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Polymer therapeutics: Top 10 selling pharmaceuticals — What next?

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ABSTRACT

At the time of the first issue of the Journal of Controlled Release (JCR), polymeric drugs, polymer–drug and protein conjugates and block copolymer micelles carrying bound drugs, i.e. polymer therapeutics, were still regarded as scientific curiosities with little or no prospect of generating practical to use medicines. How this perception has changed. Many major Pharma now have R&D programmes in this area and in 2013 two polymer therapeutics, Copaxone® and Neulasta®, are featured in the Top 10 US pharmaceutical sales list. Although there are a growing number of marketed products (e.g. PEGylated proteins, a PEG-aptamer and oral polymeric sequestrants), and the first follow-on (generic products) are emerging, the first polymer–drug conjugates and block copolymer micelle products (as covalent conjugates) have yet to enter routine clinical use. Industrial familiarity and recent advances in the underpinning scientific disciplines will no doubt accelerate the transfer of polymer therapeutics into clinically useful medicines and imaging agents. This short personal perspective reflects on the current status of polymer therapeutics and the future opportunities to improve their successful translation. It adds to recent and historical reviews that comprehensively document the evolution of the field since JCR was born.

1. Introduction

Last year, in a review written to mark the 25th Anniversary of Advanced Drug Delivery Reviews entitled "Polymer therapeutics-prospects for the 21st century: The end of the beginning" [1] we noted that the field has "… come a long way since its beginnings, and arguably polymer therapeutics have been amongst the most successful first generation nanomedicines (reviewed in [2])". Progress continues with two polymer therapeutics being featured in the US Top 10 selling drugs list for 2013 [3], Neulasta® and Copaxone®, and more products are arriving to market as innovator (new) products (e.g. Lymphoseek® (Tilmanocept), a mannonsylated dextran-based sentinel lymph node imaging agent for melanoma and breast cancer patients [4]), and also into clinical trial as 'follow-on' (generic) products (e.g. PEG-G-CSF (DA-3031) [5]). This short personal perspective adds to past comprehensive reviews that have documented, the evolution of both basic and applied research over the lifetime of JCR (e.g. [6]), the introduction of polymer therapeutics as clinically important medicines [7,8], the challenges they present for clinical development [9], and not least the future opportunities and challenges for commercialisation as medicines, imaging agents and theranostics [1,10]. Despite the above-mentioned successes, the first polymer–drug conjugates, drug conjugated micelles and polymer-based non-viral vectors designed for cytosolic delivery of biopharmaceuticals have yet to enter the market. As we celebrate the 30th birthday of the Journal of Controlled Release (JCR) it is interesting to reflect on the current status and future opportunities to increase translation of current and newly emerging technologies from lab to clinical use.

2. From hypothesis to clinically useful medicines

2.1. JCR: the emergence of polymer therapeutics into clinical use

A glance at the index pages of the first two Issues of JCR (1984) show that by far the primary interest at that time was advanced drug delivery systems/controlled release formulations for human applications with papers describing transdermal patches, vaginal pessaries, a powder dosage form for intranasal administration of insulin, and proposal of sophisticated parenteral delivery systems such as a self-regulating insulin delivery system and polymer matrices containing magnetic beads to trigger drug release. (The latter were way ahead of their time!) In 1984 there was already a rapidly growing interest in design and evaluation of first generation nanomedicines for improved drug targeting, triggered drug release, and improvement of drug passage across biological barriers. The approaches then being investigated included liposomes, polymer-based, and lipidic, nanoparticles, antibody–drug, polymer–drug and polymer–protein conjugates (this history is discussed in [2]). Surprisingly studies involving most of these technologies were not featured in the first issues of JCR (1984). The only exception being two papers of Schacht and colleagues describing the synthesis and

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characterisation of polysaccharide (dextran and inulin)-procainamide conjugates [11], and via our collaboration, their pinocytic uptake by cells *in vitro* [12]. The latter study is particularly notable given the now growing appreciation of the importance of defining cellular and whole body pharmacokinetics of polymer therapeutics [13,14]. Indeed a review on "endocytosis of nanomedicines" [15] is amongst the most cited articles in JCR over the last 5 years!

Natural polymers have been used for millennia as components of herbal remedies, so it would be wrong to suggest that polymer therapeutics per se are "novel", but the rational design of polymer-based therapeutics did begin in earnest in the second half of the 20th century following the arrival of synthetic polymer chemistry (discussed in [1]). Early contributions are worthy of note; polymers as drugs (especially antibacterial agents and immunomodulators) [16–18], radioprotectants [19], polymer–drug [6,20] and polymer–protein conjugates [21,22], and block copolymer micelles [23]. Experience gained with natural and synthetic polymers explored clinically over the last century gave first insights into polymer characteristics important for quality, safety and efficacy (i.e. those factors governing risk-benefit for clinical use). The iron–dextran complexes were first introduced as intravenous (i.v.) iron replacement infusion solutions in the 1940s and the properties (characteristics/safety) of the polymers and oligomers used to stabilise such iron complexes are still widely discussed in terms of features governing clinical safety and efficacy [24].

2.2. Learning from recent clinical successes and failures

During the lifetime of JCR several distinct classes of polymer therapeutics have progressed into first-in-man clinical trials and moreover into routine clinical use (comprehensive lists given in [1,2]). All involve a synthetic (e.g. PEG, HPMA copolymers, crosslinked polyamines), a pseudosynthetic (e.g. polyglutamic acid (PGA), lysine-based dendrimers) or a natural polymer (e.g. dextran, polysialic acid, alginate oligomers) as the core component. Products have been developed for different routes of administration (e.g. oral, intravenous (i.v.), subcutaneous (s.c.), intramuscular (i.m.), topical and intra-vitreal), and for a diversity of clinical applications as drugs, sequestrants or imaging agents. Moreover, products designed as conjugates for drug targeting and/or controlled release can contain a diverse array of therapeutic (or imaging) payloads including low molecular weight drugs (e.g. the anticancer conjugates containing doxorubicin, paclitaxel, and camptothecins), and biopharmaceuticals including peptides or proteins and aptamers/siRNA.

