



12th International VHL Medical Symposium

Selected Presentation Summaries

The 12th International VHL Medical Symposium held in Boston April 7th – 9th brought together VHL researchers, clinicians, and patients from around the world. The symposium was a great way for researchers to have the opportunity to meet and interact with physicians treating VHL, and with VHL patients and families. Most importantly, it was a venue to discuss the tremendous advances that have been made in research that is bringing us closer to effective treatments for VHL.

An entire day was devoted to presentations and discussions directed to VHL patients, their families, and friends. Several patients and caregivers

presented their unique experiences with VHL, giving a picture of the effects of VHL on self-perception, career path, family dynamics, and the transition of medical decisions from child to adult. Discussions involving the audience covered ways to work together to reduce feelings of isolation with VHL, and how to best meet the needs of caregivers and teens.

The interaction between patients and researchers is invaluable. Two researchers, in particular, were so inspired that they volunteered to help the VHLA outside of their laboratory research.

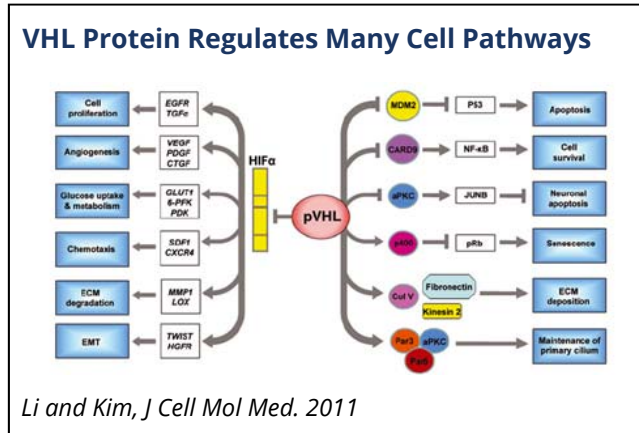
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Targeting VHL tumor pathways

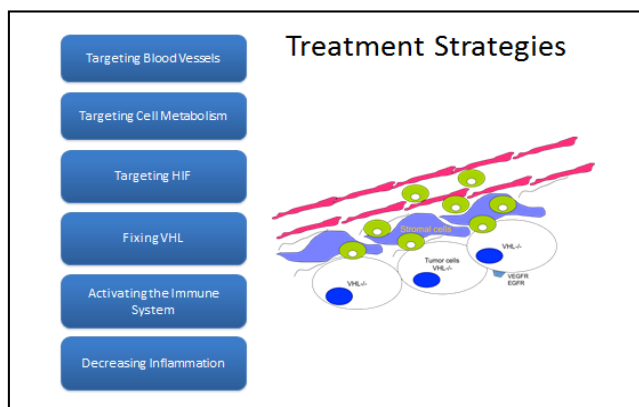
In contrast to many genetic diseases that affect a single organ or metabolic pathway, VHL is very complicated as up to ten organs can be affected. The gene's product, VHL protein (pVHL), produced by normal, non-mutated VHL genes regulates multiple metabolic (energy) pathways:



Research presented at this symposium goes into more detail about how pVHL affects metabolic pathways and how treatments may affect VHL tumors.

The ultimate goal of fully understanding how VHL tumors form is to prevent their growth in the first place. Future treatment strategies for VHL include:

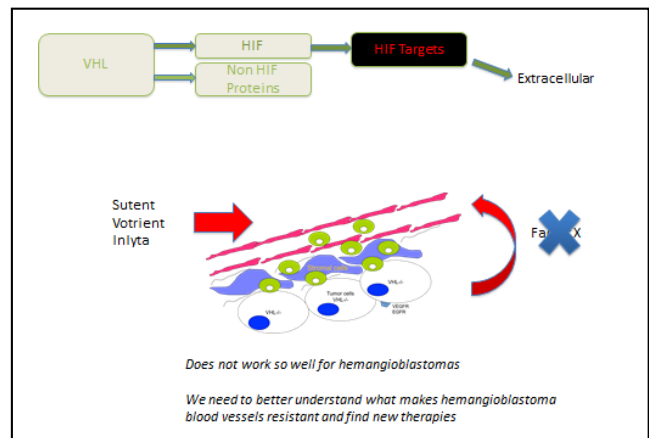
- Targeting blood vessels
- Targeting cell metabolism
- Targeting HIF
- Repairing the VHL gene, or VHL protein
- Activating the immune system
- Decreasing inflammation



