

Concept Paper

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Siderophore-Guided Strategies to Overcome Gram-Negative Barriers: β -Lactamase-Triggered Periplasmic Activation, Efflux Evasion, and Cytosolic Self-Assembly

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Abstract

Multidrug-resistant (MDR) Gram-negative pathogens pose a critical threat within the broader Antimicrobial Resistance (AMR) crisis, which caused an estimated 1.27 million direct deaths globally in 2019. Their restrictive outer membranes and broad resistance–nodulation–cell division (RND) family efflux systems severely limit antibiotic access. While siderophore–antibiotic conjugates (SACs) utilize TonB-dependent receptors (TBDRs) for outer-membrane entry, success in reaching the cytosol remains limited. Here, we outline a conceptual framework that advances testable hypotheses across three main strategies—(i) β -lactamase–triggered periplasmic activation to release a small, eNTRy-compatible cytosolic payload; (ii) efflux evasion by design to favor inner-membrane transit and residence; and (iii) siderophore-mediated intracellular self-assembly, whereby two periplasm-released precursors re-assemble an active ribosomal agent in the cytosol via bio-orthogonal chemistry—treating siderophore-guided entry as the unifying backbone across all approaches. We also consider a dual-pressure variant combining periplasmic and cytosolic action, and a minimal exporter-decoy element. Owing to technical and financial constraints, no experiments were conducted; our aim is to propose testable hypotheses.

Keywords: siderophore–antibiotic conjugate; β -lactamase trigger; eNTRy rules; efflux evasion; quinolone SAR; RND efflux; intracellular self-assembly; oxazolidinones; bio-orthogonal click chemistry

1. Introduction

1.1. Background

The challenge posed by MDR Gram-negatives—within a global AMR burden of ≈ 1.27 million direct deaths in 2019—demands innovative solutions [1]. The combination of a highly selective outer membrane (OM) and potent RND efflux pumps (e.g., AcrAB–TolC, MexAB–OprM) restricts drug accumulation across all bacterial compartments [2]. Siderophore–antibiotic conjugates leverage TonB-dependent receptors (TBDRs) to cross the OM, yet productive cytosolic delivery requires negotiating the inner membrane (IM) and persisting against trans-envelope pumps that sample both periplasmic and cytosolic pools [3,4]. A key, testable premise is to time periplasmic β -lactamase activation to release a small, eNTRy-compatible payload whose size, basicity, and shape favor IM crossing and residence [5,6]; alongside this, we pursue (ii) efflux evasion by design to favor IM transit and residence [5,6] and (iii) siderophore-mediated intracellular self-assembly from periplasm-released fragments (Section 3).

1.2. State-of-the-Art Gaps

Early cytosolic-leaning SAC exemplars include rifampicin conjugates, fluoroquinolone constructs based on enterobactin, dual-drug sideromycins, and triscatecholate platforms [7–14]. Open questions remain regarding: (i) how to synchronize periplasmic de-labeling; (ii) how linker/head mass affects deeper transport if retained; and (iii) how to limit host-side sequestration by lipocalin-2 and manage receptor idiosyncrasies that curb generalization [4,15]. Complementary envelope innovations—BamA-binding darobactins, LolCDE-inhibiting lolamicin, and outer-membrane permeabilizers (e.g., SPR741, MAC-0568743)—illustrate routes to deepen access or bypass barriers, and porin-loop dynamics increasingly inform small-molecule entry [16–20]. Lipid A biosynthesis inhibition (LpxC) further exemplifies orthogonal envelope leverage [21]. This framework centers on early periplasmic release and payload optimization to favor IM transit and sustained cytosolic residence.

1.3. Scope and Intent

This is a conceptual article. It does not prescribe chemistries or blueprints. We propose testable hypotheses and decision levers intended to guide experimental exploration. No laboratory work was conducted owing to technical–financial limitations. Section 2 details the core hypothesis; Section 3 extends it to intracellular self-assembly; Sections 4–7 provide readouts, boundary conditions, positioning vs. prior art, and conclusions.

