Review Article
Open Access
CrossMark

Active specific immunotherapy: mechanisms of action and clinical applications in bioregenerative and anti-aging medicine, autoimmune conditions and cancers

Abstract

Autologous Active Specific Immunotherapy (AASI) is a type of immunotherapy that targets complementary autoantibodies which suppress the specific immune response using anti-idiotypic antibodies. AASI entails removing immune cells (dendritic cells) from the patient's blood and subjecting them in a lab setting to a particular tumour antigen (proteins detected on the surface of cancer cells). AASI is a personalized treatment approach that has been used to treat various types of cancer, including melanoma, osteosarcoma and breast cancer.

Clinical trials have shown promising results, with some patients experiencing complete remission or long-term disease control. Although AASI has shown potential as a cancer treatment, further research is needed to optimize its effectiveness and safety. AASI is a complex and expensive therapy, and its use is currently limited to specialized cancer treatment centres.

Keywords: immunotherapy, autologous vaccines, active specific immunotherapy, immunity, immunosenescence, autoimmune disorders, allergies, cancer, regenerative medicine

Volume 7 Issue 1 - 2023

Mike KS Chan,[1,2,4] Michelle BF Wong,[2,3] Roni Moya,[1] Dmytro Klokol,[1,4] Shing Yi Pan,[3]
[1]European Wellness Biomedical Group, (Greece, EU/APAC)
[2]FCTI/ Biotech R&D GbmH, Germany
[3]Baden R&D Laboratories GbmH, Germany
[4]European Wellness Academy, Malaysia

Correspondence: Dr. Dmytro Klokol (EW Biomedical group), Email dr.dmytro@european-wellness.com

Received: February 26, 2023 | **Published:** March 10, 2023

Introduction

Active Specific Immunotherapy (ASI) was pioneered by the late Dr. Rudolph Pekar.[1] It is based on the concept of anti-idiotypic antibodies to be used as regulatory agents, which was profundly researched by Niels Jerne between 1954 and 1974.[2–4] Based on the idiotypic network theory, Jerne postulated that antigenic stimulation leads to the production of idiotypes and anti-idiotypes as a network of interacting antibodies, and the immune response is regulated by the responses to the idiotypes.[5] Idiotypes are unique determinants of immunoglobulin or T cell receptors (TCR) based upon their antigen-binding specificity.[6,7] The idiotypic network is crucial in maintaining the homeostasis of the immune system. The presence of epitopes or antigenic determinants stimulates the production of antigen-specific antibodies (Ab1), which induce the production of anti-idiotypic antibodies (Ab2), classified into Ab2α, Ab2β, or Ab2γ to maintain equilibrium.[8,9] Two categories of Ab2 known as Ab2ε and Ab2δ have been identified recently, although there is limited literature on these at present. Ab2 can stimulate the production of anti-anti-idiotypic antibodies (Ab3) which possess similar binding capacities as Ab1.[7,8] Therefore, the balance of the network equilibrium is essential to ensure that the immune system can effectively fight against exogenous antigens.

Further discussion by Gorczynski and Hoffmann discussed how anti-idiotypic antibodies can potentially be used in preventive immunotherapy through the production of cytokines, the induction of regulatory T cells, mitigation of graft intolerance and attenuation of allergic and inflammatory bowel diseases [10]. Current literature discussing the use of anti-idiotypic antibody are largely dominated by their applications in cancer treatments since anti-idiotypic antibodies mimic the shape of antigens, however researchers are now developing these as a new class of vaccine.[11–16] Furthermore, their involvement in and correlation with autoimmune diseases has also been widely reported.[17–19] Hence, AASI provides an alternative form of immunotherapy to modulate the immune system through anti-idiotypic antibodies. AASI is now used as a complementary therapy as it is well tolerated and can be applied in combination with other types of therapies. It is therefore gaining increasing interest from medical practitioners. The mechanism of action of AASI treatment will be discussed in three main areas, which includes, the autoimmune diseases, allergic disorders and cancer treatment.

