

NF NEWS

THE NEWSLETTER OF THE CHILDREN'S TUMOR FOUNDATION
SPECIAL EDITION

CHILDREN'S
TUMOR
FOUNDATION
ENDING NF
THROUGH RESEARCH

2018 Joint Global NF Conference in Paris

We are pleased to present a summary of the 2018 Joint Global Neurofibromatosis Conference, held in Paris at the Maison de la Chimie on November 2 – 6, 2018. The support and planning of this particular conference was historic in that the Children's Tumor Foundation (CTF), for the first time, combined forces with the European Neurofibromatosis Group, Association Neurofibromatoses et Recklinghausen, and the NF2/Schwannomatosis State of the Art group, to form the most comprehensive agenda and largest gathering of NF researchers, clinicians, patients, and patient advocates, with over 800 people from around the world in attendance.





About the NF Conference

The NF Conference is recognized as the premier annual scholarly gathering of international NF researchers and physicians, and is considered a critical venue for the presentation and integration of basic science discovery, translational data, and clinical trial outcomes, to both enhance the quality of ongoing research and improve clinical care.

The planning committee worked with CTF leadership to design a broad-ranging and comprehensive agenda which spanned five days. Topics that are foremost in the NF community at this time were included, to provide education about best clinical practices for the neurofibromatoses, opportunities to share major advances in research, and reinforce the growth of new investigators. The conference was further enhanced by a number of satellite meetings and workshops, which allowed particular groups, including the NF Clinic Network, time for networking and information sharing.

This year's conference presented nine plenary sessions and seven parallel sessions, along with the bi-annual NF2/Schwannomatosis State of the Art meeting which ran in parallel on days three and four. Renowned keynote speakers from outside the NF community served to stimulate fresh discussions and promote the development of new collaborations.

FROM the President

Annette Bakker, PhD

“ This Joint Global NF Conference brought together the most diverse, international expertise in the world to meet and exchange ideas, and to do so in an environment that encourages and cultivates joint efforts. ”



The Children's Tumor Foundation (CTF) has been committed to translating science into treatments for neurofibromatosis (NF) for over forty years. Tremendous progress has been made in field of NF research as a result of CTF's longstanding commitment. This was made especially evident in our 40th anniversary year, when more than 800 researchers, patients, and clinicians gathered from around the world in Paris, France for the first Joint Global NF Conference. This NF Conference brought together the most diverse, international expertise in the world to meet and exchange ideas, and to do so in an environment that encourages

and cultivates joint efforts. The five-day meeting was an assembly of men and women who are working to find treatments for the suffering of people with NF. We are excited to share with you the highlights of the work that was presented, and the promising results of the research that you have funded. Together we all play a part in the fight to end NF.

Annette Bakker, PhD
President, Children's Tumor Foundation

The 2018 Joint Global NF Conference co-chairs

Pierre Wolkenstein, MD, PhD, Hôpital Henri-Mondor (France)

Eric Pasmant, PhD, Université Paris Descartes (France)

Michel Kalamarides, MD, PhD, Hôpital Universitaire Pitié-Salpêtrière | APHP (France)

Ludwine Messiaen, PhD, University of Alabama at Birmingham (USA)

Lu Le, MD, PhD, University of Texas Southwestern (USA)

Marco Giovannini, MD, PhD, University of California, Los Angeles (USA)

Satellite Symposium on Cutaneous Neurofibromas

The Neurofibromatosis Therapeutic Acceleration Program (NTAP) led by Jaishri Blakeley, MD of Johns Hopkins School of Medicine, kicked off the working program in Paris with a satellite symposium on Developing Therapeutics for Cutaneous Neurofibromas. Although NTAP is focused on both plexiform (pNF) and cutaneous neurofibromas (cNF), this symposium was focused on cNF only. NTAP has recently activated nine projects on cNF with topics spanning from the generation of new cell and animal models of cNF, to understanding the cells of origin and genetic targets that cause the tumors to form. Ten short presentations were given; highlights included information about the identification of immunologic targets, generation of 3D organoid models of cNF, and analysis of mouse and pig models of cNF.

A clinical classification of cutaneous neurofibromas, presented by Anat Stemmer-Rachamimov, MD, of Harvard University and Pierre Wolkenstein, MD, PhD, of Hôpital Henri-Mondor in Paris, completed the session with a lively panel discussion moderated by Dr. Wolkenstein. The panel focused on the impact that cutaneous neurofibroma lesions have on patients. An NF patient on the panel named Pascal shared engaging remarks about the burden that NF has on him, and his hope for a cure or a treatment that would allow him to live a life free from NF, or at least from the cutaneous lesions. It was clear that, even if not life-threatening, the psychosocial impact of being visually affected has a major effect on patients' lives, to the point that they would be willing to risk bearing the side effects of a treatment in order to alleviate the appearance of these lesions.

Educational Symposium

The satellite educational symposium is a popular optional add-on to the NF Conference, where both novice and experienced clinicians are able to hear from experts in a variety of disciplines about best clinical practices in the treatment of a wide variety of issues facing the NF patient. Muscular weakness and its impact on lifestyle in NF1 were outlined by Juliana Souza, MD, PhD, of the University of Minas Gerais in Brazil. Another researcher, Karin Soares Goncalves Cunha, PhD, of the Universidad Federal Fluminense, Brazil, presented on oral manifestations in NF1, noting that 72-92% of NF1

patients had oral soft tissue alterations causing possible taste disturbances and hyposalivation. Jaw and dental alterations were also prevalent.

Cutaneous neurofibromas and their treatment by various methods such as electrodesiccation were reviewed by Hubert Weinberg, MD, of Mt. Sinai Hospital, who noted that these lesions should not be considered cosmetic as they are associated with pain and discomfort.

On a different note, David Largaespada, PhD, of the University of Minnesota, gave an overview of CTF-funded swine models for NF1 and their potential applications in treatment development. Eva Trevisson, MD, PhD, of the University of Padova, reviewed breast cancer screening recommendations for women with NF1.



