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Light-Controlled Active Release of Photocaged Ciprofloxacin for Lipopolysaccharide-Targeted Drug Delivery using Dendrimer Conjugates

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We report an active delivery mechanism targeted specifically to Gram(-) bacteria based on the photochemical release of photocaged ciprofloxacin carried by a cell wall-targeted dendrimer nanoconjugate.

Drug delivery for the effective treatment of bacterial infections is still an unmet need for certain localized wounds and for ocular infections.¹ Poor blood perfusion to these infected sites limits the utility of oral or systemic routes of anti-infective drug administration. Additionally, the non-selective effects of certain anti-infective agents upon topical application on the wound healing process and on non-infected tissues also hinders treatment.1 Targeted delivery of antibacterial therapeutics with multifunctional nanoparticles (NPs) conjugated with bacteria-specific ligands constitutes a promising strategy for treating localized infections.²⁻⁷ However the challenge of overcoming the thick cell wall structure⁸ which poses a barrier to both passive and active modes of NP uptake still poses a significant hurdle to these methods for antibacterial use. Here we report a proof of concept study for a novel, stimulus-controlled delivery strategy in bacteria that enables light triggered, targeted release of an antimicrobial payload at the bacterial cell wall surface.

Multivalent strategies⁹⁻¹² have played a fundamental role in the design of NPs for the targeted delivery of therapeutic agents, genes and imaging molecules to a broad range of cell types and pathogens.¹³⁻¹⁵ In particular, multivalent attachment of bacterial cell wall or outer membrane specific ligands to NPs improved their functional activity in the detection and rapid isolation of bacterial cells, and enhanced the antimicrobial activities of NPs carrying therapeutic payloads.^{2, 4-7, 16, 17} We and others have reported on the specific targeting of bacteria by NPs through the multivalent conjugation of cell walltargeting small molecule ligands including vancomycin^{2-5, 18} and polymyxin,^{16, 19} as well as cationic antimicrobial peptides.^{20, 21} Such multivalent NPs were shown to adsorb to the cell wall very tightly, and could be further modified with additional functionalities for fluorescence detection,^{3, 16} magnetic bacterial isolation^{4, 5, 19} and promotion of opsonisation by macrophages.¹⁸

Despite their tight and specific cell wall adsorption, most of these targeted NPs show suboptimal bactericidal activities^{4, 5, 16, 18} largely due to their poor intracellular uptake.⁸ Thus, a conjugate in which the advantages of a tightly binding delivery vehicle that acts to focus on a high local concentration of drug at the bacterial surface in combination with a mechanism that enables drug release at the bacterial surface is of high value.

currently Release mechanisms developed for nanoconjugates are largely based on reactions that occur in mammalian cells by endogenous factors such as low pH in endosomes,²² differences in intracellular and extracellular thiol/disulfide redox potential,²³ and hydrolytic enzymes²⁴ in lysosomes.²⁵ These mechanisms are not directly applicable to antibiotic delivery due to their irrelevance to bacterial systems and to the poor uptake of NPs in bacteria. Use of UV light has been well validated for various controlled-release applications including the spatiotemporal control of gene expression in vivo,²⁶ and tumor targeted drug delivery.^{25, 27, 28} Further, light only-based therapies which include photodynamic therapy and UVB (280-315 nm) irradiation are already in use clinically as



Fig. 1 Scheme for light-controlled, targeted delivery of photocaged ciprofloxacin (Cipro*) carried by a lipopolysaccharide (LPS)-binding dendrimer G5(Ligand)(Cipro*) adsorbed to the outer membrane (OM) of the Gram(–) cell wall. Internalized Cipro inhibits DNA gyrase. Abbreviations: PMB = polymyxin B; EA = ethanolamine, a PMB-

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mimicking lower affinity but more biocompatible ligand; PG = peptidoglycan; IM = inner membrane.

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alternative antibacterial therapies.^{29, 30} In the present study, we expand the scope of light-based therapy by combining the functionalities of light-controlled release of an antibiotic payload with the specificity of bacterial cell wall targeting on the same NP. This nanoconjugate could potentially augment current photodynamic therapy regimens.

