G-PROTEIN-COUPLED RECEPTORS: THE DEVIL IS IN THE DETAIL

As the second in our occasional series of 'Twenty Questions' features shows, GPCRs, already by far the largest class of drug targets, hold the potential to deliver very much more if we are willing to invest the effort to understand them.

Of all the tried and tested major classes of therapeutic targets, G-protein-coupled receptors (GPCRs) are surely the best characterized. Although there is still some uncertainty about the nature of the main targets of many marketed drugs, it seems safe to say the GPCRs represent the primary target of approximately half the drugs on the market. But despite this past success, current efforts to bring further classes of GPCR-targeted drugs through the pipeline are proving far less productive than might have been predicted given the accumulated knowledge on GPCRs, and very few new GPCR ligands have been recently approved as new drugs. Were previous generations simply luckier in having easier problems to tackle, or can current disappointments be ascribed to changes in the way the challenge of drug discovery is being approached?

This question is one of twenty that we pose to a group of twenty leading authorities in the field of GPCR research in the second of our 'Twenty Questions' features, to which we devote about half of this month's issue of *Nature Reviews Drug Discovery*. As with the first such feature, which we published on the topic of ion channels in March of this year, the chosen 'panellists' are all based at universities; our aim is to highlight the perspectives of a wide range of academic scientists on topics of immediate relevance to the drug industry. Once again, these questions and answers first appeared in a preliminary version as part of a joint report by *Nature Reviews Drug Discovery* and business intelligence company Decision Resources, published earlier this year, under the title *GPCR Modulators: Emerging Therapeutic Opportunities*.

Each participant was invited to answer whichever questions struck them as particularly interesting, and the answers to each question are grouped together roughly according to the nature of their content. In response to the question of why fewer GPCR-targeted drugs are being approved these days, for instance, most answers fall into two basic types (see pages 603–605). The first set of answers broadly raise the issue of how well the screening methods applied during the drug discovery process mirror the reality of a GPCR's role in the biology of a given disease. The second set address the changing emphasis of GPCR-directed drug discovery; this is shifting from a traditional focus on biogenic monoamine receptors, which have natural ligands that are readily amenable to chemical modification to produce lead compounds, to a more recent focus on peptide-activated receptors, which present an entirely different type of synthetic challenge to the drug discovery community. These two broad themes — the appropriateness of the models that are being applied to study GPCR function and the increasing complexity of the systems under study — underlie the majority of the questions and answers.

As for the successes of the past, luck must certainly have played a part, because the complications of targeting GPCRs sometimes seem to defy any logical approach. Take, for instance, the case of β-adrenoceptor antagonists in congestive heart failure (CHF), which were contraindicated for CHF for decades, on sound theoretical and experimental grounds. However, it was gradually realized that chronic dosing with beta-blockers produced opposite effects to acute dosing and could actually help to prevent CHF. Beta-blockers are now part of frontline therapy against CHF — a result that nobody could have predicted.

Given the bewildering array of possibilities presented by such complicating factors as GPCR homo- and heterodimerization, emerging regulatory protein networks and the new families of orphan GPCRs, it might sometimes seem a wonder that any targeted therapeutics aimed at GPCRs get developed at all. As the answers of our academic panel of experts make clear, committing the resources to understanding these additional aspects of GPCR biology will have a key role in the development of new GPCR-targeted therapeutics.

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