endotope
BIOSCIENCES

Next-Generation Paradigm Precision Therapy for Autoimmune Disorders

July 2023

Macro Backdrop

Autoimmune Disorders Globally Prevalent With Huge Addressable Market

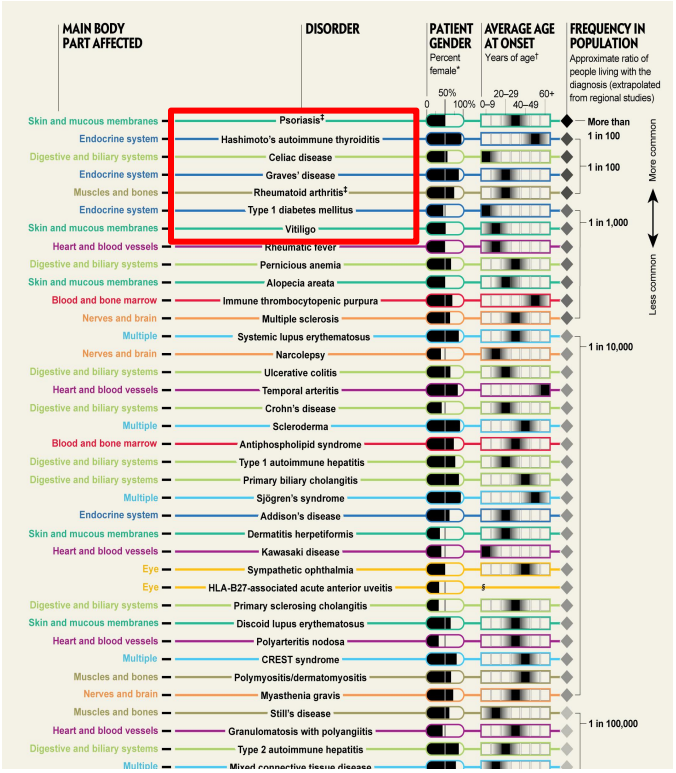
Autoimmune conditions are a spectrum of nearly 80 diseases, afflicting approximately 4.5% of the global population and representing an enormous addressable market

Autoimmune disorders, once dubbed as “horror autotoxicus” by the Nobel Laureate immunologist Paul Ehrlich in 1901, are today affecting approximately 360 million patients globally

Given pathophysiology of this broad category of diseases is yet to be fully elucidated and their chronic nature, treatment costs have surged in recent years estimated at US$149bn in 2023, up from US$32bn in 2013

The most common autoimmune disorders are usually mediated by T cells which escape immune tolerance mechanisms and react to autoantigens, with strong genetic predispositions and increasing inter-disease commonalities

A Wide Spectrum of Chronic Diseases Affecting All Ages, Gender and Ethnicity



Source: “The Terrible Toll of 76 Autoimmune Diseases”, Scientific American, September 2021; Statista

Standard of Care Lacks Specificity With Long-Term Safety Complications

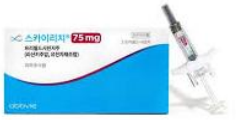
Multiple treatment modalities exist, but they lack specificity, suppressing the immune system with brute force and rendering patients susceptible to infection or malignancy risks, and yet many patients do not benefit clinically

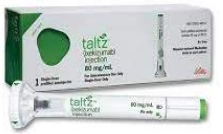
Current Treatment Modalities

General Immunosuppressants

JAK / STAT Inhibitors

Cytokine & Immune Cell Targeted Biologics





Source: corporate websites

Antigen-Specific Immune Modulation - Emerging Landscape

The next-generation treatment paradigm ideally gears towards antigen-specific immune tolerance induction leaving the regular immune functions intact, with a handful of biotechs / biopharmas pursuing various approaches in the clinic

Competitor	Country	Construct / Approach	Indications	Delivery Route
Imcyse	Belgium	Thioredox motif - synthetic peptides to augment pMHC-TCR interaction and generate cytolytic CD4+ T cells	T1D / MS	Subcutaneous
ANOKION	Switzerland	N-acetyl-galactosamine - peptides conjugate targeting liver sinusoidal endothelial cells	Celiac Disease / MS / T1D	Intravenous
TOPAS THERAPEUTICS	Germany	Super paramagnetic iron oxide nanoparticles containing autoantigen peptides	Celiac Disease / Pemphigus Vulgaris	Intravenous
BIONTECH	Germany	Lipid nanoparticles containing mRNA-encoded autoantigen peptides	MS	Intravenous
novo nordisk®	Denmark	DNA plasmids encoding autoantigens and anti-inflammatory molecules e.g. TGF-β / IL-10	T1D	Subcutaneous

Source: corporate websites

How Does the New Paradigm Compare With Current Treatment Options?

The emerging paradigm of treating autoimmune disorders with precision compares favourably to existing modalities in multiple aspects

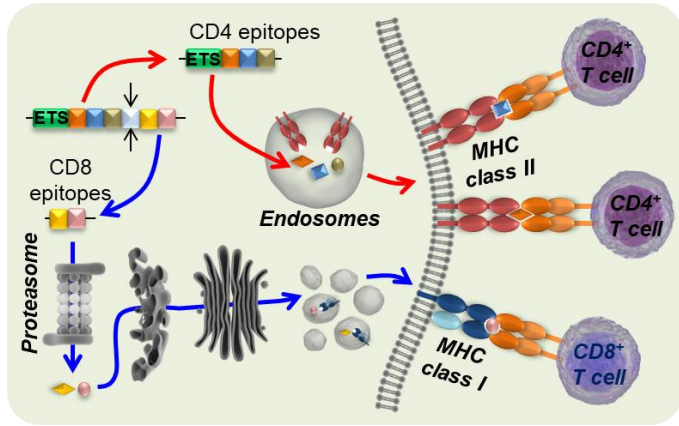
Existing Modalities	Emerging Paradigm	Superior?
• **Lack of antigen specificity** - general suppression of both the pathological immune pathways and also the normal immune functions of the patient	• **Antigen specificity** - albeit there are various approaches, the overriding feature of the new paradigm is to elicit antigen specific immune tolerance	✓
• **Significant toxicities** - heightened risk of opportunistic infections and malignancies due to long-term immune compromise	• **Excellent safety profile** - normal immune functions left intact and preliminary clinical data manifesting excellent safety profile	✓
• **Frequent dosing regimen** - often requires daily dosing in case of immunosuppressants and JAK/ STAT inhibitors or periodic infusions posing patient compliance challenges	• **Durable efficacy** - acting as “vaccines” priming the immune system for tolerance, inducing long lasting immune memory with fewer treatments	✓
• **High manufacturing costs** - biologics targeting various cytokine signaling pathways are relatively expensive to manufacture implying high treatment costs	• **Cost efficient CMC procedures** - although highly specific, the constructs are primarily synthetic peptides or nucleic acids delivered through nanoparticles, which are relatively cheap to manufacture in accordance with standard protocols	✓

The Endotope Platform

The Endotope Platform - Broad Antigen Coverage & Versatile Modalities

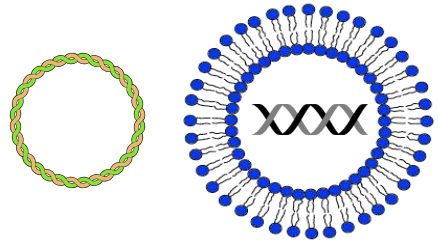
Endotope Biosciences is spun out of Professor Remi Creusot's lab at Columbia University, with the underlying "Endotope" platform designed to induce antigen-specific immune tolerance via epitopes encoded endogenously

Endogenously encoded epi**tope**s with Endotope (e.g., DNA/mRNA vaccines)

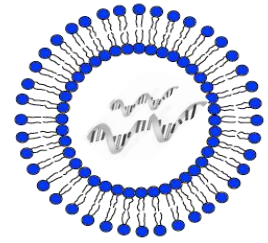


Key Features

- A selection of major epitopes from a diverse scope of disease-relevant autoantigens
- Neoepitopes not present in native autoantigens, e.g. PTM epitopes, hybrid peptides
- Optimal engagement of both CD4+ and CD8+ T cells with co-presentation guaranteed
- Epitopes are known to be loaded and presented on specific MHC haplotypes



Tolerogenic DNA vaccine



Tolerogenic mRNA vaccine

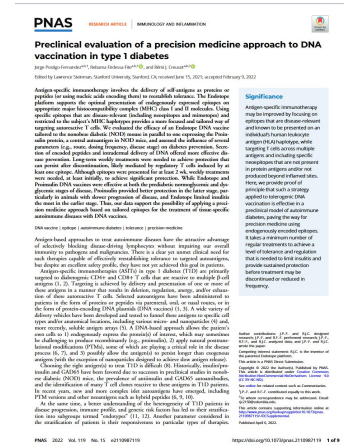

Molecular Therapy
Methods & Clinical Development
Original Article

Efficient Presentation of Multiple Endogenous Epitopes to Both CD4+ and CD8+ Diabetogenic T Cells for Tolerance