2. Core Concept and Hypothesis

Hypothesis. A siderophore– β -lactam–quinolone conjugate can exploit outer-membrane receptors and periplasmic β -lactamase activity to release a small, eNTRy-disciplined payload that achieves meaningful cytosolic exposure while reducing RND capture [3,5–14].

2.1. Core Architecture

Siderophore vehicle. A minimal catecholate-like head (or suitable alternative) engages prevalent TBDRs for TonB-dependent uptake while keeping valency/footprint modest to mitigate host sequestration and preserve receptor breadth [3,4,15].

Trigger-spacer. A cephalosporin-like β -lactam trigger couples to a compact self-immolative spacer; hydrolysis in the periplasm unmasks the payload. Direct penicillin-binding protein (PBP) engagement may occur but is not essential to the core logic [11,12,23,24].

Payload discipline. A small quinolone exemplar retains the C3/C4 pharmacophore, with judicious C7/C8 and N-1 edits to favor inner-membrane passage, target residence, and reduced efflux recognition, remaining within the eNTRy rulespace [5,6,26,27].

2.2. Mechanistic Outline

Entry: Fe(III)-loaded conjugate binds a TBDR and crosses into the periplasm [3,4].

Activation: Periplasmic β -lactamase $\rightarrow$ self-immolation $\rightarrow$ de-labeled small payload [11,12,23,24].

IM transit: The freed quinolone crosses the IM largely by passive diffusion; proton-motive-force components—the pH gradient (Δ pH) and membrane potential ($\Delta\psi$)—modulate retention [5,6].

Target residence: Productive binding to DNA gyrase and topoisomerase IV (Topo IV) with a slowed off-rate; tuned shape/basicity lessens RND capture [5,6,26,27].

2.3. Rate Competitions as a Unifying Principle

Decoupled levers: Influx, activation, efflux avoidance, and target engagement can be tuned semi-independently.

Early de-labeling: Smaller payloads face the IM and RND pumps with a kinetic advantage [11,12,23,24].

Drug-space discipline: Minimal heads + compact linkers + eNTRy-compatible payloads favor IM passage [5,6].

Rate competitions decide outcomes: Entry vs. export vs. binding ultimately governs success; subsequent sections (2.5, 3.4, and 5) reference this explicitly.

2.4. Payload Classes and Illustrative Edits

Without prescribing structures, several categories appear hypothesis-worthy (all under the eNTRy umbrella):

(A) C7 polar amines (e.g., small heteroalkyl amines via amide/urea) to balance pKa/permeability and modulate efflux recognition [5,6,26,27].

(B) C8 electronics/ π -tuning (e.g., modest substituents or short diazacycles) to influence target residence with bounded molecular weight and topological polar surface area [5,27].

(C) N-1/core shape adjustments—moderate sp³ character and rigidity—to reduce promiscuous exporter contacts while staying within eNTRy boundaries [5,6].

(D) Peripheral pruning—removing nonessential periphery—to lower globularity/rotatable bonds while preserving potency [5,6,26].

Quinolones are illustrative; other payload classes (e.g., RNA polymerase (RNAP) inhibitors, ribosomal agents) are conceptually compatible if kept within an eNTRy-like envelope [6,12]. Insights into porin-loop gating and permeability can further shape payload topology [20].

2.5. Optional Enhancements: Dual-Pressure and Efflux-Targeted Elements

2.5.1. Dual-Pressure (Periplasmic + Cytosolic)

This variant maintains β -lactam periplasmic activity (PBPs) while releasing a cytosolic payload. The viable window is narrow at 1:1 stoichiometry: overly fast triggering or an overly potent β -lactam may curtail payload delivery. Best pursued after baseline periplasmic activation timing is established [11,12,23,24]. See boundary notes in Section 5 (β -lactamase variability; species barriers).

