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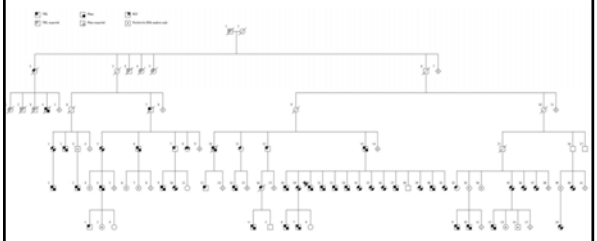
Large multi-generation VHL pedigree

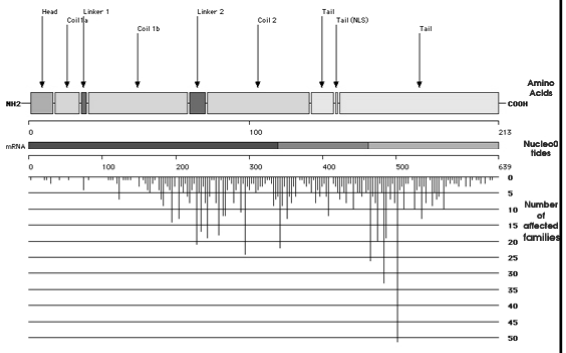


With thanks to Sarah Nielsen and Sally Carty

Some goals of the VHLFA

- To disseminate timely and accurate information about von Hippel-Lindau syndrome to patients, family members, and other interested parties
- To encourage and foster biomedical and other pertinent research on von Hippel-Lindau syndrome
- To encourage, advise, and establish standards for clinics specializing in the diagnosis and treatment of von Hippel-Lindau syndrome

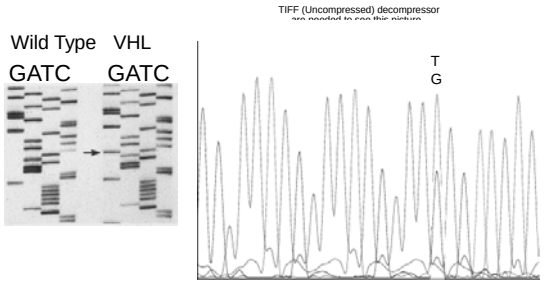
VHL germline point mutations



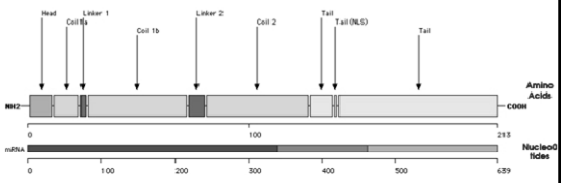
Syndromes associated with inherited renal cancer

Syndrome	Histological type	Other neoplasias	Gene
Von Hippel-Lindau Disease (VHL)	Clear cell RCC	Retinal & CNS hemangioblastomas, pheochromocytomas, pancreatic cysts and neuroendocrine tumors	*VHL,* 3p25.5
Hereditary papillary RCC (HPRC)	Type 1 papillary RCC	Papillary thyroid carcinoma (rare)	*MET,* 7q31
Hereditary leiomyomatosis RCC (HLRCC)	Type 2 papillary RCC	Uterine and cutaneous leiomyoma	*FH,* 1q42-43
Birt-Hogg-Dube' syndrome (BHD)	Chromophobe RCC; Oncocytic RCC; Oncocytoma	Fibrofolliculoma, lung cysts, spontaneous pneumothoraces, ?colon polyps	*BHD,* 17p11.2
Tuberous Sclerosis	Chromophobe RCC	Hamartomas, renal cysts & angiomyolipomas	*TSC1* *TSC2*