Photocaged ciprofloxacin, a broad-spectrum antibiotic, was attached lipopolysaccharide (LPS)-binding to а poly(amidoamine) (PAMAM) dendrimer nanoconjugate for cell wall targeted delivery (Fig. 1). The delivery system was designed using a fifth generation (G5) PAMAM³¹ dendrimer parent, conjugated with excess outer-membrane targeted ligands, polymyxin B (PMB, a polycationic cyclic peptide) or a PMB-mimicking molecule, ethanolamine (EA) as the carrier for 1 ciprofloxacin (Cipro), an inhibitor of DNA gyrase (Fig. 2). Use of these ligands with the dendrimer system for bacterial targeting has been validated in our previous study¹⁶ which demonstrated their tight and specific adsorption to a model surface immobilized with lipopolysaccharide (LPS) ($K_{\rm D}$ = 2.1– 1.4 nM)¹⁶ and to *E. coli* cells *in vitro*. First, an *N*-Boc protected form of 2 ONB-Cipro was synthesized by derivatization of ciprofloxacin at the secondary amine through a carbamate bond with a photocleavable ortho-nitrobenzyl (ONB) linker³²⁻³⁵ (Scheme S1) and its structural identity was characterized by ESI mass spectrometry (HRMS: calcd for C₃₅H₄₂FN₆O₁₂ [M+H]⁺ 757.2839, found 757.2844), UV–vis absorption (λ_{max} = 340 nm, ϵ = 3101 M $^{\text{-1}}\text{cm}^{\text{-1}}\text{;}$ 271 nm, ϵ = 7679 M $^{\text{-1}}\text{cm}^{\text{-1}}\text{)}$ and ^{1}H NMR (Fig. S1).

2 ONB-Cipro was modified at its amine terminus by attachment of an oxirane group (Scheme S2) which allowed covalent coupling to partially acetylated (Ac)₆₀G5(NH₂) dendrimer derived from $G5(NH_2)_{114}$ ($M_w = 26,600 \text{ gmol}^{-1}$, polydispersity index (PDI) = $M_w/M_n \sim 1.010)^{36}$ (Scheme S3). The remaining primary amines of the resulting dendrimer were capped with epibromohydrin for ligand conjugation with excess ethanolamine (EA) and PMB which yielded conjugates 3 $G5(EA)_n(ONB-Cipro)_m$ (n = 40; m = 8.5) and 4 $G5(PMB)_n(ONB-Cipro)_m$ $Cipro)_m$ (n = 1.1; m = 8.5). After purification by membrane dialysis (MWCO 10 kDa), each conjugate was fully characterized for its polymer purity (UPLC; >95%), molar mass (MALDI-TOF: $M_r = 31,300$ (**3**), 31,500 (**4**) gmol⁻¹), and UV-vis absorption (ONB-Cipro: λ_{max} (3) = 337 nm (ϵ = 3,315 M⁻¹cm⁻¹); λ_{max} (4) = 335 nm (ϵ = 3,857 M⁻¹cm⁻¹) in PBS, pH 7.4) as summarized in the Supplementary Information. The valency of attached ONB-Cipro (m) and PMB (n) on 3 and 4 was determined on an average basis by UV-vis analysis (m = 8.5 (mean), and 9 (median) by Poisson distribution,³⁷ Fig. S5) and by NMR integration (n = 1.1).¹⁶ Further characterization by gel permeation chromatography (GPC) led to the determination of their polymer distribution (PDI = 1.081 (3), 1.131 (4)). The basis for such increased dispersity after drug conjugation is partially attributable to the distribution of ONB-Cipro molecules attached to the dendrimer (Fig. S5). Hydrodynamic size (Zave) and zeta potential (ZP) measurements of 3 and 4 (Table S2) suggest that these conjugates are more cationic than unmodified G5(NH₂)₁₁₄ as expected for ເວີດກຸ່ມີຜູ້ສີຊັນດິດໃຫ້ເຖົາໄດ້ໄດ້ cationic EA residues, and tend to form smaller aggregates upon co-conjugation with ONB-Cipro.



Fig. 2 Structure of ciprofloxacin, photocaged ciprofloxacin (ONB-Cipro), and G5 PAMAM dendrimers **3–4** conjugated with ONB-Cipro and a cell wall targeting ligand (L) such as ethanolamine (EA) (**3**) or polymyxin B (PMB) (**4**).

