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The Process of Discovery and Development of New Antibacterial Drugs

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ABSTRACT

Antibiotic (antibacterial) resistance is a serious global problem and the need for new treatments is urgent. The current antibiotic discovery model is not delivering new agents at a rate that is sufficient to combat present levels of antibiotic resistance. This has led to fears of the arrival of a 'post-antibiotic era'. Scientific difficulties, an unfavorable regulatory climate, multiple company mergers, and the low financial returns associated with anti-biotic drug development have led to the withdrawal of many pharmaceutical companies from the field. The regulatory climate has now begun to improve, but major scientific hurdles still impede the discovery and development of novel antibacterial agents. To facilitate discovery activities there must be increased understanding of the scientific problems experienced by pharmaceutical companies. This must be coupled with addressing the current antibiotic resistance crisis so that compounds and ultimately drugs are delivered to treat the most urgent clinical challenges. By understanding the causes of the failures and successes of the pharmaceutical industry's research history, duplication of discovery programs will be reduced, increasing the productivity of the antibiotic drug discovery pipeline by academia and small companies.

INTRODUCTION:

Antibacterial drugs have revolutionized our ability to control bacterial disease, and their clinical availability has led to dramatic decreases in morbidity and mortality.[1] As such, these therapeutics underpin modern medicine. Despite the integral role of antibiotics in sustaining our modern lifestyle, they are undervalued in both cost and significance by society. Over the past century, their use has provided strong selective pressure on microorganisms, leading to preferential survival and spread of those harboring antibiotic resistance mechanisms. Multidrug resistance is now commonplace amongst bacterial pathogens with antibiotic resistance now affecting all antibiotic classes.[2] This is particularly worrisome in the case of Gram-negative bacteria (e.g. *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) for which treatment options are already limited.[3] The 'broken' economics of antibacterial research and development (R&D) is often quoted as the main reason for the lack of new therapies but the truth is that it is hard to discover new antibacterial drugs, and the science is not sufficiently advanced to allow discovery of efficient and effective drugs. This has led to fears of a 'post-antibiotic era' as it has been estimated that 5–20 novel antibacterial drugs need to enter clinical development to effectively contend with the current resistance problem. However, given the attrition rate within the existing drug discovery model, at least 200 discovery programs would be needed to achieve this outcome. Hence, new approaches to antibiotic discovery are needed.

The antibiotic pipeline

The antibiotic pipeline is not what it once was.[4] Pharmaceutical companies were once the main provider of novel antibiotic molecules but they largely withdrew in the late 1990s because of the lack of success and low financial returns in bringing new antibacterial drugs to the market.[5] The environment of discovering and developing new antibiotics was quite different during the so-called 'golden era' of drug discovery. Antibiotics worked remarkably well because resistance was low and physicians had access to a variety of efficacious antibiotics. Antibiotic R&D programs were inclined to focus on improved pharmacology to achieve less frequent dosing e.g. once a day, rather than innovative new antibiotics. Natural product screening strategies tended to result in the rediscovery of compounds rather than finding new ones. There was also no need to consider those natural products with undesirable properties such as toxicity. Today, only a few large companies such as GlaxoSmithKline, Novartis, Merck, and Roche are still actively engaged in antibiotic R&D, with many of the

original antibiotic providers e.g. Bristol-Myers Squibb, Bayer, Eli Lilly), having left the arena.

Small to medium-sized enterprises

The role previously fulfilled by industry has been taken over increasingly by academia and especially small to medium-sized enterprises (SMEs).[6,7] Furthermore, drug development programs that have recently advanced to late-stage clinical evaluation or have had marketing approval came originally from large companies and were subsequently licensed to SMEs (e.g. ceftazidime/avibactam). Innovative chemistry is also a key contributor to success as shown by the development of semi-synthetic natural products such as dalbavancin, novel natural products such as omadacycline, eravacycline, and plazomicin, and novel b-lactamase inhibitors such as vaborbactam). Fast-following approaches, in which a good candidate is quickly identified and developed, have also yielded new drugs e.g. tedizolid and cadazolid. During the last two decades, antibacterial R&D has also suffered from changing clinical and investor priorities as the focus moved from MRSA to Clostridium difficile and most recently to Gram-negative bacteria. Changes in regulatory advice also created uncertainty and additional financial risks although the recent regulatory focus for antibiotics and a collective will to create innovative regulatory pathways for antibacterial drugs should generate an environment that will stimulate discovery, research, and development. The community now needs to address the other barriers to success.

