

The 2008 NF Conference:

New Genes, New Drugs ... and NF Clinical Trials

In June, international scientists and physicians convened in Bonita Springs, FL for the 2008 NF Conference, the premier annual gathering of the NF clinical and research community. With a record attendance, breaking news on NF clinical trials, a presentation on the first NF face transplant and a session on industry drug pipelines, 2008 marked one of the most exciting NF Conferences to date. Themed *Genes to Complications to Treatments*, the meeting was hosted by **Dr. Karlyne Reilly** (NCI Frederick) and **Dr. Gareth Evans** (University of Manchester, England).

2008 marked a year of growth and change for the NF Conference on many levels. This meeting has traditionally been held in the central mountain region so Florida was a refreshing change. We set a record of over 230 attendees, with 104 speakers and 54 posters presented. For the first time, the NF Conference spanned 4 days, and included two days of clinical sessions, clinical trial and drug pipeline updates, as well as the basic 'discovery' research which has traditionally been the main element of the Conference. The growth of the Conference to include a comprehensive 'bench to bedside' agenda reflects progress in NF research. It also reflects the recent growth of CTF funding programs to include the NF Clinic Network, Drug Discovery Initiative Awards for pilot preclinical drug screens as well as the launch our recent \$5M program to include an NF Preclinical Drug Screening Consortium and funding for pilot-scale clinical trials. Many current and recent CTF awardees presented their data at the NF Conference.

Major Highlights of the 2008 NF Conference

The keynote presentation by **Dr. Laurent Lantieri** (Henri-Mondor Hospital, Paris) described the first ever NF face transplant, which was performed in his clinic. This presentation of groundbreaking work was also deeply moving. The transplant was conducted on a 29-year man with a massive plexiform neurofibroma which severely disfigured the middle and lower part of his face. Dr. Lantieri presented full and graphic details of the surgical procedure. Dr. Lantieri's presentation was prefaced by an introductory talk from his colleague at Henri-Mondor Hospital **Dr. Pierre Wolkenstein** on the importance of considering quality of life issues in NF1. The positive impact that Dr. Lantieri's surgery had on this young man's life was highlighted in two brief films about his life before and after the transplant.

On the clinical trials front, **Dr. Emmanuelle di Tomaso** (Harvard Medical School/ Massachusetts General Hospital) presented exciting preliminary results from an NF2 clinical trial on 6 patients demonstrating potential efficacy of the drug Avastin. The drug caused some shrinking NF2 vestibular schwannomas in all patients, and in five patients a restoration of some auditory function and word recognition. Avastin blocks the formation of new blood vessels and therefore effectively 'starves' tumors; it has been

developed for use in cancer. Though very preliminary, this is a breakthrough finding. More studies are underway.

Staying with clinical trials, the US Army-funded Phase II Clinical Trials Consortium announced that their first trial is now open and recruiting patients. **Dr. Brian Weiss** (Cincinnati Children's Hospital Medical Center) described the trial which will test the drug rapamycin (sirolimus) in patients with plexiform neurofibromas which are symptomatic or growing. The study will aim to reduce growth rate of these tumors. The trial is open to children of 3 years old and upwards as well as adults. CTF will shortly post on our website www.ctf.org a simple form to facilitate your application for participation in this trial. In the meantime more information can be found at www.clinicaltrials.gov.

NF Clinical Trials Updates

In addition to the NF2 Avastin and NF1 rapamycin trials highlighted above, a few other clinical trial updates were presented. **Dr. Belinda Barton** (The Children's Hospital at Westmead, Australia) reported on the status of what will be the second trial of the US Army-funded Phase II Clinical Trials Consortium - the phase II trial of Lovastatin for the treatment of learning disabilities in children with NF1. Nine centers will participate, and children aged 10-16 years old with an IQ greater than 70 are eligible to participate. The three year clinical trial will start enrollment on December 2008.

Dr. AeRang Kim (Pediatric Oncology Branch, National Cancer Institute) described the Phase I trial of Sorafenib in children and young adults with NF1 inoperable plexiform neurofibromas. This is a safety trial to evaluate the kinetics and toxicity of Sorafenib when given over an extended period, as well as preliminary analysis of the effect of Sorafenib on the growth of the tumors and on cognition. Patients will be enrolled at the NCI and the University of Alabama. The trial will open in July 2008.

