The 13th International VHL Medical Symposium held in Houston, TX on October 4-6, 2018 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. In addition to lay summaries from the previous 2 days, data from MyVHL was presented, and VHL Alliance programs, including support groups, CCC Process Improvement and Wellness Coaching were discussed.

Three major outcomes were identified:
1. Identify additional data and tools needed to assess the feasibility of genetic therapy for VHL retinal eye disease.
2. Form Task Force to reevaluate VHL Surveillance Guidelines and determine any necessary changes.

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1. Novel Insights into VHL Biology

**SIGNALLING IN cCRCC: MOLECULAR MECHANISMS AND TARGETED THERAPY**

**ERIN BRUNO RANKIN, PHD**

Renal cell carcinoma (RCC) is considered one of the most malignant tumor types that may develop in VHL patients. Metastasis is a major challenge in the treatment of RCC. Current therapeutic strategies target the abnormal tumor vasculature in VHL-related kidney tumors with antiangiogenic agents. A problem is that many of these tumors develop resistance to these agents and progress. Research is underway to address the need for the development of therapeutic strategies that will result in durable clinical responses in patients with VHL-related RCC. The focus is to identify novel therapeutic strategies that directly target the kidney cancer cells.

VHL/HIF signaling has been shown to be a critical regulator of RCC initiation and progression. AXL has been identified as a direct HIF target. Specifically, the receptor tyrosine kinase AXL has become an emerging therapeutic target for cancer. There is a molecular link between VHL/HIF signaling and AXL expression in RCC. AXL is activated by HIF-1 and HIF-2 in VHL-related RCC cells. AXL is not required for RCC cell proliferation or survival *in vitro*. The functional roles of AXL in RCC are invasion, metastasis, angiogenesis, and tumor growth. Genetic inactivation of AXL signaling in metastatic RCC cells has been shown to reverse the invasive and metastatic course of the disease. It also inhibited RCC tumor growth in the liver and reduced tumor vascularization. Therapies targeting GAS6/AXL signaling may even enhance pazopinib response based on preclinical studies in an patient derived xenograft model.

There is a lot of therapeutic potential in targeting AXL in RCC and that AXL therapy is a potent and safe option for reducing RCC tumor growth and metastatic potential. Ongoing research will help to further develop these therapeutic strategies and options.

**IDENTIFYING NOVEL THERAPEUTIC TARGETS FOR VHL DISEASE DOWNSTREAM OF A UNIQUE VHL-AURKA-HDAC6 SIGNALING AXIS**

**RUHEE DERE, PHD**

*VHL* proteins stabilize microtubules of the mitotic spindle and the cilium. Cilium (plural: cilia) are tiny organelles that project out like a finger from the apical surface of nearly every cell in animals. Cilia keep their structure because they are formed by a microtubule cytoskeleton. The VHL protein localizes to the primary cilium. People who have VHL experience a loss of this protein, which results in the loss of the primary cilia. Aurora Kinase A (*AURKA*) is an enzyme found in humans that is involved in the healthy proliferation of cells. The *VHL* gene acts as a direct regulator of *AURKA*. VHL disease is linked to elevated *AURKA* levels and fewer cilia. By understanding how these signaling pathways in the body work, researchers have identified bexarotene, a synthetic retinoid drug, as a potential treatment that can successfully rescue the cilia, by decreasing *AURKA* expression and activity.

Mouse models using this treatment method to treat RCC have shown promise, highlighting the potential for the use of bexarotene as a strategy to manage VHL-related RCC.

**VHL SUBSTRATE TRANSCRIPTION FACTOR ZHX2 AS AN ONCOCGENIC DRIVER IN RCC**

**QING ZHANG, PHD**

Researchers were able to identify proteins that bind to VHL proteins when they are hydroxylated. These proteins, known as ZHX2, were found to be a VHL target and its hydroxylation allowed VHL to regulate its protein stability.
Tumor cells from VHL-related RCC patients usually had increased accumulation of ZHX2. Depletion of ZHX2 was found to inhibit VHL-related RCC cell proliferation and growth in the lab. This research suggests that ZHX2 may be a potential therapeutic target for VHL-related RCC.

**THE HIFs IN KIDNEY CANCER – NEW INSIGHTS AND TARGETING POTENTIAL**

**MEI KOH, PHD**

RCC is the most common and aggressive form of kidney cancer and is uniquely linked to VHL. A VHL mutation results in the loss of the VHL protein, which acts as a tumor suppressor. This loss drives the accumulation of HIF factors, which are transcription factors that respond to perceived decreases in available oxygen in the cellular environment. Low oxygen levels are a feature of all solid tumors and are associated with increased metastasis. As oxygen levels go down, HIF activation levels go up. It was previously thought that in RCC, HIF-2α is a central driver of disease progression, whereas HIF-1α plays a tumor suppressor role, and is frequently deleted in high-grade tumors.

New research challenges that, indicating that the relationship is much more nuanced. The studies have shown that HIF-1α upregulation is associated with poor outcomes, while high levels of HIF-2α are associated with much better outcomes. The data therefore suggests that the notion of HIF-1α as a tumor suppressor may need to be revisited.

**SIGNALING IN cCCRCC: MOLECULAR MECHANISMS AND TARGETED THERAPY**

**EDWARD LAGORY, PHD**

VHL is associated with a high lifetime risk for the development of benign renal cysts and clear cell renal cell carcinomas (RCC). These together negatively impact kidney function and present the threat of metastasis. VHL-related RCC tumors exhibit profound metabolic alterations compared to normal kidney tissue. One of these alterations is the pronounced accumulation of lipid droplets in the cytoplasm of the tumor cells. It is currently not known what drives this accumulation or how it impacts malignancy.

Research has shown that uptake of fatty acids predominantly drives lipid droplet formation in RCC. Long chain acyl-CoA synthetase (ACSL) plays an essential role in the subsequent metabolism of fatty acids into triglycerides, the major component of lipid droplets. Studies are underway to determine which specific ACSL isoforms are important for maintaining lipid droplet formation and sustaining cellular proliferation in RCC.

Suppression of certain forms of ACSL has been shown to reduce cell growth in models, suggesting that ACSL-mediated lipid droplet formation is essential for RCC growth. Furthermore, studies have shown that by inhibiting ACSL, the oxidative stress caused by the buildup of lipid products can cause tumor cell death. All of this suggests that targeting lipid metabolism may be a useful therapeutic tool in treating RCC and that there is a possibility of using lipid-based imaging modalities for the detection and monitoring of RCC.

**MULTIPLE TUMOR SUPPRESSORS REGULATE A HIF-DEPENDENT NEGATIVE FEEDBACK LOOP THROUGH ISGF3 IN KIDNEY CANCER**

**HAIFANG YANG, PHD**

While it is known that loss of the VHL protein is the primary event in the development of RCC, how this mutation interacts with secondary mutations in other tumor suppressing genes is unclear. Analysis has shown that the VHL, PBRM,1 and KDM5C genes share a common regulation of interferon response expression signature. Further analysis reveals that the loss of VHL activate interferon stimulated gene factor 3 (ISGF3), a transcription factor that regulates the interferon signature. ISGF3 proves to be strongly tumor-suppressive, as its loss significantly enhances tumor growth while reactivation of ISGF3 stops tumor growth by PBRM1-deficient RCC cells. The suppression of any of the major secondary tumor suppressors such as PBRM1, KDM5C, SETD2, or BAP1 leads to inactivation of ISGF3, disabling the negative feedback loop. Thus this data suggests that boosting ISGF3 activity could be a novel therapeutic strategy against RCC.
2. Gene Editing: Fact or Friction for VHL Disease

**AAV TARGETED THERAPY FOR INHERITED RETINAL DYSTROPHY: BENCH TO BEDSIDE**

**DANIEL CHUNG, DO, MA**

Luxturna, a surgically administered gene therapy, is the first FDA approved gene therapy for a genetic disease. It is meant to treat patients with a very specific gene mutation that is associated with retinal dystrophy.

