

The Role of Iron and Siderophores in Infection, and the Development of Siderophore Antibiotics

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Iron is an essential nutrient for bacterial growth, replication, and metabolism. Humans store iron bound to various proteins such as hemoglobin, haptoglobin, transferrin, ferritin, and lactoferrin, limiting the availability of free iron for pathogenic bacteria. However, bacteria have developed various mechanisms to sequester or scavenge iron from the host environment. Iron can be taken up by means of active transport systems that consist of bacterial small molecule siderophores, outer membrane siderophore receptors, the TonB-ExbBD energy-transducing proteins coupling the outer and the inner membranes, and inner membrane transporters. Some bacteria also express outer membrane receptors for iron-binding proteins of the host and extract iron directly from these for uptake. Ultimately, iron is acquired and transported into the bacterial cytoplasm. The siderophores are small molecules produced and released by nearly all bacterial species and are classified according to the chemical nature of their iron-chelating group (ie, catechol, hydroxamate, α -hydroxyl-carboxylate, or mixed types). Siderophore-conjugated antibiotics that exploit such iron-transport systems are under development for the treatment of infections caused by gram-negative bacteria. Despite demonstrating high in vitro potency against pathogenic multidrug-resistant bacteria, further development of several candidates had stopped due to apparent adaptive resistance during exposure, lack of consistent in vivo efficacy, or emergence of side effects in the host. However, cefiderocol, with an optimized structure, has advanced and has been investigated in phase 1 to 3 clinical trials. This article discusses the mechanisms implicated in iron uptake and the challenges associated with the design and utilization of siderophore-mimicking antibiotics.

Keywords. β -lactams; iron transport; monobactams; siderophore; siderophore-antibiotic conjugate.

IRON HOMEOSTASIS IN HUMANS

Iron plays pivotal roles in metabolic pathways, oxygen transport, and immune function in humans, and maintaining balanced iron availability (homeostasis) is important for a healthy body. Iron deficiency leads to poor prognoses in long-term diseases and increased susceptibility to infection [1], as does iron overload [2, 3]. Iron homeostasis occurs through regulation of duodenal absorption and recycling of iron stores. Under normal physiological conditions, nearly three-quarters of body iron is found as hemoglobin, with the remainder stored intracellularly as ferritin or bound to extracellular proteins [4]. The normal serum level of iron is 10–30 μ M, giving between 12% and 50% saturation of the iron-binding capacity (60–75 μ M); higher levels are symptomatic of iron overload [5, 6].

Iron is also an essential nutrient for bacterial growth, replication, and metabolism, and the human body has numerous

defense mechanisms that reduce the availability of iron to invading pathogens [7]. Tissue damage resulting from infection can alter local iron homeostasis by enhancing iron-scavenging and macrophage sequestration of iron, heme, and hemoglobin [8, 9]. The serum protein transferrin (also called serotransferrin) creates a bacteriostatic environment by sequestering free iron [10]. The affinity of transferrin for ferric iron is high at physiological pH but decreases at lower pH [11]. This facilitates the release and internalization of complexed iron following interaction with specific receptors on erythroid cells, lymphocytes, and macrophages [12–14]. The analogous lactoferrin is widely expressed in secretory fluids (milk, saliva, and tears), in secondary granules of polymorphonuclear cells, and in some pancreatic duct cells. Its affinity for iron is 300-times higher than that of transferrin and increases further in acidic conditions. This promotes transfer of iron from transferrin to lactoferrin during inflammation, when the local pH is decreased by accumulation of organic acids [15]. Lactoferrin possesses intrinsic antimicrobial activity owing to both its binding to lipopolysaccharide and its catalyzing formation of peroxides with concomitant reduction of ferric iron, which together increase membrane permeability and trigger lysis [16–18]. Iron may also be transported around the body by mammalian siderophores, such as catechols or citrate, bound to siderocalin [19]. Siderocalin is found in neutrophil granules, uterine secretions, and, at particularly high levels,

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in serum during bacterial infection, where it contributes to the host defense [19–22]. Iron uptake in the small intestine is regulated by hepcidin, an oligopeptide hormone synthesized in the liver [23, 24]. Hepcidin production is greatly increased during infection and inflammation, and it has been reported to have direct antimicrobial activity [25, 26]. Iron bound to hepcidin is transported into cells by ferroportin, enabling macrophages, hepatocytes, and enterocytes to retain iron that would otherwise be released into the bloodstream.

