Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Evaluation of nanocoatings for the prevention of prosthetic joint infections.

Synopsis:

Prosthetic joint infections (PJI) are one of the most demanding and challenging complications for orthopedic surgeons. Total joint arthroplasties (TJA) have been steadily increasing over the past few decades [1-3]. In Portugal, PJIs lead the cause of prosthetic revision, representing 33% of all revision surgeries. Population aging, together with the increasing prevalence of osteoarthritis and other degenerative joint diseases, have led to an increased number of arthroplasties performed, and the number of cases of PJI is estimated to grow significantly in the upcoming decades. The most common microorganisms responsible for PJI are *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas* spp. [1-3]. Once the bacteria gain access to the surgical site, a biofilm develops in three-dimensional colonies in association with the prosthetic material, the adjacent tissue and, sometimes, with the bone cement itself. The persistence of the infections often leads to the failure of the prosthetic device, requiring implant replacement, and potentiating chronic and/or relapsing disease. Biomaterial-based preventive strategies have been developed (*e.g.*, local application of antibacterials or covering the prosthetic material with antibacterial film), but the increasing antibiotic resistance requires the development of novel antimicrobial approaches to reduce the incidence of PJI.

In recent years, antimicrobial peptides (AMPs) have been widely investigated as a promising alternative to conventional medicines [4-8]. Some AMPs exhibit a broad spectrum of action against bacteria, fungi, viruses and protozoa [8]. AMPs may also present other activities such as a defense (innate immune system), anti-tumour or even regenerative mechanism [8]. AMPs, often of natural origin, can significantly improve current therapy, namely because they are less likely to lead to the development of antibiotic-resistant microorganisms than conventional antibiotics [4-7].

We recently tested two peptides, Py and Pa, showing their antimicrobial activity against *E. coli*, *S. aureus* and *Klebsiella pneumoniae* at low peptide concentration, without haemolytic effects [4,7]. Both AMPs showed the ability to disturb membrane homeostasis, through changes in the membrane surface, dipole potentials and the lipid packaging profile [4,7,9].

The main goal of the proposed project is to develop an antimicrobial coating using star-shaped nanoparticles conjugated with novel antimicrobial peptides as inhibitors of bacterial biofilm in prosthetic-like material. The specific objectives to accomplish are: *i)* to evaluate the antimicrobial and cytotoxic effects of nanoconjugates in biofilms; and, *ii)* to develop nanoparticles conjugates coating by modification of titanium surface to enhance nanoparticle-surface interaction/adhesion and evaluate its antimicrobial action.

Supervisor: *Sónia Gonçalves, NSantos Lab; sabreu@medicina.ulisboa.pt.*
Co-Supervisor: *Nuno C. Santos, NSantos Lab, nsantos@medicina.ulisboa.pt*

Bibliography:

1.Song, Zhijun et al. “Prosthesis infections after orthopedic joint replacement: the possible role of bacterial biofilms.” Orthopedic reviews vol. 5,2 65-71. 14 Jun. 2013, doi:10.4081/or.2013.e14.
2.Davidson, Donald J et al. “Implant materials and prosthetic joint infection: the battle with the biofilm.” EFORT open reviews vol. 4,11 633-639. 5 Nov. 2019, doi:10.1302/2058-5241.4.180095.
3.Tande, Aaron J, and Robin Patel. “Prosthetic joint infection.” Clinical microbiology reviews vol. 27,2 (2014): 302-45. doi:10.1128/CMR.00111-13.
4.Cardoso, Marlon H et al. “A polyalanine peptide derived from polar fish with anti-infectious activities.” Scientific reports vol. 6 21385. 26 Feb. 2016, doi:10.1038/srep21385.
5.Makowski, Marcin et al. “Advances in Lipid and Metal Nanoparticles for Antimicrobial Peptide Delivery.” Pharmaceutics vol. 11,11 588. 8 Nov. 2019, doi:10.3390/pharmaceutics11110588110588.
6.Makowski, Marcin et al. “EcDBS1R4, an Antimicrobial Peptide Effective against Escherichia coli with In Vitro Fusogenic Ability.” International journal of molecular sciences vol. 21,23 9104. 30 Nov. 2020, doi:10.3390/ijms21239104.
7.Felício, Mário R et al. “Polyalanine peptide variations may have different mechanisms of action against multidrug-resistant bacterial pathogens.” The Journal of antimicrobial chemotherapy vol. 76,5 (2021): 1174-1186. doi:10.1093/jac/dkaa560.
8.Gomes, Bárbara et al. “Designing improved active peptides for therapeutic approaches against infectious diseases.” Biotechnology advances vol. 36,2 (2018): 415-429. doi:10.1016/j.biotechadv.2018.01.004.
9.Migliolo, Ludovico et al. “Structural and functional evaluation of the palindromic alanine-rich antimicrobial peptide Pa-MAP2.” Biochimica et biophysica acta vol. 1858,7 Pt A (2016): 1488-98. doi:10.1016/j.bbamem.2016.04.003.