

# VHL Research Awards 2014-2015

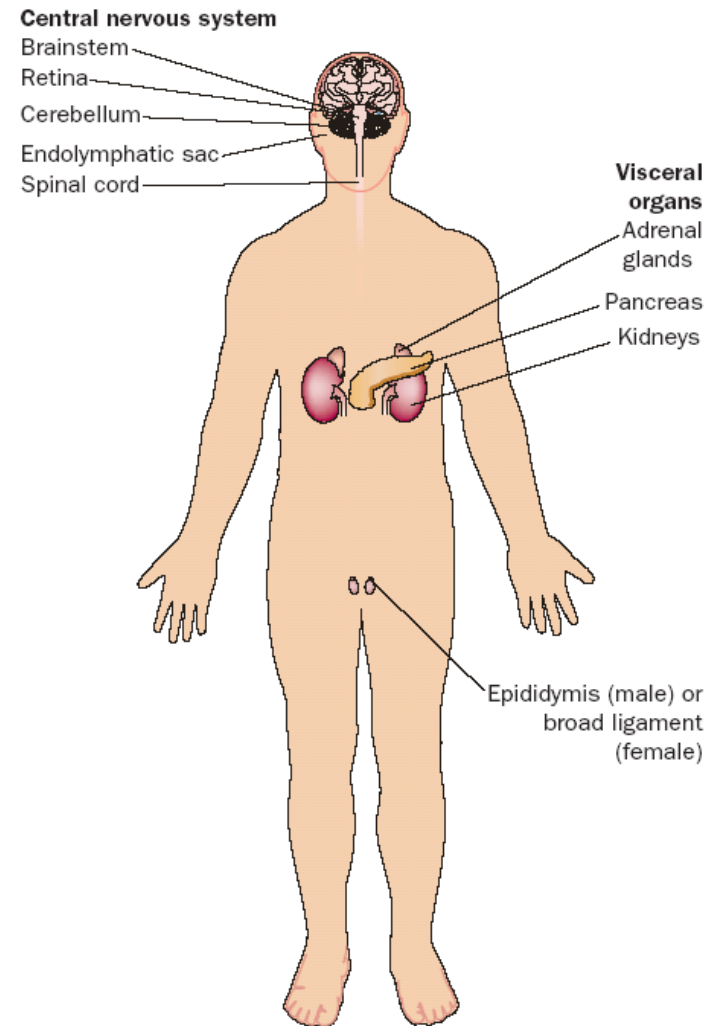
Eric Jonasch

Chair, VHL Research Council

# VHL Is a Multisystem Disorder

*Induces Blood Vessel Rich Cancerous and Noncancerous Tumors*

Malignant	Nonmalignant
Renal Cancer	Renal Cysts
Pancreatic Neuroendocrine Tumor	Pancreatic Cysts
Pheochromocytoma (rare)	Pheochromocytoma
	Hemangioblastomas (Retinal, Cerebellar, Spinal)
	Endolymphatic Sac Tumors
	Epididymal Cysts



