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(54) Title: TRUNCATED CARTILAGE-HOMING PEPTIDES AND PEPTIDE COMPLEXES AND METHODS OF USE THEREOF

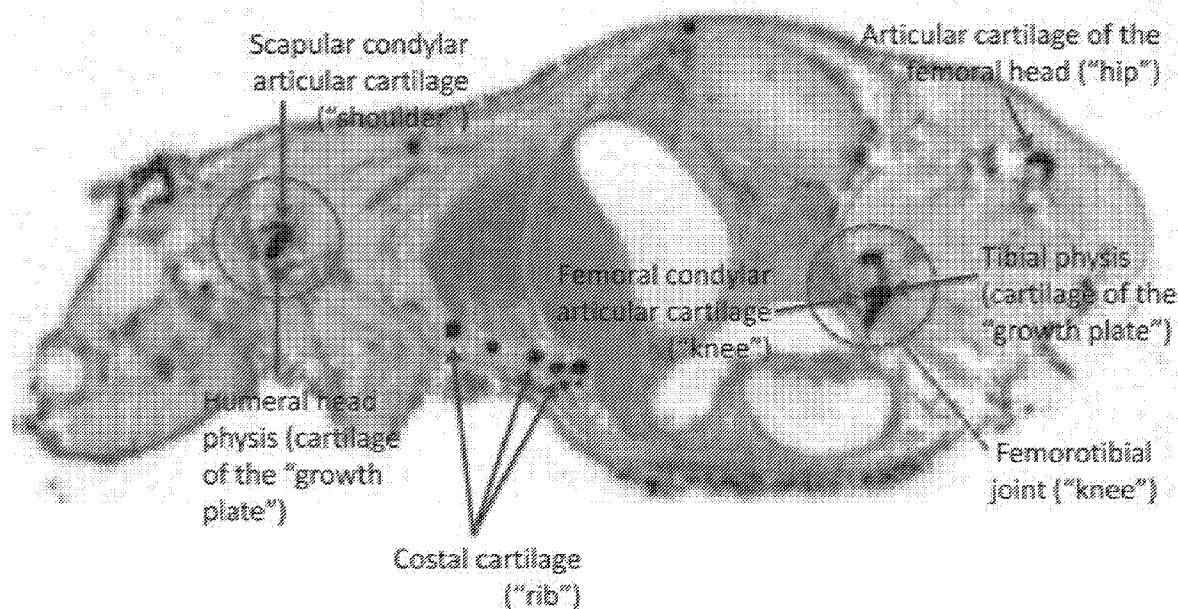


FIG. 1

(57) Abstract: Truncated, variant, or mutated peptides that home, target, migrate to, are directed to, are retained by, or accumulate in and/or bind to the cartilage or kidney of a subject are disclosed. Pharmaceutical compositions and uses for truncated or mutated peptides or truncated or mutated peptide-active agent complexes comprising such peptides are also disclosed. Such compositions can be formulated for targeted delivery of an active agent to a target region, tissue, structure or cell in the cartilage. Targeted compositions of the disclosure can deliver truncated or mutated peptide or truncated, variant, or mutated peptides or peptide-active agent complexes to target regions, tissues, structures or cells targeted by the peptide.



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TRUNCATED CARTILAGE-HOMING PEPTIDES AND PEPTIDE COMPLEXES AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/644,329 filed March 16, 2018, and U.S. Provisional Application No. 62/676,033 filed May 24, 2018, which are incorporated herein by reference in their entireties for all purposes.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 13, 2019, is named 45639-716_601_SL.txt and is 98,451 bytes in size.

BACKGROUND

[0003] Cartilage comprises chondrocytes, a specialized cell-type which produces components of the extracellular matrix, mainly including collagen, proteoglycans (e.g., aggrecan), and elastic fibers. The extracellular matrix proteins provide support, cushion, and durability to cartilage-rich portions of the body such as joints, ears, nose and windpipe. Cartilage is one of few tissues in the body which does not contain blood vessels and is considered an avascular tissue. Unlike many cells in the body which rely on a combination of blood flow and diffusion, chondrocytes rely on diffusion. Because it does not have a direct blood supply, compared to other connective tissues, cartilage grows and repairs much more slowly. As a result, cartilage disorders are particularly difficult to treat.

SUMMARY

[0004] In various aspects, the present disclosure provides a peptide comprising: a) any one of SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 219, SEQ ID NO: 223, SEQ ID NO: 225, or a functional fragment thereof; or b) any one of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221, or a functional fragment thereof and further comprising at least one amino acid in each of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221 is selected from the group consisting of: i) for SEQ ID NO: 89, wherein X¹ is selected from N, S, or G, wherein X² is selected from L or Y, wherein X³ is selected from D or E, wherein X⁴ is selected from M or T, wherein X⁵ is selected from N, Q, A, S, T, or L, wherein X⁶ is selected from S, G, or R, wherein X⁷ is selected from H or Y, and wherein X⁸ is selected from

T or Y; ii) for SEQ ID NO: 106, wherein X^1 is selected from L or Y, wherein X^2 is selected from D or E, wherein X^3 is selected from M or T, wherein X^4 is selected from N, Q, A, S, T, or L, wherein X^5 is selected from S, G, or R, wherein X^6 is selected from H or Y, and wherein X^7 is selected from T or Y; and iii) for SEQ ID NO: 221, wherein each X and X_{1-13} are individually any amino acid or no amino acid and at least one of the following residues at the denoted position, more than one of the following residues at the denoted position, or all of the following residues at the denoted position is included in SEQ ID NO: 221: X_1 is K, X_2 is Q, X_3 is Y, X_4 is E, X_5 is K, X_6 is T, X_7 is K, X_8 is M, X_9 is Q, A, S, T, or L, X_{10} is G, X_{11} is K, X_{12} is Y, or X_{13} is Y; or (iv) a corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

[0005] In some aspects, the peptide comprises any one of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221, or a functional fragment thereof, and wherein the peptide does not comprise SEQ ID NO: 128 or SEQ ID NO: 149. In some aspects, the peptide comprises a sequence of any one of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221 and further comprises at least one of KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRGMNGRC (SEQ ID NO: 105); or GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; $GRCIX^1X^2RC$ (SEQ ID NO: 229), wherein $X^1=N, Q, A, S, T$ or L and $X^2=S, G$, or R wherein each X can independently be any amino acid or amino acid analogue or null.

[0006] In some aspects, the peptide comprises a sequence of any one of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221 and the peptide further comprises at least one of RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; $GRCIX^1X^2RC$ (SEQ ID NO: 229), wherein $X^1=N, Q, A, S, T$ or L and $X^2=S, G$, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); or RFGRCI (SEQ ID NO: 259).

[0007] In some aspects, the peptide has a sequence selected from the group consisting of any one of SEQ ID NO: 106, and SEQ ID NO: 221.

[0008] In other aspects, the peptide comprises SEQ ID NO: 89 and wherein the peptide comprises one or more of the following characteristics: a) X_1 is selected from S, or G; b) X_2 is

selected from Y; c) X3 is selected from E; d) X4 is selected from T; e) X5 is selected from Q, A, S, T, or L; f) X6 is selected from G, or R; g) X7 is selected from Y; or h) X8 is selected from Y.

[0009] In some aspects, the peptide comprises two, three, four, five, six, seven or more of the characteristics, or wherein the peptide comprises all of the characteristics. In some aspects, the peptide consists of any one of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221 and wherein the peptide does not comprise SEQ ID NO: 128 or SEQ ID NO: 149.

[0010] In some aspects, the peptide is any of the above peptides, wherein a) the peptide comprises at least 70%, at least at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with a sequence selected from the group SEQ ID NO: 111 – SEQ ID NO: 126 or SEQ ID NO: 233 – SEQ ID NO: 240; or b) the peptide comprises at least 70%, at least at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with a sequence selected from the group SEQ ID NO: 134 – SEQ ID NO: 148 and SEQ ID NO: 249 – SEQ ID NO: 256.

[0011] In some aspects, the peptide is any of the above peptides, wherein a) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with any one of SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; b) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 129 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; c) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO:

130 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; d) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 131 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; e) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 132 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; f) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 133 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; g) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 260 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately

adjacent to an N-terminus or a C-terminus of the peptide and wherein i) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or ii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; or h) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

[0012] In some aspects, the peptide comprises at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 99%, or at least 100% identity with any one of SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 – SEQ ID NO: 256 and does not comprise SEQ ID NO: 128 or SEQ ID NO: 149. In some aspects, the peptide comprises any one of SEQ ID NO: 109 – SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, SEQ ID NO: 262 and does not comprise SEQ ID NO: 128 or SEQ ID NO: 149.

[0013] In some aspects, the joining sequence is at the N-terminus or a C-terminus of the peptide, or both the N-terminus and the C-terminus of the peptide. In some aspects, the joining sequence comprises from 1 to 100 amino acid residues. In some aspects, the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of SEQ ID NO: 109 – SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262 and further comprising no more than 5 additional amino acids at the N-terminus.

[0014] In some aspects, the peptide consists of a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of the peptides selected from the group consisting of SEQ ID NO: 109 – SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, or SEQ ID NO: 262.

[0015] In further aspects, the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein: a) for any one of SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262: i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A,

V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or b) for SEQ ID NO: 129, N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or c) for SEQ ID NO: 130: i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or d) for SEQ ID NO: 131: i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or e) for SEQ ID NO: 132: i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; f) for SEQ ID NO: 133: i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; g) for SEQ ID NO: 260: i) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or ii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; or h) for SEQ ID NO: 262, C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

[0016] In some aspects, the peptide is selected from the group consisting of SEQ ID NO: 109 - SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, and SEQ ID NO: 262.

[0017] In other aspects, the peptide consists of a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of the peptides selected from the group consisting of SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256.

[0018] In further aspects, the peptide is selected from the group consisting of SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256.

[0019] In various aspects, the present disclosure provides a peptide, wherein a) the peptide comprises at least 70%, at least at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with a sequence selected from the group SEQ ID NO: 111 – SEQ ID NO: 126 or SEQ ID NO: 233 – SEQ ID NO: 240; or b) the peptide comprises at least 70%, at least at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with a sequence selected from the group SEQ ID NO: 134 – SEQ ID NO: 148 and SEQ ID NO: 249 – SEQ ID NO: 256.

[0020] In various aspects, the present disclosure provides a peptide, wherein a peptide, wherein a) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with any one of SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; b) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 129 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; c) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 130 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, L, I,

M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; d) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 131 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; e) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 132 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; f) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 133 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; g) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 260 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or ii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S,

T, C, Y, N, Q, D, E, K, R, and H; or h) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

[0021] In some aspects, the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide. In some aspects, the joining sequence is at an N-terminus or a C-terminus of the peptide, or both the N-terminus and the C-terminus of the peptide. In some aspects, the joining sequence comprises from 1 to 100 amino acid residues. In some aspects, the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of SEQ ID NO: 109 - SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262 and further comprising no more than 5 additional amino acids at the N-terminus.

[0022] In some aspects, the peptide consists of a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of the peptides selected from the group consisting of SEQ ID NO: 109 - SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, or SEQ ID NO: 262.

[0023] In further aspects, the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein: a) for any one of SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262: i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or b) for SEQ ID NO: 129, N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or c) for SEQ ID NO: 130: i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or d) for SEQ ID NO: 131: i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q,

D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or e) for SEQ ID NO: 132: i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; f) for SEQ ID NO: 133: i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; g) for SEQ ID NO: 260: i) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or ii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; or h) for SEQ ID NO: 262, C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

[0024] In some aspects, the peptide is selected from the group consisting of SEQ ID NO: 109 - SEQ ID NO: 110, SEQ ID NO: 129 - SEQ ID NO: 133, SEQ ID NO: 260, and SEQ ID NO: 262. In some aspects, the peptide consists of a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of the peptides selected from the group consisting of SEQ ID NO: 111 - SEQ ID NO: 126, SEQ ID NO: 134 - SEQ ID NO: 148, SEQ ID NO: 233 - SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256. In some aspects, the peptide is selected from the group consisting of SEQ ID NO: 111 - SEQ ID NO: 126, SEQ ID NO: 134 - SEQ ID NO: 148, SEQ ID NO: 233 - SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256.

[0025] In some aspects, the peptide comprises SEQ ID NO: 28, SEQ ID NO: 45 - SEQ ID NO: 51, SEQ ID NO: 109, SEQ ID NO: 150, SEQ ID NO: 199, SEQ ID NO: 110, SEQ ID NO: 127 - SEQ ID NO: 133, SEQ ID NO: 149, or SEQ ID NO: 260 - SEQ ID NO: 263 and further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino

acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null.

[0026] In some aspects, the peptide comprises SEQ ID NO: 27, SEQ ID NO: 29 – SEQ ID NO: 44, SEQ ID NO: 52 – SEQ ID NO: 66, SEQ ID NO: 109, SEQ ID NO: 150, SEQ ID NO: 199, SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 256, and SEQ ID NO: 21 – SEQ ID NO: 26, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 108, SEQ ID NO: 219 – SEQ ID NO: 226 and further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259).

[0027] In other aspects, the peptide comprises one or more of the following peptide fragments within its sequence: GKCINKKCKC (SEQ ID NO: 90); KCIN (SEQ ID NO: 91); KKCK (SEQ ID NO: 92); PCKR (SEQ ID NO: 93); KRCSRR (SEQ ID NO: 94); KQC (SEQ ID NO: 95); GRCINRRRCRC (SEQ ID NO: 96); RCIN (SEQ ID NO: 97); RRCR (SEQ ID NO: 98); PCRR (SEQ ID NO: 99); RRCSRR (SEQ ID NO: 100); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); KKCSKK (SEQ ID NO: 103); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null, GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R (SEQ ID NO: 229), PCR (SEQ ID NO: 230), CLDPCRR (SEQ ID NO: 231), CLDPCRR (SEQ ID NO: 232), RCRGSRDC (SEQ ID NO: 257), PCRRAG (SEQ ID NO: 258), and RFGRCI (SEQ ID NO: 259).

[0028] In some aspects, the peptide comprises an N-terminal sequence comprising GG, SS, GS, SG, S, or G. In some aspects, the peptide is SEQ ID NO: 219. In other aspects, the peptide is SEQ ID NO: 220. In other aspects, the peptide is SEQ ID NO: 221 and wherein: a) the peptide further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue

or null; or b) the peptide further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRRA (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259); or c) and the peptide further comprises at least one corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

[0029] In other aspects, the peptide is SEQ ID NO: 222. In other aspects, the peptide is SEQ ID NO: 223. In other aspects, the peptide is SEQ ID NO: 224. In other aspects, the peptide is SEQ ID NO: 225. In other aspects, the peptide is SEQ ID NO: 226. In other aspects, the peptide is SEQ ID NO: 87. In other aspects, the peptide is SEQ ID NO: 89 and wherein: a) the peptide further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null; or b) the peptide further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRRA (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259); or c) and the peptide further comprises at least one corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

[0030] In other aspects, the peptide is SEQ ID NO: 106 and wherein: a) the peptide further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105);

GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null; or b) the peptide further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259); or c) and the peptide further comprises at least one corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

[0031] In other aspects, the peptide is SEQ ID NO: 110 and further comprising no more than 5 additional amino acids at the N-terminus. In other aspects, the peptide is SEQ ID NO: 219. In other aspects, the peptide is SEQ ID NO: 221 a) the peptide further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null; or b) the peptide further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259); or c) and the peptide further comprises at least one corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

[0032] In various aspects, the present disclosure provides a peptide comprising at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at

least 99%, or 100% sequence identity with any one of SEQ ID NO: 209 – SEQ ID NO: 215, wherein the peptide further comprises an active agent and wherein the active agent is complexed with the peptide to form a peptide active agent complex. In some aspects, the peptide further comprises an active agent, wherein the active agent is complexed with the peptide to form a peptide active agent complex. In some aspects, the active agent is selected from TABLE 3, TABLE 4, or TABLE 5.

[0033] In some aspects, in any of the above peptides or in any of the above peptide active agent complexes, the peptide comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or 100% sequence identity to: SEQ ID NO: 27; SEQ ID NO: 28; SEQ ID NO: 29; SEQ ID NO: 30; SEQ ID NO: 31; SEQ ID NO: 32; SEQ ID NO: 33; SEQ ID NO: 34; SEQ ID NO: 35; SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID NO: 38; SEQ ID NO: 39; SEQ ID NO: 40; SEQ ID NO: 41; SEQ ID NO: 42; SEQ ID NO: 43; SEQ ID NO: 44; SEQ ID NO: 45; SEQ ID NO: 234; SEQ ID NO: 47; SEQ ID NO: 48; SEQ ID NO: 49; SEQ ID NO: 50; SEQ ID NO: 51; SEQ ID NO: 109 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H further comprising no more than 5 additional amino acids at the N-terminus;

SEQ ID NO: 110 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H further comprising no more than 5 additional amino acids at the N-terminus; SEQ ID NO: 111; SEQ ID NO: 112; SEQ ID NO: 113; SEQ ID NO: 114; SEQ ID NO: 115; SEQ ID NO: 116;

SEQ ID NO: 117; SEQ ID NO: 118; SEQ ID NO: 119; SEQ ID NO: 120; SEQ ID NO: 121; SEQ ID NO: 122; SEQ ID NO: 123; SEQ ID NO: 124; SEQ ID NO: 125; SEQ ID NO: 126; SEQ ID NO: 87; SEQ ID NO: 129 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the joining sequence is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; SEQ ID NO: 130 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the joining sequence is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; SEQ ID NO: 131 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; , wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the joining sequence is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; SEQ ID NO: 132 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the joining sequence is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; SEQ ID NO: 133 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-

terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the joining sequence is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; SEQ ID NO: 89; SEQ ID NO: 106; SEQ ID NO: 219; or SEQ ID NO: 221; SEQ ID NO: 260 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; vii) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or viii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; or SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or vii) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

[0034] In some aspects, in the above described peptide active agent complex, the peptide comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, at least 99%, or

100% sequence identity to: SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID NO: 54; SEQ ID NO: 55; SEQ ID NO: 56; SEQ ID NO: 57; SEQ ID NO: 58; SEQ ID NO: 59; SEQ ID NO: 60; SEQ ID NO: 61; SEQ ID NO: 62; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 65; SEQ ID NO: 66; SEQ ID NO: 134; SEQ ID NO: 135; SEQ ID NO: 136; SEQ ID NO: 137; SEQ ID NO: 138; SEQ ID NO: 139; SEQ ID NO: 140; SEQ ID NO: 141; SEQ ID NO: 142; SEQ ID NO: 143; SEQ ID NO: 144; SEQ ID NO: 145; SEQ ID NO: 146; SEQ ID NO: 147; or SEQ ID NO: 148.

[0035] In some aspects, in the peptide or the peptide active agent complex, the peptide homes, targets, migrates to, accumulates in, binds to, is retained by, or is directed to cartilage, to kidney, or to cartilage and kidney. In some aspects, in the peptide or the peptide active agent complex, the peptide homes, targets, migrates to, accumulates in, binds to, is retained by, or is directed to proximal tubules of the kidney. In some aspects, in the peptide or the peptide active agent complex, the peptide is covalently complexed to the active agent. In some aspects, the peptide active agent complex homes, targets, migrates to, accumulates in, binds to, is retained by, or is directed to a cartilage or a kidney of the subject. In some aspects, in the peptide or the peptide active agent complex, the peptide comprises 4 or more cysteine residues.

[0036] In some aspects, in the peptide or the peptide active agent complex, the peptide comprises three or more disulfide bridges formed between cysteine residues, wherein one of the disulfide bridges passes through a loop formed by two other disulfide bridges. In some aspects, in the peptide or the peptide active agent complex, the peptide comprises a plurality of disulfide bridges formed between cysteine residues. In some aspects, in the peptide or the peptide active agent complex, the peptide comprises a disulfide through a disulfide knot. In some aspects, at least one amino acid residue of the peptide is in an L configuration or, wherein at least one amino acid residue of the peptide is in a D configuration. In some aspects, the sequence comprises at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58 residues, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, at least 80, or at least 81 residues.

[0037] In some aspects, any one or more K residues are replaced by an R residue or wherein any one or more R residues are replaced by for a K residue. In some aspects, any one or more M residues are replaced by any one of the I, L, or V residues. In some aspects, any one or more L residues are replaced by any one of the V, I, or M residues. In some aspects, any one or more I residues are replaced by any of the M, L, or V residues. In some aspects, any one or more V residues are replaced by any of the M, I, or L residues.

[0038] In some aspects, any one or more G residues are replaced by an A residue or wherein any one or more A residues are replaced by a G residue. In some aspects, any one or more S residues are replaced by a T residue or wherein any one or more T residues are replaced by for an S residue. In some aspects, any one or more Q residues are replaced by an N residue or wherein any one or more N residues are replaced by a Q residue. In some aspects, any one or more D residues are replaced by an E residue or wherein any one or more E residues are replaced by a D residue. In some aspects, the peptide has a charge distribution comprising an acidic region and a basic region. In some aspects, the acidic region is a nub. In some aspects, the basic region is a patch.

[0039] In some aspects, the peptide comprises 5-12 basic residues. In some aspects, the peptide comprises 0-5 acidic residues. In some aspects, the peptide comprises 6 or more basic residues and 2 or fewer acidic residues. In some aspects, the peptide comprises a 4-19 amino acid residue fragment containing at least 2 cysteine residues, and at least 2 positively charged amino acid residues. In some aspects, the peptide comprises a 20-70 amino acid residue fragment containing at least 2 cysteine residues, no more than 2 basic residues and at least 2 positively charged amino acid residues. In some aspects, the peptide comprises at least 3 positively charged amino acid residues. In some aspects, the positively charged amino acid residues are selected from K, R, or a combination thereof. In some aspects, the peptide has a charge greater than 2 at physiological pH. In some aspects, the peptide has a charge greater than 3.5 at physiological pH. In some aspects, the peptide has a charge greater than 4.5 at physiological pH. In some aspects, the peptide has a charge greater than 5.5 at physiological pH. In some aspects, the peptide has a charge greater than 6.5 at physiological pH. In some aspects, the peptide has a charge greater than 7.5 at physiological pH. In some aspects, the peptide has a charge greater than 8.5 at physiological pH. In some aspects, the peptide has a charge greater than 9.5 at physiological pH. In some aspects, the peptide is selected from a potassium channel agonist, a potassium channel antagonist, a portion of a potassium channel, a sodium channel agonist, a sodium channel antagonist, a calcium channel agonist, a calcium channel antagonist, a hadrucalcin, a theraphotoxin, a huwentoxin, a kaliotoxin, a cobatoxin or a lectin.

[0040] In further aspects, the lectin is SHL-Ib2. In some aspects, the peptide is arranged in a multimeric structure with at least one other peptide. In some aspects, at least one residue of the peptide comprises a chemical modification. In further aspects, the chemical modification is blocking the N-terminus of the peptide. In still further aspects, the chemical modification is methylation, acetylation, or acylation. In some aspects, the chemical modification is: methylation of one or more lysine residues or analogue thereof; methylation of the N-terminus; or methylation of one or more lysine residue or analogue thereof and methylation of the N-terminus. In some aspects, the peptide is linked to an acyl adduct. In some aspects, the active agent is fused with the peptide at an N-terminus or a C-terminus of the peptide. In some aspects, the active agent is another peptide. In some aspects, the active agent is an antibody.

[0041] In some aspects, the active agent is an Fc domain, Fab domain, scFv, or Fv fragment. In some aspects, the active agent is a glucocorticoid. In some aspects, the active agent is dexamethasone. In some aspects, the peptide fused with the Fc domain comprises a contiguous sequence. In some aspects, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 active agents are linked to the peptide. In some aspects, the peptide is linked to the active agent at an N-terminus, at the epsilon amine of a lysine residue, at the carboxylic acid of an aspartic acid or glutamic acid residue, or a C-terminus of the peptide by a linker. In some aspects, the peptide is linked to the active agent via a cleavable linker. In some aspects, the peptide further comprising a non-natural amino acid, wherein the non-natural amino acid is an insertion, appendage, or substitution for another amino acid. In some aspects, the peptide is linked to the active agent at the non-natural amino acid by a linker. In further aspects, linker comprises an amide bond, an ester bond, a carbamate bond, a carbonate bond, a hydrazone bond, an oxime bond, a disulfide bond, a thioester bond, a thioether bond, a triazole, a carbon-carbon bond, or a carbon-nitrogen bond. In some aspects, the linker comprises an ester bond.

[0042] In some aspects, the cleavable linker comprises a cleavage site for matrix metalloproteinases, thrombin, cathepsins, or beta-glucuronidase. In some aspects, the linker is a hydrolytically labile linker. In some aspects, the linker is pH sensitive, reducible, glutathione-sensitive, or protease cleavable. In some aspects, the peptide is linked to the active agent via a stable linker. In some aspects, the peptide has an isoelectric point of about 9. In some aspects, the peptide is linked to a detectable agent. In some aspects, the detectable agent is fused with the peptide at an N-terminus or a C-terminus of the peptide. In some aspects, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 detectable agents are linked to the peptide. In some aspects, the peptide is linked to the detectable agent via a cleavable linker. In some aspects, the peptide is linked to the detectable agent at an N-terminus, at the epsilon amine of an internal lysine residue, or a C-terminus of the

peptide by a linker. In some aspects, the peptide further comprises a non-natural amino acid, wherein the non-natural amino acid is an insertion, appendage, or substitution for another amino acid.

[0043] In some aspects, the peptide is linked to the detectable agent at the non-natural amino acid by a linker. In some aspects, the linker comprises an amide bond, an ester bond, a carbamate bond, a hydrazone bond, an oxime bond, or a carbon-nitrogen bond. In some aspects, the cleavable linker comprises a cleavage site for matrix metalloproteinases, thrombin, cathepsins, or beta-glucuronidase. In some aspects, the peptide is linked to the detectable agent via a stable linker. In some aspects, the detectable agent is a fluorophore, a near-infrared dye, a contrast agent, a nanoparticle, a metal-containing nanoparticle, a metal chelate, an X-ray contrast agent, a PET agent, a radioisotope, or a radionuclide chelator. In some aspects, the detectable agent is a fluorescent dye. In some aspects, the peptide further comprises a joining sequence. In some aspects, the joining sequence is at an N-terminus or a C-terminus of the peptide. In some aspects, the joining sequence comprises from 1 to 100 amino acid residues.

[0044] In various aspects, the present disclosure provides a pharmaceutical composition comprising any of the above peptides or a salt thereof, or any of the above peptide active agent complexes or a salt thereof, and a pharmaceutically acceptable carrier. In some aspects, the pharmaceutical composition is formulated for administration to a subject. In some aspects, the pharmaceutical composition is formulated for inhalation, intranasal administration, oral administration, topical administration, parenteral administration, intravenous administration, subcutaneous administration, intra-articular administration, intramuscular administration, intraperitoneal administration, dermal administration, transdermal administration, or a combination thereof.

[0045] In various aspects, the present disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering to the subject any of the above peptides, any of the above peptide active agent complexes, or any of the above pharmaceutical compositions.

[0046] In some aspects, the peptide active agent complex, peptide, or pharmaceutical composition is administered by inhalation, intranasally, orally, topically, parenterally, intravenously, subcutaneously, intra-articularly, intramuscularly administration, intraperitoneally, dermally, transdermally, or a combination thereof. In some aspects, the peptide active agent complex or the peptide homes, targets, or migrates to cartilage of the subject following administration. In some aspects, the condition is associated with cartilage. In some aspects, the condition is associated with a joint. In some aspects, the condition is an

inflammation, a cancer, a degradation, a growth disturbance, genetic, a tear, an infection, a disease, or an injury. In some aspects, the condition is a chondrodystrophy. In some aspects, the condition is a traumatic rupture or detachment. In some aspects, the condition is a costochondritis. In some aspects, the condition is a herniation. In some aspects, the condition is a polychondritis.

[0047] In other aspects, the condition is a chordoma. In some aspects, the condition is a type of arthritis. In some aspects, the type of arthritis is rheumatoid arthritis. In some aspects, the type of arthritis is osteoarthritis. In some aspects, the type of arthritis is lupus arthritis. In some aspects, the condition is Systemic lupus erythematosus. In some aspects, the condition is achondroplasia. In some aspects, the condition is benign chondroma or malignant chondrosarcoma. In some aspects, the condition is bursitis, tendinitis, gout, pseudogout, an arthropathy, psoriatic arthritis, ankylosing spondylitis, or an infection. In some aspects, the peptide active agent complex, peptide, or pharmaceutical composition is administered to treat the injury, to repair a tissue damaged by the injury, or to treat a pain caused by the injury. In some aspects, the peptide active agent complex, peptide, or pharmaceutical composition is administered to treat the tear or to repair a tissue damaged by the tear. In some aspects, the peptide active agent complex, peptide, or pharmaceutical composition homes, targets, or migrates to a kidney of the subject following administration. In some aspects, the condition is associated with a kidney. In some aspects, the condition is lupus nephritis, acute kidney injury (AKI), chronic kidney disease (CKD), hypertensive kidney damage, diabetic nephropathy, lupus nephritis, or renal fibrosis.

[0048] In various aspects, the present disclosure provides a method of imaging an organ or body region of a subject, the method comprising: administering to the subject any peptide described above, any peptide active agent complex described above, or any pharmaceutical composition described above; and imaging the subject.

[0049] In some aspects, the method further comprises detecting a cancer or diseased region, tissue, structure or cell. In some aspects, the method further comprises performing surgery on the subject. In some aspects, the method further comprises treating the cancer. In some aspects, the surgery further comprises removing the cancer or the diseased region, tissue, structure or cell of the subject. In some aspects, the method further comprises imaging the cancer or diseased region, tissue, structure, or cell of the subject after surgical removal.

[0050] In some aspects, any of the above described peptide active agent complexes is expressed as a fusion protein.

[0051] In various aspects, the present disclosure provides a method of treating or delivering a peptide or peptide agent complex to a subject in need thereof according to method described

above, the method further comprising administering a companion diagnostic, therapeutic, or imaging agent, wherein the companion diagnostic or imaging agent comprises a) any peptide active agent complex described above, b) any peptide described above; or c) a peptide of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, or SEQ ID NO: 233 – SEQ ID NO: 256 further comprising a diagnostic, therapeutic, or imaging agent, wherein the diagnostic or imaging agent comprises a chemical agent, a radiolabel agent, radiosensitizing agent, fluorophore, an imaging agent, a diagnostic agent, a protein, a peptide, or a small molecule.

[0052] In some aspects, the companion diagnostic, therapeutic, or imaging agent is detected by a device. In some aspects, the device is used to detect the companion diagnostic, therapeutic, or imaging agent or to assess an agent's safety and physiologic effect. In some aspects, the agent's safety and physiologic effect is bioavailability, uptake, distribution and clearance, metabolism, pharmacokinetics, localization, measurement of concentrations in blood and tissues, assessing therapeutic window, range and optimization. In some aspects, the method is combined with or integrated into a surgical microscope, confocal microscope, fluorescence scope, exoscope, endoscope, or a surgical robot comprising a KINEVO 900, QEVO, CONVIVO, OMPI PENTERO 900, OMPI PENTERO 800, INFRARED 800, FLOW 800, OMPI LUMERIA, OMPI Vario, OMPI VARIO 700, OMPI Pico, TREMON 3DHD, a PROVido, ARvido, GLOW 800, Leica M530 OHX, Leica M530 OH6, Leica M720 OHX5, Leica M525 F50, Leica M525 F40, Leica M525 F20, Leica M525 OH4, Leica HD C100, Leica FL560, Leica FL400 Leica FL800, Leica DI C500, Leica ULT500, Leica Rotatable Beam Splitter, Leica M651 MSD, LIGHTENING, Leica TCS SP8, SP8 FALCON, SP8 DIVE, Leica TCS SP8 STED, Leica TCS SP8 DLS, Leica TCS SP8 X, Leica TCS SP8 CARS, Leica TCS SPE), Leica HyD, Leica HCS A, Leica DCM8, Haag-Streit 5-1000, Haag-Streit 3-1000, and Intuitive Surgical da Vinci surgical robot. In some aspects, the device incorporates radiology or fluorescence, including the X-ray radiography, magnetic resonance imaging (MRI), ultrasound, endoscopy, elastography, tactile imaging, thermography, flow cytometry, medical photography, nuclear medicine functional imaging techniques, positron emission tomography (PET), single-photon emission computed tomography (SPECT), surgical instrument, operating microscope, confocal microscope, fluorescence scope, exoscope, or a surgical robot.

[0053] In some aspects, the peptide comprises at least two of, at least three of, at least four of, at least five of, at least six of, at least seven of, at least eight of, or all of KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); or GRCIXXRC

(SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null.

[0054] In some aspects, the peptide comprises at least two of, at least three of, at least four of, at least five of, at least six of, at least seven of, at least eight of, at least nine of, at least ten of, or all of RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); or RFGRCI (SEQ ID NO: 259).

[0055] In some aspects, the peptide comprises at least two of, at least three of, at least four of, at least five of, at least six of, at least seven of, at least eight of, at least nine of, at least ten of, at least 11 of, at least 12 of, at least 13 of, at least 14 of, at least 15 of, at least 16 of, at least 17 of, at least 18 of, at least 19 of, at least 20 of, at least 21 of, at least 22 of, at least 23 of, at least 24 of, at least 25 of, or all of GKCINKKCKC (SEQ ID NO: 90); KCIN (SEQ ID NO: 91); KKCK (SEQ ID NO: 92); PCKR (SEQ ID NO: 93); KRCSRR (SEQ ID NO: 94); KQC (SEQ ID NO: 95); GRCINRRRC (SEQ ID NO: 96); RCIN (SEQ ID NO: 97); RRCR (SEQ ID NO: 98); PCRR (SEQ ID NO: 99); RRCRR (SEQ ID NO: 100); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); KKCSKK (SEQ ID NO: 103); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null, GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R (SEQ ID NO: 229), PCR (SEQ ID NO: 230), CLDPCRR (SEQ ID NO: 231), CLDPCRR (SEQ ID NO: 232), RCRGSRDC (SEQ ID NO: 257), PCRRAG (SEQ ID NO: 258), and RFGRCI (SEQ ID NO: 259).

[0056] In some aspects, the peptide further comprises at least two of, at least three of, at least four of, at least five of, at least six of, at least seven of, at least eight of, at least nine of, at least ten of, at least 11 of, at least 12 of, at least 13 of, at least 14 of, at least 15 of, at least 16 of, at least 17 of, at least 18 of, at least 19 of, at least 20 of, at least 21 of, at least 22 of, at least 23 of, at least 24 of, at least 25 of, at least 26 of, at least 27 of, at least 28 of, at least 29, or all of the corresponding substitutions selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

INCORPORATION BY REFERENCE

[0057] All publications, patents, and patent applications mentioned, disclosed or referenced in this specification are herein incorporated by reference in their entirety and to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

[0058] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

[0059] **FIG. 1** illustrates the identification of the ^{14}C signal in the joint and other cartilage of an animal treated with the peptide of SEQ ID NO: 150.

[0060] **FIG. 2** illustrates an exemplary architecture of constructs expressing sequences of SEQ ID NO: X, where X can be any one of peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

[0061] **FIG. 3** illustrates a schematic of a method of manufacturing of a peptide of the disclosure.

[0062] **FIG. 4** illustrates the ^{14}C signal in the cartilage of an animal with intact kidneys 24 hours after treatment with a peptide of SEQ ID NO: 150.

[0063] **FIG. 5** shows white light images and corresponding whole body fluorescence images of a mouse administered 10 nmol of a peptide of SEQ ID NO: 149 (also disclosed herein as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A) at 24 hours post-administration. **FIG. 5A** illustrates an image of a frozen section of a mouse, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A). **FIG. 5B** illustrates the fluorescence signal in the mouse, corresponding to the section shown in **FIG. 5A**, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A). **FIG. 5C** illustrates an image of a different frozen section of the mouse, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 46 (also disclosed herein as SEQ ID NO: 149; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A). **FIG. 5D** illustrates the fluorescence signal in the mouse,

corresponding to the section shown in **FIG. 5C**, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A). **FIG. 5E** illustrates an image of a different frozen section of the mouse, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A). **FIG. 5F** illustrates a fluorescence signal in the mouse, corresponding to the section shown in **FIG. 5E**, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A).

[0064] FIG. 6 illustrates a multiple sequence alignment of SEQ ID NO: 198 – SEQ ID NO: 215 were used to predict enhanced peptide stability and immunogenicity or other functions. SEQ ID NO: 87 is a consensus sequence, and SEQ ID NO: 21 is the same sequence as SEQ ID NO: 87 but with an N-terminal “GS.” SEQ ID NO: 219 – SEQ ID NO: 222 are variant consensus peptide sequences, included within the family of SEQ ID NO: 87 and SEQ ID NO: 21 consensus sequences, which variant consensus sequences include further improved properties of the peptides as described herein, with or without an N-terminal GS.

[0065] FIG. 7 illustrates the identification of locations the ^{14}C signal in the nasal, spinal, tracheal, and other cartilage of an animal treated with the peptide of SEQ ID NO: 150.

[0066] FIG. 8 shows IVIS fluorescence imaging of an isolated hind limb from a first mouse and an isolated hind limb from a second mouse after administration of 10 nmol SEQ ID NO: 149 peptide conjugated to a Cy5.5 fluorophore (SEQ ID NO: 46A; also the same as SEQ ID NO: 149A, because SEQ ID NO: 46 and SEQ ID NO: 149 disclose the same sequence; the non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 is shown in SEQ ID NO: 128 and SEQ ID NO: 205). Areas of low signal intensity are shown in a thin solid line, areas of medium signal intensity are shown in a thick solid line, and areas of high signal intensity are shown in a thin dotted line. **FIG. 8A** shows the right hind limb with skin removed from a first mouse and from a second mouse 3 hours after peptide administration. **FIG. 8B** shows the right hind limb with muscle removed from a first mouse and from a second mouse 3 hours after peptide administration of 10 nmol SEQ ID NO: 149 peptide conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A). **FIG. 8C** shows the right hind limb with skin removed from a first mouse and from a second mouse 24 hours after peptide administration of 10 nmol SEQ ID NO: 149 peptide conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A). **FIG. 8D** shows the right hind limb with muscle removed from a first mouse and from a second mouse 24 hours after peptide administration of 10 nmol SEQ ID NO: 149 peptide conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A). **FIG. 8E** shows the right hind limb with skin removed from a first mouse and from a second mouse 48 hours after peptide administration of 10 nmol SEQ ID NO: 149 peptide

conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A). **FIG. 8F** shows the right hind limb with muscle removed from a first mouse and from a second mouse 48 hours after peptide administration of 10 nmol SEQ ID NO: 149 peptide conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A). **FIG. 8G** shows the right hind limb with skin removed from a first mouse and from a second mouse 72 hours after peptide administration of 10 nmol SEQ ID NO: 149 peptide conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A). **FIG. 8H** shows the right hind limb with muscle removed from a first mouse and from a second mouse 72 hours after administration of 10 nmol SEQ ID NO: 149 peptide conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A).

[0067] **FIG. 9** illustrates autoradiography images of frozen sections from a mouse, 3 hours after administration of 100 nmol of a radiolabeled peptide of SEQ ID NO: 149. **FIG. 9A** illustrates the ^{14}C signal in a different frozen section of the mouse, 3 hours after administration of 100 nmol of a radiolabeled peptide of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205). **FIG. 9B** illustrates the ^{14}C signal in a different frozen section of a mouse, 3 hours after administration of 100 nmol of a radiolabeled peptide of SEQ ID NO: 149.

DETAILED DESCRIPTION

[0068] The present disclosure relates generally to compositions and methods for cartilage therapy. In some embodiments, the compositions and methods herein utilize truncated or mutated peptides that home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage following administration to a subject. In some embodiments, the truncated or mutated cartilage homing peptides of the present disclosure exert therapeutic effect in cartilage or tissue or cell thereof. In some embodiments, the truncated or mutated cartilage homing peptides of the present disclosure are used to deliver an active agent to cartilage or tissue or cell thereof. The active agent can exert a therapeutic effect on cartilage or tissue or cell thereof. For example, in certain embodiments, the truncated or mutated peptide itself or the active agent allows for localized delivery of an anti-inflammatory or other agent to cartilage or tissue or cell thereof. As another example, the active agent is a fluorophore that can be used for imaging of cartilage. In certain embodiments, the truncated or mutated peptide itself induces therapeutic responses.

[0069] Cartilage disorders are particularly difficult to treat. A direct route for active agent administration can be parenterally (e.g., intravenously, subcutaneously, intramuscularly), intra-articularly, by inhalation, dermally, topically, or orally. However, cartilage can be avascular thus intravenous administration of drugs can fail to reach the cartilage in significant amounts. Drugs for cartilage diseases, such as osteoarthritis, can be injected directly locally

into the affected area, for example, directly injected into the joint. Few drugs aimed at treating cartilage disorders have proved therapeutically viable with lack of access to target tissue being a primary reason for failure. The lack of access to the target tissue can also lead to administration of doses that are higher than would be necessary if a drug could home, target, or be directed to, is retained by, and/or binds to a target region, tissue, structure or cell. Thus, treatment of cartilage conditions often requires the use of high concentrations of non-specific drugs. In addition, a number of therapeutics are of interest in treating joint disorders, but are problematic because of the level of side effects caused by systemic administration of the drug (Dancevic and McCulloch, *Arthritis Res Ther.* 16:429 (2014)).

[0070] Specific and potent drugs that are capable of contacting the cartilage can counteract the non-specificity of many treatments by selectively targeting and delivering compounds to specific regions, tissues, cells and structures. Such drugs can also be useful to modulate ion channels, protein-protein interactions, extracellular matrix remodeling (i.e., protease inhibition), and the like. Such targeted therapy can allow for lower dosing, reduced side effects, improved patient compliance, and improvement in therapeutic outcomes, which would be advantageous not only in acute disease of the cartilage, but in chronic conditions as well.

[0071] The present disclosure provides truncated or mutated peptides that can comprise or can be derived from cystine-dense peptides. As used herein, the term “cystine-dense peptide” can be interchangeable with the terms “knotted peptide,” “knottin,” and “optide,” and cystine-dense peptides can also be abbreviated as “CDPs.” Hitchins, amongst other disulfide-containing peptides, can also be considered “knotted peptides” or “cystine-dense peptides” for the purposes of this disclosure. Knottins, for example, are a class of cystine-dense peptides comprising from about 11 to about 80 amino acids in length that are often folded into a compact structure. Knottins and other cystine-dense peptides are typically assembled into a complex tertiary structure that is characterized by a number of intramolecular disulfide crosslinks and can contain beta strands, one or more alpha helices, and other secondary structures. The presence of the disulfide bonds can give cystine-dense peptides remarkable environmental stability, allowing them to withstand extremes of temperature and pH, to resist proteolytic enzymes in the blood stream or digestive tract, and can provide specific biodistribution, pharmacokinetic, binding interactions, cellular processing, or other properties of physiologic and therapeutic value. The truncated or mutated peptides disclosed herein can be derived from certain cystine-dense peptides. The present disclosure describes a class of cystine-dense peptides that can effectively contact cartilage and be used either directly or as carriers of active drugs, peptides, or molecules to treat a cartilage condition. For instance, osteoarthritis is a cartilage

condition that is associated with the thinning of cartilage covering the ends of bones resulting in bone directly contacting bone within the joint. Over time, the ends of the bones are subjected to increased levels of friction which ultimately causes erosion of the end of the bone. Individuals suffering from osteoarthritis experience reduced motion and increased pain. A therapeutic peptide that could contact the cartilage at the joint and ends of the bone to interact with the chondrocytes and induce increased expression of extracellular matrix proteins could be used in the treatment and prevention of osteoarthritis by increasing expression of collagen through, for example, the rate of production, amount of production, inhibition of proteins which degrade collagen, promote expression of other proteins which maintain the integrity of existing collagen proteins, or other mechanism. A peptide could also affect nearby tissues or cells such as the bone, ligaments, muscle, tendons, bursa, connective tissue, blood vessels, peripheral nerves, osteoclasts, osteoblasts, fibroblasts, synoviocytes, monocytes/macrophages, lymphocytes, plasma cells, adipocytes, endothelial cells, neurons, ligaments, muscle, tendons, and bursa. The truncated or mutated peptides of the disclosure can be used to treat the symptoms of various conditions. The truncated or mutated peptides of the disclosure can bind to, home to, migrate to, accumulate in, be retained by, or be directed to cartilage and its components, including chondrocytes, extracellular matrix, collagen, hyaluronan, aggrecan (also known as cartilage-specific proteoglycan core protein (CSPCP)), or other components of the extracellular matrix and the joint, or to other nearby components such as those described herein in joints and cartilaginous tissues as listed above.

