Starving the invader: disrupting iron uptake to defeat *Staphylococcus aureus*

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The rapid emergence of antibiotic-resistant *Staphylococcus aureus* strains underscores its role as a key contributor to the global antimicrobial-resistance crisis. A key factor in its virulence and persistence during infection is the ability to acquire iron, an essential nutrient restricted by the host's defence mechanism known as nutritional immunity. To circumvent host-imposed iron limitation, *S. aureus* employs two sophisticated iron acquisition systems: the iron-regulated surface determinant (Isd) system, which scavenges heme-bound iron directly from host hemoglobin (Hb), and the siderophore-mediated system, which captures iron from host iron-binding proteins *via* small chelators, primarily staphyloferrin B (SB), only produced by the most invasive, coagulase-positive *S. aureus* strains.

Here, we present two innovative strategies targeting *S. aureus* iron metabolism with potential therapeutic applications. The first involves a newly-identified compound (C35)[1] that selectively binds Hb and inhibits its interaction with the IsdB receptor. Using both wild-type *S. aureus* and its isogenic in frame-deletion mutant (Δ*isdB*), C35 was shown to markedly inhibit *S. aureus* growth by blocking hemophore-mediated iron uptake, an essential pathway for survival during infection.

The second approach targets SbnA, a key enzyme in SB biosynthesis. Searching for citrate (*i.e.,* an SB intermediate inhibiting SbnA at physiological concentrations) analogues, the methyl esters of 2-phenylmaleic acid (2-PhMA) and of 2-phenylsuccinic acid (2-PhSA) were found to impair siderophore-dependent iron acquisition in *S. aureus*, and its subsequent growth under iron starvation[2].

Together, these dual approaches targeting both heme- and siderophore-mediated iron uptake pathways provide a robust foundation for the development of next-generation anti-staphylococcal agents.

[1]Cozzi M, Failla M et al. Identification of small molecules affecting the interaction between human hemoglobin and *Staphylococcus aureus* IsdB hemophore. Sci Rep. 2024 Apr 9;14(1):8272. doi: 10.1038/s41598-024-55931-8.

[2]Hijazi S, Cozzi M et al. First-in-class inhibitors of SbnA reduce siderophore production in *Staphylococcus aureus*. FEBS J. 2025 Apr 2. doi: 10.1111/febs.70076.