



Annual Report issue,
2001-2002

*Family, Friends, Physicians, & Researchers dedicated
to improving diagnosis, treatment, and quality of life
for people affected by von Hippel-Lindau.*

Volume 10, Number 4

ISSN 1066-4130

December 2002

Our Second Decade - Greater Progress *with your help!*

Let's all work together to make the miracle we all
crave -- ***let's cure VHL!***

I'll probably never hold a brush
That paints a masterpiece.
Probably never find a pen
That writes a symphony.
But if I love, then I will find
That I have touched another life.
And that's something
worth leaving behind. (Lee Ann Womack)

We are all working together to leave something
behind. The VHL Family Alliance will celebrate its
tenth anniversary in January 2003. As we look back
on the growth of our organization, much progress —
much positive and innovative progress — has taken
place. It takes time, enthusiasm, and money to create
the progress you will see in this report.

The many volunteers who bring their expertise
and give of their time have brought us to where we
are today. Our Board of Directors works to enhance
the existing programs in place and add new and
informative ones where needed.

Our newly appointed Director of Volunteer
Services will encourage volunteers to offer support
and services through the existing 1-800 Line,
info@vhl.org, State Chapters and Contacts, and
online discussion groups. We are looking to introduce
some new support programs to provide more service
to our Spanish speaking population and to have
Regional meetings four times a year to bring VHL
support closer to home.

Our new Public Relations Director brings twenty
years of journalistic experience as a senior business
journalist, producer and publisher. His unique media
talents will be a tremendous asset in bringing aware-
ness about VHL to the public.

Our Finance Director has spent the last twenty
years working on the floor of the Chicago Mercantile
Exchange. His expert abilities as a broker will assist
us as an organization to move forward with our
funding needs and to continue to grow in the future.

Our Treasurer is a tax attorney having served
various positions with a number of nonprofit organi-
zations. We are fortunate indeed to have such an
experienced, concerned individual in the important
position of Treasurer.

In addition to the Directors, there are multitudes
of caring volunteers who donate much of their time
to provide services to everyone in the VHL commu-
nity, and many more who donate money. In this
issue you will read about the exciting research ***you***
are funding, and the many services ***you*** help to
sustain.

We would like our tenth anniversary year to be
the best year to date. Your generous donations will
help to accomplish our mission. Won't you help us
through and beyond the next ten years?

To help you spread the word about the VHL
Family Alliance, we have organized a special pro-
spective member section in this annual report issue.
It was designed for you to "pull it out" and share it
with a friend or acquaintance who may not know
about VHL and the Family Alliance. There is some
overlap in content, to share the essentials with your
friend.

Leave something behind. Be a part of helping the
VHL Family Alliance grow. Help us find a cure!

Take care, stay well,

Maria Shipton

Maria Shipton, Chairman of the Board

P.S. We can't do it without you!

Inside this issue!

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Special Pull-out Section to share

Research Report

by **Myriam Gorospe, Ph.D., Director of Research** and **Joyce Graff**

Nine VHL research proposals were submitted to the VHLFA this year. Because of your generosity we were able to fund five of these. Nonetheless there is a great deal more work to be done. Hospitals and universities are cutting back their own spending on research, so those of us who want VHL research to move forward swiftly need to fill this gap. Even with a modest budget, however, we have made a significant contribution to the advancement of VHL research.

One of the stated goals of our research grants program is to assist young researchers in gathering sufficient data to prove the validity of their ideas so that they can qualify for other larger grants elsewhere and continue their research. In this regard, we are very happy to announce that in 2001 Dr. Maria Czyzyk-Krzeska, whom we funded for two years (1999-2001), was able to obtain substantial funding from the U.S. National Institutes of Health and the American Cancer Society for the continuation of her research on the *Role of VHL in Pheochromocytoma*. Dr. William Rigby (funded 2000-2002) has obtained funding from NIH to continue his research on VHL and proliferation of kidney cancer cells. Similarly, Dr. Ehud Gazit at Tel-Aviv University, whom we funded last year, has won a very large grant from the Israel Cancer Research Fund, to continue his work on *'The Role of Protein Folding and Stability in the VHL Syndrome'*. Dr. William Rigby, Tien Hsu, and William Kaelin presented papers in Padua. The list of papers published by our grantees has made an important contribution to the medical literature.

There are two aspects we are focusing on in this year's grants. First, we continue to learn more about how the VHL protein (pVHL) operates in the cell – what it regulates in normal function, and what doesn't work when pVHL is not present. Second, we are trying to move from this knowledge to real therapies. This work moves ahead more quickly when there is a "biological model", preferably one that goes through many generations in a short period of time so that genetic changes can be tracked. The mouse and even the fruit fly have a VHL gene. This shows how very essential a role the VHL gene plays in the cell.



We have renewed funding for a second year for **Dr. Robert J. Duronio** of the University of North Carolina to further his research on *E3 Ubiquitin Ligase Complexes'*. He is using a very powerful genetic system (the

fruit fly) to study the function of pVHL as part of a group of proteins named "E3-ubiquitin ligase". pVHL's role within the E3-ubiquitin ligase is often compared to that of a 'garbage collector', functioning as an "off" switch by gathering up certain cellular proteins that are needed for cellular growth and proliferation. The investigators have made good progress on the goals they set out to accomplish over the past year of funding, and are continuing and extending that work.

Dr. Georges Mer of the Mayo Clinic in Minnesota is investigating how the VHL protein binds to another key protein named HIF1 α . The association between HIF1 α and pVHL has been shown by several research teams to be required for VHL to inhibit tumor growth. Dr. Mer is using Nuclear Magnetic Resonance Spectroscopy to determine the three-dimensional arrangement of pVHL and the fragment of HIF1 α important for the binding between these two proteins. These studies will provide information about why certain mutations cause a loss of interaction and result in the formation of a tumor. In addition, this investigation will increase our knowledge of how pVHL and HIF1 α interact, thus helping in the search for drug molecules that can restore the normal function of pVHL.



