Intestinal Fc receptor-targeted nanomedicines boost semaglutide effect in type 2 diabetes

Soraia Pinto

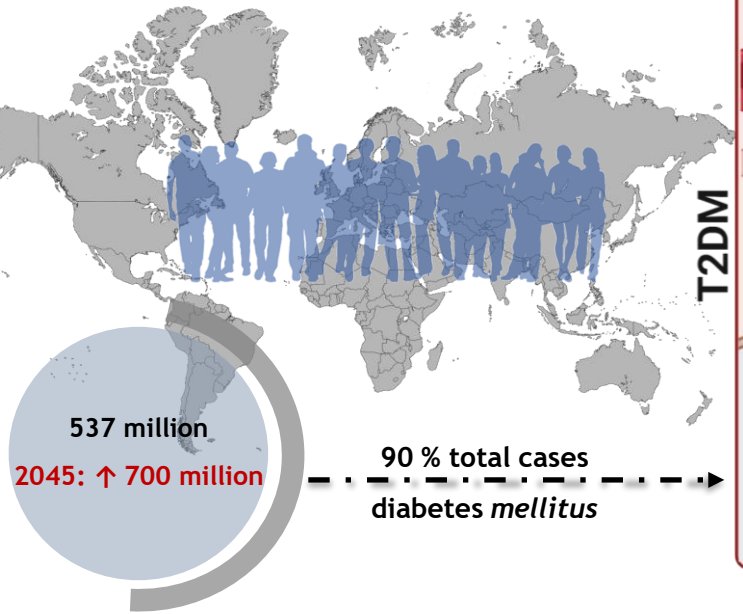
Session: Nanomedicine and Nanoscale Delivery (Focus: Oral)

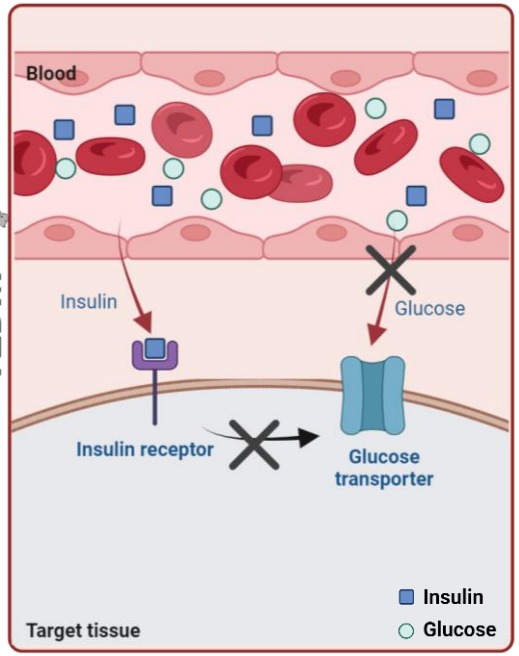
NTCD NANOMEDICINES & TRANSLATIONAL DRUG DELIVERY

