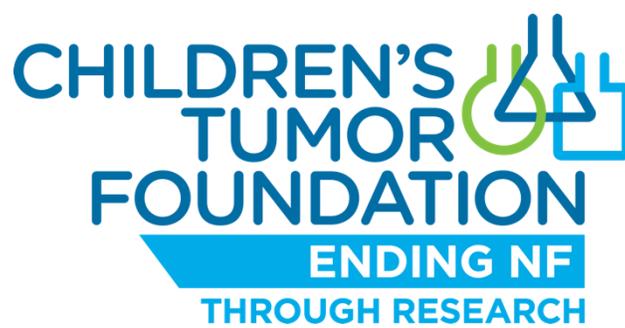


NF Preclinical Initiative



Introduction

The Children's Tumor Foundation (CTF) is a highly-recognized 501(c)(3), not-for-profit medical research organization, and the recipient for seven consecutive years of a four-star rating from Charity Navigator (placing CTF in the top 2% of charities that have earned this distinction). The Foundation is dedicated to improving the health and well-being of the more than 120,000 Americans (and over 2 million people worldwide) living with neurofibromatosis (NF), a term for three distinct genetic disorders: NF1, NF2 and schwannomatosis. NF causes tumors to grow on nerves throughout the body and can lead to deafness, blindness, bone abnormalities, disfigurement, learning disabilities disabling pain, and cancer. NF is under-recognized and underdiagnosed yet affects more people than cystic fibrosis, Duchenne muscular dystrophy and Huntington's disease combined.

CTF drives, manages and funds a research ecosystem to lower the costs and efforts needed to find treatments for NF. In addition to benefiting those who live with NF, this research is shedding new light on several forms of cancer, brain tumors, bone abnormalities and learning disabilities, ultimately benefiting the broader community.

NF Preclinical Initiatives (NFPI)

The **NF Preclinical Initiative (NFPI)** represents one of the Children's Tumor Foundation's groundbreaking models of scientific collaboration.

The NFPI is aimed at accelerating proof of concept testing of potential effective repurposed drugs in NF relevant GEM models, and frontloading the clinical pipeline with new drug candidates for NF1. Launched in 2008, the NFPI is a revolutionary method dedicated to accelerating the search for NF treatments.

Currently, the NFPI joins the forces of four leading NF1 academic laboratories from Harvard University, University of California at San Francisco, Indiana University, and the Cincinnati Children's Hospital (please see Appendix for biographies of the current members). These four labs have a successful track record in preclinical drug testing. They demonstrated in the Foundation's previous preclinical efforts that they are able to efficiently determine which drugs work, and move the efficacious ones quickly into clinical trials with NF1 patients.

In order to determine which drugs and NF1 mechanisms will be tested, the principal investigators of each NFPI lab propose projects that outline the rationale, study design, hypotheses, anticipated impact, and budget. CTF and its peer review committee carefully assess and select these proposals for funding.

During these preclinical studies, CTF acts as funder and project manager (involving CTF staff; see appendix).

To date, the NFPI has:

- Completed 116 preclinical studies to test possible new treatments in genetically engineered mouse models.
- Spurred 16 clinical trials to test the most promising treatments from the preclinical studies. The most successful study to date found that the MEK inhibitor Selumetinib shrunk tumors of at least 20% in more than 70 percent of enrolled NF patients.
- Initiated more than 12 productive research collaborations.

- Published over 13 papers in highly regarded medical journals.
- Opened and released all data transparently to the larger scientific community, so that the platform's efforts might spark additional research to find effective NF therapies quickly.

From a contract perspective, **all NFPI contracts to date have been exclusively implemented with the academic institutions**, and the **costs of the preclinical studies were entirely covered by the funding agencies**. Although CTF has partnered with pharmaceutical companies to obtain the drugs that the researchers test for effectiveness in treating NF, those companies' roles has been passive, and their level of engagement has varied widely.

However with this extensive research infrastructure and deep drug discovery expertise firmly in place, the Children's Tumor Foundation seeks to further evolve its preclinical research platform through the NF Preclinical Initiative.

In 2017, CTF plans to expand the **collaborative opportunities with the pharmaceutical industry**, embedding pharma partners directly into NF research as co-partners and co-funders of these vital efforts.

The Children's Tumor Foundation plan is to formalize pharmaceutical collaborations in a manner that these companies are financially and operationally invested in each NFPI research project. With an ever-increasing involvement of companies, CTF 's goal is to create a financially self-sustaining NFPI, which will dramatically shorten the length of time and negotiation needed to facilitate academic researchers' access to a company's available drugs. This will also strengthen the foundation for deeper corporate participation in the NF effort.

