

**MASSACHUSETTS GENERAL HOSPITAL  
CANCER CENTER**

**VHL Disease" Clinical trials and treatment concepts**

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Harvard Medical School  
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MASSACHUSETTS GENERAL HOSPITAL  
CANCER CENTER

HARVARD MEDICAL SCHOOL

**MGH: VHL/Familial Renal Cancer Clinic**

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Cayun Chan-Smutko  
Kristen Shannon  
Janette Lawrence  
Devanshi Patel  
Michele Gabree  
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Frederick Barker  
Jean Coumans  
Douglas Dahl  
Aria Olumi  
Izuo Mukai  
Carlos Fernandez

- Genetic counseling and DNA testing
- Coordination of multidisciplinary care
- Tissue and Clinical Information Banking  
markers disease activity  
"PSA" renal carcinoma  
gene discovery

**Research Activities**

**Iliopoulos Laboratory**

- Rania Baker
- Paulo Gameiro
- Laura Laviolette
- Ana Metelo
- Juanjuan Yang
- Jonas Wilson
- Michael Zimmer (Catabasis)
- Peter Hulick (U Chicago)
- Mohini Lutchman (HMS)

**Greg Stephanopoulos (MIT)**  
Kostas Pantopoulos (McGill)  
Matthias Hentze (EMBO)  
Betty Liebold (Utah)

**Broad Institute**

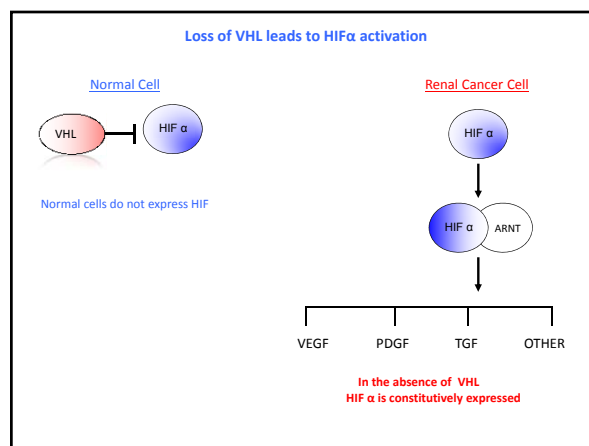
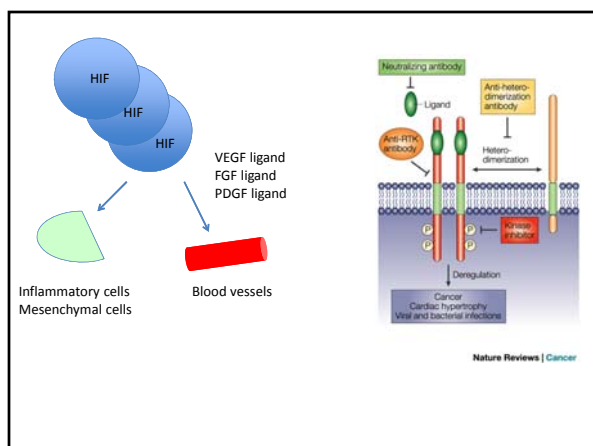
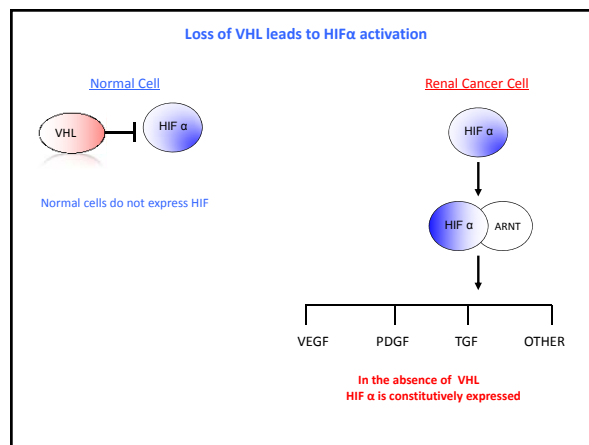
- Todd Golub
- Benjamin Ebert
- Justin Lamb

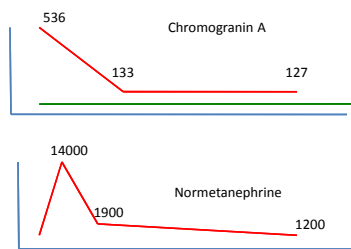
**ICCB Facility at HMS**

- Caroline Shamu
- Nicola Tolliday
- Tim Mitchison

**MGH**  
Raul Mostoslavsky  
Jonathan Whetstone  
Anders Naar  
Jeff Engelman  
.....and many others

**NIH/NCI RO1s**  
**DF/HCC SPORE Kidney Cancer**  
**MGH GU Center Bertucci Award**  
**MGH Proton Beam Therapy Center**



