Update on VHLA-Funded Research

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

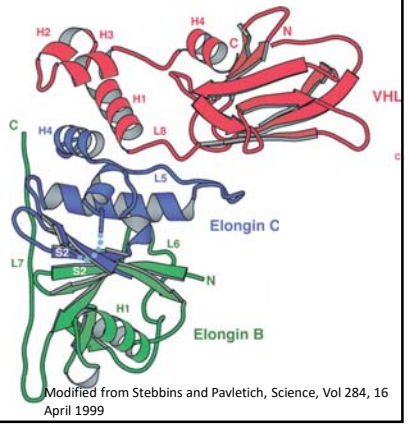
Eric Jonasch, MD
Professor of Medicine
UT MD Anderson Cancer Center

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

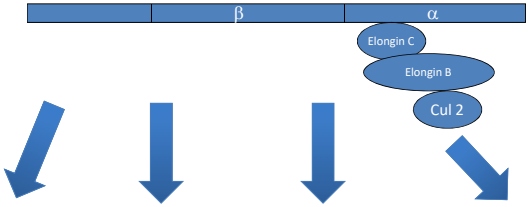
VHL Gene and Protein

- 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

VHL- A Regulatory Hub



Regulates how the cell sees its surroundings

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

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

Regulates p53

Roe and Youn Mol Cell May 2006

Controls the primary cilium

Thoma et al Nature Cell Biology Aug 2009

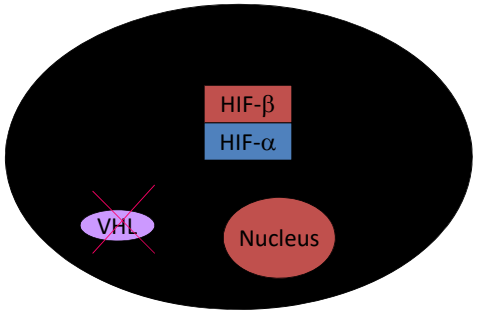
Kuehn et al Ca Res May 15, 2007

Impacts blood vessel formation

Pugh et al Narture Medicine 2003

Kerbel NEJM May 2008

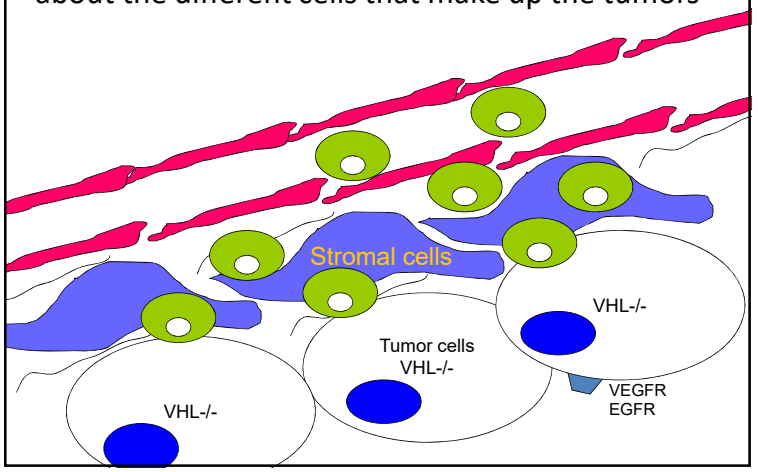
VHL Mutation Replicates the Hypoxic State



Transcription of:
VEGF
Other angiogenic factors

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

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



VHL Alliance Research Funding

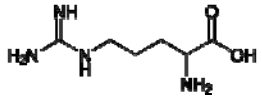
- Over 1 million dollars given for research!
- Review committee consisting of world leaders in VHL research.
- Strong emphasis on translational research which will benefit patients sooner rather than later.

2014 Pilot Project Awardee

A novel chemical chaperone for treating the VHL cancer syndrome

Danny Segal
Dept. Molecular Microbiology & Biotechnology
Tel Aviv University

Arginine



An amino acid, used as a building block to make proteins

You can get left-handed and right-handed versions

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

Ongoing work will further refine the list of candidate molecules capable of refunctionalizing 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

Rationale

- 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 en 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.

2015 Full Project Awardee

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

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.

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.

2016 Pilot Project Awardee

VHL IT-Sharing International Consortium (VISIon)

Raymond Kim PI
University of Toronto

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.

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.
5. Create a ClinGen Expert Panel.

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.

2016 Full Project Awardee

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

VHL Alliance
THE CURE FOR CANCER IS IN OUR GENES

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 heath 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**

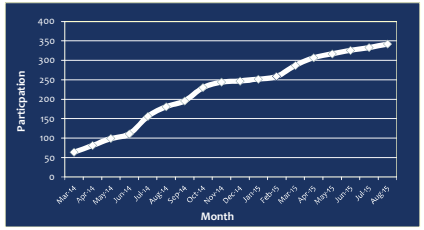
CGIP Surveys

- 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 %

- **S**

Never Smoker	67%
Ex-Smoker	23 %
Smoker	9 %

- **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?**

	Fruit/Juice	Vegetables
Daily	43%	47%
4-6 times/wk	23%	25%
2-3 times/wk	18%	22%
1 time/wk	6%	3%
Rarely/Not at all	10%	7%

CGIP Preliminary Data

Oral Health *out of 167 patients*

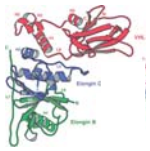
- **Dry Mouth = 29.5%**
  (normal for age 70+)
- **Mouth Sores (aphtha) = 47.9%**
  (very high digestive issues?)
- **Root Canal (one or more) = 39.5%**
  (high, generally 20%)
- **Crowns (one or more) = 43.7%**
  (consistent with high root canal)

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