VHL Gene Point Mutations



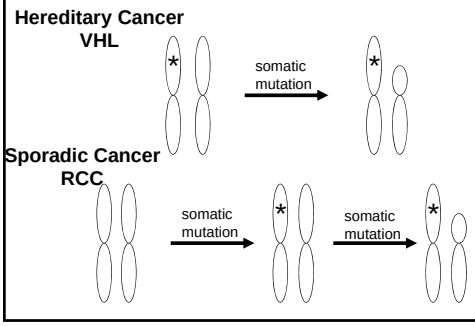
VHL germline deletions or truncations



Deletion--all or part of the entire gene is lost

Truncation--DNA sequence alterations that result in a shortened protein

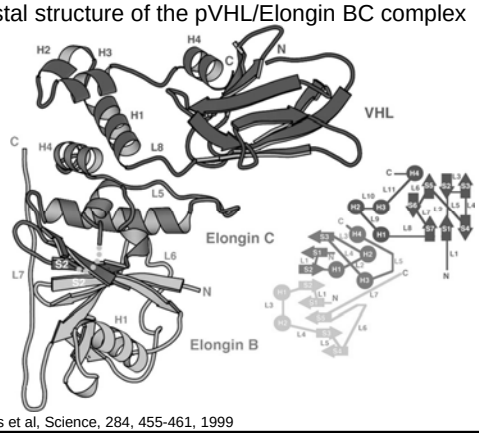
Knudson's 2-Hit Model for Tumorigenesis



VHL gene point mutation vs. deletion/truncation

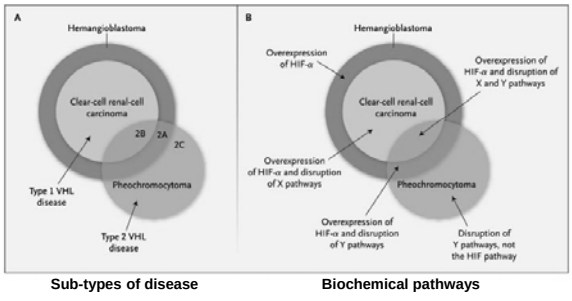
Genotype-Phenotype correlations

Crystal structure of the pVHL/Elongin BC complex



Stebbins et al, Science, 284, 455-461, 1999

Clinical Spectrum of von Hippel–Lindau Disease



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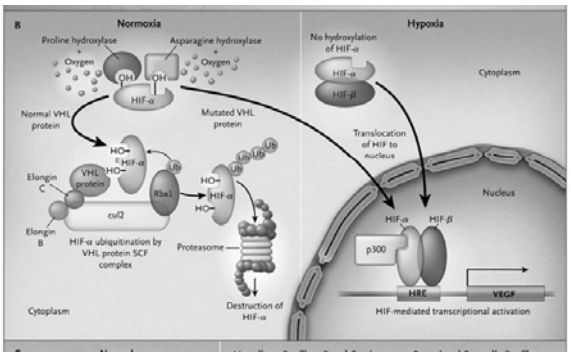
The VHL-HIF pathway



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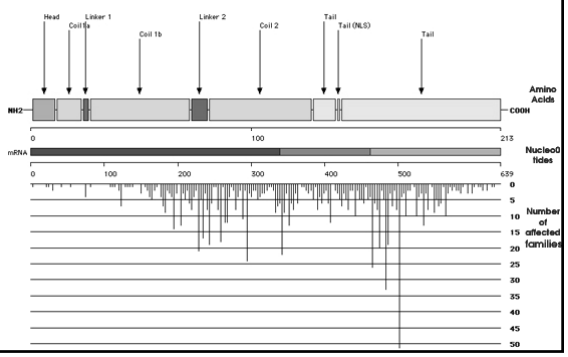
VHL germline point mutations
effects on protein interactions



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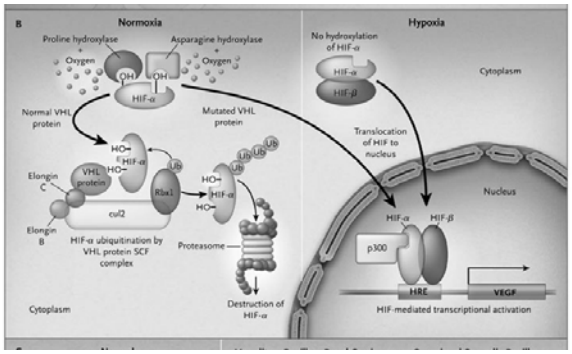