Dr. Tien Hsu of the Medical University of South Carolina is addressing how pVHL mutations cause cancer growth and metastasis. Although we know much about pVHL's involvement in blood vessel formation, important questions pertaining to cancer onset and progression (as in RCC) remain unanswered. In the fruit fly, the author has identified a pVHL-interacting

protein named nm23 (nm for non-metastatic). Mutations in the almost identical gene in humans have been correlated with many forms of metastatic tumors. He is investigating the functional relationship between this cancer-related gene and VHL disease. The implications of the study are three-fold:

- It will shed light on the function of nm23, which is not fully understood at the present time.

- It will provide evidence that pVHL can 'activate' the function of certain cellular proteins, and does not only function as a protein degradation factor.

- It will point to nm23 as a target of therapeutic intervention. Fortunately, nm23 belongs to a class of enzymes that have been very well studied, so drug development should be feasible.



Dr. Daniel George of the Dana Farber Cancer Research Institute in Boston will use the Novartis Pharmaceuticals drug PTK787/ZK22584 (PTK/ZK) to carry out a Phase II clinical trial to treat patients with VHL, especially those with advanced central nervous system disease. PTK/ZK is an angiogenesis inhibitor that blocks the activity

of two important proteins regulated by VHL: VEGF and PDGF, both of which stimulate new blood vessel growth. Early safety testing for this drug is being carried out with other kinds of cancers. The VHL study is due to open to VHL patients in December 2002.

In his proposal '**Pheochromocytoma and Altered Mental Function**,' **Pierre Jacomet** hypothesizes that there is a direct relationship between pheochromocytomas and certain psychiatric conditions. Because there often is not a great deal of communication between a patient's physicians and psychologists, the relationship may go undetected. Two out of three pheochromocytomas are discovered post-mortem. The objective is to compile data on the number of people suffering from panic attacks and other personality disorders that could be traced to undetected pheochromocytomas. With the help of statistical information, he hopes to raise the visibility of this issue so that health care professionals will be more likely to suspect and diagnose a pheochromocytoma, and possibly underlying VHL, MEN, and other pheo-related conditions. This project is being conducted in cooperation with the Catholic University Medical Center of Santiago, Chile, and Recalcine Pharmaceutical, South America.

As ever, we are very grateful to all our donors for making these grants possible. Together, we will continue to improve the management of VHL, and ultimately to find a cure.

Dr. Gorospe is Investigator Chief of the Cell Cycle Control Unit, Laboratory of Cellular and Molecular Biology, National Institute on Aging, National Institutes of Health

Watch for more information about clinical trials on the website and in the March issue of the newsletter.

None of the trial drugs is ready yet for use as a preventive. Only people for whom the standard treatment is not an option are being considered for these early trials.

Ask the Family

Question: Hi, I'm new to the group. I am going to have spinal cord surgery later this month. It is nice to think that other people have the same things wrong with them as me -- I don't mean I'm glad they have problems -- I hope you know what I mean. It is hard to talk to people who are very close to you about this. At least it is for me -- is that true for you too? -- **Stuart H., England**

Reply from Loretta: I understand how you feel about talking about VHL. I find it easier to talk to people in the online support group than I do my family and friends. They are supportive, but those who have or are experiencing anything to do with VHL seem to be more supportive and helpful.

I had a tumor removed from my brain in April and 2 tumors removed from my kidney on the in October. I was really scared about the kidney surgery, but everyone here helped me get through my fears. I knew because of them what to expect, and I found the greatest comfort here.

It is hard to deal with, but if you need someone to talk to, I am here. If I can't help you with certain things, someone here can. I still have my fears, and my down times, but the group pulls me through.

— **Loretta G., Tennessee**

Reply from Bob: I've been dealing with VHL since about 1993. In the beginning I did find it uncomfortable to talk about VHL, but you get over that. You begin learning about VHL, and you learn to explain it to your family, your friends, and most of all to your doctors. After a while it becomes less threatening and it sounds not as bad as other kinds of cancer. You can't let your guard down, you have to always stay on top of it. Good luck with your surgery.

-- **Bob K., Florida**

“

Deep inside of you there are many little sparks of potential -- all it takes is a breath to enflame them into magnificent results.

-- **Wilfred Peterson, submitted by Gilles B., Ile de la Réunion, Africa**

”

Fleckenstein Award

Dr. Sven Gläsker of the Division of Neurology, a member of Dr. Neumann's team in Freiburg, received the Fleckenstein Award in October 2002 for his doctoral dissertation on "Hemangioblastomas of the central nervous system and Von Hippel-Lindau Disease." The prize of 4000 Euros (about \$4000) is sponsored by the Bayer Company and distributed by the University of Freiburg for the outstanding thesis in 2002.

