Preclinical performance testing of medical devices with antimicrobial effects: shifting the focus from “bench” to “bedside”

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Abstract

- The rate of innovation must be considered throughout the product development pathway, including the design and development of new technologies as well as their incorporation into the clinical environment.
- Microbiological challenges play a key role in the device-associated infections, resulting in strong motivation for development of medical devices with antimicrobial effects.
- In this post, we show how preclinical testing can be improved by shifting the focus of in vitro performance testing from bench to bedside.

Moving from Bench to Bedside

The in vitro testing of many antimicrobial biomaterials often shows high performance in the literature. Large zones of inhibition, reductions in bacterial CFU, strong inhibitory effects result from optical density. Current in vitro methods do not predict clinical outcomes.

Ways to Improve Test Methods

1. Use more realistic endpoints. Antimicrobials can achieve a 3-log reduction in biofilm burden against staph, thick biofilm formed in a flow cell. But testing the same antimicrobial against large staph biofilm—a multi-day biofilm exposed to increasing concentrations of antimicrobials—may yield less realizable. Exfoliants often resemble cells seen in buildup inside, which are more resistant to antimicrobials. The duration of tests is also mismatched with clinical use time.

2. Incorporating the tissue environment into models. Bacteria have adhesions for tissue surfaces. Composite tissue may be a source of biological vectors that stimulate bacterial migration, growth, or virulence factors. Tissue can absorb antimicrobials through direct binding or sequestration, reducing the residual concentrations of the antibiotic while it is in contact with a medical device, it may provide an alternative route for migration or colonization.

3. Implement multiphysical systems (MPSs). These live tissue models that recapitulate some basic aspects of biological systems would provide even more realism.

The Product Development Pathway

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Figure 1. The medical device product development pathway is an iterative process of continual improvement. Preclinical testing is an essential part of a feedback loop that precedes clinical testing and regulatory assessment.

Current Preclinical Test Methods

- In vitro methods should identify potential safety or efficacy issues before more costly in vivo testing. But in vitro success does not always correlate with clinical benefit. Improved preclinical testing methods would lead to reduced costs and more efficient time-to-market for novel medical devices.

Figure 2. Top: surgical incision site; Bottom: biomaterial. Stars: eliciting antimicrobial agent; Pacman: immune cells. Mixed species colonies normally present on the skin surface can invade deeper tissue at the incision site, where they colonize fibrin/tissue and/or the surface of implanted biomaterials, resulting in inflammation and tissue necrosis. The foreign material response and extracellular matrix of biofilm both sequester the compound forming a barrier to cells to clear pathogenic microbes. Biomaterials with antimicrobial surface effects can kill pathogens on contact but are subject to passivation by biofouling or dead cells. Drug eluting materials can kill bacteria and other pathogens, but are limited by elution by diffusion, perfusion and neutralization of the antimicrobial. Some antimicrobials may hinder the immune response or healing process and present toxicity to mammalian cells.

Figure 3. (a,b) Testing of a thick biofilm may overestimate antimicrobial performance by not considering the importance of pericellular infection risk; (c,d) Short term testing may show reductions in biofilm, but a longer-term endpoint can reveal decreasing antimicrobial efficacy and a surface overrun by rapidly multiplying cells.

Figure 4. The combination of computational modeling and in vitro data can be used to generate more realistic starting estimates for the performance of eluting devices. For some antimicrobials, there is a very narrow therapeutic window, or none, where antimicrobial concentrations can be achieved that are sufficiently high to prevent infections, but sufficiently low to avoid toxicity (Figure 3a). This is further exacerbated by the presence of biofilms (Figure 3b). Biofilm can slow diffusion through steric hindrance and immobilize drugs through electrostatic and hydrophobic interactions. Dormant cells may not take up drugs and are difficult to kill, while changes in phenotype and propagation of resistance genes can raise the minimum effective concentration.

Figure 5. Schematic of a drug releasing orthopedic device in the physiologic space with key parameters diagrammed based on the rubric questions. a) Diagram of key systems and their interactions, b) Key parameters needed to assess performance and safety based on the systems diagram; c) Test selection to obtain key inputs. The background image (knee and spacer) have been used and annotated with permission from the American Academy of Orthopaedic Surgeons (AAOS).

Conclusions

- Preclinical testing plays an important role in our effort to further reduce the risk of medical device associated infection.
- Current in vitro methods of testing antimicrobial performance are not predictive of clinical outcomes and can be improved through more realistic environments and endpoint measurements.
- Tissue models and Medical Devices on Chips are emerging as transformative in vitro simulation technologies.
- A scalable and flexible systems approach using a consensus-based rubric will enable development of rational preclinical testing approaches that can identify new technologies with significant patient benefit.