Apart from such clinical indications for AASI as cancers, autoimmune conditions and allergic disorders, ASI is used as an effective tool of anti-aging and longevity medicine[15,20] due to its ability to reduce the burden of the senescent circulating immune memory cells, reduction of the auto-immune component of the aging and, in addition, through the significant anti-inflammatory properties of the autologous immune vaccines.[20]

ASI in Autoimmune conditions

Autoimmune diseases are common chronic conditions that have a serious influence on patients' quality of life and may even be fatal. Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and multiple sclerosis (MS) are among the most well-known autoimmune diseases. A majority of non-specific immunosuppressive medications, such as corticosteroids, mycophenolate mofetil (MMF), and azathioprine (AZA), as well as biologic therapies, such as anti-cytokine treatments, monoclonal antibodies, and biological inhibitors of T cell and B cell function, are currently used to treat autoimmune diseases.[17–19]

However, using immunosuppressive medications frequently results in unfavorable side effects linked to toxicity or the emergence of other illnesses.[21–23] These medications frequently suppress both the protective and destructive immune responses as a result of their non-selective immunosuppressive properties, which puts people at

an increased risk for infectious diseases brought on by opportunistic infections.[24] Biologic therapies similarly have side effects, which is they can increase the risk of infection, and cause other adverse reactions including liver toxicity, gastrointestinal perforation, nausea, diarrhoea and fatigue.[25]

Autoimmune diseases usually require lifelong treatment because current drugs do not restore the immune tolerance of autoantigens.[26] The ideal treatment targets disease-related antigens rather than acting as a global immunosuppressant, which minimizes side effects and concentrates on the underlying cause of the disease. AASI therapy has been reported for the treatment of several types of autoimmune diseases. Typically, autoimmune diseases are characterized by the uncontrolled production of autoantibodies, often when patients are asymptomatic and before clinical onset. For example, anti-dsDNA antibody, considered the hallmark of SLE, has been reported to be detected as early as 2 years prior to any diagnosis, while anti-P, another SLE autoantibody, was detected more than a year prior to pre-clinical diagnosis, and shows elevation during active disease episodes, and normalizing during periods of remissions.[27,28]

Based on the idiotypic network theory, which contends that an immune response results in the production of both antigen-specific antibodies (autoantibodies) and anti-idiotypic antibodies, which interact with one another to control the humoral immune response, is autologous active specific immunotherapy (AASI). The goal of AASI autologous immunomodulating therapy is to balance the immune-modulating network by stimulating the generation of anti-idiotypic antibodies and regulating regulatory T cells, then neutralizing and limiting the release of autoantibodies. Anti-idiotypic antibodies are frequently used to treat cancer, allergy conditions, and autoimmune diseases. AASI therapy is an autologous immunomodulating therapy that aims to control the immune system by strengthening the body's defences and educating the host's defence mechanisms.[29–33]

The use of anti-idiotypic antibody as an SLE vaccine was demonstrated in a small clinical trial in which five out of the nine patients administered with the mouse anti-dsDNA monoclonal antibody developed anti-idiotypic antibodies within the first 3 months, without any adverse side effects and remained disease-free during the 2 years follow up period.[17,21] Similarly, AASI can modulate the immune system by inducing the production of anti-idiotypic antibodies which will bind to autoantibodies instead of attacking the patient's own cells, thereby restoring balance to the idiotypic network.

It is well known that abnormalities in the idiotypic network can result in the expression and expansion of autoantibodies. Healthy adults usually have a low concentration of autoantibodies, however, disruption in the idiotypic network leads to the expression and elevation of circulating autoantibody levels, which can result in the development of autoimmune disease. The role of AASI is to reduce the production of anti-idiotypic antibodies by adding immune-activating substances to the autologous blood collected to convert the autoantibodies to specific harmless immunogens, which are molecules capable of eliciting an immune response.[14]

The main advantage of AASI is its ability to specifically target complementary autoantibodies, thereby effectively suppressing the specific immune response. Furthermore, unlike non-specific active immunotherapy, AASI, as its name implies, specifically targets the problematic tissue while preserving the surrounding normal tissue from non-specific toxicities.[34] The unique properties of this network have enabled therapeutic treatments for many diseases, particularly cancer and autoimmune diseases. It is most effective in treating conditions related to immunity imbalance, such as allergic disorders, rheumatoid arthritis, multiple sclerosis, psoriasis, systemic lupus erythematosus, and type I diabetes. In addition, AASI can also be applied to treat cancer of the liver, stomach, pancreas, breast, prostate, intestine, lymphatic glands, and melanoblastomas.[29,30,34]

