FISCAL YEAR 2020 REQUEST

We respectfully request $15 million for the Army's Neurofibromatosis (NF) Research Program (NFRP) in the FY2020 Department of Defense Appropriations bill.

NEUROFIBROMATOSIS CLINICAL TRIALS CONSORTIUM (NFCTC)

- The NF Clinical Trials consortium (NFCTC) was established in 2006 to develop and perform clinical trials for the treatment of NF complications in children and adults. The NFCTC was subsequently re-funded in 2011 and again in 2016 for a third award.

- The Consortium is composed of 24 clinical sites. Dr. Bruce Korf is the Principal Investigator and leads the Operations Center based at the University of Alabama at Birmingham. UAB serves as a clinical site and provides administrative, data management, and statistical support to the NFCTC. Dr. Michael Fisher at Children's Hospital of Philadelphia chairs the Steering Committee.

- The NFCTC is funded by Department of Defense through the Neurofibromatosis Research Program (NFRP), one of the Congressionally-Directed Medical Research Programs. The funding and collaboration with the DoD allows unique opportunities to partner with well-established NF Centers both nationally and internationally, pooling expertise and resources toward the common goal of new treatment opportunities and ultimately a cure for Neurofibromatosis.

- The NFCTC has allowed its investigators to develop mature protocols through collaborative discussions with various disease and discipline committees, allowing for quicker turnaround of scientific reviews and regulatory approvals.

- The consortium has leveraged its collaboration with the Department of Defense to work with pharmaceutical companies to acquire therapeutic agents and other organizations to facilitate exchange of information and assist in conducting additional trials.

PARTICIPATING SITES

The operations center and the original nine participating sites were selected by the DoD following a competitive process in 2004. The consortium was expanded to include 13 clinical sites and 9 affiliated sites when it was refunded for an additional five years in 2011 and an additional 3 sites when it was refunded in fiscal year 2017. The sites are:

- The University of Alabama at Birmingham
- Children's Hospital Boston
- Massachusetts General Hospital
- Children's National Medical Center
- Dana Farber Cancer Institute
- Cincinnati Children's Medical Center
- National Cancer Institute
- University of Chicago
- University of Utah
- Washington University (St. Louis)
- New York University Medical Center
- Children's Hospital Los Angeles
- University of California Los Angeles
- Lurie Children's Hospital of Chicago
- Johns Hopkins
- Children's Hospital of Philadelphia
- Indiana University
- Children's Hospital of Westmead (Sydney AU)
- University of Texas SW
- Children's Healthcare of Atlanta
- Murdoch Children's Research Institute (Parkville AU)
- Mayo Clinic (Minnesota)
- University of Minnesota
- University of Texas Southwestern (Dallas)
- Memorial Sloan Kettering Cancer Center

COMPLETED TRIALS

STOPN, "A Phase II Study of the mTOR Inhibitor Sirolimus in Neurofibromatosis Type 1 Related Plexiform Neurofibromas." Dr. Brian Weiss chaired this study and Drs. Michael Fisher, Brigitte Widemann, Bruce Korf and John Perentesis co-chaired. This protocol was designed to find out if sirolimus could stop or slow the growth of and/or shrink plexiform neurofibromas in patients with NF1. STOPN consisted of two strata: Stratum 1 recruited 46 evaluable participants with actively growing tumors, and Stratum 2 recruited 12 evaluable subjects with non-progressive tumors. This study yielded four publications during 2013-2015. The results showed that sirolimus is well-tolerated in NF1 participants, prolongs the time to progression of growing tumors (stratum 1), but does not result in shrinkage of these tumors (stratum 2).

STARS, "A Randomized Placebo – Controlled Study of Lovastatin in Children with Neurofibromatosis Type 1." Dr. Kathryn North chaired this study and Drs. Jonathan Payne and Belinda Barton co-chaired. STARS screened over 270 participants toward the goal of enrolling128 evaluable. This study closed to enrollment with 125 evaluable participants. STARS was designed to determine whether Lovastatin™ could improve cognitive function in children with NF1. Participants in this study were randomly assigned into one of two groups: lovastatin or a placebo control group (inactive substance). Lovastatin had no significant effect on primary outcomes of visual learning and attention (published in December 2016). This study remains open for data analysis of secondary endpoints and an ancillary study from a subset of the population.