Kidney Cancer Research

By W. Marston Linehan, Chief of Urologic Oncology, National Cancer Institute, Bethesda, Maryland



We have studied cancer of the kidney for nearly 20 years, in collaboration with many scientists and medical centers across the United States and worldwide. July 1, 2002 started my twenty-first year at the NCI. Our approach has been predicated on the thesis that understanding the fundamental basis of

kidney cancer may lead to better methods for treatment of that disease.¹

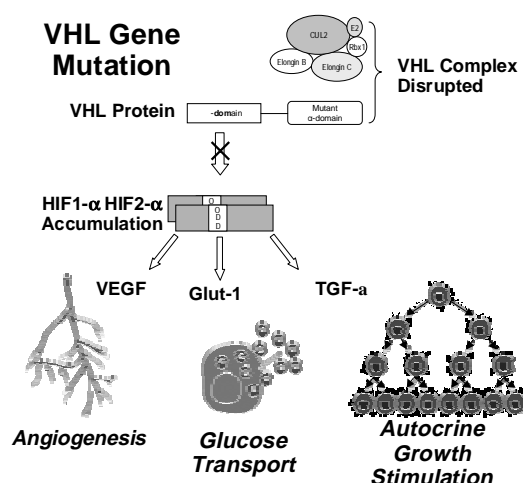
In our initial work in the search for the gene(s) for clear cell kidney cancer we identified an area of abnormality in tumor tissue from patients with kidney cancer, a loss of a segment of chromosome 3 in tumor tissue from patients with clear cell renal carcinoma.² We did further mapping studies in this region and narrowed the region of a potential kidney cancer tumor suppressor gene on chromosome 3.³ However, this region was too big to search for a disease gene by conventional methods, so we initiated study of an inherited form of renal cell carcinoma, von Hippel-Lindau.

Inherited forms of RCC: VHL

We set up a program at the NCI to evaluate patients with inherited forms of renal carcinoma in order to identify those genes. In our initial work on VHL we confirmed and further refined previous mapping to a location on the short arm of chromosome 3. In the Spring of 1993 we reported the identification of the VHL gene.⁴ Although it was not a "given" that this would be the gene we had looked for for so long, we next evaluated tumors from patients with the common form of non-inherited kidney cancer, clear cell renal carcinoma, to see if there would be mutations of the VHL gene in these tumors. We found a high percentage of tumors from patients with clear cell renal carcinoma to have mutation of the VHL gene.⁵

We next set out to understand the VHL gene, how damage to this gene leads to cancer. The hope was – and still is – to identify small molecules that would interrupt this sequence of events – this **pathway** – as a potential therapy for patients with clear cell renal carcinoma. In our initial studies we identified proteins that bind to VHL (elongins c and b and Cul-2).^{6,7} We now know that the VHL protein forms a complex with these and other proteins to target

two proteins called HIF1 alpha and HIF2 alpha for degradation, effectively turning off production of these proteins. When there is a mutation of the VHL gene, and it is inactivated, it can no longer target HIF for degradation. This allows an over-accumulation of HIF, which in turn leads to the over production of a number of proteins known to be important in cancer, such as VEGF (angiogenesis), TGF alpha (unregulated growth of the cancer), PDGF (unregulated growth of the cancer) and Glut1 (transport of glucose from the host into the cancer cells).



VHL kidney cancer gene pathway.

We are currently working on understanding the effect of HIF over accumulation in the formation of kidney cancer. We feel that this pathway provides unique opportunities for molecular targeting of kidney cancer.

Many diseases

Kidney cancer is not "one disease", it represents many types of cancer that occur in this organ. Each different type of kidney cancer is characterized by a different histologic pattern, is caused by a different gene, has a different clinical course and may respond differently to therapy. In addition to VHL we are studying other forms of hereditary and non-hereditary kidney cancer. It is our feeling that understanding the genetic basis of these cancers will provide attractive targets for molecular therapeutics – drug therapies that could reverse or prevent tumor growth. The strategy that we have been pursuing for nearly two decades has been shown to be effective in patients with a form of gastric cancer. (STI-571/Gleevec, CML/GIST tumors). We view this as "proof of principle" for such an effort.

These molecular therapeutic strategies are not separate from the efforts being pursued to develop immunologic therapies and/or vaccine strategies for

renal cell carcinoma. They are synergistic strategies which are inextricably intertwined. One example of an approach aiming to prevent formation of new tumors targets one of the events downstream from VHL, manipulating the levels of VEGF. This has already been shown to be promising in patients treated by Yang and colleagues at the NCI. Other strategies involving VHL gene pathway targets are underway and we are encouraged by the progress to date.

The VHL Family Alliance has provided enormous benefit to both clinical as well as basic investigators in the field and, most importantly, to those patients

with VHL and renal cell carcinoma that we all care for.

1. Linehan, W. M., Zbar, B., and Klausner, R. D. Renal Carcinoma. In B. Vogelstein and K. W. Kinzler (eds.), *The Genetic Basis of Human Cancer*, 2nd ed New York: McGraw-Hill 2002.
2. Zbar, B., Brauch, H., Talmadge, C., and Linehan, W. M. Loss of alleles ... renal cell carcinoma. *Nature*, 327: 721-724, 1987.
3. Anglard, P., Brauch, T. H., Weiss, G. H., Latif, F., Merino, M. J., Lerman, M. I., Zbar, B., and Linehan, W. M. Molecular analysis of genetic changes... *Cancer Res*, 51: 1071-1077, 1991.
4. Latif, F., et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*, 260: 1317-1320, 1993.
5. Gnarr, J. R., et al., Mutation of the VHL tumour Suppressor Gene in Renal Carcinoma. *Nat.Gen.*, 7: 85-90, 1994.

Our Heroes . . . are our many volunteers. These people give of their time, talents, and hearts to support others with VHL.

We honor our hotline volunteers chaired by Peggy Marshall: Altheada Johnson, Robin K., Audrey C., and Alessandra and José M., who provide toll-free service for callers from the United States, Canada,



David I. and Marilyn G. completed the Portland Marathon Racewalk twice.

Puerto Rico and the Virgin Islands. With help from Alessandra and José we will shortly be opening telephone support services in Spanish.

We honor our online discussion group moderated by Maria Shipton, Gerhard Alsmeier, Heather C., Elaine Follansbee, Gale Lugo, and Karina Villar.