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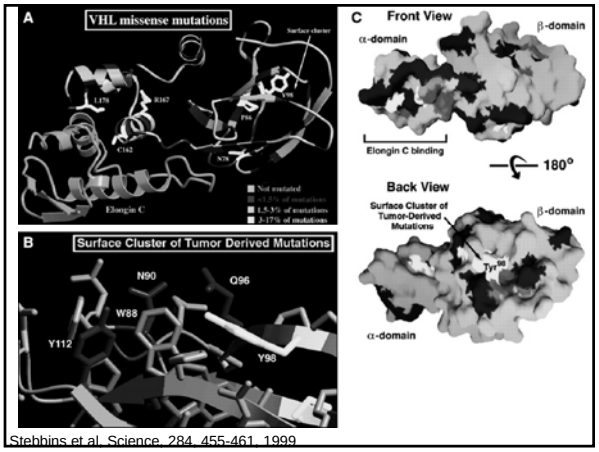
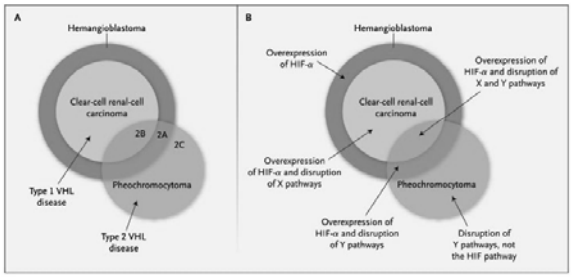


Stebbins et al. Science, 284, 455-461, 1999

Why do we care about HIF?

because it does it all

Clinical Spectrum of von Hippel–Lindau Disease



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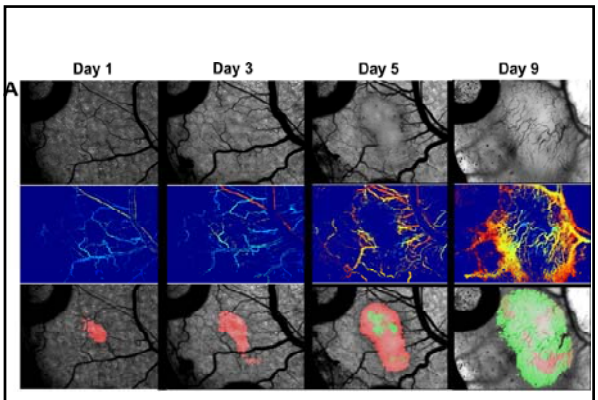
Metabolism
Adenylate Kinase-3
Carbonic Anhydrase-9
Glucose Transporter-1, -3
Glycolytic Enzymes (11)

Proliferation/Survival
Adrenomedulin, Cyclin G2
EPO, Heme Oxygenase-1
IGF, IGF-BPs
NOS isoforms, NIP3, p21
TGF-β3, VEGF

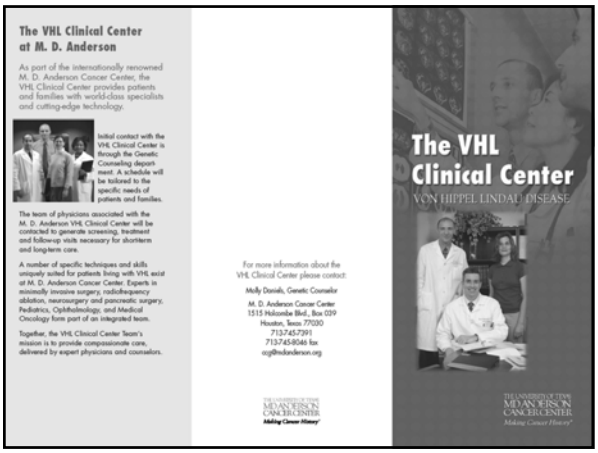
HIF-1

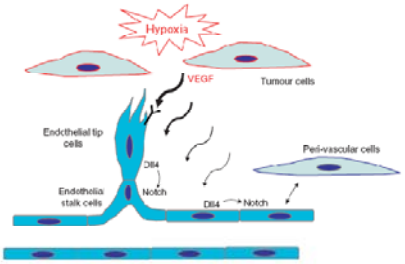
Vascular Biology
α1B Adrenergic Receptor
Endothelins, HO-1
NOS isoforms, PAI-1
VEGF, VEGFR (Flt1)
PlGF, PDGF

Iron/Erythropoiesis
Ceruloplasmin
Erythropoietin
Transferrin
Transferrin Receptor



From: Dewhirst et al, Exploring the role of HIF-1 in early angiogenesis and response to radiotherapy. Radiotherapy and Oncology 83 (2007) 249–255

