CHILDREN'S TUMOR FOUNDATION

NF2 Accelerator: A Strategic Portfolio Approach to End NF2

Drug Treatments for Patients Today, Gene Therapy to End NF2 Tomorrow

OUR MISSION TO END NF2

The Children's Tumor Foundation leads the way in confronting NF2 by bringing new treatment options to patients living with NF2, while simultaneously accelerating the development of groundbreaking gene therapies that will eliminate NF2 as an obstacle. CTF's NF2 Accelerator Program is a portfolio approach that increases the number of drugs being researched for NF2, innovates and speeds up testing for those drugs, and develops gene therapy options for the future. Patients deserve a better quality of life today, and a cure as soon as possible. The Children's Tumor Foundation is tackling new treatments and cures through the NF2 Accelerator Initiative, and we want to tell you how your support is making an impact.

CHILDREN'S TUMOR FOUNDATION
ENDING NF
THROUGH RESEARCH

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A Multi-Faceted Approach to Addressing the Needs of NF2 Patients

The Children's Tumor Foundation has developed an ongoing research portfolio to help address the clinical needs of NF2 patients, combining near-term impact with long-term results.

1) **Using gene therapy to correct or replace an ineffective protein**

Gene therapy is an incredibly promising therapeutic approach that involves using an inactivated virus (called a 'vector') to deliver genetic material (called the 'payload') to edit a variant gene or arrest the growth of tumors. CTF is supporting gene therapy research to create the tools needed to enhance the delivery of gene therapy to NF2 tumors.

2) **Accelerating the development of new therapeutics to make clinical trials more effective**

Drug development is a slow, deliberate process with many potential bottlenecks. We have found ways to reduce these bottlenecks in order to accelerate the progress of drugs in the NF2 pipeline and to incentivize the development of new drugs for NF2.

Further, the biology of NF2 tumors (while not identical) have much in common with other cancers, which enables us to repurpose existing cancer drugs for NF2 care. Based on known clinical pathways, we are already seeing known drugs being used in NF2 treatment (Avastin) and in clinical trials for NF2 (Brigatinib).

3) **Identifying new drug targets through supporting a set of unique and varied projects**

4) **Enhancing the effectiveness of existing therapies to address specific challenges in the management of NF2 clinical care**

Managing NF2 clinical care involves navigating unique challenges, such as counteracting drug resistance, and reducing side effects and collateral damage. Ensuring that therapies are most directly targeted and delivered to where they will have the most effect will minimize undesired and unintended impact. A diverse set of innovative projects supported by CTF are underway to address some of these unique challenges.

Multi-Faceted Approach to Addressing the Needs of NF2

IDENTIFYING NEW DRUGS

TARGETING NEW PATHWAYS

- Dr. David Parkinson
- Dr. Chunling Yi
- Dr. Vijaya Ramesh
- SYNODOS
- Dr. Isabelle Logan
- Dr. Jeremie Vitte
- Dr. Philipp Kulikov

DISCOVERY

BRINGING DRUGS TO PATIENTS FASTER

ANIMAL MODELS

- Dr. Marco Giovannini
- Dr. Gordon Harris

HUMAN CLINICAL TRIALS

- INTUITT
- Takeda

ACCELERATION

DEVELOPING GENE THERAPY

GENE REPLACEMENT

- NF2 Therapeutics Michael Wootton

DELIVER AND TARGET

- Dr. Samantha Ginn

CORRECTING THE ERROR

- Dr. Elisabeth Castellanos Perez
- Dr. Eduard Serra

TRANSFORMING THE FUTURE - ENDING NF2

FIGHTING DRUG RESISTANCE

Dr. Cristina Fernandez - Valle

Dr. Haley Hardin

AVOIDING SIDE EFFECTS

Dr. Tyrone Porter

BLOCKING TUMORS

Dr. Lei Xu

Identifying New Therapeutic Targets:
Exploring New Molecular Pathways

Seven innovative projects with unique and varied approaches being supported by the Children's Tumor Foundation

- The group of **Dr. David Parkinson at the University of Plymouth** in the United Kingdom is exploring an approach to block TEAD action *in vivo* in NF2 mouse models. Using two Vivace Therapeutics drugs, they have shown a reduction in the schwannomas and CTGF (connective tissue growth factor). These drugs thus act on the tumor and its surrounding area.

- The group of **Dr. Chunling Yi from Georgetown University** are testing a class of drugs called Hippo-yap/Taz inhibitors to block the RAS-RAF-MEK pathway in NF2 tumor cells.