Journal of Autoimmunity

A multi-epitope DNA vaccine enables a broad engagement of diabetogenic T cells for tolerance in Type 1 diabetes

Jorge Postigo-Fernandez, Remi J. Creusot*


PNAS

Preclinical evaluation of a precision medicine approach to DNA vaccination in type 1 diabetes


CELL & GENE THERAPY INSIGHTS

NEW HORIZONS IN CELLULAR IMMUNOTHERAPY: NEXT-GEN PLATFORMS & MODALITIES

SPOTLIGHT

INNOVATOR INSIGHT

Promising non-viral vector for efficient and versatile delivery of mRNA for antigen-specific immunotherapy

Rebuma Firdessa-Fite, Jorge Postigo-Fernandez, Valérie Toussaint-Moreau, Fabrice Stock, Alengo Nyamay'antu, Patrick Erbacher & Rémi J Creusot

Source: Dastagir et al., 2017

Well Ring-Fenced Intellectual Property Portfolio

Our core intellectual property portfolio is well ring-fenced and has been granted, underpinning future research and clinical development programmes


US010238741B2

(12) **United States Patent**
Creusot

(10) **Patent No.: US 10,238,741 B2**
(45) **Date of Patent: Mar. 26, 2019**

(54) **NUCLEIC ACID CONSTRUCTS FOR PRESENTATION OF CD4 AND CD8 EPITOPES, CELLULAR TRANSFECTION AND USES THEREOF**

(71) Applicant: **Remi J. Creusot**, New York, NY (US)

(72) Inventor: **Remi J. Creusot**, New York, NY (US)

(73) Assignee: **THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/483,889**

(22) Filed: **Apr. 10, 2017**

(65) **Prior Publication Data**

US 2017/0283810 A1 Oct. 5, 2017

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/US2015/055042, filed on Oct. 10, 2015.

(60) Provisional application No. 62/062,325, filed on Oct. 10, 2014, provisional application No. 62/416,080, filed on Nov. 1, 2016.

(51) **Int. Cl.**

C12P 21/02	(2006.01)
A61K 39/42	(2006.01)
A61K 35/76	(2015.01)
A61K 31/00	(2006.01)
C07K 14/55	(2006.01)
C07K 14/575	(2006.01)
C07K 14/735	(2006.01)
C07K 14/705	(2006.01)
C12N 9/16	(2006.01)
C12N 9/88	(2006.01)
C07K 14/47	(2006.01)
C12N 15/12	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 39/42*** (2013.01); ***A61K 31/00*** (2013.01); ***A61K 35/76*** (2013.01); ***C07K 14/55*** (2013.01); ***C07K 14/575*** (2013.01); ***C07K 14/70535*** (2013.01); ***C07K 14/70582*** (2013.01); ***C12N 9/16*** (2013.01); ***C12N 9/88*** (2013.01); *A61K 39/00* (2013.01); *C07K 2319/01* (2013.01); *C07K 2319/50* (2013.01); *C07K 2319/74* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,759,234	B1	7/2004	Geller et al.
2004/0248113	A1	12/2004	Sette et al.
2006/0216305	A1	9/2006	Lal et al.

FOREIGN PATENT DOCUMENTS

EP	0960119	B1	9/2008
WO	1997049430	A1	12/1997
WO	2002083714	A2	10/2001
WO	2003084467	A2	10/2003
WO	2013149167	A1	10/2013

Li et al., "T
Biotechnolo
Steimle et al
feron-γ Med
106-109 (19
Lee et al., "
liposomes in
Biochimica
An, Ling-Li
B-Cell, Cyto
Microbes, It
Protection a
Mar. 1997, v
Bar-Or, A., e
tiple sclerosi
protein in a m
of Neurolog
Coppieters, I
cells in insu
diabetes pati
2012.
Creusot, R.,
CD4+ T cell
cations for t
1687, 2001.
Creusot, R.,
CD4+ T cell
Immunology

Primary Ex
(74) *Attorn*
Beusse Wo

(57)

The inventi
modulating
CD4 and
transfection
non-self an
or immune
new constr
driving epi
within the
(C286) targ
the cell, to
tion in the
activator se
CD4 and CI

Spec

US 10,238,741 B2

1

NUCLEIC ACID CONSTRUCTS FOR PRESENTATION OF CD4 AND CD8 EPITOPES, CELLULAR TRANSFECTION AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation in part of PCT application No. PCT/US15/55042 filed Oct. 10, 2015 to which priority is claimed under 35 U.S.C. § 120 and claims benefit of priority under 35 U.S.C. § 119(e) to Provisional Application Ser. No. 62/062,325, filed on Oct. 10, 2014. This application also claims benefit of priority under 35 U.S.C. § 119(e) to Provisional Application Ser. No. 62/416,080, filed Nov. 1, 2016 the entire contents of which is hereby incorporated by reference as if fully set forth herein.

STATEMENT OF GOVERNMENTAL INTEREST

This invention was made with government support under DK063608 awarded by the National Institutes of Health. The government has certain rights in the invention.

REFERENCE TO SEQUENCE LISTING SUBMITTED VIA EFS-WEB

This application is being filed electronically via EFS-Web and includes an electronically submitted sequence listing in .txt format. The .txt file contains a sequence listing entitled "20170407_15003-324US1_ST25.txt" created on Apr. 7, 2017 and is 61 KB in size. The sequence listing contained in this .txt file is part of the specification and is hereby incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

Self-recognition or immune tolerance is mediated by several mechanisms including presentation of a "self" peptide to a CD4+ or CD8+ T cell, eliminating, inhibiting, or converting autoreactive (self-reactive) T cells that would potentially attack a cell producing the autoantigen (self-protein) from which the particular epitope (peptide) is derived. Autoimmune diseases such as Type 1 diabetes (T1D), rheumatoid arthritis (RA), multiple sclerosis (MS), psoriasis, systemic lupus erythematosus (SLE), and inflammatory bowel disease (IBD) can develop when this process is deficient or altered, and the immune system inappropriately attacks the body's own tissues. The National Institutes of Health estimates that 25.5 million Americans suffer from an autoimmune disease. Due to the complexity of these diseases (resulting from a combination of multiple genes and environmental factors), it has been difficult to apply drugs or biologics targeting one or a few pathways to restore tolerance efficiently and durably.

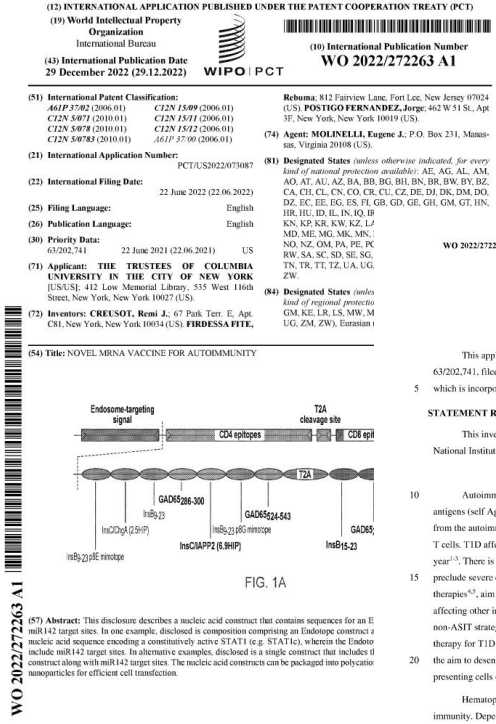
Current therapies for autoimmune disorders concentrate on symptomatic response and on mitigating the immune system as a whole, which has the inherent drawback of increasing susceptibility to infections and otherwise controlled malignancies. Antigen-specific therapy has recently emerged as a potential long-term solution to autoimmune disorders, but eliciting appropriate immune responses (i.e. tolerance-inducing or tolerogenic) and targeting sufficient numbers of disease-driving T cells has proven difficult. Immune tolerance, which prevents an immunogenic response from developing upon self-recognition, is mediated by several mechanisms, primarily involving the presentation

2

of "self" peptides to CD4+ or CD8+ T cells in a manner that results in the elimination, inhibition, or conversion of the autoreactive T cells that otherwise would potentially attack cells and tissues that are the source of autoantigens and/or support the production by B cells of antibodies that react against these autoantigens. Under normal conditions (in absence of inflammation or infection), the presentation of epitopes (peptides or regions of a protein antigen that are recognized by immune cells) by specialized antigen-presenting cells (APCs) typically instructs the immune cells not to attack cells and tissues bearing these particular autoantigens. APCs that acquire antigens exogenously (from their milieu) more effectively engage CD4+ T cells, whereas those producing antigens endogenously present epitopes mainly to CD8+ T cells. However, both CD4+ and CD8+ self-reactive T cells should be silenced in order to prevent autoimmunity.

