International Consortium Summary (1997)

The Pathogenesis of NFl and NF2: Therapeutic Strategies
By: Bruce Korf, MD, PhDHarvard Medical School/Boston Children's Hospital

(Ed. Note: The following is a report on an annual meeting of the "NNFF International Consortium for the Molecular Biology of NF1 and NF2" in modified format. In 1996 the Consortium members decided to hold annual meetings in alternate formats. They will meet every two years in the familiar, full membership gathering. During the off-years smaller, by invitation only, meetings will be held. The latter will focus on the development of long-term directions for research in NF1 and NF2. This year's meeting at the Banbury Center was such a meeting.)

An international meeting on the pathogenesis of NFl and NF2 was held from July 14-17, 1997 at the Banbury Center, Cold Spring Harbor Laboratory, New York. The meeting was sponsored jointly by the National Neurofibromatosis Foundation and by the Wilson Foundation and included 36 participants from the United States, Europe and Australia. The major focus was the consideration of possible therapeutic strategies for NFl and NF2.

Research on NF1 and NF2 has made major progress since the identification of the two genes. It is remarkable that, despite having learned a great deal about the structure and function of these genes, much remains to be discovered before we understand exactly how changes in these genes cause the various features of neurofibromatosis. This is dramatically illustrated by the finding of a role for cyclic AMP in the NF1 pathway - a new and important finding after seven years of research with the NF1 gene. Undoubtedly other new discoveries remain to be made. As this research proceeds, however, there is now renewed commitment to rapidly translating research progress to clinical application. There is also a realization that clinical trials of the first newly developed drugs that may be helpful in neurofibromatosis may not be that far off. Developing a plan for organization of clinical trials is now clinical research priority that will require close integration of basic research and clinical care.

The first session was devoted to cognitive function in NFl, and was chaired Dr. Kathryn North (Royal Alexandria Hospital, Sydney). Dr. North first reviewed current knowledge about cognitive function in NFl. The pathological basis for learning problems in NFl remains unknown. Further research, including work with MRI and functional imaging is needed. Dr. Paul Frankland (Cold Spring Harbor Laboratory) provided an update on work with NFl deficient mice. These animals display problems with spatial learning. Dr. Andre Bernards (MGH Cancer Center) and Dr. Yi Zhong (Cold Spring Harbor Laboratory) spoke about the NFl gene homolog in Drosophila. Flies with NFl gene mutations display a phenotype of small size. The phenotype is rescued by increasing levels of cyclic AMP (cAMP). This establishes a possible new physiological role for the NFl gene product that will require further study in higher organisms.

The second session, chaired by Dr. David Gutmann (Washington University) was devoted to optic glioma. Dr. Robert Listernick (Northwestern University) reviewed his experience with optic glioma in children with NFl. Although approximately 15% of his patients had MRI findings of optic glioma, only half of these children displayed symptoms, and only 3/31 showed evidence of progressive disease. Dr. Roger Packer (Children's National Medical Center) described his experience with chemotherapy for progressive optic glioma. Of 78 patients (14 with NFl) treated with Carboplatinum/vincristine, 60% displayed shrinkage of tumor. Response rate was the same in patients with or without NFl. Dr. C. David James (Mayo Foundation) summarized work on tumor suppressor genes in astrocytomas and Albert Wong (Kimmel Cancer Institute) reviewed work on signal transduction in astrocytomas. Dr. Gutmann presented evidence that the NFl gene is expressed in astrocytes subjected to ischemia. There is first a phase of cell proliferation following ischemia, and then cell differentiation. NFl expression correlates best with the differentiation phase.

The third session, on neurofibroma, was chaired by Dr. Bruce Korf (Harvard Medical Center). Dr. Korf presented a clinical classification scheme for neurofibroma and stressed the need for studies of natural history. Dr. David Viskochil (University of Utah) summarized evidence for loss of activity of the NFl gene in neurofibromas. Dr. Nancy Ratner (University of Cincinnati) described her work on the pathogenesis neurofibromas in NFl knockout mice. She has shown that neurofibroma-like tumors form in heterozygous animals after cutting of nerves. Dr. Tyler Jacks (MIT Cancer Center) reviewed his studies with homozygous and heterozygous knockout mice. Animals with chimerism for NFl -/- cells develop neurofibroma-like tumors. Animals with double knockouts of NFl and p53 develop particularly aggressive sarcomas in a fairly short time. Dr. Jonathan Epstein (University of Pennsylvania) reviewed his studies of heart defects in homozygous knockout mice. Dr. Louis Parada (UT Southwestern Medical Center) has shown that NFl -/- neurons survive in the absence of neurotrophins. Jackson Gibbs (Merck Research Laboratories) reviewed progress in development of farnesyl transferase inhibitors and Dr. Frank Lieberman (Mt. Sinai Medical Center) discussed the possible use of differentiating agents in tumor treatment.

Dr. Ephraim Casper (Memorial Sloan-Kettering Cancer Center) chaired the session on malignancy in NFl. He reviewed current data on natural history and management of malignant peripheral nerve sheath tumors (MPNST's). Dr. James Woodruff (Memorial Sloan-Kettering Cancer Center) discussed the pathology of MPNST's and Dr. Alfred Neugat (Columbia University) made comments on epidemiology. Lawrence Baker (University of Michigan) discussed his experience with sarcomas and noted seeing cafe-au-lait spots on some of his sarcoma patients. Dr. Kevin Shannon (University of California, San Francisco) described his studies of leukemia in NFl knockout mice. White blood cell counts were not altered in leukemic animals treated with a farnesyl transferase inhibitor. He also reported an increased frequency of leukemia in heterozygous mice treated with cyclophosphamide.

The final session, chaired by Dr. James Gusella (Massachusetts General Hospital) was devoted to NF2. Dr. Gusella reviewed knowledge of the structure of the NF2 gene and the types of mutations seen in patients with NF2. Dr. Vijaya Ramesh (Massachusetts General Hospital) discussed studies of localization of the NF2 protein. Dr. Richard Fehon (Duke University) showed his results with a Drosophila merlin knockout. Disruption of this gene in the fly leads to localized overgrowth. Dr. Gilles Thomas (Foundation Jean Dausset/CEPH) has created an inducible mouse NF2 knockout. These animals develop schwannomas and will be of great value in further studies of the pathogenesis of NF2. Dr. David Gutmann reviewed his findings on the structure of merlin. Dr. Mia MacCollin (Massachusetts General Hospital) discussed the possibilities of using aminoglycoside antibiotics to overcome stop mutations in NFl and NF2.

The meeting ended with a discussion of protocols for tissue collection in NFl and NF2. The next meeting of the NNFF International Research Consortium will take place in Aspen, Colorado in June, 1998.