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Themed Section: Analytical Receptor Pharmacology in Drug Discovery

EDITORIAL

BJP issue on drug discovery

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This issue is dedicated to drug discovery. Obviously, such a diverse topic could not be adequately served in volumes of books, much less in one issue of a journal. However, we have attempted to gather topical reviews and examples of works applying novel methods in the elusive search for novel and better drugs.

We are also very privileged to present a lead article written by Sir James Black titled, 'Reflections on Drug Research'. Without doubt, Sir James was one of the greatest drug discoverers of all time, and needs little introduction to readers of this issue. Suffice it to say that he was responsible for two 'first-in-class' blockbusters: propranolol, the first marketed beta-blocker, and cimetidine, the histamine H2-receptor antagonist. This article (in hard copy) was given to us on 28 November 2009, when one of us was visiting him at St Christopher's Hospice in Sydenham, London. The point of this is that even at times that most of us would consider extremely difficult, Sir James' passion for science shone as brightly as ever. Here was an 85-year-old gentleman, in a hospice, and one of his first wishes on our visit was that we 'see if this might be worth publishing'. He then added, 'I know it needs tidying of some missing references and other minor things, but of course I expect to see the reviews beforehand in case it needs more significant revision'.

As requested, the manuscript was sent out for review, and the reviewers were the experienced and successful pharmaceutical industry scientists, Daniel Hoyer and Heather Giles. Their reviews are also included immediately after the article by Sir James. Both of them thought the article was of extreme interest from not only a historical perspective, but also because Sir James, as always, continues to challenge us. The article is preceded by a short introduction from his wife, Professor Rona MacKie, who literally lived with the article's creation and was his constant reviewer and critic for the months during which Sir James was putting his ideas on paper. Unfortunately, due to Sir James' declining health, it was Rona who lovingly did most of the tidying up that was needed to put the final polishes on the published article. Finally, Rona insisted that we clarify that an abbreviated and simplified version of this article, published for a broader audience, was published in the Journal's Special Issue Celebrating the Life and Work of James Whyte Black (Black, 2010).

The issue then continues the theme of receptor-focused drug discovery with a series of articles reviewing the most common techniques and analytical methods utilised in the search for novel receptor ligands, under the overall title of 'receptor methods under the spotlight'. G protein-coupled (or seven transmembrane) receptors remain the most utilized class of protein targets in drug therapy, and for decades the characteristics of new receptor ligands have been assessed using either binding techniques or measuring intracellular second messenger levels. Now, hundreds of new receptor ligands are made each day across the pharmaceutical industry and academia, necessitating the utilisation of higher-throughput methodologies. During the gradual process of converting from tissue-based to test-tube experiments to plate-based assays, systems have been miniaturized and new detection technology has been invented. This industrialization of pharmacology has resulted in a subtle shift in priority from high assay fidelity to the high reproducibility considered essential for routinely run experiments. So, rather than focus on generating assay systems that closely represent the (patho)-physiological situation, assay developers have tended towards optimizing window size and signal strength. This series of reviews is devoted to taking a closer look at how assay design can influence observed affinity and efficacy of receptor ligands, and how this can sometimes result in large

differences in parameters that are often considered system-independent, for example, the equilibrium dissociation constant K_A. It also addresses common assay artefacts that often lead to the misinterpretation of data.

Since the 1970s, radiolabelled ligands have been utilized to study the binding properties of drugs at receptors. This series begins with a comprehensive review of radioligand binding assays by Ed Hulme and Mike Trevethick, addressing issues such as equilibration time, buffer composition and ligand depletion (Hulme and Trevethick, 2010). The next article by Philip Strange discusses methods for directly assessing activation of G proteins, contrasting the traditional GTPase assays with more modern approaches such as Galpha-specific SPA assays (Strange, 2010). Both articles demonstrate that when performed in a well-controlled manner, these assay systems offer high fidelity and are key methods for assigning mechanism of action of novel receptor drugs.

Despite this, the measurement of intracellular second messengers has become the workhorse of modern drug discovery laboratories, largely driven by technological advances in detection systems. Steven Charlton and Georges Vauquelin review the use of the calcium assay to characterize the pharmacology of novel receptor ligands, focusing in particular on complications arising from hemi-equilibrium conditions in this rapid signalling format (Charlton and Vauquelin, 2010). The alternative methods for measuring cAMP are then contrasted by Steve Hill, Lauren May and Chris Williams, highlighting differences in amplification and time dependency of the signal (Hill *et al.*, 2010).

Finally, the development of high-throughput experimental techniques has necessitated an increased reliance upon automated data analysis, often removing the ability (and seemingly responsibility) of scientists to personally interpret their data sets. In their article on fitting experimental data to pharmacological models, Chris Langmead and David Hall discuss some of the assumptions and pitfalls of commonly used analysis methods and give guidance to receptor pharmacologists on best practices for data interpretation (Hall and Langmead, 2010).

This special issue concludes with a number of original papers describing novel work in the area of drug discovery. We hope that when framed alongside the historical context of Sir James Black's achievements, it is gratifying to see that constant criticism of new technologies, and the need for rigorous quantification and proper analysis of the data continues to emphasize that analytical pharmacology remains the cornerstone of drug discovery.

Conflict of interest

None.

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