On-cell NMR screening of multivalent ligands for bacterial targeting

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Abstract: Antimicrobial resistance emerges as a threat in 21st century, with available antibiotics exerting selective pressure on essential pathways, favoring resistance development across bacterial species. The broad-spectrum nature of most antibiotics compounds the issue, causing lasting harm to the healthy human microbiota.

In addition to the development of novel antibacterial molecules exploiting new mechanisms of action, to counteract this alarming scenario there is urgent need for:
a) diagnostic tools for a fast identification of pathogen classes (Gram+, Gram-, mycobacteria) to timely select the most suitable antibiotic class.
b) novel drugs “disarming” pathogenic bacteria by disrupting their virulence mechanisms, such as those enabling bacteria to colonize, evade or inhibit the host's immune response, and scavenge nutrients. Compounds targeting virulence processes promise reduced evolutionary pressure for resistance, supplementing conventional antibiotics with increased efficacy and minimal impact on the host commensal flora.

In pursuit of these goals, we are pioneering the development of multivalent bacteria ligands. These ligands, based on calixarene or dendrimer scaffolds, target specific molecular patterns in different bacteria classes. Examples include the terminal part of peptidoglycan (D-Ala-D-Ala) and teichoic acids for Gram+ bacteria, LPS for Gram- bacteria, and mycolic acid, glycolipids, and trehalose transporter for mycobacteria. Moreover, for a specific pathogen targeting, the adhesin FimH located at the pili end of an uropathogenic strain of Escherichia coli can be targeted through the glycoside cluster effect of carbohydrate-lectin interactions. Our advanced screening approach, using on-cell STD NMR experiments, has successfully identified promising hit compounds as selective bacteria ligands and anti-virulence factors.