

CONFERENCE 2007

THE CHILDREN'S TUMOR FOUNDATION

Report from the 2007 NF Conference: From Genes to Clinical Care

In the first week of June, a record number of attendees - over 200 researchers and clinicians from all over the world - met in Park City, Utah for the 2007 Neurofibromatosis (NF) Conference, the annual meeting of the international NF scientific community organized by the Children's Tumor Foundation. This year's theme was: "Models, Mechanisms, and Therapeutic Targets" and a number of exciting new studies of NF were presented.



Dr. Kim Hunter-Schaedle opens the 2007 NF Conference

The conference included a pre-meeting Clinical Care satellite, as well as five satellite meetings focusing on NF related topics such as Optic Pathway Glioma (OPG), Learning Disabilities (LeaDNet), Clinical Care, NF2 Clinical Trials and Schwannomatosis. The 2007 conference co-chairs were Dr. Karen Cichowski (Harvard Medical School/ Brigham & Women's Hospital) and by Dr. Eric Legius (University of Leuven). The three-day event featured fifty-two scientists platform presentations and seventy posters. Four keynote presentations were from outstanding scientists from outside of NF. As last year, short presentations by patient advocates showed us a personal prospective of the NF disorder.

The Conference kicked off with the exciting announcement of the launch of the Foundation's biggest program to date: a new \$5 million commitment to accelerate progress of NF candidate drugs to clinical trials. \$4M of this funding will establish the **Drug Discovery Initiative NF Preclinical Consortium**. The Consortium will consist of

five centers - four focused on different tumors of NF1, and one on tumors of NF2. Together, these Centers will function as a fully collaborative Consortium, and will for the first time present the capability to screen drugs in parallel in multiple models of NF tumors. Applications are being sought from candidate centers this summer, and will be reviewed and the Consortium assembled this fall. Following a planning period, it is anticipated drug screening will commence by mid-2008.

\$1M of the new initiative is set aside to fund **pilot NF clinical trials** - the clinical testing of a candidate therapeutic in a small number of patients that precedes larger Phase II trials. The pilot clinical trials program is anticipated to launch in October 2007.

In a time that the NF community is looking for new drugs to be tested, Dr. **Wade Clapp** (*Indiana University School of Medicine*) presented interesting data on his work with the drug Gleevec (Novartis) which is used to treat Chronic Myeloid Leukemia (CML) and gastrointestinal stromal tumors (GIST). Dr. Clapp used genetically engineered mice, which develop NF1 plexiform neurofibromas in the spinal cord. In a preliminary clinical trial, he treated mice with Gleevec and by using PET/CT scan, he showed that the tumor volume was reduced by the drug. Far more interesting, Dr. Clapp treated a 3-year-old child with NF1 plexiform neurofibroma developed in her thoracic area. The only alternative she had to breath was to have a tracheotomy performed. After treatment with *Gleevec*, the tumor size was reduced 70% - 80% and although she is off treatment, the tumor has not grown back. Although this is only one case, it gives much hope to NF1 patients with plexiform neurofibromas for a new drug clinical trial.

Dr. **Nancy Ratner** (*Cincinnati Children's Hospital*) and Dr. Yuan Zhu (University of Michigan) gave talks showing different approaches to early inactivation of NF1 during mouse embryo development, to generate new models of NF1 tumors. The animals developed neurofibromas in the spinal cord. Both researchers used genetically engineered mice that lose NF1 expression at a specific time of embryo development and on a specific organ (spinal cord). They showed that NF1 loss causes unbalance among the different kinds of neurons by promoting unnecessary proliferation leading to neurofibromas. Understanding the mechanism how NF1 loss causes neurofibromas could help us find ways to treat it.



The laboratory of Dr. Vijaya Ramesh (*Harvard Medical School/ Massachusetts General Hospital*) has identified Magicin or MED28, a novel protein that interacts with NF2 protein, merlin. MED28 expression is elevated in many human cancers and it has been proposed that it serves as a scaffolding protein to facilitate signals within the cell. Furthermore, manipulation of MED28 expression in cells has shown that it functions as a novel regulator suppressing cell differentiation and probably maintaining proliferation which is directly linked to smooth muscle tumors.

