TUMOUR-SPECIFIC MUC1 ANTIBODIES

• Tumour targeted antibodies for therapeutic applications
• Distinct advantages and improved affinity over existing MUC1 antibodies
• Improved specificity for tumour versus normal cells demonstrated in a range of human tissue samples

THE OPPORTUNITY
MUC1 is a transmembrane mucin family protein consisting of highly conserved 20 amino acid repeats (HGVTSA.PDTRPAGSTAPP.A) decorated with a dense O-linked glycosylation pattern. MUC1 is highly expressed in an underglycosylated form in multiple tumour types of epithelial origin, including over 90% of breast cancers. The glycosylation changes expose new peptide epitopes and oligosaccharides, making MUC1 an attractive target for antibody and vaccine approaches that exploit the tumour-specific epitopes created.

5E5 antibody
Two anti-MUC1 antibodies (5E5 and 2D9) have been developed and characterised in the laboratories of Dr Henrik Clausen (Faculty of Health Sciences, University of Copenhagen) and Prof Joyce Taylor-Papadimitriou and Prof Joy Burchell (Cancer Research UK Breast Cancer Biology Group, Guy’s Hospital, London). The antibodies bind to a novel glyco-peptide epitope and demonstrate superior selectivity for tumour versus normal tissues. A patent has been filed claiming the antibodies and their epitope, which may have utility in therapeutic antibody and vaccine approaches respectively.

MUC1 antibodies SM3, HMFG-1 and HMFG-2
Several antibodies have been raised against the target MUC1, besides 5E5 and 2D9, detecting slightly different epitopes. The antibody Stripped Mucin 3 (SM3) was derived by using a glycosylation –stripped mucin core protein, which was no longer able to bind Lectins.

SM3 staining resulted in staining of 91% of the tested breast cancer tissues, but showed little or no activity against normal breast tissue or benign mammary tumours [1].

The antibodies HMFG-1 and HMFG-2 were purified from human milk, recognising human Mucin. In studies identifying staining patterns, both antibodies were found to also bind the highly-unglycosylated and non–Lectin binding Mucin [1]. These antibodies were generated in the laboratories of Prof Joyce Taylor-Papadimitriou and Prof Joy Burchell.

THERAPEUTIC RATIONALE
MUC1 is over-expressed in the majority of breast cancers, and frequently in other tumour types including pancreas, ovary, lung and colon. Evidence suggests its over-expression plays a functional role in tumour progression. High MUC1 expression is correlated with tumour progression and poor prognosis in patients, whereas expression of anti-MUC1 antibodies in patients is a favourable indicator. In cell lines, and in animal models, expression of MUC1 has been shown to induce transformation. In addition, the intracellular domain of MUC1 is known to interact with, and influence, signalling molecules including members of the ErbB family of growth factor receptors as well as FGFR3 and oestrogen receptor alpha.

Continued overleaf.
Phase 2 clinical studies of the MUC1 peptide vaccine BLP25 (Stimuvax) have demonstrated that the use of vaccines mimicking cancer-specific MUC 1 epitopes can overcome immune tolerance against MUC1, and stimulate an antitumour response in non-small lung cell cancer patients, with promising efficacy observed in a subset of patients [reviewed in 2]. Antibody approaches are also demonstrating some success, with yttrium-labelled anti-MUC1 antibodies (IMMU-107), now in Phase 3 trial in pancreatic cancer patients.

THE TECHNOLOGY

MUC1 peptide vaccines have traditionally faced the challenge of overcoming immune tolerance to MUC1, since it is expressed as a self-antigen. It was demonstrated by the inventors that immunisation of mice with a chemoenzymatically synthesised MUC1 glycopeptide with full O-glycan occupancy and Tn/STn glycoforms elicited a strong antibody response and overcame immune tolerance in human MUC1 transgenic mice [3]. Two MAbs (SE5 and 2D9) with specificity similar to the elicited immune response were generated. Characterisation of the antibodies led to the identification of a new cancer-specific combined glycopeptide epitope defined by Tn-/STn-glycosylation at the GSTA position of the MUC1 tandem repeat [4]. It is interesting that patients immunised with fully Tn-glycosylated peptide vaccine also have autoantibodies in their serum to the same epitope, suggesting it may be immunodominant.

Notably, the vast majority of MUC1 antibodies reported to date are directed to the peptide backbone in the PDTR region of the repeat, considered to be immunodominant in wildtype mice, with a small number binding the peptide backbone at different epitopes. As such, SE5 and 2D9 have unique specificity. They also seem to offer distinct advantages over existing anti-MUC1 antibodies since in immunohistology studies they demonstrate superior selectivity for tumour versus normal tissue (Figure 1). Similar results were observed in other subtypes of breast cancer, as well as tumour tissue from ovary, pancreas, small intestine, bladder and cervix. These data suggest both that the SE5/2D9 antibodies, and the Tn/STn glycopeptides make prime candidates for new therapeutic approaches to MUC1-expressing tumours.

MUC1 is commonly shed into serum in tumour patients, and is commonly used as a marker of tumour burden. Importantly, it has been demonstrated that SE5 and 2D9 do not react with forms of MUC1 shed into serum, thus further improving their profile for tumour targeting over existing MUC1 antibodies. The antibody SM3 is highly specific to tumour-associated MUC1, making this antibody a good diagnostic candidate.

COMMERCIAL OPPORTUNITY

An exclusive, multi-territory, field-specific licence is available to the SE5/2D9 clones, and associated intellectual property for therapeutic use in the antibody or vaccine field.

Exclusive, field-specific licences and know how for the antibodies SM3 and HMFG-2 are available.

INTELLECTUAL PROPERTY

A patent application has been filed covering SE5 and 2D9 and the epitope recognised by these antibodies (WO2008/040362).

REFERENCES


Figure 1. SE5 strongly stains the majority of breast carcinoma simplex tissues samples (57 of 70; right panel) but shows little/no staining of normal breast tissue (0 of 6, left panel).

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