Inverse vaccines

Friend, Not Foe: How Inverse Vaccines Tackle Autoimmune Diseases

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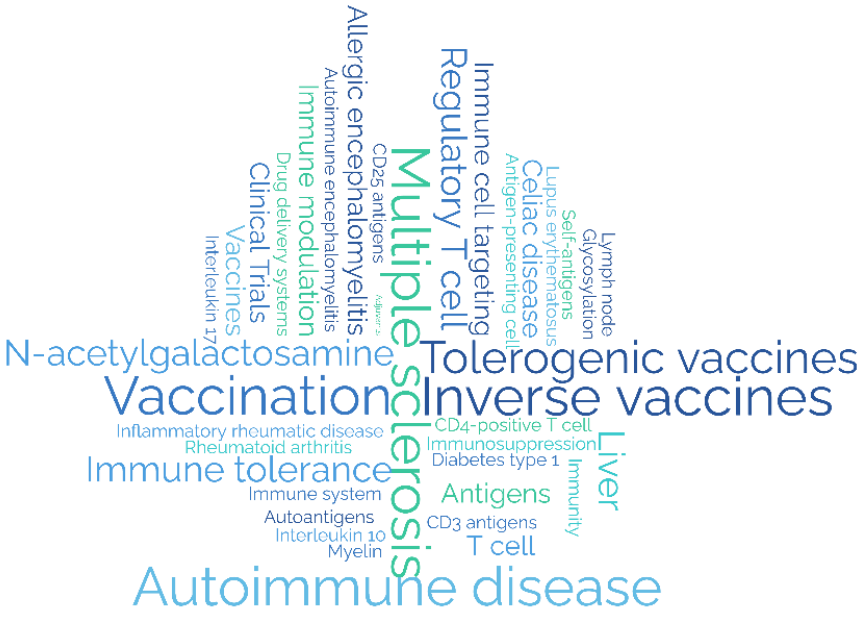
Abstract

Inverse vaccines are a new and exciting approach to treating autoimmune diseases. Unlike traditional vaccines that train the immune system to fight off pathogens, inverse vaccines aim to reprogram the immune system to stop attacking healthy tissues.

Key words: inverse vaccine; tolerogenic vaccine; autoimmune disease; multiple sclerosis; liver; T-cell



Word cloud of concepts related to inverse vaccines

Introduction

Autoimmune diseases occur when the immune system mistakenly identifies healthy body tissues as foreign invaders and launches an attack. This attack can damage cells, tissues, and organs, leading to a variety of symptoms. There is no cure for most autoimmune diseases, and current treatments focus on suppressing the immune system to reduce inflammation and slow disease progression. However, this can leave patients more vulnerable to infections and other complications.

Inverse vaccines, also called tolerogenic vaccines, offer a potential way to target the specific immune response that is causing the autoimmune disease. By introducing the body's own proteins (autoantigens) in a specific way, inverse vaccines can induce tolerance. This means that the immune system learns to recognize the autoantigens as harmless and stops attacking them.

Studies have found increased frequencies of autoimmune diseases over recent decades. [1, 2] The number of research reports focused on autoimmune diseases have grown correspondingly. According to the CAS Content Collection[3] over 150,000 research documents related to autoimmune diseases have been published since the year 2000, with over 35% growth in the last three years (2021-2023) as compared to 2019 (Figure 1).

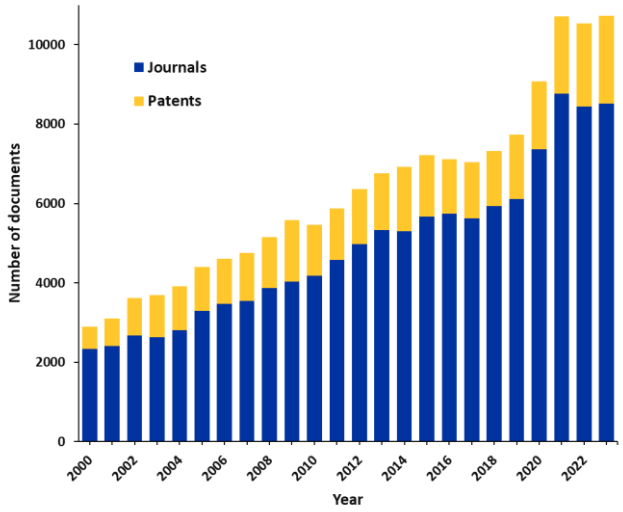


Figure 1. Number of documents related to autoimmune diseases in CAS Content Collection.