Dr. Frances Hannan (*New York Medical College*) presented a fruit fly with significant hearing defects due to loss of the NF2 corresponding gene. Further exploration of these flies will be very useful for the NF2 study. For example, they may potentially be used to screen efficacy of candidate NF drugs.

Dr. Theo Hulsebos (*University of Amsterdam*) gave an update on the *INI 1* gene, which has been found to be mutated in Schwannomatosis patients. He examined the INI expression in tumors of two Schwannomatosis patients finding partial loss of INI 1. Further studies on the INI 1 gene will help to understand the mechanisms of Schwannomatosis.

A challenging question of the NF community is what a patient should expect after being diagnosed with NF1. The variable manifestations of the disorder make developing a method to predict the disorder's outcome a priority of the NF scientific community. Dr. Karlyne Reilly (*Mouse Cancer Genetics Program, National Cancer Institute*) demonstrated that modifier genes unlinked to the NF1 gene could affect the severity of the NF-1 disorder. Dr. Reilly presented a mouse modifier gene called *Nstr3* that increases the incidence of Malignant Peripheral Nerve Sheath Tumors (MPNSTs) under certain genetic conditions and decreases the incidence of MPNSTs under different genetic conditions. The differential effect of *Nstr3* shows that the genetic background plays a significant role on the NF1 manifestation. Dr. Reilly's laboratory

works on developing a 'genetic barcode' made up of modifier genes located on multiple chromosomes, where a single 'bar' in the code has no predictive value but the combination of 'bars' produces a unique and highly predictive code. These studies will help to develop tools for early NF1 diagnosis, which will lead to early treatment and a better life for NF1 patients.

During the **Clinical Care Satellite**, **Dr. Roger Packer** (*Children's National Medical Center*) presented the latest on the NF1 Clinical Trials Consortium supported by the Department of Defense Congressionally Directed Medical Research Program. The main goals of the consortium are to develop innovative biological therapies for NF1 related tumors and biological markers, which can be used as diagnostic tools. The consortium is comprised of multidisciplinary clinics, which can each enroll 10-12 patients with NF1-plexiform neurofibromas. The consortium is ready to launch the phase II clinical trial of Rapamycin on October 1st 2007 and the Lovastatin phase II clinical trial for treatment of NF1-associated learning disabilities is expected to start at the end of the year.

Dr. Brigitte Widemann (*National Cancer Institute, Pediatric Oncology Branch*) updated the audience with the latest on clinical trials coordinated by the National Cancer Institute of the National Institutes of Health. Two drugs - Tipifarnib and Pirfenidone - are now concluding phase II clinical trials. They target patients with progressive NF1 related plexiform neurofibromas. The main objectives of these trials have been the effect of the drugs on the progression and reoccurrence of the plexiform neurofibromas and to determine the toxic effects of the drugs on the patients. In the near future, a phase I clinical trial of Sorafenib, a drug that targets Raf kinase and is used to treat sarcomas will start and it will target children with inoperable NF1 plexiform neurofibromas.

Dr. Dusica Babovic-Vuskanovic, (*Mayo Clinic*) presented the launch of the phase II clinical trial of AZD2171 (AstraZeneca), an inhibitor of angiogenesis. The study includes patients with plexiform neurofibromas and/or neurofibromas near the spine. The main objectives are to assess the effectiveness of AZD2171 on NF1 patients and measure its toxicity.

In the NF2 field, **Dr. Michel Kalamarides** (*Beaujon Hospital, Clichy, France*) gave an overview of the 2006 NF2 meeting, which took in Paris, France. (*Details about the meeting were presented in the Fall 2006 NF Newsletter*). **Dr. Scott Plotkin** (Harvard Medical School/Massachusetts General Hospital) addressed the 'Challenge

and Opportunity' of NF2 clinical trials (*see NF2 clinical trials planning report in this Newsletter for more information*).

In three moving presentations, patient advocates told their stories from the platform. **Fran Cone** talked about her son Drew's Schwannomatosis; **Barbara Franklin**, about her son Adam's NF2; and **Zoe Gerchick**, mother of two young children with NF1, about her infant son's pseudoarthrosis. These presentations were a critical part of the Conference, bringing home to the scientists the importance of their research to solve the NF puzzle.

