von Hippel-Lindau Fund for Cancer Research

Research Report

VHL Family Forum, 6.5 • ISSN 1066-4130 Special Issue, December 1998

Thanks to you and all our many friends, the VHL Fund for Cancer Research was able to award $80,000 in research grants in 1998. The research is beginning to bear fruit. In 1999 there will be at least two clinical trials of drugs that may be helpful in stopping tumors. There is still a great deal to be done, but the excitement is building.

As Dr. Gnarra says, "Our goal is to change VHL from a condition with surgical management to a condition with medical management." Instead of taking out tumors, with all the risks and discomforts of surgery, it would be nice if there were a pill for this, or a special diet. It's not such a wild dream. Last year we were hopeful, this year it seems within reach. There are four essential steps: Description, Collaboration, Understanding, and Innovation.

Description. Since Duchesne's first description of retinal angiomas in 1864 we have struggled to get a good comprehensive description of VHL. While there were some good ones, like Lindau's landmark article in 1926, most descriptions were like the proverbial three blind men and the elephant. The man holding the tail declared, "An elephant is like a rope," while the man standing next to the leg argued that "An elephant is like a tree," and the man holding the ear countered that "An elephant is like a sail." With a condition like VHL that varies so much from one individual to another, it is critically important to gather a large number of cases to see the whole elephant.

Collaboration. The Third International Symposium on VHL recently held in Paris was an excellent demonstration of the power of collaboration. Not only are there now country-level studies on VHL in the U.S., France, Germany, England, the Netherlands, Poland and Japan. Most important, the physicians heading these studies are bringing these cases together to learn from them all. Each of these countries has 35 to 600 patients; collectively they now have medical documentation on more than 1500 people with VHL. At last we have a broad enough sample that statistics are meaningful and deductions can begin to be trusted.

Understanding. To move from description to medical management, we need to fill in large gaps in our understanding of how the condition known as VHL works. What do brain tumors have in common with kidney cancer? In genetics in general, we are struggling to comprehend an entire new field of technology. Thirty years from now they'll be teaching advanced genetics to 15-year-olds. But today, we look at the DNA and we don't know what we're looking at. It's as if some brilliant scientists of the 1890's were looking at a 1998 automobile, trying to understand it. They see that if you turn the key and press the pedal the car moves. But that's all they understand. They don't understand how to fix it when the pedal doesn't produce motion. They can appreciate the posh interior, but they don't understand the mechanics and electronics in the engine.

Without that understanding, we can never fix the problem. For example, if you see a brown spot on the ceiling, you can paint the ceiling and cover up the spot. But within a short period of time you will probably have another spot on the ceiling. Until you figure out what caused the spot, and fix the source of the water, or the cause of the leak, you will never really get rid of the problem.

Innovation. In January 1999 a trial will begin at the Dana Farber Cancer Research Institute in Boston specifically focused on determining the extent to which a new drug will be able to shrink VHL tumors, or in fact keep them from occurring in the first place. It's only the beginning, but a very important beginning. We are changing from tools of war and destruction to tools of peace and prevention.

This Boston study is especially important to this VHL community. Typically what happens among rare diseases is that research is done on the rare condition to understand some fine point of how a problem is caused both in the rare condition and in the general population. But when it comes to the clinical trials, and to proving and marketing the drug, they focus on the larger market, and leave the rare disease with no proven therapy. The Boston study is focused on using this drug specifically for VHL. The same drug is being tested at three other centers for use with three other conditions, but this one will focus on VHL. As a community, we need to support this effort. We need to show the pharmaceuticals that we will do our part to support innovation in management of VHL.

Clinical trials are not for everyone, and we urge you to make an informed decision based on your own personal risks. Younger people who are basically in good health will probably not want to participate in early trials of any description. But at the same time, let us say too that we need pioneers. If no one is willing to sign on for a voyage that risks sailing off the edge of the earth, we will never find the New World. For those among us whose treatment choices are already limited, we urge you to consider becoming a pioneer. No one can promise you that this drug will be the one that will reverse tumor growth, but it's a better chance than ever before. We can promise that we as a community will learn from this study, and that it will significantly advance progress toward medical management for all of us.

We can't do it alone. For those of you who do not have VHL yourself, we need your help too. We need all of you to join with us in gathering research funding so that we can award research grants again this year to deserving projects that will move us closer to our goals.

Thank you for your generosity.
Every little bit helps!

