Reflecting on 2015 – Looking Forward to 2016

Written by Ilene Sussman, VHLA Executive Director

Looking back on the efforts of the VHL Alliance in 2015, it is my great pleasure to share what has been a fantastic year and to thank you for your support. As always, it is the generosity of VHLA’s contributors that makes possible our continued efforts to identify new programs to achieve our mission of improving awareness, diagnosis, treatment, and quality of life for those affected by VHL.

2015 was a record year for VHLA’s fund-raising. Our goal of $674,000 was exceeded by over $20,000, and in total we raised $746,317 for the fiscal year. This was made possible, in part, by the continuing success of our annual NYC Gala, which raised $260,000, and community-driven efforts like Team VHL. In 2015, Team VHL grew in size and scope. Led by Suellen, the team raised VHL awareness from Virginia to Kentucky at the Hatfield-McCoy Marathon. The Team’s annual 5K, coordinated again by Suellen with the participant and fundraising efforts spearheaded by Jill and Ellen, reached new levels in Chicagoland with over 200 participants spreading the word about VHL! Keeping the ball rolling, Team VHL is building a team for the October 2016 Baltimore Marathon. Do you run (or know someone who does) and want to be part of this team of VHL Warriors?

The last few months of 2015 have proven to be very productive in our drives for VHL awareness and education. VHLA’s website (vhla.org) and VHL Handbook were both revamped and updated. Our new modern website is now more user friendly, allowing resources to be found as quickly and intuitively as possible. The new edition of the VHL Handbook (vhla.org/handbook) includes updated screening guidelines and more in-depth information about healthy living.

There is also a good deal to look forward to in 2016, including learning more about the results from the two research projects funded in 2015. Both grant recipients will be presenting at the 12th International VHL Medical Symposium (vhla.org/symposium) being held in Boston, MA on April 7–9. These studies, along with those currently being funded by VHLA and those to be funded in the future, are crucial stepping stones on the path to finding a cure for VHL.

Of course, the progress we have seen in 2015 and expect to see this year is due to the combined efforts of many people. I am assisted in my work by Susan, Suzanne, and Heidi; the VHL Alliance would be nothing without the support of the Board, our volunteers, and the community at large. Any contribution, large or small, helps our cause. I hope you will consider joining the VHL Alliance this year in reaching our goals for 2016! These goals include updating our Strategic Plan to guide the VHL Alliance through 2018 while, at the same time, continuing to expand our efforts in education, support, and fostering research.

Propranolol: Current and Potential Uses in VHL

The VHL Alliance in Spain is working with researchers affiliated with the Higher Center for Scientific Research (CSIC) in Spain on lab and clinical studies on the effect of propranolol on VHL hemangioblastomas. VHLA Spain posted a link to the lab research results on the Facebook Discussion Group last October, spurring a great deal of conversation. With many questions left unanswered and hope for a new treatment for VHL, we have provided an overview of the drug, how it is currently used in VHL, and research with the drug.

History of propranolol and some other approved uses

Propranolol is a beta-blocker drug that was originally introduced to treat high blood pressure, although it is no longer one of the first choice medications. The drug works by blocking the beta receptors on the heart and blood vessels. This has several effects: lowered blood pressure, slower heart rate, improved symp-
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toms of ischemic heart disease, and reduced frequency and severity of migraine headaches. There are three possible mechanisms of action: vasoconstriction, angiogenesis inhibition and cellular apoptosis (programmed cell death), which could work to slow down the growth of hemangioblastomas.

Administered in an oral liquid form, propranolol was approved to treat infantile hemangiomas in 2014.1 Infantile hemangiomas are the most common tumors of infancy, and are usually visible on the surface of the skin. Although they are not related to VHL, the remarkable clinical response of these lesions to propranolol has led to consideration of propranolol as a candidate drug to test.

A beta-blocker similar to propranolol, timolol, is used as an eye drop to lower pressure in the eye in the most common type of glaucoma. Unfortunately, it is not effective in treating the type of glaucoma that can occur following a retinal detachment due to VHL retinal hemangioblastoma. While timolol is no longer the first choice for reducing pressure in the eye, it may be prescribed in situations where cost to the patient is a determining factor.2

