

Advancements in Immunomodulatory Therapies for Autoimmune Disease

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ABSTRACT

This thorough review covers the latest advancements in immunomodulation and drug discovery, as well as their effects on medicine. Immunomodulation, which involves adjusting the immune system's activity, has become a promising strategy for treating various diseases, including autoimmune disorders, cancer, infectious diseases, and inflammatory conditions. The review details the progress in personalized immunomodulatory therapies, combination treatments, the discovery of new targets and pathways, strategies for overcoming resistance, managing safety and side effects, regulatory issues, and consideration related to cost and accessibility. It also explores the potential impact of Immunomodulation and drug discovery on the future of medicine, highlighting the role of precision medicine, advancements in cancer therapy, the management of infectious diseases, the treatment of autoimmune and inflammatory disorders, and the identification of future therapeutic targets. Despite the challenges, the review emphasizes the significant potential of Immunomodulation and drug discovery to revolutionize healthcare and enhance patient outcomes.

Keywords: Immunomodulatory Therapies, autoimmune disorders, cancer, infectious diseases

INTRODUCTION

Autoimmune diseases happen when the immune system mistakenly targets the Body's own tissues, leading to disorders like rheumatoid arthritis, multiple sclerosis, Lupus and psoriasis. These conditions are long-lasting and complex, making them Difficult to treat and often requiring ongoing management. There have been notable advancements in immunomodulatory therapies, which aim To adjust the immune system to decrease inflammation and prevent damage. These Therapies have progressed from general treatments to more specific approaches, Such as biologic drugs and small molecule inhibitors, that target precise immune System pathways. This review will examine the latest progress in these therapies for autoimmune diseases. We will look at how these treatments function, recent clinical advancements, and the increasing emphasis on personalized medicine that is customized to individual patients. Additionally, we will discuss challenges like treatment resistance, safety issues, and the development of new treatment options. Our

purpose is to emphasize the potential of these new therapies to greatly enhance patient care and outcomes. Immunomodulation plays a crucial role in healthcare as it involves altering the immune system's function to achieve therapeutic outcomes. The immune system is essential for defending the body against infections, pathogens, and abnormal cells. However, when immune responses are dysregulated, it can lead to autoimmune diseases, allergies, and cancer. Immunomodulatory treatments aim to restore or adjust immune function, offering potential therapeutic benefits. Drug discovery is a multidisciplinary field critical for developing new medications to treat diseases. Traditional methods in drug discovery often face challenges in cost, time, and success rates. These advances can speed up the development of effective and safe therapeutic agents. The intersection of immunomodulation and drug discovery has created new opportunities for therapeutic interventions. Understanding how drugs modulate the immune system and their mechanisms of action has led to the repurposing of existing

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medications for new uses. Additionally, researchers are exploring new agents that can selectively modulate immune responses to treat diseases more effectively. The importance of immunomodulation, drug discovery, and medicine in healthcare is immense.

What Is Immunomodulatory?

Immunostimulants and immunomodulatory are drugs that modulate the immune response and can be used to increase the immune responsiveness of patients with immunodeficiency as in AIDS, chronic illness and cancer.

The drugs currently used for this purpose are:

• **BCG**

1. Inosiplex
2. Cytokines
3. Thymosin
4. Interferon

• **Thalidomide**

1. Immunisation

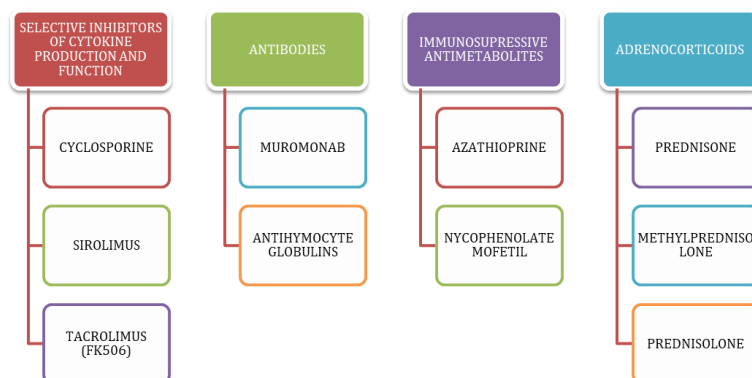
The BCG vaccine used in tuberculosis has also been tried in cancers. Levamisole, used in helminthiasis, is also found to enhance cell-mediated immunity in humans. It has been tried in some cancers.

