

CRT Licensing Opportunity



First-in-class antagonistic TACE antibody

- First ever reported antagonistic antibody to TACE (Adam17)
- Fully human IgG1 pre-clinical candidate with sub nM binding affinity
- *In-vivo* modulation of TACE substrates and efficacy demonstrated
- Broad utility in Oncology and Inflammatory disease indications

BIOLOGICAL THERAPEUTICS | Pre-Clinical Candidate

September 2011

Commercial Opportunity

The anti-TACE antibody comes with an extensive package of data demonstrating high affinity binding, potent inhibitory action against TACE *in-vitro* and *in-vivo*, a long *in-vivo* half-life and *in-vivo* efficacy in a cancer xenograft model. The antibody is a fully human IgG1 and represents a potential clinical candidate providing a unique opportunity for rapid development of this first-in-class antibody into the clinic in a short timescale.

In addition to utility in a range of common cancer types, there are clear links between TACE and a number of inflammatory indications such as rheumatoid arthritis and psoriasis where specific inhibition of TACE may be of value. CRT is seeking a licensee to take the antibody forward into clinical development.

In-vivo PK, PD Modulation and Efficacy

In-vivo pharmacokinetic studies in mice demonstrated that the antibody has an *in-vivo* half-life of around eight days. Initial *in-vivo* xenograft studies were conducted using the H630 colorectal cancer cell line which is known to be responsive to EGF pathway ligands. Once weekly treatment with the antibody caused a significant reduction in tumour volume indicating single agent activity (Fig 1a). Administration of the antibody was also shown to substantially reduce levels of the TACE substrate amphiregulin in the plasma of treated animals (Fig 1b). Further studies in colorectal, ovarian and prostate cancer xenografts are either underway or planned.

Fig 1a

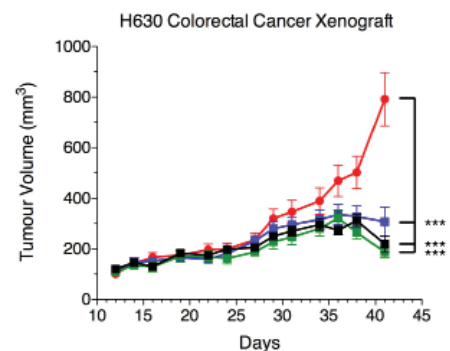


Fig 1b

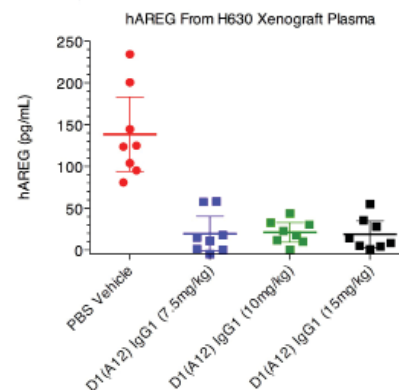


Fig 1a – H630 xenografts were established for 14 days prior to once weekly treatment with control (PBS alone – red) or the indicated dose of D1(A12) anti-TACE antibody (7.5 (blue), 10 (green) or 15mg/kg (black)) and tumour growth monitored over a period of six weeks. Each group consisted of 8 animals. Fig 1b – Levels of the TACE substrate protein amphiregulin in plasma of H630 treated tumours.

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Background and Therapeutic Rationale

TNF α converting enzyme (TACE) is a membrane bound metalloprotease also known as Adam17. TACE can function to cleave a number of membrane tethered substrates such as TNF α , EGF family growth factors (Amphiregulin, HB-EGF, TGF α , Heregulin) as well as certain receptors (IL-6R) and adhesion molecules (L-selectin, ICAM-1) (see Ref1 for review). In many instances genetic knockout studies indicate that TACE appears to be the primary metalloprotease responsible for cleavage of these substrates thereby regulating their levels. A number of TACE substrates have been linked to the development, growth, progression and therapeutic response of tumours and many of these substrates as well as TACE itself are upregulated in tumours suggesting that targeting TACE could be therapeutically useful (Ref 1).

