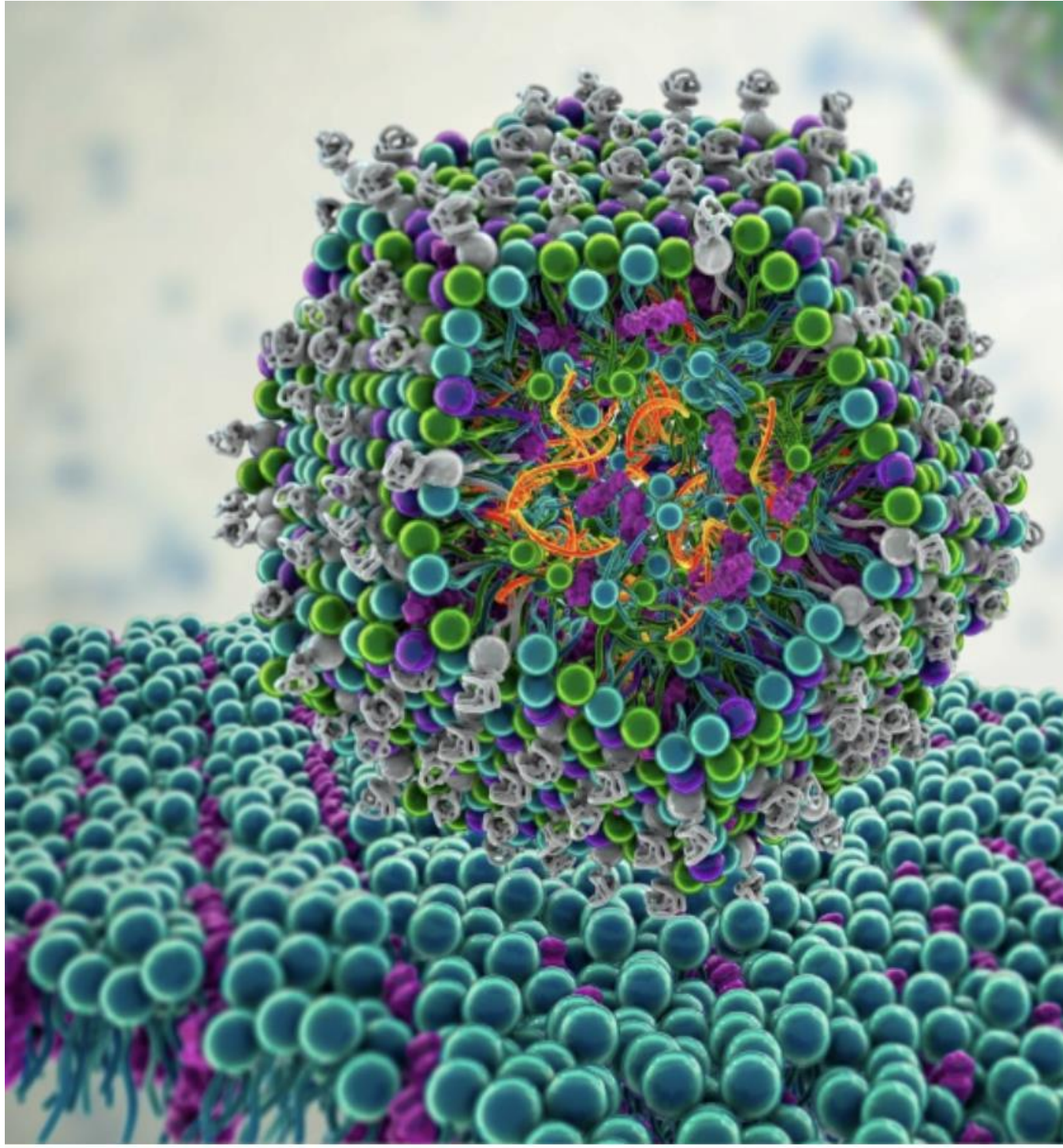
Can cancer teach us how to cure T1D?

Translating immune-evasive mechanisms from the cancer cell to the β cell



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Why we're here…

Disease

T1D is a life-threatening autoimmune disease that results in total loss of β cell mass

Children diagnosed with T1D lose ~15 years of life due to disease-related complications

Insulin is NOT a cure … significant need for new therapies that protect and preserve β cell mass

Process

Suicide induces murder

β cells are the source of their own demise* – under stress / viral infection they initiate immune activation

Once activated, immune cells attack insulin-producing β cells

β cells fail to induce immune-protective mechanisms and escape attack

Problem

Tumor biology reveals key mechanisms cancer cells use to escape immune destruction

T1D β cells fail to activate the same protective mechanisms

Targeting the regulation of these mechanisms has not been clinically feasible

emc2's unique technology and approach makes this possible

* Nat Rev Endocrinol (2023) 19(7):425–34.

emc2 βio is seeking $4M seed financing to accelerate clinical translation of a breakthrough T1D therapy

Who we are…

emc2 Bio is a pioneering biotech company leveraging world-leading expertise in islet immunology, β cell biology, bio-engineering and immune-oncology to transform Type 1 Diabetes (T1D) treatment outcomes.

Vision

Cure the β cell to Cure the Disease

emc2 Bio's Unique Approach

Developing an antibody-nanoparticle conjugate **(ANC)** to deliver genetic cargo specifically to pancreatic β cells, protecting them from immune destruction.

Scott Carmer
CEO, Co-Founder

- Former CEO at NexImmune, Inc. – a Johns Hopkins incubated company
- Prior to NEXI, held Executive Leadership positions at Amgen, Genentech, and MedImmune where he maintained responsibilities across the continuum of immune-oncology drug development and commercialization

Decio Eizirik, MD, PhD
Scientific Co-Founder

- Professor; ULB Center for Diabetes Research
- Listed by the ISI Essential Science Indicators among the top 2% most cited scientists in Clinical Medicine and Biology & Biochemistry with >430 publications (h-index 95)

