COMMERCIAL PARTNERSHIP OPPORTUNITY
Biological Therapeutics - *In Vivo* Proof of Principle
March 2018

CANCER RESEARCH UK

JAGGED1 MONOCLONAL ANTIBODY

- *In vivo* tumour growth inhibition shown with lead mAb
- Broad utility in oncology due to role of Jagged1 in multiple cell types
- A patent covering lead mAb and a novel epitope and GMP cell line available

COMMERCIAL OPPORTUNITY

The lead anti-Jagged1 monoclonal antibody (mAb) comes with a strong data package demonstrating high specificity and low pM affinity binding, and has been humanised and deimmunised by Lonza. There is strong *in vitro* and *in vivo* inhibitory action against Jagged1 and its downstream targets, with tumour killing efficacy demonstrated in 3D spheroids and xenograft models of triple-negative breast cancer. The antibody exhibits a strong safety profile, and performs to a similar degree as known pan-Notch γ-secretase inhibitors, but without any gastrointestinal toxicity, from which others in the field suffer. A patent covering a novel Jagged1 epitope has been granted in multiple territories.

Cancer Research UK is seeking a co-development partner or a licensee to take the mAb forward into clinical development.

THERAPEUTIC RATIONALE

The clinical relevance of angiogenesis has been firmly established as a rational target for cancer therapy[1,2]. Targeting tumour angiogenesis with anti-VEGF mAbs e.g. bevacizumab has been a successful strategy[3]. However many patients do not respond, or their response is temporary[1]. The Notch pathway has been implicated in vascular homeostasis and patterning, and in pathological angiogenesis within the tumour microenvironment. By endothelial specific deletion, Jagged1 has been shown to also have a Notch-independent role in vascular smooth muscle development. Combined with a role in pericytes, this suggests that Jagged1 has a crucial role in blood vessel maturation. Given that this is thought to be a factor behind the limit of efficacy of anti-VEGF therapy, this suggests a potential combination approach.

In addition, the Notch pathway is also implicated in cancer where it helps to maintain cancer stem cell populations, promote cell survival, inhibit apoptosis and metastasis, and drive cell proliferation[4]. However, pan-Notch inhibition with γ-secretase inhibitors results in gastrointestinal toxicity; while prolonged treatment with anti-Dll4 mAbs leads to the development of vascular/endothelial cell-based tumours. Other Notch ligands such as Dll1, Dll4 and Jagged2-mediated Notch signalling are required for the homeostasis of intestinal stem cells, whereas Jagged1 is not[5]. Thus, targeting Jagged1 activated signalling should be an effective mono and/or combination cancer therapy without adverse toxicity effects (the lab has authored a review of Jagged1 as a therapeutic target[6]).

SCIENTIFIC BACKGROUND

The Cancer Research UK Oxford Antibody Therapeutics Programme, led by Prof. Alison Banham, an expert in antibody production and characterisation, in conjunction with experts in Notch pathway biochemistry, Prof. Penny Handford and Prof. Susan Lea, and an academic clinician with expertise in targeting angiogenesis, Prof. Adrian Harris, have developed a series of novel anti-Jagged1 mAbs.

Notch ligands (Jagged1/2, Dll1/4) all have a Delta/Serrate/LAG-2 consensus sequence (DSL) domain, which is involved in their binding to the Notch receptors 1-4, with residues 199-207 of the Jagged1 DSL domain being critical for Notch receptor binding[6].

The lead mAb J1-65D specifically binds the DSL domain of human-Jagged1, but not Jagged2 or Dll4. Epitope mapping has shown that residue E228 is crucial for human specific binding, and therefore the antibody does not bind mouse Jagged1. 3D spheroid growth assays showed a strong correlation between Jagged1 expression and decreased spheroid growth after antibody treatment across a panel of breast cancer cell lines. The strongest spheroid growth decrease was seen in MDA-MB-231 cells (which express high levels of Jagged1), with no effect observed in MCF7 cells (which do not express Jagged1). The mechanism for inhibition of tumour spheroid growth was not via decreased proliferation (%Ki67^{+}cells), as antibody treatment was instead observed to reduce the frequency of MDA-MB-231 cancer stem cells and expression of the pro-tumorigenic cytokine IL6.

