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Boronic Acid-Functionalized Photosensitizers: a Straightforward Strategy to Target the Sweet Site of Bacteria and Implement Active Agents in Polymer Coating

Anzhela Galstyan, Roswitha Schiller and Ulrich Dobrindt*

Abstract: *Advanced methods for preventing and controlling hospital-acquired infections via eradication of free-floating bacteria and bacterial biofilms are of great interest. In this regard, the attractiveness of unconventional treatment modalities such as antimicrobial photodynamic therapy (aPDT) continues to grow. This study investigated a new and innovative strategy for targeting polysaccharides found on the bacterial cell envelope and the biofilm matrix using the boronic acid functionalized and highly effective photosensitizer (PS) silicon(IV) phthalocyanine. This strategy has been found to be successful in treating planktonic cultures and biofilms of Gram-negative E. coli. An additional advantage of boronic acid functionality is a possibility to anchor the tailor made PS to poly(vinyl alcohol) and to fabricate a self-disinfecting coating.*

Antibiotic resistance has become an urgent demand in the field of health care[1] and current challenges include not only the increasing spread of drug-resistant strains but also the ability of bacteria to form biofilms on a variety of living and non-living surfaces, inducing a new type of resistance.[2] Antibiotics targeting biosynthetic processes in growing cells become useless for the treatment of slow-growing or non-growing bacteria in biofilms. This leads to a search for more effective therapeutic modalities. Antimicrobial photodynamic therapy (aPDT) is an alternative and very effective method for treatment of bacterial infections.[3] It takes advantage of the interaction between light and a photosensitizing agent (PS) to initiate the formation of reactive oxygen species (ROS) responsible for the bacterial inactivation. However, even very effective PSs require high PS concentrations and light doses to treat biofilms.[4] The main reason behind this is the formation of multicellular bacterial communities held together via self-produced extracellular polymeric substances (EPS). They play a protective role and prevent penetration and subsequent action of the drugs. The biofilm matrix is a complex milieu where polysaccharides together with other major classes of macromolecules like proteins, nucleic acids, and lipids constitute the elastic part of the biofilm and provide mechanical stability to it.[5] Enzymes, such as the glycoside hydrolase dispersin B or alginate lyase are known to induce degradation of carbohydrates and are used to treat biofilm-related infections.[6] In this regard, PSs capable of binding to the main components of the biofilm matrix such as polysaccharides can disrupt its architecture upon irradiation and generate access to bacteria, providing an important step forward in photodynamic biofilm inactivation. Once the biofilm is dispersed, the bacterial cell can be killed by antibiotics, bacteriophages, macrophages or by the photodynamic action of the PS itself. Extracellular polysaccharides known as bacterial glycocalyx are also considered as one of the major structural components of the bacterial cell surface (up to 75% of surface) and contribute to the structural integrity of the bacterial cell.[7] This important cell membrane constituent is of crucial importance for the survival of Gram-negative bacteria: mutants unable to synthesize or export such polysaccharides are known to be highly sensitive to the killing by antibiotics and the host immune system.[8] Moreover, high amounts of lipopolysaccharides (LPS) released from bacteria can trigger an immune response, leading to endotoxic shock and in extreme cases to death. Recently, several studies have examined the efficacy of photoactive conjugates targeting LPS components. Liu *et al.* have employed LPS neutralizing peptide–porphyrin conjugates for effective photoinactivation and intracellular imaging of Gram-negative bacterial strains.[9] Wong and coworkers demonstrated that a heteromultivalent dendrimer nanoplatform binding to LPS serves as an effective method for bacterial detection or bacteria-targeted drug delivery.[10] Due to the low affinity to substrates, saccharide recognition is usually very challenging. Yet, this could be effectively achieved using the ability of boronic acids to form cyclic boronate five- or six-membered esters with *cis*-1,2- or 1,3-diols of carbohydrates through the formation of a pair of covalent bonds.[11] Lack of apparent toxicity and *in vivo* stability issues make boronic acid functionalized compounds very attractive for medical applications.[12] Due to their unique properties coupled with their stability and ease of handling boronic acids are also suitable building blocks for construction of advanced functional materials that can be used as coatings for invasive medical devices.[13]

Herein we report an effective and straightforward approach to target planktonic Gram-negative bacteria and the bacterial biofilm matrix using boronic acid functionalized PS. Photo-triggered cytotoxicity of obtained PS could be further extended via incorporation of it into poly(vinyl alcohol) (PVA) coatings to create a material with photo-bactericidal activity (Figure 1).

