Monash University and Memorial Sloan Kettering researchers have developed novel monoclonal antibodies that bind a unique epitope on a cancer associated form of the ADAM10 metalloprotease. The lead mAb (8C7) binds an active conformation of ADAM10 to inhibit its enzymatic function, and the subsequent release/activation of various ADAM10 cell surface substrate proteins essential for oncogenic development. Further, ADAM10 inhibition blocks activation of receptors linked to the ‘stem cell niche’ and depletes cancer stem cells resistant to chemotherapeutic treatments in vivo. mAb 8C7 is potentially useful as ‘cancer specific’ single agent, ADC vector and/or combination therapy medicament.

Summary of Opportunity:
- Novel monoclonal antibodies specifically binding and inhibiting a unique cancer specific form of the ADAM10 protease.
- In vivo PoC data shows single agent and combination efficacy.
- Potential use as naked and/or functionalised (ADC) therapeutic anti-cancer agents
- Targets ‘stem cell niche’ to sensitise tumours resistant to chemotherapeutics.

Background
The ADAM (‘A Disintegrin And Metalloprotease) family are cell surface proteins with a unique structure possessing both adhesion and protease domains. They function primarily on membrane bound proteins to release and activate/alter function primarily on membrane bound proteins.

ADAM10 is an essential member of this transmembrane metalloprotease family. Its substrates include Eph and erbB receptor tyrosine kinase (RTK) ligands, adhesion molecules (E-cad, NCAM), erbB RTKs, and Notch receptors and ligands. In cancer, Notch activity maintains cancer stem cells, implicated in tumour initiation, angiogenesis, metastasis and chemoresistance.

ADAM10 over-expression is clinically associated with aberrant Eph/erbB RTK and Notch activities, and correlates with poor prognosis in various indications (melanoma, colon, prostate, ovarian, lung, pancreatic cancer) including HER2(erbB2)+ breast and gastric cancer.

ADAM10 is a major determinant of HER2 shedding, leading to its constitutive activity. High ADAM10 expression correlates with shed erbB2 levels in breast cancer patients with resistance to herceptin (2, 3), and combination of herceptin and ADAM10 inhibition reduces proliferation of erbB2 overexpressing cells (4).

Thus ADAM10 inhibition provides a novel therapeutic approach to target breast and other cancers with active HER2 signalling, as well as notch-dependent drug resistance. Previous clinical trials using inhibitors targeting the active site of matrix metalloproteases (MMPs) failed due to lack of specificity, owing to conservation of this binding site across ADAMs/MMPs. No specific ADAM10 inhibitors are presently in clinical development.

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

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

As a single agent, mAb 8C7 inhibits Notch signalling and tumour growth and vascularisation, and increases apoptosis in a colorectal cancer (CRC) xenograft model. Further, it targets CD133+ tumour stem cells adjacent to vessels and with active notch signalling. Administrated in combination with irinotecan – a topoisomerase I inhibitor used clinically for cancer therapy – mAb 8C7 prevents tumour recovery post chemo, with a marked reduction in CD133+ stem cells in remaining tumours.

Humanisation of 8C7 is underway with trials in patients with metastatic breast cancer. Clinical development shows efficacy in breast cancers resistant to trastuzumab and other HER2+ indications.

Figure 1. LM1215 CRC xenograft treated with irinotecan, then +/- 8C7, as indicated. A. tumor volumes. B. change in tumor volume after irinotecan ceased. Inset, CD133+ stem cells in remaining tumors.


Key Contact
Dr Kathy Nielsen
Senior Commercialisation Manager
Monash Innovation
E: katherine.nielsen@monash.edu
T: +61 3 9905 6836
Patents: US 7,960,513 & US 61/935552