A novel means of jointly targeting IGF-1R and IR in cancer

- Exploits a common druggable site on the extracellular surface of the Type 1 insulin-like growth factor receptor (IGF-1R) and the insulin receptor (IR)
- Suitable for targeting by small molecules
- Offers advantages over antibody- and tyrosine kinase inhibitor-based strategies

Scientific team
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Background
The Type 1 insulin-like growth factor receptor (IGF-1R) plays a key role in cancer biology:
- Expression of IGF-1R is an absolute requirement for acquisition of the transformed phenotype
- IGF-1R over-expression is associated with a wide variety of cancers
- Elevated concentrations of circulating IGF-1 is associated with an increased risk of developing breast, colorectal and prostate cancer
- Activation of IGF-1R pathways appears to be an escape mechanism for therapies targeted at the epidermal growth factor receptor (EGFR)

The opportunity
Recent clinical trial outcomes lead to the conclusion that successful targeting of IGF-1R will require co-targeting with the insulin receptor (IR). In particular, anti-IGF-1R monoclonal antibodies have failed in multiple phase III trials. Structural biologists at the Walter and Eliza Hall Institute have discovered a novel, common and druggable site on the extracellular component of these receptors. As such, the finding offers a completely new strategy: co-targeting of receptors using small molecules.

The technology
IGF-1R and IR are closely related disulphide-linked homodimers. The primary IGF/insulin binding site lies on the so-called first leucine-rich repeat domain (L1) of the receptor. The α-chain (αCT) is absolutely required for ligand binding and the institute's scientists have shown that this segment has a helical conformation and interacts with the L1 surface (Figure 1). This tandem arrangement then forms the intact ligand binding site.

In a profound discovery, researchers at the Walter and Eliza Hall Institute have shown that this native peptide segment interacts only weakly with the L1 domain and can be displaced from it by certain non-native peptides that bind the L1 domain surface with higher affinity.

The nature of the interaction of these peptides with the L1 domain surface indicates that they, in turn, can be readily mimicked, for example, by small molecule helical peptide mimetics. The opportunity is thus to develop such compounds for co-targeting IGF-1R and IR in cancer.

Institute researchers have conducted a high-throughput screen against this site using the WEHI diverse library of approximately 114,000 drug-like molecules, and identified a number of lead-like small molecules with IC50 values less than 10 μM. Preliminary SAR studies are underway.

Applications
While the primary focus is on targeting IGF-1R and IR in cancer, small molecules based on this technology may have application in other disease states, including diabetes and Alzheimer's disease.

Intellectual property
The Walter and Eliza Hall Institute holds patents relating to the
The structure of the insulin receptor ectodomain (WO/2007/147213 and WO/2010/121288). The patent family describes the coordinates of the insulin receptor ectodomain and protects the use of these in the design of small molecules that target the αCT site.

Compound structures have not been publicly disclosed. An opportunity exists to generate novel composition of matter intellectual property.

Opportunity for partnership

The Walter and Eliza Hall Institute is seeking a partner to co-invest in the development of novel small molecule compounds that target the αCT site. All relevant technologies are in place to undertake this development: high-throughput screening, structural biology, hit-to-lead technologies, helical mimetic framework medicinal chemistry, cell based assays of IGF-1R and IR phosphorylation and tumour cell proliferation.

Key publications


Figure legend

Figure 1: The IGF-1R interaction. Interaction of the native C-terminal alpha-chain segment of IGF-1R (gold/green) with the L1 domain of IGF-1R (cyan/grey), based on the structure of the corresponding elements in the crystal structure of the human insulin receptor ectodomain.