This recent surge in the research on autoimmune diseases has been perhaps driven by several factors: (i) **Potential COVID-19 link:** Studies suggest a connection between COVID-19 infection and an increased risk of developing autoimmune diseases [4]; (ii) **Improved diagnostics:** Advancements in identifying biomarkers and using genetic analysis are leading to earlier and more precise diagnoses, which is crucial for developing targeted therapies [5]; (iii) **More people getting autoimmune diseases:** Data suggests a significant increase in the prevalence of autoimmune diseases. [6-9]

The concept of “inverse vaccine” is a relatively new and not a well-established concept yet, so the number of related documents identified in the CAS Content Collection is relatively low, but steadily growing (Figure 2).

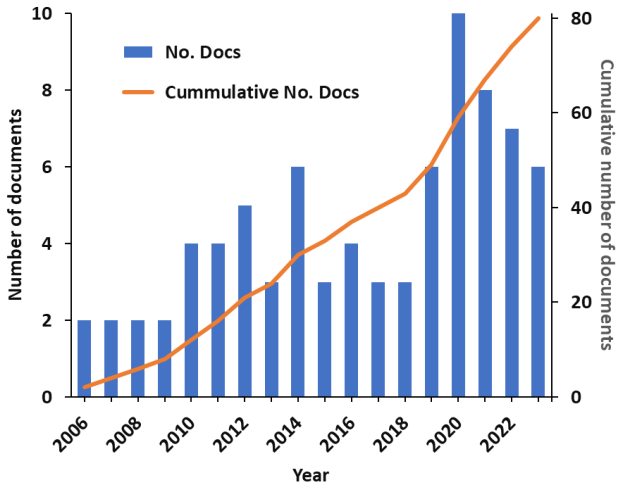


Figure 2. Number of documents related to inverse vaccines / tolerogenic vaccines in CAS Content Collection.

Researchers are still exploring the brainstorm of inverse vaccines, but early studies in animals have shown promise. If successful, inverse vaccines could revolutionize the treatment of autoimmune diseases by offering a way to target the root cause of the disease and prevent further damage.

Timeline

Researchers have been working on the idea of inverse vaccines for decades, exploring various methods for delivering the vaccine targets – antigens – without provoking an immune response. Attempts to develop peptide-based tolerogenic vaccinations against rheumatoid arthritis and systemic lupus erythematosus date almost twenty years ago. [10] However, by now the research has been based on animal models only, while data from clinical studies is still not available. A clinical trial to test a tolerogenic DNA vaccine in patients with multiple sclerosis has been performed nearly 15 years ago. [11] The vaccine was generally successful, but the efficiency was not higher than the drugs available on the market, in order to get approval. [12] The development of a tolerogenic mRNA vaccine able to restrict symptoms in several mouse models of multiple sclerosis has been reported in 2021. [13] The researchers achieved this by using modified mRNA encoding a self-antigen delivered by a non-inflammatory lipoplex carrier, which resulted in diminishing the autoimmunity through the activation of antigen-specific regulatory T cells. [13, 14]

Recent breakthrough

A breakthrough results have been reported last year on developing a technique that involves attaching a glycosylated polymer to an antigen, which directs it to the liver. The liver is crucial for establishing immune tolerance. Because of its distinctive blood supply, the liver exhibits a prominent local immune tolerogenic microenvironment. The network of hepatic regulatory immune cells is an important mechanism underlying liver immune tolerance. Multiple types of liver-resident antigen-presenting cells play immune regulatory function, and are also able to induce differentiation of circulating immune cells into regulatory cells to extend systemic tolerance. [15]

