modes of action, to anti-proliferative small molecule drugs, via anti-inflammatory, anti-viral and ion channel modulator molecules, the full scope and breadth available is yet to be realized. However, to exploit this field requires not just drug development technical know-how, but also substantial entomological expertise. Companies are rising to this challenge, with drug candidates already emerging from company pipelines, making sure that the field of 'pharma-entomology' lives up to its promise.

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The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Joanna Owens, Acting News & Features Editor, *Drug Discovery Today*, e-mail: Joanna.Owens@elsevier.com

Structural pharmacogenomics: the answer to antimicrobial drug resistance? ▼

The 20th century saw great advances in our understanding of the aetiology, transmission and prevention of infection. The introduction of chemotherapeutics in the 1930s, the advent of mass production of penicillin in 1943, rapid advances in the discovery and development of new classes of antibacterial drugs, and the introduction of safe and effective vaccines gave rise to the belief that bacterial infectious diseases could be controlled and, eventually, mastered. Although antibiotics have saved countless lives and transformed the practice of medicine, the initial widespread optimism has proven premature [1] and multiple drug resistance threatens our capacity to treat many infections [2].

Antiviral chemotherapy arrived much later; the nature of the viral lifecycle led to the belief that antiviral drugs would inevitably be toxic to the host. However, with improved understanding of viral replication, new drug candidates have been emerging in recent years, with much effort focused on the treatment of HIV infection. The problem of antiviral resistance is acute and, in this context, the surveillance of resistance genotypes is an important component in the overall strategy to keep ahead of the microbes.

Rapid sequencing of bacterial and viral genomes has created the opportunity to identify new drug targets. In a recent review in *Drug Discovery Today*, Edward Maggio and colleagues detail the use of structural pharmacogenomics as a means of rational drug design to overcome the problems of organisms that are resistant to anti-infectives [3]. By sequencing thousands of gene variants coding for HIV1 protease and reverse transcriptase, and mapping the deduced amino acid changes to the 3D structure of the proteins, inferences are made about the positions of conserved areas where mutation frequencies are low. These areas are deemed to be essential for

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protein activity and represent attractive potential binding sites for future drug candidates. Any candidates likely to suffer from low activity as a result of mutational change in the gene coding for the drug target can be removed early in the development process.

The investment in this technology will need to be substantial: 3D protein structure is required and thus a new protein target or an existing target where none is available can not be evaluated. The technique might be difficult to apply to new drugs acting on new targets as the mutation frequency in the particular gene coding for the drug target might be too low to be detected without the initial selective pressure of the drug. Furthermore, amino acid changes in the mutant proteins must be correlated with changes in drug efficacy, so drug resistance would not be detected simply by sequencing the gene.

Structural pharmacogenomics opens up new avenues for the development of both antiviral and antibacterial drugs where resistance emerges because of drug target alterations. Most antiviral drugs become less effective because of target modification, which often emerges quickly. However, it should be borne in mind that antibacterial resistance is not restricted to target modification: enzymatic inactivation or modification of the drug, drug efflux and changes in permeability also have important roles.

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Polymers in medicine; a game of chess▼

It is undeniable that the effective use of medicines has provided unparalleled benefit for the treatment of disease and infection. It is also recognized that nearly all medicines can cause harm. To attain the greatest benefit in large diverse populations, deleterious side effects and adverse interactions of medicines are continuously documented. Regulatory agencies and the pharmaceutical industry analyze voluminous amounts of often complex and incomplete information to determine the best practice for the clinical use of medicines. Clinicians require extensive training to best select and administer medicines, with close patient follow-up and treatment changes often being required. Considerable clinical experience is also essential to de-couple patient hopes and fears from the decision-making process that is required for the most effective use of medicines [1].

There is no acknowledgement in the recent article by Hunter and Moghimi [2] of the inherent complexity that typifies the development and widespread use of medicines. This is compounded by the use of not altogether appropriate comparisons and a less than representative inclusion of details about previous research. Collectively these limitations result in the loss of a balanced argument that detracts from the author's central, and important, premise that research effort is required to determine the immunotoxicology of parenteral medicines derived from physiologically soluble polymers.

It is widely accepted that constant vigilance and research are required to understand completely the toxicological implications of many chemicals used in society [3], including all the constituent components (e.g. actives and formulation excipients) of medicines. Polymers have long been widely used in consumer and healthcare applications. This includes parenteral use where many toxicological issues are well documented [4,5].

To address the toxicological implications for the parenteral administration of physiologically soluble polymers, the authors compare disparate systems; for example, cationic vectors for non-viral gene delivery, PEG-grafted liposomes and drug solubilizing polymers. These systems are complex mixtures of molecules, both small and large molecular weight. The disentanglement of the toxicological properties, including immunological issues, of these different systems is being carefully determined by the comparative study of each type of system separately [6,7], rather than grouped together as done by the authors. Comparative toxicology is entirely dependent on well defined end-use specifications and physicochemical and biological characteristics that are related to composition, formulation and processing.

Much toxicological research is predicated on knowing molecular structures before and after administration. Although the authors fittingly describe how the heterogeneities of polymer structure can obscure the determination of biological and toxicological properties, this has been well known for many years. Much remains to be done but, as the authors intimated, there has been significant progress to prepare biomedical polymers with more uniform structure [8,9]. The need for homogeneous structure and complete structure characterization has generally applied to all medicines and the author's statement that 'the absolute chemical characterization of small drug molecules is straightforward' is simply not true, considering the real complexity of medicines; for example, stereoisomers, polymorphs, pseudopolymorphs, the changes in structure caused by generally unavoidable instabilities of drug

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