p53 TCR MIMIC MONOCLONAL ANTIBODY

- Well characterised target with applications in multiple oncology indications
- Antibody directs tumour cell killing via ADCC, ADCP and CDC
- Has ability to internalise, so is suitable for Antibody Drug Conjugate approaches
- Low toxicity and multiple tumour specific peptides recognised

COMMERCIAL OPPORTUNITY

We have a novel T-Cell Receptor mimic (TCRm) monoclonal antibody (mAb) recognising an HLA-A*0201-presented wild-type p53 T-cell epitope (p53<sup>65-73</sup>).

We have selectivity and specificity data for Complement Dependent Cytotoxicity (CDC) and Antibody Dependent Cellular Phagocytosis (ADCP). Crucially, the antibody can internalise, making it suitable for use in an Antibody Drug Conjugate (ADC) approach. We have biodistribution data showing strong localisation of the antibody to the tumour site, and xenograft efficacy data in both new and established tumours.

Cancer Research UK is seeking a co-development/licensing partner to take the antibody forward into clinical development and would be happy to provide more data under CDA. A recent publication from the originating laboratory details the experiments further (Li et al 2017).

THERAPEUTIC RATIONALE

Traditionally therapeutic antibodies do not have access to proteins that are absent from the cell surface. However, intracellular proteins are degraded by the proteasome, generating short peptides for MHC class I presentation on the cell surface, allowing access by CD8<sup>+</sup> cytotoxic T cells.

mAbs that can recognise peptides presented by MHC Class I molecules, and thus mimic the action of T-cell receptors, have shown great promise as potential therapeutic agents for cancer therapy. The major issues in the field have been around a) specificity: identifying a peptide that is only expressed on the surface of cancer cells, and b) potency: that enough peptide is presented on the surface for the antibodies to induce ADCC/CDC killing of the tumour cells, both issues we have addressed in this project.

Figure 1: Increasing concentrations (μg/ml) of the p53 TCRm T1-116C antibody engages immune effector functions to achieve target cell killing of the OCI-Ly8 B cell lymphoma cell line by mouse BMDM-mediated ADCP. Anti-CD20 mAb rituximab was used as a positive control.

The lead antibody has been developed against one of the most important tumour antigens, p53, which is mutated or dysregulated in multiple tumour types. Tumour cells often have higher copy numbers of wild-type p53, and therefore display more peptide-MHC class I complexes than normal cells, due to higher turnover and peptide processing of p53, which is often mutated and therefore truncated in tumour cells. Normal cells are characterised by low levels of p53, such that p53 vaccination clinical trials have had no effect on non-cancerous tissue, regardless of their therapeutic efficacy (Vermeij et al 2011). The epitope incorporates both the target peptide and elements of the HLA-A*0201 (HLA-A2), in which the peptide is presented. This HLA-A allele is the most prevalent in the general population, being carried by over 50% of Caucasians.
The lead antibody specifically recognises HLA-A2/p53 epitopes present on multiple cancer cell lines and primary tumour samples. Crucially, no staining was observed in either HLA-A2 negative and/or p53 negative cell lines, normal cell lines or human peripheral blood mononuclear cells (PMBC). Comprehensive amino acid replacements with the p53 peptide have precisely defined the epitope, and no toxicity has been observed in humanised HLA-A2 HHD transgenic mice. The antibody has high binding efficiency, with tested cancer cell lines binding 500-15,000 PE-labelled antibody molecules per cell. This endows the antibody (T1-116C isoform) with an ability to mediate immune effector mechanisms such as CDC, ADCC, and ADCP (Figure 1), and coupled with its ability to internalise, suggests that the antibody will recruit sufficient payload for an effective ADC therapeutic approach.

The antibody has been recombinantly expressed, and subsequently humanised and de-immunised by Lonza PLC (human IgG1). The antibody shows strong tumour specific localisation in mice bearing MDA-MB-231 breast cancer cell xenografts, with minimal prolonged concentrations in the heart, carotid arteries, or liver (Figure 2). Recombinant T1-116C antibody in the mlgG2a format significantly inhibited tumour growth in vivo (Figure 3a). As expected, no tumour inhibition was seen with the hlgG1 format, due to its lack of potency against murine FcyR. The T1-116C mlgG2a antibody was further tested in established MDA-MB-231 tumours, where treatment 14 days after cell engraftment significantly reduced further growth rates (Figure 3b). Intriguingly, the antibody has also been shown to recognise several other HLA-A*0201-presented tumour-specific peptides, including the Wilm’s tumour 1 (WT1) and GP100 antigens. This suggests that the antibody could have potential applications in a wide range of malignancies. Crucially, TCRm antibodies circumvent the needs of immune cell priming and maturation, and as such do not require a competent immune system. This approach will therefore be suitable for immunosuppressed patients or as the targeting agent on chimeric antigen receptor (CAR)-T cells.

**REFERENCES**


**PATIENT STRATIFICATION**

Multiple cancers have been linked to p53 dysregulation and could potentially represent target patient populations. Due to the requirement for patients to carry the correct HLA isotype, the most straightforward method of stratification could be to use the antibody as a ‘theranostic,’ whereby patients diagnosed as ‘binders’ on a simple FACS-based or IHC biopsy screen could then receive treatment.

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