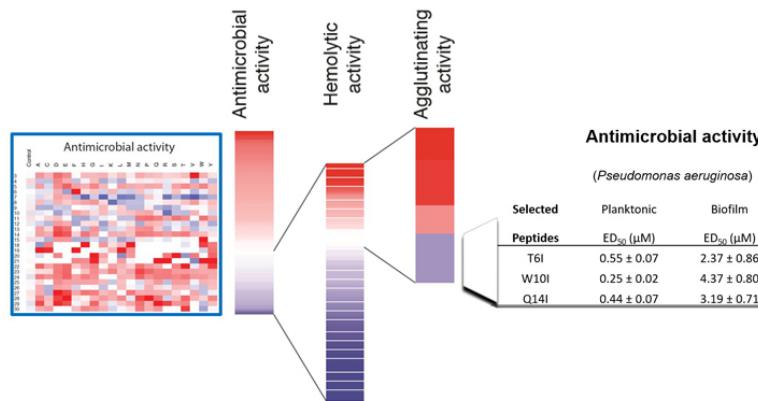


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Novel antibiotic discovery for bacterial biofilm eradication through the generation of a peptide library



Tackling bacterial resistance to conventional antibiotics poses one of the greatest challenges to the pharmaceutical industry. In particular, bacterial infection caused by biofilm-forming resistant Gram-negative bacteria is one of the most frequent causes of Hospital deaths by infectious diseases. The “Human Host Defence Ribonucleases” laboratory of the Universitat Autònoma de Barcelona has designed a novel and potent antimicrobial peptide able to eradicate *Pseudomonas aeruginosa* established biofilms.

The lack of awareness and the inappropriate use of antibiotics have promoted bacterial resistance. Therefore, the development of novel antimicrobial agents is a major priority worldwide. Luckily, our own immune system displays a wide repertoire of antimicrobial proteins and peptides that present a fast and multifaceted antimicrobial mechanism of action; being a useful source to develop new peptide-based alternative to conventional antibiotics.

Dr. Ester Boix laboratory focusses on the functional and structural characterization of the human ribonucleases, belonging to a family of proteins with key roles in the immune system of vertebrates. Specifically, ribonuclease 3, also known as eosinophil cationic protein (ECP), is a

highly cationic protein secreted by eosinophils during infection. ECP displays a high affinity towards lipopolysaccharides, anionic molecules present at the cell wall from Gram-negative bacteria. ECP interaction at the bacterial surface triggers a self-agglutination process that promotes cell lysis and death. Strikingly, the N-terminal region of the protein is able to reproduce the antimicrobial properties of the whole parental protein.

In this work we present a 500 peptide library that was generated through the SPOT technology developed in Dr. Rudolf Volkmer's laboratory at the Freie Universität of Berlin. This technology facilitates the synthesis of a large array of peptides attached to a support membrane allowing the simultaneous characterization of a large number of peptides. The library analysis suggests that ECP N-terminus has already been selected by evolutionary pressure to provide antimicrobial activity with no toxicity towards the host cells. On the other hand, the positional scanning analysis revealed the crucial residues that could be replaced inducing a drastic increment of the peptide antimicrobial activity and decreasing the cytotoxicity towards the host cells. A combination of the agglutinating and lytic activities of the peptides provided novel and potent improved peptides able to fully eradicate bacterial biofilms. The efficacy of this peptide was further evaluated against *Pseudomonas aeruginosa*, being the discovery of novel drugs against this species a top priority for the World Health Organization.

The peptide has been patented and its efficacy against mouse infection model will be tested soon. (Project funded by *Programa Indústria del Coneixement*, AGAUR: 2016 PROD-00060, co-financed by FEDER funds).

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Dra. Ester Boix

Department of Biochemistry and Molecular Biology
Faculty of Biosciences
Universidad Autónoma de Barcelona
Ester.Boix@uab.cat

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