

# CRT Licensing Opportunity



## CEA Antibodies

- High affinity anti-CEA antibodies
- Use in diagnosis, imaging and treatment of cancer
- Phase I clinical studies - autologous T cell therapy, ADEPT, RIGS, clinical imaging
- Economical methods of protein production

BIOLOGICAL THERAPEUTICS | Clinical Phase I

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## Inventors

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## Application

Antibody-targeted cancer therapy e.g. radioimmunotherapy, systemic cytokine therapy, T cell therapy, gene therapy and antibody-directed enzyme prodrug therapy (ADEPT); diagnosis and imaging of cancer.

## The Technology

CEA is a 180 kDa tumour-associated antigen expressed in the developing foetus and a wide variety of tumours, including those of the GI tract (e.g. colon, rectum, pancreas, liver), breast, lung and prostate.

A high-affinity anti-CEA single chain Fv (scFv), MFE-23, has been developed by phage display technology (1). MFE-23 has exceptional specificity for CEA and appears to have no non-specific reactivity with human tissues. Furthermore, preclinical and clinical studies indicate that MFE-23 localisation to CEA-expressing tumours is not affected by CEA protein being shed into the circulation. A humanised MFE-23 variant (hMFE) has been engineered by using a resurfacing technique and higher-affinity hMFE variants (improved off-rates) generated by mutagenesis and screening yeast-surface-displayed libraries (2). One of these variants, sm3E, has a dissociation half-

time of several days and retains approximately 80% anti-CEA binding activity after incubation for 9 days under physiological conditions (37°C) (2). MFE antibodies have been successfully radiolabelled with <sup>123</sup>Iodine, <sup>125</sup>Iodine, <sup>131</sup>Iodine and <sup>99m</sup>Tc. Economical methods of producing recombinant MFE antibodies and MFE fusion proteins to clinical grade have been developed comprising expression in bacteria (3) or *pichia pastoris* (4) and purification by immobilised metal affinity chromatography (IMAC) by virtue of an engineered hexahistidine tag.

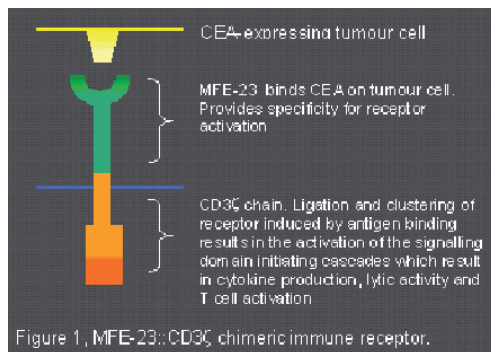
Extensive preclinical and clinical studies of the Inventors and others indicate that these antibodies are potentially useful imaging agents and have considerable therapeutic potential when linked to a suitable moiety.

## Targeted Cancer Therapy

Professor Robert Hawkins has successfully demonstrated the feasibility of a gene modified T cell therapy approach that comprises of transducing patient-derived T lymphocytes with a retroviral vector to express a chimeric immune receptor composed of MFE-23 fused to the T cell receptor CD3ζ chain (Figure 1). In these studies, MFE-23 has been shown to successfully direct the cytotoxic activity of the T cells specifically to CEA-expressing tumour cells (5). A Phase 1 clinical trial of this potential autologous T cell therapy is in progress.

MFE-23 has also been evaluated as the tumour targeting component of an ADEPT technology (antibody-enzyme fusion protein MFE-23:CPG2 and ZD2767P prodrug) and a Phase 1 clinical trial has recently been completed (led by Professor Richard Begent).

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Furthermore, *in vitro* and *in vivo* studies on an MFE-23::TNF $\alpha$  fusion protein suggest that this approach would provide an effective means of systemically administering targeted cancer therapy with cytokines such as TNF $\alpha$  (6). MFE-23 has also been shown to effectively target viruses to CEA-expressing tumours *in vivo* and thus potentially be of use to target gene therapy (7).

