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editorial

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Whither antibacterial drug discovery?

As the spectre of pan-resistant strains of bacteria has become a clinical reality, the pipeline of new antibacterial drugs capable of treating such infections is virtually bone dry. Several factors have coincided to create this evolving perfect storm, and they include industrial and biotech futility in discovering and developing novel classes of agents; an oversimplified understanding of the causes of bacterial resistance; increasing industry concentration through mergers and acquisitions; higher regulatory hurdles coupled with unrealistic public expectations, and funding agencies that have been late to the game, as well as less than insightful in their funding priorities. However, we are beginning to see some light at the end of the tunnel as some old dogma are being replaced with a better understanding of what a good molecular target looks like, so the future may not be as bleak as the present, assuming we can get there.

The emergence and dissemination of multidrug-resistant strains of bacterial pathogens has been well documented. Less well documented is the clinical impact of these resistant strains. Indeed, some have argued that, given viable therapeutic alternatives, resistance is actually clinically inconsequential, provided one makes the correct decision on the choice of antibacterial therapeutic (a choice that is often not apparent at the time a patient presents with symptoms of an infection). However, there are increasing reports of pan-resistant strains of Gram-negative bacteria [1], and it is particularly for those organisms that a growing gap between medical need and agents in development has arisen [2]. Indeed, while this gap widens it has also been well documented that fewer large companies (and probably fewer small companies) remain engaged in the hunt for new antibacterial drugs. Increasing industry concentration (through merger and acquisition activity) and larger and larger clinical trial size have resulted in ever-fewer drugs of all types making it through regulatory, commercial and medical mine fields to the market [3]. It is a fact that, for some patients, the post antibiotic era has already arrived.

Our recent failures to identify new classes of antibacterial agents, despite a wealth of new genetic and genomic data [4], is telling us something fundamental about bacterial systems and also tells us that dashing headlong into campaigns of high-throughput screening without understanding the actual physiology of perturbing a given target will be (as it has been) doomed to failure. In a commentary published last year, I derided our own superficial, incomplete, and probably inaccurate view of bacterial drug resistance [5], asking the question ''if we don't understand the biology behind bacterial drug resistance how can we prevent it?'' Likewise, we are left with the same, purely empiric, methods for antibacterial drug discovery that have been employed for over 150 years and with the increasing lack of success as the law of diminishing returns would predict. As we have learned from the study of HIV, we should realize that it is only through the study of the basic biology of bacteria (regardless and maybe even heedless as to the 'immediate impact' of that research) that we are going to have the knowledge that we need to treat ever more recalcitrant bacterial infections.

Funding matters

As a keynote speaker at last year's Interscience Conference on Antimicrobial Agents & Chemotherapy, Louis Rice of Case Western Reserve and the Cleveland VA observed that, in 2007, in the United States there will be approximately 10 000 deaths due to HIV and HIV-related causes while there will be over 90 000 deaths

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due to bacterial infections contracted in hospitals. Indeed the number of deaths due to MRSA alone surpassed HIV-associated mortality in 2005 [6]. The tremendous gains made by the biomedical research community in developing novel HIV therapeutics has clearly paid off with the discovery and development of many novel therapeutics, and this simply could not have happened without aggressive public funding to study and understand the underlying biology of HIV. However, current funding priorities seem still to reflect a 20th Century view of the world and do not reflect the stark 21st Century reality that Dr. Rice so well described. At the same time, the NIH in general, and NIAID in particular, appear less and less concerned with understanding the biology of bacterial systems and more concerned with 'impact', that is developing novel therapeutics. To apply two apt metaphors, this is putting the cart before the horse and you cannot build a good house on a rotten foundation. As a pharmaceutical industry scientist engaged in drug discovery, I can state categorically that we in industry simply cannot succeed without a solid foundation of basic biological research that was the heart and soul of NIH extramural funding in the past. By way of example, one of the most powerful technologies we in industry are now using routinely is phage display for the discovery of novel therapeutic proteins (among other applications), there are scores of monoclonal antibodies currently in development, in all therapeutic areas, that were discovered using this approach for a wide variety of diseases and syndromes. This technology simply would not have existed without many basic studies on the Ff (e.g. M13) family of bacteriophage, yet those early researchers would have been disingenuous in the extreme to suggest that their research would lead directly to novel drugs. In my own experience work on the regulation of plasmid copy number eventually translated into a decisive experiment in the development of a novel antibiotic.

This now begs the question, how should we spend our scarce public resources in funding microbiology research? I would like to see us stop following the well-beaten path, as there is a dull sameness to much currently funded research, and rather study the biology of a greater diversity of microorganisms. Not because these diverse microbes may be potential pathogens or even because they may express interesting secondary metabolites that could become therapeutics, but because they may (and frankly probably will) reveal interesting biology. By increasing the diversity of microbes we study this may also promote diversity in the scientists who receive support for their research, as the present system has concentrated much funding in the hands of relatively few people and institutions.

A new hope?

But perhaps some rays of sunshine are breaking over the storm clouds. Some recent progress has been reported in finding new agents with novel mechanisms of action [7,8]. In fact, using purely genetic criteria for judging a valid/viable novel target may be at the root of our recent futility in identifying novel antibacterial drugs as documented above. In the case of ClpP, a target now validated in animal models of infection, genetic approaches ruled it out. The riboswitches were not even elucidated by whole genome sequencing and bioinformatic analyses. What exactly makes something a good target? It is now painfully clear that genetic criteria are, at best, misleading partly because they represent the best case scenario for an inhibitor (i.e. 100% inhibition), something that is quite simply never achieved. Rather, a good target is something that, when affected (positively or negatively) causes something (irreversibly) bad to happen to the bacteria (i.e. stimulating autolysis, causing protein misfolding, stalling ribosomes on mRNA). As trite as it sounds, it is a distinctly different paradigm that resulted in hundreds of fruitless high-throughput screening campaigns, rather the 'new' paradigm actually comes from a more profound understanding of the basic biology, requiring string academic underpinnings.

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