CO

COLLABORATION OPPORTUNITY

Small Molecules – Hit to Lead Generation

Disease focus: CANCER

April 2018

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
- SVI-2506 shows a dose-response inhibition of breast cancer cell proliferation, irrespective of p53 mutational status
- X-ray crystal structures and in silico docking models to guide medicinal chemistry
- Selective 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/β-catenin signalling. Aberrant activity of LRH-1 (NR5A2) 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

- highly in ERα- positive and triple-negative breast cancer cells
- a key regulator of ERαexpression and ERαtarget genes
- highly expressed in cancer-associated fibroblasts in the tumor microenvironment where it controls cytochrome P450 aromatase expression (CYP19A1), the enzyme required for estrogen synthesis
- a critical factor in the acquisition of the anti-estrogen resistance
- controls proliferation of cancer cells by regulating CDKN1A gene expression
- LRH-1 knockdown reduces cell proliferation and spheroid growth of ERα-positive and triple negative breast cancer cells
- be associated with poor prognosis; especially in patients with high LRH-1 and low CDKN1A expression

In pancreatic cancer, genome-wide association studies establish a link between LRH-1 polymorphisms and pancreatic cancer.

siRNA-mediated LRH-1 knockdown in pancreatic cancer cells results in reduced cellular proliferation due to reduced expression of c-Myc and cyclins D1 and E1.

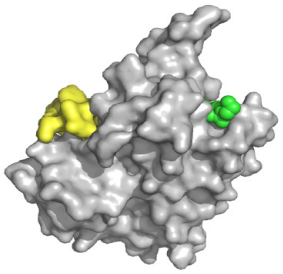
In gastrointestinal cancers, LRH-1 regulates intestinal tumour development mediated through its actions of cellular proliferation. Mutant alleles of the LRH-1 gene have been recently identified as potential markers for predicting the survival of gastric cancer patients

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 an extremely hydrophobic pocket.

Despite the discovery of phospholid binding, LRH-1 is constitutively active and regulation of its function mainly occurs through interactions with co-activator and co-repressor proteins.

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 and Dr Ashwini Chand (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 cell-based aromatase promoter-activity and proliferation assays.



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

To date, the most active compound has an IC50 of 80nM in the aromatase promoter-activity assay and inhibits proliferation of breast cancer cell lines irrespective of p53 mutational status.

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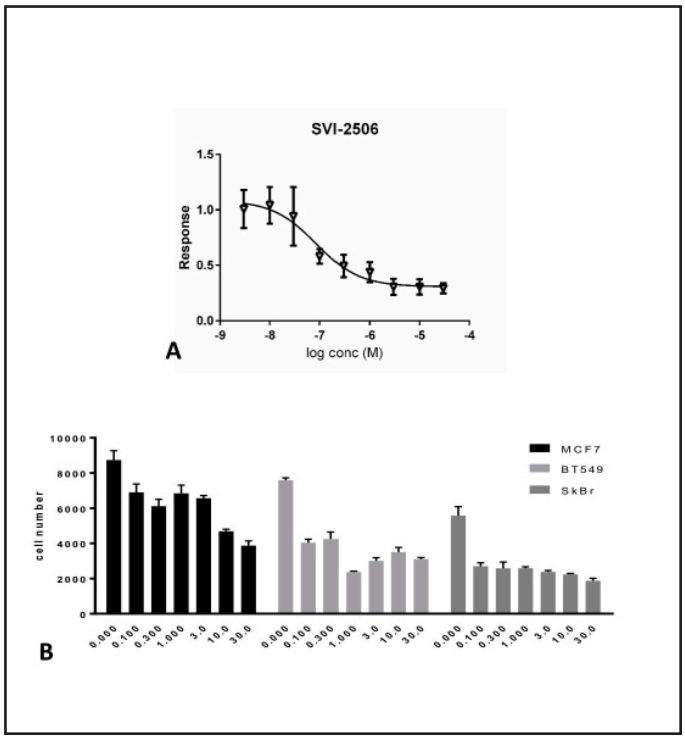

The lead series is amenable to medicinal chemistry and initial SAR analysis and docking model suggest that there are areas of the molecule that can be explored

Figure: Identification of LRH-1 interacting compounds.
A) PII aromatase promoter-luciferase cell based assay dose-response curve for Compound "A" which gives and IC50 of 80nM. Experiment was conducted in triplicate, in 3 independent experiments. Shown is the mean±SEM;
B) Cell proliferation assay data in estrogen-dependent (MCF7) and triple negative breast cancer cell lines (BT549 and SkBr). Compound SVI-2506 shows a dose-response reduction in cell number across all cell lines, irrespective of p53 mutational status

CAPABILITIES

Multidisciplinary team with capabilities in:

- structural biology (X-ray crystallography and NMR expertise)
- structure-based drug design, incl in silico screening and associated computational tools
- protein production, purification and biophysical characterisation (CD, BiaCore, DSF, DLS, ITC, MALLS, MST, SAXS)
- in vitro enzyme assays and kinetic studies
- cell-based functional screening, including transcriptional activity reporter assays, cell cycle and apoptosis analysis with flow cytometry, chromatin immunoprecipitation
- transgenic mouse in which human LRH-1 expression is inducible in mammary epithelial cells
- preclinical xenograft cancer models

COMMERCIAL OPPORTUNITY

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

ABOUT US

St Vincent's Institute of Medical Research and Hudson Institute of Medical Research are both world class medical research institutes based in Melbourne, Australia.

CONTACT

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