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THE NATIONAL NEUROFIBROMATOSIS FOUNDATION, INC.

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Scientists Discover Possible Link To Hormonal Influence In Tumors of Patients With NFI

Scientists are now learning more about what patients with NFI have been talking about for a long time. It has long been recognized that neurofibromas tend to appear or grow during puberty and pregnancy. This has suggested that hormones may influence the growth of neurofibromas, but the specific hormones responsible have not been known. In a paper published recently in the journal *Cancer Research* (Vol. 63, pages 752-755, 2003), Dr. Margaret McLaughlin and Dr. Tyler Jacks, at the Center for Cancer Research, MIT, describe a study they designed to look more carefully at this phenomenon. The authors examined 59 human neurofibromas for the presence of receptors to the hormones estrogen and progesterone. They found the presence of progesterone receptors in 75% of the tumors. Other nerve tumors, such as schwannomas, and normal nerve tissue did not have detectable progesterone receptors. Only 5% of tumors expressed the estrogen receptor.

In females, the level of progesterone is low until puberty, and increases dramatically during pregnancy. The presence of progesterone receptors in the tumors allows for

The level of progesterone receptors in the tumors varied according to the levels of progesterone in the blood, suggesting that the increase in the receptors occurred in response to the hormone's presence.

an uptake of the hormone into the tumor cells, potentially increasing their growth rate. In males, progesterone is an intermediate in the production of testosterone. The level of progesterone receptors in the

tumors varied according to the levels of progesterone in the blood, suggesting that the increase in the receptors occurred in response to the hormone's presence. The scientists also discovered that only a subset of tumor cells expressed the progesterone receptor. These cells were not the Schwann cells, which did not express neurofibromin, the NFI protein, but rather tumor-associated non-neoplastic cells.

Currently, only surgical resection is used to treat neurofibromas, and it is often impossible to completely remove the tumor tissue, especially in the plexiform or larger cutaneous tumors. Results from this study suggest that antiprogestins, such as Mifepristone (RU486) might be useful in the treatment of tumors as an alternative to surgery, to reduce the size of the tumor before surgery, or to slow progression of the plexiform tumors to malignancy. Future studies will be aimed at determining whether such a treatment will be feasible for NFI. **NF**

A Look at the Past May Clarify NF Research for the Future

It is a basic and practical question: with limited funds, is the Foundation better off funding a scientist researching new and practical treatments for NF or a scientist studying the reproduction and growth of yeast cells? The answer is less obvious than it may appear.

At the Council of Fellows 25th Anniversary reception at the University Club in New York, Dr. Jon Epstein from the University of Pennsylvania gave a speech about the keys to success in finding a cure for NF. Dr. Epstein remarked that in the past, great scientific discoveries were made from great insights stemming from serendipitous events, and that the key to finding a cure for NF lies in a two-pronged approach to research: the first prong is the clinical researchers and physicians, whose work is treating and observing patients. The second prong is made up of basic scientists, whose job it is to find the underlying causes of the disorder. Dr. Epstein pointed to some historical

examples of serendipitous scientific breakthroughs.

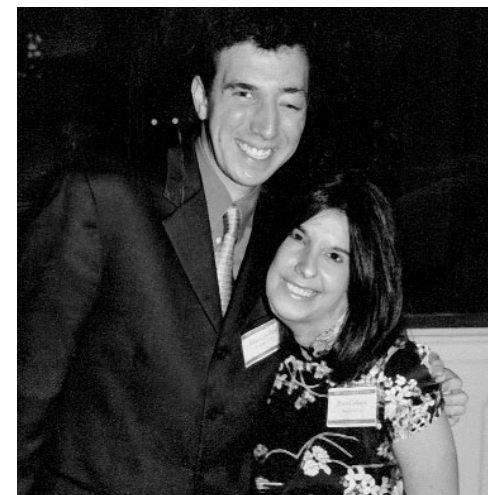
In 1928 Alexander Fleming (1881-1955) was growing bacteria in culture plates trying to prove that nasal mucus had anti-bacterial properties. By accident, he let his bacteria grow, uncovered, on his laboratory bench. Upon his return he noticed that bacteria had grown to cover the entire dish except for a small halo surrounding a patch of mold. Fleming correctly identified the mold's anti-bacterial properties. Fleming had discovered penicillin. He later commented, "My only merit was that I did not neglect the observation". Fleming was not able to develop penicillin into a working antibiotic. It took the work of Howard Florey, Ernst Chain and a team of scientific specialists to turn Fleming's accidental discovery into one of the greatest leaps in medical science.