Peggy Marshall and Joyce Graff,
Co-Chairs,
VHL Family Alliance

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1998 Research Grants Awarded

Thanks to *your generosity*, we were able to award a record $80,000 in research grants this year. This total includes donations, memorials, yard sales, raffles, a concert, a benefit cabaret, and a major gift from the Rasmussen family in Minnesota. We are hopeful that these two grants will further our knowledge of the function of the VHL gene so that we will understand better how to intervene in the process and make a difference in the outcome.

Let's do it again! Give what you can, and send brochures to others. Join Jay in going that extra mile. Together we will find a way to control VHL.

VHL Control of VEGF Expression

Dr. James R. Gnarra, Louisiana State University Medical School, New Orleans, $40,000

In this project, Dr. Gnarra proposes to continue his studies on how the VHL protein regulates the expression of the vascular endothelial growth factor (VEGF) and the growth of blood vessels. These studies continue the work we helped to fund last year. His hypothesis, which is shared by many researchers within the VHL scientific community, is that tumors of VHL do not appear until there is a change in the levels of vascular endothelial growth factor (VEGF) in the cell. Therefore, understanding how VHL regulates the production of VEGF is very important, since it may help us to identify additional targets for therapeutic intervention, additional places where a drug might intervene in this process and halt the growth of tumors. If a lowering of the amount of VHL protein in the cell results in a rise in the level of VEGF, what other processes take place in the middle? In what other ways could we modify the levels of VEGF and affect the development of VHL tumors. The regulation of VEGF expression by VHL is believed to be carried out through binding of certain proteins to the mRNA that encodes VEGF. He seeks to identify these factors and study how they work.

Dr. Gnarra received his Ph.D. in 1987 from the University of Virginia. He held a research fellowship at the NIH under Dr. Richard Klausner from 1987 to 1991. He then joined Dr. W. Marston Linehan's group at the NCI and was a member of the team headed by Drs. Berton Zbar, Michael Lerman, and Linehan that found the VHL gene. He then went on to show the role of the VHL gene in non-hereditary renal cancers. Dr. Gnarra accepted a position as Associate Professor of Biochemistry and Molecular Biology at the Louisiana State University Medical Center in New Orleans in 1996. He holds a joint appointment in the Department of Biometry and Genetics and is a member of the Stanley S. Scott Center and the Program in Human Molecular Genetics at the LSU Medical Center. (Award $40,000)

Dr. James Gnarra, Louisiana State University, speaking at a VHL Support Meeting

Dr. Robert Burk, Albert Einstein School of Medicine, New York, in his laboratory.

Studies on the VHLp18(MEA) protein

Dr. Robert D. Burk, Albert Einstein School of Medicine, New York, $40,000

Dr. Burk proposes to investigate how VHL functions normally in the cell by first trying to identify where VHL is usually located. Dr. Burk's laboratory has recently published a paper showing that the VHL gene actually makes two proteins, one large and one small which contain overlapping regions. The new, smaller protein identified by Dr. Burk's group is the more abundant VHL protein found in cells. In fact, all the mutations leading to VHL disease have been found to affect the smaller protein. By understanding precisely where the VHL proteins exists in the cell should provide important information on how an abnormal or missing VHL protein causes disease.

Dr. Burk received his M.D. from George Washington University School of Medicine in 1976. He completed a fellowship in Genetics in the Department of Pediatrics at Johns Hopkins University School of Medicine, and is Board Certified in Pediatrics and Genetics. He has been with the Albert Einstein School of Medicine in Bronx, New York, since 1983, where he holds joint appointments in Pediatrics, Microbiology and Immunology; and Epidemiology and Social Medicine. He is widely published in the field of molecular and cancer genetics. His paper "A second major native von Hippel-Lindau gene product, initiated from an internal translation start site, functions as a tumor suppressor gene," was recently published in PNAS. (Award $40,000)

$80,000 for Research in 1997 -- *Let's do it again!*

What can you contribute? Every little bit helps!

This total includes lots of small and medium personal donations, gifts honoring special occasions, memorials, yard sales, raffles, benefit concerts, a walk-a-thon team and sponsorships, and several larger gifts from families and friends.

Gifts of appreciated stock offer tax benefits to the donor as well as benefits to the Research Fund. Call to arrange transfer to the VHLFA account, 1-617-277-5667.

Pioneers Needed for the New Frontier

A medical team under Dr. William Kaelin of the Dana Farber Cancer Research Institute is proposing to conduct a Clinical Trial of a new drug which may have promise in constraining the growth of tumors in people with VHL. The trial is going through the final approvals, and is now expected to begin about January 1999.

