von Hippel-Lindau Fund for Research

Research Report

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New Hope

from Don Marshall, Vice Chair, VHL Family Alliance

The VHL Family Alliance welcomes the new millennium with renewed hope for a treatment for those people with von Hippel-Lindau Disease. Since our beginning in 1993 we have provided over a quarter million dollars to research teams focusing on the complexities of VHL. These research teams have been fast approaching the solution to finding a way to reduce the effects of VHL manifestations and identify the best means to treat VHL.

We are now reaching over 10,000 people directly affected by VHL. Our International Web site www.vhl.org has seen over 15,000 visits this past year. A visitor can find current information on the management and new treatments for VHL. One can find local support groups, Clinical Care Centers, and get answers to questions regarding living and dealing with the diagnosis of VHL.

Over 1,000 calls are answered annually on our Patient Support Line, 1-800-767-4VHL. Callers reach one of four VHL-affected volunteers who can relate directly to their needs and provide assistance in finding information, discussing health issues, locating local support people, and individual support. Support groups exist on the internet at egroups, and in 27 State Chapters and 16 International affiliates, in thirteen languages.

The year 2000 marked the Third International Symposium and Seventh Annual Patient Provider Conference held at Mayo Clinic in Rochester, Minnesota. Over 200 patients, family members and physicians attended the three and one half-day conclave. Participants from Australia, Belgium, Brazil, Canada, Denmark, England, France, Germany, Italy, Japan, the Netherlands, Poland, Sweden, Switzerland, and of course the United States joined together to share current research information and the latest techniques for diagnosis and treatment of VHL disease.

Dr. Virginia Michels, M.D., of the Department of Genetics at the Mayo Clinic in Rochester, Minnesota, and Medical Chair of the Symposium, declared that "Our accumulated knowledge about the VHL protein and its associated proteins and enzymes will lead to some major breakthroughs in the new millennium for treatment of VHL disease." One family in attendance gained insights into their own family's situation that saved the lives of a young mother and her baby only weeks after the conference.

Neatha D., celebrating her 70th birthday this year said, "Medical technology and treatment of VHL disease has 'come a long way, Baby!', since my diagnosis 36 years ago." We now have many members who have outlived the earlier predictions and we will be adding focus to their needs.

The year 2000 has begun a renewed effort to raise awareness of VHL and to emphasize the need to raise more funds for research in management of VHL. Your continued support in this research effort is deeply appreciated.

We need your help to spur research and testing and find ever better answers. Together we ***can*** achieve the extraordinary!

-- Don Marshall, Vice-Chair, VHL Family Alliance

New Drugs

from Dr. Adrian Harris, medical oncologist, Oxford, England

There are new drugs on the market today and in clinical trials that I believe will present some dynamic new treatment options for people with VHL. To get from here to there will take a great deal of patience, research, and clinical trials, but the next three to five years will be an exciting time. The study of angiogenesis, the way the body creates new blood vessels, is a key focus for VHL research and for cancer research in general.

Without a new blood supply, tumors can't grow beyond one millimeter in diameter, they can't spread to the rest of the body, and they can't grow at other sites in the body. The study of angiogenesis is a really hot area for developing anti-cancer drugs.

My main interest is in dealing with solid cancer tumors. But I recently joined the VHL team in Oxford, and have started to develop new studies to try and help patients with VHL, as part of an international collaborative effort.

We have heard a lot about the protein Vascular Endothelial Growth Factor, or VEGF, which the body normally generates when tissues need more oxygen. If you have a stroke, heart attack, or other injury, your body switches on VEGF to help repair the blood supply.

Angiogenesis is regulated in other ways as well -- so far at least seven different pathways have been identified, of which VEGF is probably the most important, as it makes the others work better. Blocking one of these pathways can help reduce the effectiveness of the others.

The amount of VEGF is much higher in most cancers than in normal tissues, and it predicts outcomes. If a cancer tumor has a lot of VEGF associated with it, it will grow more rapidly and there are more blood vessels. All of this has been good evidence that VEGF is a good target for treating cancer, and there should be some spinoff benefit for treating VHL.

VEGF comes out of the cancer cells and binds to receptors on the surface of the blood vessels to get them to grow. We can block the receptor signaling with a drug that's called a receptor kinase inhibitor. Sugen's drug SU5416 is one of these receptor kinase inhibitors. But there are also other approaches we could take that might have the same effect. We could block the receptor, destroy the VEGF, or destroy the blood vessels themselves.