The work of Nobel Laureate Barbara
continued on page 4



Dr. Jon Epstein of the University of Pennsylvania

NNFF Kicked Off Its 25th Anniversary Year With a New York Event



Adam Goodkind and Bara Colodne

In May, the NNFF hosted a Council of Fellows Cocktail Party & Reception at The University Club, in New York City, to celebrate the start of the Foundation's 25th Anniversary year. Speaking at the event, Dr. Jon Epstein, University of Pennsylvania, talked about the future of NF research and the keys to finding a cure for NF (see "A Look at the Past May Clarify NF Research for the Future"). The Foundation also announced the appointment of Bara Colodne, Adam Goodkind & Marcy Horovitz as Co-Chairs for the 25th Anniversary Gala in February 2004.

Foundation Holds 2003 International Consortium for the Molecular Biology of NF1 & NF2 in Aspen, CO

by *Judy A. Small, PhD*
NNFF Director of Clinical Trials
and Technology Transfer

125 of the world's top NF scientists and researchers gathered for the 12th Annual meeting of the "NNFF International Consortium for the Molecular Biology of Neurofibromatosis 1 and Neurofibromatosis 2" June 1-4 in Aspen CO. This annual meeting serves as an opportunity for NF researchers to exchange ideas and report progress in the many varied disciplines that NF research encompasses. This year's meeting featured over 30 oral presentations by researchers from the top laboratories in the United States and abroad and was co-chaired by Dr. David Gutmann (Washington University, St. Louis) and Dr. Marcó Giovannini (Fondation Jean Dausset, France). This year's Consortium was of special note owing to the 25th Anniversary of the NNFF and the 10th anniversary of the discovery of the NF2 gene. Below is a brief synopsis of the meeting and highlights of some presentations; for a more detailed summary of the presentations, please go to the NNFF website (www.nf.org/nf_professionals/consortium).

Two Special Occasions Noted

The Foundation noted two special occasions at this meeting. First, was the fact that the organization is celebrating its 25th Anniversary. NNFF President Peter Bellermann thanked the Foundation's co-founders Dr. Allan Rubenstein, Lynne Courtemanche Shapiro R.N., and Joel Hirschtritt, Esq. Dr. Rubenstein received a standing ovation for his 25 years of dedicated service to the NNFF.

The NNFF also celebrated the 10th Anniversary of the discovery of the gene for Neurofibromatosis Type 2, in the laboratories of Dr. James Gusella (MGH/Harvard), and Dr. Gilles Thomas (Fondation Jean Dausset, Paris) and Dr. Guy Rouleau (McGill University, Montreal). The three were honorary co-chairs of the first session, titled "Neurofibromatosis Type 2-Ten Years Later:"

Exceptional Progress During Past Year

Progress over the past year has been exceptional, and the audience was energized by the information presented during the meeting. Mouse models continue to provide a rich resource for experimental studies to understand the biology of the NF1 and NF2 genes. The spirit of communication and collaboration among NF researchers continues as use of these mouse models expands to new laboratories and research fields. Cells and tissues from these mice are an invaluable resource for studies in a number of laboratories trying to understand the role of the NF1 and NF2 genes in normal and tumor cells. There were presentations on non-tumor features of NF1, including cardiac and myeloid cell defects, bone abnormalities, and pain. Learning and memory studies were presented for both mouse and fruit fly models. Microarray technology is being used to identify the changes in gene expression in NF1 and NF2 tissues, as a promising avenue toward identi-

fying possible targets for therapeutic development. Many scientists were overheard discussing new data, possible collaborations, or projects that will be done on the return to the laboratory.

