

VHL FAMILY ALLIANCE HOME PAGE

BASIC FACTS ABOUT VHL CARING FOR YOUR HEALTH RESEARCH
PROFESSIONAL INFORMATION ABOUT THE VHL FAMILY ALLIANCE



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Frequently Asked Questions
Handbook

Dedicated to improving diagnosis, treatment, and quality of life for individuals and families affected by von Hippel-Lindau disease.

Welcome! You are visitor number **35388** since July 1, 2000

What's New

- * It's **membership renewal time**, and time to build our fund for Research grant! You can make your donation **online**. If you find value in this store of information, in the online discussion, the newsletter, and the hotline services, then please help to support those services and fund research.
- * **Larry B.** has been selected to carry the Olympic torch through Olympia, Washington. He is being acknowledged for running his "marathon" with VHL with grace and good humor. Details will follow.
- * **The September newsletter** is now online, with articles about kidney transplantation, stem cell research, report from the Palo Alto meeting, new Canadian leadership, nicotin, meetings in 2002, depression and psychological issues, and Alice

WWW.VHL.ORG

X. INTRA-OCULAR GROWTHS.

1. *Two cases, brother and sister, with peculiar vascular new growth, probably primarily retinal, affecting both eyes.*

By E. TREACHER COLLINS.

(With Plate IV.)

In vol. xii of the 'Transactions' of this Society is published a coloured drawing of the fundus of the right eye of a patient of Mr. Tweedy's, showing very peculiar enlargement of some of the retinal blood-vessels. In this patient's left eye the retina was completely detached, and he, subsequently to being shown at the Society, developed

Trans. Ophthal. Soc. U.K. 14: 141-149, 1894


Graefe Arch.Ophthal. 59: 83-106,1904

(Aus der Universitäts-Augenklinik zu Heidelberg.)

Über eine sehr seltene Erkrankung der Netzhaut.
Klinische Beobachtungen.

Von
Prof. Eugen v. Hippel
in Heidelberg.


Mit Tafel III—VI, Fig. 1—5.



AUS DEM PATHOLOGISCH-ANATOMISCHEN INSTITUT
ZU LUND (SCHWEDEN)

**ZUR FRAGE DER ANGIOMATOSIS RETINÆ
UND IHRER HIRNKOMPLIKATIONEN**


VON
ARVID LINDAU



Das ophthalmoskopische Bild einer Angiomatosis retinae ist, wenigstens in früheren Stadien der Krankheit, sehr charakteristisch. Von der Papille führen ein paar erweiterte und stark gewundene Gefässe (gewöhnlich ein »Gefässpaar«) zu einem peripher gelegenen, prominenten, kugeligen Gebilde von mehr oder weniger rötlicher Farbe (Tr. Collins (1893). v. Hinsel

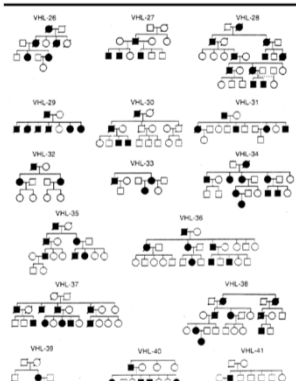
Acta. Ophthal. 4: 193-226, 1927

Watson and Crick: Structure of DNA



Circa 1950

von Hippel-Lindau (VHL) Disease Families



1) Kidney Cancer
2) Hemangioblastomas (Blood Vessel Tumors)
3) Pheochromocytomas (Adrenal Gland Tumors)

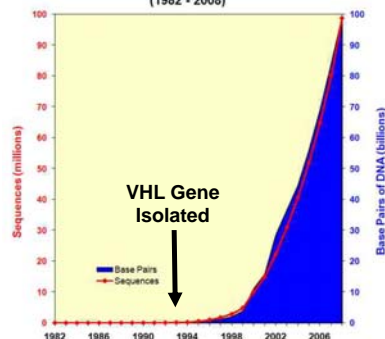
Identification of the von Hippel-Lindau Disease Tumor Suppressor Gene

Farida Latif, Kalman Tory, James Gnarra, Masahiro Yao, Fuh-Mei Duh, Mary Lou Orcutt, Thomas Stackhouse, Igor Kuzmin, William Modi, Laura Geil, Laura Schmidt, Fangwei Zhou, Hua Li, Ming Hui Wei, Fan Chen, Gladys Glenn, Peter Choyke, McClellan M. Walther, Yongkai Weng, Dah-Shuhn R. Duan, Michael Dean, Damjan Glavač, Frances M. Richards, Paul A. Crossey, Malcolm A. Ferguson-Smith, Denis Le Paslier, Ilya Chumakov, Daniel Cohen, A. Craig Chinault, Eamonn R. Maher,* W. Marston Linehan,* Berton Zbar,* Michael I. Lerman*

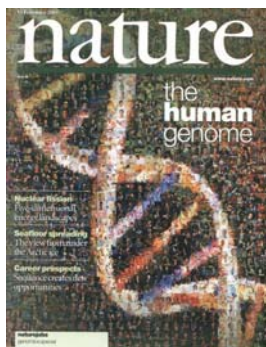
A gene discovered by positional cloning has been identified as the von Hippel-Lindau (VHL) disease tumor suppressor gene. A restriction fragment encompassing the gene showed rearrangements in 28 of 221 VHL kindreds. Eighteen of these rearrangements were due to deletions in the candidate gene, including three large nonoverlapping deletions. Intragenic mutations were detected in cell lines derived from VHL patients and from sporadic renal cell carcinomas. The VHL gene is evolutionarily conserved and encodes two widely expressed transcripts of approximately 6 and 6.5 kilobases. The partial sequence of the inferred gene product shows no homology to other proteins, except for an acidic repeat domain found in the procyclic surface membrane glycoprotein of *Trypanosoma brucei*.

Science (1993)

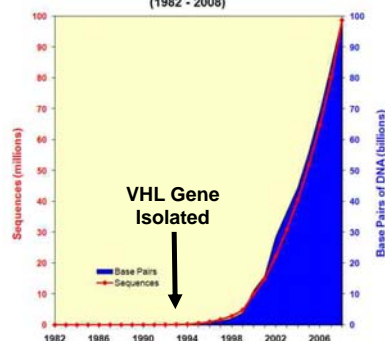
Growth of GenBank (1982 - 2008)



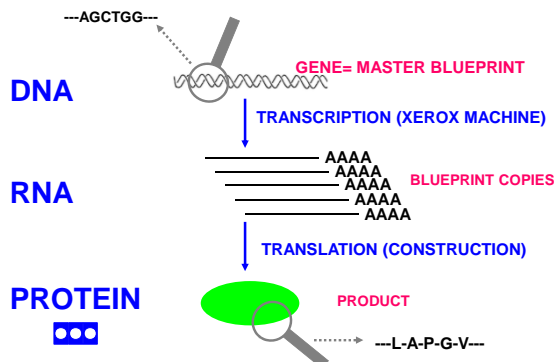
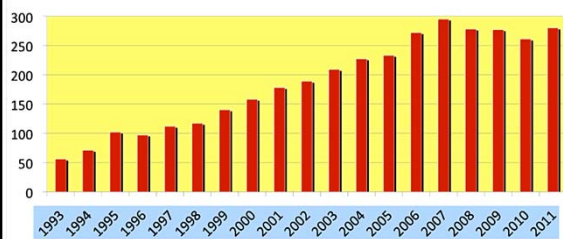
First Drafts of Human Genome (2001)

