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A REVIEW ON BIOTHERAPIES AND BIOTHERAPEUTICS

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Abstract —

The revolution in the field of medicine has currently reached a stage where researchers use microbial and human cell as versatile therapeutic engines. The detailed understanding of pathophysiology and genetic basis of various microbes has helped to change the landscape of disease management. Biological therapeutics is a thriving area of research which is expanding across the globe as a fascinating alternative methodology to treat diverse diseases. Since the first designed bio-therapeutic two decades ago, medical technology has progressed from designing small molecules to designing bio-therapeutics. These include wide range of medicinal products created by biological methods instead of chemical processes and can be proteins, nucleic acids or complex combinations of substances, may be living entities such as cells and tissues. The therapeutics includes wide range of drugs which are usually generated by recombination techniques from living organisms and are viewed to more effectively combat drug resistance, act in cases where the disease is caused because of a molecular deficiency and provide novel treatment modalities to address previously untreatable conditions. The series of discoveries in the fields of cytokine biology, monoclonal antibody development and molecular biology are the main reason for the practical advancements in this area. Precise understanding of genetic and molecular levels in diseases has helped the researchers to go through and invade the new targets which affect sub population of patients. This article provides the detailed knowledge about the Bio-therapeutics, their modes, advantages, future perspectives and challenges and highlights the issues that contribute towards development of biological drugs.

Keywords: **Antibody, Bio-therapeutics, Bio-therapy, Monoclonal antibodies, Protein**

1. INTRODUCTION

Science has seen a revolution in developing new medicinal products and new methodologies to treat the vast spectrum of medicinal conditions. From the past several decades, studies related are taken up to a qualitative understanding of the biochemical and molecular interactions of human physiology [1, 2]. Biological therapeutics is immunogenic and is recognized by the human immune system as 'non self'. Therapeutic endogenous proteins, such as erythropoietin and growth factors, possess an amino acid sequence identical to the human equivalent and can be immunogenic due to glycosylation or conformational changes, whereby new epitopes are exposed. Therapeutic antibodies carry unique complementarity determining regions, containing stretches of sequences that frequently will be recognized as foreign and induce formation of antidrug antibodies (ADAs) [3]. Natural products continued to provide key scaffolds for drug development. In the current millennium, it was discovered from genome sequencing that microbes with large genomes have the capacity to produce about ten times as many secondary metabolites as was previously recognized. Indeed, the most gifted actinomycetes have the capacity to produce around 30-50 secondary metabolites. Advances in bioinformatics, mass spectrometry, proteomics, transcriptomics, metabolomics and gene expression are driving the new field of microbial genome mining for applications in natural product discovery and development [4].

Bio-therapeutics is extracted from biological sources in contrast to conventional pharmaceutical which are chemically synthesized. It boosts our body natural defense mechanisms against diseases by using materials made by our own body or in a laboratory. The US agency FDA defines biological as "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of disease or injuries of man" [5, 6]. Curing ailments by biotherapy which was practiced in ancient times were typically plants or animal extracts. Biological therapeutics includes recombinant proteins and hormones, monoclonal antibodies, cytokines, growth factors, gene therapy products, vaccines, cell-based products, gene silencing, tissue engineering, and stem cell therapies. Plants have long been recognized for their therapeutic properties. In contrast, the rise of the modern pharmaceutical industry has been based on exploiting individual active compounds with precise modes of action. This surge has yielded highly effective drugs including many plant natural products and analogues, but has fallen short of delivering effective cures for complex human diseases with complicated causes, such as cancer, diabetes, autoimmune disorders and degenerative diseases [7].

