Disclosure

- I have a financial interest in Fibrogen, Inc., which is developing prolyl hydroxylase inhibitors for the treatment of anemia and ischemic diseases
- I have a financial interest in Agios, Inc,. which is developing cancer drugs targeting metabolism
- I am on Lilly Board of Directors
- I am a cofounder of Tango Therapeutics, Inc., which is developing cancer drugs based on synthetic lethality
- I am a cofounder of Cedilla Therapeutics, Inc., which is developing protein degraders as cancer drugs

von Hippel-Lindau Disease

Past

- Othon Iliopoulos
- Adam Kibel
- Demetri Colevas
- Kim Lonergan
- Michael Ohh
- Mircea Ivan
- Jeff Klco
- Keiichi Kondo
- Michal Safran
- William Kim
- Jim Brugarolas
- Haifeng Yang
- Archana Reddy
- Susanne Schlisio
- Qin Yan
- Arthur Young
- Jinming Gu
- Andy Minamishima
- Qing Zhang
- Jiayun Liu
- Eijiro Nakamura
- Sungwoo Lee
- Chuan Shen

Recent

- Abhishek Chakraborty
- Lianjie Li
- Javid Moslehi
- Julie Losman
- Kim Briggs
- Steven Bair
- Alan Baik
- Ben Olenchock
- Gang Lu
- Wenhua Gao
- Hyejin Cho
- Sagar Koduri
- Ben Lampson
- Jamie Pfaff
- Hilary Nicholson
- Wenyu Yu
- Laura Stransky
- Qinqin Jiang
- Nitin Shirole
- Greg Wyant
- Muhannad Abu-Remaileh

Collaborators

- Joan and Ron Conaway (Stowers)
- Nikola Pavletich (MSKCC)
- Mark Goldberg (then at Harvard)
- William Lane (Harvard)
- Vincent Chau (now at Penn State)
- William Lane (Harvard)
- Volkmar Gunzler (Fibrogen)
- David Liu (Fibrogen)
- Peppi Koivunen (Univ. of Oulu)
- Eli Wallace (Peloton Therapeutics)

David M. Livingston, M.D
Dana-Farber Cancer Institute
(Postdoctoral Mentor)

Johns Hopkins Medical Housestaff 1983

Victor McKusick, M.D.
Johns Hopkins

X. INTRA-OCULAR GROWTHS.

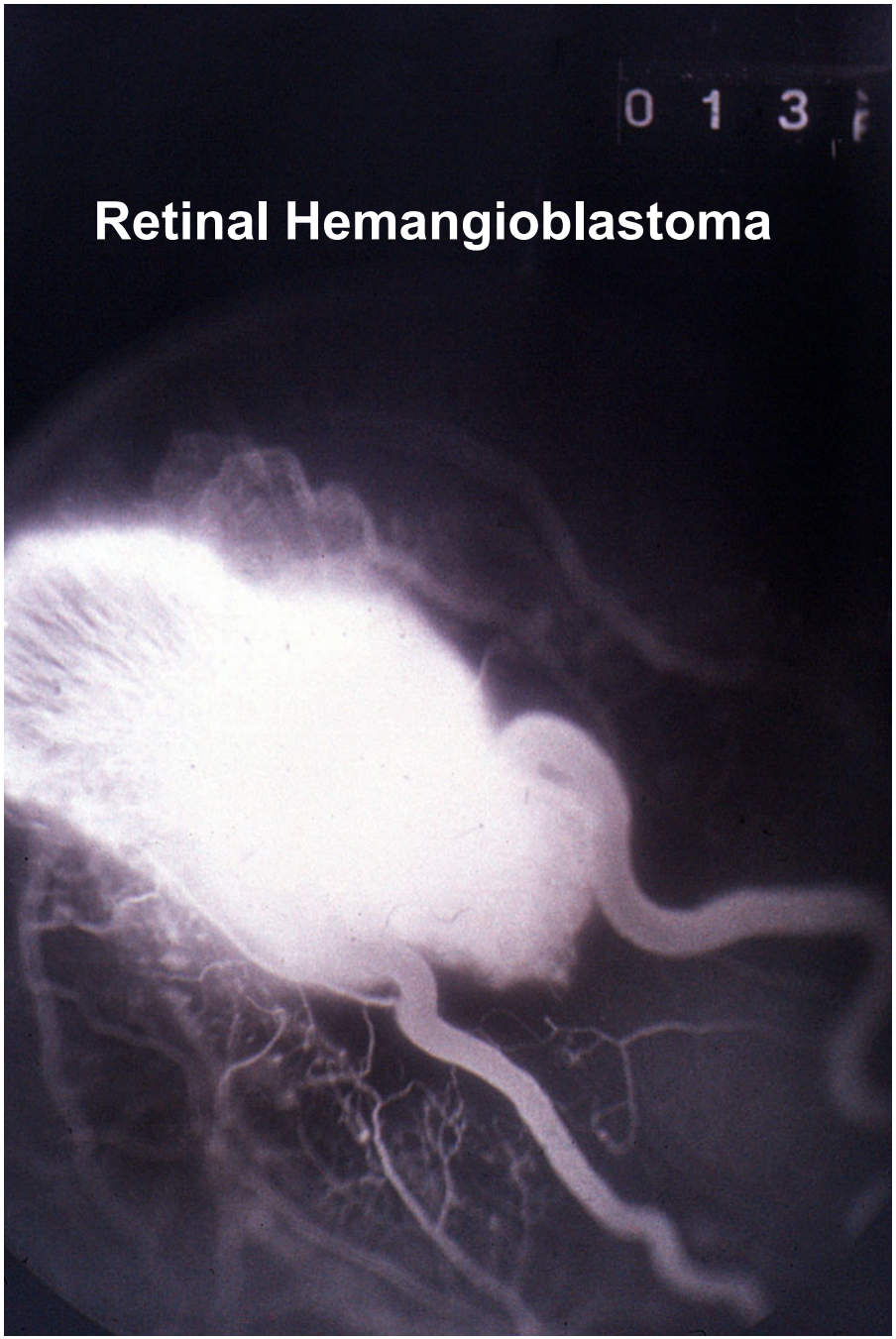
1. *Two cases, brother and sister, with peculiar vascular new growth, probably primarily retinal, affecting both eyes.*

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


0 1 3
Retinal Hemangioblastoma

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)

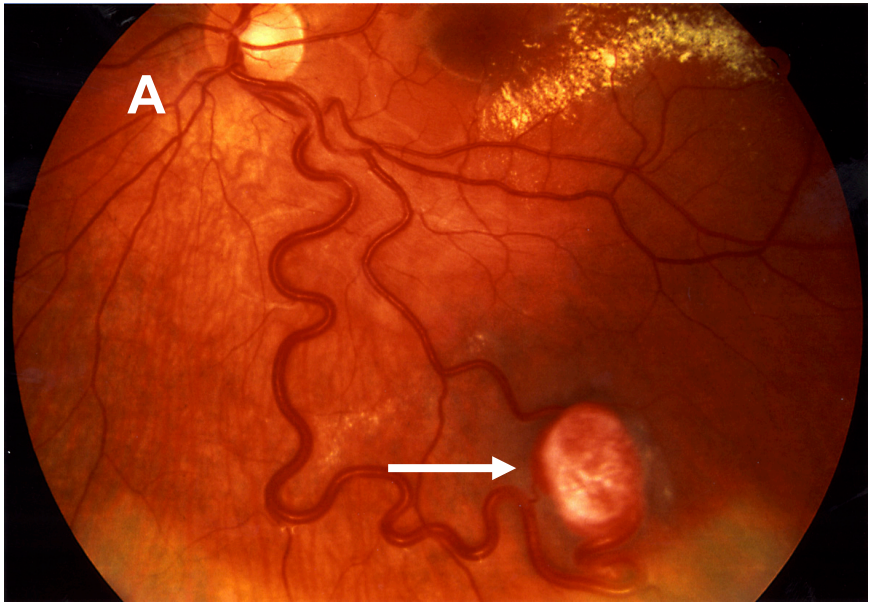
ZUR FRAGE DER ANGIOMATOSIS RETINÆ UND IHRER HIRNKOMPLIKATIONEN

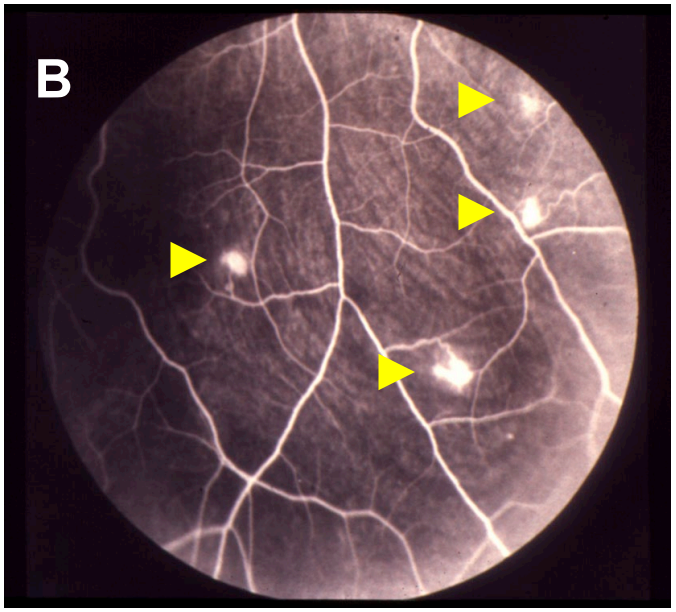
VON
ARVID LINDAU

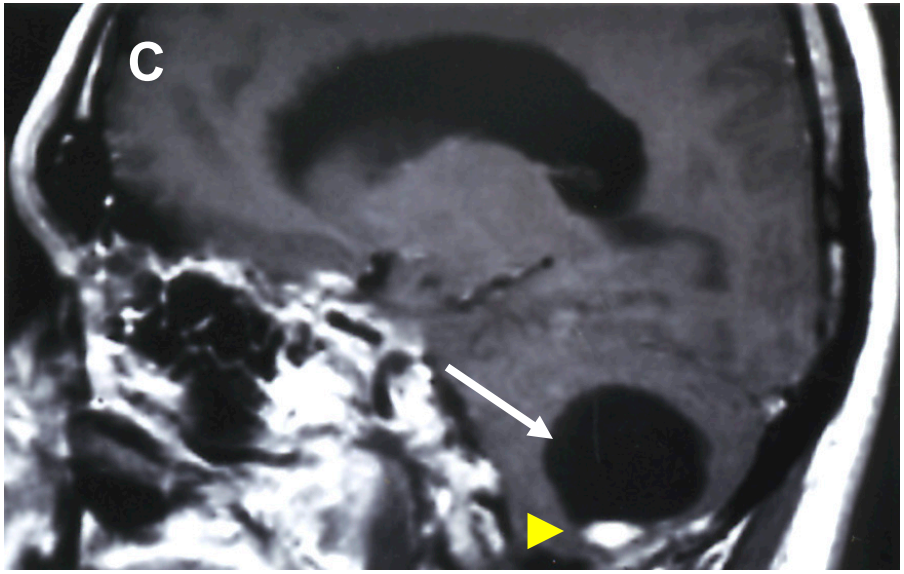
Das ophthalmoskopische Bild einer Angiomatosis retinae ist, wenigstens in früheren Stadien der Krankheit, sehr charakteristisch. Von der Papille führen ein paar erweiterte und stark gewundene Gefässe (gewöhnlich ein »Gefässpaar«) zu einem peripher gelegenen, prominenten, kugeligen Gebilde von mehr oder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

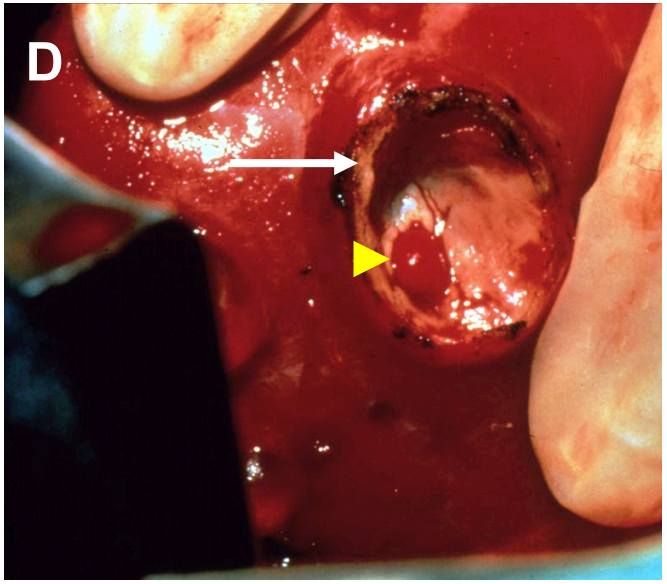
Acta. Ophthal. 4: 193-226, 1927

VHL-Associated Tumors





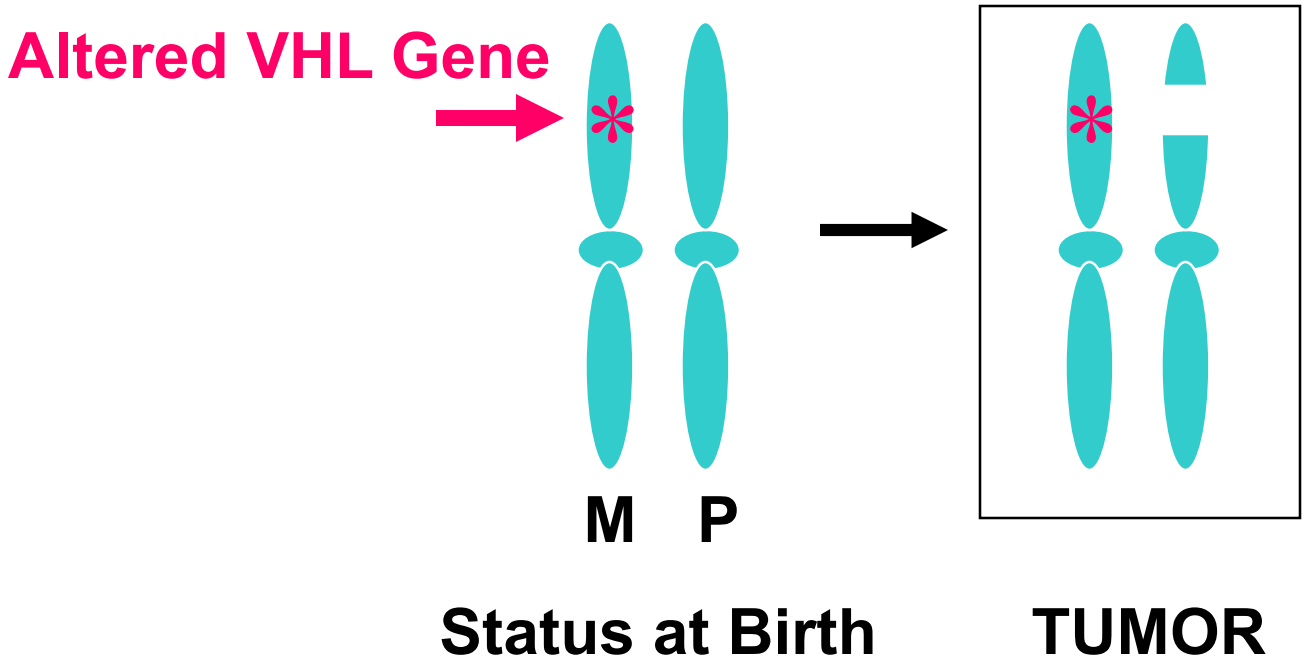




von Hippel-Lindau Disease

- **Affects ~1/35,000 people**
- **Caused by loss of function germline mutations of the *VHL* tumor suppressor gene at 3p25**
- **CNS and retinal hemangioblastomas, clear cell renal cell carcinomas, pheochromocytomas (+ a few others)**