APCs include "professional" hematopoietic cells, primarily dendritic cells (DCs) but also macrophages and B cells, and "non-professional" non-hematopoietic cells, primarily lymph node stromal cells that have most contact with immune cells. Only professional APCs have the ability to elicit a productive immune response in the presence of recognized inflammatory signals and pathogen elements. Absent such signals, professional APCs tend to induce tolerance to presented antigens, while non-professional APCs, which do not upregulate the costimulatory ligands required for full activation are by default robustly tolerogenic. Stromal cells express lower MHC levels, and some do not express MHC class II (MHCII). They also have more limited endocytosis compared to professional antigens. Thus, stromal cells primarily present endogenously expressed antigens on MHC class I (MHCI), and a specific subset of epithelial cells in the thymus expresses high levels of MHCII and is able to present endogenous antigens on MHCII via autophagy.

Stromal Cells (SCs) are non-professional APCs that inherently lack the accessory molecules needed to stimulate effector T cell responses and have limited ability to acquire exogenous antigens and present them. Lymph node stromal cells (LNSCs) are constantly in contact with circulating T cells. They can present endogenously expressed peptides to naïve $CD8^+$ T cells, leading to their deletion or anergy (Cohen, et al. *J Exp Med* 207: 681-688; Fletcher et al. (2010), *J Exp Med* 207: 689-697; and Cire, et al. (2016) *Med Ther.*). They also participate in the maintenance of Tregs (Baptista et al. (2014) *eLife* 3) although their MHC-II expression is limited to some subsets or transferred from DCs (Dubrot et al. (2014), *J Exp Med* 211: 1153-1166). SCs and parenchymal cells are more readily transfected by DNA vaccines and other non-viral vectors than DCs (Yin et al. (2014), *Nature reviews Genetics* 15: 541-555.). After the death of SCs, a limited quantity of antigens may be passed onto DCs, but the majority of endogenously expressed antigens are only presented as peptides on MHC-I to $CD8^+$ T cells. Indeed, DNA vaccines can lead to a reduction of antigen-specific $CD8^+$ T cells in T1D patients and delayed loss of C-peptide secretion without notable adverse effect (Roep et al. (2013), *Science translational medicine* 5: 191ra182). However, engagement of $CD4^+$ T cells by endogenous antigens expressed from DNA vaccines is inefficient. When targeted to MHC-II using a lysosome-targeting signal, a single endogenously expressed peptide allowed engagement of diabetogenic $CD4^+$ T cells and reduce disease incidence (Rivas et al. (2011) *J Immunol* 186: 4078-4087). However, multiple treatments (a3) were required to achieve a measurable immunological response, yet without evidence for antigen-specific Treg induction (Rivas et al. 2011).


(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
29 December 2022 (29.12.2022)

WIPO | PCT

(10) **International Publication Number**
WO 2022/272263 A1

(51) **International Patent Classification:**
A61P 37/02 (2006.01) ***C12N 15/09*** (2006.01)
C12N 5/071 (2010.01) ***C12N 15/11*** (2006.01)
C12N 5/078 (2010.01) ***C12N 15/12*** (2006.01)
C12N 5/0783 (2010.01) *A61P 37/00* (2006.01)

(21) **International Application Number:**
PCT/US2022/073087

(22) **International Filing Date:**
22 June 2022 (22.06.2022)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
63/202,741 22 June 2021 (22.06.2021) US

(71) **Applicant: THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK** [US/US]; 412 Low Memorial Library, 535 West 116th Street, New York, New York 10027 (US).

(72) **Inventors: CREUSOT, Remi J.**; 67 Park Terr. E, Apt. C81, New York, New York 10034 (US). **FIRDESSA FITE, Rebuma**; 812 Fairview Lane, Fort Lee, New Jersey 07024 (US). **POSTIGO FERNANDEZ, Jorge**; 462 W 51 St., Apt 3F, New York, New York 10019 (US).

(74) **Agent: MOLINELLI, Eugene J.**; P.O. Box 231, Manassas, Virginia 20108 (US).

(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, KN, KP, KR, KW, KZ, LA, MD, ME, MG, MK, MN, NO, NZ, OM, PA, PE, PG, RW, SA, SC, SD, SE, SG, TN, TR, TT, TZ, UA, UG, ZM, ZW.

(84) **Designated States** (*unless kind of regional protection*): GM, KE, LR, LS, MW, MZ, UG, ZM, ZW), Eurasian (

(54) **Title:** NOVEL MRNA VACCINE FOR AUTOIMMUNITY

FIG. 1A

(57) **Abstract:** This disclosure describes a nucleic acid construct that contains sequences for an E miR142 target sites. In one example, disclosed is composition comprising an Endotope construct a nucleic acid sequence encoding a constitutively active STAT1 (e.g. STAT1c), wherein the Endoto include miR142 target sites. In alternative examples, disclosed is a single construct that includes t construct along with miR142 target sites. The nucleic acid constructs can be packaged into polycatio nanoparticles for efficient cell transfection.

WO 2022/272263 A1

WO 2022/272263 PCT/US2022/073087

NOVEL mRNA VACCINE FOR AUTOIMMUNITY

CROSS-REFERENCE TO RELATED APPLICATION

This application claims benefit of United States Provisional Patent Application No. 63/202,741, filed June 22, 2021, titled "NOVEL mRNA VACCINE FOR AUTOIMMUNITY", which is incorporated herein in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under AI110812 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Autoimmunity occurs as a consequence of adaptive immune responses against self-antigens (self Ags) expressed in specific tissues. For example, Type 1 diabetes (T1D) results from the autoimmune destruction of insulin-producing β-cells by β-cell Ag-reactive diabetogenic T cells. T1D affects several millions of Americans and its incidence inexorably increases each year[1-3]. There is no cure and life-long insulin replacement with exogenous insulin does not preclude severe complications. Ag-specific immunotherapies (ASITs), unlike non-ASIT therapies[4-5], aim to target and disarm the disease-causing lymphocyte populations, without affecting other immune cells and jeopardizing our overall immune protection. Several ASIT and non-ASIT strategies have been investigated clinically[5,6] but there is still no FDA-approved therapy for T1D. ASITs involve delivery of autoantigens, under various forms and routes, with the aim to desensitize (tolerize) T cells reactive to these Ags. However, the nature of the Ag-presenting cells (APCs) involved is usually not known or not well-controlled.

Hematopoietic cells, particularly dendritic cells (DCs), play a dual role in regulating immunity. Depending on conditions, they can elicit T cell immunity ('fight signal' or immunogenic) or T cell tolerance ('stand down signal' or tolerogenic). When autoantigens are presented by immunogenic DCs, they may negate the effect of tolerogenic APCs or even exacerbate disease. Moreover, DCs have numerous reported alterations in T1D that cause them to be less tolerogenic[7]. In contrast, non-hematopoietic (stromal) cells encompass a wide variety of cell types that do not normally serve as APCs, but have yet the ability to do so under certain

1

Source: USPTO

Potential to Tackle A Wide Spectrum of Autoimmune Disorders

Endotope is a highly modular and versatile platform, amenable to treat a whole range of autoimmune indications with high prevalence

CNS

Multiple Sclerosis

Neuromyelitis Optica

Bones / Muscles

Rheumatoid Arthritis

Myasthenia Gravis

Polymyalgia Rheumatica

Glands

Type 1 Diabetes

Grave’s Disease

Hashimoto’s Disease

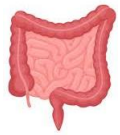
Sjogren's Syndrome

Dermis

Psoriasis

Vitiligo

Alopecia Areata



Intestines

Celiac Disease

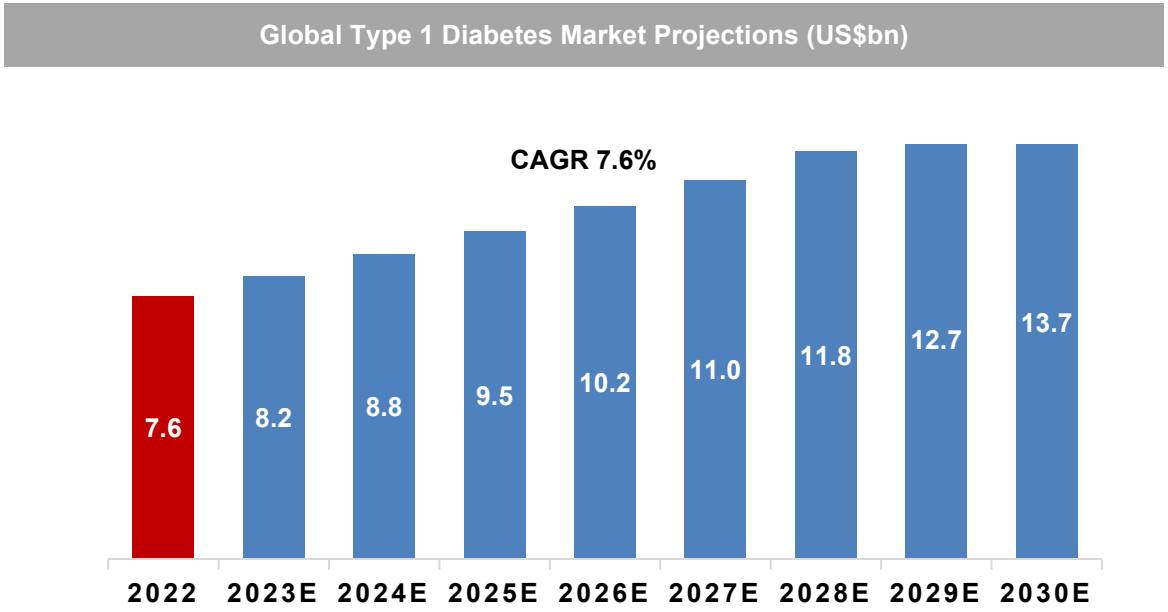
Ulcerative Colitis

Crohn’s Disease

Proof of Concept

Initial Opportunity Mapping - Type 1 Diabetes

Type 1 diabetes is projected to grow to an approximately US$14bn global market by 2030, and represents an attractive indication to pursue from a commercial perspective

