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This story board is a work in progress. To comment or request further information, please contact:

Naba Bora, Ph.D.
Program Manager, NFRP
1077 Patchel Street
Fort Detrick, MD 21702
Phone: 301-619-6881
E-mail: Naba.Bora@amedd.army.mil

OR

Jonathan Miller, Ph.D.
Program Coordinator, NFRP
1053 Patchel Street
Fort Detrick, MD 21702
Phone: 301-619-6751
E-mail: Jonathan.Miller2@amedd.army.mil

Neurofibromatosis Type 1 (NF1)

- Linked research
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1996 1997 1998

Molecular Biology & Genetics

- Genetic nature of NF1 documented by Thomson (1900), Adrian (1901), and Prieser & Davenport (1918).
- *NF1* gene localized to chromosome 17. 1987
- Loss of heterozygosity (LOH) on chromosome 17 shown for malignant peripheral nerve sheath tumors (MPNSTs). 1989
- • *NF1* gene cloned 1990
  • *NF1* classified as a tumor suppressor. 1990
- Neurofibromin identified as the product of the *NF1* gene. 1991
- Splice variants of *NF1* identified. 1992
- *NF2* gene cloned; *NF2* gene product identified as Merlin/Schwannomin. 1993
- *NF1* mRNA shows high levels of editing: potential mechanism for inactivation without mutation. 1995
- Evidence for LOH of NF1 in neurofibromas. 1995
- Identification of a point mutation in a dermal neurofibroma, which supports the tumor suppressor hypothesis. 1996
- Structure of the catalytic domain of *NF1* determined. 1998

Cellular Biology

- *NF1* shares homology with GAP proteins. 1990
- Development of intracellular Ras-GTP to Ras-GDP ratio for measuring neurofibromin-specific GAP activity. 1992
- Neurofibromin interacts with microtubules. 1993
- Ras-GTP to Ras-GDP ratio elevated in neurofibromas and MPNSTs. 1996
- *NF1*$^{-/-}$ Schwann cells proliferate in response to forskolin; *NF1*$^{+/+}$ and *NF1*$^{+/-}$ Schwann cells do not; *NF1*$^{-/-}$ Schwann cells have a growth advantage and are easily transformed. 1997
- Neurofibromin regulates protein kinase A. 1997

Pathobiology

- First recorded case of optic pathway glioma in association with NF1. 1873
- Schwann cells from neurofibromas promote angiogenesis and invasion. 1990
- Loss of *NF1* associated with MPNSTs. 1992
- NF1-related vasculopathy caused by smooth muscle cell proliferation. 1993
- p53 regulation is involved in the development of MPNSTs. 1994
- Loss of *NF1* associated with the development of leukemias and MPNSTs. 1996
- Microdeletion of *NF1* and surrounding genes associated with facial amalies and early onset 1997
- NF1$^{+/-}$ and NF1$^{-/-}$ Schwann cells are both angiogenic and invasive in culture 1997
- Sera from NF1 patients show increased mitogenic activity on Schwann cells in culture 1998
- p53 immunoreactivity is higher in MPNSTs than in benign neurofibromas 1998

Technology/ Animal Models

- *Nf1*$^{-/-}$ mice die of cardiac muscle malformation at gestational day 14. 1994
- *Nf1*$^{+/-}$ mice developed that are tumor-prone and develop myeloid leukemias and pheochromocytomas. 1994
- Improved mouse model of myeloid leukemia developed. 1996
- Mouse model of learning and memory defects developed. 1997
- Drosophila model of NF1 developed. 1997

Behavioral & Cognitive Biology

- Children with NF1 shown to have high index of specific learning disabilities. 1981
- Evidence for lower IQ scores in some children with NF1. 1986
- Magnetic Resonance Imaging (MRI) "abnormalities" associated with learning disabilities in NF1. 1994
- Pathology of NF1 correlated to MRI data; myelin edema associated with glial proliferation. 1995
- First research addressing the molecular basis of learning disabilities in NF1. 1996
- Drosophila NF1 involved in growth, learning, and memory. 1997
- Cognitive defects detected in *Nf1*$^{+/-}$ mice. 1997