LeaDNet 2007:

Phase II NF1 Learning Disabilities Clinical Trial Planning Forges Ahead

Over the past eighteen months the Children's Tumor Foundation has energized the learning disabilities community by convening them via LeaDNet - the Learning Disabilities Network. LeaDNet has been spearheaded by **Dr. Alcino Silva (UCLA)** and provides a forum for the NF1 learning disabilities community to share information and plan next steps to accelerate progress. The LeaDNet group met at the 2007 NF Conference, in a session co-chaired by **Dr. Silva** and **Dr. Kathryn North (Children's Hospital at Westmead in Sydney)**.

NF1 learning disabilities research has made significant progress in the past eighteen months. It has moved rapidly from **Dr. Silva's** 2005 findings that Lovastatin can reverse some of the learning disabilities displayed by NF1 mice, into Phase I clinical trials to test the safety of Lovastatin in children age 10-17 years with NF1 learning disabilities. These clinical trials, conducted by **Dr. Maria Acosta** at Children's National Medical Center in Washington, DC, have now concluded Phase I. At the NF Conference **Dr. Acosta** presented data on 14 patients. This demonstrated first and foremost that Lovastatin is safe at biologically active doses. It is too early to know for sure if Lovastatin is improving cognitive function, but some positive effects have been observed anecdotally in individual patients.

The next priority of the learning disabilities community, and a principal focus of the 2007 LeaDNet meeting, is to design a Phase II Lovastatin clinical trial to build on **Dr. Acosta's** Phase I findings. A major discussion point was how to determine the best endpoint measures. Ideally, one primary and one secondary measure should be used and these should be sufficiently definitive to demonstrate if there is Lovastatin efficacy. Significant progress was made at the 2007 LeaDNet gathering, and it is

hoped that the Department of Defense Congressionally Directed Medical Research Program will approve this trial to go forward within the framework of the NF1 Clinical Trials Consortium before the end of 2007.



Mr. Nate Walker, Dr. Gerard Gioia, Dr. Alcino Silva, Dr. Roger Packer

An interesting sidebar of the meeting was a discussion on the relationship between NF1 learning disabilities and attention deficit and hyperactivity disorder (ADHD), and there is a school of thought that NF1 and ADHD share common features. The group discussed whether ADHD medications might be worth testing in NF1 learning disabilities. Drugs of interest might include stimulant medications (e.g. Ritalin (methylphenidate), believed to activate certain brain regions) or non-stimulant medications (Strattera (Atomoxetine), a neurotransmitter inhibitor). Like Lovastatin, the mechanism of action of these drugs in the brain is not well understood, but there was support for testing ADHD drugs in the NF1 mouse model of learning disabilities. It would greatly certainly increase visibility of NF1 learning disabilities if a link with ADHD can be forged.

The Foundation will share updates on the Phase II Lovastatin trials as soon as these are available. Note: the clinical trial to test Lovastatin efficacy in adults with NF1 learning disabilities at UCLA has temporarily been placed on hold. However UCLA is continuing with an important research study to understand brain function in adults with NF1 learning disabilities. More information: Corinne McGown cmcgown@ctf.org.

Optic Pathway Glioma: Improving Care and Planning for Clinical Trials

A number of outstanding scientists with a wide range of expertise met at Park City in Utah on June 8, 2007 to discuss the future of Optic Pathway Glioma (OPG) in Neurofibromatosis 1 (NF1). The goal of the meeting, chaired by Dr. David Gutmann

(Washington University) was to develop criteria which can be followed by NF clinics and develop questions that will define the base of clinical trials.

The participants determined the criteria to be used to screen and detect OPG by clinics caring for children with NF1. Children with NF1 but no evident symptoms should be examined yearly by a detailed eye examination up to the age of 8 years old and MRI is not necessary. For the vision evaluation of children less than 1 year old with NF1 and showing signs of the disorder, Visual Evoked Potential (VEP) should be used along with an MRI. After discussion among the participants, it was decided that every patient showing progression should be treated. Progression is defined either by a two-drop line vision loss in a short period of time or a significant change of the tumor in consecutive MRI scans.

