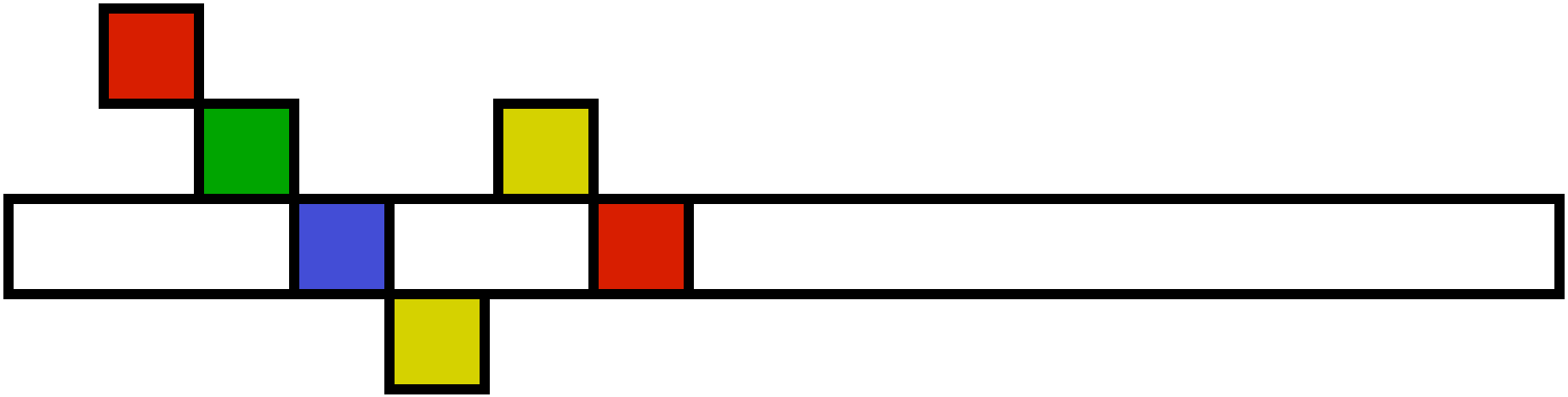

# When Neurofibromatosis 1 (NF1) Tumor Suppressors Fail: Banking the Ras Connection

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# Physiology

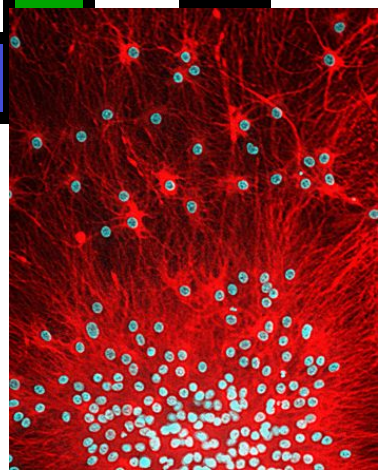

Fig 1

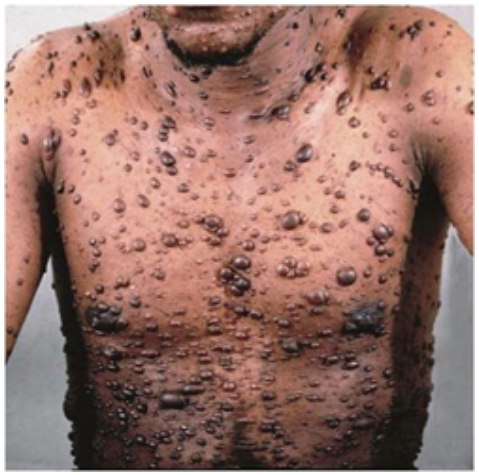

Fig 2

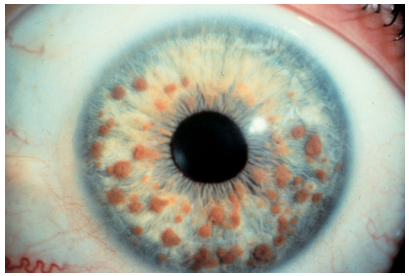

Fig 3


Fig 4

- Most common cancer predisposition syndrome: 1:2500 incidence.
- Also known as von Recklinghausen disease.
- Extreme clinical variability, multisystem disorder.
- Peripheral nervous system target: Chronic malignant lesions occur in nerve sheaths, specifically Schwann cells.
- Early childhood~late adulthood onset; malignancies eventually lethal.
- Café au lait spots and freckling, skin lesions, osseous (bone) lesions.
- Neurofibromas on skin, Lisch nodules in eye, optic gliomas (tumors).
- Common complications are cognitive/learning disability, chronic pain.