Up to this point, most research into drug treatments for VHL has focused on the HIF (Hypoxia Inducible Factor) and VEGF (Vascular Endothelial Growth Factor) pathways to target angiogenesis

(formation of new blood vessels). These medications are effective for kidney tumors, but not as effective for other VHL lesions, such as hemangioblastomas. In addition, they are accompanied by unpleasant side effects. There was much excitement about a new drug, known to be much better tolerated. It is expected to go into clinical trial for VHL patients at NIH late this year.

Research on VHL hemangioblastomas is in progress in order to learn more about their unique characteristics, how they grow, and why the blood vessels forming these tumors do not respond like ccRCC (clear cell renal cell carcinoma) blood vessels to VEGF inhibitors.



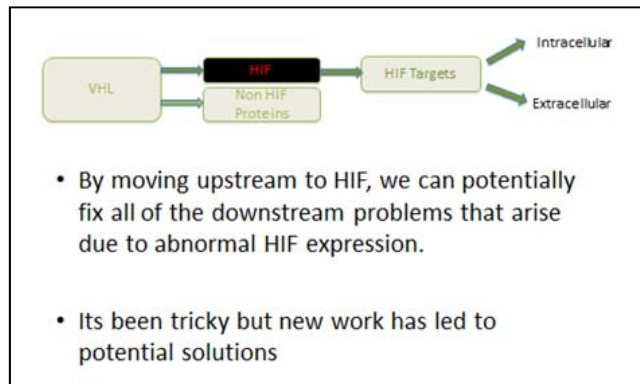
The exciting developments presented by researchers included:

- Discovery of new VHL tumor pathways that can be targeted to stop tumor growth, or selectively kill tumor cells
- A new drug that targets tumors more precisely than current anti-VEGF drugs and which should be more effective and have fewer side effects; a VHL trial begins at NIH later this year for ccRCC
- A new mouse model for VHL research
- Research into the origins of brain and spine hemangioblastomas

1. Targeting the HIF tumor pathway

Hypoxia (lack of oxygen) in solid tumors is the reason that many current cancer treatments fail. HIFs switch tumors from an energy pathway that depends upon oxygen, to one that does not (anaerobic pathway). This switch promotes angiogenesis, erythropoiesis (production of red blood cells), drug efflux (movement of a drug out of a cell – may contribute to drug resistance),

increased cell division, and a decrease in programmed cell death. HIF should be a good drug target, but it may play a protective role in kidney tumors.



HIF Proteins as Direct Drug Targets

Fraydoon Rastinejad

Proteins, whose activities can be modulated by drugs, must have “pockets” (holes or gaps) within their architectures for small molecules to bind. These pockets can be detected and analyzed using x-ray crystallography, a technique that allows the visualization of the 3-D structure of proteins. New research looked at HIF to learn how it “reads” DNA and functions differently when the protein has mutations. Five ligand (binding molecule) binding pockets were discovered in each of HIF-1 α , ARNT, and HIF-2 α . ARNT, and several mutations that had been detected in cancer patients were also noted to map directly to these pockets. The DNA binding properties of these HIF complexes can also be altered by mutations seen in human cancers. The new findings show that tumors in ccRCC can be combatted by discovering small-molecule drugs that bind to the HIF proteins, since the HIF proteins are major drivers of ccRCC.