SMEs and academia will continue to lead future efforts in antibiotic drug discovery but they can only advance new therapies so far. Full clinical development requires the capabilities and supply chain of pharmaceutical companies. Indeed, the successful delivery of new therapies will require effective partnerships between all stakeholders. By learning from their past failures and successes, pharmaceutical companies can, and should, work closely with academia, charities, and SMEs to provide a more effective model for antibiotic discovery. Antibacterial innovation is not only needed now but also in the long term. Discovering new antibiotics that circumvent resistance development is unlikely and this generation may be the last to benefit from cheap antibiotics. Consequently, we should endeavor to create a solid foundation for future generations to continually respond to the challenge posed by antimicrobial resistance (AMR).

Which antibacterials are needed?

As antibacterial discovery shifts towards academia and SMEs, there is a risk that research funding (called 'push') rather than the clinical need (called 'pull') will define the active programs. Research-led programs that fail to consider clinical use, manufacturing, regulatory practices, the feasibility of clinical study designs and reimbursement, are not only inefficient but probably doomed to failure. Recently, the WHO published a list of bacteria for which new antibiotics are urgently needed[8] so the next step will be to provide internationally agreed-on target product profiles (TPPs) that will define the properties of suitable antibacterial therapies. Pharmaceutical companies have detailed descriptions of what they consider ideal and acceptable characteristics of new antibacterials such as indication, potency, efficacy, pharmacology, toxicology, safety, and dosage. These TPPs could be used by other researchers to ensure that their research is aligned with the most urgent medical needs. TPPs could also be used by funders and investors to select the projects that are most likely to have a clinical impact. If this is not done, research on new antibiotics may well end up failing to address the most urgent needs.

Targets for monotherapy

The emergence and spread of antibiotic-resistant bacteria are responsible for the dwindling number of effective antibacterials. If the success of a new drug is to be ensured, the potential to develop resistance and the consequences of resistance must be determined. Basic studies to estimate the potential for developing resistance such as determining the MIC, resistance frequencies, minimum concentrations for preventing mutation-selection, and exploring the consequences of resistance mechanisms should be done in the early stages of drug discovery.[9] In the past, many had hoped that the lack of emergence of resistance in animal models of infection might indicate that resistance may not be an issue in the clinic, but this has not always proven to be the case (e.g. GSK2251052/AN3365).[10]Target validation, i.e. inhibiting an essential protein or process, plays a central role in the development of a successful therapeutic, and target essentiality is now considered the beginning of the validation process, as opposed to the end. A focused effort to understand the biology of the target and the impact of target inhibition is needed to develop novel drugs as this will provide insights into how resistance might occur or how essentiality could be bypassed when that target is inhibited. For instance, genetic studies to assess the mutability of a drug-binding pocket should be under-taken before screening candidate inhibitors against a potential target.

Such studies would determine how likely mutations would occur that alter the drug target and confer resistance. Studies should also be carried out to determine whether changes to the drug target affect the fitness of the bacterium and its ability to cause infection. Considerable advances have been made over the last decade in identifying gene products that are important or essential to bacterial physiology and pathogenic attributes. As a result, there have been numerous suggestions that they could provide novel targets for new antibiotics. However, there is a considerable gap between identifying an essential or important bacterial factor, and inhibitors that can form the basis for developing a new drug. This is because antibacterial discovery programs need to identify inhibitors that are amenable to chemistry thereby providing the basis of a new drug.

