Polymeric Drugs: A Novel Approach to Drug Delivery System

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ABSTRACT
This review article describes the current status and recent advances of polymeric drugs with regard to their application in drug delivery system. Essentially polymer-drug conjugation aims to achieve improved drug targeting, decrease drug toxicity and overcome mechanisms of drug resistance. First generation conjugates used linear monomethoxy PEGs and other linear polymers. Modern polymeric chemistry is increasingly producing new polymeric architectures such as dendrimers, hyper branched polymers and hybrid macromolecular structures (such as star polymers, linear graft and dendronized linear polymers and novel therapeutic siRNA. This undoubtedly can be employed for designing of second generation polymer therapeutics. Clinical approval of products such as Copaxone®, Renagel®, Vivagel® and Welchol® have been successful in developing interest in polymer therapeutics as a growing field of research and development. In conclusion, there is emerging data that polymer drug conjugation has become useful in a wide range of treatments from infectious to chronic diseases such as cancer. Polymer therapeutics holds promising future applications in the field of nanotherapeutics.

Keywords: Polymeric drugs; drug delivery; dendrimers; PEGs; Clinical trials.

Introduction

The concept of polymer drug conjugate was proposed as early as 1975. For this purpose, a drug is covalently bound to a polymeric carrier, normally via a biodegradable linker (Ringsdorf, 1975). Polymeric drug conjugate systems include polymeric drugs, polymer-drug conjugates, polymer-protein conjugates, polymeric micelles to which drug is covalently bound, multi-component polyplexes that are being developed as non-viral vectors (Duncan, 2003).

These are water soluble, multicomponent constructs considered as “new chemical entities” (NCE’s) by regulatory agencies and from the industrial standpoint they are considered as the “First Polymeric Nanomedicines” (5 – 100 nm) (Canal et al., 2011). In general polymer drug conjugates offer following advantages:

(a) Biocompatible polymer.
(b) Ability to carry the required payload of the drug.
(c) Avoid rapid liver uptake (unless targeted for delivery).
(d) Protect the premature metabolism or liberation of drug in transit.
(e) Linker chosen should be stable in circulation but amenable to specific enzymatic or hydrolytic cleavage.
(f) Drug bound must be stable in lysosomal environment.
(g) Active drug must be liberated at a rate appropriate to its mechanism of action.

The success of polymer drug conjugates can be gauged from the fact that, a number of polymeric drugs have entered the market since the 90’s, but these have still not been able to reach the desired goal. Futuristic strategies towards handling of polymer drug conjugates include:

1. Designing new polymer-drug conjugates for other diseases rather than cancer.
2. The development of polymer-based combination therapy.
3. Optimization of the characterization methods to transform the candidate for clinical evaluation.
4. Lastly, better understandings of the characteristics of polymer conjugate to avoid the risks involved and achieve new possibilities for personalized therapies.

The Evolution of Conjugates

Ringsdorf model shows that polymeric conjugates typically consist of a tripartite design: the polymer, the linker and the payload (drug or protein) (Ringsdorf, 1975) (Fig. 1).
Although in proteins, each molecule has a specific amino acid sequence, but not all polymer chains in a batch have similar structure. Hence, the molecular mass and the physiochemical properties of the polymer are the most important factors governing bioavailability of the conjugate as a whole (Markovsky et al., 2012). Polymer used must be “biocompatible” so as to justify its non-toxic or non-immunogenic (Gaspar et al., 2009) and biodegradable nature (Duncan et al., 2001). The polymeric chain mainly functions as the inert structural component of the conjugate for specific targeting or targeted drug delivery systems (Vicent, 2006).

Various natural polymers, most usually, polyanions and polycations, have been popularly known to possess antiviral and antitumor activity (Duncan, 2003). On the same origin, DIVEMA—a copolymer of divinyl ether and maleic anhydride; an immunostimulant with antineoplastic and anti infective properties was introduced as the first synthetic polyanionic medicine. However, it failed in early clinical trials due to its severe toxicity (Regelson, 1986).

Based on the lessons learnt due to early clinical failures, current efforts are directed towards more sophisticated bioconjugation approaches, which follow studies related to a pioneering work done by Davis and Abuchowski, who PEGylated proteins which heralded the birth of a new class of anticancer agents (Davis, 2002 and Nucci, 1991).

