

TUMOUR-SELECTIVE ADAM10 mAb

Novel mAbs that bind a unique epitope on a cancer-associated form of the ADAM10 metalloprotease. Inhibiting ADAM10 blocks activation of receptors linked to the 'stem cell niche' and depletes cancer stem cells resistant to chemotherapeutic treatments. The lead mAb is potentially useful as 'cancer specific' single agent, drug conjugate and/or combination therapy.

- **Proof of concept data shows single agent and combination efficacy *in vivo***
- **Potential use as naked and/or functionalised (ADC) therapeutic**
- **Targets 'stem cell niche' to sensitise chemoresistant tumours**

THE CHALLENGE

The function of oncogenic cell surface receptors and their ligands depends on shedding by the ADAM metalloproteases. ADAM10 in particular sheds ligands and receptors of the Notch, erbB, and Eph families, thereby activating receptor signaling.

Notch signaling is central in the maintenance of cancer stem cells (CSCs), is dependent on ADAM10, and is associated with drug resistance. Deregulated expression and activity of ADAM10 also correlates with poor prognosis in HER2 (erbB2)-positive breast cancer, where ADAM10-shedding of HER2 promotes signaling and anti-HER2 resistance, highlighting the potential of ADAM10 as a target for cancer therapy.

Higher levels of ADAM10 are found more frequently in high-grade tumours, is associated with adverse outcome in patients with the basal subtype of breast cancer, and is also associated with high grade serous ovarian cancer.

Metalloproteases have been tumour targets for over 20 years but previous clinical trials using inhibitors of matrix metalloproteases (MMPs) failed due to lack of specificity. Thus, there are no ADAM10 inhibitors currently in development. HER2 is the second most prominent target after checkpoint inhibitors (ASCO, 2017), with potential uses in a number of cancers aside from breast cancer including gastric, ovarian, prostate and brain cancer. Given that 60% of patients with Her2+ breast cancer develop resistance to Herceptin, agents that can prevent resistance will be of great interest.

The development of tumour-selective ADAM10 inhibitors offers an improved approach to treating aggressive cancers, such as Her2+ breast cancer, and preventing chemoresistance without the safety issues commonly associated with non-selective MMP inhibition.

THE TECHNOLOGY

The Monash University research team led by Dr. Peter Janes in collaboration with the Memorial Sloan Kettering Cancer Centre identified the substrate-binding domain of ADAM10 against which they generated antibodies, selecting a lead mAb (8C7).

8C7 preferentially binds active ADAM10 at a conformation-specific epitope prevalent in tumours but not in normal tissue. Preclinical studies showed that 8C7 inhibits ADAM10-mediated cleavage and activation of Notch and RTK signalling.^{1,2} In colorectal cancer (CRC) xenograft tumours, 8C7 preferentially targets tumours, especially CD133+ stem cells, and inhibits tumour growth as well as the expression of key ADAM10 targets. In combination with irinotecan (a topoisomerase I inhibitor used clinically for CRC) 8C7 prevents tumour relapse with a marked reduction in CD133+ stem cells in remaining tumours (Fig 1). Fully human mAb 8C7 is in development and further combination treatment studies are underway.

Intellectual property: National phase applications (CA, US, EPO, JN, NZ and AU) for PCT/AU2005/001917 on mAbs binding to ADAM10 and national phase applications (US, EPO and AU) for PCT/AU2015/050036 on anti-ADAM10 mAbs for cancer diagnosis and treatment.

THE OPPORTUNITY

Monash is now seeking a commercial partner to clinically develop and translate this opportunity.

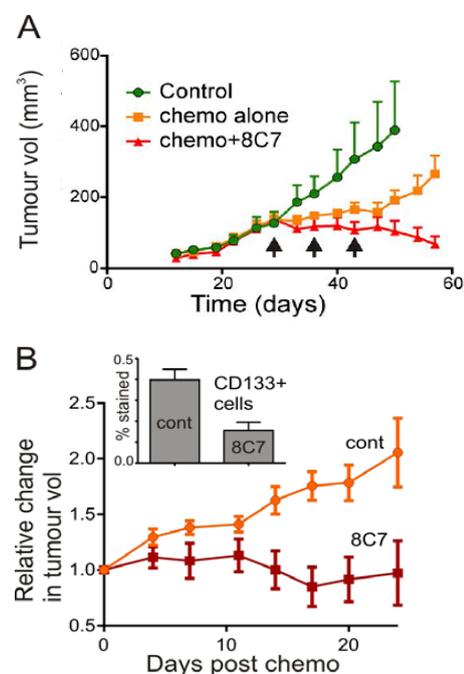


Figure 1: LIM1215 CRC xenografts treated with chemotherapy (irinotecan injections, arrows) alone or +/- mAb 8C7, as indicated. **A.** mean tumour volumes; **B.** relative change in tumour volume after cessation of irinotecan. Inset: CD133+ stem cells in remaining tumours recovered from mice treated as in A.²

References

1. Atapattu L *et al.*, (2016). An activated form of ADAM10 is tumor selective and regulates cancer stem-like cells and tumor growth. *JEM* 213(9), 1741-57.
2. Atapattu L *et al.*, (2012). Antibodies binding the ADAM10 substrate recognition domain inhibit Eph function. *J Cell Sci.* 125, 6084-93.

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