Eric Jonasch, MD, Professor in Genitourinary Medical Oncology at the University of Texas MD Anderson Cancer Center discussed the most recent research projects to which the VHL Alliance has awarded grant funding. The goal is to advance our scientific understanding of VHL disease by

1) increasing our understanding of how VHL affects the cell;
2) permitting the creation of model systems that better mimic the organ involvement of VHL; and
3) developing improved screening and treatment approaches for people living with VHL.

VHLA grants come in two sizes: a one-year $25,000 pilot grant and a two-year $100,000 research grant. Each research proposal is evaluated on rationale, approach, and significance.

**2014 Pilot Grant Awardee: Dr. Danny Segal, Tel-Aviv University**
Dr. Segal's team is trying to see if readily available materials like the amino acid arginine can be used to help refold misfolded VHL. This is especially promising because 1/3 of all VHL mutations are point mutations which mean they only have one error to fix.

**2014 Full Grant Awardee: Dr. Othon Iliopoulos, Massachusetts General Hospital**
Dr. Iliopoulos’ team uses zebrafish with VHL to screen drugs that may help treat people with VHL. Zebrafish with the VHL gene deleted display a number of VHL lesions similar to those seen in people. Since these tiny fish are relatively transparent, you can actually “see” the effect that potential drugs have on the VHL manifestations.

**2015 Pilot Grant Awardee: Dr. Horst-Shrivers, University Medical Center in Groningen, Netherlands**
Dr. Horst-Shrivers’ team is trying to understand if hormones produced by pheochromocytomas can be reliably measured in saliva. If successful, this would enable VHL patients to screen for pheos using a “spit in cup” method instead of the 24-hour urine test or the blood test which requires you to rest for 30 minutes before the blood draw.

**2015 Full Grant Awardee: Dr. Ian J. Frew, University of Zurich**
Dr. Frew's team is using a mouse model to test drugs that may be able to treat clear cell renal cell carcinoma (ccRCC), a type of kidney cancer that frequently affects VHL patients. This research will be used to guide new trials in people with VHL or other patients with noninherited ccRCC.

**2016 Pilot Grant Awardee: Dr. Raymond Kim, University of Toronto**
Dr. Kim will head the international VHL-IT Sharing International Consortium (VISIon) with the goal of developing a more efficient approach to collect information on VHL mutations and the way that VHL manifests in these individuals. This will help us better understand genotype-phenotype patterns (ie: which mutations cause which manifestations).

**2016 Full Grant Awardee: Dr. Michael Gorin, University of California Los Angeles**
Dr. Gorin will work on developing two new models to study VHL retinal lesions. One model will use inducible pluripotent stem cells. This means that undifferentiated somatic cells (ie: undifferentiated skin cells, blood cells) can be trained to act as a cell in the eye. The other model involves a VHL knockout mouse which will allow us to better understand how retinal hemangiomas form and develop new strategies for blocking the formation of these retinal tumors.

**CGIP: Cancer in our Genes International Patient Databank**
This is gives VHL patients an opportunity to contribute their own information. With more people participating longitudinally, we can better understand the natural history of the disease. One finding from the databank already is that the dry mouth, canker sores, and other oral health issues are seen at a higher incidence in VHL patients than they are in the general population. For more information, go to: vhl.org/databank.

We anticipate that these talented investigators will help move the field of VHL research forward substantially in the next few years.
VHL Research

Eric Jonasch, MD
Professor of Medicine
UT MD Anderson Cancer Center

VHL Gene and Protein

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

Regulates how the cell sees its surroundings
Regulates p53
Controls the primary cilium
Impacts blood vessel formation

VHL- A Regulatory Hub

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

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
Generate Real-World Patient Databases
Therapeutic Avenues

Regulates p53
Controls the primary cilium
Impacts blood vessel formation

Ohh et al, Mol Cell, Vol 1, 959-968, 1998
Kurban et al, Cancer Res 2006; 66: (3).
Kuehn et al, Ca Res May 15, 2007
Kerbel NEJM May 2008
Roe and Youn Mol Cell May 2006

Stubbins, Elongin C, B and Cul 2

References:
Stubbins and Pavletich, Science, Vol 284, 16 April 1999
Ohh et al, Mol Cell, Vol 1, 959-968, 1998
Kurban et al, Cancer Res 2006; 66: (3).
Stubbins, Elongin C, B and Cul 2
Kuehn et al, Ca Res May 15, 2007
Kerbel NEJM May 2008
Roe and Youn Mol Cell May 2006

VEGF = vascular endothelial growth factor; HIF = hypoxia-inducible factor.

VHL Mutation Replicates the Hypoxic State

VHL Alliance Research Funding

- Over 1 million dollars given for research!
- Review committee consisting of world leaders in VHL research.
- Strong emphasis on translational research which will benefit patients sooner rather than later.

