

Superbugs require new drugs antibiotic resistance

Anti-Infective Services: Answering the Call for Antimicrobial Development.

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Infections caused by antibiotic resistant bacteria represent a significant burden to healthcare systems worldwide today. Resistance among commonly encountered pathogens has emerged as a consequence of the selective pressures of antimicrobial use. Clinically relevant resistance to penicillin, one of the first antibiotics to be developed for clinical use, emerged within months after its introduction. Further, for virtually all other antimicrobials developed to date, resistance among target bacterial pathogens has emerged. Regardless of the time frame, the emergence of resistance appears to be not a question of “if”, but “when”.

The increased mortality and morbidity associated with infection by antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) has become an all too common problem and threat to public health. Due to their prevalence, particularly within the hospital, MRSA and VRE are likely the most well-known examples of problematic antibiotic resistant bacteria. Unfortunately, these bacteria represent the tip of the iceberg. With both the expected increase in the patient population due to aging baby boomers and the fact that hospitals provide the perfect environment for the emergence and spread of antibiotic resistance, other significant and resistant nosocomial pathogens (*Pseudomonas aeruginosa*, *Acinetobacter* spp., enteric gram-negative bacilli, etc.) have become notorious public healthcare threats similar to MRSA and VRE.

One need not look far to realize that antibiotic resistance is not strictly a hospital-based problem. The emergence of extensively drug-resistant tuberculosis (XDR-TB) has garnered much attention of late, due to its rapid spread and high mortality rate among those infected with HIV. MRSA, a significant pathogen in the hospital, is also a leading cause of skin and soft tissue infections contracted in the community today (CA-MRSA). Fortunately, CA-MRSA remain largely susceptible to other therapeutics unlike the MRSA acquired in the hospital, yet one must wonder how long that will remain the case. The spread of drug resistance among pathogens involved in communicable disease (pneumonia, meningitis, etc) is understandably a concern, as is the increased prevalence of multi-drug resistant pathogens (e.g. *Pseudomonas* and *Acinetobacter*) in our hospitals. As foreboding as the emergence of multi-drug resistant bacteria may be, new therapeutics capable of replacing currently utilized drugs that ultimately become less effective as they are used have been slow to come to market.

Where are the new drugs?

There exist many reasons to explain the dropoff in antimicrobial development, particular in the pharmaceutical industry. Steve Projan of Wyeth Pharmaceuticals stated in an article from *Current Opinion in Microbiology* (2003)¹ that the pharmaceutical industry has found better ways to invest research dollars. Although the market is the primary driving force for any business, anticipation and foresight to fulfill future needs should also play a significant role. Dr. Projan states, “The view that there is not a compelling need to address bacterial antibiotic resistance with novel agents and strategies is not only wrong, but also dangerous.”

Many pharmaceutical companies have slowed or halted their antimicrobial research and development programs over the past decade, a policy in direct contrast to the boom in antimicrobial development research observed in the 1970s, 1980s, and early 1990s. Primary reasons that are often given for this change in direction include:

- High risk, low reward (development has not been particularly successful and even if it were, the revenue is comparatively low)
- Increasing bureaucracy (harder to gain FDA approval, increased regulation regarding antimicrobial usage)

Though the landscape of antimicrobial development in large pharmaceutical companies has changed, many companies have remained committed to addressing the need for new antimicrobials, albeit on a smaller scale than in the past. In the vacuum created by the decreased trend in antimicrobial development, small biotechnology companies have also emerged in an attempt to fill the void. These companies, both new and established, have positioned themselves at the forefront of a renewed push for antimicrobial development. Nonetheless, there exist considerable challenges to developing new antimicrobials today given the limited resources available to these companies and the substantial bureaucracy involved in successfully bring their drugs to market.

To help address some of the challenges faced by depleted antimicrobial research and development programs in pharmaceutical companies and smaller biotechnology firms, a deeper partnership has emerged between pharmaceutical companies and contracted central laboratories once relied upon mainly for safety testing. The impact of infectious diseases on global health and the continued emergence of antibiotic resistance bacteria is a problem that will not disappear; rather it will likely continue to worsen.

