

# CRT Licensing Opportunity



## Boosting Antibody Response

- Platform technology: Higher and faster Antibody response
- Effective vaccination for infectious diseases and cancer
- Useful for generating monoclonal antibodies against “difficult” antigens
- Potential for generating fully human antibodies *ex vivo*

BIOLOGICAL THERAPEUTICS | *IN VIVO* PROOF-OF-PRINCIPLE

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## Lead PIs

Dr. Facundo Batista, a recently elected member of EMBO, leads the Lymphocyte Interaction Laboratory at the CRUK London Research Institute.

Professor Vincenzo Cerundolo, Professor of Immunology, leads the Oxford CRUK Tumour Immunology Programme at the Weatherall Institute of Molecular Medicine, University of Oxford.

## Commercial Opportunity

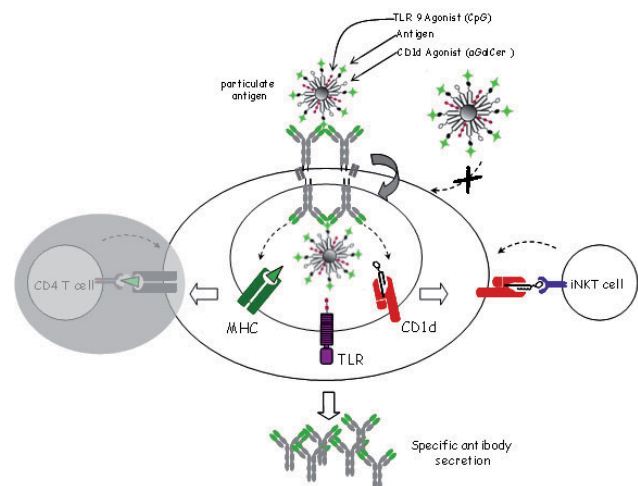
This platform technology relies on Particulate Adjuvants to enable rapid and more potent antibody response by circumventing the need for CD4 T cell help (Figure 1). The use of particulate adjuvants and its various utilities are protected by patent application filed in May 2008.

Using Particulate Adjuvant enables generation of faster and higher antibody responses *in vivo*. There are 3 key utilities of this technology:

- Boosting vaccine response: improvement of existing vaccines and generation of novel vaccines against poorly immunogenic antigens.
- Generation of monoclonal antibodies against poorly immunogenic antigens in rodent models.
- Potential for generation of fully human antibodies *ex vivo* using purified human B-cells.

CRT is seeking field specific exclusive licensees to the patent

application and associate know-how/materials to explore each of the different aspects of the technology.



**Figure 1:**  
*Activation of Antigen Specific B-Cell independent of CD4 T cell: Delivery of particulate antigen conjugated with either CD1d agonists or TLR agonists.*

## Background & Rationale

Highly regulated activation of B cells is required for the production of specific antibodies necessary to provide protection from pathogen infection. Activation of B-cells requires two signalling events: engagement of the B cell

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receptor (BCR) by the antigen and recruitment of specific helper CD4<sup>+</sup> T cells. The process is initiated by specific recognition of antigen through the BCR, leading to early intracellular signalling and internalization of accumulated antigen. The subsequent presentation of processed antigenic peptide-loaded major histocompatibility complex-II (MHC-II) molecules on the surface of the B-cell membrane stimulates the recruitment of specific helper CD4<sup>+</sup> T cells, the second signal that is required for the full activation of B cells.

In addition to CD4<sup>+</sup> T cells, recent studies have shown that there are alternative ways of activating B-cells. Interaction between CD1d restricted Natural Killer Cells (iNKT cells) and B-cells or ligation of a subset of TLR agonists can drive enhanced antibody responses.

The Invariant NKT cells are defined by their expression of a restricted TCR repertoire that recognizes and becomes activated in response to self or foreign antigenic lipids presented by nonpolymorphic CD1d molecules expressed on the surface of various antigen presenting cells including B-cells. The marine sponge-derived glycolipid  $\alpha$ -Galactosylceramide ( $\alpha$ GalCer), remains the best characterized iNKT cell antigen to date, with proven capacity to stimulate strongly both murine and human iNKT cells. Previous studies have shown that iNKT cells can provide potent activation signal to B-cells presenting CD1d loaded  $\alpha$ GalCer.

In addition to the BCR, B cells express Toll-like receptors (TLRs) more usually associated with innate immune cell function. The expression of TLR9 in humans is restricted to plasmacytoid dendritic cells and B cells. Stimulation by TLR9 agonists (such as CpG ODN) results in release of proinflammatory cytokines, promoting B-cell proliferation and antibody production.

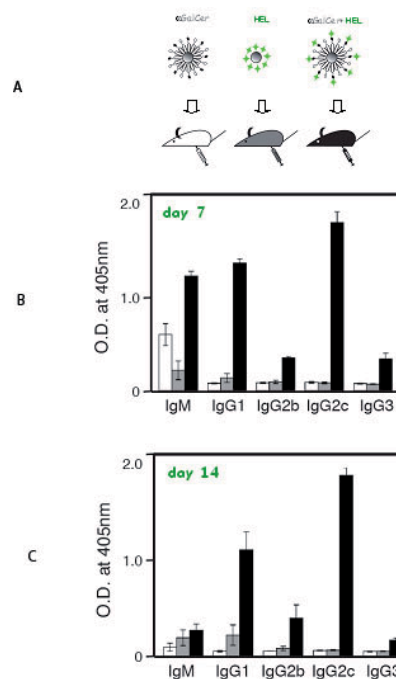
However, these soluble ligands ( $\alpha$ GalCer or TLR9 agonists) enter cells through nonspecific uptake mechanisms, and thereby result in non-discriminatory and widespread stimulation of B cells. The Particulate Adjuvant technology has been developed to allow direct conjugation of the antigen with the adjuvant on particulate support in an effort to confer specificity on the immunostimulation mediated by such adjuvants (Refs 1, 2). This approach has several advantages to delivery of non-particulate antigen/adjuvant mix:

- The greater than 500 fold numerical advantage afforded by iNKT cells over antigen specific CD4<sup>+</sup> T cells allows a significantly higher activating signal strength - resulting in a significantly higher antibody response (Figure 2)
- Only B-cells with the antigen cognate BCR uptake the Particles - hence ensuring activation of Ag specific B-cell without activation of the rest of the B-cell population.
- Circumvention of need for CD4 T cell help would allow generation of antibody response to antigens without MHC Class II epitopes - including carbohydrate and hapten

moieties.

- Potential for activation of B-cells *ex vivo* towards generation of human B-cell hybridomas: methods of generating fully human antibodies.

Further data validating this technology are available for review upon request.



**Figure 2:**  
**A:** Vaccination with model antigen Hen Egg Lysozyme (HEL): Three groups of mice were vaccinated with particulate  $\alpha$ GalCer alone, HEL alone or particles loaded with both  $\alpha$ GalCer and HEL.

**B:** HEL specific Antibody response at Day 7

**C:** HEL specific Antibody response at Day 14

Potent IgG response at Day 7 and maintained at day 14 only when particles are loaded with both  $\alpha$ GalCer and HEL (Black lines)

## References

1. Barral et al (2008): "B cell receptor-mediated uptake of CD1d-restricted antigen augments antibody responses by recruiting invariant NKT cell help in vivo"; PNAS Vol 105(24), p.8345-8350.
2. Eckl-Dorna and Batista (2009): "BCR-mediated uptake of antigen linked to TLR9 ligand stimulates B-cell proliferation and antigen-specific plasma cell formation"; Blood Vol. 113 (17) p. 3969-3977

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