The bio-therapy motivates human autoimmune system disease by interfering with the pathogenesis of diseases and there by stopping the chronic inflammatory process. Protein therapeutics hold a prominent and rapidly expanding place among medicinal products. Purified blood products, recombinant cytokines, growth factors, enzyme replacement factors, monoclonal antibodies, fusion proteins, and chimeric fusion proteins are all examples of therapeutic proteins that have been developed in the past few decades and approved for use in the treatment of human disease. Despite early belief that the fully human nature of these proteins would represent a significant advantage, adverse effects associated with immune responses to some biologic therapies have become a topic of concern. As a result, drug developers are devising strategies to assess immune responses to protein therapeutics during both the preclinical and the clinical phases of development [8, 9]. Biologic drugs have come across several challenges and opportunities. Some of the advantages are the duration of action and highly specific and strong binding to the target interest and less side effects. There are also disadvantages like the cost and the need for parenteral administration. They are also effective in neoplastic, auto immune, inflammatory cardiovascular derma logic infections and allergic reactions [10, 6]. Monoclonal antibodies and recombinant proteins have seen an immense medical and commercial success [11]. Currently, there is a significant rise in the development and clinical use of these Biopharmaceuticals or Biologics that are termed as effective class of pharmaceuticals, in the management of a range of disease conditions with, remarkable therapeutic benefits. Immunogenicity to biologics represents a significant hurdle in the continuing therapy of patients with a number of disease backgrounds. Efforts focused on the identification of factors that contribute towards the onset of immunogenic response to biologics have led to reductions in the incidence of immunogenicity. An in-depth understanding of the cellular and molecular mechanism underpinning immunogenic responses will likely improve the safety profile of biologics [12].

2. BIOTHERAPEUTICS

Biotherapeutics or biologicals are the drugs which are derived from genomes which have potential to develop complex molecules used in medicine and agriculture [13]. There are a wide range of Biotherapeutics with antibodies, cytokines, enzymes, and hormones being the most popular. The protracted application of Biotherapeutics is attributed to their specificity and binding affinity to the target [10]. Biotherapeutics play a major role in treating metabolic, immunologic, and genetic disorders which are not possible by conventional medicines. Past few decades has seen development of hundreds of clinically approved of Biotherapeutics used worldwide [14]

2.1. CLASSIFICATION OF BIOTHERAPEUTICS

Biotherapeutics are classified into several Groups based on the mode of action:

Group 1: **Therapeutics with enzymatic or regulatory activity**

a. Replacement of a protein that is deficient or abnormal. Eg- Lantus
b. Augmenting existing pathways. Eg- Neupogen
c. Providing a novel function or activity. Eg- Myoblock

Group 2: Specific targeting activity

a. Interfering with molecule or Cells. Eg- Orencia, Ontak, Stelara, Simponi, Avastin
b. Delivering other compound or protein. Eg- Epogen, Amevive

Group 3: Vaccine

a. Protection against a deleterious agent. Eg- Botox, Ngerix
b. Treating auto immune diseases. Eg- Lantus, Humira, Rituximab, Enbrel
c. Treating cancer. Eg- Herceptin, Avastin, Remicade

Group 4: Diagnostic agents Eg- Geref

2.1.1. LANTUS (INSULIN GLARGINE)

Insulin Glargine (Brand name 'Lantus') is a long acting insulin analogue produced by recombinant DNA technology using a non-pathogenic strain of Escherichia coli plasmid DNA [15, 16]. It converts dietary sugar to energy and compensates for the lack of natural insulin in diabetic patients and plays a significant role in controlling type 1 and type 2 diabetes [17, 18]. Insulin Glargine can also modulate various immune processes such as chemotaxis, phagocytosis, and cytokine production [19, 20].

2.1.2. NEUPOGEN (FILGRASTIM)

Filgrastim is the originator recombinant human Granulocyte Colony-Stimulating Factor [G-CSF] widely used for preventing neutropenia-related infections and mobilizing hematopoietic stem cells [21]. Since its approval in 1991, initial health technology assessments suggested low value due to high cost and lack of evidence for survival rate. However, recent placebo-controlled randomized trial data reveal falling costs due to biosimilar competition and absolute overall survival gains of 3.2% from filgrastim [22].

2.1.3. MYOBLOC

Myobloc is the currently available commercial formulation of type B Botulinum toxin (BoNT), a neurotoxin produced by the bacteria Clostridium botulinum used for various neurologic indications [23]. The most commonly used Botulinum toxins, the type A toxins (Botox and Dysport) affect the SNAP-25 protein whereas the type B toxin (Myobloc) affects synaptobrevi, a vesicle-associated membrane protein. Both type B and type A are antigenically distinct [24].