To improve the *in vivo* performance of MFE-23 in radioimmunotherapeutic applications, novel divalent humanised MFE-23 dimers (termed HSAbodies) have recently been engineered incorporating human serum albumin (HSA) as a backbone to genetically link two hMFE variant scFvs together (Figure 2) (8). *In vivo* studies using 125Iodine-radiolabelled HSAbodies have shown that these molecules combine MFE-23's favourable tumour localisation with the favourable pharmacokinetic properties (i.e. longer tumour retention times and systemic clearance) of larger antibody fragments. 131Iodine-radiolabelled HSAbodies have also been shown to have therapeutic effects *in vivo* in colorectal carcinoma xenografts (8). Furthermore, clearance of these HSAbodies can be controlled through engineering of Asn-linked glycosylation recognition sequences into the HSAbodies (8), which results in mannose glycosylation, accelerated systemic clearance and increased tumour: blood ratios. The GlycoHSAbodies may be particularly valuable agents for clinical imaging and RIGS.

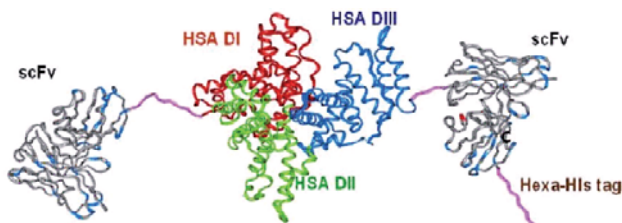


Figure 2. Proposed structure of HSAbodies. These humanised antibody molecules incorporate hMFE variant scFvs and HSA as a linker (e.g. above, whole HSA comprising HSA domains 1, 2 and 3 (DI, DII, DIII)).

## RadiolImmunoGuided Surgery (RIGS)

In RIGS, a pre-operative injection of a radiolabelled antibody is given intravenously and a hand-held gamma-detecting probe is used during surgery to detect radioactivity localised selectively in tumours. In a Phase I clinical trial, 125Iodine-labelled MFE-23-his was found to localise selectively at the site of primary colorectal cancer and metastases that could be detected by RIGS at intervals of 24-96 h between injection and scanning (3). The short interval between injection and operation and the lack of significant toxicity suggests that MFE-23-his is suitable for RIGS.

## Diagnosis and Clinical imaging

MFE-23 has potential uses in antibody-based *in vitro* diagnostic and prognostic applications, including ELISA (to measure CEA in serum). The Inventors have successfully used MFE-23 for the immunohistochemical analysis of CEA expression.

scFv antibody fragments have potential for clinical imaging because of their rapid tumour penetration and high tumour-to-blood ratios at early time points. 123Iodine-labelled MFE-23 has been successfully used for imaging CEA-expressing breast and bowel tumours in humans (9). 99mTc-labelled MFE-23 has also been shown to localise successfully to human colorectal tumours in mice (10).

## Intellectual Property

Granted US (5876691; 723288) patents and US divisional application.

## Commercial Opportunity

CRT is seeking to secure commercial partner(s) to develop these antibodies for therapeutic, imaging and/or diagnostic purposes. Collaborations and/or field-exclusive and non-exclusive licences are available.

## References

- 1 Chester KA *et al.*, 1994. *Lancet*. 343(8895):455-6
- 2 Graff CP *et al.* 2004. *Protein Eng. Des. Sel.* 17(4):293-304
- 3 Mayer A *et al* 2000. *Clin. Cancer Res.* 6(5):1711-9
- 4 Sharma SK *et al.* 2005. *Clin. Cancer Res.* 11:811-25
- 5 Sheen AJ *et al.* 2003. *Br. J. Cancer.* 88(7):1119-27
- 6 Cooke SP *et al.* 2002. *Bioconjug. Chem.* 13(1):7-15
- 7 Chowdhury S *et al.* 2004. *Mol. Ther.* 9(1):85-92
- 8 Huhlov A *et al.* British Association of Cancer Research 2004 Annual Meeting
- 9 Begent RH *et al.* 1996. *Nat. Med.* 2(9):979-84
- 10 Verhaar MJ *et al.* 1996. *J. Nuclear Med.* 37:868-872

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