



IMMUNOSTIMULANT DRUGS

Immunostimulants, **also known as immunostimulators, are substances (drugs and nutrients) that stimulate the immune system by inducing activation or increasing activity of any of its components. One notable example is the granulocyte macrophage colony-stimulating factor. Classification**

There are two main categories of immunostimulants:

1. **Specific immunostimulants** provide antigenic specificity in immune response, such as vaccines or any antigen.
2. **Non-specific immunostimulants** act irrespective of antigenic specificity to augment immune response of other antigen or stimulate components of the immune system without antigenic specificity, such as adjuvants and non-specific immunostimulators.

Innate immune response – first line of defense against an antigenic insult. Includes

- defenses like physical (skin),
- Biochemical (complement, lysozyme, interferons)
- cellular components (neutrophils, monocytes, macrophages).
- Adaptive immune response a) Humoral immunity - Antibody production – killing extracellular organisms. b) Cell mediated immunity – cytotoxic / killer T cells – killing virus and tumour cells.

IMMUNOSUPPRESSIVE DRUGS • Those drugs that suppress the immune system. • Particularly important for transplantation, autoimmune disorders, allergies, and all the cases where immune system is too active.

IMMUNOSTIMULANT DRUGS • Those drugs that stimulate the immune system. • Particularly important for the treatment of infectious diseases, tumors, immunodeficiencies and all the cases where the immune system needs a boost.

Immunotherapy deals with the idea of boosting an individual's immune system, to allow it

to destroy microbes and tumors. The boost can be biological (microbial-derived products), pharmacological, or cell-based.

IMMUNOSTIMULANT DRUGS – MICROBIAL PRODUCTS • Many bacterial products are PAMPs, and they strongly stimulate inflammation by triggering cytokine production in APCs. These, in turn, stimulate the adaptive immunity and, overall, increase leukocytes number by boosting hematopoiesis.

The *Bacillus Calmette–Guérin* (BCG) is an attenuated (less virulent, but still alive) mycobacterium bovis strain. • This is able to infect human cells, but not to induce any pathology. Rather, it can stimulate the production of Igs by B-cell and thus behave as a vaccine against mycobacterium tuberculosis. • It has a strong inflammatory effect on some tissues, and has thus been also approved as a treatment for bladder cancer.

The bad side is that PAMPs can induce massive cytokine production, which can result in fever and shock. This is especially true with cytokines, which can also have direct toxic effects.

Immunotherapy – cytokine therapies • Since cytokines control the whole immune system, and mostly stimulate it, it is logical to use them whenever there is the need to boost immune system activity. • They are used in clinical practice, but they are burdened by severe side effects.

ACTIVE VACCINATION • Active vaccination is the process of injecting individuals with microbial antigens, heat-killed microbes or attenuated living microbes to induce antibody production and memory B-cells formation. • The individual acquires the ability to respond to the microbe he/she has been vaccinated against.

To ensure memory B-cells formation, whole microbes (either killed or attenuated) are preferred, as they also trigger fever and inflammation that boost B-cells activation and memory cells formation. • Attenuated microbes are those living strains which are still able to infect an individual, but that generate a less-dangerous pathological manifestation, which is generally inflammation/flu. • Side-effects are generally low, but sometimes they can be extremely severe.

PASSIVE VACCINATION • In passive vaccination, individuals are injected with preformed immunoglobulins (from donors). Thus, individuals acquire pools of immunoglobulins (good for immunodeficiencies) and the ability to respond to certain microbes. Transfusion of immunoglobulins is called intravenous immunoglobulins (igv). generally, igvs contain igG and igA. • Anti-microbial igvs are used against hepatitis b, botulism, diphtheria, tetanus, rabies. • It's generally well-tolerated, but sporadic side-effects can be extremely severe.