MPNST, "SARC016 - Phase 2 Study of the mTOR Inhibitor Everolimus in combination with Bevacizumab in Patients with Sporadic and Neurofibromatosis Type 1 (NF1) Related Refractory Malignant Peripheral Nerve Sheath Tumors" was conducted in collaboration with the Sarcoma Alliance for Research through Collaboration (SARC), with SARC serving as the Operations Center. Dr. Brigitte Widemann represented SARC for the NF Consortium. The results of this study were presented at the American Society of Clinical Oncology 2016 Annual meeting in Chicago, IL. A total of 25 patients were enrolled on this study. With a clinical benefit rate of 12% (3 out of 25 patients), the combination of everolimus and bevacizumab did not reach the study's target response rate and is not considered active in refractory malignant peripheral nerve sheath tumors. Data analysis is complete and a manuscript has been submitted for publication.

COMPLETED ENROLLMENT

RAD001, "A Phase II Study of RAD001 (Everolimus) for Children with Neurofibromatosis Type 1 and Chemotherapy-Refractory Radiographic Progressive Low-Grade Gliomas." Dr. Mark Kieran chairs this study and Drs. John Perentesis and Alyssa Reddy co-chair. Novartis provided drug and funds for optional testing for PK, PG and PD for this study. The purpose of this research study is to learn if RAD001 can shrink or slow the growth of low-grade gliomas in children with NF1. Additionally, the safety of RAD001 in children with NF1 will be studied. A total of 23 participants were enrolled for 22 evaluable to achieve study goals. Fifteen of twenty-two patients (68%) demonstrated a response, defined as either tumor shrinkage or arrest of tumor growth (12 SD). The study remains open for central review of imaging outcomes and data analysis of the secondary endpoints. The results are expected to be published in 2019.

"A Phase II Study of Cabozantinib (XL184) for Plexiform Neurofibromas in Patients with Neurofibromatosis Type 1 – Adult Cohort" Dr. Chie-Schin Shih from Indiana University Children's Hospital chairs this study, and Drs. Michael Fisher and Jaishri Blakeley co-chair. Exelixis provides drug for this study. This phase II study is evaluating whether the targeted agent Cabozantinib shrinks plexiform neurofibromas in adolescents or adults with NF1. The study completed enrollment. 23 subjects enrolled, of which 21 are evaluable for toxicity and 19 are evaluable for response. Eight of 19 (42%) had a partial response to treatment. The study remains open for final data analysis of the primary and secondary endpoints. The results are expected to be published in 2019. Now that the pediatric dose of Cabozantinib has been identified, the study has been amended to add a separate stratum of 19 evaluable pediatric patients (<16 years of age) (see below).

"A Phase 2 Trial of the MEK Inhibitor PD-0325901 in Adolescents and Adults with NF1-Associated Morbid Plexiform Neurofibromas" Dr. Brian Weiss from Cincinnati Children's Hospital Medical Center chairs this study, and Drs. Brigitte Widemann and Scott Plotkin are co-chairs. Pfizer, Inc. provides drug and funds for optional evaluations for this study. This phase II study is evaluating whether PD-0325901 shrinks plexiform neurofibromas in adolescents or adults with NF1. This study has completed its planned enrollment of 19 evaluable subjects. Eight of 19 (42%) had a partial response to treatment. The study remains open for final data analysis of the primary and secondary endpoints. The results are expected to be published in 2019.

"An Open-label, phase 2 study of bevacizumab in children and young adults with neurofibromatosis type 2 and progressive vestibular schwannomas that are poor candidates for standard treatment with surgery or radiation." Dr. Scott Plotkin of Massachusetts General Hospital, affiliate site of Children's Hospital of Boston, chairs this study and Drs. James Tonsgard, Nicole Ullrich and Elizabeth Schorry co-chair. Genentech provides drugs and funds for patient evaluations for this study. The trial enrolled patients aged 6 years or older with NF2 and vestibular schwannoma that are growing and causing hearing loss. The primary objective of this study is to determine the hearing response rate at 24 weeks after treatment with bevacizumab. This study has met recruitment goals, but continues to follow patients on active therapy. Nine of 22 (41%) subjects achieved a hearing response at 6 months and 11/22 patients (50%) had hearing improvement at some point during induction therapy. The induction therapy results are expected to be published in 2019. Subjects remain on-study receiving maintenance therapy.