VHL GENETICS



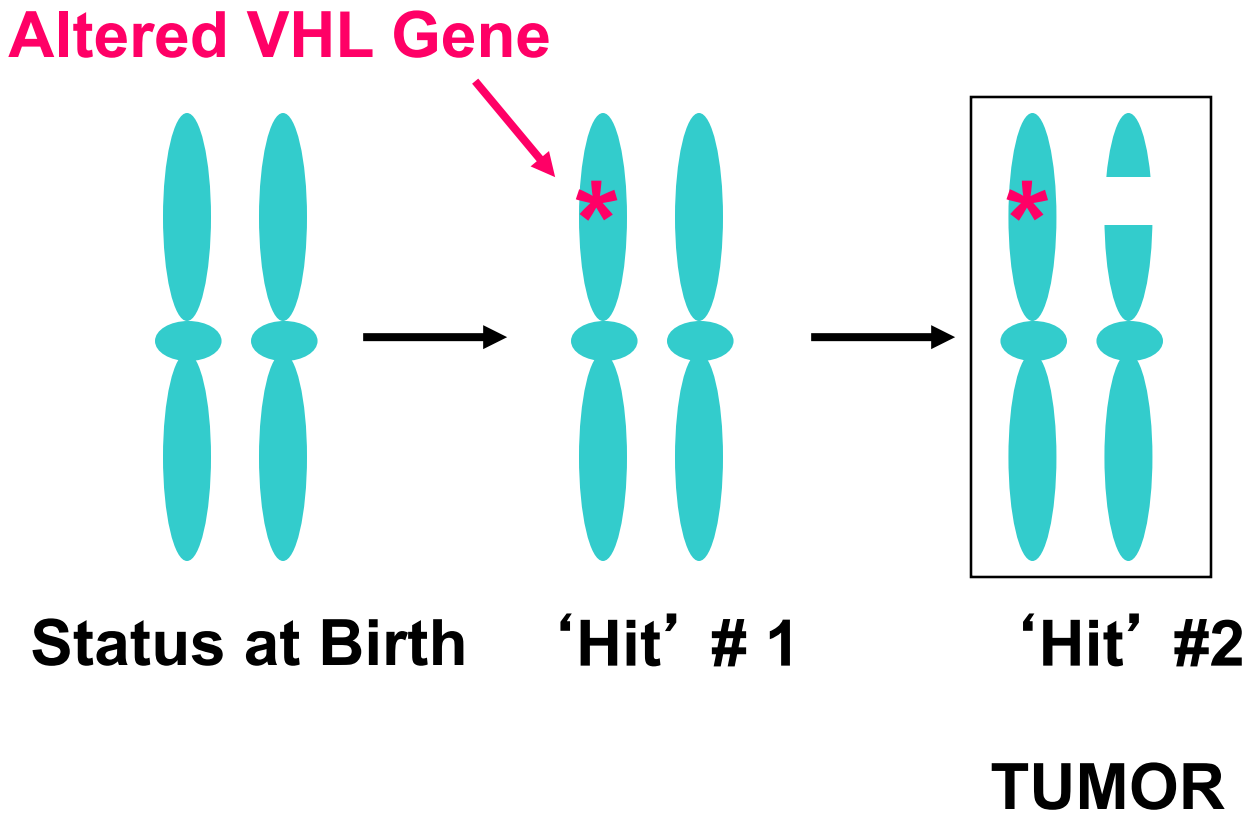
Identification of the von Hippel–Lindau Disease Tumor Suppressor Gene

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*.

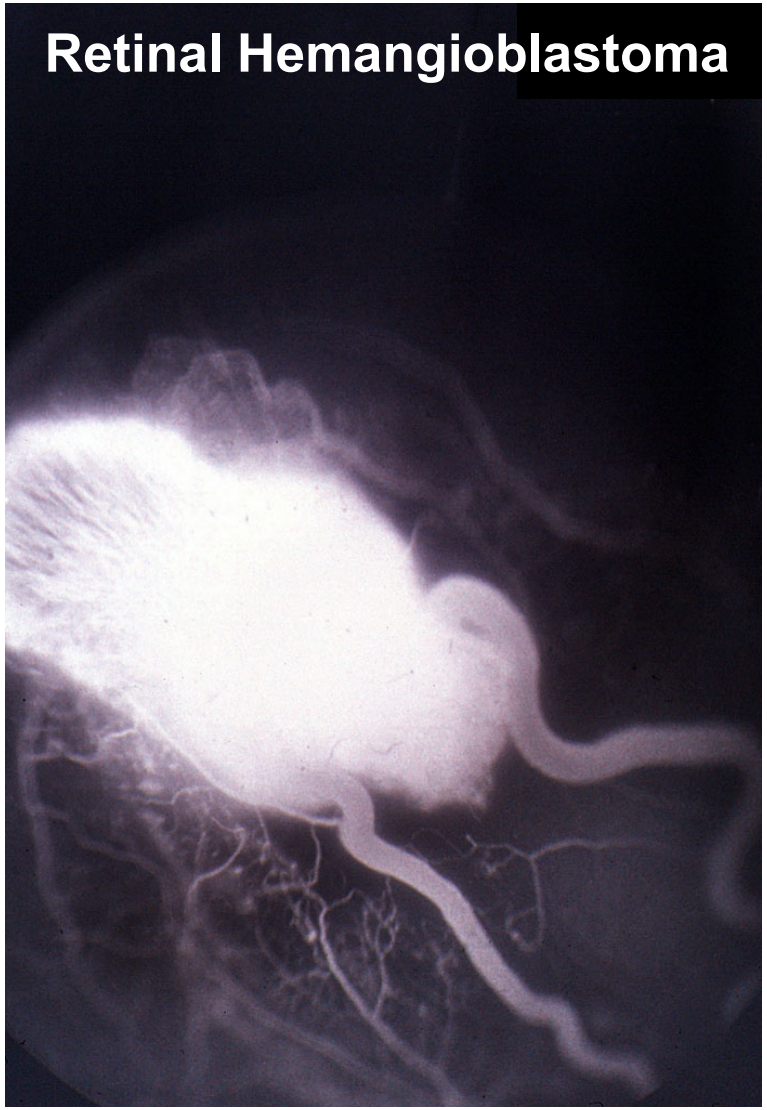
Science (1993)

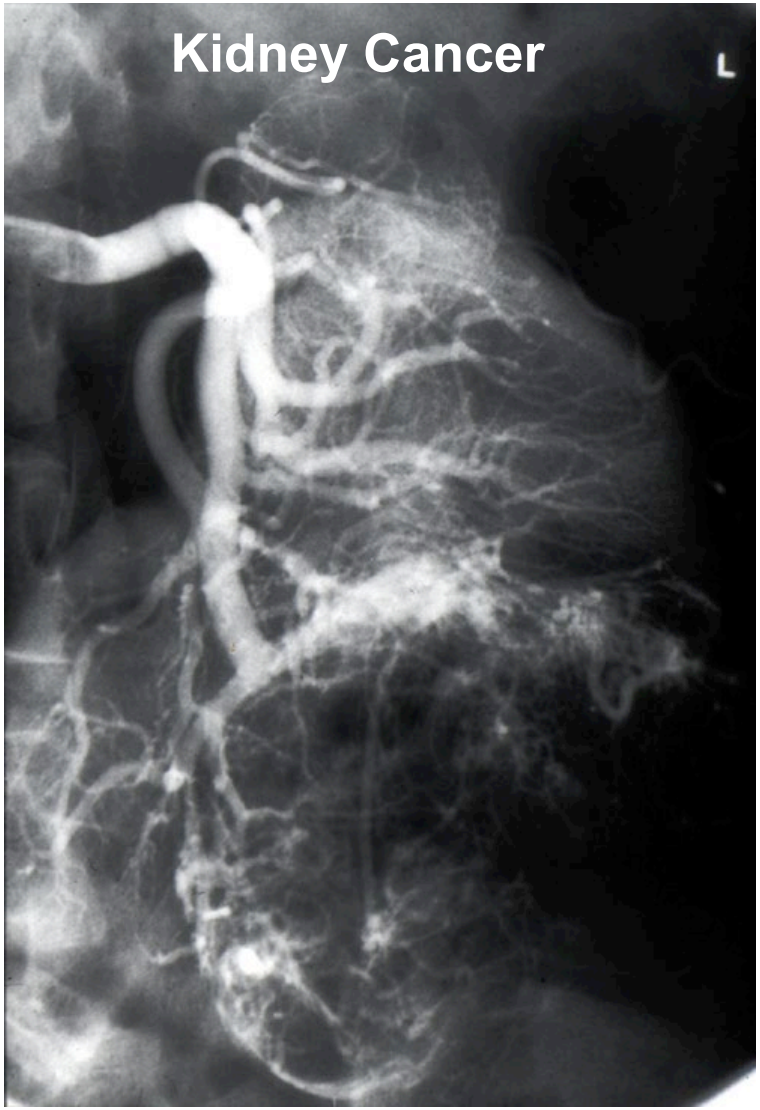
Non-Hereditary Clear Cell Renal Cell Carcinoma



The Johns Hopkins Hospital ca 1987

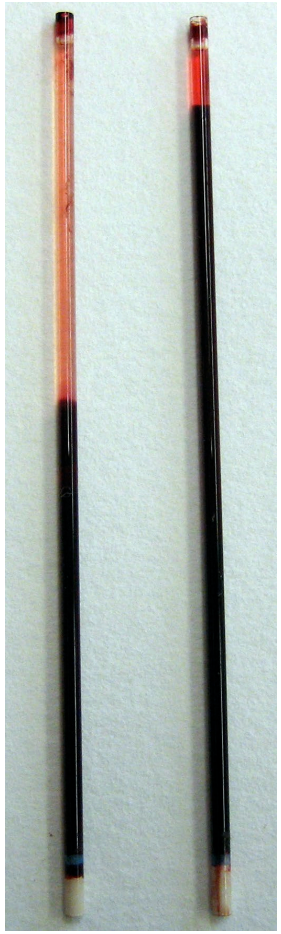
VHL Disease Tumors Are Very Angiogenic





…And Sometimes Stimulate Red Blood Cell Production

Normal Hematocrit



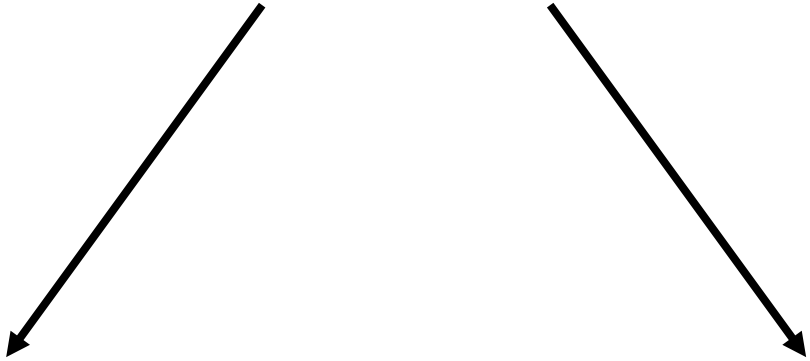
Elevated Hematocrit

Causes of Excessive Red Blood Cell Production

- Primary autonomous erythropoiesis: polycythemia rubra vera
- Secondary
  - Physiologically appropriate (decreased tissue oxygenation)
    - High altitude
    - Chronic lung disease or alveolar hypoventilation
    - Cardiovascular right-to-left shunt
    - High oxygen affinity hemoglobinopathy
    - Congenitally decreased erythrocyte 2, 3-diphosphoglycerate
    - Carboxyhemoglobinemia
    - Histiotoxic (for example, cobalt)
  - Physiologically inappropriate (normal tissue oxygenation)
    - Tumors producing erythropoietin or other erythropoietic substances
      - → Renal cell carcinoma
      - → Cerebellar hemangioblastoma
      - Hepatoma
      - Uterine leiomyoma
      - Ovarian carcinoma
      - → Pheochromocytoma
    - Renal diseases
      - Cysts
      - Hydronephrosis
      - Bartter's syndrome
      - Transplantation
    - Adrenocortical hypersecretion
- Relative polycythemia (Gaisböck's syndrome, spurious or stress erythrocytosis)

