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Global financial challenge: opportunities for strengthening R&D research in targeted drug delivery

"Cancer therapies can particularly benefit from new drug formulations based on targeted delivery as traditional cancer therapies rely on the fact that cancerous cells grow and multiply more rapidly than healthy cells."

Keywords: cancer chemotherapy ■ drug delivery ■ drug-development cost ■ drug targeting ■ R&D

Today, the pharmaceutical industry is facing an unprecedented challenge as a result of the significant increase in annual R&D costs along with a declining investment market for pharmaceutical research and a faster rise in the rate of inflation. It has been estimated that as many as 10,000 molecules are screened and tested for every one drug candidate that successfully enters the market [101], and only one in three marketed drugs is able to recoup its development costs. Even some post-marketed drugs have to be withdrawn due to concerns regarding lack of efficacy or undesirable side effects; one example is Merck's non-steroidal anti-inflammatory Vioxx®, which was voluntarily removed from the market after concerns were raised regarding increased risk of heart attack and stroke from prolonged use (**FIGURE 1**) [1,102]. According to a report published by DiMasi *et al.*, the estimated cost of developing a new pharmaceutical entity is roughly US\$802 million [2]. Although this estimate has been subjected to a great deal of scrutiny, it is generally recognized that the development of new molecular entities (NMEs) requires astronomical investment costs [101,3]. Resulting from such a high failure rate and high research and developmental premium, it is unsurprising that all big pharmaceutical companies are experiencing incredible pressure from their stakeholders. To maintain sustainability, companies are now forced to shift a significant portion of their R&D business to developing countries. Although this makes sense financially, this will have a huge negative impact on our trainees and our education systems; ultimately, this could deplete our ability to conduct R&D, and could result in poor protection of intellectual property for the big

pharmaceutical companies as the related laws vary from country to country.

To address this global concern, perhaps a shift of our current efforts in new drug development towards the area of targeted drug delivery could afford a solution. The therapeutic properties of the existing drugs are known; accordingly, new drug formulations based on improvements to old drugs will require significantly less time to develop than an NME, thus requiring far less initial investment capital. Indeed, it has been estimated that the costs associated with developing new drug formulations based on previous drug targets could be as much as one quarter of those to develop an NME [3]. By developing a more efficient and targeted method of delivery, there is an improved chance of the correct dose reaching the correct location for the desired therapeutic effects. This may also relieve some of the burden of rising healthcare costs, since less expensive drug candidates can be selected as well as lower doses administered. Most importantly, this will result in fewer side effects as only the diseased cells are targeted. Improvement to existing drugs will also allow for the extension of patents nearing expiry, allowing pharmaceutical companies to postpone the entry of generic alternatives to the market and delay the onset of substantial financial losses due to generics. For example, Prozac lost more than 80% of revenue in the US market once its patent expired, due to the entry of generic drugs [3].

Although the concept for targeted drug delivery has been known for many decades, there had not been significant breakthroughs. However, over the last few years, there have

Rachel Hevey

Alberta Glycomics Center and
Department of Chemistry,
University of Calgary, 2500
University Drive NW, Calgary

Chang-Chun Ling

Author for correspondence:
Alberta Glycomics Center and
Department of Chemistry,
University of Calgary, 2500
University Drive NW, Calgary
Alberta T2N 1N4 Canada
Tel.: +1 403 220 2768
Fax: +1 403 289 9488
E-mail: ccling@ucalgary.ca

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Figure 1. Vioxx: a non-steroidal anti-inflammatory agent voluntarily removed from the market after concerns arose regarding increased risk of heart attack and stroke after prolonged use.

been novel developments in molecular biology that help to identify biomarkers/receptors on diseased cell surfaces as well as in syntheses to obtain efficient delivery carriers; we believe that research in targeted drug delivery has never been so bright and possibly a new era is on the horizon.

Cancer therapies can particularly benefit from new drug formulations based on targeted delivery as traditional cancer therapies rely on the fact that cancerous cells grow and multiply more rapidly than healthy cells. Most existing drugs indiscriminately destroy both cell types and, thus, are cytotoxic to all fast-growing cells resulting in severe side effects, which can result in patients being unable to finish the recommended course of treatment. By using antigen–antibody or ligand–receptor targeting of

cancerous cells, healthy cells will be minimally affected as they do not contain the intended receptor or antigen, resulting in significantly lower side effects and also allowing for the administration of decreased drug doses.

