155 IGF2-TRAP: High affinity receptors to sequester growth factors linked to cancer

Asset Overview

Product Type	Peptide
Indication	Oncology
Current Stage	Proof-of-Concept
Target (MoA)	Mutations in the IGF2R that increase affinity with IGF2. These mutated receptors act as traps for IGF2 (IGF2-TRAP), thus sequestering this overexpressed ligand.
Brief Description	Researchers at the University of Oxford have identified key mutations that increase the affinity of Insulin-like Growth Factor 2 Receptor (IGFR2) for its ligand, reducing hypoglycaemia and tumour volume.
Organization	Oxford University

Differentiation

□ Unmet Needs

- Researchers at the University of Oxford have investigated the IGF2 receptor (IGF2R) and have identified mutations in domain 11 of IGF2R that increase the affinity of IGF2 to its receptor. These mutated receptors have been shown to treat hypoglycaemia and reduce tumour volume.
- Insulin-like Growth Factor 2 (IGF2) encodes a member of the insulin family of polypeptide growth factors, which are involved in development and growth. Overexpression of this growth factor gene has been reported in a wide range of cancers and is associated with an increased risk of developing early childhood tumours. IGF2 activates MAPK and PI3K pathways by binding to the ubiquitously expressed IGF1R and isoform A of the Insulin Receptor (IR-A). Unlike IGF1R, which is responsible for active signalling, IGF2R acts as an IGF2 sink to prevent excess IGF2 signalling.
- Inhibition of IGF signalling has been an area of major focus by pharma, with many failures due to either receptor redundancy (between IGF1R and IR-A) or the IGF1 feedback loop. This causes the pituitary gland to produce more growth hormone, instructing the liver to produce more IGF1, generating a potential dose limiting toxicity of hyperglycaemia.

□ Innovation

- The Oxford researchers have identified a number of key mutations in the IGF2R that increase affinity with IGF2. These mutated receptors act as traps for IGF2 (IGF2- TRAP), thus sequestering this overexpressed ligand. The mutated IGF2R have been tested in vivo – IGF2-induced hypoglycaemia in mice was abolished in the presence of the IGF2-TRAP, and a reduction in tumour volume was observed in Ewing sarcoma cells xenograft models treated with IGF2-TRAP.
- The Oxford researchers have gone on to identify two PI3 kinase inhibitors that act synergistically with the IGF2-TRAP to reduce the dose requirements of these inhibitors and improve the long-term tumour-killing efficacy of IFG2-TRAP.

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Key Data

In vivo activity of ligand trap

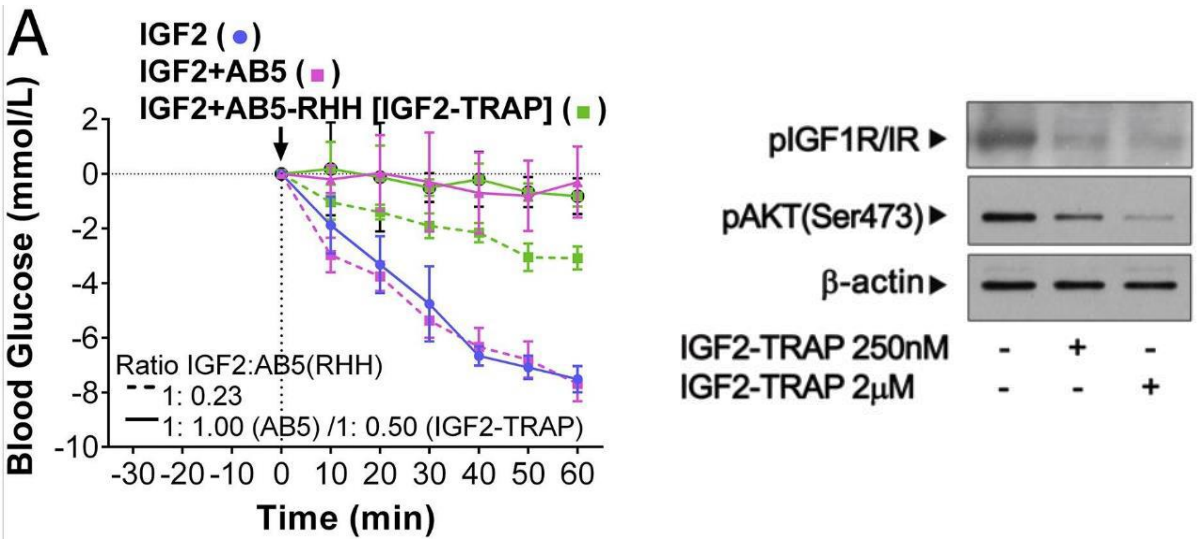
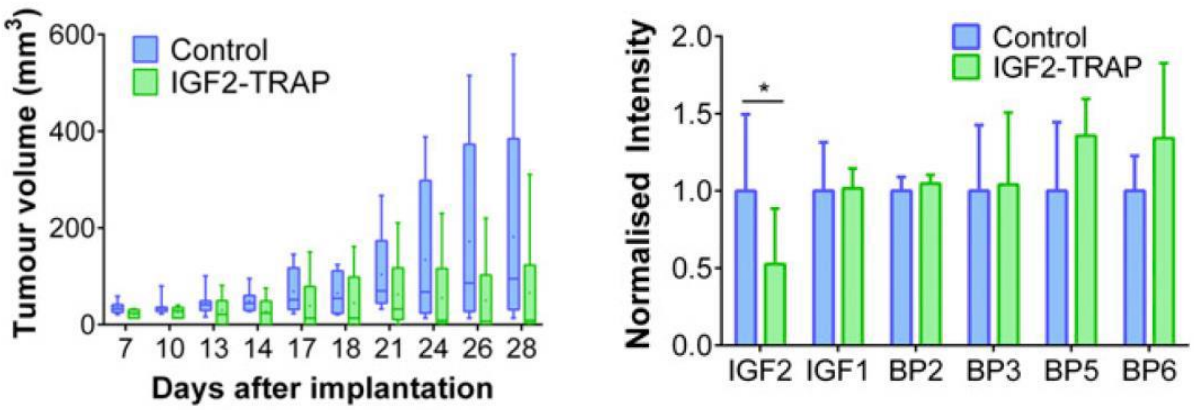