Imaging, Detection, & Diagnosis

- First identified in the literature by Dr. Friedrich von Recklinghausen. 1882
- First diagnostic test criteria developed for NF. 1988
- First comprehensive international database for NF developed. 1989
- Direct gene testing for NF1 available. 1995

Epidemiology

Experimental Therapeutics

- First national multicenter clinical trial for NF begun. 1994
- Translational Research: Compound testing for NF1 treatments begun. 1997

Symptom Management

- Neurofibromas removed surgically.
- CO_2 laser treatment used for cutaneous neurofibromas. 1987
- Assessment of surgical removal of plexiform neurofibromas – 56% of tumors did not progress and 20% of cases found improvement. 1997

Important Meetings & Symposia

- Foundation of the National Neurofibromatosis Foundation (NNFF). 1978
- National Institutes of Health (NIH) Consensus Development Conference on Neurofibromatosis: Delineated NF1 from NF2 and diagnostic criteria for each. 1987
- Foundation of Neurofibromatosis, Inc. 1988
- Department of Defense Neurofibromatosis Research Program (NFRP) established. 1996
- NNFF Clinical Care Advisory Board: Diagnostic Evaluation and Management of NF1 and NF2. 1997

NF1

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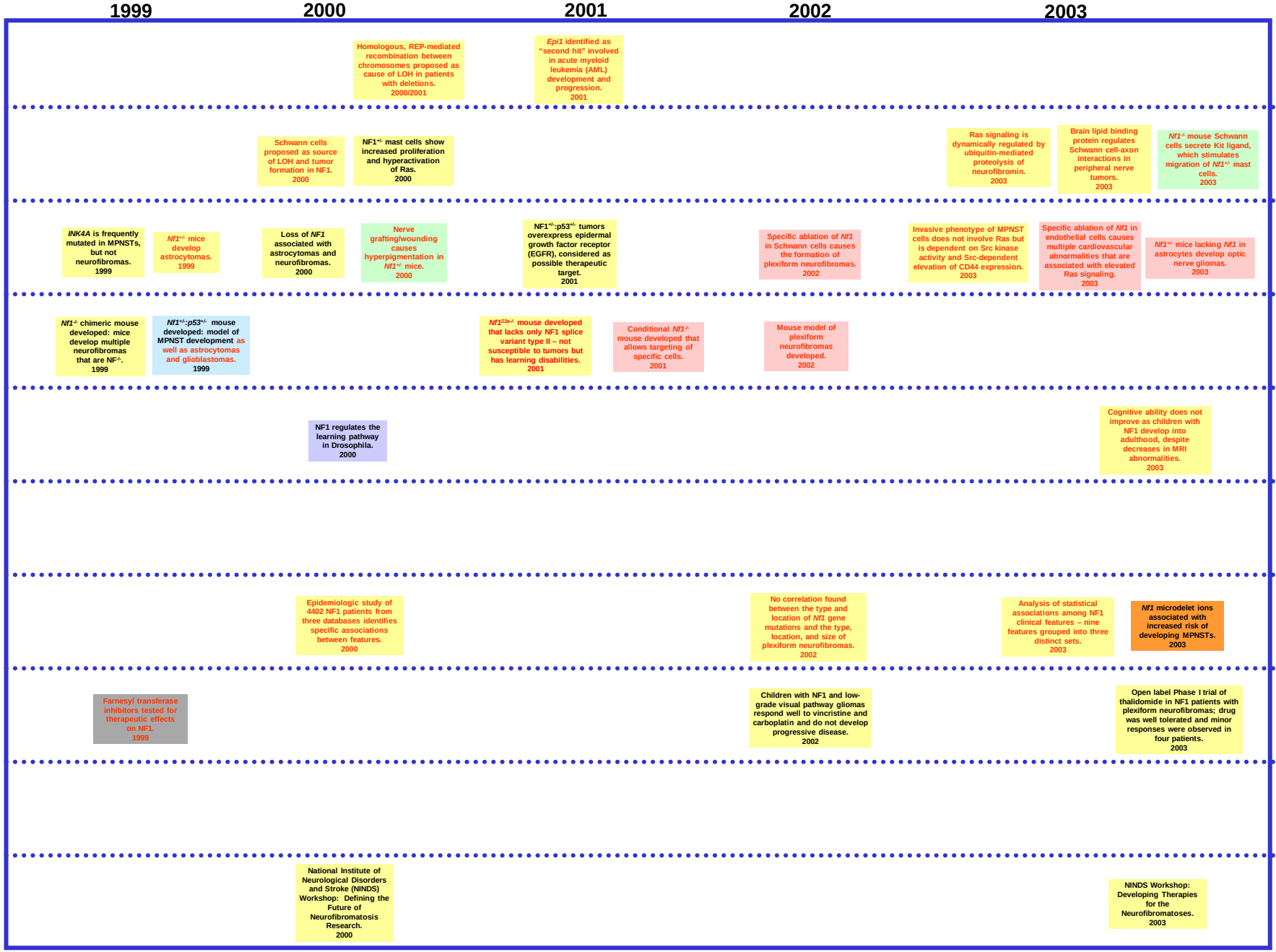

