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O1135 Regulating biofilms by small molecule chemistry

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Background: The fast increasing level of multidrug resistant bacteria, the lack in development of new antibiotics, and the implication of the biofilm life form are three factors that highlight the problematic prospects we are facing in the treatment of bacterial infections. This study is focused on preclinical drug development centered on drug discovery using novel targets to develop antimicrobials with the potentials of chemically eradicating infectious biofilms in combination with conventional antibiotics.

Materials/methods: By designing cell based monitor systems applicable in high-throughput screening both natural compound and synthetic compound libraries have been screened. The primary screening assays are focused on targeting the signaling systems quorum sensing and c-di-GMP in *Pseudomonas aeruginosa*. The most promising compounds have been evaluated in different biofilm model systems in combination with antibiotics, and the *in vivo* efficacy has been tested in a foreign implant mouse model. Target identification has been studied by transcriptomic analysis combined with e.g. different mutant strains.

Results: From diversity and focused screenings a number of potential hit compounds have been shown to lower quorum sensing and c-di-GMP activity. Our best quorum sensing inhibitors have proven to kill up to 90% of *P. aeruginosa* biofilm in combination with conventional antibiotics. They have further been shown to significantly reduce the bacterial counts in our implant mouse model as well as showing enhanced synergistic antibacterial activity with tobramycin (≥1000 fold reduction in bacterial counts).

Conclusions: By studying signaling systems as potential drug targets, compounds with diverse chemical structures showing a great potential for eradicating *P. aeruginosa* biofilms have been discovered. We continuously aim at increasing the activity of our most promising compounds by using structure-activity relationship studies.