How does it work:

1. Targeting the immune system memory of specific self-antigens. Regular vaccines activate the immune system to recognize and attack foreign pathogens. In contrast, inverse vaccines remove the immune system memory of specific self-antigens that it mistakenly attacks in autoimmune diseases. [16-19]

The responsibility of the immune system T cells is to recognize harmful cells and molecules as foreign to the body and discard them; T cells also retain a memory of the invader to eliminate it faster in the future. However, sometimes T cells mistakenly recognize healthy cells as harmful, like in the case of multiple sclerosis, where T cells attack myelin, the protective coating around nerves. An inverse vaccine works by tagging the target antigen with a sugar molecule that the liver recognizes as "safe" (Figure 3). [18, 20-24] This tricks the specialized liver cells into teaching the immune system T cells to tolerate and protect the target antigen, rather than attack it. [18, 22] In mouse models of multiple sclerosis-like disease, the inverse vaccine was able to completely reverse the autoimmune attack and restore proper nerve function. [20, 25]

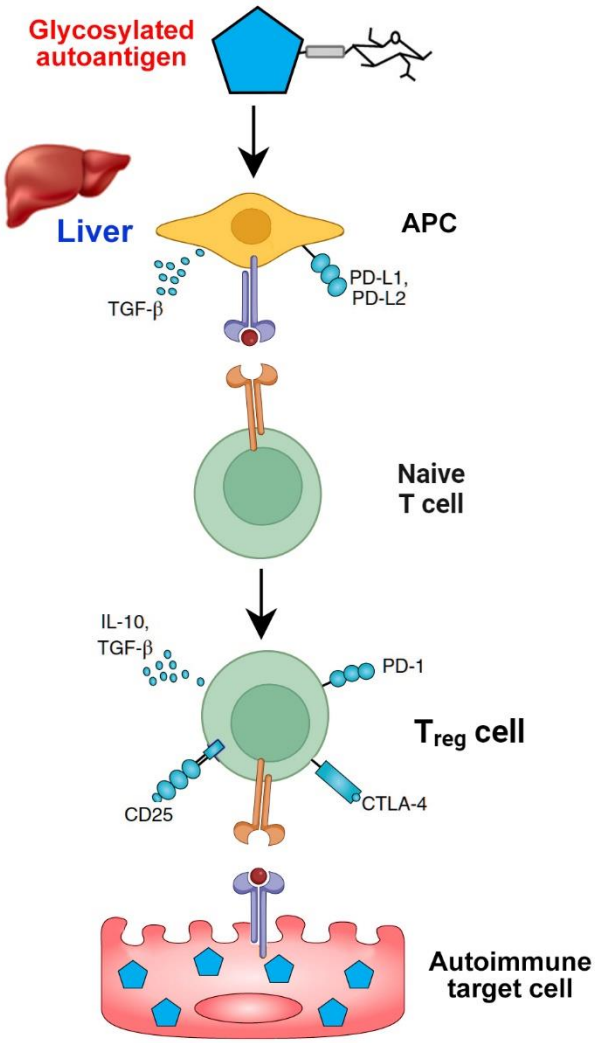


Figure 3. Induction of antigen-specific T-cell tolerance in liver: The administration of a glycosylated autoantigen results in the selective accumulation of the antigen in the liver, where it is presented to T cells by the hepatic antigen presenting cells (APCs).

2. Leveraging the liver tolerance-teaching mechanism. The liver has specialized cells that present self-antigens to T cells and teach them to tolerate those molecules as "self" rather than attack them (Figure 4). [18] The inverse vaccine couples the target autoimmune antigen with a molecule, N-acetylgalactosamine (pGal), that the liver recognizes as "safe", tricking the tolerance-teaching liver cells into reprogramming T cells to leave that antigen alone. [26]

