



Report from the  
**8th Biennial Medical Symposium on VHL**

Roskilde, Denmark  
4-6 September 2008

Joyce Wilcox Graff,  
Executive Director



## Agenda

- Who We Are
- Basic Science
- Clinical Management
- Living with VHL
- People who made it happen



## Some background . . .

- 1971 Knudson tumor suppressor gene hypothesis
- 1988 VHL gene mapped to chromosome 3p25-26
- 1993 Identification of the VHL gene
- 1994 VHL gene mutations in sporadic clear cell RCC
- 1994 Reliable methods to detect VHL gene mutations
- 1995 VHL gene mutations correlate with phenotype
- 1998 Reliable methods to detect VHL gene deletions

### Biochemistry:

- 1995 VHL protein forms a complex with Elongin and other proteins
- 1999 Crystal structure VHL-Elongin complex
- 1999 VHL is an E3 ubiquitin ligase
- 1999 VHL regulates HIF protein levels



## Mechanisms to achieve oxygen homeostasis

- Increased glucose uptake and glycolysis
  - Induction of cell survival factors
  - Vasodilation (expanding the blood vessels to carry more blood)
  - And if this state of hypoxia persists,
  - Vascular remodeling and angiogenesis (building more blood vessels to bring more oxygen)
  - Erythropoiesis – building more red blood cells to carry more oxygen to the internal organs
- HIF plays a role in the aggressiveness of all cancers, and VHL plays a role in regulating HIF.



## Cancer-associated genes

### Oncogenes

Normal protein function is to stimulate cell proliferation  
Mutational **ACTIVATION** results in uncontrolled cell proliferation

### Tumor Suppressors

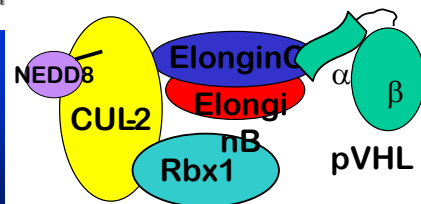
Normal protein function is to suppress cell proliferation  
Mutational **INACTIVATION** results in uncontrolled cell proliferation

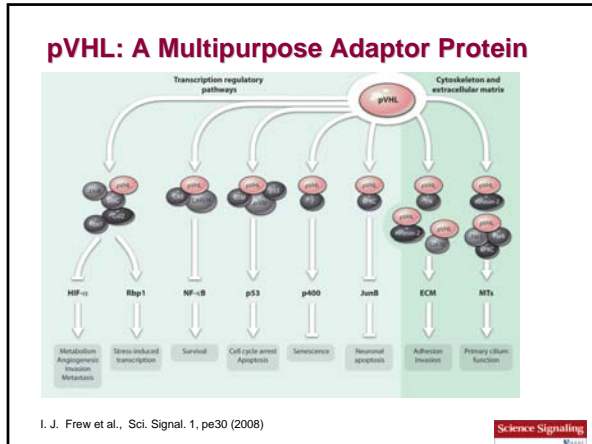
### DNA Repair Genes

Normal protein function is to repair DNA damage  
Mutational **INACTIVATION** results in genome instability

