

# CRT Licensing Opportunity



## CLEC9A: A Novel Dendritic Cell Antibody Target

- Potential for prophylactic and therapeutic anti-cancer and anti-infectious disease vaccines
- Targeted delivery of antigens to Dendritic Cells that are efficient at cross-presentation
- Significant advantages over existing antibody targeted vaccines
- Additional potential for treatment of auto-immune diseases

BIOLOGICAL THERAPEUTICS | *In Vivo* Proof-of-Principle

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### Lead Scientist

Dr Caetano Reis e Sousa, Immunobiology Laboratory, London Research Institute, Cancer Research UK.

### Background

Raising efficient immune response to target antigens is one of the rate limiting steps towards generation of effective vaccines. Generation of adaptive immune response relies on presentation of antigens by specialised antigen presenting cells. Dendritic cells (DCs) process and present self and foreign antigens to induce tolerance or immunity. However, there are a number of sub-types of DCs, some of which are highly efficient at cross-presentation of the exogenous antigen.

The CD8+ DCs in mice (but not in humans) have been known to be highly efficient at cross-presentation of antigens and activation of T cell response. Dr Reis e Sousa's laboratory have identified a C-type lectin receptor - CLEC9A (also known as DNGR-1) - that is selectively expressed in murine CD8+ DCs and, crucially, in a subset of human DCs that are highly efficient at cross-presentation (1). Proof-of-principle evidence *in vivo* demonstrates that targeted delivery of antigens using anti-CLEC9A antibodies elicits potent T-cell response that is translated in anti-cancer efficacy in both prophylactic and therapeutic setting.

A number of other C-type lectins, such as DEC205 and DC-SIGN, have been identified in the past as potential receptors for antibody targeted vaccines (2). However, these targets are expressed in a number of other cell types as well as on the target APCs. In contrast, expression of CLEC9A is highly

restricted to the subset DCs - allowing specific delivery of antigens to a small fraction of DCs that are efficient at cross-presentation.

### The Technology

Antigens linked to anti-DNGR-1 antibodies, when administered *in vivo* with appropriate adjuvant, elicit >1000 fold higher T-cell based elimination of target cells compared with non-targeted delivery of the antigen. Furthermore, in a murine model of highly metastatic B16 melanoma model - a poorly immunogenic mouse tumour that is a notoriously difficult to treat - a single 2µg dose of the anti-CLEC9A antibody conjugated vaccine given therapeutically 3 days after transfer of the cells induced nearly complete eradication of lung pseudometastases (Figure 1).

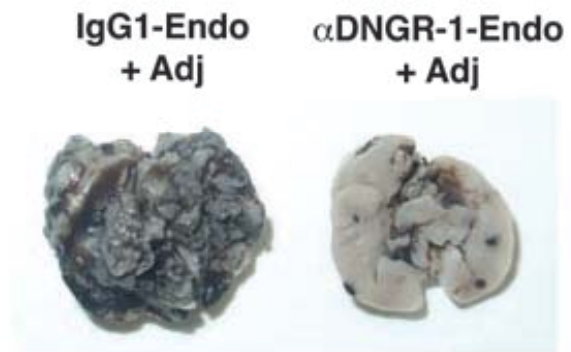


Figure 1: Immunotherapy of lung metastasis of B16 melanoma via targeting of tumor antigens to DNGR-1.\*

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In addition to induction of potent T-cell response, preliminary results indicates that antibodies to CLEC9A have potential for use in a variety of other settings:

- **Function Blocking:** Functional characterisation of CLEC9A indicates that it plays a central role in immune response to necrotic cell death (3). Furthermore, antibody based inhibition of CLEC9A inhibits cellular response to necrotic cell death. As such, CLEC9A may also be a useful target for naked antibody based treatment of diseases caused by pathological response for cell death.
- **Treatment of auto-immune diseases:** Selection of appropriate adjuvants can influence the nature of T-Helper cell response, offering possibility of further fine-tuning of the desired immune response. Furthermore, delivery of the anti-DNGR1 conjugated antigen in absence of adjuvants can result in antigen tolerance. CLEC9A may therefore constitute a promising target not only for inducing immunity but also for promoting immunological unresponsiveness.
- **Enriching DCs:** CLEC9A can be used for detection and enrichment of sub-set of DCs for treatments utilising *ex-vivo* delivery of antigens.

## Intellectual Property

Patent application: WO09013484 - "Immune modulation via C-Type Lectin". The commercial package also includes anti-CLEC9A antibodies and CLEC9A knockout mouse model.

## Commercial Opportunity

CRT is seeking to grant field specific exclusive licences to the CLEC9A patent application and the associated materials for development of anti-cancer and/or anti-infectious disease vaccines and treatment of autoimmune diseases.

## References

- (1) Sancho D, et al., Tumour therapy in mice via antigen targeting to a novel, DC-restricted C-type lectin. *J. Clin. Invest.* 2008. **118**(6):2098-110.
- (2) Keler T, He L, Ramakrishna V, Champion B. Antibody-targeted vaccines. *Oncogene.* 2007 **26**(25):3758-3767.
- (3) Sancho D, et al., Identification of a dendritic cell receptor that couples sensing of necrosis to immunity. *Nature.* 2009. published online 15th Feb 2009. (doi: 10.1038/nature07750)

## Figure Legend

*Mice were challenged with iv injection of B16 Melanoma cells. Three days after the challenge, the mice were treated with a single 2µg dose of either a non-specific antibody (IgG1) or anti-DNGR-1 antibody (αDNGR-1) coupled with peptides encoding antigenic epitopes from gp100, TRP-1 and TRP-2 (collectively labelled as "Endo") together with poly I:C and anti-CD40 as adjuvants. A single 2µg dose of the αDNGR-1 conjugate plus adjuvant is sufficient to prevent lung metastasis of B16 melanoma cells*

**Contact:** Raj Mehta, [rmehta@CancerTechnology.com](mailto:rmehta@CancerTechnology.com)

Ph: +44 (0)207 269 3640