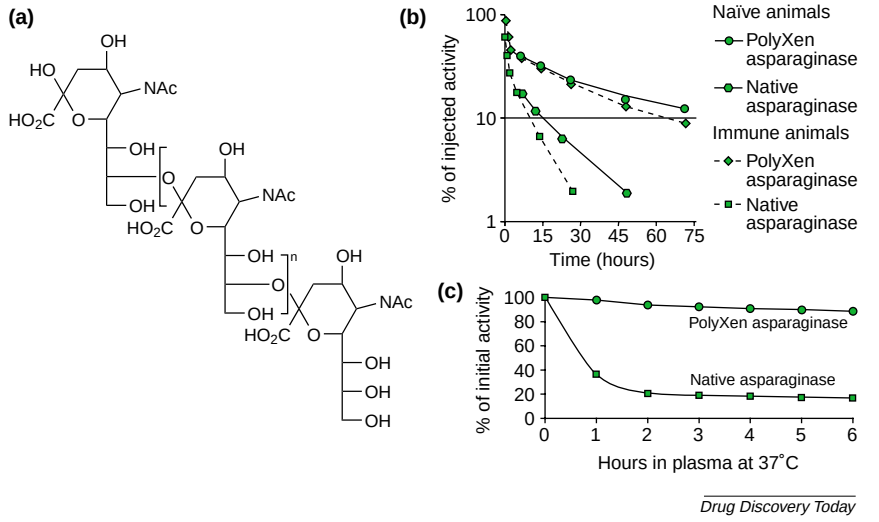

Figure 1. (a) The biopolymer polysialic acid (PSA) **(b)** extends half life (solid line) and reduces antigenicity (broken line) **(c)** and retains activity of conjugated drug .

deamidation and oxidation), that can result in heterogeneity of a monodisperse product. The issue of heterogeneity in biological materials is identified as a challenging and controversial problem facing the World Health Organization biological standardization program [3]. I agree in principle that biological materials, including biopolymers, do posses a defined structure, biological function and fate, but I am not confident that we posses all the facts in relation to either polymers or biopolymers.

Perhaps biopolymers do offer a greater potential for exploitation than synthetic polymers; biopolymers might be able to avoid the many chemical contaminates that have been suggested to exert immunotoxicity, cited by Hunter and Moghimi. Numerous groups, including Gregory Gregoriadis [4], have advocated and demonstrated the value of biopolymers in relation to drug delivery (Fig. 1). Polysialic acids (PSAs) are naturally occurring hydrophilic polymers of sialic acid, which are known to be biodegradable with non-toxic catabolic products. PSAs are used by bacteria to escape recognition by the immune system of the host and are evolved to be immunologically evasive. Although a substantial number of issues raised also need to be addressed by workers using biopolymers, the list might not be as large as for synthetic polymers.

Hunter and Moghimi suggest a paradigm shift in relation to synthetic polymer thinking; I would like to add that immunotoxicity is not all bad. This statement is supported by a recent paradigm, that of the danger model [5] introduced into the field of immunology, and has implications related to vaccine products in my own area of interest.

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Polymer therapeutics – what is missing? ▼

The recent review by Hunter and Moghimi [1] covers a broad area; polymer therapeutics, polymers used in new chemical entity (NCE) formulation and polymer–drug conjugates – I will restrict my comments to the third class of polymer. A limited range of (homo)polymers is listed by the US regulatory authorities as being biologically inert (http://www.fda.gov/cder/drug/iig), although the FDA make the point that this might not always be the case. Few of these homopolymers are listed for parenteral use and most have simple and uncharged residues.

Success for polymer therapeutics can only be judged by clinical success, which is most likely to be achieved by industrial rather than academic organizations. All of the concerns raised in the review article have been considered by companies in depth (there are pegylated drugs on the market), but they have not been effectively communicated to academia, where much of the primary research is conducted. It is easy to make a polymer conjugate but the knowledge of how to convert it into a marketable drug is often missing (compared with NCEs). The analytical burden of many polymer systems described in the literature would make them non-viable as drug candidates.

The regulatory authorities and corporate analytical departments prefer chemistries where the regiochemistry is defined and there are specific points of attachment of drugs. Bear in mind that all impurities have to be identified down to a few percent in a manufacturing process and that few reactions go to completion. Low molecular weight impurities can be quantified readily, but drugs with a polydisperse core are particularly troublesome. Techniques for analyzing the drug metabolism and pharmacokinetics (DMPK) of such polymers *in vivo* are also essentially

missing. It is difficult to find low abundance molecular ions from each species present in blood or tissue, let alone to quantify them. Polydispersity can be reduced in part using dendrimer chemistry or by controlling polymerization – currently neither approach would give what a development analyst would call a single species.

Immunogenicity is an essential part of the screening cascade for all macromolecular drugs. The problem is that such testing can only be conducted with certainty in man and must deploy a sensitive assay; a negative result can imply an inadequate assay. Immunogenicity is normally evaluated relatively late in the development process and, as such, is both costly and crucial. It is well known that the immunogenicity of polymers is raised by functionalization and for most polymer therapeutics this is unavoidable; one has to rely on the less than certain immunosuppressive properties of the homopolymer (*sic*).

It is conceivable that the technical problems can be overcome but the main driver for investment is major commercial success; to date, this has failed to materialize for polymer–drug conjugates. A current focus of polymer therapeutics is in exploiting the enhanced permeability and retention phenomena seen in animal tumour models; unfortunately, results seen in the clinic are modest. For companies to invest in a development candidate it must show a striking advantage in demanding and realistic preclinical models and also in the clinic. If it does not, corporate management will inevitably invest in more tractable candidates.

It is likely that the experience gained by companies in taking protein drugs through the clinic and onto the market will enable them to evaluate the risks with synthetic polymers. They will have the expertise in DMPK, clinical assays and physical assays to select the right candidates to progress.

Reference

1 Hunter, A.C. and Moghimi, S.M. (2002) Therapeutic synthetic polymers: a game of Russian roulette? *Drug Discov. Today* 7, 998–1001

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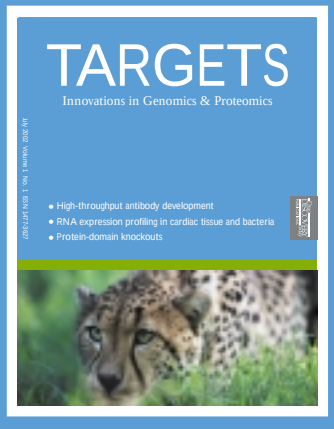

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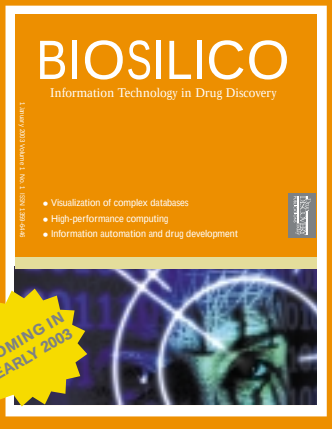

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