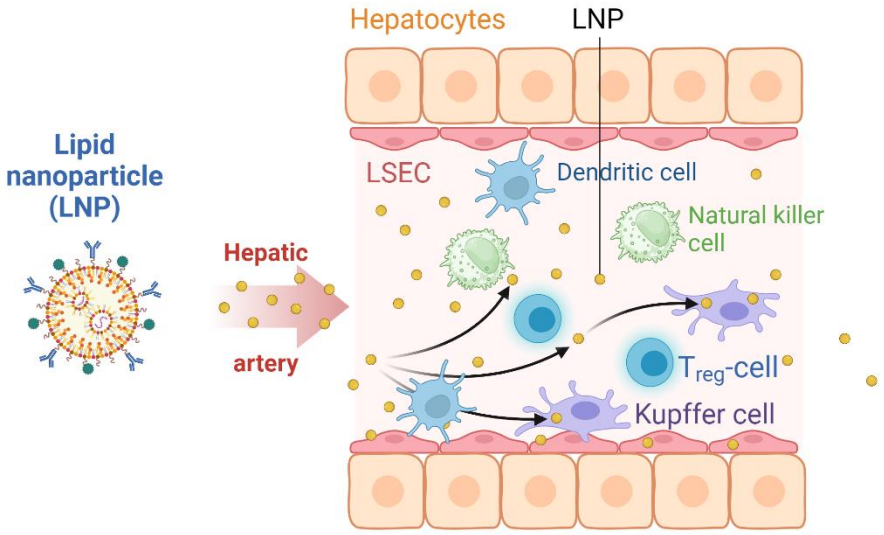


Figure 4. The liver is a potential ultimate regular pathway for immune tolerance. Vaccine is represented as being delivered through lipid nanoparticles (LNP), even though other delivery modes can be employed. (Created with BioRender.com)

A phenomenon known as peripheral immune tolerance, which is carried out in the liver, ensures that immune reactions do not take place in response to every damaged cell in the body. It has been discovered that tagging molecules with a sugar known as N-acetylgalactosamine (pGal) could mimic this process, sending the molecules to the liver where tolerance to them has been acquired. Attaching pGal to any molecule would teach the immune system to tolerate it. This way, researchers have developed an approach that can reverse autoimmune diseases by "erasing" the immune system memory of the molecule it mistakenly attacks, rather than broadly silencing the immune system.

3. Selective immune modulation. Unlike broad immunosuppressant drugs, inverse vaccines can selectively target and suppress only the specific T cells involved in the autoimmune attack, leaving the rest of the immune system intact. This more targeted approach has the potential to avoid the side effects of general immune suppression, like increased infection risk. [18]

4. Inducing durable immune tolerance. By resetting the immune system memory and tolerance of the target self-antigen, the inverse vaccine approach aims to provide long-lasting protection against the autoimmune attack, potentially offering a more durable treatment compared to chronic immunosuppressant drugs. [16, 26]

In summary, the key innovation behind inverse vaccines is their ability to selectively remove the memory of the immune system for specific self-antigens by hijacking natural tolerance-teaching mechanisms of the liver, rather than broadly suppressing the entire immune system.

Benefits of inverse vaccines

- Unlike traditional immunosuppressants that dampen the entire immune system, inverse vaccines aim to be highly targeted. [17, 20, 25] They ideally suppress only the specific immune response attacking a particular autoantigen (the body's protein mistakenly targeted for destruction). This specificity can lead to: (i) fewer side effects: because they don't suppress the whole immune system, inverse vaccines have the potential to cause fewer side effects like increased susceptibility to infections; (ii) more effective treatment: by precisely targeting the root cause of the autoimmune reaction, inverse vaccines could be more effective in controlling the disease.
- Potential for long-lasting effects: The ideal scenario is that inverse vaccines reprogram the immune system to permanently ignore the autoantigen, leading to long-term remission or even a cure for some diseases. [20]
- Addressing the root cause: Current treatments for autoimmune diseases often focus on managing symptoms by suppressing the immune system. Inverse vaccines, if successful, could address the underlying cause by retraining the immune system to recognize the autoantigen as harmless.
- Reduced treatment burden: Compared to current treatments that may require frequent dosing or monitoring, inverse vaccines could potentially offer a more convenient treatment option.
- Improved quality of life: By effectively controlling the autoimmune disease and reducing side effects, inverse vaccines could significantly improve the quality of life for patients.

