The 2009 NF Conference was held in Portland, Oregon June 13-16 and attracted a record 280 attendees from around the world. The Children’s Tumor Foundation has hosted the Conference for over 20 years, and the meeting is recognized as premier annual gathering of scientists, physicians and clinical care providers focused on neurofibromatosis. The theme of the meeting was ‘New Frontiers’, highlighting the remarkable progress made in NF research, the progress toward clinical trials and the new challenges that are emerging. It was also a nod to the location of the Conference held for the first time in the Pacific North West.

The 2009 NF Conference was hailed by many attendees as the best to date, a tribute to the comprehensive agenda created by 2009 Co-Chairs Dr. Kathryn North (Children’s Hospital at Westmead, Sydney) and Dr. Joe Kissil (The Wistar Institute), from the opening session, a full afternoon on NF clinical trials, to the final session, on new therapeutic approaches. The span of the conference was a far cry from just a few years ago when the focus was almost exclusively ‘discovery’ research and is a testament to how rapidly NF research is progressing towards finding effective drug therapies.

For the first time the NF Conference included some parallel sessions on a ‘clinical’ or ‘basic’ track offering attendees a choice. This was welcomed since the audience includes basic scientists and clinical care staff.

Also new for 2009, Foundation staff blogged throughout the NF Conference at http://ctf.org/blog.html so those not attending could keep up with the news. In addition, for the first time in 2009 the Foundation has been invited to submit a professional meeting report from the Conference for publication in the American Journal of Medical Genetics. This should be forthcoming later in 2009. In the meantime here are some NF Conference highlights.

**NF1 - Clinical Trials Update**

The Phase II NF Clinical Trials Consortium is supported by the Congressionally Directed Medical Research Program for Neurofibromatosis Research. Since this trials consortium was formed in 2005, 9 clinical sites across the US have collaborated to implement large-scale Phase II NF1 clinical trials. Cross-clinic collaboration is critical in order to identify the large number of patients (around 200) needed for these trials. Dr. Roger Packer (Children’s National Medical Center) heads this program which has already completed patient enrolment on the first trial of the drug Rapamycin for treatment of plexiform tumors. This spring the Consortium opened a learning disabilities trial (described below). In planning next are a trial of RAD001 (mTOR inhibitor) for optic pathway glioma as well as a bone abnormalities trial.

Dr. Nicole Ullrich (Children’s Hospital Boston) reviewed planning for the optic pathway glioma (OPG) trial. OPG tumors are diagnosed in children and adolescents with and without NF1 and are responsible for 5% of all brain tumors seen in children. They are low grade (benign) tumors; there will typically be 6 months before first symptoms and diagnosis; and these tumors can
spontaneously regress. Current therapeutic options are observation (‘watch and wait’), surgery, radiation or chemotherapy, with vincristine/carboplatin chemotherapy being typically first line therapy for progressive OPG. Surgery is not typically pursued and with radiation there is evidence of an elevated risk of secondary tumor formation, malignancy and radiation induced vasculopathy (blood vessel abnormalities in the brain). An OPG clinical trial is as noted above in advanced stages of planning, determining trial design, outcome measures etc.

There have been only a few clinical trials for dermal neurofibromas to date, yet these tumors impact the quality of life for many individuals with NF1. Surgery and electrodessication are among the approaches currently used to manage these tumors. Dr. Scott Plotkin (Harvard/MGH) has commenced a small trial testing the drug ranibizumab (Lucentis, prescribed for macular degeneration and targeting blood vessel growth) as a therapy for NF1 dermal neurofibromas. Tumors selected for drug treatment were of a modest size, and at least 5mm away from another tumor to facilitate measurements. Drug or a placebo is injected directly into individual tumors and tumor size – growth or shrinkage - monitored. Tumors were seen to degrade and then heal over by 85 days. Interestingly Dr. Plotkin reported it had been difficult to recruit patients for this trial as many hospital visits are required and many individuals were unable to take time off work. Though 10 patients started the trial only 5 completed it. This trial is still in its very earliest stages and it is too early to offer an assessment of drug efficacy.

Dr. Michael Fisher (Children’s Hospital of Philadelphia) presented results from a Phase I study of photodynamic therapy for tumor ablation in children with NF1 plexiform neurofibromas. The technique has been assessed in other tumors including in Japan where it is advancing through clinical trials. Light is used from with the tumor to target the cells, and appears to cause breakdown of blood vessels, cell death and an inflammatory response suggesting tumor degradation. The effectiveness of the technique appears to increase with increased light dose. In Dr. Fisher’s study, children aged 3-21 with plexiform neurofibromas of a specific size were included, and only one tumor was treated per patient. The study is now advancing to Phase Ib where more patients will be included.