We honor the many contact persons in their local states, provinces, and countries who are willing to "plant the flag" and declare "VHL spoken here," and help people to know they are not alone. We are excited to welcome new contact people in Sweden, Italy and Croatia, Peru and Costa Rica.

Most of all we honor some very special people who this year have "gone the extra mile" with creative fundraising events and extraordinary personal challenges that have inspired us all.

David I. from California completed the Racewalk at the Portland Marathon for the second year, finishing in six and one-half hours. (See VHLFF, Dec 2001)



Alice C., Seattle

Larry B. in Oregon carried the Olympic Torch in honor of his valiant battle with VHL and kidney cancer. (VHLFF, June 2002)

Alice C. from Washington completed the Seattle Danskin Triathlon in spite of her balance problems from ELST, using a "swim angel" volunteer to help keep her on course. (VHLFF, Sept 2001)

Scott C. from New Jersey was honored for having "contributed to the betterment of our community and to the lives of others while also overcoming personal challenges related to having a disability" (p. 6).

Kim P. from Illinois put on a Valentine's Day pageant for girls and boys (VHLFF, March 2002), Peggy M. from Mississippi hosted a Gospel Music Extravaganza (p. 11) and Cari E. from Ohio organized a pub music benefit, a bikini carwash, and a golf scramble (p. S2). They earned the respect of their communities and of all of us for their creative ways of raising money for VHL research. These three people alone raised \$12,217 for VHL Research.

Our thanks to all of them, and our congratulations to each and every one who is touched by VHL -- our everyday heroes who make the conscious choice each day to get up, look on the bright side, and have a happy day.



Kim P., Illinois



Larry B., Olympia, Washington

Sykes Award Ceremony Honors Scott Cannon

In October 2002, Atlantic County, New Jersey, honored ten residents with disabilities for their contributions to their communities at the 14th annual Donald J. Sykes Award Ceremony. The awards program was established by the county in 1989 to recognize outstanding individuals who help dispel the myths that typically surround individuals with disabilities. A ceremony is held each October during Disability Awareness Month.

This year's honorees include Scott Cannon, a probation officer with the Superior Court system, who has VHL. Due to complications from brain stem surgery, he had to learn to walk and talk all over again. His story appears in the June 2002 issue of **VHL Family Forum**.

"Not only have our honorees met the challenges related to their disabilities, but they have contributed to the betterment of our community. They are truly an inspiration to all of us," stated County Executive Dennis Levinson. "I am proud to honor their abilities and acknowledge their accomplishments."

The ceremony also featured guest speaker Doug Heir, a distinguished attorney, an Olympic wheelchair champion and one of the world's most decorated athletes. Paralyzed since he was 18 years old, Heir has overcome many obstacles to attain success. He serves as president of the National Spinal Cord Injury Association and is dedicated to helping others be the best they can be.

Scott too has overcome very serious obstacles that demanded perseverance and grit on his part, and loving support and hard work on the part of his family. Scott and his family maintain a delightful sense of humor and an intense cohesiveness that are marvelous to watch.

Scott's mother, Joan, is campaigning to raise the visibility of VHL both in her local community and in Congress. "Other diseases have their 'celebrity spokespeople.' Actors appear before Congress to champion their diseases, and Congress applauds. Where is the celebrity spokesperson for VHL? They should meet my son." In recognition of this award Scott also received a "Certificate of Special Congressional Recognition" emblazoned with the Great Seal of Congress.

There is no question that within his community Scott is indeed a celebrity, a valued friend, and a valued co-worker.

"I get to work early so that by 8:30 a.m. I'm at my desk and out of everyone's way. I move slower than most people because of my surgeries and I don't want a train of people stuck behind me. I've had three brain tumor surgeries. My first was eight years



Joan, Kelly, and Scott Cannon

ago. The second was five years ago. The most recent was in February 2001.

"I'm a probation officer, but technically I'm a case manager. I handle pre-trial intervention (PTI) cases. Half of this stack of cases is PTIs to be interviewed. The other stack the Prosecutor's Office has already rejected. I enjoy my job because every case is different."

Please share the pull-out section with a friend. Ask others to help find better ways to manage VHL, and find a cure!

Remembering VHLFA

You can give hope to millions of people worldwide with VHL, kidney cancer, 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, please set up a meeting with your attorney and provide him or her with the following information:

VHL Family Alliance, Inc., a non-profit corporation organized under the laws of Massachusetts
171 Clinton Road, Brookline, MA 02445
Federal tax ID 04-3180414

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 about other gift opportunities by consulting with your attorney, accountant, or tax estate planning specialist, or simply write to Director of Development, VHLFA, as above, or info@vhl.org



VHL
FAMILY
FORUM

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The many volunteers who bring their expertise
and give of their time have brought us to where we
are today. Our Board of Directors works to enhance
the existing programs in place and add new and
informative ones where needed.

We are an organization that is growing every year.
Today we serve more than half the projected number
of people with VHL in the U.S., but only 6% world-
wide. In addition, the VHL Family Alliance contin-
ues to raise more funds every year for vital research
as well as organize decisions about VHL. We are
proud to see the VHL Family Alliance grow from a
vital grass roots group to a national organization still
dedicated to individuals, family and friends who are
affected by VHL. When one person is sick, the entire
family circle is affected.

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Our Finance Director has spent the last twenty
years working on the floor of the Chicago Mercantile
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us as an organization to move forward with our
funding needs and to continue to grow in the future.

Our Treasurer is a tax attorney having served
various positions with a number of nonprofit organi-
zations. We are fortunate indeed to have such an
experienced, concerned individual in the important
position of Treasurer.