Keynote Addresses

There were two keynote speakers at the meeting. Dr. Anton Berns (The Netherlands Cancer Institute, Amsterdam) spoke about technologies that help to dissect tumorigenesis in mouse models of cancer. Dr. Mahendra Rao (NIA/NIH) spoke about neural stem cells, and the potential to use them for studying normal neural cell processes, and about the potential of these cells as therapeutic agents in disease models.

Department of Defense and NIH Representatives Participating

The Department of Defense (DOD) and the National Institutes of Health (NIH) were represented at this meeting as well. The DOD Neurofibromatosis Research Program (NFRP) funds a large portion of NF research both nationally and internationally, at a current rate of about \$20 million per year. Dr. Rick Kenyon (DOD) spoke about the NFRP and the latest call for applications. New this year is the Clinical Trials Development Award, which will be a fast

For a complete summary of the meeting and individual presentations, please visit the NF website at www.nf.org/nf_professionals/consortium.

track process for applicants for a year of funding to develop the resources necessary to propose a clinical trial for DOD funding. He also announced a new policy for allowing for resubmission of proposals, allowing for the first time a response to criticisms of the previous review. He described the NF1 and NF2 story boards, a project that the DOD has undertaken to present milestones and accomplishments in research for NF, and invited comments and corrections from the participants of the meeting. Dr. Robert Finkelstein (NINDS/NIH) was available for consultation about possible funding through the NIH, and to describe new programs that would provide funding opportunities for NF researchers.

NF2 Clinical and Research Findings

The first session of the Consortium was devoted to the accomplishments of NF2 clinical and research. Dr. Mia MacCollin (MGH/Harvard) spoke about NF2 diagnostic criteria. Since 1987, four sets of diagnostic criteria have been published, and while similar, they created the problem of not providing sufficient information for the general clinician to make a diagnosis. The presence of bilateral vestibular schwannomas (VS) is the standard criteria for diagnosis of NF2. However, other symptoms may suggest NF2, in the absence of bilateral tumors. Unilateral VS and the presence of a


meningioma, schwannoma or glioma suggests NF2. Mosaicism is a common feature in NF2 nonfamilial patients and complicates the diagnosis. Other features appear in NF2 patients, but do not appear in the diagnostic criteria. Standard imaging protocols do not meet the needs for diagnosing NF2, and specific protocols must be described to screen presymptomatic cases. A separate, adjunct meeting was held with a number of top NF2 clinicians, to discuss the NF2 diagnostic criteria and make recommendations for a consensus on NF2 diagnostic criteria.

Animal Models

Mouse models of NF1 and NF2 have become very important for understanding not only tumor formation but also many of the other symptoms of the diseases. Dr. Kevin Shannon (University of California, San Francisco) provided an update on the NNFF International Mouse Models Consortium, established to produce and characterize models of NF1 and NF2, to identify biochemical pathways and targets, and to provide a host for preclinical intervention studies. The Consortium continues to interact with the NCI's Mouse Models of Human Cancer Consortium, although it is funded through the Department of Defense NF Research Program. There are some hurdles that must be overcome in order for preclinical testing to move ahead. There are also intellectual property concerns, among both pharmaceutical and academic organizations. It is difficult to identify and obtain lead compounds. At this point, preclinical testing in the laboratory is limited to small numbers of animals, and does not yet involve high throughput testing. Mouse model scientists in academic settings typically lack the necessary expertise and resources. There will be an NNFF International Mouse Models Consortium Preclinical Therapeutics meeting in 2004 where a number of these issues will be discussed. Participating will be academic scientists and well as biotech and pharmaceutical experts.

