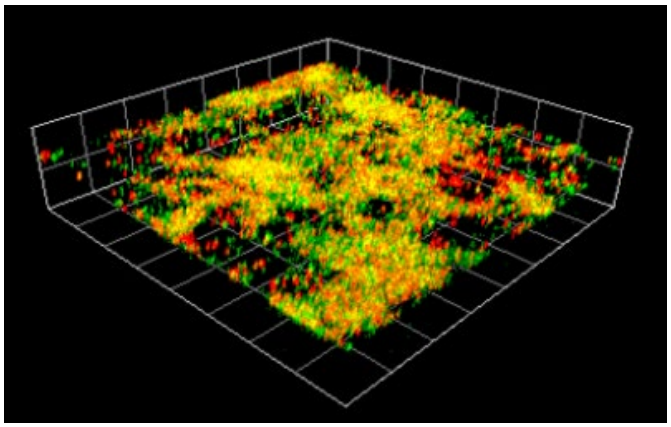
SENBIOTAR: Sensitising *Pseudomonas aeruginosa* biofilms to antibiotic and reducing virulence through novel target inhibition

Challenge

With the continuous rise of antibiotic resistance, it is becoming difficult to treat bacterial infections. The human pathogen, *Pseudomonas aeruginosa* is one of the major pathogens worldwide. It possesses a language based on the use of chemical signals which controls the production of toxic products responsible for causing diseases and potentiates mechanisms conferring resistance to antibiotics. This chemical language is called 'quorum sensing'. In SENBIOTAR, researchers have developed compounds, which do not kill the pathogen but interfere with quorum sensing, reducing the capacity of this organism to cause disease whilst making it more sensitive to antibiotics.



Research Approach

A combination of *in silico* screening of compounds library and medicinal chemistry approaches have led to the discovery 2 lead compounds: a novel antagonist of the receptor of the Pseudomonas quinolone signal pathway (PqsR) and a novel antisense molecule conjugate that has shown inhibition of quorum sensing, biofilm formation and synergistic effects with PqsR inhibitors.

Project Outcome

SENBIOTAR has studied an alternative way to treat infections caused by *P. aeruginosa*. Combinations of the newly identified compounds with tobramycin were effective in a rodent infection model to give valuable mechanistic proof-of-concept and did not show any toxicity to human cells which means they have the potential to be developed into novel treatment for human infections caused by *P. aeruginosa*. It is now continued for further development as a step closer to exploitation in the clinic.

Relevant publications

Model-Based Drug Development in Pulmonary Delivery: Pharmacokinetic Analysis of Novel Drug Candidates for Treatment of *Pseudomonas aeruginosa* Lung Infection. J Pharm Sci.108:630 (2019).

In Silico and in Vitro-Guided Identification of Inhibitors of Alkylquinolone-Dependent Quorum Sensing in *Pseudomonas aeruginosa*. Molecules. 23. 257 (2018).

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