Project Proposal for Join A*STAR Graduate Scholarship (Overseas) with the University of Cambridge:

"Computational Approaches Supporting Diversity-Oriented Synthesis (DOS) For Disrupting Bacterial Quorum Sensing"

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Background and Current Situation

Many species of bacteria use intercellular communication mechanism known as quorum sensing (QS)[1]. Such QS is mediated by small diffusible signalling molecules termed autoinducers, produced and secreted by bacterial cells. The signalling process mediated by autoinducers results in population-wide changes in gene expression and cooperative behaviour of complex, multispecies microbial communities. The dependency of QS upon a "language" of autoinducers *provides a potential opportunity for manipulation of bacterial colonies via development of novel small molecules targeted against various components of the QS pathway*. This would be of use as a means to circumvent the widening problem of bacterial resistance against antibiotics, and the emergence of pathogenic multidrug-resistant bacterial species, also known as "superbugs". This is particularly relevant given the fact that many species of clinically relevant pathogenic bacteria use QS to regulate processes associated with virulence. Moreover, it has been suggested that since QS systems are non-essential for bacterial survival, their selective disruption may be less susceptible to resistance. Targeting of QS pathways would also be of potential use in antibiofouling applications within marine environments, as well as in an agricultural context, via modulation of the behaviour of bacteria that have pathogenic or symbiotic relationships with plant crops.

Objective and Approach

Until this stage the synthesis of molecules directed at modulating QS of bacteria has been largely trial-and-error, with many ligands synthesized and tested being not bioactive. This is what we aim to change in the context of the current proposal, by also including biophysical, chemical and bioinformatics expertise about bioactive compounds, protein structures, and signalling pathways into the design process of novel bioactive compounds modulating QS. More specifically, in the group of Dr Andreas Bender at Cambridge University the researcher will be able to analyse the wealth of information about the bioactivity of compounds in public databases (such as from ChEMBL), as well as employing network information on QS, in order to suggest scaffolds and compounds more likely to modulate QS than purely random approaches [2]. The group of Dr Peter Bond at BII A*STAR will furthermore contribute the expertise to narrow down this (rather large) list of possible molecules from the structure-based perspective. In particular, molecular dynamics (MD) simulations can provide a route to characterize the conformational plasticity of proteins in atomic detail, and will be used here to suggest which types of chemical structures are likely to bind to receptors of interest, based on crystal structures now available in the public domain, and how these bound states allosterically modulate receptor conformation and hence signalling activity [3]. Molecular properties to be considered will here go beyond ligand-receptor binding alone, given that cell membrane permeability is of significant importance for autoinducer bioactivity. Finally, experimental validation of the hypotheses will be performed in the group of Prof. David Spring at the University of Cambridge, who possesses significant previous expertise in the Diversity-Oriented Synthesis (DOS) and testing of molecules for QS, and where also previous systematic studies of the activities of multiple autoinducer analgoues across several bacterial species have been performed, thereby discovering a wide range of both broad spectrum and species-selective agonists and antagonists [4]. We also expect to plan to extend this combined approach of coupling computational approaches and DOS more widely in the context of this project, in order to provide guidelines for the design of bioactive compounds in other application areas.

References

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