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Will biofilm disassembly agents make it to market?

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Abstract

Nearly twelve years after promising results suggested that anti-biofilm agents might be developed into novel therapeutics, there are no such products on the market. In our opinion, the reasons for this have been predominantly economic. Recent developments, however, suggest that there may still be emerging opportunities for the developments of such products.

When presented with a surface or an interface and conditions propitious for growth, bacteria almost invariably will assemble as groups of cells held together by a self-produced polymeric matrix. Such groups of cells, referred to as biofilms, are ubiquitous on our planet and represent a common metabolism-altering strategy in the microbial world. Rocks on riverbeds, our bodily skin, and every minute soil particle all teem with microbial life [1, 2]. Indeed, the top few dozen microns at the surface of all of the Earth's oceans are colonized by a gargantuan gelatinous biofilm [3]. That biofilms represent the predominant form of bacterial life should come as no surprise because surfaces serve as an organizing principle for bacterial growth, helping to keep cells from being carried away by uncertain currents. In addition, oftentimes surfaces are nutritious and air-liquid interfaces provide optimal access to atmospheric oxygen such that aerobes can prosper [2]. Of course, surfaces have been present since the origin of life and it is clear that as a consequence the play of bacterial evolution has been performed largely on the ecological stage of surfaces; most bacteria have evolved intricate mechanisms which allow them to form biofilms [1].

Like all forms of life, biofilms have characteristic life cycles. While the details of these life cycles exemplify the remarkable diversity of the microbial world, there are some general features characteristics of the life of all biofilms [4, 5]. A few cells, or even a single cell, can arrive at a surface and serve as the early colonizers. These cells not only will multiply but will also produce the matrix that is essential for the integrity of the biofilms [2]. But, biofilms do not last forever and they eventually disassemble. Disassembly does not just mean the demise of the existing biofilm, it also provides the means for surviving cells to leave the sessile life style for a while and achieve the dispersal of at least some members of the population. This ability of biofilms to disassemble has attracted a lot of attention because in

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many cases biofilms form where humans do not want them and we yearn for the ability to eradicate them.

In clinical settings the effects of biofilms can be devastating. If for whatever reason you need to be admitted to a hospital, chances are high that you will be catheterized. If you happen to be in the United States, your catheter would be one of an estimated 300 million that are used annually [6]. While the overwhelming majority of catheters that are used greatly aid in the physician's ability to treat the patient, a small percentage of them lead to nosocomial (hospital acquired) infections. These infections can have high mortality rates due to fact that biofilm- associated bacteria express a still poorly understood phenotypic resistance to many antibiotics [7, 8]. In the case of central venous catheters, which involve more elaborate procedures to be put into place and are therefore more complicated to replace if infected, the infection rate ranges from 1-5 per 1000 catheter days, depending on the setting [9]. Catheter-related infections are thought to result from the fact that the surface of the device is perfectly suited for bacterial and fungal colonization. Interestingly, it has been shown that all catheters, once inserted, become colonized by microbes that are originally present on the patient's skin or on the catheter's hub [7, 10]. Exactly what leads only a small fraction of catheters to cause an infection is not known but the chances of infection do increase as the time the catheter remains in place increases. Catheters are, of course, just one of many devices that routinely cause infections in a small fraction of individuals using them. Heart valves, knee and hip prostheses, surgical pins, etc., all have some probability of becoming the source of an infection [8]. The fact is that as modern medicine has made huge advances in helping patients, the placing of indwelling devices has become routine. And while such indwelling devices prove largely helpful in patients regaining their health, they always provide new surfaces on which microbes can form biofilms. In addition, many chronic infections - which by definition are difficult to eradicate - result from biofilms growing on bodily surfaces [10]. Examples of these are diabetic ulcers and lung infections in the lungs of patients with cystic fibrosis. Biofilm formation can be equally problematic in industrial settings [1]. Virtually every surface that comes in contact with fluids becomes fertile ground for biofilm growth. From water pipes to industrial machinery to air cooling towers, all can be rendered less effective as a consequence of biofilms.

