WHAT IS CLAIMED IS:

1. A method for treating or preventing joint damage in a subject with early RA or incipient RA, the method comprising, consisting or consisting essentially of eliciting an antigen-specific tolerogenic response to an aggrecan polypeptide in the subject, thereby treating or preventing the joint damage.

2. A method according to claim 1, wherein the aggrecan polypeptide is a citrullinated aggrecan polypeptide.

3. A method according to claim 1, further comprising identifying that the subject has early RA or incipient RA prior to eliciting the antigen-specific tolerogenic response.

4. A method according to any one of claims 1 to 3, wherein the subject is positive for the shared epitope (SE).

5. A method according to claim 4, further comprising identifying that the subject is positive for SE prior to eliciting the antigen-specific tolerogenic response.

6. A method according to any one of claims 1 to 5, wherein the subject has or is at risk of developing an immune response to the aggrecan polypeptide.

7. A method according to claim 6, wherein the immune response comprises an effector T lymphocyte response.

8. A method according to claim 7, wherein the immune response comprises production of at least one cytokine selected from the group consisting of interleukin-6 (IL-6), interferon-γ (IFN-γ), tumor necrosis factor (TNF), and interleukin-10 (IL-10).

9. A method according to claim 6, wherein the immune response includes a pro-inflammatory T lymphocyte response, which comprises, consists or consists essentially of production of at least one cytokine selected from the group consisting of IL-6, IFN-γ and TNF.

10. A method according to claim 9, wherein the pro-inflammatory T lymphocyte response comprises, consists or consists essentially of production of IL-6.

11. A method according to claim 6, wherein immune response is produced at least in part by $CD4^+$ lymphocytes.

12. A method according to any one of claims 1 to 11, wherein the antigen-specific tolerogenic response is effected by:

(1) increasing the number of tolerogenic antigen-presenting cells (agg-tolAPC) in the subject, which present a peptide corresponding to a portion of the aggrecan polypeptide, wherein the portion is associated with a pro-inflammatory or autoreactive T lymphocyte response to the aggrecan polypeptide;

(2) inducing anergy or apoptosis in pro-inflammatory or autoreactive T lymphocytes in the subject, which are reactive against the aggrecan polypeptide; and

(3) increasing the number of regulatory or suppressor T lymphocytes in the subject, which suppress or otherwise reduce a pro-inflammatory or autoreactive T lymphocyte response to the aggrecan polypeptide.

13. A method according to claim 12, comprising, consisting or consisting essentially of increasing the number of agg-tolAPC in the subject to thereby treat or prevent the joint damage.

14. A method according to claim 13, wherein the agg-tolAPC stimulate the production of regulatory or suppressor T lymphocytes that suppress or otherwise reduce the pro-inflammatory or autoreactive T lymphocyte response to the aggrecan polypeptide.

15. A method according to claim 13 or claim 14, wherein the agg-tolAPC are produced by contacting antigen-presenting cells in the subject with (1) an NF-κB inhibitor in an amount sufficient to inhibit NF-κB activity in the antigen-presenting cells, and/or (2) a mTOR inhibitor in an amount sufficient to inhibit mTOR activity in the antigen-presenting cells, and/or (3) a Syk inhibitor in an amount sufficient to inhibit Syk activity in the antigen-presenting cells, together with an antigenic molecule selected from an antigen that corresponds in whole, or in part, to an aggrecan polypeptide or a nucleic acid molecule from which the antigen is expressible, in an amount sufficient for the antigen-presenting cells to present the antigen or a processed form thereof on their surface.

16. A method according to claim 15, wherein the antigen comprises an amino acid sequence corresponding to a full-length aggrecan polypeptide.

17. A method according to claim 15, wherein the antigen comprises an amino acid sequence corresponding to a mature aggrecan polypeptide.

18. A method according to claim 15, wherein the antigen comprises an amino acid sequence corresponding to a domain of an aggrecan polypeptide selected from the G1 domain, the G2 domain, or the G3 domain.

19. A method according to claim 15, wherein the antigen comprises an amino acid sequence corresponding to a T cell epitope of an aggrecan polypeptide.

20. A method according to claim 19, wherein the amino acid sequence is selected from any one of SEQ ID NO: 5-35, including citrullinated forms thereof.

21. A method according to claim 19, wherein the amino acid sequence is selected from any one of SEQ ID NO: 32-35.

22. A method according to claim 15, wherein the antigen is HLA DR restricted and the subject is positive for an HLA DR allele.

23. A method according to claim 15, wherein the antigen is in the form of one or more peptides corresponding in whole or in part to an aggrecan polypeptide, including citrullinated forms thereof.