# Coming Up With A Cure: Many Layers of Knowledge are Needed!



Identification of the VHL  
Gene



Description of VHL  
Protein Function



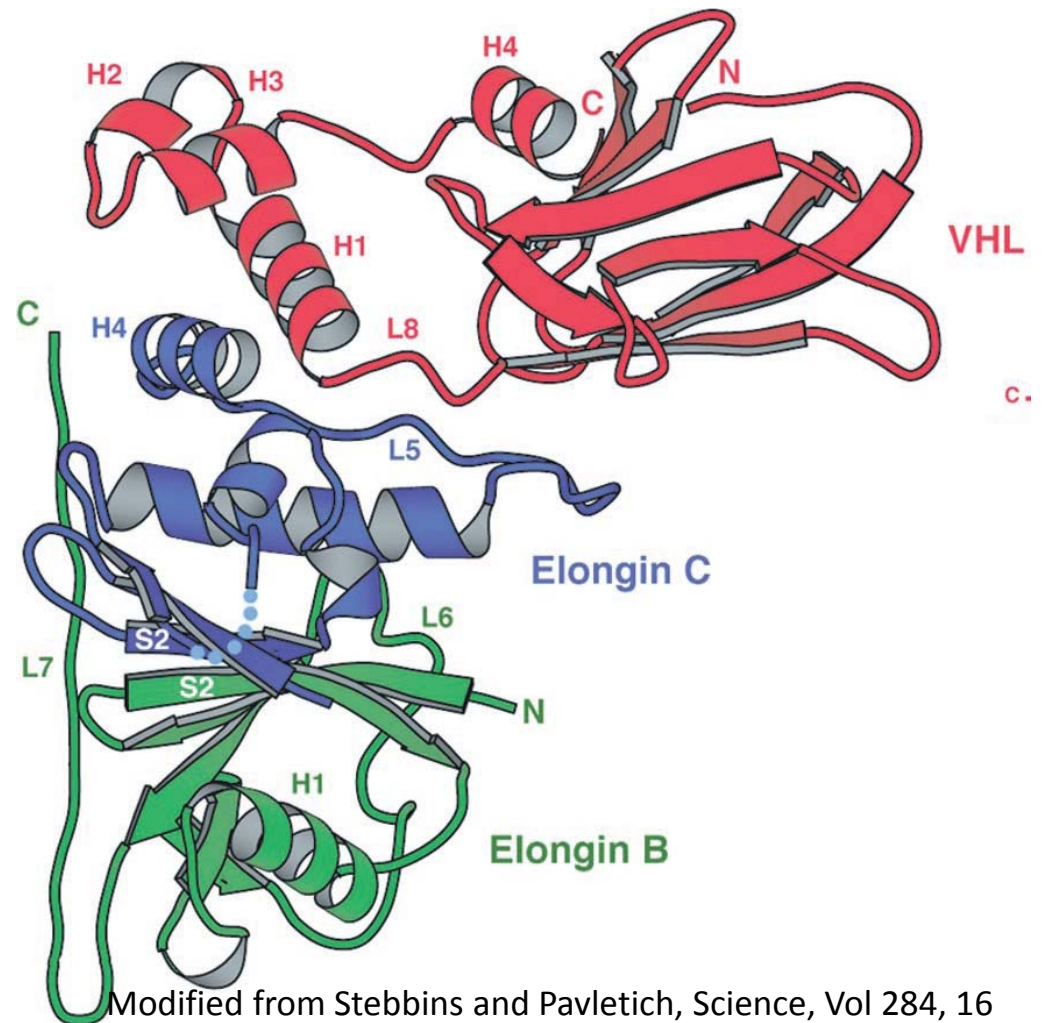
Identifying and Characterizing Additional  
Genes Disrupted in VHL Disease