Golde and Hocking, Ann Intern Med 1981

VHL-Associated Tumors



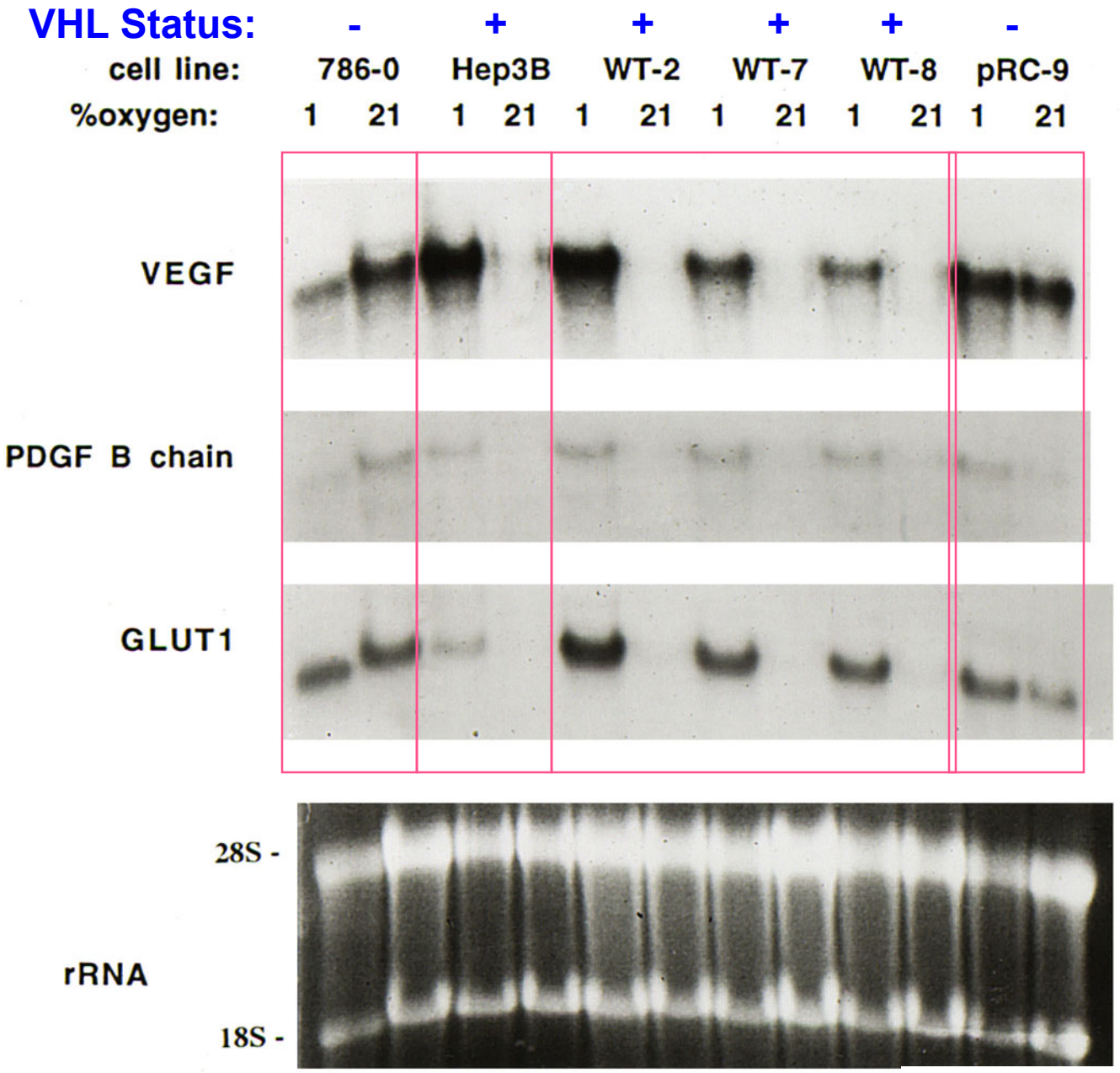
Induce Blood Vessel Formation

(Produce VEGF)

Increase Red Blood Cell Production

(Produce EPO)

Link Between VHL and Oxygen Sensing?



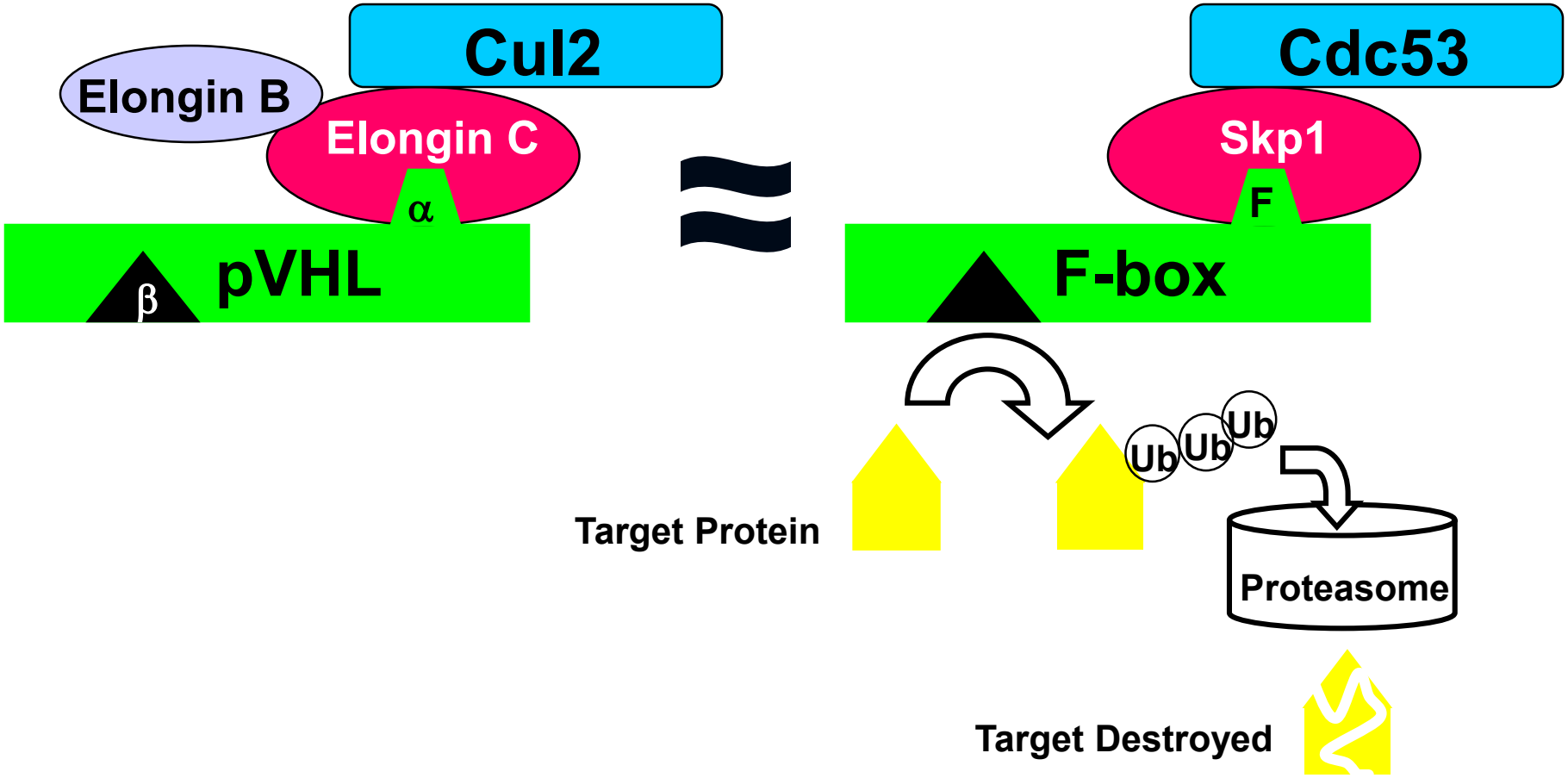
Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 10595–10599, October 1996
Biochemistry

Hypoxia (Low O2)-Inducible mRNA Status

VHL Protein	Oxygen: Low	Oxygen: High
Present	High	Low
Absent	High	HIGH

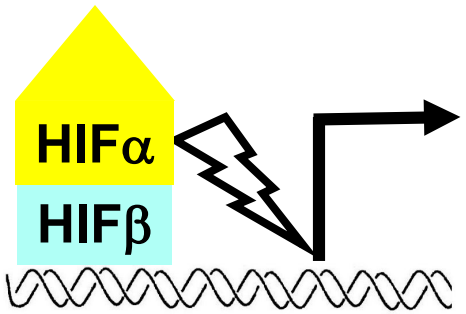
Iliopoulos et al PNAS 1996

SCF-Like Ubiquitin Ligases



Kibel et al Science 1995
Lonergan et al MCB 1998
Stebbins et al Science 1999

The HIF Transcription Factor



Glucose Uptake (e.g. GLUT1)

Anaerobic Glycolysis (e.g. PFK, LDH)

Angiogenesis (e.g. VEGF, PDGF, IL-8, TGFβ)

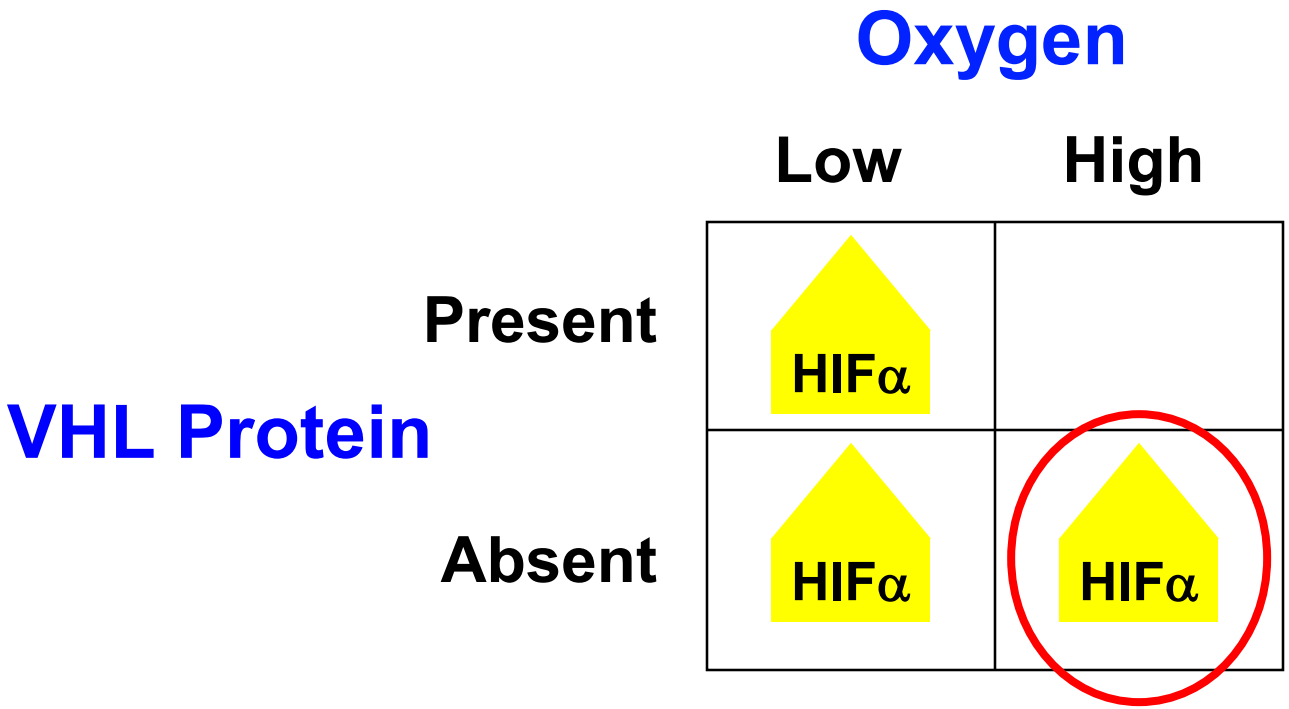
Erthropoiesis (e.g. EPO*)

Invasion/Homing (e.g. MMP2, MMP9, c-MET, CXCR4)

Mitogenesis (e.g. TGFα, Cyclin D1*)

