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A Review on Immunostimulant

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Abstract: *Humans and other vertebrates reside in a world that is occupied by a huge range of pathogenic microbes and toxic substances that menace normal homeostasis; and immunity is a specialized form of host defense mechanism that works particularly in relation to the causes and prevention ofdiseases1. Manifestation of disease due to the pathogen depends on its virulence and capability of the immune system; and to achieve resistance against disease, the most important is strengthening the immune system2. If the immune system fails become under or over active, or hits the wrong target it can vent a variety of adverse consequences. Under-activity of the immune system. The proper functioning of human immune system is essential for organism survival against infectious, toxic and oncogenic agents. The concept of immuno modulation was proposed by Edward Jenner, while working on polio vaccine in 1796. A brawny, fine-functioning immune system is the keystone of excellent health*

Keywords: Immunomodulators, Immunostimulants, Mechanism, Immune system

I. INTRODUCTION

Two main compounds are able to enhance immune responses including adjuvants and Immunostimulants. An adjuvant is a substance combined with an antigen for increasing its immune response, but an immunostimulant can induce the immune response without injection with an antigen [1]. There are several types of stimulants with different mechanisms and functions such as bacterial products, complex carbohydrates (*e.g.*, glucans, schizophyllan, scleroglucanlentinan, statolon, bestatin, acemannan), vaccines, immunoenhancing drugs (*e.g.*, Levamisole, Isoprinosine, Fluoro-quindone, Avridine, Polyribonucleotides), nutritional factors (*e.g.*, vitamins, carotenoids, lipids, trace elements, selenium), animal extracts (*e.g.*, chitosan from shrimp), cytokines (*e.g.*, macrophage activating factor, interferon, interleukin-2, tumor necrosis factor), and plant extracts (*e.g.*, Lectins, mitogens such as phytohemagglutinin, concanavalin A) [2].Humans and other vertebrates reside in a world that isoccupied by a huge range of pathogenic microbes and toxic substances that menace normal homeostasis; and immunity is a specialized form of host defense mechanism that works particularly in relation to the causes and prevention of Diseases[3]. Manifestation of disease due to the pathogen depends on its virulence and capability of the immune system; and to achieve resistance against disease, the most important is strengthening the immune system[4]. There are several types of stimulants with different mechanisms and functions such as bacterial products, complex carbohydrates (*e.g.*, glucans, schizophyllan, scleroglucan, lentinan, statolon, bestatin, acemannan), vaccines, immunoenhancing drugs (*e.g.* Levamisole, Isoprinosine, Fluoro-quindone, Avridine, Polyribonucleotides), nutritional factors (*e.g.*, vitamins, carotenoids, lipids, trace elements, selenium), animal extracts (*e.g.*, chitosan from shrimp), cytokines (*e.g.*, macrophage activating factor, interferon, interleukin-2, tumor necrosis factor), and plant extracts (*e.g.*, Lectins, mitogens such as phytohemagglutinin, concanavalin A) [5].

II. IMMUNOSTIMULANTS

Immunostimulants, also known as **immunostimulators**, are substances (drugs and nutrients) that stimulate the immune system usually in a non-specific manner by inducing activation or increasing activity of any of its components. One notable example is the granulocyte macrophage colony-stimulating factor. The goal of this stimulated immune response is usually to help the body have a stronger immune system response in order to improve outcomes in the case of an infection or cancer malignancy. There is also some evidence that immunostimulants may be useful to help decrease severe acute illness related to chronic obstructive pulmonary disease or acute infections in the lungs[6].

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III. IMMUNE SYSTEM

The immune system consist of a complex network of specialized cells, tissues, molecules and biological processes within an organism that watches out the continually to protect it against attacks by foreign antigens or invaders (basically microbes-infection causing organisms such as bacteria, viruses, parasites, and fungi or any injury, and disease)[7] Non-self-molecules are

Those recognized components that do not belong to an organism's body, they are foreign invaders. One example of non-self-molecules is antigens that cause the immune system to promote the generation of antibodies against it and then combine specifically with them to induce an immune response [8].