Immunoglobulin:

Immunoglobulin's (Ig) are human gamma globulins that carry the antibodies-like normal human gamma globulin, tetanus Ig rabies if, anti-diphtheria Ig and hepatitis- 8 Allergic reactions including serum sickness anaphylaxis can occur with antisera, while it uncommon with Is.

1. ACTIVE IMMUNISATION

2. PASSIVE IMMUNISATION



• **IMMUNOSTIMULANTS:** Immunostimulants are drugs that modulate the immune response and can be used to increase the immune responsiveness of patients with

• **Active Immunisation:**

Active immunization is the administration of antigen to the host in order to induce antibody production. Vaccines are used for active immunization.

They impart active immunity, which takes some time to develop and are therefore used prophylactically.

The antibodies so developed destroy the specific microorganism when it enters the body.

• **Passive Immunisation:**

Passive Immunization is imparting immunity to a host passively by the transfer of anti- bodies,

Eg. Antisera and immunoglobulins (Ig).

This affords immediate protection because ready-made antibodies are available. Primary immunization provides primary immunity and is usually given in children,

Eg. DPT (Triple antigen given to infants).

• **IMMUNOSUPPRESSANT:**

• Immunosuppressant drugs inhibit cellular/humoral or both immune response and have their major use in organ transplantation and autoimmune diseases.

• These drugs have met a high degree of success in organ transplant and autoimmune diseases.

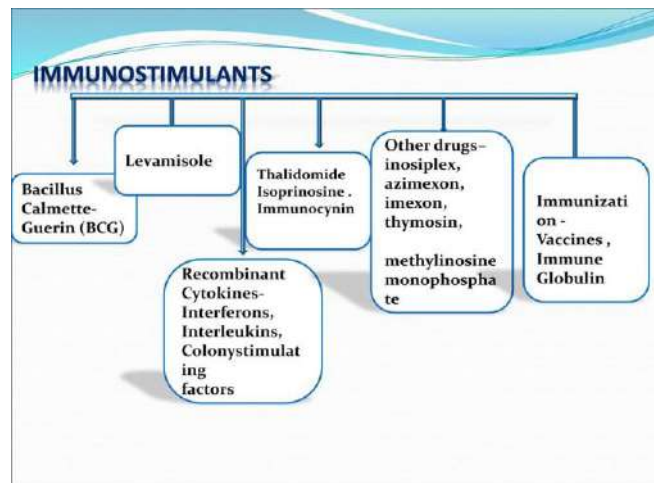
• However, such therapies require lifetime use and non-specifically suppresses the entire immune system.

• Almost everyone who receives an organ transplant has to take immunosuppressant drugs.

• When one gets an organ transplant, our body knows that the new organ is foreign.

• This triggers a response by the body's immune system to attack it.

immunodeficiency it is known as Immunostimulants



● **What Is Autoimmune Disorders?**

- Normal immune system has inbuilt capacity to distinguish 'self from non-self or foreign tissues; when confronted with a foreign invading agent, the host normally mounts an inflammatory response without causing harm to self-tissues
- Autoimmune diseases, on the other hand, are essentially due to failure of such distinction between 'self' and 'non-self', instead the body reacts by immunologic reaction against own tissues and causes tissue damage
- Autoimmunity refers to mere presence of either antibodies or T cell self-reactivity against own tissues, both of which may or may not cause tissue damage, and thus not always pathogenic.

