

Themed Section: Analytical Receptor Pharmacology in Drug Discovery

Reviewer comments on *Reflections on drug research* by Sir James Black

It was an honour and a pleasure to review these two outstanding essays in which Sir James reflects on the evolution of drug discovery, from earliest times until the present day.

The first essay, entitled *Empirical approaches, discovery and invention* is eloquent and hugely interesting. Following a trip through the ages it concludes with a description of Sir James's discovery of β -blockers. The essay provides new insights and is a hugely valuable record of those early pioneering days of drug discovery, interspersed with fascinating personal recollections and observations.

The second essay, *Rational approaches*, continues the story of Sir James's incredible record of drug discovery, taking us on an exploration of gastrointestinal physiology and pharmacology, right up to present day challenges of understanding the reasons for the huge increase in pancreatic cancer and possible links to pharmacological interventions.

There follows a description of the massive changes that have occurred in the drug discovery process since the advent of molecular biological techniques to identify and express human receptors; namely, high throughput screening and combinatorial chemistry. This has allowed identification of potential new targets for drug discovery often without any knowledge of their role of in physiology or pathophysiology. This essay is entitled 'Rational approaches' but I would argue that this approach is just as much a game of Blind Man's Bluff' as suggested in the first sentence of the first 'Empirical approaches' essay. I entirely agree that an approach to drug discovery based only on these techniques would be disastrous but I do think that their use as part of the overall discovery process – which must include whole animal physiology and ideally tissue preparations – has added to the drug discoverers armoury. It is now possible to study pharmacology and *human* receptors very early on in

the process and I contend that our ability test compounds on multiple targets during the discovery phase has increased our ability to take selective molecules into the clinic, rather than decreased it.

I found this second essay highly stimulating and thought-provoking, and inevitably more contentious as it challenges some of the paradigms that many of us currently use! It was also a more difficult read. For example, I struggle to understand the first of the seven principles, particularly the phrase 'evidence of biochemical differentiation' I am left wondering if Sir James thinks that identification of two different functional receptor sub-types based on molecular biological evidence is enough? And if not, what is? I also had difficulty in understanding the sentence starting with 'I think this becomes apparent...' I am not clear on the message here – in what way is industry expecting that the approach to treating asthma etc will be similar to hypertension...? Some elucidation would be helpful to the reader.

Sir James provides some very valuable thoughts about the role of synergy in responses in health and disease and I just wanted to read more!

In summary, these essays are a very special and unique record. Not only do they provide an interesting historical perspective, but they provide a stimulus and challenge to continue to evolve how we approach drug discovery.

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This article is part of a themed section on Analytical Receptor Pharmacology in Drug Discovery. To view the other articles in this section visit <http://dx.doi.org/10.1111/bph.2010.161.issue-6>

To view the article by Sir James Black visit <http://dx.doi.org/10.1111/j.1476-5381.2010.01019.x>