A Dynamically Degradable Surface: Can We '*Fool*' Bacteria to Delay Biofouling in Urinary Stents?

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1 Introduction

Human body has evolved multiple strategies such as the development of a complex immune system and procurement of commensal microorganisms to deal with detrimental invasion by microbes. Despite this, biofilms pose an extremely difficult mechanism for humans to cope with infections caused by both pathogenic and opportunistically pathogenic microorganisms.

Ureteral stents are deployed using minimally invasive procedures in patients to prevent or treat the blockage of the flow of urine during or after treating kidney stones, tumours or other urinary incontinence. Paradoxically, the surface of a stent also offers a breeding ground for the adhesion and colonisation by uropathogens that create biofilms.

Biofilms on these stents can lead to patient-discomfort, urinary tract infection and bacteriuria, antimicrobial resistance, stent fouling (encrustation) and obstruction. Ultimately, these stents may require extracorporeal shock wave lithotripsy, ureteroscopy or even more invasive techniques for removal. While an 'ideal' ureteral stent should be free from any such complications. There is no 'ideal' ureteral stents, however.

A 'perfect' ureteral stent should be well tolerated by the patient while ensuring optimal urine flow, resistance to infection, corrosion and encrustation. Prevention and treatment of biofilms are thus crucial for long-term patency of ureteral stents and similar indwelling devices. 'Real stents' seldom have these and may need extracorporeal shock wave lithotripsy, ureteroscopy or even more invasive techniques for removal. These post-stenting procedures cause patient trauma and add to the cost of healthcare.

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One of the major problems associated with indwelling devices is that they present novel, non-host surfaces on which microbes can colonise and form biofilms. Biofilms, especially those formed in a nutrient-limiting environments, are complex, highly structured communities designed to maximise survival, reproduction and spread of the microorganism/s. The type of biofilm that will form largely depends on the properties of surface and the microorganism/s present, the ability of the surrounding milieu to support and inhibit the growth of microorganisms and the relationship the microorganisms have with each other. It is being now recognised that biofilm formation constitutes an 'intelligent' behaviour that involves cell-cell communication such as quorum sensing rather than a matter of a complex architecture. However, the complex three-dimensional architecture that biofilms often protects microorganisms from curative treatments e.g. through antimicrobial drugs.

Currently, biofilm prevention and treatment in ureteral stents are carried out using a 'static' coating of the stent with heparin or a pH control-buffer. They increase patency but still becomes colonised by bacteria leading to biofilms. In this chapter we outline a patent-pending first-principle design strategy for a stent-coating stents that has the potential of increasing the patency by manifold and, at will. This strategy involves delaying biofouling with a 'dynamically degradable surface' and will be described in this chapter.

2 The Surface, Biofilms and Response to Antibiotics

Microorganisms are long known as capable of attaching to and grow on surfaces exposed to them [1, 2]. Surface-associated microorganisms have exhibited a distinct phenotype with respect to gene transcription and growth rate when compared to their free-floating planktonic counterpart [3]. These adherent-microorganisms can elicit specific mechanisms for initial attachment to a surface, development of a community structure and ecosystem, and detachment [4].

A microbial biofilm can be broadly defined as microorganisms adherent to a surface and enveloped within a polymeric matrix, typically comprising exopolysaccharide and proteins that develops into a complex community. The composition is often heterogeneous with water channels occurring between matrix-enclosed microorganisms in stalk- or mushroom-like structures. The structure is also a dynamic one and may include single or multiple microbial species.

Biofilms have been identified in virtually every system in the human body especially involving mucosal surface. Indwelling devices for example artificial joints, urinary catheters and stents, heart valves, biliary stents are also highly susceptible to biofilm formation. In 2004, the Centres for Disease Control and Prevention (CDC) reported that approximately 65% of all infections in developed countries are caused by biofilms [5].

The growth of a biofilm almost always leads to a large increase in resistance to antimicrobial agents compared with cultures grown in suspension (planktonic) in

conventional liquid media, with up to 1000-fold decreases in susceptibility. This poses a huge clinical problem as our current tools for fighting against infections are heavily dependent on the use of antimicrobial agents. The complex three-dimensional architecture of a biofilm, especially an extracellular polymer matrix with occasional biomineralisation makes it difficult to for antimicrobials to access the infection-causing microbes and destroy them.