Growth factor signalling via the EGF receptor family is a key driver of many cancers and this has led to the development of a number of inhibitors against EGFR. Recent studies have shown that in addition to targeting the EGF pathway directly, inhibition of TACE can lead to the downregulation of EGF family ligands and synergy with EGF inhibitor strategies (Refs 2, 3).

TACE activity has also been shown to play a key role in the response of cancer cells to chemotherapy. Treatment of colorectal cancer lines with chemotherapeutic agents leads to an increase in levels of TACE as well as the levels of several TACE substrates. Inhibition of TACE was shown to cause a synergistic increase in apoptosis in several colorectal lines and this effect was apparent in response to a range of different chemotherapies (Ref 4). As such, inhibition of TACE could be of value in combination with traditional chemotherapy interventions.

Rheumatoid Arthritis:

TNF α is one of the prime mediators of the inflammatory response and agents aimed at minimising TNF α activity have become successful treatments for arthritis (e.g. Enbrel™ anti-TNF α antibody). TACE is the key metalloprotease involved in cleaving pro-TNF α to release the soluble circulating pro-inflammatory cytokine TNF α . As such, targeting TACE activity has the potential to significantly reduce circulating levels of TNF α and hence be therapeutically useful for the treatment of a number of inflammatory conditions.

In addition to TNF α , there is growing evidence that soluble IL-6R (sIL-6R) in complex with IL-6 can drive inflammatory conditions including arthritis and a number of agents targeting the IL-6 signalling axis are in clinical development (Ref 5). A TACE inhibitor may be a highly effective anti-inflammatory agent on the basis of its ability to inhibit release of both TNF α and sIL-6R.

The Technology

Industry has devoted considerable effort to generating specific small molecule metalloprotease inhibitors but the high levels of homology in this target class have made this a real challenge. Early clinical studies using broad spectrum metalloprotease inhibitors are widely accepted to have been unsuccessful due to a lack of specificity. One of the key

advantages of monoclonal antibodies is that they are highly specific to the intended target and this combined with the long half-life of immunoglobulins in the circulation can make them ideal for delivering therapeutic inhibition of targets.

Although TACE is an attractive target for therapeutic antibody intervention, to date none of the antibodies reported against TACE have demonstrated antagonistic activity. The inventors undertook a novel antibody selection approach which included steps to identify antibodies which bound not only to the catalytic domain of TACE (which is well conserved) but also to the neighbouring cysteine rich domain. This was designed to increase the chances of obtaining both potent and selective antibodies against TACE. The approach was successful and generated a lead candidate antibody (clone D1(A12)) which has been reformatted into a fully human IgG1 framework (Ref 6). The antibody binds with very high affinity to TACE (0.4nM Kd) and is a highly effective inhibitor of TACE activity being five times more potent than the natural metalloprotease inhibitor protein N-TIMP3 in biochemical assays. The antibody was also effective against cellular TACE activity as demonstrated by the ability of the antibody to prevent the cleavage and release of a range of TACE substrates including amphiregulin, HB-EGF, TNF α and TGF α from cancer cell lines (see table 1 for summary of antibody properties).

Format	Fully human IgG1
Binding affinity to TACE (Kd)	0.4nM
Biochemical IC50 (isolated TACE protein at 1nM)	0.45nM
<i>In-vitro</i> cellular IC50 (PMA stimulated release of substrates by cancer lines)	Approx 5nM
Specificity	No binding/activity against the closely related Adam10
<i>In-vivo</i> half-life (in mouse)	8 days
<i>In-vivo</i> PD modulation	Robust inhibition of TACE substrates observed in several <i>in-vivo</i> expts.

Intellectual Property

A patent application has been filed protecting the antibody candidate along with the novel cross domain binding mode.

References

- 1) Murphy G. 2008. Nat. Rev. Cancer. 8 (12), p929-941
- 2) Zhou B.B. *et al* 2006. Cancer Cell 10, p39-50
- 3) Kenny P.A. 2007. Expert Opin Ther Targets 11, p1287-1298
- 4) Kyula J.N. 2010. Clin. Cancer Res. 16(13), p3378-3389
- 5) Jones S.A. 2011. J. Clin. Invest. 121(9), p3375-3383
- 6) Tape C.J. *et al*. 2011. PNAS. 108 (14), p5578-5583

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