TYPES OF IMMUN SYSTEM:-

INNATEIMMUNITY

ADAPTIVE IMMUNITY

Defense against infection is divided into two main forms namely innate immunity and adaptive immunity. Some of the differences between innate and adaptive immunity are shown in Table 1.

Innate immunity

Innate immunity regarded as the first line of defense from both external and internal attack, also known as natural or native immunity. It is a nonspecific and antigen-independent defensive mechanism which responds immediately and within minutes or hours of meeting an antigen[9].

The defensive barriers of innate immunity are of four types:

Anatomical barriers e.g., skin and mucous membrane, the epithelial cell layers offers tight junction so there is tight cell to cell contact, the mucus layers over the respiratory, gastrointestinal and genitourinary tract, and when foreign particles are inhaled, the mucus layer get contaminated which are constantly discarded by the epithelial cilia.

Physiological barriers e.g., temperature, low pH and chemical mediators.

Endocytic and phagocytic cells (neutrophils, macrophages), dendritic cells, natural killer (NK) cells and other innate lymphoid.

Inflammatory barriers e.g., a series of events occurs in inflammation process that plays an important role to destroy or inactivate microbes.

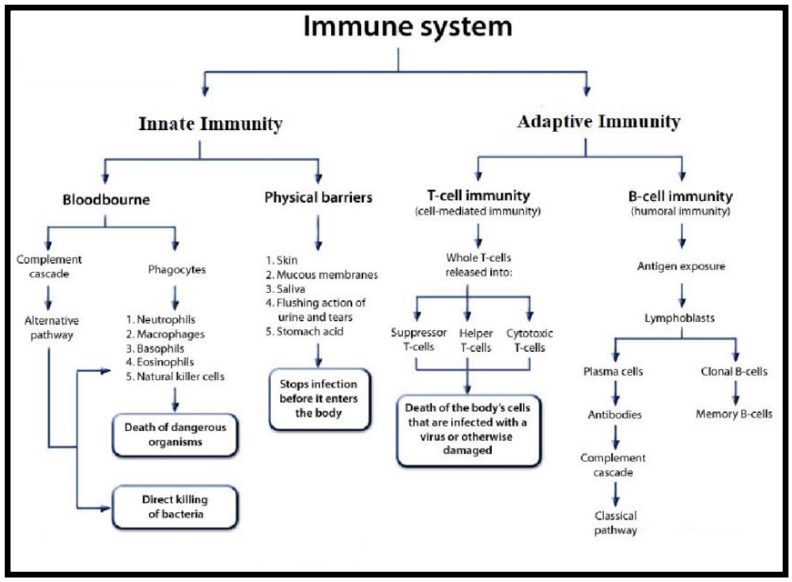

Figure 1: Flowchart of basic components of human Immune system

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Adaptive immunity

Adaptive immunity is also known as specific or acquired immunity which means the resistance acquired by human during their lifetime. It is antigen-dependent and antigen specific defensive mechanism and, thus delays the time of the antigen to get expose and to produce the maximal response. The advantage adaptive immunity is their capacity to generate memory which permits the host to elicit a more rapid, stronger and efficient immune response against consecutive exposure to the antigen [10]. This type of immunity provides the basis for effectual immunization facing infectious diseases. The two major components of adaptive immunity are Humeral (comprises of antibodies formed by B lymphocytes) and Cellular (mediated by T lymphocytes). B lymphocytes and T lymphocytes are two kind of lymphocytes found in this type of immunity that impart long lasting immunity against specific antigens by proliferating into memory cells. Lymphocytes are generated from the bone marrow and the type that mature in bone marrow turns into B lymphocytes whereas the type that leave the bone marrow and migrate to thymus gland get

Mature into T lymphocytes and based on 'cluster of differentiation' (CD) molecules on their surface they acquire certain genetic and immune surface characteristics which determines their different functions [11]. B lymphocytes are responsible for formation of specific antibodies by differentiating into plasma cells while T lymphocytes get activated in presence of appropriate antigens presented by macrophages like APC and Histocompatibility Complex (MHC). The function of B lymphocytes are like military intelligence system, they find out the target and organize defensive action, while T lymphocyte perform like soldiers, they destroy the invading substance identified by the intelligence system i.e. B lymphocytes[12]. Antigen specific receptors are encoded by genes that are assembled by somatic rearrangement of germline gene to form intact T cell receptor (TCR) and immunoglobulin (B cell antigen receptor; Ig) genes. Millions of different antigen receptors are formed from the collection of a few hundred germ-line-encoded gene elements assembly of antigen receptors, each of which are potentially unique and antigen specific1. The advantage of this diverseness of receptors helps adaptive immunity to identify any kind of pathogen [13]. They are of two types i.e., naturally acquired adaptive immunity and artificially acquired adaptive immunity.