Immune Tolerance:

Immune tolerance is a normal phenomenon present since foetal life. It is defined as the ability of an individual to recognize autoantigens and show selective unresponsiveness to autoantigens. Although clones of lymphoid cells capable of responding to

autoantigens exist in normal individuals, these cells respond selectively to autoantigens. This is based on two general processes:

- 1) Sequestration of self-antigens
- 2) Generation and maintenance of self-tolerance

1) Sequestration of self - antigens:

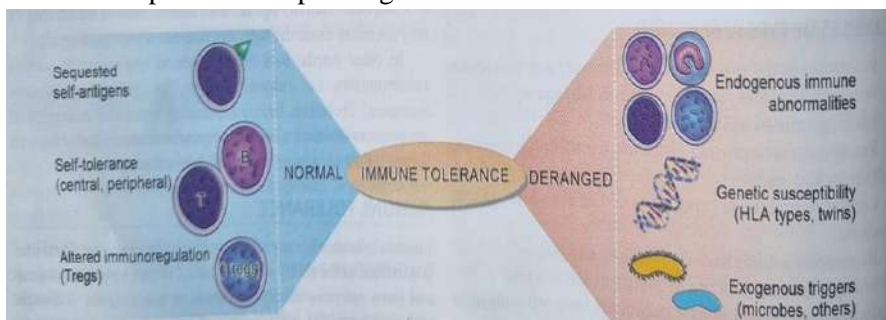
Some self-antigens reside at locations that are hidden from the immune system at 'privileged sites' that are out of circulatory reach of blood or lymph, e.g. anterior chamber of the eye, or brain. Thus, the lymphoid system remains in a state of 'immune ignorance' about these sites. Besides, there is production of immunosuppressive cytokines.

Eg:-TGF-B locally at these sites, causing apoptosis of activated T lymphocytes.

2) Generation and maintenance of self-tolerance

A state of self-tolerance is generated and maintained by one of the two mechanisms: central deletion of autoreactive lymphocytes, and peripheral silencing of autoreactive lymphocytes

● **PATHOPHYSIOLOGY:-**



Autoimmunity occurs when mechanisms of immune tolerance of the body are broken. In general, abnormal immune response in autoimmunity is explained by a combination of three factors which may be interacting:

- A) Endogenous abnormalities in the immune system.
- B) In a genetically susceptible host.

C) With triggers from exogenous agents.

A.Endogenous Abnormalities In The Immune System

1. Altered antigen presentation:-Alteration in the availability and presentation of self-antigens is an important part of autoimmunity.

2. Increased T and B cell stimulation:-

Enhanced help from T cells and increased B cell function from the following mechanisms produces autoantibodies and autoimmunity.

3. Defective clearance of apoptotic material apoptotic material is not cleared efficiently by the body's immune system, and the apoptotic debris becomes immunogenic. This activates dendritic cells and stimulates B cells forming autoantibodies against apoptotic material.

4. Release of sequestered self-antigens: which are completely sequestered may act as foreign-antigens if introduced into the circulation later. This may occur when there is damage or inflammation at these sites, and that causes significant immunologic attack by activated T cells.

For Example,

1. In multiple sclerosis, immune attack against autoantigens (myelin, non-myelin) expressed in the brain.

B.Genetic Susceptibility

Evidence has been accumulating that genetic susceptibility genes have an important role in autoimmunity:

1. HLA gene association: It has been seen that particular MHC alleles (mainly class II HLA alleles) have fairly consistent associations with susceptibility to a particular autoimmune disease. This may be owing to the difference in the ability of varying alleles of MHC molecules to present auto antigenic peptides to autoreactive T cells.

2. Other evidence:-Besides HLA association, a few other factors supporting genetic predisposition to autoimmune diseases.