Challenges

However, there are also certain challenges that need to be addressed before inverse vaccines can be used in humans.

- Accurately pinpointing the specific autoantigen (self-protein) responsible for each autoimmune disease is a major challenge. Some diseases might involve multiple autoantigens, making it trickier to design a targeted vaccine.
- Delivering the vaccine specifically to the relevant antigen-presenting cells (APCs) and ensuring it reaches the targeted T cells involved in the problematic response is another hurdle.
- While the goal is high specificity, achieving it can be difficult. Even slight variations in the presentation of the autoantigen could lead to unpredictable immune responses.
- Extensive clinical trials are needed to determine the safety and efficacy of inverse vaccines in humans. This process can be lengthy and expensive.
- Since inverse vaccines are a new approach, the long-term effects are unknown. More research is needed to understand their potential impact on the immune system over time.

Delivery systems

Additional challenge that need to be addressed before inverse vaccines can be used in humans are the drug delivery methods. Researchers are exploring different methods to deliver the vaccine, such as microparticles, nanoparticles or engineered viruses, to ensure it reaches their target effectively. [27]

- Encapsulation in PLGA microparticles: Protein antigens can be encapsulated into porous PLGA (poly(lactic-co-glycolic acid)) microspheres using methods like "self-healing encapsulation" to achieve sustained antigen release. [28] The PLGA delivery system can help protect the antigens and facilitate their targeted delivery to induce immune tolerance. [28] Antigens and other immunomodulators can be efficiently loaded onto the surface of PLGA microparticles by conjugating them with short peptides. This surface conjugation approach can help retain the integrity of the antigens during the encapsulation process. [28]

- Incorporation into polysaccharide (dextran) particles: Before encapsulation into PLGA microparticles, protein antigens can be first loaded into polysaccharide (dextran) glassy particles through freezing-induced phase separation. This two-step process can help improve the loading efficiency and stability of the antigens. [28] Microparticles made of biodegradable polymers like PLGA can provide controlled and sustained release of the encapsulated antigens over time.

- In experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis, protein-based inverse vaccines loaded in polymeric biodegradable lactic-glycolic acid (PLGA) nano/microparticles (NP) to obtain the sustained release of myelin autoantigens and regulatory adjuvants, such as interleukin (IL)-4 or IL-10. [29]

- In another study, it has been reported that tolerogenic potential of immunodominant myelin T-cell epitopes can be improved by conjugation to a carrier polyethylene glycol (PEG) in an experimental autoimmune encephalomyelitis mouse model for chronic multiple sclerosis. [30]

- In addition to PLGA microparticles, some other drug delivery systems that have been explored for inverse vaccines include, such as **liposomes** – lipid-based nanoparticles that can encapsulate and deliver vaccine antigens and adjuvants. [31] Liposomes can be engineered to target specific cells and enhance the immune response, making them a potential delivery system for inverse vaccines. **Emulsions**, such as oil-in-water emulsions, can serve as vaccine delivery platforms and have been used to enhance the immune response. The emulsion formulation could potentially be adapted to deliver inverse vaccine antigens in a targeted manner. **Virus-like particles (VLPs)**, non-infectious, self-assembling nanoparticles derived from viral structural proteins that can be used to deliver vaccine antigens. The particulate nature and ability to present antigens in a native-like conformation make VLPs an interesting option for inverse vaccine delivery. **Polymer-based nanoparticles**: in addition to PLGA microparticles, other biodegradable polymers like chitosan and poly(lactic acid) have been explored for nanoparticle-based vaccine delivery. These polymer nanoparticles could potentially be engineered to target the liver and induce immune tolerance for inverse vaccines. **Exosomes** are naturally occurring nanoparticles derived from cell membranes that can be engineered to carry

vaccine antigens and adjuvants. The inherent targeting and immune-modulating properties of exosomes make them a promising platform for inverse vaccine delivery. [31]

– In a recent patent [32], multi-vesicular **lipid nanoparticle** tolerogenic vaccines have been developed for induction of systemic immune tolerance *in vivo*.