Research with oral propranolol for retinal treatment

Oral propranolol has been tried in a few patients for treatment of retinal hemangioblastoma, but has not been shown to be effective on the tumors. One patient (who tested negative for VHL with a retinal hemangioblastoma located next to the optic nerve) was treated with oral propranolol. The size of the tumor decreased by 7%, but vision did not improve. The doctors concluded that propranolol partially improved the retinal condition, but not enough to be judged effective.3 Another patient with a retinal detachment (due to a retinal hemangioblastoma not related to VHL) of the macula (the part of the retina with the sharpest vision) was treated with oral propranolol after receiving laser treatment and ocular injection of ranibizumab (Lucentis) to inhibit blood vessel growth. The fluid under the retinal detachment was absorbed, and vision improved to 20/20. When the propranolol was discontinued, the fluid gradually came back, reducing vision. Re-starting the oral propranolol again resolved the fluid and restored vision to 20/20. The patient successfully maintained this result while taking propranolol for 18 months, so propranolol was prescribed for continuing treatment. This individual case study did not look at the hemangioblastoma, but at a detachment due to the tumor. Because of the success of this treatment, researchers feel propranolol merits further study for patients with retinal detachments.4

Current approved use of propranolol in VHL

In patients with pheochromocytomas, propranolol is used as part of the preparation for surgery. The patient is first treated with an alpha-blocker (blocks receptors in arteries and smooth muscles) to increase blood flow and lower blood pressure. Propranolol (or another non-specific beta-blocker) can then be added before or during surgery to control rapid heartbeat. In cases where pheochromocytomas are inoperable or metastatic, propranolol may be used as a treatment to block excessive beta receptor stimulation from the tumor.5

New studies of propranolol for VHL hemangioblastomas

Using hemangioblastoma cells removed from four VHL patients, a recent laboratory study performed at the Higher Center for Scientific Research in Madrid in collaboration with the Association of Neurologists Researchers at Albacete, found that cells grown in the lab and exposed to high doses of propranolol showed reduced growth in the number of tumor cells and tumor cell death.6 The hope is that this finding will apply clinically to patients with VHL hemangioblastomas. As a result, the Spanish researchers are following up with a study in patients with juxtapapillary retinal hemangioblastomas (located near the optic nerve). The clinical study at Virgen de la Salud Hospital in Toledo uses oral propranolol beginning with a low dose, with an increase to a stronger dose as individually determined safe by a cardiologist. The size of the retinal hemangioblastomas is being measured at 1 month, 3 months, 6 months, 9 months and 12 months to learn if there is any reduction in tumor size.7

Could propranolol turn out to be an effective treatment for VHL hemangioblastomas? The VHL Alliance looks forward to learning the results of the completed clinical study in Toledo. As a drug with an expired patent, propranolol is available as a generic, therefore no drug manufacturer has the financial incentive to run the clinical studies needed in the US for additional FDA approvals; propranolol would have to be used as an off-label treatment. At this point, it is important to realize that there is currently no clinical evidence showing that propranolol is an effective treatment for VHL hemangioblastomas, and the drug could be dangerous for patients with undiagnosed or untreated pheochromocytomas.

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Find the Ingredients to Handle Stress—Create Your Own “Stress-cipe”

By Leona deVinne, CPCC, ACC, Leadership and Team Coach/Consultant, Facilitator of the Monthly Telephone Support Group (vhl.org/patients/living-with-vhl/seeking-support/), and VHL Patient

My son had brain surgery this past June, and I was exposed to struggle in a new way. It was extremely challenging to say the least. It made me reflect on what helps us when we are struggling. Suffering can be so isolating. You cannot really carry another’s pain and nothing anyone does gives you a break from your own.

I reflected on what are the key pieces that can help to lighten the load. These are some of the main ingredients to manage rough times:

1. Surround yourself with supportive people. These people are the ones who are really there for you, know how to be empathic and support you the way that works for you, no drama, no agenda.

2. Ask for what you need and want. This is much harder than it sounds. When you are in a very stressful situation, it is hard to even think straight.

   Keep asking yourself “what do I want?” or “what do I need?”

   It sounds so basic. Listen to your gut response. Maybe you need a rest and if that is not an option; even a break would help.

3. Be flexible. What helps you one day, may not be helpful the next—that is ok. Life is messy, and there is no perfect road map to maneuver through all the obstacles sometimes. Go with the flow.

4. Be intentional. Notice what you say to yourself—yes, you will think you cannot do this. The circumstances can be so overwhelming, but know you CAN do this! You may be in the thick of it and do not have a choice but to soldier on. Think of how you can handle it this minute, not the next hour or tomorrow.

   Do things that make you feel better and think more positively. There is a reason we send flowers to people; it brightens things up. Tell yourself things that are supportive: this will get better, I can do this.

   Even being intentional by going out of your way to greet others, say good morning, say a sincere thank you, authentically compliment someone; it gets us out of our own heads and connects us with others.