The serious side effects reported in the US Full Prescribing Information include endophthalmitis, that may lead to blindness, permanent visual acuity loss or retinal changes causing vision loss, Other potential side effects that can be associated with Luxturna treatment include hyperemia, cataracts, increased intraocular pressure, retina tears, epiretinal membrane, corneal dellen, macular hole, subretinal deposits, conjunctival edema, eye irritation, or pain.

Clinical trial data was evaluated and provided sufficient evidence of the efficacy and safety of Luxturna, to support its approval in the U.S.

**CAS9 MEDIATED THERAPY**

**GIANNICOLA GENOVESE, MD**

Genome editing methods have revolutionized the approach to basic, as well as translational, research and enabled unprecedented clinical applications. There are three types of genome editing applications CRISPR-Cas9 technology:

- **Ex vivo** somatic editing therapy involves taking cells from a patient, editing the genetic code, and transplanting them back into the patient.
- **In vivo** somatic editing therapy is when a viral vector that carries the genetic editing system is produced in a lab and injected into the patient, after which the targeted gene is modified as instructed.
- **In vitro** germline editing medicine involves injecting genome editing nucleases into zygotes in a lab, which then edit specific DNA sequences. The zygotes will be then subjected to preimplantation genetic diagnosis (PGD), verifying the correct editing occurred. The zygotes with the proper genetic mutations are then prepared for embryo transfer to be implanted into the mother.

There are a few clinical applications of this technology. In hematology/immunology, the **ex vivo** method can potentially be used to remove pathological mutations hematopoietic stem cells and for the genetic editing of cell receptors to fight infections. The **in vivo** method can correct inborn errors of metabolism and somatic, organ specific correction of deleterious mutations such as in the liver, retinas, and lungs. There are a number of pitfalls that have come up with regard to this technology. Substantial concerns exist on the safety of CRISPR-based genome editing. There are compelling ethical issues towards genetic manipulation of human embryonic tissues.

Ongoing research into this technology includes the development of safer editing tools and new Cas9 variants with less off-targets, as well as additional effective and safe delivery methods. The field is advancing at an amazing speed as new biology of the bacterial CRISPR system is discovered. Research efforts are ongoing to use this technology to treat a variety of different disorders.
3. Bioinformatics and Data Acquisition

NEW LESSONS FROM AN OLD GENE: COMPLEX SPlicing AND A NOVEL CRYPTIC EXON IN VHL GENE CAUSE ERYTHROCYTOSIS AND VHL DISEASE

BETTY GARDIE, PhD

In 2002, a new phenotype, known as the Chuvash polycythemia, was identified and associated with a specific VHL homozygous mutation. Chuvash polycythemia is an autosomal recessive form of congenital erythrocytosis without tumors. Since then, other missense VHL mutations have been described in patients with congenital erythrocytosis. Some patients present with VHL disease in the absence of identified mutations or deletions in the VHL gene. In addition, some patients with erythrocytosis have been found to be heterozygous rather than homozygous for the expected alteration.

Through this research, a new cryptic VHL exon was identified, known as E1'. Mutations in E1' were found in seven families with erythrocytosis and in one large family with typical VHL disease but without any alteration in the other VHL exons. The evidence suggests that the E1' mutations induce dysregulation in the VHL splicing, resulting in the VHL-related manifestations. These findings open new avenues for diagnosis and research into the VHL-related hypoxia-signaling pathway.

VISION: VHL INFORMATION SHARING INTERNATIONAL CONSORTIUM

RAYMOND KIM, MD, PhD

Due to the rarity and complexity of VHL disease, scattered information about patients and gene changes has made it difficult to understand and treat VHL. To address these issues, an international team of clinicians and scientists who specialize in VHL disease (VISION) was assembled. VISION’s goal is to improve VHL disease understanding and treatment on a globally sharing genomic and clinical information.

VISION focuses on three main projects that will ensure VHL-related information is carefully gathered and made available to everyone around the world:

- Build the largest database of VHL cases.
- Develop a VHL Expert Panel to research links between genetic mutations and VHL disease symptoms.
- Freely share this data with the global medical community using existing, accessible, and reliable databases.

These efforts will advance clinical data collection strategies and spread knowledge of VHL mutations resulting in improved diagnosis, surveillance, and treatment of VHL patients.

BIOINFORMATICS TOOLS TO GAIN INSIGHT INTO PROTEOMIC AND GENOMIC DATA

CHRISTINE PETERSON, PhD

While standard analysis of gene expression typically begins with assessing differential abundance of individual genes, multivariate methods that look across pathways or sets of genes can often improve power and provide more interpretable results. In particular, gene set enrichment analysis (GSEA) and single-sample gene set enrichment analysis (ssGSEA) can be used to detect coordinated changes in expression for a given pathway, while deconvolution methods such as CIBERSORT can be used to identify the abundance of different cell types within a sample.
4. New Developments in Imaging Technology

OVERVIEW OF IMAGING MODALITIES IN THE MANAGEMENT OF VHL LIFECYCLE
W. Kimryn Rathmell, MD, PhD

The clinical management of VHL has recently undergone a series of changes in recommendations and guidelines for early detection and interventions. A recent publication by Rednam, et al, has suggested more aggressive surveillance and earlier attention to the prospective identification of lesions. Now, therapeutics targeting key pathways common to all VHL deficient cells are underway.

Current guidelines call for the following image-based screenings:

<table>
<thead>
<tr>
<th>Imaging Site</th>
<th>Pediatric</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retina</td>
<td>Annual visualization</td>
<td>Annual visualization</td>
</tr>
<tr>
<td>Brain/cerebellum (Internal auditory canal)</td>
<td>If symptomatic (if recurrent ear inf.)</td>
<td>MRI every 2-3 years or more as needed</td>
</tr>
<tr>
<td>CT/LS Spine</td>
<td>Az above</td>
<td>Az above</td>
</tr>
<tr>
<td>Adrenal/Paraganglioma</td>
<td>MRI/MIBG if blood/urine test +</td>
<td>MRI/MIBG if blood/urine test +</td>
</tr>
<tr>
<td>Kidney</td>
<td>Annual ultrasound (MRI if findings)</td>
<td>Annual US or MRI, MRI at least q2y</td>
</tr>
<tr>
<td>Pancreas</td>
<td>No recommendation</td>
<td>Annual US or MRI, MRI at least q2y</td>
</tr>
</tbody>
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Imaging of the retina should include direct visualization with a recording of the findings over time. Imaging of the brain and spine should be performed with MRI, including specialty scans to image specific regions. Imaging of the abdomen for kidney, adrenal, or pancreas tumors:
- Ultrasound is easy, non-invasive, fast, cheap, but has low sensitivity
- CT is easier to read, relatively inexpensive, easy to get, but exposes to cumulative lifetime exposure to radiation risk.
- MRI is the highest quality image, hard to read, hard to schedule, expensive, but high sensitivity and specificity

NOVEL IMAGING APPROACHES
Ivan Pedrosa, MD, PhD

Patients with VHL disease suffer from the development of benign and malignant tumors in multiple organs during their lifetime. There are currently no optimal biomarkers to screen or monitor the progression of these tumors. Accordingly, imaging plays an essential role in the screening, initial diagnosis/staging, and monitoring of the progression of these disease-associated neoplasms.

