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# Peptide vaccines against arthritis

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In this article, four distinct approaches to the development of peptide vaccines against arthritis will be reviewed. One is based on evidence that antagonizing proinflammatory cytokines can benefit patients with arthritis. The second stems from the observation that heat-shock proteins are essential arthritogenic agents in the development of arthritis. The third derives from research on the mechanisms by which specific HIV-1 peptides produce T-cell suppression, while the fourth has developed from clinical reports that children with juvenile rheumatoid arthritis (Still's disease) experience long-term remission following infection with the measles virus. The four sets of anti-arthritis peptides bear no sequence similarities but have all been tested successfully on adjuvant arthritis models, thereby providing multiple paths to the development of peptide vaccines against arthritis. Specific comparisons between methods of delivery, adjuvant requirements and dosages are reported and future directions for research suggested.

Rheumatoid arthritis (RA) affects approximately 1% of adults globally, but currently lacks any cure or effective long-term treatment. One novel approach to RA treatment and prevention is the development of peptide vaccines.

Four distinct approaches to peptide vaccine development against RA are currently being explored. Each strategy relies on isolating critical antigens from larger proteins that have been demonstrated to have anti-arthritic activity. The first is based on evidence that antagonizing certain proinflammatory cytokines can benefit people with arthritis. The second approach stems from observations that heat-shock proteins (HSPs) are critical antigens in arthritis development and blocking their actions is useful therapeutically. A third tack derives from isolation of HIV-1 peptides that specifically downregulate T cells involved in arthritis. A fourth strategy is based on observations that children with juvenile rheumatoid arthritis (JRA or Still's disease) sometimes experience long-term remissions after infections with the measles virus, the proteins of which contain anti-arthritic activity. The peptides that have been derived from these four approaches fall into three distinct sequential families and probably act through at least three separate mechanisms, thereby providing multiple approaches to developing human therapeutic agents.

## Cytokine- & T-cell-derived peptides

Extensive evidence demonstrates that blocking the proinflammatory cytokines interleukin (IL)-1 and tumor necrosis factor (TNF)- $\alpha$

results in improved treatment of RA (reviewed in [1,2]). Treatments include etanercept (TNF receptor-p75 Fc fusion protein), infliximab (chimeric antihuman TNF- $\alpha$  monoclonal antibody) and adalimumab (recombinant human anti-human TNF- $\alpha$  monoclonal antibody) (reviewed in [3,4]); anakinra, a recombinant form of an endogenous IL-1 receptor antagonist (IL-1Ra) [5], exogenous soluble IL receptors, such as IL-1 RII [6]; and the induction of autoantibodies to IL-1 receptors [7]. Interferon-inducible protein 10 has also proven effective in animal models of arthritis [8]. The basic problem with these approaches to arthritis treatment is that these cytokines and their receptors are currently prohibitively expensive to produce, require frequent injections to remain effective if used passively and result in substantial side effects whether used passively or actively as vaccines [3]. Among the commonly observed side effects are nonresponsiveness to treatment and infusion reactions; less common but serious side effects include increased susceptibility to opportunistic infections and tuberculosis and rarely demyelination, heart failure, blood dyscrasias and lymphomas have also been associated with these treatments (reviewed in [9,10]). As a consequence, efforts have begun to identify peptides that retain either the active or passive vaccinating properties of the native proteins, but are less expensive to produce and have minimal side effects.

Zagury reports that active immunization using peptides derived from the murine form of IL-1 $\beta$  protects mice against induction of