Academia can contribute towards the basic understanding of bacterial cellular processes, pathogen biology, and pathways that may influence resistance development. A better understanding of this could help to avoid some of the problems encountered in the past regarding target validation and resistance. Indeed, it is likely that small compounds and natural products have already been identified that provide a good basis for antibacterial drug monotherapies but new targets will require extensive validation before being developed further. Good monotherapies comprise a single compound that targets multiple essential protein activities.

Screening: overcoming the Gram-negative permeability barrier

The discovery of novel, broad- and narrow-spectrum inhibitors of Gram-negative bacteria has proven difficult. The quinolones were discovered in the 1960s and were the last broad-spectrum class of antibacterial agents to enter the clinic.[11] The intrinsic resistance of Gram-negative bacteria to many different drugs is largely attributed to the architecture of the cell envelope and multidrug efflux pumps. The outer membrane and the efflux machinery work together to reduce the intracellular concentration of various antibiotics so that the bacterium can resist the action of a range of structurally diverse compounds.[12] The differences in antibiotic activity between Gram-positive and Gram-negative bacteria are rarely owing to target differences between the two groups of organisms (e.g. daptomycin)[13] but instead are the result of the additional permeability and efflux barrier that Gram-negative bacteria possess.[14]

Academia plays a pivotal role in increasing our understanding of the physiology and permeability properties of the Gram-negative cell envelope by driving basic research on how to avoid efflux and ensure the entry of drugs into the bacterial cytoplasm. Generating 'rules of entry' regarding the chemical properties required for compounds to accumulate within the cytoplasm of Gram-negative bacteria and reach their respective intracellular targets will greatly aid the development of novel broad-spectrum antibiotics. The recent findings of Richter *et al*.[15] will help generate these rules. There has been some progress in improving the activity of the oxazolidinone class of drugs against *Escherichia coli* and in identifying the structural properties required to penetrate cells.[16] Furthermore, a complete understanding of the orientation and binding of LPS molecules on the exterior of the Gram-negative outer membrane could facilitate the development of cationic molecules to disrupt it. The ability of the drug to penetrate the outer membrane and its susceptibility to efflux mechanisms must be tracked throughout the drug optimization process to successfully develop new antibiotics to treat infections caused by Gram-negative bacteria. This can be achieved by including whole-cell screening assays comparing drug activity against wild-type and efflux mutants. However, care over the choice of efflux mutants is essential; point mutations inactivating the transporter process whilst preserving the protein should be used rather than deletion mutants.[17] Recent clinical isolates should be included during optimization programs to ensure compounds are effective against those bacteria currently causing the greatest clinical challenges. The importance of overcoming the barriers to antibiotic entry exhibited by Gram-negative bacteria has also been highlighted in the 'Scientific Roadmap for Antibiotic Discovery, from the Pew Charitable Trust.[18] The primary objectives outlined for antibiotic.

Sources of antibacterial compounds

Natural products dominate the existing antibacterial compendium accounting for three-quarters of available antibiotics.[19] The importance of the natural world as a source of antibacterial drugs is also evident from the history of the antibiotic pipeline, which has continued to be re-stocked with semi-synthetic derivatives of established natural product classes. However, despite previous successes, natural product drug discovery is labor-intensive, has a low throughput, and has yielded diminishing returns causing the pharmaceutical industry to stop active research in this area. During the late 1990s, the focus of attention shifted to synthetic compound libraries which were used for high-throughput screening to search for novel, target-specific inhibitors *in vitro*. This approach did not prove

fruitful as it failed to discover novel antibacterial compounds suitable for further development. The failures of the genomic era to deliver novel drug targets and scaffolds, coupled with the threat of a 'post-antibiotic era' have prompted a revival of natural product drug discovery in both academia and the biotechnology sector. However, they cannot offer a sustainable contribution to natural product discovery without involving the pharmaceutical companies; this is because many readily accessible sources of potent, broad-spectrum antibacterial compounds have already been exhausted by past discovery efforts.