C.Exogenous Agents

Certain environmental agents, in particular microbial infections, act as triggers for autoimmunity.

1. Microbial infections:-Infection with viruses (e.g. EBV infection), bacteria (e.g. streptococci, Klebsiella), and mycoplasma have been implicated in triggering autoimmunity.

● the mechanism for this can be explained by one of the two ways:

i) Molecular mimicry by which the protein products of microbes express the same antigen as self-antigen and thus activate autoreactive lymphocytes.

ii) Upregulation of costimulatory signals on antigen-presenting cells which results in clonal energy which activates T cells specific for auto-antigens.

2. Other factors besides infections, the role of other environmental agents such as cigarette smoking, tissue damage, and inflammation in triggering autoimmunity has been found.

2) CAUSES

•Genetic Factors:

- 1) Family history
- 2) Specific genes

•Environmental Triggers:

- 1) Infection
- 2) Chemical exposure
- 3) Diet

•Hormonal factory:

- 1) Gender
- 2) Pregnancy

•Immune Dysregulation:

- 1) Loss of immune tolerance
- 2) Defects in immune regulation
- 3) Stress

3) SYMPTOMS

•Digestive Symptom:

- 1) Abdominal Pain or Cramping
- 2) Diarrhoea or Constipation
- 3) Unintended Weight Loss or Gain

•Respiratory Symptoms:

- 1) Shortness of Breath
- 2) Chronic cough

•Generalized Symptoms:

- 1) Fatigue
- 2) Fever
- 3) Joint pain or swelling
- 4) Weakness

•Endocrine Symptoms:

- 1) Thyroid Dysfunction
- 2) Menstrual Irregularities

•Specific Autoimmune Disease Symptoms:

- 1) Rheumatoid Arthritis (RA)
- 2) Lupus
- 3) Multiple Sclerosis
- 4) Type 1 Diabetes
- 5) Psoriasis:

4) DIAGNOSIS

- 1) Medical History
- 2) Physical examination
- 3) Laboratory test
- 4) Organ specific test
- 5) Biopsy
- 6) Monitoring disease progression
- 7) MRI

8) Complete blood count test

9) CT scan

5) TREATMENTS:

1) Immunosuppressant's

2) Stem Cell Therapy

3) Plasmapheresis

4) Antigen-Specific Immunotherapy

5) Intravenous Immunoglobulin

6) Lifestyle and Supportive Therapies

7) Cytokine Inhibitor

8) T-cell Modulators

9) Gene Therapy

10) Regular Physical Activity

11) Stress Management

12) Smoking Cessation

13) Limiting Alcohol Consumption

14) Weight Management

15) Vitamin D Supplementation

●ROLE OF IMMUNOMODULATORY IN AUTOIMMUNE DISORDERS

Immunomodulation plays a vital role in managing and treating autoimmune diseases. Autoimmune diseases occur when the immune system mistakenly attacks healthy tissues and organs, resulting in chronic inflammation and tissue damage. Immunomodulatory Treatments aim to restore balance and regulate immune responses to prevent or alleviate symptoms of autoimmune diseases.

1) Minimizing Steroids Use

2) Modulating Immune Cell Communication

3) Long Term Management and Disease modification

4) Reducing Immune Cell Activation

5) Balancing the Immune System

6) Suppressing Overaction Immune Response

7) Cytokine Modulation

●PRINCIPAL AND MECHANISMS OF IMMUNOMODULATORS

◇Principle:-

The goal of immunomodulation is to restore the immune system's balance, which can be disrupted by conditions like autoimmune disorders or allergies to achieve a suitable immune reaction.

Specificity: - Immunomodulatory interventions can be targeted toward specific immune cell populations, signaling pathways, or cytokines, depending on the disease being treated.

Plasticity:-The immune system exhibits a degree of plasticity, meaning it can adapt and change its responses. Immunomodulation takes advantage of

this plasticity to modify immune reactions in response to different stimuli or disease states.

