# Systemic Therapy for VHL: Update on Clinical Trials

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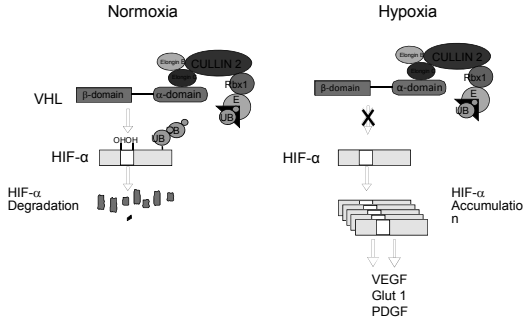
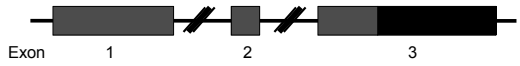
## HIFα is targeted for degradation in normoxic, but not hypoxic cells

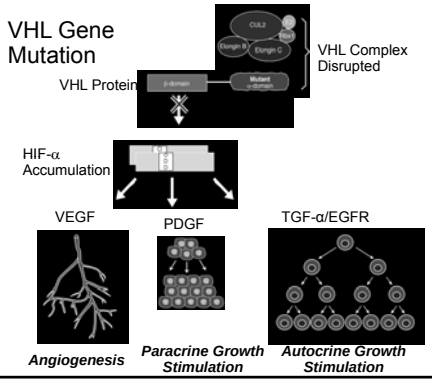



## Human VHL Gene

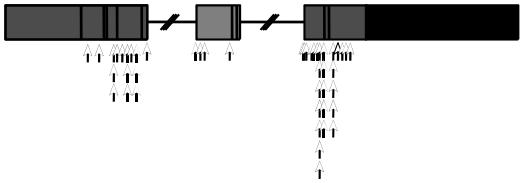



Science 260:1993

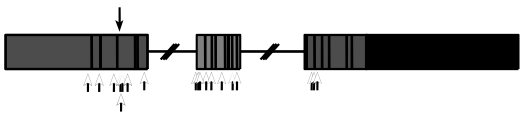
## Downstream effects of *VHL* mutation




## Germline VHL Mutations

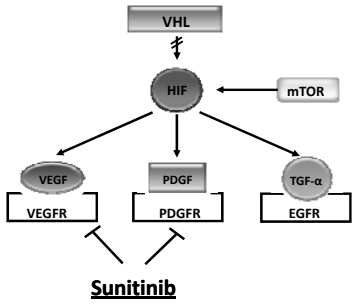


## Sporadic Clear Cell RCC VHL Gene Mutations

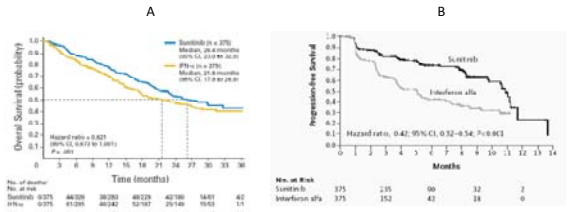


Science 260:1993
Nature Genetics 7:1994
Clin Cancer Res 14:2008

## Targeting VHL/HIF in Clear Cell RCC




## Sunitinib vs Interferon-α




From Motzer et al., JCO: 27, 2009

From Motzer et al., NEJM:356, 2007

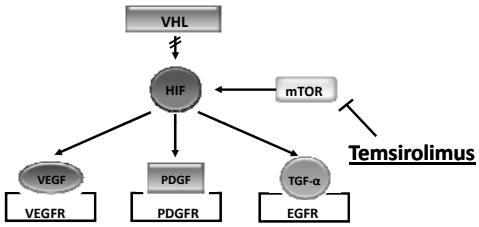
## Sunitinib Phase III Trial

Previously untreated patients with metastatic renal cell carcinoma

| | |
|---|---|
| Patients Randomized: | 750 |
| Assigned to sunitinib: | 375 |
| Assigned to interferon-α: | 375 |

Motzer, et al NEJM 356 2007

## Targeting VHL/HIF in Clear Cell RCC




## Sunitinib Phase III Trial

| Response: | Sunitinib | IFNα |
|---|---|---|
| Complete | 0 | 0 |
| Partial | 31% | 6% |
| Stable Disease | 48% | 49% |
| Prog Free Survival: | 11 mo | 5 mo |

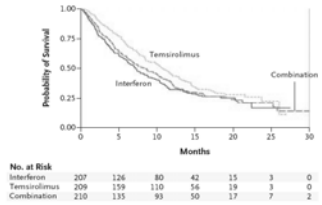
Motzer, et al NEJM 356 2007

## Temsirolimus Randomized Phase III Trial

- 626 previously untreated, poor risk patients
- TEM vs IFNA vs TEM + IFNA
  - Response rate (TEM): 8.6%
  - Progress free survival (months):
    ***3.8 (TEM) vs 1.9 (IFNA) p=0.0001***
  - Overall Survival (months):
    ***10.9 (TEM) vs 7.3 (IFNA) p=0.0069***

