Syndromes associated with inherited renal carcinoma

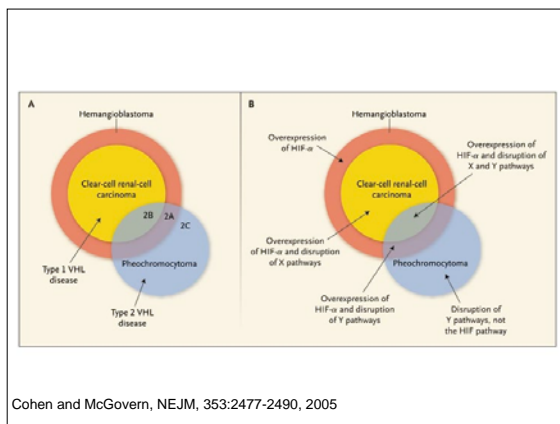| Syndrome	Histological type	Other neoplasias	Gene
Von Hippel-Lindau Disease (VHL)	Clear cell RCC	Retinal & CNS hemangioblastomas, pheochromocytomas, pancreatic cysts and neuroendocrine tumors	*VHL,* 3p25.5
Hereditary papillary RCC (HPRC)	Type 1 papillary RCC	Papillary thyroid carcinoma (rare)	*MET,* 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*

Knudson's 2-Hit Model for Tumorigenesis

VHL germline point mutations

Cohen and McGovern, NEJM, 353:2477-2490, 2005

Cohen and McGovern, NEJM, 353:2477-2490, 2005

The tumor-microvascular microenvironment
Cell-cell interactions through secreted mediators

1

Formation of new blood vessel branches

Carmeliet P et al. (2009) Branching morphogenesis and antiangiogenesis candidates: tip cells lead the way
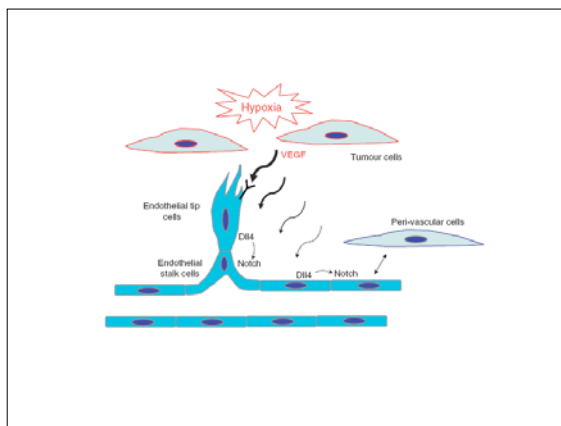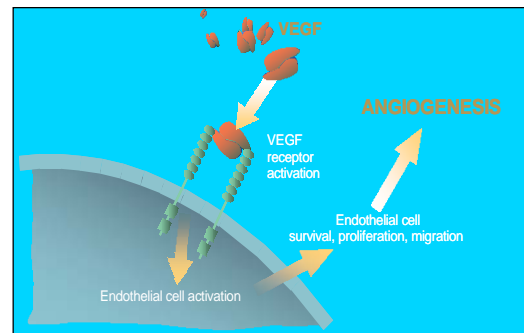Nat Rev Clin Oncol doi:10.1038/nrclinonc.2009.64

Serial observation of tumor cell – vascular interactions during early tumor growth
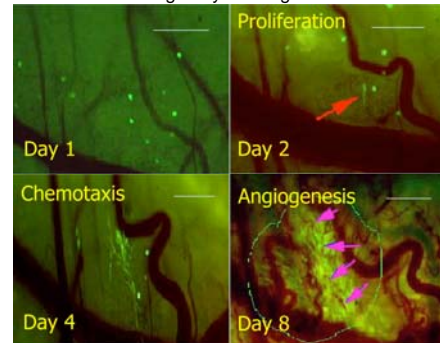
From: Dewhirst et al, Exploring the role of HIF-1 in early angiogenesis and response
to radiotherapy. Radiotherapy and Oncology 83 (2007) 249–255

The VEGF pathway

Reference: 1. Hicklin DJ, Ellis LM. *J Clin Oncol.* 2005;23:1011-1027.