ANIMAL MODEL SESSION

The Animal Model session overviewed the work done at the CTF Animal Model Workshop that took place in Palm Springs, California earlier in the fall of 2018. The workshop was hosted at the United States and Canadian Academy of Pathology (USCAP) learning center, and more than 20 new animal models were presented to a group of 10 pathologists. Slides of tumors developed by these animals, including the first pig models, were scrutinized under the microscope to understand the features of each model and whether the tumors were similar to those that developed in humans. Co-chairs of the workshop were Marco Giovannini, MD, PhD, from UCLA, Nancy Ratner, PhD, from Cincinnati Children's Hospital, and Anat Stemmer-Rachamimov, MD, from Harvard University.



David Largaespada, PhD, from the University of Minnesota and Nancy Ratner presented models that develop MPNST (malignant peripheral nerve sheath tumors) through the transition of preexisting neurofibroma. Yuan Zhu, PhD, from Children's National Medical Center and Gilbert Institute, and Rebecca Dodd, PhD, from the University of Iowa, presented models that may develop MPNST without transition from atypical or obvious pre-existing benign lesion (*ex novo*).

Adrienne Watson, PhD of Recombinetics, Inc., presented the NF pig model that has been developed within the Synodos NF1 consortium. Together with the other Synodos NF1 pig model developed by the University of Iowa and Sanford Research, these are the first large animal models of NF ever created and characterized. These models also developed plexiform and other features of NF1 pathology like lisch nodules, tibial bowling, and behavioral issues.

A number of additional animal models were presented by members of this workshop, including cutaneous, NF1-driven breast cancer, NF1-driven Rhabdomyosarcoma, NF2 models, a *SMARCB1* schwannomatosis model, and an overview of meningioma models. The work done at the workshop and the classification of all the reviewed animal models will be published in a scientific journal. The proposed histopathological classification of tumors will be used as a future reference to analyze drug testing results in these models.

Selumetinib

When the 2017 NF Conference in Washington, DC concluded, attendees were informed about Selumetinib (a MEK inhibitor) and the promise of this drug to effectively and spectacularly shrink plexiform neurofibromas in young patients where surgery was not an option. Now that the Phase 2 clinical trial is complete and the data collected is being prepared for submission to the FDA, the Paris meeting attendees were eagerly anticipating news of when the drug will be made available.

They didn't have long to wait, as the first presentation of the NF Conference was delivered by Andrea Gross, MD, from the National Cancer Institute (NCI) and part of the team that conducted the Phase 2 registration trial, called SPRINT (Selumetinib in Pediatric Neurofibroma study). Dr. Gross explained that, beyond measuring the tumor volume of patients responding to treatments, they carefully monitored safety and tolerability of the drug, motor function response,

muscle strength, pain, and the personal experience of each patient undergoing the treatment.

Having all these data points allowed the researchers to show that even with a 'modest' tumor reduction of 27% or less, one young patient now has better mobility in his arms, is more active, walks with a normal gait, sleeps better, wrestles a bit with his sister, and his clothes fit better. Other patients had over 50% tumor reduction and overall, 74% of all trial participants had a tumor reduction of more than 20% (the minimum level to classify the response as 'partial response' and considered effective).

The overall result of the SPRINT trial was even better than the results presented in the Phase 1 trial (71%). In conclusion, Dr. Gross reported that results were durable, the drug was well tolerated, and adverse effects were reversible by stopping the administration for a few weeks.

Epigenetics

The plenary session on Epigenetics presented various aspects and current knowledge on the implication of epigenetics in neurofibromatosis and schwannomatosis. Thomas De Raedt, PhD, of Children's Hospital of Philadelphia, began by presenting research into the epigenetic features of MPNSTs in mouse and human tissue and how transcription in the RAS pathway is altered by the *BRD4* gene.

Recent findings from Synodos for Schwannomatosis were reported by Sheila Mansouri, MD, of University Health Network in Toronto. This CTF-funded \$1.0 million, two-year initiative is working to develop effective treatments for schwannomatosis. The group found that schwannomatosis schwannomas are epigenetically distinct from solitary schwannomas. The potential exists for epigenetic profiling to be

Epigenetics means "above" or "on top of" genetics. It refers to external modifications to DNA that turn genes "on" or "off." These modifications do not change the DNA sequence, but instead, they affect how cells "read" genes. Epigenetics is the reason why a skin cell looks different from a brain cell or a muscle cell. All three cells contain the same DNA, but their genes are expressed differently (turned "on" or "off"), which creates the different cell types. - *livescience.com*

useful as a diagnostic criteria to distinguish schwannomatosis from solitary schwannoma.

Matt Steensma, MD, of the Van Andel Institute in Grand Rapids, Michigan, reported unique methylation profiles in cutaneous neurofibromas compared with those of plexiform neurofibromas. The implication is that correlations could be used for potential biomarkers; additionally, new drug targets could be identified that can impact expression.

Keynote Presentation 1:

Danny Reinberg, PhD

"Epigenetics: One Genome, Multiple Phenotypes"

Danny Reinberg, PhD, is the Terry and Mel Karmazin Professor of Biochemistry and Molecular Pharmacology, at the NYU Langone School of Medicine, and Howard Hughes Institute. His latest work studies the post-translational modifications of histones and their potential epigenetic character, and he is considered one of the best people working in the chromatin/transcription field.

Keynote Presentation 2:

Kristjen Jessen, PhD, University College London, UK – "Schwann Cell Biology"

Kristjen Jessen is a Professor of Developmental Biology in the Research Department of Cell and Developmental Biology at University College London. In this keynote address, Dr. Jessen presented his research on early Schwann cell development and the biology of the Schwann cell precursor, the molecular control of myelination, and the response of Schwann cells to injury and genetic disease.

Schwann Cells and Neurofibromas Session

A session on Schwann cells and neurofibromas presented the latest discoveries and knowledge on normal Schwann cell development and function, and how loss of *NF1* leads to the aberrant growth of Schwann cells, and their interaction with the cellular microenvironment which gives rise to neurofibroma.

Surgery in NF1

The main goal of this session was to invite experts in the field as well as selected abstract speakers to present the latest advances and discoveries on surgery, especially on the plexiform neurofibromas that are often located at sites with a high risk of morbidity. The session also included discussion of aesthetic outcomes in cases of facial involvement or transplant.

