Journal of Clinical & Cellular Immunology

Rosenthal et al., J Clin Cell Immunol 2019, 10:1
DOI: 10.4172/2155-9899.1000574

Review Article Open Access

Why Don't We Have a Vaccine Against Autoimmune Diseases? - A Review

Ken S Rosenthal[1,2*], **Roy Carambula**[3] **and Daniel H Zimmerman**[3]

[1]*Roseman University College of Medicine, 10530 Discovery Dr, Las Vegas, USA*

[2]*Northeast Ohio Medical University, Rootstown, OH, USA*

[3]*CEL-SCI Corporation, Vienna, VA, USA*

[*]**Corresponding author:** Ken S. Rosenthal, Roseman University College of Medicine, 10530 Discovery Dr., Las Vegas, NV 89135, USA, E-mail: krosenthal@roseman.edu

Received date: December 06, 2018; **Accepted date:** January 24, 2019; **Published date:** January 31, 2019

Abstract

This review examines some of the reasons why we don't have a vaccine against autoimmune diseases and highlights the progress that has been made. Many autoimmune diseases, such as rheumatoid arthritis (RA), multiple sclerosis (MS) and type 1 diabetes (T1D), are driven by autoimmune T cell responses. Unlike vaccines for most infectious diseases, which elicit antibody responses, are intended for immuno-naïve individuals and considered preventative, a vaccine for an autoimmune disease must be therapeutic and resolve or control the on-going autoimmune response and condition in the diseased host. Despite these differences, many of the same considerations for infectious disease vaccines must also be addressed to develop a therapeutic vaccine for autoimmune diseases. The disease initiator/triggers, antigens and autoantigens, nature of the immunopathogenic and protective/therapeutic immune response will be compared for infectious and autoimmune diseases as will approaches for developing vaccines including formulations, animal models and indicators of success. The issues for a therapeutic vaccine for RA will be discussed in greater detail with a relatively limited discussion of T1D, MS and other autoimmune diseases.

Keywords: Autoimmune; Vaccine; Immunotherapy; Rheumatoid arthritis; Type 1 diabetes; Multiple sclerosis

Introduction

The Institute of Medicine report, "Vaccines for the 21st century" [1], released over 18 years ago highlighted a list of the seven most favorable vaccine targets based on medical and economic need and benefit to society. These included cytomegalovirus (CMV), broad spectrum influenza, group B streptococcus, *S. pneumoniae* (for infants and adults) and therapeutic vaccines for type 1 diabetes (T1D), multiple sclerosis (MS), and rheumatoid arthritis (RA). Of almost 30 candidates under examination, these vaccines would improve quality of life and reduce health care costs to the greatest extent. The only vaccine from the list to be currently available is the conjugated vaccine for *S. pneumonia* for infants and adults. Previous reviews have asked the question, "Why don't we have a vaccine against…..?" common and problematic pathogenic bacteria and viruses [2-4] and it is appropriate to propose this same question for autoimmune conditions. This review will examine some of the reasons why we don't have a vaccine against autoimmune diseases focusing on the three that were mentioned highlighting the progress that has been made.

Just as for infectious diseases, such as encephalitis or pneumonia, autoimmune diseases are defined by the affected organ system and symptomatology and can be caused by different triggers or agents. Unlike vaccines for most infectious diseases, which are intended for immuno-naive individuals and therefore considered preventative, a vaccine for an autoimmune disease must be therapeutic and resolve or control an on-going inflammatory immune response and condition in the diseased individual. Design of a therapeutic vaccine is even more difficult for autoimmune diseases because the initiating trigger, the specific auto antigen and immunopathogenic response driving the disease may be different and are very individualistic. In addition, most antimicrobial vaccines induce protective antibody whereas antibody and the antigen specific B cells are likely to exacerbate autoimmune diseases. Both the autoimmune antigen and the inflammatory immune response, including the T cells and cytokines, that are driving the immunopathology and disease must be addressed for each patient.

Despite the differences in the immunological nature of infectious and autoimmune diseases, many of the same parameters must be addressed to develop a therapeutic vaccine for autoimmune diseases (Table 1) and these parameters will be discussed herein. The issues for a therapeutic vaccine for RA will be discussed in greater detail with a more limited discussion of T1D, MS and other autoimmune diseases.

Literature Review

Understanding the disease related immune responses

A. Infectious diseases are identified by the microbial agent causing the disease as well as by the symptoms. Some diseases, like pneumonia, can be caused by different microbes and others, like rabies, by only one microbe. Vaccines have been developed against several of the most common causes of serious infectious disease.

Parameters	Antimicrobial		Therapeutic Anti- Inflammatory/Autoimmune	
	Extracellular Microbe or Toxin	Intracellular Microbe	Th1 Driven	Th17 Driven
Disease Initiator	Bacteria or virus or fungi	Bacteria or virus or fungi	Unknown	Unknown
Disease Antigen	Protein or carbohydrate	Protein	Protein	Protein
Disease Generating Immune Response With Associated Cytokines	Multiple responses	Multiple responses	Th1, TNFα, IL1α, IFNγ	Th17, IL23, TNFα, IL1α
Protective / Therapeutic Response	Th2 cytokines and antibody	Th1 cytokines, CTLs and antibody	Th2, Tregs, IL10, TGFβ	Th1, Treg, IFNγ, TGFβ, IL10
Animal Model	Naïve animal before infection	Naïve animal before Infection	Auto-immunized animal	Auto-immunized animal
Vaccine Immunogens	Protein or protein peptide or carbohydrate	Protein or protein peptide	Protein peptide	Protein peptide
Indicators of Success	Protection from lethal challenge	Protection from lethal challenge	Change in ongoing immune response and reduction or blocking progression of disease	Change in ongoing immune response and reduction or blocking progression of disease
Vaccine Induced Effector Molecules	Antibodies	IFNγ, TNFα, IL1α perforin, antibodies	IL10, TGFβ*	IFNγ, TGFβ, IL10*

Note: *Based on animal studies and projected from animal studies for human conditions

NA: Not Applicable; Th1: T Helper Cells; TNFα: Tumor Necrosis Factor; IL1α: Interleukin 1 Alpha; IFNγ: Interferon Gamma; Treg: Regulatory T Cell; TGFβ: Transforming Growth Factor Beta.

Table 1: Parameters to review for vaccines.

Using a military analogy, dendritic cells (DCs) are critical to identify the microbe as the enemy and provide direction and permission to T cells to initiate a response. The nature of the immune response depends upon the type of immunogen and the route of presentation. The T cells then tell the troops what needs to be done unless regulated by a higher authority such as regulatory T cells (Tregs). T cell responses are especially important for protection against intracellular and chronic infections. T cell specialists initiate appropriate responses directed by the cytokine signaling provided by the DCs [5-7]. The Th17 cells provide antimicrobial and inflammatory epithelial and polymorphonuclear leukocyte responses and the Th1 cells provide a longer term macrophage response and antigen specific IgG and cytolytic CD8 T cell responses while the Th2 cells reinforce humoral responses (Th2). The T cell responses are defined by the cytokines that they produce. Regulation and control is provided by Treg and Tr1 cells. B cells and plasma cells produce antibody to block pathogenic microbial functions and facilitate their clearance. B cells are also powerful specialists in presentation of the epitopes from a single antigen to reinforce antigen specific CD4 T cell commands.

B. Autoimmune diseases are identified by their symptoms and also characterized by the affected tissues or organs and the type of immune response driving the disease, antibody, Th17 or Th1. These diseases are distinguished from auto inflammatory diseases which are due to excessive innate responses. Unlike an infectious disease, an autoimmune disease is directed against a self-antigen and follows the loss of immunotolerance towards this or other antigens.