CRS 2025 ANNUAL MEETING & EXPOSITION PHILADELPHIA, PA JULY 13-18, 2025

3S INSTITUTO DE INVESTIGAÇÃO E INOVAÇÃO EM SAÚDE UNIVERSIDADE DO PORTO

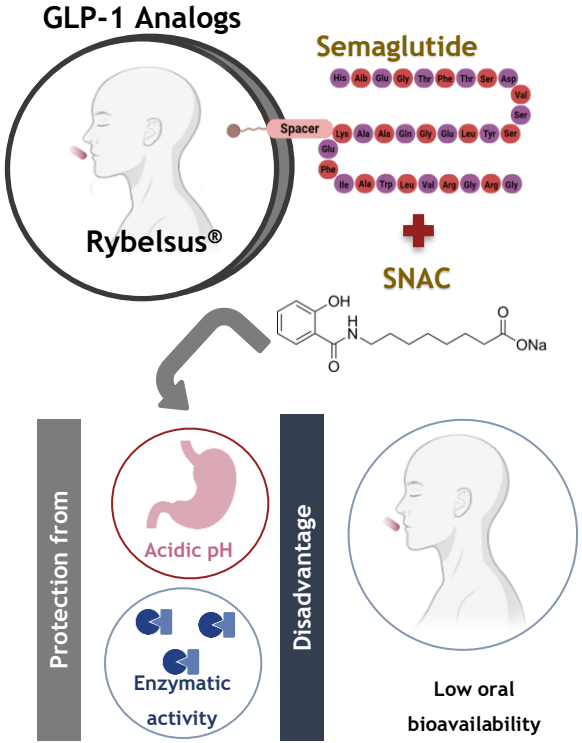
NEXT-GENERATION DELIVERY INNOVATIONS





T2DM: Type 2 diabetes *mellitus*

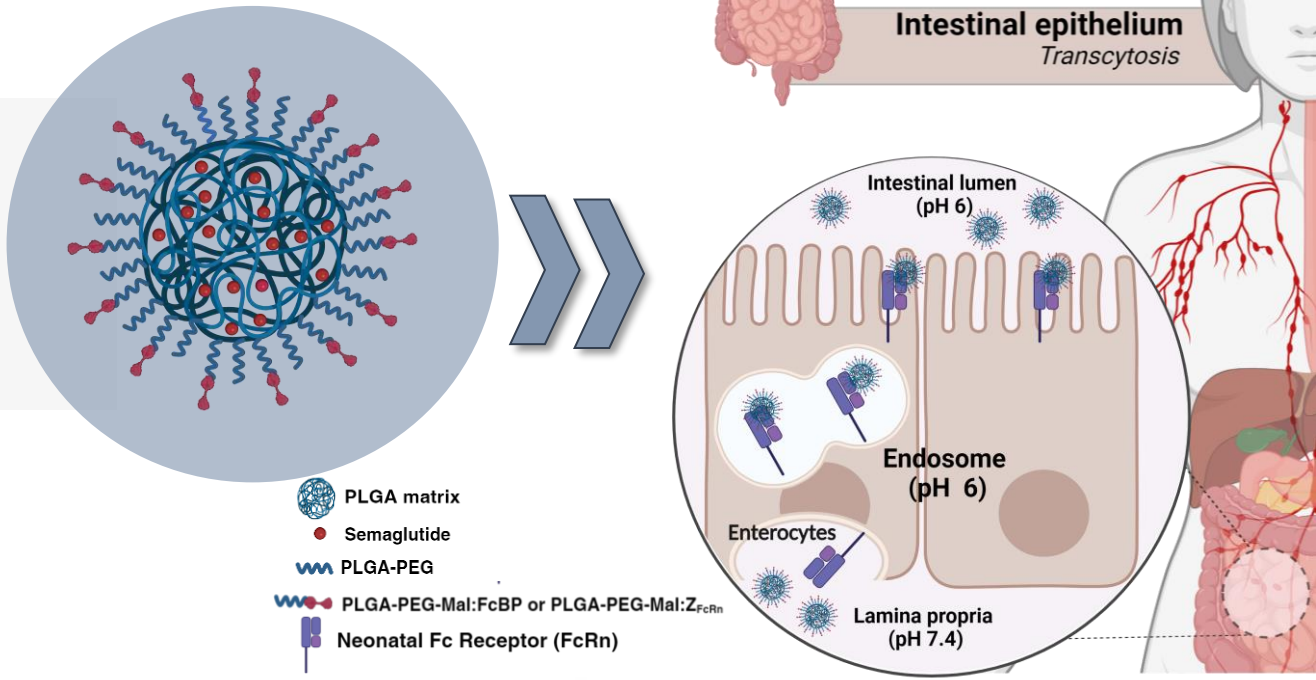
T2DM is characterized by insulin resistance and inadequate secretion of insulin



International Diabetes Federation, IDF Diabetes Atlas: 10th Editions. 2021.
Chatterjee S., *et al.*. Lancet. 389 (2017) 2239-2251.
Wu Y., *et al.*. Int. J. Med. Sci. 11 (2014) 1185-1200.

How to improve the oral delivery of semaglutide?

To incorporate **semaglutide** into polymeric NPs surface-functionalized with **FcRn-targeted ligands (Peptide, $FcBP_2$,** and **affibody, Z_{FcRn})**

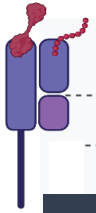


FcBP: FcRn-binding peptide

Z_{FcRn}: Affibody molecule

FcRn: Neonatal Fc receptor

Selection of FcRn-targeted ligands with affinity for hFcRn



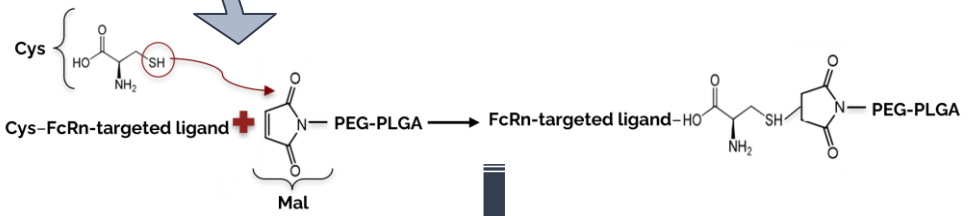
FcRn-targeted ligand	Code	K_D pH 6.0 (nM)	K_D pH 7.4 (nM)
HSA	HSA	7,300 ± 1,300	No binding
CQRFVTGHFGGLHPANG	$FcBP_1$	No binding	No binding
CQRFCTGHFGGLYPCNG	$FcBP_3$	No binding	No binding
RF-Pen-TGHFG-Sar-NMeLeu-YPC	$FcBP_4$	No binding	No binding
VDAKYAKEWMRAAHEIRWLPNLTFDQRV AFIHKLEDDPSQSSELLSEAKKLNDSQAPKC	Z_{FcRn}	72 ± 32	No binding

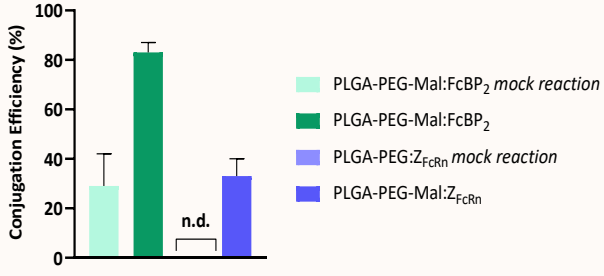
$FcBP_2$ and Z_{FcRn} bind to hFcRn in a pH-dependent manner