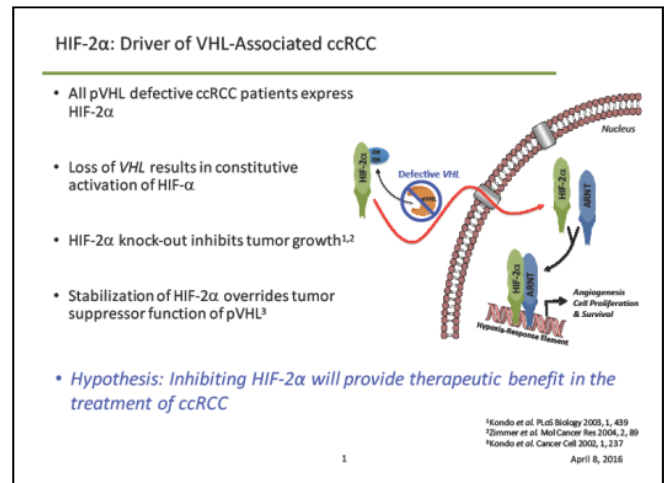
New HIF 2 α Antagonist from Peloton Therapeutics

Eli M. Wallace

Potent, Selective, Orally Bioavailable, First-In-Class HIF-2 α Antagonist

This is a new class of therapy for treatment of ccRCC with improved efficacy and reduced side effects when compared with anti-VEGF drugs. In addition to its action in kidney tumors, PT2385 crosses the blood-brain barrier. This may allow the drug to be used to treat hemangioblastomas in the brain and, possibly, in the spinal cord.

- Currently in Phase 1 clinical trial in patients with advanced or metastatic ccRCC
- VHL clinical trial planned at NIH by 2017



Drugs that target HIF-2

James Brugarolas

Most current medications such as sunitinib target the formation of blood vessels that feed kidney tumors and metastases. These drugs, however, do not directly target the tumor cells. Blood vessel formation is stimulated by the HIF-2 protein in kidney cancer cells, which also activates other processes such as the multiplication of tumor cells. A study in mice transplanted with human kidney cancer shows that a new drug that blocks HIF-2 (PT2399 analogous to PT 2385, which is in clinical trials), stops tumor growth in 56% of kidney tumors. PT2399 also stops tumor growth in tumors progressing on sunitinib. In addition, PT2399 has fewer side effects than current drugs used for kidney cancer treatment. These results suggest that HIF-2 inhibitors may one day play a role against kidney cancer in humans.

2. New VHL tumor pathways

Targeting glutaminase (GLS)

Othon Iliopoulos

Tumor cells use different metabolic (energy) mechanisms than normal cells. This means that it may be possible to develop drugs that restrict the growth of VHL -/- cells, but not the growth of normal cells that contain VHL. A metabolic target for drugs to treat tumors linked to mutations in VHL is GLS1 inhibitor (GLS1 stands for glutaminase 1, an enzyme converts the amino acid glutamate

from the amino acid glutamine). GLS1 inhibitors restrain the growth of VHL -/- cells in vitro and in vivo. A Phase 1 clinical trial with an oral GLS1 inhibitor for patients with renal cell carcinoma is underway.

Targeting DNA repair abnormalities

Herbert Cohen

Jade-1 is a repair protein and tumor suppressor in kidney cells. A drug currently used to treat multiple myeloma (blood plasma cell cancer) has been found to dramatically increase levels of Jade-1. This leads researchers to believe that a small molecule could be found to increase Jade-1, and thus inhibit tumor growth and alter DNA repair. The hope is to find a drug that can be used to treat ccRCC.

Targeting autophagy

Maria Czyzyk-Krzaska

Autophagy (enzyme breakdown of components within a cell) is an important mechanism in cancer cell survival and tumor growth, and plays both pro- and anti-oncogenic (tumor-forming) roles. Our work provides evidence for the existence of two separate autophagic programs regulated in an opposite manner by the VHL tumor suppressor. Pro-oncogenic autophagy disinhibited by loss of VHL is a potential target for the development of therapeutic approaches.