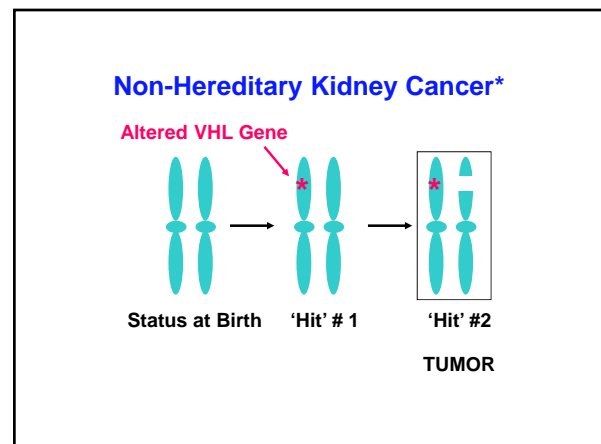
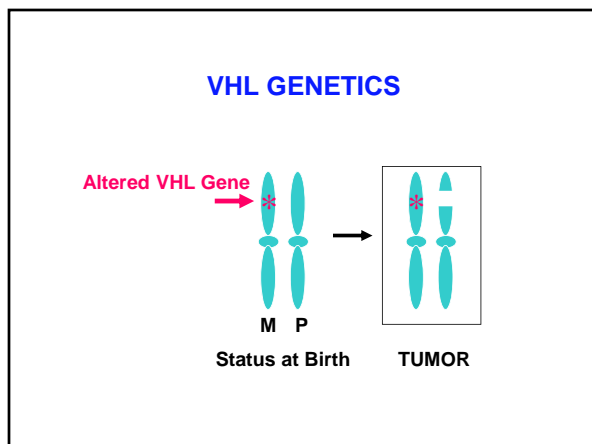
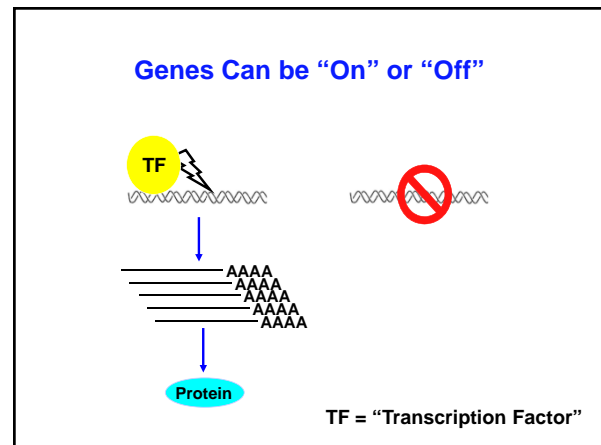
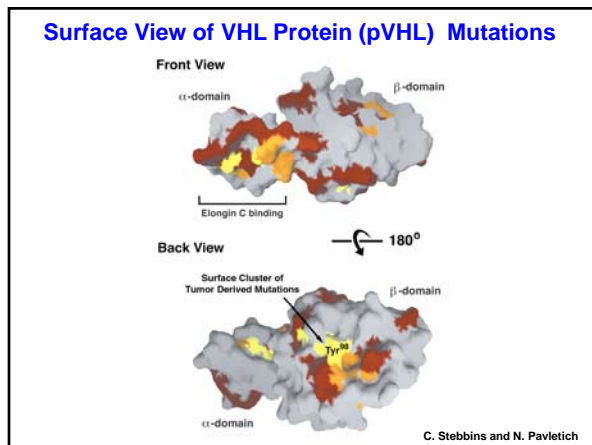
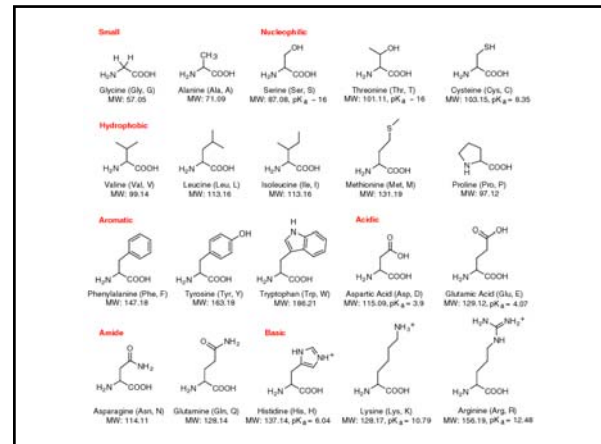
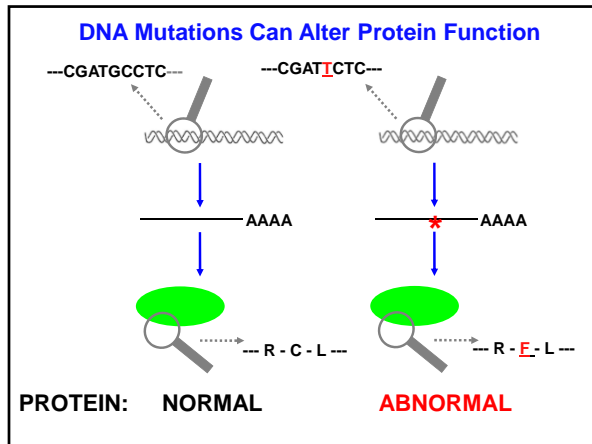