K_D: Dissociation constant

$FcBP_2$ and Z_{FcRn} covalently linked to PLGA-PEG-Mal

FcRn-ligands:PLGA-PEG-Mal Conjugation

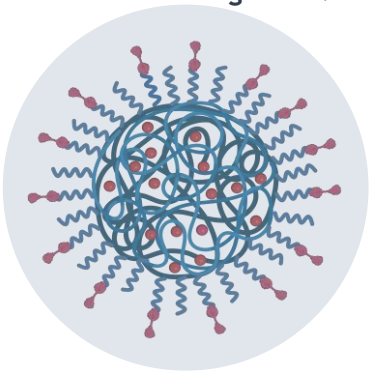


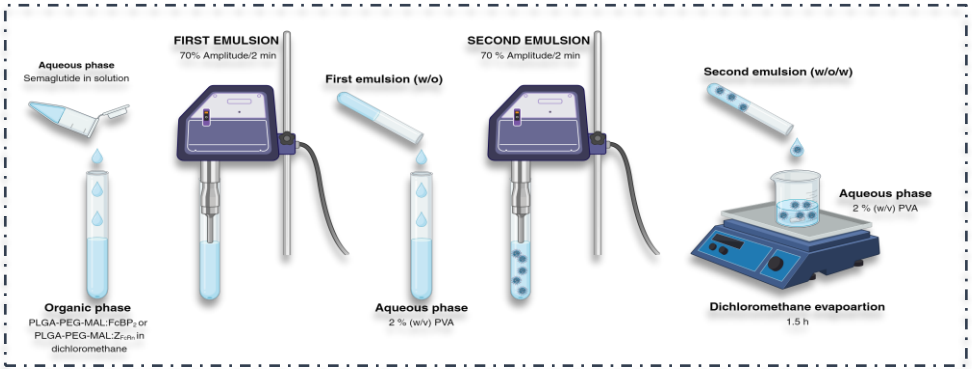


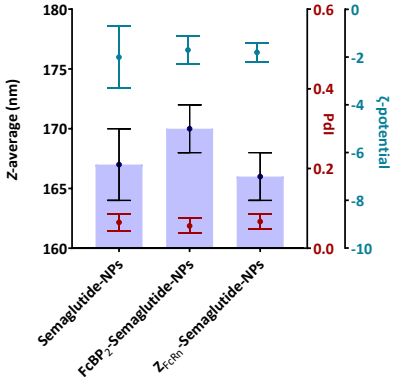
Polymer	Atomic composition (%)			
	C1s	O1s	N1s	S2p
PLGA-PEG-Mal	70.8	29.1	0.1	n.a.
PLGA-PEG-Mal:$FcBP_2$	67.5	31.5	0.9	0.09
PLGA-PEG-Mal:Z_{FcRn}	66.4	33.0	0.6	0.04

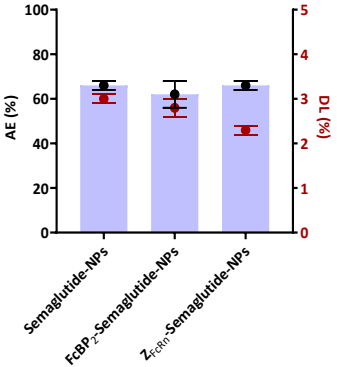
Pinto S., *et al.* J Control Release 366 (2024) 621-636.

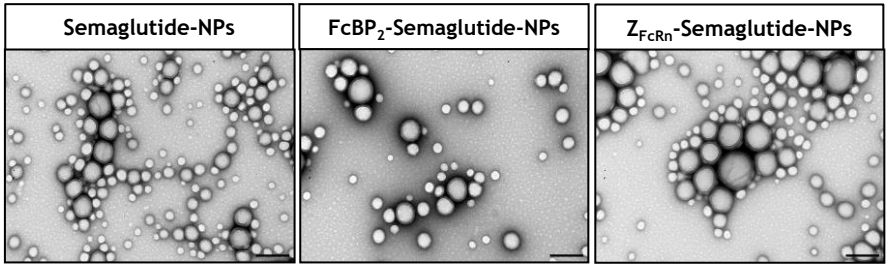
Production of FcRn-targeted Nanoparticles