BACTERIAL IRON ACQUISITION

Bacteria use a number of strategies to acquire the iron essential for growth [27]. The most important mechanisms (Figure 1) mobilize ferric iron (Fe^{3+}), the dominant iron form in oxygen-rich environments, but bacteria also take up aqueous ferrous iron (Fe^{2+}) [28] or readily utilize ferrous iron bound in heme [29–31]. Most bacteria secrete powerful ferric iron–chelating molecules called siderophores to scavenge iron from their environment [32]. Siderophores have very high ferric-ion association constants (10^{20} to 10^{30} M^{-1}), and they effectively remove iron from the host’s iron–protein complexes [33]. The iron–siderophore complexes are recognized by uptake

systems in bacteria [34]. In gram-negative bacteria, the first step is binding to specific outer membrane receptors (Figure 1), which facilitate their passage across the outer membrane. The translocation is driven by proteins of the TonB family and the energy-transducing complex ExbB/ExbD in the cytoplasmic membrane [35–39]. The iron–siderophore complexes are released into the periplasm, where they may be bound by further components of the transport systems for onward translocation to the cytoplasm or be catabolized to release the iron for uptake by alternative transport mechanisms.

The siderophore strategy is disrupted by the human protein siderocalin, which can also sequester bacterial siderophores and prevent their uptake by bacteria [40–43]. However, bacteria often display redundancy in their deployment of siderophores and can utilize alternatives, such as the fungal ferrichrome, in order to escape siderocalins [44, 45]. Some gram-negative bacteria, especially *Neisseria* spp., can acquire ferric iron directly from lactoferrin and serum transferrin [46], and many bacteria can exploit the ferrous iron bound in heme as a nutritional source. The heme or heme proteins are bound by cell surface receptors and transported into the cytoplasm, where the tetrapyrrole ring is cleaved in order to release the iron [47]. Gram-negative bacteria also secrete extracellular heme-binding