Immunotolerance is controlled by regulatory T cells (Treg and Tr1 cells). They regulate innate and immune responses and suppress inflammation with cytokines such as transforming growth factor beta (TGF-β) and Interleukin 10 (IL10) [8]. Treg cells are generated in the thymus and express high levels of the FoxP3 transcription factor. Tregs suppress by cell contact and regulatory cytokine production. Tr1 cells are Tregs generated in the periphery in response to high levels of IL10 and IL2 and produce high quantities of IL10 and TGF-β. These cells are also considered to be plastic and can morph from, and into, Th17 cells [5,7].

Responses to tissue specific antigens will result in organ-specific diseases while responses to more ubiquitous proteins would yield systemic or multi-organ autoimmune diseases (Table 2). The antigen(s) and autoimmune responses that trigger and maintain the disease may not be the same and are most likely to be different for each individual.

Normally, the discrimination between self and non-self is provided by central and peripheral immunotolerance. Many self-reactive B and T lymphocytes are deleted in the bone marrow and thymus and others are controlled by regulatory T cells (Treg and Tr1), as facilitated by DCs, myeloid derived suppressor cells (MDSC) [9], macrophages and regulatory B cells (Breg) [10,11]. These antigen presenting cells (APCs) can promote T cell tolerance by antigen presentation in the absence of inflammatory cytokines or by production of the regulatory cytokines, IL10 and TGFβ [12].

Using another military analogy, discrimination of friend (self) from foe (non-self and pathogen) is lost during autoimmunity. Autoimmunity is initiated when DCs give permission to attack targets in error resulting in attack on self and allies. Only certain major histocompatibility complex (MHC) molecules can present self-antigens to elicit friendly fire casualties, hence risk of disease is limited to certain MHC types. The autoimmune attack on self requires appropriate peptide target acquisition by MHC molecules, which is

genetically determined, and target recognition by T-cell receptors (TCRs), which is also genetically and both are experientially determined. Once triggered, cell disruption by the inflammatory immune response provides a constant presence of antigen to maintain the T cell response and reactivate memory cells.

RA	MS	T1D
Collagen	Myelin	Insulin/pre/pro-insulin
Proteoglycan (PG)	Proteolipid protein (PLP)	Islet-specific glucose-6-phosphatase catalytic subunit related protein
Vimentin, filaggrin, fibrinogen	Myelin oligodendrocyte glycoprotein (MOG)	Tyrosine phosphatase like protein
Heat shock proteins (HSP)		Glutamic acid decarboxylase (GAD65)
Nuclear proteins		Human islet amyloid polypeptide precursor protein
Citrullinated proteins	Citrullinated proteins	

Table 2: Potential antigens/immunogens for vaccines for three major autoimmune diseases.

Viral and other infections can disrupt tolerance by presenting an antigen that resembles regions of an auto antigen (molecular mimicry) [13-17] or by triggering a cytokine storm that dysregulates tolerance. Cytokine storms, induced by viral infections, sepsis, super-antigens or other triggers, can be enablers of autoimmune responses by stimulating abundant activating cytokines that override the regulatory signals to DCs. This allows the DCs and perhaps other antigen presenting cells (APC) to inappropriately process and present peptides from self-proteins and promote autoimmune Th1 or Th17 pro-inflammatory responses [18]. The cytokine storm can also promote MHC II expression on epithelial cells of the thyroid or elsewhere and inappropriate antigen presentation to CD4 T cells, as suggested for Graves' disease [19].

Autoantibody responses are often elicited to self-nuclear, cytoplasmic and extracellular molecules released upon tissue damage. These auto antigens include intracellular molecules such as DNA, ribonucleoprotein (RNP), thyroglobulin, retinol binding protein (RBP), myelin basic protein (MBP), proteolipid peptide (PLP), collagen, proteoglycan (PG), acetyl-cholinesterase (ACH) and hormones, such as insulin beta chain peptide epitopes. Many proteins become autoantigens after post translational modification (PTM), such as citrullination. Conversion of arginine to citrulline is catalyzed by the enzyme peptidyl-arginine deiminase (PADI) [20,21]. Citrullinated proteins elicit antibodies and reactive T cells in RA patients as well as patients with uveitis, MS and other autoimmune diseases. Other types of PTM involve conversion of lysine in collagen to homocitrulline and galactosylation of serine or threonine residues in these or other autoantigens.

Autoantibodies may cause or contribute to the disease process, help define the disease and are also good monitors of disease progression [22]. Goodpasture syndrome and myasthenia gravis are examples of autoimmune diseases driven by antibody and subsequent complement mediated cell disruption and inflammation. As will be described later, antibody mediated autoimmune diseases would be difficult to modulate with a vaccine.

Autoantibodies are not always the primary cause of immunopathology but their presence indicates a preponderance of B cells and plasma cells making these antibodies. The B cell is also a potent APC to CD4 T cells with a repertoire focused on the autoantigenic peptides derived from the antigen. The B cells express the autoantibody on their cell surface as an antigen receptor (sIG). The sIG binds and promotes internalization of the autoantigen for processing and presentation of its peptides on MHC II molecules to CD4 T cells and this will amplify the autoimmune response.

Autoimmune diseases driven by T cells include RA, MS, and T1D. Th17 and Th1 T cell responses promote inflammatory pathology through cytokine production and activation of neutrophils, macrophages, B cells and CD8 T cells. Presentation of autoantigenic peptides on MHC I molecules can elicit and promote localization of CD8 T cells and CD8 memory T cells to specific tissue sites. CD8 T cells can promote localized inflammation by producing inflammatory cytokines and cytotoxicity [23,24]. For Hashimoto's thyroiditis, antibodies may be present to the thyroid peroxidase, but it is the cytolytic CD8 T cells recognizing peptides on MHC I molecules of the thyroid cells that cause the autoimmune disease [25]. In some mouse models of RA, depletion of T cells alleviates disease [25] and in other models, T cells can transfer the disease from symptomatic to naïve mice [26,27].

In addition to immune attack on the infecting microbial enemy, the fog of this immune war can make discrimination of host cells and proteins difficult and allow permission to initiate friendly fire. For RA, MS and T1D, an infection or other event can cause release of specific tissue antigens and promote cytokine induced dysregulatory confusion to initiate disease. Once initiated, attack on these regional target cells or proteins (e.g. those that reside in joints, neurons or beta cells) become very difficult to resolve and the confusion and the attacks reinforce themselves and continue.

Vaccines for immunotherapy

For many infectious diseases, the vaccine immunogen that elicits protection is readily identified as an inactivated microbe, component of the microbe or a live attenuated microbe. The latter will elicit cell mediated Th1, Th2, Th17 and Treg as well as antibody responses and better memory responses while other components and inactivated microbes other than PAMPs primarily elicit a Th2 immune response sufficient to elicit protective antibody. Newer protocols using adjuvants, such as for the Shingrix vaccine for zoster [28] or the Fluad vaccine [29] for influenza, promote cell mediated as well as antibody responses to protein subunit immunogens. Although not yet licensed for humans, DNA [30] and RNA [31] vaccines provide the opportunity to rapidly produce vaccines by genetic engineering to elicit T cell responses to defined immunogens. These genomic vaccines may

require a subsequent immunization with a protein booster to elicit antibody. Immunogenic peptides, usually weak immunogens by themselves, can be converted into stronger immunogens by attachment to large carrier proteins or by use of the "helper activities" such as LEAPS (Ligand Epitope Antigen Presentation System), PaDRe (pan DR epitope), Ii-Key (MHC II binding tetrapeptide), or other technologies [32]. Adoptive transfer of antigen loaded DCs [33,34] or antigen specific T cells [35] that elicit antigen specific responses have been utilized for treatment of cancer and is also appropriate for other applications.