Dr. Brigitte Widemann (NCI, NIH) highlighted the importance of designing and conducting clinical trials solely for NF1 patients. These are typically younger than non-NF1 patients entering clinical trials and tumors are largely benign and chronic, so that any therapy developed must be able to be dosed over a long period. Dr. Widemann reported on several ongoing NF1 tumor trials including the sorafenib trial for plexiform tumors being funded in part by the Children’s Tumor Foundation. Of most excitement, by the end of 2009 another new NF1 trial will commence that combines two drugs - RAD001 and bevacizumab - for treatment of malignant peripheral nerve sheath tumors that have been resistant to other treatment. Excitingly drugs are provided by two companies - by Novartis and Genentech respectively. This combined therapy approach is being used in other tumor types and is felt to have great potential than a single drug.

In the discussion session, Dr. Widemann was asked, how do patients decide, now that there are an increasing number of clinical trials open for NF1, which trial to join? Dr. Widemann noted
there are clear cut guidelines for entry for each trial, which may limit or determine whether a patient is eligible. The physician must lay the available options out for the patient and inform them as extensively as possible, but ultimately the patient is responsible for the decision of which trial to join if any.

Given the last year’s significant expansion of clinical trials for NF1 and the inception of trials for NF2 (described below), the Children’s Tumor Foundation now offer on the homepage of our website www.ctf.org accessible information on all currently open NF trials, for the information of both patients and physicians.

**NF2 – Clinical Trials Update**

We are in an unprecedented era for NF2 clinical trials. In October 2007 the Children’s Tumor Foundation convened an expert workshop to develop consensus guidelines on how NF2 clinical trials could be best designed given our knowledge and the limitations on patient numbers. The recommendations will be published as a consensus paper this summer in the journal *Clinical Cancer Research* and importantly trials have already forged ahead, in part due to the support of the Children’s Tumor Foundation. **Dr. Jaishri Blakeley (Johns Hopkins University)** was the recipient of the first Children's Tumor Foundation Clinical Trial Award to support a Phase Zero trial to test Lapatinib in vestibular schwannomas in conjunction with **Dr. Mathias Karajannis (New York University)**. A Phase Zero trial means that drug is given to patients for a short period prior to a scheduled surgery, in this case to remove vestibular schwannomas. After tumor is removed, it can be analyzed to see if the drug reached the target and altered molecular signalling. This trial was designed using recommendations from the consensus workshop, and will commence this summer. If results prove interesting it can progress rapidly to Phase II.

The biotechnology company **PTC Therapeutics** has forged a path of developing drug therapies for orphan disorders, and this includes NF2. In conjunction with Dr. Scott Plotkin (Harvard/MGH) the company recently secured a grant from the Congressionally Directed Medical Research Program for NF Research to support a Phase I/II trial of their drug PTC-299 in NF2 vestibular schwannoma. **Dr. Harry Miao (PTC Therapeutics)** described the trial which will commence shortly. PTC-299 targets blood vessel growth and has been shown to be safe in patients with other tumor types.

**Dr. Luis Parada Recognized with the 2009 Friedrich Von Recklinghausen Award**

In 2008 the Children’s Tumor Foundation reintroduced the historical tradition of the **Friedrich von Recklinghausen Award** to recognize a researcher or physician for outstanding contributions to NF research or clinical care. Candidates are nominated by their colleagues and in 2009 the Award went to **Dr. Luis Parada (University of Texas, Southwestern)**. Dr. Parada has made wide-reaching and groundbreaking achievements in many areas of research ranging from developmental neuroscience and cancer biology, to disorders including tuberous sclerosis and autism. However, his contributions to neurofibromatosis stand out and have been nothing short of seminal. As a first-year graduate student with Dr. Robert Weinberg at the Massachusetts Institute of Technology he published his first paper in *Nature* describing the
underpinnings of Ras gene function in cancer. He went on to contribute to the development of the genetically modified mouse models of NF1 that are a baseline tool for many NF researchers today. He has utilized these mice to understand tumor development and test candidate therapeutics such as Gleevec which he, Dr. Wade Clapp and Dr. David Ingram (University of Indiana) and colleagues recently demonstrated might inhibit plexiform tumor growth by interrupting mast cell signalling.

