Flame-made nanoparticles for FcRn-mediated miRNA delivery in chemoresistant colorectal cancer therapy

Natália Teixeira[1,2]; Georgios Sotiriou[3,4]; Bruno Sarmento[1,5]

[1] Instituto de Investigação e Inovação em Saúde, Porto, Portugal

[2] Instituto de Ciências Biomédicas Abel Salazar, University of Porto, Porto, Portugal

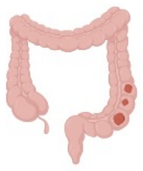
[3] Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden

[4] Department of Chemistry, Stockholm University, Stockholm, Sweden

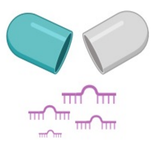
[5] Instituto Universitário de Ciências da Saúde, Gandra, Portugal

nataliat@i3s.up.pt

Background

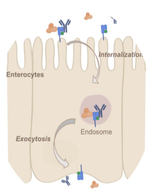


Colorectal cancer (CRC) is a leading cause of cancer mortality worldwide, with treatment often compromised by chemoresistance[1].



Restoring physiological miRNA levels can reestablish normal cellular pathways overcoming resistance[2].

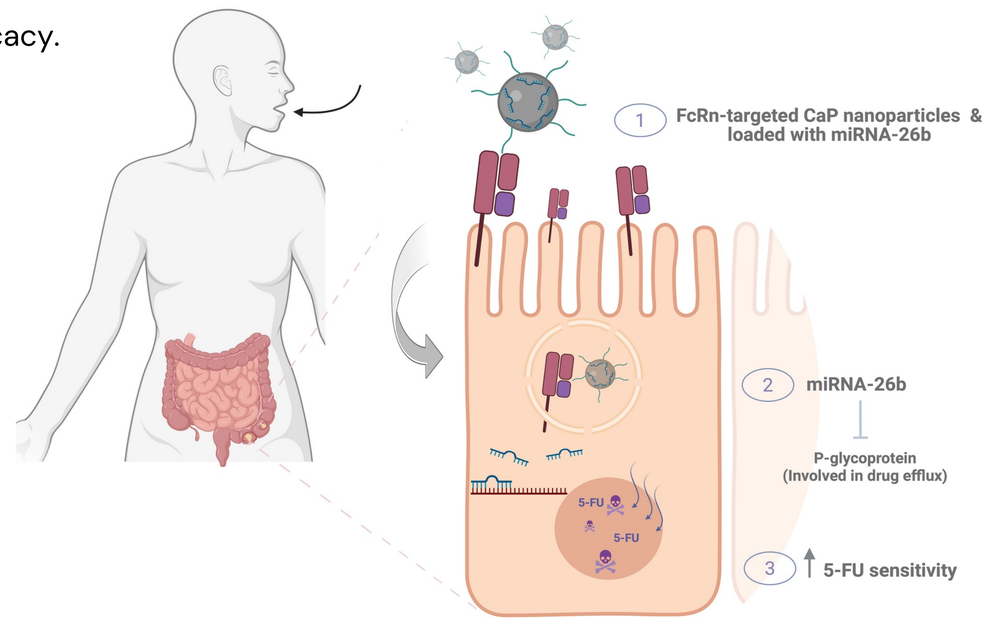
However, effective oral miRNAs' delivery is challenging due to gastrointestinal degradation and limited targeting specificity.



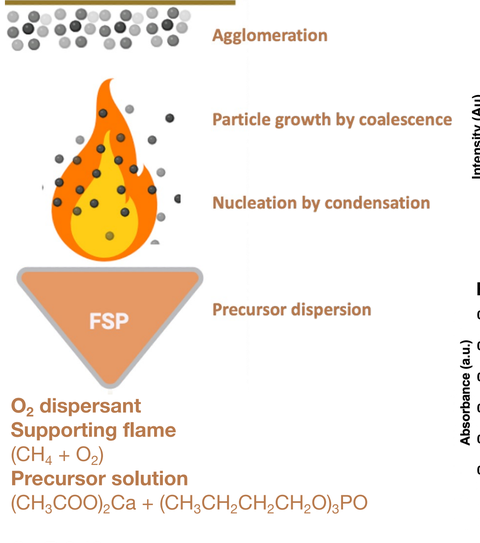
The neonatal Fc receptor (FcRn), involved in intestinal transcytosis, is overexpressed in CRC tissues and may offer a targeted route for enhancing miRNA delivery[3,4].

