## High-throughput metabolism: making the most of the technology ▼

HTS against new drug targets such as receptors and enzymes has been a core technology in drug discovery for probably the past ten, and certainly the past five, years. Although somewhat late in the game, HTS is now commonplace within industrial drug metabolism departments. But what has HTS actually delivered and should drug metabolism follow the paradigm of 'more compounds is better'.

When one examines the successful drug launches of the past decade, most new chemical entities were discovered from natural products, in particular the aminergic endogenous neurotransmitters and antacoids. Molecules such as adrenaline, 5-hydroxyhistamines and histamine are ideal lead material being small (low-MW), with nanomolar potency and being water-soluble. Even for receptors or enzymes with peptides as the agonist or substrate, serendipity rather than HTS seems to have provided the leads. For instance, simple benzyl-substituted imidazoles were found to possess weak angiotensin II (A2)-inhibitor activity (40 μM). These leads led to the discovery of losartan, the first A2 inhibitor to be marketed. All A2 inhibitors to-date are structurally related. Similarly, existing small-molecule drugs such as hypolipidemic fibrates were modified so that the proprionic acid was replaced by a potential isostere, thiazolidine-2,4-dione, to generate a new class of antidiabetic drugs, the glitazones.

HTS is seen as a necessary source of lead matter, as targets are identified that have no small-molecule ligand. To rapidly fill gaps in compound files and to increase the chance of identifying ligands, the promise of combinatorial chemistry was seized without relationship to the traditional physicochemical properties of lead matter and new molecules entering files showed little relationship to traditional ligands. Ligands would always have polar interacting groups in the correct position for activity, but because a single methyl group adds binding affinity (0.7 kcal $mol^{-1}$), and thereby potency, by displacing water, the trend has been towards large and lipophilic lead material.

The starting point for many chemistry programmes thus moved from low-MW and often water-soluble leads to high-MW lipophilic leads. Programmes based on these materials classically failed to demonstrate acceptable oral activity despite achieving high potency. Development candidates often look similar to leads and the HTS revolution has provided compounds with a large number of H-bond donors and acceptors, lipophilic substituents and a high-MW. One immediate answer is to screen this material for, say, Caco-2 permeability (oral absorption) on the chance that one, or a small number of molecules, demonstrate favourable properties. Conversely, Lipinski and colleagues analysed marketed drugs and concluded that oral bioavailability coincided in most drugs with the drug conforming to certain boundary rules ('the rules of 5'), which limit the MW (<500), number of H-bond donors (<5) and acceptors (<10), and lipophilicity (log P <5). Judged against these rules, the products of HTS normally fail. By only working on lead matter with properties bounded by these rules the need for large screening protocols for such factors as oral absorption is largely negated.

So is investment in technology wrong? The answer could be that no matter how selective the drug metabolism department is in terms of actual screening, the relentless drive for efficiency in the drug discovery process demands that technology replaces manual methods and centralised processes replace the experiments individuals traditionally performed. Ideally, this will give individuals time to think and hypothesise and move our understanding forward. If technology buys time, and we invest it wisely in acquiring wisdom and not just transmitting increasing quantities of data, we just might be in the right boat.

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## Are drug targets missed owing to lack of physical activity? – Reply ▲

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**Response from David Gurwitz**

Brenda Anderson rightfully points out that exercised laboratory animals might not always be suitable for studying human disease, and that sedentary animals might be a better choice for modeling aging-related disorders and for more sensitive detection of drug side effects. However, the commentary was not meant to discredit the massive pharmacological and behavioural research carried out using sedentary laboratory animals. Rather, a call was made for more comprehensive comparative studies in sedentary and physically active laboratory animals in the context of new drug target validation. For example, a candidate drug that shows similar efficacies in both sedentary and physically active animals is more likely to be effective in humans compared with a drug that is clearly more beneficial for sedentary animals.


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Such comparisons are crucial for ensuring that the best targets are chosen for drug development among the many new drug targets that will soon be available. Pharmacogenomics will generate scores of potential new drug targets in a relatively short time-span compared with the target discovery rate in the pre-genome era. Choosing among so many potential targets will become the most important stage in drug development, as bioinformatics and proteomics are expected to streamline the chemistry and pharmacology stages. The exclusive use of sedentary animals for taking such decisions carries the risk of failing to invest in the more favourable drug targets.

Moreover, even when sedentary animals more closely resemble human patients, such as in Alzheimer's disease, research in physically active animals could improve our insight into very early disease stages and thus be useful as an additional tool for validating preventive drug targets. This is especially relevant for immune-based therapeutics for neurological disorders[1–3], as lack of physical activity correlates with diminished immune and repair mechanisms[4–6]. Such immune-based therapies are therefore more likely to benefit physically active animals. As our genome unfolds its secrets, preventive medicine (along with personalised medicine) will become the focus for new drug development. Hence, animal models used for searching preventive drugs should better reflect the earliest possible disease stages before the patients become sedentary.

In summary, the drug industry and academic research should gear up to compare drug efficacy data in sedentary versus physically active laboratory animals and to apply this knowledge to human disease. Apparently, this is not the practice for current drug development protocols, which could in part explain why new drugs that perform well in rodent animal models often fail in clinical trials.

## References


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