Dr. Parada’s successes continues and in May 2009 his publication in Cancer Cell described the very first genetic mouse model of NF1-related dermal neurofibromas and potentially the identification of the cells that give rise to these tumors, namely skin progenitor cells (SKPs). Dr. Parada has many more discoveries ahead of him, but 2009 seems a fitting year to step back and recognize his contributions to date to unraveling neurofibromatosis. The Foundation hosted a special evening at the NF Conference to celebrate Dr. Parada with a photo slideshow that spanned the years of his career to date, roasts and presentation of the Award by his principle nominator, long-time colleague and friend Dr. Kevin Shannon (UCSF).

In his Friedrich von Recklinghausen Keynote at the Conference, Dr. Parada reviewed ‘10 years of modelling NF in the mouse’ describing much of his work. The description of his dermal mouse model was particularly exciting, since dermal neurofibromas affect the lives of some many individuals with NF1. His new model opens the way for the first time to test in mice drug therapies that might shrink these tumors.

Focus on NF1 Learning Disabilities
A special session on chaired by Dr. Kathryn North (Children’s Hospital at Westmead, Sydney) focused on cognitive deficits of NF1 tackling topics such as the challenges of translating learning disabilities mouse research findings into human trials, as well as molecular drug target updates. The second trial of the Phase II NF Clinical Trials Consortium is the recently opened trial to assess Lovastatin as a drug therapy for NF1 learning disabilities. Lovastatin has shown very promising data in mouse models of NF1 learning disabilities (the work of Dr. Alcino Silva (UCLA)) and a Phase I safety trial conducted by Dr. Maria Acosta (Children’s National Medical Center) was successful. In order to implement the Phase II trial as effectively as possible, the Consortium is collaborating with Dr. North, as she is a leading expert in NF1 learning disabilities. Dr. Ype Elgersma (Erasmus University) has focused in on the genetic underpinnings of learning disabilities implicating a potential role for NF1 Exon 9a which encodes 10 amino acids and is conserved between mice and humans. Mice lacking Exon 9a make normal levels of NF1 protein but have learning deficits and alterations in synaptic plasticity. A search is underway for Exon 9a interacting proteins.

A genetically modified Drosophila (fruit fly) has proved to be excellent models of NF1 learning disabilities. Foundation-funded Young Investigator Linnea Vose (New York State Medical College) is using both adult and larval learning-disabled fruit flies to test the effects of various drugs on behavior in learning tasks. For example the drug Rolipram, which has shown promise in treating optic pathway glioma in mouse models, may also improve task learning in flies. This is interesting because it investigates not only the correction of existing behavior (adults) but also how the developing brain might be treated to prevent incorrect learning patterns to
develop. It is emerging that the clinical features of NF1 cognitive deficits are driven by many things in the brain, including potentially the way that some of the neurons (nerve cells) develop and ‘wire up’ during development. Learning disabilities continues to be a really exciting and fast moving area of NF1 research.

In the Pipeline: Future NF Drug Therapies

Dr. David Wiemer (University of Iowa) and Dr. Karlyne Reilly (NCI, NIH) are assessing new drugs called schweinfurthins as candidate therapies for NF related tumors. The Children’s Tumor Foundation is delighted to have helped support some of this research through two Drug Discovery Initiative Awards. Schweinfurthin was first identified from African plant matter; subsequently, a panel of synthetic schweinfurthins was synthesized and these are being optimized by Dr. Wiemer as candidate drugs and tested by Dr. Reilly in cells and animal models of tumors. The schweinfurthins target Rho and Rac, and may be of interest for targeting NF1 astrocytoma, glioma, and myeloid leukemia. These drugs are in testing in a variety of patient-derived astrocytoma and MPNST cell lines. Some positive effects have been seen, but interestingly there is a difference in sensitivity between cell lines. A potential mechanism of action is that schweinfurthin blocks phosphorylation of the myosin light chain which is normally induced by EGF activation. Dr. Reilly is actively looking for more in vitro models to test the drugs in.

Dr. Ronen Marmorstein (The Wistar Institute) is using structural design to optimize novel PI3K and PAK inhibitors based on organometallic molecules. PAK inhibitors are being optimized structurally to be big enough fit the space of the active PAK site so that it is a larger and more selective inhibitor. The PAK drugs will be advanced as candidate NF2 therapies in part by a recently funded Children’s Tumor Foundation Drug Discovery Initiative Award to Dr. Joe Kissil (The Wistar Institute) which will test them in animals with NF2 tumors.