Biofilms start with a conditioning film that leads to subsequent accumulation of organic and inorganic molecules [6–11]. The conditioning films alter the nature of the device surface and facilitate bacterial adhesion. After adhesion, the biofilm is formed by materials offered by the specific environment as well as extracellular polymeric substances produced by the microorganism. Bacteria can adhere to this initial biofilm and initiate the infection process.

Three mechanisms have been proposed to explain the general resistance of biofilms to antimicrobial agents [12, 13]:

the barrier properties of the slime matrix;

the creation of starved, stationary-phase dormant zones in biofilms; and

the existence of subpopulations of resistant phenotypes, which have been referred to as 'persisters'.

It is important to note that the eradication of infection by antibiotic treatment requires elimination of all the bacteria, typically assisted by the host defences. Specifically, biofilm-resistance can be determined by the susceptibility of the most resistant cells. The inhabitants of biofilms may be up to a thousand times more resistant to antimicrobial therapy than free-floating bacteria of the same species [14]. There is significant heterogeneity within biofilms, however, and it is not the case that all cells within a biofilm are always highly resistant to antimicrobial drugs. For example, planktonic cells that are derived from these biofilms are, in most cases, fully susceptible to antibiotics. Also, biofilms do not actually grow in the presence of elevated concentrations of systemically administered antibiotics.

Cells in the biofilm are slow-growing, and many are likely to be in the stationary phase of growth due to a nutrient-starving enveloped ecosystem. A small subpopulation of cells (persisters) remain alive irrespective of the concentration of the antibiotic and the number of these persisters is greater in the non-growing stationary phase [15]. Lewis believes that the problem of antimicrobial resistance of biofilm is related to the presence of persisters [15].

Cells, whether they are rapidly dividing, slow- or non-growing cells in a biofilm, are generally susceptible to bactericidal agents such as fluoroquinolone antibiotics or metal oxyanions [16, 17]. Antibiotic treatment will kill most biofilm and planktonic cells, leaving persisters alive. The immune system can kill remaining planktonic persisters and bacteriostatic antibiotic-treated non-growing cells. Biofilm exopolymer matrix, however, protects persisters and non-growing cells against immune cells against both antibiotic treatment and the immune system [18–20]. Persisters can repopulate the biofilm and shed off new planktonic cells when the concentration of antibiotic drops off. This will cause a relapse of biofilm infection.

3 Biofouling of Ureteral Stents

Microbial ureteral stent colonisation and subsequent development of biofilm is a multistep process starting with the formation of a conditioning film made of host proteins, electrolytes, and other substances [21]. The surface of any foreign material or object introduced to the urinary system can become coated with a biofilm composed of glycoproteins, matrix and exopolymers. This can take place within a few hours [22]. Nearly half to two-thirds of stents removed from patients displayed bacterial colonies [23] with over one-fifth of these patients had required treatment for bacteriuria infection [24, 25]. Most of these stents (75–100%) that were indwelling for a period of longer than 3 months had shown the highest rate of colonization, which could not be treated with systemic administration of oral antibiotics. All 93 stents from patients became colonized with bacteria despite antibiotic prophylaxis. Oral administration of common antibiotics such as fluoroquinolones, ciprofloxacin and ofloxacin, has not been proven to reduce colonization or infection despite being present at the stent surface at a dose level that has been sufficient to inhibit bacterial growth [26, 27]. Encrustation and bacterial colonization of stents and urinary catheters are problematic and may lead to further morbidity such as infection, sepsis or renal failure [28, 29]. Undetected biofilms may serve as a reservoir for microorganisms. During stent manipulation or instrumentation, biofilm pathogens could be shed into the urine and lead to bacteriuria or funguria or even to life-threatening urosepsis [30].

In a recent systematic review, Zumstein et al. thoroughly investigated the incidence, clinical impact and prevention of biofilm formation on ureteral stents [7]. According to the review, the conditioning film may form due to contact of the stent material with body fluids such as urine and blood, and uroepithelial tissue. Glycosylated uroepithelial cell–surface proteins such as cytokeratin, blood proteins such as haemoglobin and fibrinogen, and inflammatory proteins appear to be involved in conditioning film formation in the first 72 h after insertion. The conditioning film proteins are believed to facilitate the adsorption of various molecules such as collagen, fibrinogen and albumin from the surrounding fluids and tissues, which then alter the surface of the ureteral stent and may allow microorganisms attachment for which urinary pH, ionic strength, and electrostatic and hydrophobic interactions play an important role. Other adhesion strategies such as adhesion to secreted bacterial extracellular polymeric substances may also contribute to conditioning-film formation.