ASI in cancers

The application of AASI in the treatment and management of cancers has been well documented, including malignancies such as colon cancer, melanoma and renal cell carcinomas.[29–31,34–37] A comprehensive review of the recent achievements of using anti-idiotypic antibodies as cancer vaccines to induce humoral and/or cellular immune responses has been documented by Ladjemi (2012).[38] Due to the nature of anti-idiotypic antibodies, which selectively suppress only the specific autoantibodies which they are complementary to the use of anti-idiotypic antibody has proven to be an attractive alternative form of immunotherapy capable of modulating the immune system without the side effect of non-specific immunosuppression that is often associated with conventional immunosuppressive drugs.

Once administered, the patient's own immune system will recognize the immunogens and produce anti-idiotypic antibodies which bear the internal image of the host cells. The anti-idiotypic antibodies produced will competitively bind to the autoantibodies instead of attacking the patient's own cells. This neutralizes and inhibits the further production of autoantibodies, thereby helping to restore a balanced idiotypic network in the patient's body. Maintenance of this equilibrium is essential to ensure that the immune system can effectively fight against exogenous antigens without attacking self-antigens that could potentially lead to the development of autoimmune diseases. In summary, AASI is a promising treatment for autoimmune diseases due to the immunomodulatory potential of anti-idiotypic antibodies.

The AASI preparation protocol

The AASI preparation protocol involves drawing blood or tumour tissue from the patient to produce 30 vials (1mL) of AASI. The standard protocol for one course of AASI therapy consists of 30 vials (1mL each vial), administered via subcutaneous injection of 1 vial on each alternate day for a duration of 60 days with a resting period of 3 months between treatment courses. The treatment of allergic disorders and autoimmune diseases requires 30mL or 30cc of blood to be drawn from the patient using 3x10ml syringes which are labelled with the patient's data, name, and date of birth. The syringe is stored at room temperature and in an upright position with the plunger facing downward. The waiting time of sedimentation of red blood cells and formation of the buffy coat layer should be visible within 3 days. However, collected blood samples can be stored at 4°C for longer storage. Blood samples are collected by authorized lab personnel for AASI therapy processing. Samples are then used for the preparation of 30 vials of AASI vaccine. As an alternative to vaccine preparation from the tumour specimen, the patient's autologous blood can also be used. This method is widely practiced by FCTI's laboratory, which is conducting research and development and manufacturing cancer vaccines. For cancer treatment, approximately 5-10g of tumour tissue that has never been irradiated before must be sent to the laboratory directly after surgical removal. Tumour samples are collected by authorized lab personnel and delivered to the laboratory at 4-8°C within 12 hours.[20]

Biological mechanisms of action of the AASI

Application of the ASI in treatment of allergic disorders

Allergy is an abnormal adaptive immune response directed against relatively harmless allergens which are derived from environmental and dietary substances. The incidence of allergic disorders has greatly increased over the past four decades in developed countries due to factors such as pollution, dietary changes, lifestyle, and less exposure to microbes, resulting in changes to the immune system reliance.[39] Examples of common allergic disorders include allergic dermatitis (eczema), allergic rhinitis (hay fever), allergic/atopic asthma, and food allergies. The main common allergens found in allergic disorders include the house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae are the main species), pet hair and dander, pollens, food sources, insect stings, drugs, latex, and mould spores, especially Alternaria spp. and Cladosporium spp.[40] Airborne spore levels show seasonal changes in atmospheric concentration, which are highest in summer and autumn, but vary significantly throughout the year, unlike pollens.

