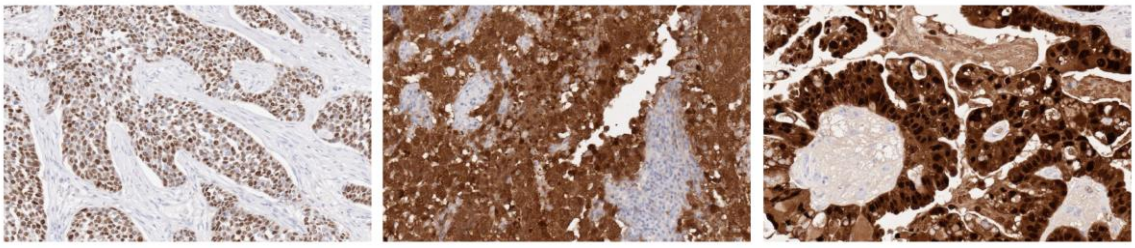
The interaction of metastasis-associated MAGE-A proteins with components of the p53 tumour suppressor network as novel anti-cancer therapeutic targets

Dr David Meek, University of Dundee
Dr Chandra Verma, A-STAR

The MAGE-A family comprises a group of highly related proteins that are expressed physiologically mainly in germ cells. However, these proteins are widely expressed in a range of human cancers where they are associated with malignancy. They can also drive metastasis in xenograft models. We are investigating how MAGE-A proteins inhibit the function of the p53 tumour suppressor and have recently established the principle that silencing MAGE-A expression is sufficient to reactivate p53-dependent apoptosis without the need to use genotoxic drugs. We are keen to exploit the MAGE-A/p53 interaction as a novel therapeutic target that would permit re-activation of the p53 response in MAGE-A-expressing cancer cells, leading to selective death of the cancer cells. In addition to interacting with p53 directly, MAGE-A also selectively blocks the turnover of the p53 inhibitor, MDM4, leading to increased p53 inhibition. Furthermore, MAGE-A can recruit modifying enzymes such as HDAC3 to deacetylate (inactivate) p53. MAGE-A proteins can therefore down-regulate p53 function by regulating specific biochemical functions in a coordinated and cooperative manner.

The aims of the project are to: (1) use parallel and complementary approaches of molecular modelling and molecular biology to characterise the sites/residues in MAGE-A that mediate association with p53 and its key regulators; (2) use mutagenesis to confirm the identity of the interacting amino acids and determine whether their substitution eliminates the ability of MAGE-A to inhibit p53-mediated cell death; (3) use molecular modelling to design and develop stapled peptides and/or small molecules that can be tested as potential inhibitors of the MAGE-A interactions; and (4) test key candidate peptides or small molecules for their ability to inhibit the p53 pathway. This innovative approach to disrupting MAGE-A interactions offers enormous potential as a novel therapeutic strategy. Moreover, since MAGE-A proteins are not expressed in healthy somatic cells, such an approach is likely to minimise potential side effects.

This study will generate an important new class of inhibitors with the potential to play a major role in cancer therapy.



Detection of MAGE-A proteins by immunohistochemistry in three independent breast cancers