ELSEVIER

Metabolomics and systems pharmacology: why and how to model the human metabolic network for drug discovery

Douglas B. Kell and Royston Goodacre

School of Chemistry and Manchester Institute of Biotechnology, The University of Manchester, 131 Princess Street, Manchester M1 7DN, UK

Metabolism represents the 'sharp end' of systems biology, because changes in metabolite concentrations are necessarily amplified relative to changes in the transcriptome, proteome and enzyme activities, which can be modulated by drugs. To understand such behaviour, we therefore need (and increasingly have) reliable consensus (community) models of the human metabolic network that include the important transporters. Small molecule 'drug' transporters are in fact metabolite transporters, because drugs bear structural similarities to metabolites known from the network reconstructions and from measurements of the metabolome. Recon2 represents the present state-of-the-art human metabolic network reconstruction; it can predict *inter alia*: (i) the effects of inborn errors of metabolism; (ii) which metabolites are exometabolites, and (iii) how metabolism varies between tissues and cellular compartments. However, even these qualitative network models are not yet complete. As our understanding improves so do we recognise more clearly the need for a systems (poly)pharmacology.

Introduction – a systems biology approach to drug discovery

It is clearly not news that the productivity of the pharmaceutical industry has declined significantly during recent years [1–14] following an 'inverse Moore's Law', Eroom's Law [11], or that many commentators, for example, see [7,8,14–47], consider that the main cause of this is because of an excessive focus on individual molecular target discovery rather than a more sensible strategy based on a systems-level approach (Fig. 1).

Arguably the two chief hallmarks of the systems biology approach are: (i) that we seek to make mathematical models of our systems iteratively or in parallel with well-designed 'wet' experiments, and (ii) that we do not necessarily start with a hypothesis [48,49] but measure as many things as possible (the 'omes) and let the data tell us the hypothesis that best fits and describes them. Although metabolism was once seen as something of a Cinderella subject [50,51], there are fundamental reasons to do with the organisation of biochemical networks as to why the metabol(om)ic level – now in fact seen as the 'apogee' of the 'omics trilogy [52] – is indeed likely to be far more discriminating than are changes in the transcriptome or proteome. The next two subsections deal with these points and Fig. 2 summarises the paper in the form of a Mind Map.

Modelling biochemical networks – why we do so

As set out previously [19,53–55], and as can be seen in every systems biology textbook [56–58], there are at least four types of reasons as to why one would wish to model a biochemical network:

- Assessing whether the model is accurate, in the sense that it reflects – or can be made to reflect – known experimental facts.
- Establishing what changes in the model would improve the consistency of its behaviour with experimental observations and improved predictability, such as with respect to metabolite concentrations or fluxes.
- Analyzing the model, typically by some form of sensitivity analysis [59], to understand which parts of the system contribute most to some desired functional properties of interest.
- Hypothesis generation and testing, enabling one to analyse rapidly the effects of manipulating experimental conditions in the model without having to perform complex and costly experiments (or to restrict the number that are performed).

Corresponding author:. Kell, D.B. (kelldb@manchester.ac.uk), (dbk@manchester.ac.uk)

1359-6446/06/$ - see front matter © 2013 Published by Elsevier Ltd. http://dx.doi.org/10.1016/j.drudis.2013.07.014

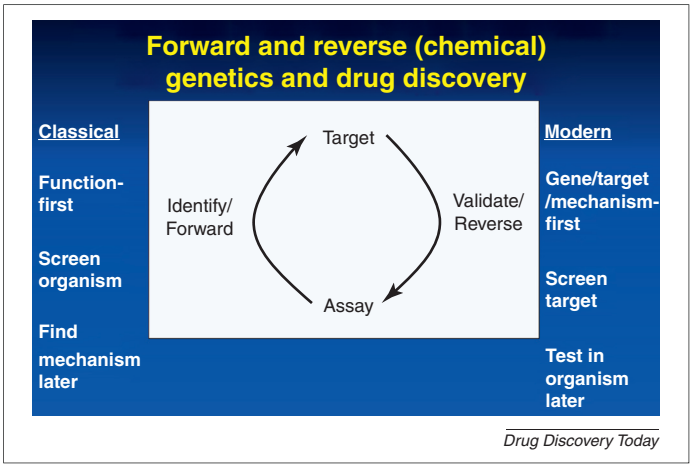

FIGURE 1

The change in drug discovery strategy from 'classical' function-first approaches (in which the assay of drug function was at the tissue or organism level), with mechanistic studies potentially coming later, to more-recent target-based approaches where initial assays usually involve assessing the interactions of drugs with specified (and often cloned, recombinant) proteins *in vitro*. In the latter cases, effects *in vivo* are assessed later, with concomitantly high levels of attrition.

In particular, it is normally considerably cheaper to perform studies of metabolic networks *in silico* before trying a smaller number of possibilities experimentally; indeed for combinatorial reasons it is often the only approach possible [60,61]. Although our focus here is on drug discovery, similar principles apply to the modification of biochemical networks for purposes of 'industrial' or 'white' biotechnology [62–68].