Development of Relevant Model Systems

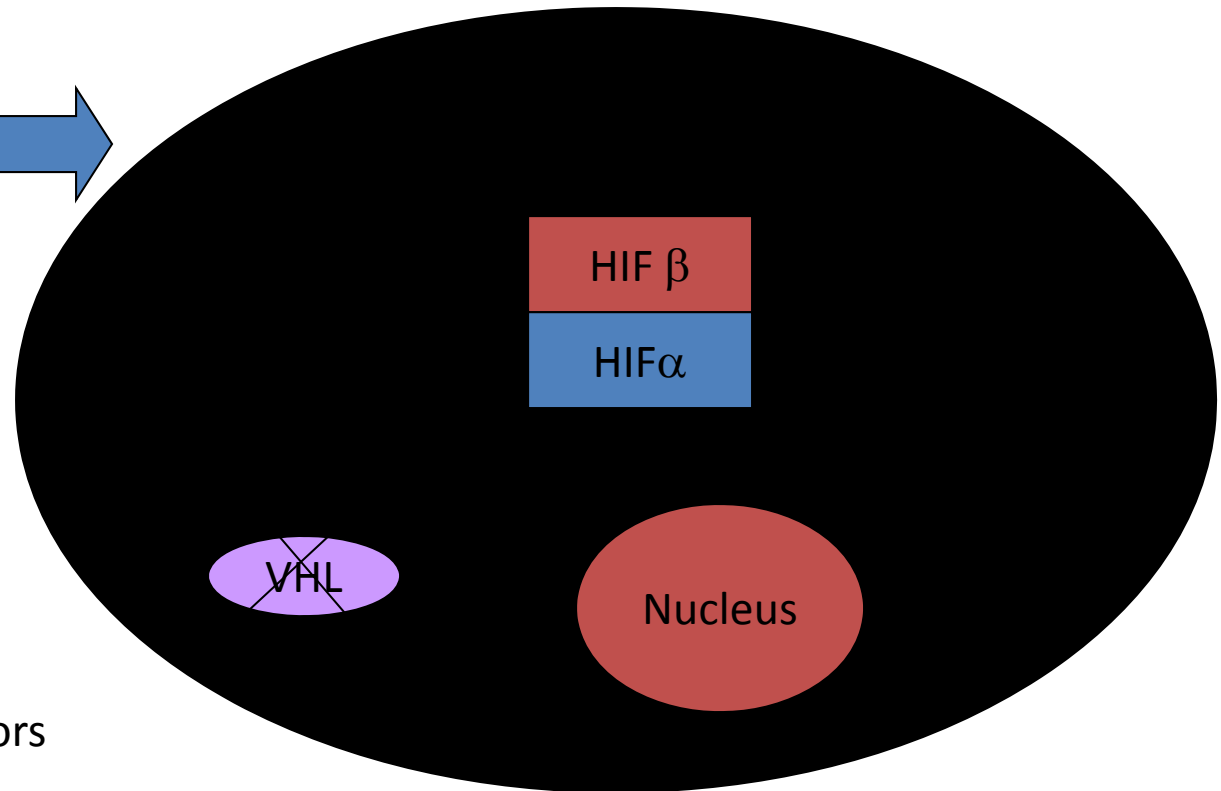
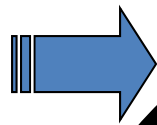
# VHL Gene and Protein

- On chromosome 3p25
- 213 amino acid protein
- Binds to Elongin C/B
- Forms “VBC complex”