HSP90: Targeting a cancer accomplice for a way to treat kidney cancer

Mehdi Mollapour

A protein called Hsp90 chaperones cancer cells, allowing them to grow and survive. This is because Hsp90 looks after deregulated and hyperactive signaling pathways that are essential for cancer cell survival. Drugging Hsp90 leads to inhibition of many signaling pathways simultaneously, therefore "killing many birds with one stone." Tumors are generally sensitive and selective toward Hsp90 inhibitors. Elevated levels and hyperactivity of a mitotic (cell division) checkpoint kinase (enzyme), Mps1 has been shown to be responsible for this phenomena. Therefore, Mps1 levels can potentially serve as a predictive indicator of the tumor's response to Hsp90 inhibitors.

Targeting PGC1 alpha

Amato Giaccia

Lipid (fat or oil) accumulation, which forms the "clear cells" in ccRCC, has a largely unknown mechanism. Mitochondria, semi-independent organelles within the cells, create ATP (adenosine triphosphate) for cell energy using oxygen. Mitochondria control both lipid accumulation and cell growth by suppression of PGC-1 α (protein that is the master regulator of external signals such as endurance exercise and cold exposure on mitochondrial energy production). This suppression increases PGC-1 α expression in ccRCC tumor cells. If PGC-1 α expression is increased, ccRCC tumor cells become sensitive to chemotherapy.

VHL kidney disease as a ciliopathy

Ruhee Dere

VHL disease in the kidneys has recently been categorized as a ciliopathy- a group of disorders with defects/loss of the primary cilium. The primary cilium (tiny hair-like cellular structure) occurs on the surface of almost every cell in the human body. They function as antennae to send and receive signals from the extracellular milieu to control cell growth and a number of critical signaling pathways in the cell. Loss of the cilium is causally related to kidney cysts, and is often associated with numerous cancers. VHL mutations stop cilia formation, and we have recently discovered that this is due to the dis-regulation of an enzyme, Aurora Kinase A (AURKA), which is directly regulated by VHL. AURKA was only thought to play a role in cell proliferation, but recent evidence suggests a novel role of this enzyme in modulating cilia. Our data linking VHL to AURKA opens up opportunities for clinical intervention. This new research demonstrates that a drug which regulates AURKA in cells with VHL mutations, restores the cells' ability to form primary cilia making this drug an attractive target for future pre-clinical studies.

3. Stabilize and re-functionalize mutated VHL

Arginine and mis-folded pVHL

Daniel Segal

Over one-third of VHL mutations are “missense,” meaning that there is a full-size pVHL for possible repair. Mutated pVHL has a shorter lifespan than normal pVHL, but may still function. A way to increase the lifespan of mutated pVHL is needed in order to improve function. Arginine in trials with fruit flies is able to “re-fold” missense pVHL into a normal, functional configuration, increasing both lifespan and, thus, levels of pVHL.

4. Chronic inflammation and tumor formation

Possible use of anti-inflammatory therapy for preventing ccRCC

Tien Hsu

The connection between chronic inflammation, VHL mutation, and development of ccRCC is poorly understood. A contributing factor to inflammation may be altered metabolism in VHL mutant cells and increased protein production in an unfolded form, causing ER (endoplasmic reticulum – part of the cell involved in making protein and lipid) stress and unfolded protein response (UPR). UPR in the kidney cells negatively impacts renal cell function, and is known to be part of the development of inflammatory kidney disease. ER stress can be measured both in cells in a culture and in animals, allowing potential inhibitors to be tested. Therefore, drugs that reduce ER stress and inflammation such as statins, hold promise to stop ccRCC development.