In coming up with treatments we have to think about the different cells that make up the tumors.

VHL Alliance Research Funding:

- Preproposal Requests (May-June)
- Invitation for Full Review (July)
- Full Proposal Submission (August)
- Peer Review and Selection
A novel chemical chaperone for treating the VHL cancer syndrome

Danny Segal
Dept. Molecular Microbiology & Biotechnology
Tel Aviv University

Dr. Segal’s lab indicates that using both D- and L-arginine may normalize HIF regulation of various mutant VHL isoforms.

Arginine

An amino acid, used as a building block to make proteins
You can get left-handed and right-handed versions

Ongoing work will further refine the list of candidate molecules capable of refunctonalizing and restabilizing VHL.
2014 Full Project Awardee

**VHL Models and Novel Therapeutics**

Othon Iliopoulos  
Dept. Oncology  
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.  
- Work is underway and will be finalized next year.

2015 Pilot Project Awardee

**Salivary, plasma metanephrines and anxiety levels in pheochromocytomas (STRESS)**

A.N.A van der Horst-Schrivers  
Department of Endocrinology  
University Medical Center Groningen

- Measurement of metabolites of catecholamines (metanephrines) is the cornerstone in diagnosing a pheochromocytoma.  
- Carriers of germline mutations such as VHL are annually screened for a pheochromocytoma using blood to measure metanephrines.  
- However, for this test rest for 30 minutes in supine position before blood sampling is obligatory.  
- Measurement of metanephrines in saliva could be less cumbersome, and more patient friendly. It has the advantage of collection at home (and subsequently send by mail to the hospital).
Approach

• This study aims to determine whether the saliva test is just as accurate and sensitive as the measurement of metanephrines in blood.
• This study will be performed in the Netherlands and at the National Institute of Health (NIH), Bethesda, USA.
• Investigators will include 145 patients with a PCC, 145 healthy controls and 145 germline mutation carriers.

Significance

• If measurement of salivary metanephrines is just as accurate as blood metanephrines, then this approach will be more time and cost effective for patients/germline mutation carriers and for the treating medical team.

Rationale

• Clear cell renal cell carcinomas (ccRCC) are kidney tumours that arise very frequently in patients with the inherited von Hippel-Lindau (VHL) disease syndrome.
• The generation of mouse models of human tumours using genetically modified mice has been a powerful tool used by scientists to not only understand the genetic causes and biological behaviour of tumours but also to test new therapies that can guide subsequent drug trials in human patients.

Using a novel mouse model of ccRCC to investigate Hif-1α and Hif-2α inhibition for cancer prevention and therapy

Prof. Dr. Ian J. Frew
Institute of Physiology, University of Zurich
Approach

• Dr. Frew and his team have recently generated a very good mouse model of ccRCC, possibly the first that truly represents what happens in patients.

• They will use mouse ccRCC model to determine whether drug treatment can prevent the formation of new tumors and efficiently treat existing tumors. They will test available compounds that block HIF.

Significance

• The information gained from this combination of a genetic and a pharmacological approach will be highly useful to guide new trials in individuals with VHL disease and in patients with noninherited clear cell renal cell carcinoma.

Rationale

• There is a dearth of consolidated databases that aggregate information on VHL genotype-phenotype correlations.

• By creating such a database, it will advance our ability understand why we see specific patterns of VHL manifestations in patients.

2016 Pilot Project Awardee

VHL IT-Sharing International Consortium (VISIon)

Raymond Kim PI
University of Toronto
**Approach**

1. Develop a standardized genotype-phenotype data collection format which can be utilized across multiple centers and compliant for ClinGen submission with multisource consistency.
2. Conduct a systematic review of published VHL studies.
3. Update the clinical phenotype for Dutch and Toronto patients.
4. Share knowledge with the VHLA Clinical Care Centers.

**Significance**

- By performing this work, Kim et al will create a template that will allow more rapid worldwide collection of VHL genotypes and phenotypes, and will contribute to our understanding of how VHL mutations affects patients.

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**iPS model for Retinal Hemangioma Pathogenesis**

Michael Gorin, MD, PhD

UCLA

**Rationale**

- No good models currently exist for hemangioblastomas.
- Induced progenitor stem cells are cells that can be modulated to develop specific cell types, including those from the eye.
- Knockout of the Vhl gene in specific regions of a mouse is possible using specific gene modulating techniques.
Approach

1. Develop VHL knockout cell lines that approximate those found in the eye by starting with an iPS cell.

2. Starting with a Vhl “floxed” mouse, knock out Vhl using a Cre injected into the eye of the mouse and assess whether lesions develop.

Significance

• If successful, this model will provide a representative model of abnormal retinal cells in VHL.