Progress is never made without pioneers, people who are willing to venture out onto the frontier and open new territory for everyone. We need people with VHL to apply to participate in this study. There is a survey form posted on the internet, or people can contact Dr. Kaelin's team directly at 617-632-4747. Remember that taking this first step is not a final commitment that you will participate, it is an expression of interest. You will be evaluated to determine that you are physically eligible, provided with more detailed information about the risks and potential benefits to you, and then given the opportunity to join the study or not.

This drug is in pill form. It has been specially designed to inhibit vascular endothelial growth factor (VEGF). Dr. Kaelin's team has been one of the key teams in learning about the function of the VHL protein – what it does normally, and what happens when the normal VHL protein is absent. What we know so far is that when there is too little normal VHL protein in a cell, there are higher levels of VEGF, and VEGF has been found in high concentrations around brain and kidney tumors, both in VHL and in other conditions. We are hopeful that this drug will be effective in limiting the growth of tumors in VHL, and also that it will be helpful against related brain and kidney tumors in the general population. This trial will help to determine whether that is true.

As we learn more about the specific effects of the VHL protein, we learn where drugs like this one might be able to intervene and make a difference. As Dr. Kaelin says, compared to drugs like this one which are specifically targeted to deal with a particular mechanism in the cell, the more general tools we have had in the past, such as interferon or thalidomide, are "blunt instruments". For example, let's say the door is locked and we want to get in. We could use a key if we had one, but we don't yet have a cure. We could shoot the lock. We could take off the hinges and remove the door. These more "blunt" approaches will succeed in opening the door, but at what cost? Or we could take a hairpin and pick the lock. Picking the lock may not be as good as having a key, but it gets the job done, and is a lot less destructive. We are hopeful that this drug will be a fine instrument like a lock-pick and may help to halt or prevent tumors.

What's the objective of the study?

Volunteers are needed to help determine correct dosage levels for this drug, and then to determine if it is effective in stopping tumors. The study will be divided into two parts. The objective of the first portion is to determine what is a therapeutic dose. Participants will be carefully monitored to see if there is an effect on tumor size, or if any side-effects appear. This portion of the study will be limited, and the criteria will exclude many people with VHL. However qualified participants with VHL will be very important in this phase.

The second portion of the trial is meant to determine the effectiveness of this drug, specifically on the tumors of VHL. Two groups of subjects will be included, measuring the effect upon brain tumors and upon kidney tumors. Participants will be monitored to determine whether brain and kidney tumors can be reduced in volume, and new tumors kept from forming. This portion of the trial will begin once sufficient information has been gathered from the initial portion to determine the dose of the drug that is safe and well tolerated. This will possibly occur as early as summer 1999. This second portion of the trial will enroll only VHL patients.

What is the time commitment?

People who are accepted into the study will be required to have DNA testing. It is a requirement that participants have a confirmed diagnosis of VHL, and that they know their mutation. DNA testing is now available through any geneticist in your own area. It is recommended that samples be sent to the University of Pennsylvania testing lab.

People who participate in the second portion of the trial will need to come to Boston for 1-2 days of testing at the beginning of the trial, and then again once a month for 1-2 days. After the fourth month the intervals may be spaced out somewhat longer, but people should plan on monthly visits.

Who is eligible?

The first portion of the trial is restricted to VHL patients with inoperable kidney cancer and no central nervous system lesions (no brain hemangioblastoma, no spinal tumors). People with VHL lesions of the brain or spinal cord may be eligible to join the second portion of the study.

Participants in the second portion of the trial must have

- One or more cerebellar hemangioblastoma(s) with a measurable solid component
- Or one or more Renal cell carcinoma tumors of less than 3 cm. in size (such that they are comfortable that the tumors can be watched and do not require conventional treatment), with or without cerebellar hemangioblastoma
- Or people with inoperable kidney cancer, with or without cerebellar hemangioblastoma

All participants must be 18 years or older, in reasonable health (not bed-ridden, not seriously anemic or suffering from other unresolved medical problems). For details on criteria for inclusion or exclusion, contact the VHL Family Alliance.

Your Donations Save Lives Now!

We have the VHLFA internet website to thank for finally coming up with a diagnosis for my husband's condition. He is adopted and did not have much information about his birth family. Ten years ago he was told his spinal cord tumors were just a freak occurrence. One day a few months ago I had some free time and looked up hemangioblastomas on the internet, and found your site. We took that information to his doctor, who performed more tests and confirmed that my husband has VHL. They also found a cancerous kidney tumor that had not yet had a chance to spread. Thank you for a wonderful and informative site! *-- P. K., California*

On the Trail for VHL!