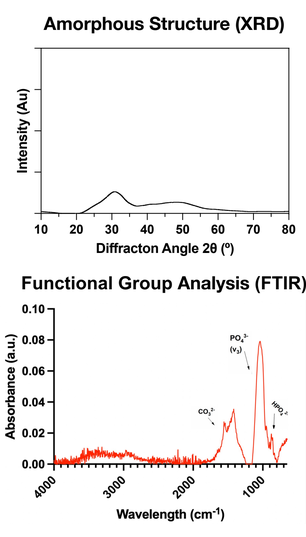
Aim

Develop an adjuvant nanodelivery system for oral colorectal cancer therapy, combining chemotherapeutics and FcRn-targeted miRNA-loaded nanoparticles to overcome chemoresistance and enhance treatment efficacy.



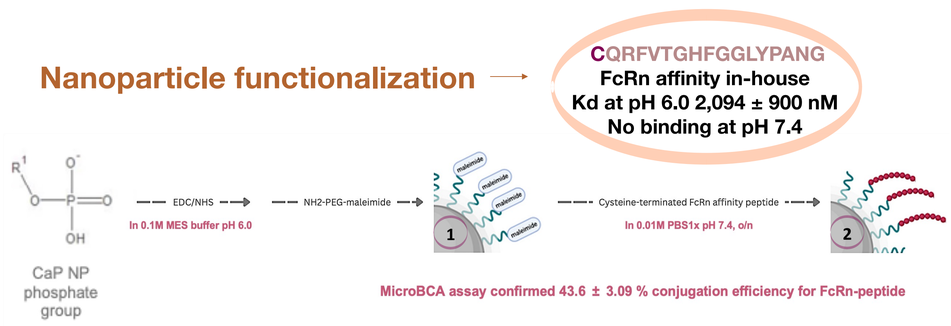
Characterization of Calcium Phosphate Nanoparticles Produced by Flame Spray Pyrolysis





Precursor (mL/min) to O_2 dispersion (L/min)	Specific Surface Area (BET measurement)	Average Particle Size (BET measurement)
3:8	259 m^2/g	7.3 nm

Nanoparticle functionalization

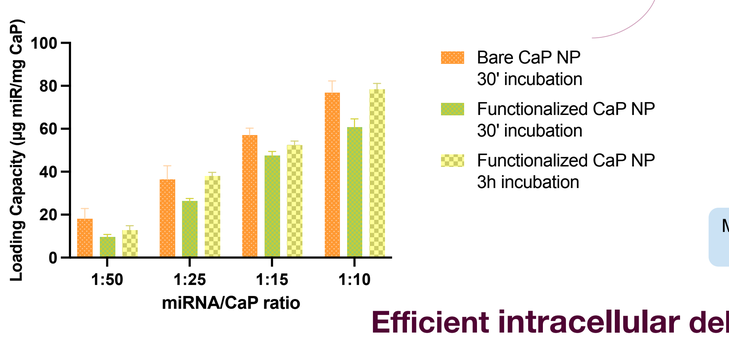


Hydrodynamic characterization

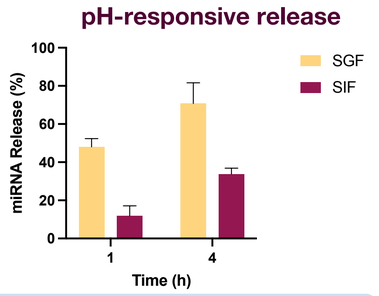
Nanoparticles	Size (nm)	PdI	ζ potential (mV)
CaP	4442 ± 173	0.28 ± 0.12	2.25 ± 0.27
CaP-PEG (1)	1072 ± 77	0.56 ± 0.10	0.98 ± 0.37
CaP-PEG-$FcRn_{PEPTIDE}$ (2)	816 ± 118	0.51 ± 0.25	1.79 ± 0.29