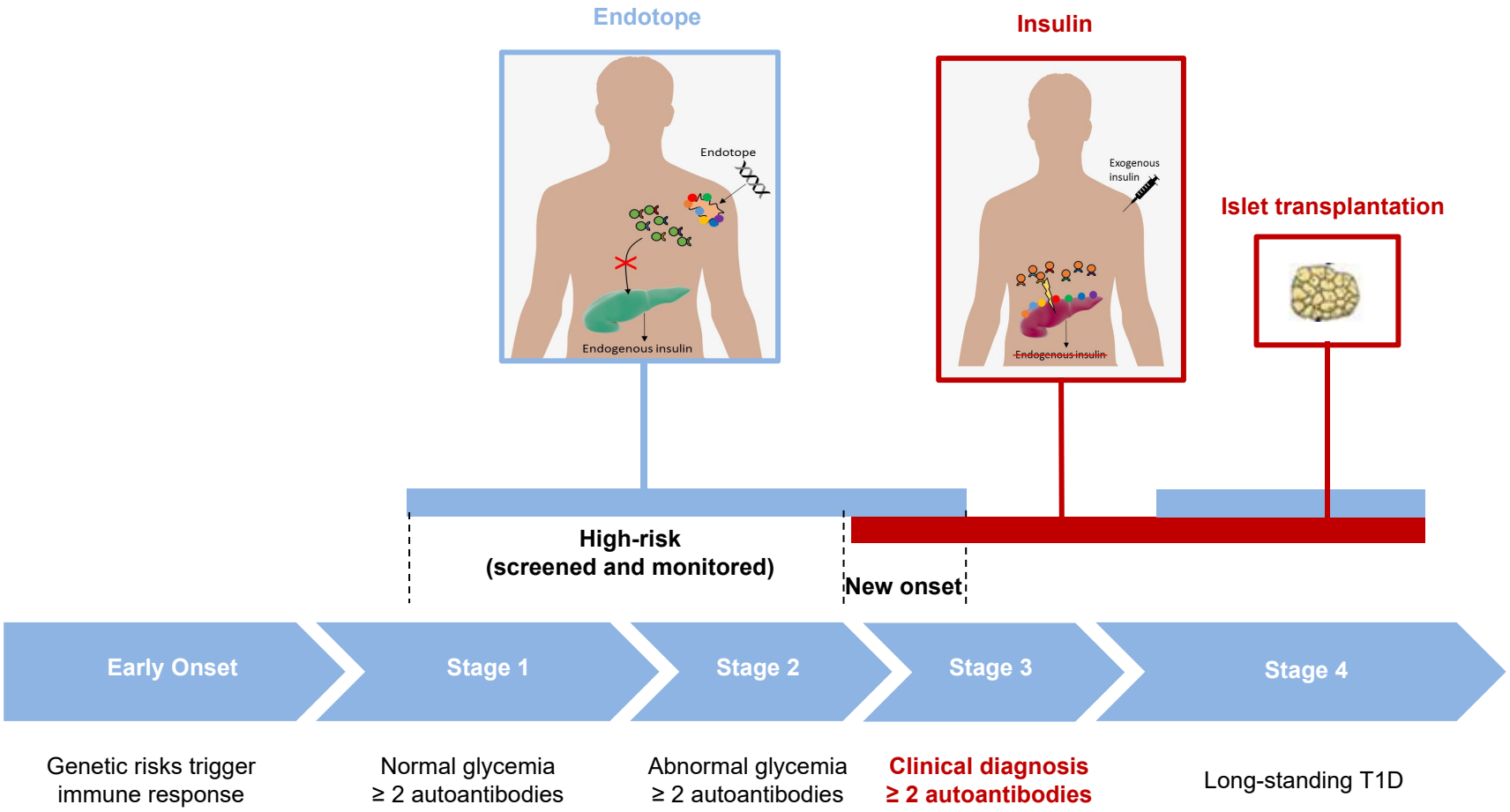


- Current “gold standard” treatment for T1D consists of life-long frequent insulin injections to regulate blood glucose levels
- However, over time, insulin resistance usually occurs, with other adverse side effects such as hypoglycemia and weight gain
- An antigen-specific approach to induce immune tolerance, with intervention in early-onset patients, is likely to prevent or halt disease occurence / progression with the remaining pancreas β cells capable of secreting endogenous insulin to keep blood glucose levels at bay, potentially transforming the current treatment regimen

Source: Frost & Sullivan

Highly Complementary & Synergistic to Existing Treatment Modalities

Our proposed Endotope constructs are highly complementary and synergistic to existing modalities along the disease progression curve

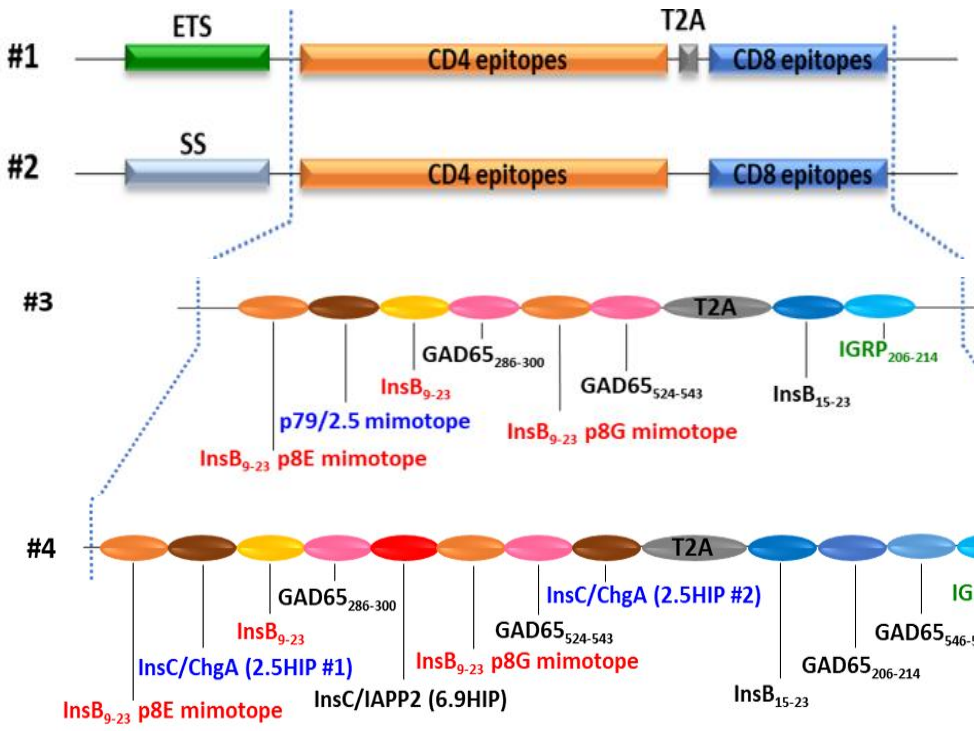


Source: Firdessa et al., 2023

Co-presentation of Multiple CD4 & CD8 Autoantigen-Derived Epitopes

Co-presentation of multiple CD4 & CD8 autoantigen-derived neoepitopes and mimotopes is achieved for T1D to induce the broadest possible magnitude of immune tolerance

NOD Mice



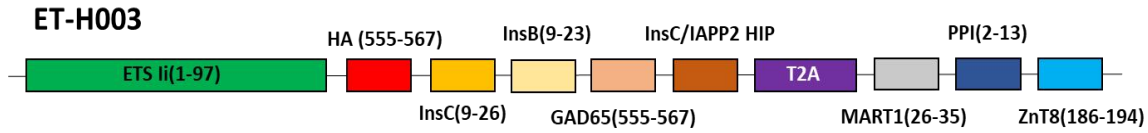
Construct for intracellular polypeptides

Construct for secreted polypeptides

5th generation Endotope T1D with mouse epitopes & mimotopes

6th generation Endotope T1D with mouse epitopes, hybrid insulin peptide neoepitopes & mimotopes

