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TOWARDS ORAL DELIVERY OF AI-PREDICTED BIOACTIVE PEPTIDES

Creating successful oral formulations of therapeutic peptides capable of forming natural peptide complexes has been perceived to be a challenge in new therapeutic development. Properties such as high molecular weight, hydrophilicity, enzyme susceptibility are thought to be inherent to peptides preventing adequate bioavailability [1, 2]. This project is assessing the permeability of a library of peptides with potential health benefits discovered through the use of bioinformatics by Nuritas Ltd. Fluorescein Isothiocyanate dextran molecular weight 4000 (FD-4) is used as control for these studies. By measuring intestinal permeability of lead peptides and hydrolysates, this may lead to oral dosage formulations.

CANDIDATE MOLECULES

Nuritas combines predictions by Machine Learning and in vitro laboratory testing approach for efficacy of bioactive peptides and protein hydrolysates. These can have consumer-health or therapeutic benefits. A set of such molecules from food(s) has been considered for studying improvements in their intestinal permeability, the main limiting factor for their oral bioavailability.

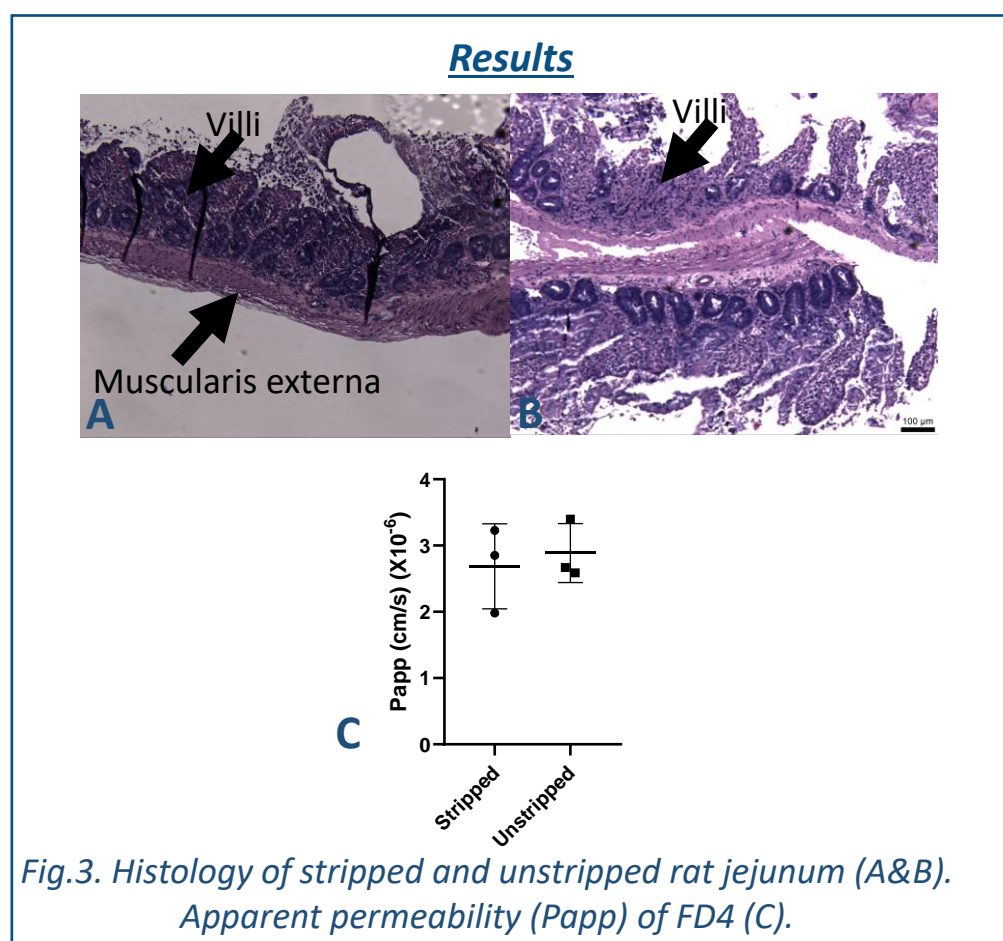
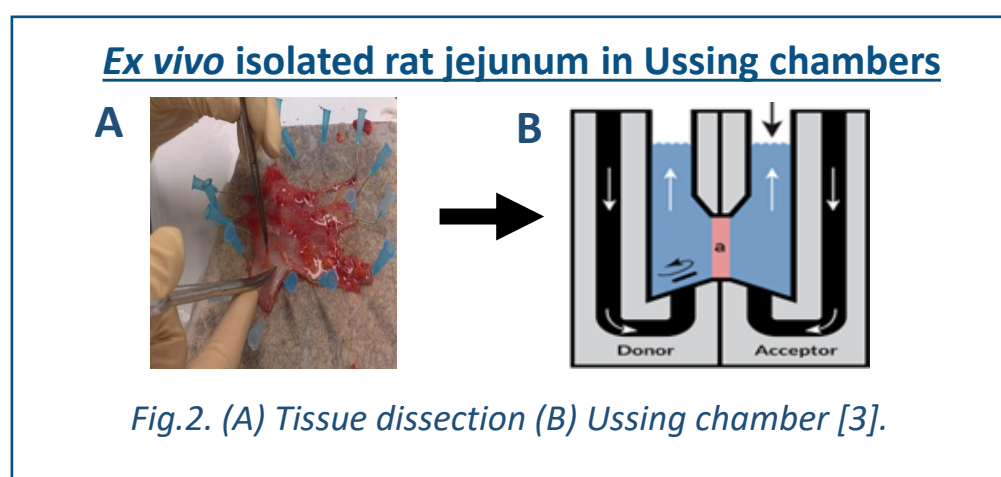
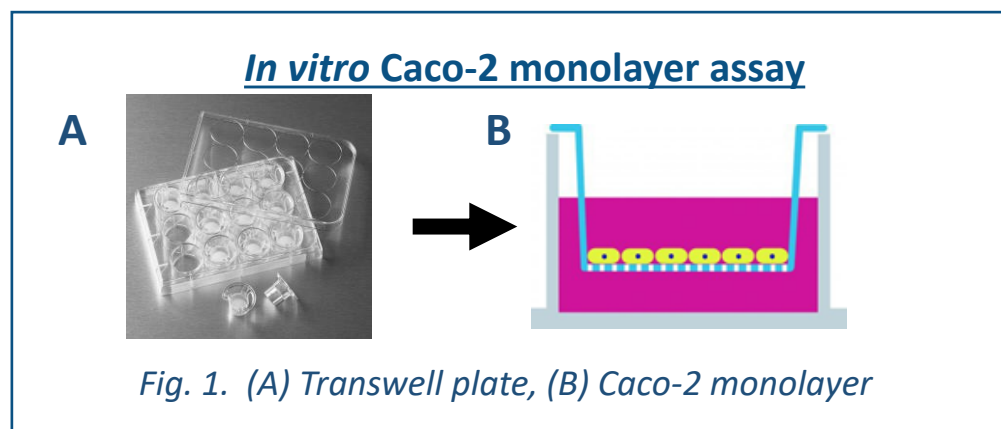
PERMEATION AND BIOAVAILABILITY ASSAYS

