Identifying the Molecular Mechanisms Underlying HIF2-Independent Tumorigenesis in ccRCC

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The VHL-HIF2 axis

A subset of ccRCC tumors are HIF2-independent

**LETTER**

Targeting renal cell carcinoma with a HIF-2 antagonist

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**LETTER**

On-target efficacy of a HIF-2α antagonist in preclinical kidney cancer models


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Conditional overexpression and knockout systems to evaluate the role of oncogenes and tumor suppressors

Doxycycline-induced reconstitution of VHL in XP258 (VHL-null line) blocks tumor growth

Loss of HIF2α in XP374 (HIF2-dependent line) blocks tumor growth

2022 Kidney Cancer Research Summit
How does the loss of known VHL targets affect tumor growth in HIF2-independent lines?

Loss of HIF1α in XP258 (HIF2-independent line) does not significantly affect the rate of tumor growth.

**VHL substrate transcription factor ZHX2 as an oncogenic driver in clear cell renal cell carcinoma**

Jing Zhang1,2, Tao Wu3, Jeremy Simon4,5, Munira Takada6, Ryuchichi Saito7, Cheng Fan8, Xian-De Liu9, Eric Jemenez10, Ling Xie11, Xian Chen11, Xiaolei Yan11, Rui Tian Yang12,13, Patrick Tan14, Xiaoguan Zhang15, Mingjie Li16, Carter Lawrence17, Jie Fan18, Jiang Gong19, Xihuan Liu20, Lianxin Hu21, Jun Wang22, Chengqiong Liao23, KaiHong9, Gaile Zulu9, Joel S. Parker24, Jeffrey A. Attia25, Charles M. Perus26, William Y. Kim27, Marc W. Kleveland27, William G. Kaehlin Jr.28, Albert H. Baldwin29, Qing Zhang13,30

**Genome-wide Screening Identifies SFMBT1 as an Oncogenic Driver in Cancer with VHL Loss**

Xijuan Liu31, Jeremy M. Simon1,2,32, Haibiao Xie33, Lianxin Hu34, Jun Wang35, Giada Zurlo36, Cheng Fan8, Travis S. Ptcak1,37, Laura Herring38,9, Xianning Tan39, Mingjie Li1,9, Albert S. Baldwin1, William Y. Kim1, Tao Wu3, Marc W. Kirschner7, Kan Gong4, Qing Zhang13,9,10,41

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**Novel VHL substrate targets SFMBT1 and ZHX2 may be important prognostic predictors in patients with ccRCC**

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VHL substrate capture to identify novel VHL-dependent onco-proteins

In collaboration with Dr. Qing Zhang at UT Southwestern:

Lysate from HIF2-independent tumorgrafts → in vitro GST-VHL pull down → Mass Spectrometry to identify novel VHL binding factors → Validate novel VHL targets and identify mis-regulated molecular pathways

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