



Probes for Biosynthesis of Bacterial Cell Wall

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Penicillin-Binding Proteins Imaging Using β -Lactone Scaffolds

Fluorophore conjugated beta-lactone (β -lactone) chemical probes can selectively label penicillin binding proteins (PBPs). The selective activity-based probes for PBP labeling in *S. pneumoniae* use novel β -lactone scaffolds and uniquely feature PBP2x localization at both the septal ring and the center of the septa during division. Adding clickable groups or affinity groups such as biotin can isolate the PBPs and proteins associated with them in the cell. The probes enable imaging and visualization of specific PBPs expressed and catalytically active in bacteria by conjugation to fluorophores and through click chemistry handles. The compounds have potential for studying specific PBPs, their physiological role in bacteria, and their mechanisms of resistance. Advancing knowledge of the physiological role of specific PBPs may allow development of new and selective PBP inhibitors. Additionally, these probes could serve as safer molecular diagnostic tools that aid in identifying resistant bacterial strains and contribute to personalized therapies.

Antibiotic-based Probes for Cell Wall Biosynthesis

Fluorescently labeled antibiotic probes bind to PBPs along an antibiotic backbone consisting of a β -lactam antibiotic. The binding process allows for specific PBP labelling so researchers can visualize activity and isolate PBPs for further use (i.e., studying bacterial cell wall biosynthesis, gel-based analysis of penicillin-binding proteins and bacterial imaging applications). Studying PBP activity in cell wall synthesis also lends important insight to bacterial resistance mechanisms.

Selective Activity-based Probes Detect Individual or Groups of PBPs

PBPs, targets for many antibacterial agents, are involved in the synthesis and crosslinking of the peptidoglycan polymeric structures that comprise bacterial cell walls. Standard methods for detecting PBPs use probes that are radioactive and difficult to handle for large scale analysis. Furthermore, current methods are insufficient in the study and characterization of individual PBPs expressed in bacteria, and analysis is time consuming. This new technology generates selective activity-based probes to evaluate PBP localization and activity in *Streptococcus pneumoniae*, where the alternative β -lactones scaffold can generate PBP-selective imaging agents for assessing PBP2x. These fluorescently labeled chemical structures can be used for gel-based analysis of penicillin-binding proteins and bacterial imaging applications. The primary advantage of these probes is their demonstrated ability to selectively probe for individual or groups of PBPs, not

currently possible with commercial PBP inhibitor-fluorophore conjugates.

BENEFITS AND FEATURES:

- Selectively labels individual or groups of PBPs
- Novel β -lactone scaffolds
- PBP2x localization in *S. pneumoniae* at both the septal ring and the center of the septa during division
- Fluorescently labeled chemical structures can be used for gel-based analysis
- Adding clickable groups or affinity groups isolates PBPs and proteins associated with them in the cell
- Safer (probes are not radioactive)
- Directly detects the activity state of the target
- Provides time resolution of cell activity
- Enables investigation of PBP2x activity in *S. pneumoniae*

APPLICATIONS:

- Cell labeling of active PBPs expressed in Gram-positive bacteria/phenotype profiling
- Selectively targeting and imaging PBP homologs expressed in bacterial cells
- Molecular probes (research tools)
- Investigating PBP2x activity
- Imaging and visualization of specific PBPs expressed and catalytically active in bacteria
- Development of new and selective PBP inhibitors
- Identification of resistant bacterial strains
- Development of personalized therapies
- Antibiotics/antibiotic resistance
- Imaging probes
- Chemical probes for direct imaging of specific bacterial PBPs and/or profiling bacterial PBP expression using fluorescence microscopy
- Discovery and screening of selective PBP inhibitors

Phase of Development - In Vitro/in vivo assessment. Molecules have been synthesized and tested in multiple bacterial organisms.

Researchers

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Publications

[*Novel Electrophilic Scaffold for Imaging of Essential Penicillin-Binding Proteins in *Streptococcus pneumoniae**](#)
ACS Chemical Biology, 12, 11, 2849-2857

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