Five different proteins, namely, alpha-1 antitrypsin, immunoglobulin kappa (Ig kappa), immunoglobulin heavy chain G1 (IgH G1), histones H2b, and H3a are present in high numbers in encrustations and biofilms. *Pseudomonas aeruginosa* and *Proteus mirabilis* secrete urease, which increases the urine pH resulting in the precipitation of struvite and hydroxyapatite crystals, adhesion factors, transporters, transcription factors and enzymes. Complex biofilm structures are formed in the last stage of stent biofilm development. Colonies of bacteria are dispersed within spaces filled with fluid and open water channels that allow the transport of oxygen and

nutrients to assure further cellular growth. Ureteral stent biofilms comprise of 10–25% cells and 75–90% of exopolysaccharide matrix characterised by a rough, and often mineralised, surface. Calcium oxalate and struvite dominate the mineralised biofilm. *Enterococcus faecalis* and *E. coli* are common pathogens colonising on ureteral stents [31]. Bacteria expressing urease, such as *Proteus* spp., *Providencia* or *Pseudomonas*, are also involved and can induce rapid growth of biofilms. Other bacteria that have been associated with stent biofilm formation are *Staphylococcus* and *Edwardsiella* spp.

As regard to the indwelling timeline, the review found that bacterial colonisation of stent was detectable 2 weeks after implantation, and that stent colonisation precedes urine colonisation. One study described an encrustation rate of 27% in < 6 weeks, 57% between 6 and 12 weeks, and 76% in > 12 weeks [32]. This compares with another study that reported a colonisation rate of 24% in < 4 weeks, 33% between 4 and 6 weeks, and 71% in over 6 weeks of indwelling time [33]. As it has been previously discussed, Riedl et al. reported 100% ureteral stent colonisation in permanently stented patients (mean stent indwelling time 39.5 days or 5–6 weeks) and 69% in the temporarily stented (mean 11 days or less than 1.5 weeks). The above also compare with a retrospective study of severely impacted ureteral stents requiring advanced removal procedures that found 43% and 76% of the stents had become encrusted within 4 months and 6 months respectively [34]. Patient risk factors such as diabetes mellitus, chronic renal failure and diabetic nephropathy can lead to a shorter stent indwelling times due to a significantly higher risk of colonisation and bacteriuria [35].

4 Resisting Biofouling of Ureteral Stents: Current and Emerging Approaches

New biomaterials, coatings and drug-eluting stents have been designed to reduce biofilm formation and subsequent infection and encrustation. Chew et al. have elaborated these approaches in terms of stent design, materials and coatings. The general strategy of protecting such stents from biofouling involved electronegative coating using heparin or a pH-buffer coating. Adhesion and colonisation by a multiplex of uropathogens (*P. mirabilis*, *E. coli*, *S. Aureus* among others) hosted within an extracellular polymeric matrix nourish and protect the pathogens at the later stages of biofilm formation.

Zumstein et al. summarises current state of the coating approaches. Heparin, hydrogel-based and diamond like coatings are commercially available as Radiance™, Hydroplus™, and VisioSafe DIAMOND™ coatings [7]. Oxalate degrading enzyme coatings and nanoscale body coatings are yet to be commercialised. So far, preventing and treating biofilms on ureteral stents have been challenging due to the conditioning film compromising the effectiveness of passive coatings (heparin, pH buffer-coat) and the involvement of multiple bacterial

species. Although heparin-coated stents significantly reduced ureteral stent encrustation and offered a 12 months indwelling, no positive effect against bacterial adhesion was seen [36, 37]. In the past, hydrogel-based coatings raised expectations that they would effectively inhibit hydroxyapatite encrustation and bacterial biofilm colonisation, and reduce general stent-related morbidity [38]. However, bacterial adhesions were found to be similar in stents with and without hydrogel-based coatings [39].