Naturally acquired adaptive immunity:

In naturally acquired active adaptive immunity, antigens enter the body naturally then the bodies develop antibodies and specialized lymphocytes whereas in naturally acquired passive adaptive

Immunity, antibodies passes from mother to fetus/infant through placenta/mother's milk. Naturally acquired active adaptive immunity lives longer than naturally acquired passive adaptive immunity.

IV. WORKING OF IMMUNE SYSTEM

The immune system comprised of cells and proteins that uphold the body from the foreign invaders [14]. These cells emanate from the pluripotent stem cells of bone marrow. Of the two pathways - (I) the myeloid pathway, in presence of IL- 3, becomes excited giving rise to the production of platelets, erythrocytes, monocytes and granulocytes. (II) The lymphoid pathway, in presence of IL-7, becomes excited giving rise to the production of innate and adaptive lymph cells (Lymphocytes). The pathways distinction relies on the chemical signals in the surrounding area [15, 16].The adaptive response takes over when the innate immune response becomes ineffective to

Eliminate pathogen. In adaptive immunity at first antigen presenting cell (APC) like macrophages and dendritic cells recognizes, engulfs and process the antigen; and displays the specific part of antigen on its surface then present it to T-cells. T-cells receptors are there that bind with the specific antigenic sites and triggers proliferation and differentiation processes in lymphoid

tissues2. There are two classes of T-cells namely, helper T-cells and Cytotoxic T-cells which can be discriminate by their presence of some molecules on their surface like CD4+ and CD8+ respectively. T-helper cells aid the immune response in recognition of antigen and then activate other T and B cells by secreting cytokines whereas Cytotoxic T-cells aid the immune response by killing pathogen infected cells or tumor cells. One other class of T-cells, known as suppressive T-cells are able to secret suppressive cytokines that can inhibit the actions of other T-cells. Antigen binding and helper T-cell can trigger the differentiation process of B-cells into plasma cells and secret antibodies which circulate in the blood and causes destruction or inactivation of the antigen[17].

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V. CONCEPT OF IMMUNOSTIMULANT

Immunostimulants known as immunostimulators are attractive substances that activate the immune system of humans and animals for prevention of diseases and improvement of the body's natural resistance to various viral and bacterial infections. These biologically active substances are the products derived from natural sources or synthetically made with different chemical properties and mechanisms of action. In general, Immunostimulants induce synthesis of specific antibodies and cytokines for treatment of infectious diseases. Two major groups of Immunostimulants contain a) specific Immunostimulants acting as antigen for stimulation of immune responses (*e.g.,* vaccines), and b) non-specific Immunostimulants without antigenic properties enhancing immune responses to other antigens (*e.g*., adjuvants and non-specific immunostimulators). Moreover, Immunostimulants were classified based on their origin and mode of action [18].

VI. FUNCTIONS OF IMMUNOSTIMULANTS

Immunostimulants activate different elements of the immune system in humans and animals. They develop the non-specific immunotherapy and immunoprevention by stimulating the major factors of the immune system including phagocytosis, propending and complement systems, protective secretory IgA antibodies, α- and γ-interferon release, T- and B-lymphocytes, synthesis of specific antibodies and cytokines, and synthesis of pulmonary surfactant [19]. There are several reasons for using the immunostimulants in the control of various infectious diseases including: a) antibiotic resistance of the bacteria; b) allergic reactions to antibiotics; c) immunosuppressive effects of antibiotics; and d) Poor effects of the antibiotics in viral infections [19].

