Biomaterials as therapeutic agents for treatment of cancer: A review

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Abstract Biomaterials can be stated as an amalgamation of science in research and development where the field of cellular biology, molecular biology, chemical sciences, materials sciences and engineering plays important role. These are substances which have been modified to interact with biological systems for therapeutic purposes and even diagnosis. They induce a synergistic effect in the environment where implanted. Although as a science, it is years old but at present it is growing as a modern-day research platform that finds its application in many fields of medical science and cancer being the most extensively researched field in the same. Such studies undertaken in the field of biomaterials has been reviewed in the paper that includes the use of biomaterials as therapeutic agents including their use as vaccines and surface modulators to enhance the antigen specific T-cell activity in the immunotherapy for cancers. The application has been found reliable in case of recurrent cancers, poorly immunogenic tumours as well as immunologically resistant tumours. Triple negative breast cancer and skin cancers have been successfully treated with the help of biomaterials. The review highlights the importance and scope of study towards field of biomaterials in cancer treatment.

1. Introduction
Biomaterials can be stated as a cocktail of science in research and development where the field of cell and molecular biology, chemistry, materials sciences and engineering are the supporting ones. The whole field is guided by these subjects and it has been a major contributor in the study of interaction of materials with their respective physiological environment called as bio interface. The development of biomaterials in the field of medical sciences have been a current topic of research which has also shown a lot of expected positive results an overview has been given in figure 1. The field of dentistry, microbiology, cancer, and many others have reported the use of biomaterials with high success rate [1, 2].
Figure 1. An overview of role of biomaterials in cancer therapeutics

1.1 The generations of biomaterials

The science of biomaterials has been divided into three successive generations, the first, which began in the 1950s, comprise of large compromise of material selected for clinical use that also ensures the minimal response from the host tissue and were considered as biocompatible. This comprises of silicone rubber, pyrolytic carbon, used for coat component of mechanical valves etc. [2].

Second generations biomaterials are those that have been found to be linked with the first generation or the early biomaterials. They are designed in such a way that get into controlled reaction with the tissues in which they are implanted to induce a therapeutic effect. They have clinical uses in orthopaedic and dental surgeries and examples includes bioactive glasses and ceramics [3]. These biomaterials also include reabsorb able materials with rates of alterable degradation. They create an interface between the site of implantation and the host tissue can be eliminated in long-term because of their biodegradable nature [4].

The third generation is in most discussion of the nowadays as it implies modern methods to deal with the modern problems. They stimulate the regeneration of functional tissues that gives backbone to tissue engineering science and regenerative medicine. Tissue engineering uses living cells to facilitate the tissue regeneration and formation producing therapeutic effects. This has been extensively used in skin, cartilage and bladder replacements with good success rates [5,6]

1.2 How biomaterials play role in cancer therapy

Cancer is a leading cause of death in the world and is a challenging disease. Most of the research in the world in carried out in the field of cancer because of its unpredictable nature and new challenges emerging in the field. The treatment of cancer is still a challenge as cancer cells includes endogenous mechanism of cell growth and division which varies from one individual to another [7].
1.3 Use of biomaterials for targeted Drug delivery system

Cancer treatment is a vast field to analyse the use of biomaterials as it includes the use of traditional as well as all kind of modern-day methods. Employing use of anti-cancerous agents and their validation in experimental set ups have been done before the clinical trials. It has been seen that most anti-cancerous drugs are hydrophobic in nature and therefore they are formulated with material that increases its solubility such as by using hydrotropic agents, micelles, etc [8]. A strong drug-delivery system is also required for proper working and to obtain desired results. Thus, nanovehicles are engineered to ensure drug delivery at targets. They are also used as diagnostic agents as well. Proper use of biomaterials to devise such polymeric drug delivery system is necessary to achieve the goals [9]. Hydrogels, self-assembling polymeric materials, micelles, dendrimers are some of the biomaterials that are been used as nanovehicles carrying anti-cancerous agents and induce the targeted effect. Therapies including combination of HPMA copolymer-anticancer drugs (DOX and photosensitizer chlorin e₆) showed curing effect against tumour better than chemotherapy. Most of the combinations produce synergistic effects [10]. Similarly, use of combination targeted polymer bound angiogenesis inhibitors (two per macromolecule: ALN and antiangiogenic TNP-470) was used as strategy against bone neoplasm that targeted both tumour epithelial and endothelial cell and could also be used to osteosarcomas and other bone related cancers [11].

1.4 Use of biomaterial as enhancers for antigen specific T-cell for cancer immunotherapy

The T-cells play an important role in the immune response against any invasion or even cancerous growth in the body. They are sometimes referred to as ‘guided missiles’ of the body. The biomaterials that can mimic the T-cell responses have been studied by Isser et al., 2020 that could be used to design immunotherapy treatments against variety of cancers and other infectious diseases. Naturally, the disease specific antigens are taken up by APC (antigen presenting cells) such as dendrite cells at the infection site [12]. When these antigens are internalized along with pathogen associated molecular pattern or danger associated molecular patterns respectively, the DCs are activated and they travel to secondary lymphoid organs in chich lymphocytes are concentrated [13]. Biomaterials have been tried on and used to develop such technology that activates the path explained and is an attractive option to deal with many challenges of cancer treatment and avoiding the ex vivo T cell proliferation [14].

