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Polymer based Drug Delivery Systems- benchtop to Bedside Transition

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ABSTRACT

Research in the field of polymers and polymeric materials has garnered immense attention in the past few decades due to the versatile functional and structural capabilities of polymers which often can be manipulated for applications in the field of therapy and diagnosis for a host of diseases and disorders. Polymer therapeutics comprises polymer-drug and polymer-protein conjugates as well as supramolecular systems used as drug delivery systems. Although the pharmacological industry invests immensely in the design and discovery of novel drug molecules, small molecular drugs are often inefficient in targeting many diseases like deep seated low vasculature tumours, metastasized cancers and various autoimmune diseases. Coupled with a rapid clearance rate, low solubility, drug resistance and high off target toxicity these small molecular drugs often present modest benefits for a host of common diseases. In order to improve the therapeutic index of pre-existing drugs and shortening the translation from preclinical validation to clinical approval, a vast area of drug delivery research focuses on the improvement of drug carriers by various alterations. The major challenges currently faced by drug delivery systems include a low payload, transition through the desmoplastic barrier for solid tumours and high hepatic and renal clearance. In order to address these issues numerous polymer–protein and polymer-drug conjugates have been engineered and have reported to enhance the stability and pharmacokinetic properties of the active drugs. Highly toxic anticancer drugs like doxorubicin, cis-platin and gemcitabine have successfully been coupled with high molecular weight polymers to formulate targeted drug delivery agents, some of which have undergone successful clinical trials. Apart from PEGylated polymers, dendritic polymers and polyplexes with DNA or RNA moieties have also been considered as candidates for improving the therapeutic index of various drugs. Ongoing efforts in the development of polymer-based therapeutics are promising and open new horizons for personalized medicine for effective cure of various life-threatening diseases.

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Polymer therapeutics comprises a vast field of materials including polymer-drug, polymer-protein conjugates as well as supramolecular assemblies. The application of polymers, both synthetic and natural, is usually in the form of carriers of low molecular weight compounds. Nanomaterials derived from such polymers which can be micelles, polymersomes or vesicles offer attractive chemical and physiologically modifiable features harnessed for drug delivery applications. While small molecular drugs have demonstrated promising results throughout history, these agents are usually associated with limitations to combat several complex diseases including but not limited to cancer, various autoimmune and rheumatic diseases and diabetes. Not only do such diseases exhibit aggressive resistance against small molecular drugs, but these drug molecules exhibit high hydrophobicity, rapid renal, hepatic and splenic clearance, off-target toxicity, high dosage and low penetration and accumulation across the desmoplastic barrier in low vasculature tumor tissues [1-22]. To overcome these challenges extensive research has been carried out to develop and enhance targeted delivery of active therapeutic agents, thereby resulting in phenomenal achievements in nanotechnology drug delivery approaches such as improved solubility, controlled and sustained release of drugs, higher circulation times, lower clearance rates, adaptable release profile and reduced off-target toxicity [1,2,4,5]. Variation of surface functionalities and use of biomolecules and ligands enhance the targeting capacity of these nanocarriers. The use of passive (pH, hypoxia, temperature, enzyme, ROS) and active (targeting ligands, aptamers etc.) stimuli can selectively deliver the therapeutic cargo at the intended site with least collateral damage (Figure 1).

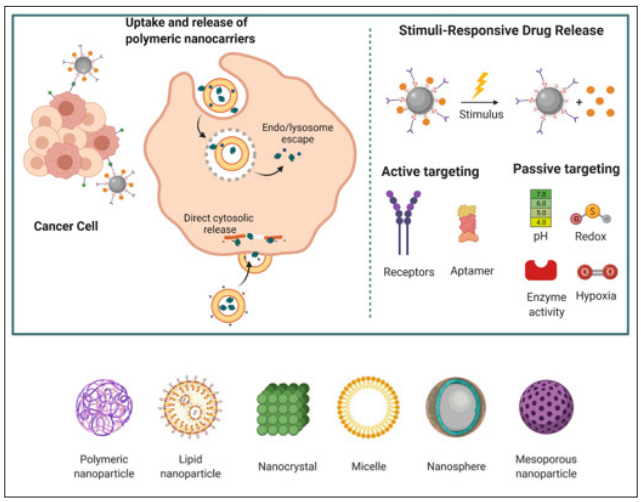

Figure 1: The various stimuli used for release of drug into cancer cells along with the uptake mechanism in cancer cells and (below) some varieties of nanoparticles used for drug delivery (Created using BioRender)

Currently most drug delivery systems rely on small molecular drugs to address a disease and thus still face a drug's inherent limitations. Despite the fact that these delivery systems are efficient to sustain a desired concentration of drugs at a targeted location, cellular barriers and resistance mechanisms of targeted tissues may still reduce the overall efficiency of a drug [22-33]. Additionally, such systems are prone to other drawbacks such as burst release that raises safety concerns for a drug, enzymatic drug degradation, and activation of the immune system [6,5]. To address safety concerns, complex strategies have been utilized involving simultaneous-loading of several small molecular drugs and multifunctional nanoparticles [31,34,35]. As a result, design of a simple effective delivery system remains a challenge, considering the stringent biocompatibility requirement of nanoscale drug delivery systems.

The inherent ability of polymers to interact with a target at multiple sites locations simultaneously grants them a distinguishable property. Multivalent interactions, concurrent binding between multiple ligands and receptors of two molecular entities, is the key characteristics of many biological processes, such as adhesion of bacteria to the surface of a host cell, cell-cell interactions, or binding between transcription proteins and DNA (deoxyribonucleic acid). The multivalent interactions are reversible and play a role in activation/inhibition of biological processes. While small molecular drugs are typically monovalent, the multivalent interaction of macromolecules offers unprecedented benefits that are not reachable by the small drugs. The inherent benefits result from the repeating units of polymers that allows multivalent interaction, generating enhanced affinity, favorable entropy, and cooperativity [7,11]. The multivalent interactions opens the door for simple applications like polymeric sequesters. Further, the use of nanoparticles offers a wide range of size and shape tunability to adapt for desired use [36-49].

The potential of polymers as therapeutic agents is highly underestimated. Polymers possess a multi-ligand property allowing them to mimic the natural multi-ligand processes and bind simultaneously to multiple binding-sites [12,13]. Binding to receptors is a reversible process, meaning when a receptor disconnects, another ligand of a polymeric drug is situated in a position to rebind, offering a statistical rebinding mechanism [8,16]. This process is more energy efficient than recruiting another small molecule following each release and macromolecular drugs establish a hindrance stabilizing effect which prevents association of the surrounding medium with the targeted detrimental biological agents like viruses [17,18].

Polymeric drugs are promising candidates to fight against many diseases. The discoveries in the past few decades have resulted in multiple FDA approved polymeric drugs which offer commercial viability and feasibility to be produced in large quantities in comparison to labor-extensive preparation of small drugs or conjugated peptide-polymeric agents. Recent research strongly supports the potential of polymers as drugs where the target cells are killed while the constructs themselves did not demonstrate multidrug resistance behavior. As the field of polymeric drugs field is relatively new, there is a huge potential of investigating their properties and tuning them for personalized medicine.

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