Current therapy for autoimmune diseases ablate a proinflammatory cytokine or T or B cell function and leaves the patient immunocompromised with respect to those immune functions. Therapies have been proposed to generically activate Treg and immunosuppressive cells but this would still have effects on the entire immune system and all specificities.

Rather than eliminate or limit helpful responses, an immunotherapeutic vaccine for an autoimmune disease should suppress or modify the disease driving inflammatory immune response and focus the response to the relevant autoantigen(s). The vaccine could stimulate antigen specific Treg cells or initiate a cytokine response to modulate the antigen specific pro-inflammatory Th1 or Th17 responses that are driving the disease.

For Th2 driven allergies, immunization with the offending antigen is the approach used for treatment. Repeated immunization with low doses of allergen (antigen) promotes a shift in the immunoglobulin response away from an allergic disease promoting IgE, to an IgG response, rather than promoting immunotolerance [36]. This approach usually has not been effective for autoimmune diseases for which antibody and expansion of B cell numbers can be detrimental.

Most immunotherapies focus on the aberrant T cell and its cytokine response (Table 3). Antigen specific stimulation of Tregs and tolerance has been attempted by co-administration of antigen and an immunosuppressive treatment, such as IL4, IL10, or a DNA plasmid encoding these cytokines [37]. The suppressive action of intravenous immunoglobulin (IVIG) treatments can be utilized with a set of peptides from IgG called Tregitopes which stimulate Treg cells and induce tolerance when co-administered with autoantigen [38,39]. The antigen and the adjuvant-like treatment can be co-administered as separate components but co-delivery by covalently linking the molecules, encoding them within the same DNA plasmid or embedding them within a nanoparticle, ensures that the relevant cells are affected simultaneously by all of the components. Intravenous administration of apoptotic antigen-expressing cells or particles from these cells can also promote tolerance [40]. Apoptotic cells expose tolerizing structures that suppress responses to covalently affixed peptide or protein autoantigens [41]. Similarly, IV infusion of an autoantigenic peptide coupled to biodegradable poly (lactic-coglycolic acid) nanoparticles can elicit tolerizing responses [42], as shown for the relapsing-remitting experimental autoimmune encephalomyelitis model for multiple sclerosis [43].

Of the different vaccine approaches that have been suggested, the LEAPS approach is unique in that the vaccine can be designed to deliver either a Th1 or a Th2/Treg immune response to an immunogenic peptide depending upon the attached immune cell binding ligand (ICBL). The ICBL attached to the antigenic peptide in a LEAPS vaccine acts like an adjuvant to activate and direct the subsequent immune response. Its uniqueness is also seen by the up and down regulation of different elements such as cytokines. Still to be determined is whether this is a direct effect of the LEAPS immunogen on T cells or indirect perhaps elicited by the cytokines from the activated cell (like a bystander effect). Attachment of the J-ICBL, a peptide from the beta-2-microglobulin component of the MHC I molecule (DLLKNGERIEKVE, aa 38-50) [44-47] converts a peptide containing a CD8 T cell epitope as small as 8 amino acids into an immunogen that elicits interferon γ (IFNγ) directed Th1 immune responses. The J-LEAPS vaccines promote the maturation of mouse and human precursors into DC1s that produce IL12p70, present antigen to CD4 and CD8 T cells and are sufficient to elicit protection from lethal herpes simplex virus type 1 (HSV-1) infection [48] and therapy to influenza infection (49). Attachment of the G-ICBL, or the more stable DerG (DGQEEKAGVVSTGLI) ICBL, peptides from the beta chain of the MHC II molecule (NGQEEKAGVVSTGLI, aa 135-149, [44-46,49-54] promotes Th2 and Treg responses. The G and DerG ICBLs bind directly to the CD4 molecule to affect the function of CD4 T cells. J-LEAPS vaccines have demonstrated protection or therapy in mouse models for HSV-1, influenza, breast cancer, collagen-induced arthritis (CIA) mouse model for RA and autoimmune myocarditis (46,52,55-58), and a G-LEAPS vaccine demonstrated therapeutic efficacy for the PGIA/GIA mouse models of RA [32,55-60].

Animal models

The first step in developing a therapeutic agent, including a vaccine, is to test it in an animal model (Table 3). Appropriate animal models for infectious diseases are often available since most, but not all, human pathogens infect animals causing disease signs similar to that of humans. The efficacy of an antimicrobial drug or vaccine can be surmised by protection from morbidity and mortality and reduction in microbial load following challenge in the animal model. Mice are often the animal model because they are relatively inexpensive, their immune systems are well characterized and there is a large library of immunological reagents to facilitate the analysis of the response. In addition, inbred and or transgenic (for MHC or other human immune system genes) strains are available to enhance reproducibility and minimize histocompatibility issues. Ultimately, however, a mouse, ferret, cotton rat, mini-pig, dog, cat, rabbit or even a non-human primate (NHP) are not a human. Subtle differences in the optimal microbial strain that can infect the mouse, the course of disease and the immune response in the highly inbred laboratory mouse and the comparatively very short life span of the mouse limit the translation of findings to humans.

Animal models are even more difficult to develop for autoimmune human diseases than for infections. By definition, an autoimmune human disease involves human proteins and human immune components and these can differ from that of animals. Although the animal models may express similar disease signs as for humans, the initiators, immune responses, disease markers, time course for initiation, rate of progression, and severity that is elicited in the model may differ substantially from human disease.

Autoimmune disease in animal models can occur spontaneously in genetically manipulated models, be induced by immunization with an autoantigenic protein or by other treatments.

Format	Description	Animal or Human Disease*
LEAPS	Heteroconjugates peptides of T cell antigenic peptide and immune cell binding ligand	Murine: RA (PGIA/GIA, CIA), EAM, Influenza A, HSV, HER2/NEU(44-46,48,49,52–58)
Co-administration of antigen and modulator	Apoptotic cells exposing tolerizing structures	Murine: RA (40)
Nanoparticle	Poly lactic-coglycolic acid	Murine: EAE (42)
Adoptive transfer T cells	Autologous regulatory T cells induced and expanded *ex vivo*	Murine: MS, RA, T1D, SLE(92)
Adoptive transfer DCs	Autologous suppressive or tolerogenic DCs activated and loaded with antigen, *ex vivo*	Human phase I: T1D, RA, Crohn's disease (90)
Note: *RA: Rheumatoid Arthritis; CIA: Collagen Induced Arthritis; PGIA/GIA: Cartilage Proteoglycan (PG)-Induced Arthritis (PGIA) and PG G1-Domain-Induced Arthritis (GIA); EAM: Experimental Autoimmune Myocarditis; EAE: Experimental Autoimmune Encephalitis; T1D: Type 1 Diabetes; SLE: Systemic Lupus erythematosus;		

Table 3: Examples of formats of immunotherapeutic autoimmune vaccines and animal or human trials.

The models, described for the different diseases, are mostly in specific mouse or rat strains. The spontaneous models may resemble human disease in that they are chronic and progressive with much defined genetic backgrounds but compared to other models, they are less predictable regarding age of initiation and severity of disease course. The inducible models utilize known initiators, usually autoantigens, and have a relatively reproducible time course for initiation and disease progression. The autoantigens are usually administered with a strong adjuvant, such as complete Freund's adjuvant or endotoxin, to activate inflammatory responses. Some models require multiple inoculations over an extended period of time to induce disease and others have a rapid onset following a single incident. These and other factors could diminish the resemblance of the animal model to human disease.

The route of administration of auto-antigen is an important consideration in determining how the antigen will be presented and plays a key role in determining whether the disease is driven by a Th1 or Th17 immune response. This has been demonstrated for the experimental autoimmune encephalitis (EAE) model for MS [59], the experimental autoimmune uveitis (EAU) model for uveitis [60], and for RA, in the cartilage proteoglycan PGIA and PG G1-domain-induced arthritis (GIA) models for RA [61]. Similarly, each individual may experience the autoimmune trigger in a different way and experience a different immunopathogenic response.