APPENDIX

NF Preclinical Initiative: Children's Tumor Foundation Leadership



**SALVATORE LA ROSA, PHD
VP OF RESEARCH AND DEVELOPMENT**

Dr. La Rosa is responsible for the implementation of the Foundation's business strategy into research projects. He manages research activities, providing scientific and knowledgeable review of discovery, preclinical and early development programs in neurofibromatosis. He leads a team of seven experts who run all CTF research, clinical and patient support activities. They develop and manage novel partnerships and initiatives with academic research groups and biotech/pharmaceutical companies to address unmet needs in NF.

The research division of Dr. La Rosa's team acts as project manager for the NF Preclinical Initiative and Synodos. Within NFPI, Dr. La Rosa oversees all operational activities, providing medicinal chemistry expertise in the phase of drug selection and experimental design.

Dr. La Rosa has participated in many international working groups on topics of Open Science, Open Data and Science Transparency, including serving on the Advisory Committee for 'Building the Medical

Information Commons' and the Health and Research Alliance (HRA) initiative on implementing Open Science and Data Sharing. He has co-authored more than 20 peer-review research articles and served as Group Leader and Project Leader for Siena Biotech (Italy), Nikem Research (Italy) and Evotec (UK). He holds a PhD in Medicinal Chemistry from the University of Strathclyde in Glasgow (Scotland, UK) and an MSc in Organic Chemistry from the University of Messina (Italy).



**ANNETTE BAKKER, PHD
PRESIDENT AND CHIEF SCIENTIFIC OFFICER**

Dr. Bakker currently leads a staff of 45 people at the Children's Tumor Foundation. Together with a highly experienced executive team, she is responsible for the strategic, programmatic, and financial operations of the Foundation to ensure that the mission and core values are put into practice, and that a success-oriented and accountable environment exists throughout the Foundation.

As Chief Scientific Officer, Dr. Bakker works with the Foundation's research staff to design and implement innovative strategies that accelerate the translation from top science into therapeutic benefit. In the NFPI, she explores partnerships with pharmaceutical companies.

She also advises CTF's Board on its research direction and portfolio, and is the liaison to four external committees that coordinate NF research nationally. She is constantly breaking through traditional ways of thinking, and encourages Foundation staff to do the same. Dr. Bakker effectively implements her personal network of world-class centers of excellence to advance NF research and attract top scientists and clinicians to the field of NF.

She holds a PhD in Biochemistry from the University of Antwerp in Belgium. Her past experience includes serving as NeuroOncology Division head at Siena Biotech, Oncology Group Leader at Janssen Pharmaceutica, Assistant Professor Physiology and Biomechanics at the University of Paris and postdoctoral fellowships at Yale University and La Salpetriere, Paris. Dr. Bakker's research is internationally recognized by numerous publications, patents, and awards, and she has extensive experience liaising and negotiating with biotechnology and pharmaceutical companies. She has won multiple leadership awards and was a 2016 scholar of the Harvard Business School's Strategic Perspectives in Nonprofit Management program.

Because of her breakthrough innovative approaches in Research and Development, she was invited as an active participant in the Cancer Moonshot Initiative that was led by Vice President Joseph Biden.



**MARCO NIEVO, PHD
PROJECT MANAGER OF NFPI**

Dr. Nievo acts as consultant for the Children's Tumor Foundation, mainly in the field of intellectual property, contract drafting and negotiations, and runs the industry-academia liaison activities of the Foundation. Within NFPI, he assists Drs. Bakker and La Rosa in developing partnerships with pharmaceutical companies, project management, and in potential drug candidate scouting activities.

Dr. Nievo received his PhD in Biological Chemistry from Imperial College London. He then worked in the pharmaceutical industry for nearly a decade specializing in the area of Competitive Intelligence, Intellectual Property and Project Management. Shortly after becoming a Patent Attorney in 2011, he went freelance and operates with an international client base.

NF Preclinical Initiative: Collaborating Laboratory Members



KAREN CICHOWSKI, PHD

Brigham and Women's Hospital/Harvard University

Dr. Karen Cichowski is Professor of Medicine at Brigham and Women's Hospital and Harvard Medical School and is a Ludwig Center Investigator within the Dana-Farber/Harvard Cancer Center. She is the founder and Director of the Center for Developing Targeted Cancer Therapies at BWH/DFCI and in 2011 became the Scientific Director of the NFPI.