A multi-stage approach of sterilisation following Bigger was proposed by Lewis to eradicate persisters in biofilms [40]. It was proposed to kill bacterial cells with a high initial dose of an antibiotic. The concentration of the antibiotic would then decrease to enable persisters to resuscitate and start to grow. If a second dose of antibiotic was then administered shortly after persisters had started to grow, a complete sterilization might have been achieved. While it was suggested for systemic pharmaceutical/biopharma treatment of biofilms, a similar approach can be adopted in coating designs using antiseptics/antimicrobials [41, 42]. Once attached to the surface, an antimicrobial molecule is immobilized and is unable to reach and kill the pathogen. Long, flexible polymeric chain linkers are needed to covalently anchor these antimicrobials to the surface of a material.

5 A Dynamically Degradable Surface

The coatings mentioned in the previous section are essentially ‘static’ means they degrade at a very slow rate. This allows sufficient time for the formation of the conditioning film and microbial attachment. In fact, micro-organisms are ‘intelligent’ to find mechanisms to colonise any abiotic surface that allows sufficient time to do so. This is because a ‘static’ surface offers to incoming molecules and microbes a relatively low-entropy boundary that eventually leads to a lowering of free energy for molecules and microbes to attach. If this ‘static’ condition of the coating surface could be replaced with a coating that is degrading at a constant or a variable speed, a relatively higher entropy condition can be created that would ‘delay’ the attachment of molecules and cells to the surface. This is analogous to a ‘pulling the rug from under somebody’s feet’. It would delay the formation of the conditioning films, and in turn delay the bacterial adhesion by constantly ‘fooling’ away bacteria from landing on a ‘low-entropy’ surface.

Biodegradation means that coatings do not have a static surface on which microbes can colonise to lead towards biofilm formation. The coating can be designed to suit the specific ecosystem in which it would have to prevent biofouling and its degradation rate tuned to suit the time it takes to form the conditioning film or the first few layers of microorganism colonisation.

Obviously, such a coating has to be degradable i.e. it would decay, corrode, erode or peel in response to its environment. The coating can also be multilayers or functionally graded to tune the degradation. Furthermore, the coating can itself be antimicrobial or can be loaded with antimicrobial, antiadhesive or cell-polarising agents.

A simple coating of electrically polar fluoropolymer (pyro and piezoelectric) can reduce encrustation significantly through mediating electrostatic interactions [7–9]. Biodegradable molecular crystals show very strong antimicrobial effects which can be engineered for sterilisation for clinical applications [43]. Polycationic or polyanionic surface offered by such polar molecular crystals can either cause cellular lysis or repulsion, respectively. Electrically polar biomolecules such as amino acids (e.g. glycine, cysteine), their derivatives (e.g. triglycine sulfate TGS), metabolites (e.g. peptide nanotubes) or enzymes (e.g. lysozyme) have also demonstrated very high electrically polar properties [10–14] which makes them responsive to changes in local environment such as pressure and temperature. Electrically polarised fluoropolymer, polyvinylidene difluoride (PVDF) stent has demonstrated 40% increase inhibition of calcification (oxalate and hydroxyapatite) after 30 days patency in ASME standard artificial urine in comparison to commercial polyurethane, unpoled PVDF, heparin coated polyurethane and hydrogel coated polyurethane. The use of an electrically polar, molecular crystals in the coating can produce a 'dynamic' surface that can combine biocompatibility with electro negativity and functional grading to reduce biofouling of ureteral stents. Biodegradable and functionally gradable polymers can also be used to create the 'dynamic' surface. Metallic materials such as magnesium and zinc-based coatings are also possible.

6 Conclusions

Biofouling complicates and compromises indwelling of ureteral stents. It causes patient discomfort, infection and trauma and its removal is expensive. Commercially available stents uses anti-fouling coatings with variable successes. These coatings are static and inadequate in resisting bacterial colonization that eventually leads to encrustation. In this chapter we introduced the concept of a dynamic surface which may be successful in 'fooling' bacteria due to constant degradation of the surface during indwelling. The concept is new and currently being experimented at the authors' group. It offers to use biodegradable, electrically polar molecular crystals as the anti-fouling coating, which can be functionally graded to tune the biodegradation and anti-encrustation effect.

