Harnessing the power of scientific advances for treatment of VHL

Othon Iliopoulos, MD, PhD
Associate Professor of Medicine
Harvard Medical School
Director, MGH Hereditary Renal Cell Carcinoma Clinic
Co-Leader, Dana-Farber/Harvard Cancer Center Kidney Cancer Program

Loss of VHL leads to HIFα activation

Normal Cell

Renal Cancer Cell

VEGF  PDGF  TGF  OTHER

In the absence of VHL, HIF α is constitutively expressed

Targeted therapy

Direct targeting of HIF2α with small molecule inhibitors
Direct targeting of HIF2α with small molecule inhibitors

TUMOR HYPOXIA

EGFR
HER2/Neu

TCA/ROS

FH

EGLN

SDH

TSC1/2

PI3K

AKT

mTOR

HIFα mRNA

VEGF

PDGF

TGF

OTHER

The power of next generation sequencing (NGS)

SORTING OUT HETEROGENEOUS TUMORS: Sequencing of the whole genome (exome)

Significantly mutated genes

372 ccRCC tumor samples

Frequent VHL alterations
(91% copy, 55% mutation, 7% methylation)
TUMORS ARE HETEROGENEOUS

Metabolism: Cancer cells have their own appetite preferences

Reprogramming of metabolism by HIF2a: opportunities for synthetic lethality

Glutaminase 1 Inhibitors synergize with Olaparib in killing VHL-Deficient Cells
Can we wake up or educate our immune system?

Can the immune system help us?

Anti-PD1 antibodies
Anti-PD1-L antibodies
“Educated” T cells

New methods to edit DNA errors

Specifity
Delivery
Thank you!
Or
Do NOT be afraid to ask