5. Be present. Stress can be overwhelming and ‘future surfing’ statements that start with “what if?” can be terrifying. Any questions that start with “why” are not helpful at this moment.

   What if this gets worse? You know that thought. It is so rarely positive and the truth is you do not know. Why is this happening to me? This is not helpful either—not to say that it is not ok to talk with a friend about it, but when you are in the height of a big challenge, this takes away the much needed energy to get through the present moment.

   Be present: I am in the hospital, I am drinking coffee, I am comforting a sick child. Being present reduces stress and helps us to simply “be” with what is.

6. Be kind to yourself. Your situation may feel awful. Do not beat yourself up for not doing this the way you hoped, or for not reacting, or being as engaged or energized as you would like to be. Speak to yourself like you would to a friend, with compassion and kindness. You are doing the best you can.

   That does not mean we candy-coat our feelings, but it does mean we make a choice of how we interact with our circumstances, and we choose what serves us.

   There are many ways to handle stress—some that work uniquely for us and some that do not. Develop and hone the tools that work well for you in stressful times.

   See Leona’s blog at http://accentdoconsulting.ca/category/blog/

2015 Annual Meeting

SELECTED PRESENTATION SUMMARIES

The 2015 VHL Alliance Annual Conference was held outside of Chicago, IL, on Saturday, October 17, 2015. The agenda included eight scientific presentations and a talk on how to speak with children about genetic disorders. In addition, the meeting included an update from the VHLA Board Chair on the State of VHL, and two facilitated break-out sessions: one for VHL patients and one for family members and caregivers.

Summaries of selected presentations are below. All presentation summaries and slides from most presentations may be viewed on the VHLA website (vhl.org/wp-content/uploads/2016/01/2015-Annual-Meeting-Summary.pdf).

Update on VHLA-Funded Research
Eric Jonasch, MD
MD Anderson Cancer Center, Houston, TX

The goal of the VHL Alliance funded research is to talk about effective treatments beyond surgery in 10–15 years. In order to find a cure, many layers of research are required. The process is like peeling an onion. The knowledge gained in one project suggests new projects that were not even thought of previously. The VHL gene was identified in 1993; now we are looking at how specific VHL mutations affect cellular function.

We are learning that VHL is not just about HIF (Hypoxia Inducible Factor), but also about how a cell sees its neighbors and how it interacts with neighbors and how it interacts with. Continued on Page 4
tumor cells, blood vessels, and connective tissue. Questions that need to be answered include: Can the VHL protein be fixed? Can we directly kill the VHL mutated tumor cells? Can the immune system be used to stop tumor growth?

Research funded in fiscal year 2015 included two exciting projects. The first, A novel chemical chaperone for treating the VHL cancer syndrome, looked at the possibility of repairing the full-sized VHL proteins that occur in VHL missense mutations (over 1/3 of VHL mutations). An amino acid, arginine, is showing positive results in cell lines. The second project, Zebrafish-Based Discovery of VHL Disease Targeting Drugs, was funded for two years and is testing 25,000 chemical compounds that have “drug-like” properties in zebrafish with VHL.

Two new research projects are being funded in fiscal year 2016. The first is Dr. van der Horst-Schrivers’ new process for testing for pheochromocytomas (pheos) using a saliva sample. This will be an exciting advance in both ease and accuracy over the current blood and urine tests. The second is Dr. Frew’s mouse model of renal cell carcinoma to test a recently developed promising treatment. The information as well as the new mouse model are important steps in our quest for discovering an approvable therapy.

Finally, the VHL Alliance is continuing the Cancer in our Genes International Patient Databank. This VHL patient registry resulted from the 2012 VHL International Medical Symposium in response to the top unmet research needs for VHL: detailed natural history of the disease, genotype/phenotype correlations, impact of lifestyle, and impact of geographical location. This registry is unique and does not duplicate the information for any registry you may already be enrolled in. Data security has been approved by an Institutional Review Board and your information is kept confidential. Your participation in the Databank is a critical part of finding and measuring the success of VHL treatments.