NF1

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2004 2005 2006

Molecular Biology & Genetics

Epigenetic methylation does not play a broad role in *NF1* inactivation but may be an important factor in some tumors. 2005

TATA-binding protein (TBP) and TBP-like factors (TLFs) reciprocally regulate *Nf1* transcription. 2005

Identification of a highly homologous sequence in the NF1 gene that may contain the core promoter element for Nf1 transcription. 2005

Identification of a 159-gene molecular signature distinguishing MPNST cell lines from normal Schwann cells. 2006

Cellular Biology

Nf1-deficient mast cells have reduced surface Fas antigen expression in response to Kit ligand and are resistant to Fas-ligand-mediated apoptosis. 2004

Neurofibromin contains a nuclear localization signal. 2004

Omega-3 and omega-6 fatty acids differentially modulate MPNST growth. 2005

Neurofibromin enhances cell motility and adhesion by regulating actin filament dynamics via the Rho-ROCK-LIMK2-cofilin pathway. 2005

Heterozygosity of Nf1 in endothelial and inflammatory cells augments angiogenesis, which may promote neurofibroma formation. 2005

Identification of a negative feedback signaling pathway that underlies oncogene-induced senescence, a mechanism that protects benign lesions from becoming malignant. 2006

In response to EGF, neurofibromin is phosphorylated on serine residues by PKC-alpha, which increases neurofibromin's association with the actin cytoskeleton. 2006

Neurofibromin possesses functions outside the GAP-related domain; therefore, therapies solely aimed at Ras may not be sufficient. 2006

Hyperactivation of p21ras and PI3K cooperate to alter osteoclast functions involved in the pathogenesis of NF1 bone disease. 2006

Pathobiology

Somatic inactivation of *Nf1* in hematopoietic cells causes progressive myeloproliferative disease. 2004

Expression of activated TC21/R-Ras2 enhances migration of *Nf1*-deficient mouse Schwann cells. 2004

Aberrant activation of the calcium signaling pathway by PDGF B chains contributes to MPNST formation. 2005

EGFR expression in Schwann cells causes nerve hyperplasia with occasional neurofibroma formation; reduction of EGFR expression in *Nf1*$^{+/-}$*;p53*$^{+/-}$ mice decreases tumor formation and mortality. 2005

Nf1 loss in mouse astrocytes preferentially activates K-Ras; astrocyte K-Ras activation mimics effects of *Nf1* loss in vitro and in vivo. 2005

Characterization of the natural history of optic nerve gliomas in *Nf1*$^{+/-}$ mice lacking *Nf1* in astrocytes. 2005

mTOR (mammalian target of rapamycin) pathway is activated in *Nf1* mutant optic nerve gliomas and mTOR inhibition restores normal growth in *Nf1*$^{-/-}$ astrocytes. 2005

Gastrointestinal stromal tumors in NF1 patients have a different pathogenesis than sporadic gastrointestinal stromal tumors. 2006

Technology/ Animal Models

Development of a mouse model for assessing mutagenic potential of NF1 tumor therapies. 2005