The nature of the inflammatory disease-promoting immune response in the animal model must be reproducible, definable and resemble as closely as possible immune responses in humans. Onset of human autoimmune diseases often occurs later in life whereas many animal models utilize sequestered, inbred, male or female and younger animals and disease develops more aggressively than in man and studies tend to focus on early stages and not late stage disease where clinical presentation often occurs.

To mimic a chronic disease in humans and allow time to elicit therapeutic immune responses by a vaccine, the autoimmune disease in the animal model must progress sufficiently slowly and the animals must survive long enough to allow monitoring of the consequences of the treatment.

Some rat models for RA progress so quickly that there is inadequate time to induce a response to a therapeutic vaccine immunotherapy. For example, the streptococcal wall induced arthritis (SCWIA) or collagen antibody induced arthritis models (CAIA) progress to aggressive disease in less than two weeks [62]. In contrast, RA disease progression for the collagen induced arthritis DBA mouse model (CIA) is 3-4 weeks and for the PGIA or GIA models in the Balb/c strain is 6-8 weeks, sufficient time for immunotherapy [32,54].

To approach a human immune response in a mouse model, immunodeficient mice can be reconstituted with human hematopoietic stem cells that develop into functional human immune systems and even human tissues [63-65]. For T cell driven diseases such as RA, T1D and MS, these models provide opportunity to manipulate the immune response. However, the engrafted immune system must be of the appropriate MHC background and capable of appropriate autoimmune responses.

Use of the animal model can provide insight into the efficacy and immunological response of a therapeutic vaccine but other considerations must be considered for translation to humans. Studies with NHP, although a desired step in the Food and Drug Administration (FDA) approval process of a therapeutic vaccine, still does not deal with the species differences in disease initiation, presentation, disease driving autoantigen and immune response.

Ultimately, each person may have to be their own experimental model for testing personalized immunotherapies that address their specific autoantigen and disease generating pro-inflammatory T cell immune response [66]. Human cell culture systems may be a way to help find the answer(s). Like an allergen patch test, the cytokine response of the individual's buffy coat white blood cells to a panel of autoantigens could be used to indicate reactivity and the generated cytokines would indicate the nature of the predominant response for each individual patient. Such an assay was used to identify the antigen specific T cell response, Th1 or Th17, driving the disease in the PGIA animal model [54].

Rheumatoid arthritis

RA is a T cell driven disease and animal studies suggest that within an individual either a Th1 or a Th17 proinflammatory response predominates to drive the disease [61] but disease and pathological presentation may result from a combination of these pro-inflammatory responses. The cytokine repertoire induced by these T cells promotes

tissue disruptive inflammatory neutrophil and macrophages responses and the proliferation of synoviocytes (pannus formation) that degrade and compromise joint structure and function [62].

The autoantigens suggested to be associated with RA include collagen II, IX and XI, proteoglycan (PG or aggrecan), vimentin, filaggrin, fibrinogen, heat shock proteins (HSP), nuclear proteins and citrullinated and other modified versions of these and other proteins [67]. Many of the citrullinated proteins are present in joints that can be affected by RA. These antigens, other antigens or a combination of antigens could be the inducers of RA in humans. Prime candidates are collagen II and proteoglycan [20,57,62,66-71] which can induce RA-like disease in mice, are prone to citrullination and elicit potent T cell responses.

For RA disease, the characteristics of an ideal animal model include: age and gender of the susceptible individual; disease signs; the inflammatory T cell response driving the disease; expression of autoantibodies, including those against citrullinated proteins; and presence of rheumatoid factor (Rf). Models for RA include: collagen induced arthritis (CIA) in young male DBA/1j mice, cartilage proteoglycan (PG)-induced arthritis (PGIA) and PG G1-domain-induced arthritis (GIA) models in adult older (retired breeder) female BALB/c mice, antibody (anti-collagen) induced collagen arthritis (CAIA), pristane induced arthritis (PIA), adjuvant induced arthritis (AA), methylated BSA induced arthritis (often inoculated in a joint cavity), and streptococcal wall induced arthritis (SCWIA) (for references on these various models see review [32]).

Disease progression in the CIA model mimics human disease in terms of joint pathology, inflammation, bone erosion, bone remodeling, cartilage alterations and pannus formation (57,72-78). Disease is initiated by immunization with bovine or human collagen in complete Freund's adjuvant and then repeated in incomplete Freund's adjuvant. Initial signs of disease are noticeable approximately 14-35 days after the second injection and progress over time. This is sufficient time to initiate and test a vaccine induced immunotherapy. The disease in this model is driven by Th17 immune responses, as indicated by the generation of IL17 (57) and that disease does not occur in mice lacking the IL23 gene, a key cytokine that promotes the Th17 response [72-80].

The PGIA and GIA models in adult (retired breeder) female BALB/c mice are predominantly driven by Th1 responses producing IFNγ [81-84] but the mice also generate Th17 and other pro-inflammatory cytokine responses. The PGIA [85,86] and GIA [81] models resemble human RA more than other animal models in that disease is induced in older females, and anti-citrullinated protein, autoantibody to anti-citrulline peptide (ACPA) and Rf are produced. This combination is not commonly seen in other models such as the CIA, PIA, or AA models in mice, rabbits or rats [32].

A J-LEAPS vaccine, CEL-2000, incorporating a peptide from human collagen (huCII254-273) was effective in the Th17 driven CIA model of RA as therapy to block the progression of disease after disease initiation. Neither a mixture of the unconjugated J-ICBL and the huCII254-273 peptide nor the DerG version of this vaccine was effective. Mice immunized with CEL-2000 had greatly reduced levels of IL17 and Tumour Necrosis Factor alpha (TNFα) and increased levels of IFNγ and IL10, a regulatory cytokine. TGFβ, another regulatory cytokine, was not assayed. The therapeutic and serum cytokine results following biweekly CEL-2000 treatments were comparable to those for mice treated every other day with the TNFα antagonist, etanercept [57]. It can be suggested that the IFNγ generated by CEL-2000 immunization converts the antigen specific Th17 cells into Tr1 cells. Interestingly, Tr1 cells produce low levels of IFNγ in addition to IL10 and TGFβ [87]. The antigen specific Tr1 cells would then modulate the proinflammatory condition.

CEL-4000, consisting of a heteroconjugate of the derG-ICBL and the ATEGRVRVNSAYQDK (PG70) peptide from human proteoglycan, stopped progression of disease and reduced Th1 as well as Th17 related cytokine and inflammatory responses in the Th1 driven PGIA and GIA mouse models of RA [54]. The J-LEAPS version of this vaccine was not effective in this model. The importance of a vaccine's ability to modulate the specific disease-driving proinflammatory immune response within an individual is demonstrated by the difference in efficacy of the J-ICBL (Th1 promoting) and G-ICBL (Th2/Treg promoting) versions of the CEL-2000 and CEL-4000 LEAPS vaccines in the CIA and PGIA/GIA mouse models.

With both CEL-4000 and CEL-2000, single epitope LEAPS vaccines appear to evoke therapeutic immune responses against a multiple epitope driven disease in their respective animal models for at least 35 days ((PGIA/GIA) or more (CIA) days. Therapy was tailored to modulate the disease driving immune response.

