The Past, Present, and Future of VHL: A Clinical and Research Perspective

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Unmet Needs

- Basic Science
- Models of Disease
- Data Collection
- Screening Tools
- Imaging Technology
- New Therapies

VHL Gene and Protein

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

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
- Follow up
- Treatment

Modified from Stabinski and Pavletic, Science, Vol 284, 16 April 1999
VHL - A Regulatory Hub

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

VHL Mutation Increases Production of Growth Factors, like VEGF

- Transcription of:
  - VEGF
  - Other angiogenic factors

VHL Loss Results in Abnormal Production of Blood Vessels, Fueled by VEGF

Can We Block The Consequences of VHL Loss?
Agents Exist or Are in Development That Block VEGF or VEGF Receptors

Pazopanib: Tumor Response

If VHL Is Broken, Cells Don’t Control HIF

**VHL Alliance, 2017**
If VHL Is Broken, Cells Don’t Control HIF

- HIF-\(\beta\)
- HIF-\(\alpha\)
- VHL
- Nucleus

VEGF

If VHL Is Broken, Cells Don’t Control HIF

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VEGF

Can we block HIF?

If VHL Is Broken, Cells Don’t Control HIF

- HIF-\(\beta\)
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- Nucleus

VEGF

Peloton HIF 2 Alpha Blocker

New Therapies
A clinical trial is being developed to test PT2977 in VHL patients!

Peloton HIF 2 Alpha Blocker

• PT2977 is a next-generation HIF2a blocker that is administered in pill form.

• A study will be launched in 2018 to test the effect of PT2977 on kidney and other manifestations in individuals with VHL.

• Primary goal of study will be to see whether kidney tumors shrink - will also assess impact in other sites.
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.

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 used zebrafish to discover new drugs that may rescue consequences of VHL mutation.
• Work is almost complete and will be published soon.

**Approach and Significance**

• The team will assess salivary metanephrine levels and compare to blood levels to determine accuracy

• 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.

**Screening Tools**

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

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

**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) that arise frequently in patients with von Hippel-Lindau (VHL) disease.

- The generation of mouse models has been a powerful tool used by scientists to not only understand the genetic causes and biological behaviour of tumors but also to test new therapies that can guide subsequent drug trials in human patients.

**Approach and Significance**

- 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.

- If successful, this will allow us to more rapidly screen for new drugs that can treat kidney cancer.

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**VHL IT-Sharing International Consortium (VISIon)**

Raymond Kim PI
University of Toronto

2016 Pilot Project Awardee
Approach and Significance

- Dr. Kim will develop an interactive database to collect genotypic and phenotypic data on VHL patients worldwide.
- By performing this work, Dr. Kim’s team will create a template that will allow more rapid collection of VHL genotypes and phenotypes, and will contribute to our understanding of how VHL mutations affect patients.

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.

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.
VHL Patient Natural History Study

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

**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

**Data Collection**

**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

**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
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

Challenges

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

2017 Grant Cycle

- Basic Science
- Models of Disease
- Data Collection
- Screening Tools
- Imaging Technology
- New Therapies

Past Present and Future

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