From Bench to Bedside: The NF Conference 2006

Over 185 international researchers & physicians convened in Aspen, CO in early June, for the 2006 NF Conference. This is the premier annual gathering of the NF community, and is convened by the Children's Tumor Foundation.

The 2006 meeting - 'Progress: From Bench to Bedside' – presented the very latest of 'what's new' in NF, from basic research to clinical trials. The three-day event, chaired by Dr. Vijaya Ramesh *(Harvard University)* and Dr. David Viskochil *(University of Utah)*, included 49 talks and 53 posters. Two special satellite sessions addressed NF Clinical Care Standards, and Learning Disabilities, current 'hot topics' for the NF community.

The 2006 Conference was augmented by two lay presentations by 'patient advocates' Jason Pontin and Barbara Franklin, who laid out the day-to-day reality of living with NF. These moving & powerful presentations brought home, especially to those in basic research who do not see patients, the urgency of need for effective NF therapies.

Some highlights of the 2006 meeting are presented below.

Cell & Molecular Biology Update

Why do some tumor cells keep multiplying, when others don't? Dr. Karen Cichowski *(Harvard University)* showed that while in some tumor cells, loss of the *Nf1* gene product – the tumor suppressor neurofibromin - causes cells to divide extensively, other cells actually do the opposite and become senescent – that is, they lose the ability to divide. Dr. Cichowski is investigating what molecular characteristics invoke these very different responses. Importantly, these studies may pave the way to a better understanding how NF1 tumor cells keep the tumor growing, and how we might target these cells to induce them to adopt features of senescence and halt tumor growth.

The *Nf2* gene product merlin is like neurofibromin a tumor suppressor. However merlin acts specifically by regulating interactions between the cell's 'skeleton' and the surface membrane. Merlin also plays a key role when cell form junctions with each other, communicate and receive signals from their surroundings. When normal cells contact each other, they form junctions and signal to stop growing; when merlin function is disrupted in NF2, cells do not recognize these 'stop growing' signals and a tumor results. Dr. Andrea McLatchey *(Harvard University)* has demonstrated that a contributor to this mechanism seems to be the EGF cell surface receptor, which is hyperactive in NF2 tumor cells. The EGFR inhibitor Iressa (gefitinib) will block the proliferation of NF2 tumor cells in culture, demonstrating that EGFR hyperactivity may play a key role in tumor cell proliferation. Dr. McLatchey is now homing in on specific regions of merlin protein that are critical for the protein's normal function.

Dr. Oliver Hanemann *(Universities of Exeter & Plymouth)* is studying how NF2 schwannoma cells are physically & behaviorally different from normal Schwann cells, while Dr. Marianne James *(Harvard University)* is studying cell phenotype in NF2 meningioma cells to understand what physical changes in the cell are associated with malignancy. Dr. Hanemann observed that NF2 schwannoma cells tend to ruffle their membrane and have increased remodeling of the cell skeleton. Dr. James has observed cytoskeletal abnormalities in malignant NF2 meningioma cells. These changes suggest that physical & behavioral abnormalities make NF2 tumor cells less able than normal cells to form stabilizing junctions. Understanding these functional abnormalities could help identify future drug targeting approaches to 'normalize' cell behavior and inhibit tumor growth.

Dr. Fisun Hamaratoglu *(Baylor College of Medicine)* is unraveling what happens in cells 'downstream' - or as a consequence - of merlin signaling. By studying merlin function in the fruit fly *drosophila,* she has linked merlin function to a tumor/growth suppressor pathway involving the cell cytoplasm genes *Hippo* and *Warts*, and the nuclear target gene *Yorkie*. The human homolog (equivalent gene) of *Yorkie* is the gene *YAP*. These studies open the way to future studies & drug targeting of *YAP* and other molecular elements of this signaling pathway in NF2 tumors.