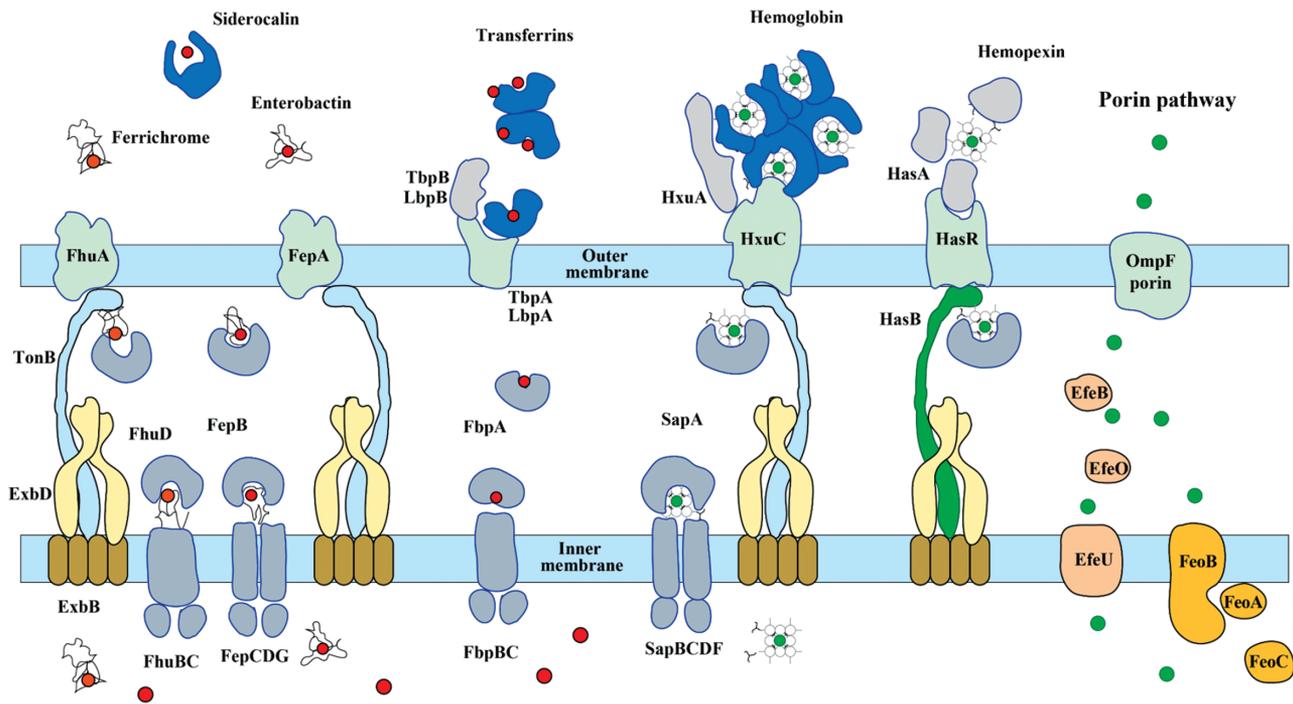


Figure 1. Iron transporters in gram-negative bacteria and metal availability in the host during infection. In a healthy individual, ferric iron (Fe^{3+} ; red circles) circulates bound by transferrin in the blood, and ferrous iron (Fe^{2+} ; green circles) is complexed in heme, which is bound by hemoglobin within red blood cells but can be released by hemolysis during infection. Free Fe^{2+} is uncommon; however, when available, it enters through the general porin pathway. Free heme is scavenged by hemopexin. Secreted bacterial siderophores remove iron from transferrins and ferritin, and the siderophore–iron complexes are bound by cognate receptors at the bacterial surface. Similarly, secreted hemophores such as HasA and HxuC can remove heme from hemoglobin and hemopexin. Enterobacteria also possess outer membrane receptors for heme. In *Neisseria*, iron transferrins are bound by outer membrane receptors comprising 2 subunits (eg, LbpA and LbpB for lactoferrin) and forced to release 1 of the bound iron ions. Catecholate-mediated iron acquisition (eg, by enterobactin) can be inhibited by the innate immune protein lipocalin-2 (siderocalin or neutrophil gelatinase-associated lipocalin), which binds and sequesters catechols.

proteins (hemophores), such as hemopexin, which sequester heme and deliver it to active uptake systems [48–50].

Bacteria use a wide variety of ligands in their siderophores [32], the principal ligands being α -hydroxy acids (eg, citrate, vibrioferrin, staphyloferrin A), catechols (eg, enterobactin, bacillibactin), and hydroxamates (eg, ferrichrome, deferoxamine, ornibactin). Some species produce siderophores that combine different ligands (eg, azotobactin, pyoverdine) [41]. The ligands are typically bidentate and, together with other ligands, form pseudo-octahedral, hexadentate coordination complexes with ferric iron [51]. Siderophores such as enterobactin or ferrichrome are optimized for binding, as each molecule carries 3 bidentate ligands.

ILLICIT TRANSPORT BY IRON UPTAKE SYSTEMS

The iron–siderophore uptake systems provide access to the periplasm across the otherwise poorly permeable outer membrane. It is therefore not surprising that bacteria have evolved ways to exploit these systems to deliver toxic compounds that hinder the growth of competing species. The natural antibiotics, known as sideromycins, mimic hydroxamate siderophores [52]. This small group of antibiotics includes albomycin, produced by *Actinomyces subsp. tropicus*; ferrimycin A1, produced by *Streptomyces griseoflavus*; and salmycins A–D, produced by *Streptomyces violaceus* [53–55]. No new members of this structurally diverse group have been identified, although a genome-mining approach has paved the way for structural variation around albomycin [56]. Many Enterobacteriaceae secrete microcins that are conjugated post-translationally with endogenous catecholate siderophores [57–59]. Genome mining, using the readily identified genes responsible for conjugating the siderophore and peptide [60], has yielded many new variants [61].

SYNTHETIC SIDEROPHORE-DRUG CONJUGATES

Research efforts exploiting a “Trojan horse” strategy started in the 1980s, with the aim of developing agents that would facilitate the uptake of antibiotics into gram-negative bacteria in a way similar to albomycin [32, 62, 63]. For the most part, the activity of these model compounds was not greater than that of the parent antibiotic [32], and additional challenges emerged including solubility issues, inadequate passage across the cytoplasmic membrane, and a lack of release of the active antibiotic [64]. The β -lactam antibiotics, whose targets (the penicillin-binding proteins [PBPs] essential for cell wall biosynthesis) are located in the periplasmic space, have been the antibiotic class where this strategy has been most successfully used, with 4 compounds, cefetecol, BAL30072, GSK3342830, and cefiderocol, reaching clinical trials [32, 65].