Figure 1. FC domain 11AB5 and domain11AB5-RHH ligand trap inhibit IGF2 signalling in vivo. Both ligands abrogate IGF21-67 induced hypoglycaemia in a mouse model(a), at various molar ratios. This effect is attributable to reduction in downstream activation of AKT signalling, as measured by a reduction in phosphorylation (b).

Effect on xenograft growth and serum levels



An autocrine-IGF21-67 dependent tumour model was developed using the Ewing sarcoma cell line (SKNMC). Retroviral-transformed SKNMC cells were injected into adult mice (which do not express IGF2), 24 hours after IgG2-Fc Domain11AB5-RHH was infused into the mice using an osmotic minipump. A modest effect on tumour volume was observed (Figure 2a) and circulating IGF21-67 was less evident in treated mice, without any alteration in either total serum IGF1, GH or IGFBP levels (Figure 2b).

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Key Data

Identifying synergistic compounds

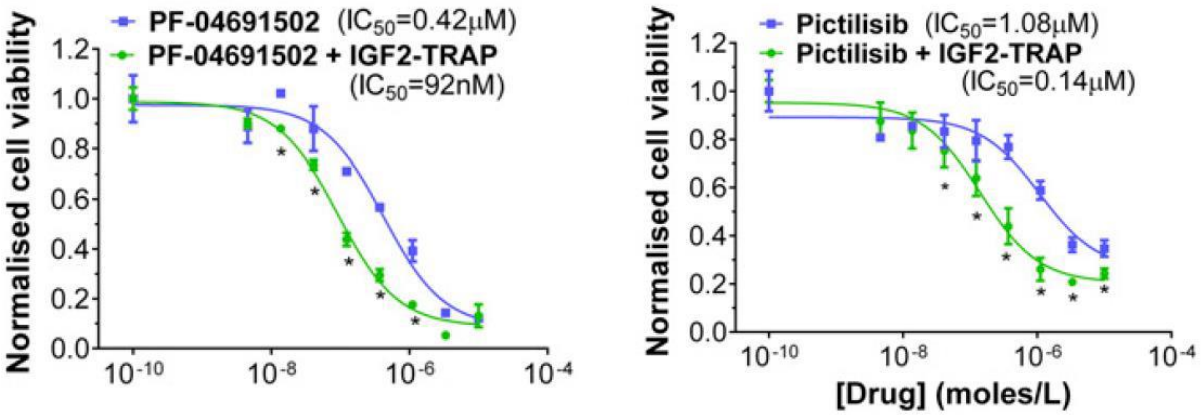

Figure 3. Validation dose-response curves for PI3 kinase inhibitors (PF-04691502 and Pictilisib) in the presence (green) or absence (blue) of IGF2-TRAP.IC50 values are shown.

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Intellectual Property

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Status	Registered
Country	US, EP

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