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Teaching Old Drugs New Smart Tricks: Rethinking Cancer Therapeutics via Bioconjugate Technologies

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Editorial

Targeting cancer cells while circumventing non-cancerous cells is the main challenge in cancer therapy. Over the past two decades, numerous systems and strategies have been designed for overcome this problem. Initiatives to overcome this problem either involved the design and development of novel new chemotherapeutic agents or chemical or physical modifications of currently used chemotherapeutic agents [1].

For the past couple of decades, academic research has been mainly focusing on novel carrier systems and nano particulate colloidal technologies for drug delivery, such as nanoparticles, nanospheres, vesicular systems, liposomes or nanocapsules to impart novel functions and targeting abilities to currently used chemotherapeutic agents. Such efforts aided in the creation of newly marketed products such as Doxil® (Doxorubicin encapsulated in PEGylated liposomal vesicles) in the market [2,3]. Such systems provide the tools to custom design a superior drug delivery system, impart novel functions to old drugs such as longer half-life and stealth properties (as in the case of Doxil®), and provide them with either passive or active targeting properties via grafting the carrier system with targeting moieties and/or imaging agents or another drug within the same carrier system [4]. Such technologies opened the gate towards more sophisticated and effective multi-acting platform(s) which can offer site-targeting, imaging, and treatment using a single multi-functional system [5]. Unfortunately, such technologies are faced with major problems including high cost, low stability profile, short shelf-life, and poor reproducibility across and within production batches leading to harsh bench-to-bedside transformation. Major process and formulation development concerns exist with respect to scale-up processes of complex nanoparticluate carriers. Most of the reagents and inactive moieties in the formulation of such novel therapeutic systems are not included in the FDA approved Inactive Ingredient Database (IID).

Currently, pharmaceutical industry along with academic research are investing heavily in bioconjugate structures. Bioconjugate technologies offer an appealing and advantageous alternative to nanoparticulate delivery systems with all its flexible benefits when it comes to custom design and tailor grafting along with avoiding most of its shortcomings. Bioconjugates offer the flexibility of custom designing personalized products. Bioconjugates facilitate simple and easy drug (active

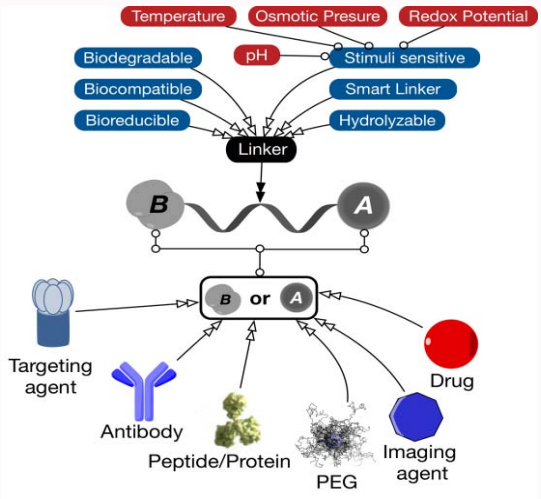

Figure 1: Bioconjugate molecules structural design.

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pharmaceutical ingredient) conjugation, using various smart biocompatible, bio-reducible, or biodegradable linkers, to targeting agents, PEG layer or another drug (Figure 1). Such technology enables the formation of smart multi-functional platform(s) offered by nanoparticulate carriers. Furthermore, conjugates are still considered chemical compounds.

This fact simply allows the use of traditional analytical and manufacturing technologies in the characterization and manufacturing of traditional active pharmaceutical ingredients offering high probability for their successful transition from bench-to-bedside. Moreover, the final formulation could be a simple injectable or solid formulation, which offers long shelf-life and enhanced stability profile. The main aim of bioconjugation is to form a stable biologically-cleavable covalent link between two molecules, at least one of which is a biomolecule [6]. Bioconjugation aims to increase stability, protect drug from proteolysis, or to enhance the targeting properties of the delivery system. Inspite of the historic fact that bioconjugates are older than nanoparticles, research is currently being diverted back to it. The design of a useful bioconjugate will depend mainly on its use, purpose and the desired properties needed. Thus one could choose a suitable molecule and suitable cross-linker to form the bioconjugate [7]. Bioconjugates can be synthesized by using cross linkers (couplers) that have been designed for this purpose, or by using a reactive group on one of the two molecules to facilitate the reaction [6]. Most of these reactions couplers are used to enhance the conjugation yield such as 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC, EDAC or EDCI) and *N,N′*-Dicyclohexylcarbodiimide (DDC). EDC is often used in combination with N-Hydroxysuccinimide (NHS) for the immobilisation of large biomolecules [6]. Bioconjugation can also be carried out by using a secondary activating agent, that forms an intermediate reactive group on one of the two molecules and thus facilitates the coupling reaction. Thus the key to forming a successful bioconjugate is choosing the suitable cross linker between the molecules [6]. Bioconjugation technologies can aid in creating safer, cheaper, stable, and effective novel therapeutics. It can also be a rate-limiting step in reinventing old drugs and imparting new functions to them that would enhance their target ability, pharmacokinetic and pharmacodynamic parameters, and their overall formulation patient compliance, easing their transition to market. A major focus should be the transformation of such novel bioconjugates' technologies from bench-to-bedside. The use of click chemistry, bioconjugation technologies, ligand post-insertion, and labeling techniques need to be extensively researched for ease of scale up and proper bench-to-bedside transformation.

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