Scientific Meeting
AuPS | ASB
HOBART · 2022

AUSTRALIAN SOCIETY FOR BIOPHYSICS

Abstract: 101O

Rational design of potent ultrashort antimicrobial peptides with programmable assembly into nanostructured hydrogels

Priscila Cardoso[1,2], Samuel Appiah Danso[1,3], Andrew Hung[2], Chaitali Dekiwadia[4], Nimish Pradhan[1], Jamie Strachan[1,2], Brody McDonald[1], Kate Firipidis[5], Jacinta White[3], Arturo Aburto-Medina[2], Charlotte E. Conn[2], Céline Valéry[1*]

[1]School of Health and Biomedical Sciences, NanoBioPharm Research Group, RMIT University, Australia [2]School of Science, STEM College, RMIT University, Australia [3]Electron Microscopy Laboratory, CSIRO Manufacturing, Australia [4]RMIT Microscopy and Microanalysis Facility (RMMF), RMIT University, Australia [5] Biofab3D, Aikenhead Centre for Medical Discovery, St Vincent's Hospital Melbourne, Australia [6] Biomedical and Electrical Engineering, School of Engineering, RMIT University, Australia

Microbial resistance to common antibiotics is threatening to cause the next pandemic crisis. In this context, antimicrobial peptides (AMPs) are receiving increased attention as an alternative approach to the traditional small molecule antibiotics[1-2]. Here, we report the bi-functional rational design of Fmoc-peptides as both antimicrobial and hydrogelator substances[3]. The tetrapeptide Fmoc-WWRR-NH_2 - termed Priscilicidin - was rationally designed for antimicrobial activity and molecular self-assembly into nanostructured hydrogels. Molecular dynamics simulations predicted Priscilicidin to assemble in water into small oligomers and nanofibrils, through a balance of aromatic stacking, amphiphilicity and electrostatic repulsion. Antimicrobial activity prediction databases supported a strong antimicrobial motif via sequence analogy. Experimentally, this ultrashort sequence showed a remarkable hydrogel forming capacity, combined to a potent antibacterial and antifungal activity, including against multidrug resistant strains. Using a set of biophysical and microbiology techniques, the peptide was shown to self-assemble into viscoelastic hydrogels, as a result of assembly into nanostructured hexagonal mesophases (figure 1). To further test the molecular design approach, the Priscilicidin sequence was modified to include a proline turn - Fmoc-WPWRR-NH_2, termed P-Priscilicidin – expected to disrupt the supramolecular assembly into nanofibrils, while predicted to retain antimicrobial activity. Experiments showed P-Priscilicidin self-assembly to be effectively hindered by the presence of a proline turn, resulting in liquid samples of low viscosity. However, assembly into small oligomers and nanofibril precursors were evidenced. Our results augur well for fast, adaptable, and cost-efficient antimicrobial peptide design with programmable physicochemical properties.

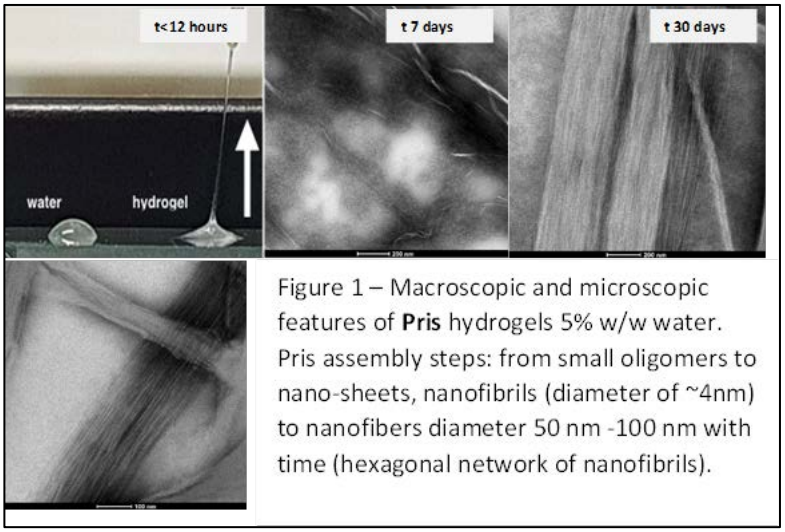

Figure 1 – Macroscopic and microscopic features of **Pris** hydrogels 5% w/w water. Pris assembly steps: from small oligomers to nano-sheets, nanofibrils (diameter of ~4nm) to nanofibers diameter 50 nm -100 nm with time (hexagonal network of nanofibrils).

References

1. Cardoso, P., Glossop, H., Meikle, T.G. et al. Biophys Rev, 2021, 13, 35–69.
2. Glossop H., Zoysa G., Hemar Y., Cardoso P., et al. 2019, 20 (7), 2515-2529.
3. **Cardoso P.**, Appiah Danso S., et al. Rational design of potent ultrashort antimicrobial peptides with sequence-controlled assembly into nanostructured hydrogels. Frontiers in Chemistry. Women in Nanoscience article collection. *In press*