As alternatives to immunization with a peptide, autologous cells that are activated and expanded *ex vivo* can be used to deliver antigen specific vaccine-like therapy. DCs generated with LEAPS J-influenza peptides rapidly modulated the inflammatory immune responses and also limited influenza A virus production and promoted survival of mice when administered up to 2 days after lethal infection [49]. Also observed was a reduction in proinflammatory cytokines and IL4 and increase in Th1 cytokines. As mentioned earlier it was not possible to determine which were primary and which were secondary because of bystander effect. Rapid modulation of Th17 inflammatory responses in RA might also be possible with autologous DCs activated *ex vivo* with CEL-2000, also a J-LEAPS vaccine. In addition to the LEAPS DCs, tolerogenic autologous DCs can be activated *ex vivo* [88-91] and then loaded with the relevant autoantigen prior to reinfusing into the patient. This approach has been examined in animal models of RA, T1D, atherosclerosis, inflammatory bowel disease and MS; and human phase 1 trials have been performed for RA and T1D. Preliminary findings indicate safety but it is premature to determine efficacy. Immunomodulatory antigen specific autologous T cells can be activated and expanded *ex vivo* and have been tested in animal models for RA as well as MS, SLE and T1D [92].

Multiple sclerosis

Multiple sclerosis (MS) is believed to be mediated primarily by Th17, Th1 and CD8 T cell anti-myelin inflammatory responses. The trigger for MS is not known but MS may follow a virus infection with Epstein Barr virus (EBV), influenza A virus, herpes simplex virus, human papilloma virus, or human herpesvirus-6 [93,94]. In addition to inducing responses to virus induced tissue damage, these viruses express proteins with peptides that mimic peptides from myelin that might induce autoimmune responses [93,94]. Peptides from proteolipid protein (PLP) or myelin oligodendrocyte glycoprotein (MOG) induce an autoimmune condition in the experimental autoimmune encephalitis (EAE) mouse model for MS and either a Th1 or Th17 signature phenotype may occur depending on how the disease is induced [59].

For multiple sclerosis (MS), the three most popular models are the Theiler's murine encephalomyelitis (TME) virally induced chronic

demyelinating; experimental autoimmune/allergic encephalomyelitis (EAE); and the toxin-induced demyelination models [95]. Models that utilize adoptive transfer of MBP specific activated T cells are also useful for analyzing the disease process [96]. The importance of CD8 T cells to the pathophysiology is shown in this model. As for the animal models for RA, each MS model has its advantages and disadvantages. The EAE model is initiated by injection of myelin containing material with complete Freund's adjuvant and pertussis toxin into SJL/J mice. Disease is initiated against a peptide from the proteolipid protein of myelin basic protein and induces a relapsing and remitting paralysis. Unlike MS in which lesions are primarily in the brain, in some cases EAE primarily affects spinal cord white matter. Although several viral infections have been implicated as providing the triggers for MS, there is no clear cause and effect relationship for human disease. For the MS-like disease induced by TME virus, the virus triggers immune responses secondary to the infection. For demyelination induced by the toxic actions of cuprizone or lysolecithin treatments, MS-like disease occurs due to the death of oligodendrocytes or dissolution of myelin, neither of which are initiated by immune mechanisms. The EAE model is the most favored of the three.

For MS, immune responses against myelin associated proteins, including myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP), appear to drive the disease. Therapeutic vaccine preparations of these proteins and CD4 T and CD8 T cell antigenic peptides from these proteins have been evaluated in human trials with little efficacy. Continued oral exposure to a protein can elicit T cell tolerance, as it does for food and intestinal flora. This approach was attempted with myelin for MS and other antigens for T1D but with very limited success [97-99].

Type 1 diabetes

Type 1 diabetes (T1D) appears to be a CD8 T cell mediated cytolytic disease with CD4 helper influence. The autoimmunity can be initiated by infection with coxsackie B4 virus with a genetic predilection towards individuals with specific MHC II genotypes [100]. The CD8 T cells are directed towards peptides from insulin, preproinsulin, islet-specific glucose-6-phosphatase catalytic subunit related protein, tyrosine phosphatase like protein, glutamic acid decarboxylase (GAD65) and human islet amyloid polypeptide precursor protein [100]. For more recent findings and other details, see the following articles [101-103]. Autoantibodies are also generated against the insulin beta chain epitope and other proteins during T1D.

For type 1 diabetes (T1D), CD8 T cell mediated inflammatory destruction of the islets of Langerhans results in spontaneous development of diabetes in the nonobese diabetic (NOD) mouse model [104]. The NOD model is the most used model [105]. Various transgenic mice are used for other models. For example, lymphocytic choriomeningitis virus (LCMV) infection of genetically modified mice that express the LCMV glycoprotein under control of the insulin promotor elicits CD8 T cell mediated beta cell cytolysis mimicking the coxsackie virus induced diabetes that occurs in humans [106,107]. Humanized NOD-scid mice grafted with human lymphoid cells allows evaluation of the role of human CD8 T cells in diabetes [108]. Although driven by CD8 cytolytic T cells, as for humans, the autoantigenic peptides are not necessarily the same as for humans which limits the translatability to an effective vaccine for human usage.

For T1D, pancreatic proteins, including insulin, proinsulin, pancreatic glutamic acid hydrolase and 60kD heat shock protein are possible sources of tolerogenic peptides [109,110]. Tolerogenic peptides from insulin and proinsulin have been identified and tested as therapeutic vaccines in mice and humans [111-114]. Specific peptides from insulin/proinsulin promote FoxP3 Treg and antigen specific IL-10 producing T cells. As peptides, their action is MHC specific which would limit their use to only those who express that MHC. Although well tolerated in a Phase 1 trial, there is still the potential for induction of undesired autoimmune responses against the peptide. This possibility could be minimized by conjugating the peptide to an immunomodulating carrier, such as a derG LEAPS peptide, or co-administration with a regulatory cytokine.

Discussion and Conclusion

Why don't we have a vaccine for autoimmune diseases?

Although the challenge set forth in the Institute of Medicine (IOM) report for development of a therapeutic vaccine for autoimmune diseases has not been met, there has been some substantial progress towards identifying the disease driving antigens and immune responses, developing appropriate models for disease induction and vaccine testing, markers for monitoring disease progression, the disease causing immune responses and the efficacy of therapy. Probably the most important realization is that each autoimmune condition is actually a collection of immunological diseases that are initiated and maintained by different autoantigen(s) and maintained by different proinflammatory immune responses. This will likely to require that the antigens and immune responses for a therapeutic vaccine will be different for different patients. To reach the same expectations as for antimicrobial vaccines, vaccines for autoimmune diseases will most likely have to be customized for each patient so that they modulate the individual's disease driving immune response to the relevant autoantigen.

These vaccines will have to take into consideration the diversity of MHC backgrounds of humans and its importance in driving the disease. Development of effective therapies, whether by current means or vaccine, will need to take advantage of recent advances in personalized medicine that determine the disease directing immune response and antigen.

Analysis of the patient's serum for signature cytokines and evaluation of the cytokine responses of their T cells *ex vivo* to panels of auto-antigens can allow intelligent choice of appropriate vaccine therapy. Vaccines, such as the LEAPS vaccines, that can direct and specifically modulate the subsequent antigen specific immune response, can then provide the necessary personalized therapy for the human patient.

Acknowledgements

DH Zimmerman is supported by grants from the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) of USA (NIAMS) under award numbers R43AR063504.

References

1. Stratton KR, Durch JS, Lawrence RS (2000) Vaccines for the 21st Century: A Tool for Decisionmaking. Washington, DC: National Academies Press, 476.
2. Rosenthal KS, Sikon J, Kuntz A (2015) Why don't we have a vaccine against…….? Part 1. Viruses. Infect Dis Clin Pract 23: 202-210.