Psychology Workshop

This "by-invitation" workshop was for psychologists only and was created to provide a platform for discussing critical issues in the treatment of NF patients.

Psychosocial Impact of the Neurofibromatoses

Ana-Maria Vranceanu, PhD, director of the Integrated Brain Health program at Massachusetts General Hospital, reported that a Skype-based psychosocial intervention, the Relaxation Response Resiliency Program, can improve quality of life in people with any form of NF. Dr. Vranceanu also reported that Acceptance and Commitment Therapy (ACT) benefitted people with NF1 plexiforms, decreasing their perceived pain, depression, and anxiety, and improving their quality of life. Pamela Wolters, PhD, of the Pediatric Oncology Branch of NIH, showed that the use of patient-reported outcomes (PROs) was helpful in documenting clinical benefit in a trial of selumetinib in treating plexiforms. Since the FDA emphasizes the importance of documenting clinical benefit in addition to tumor shrinkage, incorporating PROs in clinical trials has the potential to speed drug approvals. Dr. Belinda Barton, PhD, of the University of Sydney, spoke about international perspectives on supporting psychosocial needs. She noted that concerns vary among the various types of NF, but within the same type are fairly consistent across age groups and geographic regions.

AstraZeneca Satellite Meeting

AstraZeneca, the pharmaceutical company that has developed Selumetinib, had a strong presence at the meeting. The AstraZeneca team organized meetings with patient organizations, researchers, and clinicians to educate them about the drug and discuss the options available for patients with current and emerging treatments. A satellite meeting entitled “NF1-PN: Are We MEKing Progress” was organized by the company and chaired by Roger Packer, MD, with the participation of Gareth Evans, MD, Brigitte Widemann, MD, and David Mowatt, MD.

The session analyzed various individual NF1 cases and highlighted options that either surgery or other treatments (in development) could offer. It was concluded that the greater the medicines,



equipment, and techniques at the disposal of doctors, the better the outcome for patients. In cases where surgery would be riskier than the condition itself, a drug would be needed. And the more drugs available, targeting different aspects of the tumor, the less we will need surgery and invasive treatments. Finally, from the latest update we received from AstraZeneca, their plan is to submit to the FDA in the first half of 2019, meaning that approval could well happen before the end of this year.

NF Clinics Network Satellite Meeting: Addressing the Shortage of Qualified NF Providers

Each year, the Foundation organizes a satellite session for NF clinicians at the NF Conference. This year's session focused on addressing the shortage of qualified NF providers and offered four presentations on ways to enhance care. The value of telehealth and the need to encourage young professionals to train in relevant specialties were the main themes.

David Stevenson, MD, director of the NF clinic at Stanford University, had gathered data demonstrating a stalling pipeline of future NF providers. He found that residency programs in medical genetics, the most common specialty among NFCN directors, are going unfilled. Almost three-quarters of these programs recently reported being unable to fill all available placements. As a result, employment opportunities in medical genetics are also going unfilled. Pediatric neurologists, who make up the next largest cohort of NFCN directors, are in a similar situation with demand exceeding supply, and

this national shortfall is expected to increase from 11% in 2012 to 29% by 2025. Stevenson made the point that encouraging medical students' interest in these areas early in their training is crucial to attracting and retaining them in the areas that feed into NF care.

Justin Jordan, MD, MPH, a neuro-oncologist at Massachusetts General Hospital (MGH), presented on the use of telehealth to increase access to NF care. He noted that telehealth eases travel burdens for patients, and scheduling and space challenges for clinicians, while avoiding emergency room visits. Jordan reported on a pilot study at MGH in which 109 NF patients used telehealth services. The majority were routine follow-ups, but one-quarter of them were to communicate test results, with another 12% evaluating a new health issue or on-therapy follow-up.

Sally Trump, a registered general

nurse at Guy's and St. Thomas Trust in the United Kingdom, described existing nurse-led telephone clinics for complex and non-complex NF1 cases. For non-complex patients, telehealth calls take the place of annual appointments and are used to monitor, triage, and advise on self-management.

Nicole Ullrich, MD, PhD, at Boston Children's Hospital, chair of the mentorship committee of CTF's Clinical Care Advisory Board (CCAB), reported the results of a needs assessment survey concerning mentorship within the NFCN. Half of the respondents to the survey said they would like to be mentored by an experienced NF clinician to discuss matters such as increasing clinic volume, building research capabilities, and consulting on complex cases. Based on the results of the assessment, the CCAB Mentorship Committee will soon create a formal process to implement mentoring relationships.

Keynote Presentation 3:

Paolo G. Casali, MD

“Malignant Nerve Sheath Tumor: Improving the Prognosis”

Paolo G. Casali, MD, is Associate Professor of Medical Oncology at University of Milan, Italy, and spoke about his clinical and research activities, with a focus on adult soft tissue sarcomas and gastrointestinal stromal tumors (GIST). He is Secretary of the Italian Sarcoma Group and a member of the European Organisation for Research and Treatment of Cancer Soft Tissue & Bone Sarcoma Group.

Mutations in Other Cancers Session

Speakers presented on the presence of somatic *NF1* mutations in tumors that are not necessarily considered *NF1*-associated

tumors. In addition, somatic mutations in many genes may be critical drivers in *NF1*-associated cancers. The landscape of somatic mutations should provide novel insights into our understanding of the pathophysiology of cancer and identify new therapeutic targets.