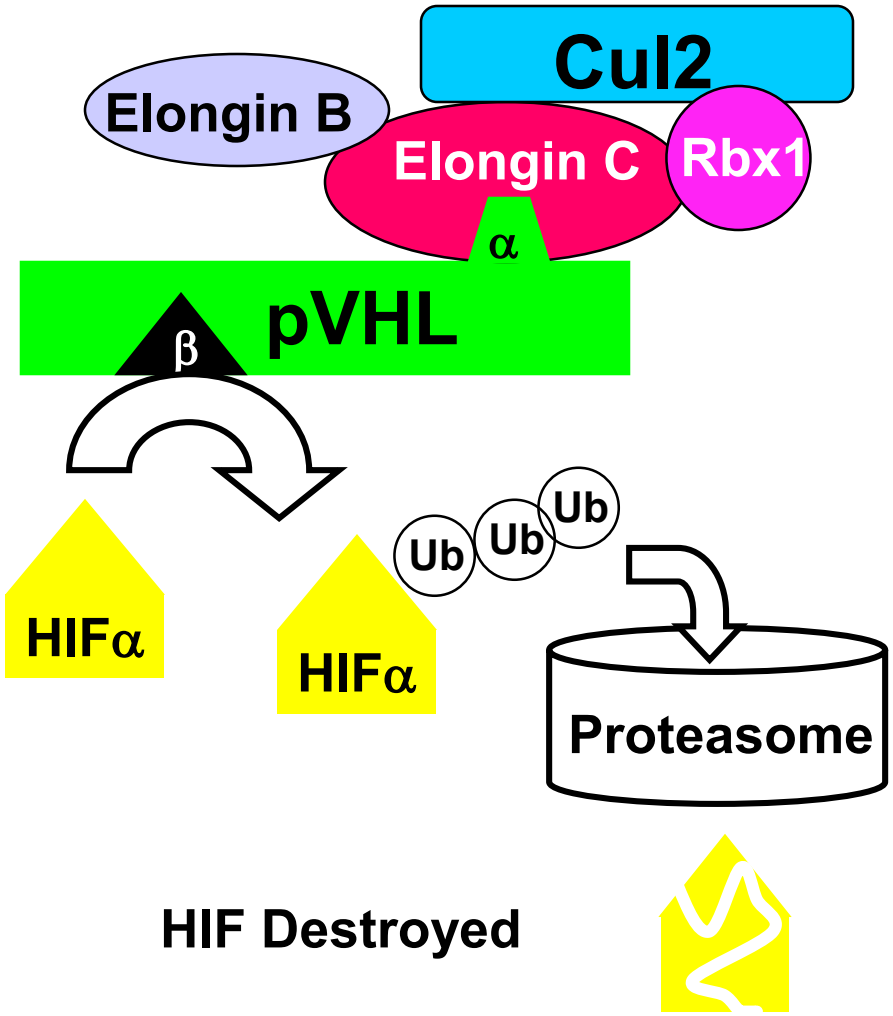
* Tissue specific

VHL-/- Cells Don't Degrade HIFα Under Normoxic Conditions



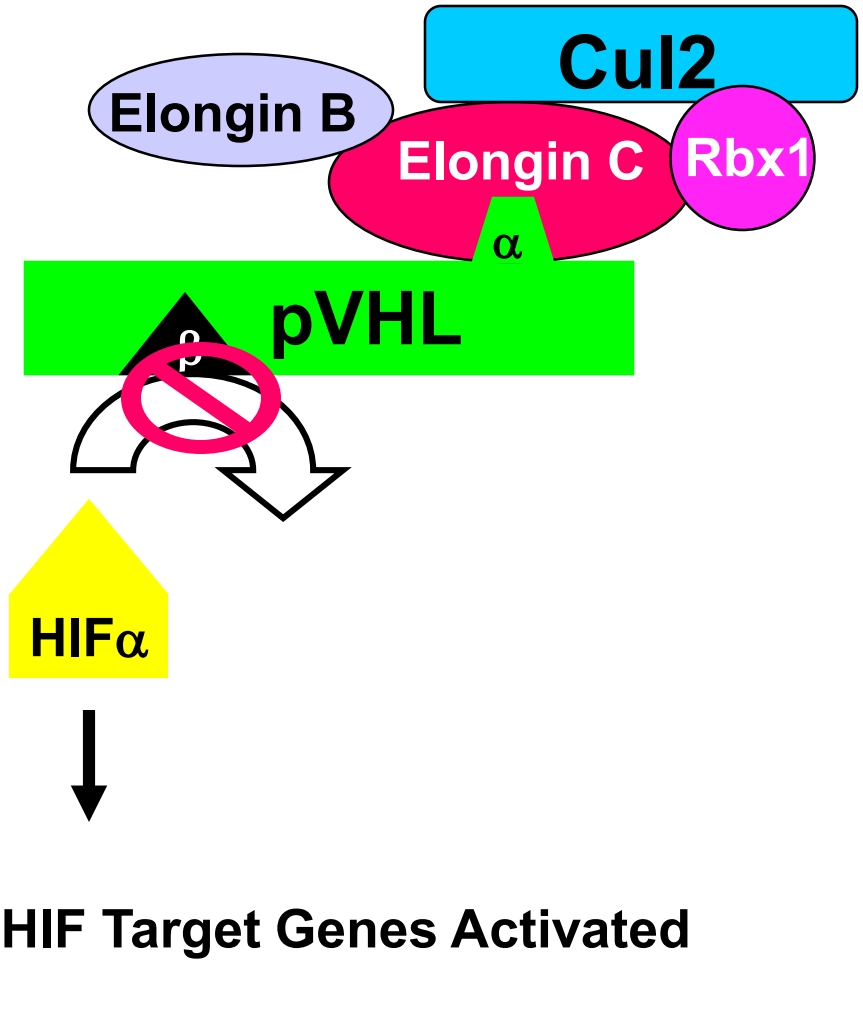
Maxwell et al (Ratcliffe Laboratory) Nature 1999

O2 Present



HIF Destroyed

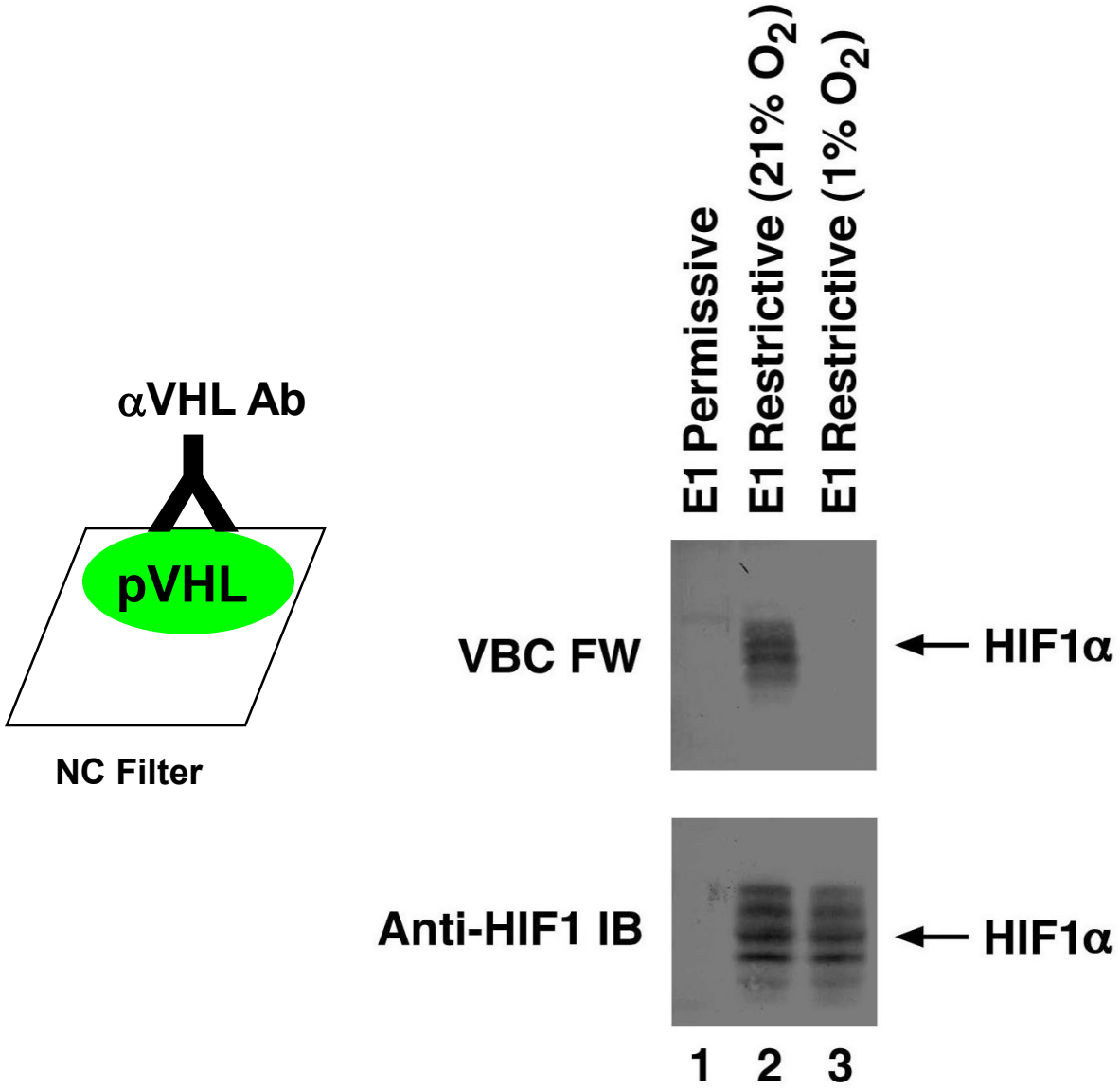
O2 Absent



HIF Target Genes Activated

Ohh et al NCB 2001

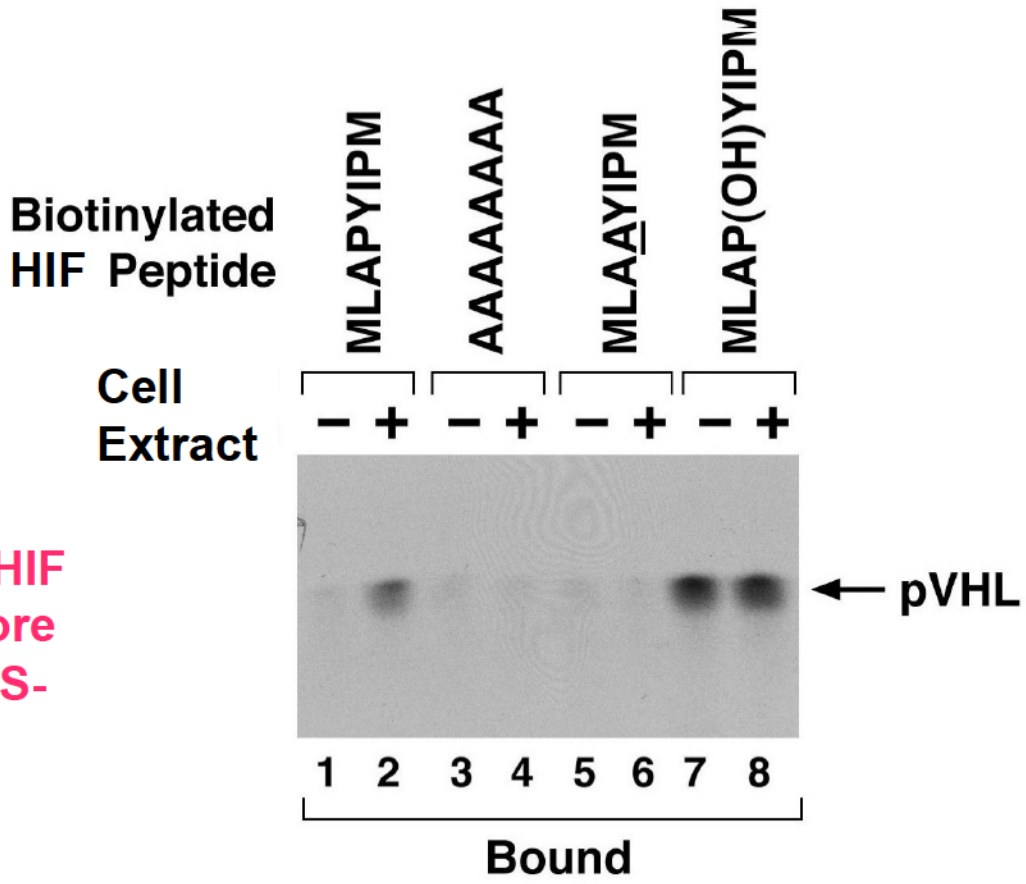
HIF1α Undergoes an Oxygen-Dependent Modification that Regulates its Direct Binding to pVHL



ts20 (VHL +/+) mouse fibroblasts (TS E1 Mutant)