Environmental organisms may represent a large potentially untapped resource of novel antibiotics, and recent innovations could allow natural product discovery to be carried out sustainably. For instance, the development of the *in situ* culture device, the iChip, has allowed the high throughput cultivation of environmental microorganisms.[20] The merit of this device can be seen from the discovery of teixobactin, a compound of a novel antibiotic class that possesses activity against the cell wall biosynthesis of Gram-positive bacteria.[21] Alternatively, cryptic biosynthetic pathways could be activated leading to the production of novel secondary metabolites with antibiotic activity.[22] Metagenomics (analysis of the genomes of DNA from microorganisms in environmental samples) could be used to investigate the secondary metabolite diversity of non-cultivatable environmental organisms. Lastly, a key process in natural product drug discovery is the inclusion of de-replication techniques such as high-resolution LC-MS/MS, which ensures the elimination of previously characterized compounds from further study.

It is always possible that all the potentially antibacterial molecules amenable to medicinal chemistry have already been identified and that the search for novelty may not pay off. In this case, substantial investment in innovative chemistry on, and around, the known molecules would be prudent to determine whether any advances are possible. This is surprisingly difficult to fund and yet has proved a successful strategy to overcome resistance and side effects. It may also be the case that all the good targets for single-drug therapy have already been identified, making it necessary to seek alternative chemical classes to inhibit these targets by employing innovative chemistry.

Efficacy

Animal models of bacterial infection can be highly predictive of efficacy in clinical use. Marketed antibiotics perform well in these models and researchers have come to expect high

levels of bacterial kill by candidate drugs. However, some compounds with modest potency *in-vivo* may have been overlooked or de-prioritized in optimization programs. Nor do we know what the minimum level of efficacy is to deliver meaningful clinical benefit for monotherapy. Until recently, a 3 log reduction (99.9%) in bacterial burden was considered the minimum level of efficacy necessary for a pharmaceutical company to continue research and development. Many now consider a 2 log reduction adequate and indicative of potential clinical utility.[23] However, perhaps a 1 log reduction or just bacteriostasis is sufficient in most circumstances but further research on this area is urgently needed.

Resistance

There needs to be an agreement between the community and regulators as to what level of *in vitro* evolution to give drug resistance would be considered acceptable for a drug candidate. This metric may depend on the consequences of resistance, for instance, a marked increase in MIC but also whether the infection is attenuated in infection models. Understanding all aspects of resistance and transmission of drug-resistant bacteria is essential if new drugs are to possess longevity.[24]The mutant prevention concentration (MPC) i.e. the drug concentration at which no mutants survive, is a key metric when considering an antibiotic for monotherapy. When a culture of drug-susceptible bacteria is exposed to a new antibacterial compound, rare, pre-existing point mutations that confer resistance to the compound may be selected.[25] The activity of the compound against these insusceptible mutants is likely to be less than seen against wild-type bacteria and multiples of the MIC of the compound may be required to kill a mutant or inhibit its growth. To suppress resistance development in clinical use, bacteria must be exposed to a concentration of the antibiotic that kills both the susceptible and first-step mutants of the species. Typically, bacteria require two or more mutations to become insusceptible at the MPC. This rarely happens *in vitro*, and is seldom encountered during registration studies but is not uncommon once the drug has been licensed. The fluoroquinolones provide a good example of this though it should be noted that mutations have been found in the same gene as well as different genes.[26]

If the MIC against a strain with a first-step mutation does not greatly increase, only a modest increase in drug concentration is required to achieve the MPC. However, if there is a big increase in the MIC, a much higher dose is required to achieve the MPC. To stop resistance developing in clinical use, bacteria at the site of infection must be exposed to free-drug concentrations above the MPC for a significant period of the dosing interval (e.g. 8 h). In

practice, this means that antibacterials have to be potent and well-tolerated to achieve these exposures. Too few antibacterial drug R&D programs demonstrate understanding of the pharmacology of managing resistance and fail to build this into their testing. When thoroughly analyzed, many of the novel target and new compounds.

