p53 TCR MIMIC MONOCLONAL ANTIBODY

- Well characterised target in multiple oncology indications
- Ability to function via ADCC, CDC, or ADC
- Low potential toxicity

COMMERCIAL OPPORTUNITY

This opportunity has produced a lead T-Cell Receptor mimic (TCRm) monoclonal antibody (mAb) against an HLA-A*0201 presented peptide derived from the cancer target p53, that is mutated in 50% of human tumours and deregulated in many more. Currently we have selectivity and specificity data on the lead mAb, with positive preliminary data for Antibody Dependent Cell-mediated Cytotoxicity (ADCC), Complement Dependent Cytotoxicity (CDC), Antibody Dependent Cellular Phagocytosis (ADCP), as well as in vivo efficacy data in a mouse xenograft model. In addition the antibody is shown to internalise making it suitable for use in an Antibody Drug Conjugate (ADC) approach.

CRT 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.

THERAPEUTIC RATIONALE

Traditionally intracellular proteins are not seen as antibody targets because of their inherent position within the cell. However, there is an endogenous mechanism that the immune system uses to inspect the internal health of a cell. Intracellular proteins are degraded by the proteasome, these short peptides are transported (via TAP) into the endoplasmic reticulum, and loaded onto MHC class I proteins. MHC:Peptide complexes are then transported to the cell surface for presentation /inspection by CD8+ T cells (Figure 1).

mAbs that can recognise peptides presented on the surface by MHC class I molecules, and thus mimic T-cell receptors have long been hoped to be potential therapeutic agents for cancer therapy [1]. 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 (Figure 2).

Figure 1: diagram showing how internal proteins can be expressed on the surface of cells, from Yewdell, J.W., Reits, E., Neefjes, J., Making sense of mass destruction: quantitating MHC class I antigen presentation Nat Rev Immunol. 3(12):952-61 (2003). PMID:14647477

Figure 2: diagram showing comparison of CD8+ T-cells and TCR mimic mAbs

Read more overleaf
The Cancer Research UK Oxford Antibody Therapeutics Programme, led by Prof. Alison Banham, an expert in monoclonal antibody production and characterisation, is interested in developing a number of TCR mimic mAbs for cancer immunotherapy. Together with an experienced immunologist, Dr Demin Li, and experts in proteomics Prof Benedikt Kessler and Nicola Ternette the team are also using mass spectrometry to identify the most abundantly MHC class I-presented peptides derived from future target antigens. The most advanced antibody has been developed against one of the most important tumour antigens, p53, which is mutated or deregulated in multiple tumour types, and was identified as a top target in a National Cancer Institute cancer antigen prioritisation paper aiming to accelerate translational research [2]. The wild type p53 peptide selected was derived from the N-terminus of the protein, so that truncated forms of the p53 protein should also present the target epitope. There was already evidence in the scientific literature reporting the endogenous processing and presentation of the target epitope in cancer cells. Importantly although p53 vaccination clinical trials using this peptide failed due to lack of efficacy, they did not induce any damage to normal tissues in mice or patients. This is consistent with reports in the literature that that malignant cells exhibit increased presentation of p53 peptides on their cell surface. The target peptide is presented by HLA-A*0201 (HLA-A2), which is one of the most prevalent HLA-A alleles in Caucasians (50%), which will also comprise part of the epitope recognised by the antibody.

Multiple TCRm mAbs have been successfully generated. The lead antibody specifically recognises T2 cells pulsed with the target peptide. The lead antibody has been further tested and shows cell surface labelling of a number of HLA-A2+/p53+ cancer cell lines (from different tissue types). Staining of HLA-A2-negative and p53-negative cell lines has not been observed. No staining of peripheral blood mononuclear cells (PMBC) from 13/14 healthy HLA-A2+ donors was observed, weak labelling in one patient was accompanied by an abnormal expansion of granulocytes, suggesting that there may have been some abnormality.

The lead antibody has been cloned and sequenced. The p53 epitope has been further mapped to allow in silico prediction of potential cross-reactivity, which is currently being experimentally tested. It was then recombinantly expressed to generate purified antibodies with isotypes (mouse IgG2a and human IgG1) to allow for preliminary ADCC/ADCP/CDC assays, and for initial in vivo mouse xenograft models. In addition the human IgG1 isotype would be suitable for ADC testing. The initial ADCC/CDC/ADCP and xenograft experiments have all shown positive anti-cancer efficacy, and thus this opportunity has the ability to work as a therapeutic through multiple mechanisms (Figure 2). The antibody has also been humanised and de-immunised in silico by Lonza PLC.

REFERENCE

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