Hai-Quan Mao, PhD
Scientific Co-Founder

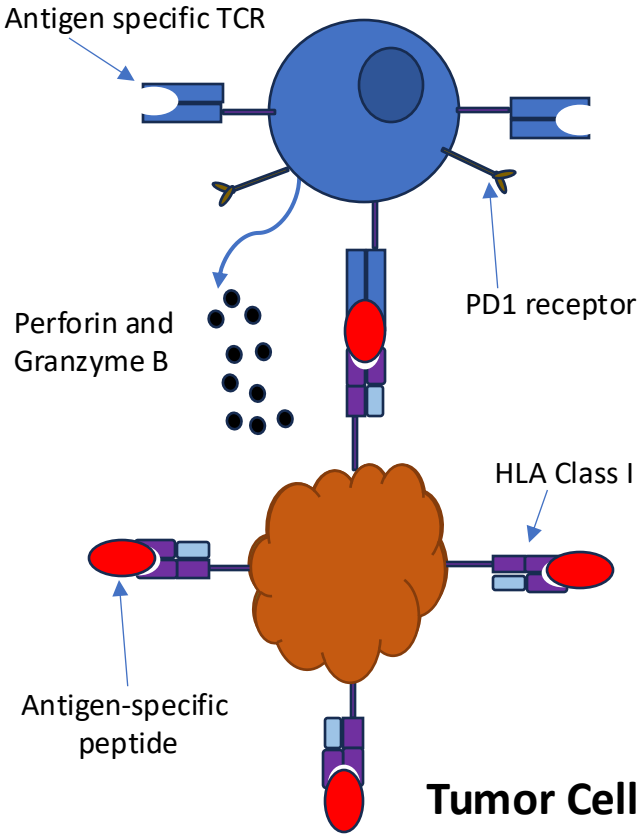
- Director, Institute of NanoBioTech; Professor, Depts of Materials Science Engineering & Biomedical Engineering - Johns Hopkins University
- He has published more than 200 peer-reviewed research articles and is a co-inventor of 36 U.S. patents and more than a dozen provisional applications.

Translating Success from Immuno-oncology to T1D

Problem: T1D β cells and tumor cells present as similar 'non-self' targets to the immune system…Tumor cells induce escape mechanisms – β cells don't

Immune Detection
(Tumor Destruction)

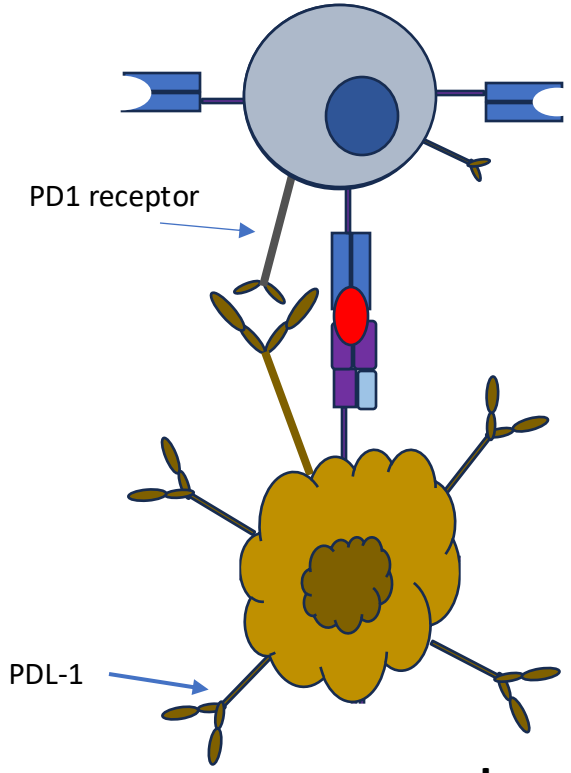
Activated CD8 T cell



Tumor Cell / T1D β cell

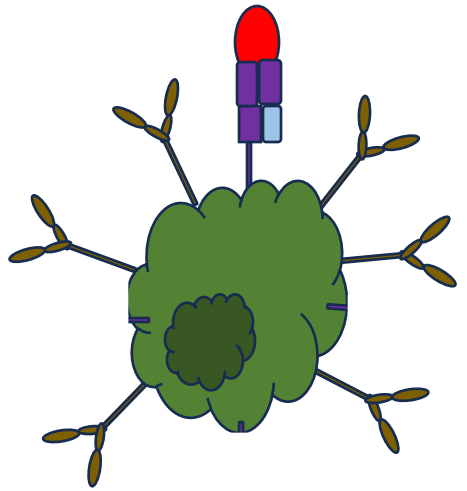
Immune Pressure
(Tumor Defense)

Tolerized CD8 T cell



Immune-Adaptive Tumor Cell

Immune Escape
(Tumor Survival)



Immune Evasive Tumor Cell

Int. J. Mol. Sci. 2023, 24, 6736

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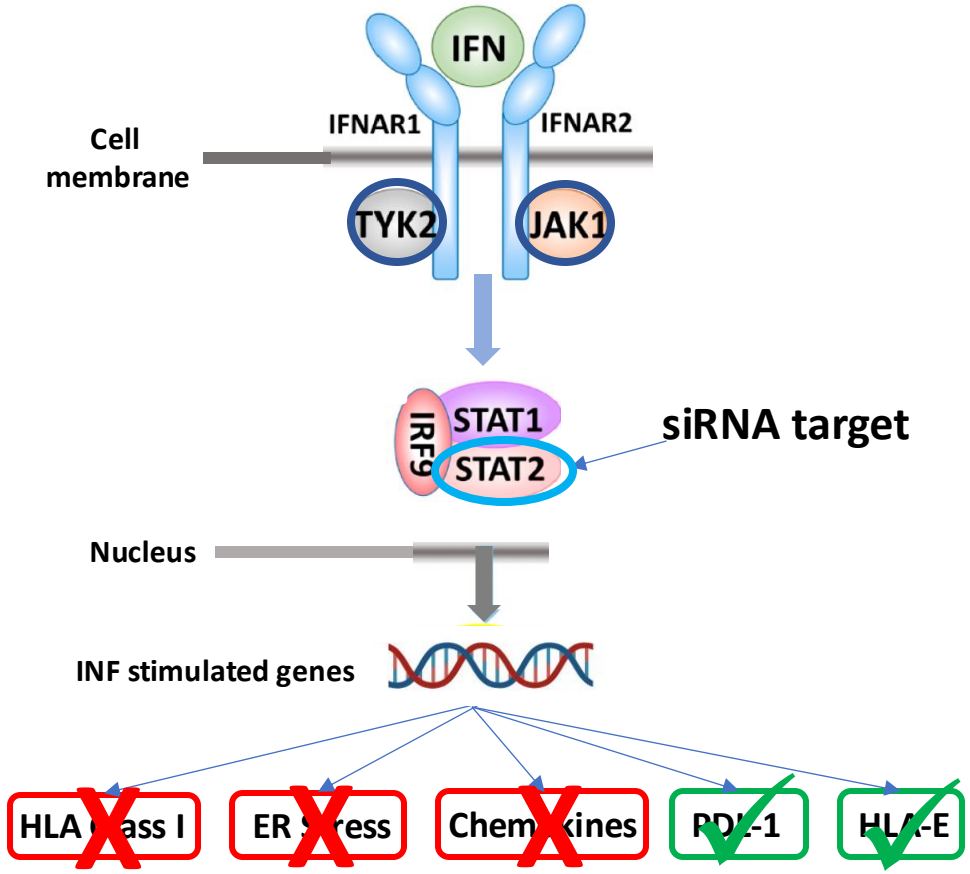
IFN signaling pathway: STAT2 is a KEY downstream regulator of immune-protective mechanisms and gene expression in human β cells