ADJUVANTS USED FOR VACCINATION • Injecting a living microbe can be dangerous, and reducing the amount of microbe to the minimum is mandatory. Here's the need for adjuvants. • Adjuvants are chemical or biological products that can either boost T-cells, activate inflammation or help to stabilize the antigen so that it can stimulate B-cells for a longer time. • Adjuvants have been also implicated in clinical side-effects of vaccinations, like the onset of juvenile diabetes in the case of Freund's adjuvant.

ADOPTIVE CELL TRANSFER • Adoptive cell transfer deals with the idea of isolating immune cells from individuals, expand them in culture and then re-infuse them. This is a wonderful strategy to kill tumors. • Tumor-infiltrated lymphocytes (TIL) are a heterogeneous population which includes Th and CTLs able to recognize and kill the tumor. The problem is that the cytokines released from the tumor suppress them. Taking these "good cells" out of the tumor mass and re-injecting them upon expansion strongly increases the ability of the immune system to react against tumors.

CELL-BASED VACCINATION • Dendritic cells can be "prepared" in vitro to show tumor antigens, and then re-injected into the patient to stimulate tumor antigens' recognition and tumor killing. This is currently defined as cell-based vaccination.

IMMUNOSTIMULANTS USES • Immunodeficiency disorders • Chronic infections • Cancer
Thalidomide Isoprinosine . Immunocynin Recombinant Cytokines- Interferons, Interleukins, Colonystimulating factors Bacillus Calmette- Guerin (BCG) Levamisole Other drugs- inosiplex, azimexon, imexon, thymosin, methylinosine monophosphate
Immunization - Vaccines , Immune Globulin

Bacillus Calmette-Guerin (BCG) • Live, attenuated culture of BCG strain of Mycobacterium Bovis
MOA • Induction of a granulomatous reaction at the site of administration. It causes

activation of macrophages to make them more effective killer cells

Therapeutic uses • Treatment and prophylaxis of carcinoma of the urinary bladder, Prophylaxis of primary and recurrent stage of papillary tumors after transurethral resection.

Adverse effects • Hypersensitivity, shock, chills, fever, malaise, and immune complex disease.

Levamisole /Ergamisol • synthesized originally as an anthelmintic but appears to restore depressed immune function of B lymphocytes, T lymphocytes, monocytes and macrophages

Therapeutic uses: • Adjuvant therapy with 5-fluorouracil colon cancer, agranulocytosis. Used to treat immunodeficiency associated with Hodgkins disease Adverse effects : • Flu-like symptoms, allergic manifestation, nausea and muscle pain .

Thalidomide MOA • Enhanced T-cell production of cytokines – IL-2, IFN- γ • NK cell-mediated cytotoxicity against tumor cells. Decrease circulating TNF- α in patients with erythema nodosum leprosum, but increase in HIV-seropositive patients, It affects angiogenesis also. Therapeutic uses • Severe, refractory rheumatoid arthritis. Multiple myeloma Adverse effects • Teratogenicity

• Hormone like, small low molecular weight polypeptides. • Maintain communication among cells to co-ordinate immune response. • Act synergistically or antagonistically thereby enhancing or suppressing their own production • Autocrine, paracrine or endocrine in action.

• Causes tissue repair and provide resistance to infection

• Cytokines : Properties Cytokine: Action TMAutocrine TMParacrine TMEndocrine

Cytokines-based therapies in clinical use

• **Isoprinosine (Inosiplex)** • Complex of the acetamidobenzoate salt of N,N- dimethylamino-2- propanol: inosine in a 3:1 molar ratio MOA • Augment production of cytokines such as IL-1, IL-2 and IFN- γ ,increases proliferation of lymphocytes in response to mitogenic or antigenic stimuli, increases active T-cell rosettes and induces T-cell surface markers on prothymocytes

• Nonspecific immunoglobulins TMAntibody-deficiency disorders TMSpecific immune globulins.

High titers of desired antibody TMHepatitis B, Rabies, Tetanus