The use of silicon(IV)phthalocyanine (SiPc) as a photosensitizer is very attractive due to its long-wavelength absorption, high singlet oxygen generation and suitable toxicology and biocompatibility profiles.[14] The diversity of modification sites of SiPcs enables the design of PSs with additional characteristics, such as water solubility, favorable photophysical properties, and target specificity.[15]

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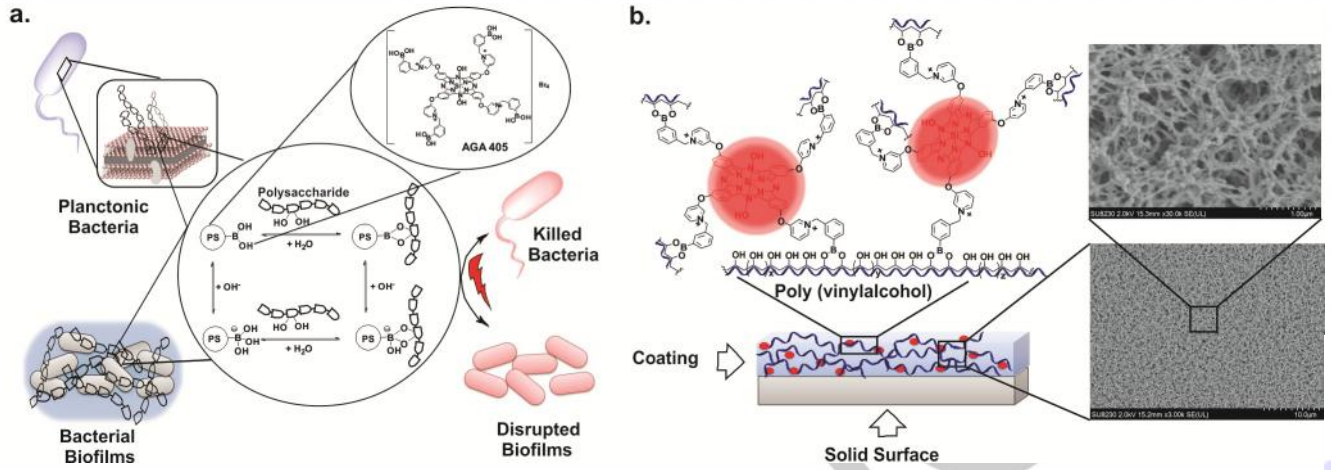

Figure 1. a) Schematic illustration of the interaction between the photosensitizer and polysaccharides of the bacterial cell membrane and the biofilm matrix; b) Schematic illustration of the implementation of **AGA405** into a poly(vinyl alcohol) matrix and SEM images of swollen and freeze-dried hydrogel coating.

The boronic acid functionalized photosensitizer **AGA405** and an appropriate control phthalocyanine lacking the boronic acid substituents **Pc1** were synthesized starting from 4-nitrophthalonitrile and 3-hydroxypyridine.[16] Synthesis of diiminoisoindoline in an intermediate step was conducted to increase the tendency towards cyclization. SiPc was readily formed in the presence of $SiCl_4$. Exchange of chlorine atoms was achieved via hydrolysis with ammonium hydroxide solution. To this end, boronic acid functionality was introduced via quaternization of the pyridine units on the peripheral positions of the macrocycle yielding **AGA405**. Methylation of pyridine units using dimethylsulfate yielded **Pc1** (for details see section 1.2 in the Supporting Information). For both PSs, the partition coefficients obtained were similar ($Log P_{AGA405}$= -1.07, $Log P_{Pc1}$ = -0.98).