3. Rosenthal KS, Kuntz A, Sikon J (2016) Why don't we have a vaccine against…….? Part 2. Bacteria. Infect Dis Clin Pract Mar 24: 119-123.
4. Rosenthal KS, Sikon JR, Kuntz A (2016) Why don't we have a vaccine against…….? Part 3. Bacteria Too. Infect Dis Clin Pract 24: 183-189.
5. Nistala K, Adams S, Cambrook H, Ursu S, Olivito B, et al. (2010) Th17 plasticity in human autoimmune arthritis is driven by the inflammatory environment. Proc Natl Acad Sci 107: 14751-14756.
6. Maggi L, Santarlasci V, Capone M, Rossi MC, Querci V, et al. (2012) Distinctive features of classic and nonclassic (Th17 derived) human Th1 cells. Eur J Immunol 42: 3180-3188.
7. Lee YK, Mukasa R, Hatton RD, Weaver CT (2009) Developmental plasticity of Th17 and Treg cells. Curr Opin Immunol 21: 274-280.
8. Yu H, Paiva R, Flavell RA (2018) Harnessing the power of regulatory T-cells to control autoimmune diabetes: [An] overview and perspective. Immunol 153: 161-170.
9. Cripps JG, Gorham JD (2011) MDSC in autoimmunity. Int Immunopharmacol 11: 789-793.
10. Wortel C, Heidt S (2017) Regulatory B cells: Phenotype, function and role in transplantation. Transpl Immunol 41: 1-9.
11. Rosser EC1, Mauri C2 (2015) Regulatory B cells: Origin, phenotype, and function. Immunity 42: 607-612.
12. Arango Duque G, Descoteaux A (2014) Macrophage cytokines: Involvement in immunity and infectious diseases. Front Immunol 5: 491.
13. Darabi K, Karulin AY, Boehm BO, Hofstetter HH, Fabry Z, et al. (2004) The third signal in T cell-mediated autoimmune disease? J Immunol 173: 92-99.
14. Cusick MF, Libbey JE, Fujinami RS (2012) Molecular mimicry as a mechanism of autoimmune disease. Clin Rev Allergy Immunol 42: 102-111.
15. Rose NR (2015) Molecular mimicry and clonal deletion: A fresh look. J Theor Biol 375: 71-76.
16. Proal AD, Marshall TG (2018) Re-framing the theory of autoimmunity in the era of the microbiome: persistent pathogens, autoantibodies, and molecular mimicry. Discov Med 25: 299-308.
17. Gianani R, Sarvetnick N (1996) Viruses, cytokines, antigens, and autoimmunity. Proc Natl Acad Sci USA 93: 2257-2259.
18. Banchereau J, Pascual V, Palucka AK (2004) Autoimmunity through cytokine-induced dendritic cell activation. Immunity 20: 539-550.
19. Hanafusa T, Pujol-Borrell R, Chiovato L, Russell RC, Doniach D, et al. (1983) Aberrant expression of HLA-DR antigen on thyrocytes in Graves' disease: relevance for autoimmunity. Lancet 2: 1111-1115.
20. Law SC, Street S, Yu CHA, Capini C, Ramnoruth S, et al. (2012) T cell autoreactivity to citrullinated autoantigenic peptides in rheumatoid arthritis patients carrying HLA-DRB1 shared epitope alleles. Arthritis Res Ther 14: R118.
21. Schellekens G, De Jong B, Van den Hoogen FH, Van de Putte LB, Van Venrooij WJ (1998) Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. J Clin Invest 101: 273-281.
22. Rowley M, Whittingham S (2015) The role of pathogenic autoantibodies in autoimmunity. Antibodies 4: 314-353.
23. Carvalheiro H, Duarte C, Silva-Cardoso S, Da Silva JAP, Souto-Carneiro MM (2015) CD8+ T Cell Profiles in Patients With Rheumatoid Arthritis and Their Relationship to Disease Activity. Arthritis Rheumatol 67: 363-371.
24. Petrelli A, Van Wijk F (2016) CD8+ T cells in human autoimmune arthritis: the unusual suspects. Nat Rev Rheumatol 12: 421-428.
25. Kang YM, Zhang X, Wagner UG, Yang H, Beckenbaugh RD, et al. (2002) CD8 T cells are required for the formation of ectopic germinal centers in rheumatoid synovitis. J Exp Med 195: 1325-1336.
26. Hesse M, Mitchison NA (2000) Relapsing arthritis induced by cell transfer from collagen-immunised mice. Autoimmunity 32: 27-32.
27. Kadowaki KM, Matsuno H, Tsuji H, Tunru I (1994) CD4+ T cells from collagen-induced arthritic mice are essential to transfer arthritis into severe combined immunodeficient mice. Clin Exp Immunol 97: 212-218.
28. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, et al. (2015) Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 372: 2087-2096.
29. Goldeck D, Theeten H, Hassouneh F, Oettinger L, Wistuba-Hamprecht K, et al. (2017) Frequencies of peripheral immune cells in older adults following seasonal influenza vaccination with an adjuvanted vaccine. Vaccine 35: 4330-4338.
30. Ferraro B, Morrow MP, Hutnick NA, Shin TH, Lucke CE, et al. (2011) Clinical applications of DNA vaccines: Current progress. Clin Infect Dis 53: 296-302.
31. Deering RP, Kommareddy S, Ulmer JB, Brito LA, Geall AJ (2014) Nucleic acid vaccines: Prospects for non-viral delivery of mRNA vaccines. Expert Opin Drug Deliv 11: 885-899.
32. Rosenthal KS, Mikecz K, Steiner HL, Glant TT, Finnegan A, et al. (2015) Rheumatoid arthritis vaccine therapies: perspectives and lessons from therapeutic ligand epitope antigen presentation system vaccines for models of rheumatoid arthritis. Expert Rev Vaccines 14: 891-908.
33. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, et al. (2010) Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363: 411-422.
34. Koski GK, Koldovsky U, Xu S, Mick R, Sharma A, et al. (2012) A novel dendritic cell-based immunization approach for the induction of durable Th1-polarized anti-HER-2/neu responses in women with early breast cancer. J Immunother 35: 54-65.
35. Rosenberg SA, Restifo NP (2015) Adoptive cell transfer as personalized immunotherapy for human cancer. Science 348: 62-68.
36. Wisniewski J, Agrawal R, Woodfolk JA (2013) Mechanisms of tolerance induction in allergic disease: integrating current and emerging concepts. Clin Exp Allergy 43: 164-176.
37. Northrup L, Christopher MA, Sullivan BP, Berkland C (2016) Combining antigen and immunomodulators: Emerging trends in antigen-specific immunotherapy for autoimmunity. Adv Drug Deliv Rev 98: 86-98.
38. Cousens L, Najafian N, Martin WD, De Groot AS (2014) Tregitope: Immunomodulation Powerhouse. Hum Immunol 75: 1139-1146.
39. Su Y, Rossi R, De Groot AS, Scott DW (2013) Regulatory T cell epitopes (Tregitopes) in IgG induce tolerance in vivo and lack immunogenicity per se. J Leukoc Biol 94: 377-383.
40. Saas P, Bonnefoy F, Toussirot E, Perruche S (2001) Harnessing apoptotic cell clearance to treat autoimmune arthritis. Front Immunol 8: 1191.
41. Birge RB, Boeltz S, Kumar S, Carlson J, Wanderley J, et al. (2016) Phosphatidylserine is a global immunosuppressive signal in efferocytosis, infectious disease and cancer. Cell Death Differ 23: 962-978.
42. Serra P, Santamaria P (2015) Nanoparticle-based autoimmune disease therapy. Clin Immunol 160: 3-13.
43. Hunter Z, McCarthy DP, Yap WT, Harp CT, Getts DR, et al. (2010) A biodegradable nanoparticle platform for the induction of antigen-specific immune tolerance for treatment of autoimmune disease. ACS Nano 8: 2148-2160
44. Zimmerman D, Bergmann K, Rosenthal K, Elliott D (1996) A new approach to T-cell activation: Natural and synthetic conjugates capable of activating T cells. Vaccine Res 5: 91-102.
45. Zimmerman DH, Morris S, Rouse D, Worthington K, Elliott D, et al. (1996) Immunization with peptide heterconjugates primes a t helper cell type 1-associated antibody (IgG2a) response that recognizes the native epitope on the 38-kDA protein of Mycobacterium tuberculosis. Vaccine Res 5: 103-118.
46. Rosenthal KS, Mao H, Horne WI, Wright C, Zimmerman D (1999) Immunization with a LEAPS heteroconjugate containing a CTL epitope and a peptide from beta-2-microglobulin elicits a protective and DTH response to herpes simplex virus type 1. Vaccine 17: 535-542.
47. Parham P, Androlewicz MJ, Holmes NJ, Rothenberg BE (1983) Arginine 45 is a major part of the antigenic determinant of human beta 2-microglobulin recognized by mouse monoclonal antibody BBM. J Biol Chem 258: 6179-86.