J1-65D effectively binds rat Jagged1 to block rat Notch signalling, enabling stromal targeting and toxicity studies to be performed in nude rat models. Strong repression of endogenous Notch signalling leads to a dramatic decrease in the relative expression of Notch target gene HES1 (Fig. 1), and a significant reduction in tumour volume in breast cancer MDA-MB-231 xenografts (Fig. 2). A similar result was seen with an U87 glioblastoma xenografts overexpressing Jagged1, in which the effect of overexpression in tumour growth was severely minimised when xenografts were treated with J1-65D (Fig. 3).

Read more overleaf

The lead antibody 65D has been successfully humanised and deimmunised by Lonza with no detrimental effect on specificity, but a log-fold increase in affinity (14pM). A GMP-grade cell line is available for production. Further xenograft experiments are ongoing with the higher affinity humanised antibody. The team have also recently developed a mouse model carrying humanised exon 4 of Jagged1, to enable testing of both tumour and stromal Jagged1 targeting.

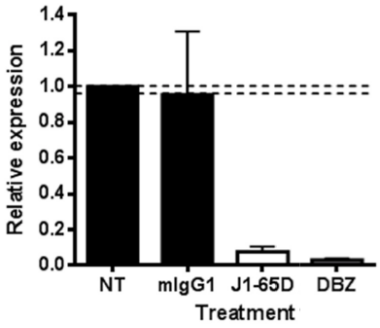

Figure 1. Hes1 expression in MDA-MB-231 breast cancer cells cultured with 10µg/ml J1-65D Jagged1 mAb. The γ-secretase inhibitor DBZ was used to represent pan-Notch inhibition (NT = no treatment; mIgG1 isotype control).

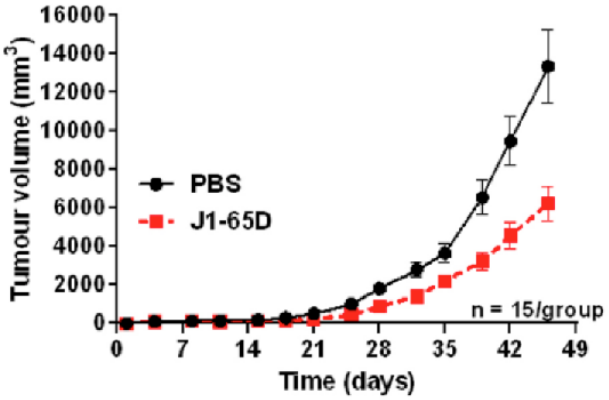

Figure 2. *In vivo* MDA-MB-231 rat xenograft data. 15 animals per group, treated with 20mg/kg J1-65D Jagged1 mAb injected one day after tumour grafting and then bi-weekly (P<0.05).

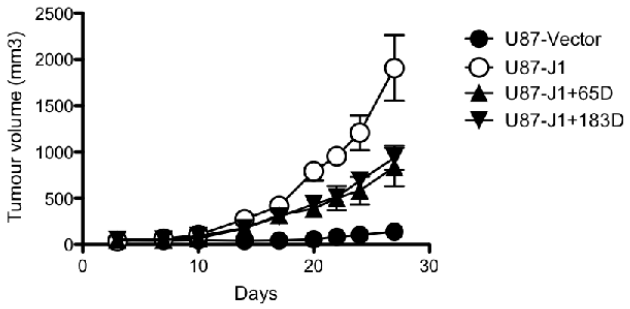

Figure 3. Jagged1 overexpression in glioblastoma U87 cells is rescued with 10mg/kg biweekly injection of J1-65D Jagged1 mAb injection. A related antibody J1-183D also has a similar effect on growth.

INTELLECTUAL PROPERTY

A PCT patent application WO2014111704 "Antibodies that bind to jagged 1" is granted in multiple territories, protecting the lead mAb based on an unique Jagged1 epitope sequence.

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