2024

GLOBAL NF CONFERENCE HIGHLIGHTS:

Fueling the Drug Discovery Engine for NF

Hosted by:

CHILDREN'S TUMOR FOUNDATION EUROPE

Organized by:

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

EUROPEAN NF GROUP

2024
NF CONFERENCE HIGHLIGHTS:

A Letter from the CEO

Annette Bakker, PhD
CEO, Children's Tumor Foundation

I am delighted to share the key highlights from the groundbreaking research presented at the 2024 Global NF Conference. Organized by the Children's Tumor Foundation (CTF) and the European NF Group and hosted by CTF Europe, this conference remains the premier event for the NF research and clinical communities. Our collective focus is on advancing outcomes for individuals with neurofibromatosis type 1 (NF1) and all forms of schwannomatosis (SWN), including *NF2*-related schwannomatosis (*NF2*-SWN).

Held June 20-25, 2024, in the magnificent city of Brussels, Belgium's historic capital, the Global NF Conference welcomed 849 registrants from 43 countries, with 37% of attendees participating for the first time. Each of the five days was dedicated to a specific aspect of NF, allowing us to delve deeper into topics such as Gene Therapy, Comprehensive Care, Schwannomatosis, Novel Therapeutics, and "AI, Novel Tech, Biomarkers."

I am deeply grateful to our European and American planning committee: **Hilde Brems** from Belgium, **Ignacio Blanco Guillermo** from Spain, and **Justin Jordan** and **Laura Klesse** from the United States.

We were honored to have **Dr. Nathalie Moll**, Director General of the European Federation of Pharmaceutical Industries and Associations (EFPIA), give an inspiring address to open our conference. **Dr. Niklas Blomberg**, Executive Director of the Innovative Health Initiative, and **Magda Chlebus**, Executive Director of Scientific & Regulatory Affairs at EFPIA and board member of CTF Europe, engaged in a fireside chat to discuss Europe's unique public-private partnerships and opportunities in rare disease research.

Our conference co-chairs selected top keynote speakers with diverse and impressive backgrounds:

- **Luigi Naldini, MD, PhD**, from San Raffaele University in Italy, delivered a keynote on the journey from "Bench to Bedside and the Market: A Roadmap to the Development of New Advanced Gene and Cell Therapies."
- **Abby Rosenberg, MD**, from Boston Children's Hospital/ Harvard University, presented the Comprehensive Care Keynote, sharing insights on "Science and the Art of Resilience: 5 Lessons Learned from Patients, Communities, and Society."
- **Andrew Rice, MD**, from Imperial College London, provided an "Update on the Diagnosis and Management of Chronic Neuropathic Pain" during the SWN session.
- **Dan Nomura, PhD**, from the University of California, Berkeley, spoke on "Reimagining Druggability Using Chemoproteomic Platforms" during the Novel Therapeutics session.
- **Casey Greene, PhD**, from the University of Colorado, delivered the final keynote on "Engineering Serendipity: AI's Rapidly Expanding Role in Research and Care" for the AI, Novel Technologies, Biomarkers session.

The first-ever **Young Investigator Day** and the second **Patient Day** occurred before the conference. Our partners at Sage Bionetworks hosted two essential data workshops, and our long-term friends and partners organized highly focused satellite meetings on specific topics.

Throughout the meeting, we remembered our longtime friend and colleague, Ludwine Messiaen, PhD, to whom we dedicated the 2024 Global NF Conference.

This conference is a cornerstone of CTF's efforts. Each year, I leave more convinced that our community, united in purpose, will help us achieve our mission to end NF.

Annette Bakker, PhD
CEO, Children's Tumor Foundation

Inaugural Young Investigator Day

Supporting the growth of young investigators as independent NF researchers is a key objective of the Children's Tumor Foundation. To advance this goal, CTF organized the Young Investigator Day (YI Day), a one-day event dedicated to networking, scientific exchange, and mentorship. This event aims to further the research of emerging scientists while also guiding their future career development.

The YI Day was planned and led by a committee composed of both veteran and junior NF faculty. The committee included Andrea McClatchey (Massachusetts General Hospital), Helen Morrison (Leibniz Institute on Aging, Germany), Eduard Serra-Arenas (Germans Trias i Pujol Research Institute (IGTP), Spain), Vanessa Merker (Massachusetts General Hospital), and Daochun Sun (Medical College of Wisconsin).

CTF launched a call for applications for the YI Day in March 2024, and, in response, 62 applications from early-stage researchers focused on NF, including trainees, graduate students, and postdoctoral researchers, were received. Through a rigorous selection process, 55 applicants were invited to participate in the YI Day.

The YI Day included research presentations by participating young investigators, interspersed with mentoring sessions organized by the planning committee. The "NF Research Brainstorming" session was particularly noteworthy in which attendees were divided into groups. Each group was asked to identify and present an unmet research or clinical need in NF. Ideas ranged from creating unique social media platforms for spreading awareness and improving interactions among the community to developing precision medicine approaches for NF.

Another session, structured in the form of a two-way conversation between mentors and participants, aptly named "Mentor-Trainee Town Hall," encouraged participants to share their concerns about topics such as establishing research collaborations, applying for research funding, writing successful grant applications, and getting the most out of attending large conferences and meetings. The mentors shared real-world examples from their career paths and provided valuable advice to participants.

All participants were asked to submit and present a poster of their work. A poster session allowed participants to present posters on their research, and mentors advised the presenters on possible future directions for their work. One poster was voted to be presented at the Global NF Conference.

The YI Day culminated in a keynote presentation by **Dr. David Largaespada*** from the University of Minnesota. Dr. Largaespada is a well-established NF1 researcher, a past recipient of numerous CTF Drug Discovery Initiative (DDI) awards, and also served as a principal investigator for CTF's Synodos for NF1 consortium. He has spent much of his professional career mentoring trainees in research. During his keynote presentation, Dr. Largaespada talked about his research and shared with the audience different "recipes to success" behind the key milestones in his career.

Overall, the early career NF research community received and appreciated the inaugural Young Investigator Day, which will now become a regular feature of CTF's annual NF conference.

