

# 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 development of tumour-selective ADAM17 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 MP 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.

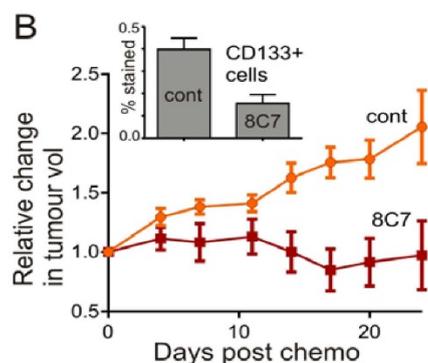
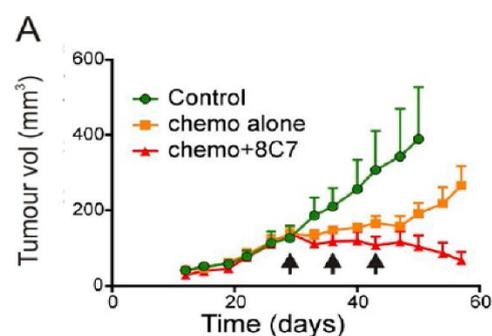
8C7 preferentially binds active ADAM10 at a conformation-specific epitope prevalent in tumours but not in normal tissue. Preclinical studies showed that 8C7 inhibits ADAM10-mediated cleavage and activation of Notch and RTK signalling.<sup>1,2</sup>

In colorectal cancer (CRC) xenograft tumors, 8C7 preferentially targets tumors, especially CD133+ stem cells, and inhibits tumor 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.

## THE OPPORTUNITY

Fully human mAb 8C7 is in development and further combination treatment studies are underway. Monash is now seeking a commercial partner to clinically develop and translate this opportunity.

**Intellectual property:** National phase applications filed (CA, US, EPO, JN, NZ and AU) from PCT/AU2005/001917 on Abs binding to ADAM10 and National phase applications filed (US, EPO and AU) from PCT/AU2015/050036 on anti-ADAM10 Abs for diagnosis and treatment of cancers.



## References

1. Atapattu L et al., (2012). Antibodies binding the ADAM10 substrate recognition domain inhibit Eph function. *J Cell Sci.* 125:6084-93.
2. 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.

## CONTACT US

**Monash Innovation**  
T: +61 3 9905 9910  
E: [innovation@monash.edu](mailto:innovation@monash.edu)  
[monash.edu/industry](http://monash.edu/industry)

## THE CHALLENGE

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

Notch signalling is central in 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 cancers, where ADAM10-shedding of HER2 promotes signalling and anti-HER2 resistance, highlighting the potential of ADAM10 as a target for cancer therapy.

Metalloproteases have been tumour targets for over 20 years but previous clinical trials using inhibitors of matrix metalloproteases have failed due to lack of specificity. Accordingly, there are no ADAM10 inhibitors presently in clinical development.

60% of patients with Her2+ breast cancer develop resistance to tyrosine kinase inhibitors such as Trastuzumab.

Higher levels of ADAM10 are found more frequently in high-grade vs low-grade tumours, in oestrogen receptor (ER)-negative compared with ER-positive tumours and are associated with adverse outcome in patients with the basal subtype of breast cancer, and is also associated with high grade serous ovarian cancer.