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collagen-induced arthritis [11]. Murine (m) IL-1 $\beta$  has a 3D structure similar to that of endogenous human (h) IL-1Ra. mIL-1 $\beta$  also binds to hIL-1Ra, but the structural details of that binding are unknown. Based on studies of how hIL-1Ra binds to the hIL-1 receptor (hIL-1R), Zagury's group identified three loops in the mIL-1 $\beta$  protein that were likely to be involved in mIL-1 $\beta$  binding to hIL-1R and synthesized peptides derived from these three regions. The peptides were synthesized either as linear sequences or as loops (by adding cysteines at each end to form a disulfide bridge) and these peptides were delivered either as free peptides in Freund's complete adjuvant (FCA) or as keyhole limpet hemocyanin (KLH)-conjugated peptides in FCA. Three booster shots were given following the initial inoculation. Only two peptides induced significant antibody responses, the cyclic form of mIL-1 $\beta$  29–39 and the cyclic form of mIL-1 $\beta$  123–132, both conjugated to KLH (Figure 1). Of these, only the second peptide (mIL-1 $\beta$  123–132) displayed significant protection against collagen II-induced arthritis in mice, delaying and reducing clinical and histological measures of joint disease.

Zagury's group has also identified TNF- $\alpha$  peptides that protect weakly against a septic shock model but the group has not reported any tests of these peptides as protective agents against arthritis [12].

T-cell receptors (TCRs) associated with RA have also been targeted for peptide therapies. Several investigators have found that V $\beta$ 3, V $\beta$ 14 and particularly V $\beta$ 17 TCR proteins were preferentially expressed in activated cells from RA patients [13–16]. Moreland and colleagues therefore initiated human clinical trials of a V $\beta$ 17 TCR peptide (Figure 1) that was determined to be safe enough for Phase II clinical trials [17,18]. Since there appear to be no further publications regarding this peptide, one must assume that it was not found to confer significant clinical benefits for arthritis patients.

#### Peptides derived from mycobacterial HSPs

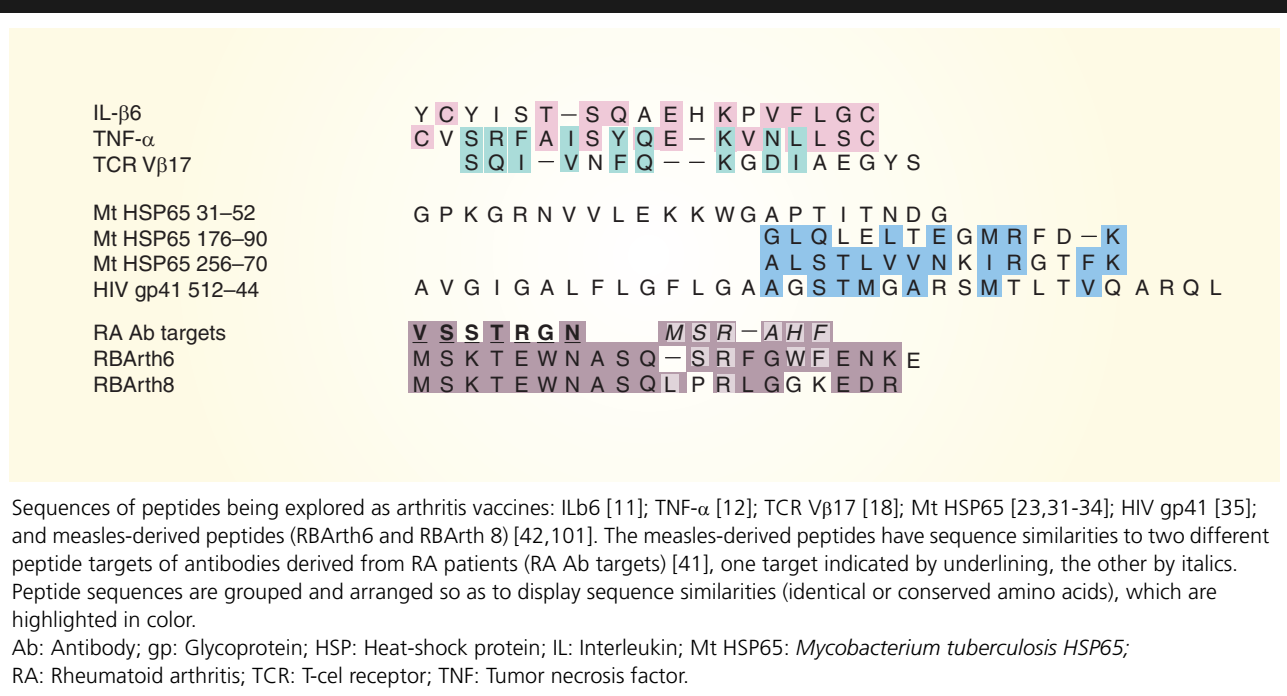
Rather than addressing the immunological response involved in RA, some investigators have chosen instead to address antigens involved in RA onset. HSPs are one such set of antigens. Antibody and T-cell responses to the 65 kDa HSP of *Mycobacterium tuberculosis* (HSP65), and its corresponding human equivalent,