All these approaches are now in early, or "Phase 1", clinical trials. But we don't actually know the safe dosage levels of the drugs involved. We begin with a very low dose and gradually build the dose up in successive groups of patients. If you have VHL, you don't want to be in Phase 1 because you're likely to need long-term treatment. You want to know the right dose, and the safe dosage level. So we need to take the lead from the cancer trials and apply those results across to VHL. In our early studies with SU5416 we have accepted only very severe cases of VHL, where there is no standard treatment that will make things better.

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What are the drugs available? We do not yet have any drugs directly helpful for VHL. There are some drugs on the market today for other things that also have anti-angiogenic properties. *Interferon,* which is a standard treatment for kidney cancer, is used to treat rare blood vessel syndromes in childhood. *Thalidomide*, which is becoming more widely used in cancer, seems to be able to block the blood supply to tumors, but is toxic to nerve tissue in long-term use. It can cause fetal malformation, so if you use it you have to use two forms of contraception. *Captopril* is used to treat hypertension. And there's a new sort of anti-inflammatory drug known as a *Cox-2 (cyclooxygenase) inhibitor* which has recently been shown to prevent development of colon cancer from colon polyps.

These drugs are not very potent, but they do have some anti-angiogenic activity. Of those thalidomide is the most potent, but is difficult to use in the long term. Interestingly, these drugs that block blood vessel formation do not block wound healing. It may be that wound healing uses multiple pathways and blocking one is not enough. In other words, the drugs currently on the market are certainly not optimal for VHL. They were not designed to block angiogenesis, they are not specific to VHL, they are toxic, and there is little data to support them apart from thalidomide.

In our current study, we wanted to get the latest VEGF kinase, to block the receptor for VEGF. It is not easy to get access to these drugs for rare diseases. Most drug companies are concentrating first on cancer, because cancer is big business. It takes a lot of persuasion to test the drugs for rarer diseases. Because our team is very actively involved in drug trials for cancer patients with VEGF inhibitors, we have been able to persuade companies to link up with us to do this kind of specialized test. Sugen is also linked up with Dr. William Kaelin in Boston, and with trials in Poland and France. This is what we call a pilot study. We did it to get experience on safety and toxicity at the top dose used to treat cancer patients, to make sure that VHL patients tolerated it well, and that it was compatible with their lifestyle, before beginning a proper Phase 2 trial.

The Sugen drug is a small molecule. It has to be given intravenously. There will be a version of this in 2001 that is oral, and there are at least two other companies with oral versions coming through, and within 2-3 years there will be much better ones. It is a rapidly changing field, and we need to convince companies to support us with the latest drugs once they have the Phase 2 levels available.

We have tried SU5416 with three patients in very grave condition, and one patient with a serious eye tumor but otherwise in relatively good health. Two stabilized but did not improve, and in two patients the lesions stayed the same but the symptoms got worse. So it's very early days. We need to recruit a larger number of patients in multiple centers. We also think that when we begin to treat patients earlier in the disease process, we should have more success.

Level of activity. One of the challenges is to detect the level of activity biochemically in the lesion. Can we tell if it has stopped growing, or become less active? We are trying various techniques that have been developed for treating common cancers to see if we can apply them to the VHL lesions to get an indication of activity. One is to use special techniques of MRI to measure uptake and diffusion of the contrast agent, which tells us about the blood flow and the vascular permeability. Cancer tumors with a very high uptake rate may respond to SU5416. It may be that after VHL tumors have been there for many years and the blood vessels are very well organized, it may be much harder to get them to shrink away. In people with VHL you have a mixture of leaky vessels which you might be able to modify, and old vessels that are well differentiated and that will be hard to shrink.

Tissue Bank donations are very important, because we really need to know more about what's going on in these different tissues. Various tumors have different rates of growth -- some speed up, some stay stable -- and thre is great heterogeneity here. We would like to analyze many tumors to see if we can predict which ones will grow and which ones will remain stable.