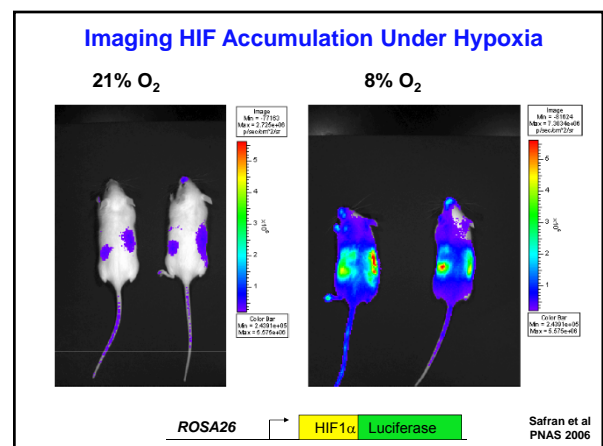
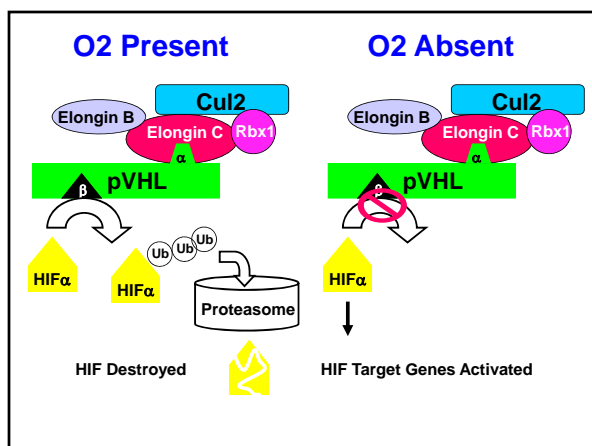
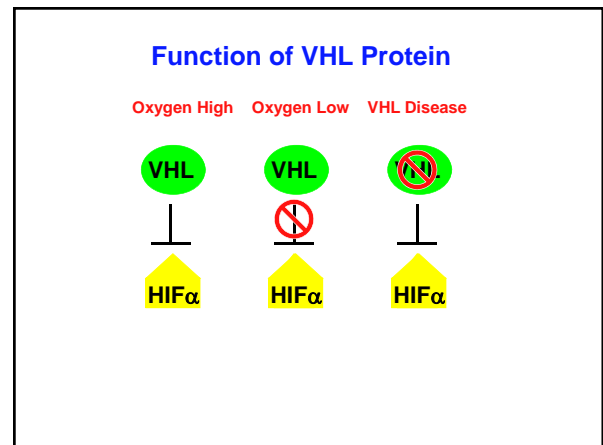
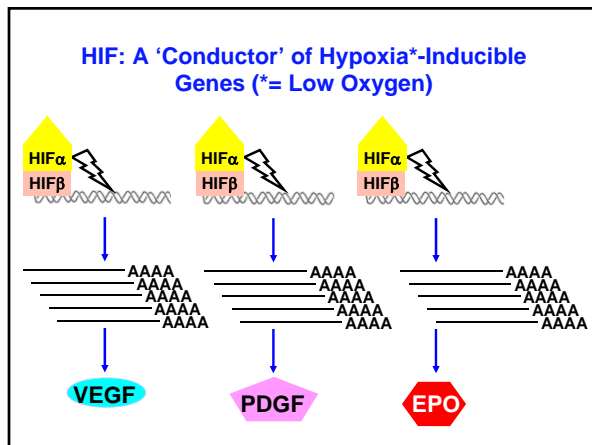
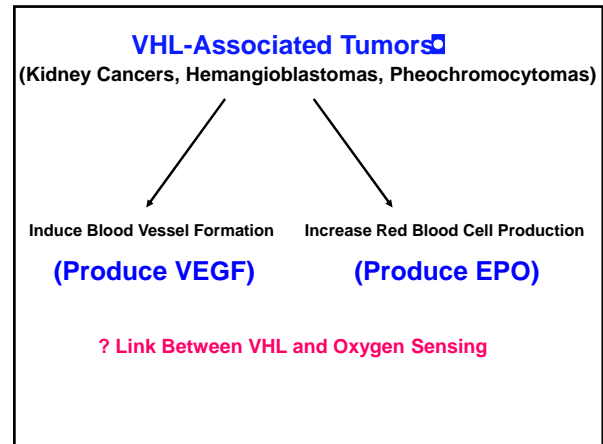
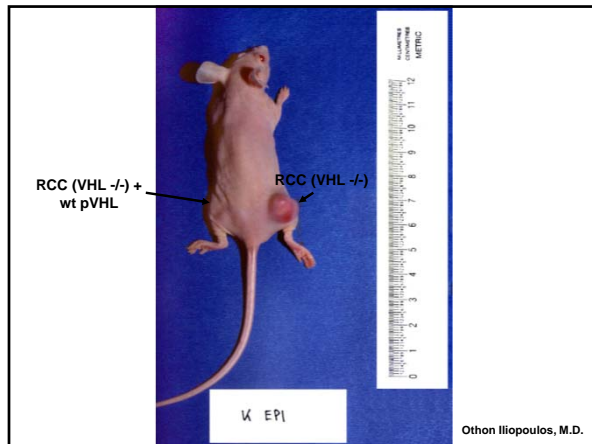
Growth of GenBank (1982 - 2008)

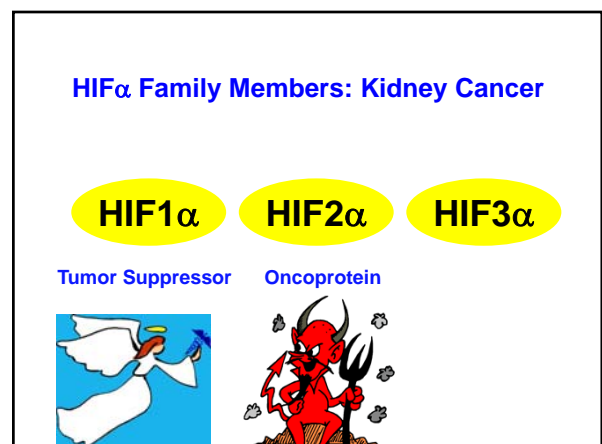
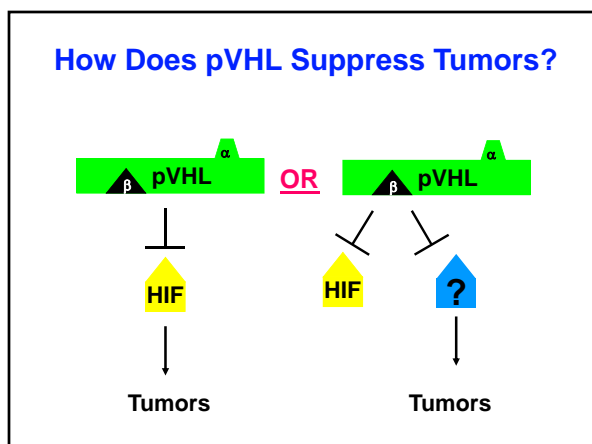
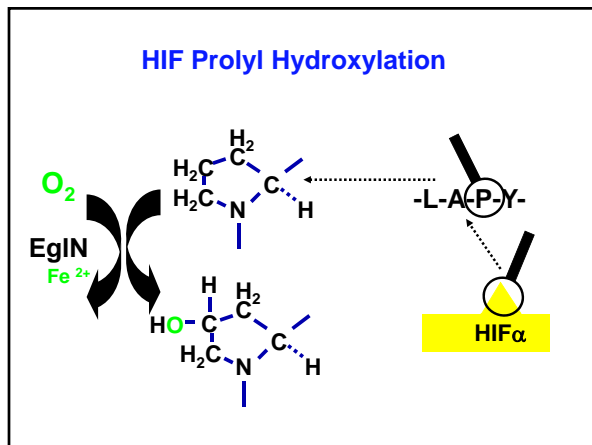
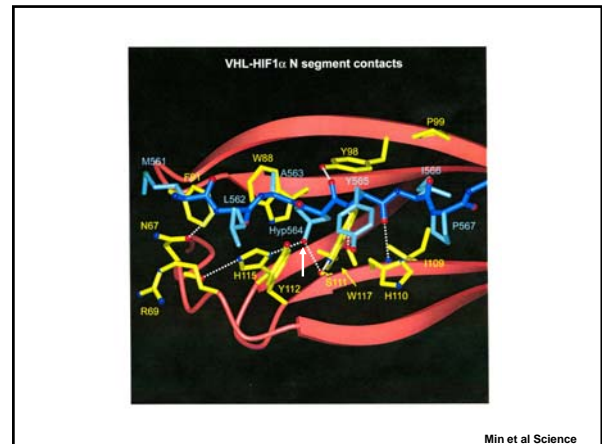
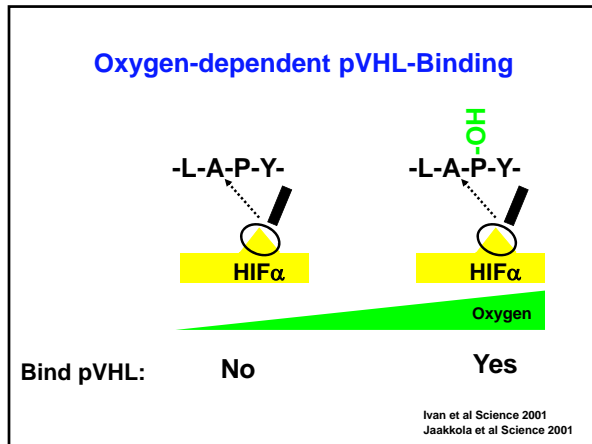