- As in cancer cells, the IFN signaling pathway regulates immune-protective gene networks in β cells
- In β cells, IFN signaling elicits paradoxical effects – inducing both pro-inflammatory and protective mechanisms
- Inhibiting upstream TYK2 and/or JAK1 activation with small molecules **DOES NOT** de-couple IFN signaling effects
- **STAT2 is a crucial downstream transcription factor that mediates IFN-induced expression of immune-protective mechanisms**
- Inhibiting STAT2 activation with siRNA **DOES** de-couple IFN signaling effects



"There is sufficient evidence to strongly support that targeting of IFN-mediated pathways will provide benefit to individuals with T1D"

doi: 10.3389/fendo.2023.1270325

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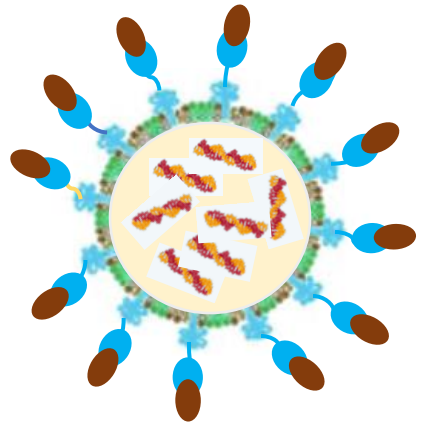
‘Saving the β cell from itself’: Components and Design Concepts of β cell-targeting ANC system

A	**Therapeutic Concept:**	**Target STAT2 gene pathway to modulate β cell / immune cell crosstalk and reduce β cell stress**
B	**Targeting Concept 1:**	**Receptor-specific targeting enhances cell binding and uptake**
C	**Targeting Concept 2:**	**NP formulation enhances β cell-selective gene delivery**



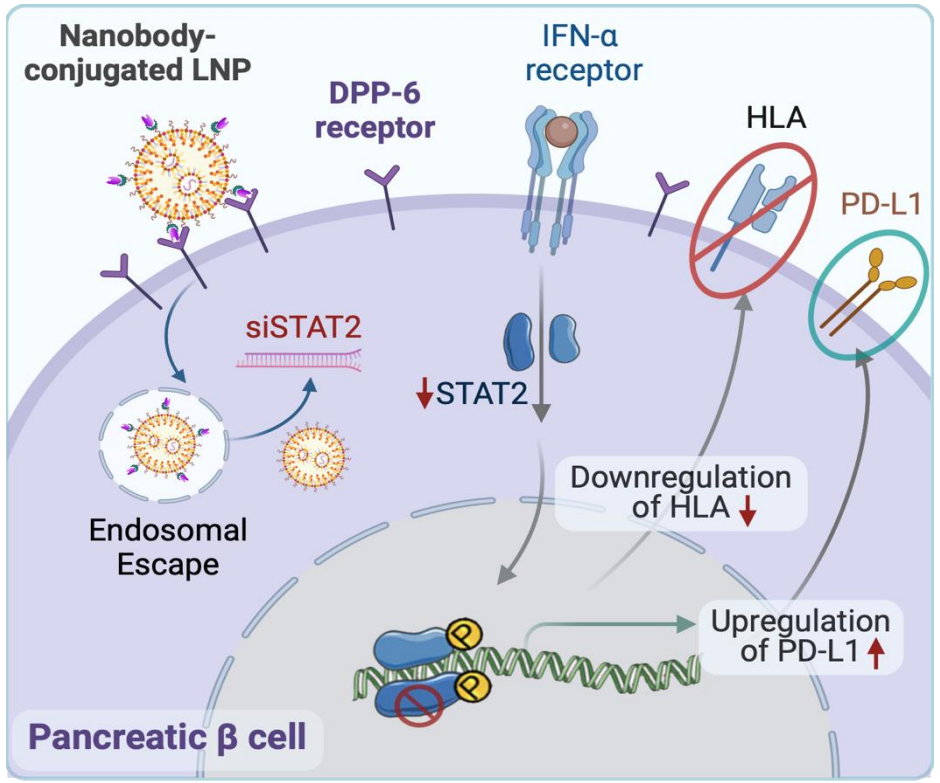
siRNA-STAT2 loaded ANC

STAT 2 knockdown induces protective effects of IFNα signaling

Lead Product (emc-011): Translating immune-evasive mechanisms from the cancer cell to the β cell by modulating immune-protective gene pathways

- We aim to target STAT2 regulated gene pathways to prevent:
  1) Immune detection: ***inhibit*** signals that promote immune recognition (e.g., HLA class I expression)
  2) Immune destruction: ***induce*** signals that protect β cells (e.g., PDL-1 and HLA-E expression)
- Gene networks that modulate immune-protective pathways are ubiquitously expressed
- EMC2's ANC is designed to enable β cell-specific delivery of protective genetic cargo

Promoting Immune-Protective Mechanisms



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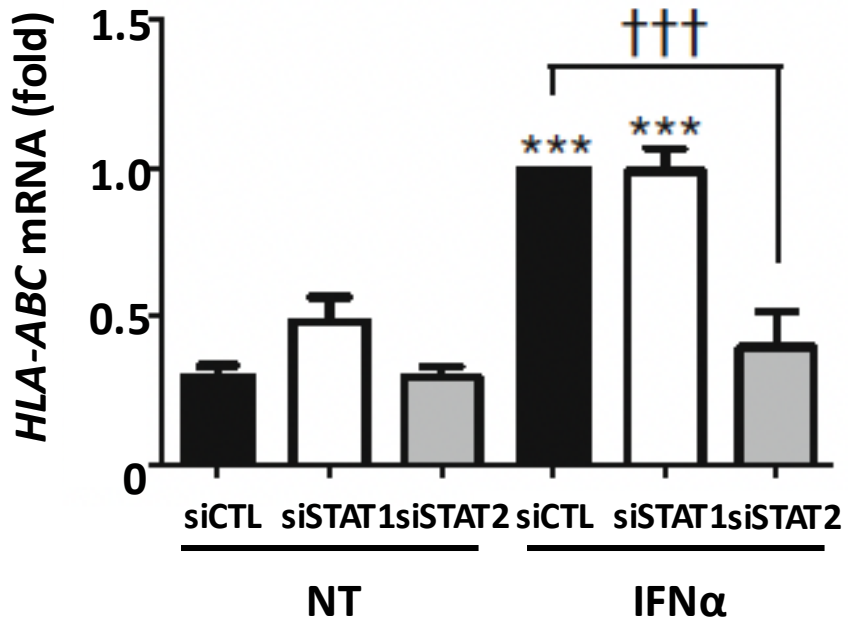
siRNA-mediated STAT2 knockdown induces β cell protective mechanisms in response to IFNα exposure (results from two independent studies)