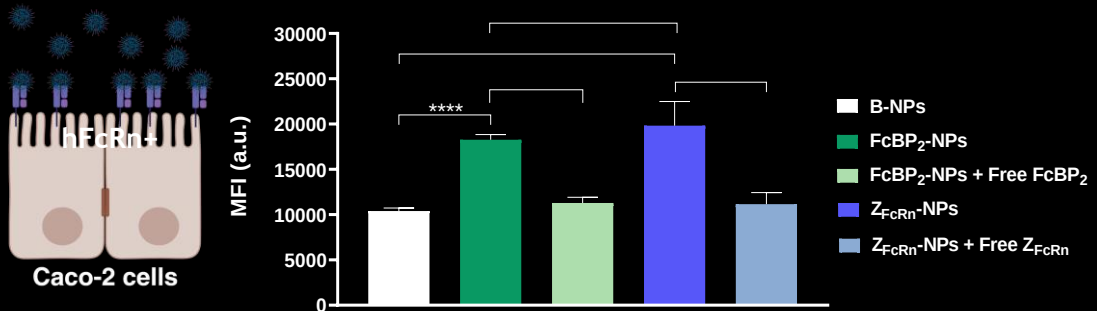


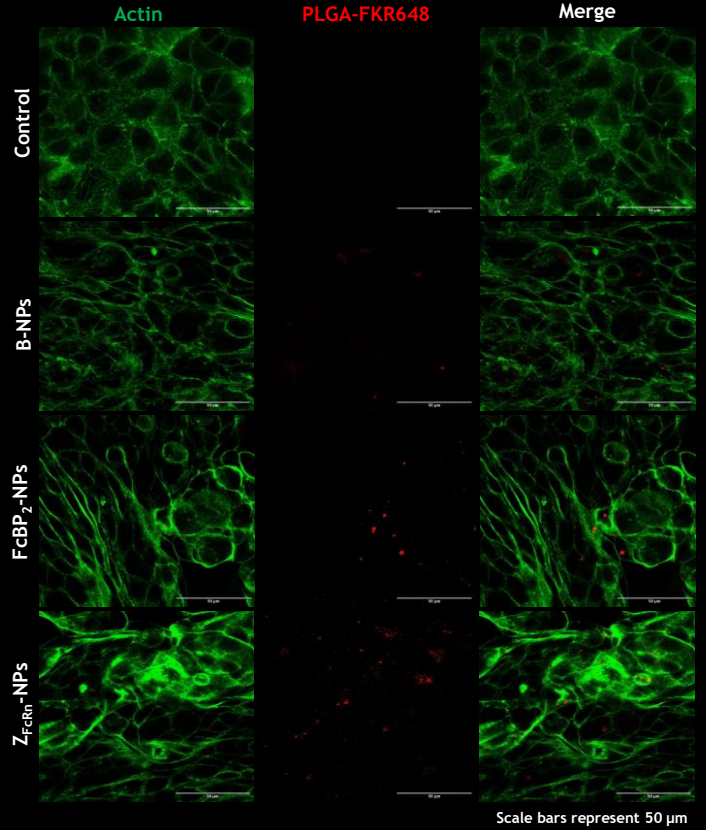


Scale bars represent 200 nm

Pinto S., *et al*. J Control Release 366 (2024) 621-636.

In vitro uptake of FcRn-targeted NPs by intestinal cells





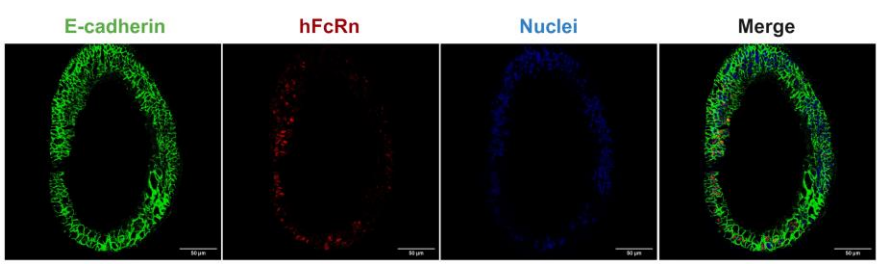
Scale bars represent 50 µm

Pinto S., *et al.* J Control Release 366 (2024) 621-636.

Microinjection of FcRn-targeted NPs into Human Intestinal Organoids lumen

University Medical Center Groningen

BBT BIOMATERIALS AND BIOMEDICAL TECHNOLOGY



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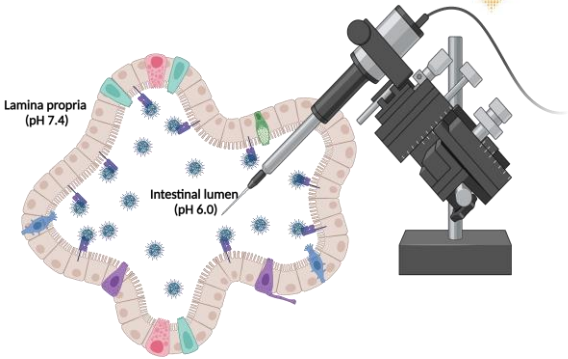
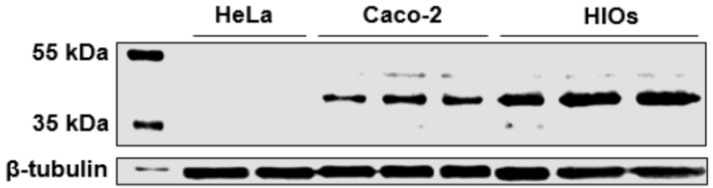
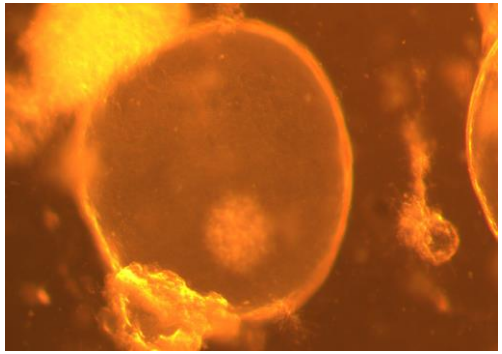
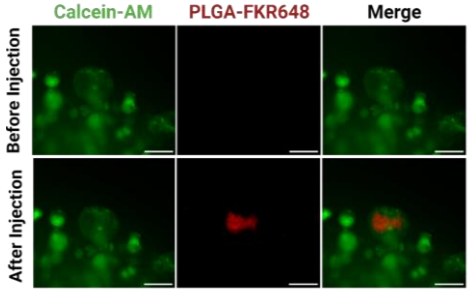