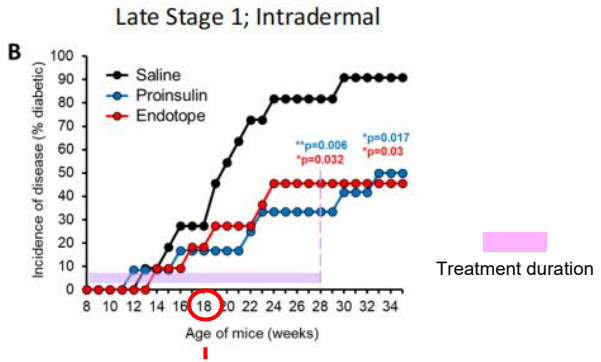
Human

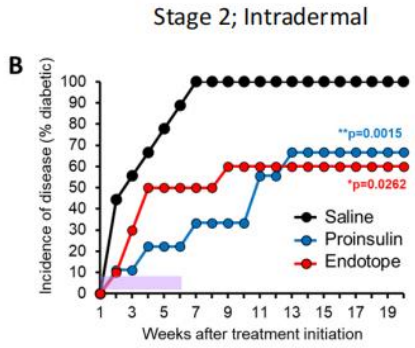


Source: Postigo et al., 2019 & 2022

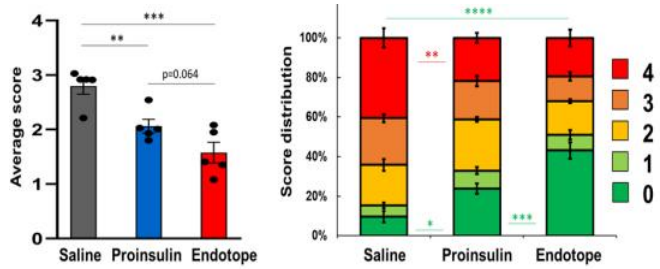
Tolerogenic DNA Vaccine Construct - Preclinical Proof of Concept

Naked plasmids encoding various CD4 & CD8 autoantigen-derived neoepitopes and mimotopes for T1D are administered intradermally into NOD mice, with durable efficacy witnessed

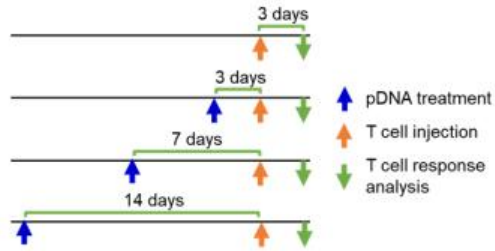


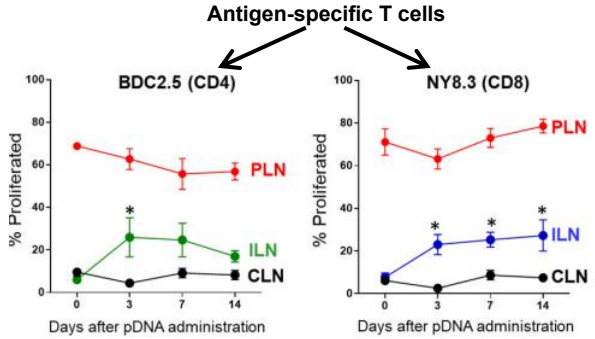


Treatment with Endotope provides
significant therapeutic benefit
at both late stage 1 and stage 2 of disease



Treatment with Endotope results in a high
degree of protection from insulitis
(score of 0, no insulitis; score of 4, completely infiltrated islet)



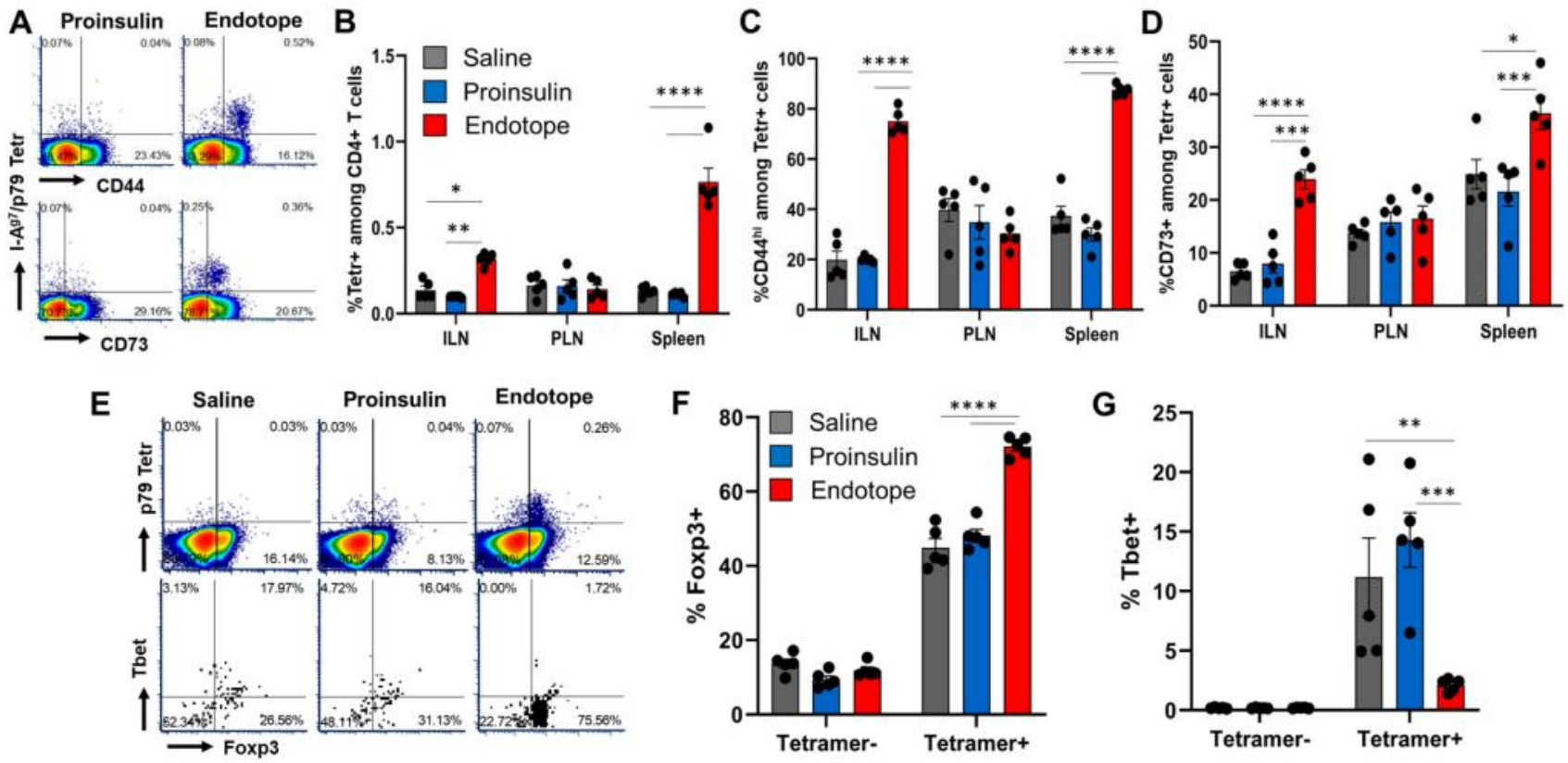


Persistence - antigen is still being presented 2 weeks after a single injection,
assessed by the response of antigen-specific CD4+ and CD8+ T cells
adoptively transferred at different times
(ILN - inguinal lymph nodes, draining the site of administration; CLN -
cervical lymph nodes, negative control; PLN - pancreatic lymph nodes,
positive control)

Source: Postigo et al., 2019 & 2022

Tolerogenic DNA Vaccine Construct - Preclinical Proof of Concept

The treatment targets only a specific set of disease-relevant antigen-specific T cells, expands them and reprograms them to acquire a regulatory phenotype

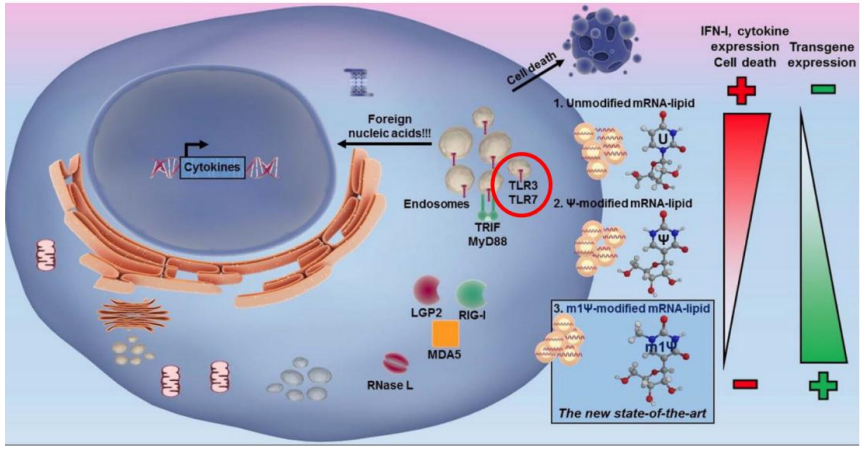


Ag-specific response detected by MHC tetramers after 10 weekly injections
(50 µg, i.d.), showing acquisition of tolerance-associated markers (e.g., CD73) in spleen and draining lymph nodes, and switch from Tbet (Th1 marker) to Foxp3 (Treg marker) expression in spleen