Molecular Genetics & Biology

Molecular Genetics and Biology continue to be a rich area of research. Among the studies reported on at the Consortium meeting were reviews of natural history and risk factors for NF1; mutation analysis; a research project looking for genetic modifiers that might control the number or density of cutaneous neurofibromas in NF1 patients; and, one of the first studies of hormonal influences in neurofibromatosis, a phenomenon often noted by patients with NF1.

In addition to the oral presentations, there were 36 abstracts presented as posters. These posters covered a number of areas of both NF1 and NF2 research, and added to the overall scientific contributions to the meeting. For a complete summary of the meeting and individual presentations, please visit the NF website at www.nf.org. 

**Touch the Future:
Invest in NF Research**

NF PROFILE

Gunnar Johanson: Scientist Fighting NF for Personal Reasons

There are very few researchers with the intimate connection to NF that Gunnar Johanson has. Living in Umeå, Sweden, Gunnar was five-years-old when he was diagnosed with NF1. He was not the only person in his family to be diagnosed with NF. When Gunnar was diagnosed it was also found that his Father, Sister, Grandmother, Aunt and Cousins all had the same condition. Fortunately none of his family members have had any major medical problems associated with NF.

Attending a conference in Ulm, Germany in 1999, Gunnar heard Dr. Nancy Ratner and was enthralled by the quality and content of her research. In 2001 as Gunnar was working on his master's thesis, he decided to email Dr. Ratner and ask her if it was possible to finish up his masters degree while working in her lab. In January of 2002, Gunnar joined Dr. Ratner's Lab in Cincinnati, OH to complete his masters thesis. They quickly developed a good working relationship and Gunnar applied, and was accepted, to stay on as a Ph.D. candidate in Dr. Ratner's lab.

The Ratner lab is studying the changes in Schwann cells that occur during the formation of neurofibromas. They

have shown that a protein called Brain Lipid Binding Protein (BLBP) is linked to the loss of connection of a Schwann cell to its nerve fiber during tumor develop-



Dr. Nancy Ratner and Gunnar Johanson

ment. When BLBP is blocked, the SC/nerve fiber association is restored. BLBP expression has been linked to the Epidermal Growth Factor Receptor (EGFR) cell signaling pathway, an impor-

tant growth signaling pathway in many cells. However, EGFR is not normally found in Schwann cells, but is expressed in malignant peripheral nerve sheath tumors (MPNST), suggesting that EGFR may play a role in neurofibroma formation. Current research is focused on developing genetically engineered mice that have high levels of BLBP in the SC, to study the effect on tumor formation and changes in nerve structure. In a similar study, mice with high levels of EGFR developed enlarged nerves and mast cell recruitment mimicking neurofibroma formation. These studies will lead to a better understanding of the role of BLBP in SC-nerve interactions and in neurofibroma formation.

Although Gunnar says that he has always had an interest in science, the fact that he is a patient with NF led him to biochemistry and NF research. "I think its interesting and stimulating work, trying to find out something that no one else knows." In order to inspire other young patients with NF to explore careers in science, and NF research specifically, Gunnar will be running a "Day At the Lab" for Children with NF in the Cincinnati, OH area. **NF**

The NNFF Young Investigators Awards Announced

Summaries of 2003 Award Projects

The Foundation has announced the list of Young Investigators it is funding in 2003/04. "This list represents an extraordinary group of young scientists in the fields of NF1 and NF2. Most of them are new to the field," NNFF President Peter Beller-mann said, "They came from outstanding laboratories in the United States and abroad, and we hope that many of them will make careers in our field."