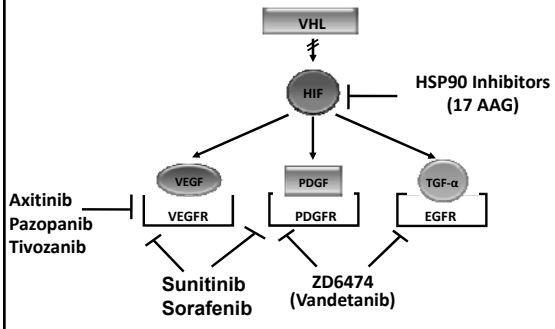
Hudes, et al NEJM 356:2007

## Temsirolimus Alone, Interferon-a Alone or the Combination

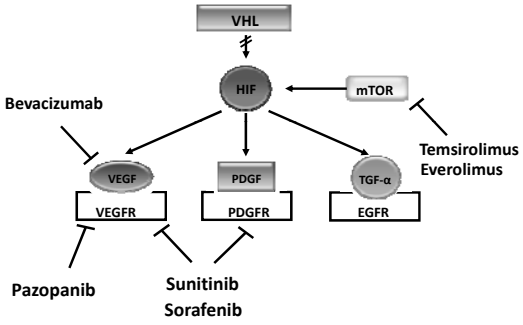



From Hudes et al. NEJM:356, 2007

## Targeting VHL/HIF

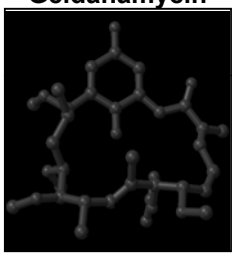



## Targeting VHL/HIF in Clear Cell RCC




## Benzoquinone Ansamycins: The First Identified HSP90 Inhibitors

### Geldanamycin

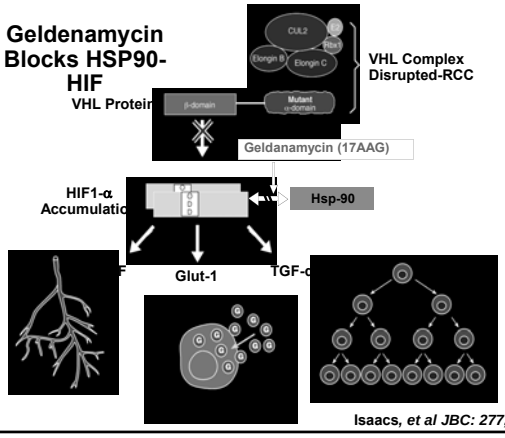


- Proposed mechanism: tyrosine kinase inhibition
- Later found to be caused by drug-induced kinase degradation
- Direct binding of this drug to HSP90: its true molecular target (Whitesell et al. *PNAS*, 91:8324, 1994)

## VHL Patients and Clinical Trial Participation

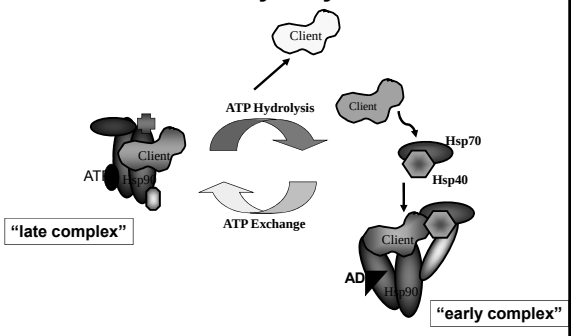
- Relatively rare disease
- Clinical characteristics that may pose specific risks
  - CNS hemangioblastomas, ELSTs
  - Pheochromocytoma
- Drug tolerability
- Stringent protocol requirements/logistics
- Reluctance to participate in clinical trials

## Geldenamycin Blocks HSP90-HIF




Isaacs, *et al JBC: 277, 2002*

## The Hsp90 chaperone machine Is driven by ATP hydrolysis




## 17AAG in VHL

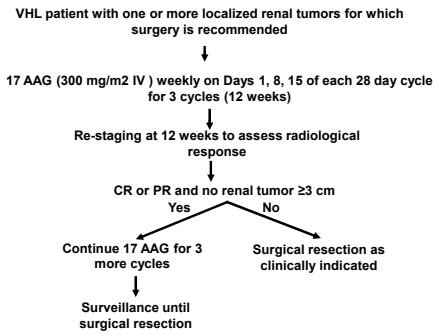
### Key Eligibility Criteria

- Clinical diagnosis of VHL
- One or more measurable tumors
- Adequate organ function
- ECOG ≤ 2

**04-C-0238: A Phase 2 Study of 17-allylamino-17-demethoxygeldanamycin (17AAG) in Patients with von Hippel Lindau (VHL) Disease and Renal Tumors**

## 17AAG in VHL

**Design: Open Label Phase II Study**




## 17AAG in VHL

- **Study Objectives**
  - Primary: Evaluate efficacy (overall response rate) of single agent 17 AAG on renal tumors in patients with VHL disease
  - Secondary-Safety and tolerability in VHL patients, Effect on non-renal VHL tumors, HSP90 modulation in PBMC and tumor tissue, feasibility of PET and DCE-MRI in evaluating VHL renal tumors