60 kDa HSP (HSP60), have been documented in experimental and human arthritis [19–22]. Vaccinating animals with either HSP65 or HSP60 induces antibodies that prevent induction of adjuvant arthritis [23,24], as well as arthritis induced with streptococcal cell walls, collagen Type II and the lipoidal amine CP20961 [25,26]. Because HSP60 is highly homologous to and cross-reactive with HSP65 [27–29], and HSP60 expression is increased in the synovial fluid of human patients with arthritis [20,22,30], research has focused on finding epitopes shared by HSP60 and HSP65 that may provide the same type of protection in human arthritis patients that is seen in animal models of arthritis.

A variety of different HSP peptides have been reported to vaccinate against various animal models of arthritis. Yang and colleagues have reported that the nonapeptide HSP65 180–188 protects against adjuvant arthritis in Lewis rats via a T-cell-mediated mechanism [31,32], but Anderton and colleagues found that a slightly longer peptide inclusive of the nonapeptide (HSP65 176–190) had no protective effect in the same model [23]. The different outcomes are probably due to significant differences in immunization procedures. Yang and colleagues preinoculated intraperitoneally 35, 20 and 5 days prior to arthritis induction, whereas Anderton and colleagues inoculated subcutaneously in the footpad only once, 7 days prior to arthritis induction. The probability that this procedural difference caused the difference in results is strengthened by the fact that Anderton's group subsequently demonstrated that HSP65 176–190 could induce a strong protective effect against several types of experimentally induced arthritis when delivered intranasally on days 15, 10 and 5 prior to induction of arthritis [33].

Anderton and colleagues also identified another HSP65 peptide with significant anti-arthritic activity using their single-dose vaccination method: HSP65 256–270 [23]. Notably, HSP65 176–190 (which includes Yang and colleagues 180–188) and HSP 256–270 are sequentially similar (Figure 1), suggesting that both peptides may be activating similar sets of T-cell responses. HSP65 256–270 also protected against lipoidal amine CP20691-induced arthritis in these experiments, as did HSP65 176–190 in the nasal tolerance studies, suggesting that the peptides are interfering with a general arthritic mechanism.

**Figure 1. Regions of homology within peptides being explored as vaccines for rheumatoid arthritis.**



Finally, Ulmansky and colleagues have demonstrated that two peptides derived from the sequence 31–52 of HSP65 induce antibodies that vaccinate against adjuvant arthritis [34]. These antibodies cross-react with host HSPs and also release IL-10, suggesting that their mechanism of protection involves several pathways. The Ulmansky peptides appear to have no sequence similarity to any other peptide currently being investigated as an arthritis vaccine (Figure 1).

#### HIV-1 glycoprotein-41 fusion peptide

An unexpected contributor to arthritis peptide vaccine research may be HIV. The N-terminus of the extracellular region of HIV-1 glycoprotein (gp)41 envelope protein contains a fusion peptide (gp41 512–544) that is essential to viral fusion with host cell membranes. Investigators at the Weizmann Institute report that this fusion peptide is specific for CD4 lymphocytes and binds specifically to TCRs, inhibiting T-cell proliferation and proinflammatory cytokine production [35]. HIV fusion protein, when administered at the time of adjuvant arthritis induction in Lewis rats, resulted in a significant reduction in arthritis development, as well as inhibition of the delayed type hypersensitivity (DTH) response [35]. While these results do not technically constitute demonstration of a vaccine effect, the fusion peptide

approach looks promising as both an active and passive vaccine. Notably, the peptide has significant sequence similarity with some regions of the 65 kDa mycobacterial HSP (Figure 1).