Since then PEGylation has been the technique of choice in the last three decades (Harris, 2003) as it fulfilled all the specific requirements needed for optimized synthesis of the conjugates such as site-specific modification and appropriate linking, to maintain biological activity without liberation of toxic by-products (Pasut et al., 2004). Besides, PEG does not present any risk to humans due to its low quantity and low toxicity profile (Webster, 2007).

Moreover, regulatory approval of polymer-protein conjugates (such as PEG-adenosine deaminase namely, ADAGEN for severe combined immunodeficiency (SCID) syndrome in 1990 (Levy et al., 1988) and PEG–L–asparaginase (ONCASPAR) (Graham, 2003) used to treat acute lymphoblastic leukemia in the year 1994 has been a breakthrough that lead to the exponential growth of interest in this field.

The past two decades have effectively lead to the foundation for the design of each of the sub-class of polymer therapeutics and this has given birth to a pipeline of compounds that are suitable for both clinical development and routine clinical use (Table 1). Apart from PEG, another polymer i.e. hydroxy propyl methacrylamide (HPMA) is a milestone in the clinical development of this field (Table 2). Due to its appealing properties such as non – toxic, non – immunogenic, multiple pendant side chains to carry drug (in contrast to PEG having two functional groups) made HPMA the preferred linker for development as an anticancer drug carrier platform (Duncan, 2009). However, early studies and clinical failure of PNU166945Tm (HPMA copolymer PTX conjugate; caused drug liberation during renal elimination) (Meerum, 2001) and MAG-CPT (HPMA copolymer-PTX conjugate; caused neurotoxicity) yielding unspecific drug release (Schoemaker et al., 2002) warrant a second opinion.

### Table 1
PEGylated protein/drug/aptamer conjugates on the market or in clinical development.

<table>
<thead>
<tr>
<th>Description</th>
<th>Name</th>
<th>Indication</th>
<th>Stage</th>
<th>Year</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG–adenosine deaminase</td>
<td>ADAGEN</td>
<td>SCID syndrome</td>
<td>Market</td>
<td>1990</td>
<td>Enzon</td>
</tr>
<tr>
<td>PEG–interferon-α-2b</td>
<td>PEGINTRON®</td>
<td>Hepatitis C</td>
<td>Market</td>
<td>2000</td>
<td>Enzon</td>
</tr>
<tr>
<td>Styrene maleic anhydride- neocarzinostatin (SMANCS)</td>
<td>ZINOSTATIN, STIMALMER®</td>
<td>Hepato cellular carcinoma</td>
<td>Market</td>
<td>1993 (Japan)</td>
<td>Schering-Plough</td>
</tr>
<tr>
<td>PEG–interferon-α-2a</td>
<td>PEGASYS®</td>
<td>Hepatitis C</td>
<td>Market</td>
<td>2002</td>
<td>Roche</td>
</tr>
<tr>
<td>PEG–human growth hormone(HGH)</td>
<td>PEGVISOMANT SOMAVER®*</td>
<td>Acromegaly</td>
<td>Market</td>
<td>2003</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>PEG–granulocyte– colony stimulating factor (G-CSF)</td>
<td>PEG-filgrastim, (Neulasta®or Neupogen (filgrastim))</td>
<td>Prevention chemotherapy associated neutropenia</td>
<td>Market</td>
<td>2002</td>
<td>Amgen</td>
</tr>
<tr>
<td>PEGylated Fab fragment of a humanized TNF inhibitor monoclonal antibody</td>
<td>CIMZIA®*</td>
<td>Treatment of Crohn’s disease Rheumatoid a.rthritis</td>
<td>Market</td>
<td>2009</td>
<td>UCB Pharma</td>
</tr>
<tr>
<td>PEGylated anti – VEGF aptamer</td>
<td>PEGAPTANIB (MACUGEN®*)</td>
<td>Treatment of neovascular age related macular degeneration</td>
<td>Market</td>
<td>2004</td>
<td>Pfizer</td>
</tr>
<tr>
<td>PEGylated pegaptanib</td>
<td>PEGESPATIDE®*</td>
<td>Anemia associated with CKD patients</td>
<td>Phase III</td>
<td>Pending approval</td>
<td>Affymax and Takedo</td>
</tr>
<tr>
<td>PEG-EPO</td>
<td>MIRCERA®</td>
<td>Anemia associated with chronic kidney disease (CKD)</td>
<td>Market</td>
<td>2007</td>
<td>Roche</td>
</tr>
<tr>
<td>PEG-Uricase</td>
<td>KRYSTEXXA® (pegulase )(formerly known as PURICASE®)</td>
<td>Gout</td>
<td>Market</td>
<td>2010</td>
<td>Savient</td>
</tr>
<tr>
<td>PEG-Camtothecin</td>
<td>PROTHECAN</td>
<td>Various cancers</td>
<td>Market</td>
<td>1999</td>
<td>Enzon</td>
</tr>
</tbody>
</table>

SCID, severe combined immunodeficiency; TNF, tumour necrosis factor; PEG, polyethylene glycol.

