Introduction

Why Design Multi-Target Drugs?

The promiscuity of a drug, that is, its tendency to bind to multiple drug targets is both a challenge and an opportunity for medicinal chemists. Drug designers attempt to reduce the 'off-target' toxicity liabilities of a compound by increasing the selectivity of a drug for one target over others. Analysis of the physicochemical properties of failed and successful drug candidates illustrate that drug target promiscuity, due to high lipophilicity, is linked to an increased risked of toxicity and failure in the clinic:[1,2] hence the traditional label of promiscuous compounds as 'dirty'.[3] Guiding the design principle of selectivity is not only a reduction in potential toxicity but also the assumption that the direct modulation of single proteins will produce clinical benefits: a reductionist paradigm summarised as 'one gene, one disease, one drug'.

Since the completion of the sequencing of the first draft of the human genome, evidence has been accumulating from functional genomics and the new field of network biology that biological systems are robust to perturbation of individual genes. The new insights are challenging the dominant assumption of single target-based drug discovery.[4–8] Insights into the robustness of phenotype to perturbation can be found from understanding the function of biological networks. The fundamental architecture of networks contributes to the robustness and redundancy of biological systems. Network analysis of biological pathways and interactions has revealed that much of the robustness of biological systems is derived from the structure of biological networks.[9,10] The scale-free nature of many biological networks produces systems that are resilient against random deletion of any one protein (node) but also critically dependent on a few highly connected hubs. Network biology analysis predicts that if, in most cases, deletion of individual nodes may have little effect on disease networks, modulating multiple proteins may be required to perturb

RSC Drug Discovery Series No. 21
Designing Multi-Target Drugs
Edited by J. Richard Morphy and C. John Harris

Published by the Royal Society of Chemistry, www.rsc.org

robust phenotypes.[6,9,11] A network approach to pharmacology[12] suggests two strategies: targeting highly connected hub proteins, which exhibit pleiotropic effects (such as the role of HSP90 in cancer) or the targeting of multiple proteins to increase the perturbation of a network.

The robustness of individual proteins to perturbation is also revealed by metabolic flux analysis where modulation of single components in a pathway rarely results in large changes in metabolic flux and therefore phenotype.[13–15] A greater degree of perturbation of phenotype is observed in systems where more than one gene product is modulated. The emergent phenotype that occurs from the perturbation of multiple proteins is demonstrated by the systematic experiments on synthetic lethality. Dual gene deletion experiments in model systems have shown that, whilst the deletion of any one of two genes by itself may show no effect, the deletion of both genes can lead to 'synthetic lethality' or 'synthetic sickness'.[16] When dual perturbations are introduced, by combining single gene genetic knock-outs with a second chemical perturbation, the number of essential genes in yeast is predicted to significantly expand the 18% of the genes for which singleton gene knockouts are lethal. A large-scale study by Hillenmeyer *et al*. demonstrates the extent of synthetic lethality when gene deletions are augmented by chemical interventions.[17] Under ideal conditions only 34% of single gene deletions result in lethality or sickness. When the whole genome panel of yeast single gene knock-outs was screened against a diverse, small molecular library and assayed against a wide range of environment conditions an additional 63% of gene knock-outs showed a growth phenotype.[17] Thus 97% of genes demonstrate a fitness defect when challenged with a small molecule under at least one environmental condition. The vast majority of genes may be redundant under any one environmental condition but there appears to be little redundancy across a spectrum of conditions when a genetic perturbation is combined with a chemical insult. Genes that may appear dormant and dispensable under one set of specific conditions may prove essential under other stresses.[18,19]

The fundamental property of inherent robustness of biological networks has profound implications for drug discovery; instead of searching for a single 'disease-modifying' gene, network biology suggests that the strategy should be to perturb the disease network.[20,21] Hellerstein has argued that the true targets of drugs are not individual proteins but functionally important biochemical pathways embedded in larger biological networks.[22]

The intellectual foundations of network pharmacology challenge deep assumptions behind target selection and validation. Responding to the new biological insights into the complexity, robustness and redundancy in disease phenotype is helping to drive the emergence of a new approach to drug discovery, that of polypharmacology or multi-target drug discovery (MTDD).[3–6,11,12,23–30] Therefore, understanding the polypharmacology of a drug and its effect on biological networks and phenotype is essential if we wish to improve efficacy and understand toxicity.

Over the past decade the assumption of the desirability of single drug target mechanisms has begun to be questioned.[6,12,31] In certain

circumstances, it may be advantageous for a drug to act on multiple drug targets, deliberately and specifically, rather than be too selective. The chapters written for this book gather together in one volume the state-of-the-art of the emerging new field of MTDD. Successes in rational MTDD have already been reported, such as the approval of lapatinib, discussed in Chapter 8. Moreover, new tools are now emerging to aid the medicinal chemists to discover multi-target drugs. We hope this book serves as a record of the achievements of the field to date and provides inspiration for the development of rational MTDD as the next paradigm in drug discovery.

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