Clockwise from left: Drs. Eduard Serra Arenas Daochun Sun*, Vanessa Merker*, Helen Morrison*, David Largaespada*, Vidya Browder, Andrea McClatchey**

** CTF-funded researcher*

Patient Day

CTF proudly hosted its second Patient Day during the Global NF Conference. This day was dedicated to providing education and community to an international group of NF patients and caregivers and soliciting their feedback on important issues. Nearly 60 patients attended and were overwhelmingly positive about their experience.

The planning for this day started months in advance with a survey designed to capture the differences and similarities in priorities between families living with NF compared to NF clinicians or researchers. The survey identified a few critical areas of discrepancy. For example, patients reported weakness and numbness as a significant concern, whereas physicians reported that patients rarely bring that to them as a complaint. However, we also found both groups have the greatest hope for gene therapy as a definitive treatment option for the NF patients of the future.

The morning was dedicated to providing education on topics identified in the survey, and the afternoon to brainstorming suggestions for tackling the biggest concerns for the NF community. Highlights from the morning included an interview by NF parent Kimberly McCoy, who asked Wendy Erler, Alexion VP of Patient Engagement, about the research community's efforts to increase the diversity and access to clinical research

Patient Day

opportunities and an open Q&A panel with three leading NF clinicians.

In the afternoon, attendees broke into groups to discuss concerns and solutions around pain management, clinical trial participation, education for those outside the NF community, and access to care. CTF has committed to delivering on at least two initiatives identified through this brainstorming session within the following year. Attendees shared that Patient Day allowed them to connect with others in the NF community, made them feel valued, and that their voices are essential to ending NF.

Data Workshops

CTF took a significant leap forward this year with a morning dedicated to two pivotal data workshops hosted by Sage Bionetworks. These workshops aimed to equip the NF research community with the tools and knowledge to harness the extensive data available on the NF Data Portal, thereby accelerating research efforts and fostering collaboration.

The first workshop was a deep dive into the practicalities of requesting, reusing, and analyzing data on the NF Data Portal. Participants were introduced to tools like cBioPortal and Cavatica, learning to transform raw data into insightful visualizations and analyses. The session catered to various technical skill levels, shedding light on user-friendly interfaces and R and Python programming approaches. Attendees engaged in hands-on exercises, exploring different data sets and learning to navigate the complexities of data analysis. During this session, the team also introduced Pluto.bio, an innovative no-code analysis platform that promises to be a game-changer. In collaboration with CTF and the Sage Bionetworks team, Pluto.bio is conducting a pilot project using data from

CTF's team-science initiative, Synodos for Low-Grade Glioma. This pilot showcases the potential for streamlined, accessible data analysis without requiring extensive coding expertise.

The second session delved into large language models (LLMs) and their application in data curation, specifically tailored for NF research. The Sage team provided a comprehensive overview of artificial intelligence, machine learning, and deep learning concepts, setting the stage for a detailed exploration of LLMs in research workflows. They highlighted the challenges of finding suitable research tools for NF and introduced the NF Research Tools Central database as a promising solution.

Participants learned how LLMs can revolutionize data curation by extracting information from scientific literature, summarizing complex texts, and generating accessible versions of scientific documents. The session featured real-world examples of LLMs curating observations from publications and automating the population of metadata templates. The potential for creating chatbots to answer NF-related queries was also discussed, illustrating the future possibilities of AI-driven assistance in research.
These workshops provided invaluable insights and practical training, empowering the NF research community to leverage data and AI tools effectively. With the knowledge and skills gained, researchers are now better equipped to tackle critical questions and drive forward the mission of improving the lives of those affected by NF.

Gene Therapy

Gene therapy holds tremendous potential to transform NF treatment by targeting the underlying genetic causes of the disease. Continued support for research in this area is crucial to overcome remaining challenges and advance toward more effective, personalized therapies for those living with NF.

The gene therapy session at this year's conference began with **Dr. Santiago Vernia** from Imperial College London, who presented his work on RNA therapeutics for NF1. RNA therapeutics is a new field using RNA molecules to treat diseases. Dr. Vernia showed that RNA-based oligonucleotides (short, single-stranded DNA or RNA molecules) can promote the production of more stable isoforms of tumor suppressor proteins, which in NF1 are often degraded. This approach follows the success of FDA-approved RNA therapeutics like Spinraza and Exondys 51. One of the identified challenges in gene therapy is precise delivery of the gene to the affected cells for that condition. Researchers are exploring methods of delivery such as viral carriers, synthetic particles, and exosomes—tiny cell-released bubbles that transport genetic materials. Dr. Vernia's team has enhanced a delivery system using exosomes. They did this by modifying a protein on the exosome surface, improving attachment to Schwann cells, the primary cells affected in NF1. This allows for more precise delivery of the genetic material, including *NF1* gene segments, to Schwann cells. The next step is testing these engineered exosomes in lab models to evaluate that they get to where they need to and express the protein at levels required to correct the expression of the normal protein needed and understand their treatment potential.

Dr. Deeann Wallis from the University of Alabama at Birmingham is also developing RNA oligonucleotides to selectively skip specific regions ("exons") containing pathogenic variants within the NF1 RNA. Using this approach, targeted skipping of exon 17 harboring two known pathogenic variants was achieved in NF1

Dr. Nathalie Moll delivering the conference's Opening Address.

Gene Therapy
continued

mouse models, and production of functionally active neurofibromin was restored. The Wallis lab developed synthetic agents for delivering these oligonucleotides in mice. This study offers more proof that using antisense oligonucleotides to modify gene splicing could be an effective treatment for NF1.

Another method of gene correction, CRISPR-based gene editing, is revolutionizing the field of genetic engineering and is being extensively investigated in several genetic diseases, including NF. **Ms. Madeleine Sitton** from Duke University applied a newer gene editing technique called 'base editing' to correct one known pathogenic variant in the *NF1* gene. This nonsense/stop variant is observed in individuals with NF1 and results in premature termination of neurofibromin synthesis. The base editing strategy corrected this variant and restored neurofibromin production with modest efficiency in cells.