VON HIPPEL-LINDAU PAPERS PUBLISHED

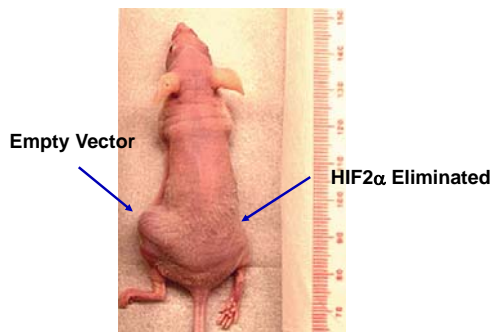






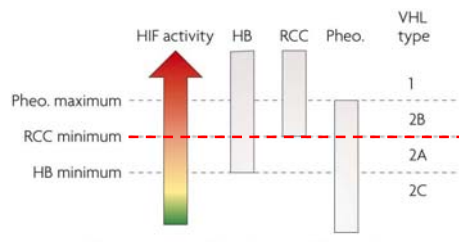


HIF2 α Elimination Mimics Restoration of pVHL Function



Keiichi Kondo

Degree of HIF Deregulation Predicts Cancer Risk in VHL Families



HB = Hemangioblastoma; RCC = Renal Cell Carcinoma; Pheo= Pheochromocytoma

HIF α Family Members: Kidney Cancer

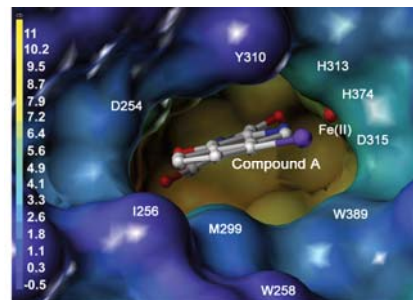
HIF1 α HIF2 α HIF3 α

Tumor Suppressor

Oncoprotein

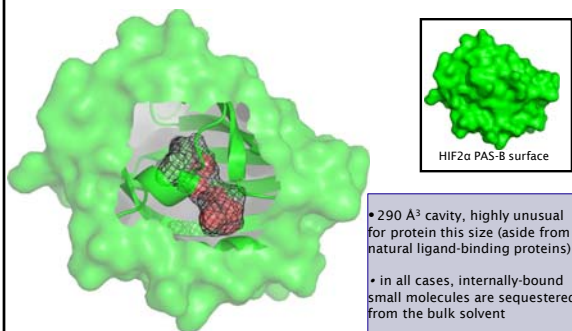


EglN1 (PHD2) Has a Druggable Pocket



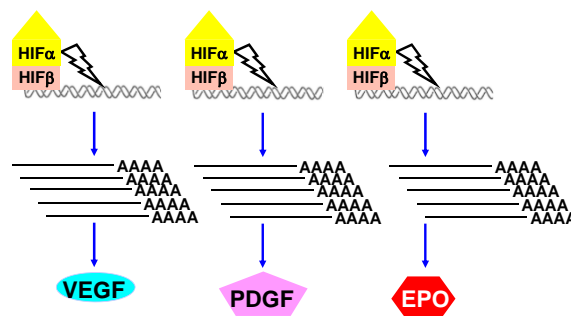
McDonough et al Proc Natl Acad Sci U S A. 2006 Jun 27;103(26):9814-9.

Possible Druggable Pocket in HIF2 α

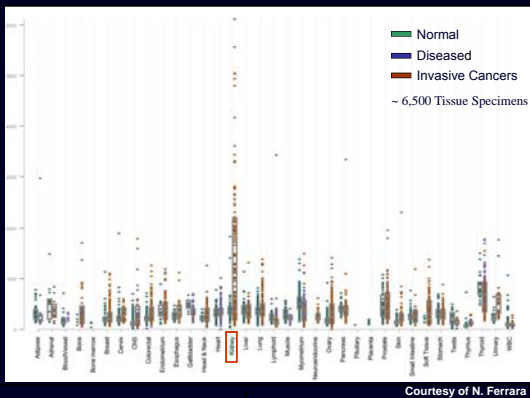


Scheuermann et al., 2000

HIF: A 'Conductor' of Hypoxia*-Inducible Genes (= Low Oxygen)



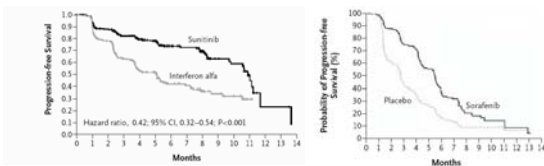
Expression of VEGF-A in Human Tissues – GeneLogic / Affymetrix®



VEGF Inhibitors Displaying Activity against Kidney Cancer

- Bevacizumab *FDA Approved
- Sunitinib *FDA Approved
- Sorafenib *FDA Approved
- Axitinib
- Pazopanib *FDA Approved
- ~30 more on the way!

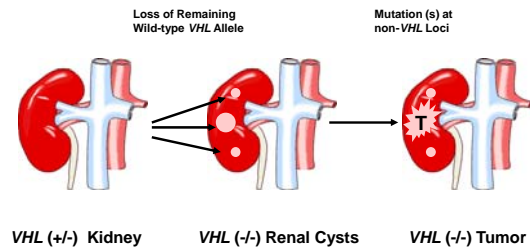
Treatment of Clear Cell Renal Carcinoma with KDR inhibitors



Motzer, R. J., et al, N Engl J Med, 356: 115-124, 2007.