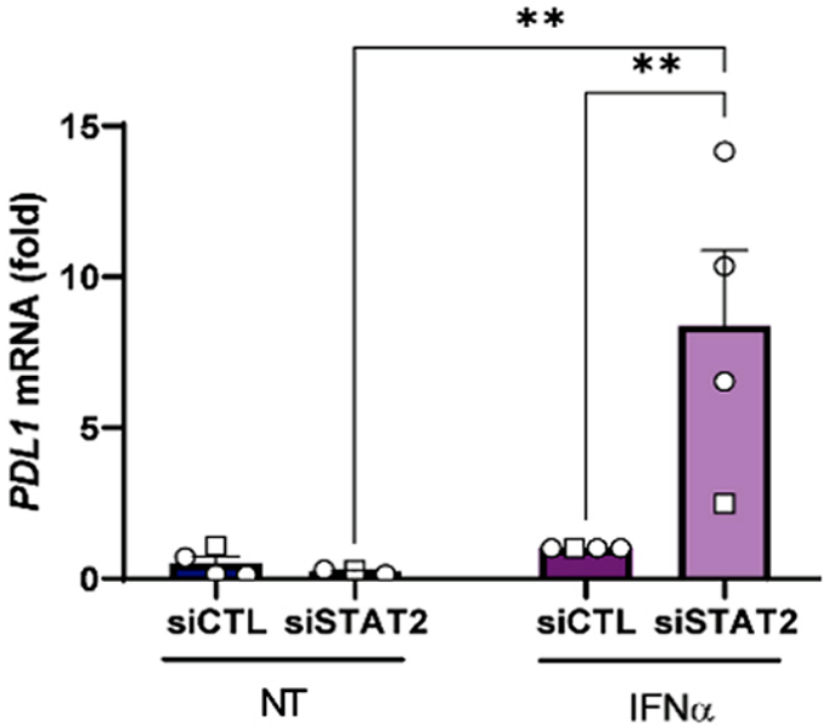
Downregulation of HLA-ABC mRNA expression



IFNα-induced upregulation of MHC class I and increased ER stress increases presentation of auto/**neoantigens** to the immune cells

Diabetologia (2017) 60:656–667

Upregulation of PDL-1 mRNA expression

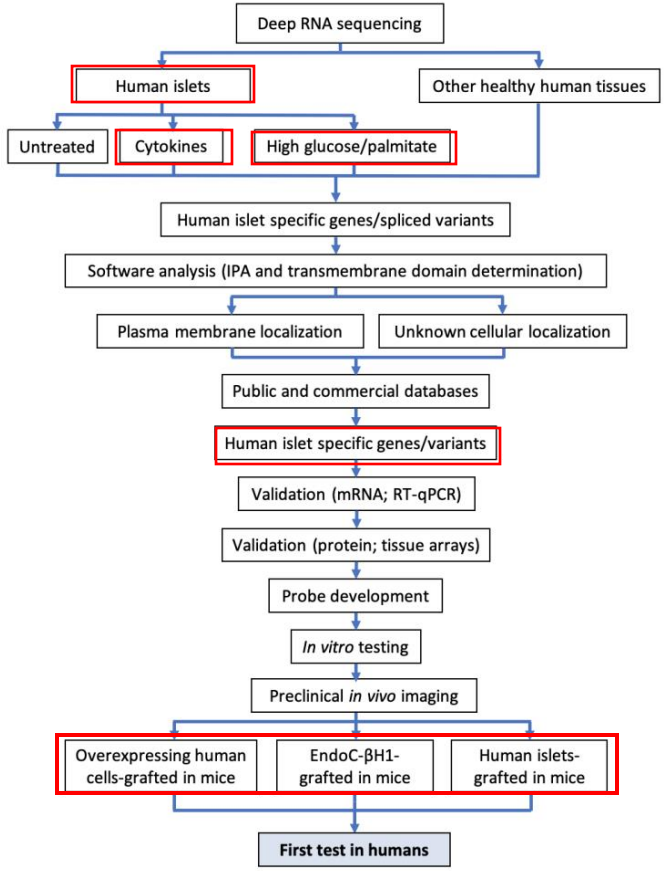


PD-1-PDL1 system is crucial to the preservation of tolerance to beta cell antigens