1.5 Biomaterials for cancer immunotherapy

Cancer immunotherapy provides hopes for the treatment of cancers in the patients and has been in use for ages. But a new upgradation was required as it has certain limitations to be cleared. Some limitations associated includes undesirable adverse and side effects, localised delivery on immunomodulators and overactivation of systemic immune system [15].

To eliminate them, use of biomaterials as implants, injectables or transdermal fabrication of drug delivery devices can help in localized delivery of cancer immunotherapy and hence solving the problem. Some of them are discussed below.

1.5.1 Implantable biomaterials. They include biomaterials scaffold are implanted in place of excised tissue, subcutaneously with help of a minor surgery. Before the implantation, the biomaterials are preloaded with factors, anti-cancerous agents, cells or whatever required for the treatment and then are released in a controlled manner from large scaffolds that are specially designed for them.

Immune cells are recruited to the implantation site from these designed porous scaffolds. Examples includes poly(lactide-coglycolide), alginate, polyglyconate and porcine gelatin, collagen and hyaluronic acid [16,17].

1.5.1 Injectable biomaterials. They include injectables biomaterial scaffolds so that surgery and implants related problems could be ruled over. They are well suited for the combination therapies
given in cancers such as chemotherapeutics or radioisotope therapy. The injectables possess property of biocompatibility, liquid like state at room temperature and convert it into gel form at body temperature. Examples includes hydrogel, cryogel, inorganic scaffolds that enable the localized and controlled release of anti-cancerous drugs [18].

Many researchers have shown many positive results in tumours and other cancers after the use of injectable scaffolds. To quote one of the, Wang et al., demonstrated the use of fibrin hydrogel with biodegradability and compatibility to load the cyclophosphamide, an anti-cancerous drug in mouse model against ovarian and breast cancer and showed inhibition in tumours recurrence after surgery [19,20].

1.5.2 Transdermal biomaterials. They include the injections or surgically implanted devices in the transdermal region. Melanoma, a primary form of skin cancer is been tried to treat through this approach. The drugs are transported from the patch through the skin and in the systemic circulation at a particular rate. The transdermal biomaterials should have the characteristics including low permeability. They mainly address electric fields (iontophoresis and electroporation), lipid enhancers, chemical enhancers and pressure waves generated by ultrasound or photoacoustic effects. Microneedles are used as approach to puncture through the skin. Examples includes poly (lactic-co-glycolic acid), Granulocyte-macrophage colony-stimulating factor, Polycaprolactone, Hyaluronic acid, trimethylene carbonate, Poly etc [20,21]

1.6 3D cell culture and tumour microenvironment engineering using biomaterials
The latest concept of artificially engineered microenvironment by using the biomaterials has been recognised as an important approach for pre-clinical studies of therapeutic drugs and vaccines too. 3D matrices encapsulating In vitro cancer model of tumour microenvironment have been developed for the studies and has revealed new pathways and concepts in the field of cancer biology [22]. In contrast to 2D monoculture models that have been the conventional use as In vitro studies in for drug testing, 3D extracellular matrix also called as the ECM have shown the change in behaviours of cell from 2D to 3D model giving much more resemblance of 3D model to tumour microenvironment which makes it more understandable and easier to draw inferences [23]. For encapsulating, the 3D ECM of tumour, many natural and synthetic materials have been developed to provide support to the growing cells [24]. Biomaterials such as collagen, hyaluronic acid, laminin, alginate, chitosan, matrigel that are derived naturally are commonly used in 3Dcell culture due to their cell adhesion properties, cytocompatibility and remoldable ability by cells [23]. Synthetic materials such as PEG and poly(lactide-co-glycolide) (PLG) are also used for the same. The 3D ECM is able to model many hypoxic conditions by hydrogel spatial configuration control which allowed studies of secretion of interleukin 8 (IL-8) and VEGF factors from cancer cells. To control the spatiotemporal capability of growth factors in 3D tumour model, controlled drug delivery has been used for example, a hyaluronic acid hydrogel bilayer system was developed to study the functioning of heparin-binding EGF-like growth factor on growth of prostate cancer. As heparin-binding EGF-like growth factor are found in prostate stroma and bound to ECM, heparin-binding EGF-like growth factor was capasulated in microparticles to control the availability. Controlled release of HB-EGF microparticles from top layer hydrogel promoted the growth of tumour in bottom layer and increased VEGF and IL-8 expression in the cancer cells. These kinds of approaches are useful to study the tumour cell response to spatiotemporally controlled cytokines with respect to immunotherapy [25].