VEGF stimulates multiple downstream signaling pathways

Anti-VEGF Therapy

Tyrosine kinase inhibitors

Rini BI, Small EJ. *J Clin Oncol.* 2005;23:1028-1043. Reprinted with permission
from the American Society of Clinical Oncology.
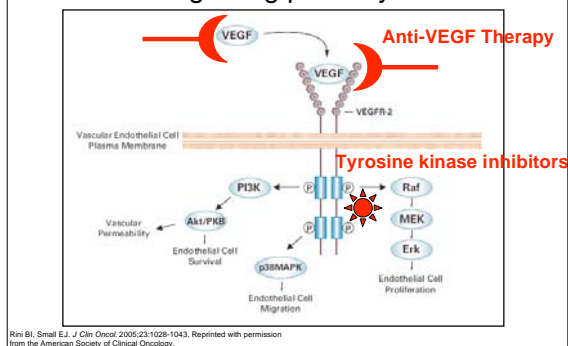
Studies on imaging in hereditary tumor syndromes: VHL and MEN 1

**University Medical Center Groningen
Groningen, the Netherlands**

Anatomic Imaging
  size shape density
  e.g. CT, MRI, ultrasound
      => tumor response by changes in size
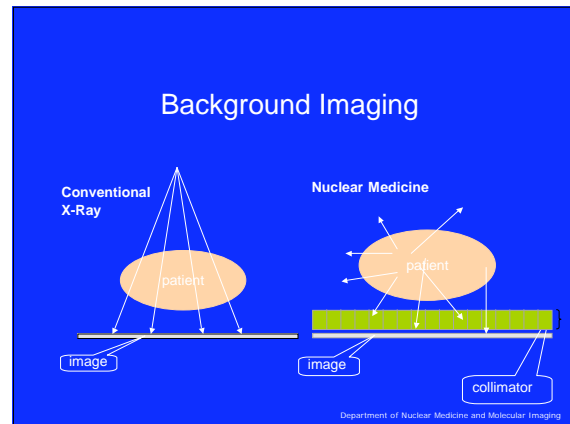**Molecular Imaging**
 tumor biology in vivo
  e.g. PET,SPECT,MRI
      => tumor response by changes in size

Background Imaging

Conventional X-Ray

Nuclear Medicine

patient

patient

image

image

collimator

Department of Nuclear Medicine and Molecular Imaging

PET camera: positron emission

Department of Nuclear Medicine and Molecular Imaging

Promising Developments
in Nuclear Medicine :

^{18}F-DOPA

^{11}C-5-HTP PET

^{18}F-DOPA PET

Feochromocytoma: ^{18}F-DOPA >> ^{123}I-MIBG
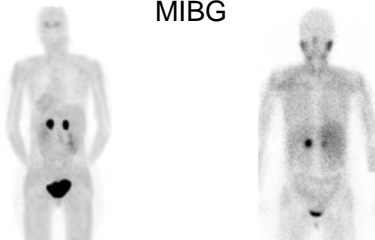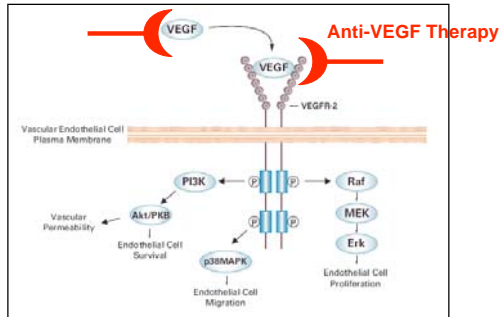
Asco 2009 H.B. Fiebrich

2
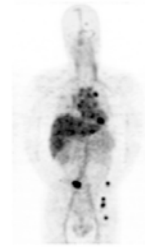Visualizing VEGF producing
lesions in Von Hippel- Lindau
disease
AIM

To perform ^{89}Zr-bevacizumab PET
scans in patients with VHL to detect
and quantify non-invasively VEGF
production in VHL associated lesions