The electronic absorption and basic photophysical data of **AGA405** and **Pc1** were measured in *N,N*-dimethylformamide (DMF), water and phosphate buffered saline (PBS) and the data are summarized in Table 1 and section 2 of the Supporting Information. **AGA405** displays typical absorption spectra of non-aggregated phthalocyanines, with a B-band around 355 nm, and an intense and sharp Q-band at 674 nm in DMF and 678 nm in water, which strictly followed the Beer-Lambert law (Figure S1, Supporting Information). Upon excitation at 610 nm in DMF solution **AGA405** showed a strong fluorescence emission at 686 nm with a fluorescence quantum yield Φ_F = 0.33. The behavior of **AGA405** in water (λ_{max} = 692, Φ_F = 0.29) is almost similar to that of measured in DMF. The fluorescence lifetimes were also fully comparable in both solvents. Lowered molar absorption coefficients of **AGA405** in PBS point towards the formation of aggregates, most likely due to the self-condensation of boronic acid groups. The aggregation-disaggregation equilibrium was found to be temperature and pH dependent (Supporting Information, section 2.9) Upon excitation at 610 nm, **AGA405** generates singlet oxygen $O_2(^1\Delta_g)$, evidenced by its near-infrared photoluminescence at 1270 nm. In DMF the singlet oxygen quantum yield (Φ_Δ) was determined relative to the *tetra*-t-butylphthalocyaninato zinc(II) using the direct method. The rate of 9,10-anthracenediyl-*bis*(methylene)dimalonic acid (ABMDMA) photobleaching was used to obtain Φ_Δ in aqueous media.(Figure 2 and Table 1). Relevant photophysical data for the **Pc1** are summarized in the Supporting Information.

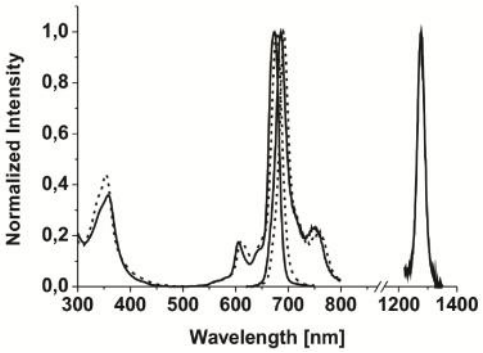

Figure 2. Absorption, fluorescence and $^1O_2$ emission spectra (λ_{exc} = 610 nm) of **AGA405** in *N,N*-dimethylformamide (solid line) and water (dashed line).

Table 1. Electronic absorption and photophysical data for **AGA405**.

AGA 405	λ^{abs}/nm (log ε)	λ_{em} /nm[a]	τ / ns[b]	Φ_F[c]	Φ_Δ[d,e]
in DMF	356 (4.64) 604 (4.36) 674 (5.08)	686 750	4.57	0.33	0.51[d]
in H_2O	353 (4.45) 611 (4.12) 678 (4.92)	692 760	4.55	0.29	0.18[e]

[a] Excited at 610 nm. [b] Excited at 635 nm. [c] Quantum yields were measured in an integrating sphere system. [d] Quantum yield was measured using the relative method and ZnPc as the reference. [e] Quantum yield was measured using photochemical monitor bleaching rates and methylene blue as the reference.

The chemical composition of the carbohydrates in biofilms and outer membrane-associated lipopolysaccharides is often unique to a specific bacterial strain.[17] To investigate the feasibility of our hypothesis, the binding affinity of **AGA405** to different carbohydrates were examined. Five representative carbohydrates D-glucose, D-fructose, D-mannose, D-galactose

and 3-deoxy-D-manno-2-octulopyranosonic acid (KDO) were used as a substrate model for the compounds of biological interest that would represent potential targets of PS binding. Intrinsic fluorescence of **AGA405** in PBS buffer was changed to a different extent depending on the added saccharides, indicating the proposed boronic acid-diol binding interaction (Figure S8, Supporting Information).

As a consequence of the different membrane composition the light activated mode of microbial killing is significantly higher for Gram-positive rather than Gram-negative organisms.[18] In addition, the increasing incidence of antibiotic-resistant infections by Gram-negative bacteria [19] calls for renewed efforts to develop more effective PSs for combating Gram-negative pathogens. Although the bacterial membrane is likely to be the main target of PS, studies regarding the dependency of PS phototoxicity on the outer membrane composition of closely related bacteria are scarce. To address this issue, four extraintestinal pathogenic *E. coli* strains with distinct surface polysaccharide structures 536, 04441/201/06, 3025/11 and 3588/11 were used to assess the photoinactivation efficiency of **AGA405** and **Pc1**. The introduction of positive charges not only provides solubility to the otherwise highly insoluble phthalocyanine macrocycle, but also provokes electrostatic interaction with the negatively charged outer membrane of *E. coli.* Together with the multipoint binding of **AGA405** to LPS-constituents through boronic acid-diol interactions, an incubation time of less than 15 min is sufficient in order to achieve significant binding of PS to microbial cells, even after three washing steps. In contrast, binding of **Pc1** under these conditions was substantially low, emphasizing the importance of the PS-membrane interaction.[20]