"A Role for Merlin in Membrane Trafficking"

Dr. Julie Hughes, PhD
Cornell University
Two-Year Young Investigator Award

"Development of Neural Prosthetic to Cause Blink"

Dr. S. Tonya Stefko
The University of Pittsburgh
Two-Year Young Investigator Award

"Identification of Meningioma Tumor Suppressor Loci"

Dr. Fabio Nunes
Massachusetts General Hospital
Two-Year Young Investigator Award

"Analysis of the Mechanism and Significance of Merlin Lipid Raft Localization"

Dr. John T. Stickney
University of Cincinnati
Two-Year Young Investigator Award

"Signaling Pathways Mediated Through PDGF in NF2 Tumors"

Dr. Marianne James
Massachusetts General Hospital
Two-Year Young Investigator Award

"Neurofibromatosis 2 Tumor Suppressor, Merlin, Inhibits PIKE/PI3-Kinase Signaling"

Dr. Shyra Miller
University of Cincinnati
Two-Year Young Investigator Award

"A Clinical Screening Package for Cognitive Deficits in NF1"

Dr. Shelley Hyman
Children's Hospital Westmead, Australia
Two-Year Young Investigator Award

"The Actions of Nerve Growth Factor and Vascular Endothelial Growth Factor on the Function of Haploinsufficient NF1 Sensory Neurons"

Dr. Cynthia M. Hingtgen
Indiana University
Two-Year Young Investigator Award

"Genetic and Molecular Identification and Characterization of Drosophila Merlin/NF2 Modifiers"

Dr. Sarah Hughes
Duke University
Two-Year Young Investigator Award

"The Role of Genomic Instability in NF2-Related Tumors"

Dr. Angela A. G. van Tilborg
Erasmus University Rotterdam,
The Netherlands
Two-Year Young Investigator Award

"Mechanism of Protein 4.1B Growth Suppression"

Dr. Victoria A. Robb
Washington University School of Medicine
Two-Year Young Investigator Award

"Recruitment of Stem/Progenitor Cells to Brain Tumor Vasculature"

Dr. Kenneth S. Cohen
Harvard Medical School/MGH
Two-Year Young Investigator Award

"Analysis of Gene Expression in Drosophila NF1 Mutants using DNA Microarrays."

Dr. James Walker
Harvard Medical School/MGH
Two-Year Young Investigator Award

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RESEARCH STUDY OF ADULTS WITH NEUROFIBROMATOSIS TYPE I

The Department of Genetics at the University of Alabama at Birmingham, as part of a multi-center study, is looking for adults diagnosed with Neurofibromatosis type I (NF1) to participate in research examining factors affecting Quality of Life. Enrolled participants will be screened for eligibility and then asked to complete two questionnaires on two separate occasions. No remuneration will be offered.

If you are diagnosed with neurofibromatosis type I, and you are interested in participating in our research study, please contact the principle investigator, Bruce Korf, MD, PhD at (205) 934-9411 or by email bkorf@genetics.uab.edu, or the study coordinator, Tricia Page, M.S. at (205) 934-4983 or by email ppage@genetics.uab.edu.

Epstein *continued from page 1*

McClintock, a biologist studying how corn can be produced with so many different colored kernels, deduced that genes must be at work and that these genes can move around a chromosome. Although her peers shunned her theories, she was later proven correct, and her work, among others, laid the foundation for the molecular work being done in NF research today.

Dr. Barbara McClintock's work is responsible for the ability to genetically develop animals that express symptoms of NF, or what is called animal modeling. The use of animal models is allowing scientists to see how NF development affects animal growth and behavior. It is also allowing scientists to test new treatments on a scale that would have been previously impossible. Scientists working on animal models are a necessary step towards developing treatments for use in a human clinical setting. 

WEB UPDATE

**There is a new Schwannomatosis
Section of our Bulletin Board**
Check it out at:
<http://www.nf.org/bb2/bbentry.htm>

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The purpose of the National Neurofibromatosis Foundation, Inc. (NNFF) is to improve the well-being of patients and families affected by NF1 and NF2. The Foundation therefore sponsors scientific research aimed at finding the causes and cures for the neurofibromatoses, promotes the development of clinical activities, works to create public awareness and provides patient support services.

The National Neurofibromatosis Foundation is a founding member of the International Neurofibromatosis Association.