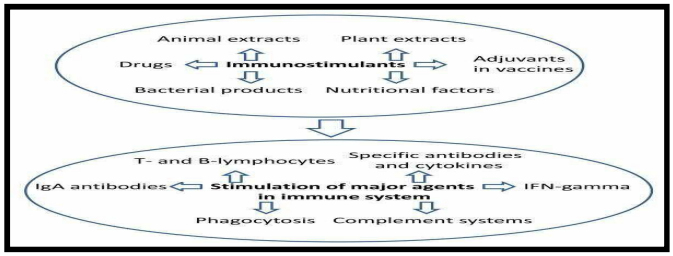

Figure 2 shows some types of immunostimulants and their general functions

TYPES OF IMMUNOSTIMULANTS:

For simplification, we divided the types of Immunostimulants as seven groups such as:-
bacterial products
complex carbohydrates
vaccines (antigens and adjuvants)
cytokines
immunoenhancing drugs
plant extracts
animal extracts

IMMUNOSTIMULATORY DRUGS

A few immunostimulatory drugs (Endogenous Immunostimulantsor Synthetic Immunostimulants) have been developed to induce humoral or cellular immune responses or both of them against bacterial or viral infections, immunodeficiency diseases, and cancer.
They were classified as follows: -

A) Levamisole (Ergamisol):-

Levamisole is a synthetic drug inducing B and T lymphocytes, monocytes, and macrophages. It was used in adjuvant therapy with 5-fluorouracil after surgical resection in patients with Duke's stage C colon cancer. Its disadvantages are allergy, nausea, flu, and muscle pain. Levamisole has been successfully used in combination with polymers for

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treatment of dermatologic disorders. For example, it was combined with cimetidine for treating recalcitrant warts, and with prednisolone for treating aphthous ulcers of the mouth [20,21].

Fig .3 Levamisole Hydrochloride Tablet IP 150 mg

B) Thalidomide: Thalidomide or Immunoprin (C13H10N2O4) is an immunomodulatory drug. Thalidomide could decrease circulating TNF-α in patients with erythema nod sumleprous. In contrast, it increased TNF-α in HIV-seropositive patients. Furthermore, its therapeutic effects were determined in severe rheumatoid arthritis and angiogenesis [20].

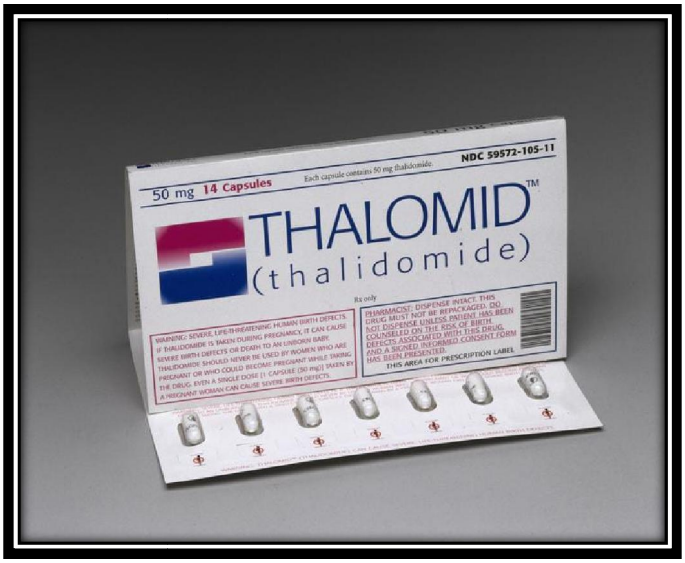

Fig .4 Thalomid (Thalidomide)

C) Isoprinosine (Inosiplex/ Imunovir): Isoprinosine (C52H78N10O17) is a combination of inosine, acetamidobenzoic acid, and dimethylaminoisopropanol. Isoprinosine could enhance the levels of cytokines including

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IL-1, IL-2, and IFN-γ. It increased the proliferation of lymphocytes against mitogenic or antigenic stimuli. Moreover, Isoprinosine augmented active T-cells and induced T-cell surface markers on prothymocytes. It was used to treat Herpes simplex infections, Epstein-Barr, and Measles viruses. Its disadvantages are minor CNS depressant, transient nausea, and increased level of uric acid in serum and urine [20].