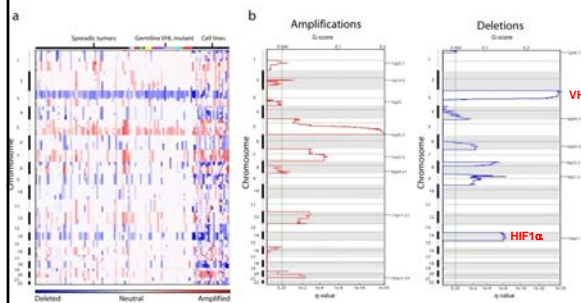
Escudier, B., et al, N Engl J Med, 356: 125-134, 2007.

VHL Loss is Not Sufficient for Human Kidney Cancer



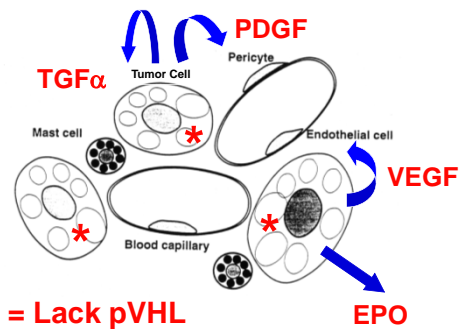
Development of Kidney Cancer in VHL Patients

Kidney Cancer Copy Number Changes

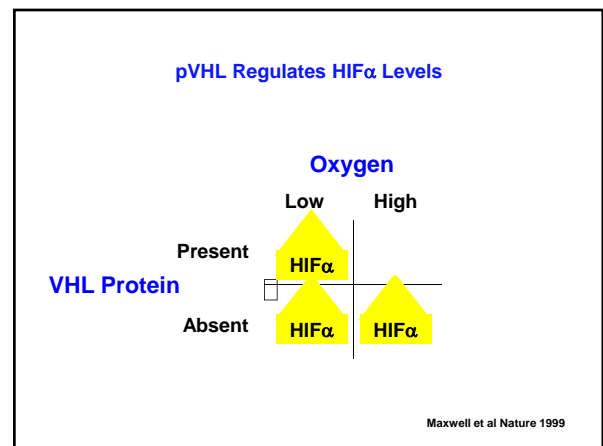
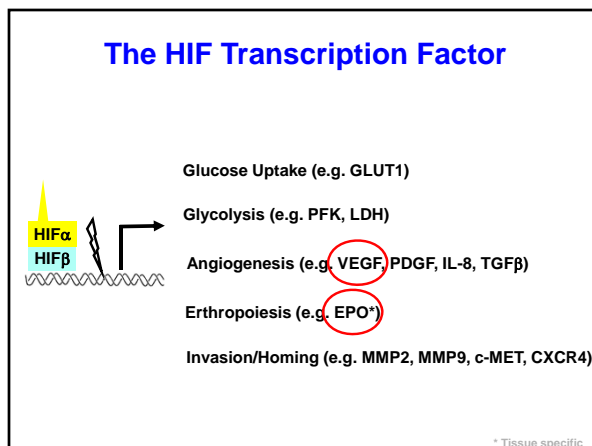
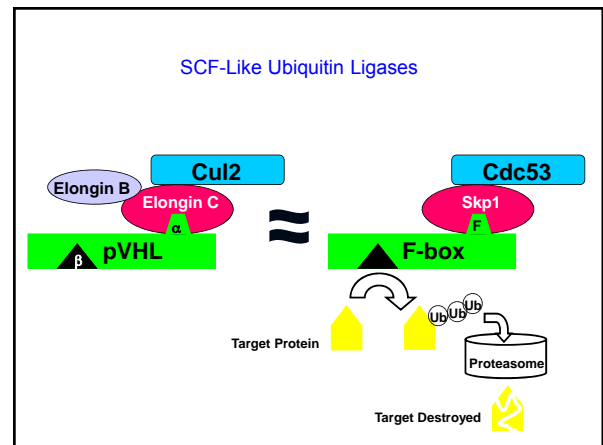
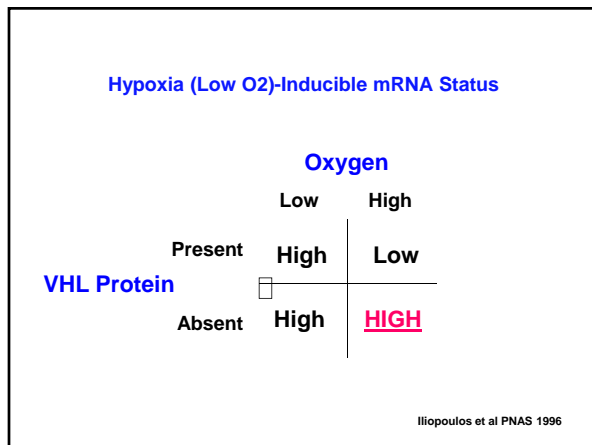
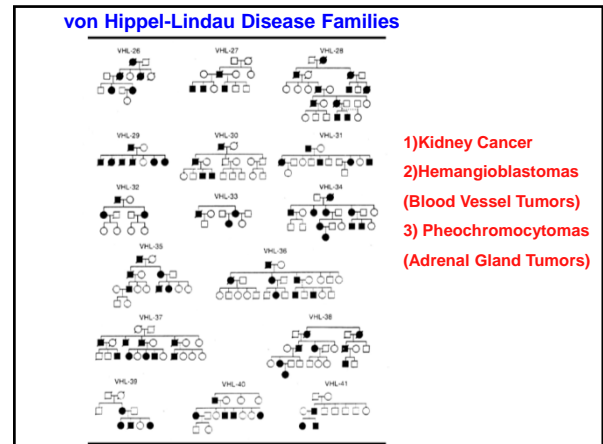
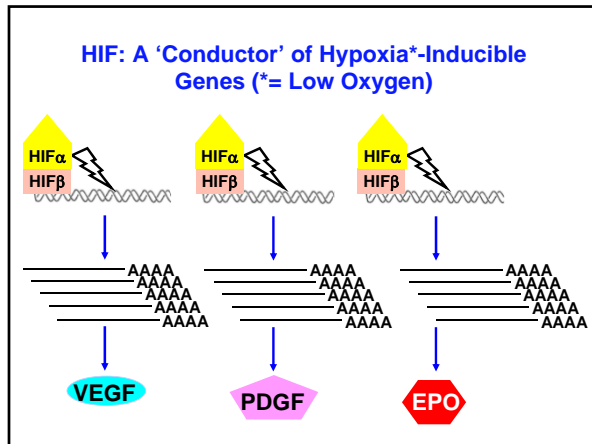