2.1.4. BOTOX (BOTULINUM TOXIN)

Botulinum toxin (Brand name 'Botox') is a protease exotoxin produced from gram positive bacterium called *Clostridium botulinum,* strain type A. It blocks the release of acetyl choline from cholinergic nerve ending which causes inactivity of glands or muscles [25]. Since its approval in 1989 by FDA it is used in treatment of strabismus, blepharospasm and hemifacial spasm [26]. It is also used to treat tremors, to improve appearance of dynamic facial wrinkles, parafunctional clenching, extracapsular myogenic temporomandibular disorder and the associated headaches [26, 27].

2.1.5. ORENCIA (ABATACEPT)

Abatacept is a humanized drug, a fusion human protein which is specifically designed to interfere with the T-cell costimulation by binding to costimulatory receptor followed by blocking the interaction with costimulatory receptor [28] and is approved by FDA for the treatment of moderate to severe rheumatoid arthritis [29]. It may be used as monotherapy or in combination with other drugs like methotrexate (MTX). Abatacept attaches to the surface of inflammatory cells and blocks communication between these cells reducing inflammation [30].

2.1.6. HUMIRA (ADALIMUMAB)

Adalimumab is a recombinant humanized monoclonal immunoglobin [IgG1] with anti-TNF-α activity. It is approved to treat rheumatoid arthritis as well as psoriatic arthritis [31] ankylosing spondylitis and ulcerative colitis [32]. It was developed by harvesting B-cells which produce antibodies and it is produced by recombinant DNA technology in a mammalian cell expression system and it is purified by the process which has specific viral inactivation and removal steps [33].

2.1.7. HERCEPTIN (TRASTUZUMAB)

Herceptin is a manmade bioengineered monoclonal antibody to target the human epidermal growth receptor 2 (HER2) which is over expressed by some cancer cells of breast cancers ovarian cancer, stomach cancer and oesophageal cancer [34].

2.1.8. AVASTIN (BEVACIZUMAB)

Bevacizumab (Brand name 'Avastin') is synthetic recombinant monoclonal immunoglobin IgG1 that acts against vascular endothelial growth factor (VEGF). It is classified as anti-angiogenesis and is approved by the FDA for the treatment of metastatic colorectal cancer and is in Phase III trials for advanced breast cancer and advanced renal cancer [35, 36]. It works effectively when combined with chemotherapeutic drugs like fluorouracil and irinotecan [37]. Bevacizumab is used to treat kidney, cervical, ovarian, lung, colon and rectal melanoma [38].

2.1.9. AMEVIVE (ALEFACEPT)

Alefacept (Brand name 'Amevive') is a genetically engineered immunosuppressive drug approved by the FDA in 2003 for the treatment of chronic and severe plaque type psoriasis [39, 40]. Clinical trials have demonstrated the safety and efficiency of Alefacept as monotherapy [41, 42]. Its uses in several countries is attributed to its efficiency and low side effects as a cure for immune-mediated dermatology conditions including *Lichen planus*, *Alopecia areata*, scleroderma, nail psoriasis, atopic dermatitis, *Palmoplantar pustulosis*, eczema, *Pyoderma gangrenosum* and mucosal disease [40].

2.2.0. EPOGEN (ERYTHROPOIETIN)

Erythropoietin (EPO), the principal hematopoietic hormone produced by the kidney and the liver in fetuses, regulates mammalian erythropoiesis and exhibits diverse cellular effects in nonhematopoietic tissues. Epogen is a recombinant human erythropoietin that stimulates erythropoiesis. The introduction of recombinant human EPO (rhEPO) has marked a significant advance in the management of anemia associated with chronic renal failure [43, 44]. Athletes however use recombinant human erythropoietin illicitly to dope and boost the delivery of oxygen to the tissues and enhance their performance in endurance sports [45].

2.2.1. ENBREL (ETANERCEPT)

Etanercept was the first anti-tumor necrosis factor inhibitor (TNFi) as a part of specific anticytokine therapy approved by US-FDA and EMA for the treatment of rheumatoid arthritis (RA) after several clinical trials [46]. Etanercept, along with other TNF inhibitors with similar structures, have revolutionized management of RA and dramatically improved disease activity, function, quality of life and mortality for these patients [47].