[0072] Also described herein are truncated or mutated peptides that selectively home, target, are directed to, migrate to, are retained by, or accumulate in and/or bind to specific regions, tissues, structures or cells of the cartilage that aid in managing, decreasing, ablating or reducing pain (e.g., joint pain) due to chronic disease or cartilage injury or other therapeutic indications as described herein. A truncated or mutated peptide that homes, targets, migrates to, is directed to, is retained by, or accumulates in and/or binds to one or more specific regions, tissues, structures or cells of the cartilage can have fewer off-target and potentially negative effects, for example, side effects that often limit use and efficacy of pain drugs. In addition, such truncated or mutated peptides can reduce dosage and increase the efficacy of existing drugs by directly targeting them to a specific region, tissue, structure or cell of the cartilage and helping the contact the cartilage or increasing the local concentration of agent. The truncated or mutated peptide itself can modulate pain or it can be complexed, conjugated, or fused to an agent that modulates pain. Such pain modulation may operate by various mechanisms such as modulating inflammation, autoimmune responses, direct or indirect

action on pain receptors, cell killing, or programmed cell death (whether via an apoptotic and/or non-apoptotic pathway of diseased cells or tissues, and the like (Tait et al., *J Cell Sci* 127(Pt 10):2135-44 (2014))).

[0073] Truncated or mutated peptides of this disclosure that home, target, are directed to, migrate to, are retained by, accumulate in, or bind to specific regions, tissues, structures or cells of the cartilage can do so with different degrees of efficiency. Truncated or mutated Peptides can have a higher concentration in cartilage than in other locations, such as blood or muscle. Peptides can be recorded as having a signal in cartilage as a percentage of signal in blood. For example, a cartilage signal of 200% indicates that the signal in cartilage is twice as high as the signal in blood. In some embodiments, peptides that have cartilage homing properties can have a cartilage signal of >170% by radiographic densitometry measurements. In other embodiments, peptides that are cartilage homers can have a cartilage signal of >200% by radiographic densitometry measurements. In other embodiments, peptides that are more efficient cartilage homers can have a cartilage signal of >300% by radiographic densitometry measurements. In other embodiments, peptides that are more efficient cartilage homers can have a cartilage signal of >400% by radiographic densitometry measurements. In other embodiments, peptides that are strongest cartilage homers of highest interest can have a cartilage signal of >500% by radiographic densitometry measurements. In some embodiments, measurement of the ratio of peptide concentration in blood, muscle, or other tissues relative to the peptide concentration in cartilage can be performed using various methods including measuring the densitometry signal of peptides labeled with radioisotopes (as described above), or by using other assays.

[0074] Truncated or mutated peptides that selectively home, target, are directed to, migrate to, are retained by, or accumulate in and/or bind to specific regions, tissues, structures or cells of the cartilage can occur after administration of the peptide to a subject. A subject can be a human or a non-human animal.

[0075] The truncated or mutated peptides disclosed herein can be used as active agents, or complexed, conjugated, or fused to detection agents such a fluorophores, iodide-containing X-ray contrast agents, lanthanide chelates (e. g., gadolinium for MRI imaging), perfluorocarbons (for ultrasound), or PET tracers (e. g., 18F or 11C) for imaging and tracing the truncated or mutated peptide, or complexed, conjugated, or fused to agents such as anti-inflammatory active agents or other active agents to the joint to treat inflammation or other disease.

[0076] The truncated or mutated peptides disclosed herein can be used to bind cartilage explants ex vivo. Cartilage explants can be from any subject, such as a human or an animal. Assessment

of truncated or mutated peptide binding to cartilage explants can be used to screen peptides that may efficiently home to cartilage in vivo

[0077] In some embodiments, truncated or mutated peptides of this disclosure home, target, are directed to, migrate to, are retained by, accumulate in, or bind to specific regions, tissues, structures or cells of the kidneys. For example, in some embodiments, truncated or mutated peptides of this disclosure home, target, are directed to, migrate to, are retained by, accumulate in, or bind to the proximal tubules of the kidneys, kidney nephrons, or podocytes. Peptides that selectively home, target, are directed to, migrate to, are retained by, or accumulate in and/or bind to specific regions, tissues, structures or cells of the kidney can occur after administration of the peptide to a subject. A subject can be a human or a non-human animal. The truncated or mutated peptides disclosed herein can be used as active agents, or complexed, conjugated, or fused to detection agents such as fluorophores, iodide-containing X-ray contrast agents, lanthanide chelates (e. g., gadolinium for MRI imaging), perfluorocarbons (for ultrasound), or PET tracers (e. g., ¹⁸F or ¹¹C) for imaging and tracing the truncated or mutated peptide, or complexed, conjugated, or fused to agents such as anti-inflammatory agents or other agents to the kidney to treat renal cancer, chronic kidney failure or other kidney disease.

[0078] One roadblock in the advancement and wide spread use of peptides as a therapeutic is that peptides can be chemically and physically unstable. During the process of manufacturing of therapeutic peptides essential considerations can include storage conditions, sustained biochemical function, and in vivo delivery. Peptide degradation products can result in the formation of species that alter the safety profile, potency, and immunogenicity of the peptide. These peptide degradation products can form during manufacture and storage, as well as in vivo after delivery to a patient. Furthermore, peptide degradation may limit the shelf-life and increase production cost due to unstable peptides requiring refrigeration or shipment on dry ice. The latter can necessitate continual monitoring and validation of peptides as degradation products could have formed during the manufacturing process. Hence, there is an urgent need for the rationale design and production of therapeutic peptides that have enhanced stability, for example, in the ambient environment, during the process of manufacturing, in storage, and that prevent the likelihood of peptide degradation under a variety of conditions.

[0079] In some embodiments, the truncated or mutated peptides and truncated or mutated peptide-drug conjugates of the present disclosure have stability properties that minimize truncated or mutated peptide or truncated or mutated peptide-drug conjugate degradation to enable adequate storage. Long term, accelerated, and intermediate storage conditions for the

truncated or mutated peptides and truncated or mutated peptide-drug conjugates of the present disclosure can include long term storage conditions of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$, or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ for at least 6 months, at least 12 months, and up to 1 year, up to 2 years, up to 3 years, up to 4 years, or longer than 4 years. In addition, intermediate and short term storage conditions (e.g., during transport, distribution, manufacturing, or handling), or long term storage conditions for certain climates and infrastructures, can include storage conditions of $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ or $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$ for up to 1 hour, for up to 8 hours, for up to 1 day, for up to 3 days, for up to 1 week, for up to 1 month, for up to 3 months, for up to 6 months or at least 6 months, up to 1 year, up to 2 years, up to 3 years, up to 4 years, or longer than 4 years. Moreover, the truncated or mutated peptides and truncated or mutated peptide-drug conjugates of the present disclosure can be refrigerated, for example between $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for at least 6 months, at least 12 months, and up to 1 year, up to 2 years, up to 3 years, up to 4 years, or longer than 4 years. In addition, intermediate and short term refrigeration conditions (e.g., during transport, distribution, manufacturing, or handling) can include $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ for up to 1 hour, for up to 8 hours, for up to 1 day, for up to 3 days, for up to 1 week, for up to 1 month, for up to 3 months, for up to 6 months or at least 6 months, and potentially longer (at least 12 months and up to 1 year, up to 2 years, up to 3 years, up to 4 years, or longer than 4 years). Such conditions for storage, whether based on ambient or refrigerated conditions can be adjusted based upon the four zones in the world (e.g., the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) stability Zone I, II, III, or IV) that are distinguished by their characteristic prevalent annual climatic conditions. In addition, formulation components can be principally chosen for their ability to preserve the native conformation and chemical structure of the peptides and peptide-drug conjugates of the present disclosure in storage by preventing denaturation due to hydrophobic interactions and aggregation, as well as by preventing chemical degradation, including truncation, oxidation, deamidation, cleavage, hydrolysis, isomerization, disulfide exchange, racemization, and beta elimination (Cleland, et al., *Crit Rev Ther Drug Carrier Syst* 10(4): 307-377 (1993); Shire et al., *J Pharm Sci* 93(6): 1390-1402 (2004); Wakankar and Borchardt, *J Pharm Sci* 95(11): 2321-2336 (2006)).

[0080] In some embodiments, the truncated or mutated peptides and truncated or mutated peptide-drug conjugates of the present disclosure have incorporated properties that minimize immunogenicity of the peptides and peptide-drug conjugates. Immunogenicity can be a major concern with the development of therapeutic peptides and proteins, and there is an urgent need for the rationale design and production of therapeutic peptides that have reduced

immunogenicity and that increase their safety and efficacy. Immunogenicity can occur against a desired peptide sequence or a peptide degradation product. Immunogenicity can occur when a patient develops an immune response to the therapeutic peptide, protein, conjugate, or other drug, such as by producing antibodies that bind to and/or neutralize the therapeutic peptide, protein, conjugate, or other drug. The likelihood of immunogenicity can increase when drugs are administered more than once or chronically. Immunogenicity can reduce patient exposure to the drug, can reduce effectiveness of the drug, and can also result in safety risks for the patient, such as generating an immune response to self-proteins or other adverse responses related to increased immunogenicity to the therapeutic peptide, protein, conjugate, or other drug. Immunogenic responses can vary from patient to patient and also amongst different groups of HLA alleles, as well as over time. As such, minimizing risk of immunogenicity with a therapeutic peptide or protein can be important for developing a drug that can be effectively and safely used for treatment. Various methods exist for assessment of immunogenic potential, which can include *in silico* methods, in vitro testing, preclinical in vivo testing, and assessment during clinical dosing. Evaluation early in product design and development of the therapeutic peptides and peptide-drug conjugates of the present disclosure in the in vivo milieu in which they function (e.g., in inflammatory environments or at physiologic pH) can reveal susceptibilities to modifications (e.g., aggregation and deamidation) that can result in loss of efficacy or induction of immune responses. Such information can be used to facilitate product engineering to enhance the stability of the product under such in vivo conditions or reduce immunogenicity. Moreover, the therapeutic truncated or mutated peptides and truncated or mutated peptide-drug conjugates of the present disclosure can be designed to minimize protein aggregation. Strategies to minimize aggregate formation can be used early in drug development, for example, by using an appropriate cell substrate, selecting manufacturing conditions that minimize aggregate formation, employing a robust purification scheme that removes aggregates to the greatest extent possible, and choosing a formulation and container closure system that minimize aggregation during storage.

[0081] Additional aspects and advantages of the present disclosure will become apparent to those skilled in this art from the following detailed description, wherein illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

[0082] As used herein, the abbreviations for the natural L-enantiomeric amino acids are conventional and are as follows: alanine (A, Ala); arginine (R, Arg); asparagine (N, Asn); aspartic acid (D, Asp); cysteine (C, Cys); glutamic acid (E, Glu); glutamine (Q, Gln); glycine (G, Gly); histidine (H, His); isoleucine (I, Ile); leucine (L, Leu); lysine (K, Lys); methionine (M, Met); phenylalanine (F, Phe); proline (P, Pro); serine (S, Ser); threonine (T, Thr); tryptophan (W, Trp); tyrosine (Y, Tyr); valine (V, Val). Typically, Xaa can indicate any amino acid. In some embodiments, X can be asparagine (N), glutamine (Q), histidine (H), lysine (K), or arginine (R).

[0083] Some embodiments of the disclosure contemplate D-amino acid residues of any standard or non-standard amino acid or analogue thereof. When an amino acid sequence is represented as a series of three-letter or one-letter amino acid abbreviations, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxyl terminal direction, in accordance with standard usage and convention.

Peptides

[0084] The cystine-dense peptides herein can bind targets with antibody-like affinity. The cystine-dense peptides can modulate the activity of a plurality of cartilage regions, tissues, structures or cells. For example, in some embodiments, the cystine-dense peptide complexed, conjugated, or fused to a bone-modifying drug homes to the cartilage of a diseased joint and releases the drug, creating a higher local concentration of drug in an area of eroded or damaged bone than would be achieved without the cartilage targeting function of the peptide. The cystine-dense peptide can be complexed, conjugated, or fused to a drug that can affect nearby tissues or cells such as the ligaments, muscle, tendons, bursa, connective tissue, blood vessels, peripheral nerves, osteoclasts, osteoblasts, fibroblasts, synoviocytes, monocytes/macrophages, lymphocytes, plasma cells, adipocytes, endothelial cells, neurons, ligaments, muscle, tendons, and bursa. The cystine-dense peptide complexed, conjugated, or fused to a drug can bind to, home to, migrate to, accumulate in, be retained by, or be directed to cartilage and its components, including chondrocytes, extracellular matrix, collagen of any type, hyaluronan, aggrecan (also known as cartilage-specific proteoglycan core protein (CSPCP)), proteoglycans, glycoasminoglycans, glycoproteins, decorin, biglycan, fibromodulin, or other components of the extracellular matrix and the joint, or to other nearby components such as those described herein in joints and cartilaginous tissues as listed above. Some of the cartilage regions, tissues, and structures that peptides and peptide-drug conjugates can target to treat a cartilage-associated disorder include: (a) elastic cartilage; (b) hyaline cartilage, such as articular cartilage and physeal cartilage; (c) fibrocartilage; and (d) any cells or cell types in (a) -(c) above. Some of the areas where the peptide and peptide-drug conjugates can target to treat a cartilage-

associated disorder include: cartilage includes joints such as knees, hips, or digits, nasal cartilage, spinal cartilage, tracheal cartilage, and rib cartilage. In various aspects, cartilage components include aggrecan and type II collagen. Additionally, in some embodiments, cystine-dense peptides can penetrate into cells. In other embodiments, cystine-dense peptides do not enter cells. In other embodiments, cystine-dense peptides exhibit more rapid clearance and cellular uptake compared to other types of molecules.

[0085] The peptides of the present disclosure can comprise cysteine amino acid residues. In some cases, the peptide has at least 4 cysteine amino acid residues. In some cases, the peptide has at least 6 cysteine amino acid residues. In other cases, the peptide has at least 8 cysteine amino acid residues, at least 10 cysteine amino acid residues, at least 12 cysteine amino acid residues, at least 14 cysteine amino acid residues or at least 16 cysteine amino acid residues.

[0086] A cystine-dense peptide can comprise disulfide bridges. A cystine-dense can be a peptide wherein 5% or more of the residues are cysteines forming intramolecular disulfide bonds as cystines. A disulfide-linked peptide can be a drug scaffold. In some embodiments, the disulfide bridges form an inhibitor knot. A disulfide bridge can be formed between cysteine residues, for example, between cysteines 1 and 4, 2 and 5, or, 3 and 6. In some cases, one disulfide bridge passes through a loop formed by the other two disulfide bridges, for example, to form the inhibitor knot. In other cases, the disulfide bridges can be formed between any two cysteine residues.

[0087] The present disclosure further includes peptide scaffolds that, e.g., can be used as a starting point for generating additional peptides that can target and home to cartilage. In some embodiments, these scaffolds can be derived from a variety of cystine-dense peptides. In certain embodiments, cystine-dense peptides are assembled into a complex tertiary structure that is characterized by a number of intramolecular disulfide crosslinks, and optionally contain beta strands and other secondary structures such as an alpha helix. For example, cystine-dense peptides include, in some embodiments, small disulfide-rich proteins characterized by a disulfide through disulfide knot. This knot can be, e.g., obtained when one disulfide bridge crosses the macrocycle formed by two other disulfides and the interconnecting backbone. In some embodiments, the cystine-dense peptides can include growth factor cysteine knots or inhibitor cysteine knots. Other possible peptide structures can include peptide having two parallel helices linked by two disulfide bridges without β - sheets (e.g., hefutoxin).

[0088] A cystine-dense peptide can comprise at least one amino acid residue in an L configuration. A cystine-dense peptide can comprise at least one amino acid residue in a D configuration. In some embodiments, a cystine-dense peptide is 15-40 amino acid residues long.

In other embodiments, a cystine-dense peptide is 11-57 amino acid residues long. In further embodiments, a cystine-dense peptide is at least 20 amino acid residues long.

[0089] In some embodiments, cartilage homing peptides are family members of the sequences GSXVXIXVKCXGSXQCLXPCKXAXGXRXGKCMNGKCXCXPXX (SEQ ID NO: 21) or XVXIXVKCXGSXQCLXPCKXAXGXRXGKCMNGKCXCXPXX (SEQ ID NO: 87), wherein each X can independently be any amino acid or amino acid analogue or null, in which these sequences are based on the most common elements found in the following sequences:

-VRIPVSCKHSGQCLKPCKDA-GMRFGKCMNGKCDCTPK- (SEQ ID NO: 198),
 GVPINVKCRGSRDCLDPCKKA-GMRFGKCINSKCHCTP-- (SEQ ID NO: 199), ---
 EVIRCSGSKQCYGPCKQQTGCTNSKCMNKVCKCYGCG (SEQ ID NO: 200),
 GVIINVKCKISRQCLEPCKKA-GMRFGKCMNGKCHCTPK- (SEQ ID NO: 201),
 GVPTDVKCRGSPQCIQPKCKDA-GMRFGKCMNGKCHCTPK- (SEQ ID NO: 202),
 GVPINVSTGSPQCIKPKCKDA-GMRFGKCMNRKCHCTPK- (SEQ ID NO: 203),
 -VGINVKCKHSGQCLKPCKDA-GMRFGKCINGKCDCTPK- (SEQ ID NO: 204),
 GVPINVRGSRDCLDPCRRRA-GMRFGRCINSRCHCTP-- (SEQ ID NO: 205; also disclosed herein as SEQ ID NO: 128; GS versions of SEQ ID NO: 205 and SEQ ID NO: 128 are shown in SEQ ID NO: 46 and SEQ ID NO: 149),

QKILSNRCNNSSECIPHICIRIFGTRAAKCINRKCYCYP-- (SEQ ID NO: 206),
 -VFINVKCRGSPECLPKCKEAIGKSAGKCMNGKCKCYP-- (SEQ ID NO: 207),
 -VPTDVKCRGSPQCIQPKCKDA-GMRFGKCMNGKCHCTP-- (SEQ ID NO: 208),
 --AEIIRCSGTRECYAPCQKLTGCLNAKCMNKACKCYGCV (SEQ ID NO: 209),
 -RPTDIKCSASYQCFPVCKSRFGKTNGRCVNGLCDCF--- (SEQ ID NO: 210),
 -QFTDVKCTGSKQCWPVCKQMFGKPNGKCMNGKCRCYS-- (SEQ ID NO: 211),
 -VGINVKCKHSRQCLKPCKDA-GMRFGKCTNGKCHCTPK- (SEQ ID NO: 212),
 -VVIGQRCYRSPDCYSACKKLVGKATGKCTNGRCDC---- (SEQ ID NO: 213),
 --NFKVEGACSKPCRKYCIDK-GARNGKCINGRCHCYY-- (SEQ ID NO: 214), and
 QIDTNVKCSGSSKCVKICIDRYNTRGAKCINGRCTCYP-- (SEQ ID NO: 215). Furthermore, peptides denoted as SEQ ID NO: 128 (also shown as SEQ ID NO: 205), and SEQ ID NO: 149 (also shown as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) are excluded from (or not included in) peptides comprising SEQ ID NO: 21 and SEQ ID NO: 87.

[0090] In some embodiments, the cartilage homing peptides are family members of the sequences GSXVXIXVRCXGSXQCLXPCRAXGXRXGRCMNGRCXCXPXX (SEQ ID NO: 22) or XVXIXVRCXGSXQCLXPCRAXGXRXGRCMNGRCXCXPXX (SEQ ID NO: 88)

wherein each X individually can be any amino acid or amino acid analogue or null, in which these sequences are based on the most common elements found in the following sequences and with K interchanged with R: SEQ ID NO: 198 – SEQ ID NO: 215.

[0091] In some embodiments, a peptide comprises the sequence

GSGVPIX¹VRCRGSRDCX²X³PCRRAGX⁴RFGRCIX⁵X⁶RCX⁷CX⁸P (SEQ ID NO: 23) or
GVPIX¹VRCRGSRDCX²X³PCRRAGX⁴RFGRCIX⁵X⁶RCX⁷CX⁸P (SEQ ID NO: 89), where the following residues where X¹ is selected from N, S, or G, wherein X² is selected from L or Y, wherein X³ is selected from D or E, wherein X⁴ is selected from M or T, wherein X⁵ is selected from N, Q, A, S, T, or L, wherein X⁶ is selected from S, G, or R, wherein X⁷ is selected from H or Y, and wherein X⁸ is selected from T or Y. In some embodiments, zero or one or more of the R residues in SEQ ID NO: 23 or SEQ ID NO: 89 can be replaced with K residues. In some embodiments, zero or one or more of the R residues in SEQ ID NO: 23 or SEQ ID NO: 89 can be replaced with A residues in any combination. In other embodiments, zero or one or more R residues in SEQ ID NO: 23 or SEQ ID NO: 89 can each be replaced with either a K or an A residue. In some embodiments, at least one but not all eight of the residues X¹ through X⁸ in SEQ ID NO: 23 or SEQ ID NO: 89 is excluded at the following residue at the denoted position: wherein X¹ is N, wherein X² is L, wherein X³ is D, wherein X⁴ is M, wherein X⁵ is N, wherein X⁶ is S, wherein X⁷ is H and wherein X⁸ is T. Furthermore, the following peptide (also denoted as SEQ ID NO: 128 or SEQ ID NO: 205, and SEQ ID NO: 149 or SEQ ID NO: 46 respectively) is excluded from (or not included in) the peptides of this disclosure: wherein all eight of the residues X¹ through X⁸ in of SEQ ID NO: 23 or SEQ ID NO: 89 include the following residues at the denoted position: X¹ is N, wherein X² is L, wherein X³ is D, wherein X⁴ is M, wherein X⁵ is N, wherein X⁶ is S, wherein X⁷ is H and wherein X⁸ is T. Furthermore, peptides denoted as SEQ ID NO: 128 (also shown as SEQ ID NO: 205), and SEQ ID NO: 149 (also shown as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) are excluded from (or not included in) peptides comprising SEQ ID NO: 23 and SEQ ID NO: 89.

[0092] In some embodiments, cartilage homing peptides are family members of the sequences

GSRCRGSRDCX¹X²PCRRAGX³RFGRCIX⁴X⁵RCX⁶CX⁷P (SEQ ID NO: 24) or
RCRGSRDCX¹X²PCRRAGX³RFGRCIX⁴X⁵RCX⁶CX⁷P (SEQ ID NO: 106), wherein X¹ is selected from L or Y, wherein X² is selected from D or E, wherein X³ is selected from M or T, wherein X⁴ is selected from N, Q, A, S, T, or L, wherein X⁵ is selected from S, G, or R, wherein X⁶ is selected from H or Y, and wherein X⁷ is selected from T or Y. Furthermore, peptides denoted as SEQ ID NO: 128 (also shown as SEQ ID NO: 205), and SEQ ID NO: 149 (also

shown as SEQ ID NO: 46) are excluded from (or not included in) peptides comprising SEQ ID NO: 24 and SEQ ID NO: 106. In some embodiments, cartilage homing peptides are family members of the sequences GSKCXGSXQCLXPCKXAXGXRXGKCMNGKCXCXPXX (SEQ ID NO: 25) or KCXGSXQCLXPCKXAXGXRXGKCMNGKCXCXPXX (SEQ ID NO: 107), wherein each X can individually be any amino acid or amino acid analogue or null. In some embodiments, cartilage homing peptides are family members of the sequences GSRCXGSXQCLXPCRAXGXRXGRCMNGRCXCXPXX (SEQ ID NO: 26) or RCXGSXQCLXPCRAXGXRXGRCMNGRCXCXPXX (SEQ ID NO: 108), wherein each X can individually be any amino acid or amino acid analogue or null.

[0093] In some embodiments, a peptide comprises the sequence

XVXIXVX₁CXGSXX₂CX₃X₄PCX₅XAXGX₆RXGX₇CX₈X₉X₁₀X₁₁CX₁₂CX₁₃P (SEQ ID NO: 219), wherein each X and X₁₋₁₃ are individually any amino acid or no amino acid and at least one of the following residues at the denoted position, more than one of the following residues at the denoted position, or all of the following residues at the denoted position is included in SEQ ID NO: 219: X₁ is K, X₂ is Q, X₃ is Y, X₄ is E, X₅ is K, X₆ is T, X₇ is K, X₈ is M, X₉ is Q, A, S, T, or L, X₁₀ is G, X₁₁ is K, X₁₂ is Y, or X₁₃ is Y or

GSXVXIXVX₁CXGSXX₂CX₃X₄PCX₅XAXGX₆RXGX₇CX₈X₉X₁₀X₁₁CX₁₂CX₁₃P (SEQ ID NO: 220), wherein each X and X₁₋₁₃ are individually any amino acid or no amino acid and at least one of the following residues at the denoted position, more than one of the following residues at the denoted position, or all of the following residues at the denoted position is included in SEQ ID NO: 220: X₁ is K, X₂ is Q, X₃ is Y, X₄ is E, X₅ is K, X₆ is T, X₇ is K, X₈ is M, X₉ is Q, A, S, T, or L, X₁₀ is G, X₁₁ is K, X₁₂ is Y, or X₁₃ is Y. SEQ ID NO: 219 and SEQ ID NO: 220 are variant consensus peptide sequences, included within the family of SEQ ID NO: 87 and SEQ ID NO: 21 consensus sequences, which variant consensus sequences include variants with further improved properties of the peptides as described herein, with or without an N-terminal GS. In some embodiments, at least two of the following residues at the denoted position, at least three of the following residues at the denoted position, at least four of the following residues at the denoted position, at least five of the following residues at the denoted position, at least six of the following residues at the denoted position, at least seven of the following residues at the denoted position, at least eight of the following residues at the denoted position, at least nine of the following residues at the denoted position, at least 10 of the following residues at the denoted position, at least 11 of the following residues at the denoted position, or at least 12 of the following residues at the denoted position are included in SEQ ID NO: 219 and SEQ ID NO:

220, respectively: X₁ is K, X₂ is Q, X₃ is Y, X₄ is E, X₅ is K, X₆ is T, X₇ is K, X₈ is M, X₉ is Q, A, S, T, or L, X₁₀ is G, X₁₁ is K, X₁₂ is Y, or X₁₃ is Y in SEQ ID NO: 219 and SEQ ID NO: 220.

[0094] In some embodiments, a peptide comprises the sequence

X₁CXGSXX₂CX₃X₄PCX₅XAXGX₆RXGX₇CX₈X₉X₁₀X₁₁CX₁₂CX₁₃P (SEQ ID NO: 221),

wherein each X and X₁₋₁₃ are individually any amino acid or no amino acid and at least one of the following residues at the denoted position, more than one of the following residues at the denoted position, or all of the following residues at the denoted position is included in SEQ ID NO: 221: X₁ is K, X₂ is Q, X₃ is Y, X₄ is E, X₅ is K, X₆ is T, X₇ is K, X₈ is M, X₉ is Q, A, S, T, or L, X₁₀ is G, X₁₁ is K, X₁₂ is Y, or X₁₃ is Y or

GSX₁CXGSXX₂CX₃X₄PCX₅XAXGX₆RXGX₇CX₈X₉X₁₀X₁₁CX₁₂CX₁₃P (SEQ ID NO: 222),

wherein each X and X₁₋₁₃ are individually any amino acid or no amino acid and at least one of the following residues at the denoted position, more than one of the following residues at the denoted position, or all of the following residues at the denoted position is included in SEQ ID NO: 222: X₁ is K, X₂ is Q, X₃ is Y, X₄ is E, X₅ is K, X₆ is T, X₇ is K, X₈ is M, X₉ is Q, A, S, T, or L, X₁₀ is G, X₁₁ is K, X₁₂ is Y, or X₁₃ is Y. SEQ ID NO: 221 and SEQ ID NO: 222 are variant consensus peptide sequences, included within the family of SEQ ID NO: 87 and SEQ ID NO: 21 consensus sequences, which variant consensus sequences include truncated variants with further improved properties of some of the peptides and fragments of the peptides of the disclosure as described herein, with or without an N-terminal GS. Furthermore, peptides denoted as SEQ ID NO: 128 (also shown as SEQ ID NO: 205), and SEQ ID NO: 149 (also shown as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) are excluded from (or not included in) peptides comprising SEQ ID NO: 221 and SEQ ID NO: 222. In some embodiments, at least two of the following residues at the denoted position, at least three of the following residues at the denoted position, at least four of the following residues at the denoted position, at least five of the following residues at the denoted position, at least six of the following residues at the denoted position, at least seven of the following residues at the denoted position, at least eight of the following residues at the denoted position, at least nine of the following residues at the denoted position, at least 10 of the following residues at the denoted position, at least 11 of the following residues at the denoted position, or at least 12 of the following residues at the denoted position are included in SEQ ID NO: 221 or SEQ ID NO: 222, respectively: X₁ is K, X₂ is Q, X₃ is Y, X₄ is E, X₅ is K, X₆ is T, X₇ is K, X₈ is M, X₉ is Q, A, S, T, or L, X₁₀ is G, X₁₁ is K, X₁₂ is Y, or X₁₃ is Y in SEQ ID NO: 221 and SEQ ID NO: 222.

[0095] In some embodiments, a peptide comprises the sequence

KCRGSRQCX¹X²PCKRAX⁸GX³RFGKCMX⁴X⁵KCX⁶CX⁷P (SEQ ID NO: 223) or GSKCRGSRQCX¹X²PCKRAX⁸GX³RFGKCMX⁴X⁵KCX⁶CX⁷P (SEQ ID NO: 224), wherein X¹ is selected from L or Y, wherein X² is selected from D or E, wherein X³ is selected from M or T, wherein X⁴ is selected from N, Q, A, S, T, or L, wherein X⁵ is selected from S, G, or R, wherein X⁶ is selected from H or Y, wherein X⁷ is selected from T or Y, and X⁸ is any amino acid or null. SEQ ID NO: 223 and SEQ ID NO: 224 are variant consensus sequences, and include variants with further improved properties of some of the peptides and fragments of the peptides of the disclosure, with or without an N-terminal GS.

[0096] In some embodiments, a peptide comprises the sequence

XVXIXVKCRGSRQCX¹X²PCKRAX⁸GX³RFGKCMX⁴X⁵KCX⁶CX⁷P (SEQ ID NO: 225) or GSXVXIXVKCRGSRQCX¹X²PCKRAX⁸GX³RFGKCMX⁴X⁵KCX⁶CX⁷P (SEQ ID NO: 226), wherein X¹ is selected from L or Y, wherein X² is selected from D or E, wherein X³ is selected from M or T, wherein X⁴ is selected from N, Q, A, S, T, or L, wherein X⁵ is selected from S, G, or R, wherein X⁶ is selected from H or Y, wherein X⁷ is selected from T or Y, and X⁸ is any amino acid or null. SEQ ID NO: 225 and SEQ ID NO: 226 are variant consensus sequences, and include variants with further improved properties of some of the peptides and fragments of the peptides of the disclosure, with or without an N-terminal GS.

[0097] In some embodiments, a peptide comprises the sequence

KCRGSRDCLDPCKKAGMRFGKCINSKCHCTP (SEQ ID NO: 109), with or without an N-terminal GS. Furthermore, peptides denoted as SEQ ID NO: 150 and SEQ ID NO: 199 (non-GS version of SEQ ID NO: 150) are excluded from (or not included in) peptides comprising SEQ ID NO: 109.

[0098] In some embodiments, a peptide is a fragment comprising the sequence GRCINSRC (SEQ ID NO: 227).

[0099] In some embodiments, a peptide is a fragment comprising the sequence GRCIXXRC (SEQ ID NO: 228), wherein each X can independently be any amino acid or amino acid analogue or null.

[0100] In some embodiments, a peptide is a fragment comprising the sequence GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N, Q, A, S, T or L and X²=S, G, or R.

[0101] In some embodiments, a peptide is a fragment comprising the sequence PCR (SEQ ID NO: 230).

[0102] In some embodiments, a peptide is a fragment comprising the sequence CLDPCRRRA (SEQ ID NO: 231).

[0103] In some embodiments, a peptide is a fragment comprising the sequence CLDPCR (SEQ ID NO: 232).

[0104] In some embodiments, a peptide is a fragment comprising the sequence RCRGSRDC (SEQ ID NO: 257).

[0105] In some embodiments, a peptide is a fragment comprising the sequence PCRRAG (SEQ ID NO: 258).

[0106] In some embodiments, a peptide is a fragment comprising the sequence RFGRCI (SEQ ID NO: 259).

[0107] The peptide fragments disclosed herein can be used as immunogenic epitopes (i.e., for the creation of antibodies, antibody fragments or CDRs that would bind such fragments) or otherwise used to identify the peptides of the disclosure, or screen additional related variants to the peptides of the disclosure from expression libraries and the like, or to purify the peptides of the disclosure, using variety of methods known in the art including western blot, affinity chromatography, FACS, and the like. Moreover, polynucleotide sequences to such fragments can be used as molecular probes or in PCR screens to isolate and identify polynucleotides encoding the peptides of the present invention or screen additional related variants to the peptides of the disclosure from expression libraries and the like. For example, the fragments of SEQ ID NO: 227 – SEQ ID NO: 232, and SEQ ID NO: 257 – SEQ ID NO: 259 can be used for this purpose.

[0108] The N-terminal GS sequence can be included or excluded between the peptides of the present disclosure.

[0109] Moreover certain small fragments identified herein are conserved or functional peptide sequences or peptide domains that can be used to create further variant peptides of the disclosure with enhanced functionality with respect to immunogenicity, stability, manufacturability, cartilage binding, and the like as disclosed herein. For example, the following fragments can be used to enhance the functionality of a peptide comprising SEQ ID NO: 28, SEQ ID NO: 45 - SEQ ID NO: 51, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 128 - SEQ ID NO: 133, SEQ ID NO: 149, or SEQ ID NO: 260 - SEQ ID NO: 263 and includes one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N, Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null, the peptide having one or more of the

foregoing peptide fragments located at the corresponding location in the peptide relative to those fragments (or with reference to those fragments) as located within SEQ ID NO: 128 or SEQ ID NO: 149, SEQ ID NO: 28, SEQ ID NO: 109, SEQ ID NO: 150, SEQ ID NO: 199, SEQ ID NO: 110, SEQ ID NO: 127, SEQ ID NO: 260 or SEQ ID NO: 262, , with or without an N-terminal GS (for example, using a sequence alignment or other methodology). Moreover certain fragments identified herein are conserved or functional peptide sequences or peptide domains that can be incorporated into variant peptides of the disclosure to enhanced functionality with respect to cartilage homing, stability, manufacturability, cartilage binding, and the like as disclosed herein. For example, the following fragments can be used to enhance the functionality of a peptide comprising SEQ ID NO: 27, SEQ ID NO: 29 – SEQ ID NO: 44, SEQ ID NO: 52 – SEQ ID NO: 66, SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 256, and SEQ ID NO: 21 – SEQ ID NO: 26, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 108, SEQ ID NO: 219 – SEQ ID NO: 226 and includes one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRRA (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259), the peptide having one or more foregoing fragment sequences located at such corresponding location within the peptide of any one of SEQ ID NO: 87, SEQ ID NO: 89 or SEQ ID NO: 106, SEQ ID NO: 109, SEQ ID NO: 150, SEQ ID NO: 199, SEQ ID NO: 110, SEQ ID NO: 219 or SEQ ID NO: 221, or SEQ ID NO: 224 or SEQ ID NO: 226, with or without an N-terminal GS (for example, using a sequence alignment or other methodology).

[0110] In some embodiments, a peptide of the present disclosure comprises one or more of the following peptide fragments within its sequence: GKCINKKCKC (SEQ ID NO: 90); KCIN (SEQ ID NO: 91); KKCK (SEQ ID NO: 92); PCKR (SEQ ID NO: 93); KRCSRR (SEQ ID NO: 94); KQC (SEQ ID NO: 95); GRCINRRRCRC (SEQ ID NO: 96); RCIN (SEQ ID NO: 97); RRRCR (SEQ ID NO: 98); PCRR (SEQ ID NO: 99); RRCSRR (SEQ ID NO: 100); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); KKCSKK (SEQ ID NO: 103); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCINSRC (SEQ ID NO: 227), GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null, GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R (SEQ ID NO: 229), PCR (SEQ ID NO: 230), CLDPCRRA (SEQ ID NO: 231), CLDPCRR (SEQ

ID NO: 232), RCRGSRDC (SEQ ID NO: 257), PCRRAG (SEQ ID NO: 258), and RFGRCI (SEQ ID NO: 259). In another embodiment, the peptide of the present disclosure comprises a peptide 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to any of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 256 and further comprises one or more of the following peptide fragments within its sequence: GKCINKKCKC (SEQ ID NO: 90); KCIN (SEQ ID NO: 91); KKCK (SEQ ID NO: 92); PCKR (SEQ ID NO: 93); KRCSRR (SEQ ID NO: 94); KQC (SEQ ID NO: 95); GRCINRRRCRC (SEQ ID NO: 96); RCIN (SEQ ID NO: 97); RRCR (SEQ ID NO: 98); PCRR (SEQ ID NO: 99); RRCSSR (SEQ ID NO: 100); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102), KKCSKK (SEQ ID NO: 103), GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCINSRC (SEQ ID NO: 227), GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null, GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R (SEQ ID NO: 229), PCR (SEQ ID NO: 230), CLDPCRR (SEQ ID NO: 231), CLDPCRR (SEQ ID NO: 232), RCRGSRDC (SEQ ID NO: 257), PCRRAG (SEQ ID NO: 258), and RFGRCI (SEQ ID NO: 259). In another embodiment, the peptide having one or more of the foregoing peptide fragments within its sequence has the fragment sequences located at the corresponding location in the peptide relative to those fragments (or with reference to those fragments) as located within SEQ ID NO: 128 or SEQ ID NO: 149 (for example, using a sequence alignment or other methodology) (SEQ ID NO: 149 is also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205). In another embodiment, the fragment sequences disclosed herein are located at such corresponding location within the peptide of any one of SEQ ID NO: 21 – SEQ ID NO: 26, SEQ ID NO: 220, SEQ ID NO: 222, SEQ ID NO: 224, SEQ ID NO: 226. In another embodiment, the fragment sequences disclosed herein are located at such corresponding location within the peptide of any one of SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 108, SEQ ID NO: 219, SEQ ID NO: 221, SEQ ID NO: 223, SEQ ID NO: 225. In another embodiment, the fragment sequences disclosed herein are located at such corresponding location within the peptide of any one of SEQ ID NO: 87, SEQ ID NO: 89 or SEQ ID NO: 106, SEQ ID NO: 110, SEQ ID NO: 219 or SEQ ID NO: 221, or SEQ ID NO: 260 or SEQ ID NO: 262 (for example, using a sequence alignment or other methodology).

[0111] In some embodiments, any peptide disclosed herein having an N-terminal GS sequence can have further have one or more of a mutation or corresponding substitution selected from the

group consisting of N7S, D18E, M25T, N32Q, N32A, N32S, N32T, N32L, S33G, S33R, L17Y, H36Y, and T38Y.

[0112] In some embodiments, any peptide disclosed herein without an N-terminal GS sequence can have further have one or more of a mutation or corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, and T36Y.

[0113] In some embodiments, any peptide disclosed herein without an N-terminal GS sequence can have further have one or more of a mutation or corresponding substitution selected from the group consisting of D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K and R26K.

[0114] In some embodiments, any peptide disclosed herein having an N-terminal GS sequence can have further have one or more of a mutation or corresponding substitution selected from the group consisting of D12E, M19T, N26Q, N26A, N26S, N26T, N26L, S27G, S27R, L11Y, H30Y, T32Y, R3K, R15K, R16K, R23K and R28K.

[0115] **TABLE 1** lists some exemplary peptides according to the present disclosure.