24. A method according to claim 15, wherein the antigen is in the form of a plurality of contiguous overlapping peptides whose sequences span at least a portion of an aggrecan polypeptide, including citrullinated forms thereof.

25. A method according to claim 15, wherein the overlapping peptides comprise, consist or consist essentially of an amino acid sequence selected from SEQ ID NO: 49-531, including citrullinated forms thereof.

26. A method according to claim 15, wherein the inhibitor is an NF-κB inhibitor (*e.g.*, an NF-κB inhibitor selected from any one of the inhibitors listed in Tables 2, 3A, 3B or 4).

27. A method according to claim 26, wherein the NF-κB inhibitor is curcumin or a curcumin derivative.

28. A method according to claim 15, wherein the inhibitor and the antigenic molecule are co-administered in soluble form.

29. A method according to claim 15, wherein the inhibitor and the antigenic molecule are co-administered in particulate form.

30. A method according to claim 29, wherein the inhibitor and the antigenic molecule are co-administered in the same particle.

31. A method according to claim 29, wherein the particle is a polymeric particle.

32. A method according to claim 29, wherein the particle is a liposome.

33. A method according to claim 12, wherein the agg-tolAPC are produced by expressing in B lymphocytes a nucleic acid molecule that encodes an antigen that corresponds in whole, or in part, to an aggrecan polypeptide, wherein the expression of the nucleic acid molecule leads to presentation of the antigen or processed form thereof on the surface of the B lymphocytes.

34. A method according to claim 33, wherein the nucleic acid molecule further encodes an immunoglobulin or an immunoglobulin fragment fused directly or indirectly to the antigen.

35. A method according to claim 12, comprising administering to the subject regulatory or suppressor T lymphocytes, which suppress or otherwise reduce the pro-inflammatory or autoreactive T lymphocyte response to the aggrecan polypeptide.

36. A method according to claim 1, comprising administering to the subject a MHC-peptide complex consisting essentially of an antigen that corresponds in whole, or in part, to the aggrecan polypeptide and an isolated MHC component having an antigen-binding site, wherein the antigen is associated with the antigen-binding site.

37. A method according to claim 1, comprising administering to the subject a chimeric construct comprising an immunomodulatory peptide and an immune- or T cell-binding ligand (I/TCBL), wherein the immunomodulatory peptide comprises, consists or consists essentially of an amino acid sequence corresponding to a portion of an aggrecan polypeptide, and which binds to an antigen receptor on pro-inflammatory or autoreactive T lymphocytes, and wherein the I/TCBL binds to a class or subclass of T cell selected from the group consisting of helper T cells, suppressor T cells and cytotoxic T cells and modulates T cell activity.

38. A method according to claim 37, wherein the I/TCBL comprises at least a portion of a molecule selected from a MHC class I molecule, a MHC class II molecule, an accessory molecule such as β2-microglobulin, lymphocyte function associated molecule-3 (LFA-3), the Fc region of the heavy chain of an immunoglobulin molecule, Ia^+ molecules, an antibody to CD2, an antibody to CD3, an antibody to CD4, an antibody to CD8, an antibody to lectin, a lymphokine.

39. Use of an agent or combination of agents that elicits an antigen-specific tolerogenic response to an aggrecan polypeptide for treating or preventing joint damage in a subject with early RA or incipient RA.

40. A use according to claim 39, wherein the agent or combination of agents is selected from: (1) an inhibitor of the NF-κB pathway and an antigenic molecule selected from an antigen that corresponds in whole, or in part, to an aggrecan polypeptide or a nucleic acid molecule from which the antigen is expressible; (2) an mTOR inhibitor and an antigenic molecule selected from an antigen that corresponds in whole, or in part, to an aggrecan polypeptide or a nucleic acid molecule from which the antigen is expressible; (3) an inhibitor of the Syk pathway and an antigenic molecule selected from an antigen that corresponds in whole, or in part, to an aggrecan polypeptide or a nucleic acid molecule from which the antigen is expressible; (4) a nucleic acid molecule that encodes an antigen that corresponds in whole, or in part, to an aggrecan polypeptide for introduction into B lymphocytes; (5) a MHC-peptide complex consisting essentially of an antigen that corresponds in whole, or in part, to an aggrecan polypeptide and an isolated MHC component having an antigen-binding site, wherein the antigen is associated with the antigen-binding site; (6) a chimeric construct comprising an immunomodulatory peptide and an immune- or T cell-binding ligand (I/TCBL), wherein the

immunomodulatory peptide comprises, consists or consists essentially of an amino acid sequence corresponding to a portion of an aggrecan polypeptide; (7) aggrecan-specific tolerogenic antigen-presenting cells; or (8) an APL that comprises, consists or consists essentially of an amino acid sequence corresponding to a portion of an aggrecan polypeptide.