HIOs endogenously express hFcRn



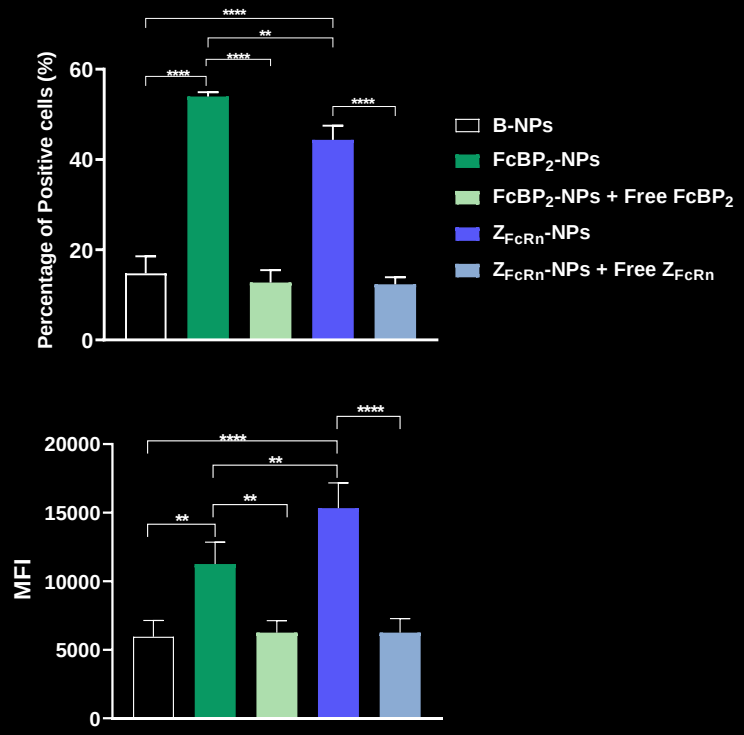


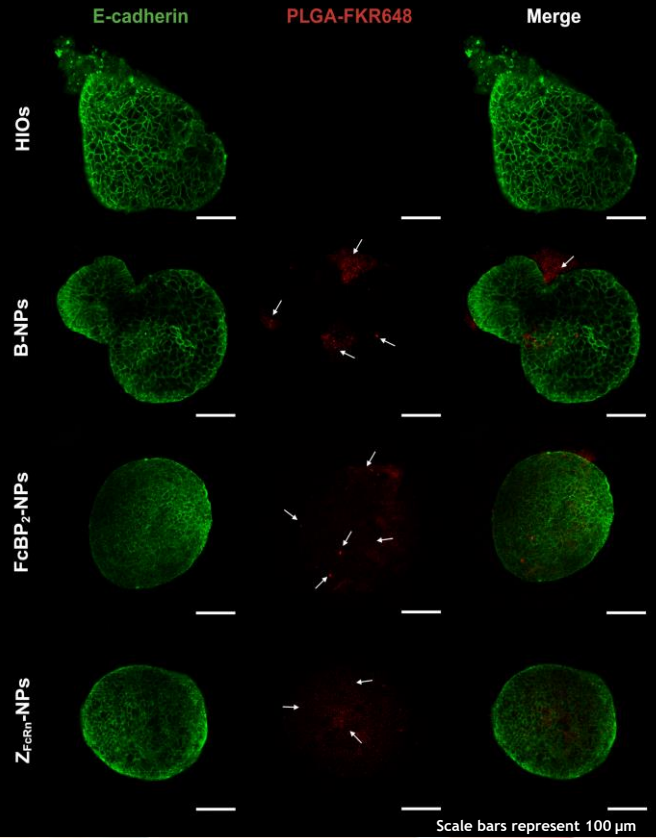
Scale bars represent 500 µm

HIOs: Human Intestinal Organoids

Pinto S., *et al*. J Control Release 366 (2024) 621-636.