MPNST, "SARC023 - Phase 1/2 Study of ganetespib in combination with sirolimus for refractory sarcomas and malignant peripheral nerve sheath tumors" is being conducted in collaboration with SARC, with SARC serving as the Operations Center. Dr. AeRang Kim serves as the Principal Investigator and Dr. Brigitte Widemann as co-Principal Investigator. The study is closed to accrual. The phase 1 portion is completed. The study did not meet criteria to progress to the phase 2 portion. Data analysis is complete, and a manuscript has been submitted for publication. Drs. Kim and Widemann are planning the successor MPNST trial with the pre-clinical consortium and NFCTC Biology committee along with DoD and SARC support.

TRIALS IN PROGRESS

"A Study of INFUSE Bone Graft ((recombinant human Bone Morphogenetic Protein-2/absorbable collagen sponge) in the treatment of Tibial Pseudarthrosis in Neurofibromatosis Type 1 (NF1)" Dr. Elizabeth Schorry of Cincinnati Children's Hospital chairs this study and Drs. B. Stephens Richards, David Viskochil and David Little co-chair. Medtronic provides the INFUSE device for this study. The goal of this trial is to determine if use of an osteogenic agent (rhBMP-2) at the time of surgical treatment for tibial pseudarthosis in NF1 patients will result in improved bone healing when compared to NF1 patients treated with the same surgical treatment but without BMP-2. Bone morphogenetic proteins (BMPs) are naturally occurring substances that are involved in bone formation. When applied to bone at the time of surgery, BMPs induce mesenchymal stem cells to infiltrate the fracture zone and to differentiate into osteoblasts, which subsequently form new bone. The application of these substances at the time of surgery may increase the chance of tibial fracture healing. Bone morphogenetic protein-2 (BMP-2), as a collagen sponge device marketed as INFUSE, has shown efficacy in healing of complex traumatic tibial fractures in adult populations. The current study proposes adding BMP-2 (INFUSE) at the surgical site of tibial pseudarthosis repair in children with NF1, compared to a control group of patients treated surgically without BMP-2. The INFUSE BMP2 Study is currently open for enrollment with a goal of enrolling up to 54 participants for 50 evaluable.

"Phase II Study of Binimetinib in Children and Adults With NF1 Plexiform Neurofibroma" Dr. Sabine Mueller of the University of California, San Francisco chairs this study and Dr. Michael Fisher of Children's Hospital of Philadelphia co-chairs. Array BioPharma provides drugs and funds for this study. The goal of this trial is to evaluate children ≥ 1 year of age and adults with neurofibromatosis type 1 (NF1) and plexiform

neurofibromas treated with the MEK inhibitor, binimetinib. The primary objective is to determine if there is an adequate level of disease responsiveness to binimetinib in children and adults with NF1 and inoperable plexiform neurofibromas. The objective response to binimetinib is defined as ≥ 20% decrease in tumor volume reduction by 12 courses. The NFCTC is partnering with the Pacific Pediatric Neuro-Oncology Consortium (PNOC) to enroll for this trial. The Binimetinib Study is currently open for enrollment with a goal of enrolling up to 20 subjects in each cohort for 34 evaluable.

"A Phase II Study of Cabozantinib (XL184) for Plexiform Neurofibromas in Patients with Neurofibromatosis Type 1 – Pediatric Cohort" Dr. Michael Fisher from The Children's Hospital of Philadelphia chairs this study, and Dr. Jaishri Blakeley co-chairs. Exelixis provides drug for this study. This phase II study is evaluating whether the targeted agent Cabozantinib shrinks plexiform neurofibromas in children with NF1. The study enrollment goal is19 evaluable subjects. The study is open and has started enrolling. The pediatric cohort of the study is expected to reach enrollment goals in 2019.

CLINICAL TRIALS OPENING IN 2019

Successor Trial to RAD001 - A targeted chemotherapy trial is in design to treat gliomas in NF1 patients to follow on the results of the RAD001 trial. The anticipated date for open enrollment is within the next three months.

MPNST/SARC - Drs. Kim and Widemann are planning the successor MPNST trial with the pre-clinical consortium and NF Biology committee with DoD and SARC support.

Schwannomatosis – The NFCTC Schwannomatosis Committee is planning a study of targeted chemotherapy for children and adults. The anticipated date for open enrollment is June 2019.

Neurofibromatosis Type 2 – The NFCTC Neurofibroma (NF2) Committee is planning a study of targeted chemotherapy for children and adults with NF2. The anticipated date for open enrollment is March 2019.