#### Measles virus-derived peptides

Another virus that may provide useful peptides for therapeutic use is measles. Patients with JRA (Still's disease) have been reported to experience long-term remissions of symptoms and, rarely, outright cures following measles infections [36–39]. Some measles virus proteins have significant homologies with myelin basic protein [40] and, oddly, Lewis rats inoculated with arthritogenic doses of mycobacterial adjuvant in the presence of myelin basic protein develop experimental allergic encephalomyelitis, but no symptoms of adjuvant arthritis. These observations suggested to the author that anti-arthritic peptides might exist among the homologous regions shared by measles proteins and myelin basic protein. Such was the case. Two peptides with significant homologies to peptides that are recognized by synovial fluid antibodies from RA patients (Figure 1) [41] have been found to have significant anti-arthritic activity as both active and passive immunogens in the Lewis rat model of adjuvant arthritis. In particular, a single dose of 1.0 mg/animal of one of the peptides (RBArth6) in incomplete Freund's adjuvant 3 weeks prior to induction of adjuvant arthritis completely prevented induction of

arthritis. In the same way, a 1.0 mg/animal dose delivered subcutaneously on the day of first overt adjuvant arthritis symptoms significantly decreased the subsequent development of arthritis [42,101].

### Conclusions

Six different agents (ILs, TNFs, TCR proteins, HSPs, HIV and measles) are currently sources for peptide vaccines against animal models of arthritis. Only the TCR proteins have thus far been tested in human clinical trials. The peptides so far derived from these agents can be organized roughly into three groups based on sequence similarities (Figure 1). The three groups appear to share no intergroup sequence similarities and thus represent distinct approaches to the field.

There appear to be significant differences in the mechanisms of action reported for the different groups of peptide vaccines. The anti-inflammatory cytokine peptides appear to work via antibody responses. The TCR peptides, antimycobacterial and HIV peptides appear to work via T-cell responses. The mechanism of action of the measles-derived peptides is currently unknown, but the fact that these peptides mimic targets of antibodies produced by RA patients suggests an antibody-mediated mechanism. Perhaps because some of the antimycobacterial peptides work through T-cell responses, they proved to be effective against induction not only of adjuvant arthritis, but also of arthritis induced by collagen type II, lipoidal amines and *Streptococcal* cell wall (SCW). The effectiveness of the other peptide vaccines, particularly those known to induce antibody responses, against collagen, SCW and other forms of arthritis, is unknown. Only in one case – the HIV fusion peptide – were direct studies of general immune suppression (the DTH reaction) investigated, although it may be presumed that vaccination against inflammatory cytokines will have general immunosuppressive effects of some degree. Peptides derived from mycobacteria and measles may also have such general anti-inflammatory effects, but appropriate tests will need to be run. Clearly, the ultimate goal of any attempt to produce an active or passive vaccine against arthritis must be to develop peptides with great specificity for the arthritic process and without general immunological effects.

The methods used to vaccinate against arthritis in the various studies vary widely, which creates difficulties in comparing their

efficacy directly. The only effective IL-1 $\beta$  and TNF- $\alpha$  peptides were cyclized, KLH-conjugated ones delivered in FCA [11,12]. Unmodified HIV-1 fusion protein (FP) and measles-derived peptides were also inoculated in FCA emulsion [35,42,101]. Unmodified and unconjugated HSP peptides, however, were inoculated in phosphate buffered saline (PBS) alone [34] or in a PBS-dimethyldioctadecylammonium bromide (DDA) adjuvant [33]. The fact that the HSP peptides were effective without the use of a conjugate, such as KLH, or an adjuvant is especially heartening as it suggests the possibility that arthritis vaccines appropriate for human clinical use are possible.