Allergy is an IgE mediated type I hypersensitivity characterized by the degranulation of mast cells and basophils.[41] In sensitized individuals, these mast cells and basophils already possess allergen-specific IgE bound to their surface receptor (FcεRI). When crosslinking of adjacent IgE molecules by allergens happens, the activation and degranulation of mast cells and basophils is induced and results in the release of inflammatory mediators that trigger allergic inflammation such as mucous secretion, vasodilation, and smooth muscle contraction, which then further contribute to the allergic symptoms. The allergic symptoms vary from mild allergies, including itchiness, rashes, hay fever, rhinitis, eczema, conjunctivitis to chronic asthma and severe life-threatening anaphylaxis.

The conventional allergy treatment is to avoid exposure to allergens and the use of symptom-reducing medications. However, avoiding exposure to allergen becomes difficult due to the dispersed allergens in the air that can be easily inhaled by sensitized individuals without any notice or ability to control. When allergen exposure is inevitable, pharmacotherapy is an alternative to ease the allergen-induced symptoms. Common drugs such as antihistamines and anti-leukotrienes are used as antagonists to allergic mediators and block allergic symptoms.[40] In cases where the offending allergen is identified, immunotherapy to desensitize the response to targeted allergen is a promising way to treat allergic disorders. Allergen-specific immunotherapy has been proven to be a highly effective treatment for allergic disorders, especially allergic respiratory disorders that respond inadequately to conventional therapies.[42]

AASI is also a promising targeted therapy that has proven to be safe and effective in treating allergic disorders such as allergic respiratory disorders and eczema. AASI vaccines modulate the immune system to produce anti-idiotypic antibodies that competitively bind to the cell-bound IgE antibodies and inhibit the release of the chemical mediators that cause allergic reactions.[41] Therefore, AASI plays an important role in the recovery of the correct immune tolerance response in patients with allergic disorders.

An allergic reaction requires the sensitization of a specific antigen which is recognized by naïve T and B lymphocytes. During sensitization, the immune system first encounters the antigen (allergen) and antigen-presenting cells (APCs) then recognizes it as a foreign antigen. APCs then phagocytose the antigen and present it through specific major histocompatibility complex (MHC) class II (MHC-II) antigens. The naïve T cells recognize the MHC-II antigens on the APCs and induce the differentiation and expansion of T helper cells (Th-2), leading to the production of inflammatory interleukins IL-4, IL-5 and IL-13. These interleukins act on naïve B cells and promote immunoglobulin (Ig) class switching to IgE. The IgE antibodies bind to FcεRI expressed on mast cells and basophils. The occurrence of repeated exposure to the allergen results in the cross-linkage of FcεRI-bound IgE and initiates the degranulation of the allergic mast cells and basophils. The release of histamine and other types of mediators then contributes to the characteristic symptoms of allergy.[42]

The mechanism of action of AASI in allergic disorders is to induce the production of anti-idiotypic antibodies by the collection of autologous blood followed by the addition of an immune adjuvant. Doing so converts the main antibodies responsible for allergic reactions, IgE, into harmless immunogens. Once administered back to the patient, the immune system recognizes the immunogens and induces the production of anti-idiotypic antibodies (Ab2). The anti-idiotypic antibodies competitively bind with IgE, thereby inhibiting the cross-linkage of FcεRI-bound IgE and consequently preventing the release of chemical mediators which cause allergic reactions. In this way, AASI vaccines modulate the production of anti-idiotypic antibodies which can dampen the allergic reactions.[20]

In case report, a 31-year-old male with a 5-month history of nummular eczema after showing no improvement to the skin after the application of lotions and topical corticosteroids. On 23rd November 2016, the patient began a 30-day treatment protocol including one course of AASI (30 vials) as the main therapy, following one course of Super Transfer Factor (every alternate day for one month) as complementary therapy together with the application of topical moisturizers on the skin lesions. Upon completion of the first treatment course, the patient showed remarkable improvement with dramatic reduction of skin lesions and inflammation with few remaining scars. In February 2017, the patient entered his second course of treatment which included one course of AASI (30 vials) and a repeated course of Super Transfer Factor. The treatment was given for 30 consecutive days consecutively. After completing the course of treatment, the patient gradually recovered from skin lesions and the symptoms of weeping and oozing had healed entirely. The patient has also stopped taking medications for eczema he used to take previously. A stable lasting remission of eczema was achieved for at least a year.[32]