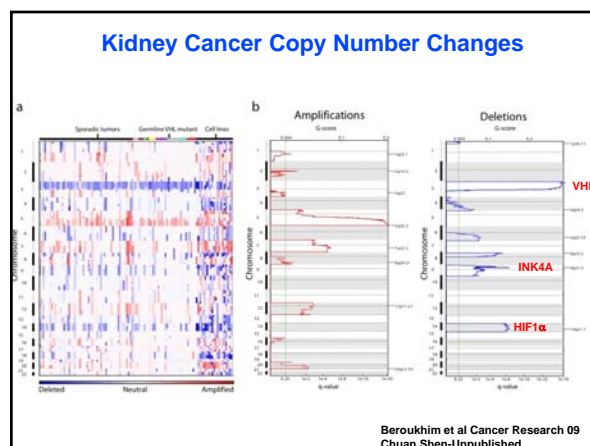
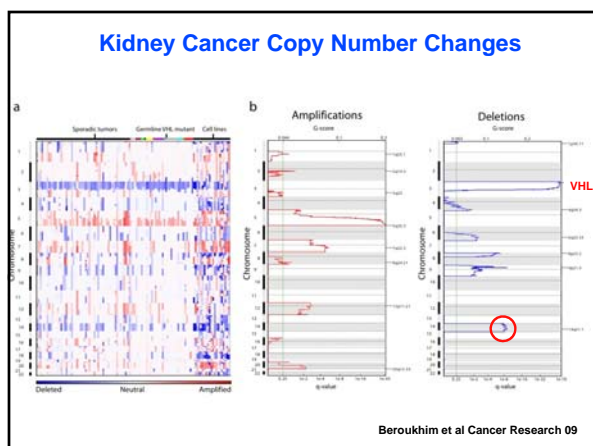
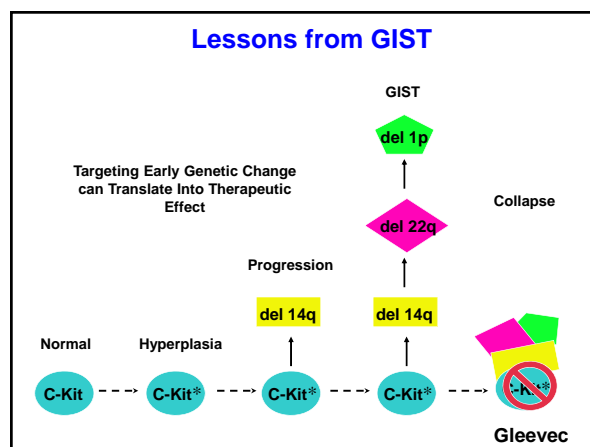
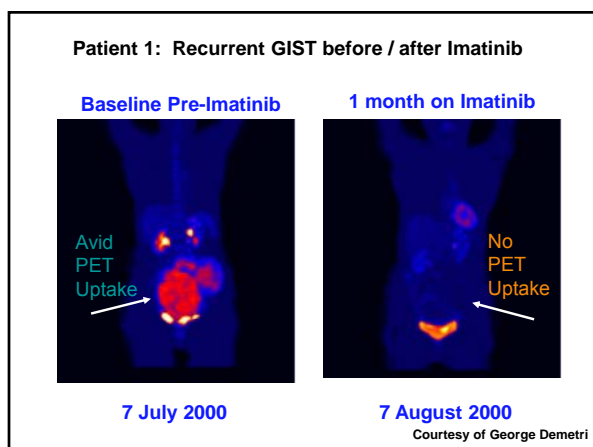
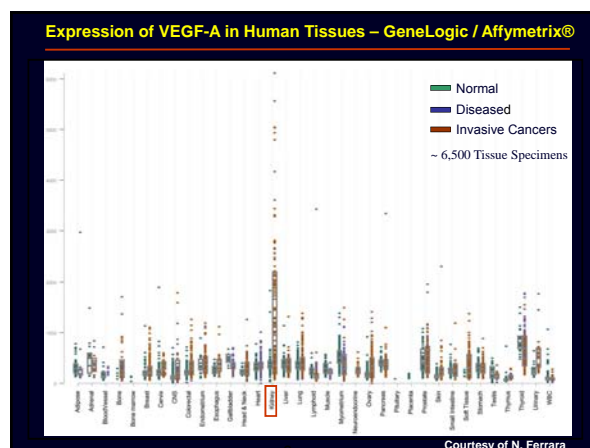
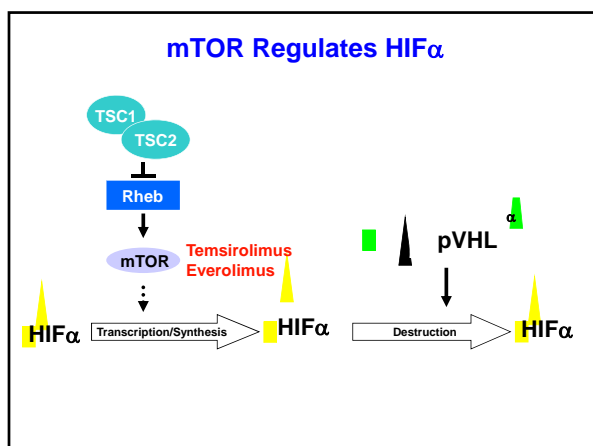
Beroukhi et al Cancer Research 09
Shen et al Cancer Discovery 11