Haifeng Yang

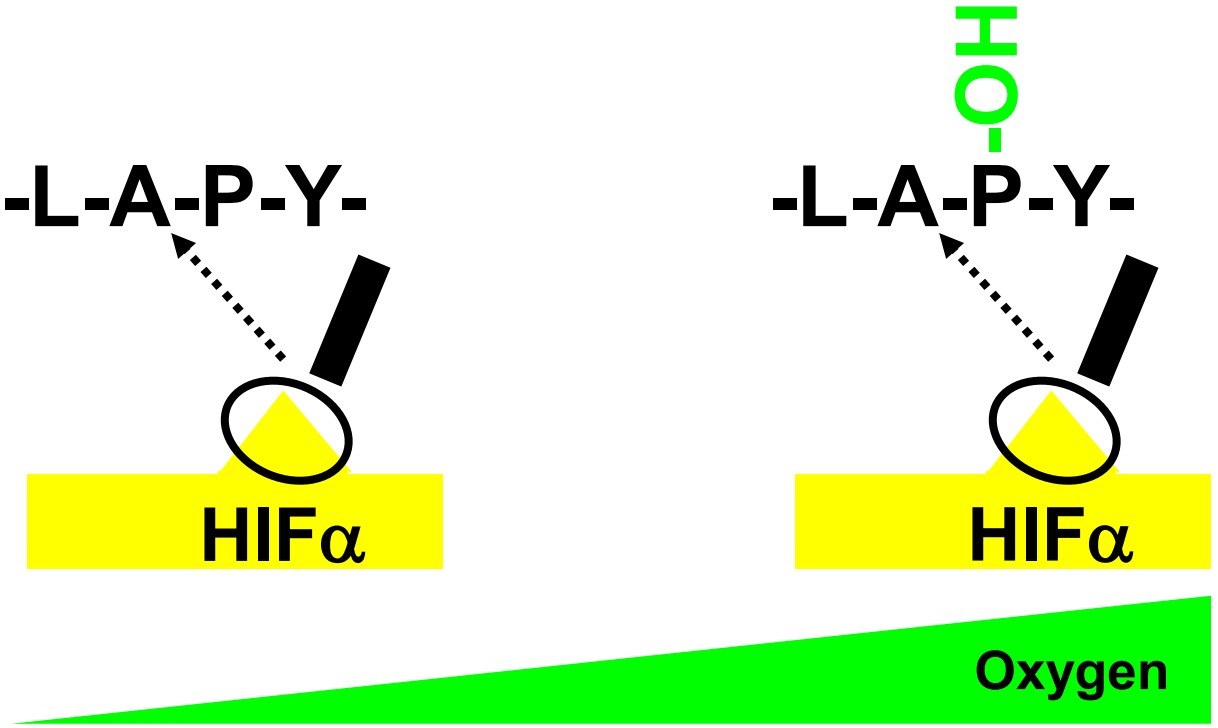
pVHL Binds to Prolyl Hydroxylated HIF1α



Biotinylated HIF Peptide ? Score Capture of ^{35}S-pVHL

Mircea Ivan

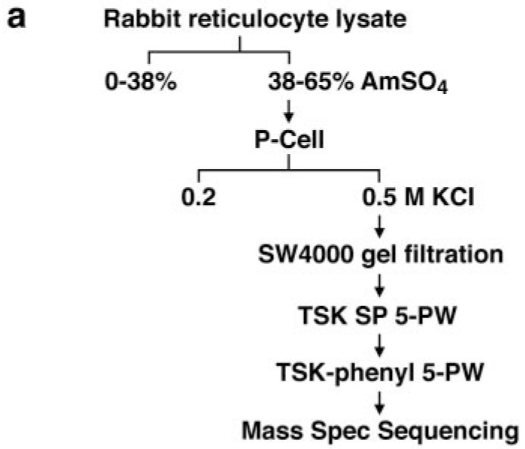
Oxygen-dependent pVHL-Binding

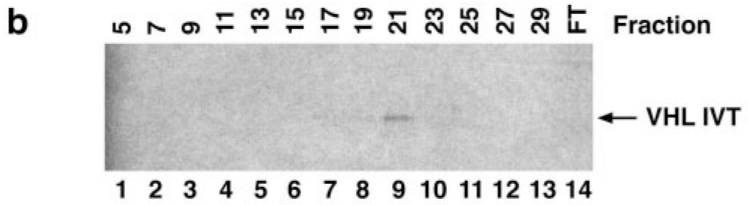


Bind pVHL: **No** **Yes**

Ivan et al Science 2001
Jaakkola et al Science 2001

Purification of the HIF Prolyl Hydroxylase EglN1



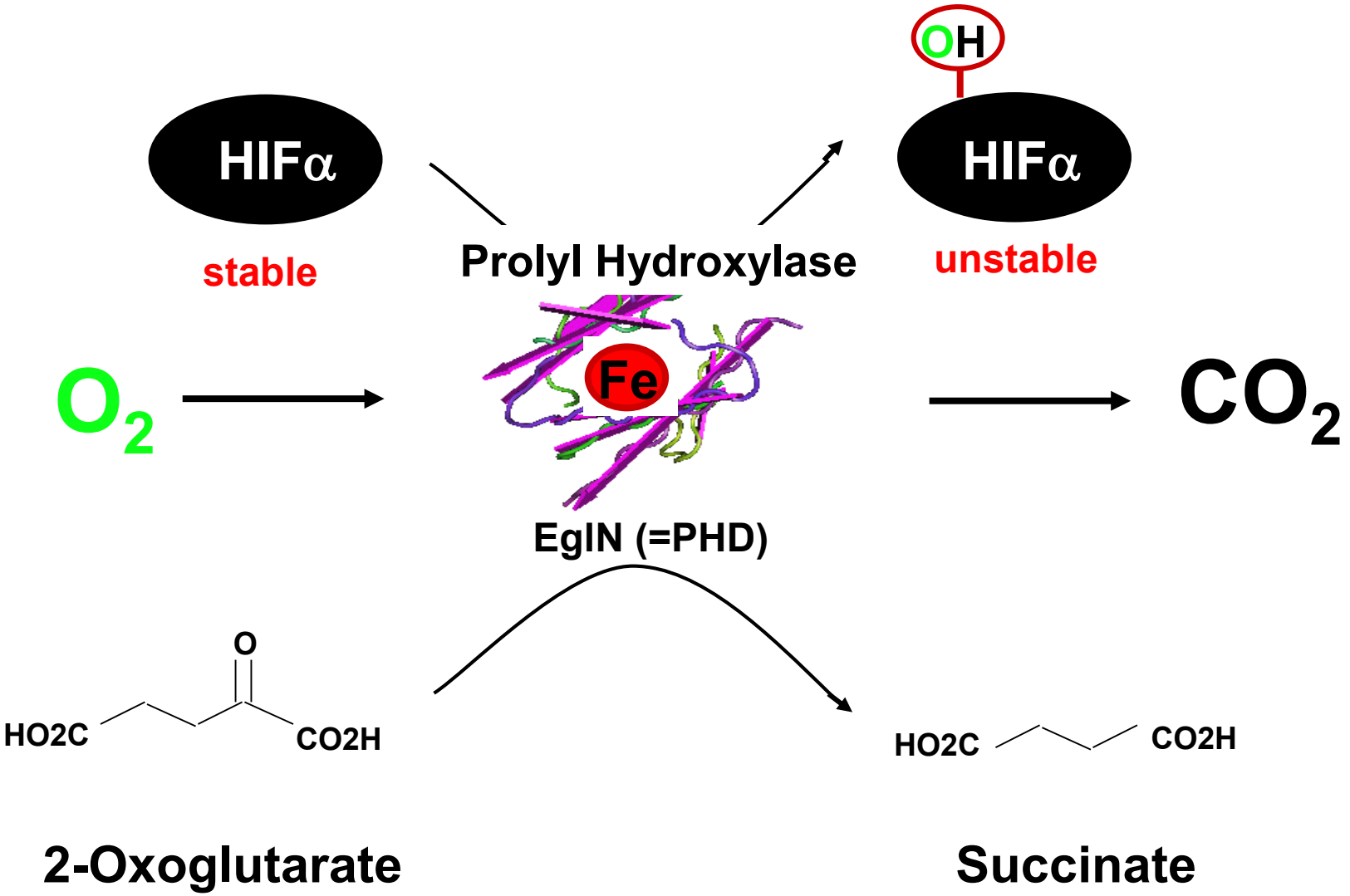


c

MANDSGGPGGPSPSERDRQYCELCGKMENLLRCSRCRS
SFYCCKEHQRQDWKKHKLVCQGSEGALGHGVGPHQHS
GPAPPAAVPPPRAGAREPRKAAARRDNASGDAAKGKVKA
KPPADPAAAASPCRAAAGGQGSAVAAEAEPGKEEPPARS
SLFQEKANLYPPSNTPGDALSPGGGLRPNGQTKPLPALKL
ALEYIVPCMNKHGICVVDDFLGK*ETGQQIGDEVRALHDTG*
*KFTDGQLVSQK*SDSSKDIRGDKITWIEGKEPGCETIGLLMS
SMDDLIRHCNGKLGSYKINGRTKAMVACYPGNGTGYVRH
VDNPNGDGRCVTCIYYLNKDWDAKVSGGILRIFPEGKAQF
ADIEPKFDRLLFFWSDRRNPHEVQPAYATRYAITVWYFDA
DERARAK*VKYLTGEK*GVRVELNKPSDSVGKDVF

Ivan et al, PNAS 2002

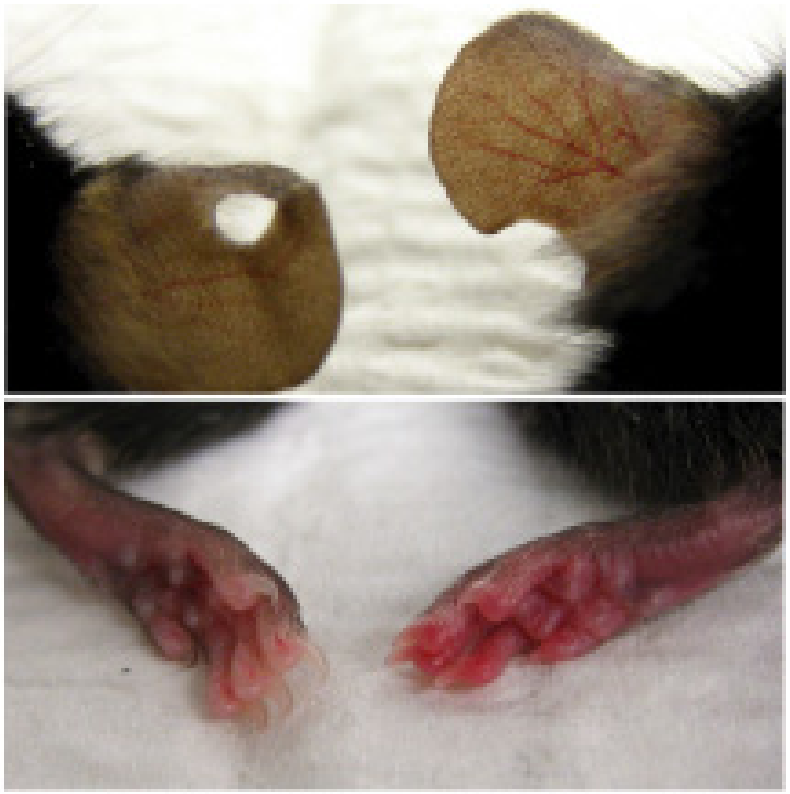
HIF Prolyl Hydroxylase Reaction



EglN Family Members

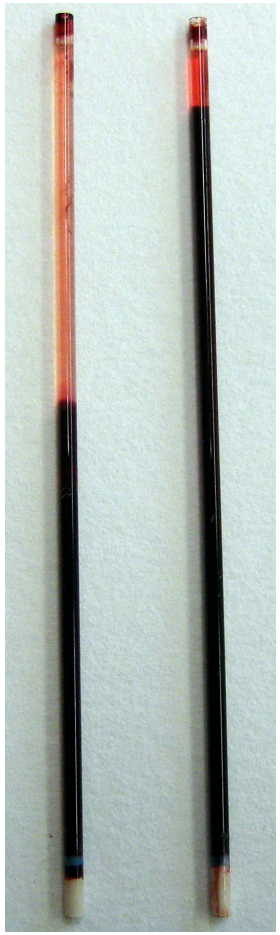
- **EglN1 (= PHD2)**
  - **EglN1-/- embryonic lethal**
- **EglN2 (= PHD1)**
  - **EglN2-/- mice viable; grossly normal**
- **EglN3 (= PHD3)**
  - **EglN3-/- mice viable; grossly normal**

Conditional Inactivation of EglN1 (= PHD2) in Mice



+/+;Cre-ER TAM(+)

F/F;Cre-ER TAM(+)



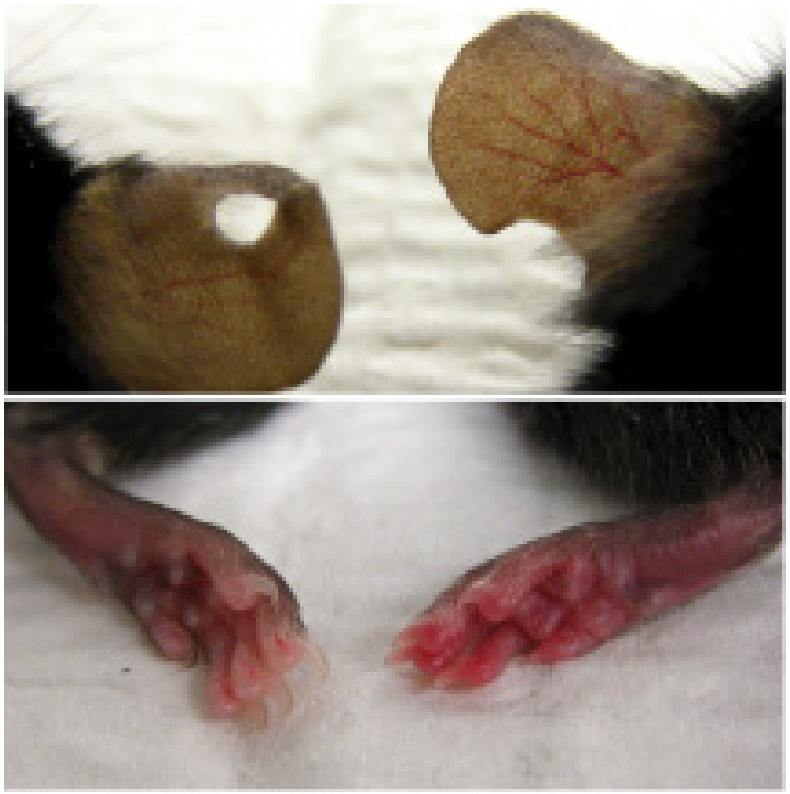
+/+ Δ/Δ

Minamishima et al Blood 08

Human Familial Polycythemia and HIF

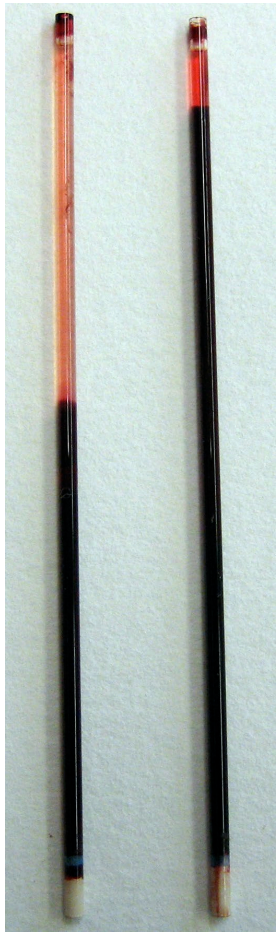
- **Homozygous (or compound heterozygous), hypomorphic, *VHL* Mutations (Chuvash Polycythemia)**
- **Heterozygous, hypomorphic, *EglN1* Mutations**
- **Heterozgous, hypermorphic, *HIF2α* Mutations**

Conditional Inactivation of EglN1 (= PHD2) in Mice



+/+;Cre-ER TAM(+)

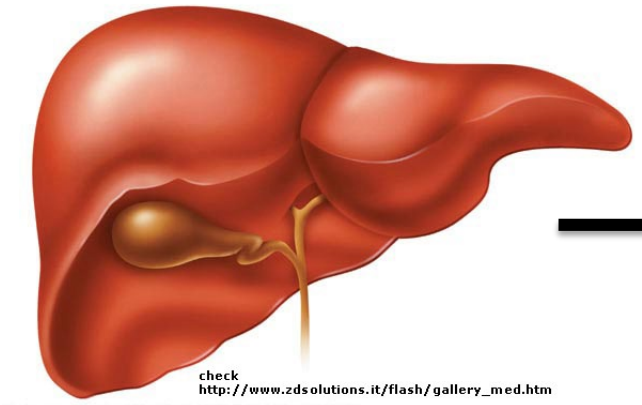
F/F;Cre-ER TAM(+)