◇Mechanism

Suppression:-Immunomodulation can include the reduction of immune responses to decrease inflammation or prevent immune-mediated damage. This can be accomplished by inhibiting pro-inflammatory cytokines, down regulating immune cell activation, that help suppress excessive immune reactions.

Stimulation:-Immunomodulation can also aim to enhance immune responses to improve immune function. This can be achieved by promoting the activation and proliferation of immune cells, such as T cells or by increasing the production of specific cytokines or antibodies.

Immune Cell Modulation:-Interventions can target immune cells directly to modify their function.

Eg: - monoclonal antibodies can bind to specific cell surface receptors.

Cytokine Modulation:-Cytokines are critical in immune regulation, and immunomodulation can involve modifying cytokine production. This can be done by blocking and enhancing specific cytokines and adjusting the balance between proinflammatory and anti-inflammatory cytokines.

Tolerance Induction: Immunomodulation can focus on inducing immune tolerance, especially in cases of autoimmune diseases or organ transplantation. This involves fostering immune tolerance towards self-antigens or transplanted tissues through mechanisms such as inducing energy or deleting autoreactive immune cells.

●THE INTERPLAY BETWEEN IMMUNOMODULATORY AND DRUG DISCOVERY

Immunomodulatory therapies are a key focus in drug discovery due to their ability to modulate the immune system's response, which is crucial for treating various diseases, including cancer, autoimmune disorders, and infections. The interplay between these therapies and drug discovery involves several key aspects:

1) **Target Identification and Validation:**- Researchers identify specific molecules or pathways involved in immune regulation that could be targeted by new drugs.

Eg: - checkpoint inhibitors target molecules like PD-1/PD-L1 to enhance immune responses against cancer cells.

2) Drug Design and Development:-Based on target identification, scientists design drugs that can modulate immune functions. This includes small molecules, monoclonal antibodies, and other biologics. The challenge is to design drugs that effectively alter immune responses without causing unwanted side effects.

3) Preclinical and Clinical Testing:-New immunomodulatory drugs undergo rigorous testing to assess their efficacy and safety. Preclinical studies in animal models help to predict how the drugs will behave in humans, while clinical trials test the drugs in human populations.

4) Mechanism of Understanding how these drugs work at a molecular level helps in optimizing their use. For instance, elucidating the exact mechanism by which a drug alters immune cell activity can lead to better patient selection and personalized treatments.

5) Combination Therapies:-Researchers explore combinations of

Immunomodulatory drugs with other therapies, such as chemotherapy, targeted therapies, or radiation.

1. Pharmacological Treatments:-

1) Corticosteroids:-

•**Mechanism:**-reduce inflammation and suppress the immune response.

•**Examples:**-Prednisone, hydrocortisone.

•**Indications:**- In conditions like rheumatoid arthritis, lupus, and multiple sclerosis.

•**Considerations:**-Long-term use can lead to side effects like osteoporosis, diabetes, and hypertension.

2) Biologics:-

•**Mechanism:**-Target specific components of the immune system or inflammatory pathways.

•**Examples:**-

TNF Inhibitors: - Etanercept, infliximab.

IL-6 Inhibitors: - Tocilizumab.

B-cell Depleting Agents:-Rituximab.

•**Indications:**-Used in rheumatoid arthritis, ankylosing spondylitis, and lupus.

•**Considerations:**-Can increase susceptibility to infections and may have other immune-related side effects.

•**Lifestyle Modifications:-**

3) Diet:-

•**Purpose:**-A balanced diet can help manage inflammation and overall health.

•**Considerations:**-Specific dietary changes may be recommended based on the disease and individual needs.

4) Stress Management:-

•**Purpose:**-Reducing stress can help manage autoimmune symptoms.

•**Methods:**-Includes relaxation techniques, mindfulness, and therapy.

