



## **"Dramatic Advances" Reported At 2005 CTF Consortium in Aspen, CO**

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The annual scientific meetings of the Children's Tumor Foundation Consortium for the Molecular Biology of NF1, NF2 and Schwannomatosis was held in Aspen, Colorado June 5 to 8, 2005. The meeting was characterized by an astounding array of basic science and clinical advances that were presented to the 150 assembled researchers and physicians from around the world.

Dr. Arnold Levine, a distinguished professor at the Institute for Advanced Study in Princeton, NJ and the Robert Wood Johnson School of Medicine, and past president of the Rockefeller University in New York, delivered the plenary lecture. Dr. Levine is the discoverer of the tumor suppressor gene p53, known as the "guardian of the genome," which is mutated in up to 50% of human cancers. In animal models, and perhaps in humans, p53 mutations augment tumor formation in NF. Dr. Levine discussed cutting-edge techniques to identify genetic factors that influence cancer risk.

The meeting featured five additional invited experts who had not previously contributed directly to NF-related investigations. Dr. Benjamin Neel, Professor of Medicine at Harvard Medical School and Director of the Cancer Biology Program at the Beth Israel-Deaconess Medical Center presented evidence that mutations in a signaling molecule called Shp2, which acts as a protein phosphatase, cause Noonan's syndrome and Leopard syndrome. These childhood disorders bear striking resemblance to NF1, and work in animal models suggests that Shp2 may function in the same molecular pathway as NF1. Kinases and phosphatases act to add or remove, respectively, phosphate molecules from cellular proteins, and some of the most effective recent treatments for human cancers target these proteins.

Several investigators presented evidence that the predominant role of NF1 is to regulate the level of a critical signaling molecule called Ras. Exciting new data from Dr. Karen Cichowski's laboratory at Harvard Medical School and from [Dr. David Gutmann's](#) laboratory at Washington University at St. Louis suggested that a molecule called mTOR is activated when NF1 is mutated and Ras is activated. This is important because chemical inhibitors of mTOR, including rapamycin, are available and can be tested in animal models as potential treatments for NF1. Dr. Roman Herrera from Pfizer Pharmaceuticals presented the most recent updates on safety trials that are underway in people to assess inhibitors that block other known pathways that are activated by Ras. These phase I clinical trials suggest that a class of inhibitors that

block a protein called Mek can be relatively well tolerated by patients. The next step is to perform larger clinical trials to assess efficacy.

Dr. Luis Parada, a leader in the NF research community, presented data suggesting that excessive growth of nerves and glia in animals lacking neurofibromin might offer important insights relevant to the study of nerve regeneration and repair. Mice with mutations in Nf1 were shown to recover from spinal cord nerve injury more rapidly and to a greater degree than normal litter mates due to enhanced sprouting of uninjured nerves. This exciting line of investigation may provide critical clues for developing therapies aimed towards nerve regeneration for the treatment of paralysis due to spinal cord injury.

Another highlight of the meeting involved the presentation of data from Dr. Freda Miller who works at the University of Toronto. Dr. Miller, an invited expert, has discovered an adult stem cell population that resides in the skin. These stem cells are able to differentiate into nerve tissue when cultured and stimulated in the laboratory. Many experts now believe that adult stem cells are the cells of origin of many cancers, and Dr. Miller's work suggests that the stem cells that she has identified could be the cells that give rise to café-au-lait spots and cutaneous neurofibromas.

Several investigators presented new data concerning the function of merlin, the protein encoded by the NF2 gene. Merlin is related to several other structural proteins in the cell, and cells that lack merlin show abnormal shape and sometimes fail to develop normal connections with neighboring cells. However, accruing evidence indicates that merlin also regulates signaling pathways in cells, in a fashion somewhat related to the role of NF1. A signaling protein called Rac, which is related to Ras, is regulated by merlin, and Rac is known to affect cell migration, shape and growth. The precise mechanism by which merlin affects Rac is being investigated, and these studies are likely to suggest specific proteins and pathways that will be targets for therapeutic intervention in NF2.

Dr. Mia MacCollin, a physician and researcher at Harvard Medical School and the Massachusetts General Hospital, presented her recent analysis of the genetics of Schwannomatosis, suggesting that a gene(s) on chromosome 22 located near to, but distinct from, NF2 is responsible for this disorder. Finally, Dr. Scott Plotkin, also at Massachusetts General Hospital, presented results of a survey of NF patients and care-givers which suggested that both groups were eager to participate in clinical trials even when additional burdens and uncertainty that can accompany these efforts were considered.

This year's meeting concluded with a general sense of significant progress and excitement. There was recognition that basic scientific investigations have successfully identified a series of potential molecular targets that offer the possibility of developing and testing medications to treat these diseases. This represents a dramatic advance. While development and testing in animal models and in clinical trials are time consuming and difficult processes, a path forward from these scientific sessions has emerged.