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Streamlining drug discovery: finding the right drug against the right target to treat the right disease

Genomics and proteomics technologies have created a paradigm shift in the drug discovery process. Until about 20 years ago, drug discovery was chemistry-driven, conducted by trial-and-error and with a paucity of defined targets. The introduction of genomics and proteomics in the past decade has given birth to the new paradigm of a biology-driven process, leading to a plethora of drug targets. This transition has led to a major discontinuity in drug discovery. Despite significant increases in R&D expenditures, there has been no corresponding increase in output, in terms of new drugs brought to the market. The lack of immediate results has raised doubts about the value of genomics/proteomics for drug discovery. However, in-depth analysis suggests that the current situation is typical of any technological revolution's early phase – termed 'an era of ferment', or the period between the invention and adaptation stages, where different paradigms are explored and from which, a robust standard emerges [1].

The genomics paradigm for early drug discovery can be broken into the following steps: (1) target identification, (2) target validation and (3) lead identification. The later stages include lead optimization, preclinical and clinical development. The costs in early drug discovery represent nearly 50% of the total costs in developing a drug, hence, optimization in the early stages would benefit both the industry and its consumers. Using the different types of technologies that have been developed, genomics and proteomics address different aspects in early drug discovery but clearly divide the entire process. This segmented approach is the usual suspect that leads to the resulting array of 'potential druggable targets', and a reason for the confusion surrounding the definitions of and differentiation between target identification and target validation. During this genomics and proteomics era of ferment, it is evident that there is no clear effective standard on how to convert genomics/proteomics information into methods to produce better and safer drugs. A major weakness in this segmented approach is the narrow focus on identifying or validating targets and generating leads, without giving due consideration to the question: which is the right drug lead molecule to modulate the right target for treating a particular disease?

An emerging paradigm that addresses the current limitations in applying genomics/proteomics to drug discovery is the streamlining of the early drug discovery phase by integrating target identification, target validation and lead identification. Rather than having distinct and independent steps, there should be a unified approach. The key issue is to identify the right drug lead compound against the corresponding validated target to modulate the key disease process.

Recently, Brown and Superti-Furga described one approach to this [2]. By combining protein-interaction mapping of biological pathways with corresponding target information of known small-molecule compounds that have shown efficacy, it might be possible to improve on these small molecules, to make them safer and more adequate at treating other specific disease indications. Although the approach they described provides a compelling way to improve the early drug discovery phase or, in their words, to 'rediscover the sweet spot', it represents only one of a few emerging approaches. Others include the use of chemical genetics and diversity-oriented synthesis in combination with phenotypic screens to generate new drug leads and accompanying validated targets [3,4]. Analogous phenotypic screens combined with antibody-based methods to generate novel targets and corresponding therapeutic antibody leads are also currently being pursued [4,5]. Only time will tell, by the conclusion of this era of ferment, which approach will emerge as the robust standard in streamlining drug discovery by finding the right drug for the right target to treat the right disease.

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The dangers of generalization in nanotechnology

In a recent article in *Drug Discovery Today*, Sahoo and Labhasetwar [1] provided a highly optimistic account of the potential of nanotechnology in drug delivery and in diagnosis. One of the dangers of such a review, or 'preview', of nano-sized carrier systems is that a wide range of systems are considered as if they all behave similarly. Some nanotechnology approaches will work and some will not. The authors have, rightfully, selected data from a wide variety of literature sources, which generally illustrate the advantages of nanosystems; this technology thus appears to be solely beneficial. Readers should be reminded that many were working in the field before the modern, encompassing nomenclature was invented. It was Peter Speiser who, in the early 1970s, produced by micellar polymerisation what he quaintly termed 'nanoparts' [1]. He differentiated these nanoparts into nanoparticles and nanocapsules, and studied them as vaccine carriers. There has, therefore, been a quarter of a century for nanoparticles to be developed. Marty *et al.* discussed progress in 1978 [1], and Kreuter reviewed the topic in the same year [2].

The unifying feature of the field of pharmaceutical nanotechnology is, of course, the size range of the particles or system. The nanometer size range is, indeed, important in allowing, as the authors state, access to tissues from which larger carriers are excluded. But at the same time, extremely small size provides two features: low volumetric capacity and high surface area. Both characteristics, in fact, pose problems – a limited capacity for active compounds and the potential for instability, respectively. With dendrimers, whose maximum size will be of the order of 10 nm, the capacity of the interior is low and, unlike micellar structures with their 'liquid' interiors, dendrimers usually possess a largely inflexible branched core. Proteins often have a diameter that is equivalent to many carriers in the nanometer size range, thus, as protein carriers, the smallest nanoparticles have their limitations. Aggregation of primary nanoparticles also determines their effective particle size. Nanosized dendrimers, when added to tissue culture media, can often flocculate to an extent that is dependent on the nature and, particularly, ionic strength of the medium. Their state of aggregation *in vivo* is difficult to ascertain, but it is unlikely that they will remain in their native state in blood, tissue and organs. Hydrophilic nanosystems are more immune to such problems, but their hydrophilic nature might influence uptake adversely.

The absorption or covalent attachment of specific ligands to the surface of nanoparticles can lead to specific interactions with biological surface receptors, but these surface ligand molecules, without doubt, change the physical nature of the surface. They might, or might not, reduce the likelihood of flocculation or aggregation. What is yet to be ascertained is the optimal spacing and conformation of ligand molecules on the surface of carriers. With improved knowledge of the molecular topology of receptors, this issue could be addressed more precisely, particularly with the pre-determined chemical architecture of dendrimeric systems.

One topic that has, perhaps, been neglected is the behaviour of particles in the circulatory system. This will be determined by: i) the interaction of nanoparticles with erythrocytes and other blood components; ii) the association of primary nanoparticles with themselves and with vessel walls and; iii) the influence of elasticity, when the diameter of the system exceeds that of the capillary vessels. The last point is unlikely to be an issue with nanoparticles, unless the particles have aggregated; here, the reversibility of any such particle–component or particle–particle interactions is key. Any significant number of nanoparticles, for example in the lymphatic vessels, is likely, at least, to influence lymphatic flow. We are presently studying the flow behaviour of blood–nanoparticle and microparticle mixtures.

It is undoubtedly true that nanosystems offer the potential for enhanced delivery and targeting. The sheer variety of structures that can be built up by self-assembly or covalent attachment of components, say, of dendrimers or dendrons, offers much scope, particularly if these structures can be fabricated at will. One approach that is frequently neglected is the combination of two or more technologies, for example, the incorporation of nanosystems within other carriers, such as emulsions and liposomes.

There is a general issue centred around the enhanced permeation and retention effect in targeting and diagnostic systems. The criteria for success in drug targeting are much more severe than those for diagnostic success, where, essentially, only an enhancement of signal over background is required. In treatment, if there is to be true success, accumulation at the target site should, ideally, be complete. So far, this has not been achieved – the balance of drug concentration has only been shifted moderately in favour of the target.

The potential of nanosystems to cause adverse effects needs to be thoroughly investigated, as size partly determines organ distribution.

Fascinating phenomena are reported with nanoparticles: polysorbate 80-coated nanoparticulates have been shown to penetrate the blood–brain barrier [3], but this can not yet be generalized. If this was the case, then it

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