●THERAPEUTIC USES

1. Medications:-

Anti-inflammatory drugs, corticosteroids, immunosuppressant, and pain-killing medications can help manage symptoms.

2. Supplements:-

Supplements can replace substances the body lacks, such as insulin, vitamin B12, or thyroid hormone.

3. Blood Transfusions:-

Blood transfusions can help if blood is affected.

4. Physical Therapy:-

Physical therapy can help with movement if the bones, joints, or muscles are affected.

5. Precision Therapies:-

Precision engineered CAR-T cells can seek out and kill B cells that cause autoimmune disease.

6. Biologic Response Modifiers:-

Also known as immunomodulatory, these medications target the disease-causing mechanism.

●IMMUNOMODULATORY IN CANCER THERAPY

1. Monoclonal Antibodies:-

Mechanism: - These are antibodies designed to bind to specific antigens on cancer cells or on immune cells, enhancing the immune system's ability to recognize and kill cancer cells.

Examples: - Rituximab (Rituxan) targets CD20 on B cells; trastuzumab (Herceptin) targets HER2 on some breast cancer cells

2. Cancer Vaccines:-

Mechanism: - Cancer vaccines aim to stimulate the immune system to recognize and attack cancer-specific antigens. They can be preventive (for high-risk individuals) or therapeutic (to treat existing cancer).

Examples: - The HPV vaccine (Gardasil) helps prevent cervical cancer; Provenge (sipuleucel-T) is a therapeutic vaccine for prostate cancer.

3. Cytokine Therapy:-

Mechanism: - Cytokines are proteins that can influence immune cell activity. Administering specific cytokines can enhance immune responses against cancer cells.

Examples: - Interleukin-2 (IL-2) and interferon-alpha are used to boost the immune response in some cancers.

4. Oncolytic Virus Therapy:-

Mechanism: - This involves using genetically modified viruses that selectively infect and kill cancer cells while stimulating an immune response against the cancer.

Examples: - Alipogene laherparepvec (T-VEC) is an oncolytic virus therapy approved for melanoma.

5. Immune Modulators:-

Mechanism: - These drugs modify the immune system's activity to enhance its ability to fight cancer. They can act on various immune cells and signaling pathways.

Examples: - Thalidomide, lenalidomide, and pomalidomide are used in multiple myeloma and certain other cancers.

● Immunomodulatory Intervention For Allergic Disorder

1. Allergies Immunotherapy:-

Mechanism:-This treatment involves administering gradually increasing doses of an allergen to desensitize the immune system and reduce sensitivity over time. It can be delivered via subcutaneous injections or tablets/drops.

Examples:-Grass pollen, ragweed, and house dust mites, various allergens including pollen, mould, and insect stings.

2. Biologic Therapies:-

Mechanism:-Biologics are targeted therapies that modify specific immune responses involved in allergic reactions. They can block inflammatory cytokines or other molecules critical to allergy development.

Examples:-

1. Anti-IgE Antibodies: - Omalizumab (Xolair) binds to IgE antibodies, preventing them from triggering allergic reactions.

2. Anti-IL-4/IL-13 Antibodies: - Dupilumab (Dupixent) inhibits IL-4 and IL-13, which are involved in allergic inflammation and asthma

3. Immunosuppressive Agents:-

Mechanism:-These drugs suppress overall immune activity and are used in severe cases where

conventional treatments are ineffective. They are generally severe cases of allergic diseases.

Examples:-Methotrexate and cyclosporine may be used in severe cases of allergic disorders such as atopic dermatitis.

4. Allergen Avoidance and Environmental Control:-

Mechanism:-While not a therapy per se, managing environmental factors and avoiding known allergens can complement other treatments and reduce symptom burden.

Examples: - Using air purifiers, controlling indoor humidity, and minimizing exposure to allergens like dust mites, pet dander, and mould.

● Advancement In Medicine

1. Biological agents:-

Monoclonal Antibodies: - These engineered molecules target specific immune system components.