## 17AAG in VHL

### Results and Conclusions

- 9 patients enrolled (7 evaluable)
  - Mean age 48
  - Avg # of tumors 3.3
  - Avg size 3.1 cm

## 17AAG in VHL

- Safety:
  - No Grade ¾ events related to drug
  - Most common toxicities include
    - Nausea (88%)
    - Fatigue (63%)
    - Cardiac (63%)
      - 1st and 2nd degree AV block
      - Sinus Brady and Sinus Tach
      - Non-sustained V-tach
      - One patient developed asymptomatic high grade AV block
    - Altered Taste (50%)
    - Elevated glucose (50%)
    - Muscle pain (38%)

## Sunitinib in VHL

**(MD Anderson CC-Drs. Jonasch, Mateen et al)**

- Phase II study
- Patients with renal or pancreatic tumors, CNS hemangioblastomas, or retinal angiomas
- Sunitinib administered at standard doses for 6 months

## 17AAG in VHL

- All 7 evaluable patients were found to have stable disease following 3 cycles of therapy
- No objective responses by RECIST
- Accrual halted/trial closed due to slow accrual

## Sunitinib in VHL

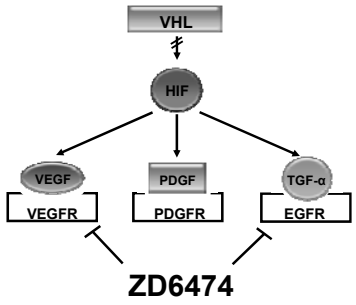
- 12 patients enrolled
- Tumor regression seen in
  - 16/19 renal tumors
  - 3/5 pancreatic tumors
  - 6/19 hemangioblastomas
- Two patients taken off study due to drug toxicity

## 17AAG in VHL- Summary

- Acceptable safety profile
- Efficacy-No objective responses, but drug may be cytostatic
- Newer generation HSP90 analogues now available and may bear further investigation as single agents or in combination

**08-C-0020: Phase II Study of ZD6474 (vandetanib) in Patients with von Hippel Lindau (VHL) Disease and Renal Tumors**

## Targeting VHL/HIF in Clear Cell RCC




## Vandetanib in VHL

**Study Design**

- Single arm, open label phase 2 study
- ZD6474 oral
  - Continuous daily dosing-300mg/day
- Simon optimal two stage design
  - Initial stage: 12 patients
  - If 1 or more of initial 12 respond, maximum of 37 patients will be enrolled
- Assess response by RECIST q 12 weeks

## Vandetanib in VHL

- Vandetanib is a dual tyrosine kinase inhibitor with activity against:
  - VEGF2 (mediates tumor angiogenesis)
  - EGFR (mediates tumor growth and proliferation

## Vandetanib in VHL

**Key Eligibility Criteria**

- Clinical diagnosis of VHL
- One or more measurable tumors
- Adequate organ function
- ECOG ≤ 2

## Vandetanib in VHL

**Objectives**

- Primary
  - Overall response rate in VHL patients with renal tumors
- Secondary
  - Safety and tolerability in VHL patients
  - Progression-free survival
  - Effect of ZD6474 on VHL non-renal tumors
  - PD endpoints
    - surrogates of angiogenesis inhibition- *Jane Trepel, MOB*
      - circulating endothelial cells, plasma VEGF and soluble VEGFR2

## Vandetanib in VHL

**Study Contact**

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- Sally Fowler, RN
  Research Nurse
  Tel: 301-435-6255
  e-mail: fowlers@mail.nih.gov

## Bevacizumab for CNS Hemangioblastoma

**NCT01015300 (Dartmouth-Hitchcock Med Ctr)**

Eligibility Criteria:
-CNS hemangioblastomas (at least 5mm), not amendable to surgical resection
-Confirmed diagnosis of von-Hippel-Lindau disease
-No prior treatment with VEGF inhibitors
-No major bleeding event from hemangioblastoma within 90 days
-KPS > or equal to 60%
-Age > or equal to 18 years

## Conclusions

- Several HIF/VEGF pathway inhibitors in clinical evaluation
- VEGF pathway inhibitors have demonstrated activity
- Development and clinical testing of agents with less toxicity ongoing
- Strategies to enhance and encourage clinical trial access and participation required

## Sunitinib for Retinal Angiomas

NCT00673816 (National Eye Institute)
PI-Catherine Meyerle, M.D.

- Eligibility Criteria
  - Confirmed VHL
  - Optic nerve angioma
  - Best corrected visual acuity 20/40 or less
  - Age >18 yrs
  - Adequate organ function
  - Good Performance Status

## Acknowledgements


- VHL Patients and their Families
- VHLFA
- Urologic Oncology Branch and Collaborators, NIH


## Future Studies

- Selective VEGF receptor inhibitors
  - Tivozanib, Axitinib, Pazopanib
  - Better toxicity profile
  - ?Efficacy
- Novel agents
  - HIF antagonists
- Inclusion of CNS hemangioblastomas, pheochromocytomas