Gene editing as a therapeutic strategy can potentially be a one-time permanent cure for a disease. However, there are over 3,000 disease-causing variants in the *NF1* gene, so editing one variant at a time is a personalized medicine approach but not viable as a single remedy for all NF1 patients. Improving the editing efficiency to clinically relevant levels, minimizing editing at sites other than the site of interest, and discovering an efficient delivery vehicle remain ongoing challenges.

While gene editing presents one approach, gene replacement using viral delivery systems is another promising avenue for addressing NF's complex genetic challenges. **Dr. Gary Brenner** from Massachusetts General Hospital used an AAV vector to deliver the ASC gene to human schwannoma models for *NF2*-SWN. The ASC protein activates caspases, enzymes that induce apoptosis, or cell death. Dr. Brenner demonstrated that injecting the AAV-ASC vector into *NF2* schwannomas in a mouse model significantly inhibited tumor growth, even with pre-existing immunity to AAV in the animal model. This is important because prior AAV exposure can limit the effectiveness and safety of AAV-mediated gene therapy. AAV gene therapy is already approved for several genetic diseases (e.g., Zolgensma, Luxturna), and this study is now being considered for clinical trial development.

Krizelle Alcantara, also an *NF2*-SWN patient from Nationwide Children's Hospital, reported the development of novel AAV vectors for gene replacement therapy for *NF2*-SWN. Delivering the *NF2* gene to cell and mouse models produced the desired effects, including a significant reduction in the size of tumors. AAV-mediated *NF2* gene replacement could thus be an effective therapy for *NF2*-SWN.

In addition to AAV gene replacement therapy, researchers are investigating other innovative approaches to treat *NF2*-SWN. One such approach involves using antisense oligonucleotides, as demonstrated by **Gemma Casals Sendra** from the Germans Trias I Pujol Research Institute in Spain. Dr. Sendra used antisense oligonucleotides for skipping exon 11 of the *NF2* gene. The skipping of exon 11 resulted in the synthesis of partially functional merlin. These results provide hope for applying this approach to treat patients harboring truncating variants in exon 11. Part of this study was funded by two Drug Discovery Initiative grants from the Children's Tumor Foundation.

Advances in gene therapy for NF include identifying the challenges faced and looking at solutions to find the best approach. The research involves investigating gene replacement vs gene editing, identifying the best delivery system, and using RNA vs DNA. While challenges remain, progress in these areas underscores the promise of personalized and precision medicine approaches to treating NF, bringing hope for more effective future therapies.

Comprehensive Care

Comprehensive care can include anything involved in the care of individuals with NF, which often requires a team approach that can be quite complex. The highlights of what was reported include a thought-provoking talk on the science and art of resilience, "Five Lessons Learned from Patients, Communities and Society," delivered by **Dr Abby Rosenberg** of Harvard University. Based on her research, resilience has to do with gathering internal, external, and existential resources. Helping people identify and connect with these resources is an important part of comprehensive care. Her team has learned from patients how this can be improved and is focused on ways to help patients manage the stress of illness and tools to make what they are experiencing more manageable.

Dr. Miriam Bornhorst* from Ann & Robert H. Lurie Children's Hospital of Chicago presented her work on understanding the metabolic phenotype of patients with NF1. The metabolic presentation in patients can include decreased weight, height, bone mineral density (BMD), muscle bulk and strength, and reports of fatigue. However, the mechanisms behind these findings are still under investigation. Even in individuals with NF1 who consume a diet high in saturated fats, weight is often decreased. A higher plexiform neurofibroma burden is also linked to trends toward low weight, lower height potential, decreased BMD, low glucose levels, and increased insulin sensitivity. Mouse studies suggest NF1 deficiency leads to increased energy expenditure and prolonged insulin sensitivity. Studies in mice and patients indicate that MEK inhibition affecting the Ras/MAPK pathway may reduce lipid oxidation energy expenditure, thus possibly explaining why we see weight gain in patients during some MEK treatments.

Now that there is a better understanding of why NF1 patients present with this metabolic phenotype, the following steps will be to look at interventions that can treat or prevent these symptoms and, in addition, look at other aspects of metabolism in patients with NF1.

Sleep disturbance or lack of sleep can negatively impact attention, learning, and memory. Many children with NF1 report sleep disturbances. However, associations between sleep, learning, and attention in NF1 have not been well established. Studies done in mice with NF1 suggest that disrupted sleep rhythms are thought to be linked to the loss of neurofibromin. **Dr. Karin Walsh*** from Children's National Hospital presented data from a survey collected through the NF registry of 202 parents of a child with NF1 and 27 adolescents (13-17 years) with NF1. The survey showed the highest rates of sleep disturbances in NF1 patients include insomnia (48%), sleep maintenance (32%), and nightmares (21%). Parents reported fewer sleep impairments than adolescents self-report. Individuals with ADHD were more likely to report sleep problems ($p < .001$), but no differences were seen based on gender or diagnosis of anxiety or depression. We know from previous work that loss of neurofibromin disrupts the circadian rhythm.

The comprehensive care session also presented evidence that the characteristics of nodular plexiform neurofibromas (PN) can change over time. By looking at a subgroup of patients enrolled and followed in the NCI NF1 longitudinal natural history study, **Dr. Eva Dombi** from the NCI discussed age-related changes in MRI characteristics of plexiform neurofibromas (PN) in NF1. They retrospectively identified 17 NF1 patients at least 30 years old at their last imaging and had at least one PN with over 10 years of MRI follow-up. In most of the 17 adult NF1 patients (71%) with nodular PN reviewed, there was a decrease in signal intensity within some areas of their PN as they aged. This reduced signal intensity may complicate the use of volumetric MRI, a standard measure used to monitor PN size, thus indicating that alternative methods may be needed.