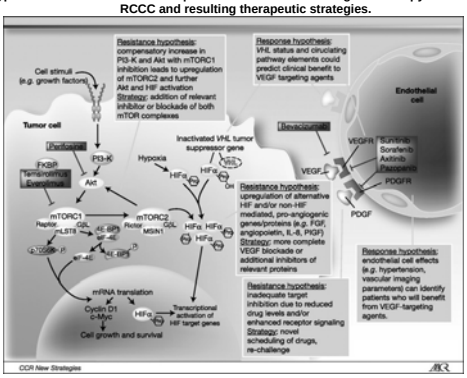




Hypothesis

- Treatment with antiangiogenic therapy should impact all VHL derived lesions, independent of organ site.
- Using a relatively potent agent should provide best clinical outcome.

Hypothesized mechanisms of response and resistance to targeted therapy in metastatic RCCC and resulting therapeutic strategies.



Rini B I Clin Cancer Res 2010;16:1348-1354

Clinical Cancer Research

MDACC Trial of Sunitinib in VHL Patients

- Endpoints:
  - Response in VHL lesions.
- Eligibility:
  - VHL patients with measurable lesions:
    - RCC between 1 and 3 cm
    - NET between 1 and 3 cm
    - Hemangioblastoma $\geq$ 5mm
  - Pheochromocytomas excluded.
  - Performance status 2 or higher.
  - Not requiring imminent surgery.

MDACC Sunitinib VHL Trial

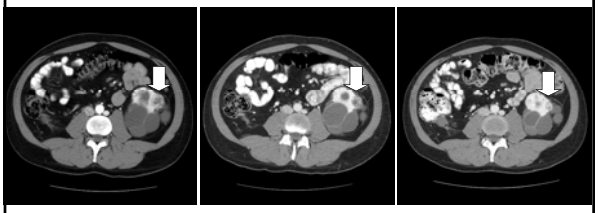
Confirmed VHL Baseline Imaging → Sunitinib 50 mg By mouth daily 4 out of 6 weeks For 24 weeks Imaging at weeks 12 and 24 → Restaging week 48

Response To Therapy

Lesion site	Number of Lesions	PR (%)	SD (%)	PD (%)
Hemangioblastoma*	**21**	**0**	**19(91)**	**2(9)**
Renal cell carcinoma*	**18**	**6 (33)**	**10(67)**	**2(10)**
Renal cyst	**9**	**0**	**9 (100)**	**0**
Retinal angiomas	**7**	**0**	**7 (100)**	**0**
Pancreatic NET	**5**	**0**	**5 (100)**	**0**
Pancreatic cyst	**3**	**0**	**3 (100)**	**0**

*(P=0.014)

Renal Masses
partial response



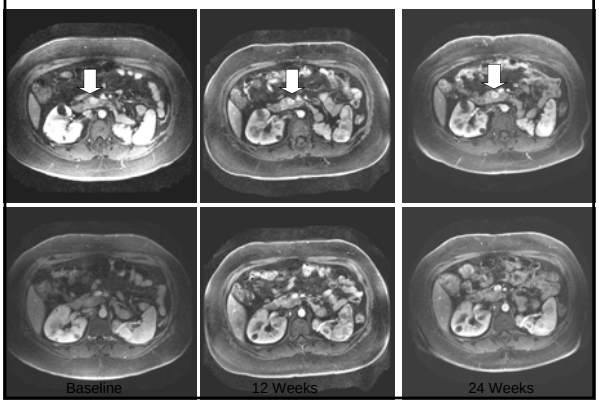
Baseline 12 Weeks 24 Weeks

Eric Jonasch, M.D. Anderson

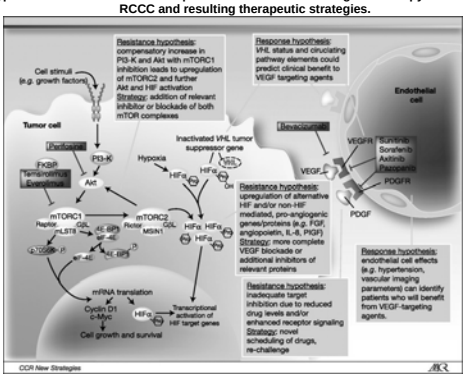
Two Trials with Industry Approval

1. Single center pilot study testing TKI258 in VHL patients with hemangioblastomas
   - Novartis oral anti-FGF receptor inhibitor
   - Also blocks VEGFR, c-Kit and Flt3
2. Multicenter 40 patient pazopanib trial for VHL patients with RCC
   - Relatively specific VEGFR inhibitor with better toxicity profile compared with sunitinib
   - Lower affinity for “off target” receptors
   - Daily oral dosing

Pancreatic Masses



Hypothesized mechanisms of response and resistance to targeted therapy in metastatic RCCC and resulting therapeutic strategies.