Apart from retinal hemangioblastomas, which are diagnosed by direct retinal examination, the most common tumors assessed by imaging involve the central nervous system (CNS), kidneys, pancreas, adrenals/retroperitoneum, and epididymis. The wide variety of organs involved require extensive anatomic coverage while maintaining high-resolution strategies that permit the evaluation of complex anatomy. Furthermore, because many of these tumors can develop early in life, patients require multiple diagnostic imaging examinations during their lifetime. Moreover, some patients suffer renal function impairment secondary to renal tumors or their treatment. As a result, exposure to repeated doses of radiation and/or contrast during computed tomography (CT) exams is particularly problematic in this patient population. There are some novel CT technologies that offer an opportunity to reduce the radiation dose and intravenous contrast requirements.

Magnetic resonance imaging (MRI) provide excellent detail of the CNS and abdomen, the most common locations for VHL-related tumors. However, it is frequently associated to long examination times. Similarly, recent concerns have been raised about the administration of repeated doses of gadolinium-based contrast agents for MRI. In response, there are novel approaches for short MRI protocols and non-contrast MRI techniques. Contrast-enhanced ultrasound is
another option, particularly in the context of abdominal neoplasms.

In the era of personalized medicine, there will are specific scenarios for the use of each type of imaging, with machine learning and artificial intelligence expected to play a greater role in diagnostics and treatment moving forward.

**[18F]FAZA PET IMAGING REVEALS PRECISE PHARMACODYNAMICS IN VIVO OF THE NOVEL CHEMOTHERAPEUTIC IACS-010759**

**Seth Gammon, PhD**

Genetic deletions and mutations that result in defects in the cell’s ability to breakdown glucose, force the resultant tumors to depend on energy released from enzymes oxidizing nutrients for growth. Tumors, particularly those that rely on oxidized nutrients, yield low oxygen environments. Researchers have uncovered a way to use FASA, an imaging agent, to highlight these low oxygen areas existing in tumors.

As stereotactic ablative radiotherapy (SABR) plays a bigger role in RCC treatment options, identifying areas of hypoxia, particularly those that are drug-induced, may help enable personalized treatment and medication plans. Studies have shown that manipulating oxygen levels may influence treatments outcome. This method may also be applicable to other therapies that modulate oxygen consumption.

**NOVEL KIDNEY IMAGING**

**Emily Chang, MD**

VHL disease comes with the need for a lifetime of surveillance, the primary method of which is medical imaging. Beginning at age 16, the current surveillance guidelines recommend abdominal imaging with contrast-enhanced magnetic resonance imaging (MRI) annually, although this can be replaced with a quality ultrasound every other year. In the central nervous system (CNS), contrast-enhanced MRI is recommended every 2 to 3 years. For an individual who lives to their 70s, this can mean upwards of 45 lifetime MRI scans, which also means exposure to high lifetime doses of gadolinium-based contrast agents. Historically, these contrast agents have been known to be quite safe with few significant adverse effects, but more recent findings have suggested that gadolinium can deposit in certain areas of the brain. The clinical importance of this is not yet known. In addition, MRI is also costly and can be difficult to tolerate for some patients. Patients with metal implants cannot get MRI. Computed tomography (CT) is an appropriate alternative, but repeating CT scans can lead to a cumulative high dose of radiation.

Identification of a safe imaging technique that has equivalent sensitivity to contrast-enhanced MRI for detection of the abdominal VHL manifestations would allow minimization of total lifetime MRI exposure. Contrast-enhanced ultrasound (CEUS) is an emerging ultrasound technique that has been in use for decades for cardiac imaging. It has been more recently investigated for abdominal applications. CEUS uses microbubble contrast agents that can be used to monitor blood flow and tissue perfusion. It is cost efficient, safe, and can yield images in real-time. However, it is not yet FDA-approved for the kidneys, has a short enhancement and circulation time and only provides imaging in a single plane. The microbubble contrast agents are breathed off after minutes of circulation. They are not cleared through the kidneys and are not toxic to the kidneys.

While CEUS may prove to be a very valuable tool in the surveillance of kidney lesions, it is not a complete replacement for MRI. However, by reducing the frequency of gadolinium-enhanced MRI over a patient’s lifetime, it reduces the total lifetime requirement of MRI and the total lifetime exposure to gadolinium. There are still hurdles to clear as far as diagnostic accuracy, optimal imaging protocol, availability, clinical acceptance and implementation.

In the future, this technology may also be used for molecular imaging, directed therapies and surveillance for other organs. More studies to determine feasibility and accuracy are required.

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**Conclusions**

- Contrast-enhanced ultrasound is a potential novel imaging tool that may prove useful in kidney cyst/mass surveillance in VHL patients
  - Screening
  - Diagnosis
- Requires studies to determine feasibility and accuracy

In the future, this technology may also be used for molecular imaging, directed therapies and surveillance for other organs. More studies to determine feasibility and accuracy are required.
IN SILICO EXPLORATION OF VON HIPPEL-LINDAU (pVHL) TUMOR SUPPRESSOR MOLECULAR FUNCTIONS: CORRELATIONS BETWEEN DISEASE MUTATIONS, INTERACTORS AND PATHWAYS

GIOVANNI MINERVINI, PHD

VHL disease is associated with a functional inactivation of the VHL protein (pVHL) and is characterized by tumor development in different target organs. Since its discovery, efforts in correlating pVHL mutations and types of developed tumors have been made. Researchers investigated the correlation between genetic mutations and manifestations. Evidence of patients developing different manifestations, despite harboring the same mutations, suggests that molecular details about VHL are far from being clear.

Researchers speculate that the VHL protein presents different binding interfaces and their alteration affects its interaction with multiple proteins driving development of different tumors. Research is underway to learn more about the VHL protein, how it triggers tumor transformation and the general development of VHL-related tumors.

5. CNS Hemangioblastomas

TARGETING METABOLISM AND ANGIOGENESIS IN VHL RELATED TUMORS

OTHON ILOPOULOS, MD, PHD

Evidence exists showing that tumor hypoxia (lack of oxygen) and cancer-associated mutations (such as VHL) promote HIF (Hypoxia-inducible factor) activity. Based on this evidence, HIF has been established as a validated target for RCC and other cancers. It has also provided insight into the biology of hemangioblastomas.

HIF2α inhibitors are drugs that decrease abnormal production of red blood cells and angiogenesis. Animal models are being used to learn more about using HIF2 alpha inhibitors to downregulate HIF2α signaling. Peloton’s PT2977 drug that is currently undergoing clinical trials, is an example of directly targeting HIF2α with small molecule inhibitors. Preliminary results have shown that PT2977 is well tolerated and has activity in heavily pre-treated metastatic RCC patients.