Another important area of comprehensive care for patients with NF includes access to care and regular follow-up throughout their life. Thus, it is vital to have a clear transition plan for pediatric patients as they enter adulthood. **Dr. Rosalie Ferner** from Guy's and St. Thomas' NHS Foundation Trust presented information about the transition from pediatric to adult healthcare services in Manchester, UK. This ideal model of a transition program starts at around the age of 14, based on individual needs, and is based on a

** CTF-funded researcher*

multidisciplinary transition service. The aim is to promote autonomy by teaching the young person and their family about diagnosis, treatment, and management of their condition. Specific areas of the program include social services (housing, finance, college support, employment, safeguarding), signpost to NF lay organizations, and education promotion (symptom management, lifestyle, and mental health; sexual health, pre-conception, genetic testing/counseling).

In addition, **Dr. Jane Fleming** and colleagues from Royal North Shore Hospital in Australia shared insights on supporting reproductive choices for adults with NF. They have found that many patients with NF need to be made aware of their options and have misinformation and noted that there is limited literature on this subject. They aimed to develop educational resources based on the feedback they received from patients. Following feedback from NF patients and partners, three main themes emerged: Barriers (access to services, IVF/PGT costs), Enablers (robust support systems, positive healthcare experiences), and Support Needs. Key factors identified in reproductive decision-making for patients with NF included mental health, NF experiences, concern for their health, and cultural norms. A patient resource developed from this survey is available on their website.

Another important area of care for women with NF1 is their increased risk of breast cancer. **Dr. Yermina Berman*** from the University of Sydney, Australia, presented her data recommending MRI as the preferred method for women with NF1 due to their increased breast density. If MRI is unavailable, a 3D mammogram is advised. Additionally, the Australian team created an animated resource to help women understand their heightened breast cancer risks and screening options.

Schwannomatosis

Dr. Gareth Evans* from the University of Manchester, UK, presented some interesting epidemiologic data collected from four centers in England using registries covering over 50 million individuals. This revealed an *NF2*-SWN prevalence of 1 in 55,000. Approximately three-quarters of *NF2*-SWN cases are de novo (not inherited), with different rates associated with genotype. Nonsense pathogenic variants (PV) lead to the most severe cases of *NF2*-SWN, with 90% of the cases de novo, some of the milder genetic variants having a lower de novo rate. The estimated prevalence of non-*NF2*-related schwannomatosis is 1 in 150,000, with *LZTR1*-associated SWN being twice as prevalent as *SMARCB1*-associated SWN. Most non-*NF2*-related SWN patients do not carry either of these genes, suggesting other disease-causing genes.

During the conference, **Dr. Barbara Rivera** and her team from McGill University Canada presented data confirming that a third gene called *DGCR8*, also located on chromosome 22q, has been identified. Patients with this altered gene present with peripheral schwannomas and multinodular goiter (thyroid tumors). Schwannomas from patients with *DGCR8*-associated SWN showed some features similar to other non-*NF2* schwannomas but with additional unique characteristics. Identifying *DGCR8* as a contributing gene significantly contributes to determining the cause of non-*NF2*-SWN in more patients.

A common symptom of non-*NF2*-SWN is pain that is often not correlated with the presence, size, or location of a tumor and is very diverse in the way patients experience or describe it. However, the mechanisms generating this pain still need to be fully understood. Patients with *LZTR1*-mediated SWN experience higher levels of pain compared to SWN patients with other genetic variants. CTF Young

** CTF-funded researcher*

Schwannomatosis
continued

Investigator Awardee **Georgia Daraki*** from the Fritz Lipmann Institute-Leibniz Institute on Aging, Germany, showed that loss of *LZTR1* leads to nerve inflammation, a malformed and defective myelin sheath, a protein and fatty layer around nerves, and increased sensitivity to pain. At the molecular level, *LZTR1* loss affected lipid metabolism. Since lipid metabolism is crucial for the structure and function of the myelin sheath, *LZTR1* loss disrupts nerve myelination leading to neuropathic pain development.

Dr. Larry Sherman* from Oregon Health and Science University presented data showing that loss of *SMARCB1* or *LZTR1* in Schwann cells leads to increased expression of inflammation-inducing factors such as IL-6. Anti IL-6 antibody reversed the pain effects, suggesting that targeting specific proteins secreted by mutant Schwann cells can treat non-*NF2*-SWN pain. The Children's Tumor Foundation funds Dr. Sherman and his collaborators to investigate SWN pain mechanisms further.

CTF Drug Discovery Initiative Awardee **Dr. Lei Xu*** from Massachusetts General Hospital developed new mouse models to study pain in non-*NF2* SWN, discovering that tumors formed in these mice produce higher levels of inflammatory substances like IL-6, which cause pain. Xu's research revealed that when peripheral schwannomas form, nerve cells produce CCL2 (a substance that attracts inflammatory cells), macrophages collect and release IL-6, leading to pain. Blocking IL-6 in mice reduced pain but did not stop tumor growth. She explains that is because another protein, EGFR, was produced to support tumor survival. Xu found that targeting both IL-6 and EGFR was more effective, reducing pain and slowing tumor growth. This preclinical data has led to a clinical trial led by Dr. Scott Plotkin, testing siltuximab, an FDA-approved anti-IL6 antibody, for pain relief in non-*NF2* SWN patients.

Dr. Joseph Kissil* from the Moffitt Cancer Center described their exploratory work on immunotherapy for *NF2*-SWN. *NF2*-associated schwannomas show the presence of different cells and other components of the immune system within their microenvironment. The Kissil lab observed that schwannoma cells have increased

CTF Young Investigator Awardee Georgia Darakia

levels of an immune component called the Major Histocompatibility Complex (MHC) class I (MHC-I). In principle, by identifying the antigens (proteins) bound to MHC-I in schwannomas, a vaccine can be designed that, upon injection, would trigger an immune response, resulting in T cells attacking the schwannoma. The Kissil lab uses mouse models and patient tumor samples to examine the antigens bound to MHC-I in *NF2* schwannomas. Once they identify an antigen of interest, they will investigate a vaccine-based approach for this disease.