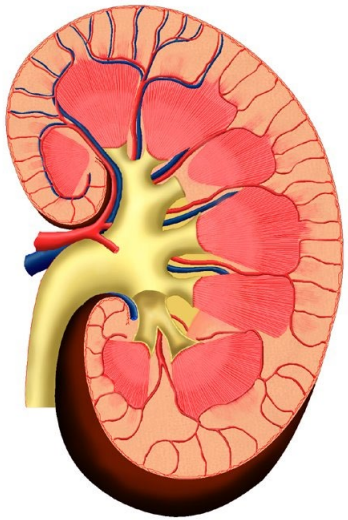


+/+ Δ/Δ

Minamishima et al Blood 08

EPO Production



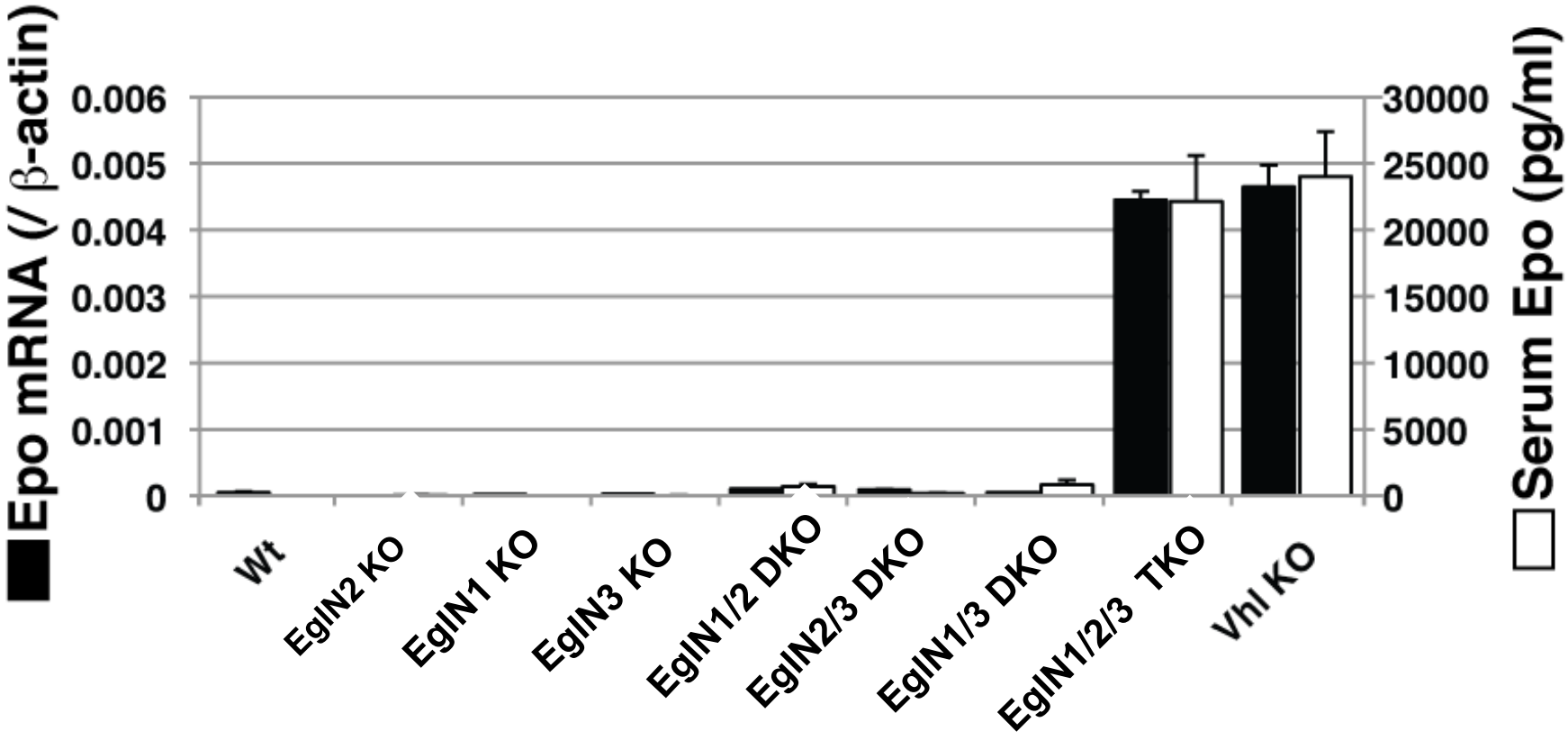


Fetal Life

Adult

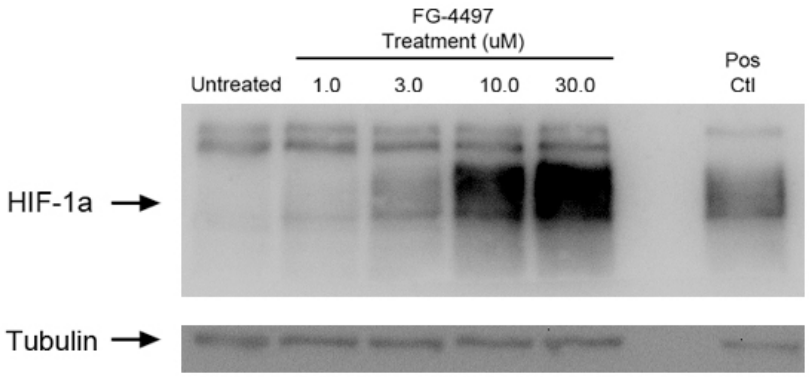
~ 20 million Americans with Chronic Renal Failure
2-4 million of these are Anemic

Reactivation of Hepatic EPO Production after Loss of all 3 EglN Members



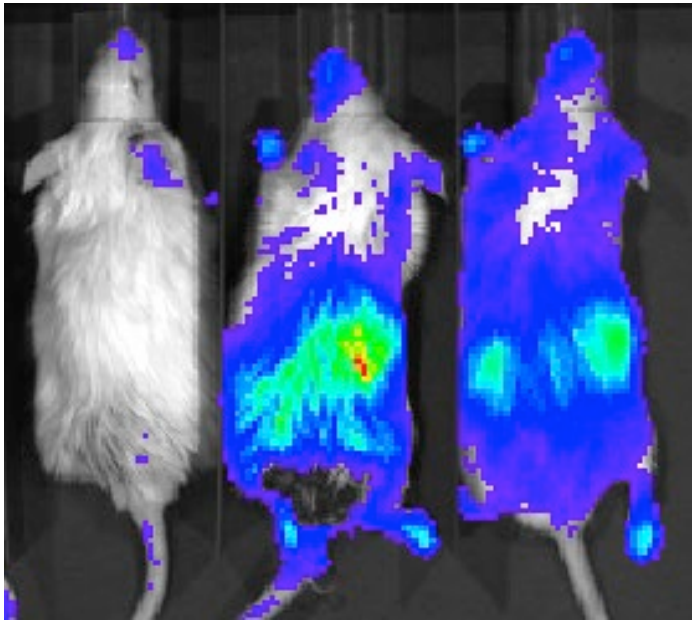
Minamishima and Kaelin, Science, 2010

Pharmacologic Stabilization of HIF



FG-4497 (mg/kg)

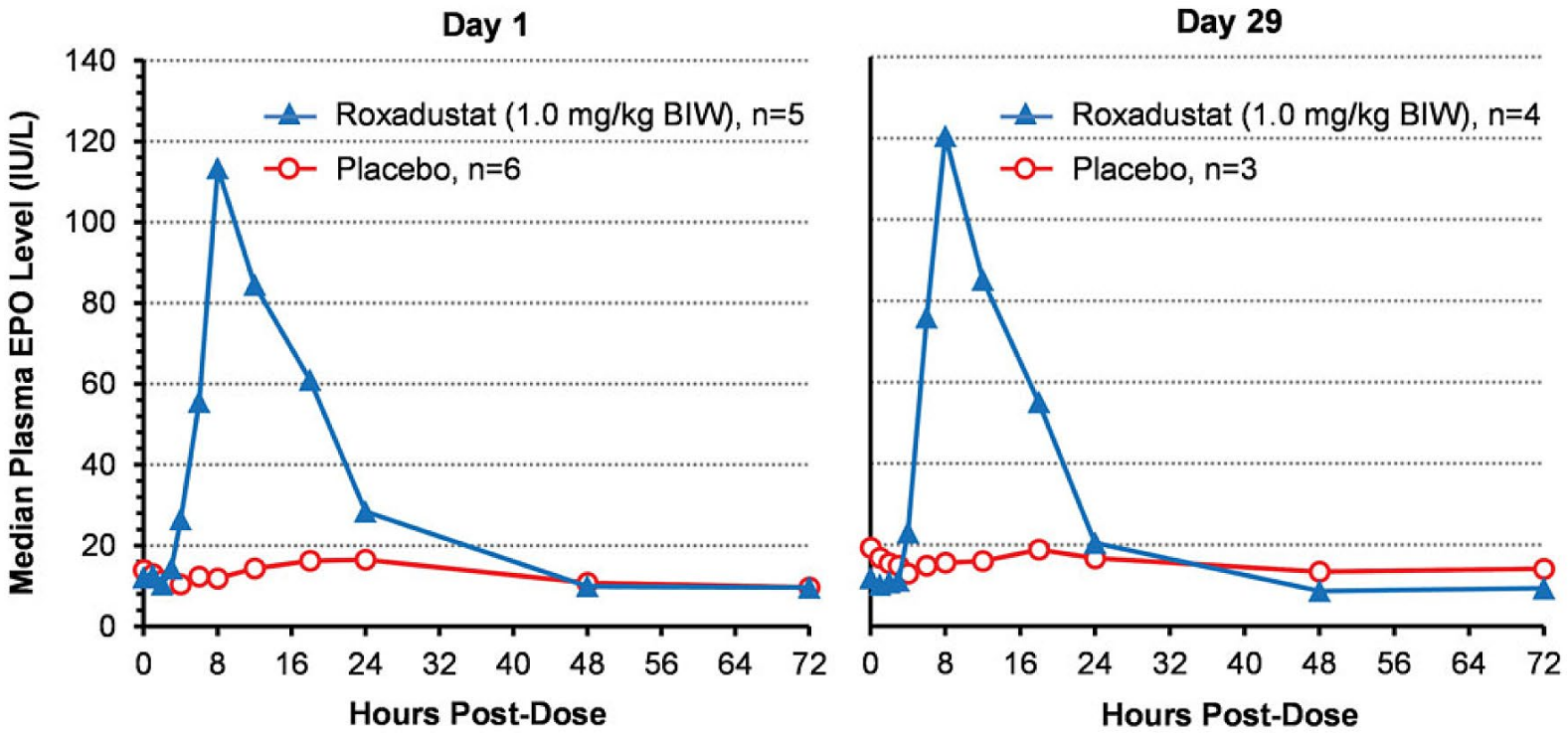
0 50 100



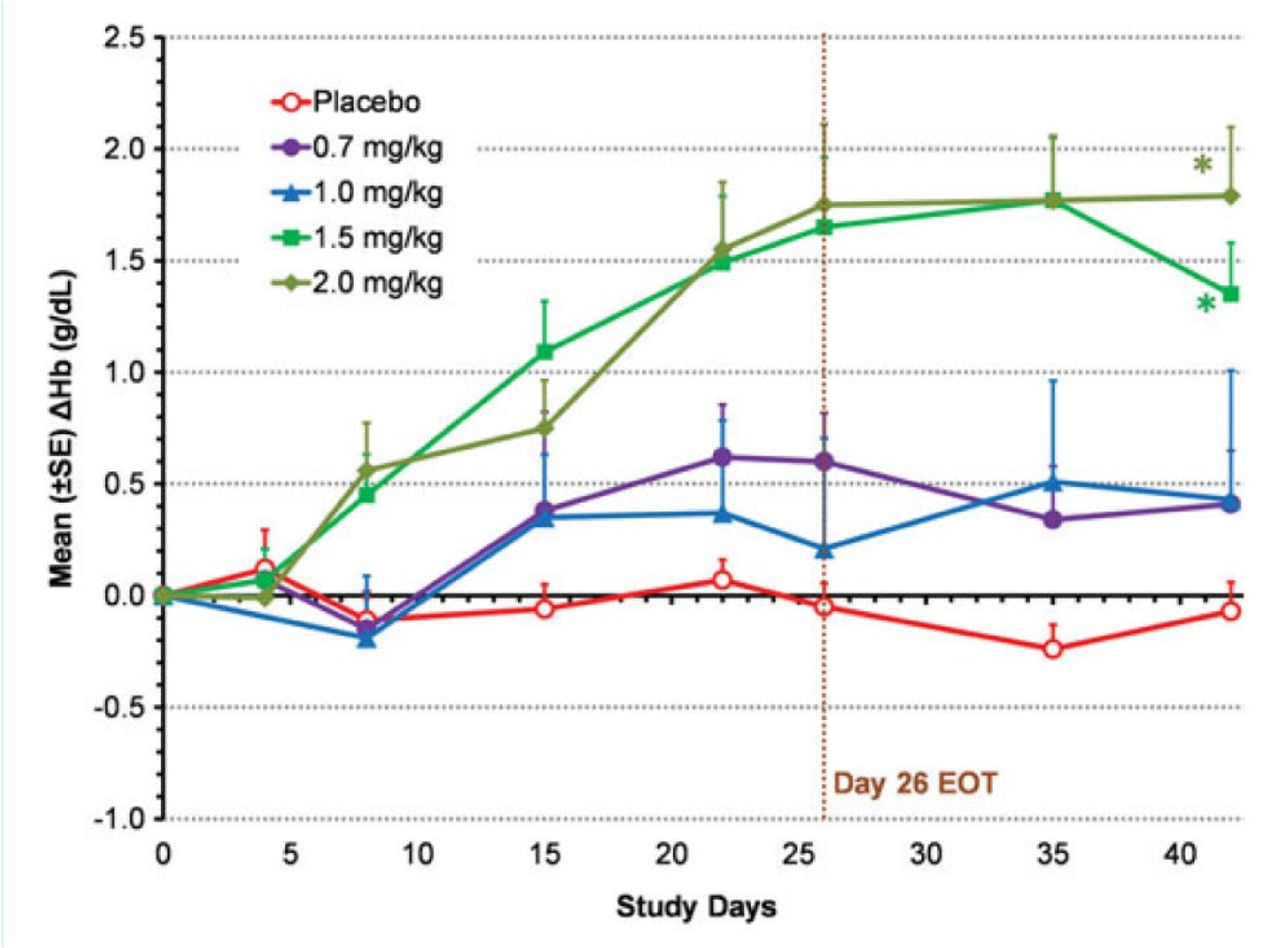
HIF-Luc Reporter Mice

e.g. Ivan et al PNAS 2002
Safran et al PNAS 2006

Treatment of Anemia with Oral EglN Inhibitor: Predialysis Chronic Kidney Failure



Treatment of Anemia with Oral EglN Inhibitor: Predialysis Chronic Kidney Failure



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis

N. Chen, C. Hao, X. Peng, H. Lin, A. Yin, L. Hao, Y. Tao, X. Liang, Z. Liu, C. Xing, J. Chen, L. Luo, L. Zuo, Y. Liao, B.-C. Liu, R. Leong, C. Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

