New Treatment for Cancer and Metabolic Diseases: Vitamin D Receptor Coregulator Inhibitors

(OTT ID 1250)

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Shortfalls of current therapies for Cancer and Metabolic Disease

Problems/Unmet Needs:
• Leukemia (57.1%) estimated deaths 24,090
• Ovarian cancer (44.6%) estimated deaths 14,270
• Surgery not possible/difficult; radiation not applicable
• Current chemotherapy drugs are non-specific/toxic
• Poor quality of life outcomes/survival

Technological Solution:
• The inventor has discovered novel small molecules that can disrupt the interaction between the vitamin D receptor (VDR) and coregulator proteins that modulate VDR-mediated gene transcription
• Focus on a new tissue-selective cancer treatment
• Reprogramming the cancer cells to stop growing
• VDRCI are expected to be more effective and safer than current treatments with less side effects
• VDRCI are expected to be more metabolically stable than current secosteroid-based ligands enabling systemic treatments
• The inhibitors can be easily generated in a one-step synthesis
Market
- Ave Ca drug price - >$10,000/mo; $70,000-115,000 annually
- Avail mkt (ovarian Ca) – 30,000 patients x $100,000/an = $300MM
- Ovarian cancer diagnostics and treatment market is forecast to reach $35 billion in 2018 (BCC Research)
- The current market for nuclear receptor targeted drugs is estimated to be 10%-15% of the global pharmaceutical market of US $400 billion

Intellectual Property
- US Utility Patent application filed February 2014:
- Continue to aggressively pursue US and foreign patent protection

Partnering
- Looking for a development partner to:
  - Support pharmacokinetic and pharmacodynamic analysis for IND filing
  - License novel compounds
  - Conduct clinical trials for effective lead compounds
VDR Function

- VDR is a transcription factor in the nuclear receptor family
- VDR forms a heterodimer with the retinoid-X receptor and is activated by vitamin D analogs
- Coregulators can bind to the VDR heterodimer regulated by the vitamin D ligand to either activate or repress transcription of target genes
- **VDR-coregulator inhibitors** have the potential to cell-specifically inhibit the activation or repression of genes

TF = vitamin D receptor (VDR)

Compounds that inhibit the interaction between VDR and coactivators
Vitamin D Receptor Function

**Differentiation**
- Stem Cell
- Erythroid
- Structural Glycoprotein Osteoblast
- Neural Astrocyte Microrthio Glycosylated Osteocyte Photoreceptor
- Myogenesis Cardiomyocyte Smooth muscle
- Hematopoiesis B-cells Macrophages Teeth

**Proliferation**
- Mitotic Phase
- Cell division
- Cycle begins
- Cell attaches to substrate
- Cell cycle is driven by CDKs
- Cdk1, Cdk2, Cdk4, Cdk6

**Apoptosis**
- Final stage of apoptosis
- Apoptotic cell

**Cancer**
Disease Targets

New Compounds Developed

- Developed a compound 31B against ovarian cancer
- Developed a compound PS121912 against leukemia
- In vivo activity was demonstrated

Vitamin D-based treatments

- Limited systemic application because of high risk to cause hypercalcemia and hypercalciurea
- Limited tissue selectivity because of a general expression profile of VDR
- The majority of these drugs are used topically
31B to Treat Ovarian Cancer

Ovarian Cancer xenograft (10 mg/kg)

Control  31B (25μM)

0 Hours

24 Hours

Tumor Size (mm)

Days

Untreated (5)  Treated (5)

Vehicle-treated mice with xenograft tumors

31B-treated animals (10mg/kg, 3 times/week)
PS121912 to treat leukemia

Leukemia xenograft (1 mg/kg)

Tumor weight P = 0.026
Proliferation studies with PS121912 and 1,25(OH)$_2$D$_3$ in DU145, and HL60.

A) Anti-proliferation induced by PS191219 after 18 hours with different cancer cells;

B)/C) Long term anti-proliferation study in DU145 and HL60. Cell viability was determined using Cell Titer-Glo (Promega).

- The anti-proliferation effect of 1,25-(OH)$_2$D$_3$ was significantly amplified for all cancer cells in the presence of 0.5 μM PS121912 for HL60 and 2 μM for all other cell lines.
- 100% viability was confirmed at the same PS121912 concentrations in the absence of 1,25-(OH)$_2$D$_3$ over 6 days.
- The crucial influence of 1,25-(OH)$_2$D$_3$ in respect to cell viability is strong evidence that VDR is mediating the anti-proliferation effects of PS121912.
Regulation of cytochrome \( \text{P}_450 \) enzyme 24-hydroxylase

- CYP24A1 (24-Hydroxylase gene) is regulated by VDR
- 24-Hydroxylase regulates the function VDR through metabolic degradation of vitamin D ligands
- CYP24A1 is over-expressed in many cancers
- Cancer patients with elevated CYP24A1 levels have poor prognoses

Application of VDR-coregulator inhibitors as transcriptional regulators of CYP24A1 represents a novel strategy to fight cancer proliferation and differentiation

Methods: rt-PCR in HL60 cell after 18h treatments (20/100 nM 1,25(OH)\(_2\)D\(_3\) and 0.5/2 uM PS121912)
PS121912 Induces Apoptosis

Cancer cell lines were treated with PS121912 in a dose-dependent manner and caspase 3/7 activity was quantified using Apo-Glo after 18 hrs (left).

PS121912 activated caspase 3/7; HL60 were most sensitive.

HL-60 cells were treated for 4 days (right) with vehicle (1) or 1,25(OH)$_2$D$_3$ (20nM) and PS121912 (500nM) (2).

The antibody array showed down-regulation of apoptosis inhibitor XIAP, increase of Fas/APO1, decrease of HSP60, and increase of TNFR2.

Apoptosis Antibody Array
### Collaborative Projects

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Next Steps

1. Intensify the search for pharmaceutical partners to license IP

2. Pharmacokinetic analysis (how is the drug candidate distributed in vivo)

3. Pharmacodynamics analysis (discreet effects in vivo)

4. IND filing with commercial partner

Path A

Path B

1. Grant application (current pending R01)

2. In house pharmacokinetics/pharmacodynamics

3. Apply for SBIR funding and venture capital

4. IND filing at UWM
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