The binding avidity of these two conjugates to the bacterial surface was evaluated with a Gram(-) cell wall model by surface plasmon resonance (SPR) spectroscopy as described previously.^{4, 16} Each conjugate showed tight binding to the sensor chip surface containing immobilized LPS in a dosedependent manner (Fig. 3). Sensorgram kinetic analysis showed markedly slow dissociation rates for both dendrimers, reflecting the tight association imparted by multivalent ligand binding.⁹⁻¹¹ Langmuir fitting analyses³⁸ performed for each sensorgram set yielded dissociation constant ($K_{\rm D}$) values of 7.0 nM (3) and 5.7 nM (4) ($K_D = k_{off}/k_{on}$; Table S3). Conjugates 3 and 4 thus bounnd tighter than free monovalent PMB (K_D = 150 nM¹⁶), with a multivalent enhancement (β) factor of 21 and 26 over PMB, respectively. These values are consistent with previous results¹⁶ observed for the dendrimer modified with only PMB ligand and/or excess EA as an auxiliary ligand



Fig. 3 (A, B) Overlaid SPR sensorgrams of **3** G5(EA)₄₀(ONB-Cipro)_{8.5} and **4** G5(PMB)_{1.1}(ONB-Cipro)_{8.5} binding to a LPS-immobilized cell wall model surface. Experimental (solid line); simulated global fit (dotted line). (C, D) Confocal fluorescence images of *E. coli* treated with the control dendrimer FITC-G5(GA)¹⁶ (C) or with FITC-**4**

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 $G5(PMB)_{1.1}(ONB-Cipro)_{8.5} \ (D). \ Inset: \ an \ enlarged \ view. \ FITC \ fluorescence \ is \ shown \ (green). Bacterial cells were also stained with SYTO59 (red).$

AUC analysis of each UPLC trace. (C, D) UPLC and UV-vis traces (inset, top) measured for the release kinetics of **3** and **4** (31.7 μ M in water) as af mction of 33/2 (as a straight of 33) and 33 a

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without the photocaged ciprofloxacin (ONB-Cipro), demonstrating that the attached ONB-Cipro does not affect the binding avidity. In addition, SPR experiments performed using a model surface for Gram(+) bacteria (immobilized with (D)-Ala-(D)-Ala) demonstrated a lack of binding by conjugate **3** or **4**, supporting their LPS-targeting specificity (Fig. S6).

We investigated the binding of fluorescein 5(6)isothiocyanate (FITC)-labeled conjugate **4** to *Escherichia coli* (XL-1) by confocal fluorescence microscopy (Fig. 3C, 3D). *E. coli* treated with FITC-labeled **4** showed intense areas of green fluorescence, indicating adsorption of conjugate to the cell wall. In contrast, a negatively charged control dendrimer FITC-G5(GA)¹⁶ lacking a targeting ligand did not show any adsorption. Treatment with **4** led to aggregates of *E. coli* which might be attributable to crosslinking of the multivalent dendrimers with multiple cells.^{4, 16}

The photochemical release of ciprofloxacin from **2** ONB-Cipro was evaluated by exposing it to UVA light (365 nm; exposure time = 0–30 min) followed by reversed phase UPLC analysis of the photolysed product as a function of exposure time (Fig. 4A). After brief irradiation, a new peak appeared with a retention time of t_R = 7.2 min which was identical to that of free ciprofloxacin. The peak grew as a function of exposure time with the concomitant consumption of ONB-Cipro **2** (t_R = 9.5 min). Area under the curve (AUC) analysis (Fig. 4B) provided a half-life ($t_{1/2}$) of 15 min for the decay of ONB-Cipro which occurred with a first-order rate constant of



Fig. 4 Light-controlled release of ciprofloxacin from ONB-Cipro 2 (top) or from the ONB-Cipro conjugated G5 dendrimer 4 (bottom) through cleavage of the ONB cage. (A) UPLC traces for release kinetics of Cipro by UVA (365 nm) irradiation of 2 (0.13 mM in 10% aq. MeOH), and (B) a plot of Cipro release (%) against exposure time determined by

Light-controlled ciprofloxacin release was next investigated for conjugates 3 G5(ONB-Cipro)_{8.5} and 4 G5(PMB)_{1.1}(ONB-Cipro)₈₅ and monitored by UPLC and UV-vis spectrometry (Fig. 4C, 4D). Overlaid UPLC traces acquired for each conjugate after UV exposure showed a sharp peak for free ciprofloxacin (t_R = 7.2 min) which grew within the broad dendrimer peak. Ciprofloxacin release was also evidenced by the shift in the broad dendrimer peaks to faster retention times over the course of UV exposure, reflecting their reduction to smaller NPs due to the loss of the drug payload. No significant fraction of intact 3 was observed after ≥15 min of irradiation. UV-vis spectral traces (top, inset) acquired over the irradiation time course showed a notable change in the absorbance at 280 nm which reflects photocleavage of the ONB linker (quantum efficiency $\Phi = 0.29$ ³² as observed in other drug release systems.³²⁻³⁴ These analyses demonstrate the effectiveness of UV in the active control of ciprofloxacin release from its ONB photocaged form on LPS-targeted dendrimers 3 and 4.