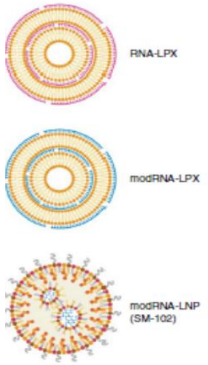
Source: Postigo et al., 2022

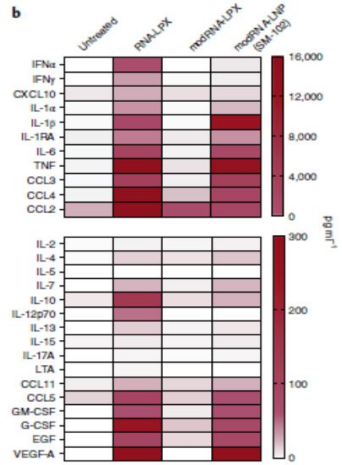
Tolerogenic mRNA Vaccine Construct - Safety Considerations

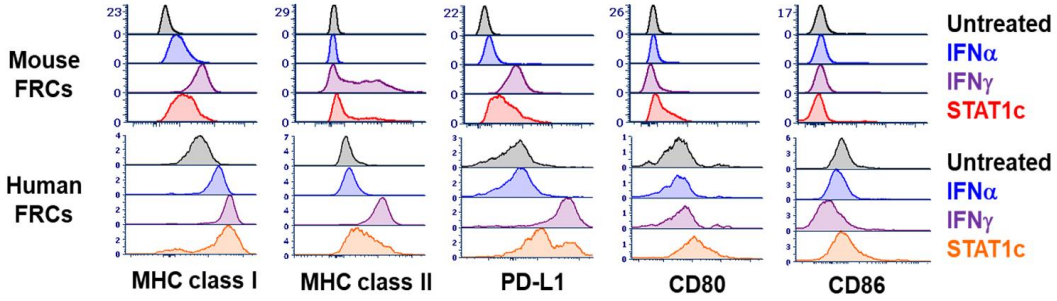
Both mRNAs and nanoparticles have adjuvant properties, and therefore stromal cells are leveraged as substitute antigen-presenting cells (APCs) for dendritic cells to maintain the tolerogenic context

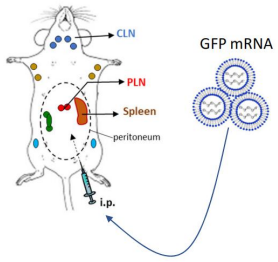


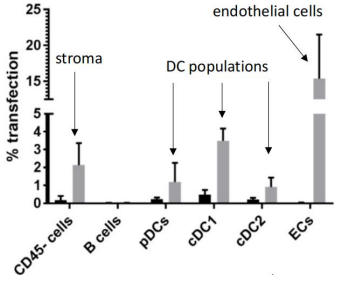
mRNA modification can extinguish its adjuvant properties, but nanoparticle formulations may have inherent adjuvant properties that activate professional APCs such as dendritic cells to become immunogenic











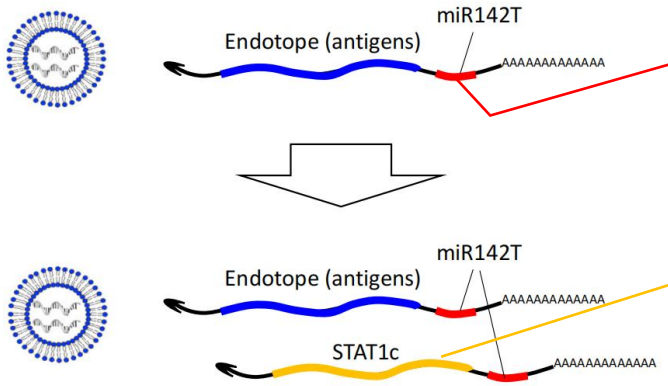
Expression of constitutively active STAT1 (STAT1c) can partially recapitulate the effect of IFNγ; FRCs (fibroblastic reticular cells) are a type of tolerogenic lymph node stromal cells, its antigen presentation capability can be enhanced by IFNγ / STAT1 signaling (higher MHC, higher PD-L1 expression with no or limited effect on CD80/CD86)

Source: Andries et al., 2015; Tahtinen et al., 2022

mRNA nanoparticles can target both professional & non-professional APCs in lymph nodes

Tolerogenic mRNA Vaccine Construct - Endotope's Novel Design

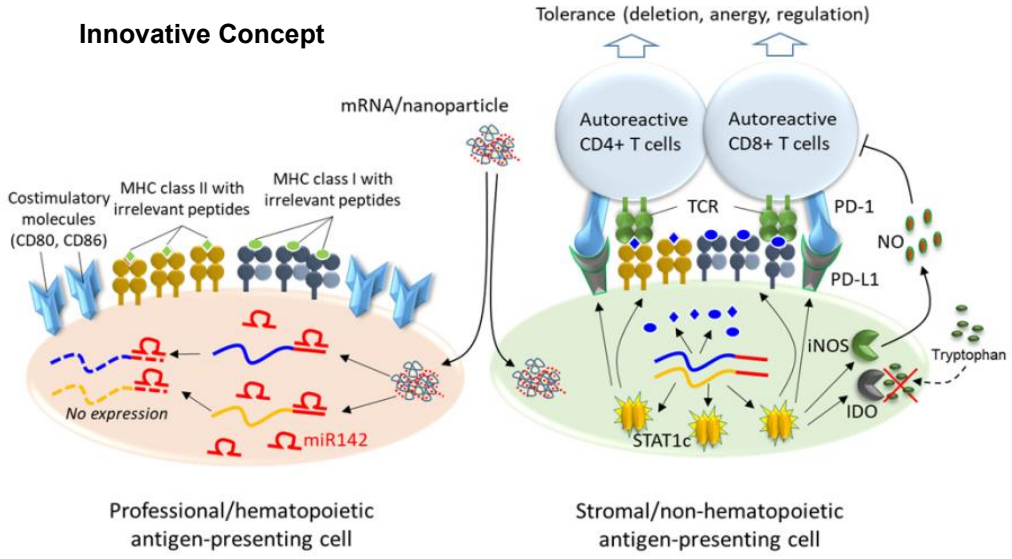
Our new concept leverages the unique potential of stromal cells as tolerogenic APCs



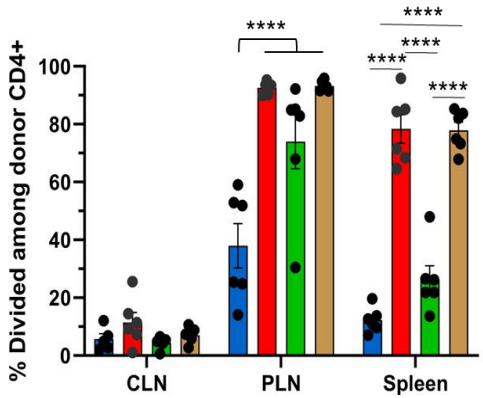
miR142T restricts expression in stromal cells and NOT in hematopoietic APCs such as dendritic cells or B cells

STAT1c potentiates APC function and tolerogenicity of stromal cells

Innovative Concept



Response of antigen-specific CD4+ T cells (adoptively transferred BDC2.5 T cells) after a single i.p. injection (5 µg mRNA)



GFP/GFP-miR142T

Endotope + GFP

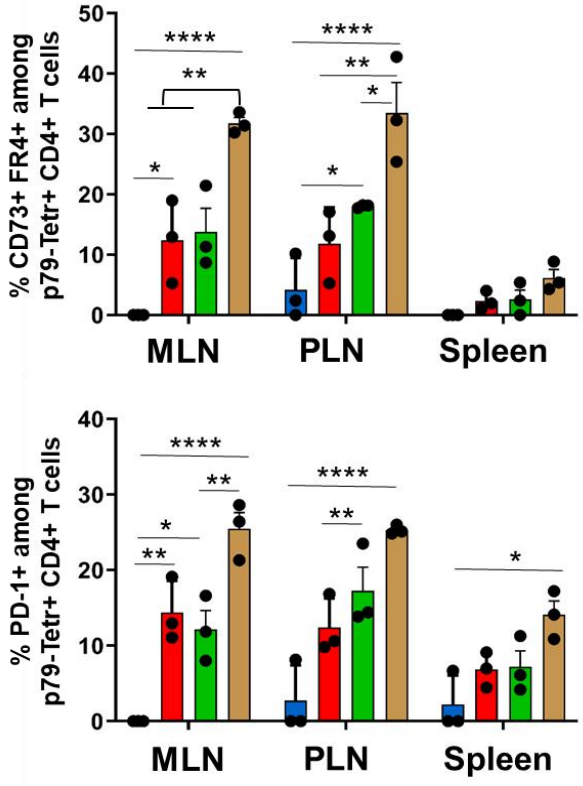
Endotope-miR142T + GFP-miR142T

Endotope-miR142T + STAT1c-miR142T

Tolerogenic mRNA Vaccine Construct - Effect On CD4+ T Cells (Early)