TABLE 1 – Exemplary Amino Acid Sequences

SEQ ID NO:	Amino Acid Sequence
SEQ ID NO: 27	GSKCRGSRDCLDPCKKAGMRFGKCINSKCHCTP
SEQ ID NO: 28	GSRCRGSRDCLDPERRAGMRFGRCINSRCHCTP
SEQ ID NO: 29	GSRCRGSRDCLEPCRRAGTRFGRCINGRCHCTP
SEQ ID NO: 30	GSRCRGSRDCLEPCRRAGTRFGRCINRRCHCTP
SEQ ID NO: 31	GSRCRGSRDCLEPCRRAGTRFGRCINSRCHCTP
SEQ ID NO: 32	GSRCRGSRDCLEPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 33	GSRCRGSRDCLEPCRRAGTRFGRCIQSRCHCYP
SEQ ID NO: 34	GSRCRGSRDCYEPERRAGTRFGRCIQSRCHCTP
SEQ ID NO: 35	GSRCRGSRDCLEPCRRAGTRFGRCIQSRCYCTP
SEQ ID NO: 36	GSRCRGSRDCLEPCRRAGTRFGRCIASRCHCYP
SEQ ID NO: 37	GSRCRGSRDCLEPCRRAGTRFGRCISSRCHCYP
SEQ ID NO: 38	GSRCRGSRDCLEPCRRAGTRFGRCITSRCHCYP
SEQ ID NO: 39	GSKCRGSRDCLDPERRAGMRFGRCINSRCHCTP
SEQ ID NO: 40	GSRCRGSRDCLDPCKRAGMRFGRCINSRCHCTP
SEQ ID NO: 41	GSRCRGSRDCLDPCKKAGMRFGRCINSRCHCTP
SEQ ID NO: 42	GSRCRGSRDCLDPERRAGMRFGKCINSRCHCTP
SEQ ID NO: 43	GSRCRGSRDCLDPERRAGMRFGRCINSKCHCTP
SEQ ID NO: 44	GSRCRGSRDCLEPCRRAGTRFGRCINSRCHCYP
SEQ ID NO: 45	GSSGVPINVRGSRDCLDPERRAGMRFGRCINSRCHCTP
SEQ ID NO: 46	GSGVPINVRGSRDCLDPERRAGMRFGRCINSRCHCTP
SEQ ID NO: 47	GSVPINVRGSRDCLDPERRAGMRFGRCINSRCHCTP
SEQ ID NO: 48	GSPINVRGSRDCLDPERRAGMRFGRCINSRCHCTP

SEQ ID NO:	Amino Acid Sequence
SEQ ID NO: 49	GSINVRCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 50	GSNVRCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 51	GSVRCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 52	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCINGRCHCTP
SEQ ID NO: 53	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 54	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCINRRCHCTP
SEQ ID NO: 55	GSGVPINVRCSRDCLDPCRRAGTRFGRCINSRCHCTP
SEQ ID NO: 56	GSGVPINVRCSRDCLDPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 57	GSGVPINVRCSRDCLDPCRRAGTRFGRCIQSRCHCYP
SEQ ID NO: 58	GSGVPINVRCSRDCLDPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 59	GSGVPINVRCSRDCLDPCRRAGTRFGRCIQSRCYCTP
SEQ ID NO: 60	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCYP
SEQ ID NO: 61	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 62	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCIQSRCYCTP
SEQ ID NO: 63	GSGVPINVRCSRDCLDPCRRAGTRFGRCIASRCHCYP
SEQ ID NO: 64	GSGVPINVRCSRDCLDPCRRAGTRFGRCISSRCHCYP
SEQ ID NO: 65	GSGVPINVRCSRDCLDPCRRAGTRFGRCITSRCHCYP
SEQ ID NO: 66	GSGVPINVRCSRDCLDPCRRAGTRFGRCINSRCHCYP
SEQ ID NO: 109	KCRGSRDCLDPCRRAGMRFGKCINSKCHCTP
SEQ ID NO: 110	RCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 111	RCRGSRDCLDPCRRAGTRFGRCINGRCHCTP
SEQ ID NO: 112	RCRGSRDCLDPCRRAGTRFGRCINRRCHCTP
SEQ ID NO: 113	RCRGSRDCLDPCRRAGTRFGRCINSRCHCTP
SEQ ID NO: 114	RCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 115	RCRGSRDCLDPCRRAGTRFGRCIQSRCHCYP
SEQ ID NO: 116	RCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 117	RCRGSRDCLDPCRRAGTRFGRCIQSRCYCTP
SEQ ID NO: 118	RCRGSRDCLDPCRRAGTRFGRCIASRCHCYP
SEQ ID NO: 119	RCRGSRDCLDPCRRAGTRFGRCISSRCHCYP
SEQ ID NO: 120	RCRGSRDCLDPCRRAGTRFGRCITSRCHCYP
SEQ ID NO: 121	KCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 122	RCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 123	RCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 124	RCRGSRDCLDPCRRAGMRFGKCINSRCHCTP
SEQ ID NO: 125	RCRGSRDCLDPCRRAGMRFGRCINSKCHCTP
SEQ ID NO: 126	RCRGSRDCLDPCRRAGTRFGRCINSRCHCYP
SEQ ID NO: 127	SGVPINVRCSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 128	GVPINVRCSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 129	VPINVRCSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 130	PINVRCSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 131	INVRCSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 132	NVRCSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 133	VRCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
SEQ ID NO: 134	GVPIVRCRGSRDCLDPCRRAGTRFGRCINGRCHCTP
SEQ ID NO: 135	GVPIVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP

SEQ ID NO:	Amino Acid Sequence
SEQ ID NO: 136	GVPISVRCRGSRDCLPCRRAGTRFGRCINRRCHCTP
SEQ ID NO: 137	GVPINVRCRGSRDCLPCRRAGTRFGRCINSRCHCTP
SEQ ID NO: 138	GVPINVRCRGSRDCLPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 139	GVPINVRCRGSRDCLPCRRAGTRFGRCIQSRCHCYP
SEQ ID NO: 140	GVPINVRCRGSRDCLPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 141	GVPINVRCRGSRDCLPCRRAGTRFGRCIQSRCHCYP
SEQ ID NO: 142	GVPISVRCRGSRDCLPCRRAGTRFGRCIQSRCHCYP
SEQ ID NO: 143	GVPISVRCRGSRDCLPCRRAGTRFGRCIQSRCHCTP
SEQ ID NO: 144	GVPISVRCRGSRDCLPCRRAGTRFGRCIQSRCHCYP
SEQ ID NO: 145	GVPINVRCRGSRDCLPCRRAGTRFGRCIASRCHCYP
SEQ ID NO: 146	GVPINVRCRGSRDCLPCRRAGTRFGRCISSRCHCYP
SEQ ID NO: 147	GVPINVRCRGSRDCLPCRRAGTRFGRCITSRCHCYP
SEQ ID NO: 148	GVPINVRCRGSRDCLPCRRAGTRFGRCINSRCHCYP
SEQ ID NO: 233	RCRGSRDCLPCRRAGTRFGRCILSRCHCTP
SEQ ID NO: 234	RCRGSRDCLPCRRAGTRFGRCILSRCHCYP
SEQ ID NO: 235	RCRGSRDCLPCRRAGTRFGRCILSRCHCYP
SEQ ID NO: 236	RCRGSRDCLPCRRAGMRFGRCIQSRCHCTP
SEQ ID NO: 237	RCRGSRDCLPCRRAGMRFGRCIASRCHCTP
SEQ ID NO: 238	RCRGSRDCLPCRRAGMRFGRCISSRCHCTP
SEQ ID NO: 239	RCRGSRDCLPCRRAGMRFGRCITSRCHCTP
SEQ ID NO: 240	RCRGSRDCLPCRRAGMRFGRCILSRCHCTP
SEQ ID NO: 241	GSGVPINVRCRGSRDCLPCRRAGTRFGRCILSRCHCTP
SEQ ID NO: 242	GSGVPINVRCRGSRDCLPCRRAGTRFGRCILSRCHCYP
SEQ ID NO: 243	GSGVPINVRCRGSRDCLPCRRAGTRFGRCILSRCHCYP
SEQ ID NO: 244	GSGVPINVRCRGSRDCLPCRRAGMRFGRCIQSRCHCTP
SEQ ID NO: 245	GSGVPINVRCRGSRDCLPCRRAGMRFGRCIASRCHCTP
SEQ ID NO: 246	GSGVPINVRCRGSRDCLPCRRAGMRFGRCISSRCHCTP
SEQ ID NO: 247	GSGVPINVRCRGSRDCLPCRRAGMRFGRCITSRCHCTP
SEQ ID NO: 248	GSGVPINVRCRGSRDCLPCRRAGMRFGRCILSRCHCTP
SEQ ID NO: 249	GVPINVRCRGSRDCLPCRRAGTRFGRCILSRCHCTP
SEQ ID NO: 250	GVPINVRCRGSRDCLPCRRAGTRFGRCILSRCHCYP
SEQ ID NO: 251	GVPINVRCRGSRDCLPCRRAGTRFGRCILSRCHCYP
SEQ ID NO: 252	GVPINVRCRGSRDCLPCRRAGMRFGRCIQSRCHCTP
SEQ ID NO: 253	GVPINVRCRGSRDCLPCRRAGMRFGRCIASRCHCTP
SEQ ID NO: 254	GVPINVRCRGSRDCLPCRRAGMRFGRCISSRCHCTP
SEQ ID NO: 255	GVPINVRCRGSRDCLPCRRAGMRFGRCITSRCHCTP
SEQ ID NO: 256	GVPINVRCRGSRDCLPCRRAGMRFGRCILSRCHCTP
SEQ ID NO: 260	RCRGSRDCLPCRRAGMRFGRCINSRCHC
SEQ ID NO: 261	GSRCRGSRDCLPCRRAGMRFGRCINSRCHC
SEQ ID NO: 262	RCRGSRDCLPCRRAGMRFGRCINSRCHCT
SEQ ID NO: 263	GSRCRGSRDCLPCRRAGMRFGRCINSRCHCT

[0116] In some embodiments, a peptide of the present disclosure comprises at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least

58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 85.5%, at least 86%, at least 86.5%, at least 87%, at least 87.5%, at least 88%, at least 88.5%, at least 89%, at least 89.5%, at least 90%, at least 90.5%, at least 91%, at least 91.5%, at least 92%, at least 92.5%, at least 93%, at least 93.5%, at least 94%, at least 94.5%, at least 95%, at least 95.5%, at least 96%, at least 96.5%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, or 100% sequence identity with any one of SEQ ID NO: 89, SEQ ID NO: 106, SEQ ID NO: 221, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 219, SEQ ID NO: 223, SEQ ID NO: 225, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 220, SEQ ID NO: 222, SEQ ID NO: 224, SEQ ID NO: 226, SEQ ID NO: 109 – SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, SEQ ID NO: 262, SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 – SEQ ID NO: 256, SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 241 – SEQ ID NO: 248, SEQ ID NO: 261, and SEQ ID NO: 263, or SEQ ID NO: 209 – SEQ ID NO: 215. In some embodiments, a peptide of the present disclosure has at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 85.5%, at least 86%, at least 86.5%, at least 87%, at least 87.5%, at least 88%, at least 88.5%, at least 89%, at least 89.5%, at least 90%, at least 90.5%, at least 91%, at least 91.5%, at least 92%, at least 92.5%, at least 93%, at least 93.5%, at least 94%, at least 94.5%, at least 95%, at least 95.5%, at least 96%, at least 96.5%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, or 100% sequence identity with a sequence selected from the group consisting of SEQ ID NO: 89, SEQ ID NO: 106, SEQ ID NO: 221, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 219, SEQ ID NO: 223, SEQ ID NO: 225, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 220, SEQ ID NO: 222, SEQ ID NO: 224, SEQ ID NO: 226, SEQ ID NO: 109 – SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, SEQ ID NO: 262, SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO:

148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256, SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 241 – SEQ ID NO: 248, SEQ ID NO: 261, and SEQ ID NO: 263, and SEQ ID NO: 209 – SEQ ID NO: 215. In some embodiments, a peptide of the present disclosure consists of a sequence selected from the group consisting of SEQ ID NO: 89, SEQ ID NO: 106, SEQ ID NO: 221, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 219, SEQ ID NO: 223, SEQ ID NO: 225, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 220, SEQ ID NO: 222, SEQ ID NO: 224, SEQ ID NO: 226, SEQ ID NO: 109 – SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, SEQ ID NO: 262, SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256, SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 241 – SEQ ID NO: 248, SEQ ID NO: 261, and SEQ ID NO: 263, and SEQ ID NO: 209 – SEQ ID NO: 215.

[0117] In some embodiments, any peptide of the present disclosure further comprises a joining sequence. A joining sequence can be at the N-terminus or the C-terminus. In some embodiments, the joining sequence comprises of one or more amino acid residues and is located immediately adjacent to the N-terminus or the C-terminus of the peptide. A joining sequence can be at least 1 amino acid residue, at least 2 amino acid residues at least 1 amino acid residues, at least 2 amino acid residues, at least 3 amino acid residues, at least 4 amino acid residues, at least 5 amino acid residues, at least 6 amino acid residues, at least 7 amino acid residues, at least 8 amino acid residues, at least 9 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 35 amino acid residues, at least 40 amino acid residues, at least 45 amino acid residues, at least 50 amino acid residues, at least 55 amino acid residues, at least 60 amino acid residues, at least 65 amino acid residues, at least 70 amino acid residues, at least 75 amino acid residues, at least 80 amino acid residues, at least 85 amino acid residues, at least 90 amino acid residues, at least 95 amino acid residues, up and including 100 amino acid residues, from 1 to 5 amino acid residues, from 5 to 10 amino acid residues, from 10 to 15 amino acid residues, from 15 to 20 amino acid residues, from 20 to 25 amino acid residues, from 25 to 30 amino acid residues, from 30 to 35 amino acid residues, from 35 to 40 amino acid residues, from 40 to 45 amino acid residues, from 45 to 50 amino acid residues, from 50 to 55 amino acid residues, from 55 to 60 amino acid residues, from 60 to 65 amino acid residues, from 65 to 70 amino acid residues, from 70 to 75 amino acid residues, from 75 to 80 amino acid residues, from 80 to 85 amino acid residues, from 85 to 90 amino acid residues, from 90 to 95 amino acid residues, from

95 to 100 amino acid residues, from 1 to 100 amino acid residues, from 5 to 100 amino acid residues, from 20 to 80 amino acid residues, or from 1 to 10 amino acid residues.

[0118] A joining sequence can be immediately adjacent to the N-terminus, the C-terminus, or the N-terminus and the C-terminus of a peptide disclosed herein. Residues located in the joining sequence immediately adjacent to the N-terminus of a peptide are referred to as N-1 (the residue immediately N-terminally of the peptide), N-2 (the residue immediately N-terminally of the N-1 residue), N-3 (the residue immediately N-terminally of the N-2 residue), N-4 (the residue immediately N-terminally of the N-3 residue), N-5 (the residue immediately N-terminally of the N-4 residue), N-6 (the residue immediately N-terminally of the N-5 residue), and so on and so forth. In other words, if a joining sequence is placed at the N-terminus of the peptide, the last residue (reading from left to right, or N-terminus to C-terminus) of said joining sequence is the N-1 residue, the second to last residue of said joining sequence is the N-2 residue, the third to last residue of said joining sequence is the N-3, the fourth to last residue of said joining sequence is the N-4 residue, the fifth to last residue of said joining sequence is the N-5 residue, the sixth to last residue of said joining sequence is the N-6 residue, and so on and so forth.

[0119] Residues located in the joining sequence immediately adjacent to the C-terminus of a peptide are referred to as C+1 (the residue immediately C-terminally of the peptide), C+2 (the residue immediately C-terminally of the C+1 residue), C+3 (the residue immediately C-terminally of the C+2 residue), C+4 (the residue immediately C-terminally of the C+3 residue), C+5 (the residue immediately C-terminally of the C+4 residue), C+6 (the residue immediately C-terminally of the C+5 residue), and so on and so forth. In other words, if a joining sequence is placed at the C-terminus of the peptide, the first residue (reading from left to right, or N-terminus to C-terminus) of said joining sequence is the C+1 residue, the second residue of said joining sequence is the C+2 residue, the third residue of said joining sequence is the C+3, the fourth residue of said joining sequence is the C+4 residue, the fifth residue of said joining sequence is the C+5 residue, the sixth residue of said joining sequence is the C+6 residue, and so on and so forth.

[0120] In some embodiments, the peptide has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of: a) SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at the C-terminus of the joining sequence is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; b) SEQ ID NO: 129, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the

joining sequence is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; c) SEQ ID NO: 130, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the joining sequence is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; d) SEQ ID NO: 131, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the joining sequence is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; e) SEQ ID NO: 132, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the joining sequence is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; f) SEQ ID NO: 133, wherein the peptide further comprises a joining sequence at the N-terminus, and wherein a last residue at a C-terminus of the joining sequence is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H; g) SEQ ID NO: 260, wherein the peptide further comprises a joining sequence at the C-terminus, and wherein a first residue at an N-terminus of the joining sequence is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or h) SEQ ID NO: 262, wherein the peptide further comprises a joining sequence at the C-terminus, and wherein a first residue at an N-terminus of the joining sequence is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

[0121] In any of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 or fragment thereof, any one or more K residues can be replaced by an R residue or an A residue, any one or more R residues can be replaced by a K residue or an A residue, any one or more A residues can be replaced by a K residue or an R residue, all K residues can be replaced by R residues or A residues, all but one K residue can be replaced by R or A residues, all but two K residues can be replaced by R residues or A residues, or in any combination thereof. In any of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 or any fragment thereof, any one or more M residues can be replaced by any one of I, L, or V residues, any one or more L residues can be replaced by any one of V, I, or M residues, any one or more I residues can be replaced by any one of M, L, or V residues, or any one or more V residues can be replaced by any one of I, L, or M residues. In any embodiment, at least one of the amino acids alone or in combination can be interchanged in the peptides or peptide fragments as follows:

K/R, M/ I/ L/V, G/A, S/T, Q/N, and D/E wherein each letter is each individually any amino acid or amino acid analogue. In some instances, the peptide can contain only one lysine residue, or no lysine residue. In any of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 or fragment thereof, any amino acid can be replaced with citrulline. In any of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 or any fragment thereof, X can independently be any number of any amino acid or no amino acid. In some cases, a peptide can include the first two N-terminal amino acids GS, as with peptides of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 220, SEQ ID NO: 222, SEQ ID NO: 224, SEQ ID NO: 226, SEQ ID NO: 241 – SEQ ID NO: 248, SEQ ID NO: 261, and SEQ ID NO: 263 or such N-terminal amino acids (GS) can be substituted by any other one or two amino acids. In other cases, a peptide does not include the first two N-terminal amino acids GS, as with peptides of SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 108, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219, SEQ ID NO: 221, SEQ ID NO: 223, SEQ ID NO: 225, SEQ ID NO: 233- SEQ ID NO: 240, SEQ ID NO: 249 – SEQ ID NO: 256, SEQ ID NO: 260, and SEQ ID NO: 262. In some cases, the N-terminus of the peptide is blocked, such as by an acetyl group; in other instances the C-terminus of the peptide is block, such as by an amide group.

[0122] In some instances, the peptide is any one of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 or a functional fragment thereof. In other embodiments, the peptide of the disclosure further comprises a peptide with 99%, 95%, 90%, 85%, or 80% homology to any one of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263. In further embodiments, the peptide fragment comprises a contiguous fragment of any one of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID

NO: 219 – SEQ ID NO: 263 that is at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46 residues long, wherein the peptide fragment is selected from any portion of the peptide. In some embodiments, such peptide fragments contact the cartilage and exhibit properties of those described herein for peptide and peptide-active agent conjugates.

[0123] The peptides of the present disclosure can further comprise negative amino acid residues. In some cases, the peptide has 2 or fewer negative amino acid residues. In other cases, the peptide has 4 or fewer negative amino acid residues, 3 or fewer negative amino acid residues, or 1 or fewer negative amino acid residues. The negative amino acid residues can be selected from any negative charged amino acid residues. The negative amino acid residues can be selected from either E or D, or a combination of both E and D.

[0124] The peptides of the present disclosure can further comprise basic amino acid residues. In some embodiments, basic residues are added to the peptide sequence to increase the charge at physiological pH. The added basic residues can be any basic amino acid. The added basic residues can be selected from K or R, or a combination of K or R.

[0125] In some embodiments, the peptide has a charge distribution comprising an acidic region and a basic region. An acidic region can be a nub. A nub is a portion of a peptide extending out of the peptide's three-dimensional structure. A basic region can be a patch. A patch is a portion of a peptide that does not designate any specific topology characteristic of the peptide's three-dimensional structure. In further embodiments, a cystine-dense peptide can be 6 or more basic residues and 2 or fewer acidic residues.

[0126] The peptides of the present disclosure can further comprise positively charged amino acid residues. In some cases, the peptide has at least 2 positively charged residues. In other cases, the peptide has at least 3 positively charged residues, at least 4 positively charged residues, at least 5 positively charged residues, at least 6 positively charged residues, at least 7 positively charged residues, at least 8 positively charged residues or at least 9 positively charged residues. The positively charged residues can be selected from any positively charged amino acid residues. The positively charged residues can be selected from either K or R, or a combination of K and R.

[0127] In addition, the peptides herein can comprise a 4-19 amino acid residue fragment of any of the above sequences containing at least 2 cysteine residues, and at least 2 or 3 positively charged amino acid residues (for example, arginine, lysine or histidine, or any combination of arginine, lysine or histidine). In other embodiments, the peptides herein is a 20-70 amino acid

residue fragment of any of the above sequences containing at least 2 cysteine residues, no more than 2 basic residues, and at least 2 or 3 positively charged amino acid residues (for example, arginine, lysine or histidine, or any combination of arginine, lysine or histidine). In some embodiments, such peptide fragments contact the cartilage and exhibit properties of those described herein for peptide and peptide-active agent conjugates.

[0128] Furthermore, peptides denoted as SEQ ID NO: 128 (also shown as SEQ ID NO: 205), and SEQ ID NO: 149 (also shown as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) are excluded from (or not included in) peptides comprising any one of the peptides comprising SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263. Peptides denoted as SEQ ID NO: 128 (also shown as SEQ ID NO: 205), and SEQ ID NO: 149 (also shown as SEQ ID NO: 46) are specifically excluded from (or not included in) peptides comprising any one of the peptides comprising SEQ ID NO: 110, SEQ ID NO: 260, SEQ ID NO: 262.

[0129] In some embodiments, the peptide contains one or more disulfide bonds and has a positive net charge at neutral pH. At physiological pH, peptides can have a net charge, for example, of -5, -4, -3, -2, -1, 0, +1, +2, +3, +4, or +5. When the net charge is zero, the peptide can be uncharged or zwitterionic. In some instances, the peptide can have a positive charge at physiological pH. In some instances, the peptide can have a charge $\geq +2$ at physiological pH, $\geq +3.5$ at physiological pH, $\geq +4.5$ at physiological pH. In some embodiments, the peptide contains one or more disulfide bonds and has a positive net charge at neutral pH where the net charge can be +0.5 or less than +0.5, +1 or less than +1, +1.5 or less than +1.5, +2 or less than +2, +2.5 or less than +2.5, +3 or less than +3, +3.5 or less than +3.5, +4 or less than +4, +4.5 or less than +4.5, +5 or less than +5, +5.5 or less than +5.5, +6 or less than +6, +6.5 or less than +6.5, +7 or less than +7, +7.5 or less than +7.5, +8 or less than +8, +8.5 or less than +8.5, +9 or less than +9.5, +10 or less than +10. In some embodiments, the peptide has a negative net charge at physiological pH where the net charge can be -0.5 or less than -0.5, -1 or less than -1, -1.5 or less than -1.5, -2 or less than -2, -2.5 or less than -2.5, -3 or less than -3, -3.5 or less than -3.5, -4 or less than -4, -4.5 or less than -4.5, -5 or less than -5, -5.5 or less than -5.5, -6 or less than -6, -6.5 or less than -6.5, -7 or less than -7, -7.5 or less than -7.5, -8 or less than -8, -8.5 or less than -8.5, -9 or less than -9.5, -10 or less than -10. In some cases, the engineering of one or more mutations or corresponding substitutions within a peptide yields a peptide with an altered isoelectric point, charge, surface charge, or rheology at physiological pH. Such

engineering of a mutation or corresponding substitutions to a peptide derived from a scorpion or spider can change the net charge of the complex, for example, by decreasing the net charge by 1, 2, 3, 4, or 5, or by increasing the net charge by 1, 2, 3, 4, or 5. In such cases, the engineered mutation or corresponding substitutions may facilitate the ability of the peptide to contact the cartilage. Suitable amino acid modifications for improving the rheology and potency of a peptide can include conservative or non-conservative mutations or corresponding substitutions. A peptide can comprises at most 1 amino acid mutation or corresponding substitution, at most 2 amino acid mutations or corresponding substitutions, at most 3 amino acid mutations or corresponding substitutions, at most 4 amino acid mutations or corresponding substitutions, at most 5 amino acid mutations or corresponding substitutions, at most 6 amino acid mutations or corresponding substitutions, at most 7 amino acid mutations or corresponding substitutions, at most 8 amino acid mutations or corresponding substitutions, at most 9 amino acid mutations or corresponding substitutions, at most 10 amino acid mutations or corresponding substitutions, or another suitable number as compared to the sequence of the venom or toxin that the peptide is derived from. In other cases, a peptide, or a functional fragment thereof, comprises at least 1 amino acid mutation or corresponding substitution, at least 2 amino acid mutations or corresponding substitutions, at least 3 amino acid mutations or corresponding substitutions, at least 4 amino acid mutations or corresponding substitutions, at least 5 amino acid mutations or corresponding substitutions, at least 6 amino acid mutations or corresponding substitutions, at least 7 amino acid mutations or corresponding substitutions, at least 8 amino acid mutations or corresponding substitutions, at least 9 amino acid mutations or corresponding substitutions, at least 10 amino acid mutations or corresponding substitutions, or another suitable number as compared to the sequence of the venom or toxin that the peptide is derived from. In some embodiments, mutations or corresponding substitutions can be engineered within a peptide to provide a peptide that has a desired charge or stability at physiological pH.

[0130] Peptides can be mutated to add function or remove function. For example, peptides and peptide-conjugates of the present disclosure can be mutated to retain, remove, or add the ability to bind to ion channels, or to promote agonizing or antagonizing ion channels, such as potassium channel binding that may occur with the peptide or peptide-conjugates (e.g., the potassium channel hERG). In some instances, it can be advantageous to remove potassium channel binding from a peptide used for delivery of an active agent. Mutations and or corresponding substitutions can include one or more N to S, D to E, M to T, N to Q, N to A, N to S, N to T, N to L, S to G, and S to R amino acid substitutions, or one or more L to Y, H to Y, and T to Y amino acid substitutions, or any combination of thereof, depending on whether the variant is designed to

retain function or to remove function of binding to the ion channel. In some embodiments the peptides and peptide-drug conjugates of the present disclosure are mutated to minimize ion channel binding in order to minimize side effects or enhance the safety either in the target tissue or systemically.

[0131] In some embodiments, charge can play a role in cartilage homing. The interaction of a peptide of this disclosure in solution and in vivo can be influenced by the isoelectric point (pI) of the peptide and/or the pH of the solution or the local environment it is in. The charge of a peptide in solution can impact the solubility of the protein as well as parameters such as biodistribution, bioavailability, and overall pharmacokinetics. Additionally, positively charged molecules can interact with negatively charged molecules. Positively charged molecules such as the peptides disclosed herein can interact and bind with negatively charged molecules such as the negatively charged extracellular matrix molecules in the cartilage including hyaluronan and aggrecan. Positively charged residues can also interact with specific regions of other proteins and molecules, such as negatively charged residues of receptors or electronegative regions of an ion channel pore on cell surfaces. As such, the pI of a peptide can influence whether a peptide of this disclosure can efficiently home to cartilage. Identifying a correlation between pI and cartilage homing can be an important strategy in identifying lead peptide candidates of the present disclosure. The pI of a peptide can be calculated using a number of different methods including the ExPASy pI calculator and the Sillero method. The ExPASy pI can be determined by calculating pKa values of amino acids as described in Bjellqvist et al., which were defined by examining polypeptide migration between pH 4.5 to pH 7.3 in an immobilized pH gradient gel environment with 9.2M and 9.8M urea at 15°C or 25°C (Bjellqvist et al. Electrophoresis. 14(10):1023-31 (1993)). The Sillero method of calculating pI can involve the solution of a polynomial equation and the individual pKas of each amino acid. This method does not use denaturing conditions (urea) (Sillero et al. 179(2): 319-35 (1989)) Using these pI calculation methods and quantifying the cartilage to blood ratio of peptide signal after administration to a subject can be a strategy for identifying a trend or correlation in charge and cartilage homing. In some embodiments, a peptide with a pI above biological pH (~pH 7.4) can exhibit efficient homing to cartilage. In some embodiments, a peptide with a pI of at least 8, at least 9, at least 10, or at least 11 can efficiently home to cartilage. In other embodiments, a peptide with a pI of 11 – 12 can home most efficiently to cartilage. In certain embodiments, a peptide can have a pI of about 9. In other embodiments, a peptide can have a pI of 8 – 10. In some embodiments, more basic peptides can home more efficiently to cartilage. In other embodiments, a high pI alone may not be sufficient to cause cartilage homing of a peptide.

[0132] In some embodiments, the tertiary structure and electrostatics of a peptide of the disclosure can impact cartilage homing. Structural analysis or analysis of charge distribution can be a strategy to predict residues important in biological function, such as cartilage homing. For example, several peptides of this disclosure that home to cartilage can be grouped into a structural class defined herein as “hitchins,” and can share the properties of disulfide linkages between C1-C4, C2-C5, and C3-C6. The folding topologies of peptides linked through three disulfide linkages (C1-C4, C2-C5, and C3-C6), can be broken down into structural families based on the three-dimensional arrangement of the disulfides. Some cystine-dense peptides have the C3-C6 disulfide linkage passing through the macrocycle formed by the C1-C4 and C2-C5 disulfide linkages, hitchins have the C2-C5 disulfide linkage passing through the macrocycle formed by the C1-C4 and C3-C6 disulfide linkages, and yet other structural families have the C1-C4 disulfide linkage passing through the macrocycle formed by the C2-C5 and C3-C6 disulfide linkages. Variants of “hitchin” class peptides with preserved disulfide linkages at these cysteine residues, primary sequence identity, and/or structural homology can be a method of identifying or predicting other potential peptide candidates that can home to cartilage.

Additionally, members and related members of the calcin family of peptides can also home to cartilage, despite having a distinct tertiary structure from the “hitchin” class of peptides. Calcin peptides are structurally a subset of the cystine-dense peptides, with cystine-dense disulfide connectivity and topology, but are further classified on the basis of functioning to bind and activate ryanodine receptors (RyRs). These receptors are calcium channels that act to regulate the influx and efflux of calcium in muscle (Schwartz et al. Br J Pharmacol 157(3):392-403. (2009)). Variants of the calcin family of peptides with preserved key residues can be one way to predict promising candidates that can home to cartilage. In some embodiments, structural analysis of a peptide of this disclosure can be determined by evaluating peptides for resistance to degradation in buffers with various proteases or reducing agents. Structural analysis of the distribution of charge density on the surface of a peptide can also be a strategy for predicting promising candidates that can home to cartilage. Peptides with large patches of positive surface charge (when at pH 7.5) can home to cartilage.

[0133] The NMR solution structures, x-ray crystallography, or crystal structures of related structural homologs can be used to inform mutational strategies that can improve the folding, stability, and manufacturability, while maintaining the ability of a peptide to home to cartilage. They can be used to predict the 3D pharmacophore of a group of structurally homologous scaffolds, as well as to predict possible graft regions of related proteins to create chimeras with improved properties. For example, this strategy can be used to identify critical amino acid

positions and loops that can be used to design drugs with improved properties or to correct deleterious mutations that complicate folding and manufacturability for the peptides. These key amino acid positions and loops can be retained while other residues in the peptide sequences can be mutated to improve, change, remove, or otherwise modify function, homing, and activity of the peptide.

[0134] Additionally, the comparison of the primary sequences and the tertiary sequences of two or more peptides can be used to reveal sequence and 3D folding patterns that can be leveraged to improve the peptides and parse out the biological activity of these peptides. For example, comparing two different peptide scaffolds that home to cartilage can lead to the identification of conserved pharmacophores that can guide engineering strategies, such as designing variants with improved folding properties. Important pharmacophore, for example, can comprise aromatic residues or basic residues, which can be important for binding.

[0135] Improved peptides can also be engineered based upon immunogenicity information, such as immunogenicity information predicted by TEPITOPE and TEPITOPEpan. TEPITOPE is a computational approach which uses position specific scoring matrix to provide prediction rules for whether a peptide will bind to 51 different HLA-DR alleles, and TEPITOPEpan is method that uses TEPITOPE to extrapolate from HLA-DR molecules with known binding specificities to HLA-DR molecules with unknown binding specificities based on pocket similarity. For example, TEPITOPE and TEPITOPEpan can be used to determine immunogenicity of peptides that home to cartilage. Immunogenicity information can also be predicted using the program NetMHCII version 2.3, which can determine the likelihood that a sequence might be presented as an immunogenic peptide via the major histocompatibility complex (MHC) presentation system of antigen presenting cells (APCs). (Nielson, M et al. *BMC Bioinformatics*, 8: 238 (2007); Nielsen, M. et al. *BMC Bioinformatics*, 10: 296 (2009)). This program can create an immunogenicity score by predicting the binding of a peptide to MHC alleles. Strong binding alleles and weak binding alleles in each major MHC allele group (DR, DQ, and DP) can be tallied separately. The number of peptides of a specific length within the sequence (e.g., a 'core' peptide that can be nine residues long) that are immunogenic can also be tallied. Comparison of peptides or 'core' peptides with high immunogenicity to peptides or 'core' peptides with low immunogenicity can guide engineering strategies for designing variants with decreased immunogenicity. Stronger binding peptides can be more likely to generate an immune response in patient carrying that given MHC alleles. Mutating stronger binding amino acids or peptides out of a peptide sequence can reduce the immunogenicity of the entire peptide. Another aspect of immunogenicity, in addition to whether a peptide binds to a patient's MHC allele, can be whether the patient's

immune cells, such as a professional antigen presenting cells such as a macrophage, a B cell, or a dendritic cell, can process the peptide. A dendritic cell can take up a protein or peptide, and then can process a peptide, such as by cleaving to form a nine residue long peptide, which then can bind to the MHC and can be presented on the surface of the dendritic cell to the immune system's various T cells, including helper T cells and cytotoxic T cells, and thus can stimulate an immune response. The processing can involve peptide bond cleavage by enzymes and disulfide bond reduction, and thus a peptide or protein that is resistant to enzymatic cleavage and/or reduction can be resistant to processing and subsequent MHC presentation to the immune system. Therefore, having a peptide or protein that is resistant to enzymatic cleavage and/or reduction can reduce its immunogenic potential.

[0136] Furthermore, multiple sequence alignment can also be used to inform mutational strategies using previously identified sequences, and thus providing a guide to making changes that would eliminate labile residues and immunogenic regions of a peptide sequence. Peptides can be evaluated for residues of potential biochemical instability and regions of potential immunogenicity. Then, a residue that can allow for greater peptide stability at a certain location in a peptide can be identified from a multiple sequence alignment. For example, a specific residue can be identified from a multiple sequence alignment as providing greater stability for a peptide at position previously identified as a possible risk for a significant rate of deamidation, cleavage, degradation, oxidation, hydrolysis, isomerization, disulfide exchange, racemization, beta elimination, or aggregation. This information can then be used to create peptides with greater stability or reduced immunogenicity.

[0137] In addition to utilizing co-crystal x-ray structures, NMR solution structures, and mutagenesis studies, a multiple alignment of peptide sequences can be used to identify specific amino acids or regions of high conservation that indicate an important interaction with a target or receptor (e.g., binding to a potassium channel protein) or are important for folding and structure or other properties. Once the conserved amino acid or region is identified, then amino acids replacements can be determined that maintain the important properties of the peptide, such as maintenance of the structure, reduction in immunogenicity, reduction in binding to an ion channel protein, increased stability, or any combination of thereof.

[0138] The multiple sequence alignment can also identify possible locations to add a tyrosine or tryptophan residue for spectrophotometric reporting. Incorporation of aromatic amino acids such as Tyrosine or Tryptophan into a peptide such as SEQ ID NO: 149 (also disclosed herein as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205), which otherwise contains only amino acids of low UV absorbance at 280

nm, can be analytically advantageous. Tyrosine and Tryptophan amino acids contain aromatic ring structures. These residues have distinct absorption and emission wavelengths and good quantum yields, as shown in **TABLE 2**, not present in other amino acids. Both Tyrosine and Tryptophan can provide a good 'handle' for analytical detection of a peptide in solution since UV absorbance in the 250-300 nm range and peptide fluorescence is specific for these aromatic molecules. While chromatographic detection of a peptide such as SEQ ID NO: 149 relies on the absorbance of the peptide bond at 220 nm, where many other materials including minor impurities in solvents also often contribute to signal, the absorbance and fluorescence properties of Tryptophan and Tyrosine containing peptides can provide for a significantly more selective and sensitive detection. Thus incorporating an aromatic amino acid can create peptides better suited for concentration and purity measurements, which can be useful during analytics, process development, manufacturing, and other drug development and drug manufacturing activities. Incorporation can be achieved either through substitutions of one or more amino acids in the peptide to Tyr and/or Trp, insertion of Tyr and/or Trp into the peptide, or via addition of Tyr and/or Trp to the N-terminus or C-terminus of the peptide.

TABLE 2. Absorbance and Fluorescence Characteristics of Tryptophan and Tyrosine.

Amino Acid	Absorbance		Fluorescence	
	Wavelength (nm)	Absorbivity (M*cm) ⁻¹	Wavelength (nm)	Quantum Yield
Tryptophan	280	5,600	348	0.20
Tyrosine	274	1,400	303	0.14

[0139] A peptide of this disclosure can bind to chloride, potassium, or sodium channels. The peptide can also bind to calcium channels. The peptide can block potassium channels and/or sodium channels. The peptide can block calcium channels. In some embodiments, the peptide can activate any one or more of such channels. In some embodiments, the peptide can block any one or more of such channels. In some embodiments, the peptide cannot interact with any of such channels or can be mutated to reduce or remove binding to any such channels. In still other embodiments, the peptide can be a potassium channel agonist, a potassium channel antagonist, a portion of a potassium channel, a sodium channel agonist, a sodium channel antagonist, a chloride channel agonist, a chloride channel antagonist, a calcium channel agonist, a calcium channel antagonist, a hadrucalcin, a theraphotoxin, a huwentoxin, a kaliotoxin, a cobatoxin or a lectin. In some embodiments, the lectin can be SHL-Ib2. In some embodiments, the peptide can interact with, binds, inhibits, inactivates, or alters expression of ion channels or chloride

channels. In some embodiments, the peptide can interact with an Nav1. 7 ion channel. In some embodiments, the peptide can interact with a Kv 1. 3 ion channel. In still other embodiments, the peptide interacts with proteases, matrix metalloproteinase, inhibits cancer cell migration or metastases, has antimicrobial activity, or has antitumor activity. In addition to acting on matrix metalloproteinases, the peptide can interact with other possible proteases (e.g., elastases). In some embodiments, a peptide of this disclosure can bind to multidrug resistance transporters. Peptide and peptide drug conjugate binding to and blocking multidrug resistance transporters can be used to treat bacterial infections or cancers of the joint and/or bone.

[0140] In some embodiments, the peptide has other therapeutic effects on the cartilage or structures thereof or nearby. Beta defensin expression in articular cartilage can be correlated with immunomodulatory functions as well as osteoarthritis, autoimmune rheumatic disorders such as systemic lupus erythematosus and rheumatoid arthritis (Vordenbäumen and Schneider 2011, Varoga 2004 and Varoga 2005). In some embodiments, the peptides or their mutants inhibit beta defensins, supplement beta defensins, are competitive inhibitors of beta defensins, active or block activation of beta defensin targets, and are used as immune modulators, or to treat autoimmune, arthritis, infections, and other articular disorders.

[0141] The present disclosure can also encompass multimers of the various peptides described herein. Examples of multimers include dimers, trimers, tetramers, pentamers, hexamers, heptamers, and so on. A multimer can be a homomer formed from a plurality of identical subunits or a heteromer formed from a plurality of different subunits. In some embodiments, a peptide of the present disclosure is arranged in a multimeric structure with at least one other peptide, or two, three, four, five, six, seven, eight, nine, ten, or more other peptides. In certain embodiments, the peptides of a multimeric structure each have the same sequence. In alternative embodiments, some or all of the peptides of a multimeric structure have different sequences.

[0142] The present disclosure further includes peptide scaffolds that, e.g., can be used as a starting point for generating additional peptides. In some embodiments, these scaffolds can be derived from a variety of cystine-dense peptides. Some suitable peptides for scaffolds can include, but are not limited to, chlorotoxin, brazzein, circulin, stecrisp, hanatoxin, midkine, hefutoxin, potato carboxypeptidase inhibitor, bubble protein, attractin, α -GI, α -GID, μ -PIIIA, ω -MVIIA, ω -CVID, χ -MrIA, ρ -TIA, conantokin G, contulakin G, GsMTx4, margatoxin, shK, toxin K, chymotrypsin inhibitor (CTI), and EGF epiregulin core.

[0143] In some embodiments, the peptide sequences of the disclosure are flanked by additional amino acids. One or more additional amino acids can, for example, confer a desired in vivo

charge, isoelectric point, chemical conjugation site, stability, or physiologic property to a peptide.

[0144] Identifying sequence homology can be important for determining key residues that preserve cartilage homing function. For example, in some embodiments identification of conserved positively charged residues can be important in preserving cartilage homing in any homologous variants that are made. In other embodiments, identification of basic or aromatic dyads, can be important in preserving interaction and activity with Kv ion channels in homologous variants.

[0145] Two or more peptides can share a degree of homology and share similar properties in vivo. For instance, a peptide can share a degree of homology with a peptide of the present disclosure. In some cases, a peptide of the disclosure can have up to about 20% pairwise homology, up to about 25% pairwise homology, up to about 30% pairwise homology, up to about 35% pairwise homology, up to about 40% pairwise homology, up to about 45% pairwise homology, up to about 50% pairwise homology, up to about 55% pairwise homology, up to about 60% pairwise homology, up to about 65% pairwise homology, up to about 70% pairwise homology, up to about 75% pairwise homology, up to about 80% pairwise homology, up to about 85% pairwise homology, up to about 90% pairwise homology, up to about 95% pairwise homology, up to about 96% pairwise homology, up to about 97% pairwise homology, up to about 98% pairwise homology, up to about 99% pairwise homology, up to about 99.5% pairwise homology, or up to about 99.9% pairwise homology with a second peptide. In some cases, a peptide of the disclosure can have at least about 20% pairwise homology, at least about 25% pairwise homology, at least about 30% pairwise homology, at least about 35% pairwise homology, at least about 40% pairwise homology, at least about 45% pairwise homology, at least about 50% pairwise homology, at least about 55% pairwise homology, at least about 60% pairwise homology, at least about 65% pairwise homology, at least about 70% pairwise homology, at least about 75% pairwise homology, at least about 80% pairwise homology, at least about 85% pairwise homology, at least about 90% pairwise homology, at least about 95% pairwise homology, at least about 96% pairwise homology, at least about 97% pairwise homology, at least about 98% pairwise homology, at least about 99% pairwise homology, at least about 99.5% pairwise homology, at least about 99.9% pairwise homology with a second peptide. Various methods and software programs can be used to determine the homology between two or more peptides, such as NCBI BLAST, Clustal W, MAFFT, Clustal Omega, AlignMe, Praline, or another suitable method or algorithm.

[0146] In still other instances, the variant nucleic acid molecules of a peptide of any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 can be identified by either a determination of the sequence identity or homology of the encoded peptide amino acid sequence with the amino acid sequence of any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263, or by a nucleic acid hybridization assay. Such peptide variants can include nucleic acid molecules (1) that remain hybridized with a nucleic acid molecule having the nucleotide sequence of any one of S SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 (or any complement of the previous sequences) under stringent washing conditions, in which the wash stringency is equivalent to $0.5 \times -2 \times$ SSC with 0.1% SDS at 55-65° C, and (2) that encode a peptide having at least 70%, at least 80%, at least 90%, at least 95% or greater than 95% sequence identity or homology to the amino acid sequence of any one SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Alternatively, peptide variants of any one SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 can be characterized as nucleic acid molecules (1) that remain hybridized with a nucleic acid molecule having the nucleotide sequence of any one SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 (or any complement of the previous sequences) under highly stringent washing conditions, in which the wash stringency is equivalent to $0.1 \times -0.2 \times$ SSC with 0.1% SDS at 50-65° C. , and (2) that encode a peptide having at least 70%, at least 80%, at least 90%, at least 95% or greater than 95% sequence identity or homology to the polynucleotide encoding the amino acid sequence of any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO:

129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

[0147] Percent sequence identity or homology can be determined by conventional methods. See, for example, Altschul et al., *Bull. Math. Bio.* 48:603 (1986), and Henikoff and Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1992). Briefly, two amino acid sequences are aligned to optimize the alignment scores using a gap opening penalty of 10, a gap extension penalty of 1, and the “BLOSUM62” scoring matrix of Henikoff and Henikoff (*Id.*). The sequence identity or homology is then calculated as: $([\text{Total number of identical matches}]/[\text{length of the longer sequence plus the number of gaps introduced into the longer sequence in order to align the two sequences}])(100)$.

[0148] Additionally, there are many established algorithms available to align two amino acid sequences. For example, the “FASTA” similarity search algorithm of Pearson and Lipman is a suitable protein alignment method for examining the level of sequence identity or homology shared by an amino acid sequence of a peptide disclosed herein and the amino acid sequence of a peptide variant. The FASTA algorithm is described by Pearson and Lipman, *Proc. Nat'l Acad. Sci. USA* 85:2444 (1988), and by Pearson, *Meth. Enzymol.* 183:63 (1990). Briefly, FASTA first characterizes sequence similarity by identifying regions shared by the query sequence (e.g., a reference sequence such as SEQ ID NO: 128, SEQ ID NO: 110 or SEQ ID NO: 260) and a test sequence that has either the highest density of identities (if the ktup variable is 1) or pairs of identities (if ktup=2), without considering conservative amino acid substitutions, insertions, or deletions. The ten regions with the highest density of identities are then rescored by comparing the similarity of all paired amino acids using an amino acid substitution matrix, and the ends of the regions are “trimmed” to include only those residues that contribute to the highest score. If there are several regions with scores greater than the “cutoff” value (calculated by a predetermined formula based upon the length of the sequence and the ktup value), then the trimmed initial regions are examined to determine whether the regions can be joined to form an approximate alignment with gaps. Finally, the highest scoring regions of the two amino acid sequences are aligned using a modification of the Needleman-Wunsch-Sellers algorithm (Needleman and Wunsch, *J. Mol. Biol.* 48:444 (1970); Sellers, *Siam J. Appl. Math.* 26:787 (1974)), which allows for amino acid insertions and deletions. Illustrative parameters for FASTA analysis are: ktup=1, gap opening penalty=10, gap extension penalty=1, and substitution matrix=BLOSUM62. These parameters can be introduced into a FASTA program by modifying the scoring matrix file (“SMATRIX”), as explained in Appendix 2 of Pearson, *Meth. Enzymol.* 183:63 (1990).