Anti-Infective Services

Because of the microbiological and business dynamics discussed above, biopharmaceutical companies look to central laboratory service providers that can play a critical role in support of anti-infective drug development. To address this need, Eurofins Medinet Anti-Infective Services provides both laboratory services and expert solutions to support the complex process of anti-infective drug development to assist biopharmaceutical industry in the timely and efficient development of new agents.

Key areas include:

1. Clinical Trial Support

- Full spectrum centralized testing of bacteriological and mycology samples (specimens and isolates)
 - Culture processing
 - Organism identification
 - Characterization (molecular and phenotypic) of isolates
 - Susceptibility testing via conventional, automated, and molecular methods
- Safety lab testing
 - Chemistry
 - Hematology
 - Urine analysis
- Specialty testing (e.g. biomarkers)
- Project management
- Data management
- Logistics and courier management
- Quality assurance
- Regulatory compliance
- Global standard operating procedures

2. Antimicrobial Surveillance

- Profiling agents in clinical and pre-clinical development via retrospective studies
- Long term prospective monitoring of the ongoing in vitro activity of several leading antimicrobial agents
- Passive surveillance and resistance mapping

3. Specialty Microbiology

- Capability to provide a wide array of laboratory testing and characterization required by the FDA for New Drug Applications (NDAs), such as:
 - Molecular characterization (PCR, sequencing)
 - Molecular typing (PFGE, ribotyping)
 - Lead compound screening
 - Resistance development
 - Bactericidal activity by timekill analysis
 - Drug synergy/antagonism studies
 - Post-antibiotic effect (PAE) analysis
 - Disk diffusion and MIC method validation
 - Quality control range development
 - Interpretive breakpoint determinations

4. Scientific Consultative Services

- Qualified staff with extensive experience in all areas of drug development readily available for scientific consultation and guidance throughout development
- Experience in the execution of clinical trials for a wide variety of indications (community acquired and hospital acquired pneumonia, intra-abdominal infections, surgical site prophylaxis, skin and soft tissue infections, etc.)
- Experience in dealing with the relevant regulatory agencies and their requirements for new drugs (FDA filings, CLSI methodology, EUCAST, and EMEA)
- Production of reports, peer-reviewed publications, and presentations to be given at scientific conferences (ICAAC, ECCMID, IDSA, and ASM) to increase visibility and for use in filing with regulatory agencies

Summary

Are we prepared to face the challenges of infectious disease in the 21st century?

The continued emergence of drug resistance among commonly encountered pathogens and the evolution of multi-drug resistant pathogens refractory to the majority of currently utilized therapeutics represents a challenge for the treatment of infectious disease both today and in the future. Infectious diseases remain the second leading cause of death worldwide and are the third leading cause of death among the developed world.² These developments have

created an increasing need for new antimicrobials that will enable clinicians to better manage infections caused by these pathogens. However, antimicrobial research and development has been less of a focus of the pharmaceutical industry than in the past. Although new leads continue to be generated from both the pharmaceutical and biotechnology industries that have remained committed to generating new antimicrobials, the climate both within their own companies and within the regulatory agencies has made it more difficult to get these compounds through the drug development pipeline and into the market.

These developments have created a unique opportunity for the central laboratory to help pharmaceutical and biotechnology companies turn their leads into clinically approved therapeutics. Through the process of acquisition and the building of programs specifically tailored to serve their clients in all aspects of drug development, central laboratory services within companies like Eurofins Medinet, Inc. have evolved to the point where they can provide their clients with active contributions and guidance throughout all phases of a drugs development. Thankfully, this partnership between anti-infectives services and the research and development programs within the pharmaceutical and biotechnology industries has been shown to be successful in bringing new antimicrobials to market where they are so badly needed. The ongoing battle between clinicians and antibiotic resistant pathogens is analogous to war, and in war one should never go to battle unprepared. As has been said, “We don’t know if we can win the war against infectious diseases, but we surely can not afford to lose it.” The ongoing collaboration between pharmaceutical companies, biotechnology companies, and companies capable of providing anti-infective services, will continue to have a significant impact on the arsenal available to clinicians to battle infectious diseases today and in the future.

¹ Projan SJ. *Why is big Pharma getting out of antibacterial drug discovery?*
Curr Opin Microbiol 2003, 6:427-430.

² Fauci AS. *Infectious diseases: considerations for the 21st century.*
Clin Infect Dis 2001, 32:675-685.



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