BAL30072 (Figure 2) is a monocyclic β -lactam, an analog of the monosulfactam tigemonam, conjugated with the catechol isostere, hydroxypyridone [66]. Other

hydroxypyridone-conjugated monocyclic β -lactams that have recently received experimental investigation include a monobactam MB-1 [67] and 2 monocarbams MC-1 and SMC-3176 [68, 69]. These 4 compounds (Figure 2) exhibited potent activity against β -lactamase-producing Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*, but the activities of MB-1, MC-1, and SMC-3176 against *Acinetobacter* spp. were limited. Monocyclic β -lactams are not readily hydrolyzed by the class B metallo- β -lactamases and class C serine- β -lactamases [68, 69]. MB-1, MC-1, and SMC-3176 carry bulky substituents that improve stability toward class A, C, and D extended-spectrum β -lactamases and carbapenemases, but the bulk of these substituents prevents binding to the active site of the target PBP3 in *Acinetobacter* spp. [70, 71]. Of these 4 molecules, only BAL30072 entered into clinical trials, but its development by Basilea Pharmaceutica was suspended in phase 1.

Catechol-conjugated cephalosporins have been investigated experimentally by many research groups [32, 72]. Of the early conjugates, cefetecol (Figure 3, compound 1) entered into human clinical trials, but its development was terminated in phase 1. The potent in vitro activity of these early compounds did not translate into good in vivo efficacy, largely because mammalian catechol O-methyltransferase (COMT) methylates 1 phenol group of the catechol [72], leading to loss of activity as the metabolized compound is no longer a substrate for the uptake systems. Decreasing the pK_a of the catechol moiety by the introduction of an electron-withdrawing halogen atom (eg, Figure 3, compound 2) led to compounds that retained excellent potency, were more stable toward COMT, and had extended pharmacokinetic half-lives [73]. However, none of these compounds reached the market owing to a lack of stability against β -lactamase-mediated hydrolysis, unwanted side effects, and, in some cases, simple economics. More recently, Shionogi and GlaxoSmithKline (GSK) ran a joint discovery program around such conjugated cephalosporins. GSK registered a phase 1 trial to evaluate safety, tolerability, and pharmacokinetics of an ascending intravenous single-dose and repeat dose of GSK3342830 (NCT02751424) [74]; however, the trial was suspended, and no details of activity or structure of the compound are available. Shionogi pursued S-649266 (previously also known as GSK2696266), now called cefiderocol (Figure 3, compound 6), which has progressed satisfactorily through clinical trials (see below).

Hydroxypyridone, the catechol isostere, has also been investigated with cephalosporins [32], and GT-1 (LCB10-0200) is a new hydroxypyridone-conjugated cephalosporin in development by Geom Therapeutics and LegoChem Biosciences, alone and in combination with a β -lactamase inhibitor (GT055, LCB18-055). GT-1 (Figure 3, compound 3) is active against many gram-negative pathogens, including *P. aeruginosa* and *Acinetobacter baumannii*. Addition