48. Taylor PR, Koski GK, Paustian CC, Bailey E, Cohen P, et al. (2010) J-LEAPS vaccines initiate murine Th1 responses by activating dendritic cells. Vaccine 28: 5533-5542.
49. Boonnak K, Vogel L, Orandle M, Zimmerman D, Talor E, et al. (2013) Antigen-activated dendritic cells ameliorate influenza A infections. J Clin Invest 123: 2850-2861.
50. Cammarota G, Scheirle A, Takacs B, Doran DM, Knorr R, et al. (1992) Identification of a CD4 binding site on the beta 2 domain of HLA-DR molecules. Nature 356: 799-801.
51. König R, Huang LY, Germain RN (1992) MHC class II interaction with CD4 mediated by a region analogous to the MHC class I binding site for CD8. Nature 356: 796-798.
52. Goel N, Rong Q, Zimmerman D, Rosenthal KS (2003) A L.E.A.P.S. heteroconjugate vaccine containing a T cell epitope from HSV-1 glycoprotein D elicits Th1 responses and protection. Vaccine 21: 4410-4420.
53. Goel N, Zimmerman DH, Rosenthal KS (2005) Ligand epitope antigen presentation system vaccines against herpes simplex virus. Front Biosci 10: 966-974.
54. Mikecz K, Glant TT, Markovics A, Rosenthal KS, Kurko J, et al. (2017) An epitope-specific DerG-PG70 LEAPS vaccine modulates T cell responses and suppresses arthritis progression in two related murine models of rheumatoid arthritis. Vaccine 35: 4048-4056.
55. Cihakova D, Barin JG, Baldeviano GC, Kimura M, Talor MV, et al. (2008) L.E.A.P.S. heteroconjugate is able to prevent and treat experimental autoimmune myocarditis by altering trafficking of autoaggressive cells to the heart. Int Immunopharmacol 8: 624-633.
56. Taylor PR, Paustian CC, Koski GK, Zimmerman DH, Rosenthal KS (20100 Maturation of dendritic cell precursors into IL12-producing DCs by J-LEAPS immunogens. Cell Immunol 262: 1-5.
57. Zimmerman DH, Taylor P, Bendele A, Carambula R, Duzant Y, et al. (2010) CEL-2000: A therapeutic vaccine for rheumatoid arthritis arrests disease development and alters serum cytokine/chemokine patterns in the bovine collagen type II induced arthritis in the DBA mouse model. Int Immunopharmacol 10: 412-421.
58. Rosenthal KS, Stone S, Koski G, Zimmerman DH (2017) LEAPS vaccine incorporating HER-2/neu epitope elicits protection that prevents and limits tumor growth and spread of breast cancer in a mouse model. J Immunol Res 2017: 1-8.
59. Domingues HS, Mues M, Lassmann H, Wekerle H, Krishnamoorthy G (2010) Functional and pathogenic differences of Th1 and Th17 cells in experimental autoimmune encephalomyelitis. PLoS One 5: e15531.
60. Luger D, Silver PB, Tang J, Cua D, Chen Z, et al. (2008) Either a Th17 or a Th1 effector response can drive autoimmunity: conditions of disease induction affect dominant effector category. J Exp Med 205: 799-810.
61. Rodeghero R, Cao Y, Olalekan SA, Iwakua Y, Glant TT, et al. (2013) Location of CD4+ T cell priming regulates the differentiation of Th1 and Th17 cells and their contribution to arthritis. J Immunol 190: 5423-5435.
62. Hu Y, Cheng W, Cai W, Yue Y, Li J, et al. (2013) Advances in research on animal models of rheumatoid arthritis. Clin Rheumatol 32: 161-165.
63. Friese MA, Jensen LT, Willcox N, Fugger L (2006) Humanized mouse models for organ-specific autoimmune diseases. Curr Opin Immunol 18: 704-709.
64. Serreze DV, Niens M, Kulik J, DiLorenzo TP (2016) Bridging Mice to Men: Using HLA Transgenic Mice to Enhance the Future Prediction and Prevention of Autoimmune Type 1 Diabetes in Humans. In: Proetzel G, Wiles M, editors. Mouse Models for Drug Discovery Methods in Molecular Biology. Humana Press, New York, NY.
65. Walsh NC, Kenney LL, Jangalwe S, Aryee KE, Greiner DL, et al. (2017) Humanized mouse models of clinical disease. Annu Rev Pathol 12: 187-215.
66. Castiblanco J, Anaya JM (2015) Genetics and vaccines in the era of personalized medicine. Curr Genomics 16: 47-59.
67. Mewar D, Wilson AG (2001) Autoantibodies in rheumatoid arthritis: a review. Biomed Pharmacother 60: 648-655.
68. Von Delwig A, Locke J, Robinson JH, Ng WF (2010) Response of Th17 cells to a citrullinated arthritogenic aggrecan peptide in patients with rheumatoid arthritis. Arthritis Rheum 62: 143-149.
69. Wegner N, Lundberg K, Kinloch A, Fisher B, Malmström V, et al. (2010) Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunol Rev 233: 34-54.
70. Burkhardt H, Holmdahl R, Deutzmann R, Wiedemann H, von der Mark H, et al. (21991) Identification of a major antigenic epitope on CNBr-fragment 11 of type II collagen recognized by murine autoreactive B cells. Eur J Immunol 21: 49-54.
71. Terato K, Hasty KA, Cremer MA, Stuart JM, Townes AS, et al. (1985) Collagen-induced arthritis in mice. Localization of an arthritogenic determinant to a fragment of the type II collagen molecule. J Exp Med 162: 63-646.
72. Krco CJ, Pawelski J, Harders J, McCormick D, Griffiths M, et al. (1996) Characterization of the antigenic structure of human type II collagen. J Immunol 156: 2761-2768.
73. Myers LK, Terato K, Seyer JM, Stuart JM, Kang AH (1992) Characterization of a tolerogenic T cell epitope of type II collagen and its relevance to collagen-induced arthritis. J Immunol 149: 1439-1443.
74. Brand DD, Marion TN, Myers LK, Rosloniec EF, Watson WC, et al. (1996) Autoantibodies to murine type II collagen in collagen-induced arthritis: a comparison of susceptible and nonsusceptible strains. J Immunol 157: 5178-5184.
75. Myers LK, Tang B, Rosloniec EF, Stuart JM, Chiang TM, et al. (1998) Characterization of a peptide analog of a determinant of type II collagen that suppresses collagen-induced arthritis. J Immunol 161: 3589-3595.
76. Kannan K, Ortmann RA, Kimpel D (2005) Animal models of rheumatoid arthritis and their relevance to human disease. Pathophysiol 12: 167-181.
77. Hegen M, Keith JC, Collins M, Nickerson-Nutter CL (2008) Utility of animal models for identification of potential therapeutics for rheumatoid arthritis. Ann Rheum Dis 67: 1505-1515.
78. Williams RO (2007) Collagen-induced arthritis in mice. Methods Mol Med 136: 191-199.
79. Hildner K, Edelson BT, Purtha WE, Diamond M, Matsushita H, et al. (2008) Batf3 deficiency reveals a critical role for CD8alpha+ dendritic cells in cytotoxic T cell immunity. Science 322: 1097-1100.
80. Murphy CA, Langrish CL, Chen Y, Blumenschein W, Mcclanahan T, et al. (2003) Brief Definitive Report Divergent Pro-and Antiinflammatory Roles for IL-23 and IL-12 in Joint Autoimmune Inflammation. J Exp Med J Exp Med 12700: 1951-1957.
81. Glant TT, Radacs M, Nagyeri G, Olasz K, Laszlo A, et al. (2011) Proteoglycan-induced arthritis and recombinant human proteoglycan aggrecan G1 domain-induced arthritis in BALB/c mice resembling two subtypes of rheumatoid arthritis. Arthritis Rheum 63: 1312-1321.
82. Doodes PD, Cao Y, Hamel KM, Wang Y, Farkas B, et al. (2008) Development of proteoglycan-induced arthritis is independent of IL-17. J Immunol 181: 329-337.
83. Finnegan A, Mikecz K, Tao P, Glant TT (1999) Proteoglycan (aggrecan)-induced arthritis in BALB/c mice is a Th1-type disease regulated by Th2 cytokines. J Immunol 163: 5383-5390.
84. Hanyecz A, Berlo SE, Szántó S, Broeren CPM, Mikecz K, et al. (2004) Achievement of a synergistic adjuvant effect on arthritis induction by activation of innate immunity and forcing the immune response toward the Th1 phenotype. Arthritis Rheum 50: 1665-1676.
85. Glant TT, Mikecz K, Arzoumanian A, Poole AR (1987) Proteoglycan-induced arthritis in BALB/c mice. Clinical features and histopathology. Arthritis Rheum 30: 201-212.
86. Mikecz K, Glant TT, Poole AR (1987) Immunity to cartilage proteoglycans in BALB/c mice with progressive polyarthritis and ankylosing spondylitis induced by injection of human cartilage proteoglycan. Arthritis Rheum 30: 306-318.
87. Zeng H, Zhang R, Jin B, Chen L (2015) Type 1 regulatory T cells: A new mechanism of peripheral immune tolerance. Cell Mol Immunol 12: 566-571.