In vitro uptake of FcRn-targeted NPs by HIOs

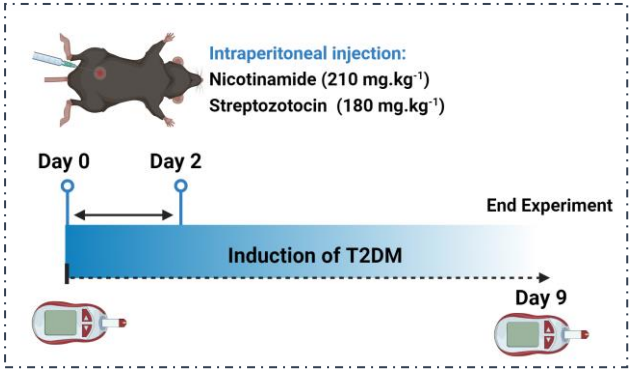


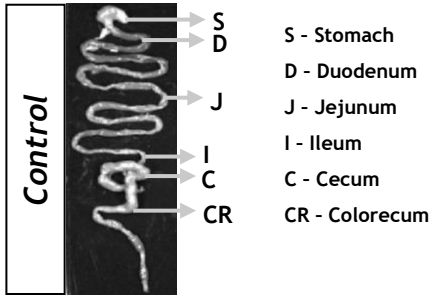


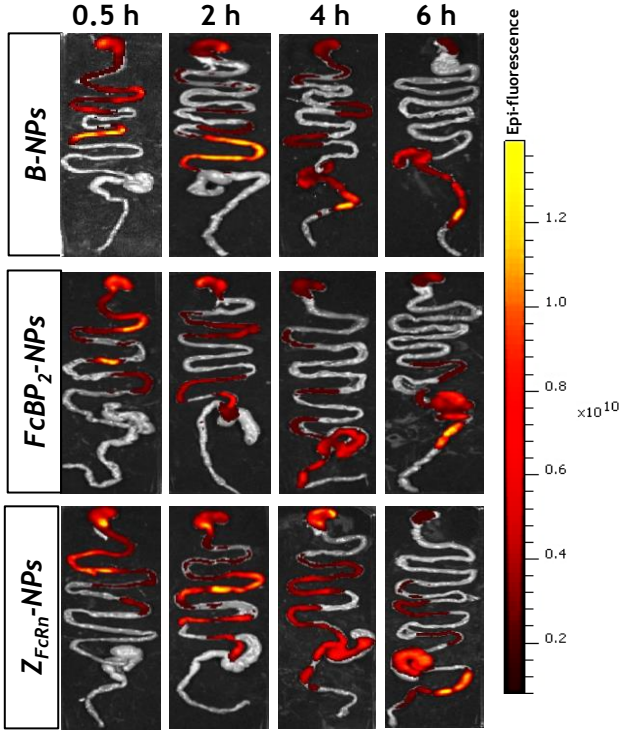
Scale bars represent 100 µm

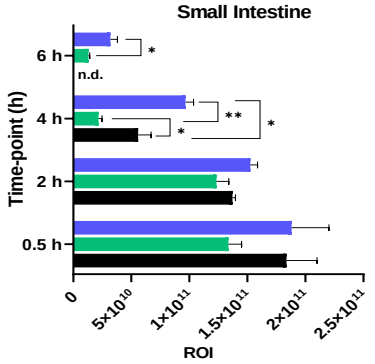
Pinto S., *et al.* J Control Release 366 (2024) 621-636.

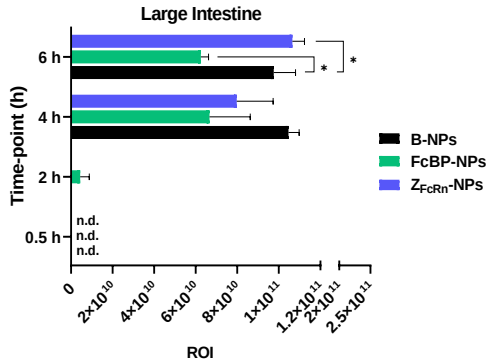
Biodistribution of FcRn-targeted NPs through the gastrointestinal tract of T2DM-induced mice





