**TARGETED CATHELICIDIN NANOMEDICINES AS NOVEL GLUCOREGULATOR FOR DIABETES THERAPY**

Cecília Cristelo[1,2,3], Francisco Miguel Gama[3], Bruno Sarmento[1,2]

[1] – i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal;
[2] – Nanomedicines & Translational Drug Delivery Group, INEB - Instituto de Engenharia Biomédica, Portugal;
[3] – Centre of Biological engineering, Universidade do Minho, Braga, Portugal.

**Background:** Type 1 diabetes (T1D) results from autoimmune destruction of the insulin-producing β cells. Given that cathelicidin antimicrobial peptide has shown to improve β cell function and neogenesis, this work aims to use a cathelicidin-derived peptide, LLKKK18, loaded on targetable PLGA nanoparticles and assess the ability of the formulation to recover β cell mass and pancreatic function, reverting T1D. For targeting, functionalization of NPs with exenatide, an agonist of the glucagon-like peptide-1 receptor (GLP-1R), which is expressed by β cells, is proposed.

**Methods:** NPs were characterized using DLS, NTA and TEM. The association efficiency (AE) and drug loading (DL) of LLKKK18 were determined using fluorescamine. Peptide cumulative release from the NPs was studied in phosphate buffer (PB) at 37ºC, up to one week. Functionalization of the nanoparticles was performed using the thiol–maleimide "click" chemistry and conjugation efficiency determined using fluorescamine. The effects from blank, LLKKK18-loaded and exenatide-functionalized NPs on the cell viability of L929 and INS1E cell lines were evaluated using MTT.

**Results:** The obtained results from NP characterization indicate a mean size around 100 nm, for blank, LLKKK18-loaded and exenatide-funtionalized NPs and a narrow size distribution (PdI of 0.10). After loading of LLKKK18, zeta potential of -3.1 mV, with stability up to 20 days at 4 ºC in PB. NP functionalization decreased the surface charge of NPs to -12 mV, which may contribute to further stability. LLKKK18 AE and DL of 88 % and 0.9 %, respectively, with a sustained *in vitro* release. The conjugation efficiency of exenatide to the surface of NPs was around 80%, as determined by indirect method, using the molar ratio of 2:1 of maleimide:exenatide. Furthermore, 125 µg/mL of nanoformulation showed no cytotoxic effects on both cell lines and will be used in the future for the following assays.

**Conclusions:** In the near future, the bio-functionality of NPs will be evaluated, to address the ability of the NPs to favor interaction with β cells and the ability of the formulation to promote glucose-mediated insulin release and improve β cell replication.