2.2.2. REMICADE (INFLIXIMAB)

Infliximab is a chimeric immunoglobulin G1κ monoclonal antibody that binds with high affinity and specificity to the soluble form of tumor necrosis factor (TNF)-α, preventing it from binding to cellular receptors. Infliximab also binds to membrane bound TNF-α found on inflammatory cell surfaces, inducing apoptosis. Currently, infliximab is successfully used for the induction and maintenance of remission in Crohn's disease (CD). Infliximab's efficacy in the treatment of ulcerative colitis (UC) is now being investigated due to the similarities in the pathophysiology of CD and UC [48].

2.2.3. STELARA (USTEKINUMAB)

Ustekinumab is a monoclonal antibody effectively targeting p40 subunit of interleukins-12 and -23 in Crohn's disease (CD) [49] and an alternative therapeutic especially to adult patients intolerant to other anti-TNFα drugs, Immunomodulators and corticosteroids [50, 51]. Ustekinumab has also demonstrated an improvement in mucosal healing parameters.

2.2.4. SIMPONI (GOLIMUMAB)

Golimumab (Brand name 'Simponi') is a fully human monoclonal antibody against tumour necrosis factor-alpha (TNFα) subcutaneously administered once a month with an advantage of requiring less frequent administration as compared to the other TNF antagonists. In the EU, golimumab is approved as monotherapy and/or in combination with methotrexate for the treatment of inflammatory arthritis, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis in adults, and polyarticular juvenile idiopathic arthritis (pJIA) in children. Infliximab and Adalimumab were the first biological agents used to induce and maintain remission in ulcerative colitis. More recently, a third tumor necrosis factor antagonist, Golimumab, was approved, extending the therapeutic approach for moderate-to-severe ulcerative colitis [52].

2.2.5. RITUXIMAB (RITUXAN)

Rituximab (RTX) is a chimeric monoclonal antibody against CD20, commonly used in the

treatment of hematological malignancies and autoimmune diseases [53]. It is the first antibody approved for immunotherapy in nonmalignant autoimmune disease like rheumatoid arthritis, non-Hodgkin's B-cell lymphoma and other B-cell lymphoproliferative disorders [54].

2.2.6. GEREF (SERMORELIN)

Sermorelin, a 29 amino acid analogue to human growth hormone-releasing hormone (GHRH), is the shortest synthetic peptide with full biological activity of GHRH. Intravenous and subcutaneous Sermorelin specifically stimulate growth hormone secretion from the anterior pituitary [55] leading to maintenance, regeneration and repair functions, regulation of carbohydrate and lipid metabolism, cardiovascular, immune, and brain function, bone density and skin integrity. Sermorelin targets the stimulation by the hypothalamus to combat age-related GHRH decline. Major advantage of Sermorelin over rhGH (Recombinant Human Growth Hormone) injections is formulation and ease of use [56].

3. BIOTHERAPIES

Bio-therapies are the treatment strategies for curing hazardous diseases with the help of modalities with natural origin like vaccines, blood and blood components, gene therapy, and recombinant protein sources [8, 57]. The current understanding about molecular and cellular biology and pathophysiology of diseases has helped identify the cellular sources and molecular processes which allowed the production of diverse biological therapies such as monoclonal antibodies [8]. Biotherapies are more effective because they target the molecules which are involved in pathogenesis of disease which is quite difficult in conventional treatments [6]. Recently, scope for biotherapies has spread across to treat cancer, inflammation/autoimmunity and cardiovascular-metabolic disorders [58]. Due to their high efficiency, minimal side effects and targeted nature they are now playing a major role in treating acute and chronic diseases like common cold, rheumatoid arthritis, psoriasis, diabetes, blood disorders, cancer, chronic kidney disease, vaccines and inflammatory bowel diseases [58].

3.1. CLASSIFICATION OF BIOTHERAPIES

1. Immune system-targeted therapies

1.1 Non-specific immune stimulators: Eg- Interleukin 2
1.2 Monoclonal antibodies therapy
1.3 Cytokines: Eg- Interferons, Anti-tumour necrosis factor
1.4 Vaccines

2. Endocrinological (hormonal) therapies

2.1 Exogenous Hormones
2.2 Hormone receptor inhibitors

3. Tyrosine kinase inhibitor therapy
4. Adoptive cellular therapy
5. DNA repair enzyme inhibitors therapy
6. Gene therapy

3.1.1. MONOCLONAL ANTIBODIES

Monoclonal antibodies are **antibodies** that are made by identical immune cells that are all clones of a unique parent cell [see **FIG 1**] that are designed to recognise and bind to specific receptors found on cell surface. It is used as a therapy for diseases like cancer, arthritis and metabolic diseases. There are 4 broad types of monoclonal antibodies: murine (made from mouse protein), chimeric (made from mice and human proteins), humanized (made from small parts of mouse protein attached to human protein), human (made fully from human) [59]. The monoclonal antibodies can be produced by different techniques like phage display, using transgenic mice or single B cell antibody technology. However widely used technology for the *In Vitro* antibody selection is phage display [60].

