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Discovering peptide inhibitors against FtsY, an antibiotic target

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The rapid rise of antibiotic resistance has caused an urgent demand for new antibiotics. One way to address this is by manipulating essential bacterial interactions not targeted by current antibiotics. The interaction between the Signal Recognition Particle (SRP) and its receptor (FtsY) is critical for cell viability but is mediated by RNA:protein interactions in bacteria versus protein:protein interactions in eukaryotes. We have used a new technology known as RaPID (Randomised non-standard Peptide Integrated Discovery) to identify cyclic peptides that bind to FtsY. Sequence enrichment was observed after seven rounds of selection and eight representative peptides were selected for further characterisation.

To determine whether the peptides can bind the intended RNA-binding interface on FtsY, Nuclear Magnetic Resonance Spectroscopy (NMR) spectra were collected on 2H13C15N-FtsY produced by ANSTO. High deuteration level has facilitated good quality NMR spectra despite the large size of FtsY (35 kDa). In total, ~220 amide groups were mapped onto the “fingerprint” 15N-1H-HSQC spectrum with >75% of backbone resonances assigned. Following peptide synthesis, we will titrate selected peptides into labelled FtsY for chemical shift perturbation experiments. This will provide binding affinity data for the different peptides and enable the mapping of binding residues onto our previously solved crystal structure. The highest affinity binders will be subjected to soaking and co-crystallisation experiments with FtsY to further characterise the mode of interaction. Taken together, the data obtained will inform the future development of cyclic peptides into FtsY inhibitors with high affinity and specificity as potential antibiotic leads.

Level of Expertise

Student

Presenter Gender

Woman

Pronouns

She/Her

Which facility did you use for your research

National Deuteration Facility

Students Only - Are you interested in AINSE student funding

Yes

Do you wish to take part in the Student Poster Slam

Yes

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Yes

Primary author(s) : ZHAO, Jennifer (University of Sydney)

Co-author(s) : Dr PASSIOURA, Toby (University of Sydney); Dr DUFF, Anthony (ANSTO); Dr WILKINSON-WHITE, Lorna (University of Sydney); Dr ATAIDE, Sandro (University of Sydney); Dr KWAN, Ann (University of Sydney)

Presenter(s) : ZHAO, Jennifer (University of Sydney)

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