VHL
FAMILY
ALLIANCE

3

VEGF stimulates multiple downstream signaling pathways

Anti-VEGF Therapy

Rini Bl, Small EJ. *J Clin Oncol.* 2005;23:1028-1043. Reprinted with permission from the American Society of Clinical Oncology.
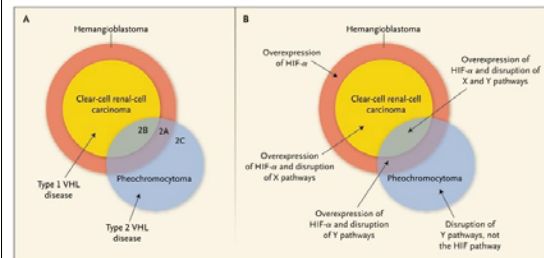

Whole-body image 4 days after tracer injection. Multiple bone, lung and brain metastases are visualized in a patient with renal cell carcinoma

⁸⁹Zr- bevacizumab tumor visualization

The First Animal Model to study the Early Diagnosis and Treatment of Retinal Hemangioblastomas in Patients with von Hippel-Lindau Disease

James Handa, MD
Wilmer Eye Institute

Cohen and McGovern, NEJM, 353:2477-2490, 2005

Retinal Hemangioblastomas in VHL Disease

- Retinal hemangioblastomas
  - Most common manifestation of VHL disease

- Patient problems
  - Vision loss
    - Risk of blindness is high if untreated
  - Secondary glaucoma
    - Pain
    - Possible loss of the eye

- Early diagnosis to save vision is essential.

- Current treatment
  - Limited options
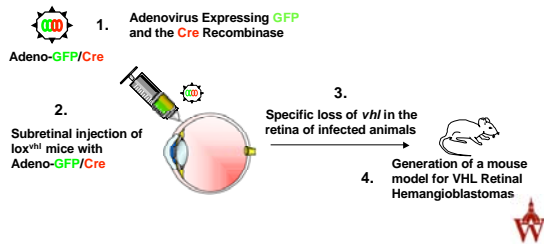 - Prognosis can be poor for good visual outcome.

Animal Model for VHL Hemangioblastomas

- Animal model of VHL retinal hemangioblastoma
  - Simulate the retinal tumors
  - Understand how they develop due to the VHL gene defect
  - Test new methods for early detection
  - Test new methods for early treatment

- Goal: Prevent or delay disease development before vision loss.

Animal Model for VHL Hemangioblastomas

- Support by the VHL Foundation:
  - Development of an animal model of VHL hemangioblastomas.

  - Reproduces loss of the *vhl* gene in the eye.

1. **Adenovirus Expressing GFP and the Cre Recombinase**

Adeno-GFP/Cre

2. **Subretinal injection of lox^vhl mice with Adeno-GFP/Cre**

3. **Specific loss of *vhl* in the retina of infected animals**

4. **Generation of a mouse model for VHL Retinal Hemangioblastomas**

Animal Model for VHL Hemangioblastomas

- Retinal lesions are similar to those in patients with VHL disease.
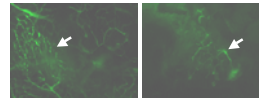
Representative Early Lesions from Mouse Model for VHL Retinal Hemangioblastomas

- The first animal model for VHL retinal hemangioblastomas.

- Current investigation
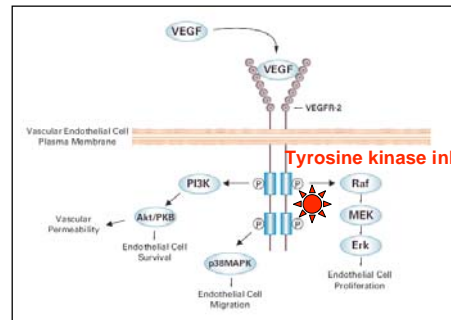 - Identify new targets for the early diagnosis and treatment.

Sodhi, et. al., 2009 (manuscript in preparation)

Role of the Interferon Gamma Pathway in Resistance to Antiangiogenic Therapy

Rupal Bhatt, M.D.

VHLFA

VEGF stimulates multiple downstream signaling pathways

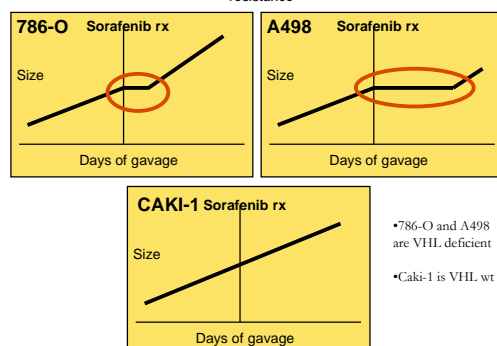**Tyrosine kinase inhibitors**

Rini BI, Small EJ. *J Clin Oncol.* 2005;23:1028-1043. Reprinted with permission from the American Society of Clinical Oncology.