VHL renders RCC tumors sensitive to glutaminase inhibition. Glutamine dependence is a critical feature and a vulnerability of VHL-related RCC, suggesting that glutaminase 1 (GLS1) inhibitors are novel therapeutic agents for RCC. The glutaminase inhibitor CB-839 is now in clinical trials for the treatment of RCC and other HIF-driven cancers.

Further research revealed that a complete inactivation of VHL proteins is necessary for CNS hemangioblastoma formation and that these tumors have a high lipid content. While HIF is known to reprogram cancer cell metabolism and renders VHL cells dependent on Glutamine, this remains to be proven for hemangioblastomas.
Research is ongoing to reveal if there might be a synergistic effect when certain drugs are used in combination to treat these tumors. A xenograft mouse model may guide the development of targeted therapy for CNS hemanigoblastomas.

6. Renal Cell Carcinoma

HIF2 IN RENAL CANCER
JAMES BRUGAROLAS, MD, PhD

*VHL* is arguably the most important gene in the development of ccRCC. *VHL* is inactivated in the majority of tumors. Furthermore, *VHL* is the only consistently inactivated gene in ccRCC and its inactivation may precede tumor development by several years.

*VHL* loss results in upregulation of the HIF2α protein, which is essential for tumor development. This makes HIF2α an attractive target for drug development.

While HIF2α was previously thought to “undruggable,” structural analyses of the HIF2α protein at UT Southwestern identified a potential vulnerability. A cavity was discovered, which could provide a foothold for a drug. Drugs are currently being tested in patients that specifically target HIF2α, specifically Peloton’s PT2977, which is being evaluated in patients with VHL syndrome. PT2977 is a promising strategy against RCC as it is also quite well tolerated.

DNA DAMAGE SIGNALING AND THERAPEUTIC OPPORTUNITIES IN VHL DISEASE
ERIC JONASCH, MD

RCC displays a moderate level of genomic instability, suggesting that there may be a shortcoming in DNA damage response (DDR). However, RCC does not harbor frequent mutations in recognized DDR genes, but nearly always has a mutation in the *VHL* gene and loss of chromosome 3p.

Research has shown that pVHL (VHL protein) loss is sufficient to cause homologous repair deficiency (HRD) early in RCC development. Early stage RCC tumors display dysregulated DDR signaling, significantly more than in late stage disease, and data show a functional HRD signature in RCC tumors and an association with a VHL mutation and early stage disease.

These findings establish *VHL* as a key regulator of DDR signaling in early RCC development.

CLINICAL AND SURGICAL MANAGEMENT OF VHL-RELATED CYSTS AND CYSTIC RCC
Mark Ball, MD

Renal cysts and cystic renal cell carcinoma (RCC) are common manifestations of VHL. They occur in 25%-60% of people with VHL. Of those VHL patients who do develop kidney manifestations, about 70% will be before the age of 60. Management of these lesions can include active surveillance and surgical removal. The vast majority of lesions that appear to be simple cysts on imaging end up being benign cysts. VHL-related solid kidney tumors will usually exhibit linear growth.

Most interventions are based on solid tumors. Research has shown that when patients are managed using the 3cm surgical guideline, they are very unlikely to develop metastatic disease. Patients who have developed metastatic disease have had large (> 3cm) solid tumors. While removal of the cyst cover is not recommended in surgery, removal of all tumor tissue enucleation is and intraoperative ultrasound is critical.
**EVOLUTION OF CLINICAL STUDIES IN VHL DISEASE**

Ramaprasad Srinivasan, MD, PhD

Patients with VHL are at risk for developing tumors in multiple organs, including the kidney (clear cell renal cell carcinoma), the pancreas (pancreatic neuroendocrine tumor), pheochromocytomas, CNS hemangioblastomas, and retinal hemangioblastomas. VHL associated tumors are managed surgically in most organ systems affected, with tumors resected periodically. The goal of surgery is to minimize the risk of metastases and to control local symptoms and systemic complications. Since repeated surgeries are associated with significant long term morbidity, there is significant interest in the development of nonsurgical approaches for VHL patients.

VHL is caused by germline mutations in the VHL tumor suppressor gene. One of the better characterized consequences of loss of VHL function is the dysregulated expression of hypoxia inducible factors, particularly HIF-2 alpha, and consequent overexpression of growth factors such as Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR).

A variety of approaches targeting the downstream consequences of VHL inactivation have been evaluated in the clinic. While approaches targeting the VEGF-axis are associated with antitumor activity, the toxicity profile is not tolerable to many VHL patients and the long term clinical utility of these approaches remains unclear. More recently, approaches targeting HIF-2 alpha have attracted significant interest and are currently undergoing clinical evaluation in VHL patients.

**VHL KNOCKDOWN KIDNEY CELLS INDUCES MACROPHAGE EXTRAVASATION AND POLARIZATION TOWARD TUMOR-ASSOCIATED MACROPHAGE (TAM) IN PROGRESSION OF CLEAR-CELL-RENAL CELL CARCINOMA**

Tien Hsu PhD

Kidney cancer is a worldwide health concern. It is predicted that from 2012 - 2020, kidney cancer will increase globally by 22%. The VHL tumor suppressor gene is closely linked with renal cell carcinoma (RCC). Up to 80% of sporadic clear cell RCC carry VHL mutations or epigenetic modifications. Nearly 100% of the familial RCC (in VHL disease) are related to VHL.

There is a very close causal correlation between RCC and inactivation of the VHL tumor suppressor gene. To study this correlation, a previously developed mouse model was used to demonstrate a critical link between tissue inflammation and RCC formation. The results showed an abundance of infiltrating macrophages and lymphocytes, which are white blood cells that are an important part of our immune system, in inflammatory kidney tissue of the VHL mouse, accompanied by abnormal clear cells and hyperplastic cysts. Monocyte-derived tissue effector cells, macrophages, is a crucial player in connection of inflammation and cancer formation. Macrophage infiltration in the inflammatory microenvironment has been observed in previous studies of RCC models containing VHL mutations. However, the mechanism by which VHL cells attract macrophage during RCC formation has remained unclear.

Research was conducted to study the interaction between VHL loss-of-function kidney cells and macrophage in progression of clear-cell-renal cell carcinoma. Researchers found that VHL cells recruit macrophages through secreting relevant cytokines. It is thought that in the inflammatory microenvironment induced by VHL, macrophages aggregate and polarize promoting tumor formation. The cytokines secreted from VHL cells, or tumor-promoting cytokines released by invasive macrophage, may present novel targets for anti-RCC therapy.
GERMLINE GENOTYPE ANALYSIS AS A CLINICAL TOOL IN THE MANAGEMENT OF PATIENTS WITH VHL ASSOCIATED PANCREATIC NEUROENDOCRINE TUMORS
Amit Tirosh, MD

The specific mutation in the VHL gene that each person has is associated with a clinical phenotype of VHL. 35-70% of VHL patients will develop pancreatic tumors or cysts. 8-17% of VHL patients will develop pNETs, of which 30-50% will develop multiple pNETs AND 8.3%-12.8% will develop metastatic disease. Current guidelines suggest that those with pNETs with a diameter greater than 3cm, a doubling time less than 500 days, and/or a mutation in exon 3 of the VHL gene should be considered for surgery. Research is being conducted to determine which VHL mutations may be associated with VHL-related pNETs. Studies have shown that:

- VHL patients with a missense mutation may have shorter disease-free intervals, higher rate of metastases, and more often require surgical intervention than those VHL patients with non-missense mutations.
- Patients with solid pancreatic lesions that are less than 1.2cm in diameter may have a lower risk for metastasis or requiring surgical intervention. Those with solid lesions greater than 3cm may have a higher risk for metastases.
- Patients with a tumor diameter between 1.2cm and 3cm with a missense VHL mutation, and/or mutations in exon 3 of the VHL gene may have a higher risk of requiring surgical intervention.