Fig .5 Isoprinosine (Inosina pranobex TABLETAS 500mg)

D) Immunocynin: Immunocynin is a stable form of haemocynin, a copper-containing protein, found in molluses and arthropods. It was used to treat urinary bladder cancer with poor side effects such as rare-mild fever [21].

E) Bestatin: Bestatin, a dipeptide [(2S, 3R)-3-amino-2-hydroxy-4-phenylbutanoyl]-L-leucine, is an immuno-stimulant with low toxicity which binds to the cell surface of lymphocytes and macrophages and enhances both humoral and cellular immune responses. It is a leucine aminopeptidase and aminopeptidase-B inhibitor. Bestatin possesses antitumor activity and also increase the antitumor activity of bleomycin and adriamycin. Bestatin efficiently prevented the metastasis of P388 leukemia when the antibiotic was constantly injected after tumor inoculation [22]

Fig.6 Bestatin 20

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VII. MARKETED IMMUNO STIMULANT

Immunostimulants used in vaccines

Vaccines contain a wide range of immunostimulants [23]. For example, an adjuvant heat-labile enterotoxin from *Escherichia coli* (LT), administered as an immunostimulant (LT-IS) patch on the skin may further enhance immune responses to influenza vaccine in the elderly [24]. Also, the immune activation mediated by LT-IS improved the potency of generating Alzheimer's disease (AD)-specific vaccination responses as an adjuvant in the clinical trial [25]. Co-administration of a potent adjuvant in IS patches containing heat-labile enterotoxin from *E. coli* placed on the skin at the site of DNA vaccination significantly increased anti-influenza antibody immune response [26]. Adjuvants enhance and modulate immune responses to antigens. This is important when the purified antigens do not elicit the effective innate or adaptive immune systems. Adjuvants are different in the types and levels of immune responses. Expected advantages of adjuvants contain stronger immune priming, effective immune responses in low-response populations (*e.g.*, the elderly or immuno-compromised patients), the use of smaller amounts of the antigen, and safety profile [27]. New adjuvants have already applied to more efficient influenza vaccines, as well as vaccines targeting hepatitis B (HBV) and human papillomavirus (HPV) [28]. On the other hand, CpG oligonucleotides and imiquimod drugs (an anti-viral agent) could activate dendritic cells, induce *in situ* maturation and migration of DCs, and augmented both humoral and cellular immune responses [29].

REFERENCES

[1]. Carter D, Reed SG. Role of adjuvants in modelling the immune response. Cur Opin HIV AIDS. 2010; 5 (5): 409-13.
[2]. Galeotti M. Some aspects of the application of Immunostimulants and a critical review of methods for their evaluation. J Appl Ichthyol. 1998; 14 (3-4): 189-99.
[3]. Chaplin DD. Overview of the Immune Response. J Allergy ClinImmunol. 2015; 125:1-41
[4]. Meagher MW. Immune system structure and function. Encyclopediaof Health Psychology. 2014; 1-9.V
[5]. Galeotti M. Some aspects of the application of immunostimulants and a critical review of methods for their evaluation. J ApplIchthyol. 1998; 14 (3-4): 189-99. https://doi.org/10.1111/j.1439-0426.1998.tb00641.x.
[6]. https://en.wikipedia.org › wiki › Immunostimulants
[7]. Schultz KT, Grieder F. Structure and Function of the ImmuneSystem. Toxicol Paolo. 1987; 15(3):262-264.https://doi.org/10.1177/019262338701500301
[8]. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy, Asthma ClinImmunol. 2018; 14:49-59. https://doi.org/10.1186/s13223-018-0278-1
[9]. Cruvinel WDM, Júnior DM, Antônio J, Araújo P, Tieko T, Catelan Fundamentals of innate immunity with emphasis on molecular and cellular mechanisms of inflammatory response. Bras JRheumatol. 2010; 50(4):434-461.https://doi.org/10.1590/S0482-50042010000400008
[10]. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy, Asthma ClinImmunol. 2011; 7:1-8. https://doi.org/10.1186/1710-1492-7-S1-S1
[11]. Nielsen HG. Exercise and Immunity. In: Current Issues in Sportsand Exercise Medicine. 2016. p. 121-42. Available from:https://www.intechopen.com/books/advanced-biometrictechnologies/liveness-detection-in-biometrics.
[12]. Advances in Exercise Immunology - UQ eSpace. Available from:https://espace.library.uq.edu.au/view/UQ:145869.
[13]. Turvey SE, Broide DH. Innate Immunity. J Allergy Clin Immunol.2010; 125:24-32. https://doi.org/10.1016/j.jaci.2009.07.016
[14]. Sattler S. The Role of the Immune System beyond the Fight against Infection. 1003rd ed. London: Springer International Publishing; 2017. p. 3-14. https://doi.org/10.1007/978-3-319-57613-8_1
[15]. John H Humphrey SSP. Evolution of the immune system. Encycl Br.2020; 1-3.
[16]. Travis J. On the Origin of the Immune System. Science. 2009;324(5927):580-582. https://doi.org/10.1126/science.324_580