Role of AASI in cancer treatment

Cancer therapy has long depended on strategies that directly attack tumour cells. Multimodal cancer immunotherapy combined with other biological treatments, such as, systemic hyperthermia and high- dose vitamin supplementation) are now emerging as important additions to conventional therapies. Metastatic cancer is often a fatal disease with a low survival rate. The course of cancer development involves a pathogenic cascade that includes inflammation, the overexpression of reactive oxygen species, loss of DNA repair, genome instability, neovascularization, epithelial infiltration, collagen destruction, immunosuppression of cancer cells and their evasion of apoptosis.[42]

Immunotherapy has recently been described as the fourth pillar of cancer treatment in addition to surgery, chemotherapy, and radiation therapy.[20] It is of utmost importance to understand both the cross-interaction mechanism between the immune co-stimulatory and inhibitory molecules as well as tumour cells in the development of a successful immunotherapeutic strategy to fight aggressive cancers. An optimal protective immune system must balance eliminating foreign pathogens and tolerance of self-antigens to be successful. Immunotherapy works by modulating the immune system to attack malignant or hyperreactive inflammatory cells.[20,31] The idea

of advanced immunotherapeutic methods must also incorporate personalized agents that can induce more specific immune responses against malignant cells.

AASI can reactivate and strengthen the immune system by explicitly producing anti-anti-idiotypic antibodies to target against cancer. Autologous AASI vaccines have so far shown promising results in cancer prevention and the early or intermediate stages of cancer and are most often used in cancers of the liver, stomach, pancreas, breast, prostate, intestine, lymph glands, and melanoblastomas. The ability of AASI therapy to initiate tumour antigen-specific immune responses through the production of anti-anti-idiotypic antibodies against tumour cells and consequently regulate the immune system, makes it an attractive approach in treatment of cancer patients.[30,31,36]

The use of anti-idiotypic antibodies to stimulate antitumor activity is deemed as a promising immunological approach to cancer treatment.[37] According to the idiotypic network theory, the presence of tumour antigens will induce the production of Ab1 and generate the production of anti-idiotypic antibodies (Ab2), with Ab2β playing an essential role by inducing anti-anti-idiotypic antibodies (Ab3).[37] The fundamental concept of AASI is to initiate tumour antigen-specific immune responses by isolating tumour tissue and adding an immunological adjuvant. Administration of an AASI vaccine consisting of harmless immunogens induces the production of anti-idiotypic antibodies (Ab2) followed by the production of anti-anti-idiotypic antibodies (Ab3) which specifically target tumour antigens. AASI vaccines have been shown to effectively inhibit the growth of solid tumours in early or intermediate stages of cancer.

For instance, a female patient with osteosarcoma at the age of 31 had treatment in 2015. After undergoing various chemotherapy regimens and integrated immunotherapy (dendritic cells and vitamins infusion), the patient went into remission. She was immediately treated with the standard protocol of intravenous gemcitabine + irinotecan every 15 days, with cyclophosphamide daily as an oral immunosuppressant, after experiencing a relapse of the same osteosarcoma with lung metastases in November 2018. The patient started getting ASI treatment with 60mcg/ml/200 ml of ozone therapy and general hyperthermia once a month in April 2019 along with combined conventional chemotherapy. A normal immune hemogram, phenotyping profile, and the absence of anaemia or liver toxicity are all revealed by subsequent CT scans, which also show no overall deterioration.[31]

Another study had shown a different patient, a 44-year-old female patient was diagnosed with right breast cancer (BRCA-2 positive) in 2003. She underwent a mastectomy and 5 years of Tamoxifen. She was then diagnosed with left breast cancer and underwent a further left mastectomy and one year of Tamoxifen in 2013. In 2015, she was diagnosed with multiple metastases (liver, lungs, and bones) and subsequently underwent radiotherapy and chemotherapy with Docetaxel and Carboplatin for 6 months. In 2016, she was further prescribed with letrozole therapy with zolendronic acid. Parallel to the conventional oncological treatment, the patient also underwent six sessions of systemic hyperthermia. Subsequent PET scans indicated a reduction in metastatic lesions size and quantity. However, a PET scan in January 2018 showed worsening of lymphadenopathy in the lungs, the presence of five new liver lesions, and overall spreading of metastases to the spine and iliac bones, with CEA and CA-15-3 markers of 8.17U/ml and 120.8U/ml respectively. Capecitabine 3000 mg per day was initiated, resulting in an increase in her CEA (9.71U/ml) and CA 15-3 (290.5U/ml) markers and the development of anemia.[31]