Dr. Cichowski has been working on NF1 and other Ras driven tumors for over 20 years. She developed the first mouse models of neurofibromas and MPNSTs, and has made seminal contributions in understanding how NF1 mutations promote neurofibroma, MPNST, and glioma development. Since 2007 she has been dedicated to developing therapies for individuals with NF1, in particular for MPNSTs. The work from her laboratory has resulted in the development of several clinical trials, which are currently ongoing. She continues to identify and refine new "smart" therapies and is committed to partnering with physicians and pharmaceutical companies to bring the most promising therapies into the clinic.



D. WADE CLAPP, MD

Indiana University School of Medicine

The major area of focus in Dr. Clapp's laboratory is understanding the molecular pathogenesis of NF1. Neurofibromatosis type 1 is the most common human genetic disease with a predisposition to cancer, and one of a series of developmental disorders called Rasopathies. His laboratory provided the first genetic, cellular and biochemical evidence that loss of a single allele of NF1 alters neurofibromin protein levels, Ras activation and cellular fates. This concept is called haploinsufficiency. They subsequently established that haploinsufficient loss of *NF1* in hematopoietic cells was a key driver of tumorigenesis in the neural crest derived cancers, plexiform neurofibromas, which affect cranial and peripheral nerves in infants and young children. A long-term key goal of their laboratory is to elucidate key pathological and

hyperactive Ras-mediated signaling pathways using genetically engineered murine models. Collectively, this work in his lab and with colleagues in the preclinical consortium and NCI SPORE has resulted in the identification of 3 drugs that have shown a clinical response in human plexiform neurofibromas and multicenter trials on each of these drugs are ongoing.

Recently, they have become interested in the function of NF2 in tumor initiation and in pursuing a parallel strategy of utilizing genetically engineered models to test experimental therapeutics in mice and then move successful compounds forward into clinical trials. Their lab has now generated a genetically engineered model of NF2 that acquires spinal Schwannomas and vestibular Schwannomas with 100% penetrance. All mice develop functional hearing and vestibular deficits. This unique reagent allows for the testing of rational drugs utilizing physiologically meaningful clinical endpoints that have applications to human trials.



NANCY RATNER, PHD
Cincinnati Children's Hospital

Dr. Ratner is interested in peripheral nerve tumors that occur in the neurofibromatoses, NF1 and NF2, and studies the brain in neurofibromatosis type 1. She uses genomics to study neurofibroma formation and carries out neurofibroma and MPNST preclinical therapeutics. Ratner received her bachelor's degree from Brown University, her doctorate from Indiana University, Bloomington (during which time she was a student in the Neurobiology Course at the Marine Biological Laboratory), and was a postdoctoral fellow at Washington University in St. Louis where she studied Schwann cells in nerve development under Richard Bunge and Luis Glaser. A member of the faculty at the University of Cincinnati 1987 – 2004, she is currently a Professor in the Department of Pediatrics, Cincinnati Children's

Hospital, University of Cincinnati, where she holds the Beatrice C. Lampkin Endowed Chair in Cancer Biology.

She co-leads the Rasopathy Program and serves as the Program Leader for the Cancer Biology and Neural Tumors Program in the Cancer and Blood Disorders Institute. She has served on numerous national and international review panels and authored over 100 peer-reviewed manuscripts and 30 reviews. She was awarded the von Recklinghausen Award in 2010, and a Jacob K. Javits Neuroscience Investigator Award (NIH-NINDS Merit Award) in 2014. She has been an active member of the Preclinical Platform since its inception.



KEVIN SHANNON, MD
University of California San Francisco

Kevin Shannon, M.D. is the Auerback Distinguished Professor of Molecular Oncology in the UCSF Department of Pediatrics. He led the Hematopoietic Malignancies Program at the UCSF Helen Diller Family Comprehensive Cancer Center from 2002-2012, and was Director of the UCSF Medical Scientist Training Program from 2006-2012. Dr. Shannon received his MD from Cornell University, obtained residency training in pediatrics at UT Southwestern Medical Center in Dallas, and completed a fellowship in pediatric hematology/oncology at UCSF. He served 10 years as in the US Navy Medical Corps before joining the full-time UCSF faculty in 1992.

His laboratory has discovered inherited and somatic mutations that cause human developmental disorders and contribute to leukemia. His current research focuses on normal and leukemic hematopoiesis with an emphasis on genetic mechanisms underlying leukemia development, aberrant Ras signaling, mouse cancer modeling, molecular therapeutics, and drug resistance. Dr. Shannon holds a MERIT Award from the National Cancer Institute (NCI) and an American Cancer Society (ACS) Research Professorship. He was the Scientific Co-Chair of the 2013 American Society of Hematology meeting, currently serves on the NCI Board of Scientific Advisors and the ACS Extramural Research Council, and was a member of the Pediatric Cancer Working Group of the Vice President's Cancer "Moonshot" Initiative.