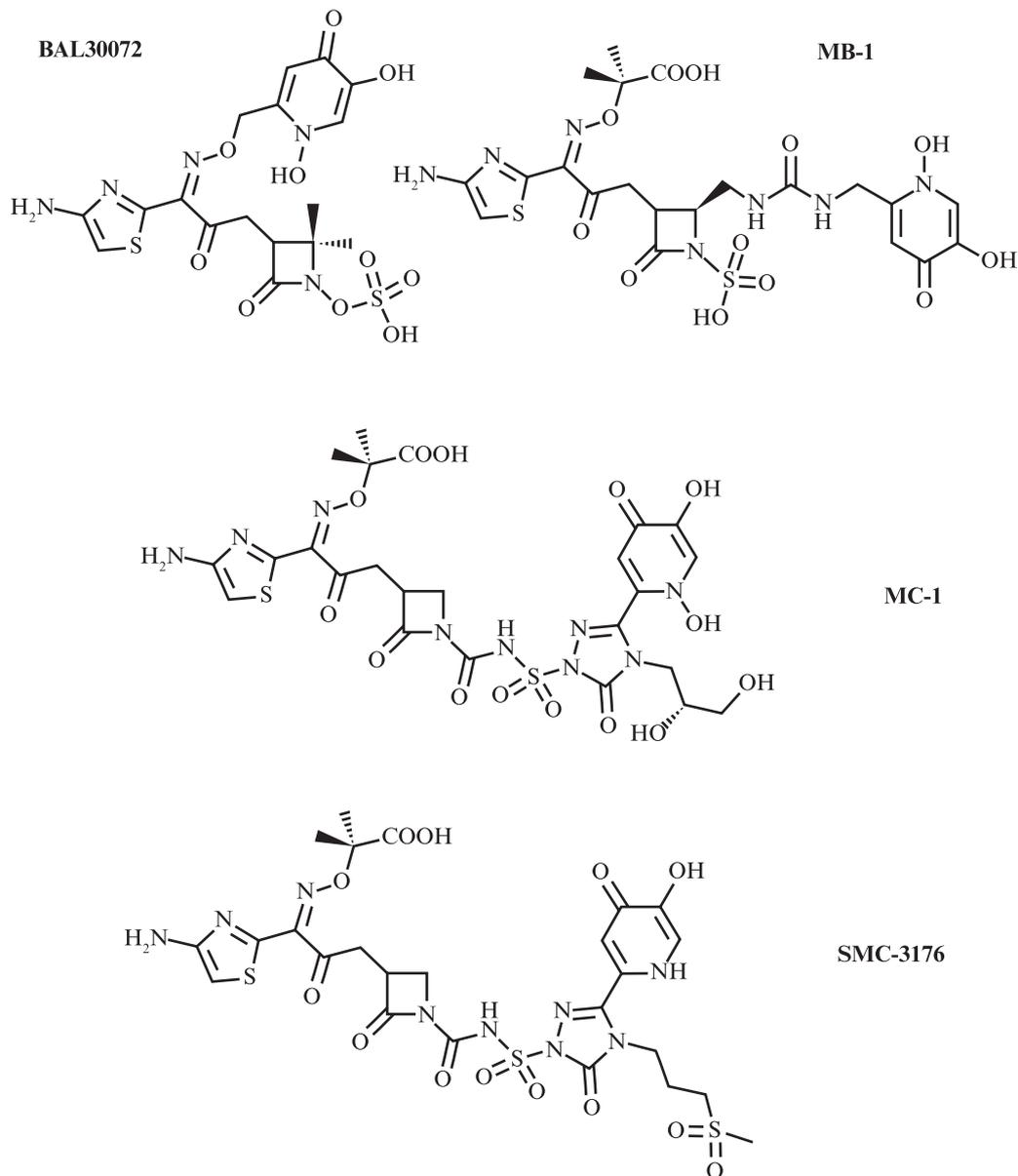


Figure 2. Structures of the monocyclic β -lactam-siderophore conjugates that have been evaluated for clinical development—BAL30072 (terminated in phase 1), MB-1 (preclinical investigation only), MC-1 (preclinical investigation only), and SMC-3176 (preclinical investigation only).

of the new β -lactamase inhibitor improves activity against Enterobacteriaceae [75].

RESISTANCE TO SIDEROPHORE-CONJUGATED β -LACTAMS

Resistance to any of the conjugates with a catechol ligand, or catechol isosteres, can be acquired in *Escherichia coli* (and other Enterobacteriaceae) through loss of the TonB energy-transducing protein or the catecholate receptors Cir and Fiu, which preferentially transport monomeric catecholate siderophores [76–78]. Similarly, loss of the putative catecholate receptors PiuA, PiuD, and PirA or TonB in *P. aeruginosa* and

A. baumannii results in elevated minimum inhibitory concentrations (MICs) for the conjugated monocyclic β -lactams and cefiderocol [77, 79–83].

In addition, MB-1 and SMC-3176 may be vulnerable to adaptive resistance (ie, reversible resistance observed only in the presence of the antibiotic) in *P. aeruginosa* [81, 84], a phenomenon that has previously been observed for this organism exposed to aminoglycosides and polymyxins [85–89]. The mechanisms underlying adaptive resistance are unclear and the net effect probably depends on specific combinations of environmental conditions, strains, and antibiotics. Adaptive resistance has been attributed to decreased outer membrane permeability and