In February 2018, the patient presented to our clinic and started in-house integrative protocol (nutrient infusion) and made changes in her diet to adopt a dairy-free, low sugar, Mediterranean-like diet, enriched with fermented natural probiotics, polyphenols, and polyunsaturated fatty acids. No significant changes were reported in her metastatic tumor status, although the patient had a dramatically improved quality of life and improved performance, without any hospitalization or anemia.[20,31]

In April 2018, the patient commenced a protocol combining ASI with GcMAF Forte. In May 2018, one week after completion of ASI and GcMAF protocol, her α-N-acetylgalactosaminidase (nagalase) activity was 1.05 nmol, slightly over the normal reference (<0.95nmol). Immune phenotype analysis indicated maintenance of the dendritic, B, NK, and T cell populations and no sign of severe anemia. The PET scan and the cancer markers (CEA and CA 15-3) indicated stable disease. The patient continued receiving regular systemic hyperthermia. She reported a relatively good quality of life, with regular light physical exercises, social activities, and had good pain control with a low dosage of painkillers on a pro re nata basis. The patient currently continues to receive the same biomedical integrative regimen protocol, with regular follow up at the palliative care department at the hospital.[20,31]

A 63-year-old female patient was identified as having multiple myeloma and multiple inflammatory bones in May 2019. The patient chose to begin the ASI protocol with 50g vitamin C infusions because she was experiencing joint discomfort, constipation, and exhaustion at the same time before the conventional healthcare protocol was established. She had more energy, was sleeping soundly, and was more active three weeks following the ASI introduction. The right arm and hip pain had been the only areas of pain, and the constipation had eased. The patient also no longer need painkillers. Compared to the typical range of 0.310 to 1.560, the kappa/lambda ratio was slightly higher (2.45). Her CT scan didn't reveal any compatible multiple myeloma lesions in June 2019. Hence, she was kept under observation with no further treatment needed.[20,31]

The expected outcomes of AASI

AASI promotes the production of anti-idiotypic antibodies that neutralise and inhibit the release of autoantibodies, thereby maintaining a balanced immune-modulating network. This helps treat and prevent diseases like autoimmune disease, allergy, and cancer that are brought on by immune system imbalance. One of the main advantages of anti-idiotypic antibodies is that they can selectively inhibit the specific autoantibodies that are complementary.[6,9,14] In contrast, most conventional drugs and immunotherapies are non-selective and suppress protective and destructive immune responses, making individuals susceptible to a higher risk of infectious diseases caused by opportunistic pathogens.[9,20,25] In addition, anti-idiotypic antibodies induce a memory response by generating T helper memory cells that persist after treatment and prevent relapses from occurring,[38] thus promoting longer-lasting immunity. AASI is therefore an alternative to immunosuppressants in the management of immune diseases. Since anti-idiotypic antibodies are naturally present in the body and the immune response evoked mimics those caused by nominal antigens, they are safe and without toxicity.[20,35,39] Additionally, incompatibility issues and the risk of rejection by the recipient is practically non-existent since anti-idiotypic antibodies are obtained from the patient.[20] According to reports, anti-idiotypic antibodies are effective in patients who do not respond well to traditional therapies, improving their quality of life, reducing their pain and weariness, and lengthening their life expectancy.[43]

Conclusion

AASI, or autologous active specific immunotherapy, is a promising method for treating cancer. AASI can train the immune system to recognize and destroy cancer cells that express particular tumor antigens by exposing immune cells to those antigens. Patients with numerous cancers, including osteosarcoma, breast cancer, and multiple myeloma, have responded positively in clinical studies. Therefore, AASI and other immunotherapy strategies are anticipated to eventually enhance outcomes and quality of life for cancer patients as research in this field advances.