References

1. Heukelekian H, Heller A. Relation between food concentration and surface for bacterial growth. J Bacteriol. 1940;40:547–58.
2. Zobell CE. The effect of solid surfaces on bacterial activity. J Bacteriol. 1943;46:39–56.
3. Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis. 2002;8(9):881–90.
4. Robin S, et al. Interactions of biofilm-forming bacteria with abiotic surfaces. In: Tofail SAM, editor. Biological interactions with surface charge in biomaterials. London: RSC Publishing; 2011.

5. Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. Nat Rev Microbiol. 2004;2:95–108.
6. Zelichenko G, Steinberg D, Lorber G, Friedman M, Zaks B, Lavy E, Hidas G, Landau EH, Gofrit ON, Pode D, Duvdevani M. Prevention of initial biofilm formation on ureteral stents using a sustained releasing varnish containing chlorhexidine: in vitro study. J Endourol. 2013;27:333–7.
7. Zumstein V, Betschart P, Albrich WC, Buhmann MT, Ren Q, Schmid HP, Abt D. Biofilm formation on ureteral stents—incidence, clinical impact, and prevention. Swiss Med Wkly. 2017;147:w14408.
8. Reid G, Denstedt JD, Kang YS, Lam D, Nause C. Microbial adhesion and biofilm formation on ureteral stents in vitro and in vivo. J Urol. 1992;148(5):1592–4.
9. Buhmann MT, Abt D, Altenried S, Rupper P, Betschart P, Zumstein V, Maniura-Weber K, Ren Q. Extraction of biofilms from ureteral stents for quantification and cultivation-dependent and -independent analyses. Front Microbiol. 2018;9:1470.
10. Zhang JM,·Liu J,·Wang K,·Zhang X, Zhao T,·Luo HMObservations of bacterial biofilm on ureteral stent and studies on the distribution of pathogenic bacteria and drug resistance Urol Int 2018, 101(3): 320-326
11. Gandhi AA, Korostynska O, Robin S, Laffir F, Soulimane T, Lavelle S, Tofail SAM. Contact poling of polyurethane, charge stability and interactions with *P. mirabilis*. In: Tofail SAM, Bauer J, editors. Electrically active materials for medical devices. Singapore: World Scientific; 2016.
12. Spoering AL, Lewis K. Biofilms and planktonic cells of *Pseudomonas aeruginosa* have similar resistance to killing by antimicrobials. J Bacteriol. 2001;183(23):6746–51.
13. Suci PA, Tyler BJ. A method for discrimination of subpopulations of *Candida albicans* biofilm cells that exhibit relative levels of phenotypic resistance to chlorhexidine. J Microbiol Methods. 2003;53(3):313–25.
14. Parsek MR, Singh PK. Bacterial biofilms: an emerging link to disease pathogenesis. Annu Rev Microbiol. 2003;57:677–701.
15. Lewis K. Persister cells, dormancy and infectious disease. Nat Rev Microbiol. 2007;5:48–56.
16. Harrison JJ, et al. Persister cells mediate tolerance to metal oxyanions in *Escherichia coli*. Microbiology. 2005;151:3181–95.
17. Harrison JJ, Turner RJ, Ceri H. Persister cells, the biofilm matrix and tolerance to metal cations in biofilm and planktonic *Pseudomonas aeruginosa*. Environ Microbiol. 2005;7:981–94.
18. Leid JG, Shirtliff ME, Costerton JW, Stoodley AP. Human leukocytes adhere to, penetrate, and respond to *Staphylococcus aureus* biofilms. Infect Immun. 2002;70:6339–45.
19. Jesaitis AJ, et al. Compromised host defense on *Pseudomonas aeruginosa* biofilms: characterization of neutrophil and biofilm interactions. J Immunol. 2003;171:4329–39.
20. Vuong C, et al. Polysaccharide intercellular adhesin (PIA) protects *Staphylococcus epidermidis* against major components of the human innate immune system. Cell Microbiol. 2004;6:269–75.
21. Bonkat G, Rieken M, Siegel FP, Frei R, Steiger J, Groschl I, Gasser TC, Dell-Kuster S, Rosenthal R, Gurke L, Wyler S, Bachmann A, Widmer AF. Microbial ureteral stent colonization in renal transplant recipients: frequency and influence on the short time functional outcome. Transpl Infect Dis. 2012;14:57–63.
22. Tieszer C, Reid G, Denstedt J. Conditioning film deposition on ureteral stents after implantation. J Urol. 1998;160:876–81.
23. Chew BH, Duvdevani M, Denstedt J. New developments in ureteral stent design, materials and coatings. Expert Rev Med Devices. 2006;3(3):395–403.
24. Riedl CR, Plas E, Hubner WA, Zimmerl H, Ulrich W, Pfluger H. Bacterial colonization of ureteral stents. Eur Urol. 1999;36(1):53–9.
25. Paick SH, Park HK, Oh SJ, Kim HH. Characteristics of bacterial colonization and urinary tract infection after indwelling of double-J ureteral stent. Urology. 2003;62(2):214–7.
26. Reid G, Habash M, Vachon D, Denstedt J, Riddell J, Beheshti M. Oral, fluoroquinolone therapy results in drug adsorption on ureteral stents and prevention of biofilm formation. Int J Antimicrob Agents. 2001;17(4):317–9.