*CIMZIA (Certolizumab pegol)(CDP870) is a therapeutic monoclonal antibody mainly directed against tumour necrosis factor alpha.

**PEGESPATIDE is a synthetic, PEGylated peptidic compound that binds to and stimulates the erythropoietin receptor and thus acts as an erythropoiesis stimulating agent (ESA). If approved, PEGESPATIDE will be the first once – monthly ESA available for the treatment of anemia associated with CKD patients on dialysis in the US. FDA had announced an action date of March 27, 2012 under the Prescription Drug User Fee Act, (PDUFA) which is still pending.
A stream of modified polysaccharides, synthetic polypeptides and synthetic polymers has also been successfully transferred into the market as polymeric drugs (Breslow, 1976). For example, in gel form, dextrin-2-sulphate (Emmelle®) is now approved for use as an intravaginal virucide (Beer, 2002).

Although most of the linear polymers such as polyethylene glycol (PEG), N-(2-hydroxypropyl) methacrylamide (HPMA), poly (vinyl-pyrrolidone) (PVP), dextrin etc. and their conjugates have been successfully transferred to the clinics, yet, there is a pressing need to move towards better defined polymers.

To meet this need of the hour pharmaceutical companies have moved forward to develop different polymers with superior qualities as compared to the existing ones. Certain examples in this category include pH – responsive polyacetal Fleximer®, a biodegradable polymer developed by Mersana Therapeutic Inc. which has been utilized for advancing in the category of next generation antibody-drug conjugate (ADC) with superior properties not found with current generation ADCs (Papson, 2005). Mersana’s product pipeline includes XMT-1001 (novel camptothecin conjugate, currently being investigated in a phase 2 clinical trial in patients with lung cancers) (Yurkovtskiy, 2009 and Mersana Therapeutics). The company is also conducting a phase 1 study of intravenous XMT-1001 in patients with Stage IV non-small cell lung carcinoma (NSCLC) and small cell lung cancer to study its safety, tolerability, and pharmacokinetics. The study is reported in clinicaltrials.gov under license number NCT00455052. The antitumor efficacy of XMT-1001 was also compared to irinotecan (CPT-11) in mice bearing HT-29 human colon carcinoma xenografts, which demonstrated an improved antitumor effect (Walsh, 2012).

Another candidate is XMT-1107, licensed to Teva in 2010, is an anti-angiogenic fumagillin (TNP470) analog conjugate (Akullian, 2009). Earlier drugs in this class have shown promising activity in the clinic but were discontinued due to reversible neurologic toxicity. However, conjugation of fumagillin to Fleximer using a specific linker technology reduced CNS exposure in animal models (Fumagillin, 2012). The company is still recruiting participants in a phase 1 study of XMT-1107 to determine the maximum tolerated dose when given via IV once every three weeks to patients with advanced solid tumors. The study is reported in clinicaltrials.gov under license number NCT01011972.

Many other pharmaceutical industries are entering the race to develop novel polymeric drug conjugates. Another example includes that of Serina Therapeutics Inc., a relatively new company created pharmaceutical candidates using POZ (polyoxazoline), a safe, water soluble polymer with PEG-like properties (Adams, 2007 and Viegas, 2011). SER-201, SER-203 and SER-207 are the three major pipeline products of the company. Serina is advancing its lead clinical oncology candidate SER-203 into Phase I study in refractory cancer in early 2013 (Serina Therapeutics) Novel POZ conjugates of rotigotine have also been prepared with three linker chemistries allowing different rates of release, i.e. SER-212 (fast), SER-213 (intermediate) and SER-214 (slow) for treatment of Parkinson’s disease. It was reported that SER-214 showed significant duration of anti-Parkinson activity in comparison to un-conjugated rotigotine or any other dopamine therapies. It is being investigated as once a week injection (s.c.) to treat Parkinson patients and by 2013 the company reports to advance into Phase I study in humans (Moreadith, 2012 or Serina Therapeutics). Cerulean Pharma Inc. a clinical – stage company specializing in the design and development of tumour–targeted nanoporpharmaceuticals has developed CRLX101 (formerly IT-101, conjugate comprising of camptothecin coupled with cyclodextrin) (Davis, 2009). The conjugate has effectively demonstrated positive results in phase I/IIa trials in patients with NSCLC. Based on these encouraging phase I/IIa clinical data and non-clinical findings, the company enrolled patients in a randomized phase 2 clinical trial in NSCLC patients, who have progressed through one or two prior regimens of chemotherapy and successfully achieved its target of enrolling 150 patients in July, 2012 (Cerulean Therapeutics, 2012). Cerulean has even begun phase I b/II study of CRLX101 in combination with Avastin in renal cancer as well as the company has dosed its first patient in a phase II study in a platinum-resistant ovarian cancer patients (Cerulean Therapeutics, 2012) (Fig. 2).