88. Van Brussel I, Lee WP, Rombouts M, Nuyts AH, Heylen M, et al. (2014) Tolerogenic dendritic cell vaccines to treat autoimmune diseases: can the unattainable dream turn into reality? Autoimmun Rev 13: 138-150.
89. Rodriguez-Calvo T, Suwandi JS, Amirian N, Zapardiel-Gonzalo J, Anquetil F, et al. (2015) Heterogeneity and Lobularity of Pancreatic Pathology in Type 1 Diabetes during the Prediabetic Phase. J Histochem Cytochem 63: 626-636.
90. Jansen MAA, Spiering R, Broere F, van Laar JM, Isaacs JD, et al. (2017) Targeting of tolerogenic dendritic cells towards heat-shock proteins: a novel therapeutic strategy for autoimmune diseases? Immunol 153: 51-59.
91. Suwandi JS, Toes REM, Nikolic T, Roep BO (2015) Inducing tissue specific tolerance in autoimmune disease with tolerogenic dendritic cells. Clin Exp Rheumatol 33: 97-103.
92. Huang X, Wu H, Lu Q (2014) The mechanisms and applications of T cell vaccination for autoimmunediseases: a comprehensive review. Clin Rev Allergy Immunol 47: 219-233.
93. Wucherpfennig KW, Strominger JL (1995) Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell 80: 695-705.
94. Tejada-Simon MV, Zang YCQ, Hong J, Rivera VM, Zhang JZ (2003) Cross-reactivity with myelin basic protein and human herpesvirus-6 in multiple sclerosis. Ann Neurol 53: 189-197.
95. Procaccini C, De Rosa V, Pucino V, Formisano L, Matarese G (2015) Animal models of Multiple Sclerosis. Eur J Pharmacol 759: 182-191.
96. Huseby ES, Liggitt D, Brabb T, Schnabel B, Ohlén C, et al. (2001) A pathogenic role for myelin-specific CD8(+) T cells in a model for multiple sclerosis. J Exp Med 194: 669-676.
97. Mayer L, Shao L (2004) Therapeutic potential of oral tolerance. Nat Rev Immunol 4: 407-419.
98. Faria AMC, Weiner HL (2005) Oral tolerance. Immunol Rev 206: 232-259.
99. Weiner HL, Mackin GA, Matsui M, Orav EJ, Khoury SJ, et al. (1993) Double-blind pilot trial of oral tolerization with myelin antigens in multiple sclerosis. Science 259: 1321-1324.
100. In't Veld P (2014) Insulitis in human type 1 diabetes: A comparison between patients and animal models. Semin Immunopathol 36: 569-579.
101. Christoffersson G, Rodriguez-Calvo T, von Herrath M (2016) Recent advances in understanding Type 1 Diabetes. F1000 Res.
102. Herrath MG, Korsgren O, Atkinson MA (2016) Factors impeding the discovery of an intervention-based treatment for type 1 diabetes. Clin Exp Immunol 183: 1-7.
103. Walker LSK, Von Herrath M (2016) CD4 T cell differentiation in type 1 diabetes. Clin Exp Immunol 183: 16-29.
104. Van Belle TL, Taylor P, Von Herrath MG (2009) Mouse models of type1 diabetes. Drug Discov Today Dis Model 6 : 41-45.
105. King AJF (2012) The use of animal models in diabetes research. Br J Pharmacol 166: 877-894.
106. Ohashi PS, Oehen S, Buerki K, Pircher H, Ohashi CT, et al. (1991) Ablation of "tolerance" and induction of diabetes by virus infection in viral antigen transgenic mice. Cell 65: 305-317.
107. Oldstone MB, Nerenberg M, Southern P, Price J, Lewicki H (1991) Virus infection triggers insulin-dependent diabetes mellitus in a transgenic model: role of anti-self (virus) immune response. Cell 65: 319-331.
108. Pearson T, Greiner DL, Shultz LD (2008) Humanized SCID mouse models for biomedical research. Curr Top Microbiol Immunol 324: 25-51.
109. Coppieters KT, Harrison LC, Von Herrath MG (2013) Trials in type 1 diabetes: Antigen-specific therapies. Clin Immunol 149: 345-355.
110. Christen S, Coppieters K, Rose K, Holdener M, Bayer M, et al. (2013) Blockade but not overexpression of the junctional adhesion molecule C influences virus-induced type 1 diabetes in mice. PLoS One 8: e54675.
111. Daniel D, Wegmann DR (1996) Protection of nonobese diabetic mice from diabetes by intranasal or subcutaneous administration of insulin peptide B-(9-23). Proc Natl Acad Sci U S A 93: 956-960.
112. Orban T, Farkas K, Jalahej H, Kis J, Treszl A, et al. (2010) Autoantigen-specific regulatory T cells induced in patients with type 1 diabetes mellitus by insulin B-chain immunotherapy. J Autoimmun 34: 408-415.
113. Cetkovic-Cvrlje M, Gerling IC, Muir A, Atkinson MA, Elliott JF, et al. (1997) Retardation or acceleration of diabetes in NOD/Lt mice mediated by intrathymic administration of candidate beta-cell antigens. Diabetes 46: 1975-1982.
114. Thrower SL, James L, Hall W, Green KM, Arif S, et al. (2009) Proinsulin peptide immunotherapy in type 1 diabetes: report of a first-in-man Phase I safety study. Clin Exp Immunol 155: 156-165.