Behavioral & Cognitive Biology

Attention deficit hyperactivity disorder is the major risk factor for poor social functioning in children with NF1. 2004

Imaging, Detection, & Diagnosis

NF1 blood gene expression profiles characterized: potential diagnostic and prognostic markers. 2005

Development and clinical application of five pre-implantation genetic diagnosis protocols for NF1. 2005

Matrilin-2 identified as a specific and clinically useful biomarker for discriminating between indolent and clinically aggressive pilocytic astrocytoma. 2006

Standardized uptake values obtained by FPET is a significant parameter for prediction of survival in NF1 patients with MPNSTs while histopathological tumor grading did not predict outcome. 2006

Epidemiology

No correlation found between the development of café-au-lait spots and neurofibromas in individual body segments of NF1 patients, but the number of body segments affected is influenced by genetic factors. 2004

Deletion of the *NF1* gene responsible for disease phenotype in at least 4.4% of a cohort of 500 unrelated unselected NF1 patients. 2004

Optic pathway gliomas may present in older children with NF1 and progress years after diagnosis. 2004

Subcutaneous neurofibromas associated with increased mortality in adults with NF1; facial plexiform neurofibromas and itching associated with elevated mortality in children with NF1. 2005

Oral contraceptives do not stimulate neurofibroma growth in women with NF1. 2005

NF1 patients with internal plexiform neurofibromas were 20 times more likely to develop MPNSTs than patients without. 2005

Experimental Therapeutics

FK228, an anti-PAK1 drug, causes complete regression of MPNST xenografts. 2005

Lovastatin reverses cognitive deficits in a mouse model of NF1. 2005

Phase II trial of pirfenidone in adults for the treatment of NF1-associated tumors. 2006

Fumagillin, an inhibitor of methionine aminopeptidase 2, significantly reduces Nf1 -/- astrocyte proliferation in vitro. 2006

Phase 1 trial of the farnesyltransferase inhibitor tipifarnib for the treatment of plexiform neurofibromas in children with NF1. 2006

The MEK inhibitor PD184352 selectively induces apoptosis in malignant Schwannoma cell lines. 2006

Symptom Management

Radiation cooperates strongly with heterozygous *Nf1* inactivation in tumorigenesis. 2005

Important Meetings & Symposia

NF Clinical Trials Consortium established. 2006

NF1

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2007 → 2008

Molecular Biology & Genetics

By expressing clinically relevant human NF1 mutations and deletions in Drosophila Nf1-null mutants, it was demonstrated that the GAP-related domain of NF1 was necessary and sufficient for long-term memory, whereas the C-terminal domain of NF1 was essential for immediate memory.
2007

The somatic mutational spectrum in NF-associated MPNSTs is different from the germline mutational spectrum, indicative of the involvement of different mutational mechanisms in the germline and the somatic tissues. Subsequent inactivation of the TP53 gene is seemingly required for progression to malignancy
2008

Cellular Biology

Cytokine-induced NF1 transcription involves phosphorylation-dependent assembly of an activation complex that includes PU.1, Interferon Regulatory Factor (IRF) 2, and the Interferon Consensus Sequence-binding Protein (ICSBP/IRF8). This study provides a mechanism by which both PU.1 and IRF2 influence proliferation in differentiating myeloid cells. Clarification of such molecular mechanisms may suggest rational therapeutic targets for malignant myeloid disorders.
2007

K-ras is required for c-kit-mediated mast cell proliferation, survival, migration, and degranulation in vitro and in vivo. The hyperactivation of these cellular functions in Nf1+/- mast cells is decreased in a K-ras gene dose-dependent fashion in cells containing mutations in both loci. K-ras identified as a key effector in multiple mast cell functions and neurofibromin identified as a GAP for K-ras in mast cells.
2007

Nf1 deletion in sensory primary afferents conveys these cells with an enhanced capacity for functional collateral sprouting in response to spinal cord denervation injury. These results underline neurofibromin as a useful therapeutic target to increase the sprouting capacity of spared neurons after neural trauma.
2007

Discovery that neurofibromin/mTOR signaling regulates actin cytoskeleton dynamics and cell proliferation in astrocytes through Nucleophosmin.
2007

