VHL Research Awards 2014-2015

Eric Jonasch
Chair, VHL Research Council
VHL Is a Multisystem Disorder

Induces Blood Vessel Rich Cancerous and Noncancerous Tumors

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Nonmalignant</th>
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</thead>
<tbody>
<tr>
<td>Renal Cancer</td>
<td>Renal Cysts</td>
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<tr>
<td>Pancreatic Neuroendocrine Tumor</td>
<td>Pancreatic Cysts</td>
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<tr>
<td>Pheochromocytoma (rare)</td>
<td>Pheochromocytoma</td>
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<tr>
<td></td>
<td>Hemangioblastomas (Retinal, Cerebellar, Spinal)</td>
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<td></td>
<td>Endolympathic Sac Tumors</td>
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<tr>
<td></td>
<td>Epididymal Cysts</td>
</tr>
</tbody>
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Lonser et al, Lancet 2003
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

Extracellular Matrix Control

p53 Regulation

Primary Cilium Function

Angiogenesis

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

Kuehn et al Ca Res May 15, 2007

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

Pugh et al Nature Medicine 2003

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

150 000 Dollars

Pilot Grants
25 000

Full Grant
100 000
(50 000/yr x 2 yrs)
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