Clearly, there is an unmet need of controlling biofilms in many settings. While this fact was recognized for many years, the application of molecular genetics approaches to the study of biofilms in the late 1990s led to a large increase in the interest among scientists in the development of biofilm control strategies. A key finding at that time was the discovery, in 1998, of the fact *Pseudomonas aeruginosa* biofilm formation required cell-cell signaling [11]. This led to the general feeling among biofilm investigators that small molecules that would interfere with these signaling pathways might prove useful for eradicating undesirable biofilms. In 1999 the mood was upbeat, the path to biofilm control was clear as is made evident in this quote from a review of that year:

> "Our modern view of biofilm infections leads to the realization that their effective control will require a concerted effort to develop therapeutic agents that target the biofilm phenotype and community signaling based agents that prevent the formation, or promote the detachment, of biofilms. The techniques are now available to undertake such efforts." [10]

Here we are, a dozen years later. What have we accomplished? Are there any widely used anti-biofilm products? As far as we know, no. To date there is no great success story in this field. Up to now we have limited ourselves to describing the landscape. Yet this is to be an opinionated essay. We were simply setting the stage. Now reader, read on for our opinion. Of course, throughout your reading be mindful of why we might have been asked to give our opinion. We work in the field and are thus likely to have strong biases. In the spirit of full

disclosure you should know that indeed we are very interested in seeing anti-biofilm agents make it to market (see Disclosure statement).

We feel that research in the area of biofilm disassembly has yielded some very promising results. Aside from the early discovery of cell-cell signaling involvement in biofilm formation, many discoveries have been made on the process of biofilm disassembly itself. We do not intend to describe those here, readers are referred to two excellent recent reviews that cover this matter thoroughly [5, 12]. Suffice it to say that we now know that biofilm disassembly often involves the induction of enzymes that destroy components of the matrix and thus liberate the biofilm-associated cells [12]. A recent study that we were involved in demonstrated that the incorporation of specific D-amino acids into the peptidoglycan led to cells being released from the matrix [13]. In addition, synthetic biology has come into the picture with the development of recombinant phage that both attack biofilm cells and produce matrix-degrading enzymes [14]. Thus, there is now a significant armamentarium aimed at biofilm disassembly.

Despite the early enthusiasm and recent successes, why are there no anti-biofilm products on the market yet? It certainly is not for lack of trying. Early on, many patent applications were filed and many start-up companies got off the ground searching for anti-biofilm agents. Indeed, in academic and industrial laboratories promising agents were discovered. Yet, today, many of those start-up companies have either failed or they have moved on to other pursuits. We do not think that the failure to develop a product has been due to the fact that the anti-biofilm approach is intrinsically flawed. Rather, we feel that the path to product development is long and expensive and the potential market is not as lucrative as corporations would like it to be. Add to that the unfortunate timing of historical events. As companies were tooling up a decade ago, the market downturn of 2001 led to the first flight of interest from potential investors. Then, as interest began to grow again in development of these sorts of therapeutics, the worldwide recession that started in 2008 sent most investors into a deep retreat. In many ways, the development of any specialized anti-biofilm agents has paralleled what has happened to the development of novel antibiotics. And therein lies the very heart of the problem. The development of these novel agents requires an enormous investment up front. Yet, the chances of success are extremely small. Therefore, corporations are only willing to invest in what they believe will be potentially huge money makers.