2.5.2. Efflux-Targeted Adjuncts

Rather than global pump inhibition, two localized strategies can tilt rate competitions (cf. Section 2.3):

(a) Covalently linked efflux-resistance element (intrinsic). An element covalently appended to the antibiotic payload and positioned to share the same RND export route can transiently occupy or misdirect that pathway—without compromising size, polarity, or shape—thereby improving net cytosolic exposure (built atop the intrinsic eNTRy-guided design of Section 2.1).

(b) Export decoy (extrinsic). A small, well-penetrant motif embedded in the conjugate scaffold or co-released upon periplasmic triggering that preferentially engages the same RND transport pathway as the freed payload and transiently occupies export capacity. This favors local, short-lived micro-concentrations near the IM and avoids broad systemic exposure. Discriminate by loss-of-benefit tests (efflux-deficient backgrounds or payload-decoy route separation).

Efflux-focused readouts applicable to both (a) and (b) are summarized in Section 4, with additional references to entry/activation assays in Sections 2.2 and 4.

3. Siderophore-Mediated Intracellular Self-Assembly: A Forward-Looking Extension

3.1. Rationale

Many potent ribosomal agents (e.g., oxazolidinones) struggle in Gram-negatives due to permeability/efflux rather than target insensitivity. Here we posit delivery of two small Pro-

Fragments, each IM-permeant and bio-orthogonally complementary, that are released periplasmically and assemble only in the cytosol [9,25].

3.2. Minimal Workflow

Distinct siderophore–antibiotic conjugates → TBDR entry → β -lactamase cleavage → two Pro-Fragments cross the IM → fast click assembly near the ribosome [8,9,11,12,23–25].

3.3. Advantages and Constraints

Advantages: Smaller fragments ease IM transit; distinct chemotypes may reduce coordinated efflux; cytosol-restricted assembly; possibility to use different heads for broader receptor coverage.

Constraints: Assembly must outpace export/back-diffusion; cleavage must be clean; synthetic complexity must be managed. Use intracellular ligation reporters and two-fragment synergy as primary readouts [25].

3.4. Feasibility Notes and Rate Considerations

Efflux, membrane transit, and intracellular ligation operate on competing timescales; practical success requires that fragment pairing and assembly be sufficiently rapid under cellular conditions. Bio-orthogonal pairs that have shown efficient cellular reactivity (e.g., tetrazine–strained alkene/alkyne chemistries) may offer useful starting points, and fragment designs whose physicochemical properties align with eNTRY-like constraints could support IM transit and residence. Oxazolidinones are one plausible payload family; in metallo- β -lactamase–dominant periplasms, reductase-responsive motifs (e.g., disulfides) or esterase-labile caps are potential trigger-level options to examine [24,25]. See also Section 2.3 for the rate-competition perspective.

4. Readouts and Exemplary Assays

Chemistry/Triggering: Serum stability; β -lactamase panels—extended-spectrum β -lactamase (ESBL), AmpC β -lactamase (AmpC), and metallo- β -lactamase (MBL); self-immolation half-lives in periplasm-like buffers; LC–MS confirmation of scar-free payload [11,12,23,24].

Entry/Activation: TonB dependence ($\pm$ chelators) and receptor knockouts; radiolabeled/fluorescent uptake; spheroplast assays; real-time de-labeling reporters [3,4,11,12].

Cytosolic Exposure and Pharmacodynamics (PD): Fractionation + LC–MS; perturbations of $\Delta\text{pH}/\Delta\psi$; DNA gyrase and Topo IV engagement assays; MIC and time-kill across MDR panels; RND sensitivity pre/post de-labeling [5,6,26,27].

Efflux-targeted adjuncts (cf. 2.5.2): Nile Red/ethidium efflux competition; impact in efflux-deficient strains; pocket/tunnel specificity with informed mutants; checks for outer-membrane perturbation and induction of efflux operons [2].