Dr. Vijaya Ramesh (Harvard/MGH) reported that cell signalling element mTORC, long recognized as an important candidate drug target for the treatment of NF1 tumors, may also be a key drug target in NF2 tumors meningioma and vestibular schwannoma. mTORC is hyperactive in human meningioma cells, as well as in vestibular schwannoma cells. Blocking hyperactive merlin protein (NF2 gene product) blocks the activation of mTORC1. The drug rapamycin which targets mTORC was able to shrink human meningioma tumor cells - which are overly large - back to a more normal size. Interestingly, mTORC appears to be acting independently of Akt activation. This opens up the possible value of using dual therapies approach to target mTORC and Akt simultaneously.

Exploring NF Signaling and Drug Targets

A number of presentations explored the Ras pathway and various signaling elements that are dysfunctional in tumor cells and may be good drug targets. The stage was nicely set for this by two outstanding Keynote Speakers. Dr. Allan Balmain (UCSF) examined ‘the many faces of Ras’; and Dr. David Kwiatkowski (Harvard School of Public Health) provided a perspective from his work on the tuberous sclerosis TSC1/TSC2 complex which also signals through PI3K, AKT and mTOR. Tuberous sclerosis causes tuberous growths to develop throughout the body and there is a mouse model with tubers in kidney and liver. Both RAD001 (mTOR inhibitor) and BEZ-235 (PI3K/mTOR inhibitor) have been assessed in mice as TS therapeutics. Both drugs worked
individually to shrink kidney (though not liver) but once drug stops being dosed – at 6 months –
the tumors grow back robustly. Its thought the drugs simply paused growth rather than killed
the tumor as no evidence of apoptosis (cell death) was seen. This could lend interesting lessons
to NF.

**Dr. Frank McCormick (UCSF)** reviewed some of the conundrums of targeting the hyperactive
Ras pathway we see in NF, and how cells are essentially ‘addicted’ to dysfunctional signaling
elements. Inhibiting ERK phosphorylation leads to upregulation of EGFR-PI3kinase signaling and
as a result tumor cells become insensitive to the ERK inhibitor. On the other hand cells that
contain mutant bRaf appear ‘addicted’ to the hyperactive Ras pathway, and will die when
exposed to mEK inhibitors at low levels that would not be toxic to healthy cells or cells lacking
mutant bRaf. On the other hand MEK inhibitors can also allow some cells to become
‘unaddicted’ to Ras and as a result escape therapy. A way forward may the emerging dual
therapy approaches that target the pathway from two points. **Dr. Nancy Ratner (Cincinnati
Children’s Hospital Medical Center)** described new findings showing that the transcription factor
Sox9, which has an established role in bone chondrocyte differentiation and is expressed in
eyearly development in the neural crest, is also a biomarker of NF1 neurofibroma and MPNST. **Dr.
Jonathan Cooper (Memorial Sloan Kettering Cancer Center)** is examining the structure of merlin
protein and has developed mutant forms of merlin to understand if this protein localizes to the
nucleus as well as to the more traditionally recognized cell membrane region within the cell.
Foundation Young Investigator Award recipient **Geoffrey Killili (Tufts University)** is focused on
the mammalian homolog of drosophila HIPPO called Ste20 like kinase 2 (MST2) which unlike
HIPPO is not downstream of merlin.

The generation of new mouse models is a vital resource for NF research. In addition to the
report of **Dr. Luis Parada**’s new mouse model of dermal neurofibromas, **Dr. Michel
Kalamardies (Hopital Beaujon, Paris)** reported his mouse model of NF2 meningioma, in which
these tumors can only develop if the NF2 gene is inactivated at a certain point in embryonic
development. **Dr. Yuan Zhu (University of Michigan)** presented a new mouse model that
develops NF1 related of plexiform neurofibromas, dermal tumors and MPNSTs that are
progressive and somewhat mimic the human state.