Data presented on the treatment of patients with NF2-SWN include analysis from one study presented by **Dr. Scott Plotkin**** from Massachusetts General Hospital demonstrating the effect of bevacizumab (Avastin) on meningiomas and non-vestibular schwannomas. Bevacizumab is an anti-vascular endothelial growth factor (VEGF) antibody and has shown efficacy in tumor growth control and hearing improvement in some *NF2*-SWN patients. A retrospective data analysis assessed the effect of bevacizumab on meningiomas and non-vestibular schwannomas in these patients. A marginal response, as measured by tumor volume reduction, was observed in both these tumor types. While these tumors are not a direct objective of this clinical trial, examining the drug's effect on all types of tumors occurring in *NF2*-SWN patients would provide a reference standard for comparison for future studies.

In another presentation, **Dr. Masahiro Toda** from Keio University, Japan, presented results from an

** CTF-funded researcher*
***CTF-funded researcher and Co-Chair of CTF's Clinical Care Advisory Board.*

Drs. Ferner and Upadhyyaya in front of a poster announcing a new essay series, Women in NF, that launched at the conference.

immunotherapy clinical trial of a vascular endothelial growth factor receptor (VEGFR) vaccine in patients with *NF2*-SWN. In tumors, VEGF and its receptors, essential for blood vessel development ("angiogenesis"), are highly expressed in *NF2*-related schwannomas. The anti-VEGF receptor vaccine induces an immune response that attacks and destroys cells expressing these receptors, inhibiting tumor angiogenesis and, consequently, tumor growth. The vaccine was administered to 16 patients. Unlike the bevacizumab antibody, this vaccine was slow to act but produced long-lasting effects. Hearing improvement and tumor reduction were observed after treatment, and no severe side effects were reported, demonstrating the safety and efficacy of this vaccine.

Dr. Sylwia Ammoun*, a CTF Drug Discovery Initiative Awardee from the University of Plymouth, UK, presented another novel therapeutic approach for *NF2*-SWN that involves using anti-retroviral drugs, which are drugs against retroviruses such as the HIV/AIDS virus. The human genome contains sequences from the genomes of ancient retroviruses that were incorporated due to infections and subsequently established. Human Endogenous Retrovirus (HERV) type K is one such example. Interestingly, HERVK proteins are overexpressed in *NF2*-deficient schwannoma and meningioma tumors. Dr. Ammoun showed that the anti-HIV drugs Ritonavir and Lopinavir decrease the growth and survival of schwannoma and meningioma cells. This study is now being developed into a clinical trial, funded by the Children's Tumor Foundation, to get insights into their effects on schwannoma and any toxicity.

Novel Therapeutics

The Novel Therapeutics session kicked off with **Dr. Daniel Nomura** from the University of California delivering a remarkable keynote focused on druggability and the use of chemoproteomics platforms. The Nomura Research Group pioneers the future of drug discovery by tackling one of its most significant challenges: the "undruggable" proteins. Over 90% of proteins are not druggable, meaning it is difficult for a small molecule to gain access and bind the specific protein target. By leveraging cutting-edge chemoproteomic platforms, the group identifies and targets unique "ligandable hotspots" on these proteins, paving the way for transformative medicines. The Nomura Research Group is advancing such innovative chemical technologies, pushing the boundaries of what's possible in drug discovery.

Several exciting sessions focused on better understanding the transformation of plexiform neurofibroma (pNF) into more aggressive tumors known as malignant peripheral nerve sheath tumors (MPNSTs) and identifying potential new therapeutic targets and treatment strategies.

Dr. Lu Le** from the University of Virginia School of Medicine emphasized the essential role of the tumor microenvironment in neurofibroma genesis. Dr. Le is also

** CTF-funded researcher*
***CTF-funded researcher and Co-Chair of CTF's Clinical Care Advisory Board.*

Dr. Lu Lei

the Chair of the CTF Research Advisory Board. His work focused on understanding how the extracellular matrix (ECM) changes during the development of a pNF. Using a novel mutant mouse model, Dr. Le noted faster growth of pNF and transformation into MPNSTs, which become less responsive to the immune system. To address this, they developed a new approach. By activating a pathway in the innate immune system called cGAS-STING, the group was able to transform MPNSTs from "cold" tumors (with low immune activity) into "hot" tumors. This change made the tumors more susceptible to treatments that boost the immune system's ability to fight cancer cells (checkpoint inhibitors), leading to reduced tumor growth by causing more cancer cells to die.

The work of **Dr. Kyle Williams*** from the University of Minnesota further shed light on MPNSTs. By using advanced genetic tools like CRISPR/Cas9, the lab recreated the genetic conditions seen in these tumors, which allowed for the screening of a specialized library of epigenetic drugs to pinpoint compounds specifically lethal to cells lacking both NF1 and SUZ12. These efforts identified HDAC inhibitors (HDACi) as promising candidates. When combined with MEK inhibitors (MEKi), which target another critical pathway in cancer growth, the group observed a powerful synergy against NF1/SUZ12-deficient MPNST cells both in vitro and in vivo. Encouraged by these results, Dr. Williams and team are advancing towards a groundbreaking phase 0 clinical trial to assess the safety and effectiveness of combining the MEK inhibitor mirdametinib with the HDAC inhibitor vorinostat in patients with MPNSTs lacking H3K27 trimethylation. This unique approach aims to validate the preclinical findings in a clinical setting, offering a new treatment avenue for patients facing limited options.

In the continued pursuit of effective treatments for MPNSTs, **Dr. Jiawan Wang** (Johns Hopkins University School of Medicine) presented her work exploring innovative combinatorial approaches targeting MEK and other pathways crucial in MPNST pathogenesis. Her results, using several in vitro and in vivo models, underscore the potential of combined C/BRAF and MEK inhibition as a compelling therapeutic strategy for NF1-MPNSTs. Moreover, **Dr. Özlem Yüce Petronczki** from Böhringer Ingelheim provided an interesting industry perspective and shed light on another potential new combination using SOS1 and KRAS inhibition as a compelling new treatment strategy for MPNSTs.