M.L. Colli et al. / EBioMedicine 36 (2018) 367–375

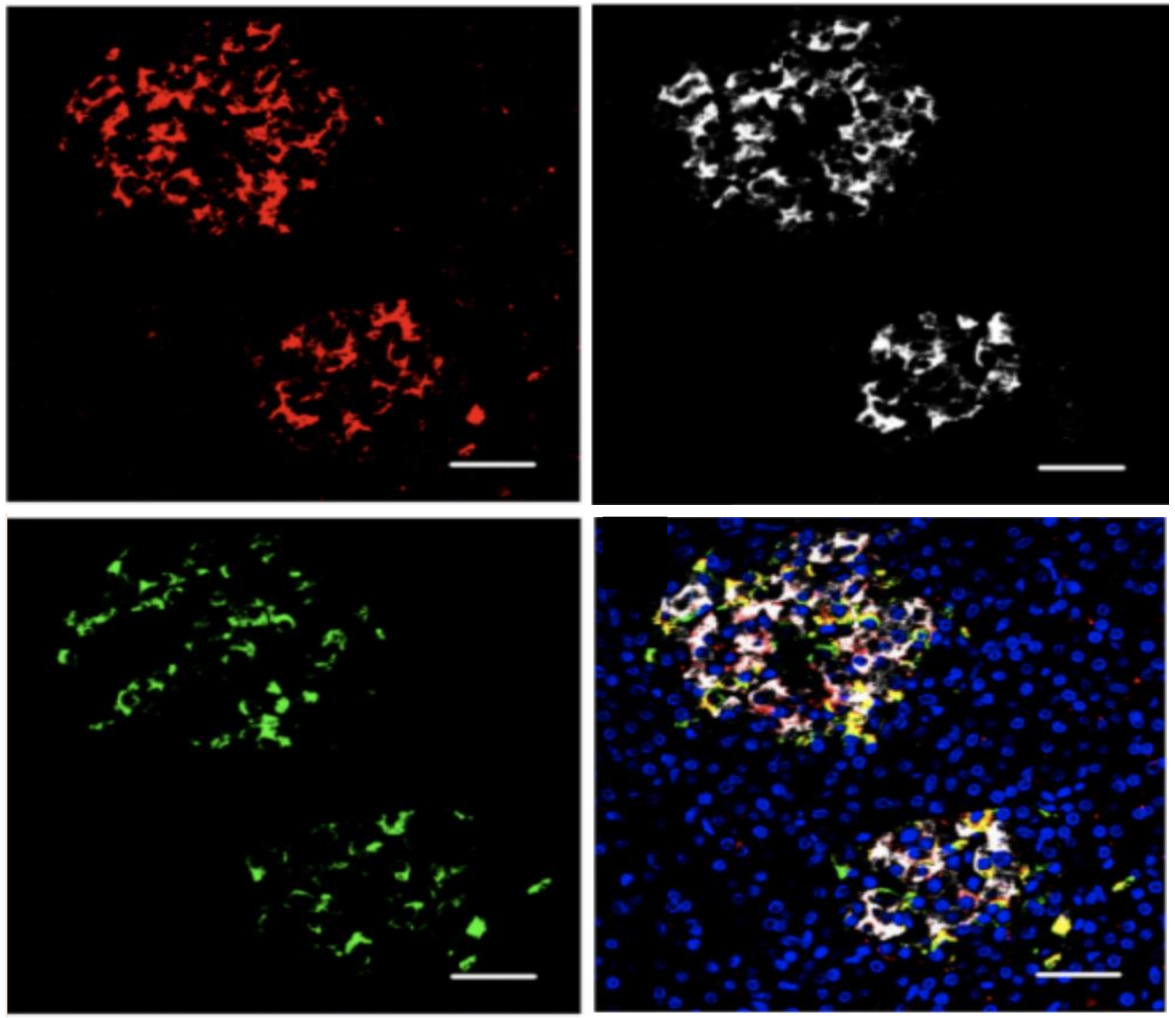
β cell receptor-specific targeting

β Cell Target: DPP6 is a stable and highly expressed pancreatic β cell-specific protein



Step-by-step workflow used to identify new β cell biomarkers and to generate corresponding imaging probes. A schematic overview of the methodology used to mine RNA sequencing data for discovery of novel pancreatic islet biomarkers is shown.

Demine et al; Int. J. Mol. Sci. 2020, 21, 7274; doi:10.3390/ijms2119727



A representative human pancreas stained for DPP6 (red), insulin (white), glucagon (green); and overlay of DPP6 (red), insulin (white) and glucagon (green). Data indicate co-staining of both insulin and glucagon with DPP6

Balhuizen A et al. SCIENTIFIC REPORTS | 7: 15130 | DOI:10.1038/s41598-017-15417-2

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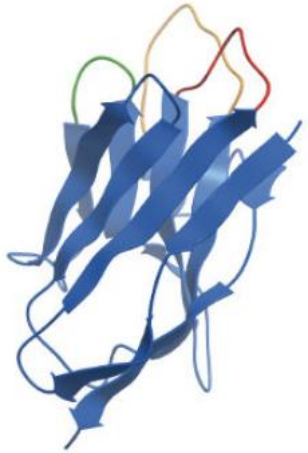
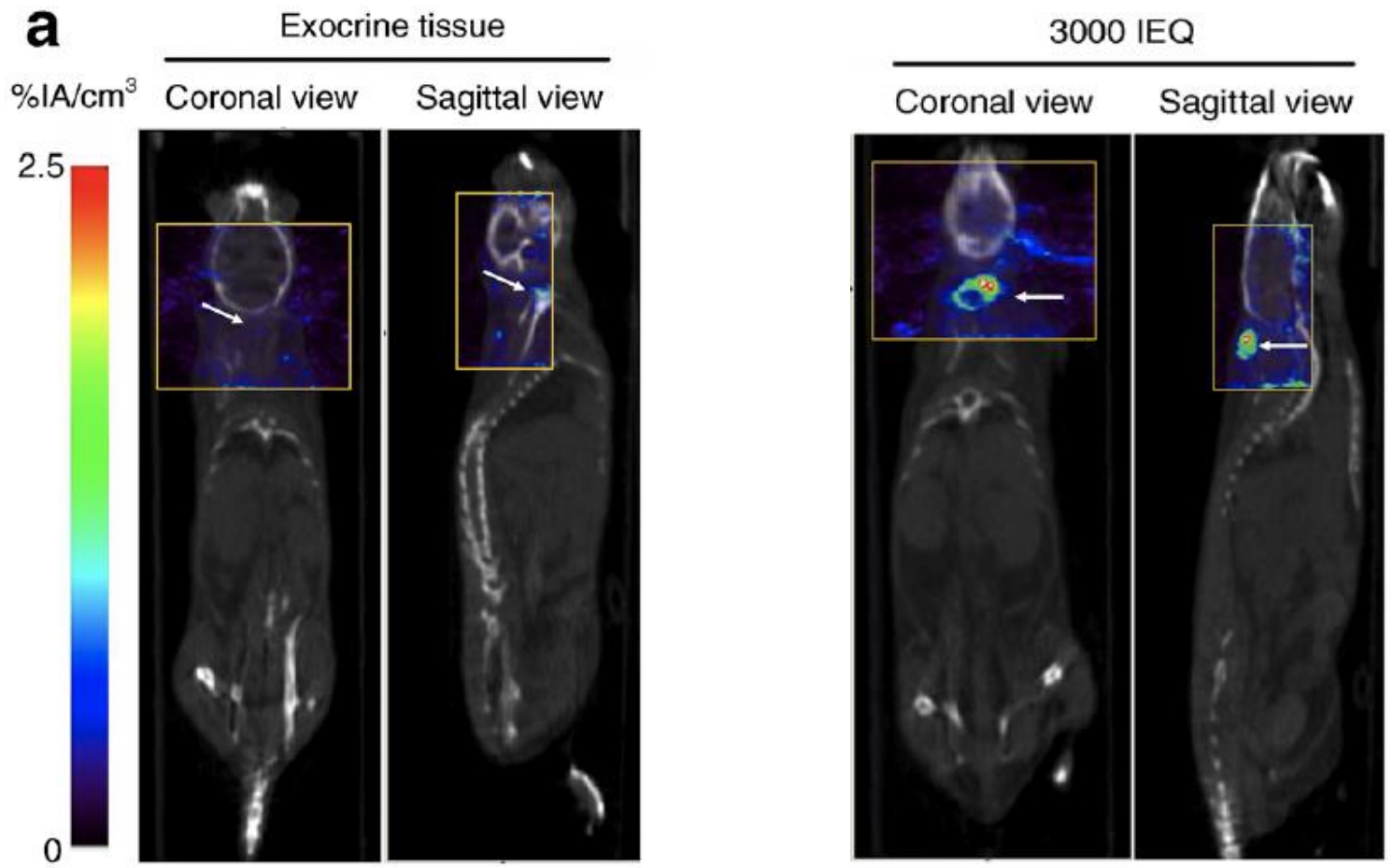
Targeting Moiety: 4hD29 is a high affinity nanobody targeting human DPP6