Why we choose to model metabolic networks more than transcriptomic or proteomic networks comes from the recognition – made particularly clear by workers in the field of metabolic control analysis [69–77] – that, although changes in the activities of individual enzymes tend to have rather small effects on metabolic fluxes, they can and do have very large effects on metabolite concentrations (i.e. the metabolome) [78–81]. Thus, the metabolome serves to amplify possibly immeasurably small changes in the transcriptome and the proteome, even when derived from minor changes in the genome [82–84]. Note here that in metabolic networks the parameters are typically the starting enzyme concentrations and rate constants, whereas the system variables are the metabolic fluxes and concentrations, and that as in all systems the parameters control the variables and not vice versa. This recognition that small changes in network parameters can cause large changes in metabolite concentrations has led to the concept of metabolites as biomarkers for diseases. Although an important topic, it has been reviewed multiple times recently [85–105] and, for reasons of space and the rarity of their assessment via network biology, disease biomarkers are not our focus here.

Modelling biochemical networks – how we do so

Although one could seek to understand the time-dependent spatial distribution of signalling and metabolic substances within individual cellular compartments [106,107] and while spatially discriminating analytical methods such as Raman spectroscopy [108] and mass spectrometry [109–113] do exist for the analysis of drugs *in situ*, the commonest type of modelling, as in the spread of substances in ecosystems [114], assumes 'fully mixed' compartments and thus 'pools' of metabolites, cf. [115,116]. Although an approximation, this 'bulk' modelling will be necessary for complex ecosystems such as humans where, in addition to the need for tissue- and cell-specific models, microbial communities inhabit this superorganism and the gut serves as a source for nutrients courtesy of these symbionts [117]. The gut microflora contain some 10^{13}–10^{14} bacteria (over 1000 bacterial species, each with their own unique metabolic network) that allow metabolite transformation and cross-feeding within the prokaryotic group and to our gut epithelia; it is also noteworthy that, although antibiotics have an obvious effect here, other human-targeted pharmaceuticals will also undergo microbial drug

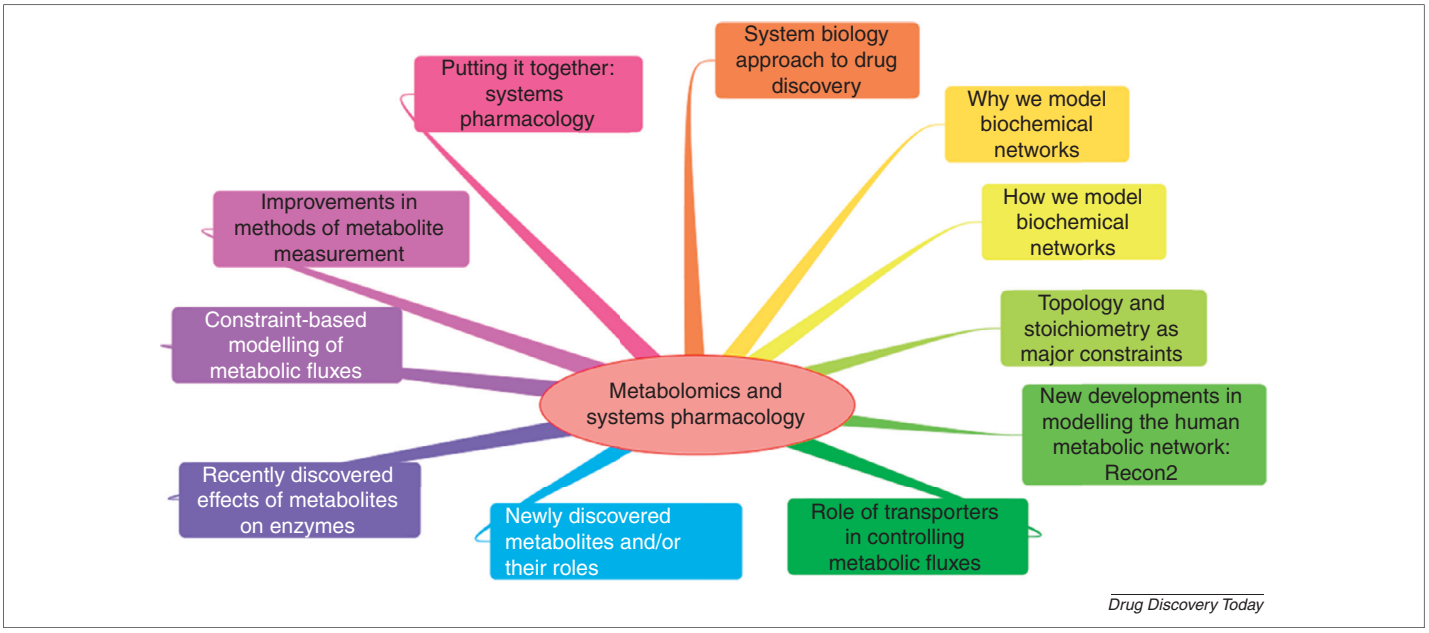

FIGURE 2

A Mind Map summarising this paper.