Combinations

As monotherapies have proven so challenging to discover and develop, much focus has turned towards antibacterial combinations and it is here that academia has much to offer. This approach is much like those adopted for the treatment of HIV or tuberculosis, in which different drugs with different modes of action are used as part of a combination treatment. When current combinations of antibiotics are used, such as those used to treat patients with sepsis, the focus is on covering Gram-positive and Gram-negative bacteria as well as ensuring adequate drug concentration at the probable site of infection.[27] There is much literature on ad-hoc combinations of antibiotics and their effects on laboratory strains and clinical isolates; this has led to suggestions of novel combinations that could be used to treat Gram-negative bacterial infections. However, definitive large-scale studies have been lacking. This area would be enabled by wide-spread open access to well-characterized drug-resistant and multidrug-resistant isolates. Double, triple, and quadruple combinations that can inhibit challenging strains may be feasible but might be unpredictable. As resources are the only barrier, exhausting combination opportunities now from drugs already available for human use should be investigated. Unfortunately, such studies are rare; the focus of resolving the crisis of AMR has been on establishing economic incentives to stimulate pharmaceutical companies to stay in, or return to, this field. Furthermore, companies have no incentive to support studies on combinations of old drugs and have been generally unsupportive of this approach.

There are examples in the literature of antibiotics and non-antibacterial marketed drugs that could be used to potentiate the activity of an antibiotic against insusceptible or drug-resistant bacteria sometimes called ‘resistance breakers’.[28] The marketed drug may alter permeability through the bacterial cell membrane, interfere with efflux or act via alternative mechanisms. While the titles of some publications look appealing it is unclear whether any clinically useful new combinations have emerged. Not only does the activity of drug combinations against multidrug-resistant clinical isolates need to be established, but the primary pharmacology of the drug to be combined with an antibiotic may not be amenable to clinical use when given as

a combination. For example, the dose may be much higher than the approved dose. Alternatively, the toxicity and safety at higher doses, plus the requirement for matched or manageable pharmacology of the combination must be considered.

CONCLUSIONS AND FUTURE PERSPECTIVES

Academia has an essential role to play as there is still much to learn about bacterial physiology to benefit the field of antibiotic R&D. This can be achieved by employing a systems biology approach to understand potential targets and deepen our knowledge of the permeability barrier and multidrug efflux exhibited by Gram-negative bacteria. A new paradigm for preclinical research has been proposed that should aid those engaged in early drug discovery. However, early discovery research should be in partnership with SMEs and large companies and not in isolation in academia. Otherwise, there is the danger of spending considerable time and funding on research that will never deliver a new drug.

The natural world remains the largest source of novel drug scaffolds making this a viable option in the search for new antibiotic compounds. Advances in bacterial culture techniques, molecular biology, and metagenomics will make natural product drug discovery easier and more cost-effective, obviating these limiting factors. Screening procedures must include whole-bacterial cell assays, addressing the issue of bacterial permeability and efflux early in the discovery process. Additionally, the generation of training schemes by, and with, pharmaceutical companies that cover all aspects of the pipeline and include natural product drug discovery, are essential and will ensure that expertise is passed on to future researchers.

Investment should also be made into the study of previously characterized lead compounds that did not reach the clinic, so-called ‘old leads’. The reasons that led to these compounds being dropped from further development vary, ranging from financial issues to trial design, dosing problems, and toxicity. It may be that there is now sufficiently improved technology and expertise to develop these as safe and efficacious antibacterials. The revival of interest in old leads could also provide an additional source of novel antimicrobials. A freely accessible database of antibiotics that were never developed has recently been launched, Antibiotic DB to reduce unnecessary duplication of discovery efforts. Another database comprising ‘old natural product leads’ would also help the community. However, care must be taken to review all the previous research on any compound of interest to ensure that the failures of the past are not repeated.

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