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Antimicrobial peptide prodrugs activated by neutrophil elastase

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For millions of years, the first line of defense against infections in multicellular organisms has relied on peptides with cationic and amphipathic properties. These Antimicrobial Peptides (AMPs) represent promising leads for the development of antibiotics delaying the emergence of resistance in bacteria. However, their clinical applications have been limited by inadequate margins of safety. A prodrug approach can overcome a toxicity barrier in drug delivery. With AMPs, prodrugs can be generated by reducing their net positive charge, through a modification which can be selectively removed by an enzyme (bacterial or human) confined to sites of infection. For example, Neutrophil Elastase (NE), a human protease involved in chronic airway inflammation and infections associated with Cystic Fibrosis (CF) can disconnect an oligo-glutamate promoiety masking the net positive charge and therefore activity of AMP candidates (Bac8c, P18, HB43, WMR and WR12). Their bactericidal activities against reference and clinical isolates of the CF pathogen *P. aeruginosa* are restored by NE in CF bronchoalveolar lavage fluids. Toxicity differentials are also achieved with the active peptides consistently more hemolytic and cytotoxic against representative epithelial and immune cells than their prodrug forms with the exception of WMR. While no toxicity was observed *in vitro* with both active and prodrug forms of this candidate, *in vivo* studies indicated that the prodrug was better tolerated than the active peptide. Finally, an *in vitro* nebulization study performed with a vibrating mesh nebulizer showed that a high level of dosing in the lung can be achieved for this AMP prodrug.

Biography

Marc Devocelle has completed his PhD at the University of Lille, France under contract with a Pharmaceutical Company. He subsequently joined RCSI in 1999 as a Postdoctoral Researcher and became Manager of the Peptide Synthesis Laboratory in 2000. He has been appointed as a Lecturer in 2004, a Senior Lecturer in 2008 and an Associate Professor of Chemistry in 2014. His laboratory is involved in over 25 collaborations with 14 academic groups across 8 HEIs in Ireland, 2 SMEs and 1 MNC.

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