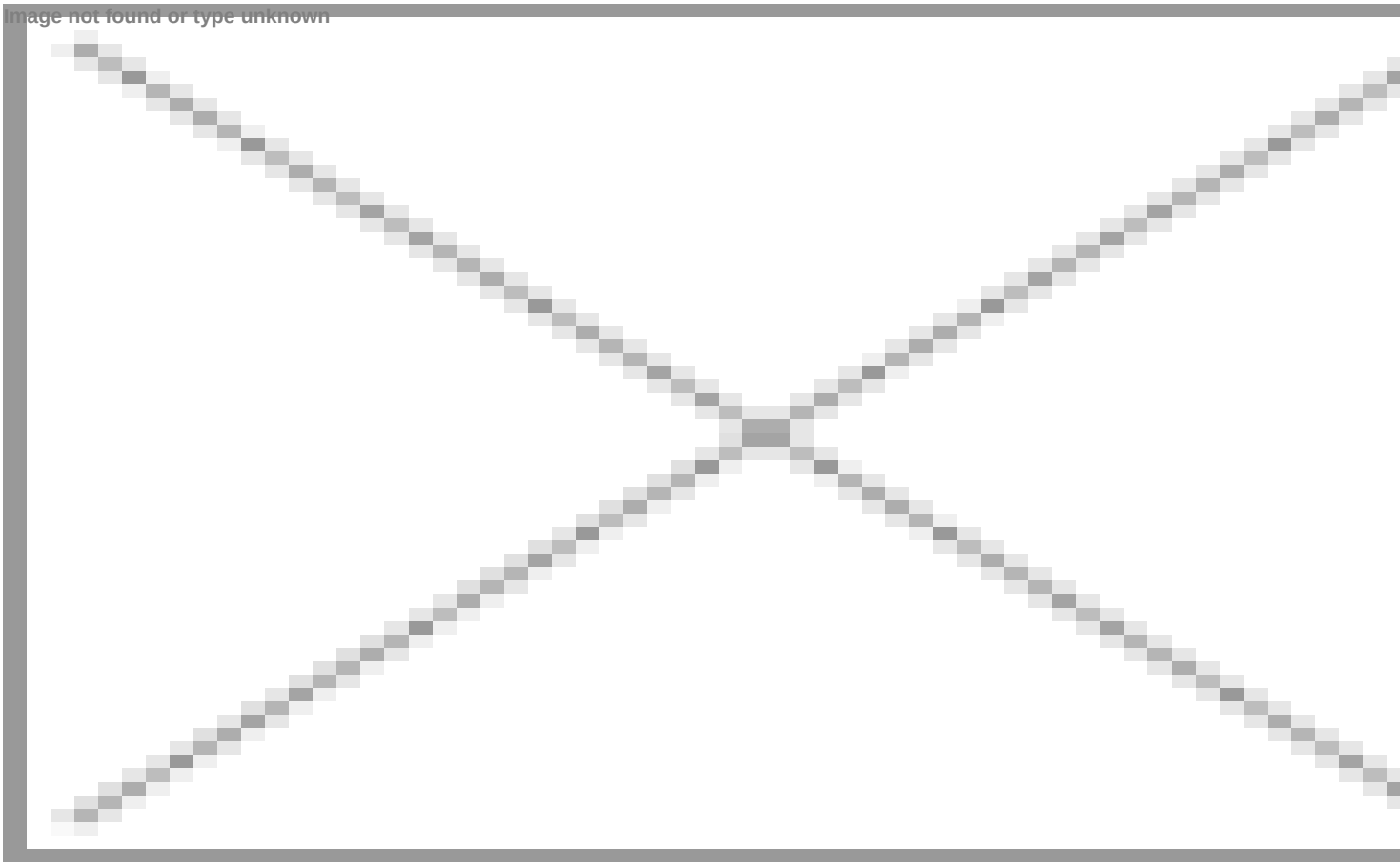
Overview



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To fight back the emergence of the ever-evolving resistance in superbugs as *S.aureus*, we created the NEWAIMS project, a multidisciplinary platform shared among pharmaceutical chemistry, biochemistry and microbiology research groups.

In this framework we aim at developing a new class of antimicrobials able to iron-starve multi-resistant *S. aureus* through a yet unexplored mechanism of action.

The preferred and most abundant iron source for *S. aureus*, and for other Gram+ and Gram- bacteria is hemoglobin (Hb) and bacterial iron acquisition relies on heme capturing from this circulating hemoprotein. *S.aureus* expresses proteins, called hemophores, or iron-regulated surface determinants (Isd), which scavenge heme iron and transport it into the cytoplasm. Heme capture is catalyzed by IsdB and IsdH, formed of two and three NEAr-iron transporter (NEAT) domains, respectively. Once extracted the heme is transferred through the cell wall by means of a relay system of Isd proteins having different affinities for the heme.

S. aureus is able to satisfy its iron requirement by acquiring heme from host hemoglobin in the

context of infection. Several works have demonstrated the essential role of IsdB/IsdH to achieve full virulence by *S. aureus*.

Nevertheless, to our knowledge, no ligand targeting and inhibiting the first hemophore-Hb interaction has been developed. Crystal structures of hemophore-Hb complexes have been recently solved, laying the basis for the design of new antimicrobials inhibiting the formation of Hb-hemophore complexes.

We developed the NEWAIMS platform, integrating *in silico* and *in vitro* approaches, to validate Hb-hemophore complexes as new antimicrobial targets, and identify new inhibitors blocking Superbugs growth and survival in human hosts.

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