Positron emission tomography (PET) scanning, is offering some very interesting possibilities. We are using an antibody to VEGF and labelling it so that it shows on PET scans. We inject the tracer into patients with cancer, and on the scan we can see the individual lesions which are making VEGF, and the levels of VEGF in each, without having to biopsy or stick a needle in the lesions. All the lesions light up with varying intensity indicating the relative levels of VEGF. This antibody is now in clinical trials for cancer treatment. As we get more experience with it we will want to move on to VHL patients to see if the lesions differ in the amount of VEGF they make. Our thought is that this might determine why they are behaving in different ways.

There is a long list of other proteins known to be regulated by VHL, all of which are known to be important in tumor angiogenesis and might be important in VHL angiogenesis. We just don't know yet. We'd like to analyze a wide variety of lesions to see if any of these factors are actually switched on or not. There are drugs that will block most of these, either on the market or now in cancer therapy trials. It will be important to understand which of these pathways are the most important, and to understand the heterogeneity.

We have all seen the heterogeneity in VHL – different kinds of tumors, different growth rates, variations between families, between patients within families, and between lesions in the same patient. Obviously there are multiple things going on. Similarly in cancer understanding heterogeneity is important. Our team did a study correlating the number of blood vessels around a cancer tumor with the long-term outcome of the patient. We just counted the number of blood vessels, and the higher the number of blood vessels in a cancer the worse they did. We also found that there was an even higher correlation between high concentrations of VEGF and more aggressive cancers. Similarly in VHL, if there is a variability in the amount of VEGF made or bound by lesions, this might explain some of the variability we see, and might help us understand which drugs we might need to use.

In conclusion, anti-angiogenesis therapy is a rational approach to VHL. Long-term use may be necessary. Drugs blocking VEGF are the highest priority, but we should not ignore other pathways. And we may not be able to regress established vessels, which would be an argument for treating early. A broad spectrum or combination of drugs may be the most useful, to block multiple pathways. But we do need more investigation into the pathways involved in blood vessel formation. If VEGF turns out to be a key driver, as we think, in the formation of renal cysts as well, then the controls we use for hemangioblastomas might prevent the loss of kidneys as well.

There is a lot happening out there, and there is much to learn about the applicability of these new cancer drugs to the treatment of VHL. As soon as we know the right doses of a drug, and something about its safety, we will initiate trials. The next three to five years will tell us a lot about long-term safety in cancer, with direct application to VHL and the prevention of cancer.

Dr. Harris is Professor of Clinical Oncologist, Churchill Hospital, associated with Oxford University in England. His work is supported by the Imperial Cancer Research Fund in the U.K. This article is based on his talk at the VHL Symposium, July 2000.

Research Grants

In the past year, the VHL protein has come to be appreciated as a regulator of the levels of other proteins in the cell. It teams up with Elongin B, Elongin C, and Cul-2 to form a VHL Complex. This team then sorts proteins and marks certain ones for degradation, in much the same way that a forester would go through a forest and paint X's on the trees that should be cut down. It's not just one protein that it is controlling. Scientists have already identified several such proteins. This helps to explain why VHL seems to have such a wide variety of effects. If we think of that forester — cutting down a tall tree brings more light into the forest floor. Cutting down a tree that is too close to another gives the second tree room to grow. We are trying to understand what happens when VHL is working properly, and what doesn't happen when VHL is not working properly, so that we can discover new ways to intervene and make the end result turn out right.

Dr. William Rigby, Dartmouth-Hitchcock Medical Center, Dartmouth, Massachusetts, in his project "VHL regulates hnRNP A2 expression," will study one of the ways that the breakdown of VHL function in the cell may lead to cancer only in some kinds of cells. *Funding $30,000 from the VHL Family Alliance.*

This project will examine the finding that hnRNP A2, an RNA-binding protein, appears to be found in over-supply only in kidney cancer cells that lack the VHL protein. The overexpression of hnRNP A2 has been found in other tumors and may therefore play a role in the development of cancer when the VHL protein is absent. The project will examine the mechanism by which VHL regulates levels of hnRNP A2, and will correlate this finding with the mutations of the VHL gene that are associated with various cancers."

$90,000 for Research in 2000 -- *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.