**Clinical Diagnosis and Management of NF: What We Do, and Don’t, Know**
A number of sessions focused squarely upon the issues impacting on the diagnosis and clinical
management of NF. **Dr. Bruce Korf (University of Alabama at Birmingham)** reviewed current
diagnostic criteria for NF1 and noted that though there is always a drive to reach consensus –
agreement – in the community about how NF1 is diagnosed, what we actually need is more
data to be accumulated from patients so that we can have a more comprehensive view of the
disorder on which to base these criteria. **Dr. John Mulvihill (University of Oklahoma)** focused
on NF1 in old age and the fact that individuals with NF1 have accelerated mortality, usually with
social issues and poor access to care as impacting factors on this.

**Dr. Anat Stemmer-Rachamimov (Harvard/ MGH)** presented results from a working group that
took place at the European NF Meeting in Killarney, Ireland November 2008, to better classify
the terminology used to describe neurofibromas, since currently used terminology can be
confusing when the same term is being used to describe different things. These tumors should
be classified by location, growth pattern (localized, diffuse or plexiform), association with nerve
(tumor expands nerve fascicle and goes outside fascicle), and other histological features. She also addressed the concept that dermal tumors are actually offshoot of plexiform neurofibromas. If you will see a diffuse neurofibroma affecting dermal and subcutaneous layers it is important to examine if the tumor has a relationship to a known plexiform.

**Dr. Ian McCutcheon (University of Texas M.D. Anderson Cancer Center)** addressed the clinical variability of malignant peripheral nerve sheath tumors (MPNST) in NF1. These tumors affect an estimated 10% of individuals with NF1, but are also seen in the general population as sarcomas. These tumors can appear in diverse sites and usually have a poor prognosis. Chemotherapy will often have only a temporary therapeutic effect, and there is a high mortality rate from these tumors. Radical surgery is often used, taking out tissue beyond the tumor boundaries to ensure the tumor will not return. The MPNSTs seen in NF1 have unique characteristics rendering them different from non-NF1 related MPNSTs, and this will need to be better understood by clinicians as they develop drug treatment strategies.

**Andre Bernards (Harvard/MGH)** examined what genetics can help us predict in NF1 manifestations. For example patients with microdeletions are at greater risk of early onset tumors. Ras clearly has a central role in causing NF1, but Dr. Bernards presented the case for investigating new off-pathway drug targets Ret and Alk receptor tyrosine kinases as well as looking at the role of other gene modifiers, suppressors and enhancers. One session examined the parallels between NF and other disorders with mutations that affect signaling in the Ras pathway such as Noonan’s syndrome. **Michelle Strecker (UCSF)** described her clinics ‘Ras Pathway’ approaches to managing these related disorders, as they share many parallels. Families are followed through life following diagnosis, and close links are held with advocacy group networks such as the Children’s Tumor Foundation to ensure family support is provided. A close interface is in place with research, translational studies and clinical trials, to ensure patients have rapid access to participating in new studies and newly available therapies. Overall there is a focus on the big picture and quality of life for the patient.

Finally, a popular session chaired by **Dr. Rosalie Ferner (Guys and St. Thomas’ NHS Trust) and Dr. Kathryn North (Children’s Hospital at Westmead)** pitted the United States against the ‘Rest of World’ in a friendly face-off to evaluate and share opinions on ‘clinical cased that taught me something new’.

**Schwannomatosis Progress**

Schwannomatosis is the rarest form of NF, affecting an estimated 1:40,000 individuals, and causes peripheral nerve tumors and unmanageable pain. Our understanding of schwannomatosis has made significant progress in the last 2 years since the first candidate gene for the disorder, variably known as \textit{INI1/Snf5/SmarcB1}, was announced, but much remained to be learned. **Dr. Anat Stemmer-Rachamimov (Harvard/MGH)** presented data to suggest that maybe as few as 10-30% of schwannomatosis cases have mutations in the NF1 gene, and these are the cases where there seems to be some sort of inheritance pattern. In spontaneous (first in family) cases, there are some cases where a mutation in both \textit{INI1} and \textit{Nf2} genes is seen. This emphasizes the importance of continuing the search for additional genes that are important in schwannomatosis.

This area is being significantly advanced by grant investments from the Children’s Tumor Foundation. One ongoing question is whether there is a link between NF2 and
schwannomatosis, or whether there are further as yet unknown genes that contribute to the development of schwannomatosis. To get a better understanding of how these tumors develop Dr. Marco Giovannini (House Ear Institute) and Dr. Larry Sherman (Oregon Health Sciences University) have been funded by the Foundation to develop the first animal models of the disorder. Dr. Giovannini is exploring conditional knockout of the candidate gene INI1/Snf5/SmarcB1, in some cases in combination with the Nf2 gene, and early efforts have generated tumor bearing mice. Dr. Sherman is exploring a different approach with conditional knockout of the gene Brg1 which is involved in INI1/Snf5/SmarcB1 signaling, and early results suggest that this gene may be involved with the pain that is characteristic of schwannomatosis. Interestingly Schwann cells from these animals make too much of a growth factor called BDNF, which for example is also present at high levels in persons with phantom limb pain, and might be important in propagating pain of schwannomatosis.