Permeability assays:

- In vitro Caco-2 (human colorectal adenocarcinoma) cell monolayer assay on filter supports)
- Ex vivo rat jejunum assay on the Ussing chambers

Bioavailability assay:

- In vivo intestinal instillations



CONCLUSIONS

Stripped rat jejunum shows lack of muscular layer in histological examinations, which has been traditionally used for permeability analysis. Further, the two variations of rat jejunum have comparable P_{app} values of FD-4 while treated with permeation enhancer or without it. Peptide candidates arising from bioinformatics screens of food isolates have been selected to assess permeability across Caco-2 monolayers and isolated rat intestinal tissue mucosae on the basis of ongoing results.

1. Presas, E., et al., *Physicochemical, pharmacokinetic and pharmacodynamic analyses of amphiphilic cyclodextrin-based nanoparticles designed to enhance intestinal delivery of insulin*. J. Controlled Release, 2018. 286: p. 402-414.
2. Aguirre, T.A.S., et al., *Current status of selected oral peptide technologies in advanced preclinical development and in clinical trials*. Adv. Drug Deliv. Rev, 2016. 106: p. 223-241.
3. Kristin, F., et al., *Dissolution and dissolution/permeation experiments for predicting systemic exposure following oral administration of the BCS class II drug clarithromycin*. Eur. J. Pharm. Sci., 2017. 101: p. 211-219.