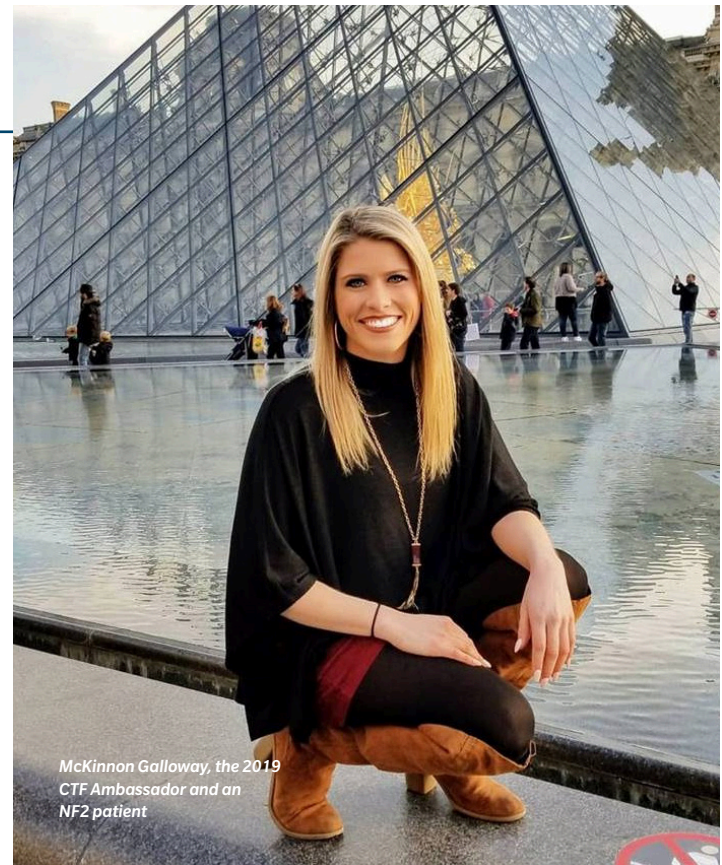
NF2 and Schwannomatosis State of the Art

The NF2 State of the Art session began with the inspiring words of McKinnon Galloway, the 2019 CTF Ambassador and an NF2 patient. In her speech, McKinnon explained how NF2 entered her life, and the impact of hundreds of doctor’s appointments, countless hours spent in the hospital for MRIs, and numerous surgeries. NF has taken a toll on her body and her life. Yet thanks to her strong spirit, coupled with hope in medicine and science, she is fighting back and undeterred to live her life in full. Her plea to the NF experts gathered at the Conference was to continue to search for a cure or treatment that would stabilize or shrink tumors and ultimately allow NF patients around the world to live a normal life.

The NF2 State of the Art session continued with a presentation by Gareth Evans, MD, from the University of Manchester, UK, reporting on progress made in the use of genetic tests to identify pathogenic variants that cause

NF2. A combined approach with Next Generation Sequencing and MLPA (a test for identification of large rearrangements) alongside additional tests, is a highly sensitive technique to identify mosaic NF2 patients (those patients whose mutation is often detected only in tumor material and not in blood). Indeed 25-30% of new NF2 cases are mosaic and therefore difficult to diagnose. This new technique offers a major advantage in identifying mosaic NF2 and can provide estimates for offspring transmission.

Scott Plotkin, MD, PhD, from Massachusetts General Hospital, gave an update on current and emerging drug treatments options for NF2. After years invested in understanding the underlying cause of NF2 and experimentation in clinical trials, there is now a portfolio of drugs and targets that work on the many aspects of NF2 biology. Starting with drugs like Lapatinib, Everolimus, Vistusertib, and Crizotinib (that should work by inhibiting critical pathways



McKinnon Galloway, the 2019 CTF Ambassador and an NF2 patient

used by tumors to survive) to Bevacizumab and Axitinib (that should tackle the tumor microenvironment), to emerging drugs like Brigatinib, TAK228, and Dasatinib, that were recently identified in the Synodos for NF2 project. Dr. Plotkin also pointed to many other drugs that are on the horizon as well as immunotherapy and gene replacement therapy that could soon find application in NF2.

The clinic section of the NF2

mini-symposium highlighted the management and treatment of the various tumor types, including vestibular schwannomas (VS), meningiomas, hearing rehabilitation, spinal tumors, and peripheral nerve schwannomas. Michael Link, MD, from Mayo Clinic, reported that management of NF2-associated VS remains very challenging and that their practice maintains an extremely nuanced and individualized treatment strategy. The primary goals remain



As a result of the promising discoveries made in CTF's Synodos for NF2 project, the Foundation is collaborating on a new clinical trial for NF2 patients, which will launch later this year.

tumor control to avoid life-threatening complications from progressive mass effect, and the maintenance or restoration of cranial nerve function.

In a similar fashion, John Golfinos, MD, from NYU, presented numerous cases of patients with NF2 meningiomas. Being an expert surgeon, he explained that NF2, similarly to NF1, requires a full NF-center team approach with multiple expertise. Surgery should be limited to the management of symptomatic lesions as it remains very challenging and applauded the arrival of the molecular era for meningiomas as well as the opportunity to use non-invasive treatments like drugs or biologics. For schwannomatosis, Allan Belzberg, MD, FRCS, from Johns Hopkins reported the state of the art in schwannomatosis treatment and surgery. Today surgery remains the #1 option for patients, with radiosurgery and medications (pain/chemo) following. Also, schwannomatosis requires a multi-discipline approach for its management, including neurological evaluation, imaging, genetic testing, tissue diagnosis, and pain.

An interesting view of the management

of NF2 in China was provided by Dr. Hao Wu, from the Shanghai Jiaotong University, where the center offers a multi-disciplinary approach to patients. With an estimate of 35,000 NF2 patients in China, only 60 patients are referred to the center every year. Researchers in China are eager to get more internationally involved and increase the quality of life of many patients that remain untreated or undiagnosed. So far there is no systemic NF2 data in China, and most NF2 patients lack appropriate management and have a poor quality of life.

In a platform talk, Matthias Karajannis, MS, MD, from Memorial Sloan Kettering Cancer Center explained the results of a Phase 0 study of the drug Everolimus in VS and meningioma patients. In his conclusions, he suggests that exploiting this resistance mechanism with combination therapies could be a more effective way to target NF2 tumors.

In another platform talk, Long-Sheng Chang, PhD, from Ohio State University, reported on the results of the CTF-sponsored Synodos NF2 consortium and the identification of the drug Brigatinib. The project involved the collaboration of 12 different labs with different expertise and 3 years of research. The \$3.3 million investment made by CTF in Synodos NF2 paid off, with the results in both VS and meningioma animal models showing tumor shrinkage. After assessing the results produced by the team, Takeda, the pharmaceutical company that owns the drug, has agreed to start a clinical trial in NF2 patients in collaboration with CTF. The trial will be started in 2019.