Modified from Stebbins and Pavletich, Science, Vol 284, 16 April 1999

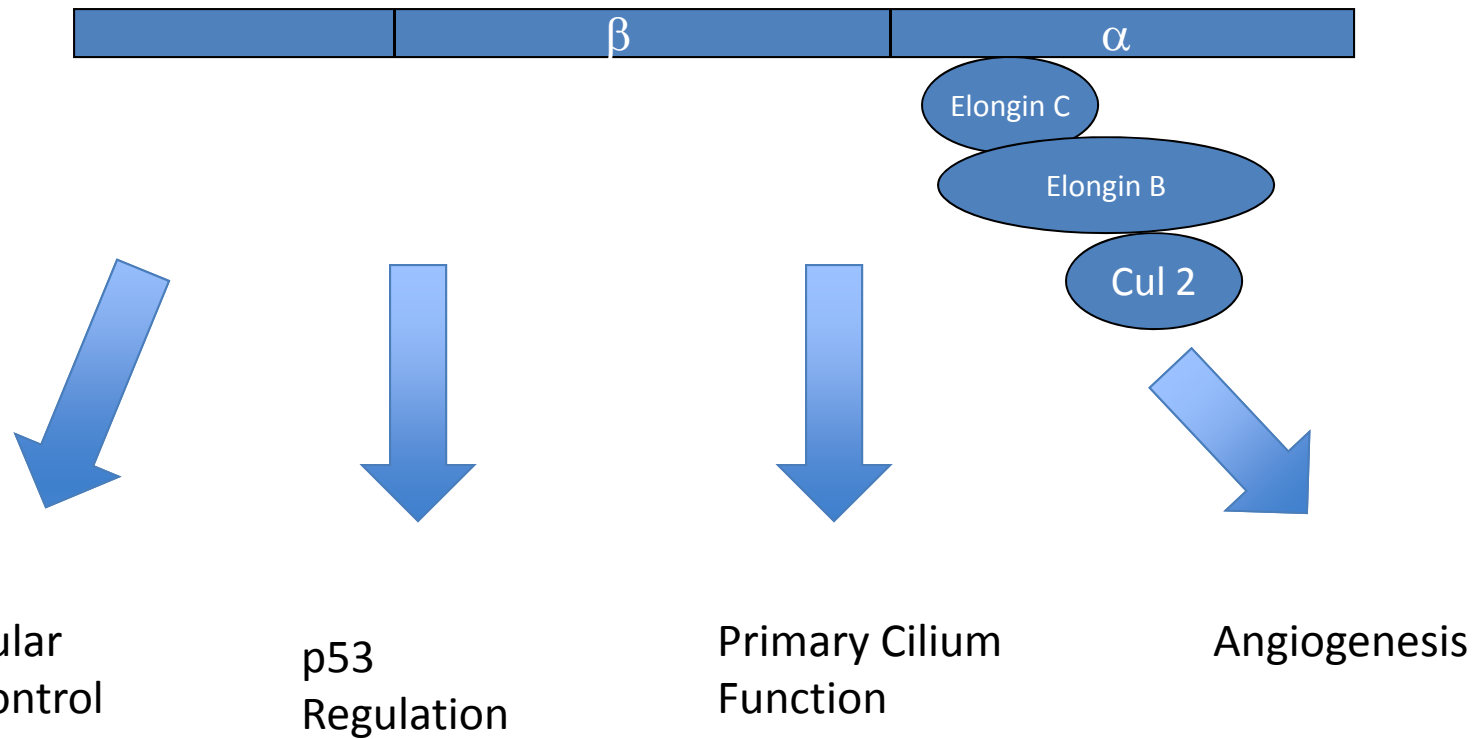
Low Oxygen  
Or Mutation



Generates  
VEGF  
Other angiogenic factors

*We have drugs that target VEGF pathway upregulation,  
including Votrient, Sutent and Avastin*

# VHL- A Regulatory Hub



Ohh et al, Mol Cell, Vol 1, 959-968, 1998

Roe and Youn Mol Cell May 2006

Thoma et al Nature Cell Biology Aug 2009

Pugh et al Nature Medicine 2003

Kurban et al, Cancer Res 2006; 66: (3).

Kuehn et al Ca Res May 15, 2007

Kerbel NEJM May 2008

# And It's Not Only *VHL* That is Mutated!

- Renal Cell Carcinoma:
  - *SETD2, PBRM1, BAP1*
- Hemangioblastomas:
  - *HNF1B*