**Sunitinib in a VHL patient with metastatic malignant pheochromocytoma**

IMPROVEMENT pain, tumor size in metastatic areas, catecholamine symptoms  
Blood pressure

Jimenez et al J Clin Endo Metabolism 2009

**Pilot study of Sunitinib in a 15 VHL patient**

TREATMENT: 4 weeks ON + 2 weeks OFF for UP to 4 cycles

	Partial Response rate	Progression
18 RCC lesions	6/18 (33%)	2/18 (9%)
21 HB lesions	0/18 (0%)	2/21 (10%)

15 patients treated  
10/15 dose reduction because of fatigue or other toxicity  
4/15 discontinued due to toxicity

Jonasch et al Annals Oncology 2011

**Pilot study of Sunitinib in a 15 VHL patient: toxicity**

Fatigue	15/15
Diarrhea	13/15
Mucositis	13/15
Anemia	10/15
Rash	9/15
Nausea	9/15
High Blood pressure	6/15
HA	6/15

Jonasch et al Annals Oncology 2011

**Second and Third generation RTK inhibitors**

	Sunitinib	Axitinib	Pazopanib	XL148
VEGFR1	++	++	++	+
VEGFR2	+	++	+	++
VEGFR3	+	++	++	+
PDGF	++	++	+	++
C-MET				++
FGF			++	
RET	++			

**Treatment of RETINAL HB with intraocular injections****Participants**

Five patients with VHL associated exudative changes and visual loss

**Methods**

Monthly intravitreal injections of ranibizumab

Course of 6 months for a total of 7 injections

The final study visit was designated as 8 weeks after the final study injection.

**The primary outcome**

Change in best-corrected visual acuity (BCVA) of  $\geq 15$  letters

**Secondary outcomes**

included change in lesion size

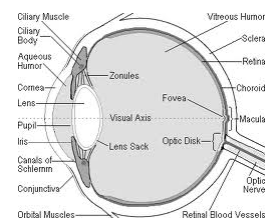
exudation as assessed clinically and by fluorescein angiography,  
change in retinal thickness as evaluated by optical coherence tomography  
and adverse events

**Results**

Mean change in BCVA was a decrease of  $9 \pm 20$  letters.

Changes in both lesion size and exudation were variable.

Wong et al Ophthalmology. 2008 November ; 115(11): 1957-1964

**Intraocular injections vs systemic delivery**

Aiello LP, George DJ, Cahill MT, Wong JS, Cavallerano J, Hannah AL, Kaelin WG Jr.  
Rapid and durable recovery of visual function in a patient with von  
hippel-lindau syndrome after systemic therapy with vascular endothelial growth factor  
receptor inhibitor su5416. Ophthalmology. 2002 Sep;109(9):1745-51.

### Questions and Resources

Which inhibitor for which VHL-associated lesion (HB, RCC, retina, PNET)

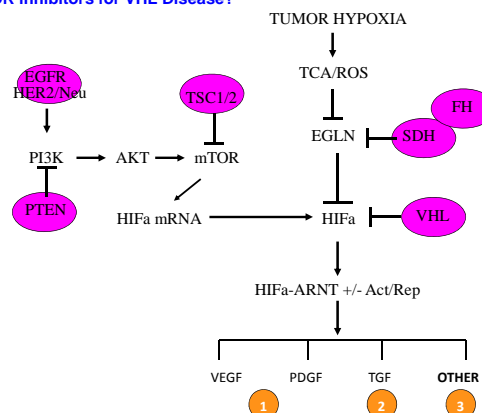
When to give them?  
When to start and when to stop  
Prevention?

How to combine them with surgery and radiation ?

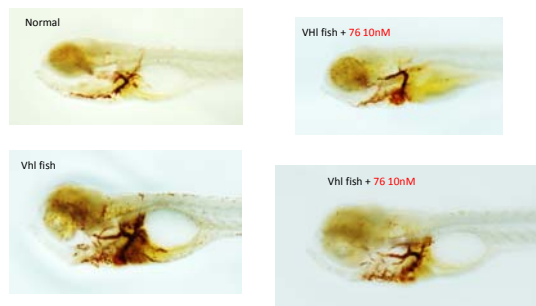
[Clinictrials.gov](http://Clinictrials.gov)

VHL Clinical Task Force

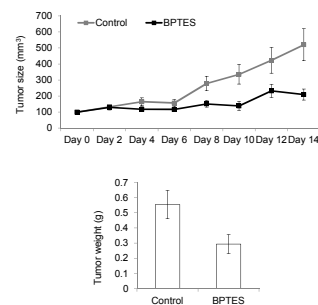
### mTOR inhibitors for VHL Disease?



### HIF inhibitor compound suppresses angiogenesis in *vhl* zebrafish



### Systemic administration of Glutaminase inhibitors suppresses growth of VHL-deficient RCC mouse xenografts



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