Effectively labels DPP6 expressing human β-cells implanted in SCID mouse model

DPP6 protein

DPP6 camelid nanobody





In vivo SPECT imaging of primary human islets transplanted into SCID mice. Four weeks post-transplantation, the mice were imaged by total body CT, followed by a focal SPECT imaging scan using the anti-DPP6 4hD29 nanobody. The yellow square indicates the field-of-view of the SPECT camera; white arrows indicate the graft localization

Demine et al Diabetologia (2020) 63:825–836

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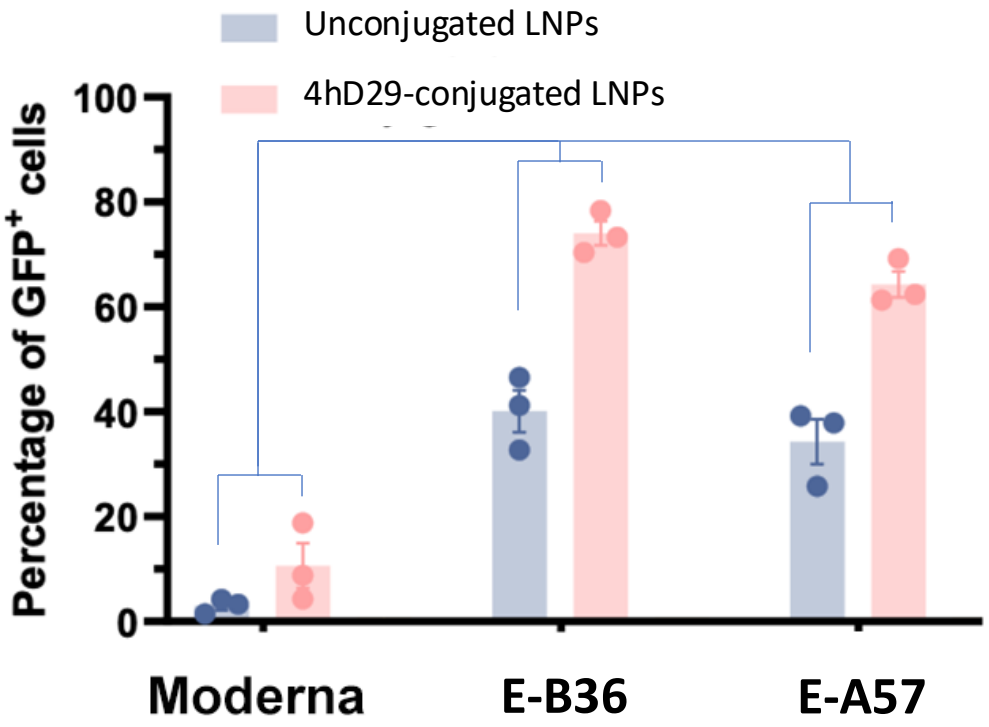
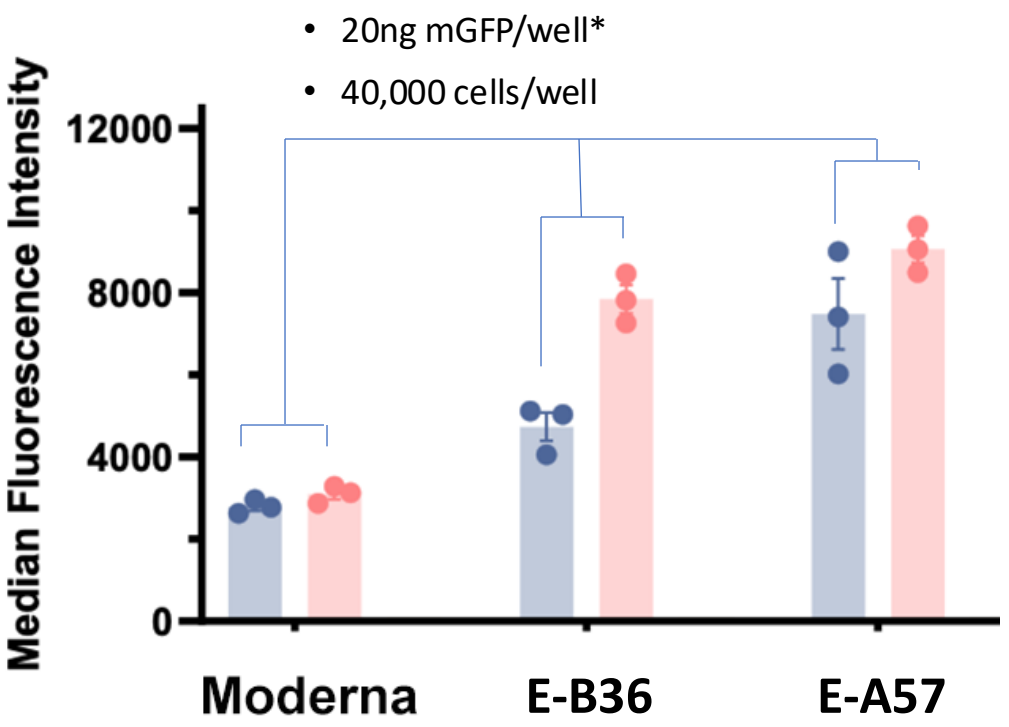
β cell-specific gene cargo delivery

