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# Polymer therapeutics-prospects for 21st century: The end of the beginning ☆

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ABSTRACT

The term "polymer therapeutics" was coined to describe polymeric drugs, polymer conjugates of proteins, drugs and aptamers, together with those block copolymer micelles and multicomponent non-viral vectors which contain covalent linkages. These often complex, multicomponent constructs are actually "drugs" and "macromolecular prodrugs" in contrast to drug delivery systems that simply entrap (non-covalently) therapeutic agents. They have also been described as nanomedicines. First polymer–protein conjugates entered routine clinical use in 1990 and a growing number of polymeric drugs/sequestrants and PEGylated proteins/aptamers have since come into the market. Valuable lessons have been learnt over >3 decades of clinical development, especially in relation to critical product attributes governing safety and efficacy, the validated methods needed for product characterisation. Not least there has been improved understanding of polymer therapeutic-specific biomarkers that will in future enable improved selection of patients for therapy. Advances in synthetic polymer chemistry (including control of 3D architecture), the move towards greater use of biodegradable polymers, polymers delivering combination therapy, increased understanding of polymer therapeutic critical product attributes to guide pharmaceutical development, and advances in understanding of endocytosis and intracellular trafficking pathways in health and disease are opening new opportunities for design and clinical use of polymer-based therapeutics in the decades to come.



**Contents**



## 1. The beginnings

### 1.1. Introduction

On the occasion of the "25th birthday" of Advanced Drug Delivery Reviews it is timely to reflect on the progress made across the polymer therapeutics sector (Fig. 1a), and consider the potential for further developments into the 21st Century. The field has certainly come a long way since its beginnings, and arguably polymer therapeutics have been amongst the most successful first generation nanomedicines (reviewed in Ref. [1]) considering the relatively modest investment made in these technologies (active researchers and funding) during the last quarter of the 20th Century compared to liposomes, nanoparticles, biodegradable polymeric implants and immunoconjugates and other advanced drug delivery systems for oral delivery. It is truly the "end of the beginning"! In 2013 we celebrate the 60th anniversary of the 1953 Hermann Staudinger Nobel Prize, the first awarded for "polymer" chemistry. Not only did Staudinger give us the concept of covalently linked "macromolecules" he foresaw the potential of their use in

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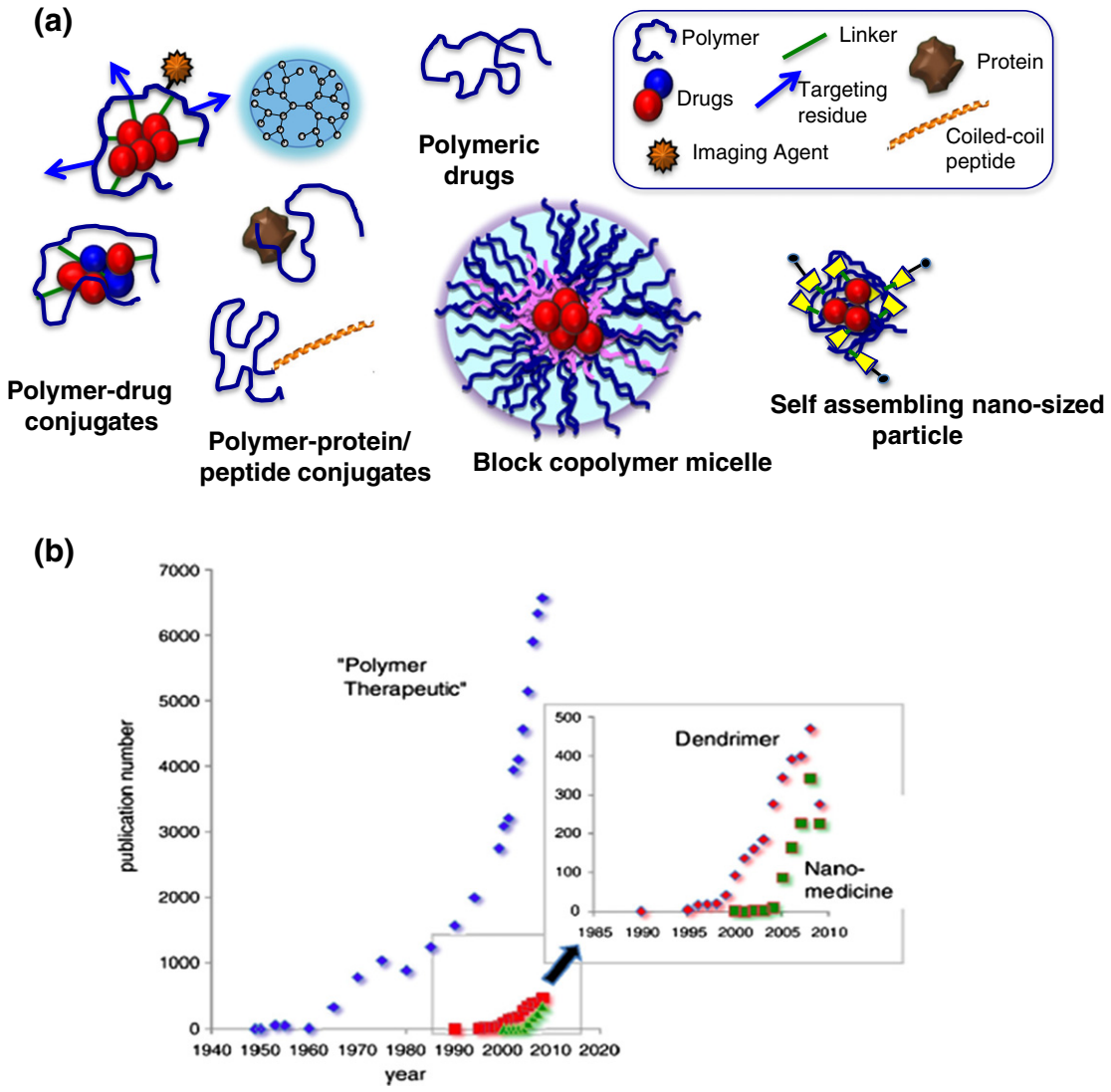