 EZN2208, a water soluble polyethylene glycol (PEG) conjugate of SN38 (10-hydroxy-7-ethyl-camptothecin: derivative of camptothecin family) - a potent topoisomerase I inhibitor and the active moiety of CPT-II (camptostar, irinotecan) was used as an anticancer drug in humans, but it was unsuccessful due to its poor solubility in any pharmaceutically acceptable excipient. However, the PEGylated version allows increased solubility, parenteral delivery, inhibition of angiogenesis, and longer apparent half – life of SN38 (Zhao, 2008) (Fig. 3).
Through in vitro and in vivo studies of Epratuzumab-SN-38 conjugates (Emab-SN-38), it was found that the new antibody drug conjugate was a successful candidate in the treatment of B-cell malignancies. Emab-SN-38 was active against leukemia and lymphoma at doses below toxic levels thus proving to be a potential agent alone or in combination with antibody therapy (Sharkey, 2011a). Studies have also been conducted to study the combined effect of radioimmunotherapy and chemotherapy in mice bearing human pancreatic cancer xenografts (Capan-1 and BxPC-3). These were treated by using single dose of 90Y-labeled antimucin antibody alone or in combination with anti-Trop-2-SN-38 conjugate twice weekly over 4 weeks along with radiation. The studies thus conducted proved to be beneficial in improving the efficacy of the treatment without causing increased toxicity (Sharkey, 2011b).

Another example in the same category includes that of OPAXIO (CT-2103, Paclitaxel Poliglumex), formerly branded as XYOTAX®, and is closest to the market. In March 2008, Cell Therapeutics, Inc. ("CTI") submitted a marketing authorization application for OPAXIO for treatment of patients with non small cell lung cancer (NSCLC). In this conjugate, PTX is linked to the carrier via an ester bond. This type of linkage had proved unsuccessful for HPMA copolymer Camptothecin and HPMA- Paclitaxel, since it led to premature drug release by blood esterase (Vicent et al., 2007). OPAXIO was designed to improve the delivery of paclitaxel to tumor tissue while protecting normal tissue from toxic side effects (Li et al., 1998) (Table 3).

With the success report of OPAXIO in ovarian patients, it was further tried for advanced esophageal cancer with combination of radiation (Dipetrillo et al., 2006).

Moreover, Cell Therapeutics, Inc. announced encouraging interim results of a phase II clinical study of OPAXIO combined with temozolomide ("TMZ") and radiotherapy ("RT") in patients with newly diagnosed high – grade malignant brain tumors, (anaplastic astrocytomas (AA) and glioblastoma multiforme (GBM). This study resulted in a median progression free survival (PFS) of 13.5 months. The addition of OPAXIO to the treatment of GBM represents a major advancement in prolonging survival in this otherwise rapidly fatal disease (OPAXIO) (Fig. 6).

### TABLE 2

<table>
<thead>
<tr>
<th>POLYMER – DRUG CONJUGATE</th>
<th>PRODUCT NAME</th>
<th>USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMA copolymer doxorubicin</td>
<td>PK1:FCE 28068</td>
<td>Various cancers, particularly lung and breast.</td>
</tr>
<tr>
<td>HPMA copolymer doxorubicin-galactosamine</td>
<td>PK2:FCE28069</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>HPMA copolymer paclitaxel</td>
<td>PNU166945</td>
<td>Various cancers</td>
</tr>
<tr>
<td>HPMA copolymer carboplatin palatinate</td>
<td>AP5280</td>
<td>Various cancers</td>
</tr>
<tr>
<td>HPMA copolymer DACH-palatinate</td>
<td>AP5346, Prolindac</td>
<td>Various cancers, particularly ovarian and colorectal.</td>
</tr>
<tr>
<td>HPMA copolymer-camptothecin</td>
<td>MAG-CPT</td>
<td>Various cancers.</td>
</tr>
</tbody>
</table>

DACH: Diaminocyclohexane; HPMA: N-2-(hydroxypropyl) methacrylamide.