• This model will allow the Gorin team to test how retinal hemangiomas influence blood vessels in the eye, and to screen for potential strategies that will overcome blood vessel formation.

Cancer in Our Genes International Patient (CGIP) Databank

A patient-driven databank dedicated to finding a cure for VHL, BHD, HLRCC, SDH, and related disorders
CGIP Origins

• Outcome of 10th International VHL Medical Symposium (Houston, 2012)
  – VHLA Research Council

• Collaborative effort includes National Organization of Rare Disorders (NORD)
  – NORD = Software Provider
  – VHLA = Databank Owner

CGIP: A Complementary Effort

• Joint effort between VHLA and health care professionals
• Complementary to existing institutional databanks
  – Information best answered by patients, i.e. lifestyle (diet, exercise, sleep, nutritional supplements, mood, altitude, oral health)
• De-identified data available to researchers
• Match participants within a specific research criteria
• Provide baseline data for clinical trial

CGIP Goals

• Further understand natural history
  - Longitudinal
• International study
  - Wide range of genotype
  - Study geographical differences
• Comprehensive patient-driven data
  - Impact of lifestyle on disease progression and/or tumor growth rate
• Learn from all experimentation
• Learn from commonalities and differences between disorders

CGIP Features

• Privacy and Confidentiality: Primary concerns and factor built into CGIP
• Confidential/Secure
• IRB Approved
• Data curation process incorporated
• Online: no geographic limitations
• Language = English
• No age limitations
CGIP Surveys

- About the Participant
- Diagnosis and Medical History
- Genetics
- Eye
- Ear
- Kidney
- Neurology
- Pancreas and Digestive Issues
- Adrenal
- Heart
- Reproductive Tract
- Thyroid
- Lung
- Skin
- Nutrition and Exercise
- Oral Health and Tobacco Use
- Measuring your Mood
- Other Information and Updates

CGIP Status

- Launched March 2014
- “Living Registry”: Updates based on learnings
- Registrants vs. Participants
  502 vs. 344 or 68.5%

CGIP Demographics

- Gender
  Female 66%
  Male 34%

- Age
  Median 43 yrs
  Min 13 yrs
  Max 81 yrs

- Country of Residence
  US 76%
  EU 11%
  Canada 6%
  Pacific/Asia 4%
  South America 2%
  Other 1%

- Diagnosis (self reported)
  VHL 84%
  HLRCC 7%
  BDH 6%
  SDH 2%
  Other/Undiagnosed 1%

CGIP Data

- General Health (self reported)
  Excellent 12%
  Very Good 31%
  Good 31%
  Fair 19%
  Poor 6%

- Alcohol Consumption
  Daily 6%
  4-6 times/wk 7%
  2-3 times/wk 14%
  1 times/wk 15%
  Rarely/Not at all 57%

- BMI
  Underweight: < 18.5 3%
  Normal weight: 18.5 - 24.9 36%
  Overweight: 25.0 - 29.9 33%
  Obese: ≥ 30 29%
CGIP Data

• Does your health now limit you in doing vigorous activities?
  - Not at all 32%
  - Sometimes 19%
  - Very little 24%
  - Quite a lot 18%
  - Cannot do 6%

• How often do you feel fatigued?
  - Never/Rarely 25%
  - Sometimes 33%
  - Often/Always 42%

• How frequently do you do at least 10 minutes of sustained exercise in a day? (walking, yoga, weight training)
  - Daily 28%
  - 4-6 times/wk 22%
  - 2-3 times/wk 24%
  - 1 time/wk 9%
  - Rarely 12%
  - Not at all 5%

CGIP Data

• How frequently do you eat at least 1 cup of fruit or fruit juice or 1/2 cup of fresh or frozen vegetables?
<table>
<thead>
<tr>
<th></th>
<th>Fruit/Juice</th>
<th>Vegetables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>43%</td>
<td>47%</td>
</tr>
<tr>
<td>4-6 times/wk</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>2-3 times/wk</td>
<td>18%</td>
<td>22%</td>
</tr>
<tr>
<td>1 time/wk</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Rarely/Not at all</td>
<td>10%</td>
<td>7%</td>
</tr>
</tbody>
</table>

CGIP Preliminary Data

**Oral Health out of 167 patients**

- Dry Mouth = 29.5% (normal for age 70+)
- Mouth Sores (aphtha) = 47.9% (very high digestive issues?)
- Root Canal (one or more) = 39.5% (high, generally 20%)
- Crowns (one or more) = 43.7% (consistent with high root canal)

CGIP Challenges

- Global support and participation by researchers
- Increased awareness among patients
  - VHL, BHD, HLRCC, SDH, etc.
- Increasing participation
- Patient follow-through
  - Surveys
  - Medical information
Past Present and Future

- Identification of the VHL Gene
- Determining how VHL deficiency affect patients
- Developing new ways to treat VHL disease