- **Dr. Vijaya Ramesh from Massachusetts General Hospital** is evaluating combination therapy using three drugs targeting the proteasome. Two drugs are NUAK2 inhibitors, and one is an mTOR inhibitor for meningioma.

- New drug targets emerged from the **SYNODOS-NF2 project**: HDAC, proteasomes, kinases, tubulin (form the cytoskeleton), topoisomerase. All inhibitors of these molecules can potentially become new treatments for NF2. The data generated characterized a few combinations from thousands of drugs, and identified Brigatinib as a new potential treatment which is now in clinical trials for NF2.

- A very innovative pathway is a focus of **Dr. Philipp Kulikov from the Russian National Medical Research University** to use statins and bisphosphonates in combination and estimate the activity of Rac1.

- In NF2, the tumor increases a process called macropinocytosis, which triggers an increase in proliferation. CTF funds a very innovative study run by **Dr. Jeremie Vitte from UCLA** to block macropinocytosis.

- **Dr. Isabelle Logan at Oregon State University** is the first to characterize and block the nitrated protein formation responsible for the aberrant behavior of proteins. This is a highly inventive discovery in NF2.

Accelerating the Development of New Therapeutics for Patients

Animal Models

Improving the Selection of Drugs

A major challenge of drug development has been creating physiologically relevant models to test a drug, meaning that the model acts similarly in a human as it does in a preclinical model. The Children's Tumor Foundation is focused on reducing this hurdle by creating new animal models that better mirror human NF2.

A key initiative in this work is CTF's support of the research of Dr. Marco Giovannini of UCLA. His focus is the observation of NF2 characteristics in new NF2 mini pig models.

Providing Better Access to Testing

Until now, all NF2 models have been exclusively owned by the universities that produce them, which sounds logical until one realizes this often means access to these models by other research labs can be restricted, or become quite costly.

We're committed to breaking down the barriers that slow down research. The Children's Tumor Foundation has partnered with Taconic to make animal models that the Foundation owns, but offers for free to labs testing potential new NF2 treatments.

Human Testing: From Innovation to Clinical Trials

Reducing Timelines

The main hurdles that we experience when running clinical trials in rare disease are: 1. the time it takes to recruit the patients; 2. the lack of a clinical trial network who run the trial together; 3. the trial can only address one of the multiple manifestations of the rare disease.

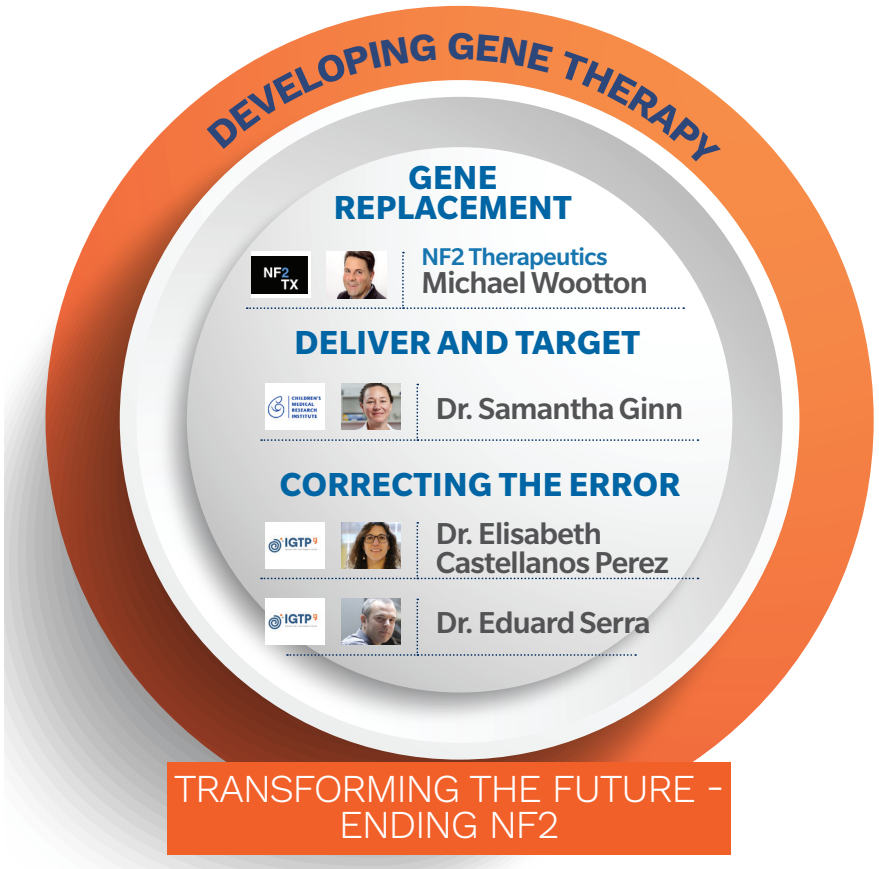
We're investing in a 'better way' to reduce both the time this takes as well as the hoops that patients deal with. CTF is co-funding with Takeda Pharmaceuticals the creation of a fast and efficient trial enrollment tool, being utilized in a unique platform-basket trial run in 6 sites called INTUITT-NF2. This protocol regroups studies for all different types of NF2 tumors and increases the potential of success even when the patient group size is small.

