

**Call:** 6<sup>th</sup> transnational call for the JPIAMR within the ERA-NET JPI-EC-AMR:  
Innovations against antibiotic-resistant bacteria: New targets, compounds and tools

**Title:** Design, synthesis and lead generation of novel siderophore conjugates for the detection and treatment of infections by Gram-negative pathogens

**Acronym:** SCAN

#### Consortium composition

Type	Name	Institute	Country
Coordinator	Mark Brönstrup	Helmholtz Centre for Infection Research	Germany
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#### Abstract

There is a strong need for novel, innovative therapeutic solutions for infections caused by Gram-negative pathogens. In addition, there is a lack of tools to diagnose bacterial infections at deep body sites, e.g. on implant surfaces. In the project SCAN (Siderophore Conjugates Against Gram-Negatives), we apply a rational design approach to establish a targeting conjugate platform that can be used to both diagnose as well as treat bacterial infections ('theranostics' principle). The conjugates are actively transported into bacteria through their iron transport machinery that accepts siderophores as substrates. This concept has recently been validated clinically and addresses a key issue of Gram-negative pathogens, the impaired translocation into the cell. We will design and synthesise novel siderophores that employ novel central scaffolds and combinations of iron-binding motifs. Those will be coupled with hitherto unexplored effectors: RNA polymerase inhibitors are employed as potent antibiotics, and dioxetane-based chemiluminescent probes will be used for imaging. As a linkage between siderophore and antibiotic, cleavable, self-immolative linkers (e.g. trimethyl lock) will be constructed. The conjugates will be characterised in cellular assays and in infection models in mice. Their translocation and resistance mechanisms will be investigated by genetic and proteomic methods. The project should yield novel antibiotic lead structures with proven efficacy *in vivo*.