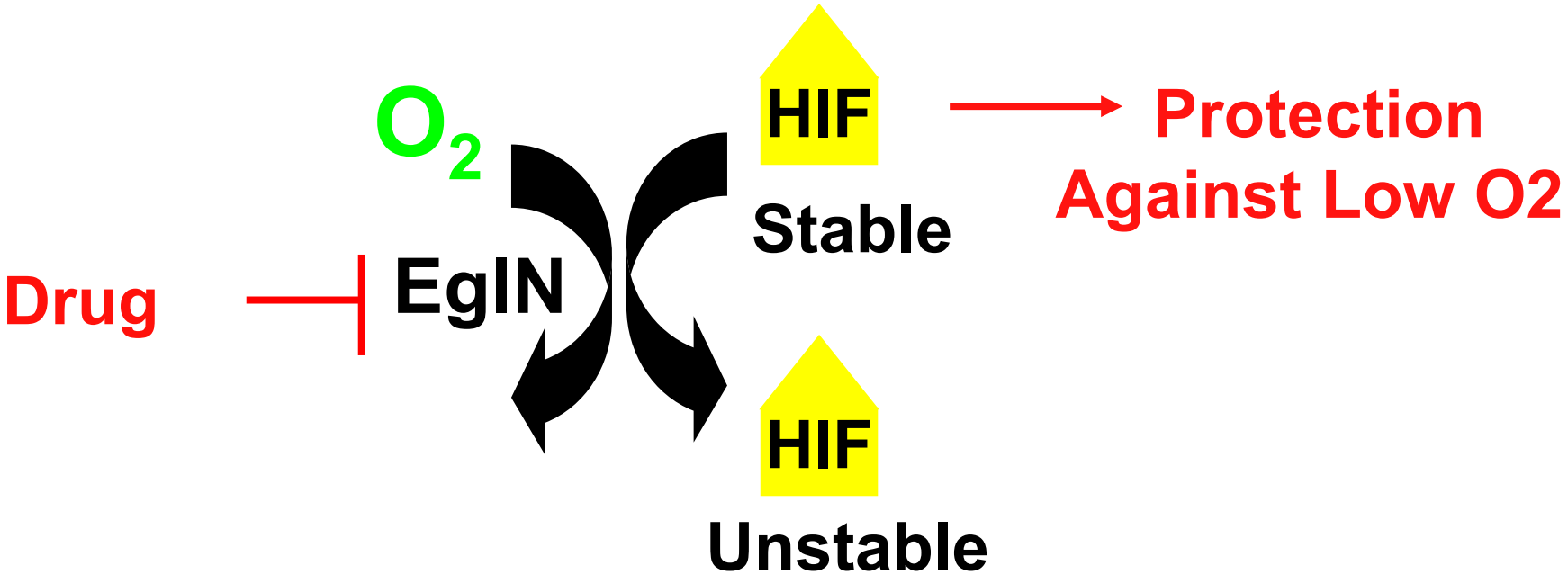
ORIGINAL ARTICLE

Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

N. Chen, C. Hao, B.-C. Liu, H. Lin, Caili Wang, C. Xing, X. Liang, G. Jiang, Zhengrong Liu, X. Li, L. Zuo, L. Luo, J. Wang, M. Zhao, Zhihong Liu, G.-Y. Cai, L. Hao, R. Leong, Chunrong Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

July 24, 2019

Treatment for Ischemic Diseases?

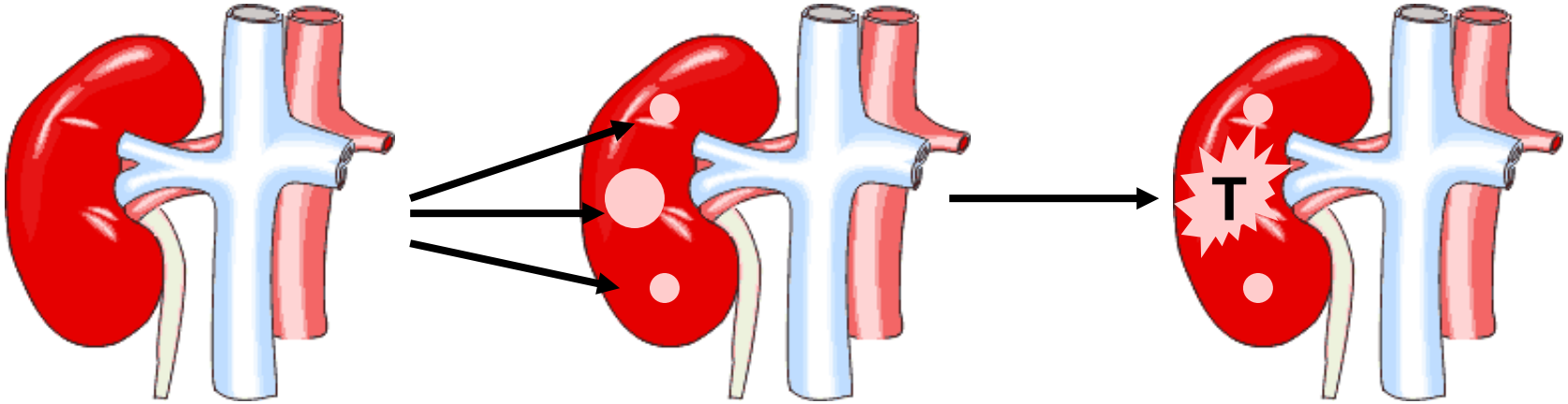


e.g. Olenchock et al Cell 2016

Kidney Cancer Arising in VHL Patients

Loss of Remaining Wild-type *VHL* Allele

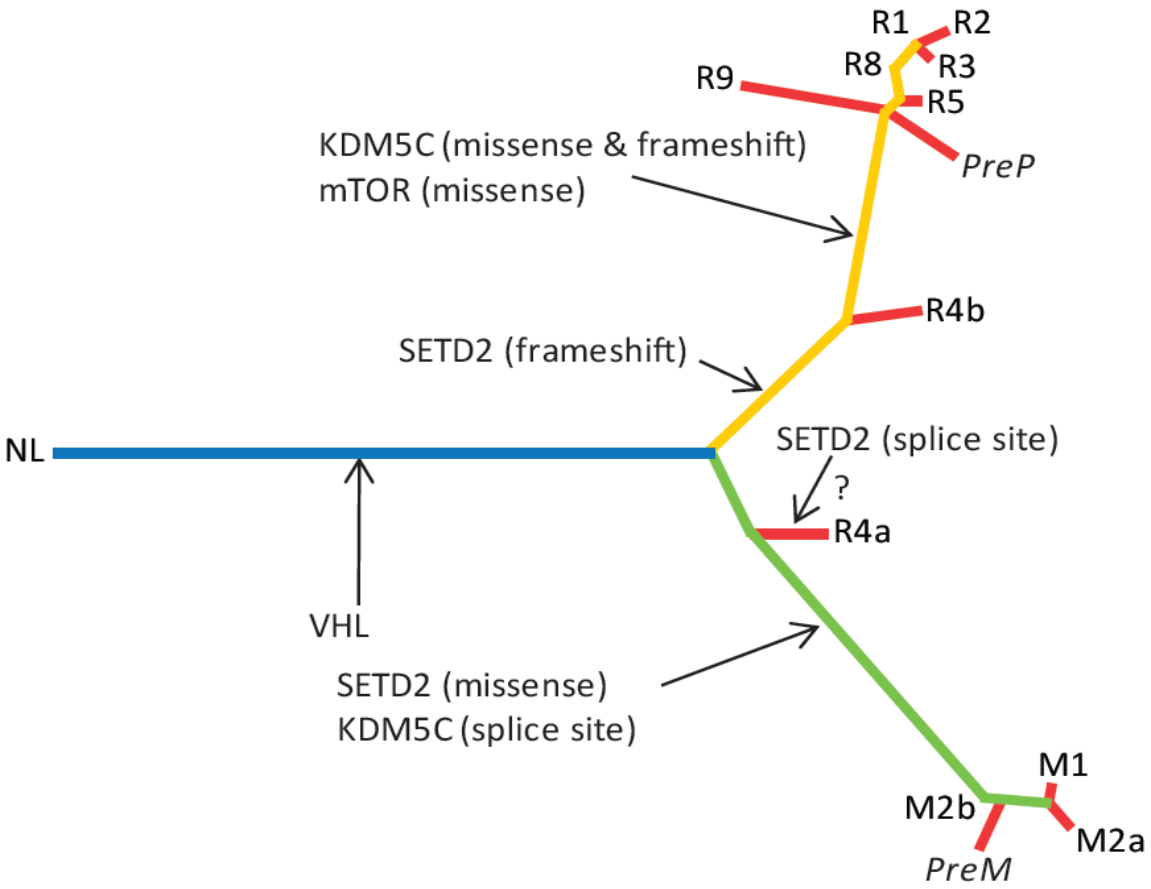
Mutation (s) at non-*VHL* Loci



***VHL* (+/-) Kidney** ***VHL* (-/-) Renal Cysts** ***VHL* (-/-) Tumor**

Inactivation of VHL is not Sufficient for Renal Carcinogenesis

VHL Loss is the Initiating Event in Most Sporadic Clear Cell Renal Cell Carcinomas- One Example



Gerlinger M et al. N Engl J Med 2012;366:883-892.

Inhibition of HIF2 is *Necessary* and *Sufficient* for Kidney Tumor Suppression by pVHL

VHL (-/-) RCC → TUMORS

VHL (-/-) RCC + pVHL → NO TUMORS

VHL (-/-) RCC + pVHL + HIF2α P -> A → TUMORS

VHL (-/-) RCC + HIF2α shRNA → NO TUMORS

Iliopoulos et al Nat Med 1995
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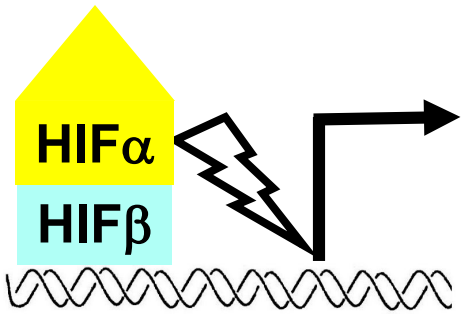
The HIF Transcription Factor



Glucose Uptake (e.g. GLUT1)

Anaerobic Glycolysis (e.g. PFK, LDH)

Angiogenesis (e.g. VEGF, PDGF, IL-8, TGFβ)