Glioma - In/Out of NF

This session discussed whether and how gliomas occurring in NF1 patients classify in the context of the comprehensive landscape of genetic and epigenetic alterations reported in patients who have sporadic glioma (patients not diagnosed with NF). This information will shed light on the question of whether the formation of gliomas in NF1 syndrome recapitulates any of the specific events that characterize sporadic gliomas. We anticipate that the ability to address this yet unanswered question will cause a re-evaluation of the guidelines for the classification of sporadic glioma and will elucidate new points of therapeutic intervention for these tumors.

Antonio Iavarone, MD, from Columbia University and David Jones, PhD, from German Cancer Research Center presented results from the CTF-funded Synodos NF1 Glioma projects. They have collected over 100 high-quality glioma samples from across the world, and have carried out comprehensive analyses to identify genetic, epigenetic, and metabolic alterations driving these tumors. These analyses revealed several novel insights, which will have significant implications for improving diagnosis and treatment of NF1 gliomas.

One of the challenges with NF1 gliomas is determining whether the tumor will remain asymptomatic or if it will progress and require therapeutic intervention. Robert Avery, DO, MSCE of Children's Hospital of Philadelphia presented on correlations between optic pathway glioma (OPG) dimensions, extent of nerve damage, and vision loss. He presented data from a study involving 26 children with NF1 OPGs, revealing that larger tumor size as measured by MRI was associated with more severe nerve damage and increased vision loss. These observations may be helpful in identifying NF1 OPG patients with higher risk and, therefore, greater need for medical intervention.

The session concluded with Dr. Amedeo Azizi from the Medical University of Vienna, who gave a presentation emphasizing the importance of selection criteria for timely and accurate identification of NF1 OPG patients that can benefit from treatment. He presented data from a clinical trial showing that even though the drugs vincristine and carboplatin were effective in many NF1 OPG patients, it is not easy to predict which patients would benefit from such therapy. Close medical observation to follow the natural progression of the glioma is essential for identifying the best time for initiating treatment.

Neurocognitive/Learning Disabilities

Autism spectrum disorder is thought to affect 10-40% of children with NF1, and ADHD incidence in NF1 is estimated at 40-60%. Shruti Garg, PhD, of the University of Manchester, UK, reported preliminary results toward measuring the effect of the drug simvastatin in children with NF1 autism, demonstrating proof-of-concept that parametric brain imaging of unmedicated children in this population was feasible and looked capable of showing changes related to treatment.

Hilda Brems, PhD, of KU Leuven, Belgium, discussed a mouse model of social deficits in Legius syndrome, and results showing that MEK inhibition can reverse these deficits.

Andre Rietman, PhD, of Erasmus Medical Center, Netherlands, presented research

into genotype and behavioral phenotype on NF1. Non-truncating mutations were associated with more autistic traits than truncating mutations but did not associate with more general behavioral or attention problems.

Peter de Blank, MD, Cincinnati Children's Hospital, reported findings of the Childhood Cancer Survivor Study that NF1 cancer survivors may be at increased risk for chronic health conditions and cognitive/psychosocial impairments. NF1 cancer survivors had lower survival rates than other cancer survivors 20 years after diagnosis, which were not improved even if they had avoided radiation and



alkylating chemotherapy.

Karin Walsh, PsyD, of Children's National Health System, reported the results of patient surveys, showing that most knew of cognitive and social-emotional research in NF1, but few had participated in such research. Barriers to participation and ways to engage patients in this area were explored.

GENOTYPE / PHENOTYPE SESSION

Patients and families with NF1 are often told to 'watch and wait' as it is not possible to precisely anticipate which NF1 symptoms will develop, or the severity of these manifestations.

The Genotype/Phenotype session focused on recent advances in the understanding of genotype-phenotype correlations specifically in NF1, including clinically relevant phenotypes associated with specific recurrent *NF1* missense mutations, impact of mosaicism on the phenotype, timing of and cell of origin for second hits, and the influence of modifier genes.

Ludwine Messiaen, PhD, heads the Medical Genomics Laboratory at the University of Alabama in Birmingham and is a recognized leader in genetic testing. She has a long-standing interest in researching the potential relationship between the specific *NF1* mutation or variant (genotype), and the *NF1* manifestations (phenotype). These investigations are complicated by the large size of the *NF1* gene, and the thousands of different variants reported. Dr. Messiaen has, however,

identified *NF1* variants and associated features in over 8,100 unrelated NF1 individuals. The Children's Tumor Foundation funded Dr. Messiaen's promising work with the Isaac and Sadie Fuchs Genotype-Phenotype Grant in order to facilitate the discovery of additional NF1 genotype-phenotype correlations.

As part of the NF1 genetic analysis at UAB, referring physicians that submit a sample for testing also complete a phenotypic checklist, documenting the patient's features and NF manifestations. This increases the understanding and awareness of the complexity and variability of NF1-associated signs and helps with the identification of potential genotype-phenotype correlations.

Read more about Dr. Messiaen, who was awarded this year's von Recklinghausen award, on page 13.

The **genotype** is the set of genes in our DNA which is responsible for a particular trait. The **phenotype** is the physical expression, or characteristics, of that trait. For example, two organisms that have even the minutest difference in their genes are said to have different **genotypes**.

- YourDictionary.com



Keynote Presentation 4:

Pier Paolo Pandolfi, MD, PhD
Translational Mouse: From Genetic Models to the Mouse Hospital, and Co-Clinical Trials for Understanding and Treatment of Cancer

Pier Paolo Pandolfi, MD, PhD, is the Director of the Cancer Center & Cancer Research Institute, Beth Israel Deaconess Medical Center at Harvard Medical School in Boston. His research has been revolutionary with the development of the “Co-Clinical” Trial Platform approach for cancer therapy optimization. With this approach, the mouse models of cancer, which are representative of the diversity of human cancer, are treated with the same drug, and follow the very same clinical protocol offered to human patients enrolled in experimental clinical trials. This allows for “mice-to-human-to-mouse” stratification and cross-validation of response and resistance to specific treatment modalities, and for the identification of effective therapies that overcome such resistance. Dr. Pandolfi explained the story of how Acute Promyelocytic Leukemia (APL) was cured with a targeted therapy developed with the aid of specific mouse models. Interestingly, the NF research community has developed mouse models that could be used in a similar setting and could prove very effective in the identification of specific treatments for MPNST.