In addition to the Directors, there are multitudes
of caring volunteers who donate much of their time
to provide services to everyone in the VHL commu-
nity, and many more who donate money. In this
issue you will read about the exciting research ***you***
are funding, and the many services ***you*** help to
sustain.

We would like our tenth anniversary year to be
the best year to date. Your generous donations will
help to accomplish our mission. Won't you help us
through and beyond the next ten years?

Leave something behind. Be a part of helping the
VHL Family Alliance grow. Help us find a cure!

Take care, stay well,

Maria Shipton

Maria Shipton, Chairman of the Board

P.S. We can't do it without you!

Let's make a miracle!

Let's cure VHL!

1.. "Something Worth Leaving Behind," by Lee Ann Womack,
(MCA, 2002, UPC 8817028729). Song written by: Brett Beavers &
Tom Douglas, Rutledge Press.

Ohio Woman Fights VHL Disease

When Cari E. was in labor in October, 2001, her blood pressure spiked repeatedly. After giving birth to her daughter, it was discovered Cari had a large tumor on her adrenal gland.

The tumor was the result of Von Hippel-Lindau Syndrome, a genetic condition caused by a dominant gene that leads to an abnormal growth of blood vessels in some parts of the body. Most VHL tumors are benign, but some can grow to be malignant.

In addition to the adrenal tumor, Cari has also had a brain tumor removed. She knows that more tumors are possible because of the nature of VHL.

Cari, an Ohio native who works as an administrative assistant, said the disease is generally not life-threatening, but she will likely develop more tumors.

"The key to living with this is early detection," she said. "I will have to go through yearly CT scans."

Cari, 27, said she believes she inherited VHL from her mother, who died from a brain tumor in 1982, and there is a 50 percent chance her daughter, Siera, has inherited the disease.

"We're going through genetic counseling at the Cleveland Clinic to see if my daughter has this disease," she said. "It was once considered rare, but now we know it's not so rare. There are thousands of people with undiagnosed tumors."

According to the VHL Family Alliance, the disorder is more common than previously thought. More people are now diagnosed in time to help because of the use of more sophisticated imaging techniques, such as Magnetic Resonance Imaging. MRI is used to produce high quality images of the inside of the human body.

"[VHL is] one of many recently recognized and described genetic diseases that predispose people to cancer," said Dr. Steve Roshon of North Coast Cancer Center of Sandusky, Ohio. "It's fairly rare, but the scientific interest is huge, especially among those who are in genetic research."

Cari, her family and friends planned and held a series of fund-raising events to raise money for VHL research.

"Research is confident that there will one day be a pill which will suppress tumor growth," she said. "The money will go to the VHL Family Alliance."

VHL Family Alliance, Brookline, Mass., is a non-profit organization, dedicated to the diagnosis,



Cari and Siera

treatment and quality of life for people affected by VHL.

The first event was a benefit day at D.J.'s Sports Bar in Sandusky. Area bands donated their time, including TwoTheMax, Funk 'n Bluez, Dave James, Pete Bernel, Island Fever, Daisy Chain, Surrender Dorothy and Donny G. In addition, Greg Michaels of WNRR 92.1 broadcast live on the radio throughout the day. Area businesses donated door prizes, including Cleveland Indians tickets, Island Rocket tickets and 18 holes of golf for two with a cart from Sawmill Creek. The \$10 admission included entertainment, food and participation in a poker run, with a cash prize of \$150 for first place.

This was followed by a bikini car wash, which attracted a great deal of attention. And finally, Cari's dad, Dan P., held a golf scramble.

Altogether Cari, her family and friends raised \$6,117 to go toward funding research on VHL. We are all grateful to them for their efforts and join them in hope that by understanding more of what is going on in the cell we can finally get the maintenance drugs we need to keep tumors small, or keep them from ever appearing at all.

Based on an article by Trish Doller, *Sandusky Register*, June 10, 2002

*We Need Your Help Too!
Please Give Generously
Thank you!*

Research Digest

by Myriam Gorospe, Ph.D., Director of Research and Joyce Graff

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in 2001 Dr. Maria Czyzyk-Krzeska, whom we funded for two years (1999 – 2001), was able to obtain substantial funding from the NIH (National Institutes of Health) and the ACS (American Cancer

Society) for the continuation of her research on the **Role of VHL in Pheochromocytoma**. Similarly, Dr. Ehud Gazit at Tel-Aviv University, whom we funded last year, has won a very large grant from the Israel Cancer Research Fund, to continue his work on **'The Role of Protein Folding and Stability in the VHL Syndrome'**.

There are two aspects we are focusing on in this year's grants. First, we continue to learn more about how the VHL protein (pVHL) operates in the cell – what it regulates in normal function, and what doesn't work when pVHL is not present. Second, we are trying to move from this knowledge to real therapies. This work moves ahead more quickly when there is a "biological model", preferably one that goes through many generations in a short period of time so that genetic changes can be tracked. The mouse and even the fruit fly have a VHL gene. This shows how very essential a role the VHL gene plays in the cell.

We have renewed funding for a second year for **Dr. Robert J. Duronio** of the University of North Carolina to further his research on **E3 Ubiquitin Ligase Complexes**. pVHL's role within the E3-ubiquitin ligase is often compared to that of a 'g Page 9arbage collector', functioning as an "off" switch by gathering up certain cellular proteins that are needed for cellular growth and proliferation. The investigators have made good progress on the goals they set out to accomplish over the past year of

funding, and are continuing and extending that work.

Dr. Georges Mer of the Mayo Clinic in Minnesota is investigating how the VHL protein binds to another key protein named HIF α . These studies increase our knowledge of how pVHL and HIF1 α interact, thus helping in search for drug molecules that can restore the normal function of pVHL.