To address the critical challenge of reprogramming the suppressive immune microenvironment of tumors in immunotherapy, **Dr. Lei Xu** from Massachusetts General Hospital and Harvard Medical School explored the potential of anti-vascular endothelial growth factor (anti-VEGF). This work was funded by CTF and focused on using anti-VEGF treatment to normalize the tumor microenvironment and enhance the effectiveness of immune checkpoint inhibitor (ICI) therapy. The results, gathered in several mouse models of vestibular schwannomas (VS), are encouraging and suggest that combining anti-VEGF with anti-PD1 treatment significantly improved outcomes by normalizing tumor vasculature, thereby increasing anti-PD1 drug delivery and preventing tumor-induced hearing loss.

With all the recent success in the clinic using antisense oligonucleotides (ASOs) to skip problematic exons in pre-mRNA splicing for diseases, **Cameron Church** from the University of Alabama at Birmingham presented his recent research highlighting NF1 exon 52 as a prime candidate for a similar approach. These findings underscore the therapeutic potential of exon skipping for treating NF1 exon 52 mutations, offering a promising new avenue for

** CTF-funded researcher*

patients with this genetic disorder.

We were excited to have **Dr. Kavita Sarin** from Stanford University Medical Center share results from the **CTF-Funded Phase 2b study of NFX-179** (Nedometinib) topical gel for treating cutaneous neurofibromas (cNF) in NF1. This was a randomized, double-blind, vehicle-controlled study design. The findings suggest that NFX-179 Topical Gel 1.5% significantly reduced cNF size with minimal side effects, marking a significant step forward in treating these tumors. Interestingly, nearly half of the participants in the 1.5% gel group rated their tumors as "better" after treatment, compared to just over 20% in the placebo group. This successful Phase 2b trial paves the way for further research and development in a Phase 3 trial. Additional details for this study can be found at **ctf.org/NFX-179**.


Dr. Kavita Sarin

Bringing in a broader perspective, our invited speaker, **Dr. Darren Hargrave** from the Great Ormond Street Institute of Child Health, shared some impactful lessons from Pediatric Oncology that can be applied to drug discovery efforts for children. He stressed the importance of having a consortium, strong patient engagement, a robust registry, strong knowledge of natural history, early and often communication with regulatory agencies, validated biomarkers for clinical trial design, as well as standardized and accessible preclinical models and endpoints. These are all valuable lessons that apply to the general NF community and the ongoing initiatives in drug development.

AI, Novel Tech, Biomarkers

Dr. Casey Greene from the University of Colorado opened our AI session with a keynote on "engineering serendipity." He discussed how Artificial Intelligence (AI) and Machine Learning (ML) are revolutionizing healthcare by improving patient outcomes and accelerating research. Dr. Greene reviewed successful AI/ML implementations in clinical and research settings, citing genome-wide association studies in human genetics. A key example was the University of Colorado's oncology pharmacogenomic screening program, enhancing treatment selection. Dr. Greene's keynote demonstrated the transformative potential of AI/ML in advancing research, particularly in rare diseases, while addressing ethical considerations.

The AI morning session began with a long-time CTF-funded investigator, **Dr. Scott Plotkin***, from Massachusetts General Hospital, discussing a multicenter radiomics model for diagnosing NF1-associated MPNSTs. Dr. Plotkin highlighted the crucial role of radiology in diagnosing MPNSTs. His team developed a multicenter

** CTF-funded researcher*

MRI and clinical data repository to achieve this, aiming to standardize imaging protocols across institutions. The findings from these efforts indicate that multicenter radiomics models can effectively classify tumors as (pNFs vs. MPNSTs and pNFs vs. atypical neurofibromas (ANFs) plus MPNSTs using clinically available MRI sequences. The short tau inversion recovery (STIR)-based model performed the best among these models. This ongoing work aims to create a validated model to predict malignant transformation and achieve computer-enhanced diagnosis.

In a similar endeavor, CTF Clinical Research Award recipient **Dr. Inka Ristow*** from the Medical Center Hamburg-Eppendorf presented her work on using radiomics and deep learning for MRI image analysis, which focuses on differentiating between benign and malignant tumors in NF1 patients. Dr. Inka presented evidence that the machine learning approach using MRI-based radiomics shows great potential in accurately distinguishing between benign and malignant tumors, with atypical tumors exhibiting features that fall between the two.

Taking a closer look at the mechanisms of malignant progression of MPNSTs, **Dr. Bernat Gel*** (currently funded by CTF) from the Germans Trias i Pujol Research Institute analyzed samples from different stages of tumor progression (control nerves, pNF, ANF, and MPNST) using advanced technologies: scRNA-seq, scATAC-seq, SMARTseq2, scDNA-seq. One of the most interesting findings from the presented work identified the specific cell populations affected by the inactivation of NF1, CDKN2A, and PRC2 genes, pinpointing cells likely responsible for tumor development. Moreover, spatial transcriptomics mapped the organization of different cell populations within the tumor tissue. This study provides new insights into the progression of MPNSTs and potential clinical applications. Knowing that the comprehensive dataset will be available to the NF1 research community for further exploration is exciting.

In a continued pursuit of understanding MPNST transformation, **Dr. Xiyuan Zhang** from the National Cancer Institute looked at changes in the tumor environment using single-cell RNA sequencing (scRNAseq) and discovered a unique "transitioning" cell type in some pNF and ANF that might indicate a higher risk of becoming malignant. Using these "transitioning" cells and the malignant cell signatures, they developed an algorithm to identify high-risk tumors early, suggesting that a new diagnostic tool using scRNAseq could potentially help identify these tumors in clinical practice.

Dr. Catena Kresbach from the University Hospital Hamburg-Eppendorf also analyzed tissue samples from patients using histology and global methylation profiling and found that epigenetic changes occur early, even in areas that look benign. The study is ongoing, with plans to expand the sample size and correlate findings with MRI and PET-CT scans, along with transcriptomic and genome sequencing data.

Beyond malignant transformation, it was fascinating to hear **Dr. Zhifan Jiang** from Children's National Hospital present his work on an automatic deep-learning framework that predicts visual acuity loss in children with optic pathway gliomas (OPG) using MRI features. MRIs from 135 children with NF1-OPG from Children's National Hospital and Children's Hospital of Philadelphia were analyzed, and the findings concluded that this automated MRI analysis method enhances the ability to predict vision loss in children with NF1-associated OPGs.