In the future, determining the specific VHL mutation may be used to assess the risk of patients with VHL for having a solid pancreatic lesion, and may be a complementary tool to tumor diameter for determining the risk of metastases and requiring surgical intervention. More research into predicting the impact of missense VHL gene mutations may further define the prognosis of patients with pancreatic manifestations of VHL.

SURGICAL MANAGEMENT OF VHL ENDOCRINE MANIFESTATIONS
Electron Kebebew, MD

VHL disease is an inheritable cancer-predisposition syndrome with multi-organ involvement. Pheochromocytoma (pheos) and pancreatic neuroendocrine tumors (pNETs) are common manifestations of VHL that require a multidisciplinary team. Pheos occur in about 10%-20% of people with VHL and pancreatic tumors or cysts occur in 35%-70% of patients.

There have been significant advances in our understanding of the natural history of VHL-related pheos and pNETs, genotype-phenotype associations that impact patient outcome, new generation tumor specific imaging studies, and treatment alternatives for these tumors. Pheos are diagnosed using 24-hour urine testing or plasma free fractionated normetanephrine/metanephrine using blood. Surgical intervention may be required and preoperative alpha-blockade and volume repletion is essential. Guidelines recommend biochemical and radiological screening every 1–2 years for pheos in patients with VHL. With regard to surgery, a partial adrenalectomy might be appropriate and may prevent the patient needing steroid replacements. It is the best approach if there are no signs of malignancy and no family history of malignant pheos. It is easiest to perform when the tumor is small. A total adrenalectomy will avoid risk of recurrence.

PNETs occur in about 8%-12% of VHL patients. Enucleation is the optimal surgical solution if there is a low risk for malignancy. If there is a high risk for malignancy, there is pancreatic duct involvement or if there are multiple lesions in the region, a pancreatectomy may be required.
Screening and surveillance for pheos and pNETs is essential to reduce morbidity and mortality. For localized and low-risk pheos, adrenal preserving surgical intervention is preferable. For pNETs, surgical intervention that preserves pancreas function is optimal, but dependent on the situation.

**MALIGNANT PHEOCHROMOCYTOMAS IN VHL**

Camilo Jimenez, MD

About 10-20% of patients with VHL will develop pheochromocytomas and sympathetic paragangliomas (pheos). These tumors frequently secrete excessive amounts of noradrenaline, predisposing patients to hormonal disease. 90% of these tumors are non-metastatic, which means that they are not at risk for spreading to other organs, and could be cured with surgery. Only 10% of these tumors are metastatic and may spread to organs, such as the bones, lymph nodes, liver, and lungs.

Patients with malignant tumors are at risk for cardiovascular (heart attacks, arrhythmias) and gastrointestinal complications (severe constipation) because of the excessive secretion of noradrenaline. Furthermore, metastatic disease can predispose the person to severe tumor burden related complications such as skeletal related events (fractures, cord compression, hypercalcemia), lung and liver failure, and urinary tract obstruction. There are limited therapies for those with metastatic pheos. Resection of the primary tumor may improve survivorship and quality of life. Chemotherapy (CVD) works in about 37% of patients and conventional MIBG (metaiodobenzylguanidine) therapy works in about 30% of patients.

Over the last decade, the value of chemotherapy has been recognized and several potential systemic therapies have been identified. There is a need to study therapies with novel mechanisms of action. Therapies should usually be initially studied alone; nevertheless, clinical trials combining therapies in a simultaneous and sequential manner are an essential goal. Some therapies that are currently being investigated are High Specific Activity MIBG, sunitinib, cabozantinib, and HIF-2A inhibitors. Additional clinical trials into the use of tyrosine kinase inhibitors, radionuclide agents, and HIF inhibitors may yield promising results.

**VHL IN THE GENOMIC LANDSCAPE OF PHEOCHROMOCYTOMA AND PARAGANGLIOMA**

Anne Paule Gimenez-Roqueplo, MD

PPGLs are neuroendocrine tumors with a strong genetic component. A germline mutation in one of the fifteen susceptibility genes identified so far explains about 40% of all cases. About 7%-10% of these mutations are located on the VHL gene.

Research has revealed the crucial role of predisposing gene mutations as being the main drivers of PPGL tumor development. Additionally, PPGL subtypes can be defined by a set of unique genomic alterations that represent different molecular entities. Studies have identified two main molecular pathways, activating either the hypoxic pathway or the MAP kinase/mTOR signaling pathway. VHL-related tumors are all classified in the hypoxic pathway and are distinguishable from other pseudo-hypoxic tumors.
Currently, next-generation sequencing (NGS) is the ideal technology to screen the high number of PPGL susceptibility genes and to precise molecular classification at tumoral level. New tools have been developed for helping the interpretation of genetic variants identified and research data have helped the deciphering of tumors, notably VHL-related tumors, within the genomic landscape of PPGL. This has opened the door to a personalized medical management for the affected patients and their relatives.

**SYNONYMOUS but not SILENT: A SYNONYMOUS VHL MUTATION CONFERS SUSCEPTIBILITY to PHEOCHROMOCYTOMAS IN A FOUR-GENERATION FAMILY**

Shahida Flores, MS

Pathogenic mutations in the *VHL* gene predispose individuals to a variety of clinical presentations including renal cell carcinomas, pheochromocytomas (PCCs), hemangioblastomas of the central nervous system, and other manifestations. There are several different types of pathogenic mutations. Synonymous, or "silent" mutations, are presumed to have a neutral effect. This means that there is a change in the nucleotide sequence, but not the amino acid sequence. However, synonymous mutations are not always silent and can be pathogenic.

The *VHL* gene consists of three exons and encodes for two main naturally occurring transcripts – a full length transcript with includes exon 1, 2 and 3, and a shortened transcript which skips exon 2 and includes only exon 1 and 3. *VHL* exon 2 is critical for the HIF binding domain; predominant expression of the shorter isoform leads to elevated HIF targets associated with the development of tumors. Research has demonstrated in other genes and other cancers, that synonymous mutations can actually alter pre-mRNA splicing and act as driver mutations. It is likely more complex that this for VHL, but it is only a matter of time until we define an exact mechanism.

We report a four-generation family with a history of PCCs and demonstrate that a synonymous VHL mutation, c.414A>G, is pathogenic because it promotes skipping of exon 2. Most genetic screening workflows exclude synonymous mutations. The presented findings show that synonymous variants in coding regions of *VHL* should be taken into consideration, as they may have splicing disruptions and affect protein function. Families presenting with clinical features of VHL but with no reported pathogenic mutations, should be tested to see if any synonymous mutations are present.