Dr. Tien Hsu of the University of South Carolina is interested in addressing how pVHL mutations cause cancer growth and metastasis. Dr. Hsu has identified a pVHL-interacting protein named nm23 (nm: non-metastatic), which may be a good target for therapeutic intervention.

Thank you very much for giving me this grant. I can assure you that the funding will be put to good use. My gratitude to the VHL Family Alliance for this great opportunity.

-- **Georges Mer, Mayo Clinic**

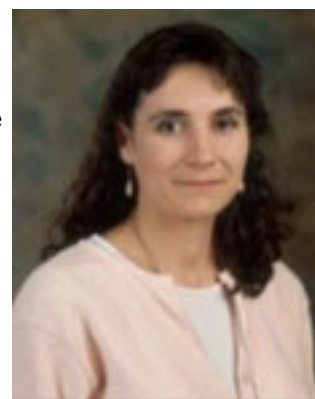
Fortunately, nm23 belongs to a class of enzymes that have been very well studied, so drug development should be feasible.

Dr. Daniel George of the Dana Farber Cancer Research Institute in Boston proposes to use the Novartis Pharmaceuticals drug PTK/ZK to carry out a Phase II clinical trial to treat patients with VHL, especially those with advanced central nervous system disease. The VHL study is due to open to VHL patients in December 2002.

Pierre Jacomet and a team at the Catholic University Medical Center in Santiago, Chile, are studying **"Pheochromocytoma and Altered Mental Function."** The objective is to compile data on the number of people suffering from panic attacks and other personality disorders that could be traced to undetected pheochromocytomas. With the help of statistical information, he hopes to raise the visibility of this issue so that health care professionals will be more likely to suspect and diagnose a pheochromocytoma. Dr. Gorospe is Investigator Chief of the Cell Cycle Control Unit, Laboratory of Cellular and Molecular Biology, National Institute on Aging, National Institutes of Health

The VHL Family Alliance has provided enormous benefit to both clinical as well as basic investigators in the field and, most importantly, to those patients with VHL and renal cell carcinoma that we all care for. Keep up the good work, you are helping and giving hope to thousands of people. I am optimistic about the future for therapy.

-- **W. Marston Linehan, M.D., Chief of Urologic Oncology, U.S. National Cancer Institute, National Institutes of Health**



Teamwork for Health

I just came across the VHL Family Alliance Homepage. What a wonderful site! I am in awe of what an obviously dedicated organization you belong to! -- **Erica T., genetic counselor, Mass.**

It's so wonderful to know that we are not alone with VHL. There's a community of support here to help. -- **Fran M., Michigan**

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!

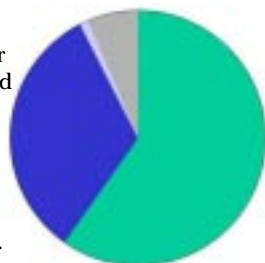
We are now reaching more than 13,000 people in 72 countries. We are in touch with more than half the projected number of people with VHL in the U.S., but only 6% worldwide. Service for English-speaking U.S. citizens has moved significantly to the internet, while service to the Spanish-speaking population in the U.S. and Latin America is beginning to build rapidly. This year we distributed 18,000 copies of the **VHL Handbook** in English, 500 copies in Spanish, and 80 in Portuguese. Operating expenses were down 7% from the prior year.

The money we raise goes directly into programming and research, with only 6% for administrative costs. We are able to do this because of the hard work of a large number of dedicated volunteers in 19 countries around the world, providing outreach in their local areas.

This year, **thanks to you**, we awarded \$131,000 in research grants, bringing the total to \$571,000 over the last six years. **Let's do it again!**

Call or write for a list of special projects that need funding. For example, we want to set up an inquiry line in Spanish language, and design better support for asymptomatic youth diagnosed through DNA testing.

Total Revenue for Fiscal 2002 (ended June 30, 2002) was \$222,152. Of this, a total of \$131,000 was allocated to research funding.



61% Research
32% Education
and support
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Remember VHLFA in Your Will

You can give hope to millions of people worldwide with VHL, kidney cancer, 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.

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171 Clinton Road, Brookline, MA 02445
Federal tax ID 04-3180414

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Mail to: VHLFA, 171 Clinton Rd., Brookline, MA 02445

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Fowler Family Touches Hearts with Song

by Peggy Marshall, Mississippi

The Fowler family of Tennessee and Mississippi is a large family with many talented people. One of the talents prevalent in the group is the gift of song. Four generations of Fowlers have been professional gospel singers for as much as sixty years. It is said within the family that "if a newborn doesn't come out singing, we send them back!"

The idea began after Eva Logan passed away, with a phone call from a musically talented and sincerely caring cousin, John Blankenship, who said "we want to help." He suggested holding a benefit to raise funds for VHL research.

In September 2002 several prominent groups participated in a Gospel Music Extravaganza in a very beautiful, ornate auditorium in Corinth, Mississippi. Friends and relations gathered to remember Eva, to honor those who are still living with VHL, and to raise money for VHL research. The evening was a stunning success that not only raised \$5100 for research on VHL but raised awareness of VHL among Northeast Mississippi and West Tennessee folks.

Altogether nine groups donated their time and talent and helped to raise \$5,100 for VHL research. We were thrilled with the event, and with the warmth and comradeship everyone experienced. We were very moved by the support we received from the performers and from our community.

Mary Ann Johnson and Starr Gunn sang duets including a particular favorite, "There is Always Enough. The reason, they say, is "No matter what the case may be, and there always seems to be a case these days, there is always enough of God's love and grace and mercy to get us through whatever situation



Jerry Carr (tenor), Jeremy Ballinger (lead), Mark Brantley (baritone), and Bobby Smith (bass guitar) of Under Grace we have to face."