This is just a brief message to thank you for the most complete and effective website I've visited. As a Clinical Geneticist, I'm constantly searching for clear, concise information for my patients and for my own use. You certainly exceeded my expectations. -- *Patricia Gordon, M.D., St. Jude's Children's Cancer Research Center, Memphis, Tennessee*

Dr. Maria Czyzyk-Krzeska, University of Cincinnati, Ohio, will be continuing her stody of "VHL Function in Pheochromocytoma." *Funding: $30,000 from the VHL Family Alliance.*

We are renewing the grant awarded to her last year to study the role of the VHL protein in the creation of a pheochromocytoma. In the work completed to date she has established that pVHL regulates the expression of the hypoxia-inducible tyrosine hydroxylase (TH), an enzyme that controls the amount of catecholamines the body makes. This year's project will focus on the mechanism by which pVHL regulates the levels of TH, and the influence of cell density on the amount of TH manufactured in the cell.

"The major significance of our preliminary results is that VHL, the gene linked to pheochromocytoma tumors in VHL disease, is also a strong regulator of catecholamine synthesis. Disruption of normal VHL protein function, as in VHL disease, results not only in the pheochromocytoma tumor formation, but also in augmented catecholamine synthesis and release. These results will provide new and unique insights into the understanding of VHL function in the pheochromocytoma tumors and VHL disease."

Dr. Czyzyk-Krzeska and her entire team attended and participated in the Symposium.

Dr. Shahriar Koochekpour, University of Louisiana, New Orleans, working in the laboratory of Dr. Jim Gnarra, will investigate the mechanisms whereby the VHL protein influences the interaction of cells with their surrounding matter (the "extracellular matrix" or ECM) through the so-called fibronectin-integrin system. *Funding: $30,000 from the VHL Family Alliance.*

The extracellular matrix serves as a fence for cells. It keeps cells organized and working properly. This is done in part through proteins on the surface of cells called integrins. The integrins reach out and touch the ECM proteins and this interaction helps to maintain order. Understanding how cells communicate with their environment is critical because these interactions can regulate the rate at which cells proliferte, and they can also prevent cells from invading other tissues and forming metastases. In cells lacking the VHL protein, this communication is deficient, and cells can grow into a tumor, and eventually invade other tissues and metastasize. This research will build upon the finding of Dr. James Gnarra's team renal cell carcinoma (RCC) cells lacking pVHL over-produce proteases, proteins that break down the ECM, allowing the cancer cells to escape.

Information is Power

We are so very grateful for the VHL Family Alliance and the meeting in Minnesota, and for Joyce's "VHL 101" class. At least three times we were reminded that everyone with VHL should be checked for a pheo before any surgery, before or during pregnancy, and before labor and delivery. We finally heard it, and used that information to protect my niece Emily and her baby Hanna.

Our family wants to thank everyone for sharing their stories, Dr. Michels and the VHL Board of Directors for providing us with the valuable information that saved Emily's life, and will help keep her and her sister monitored and safe. Our family has been through a great emotionally stressful ordeal in the past few months, and we sure appreciate the support and help we have received. Thank you so much! — *Laurie D., Minnesota*

Let's Cure VHL in this Decade

Improve Diagnosis: Let's find all those people with VHL who are struggling to find a diagnosis for all their mysterious symptoms.

Improve Treatment: Let's find improvements in imaging and surgical techniques that will make it easier to treat individual tumors and keep people healthy and productive.

Improve Quality of Life: By supporting one another, by keeping our spirits up, by focusing on the positive and creating real progress, we can live happier lives.

Progress!

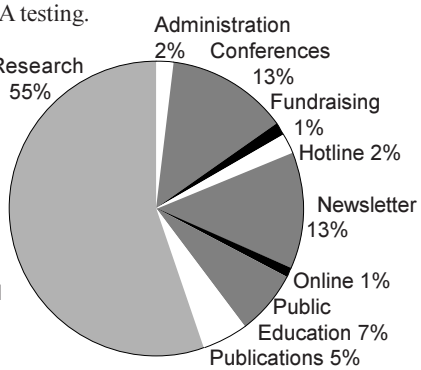
We are now reaching more than 10,000 people in 63 countries. While the population served has grown 17% per year over the last two years, the operating budget has grown only 12% per year in that same time.

We pay no staff, we do not rent office space. The money we raise goes directly into programming and research, with only 2% for administrative costs. 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.

This year we awarded $90,000 in research grants, bringing the total to $340,000 over the last four years.

Call or write for a list of special projects that need funding. For example, we want to design better support for children diagnosed through DNA testing.

Total Revenue for Fiscal 2000 (ended June 30, 2000) was $153,702.
Of this, a total of $94,350 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

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