CaP Nucleic Acid Loading & Bioactivity

miRNA-26b high loading onto CaP

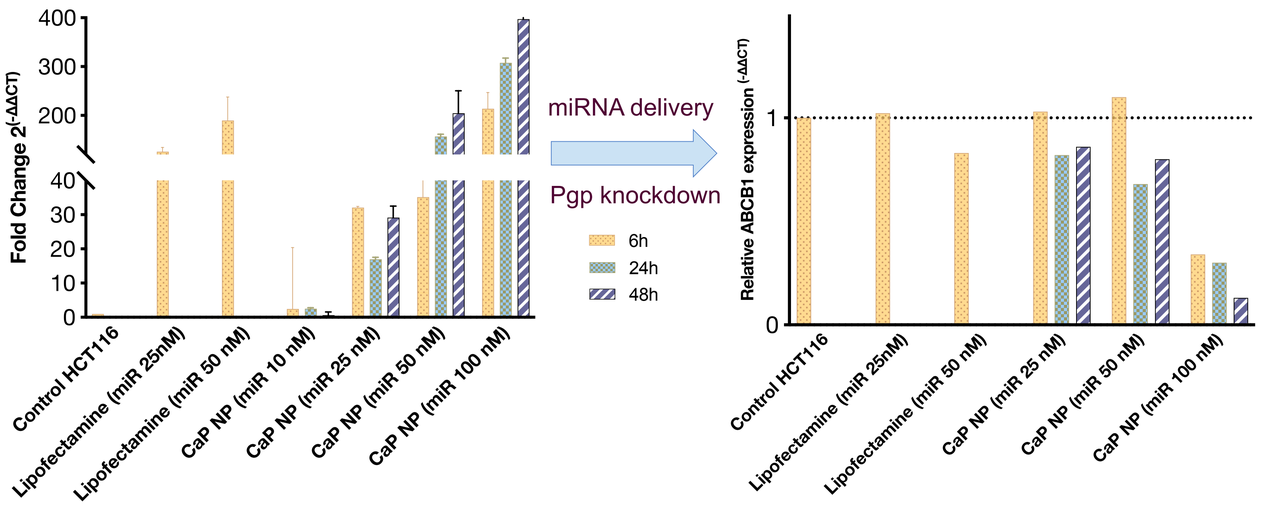


pH-responsive release



Measure absorbance at 260 nm using NanoDrop
Confirmation by RiboGreen Quant-iT Assay

Efficient intracellular delivery of miRNA

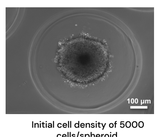


Take-home message

Flame-sprayed CaP nanoparticles enabled efficient intracellular miRNA delivery and functional target gene knockdown in colorectal cancer cells, demonstrating their potential as a miRNA delivery platform.

Next Steps

- Evaluate nanoparticle uptake using fluorescently labelled formulations and determine the influence of FcRn-mediated targeting.
- Assess the therapeutic efficacy of miRNA-loaded nanoparticles in triple co-culture spheroid model that better recapitulates tumour microenvironment.



Initial cell density of 5000 cells/spheroid,
1:4:4
HCT116 : monocytes : HIF

References

[1]Teixeira N, et al. Expert Opin Drug Discov. 2024 [2]Rezayatmand H, et al. Stem Cell Res Ther. 2022;13:181 [3]Larsen MT, et al. J Control Release. 2020;322:53–63 [4]Hameedat F, et al. Eur J Pharm Sci. 2022;176:106259.