Differences among the studies in the number, mode and timing of vaccinations are also instructive. Measles- and HIV-FP-derived peptides have proven effective after single dose, subcutaneous injections, but these required FCA [35,42,101]. Single-dose, subcutaneous injections of measles-derived peptides in saline were not effective [42]. Notably, among the HSP65 peptides, only HSP65 176–190 was an effective vaccine after subcutaneous or intranasal inoculation in PBS without any adjuvant [23]. The other effective HSP-derived peptides in PBS were ineffective after a single vaccination but some were highly active after an intraperitoneal triple-vaccination regimen. These observations suggest that it would be worthwhile testing a PBS-only triple inoculation strategy, both subcutaneous and intranasal, for measles- and HIV-derived peptides [23,31–34]. A similar approach with nonconjugated peptides has already failed for IL-1 $\beta$  and TNF- $\alpha$  peptides [11,12]. These data therefore suggest that microbially derived peptides may provide a higher probability of inducing protection against arthritis using the safest and least invasive inoculation procedures.

The ability to develop peptide vaccines that are easy to manufacture, effective, require minimal adjuvant support and induce immunity via patient-acceptable procedures (e.g., subcutaneous or intranasal administration) will play a substantial role in determining which of the current peptide vaccines (if any) go on to be developed for human use. Clearly, an effective intranasal vaccine would be highly desirable, although most arthritis patients would probably endure more or less frequent subcutaneous or intramuscular injections. Equally clearly, some of the adjuvants and conjugates currently being used in experimental protocols (e.g., FCA and KLH) will probably not be used in human patients. Similarly,

repeated intraperitoneal inoculations have limited appeal from a patient stand point. The inoculation route and adjuvant requirements will, therefore, be key properties differentiating successful peptide vaccines from failures.

### Future perspective

In sum, many approaches to peptide vaccine development against arthritis are being explored and, although most results are still from the early stage of animal studies, several of these show great promise. The fact that TCR peptides successfully entered Phase II human trials bolsters hopes that other peptide vaccines against arthritis will be successful in the clinic. In order to achieve clinical success, however, investigators focusing on each of the approaches outlined here will need to learn from each other in terms of the best methods for inducing a strong vaccine response with minimal adjuvant. I would urge drug developers

to consider the current set of options, not as alternatives or competitors, but possibly as synergistic. If a single peptide is effective against mixed models of arthritis, what might a mixture (or polymer) of several effective peptides achieve, each working concurrently against a different aspect of the autoimmune process? My prediction is that a new class of peptide vaccines will shortly follow the ones listed here, and that these new peptides will be chimeras composed of TCR cytokine, TNF-IL sequences, multiple HSP, HIV-measles sequences or even combined cytokine-HSP-viral sequences. Such peptides will still be quite short compared with the recombinant proteins and monoclonal antibodies currently being used clinically and thus costs can be minimized. By targeting multiple steps in the arthritis process through several highly specific immune responses, the probability of obtaining a highly effective vaccine with minimal side effects will be maximized.

## Executive summary

### Approaches to peptide vaccine development

- Several distinct approaches are currently being explored to produce active and passive peptide vaccines against arthritis.
- Peptides from tumor necrosis factor- $\alpha$  are effective against several animal models of arthritis.
- Peptides from interleukin-1 are effective against several animal models of arthritis.
- A peptide from the T-cell receptor V $\beta$ 17 is effective against arthritis and has entered Phase II human trials, although no recent reports are available.
- Several peptides derived from regions of homology shared by human and mycobacterial heat-shock proteins are effective in various animal models of arthritis.
- A peptide derived from HIV Type 1 fusion protein is effective against adjuvant arthritis.
- Several peptides derived from measles virus are effective against adjuvant arthritis and natural measles infection has been reported to produce long-term remissions in human juvenile rheumatoid arthritis.

### Conclusion

- In summary, proteins associated with inducing arthritis, as well as with specific immune responses regulating arthritis, have been used as sources of peptides which have shown promise as vaccines in multiple animal models of arthritis.

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## Patent

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