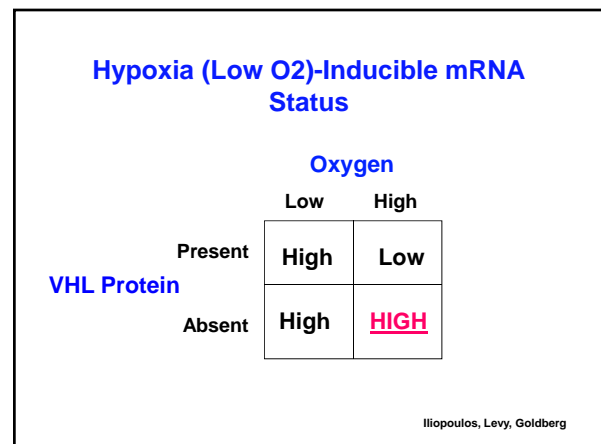
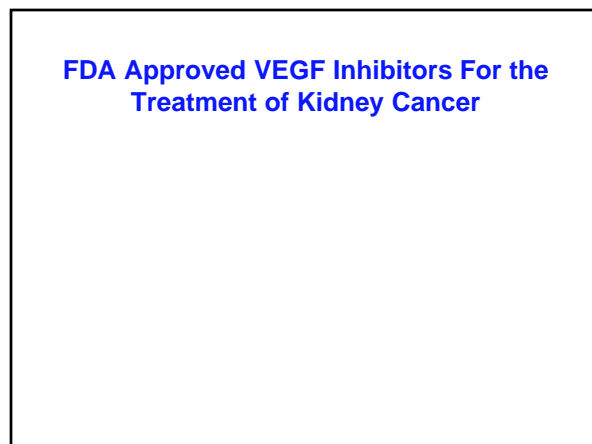
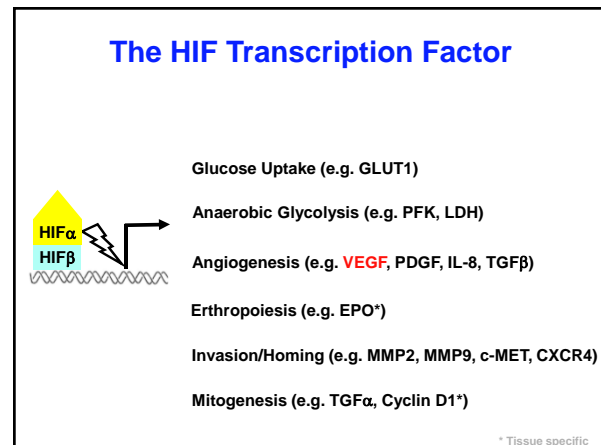
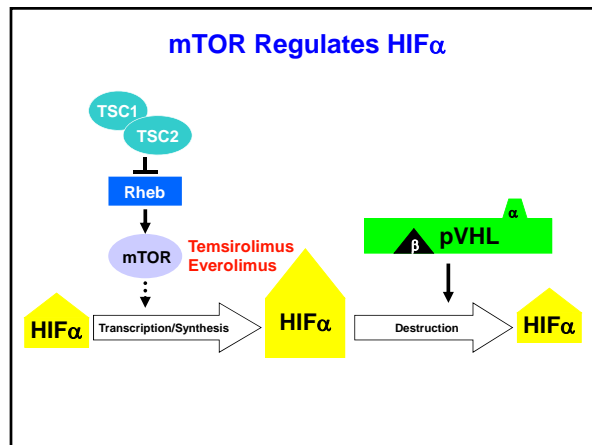
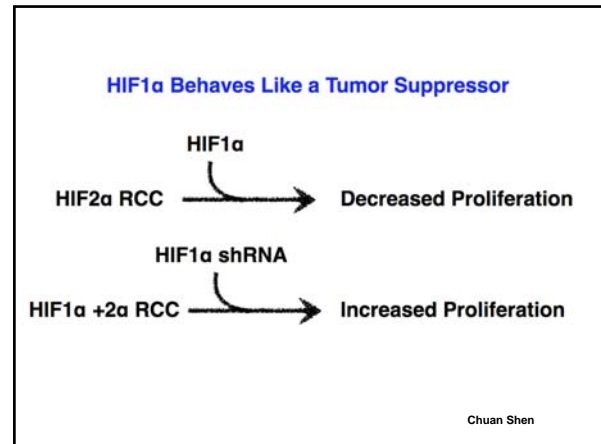
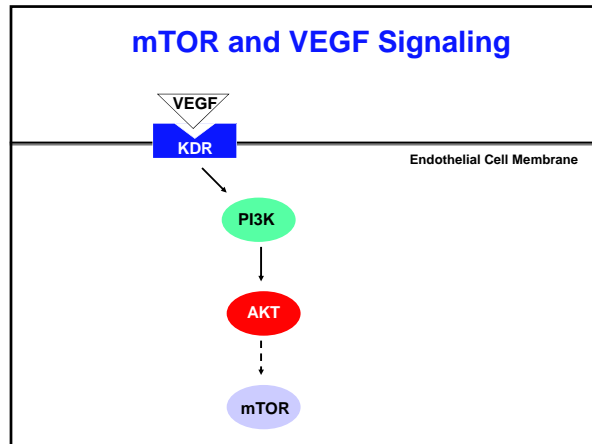
pVHL-defective Tumor (e.g. Kidney Cancer)



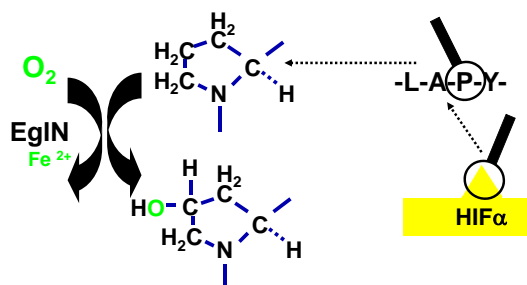
Modified from Richard et al J. Int. Med. 243:547-553, 1998



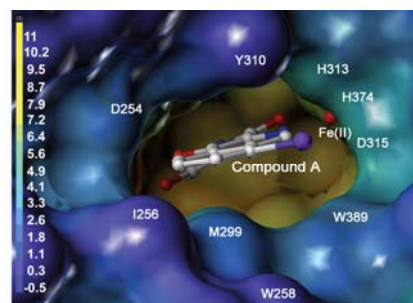




HIF Prolyl Hydroxylation



EglN1 (PHD2) Has a Druggable Pocket



McDonough et al Proc Natl Acad Sci U S A. 2006 Jun 27;103(26):9814-9.

Therapeutic Implications

Want to Increase HIF in :

Anemia (Too Few Red Blood Cells)
Heart Attack
Stroke
Adaptation to High Altitude

Want to Decrease HIF in

Many Cancers (Especially Kidney Cancer)

Picking a Career: Two Roads to Happiness*

Pick a Career You Enjoy Every Day

Pick a Career That Pays You Well Enough to Enjoy Life OUTSIDE of your Work

*Fortunately There are Others

Why Did I Become a Scientist?

Like Solving Interesting Puzzles

Feels Like I am Getting Paid to Have Fun

I Am Still My Own Boss

Meet Brilliant People

Can Potentially Help More Patients Than When I was A Clinician



Dear Dr. Kaelin,

I'm one of the patients featured in the article about advances in the treatment of kidney cancer. The article mentions the wonderful work that you and (your colleagues) have done. You are the true heroes in the story.

What the story didn't say is that **my disease was so extensive that I was deemed inoperable and was in excruciating pain.** I couldn't walk more than a hundred yards. My quality of life was not great.

Today I am totally painless and can walk as long and as far as anyone I know. In Feb 2007 I was told that I would never swing a golf club again and was OK with that. Last spring I was told that I could start playing as long as it didn't hurt. I played all summer. **In the 3+ years since my diagnosis I've been able to witness many things that I didn't expect to live long enough to see.** In March of 2008 my oldest daughter and her husband presented my wife and I with **our first grandchild.** Later that year I **escorted my 2nd daughter down the aisle at her wedding** and in July 2009, **I served as my son's best man!** We have **another grandchild due to be born on the 4th of July.** Intermixed there are thousands of other very important memories and events that would not have been possible without the work of yourself and so many others. For example, **my son and I were at Fenway Park the night Jon Lester threw the no hitter.** That's a father son memory that ...no one will ever take away from either of us.

VON HIPPEL-LINDAU DISEASE

- Described in Late 19th Century
- Affects 1 / 35,000 People
- Caused by Germline Mutation of *VHL* Tumor Suppressor Gene (3p25)
- Conforms to Knudson Two-Hit Model
- Tumors Develop in 2nd, 3rd, 4th decades of Life
- Life Expectancy ~ 50 years old (highly variable)

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Graefe Arch.Ophthal. 59: 83-106,1904

(Aus der Universitäts-Augenklinik zu Heidelberg.)

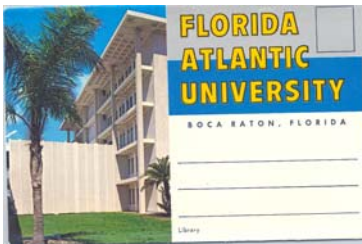
Über eine sehr seltene Erkrankung der Netzhaut.

Klinische Beobachtungen.