Looking closely at Schwann cells, **Dr. Gregory P. Way** from the University of Colorado shared his current research

** CTF-funded researcher*

efforts to identify unique cell shapes and structures in these cells affected by the *NF1* gene. Researchers used Cell Painting to study three types of Schwann cells with different *NF1* gene statuses (healthy, partially affected, and fully affected). Dr. Way showed that machine learning successfully predicted the NF1 status from cell images, something that can't be seen with the naked eye. This research shows promise in using cell shape analysis to identify drugs that can improve the health of NF1 patient cells without causing toxicity.

Finally, **Dr. Sara JC Gosline** from Pacific Northwest National Laboratory addressed data harmonization, a vital topic in AI. Dr. Gosline introduced the Cancer Omics and Drug Experiment Response Data (coderdata) Python package, standardizing cancer omics and drug response data to support AI-based drug sensitivity predictions in NF1 tumors. This effort addresses the challenge that current AI algorithms for predicting drug sensitivity in tumors must be revised for NF1 tumors due to limited and inconsistent data. The goal is to create a unified dataset and platform to enhance AI-based predictions specifically for NF1 tumors. The study has compiled molecular data from around 5000 samples, including various model systems like cell lines, organoids, patient-derived xenografts, and actual tumor data, including NF1-related tumors such as malignant peripheral nerve sheath tumors and cutaneous neurofibromas. By harmonizing this diverse dataset, AI algorithms can better predict drug sensitivity in rare tumors like NF1.

Poster Winners

BASIC SCIENCE

1st place – Helena Mazuelas

NF1 / Schwann cell differentiation as a therapeutic approach for cutaneous Neurofibromas

Hereditary Cancer Group, Germans Trias i Pujol Research Institute (IGTP)

2nd place – Franceska Kovaci

Spine Deformity in Mice Lacking NF1 Gene in Boundary Cap-Derived Osteoblasts

Mondor Institute for Biomedical Research (IMRB)

3rd place – Jamie Blake

TEAD Inhibitors in Combination with Brigatinib Prevent NF2-Deficient Meningioma

Peninsula Medical School, University of Plymouth

CLINICAL SCIENCE

1st place – Omar Roman

The Effect of Selumetinib Treatment Interruptions on Plexiform Neurofibroma Growth

National Cancer Institute - Pediatric Oncology Branch

2nd place – Aditya Sheth*

CENPF as a Biomarker and Therapeutic Target for NF1-Associated MPNST

Indiana University School of Medicine

3rd place (tie) – Matthieu Peyre

Surgical Management of Peripheral Nerve Tumors in NF2-Independent Schwannomatosis

Department of Neurosurgery, APHP.Sorbonne Université, Hôpital Pitié-Salpêtrière, Assistance Publique