Reprogramed stromal cells induce a more pronounced anergic/exhausted phenotype of specific CD4+ T cells

Upregulation of anergy/exhaustion markers after 3 injections (i.p.) of 5 µg Endotope mRNA



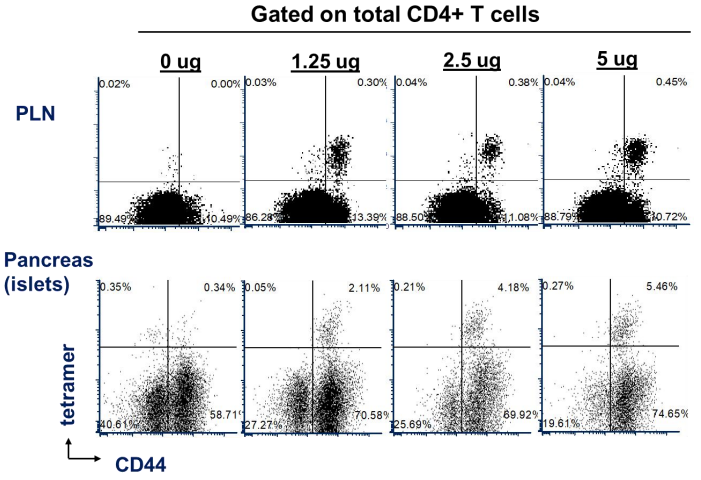
GFP/GFP-miR142T

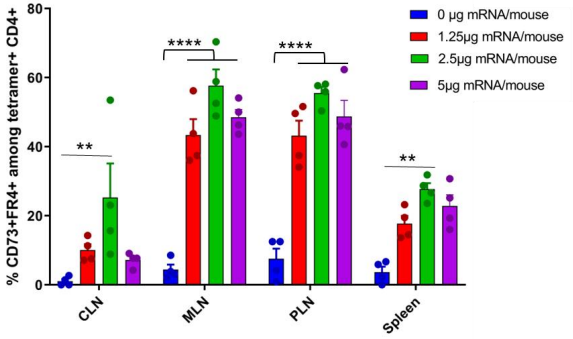
Endotope + GFP

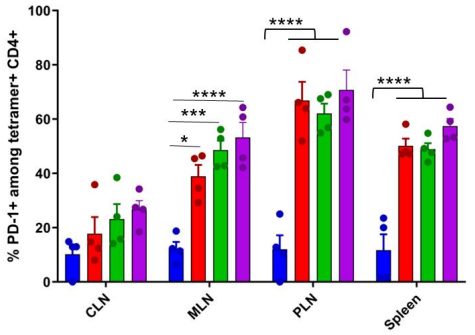
Endotope-miR142T + GFP-miR142T

Endotope-miR142T + STAT1c-miR142T

Ag-specific response detected by MHC tetramers after 3 injections (i.p.), with as low as 1.25 µg Endotope mRNA





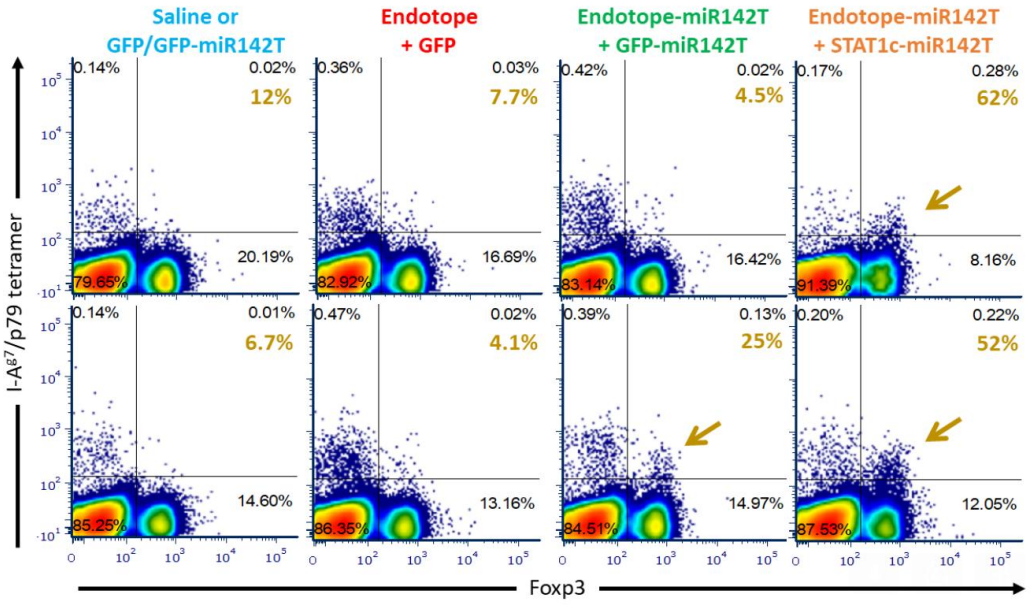


Unpublished

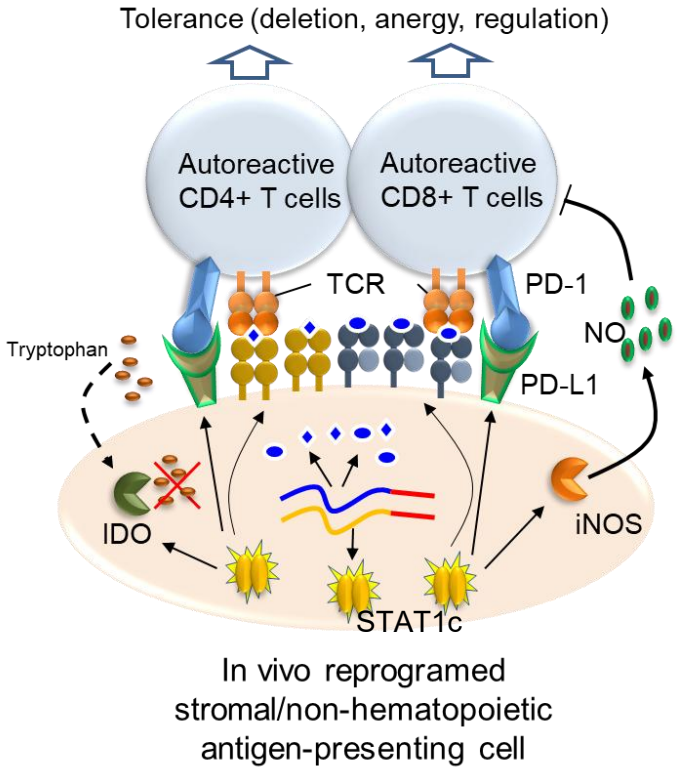
Tolerogenic mRNA Vaccine Construct - Effect On CD4+ T Cells (Late)

Reprogramed stromal cells induce substantially higher Foxp3+ expression among specific CD4+ T cells

Antigen-specific response detected in spleen by MHC tetramers
after 7 injections (i.p.) of 1.5 µg Endotope mRNA