Antibody-Nanoparticle Conjugate: 4hD29-conjugation enhances functional performance of β cell-specific LNP formulations





* Lowest dose evaluated used for initial conjugation testing

H-Q Mao et al: data on file Unpublished results

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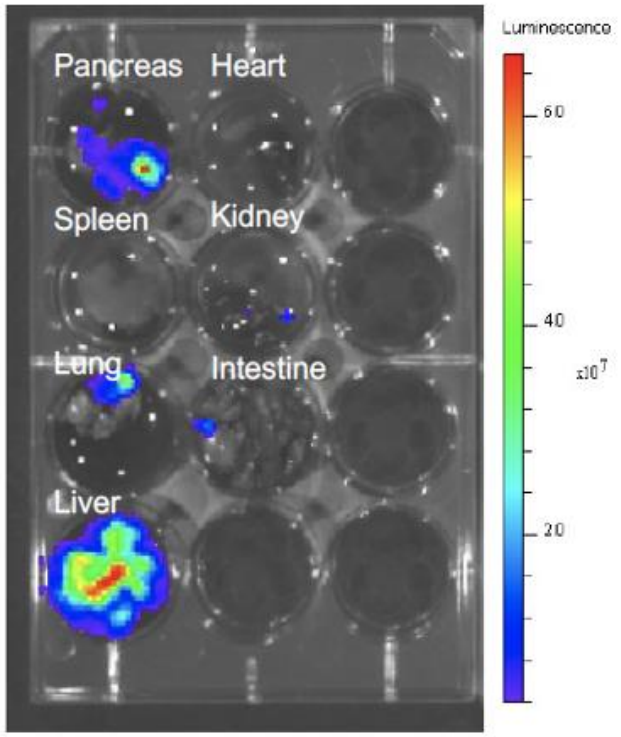
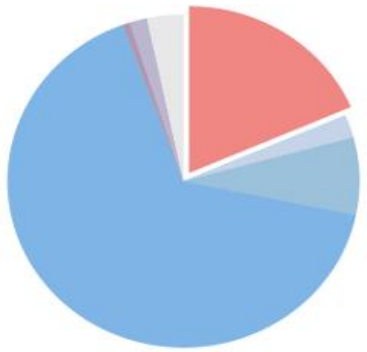
LNP formulation: emc2 ANCs exhibit significantly greater pancreas-selective distribution and gene transfection in healthy mice vs Moderna ANC control

mAb-conjugated Moderna LNP



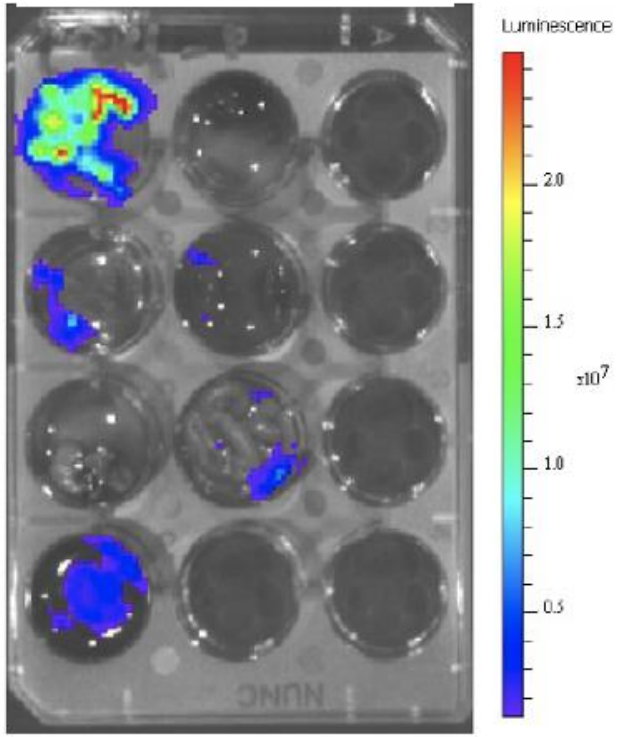


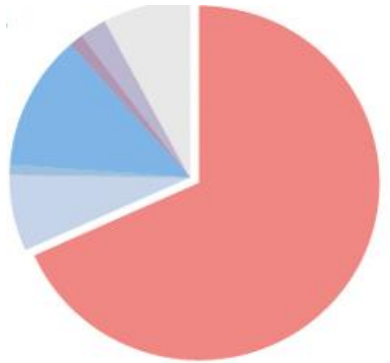
18.52% Pancreas
2.25% Spleen
7.51% Lung
66.11% Liver
0.67% Heart
1.61% Kidney
3.33% Intestine

H-Q Mao et al; data on file

Unpublished results

mAb-conjugated EMC2 LNP





68.29% Pancreas
6.95% Spleen
0.94% Lung
12.35% Liver
1.24% Heart
2.42% Kidney
7.81% Intestine

* Murine reactive β cell-specific antibody analog – research purposes only

Pipeline: Progress to-date

Program (Target)	Target Indication	Modality	Proof of Mechanism	Proof of Concept	IND	Funding / Sponsor
emc-011 (STAT2)	Stage 3 T1D (recent onset)	Antibody-NP conjugate				Seed Financing
emc-440	β cell Imaging	Radiolabeled Nb-probe				THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST; Breakthrough T1D™

$4M Seed funds company through significant value creating milestones – mitigates future product development and investment risk

AIM	Milestones	Year 1												Year 2											
		M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
1	**Proof of Concept - SCID Mouse**																								
	> Confirm safety and toxicity meets TPP > Confirm biodistribution, % transfection and STAT2 knockdown meets TPP > Confirm disease modifying activity in disease model meets / exceeds TPP > Dose response/interval and associated toxicity meets target product profile																								
2	**Proof of Concept - NHP**																								
	> See quantifiable results above - all compared to TPP metrics																								
3	**Proof of Concept - β cell imaging**																								
	> Synthesize probe-conjugated LNPs for β cell-targeted delivery > Confirm labeling of probe-conjugated LNPs in islet cell-engrafted SCID mice																								
4	**Proof of Mechanism - Multi-target gene expression**																								
5	**Series A Fianancing**																								

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Summary and Conclusions

- T1D is a life-threatening disease wherein “suicide” induces “murder”
- Cancer biology teaches us ‘how to save the β cell from itself’
- New treatment strategies require three key components:
  1. The right therapeutic target
  2. β cell-specific targeting
  3. β cell-specific gene delivery
- emc2 βio has the only technology that delivers all three
- $4M seed investment creates significant value, mitigates technical risk and sets up Series A syndicate