8. Retinal Hemangioblastomas

**MURINE MODEL OF VHL RETINAL HEMANGIOBLASTOMAS**

Herui Wang, PhD

VHL disease is an autosomal dominant tumor predisposition syndrome characterized by the development of highly vascularized tumors and cysts. Loss of heterozygosity (LOH) of the *VHL* gene results in an increase of hypoxia-inducible factors (HIF) and has been associated with tumor formation. Hemangioblastomas of the central nervous system and retina represent the most prevalent VHL-associated tumors, but no VHL animal model has reproduced retinal capillary hemangioblastomas (RCH), the hallmark lesion of ocular VHL.

Researchers developed a mouse model. The VHL-affected mice demonstrated retinal vascular lesions associated with prominent vasculature, abnormal capillary networks, hemorrhage, exudates, and localized fibrosis. Histological analysis showed RCH-like lesions characterized by tortuous, dilated vasculature surrounded by "tumorlet" cell clusters and isolated foamy stromal cells, which are typically associated with RCH. Fluorescein angiography suggested increased vascular permeability of the irregular retinal vasculature and hemangioblastoma-like lesions. VHL deletion was detected in "tumorlet" cells via microdissection.
The study provided a mouse model of VHL-related RCH that may be useful to study RCH pathogenesis and therapeutics aimed at treating ocular VHL.

**VASCULAR ABNORMALITIES WITH VHL MUTATIONS**

*John Chappell, PhD*

Mutations in the *VHL* gene often give rise to hemangioblastomas in neural tissue, in addition to highly vascular renal cell carcinoma (RCC) lesions. Hypoxia Inducible Factors (HIFs) and Vascular Endothelial Growth Factor-A (VEGF-A) are among many downstream genes and pathways that contribute to pathological vascular remodeling.

Recent research found that Type 1 (null) and Type 2B *VHL* mutations also compromise Notch signaling, leading to vascular perturbations specific to each mutation type. Induction of both conditional *VHL* mutations in the developing mouse retina had relatively little effect on early stages of vessel branching, though arterial and venous branching was severely reduced at later time points.

Both *VHL* mutations also accelerated maturation of vessels towards an arterial phenotype, reflected in increased artery diameter and arterial-venous shunts, and aberrant expression of alpha-smooth muscle actin, particularly by vascular pericytes. RNA sequencing analysis of whole retina revealed gene transcription changes within several vascular-related pathways, including VEGF-A, Notch, and smooth muscle cell contractility.

Disrupting Notch signaling in both mutant backgrounds did not reverse later-stage changes in vessel branching but did rescue the accelerated arterial phenotype. Inducing the Type 2B *VHL* mutation caused stage-specific changes in vascular branching as well as an accelerated progression towards arterialization. Notch inhibition in this context increased vessel branching within arterial and venous regions, but rescued arterial maturation back toward non-mutant outcomes.

The differential effects of the Type 1 (null) and Type 2B *VHL* mutations on retina vessel branching and maturation offer insight into the variability of VHL-related vascular anomalies. These observations also suggest the Notch pathway as a viable option for treating vascular-related complications arising from *VHL* mutations.

**REPURPOSING PROPRANOLOL FOR THE TREATMENT OF VON HIPPEL-LINDAU DISEASE**

*Angel Cuesta, PhD*

Researchers and physicians are looking to find a non-invasive, safe, and long-term therapy for VHL disease, that is able to impair, or even stop, the growth of central nervous system (CNS) and retinal hemangioblastomas, as well as renal cell carcinoma (RCC). The most frequent tumors in VHL are CNS and retinal hemangioblastomas and RCC. Since the systemic medical approaches have not provided long-term cessation of tumor growth up to now, standard treatments involve repeated surgeries and other invasive procedures.

Propranolol, a non-selective beta blocker that is used for the treatment of hypertension and other cardiac and neurological diseases, has proven effective for infantile hemangioma due to its anti-angiogenic and proapoptotic properties. It could also be a useful treatment for hemangioblastomas and RCC in VHL. In line with these findings, propranolol has been also recently used in combination therapies for cancer. In order to avoid the multiple surgical interventions and provide a non-invasive, safe, and long-term therapy for VHL, propranolol repurposing has been tested for its therapeutic application.

Our lab has performed some experiments with propranolol and CNS hemangioblastoma cells derived from different patients. In our hands, propranolol is able to selectively kill the tumor cells and avoid pathologic tumor-related processes. In addition, we have also seen an impairment of tumor growth by propanolol in mouse models bearing human RCC cells.

A clinical trial developed in Spain shows a stabilization of all retinal tumors and the absence of new tumors when treated with propranolol. Reabsorption of retinal exudation was noted and no adverse effects were recorded, except for hypotension in one patient. Analysis of VEGF, EPO, and SOX2 had shown a reduction after propranolol treatment, becoming as possible biomarkers of VHL. Propranolol also showed a synergistic effect together with temozolomide in a metastatic paraganglioma case by potentiating the apoptosis and decreasing the viability in the VHL derived treated cells.

This research into propranolol may open new doors for clinical applications on VHL and another diseases.
NEW IN VIVO MODEL FOR VHL RETINAL HEMANGIOMAS
Anna Matynia, PhD

Retinal hemangioblastomas are often the first manifestations of VHL and have significant consequences for vision. At presentation, retinal hemangiomas are often large, highly vascular, characterized by giant foamy cells of unidentified origin, located in the superficial layers of the retina and project into the vitreous. Retinal hemorrhage and exudation from leaky blood vessels can lead to retinal damage and detachment resulting in vision loss.

Researchers have generated a mouse model of retinal hemangioblastomas in which the effects of loss of expression of the VHL gene is limited to the eyes so as to not compromise their overall health and survival. Vascular alterations, consistent with outward growing retinal hemangiomas described in VHL patients prior to formation of overt hemangioblastomas, are observed as an early phenotype in this novel ocular mouse model of VHL. Abnormal superficial blood vessels, consistent with small hemangioblastomas, are observed as a later phenotype. The researchers hypothesized that the earliest lesions form at the RPE/photoreceptor layer and grow inwards to break through the retina. There unrestricted growth leads to a classic hemangioblastoma with exudation and bleeding that threatens vision. This targeting of retinal cells causing genetic loss of VHL proteins enables us to identify key cell types in the initiation and progression of disease. A major use of this model system will be determining and testing new strategies for retinal hemangioblastoma prevention and treatment.

9. Clinical Guidelines

UNIVERSAL REFLEX REFERRAL TO VHL COMPREHENSIVE CLINICAL CARE CENTER OF PATIENTS PRESENTING TO OPHTHALMOLOGISTS LEADS TO DRAMATIC IMPROVEMENT IN GUIDELINE-CONCORDANT SCREENING: RESULTS OF A PILOT STUDY
Anthony Daniels, MD

VHL affects many organ systems and requires treatment by multiple specialists. Thus, care is often fragmented. It is difficult for a physician seeing a VHL patient for the first time to ascertain which other specialists are ordering screening studies, and whether the patient's screening is up-to-date and guideline-concordant. In 2017, Vanderbilt became one of a dozen CCCCs in the U.S. At that point, the hospital instituted a quality improvement initiative to improve guideline-concordant screening. All VHL patients who came to their ophthalmology clinic were referred directly to the Vanderbilt CCC oncologist for surveillance imaging. This was done regardless of whether they were being followed by other specialists.

