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editorial

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Fragment-based approaches and the prospect of fragmented prodrugs

Drug discovery and development is a dynamic and interdisciplinary process that is constantly aggregating new technologies in the search for new therapeutics. Fragment-based drug design (FBDD) has gained momentum through the last ten years and can now be considered an established methodology which is widely used in medicinal chemistry projects in both industry and academia. The details and applications of FBDD have been extensively reviewed in the literature [1–3]. Following from this line of research, target-guided synthesis (TGS) is emerging as a new fragment-based approach that suggests the involvement of the molecular target (e.g. protein or DNA) to assemble its own ligand (Fig. 1). TGS advocates the formation of highly efficient ligands templated by the targeted biomolecule in near-physiological conditions [4]. Thus, by actively engaging the target in the assembly of its inhibitor TGS aims to reduce the number of inactive compounds to be synthesised for screening and overcome intrinsic errors associated with computational analysis [5].

The first TGS can be attributed to carnitine acetyltransferase inhibition experiments reported by Chase and Tubbs in 1969 [6]. However, the use of biological targets for the design and synthesis of drug-like compounds was first demonstrated by Rideout in 1986 in studies of synergism between molecular fragments [7]. In this case, aldehyde- and hydrazine-containing fragments react covalently to form hydrazone bonds in the final ligands. Perhaps labile hydrazone bonds were not appealing for biological applications and this concept of ligand self-assembling remained unexploited until recently when advances in the area of bioorthogonal reactions were provided by *in situ* 'click' chemistry [8,9]. A significant contribution was reported by Lewis and co-workers who showed that acetylcholinesterase can be strongly inhibited by incubating the enzyme with a library of building blocks containing azide and alkyne functionalities [10]. The azide and alkyne reagents are structurally selected to partially interact with the enzymatic binding site. Thus, fragments that interact favourably with the enzyme are selected, and the 1,3-dipolar cycloaddition 'click' reaction connects the fragments to form the final inhibitor (Fig. 1) [11].

FBDD and TGS have both in common the fact that they capitalise on molecular recognition patterns imprinted on molecular targets to select suitable molecular fragments '*ex vivo*', which are then tethered through synthetic optimization (FBDD) or *in situ* self-assembling (TGS) to form the final ligands. These ligands can then be re-synthesized and scaled-up for subsequent biological evaluations through the drug development stages (i.e. *in vivo* animal models and clinical development). However, when considering Rideout's ideas and recent developments in TGS together, one could shift this paradigm of fragment-based approaches a step forward towards the use of molecular fragments for direct clinical use (Fig. 2). The approach would allow for the *in vivo–in situ* synthesis of the final ligand already in close proximity to its biological target (protein or DNA) in the host. This innovative research envisages a gene/protein-specific pharmaceutical composition which contains the encoded combination of bioorthogonally fragmented prodrugs (two or more than two) to be

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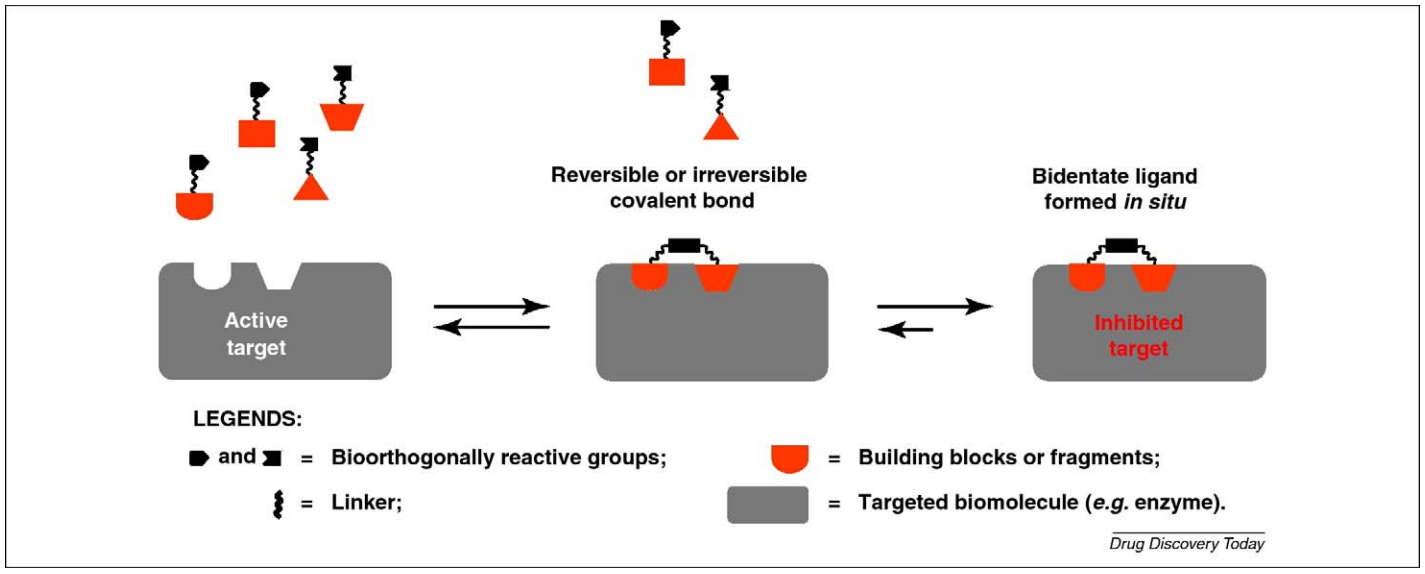

FIGURE 1

Schematic representation for the targeted-guided synthesis (TGS) of, for example, enzyme inhibitors.