**Fig. 1.** Polymer therapeutics. Panel (a) shows a schematic of the sub-classes of polymer therapeutic and panel (b) a comparative "pubmed" literature search against the phrase "Polymer Therapeutic" and the words "Dendrimer" and "Nanomedicine" (from Ref. [58]).

biomedical applications [2,3]. (Staudinger liked to use the overarching term "macromolecules" but to note polymer therapeutics discussed here natural, pseudo-synthetic and synthetic polymers as seen as the platform not biotech drugs and delivery systems). His Nobel lecture also acknowledged that "..... macromolecular chemistry appears today to fit between low molecular organic chemistry and cytology....." [2], wise words indeed given our continuing interdisciplinary attempts to treat diseased cells using polymer-based therapeutics often designed to navigate their endocytic pathways for lysosomotropic or endosomotropic (cytosolic) drug delivery [4,5]. Just as the turn of the last century witnessed landmark changes in our understanding of macromolecular chemistry (Staudinger [2]), phagocytosis (Mechnikov [6]), and the potential of synthetic low molecular weight chemotherapy and drug targeting (Ehrlich [7]), the beginnings of the 21st century have been equally inspiring. The last decade has witnessed some remarkable advances in the understanding of the molecular basis of many diseases [8], the molecular basis of the endocytic machinery in health and disease [9], and not least, in nano- and material-science focused towards medical applications—the birth of "nanomedicine" as a new discipline (reviewed in Ref. [1] and references therein). Thus the landscape for design, preclinical evaluation, and clinical use of polymer therapeutics is rapidly changing and future successes will rely on our ability to embrace all the emerging opportunities and apply them to design and development of the next generation technologies.

It would be inappropriate to simply revisit all of the topics/primary papers that we have already comprehensively reviewed in recent reviews published in this journal and elsewhere (see Refs. [10–19]). Therefore here, and in the spirit of this "birthday" issue, we have collated some of the key points to illustrate the historical journey of polymer therapeutics from lab to clinic, to briefly discuss the current status, and most importantly try to highlight some of the emerging opportunities and challenges facing polymer therapeutics today, and in the foreseeable future. It is interesting to consider how polymer therapeutics might be used clinically as this century progresses and what percentage of the therapeutic market will they hold? To note, this short overview relies heavily on these recent key reviews as a reference point, so the reader is directed to their extensive bibliography for a more comprehensive listing of landmark primary papers.

### *1.2. Evolution of polymer therapeutics*

Since the 1940s synthetic polymers have been explored as therapeutics with a dramatic increase in publications year on year (Fig. 1b). The number of papers in 2011 interestingly rose to ~9.000, still some 10-fold