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COLLABORATION OPPORTUNITY
Small Molecules – Lead Generation
Disease focus: CANCER
March 2016

SVI ST VINCENT'S INSTITUTE MEDICAL RESEARCH

HUDSON INSTITUTE OF MEDICAL RESEARCH

Small molecule inhibitors of Liver Receptor Homolog-1 (LRH-1)

- **Validated target for small molecule-based cancer therapy**
- **Potent (<100nM), small drug-like molecules predicted to bind to the co-regulator interaction domain of LRH-1**
- **X-ray crystal structures and in silico docking models to guide medicinal chemistry**
- **biological assays in place**

THERAPEUTIC RATIONALE

LRH-1 (NR5A2) is a member of the nuclear receptor family of regulatory transcription factors, linked to multiple developmental pathways, including Hedgehog and Wnt/ -catenin signalilng. Aberrant activity of LRH-1 has been linked to different malignancies, including breast as well as pancreatic, gastric and colon cancer.

In breast cancer, LRH-1:has been shown to

- be over-expressed in breast cancer cells, including ER -positive and triple-negative cells
- be a key regulator of ER expression and ER target genes
- be expressed in adipose tissue and cancer-associated fibroblasts surrounding the tumor microenvironment where it controls cytochrome P450 aromatase expression (CYP19A1), the enzyme required for estrogen synthesis, thereby acting in a paracrine manner on neighboring tumor cells
- be a critical factor in the acquisition of the anti-estrogen resistance
- control proliferation of breast cancer cells by regulating CDKN1A gene expression; LRH-1 knockdown affects two- and three-dimensional cell proliferation of ER -positive and triple-negative cells
- be associated with poor prognosis; especially in patients with high LRH-1 and low CDKN1A expression

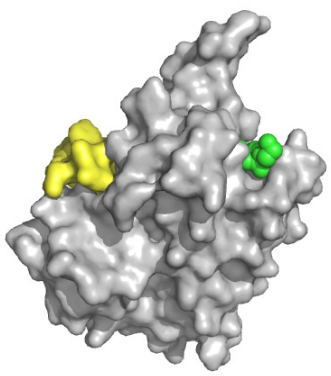
In pancreatic cancer, genome wide association studies have established a link between LRH-1 polymorphism and pancreatic cancer, and siRNA-mediated LRH-1 knockdown in pancreatic cancer cell lines results in impaired cellular proliferation, linked to reduced expression of c-Myc and the cyclins D1 and E1. Finally, LRH-1 has been implicated in intestinal tumour formation and studies have shown that inhibition of LRH-1 via shRNA in colon cancer cell lines leads to decreased CRC proliferation. Mutant alleles of the NR5A2 gene have been recently identified as potential markers for predicting the survival of gastric cancer patients.

THE OPPORTUNITY

Targeting LRH-1 from a drug discovery perspective remains a challenge due to the fact that its natural ligand appears to be a phospholipid, which binds to a extremely hydrophobic pocket and that LRH-1 is constitutively active, meaning regulation of its function mainly occurs through interactions with co-activators and co-repressors.

Using in-house X-ray crystal structures of LRH-1 and in silico docking, the research team, led by Prof Michael Parker at SVI in collaboration with Prof Colin Clyne (Hudson Institute of Medical Research), has identified a number of potent, small drug-like molecules that are predicted to bind to the co-regulator interaction domain of LRH-1. Analogues have been purchased and further validated using in vitro binding and biological assays, including a cell-based PII aromatase promoter-luciferase assay. To date, the most active compound has an IC50 of 80nM in the PII aromatase promoter-luciferase assay.

The lead series is amenable to medicinal chemistry and initial SAR analysis and docking model suggest that there are areas of the molecule that can be explored.



Three-dimensional structure of LRH-1, showing phospholipid (green) and co-regulator binding sites (yellow)

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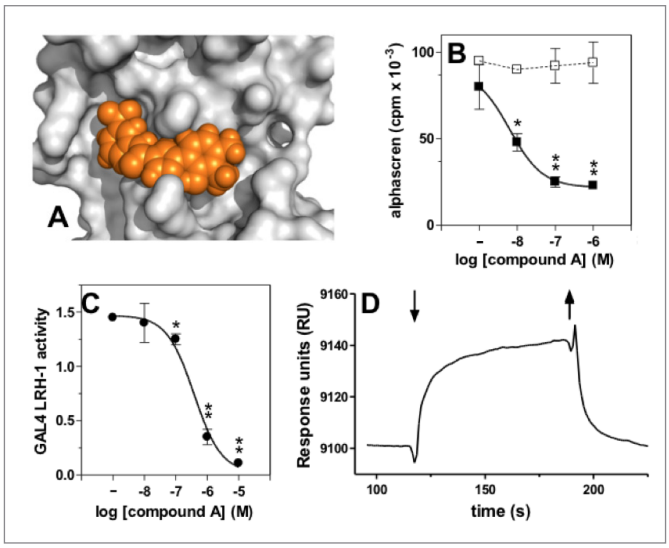

In silico identification of LRH-1 interacting compounds: (A) example of a drug-like compound (compound "A", orange) predicted to bind to the LRH-1 co-activator interaction domain (grey); (B) compound "A" inhibits LRH-1 co-regulator recruitment in alphascreen assay (■), whereas a non-binding control compound (□) is inactive; (C) compound "A" inhibits transcriptional activity of GAL4-LRH-1 transfected into HepG2 cells; (D) compound "A" (50μM) binds directly to LRH-1 as demonstrated by surface plasmon resonance using biotinylated LRH-1 protein immobilised on an SA sensor chip. */** = $p<0.05$ / 0.01 *vs* control

COMMERCIAL OPPORTUNITY

SVI is seeking a commercial partner interested in pursuing a co-development arrangement.

ABOUT US

St Vincent's Institute of Medical Research (SVI) is a world class medical research institute based in Melbourne, Australia. Diseases studied at SVI include type 1 diabetes, cancer, obesity and type 2 diabetes, heart disease, arthritis and osteoporosis, infectious disease and Alzheimer's disease.

Hudson Institute of Medical Research specialises in driving innovative, cutting-edge research towards improved prevention, diagnosis and treatments for our greatest health challenges. The Institute resulted from the 2014 merger of two of Australia's most trusted names in medical research, Monash Institute of Medical Research (MIMR) and Prince Henry's Institute (PHI).

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