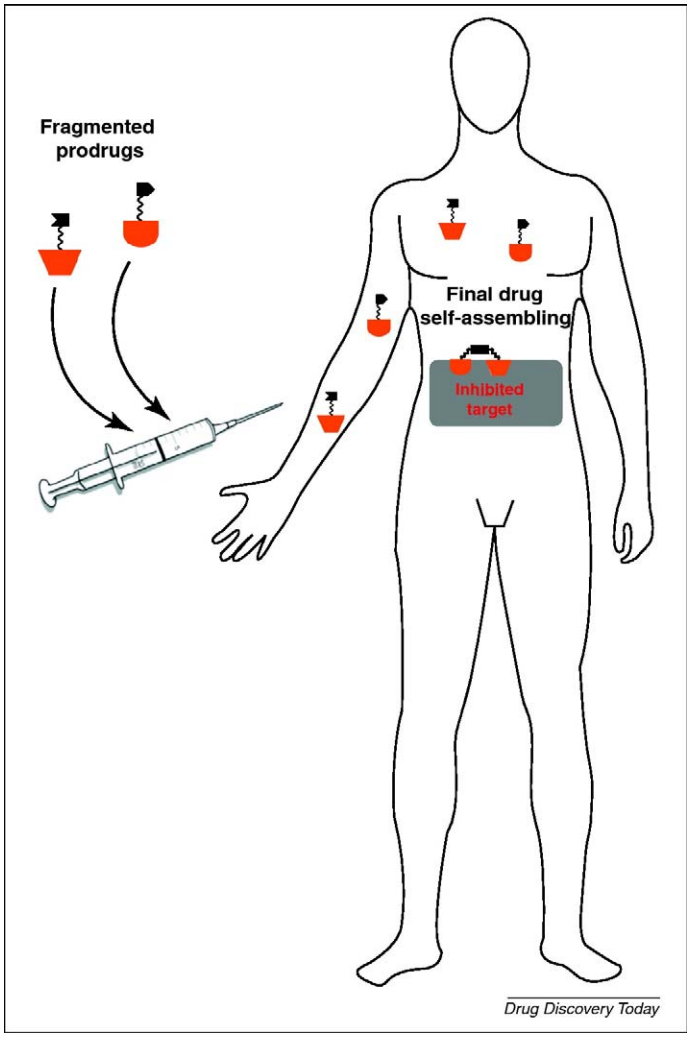

FIGURE 2

Schematic representation for the application of fragmented prodrugs for *in vivo–in situ* self-assembling of the final drug templated by the targeted biomolecule (e.g. enzyme) in the patient's body.

simultaneously or sequentially administered for *in vivo* self-assembling of the drug through a synergetic target-driven mechanism. As a consequence, highly desirable pharmacological properties associated with low molecular weight drugs could be maintained while biodistribution problems related to large molecules could be minimized at the plasma level for an optimal clinical application. Another potential benefit could be evasion of drug resistance mechanisms associated with host recognition/metabolization of non-fragmented drugs. In the context of cancer, formation of the final drug only at close proximity of its biological targeted can lead to amplification of selectivity between neoplastic and normal cells [7]. Thus, it is foreseeable that in the future, purposely prepared pharmaceutical compositions of closely related but different fragmented prodrugs could be designed to synergistically interact with specific molecular targets that have different isoforms (i.e. proteins) or polymorphism (i.e. genes) within patients, paving the way for personalized prodrugs. Furthermore, the valuable aspect associated with the uniqueness of molecular scaffolds constructed from fragment-based approaches could not only be maintained but also applied to current drugs that could be retrosynthetically fragmented, thus creating an attractive setting from the intellectual property standpoint.

Although tantalising, the above statements do not take into account the wide gulf that researchers will have to sail across in order to ascertain the benefits of fragmented therapeutics. Unknown questions related to the pharmacodynamics and pharmacokinetics of fragmented chemotherapies can be expected to arise before this concept becomes a clinical reality. Even so, the prospects for fragmented prodrugs are vast but hitherto lack *in vivo* and clinical data, which preclude their validation for therapeutic applications. Also, new ideas for drug discovery/development that include clinical studies will inevitably involve high financial risks. However, the lack of clinical data and risks associated with developing new therapeutics should not discourage funding agencies and the pharmaceutical industry from considering highly innovative research initiatives such as fragmented prodrugs.

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