2.2.1. Polymer conjugates of biopharmaceuticals

Market approval in the early 1990s of the first polymer–protein conjugates (e.g. Zinostatin stimalmer (styrene maleic anhydride neocarzinostatin, SMANCS) in Japan, PEG-adenosine deaminase (Adagen®) and PEG-asparaginase (Oncaspar®)) was a pivotal landmark in the history of polymer therapeutics (discussed in [7]). PEGylation [22] is now an accepted tool, and the composition of biopharmaceutical conjugates is increasingly well-defined (usually a 1:1, PEG: protein/aptamer). Many improved synthetic routes have emerged (current status reviewed in [25]), and products developed for a diverse array of clinical indications, e.g. as antiviral agents, anticancer agents, as an adjunct to chemotherapy, and to treat arthritis, gout and age-related macular degeneration. FDA approval in the early 2000s of two PEG-interferon conjugates (PEG-Intron®; PEG-ASYS®) for s.c. injection to treat chronic hepatitis C gave the field heightened visibility. Their use has subsequently been broadened to other indications with PEG-interferon α-2b (Sylatron™) now approved (2011) as an adjuvant therapy for treatment of high-risk melanoma [26], and a PEG-interferon-β-1a conjugate is currently being tested in Phase III clinical trials as a treatment for multiple sclerosis [27].

PEG conjugation of proteins, peptides and more recently aptamers (Macugen® was the first approved aptamer-based drug, discussed in [28]), is typically undertaken to improve the pharmacokinetic profile (increased plasma half-life, longer absorption profile), and reduce antigenicity and immunogenicity, especially of non-human proteins. The molecular weight of the PEG, site of conjugation and linking chemistry used, together with the clinical indication for use can all influence performance in terms of safety/efficacy. Although both PEG–interferon conjugates are used in combination with ribavirin to treat hepatitis C their composition is very different. PEGASYS® consists of recombinant human alfa-2a interferon conjugated to a single branched PEG of molecular weight ~40,000 g/mol whereas PEG-Intron® contains recombinant human interferon alfa-2b conjugated to a single chain PEG of molecular weight ~12,000 g/mol. The impact of the pharmacokinetic–pharmacodynamic (PKPD) properties of these conjugates on their relative safety and efficacy is still much debated [29]. The PEG-recombinant granulocyte colony-stimulating factor (G-CSF) (Neulasta®) contains ~20,000 g/mol PEG, and it perfectly illustrates the benefit of prolonged circulation compared to the unmodified protein. Neulasta® was approved by the FDA in 2002 for s.c. administration to cancer patients in order to minimise chemotherapy-induced neutropenia. The reduced rate of renal elimination of GCSF by PEGylation enables a single injection per chemotherapy cycle, which is a significant advantage for the patient compared to the ~10 daily injections required when using G-CSF alone (reviewed in [30]).

Two decades of clinical experience with PEG conjugates has generated a significant post-marketing database relating to clinical outcomes. In most cases benefits of PEGylation have been clearly shown to outweigh disadvantages. Moreover, although it was often suggested that cost of manufacture of polymer therapeutics would prohibit their commercialisation, pharmacoeconomic studies have demonstrated the cost-effectiveness of PEGylated products in almost all cases (discussed in [31]). As early PEG conjugates now start to come off patent, their healthcare contribution and commercial success have stimulated an eagerness to enter the market with first "follow-on" products, e.g. Phase II evaluation of DA-3031, a PEGylated G-CSF [5]. There is currently considerable debate as to the regulatory requirements needed to ensure equivalence of quality, safety and efficacy of complex, multi-component "follow-on" nanomedicines in general as they cannot simply be assessed using the classical procedures established to define bioequivalence of low molecular weight generic drugs (discussed in [32,33]). In parallel studies describing the design of more controlled industrial scale manufacturing processes [34], improved purification techniques [34,35] and improved validated analytical methods for conjugate characterisation [36] can be seen.

Safety concerns have however been voiced regarding the use of PEGylation. Intravenous administration of Doxil® (a PEGylated liposomal doxorubicin) can cause infusion reactions, albeit this is in <10% of patients and can be easily managed clinically. Certain PEG–protein conjugates have also demonstrated hypersensitivity reactions, which it has been suggested, is due to induced or pre-existing anti-PEG antibodies. Immunosuppressive strategies were recently proposed to minimise risk of infusion reactions when treating gout in patients using PEG-recombinant porcine uricase given i.v. (Krystexxa®) [37]. Why some patients exhibit infusion reactions while others do not remains unclear. Some argue that the PEG component triggers production of anti-PEG IgM antibodies [38]. However others state that, "most, if not all assays for anti-PEG antibodies are flawed and lack specificity" highlighting the need for "standardisation of the anti-PEG assays and the development of reference sera" [39]. The debate continues, but it is important to remember that the diversity of therapeutic, PEG molecular weight and linking chemistry will all play a part in the product toxicological profile seen in a particular clinical setting.

Certain PEG conjugates have recently displayed unacceptable toxicity which caused termination of clinical trial/use. While PEG–L-asparaginase (Oncaspar®) is now a standard therapy for paediatric acute lymphocytic leukaemia (ALL), in a recent Phase II clinical trial in advanced ovarian cancer patients, PEG–L-asparaginase was very poorly

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