Novel antibodies directed to c-Met: A therapeutic target in cancer

A Monash University led research team have used a unique immunisation strategy to generate 3 distinct classes of monoclonal antibodies (mAbs) targeting the proto-oncogene receptor c-Met. These agents have potential utility as anti-cancer medicaments that directly inhibit c-Met signalling or target a tumour specific version of c-Met as vectors for the delivery of cytotoxic drug conjugates.

Benefits over existing treatments

- ‘First in Class’ tumour specific and ‘partial’ antagonist c-Met mAbs.
- Mechanisms of Action suitable for ADC and/or ADCC effector functions.
- Active in ligand independent c-Met tumours
- No receptor agonism – clinically derisked.

Background

The oncology market has shown rapid growth in recent years with the anti-neoplastic monoclonal antibodies (mAbs) segment primarily driving this expansion. Recently, antibody drug conjugates (ADC), that exploit the specificity of an antibody to deliver a toxic or radioactive agent to tumours have emerged as a drug class with significant potential. The recent FDA approval of Kadcyla (trastuzumab (anti-Her2) with a chemotherapy agent DM1) represents the first approval for this class of therapy.

Hepatocyte growth factor/scatter factor (HGF/SF) and its receptor c-Met, are involved in human cancer and are clinically validated therapeutic targets. mAbs targeting c-Met have been difficult to generate due to bivalent, intact anti-c-Met antibodies frequently activating the signalling pathway.

The opportunity

Using a novel immunisation strategy in mice, Monash researchers from the Oncogenic Signalling Laboratory, led by Associate Professor Terry Johns, have generated a panel of mAbs directed to c-Met with a range of novel properties.

These mAbs have been assessed biochemically for their influence on c-Met activation and function. The team created three classes of c-Met mAbs.

- Novel tumour specific antibodies that bind exclusively to the unprocessed form of c-Met, a form that is only found on the surface of cancer cells (and not normal cells), to induce its internalisation.
- Antibodies that directly activate c-Met as intact molecules, but block HGF (ligand) activation when produced in a monovalent (eg scFv, Fab) form. These antibodies have potential as anti-tumour agents by inhibiting HGF/c-Met axis signalling.
- Antibodies that bind a novel and defined epitope on c-Met and that inhibit signalling by stimulating c-Met internalisation, in the absence of receptor activation, and have anti-tumour activity in animal models. These antibodies should preferentially target cancer cells that overexpress the receptor and are thus susceptible to this mechanism of action. In addition, these ‘partial antagonist’ antibodies do not inhibit HGF binding and should have low level ‘on-target’ side effects. These mAbs are candidates for single agent and combination therapy applications, and display mechanisms of action consistent with utility as ADC vectors.

The Monash Laboratory has extensive experience in commercial mAb development. A/Prof Johns was a key leader in the development of mAb 806: a novel antibody directed to a tumour specific form of the EGFR that is currently in clinical trials with Abbvie Pharmaceuticals.

Key contact:

Dr Rocco Iannello
Director – Business Development
Monash Institute of Pharmaceutical Sciences
Monash University
rocco.iannello@monash.edu
Phone: +61 3 9903 9054
Mobile: +61 408 547 394