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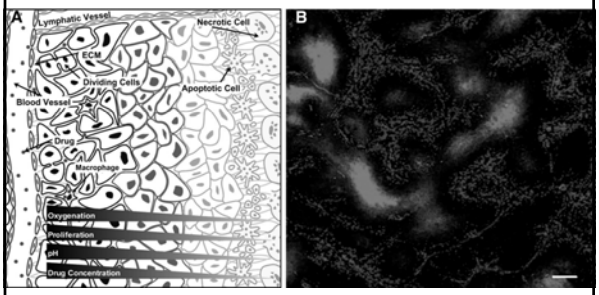
Clinical Cancer Research

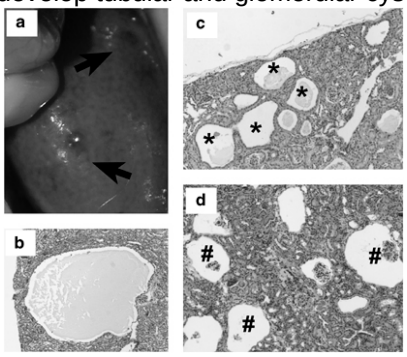
Why don't the drugs work better?

accessibility, development of resistance ….



Egeblad, et al. Tumors as Organs: Complex Tissues that Interface with the Entire Organism Developmental Cell 18, 884-901, 2010)

Mice that lack pVHL in the proximal renal tubule develop tubular and glomerular cysts

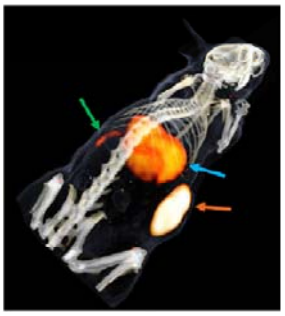


Kapitsinou, PP and Haase, VH. The VHL tumor suppressor and HIF: insights from genetic studies in mice. Cell Death and Differentiation (2008) 15, 650–659.

How to improve treatment

clinical trials

pre-clinical trials



Stillebroer AB, et al. Carbonic Anhydrase IX in Renal Cell Carcinoma: Implications for Prognosis, Diagnosis, and Therapy. Eur Urol (2010), doi:10.1016/j.eururo.2010.03.015

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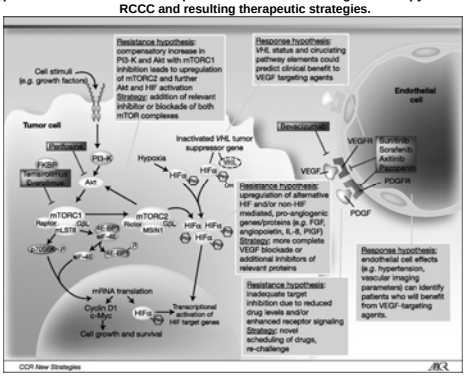

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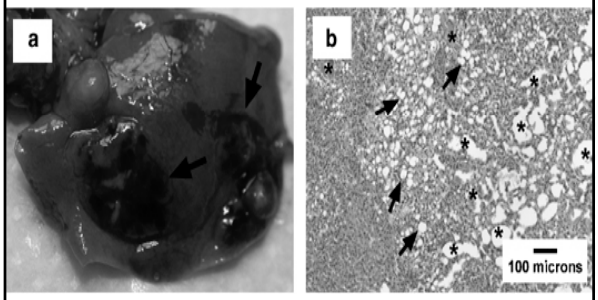
Hepatic vascular tumors in mice that lack pVHL in hepatocytes



Kapitsinou, PP and Haase, VH. The VHL tumor suppressor and HIF: insights from genetic studies in mice. Cell Death and Differentiation (2008) 15, 650–659.

VHL research papers listed in PubMed 1970-2009

Tien Hsu, Boston University