### TABLE 3

<table>
<thead>
<tr>
<th>S. NO.</th>
<th>COMBINATION THERAPY</th>
<th>DISEASE TARGETED</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pegasys (Peg-interferon- α-2a) and Copegus® (ribavirin)</td>
<td>Chronic hepatitis C (HCV)</td>
<td>Sakai et al., 2006</td>
</tr>
<tr>
<td>2.</td>
<td>PEG-Intron and Rabetol</td>
<td>Retreating both HCV relapers and non responders</td>
<td>Kapustayan, 2001</td>
</tr>
<tr>
<td>3.</td>
<td>Pegvisomant and somatostatin analogues</td>
<td>Acromegaly</td>
<td>Negrers et al., 2011</td>
</tr>
<tr>
<td>4.</td>
<td>PEGylated-D-amino acid oxidase (PEG-DAO) and its substrate D-proline</td>
<td>Generates H2O2 intratumorally, leading to in vivo anti-tumor activity</td>
<td>Fang et al., 2008</td>
</tr>
<tr>
<td>5.</td>
<td>HPMA copolymer, the aromatase inhibitor aminoglutethimide (an endocrine therapy) and doxorubicin (a chemotherapy)</td>
<td>Chemotherapy resistant breast cancer</td>
<td>Vicent et al., 2005</td>
</tr>
<tr>
<td>6.</td>
<td>HPMA copolymer conjugate of both gemcitabine and doxorubicin</td>
<td>Inhibition of tumor growth</td>
<td>Lammers et al., 2009</td>
</tr>
</tbody>
</table>

Table 3 Contd...
Techniques other than Pegylation

PEGylation, no doubt, is a well established tool for polymer conjugate design. However, continuous search has lead to improved alternative techniques like recombinant DNA and monoclonal antibody technology that have helped in creating a number of peptide, protein and antibody–based drugs (Duncan, 2011).

Better conjugation techniques for extracellular drug delivery have been developed which have indeed proved out to be a boon over the existing problems related to intracellular delivery via lysosomotropic or endosomotropic routes (Vicent et al., 2006). These utilize a two – way approach i.e. polymer – directed enzyme prodrug therapy (PDEPT) combines both polymer – drug and polymer – enzyme conjugates. For example, HPMA copolymer – cathepsin B combined with HPMA copolymer-Gly-Phe-Leu-Gly-doxorubicin (Satchi et al., 2001) and an HPMA copolymer – β-lactamase conjugate (HPMA – Gly-Gly-β-L) with HPMA copolymer-Gly-Gly-cephalosporin-doxorubicin have shown in vivo proof of concept, (Satchi et al., 2003) and PELT (polymer-enzyme liposome therapy) in which drug is liberated from liposomes by the action of polymer-phospholipase conjugate. For example, HPMA copolymer – phospholipase C conjugates increase drug release from liposomes (Duncan et al., 2001).

On the same pathway, it has been reported that dextrin-phospholipase A₂ (PLA₂) conjugates show a significant role as anticancer agents and these work via PUMPT concept (Polymer-Masked Unmasked Protein Therapy). This utilizes a biodegradable polymer to transiently mask a protein during its transportation, simultaneously allowing triggered polymer degradation, protein unmasking and thus restoration of bioactivity (Duncan et al., 2008). Further work has been carried out using Hyaluronic acid – protein conjugates as modulators of tissue repair (Fergusan et al., 2010) (Fig. 4).

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**Table 4.2**

<table>
<thead>
<tr>
<th>S. NO.</th>
<th>COMBINATION THERAPY</th>
<th>DISEASE TARGETED</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>HPMA copolymer conjugate containing amino-bis-phosphonate alendronate and the anti-angiogenic agent TNP-470 bound using a Cathepsin K peptidyl linker</td>
<td>Angiogenesis – dependent tumors in bone</td>
<td>Satchi-Fainaro R et al., 2004</td>
</tr>
<tr>
<td>8</td>
<td>HPMA copolymer conjugates containing both doxorubicin and mesochlorin e6(photoactivatable compound) combined with OV-TL16 antibody</td>
<td>Anti-tumor activity</td>
<td>Shiah et al., 2001</td>
</tr>
<tr>
<td>9</td>
<td>GlutaDON (a combination of PEGylated glutaminase plus 6-diazo-5-oxo-L-norleucine)</td>
<td>Advanced, refractory, solid tumors. Refractory colorectal, renal or non small cell lung cancer</td>
<td>Unger et al., 2005</td>
</tr>
</tbody>
</table>