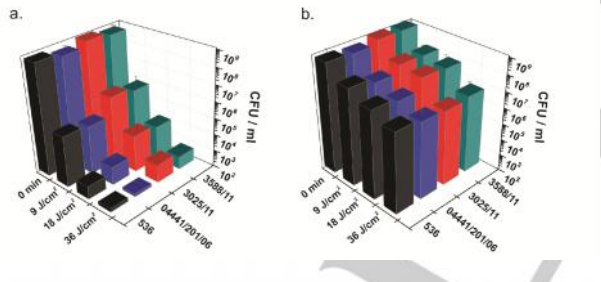

Figure 3. Histograms showing the photodynamic inactivation of *E. coli* in planktonic cultures treated with a) **AGA405** and b) **Pc1** ([PS]=10 µM). The number of colony forming units (CFU) indicates the presence of live bacteria in the aliquots that were plated. Results are presented as mean ± SD.

The bacterial cellular uptake efficiency was cell-line dependent and uptake levels showed to be influenced by the composition of the bacterial glycan coat (Figure S11, Supporting Information). Nevertheless, **AGA405** can efficiently label all *E. coli* strains tested, as seen in the fluorescence microscopy images (Figure S12, Supporting Information).

Illumination of *E. coli* cells which had been exposed to 10 µM **AGA405** caused a considerable decrease in cell survival exhibiting strain-dependent photocytotoxicity (Figure 3a). *E. coli* strains 536 and 04441/201/06 photosensitized under identical conditions showed similar decreases in CFU/ml. For *E. coli* strains 3025/11 and 3588/11 the photo bactericidal effect was lower. This could be explained by the presence of thick polysaccharide layers on the outer membrane of these strains, which increases the cell surface's impassibility. All *E. coli* strains exhibit low sensitivity to photosensitization by **Pc1** due to the weak binding of the PS to bacterial outer membrane. Analog of **Pc1** differing only in the nature of the counter ions was previously reported by Mantareva *et al.* also found to exhibit reduced binding to bacterial cells.[21] Their studies on Gram-positive (*S. mutants, E. faecalis*) and Gram-negative (*A. actinomycetemcomitans, P. intermedia*) bacteria showed a very low photodynamic response.[21]

The *E. coli* biofilms used in this study were developed during 48 h and treated with a 10°µM solution of **AGA405** for an incubation period of 30 min. In combination with the light fluency of 18 J/cm^2, **AGA405** significantly decreased biofilm metabolism (measured by the application of the XTT reduction assay, Figure 4a) as well as biofilm biomass (measured by crystal violet staining, Figure 4b). The observed biofilm mass of the *E. coli* strains 536, 3025/11 and 3588/11 was reduced by approx. 50% in comparison to the untreated control. The reduction of biofilm mass was accompanied by an almost complete loss of metabolic activity of the bacteria**.** Although a PDT-induced reduction of the cellular metabolism occurred for *E. coli* strain 04441/201/06 as well, the reduction of the biomass was less profound in this case. This could be attributed to the tendency of this strain to form more robust biofilm.

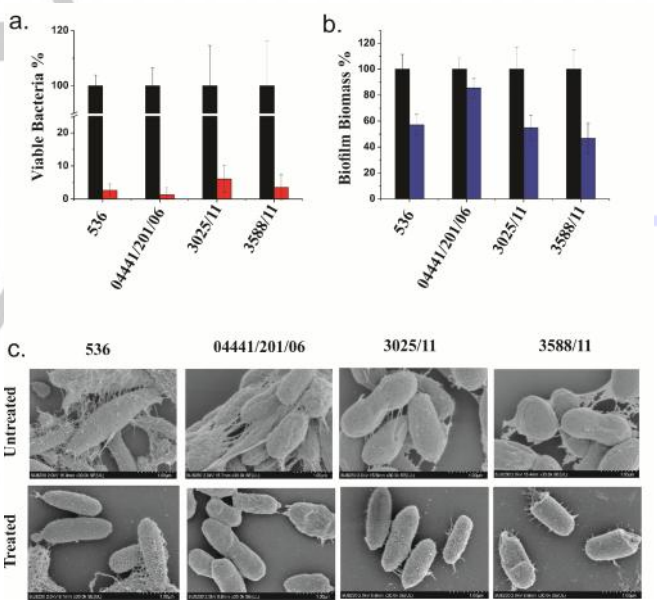

Figure 4. Histograms showing the a) viability and b) biomass reduction of 48 h biofilm of *E. coli* cells upon photodynamic treatment ([PS] = 10 µM, control-black, light dose = 18 J/cm^2). Results are presented as mean ± SD. c) Representative scanning electron microscopy (SEM) images of treated and untreated biofilm samples.