DdNF1 identified as an ortholog of mammalian NF1 and as a regulator of Ras activity in Dictyostelium
2008

Pak1 regulates c-Kit mediated Nf1+/- mast cell proliferation through Erk and migration through p38 pathways
2008

PKA dysregulation triggered by loss of Prkar1a causes Schwann cell tumorigenesis and loss of NF1/2 protein expression, through pathways that overlap, but are distinct from, those that cause NF1 and NF2
2008

Pathobiology

NF+/- brain microglia promote NF1-/- astrocyte growth through paracrine factors in vitro and in vivo. Hyaluronidase is one of these paracrine factors.
2007

Discovery that inactivation of Nf1 results in bowing of long bones in mice. These skeletal defects were attributed to immature development of osteoblasts lacking the neurofibromin gene.
2007

Identification of EGFR+ cells within human neurofibroma that form colonies and spheres, undergo multilineage differentiation, and grow in nude mice, and EGFR+ cells in DhhCre;Nf1^{lox} GEM-neurofibromas form EGFR-dependent, multipotent spheres
2008

Technology/ Animal Models

Unique profile of gene expression opens the mouse pheochromocytoma model to new applications pertinent to neural stem cells and suggests potential new targets for treatment of pheochromocytomas or eradication of their precursors.
2007

Rac1 critically contributes to increased osteoclast function induced by haploinsufficiency of Nf1 and implicates Rac1 as a rational therapeutic target for osteoporosis.
2007

Neurofibromin regulates longevity and stress resistance through cAMP regulation of mitochondrial respiration and ROS production, and NF1 may be treatable using catalytic antioxidants.
2007

Development of a practical, reproducible NF1 tumor xenograft model by transplantation of the human NF1 tumor-derived Schwann cell line, sNF94.3, into the peripheral nerve of SCID mice. Like human NF1 plexiform neurofibroma, intraneural sNF94.3 xenografts displayed hypocellularity, a low proliferative index, an extracellular matrix-rich stroma, and basal laminae. This is the first xenograft model allowing the properties of human NF1 tumor-derived cells to be examined in a relevant cellular environment.
2007

NF1 regulates hypothalamic function and pituitary development in the mammalian CNS by modulating intracellular cAMP levels.
2008

Nf1+/- mice lacking Nf1 in astrocytes recapitulates genetic and cellular abnormalitieis seen in human NF-1 optic glimoas.
2008

Behavioral & Cognitive Biology

The deletion of NF1 in inhibitory neurons causes learning disabilities due to increases in GABA release, an effect reversed with GABA antagonists. Nf1 modulates ERK/synapsin I-dependent GABA release, which modulates hippocampal long-term potentiation and learning.
2008

Imaging, Detection, & Diagnosis

Longitudinal study shows value of volumetric MRI to measure changes in plexiform neurofibromas.
2007

Individuals with NF1 have a unique generalized skeletal dysplasia, predisposing them to localized osseous defects. Dual energy X-ray absorptiometry may prove useful to identify individuals with NF1 who are at risk for clinical osseous complications, and monitoring therapeutic trials.
2007

Biomarkers CUGBP2, IFNGR, INFGR1, and RANBP9 proteins are expressed in NF1-Pilocytic astrocytomas (PA) and not in sporadic –PAs.
2008

Epidemiology

Experimental Therapeutics

Oncolytic herpes simplex virus (HSV) and EGFR inhibitor, erlotinib, inhibit tumor growth and angiogenesis in an MPNST mouse model.
2007

Sorafenib, a B-Raf inhibitor, inhibits MPNST proliferation and MAPK signaling. Based on preclinical data, sorafenib is in a multicenter Phase II clinical trial for NF-1 MPNST.
2008

Rapamycin, an inhibitor of mTOR, suppresses the growth of MPNSTs in NF1+/-p53+/- mice.
2008

mTOR inhibitor RAD001 (Everolimus) delayed tumor growth of NF1 patient MPNST cell and sporadic MPNST STS26T cell xenografts.
2008

Symptom Management

Important Meetings & Symposia

NF1

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