Another approach being explored for NF is Phase 0 trials where drug is given to the patient for a period of time prior to surgery, and the tumor can then be removed and analyzed. These types of study can be done for fairly limited amounts of funding but can provide valuable information to help identify the most promising candidate therapeutics and move them forward quickly to larger and more advanced trials. **Dr. Matthias Karajannis** (New York University) described a forthcoming Phase 0 trial, where the drug Lapatinib (targets EGFR/ErbB2) will be given to NF2 patients prior to vestibular schwannoma surgery.

What Drugs Will Be Next in the Pipeline for NF Treatment?

The 2008 NF Conference included a significant number of presentations on preclinical studies testing candidate drugs for NF in mouse and fly models of tumors, bone dysplasia, learning disabilities etc. It is from studies like this that future clinical trial drugs are identified.

Many of the presentations at the NF Conference were from current or recent CTF Drug Discovery Initiative Award recipients. **Dr. Abraham Jacob** (The Ohio State University, and a DDI Award recipient) presented data on the effect of an inhibitor of the PI3K/AKT pathway, OSU03012. This drug may represent a potent therapeutic approach to treat NF2 related vestibular schwannomas and malignant schwannomas. OSU03012 was recently licensed to Arno Therapeutics. **Dr. Joshua Rubin** (Washington University School of Medicine and a DDI Award recipient) showed that Rolipram blocked optic pathway gliomas. Preliminary data showed that the combination of Temozolomide and Rolipram have a better effect than the individual treatments. **Dr. Tommy Turbyville** (SAIC-Frederick) talked about Schweinfurthin A (SA), a natural product which represents a candidate drug therapy for NF1. The drug inhibited growth of a Grade 3 anaplastic astrocytoma cell line through Rho signaling mechanisms and cytoskeletal reorganization. CTF funds Schweinfurthin research through a DDI Award to Dr. David Wiemer, University of Iowa. **Ms. Priya Bhola** (University of Toronto) showed that ARRY-509 an MEK inhibitor significantly attenuated tumor growth of a MPNST xenograft mouse model. Finally, **Dr. Mateusz Kolanczyk** (University of Berlin, Germany), 2007 YIA recipient, showed that Lovastatin treated animals exhibit better healing in an NF1 tibia cortical bone injury animal model. This demonstrates potential therapeutic roles for Lovastatin that go beyond cognition.

For the first time the NF Conference included a session of presentation by representatives from biotechnology companies. The session was chaired by **Dr. Jay Gibbs (AstraZeneca)**, who also chairs the Oversight Committee of the NF Preclinical Consortium. Though there is currently little NF research activity in industry, CTF is striving to change this by building relationships with companies and connecting them with our programs through the Drug Discovery Initiative Toolbox, where they can make drugs available to NF researchers, and through the NF Preclinical Consortium. **Gideon Bollag** (Plexikon) described the kit/fms inhibitor, PLX3397, which has shown to be effective on multiple sclerosis animal models. Preliminary data testing this drug on NF1 animal models looks optimistic, and the studies will continue. **Ruihong Chen** (NexGenix) talked about NXD3000 series of HSP90 inhibitors. NXD3001 inhibits the growth of NF2 knockout Schwann cells, showing NXD3001 as a possible therapeutic candidate for NF2 tumors.

Finally, two presentations touched on therapeutic approaches for a lesser studied aspect of NF1, namely cardiovascular defects. **Dr. David Ingram** and **Dr. Elisabeth Lasater** (Indiana University School of Medicine) have established a mouse carotid artery injury model of vascular lesion resulting in smooth muscle accumulation in the vessel, to recapitulate the human disease. NF1+/- mice develop increased vessel thickening upon arterial injury. However, pre-administration of Gleevec, the drug which is used successfully for the treatment of acute myeloid leukemia, completely reduced the vessel thickening upon arterial injury.

Learning Disabilities Update

As well as the exciting news described above that the Phase II Lovastatin trials for learning disabilities should be open before year's end, there were other presentations that expanded upon our current

thinking on learning disabilities. Two presentations highlighted the fact that we may be able to detect learning and developmental impairments difficulties in very young children with NF1. **Heather Thompson** (University of Utah) showed that the rate of speech and/or language delay in the children aged 3-5 with NF1 was significantly higher than in the general population. **Dr. Jennifer Lorenzo** (The Children's Hospital at Westmead, Australia) showed that cognitive difficulties can similarly be detected in very young children with NF1. **Dr. Maria Acosta** (Children's National Medical Center) showed results from 604 NF1 patients in the Children's National Medical Center database who were evaluated for any indication the presence of brain malformations. Comparisons between NF1 patients and unaffected individuals showed that brain malformations are more frequent in NF1 patients. **Ms. Monica Buchanan** (Baylor College of Medicine), 2006 YIA recipient, has studied fly models of NF1 learning disabilities to gain a deeper insight. She has identified a discrete region of the *Drosophila* brain in which NF1 is required during the acquisition of olfactory (smell) memories. Finally, **Dr. Frances Hannan** (New York Medical College) showed that Lovastatin treated NF1 flies had improved learning scores than controls. Dr. Hannan is now looking as rapamycin and other drugs for their effects on fly learning.