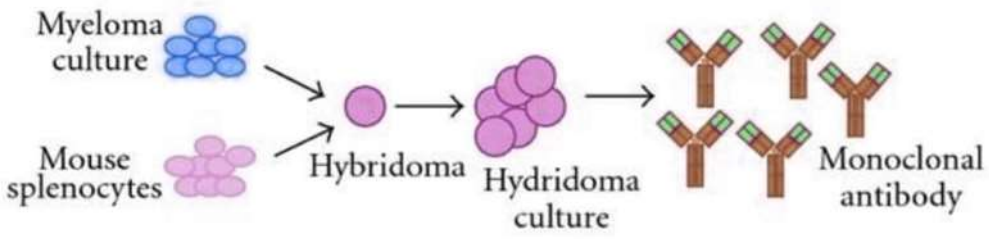

FIG 1: Schematic Representation of the production of monoclonal antibodies [84].

3.1.2. INTERFERONS

Interferons naturally occurring defence proteins that are activated upon entry of viral particles. They trigger the Natural killer cells for an effective response. Interferons got their name because they 'interfere' with virus and keep them multiply. Apart from anti-viral properties, interferons possess pleiotropic effects on cell growth, cell motility and cell function [61].

3.1.3. INTERLEUKIN

Interleukin (IL-2 specifically) is a cytokine which is secreted by the activated T-lymphocytes responsible for stimulating the growth of defence cells in the immune system [62]. IL-2 is used as an immunotherapeutic agent to treat many diseases like leishmania, leprosy and HIV- infection [63]. The availability of recombinant IL-2 has made it feasible to develop interleukin-2 as an in vivo therapeutic reagent. With deeper understanding of their applications, IL-2 can be viewed to play an effective major role in the medicinal field [64]

3.1.4. ONCOLYTIC THERAPY

Oncolytic Virotherapy is a promising form of gene therapy for cancer, employing nature's own agents to find and destroy malignant cells [65].Oncolytic viruses (OVs) are emerging as important agents in cancer treatment. Oncolytic viruses offer the attractive therapeutic combination of tumor-specific cell lysis together with immune stimulation, therefore acting as potential *In Situ* tumor vaccines [see **FIG 2**]. The effectiveness of OVs has been demonstrated in many preclinical and clinical studies [66]. Because of the advances in biotechnology and virology, the field of virotherapy has rapidly evolved over the past two decades with innovative recombinant selectivity-enhanced viruses (second generation oncolytic viruses) being developed. Nowadays, therapeutic transgene-delivering "armed" oncolytic viruses (third generation oncolytic viruses) have been engineered using many kinds of viruses [67]. Oncolytic virus therapy is perhaps the next major breakthrough in cancer treatment following immunotherapy [68].

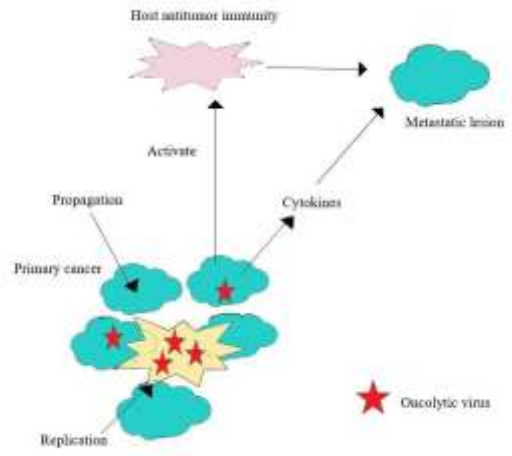

FIG 2: Different mechanisms of tumor-specific cell lysis by Oncolytic virus [68].