Percentage of Foxp3+ cells among p79-Tetr+ CD4+ T cells



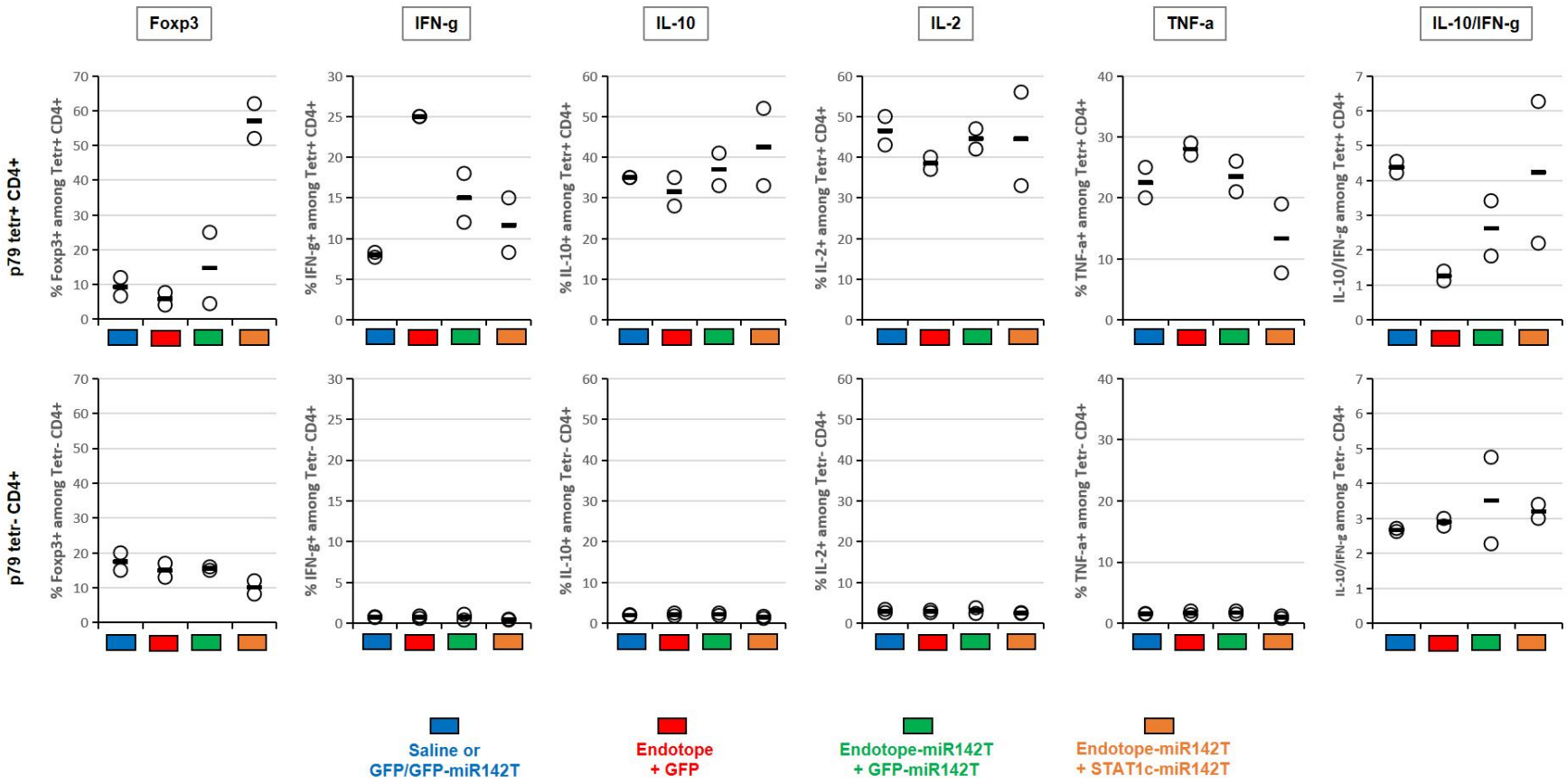
In vivo reprogramed
stromal/non-hematopoietic
antigen-presenting cell

Unpublished and preliminary

Tolerogenic mRNA Vaccine Construct - Effect On Transcription Factor / Cytokines

Reprogramed stromal cells increase Foxp3/IL-10 expression and reduce IFNγ and TNFα expression among specific CD4+ T cells

Antigen-specific response detected by MHC tetramers after 7 injections (i.p.) of 1.5 µg Endotope mRNA

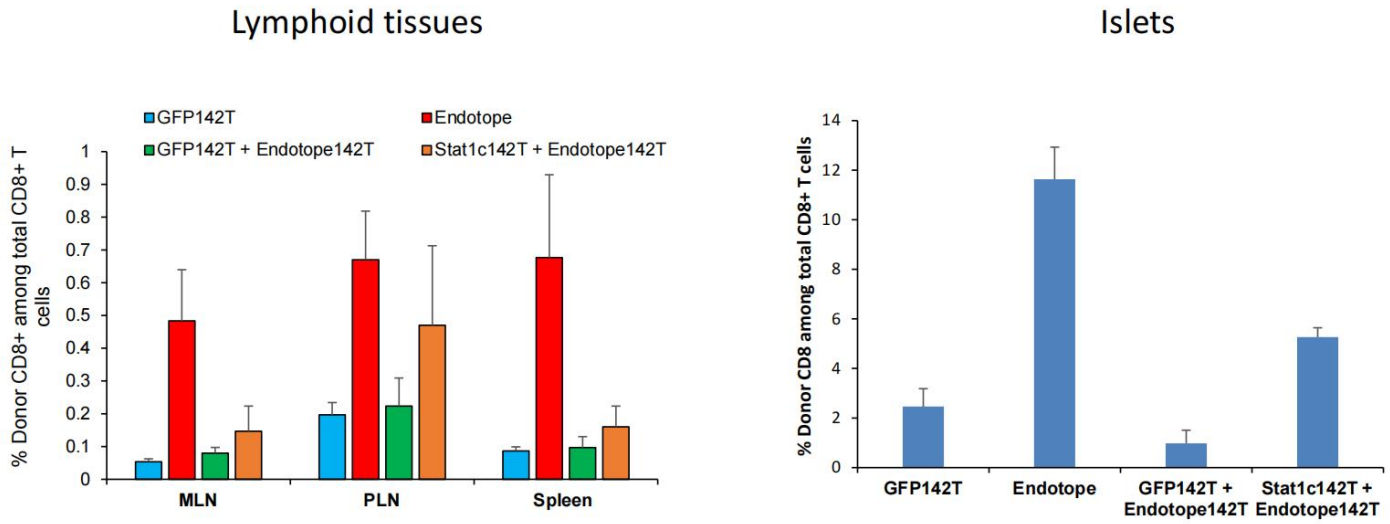


Unpublished and preliminary

Tolerogenic mRNA Vaccine Construct - Effect On CD8+ T Cells

Restricting CD8+ T cell stimulation to stromal cells limits their expansion

Response of antigen-specific CD8+ T cells
(adoptively transferred NY8.3 T cells)
after three i.p. injections (5 µg Endotope mRNA)



Note: continuous antigen presentation by lymph node stromal cells is known to result in CD8 T cell deletional tolerance

Unpublished

Founding Team /
Scientific Advisory Board

Pioneering Scientist Founder Driving Cutting-Edge Discovery

Professor Remi Creusot from Columbia University is our founding scientist and chairs the scientific advisory board

Scientific Founder / Advisor

Professor Remi Creusot

COLUMBIA UNIVERSITY

Stanford University

gsk GlaxoSmithKline

UCL

Entrepreneurial Founders Bringing Deep Industry Insight

Two entrepreneurial founders collectively bring deep industry know-how, collectively with decades of experience spanning across geographies

Entrepreneurial Founders

Adrian Chan

UNIVERSITY OF OXFORD

Linklaters

Goldman Sachs

UBS

SEDGWICK YARD

Richard Shen

UNIVERSITY OF CAMBRIDGE

UNIVERSITY OF OXFORD

Goldman Sachs

UBS

SEDGWICK YARD

Supported and Advised By Leading Immunologists

Our SAB comprises three world renowned immunologists, Professor Lawrence Steinman from Stanford, Professor Roberto Mallone from INSERM and Professor Jianzhu Chen from MIT

Scientific Advisors

Professor Lawrence Steinman

Stanford University

Weizmann Institute of Science

Harvard Medical School

Dartmouth

Neurocrine Biosciences

centocor

Professor Roberto Mallone

Inserm
La science pour la santé
From science to health

Benaroya Research Institute

Università di Torino

Professor Jianzhu Chen

Massachusetts Institute of Technology

Koch Institute for Integrative Cancer Research at MIT

Harvard Medical School

Boston Children's Hospital
Until every child is well

Columbia University

Stanford University

Note: SAB members are currently going through conflict clearance process

Value Proposition

Value Proposition

Endotope Biosciences is a best-in-class opportunity in the emerging realm of antigen specific immune modulation, and presents a compelling value proposition

1. Modular “plug & play” platform encoding multiple native and neoepitopes in single vector constructs
2. Optimal engagement of both CD4+ and CD8+ T lymphocytes maximizing immune tolerance induction
3. Customized precision therapy tailored to patients’ specific HLA haplotypes in a vast array of indications
4. Antigen specific immune modulation achieved in a non-integrating & non-replicating fashion
5. Cost efficient manufacturing in accordance with standard CMC protocols
6. Pioneering scientific founder / advisors from prestigious institutions backed by seasoned financial sponsors

Disclaimer

By accepting this document, the recipient agrees to be bound by the following obligations and limitations.

The purpose of this document is to provide information solely to the addressee. By accepting this document, the recipient agrees to keep confidential at all times information contained in it or made available in connection with this or any further investigation. This document is for the exclusive use of the persons to whom it is addressed and their advisers and shall not be copied or reproduced or distributed, communicated or disclosed in whole or in part by recipients to any other person nor should any other person act on it. The recipient has further agreed, on request, to return all documents and other material (including this document) received from Endotope Biosciences Inc. (“Endotope”) relating to proposals contained herein.

The information in this document has not been independently verified by Endotope Biosciences. Except in the case of fraudulent misrepresentation, no responsibility, liability or obligation is accepted by Endotope Biosciences or by any of its officers, employees or agents as to or in relation to the accuracy or sufficiency of this document or any other written or oral information made available to any interested party or its advisers and any such liability is expressly disclaimed.

Endotope Biosciences gives no undertaking, and is under no obligation, to provide the recipient with access to any additional information or to update this document or any additional information or to correct any inaccuracies in it which may become apparent, and it reserves the right, without giving reasons, at any time and in any respect to amend or terminate the proposals described herein.

Without prejudice to any liability for fraudulent misrepresentation, Endotope Biosciences and each of its officers, employees and agents disclaims any liability which may arise from this document, or any other written or oral information provided in connection therewith, and any errors contained therein and/or omissions therefrom.

By accepting this document, the recipient agrees to be bound by the foregoing limitations.