Is there a potential huge money maker in the anti-biofilm agent arena? We presented the case of catheters above because it helps to illustrate the situation. At first glance, it does seem like a remarkable opportunity - 300 million catheters used annually in the United States. A catheter that would achieve zero infection rates would certainly be welcome. But even if that were possible, perhaps developing a coating that includes an antibiotic and an anti-biofilm agent, how much more would such a catheter cost to be able to recover the costs of its development? And would the healthcare system, in its current tight budget, be willing to pay that premium to reduce a risk that is currently 1-5 infections per 1000 catheter days; especially when most of those infections could be controlled by replacing the catheter and treating with antibiotics? We feel that similar economic arguments are being made by potential investors for almost all anti-biofilm applications. The costs of development in relation to the possible profits are likely sending most potential investors away from this area. Thus, we feel that the major reasons for the fact that we have no anti-biofilm agents in the market today are economic and not necessarily scientific. While such agents may be feasible and perhaps even efficacious, the expected profits are not seen as large enough by investors to justify the required investment. Of course, this is a gross oversimplification of what is without a doubt a very complex issue where many factors come into play. There clearly are many hurdles that involve, among others, technical problems in reducing

laboratory discoveries to practice, clinical practice ‘culture’, and vagueness in the regulatory steps towards approval. Still, when it is all said and done, it is the expected high cost of overcoming these hurdles, packaged above in the term ‘costs of development’, that may be keeping anti-biofilm agents from hitting the market.

Amid the rather grim view expressed above, we do see glimmers of hope. Ongoing research in academic laboratories has indeed provided evidence that biofilm disassembly can be accomplished with enzymes, phage and small molecules [14, 15]. There are signs that some corporate interests are seeing these as potentially profitable areas to invest in. Importantly, there may be an emerging shift away from development of therapeutic applications. We feel it does make sense for the translation of these technologies into products to start in non-medical arenas, were the route to market may be shorter. Whatever is learned from those attempts should prove useful for the eventual development of therapeutic applications. Most important of all, we feel that continued research efforts in academic laboratories will in all likelihood yield additional promising avenues that might some day be translated into products.

References

1. Hall-Stoodley L, et al. Bacterial biofilms: from the natural environment to infectious diseases. Nat Rev Microbiol. 2004; 2:95–108. [PubMed: 15040259]
2. Lopez D, et al. Biofilms. Cold Spring Harb Perspect Biol. 2010; 2:a000398. [PubMed: 20519345]
3. Cunliffe M, Murrell JC. The sea-surface microlayer is a gelatinous biofilm. ISME J. 2009; 3:1001–1003. [PubMed: 19554040]
4. Kolter R, Greenberg EP. Microbial sciences: the superficial life of microbes. Nature. 2006; 441:300–302. [PubMed: 16710410]
5. Karatan E, Watnick P. Signals, regulatory networks, and materials that build and break bacterial biofilms. Microbiol Mol Biol Rev. 2009; 73:310–347. [PubMed: 19487730]
6. Edgeworth J. Intravascular catheter infections. J Hosp Infect. 2009; 73:323–330. [PubMed: 19699555]
7. Raad I. Intravascular-catheter-related infections. Lancet. 1998; 351:893–898. [PubMed: 9525387]
8. Davies D. Understanding biofilm resistance to antibacterial agents. Nat Rev Drug Discov. 2003; 2:114–122. [PubMed: 12563302]
9. Edwards JR, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control. 2009; 37:783–805. [PubMed: 20004811]
10. Costerton JW, et al. Bacterial biofilms: a common cause of persistent infections. Science. 1999; 284:1318–1322. [PubMed: 10334980]
11. Davies DG, et al. The involvement of cell-to-cell signals in the development of a bacterial biofilm. Science. 1998; 280:295–298. [PubMed: 9535661]
12. Kaplan JB. Biofilm dispersal: mechanisms, clinical implications, and potential therapeutic uses. J Dent Res. 2010; 89:205–218. [PubMed: 20139339]
13. Kolodkin-Gal I, et al. D-amino acids trigger biofilm disassembly. Science. 2010; 328:627–629. [PubMed: 20431016]
14. Donlan RM. Preventing biofilms of clinically relevant organisms using bacteriophage. Trends Microbiol. 2009; 17:66–72. [PubMed: 19162482]
15. Richards JJ, Melander C. Controlling bacterial biofilms. Chembiochem. 2009; 10:2287–2294. [PubMed: 19681090]