[0149] FASTA can also be used to determine the sequence identity or homology of nucleic acid molecules using a ratio as disclosed above. For nucleotide sequence comparisons, the ktup value can range between one to six, preferably from three to six, most preferably three, with other parameters set as described above.

[0150] Some examples of common amino acids that are a “conservative amino acid substitution” are illustrated by a substitution among amino acids within each of the following groups: (1) glycine, alanine, valine, leucine, and isoleucine, (2) phenylalanine, tyrosine, and tryptophan, (3) serine and threonine, (4) aspartate and glutamate, (5) glutamine and asparagine, and (6) lysine, arginine and histidine. The BLOSUM62 table is an amino acid substitution matrix derived from about 2,000 local multiple alignments of protein sequence segments, representing highly conserved regions of more than 500 groups of related proteins (Henikoff and Henikoff, *Proc. Nat'l Acad. Sci. USA* 89:10915 (1992)). Accordingly, the BLOSUM62 substitution frequencies can be used to define conservative amino acid substitutions that may be introduced into the amino acid sequences of the present invention. Although it is possible to design amino acid substitutions based solely upon chemical properties (as discussed above), the language “conservative amino acid substitution” preferably refers to a substitution represented by a BLOSUM62 value of greater than -1 . For example, an amino acid substitution is conservative if the substitution is characterized by a BLOSUM62 value of 0, 1, 2, or 3. According to this system, preferred conservative amino acid substitutions are characterized by a BLOSUM62 value of at least 1 (e. g., 1, 2 or 3), while more preferred conservative amino acid substitutions are characterized by a BLOSUM62 value of at least 2 (e. g., 2 or 3).

[0151] Determination of amino acid residues that are within regions or domains that are critical to maintaining structural integrity can be determined. Within these regions one can determine specific residues that can be more or less tolerant of change and maintain the overall tertiary structure of the molecule. Methods for analyzing sequence structure include, but are not limited to, alignment of multiple sequences with high amino acid or nucleotide identity or homology and computer analysis using available software (e.g., molecular modelling software such as PyMol, Chimera, Rosetta, Modeller, the Insight II, Discover or CHARMM and the like, homology modeling tools, or other appropriate program), secondary structure propensities, binary patterns, complementary packing and buried polar interactions (Barton, G. J. , *Current Opin. Struct. Biol.* 5:372-6 (1995) and Cordes, M. H. et al. , *Current Opin. Struct. Biol.* 6:3-10 (1996)). In general, when designing modifications to molecules or identifying specific fragments, determination of structure can typically be accompanied by evaluating activity of modified molecules.

[0152] Pairwise sequence alignment is used to identify regions of similarity that may indicate functional, structural and/or evolutionary relationships between two biological sequences (protein or nucleic acid). By contrast, multiple sequence alignment (MSA) is the alignment of three or more biological sequences. From the output of MSA applications, homology can be inferred and the evolutionary relationship between the sequences assessed. One of skill in the art would recognize as used herein, “sequence homology” and “sequence identity” and “percent (%) sequence identity” and “percent (%) sequence homology” have been used interchangeably to mean the sequence relatedness or variation, as appropriate, to a reference polynucleotide or amino acid sequence.

Chemical Modifications

[0153] A peptide can be chemically modified one or more of a variety of ways. In some embodiments, the peptide can be mutated to add function, delete function, or modify the in vivo behavior. One or more loops between the disulfide linkages can be modified or replaced to include active elements from other peptides (such as described in Moore and Cochran, *Methods in Enzymology*, 503, p. 223-251, 2012). Amino acids can also be mutated, such as to increase half-life or bioavailability, modify, add or delete binding behavior in vivo, add new targeting function, modify surface charge and hydrophobicity, or allow conjugation sites. N-methylation is one example of methylation that can occur in a peptide of the disclosure. In some embodiments, the peptide can be modified by methylation on free amines. For example, full methylation can be accomplished through the use of reductive methylation with formaldehyde and sodium cyanoborohydride.

[0154] A chemical modification can, for instance, extend the terminal half-life, the absorption half-life, the distribution half-life of a peptide, change the biodistribution or pharmacokinetic profile, or the modification itself can be useful to provide viscosupplementation to a joint. A chemical modification can comprise a polymer, a polyether, polyethylene glycol, a biopolymer, a polyamino acid, a fatty acid, a dendrimer, an Fc region, a simple saturated carbon chain such as palmitate or myristolate, sugars, hyaluronic acid, or albumin. The chemical modification of a peptide with an Fc region can be a fusion Fc-peptide. A polyamino acid can include, for example, a polyamino acid sequence with repeated single amino acids (e. g., polyglycine), and a polyamino acid sequence with mixed polyamino acid sequences (e. g., gly-ala-gly-ala (SEQ ID NO: 264)) that can or cannot follow a pattern, or any combination of the foregoing.

[0155] In some embodiments, the peptides of the present disclosure may be modified such that the modification increases the stability and/or the half-life of the peptides. In some embodiments, the attachment of a hydrophobic moiety, such as to the N-terminus, the C-terminus, or an

internal amino acid, can be used to extend half-life of a peptide of the present disclosure. In other embodiments, the peptide of the present disclosure can include post-translational modifications (e. g., methylation and/or amidation), which can affect, e.g., serum half-life. In some embodiments, simple carbon chains (e. g., by myristoylation and/or palmitylation) can be complexed, conjugated, or fused to the peptides. In some embodiments, for example, the simple carbon chains may render complexed, conjugated, or fused peptides easily separable from uncomplexed, unconjugated, or non-fused material. For example, methods that may be used to separate the desired peptides of the invention from uncomplexed, unconjugated, or non-fused material include, but are not limited to, solvent extraction and reverse phase chromatography. In some embodiments, lipophilic moieties can be complexed, conjugated, or fused to the peptide and can extend half-life through reversible binding to serum albumin. Moreover, the complexed, conjugated, or fused moieties can be lipophilic moieties that extend half-life of the peptides through reversible binding to serum albumin. In some embodiments, the lipophilic moiety can be cholesterol or a cholesterol derivative including cholestenes, cholestanes, cholestadienes and oxysterols. In some embodiments, the peptides can be complexed, conjugated, or fused to myristic acid (tetradecanoic acid) or a derivative thereof. In other embodiments, the peptides of the present disclosure are coupled (e. g., complexed, conjugated, or fused) to a half-life modifying agent. Examples of half-life modifying agents include but are not limited to: a polymer, a polyethylene glycol (PEG), a hydroxyethyl starch, polyvinyl alcohol, a water soluble polymer, a zwitterionic water soluble polymer, a water soluble poly(amino acid), a water soluble polymer of proline, alanine and serine, a water soluble polymer containing glycine, glutamic acid, and serine, an Fc region, a fatty acid, palmitic acid, antibodies, or a molecule that binds to albumin.

[0156] In some embodiments, the first two N-terminal amino acids (GS) of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 220, SEQ ID NO: 222, SEQ ID NO: 224, SEQ ID NO: 226, SEQ ID NO: 241 – SEQ ID NO: 248, SEQ ID NO: 261, and SEQ ID NO: 263 can serve as a spacer or linker in order to facilitate conjugation or fusion to another molecule, as well as to facilitate cleavage of the peptide from such complexed, conjugated, or fused molecules. In some embodiments, the peptides of the present disclosure can be complexed, conjugated, or fused to other moieties that can modify or effect changes to the properties of the peptides.

Active Agent Conjugates

[0157] As used herein, peptides according to the present disclosure can be complexed to an active agent. Such “complexes” can interchangeably be used herein with the terms “conjugates”,

“linked”, “attached”, “joined”, “fused” (e.g., as a result of peptide fusion, expression via one or more vectors, viral methods, recombinant methodologies, or otherwise), or any combination of the foregoing can be used, to describe complexing of any peptide of the present disclosure to one or more active agent disclosed herein. Complexes can be formed by creating chemical bonds linking molecules such as linking the peptide and the active agent, including by chemical synthesis or conjugation or by recombinant expression. Complexes can also be formed non-covalently, such as by inclusion in particles, nanoparticles, liposomes, cells, cell fragments, membranes, or other methods of physical or chemical association. It is understood that the peptide-active agent complexes of the present disclosure are not limited by the methodology used to complex, conjugate, fuse, or link the active agent to the peptide. Peptides according to the present disclosure can be complexed, conjugated, or fused to a peptide biological agent or other agent comprising amino acids (e.g., an antibody or antibody fragment, receptor or receptor fragment, ligand or ligand fragment, hormone or hormone fragment, growth factors and growth factor fragments, biological toxins and fragments thereof, or other active portion of a peptide), a protein, a peptide, or to a small molecule, RNA, DNA, or other active agent molecular structure for use in the treatment of cartilage diseases, disorders, or injuries. A small molecule active agent can include a corticosteroid or glucocorticoid. A peptide active agent conjugate can be a peptide complexed, conjugated, or fused to an active agent by any mechanism described herein. For example, a peptide can be covalently complexed, conjugated, or fused to an active agent to form a peptide active agent conjugate. A peptide can be chemically complexed, conjugated, or fused to an active agent to form a peptide active agent conjugate. A peptide and active agent can be expressed as a fusion protein to form a peptide active agent conjugate. For example, an antibody or fragment thereof and a peptide can be expressed as a fusion protein to form a peptide active agent conjugate. For example, in certain embodiments, a peptide as described herein can be fused to another molecule, such as an active agent that provides a functional capability. A peptide can be complexed, conjugated, or fused with an active agent through expression of a vector containing the sequence of the peptide with the sequence of the active agent. In various embodiments, the sequence of the peptide and the sequence of the active agent are expressed from the same Open Reading Frame (ORF). In various embodiments, the sequence of the peptide and the sequence of the active agent can comprise a contiguous sequence. Various vectors and recombinant systems known in the art can be employed to make such fusion peptides. The peptide and the active agent can each retain similar functional capabilities in the fusion peptide compared with their functional capabilities when expressed separately.

[0158] Furthermore, for example, in certain embodiments, the peptides described herein are attached to another molecule, such as an active agent that provides a functional capability. In some embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 active agents can be linked to a peptide. Multiple active agents can be attached by methods such as conjugating to multiple lysine residues and/or the N-terminus, or by linking the multiple active agents to a scaffold, such as a polymer or dendrimer and then attaching that agent-scaffold to the peptide (such as described in Yurkovetskiy, A. V. , *Cancer Res* 75(16): 3365–72 (2015).

[0159] Described herein are active agents that can be complexed, conjugated, or fused to the peptides of the present invention for use in either cartilage disorders or kidney disorders, or both. In some embodiments, certain compounds or drugs are appropriate for use in either cartilage or kidney disorders, certain drug classes may be preferred for specific treatment depending on the indication or disorder. As described herein, it is understood that certain active agents are described in a non-limiting exemplary manner for use in treatments of cartilage and/or kidney indications. One or more of such active agents can be complexed, conjugated, or fused to a peptide of the present invention alone or in combination with one or more detectable agents described herein. In some embodiments, active agents that can be complexed, conjugated, or fused to any peptide of this disclosure can be classified by mechanism. For example, active agents can belong to the class of anti-inflammatory drugs, immunosuppressive (immune suppression) drugs, analgesics/pain relief drugs, disease modifying osteoarthritic drugs (DMOADs), cell depleting agents/apoptosis modifiers, bone resorptive agents and viscosupplementing agents, and tissue normalization (disease modifying) drugs.

[0160] Anti-inflammatory active agents can include, but are not limited to, corticosteroids, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), biologics, and other small molecules. Examples of corticosteroid active agents that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints and kidneys include triamcinolone dexamethasone, budesonide, dexamethasone, and triamcinolone acetate. Examples of NSAID active agents that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints and kidneys include naproxen and ibuprofen. Other active agents include acetylsalicylic acid and acetaminophen. NSAID active agents can be further classified into COX2 inhibitors. An example of a COX2 inhibitor active agent directed to a prostaglandin pathway that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joint includes celecoxib. An example of a COX2 inhibitor active agent with anti-leukotriene receptor antagonist that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joint includes montelukast. An example of a COX2 inhibitor active

agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the kidneys includes iguratimod. Biologic active agents can be further classified into active agents that are IL-1 family inhibitors, IL-17 or IL-23 pathway inhibitors, IL-6 family inhibitors, interferon receptor inhibitors, tumor necrosis factor (TNF) inhibitors, RANK pathway inhibitors, B cell inhibitors, anti-IgE active agents, and co-stimulation inhibitors. An example of an IL-1 family inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes anakinra. An example of an IL-17/IL-23 pathway inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes secukinumab. An example of an IL-6 family inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the kidneys includes sirukumab. An example of an interferon receptor inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the kidneys includes anifrolumab. An example of a TNF inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes infliximab or etanercept. An example of a RANK pathway inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes denosumab. An example of a B cell inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints and kidneys includes rituximab. An example of an anti-IgE active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the kidneys includes omalizumab. An example of a co-stimulation inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes abatacept.

[0161] Pain relief active agents can include, but are not limited to analgesics, counter-irritants, and pain receptor blocking drugs. Analgesics can be further classified into non-narcotic agents and narcotic agents. An example of a non-narcotic active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes acetaminophen. An example of a narcotic active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to joints includes oxycodone. Counter-irritant active agents can be further classified as natural products. An example of a natural product that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes capsaicin. Pain receptor blocking active agents can be further classified as TRPV4 inhibitors. An example of a TRPV4 inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes GSK2193874.

[0162] Apoptosis modifier active agents can include, but are not limited to, biologics and small molecules. Biologic apoptosis modifier active agents can be further classified as Fas/FasL inhibitors, TNF/TNFR inhibitors, TRAIL/TRAILR inhibitors, TWEAK/Fn14 inhibitors, IL-1 inhibitors, IL-1 receptor antagonists, growth factors, and sclerostin inhibitors. An example of a TNF/TNFR inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes infliximab. An example of a TRAIL/TRAILR inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes osteoprotegerin. An example of a TWEAK/Fn14 inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the kidneys includes BIIB023. An example of an IL-1 receptor antagonist that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes anakinra. An example of a growth factor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes IGF-1. An example of a growth factor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the kidneys includes EGF. An example of a sclerostin inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes romosozumab. Small molecule apoptosis modifier active agents can be further classified as caspase inhibitors, iNOS inhibitors, surfactants, and bisphosphonates. An example of a caspase inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes ZVAD-fmk. An example of an iNOS inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints include S-methylisothiourrea. An example of a surfactant active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints include P188. An example of a bisphosphonate active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes alendronate. Moreover, the known class of drugs called senotherapeutics, also referred to as senolytics or senolytic drugs or senolytic compounds, refers to small molecules that can selectively induce death of senescent cells and for example by directly or indirectly inducing apoptosis in senescent cells. In addition, senolytics may also act via non-apoptotic mechanisms of cell death including by necroptosis, autophagic cell death, pyroptosis and caspase-independent cell death (Journal of Cell Science 127; 2135-2144 (2014)). Such drugs can attenuate age-related deterioration of tissues or organs. Examples of drugs that can be complexed, conjugated, or fused to any peptide of this disclosure to induce apoptosis or induce cell death via non-apoptotic mechanisms include quercetin, dasatinib, bortezomib,

carfilzomib, and navitoclax amongst other compounds disclosed herein. Additional active agents are described in the following references: Zhu, Y et al., *Aging Cell* 14(4):644-58 (2015); Kirkland, JL, *Exp Gerontol.* 48(1): 1-5 (2013); Kirkland JL and Tchkonian T, *Exp Gerontol.* 68: 19-25 (2015) Tchkonian, T et al., *J Clin Invest.*, 123(3): 966-72 (2013); WO2016118859; Sugumar, D et al., *Pharmagenomics Pers Med.* 8: 23-33 (2015); Jiafa, R et al., *Sci Rep.* 6: 23968 (2016); Swanson, CD et al., *Nat Rev Rheumatol.*, 5(6): 317-324 (2009); Oh, CJ et al., *PLoS One*, 7(10): e45870 (2012); and Adebajo, A and Boehncke, W, *Psoriatic Arthritis and Psoriasis: Pathology and Clinical Aspects*, Springer (2016).

[0163] Tissue normalization (disease modifying) active agents can include, but are not limited to, biologics and small molecules. Biologic active agents can be further classified as chemokines (e.g., for stem cell recruitment) and growth factors. An example of a tissue normalization chemokine active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes MIP-3 α . An example of a tissue normalization growth factor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes BMP-2. Small molecule active agents can be further classified as flavonoids, ACE inhibitors, and anti-proliferative active agents. An example of a tissue normalization flavonoid active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes icariin. An example of a tissue normalization ACE inhibitor active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the kidneys includes captopril. An example of a tissue normalization anti-proliferative active agent that can be complexed, conjugated, or fused to any peptide of this disclosure for delivery to the joints includes methotrexate. As used herein, corticosteroid can refer to both a glucocorticoid and a mineralocorticoid compound (e.g., as, for example, mimics of hormones produced by the adrenal cortex), but corticosteroid is also used herein in a non-limiting manner as a synonym for glucocorticoid.

[0164] **TABLE 3** describes active agents for treatment of a cartilage disorder that can be complexed, conjugated, or fused to any peptide of the present disclosure to form peptide-drug conjugates.

TABLE 3 – Exemplary Active Agents for Cartilage Disorders

Active Agent Class	Active Agent
Gold compound	Gold
Gold compound	Auranofin
Gold compound	Gold Sodium Thiomalate
Gold compound	Gold Thioglucose
Gold compound	Thiomalic Acid
Gold compound	Gold Thiosulphate

Active Agent Class	Active Agent
Analgesics	Tramadol (e.g., Ultram, Ultracet) and derivatives
Analgesics	Oxycodone (e.g., Percocet, Oxycontin) and derivatives
Analgesics	Hydrocodone (e.g., Norco, Vicoprofen)
Analgesics	Morphine
Analgesics	Fentanyl
Analgesics	Oxymorphone
Analgesics	Hydromorphone
Analgesics	Meperidine
Analgesics	Buprenorphine
Analgesics	Methadone
Bisphosphonate	Alendronate
Bisphosphonate	Ibandronate
Bisphosphonate	Risedronate
Bisphosphonate	Pamidronate
Bisphosphonate	Zoledronate
Non-Nitrogen Containing First Generation Bisphosphonate	Clodronate
Non-Nitrogen Containing First Generation Bisphosphonate	Etidronate
Non-Nitrogen Containing First Generation Bisphosphonate	Tiludronate
Bone resorption Inhibitors	Osteoprotegerin (OPG)
Sclerostin Antagonist Apoptosis Inhibitors	AMG785 (Romosozumab)
Caspase-1 ICE Inhibitors	VX-740 (Pralnacasan)
Counter-irritants	Menthol
Counter-irritants	Capsaicin
RANKL Targeting Agents	Denosumab
Cathepsin K Targeting Agents	Odanacatib
TNF- α Antagonists	CDP571
TNF- α Antagonists	ISIS 104838
Anti-Pain Drugs	Duloxetine
Polymers	Low Molecular Weight Chitosan
Matrix Drugs	Chondroitin sulfate glucosamine
Cytokines/Growth Factors	TGF-beta
Matrix	Laminin
Matrix	Fibronectin
Matrix	Lubricin
Matrix	Hyaluronic acid injections
Matrix	Glucosamine
Immunosuppressants	Rapamycin
HIF-1 α Modulators	
HIF-2 α Modulators	
Corticosteroid	Tixocortol pivalate
Glucocorticoid/Corticosteroid	Hydrocortisone Acetate
Glucocorticoid/Corticosteroid	Hydrocortisone t-Butyl Acetate
Glucocorticoid/Corticosteroid	Prednisolone Acetate
Glucocorticoid/Corticosteroid	Prednisolone t-Butyl Acetate
Corticosteroid	Dexamethasone Acetate

Active Agent Class	Active Agent
Corticosteroid	Dexamethasone t-Butyl Acetate
Glucocorticoid/Corticosteroid	Triamcinolone Diacetate

[0165] **TABLE 4** describes active agents for treatment of a kidney disorder that can be complexed, conjugated, or fused to any peptide of the present disclosure to form peptide-drug conjugates

TABLE 4 – Exemplary Active Agents for Kidney Disorders

Active Agent Class	Active Agent
ACE Inhibitors	Captopril
Angiotensin receptor blockers	Angiotensin receptor blocker losartan (Cozaar)
Hormones	Adrenocorticotrophic hormone
Hormones	corticotropin-releasing hormone
Anti-fungal	amphotericin B
Cardiac glycoside	digitalis (and related glycosides)
Diuretics	potassium-depleting diuretics
Anti-coagulant	Coumadin
NLRP3 Inflammosome Targeted Drugs	MCC950
NLRP3 Inflammosome Targeted Drugs	BHB
NLRP3 Inflammosome Targeted Drugs	Type I interferon / interferon alpha
NLRP3 Inflammosome Targeted Drugs	IFN-beta
NLRP3 Inflammosome Targeted Drugs	Resveratrol
NLRP3 Inflammosome Targeted Drugs	Arglabin
NLRP3 Inflammosome Targeted Drugs	CB2R agonist
NLRP3 Inflammosome Targeted Drugs	MicroRNA-223
Biguanide	metformin
Immunosuppressive	mTOR modulators
Immunosuppressive and antiproliferative	FOXO4 peptide
Anti-inflammatory, immunosuppressive	Triptolide
Antioxidant	Alpha-lipoic acid
Checkpoint inhibitors	Nivolumab
Checkpoint inhibitors	Pembrolizumab
Checkpoint inhibitors	Pidilizumab
Checkpoint inhibitors	Bmx-936559
Checkpoint inhibitors	Atezolizumab
Checkpoint inhibitors	Avelumab
Antibiotics	Penicillins

Active Agent Class	Active Agent
Penicillins	Amoxicillin
Antibiotics	Cephalosporins
Cephalosporins	Cephalexin
Antibiotics	Macrolides
Macrolides	Azithromycin
Antibiotics	Fluoroquinolones
Fluoroquinolones	Ciprofloxacin
Antibiotics	Sulfonamides
Sulfonamides	Co-trimoxazole
Antibiotics	Tetracyclines
Tetracyclines	Doxycycline
Antibiotics	Aminoglycosides
Diuretics	Loop Diuretics
Diuretics	Potassium Sparing Diuretics
Diuretics	Chlorothiazide
Diuretics	Chlorthalidone
Diuretics	Metolazone
Diuretics	Indapamide
Mineralocorticoid	
Renin Inhibitors	
Renin Inhibitors	aliskiren
Renin Inhibitors	pepstatin
Renin Inhibitors	statine
Renin Inhibitors	cgp2928
Renin Inhibitors	remikiren
Renin Inhibitors	enalkiren
Renin Inhibitors	zankiren
SGLT modulator	Dapagliflozin
SGLT modulator	Canagliflozin
SGLT modulator	Empagliflozin
	Acetylsalicylic acid
Steroid	Beclomethasone monopropionate
IL-17 inhibitor	
	Caspaicin
	Deferasirox
	Olmesartan
	L-glutamic acid polymer
	Tirilazad
Dietary flavonols	
siRNA	
Rapamycin analogs	RAD001
Counter-irritants	Piperine
Counter-irritants	Mustard Oil
Counter-irritants	Eugenol
Counter-irritants	Curcumin
Counter-irritant capsaicin-like molecule	Resiniferatoxin (RTX)

[0166] **TABLE 5** describes active agents for treatment of a cartilage disorder and a kidney disorder that can be complexed, conjugated, or fused to any peptide of the present disclosure to form peptide-drug conjugates.

TABLE 5 – Exemplary Active Agents for Cartilage Disorders and Kidney Disorders

Active Agent Class	Active Agent
IL-6 Receptor Modulators	Tocilizumab
IL-6 Receptor Modulators	Sarilumab
IL-6 Receptor Modulators	ALX-0061
IL-6 Receptor Modulators	Sirukumab
IL-6 Receptor Modulators	Clazakizumab
IL-6 Receptor Modulators	Olokizumab
IL-6 Receptor Modulators	MEDI5117
IL-17 Antagonists	Secukinumab
IL-17 Antagonists	Brodalumab
IL-17 Antagonists	Ixekizumab
Antagonists of p40 Subunit of IL-12/IL-23	Ustekinumab
Antagonists of p40 Subunit of IL-12/IL-23	Briakinumab
Antagonists of p19 Subunit of IL-23	Tildrakizumab
Antagonists of p19 Subunit of IL-23	Guselkumab
IL-23 Antagonists	Soluble IL-23 (or cytokine-binding homology region of soluble IL-23)
IL-1 Antagonists	Canakinumab
IL-1 Antagonists	Rilonacept
IL-1 Antagonists	Gevokizumab
IL-1 Antagonists	LY2189102
IL-1 Antagonists	Lentiviral-mediated RNAi
IL-12 Antagonists	
IL-1 Receptor Antagonists	Anakinra/Kineret
IL-1 Receptor Antagonists	MEDI-8968
IL-1 Antagonists	AMG-108
Interleukins/Pro-Inflammatory Cytokines	Pro-inflammatory IL-1 α or IL-1 β
Interleukins	IL-8
Interleukins	IL-15
Interleukins	IL-18

Active Agent Class	Active Agent
Interleukins	IL-4
Interleukins	IL-10
Interleukins	IL-13
Interleukins	IL-22
Interleukins	IL-17
Interleukins	IL-6, IL-12, IL-23
p38 Inhibitors	VX-745
p38 Inhibitors	BIRB 796
p38 Inhibitors	SCIO-469
p38 Inhibitors	VX-702
p38 Inhibitors	Pamapimod
p38 Inhibitors	ARRY-797
Corticosteroids	beclomethasone 17-monopropionate
Corticosteroids	Desciclesonide (also known as des-isobutyrylciclesonide, des-ciclesonide, C21-desisobutyryl-ciclesonide, or RM1)
Corticosteroids	Flunisolide
Corticosteroids	Mometasone furoate
Corticosteroids	22-hydroxy intermediate budesonide derivative
Corticosteroids	6 β -hydroxy budesonide derivative
Corticosteroids	Δ 6-budesonide derivative
Corticosteroids	23-hydroxy budesonide derivative
Corticosteroids	16 α -butyryloxyprednisolone budesonide derivative
Corticosteroids	16 α -hydroxyprednisolone budesonide derivative
Corticosteroid (Beclomethasone)	QVAR inhalation
Corticosteroid (Budesonide)	pulmicort respules
Corticosteroid	Flovent HFA 44
Corticosteroid (Mometasone)	Asmanex HFA
Corticosteroid (Mometasone)	Budesonide symbicort
Corticosteroid	Dexamethasone sodium phosphate
Corticosteroid	Tixocortol pivalate
Corticosteroid	Ciclesonide
Glucocorticoids	21-nortriamcinolone acetonide
Glucocorticoids	Δ 6-triamcinolone
Glucocorticoids	6b-hydroxy triamcinolone acetonide
Glucocorticoids	21-carboxy triamcinolone acetonide
Glucocorticoids	6b-OH, 21-COOH triamcinolone acetonide

Active Agent Class	Active Agent
Glucocorticoids	6 α fluorocortisol
Glucocorticoids	9 α fluorocortisol
Glucocorticoids	Δ 1-dehydro configuration in prednisolone
Glucocorticoids	16-methylene dexamethasone derivative
Glucocorticoids	16 α -methyl dexamethasone derivative
Glucocorticoids	16 β -methyl betamethasone derivative
Glucocorticoids	Cyclophosphamide
Immunosuppressive	Mycophenolate
Glucocorticoids/Mineralocorticoids	Cortisol
Glucocorticoids/Mineralocorticoids	Hydrocortisone
Glucocorticoids/Mineralocorticoids	Prednisolone
Glucocorticoids/Mineralocorticoids	Betamethasone
Glucocorticoid	Fluticasone
Glucocorticoid	Fluticasone propionate
Steroid (flunisolide)	Aerobid
Steroid (flunisolide)	Aerobid-M
Steroid (flunisolide)	Aerospan
Steroid (Flunisolide)	Fluticasone Furoate
Steroid (Fluticasone)	Flovent HFA 110
Steroid (Fluticasone)	Flovent HFA 220
Steroid (Fluticasone)	Flovent Diskus 50
Steroid (Fluticasone)	Asmanex
Steroid	Betamethasone acetate
Steroid	Betamethasone sodium phosphate
Steroid	Betamethasone valerate
Steroid	Beclomethasone dipropionate
Local Anesthetic	procaine hydrochloride
Local Anesthetic	Novacain
Anesthetic	bupivacaine hydrochloride
Anesthetic	lidocaine hydrochloride
Local Anesthetic	ropivacaine hydrochloride
Analgesics	Morphine
Analgesics	Fentanyl
Quinazolines	Feitinib/Iressa
Quinazolines	Sorafenib/Nexavar

Active Agent Class	Active Agent
Quinazolines	Lapatinib ditosylate/Tykerb/Tyverb
Quinazolines	Sunitinib/Sutent
Quinazolines	Bortezomib/Velcade/Cytomib
Quinazolines	Everolimus/Temsirolimus
Quinazolines	Inhibitors of IAPS
Quinazolines	Activators of caspase pathway
Quinazolines	Activators of AKT pathway
Quinazolines	Propylpeptidase inhibitors
Quinazolines	Activators of p53
Quinazolines	Inhibitors of anti-apoptotic protein inhibitors
Prolyl Hydroxylase (PHD) Inhibitors	Desferrioxamine
Prolyl Hydroxylase (PHD) Inhibitors	Dimethyloxalylglycine (DMOG)
Prolyl Hydroxylase (PHD) Inhibitors	L-mimosine (L-mim)
Aptamers	Peptide aptamers
Aptamers	RNA aptamer A-p50
Aptamers	Peptide A aptamer TrxLef1D
Aptamers	Aptamer E07
Aptamers	Aptamer gemcitabine polymers
Aptamers	RAGE
Aptamers	Pegaptanib
Proteosome Inhibitors	Bortezomib
Proteosome Inhibitors	Carfilzomib
Second Generation Proteosome Inhibitors	Ixazomib
Second Generation Proteosome Inhibitors	Delanzomib
Second Generation Proteosome Inhibitors	Oprozomib
Second Generation Proteosome Inhibitors	Marizomib
Apoptosis Inhibitors	FLIP agonist
Apoptosis Inhibitors	nitric oxide synthase inhibitors
Apoptosis Inhibitors	caspase-3 inhibitors (Z-DEVD-fmk (SEQ ID NO: 265))
Apoptosis Inhibitors	caspase-9 inhibitors (Z-LEHD-fmk (SEQ ID NO: 266))
Apoptosis Inhibitors	Sclerostin antagonists

Active Agent Class	Active Agent
Apoptosis Inhibitors/Growth Factor	IGF-1
BCL-2 Agonist Apoptosis Inhibitors	Oblimersen
BCL-2 Agonist Apoptosis Inhibitors	Obatoclax
BCL-2 Agonist Apoptosis Inhibitors	Navitoclax
BCL-2 Agonist Apoptosis Inhibitors	Venetoclax (ABT-199)
BCL-2 Agonist Apoptosis Inhibitors	Navotoclax (ABT-263)
BCL-2 Agonist Apoptosis Inhibitors	GX01 series of compounds
BCL-2 Agonist Apoptosis Inhibitors	BCL-2 small molecule antagonists
BCL-2 Agonist Apoptosis Inhibitors	Tetraocarcin-A derivatives
BCL-2 Agonist Apoptosis Inhibitors	Chelerythrine
BCL-2 Agonist Apoptosis Inhibitors	Antimycin A derivatives
BCL-2 Agonist Apoptosis Inhibitors	HA14-1
BCL-2 Agonist Apoptosis Inhibitors	Synthetic compound antagonist of BH3
BCL-2 Agonist Apoptosis Inhibitors	Genasense
BCL-2 Agonist Apoptosis Inhibitors	ISIS 22783
BCL-2/BCL-XL Agonist Apoptosis Inhibitors	Bispecific Antisense
Proapoptotic BCL-2 Targeting Drugs	Bax, Bak, Bid, Bad-derived BH3 Peptides
Proapoptotic BCL-2 Targeting Drugs	SAHBs
Proapoptotic BCL-2 Targeting Drugs	BH3Is
BCL-2/BCL-XL Agonist Apoptosis Inhibitors	ABT-737
BCL-X Inhibitors	
Apoptosis Modifiers	Caspase-1 Inhibitors

Active Agent Class	Active Agent
Apoptosis Modifiers	Caspase-8 Inhibitors
Pan-caspase Caspase Inhibitor	IDN-6556
Pan-caspase Caspase Inhibitor	IDN-6734
Pan-caspase Caspase Inhibitor	VX-799
Pan-caspase Inhibitor	MX1013
Pan-caspase Caspase Inhibitor	M-920
Pan-caspase Caspase Activator	MX-2060 derivatives
Pan-caspase Caspase Activators	Small-molecule compounds
Pan-caspase Caspase Activators	RGD peptides
Pan-caspase inhibitors	ZVAD-fmk
Caspase-1 ICE Inhibitors	IDN-11104
Caspase-1 ICE Inhibitors	VX-756
Caspase-3 Inhibitors	M-826
Caspase-3 Inhibitors	M-791
Caspase-3 Inhibitors	Immunocasp-3
Caspase-3 Inhibitors	Ad-G/iCasp3
Caspase-3 Inhibitors	PEF-F8-CP3
Caspase-6 Inhibitors	Immunocasp-6
Caspase-9 Inhibitors	FKBP12/caspase-9 fusion protein
IAP Antagonists	BIR3 antagonists
XIAP Antagonists	Capped tripeptide XIAP Antagonists
XIAP Antagonists	Smac-mimetic compounds
XIAP Antagonists	AEG35156/GEM®640
XIAP Inhibitors	Embelin
XIAP Inhibitors	XIAP antisense and RNA constructs
XIAP/cIAP-1/cIAP-2 Inhibitors	Small molecule SMAC mimetics
IAP/Caspase Inhibitors	HIV-Tat/polyarginine-complexed SMAC peptides
BIR2/Caspase-3 Inhibitors	TWX024
BIR2 Inhibitors	Polyphenylurea derivatives
Survivin Targeting Drugs	LY2181308
Survivin Targeting Drugs	Ad-Survivin T34A
Anti-TWEAK Apoptosis Modifiers	BIIB023
Xanthine Oxidase Inhibitors	Allopurinol
Xanthine Oxidase Inhibitors	Febuxostat
Xanthine Oxidase Inhibitors	Zyloprin
Growth Factor	bFGF
Growth Factor	IGF
Growth Factor	TFG-beta
Growth Factor	BMP-2

Active Agent Class	Active Agent
Growth Factor	BMP-9
Growth Factor	BMP-13
Growth Factor	BMP-7
Growth Factor	BMP-3 inhibitors
Growth Factor	TFG- β 1
Growth Factor	OP-1
Growth Factor	PDGF
Growth Factor	PTH
Growth Factor	PTHrP
Growth Factor	MIP-3 α
Growth Factor	EPO
Growth Factor	FGF
Growth Factor	FGF-2
Growth Factor	FGF-18
Growth Factor	TGF- β 3
Growth Factor	VEGF
Growth Factor	Wnt proteins
Growth Factor	EGF
Growth Factor	GM-CSF
Flavonoid	Icariin
Flavonoid	Quercetin
Tyrosine Kinase Inhibitor (Lck/Btk Inhibitor)	Dasatinib
TRPV4 Activators	GSK1016790A
TRPV4 Activators	4 α -PDD
TRPV4 Inhibitors	HC-067047
TRPV4 Inhibitors	GSK2193874
NSAID	Ampion
NSAID	Phenylbutazone
NSAID	Naproxen lysozyme conjugate
NSAID	Acetal salicylic acid
DMARDs	Sulfasalazine
DMARDs	Leflunomide
DMARDs	Hydroxychloroquine (Plaquenil)
Disease-Modifying Osteoarthritis Drugs (DMOADs)	FGF-18
Uricosurics	Sulfinpyrazone
MSC Matrix	Collagen
MSC Matrix	Fibrin
MSC Matrix	Polylactatous
Surfactant	P188 and other surfactants

Active Agent Class	Active Agent
Molecules for Bone Marrow Niches	Angiopoetin
Molecules for Bone Marrow Niches	Bone morphogenetic proteins
Catecholamines	Epinephrine
Molecules for Bone Marrow Niches	Norepinephrine
Molecules for Bone Marrow Niches	GDF5
Molecules for Bone Marrow Niches	ICAN1
Molecules for Bone Marrow Niches	Jagged1
Molecules for Bone Marrow Niches	Osteopontin
Molecules for Bone Marrow Niches	parathyroid hormone
Molecules for Bone Marrow Niches	Calcitonin
Molecules for Bone Marrow Niches	steel factor
Molecules for Bone Marrow Niches	Thrombopoetin
Molecules for Bone Marrow Niches	vascular cell adhesion molecule 1
Chemokine Molecules for Bone Marrow Niches	CXCL12
B Cell Targeting Agents	Rituximab
B Cell Targeting Agents	BLys
B Cell Targeting Agents	TACI
T Cell Co-stimulation Antagonists	Abatacept
JAK Targeting Agents	Tofacitinib
Calcineurin Inhibitors	Tacrolimus
Calcineurin Inhibitors	Cyclosporin
Calcineurin Inhibitors	Voclosporin
COX-2 Inhibitors	Iguratimod
Leukotriene inhibitor	Montelukast
COX-2 Inhibitors	Rofecoxib
COX-2 Inhibitors	Valdecoxib
Interferon Receptor Inhibitors	Anifrolumab
IFN- α Inhibitors	Sifalimumab

Active Agent Class	Active Agent
Anti-IgE Agents	Omalizumab
iNOS Inhibitors	S-methylisothiourea
CD20 Antagonists/B Cell Inhibitors	Ocrelizumab
BAFF Antagonists/B Cell Inhibitors	Belimumab
TNF Superfamily BAFF and APRIL Antagonists/B cell Inhibitors	Atacicept
TNF- α Antagonists	Thalidomide
TNF- α Antagonists	Lenalidomide
TNF- α Antagonists	Pomalidomide
TNF- α Antagonists	Pentocifylline
TNF- α Antagonists	Bupropion
TNF Antagonists	Lentiviral-mediated RNAi
TNF Agonists	Recombinant TNF- α
TRAIL Receptor Agonists	HGS-ETR1
TRAIL Receptor Agonists	HGS-ETR2
TRAIL Receptor Agonists	HGS-TR2J
TRAIL Receptor Agonists	PRO1762
TRAIL Receptor Agonists	TRA-8
CD95/Fas Agonists	CD95-Fc
Marine Bioactive Compounds	TRAIL-Resistance Overcoming Marine Bioactive Compounds
Marine Bioactive Compounds	mazamine A
Marine Bioactive Compounds	marine-derived chromomycins
Marine Bioactive Compounds	Carotenoids
Marine Bioactive Compounds	Aplysin
Marine Bioactive Compounds	Aplidin
Marine Bioactive Compounds	Siphonaxanthin
Marine Bioactive Compounds	pectinotoxin-2
Anti-Complement Drugs	Eculizumab
PAR-2 Modulators	Pepducin P2pal-18
miR-2013 Blockers	Anti-sense oligonucleotides
Nrf2 Activator	Dimethyl fumarate
p53 Targeting Drugs	INGN201
p53 Targeting Drugs	SCH58500
p53 Targeting Drugs	ONYX-015
p53 Targeting Drugs	C-terminal p53 peptides
p53 Targeting Drugs	CDB3
p53 Targeting Drugs	CP31398

Active Agent Class	Active Agent
p53 Targeting Drugs	Prima-1
p53 Targeting Drugs	HPV E6-binding peptide aptamers
p53 Targeting Drugs	Nutlins
p53 Targeting Drugs	Chalcones
p53 Targeting Drugs	Small peptides
p53 Targeting Drugs	Pifithrin- α
p53 Targeting Drugs/Apoptosis Modifiers (T cells)	QP1-1002
Apaf-1 Targeting Drugs/Apoptosis Modifiers (T cells)	QM56
Apaf-1 Targeting Drugs/Apoptosis Modifiers (T cells)	SVT016426
Ferrostatin	16/86
BASP1 Targeting Drugs/Apoptosis Modifiers (T cells)	BASP siRNA
Anti-Inflammatory Drugs	CCX140
Anti-Inflammatory Drugs	CXA-10
Anti-Inflammatory Drugs/Anti-Fibrotic Drugs	Alkaline phosphatase
Anti-Fibrotic Drugs	Dnmt1 inhibitors
Anti-Inflammatory Drugs/Apoptosis Modifiers (T cells)	THR-184
Immunomodulation	Lithium
β 2-Adrenergic Agonists	Formoterol
Anti-Inflammatory Drugs	CRMD-001
Endothelin-1 Targeting Drugs	Astrasentan
Vasopressin Receptor Antagonists	Tolvaptan
Vasopressin Receptor Antagonists	RWJ-676070
Immunosuppressants	Azathioprine
Immunosuppressants	Mycophenolic acid
Immunosuppressants	Cyclosporine
Immune Modulators	Laquinimod
Slow-acting antirheumatic drugs (SAARDs)	
	Colcrys

Active Agent Class	Active Agent
Hormones	parathyroid hormone
Hormones	growth hormone
	11-beta hydroxysteroid dehydrogenases
	Mineralocorticoid
	Proopiomelanocortin
	fludrocortisonesoxycorticosterone acetate
	vaccines from live attenuated viruses
	Aspirin
	Insulin
	Isonizaid
	Oral hypoglycemic agents
	Antacids
	Carbamazepine
	Cholestyramine
	Colestipol
	Ephedrine
	Erythromycin
	Mitotane
	oral contraceptives
	Phenobarbital
	Phenytoin
	Rifampin
	Troleandomycin
	Non-selective caspase inhibitor
	okadaic acid
	Camptothetic
	Staurosporine
	HFA
	Alvesco inhalation
	Breo Ellipta
	Advair
	Mometasone
	Dulera
	Umeclidinium
	Anoro
Reactive Oxygen Species Targeting Drugs	
Cytokines/Growth Factors	TGF-beta

Active Agent Class	Active Agent
NOD-like receptor protein 3-dependent caspase 1 Targeting Drugs	
NSAID	Etoricoxib
Apoptosis Modifiers	MCL1 inhibitors
	Teriparatide
	BH3 mimetics
	AZD 4320
Carrier Proteins	Low molecular weight human serum albumin
Ceramide Targeting Drugs	
DMARDs	Penicillamine
Chondrogenic factors	
Anti-oxidative factors	
A(1)AR agonist	
S1P(2)R antagonist	
Antimalarials	
BAX/BAK activating drugs	
Selective GR Activators (SEGRAs)	
Rap1 Targeted Drugs	
Senolytic	Ephrin Ligand (EFN) B1 blockers
Senolytic	Cyclin-dependent kinase inhibitor 1A (p21) phosphatidylinositol-4,5-bisphosphate 3-kinase delta catalytic subunit (PI3KCD) blockers
Senolytic	Plasminogen-activated inhibitor-2 (PAI-2) blockers
Senesce-associated secretory phenotype (SASP) inhibitors	
Hormone	Tetracosactide
Peptide	Oligopeptide
Peptide	Polypeptide
Peptide	Peptidomimetic
Nucleic Acid	Polynucleotide
Nucleic Acid	Polyribonucleotide
Nucleic Acid	Oligonucleotide
Nucleic Acid	DNA
Nucleic Acid	cDNA
Nucleic Acid	ssDNA
Nucleic Acid	RNA
Nucleic Acid	dsRNA

Active Agent Class	Active Agent
Nucleic Acid	micro RNA
Nucleic Acid	Interfering RNA
Nucleic Acid	Aptamer
Antibody	single chain variable Fragment (scFv)
Antibody	Antibody Fragment
Peptide	Aptamer
Antibody	Fc domains
Antibody	Fc regions
Antibody	Fc active fragments or modifications thereof
Cytokine	
Cytokine antagonists	Mavrilimumab
Cytokine antagonists	Ixekizumab
Cytokine antagonists	Tocilizumab
Cytokine antagonists	Anakinra
Cytokine antagonists	Ustekinumab
Cytokine antagonists	Secukinumab
Interferon	
Hormone	
Enzymes	
Growth Factor	
Checkpoint Inhibitor	
CD Antigen	
Chemokines	
Neurotransmitters	
Ion Channel Inhibitors	
G-protein coupled receptor inhibitors	
G-protein coupled receptor activators	
Tumor necrosis factor inhibitors	
Chemical Agents	
Radiosensitizers	
Radioprotectants	
Radionuclide	
Therapeutic Small Molecules	
Steroids	
Corticosteroids	
Anti-inflammatory Agents	
Immune Modulators	Abatacept

