Identifying Novel Therapeutics for VHL Disease Downstream of a Unique VHL-AURKA-HDAC6 Signaling Axis

Ruhee Dere, Ph.D.
Assistant Professor
Baylor College of Medicine
4th October, 2018
13th International VHL Medical Symposium

VHL and the Primary Cilium

- VHL stabilizes microtubules of the mitotic spindle and the cilium
- VHL localizes to the primary cilium
- Loss of VHL results in loss of primary cilia
- VHL-deficient tumor tissue was reported to have a decreased frequency of ciliation as compared to the adjacent parenchymal tissue

VHL and the Primary Cilium

- VHL stabilizes microtubules of the mitotic spindle and the cilium
- VHL localizes to the primary cilium
- Loss of VHL results in loss of primary cilia
- VHL-deficient tumor tissue was reported to have a decreased frequency of ciliation as compared to the adjacent parenchymal tissue

AURKA — Non-Mitotic Role in Cilia Disassembly

- AURKA stabilizes microtubules of the mitotic spindle and the cilium
- AURKA localizes to the primary cilium
- Loss of AURKA results in loss of primary cilia
- AURKA-deficient tumor tissue was reported to have a decreased frequency of ciliation as compared to the adjacent parenchymal tissue

AURKA — Non-Mitotic Role in Cilia Disassembly

- AURKA stabilizes microtubules of the mitotic spindle and the cilium
- AURKA localizes to the primary cilium
- Loss of AURKA results in loss of primary cilia
- AURKA-deficient tumor tissue was reported to have a decreased frequency of ciliation as compared to the adjacent parenchymal tissue

VHL Directly Ubiquitinates AURKA

- In Vitro Ubiquitination Assay
- In Vivo Ubiquitination Assay

VHL Directly Ubiquitinates AURKA

- In Vitro Ubiquitination Assay
- In Vivo Ubiquitination Assay
VHL Regulates AURKA Protein Half-Life

VHL Mediates AURKA Ubiquitination Independent of Prolyl Hydroxilation

VHL Promotes AURKA Degradation to Regulate Ciliogenesis

Ongoing Efforts:
1. What is the signal on AURKA that is recognized by VHL?
2. Is there a genotype-phenotype correlation between pathogenic VHL mutants and their ability to regulate AURKA?

Primary Image Based High Throughput Screening (HTS) Assay

Chowdhury P. et al., under revision
Bexarotene as a Positive Regulator of the Primary Cilium

Chowdhury P. et al., under revision

Bexarotene is a FDA approved synthetic retinoid that binds and activates retinoid X receptors (RXRs).

Bexarotene as A Positive Regulator of the Primary Cilium in hTERT RPE-1 Cells

Chowdhury P. et al., under revision

Bexarotene Rescues Cilia By Regulating AURKA Expression

Chowdhury P. et al., under revision
**SUMMARY**

1. Developed a highly robust and reproducible HTS assay using a dual labelling strategy to identify small molecules that rescue the cilia defect in the setting of VHL-deficiency

2. Identified bexarotene, a synthetic retinoid as a bona fide positive regulator of the cillum

3. Bexarotene modulates the cillum via its regulation of AURKA expression

4. Bexarotene is efficacious in decreasing AURKA activity in a tumor xenograft model of RCC

**ACKNOWLEDGEMENTS**

**Baylor College of Medicine**
Pratim Chowdhury, M.S.
Menuka Karki, Ph.D.
Durgi Nand Tripathi, Ph.D.
Tiq Berry, B.S.
Cheryl L. Walker, Ph.D.
Mike Mancini, Ph.D.

**Vanderbilt University**
W. Kimryn Rathmell, M.D., Ph.D.

**Texas A&M Health Science Center, IBT**
Peter Davies, M.D.
Clifford Stephan, Ph.D.
Red Powell, Ph.D.
Yong Song Park, Ph.D.

**University of Debrecen, Hungary**
Ivan Uray, M.D., Ph.D.

**Funding**

VHL Alliance
Gilson Longenbaugh Foundation