Poster

DESIGN PEPTIDES NANOSTRUCTURES HAVING ANTIMICROBIAL ACTIVITY

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Many people receive health care every day in hospitals.(1) These individuals may be more vulnerable to infection, or may themselves be carrying a transmissible infection. The following bacteria that cause nosocomial infections are currently of particular concern: *C. difficile* (*Clostridium difficile*), VRE (Vancomycin-resistant *Enterococci*) and MRSA (Methicillin-resistant *Staphylococcus Aureus*) and many more gram negative bacteria. In Québec, 80,000 to 90,000 people in health institutions, or 10% of admissions, are thought to have a nosocomial infection. The prevention and control of nosocomial infections is nothing new in Québec. For many years, health professionals, particularly microbiologists, infectious disease specialists and infection prevention and control nurses, have been devoting time and energy in this area at health network institutions, which form the front line in the battle against these infections and have the main responsibility for preventing and controlling them. Our role is to create new antimicrobial generations which will use different mechanism of action that won't develop any resistance mechanism. On that basis, our group devotes efforts to develop novel peptide nanostructures for such purposes.

Cationic antimicrobial peptides (AMPs) have become important candidates as potential therapeutic agents. Cationic AMPs are found in organisms that are evolutionarily quite distant, ranging from plants and insects to birds, animals (including molluscs, crustaceans, amphibians, fish, and mammals), and humans.(3; 4) Cationic AMPS have usually broad spectra of "antimicrobial" activity, which include an ability to kill or neutralize bacteria (gram-positive and gram-negative), fungi, parasites, cancer cells, and even viruses like HIV and herpes simplex virus.(5)

Although the exact mode of action of AMPs has not been established, it is generally accepted that the cytoplasmic membrane is the main target of many AMPs, whereby peptide accumulation in the membrane causes increased permeability and a loss of barrier function, resulting in leakage of cytoplasmic components and cell death. The development of resistance to membrane active peptides whose sole target is cytoplasmic membrane is tought to be considerably reduced when compared with that of many current antibiotics, which have more specific molecular targets. The prediction has been substantiated in several studies.(2; 6; 7) However, the major barrier for the use of AMPs as antibiotics is their toxicity or ability to lyse eukaryotic cells, normally expressed as haemolytic activity (toxicity to human red blood cells). This is the main reason preventing their applications as injectable therapeutics.

Although numerous studies on AMPs have been done on their biological and structural activity, the amount of information about their actives structures and their molecular determinants responsible for their various biological activities is poor. Among the reasons to explain this lack of information we find the chemical and structural complexity. In fact, the minor molecular modifications on those peptides result in enormous modifications on their conformation, structure, solubility and auto-association.

In our previous studies about peptide nanostructures with membrane activity, our group has demonstrated that neutral non-natural peptide composed of 14 residues (10 leucines and 4 phenylalanines modified with crown ether acts similarly to some cationic peptides. Preliminary biophysical studies suggested that peptide nanostructure in **Figure 1** was a unique structural model to identify the molecular determinants responsible of the biological activity of natural cationic peptide.

In this presentation, we will described the design rational and the synthesis of a library of analogous crown peptide nanostructures. The resultats obtained about the antibiotic activity

and the effect of these compounds on the transcriptome of *Escherichia coli* ATCC 25922 to acquire detailed information on their mode of action will be described also. Moreover, we will present the results of various biophysical and biochemical studies, including circular dichroism (CD), fluorescence spectroscopy to explore the properties of such peptide nanostructures and their interactions with various bacteria and model membranes.

References :

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Figures :

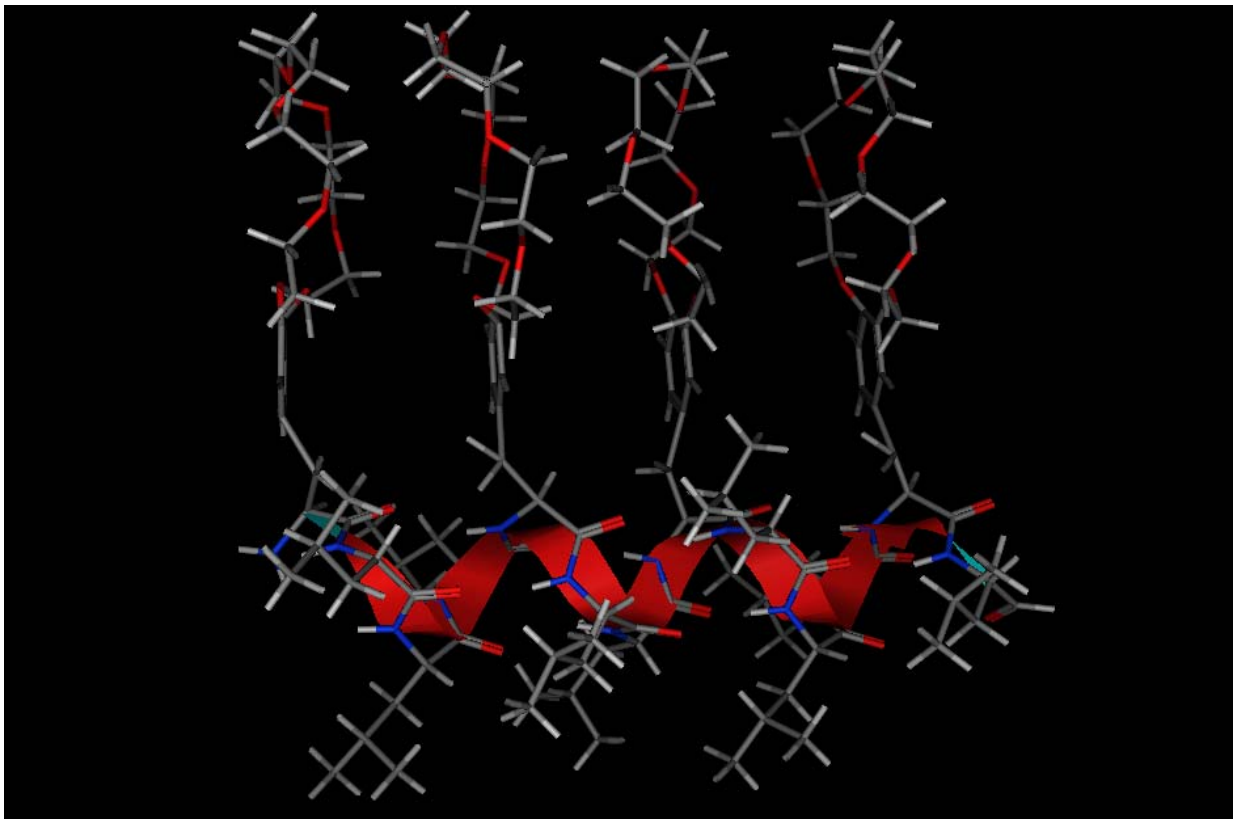

Figure 1