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Bioengineered nanomedicines for modulation of intestinal anti-diabetic peptide delivery

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Introduction: Diabetes mellitus is a high prevalence and one of the most severe and lethal diseases in the world with tremendous impact on health worldwide. Anti-diabetic peptides as insulin or GLP-1 are commonly used to treat diabetes in order to give patients a better life condition. However, due to bioavailability problems, their most common route of administration is the subcutaneous route. Invasive delivery route is, still, the most efficient, but less desired by patients. Non-invasive delivery systems have potential to overcome the most pressing problem regarding effective treatment of diabetic patients - therapy compliance, and are thus considered as convenient alternative, but it faces important challenges. Therefore, the nanoencapsulation of antidiabetic peptides into nanoparticles is presented as a good strategy to improve bioavailability.

Results: In our research group, we have developed and characterized nanoparticles containing insulin and/or GLP-1 peptides, following their evaluation as medical products to control diabetes upon oral delivery. In particular, we use poly(lactic-co-glycolic acid) (PLGA) modified with chitosan and a cell-penetrating peptide. Afterwards, glucagon like peptide -1 (GLP-1) loaded NPs were encapsulated into a pH-sensitive polymer and loaded with dipeptidyl peptidase-4 (DPP4) inhibitor, using a microfluidics technique. *In vivo* tests were performed in a rat type 2 diabetes mellitus model by oral gavage, and the blood glucose levels were quantified. The plasmatic insulin levels, as well as the pancreatic insulin content, were also evaluated. Our no-invasive technologies have demonstrated a clear efficacy in lowering the blood glucose levels in diabetic animal models. Not only nanoparticles have demonstrated to be able to cross biological barriers, but also provide sustain release of their peptide payloads. The interaction between the nanoparticles and the intestinal co-culture cells showed that there was a clear increase in the interaction between the modified nanoparticles with the cells. In the in vivo assays, the blood glucose levels decreased after 4 h of the administration of the particles and were kept low thereafter. The insulin levels increased along the time and the insulin pancreatic content was higher in the experimental groups in comparison with the control. No inflammation, cytotoxicity or tissue damage has been associated with chronic use of such nanoparticles, giving promising clinical application in a near future.

Conclusions: The developed particles were sensitive to different pH, showing high interaction with intestinal cells. They allowed the dual-delivery of two different drugs in a single formulation. The very low activity of DPP4 enzyme prolonged the GLP-1's half-life, thus increasing the insulin levels and decreasing the blood glucose levels along the time in vivo. In this presentation, the feasibility of nanomedicines to improve the bioavailability and efficacy of anti-diabetic biopharmaceutical drugs will be demonstrated.

Biography

Bruno Sarmento has comleted his PhD in Pharmaceutical Technology and Degree in Pharmaceutical Sciences from University of Porto, Portugal; Affiliated Researcher at Institute of Investigation and Innovation in Health (i3S) and Institute of Biomedical Engineering (INEB), University of Porto, Portugal; Assistant Professor of Pharmaceutical and Biopharmaceutical Technology at IUCS, Gandra, Portugal. His current research is focused on the development of functionalized nanomedicines and their application in the pharmaceutical and biomedical fields. In particular, nanoformulations of biopharmaceutical drugs with interest in diabetes, cancer and infectious diseases. He has also specialized in mucosal tissue engineering models to validate functionalized nanomedicines and to perform *in vitro/in vivo* correlation. He published more than 160 papers in international peer reviewed (ISI) journals, most in top journals (Q1 in *Pharmaceutical Sciences*; Q1 in *Nanoscience and Nanotechnology*; total citations 3350; accumulated impact factor 627; H-index 29), 34 book chapters and more than 180 proceedings. He edited 4 books, participated in more than 50 invited/selected talks in national and international meetings and was awarded several distinctions. He is member of the Editorial Advisory Board of 10 international journals and has acted as referee for top-ranked journals in his area of expertise, and for international funding agencies.

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