

CRT Licensing Opportunity



DNA Fusion Vaccines

- Technology platform based on an antigen of choice fused to an immunoenhancing sequence derived from Fragment C of tetanus toxin
- Clinical trials in lymphoma, myeloma, prostate cancer and colorectal cancer confirm the safety and immunogenicity of these vaccines
- Induction of immunity against tumour-associated antigens seen in all clinical studies
- Strong patent portfolio covering protection of DNA fusion vaccine concept

BIOLOGICAL THERAPEUTICS | Clinical Phase II

OCTOBER 2010

Originating Institute

This programme originates from Prof Freda Stevenson and Prof Christian Ottensmeier at the University of Southampton, world leaders in the field of DNA vaccines, who can provide invaluable expertise on the technology and its clinical application.

The Technology

Prof Freda Stevenson has developed therapeutic DNA fusion gene vaccines encoding tumour antigens fused to an immunoenhancing sequence, which significantly promotes the immune response to the DNA vaccine (1). These vaccines can be designed to activate antibody and/or T cell responses, providing focused immune attack on selected antigens. Immunoenhancing sequences incorporated into the vaccines include Fragment C of tetanus toxin (FrC) or domain 1 of Fragment C (pDOM, see Figure 1).

The key to bypassing immune tolerance and activating high levels of anti-tumour antibody or cytotoxic T lymphocytes (CTLs) lies in inducing CD4⁺ T cell help. Incorporation of sequences derived from FrC provides for the engagement of T helper cells from a large anti-microbial repertoire to help immune responses against the tumour antigen.

Research initially focused on the development of patient-specific vaccines using idiotypic determinants found on B cell malignancies. The vaccines were designed to induce high levels of anti-idiotypic antibody by fusing idiotypic determinants expressed as single chain Fv to FrC. For solid

tumours, vaccination is commonly aimed at inducing CTLs that are able to kill target cells directly. Fusion of MHC class I binding epitopes to a single domain of FrC, pDOM, induced substantial levels of protective epitope-specific CTLs supported by CD4⁺ T cells activated from the large anti-FrC repertoire. Using a single domain of FrC significantly decreased the potential for peptide competition. Both approaches can be applied to any antigen and have been tested in the clinic. Phase II testing is currently ongoing.

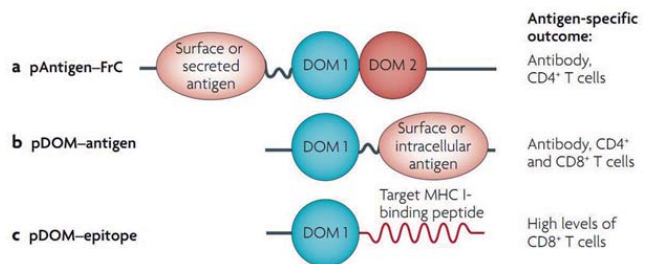


Figure 1: DNA fusion vaccine design based on help from Fragment C. Fragment C of tetanus toxin contains two linked domains (DOM1 and DOM2). **a** For the induction of antibody and/or CD4⁺ T cell responses against tumour, full-length Fragment C is fused to the 3' end of the tumour antigen sequence. **b** For induction of CD8⁺ T cells against tumour, DOM2, which contains potentially competitive MHC I-binding peptides, is removed. DOM1, containing a known MHC II-binding peptide, is retained and fused to the 5' (or 3') position of the tumour antigen sequence. **c** For induction of high levels of CD8⁺ T cells against single tumour peptides, DOM1 is fused to the 5' position of the peptide-encoding sequence.

CRT Licensing Opportunity

Preclinical Data

In mouse models of lymphoma and myeloma, fusion of idiotypic determinants expressed as single chain Fv to FrC induced high levels of anti-idiotypic antibody and protective immunity (2,3). Fusion of the poorly immunogenic variable region sequences to FrC converted these sequences to potent immunogens.