Self-assembly: Activity only with both fragments; intracellular ligation reporters; conditioned-media controls to exclude extracellular assembly [25].

5. Boundary Conditions and Conceptual Caveats

Receptor heterogeneity: TBDR repertoires vary across *Enterobacterales*, *Pseudomonas*, *Acinetobacter*; consider stealth heads and species-matched choices [3,4,15].

β -Lactamase variability: ESBL/AmpC/MBL profiles will tune periplasmic activation efficiency; alternate triggers (esterase/reductase) remain in scope [11,12,23,24].

Host sequestration: Lipocalin-2 and immune recognition can reduce exposure; favor stealthier heads and early PK/immunogenicity checks [4,15].

Premature/periplasmic loss: Export or hydrolysis before payload release argues for compact linkers and earlier de-labeling [11,12,23,24].

Efflux dominance: Payloads outside eNTRY space are rapidly exported; discipline edits toward low globularity and bounded TPSA/rotatable bonds [5,6,26,27].

Species barriers: *Pseudomonas/Acinetobacter* present dense OM/porin scarcity; a periplasmic branch remains viable [16,17]; porin-loop dynamics and LPS remodeling pressures should be considered [20,21].

Synthetic complexity: Dual-conjugate self-assembly raises build burden; modular click logic can simplify [25].

Off-target risks: Transferrin mimicry and unintended eukaryotic uptake necessitate bacteria-specific heads [4,15].

6. Positioning vs. Prior Art

Siderophore-guided OM entry is clinically validated (e.g., cefiderocol) [22]. Cephalosporin-based self-immolative triggers are established in principle [11,12,23,24]. Cytosolic-leaning SACs (e.g., rifampicin conjugates) are emerging [7]. This framework differs in several key aspects:

- Activation timing: Periplasmic β -lactamase + self-immolation vs. esterase activation in enterobactin–ciprofloxacin constructs [8].
- Efflux strategy: eNTRY-guided edits to reduce exporter engagement vs. largely empirical tuning in some precedents [5,6]; localized efflux-targeted adjuncts (intrinsic appendage or co-released decoy) offer a route distinct from global efflux pump inhibition and complement OM-permeabilizer concepts (e.g., SPR741, MAC-0568743) [18,19].
- Cytosolic delivery: A self-assembly route enables cytosolic formation of otherwise impermeant payloads, in contrast to DOTAM-based macrocyclic constructs focused periplasmically and to non-assembling cytosolic attempts [14].
- Envelope context: Complementary innovations—BamA-targeting darobactins, LolCDE-inhibiting lolamicin, OM permeabilizers (SPR741, MAC-0568743), and LpxC inhibition—frame alternative or adjunctive paths to access and potency [16–19,21].

7. Concluding Remarks

We proposed testable hypotheses that combine siderophore-guided entry, timely periplasmic activation, and eNTRY-disciplined payloads, alongside optional enhancements (dual pressure and efflux-targeted adjuncts) and a forward-looking self-assembly extension. Demonstrating periplasmic activation that yields useful cytosolic exposure would be a meaningful step; subsequent exploration can escalate complexity as rate-limiting steps become clearer. As outlined in the abstract, no experiments were performed due to technical and financial constraints; this work aims to expand the hypothesis space and provide clear waypoints that experimental groups can refine.

Provenance and Generative AI Use

This manuscript's central idea and wording resulted from iterative author–LLM exchanges using ChatGPT (GPT-5 Thinking), Grok-4 Specialist, Gemini 2.5 Pro, DeepSeek 3.2, and ai2asta. The systems assisted with (i) hypothesis brainstorming and reframing, (ii) literature surfacing and scoping, and (iii) drafting and language polishing. All citations and DOIs were verified by the author. No experimental data, images, or numerical results were generated by AI. The author curated prompts and outputs, reconciled inconsistencies, performed independent accuracy checks, and accepts full responsibility for the content and any errors. No proprietary, confidential, or personally identifiable information was shared with these systems.

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