New Clinical Ideas ... and Clinical Controversies

Dr. Susan Huson (University of Manchester, England) proposed that clinicians might need to develop a more detailed diagnostic approach for NF1 is diagnosed, since it includes such a broad range of manifestations. Dr. Huson recommended that a genetic test be mandated as part of a clinical NF1 diagnosis. This issue has come to the fore with the identification of a new 'NF1-like' syndrome associated with the gene SPRED-1 which is on Chromosome 15. **Dr. Eric Legius** (Centre of Human Genetics, Catholic University of Leuven, Belgium) recently published a paper showing SPRED1 syndrome in humans, who develop café-au-lait spots, can have learning disabilities but do not seem to develop tumors. Dr. Legius presented data at the Conference on a SPRED1 knock-out mice showing they have learning disabilities but normal basic neuromotor and sensory abilities. The question remains open as to whether SPRED1 syndrome has similar pathogenic mechanisms as NF1.

A recurring controversy in the NF clinical community is whether radiotherapy should be utilized for NF patients, and what is the risk of this causing malignancy. The 2008 NF Conference was no different with **Dr. Dade Lunsford** (University of Pittsburgh Medical Center) provoking heated debate following his presentation on the positive aspects of using radiotherapy for NF2 tumor management. In the same vein, **Dr. Jean Nakamura** (University of California, San Francisco) showed data from NF1+/- mice where secondary malignancies developed after radiotherapy treatment of NF1 tumors. Mice treated with 15 Gy dose develop predominately hematologic abnormalities, but a 30 Gy dose will induce predominately solid tumors. This data supports the argument against using radiotherapy for NF tumor management and also suggests that there is a radiation dose threshold for hematological and non-hematological cancers.

One of the most engaging sessions of the 2008 NF Conference was chaired by **Dr. Rosalie Ferner** (Guy's Kings and St Thomas Hospitals, England). Individual clinical cases were unfolded piece by piece, and

physician audience members were asked to comment on how to proceed with diagnosis and clinical management. Some of the most interesting cases were those on which the experts had different opinions, making the session educational for all.

Schwannomatosis Research Progress

Schwannomatosis played a bigger role in the Conference agenda than in previous years due to the explosion of research activity that followed the identification of a candidate Schwannomatosis gene in early 2007. This has been fuelled by CTFs commitment to the field, funding Schwannomatosis Awards for research and hosting a Schwannomatosis Workshop in February 2008.

Three groups focused on the genetics of Schwannomatosis presented their findings. **Dr. Gareth Evans** and **Dr. Kristen Hadfield** (University of Manchester, England) and **Dr. Scott Plotkin** (Harvard Medical School/ Massachusetts General Hospital) presented independent data supporting the role of both the *NF2* and *INI1/SmrcB1* genes in causing the Schwannomatosis tumor phenotype. This is known as the “four hit” hypothesis because it requires 4 individual mutations to occur in each of 2 copies of the 2 genes. **Dr. Theo Hulsebos** (University of Amsterdam, The Netherlands) was the first to report the role of *INI1/SmrcB1* in Schwannomatosis. He presented a Schwannomatosis medical case where two brothers had *INI1/SMARCB1* mutations but the parents did not have any mutation suggesting *de novo* development of the mutation in the germline (egg or sperm) of one of the parents and transmission to both brothers. Using genetic analysis, Dr. Hulsebos showed that the *INI1/SMARCB1* mutations were developed in the germline of the mother. Dr. Hulsebos concluded that this was only one case and more cases are required to determine whether the maternal origin of the mutation has any significance. Intriguingly, new *INI1/SMARCB1* germline mutations reported in children with rhabdoid tumors have all, with the exemption of one, been of maternal origin.

What Can NF Learn from Other Disorders?

