International Consortium Summary (1999)

NNFF Scientific Consortium Meets at MIT

While the NF1 and NF2 genes are large and complex, their mysteries are played out at a much more specific level. The molecular biology of NF involves the exacting task of breaking down the most minute actions and reactions within and between the cells to better understand how the NF genes function.

This challenge is one that dozens of scientists from around the world take on every day in their labs. The National Neurofibromatosis Foundation is instrumental in moving this research process along. One way the NNFF manages research in the molecular biology of NF is to host the"NNFF Consortium on Molecular Biology of NF1 and NF2" so that researchers can share their up-to-the minute findings with their colleagues. This year's meeting took place during the summer at MIT's prestigious Whitehead Institute for Biomedical Research and was organized by Tyler Jacks, Ph.D., MIT Center for Cancer Research; and André Bernards, Ph.D., Massachusetts General Hospital Cancer Center.

Although the NF2 gene was identified after the NF1 gene, progress in NF2 research is moving more rapidly than expected, according to Dr. Jacks. The presentations by NF2 researchers noted progress on three fronts - biochemical studies, regulation of and by Merlin/schwannomin (the NF2 gene product), and in modeling of NF2 in animals. Dr. James Gusella of Harvard Medical School/MGH and Dr. Gilles Thomas of the CEPH Foundation Jean Daussett in France chaired the NF2 portion of the meeting.

In addition, new researchers were brought into the consortium to expand the fields of research with potential impact on NF2. While Dr. Elizabeth Luna of University of Massachusetts and Dr. Mitsuyoshi Nakao of Kumamoto University, Japan do not conduct research into NF2 specifically, their interests within molecular biology may provide additional clues to the behavior of the gene.

Biochemical studies explore the relationship of the NF2 protein, Merlin, to other similar proteins found in cells. Discovering the interaction between these various ERM proteins will help scientists understand why the loss of the Merlin protein that occurs in NF2 occurs and how it affects the functioning of the NF2 gene.

One of the most significant discoveries shared was the first 3-D model of ERM proteins, which interact with Merlin. The detailed atom-by-atom structure developed by Dr. Anthony Bretscher of Cornell University is the most detailed view of this class of protein that has ever been developed. "Dr. Bretscher's model gives us a better sense of what Merlin's structure may look like," Dr. Jacks said. "This is a monumental discovery that will help in making progress towards understanding Merlin's function."

In a related area of research, several scientists discussed their findings of the regulation of and by Merlin and the signaling pathways among cells. Some of the researchers found new proteins that interact with Merlin. These discoveries reveal more about the signaling pathways and their functions than was previously known. For example, Dr. Andrea McClatchey of Harvard/Massachusetts General Hospital suggested that NF2 might function indirectly in the Ras signaling pathway, which is implicated in cell growth and division. Traditionally, only NF1 was thought to have an interaction with Ras. This finding suggests that NF2 and NF1 may have more in common than was previously thought, according to Dr. Jacks.

Other researchers focus beyond the cellular level to explore NF in the context of a traditional genetic model. The area of realistic disease modeling in fruit flies and laboratory mice is critical to the development of effective treatments. The presentations marked a significant improvement in

animal models that mimic NF in humans. Dr. Marco Giovannini of the CEPH Foundation Jean Daussett in France discussed a refined mouse model for NF2 that produces Schwann cell tumors. Dr. Richard Fehon of Duke University has been able to substitute a human gene for NF2 for a fly gene. This opens up the possibility of studying human derived mutations in the fruit fly. Experiments could then be conducted on the altered flies to learn more about signaling pathways and the consequences of the loss of Merlin in the cells.

Other presentations given during the NF2 session focused on various aspects of the NF2 gene product (merlin/schwannomin). The following researchers discussed their findings about the NF2 gene product: Dr. David Gutmann, Washington University; Dr. Vijaya Ramesh, Massachusetts General Hospital; Dr. Markku Sainio, University of Helsinki; Dr. Guy Rouleau, McGill University; Dr. Stefan Pulst, UCLA.

During the NF1 session, which was chaired by Dr. Bernards, progress was reported in the areas of animal studies, the role and function of the NF1 gene product (neurofibromin), and the role of the NF1 gene in development.

Among the most important developments in the NF1 field was the news that Dr. Luis Parada of the University of Texas has developed a second-generation mouse model. "Dr. Parada has developed an elegant model that will enable scientists to better define neurofibromin's precise role in various cell types such as peripheral nerve cells," Dr. Bernards said.

It has been known for several years that neurofibromin inactivates the Ras protein, which serves as an on-and-off switch that controls cell growth and cell division. "In a new twist to the tale of the NF1 protein and Ras relationship, Dr. Jacks shared research results that suggest that neurofibromin may actually play a dynamic role and promote Ras activity," Dr. Bernards said.

Dr. Iswar Hariharan of Massachusetts General Hospital reported on a fly model that yielded further evidence to support the theory that c-AMP is regulated by neurofibromin. "This finding is important because c-AMP is a molecule involved in learning and memory in various organisms," Dr. Bernards noted.

Several researchers presented on growth factors in NF1: Dr. Kristine Vogel, Louisiana State University; Dr. George deVries, Loyola University; and Dr. Kevin Shannon, UCSF. Dr. Nancy Ratner, University of Cincinnati, reported on defective wound healing in NF1 mutant mice. Dr. Wade Clapp, Indiana University, reported on a potential dominant effect of NF1 on coat color pigmentation in mice. Dr. Jeffrey DeClue, National Cancer Institute, discussed NF1 tumors and Schwann cell transformation. Dr. David Largaespada, University of Minnesota, and Dr. Camilynn Brannan, University of Florida, presented findings on myeloid leukemia. Dr. Jon Epstein, University of Pennsylvania, discussed NF1's impact on the neural crest and development of the heart. Dr. Mladen Golubic, Cleveland Clinic Foundation, presented findings on the neurofibromin's relationship with lipids and mitochondria.