Many targeting strategies have been reported: peptides, proteins and antibody fragments have been utilized as tags to deliver therapeutic agents to target cells [4,5]. In fact, the targeted moieties do not need to be internalized into the diseased cell. An example involving paclitaxel-loaded nanoparticles to target cancer cells illustrated that a strong antigen–antibody interaction at the cell surface (without internalization) resulted in localized drug activity in the tumor microenvironment, which successfully destroyed the intended tumor cells [6].

In cancer targeting, a large degree of research has been focused on folate receptors (FRs) which are over-expressed (100- to 300-fold increase) [7] on the surface of several types of cancer cells (FR α receptor), since folate conjugates can be internalized into FR-expressing tumor cells via receptor-mediated endocytosis. Studies on conjugates containing an imaging agent have illustrated that the conjugates are selectively internalized into tumor cells (and kidney cells where they are rapidly recycled back into the bloodstream), and studies involving folate–drug conjugates have demonstrated the selective destruction of FR-positive cell lines [8]. Folate has also been conjugated to paclitaxel-loaded micelles and nanoparticles, both of which display cytotoxicity selective for

Figure 2. Anticancer conjugate vaccine composed of a Tn tumor antigen and an L-rhamnose targeting moiety, which improves internalization of the vaccine into immune cells [12].

the FR-expressing cell lines [9,10]. The related FR β receptor is over-expressed on activated immune cells, and has been used for targeted delivery of drugs to treat inflammatory and autoimmune diseases; a recent example used folate conjugates to target activated macrophages for treatment against rheumatoid arthritis [11].

Targeting has also been used in vaccines to improve the immune response of poorly immunogenic antigens. Naturally present serum antibodies (e.g., those against L-rhamnose) can interact with the Fc-binding region on antigen presenting cells and, therefore, by using antigens conjugated to epitopes, which bind these serum antibodies, the vaccine constructs are better internalized by the antigen-presenting cells resulting in enhanced immunogenicity. This approach has been utilized in an anticancer vaccine in an effort to improve

immunogenicity of the Tn self-antigen, and, consequently, resulted in a twofold increase in the anti-Tn titer response in mice (**FIGURE 2**) [12].

Recently, a number of other carbohydrates have been used for cellular targeting; their extensive structural variation often results in the expression of novel structures on particular cell types. For example, the Lewis Y oligosaccharide is overexpressed on a number of epithelial cancers, and a recent study illustrated that a monoclonal antibody recognizing the Lewis Y structure could be used to selectively deliver siRNA to tumor cells [13]. Plant lectins have also been studied in an effort to establish whether or not they can selectively bind the unique carbohydrates expressed at the surface of human urothelial carcinoma cells [14]. It was observed that wheat germ agglutinin was most successful in entering the diseased cells, although peanut agglutinin illustrated the best

Figure 3. Functionalized polycationic cyclodextrin that can be used as a vehicle for targeted DNA and RNA delivery.

selectivity between healthy and cancerous cells. Carbohydrates can also be used as ligands to target cell surface receptors. For example, galactosylated chitosan is selectively recognized by asialoglycoprotein receptors expressed on hepatocytes, and studies have illustrated that galactosylated chitosan–DNA complexes can be selectively internalized into the liver as a method of delivering therapeutic DNA sequences to diseased cells [15]. In addition, mannose has been conjugated to polycationic cyclodextrin, loaded with plasmid DNA, and then selectively transfected into cells expressing mannose-specific lectins, such as concanavalin A or the human macrophage mannose receptor (FIGURE 3) [16].

Receptor targeting has also been used to develop new routes of drug administration, which can improve patient compliance by developing less invasive administration methods. This has been achieved by targeting the Fc receptor expressed in the upper airway (characteristic of primates), which can internalize IgG–drug conjugates upon inhalation of the compound into the lungs [17]. The conjugates are internalized via pinocytosis and then transported into the patient's circulatory system. One of the more promising examples involves an erythropoietin conjugate where inhalation administration has been demonstrated to have a comparable efficacy to traditional subcutaneous injection [18]. In fact, the pulmonary administration of conjugates targeting these bronchial Fc receptors (in a

number of cases) has demonstrated comparable bioavailability to more standard approaches of administration [17].

In conclusion, in a challenging market with decreasing investment capital and rapidly increasing research costs, we believe that there are multifaceted benefits if we shift our major R&D efforts to the development of new drug formulations to improve an old drug's efficacy. This could especially benefit the field of cancer chemotherapeutics, since the lower doses and selective nature of targeted drugs should enable a greater number of patients to proceed further in their desired treatment protocols. A number of recent examples have been shown to enhance an existing drug's activity, decrease its side effects, and even lead to the development of new therapeutic avenues. Such an adjustment in the R&D strategy will ultimately prove to alleviate the financial burden faced by all pharmaceutical companies and ultimately benefit society.

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