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Biodegradable Polymer-Based Nanoparticles as Antimicrobial Drugs

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The development of antibiotic-resistant organisms has prompted substantial interest in finding new ways to target and eliminate harmful bacteria. The high global mortality rates associated with many of these pathogens, as well as the side effects of antibiotics when they are used, are two additional concerns behind this effort (Lamprecht, 2009). Antibiotics, a form of antimicrobial drug which act by penetrating the target microbes and disrupting their functionality on a subcellular level, play a prominent role in modern medicine's treatment of bacterial diseases. The process by which these chemical compounds function includes the destruction of DNA, interference in cell division, and initiation of autolysis (Greenemeier, 2011; Nederberg et al., 2011). However, the nature of the interaction between conventional antibiotics and the microorganisms they seek to destroy poses a number of inherent problems in their practical application. Some of the targeted microbes inevitably remain, maintaining bacterial morphology, which results in the evolution of the bacterial colony to develop immunity to the antibiotics used for treatment (Bourzac, 2011; Lamprecht, 2009). For example, the US Centers for Disease Control and Prevention attributed approximately 19,000 American deaths in 2005 to Methicillin-resistant Staphylococcus aureus (MRSA) alone (Klevens et al., 2007). Lack of target specificity commonly results in the devastation of healthy cells, and the absence of degradability leads to antimicrobial buildup in the body's organs (Lamprecht, 2009).

The shortcomings of present-day antibiotics may be offset by new forms of synthetic, polymer-based nanostructures that have been identified by preliminary in vitro and in vivo testing as promising. The advantage of using nanostructures is that they are capable of seeking out and destroying gram-positive bacteria, including those which have developed antibiotic resistance (such as MRSA). They are highly selective in their targeting of cells, nontoxic and completely biodegradable. In addition, nanoparticles can be synthesized on a large scale at a relatively low cost, suggesting a potential positive global impact on bacterial disease-related mortality (Nederberg et al., 2011).

Composition and function of the nanostructures

The polymer-based nanostructures used for drug applications are composed of amphiphilic polycarbonates which, when submerged in a fluid such as water or blood, autonomously reassemble into new polymer structures approximately 200 nanometers in length (Boyle, 2011). In order to eliminate targeted bacteria cells, these self-assembled nanoparticles employ a strategy which is of an intrinsically different nature than that of antibiotics (Bourzac, 2011). Rather than penetrate the cells and attack chemically from within, they operate in an entirely physical manner via electrostatic interaction (Cho et al., 2007; Nederberg et al., 2011). The nanoparticles possess cationic charges, which provides them with the ability to attack a cell's anionic protective membrane by employing a method known as electroporation. As the positively charged nanoparticles align themselves with the cell's negatively charged membrane, strong electric fields randomly stretch the cell's surface in different directions, culminating in the formation of pores in the membrane, as shown in Figure 1.

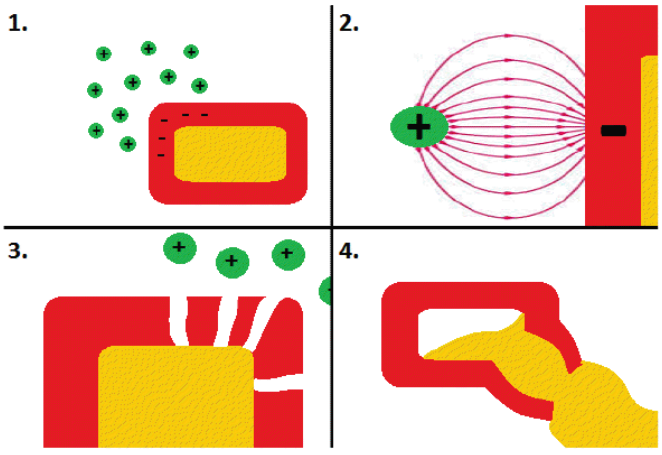

Figure 1. (1) Positively charged nanoparticles (green) surround the cell's negatively-charged outer membrane (red). Electric fields between these opposing charges (2, arrowed lines) pull the phospholipids in different directions, randomly rearranging them to create pores in the surface (3). The cell membrane ruptures and cell lysis is observed (4).

