Structure-activity studies of biologically active peptides and analogues

1. Peptide-based antibiotics.

WHO has predicted that within a decade, it will be common to encounter pathogenic bacteria resistant to all known antibiotics. Antimicrobial peptides are produced by all living organisms as part of their natural first line of defense against and hold promise as novel antibiotics. The aim of this Master Project is to improve the antimicrobial activity and proteolytic stability of an antimicrobial peptide lead compound. You will first perform i) structure-activity studies and then ii) optimize the activity by inserting *N*-substituted glycine units (peptoids) in selected positions. The derivatives will be synthesized by solid-phase peptide synthesis, purified by preparative HPLC and characterized by MALDI-TOF-MS/LC-MS. You will test the antimicrobial activity of the derivatives against both human and veterinary pathogens.

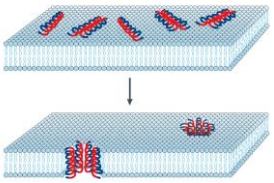

Figure: Antimicrobial peptides kill bacteria by disrupting the membrane

2. Peptide ligands for the cancer specific receptor EGFRVIII.

One of the few known cancer specific surface markers is the epidermal growth factor tyrosine kinase receptor mutation (EGFRvIII). EGFRvIII is present in number of human malignancies, in particular ovarian and breast cancer, and glioblastomas. However, this mutation has never been identified in normal tissue. The aim of this Master Project is to synthesize radiolabelled peptides which specifically bind to EGFRvIII.
Peptides will be adapted to enable radiolabelling with the positron emitting radionuclides, fluorine-18, gallium-68 and copper-64. Fluorine-18 based tracers will be radiolabelled by conjugation of small fluorine-18 labelled precursors. Labelling precursors for gallium-68 or copper-64 will be prepared by conjugation of chelators such as DOTA, NOTA or NODAGA to the peptides. Radiolabelled peptides will be tested *in vitro* using cell binding assays and the most promising candidates will be evaluated in vivo in mice xenografted subcutaneously with EGFRviii expressing tumours using PET imaging.

3. Fluorescent and fatty acid analogues of Calcitonin gene-related peptide.

Calcitonin gene-related peptide (CGRP) is a naturally occurring, 37 amino acid neuropeptide which is widely distributed throughout the CNS and PNS and possesses potent vasodilatory effect. CGRP plays an important role in various circulatory diseases such as hypertension, ischemic heart diseases, subarachnoid haemorrhage (SAH) and migraine. The aim of the present study is to synthesize different single-labelled fluorescent analogues and fatty acid analogues of CGRP using Fmoc solid-phase peptide synthesis in order to increase the half-life of the peptide and to study its chronic effects.

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