DEPARTMENT OF PHYSICS COLLOQUIUM

Characterization of oritavancin mode of action and *Staphylococcus aureus* peptidoglycan structure by solid-state NMR

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ZOOM Link:

https://uchicagogroup.zoom.us/j/96367028599?pwd=VU9nOHZ1YW1hUnZGVXNPTVBhOWdkdz09

Solid-state NMR was used to characterize the mode of action of oritavancin, a second-generation glycopeptide antibiotic reserved for the treatment of serious infections by multi-drug resistant Gram-positive pathogens. Oritavancin inhibits bacterial cell wall biosynthesis by targeting the nascent peptidoglycan. Rotational-echo double resonance (REDOR) NMR was used to determine the internuclear distances from the 19F of oritavancin to the specific 31P, 13C, and 15N labels that are incorporated into the cell walls of *Staphylococcus aureus*. $^{13}C\{^{15}N\}$ and $^{15}N\{^{13}C\}$ REDOR NMR confirmed that the potent bactericidal activity of oritavancin is due to dual inhibition of transglycosylation and transpeptidation steps of peptidoglycan biosynthesis by targeting the lipid transporter C_{55}. Since C_{55} is a shared transporter required for both peptidoglycan and wall teichoic acid (WTA) biosyntheses, we found that *S. aureus* treated with a sub-inhibitory concentration of oritavancin rapidly inhibited WTA biosynthesis, but without detectable changes to the peptidoglycan cross-link or stem-link densities. The result is consistent with oritavancin targeting WTA prior to the peptidoglycan biosynthesis in *S. aureus*.