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The cell wall ruptures in the process, resulting in its disintegration and a subsequent cell lysis through the outpouring of its contents (Chan, Prenner, & Vogel, 2006; Nederberg et al., 2011). During in vitro testing, the nanoparticles killed 100% of the gram-positive bacteria they were set out to destroy, including *Bacillus subtilis*, *Enterococcus faecalis*, *Staphylococcus aureus*, MRSA, as well as the *Cryptococcus neoformans* fungus. The methodology deployed by the nanostructures in their destruction of bacteria cells permits them to effectively obliterate antibiotic-resistant species, as well as prevent any species from developing immunity to the treatment (Nederberg et al., 2011).

Evaluation of toxicity resulting from selective targeting

Difference in electric charge is a major distinguishing characteristic between cells that are healthy and those that are bacteria-infected: The charges of bacteria cells are substantially larger in magnitude (Greenemeier, 2011). This contrast in electronegativity results in the cationic nanoparticles maintaining a significantly greater electrostatic interaction with bacteria cells over healthy cells due to the higher level of attractive electric force. This translates directly into an inherent ability in the nanoparticles to target specific cells in the body with near-perfect precision, thus preserving the integrity of those that are healthy (Cho et al., 2007; Nederberg et al., 2011). In practical application, this results in insignificant haemolysis, no acute toxicity damage to organs and maintenance of the blood's electrolyte balance, even when administered at extremely high concentrations (Nederberg et al., 2011). To evaluate these qualities, in vivo testing was carried out by injecting the nanostructures into mice at a concentration ten times that of the established minimum inhibitory concentration. Among those properties analyzed were changes in the levels of alanine transaminase, aspartate transaminase, creatinine, urea nitrogen, and sodium and potassium ions in the blood of the mice. Forty-eight hours following the injection, the functional levels remained unchanged. This was reevaluated 14 days post-injection, only to reveal an identical outcome. No mice involved in the experiment died and no deviations in colour were observed in their urine and serum samples. These results suggest virtually no disintegration of red blood cells, no acute damage to the liver and kidney, and no effect on electrolyte balance, effectively implying an induction of negligible toxicity to the mice (Nederberg et al., 2011).

Biodegradability of the nanostructures

Unlike other polymer-based antimicrobial drugs, which produce harmful by-products that can remain in the body and accumulate in organs, these polymer nanostructures are biodegradable (Nederberg et al., 2011). The nanoparticles are broken down by enzymes into harmless, lightweight carbon dioxide and alcohol molecules and are eliminated from the body in the same manner as any other innocuous by-product (Boyle, 2011; Greenemeier, 2011). Despite this conversion, testing in rats proved that the deterioration of the structures was a slow process, with the nanoparticles shedding a mere 21.1% of their weight over a 24 week period. This result indicates long-acting antimicrobial functionality and high stability (Nederberg et al., 2011). These qualities strengthen any potential application due to the prolonged effectiveness of the nanostructures in vivo combined with the body's natural ability to ultimately remove them in their entirety.

Further research required for human use

Although current research and evidence suggest much promise for future application of these nanoparticles in the treatment of human infections, many hurdles still remain to be cleared in order to achieve that potential reality. Currently, the polymer nanostructures are effectively limited to gram-positive bacteria and certain fungi. They show no efficacy in the treatment of gram-negative bacteria, which possess significantly more complex protective membranes that existing iterations of the nanostructures are unable to penetrate. Scientists would also like to further manipulate and refine the shape of the nanoparticles, predicting that elongation would permit for easier travel through a system (Greenemeier, 2011). It still remains unclear as to how the nanoparticles would be administered to humans (Boyle, 2011). Eventually, the matter of safety for human use will have to be addressed. However, this issue is presently purely speculative: Toxicity over longer-term periods should first be appraised prior to commencing clinical testing (Nederberg et al., 2011).

Conclusion

Despite the present early stage of development and evaluation, promising results for the poly-mer-based nanostructures have resulted from current in vivo testing in mice and rats. Capable of destroying 100% of gram-positive bacteria without susceptibility to the evolution of resistance in the attacked species, they are highly specific in their targeting, induce negligible haemolysis and acute toxicity to major organs, and biodegrade completely upon completion of their task. Furthermore, the projected ability to manufacture the nanoparticles in abundant quantities at affordable prices may very well translate into widespread availability, potentially implicating global accessibility even in impoverished regions. These highly desirable properties provide a prospective solution to the growing concerns which existing antibacterial treatments are unable to address. While clinical administration remains a distant matter, these nanoparticles are a hopeful candidate for future deployment as antimicrobial drugs in the treatment of infectious diseases.

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