5. Research into the origins and treatment of brain and spine hemangioblastomas

VHL research with zebrafish

Rachel Giles

Hemangioblastomas and ccRCC are the top concerns of those living with VHL, but up until this point, most research has focused on ccRCC. Zebrafish in which both VHL genes are non-functioning (VHL -/-) have growth of new blood

vessels that mimics brain and spine hemangioblastomas. The use of an anti-molecular hypoxic response (antiMIR) agent (a regulator of gene expression) that is increased when VHL is not functioning) was shown in zebrafish to decrease new blood vessel growth. This suggests an interesting opportunity for drug development to stop or slow down tumor growth in ccRCC as well as a possible intervention for VHL hemangioblastomas.

VHL research with zebrafish (Poster Presentation)

Haley Noonan

A zebrafish model with a homozygous (matching copies of a gene) inactivation in the *VHL* gene (*VHL*^{-/-}) recapitulates several aspects of human VHL disease, including the development of highly vascular lesions in the brain and the retina, resembling hemangioblastomas, and erythrocytosis (increased red blood cells). The epithelial (surface layer cell) abnormalities present in the kidney of the *VHL*^{-/-} zebrafish larvae were characterized as a first step in building a model of clear cell renal cell carcinoma (ccRCC) in zebrafish. The phenotype of the *VHL*^{-/-} pronephros (first stage of embryonic kidney development) is reminiscent of “clear cell” histology, indicating that the *VHL*^{-/-} mutant zebrafish may serve as a model of early stage ccRCC. Treatment of *VHL*^{-/-} zebrafish embryos with a small molecule HIF2a inhibitor rescued the pronephric abnormalities, underscoring the value of the zebrafish model in drug discovery for treatment of VHL disease and ccRCC. These zebrafish can be used to screen a collection of 25,000 previously discovered and/or FDA approved chemical compounds, for drugs that improve the *VHL*^{-/-} zebrafish kidney phenotype (observed physical traits). *This research is being funded through a VHLA Research Grant.*

New tumor pathways in CNS hemangioblastomas

Ana Marguerita Martins Metelo

Hemangioblastomas, like other VHL tumors, show loss of VHL function in both alleles (one member of a pair of genes; VHL -/-). There are other chromosomal abnormalities in hemangioblastomas, but these have not been identified yet. Hemangioblastomas are composed of multiple cell types and the origin of the tumor cells is unclear. In order to understand the genetic changes that occur in VHL hemangioblastomas (in addition to the VHL mutations), next-generation whole exome sequencing was performed. The samples from 8

VHL patients were tested and the tumors all had VHL mutations on chromosome 3, plus 2 tumors showed complete loss of chromosome 8. Furthermore, hemangioblastoma-derived cell lines were established from fresh tumor samples. These cells express PDPN (clinical marker used to identify hemangioblastoma tumor cells), VEGF (angiogenic factor), and CD31 (endothelial marker), and have a strong HIF expression profile.

6. New VHL mouse model for ccRCC

New mouse replicates human VHL ccRCC Ian Frew

Despite many attempts by many research groups over two decades, it has not been possible to genetically engineer mice that fully reproduce human ccRCC. Unlike in humans, mice lacking the VHL gene do not develop ccRCC. Researchers have needed to graft human kidney tumor cells onto test mice in order to conduct VHL experiments. This is not ideal since the tumor environment (the surrounding cells, inflammation levels, organ function, etc.) is different from that natural environment of VHL ccRCC growing in the kidney.

By generating mice with the VHL mutation plus mutation of two additional tumor suppressor genes, it has now been possible to recreate ccRCC in the mouse kidney, proving a long sought-after experimental model in the context of the complete kidney environment and in the presence of a functioning immune system. The new mouse model will allow researchers to learn more about the biology of VHL ccRCC and to test possible therapies including drugs that inhibit HIF1 α , HIF2 α , and drugs which re-activate the anti-tumor activities of the immune system. *This research is being funded through a VHLA Research Grant.*