41. An agent or combination of agents as defined in claim 39 or claim 40 for use in treating or preventing joint damage in a subject with early RA or incipient RA.

WHAT IS CLAIMED IS:

1. Use of an agent or combination of agents that elicits an antigen-specific tolerogenic response to an aggrecan polypeptide for treating or preventing joint damage in a subject with early RA or incipient RA.

2. A use according to claim 1, wherein the agent or combination of agents is selected from: (1) an inhibitor of the NF-κB pathway and an antigenic molecule selected from an antigen that corresponds in whole, or in part, to an aggrecan polypeptide or a nucleic acid molecule from which the antigen is expressible; (2) an mTOR inhibitor and an antigenic molecule selected from an antigen that corresponds in whole, or in part, to an aggrecan polypeptide or a nucleic acid molecule from which the antigen is expressible; (3) an inhibitor of the Syk pathway and an antigenic molecule selected from an antigen that corresponds in whole, or in part, to an aggrecan polypeptide or a nucleic acid molecule from which the antigen is expressible; (4) a nucleic acid molecule that encodes an antigen that corresponds in whole, or in part, to an aggrecan polypeptide for introduction into B lymphocytes; (5) a MHC-peptide complex consisting essentially of an antigen that corresponds in whole, or in part, to an aggrecan polypeptide and an isolated MHC component having an antigen-binding site, wherein the antigen is associated with the antigen-binding site; (6) a chimeric construct comprising an immunomodulatory peptide and an immune- or T cell-binding ligand (I/TCBL), wherein the immunomodulatory peptide comprises, consists or consists essentially of an amino acid sequence corresponding to a portion of an aggrecan polypeptide; (7) aggrecan-specific tolerogenic antigen-presenting cells; or (8) an APL that comprises, consists or consists essentially of an amino acid sequence corresponding to a portion of an aggrecan polypeptide.

3. A use according to claim 2, wherein the antigen comprises an amino acid sequence corresponding to a full-length aggrecan polypeptide.

4. A use according to claim 2, wherein the antigen comprises an amino acid sequence corresponding to a mature aggrecan polypeptide.

5. A use according to claim 2, wherein the antigen comprises an amino acid sequence corresponding to a domain of an aggrecan polypeptide selected from the G1 domain, the G2 domain, or the G3 domain.

6. A use according to claim 2, wherein the antigen comprises an amino acid sequence corresponding to a T cell epitope of an aggrecan polypeptide.

7. A use according to claim 6, wherein the amino acid sequence is selected from any one of SEQ ID NO: 5-35, including citrullinated forms thereof.

8. A use according to claim 6, wherein the amino acid sequence is selected from any one of SEQ ID NO: 32-35.

9. A use according to claim 2, wherein the antigen is HLA DR restricted and the subject is positive for an HLA DR allele.

10. A use according to claim 2, wherein the antigen is in the form of one or more peptides corresponding in whole or in part to an aggrecan polypeptide, including citrullinated forms thereof.

11. A use according to claim 2, wherein the antigen is in the form of a plurality of contiguous overlapping peptides whose sequences span at least a portion of an aggrecan polypeptide, including citrullinated forms thereof.

12. A use according to claim 11, wherein the overlapping peptides comprise, consist or consist essentially of an amino acid sequence selected from SEQ ID NO: 49-531, including citrullinated forms thereof.

13. A use according to claim 2, wherein the inhibitor of the NF-κB pathway is curcumin or a curcumin derivative.

14. A use according to claim 2, wherein the inhibitor of the NF-κB pathway, the mTor inhibitor or the inhibitor of the Syk pathway, and the antigenic molecule are co-administered in soluble form.

15. A use according to claim 2, wherein the inhibitor of the NF-κB pathway, the mTor inhibitor or the inhibitor of the Syk pathway, and the antigenic molecule are co-administered in particulate form.

16. A use according to claim 2, wherein the inhibitor of the NF-κB pathway, the mTor inhibitor or the inhibitor of the Syk pathway, and the antigenic molecule are co-administered in the same particle.

17. A use according to claim 16, wherein the particle is a polymeric particle.

18. A use according to claim 16, wherein the particle is a liposome.

19. A use according to claim 2, wherein the nucleic acid molecule further encodes an immunoglobulin or an immunoglobulin fragment fused directly or indirectly to the antigen.