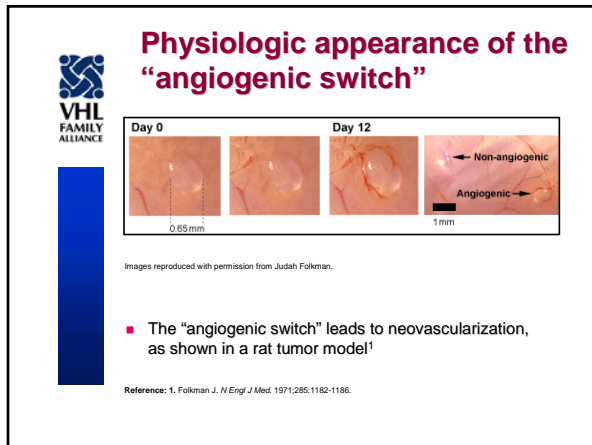


## The pVHL E3 Ubiquitin Ligase Complex

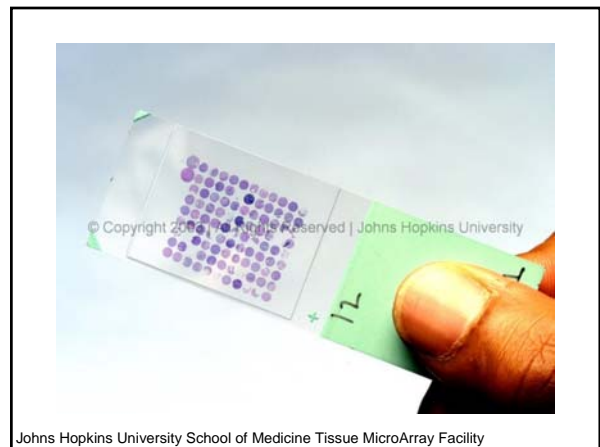
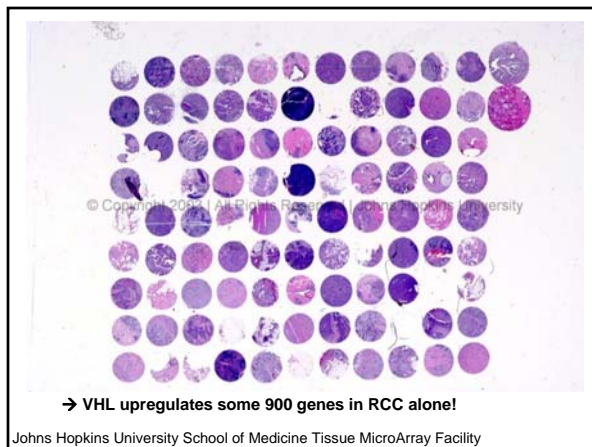




- ### Significant VHL Findings
- #### Cell Biology
- 1996 Molecular link between VHL and angiogenesis
  - 1998 VHL associates with fibronectin
  - 1999 VHL controls cell motility and invasion
  - 2001 VHL regulates cell-cell and cell-extracellular matrix interactions
  - 2006 VHL regulates primary cilium formation and cystogenesis
  - 2008 VHL associates with collagen



- ### Drug development
- 2005 Sorafenib (VEGF R small molecule inhibitor) approved by FDA for advanced RCC
  - 2006 Sunitinib (VEGF R small molecule inhibitor) approved by FDA for advanced RCC
  - 2007 Temsirolimus (mTOR inhibitor) approved by FDA for advanced RCC





### What do these animals have in common?

- Fruit fly
- Earthworm
- Sea urchin
- Zebra fish
- Mouse
- Rat
- Dog
- Human



### Summary of Thursday

- Dr. Peter Maxwell noted that when he began attending these meetings ten years ago we were only beginning to understand what VHL did. Now we know a number of additional steps in the many pathways where VHL plays a role. We have learned a great deal, which in turn has taught us more about what we don't know.



### Clinical Management

- Types of VHL
  - Percentage risk varies, but none are zero.
- Genotype/phenotype alignment is helping us understand the biochemical mechanisms



### Dr. Maher and the UK registry

- 40% of "sporadic" pheo patients proved to have an underlying VHL mutation.
- Of 198 people diagnosed with sporadic hemangioblastoma, 4% had VHL mutations; more may have been mosaic
- Among people in the registry who had familial clear cell renal cancer (ccRCC), he found considerable underlying VHL, 4% BHD (with a folliculin mutation), and a few SDHB mutations.



### Genotype/phenotype alignments

- This year added Brazil, India
- 43 families in Brazil
  - 50% de novo
- 4 families in Kerala, India
  - No retinal tumors



### Familial Pheochromocytoma

- Hartmut Neumann of Germany has DNA mutation information on 1331 patients with symptomatic pheochromocytoma and/or paraganglioma, and 271 non-syndromic pheos.
  - RET 7%
  - VHL 13%
  - SDH 6%
  - SDH 2%
  - SDHD 6%
  - NF1 4%
- Total with any mutation 37%





## Founder Effect

- Dr. Giuseppe Opocher is studying an Italian family
  - He believes it to be a family of German origin that immigrated to Italy about AD1400 when some mines were discovered.
  - This same mutation has also been seen in Germany and Poland, which may be other branches of this same family.