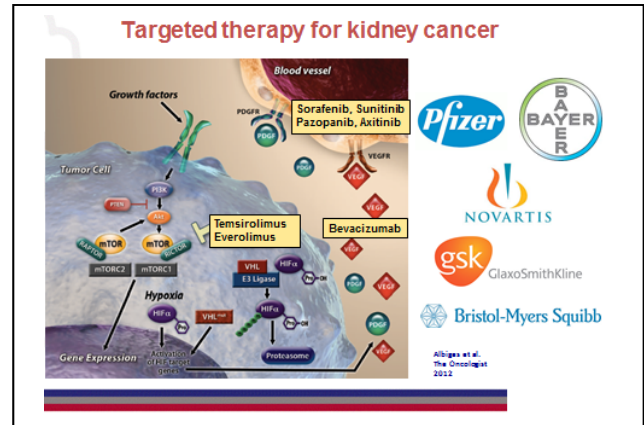
7. Clinical Treatment of VHL

Need for new drugs that target tumors more precisely than current anti-VEGF drugs

Eric Jonasch

Current available drugs approved for sporadic ccRCC provide small improvements in VHL kidney tumors, but show inconsistent results in hemangioblastomas and other VHL lesions. The hope is that better understanding of VHL heman-

gioblastomas, ccRCC, and other lesions will lead to the development of more effective treatments with fewer side effects. Future treatments that actually prevent VHL tumors need to be approached with caution. To intervene at this level, we have to be sure preventive treatments are safe, in particular because a number of people with VHL will never develop certain lesions.



A review of small studies of VHL patients and case reports using receptor tyrosine kinase (RTK) inhibitor chemotherapy drugs show that there are only modest reductions in the size of kidney lesions and varied results from patient to patient in brain and spine hemangioblastomas. The RTK inhibitors tested are primarily VEGF receptor inhibitors and interfere with the blood vessel formation which occurs in both ccRCC and hemangioblastomas. However, the data suggests that there is a difference in the angiogenic receptors between ccRCC and hemangioblastomas. This is likely due to the increased activation of both the VEGF receptor and the FGF (fibroblast growth factor) receptor in hemangioblastomas as compared with ccRCC.

A different approach is to stop tumors from becoming malignant (spreading beyond the original organ where they formed). Silmitasertib selectively targets cancer cells by stopping the CK2 enzyme (a protein kinase), which appears to cause tumor growth and transformation of tumors from benign to malignant. This drug is currently in clinical trials for other diseases.

Silmitasertib

- AKA CX4945
- Highly specific CK2 inhibitor
- In clinical trials for other diseases
- Relatively well tolerated
- Trial design in discussion with Senhwa Biosciences

8. Integrated Care

The Value of Integrated Care Channing Paller

Integrated care is important to living the best life with VHL. In addition to conventional medical treatment of VHL, one should treat the stress, fatigue, pain, and relationship issues that are part of living with a chronic disease. Complimentary medicine addresses these issues in ways that may even make conventional medical treatments more effective. In the past, there has been very little data for doctors to use when recommending these integrative medical treatments. The treatment with the highest success rate in studies is participation in a support group. The table shows that support groups for both patients and family members receive the highest level of evidence scores (1A), followed by exercise, healthy diet, and meditation/ yoga (all classified as 1B). Nutritional supplements have less evidence to support their use and are classified as 2B.

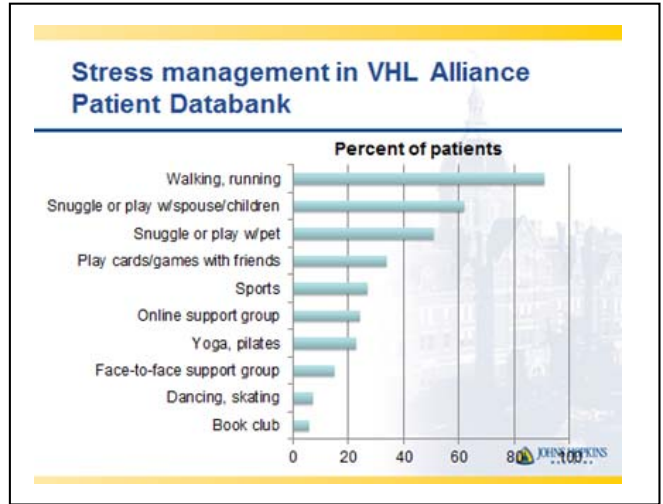
Society of Integrative Oncology Data: Strength of evidence on which to make recommendation