Acknowledgments

None.

Funding

None.

Conflicts of interest

There is no competing interests between the authors.

References

1. Pekar R, Korpan NN. Cancer. The biological and the medical tragedy: bio-oncology. The crisis in cancer medicine and new ways to solve it. Maudrich Verlag; 2002. ISBN 10: 3851757769/ISBN 13: 9783851757767.
2. Niels KJ. The natural-selection theory of antibody formation. *Proc Nat Acad Sci*. 1955;41(1955):849–857.
3. Niels KJ. The natural selection theory of antibody formation, ten years later in phage and the origins of molecular biology. In: John C, Gtinther SS, James DW, editors. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory of Quantitative Biology; 1966. 306 p.
4. Söderqvist T. Darwinian overtones: Niels K Jerne and the origin of the selection theory of antibody formation. *J Hist Biol*. 1994;27(3):481–529.
5. Jerne NK. Towards a network theory of the immune system. *Ann Immunol (Paris)*. 1974;125C(1-2):373—389.
6. Zanetti M. Anti-idiotypic antibodies and autoantibodies. *Ann New York Acad Sci*. 1983;418(1):363–378.
7. Abu-Shakra M, Shoenfeld Y. Idiotypes and anti-idiotypes. Autoantibodies, Elsevier; 2013.
8. Uner A, Gavalchin J. Idiotypes. 2006:1–5.
9. Stanova AK, Ryabkova VA, Tillib SV, et al. Anti-idiotypic agonistic antibodies: candidates for the role of universal remedy. *Antibodies*. 2020;9(2):19.
10. Gorczynski R, Hoffmann G. Toward a new kind of vaccine: a logical extension of the symmetrical immune network theory. *Interact J Med Res*. 2017;6(2):e8.
11. Vermorken JB, Claessen AM, van Tinteren H, et al. Active specific immunotherapy for stage II and stage III human colon cancer: A randomised trial. *Lancet*. 1999;353:345–350.
12. Morton DL, Foshag LJ, Hoon DSB, et al. Prolongation of survival in metastatic melanoma after active specific immunotherapy with a new polyvalent melanoma vaccine. *Ann Surg*. 1992;216(4):463–482.
13. Bhattacharya-Chatterjee M, Chatterjee SK, Foon KA. Anti-idiotype vaccine against cancer. Immunol Lett. 2000;74:51–58.
14. Daigleish AG, Kennedy RC. Anti-idiotypic antibodies as immunogens: Idiotype-based vaccines. *Vaccine*. 1988;6(3):215–220.
15. Bhattacharya-Chatterjee M, Chatterjee SK, Foon KA. The anti-idiotype vaccines for immunotherapy. *Curr Opin Mol Ther*. 2001;3(1):63–69.
16. McCarthy H, Ottensmeier CH, Hamblin TJ, et al. Anti-idiotype vaccines. *Br J Haematol*. 2003;123(5):770–781.
17. Spertini F, Leimgruber A, Morel B, et al. Idiotypic vaccination with a murine anti-dsDNA antibody: Phase I study in patients with nonactive systemic lupus erythematosus with nephritis. *J Rheumatol*. 1999;26(12):2602–2608.
18. Paschke R, Teuber J, Enger I, et ak. Evidence for a role of anti-idiotypic antibodies in the induction of remission in Graves' disease. *J Autoimmun*. 1990;3(4):441–448.
19. Sikorska HM. Anti-thyroglobulin anti-idiotypic antibodies in sera of patients with Hashimoto's thyroiditis and Graves' disease. *J Immunol*. 1986;137(12):3786–3795.
20. Klokol D, Chan DSMK, Moya RL. Immunotherapy in bioregenerative medicine. European Wellness Academy; 2022. 239 p.
21. Ginzler E, Dooley M, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med*. 2005;353(21):2219–2228.
22. Le Ray C, Coulomb A, Elefant E, et al. Mycophenolate mofetil in pregnancy after renal transplantation: A case of major fetal malformations. *Obstet Gynecol*. 2004;103(5):1091–1094.
23. Björnsson ES, Gu J, Kleiner DE, et al. Azathioprine and 6-mercaptopurine induced liver injury: Clinical features and outcomes. *J Clin Gastroenterol*. 2017;51(1):63–69.
24. Trabelsi AB en S, Hamami E, Souguir A, et al. Suspected azathioprine induced liver cirrhosis: An unusual side effect. *Pan Afr Med J*. 2014;17:174.
25. Miller E. Immunosuppressive therapy in the treatment of immune-mediated disease. *J Vet Intern Med*. 1992;6(4):206–213.
26. Rosato E, Pisarri S, Salsano F. Current strategies for the treatment of autoimmune diseases. *J Biol Regul Homeost Agen–ts*. 2010;24(3):251–259.
27. Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med*. 2003;349:1526–1533.
28. Heinlen LD, Ritterhouse LL, Mcclain MT, et al. Ribosomal P autoantibodies are present before SLE onset and are directed against non-C terminal peptides. *J Mol Med*. 2011;88(7):719–727.
29. Moya R, Chan MKS, Klokol D, et al. Active specific immunotherapy (ASI) and GcMAF Forte in management of metastatic invasive carcinoma-overview of the therapeutic modalities and a case report. *J Clin Exp Immunol*. 2018;3(2):1–4.
30. Ciardiello D, Vitiello PP, Cardone C, et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. *Cancer Treat Rev*. 2019;76:22–32.
31. Moya R, Chan MKS, Wong MBF, et al. Active specific immunotherapy (ASI) in cancer treatment: five case reports. J Cancer Sci Ther. 2019;11(9):256–259.
32. Klokol D, Pan SY, Chan MKS, et al. Management of eczema with active specific immunotherapy and super transfer factor : A case report. J Clin Immunol Allergy. 2018;4(1).
33. Moya R, Chan MKS, Wong MBF, et al. Integration of active specific immunotherapy and cell therapy into the protocols of biomedical management of interstitial pneumonia with autoimmune features. Clin Med Rep. 2020;3:1–5.
34. Mirasol F. New biotherapies push technological innovation forward. Pharmaceutical Technology Europe. 2021:9–13.