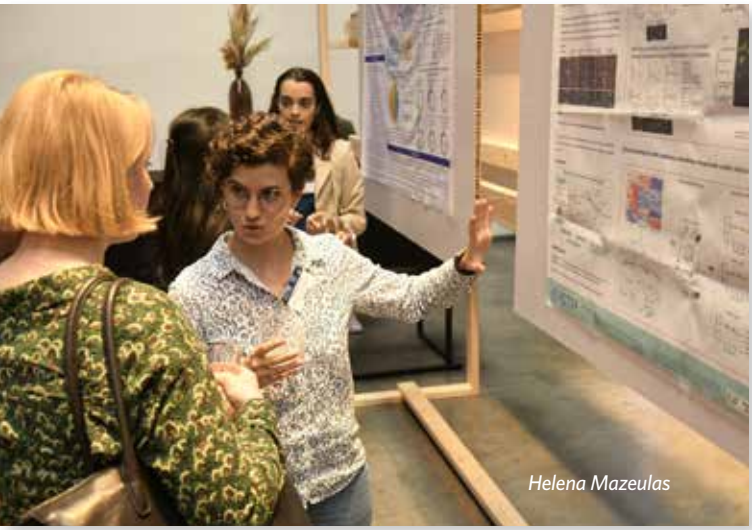
3rd place (tie) – Christy Soares

Real-World Evidence for Quality of Schwannomatosis Care

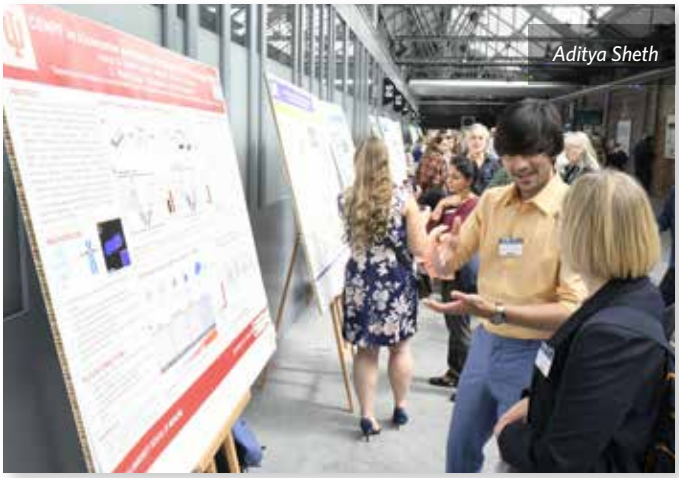
Emory University School of Medicine

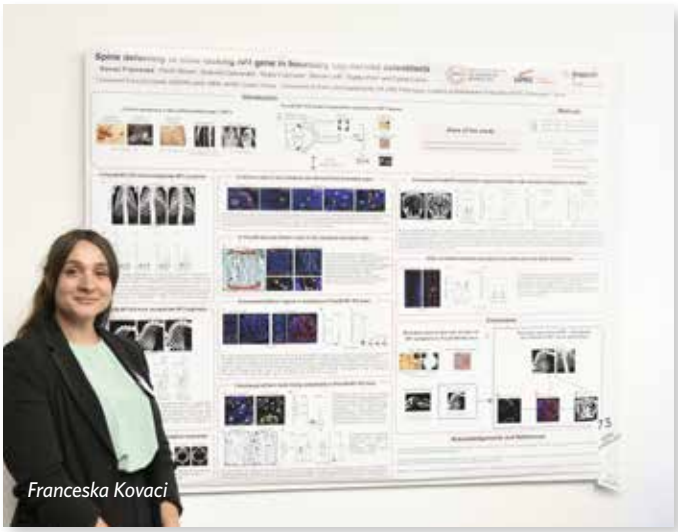
**CTF Young Investigator Awardee*

Poster Winners
continued

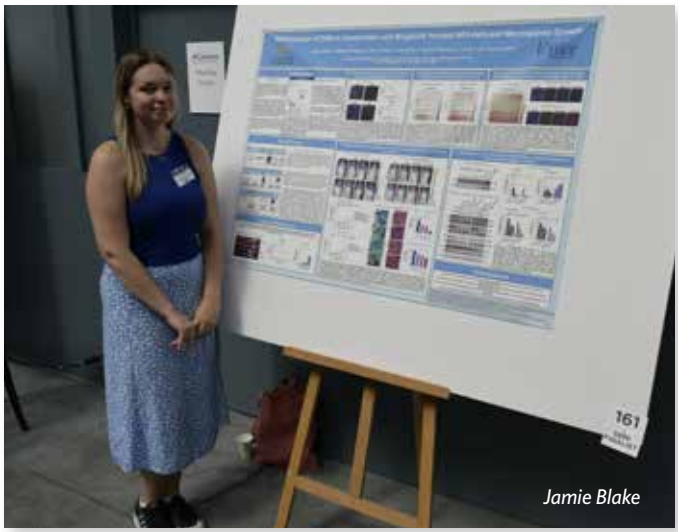

Helena Mazeulas


Omar Roman


Aditya Sheth


Franceska Kovaci

Matthieu Peyre



Jamie Blake

Christy Soares

2024 Friedrich von Recklinghausen Award Winner

The Children's Tumor Foundation's Friedrich von Recklinghausen Award is given to individuals in the professional NF community who have significantly contributed to neurofibromatosis or schwannomatosis research or clinical care. It is named after Friedrich Daniel von Recklinghausen (1833-1910), the German physician who first described 'von Recklinghausen's disease' – what we now know as neurofibromatosis type 1.

At the 2024 Global NF Conference, CTF announced **Professor Rosalie Ferner, MD**, consultant neurologist of Guys and St. Thomas NHS Foundation Trust London (GSTT), UK, as the 2024 Friedrich von Recklinghausen Award recipient.

CTF CEO Annette Bakker with Von Recklinghausen Award Winner Rosalie Ferner

After an early academic career studying modern languages, Dr. Ferner shifted gears and moved on to study medicine. Hence, she has spent her lifetime dedicated to improving the lives of those afflicted with neurofibromatosis and schwannomatosis. Dr. Ferner has consistently demonstrated all the considerable attributes and accomplishments that make her a most worthy awardee.

Dr. Ferner established and has been the national lead for the nationally commissioned NF1 service in the UK since 2009 and was the lead for the London NF2 service from 2010 to 2015. In these roles, she has been a passionate champion for patients with all forms of neurofibromatosis and schwannomatosis but has had a particular impact in the field of NF1. She is a clinician's clinician—skilled, precise, compassionate, creative, and dedicated.

As a researcher, she has driven entire chapters of NF1 research to improve clinical care for people with NF1. She has miraculously created pathways for care for people with NF in the UK that follow the best evidence in the face of many hurdles. She was instrumental in developing QOL patient-focused outcome measures for NF1 and *NF2*-SWN and has delivered multiple publications on elucidating the phenotype of NF1, OPG, and MPNST. Indeed, she is one of the most published researchers in NF and is still active in the field. Dr. Ferner recruits and trains early-stage clinician investigators and is the consummate collaborator – expert, reliable, respectful, dedicated, and clear about her mission and the importance of the work. Much of what we know about optic pathway gliomas, plexiform neurofibromas, and MPNST is due to her efforts. She is driven by concern for the person facing a challenging illness and parlays this concern into critical research and national program building. Finally, no one can match her wit or sincere warmth, caring, and compassion.

The Children's Tumor Foundation, along with her colleagues and peers, is proud and thrilled to recognize Professor Ferner with the 2024 Friedrich von Recklinghausen Award, not only for her many outstanding achievements over her years in the field but also for her dedicated efforts in supporting the entire NF community.

SAVE THE DATE

2025

NF CONFERENCE

JUN 21-24, 2025

Omni Shoreham Hotel
Washington, DC

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

nfconference.org

For more information, contact nfconference@ctf.org

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

engage
PATIENT ENGAGEMENT INITIATIVE

ANNOUNCING CTF ENGAGE:

A Patient Engagement Initiative from the Children's Tumor Foundation

CTF Engage is the Foundation's Patient Engagement initiative, designed to prepare individuals with NF and their families to add their perspective during all phases of the research process – from the laboratory, to the clinic, to the community.

Patient Representatives team up with researchers and other drug development stakeholders as advisors, consultants, and co-investigators to help these experts understand what it is like to live with NF and what outcomes are important to patients.

Over the past several years, CTF has trained patients and their family members to become effective advocates in NF research. Moving forward, we are building upon this success and are looking to add new Patient Representatives to this program.

We are looking for NF-affected adults and NF care advocates of all backgrounds. Must be 18 or older to apply. There is no experience required.

To indicate your interest in becoming a Patient Representative, please scan the QR code or go to **ctf.org/patientengagement** to learn more.

If you have any questions, please direct them to Emily Greaves, egreaves@ctf.org.

National Office:
Children's Tumor Foundation
697 Third Avenue
Suite 418
New York, NY 10017

Mail Donations To:
Children's Tumor Foundation
Mail Code: 6895
P.O. Box 7247
Philadelphia, PA 19170 - 0001

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

Tel. 212-344-6633 . 1-800-323-7938 . info@ctf.org

ctf.org