1.7 Biomaterials as an alternative for vaccine development for cancers
Biomaterial based cancer vaccines have many additional advantages over the regular ones as demonstrated by many researchers. Firstly, they can be easily delivered to any targeted organ or spot with the help of nanovesicles that too in a controlled manner [26]. The challenges faced by any cancer vaccine includes weak immune system, toxicity and off targets effects. They are the main obstacles that remain in path of success of any vaccine. The conventional vaccines have several classes based upon DNA, mRNA and protein based. The use of biomaterials in cancer vaccine range from large implants or injectable scaffolds or use as nanovesicles in face of polymeric and liposomes [27]. The latest example includes vaccine designed by Mooney and colleagues i.e., PLGA-based scaffold vaccine (WDVAX) which is recently been licensed by Novartis for commercial use [28].

1.8 Biomaterials in adoptive cell transfer
Tumour infiltration by lymphocytes, chimeric antigen receptor T cells, T cell-based ACT has become a highlighted development in cancer immunotherapy [29]. However, it includes the challenge of expansion of T cells and fails to maintain their effector function during ex vivo cell production and in vivo after transplantation. Apart from this, these therapies require large number of autologous tumour specific T cells. The T cells collected directly from patients’ blood can be hyporesponsive [30].

In this case, the biomaterials play role where microparticles coated with anti-CD3 and anti-CD28 antibodies have been developed as “artificial APCs” to provide primary and co-stimulatory signals. They also contain superparamagnetic iron oxide for separation from cells via magnetic field. This has now become a common method. PLG microparticles having additional signal the T cell growth factor IL-2, further enhanced T cell expansion, especially of CD8+ T cells [31]. They also allow the prevention in viability and function of transplanted cells in ACT by creating optimal cytokine presentation in cellular environment.

1.9 Biomedical polymers as intra-arterial occlusion devices
Use of beads composed of sulfonate-modified poly (vinyl alcohol) (PVA) hydrogel (DC Bead®) have been reported by Lewis, 2013 as degradable embellishment devices that could be helpful in hyper vascular benign and malignant tumours and specially in arterio-venous malfunction. The embolization of blood vessels could be said to be the process of helping and treating in bleeding problems. Beads composed of sulfonate-modified poly (vinyl alcohol) (PVA) hydrogel have been found to deliver chemotherapeutic drugs directly to the vasculature of liver tumour and are called as DEB (drug eluting beads). They can release positively charged anticancer drugs by ion-exchange mechanism and has found its place in treatment of liver cancer as quoted by Lewis, 2013 [32].

1.10 Uses of some biomaterials for cancer therapeutics.
Polyamine analogues can inhibit cell growth and kill cancer cells. The bioactive polymers show direct and indirect effect in damaging cancer cells either by killing cancer cells and inhibiting their growth and/or by eliminating multi-drug resistance by inhibiting the function of P-glycoprotein (Pgp). Each class has unique function based on its structure activity relationship and cytotoxicity mechanism [33].

Gold particles as biomaterials with their conjugates have wide range use in field of biomedical sciences. The use ranges from drug carries, in biomedical imaging, as photothermal agents in biomedical imaging and as sensitzers in radiation therapies [34].

Similarly, Zhang et al. recently in 2020 highlighted their work, which included use of Cu as biomaterial for cancer therapy by enhancing hypoxia. Copper metal-organic framework nanoparticles (Cu-MOF NPs) which were a novel hypoxia-responsive were used for chemo dynamic therapy and sonodynamic therapy (CDT/SDT). The nanoparticles for drug delivery into deep tumour showed great affect and killing of cancer cells. The nanoparticles showed good stability under normal oxygen partial pressure and enhance tumour accumulation that degrades and released Copper ions when exposed to hypoxic tumour microenvironment that reinforced intratumorally penetration [27].
2. Conclusion

Cancer is a leading cause of death in the world with increasing no of patients’ day by day. The complex nature of cancer, the variation in the progression at cellular level, heterogeneity and the different origins makes it a more challenging disease every time to treat. Along with the conventional treatments given, adjuvant therapies for the treatment of cancers have been in use nowadays to prevent its progression, recurrence and treat to drug resistant cancers. Biomaterials as an approach in the field of cancer therapeutics play synergistic roles in the therapies given for cancers that includes immunotherapies, targeted nanoparticle drug delivery system, as vaccines etc. apart from this, multi-modulating cancer imaging can also be one of the use of biomaterials in field of medical research. Apart from this, the modelling of an artificial microenvironment for the experimental or pre-clinical studies of the therapeutic drugs and vaccines using biomaterials has also laid a new path in drug discovery for cancer treatment making use of biomaterials a more promising approach. Biomaterials as therapeutic and assistive agents in the field of cancer have shown reliable results and laid path for future researches in the same field. This calls for attention requirement of clinical adaptation of biomaterials and those of researchers, physicians and pharmaceutics towards this growing field.

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