3.1.5. HORMONE THERAPY FOR METASTATIC BREAST CANCER

In the recent years there are multiple approaches to anticancer therapy, among those hormone therapies [see **FIG 3**] is of them which plays an important role in curing many diseases like metastatic breast cancer [69]. In Estrogen receptor-positive breast cancer, Tamoxifen is a first line therapy in postmenopausal women with a Selective Estrogen Receptor Modulator (SERM) [70, 71]. It modifies the Estrogen receptors on the cancer cells, blocks their binding to the hormone and prevents the proliferation of cancer cells. Aromatase is a cytochrome P450 with Anti- Estrogen activity and is used as an effective endocrine treatment for post-menopausal breast cancer [70].

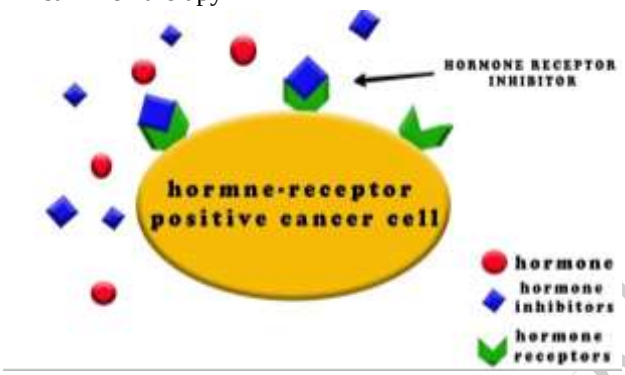

FIG 3: Schematic representation of Hormone therapy for cancer treatment.

3.1.6. TESTOSTERONE WITHDRAWAL FOR PROSTATE CANCER

Prostate cancer is a common cancer in men [72]. Activation of androgen receptors is the main reason for prostate cancer. Androgen withdrawal therapy can slow down the growth of cancer cells [see **FIG 4**] [73]. Hormonal therapy decreases the growth of prostate cancer by the withdrawing the circulation of testosterone to the cancer cells. It can be done by the various methods like oral Estrogen administration, orchiectomy, antiandrogens and also luteinising hormone releasing hormone agonists [74].

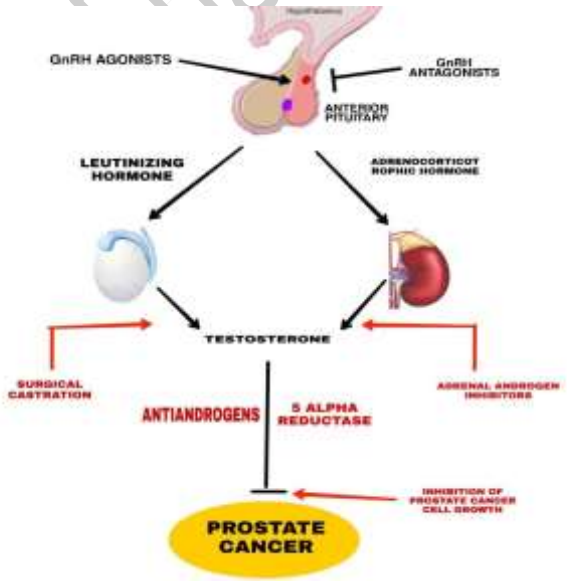

FIG 4: Schematic representation of Androgen withdrawal therapy for prostate cancer treatment.

3.1.7. TYROSINE KINASE INHIBITOR THERAPY

Protein tyrosine kinase (PTK) is one of the major signalling enzymes in cell signal transduction that catalyses the transfer of ATP-γ-phosphate to the tyrosine residues of the substrate protein, regulating cell growth, differentiation, and a series of physiological and biochemical processes. Abnormal expression of PTK usually leads to cell proliferation disorders, and is closely related to tumor invasion, metastasis and tumor angiogenesis. PTKs are major targets to anti-tumor drugs. Tyrosine kinase inhibitors (TKIs) compete with ATP for the ATP binding site of PTK and reduce tyrosine kinase phosphorylation, thereby inhibiting cancer cell proliferation [75]. Studies reveal that Tyrosine kinase inhibitors (TKIs) have markedly improved the prognosis of patients with certain Leukemia [76]. Recently, tyrosine kinase inhibitors (TKI) have emerged as new classes of anticancer therapies. However they are associated with side effects including thyroid dysfunction [77].