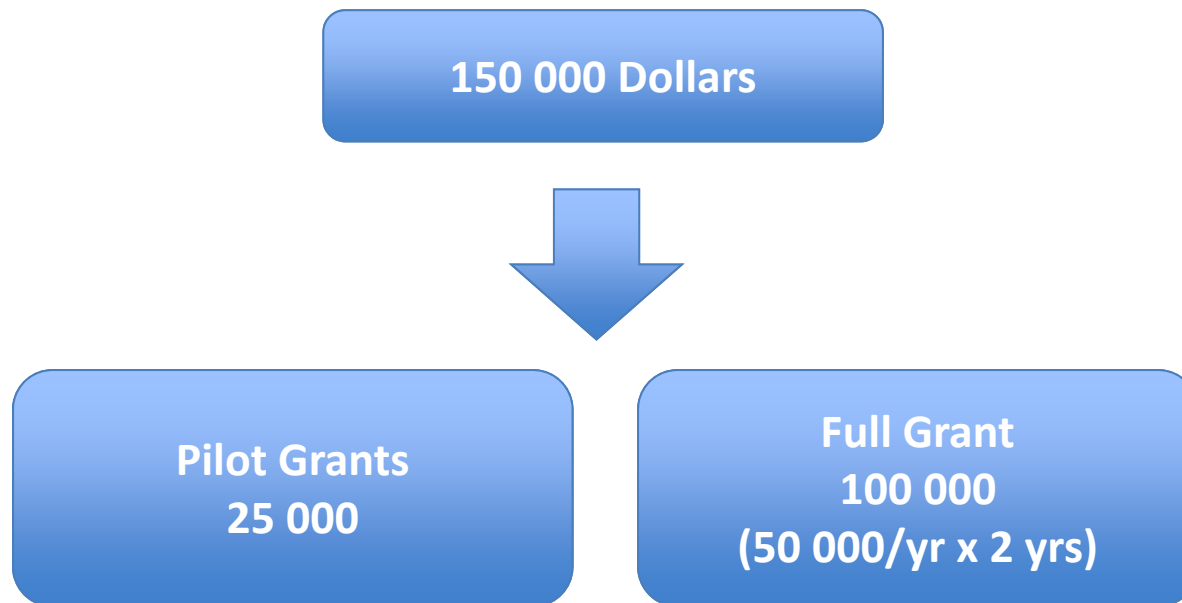
*Knowing how these genes interact will be critical to fully understanding VHL disease and develop relevant model systems*

# What Do We Need?

1. New ways to either replace or repair defective VHL function
2. An analysis of the other “broken” genes that conspire with VHL loss to cause tumors
3. Model systems that replicate organ specific manifestations



# Research Grants 2014



# Research Grants 2014

Request for Letters of  
Intent June 2014

3 Pilots and 11 Full Applications Received

Review for  
Compliance/Significance  
and Invite Full Grant  
Submission  
July 2014

3 Pilots and 9 Full Applications Invited

Send out Grants for  
Independent Review  
(3 reviewers per grant)  
August 2014

Final Decision:  
Research Council  
Executive  
Sept 2014

# Awards 2014

## **Pilot Project**

*Danny Segal, PhD*

“A novel chemical chaperone for treating the VHL cancer syndrome”



## **Full Proposal**

*Othon Iliopoulos, MD*

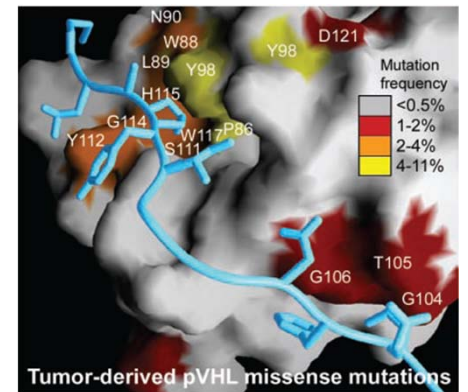
Zebrafish Based Discovery of VHL Disease Targeting Drugs”



# Daniel Segal: Fixing Broken VHL

Tel Aviv University, Tel Aviv

- Some mutant VHL proteins can still function but are broken down very quickly by the cell.
- Finding ways to stabilize these VHL proteins may act as a therapy.
- Dr. Segal will study a candidate substance, D-Arginine, which may repair VHL function in a subset of patients.



# Othon Iliopoulos: VHL Models and Novel Therapeutics

Massachusetts General Hospital, Boston MA

- Zebrafish are tiny fish that can be genetically modified
- VHL mutation in zebrafish can represent aspects of human biology
- Dr. Iliopoulos will use zebrafish to discover new drugs that may rescue consequences of *VHL* mutation.



# Past Present and Future

Identification of the VHL Gene



Targeting VHL Gene Deficiency



Identifying and Characterizing Additional Genes Disrupted in VHL Disease