Talking to Children about Genetic Disorders
Ken Onel, MD
University of Chicago
Lindsay Rhodes, MS, CGC
Gene Dx, Gaithersburg, MD

VHL is one of the inherited diseases for which it is appropriate to perform genetic testing in children; the results will guide the child’s health management. Genetic testing may be “diagnostic” to find the cause of specific clinical findings, or “pre-symptomatic” to test a healthy child for the presence of an already known familial mutation. Special considerations apply when testing minor children and there is no single approach for every family. The child may not be part of the initial discussion if too young, or if the family wants to prolong childhood and protect the child from knowledge of the disease. Family experience with VHL will also be a factor. However, it is important never to assume that just because a child has family members with VHL, that child knows about VHL. Frequently, what a child imagines is far worse than reality, and so, it is critical for family members and medical professionals to assess a child’s understanding and share facts in a developmentally appropriate manner. Additionally, another possible consequence of having multiple family members with VHL is “screening fatigue,” because of the lifelong commitment to screening required of each affected individual. It is important to follow the suggested screening schedule for each family member, both to successfully manage VHL, and to instill a good example for each child to follow as an adult.

Researchers have found from studies with both parents and children, that keeping discussions of VHL informal and gradually adding to the child’s knowledge of VHL over time is the most effective approach. Learning all of the details about VHL at once can be overwhelming. Gradual learning results in children who feel that they had always known about VHL. VHL becomes part of the shared family identity. Children generally want to learn about VHL between 6–10 years of age, and almost always ask questions by age 14. In cases where parents avoided discussion of VHL, children were often reluctant to ask questions as a way of protecting their parents from distressing conversations, and this could affect healthy parent-child relationships. The child’s healthcare provider can facilitate parent-child communication during visits, and parents can meet privately with a genetic counselor to ask questions and practice how to communicate VHL information to their children. No parent we have worked with has regretted being open and honest with their children about VHL.

Brain and Spinal Lesions: Not Just a Science
Rimas V. Lukas, MD
University of Chicago

VHL can result in progressive central nervous system (CNS) hemangioblastomas that, although benign, may cause significant symptoms. The median age at which CNS hemangioblastomas are first diagnosed is 20–30 years. Most tumors do not cause symptoms prior to diagnosis. Usually the tumors grow in a stepwise pattern. Tumors may also develop cysts which occupy space and can compress adjacent tissue. CNS hemangioblastomas occur in 60–90% of VHL patients and approximately half of these patients have lesions in two or more regions. The location of current lesions does not predict that there will be more lesions in the same region. Fewer than 1% of VHL lesions are located in the cerebral cortex; most are in the cerebellum, brain stem, spinal cord, or spinal nerve roots.

Surgery is a mainstay of treatment of CNS hemangioblastoma. Surgery can often completely remove the tumor. Treatment decisions are made on an individualized basis and take into account the size of the tumor, the size of the associated cyst, the rate of growth, the tumor’s location, the prior treatments administered, and a patient’s other medical conditions. Another focal therapy which can be utilized for treating CNS hemangioblastomas is stereotactic radiosurgery.
nerves in the chest, abdomen, and pelvis. Paragangliomas in the chest, abdomen, and pelvis are more likely to produce excess adrenaline. VHL-related adrenal tumors are most commonly first diagnosed between ages 12-25 and approximately 10-20% of VHL patients will develop a pheo or para, with pheos being 80% of VHL cases.

Diagnosis of a pheo or para can be challenging as not all produce symptoms and many medications can interfere with testing. Ideally, testing should be done in an outpatient clinic as many patients find hospitals stressful. CT and MRI can be used to locate and confirm pheos and paras. Surgery is the best treatment, but if surgery is not possible, high adrenaline levels must be treated with medications. Radiotherapy is used in a few patients. Lifelong follow-up is needed, even if both adrenal glands are removed, to detect recurrent or metastatic disease.

**Clinical Care Center Update**

**New Comprehensive Clinical Care Center:** Suny Upstate

**New Clinical Care Center:** University of Michigan

**VHL Handbook, New Edition**

Updated in 2015, the VHL Handbook is a compact summary of information essential to managing the health of a person with von Hippel-Lindau disease (VHL). Designed to be read by patients, families, their physicians and members of their health care teams, it explains how VHL occurs, how to monitor and test for possible medical issues, and common treatment options to be considered. Order your new handbook at vhl.org/product/vhl-handbook or download it at vhl.org/handbook.

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Join us for the 2016 International VHL Medical Symposium, Boston, MA

The 12th VHL International Medical Conference will provide a diverse and unique opportunity for attendees to share, discuss and learn the latest advancements in von Hippel-Lindau disease.

While the content is directed to medical researcher and healthcare professionals, patients and caregivers are encouraged to attend. Their participation is highly valued as they are the true authorities on von Hippel-Lindau.

Please see the VHL website at vhl.org/symposium for more information, write to vhlmedsymp@vhl.org or call the office at 617.277.5667 x4 or toll free 800.767-4845 x4.