The Father's Four sang selections from their latest album. "Our earthly fathers and mothers played a vital part in nurturing, training, and encouraging us to sing for The Lord since our youth. Our desire is to pass this tradition on to future generations through our sons and daughters."

Trevor Williams, a local pharmacist, added his beautiful tenor to the evening. Brenda Barbour added her strong alto voice and spirit-filled delivery. Courtney Johnson, age 13, was the youngest talent in the show. She has won several local talent contests in the West Tennessee Area.

The Harmony Trio, made up of Linda Fowler Skinner, Brenda Fowler Jones and Cornelia Hall, daughter of Carrie Fowler Thomas, grew up a singing family. "Our grandfather Fowler taught singing in schools. Out of grandfather and grandmother's children there was a sisters quartet who sang mostly at the home church and surrounding churches, and a brothers quarter (The Fowler Brothers Quartet) who traveled around the country singing for sixty years." Most of their singing is in churches, schools, and for fundraisers in their local communities around Beech Bluff, Tennessee.

Under Grace, a traditional Southern Gospel Group, sang older Southern Gospel songs with a good mix of original material.

Grady Fowler of Beech Bluff, Tennessee, sings tenor with a group called The Living Truth. Gary Fowler sings baritone and John Blankenship sings the lead with The Jubilaires.

It was indeed a memorable event and one we are still hearing compliments about. In fact, we have been asked to make it an annual event. This family and its wide circle of friends is dedicated to the mission of finding a cure for VHL. "We will continue that mission with determination and passion until a cure is found." They are already planning to do it again next year!

For bookings, contact Mary Ann or Starr at 662-287-5666; Father's Four at 731-787-6900 www.thefathers4.com; Brenda Barbour at 662-287-4608; The Living Truth at 731-645-3161; The Jubilaires at 713-668-0890; Under Grace at 731-662-4171 www.undergrace.net



Tom Richerson, Larry Evans, James Richerson, and Eddie Long of The Father's Four

Please share the pull-out section with a friend. Ask others to help us find a cure for VHL!

Update on VHL: Cleveland 2002

The U.S. National Conference was held in conjunction with the Cleveland Clinics. Dr. David Goldfarb, Head of Renal Transplantation at the Cleveland Clinic and Dr. Robert Uzzo of Fox Chase Cancer Center in Philadelphia co-chaired an outstanding continuing medical education event. Fifteen physicians, two nurses, two genetic counselors, and 55 patients and family members met at the Cleveland Marriott to learn the latest advice in health management with VHL.

Fifteen outstanding presenters gave us a clear and concise overview of the major issues in VHL. The material was carefully prepared and well-honed for a well-informed lay audience.

On Friday morning before the medical meeting began Joyce Graff met with 42 family attendees for "VHL 101," an introductory session on the concepts and terminology that would be used in the medical sessions. As each person told his or her story we heard clearly the diversity of experience among people with VHL, and the breadth of topics needed to cover the interests of the entire group. Experiences ranged from people in their fifties with no more than a retinal angioma or two, to people with serious deficits.

The one theme predominant throughout was that early diagnosis, conscientious screening, and appropriate treatment are the keys to living well with VHL. While this is in part the responsibility of the physicians, the primary person in charge of patient care is the patient himself or herself. The patient has a responsibility to make the appointments, show up for testing, and share sufficient information with the physician so that the physician can do a good job. And it is also the responsibility of the patient to manage the health care team.

Often there is not one clear course of action. The patient has to approach the problem as objectively as if it were car repair or house repair -- gather information from multiple experts, listen to their recommendations and estimates (not just money but human cost), and then choose the course of action that feels right. As Patricia Rasmussen, VHLFA Director of Clinical Care, told the audience, "You are the Chief Executive Officer (CEO) of your body."

In his opening remarks, Dr. Goldfarb noted that "As a medical community, we know more about the location and mutation of this gene than perhaps any other. Practically speaking, this means that patients and their family members at risk are diagnosed earlier than ever before and therefore receive medical attention long before they become symptomatic, allowing them an unprecedented opportunity to be proactive in the approach to their care." We still face significant challenges in ensuring that new patients

whose families do not realize they are at risk for VHL obtain timely diagnosis.

"It is our collective medical hope," he said, "that the familiarity we have with the VHL gene will provide unique insight into the mechanisms of malignant transformation, namely how a mutated gene, through its protein products, induces uncontrolled cellular growth and proliferation. The protein product of the VHL gene has been identified (pVHL) and an intense search is now underway to identify the pathways and targets of pVHL in an effort to develop novel therapeutic strategies for treatment. This search has profound implications not only for patients afflicted with hereditary forms of cancer such as VHL, but for patients with sporadic cancers as well."

Dr. Uzzo defined the problem of VHL. As a multi-system disorder, it is a challenge to all the doctors involved to analyze the presenting problem and delegate it to the right specialist. We don't yet know why it affects so many organ systems in different ways.

Dr. Louis Liou and Dr. Brian Clark explained the intricacies of DNA testing, and Dr. Clark spoke about preimplantation testing, a process of fertilization in vitro, DNA testing, and then implanting an unaffected fertilized egg into the womb.

Dr. Erick Remer presented advances in diagnostic imaging. Dr. Peter Weber spoke about ELST, and Dr. Jonathan Sears about the eye. The Central Nervous system tumors and treatments were explained by Dr. Gene Barnett, and the pancreas by Dr. Matthew Walsh. Drs. Uzzo, Novick, Goldfarb, and Olencki gave an excellent series on the state of the art in kidney diagnosis and treatment, followed by an explanation of laparoscopic approaches to the adrenals by Dr. Andrew Steinberg.