Microenvironment Session

Speakers presented on the presence of somatic NF1 mutations in tumors that are not necessarily considered NF1-associated tumors. In addition, somatic mutations in many

genes may be critical drivers in NF1-associated cancers. The landscape of somatic mutations should provide novel insights into our understanding of the pathophysiology of cancer and identify new therapeutic targets.

Pain and Pruritis in Neurofibromatosis

Pain and pruritis (itching) are a prominent feature in the neurofibromatoses. Nerve and tissue damage, as well as inflammation cause pain and itch, which are associated with significant distress and impaired quality of life. The

molecular and cellular mechanisms underlying our sense of pain and itch were discussed along with implications for therapy and current management of these symptoms.

BASIC SCIENCE PLATFORM SESSION

This session, chaired by Yuan Zhu, PhD, of the Children’s National Medical Center, and Conxi Lazaro PhD, of the Institut Catala d’Oncologia, was opened by German Luis Velez Reyes, PhD candidate of the University of Minnesota, who gave an overview of genes recently identified as involved in the transformation to MPNST.

This talk was followed by a presentation by Anna Kolesnik, PhD candidate from Birbeck University London, on ongoing studies in Autism Spectrum Disorder symptoms in NF1 infants, showing that signs of social and communication difficulties can arise very early in children with NF1.

Michael Daniel, PhD, of the University of Alabama at Birmingham then presented ongoing work in exon skipping in NF1, a gene therapy technique whereby the fragment of NF1 gene (exon) which contains the mutation is “skipped” when the gene is translated into the NF1 protein, so as to produce a protein which does not contain

the defective portion, albeit not being the full NF1 protein. This work may be able to identify exons that can be skipped and at the same time produce a truncated NF1 protein that is functional.

In the same area of work (gene therapy), Verena Staedtke, MD, PhD of Johns Hopkins University then presented *in vitro* work showing that the GAP-binding portion of the NF1 gene (the one responsible for the repression of the RAS pathway when the gene is not mutated, i.e. the one repressing the formation of tumors) has potential for use in gene therapy, as it can be delivered to cells using a virus, inhibiting the proliferation of MPNST cells.

Moving on to NF2, Cristina Fernandez Valle, PhD, of the University of Central Florida presented *in vitro* and *in vivo* work showing that MEK inhibitors also have a potential for treatment of NF2 Schwannomas, and that in the context of NF2, different MEK inhibitors do not

necessarily act in the same way. The session was closed with a presentation by Long Cheng, PhD, on behalf of the CTF-identified and funded Synodos NF2 Consortium, highlighting how the consortium’s 4-year effort has led to the identification of Brigatinib, alone or in combination with an AKT inhibitor, as a novel and promising clinical candidate for the treatment of NF2 tumors.

On top of having identified these clinical candidates, the consortium has generated a very large amount of data, now publicly available through the CTF-funded NF Data Portal, which can be used by researchers worldwide to explore other possibilities beyond Brigatinib, which had emerged as the best possible candidate, but not the only one. Moreover, the fact that all data produced is now available to the wider public will make it possible for researchers worldwide to avoid focusing on compounds that the consortium has identified as ineffective.

Keynote Presentation 5:

Caroline Robert, MD, PhD “Targeted Therapy in Melanoma”

Prof. Robert is the Head of the Dermatology Unit at the Institut GustaveRoussy in Paris. She is Board Member, European Association of Onco-Dermatology; Melanoma Board Secretary for European Organization for the Research and Treatment of Cancer; French Society of Dermatology and Venerology, AACR, ASCO, France.

About half of all melanomas have changes (mutations) in the BRAF gene. Melanoma cells with these changes make an altered BRAF protein that helps them grow. Melanoma therapy was revolutionized by two strategies in recent years: targeted therapy for BRAF-mutant melanoma, and immunotherapy relying on checkpoint inhibitors, regardless of BRAF mutation.

Therapies targeting the BRAF and MEK proteins have shown to achieve the highest response rate - around 70% - in patients with metastatic BRAF-mutant melanoma; however, secondary resistances are frequent. After one year of treatment, half of the patients show signs of resistance to the drug. A vast variety of resistance mechanisms have been identified and several treatment strategies are being evaluated in order to delay the occurrence of resistance.

Medical and Surgical Care: A Multidisciplinary Approach for NF

A multidisciplinary approach is the rule for the management of neurofibromatosis 1 and 2. The action of the paired Physician/Surgeon is a fine-tuned adjustment. This session provided attendees the state of the art for this approach, taking into account the vast number of NF complications to be treated, from plexiform neurofibromas to vestibular schwannomas.

The Biology of NF2 and Schwannomatosis

A group of Schwann cell researchers discussed and exchanged data on key cell intrinsic and extrinsic signaling mechanisms important for peripheral nerve maintenance and repair, and discussed how merlin functions as a tumor suppressor.

Clinical Science Platform Session

In a study report prepared by Rosalie Ferner, MD, of Guy’s and St. Thomas’ Hospital, U.K., a five-year survival rate of 59%, much higher than generally reported for MPNST, was found in a case series of 83 MPNST cases followed at her institution. Earlier diagnosis and/or improved management in cohesive national centers in the U.K. may explain the improved survival. The David Miller, MD, PhD, Boston Children’s Hospital, reported on the organization of the Genomics of MPNST (GEM) Consortium, a collaboration focused on defining the genomic and clinical features of a set of over 100 MPNST samples. Its goal is to serve as a data resource for pre-clinical research.

Dorothy Halliday of Oxford University Hospitals, UK, reported on the benefits of incorporating genotype information into routine NF2 care. Her group uses a metric that combines type of NF2 mutation (missense, truncating, whole-gene deletion, etc.) with mosaicism status to yield a genetic severity score for each patient. The validity of the genetic severity score was examined and found relevant to observed natural history status, including rate of progression of hearing loss, eye disease, and age at first manifestation. It has proved useful in discussions of individual prognosis and management.