A major challenge to advancing schwannomatosis research is the fact that there are so few patients, and the fact even a well recognized NF clinic will probably only see a tiny number of schwannomatosis patients. Because schwannomatosis is not a well known disorder, it is possible there are many undiagnosed cases and that many patients are being seen elsewhere perhaps in pain management or plastic surgery clinics. For this reason the Children's Tumor Foundation is supporting a special initiative headed by Dr. Allan Belzberg (Johns Hopkins University) to establish a collaborative schwannomatosis database that will collect patient data from as many clinics as possible. At a special workshop at the NF Conference, representatives from about ten clinics US and international met to hammer out the questions this database must ask - these need to be detailed enough to make the data collected 'mineable' (searchable, meaningful) to be able to identify patients for follow up studies. Also, at the first cut, the amount of data to be entered can't be too onerous as to put clinics off taking the time to enter it. The Foundation is providing initial funding to get this database up and running, but perhaps our most important role in this will be to encourage and drive as many clinics as possible to participate.

Legius Syndrome: An Update

Last year saw the emergence of Legius Syndrome, a new NF1-like disorder associated with mutations in the gene Spred-1 on Chromosome 15 (the Nf1 gene is on Chromosome 17). The name was given to this new disorder by consensus of the NF clinical community at the 2008 European NF Conference in Killarney, Ireland recognizing that this was a fundamental discovery made by Dr. Eric Legius (Catholic University of Leuven beginning with his research in the SPRED-1 mouse model and progressing to human studies. Dr. Ludwine Messiaen University of Alabama at Birmingham) presented an update on the genetics of Legius Syndrome. Spred-1 mutations have now been reported by a few independent studies in patients presenting with café au lait spots and learning disabilities but no tumors or other features of NF1 and no mutations in the Nf1 gene. Dr. Messiaen has identified Spred-1 mutations in 34 patient samples from a library of samples from 1318 patients who presented with apparent clinical NF1 but no Nf1 gene mutations. The Spred-1 gene appears to have 3 functional domains and can have a variety of mutations spread across the gene. Almost half the patients with Spred-1 mutations actually meet the NIH clinical diagnostic criteria for NF1, including café au lait spots. A quarter had speech problems; there were occasional cases of pectus excavatum (chest wall deformities
sometimes seen in NF1); but no patients had tumors. Interestingly a small percentage of NF1 patients with *Nf1* gene mutations also have mutations in the *Spred-1* gene and this is particularly seen in families with characteristic café au lait spots, freckling but no other features of NF1. **Dr. Meena Uphadyaya (Cardiff University)** followed Dr. Messiaen’s presentation with parallel data on a UK population study on 110 patients with clinical NF1 but no *Nf1* gene mutations; 8% had *Spred-1* mutations. Future unraveling of Legius Syndrome will be very important particularly with regards to genetic counseling. Though Legius Syndrome may appear clinically to be like NF1, it looks as though Legius Syndrome will have a far more reduced spectrum of manifestations in the long term than NF1.

**Dr. Eric Legius (Catholic University of Leuven)** provided an update on his own continuing studies of *Spred-1* and particularly the impact of these mutations on cognitive function. In a small study of 9 children with *Spred-1* mutations he saw speech difficulties, ADHD, learning disabilities, and pectus excavatum. Most cases are inherited, with a few being sporadic (first in family) cases. Dr. Legius also continues work on his mouse model of SPRED-1 where his observations of this disorder began. Like *Nf1 +/-* genetic mouse models the *Spred-1 +/-* mice have learning disabilities. Dr. Legius did a small study treating these mice with Lovastatin, which corrects learning deficits in *Nf1 +/-* mice and is now in NF1 clinical trials to treat NF1 learning disabilities. However the drug had no effect in the *Spred-1 +/-* mice. This may signify that the underlying cognitive issues have a different molecular basis than in NF1 or that potentially the deficit is less severe in SPRED-1.

Legius Syndrome is emerging as a fascinating disorder and we look forward to continued progress in understanding its basis.