The data collected shows that prior to creating the CCC in 2017, 0% of patients were guideline-concordant at the time they presented to ophthalmology, while only 29% were concordant afterwards. After creating the CCC and the reflex referral initiative, rates of guideline-concordant surveillance imaging increased to 100%, following the reflex referral. The data also showed that 50% of patients referred from ophthalmology to CCC oncology had (non-ocular) tumors requiring intervention at the time of initial screening imaging.

Conclusions

- Simple intervention: Refer ALL pts to oncologist
- Dramatic improvement in guideline-concordance
  – From 0% to 100%
- HALF of all patients seeing ophthalmology had another tumor – and didn’t know it!
- For any specialist seeing a patient with VHL, think about what other cancers you are sending out the door...
Rates of guideline-concordant screening have historically been poor, even for patients being followed for VHL-related tumors by subspecialists. The evidence suggests that the simple intervention of implementing a universal reflex referral policy for VHL patients to a CCCC, dramatically improved guideline-concordant screening rates to 100%. Half of all patients have a (non-ocular) tumor requiring treatment at the time they present to ophthalmology, underscoring the importance of expeditious referral.

**RECOMMENDATIONS FOR VON HIPPEL–LINDAU TUMOR SURVEILLANCE IN CHILDHOOD AND ADOLESCENCE**

Surya Rednam, MD

Von Hippel–Lindau disease (VHL) is a hereditary tumor predisposition syndrome that places affected individuals at risk for multiple tumors. These tumors are predominantly benign and generally occur in the central nervous system or abdomen. While the majority of tumors occur in adults, children and adolescents with the condition develop a significant proportion of VHL manifestations and are vulnerable to delayed tumor detection and its consequences.

Multiple tumor screening paradigms are currently being utilized for patients with VHL. Surveillance should be reassessed as the available relevant clinical information continues to expand.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Surveillance</th>
<th>Starting</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal hemangioblastoma</td>
<td>Eye exam</td>
<td>Birth</td>
<td>Annual</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>BP at all visits</td>
<td>2 years</td>
<td>Annual</td>
</tr>
<tr>
<td>Endolymphatic sac tumor</td>
<td>Audiogram</td>
<td>5 years</td>
<td>Biennial</td>
</tr>
<tr>
<td>CNS hemangioblastoma</td>
<td>MRI brain</td>
<td>8 years</td>
<td>Biennial</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td>MRI abdomen</td>
<td>10 years</td>
<td>Annual</td>
</tr>
<tr>
<td>Pancreatic NET</td>
<td>MRI abdomen</td>
<td>10 years</td>
<td>Annual</td>
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The rationale for most of the recommended screening guidelines updates was that the risk is significant and that they may present early in life. For retinal hemangioblastomas, pre-symptomatic detection is possible and early intervention may prevent permanent vision loss. For pheochromocytomas, pre-symptomatic detection is also possible. Early intervention may prevent severe hypertension, facilitate less invasive surgical approach, and reduce the risk of metastases. For endolymphatic sac tumors (ELSTs), pre-symptomatic detection is possible and early intervention may prevent irreversible neurologic symptoms. For CNS hemangioblastomas, most new lesions appear in the first two decades of life. Pre-symptomatic detection is possible and early intervention may prevent severe, possibly irreversible neurologic symptoms. For renal cell carcinoma (RCC) and pancreatic neuroendocrine tumors (pNETs), early detection is possible, prior to functional impact and/or metastases. Early intervention may prevent morbidity/mortality.

As more evidence becomes available and new technologies and paradigms emerge, questions about reasonability for compliance, risk/benefit ratio and adult implications will be brought up and addressed. This information will all be used to continue to identify and refine best practices in the surveillance of children with VHL.
10. The Patient’s Perspective

HIGHLIGHTS OF BASIC RESEARCH
Tien Hsu, PhD

The classic view of cancer is that when there are mutations in a cell, they result in uncontrolled proliferation of those cells which causes cancer. Some new cell-intrinsic factors that have been discovered to be involved in VHL pathobiology are:

- AXL: a receptor tyrosine kinase
- AURKA: primary cilia function
- ZHX2: a HIF-independent transcription factor; NFkB pathway
- ISGF3: a feed-back tumor suppressor gene
- VHL deficiency directly leads to genome instability, but the mechanism remains unclear. Future studies are needed.

MicroRNA profiling in ccRCC has identified some of these unique molecules (microRNAs) that may contribute to tumor formation.

New therapeutic options that are being developed include:

- HIF2 inhibitors:
  - PT2399 and PT2977 in Phase 2 trials
- GLS1 inhibitor:
  - Phase I trial
- MIBG for metastatic pheochromocytoma, phase 2 trial
- Propranolol (reduces HIF expression) in clinical trials:
- Reduces VEGF plasma levels in hemangioblastoma
- Gene therapies:
  - Gene delivery system; Cas9

Researchers have discovered that renal cell carcinoma (RCC) is a metabolic/immune disease. They are working on how to use precision medicine with VHL patients, with a goal being the establishment of a genotype-phenotype correlation. Single-cell sequencing may soon reveal the cellular origin of hemangioblastomas. The concept of a tumor microenvironment, with an immune component, is beginning to gain notice. There have been some tremendous advances in the research and clinical care of VHL. The research that is going on now will lead to many more breakthroughs. The future is very bright.

CLINICAL ADVANCES
W. Kimryn Rathmell, MD, PhD

One major change in the clinical management of VHL has to do with diagnosis. New (previously undetectable) disease-causing mutations in VHL have been identified. These include alternative exon mutations, mutations in cryptic exons and synonymous mutations with pathogenic potential. There has been a diagnosis focus to identify new families based on VHL mutation detected in about 84% of apparently sporadic hemangioblastomas and higher than expected germline VHL in apparently sporadic pheos and paragangliomas.

Another major change has to do with screening. There are current ongoing efforts to review and update screening guidelines to better reflect updated research. This includes an assessment for phenotypic onset, as well as of modality sensitivity and specificity for detection.

New advances with regard to VHL-related retinal hemangioblastoma interventions include: laser therapy, radiation, photocoagulation, photodirected therapy, thermotherapy, intravitral anti-VEGF, and propranolol therapy. In the field of CNS hemangioblastomas and RCC, new imaging techniques, including 3D reconstruction, are changing the way surgeons approach tumors. Updated techniques for resected symptomatic and dangerous lesions are being developed that can restore functions lost due to tumors.

The establishment and continued improvement of the VHL Clinical Care Center network has allowed for patients to receive the latest and most accurate information, while creating a powerful network of VHL-experienced physicians, enabling them to share information efficiently. Efforts are ongoing to further prove the effectiveness of this initiative.

CLINICAL TRIALS: PAST AND PRESENT
Ramaprasad Srinivasan, MD, PhD

Currently, the management of VHL-related tumors calls for the establishment of local control, using surgery or ablation. The goal is to minimize the risk of metastases (RCC, pNET, pheos) and control local symptoms (CNS, retinal, ELST) and systemic complications (pheos). These interventions are associated with significant lifetime morbidity, with complications from surgery, gradual loss of renal function and neurologic complications all being issues.