Finally, they discussed the advantages and disadvantages of the **treatments available**: surgery, radiotherapy, and chemotherapy. There was a negative feeling among the participants towards the use of radiotherapy due to high risk of developing secondary tumors. They talked about the great need of **biological therapies**, which include inhibitors of specific pathways related to OPG in NF1.

The participants decided that this meeting was very successful because they had the chance to clarify certain aspects of diagnosis and treatment of NF1. They decided to do a retrospective study, which will include data of why a patient was treated and if the treatment improved or stabilized vision. A prospective study will define the use of alternative diagnostic methods and possible candidates for clinical trials. It is the hope of the participants that an **OPG consortium** will be formed to include 5-10 centers that have the means for standard visual tests, VEP and MRI. This consortium will lead to development of **clinical trials**. The participants expressed the need to potentially meet potentially biannually to maintain momentum.

Planning for NF2 Clinical Trials: International Experts Tackle the Issue

To date, there have been no major clinical trials specifically for NF2. Unfortunately, this is a Catch 22 situation: because no NF2 trial has ever been set up, many parameters remain in question - what patient subpopulation to treat; what tumor to monitor; how long to treat for; and of course what are the most rational drugs to test? Nevertheless it is critical that the NF2 community prepare for clinical trials in the near future to be ready as drug candidates emerge from preclinical screening.

The Foundation convened an **NF2 Clinical Trials Roundtable** at the 2007 NF Conference, chaired by **Dr. Marco Giovannini** (*Inserm, Paris*) and **Dr. Scott Plotkin** (*Harvard/MGH*). Over 25 physicians from around the world participated. Some of the topics addressed are summarized below.

A 2006 Foundation survey clearly demonstrated that the NF2 patient community is highly motivated to participate in trials. Nevertheless physicians have to determine the most appropriate subgroup of **NF2 patients to participate** in initial trials. These patients must have tumors that are still progressing (so change can be monitored) but may have exhausted standard therapy approaches and have few options. It was noted that the NF2 pediatric population might be a target, as they have the greatest potential to benefit from effective therapeutics. Benefit versus risk remains a critical factor in NF2 patient population selection.

Regarding which **NF2 tumor** is the best initial target to monitor in a clinical trial, vestibular schwannomas stand out due to their impact on quality of life. Small tumors were proposed as a target, as effective drug treatment could potentially rescue hearing loss. Meningioma trials could potentially have outreach beyond NF2 since it is estimated 1:500 persons will develop a spontaneous meningioma in their life and their may be common drug targets with NF2 meningiomas. In contrast spinal schwannomas were felt not to be good tumors to monitor in a trial: once these grow, which tumors must to give meaningful measures in a trial, they become risky and have to be resected as soon as possible. However, spinal schwannomas can provide helpful secondary measures.

Defining endpoints for NF2 clinical trials is critical as this is the means by which drug effect is monitored and assessed. The time it takes for the tumor to progress (grow) is clearly a primary measure. For this, volumetric imaging (the technology developed by Dr. Gordon Harris at Harvard/MGH with support from a Children's Tumor Foundation Contract Award) is far more meaningful than diameter measures of tumors, since volume can change significantly while diameter remains the same. Volumetric imaging can be used for other tumors such as intracranial meningioma. Some other vestibular tumor measures include audiology, radiology, electrophysiology, and an important quality of life measure - extra years of hearing added.

Drug selection was hotly debated. It was agreed that well known candidate drugs with established safety profiles are attractive, since these would be easier to

accelerate to the clinic. It is likely that combinations of drugs will be required to treat NF2 tumors (e.g. chemotherapy drug + biologic drug) and this should be kept in mind when designing clinical trials. Available candidate drugs need to be prioritized, and there may be value in gathering data on the successful and non-successful drugs that have been tested in small numbers of NF2 patients to date.