Genetics Update

Dr. Ludwine Messiaen *(University of Alabama)* reported that from analyses of over 1,000 international patient samples, there are now around 700 identified mutations of the *Nf1* gene. The next challenge for the NF1 community is to see if we can correlate certain gene mutations with specific clinical features of NF1. On that note, Dr. Meena Upadhyaya *(Cardiff University)* showed data to suggest that there is indeed a correlation between certain *Nf1* mutations and the appearance of dermal neurofibromas in those individuals. This analysis of 'genotype-phenotype' connection will help us eventually better understand what therapies might be most effective for specific features of NF.

Dr. Gareth Evans *(University of Manchester)* presented an update on the NF2 mutation spectrum. An analysis of 440 families affected by NF2 has also started to reveal a potential genotype-phenotype association. Truncating mutations (normal 'full length' merlin protein is not made) appear to be associated with the most severe forms of NF2, with early onset and poor prognosis, and the appearance of meningiomas and spinal tumors. Missense mutations (merlin is non-functional due to discrete defects) appear to be associated with the mildest NF2 cases. Dr. Evans and his collaborators have been able to identify the responsible mutation in 85% of familial (inherited) cases, and 55% of isolated cases.

Dr. Lan Kluwe *(Harvard University)* provided a progress update on identifying the Schwannomatosis gene, which has now been narrowed to a 3-5MB section of Chromosome 22, estimated to contain 30-60 genes.

Animal Models Update

It has been difficult to develop useful mouse models of NF2 that are representative of the human condition, but such models are vital for screening candidate drugs. Dr. Marco Giovannini *(INSERM)* described a new NF2 mouse model, developed by selectively disrupting gene expression in Schwann cells. A third of these mice go on to develop schwannomas within 9 months of life. Analysis of gene expression changes in these tumors has shown these to be similar to those gene changes seen in human NF2 schwannomas and meningiomas. Therefore, these models are representative of the human condition, and will be a powerful valuable tool for screening candidate NF2 drug therapies, something Dr. Giovannini is pursuing.

Optic gliomas are seen in up to 20% of children with NF1, typically younger than 7 years old, appearing in the optic nerve, optic chiasm or hypothalamus. Though rarely malignant, if they need to be surgically resected this can lead to blindness. Dr. David Gutmann *(Washington University)* has been studying the cellular events that cause optic gliomas to arise from astrocytes in the optic nerve. He has identified a role for resident microglia, cells known to play a role in inflammation & immune function in the nervous system, in prompting astrocytes to initiate tumor formation. These studies should help identify new drug targets for the treatment of optic gliomas. Currently Dr. Gutmann is testing rapamycin as a candidate therapeutic in these mouse models.

Tuberous sclerosis complex (TSC) is, like NF, a neurocutaneous tumor disorder, and there are crossovers in the signaling pathways involved in the two groups of disorders. 60% of children with TSC suffer from autism. Dr. Luis Parada *(University of Texas)* established an autism mouse model by blocking the tumor suppressor PTEN in postmitotic mouse neurons. These mice had large brains with visibly incorrect 'wiring' patterns. The mice had behavioral features of autism, which are partially resolved by giving the mice the drug rapamycin (which is also soon to be clinically assessed as a treatment for NF tumor growth - see below). These studies complement the NF1 mouse model work presented by Dr. Alcino Silva & Children's Tumor Foundation Young Investigator Awardee Ms. Carrie Shilyansky *(UCLA)* showing that *Nf1* mice have a variety of cognitive disabilities that at least in part may be restored by Lovastatin. (The statin studies have progressed to clinical trials: see below).

These studies on brain function are opening up a new understanding of cognition itself, by showing that tumor suppressors may in fact have a role in the normal brain

function. Next we need to understand how this signaling becomes disrupted in NF1, potentially by also studying TSC; and how we might therapeutically restore normal brain function.

Clinical Trials Update

Keynote Speaker Dr. Evan Snyder (Burnham Institute) addressed the potential role of stem cells in tumor treatment. Stem cells naturally 'home' to tumors; this is a feature that researchers may be able to capitalize on, especially in the difficult-to-access brain. Homing stem cells could be used both to better understand tumor growth, and to deliver therapies to stop it.