Michael Fisher, MD, of Children’s Hospital of Philadelphia presented on the risk of subsequent neoplasms (SN) after a primary tumor in NF1 based on a DHART SPORE collaboration. They found a 3.1-fold higher risk for NF1 patients with a primary tumor to later develop a SN, compared with non-

NF1 cancer patients, especially if exposed to radiation therapy. However, treatment of a primary tumor in NF1 with alkylating chemotherapy was not associated with increased SN risk over the risk conferred by their NF1 status.

Dr. Fisher also reported results of a NF Clinical Trial Consortium study of cabozantinib (XL184) for treatment of plexiform neurofibromas. Cabozantinib targets the tumor microenvironment and angiogenesis and reduced PN size and number in a mouse model. In the clinical trial, a partial response, defined as 20% reduction in tumor volume, was achieved by 8 or 19 subjects (42%). In this group of responders, a significant decrease in patient-reported pain intensity was observed.

In a late-breaking abstract, Gareth Evans, MD, of St. Mary’s Hospital in Manchester, UK, reported the results of a multicenter study of the risk of contralateral breast cancer. It has often been reported that women with NF1 carry a higher risk of breast cancer, in the range of 6-fold in women ages 30-39, and have poorer survival rates. Using case records and cancer registry data from Turku, Manchester, Paris, Hamburg, and Padova, the incidence of second breast cancers in NF1 and non-NF1 women was assessed. Together the study sites contributed data on 146 women with NF1 and 335 controls. Of the women with NF1, 13 developed a second cancer in the contralateral breast at a median age of 53 years. Screening recommendations for annual mammography beginning at age 30 or 35, plus MRI if available, were proposed.

NF: Present, Past, and Future

This session was a retrospective and prospective view of the field of NF research and NF clinical care, delivered by the most experienced and respected “NFologists” in the world.

The session began with presentations from Drs. Vincent Riccardi, Susan Huson, and Arvid Heiberg, who are three of the “originals” in the field of NF. Each delivered a personal and unique perspective of the “way we were,” followed by presentations from Luis Parada and Gareth Evans on “where we’re headed.”

Dr. Luis Parada from Memorial Sloan Kettering Cancer Center presented an overview of the complex interplay of various molecular factors in the development of NF1. Although NF1 is caused by a mutation in the NF1 tumor suppressor gene, the nature of the mutation alone does not explain the high variability of NF1 manifestations. Dr. Parada elaborated on how the identity of the tumor-originating cell, NF1 gene dosage state, and factors in the tumor microenvironment all play an essential role in influencing and modulating disease

development. He also presented data from his laboratory demonstrating the occurrence of cancer stem cell-like tumor cells in MPNSTs that mediate MPNST formation, progression, and regrowth after chemotherapy.

Dr. Gareth Evans from University of Manchester presented an overview of NF2 and schwannomatosis, with emphasis on improved treatment possibilities and future directions for both conditions. He summarized data from several studies that showed how bevacizumab

treatment decreased vestibular schwannoma growth rates and the need for surgeries, as well as improved hearing and overall quality of life in NF2 patients. He also emphasized the potential of new strategies, such as antisense oligonucleotides and exon skipping as therapeutic options for NF2. Dr. Evans also described the complexity of pain in schwannomatosis patients and expressed optimism that initiatives such as the Synodos can tremendously increase understanding of the disease.

NF Patient Advocacy meetings were held in parallel with the medical and scientific conference.

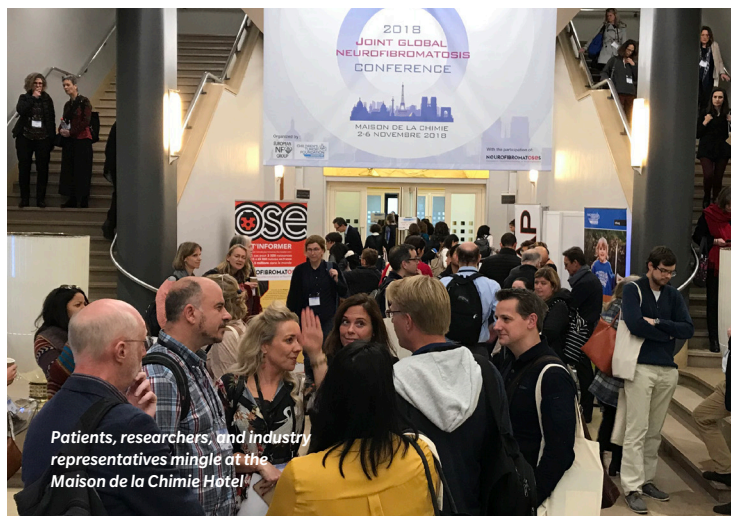
Global NF1 Patient Advocacy Exchange - AZ & Patient Groups

The inaugural Global NF1 Patient Advocacy Exchange between AstraZeneca, US, and EU patient organizations, was held alongside the scientific NF Conference in Paris. There was representation from key stakeholders in patient organizations, with US-based organizations including the Children’s Tumor Foundation, Texas NF, and the Littlest Tumor Foundation; and European organizations including Patients United and Les Neurofibromatoses.

The objective of the meeting was for AstraZeneca to build strong relationships with patient advocacy groups and understand how to support patients and physicians in the treatment of NF1 plexiform neurofibromas. The discussions at the meeting were very informative and inspiring for both patient groups and AstraZeneca. The discussions focused on clarifying the goals of the patient groups to foster better collaboration with pharma, and soliciting input on access to treatment and patient support. Patient groups gave feedback on what materials/activities would most add value to ensure patients stay on, and understand the value of, continuing therapy, as well as what non-treatment related patient support AZ could consider supporting, without duplicat-

ing the effort of NF1 Patient Advocacy Groups.

The session concluded with a hopeful feeling that working together can ensure access to selumetinib treatment for patients at the right place and time.



Patients, researchers, and industry representatives mingle at the Maison de la Chimie Hotel!