Linking domain 1 of FrC of tetanus toxin (pDOM) to a peptide sequence from a tumour antigen was shown to break tolerance and allowed induction of epitope-specific CD8+ T cell responses, thereby controlling the development of tumours in murine models (4). These vaccines were also able to break tolerance against persistent antigens and to induce durable T cell memory (5,6).

Clinical Data

Targeting the Tumour Idiotype by Vaccination

Phase I/II testing of patient-specific anti-idiotypic vaccines is complete in patients with follicular lymphoma (LIFTT study) and ongoing in patients with multiple myeloma (MMIFTT study). In the LIFTT Phase I/II multi-centre dose-escalation study, a separate vaccine was produced for each patient after identification of the variable region gene sequences from a tumour biopsy. The vaccine was safe, and patients showed antibody and/or CD4+ T cell responses against FrC and responses to the tumour-specific idiotypic antigen. The MMIFTT study is a single-dose single-centre study with toxicity and immune responses as the key clinical endpoints. 15 patients were recruited; immunological evaluation is ongoing.

ACVA DNA Vaccination Study

A two-arm, single-dose Phase I/II study to examine the safety and immunogenicity of the DNA fusion vaccine based on the pDOM design (see Figure 1) was conducted in CEA-expressing malignancies (bowel, lung, breast). The target peptide was the HLA A2 binding sequence CAP-1 (CEA605-613). 15 patients with measurable disease and 12 patients without radiological evidence of disease, but at risk of progression, were recruited. Humoral and cellular responses to the vaccine were induced in both arms. FrC and CAP-1 cellular responses and CAP-1-specific CD8+ T cells were detected. High incidence of gastrointestinal adverse events in vaccinated patients coincided with increased time to clinical and radiological disease progression, longer on-study follow-up, decreases in, or stable levels of, CEA, and longer duration of positive anti-DOM cellular responses.

PSMA DNA Vaccination Study

A Phase I/II study employing the pDOM-epitope design encoding PSMA27 was conducted as an open-label, two-arm, dose escalation study in HLA A2+ patients with recurrent prostate cancer. The vaccine was shown to be safe and induced significant, robust and reproducible humoral and

cellular immune responses. CD8+ T cell responses against the PSMA peptide were induced in 65% of patients with long persistence of T cell responses of up to 18 months. In the vaccinated patient group, time to next treatment was longer and fewer patients died after a follow-up of 5 years than in the unvaccinated group. Delivery of the DNA vaccine by electroporation was shown to increase the potency of the vaccine significantly.

WT1 DNA Vaccination Study

An open-label, single-dose randomised Phase II study in two patient groups (CML and AML) has just started. HLA A2+ patients will be vaccinated with two pDOM-based DNA vaccines targeting different WT1-derived epitopes; HLA A2- patients will be followed up with monthly monitoring only. 37 patients will be recruited in each treatment group. CML patients will be recruited first and an interim analysis will occur after the first 12 patients; if one or more molecular responders are observed at 6 months, an additional 25 patients will be recruited into this group. Two well-established molecular markers, BCR-ABL and WT1, will be employed to quantify the clinical efficacy of vaccination.

Intellectual Property

A portfolio of patents covering DNA fusion vaccines is available for licensing:

- WO9408008A1 (granted US): Improvements in or relating to immune response modification
- WO0179510A1 (granted US/EP, JP pending): Materials and methods relating to immune responses to fusion proteins

Commercial Opportunity

CRT is seeking a commercial partner to facilitate further development of this technology for the treatment of cancer and/or infectious diseases under an exclusive or non-exclusive licence or via a collaborative arrangement.

References

1. Rice et al. 2008. Nature Reviews Cancer 8(2):108-120.
2. Spellerberg et al. 1997. Journal of Immunology 159:1885-1992.
3. King et al. 1998. Nature Medicine 4:1281-1286.
4. Rice et al. 2001. Journal of Immunology 167:1558-1565.
5. Rice et al. 2006. Cancer Research 66:5436-5442.
6. Rice et al. 2004. Journal of Immunology 173:4492-4499.

Contact: Ruth Nebauer, rnebauer@CancerTechnology.com

Ph: +44 (0)203 469 6300