Active Agent Class	Active Agent
Immune Modulators	Rituximab
Complement Fixing Peptides or Proteins	
Tumor Necrosis Factor Family Inhibitors	Tumor Necrosis Factor (TNF) soluble receptor or antibody
Tumor Necrosis Factor Family Activators	
Tumor Necrosis Factor (TNF) soluble receptor or antibody	
Caspase protease inhibitors or activators	
NF-kB, RIPK1 and/or RIPK3 Inhibitors	
NF-kB, RIPK1 and/or RIPK3 Activators	
Death-receptor ligand activator or inhibitor	
Tumor Necrosis Factor Family Agonists	TNFR1
Tumor Necrosis Factor Family Agonists	TNFR2
Tumor Necrosis Factor Family Agonists	CD27/TNFRSF7
Tumor Necrosis Factor Family Agonists	CD30/TNFRSF8
Tumor Necrosis Factor Family Agonists	OX40/TNFRSF4
Tumor Necrosis Factor Family Agonists	CD40/TNFRSF5
Tumor Necrosis Factor Family Agonists	4-1BB/TNFRSF9
Tumor Necrosis Factor Family Agonists	RANK (receptor activator of NF-kappa B/TNFRSF11A)
Tumor Necrosis Factor Family Agonists	TWEAK receptor/TNFRSF12A
Tumor Necrosis Factor Family Agonists	TAC1/TNFRSF13B
Tumor Necrosis Factor Family Agonists	BAFF-R (BAFF receptor/TNFRSF13C)

Active Agent Class	Active Agent
Tumor Necrosis Factor Family Agonists	HVEM (herpes virus entry mediator/TNFRSF14)
Tumor Necrosis Factor Family Agonists	REL1/TNFRSF19L
Tumor Necrosis Factor Family Agonists	ectodysplasin A2 isoform receptor/TNFRSF27
Tumor Necrosis Factor Family Agonists	ectodysplasin A1
TNF Family Member	Anhidrotic Receptor
Tumor Necrosis Factor Family Antagonists	Decoy Receptor 3/TNFRSF6B
Tumor Necrosis Factor Family Antagonists	Decoy Receptor 1/TNFRSF10C
Tumor Necrosis Factor Family Antagonists	Decoy Receptor 2/TNFRSF10D
Tumor Necrosis Factor Family Antagonists	DR3 (death receptor 3/TNFRSF25)
Tumor Necrosis Factor Family Antagonists	DR4 (death receptor 4/TNFRSF10A)
Tumor Necrosis Factor Family Antagonists	DR5 (death receptor 5/TNFRSF10B)
Tumor Necrosis Factor Family Antagonists	DR6 (death receptor 6/TNFRSF21)
Tumor Necrosis Factor Family Antagonists	Fas/TNFRSF6
Tumor Necrosis Factor Family Antagonists	Lymphotoxin b receptor/TNFRSF3
Tumor Necrosis Factor Family Antagonists	OPG (osteoprotegerin/TNFRSF11B)
Tumor Necrosis Factor Family Antagonists	Nerve Growth Factor Receptor/TNFRSF16
Tumor Necrosis Factor Family Antagonists	BCMA (B Cell Maturation Antigen/TNFRSF17)
Tumor Necrosis Factor Family Antagonists	GITR (Glucocorticoid-Induced TNF Receptor/TNFRSF18)
Tumor Necrosis Factor Family Antagonists	TAJ (Toxicity and JNK Inducer/TNFRSF19)
Tumor Necrosis Factor Family Antagonists	TNFRSF22
Tumor Necrosis Factor Family Antagonists	TNFRSF23

Active Agent Class	Active Agent
TNF Receptor Superfamily Ligands	TNF alpha
TNF Receptor Superfamily Ligands	Lymphotoxin-a
TNF Receptor Superfamily Ligands	Tumor Necrosis Factor Membrane Form
TNF Receptor Superfamily Ligands	Tumor Necrosis Factor Shed Form
TNF Receptor Superfamily Ligands	LIGHT
TNF Receptor Superfamily Ligands	Lymphotoxin b2a1 heterotrimer
TNF Receptor Superfamily Ligands	OX-40 Ligand
TNF Receptor Superfamily Ligands	Compound 1 [PMID: 24930776]
TNF Receptor Superfamily Ligands	CD40 Ligand
TNF Receptor Superfamily Ligands	Fas Ligand
TNF Receptor Superfamily Ligands	TL1A
TNF Receptor Superfamily Ligands	CD70
TNF Receptor Superfamily Ligands	CD30 Ligand
TNF Receptor Superfamily Ligands	TRAF1
TNF Receptor Superfamily Ligands	TRAF2
TNF Receptor Superfamily Ligands	TRAF3
TNF Receptor Superfamily Ligands	TRAIL
TNF Receptor Superfamily Ligands	RANK Ligand
TNF Receptor Superfamily Ligands	APRIL
TNF Receptor Superfamily Ligands	BAFF
TNF Receptor Superfamily Ligands	B and T lymphocyte Attenuators

Active Agent Class	Active Agent
TRK Receptor Superfamily Ligands	NGF
TRK Receptor Superfamily Ligands	BDNF
TRK Receptor Superfamily Ligands	Neurotrophin-3
TRK Receptor Superfamily Ligands	Neurotrophin-4
TNF Receptor Superfamily Ligands	TL6
TNF Receptor Superfamily Ligands	Ectodysplasin A2
TNF Receptor Superfamily Ligands	Ectodysplasin A1
TNF blockers	Remicade (infliximab)
TNF blockers	Enbrel (etanercept)
TNF blockers	Humira (adalimumab)
TNF blockers	Cimzia (certolizumab pegol)
TNF blockers	Simponi (golimumab)
Tumor Necrosis Factor Receptor Family Agonists	
Toll Like Receptors Agonist	
TIMP-3 Inhibitors	
BCL-2 Family Inhibitors	
IAP Disruptors	
Protease Inhibitors	
Amino Sugars	
Chemotherapeutic	
Cytotoxic chemical	
Toxins	
Tyrosine Kinase inhibitors	Imatinib Mesylate
Protons	
Antivascular Agents	Bevacizumab
EGFR Inhibitors	Erlotinib
Anti-Infective Agents	
Antibiotics	
Anti-Viral Agents	
Anti-Fungal Agents	
Aminoglycoside	
Statins	
Nanoparticles	

Active Agent Class	Active Agent
Liposomes	
Polymers	Biopolymers
Polysaccharide	
Proteoglycan	
Glycosaminoglycans	
Polyethylene glycol	
Lipids	
Dendrimers	
Fatty Acids	
Glucocorticoid	
Corticosteroid	
Collagenase Inhibitor	
Matrix Metalloprotease Inhibitors	MMP-13 inhibitor
Vitamins	Vitamin D
Antibiotics	
Antiviral	
Antifungal	
Statins	
Immune Modulators	
Radioisotopes	
Toxins	
Enzymes	
Sensitizing drugs	
Anti-Angiogenic Agents	Cisplatin
Anti-Angiogenic Agents	Anti-Metabolites
Anti-Angiogenic Agents	Mitotic Inhibitors
Anti-Angiogenic Agents	Growth Factor Inhibitors
Chemotherapeutic Agent	Paclitaxel
Chemotherapeutic Agent	Temozolomide
Chemotherapeutic Agent	Topotecan
Chemotherapeutic Agent	Fluorouracil
Chemotherapeutic Agent	Vincristine
Chemotherapeutic Agent	Vinblastine
Chemotherapeutic Agent	Procarbazine
Chemotherapeutic Agent	Decarbazine
Chemotherapeutic Agent	Altretamine
Chemotherapeutic Agent	Methotrexate
Chemotherapeutic Agent	Mercaptopurine
Chemotherapeutic Agent	Thioguanine
Chemotherapeutic Agent	Fludarabine Phosphate
Chemotherapeutic Agent	Cladribine

Active Agent Class	Active Agent
Chemotherapeutic Agent	Pentostatin
Chemotherapeutic Agent	Cytarabine
Chemotherapeutic Agent	Azacitidine
Chemotherapeutic Agent	Etoposide
Chemotherapeutic Agent	Teniposide
Chemotherapeutic Agent	Irinotecan
Chemotherapeutic Agent	Docetaxel
Chemotherapeutic Agent	Doxorubicin
Chemotherapeutic Agent	Daunorubicin
Chemotherapeutic Agent	Dactinomycin
Chemotherapeutic Agent	Idarubicin
Chemotherapeutic Agent	Plicamycin
Chemotherapeutic Agent	Mitomycin
Chemotherapeutic Agent	Bleomycin
Chemotherapeutic Agent	Tamoxifen
Chemotherapeutic Agent	Flutamide
Chemotherapeutic Agent	Leuprolide
Chemotherapeutic Agent	Goserelin
Chemotherapeutic Agent	Aminogluthimide
Chemotherapeutic Agent	Anastrozole
Chemotherapeutic Agent	Amsacrine
Chemotherapeutic Agent	Asparaginase
Chemotherapeutic Agent	Mitoxantrone
Chemotherapeutic Agent	Mitotane
Chemotherapeutic Agent	Amifostine
Apoptotic Agents	
Cell Death or Cell Killing Agents	Caspases
Apoptosis Activators	
Apoptosis Inhibitors	XBP-1
Apoptosis Inhibitors	Bcl-2
Apoptosis Inhibitors	Bcl-Xl
Apoptosis Inhibitors	Bcl-w
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	COX-2 Inhibitors
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Ketorolac
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Indomethacin
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Etodolac

Active Agent Class	Active Agent
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Tolemetin
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Naproxen
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Enolic Acid Derivatives
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Anthranilic Acid Derivatives
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Celecoxib
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Sulfonanilides
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Salicylates
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Aceclofenac
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Nabumetone
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Sulindac
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Diclofenac
Nonsteroidal Anti-Inflammatory Drugs (NSAID)	Ibuprofen
Steroids	Dexamethasone
Steroids	Budesonide
Steroids	Triamcinolone
Steroids	Triamcinolone acetonide
Steroids	Cortisone
Steroids	Prednisone
Steroids	Prednisolone
Steroids	Triamcinolone Hexacetonide
Steroids	Methylprednisolone
Pain Reliever	Acetaminophen
Opioids	
Local Anesthetics	
Anti-Depressants	
Glutamate Receptor Antagonists	
	Adenosine
Neuropeptides	
Uricase	

Active Agent Class	Active Agent
Elastase	

[0167] Further examples of active agents include but are not limited to: a peptide, an oligopeptide, a polypeptide, a peptidomimetic, a polynucleotide, a polyribonucleotide, a DNA, a cDNA, a ssDNA, a RNA, a dsRNA, a micro RNA, an RNAi, an oligonucleotide, an antibody, a single chain variable fragment (scFv), an antibody fragment, an aptamer, a cytokine, an interferon, a hormone, an enzyme, a growth factor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a CD antigen, a chemokine, a neurotransmitter, an ion channel inhibitor, a G-protein coupled receptor inhibitor, a G-protein coupled receptor activator, a chemical agent, a radiosensitizer, a radioprotectant, a radionuclide, a therapeutic small molecule, a steroid, a corticosteroid, an anti-inflammatory agent, an immune modulator, a complement fixing peptide or protein, a tumor necrosis factor inhibitor, a tumor necrosis factor activator, a tumor necrosis factor receptor family agonist, a tumor necrosis receptor antagonist, a tumor necrosis factor (TNF) soluble receptor or antibody, caspase protease activator or inhibitor, an NF- κ B a RIPK1 and/or RIPK3 inhibitor or activator (e.g., through Toll-like receptors (TLRs) TLR-3 and/or TLR-4, or T-cell receptor (TCR) and the like), a death-receptor ligand (e.g., Fas ligand) activator or inhibitor, TNF receptor family (e.g., TNFR1, TNFR2, lymphotoxin β receptor/TNFRSF3, OX40/TNFRSF4, CD40/TNFRSF5, Fas/TNFRSF6, decoy receptor 3/TNFRSF6B, CD27/TNFRSF7, CD30/TNFRSF8, 4-1BB/TNFRSF9, DR4 (death receptor 4/TNFRSF10A), DR5 (death receptor 5/TNFRSF10B), decoy receptor 1/TNFRSF10C, decoy receptor 2/TNFRSF10D, RANK (receptor activator of NF-kappa B/TNFRSF11A), OPG (osteoprotegerin/TNFRSF11B), DR3 (death receptor 3/TNFRSF25), TWEAK receptor/TNFRSF12A, TACI/TNFRSF13B, BAFF-R (BAFF receptor/TNFRSF13C), HVEM (herpes virus entry mediator/TNFRSF14), nerve growth factor receptor/TNFRSF16, BCMA (B cell maturation antigen/TNFRSF17), GITR (glucocorticoid-induced TNF receptor/TNFRSF18), TAJ (toxicity and JNK inducer/TNFRSF19), RELT/TNFRSF19L, DR6 (death receptor 6/TNFRSF21), TNFRSF22, TNFRSF23, ectodysplasin A2 isoform receptor/TNFRSF27, ectodysplasin 1, and anhidrotic receptor, a TNF receptor superfamily ligand including – TNF alpha, lymphotoxin- α , tumor necrosis factor membrane form, tumor necrosis factor shed form, LIGHT, lymphotoxin $\beta_2\alpha_1$ heterotrimer, OX-40 ligand, compound 1 [PMID: 24930776], CD40 ligand, Fas ligand, TL1A, CD70, CD30 ligand, TRAF1, TRAF2, TRAF3, TRAIL, RANK ligand, APRIL, BAFF, B and T lymphocyte attenuator, NGF, BDNF, neurotrophin-3, neurotrophin-4, TL6, ectodysplasin A2, ectodysplasin A1 – a TIMP-3 inhibitor, a BCL-2 family inhibitor, navitoclax (Aging Cell. 15(3): 428–435. (2016)) an IAP disruptor, a protease inhibitor,

an amino sugar, a chemotherapeutic (whether acting through an apoptotic or non-apoptotic pathway) (Ricci et al. *Oncologist* 11(4):342-57 (2006)), a cytotoxic chemical, a toxin, a tyrosine kinase inhibitor (e.g., imatinib mesylate), protons, bevacuzimab (antivascular agent), erlotinib (EGFR inhibitor), an anti-infective agent, an antibiotic, an anti-viral agent, an anti-fungal agent, an aminoglycoside, a nonsteroidal anti-inflammatory drug (NSAID), a statin, a nanoparticle, a liposome, a polymer, a biopolymer, a polysaccharide, a proteoglycan, a glycosaminoglycan, polyethylene glycol, a lipid, a dendrimer, a fatty acid, or an Fc domain or an Fc region, or an active fragment or a modification thereof. Any combination of the above active agents can be co-delivered with peptides or peptide conjugates of this disclosure. Additionally, in some embodiments, other co-therapies such as proton therapy or ablative radiotherapy can be administered to a subject in need thereof along with peptides or peptide conjugates of this disclosure. In some embodiments, the peptide is covalently or non-covalently linked to an active agent, e.g., directly or via a linker. TNF blockers suppress the immune system by blocking the activity of TNF, a substance in the body that can cause inflammation and lead to immune-system diseases, such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. The drugs in this class include Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab pegol) and Simponi (golimumab). The peptide disclosed herein can be used to home, distribute to, target, directed to, is retained by, accumulate in, migrate to, and/or bind to cartilage, and thus also be used for localizing the attached or fused active agent. Furthermore, cystine-dense chlorotoxin peptide can be internalized in cells (Wiranowska, M. , *Cancer Cell Int.* , 11: 27 (2011)). Therefore, cellular internalization, subcellular localization, and intracellular trafficking after internalization of the peptide itself, or an active agent peptide conjugate or fusion peptide can be important factors in the efficacy of an active agent conjugate or fusion. (Ducry, L., *Antibody Drug Conjugates* (2013); and Singh, S. K., *Pharm Res.*, 32(11): 3541–3571 (2015)). Exemplary linkers suitable for use with the embodiments herein are discussed in further detail below.

[0168] The peptides or peptide-active agent fusions of the present disclosure can also be complexed, conjugated, or fused to other moieties that can serve other roles, such as providing an affinity handle (e.g., biotin) for retrieval of the peptides from tissues or fluids. For example, peptides or peptide-active agent fusions of the present disclosure can also be complexed, conjugated, or fused to biotin. In addition to extension of half-life, biotin could also act as an affinity handle for retrieval of peptides or peptide-active agent fusions from tissues or other locations. In some embodiments, fluorescent biotin conjugates that can act both as a detectable label and an affinity handle can be used. Non limiting examples of commercially available

fluorescent biotin conjugates include Atto 425-Biotin, Atto 488-Biotin, Atto 520-Biotin, Atto-550 Biotin, Atto 565-Biotin, Atto 590-Biotin, Atto 610-Biotin, Atto 620-Biotin, Atto 655-Biotin, Atto 680-Biotin, Atto 700-Biotin, Atto 725-Biotin, Atto 740-Biotin, fluorescein biotin, biotin-4-fluorescein, biotin-(5-fluorescein) conjugate, and biotin-B-phycoerythrin, Alexa fluor 488 biocytin, Alexa flour 546, Alexa Fluor 549, lucifer yellow cadaverine biotin-X, Lucifer yellow biocytin, Oregon green 488 biocytin, biotin-rhodamine and tetramethylrhodamine biocytin. In some other examples, the conjugates could include chemiluminescent compounds, colloidal metals, luminescent compounds, enzymes, radioisotopes, and paramagnetic labels. In some embodiments, the peptide-active agent fusions described herein can be attached to another molecule. For example, the peptide sequence also can be attached to another active agent (e.g., small molecule, peptide, polypeptide, polynucleotide, antibody, aptamer, cytokine, growth factor, neurotransmitter, an active fragment or modification of any of the preceding, fluorophore, radioisotope, radionuclide chelator, acyl adduct, chemical linker, or sugar, etc.). In some embodiments, the peptide can be fused with, or covalently or non-covalently linked to an active agent.

[0169] Additionally, more than one peptide sequence can be present on or fused with a particular peptide. A peptide can be incorporated into a biomolecule by various techniques, for example by a chemical transformation, such as the formation of a covalent bond, such as an amide bond, or by solid phase or solution phase peptide synthesis, or by preparing a nucleic acid sequence encoding the biomolecule, wherein the nucleic acid sequence includes a subsequence that encodes the peptide. The subsequence can be in addition to the sequence that encodes the biomolecule, or can substitute for a subsequence of the sequence that encodes the biomolecule.

Detectable Agent Conjugates

[0170] Described herein are agents that can be complexed, conjugated, or fused to the peptides of the present invention for use in detection and tracing either cartilage disorders or kidney disorders, or both. As described herein, it is understood that certain active agents are described in a non-limiting exemplary manner for use in diagnostics, aiding surgery and treatment, prognosis and tracking of progress or remission of cartilage and/or kidney disorders, diseases or injury. One or more of such detectable agents can be complexed, conjugated, or fused to a peptide of the present invention alone or in combination with one or more active agents described herein. Moreover some detectable agents (e.g., radionuclides, radioisotopes, radiosensitizers and photosensitizers amongst others) may also exert therapeutic activity as well. A peptide can be complexed, conjugated, or fused to an agent used in imaging, research, therapeutics, theranostics, pharmaceuticals, chemotherapy, chelation therapy, targeted drug delivery, and

radiotherapy. The agent can be a detectable agent. In some embodiments, a peptide of the present invention is complexed, conjugated, or fused to detectable agents, such as a metal, a radioisotope, a dye, fluorophore, or another suitable material that can be used in imaging. Non-limiting examples of radioisotopes include alpha emitters, beta emitters, positron emitters, and gamma emitters. In some embodiments, the metal or radioisotope is selected from the group consisting of actinium, americium, bismuth, cadmium, cesium, cobalt, europium, gadolinium, iridium, lead, lutetium, manganese, palladium, polonium, radium, ruthenium, samarium, strontium, technetium, thallium, and yttrium. In some embodiments, the metal is actinium, bismuth, lead, radium, strontium, samarium, or yttrium. In some embodiments, the radioisotope is actinium-225 or lead-212. In some embodiments, the fluorophore is a fluorescent agent emitting electromagnetic radiation at a wavelength between 650 nm and 4000 nm, such emissions being used to detect such agent. In some embodiments the fluorophore is a fluorescent agent is selected from the group consisting of non-limiting examples of fluorescent dyes that could be used as a conjugating molecule (or as applied to each class of molecules) in the present disclosure include DyLight-680, DyLight-750, VivoTag-750, DyLight-800, IRDye-800, VivoTag-680, Cy5, 5, or indocyanine green (ICG class of dyes). In some embodiments, near infrared dyes include cyanine dyes. Additional non-limiting examples of fluorescent dyes for use as a conjugating molecule in the present disclosure include acradine orange or yellow, Alexa Fluors and any derivative thereof, 7-actinomycin D, 8-anilinonaphthalene-1-sulfonic acid, ATTO dye and any derivative thereof, auramine-rhodamine stain and any derivative thereof, bensanthrone, bimean, 9-10-bis(phenylethynyl)anthracene, 5,12 – bis(phenylethynyl)anthracene, bisbenzimidazole, brainbow, calcein, carboxyfluorescein and any derivative thereof, 1-chloro-9,10-bis(phenylethynyl)anthracene and any derivative thereof, DAPI, DiOC6, DyLight Fluors and any derivative thereof, epicocconone, ethidium bromide, FAsH-EDT2, Fluo dye and any derivative thereof, FluoProbe and any derivative thereof, Fluorescein and any derivative thereof, Fura and any derivative thereof, GelGreen and any derivative thereof, GelRed and any derivative thereof, fluorescent proteins and any derivative thereof, m isoform proteins and any derivative thereof such as for example mCherry, hetamethine dye and any derivative thereof, hoeschst stain, iminocoumarin, indian yellow, indo-1 and any derivative thereof, laurdan, lucifer yellow and any derivative thereof, luciferin and any derivative thereof, luciferase and any derivative thereof, mercocyanine and any derivative thereof, Nile dyes and any derivative thereof, perylene, phloxine, phyco dye and any derivative thereof, propidium iodide, pyranine, rhodamine and any derivative thereof, ribogreen, RoGFP, rubrene, stilbene and any derivative thereof, sulforhodamine and any derivative thereof, SYBR

and any derivative thereof, synapto-pHluorin, tetraphenyl butadiene, tetrasodium tris, Texas Red, Titan Yellow, TSQ, umbelliferone, violanthrone, yellow fluorescent protein and YOYO-1. Other Suitable fluorescent dyes include, but are not limited to, fluorescein and fluorescein dyes (e.g., fluorescein isothiocyanine or FITC, naphthofluorescein, 4', 5'-dichloro-2',7' - dimethoxyfluorescein, 6-carboxyfluorescein or FAM, etc.), carbocyanine, merocyanine, styryl dyes, oxonol dyes, phycoerythrin, erythrosin, eosin, rhodamine dyes (e.g., carboxytetramethyl-rhodamine or TAMRA, carboxyrhodamine 6G, carboxy-X-rhodamine (ROX), lissamine rhodamine B, rhodamine 6G, rhodamine Green, rhodamine Red, tetramethylrhodamine (TMR), etc.), coumarin and coumarin dyes (e.g., methoxycoumarin, dialkylaminocoumarin, hydroxycoumarin, aminomethylcoumarin (AMCA), etc.), Oregon Green Dyes (e.g., Oregon Green 488, Oregon Green 500, Oregon Green 514. , etc.), Texas Red, Texas Red-X, SPECTRUM RED, SPECTRUM GREEN, cyanine dyes (e.g., CY-3, Cy-5, CY-3. 5, CY-5. 5, etc.), ALEXA FLUOR dyes (e.g., ALEXA FLUOR 350, ALEXA FLUOR 488, ALEXA FLUOR 532, ALEXA FLUOR 546, ALEXA FLUOR 568, ALEXA FLUOR 594, ALEXA FLUOR 633, ALEXA FLUOR 660, ALEXA FLUOR 680, etc.), BODIPY dyes (e.g., BODIPY FL, BODIPY R6G, BODIPY TMR, BODIPY TR, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY 630/650, BODIPY 650/665, etc.), IRDyes (e.g., IRD40, IRD 700, IRD 800, etc.), indocyanine green dyes, and the like. For each of the above listed fluorescent dyes various activated forms can be used for conjugation. Additional suitable detectable agents are described in PCT/US14/56177. Non-limiting examples of radioisotopes include alpha emitters, beta emitters, positron emitters, and gamma emitters. In some embodiments, the metal or radioisotope is selected from the group consisting of actinium, americium, bismuth, cadmium, cesium, cobalt, europium, gadolinium, iridium, lead, lutetium, manganese, palladium, polonium, radium, ruthenium, samarium, strontium, technetium, thallium, and yttrium. In some embodiments, the metal is actinium, bismuth, lead, radium, strontium, samarium, or yttrium. In some embodiments, the radioisotope is actinium-225 or lead-212.

[0171] Other embodiments of the present disclosure provide peptides complexed, conjugated, or fused to a radiosensitizer or photosensitizer. Examples of radiosensitizers include but are not limited to: ABT-263, ABT-199, WEHI-539, paclitaxel, carboplatin, cisplatin, oxaliplatin, gemcitabine, etanidazole, misonidazole, tirapazamine, and nucleic acid base derivatives (e.g., halogenated purines or pyrimidines, such as 5-fluorodeoxyuridine). Examples of photosensitizers include but are not limited to: fluorescent molecules or beads that generate heat when illuminated, porphyrins and porphyrin derivatives (e.g., chlorins, bacteriochlorins,

isobacteriochlorins, phthalocyanines, and naphthalocyanines), metalloporphyrins, metallophthalocyanines, angelicins, chalcogenapyrrillium dyes, chlorophylls, coumarins, flavins and related compounds such as alloxazine and riboflavin, fullerenes, pheophorbides, pyropheophorbides, cyanines (e.g., merocyanine 540), pheophytins, sapphyrins, texaphyrins, purpurins, porphycenes, phenothiaziniums, methylene blue derivatives, naphthalimides, Nile blue derivatives, quinones, perylenequinones (e.g., hypericins, hypocrellins, and cercosporins), psoralens, quinones, retinoids, rhodamines, thiophenes, verdins, xanthene dyes (e.g., eosins, erythrosins, rose bengals), dimeric and oligomeric forms of porphyrins, and prodrugs such as 5-aminolevulinic acid. Advantageously, this approach allows for highly specific targeting of diseased cells (e.g., cancer cells) using both a therapeutic agent (e.g., drug) and electromagnetic energy (e.g., radiation or light) concurrently. In some embodiments, the peptide is covalently or non-covalently linked to the agent, e.g., directly or via a linker. Exemplary linkers suitable for use with the embodiments herein are discussed in further detail below.

[0172] The peptides or peptide-agent complexes of the present disclosure can be administered alone or in combination with a companion diagnostic, therapeutic agent, or imaging agent (said diagnostic or imaging agent can be linked to the peptides or peptide-agent complexes or, alternatively, can be used as a separate companion diagnostic, therapeutic agent, or imaging agent linked to the peptide for use in conjunction with the peptides or peptide-agent complex), such as chemical agents, radiolabel agents, radiosensitizing agents, fluorophores, imaging agents, diagnostic agents, proteins, peptides, or small molecules, wherein said agents are intended to have or have diagnostic or imaging effects. Agents used for companion diagnostic agents and companion imaging agents can include the diagnostic, therapeutic agent, and imaging agents described herein, or other diagnostic, therapeutic agent, and imaging agents consistent with the present disclosure. Diagnostic tests can be used to enhance the use of therapeutic products, such as those disclosed herein. The development of therapeutic products with a corresponding diagnostic test, such as a test that uses diagnostic imaging (whether in vivo or in vitro) can aid in diagnosis, treatment, identification of patient populations for treatment, and enhancement of the therapeutic effect of the corresponding therapy. Detection of therapeutic agents, such as those peptide and peptide agent complexes disclosed can also aid in the application of a therapy and to measure it to assess the agent's safety and physiologic effect, e.g. to measure bioavailability, uptake, distribution and clearance, metabolism, pharmacokinetics, localization, measurement of concentrations in blood and tissues, assessing therapeutic window, range and optimization, and the like of the therapeutic agent. Thus systems and methods can be employed in the context of therapeutic, imaging and diagnostic applications of such agents including peptides or peptide-

agent complexes disclosed herein. Tests also aid therapeutic product development to obtain the data FDA uses to make regulatory determinations. For example, such a test can identify appropriate subpopulations for treatment or identify populations who should not receive a particular treatment because of an increased risk of a serious side effect, making it possible to individualize, or personalize, medical therapy by identifying patients who are most likely to respond, or who are at varying degrees of risk for a particular side effect. Thus, the present disclosure, in some embodiments, includes the joint development of therapeutic products and diagnostic devices (used to detect the peptide or peptide agent complexes themselves, or used to detect the companion diagnostic, therapeutic, or imaging agent, whether said diagnostic, therapeutic, or imaging agent is linked to the peptides or peptide-agent complex or used as a separate companion diagnostic, therapeutic, or imaging agent linked to the peptide for use in conjunction with the peptides or peptide-agent complex) that are used in conjunction with safe and effective use of the peptides or peptide-agent complexes as therapeutic products. Non-limiting examples of companion devices include a surgical instrument, such as an operating microscope, confocal microscope, fluorescence scope, exoscope, endoscope, or a surgical robot and devices used in biological diagnosis or imaging or that incorporate radiology, including the imaging technologies of X-ray radiography, magnetic resonance imaging (MRI), medical ultrasonography or ultrasound, endoscopy, elastography, tactile imaging, thermography, medical photography, and nuclear medicine functional imaging techniques, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Companion diagnostics, therapeutics, imaging agents, and devices can comprise tests that are conducted ex vivo, including detection of signal from tissues or cells that are removed following administration of the companion diagnostic to the subject, or application of the companion diagnostic, therapeutics, or companion imaging agent directly to tissues or cells following their removal from the subject and then detecting the signal. Examples of devices used for ex vivo detection include fluorescence microscopes, flow cytometers, and the like. Moreover, the systems and devices for such use in companion diagnostics include a surgical microscope, confocal microscope, fluorescence scope, exoscope, endoscope, or a surgical robot, including a KINEVO system (e.g., KINEVO 900), QEVO system, CONVIVO system, OMPI PENTERO system (e.g., PENTERO 900, PENTERO 800), INFRARED 800 system, FLOW 800 system, YELLOW 560 system, BLUE 400 system, OMPI LUMERIA systems OMPI Vario system (e.g., OMPI Vario and OMPI VARIO 700), OMPI Pico system, TREMON 3DHD system (and any additional exemplary surgical microscope, confocal microscope, fluorescence scope, exoscope, endoscope, and surgical robot systems from Carl Zeiss A/G); a PROVido system, ARvido

system, GLOW 800 system, Leica M530 system (e.g., Leica M530 OHX, Leica M530 OH6), Leica M720 system (e.g., Leica M720 OHX5), Leica M525 System (e.g., Leica M525 F50, Leica M525 F40, Leica M525 F20, Leica M525 OH4), Leica HD C100 system, Leica FL system (e.g., Leica FL560, Leica FL400, Leica FL800), Leica DI C500, Leica ULT500, Leica Rotatable Beam Splitter, Leica M651 MSD, LIGHTENING, Leica TCS and SP8 systems (e.g., Leica TCS SP8, SP8 FALCON, SP8 DIVE, Leica TCS SP8 STED, Leica TCS SP8 DLS, Leica TCS SP8 X, Leica TCS SP8 CARS, Leica TCS SPE), Leica HyD, Leica HCS A, Leica DCM8 (and any additional exemplary surgical microscope, confocal microscope, fluorescence scope, exoscope, endoscope, and surgical robot systems from Leica Microsystems or Leica Biosystems); Haag-Streit 5-1000 and Haag-Streit 3-1000 systems (and any additional exemplary surgical microscope, confocal microscope, fluorescence scope, exoscope, endoscope, and surgical robot systems from Haag-Streit A/G); Intuitive Surgical da Vinci surgical robot systems (and any additional exemplary surgical microscope, confocal microscope, fluorescence scope, exoscope, endoscope, and surgical robot systems from Intuitive Surgical, Inc.).

Linkers

[0173] Peptides according to the present disclosure that home, target, migrate to, are retained by, accumulate in, and/or bind to, or are directed to the cartilage can be attached to another moiety (e.g., an active agent), such as a small molecule, a second peptide, a protein, an antibody, an antibody fragment, an aptamer, polypeptide, polynucleotide, a fluorophore, a radioisotope, a radionuclide chelator, a polymer, a biopolymer, a fatty acid, an acyl adduct, a chemical linker, or sugar or other active agent described herein through a linker, or directly in the absence of a linker.

[0174] A peptide can be directly attached to another molecule by a covalent attachment. For example, the peptide is attached to a terminus of the amino acid sequence of a larger polypeptide or peptide molecule, or is attached to a side chain, such as the side chain of a lysine, serine, threonine, cysteine, tyrosine, aspartic acid, a non-natural amino acid residue, or glutamic acid residue. The attachment can be via an amide bond, an ester bond, an ether bond, a carbamate bond, a carbon-nitrogen bond, a triazole, a macrocycle, an oxime bond, a hydrazone bond, a carbon-carbon single double or triple bond, a disulfide bond, or a thioether bond. In some embodiments, similar regions of the disclosed peptide(s) itself (such as a terminus of the amino acid sequence, an amino acid side chain, such as the side chain of a lysine, serine, threonine, cysteine, tyrosine, aspartic acid, a non-natural amino acid residue, or glutamic acid residue, via an amide bond, an ester bond, an ether bond, a carbamate bond, a carbon-nitrogen bond, a triazole, a macrocycle, an oxime bond, a hydrazone bond, a carbon-carbon single double or triple

bond, a disulfide bond, or a thioether bond, or linker as described herein) can be used to link other molecules.

[0175] Attachment via a linker can involve incorporation of a linker moiety between the other molecule and the peptide. The peptide and the other molecule can both be covalently attached to the linker. The linker can be cleavable, labile, non-cleavable, stable, stable self-immolating, hydrophilic, or hydrophobic. As used herein, the term “non-cleavable” or “stable” (such as used in association with an amide, cyclic, or carbamate linker or as otherwise as described herein) is often used by a skilled artisan to distinguish a relatively stable structure from one that is more labile or “cleavable” (e.g., as used in association with cleavable linkers that may be dissociated or cleaved structurally by enzymes, proteases, self-immolation, pH, reduction, hydrolysis, certain physiologic conditions, or as otherwise described herein). It is understood that “non-cleavable” or “stable” linkers offer stability against cleavage or other dissociation as compared to “cleavable” linkers, and the term is not intended to be considered an absolute non-cleavable or non-dissociative structure under any conditions. Consequently, as used herein, a “non-cleavable” linker is also referred to as a “stable” linker. The linker can have at least two functional groups with one bonded to the peptide, the other bonded to the other molecule, and a linking portion between the two functional groups.

[0176] Non-limiting examples of the functional groups for attachment can include functional groups capable of forming an amide bond, an ester bond, an ether bond, a carbonate bond, a carbamate bond, or a thioether bond. Non-limiting examples of functional groups capable of forming such bonds can include amino groups; carboxyl groups; hydroxyl groups; aldehyde groups; azide groups; alkyne and alkene groups; ketones; hydrazides; acid halides such as acid fluorides, chlorides, bromides, and iodides; acid anhydrides, including symmetrical, mixed, and cyclic anhydrides; carbonates; carbonyl functionalities bonded to leaving groups such as cyano, succinimidyl, and *N*-hydroxysuccinimidyl; hydroxyl groups; sulfhydryl groups; and molecules possessing, for example, alkyl, alkenyl, alkynyl, allylic, or benzylic leaving groups, such as halides, mesylates, tosylates, triflates, epoxides, phosphate esters, sulfate esters, and besylates.

[0177] Non-limiting examples of the linking portion can include alkylene, alkenylene, alkynylene, polyether, such as polyethylene glycol (PEG), hydroxy carboxylic acids, polyester, polyamide, polyamino acids, polypeptides, cleavable peptides, valine-citrulline, aminobenzylcarbamates, D-amino acids, and polyamine, any of which being unsubstituted or substituted with any number of substituents, such as halogens, hydroxyl groups, sulfhydryl groups, amino groups, nitro groups, nitroso groups, cyano groups, azido groups, sulfoxide groups, sulfone groups, sulfonamide groups, carboxyl groups, carboxaldehyde groups, imine

groups, alkyl groups, halo-alkyl groups, alkenyl groups, halo-alkenyl groups, alkynyl groups, halo-alkynyl groups, alkoxy groups, aryl groups, aryloxy groups, aralkyl groups, arylalkoxy groups, heterocyclyl groups, acyl groups, acyloxy groups, carbamate groups, amide groups, urethane groups, epoxides, and ester groups.

[0178] A peptide and drug complexed, conjugated, or fused via a linker is described with the formula Peptide-A-B-C-Drug, wherein the linker is A-B-C. A can be a stable amide link, is an amine on the peptide and the linker and can be achieved via a tetrafluorophenyl (TFP) ester or an NHS ester. B can be $(-\text{CH}_2-)_x$ - or a short PEG $(-\text{CH}_2\text{CH}_2\text{O}-)_x$ (x is 1-10), and C can be the ester bond to the hydroxyl or carboxylic acid on the drug. In some embodiments, C can refer to the “cleavable” or “stable” part of the linker. In other embodiments, A can also be the “cleavable” part. In some embodiments, A can be amide, carbamate, thioether via maleimide or bromoacetamide, triazole, oxime, or oxacarboline. The cleaved active agent or drug can retain the chemical structure of the active agent before cleavage, or can be modified as a result of cleavage. Moreover, depending on the desired therapeutic properties of the peptide-drug conjugate, such active agent can be active while linked to the peptide, remain active after cleavage or become inactivated, be inactive while linked to the peptide, or it can be activated upon cleavage.

[0179] In some embodiments, peptide conjugates have stable linkers. A peptide of the disclosure can be expressed recombinantly or chemically synthesized. The peptide can be complexed, conjugated, or fused to a detectable agent or an active agent via a stable linker, such as an amide linkage or a carbamate linkage. The peptide can be complexed, conjugated, or fused to a detectable agent or an active agent via a stable linker, such as an amide bond using standard 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) or dicyclohexylcarbodiimide (DCC) based chemistry or thionyl chloride or phosphorous chloride-based bioconjugation chemistries. A stable linker may or may not be cleaved in buffer over extended periods of time (e.g., hours, days, or weeks). A stable linker may or may not be cleaved in body fluids such as plasma or synovial fluid over extended periods of time (e.g., hours, days, or weeks). A stable linker, may or may not be cleaved after exposure to enzymes, reactive oxygen species, other chemicals or enzymes that can be present in cells (e.g., macrophages), cellular compartments (e.g., endosomes and lysosomes), inflamed areas of the body (e.g., inflamed joints), tissues or body compartments. A stable linker may be cleaved by unknown mechanisms. A stable linker may or may not be cleaved in vivo but remains an active agent after peptide conjugation.

[0180] A peptide and drug complexed, conjugated, or fused via a linker can be described with the formula Peptide-A-B-C-Drug, wherein the linker is A-B-C. A can be a stable amide link such

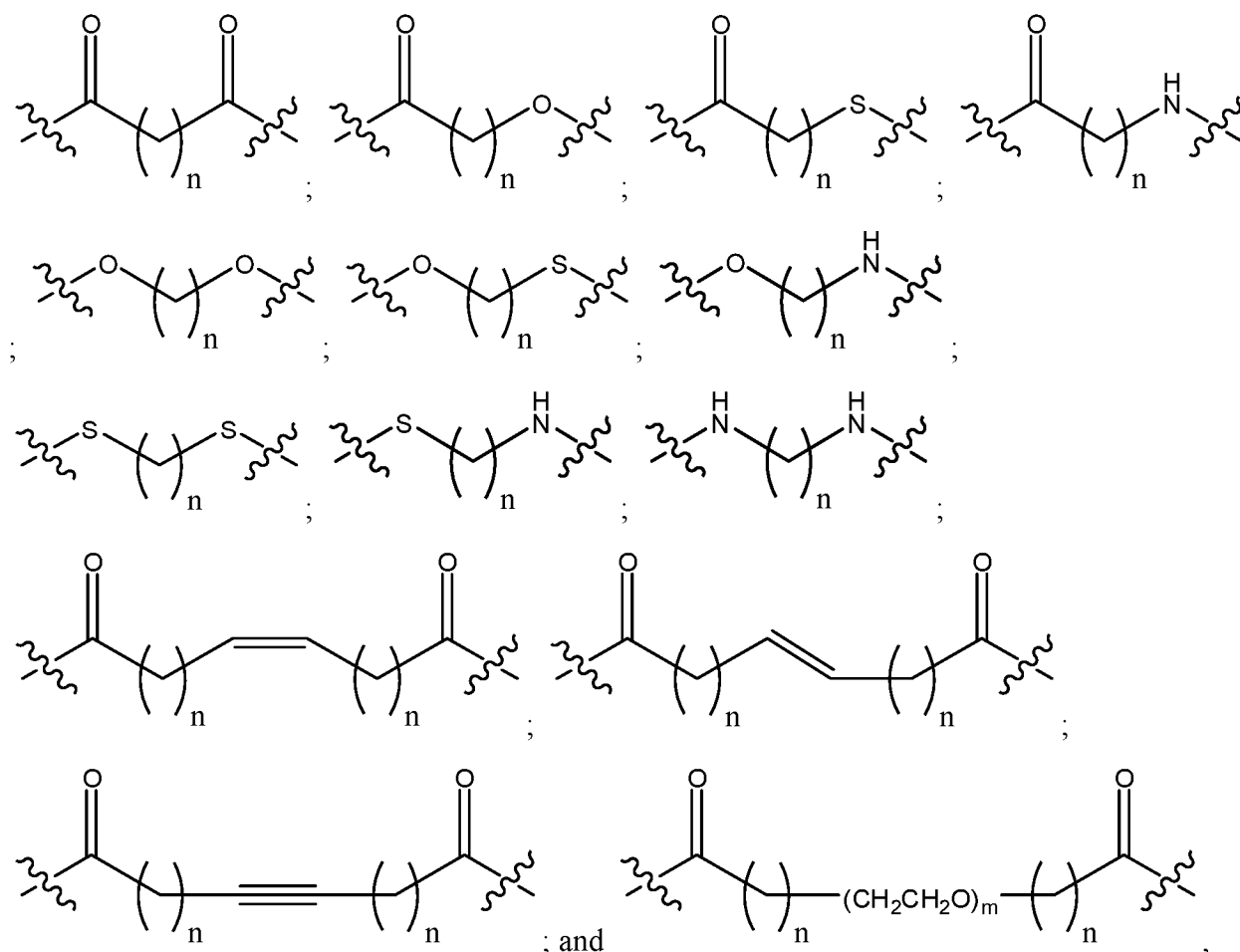
as that formed by reacting an amine on the peptide with a linker containing a tetrafluorophenyl (TFP) ester or an NHS ester. A can also be a stable carbamate linker such as that formed by reacting an amine on the peptide with an imidazole carbamate active intermediate formed by reaction of CDI with a hydroxyl on the linker. A can also be a stable secondary amine linkage such as that formed by reductive alkylation of the amine on the peptide with an aldehyde or ketone group on the linker. A can also be a stable thioether linker formed using a maleimide or bromoacetamide in the linker with a thiol in the peptide, a triazole linker, a stable oxime linker, or an oxacarboline linker. B can be $(-\text{CH}_2-)_x$ - or a short PEG $(-\text{CH}_2\text{CH}_2\text{O}-)_x$ (x is 0-20) or other spacers or no spacer. C can be an amide bond formed with an amine or a carboxylic acid on the drug, a thioether formed between a maleimide on the linker and a sulfhydryl on the drug, a secondary or tertiary amine, a carbamate, or other stable bonds. Any linker chemistry described in "Current ADC Linker Chemistry," Jain et al. , Pharm Res, 2015 DOI 10. 1007/s11095-015-1657-7 can be used.