Symptom relief

| Intervention | Stress | Anxiety, depression | Cognitive function | Fatigue | Pain | Sexual Function | Sleep disorder | Progression/recurrence of cancer |
|------------------------------------|--------|---------------------|--------------------|----------|------|-----------------|----------------|----------------------------------|
| Exercise and physical activity* | 1B | 1B | 1B, NCCN | 1B | | | 1B | |
| Healthy Diet | 1B | 1B | 1C | 1B | | | 1B | 1B |
| Nutritional supplements | 2B | 2B | 2B | 2B | 2B | 2B | 2B | |
| Meditation, yoga, relaxation, etc. | 1B | 1B | 1B | 1B | 1B | 1B | 1B | |
| Support groups | 1A | 1A | 1A | 1A | 1A | 1A | 1A | |
| Massage Therapy** | | 1C | | 1A, NCCN | 1C | | | |
| Energy therapy | | 1B | | 1C | 1C | | | |
| Acupuncture | | | | | 1B | | | |

*1A for breast cancer; NCCN says exercise also improves cognitive function
** Massage is 1A for fatigue at NCCN

Data from VHLA's Patient Databank (vhl.org/databank) shows that over 30 percent of patients participate in online and/or in-person support groups as one way of managing stress:



The VHL Alliance offers online support (social media discussion groups), a facilitated telephone discussion group, and in-person guided discussion groups at the annual VHLA meeting.

9. The VHL Patient Databank

Early Data from the Databank Ilene Sussman

The VHL Alliance launched an ongoing, longitudinal online clinical study of the natural history of VHL, the Cancer in our Genes International Patient Databank (vhl.org/databank). This study is completed by individual patients located around the world and includes detailed lifestyle, nutrition, and exercise questions, supplementing the medical questions. The Databank does not duplicate medical institution registries – it complements them with additional information.

CGIP Data: Demographics

579 Registrants with 389 Participants (67%)

- 369 (97%) alive; 11 deceased (3%) (n= 380)

- Age (n= 326)
Median = 43 years
 Range = 13-81 years

- Gender (n= 326)
 Female = 66.1%
 Male = 33.9%

| Country of Residence (n=327) | |
|------------------------------|-------|
| United States | 72.2% |
| United Kingdom | 9.2% |
| Canada | 6.4% |
| Australia/New Zealand | 2.1% |
| European Union | 5.5% |
| South America | 1.2% |
| Asia | 1.2% |
| Other | 2.1% |



CGIP Data: Oral Health Perspective

Oral Health (n=~170 patients)

Xerostomia (dry mouth)= 32.3%: **Normal for age 70+**

Aphtha (mouth sores)= 47.1%: **Very High Digestive Issues**

Root Canal (≥ 1) = 40.2%: **High, Generally 20%**

Crowns (≥ 1) = 44.5%: **Consistent with High Root Canal**



Many people living with VHL are also living with additional health concerns. Fortunately, 52.0% of respondents reply that their physical activity is “not at all limited” or only “limited very little.” This is true although 59.4% of respondents have BMIs in the overweight or obese categories, and only 2.5% are underweight. These subgroups of people living with VHL will be looked at in more detail to see if there are any possible associations with VHL tumor location and growth.

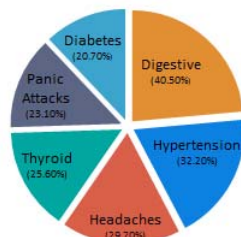
The most commonly reported health problem of those living with VHL is digestive issues – this is not surprising as it can be a symptom of VHL lesions in the pancreas.