35. Ma J, Zhou L, Wang D. Functional mimicry of an anti-idiotypic antibody to nominal antigen on cellular response. 2002;01:78–84.

36. Li G, Xie L, Zhou G, et al. A clinical trial of active immunotherapy with anti-idiotypic vaccine in nasopharyngeal carcinoma patients. Chin Med J (Engl). 2002;115(4):567–570.

37. López-rRquena A, Burrone OR. Anti-idiotypic antibodies and "tumor-only" antigens : an update. Open Immunol J. 2009;2:1–8.

38. Mirasol F. New biotherapies push technological innovation forward. Pharmaceutical Technology Europe. 2021:9–13.

39. Pramod SN. Immunological basis for the development of allergic diseases-prevalence, diagnosis and treatment strategies. Cell Interaction-Molecular and Immunological Basis for Disease Management. IntechOpen; 2021.

40. Jenerowicz D, Silny W, Danczak-Pazdrowska A, et al. Environmental factors and allergic diseases. Ann Agric Environ Med. 2012;19(3).

41. Bonyadi MR, Hassanzadeh D, Seyfizadeh N, et al. Assessment of allergen-specific IgE by immunoblotting method in atopic dermatitis. Eur Ann Allergy Clin Immunol. 2017;49(5):213–219.

42. O'Brien RM. Immunotherapy for allergic disorders. Aust Prescr. 2003;26:91–93.

43. Ciardiello D, Vitiello PP, Cardone C, et al. Immunotherapy of colorectal cancer: Challenges for therapeutic efficacy. Cancer Treat Rev. 2019;76:22–32.

Citation: Chan MKS, Wong MBF, Moya R, et al. Active specific immunotherapy: mechanisms of action and clinical applications in bioregenerative and anti-aging medicine, autoimmune conditions and cancers. *Int J Vaccines Vaccin.* 2023;7(1):33–38. DOI: 10.15406/ijvv.2023.07.00117