NACPLI: Non-conventional approaches for peptidoglycan cross-linking inhibition

Challenge

Bacterial resistance to antibiotics has been mainly fought by modifications of molecules discovered more than 50 years ago. Consequently, antibiotics available in the clinics belong to a very limited number of chemical classes. This JPIAMR-funded project has evaluated new ways to inhibit “old” drug targets, those of β-lactams.

Research Approach

The consortium designed new inhibitors with antibacterial activity that could act alone or in synergy with β-lactams. It has identified new binding sites that are distinct from that of penicillin and are essential for the activity of the targets. A new lead molecule that is an analog of peptidoglycan fragment and acts as a bi-substrate inhibitor of L,D-transpeptidases has been identified which are involved in distinct β-lactam resistance mechanisms.

Project Outcome

The impact of the project is to show how furthering the understanding of peptidoglycan synthesis contributes to the development of new strategies for drug development in academic laboratories with complementary expertise in structural biology, in chemistry and in biochemistry.

The collaboration has received further support through other funding including CARBX for academia-industry research partnership.

Relevant publications

Peptidoglycan Remodeling Enables Escherichia coli To Survive Severe Outer Membrane Assembly Defect. MBio.10:e02729 (2019).

Copper inhibits peptidoglycan LD-transpeptidases suppressing β-lactam resistance due to bypass of penicillin-binding proteins. PNAS. 115. 10786 (2018).

Factors essential for L, D-transpeptidase-mediated peptidoglycan cross-linking and β-lactam resistance in Escherichia coli. eLife.5:e19469 (2016).

Research team

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