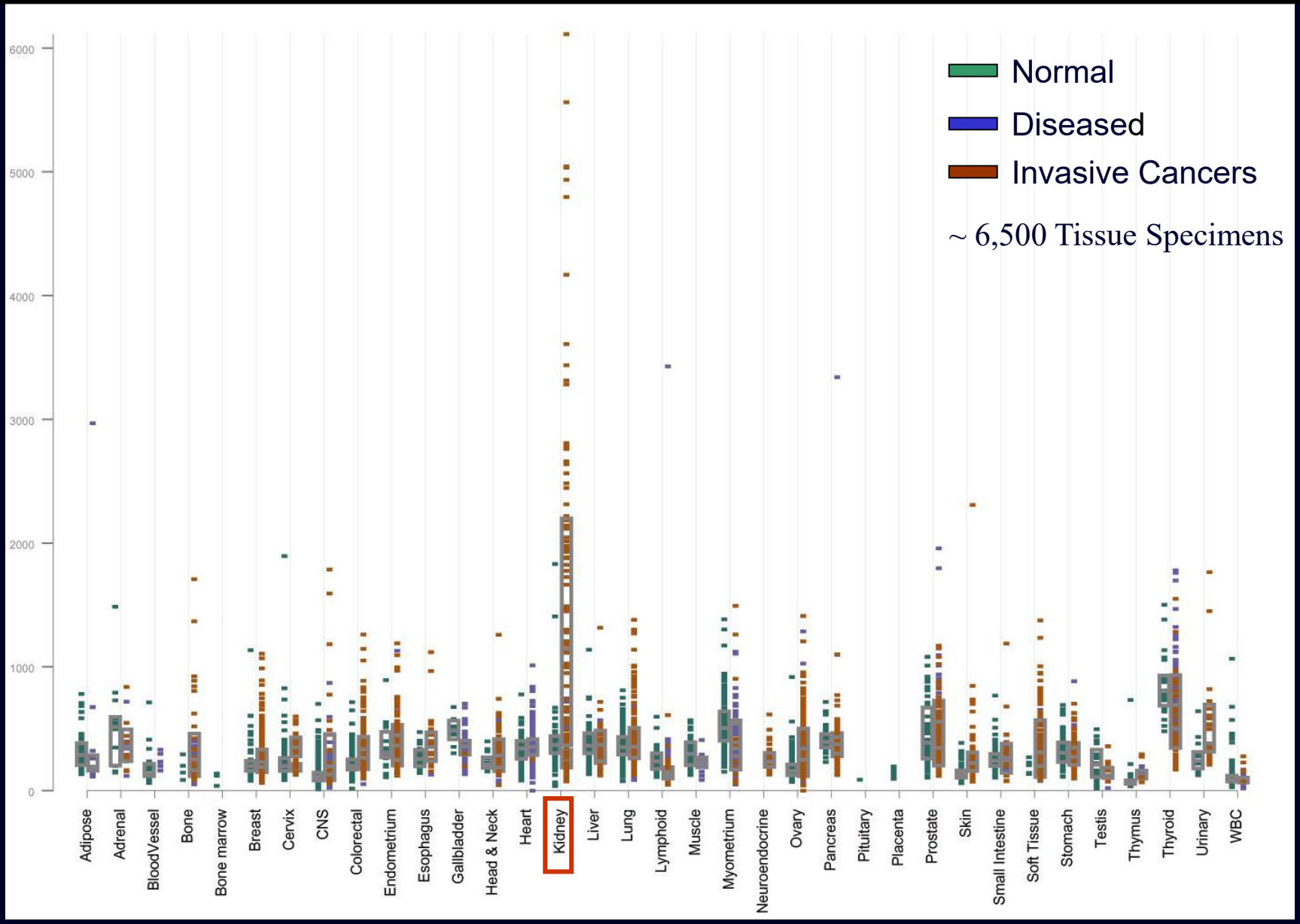
Erthropoiesis (e.g. EPO*)

Invasion/Homing (e.g. MMP2, MMP9, c-MET, CXCR4)

Mitogenesis (e.g. TGFα, Cyclin D1*)

* Tissue specific

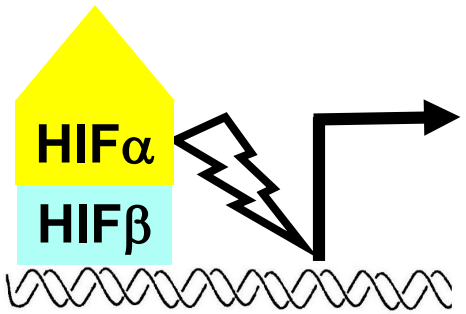
Expression of VEGF-A in Human Tissues – GeneLogic / Affymetrix®



FDA Approved VEGF Inhibitors for Treating Kidney Cancer

- **Bevacizumab**
- **Sunitinib**
- **Sorafinib**
- **Axitinib**
- **Pazopanib**
- **Cabozantib**
- **Levantinib**

The HIF Transcription Factor



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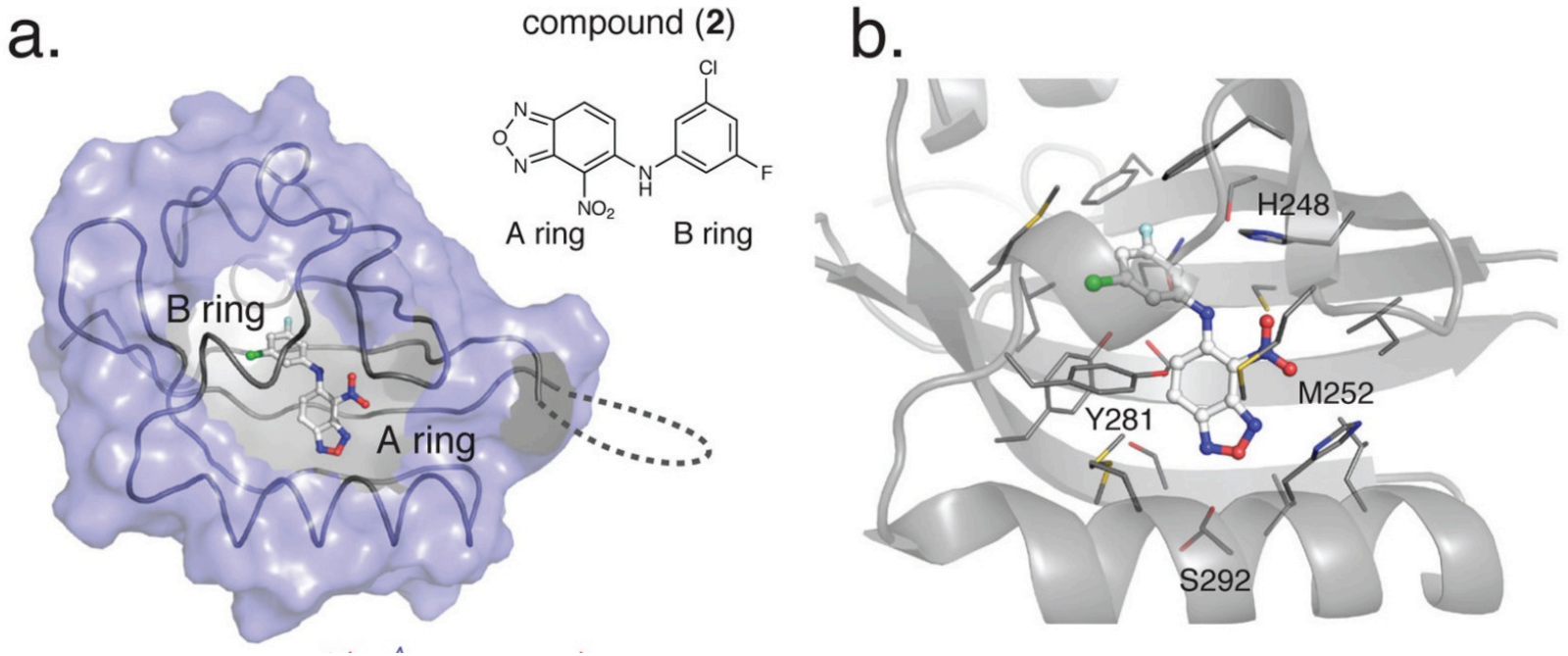
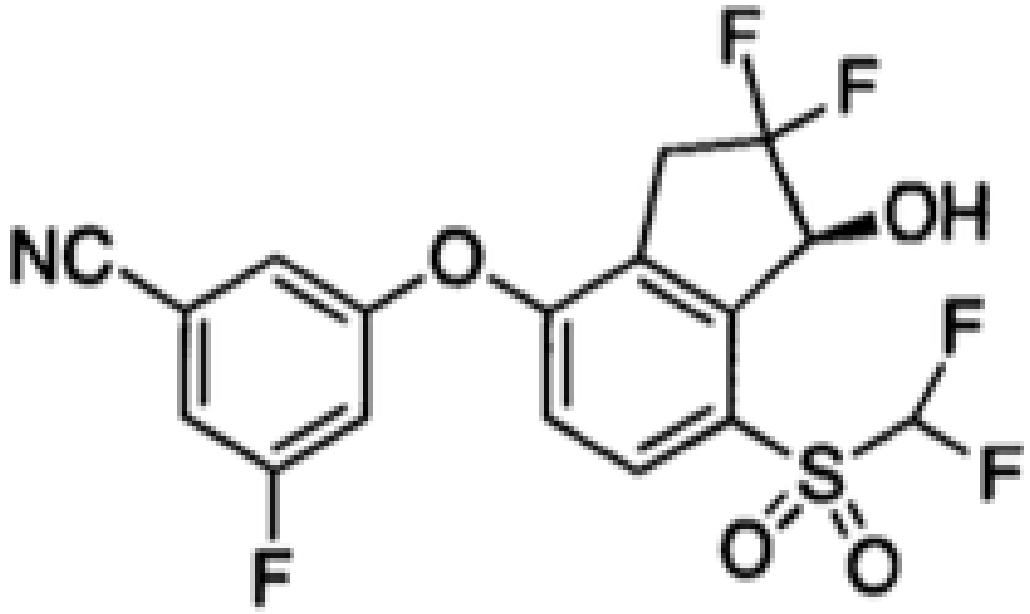
First Generation HIF2α Inhibitors



Rick Bruick and Kevin Gardner-UTSW

Peloton Therapeutics

HIF2α Inhibitor



PT2399

John Josey, Eli Wallace, et al

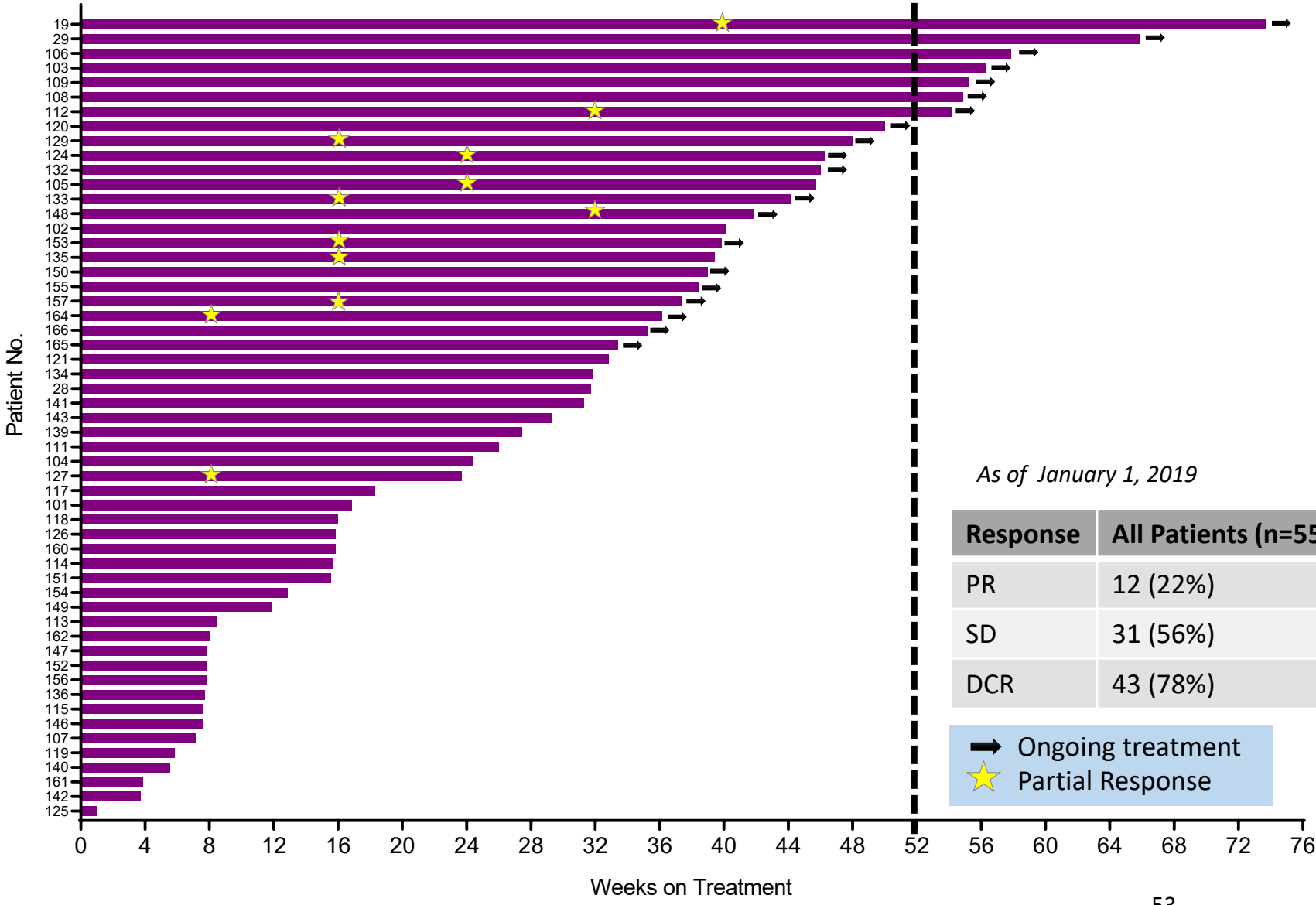
LETTER

doi:10.1038/nature19795

On-target efficacy of a HIF-2α antagonist in preclinical kidney cancer models

Hyejin Cho[1], Xinlin Du[2], James P. Rizzi[2], Ella Liberzon[1], Abhishek A. Chakraborty[1], Wenhua Gao[1], Ingrid Carvo[1,3], Sabina Signoretti[1,3], Richard K. Bruick[4], John A. Josey[2], Eli M. Wallace[2] & William G. Kaelin Jr[1,5]

HIF2 Inhibitor in Patients with Advanced Kidney Cancer (Phase 2)



As of January 1, 2019

Response	All Patients (n=55)
PR	12 (22%)
SD	31 (56%)
DCR	43 (78%)

Ongoing treatment
Partial Response

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

WWW.VHL.ORG

VHL Alliance

PATIENTS CLINICIANS RESEARCHERS GIVE ABOUT

Patients

What is VHL?

Manifestations >

Genetics >

First in Family >

[redacted]

VHL: Spreading Awareness of von Hippel-Lindau

36 mins ·

Hey all- wanted to update my fellow VHL warriors on my 24 week scans for the PT2977 clinical trial! More great results! I never thought I'd see this day

Kidney: 1.3cm decreased to 1.1cm (started off at 2.9x2.2cm)
The lesions that have decreased from my previous scans are stable, which is great.
Brain : 4mm now 3mm (started at 7mm)
5mm which is stable.
3 brain tumors disappeared

Carolyn M. Kaelin M.D. (April 4, 1961– July 28, 2015)

Neuroprotection in Rodent Stroke Model

- **FG-4539 administered i.v. at time of MCAO (60 mg/kg shown)**
- **Significant reduction in infarct volume**

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