Improving the Readout

A more precise measurement of tumors enables better visibility into the effectiveness of a therapeutic and a better estimate of the tumor burden in a patient. CTF is working with Dr. Gordon Harris of Massachusetts General Hospital to develop more effective and reliable approaches to measurement.

Developing Gene Therapy

Targeting New Pathways



Deliver and Target

A primary challenge in gene therapy is to bring the right level of 'biological payload' (i.e. something to edit the gene or a fully functioning gene) to the cells that need it while impacting as minimally as possible the other cells.

The Children's Tumor Foundation is funding significant work to create an NF2 gene vector (to transport the biological payload that produces healthy protein) focused on the NF2 tumor cells.

Dr. Samantha Ginn's group at the Children's Medical Research Institute in Australia, has engineered and tested several millions of new types of AAV vectors (a mode of gene transportation and delivery) to assess how effectively they penetrate into Schwann cells.

The result is three new extremely selective and efficient vectors for NF2.

Gene Replacement

The Children's Tumor Foundation has partnered with NF2 Therapeutics, a start-up that is accelerating promising approaches to gene therapy specifically in NF2. Their approach, currently being tested in non-human primates, is to deliver the 'new gene' that restores the NF2 function, which is delivered into the suitable cells, and decreases the size of the tumors. The pathology studies to date have not shown signs of toxicity, which is incredibly promising. The company's CEO has announced that trials in humans could start in 2023.

Correcting the Error

In order to facilitate studies that look into 'correcting the error' caused by the mutation in the *NF2* gene, CTF is funding Dr. Eduard Serra and Dr. Elisabeth Castellanos Perez of the Germans Trias i Pujol Research Institute (IGTP) in Spain. Their work is in modifying the gene product by skipping the part of the gene with the error. This produces a partial Merlin protein, which should still show a high degree of functionality.

Innovations in NF2 Research

Fighting Drug Resistance

Oftentimes, treatments can stop working because the tumor evolves in a way that escapes the biological mechanism that had previously worked to arrest the growth of that tumor. The Foundation's SYNODOS for NF2 collaborative led to a promising study by Dr. Haley Hardin of Dr. Cristina Fernandez-Valle's team at the University of Central Florida. The group has developed an approach of combinational treatment (i.e. using two or more drugs together in combination) on an NF2 schwannoma cellular model. They have tested 32 drugs in-pairs, and the best results give an indication of which pathways to target to reduce drug resistance, as well as overcome the resistance that a tumor can develop over time.

Avoiding Side Effects

Focusing the Treatment on the Tumor Being Targeted

The Children's Tumor Foundation has partnered with the Focused Ultrasound Foundation to fund Dr. Tyrone Porter of the University of Texas at Austin to develop a new and innovative drug delivery method.

Dr. Porter will pack afatinib in a specialized delivery vehicle called a liposome, which will transport the drug and release the drug only when ultrasounds heat them. This enables focused ultrasounds to be applied at the tumor site, avoiding a whole-body exposure, and thereby minimizing its side effects. Therefore the drug is delivered when and where it's wanted, for maximum benefit and minimized side effects.

Blocking the Tumor

Acting on the Tumor Microenvironment

The hearing loss associated with NF2 vestibular schwannomas depends on both the tumor and the cell in its immediate environment. Fibrosis induces the production of a net of fibers and inflammation.

The Foundation is supporting Dr. Lei Xu's group at Harvard Medical School in identifying a drug to act on both indications. The study observed a decrease in hearing loss, and these results could lead to a clinical trial of Losartan, a currently prescribed hypertension drug in patients with vestibular schwannomas. Additional trials will explore this approach further.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