# Molecular Cause

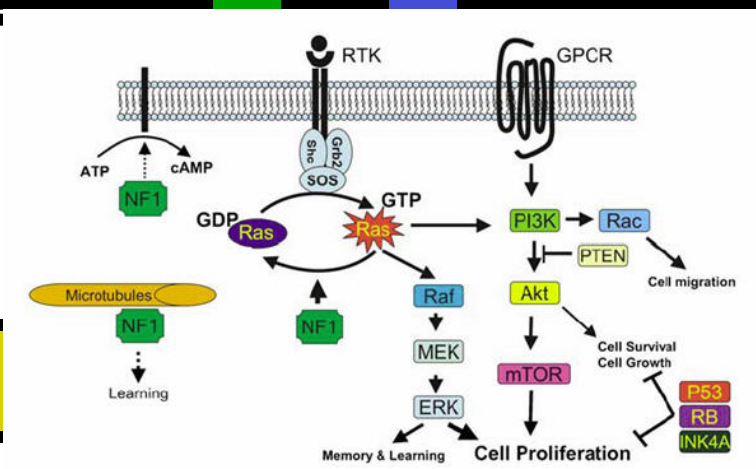


Fig 5

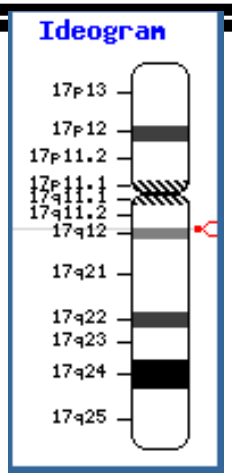


Fig 6

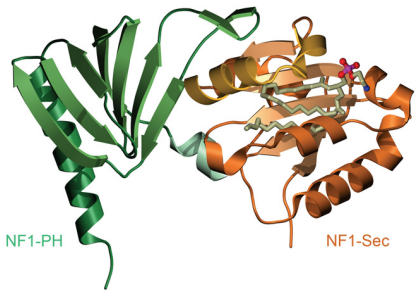


Fig 7

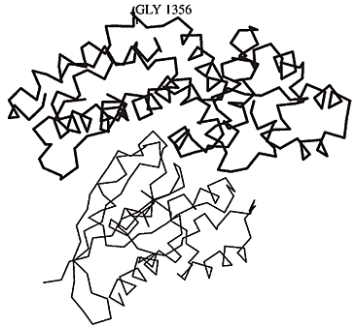


**Figure 1** - Cα-backbone for the complex NF1(E1356G)-Ras, showing the G1356 position in the structure. NF1 is drawn with thick lines and Ras with thin lines.

Fig 8

- NF1 is a natural Tumor Suppressor in humans.
- Transmission: Autosomal Dominant Loss-of-Function; only one mutated NF1 allele is sufficient for disease manifestation. Disease paradigm is extremely similar to that of Retinoblastoma (Rb). Spontaneous mutation and mosaic manifestations are common.
- Most common mutations are on long arm of chromosome 17, location 17q11.2; premature exonic stop codon truncates NF1 protein.
- Overactivated Ras (K-ras) is implicated in 30% of human tumors.
- NF1 is a natural downregulator of Ras activity; NF1 temporally holds Ras in an inactive, GDP-bound state. The absence of NF1 allows Ras to remain GTP-bound, super-active. This lack of NF1 promotes tumorigenesis, as GTP-Ras is a potent stimulator of cell division.

# Treatments/Risks and Limits

- NF1 disease is unpredictable and there is no cure.
- One-step-ahead approach to symptoms and presentation.
- Must manage disease with a team of specialists.
- Multidisciplinary clinics specialize in NF.
- Malignant peripheral nerve sheath tumors and surrounding healthy tissue must be removed with surgery.
- Obtrusive skin lesions are removed surgically, but tend to grow back.
- Social isolation due to disfigurement and attention deficit/cognitive delay both require constant psychological care and monitoring.
- 3 drugs are currently being tested to interfere with NF-1 based disease.
- They are all farnesyltransferase inhibitors, and work in a compensatory manner to diminish hyperactive GTP-Ras activity by preventing it from localizing to the inside of the cell membrane where Ras typically resides.
- No drugs have made phase II clinical trials, but Lovastatin (similar to Lipitor) and Imatinib (Gleevec, for leukemia) are in phase I trials.