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[17]. Janeway CA JR, Travers P WM. Immuno biology: The ImmuneSystem in Health and Disease. 5th Ed. New York: Garland Science; 2001. 1-884 pp.

[18]. Labh SN, Shakya SR. Application of Immunostimulants as an alternative to vaccines for health management in aquaculture. Int J Fish Aquat St. 2014; 2 (1): 153-6.

[19]. Petrunov B, Nenkov P, Shekerdjiisky R. The role of Immunostimulants in immunotherapy and immunoprophylaxis. Biotechnol & Biotechnol Eq. 2007; 21(4): 454-63.

[20]. Patil US, Jaydeokar AV, Banda wane DD. Immunomodulators: A pharmacological review. Int J Pharm Pharm Sci. 2012; 4 (1): 30-6.

[21]. Biswajit D, Surakarta D, Chandra CR, Jashabir C. An overview of levamisole hydrochloride with Immunostimulants activity. Am J Pharm Health Res. 2014; 2 (4): 1-9.

[22]. Tsuruo T, Naganuma K, Iida H, Yamori T, Tsukagoshi S, Sakurai Y. Inhibition of lymph node metastasis of P388 leukemia by bestatin in mice. J Antiriot (Tokyo). 1981; 34 (9): 1206-9.

[23]. Dhama K, Sami Nathan M, Jacob SS, Singh M, Karthik K, Amarpal, Tiwari R, Sunkara LT, Malik YS, Singh RK. Effect of immunomodulation and immunomodulatory agents on health with some bioactive principles, modes of action and potent biomedical applications. Int J Pharmacol. 2015; 11 (4): 253-90.

[24]. Frech SA, Kenney RT, Spyr CA, Lazar H, Viret JF, Herzog C, Glück R, Glenn GM. Improved immune responses to influenza vaccination in the elderly using an Immunostimulants patch. Vaccine. 2005; 23 (7): 946-50.

[25]. Davtyan H, Ghochikyan A, Hovakimyan A, Petrushina I, Yu J, Flyer D, Madsen PJ, Pedersen LO, Cribbs DH, Agadjanyan MG. Immunostimulants patches containing Escherichia coli LT enhance immune responses to DNA- and recombinant protein-based Alzheimer's disease vaccines. J Neuroimmunology. 2014; 268 (1-2): 50-7.

[26]. Mkrtichyan M, Ghochikyan A, Movsesyan N, Karapetyan A, Begoyan G, Yu J, Glenn GM, Ross TM, Agadjanyan MG, Cribbs DH. Immunostimulant adjuvant patch enhances humoral and cellular immune responses to DNA immunization. DNA Cell Biol. 2008; 27 (1): 19-24.

[27]. Garçon N, Leroux-Roels G, Cheng WF. Understanding modern vaccines: Perspectives in Volcanology. Elsevier BV. 2011; 1: 89-113.

[28]. Pasquale AD, Preiss S, Da Silva FT, Garçon N. Vaccine adjuvants: from 1920 to 2015 and Beyond. Vaccines (Basel). 2015; 3 (2): 320-43.

[29]. Mizumoto N, Gao J, Matsushima H, Ogawa Y, Tanaka H, Takashima A. Discovery of novel Immunostimulants by dendritic-cell based functional screening. Blood. 2005; 106 (9): 3082-9.