Attempts are currently being made to develop a systemic therapy alternative to surgery. The goals
of this type of therapy would be to delay or avoid surgery by preventing tumor growth or shrinking tumors, prevent metastasis, improve quality of life, and preserve organ function, ideally with tolerable/manageable side effects. Therapies that target blood vessel growth (angiogenesis) as well as other approaches (including a group of proteins called hypoxia inducible factors or HIF) are being investigated. Some systemic therapy trials that utilize drugs that inhibit angiogenesis include sunitinib, pazopanib and vandetanib. Some systemic trials that utilize drugs that target HIF include 17AAG, PT2385, and PT2977.

**Clinical Trials in VHL-Summary**

- Experience restricted to small single arm phase 2 studies
- VEGFR and HIF primary targets pursued
- Tumor regression with VEGFR inhibitors, but patient tolerability a significant issue: long term clinical benefit unknown
- HIF 2 inhibitors offer a new avenue of investigation

So far, VHL-related clinical trials have been restricted to small single arm phase 2 studies. VEGFR and HIF are the primary targets being pursued. Tumor regression with VEGFR inhibitors has been seen, but patient tolerability has proven to be a significant issue and the long term clinical benefits are currently unknown. HIF2 inhibitors offer a new avenue of investigation and are being pursued in clinical trials.

**MYVHL: PATIENTS CONTRIBUTING TO VHL RESEARCH**

Ilene Sussman, PhD

Over the past number of years, the rare disease community has embraced the importance of natural history studies focused on data entered by the patient. Since information known only by the given patient is entered, this approach enhances existing and developing knowledge of registries/databanks collected by the clinical and research communities.

MyVHL: Patient Natural History Study (formally known as Cancer in Our Genes International Patient (CGIP) Databank) was recreated in response to a mandate from the VHL Alliance’s Research Council. Launched in 2014 as a longitudinal study, MyVHL includes a comprehensive series of surveys designed to collect data on each organ impacted by VHL. In addition, information about lifestyle factors (nutrition, exercise, mood) is collected with the hope of understanding how these factors influence VHL progression.

MyVHL participants can feel confident knowing that their personal identifying information will always be kept private. Only de-identified data will ever be made available to the VHL research community. No one will have access to the complete database. Only data requested will be given to researchers, after they submit a formal request explaining the proposed usage and research question being addressed. The request must be reviewed and approved by a committee before VHLA will provide any data. Additionally, MyVHL is an IRB, or Institutional Review Board, approved study. IRB approval is needed for any clinical trial and helps ensure patient privacy and safety, as well as allows research outcomes to be publishable.

With over 600 consented participants, we now have a good understanding of the populations entering data and have identified some interesting findings. Twice as many females than males have participated in MyVHL. About 24% of participants are first-in-family, with another 11% of participants who do not know if they have a family history of VHL. Only 27% of participants go to a VHL Clinical Care Center (CCC) on a regular basis, with an additional 14% of participants saying that they have only done one round of checkups at a CCC. Almost 35% of participants say that they would prefer to see clinicians close to their home.

While 20% of participants describe their general health as fair to poor, the majority feel that they are in good to excellent health. That being said, about 40% of patients often or always experience fatigue, with another 36% of participants feeling fatigued at times.
15% of participants describe feeling depressed often or always, with another 25% sometimes experiencing feelings of depression. 7% of participants would be described as clinically depressed, with another 11% who may possibly be clinically depressed. 23% of participants fall into an anxiety level of a probably clinical disorder, with another 16% possibly being clinically anxious. 25% of participants report experiencing panic attacks, which is five times more frequent than the general public, according to the National Institute of Mental Health.

40% of participants indicate digestive complaints, which is about double the frequency noted by the National Institute of Diabetes and Digestive and Kidney Disease. 24% of patients complain of persistent headaches. 21% of participants indicate thyroid problems, which is almost double the frequency in the general public, noted by the American Thyroid Association.

While offering insightful information, current enrollment in MyVHL is insufficient to do in-depth analysis. It is important to expand the reporting patient population. As such, we need to fully engage the VHL patient community to participate in MyVHL on at least an annual basis. It is also incumbent on the VHL medical and research communities to encourage them to do so.

### New VHLA Programmatic Initiatives

**Joshua Mann, MPH**

People with a hereditary disease commonly experience a heightened sense of stress and anxiety. The unpredictable nature of VHL, can cause an even greater risk in patients as well as their families and loved ones. It can help to connect with others who are on the same journey. The VHL Alliance has developed a portfolio of initiatives meant to help mitigate the psychosocial impact of VHL.

These initiatives include:

- **MyVHL: Patient Natural History Study** – vhl.org/MyVHL
- **Phone Hotline** – (800) 767-4845 x1
- **Discussion Calls**
  - Patient/Caregiver Call - vhl.org/ptcgcall
  - Parents of VHLers Call - vhl.org/parentscall
  - Low/No Vision Call - vhl.org/lownovisioncall
- **Peer Mentoring Program**
- **Young Adult Retreat** – vhl.org/iar
- **VHL Birthday Club** – vhl.org/birthdayclub
- **Well Wishes Program** – vhl.org/wellwishes
- **VHLApp** – vhl.org/VHLApp
- **VHLentines** – vhl.org/VHLentine

### Medical Coaching: What Is It All About?

**Leona deVinne, CPCC, ACC**

Medical coaching involves addressing the entire person, not simply addressing their medical situation. A medical coach works with patients that are currently undergoing medical care for a recently diagnosed condition or chronic illness. Medical coaches have expertise in the condition they’re supporting the patient with, as well as coaching skills to have a collaborative, instead of a directive approach, to achieve desired outcomes set out by the patient and medical care team.

Research shows that the impact is long lasting and results in decreased healthcare costs, increased overall wellbeing and more informed and greater adherence to advised medical protocols.
**CCC Process Improvement**

*Stacy Lloyd, MPH*

The VHL Alliance’s CCC program recognizes healthcare organizations that are providing multi-specialty, coordinated care for patients with VHL. In an effort to continue to improve the experience for both patients and CCC care teams, the VHL Alliance created the Clinical Care Center Process Improvement Committee in 2018.

The goals of the CCC program are to improve diagnosis and treatment of VHL, provide coordination of care across medical specialties, provide resource centers to patients and physicians who are new to VHL, provide a ready channel for communicating advances to these centers of expertise, provide a model that can be replicated elsewhere, and increase awareness of MyVHL and the importance of patient and caregiver emotional well-being. Clinical Care Centers that have been active for two years and have showed exemplary service may become Comprehensive Clinical Care Centers (CCCCs). Institutions designated as a CCCC also have additional multi-specialty care team members. There are currently 22 CCCs, 12 CCCCCs, and 19 International CCCs.

The mission of the VHLA CCC Process Improvement Committee is to improve the experience at designated clinical care centers (C/CCC) for both patients and physicians through support, collaboration, and enhanced communication. The vision is for Patients, physicians and care teams, and the VHL Alliance collaborating to achieve coordinated, quality care and improved quality of life for VHL patients. The committee plans on achieving this by identifying ways to increase accountability of designated clinical care centers, enhance the VHL patient experience with clinical care centers and provide support and resources for clinical care centers to improve patient care, quality of life, and patient experience.