[0181] The resulting peptide conjugates can be administered to a human or animal subcutaneously, intravenously, orally, or injected directly into a joint to treat disease. The peptide is not specifically cleaved from the detectable agent or active agent via a targeted mechanism. The peptide can be degraded by mechanisms such as catabolism, releasing a drug that is modified or not modified from its native form (Antibody-Drug Conjugates: Design, Formulation, and Physicochemical Stability, Singh, Luisi, and Pak. Pharm Res (2015) 32:3541-3571). The peptide drug conjugate exerts its pharmacological activity while still intact, or while partially or fully degraded, metabolized, or catabolized.

[0182] In some embodiments, peptide conjugates can have cleavable linkers. In some embodiments, a peptide and drug can be complexed, conjugated, or fused via a linker and can be described with the formula Peptide-A-B-C-Drug, wherein the linker is A-B-C. In some embodiments, A can be a stable amide link such as that formed by reacting an amine on the peptide with a linker containing a tetrafluorophenyl (TFP) ester or an NHS ester. In certain embodiments, A can also be a stable carbamate linker that is formed by an amine reaction on the peptide with an imidazole carbamate active intermediate formed by reaction of CDI with a hydroxyl on the linker. In other embodiments, A can also be a stable secondary amine linkage such as that formed by reductive alkylation of the amine on the peptide with an aldehyde or ketone group on the linker. In some embodiments, A can also be a stable thioether linker formed using a maleimide or bromoacetamide in the linker with a thiol in the peptide, a triazole linker, a stable oxime linker, or an oxacarboline linker. B can be $(-\text{CH}_2-)_x$ - or a short PEG $(-\text{CH}_2\text{CH}_2\text{O}-)_x$ (x is 0-20) or other spacers or no spacer. C can be an ester bond to the hydroxyl or carboxylic

acid on the drug, or a carbonate, hydrazone, or acylhydrazone, designed for hydrolytic cleavage. The hydrolytic rate of cleavage can be varied by varying the local environment around the bond, including carbon length (-CH₂-)_x, steric hindrance (including adjacent side groups such as methyl, ethyl, cyclic), hydrophilicity or hydrophobicity. In some embodiments, peptide conjugates can have a linear or cyclic ester linkage, which can include or do not include side chains such as methyl or ethyl groups. A linear ester linkage can be more susceptible to cleavage (such as by hydrolysis, an enzyme such as esterase, or other chemical reaction) than a cyclic ester due to steric hindrance or hydrophobicity/hydrophilicity effects. Likewise, side chains such as methyl or ethyl groups on the linear ester linkage can optionally make the linkage less susceptible to cleavage than without the side chains. In some embodiments, hydrolysis rate can be affected by local pH, such as lower pH in certain compartments of the body or of the cell such as endosomes and lysosomes or diseased tissues. In some embodiments, C can also be a pH sensitive group such as a hydrazone or oxime linkage. In other embodiments, C can be a disulfide bond designed to be released by reduction, such as by glutathione. In other embodiments, (or A-B-C) can be a peptidic linkage design for cleavage by enzymes. Optionally, a self-immolating group such as pABC can be included to cause release of a free unmodified drug upon cleavage (Antibody-Drug Conjugates: Design, Formulation, and Physicochemical Stability, Singh, Luisi, and Pak. Pharm Res (2015) 32:3541-3571). The linker can be cleaved by enzymes such as esterases, matrix metalloproteinases, cathepsins such as cathepsin B, glucuronidases, a protease, or thrombin. Alternatively, the bond designed for cleavage can be at A, rather than C, and C can be a stable bond or a cleavable bond. An alternative design can be to have stable linkers (such as amide or carbamate) at A and C and have a cleavable linker in B, such as a disulfide bond. The rate of reduction can be modulated by local effects such as steric hindrance from methyl or ethyl groups or modulating hydrophobicity/hydrophilicity. In some embodiments, peptide conjugates can have an ester carbonyl linkage, a long hydrocarbon linker, or carbamate linker, each of which can include hydrophilic groups, such as alcohols, acids, or ethers, or include a hydrocarbon side chain or other moiety that tunes the rate of cleavage. For example, the rate of hydrolysis can be faster with hydrophilic groups, such as alcohols, acids, or ethers, near an ester carbonyl. In another example, hydrophobic groups present as side chains or as a longer hydrocarbon linker can slow the cleavage rate of the ester. Likewise, cleavage of a carbamate group can also be tuned by hindrance, hydrophobicity, and the like. In another example, using a less labile linking group, such as a carbamate rather than an ester, can slow the cleavage rate of the linker.

[0183] Non-limiting examples of linkers include:



wherein each n is independently 0 to about 1,000; 1 to about 1,000; 0 to about 500; 1 to about 500; 0 to about 250; 1 to about 250; 0 to about 200; 1 to about 200; 0 to about 150; 1 to about 150; 0 to about 100; 1 to about 100; 0 to about 50; 1 to about 50; 0 to about 40; 1 to about 40; 0 to about 30; 1 to about 30; 0 to about 25; 1 to about 25; 0 to about 20; 1 to about 20; 0 to about 15; 1 to about 15; 0 to about 10; 1 to about 10; 0 to about 5; or 1 to about 5. In some embodiments, each n is independently 0, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, or about 50. In some embodiments, m is 1 to about 1,000; 1 to about 500; 1 to about 250; 1 to about 200; 1 to about 150; 1 to about 100; 1 to about 50; 1 to about 40; 1 to about 30; 1 to about 25; 1 to about 20; 1 to about 15; 1 to about 10; or 1 to about 5. In some embodiments, m is 0, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about

36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, or about 50.

[0184] In some cases a linker can be a succinic linker, and a drug can be attached to a peptide via an ester bond or an amide bond with two methylene carbons in between. In other cases, a linker can be any linker with both a hydroxyl group and a carboxylic acid, such as hydroxy hexanoic acid or lactic acid.

[0185] The linker can be a cleavable or a stable linker. The use of a cleavable linker permits release of the complexed, conjugated, or fused moiety (e.g., a therapeutic agent) from the peptide, e.g., after targeting to the cartilage. In some cases the linker is enzyme cleavable, e.g., a valine-citrulline linker. In some embodiments, the linker contains a self-immolating portion. In other embodiments, the linker includes one or more cleavage sites for a specific protease, such as a cleavage site for matrix metalloproteases (MMPs), thrombin, or a cathepsin. Alternatively or in combination, the linker is cleavable by other mechanisms, such as via pH, reduction, or hydrolysis. A hydrolytically labile linker, (amongst other cleavable linkers described herein) can be advantageous in terms of releasing active agents from the peptide. For example, an active agent in a conjugate form with the peptide may not be active, but upon release from the conjugate after targeting to the cartilage, the active agent is active.

[0186] The rate of hydrolysis of the linker can be tuned. For example, the rate of hydrolysis of linkers with unhindered esters is faster compared to the hydrolysis of linkers with bulky groups next an ester carbonyl. A bulky group can be a methyl group, an ethyl group, a phenyl group, a ring, or an isopropyl group, or any group that provides steric bulk. In some cases, the steric bulk can be provided by the drug itself, such as by ketorolac when complexed, conjugated, or fused via its carboxylic acid. The rate of hydrolysis of the linker can be tuned according to the residency time of the conjugate in the cartilage. For example, when a peptide is cleared from the cartilage relatively quickly, the linker can be tuned to rapidly hydrolyze. In contrast, for example, when a peptide has a longer residence time in the cartilage, a slower hydrolysis rate can allow for extended delivery of an active agent. This can be important when the peptide is used to deliver a drug to the cartilage. “Programmed hydrolysis in designing paclitaxel prodrug for nanocarrier assembly” Sci Rep 2015, 5, 12023 Fu et al. , provides an example of modified hydrolysis rates.

Peptide Stability

[0187] A peptide of the present disclosure can be stable in various biological conditions, as well as during manufacturing, handling, storage, and other conditions in either a liquid or a dried state. Additionally, a peptide of the present disclosure can be resistant to enzymatic cleavage

needed for peptide processing by the immune system. For example, any peptide of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 can exhibit resistance to reducing agents, proteases, oxidative conditions, or acidic conditions.

[0188] In some cases, biologic molecules (such as peptides and proteins) can provide therapeutic functions, but such therapeutic functions are decreased or impeded by instability caused by the in vivo environment. (Moroz et al., *Adv Drug Deliv Rev* 101:108-21 (2016), Mitragotri et al., *Nat Rev Drug Discov* 13(9):655-72 (2014), Bruno et al., *Ther Deliv* (11):1443-67 (2013), Sinha et al., *Crit Rev Ther Drug Carrier Syst.* 24(1):63-92 (2007), Hamman et al., *BioDrugs* 19(3):165-77 (2005)). Peptide degradation can be a result of a number of processes involving hydrolytic pathways, peptide oxidation such as oxidation of methionine (Met) residues, deamidation of asparagine (Asn) and glutamine (Gln) residues, and isomerization and hydrolysis of an adjacent asparagine (Asp) residue. (Manning et al., *Pharmaceutical Research*, Vol. 27 No. 4 (2010)). The amino acid immediately following the Asn or Gln residue can also affect the rate of deamidation, whereas: Asn-Gly, Asn-Ser, Asn-His, and Gln-Gly can be more likely to undergo deamidation. Additionally, the peptide bond adjacent to amino acids such as Asp can undergo hydrolysis with amino acid pairings such as Asp-Gly, Asp-Ser, Asp-Tyr, and Asp-Pro, which can be more likely to undergo hydrolysis. Oxidation of amino acid residues such as Met can form a sulfoxide species. The specific degradation reactions rates can vary for any given peptide or protein sequence.

[0189] Furthermore, the microenvironment within the molecular structure of the peptide, solvent accessibility, and conformational stability of each residue can impact the likelihood of peptide degradation. Therefore, by modifying a peptide sequence to reduce occurrence of such degradation events, a the modified peptide or peptide-conjugate can have increased beneficial properties over unmodified peptides or peptide-drug conjugates, such as improved therapeutic efficacy, an increased safety profile, and can be less expensive to manufacture and develop. Key formulaic considerations that can prevent peptide decay can include the use of excipients, formulation at a desired pH, and storage under specific conditions (e.g., temperature, oxygen, light exposure, solid or liquid state, and container excipient materials). To circumvent degradation, peptide residues can be substituted with amino acids that increase stability, which can result in more efficacious and durable therapeutic peptides.

[0190] With respect to in vivo stability, the GI tract can contain a region of low pH (e.g., pH ~1), a reducing environment, or a protease-rich environment that can degrade peptides and proteins.

Proteolytic activity in other areas of the body, such as the mouth, eye, lung, intranasal cavity, joint, skin, vaginal tract, mucous membranes, and serum, can also be an obstacle to the delivery of functionally active peptides and polypeptides. Additionally, the half-life of peptides in serum can be very short, in part due to proteases, such that the peptide can be degraded too quickly to have a lasting therapeutic effect when administering a therapeutic and safe dosing regimen. Likewise, proteolytic activity in cellular compartments, such as lysosomes, and reduction activity in lysosomes and the cytosol can degrade peptides and proteins such that they may be unable to provide a therapeutic function on intracellular targets. Therefore, peptides that are resistant to reducing agents, proteases, and low pH may be able to provide enhanced therapeutic effects or enhance the therapeutic efficacy of co-formulated or complexed, conjugated, or fused active agents in vivo.

[0191] Additionally, oral delivery of drugs can be desirable in order to target certain areas of the body (e.g., disease in the GI tract such as colon cancer, irritable bowel disorder, infections, metabolic disorders, and constipation) despite the obstacles to the delivery of functionally active peptides and polypeptides presented by this method of administration. For example, oral delivery of drugs can increase compliance by providing a dosage form that is more convenient for patients to take as compared to parenteral delivery. Oral delivery can be useful in treatment regimens that have a large therapeutic window. Therefore, peptides that are resistant to reducing agents, proteases, and low pH can allow for oral delivery of peptides without nullifying their therapeutic function.

[0192] Peptide Resistance to Reducing Agents. Peptides of this disclosure can contain one or more cysteines, which can participate in disulfide bridges that can be integral to preserving the folded state of the peptide. Exposure of peptides to biological environments with reducing agents can result in unfolding of the peptide and loss of functionality and bioactivity. For example, glutathione (GSH) is a reducing agent that can be present in many areas of the body and in cells, and can reduce disulfide bonds. As another example, a peptide can become reduced upon cellular internalization during trafficking of a peptide across the gastrointestinal epithelium after oral administration a peptide can become reduced upon exposure to various parts of the GI tract. The GI tract can be a reducing environment, which can inhibit the ability of therapeutic molecules with disulfide bonds to have optimal therapeutic efficacy, due to reduction of the disulfide bonds. A peptide can also be reduced upon entry into a cell, such as after internalization by endosomes or lysosomes or into the cytosol, or other cellular compartments. Reduction of the disulfide bonds and unfolding of the peptide can lead to loss of functionality or affect key pharmacokinetic parameters such as bioavailability, peak plasma concentration, bioactivity, and

half-life. Reduction of the disulfide bonds can also lead to increased susceptibility of the peptide to subsequent degradation by proteases, resulting in rapid loss of intact peptide after administration. In some embodiments, a peptide that is resistant to reduction can remain intact and can impart a functional activity for a longer period of time in various compartments of the body and in cells, as compared to a peptide that is more readily reduced.

[0193] In certain embodiments, the peptides of this disclosure can be analyzed for the characteristic of resistance to reducing agents to identify stable peptides. In some embodiments, the peptides of this disclosure can remain intact after being exposed to different molarities of reducing agents such as 0.00001M – 0.0001M, 0.0001M – 0.001M, 0.001M – 0.01M, 0.01M – 0.05M, 0.05M – 0.1M, for greater 15 minutes or more. In some embodiments, the reducing agent used to determine peptide stability can be dithiothreitol (DTT), Tris (2-carboxyethyl) phosphine HCl (TCEP), 2-Mercaptoethanol, (reduced) glutathione (GSH), or any combination thereof. In some embodiments, at least 5%-10%, at least 10%-20%, at least 20%-30%, at least 30%-40%, at least 40%-50%, at least 50%-60%, at least 60%-70%, at least 70%-80%, at least 80%-90%, or at least 90%-100% of the peptide remains intact after exposure to a reducing agent.

[0194] Peptide Resistance to Proteases. The stability of peptides of this disclosure can be determined by resistance to degradation by proteases. Proteases, also referred to as peptidases or proteinases, can be enzymes that can degrade peptides and proteins by breaking bonds between adjacent amino acids. Families of proteases with specificity for targeting specific amino acids can include serine proteases, cysteine proteases, threonine proteases, aspartic proteases, glutamic proteases, esterases, serum proteases, and asparagine proteases. Additionally, metalloproteases, matrix metalloproteases, elastase, carboxypeptidases, Cytochrome P450 enzymes, and cathepsins can also digest peptides and proteins. Proteases can be present at high concentration in blood, in mucous membranes, lungs, skin, the GI tract, the mouth, nose, eye, and in compartments of the cell. Misregulation of proteases can also be present in various diseases such as rheumatoid arthritis and other immune disorders. Degradation by proteases can reduce bioavailability, biodistribution, half-life, and bioactivity of therapeutic molecules such that they are unable to perform their therapeutic function. In some embodiments, peptides that are resistant to proteases can better provide therapeutic activity at reasonably tolerated concentrations in vivo.

[0195] In some embodiments, peptides of this disclosure can resist degradation by any class of protease. In certain embodiments, peptides of this disclosure resist degradation by pepsin (which can be found in the stomach), trypsin (which can be found in the duodenum), serum proteases, or any combination thereof. In certain embodiments, peptides of this disclosure can resist

degradation by lung proteases (e. g., serine, cysteinyl, and aspartyl proteases, metalloproteases, neutrophil elastase, alpha-1 antitrypsin, secretory leucoprotease inhibitor, elafin), or any combination thereof. In some embodiments, the proteases used to determine peptide stability can be pepsin, trypsin, chymotrypsin, or any combination thereof. In some embodiments, at least 5%-10%, at least 10%-20%, at least 20%-30%, at least 30%-40%, at least 40%-50%, at least 50%-60%, at least 60%-70%, at least 70%-80%, at least 80%-90%, or at least 90%-100% of the peptide remains intact after exposure to a protease. Peptides of, SEQ ID NO: 150, and SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) can have particular structural qualities, which make them more resistant to protease degradation. For example, peptide of SEQ ID NO: 150 and SEQ ID NO: 149 exhibit the “hitchin” topology as described previously, which can be associated with resistance to protease and chemical degradation.

[0196] Peptide Stability in Acidic Conditions. Peptides of this disclosure can be administered in biological environments that are acidic. For example, after oral administration, peptides can experience acidic environmental conditions in the gastric fluids of the stomach and gastrointestinal (GI) tract. The pH of the stomach can range from ~1-4 and the pH of the GI tract ranges from acidic to normal physiological pH descending from the upper GI tract to the colon. In addition, the vagina, late endosomes, and lysosomes can also have acidic pH values, such as less than pH 7. These acidic conditions can lead to denaturation of peptides and proteins into unfolded states. Unfolding of peptides and proteins can lead to increased susceptibility to subsequent digestion by other enzymes as well as loss of biological activity of the peptide.

[0197] In certain embodiments, the peptides of this disclosure can resist denaturation and degradation in acidic conditions and in buffers, which simulate acidic conditions. In certain embodiments, peptides of this disclosure can resist denaturation or degradation in buffer with a pH less than 1, a pH less than 2, a pH less than 3, a pH less than 4, a pH less than 5, a pH less than 6, a pH less than 7, or a pH less than 8. In some embodiments, peptides of this disclosure remain intact at a pH of 1-3. In certain embodiments, at least 5%-10%, at least 10%-20%, at least 20%-30%, at least 30%-40%, at least 40%-50%, at least 50%-60%, at least 60%-70%, at least 70%-80%, at least 80%-90%, or at least 90%-100% of the peptide remains intact after exposure to a buffer with a pH less than 1, a pH less than 2, a pH less than 3, a pH less than 4, a pH less than 5, a pH less than 6, a pH less than 7, or a pH less than 8. In other embodiments, at least 5%-10%, at least 10%-20%, at least 20%-30%, at least 30%-40%, at least 40%-50%, at least 50%-60%, at least 60%-70%, at least 70%-80%, at least 80%-90%, or at least 90%-100% of the peptide remains intact after exposure to a buffer with a pH of 1-3. In other embodiments, the

peptides of this disclosure can be resistant to denaturation or degradation in simulated gastric fluid (pH 1-2). In some embodiments, at least 5%-10%, at least 10%-20%, at least 20%-30%, at least 30%-40%, at least 40%-50%, at least 50%-60%, at least 60%-70%, at least 70%-80%, at least 80%-90%, or at least 90%-100% of the peptide remains intact after exposure to simulated gastric fluid. In some embodiments, low pH solutions such as simulated gastric fluid or citrate buffers can be used to determine peptide stability.

[0198] Peptide Stability at High Temperatures. Peptides of this disclosure can be administered in biological environments with high temperatures. For example, after oral administration, peptides can experience high temperatures in the body. Body temperature can range from 36°C to 40°C. High temperatures can lead to denaturation of peptides and proteins into unfolded states. Unfolding of peptides and proteins can lead to increased susceptibility to subsequent digestion by other enzymes as well as loss of biological activity of the peptide. In some embodiments, a peptide of this disclosure can remain intact at temperatures from 25°C to 100°C. High temperatures can lead to faster degradation of peptides. Stability at a higher temperature can allow for storage of the peptide in tropical environments or areas where access to refrigeration is limited. In certain embodiments, 5%-100% of the peptide can remain intact after exposure to 25°C for 6 months to 5 years. 5%-100% of a peptide can remain intact after exposure to 70°C for 15 minutes to 1 hour. 5%-100% of a peptide can remain intact after exposure to 100°C for 15 minutes to 1 hour. In other embodiments, at least 5%-10%, at least 10%-20%, at least 20%-30%, at least 30%-40%, at least 40%-50%, at least 50%-60%, at least 60%-70%, at least 70%-80%, at least 80%-90%, or at least 90%-100% of the peptide remains intact after exposure to 25°C for 6 months to 5 years. In other embodiments, at least 5%-10%, at least 10%-20%, at least 20%-30%, at least 30%-40%, at least 40%-50%, at least 50%-60%, at least 60%-70%, at least 70%-80%, at least 80%-90%, or at least 90%-100% of the peptide remains intact after exposure to 70°C for 15 minutes to 1 hour. In other embodiments, at least 5%-10%, at least 10%-20%, at least 20%-30%, at least 30%-40%, at least 40%-50%, at least 50%-60%, at least 60%-70%, at least 70%-80%, at least 80%-90%, or at least 90%-100% of the peptide remains intact after exposure to 100°C for 15 minutes to 1 hour.

Pharmacokinetics of Peptides

[0199] The pharmacokinetics of any of the peptides of this disclosure can be determined after administration of the peptide via different routes of administration. For example, the pharmacokinetic parameters of a peptide of this disclosure can be quantified after intravenous, subcutaneous, intramuscular, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, optic, nasal, oral, sublingual, inhalation, dermal, intrathecal, intranasal, intra-articular,

peritoneal, buccal, synovial, or topical administration. Peptides of the present disclosure can be analyzed by using tracking agents such as radiolabels or fluorophores. For example, a radiolabeled peptide of this disclosure can be administered via various routes of administration. Peptide concentration or dose recovery in various biological samples such as plasma, urine, feces, any organ, skin, muscle, and other tissues can be determined using a range of methods including HPLC, fluorescence detection techniques (TECAN quantification, flow cytometry, iVIS), or liquid scintillation counting.

[0200] The methods and compositions described herein can relate to pharmacokinetics of peptide administration via any route to a subject. Pharmacokinetics can be described using methods and models, for example, compartmental models or noncompartmental methods. Compartmental models include but are not limited to monocompartmental model, the two compartmental model, the multicompartmental model or the like. Models can be divided into different compartments and can be described by the corresponding scheme. For example, one scheme is the absorption, distribution, metabolism and excretion (ADME) scheme. For another example, another scheme is the liberation, absorption, distribution, metabolism and excretion (LADME) scheme. In some aspects, metabolism and excretion can be grouped into one compartment referred to as the elimination compartment. For example, liberation can include liberation of the active portion of the composition from the delivery system, absorption includes absorption of the active portion of the composition by the subject, distribution includes distribution of the composition through the blood plasma and to different tissues, metabolism, which includes metabolism or inactivation of the composition and finally excretion, which includes excretion or elimination of the composition or the products of metabolism of the composition. Compositions administered intravenously to a subject can be subject to multiphasic pharmacokinetic profiles, which can include but are not limited to aspects of tissue distribution and metabolism/excretion. As such, the decrease in plasma or serum concentration of the composition is often biphasic, including, for example an alpha phase and a beta phase, occasionally a gamma, delta or other phase is observed

[0201] Pharmacokinetics includes determining at least one parameter associated with administration of a peptide to a subject. In some aspects, parameters include at least the dose (D), dosing interval (τ), area under curve (AUC), maximum concentration ($C_{\max}$), minimum concentration reached before a subsequent dose is administered ($C_{\min}$), minimum time ($T_{\min}$), maximum time to reach $C_{\max}$ ($T_{\max}$), volume of distribution (V_d), steady-state volume of distribution (V_{ss}), back-extrapolated concentration at time 0 (C_0), steady state concentration (C_{ss}),

elimination rate constant (k_e), infusion rate (k_{in}), clearance (CL), bioavailability (f), fluctuation (%PTF) and elimination half-life ($t_{1/2}$).

[0202] In certain embodiments, the peptides of any of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 exhibit optimal pharmacokinetic parameters after oral administration. In other embodiments, the peptides of any of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 exhibit optimal pharmacokinetic parameters after any route of administration, such as oral administration, inhalation, intranasal administration, topical administration, parenteral administration, intravenous administration, subcutaneous administration, intra-articular administration, intramuscular administration, intraperitoneal administration, transdermal administration, dermal administration, or any combination thereof.

[0203] In some embodiments any peptide of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 exhibits an average T_{max} of 0.5 – 12 hours, or 1-48 hours at which the C_{max} is reached, an average bioavailability in serum of 0.1%-10% in the subject after administering the peptide to the subject by an oral route, an average bioavailability in serum of less than 0.1% after oral administration to a subject for delivery to the GI tract, an average bioavailability in serum of 10-100% after parenteral administration, an average $t_{1/2}$ of 0.1 hours – 168 hours, or 0.25 hours – 48 hours in a subject after administering the peptide to the subject, an average clearance (CL) of 0.5-100 L/hour or 0.5 – 50 L/hour of the peptide after administering the peptide to a subject, an average volume of distribution (V_d) of 200 – 20,000 mL in the subject after systemically administering the peptide to the subject, or optionally no systemic uptake, any combination thereof.

Methods of Manufacture

[0204] Various expression vector/host systems can be utilized for the production of the recombinant expression of peptides described herein. Non-limiting examples of such systems include microorganisms such as bacteria transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing a nucleic acid sequence encoding peptides or peptide fusion proteins/chimeric proteins described herein, yeast transformed with

recombinant yeast expression vectors containing the aforementioned nucleic acid sequence, insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing the aforementioned nucleic acid sequence, plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus (CaMV), tobacco mosaic virus (TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing the aforementioned nucleic acid sequence, or animal cell systems infected with recombinant virus expression vectors (e.g., adenovirus, vaccinia virus) including cell lines engineered to contain multiple copies of the aforementioned nucleic acid sequence, either stably amplified (e.g., CHO/dhfr, CHO/glutamine synthetase) or unstably amplified in double-minute chromosomes (e.g., murine cell lines). Disulfide bond formation and folding of the peptide could occur during expression or after expression or both.

[0205] A host cell can be adapted to express one or more peptides described herein. The host cells can be prokaryotic, eukaryotic, or insect cells. In some cases, host cells are capable of modulating the expression of the inserted sequences, or modifying and processing the gene or protein product in the specific fashion desired. For example, expression from certain promoters can be elevated in the presence of certain inducers (e.g., zinc and cadmium ions for metallothionein promoters). In some cases, modifications (e.g., phosphorylation) and processing (e.g., cleavage) of peptide products can be important for the function of the peptide. Host cells can have characteristic and specific mechanisms for the post-translational processing and modification of a peptide. In some cases, the host cells used to express the peptides secrete minimal amounts of proteolytic enzymes.

[0206] In the case of cell- or viral-based samples, organisms can be treated prior to purification to preserve and/or release a target polypeptide. In some embodiments, the cells are fixed using a fixing agent. In some embodiments, the cells are lysed. The cellular material can be treated in a manner that does not disrupt a significant proportion of cells, but which removes proteins from the surface of the cellular material, and/or from the interstices between cells. For example, cellular material can be soaked in a liquid buffer or, in the case of plant material, can be subjected to a vacuum, in order to remove proteins located in the intercellular spaces and/or in the plant cell wall. If the cellular material is a microorganism, proteins can be extracted from the microorganism culture medium. Alternatively, the peptides can be packed in inclusion bodies. The inclusion bodies can further be separated from the cellular components in the medium. In some embodiments, the cells are not disrupted. A cellular or viral peptide that is presented by a cell or virus can be used for the attachment and/or purification of intact cells or viral particles. In

addition to recombinant systems, Peptides can also be synthesized in a cell-free system using a variety of known techniques employed in protein and peptide synthesis.

[0207] In some cases, a host cell produces a peptide that has an attachment point for a drug. An attachment point could comprise a lysine residue, an N-terminus, a cysteine residue, a cysteine disulfide bond, or a non-natural amino acid or a unique peptide sequence such as targeted by an enzyme. The peptide could also be produced synthetically, such as by solid-phase peptide synthesis, or solution-phase peptide synthesis. The peptide could be folded (formation of disulfide bonds) during synthesis or after synthesis or both. Peptide fragments could be produced synthetically or recombinantly and then joined together synthetically, recombinantly, or via an enzyme.

[0208] **FIG. 3** illustrates a schematic of a method of manufacturing a construct that expresses a peptide of the disclosure, such as the constructs illustrated in **FIG. 2** and as described throughout the disclosure and in SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 provided herein.

[0209] In other aspects, the peptides of the present disclosure can be prepared by conventional solid phase chemical synthesis techniques, for example according to the Fmoc solid phase peptide synthesis method (“Fmoc solid phase peptide synthesis, a practical approach,” edited by W. C. Chan and P. D. White, Oxford University Press, 2000), Boc solid phase peptide synthesis, or solution phase peptide synthesis. The disulfide bonds can be formed after cleavage from the resin, such as by air oxidation or a buffer system with a set pH range such as from 7-10 and can contain a redox system such as glutathione/oxidized glutathione or cysteine/cystine. The disulfide bonds can also be formed by selective protection and deprotection of specific cysteine residues followed by oxidation, or on the resin. The peptide can be purified, such as by reversed-phase chromatography at any one or more steps during the production process. The peptide can be isolated by lyophilization and can be in various salt forms, such as TFA salt or ammonium and acetate salt.

Pharmaceutical Compositions of Peptides

[0210] A pharmaceutical composition of the disclosure can be a combination of any peptide described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, antioxidants, solubilizers, buffers, osmolytes, salts, surfactants, amino acids, encapsulating agents, bulking agents, cryoprotectants, and/or excipients. The pharmaceutical composition facilitates administration of a peptide

described herein to an organism. Pharmaceutical compositions can be administered in therapeutically-effective amounts as pharmaceutical compositions by various forms and routes including, for example, intravenous, subcutaneous, intramuscular, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, optic, nasal, oral, sublingual, inhalation, dermal, intrathecal, intranasal, intra-articular, and topical administration. A pharmaceutical composition can be administered in a local or systemic manner, for example, via injection of the peptide described herein directly into an organ, optionally in a depot.

[0211] Parenteral injections can be formulated for bolus injection or continuous infusion. The pharmaceutical compositions can be in a form suitable for parenteral injection as a sterile suspension, solution or emulsion in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of a peptide described herein in water soluble form. Suspensions of peptides described herein can be prepared as oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. The suspension can also contain suitable stabilizers or agents which increase the solubility and/or reduce the aggregation of such peptides described herein to allow for the preparation of highly concentrated solutions. Alternatively, the peptides described herein can be lyophilized or in powder form for re-constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. In some embodiments, a purified peptide is administered intravenously.

[0212] A peptide of the disclosure can be applied directly to an organ, or an organ tissue or cells, such as brain or brain tissue or cancer cells, during a surgical procedure. The recombinant peptides described herein can be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams, and ointments. Such pharmaceutical compositions can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0213] In practicing the methods of treatment or use provided herein, therapeutically-effective amounts of the peptide described herein described herein can be administered in pharmaceutical compositions to a subject suffering from a condition that affects the immune system. In some embodiments, the subject is a mammal such as a human. A therapeutically-effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compounds used, and other factors.

[0214] Pharmaceutical compositions can be formulated using one or more physiologically-acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations that can be used pharmaceutically. Formulation can be modified depending upon the route of administration chosen. Pharmaceutical compositions comprising a peptide described herein can be manufactured, for example, by expressing the peptide in a recombinant system, purifying the peptide, lyophilizing the peptide, mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or compression processes. The pharmaceutical compositions can include at least one pharmaceutically acceptable carrier, diluent, or excipient and compounds described herein as free-base or pharmaceutically-acceptable salt form.

[0215] Methods for the preparation of peptides described herein comprising the compounds described herein include formulating the peptide described herein with one or more inert, pharmaceutically-acceptable excipients or carriers to form a solid, semi-solid, or liquid composition. Solid compositions include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories. These compositions can also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and other pharmaceutically-acceptable additives.

[0216] Non-limiting examples of pharmaceutically-acceptable excipients can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa. : Mack Publishing Company, 1995); Hoover, John E. , Remington's Pharmaceutical Sciences, Mack Publishing Co. , Easton, Pennsylvania 1975; Liberman, H. A. and Lachman, L. , Eds. , Pharmaceutical Dosage Forms, Marcel Decker, New York, N. Y. , 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), each of which is incorporated by reference in its entirety.

Administration of Pharmaceutical Compositions

[0217] A pharmaceutical composition of the disclosure can be a combination of any peptide described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of a peptide described herein to an organism.

Pharmaceutical compositions can be administered in therapeutically-effective amounts as pharmaceutical compositions by various forms and routes including, for example, intravenous, subcutaneous, intramuscular, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, optic, nasal, oral, inhalation, dermal, intra-articular, intrathecal, intranasal, and topical administration. A pharmaceutical composition can be administered in a local or systemic

manner, for example, via injection of the peptide described herein directly into an organ, optionally in a depot.

[0218] Parenteral injections can be formulated for bolus injection or continuous infusion. The pharmaceutical compositions can be in a form suitable for parenteral injection as a sterile suspension, solution or emulsion in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of a peptide described herein in water-soluble form. Suspensions of peptides described herein can be prepared as oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. The suspension can also contain suitable stabilizers or agents which increase the solubility and/or reduce the aggregation of such peptides described herein to allow for the preparation of highly concentrated solutions. Alternatively, the peptides described herein can be lyophilized or in powder form for re-constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. In some embodiments, a purified peptide is administered intravenously. A peptide described herein can be administered to a subject, home, target, migrates to, is retained by, and/or binds to, or be directed to an organ, e.g., the cartilage.

[0219] A peptide of the disclosure can be applied directly to an organ, or an organ tissue or cells, such as cartilage or cartilage tissue or cells, during a surgical procedure. The recombinant peptides described herein can be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams, and ointments. Such pharmaceutical compositions can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0220] In practicing the methods of treatment or use provided herein, therapeutically-effective amounts of the peptide described herein described herein are administered in pharmaceutical compositions to a subject suffering from a condition. In some instances the pharmaceutical composition will affect the physiology of the animal, such as the immune system, inflammatory response, or other physiologic affect. In some embodiments, the subject is a mammal such as a human. A therapeutically-effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compounds used, and other factors.

[0221] Pharmaceutical compositions can be formulated using one or more physiologically-acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the

active compounds into preparations that can be used pharmaceutically. Formulation can be modified depending upon the route of administration chosen. Pharmaceutical compositions comprising a peptide described herein can be manufactured, for example, by expressing the peptide in a recombinant system, purifying the peptide, lyophilizing the peptide, mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or compression processes. The pharmaceutical compositions can include at least one pharmaceutically acceptable carrier, diluent, or excipient and compounds described herein as free-base or pharmaceutically-acceptable salt form.

[0222] Methods for the preparation of peptides described herein comprising the compounds described herein include formulating the peptide described herein with one or more inert, pharmaceutically-acceptable excipients or carriers to form a solid, semi-solid, or liquid composition. Solid compositions include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories. These compositions can also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and other pharmaceutically-acceptable additives.

[0223] Non-limiting examples of pharmaceutically-acceptable excipients can be found, for example, in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa. : Mack Publishing Company, 1995); Hoover, John E. , *Remington's Pharmaceutical Sciences*, Mack Publishing Co. , Easton, Pennsylvania 1975; Liberman, H. A. and Lachman, L. , Eds. , *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N. Y. , 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins 1999), each of which is incorporated by reference in its entirety.

Use of Peptide in Imaging and Surgical Methods

[0224] The present disclosure generally relates to peptides that home, target, migrate to, are retained by, accumulate in, and/or bind to, or are directed to specific regions, tissues, structures, or cells within the body and methods of using such peptides. These peptides have the ability to contact the cartilage, which makes them useful for a variety of applications. In particular, the peptides can have applications in site-specific modulation of biomolecules to which the peptides are directed to. End uses of such peptides can include, for example, imaging, research, therapeutics, theranostics, pharmaceuticals, chemotherapy, chelation therapy, targeted drug delivery, and radiotherapy. Some uses can include targeted drug delivery and imaging.

[0225] In some embodiments, the present disclosure provides a method for detecting a cancer, cancerous tissue, or tumor tissue, the method comprising the steps of contacting a tissue of interest with a peptide of the present disclosure, wherein the peptide is complexed, conjugated,

or fused to a detectable agent and measuring the level of binding of the peptide, wherein an elevated level of binding, relative to normal tissue, is indicative that the tissue is a cancer, cancerous tissue or tumor tissue.

[0226] In some embodiments, the disclosure provides a method of imaging an organ or body region or region, tissue or structure of a subject, the method comprising administering to the subject the peptide or a pharmaceutical composition disclosed herein and imaging the subject. In some embodiments such imaging is used to detect a condition associated with cartilage, or a function of the cartilage. In some cases the condition is an inflammation, a cancer, a degradation, a growth disturbance, genetic, a tear or an injury, or another suitable condition. In some cases the condition is a chondrodystrophy, a traumatic rupture or detachment, pain following surgery in regions of the body containing cartilage, costochondritis, herniation, polychondritis, arthritis, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis (AS), Systemic Lupus Erythematosus (SLE or “Lupus”), Psoriatic Arthritis (PsA), gout, achondroplasia, or another suitable condition. In some case the condition is associated with a cancer or tumor of the cartilage. In some cases the condition is a type of chondroma or chondrosarcoma, whether metastatic or not, or another suitable condition. In some embodiments, such as those associated with cancers, the imaging may be associated with surgical removal of the diseased region, tissue, structure or cell of a subject.

[0227] Furthermore, the present disclosure provides methods for intraoperative imaging and resection of a diseased or inflamed tissue, cancer, cancerous tissue, or tumor tissue using a peptide of the present disclosure complexed, conjugated, or fused with a detectable agent. In some embodiments, the diseased or inflamed tissue, cancer, cancerous tissue, or tumor tissue is detectable by fluorescence imaging that allows for intraoperative visualization of the cancer, cancerous tissue, or tumor tissue using a peptide of the present disclosure. In some embodiments, the peptide of the present disclosure is complexed, conjugated, or fused to one or more detectable agents. In a further embodiment, the detectable agent comprises a fluorescent moiety coupled to the peptide. In another embodiment, the detectable agent comprises a radionuclide. In some embodiments, imaging is achieved during open surgery. In further embodiments, imaging is accomplished using endoscopy or other non-invasive surgical techniques.

Treatment of Cartilage Disorders

[0228] The term “effective amount,” as used herein, can refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a

biological system. Compositions containing such agents or compounds can be administered for prophylactic, enhancing, and/or therapeutic treatments. An appropriate “effective” amount in any individual case can be determined using techniques, such as a dose escalation study.

[0229] The methods, compositions, and kits of this disclosure can comprise a method to prevent, treat, arrest, reverse, or ameliorate the symptoms of a condition. The treatment can comprise treating a subject (e.g., an individual, a domestic animal, a wild animal or a lab animal afflicted with a disease or condition) with a peptide of the disclosure. In treating a disease, the peptide can contact the cartilage of a subject. The subject can be a human. A subject can be a human; a non-human primate such as a chimpanzee, or other ape or monkey species; a farm animal such as a cattle, horse, sheep, goat, swine; a domestic animal such as a rabbit, dog, and cat; a laboratory animal including a rodent, such as a rat, mouse and guinea pig, or the like. A subject can be of any age. A subject can be, for example, an elderly adult, adult, adolescent, pre-adolescent, child, toddler, infant, or fetus in utero.

[0230] Treatment can be provided to the subject before clinical onset of disease. Treatment can be provided to the subject after clinical onset of disease. Treatment can be provided to the subject after 1 day, 1 week, 6 months, 12 months, or 2 years or more after clinical onset of the disease. Treatment may be provided to the subject for more than 1 day, 1 week, 1 month, 6 months, 12 months, 2 years or more after clinical onset of disease. Treatment may be provided to the subject for less than 1 day, 1 week, 1 month, 6 months, 12 months, or 2 years after clinical onset of the disease. Treatment can also include treating a human in a clinical trial. A treatment can comprise administering to a subject a pharmaceutical composition, such as one or more of the pharmaceutical compositions described throughout the disclosure. A treatment can comprise a once daily dosing. A treatment can comprise delivering a peptide of the disclosure to a subject, either parenterally, intravenously, subcutaneously, intramuscularly, by inhalation, dermally, intra-articular injection, orally, intrathecally, transdermally, intranasally, via a peritoneal route, or directly onto or into a joint, e.g., via topical, intra-articular injection route or injection route of application. A treatment can comprise administering a peptide-active agent complex to a subject, either parenterally, intravenously, subcutaneously, intramuscularly, by inhalation, dermally, intra-articular injection, orally, intrathecally, transdermally, intranasally, via a peritoneal route, or directly onto or into a joint or directly onto, near or into the cartilage, e.g., via topical, intra-articular injection route or injection route of application.

[0231] Types of cartilage diseases or conditions that can be treated with a peptide of the disclosure can include inflammation, pain management, anti-infective, pain relief, anti-cytokine, cancer, injury, degradation, genetic basis, remodeling, hyperplasia, surgical injury/trauma, or the

like. Diseases or conditions of bone adjacent to cartilage can also be treated with a peptide of the disclosure. Examples of cartilage diseases or conditions that can be treated with a peptide of the disclosure include Costochondritis, Spinal disc herniation, Relapsing polychondritis, Injury to the articular cartilage, any manner of rheumatic disease (e.g., Rheumatoid Arthritis (RA), ankylosing spondylitis (AS), Systemic Lupus Erythematosus (SLE or “Lupus”), lupus arthritis, Psoriatic Arthritis (PsA), Osteoarthritis, Gout, and the like), Herniation, Achondroplasia, Benign or non-cancerous chondroma, Malignant or cancerous chondrosarcoma, Chondriodystrophies, Chondromalacia patella, Costochondritis, Halus rigidus, Hip labral tear, Osteochondritis dissecans, Osteochondrodysplasias, Torn meniscus, Pectus carinatum, Pectus excavatum, Chondropathy, Chondromalacia, Polychondritis, Relapsing Polychondritis, Slipped epiphysis, Osteochondritis Dissecans, Chondrodysplasia, Costochondritis, Perichondritis, Osteochondroma, Knee osteoarthritis, Finger osteoarthritis, Wrist osteoarthritis, Hip osteoarthritis, Spine osteoarthritis, Chondromalacia, Osteoarthritis Susceptibility, Ankle Osteoarthritis, Spondylosis, Secondary chondrosarcoma, Small and unstable nodules as seen in osteoarthritis, Osteochondroses, Primary chondrosarcoma, Cartilage disorders, scleroderma, collagen disorders, Chondrodysplasia, Tietze syndrome, Dermochondrocorneal dystrophy of Francois, Epiphyseal dysplasia multiple 1, Epiphyseal dysplasia multiple 2, Epiphyseal dysplasia multiple 3, Epiphyseal dysplasia multiple 4, Epiphyseal dysplasia multiple 5, Ossified Ear cartilages with Mental deficiency, Muscle Wasting and Bony Changes, Periosteal chondrosarcoma, Carpotarsal osteochondromatosis, Achondroplasia, Genochondromatosis II, Genochondromatosis, Chondrodysplasia -- disorder of sex development, Chondroma, Chordoma, Atelosteogenesis, type 1, Atelosteogenesis Type III, Atelosteogenesis, type 2, Pyknoachondrogenesis, Osteoarthropathy of fingers familial, Dyschondrosteosis – nephritis, Coloboma of Alar-nasal cartilages with telecanthus, Alar cartilages hypoplasia – coloboma – telecanthus, Pierre Robin syndrome – fetal chondrodysplasia, Dysspondyloenchondromatosis, Achondroplasia regional – dysplasia abdominal muscle, Osteochondritis Dissecans, Familial Articular Chondrocalcinosis, Tracheobronchomalacia, Chondritis, Dyschondrosteosis, Jequier-Kozlowski-skeletal dysplasia, Chondrodystrophy, Cranio osteoarthropathy, Tietze's syndrome, Hip dysplasia – ecchondromata, Bessel-Hagen disease, Chondromatosis (benign), Enchondromatosis (benign), Chondrocalcinosis due to apatite crystal deposition, Meyenburg-Altherr-Uehlinger syndrome, Enchondromatosis-dwarfism-deafness, premature growth plate closure (e.g., due to dwarfism, injury, therapy such as retinoid therapy for adolescent acne, or ACL repair), Astley-Kendall syndrome, Synovial osteochondromatosis, Severe achondroplasia with developmental delay and acanthosis nigricans, Chondrocalcinosis, Stanescu syndrome, Familial osteochondritis dissecans, Achondrogenesis

type 1A, Achondrogenesis type 2, Achondrogenesis, Langer-Saldino Type, Achondrogenesis type 1B, Achondrogenesis type 1A and 1B, Type II Achondrogenesis-Hypochondrogenesis, Achondrogenesis, Achondrogenesis type 3, Achondrogenesis type 4, Chondrocalcinosis 1, Chondrocalcinosis 2, Chondrocalcinosis familial articular, Diastrophic dysplasia, Fibrochondrogenesis, Hypochondroplasia, Keutel syndrome, Maffucci Syndrome, Osteoarthritis Susceptibility 6, Osteoarthritis Susceptibility 5, Osteoarthritis Susceptibility 4, Osteoarthritis Susceptibility 3, Osteoarthritis Susceptibility 2, Osteoarthritis Susceptibility 1, Pseudoachondroplasia, Cauliflower ear, Costochondritis, Growth plate fractures, Pectus excavatum, septic arthritis, gout, pseudogout (calcium pyrophosphate deposition disease or CPPD), gouty arthritis, bacterial, viral, or fungal infections in or near the joint, bursitis, tendinitis, arthropathies, or a joint disease condition. Examples of bone diseases or conditions that can be treated with a peptide of the disclosure include osteopenia, post-menopausal bone loss, bone maintenance, bone fracture, arthroplasty recovery, osteoporosis, bone loss due to metastatic cancer, fractures due to bone loss (e.g., hip fractures in patients with osteoporosis), pathological fracture, or atypical fracture.