Even for a Marine of sound body conquering the 2,160 miles of southbound wilderness known as the Appalachian Trail would be a remarkable feat, something about 300 humans have accomplished.

But 32-year-old Jay Platt who is now marching down the trail's lush footpaths in Virginia has undertaken the grueling, five-month journey despite surgeries to remove his left eye and part of his kidney Platt is determined to complete the tour as a fund-raiser to help others with VHL, the condition he has battled for 11 years - von Hippel-Lindau Syndrome. He is leading the VHLFA's effort to raise money for research.

"I believe that everyone will be generous when they understand the way this disease hits families like theirs," says Platt. "if it means walking this trail when I'm tired, I will do it to help those who have supported me." Platt, known as "Patch" on the Trail, has already walked across ten states, and is now hiking across Virginia.

Why is Platt walking this Trail? "Because it challenges your mental and physical toughness," he said. "Not only Marines, but persons with VHL and their families must have perseverance and courage. We are challenged to manage this disease until all of us working together find the cure for VHL and cancer."

Let's Keep Up with Jay!
Send your donation now!

Follow Jay's progress at www.vhl.org

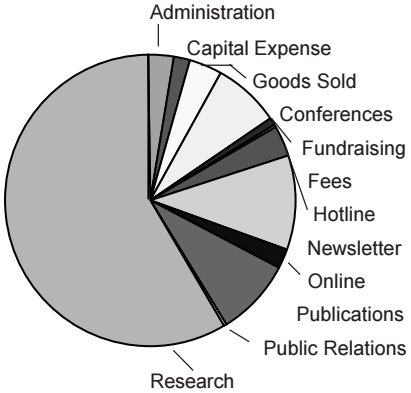
Progress!

This year we reached ten more countries, and a thousand more people. We are now reaching more than 8000 people in 47 countries, up 16.2% over last year. Over 150 doctors attended the Paris meeting alone. At the same time, our operating budget is up 28% to a total of only $61,620.

We pay no staff, we do not rent office space. The money we raise goes directly into programming and research. We are able to do this because of the hard work of a large number of dedicated volunteers in twelve countries around the world. Volunteers provide telephone and internet inquiry service, maintain our web site at www.vhl.org, and provide outreach in their local areas.

The Rasmussen Family grant gives an extra boost to our research funding power. Call or write for a list of special projects that need funding.

Total Revenue for Fiscal 1998 (ended June 30, 1998) was $160,730. Of this, a total of $87,573 was allocated to research funding.



Remember VHLFA in Your Will

You can give hope to millions of people worldwide with VHL and other tumors by extending your support of VHL Family Alliance programs beyond your lifetime. Whether your legacy is large or small, you can support our programs of education, service, and research by remembering VHLFA in your will.

To make a bequest of cash or other property to VHLFA, your will (or supplemental codicil, if you do not wish to write a new will) should state:

"I give and bequeath to the VHL Family Alliance, Inc., a non-profit corporation, organized under the laws of the Commonwealth of Massachusetts, and having its principal office at 171 Clinton Road, Brookline, MA 02445, the sum of $_____ or __ percent of the rest, residue, and remainder of my estate to be used for general purposes of the organization."

A bequest to VHLFA is fully deductible for estate tax purposes. In addition, remembering VHLFA in your will is an important and personal way of providing hope to people with von Hippel-Lindau disease for generations to come. You may wish to learn more about other gift opportunities by consulting your attorney, accountant, and/or tax estate planning specialist, or simply write to VHLFA's Chairman of Development, 171 Clinton Road, Brookline, MA 02445, info@vhl.org.

Mail to: VHL Family Alliance, 171 Clinton Rd., Brookline, MA 02445

Enclosed is my tax-deductible gift to support the:

❑ Fund for Cancer Research ❑ VHL Educational Programs

❑ Both Education and Research

❑ $1000 ❑ $500 ❑ $100 ❑ $50 ❑ $25 ❑ $____

(Please make checks payable to VHL Family Alliance)

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❑ Send quarterly newsletter ❑ Audio version needed

❑ My employer will match my donation. I have enclosed the necessary form.

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VHLFA is a non-profit organization. Our IRS Tax ID number is 04-3180414

My donation is ❑ In Honor of... ❑ In Memory of ... _____

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