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Fig. 4. (a) Polymer–drug conjugates designed for lysosomotropic delivery of small-molecule drugs. Also shown is the use of bioresponsive, endosomolytic polymers to facilitate cytosolic access of genes and proteins from the endosome. (b) Use of polymer-based systems to deliver drug within the tumour interstitium, or to destroy tumour cells following interaction with the cell membrane. Polymer-directed enzyme prodrug therapy (PDEPT) is a two-step approach that relies on activation of a polymer–drug conjugate by a complementary polymer–enzyme conjugate. Polymer–enzyme liposome therapy (PELT) relies on the liberation of drug from liposomes by the action of a polymer–phospholipase conjugate. Polymers that are conjugated to membrane active peptides or drugs that are known to activate the apoptosis pathway also have the potential to act at the level of the plasma membrane. Reproduced with permission from Duncan, 2003.
Dendrimers due to their basic advantages over linear polymers such as their precise 3D globular shape, monodispersity, defined number of functional groups and their distinct inner and outer surfaces have been widely explored in the field of drug delivery as anticancer, antiviral or antibacterial drugs, MRI contrast agents and as DNA transfection agents (Duncan, 2005, Canal et al., 2011). For e.g., the first dendrimer based magnetic resonance imaging (MRI) agent (SH-L 643A; Gadomar®) (Jaspers et al., 2011) and HPMA copolymers containing either F probes (t1/2 ~1.8h) or longer – living positron emitters (t1/2 ~26h) or As (t1/2 ~17.8d) have been described by Herth and colleagues which proves to be an important development for positron emission tomography (PET) imaging (Herth et al., 2010).

Presently, dendrimers as PAMAM (poly(amidoamine) (Menjoge et al., 2011), poly(ethylene oxide) (PEO) grafted carboxilane or poly(propyleneimine) (DAB) are being focused for further research and improvement of this field (Gaspar et al., 2009).

**Combination Therapy**

Polymer – based systems have been extensively explored as monotherapies. Furthermore, combination therapy is being widely applied to achieve medical treatments with highly enhanced therapeutic value (Greco et al., 2009). On one hand, as already quoted the example of OPAXIO with drugs (like carboplatin and temozolamide) and radiotherapy proved to be efficacious. On the other hand, certain other examples have been quoted in Table 4.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Clinical trials of OPAXIO</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>NAME</th>
<th>DISEASE</th>
<th>COMPARISON</th>
<th>RESULT</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>STELLAR 3</td>
<td>Advanced NSCLC who were chemotherapy-naïve and had poor performance status.</td>
<td>STELLAR 3 compared the effect of standard paclitaxel/carboplatin to OPAXIO/carboplatin. STELLAR 4 compared OPAXIO to standard single-agent therapy with either gemcitabine or vinorelbine.</td>
<td>Survival benefit for women receiving OPAXIO compared to the control arms.</td>
<td>Ross et al., 2006; O’Brien et al., 2006.</td>
</tr>
<tr>
<td>AND STELLAR 4</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 3 Contd...
In short, polymer-drug conjugation aims to achieve improved drug targeting. Reduce drug toxicity and overcome mechanisms of drug resistance. First generation conjugates used linear monomethoxy PEGs and other linear polymers. Modern polymeric chemistry is increasingly producing new polymeric architectures such as dendrimers, hyper branched polymers and hybrid macromolecular structures (such as star polymers, linear graft and dendronised linear polymers, novel therapeutic siRNA etc.) this undoubtedly can be employed for designing of second generation polymer therapeutics. Clinical approval of products (e.g. Copaxone®, Renagel®, Vivagel®, Welchol®) have been successful in developing interest in polymer therapeutics as a growing field of research and development.

There is a growing realization that polymer drug conjugation has become useful in a wide range of treatments from infectious to chronic diseases such as cancer. On the basis of sound biological rationale, scientists have successfully developed nanovectors for targeted delivery of anticancer drugs, imaging contrast agents and detection systems such as nanowires and nanocantilever arrays for early detection of precancerous and malignant lesions in biological fluids. It should not be an exaggeration to pronounce polymer therapeutics as a future of nanomedicines.

**Conclusions**

**References**


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