VEGFR TKI: Sorafenib/sunitinib

- Activity is robust, but there are few, if any, complete responses

- Continued treatment appears required to maintain efficacy

- Disease resistance usually develops within 6-12 months

- Mechanism of resistance is unknown and treatment of resistant disease are suboptimal

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Sorafenib treatment of mouse tumors lead to tumor stabilization followed by resistance

786-O Sorafenib rx — Size — Days of gavage

A498 Sorafenib rx — Size — Days of gavage

CAKI-1 Sorafenib rx — Size — Days of gavage

- 786-O and A498 are VHL deficient
- Caki-1 is VHL wt

*Tumor size represented by long axis

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5

Importance to VHL

- VHL patients who have metastatic RCC may require prolonged exposure to VEGFR TKIs.
- There is also much interest in the utility of these agents for patients with VHL without metastases in an effort to delay complications related to RCC progression.
- Importantly, if used in this setting, sorafenib or sunitinib may be needed for long periods of time.
- This could be a major predisposing factor to the development of resistance.
- It is in this population of patients that understanding the mechanisms of resistance to sunitinib and sorafenib would be particularly useful.

Goals

- Establish a murine model of RCC resistance to VEGF R blockade to elucidate and validate the molecular mechanisms of resistance
- Develop imaging techniques to follow response and resistance
- Develop tissue and blood biomarkers to study response and relapse
- Design clinical trials to combat resistance

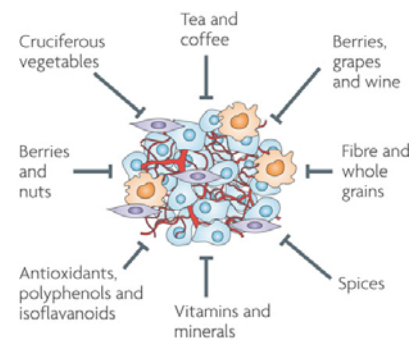## VEGF stimulates multiple downstream signaling pathways
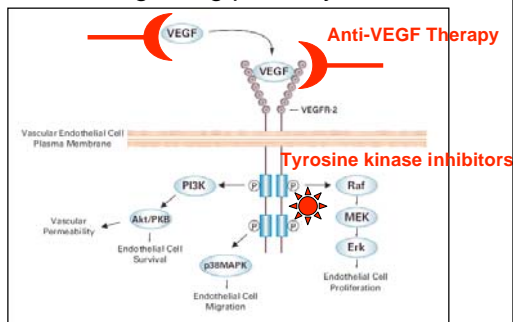
Rini BI, Small EJ. *J Clin Oncol.* 2005;23:1028-1043. Reprinted with permission from the American Society of Clinical Oncology.

Prevention & Chemoprevention
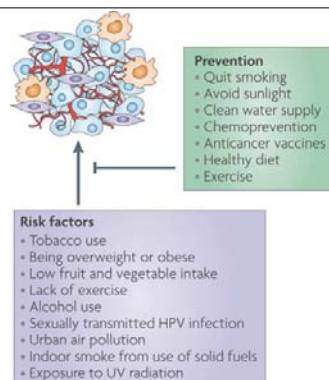
Bode and Dong, 9, 508-516 (2009)   Nature Reviews | Cancer

Bode and Dong, 9, 508-516 (2009)   Nature Reviews | Cancer

Nature Reviews | Cancer

1X / week
for 8 weeks

Started PEITC-NAC
+ myo-I after 4 weeks

Vehicle control

BaP + NNK

BaP + NNK + PEITC-NAC
+ myo-inositol

Hecht et al., 9, 476-488

Nature Reviews | Cancer

PEITC

Hypoxia → HIF → VEGF → Angiogenesis

Wang et al., Biochemical Pharmacology, 78, 261-272, 2009

Bode and Dong, 9, 508-516 (2009)

Nature Reviews | Cancer

7