27. Wollin TA, Tieszer C, Riddell JV, Denstedt JD, Reid G. Bacterial biofilm formation, encrustation, and antibiotic adsorption to ureteral stents indwelling in humans. J Endourol. 1998;12(2):101–11.
28. Damiano R, Oliva A, Esposito C, De Sio M, Autorino R, D'Armiento M. Early and late complications of double pigtail ureteral stent. Urol Int. 2002;69(2):136–40.
29. Singh I, Gupta NP, Hemal AK, Aron M, Seth A, Dogra PN. Severely encrusted polyurethane ureteral stents: management and analysis of potential risk factors. Urology. 2001;58(4):526–31.
30. Gautam G, Singh AK, Kumar R, Hemal AK, Kothari A. Beware! Fungal urosepsis may follow endoscopic intervention for prolonged indwelling ureteral stent. J Endourol. 2006;20(7):522–4.
31. Brotherhood H, Lange D, Chew BH. Advances in ureteral stents. Transl Androl Urol. 2014;3(3):314–9.
32. Kawahara T, Ito H, Terao H, Yoshida M, Matsuzaki J. Ureteral stent encrustation, incrustation, and coloring: morbidity related to indwelling times. J Endourol. 2012;26(2):178–82.
33. Rahman MA, Alam MM, Shamsuzzaman SM, Haque ME. Evaluation of bacterial colonization and bacteriuria secondary to internal ureteral stent. Mymensingh Med J. 2010;19(3):366–71.
34. Bultitude MF, Tiptaft RC, Glass JM, Dasgupta P. Management of encrusted ureteral stents impacted in upper tract. Urology. 2003;62(4):622–6.
35. Kehinde EO, Rotimi VO, Al-Awadi KA, Abdul-Halim H, Boland F, Al-Hunayan A, et al. Factors predisposing to urinary tract infection after J ureteral stent insertion. J Urol. 2002;167(3):1334–7.
36. Lange D, Chew BH. Update on ureteral stent technology. Ther Adv Urol. 2009;1(3):143–8.
37. Cauda F, Cauda V, Fiori C, Onida B, Garrone E. Heparin coating on ureteral double J stents prevents encrustations: an in vivo case study. J Endourol. 2008;22(3):465–72.
38. Lange D, Chew BH. Biomaterials and tissue engineering in urology. Amsterdam: Elsevier; 2009. p. 85–103.
39. John T, Rajpurkar A, Smith G, Fairfax M, Triest J. Antibiotic pretreatment of hydrogel ureteral stent. J Endourol. 2007;21(10):1211–6.
40. Bigger JW. Treatment of staphylococcal infections with penicillin. Lancet. 1944;244:497–500.
41. Tiller JC, Liao CJ, Lewis K, Klibanov AM. Designing surfaces that kill bacteria on contact. Proc Natl Acad Sci USA. 2001;98:5981–5.
42. Lewis K, Klibanov AM. Surpassing nature: rational design of sterile-surface materials. Trends Biotechnol. 2005;23:343–8.
43. McCloskey AP, Gilmore BF, Laverty G. Evolution of antimicrobial peptides to self-assembled peptides for biomaterial applications. Pathogens. 2014;3:791–821.