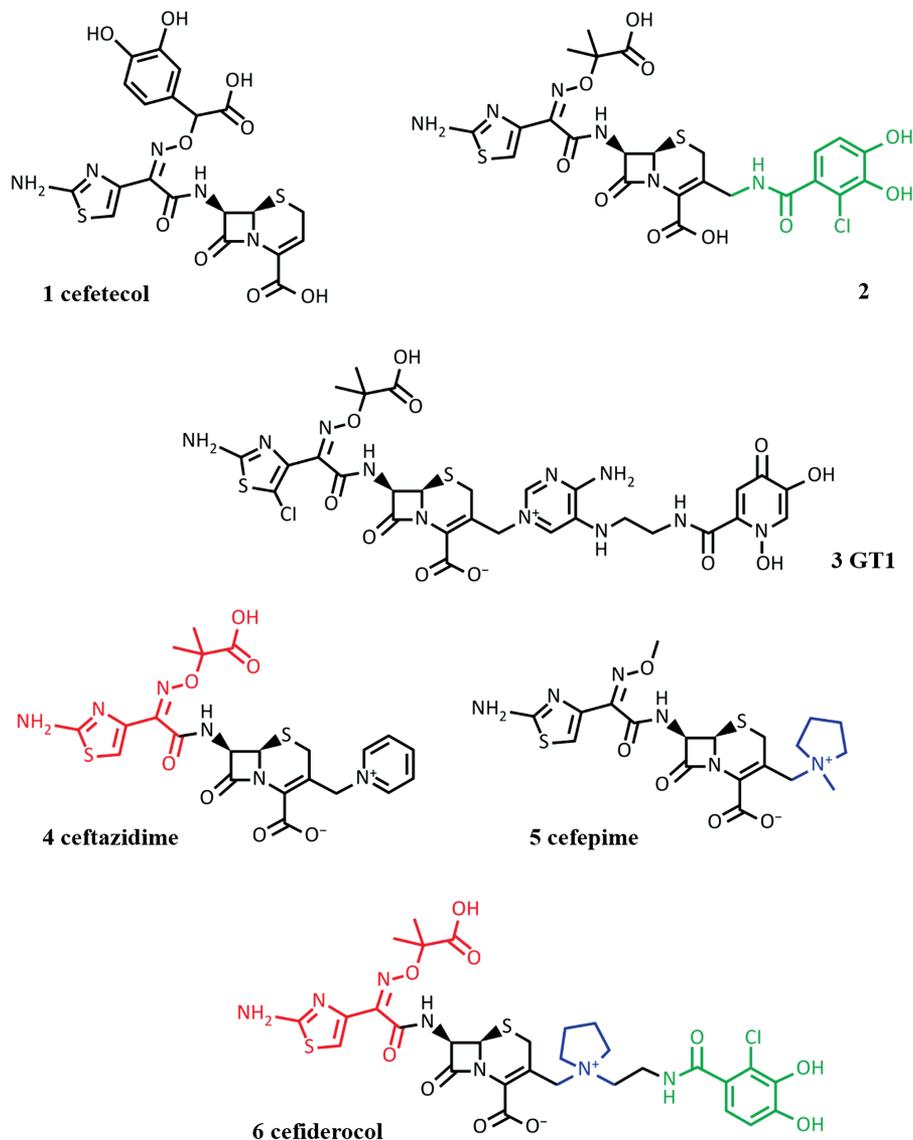


Figure 3. Structures of the siderophore-conjugated cephalosporins that have been evaluated for clinical development. Compound 1: cefetecol (terminated in phase 1). Compound 2 (preclinical investigation only [73]): the halogen-substituted catechol moiety (highlighted in green), optimized for in vivo stability. Compound 3: GT-1 (currently in preclinical investigation). Compound 6: cefiderocol (phase 1 to phase 3 clinical development), which shares the halogen-substituted catechol moiety shown in compound 2. For comparison, structures are also shown for ceftazidime (compound 4), with which cefiderocol shares the bulky 7-acylamino side chain (highlighted in red) that confers β -lactamase stability, and cefepime (compound 5), with which cefiderocol shares the 3' side chain with a quaternary ammonium function (highlighted in blue) that confers β -lactamase stability and good penetration into gram-negative bacteria.

action of efflux pumps [85, 90, 91]. Indeed, MB-1 was potentiated by combination with an efflux pump inhibitor [92]. It was also suggested that, for MB-1, competition between the natural siderophores and the synthetic conjugate may contribute to the effect [92]. However, activity of BAL30072 against *Burkholderia pseudomallei* is independent of the ability of the bacteria to take up malleobactin and pyochelin, the siderophores utilized by this organism [93], and activity against *P. aeruginosa* was not affected by competition with endogenous siderophores at physiological expression levels [94]. Furthermore, extensive in vivo testing did not suggest a propensity for adaptive resistance