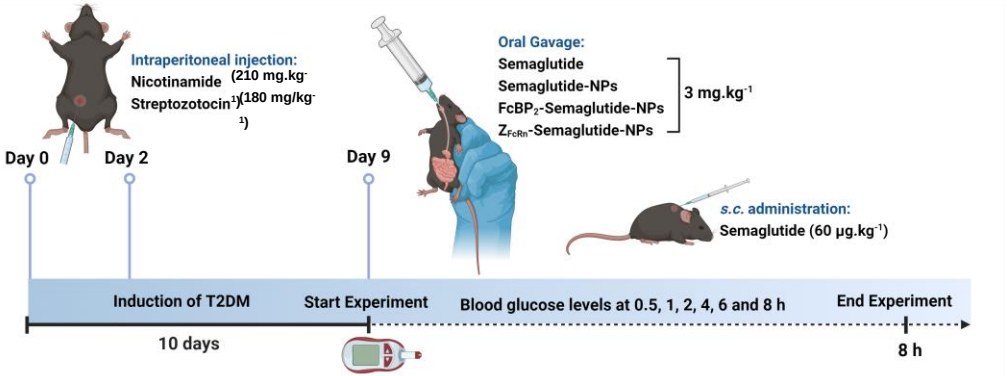


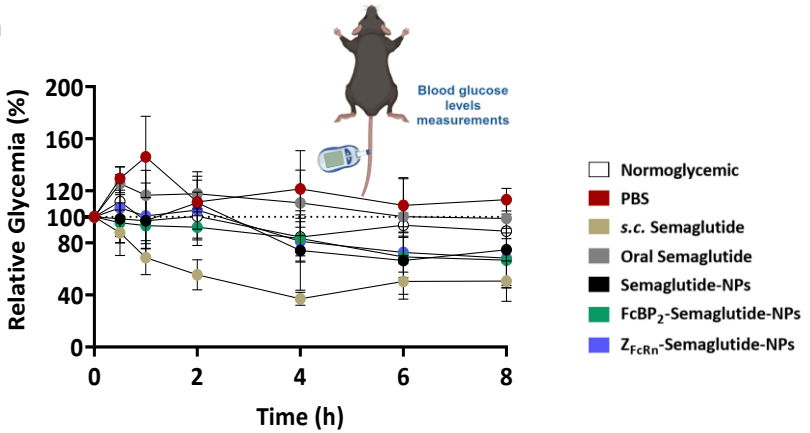


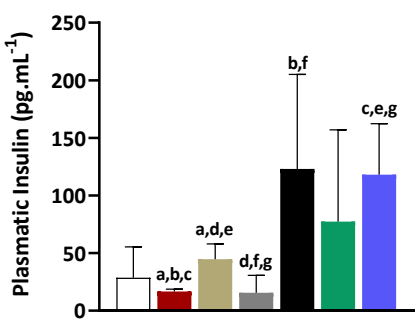


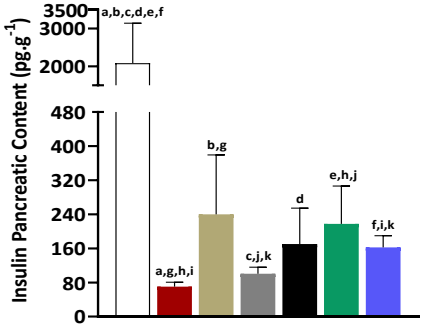
Pinto S., *et al*. *ACS Nano* 18 (2024) 28406-28424.

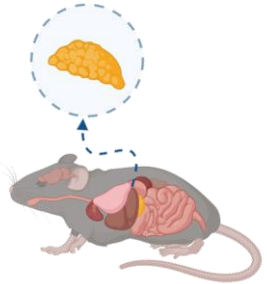
FcRn-targeted NPs induced a glucoregulatory effect after single administration