Dr. Frederick Frost surveyed advances in rehabilitation following surgery, and Dr. Joseph Locala explained psychosocial concerns. Dr. Victoria Vance gave an excellent talk on insurance issues and legal concerns.

Dr. Goldfarb again stressed the importance of being a proactive patient. "Patients with VHL and their families face unique circumstances and problems. We hope that this "Update on VHL" provides some insight into the basic mechanisms of the disease, its diagnosis and the latest treatment strategies. Patients with VHL must use their physicians and other health care providers, their genetic counselors, social workers, and lawyers as resources to guide them through these issues. However, they must also remain proactive in the management of their disease through organizations such as the VHL Family Alliance."

Forthcoming Meetings

The first National Canadian meeting on VHL will be held in **London, Ontario**, in May 2003, co-sponsored with the University of Western Ontario. Dr. Stephen Pautler of the Division of Urology will chair the meeting. The final date is still being arranged and will be posted when available. Watch for further details in the March issue, or contact Jill Shields.

This meeting is being designed for primary care physicians and patients and families, to provide a good understanding of VHL management.

Instead of one large **U.S. meeting in 2003** we are planning at least two regional meetings in a one-day format, in hopes of making the meetings more available to more people. If you would like to host a meeting in your local area, please contact the Hotline 1-800-767-4VHL. The first meeting will be in the June timeframe, probably in Nashville, Tennessee. Watch the March newsletter or the website for further information.

The next Medical Symposium is being planned for **April 2004 in Japan**, hosted by Dr. Taro Shuin of the Department of Urology, Kochi University Medical School. Dr. Shuin heads one of the large research studies on VHL, the largest in Asia and one of the five top centers in the world. This meeting is designed as a forum for experts in VHL -- clinicians and researchers -- to share their latest findings and accelerate progress in management of VHL. Abstracts will be solicited for this meeting in late 2003. The language of the Symposium will be English. A separate conference designed for families will be held in Japanese adjacent to this meeting.



Dr. Stephen Pautler



Dr. Taro Shuin

Ontario May 2003
Nashville June 2003
Kochi, Japan, April 2004

To the Editor: DNA Testing

In the September issue of the **VHL Family Forum** there was an article called, "Our Experiences with DNA Testing." I was terribly sorry to hear about this family's unnecessary, frustrating, and confusing experience. I am writing to tell you a little more about genetic counseling, mentioned in your article in the section under "How to avoid confusion."

A Genetic Counselor's area of expertise specifically includes explaining and facilitating the genetic testing process. Most genetic counselors would have spent 1-2 hours with this family prior to testing, arranged the testing for them (including arranging the blood draw and shipping) and then would have followed up with disclosure and review of results at a second appointment (30-60 minutes, as mentioned in the article), allowing plenty of time for questions. A follow-up written communication to summarize these visits would have been included. Genetic counselors can also help to communicate test results and implications to other family members and to medical professionals involved in the family's care. Genetic Counselors often have Master's Degrees in Medical Genetics or Genetic Counseling, or a related area. Their training is specific to help identify and explain genetic diseases in terms that are understandable to the family. I have often heard Genetic Counselors describe themselves as "translators" of the complex language and technology of genetics now available to us.

Genetic counseling is an option and a good choice for anyone considering genetic testing. Some would argue that it should be required for anyone seeking genetic testing; currently it is often not required. Genetic counseling is also a good option for people who do not want genetic testing, who would simply like to have information about their genetic disease presented in a detailed and understandable manner.

To find a genetic counselor near you, go to <http://www.nsgc.org/resource/link.asp>

—**Anna Leininger, M.S., Certified Genetic Counselor,
Minnesota Colorectal Cancer Initiative, St. Paul, MN.
Phone: 651-312-1557**

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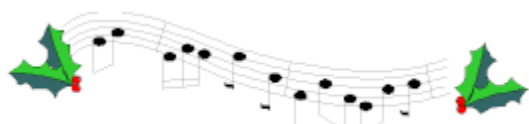
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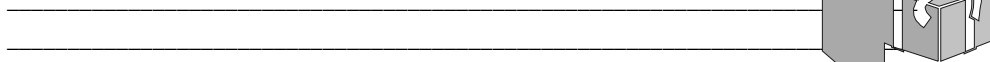
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Progress!

We are now reaching more than 13,000 people in 72 countries. We are in touch with nearly half the projected number of people with VHL in the U.S., but only 6% worldwide. Service for English-speaking U.S. citizens has moved significantly to the internet, while service to the Spanish-speaking population in the U.S. and Latin America is beginning to build rapidly. This year we distributed 18,000 copies of the **VHL Handbook** in English, 500 copies in Spanish, and 80 in Portuguese. Operating expenses were down 7% from the prior year.

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Teamwork for Health

I just came across the VHL Family Alliance Homepage. What a wonderful site! I am in awe of what an obviously dedicated organization you belong to! -- *Erica T., genetic counselor, Mass.*

It's so wonderful to know that we are not alone with VHL. There's a community of support here to help. -- *Fran M., Michigan*

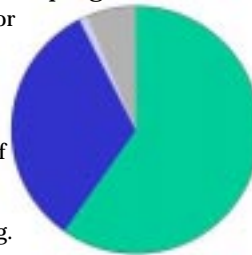
Let's Cure VHL in this Decade

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.

Total Revenue for Fiscal 2002 (ended June 30, 2002) was \$222,152. Of this, a total of \$131,000 was allocated to research funding.



61% Research
32% Education and support
1% Fundraising
6% Administration

Let's Make a Miracle! We Need Your Help!



Newsletter of the VHL Family Alliance
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