c-MET ANTIBODIES FOR CANCER THERAPY

OVERVIEW

• Novel high affinity antagonistic c-Met antibodies with in vitro (anti-migratory and proliferative) and in vivo efficacy.
• Cellular efficacy assays indicate best in class potential — compared to leading clinical competitor.
• Novel binding site may confer novel phenotypic attributes; epitope claims filed.
• Selective cancer expression may make this target of interest for an Antibody Drug Conjugate (ADC) approach.

THE OPPORTUNITY

c-Met is a well validated exciting oncology target which has attracted significant commercial interest in major cancers such as NSCLC, breast and colon cancer. We believe that this project represents an attractive opportunity for a company interested in this target to rapidly reach the forefront of this field. CRT is currently seeking a commercial partner interested in the licensing of the antibodies.

BACKGROUND

The Met receptor tyrosine kinase is aberrantly expressed in many cancers and is involved in transmitting both migratory and proliferative signals. In addition, autocrine expression of the ligand (HGF) is also found in many tumours and cancers driven by this mechanism should also be sensitive to Met inhibition. Extensive validation of the target exists in the literature and Met is accepted as an attractive anti-cancer target [1]. Clinical development of c-Met targeting antibodies has shown initial evidence of clinical efficacy and no serious toxicological concerns (e.g. MetMAb (5D5) by Genentech, now in Phase 3) [2]. Small molecule inhibitors often suffer from selectivity issues and this is one of the key reasons why antibody therapeutics against such receptor targets are attractive.

Dr Gherardi is an acknowledged expert on the Met system and was part of the first group to identify HGF, the Met receptor ligand [3]. Dr McCafferty is a leader in the development of phage display and was one of the founders of Cambridge Antibody Technology and the addition of his expertise in the areas of phage display and antibody engineering make this an impressive project team.
TECHNOLOGY

The aim of the project was to generate best in class function blocking antibodies against the Met receptor tyrosine kinase. Following affinity maturation efforts, lead antibodies have been identified and their activity and affinity profiles suggest that they represent an improvement over the existing commercial programmes. Our antibodies bind to a different site in c-Met than other commercial antibodies (see Figure 1 for comparison to 5D5) and show good function blocking activity in in vitro migration assays (see Table 1). Our antibody also shows potent anti-proliferative activity in HGF driven BxPC-3 pancreatic cancer cells and in vivo efficacy in a glioma tumour model (Figure 2).

7A2 antibody binds to IG1/IG2 stalk region

![Figure 1: Our antibody 7A2 does not compete with 5D5 for binding to c-Met. Biacore Assay shows binding of our parent antibody 7A2 and its derivatives only once the stalk region is present (contained within region 567-741, contains IG1 and IG2 regions). In contrast, 5D5 binds to the SEMA domain present in Met567 construct.](image)

7A2 is a potent inhibitor of HGF driven migration

<table>
<thead>
<tr>
<th>IC50 (scFv)</th>
<th>7A2</th>
<th>5D5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay 1</td>
<td>2.1</td>
<td>115.5</td>
</tr>
<tr>
<td>Assay 2</td>
<td>2.5</td>
<td>83.6</td>
</tr>
<tr>
<td>Mean (nM)</td>
<td>2.3</td>
<td>99.6</td>
</tr>
</tbody>
</table>

Table 1: Our antibody 7A2 has a more potent anti-migratory activity than 5D5. Table shows migration of SKOV-3 cells towards 300pM HGF. A scFv version of MetMab (5D5) as a control shows reduced inhibitory activity compared to our parent antibody.

INTELLECTUAL PROPERTY

PCT application was filed on 30th November 2012 (WO2013/079973). Application claims the parent antibody 7A2 and its affinity matured derivatives. Claims to the novel c-Met epitope identified in this project are also included.

COMMERCIAL OPPORTUNITY

An exclusive license is available to develop these high affinity antagonistic c-Met antibodies. Using this antibody in combination with other technologies, e.g. as part of an ADC approach may also be of interest.

REFERENCES

2. NCT01456325: A Study of Onartuzumab (MetMAb) in Combination With Tarceva (Erlotinib) in Patients With Met Diagnostic-Positive Non-Small Cell Lung Cancer Who Have Received Chemotherapy For Advanced or Metastatic Disease (MetLung) Genentech; Hoffmann-La Roche
3. Scatter factor is a fibroblast-derived modulator of epithelial cell motility., Stoker et al., Nature 1987

CONTACT

Angus Lauder, Business Development Executive
alauder@cancertechnology.com
+44 (0)20 3469 6300

www.cancertechnology.com