The morphology of bacterial cells and extracellular surfaces of biofilms were visualized by scanning electron microscopy. Upon irradiation in the presence of 10°µM **AGA405** marked changes in the EPS architecture and the bacterial cell membrane was observed (Figure 4c). Biofilms were mostly disrupted and non-aggregated single bacterial cells were detected. The surface structures of bacterial cells also showed obvious changes upon

irradiation: they became wrinkled and some cells lost their cellular integrity. The photodynamic action of **Pc1** on biofilms was significantly lower as compared with **AGA405** (Figure S15 and Figure S16, Supporting Information). Even though further detailed studies are required to determine the target specificity, the dependence of the uptake of PS, and the photo bactericidal activity in planktonic cultures and biofilms from bacterial glycan coat suggests an important role of the nature of polysaccharides in aPDT.

One of the favorable attributes for a PS to be used in aPDT is the possibility to implement it in formulations for delivery or for antibacterial coatings.[22] So far two main strategies were used for immobilization of PSs to a substrate: covalent coupling[23] and physical adsorption.[24] The use of reversible bonds such as boronate esters can enable the design of new systems with favorable characteristics.[13, 25] Boronic acids are known to be very efficient cross-linkers of poly(vinyl alcohol)(PVA),[26] which is a water soluble polymer with excellent film-forming and adhesive properties. The use of PVA-based materials in the biomedical field is steadily increasing, also due to the wide availability and low cost of this polymer. We used **AGA405** to promote the cross-linking of PVA via formation of reversible covalent bonds with the hydroxyl groups present in PVA repeating units. Indeed, SEM images of obtained the PVA-**AGA405** composite produced by the drop-casting method showed the formation of a uniform network pattern (Figure 1b). Light-activated antimicrobial properties of the coverslips coated with the optimized formulation of PVA-**AGA405** were explored using *E. coli* strain 536. The extent of the cell inactivation correlated well with the concentration of the released PS (Figure S18, Supporting Information). This is consistent with the reports suggesting that the short life and minimal diffusion of the generated ROS restrict the oxidative damage to the PS in close proximity to bacteria. Most likely the highly hydrophilic surface of the PVA-**AGA405** coating resulting from the uptake of water into the polymeric backbone prevents bacterial adhesion to the surface.[27] This is a very important and desirable feature of antibacterial coatings that prevents biofilm formation.[28]

In conclusion, we suggest an effective strategy to modify PSs in a way that they are able to bind to polysaccharides of the bacterial cell membrane and biofilm matrix via boronic acid-diol interaction and destroy it using near-infrared light-mediated PDT. Moreover the same functionality could be used to implement PS into PVA based coating. The current results provide new insights into the formation of dynamic coatings that may have a big impact in reducing the risk of device-associated infections or can be used to seal surgical wounds and simultaneously prevent wound infection. The PVA-**AGA405** composite represents a versatile platform for the development of new materials with a wide range of application in modern medicine.

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Conflict of interest

AG has received travelling grant from GlaxoSmithKline.

Keywords: antibiotic resistance • *E. coli* • bacterial biofilm • silicon(IV)phthalocyanine • antibacterial coating

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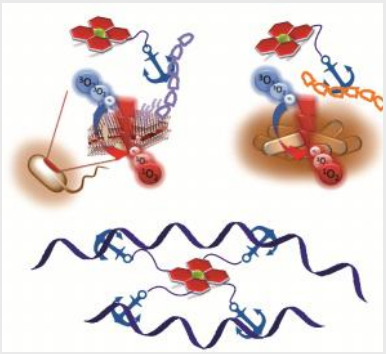
Entry for the Table of Contents

COMMUNICATION

Making and Breaking Barriers:

Boronic acid-diol interaction was used to anchor a photosensitizer into the bacterial cell surface and biofilm matrix and break the barrier via photodynamic action. Moreover, the same functional group enables implementation of the active agent in a poly(vinylalkohol) coating providing a photo-bactericidal barrier against microbial adhesion.



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