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CREATE CHANGE

AVAILABLE TECHNOLOGY

ASITI Therapeutic Tolerance

Key features

- Antigen Specific Immune Tolerance Induction nanoparticle technology in Phase 1b study and subsequent reverse translation studies elucidate dosing strategy to optimize the expansion of regulatory T cells for tolerance.
- Targets self-antigen which is the underlying cause of the autoimmune disease rather than treating the symptoms alone and hampering the immune system ability to fight infections.
- Seeking partner to help prioritise and develop therapeutic programs in rheumatoid arthritis, type 1 diabetes and other autoimmune diseases.

Background

Autoimmune diseases develop and persist due to the failure of immune self-tolerance mechanisms, which regulate inflammatory responses to injury or infection.

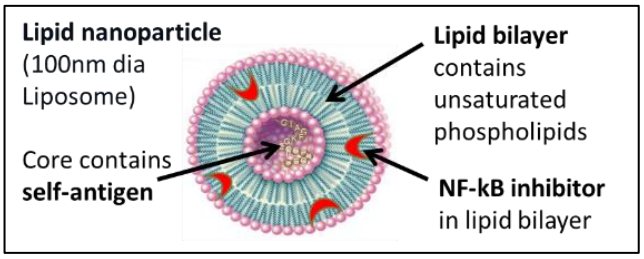
The team, led by Professor Ranjeny Thomas, discovered that the body's immune response could be "re-educated" to turn-off, rather than react to a self-antigen responsible for an autoimmune disease. This discovery led to the development of two drug formats for rheumatoid arthritis (RA) that have progressed in to Phase 1 clinical trials. The first was an ex vivo antigen-exposed tolerising dendritic cell therapy, followed by an injectable antigen-encapsulated tolerising liposome formulation which has since been the focus of translation and commercialisation. The antigen specific immune tolerance induction (ASITI) technology addresses the immunological cause of autoimmune disease by re-establishing disease-specific tolerance in patients, without impairing normal immunity and the ability to fight infections.

The technology

Antigen specific immune tolerance induction is a strategy to restore self-tolerance in patients with specific high-risk HLA genotypes, based on delivery of self-antigenic peptide to lymph node dendritic cells, while simultaneously modulating dendritic cell function.

The ASITI technology comprises a single liposome nanoparticle, which co-delivers NF-kB inhibitor and disease-specific self-antigen to dendritic cells, administered subcutaneously. The nanoparticle drains to the lymph node where it targets and inhibits NF-kB in lymph node dendritic cells, which present antigen to autoreactive T cells. This dendritic cell NF-kB inhibition promotes the induction of antigen-specific Treg but does not block NF-kB in the Treg that respond to them.

Hence, dendritic cell uptake leads to presentation of self-peptide to promote immune regulation of antigen-experienced memory T cells to increase antigen-specific T cell unresponsiveness and reduce auto-antibody responses.



Liposomes as the nanoparticle have the advantage of a long clinical track record as drug delivery vehicles such as Amphotericin and Doxorubicin.

ASITI therapeutic development

POC has been demonstrated in animal models of ovalbumin, proteoglycan aggrecan induced arthritis (PGIA), Goodpasture's vasculitis, Experimental autoimmune uveoretinitis (EAU), HLA-DR1 transgenic collagen-induced arthritis (CIA) and type 1 diabetes (multiple epitopes tested in NOD mouse model).

The first antigen-encapsulated liposome for clinical studies was DEN-181 for rheumatoid arthritis patients. It proceeded through preclinical development, CMC and a Phase 1b single ascending dose trial in patients.

The first-in-human study found that DEN-181 was safe and modulated antigen-specific T cells in RA patients of appropriate HLA type. The lowest dose tested reduced the antigen-specific memory T cells by 7 days post dose. This reduction persisted for 28 days and was associated with reduced disease activity. The FIH study and subsequent reverse translation studies have elucidated a dosing strategy to optimize the expansion of regulatory T cells for tolerance which does not follow normal dose-response principles.

We are now applying the learnings from the Phase 1b and reverse translation studies to the formulation optimisation, clinical strategy and development of our therapeutic tolerance pipeline.