**Driving Bench-to-Bedside Progress**

Each year the NF Conference provides an opportunity for many vital NF community activities such as meetings of Foundation Boards and Committees, as well as meetings of research consortia such as the Foundation’s NF Preclinical Consortium and the CDMRP NFRP-supported NF Clinical Trials Consortium. Meetings included a pre-conference meeting of the Children’s Tumor Foundation NF Preclinical Consortium (NFPC). This is a collaboration of six top-tier labs - at UCSF, House Ear Institute, Washington University, Cincinnati Children’s Hospital Medical Center and two groups at Harvard Medical School - each focused on genetically-engineered mouse models of different NF tumors. Drugs are tested in parallel in the multiple tumor types of NF1 and NF2 to ensure that if a drug is not effective in one NF tumor type we can see if it might be effective in another. NFPC is overseen by a committee of representatives from academia and industry. A $4M multi-year commitment for the Children’s Tumor Foundation, NFPC should maximize our chances of identifying drug candidates for NF clinical trials. So far NFPC has made tremendous strides, establishing collaboration with Novartis; further industry partnerships will be announced later this year.

An important element of advancing interesting preclinical drug candidates is to establish a link with those who are doing the clinical trials. NFPC met Friday in a ‘crossover' meeting with the physicians of the CDMRP NFRP Phase II NF clinical trials consortium. This group is a clinical trials version of NFPC connecting multiple clinical sites. Because of the variety of tumor types (plexiform, optic pathway etc.) and other manifestations (bone abnormalities, learning disabilities) seen in NF, an effort like this is required in order to recruit sufficient patients for a
Clinical trial in a timely manner. In the past year or so the Clinical Trials Consortium has launched 2 trials (for plexiform tumors and learning disabilities) and more are pending. Scientists and clinicians can often live in two different worlds but the joint meeting of the 2 groups opened a dialog on the drugs in the preclinical pipeline, and those most likely to be of clinical interest. Though early days, this meeting emphasizes the importance of collaboration and open communication among our NF community to ensure that we advance promising drug treatment as quickly as possible to the clinic.

Connecting with the Local Community
For the past few years the NF Conference has included presentations from lay persons living with NF1, NF2 and schwannomatosis, either themselves or in their family. This has proved to be a popular segment of the NF Conference particularly for the scientists, who do not see patients. This year’s lay presenters were all from the local community: Ms. Nikole Hadley, Ms. Sarah Marugg and Ms. Lora Stradley. We thank them for their participation. On Thursday June 11, the Oregon Affiliate of the Children’s Tumor Foundation hosted an NF Symposium for local NF patients and families at Oregon Health Sciences University. Around 45 attendees heard Foundation program updates as well as clinical trial and research updates from Dr. David Viskochil (University of Utah) and local Foundation-funded researcher Dr. Larry Sherman (OHSU). Thank you to the local Foundation Affiliate particularly Ms. Jean Fitzgerald for coordinating both the local symposium and the lay participation in the NF Conference.

Closing Thoughts, and Looking Ahead
Best 2009 Poster Prizes were up for grabs this year, with all meeting attendees eligible to vote for their favourite basic research and clinical poster. This emerged to be a coup for Finland: Minja Laulajainen, University of Helsinki won Basic Science category for a merlin-focused study, and Lotta Alivuotila, University of Turku won Clinical category for a cognitive-focused NF1 study. The 2009 NF Conference closed with the announcement of the 2011 NF Conference Chairs, Nancy Ratner and Michel Kalamarides. Before then of course, the 2010 NF Conference (‘NF- Back to the Future’) - will take place in Baltimore, MD June 5-8, 2010 and will be co-chaired by Dr. Susan M. Huson (University of Manchester) and Dr. Filippo Giancotti (Memorial Sloan Kettering Cancer Center). Special thanks go to the 2009 NF Conference Chairs Dr. Kathryn North and Dr. Joe Kissil for their significant efforts to plan and ensure the success of the 2009 NF Conference.

We are delighted to recognize the supporters of the 2009 NF Conference: the National Institutes of Health, Novartis Institutes for Biomedical Research, the Biotechnology Industry Organization and PTC Therapeutics. In addition we thank the New York University Office of Continuing Medical Education for their patience and guidance in facilitating CME accreditation for the 2009 NF Conference. Look out for the professional published report from the NF Conference in the American Journal of Medical Genetics later this year.