Inspired by siderophores: from structural probes of ferric ions assimilation to Ga-68/Zr-89 nuclear imaging

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Under iron-deficient conditions most aerobic microorganisms secret low molecular-weight, highly specific iron(III) chelating compounds – siderophores, which actively transport ferric ions into the cells via specific receptors in the microbial membranes.[1] The difficulties in synthesis of structurally complicated natural siderophores has directed the siderophore research towards biomimetic chemistry, aiming at mimicking or reproducing the function of the natural product rather than its detailed structure. This approach allowed us to diversify the arsenal of biologically active siderophore-type molecules, introduce additional desired chemical and/or physical properties, and provide means to identify general motifs governing an interplay between structure and function in biological activity.[1-4]

Taking into account, that siderophores are absent in the host cells, they are tempting targets for microbial imaging; ^{68}Ga and ^{89}Zr are positron emitters that have recently become the subject of great interest for molecular imaging applications using positron emission tomography (PET). Of the evaluated siderophores, ^{68}Ga-ferrioxamine E (FOXE) and its close biomimetic analogs were shown as the most promising for possible applications in PET imaging of *S. aureus*.[4] On the other hand, desferrioxamine B (DFO) is currently the most commonly used chelator to radiolabel biomolecules with ^{89}Zr.[5] However, its *in vivo* stability has proven insufficient, and transchelation has been observed. Our Zr(IV) – DFO solution studies provided information on the actual chemical form of the complex in biological media, and this can contribute to a better understanding of the *in vivo* speciation and differences in the biological activity of this and other chelators.[6,7]

Overall, proposed derivatives may hold potential as inert and stable carrier agents for Fe(III), Ga(III) and Zr(IV) ions for diagnostic medical applications. They could also allow identifying critical microbial compartments in which siderophores accumulate and thus illuminate key targets for specific drugs against bacterial/fungal diseases.

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