We then investigated the light-controlled bactericidal activity of conjugates **3** and **4** using a turbidity assay.¹⁶ The optical density at 650 nm (OD₆₅₀) of E. coli cultures treated with the conjugates was measured over time. A drop in OD reflects a decrease in bacterial viability. Fig. 5A shows control experiments involving free ciprofloxacin, photocaged ciprofloxacin (2) and a control dendrimer. Free ciprofloxacin displayed potent antibacterial activity with an MIC₅₀ value of 80 nM (lit. $MIC_{50} = 94 \text{ nM}^{39}$). In contrast, a glutarateterminated control dendrimer lacking the conjugated drug G5(GA) showed no significant effect on the cell viability at concentrations of up to 2.5 μ M. UVA exposure did not impact the activity of free ciprofloxacin or the dendrimer control. However 2 ONB-Cipro showed bactericidal activity as potent as free Cipro after UVA exposure, demonstrating the efficient release of drug in a functional form by long wavelength UV (365 nm). Fig. 5B summarizes the viability of E. coli treated with conjugates **3** or **4**, each carrying photocaged ciprofloxacin. Unlike bactericidal UVC (200-280 nm), exposure to longer wavelength UVA (315-400 nm) alone had no effect on the viability of untreated bacterial cells (Fig. 5B).³⁰ Likewise treatment of bacterial cells with each conjugate without UV exposure (-UV) led to minimal changes in viability. These results suggest that tight LPS binding by each conjugate is insufficient for cytotoxicity, likely due to poor penetration of the conjugate into the inner cell wall structure and/or to the lack of intracellular ciprofloxacin release if uptake occurs (Fig. 1). In contrast, treatment of bacteria with 3 and 4 with concomitant UVA irradiation for 30 min dramatically increased the antibacterial efficacy of the conjugates. This decrease occurred as a function of dose with an MIC₅₀ value of ≈ 230 nM (2.0 µM) on a dendrimer (or Cipro) basis. Although this antibacterial activity is lower than that of free ciprofloxacin, perhaps in part due to incomplete drug release, these results

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clearly demonstrate the effectiveness of using a photocage and light as a means to temporally modulate the activity of ciprofloxacin in bacteria-targeted delivery. Finally, **3** and **4** showed a lack of phototoxicity in human KB cells, and caused no hemolysis of red blood cells, supportive of their selectivity and potential biocompatibility (Figure S7, S8).

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Fig. 5 Light control of antibacterial activity against *E. coli* (XL-1) as determined by a turbidity assay. (A) Effect of UVA (365 nm) exposure on the cells treated with ciprofloxacin, **2** or control dendrimer G5(GA). (B) UVA-triggered enhancement in antibacterial activity of **3** and **4**. Bacterial cells (1×10^6 CFU) were treated with each, exposed to UVA for 30 min and then incubated at 37° C for 24 h. Data are the average of replicate experiments (N = 2) with error bars representing SD.

In conclusion, the present study validated, for the first time, an actively controlled, release mechanism in bacteria for the effective delivery of ciprofloxacin using an LPS-targeted dendrimer nanoconjugate. Use of this novel approach for bacteria-targeted drug delivery provides potential benefits in enhancing the selectivity, and thus the therapeutic index of the payload drug molecule. As potent antibiotics such as Ciprofloxacin tend to exhibit unwanted side effects, greater selective targeting and control of delivery is highly desirable. We believe this light-based release mechanism has the potential to improve targeted NP delivery of antimicrobial compounds to bacterial and fungal pathogens, which unlike cancer cells resist NP penetration. Future efforts will be made to validate the applications of this temporally-controlled delivery against drug resistant pathogens.

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A Graphical and Textual Abstract



We report a light-controlled release mechanism for photocaged ciprofloxacin carried by a cell wall-targeted dendrimer nanoconjugate. Validation of this bacteria-targeted strategy adds a novel modality to existing light-based therapies for wound treatments.