during exposure to BAL30072 [95–100]. Similarly, cefiderocol has demonstrated good in vivo efficacy in rat models of respiratory infection [101] and the neutropenic mouse thigh infection model [102–104]. In a recent study comparing the in vivo efficacies of cefiderocol, MB-1, and SMC-3167 against *P. aeruginosa* strains that exhibited variable susceptibility toward MB-1 and SMC-3167 in previous investigations [81, 84], the attenuated efficacies of MB-1 and SMC-3167 were confirmed, whereas cefiderocol showed sustained inhibitory effects consistent with expectation from the MICs determined in iron-depleted medium [103]. It remains to be proven that the

discrepancy between observed activity of some of the siderophore conjugates in vitro and their efficacy in animal models of infection in vivo is caused by a resistance phenomenon. It is possible that the inconsistency is simply attributable to differences in expression of the multiple iron uptake pathways between the in vitro test medium and the infection site in vivo.

Normal growth media recommended for susceptibility testing contain iron at concentrations that are many times higher than the normal free iron concentration in blood. These concentrations are sufficient to repress the expression of siderophores and most iron-uptake pathways. These media are clearly inappropriate for determination of the activity of the siderophore compounds and it has been customary to add a chelating agent, such as ovotransferrin (conalbumin) [105] or 2,2' bipyridyl [66] or to remove iron using ion-exchange resins [81]. This results in increased siderophore production, induction of the iron-uptake systems, and, consequently, increased susceptibility toward the siderophore-conjugated antibiotics. However, *P. aeruginosa* is well known to adapt its iron homeostasis to local conditions of infection [106, 107]. Without information about the actual expression levels under the various in vitro susceptibility testing conditions, it is unclear whether any of the proposed in vitro tests is appropriate for prediction of in vivo efficacy and, therefore, for properly identifying adaptive resistance for this species.

SIDEROPHORE CONJUGATES CURRENTLY IN DEVELOPMENT

Cefiderocol is an advanced-generation cephalosporin that combines the optimized chloro-catechol iron-binding moiety, similar to earlier siderophore cephalosporins (Figure 3, compounds 1, 2), with features conferring β -lactamase stability, such as the quaternary ammonium function in the 3' side chain, similar to cefepime (Figure 3, compound 5), and a bulky 7-acylamino side chain, similar to ceftazidime (Figure 3, compound 4). Cefiderocol therefore shows potent activity against a wide range of gram-negative bacteria that produce serine- β -lactamases [108–115] because it is poorly hydrolyzed by these enzymes, including the *Klebsiella pneumoniae* carbapenemases [116]. It is not clear which structural features lead to the remarkable stability of cefiderocol toward metallo- β -lactamases, where unexpectedly low catalytic efficiencies (k_{cat}/K_M) were reported for imipenemase metallo- β -lactamase-1 (IMP-1), Verona integron-encoded metallo- β -lactamase (VIM-2), L1, and New Delhi metallo- β -lactamase-1 (NDM-1) [116].

The molar ratio of cefiderocol to ferric iron in the equilibrium complex was found to be 1:1 [108], lower than the expected 3:1 reported for monocarbams [117]. It seems likely that, as observed with BAL30072 [118], other parts of the molecule provide secondary ligands to fulfill the coordination requirements of the ferric ion. The example of BAL30072 strongly suggests that a lower stoichiometry might be the one recognized by the receptor, so that to focus only on the highest stoichiometry

might be misleading for siderophores with fewer than 6 donors. The possibly unique iron-chelating modality of cefiderocol may allow it to escape the mechanisms that underlie the putative adaptive resistance observed with MB-1, MC-1, and SMC-3167. The clinical development of cefiderocol is continuing, with the recent completion of a phase 2 trial to study efficacy and safety of intravenous cefiderocol vs imipenem/cilastatin in complicated urinary tract infections (APEKS-cUTI) [119] and an ongoing phase 3 trial studying the efficacy of cefiderocol in the treatment of adult patients with serious infections caused by carbapenem-resistant gram-negative pathogens (CREDIBLE-CR) [120].

CONCLUSIONS

Cefiderocol is the first siderophore-conjugated antibiotic to progress beyond phase 1 human safety trials. Its unique combination of structural features has helped to avoid problems earlier conjugated cephalosporins encountered. Developing a standardized in vitro testing method should be feasible based on the apparent robust correlation between in vitro and in vivo models. The further development and use of cefiderocol in clinical practice for the treatment of infection will be watched with interest.

Notes

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