Examples include:-

●**TNF-alpha Inhibitors:**-A cytokine involved in inflammation. These are used for conditions like rheumatoid arthritis and Crohn's disease.

●**IL-6 Inhibitors:**-They are applied in treating rheumatoid arthritis and other inflammatory disorders.

●**B-Cell Depleting Agents:**-Rituximab targets and depletes B-cells, which play a role in autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus.

●**Checkpoint Inhibitors:-**

Immune Checkpoint Inhibitors: - Primarily used in cancer treatment, these inhibitors, such as PD-1 inhibitors, are being explored for their potential to modulate autoimmune responses by adjusting specific immune pathways.

3. Vaccines and Tolerance Induction:-

●**Therapeutic Vaccines:**-Research is focusing on vaccines designed to induce immune tolerance in autoimmune conditions. These vaccines target specific antigens involved in autoimmune reactions.

4. Combination Therapies:-

●**Integrated Approaches:**-Combining various immunomodulatory therapies can enhance treatment effectiveness and reduce side effects.

For example, using biologics alongside small molecule drugs to improve disease management.

- **Future Direction And Potential Challenges In Advancing Immunomodulation, Drug Discovery**

1. Advancing Immunomodulation Therapy:-

A.Precision Medicine:-

Immunomodulation therapies are increasingly tailored to individual genetic, molecular, and environmental profiles. Advances in genomics and proteomics allow for the development of personalized immunotherapies that target specific immune pathways improving efficacy and reducing side effects.

Immune System Reprogramming:-

Techniques to reprogram or modulate the immune system, such as cytokine therapy or immune checkpoint inhibitors, are advancing. These approaches aim to harness the immune system's power more effectively against diseases, including cancer and chronic infections.

Microbiome and Immunity:-

Research into the gut microbiome's impact on immune function is expanding. Modulating the microbiome could influence immune responses, potentially leading to novel therapies for autoimmune diseases and allergies.

- **Drug Discovery:-**

A.Artificial Intelligence and Machine Learning:-

AI and machine learning are revolutionizing drug discovery by predicting drug interactions, identifying new drug targets, and optimizing compound screening processes. These technologies enable faster and more cost-effective drug development.

Targeted and Rational Drug Design:-

The use of structural biology and computational modelling to design drugs that specifically interact with disease-related molecules is becoming more refined. This targeted approach enhances the precision and effectiveness of new drugs.

- **Medicine:-**

A.Regenerative Medicine and Stem Cells:-

Regenerative medicine, including stem cell therapy and tissue engineering, is advancing towards more effective treatments for degenerative diseases and injuries. Stem cells have the potential to replace damaged tissues and organs, offering new therapeutic options.

Preventive and Predictive Medicine:-

There is a growing emphasis on preventive and predictive medicine, driven by advances in

biomarkers and risk assessment tools. Early detection and lifestyle interventions are becoming central to managing chronic diseases and improving overall health outcomes.

Integration of Health Data:-

The integration of electronic health records (EHRs), health information exchanges, and patient-generated health data is improving care coordination and decision-making. This comprehensive data approach supports more accurate diagnoses and personalized treatment plans.

CONCLUSION:

In conclusion, advancements in immunomodulatory therapies for autoimmune diseases represent a significant leap forward in the treatment landscape. The development of targeted biologics, such as monoclonal antibodies and checkpoint inhibitors, has enabled more precise modulation of the immune system, improving efficacy and reducing off-target effects. Advances in understanding the role of the microbiome and immune system interactions are opening up innovative treatment strategies. The integration of these advancements promises not only to enhance the management of autoimmune diseases but also to improve patient's quality of life by offering more targeted, effective, and safer treatment options. As research continues to evolve, these therapies will likely become increasingly refined, offering hope for better disease control and potentially transformative outcomes for patients with autoimmune disorders.

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