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Commentary

Current Challenges and Potential Opportunities for the Pharmaceutical Sciences to Make Global Impact: An FIP Perspective

Geoffrey Tucker [1,*], Binodh DeSilva [2], Jennifer Dressman [3], Michiho Ito [4], Takuya Kumamoto [5], Don Mager [6], Hanns-Christian Mahler [7], Anke H. Maitland-van der Zee [8], Giovanni M. Pauletti [9], Hitoshi Sasaki [10], Vinod Shah [11], Daniel Tang [12], Michael Ward [13]

[1] *Department of Human Metabolism (Emeritus), Medicine and Biomedical Sciences, University of Sheffield, Sheffield, UK*
[2] *Immunochemistry and Biomarker Development, Bristol-Myers Squibb, Lawrenceville, Princeton, New Jersey 08648*
[3] *Institute of Pharmaceutical Technology, Biocenter, Johann Wolfgang Goethe University, Frankfurt, Germany*
[4] *Department of Pharmacognosy, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan*
[5] *Department of Synthetic Organic Chemistry, Research Institute for Pharmaceutical Sciences, Musashino University, Nishitokyo, Tokyo, Japan*
[6] *Department of Pharmaceutical Science, School of Pharmacy and Pharmaceutical Science, State University of New York at Buffalo, Buffalo, New York 14214*
[7] *Drug Product Services, Lonza AG, Basel, Switzerland*
[8] *Division of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands*
[9] *James L. Winkle College of Pharmacy, University of Cincinnati, Cincinnati, Ohio 45219*
[10] *Department of Hospital Pharmacy, Nagasaki University Hospital, Nagasaki, Japan*
[11] *Pharmaceutical Consultant, North Potomac, Maryland 20878*
[12] *United-Power Pharma Tech, Beijing, China*
[13] *School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia 5000, Australia*

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ABSTRACT

The chairs of each of the 8 Special Interest Groups of the Board of Pharmaceutical Sciences of the International Pharmaceutical Federation have compiled opinions with regard to major challenges for the pharmaceutical sciences over the next 5-10 years. Areas covered are drug design and discovery, natural products, formulation design and pharmaceutical technology, pharmacokinetics/pharmacodynamics and systems pharmacology, translational and personalized medicine, biotechnology, analytical sciences and quality control, and regulatory science.

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Introduction

The International Pharmaceutical Federation (FIP) is a global organization representing 2 million pharmacists and pharmaceutical scientists, with 137 member groups, including the American Association of Pharmaceutical Scientists. It sets standards through professional and scientific guidelines, policy statements and declarations, as well as by collaboration with other international organizations, including the World Health Organization (WHO).

In 2007, the President of FIP commissioned its Board of Pharmaceutical Sciences (BPS) to develop an article on the impact of pharmaceutical sciences, a reflection on progress over the last 50 years.[1] The aim was to acquaint fellow scientists with the contributions of pharmaceutical scientists and to increase awareness of the role that they have played in improving health care. Based on

Geoffrey Tucker is also Chair of the Board of Pharmaceutical Sciences of FIP.

* *Correspondence to:* Geoffrey Tucker (Telephone: 00447968840775).
E-mail address: g.t.tucker@sheffield.ac.uk (G. Tucker).

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this review, a concise flyer was also produced to stimulate interest in the pharmaceutical sciences as a career choice for graduates.[2] Having looked back at past achievements, BPS now looks forward in an attempt to identify the main challenges across the spectrum of activities that comprises the pharmaceutical sciences.

Whereas the impact article was prepared by individuals who had witnessed the development of the pharmaceutical sciences over much of the last 50 years, the main contemporary challenges have been addressed in this article by a mostly younger generation. Accordingly, the chairs of each of the BPS Special Interest Groups (SIGs) were invited to seek the opinions of 5-10 global opinion leaders in their area as to the main issues and to use their responses to identify up to 5 key challenges. Currently, there are 8 SIGs with global outreach within FIP, namely Drug Design and Discovery, Natural Products, Formulation Design and Pharmaceutical Technology, Pharmacokinetics or Pharmacodynamics and Systems Pharmacology, Translational and Personalized Medicine, Biotechnology, Analytical Sciences and Quality Control, and Regulatory Science. It should be noted that other areas such as drug metabolism, pharmacoeconomics, pharmacovigilance, and social and behavioral sciences are not represented as SIGs. Together with the Board of Pharmaceutical Practice within FIP, BPS is currently seeking to establish joint interest groups around the last 3 areas.