[0232] In some embodiments, a peptide or peptide conjugate of this disclosure can be administered to a subject in order to target, an arthritic joint. In other embodiments, a peptide or peptide conjugate of this disclosure can be administered to a subject in order to treat an arthritic joint.

[0233] In some embodiments, the present disclosure provides a method for treating a cancer, the method comprising administering to a subject in need thereof an effective amount of a peptide of the present disclosure.

[0234] In some embodiments, the present disclosure provides a method for treating a cancer, the method comprising administering to a patient in need thereof an effective amount of a pharmaceutical composition comprising a peptide of the present disclosure and a pharmaceutically acceptable carrier.

[0235] In some embodiments, the peptides of the present disclosure can be used to treat chondrosarcoma. Chondrosarcoma is a cancer of cartilage producing cells and is often found in bones and joints. It falls within the family of bone and soft-tissue sarcomas. In certain embodiments, administration of a peptide or peptide conjugate of the present disclosure can be used to image and diagnose or target and treat a subject with chondrosarcoma. The administration of a peptide or peptide conjugate of the present disclosure can be used in combination with ablative radiotherapy or proton therapy to treat chondrosarcoma. The subject can be a human or an animal.

[0236] In some embodiments, a peptide or peptide conjugate of this disclosure can be used to treat Chordoma. In certain embodiments, administration of a peptide or peptide conjugate of the present disclosure can be used to image and diagnose or target and treat a subject with chordoma. The administration of a peptide or peptide conjugate of the present disclosure can be used in combination with a tyrosine kinase inhibitor, such as imatinib mesylate, and ablative radiotherapy or proton therapy to treat chordoma. The administration of a peptide or peptide conjugate of the present disclosure can be used in combination with an antivascular agent such as bevacizumab and an epidermal growth factor receptor inhibitor such as erlotinib to treat chordoma. The subject can be a human or an animal.

[0237] In some embodiments, the present disclosure provides a method for inhibiting invasive activity of cells, the method comprising administering an effective amount of a peptide of the present disclosure to a subject.

[0238] In some embodiments, the peptides of the present disclosure are complexed, conjugated, or fused to one or more therapeutic agents. In further embodiments, the therapeutic agent is a chemotherapeutic, anti-cancer drug, or anti-cancer agent selected from, but are not limited to: anti-inflammatories, such as for example a glucocorticoid, a corticosteroid, a protease inhibitor, such as for example collagenase inhibitor or a matrix metalloprotease inhibitor (i.e., MMP-13 inhibitor), an amino sugar, vitamin (e.g., Vitamin D), and antibiotics, antiviral, or antifungal, a statin, an immune modulator, radioisotopes, toxins, enzymes, sensitizing drugs, nucleic acids, including interfering RNAs, antibodies, anti-angiogenic agents, cisplatin, anti-metabolites, mitotic inhibitors, growth factor inhibitors, paclitaxel, temozolomide, topotecan, fluorouracil, vincristine, vinblastine, procarbazine, decarbazine, altretamine, methotrexate, mercaptopurine, thioguanine, fludarabine phosphate, cladribine, pentostatin, cytarabine, azacitidine, etoposide, teniposide, irinotecan, docetaxel, doxorubicin, daunorubicin, dactinomycin, idarubicin, plicamycin, mitomycin, bleomycin, tamoxifen, flutamide, leuprolide, goserelin, aminogluthimide, anastrozole, amsacrine, asparaginase, mitoxantrone, mitotane and amifostine, and their equivalents, as well as photo-ablation. Some of these active agents induce programmed cell death such as apoptosis in target cells and thereby improve symptoms or ameliorate disease. Apoptosis can be induced by many active agents, including, for example, chemotherapeutics, anti-inflammatories, corticosteroids, NSAIDS, tumor necrosis factor alpha (TNF- α) modulators, tumor necrosis factor receptor (TNFR) family modulators. In some embodiments, peptides of this disclosure can be used to target active agents to pathways of cell death or cell killing, such as caspases, apoptosis activators and inhibitors, XBP-1, Bcl-2, Bcl-XL, Bcl-w, and other disclosed herein. In other embodiments, the therapeutic agent is any nonsteroidal anti-inflammatory drug

(NSAID). The NSAID can be any heterocyclic acetic acid derivatives such as ketorolac, indomethacin, etodolac, or tolemetin, any propionic acid derivatives such as naproxen, any enolic acid derivatives, any anthranilic acid derivatives, any selective COX-2 inhibitors such as celecoxib, any sulfonanilides, any salicylates, aceclofenac, nabumetone, sulindac, diclofenac, or ibuprofen. In other embodiments, the therapeutic agent is any steroid, such as dexamethasone, budesonide, beclomethasone monopropionate, dexamethasone, triamcinolone, cortisone, prednisone, prednisolone, triamcinolone hexacetonide, or methylprednisolone. In other embodiments, the therapeutic agent is a pain reliever, such as acetaminophen, opioids, local anesthetics, anti-depressants, glutamate receptor antagonists, adenosine, or neuropeptides. In some embodiments, a treatment consists of administering a combination of any of the above therapeutic agents and a peptide conjugate, such as a treatment in which both a dexamethasone-peptide conjugate and an NSAID are administered to a patient. Peptides of the current disclosure that target the cartilage can be used to treat the diseases conditions as described herein, for example, any diseases or conditions including tears, injuries (i.e., sports injuries), genetic factors, degradation, thinning, inflammation, cancer or any other disease or condition of the cartilage or to target therapeutically-active substances to treat these diseases amongst others. In other cases, a peptide of the disclosure can be used to treat traumatic rupture, detachment, chondrochondritis, spinal disc herniation, relapsing and non-relapsing polychondritis, injury to the articular cartilage, osteoarthritis, arthritis or achondroplasia. In some cases, the peptide or peptide-active agent can be used to target cancer in the cartilage, for example benign chondroma or malignant chondrosarcoma, by contacting the cartilage by diffusion into chondrocytes and then having antitumor function, targeted toxicity, inhibiting metastases, etc. As well, such peptide or peptide-active agent can be used to label, detect, or image such cartilage lesions, including tumors and metastases amongst other lesions, which may be removed through various surgical techniques or by targeting with peptide-active agents that induce programmed cell death or kill cells.

[0239] Venom or toxin derived peptide(s), peptides, modified peptides, labeled peptides, peptide-active agent conjugates and pharmaceutical compositions described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the composition can be administered to a subject already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition, or to cure, heal, improve, or ameliorate the condition. Such peptides described herein can also be administered to prevent (either in whole or in part), lessen a likelihood of developing, contracting, or worsening a condition. Amounts effective for this use can vary based on the severity and course of the disease or condition, previous therapy, the subject's health status,

weight, response to the drugs, and the judgment of the treating physician. Venom or toxin derived peptide(s), peptides, modified peptides, labeled peptides, peptide-active agent conjugates and pharmaceutical compositions described herein can allow for targeted homing of the peptide and local delivery of any conjugate. For example, a peptide complexed, conjugated, or fused to a steroid allows for local delivery of the steroid, which is significantly more effective and less toxic than traditional systemic steroids. A peptide complexed, conjugated, or fused to an NSAID is another example. In this case, the peptide complexed, conjugated, or fused to an NSAID allows for local delivery of the NSAID, which allows for administration of a lower NSAID dose and is subsequently less toxic. By delivering an active agent to the joint, pain relief can be more rapid, may be more long lasting, and can be obtained with a lower systemic dose and off-site undesired effects than with systemic dosing without targeting.

[0240] Peptides of the current disclosure that target the cartilage can be used to treat or manage pain associated with a cartilage injury or disorder, or any other cartilage or joint condition as described herein. The peptides can be used either directly or as carriers of active drugs, peptides, or molecules. For example, since ion channels can be associated with pain and can be activated in disease states such as arthritis, peptides that interact with ion channels can be used directly to reduce pain. In another embodiment, the peptide is complexed, conjugated, or fused to an active agent with anti-inflammatory activity, in which the peptide acts as a carrier for the local delivery of the active agent to reduce pain. Peptides or peptide-active agent complexes may exert their effects via a variety of activities including anti-inflammatory, stopping cartilage destruction, stimulating cartilage regrowth, restoring cartilage, amongst other effects described herein.

[0241] In some embodiments, the peptides described herein provide a method of treating a cartilage condition of a subject, the method comprising administering to the subject a therapeutically-effective amount of a peptide comprising the sequence SEQ ID NO: 110, SEQ ID NO: 115, SEQ ID NO: 234, SEQ ID NO: 242, SEQ ID NO: 139, SEQ ID NO: 242, SEQ ID NO: 260, or fragment thereof. In some embodiments, the peptides described herein provide a method of treating a cartilage condition of a subject, the method comprising administering to the subject a therapeutically-effective amount of a peptide comprising the sequence SEQ ID NO: 52 – SEQ ID NO: 66, SEQ ID NO: 241 – SEQ ID NO: 248, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 249 – SEQ ID NO: 256, SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 233 – SEQ ID NO: 240, or fragment thereof. In some embodiments, the peptides described herein provide a method of treating a cartilage condition of a subject, the method comprising administering to the subject a peptide of any one of SEQ ID NO: 21 – SEQ ID NO: 45, SEQ ID

NO: 47 – SEQ ID NO: 66, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 219 – SEQ ID NO: 263 or fragment thereof. Optionally, the peptide or fragment thereof may be administered itself, or may be administered as a peptide-active agent complex.

Treatment of Kidney Disorders

[0242] In some embodiments, peptides of this disclosure that home, target, are directed to, migrate to, are retained by, accumulate in, or bind to specific regions, tissues, structures or cells of the kidneys can be used to treat a kidney disorder. In other embodiments, peptides are used in peptide conjugates of the present disclosure to deliver an active agent for treatment of a kidney disorder.

[0243] In some embodiments, the peptides and peptide-conjugates of the present disclosure are used to treat a condition of the kidney, or a region, tissue, structure, or cell thereof. In certain embodiments, the condition is associated with kidney, or a function of a subject's kidneys. The present disclosure encompasses various acute and chronic renal diseases, including glomerular, tubule-interstitial, and microvascular diseases. Examples of conditions applicable to the present disclosure include but are not limited to: hypertensive kidney damage, acute kidney diseases and disorders (AKD), acute kidney injury (AKI) due to ischemia-reperfusion injury, drug treatment such as chemotherapy, cardiovascular surgery, surgery, medical interventions or treatment, radiocontrast nephropathy, or induced by cisplatin or carboplatin, which can be treated prophylactically, established AKI including ischemic renal injury, endotoxemia-induced AKI, endotoxemia/sepsis syndrome, or established nephrotoxic AKI (e.g., rhabdomyolysis, radiocontrast nephropathy, cisplatin/carboplatin AKI, aminoglycoside nephrotoxicity), end stage renal disease, acute and rapidly progressive glomerulonephritis, acute presentations of nephrotic syndrome, acute pyelonephritis, acute renal failure, chronic glomerulonephritis, chronic heart failure, chronic interstitial nephritis, graft versus host disease after renal transplant, chronic kidney disease (CKD) such as diabetic nephropathy, hypertensive nephrosclerosis, idiopathic chronic glomerulonephritis (e.g., focal glomerular sclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, minimal change disease transition to chronic disease, anti-GBM disease, rapidly progressive crescentic glomerulonephritis, IgA nephropathy), secondary chronic glomerulonephritis (e.g., systemic lupus, polyarteritis nodosa, scleroderma, amyloidosis, endocarditis), hereditary nephropathy (e.g., polycystic kidney disease, Alport's syndrome), interstitial nephritis induced by drugs (e.g., Chinese herbs, NSAIDs), multiple myeloma or sarcoid, or renal transplantation such as donor kidney prophylaxis (treatment of

donor kidney prior to transplantation), treatment post transplantation to treat delayed graft function, acute rejection, or chronic rejection, chronic liver disease, chronic pyelonephritis, diabetes, diabetic kidney disease, fibrosis, focal segmental glomerulosclerosis, Goodpasture's disease, hypertensive nephrosclerosis, IgG4-related renal disease, interstitial inflammation, lupus nephritis, nephritic syndrome, partial obstruction of the urinary tract, polycystic kidney disease, progressive renal disease, renal cell carcinoma, renal fibrosis, and vasculitis. For example, in certain embodiments, the peptides and peptide-conjugates of the present disclosure are used to reduce acute kidney injury in order to prevent it from progressing to chronic kidney disease.

[0244] Alternatively or in combination, in some embodiments, the peptide and peptide-conjugates of the present disclosure are used to elicit a protective response such as ischemic preconditioning and/or acquired cytoresistance in a kidney of the subject. In some embodiments, ischemic preconditioning and/or acquired cytoresistance is induced by administering an agent (e.g., a peptide or peptide-conjugate of the present disclosure) that upregulates the expression of protective stress proteins, such as antioxidants, anti-inflammatory proteins, or protease inhibitors. In certain embodiments, the induced response protects the kidney by preserving kidney function in whole or in part and/or by reducing injury to renal tissues and cells, e.g., relative to the situation where no protective response is induced. The peptides and peptide-conjugates of the present disclosure can provide certain benefits compared to other agents for inducing ischemic preconditioning and/or acquired cytoresistance, such as a well-defined chemical structure and avoidance of low pH precipitation.

[0245] In some embodiments, the protective response is induced in order to protect the kidney or tissues or cells thereof from an injury or insult that is predicted to occur (e.g., associated with a planned event such as a medical procedure, is likely to occur due to a condition in the subject) or has already occurred. In certain embodiments, the induced response prevents or reduces the extent of damage to the kidney or tissues or cells thereof caused by the injury or insult. For instance, in certain embodiments, the peptides and peptide-conjugates induce acquired cytoresistance by activating protective pathways and/or upregulating expression of protective stress proteins. Optionally, the peptides and peptide-conjugates are capable of inducing such protective responses while causing minimal or no injury to the kidney.

[0246] In various embodiments, the injury or insult is associated with one or more of: surgery, radiocontrast imaging, cardiopulmonary bypass, balloon angioplasty, induced cardiac or cerebral ischemic-reperfusion injury, organ transplantation, sepsis, shock, low blood pressure, high blood pressure, kidney hypoperfusion, chemotherapy, drug administration, nephrotoxic drug administration, blunt force trauma, puncture, poison, or smoking. For instance, in certain

embodiments, the injury or insult is associated with a medical procedure that has been or will be performed on the subject, such as one or more of: surgery, radiocontrast imaging, cardiopulmonary bypass, balloon angioplasty, induced cardiac or cerebral ischemic-reperfusion injury, organ transplantation, chemotherapy, drug administration, or nephrotoxic drug administration.

[0247] In some embodiments, the peptide itself exhibits a renal therapeutic effect. For example, in certain embodiments, the cystine-dense peptide interacts with a renal ion channel, inhibits a protease, has antimicrobial activity, has anticancer activity, has anti-inflammatory activity, induces ischemic preconditioning or acquired cytoresistance, or produces a protective or therapeutic effect on a kidney of the subject, or a combination thereof. Optionally, the renal therapeutic effect exhibited by the peptide is a renal protective effect or renal prophylactic effect (e.g., ischemic preconditioning or acquired cytoresistance) that protects the kidney or a tissue or cell thereof from an upcoming injury or insult. Peptides or peptide-active agent complexes may exert their effects via a variety of activities including anti-inflammatory, stopping kidney destruction, stimulating kidney regrowth, restoring kidney function, amongst other effects described herein.

[0248] For example, in certain embodiments, a peptide of the present disclosure activates protective pathways and/or upregulates expression of protective stress proteins in the kidney or tissues or cells thereof. As another example, in certain embodiments, a peptide of the present disclosure accesses and suppresses intracellular injury pathways. In yet another example, in certain embodiments, a peptide of the present disclosure inhibits interstitial inflammation and prevents renal fibrosis. As a further example, in certain embodiments, a peptide of the present disclosure is administered prior to or currently with the administration of a nephrotoxic agent (e.g., aminoglycoside antibiotics such as gentamicin and minocycline, chemotherapeutics such as cisplatin, immunoglobulins or fragments thereof, mannitol, NSAIDs such as ketorolac or ibuprofen, cyclosporin, cyclophosphamide, radiocontrast dyes) in order to minimize its damaging effects, e.g., by blocking megalin-cubulin binding sites so that the nephrotoxic agent passes through the kidneys.

[0249] In some embodiments, the present disclosure provides that any peptide of the disclosure including SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 can as a peptide conjugate with an active agent for treatment of a kidney

disorder can be complexed, conjugated, or fused to an active agent and administered to a subject in need thereof to treat a kidney disorder.

[0250] In some embodiments, homing of a peptide of this disclosure to cartilage or the kidneys can be assessed in an animal model such as those described in Alves et al. (Clin Rev Allergy Immunol. 2016 Aug;51(1):27-47. doi: 10. 1007/s12016-015-8522-7), Kuyinu et al. (J Orthop Surg Res. 2016 Feb 2;11:19. doi: 10. 1186/s13018-016-0346-5), Li et al. (Exp Biol Med (Maywood). 2015 Aug;240(8):1029-38. doi: 10. 1177/1535370215594583), and Mullins et al. (Dis Model Mech. 2016 Dec 1;9(12):1419-1433), all of which are incorporated herein by reference.

[0251] Multiple peptides described herein can be administered in any order or simultaneously. In some cases, multiple functional fragments of peptides derived from toxins or venom can be administered in any order or simultaneously. If simultaneously, the multiple peptides described herein can be provided in a single, unified form, such as an intravenous injection, or in multiple forms, such as subsequent intravenous dosages.

[0252] Peptides can be packaged as a kit. In some embodiments, a kit includes written instructions on the use or administration of the peptides.

EXAMPLES

[0253] The following examples are included to further describe some embodiments of the present disclosure, and should not be used to limit the scope of the disclosure.

EXAMPLE 1

Manufacture of Peptides

[0254] The peptide sequence was reverse-translated into DNA, synthesized, and cloned in-frame with siderocalin using standard molecular biology techniques. (M. R. Green, Joseph Sambrook. Molecular Cloning. 2012 Cold Spring Harbor Press.). The resulting construct was packaged into a lentivirus, transfected into HEK293 cells, expanded, isolated by immobilized metal affinity chromatography (IMAC), cleaved with tobacco etch virus protease, and purified to homogeneity by reverse-phase chromatography. Following purification, each peptide was lyophilized and stored frozen.

EXAMPLE 2

Radiolabeling of Peptide

[0255] This example describes radiolabeling of peptides with standard techniques. *See* J Biol Chem. 254(11):4359-65 (1979). The sequences were engineered to have the amino acids, “G” and “S” at the N terminus. *See* Methods in Enzymology V91:1983 p. 570 and Journal of

Biological Chemistry 254(11):1979 p. 4359. An excess of formaldehyde was used to ensure complete methylation (dimethylation of every free amine). The labeled peptides were isolated via solid-phase extraction on Strata-X columns (Phenomenex 8B-S100-AAK), rinsed with water with 5% methanol, and recovered in methanol with 2% formic acid. Solvent was subsequently removed in a blowdown evaporator with gentle heat and a stream of nitrogen gas.

EXAMPLE 3

Peptide Detectable Agent Complexes

[0256] This example describes the dye labeling of peptides. A peptide of the disclosure is expressed recombinantly or chemically synthesized, and then the N-terminus of the peptide is complexed, conjugated, or fused to a detectable agent via an NHS ester using DCC or EDC to produce a peptide-detectable agent conjugate. The detectable agent is the fluorophore dye is a cyanine dye, such as Cy5. 5 or an Alexa fluorophore, such as Alexa647.

[0257] The peptide detectable agent conjugates are administered to a subject. The subject can be a human or a non-human animal. After administration, the peptide detectable agent conjugates home to cartilage. The subject, or a biopsy from the subject, can be imaged to visualize localization of the peptide detectable agent conjugates to cartilage. In some aspects, visualization of the peptide detectable agent conjugates in cartilage after administration results in diagnosis of arthritis, cartilage damage, or any cartilage disorder.

EXAMPLE 4

Dosing of Peptide with Kidney Ligation

[0258] This example describes a dosing scheme for administering peptides to mice in conjunction with kidney ligation. Different dosages of the peptides of SEQ ID NO:149 and SEQ ID NO:150 were administered to Female Harlan athymic nude mice, weighing 20g – 25g, via tail vein injection (n = 2 mice per peptide). The experiment was done in duplicates. The kidneys were ligated to prevent renal filtration of the peptides. Each peptide was radiolabeled by methylating lysines and the N-terminus, so the actual binding agent may contain methyl or dimethyl lysine(s) and a methylated or dimethylated amino terminus.

[0259] A target dosage of 50-100 nmol of each peptide carrying 10-25 uCi of ^{14}C was administered to Female Harlan athymic nude mice while anesthetized. Each peptide was allowed to freely circulate within the animal before the animals were euthanized and sectioned.

[0260] This method is applied to any of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID

NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

EXAMPLE 5

Peptide Homing with Kidney Ligation

[0261] This example illustrates peptide homing to cartilage of mice with kidneys that were ligated prior to peptide administration. At the end of the dosing period in **EXAMPLE 4**, mice were frozen in a hexane/dry ice bath and then frozen in a block of carboxymethylcellulose. Whole animal sagittal slices were prepared that resulted in thin frozen sections being available for imaging. Thin, frozen sections of animal including imaging of tissues such as brain, tumor, liver, kidney, lung, heart, spleen, pancreas, muscle, adipose, gall bladder, upper gastrointestinal tract, lower gastrointestinal tract, bone, bone marrow, reproductive track, eye, cartilage, stomach, skin, spinal cord, bladder, salivary gland, and other types of tissues were obtained with a microtome, allowed to desiccate in a freezer, and exposed to phosphorimager plates for about ten days.

[0262] These plates were developed, and the signal (densitometry) from each organ was normalized to the signal found in the heart blood of each animal. A signal in tissue darker than the signal expected from blood in that tissue indicates peptide accumulation in a region, tissue, structure or cell. For instance, the cartilage is avascular and contains minute amounts of blood. A ratio of at least 170% signal in the cartilage versus heart ventricle was chosen as a reference level for significant targeting to cartilage, which also correlated with clear accumulation in cartilaginous tissues in the images of the slices. **FIG. 1** identifies the locations of the SEQ ID NO: 150 peptide distribution in joint and other cartilage. **FIG. 7** identifies the locations of the SEQ ID NO: 27 peptide distribution in nasal, spinal, tracheal, and other cartilage, including to hyaline cartilage such as articular cartilage and physal cartilage, as well as fibrocartilage.

[0263] Additionally, the peptide can be retained in cartilage for hours after treatment. The SEQ ID NO: 150 peptide was radiolabeled as in **EXAMPLE 4** and 100 nmol of peptide was injected into a mouse with intact kidneys. **FIG. 4** illustrates the retention of and the tissue distribution in the cartilage of a peptide of SEQ ID NO: 150, 24 hours after administration.

[0264] This method is applied to any of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

EXAMPLE 6**Dosing of Peptide without Kidney Ligation**

[0265] This example describes a dosing scheme for administering peptides to mice without kidney ligation. The peptide administered had the sequence of SEQ ID NO: 150. The peptide was radiolabeled by methylating lysines and the N-terminus, so the actual binding agent may contain methyl or dimethyl lysine(s) and a methylated or dimethylated amino terminus.

[0266] A target dosage of 100 nmol of each peptide carrying 10-25 μ Ci of 14 C was administered to Female Harlan athymic nude mice by a tail vein injection. Each peptide was allowed to freely circulate within the animal for either 4 hours or 24 hours before the animals were euthanized and sectioned.

[0267] This method is applied to any of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

EXAMPLE 7**Peptide Homing with Intact Kidneys**

[0268] This example illustrates peptide homing to cartilage in animals with intact kidneys. At the end of the 4 hour or 24 hour dosing periods in **EXAMPLE 6**, mice were frozen in a hexane/dry ice bath and then frozen in a block of carboxymethylcellulose. Whole animal sagittal slices were prepared that resulted in thin frozen sections being available for imaging. Thin, frozen sections of animal including imaging of tissues such as brain, tumor, liver, kidney, lung, heart, spleen, pancreas, muscle, adipose, gall bladder, upper gastrointestinal track, lower gastrointestinal track, bone, bone marrow, reproductive track, eye, cartilage, stomach, skin, spinal cord, bladder, salivary gland, and other types of tissues were obtained with a microtome, allowed to desiccate in a freezer, and exposed to phosphorimager plates for about ten days.

[0269] These plates were developed. A signal in tissue darker than the signal expected from blood in that tissue indicates peptide accumulation in a region, tissue, structure or cell. For instance, the cartilage is avascular and contains minute amounts of blood. High signal in the kidneys indicates presence and accumulation of the peptide in the kidneys. **FIG. 1** identifies the locations of the SEQ ID NO: 150 peptide distribution in joint and other cartilage as well as kidneys.

[0270] This method is applied to any of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

EXAMPLE 8

Peptide Homing with Therapeutic Agents

[0271] This example describes certain exemplary therapeutic agents that are complexed, conjugated, or fused to a peptide. A peptide of the disclosure is expressed recombinantly or chemically synthesized and then is complexed, conjugated, or fused to an exemplary drug, such as paclitaxel or triamcinolone acetonide or budesonide using techniques known in the art, such as those described in Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). One or more drugs are complexed, conjugated, or fused per peptide, or an average of less than one drug is complexed, conjugated, or fused per peptide.

[0272] Coupling of these drugs to a peptide of any of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 targets the drug to the cartilage of the subject. One or more drug-peptide conjugates are administered to a human or animal.

EXAMPLE 9

Peptide Homing to an Arthritic Joint

[0273] This example illustrates peptide homing to cartilage in humans or animals with arthritis. A peptide of the present disclosure is expressed recombinantly or chemically synthesized and is used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound. A peptide is selected from any one of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. The peptide or peptide conjugate is administered to a human or animal subcutaneously, intravenously, or orally, or is injected directly into a joint intraarticularly. The peptide or peptide conjugate homes to cartilage.

EXAMPLE 10

Peptide Homing to Cartilage in Non-Human Animals

[0274] This example illustrates a peptide or peptide conjugate of this disclosure homing to cartilage in non-human animals. Non-human animals include but are not limited to guinea pigs, rabbits, dog, cats, horses, rats, mice, cows, pigs, non-human primates, and other non-human animals. A peptide of the present disclosure is recombinantly expressed or chemically

synthesized and are used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound. The peptide is selected from any one of the peptides SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. The resulting peptide or peptide conjugate is administered to a non-human animal subcutaneously, intravenously, or orally, or is injected directly into a joint intra-articularly. Biodistribution is assessed by LC/MS, autoradiography, positron emission tomography (PET), or fluorescence imaging. A peptide or peptide conjugate is homed to cartilage in non-human animals.

EXAMPLE 11

Whole Body Fluorescence and Isolated Limb Fluorescence of Homing Peptides

[0275] This example illustrates whole body fluorescence and isolated limb fluorescence of peptide homers of this disclosure. Any peptide of the present disclosure is chemically complexed, conjugated, or fused to one molecule of a near infrared fluorophore, at the N-terminus of the peptide via an active NHS ester on the dye. A dose of 10 nmol of each peptide complexed, conjugated, or fused to a fluorophore is administered to Female Harlan athymic nude mice, weighing 20-25 g, and is administered via tail vein injection. Each experiment is done at least in duplicate (n=2 mice per group). The peptide fluorophore conjugate is allowed to freely circulate for the described time period before the mice were euthanized at various time points. Mice are evaluated for peptide distribution of the peptide fluorescence in whole body imaging and in isolated hind limb imaging.

[0276] For Whole body fluorescence (WBF), at the end of the dosing period, mice are frozen in a hexane/dry ice bath and then embedded in a frozen block of carboxymethylcellulose. Whole animal sagittal slices are prepared that resulted in thin frozen sections for imaging. Thin frozen sections are obtained using a microtome and allowed visualization of tissues. Sections are allowed to dessicate in a freezer prior to imaging. WBF is performed on fluorescent sections, which are scanned on a Li-Cor Odyssey scanner at a setting of 169 μ m resolution, medium quality, 700 channel, L-2. 0 intensity.

[0277] For isolated hind limb fluorescence studies, mice are euthanized by CO₂ asphyxiation at the end of the dosing period. The right hind limb is removed at the hip joint and imaged on a Sepctrum IVIS imager (ex/em: 675 nm. 720 nm) with a 1 second exposure length and a focal height of 0. 5 cm. Limbs are imaged with skin removed and with muscle removed.

EXAMPLE 12**Whole Body Autoradiography of Homing Peptides**

[0278] This example illustrates whole body autoradiography of peptide homers of this disclosure. Peptides are radiolabeled by methylating lysines at the N-terminus as described in **EXAMPLE 2**. As such, the peptide may contain methyl or dimethyl lysines and a methylated or dimethylated amino terminus. A dose of 100 nmol radiolabeled peptide is administered via tail vein injection in Female Harlan athymic nude mice, weighing 20-25 g. The experiment is done in at least duplicate (n=2 animals per group). In some animals, kidneys are ligated to prevent renal filtration of the radiolabeled peptides and extend plasma half-life. Each radiolabeled peptide is allowed to freely circulate within the animal for the described time period before the animals were euthanized and sectioned.

[0279] Whole body autoradiography (WBA) sagittal sectioning is performed as follows. At the end of the dosing period, mice are frozen in a hexane/dry ice bath and then embedded in a frozen block of carboxymethylcellulose. Whole animal sagittal slices are prepared that resulted in thin frozen sections for imaging. Thin frozen sections are obtained using a microtome and allowed visualization of tissues such as brain, tumor, liver, kidney, lung, heart, spleen, pancreas, muscle, adipose, gall bladder, upper gastrointestinal tract, lower gastrointestinal tract, bone, bone marrow, reproductive tract, eye, cartilage, stomach, skin, spinal cord, bladder, salivary gland, and more. Sections are allowed to dessicate in a freezer prior to imaging.

[0280] For the autoradiography imaging, tape mounted thin sections are freeze dried and radioactive samples were exposed to phosphorimager plates for 7 days. These plates are developed and the signal (densitometry) from each organ was normalized to the signal found in the cardiac blood of each animal. A signal in tissue darker than the signal expected from blood in that tissue indicates accumulation in a region, tissue, structure, or cell.

EXAMPLE 13**Peptide Localization in Chondrocytes**

[0281] This example illustrates binding of peptides of this disclosure to chondrocytes within cartilage in animals with intact kidneys. In one embodiment, animals are dosed and are processed as described in **EXAMPLE 11** and **EXAMPLE 12**. At the end of the dosing period, animals are euthanized and cartilage is optionally removed for use in staining and imaging procedures. Whole animal sagittal slices are prepared that result in thin frozen sections being available for staining and imaging. One or more of the following cartilage components are identified in thin frozen sections or live cartilage explants using standard staining techniques: collagen fibrils, glycosaminoglycans, or chondrocytes. A peptide of this disclosure is found to

localize to chondrocytes in cartilage, localized intracellularly or extracellularly bound or both. Localization is visualized and confirmed by microscopy.

[0282] In another embodiment, peptides or peptide-drug conjugates of this disclosure are administered in humans and are localized on or in chondrocytes in cartilage.

EXAMPLE 14

Peptide Localization in Cartilage Extracellular Matrix

[0283] This example illustrates localization of peptides of this disclosure in cartilage extracellular matrix. In one embodiment, animals are dosed and are processed as described in **EXAMPLE 11** and **EXAMPLE 12** in animals with intact kidneys. At the end of the dosing period, animals are euthanized and cartilage is optionally removed for use in staining and imaging procedures. Whole animal sagittal slices are prepared that result in thin frozen sections being available for staining and imaging. Thin frozen sections or live cartilage explants are acquired, stained, and visualized as described in **EXAMPLE 13**. A peptide of the present disclosure is found to localize to the extracellular matrix in cartilage. The peptide may be bound to one or more components of the extracellular matrix, such as proteoglycans, glycosaminoglycans, aggrecan, decorin, or collagen. Localization is visualized and confirmed by microscopy.

[0284] In another embodiment, peptides or peptide-drug conjugates of this disclosure are administered in humans and are localized in cartilage extracellular matrix.

EXAMPLE 15

Peptide Binding to Cartilage Explants

[0285] This example illustrates a peptide or peptide conjugation of this disclosure homing, targeting, being directed to, migrating to, being retained by, accumulating in, or binding to human and animal cartilage explants in culture. A peptide is selected from any one of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Peptides are recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound. A peptide of peptide conjugate of this disclosure is incubated with cartilage explants derived from humans or animals. Peptides of peptide conjugate are found to bind to cartilage explants. The interaction with cartilage is confirmed using various methods that include but are not limited to liquid scintillation counting, confocal microscopy, immunohistochemistry, HPLC, or LC/MS. The

peptide shows a higher level of signal than a control peptide that is administered that is not a cartilage binding peptide.

EXAMPLE 16

Effects of Peptide on Ion Channels

[0286] This example describes the interaction between peptides of the present disclosure and ion channels. Ion channels can be associated with pain and can be activated in disease states such as arthritis. A peptide of the disclosure is expressed and administered in a pharmaceutical composition to a patient to treat a joint condition or disease associated with an ion channel and treatable by binding, blocking, or interacting with the ion channel. Ion channels, such as Nav 1.7, are inhibited by peptides of the present disclosure. A given peptide is expressed recombinantly or chemically synthesized, wherein the peptide selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Following expression or synthesis, the peptide is used directly or complexed, conjugated, or fused to a therapeutic compound, such as those described herein. A peptide of the present disclosure selectively interacts with ion channels, or is mutated in order to interact with ion channels. For example, a peptide of this disclosure is bound to Nav 1.7 or Nav 1.7 is blocked by a peptide of this disclosure. When the peptide is administered to a human subject, Nav 1.7 signaling is reduced in the tissues in proximity to the joints, and pain relief is thereby provided.

EXAMPLE 17

Peptide-Fc Protein Fusions

[0287] This example illustrates making and using peptide-Fc protein fusions. A peptide of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) was recombinantly expressed with the sequence for the human IgG1 Fc protein in HEK293 cells to yield a sequence of SEQ ID NO: 216

(METDTLLLWVLLLWVPGSTGGSGVPINVRCRGSRDCLDPCRRAGMRFGRCINSRCHCT
PGGSGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMHEALHNHYTQKSLSLSPGK)

[0288] The sequence of any peptide of this disclosure is expressed as a fusion protein with either murine or human Fc by adding a secretion signal sequence to the N-terminus and an Fc sequence to the C-terminus. This creates a bivalent molecule with improved secretion properties. The larger peptide-Fc fusion is expressed in different mammalian or insect cell lines and is useful as a research reagent and a therapeutic.

[0289] Fc fusion to a peptide of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) to yield a sequence of SEQ ID NO: 216 extends half-life and improves biodistribution of the peptide to cartilage. Any peptide of this disclosure is co-expressed with Fc protein to yield Fc-fusion peptides with longer half-life and improved homing to cartilage. In SEQ ID NO: 216, the secretion signal sequence METDTLLLWVLLLWVPGSTG (SEQ ID NO: 217) is followed by the peptide of SEQ ID NO: 149, and is followed by the sequence for Fc protein. Cleaving can be imprecise, resulting in cleavage at position 20 or position 21 of SEQ ID NO: 216.

EXAMPLE 18

Peptide Conjugate Hydrolysis

[0290] This example describes preparation of peptide conjugates having tunable hydrolysis rates. The peptide-drug conjugates described below are synthesized with the modification that instead of using succinic anhydride, other molecules are used to provide steric hindrance to hydrolysis or an altered local environment at the carbon adjacent to the final hydrolyzable ester. In one exemplary conjugate, the peptide-drug conjugate is synthesized with tetramethyl succinic anhydride to generate hindered esters, which causes a decreased rate of hydrolysis. In another exemplary conjugate, one methyl group is present at the adjacent carbon. In another exemplary conjugate, two methyl groups are present at the adjacent carbon. In another exemplary conjugate, one ethyl group is present at the adjacent carbon. In another exemplary conjugate, two ethyl groups are present at the adjacent carbon. In another exemplary conjugate, the carbon linker length is increased such as by using glutaric anhydride instead of succinic anhydride, increasing the local hydrophobicity and lowering the hydrolysis rate. In another exemplary conjugate, a hydroxyl group is located on the adjacent carbon, increasing the local hydrophilicity and increasing the hydrolysis rate. The rate of hydrolysis in these exemplary conjugates is therefore adjusted, preventing premature cleavage and ensuring that the majority of peptide-dexamethasone conjugates accumulate in cartilage prior to release of the drug by hydrolysis but that the dexamethasone is also released in the cartilage in a timely manner.

[0291] The resulting peptide conjugates are administered to a human or animal subcutaneously, intravenously, orally, or injected directly into a joint to treat disease.

EXAMPLE 19**Peptide Complexes with Stable Linkers**

[0292] This example describes preparation of peptide conjugates with stable linkers. A peptide of the disclosure is expressed recombinantly or is chemically synthesized. The peptide is complexed, conjugated, or fused to a detectable agent or an active agent via a stable linker, such as an amide linkage or a carbamate linkage. The peptide is complexed, conjugated, or fused to a detectable agent or an active agent via a stable linker, such as an amide bond using standard 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) or dicyclohexylcarbodiimide (DCC) based chemistry or thionyl chloride or phosphorous chloride-based bioconjugation chemistries.

[0293] A peptide and drug complexed, conjugated, or fused via a linker are described with the formula Peptide-A-B-C-Drug, wherein the linker is A-B-C. A can be a stable amide link that is formed by reacting with an amine on the peptide with a linker containing a tetrafluorophenyl (TFP) ester or an NHS ester. A can also be a stable carbamate linker that is formed by reacting with an amine on the peptide imidazole carbamate active intermediate formed by the reaction of CDI with a hydroxyl on the linker. A can also be a stable secondary amine linkage that is formed by reductive alkylation of the amine on the peptide with an aldehyde or ketone group on the linker. A can also be a stable thioether linker formed using a maleimide or bromoacetamide in the linker with a thiol in the peptide, a triazole linker, a stable oxime linker, or an oxacarboline linker. B is $(-\text{CH}_2-)_x$, a short PEG $(-\text{CH}_2\text{CH}_2\text{O}-)_x$ (x is 0-20). Alternatively, spacers within the linker is optional and can be included or not at all. C is an amide bond formed with an amine or a carboxylic acid on the drug, a thioether formed between a maleimide on the linker and a sulfhydryl on the drug, a secondary or tertiary amine, a carbamate, or other stable bonds. Any linker chemistry described in “Current ADC Linker Chemistry,” Jain et al., *Pharm Res*, 2015 DOI 10. 1007/s11095-015-1657-7 can be used.

[0294] The resulting peptide conjugates are administered to a human or animal subcutaneously, intravenously, orally, or injected directly into a joint to treat disease. The peptide is not specifically cleaved from the detectable agent or active agent via a targeted mechanism. The peptide can be degraded by mechanisms such as catabolism, releasing a drug that is modified or not modified from its native form (Singh, Luisi, and Pak, *Pharm Res* 32:3541-3571 (2015)). The peptide drug conjugate exerts its pharmacological activity while still intact, or while partially or fully degraded, metabolized, or catabolized.

EXAMPLE 20**Peptide Complexes with Cleavable Linkers**

[0295] This example describes preparation of peptide conjugates having cleavable linkers. A peptide of the disclosure is expressed recombinantly or chemically synthesized. A peptide and drug are complexed, conjugated, or fused via a linker and is described with the formula Peptide-A-B-C-Drug, wherein the linker is A-B-C. A is a stable amide link such as that formed by reacting an amine on the peptide with a linker containing a tetrafluorophenyl (TFP) ester or an NHS ester. A can also be a stable carbamate linker such as that formed by reacting an amine on the peptide with an imidazole carbamate active intermediate formed by reaction of CDI with a hydroxyl on the linker. A can also be a stable secondary amine linkage such as that formed by reductive alkylation of the amine on the peptide with an aldehyde or ketone group on the linker. A can also be a stable thioether linker formed using a maleimide or bromoacetamide in the linker with a thiol in the peptide, a triazole linker, a stable oxime linker, or a oxacarboline linker. B is $(-CH_2-)_x$ - or a short PEG $(-CH_2CH_2O-)_x$ (x is 0-20) or other spacers or no spacer. C is an ester bond to the hydroxyl or carboxylic acid on the drug, or a carbonate, hydrazone, or acylhydrazone, designed for hydrolytic cleavage. The hydrolytic rate of cleavage is varied by varying the local environment around the ester, including carbon length $(-CH_2-)_x$, steric hindrance (including adjacent side groups such as methyl, ethyl, cyclic), hydrophilicity or hydrophobicity. Hydrolysis rate is affected by local pH, such as lower pH in certain compartments of the body or of the cell such as endosomes and lysosomes or diseased tissues. C is a pH sensitive group such as a hydrazone or oxime linkage. Alternatively C is a disulfide bond designed to be released by reduction, such as by glutathione. Alternatively C (or A-B-C) is a peptidic linkage design for cleavage by enzymes. Optionally, a self-immolating group such as pABC is included to cause release of a free unmodified drug upon cleavage (Antibody-Drug Conjugates: Design, Formulation, and Physicochemical Stability, Singh, Luisi, and Pak. Pharm Res (2015) 32:3541-3571). The linker is cleaved by enzymes such as esterases, matrix metalloproteinases, cathepsins such as cathepsin B, glucuronidases, a protease, or thrombin. Alternatively, the bond designed for cleavage is at A, rather than C, and C could be a stable bond or a cleavable bond. An alternative design is to have stable linkers (such as amide or carbamate) at A and C and have a cleavable linker in B, such as a disulfide bond. The rate of reduction is modulated by local effects such as steric hindrance from methyl or ethyl groups or modulating hydrophobicity/hydrophilicity.

[0296] The resulting peptide conjugates are administered to a human or animal subcutaneously, intravenously, orally, or injected directly into a joint to treat disease.