Von

Prof. Eugen v. Hippel
in Heidelberg.

Mit Tafel III—VI, Fig. 1—5.



QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

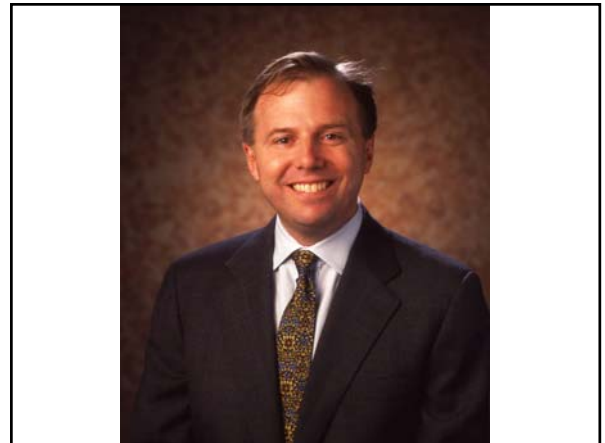
Two Ways to "Drug" Abl



"May you Live in Interesting Times"

Why Did I Succeed as a Postdoc?

- Great Mentorship
- Great Problem to Work On (RB Gene)
- Too Naïve to Know What "Should Not Work" (Tried Lots of Things)
- M.D.s are Great Multitaskers and are Used to Working Hard
- Good M.D.s Know How to Weigh Conflicting Data
- Most M.D.s are Obsessive-Compulsive



- Ask Important, Tractable, Questions
- Be Your Own Worst Critic

High School

Liked:

Learning Concepts & Ideas
Objective Subjects
Playing

Disliked:

Memorizing Facts
Subjective Subjects
Studying

High School

Freshman	B (except for Math)
Sophomore	B (except for Math)
Junior	B (except for Math)

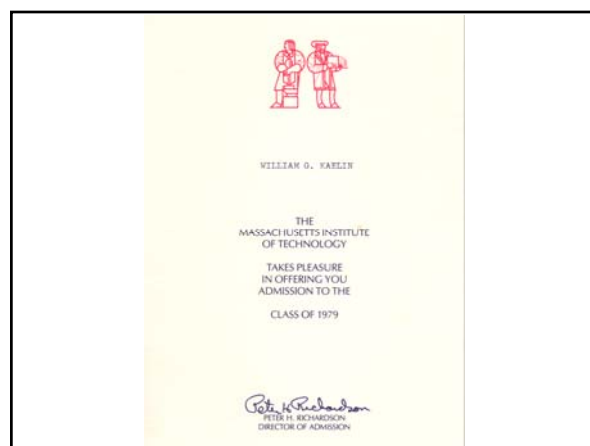


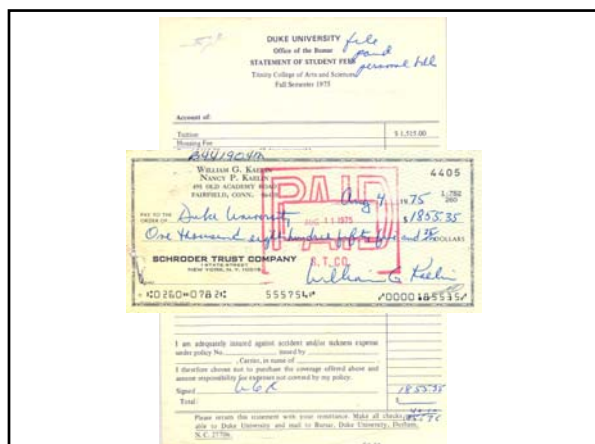
High School

Sit in Front of Classroom Instead of the Back
Spend More Time with the Smart Kids (a.k.a. "Nerds")
Do Homework First Rather than Last
Review the Day's New Material Every Evening
Do Extra Work Rather than the Minimum
Earn your Playtime!

High School

Freshman	B (except for Math)
Sophomore	B (except for Math)
Junior	B (except for Math)
Senior	A+





Picking a Career (High School/College)

Liked Math and Science

Wanted to Be My Own Boss

Wanted New Intellectual Challenges Every Day

Liked Interacting with People

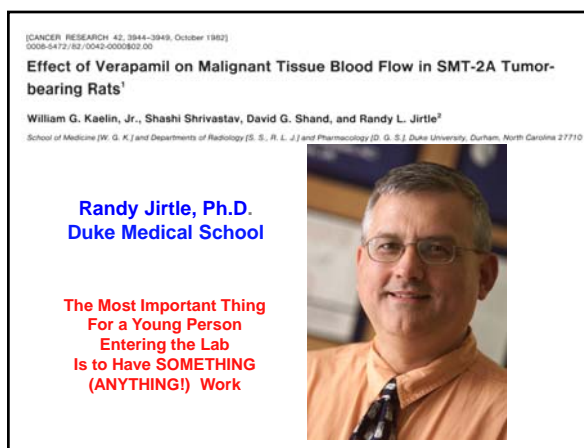
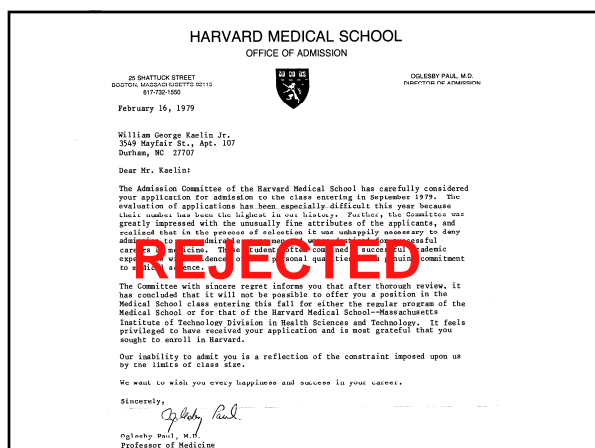
Wanted Good Income to Support my (Future) Family

Wanted to Help Others

“All 7 of your predecessors have gotten into medical school”

- unnamed Duke Chemistry Professor

“Mr. Kaelin appears to be a bright young man whose future lies outside the laboratory”





The Johns Hopkins Hospital ca 1987

Victor McKusick, M.D.
Johns Hopkins

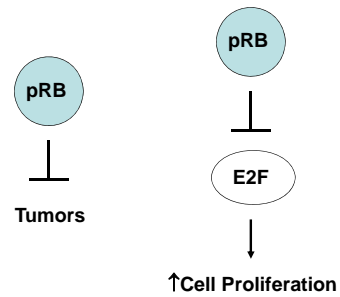


David M. Livingston, M.D.
Dana-Farber Cancer Institute

- Ask Important Questions
- Be Your Own Worst Critic



The Retinoblastoma Tumor Suppressor Protein



Why Did I Succeed as a Postdoctoral Fellow?

- Great Mentorship
- Given a Great Problem to Work On
- Too Naïve to Know What “Should Not Work” (Tried Lots of Things)
- Good M.D.s Know How to Multitask and to Weigh Conflicting Data
- Most M.D.s are Trained to be Careful