Intellectual property

The foundation patent WO2008043157 titled "Compositions and methods for modulating immune responses" is granted in US, CN, CH, IN and AU, and is proceeding in EU. The breadth of the patent family is illustrated by the US filing Claim 1: "A method for eliciting a tolerogenic immune response to a target antigen in a subject, comprising administering concurrently to the subject an NF-kB inhibitor and an antigen that corresponds to at least a portion of the target antigen, wherein the inhibitor and the antigen are in a particulate form comprising at least one particle that is capable of being taken up by an immune cell".

Know-how includes encapsulation of immune modulators, in vitro and in vivo assays to characterize and optimize immune responses; liquid nanoparticle formulation; CMC and quality control assays; in vivo stability assays; and dosing strategy for efficacy.

Strategy for new IP filings ranges from lipid nanoparticle formulation approaches to specific compositions of matter.

Commercialisation opportunity

UniQuest is seeking a partner to help prioritise and develop one or more therapeutic development programs including rheumatoid arthritis and type 1 diabetes. We have significant experience in rheumatoid arthritis and have been awarded over US $1M in non-diluting funding from JDRF and the Helmsley Foundation to advance the T1D program up to clinical trials. Other tractable diseases include those with known or identified epitopes and assay readout (e.g. pemphigus vulgaris or celiac disease) or where antigens are known, but epitope discovery is required using a known assay (e.g. systemic lupus erythematosus).

Key Publications

- Benham et al., *Citrullinated peptide dendritic cell immunotherapy in HLA risk genotype-positive rheumatoid arthritis patients*. Sci Transl Med. 2015;7(290):290ra87
- Galea et al., *PD-L-1- and calcitriol-dependent liposomal antigen-specific regulation of systemic inflammatory autoimmune disease*. JCI Insight. 2019;4(18):126025.
- Maradana et al., *Immunomodulatory liposomes targeting liver macrophages arrest progression of non-alcoholic steatohepatitis*. Metabolism. 2018;78:80-94.
- Sonigra et al., *A Phase I, randomized, double-blind, placebo-controlled, single center, single-dose escalation to investigate the safety, tolerability, and pharmacodynamics of subcutaneously administered DEN-181 in adult patients with ACPA+ rheumatoid arthritis on stable methotrexate*. Arthritis Rheumatol 71, 4920-4921 (abstract presented, ACR 2019).
- Bergot et al., *Regulatory T cells induced by single peptide liposome immunotherapy suppress islet-specific T cell responses to multiple antigens and protect from autoimmune diabetes.* J Immunol 2020, In press.
- Musthaffa et al., *Proinsulin-specific T-cell responses predict current and future beta-cell function in type 1 diabetes* (abstract presented APEG 2019).

Research leader

Professor Ranjeny Thomas (MBBS, FRACP, MD) is the Arthritis Qld Chair of Rheumatology at the University of Queensland Diamantina Institute in the Faculty of Medicine at UQ, consultant Rheumatologist at Princess Alexandra Hospital and fellow of the Australian Academy of Health and Medical Sciences. Professor Thomas' research is focused on the study of the biology and clinical use of human dendritic cells in autoimmune disease. Professor Thomas is a co-inventor of the ASITI technology, a co-founder of Dendright Pty Limited, held the positions of Chief Technology Officer and Director of Dendright, and has a track record of conducting industry-funded research projects. She has been a keynote speaker at the American College of Rheumatology's annual conference and is an invited member of the RTCure (Rheuma Tolerance for Cure) initiative. RTCure consists of 20 partners from academical institutions, pharmaceutical companies and small-medium enterprises, who have teamed up, together with patient research partners, to work towards earlier detection and prevention of rheumatoid arthritis.

About UniQuest

UniQuest is Australia's leading technology transfer company. We manage and commercialise the intellectual property of The University of Queensland to create change and deliver solutions for a better world.

Our innovation portfolio has seen the creation of more than 100 startup companies, and includes Australia's first blockbuster vaccine Gardasil®, the internationally acclaimed Triple P-Positive Parenting Program and superconductor technology used in most of the world's MRI machines. In 2015, our spinout company Spinifex Pharmaceuticals secured Australia's largest ever biotechnology acquisition.

Contact

David Markwell
Director, Commercialisation (Health)
P: +61 428 385 705
E: d.markwell@uniquest.com.au