Drug Design and Discovery

The Need for New Drugs to Combat Diseases With Major Impact on Health and Economics

New Anti-Infective Drugs

For several years now, the world has been confronted with the rapid evolution of bacteria and other microorganisms resistant to current antimicrobial treatment (e.g., methicillin-resistant *Staphylococcus aureus* and carbapenem-resistant *Klebsiella pneumonia*), many being unaffected by more than one compound. Once the efficacy of “reserve” antibiotics such as teicoplanin has been overcome, patients will begin to die and, indeed, are already dying from otherwise easily treatable conditions such as septicemia. Regrettably, few new antibiotics, especially ones with novel mechanisms of action, have yet to reach the clinic. They are urgently needed. Classical approaches to the development of antibiotics involving impairment of protein synthesis or cell wall formation may not provide sufficiently lethal agents; new strategies are required including those designed to inhibit efflux pumps and to impair the cellular penetration and dissemination of the microorganism. The development of new anti-infective agents capable of addressing major unmet needs in developing countries for the treatment of malaria, tuberculosis, dengue, Ebola, and other tropical diseases also remains a global health priority. In this context, a challenge is to develop alternative reimbursement models, to refine and evolve public-private partnerships with open access to relevant information across national borders, and, in common with all aspects of drug development, to ensure data integrity and scientific honesty.

New Drugs for the Treatment of Diseases of CNS Disorders

As people live longer, the number of patients with dementia is increasing rapidly. Although acetylcholinesterase inhibitors, including donepezil, galantamine, and rivastigmine, and NMDA receptor agonists, such as memantine, have been developed to treat the symptoms, compounds such as amyloid β inhibitors that delay disease progression are needed.[3] The same applies to other major neurological diseases such as Parkinsonism and schizophrenia. Development of new CNS drugs is particularly challenging, while the mechanisms underlying disease remain obscure and the clinical assessment of efficacy is difficult.

Drug Discovery Based on New Understanding of Mechanism of Action

Selective Agonists at (Oligomeric) G-Protein—Coupled Receptors

In the past, it has been very difficult to activate G-protein—coupled receptors (GPCRs) selectively to avoid off-target side effects mediated by other receptors or receptor subtypes. This reflects the fact that the orthosteric pockets of cognate receptors and receptor families are structurally very similar. However, it is evident from recent X-ray analysis of the structure of GPCRs that many of them exhibit allosteric binding that could be addressed in developing more selective compounds. Dualsteric or bitopic ligands occupying both the allosteric and orthosteric binding sites can enhance agonist activity or can trigger partial agonism. Understanding the functional consequences of the oligomerization of GPCRs is a further challenge. If a single receptor can form multiple homo- or hetero-oligomers, drugs designed to bind to the monomer may still interact with the oligomers, resulting in multiple unintended responses. Therefore, in designing and screening compounds that target a specific oligomer, it will be vital to elucidate the location of the oligomer interface and the distances between respective ligand-binding pockets in the receptors.[4]

Epigenetic Inhibitors

The development of inhibitors of epigenetic events mediated by DNA methylation or histone modification is in its infancy but is a potentially fruitful area for new drug development.[5] Challenges include elucidation of downstream signaling pathways and crosstalk mechanisms between DNA methylation and histone modification and understanding of individual epigenetic enzyme isoforms.

Protein-Protein Interactions as Drug Targets

Protein-protein interactions (PPIs) have been recognized as key features of diseases such as cancer and HIV.[6] For example, HDM2 is responsible for the ubiquitination of p53 tumor suppressor, and the complex is a potential anticancer target; the LEDGF/p75 integrase interaction is a target for anti-HIV therapy. Although PPIs were originally thought to be undruggable targets, advances in systems biology and the application and improvement of techniques such as surface plasmon resonance and nuclear magnetic resonance as well as the elucidation of crystal structures should accelerate drug design against them. Challenges include how to inhibit the PPIs directly or allosterically, which interface to be targeted and how much of it, and how to maximize bioavailability.

The Application of Systems Biology and Organ- and Body-on-a-Chip

Through the understanding of signaling pathways and metabolic networks, systems biology is being applied to the elucidation of biomarkers of disease and drug response and is expected to expand its role in the design and development of small molecules by targeting key network nodes and by exploiting the use of drug combinations to offset homeostatic mechanisms and enhance synergy.[7] The emerging technology of organ- and body-on-a-chip also promises to open new opportunities in drug discovery with respect to target identification and validation, target-based screening, and phenotype screening.[8]

Increased Use of Human Tissue

In those cases where animal models are of limited use for establishing proof-of-concept for efficacy in humans, a challenge is to expedite the development and application of *in vitro* test systems based on human tissue, with due regard to ethical, legal, and

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