3.1.8. DNA REPAIR ENZYME INHIBITORS

Modern cancer therapies mainly target DNA and disrupt the genome preventing cancer cells from dividing and proliferating. However, cancer cells can survive by over-activating a wide range of DNA repair pathways to eliminate the induced damage. In this context, DNA repair mechanisms are considered to be a vital target to improve cancer therapy [78]. Homologous recombination (HR) and Non-homologous end joining (NHEJ) are major Double Stranded DNA Break repair pathways in higher eukaryotes. It is known that expression of DSB repair genes is altered in various cancers. Activation of DSB repair genes is a prime reason for chemo- and radio resistance. Targeting DSB repair is therefore an attractive strategy to eliminate cancer. Blocking the residual repair using inhibitors can potentiate the efficacy of cancer treatment. [79]

3.1.9. B CELL VACCINE

Generally, vaccine stimulates the immune system and is based on antibody mediated protection from the disease where B cells and T cells play a major role. B cells activated by vaccines produce antibody against antigen or antigen bearing particles [see **FIG 5**] [80]. B cell vaccines are therapeutically effective in treating diseases like autoimmune skin diseases, autoimmune neurologic disorders, myasthenia gravis, or antibody/immune-complex-mediated Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA) and also increase the anti-tumour response and improve the efficacy of therapeutic cancer vaccines [81, 82, 83]. B cell vaccines are also a cure for Human Papilloma Virus (HPV) 16 and 18 [84].

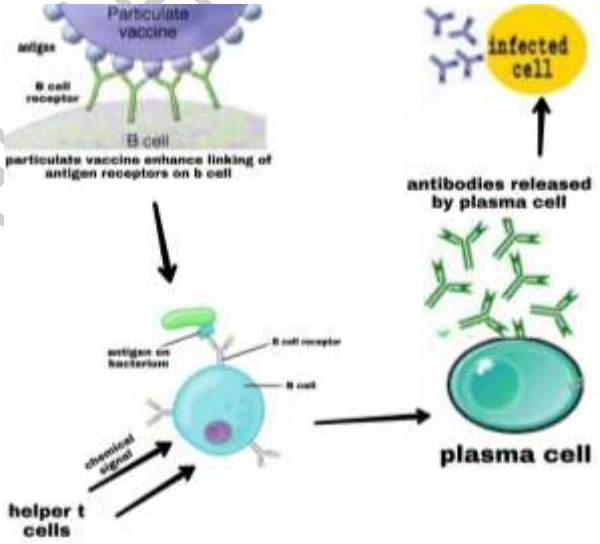

FIG 5: B-Cell activation by Particulate vaccines [85].

4. CONCLUSION

Bio-therapies and Bio-therapeutics are a new approach to treat life threatening diseases which cannot be tackled by conventional treatments. The main source of these therapies and therapeutics are proteins, peptides and blood derived naturally from plants and animals. The current global scenario of newer heath complications developing because of

the increasing population emphasises the need for these alternate therapies that are considered as revolutionized treatment for various diseases because they target the specific molecular mechanism to influence the activity of microorganisms aiming to limit the side effects. They have resolved the diseases like diabetes, heart disease, cancer, rheumatoid arthritis, schizophrenia, and Alzheimer's illness which are difficult to be treated by conventional medicines. Bio-therapeutics has the potential to destroy microbes which are unsafe and resistant to antibiotics. Deeper understanding of specific mechanism of immune system has helped find new target structures for therapeutic mediation. Researchers globally should focus on developing new therapeutics or therapies which are more convincing and efficient.

5. FUTURE PROSPECTIVES

Bio-therapeutics and Bio-therapies are one of the fastest growing sectors in the field of medicines originated from living cells used to treat many life threatening and rare diseases. In recent years, the use of Biologics has expanded significantly. Ideal biologics should be affordable, targeting the specific cells with minimum side effects. However Biologics used currently have yet to meet the expectation with numerous downsides still persisting like discovering most ideal structured bio-therapeutics, minimizing off target effects, raising and predicting the absorption, distribution, metabolism and excretion of therapeutics. Bio therapeutics are only going to grow in clinical importance and are set to herald a new generation of disease management and cure. This article emphasizes the new age researchers to improve and develop therapeutics and therapies with a greater specificity, efficacy and minimum side effects.

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