Dr. Brigitte Widemann (NCI) presented her clinical trials on malignant peripheral nerve sheath tumors (MPNSTs) which can develop deep inside benign plexiform neurofibromas. Currently the only option to treat these tumors is complete surgical resection of the plexiform tumor; Dr. Widemann and colleagues are shortly beginning a trial to test efficacy of sorafenib, a raf kinase inhibitor, to treat MPNSTs.

Drs. Alcino Silva *(UCLA)*, Maria Acosta *(Children's National Medical Center)* & Ype Elgersma *(Erasmus University)* presented updates on the clinical trials to test efficacy on statins in NF1 learning disabilities (see the full summary by Dr. Acosta in this issue of the *NF Newsletter*).

Dr. Jeanette Lee heads the Coordinating Center of the newly established Department of Defense NF Clinical Trials Consortium, which includes 9 clinical trials sites across the US. The Consortium was assembled by matchmaking of individual applicant centers, each selected on the strengths of their abilities to conduct clinical trials. The Consortium has already received funding from the DOD to organize the trial structure; full 3-year funding, to commence trials, is anticipated in late 2006/early 2007. The first two trials proposed to be conducted will be a Phase II trial of lovastatin in NF1 learning disabilities; and a Phase II trial of rapamycin for NF1 plexiform neurofibromas. Subsequent trials will focus on MPNSTs and optic pathway tumors. Though initially limited to 9 centers, the Consortium plans in time to open up to other clinical centers.

Dr. William Slattery gave an overview of the NF2 natural history study, which has now completed data collection. The study outcome is anticipated to impact both on the basic understanding of NF2 disease processes, thereby aid the search for effective NF2 therapies, and to improve clinical management.

Clinical Care Satellite

As reported in the last issue of the *NF Newsletter*, the Foundation is developing NF Clinic Guidelines with the aim of standardizing & ensuring good NF clinical care across the US. This topic was discussed in a special satellite session of the NF Conference, where members of the Foundation's Clinical Care Advisory Board led discussions on care guidelines & outcome monitoring for different clinical aspects of NF. Though it was the first

time such a session had been held, it was popular, with over 80 attendees arriving prior to the main NF Conference in order to participate. This satellite looks likely to become a regular fixture of the NF Conference.

The NF Clinical Database (NFDB) is an NF patient registry whose development has been funded by the Foundation. Registries are critical resources both for identifying clinical trial participants, and for doing clinical research studies. NFDB currently has 5,000 patients logged. All NF Conference attendees received a CD with a demo copy of NFDB to take home & try out. We hope this will encourage increased registry submissions.

Learning Disabilities Satellite

The Foundation convened this satellite meeting as a follow on to the February meeting reported in the last issue of the *NF Newsletter*. A review of this satellite meeting by Dr. Maria Acosta is presented elsewhere in this issue.

Importantly the group reviewed the status of ongoing statin clinical trials in the US and Europe. In addition there was serious discussion on how we can better understand & monitor the learning disabilities of NF1.

As a result of this meeting the Foundation is spearheading the formation of the Learning Disabilities Network (LeaD Net, an open communication forum for researchers & clinicians. We spearhead LeaD Net as a direct response to a request from the research community, quite simply to develop a way for this international and diverse group to keep working together as we learn more about this rapidly progressing & complex area of NF1. LeaD Net web page for information sharing will be established this summer at www.ctf.org

Finally, the Foundation took the opportunity of the NF Conference to launch the Drug Discovery Initiative – learn more in the DDI article in this issue of the *NF Newsletter*.

Looking ahead, the 2007 NF Conference will be chaired by Dr. Karen Cichowski and Dr. Eric Legius; and the 2008 NF Conference by Dr. Gareth Evans & Dr. Karlyne Reilly.

To download the 2006 NF Conference agenda & abstract book please visit http://www.ctf.org/professionals/meetings.htm

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