# Proposed Cure/Limits

- There has been an active effort to generate a viable NF1 mouse knockout because it would allow a model for drug development.
- *Mus musculus* NF1 is 99.2% identical to *Homo sapiens* NF1.
- Double NF1 ("traditional" homozygous) knockouts in mice are consistently embryonic lethals.
- NF1 heterozygous mouse mutants are viable but are extremely susceptible to tumorigenesis, and show overactivation of Ras and related pro-proliferative molecules. NF1 mutant chimeras develop similar tumorigenic phenotypes at the site of the affected cells. Scientists are developing tissue-specific conditional NF1 knockouts in mice that allow the mutant phenotype to be switched on or off.
- Proposal is to first deliver potent molecular inhibitors of Ras to all three of the above mouse models.
- Scientists have demonstrated successful inhibition of mutant K-ras in pancreatic carcinomas using RNA interference.
- The inhibitor of choice should be dsRNA interference: RNA Interference Silencing Complex (RISC) dicer silences the translation of an mRNA; while RNAi delivery can be a problem, if targeting the overactive Ras in these mouse models made their tumors recede, this would suggest a compensatory intervention for human NF1 patients based on the mouse response.
- Submit successful RNAi-Ras sequences for clinical trials upon NF1 humans.

# References


**Physiology slide:**

Content:

->Thompson 7th edition (2007) pp 292-293

->http://www2.mdanderson.org/depts/oncolog/articles/09/11-12-novdec/11-12-09-1.html
Chalaire, D.: Treating Neurofibromatosis; OncoLog: November-December 2009, V 54 No 11-12

->http://en.wikipedia.org/wiki/Neurofibromatosis_type_I

->http://www.cdc.gov/ncbddd/bd/nf1sonja.htm
excerpt from American Journal of Epidemiology 2000; 151: 33-40.

Images:

Skin Lesions and Face tumor (figures 2 and 4):
http://www2.mdanderson.org/depts/oncolog/articles/09/11-12-novdec/11-12-09-1.html

Mouse schwann cells (figure 1):
www.curingdeath.com/Archives/February_2008.asp

Lisch nodules in iris (figure 3):
usmlemd.wordpress.com
1189694-1219222-34.jpg

**Molecular Slide:**

Content:

-> Thompson 7th edition (2007) pp 292-293

->
www.ncbi.nlm.nih.gov
-mapview search for Neurofibromatosis 1; screentraps of chromosome 17 data

->
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1531708
-Guttmann, DH and M Giovannini: Mouse Models of Neurofibromatosis 1 and 2: Neoplasia 2002 July 4(4): 279-290.

->
http://hmg.oxfordjournals.org/cgi/content/short/ddl114v1?ck=nck
-Li et al: Neurofibromin is a Novel Regulator of Ras Induced Signals in Primary Vascular Smooth Muscle Cells: Human Molecular Genetics (advanced online access published April 27, 2006): doi: 10.1093/hmgddl114

-> http://www.nature.com/nature/journal/v410/n6832/abs/4101111a0.html
-Johnson et al: Somatic activation of the K-ras oncogene causes early onset lung cancer in mice: Nature 410, 1111-1116 (26 April 2001): doi:10.1038/35074129

**Molecular Slide:**

Images:

Pathway (figure 5) from Le and Parada: Oncogene 26, 4609-4616 (12 July 2007) | doi:10.1038/sj.onc.1210261
http://www.nature.com/onc/journal/v26/n32/fig_tab/1210261f2.html

Chromosome (figure 6)
www.ncbi.nlm.nih.gov
-trap of mapview search for NF1 on chromosome 17

NF1 subunit structure (figure 7)
www.embl.de/research/units/scb/scheffzek/402.jpg

NF1 plus Ras complex (figure 8)
www.scielo.br/img/revistas/gmb/v27n3/a03fig01.gif

**Treatment Slide:**

Content:

->Thompson 7th edition (2007) pp 292-293

->http://www2.mdanderson.org/depts/oncolog/articles/09/11-12-novdec/11-12-09-1.html
Chalaire, D.: Treating Neurofibromatosis; OncoLog: November-December 2009, V 54 No 11-12

->http://en.wikipedia.org/wiki/Neurofibromatosis_type_I

Proposal slide:

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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1531708
-Guttmann, DH and M Giovannini: Mouse Models of Neurofibromatosis 1 and 2: Neoplasia 2002 July 4(4): 279-290.

->
http://www.ninds.nih.gov/news_and_events/news_articles/news_neurofibroma_mouse_model.htm
-New Mouse Model for Neurofibromatosis Yields Insights into Disease Process and Treatment: April 2008

->
http://www.ncbi.nlm.nih.gov/pubmed/17106254
Zhu et al: Small Interfering RNAs targeting mutant K-ras inhibit human pancreatic carcinoma cells growth in vitro and in vivo.: Cancer Biol Ther. 2007 Feb:6(2): 293-4