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 in vivo. The lead mAb is potentially useful as ‘cancer specific’ single agent, drug conjugate and/or combination therapy.

THE CHALLENGE
Cancers figure among the leading causes of morbidity and mortality worldwide, with ~14 million new cases and 8 million cancer related deaths annually. Despite clinically validated treatment and positive initial response, chemoresistance can develop. Subpopulations of cancer stem cells are not only capable of self-renewal and proliferation but are implicated in treatment resistance and relapse.

ADAM10 is a member of the A Disintegrin And Metalloprotease family. Over-expression is clinically associated with aberrant activity of its substrates, Eph/erbB receptor tyrosine kinase (RTK) ligands and Notch activities (which maintains cancer stem cells implicated in tumour initiation, angiogenesis, metastasis and chemoresistance). This over-expression correlates with poor prognosis in various cancers, including ER2(erbB2)+ breast and gastric cancer.

ADAM10 is a major determinant of HER2 shedding, leading to its activity. Combining Herceptin and ADAM10 inhibition reduces proliferation of erbB2 overexpressing cells.

ADAM10 inhibition provides a novel therapeutic approach to target breast and other cancers with active HER2 signalling and notch-dependent drug resistance.

Previous clinical trials using inhibitors of matrix metalloproteases (MMPs) failed due to lack of specificity. No ADAM10 inhibitors are presently in clinical development.

These data suggest a strong clinical need for the development and translation of specific ADAM10 inhibitors as single agent or combination medicaments for drug-resistant and HER2-positive cancers.

THE TECHNOLOGY
Monash University and Memorial Sloan Kettering researchers identified the substrate-binding domain of ADAM10 against which they generated antibodies, selecting a lead mAb (8C7).

mAb 8C7 binds ADAM10 with high affinity at a conformation-specific epitope prevalent in tumours but not in normal tissue, correlating with high protease activity. mAb 8C7 specifically inhibits ADAM10-mediated proteolysis – including cleavage of RTK ligands from cell surfaces – and thus blocks RTK function.1

mAb 8C7 inhibits Notch signalling and tumour growth and vascularisation, and increases apoptosis in colorectal cancer. It also targets CD133+ tumour stem cells adjacent to vessels with active notch signalling.

Administered in combination with irinotecan (a topoisomerase I inhibitor used clinically for CRC) mAb 8C7 prevents tumour recovery post chemotherapy, with a marked reduction in CD133+ stem cells in remaining tumours.


THE OPPORTUNITY
Humanisation of 8C7 is underway, with functional evaluation in additional tumour models. 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 +/- 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.

Reference

KEY CONTACT
Dr Kathy Nielsen
Senior Commercialisation Manager
Monash Innovation
T: +61 3 9905 5918
E: katherine.nielsen@monash.edu