Regarding **clinical trial design** this too was hotly debated. One popular proposal was to do short-term 'research trials' giving test drugs to NF2 patients who have scheduled surgery to remove a tumor. Drug is given for a period of time before surgery. Once the tumor is removed, it can be studied to see if the drug was effective in hitting its target. Such studies have been used in other sectors of oncology, and can rapidly yield data that can then accelerate the best candidate drugs into larger and more advanced clinical trials.

Having stimulated these conversations with the NF2 community, the Foundation will host a 2-day meeting this fall to reconvene them, with an outcome goal of developing concrete plans to conduct collaborative NF2 clinical trials. This meeting is timely: as described elsewhere in this NF NewsLetter, the Foundation plans to launch our pilot clinical trials initiative this fall and is intended to fund both NF1 and NF2 trials.

Schwannomatosis Strategic Planning: Defining Priorities for Research and Clinical Care

This has been an exciting year for Schwannomatosis: the first candidate gene for the disorder, the tumor suppressor *INI1*, was announced this spring by Dr. Theo Hulsebos of the University of Amsterdam. Schwannomatosis is a debilitating and poorly understood type of NF that affects an estimated 1:40,000 persons, causing a myriad of extremely painful tumors to grow on peripheral nerves. The finding of a candidate gene (as reported in the Spring 2007 *NF NewsLetter*) is a major step forward to understanding this disorder.

Over 25 physicians and scientists convened for a satellite of the 2007 NF Conference to review the status of Schwannomatosis research and clinical care practices, and set future priorities for the field. The meeting was co-chaired by Dr. Anat Stemmer-Rachamimov (*Harvard Medical School/MGH*) and Dr. Gareth Evans (*University of Manchester*).

The group identified six priority areas of Schwannomatosis that can accelerate research: Genetics, Clinical Diagnostic Criteria, Pathology, Cell and Animal Models, Clinical Care Practices and Pain Management.

The highlight of the satellite was in genetics, and learning that as well as Dr. Hulsebos, an additional four research groups have identified INI1 mutations in a significant number of additional Schwannomatosis patients. INI1 mutations have been identified in both familial (inherited) and sporadic (spontaneous) cases of the disorder. This validates Dr. Hulsebos' initial finding and suggests that the INI1 gene does indeed play an important role in Schwannomatosis. Pathology studies on human tumors are yielding information about the cellular role of INI1 protein. However much remains to be understood - about INI1 function, and about other genes that may be implicated in Schwannomatosis.

The clinical diagnostic criteria for Schwannomatosis were first published by the Foundation in 2005, but may need revising as we learn more about the disorder and in the advent of progress in its genetics. As the patient group affected by Schwannomatosis is so small, there is not much data available. It was recommended that to accrue more information, the Foundation gather data both via clinical measures as well as via a patient survey.



Dr. Theo Hulsebos, Dr. Els Robanus-Maandag, Mr & Mrs Fran and Jon Cone

Today, surgery is the main line of clinical care for Schwannomatosis: there are no drugs yet known to be effective in the disorder. It is certainly too early to think about clinical trials for Schwannomatosis - we first need to unravel the biology further - but we may gain some helpful information from future NF2 trials as to what drugs might be worth also testing in Schwannomatosis.

Currently there are no good cell and animal models of Schwannomatosis, which are critical for biological studies. The group discussed strategies for developing these, including both mouse and fly models of Schwannomatosis.

Untreatable and debilitating pain is commonly a primary issue for those with Schwannomatosis, and figuring out how to treat it has been challenging for clinicians. The group agreed we need to summarize those drugs known to work - or not - in Schwannomatosis pain management, and to look for new candidate drugs. The patient survey mentioned above can be designed to find out how an individual's pain was managed and what was effective. In addition, extensive biology and genetic studies need to be done on Schwannomatosis tumors to understand the mechanism of pain. What causes certain tumors to be painful, location, or is genetics involved too? If so, are there Schwannomatosis pain-associated genes? What alterations of cell function in the tumor are involved in pain?

The priorities emerging from this meeting will inform future programs of the Children's Tumor Foundation targeted at accelerating progress in understanding Schwannomatosis and moving toward effective therapies.

The group will convene again early in 2008 to continue sharing data and plan collaborations.

THANK YOU TO OUR 2007 SPONSORS:

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OPG Satellite: the Gilbert Family.

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