APPENDIX

Intellectual Property – Issued & Planned

Independently Owned IP

- Eizirik DL and co-workers. A new biomarker expressed in pancreatic b-cells useful in imaging or targeting b-cells. Submitted to the European Patent Office on April, 2016, EP16166588.0; PCT/EP201/059459; WO 2017/182603 A1; USA patent US 11,243,214 granted on 08.02.2021, EP17721559 intention to grant issued on 18.01.2024 (national validation to be performed BE, CH, DE, FR, GB, IE, NL)
  Patent covers the beta-cell biomarker DPP6 and approaches to target it, including nanobodies; co-ownership with Vrije Universiteit Brussel
- Tang K, Eizirik DL and co-workers. Anti-DPP6 chimeric antigen receptor bearing regulatory T-cells. Submitted to the United States Patent and Trademark Office on October 29, 2021, (63/107.110), published on 05.05.2022; PCT/US2021/072139; WO 2022/094614 A1; pending applications: US2023381228A1 and EP4236987A1
  Patent covers the use of DPP6 to target T-regs to the beta-cells; developed in collaboration with UCSF, USA
- Eizirik DL and co-workers. Plasma membrane biomarkers preferentially expressed in pancreatic b-cells useful in imaging or targeting b-cells. Patent No. WO/2009/101181, International Application Number, PCT/EP2009/051721, 2009; US 8,425,878 granted on 23.04.2013 (patent only in force in the US at this stage),
  Patent covers the beta-cell biomarker FXYDgamma2A (completely b-cell specific) and approaches to target it. Developing nanobodies against this target, co-ownership with ISB and Kaneka Eurogentec
- **C17083**: Compositions of Lipid Nanoparticles for Plasmid DNA Delivery to the Liver and Methods for Preparing the Same
  Patent covers LNP library. Expanded to include different nucleic acid cargos. Continuing to add filings to cover cell type specific formulations and utilities

Planned (Project-related) IP To Be Generated

- New β-cell specific LNP formulations will be jointly filed and owned between JHU and EMC2 βio
- The nanobody-conjugated LNP compositions will be jointly owned between JHU, ULB and EMC2 βio
- The utilities for T1D treatment and specific dosing and formulation compositions will be filed separately as jointly owned IP between JHU, ULB and EMC2 βio

Supporting Publications

1. *A nanobody-based nuclear imaging tracer targeting dipeptidyl peptidase 6 to determine the mass of human beta cell grafts in mice*
   Stéphane Demine; Rita Garcia Ribeiro; Julien Thevenet; Lorella Marselli; Piero Marchetti; François Pattou; Julie Kerr-Conte; Nick Devoogdt; and **Decio L. Eizirik**
   Diabetologica (2020) 63:825–836

2. *Beta Cell Imaging—From Pre-Clinical Validation to First in Man Testing*
   Stephane Demine, Michael L. Schulte, Paul R. Territo and **Decio L. Eizirik**
   Int. J. Mol. Sci. 2020, 21, 7274; doi:10.3390/ijms21197274

3. *A nanobody-based tracer targeting DPP6 for non-invasive imaging of human pancreatic endocrine cells*
   Alexander Balhuizen, Sam Massa, Iris Mathijs, Jean-Valery Turatsinze, Jens DeVos, Stéphane Demine, Catarina Xavier, Olatz Villate, Isabelle Millard, Dominique Egrise, Carmen Capito, Raphaël Scharfmann, Pieter Veld, Piero Marchetti, Serge Muyldermans, Serge Goldman, Tony Lahoutte, Luc Bouwens, **Decio L. Eizirik**, and Nick Devoogdt
   Sci Rep. 2017 Nov 9;7(1):15130. doi: 10.1038/s41598-017-15417-2

4. *Multi-step screening of DNA/lipid nano-particles and co-delivery with siRNA to enhance and prolong gene expression*
   Yining Zhu, Ruouchen Shen, Ivan Vuong, Rebekah Reynolds, Melanie Shears, Ahi-Chang Yao, Yizong Hu, Won June Cho, Juayuan Kong, Sashank Reddy, Sean Murphy, **Hai-Quan Mao**
   Nature Communications; https://doi.org/10.1038/s41467-022-31993-γ

5. *Screening for lipid nanoparticles that modulate the immune activity of helper T cells towards enhanced anti-tumour activity*
   Yining Zhu, Jingyao Ma, Ruochen Shen, Jinghan Lin, Shuyi Li, Xiaoya Lu, Jessica L. Stelzel, Jiayuan Kong, Leonardo Cheng, Ivan Vuong, Zhi-Cheng Yao, Christine Wei, Nicole M. Korinetz, Wu Han Toh, Joseph Choy, Rebekah A. Reynolds, Melanie J. Shears, Won June Cho, Natalie K. Livingston, Gregory P. Howard, Yizong Hu, Stephany Y. Tzeng, Donald J. Zack, Jordan J. Green, Lei Zheng, Joshua C. Doloff, Jonathan P. Schneck, Sashank K. Reddy, Sean C. Murphy & **Hai-Quan Mao**
   Nature Biomedical Engineering https://doi.org/10.1038/s41551-023-01131-0

Comparing therapeutic approaches that target the INFσ/JAK/STAT pathway

	Pro-Inflammatory Effects			Protective Effects				
	HLA Class I Hyperexpression	ER Stress (Oxidative, Mitochondria, Neoantigens)	Inflam Chemokines (CXCL10)	HLA-E	PDL-1	Modality	Beta cell specific	T1D clinical trials
JAK1 inh	Prevents	Improves ER stress markers	Inhibits	No effect	Prevents induction	small molecule	No	Yes
JAK2 inh	Prevents	No effect	Inhibits	No effect	No effect	small molecule	No	Yes
TYK2 inh	Prevents	Improves ER stress markers	Unknown	No effect	Prevents induction	small molecule	No	IND approved
STAT1 inh	Prevents	Reduces ER stress	Inhibits	No effect	No effect	siRNA	Possible	No
STAT2 inh	Prevents	Reduces ER stress	Inhibits	Upregulation	Upregulation	siRNA	Possible	No

Adapted from: Eizirik et al., Diabetes 2021;

"New drugs should be developed to prevent IFNα-induced proinflammatory effects, i.e. HLA class I up-regulation, chemokine production and ER stress, while preserving up-regulation of the protective PDL1 and HLA-E expression"

Eizirik et all, Diabetes 2021

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