSN.

- **Kentucky Neuroscience Institute through the University of Kentucky** in Lexington, KY
  with Clinic Director Donita Lightner, MD, and Clinic Coordinator Kim Osborne.

All Affiliate Clinics must submit an annual report that demonstrates that the clinic provides appropriate NF care through implementation of current consensus clinical care guidelines for NF. As part of this reporting process, Affiliate Clinics are eligible to apply for NF clinic stipends, which provide funding for hosting medical symposia and/or professional attendance at the annual CTF NF Conference, which gathers NF experts and researchers from all over the world.

CTF welcomes the newly appointed clinics who join our other NFCN colleagues in striving to provide excellent patient care and support to families throughout the country. To learn more please visit ctf.org/nfcn.

IMPORTANT 2016 DATES FOR NF RESEARCHERS

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<tr>
<th>Date</th>
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<tr>
<td>April 18</td>
<td>Drug Discovery Initiative Award (A) deadline</td>
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<tr>
<td>June 18-21</td>
<td>NF Conference, Austin, Texas</td>
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<tr>
<td>June 20</td>
<td>Clinical Research Award Letter of Intent due</td>
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<tr>
<td>September 19</td>
<td>Clinic Award applications due</td>
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<td>September 26</td>
<td>Drug Discovery Initiative Award (B) deadline</td>
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To learn more go to ctf.org/research.
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.
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.

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 Ulrich, 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.

NF Research: Seeing the Big Picture and Promoting Collaboration

It is extremely difficult for a single scientific laboratory or a single clinician to find a cure for NF. Therefore, the Children's Tumor Foundation is committed to fostering collaboration.

Attempts to Find Effective Treatments for NF

In 2012, CTF analyzed the current state of neurofibromatosis research and development and drug discovery. The issues and bottlenecks were identified, and efforts were made to solve the problems.

In order to develop new treatments for NF, the different steps of drug discovery have to be freed from logistics problems; the first step is to get access to the material necessary for scientific testing.

continued on page 4
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**
*Micheal 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*

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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](http://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

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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: laptinib 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 laptinib, is near conclusion and has been a collaboration between Dr. Jaishri Blakeley (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

> **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 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.