Despite these challenges, inverse vaccines hold great promise for the future of autoimmune disease treatment.

Targeted diseases

The **autoimmune diseases for which inverse vaccines are currently being explored** include:

- Initial studies in animal models have shown the inverse vaccine can completely reverse autoimmune attacks in diseases like **multiple sclerosis** and **type 1 diabetes**. [21, 26]
- Early phase I safety trials have been conducted in people with **celiac disease**, and further trials are underway for multiple sclerosis. [21, 26]
- Researchers are exploring the use of this new inverse vaccine approach for other autoimmune conditions like autoimmune inflammatory rheumatic disease such as **rheumatoid arthritis** and **systemic lupus erythematosus** as well. [33]

Other potential applications

Other potential applications of inverse vaccines extend beyond just autoimmune diseases:

– **Allergic conditions**: The search results mention that researchers are exploring the use of inverse vaccines for treating allergic asthma, in addition to autoimmune diseases. [34] The ability of inverse vaccines to selectively modulate the immune response could make them a promising approach for managing allergic reactions.

– **Organ transplant rejection**: The search results indicate that the inverse vaccine platform could potentially be used to prevent rejection of transplanted organs by inducing tolerance to the transplanted tissue. [34] By resetting the immune system's memory and attack response, inverse vaccines may help maintain long-term acceptance of the transplanted organ.

– **Anti-drug antibody reactions**: Inverse vaccines could also be explored for managing unwanted immune responses to therapeutic drugs, such as the development of anti-drug antibodies. By inducing tolerance to the drug molecule, inverse vaccines may help prevent these problematic immune reactions. [34]

– Infectious diseases: While the search results focus on autoimmune and allergic conditions, the inverse vaccine approach could potentially be adapted to infectious diseases as

well. By selectively modulating the immune response, inverse vaccines may be able to enhance protective immunity while avoiding excessive inflammation or autoimmunity. [34]

Companies

Initial phase I clinical trials of a glycosylation-modified antigen therapy described above, based on preclinical research, are being carried out in patients with celiac disease and multiple sclerosis by the pharmaceutical company **Anokion** [35], a company co-founded by Jeffrey Hubbell, one of the researchers behind the inverse vaccine concept. [35, 36] Anokion has already launched clinical trials to test whether this type of inverse vaccine might help people with multiple sclerosis. [35]

Another company exploring inverse vaccine platform with the potential to treat autoimmune diseases is **Nykode Therapeutics**, a clinical-stage biopharmaceutical company dedicated to the discovery and development of novel immunotherapies. [37, 38] The company is utilizing its antigen presenting cells-targeted technology to create an inverse vaccine platform for the potential use in autoimmune disorders, organ transplant rejections, anti-drug antibody reactions and allergy. [37] Nykode has demonstrated significant effects of its inverse vaccine platform in preclinical models of multiple sclerosis and type 1 diabetes. [38] The data, which were presented in a poster [39] at the 7th Antigen-Specific Immune Tolerance Drug Development Summit in 2024, "provide motivation to pursue a completely new approach to treating autoimmune diseases". [37] Nykode's inverse vaccine technology is devised to deliver small circular DNAs to muscle cells, providing instructions for making the Vaccibody proteins, which are subsequently secreted by the cells and target antigen-presenting cells. [40]

Pasithea Therapeutics [41] dedicated to developing drugs for nervous system disorders, has recently announced hopeful preclinical results for a tolerogenic, inverse DNA vaccine for multiple sclerosis. [42] Intramuscular injections of the candidate vaccine (PAS002) is reported to delay the onset of paralysis, and reduce severity of disease. Prophylactic administration also reduced the incidence and severity of relapse in the mouse model. [42]

Overall, the future of inverse vaccine research appears bright, showing promising potential. With continued investment, scientific breakthroughs, and careful clinical evaluation, these novel vaccines have the potential to transform the treatment of autoimmune diseases, but it will require further development and testing to ensure safety and efficacy in humans.

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