CHIMERIC ANTIGEN RECEPTORS vs CLEC14A

OVERVIEW

- Two novel Chimeric Antigen Receptors (CARs) have been developed against the endothelial factor CLEC14a showing promising anti-solid tumour activity in vivo.
- No toxicity was observed in preliminary mouse models.
- CLEC14a represents an ideal anti-vasculature target for CARs, and is over-expressed across a wide range of cancers.
- Targeting of untransformed cells bypasses standard resistance mechanisms.
- CRT owns a patent on the target, and the sequences of the CARs themselves remain patentable.

BACKGROUND

Targeting T-lymphocytes to recognise and destroy cancer cells by engineering them to express receptors for tumour-specific antigens is proving to be a potent treatment modality, as demonstrated in recent clinical trials of Chimeric Antigen Receptors, or CARs (1,2). However, T-cell therapies can result in immune evasion by malignant cells as antigen-loss variants may arise.

As previously demonstrated by CRT and researchers at the University of Birmingham, the endothelial factor CLEC14a is preferentially presented on tumour-associated vessels in a wide range of common cancers, and makes an exciting target to bypass acquired resistance and immunological silencing mechanisms (3).

THE TECHNOLOGY

A novel series of active second generation CARs which selectively target CLEC14a have been rationally designed and developed, utilising the world-leading expertise on the target at the University of Birmingham. These CARs show promising anti-tumour activity through an anti-vascular mechanism in Lewis lung carcinoma (Figure 1) and RipTag2 pancreatic mouse solid tumour models, and are primed for late-stage pre-clinical testing.

Figure 1. CLEC14a CAR-transduced T-cells show tumour growth reduction in Lewis lung carcinoma mouse model by photoluminescence. The Mock cohort received T-cells which were subjected to the transduction process but were not exposed to retrovirus.

ABOUT CRT

CRT develops and commercialises exciting new discoveries in cancer research. We’re the meeting point between academia and industry. Our deep understanding of both perspectives enables us to translate promising research into commercial propositions for the greatest patient benefit and maximum final return.

cancertechnology.com

Read more overleaf
NO TOXICITY OBSERVED IN PRELIMINARY MOUSE MODELS

Alongside anti-tumour activity, these CARs also show a lack of general toxicity. Healthy mice dosed with CLEC14a CAR-transduced T-cells continued to gain weight (Figure 2) and subsequent histopathological analysis demonstrated no observable toxicity in brain, lung, liver, kidney, heart or colon.

Figure 2. Weight gain over time of healthy mice treated with Mock- or CLEC14a CAR-transduced T cells. The Mock cohort received T-cells which were subjected to the transduction process but were not exposed to retrovirus.

PANCREATIC CANCER MOUSE MODEL

In addition to the promising activity observed in the Lewis lung mouse model, the CARs also demonstrate activity in the RipTag2 mouse model, known to be representative of human disease. Even at low transduction levels (average T-cell transduction was 15%), the therapy was able to reduce tumour growth compared to controls. Preliminary results suggest this activity is comparable to that of sunitinib in the same model. As higher transduction percentages are achieved, higher anti-tumour activity would be anticipated in all in vivo models.

REFERENCES

4. PCT/GB2010/001689

COMMERCIAL OPPORTUNITY

CRT is seeking a partner experienced in the field of T-cell therapy development to take this CAR technology through to first-in-man clinical trials. The technology is well positioned for mid- to late-stage preclinical development, including process development and further disease positioning. CRT holds a patent on the target (4). The specific sequences of the CARs, whilst not protected, have not been disclosed and remain patentable.

CONTACT

Tommy Rennison, Project Development Manager
trennison@cancertechnology.com
+44 (0)20 3469 6300