Global Patient Representatives Congress

The Global Patient Representative Meeting was a gathering of patient advocacy groups from around the world, with much representation from the EU and USA, along with newcomers such as Russia. The meeting was spearheaded by new patient organization Patients United, and patient advocate Claas Röhl. During the day-and-a-half congress, patient groups shared ideas and learned about best practices in their respective organizations and countries. The enthusiasm and energy within the group was infectious. It is evident that there is much good happening globally to support NF patients. Throughout the day, NF experts such as Dr. Gareth Evans presented on the work of ERN GENTURIS (European Reference Network) and the inclusion of neurofibromatosis as a part of that network. ERN is a network connecting health care providers and centers of expertise of highly specialized healthcare, for the purpose of improving access to diagnosis, treatment, and the provision of high-quality healthcare for patients with Rare Diseases no matter where they are in Europe. Patient representatives are involved in the governance of ERNs.

Children's Tumor Foundation President Annette Bakker discussed the vision, mission, strategy and strategic fit of the CTF existing organization and future plans. There was an excellent interactive panel discussion about patients being partners, instead of victims. Traceann Rose, CTF Director of Patient Education, discussed the patient representative training program as a means of building patient capacity and empowering

patients to become advocates. Nicole Martin, NF1 patient from the UK shared a story of motivating and inspiring youths through creating a camp program in the UK. Claas Röhl (Eupati trainee) discussed his journey as an advocate and graduate of the Eupati training program and how it inspired him to start his NF Foundation (NF Kinder) in Austria. Onno Faber, NF2 patient, also gave his perspective on the value and importance of getting behind research and the solution he chose because of his journey. Onno's startup company, RDMD, streamlines patients' journeys through two tools: a referral engine for rare-disease specialists, and a medical-history app that's a more organized, elegant, portable version of that bulky binder.

Simon Vukelj, the Chief Marketing Officer of the Children's Tumor Foundation, presented CTF's 'Shine a Light on NF' initiative, which launched in 2014. In this annual campaign, hundreds of buildings, bridges, monuments, and landmarks around the world show their support in the fight against NF by lighting up each May in blue and green, the official colors of NF. The Shine a Light on NF campaign grew to 205 landmarks around the world in 2018, and included well-known locations in the United States, including Niagara Falls, as well as in the United Kingdom, Canada, Italy, Austria, and New Zealand.

The program had many opportunities for open discussions and a question and answer session that generated a lot of ideas and discussions around what other groups had done to raise awareness and funds for NF, support patients, facilitate access to better NF care, and how we can create a system to share ideas and resources.

NF News is the official publication of the Children's Tumor Foundation. All issues are available on our website at www.ctf.org. Please direct any questions or feedback to info@ctf.org.

The Children's Tumor Foundation is a 501(c)(3) not-for-profit organization dedicated to funding and driving innovative research that will result in effective treatments for the millions of people worldwide living with neurofibromatosis (NF), a term for three distinct disorders: NF1, NF2, and schwannomatosis. NF causes tumors to grow on nerves throughout the body and may lead to blindness, deafness, bone abnormalities, disfigurement, learning disabilities, disabling pain, and cancer. NF affects 1 in every 3,000 births across all populations equally. There is no cure yet – but the Children's Tumor Foundation mission of driving research, expanding knowledge, and advancing care for the NF community fosters our vision of one day ending NF. For more information, please visit www.ctf.org.

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2018 Friedrich von Recklinghausen Recipient

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



Ludwine Messiaen, PhD, von Recklinghausen Award recipient, and Annette Bakker, PhD, CTF President

The Children's Tumor Foundation is delighted to announce the 2018 von Recklinghausen Award recipient: Ludwine M. Messiaen, PhD, Professor of Genetics and Director of the Medical Genomics Laboratory at the University of Alabama at Birmingham.

Dr. Messiaen's extensive training and experience in the field of molecular genetics and genetic testing has gained her and her lab international recognition for her many accomplishments in the molecular diagnosis of all the neurofibromatoses.

She established the best and most comprehensive *NF1* mutation screening technique in the world at UAB, and provided a diagnostic service to the patients in the US and abroad. She also invested in mutation analysis on melanocytes from café au lait spots and on Schwann cells from neurofibromas. She was the first to find a second hit in melanocytes derived from a café au lait spot on a person with *NF1*. She was also the first to investigate pseudarthrosis tissue for a second hit in the *NF1* gene.

She collaborated with Dr. Eric Legius on the identification and characterization of

SPRED1 mutations in Legius syndrome, and she published in *JAMA* on the clinical and molecular spectrum of *SPRED1* mutations. Dr. Messiaen also created an enormous database with the molecular and clinical data of *NF1* patients. She is using this impressive resource successfully to discover new genotype-phenotype correlations, and to unravel different types of mutational mechanisms. She also is offering diagnostic testing for *NF2* and schwannomatosis, both on DNA extracted from blood and on DNA extracted from tumor

“If a genotype-phenotype correlation exists for a particular mutation, it will help families have some perspective of what the future will bring, and it will help them cope with the disease.”

—LUDWINE MESSIAEN, PhD

tissue. This led her to identify a set of families with schwannomatosis but without a *SMARCB1* mutation on chromosome 22. She found that schwannomas from these individuals showed loss of one chromosome 22 and a schwannoma-specific *NF2* mutation similar to the mechanism seen in *SMARCB1* families. This directed her to chromosome 22 and further work by her led to the conclusion that *LZTR1* is a second gene involved in schwannomatosis.

Her discoveries and conclusions were published in the journal *Nature Genetics* in 2014. She followed up on the function of *LZTR1*, and in 2018 was a co-author on a science paper showing that the *LZTR1-CUL3* complex ubiquitinates all RAS-isoforms.

Ludwine is also currently serving as a member of the steering committee reviewing and revising the diagnostic criteria for *NF1*, *NF2*, and schwannomatosis and her expertise in the molecular aspects of these disorders is of tremendous value to the committee's formulation of the new criteria.

Please join us in congratulating Dr. Messiaen for this much-deserved award.



Children's Tumor Foundation Europe launched on November 7, 2018. The focus of CTF Europe is to further build out relationships with European agencies and partners while maintaining our commitment to funding innovative research worldwide that will result in effective treatments for NF. To read more more about the formation of CTF Europe, and watch videos from the launch event in Brussels, please go to: ctf.org/europe

Children's Tumor Foundation Europe Launched November 7, 2018

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ENDING NF THROUGH RESEARCH



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