There are a number of unanswered questions about VHL and pregnancy. The Databank already has more participants for pregnancy and VHL than any published study. This will allow researchers to look at which VHL tumors are present in women before and after pregnancy, look at tumor growth over time and compare it with women who have never been pregnant.

VHLA and our constituents living with VHL are excited to be an important part of VHL research and to help advance research with the Databank. Researchers may contact VHLA with proposals for research utilizing the Databank.

Databank: Top General Health Issues

VHL Patients: General Health Issues
 Number of participants = 121



A surprising finding from the Databank is the relationship between VHL and poor oral health. Most everyone is brushing, flossing, and getting dental care (and only 10.6% smoke), but dry mouth and related problems with gum disease and tooth decay are more typical of an elderly group. The cause of these problems is not yet known (it could be related to digestive issues, number of surgeries, or medications).

10. Advances in science that may be applicable to VHL

Directly fix mutated VHL using CRISPR-Cas9 technology

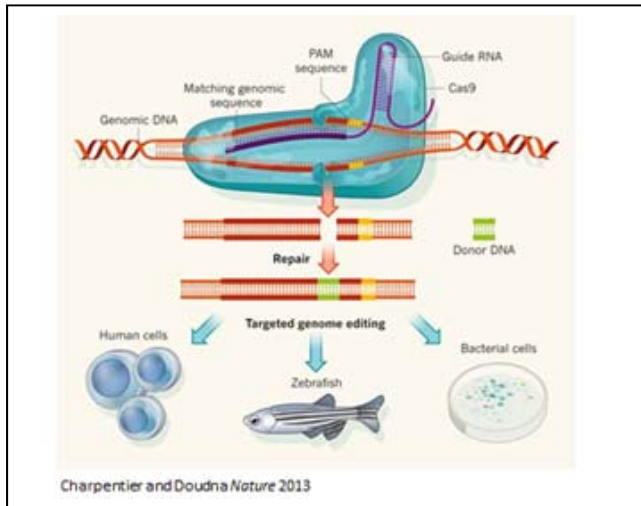
Targeted gene editing

J. Keith Joung

Gene editing that can delete, replace, or repair genes, can potentially enable corrections to be made to genes with mutations such as VHL that result in non-functioning pVHL. One important goal of gene editing is to “fix” the gene so that the protein coded for is functional. When cutting and pasting genes into a genome, it is very important not to cause other unintended mistakes. This topic has been a major emphasis of ongoing research.

CRISPR-Cas9 was developed from bacteria in 2012 as a genetic engineering tool that is simple, accurate, and can be used in any cell. CRISPR-Cas9 is being developed to treat different diseases, including a rare genetic form of blindness known

as Leber's Congenital Amaurosis, and clinical trials have been projected to potentially begin as soon as 2017. Genome editing will provide an important research tool that will potentially impact a wide range of human diseases including VHL.



Direct the immune system to target VHL tumor cells

Immune cell checkpoints for tumor immunotherapy

Gordon Freeman

The immune system normally recognizes tumor cells and eliminates many tumors at an early stage, before they become a medical problem. However, immunosuppression can develop which is when tumor cells evolve to resist the immune system and evade attack. The strength and duration of all immune responses are regulated by a number of immunological checkpoints. Three checkpoints (PD-1, PD-L1, CTLA-4) are already effective targets that can be blocked by antibody drugs either singly, or in combination, in immunotherapy for treatment of a variety of cancers, including kidney cancer. In the future, we may learn that VHL tumors will respond to immunotherapy. If so, the T cells which carry out the immune response are possible targets for genetic modification to generate an even better immune response to VHL tumor cells. This methodology has already been developed to treat glioblastomas (a brain tumor unrelated to VHL hemangioblastomas). It is crucial to be careful that there is not an immune response to pVHL in normal tissue.