The Conference took lessons from other disorders with the inclusion of some prominent presentations. **Dr. Heidi Greulich** (Dana Farber Cancer Institute) shared with the NF conference attendees the exciting findings that *NF1* mutations have been found in lung adenocarcinomas and in gliomas. This data emerged from analysis looking for novel genes associated with these tumors, and might suggest a broader role for the *NF1* gene in tumors and cancer. **Dr. Kathryn Rauen** (University of California, San Francisco) gave an overview of all ‘Ras related disorders’ - those with have mutations in genes that include components of the Ras/MAPK signaling pathway. The clinically distinct syndromes have overlapping features and are caused by mutations in proteins that have distinct roles within the pathway. Many of these syndromes have characteristic craniofacial dysmorphology, cardiac malformations/abnormalities, cutaneous abnormalities, musculoskeletal issues, ocular abnormalities, varying degrees of developmental delay and some are associated with an increased risk of cancer. It is important to study these other disorders because they can potentially help us better understand *NF1*

and identify candidate treatment approaches. In addition to NF1 and SPRED-1 associated NF1-like phenotype (described above) these disorders include Noonan syndrome, LEOPARD syndrome, Gingival Fibromatosis 1, Capillary malformation-AV malformation syndrome, Costello syndrome and Cardio-Facio-Cutaneous syndrome.

The NF community is avidly watching the progression of clinical trials using rapamycin for treatment of tumors in tuberous sclerosis complex (TSC), since this drug is now in Phase II clinical trials for plexiform tumors. **Dr. Sandra Dabora** (Harvard Medical School) has headed the TS Phase II trials of rapamycin and provided an update. Thirty TSC patients were treated with rapamycin for one year. 8 patients had tumor shrinkage, while 22 twenty-two showed stabilized disease. From her experience with the TSC trial, Dr. Dabora highlighted the importance of now testing rapamycin at lower amounts over a longer period of time, since, like NF, TSC tumors are chronic and will need long term management. **Dr. Fergus Couch** (Mayo Clinic) provided an update on the international consortium to identify genetic modifiers in carriers of the breast cancer susceptibility genes BRCA1 and BRCA2. A similar consortium could be established for NF. Modifier genes regulate gene function: if they have a role in NF1 this could help explain why so many different manifestations can develop from mutation of a single gene. **Finally, Dr. Bernard Maria** (University of South Carolina) highlighted his work using drugs called hyaluronan oligomers which can decrease growth of certain benign and malignant pediatric central and peripheral nervous system tumors. Dr. Maria is currently a recipient of CTF Drug Discovery Initiative Award to explore the use of oligomers as a therapeutic approach for NF-related tumors.

Patient Advocates Tell Their Stories

As in the past few years, the NF Conference including deeply moving presentations by patient advocates who are personally affected by NF1, NF2 and Schwannomatosis. **Lesley Oslica** (Arkansas) talked about her teenage daughter, sharing the personal experience as mother of a child and living every day with 'it' - the uncertainty of NF and what will happen next. Mrs. Oslica explained how, instead of feeling helpless against 'it' her family had turned their energies to fundraising for CTF research by running marathons, organizing local events and working with her local NF Clinic to have them apply to CTF-NFCN. **Ken Shigley** (Georgia) talked about his daughter's life with NF2 and challenged the NF community to collaborate and accelerate the development of NF treatments. **Bob Beck** described living with Schwannomatosis, the pain of which has impacted on every aspect of his life and decision making. CTF was honored to host these remarkable individuals for attending the Conference to share their stories.

Poster Prize Winners

For the first time, in 2008 CTF offered prizes to Best Clinical Poster and Best Research Poster. Many thanks to our extensive poster judging committee! **Dr. Jonathan Payne** (The Children's Hospital at Westmead, Australia) was awarded Best Clinical Poster for "Examination of visuospatial memory function in children with NF1: implications for clinical trials". **Dr. Stephane Coutagny** (Hospital Beaujon,

France) for his poster: “Genomic profiling reveals alternative genetic pathways of meningioma malignant progression determined by NF2 status”.

Looking ahead, the 2009 NF Conference will be chaired by Dr. Joseph Kissil (The Wistar Institute) and Dr. Kathryn North (The Children’s Hospital at Westmead, Australia). The 2010 NF Conference will be chaired by Dr. Filippo Giancotti (Memorial-Sloan Kettering Cancer Center) and Dr. Susan Huson (University of Manchester, England).

With sincere thanks to our 2008 NF Conference sponsors: National Institute for Neurological Disorders and Stroke; NIH Office of Rare Disorders; Irving Berlin Charitable Fund; Genentech; Nexgenix Pharmaceuticals; PTC Therapeutics; Biotechnology Industry Organization.