## Dr. Kim on ELST

- All ELST will eventually lead to sudden or step-wide progressing hearing loss, not related to size. The goal should be to detect ELST early, especially when they are small and hearing is still present. At that point they may be treating surgically and the hearing preserved.
- More tumors tend to develop on the left than on the right. In his series of 22 patients since 1998, 86% have hearing loss, 52% severe and profound, 55% sudden and step-wise, and one bilateral. He performed a complete resection in 20 ears. There was some postoperative dizziness and vertigo (sometimes delayed) which can be treated as for Meniere's.



## Dr. Hammel on Pancreas

- **Pascal Hammel of France** reported on endocrine tumors of the pancreas. In the French series, 75% of VHL patients have pancreatic involvement
  - 90% have isolated or multiple cysts
  - 12% have serous cystadenomas
  - 12-17% have pancreatic neuroendocrine tumors (PNET)
- In order to determine whether or not it is a PNET, he uses ultrasound and CT, and sometimes somatostatin receptor scintigraphy (SRS). SRS is positive in 59% of cases (versus more than 80% among sporadic PNET)
- The size of the tumor is not a clear indicator of its nature.
- Fine needle aspiration may also be used to characterize the tumor.
- Malignancy is frequent among PNETs. About 25% have liver metastases, about one-third are very locally aggressive tumors that may invade the duodenum, aggressive but not metastatic.
- He advises only to resect a dangerous lesion the small ones can be left in order to preserve pancreatic function.
- He is beginning clinical trials with Sunitinib.



## Predicting outcome of RCC

- **Yin Hunang** from Dr. Nakamura's lab in Kyoto, presented a three-gene expression signature which he has determined can predict the clinical outcome of clear cell renal cell carcinoma (ccRCC).
- By evaluating the levels of VCAM1, EDNRB, and RGS5 they have been able to predict the outcome for people with ccRCC.
- They are evaluating additional candidate genes in an effort to improve their scoring model.



## Cost/benefit of screening

- The Danish group has done some very interesting evaluations of the cost/benefit of screening, to evaluate the recommended frequency of screening.
  - After examining the medical records of the 59 patients in the study, they determined that the risk of CNS manifestations was twice as great (6%) after 24 months than after 12 (2%) or 15.5 (3%) months.



## Living with VHL

- Patients have access to more information today than ever before
- General information is nice, but you need the doctor to put this into context in YOUR situation
- Patients and physicians must form constructive partnerships



## Psychosocial Issues

- Clinical genetics in Sydney, Australia is piloting a questionnaire
- They would love to have international participation
- Measuring quality of life, and accompanying complaints
- Chantal Lammens of the Netherlands and Frauke Pelz of Wales are also studying these effects.



## Issues to Debate this Year

- Are changes needed for the screening protocol?
- Changes to the pancreas section
- When to begin screening?
  - US and Sweden both have several children with serious eye involvement by age 5.



## Who We Are

Families and Health Care Professionals working together

## Our Mission

to improve diagnosis, treatment, and quality of life for individuals and families affected by von Hippel-Lindau



## People Who Made it Happen

- Marie Luise Bisgaard, MD
- Vibeke Harbud
- Richard Harbud
- Many wonderful presenters
- One hundred twenty-four people from 16 countries on five continents
  - 82 people from 10 countries of Europe, 17 from the U.S., 2 from Canada, one from Brazil, 4 from Australia, 5 from Japan, 2 from China, and for the first time, one from India.
- Thanks to Dr. Jim Gnarra for several slides



VHL Family Alliance

Joyce Wilcox Graff  
[director@vhl.org](mailto:director@vhl.org)  
[www.vhl.org](http://www.vhl.org)



## Questions?

Joyce Wilcox Graff

[director@vhl.org](mailto:director@vhl.org)

[www.vhl.org](http://www.vhl.org)



## **Teamwork for Health**

Families and Health Care Professionals  
working together  
to improve diagnosis, treatment, and  
quality of life  
for individuals and families  
affected with von Hippel-Lindau

**VHL Family Alliance**