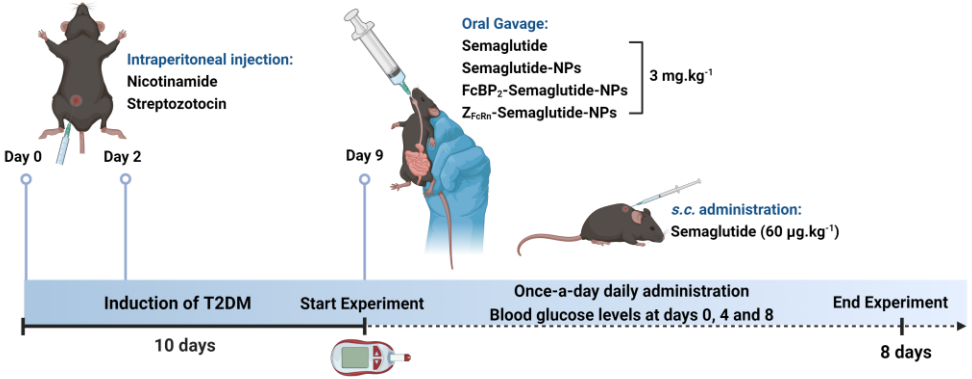


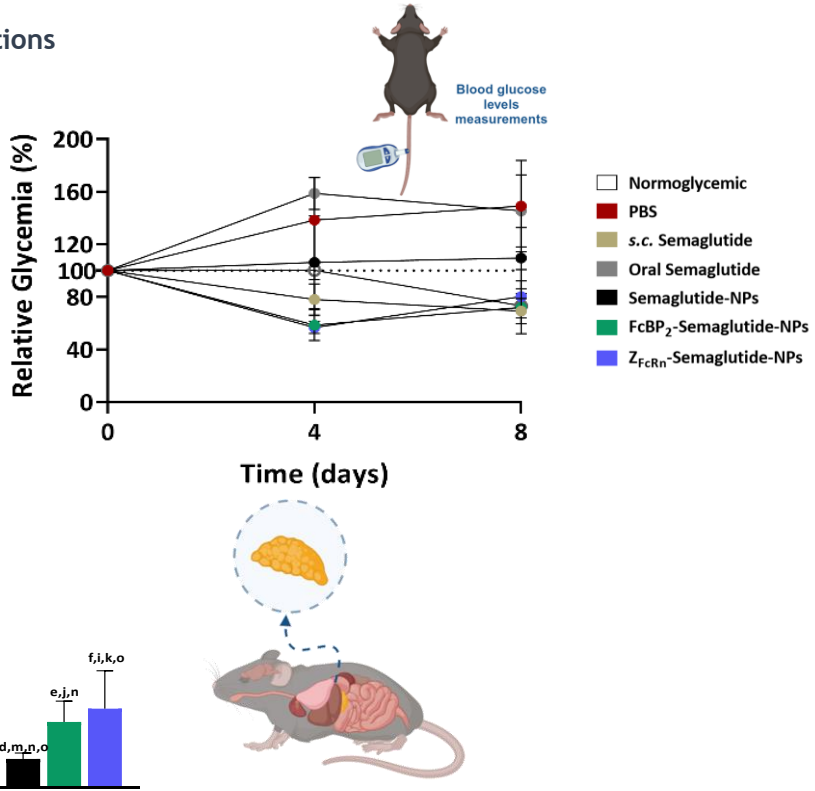


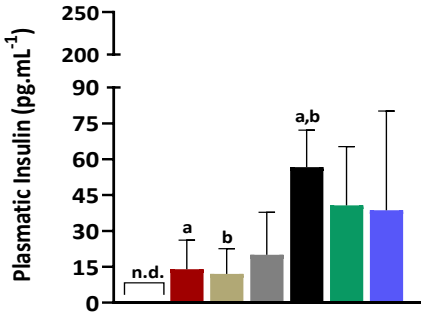


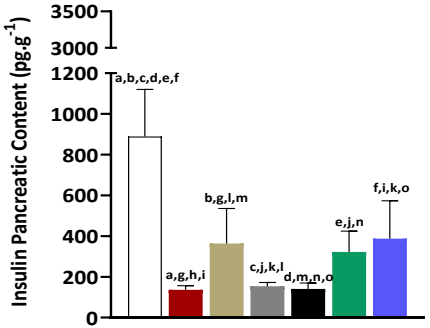
Pinto S., *et al*. *ACS Nano* 18 (2024) 28406-28424.

FcRn-targeted NPs induced a glucoregulatory effect after multiple administrations









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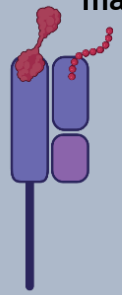
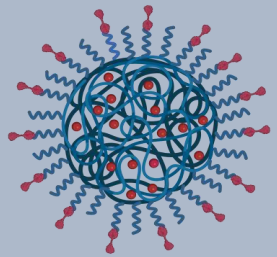
FcRn-targeted ligands **$FcBP_2$** and **Z_{FcRn}** interacted with hFcRn at an **acidic pH-dependent manner**

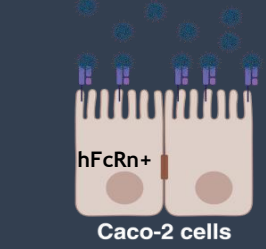


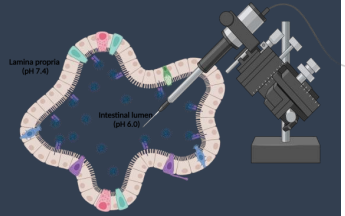
$FcBP_2$ and **Z_{FcRn}** were successfully **conjugated to PLGA-PEG-Mal** *co*-polymer *via* **Mal-thiol chemistry**

Semaglutide was incorporated into PLGA-PEG NPs, surface functionalized with **$FcBP_2$** and **Z_{FcRn}**

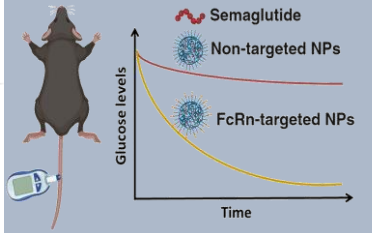


FcRn-targeted NPs interacted with **intestinal cells** and **HIOs** that endogenously express hFcRn





FcRn-targeted semaglutide-NPs induce a **suitable glucoregulatory response** than non-targeted NPs and oral semaglutide



FcRn-targeted ligands $FcBP_2$ and Z_{FcRn} interacted with hFcRn at an **acidic**

$FcBP_2$ and Z_{FcRn} were successfully **conjugated to PLGA-PEG-Mal** *co*-polymer *via* **Mal-thiol chemistry**

Semaglutide was incorporated into PLGA-PEG NPs, surface functionalized with $FcBP_2$ and

FcRn-targeted NPs interacted with **intestinal cells** and **HIOs** that endogenously express hFcRn

FcRn-targeted semaglutide-NPs induce a **suitable glucoregulatory response** than non-targeted NPs and

FcRn-targeted NPs demonstrated to be a promising nanoplatform for **improving the oral delivery of semaglutide** and for **enhancing the treatment of T2DM**

Acknowledgments

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Juliana Viegas

Sofia Barros

Cecília Cristelo

Catarina Pacheco

All NTDD members

All BBT members

Scientific Platforms

Intestinal Fc receptor-targeted nanomedicines boost semaglutide effect in type 2 diabetes

Soraia Pinto

Session: Nanomedicine and Nanoscale Delivery (Focus: Oral)

NTCD NANOMEDICINES & TRANSLATIONAL DRUG DELIVERY

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NEXT-GENERATION DELIVERY INNOVATIONS