EXAMPLE 21**Acetylsalicylic Acid Peptide Complex**

[0297] This example describes the conjugation of acetylsalicylic acid to a peptide using a lactic acid linker. A conjugate is produced from a mixture of (*R,S*)- acetylsalicylic acid, lactic acid, and a peptide:

[0298] The acetylsalicylic acid -lactic acid linker conjugate depicted above is then reacted with a lysine or the N-terminus of a cystine-dense peptide to create an acetylsalicylic acid -lactic acid-peptide conjugate. The cystine-dense peptide is selected from the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

[0299] Acetylsalicylic acid is currently dosed as an enantiomeric mixture, in which enantiomers with a single racemic stereocenter are very difficult to separate. As in the reaction scheme (I), a diastereomer with two chiral centers is created by the addition of a chiral linker such as L-lactic acid. Since diastereomers are easily separated, the active enantiomer of acetylsalicylic acid complexed, conjugated, or fused to the lactic acid linker can be purified prior to conjugation to a cystine-dense peptide. The chemical synthesis can use any conjugation techniques known in the art, such as described in Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013) and in “Ketorolac-dextran conjugates: synthesis, in vitro, and in vivo evaluation,” Acta Pharm. 57 (2007) 441-450, Vyas, Trivedi, and Chaturvedi. The conjugate can display anti-inflammatory activity, or free acetylsalicylic acid is released from the conjugate to provide anti-inflammatory activity. The free acetylsalicylic acid can result from hydrolysis that occurs after administration, such as hydrolysis at the ester bond. By dosing the conjugate containing the cartilage homing peptide, a higher AUC of acetylsalicylic acid delivery to the joint may be achieved than would be achieved by systemic dosing of acetylsalicylic acid alone.

[0300] Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 22**Ibuprofen Peptide Complex**

[0301] This example describes the conjugation of ibuprofen to a peptide using a PEG linker. A conjugate is produced using ibuprofen and a PEG linker, which forms an ester bond that can hydrolyze as described in “In vitro and in vivo study of poly(ethylene glycol) complexed, conjugated, or fused ibuprofen to extend the duration of action,” Scientia Pharmaceutica, 2011,

79:359-373, Nayak and Jain. Fischer esterification is used to conjugate ibuprofen with a short PEG, e.g., with triethylene glycol, to yield ibuprofen-ester-PEG-OH.

[0302] Following preparation of the PEG-ibuprofen conjugate as shown above, the hydroxyl moiety of PEG is activated with N,N'-disuccinimidyl carbonate (DSC) to form ibuprofen-ester-PEG-succinimidyl carbonate, which is then reacted with a lysine or the N-terminus of a cystine-dense peptide to form an ibuprofen-ester-PEG-peptide conjugate. The cystine-dense peptide is selected from any one of the peptides of sequence SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. The conjugate can display anti-inflammatory activity, or free ibuprofen is released from the conjugate to provide anti-inflammatory activity. The free ibuprofen can result from hydrolysis that occurs after administration, such as hydrolysis at the ester bond.

[0303] Ibuprofen-peptide conjugates are administered to a subject in need thereof. The subject can be a human or a non-human animal.

[0304] Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**). Similar peptide-drug conjugates can be made using acetylsalicylic acid.

EXAMPLE 23

Dexamethasone Peptide Complex

[0305] This example describes different methods of complexing dexamethasone with a peptide of this disclosure. A peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 was recombinantly expressed. Dexamethasone was readily chemically conjugated to a peptide of this disclosure using a dicarboxylic acid linker. The peptide-dexamethasone conjugate was made by first converting dexamethasone to a hemisuccinate by reacting it with succinic anhydride. The hemisuccinate was then converted to a succinate carboxylic acid containing an active ester, using dicyclohexyl carbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in the presence of N-hydroxy succinimide (NHS). This active ester was then reacted with a lysine or the N-terminus of a cystine-dense peptide to create a dexamethasone-carboxylic acid-peptide conjugate. Methods such as those described in “Functionalized derivatives of hyaluronic acid oligosaccharides: drug carriers and novel biomaterials” Bioconjugate Chemistry 1994, 5, 339-347, Pouyani and Prestwich, and Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013) can be used.

[0306] Peptide-dexamethasone conjugates were prepared by coupling dexamethasone to the peptides of this disclosure using standard coupling-reagent chemistry. For example, dexamethasone conjugates were made by reacting dexamethasone hemiglutarate with 1.05 molar equivalents of 1,1'-carbonyldiimidazole in anhydrous DMSO in an inert atmosphere. After 30 minutes, excess dexamethasone in anhydrous DMSO was added along with two molar equivalents of anhydrous trimethylamine. The N-hydroxysuccinimide ester of the peptide-dexamethasone conjugate was generated to form a shelf-stable intermediate for later reaction with an amine-containing carrier. The N-terminal dexamethasone-peptide conjugate (SEQ ID NO: 108B) was verified by electrospray mass spectrometry (ES-MS) within a 10 ppm error.

[0307] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. A peptide of any of the sequences of this disclosure including SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263, are conjugated to dexamethasone using the methods described above.

[0308] Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

[0309] Any peptide of any sequence of this disclosure can be complexed, conjugated, or fused to dexamethasone.

EXAMPLE 24

Beclomethasone monopropionate Peptide Complexes

[0310] This example describes conjugation of a peptide any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to beclomethasone monopropionate. Beclomethasone monopropionate is readily complexed, conjugated, or fused to any peptide disclosed herein via a dicarboxylic acid linker. The dicarboxylic acid linker is a linear dicarboxylic acid, such as succinic acid, or a related cyclic anhydride, such as succinic anhydride. Reactions with anhydrides can proceed under simple conditions. For example, the reaction of beclomethasone monopropionate with five molar equivalents of glutaric anhydride is carried out in anhydrous pyridine at room temperature. Reactions with dicarboxylic acids can occur using standard carbodiimide coupling methods. For example, beclomethasone monopropionate is reacted with one molar equivalent dimethylsuccinic acid, one molar equivalent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (or another carbodiimide), and 0.2 molar equivalents of 40-dimethylamino pyridine.

[0311] The same methods as described in **EXAMPLE 18** are used to adjust the rate of hydrolysis of peptide- beclomethasone monopropionate conjugates, preventing premature cleavage and ensuring that the beclomethasone monopropionate of peptide- beclomethasone monopropionate conjugates accumulate in cartilage.

[0312] Peptide- beclomethasone monopropionate conjugates are prepared by coupling beclomethasone monopropionate to the peptides of this disclosure using standard coupling-reagent chemistry. The peptide- beclomethasone monopropionate conjugate was made by first converting beclomethasone monopropionate to a hemisuccinate by reacting it with succinic anhydride. The hemisuccinate was then converted to a succinate carboxylic acid containing an active ester, using dicyclohexyl carbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in the presence of N-hydroxy succinimide (NHS). This active ester was then reacted with a lysine or the N-terminus of a peptide to create a beclomethasone monopropionate -carboxylic acid-peptide conjugate. Methods such as those described in "Functionalized derivatives of hyaluronic acid oligosaccharides: drug carriers and novel biomaterials" Bioconjugate Chemistry 1994, 5, 339-347, Pouyani and Prestwich, and Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013) can be used.

[0313] Peptide- beclomethasone monopropionate conjugates were prepared by coupling beclomethasone monopropionate to the peptides of this disclosure using standard coupling-reagent chemistry. For example, beclomethasone monopropionate conjugates were made by reacting beclomethasone monopropionate hemiglutarate with 1.05 molar equivalents of 1,1'-carbonyldiimidazole in anhydrous DMSO in an inert atmosphere. After 30 minutes, excess beclomethasone monopropionate in anhydrous DMSO was added along with two molar equivalents of anhydrous trimethylamine. The N-hydroxysuccinimide ester of the peptide-beclomethasone monopropionate conjugate was generated to form a shelf-stable intermediate for later reaction with an amine-containing carrier.

[0314] Beclomethasone monopropionate is also readily complexed, conjugated, or fused to any peptide disclosed herein via a dicarboxylic acid linker. The dicarboxylic acid linker is a linear dicarboxylic acid, such as succinic acid, or a related cyclic anhydride, such as succinic anhydride. Reactions with anhydrides can proceed under simple conditions. For example, the reaction of beclomethasone monopropionate with five molar equivalents of glutaric anhydride is carried out in anhydrous pyridine at room temperature. Reactions with dicarboxylic acids can occur using standard carbodiimide coupling methods. For example, beclomethasone monopropionate is reacted with one molar equivalent dimethylsuccinic acid, one molar equivalent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (or another carbodiimide), and 0.2

molar equivalents of 40-dimethylamino pyridine. The peptide- beclomethasone monopropionate conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage and/or kidneys. The subject is a human or animal and has inflammation in the cartilage or kidney tissues. Upon administration of the peptide- beclomethasone monopropionate conjugates, the cartilage and/or kidney inflammation is alleviated.

[0315] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

[0316] Such peptide-drug conjugates are made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 25

Desciclesonide Peptide Complexes

[0317] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to desciclesonide. Ciclesonide is a prodrug that is metabolized in vivo to the active metabolite desciclesonide. By conjugating desciclesonide to a peptide via an ester linker, upon hydrolysis the released drug would be desciclesonide, just as after systemic administration of ciclesonide the active metabolite desciclesonide is present and active. Desciclesonide is readily complexed, conjugated, or fused to any peptide disclosed herein via a dicarboxylic acid linker. The dicarboxylic acid linker is a linear dicarboxylic acid, such as succinic acid, or a related cyclic anhydride, such as succinic anhydride. Reactions with anhydrides can proceed under simple conditions. For example, the reaction of desciclesonide with five molar equivalents of glutaric anhydride is carried out in anhydrous pyridine at room temperature. Reactions with dicarboxylic acids can occur using standard carbodiimide coupling methods. For example, desciclesonide is reacted with one molar equivalent dimethylsuccinic acid, one molar equivalent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (or another carbodiimide), and 0.2 molar equivalents of 40-dimethylamino pyridine.

[0318] The same methods as described in **EXAMPLE 18** are used to adjust the rate of hydrolysis of peptide- desciclesonide conjugates, preventing premature cleavage and ensuring that the desciclesonide of peptide- desciclesonide conjugates accumulate in cartilage.

[0319] Desciclesonide is also readily complexed, conjugated, or fused to any peptide disclosed herein via a dicarboxylic acid linker. The dicarboxylic acid linker is a linear dicarboxylic acid, such as succinic acid, or a related cyclic anhydride, such as succinic anhydride. Reactions with anhydrides can proceed under simple conditions. For example, the reaction of desciclesonide with five molar equivalents of glutaric anhydride is carried out in anhydrous pyridine at room temperature. Reactions with dicarboxylic acids can occur using standard carbodiimide coupling methods. For example, desciclesonide is reacted with one molar equivalent dimethylsuccinic acid, one molar equivalent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (or another carbodiimide), and 0.2 molar equivalents of 40-dimethylamino pyridine. The peptide-desciclesonide conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage and/or kidneys. The subject is a human or animal and has inflammation in the cartilage or kidney tissues. Optionally, the subject has osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, lupus arthritis, systemic lupus erythematosus, or lupus nephritis. Upon administration of the peptide-desciclesonide conjugates, the cartilage and/or kidney inflammation is alleviated.

[0320] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be a peptide of SEQ ID NO: 114, SEQ ID NO: 126, or SEQ ID NO: 109. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

[0321] Such peptide-drug conjugates are made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 26

Desciclesonide Peptide Complexes

[0322] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to desciclesonide. Ciclesonide is a prodrug that is metabolized in vivo to the active metabolite desciclesonide. By conjugating desciclesonide to a peptide via a linker such as an ester, a carbonate, or a carbamate, upon hydrolysis the released drug can be desciclesonide, just as after systemic administration of ciclesonide the active metabolite desciclesonide is present and active. Desciclesonide is readily complexed, conjugated, or fused to any peptide disclosed herein via a stable or cleavable linker.

[0323] The peptide- desciclesonide conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage

and/or kidneys. The subject is a human or animal and has inflammation in the cartilage or kidney tissues. Upon administration of the peptide- dexamethasone conjugates, the cartilage and/or kidney inflammation is alleviated.

[0324] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be a peptide of SEQ ID NO: 114, SEQ ID NO: 126, or SEQ ID NO: 109. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

[0325] Such peptide-drug conjugates are made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 27

Peptide-Ustekinumab Complexes

[0326] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to ustekinumab. Ustekinumab is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). Alternatively the peptide-active agent of this Example can be expressed as a fusion protein. From one to eight peptides are linked to ustekinumab.

[0327] The peptide-ustekinumab conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has psoriatic arthritis. Upon administration of the peptide-ustekinumab conjugates, the psoriatic arthritis condition is alleviated.

[0328] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

EXAMPLE 28

Peptide-Xeljanz Complexes

[0329] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to xeljanz. Xeljanz is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those

described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to xeljanz.

[0330] The peptide-xeljanz conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has rheumatoid arthritis. Upon administration and homing of peptide-xeljanz conjugates, the rheumatoid arthritis condition is alleviated.

[0331] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 29

Peptide-IL-17 Inhibitor Complexes

[0332] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to an IL-17 inhibitor. An IL-17 inhibitor is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0333] The peptide-IL-17 inhibitor conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has ankylosing spondylitis. Upon administration and homing of peptide-IL-17 inhibitor conjugates, the ankylosing spondylitis condition is alleviated.

[0334] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 30**Peptide-Iguratimod Complexes**

[0335] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to iguratimod. Iguratimod is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0336] The peptide- iguratimod conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to kidneys. The subject is a human or animal and has rheumatoid arthritis. Upon administration and homing of peptide-iguratimod conjugates, the rheumatoid arthritis condition is alleviated.

[0337] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 31**Peptide Mycophenolic Acid Complexes**

[0338] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to mycophenolic acid. Mycophenolic acid is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0339] The peptide- mycophenolic acid conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to kidneys. The subject is a human or animal and has organ transplantation, infection, cancer, or other kidney disorders. Upon administration and homing of peptide-mycophenolic acid conjugates, the organ transplantation, infection, cancer, other kidney disorders condition is alleviated.

[0340] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ

ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 32

Peptide-Tacrolimus Complexes

[0341] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to tacrolimus. Tacrolimus is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0342] The peptide-tacrolimusconjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to kidneys. The subject is a human or animal and has organ transplantation, any other kidney disease. Upon administration and homing of peptide-tacrolimus conjugates, the organ transplantation, any other kidney disease condition is alleviated.

[0343] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 33

Peptide-Secukinumab Complexes

[0344] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to secukinumab. Secukinumab is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to secukinumab. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0345] The peptide-secukinumab conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage.

The subject is a human or animal and has ankylosing spondylitis. Upon administration and homing of peptide-secukinumab acid conjugates, the ankylosing spondylitis condition is alleviated.

[0346] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 34

Peptide-Sirukumab Complexes

[0347] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to sirukumab. Sirukumab is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to sirukumab. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0348] The peptide- sirukumab conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to kidneys. The subject is a human or animal and has rheumatoid arthritis, immune diseases of the kidneys. Upon administration and homing of peptide-sirukumab conjugates, the rheumatoid arthritis, immune diseases of the kidneys condition is alleviated.

[0349] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 35**Peptide-Anifrolumab Complexes**

[0350] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to anifrolumab. Anifrolumab is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to anifrolumab. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0351] The peptide- anifrolumab conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to kidneys. The subject is a human or animal and has lupus nephritis. Upon administration and homing of peptide-anifrolumab conjugates, the lupus nephritis condition is alleviated.

[0352] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 36**Peptide-Denosumab Complexes**

[0353] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to denosumab. Denosumab is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to denosumab. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0354] The peptide-denosumab conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has osteoporosis. Upon administration and homing of peptide-denosumab conjugates, the osteoporosis condition is alleviated.

[0355] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID

NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 37

Peptide-Rituximab Complexes

[0356] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to rituximab. Rituximab is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to rituximab. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0357] The peptide-rituximab conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage or kidneys. The subject is a human or animal and has rheumatoid arthritis, kidney transplant. Upon administration and homing of peptide-rituximab conjugates, the rheumatoid arthritis, kidney transplant condition is alleviated.

[0358] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 38

Peptide-Omalizumab Complexes

[0359] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to omalizumab. Omalizumab is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to omalizumab. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0360] The peptide- omalizumab conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to kidneys. The subject is a human or animal and has kidney inflammation. Upon administration and homing of peptide- omalizumab conjugates, the kidney inflammation condition is alleviated.

[0361] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 39

Peptide-Abatacept Complexes

[0362] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to abatacept. Abatacept is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to abatacept. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0363] The peptide- abatacept conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to kidneys. The subject is a human or animal and has rheumatoid arthritis, lupus nephritis, organ transplant, focal segmental glomerulosclerosis. Upon administration and homing of peptide-abatacept conjugates, the rheumatoid arthritis, lupus nephritis, organ transplant, focal segmental glomerulosclerosis condition is alleviated.

[0364] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 40**Peptide-Oxycodone Complexes**

[0365] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to oxycodone. Oxycodone is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0366] The peptide- oxycodone conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has cartilage or kidney-related pain. Upon administration and homing of peptide- oxycodone conjugates, the cartilage-related pain condition is alleviated.

[0367] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 41**Peptide Capsaicin Complexes**

[0368] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to capsaicin. Capsaicin is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0369] The peptide-capsaicin conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has cartilage-related pain. Upon administration and homing of peptide-capsaicin conjugates, the cartilage or kidney-related pain condition is alleviated.

[0370] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug

conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 42

Peptide-GSK2193874 Complexes

[0371] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to GSK2193874. GSK2193874 is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0372] The peptide- GSK2193874 conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to GSK2193874. The subject is a human or animal and has cartilage-related pain. Upon administration and homing of peptide- GSK2193874 conjugates, the cartilage-related pain condition is alleviated.

[0373] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 43

Peptide BIIB023 Complexes

[0374] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to BIIB023. BIIB023 is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to BIIB023. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0375] The peptide- BIIB023 conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has lupus nephritis or rheumatoid arthritis. Upon administration

and homing of peptide- BIIB023 conjugates, the lupus nephritis or rheumatoid arthritis condition is alleviated.

[0376] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 44

Peptide-Anakinra Complexes

[0377] This example describes conjugation or fusion of a peptide any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to anakinra. A linker is optionally used to conjugate the peptide to anakinra. Anakinra is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to anakinra. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0378] The peptide-anakinra conjugates or fusions are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has lupus nephritis or rheumatoid arthritis. Upon administration and homing of peptide-anakinra conjugates or fusions, the lupus nephritis or rheumatoid arthritis condition is alleviated.

[0379] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 45**Peptide-IGF-1 Complexes**

[0380] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to IGF-1. IGF-1 is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to IGF-1. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0381] The peptide- IGF-1 conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has renal cancer or arthritis. Upon administration and homing of peptide-IGF-1 conjugates, the renal cancer or arthritis condition is alleviated.

[0382] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 46**Peptide-Romozumab Complexes**

[0383] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to Romozumab. Romozumab is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to romozumab. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0384] The peptide- romozumab conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has osteoporosis. Upon administration and homing of peptide- romozumab conjugates, the osteoporosis condition is alleviated.

[0385] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ

ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 47

Peptide-ZVAD-fmk Complexes

[0386] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to ZVAD-fmk. ZVAD-fmk is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to ZVAD-fmk.

[0387] The peptide- ZVAD-fmk conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has cartilage grafting, arthritis, surgical intervention, surgery for cartilage repair. Upon administration and homing of peptide- ZVAD-fmk conjugates, the cartilage grafting, arthritis, surgical intervention, surgery for cartilage repair condition is alleviated.

[0388] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 48

Peptide-S-methylisothiourea Complexes

[0389] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to S-methylisothiourea. S-methylisothiourea is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0390] The peptide- S-methylisothiourea conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to

cartilage. The subject is a human or animal and has arthritis surgery, kidney iron overload, renal ischemia reperfusion injury, or acute kidney injury. Upon administration and homing of peptide-S-methylisothiourea conjugates, the arthritis surgery, kidney iron overload, renal ischemia reperfusion injury, or acute kidney injury condition is alleviated.

[0391] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 49

Peptide-P188 Complexes

[0392] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to P188. P188 is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0393] The peptide- P188 conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has arthritis surgery. Upon administration and homing of peptide- P188 conjugates, the arthritis surgery condition is alleviated.

[0394] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 50

Peptide-Alendronate Complexes

[0395] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to alendronate. Alendronate is readily

complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0396] The peptide- alendronate conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has bone erosion. Upon administration and homing of peptide- alendronate conjugates, the bone erosion condition is alleviated.

[0397] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 51

Peptide-MIP-3 α Complexes

[0398] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to MIP-3 α . MIP-3 α is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to MIP-3 α . Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0399] The peptide- MIP-3 α conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has Joint injury, repair and regeneration of cartilage and bone. Upon administration and homing of peptide- MIP-3 α conjugates, the Joint injury, repair and regeneration of cartilage and bone condition is alleviated.

[0400] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 52**Peptide-BMP-2 Complexes**

[0401] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to BMP-2. BMP-2 is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to BMP-2. Alternatively the peptide-active agent of this Example can be expressed as a fusion protein.

[0402] The peptide- BMP-2conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has Joint repair. Upon administration and homing of peptide-BMP-2conjugates, the Joint repair condition is alleviated.

[0403] The peptide can also be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 53**Peptide-Icariin Complexes**

[0404] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to icariin. Icariin is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0405] The peptide- icariin conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has Joint repair. Upon administration and homing of peptide-icariin conjugates, the Joint repair condition is alleviated.

[0406] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ

ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or a stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 54

Peptide-Captopril Complexes

[0407] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to captopril. Captopril is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, *Bioconjugate Techniques* by Greg Hermanson (Elsevier Inc., 3rd edition, 2013).

[0408] The peptide-captopril conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to kidneys. The subject is a human or animal and has diabetic nephropathy. Upon administration and homing of peptide- captopril conjugates, the diabetic nephropathy condition is alleviated.

[0409] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 55

Peptide-Tofacitinib Complexes

[0410] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to tofacitinib. Tofacitinib is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, *Bioconjugate Techniques* by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). From one to eight peptides are linked to tofacitinib.

[0411] The peptide- tofacitinib conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage. The subject is a human or animal and has rheumatoid arthritis and kidney transplant, ankyloses spondylitis. Upon administration and homing of peptide- tofacitinib conjugates, the rheumatoid arthritis and kidney transplant, ankyloses spondylitis condition is alleviated.

[0412] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 56

Peptide-Dimethyl fumarate Complexes

[0413] This example describes conjugation of a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133 to dimethyl fumarate. Dimethyl fumarate is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013). Alternatively, peptide-dimethyl fumarate conjugates can be synthesized by Michael addition of a thiol (on the peptide or linker) to dimethyl fumarate as described by Schmidt et al. (Bioorg Med Chem. 2007 Jan 1;15(1):333-42. Epub 2006 Sep 29.).

[0414] The peptide- dimethyl fumarate conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to kidneys. The subject is a human or animal and has Kidney fibrosis, psoriatic arthritis, rheumatoid arthritis . Upon administration and homing of peptide- dimethyl fumarate conjugates, the Kidney fibrosis, psoriatic arthritis, rheumatoid arthritis condition is alleviated.

[0415] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can be any peptide with the sequence selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 57

Intra-articular Administration of Peptides and Peptide Complexes

[0416] This example illustrates intra-articular administration of peptides or peptide conjugates of this disclosure. A peptide of this disclosure is expressed recombinantly or chemically synthesized. In some cases, the peptide is subsequently complexed, conjugated, or fused to a

detectable agent or an active agent. The peptide or peptide conjugate is administered to a subject in need thereof via intra-articular administration. The cartilage is penetrated by the peptide or peptide conjugate due to the small size of the peptide or peptide conjugate, and due to binding of cartilage components by the peptide or peptide conjugate. The peptide or peptide conjugate is bound to cartilage and the residence time in the cartilage is longer due to this binding.

Optionally, the injected material is aggregated, is crystallized, or complexes are formed, further extending the depot effect and contributing to longer residence time.

[0417] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 58

Treatment of Osteoarthritis

[0418] This example describes a method for treating osteoarthritis using peptides of the present disclosure. This method is used as a treatment for acute and/or chronic symptoms associated with osteoarthritis. A peptide of the present disclosure is expressed recombinantly or chemically synthesized and then is used directly or complexed, conjugated, or fused to an anti-inflammatory compound, such as aspirin, dsciclesonide, or secukinumab. The resulting peptide or peptide-drug conjugate is administered in a pharmaceutical composition subcutaneously, intravenously, or orally, or is injected directly into a joint of a patient and targeted to cartilage. The formulation can be modified physically or chemically to increase the time of exposure in the cartilage. One or more anti-inflammatory peptide conjugates are administered to a human or animal.

[0419] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 59**Treatment of Cartilage Degradation**

[0420] This example describes a method for treating and/or preventing cartilage degradation using a peptide of the present disclosure. This method is used as a treatment for acute and/or chronic symptoms associated with cartilage degradation. Progressive degradation or thinning of the cartilage is difficult to treat in part because molecules such as small molecule drugs and antibodies typically do not reach the avascular cartilage. A peptide of the present disclosure is used for its homing and/or native activity, or is mutated to generate activity such as MMP protease inhibition. It is expressed recombinantly or chemically synthesized and then is used directly or complexed, conjugated, or fused to an extracellular matrix targeting active agent, such as an inhibitor of MMP activity or an anti-apoptosis agent (e. g., osteoprotegrin, romosozumab, P188, ZVAD-fmk, quercetin, dasatinib, dimethyl fumarate, bortezomib, carilzomib, or navitoclax). The resulting peptide or peptide-drug conjugate is administered in a pharmaceutical composition subcutaneously, intravenously, or orally, or is injected directly into a joint of a patient and targeted to extracellular matrix. One or more extracellular matrix targeting conjugates are administered to a human or animal.

[0421] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 60**Treatment of a Cartilage Injury**

[0422] This example describes a method for treating a cartilage injury using a peptide of the present disclosure. A peptide of the present disclosure is expressed recombinantly or chemically synthesized and then is used directly or complexed, conjugated, or fused to a therapeutic compound, such as those described herein, including, but not limited to BMP-2, BMP-7, BMP-9, BMP-13, PDGF, PTH, PTHrP, IL-8, MIP-3 α . The resulting peptide or peptide-drug conjugate is administered in a pharmaceutical composition to a patient and targeted to cartilage. One or more therapeutic compound-peptide conjugates are administered to a human or animal.

[0423] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 61

Treatment of Rheumatoid Arthritis

[0424] This example describes a method for treating rheumatoid arthritis. This method is used as a treatment for acute and/or chronic symptoms associated with rheumatoid arthritis. A peptide of the present disclosure is expressed recombinantly or chemically synthesized and then is used directly, or is complexed, conjugated, or fused to an anti-inflammatory compound, such as adalimumab, certolizumab, golimumab, thalidomide, lenalidomide, pomalidomide, pentocifylline, bupropion, or dexamethasone. Optionally, when the peptide is used directly, the peptide can, for example, bind or inhibit ion channels such as Kv 1.3. The resulting peptide or peptide-drug conjugate is administered in a pharmaceutical composition to a patient and is targeted to cartilage. One or more anti-inflammatory compound-peptide conjugates are administered to a human or animal subcutaneously, intravenously, or orally, or is injected directly into a joint.

[0425] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 62

Treatment of Gout

[0426] This example describes a method for treating gout using peptides of the present disclosure. This method is used as a treatment for acute and/or chronic symptoms associated with

gout. A peptide of the present disclosure is expressed and administered in a pharmaceutical composition to a patient as a therapeutic for gout. A peptide of the disclosure is recombinantly or chemically synthesized and then is used directly or complexed, conjugated, or fused to pegloticase to treat a cartilage disorder. A peptide of the disclosure is recombinantly or chemically synthesized and then is used directly or complexed, conjugated, or fused to probenecid to treat a kidney disorder. The peptide is administered in a pharmaceutical composition to a patient and the peptide is targeted to the cartilage or kidney affected by gout. One or more peptides are administered to a human or animal subcutaneously, intravenously, or orally, or is injected directly into a joint.

[0427] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 63

Treatment or Management of Pain

[0428] This example describes a method for treating or managing pain associated with a cartilage injury or disorder. This method is used as a treatment for acute and/or chronic symptoms associated with a cartilage injury or disorder. A peptide of the disclosure is expressed and administered in a pharmaceutical composition to a patient as a therapeutic for pain as a result of injury or other cartilage or joint condition as described herein. The peptide of the present disclosure inhibits ion channels, such as Nav 1. 7. The peptide is expressed recombinantly or chemically synthesized, wherein the peptide selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Alternatively, the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 are mutated to maintain the cartilage homing function, but to add or increase ion channel inhibition, such as to Nav 1. 7. Following expression or synthesis, the peptide is used directly or complexed,

conjugated, or fused to a narcotic (e.g., oxycodone), a non-narcotic analgesic, a natural counter-irritant (capsaicin), or a pain receptor channel inhibitor (such as the TRPV4 inhibitor GSK2193874). Following administration of the peptide, the peptide targets to the cartilage affected by pain. One or more peptides are administered to a human or animal subcutaneously, intravenously, or orally, or is injected directly into a joint.

[0429] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 64

Treatment or Management of Pain with Peptides Only

[0430] This example describes a method for treating or managing pain associated with a cartilage injury or disorder. This method is used as a treatment for acute and/or chronic symptoms associated with a cartilage injury or disorder. A peptide of the disclosure is expressed and administered in a pharmaceutical composition to a patient as a therapeutic for pain as a result of injury or other cartilage or joint condition as described herein. The peptide of the present disclosure inhibits ion channels, such as Nav 1. 7. The peptide is expressed recombinantly or chemically synthesized, wherein the peptide selected from SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Alternatively, the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 are mutated to maintain the cartilage homing function, but to add or increase ion channel inhibition, such as to Nav 1. 7. Following expression or synthesis, the peptide is used directly. Following administration of the peptide, the peptide targets to the cartilage affected by pain. One or more peptides are administered to a human or animal subcutaneously, intravenously, or orally, or is injected directly into a joint.

[0431] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

EXAMPLE 65

Treatment of Chondrosarcoma

[0432] This example illustrates treatment of chondrosarcoma using peptides of the present disclosure. A peptide of the present disclosure is recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound, such as dasatinib. The peptide or peptide conjugate is administered in a pharmaceutical composition to a subject as a therapeutic for chondrosarcoma. One or more peptides or peptide conjugates of the present disclosure are administered to a subject. A subject can be a human or an animal. The pharmaceutical composition is administered subcutaneously, intravenously, orally, or injected directly into a joint. The peptides or peptide conjugates target cartilage affected by chondrosarcoma.

[0433] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 66

Treatment of Chordoma

[0434] This example illustrates treatment of chordoma using peptides of the present disclosure. A peptide of the present disclosure is recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound, such as dasatinib. The peptide or peptide conjugate is administered in a pharmaceutical composition to a subject as a therapeutic for chordoma. One or more peptides or peptide

conjugates of the present disclosure are administered to a subject. A subject can be a human or an animal. The pharmaceutical composition is administered subcutaneously, intravenously, orally, or injected directly into a joint. The peptides or peptide conjugates target cartilage affected by chordoma.

[0435] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 67

Treatment for Rapid Pain Relief

[0436] This example illustrates rapid pain relief in patients treated for rheumatoid arthritis or osteoarthritis with the peptides or peptide conjugates of this disclosure. A peptide of this disclosure is expressed recombinantly or chemically synthesized, and then the N-terminus of the peptide is complexed, conjugated, or fused to an active agent via an NHS ester to produce a peptide-active agent conjugate. In some aspects the active agent such as a kidney therapeutic from **TABLE 4** or **TABLE 5**. In some cases, the peptide alone is administered to the subject.

[0437] The peptide or peptide-active agent conjugate is administered to a subject in need thereof. The subject is a human or non-human animal. The subject in need thereof has rheumatoid arthritis or osteoarthritis. The peptide or peptide conjugate is delivered via intravenous administration. Upon administration, the peptide or peptide conjugate rapidly homes to cartilage. Rapid pain relief within five minutes to an hour is experienced by the subject, and pain relieve can last as long as over 3 hours.

[0438] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 68**Treatment for Systemic Lupus Erythematosus**

[0439] This example illustrates treatment of systemic lupus erythematosus, including forms of the disease known as lupus nephritis and/or lupus arthritis using peptides or peptide conjugates of this disclosure. A peptide of the present disclosure is recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation or fusion to a fluorophore or therapeutic compound, such as abatacept or BIIB023 or desciclesonide.

[0440] The peptide or peptide conjugate is administered in a pharmaceutical composition to a subject as a therapeutic for lupus. The peptide is selected from any one of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. One or more peptides or peptide conjugates of the present disclosure are administered to a subject. A subject can be a human or an animal. The pharmaceutical composition is administered subcutaneously, intravenously, orally, or injected directly. The peptides or peptide conjugates target kidney affected by lupus nephritis and/or cartilage affected by lupus arthritis. The lupus condition of the subject is slowed, mitigated or improved.

[0441] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 69**Treatment for ankylosing spondylitis**

[0442] This example illustrates treatment of ankylosing spondylitis using peptides or peptide conjugates of this disclosure. A peptide of the present disclosure is recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation or fusion to a fluorophore or therapeutic compound, such as abatacept or BIIB023 or desciclesonide.

[0443] The peptide or peptide conjugate is administered in a pharmaceutical composition to a subject as a therapeutic for ankylosing spondylitis. The peptide is selected from any one of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO:

109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. One or more peptides or peptide conjugates of the present disclosure are administered to a subject. A subject can be a human or an animal. The pharmaceutical composition is administered subcutaneously, intravenously, orally, or injected directly. The peptides or peptide conjugates target cartilage affected by ankylosing spondylitis. The ankylosing spondylitis condition of the subject is improved.

[0444] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 70

Treatment for Acute Kidney Injury (AKI)

[0445] This example illustrates treatment of acute kidney injury (AKI) using peptides or peptide conjugates of this disclosure. A peptide of the present disclosure is recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound, such as such as a kidney therapeutic from **TABLE 4** or **TABLE 5**.

[0446] The peptide or peptide conjugate is administered in a pharmaceutical composition to a subject as a therapeutic for acute kidney injury (AKI). The peptide is selected from any one of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. One or more peptides or peptide conjugates of the present disclosure are administered to a subject. A subject can be a human or an animal. The pharmaceutical composition is administered subcutaneously, intravenously, orally, or injected directly into a joint. The peptides or peptide conjugates target cartilage affected by acute kidney injury (AKI).

[0447] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence

selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 71

Treatment for Chronic Kidney Disease (CKD)

[0448] This example illustrates treatment of chronic kidney disease (CKD) using peptides or peptide conjugates of this disclosure. A peptide of the present disclosure is recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound, such as a kidney therapeutic from **TABLE 4** or **TABLE 5**.

[0449] The peptide or peptide conjugate is administered in a pharmaceutical composition to a subject as a therapeutic for chronic kidney disease (CKD). The peptide is selected from any one of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. One or more peptides or peptide conjugates of the present disclosure are administered to a subject. A subject can be a human or an animal. The pharmaceutical composition is administered subcutaneously, intravenously, orally, or injected directly into a joint. The peptides or peptide conjugates target cartilage affected by chronic kidney disease (CKD).

[0450] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 72**Treatment for Hypertensive Kidney Damage**

[0451] This example illustrates treatment of hypertensive kidney damage using peptides or peptide conjugates of this disclosure. A peptide of the present disclosure is recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound, such as such as a kidney therapeutic from **TABLE 4 or TABLE 5**.

[0452] The peptide or peptide conjugate is administered in a pharmaceutical composition to a subject as a therapeutic for hypertensive kidney damage. The peptide is selected from any one of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. One or more peptides or peptide conjugates of the present disclosure are administered to a subject. A subject can be a human or an animal. The pharmaceutical composition is administered subcutaneously, intravenously, orally, or injected directly into a joint. The peptides or peptide conjugates target cartilage affected by hypertensive kidney damage.

[0453] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 73**Treatment for Diabetic Nephropathy**

[0454] This example illustrates treatment of diabetic nephropathy using peptides or peptide conjugates of this disclosure. A peptide of the present disclosure is recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound, such as such as a kidney therapeutic from **TABLE 3 or TABLE 4**.

[0455] The peptide or peptide conjugate is administered in a pharmaceutical composition to a subject as a therapeutic for diabetic nephropathy. The peptide is selected from any one of the

peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. One or more peptides or peptide conjugates of the present disclosure are administered to a subject. A subject can be a human or an animal. The pharmaceutical composition is administered subcutaneously, intravenously, orally, or injected directly into a joint. The peptides or peptide conjugates target cartilage affected by diabetic nephropathy.

[0456] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 74

Treatment for Renal Fibrosis

[0457] This example illustrates treatment of renal fibrosis using peptides or peptide conjugates of this disclosure. A peptide of the present disclosure is recombinantly expressed or chemically synthesized and are used directly, after radiolabeling, or after conjugation to a fluorophore or therapeutic compound, such as such as a kidney therapeutic from **TABLE 3** or **TABLE 4**.

[0458] The peptide or peptide conjugate is administered in a pharmaceutical composition to a subject as a therapeutic for renal fibrosis. The peptide is selected from any one of the peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. One or more peptides or peptide conjugates of the present disclosure are administered to a subject. A subject can be a human or an animal. The pharmaceutical composition is administered subcutaneously, intravenously, orally, or injected directly into a joint. The peptides or peptide conjugates target cartilage affected by renal fibrosis.

[0459] The peptide can be a peptide of SEQ ID NO: 115. The peptide can be a peptide of SEQ ID NO: 234. The peptide can also be a peptide of any one of SEQ ID NO: 109 – SEQ ID NO: 126 or SEQ ID NO: 129 – SEQ ID NO: 133. The peptide can be any peptide with the sequence selected SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO:

109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263. Such peptide-drug conjugates can be made using either a cleavable or stable linker as described herein (e. g., **EXAMPLES 19 and 20**).

EXAMPLE 75

Peptide Variants Based on Multiple Sequence Alignment

[0460] This example illustrates using multiple sequence alignment to design peptide variants with increased stability and decreased immunogenicity. An alignment was generated using R language and an “msa” software package, which codes for R language specific for multiple alignments (Bodenhofer, U et al. *Bioinformatics*, 31 (24): 3997–3999 (2015)). **FIG. 6** illustrates a multiple sequence alignment of SEQ ID NO: 198 – SEQ ID NO: 215. The alignment identified permissive or preferred amino acids at a given location, and provided a guide for discovery of novel peptide variants that could be generated and that could retain essential properties such as structure, function, peptide folding, biodistribution, or stability. SEQ ID NO: 21 and SEQ ID NO: 87 are consensus sequences based on the above multiple sequence alignment. SEQ ID NO: 21 is the same sequence as SEQ ID NO: 87 but with an N-terminal “GS.” SEQ ID NO: 219 – SEQ ID NO: 222 show peptide sequences, wherein the SEQ ID NO: 87 and SEQ ID NO: 21 consensus sequences were fit to SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205), with or without an N-terminal GS. SEQ ID NO: 219 – SEQ ID NO: 222 are variant consensus peptide sequences, included within the family of SEQ ID NO: 87 and SEQ ID NO: 21 consensus sequences, which variant consensus sequences include variants with improved properties of the peptides. Furthermore, based on the ability to substitute K residues with R residues the multiple sequence alignment identified peptides of the family of sequences of SEQ ID NO: 22 and SEQ ID NO: 88 as potential peptide variants that could be generated and that could retain essential properties such as structure, function, peptide folding, biodistribution, or stability. Additionally, the multiple sequence alignment identified SEQ ID NO: 104 as a conserved region within the sequences of the alignment, which may, at least in part, be important for maintaining the essential properties such as structure, function, peptide folding, biodistribution, binding, accumulation, retention, or stability. Other conserved regions within sequences of the present disclosure can be any one of SEQ ID NO: 227 – SEQ ID NO: 232.

EXAMPLE 76**Peptide Immunogenicity**

[0461] This example illustrates the testing of the immunogenicity of a peptide. NetMHC II version 2.3 prediction software was used to identify immunogenic peptides based on a neural network alignment algorithm that predicts peptide binding to MHC Class II molecules.

[0462] The NetMHC II prediction software was utilized to determine the putative peptide binding capability to DR, DQ, and DP MHC II alleles and the strength of the interaction between peptide and MHC II molecules. **TABLE 6** shows the resulting immunogenicity score of some select peptides. The numbers of strong versus weak peptides are tallied into each major MHC allele group (DR, DQ, and DP). Additionally, the numbers of ‘unique strong’ and ‘unique weak core’ peptides are also tallied. This data were used to predict which peptides are less likely to induce an immunogenic response in patients. For example, the stronger a peptide binds to an allele, the more likely it is to be presented in a MHC/peptide combination on an antigen presenting cell, thus triggering an immune response, and a peptide that is predicted to bind to fewer alleles is more likely to have weaker binding to given alleles and should be less immunogenic.

TABLE 6 – Immunogenicity Scores of Peptides

SEQ ID NO:	Strong Binding Alleles (DR + DQ + DP)	Unique Strong Core Peptides	Weak Binding Alleles (DR + DQ + DP)	Unique Weak Core Peptides
149	1 + 0 + 0	1 + 0 + 0	7 + 1 + 0	7 + 2 + 0
52	0 + 0 + 0	0 + 0 + 0	4 + 1 + 3	6 + 1 + 1
53	0 + 0 + 0	0 + 0 + 0	4 + 1 + 3	6 + 2 + 1
54	1 + 0 + 0	2 + 0 + 0	5 + 1 + 3	7 + 1 + 1
55	1 + 0 + 0	2 + 0 + 0	6 + 1 + 3	5 + 1 + 1
56	0 + 0 + 0	0 + 0 + 0	4 + 1 + 3	6 + 2 + 1
57	0 + 0 + 0	0 + 0 + 0	5 + 1 + 3	7 + 2 + 1
63	0 + 0 + 1	0 + 0 + 1	7 + 4 + 1	8 + 6 + 2
66	0 + 0 + 0	0 + 0 + 0	5 + 4 + 1	5 + 4 + 2
128	1 + 0 + 0	1 + 0 + 0	7 + 1 + 0	7 + 1 + 0
134	0 + 0 + 0	0 + 0 + 0	4 + 0 + 3	6 + 0 + 1
135	0 + 0 + 0	0 + 0 + 0	4 + 1 + 3	6 + 1 + 1
136	1 + 0 + 0	2 + 0 + 0	5 + 0 + 3	7 + 0 + 1
137	1 + 0 + 0	2 + 0 + 0	6 + 0 + 3	5 + 0 + 1
138	0 + 0 + 0	0 + 0 + 0	4 + 1 + 3	6 + 1 + 1
139	0 + 0 + 0	0 + 0 + 0	5 + 1 + 3	7 + 1 + 1
145	0 + 0 + 1	0 + 0 + 1	7 + 4 + 1	8 + 6 + 2
148	0 + 0 + 0	0 + 0 + 0	5 + 4 + 1	5 + 5 + 2
109	0 + 0 + 0	0 + 0 + 0	2 + 0 + 0	2 + 0 + 0
110	0 + 0 + 0	0 + 0 + 0	6 + 2 + 1	5 + 3 + 2
111	0 + 0 + 0	0 + 0 + 0	4 + 2 + 1	3 + 2 + 1
112	0 + 0 + 0	0 + 0 + 0	4 + 2 + 1	3 + 3 + 1
113	0 + 0 + 0	0 + 0 + 0	4 + 2 + 1	3 + 3 + 2

SEQ ID NO:	Strong Binding Alleles (DR + DQ + DP)	Unique Strong Core Peptides	Weak Binding Alleles (DR + DQ + DP)	Unique Weak Core Peptides
114	0 + 0 + 0	0 + 0 + 0	2 + 2 + 1	1 + 4 + 2
115	0 + 0 + 0	0 + 0 + 0	2 + 2 + 1	2 + 4 + 2
118	0 + 0 + 1	0 + 0 + 1	7 + 2 + 1	4 + 5 + 2
126	0 + 0 + 0	0 + 0 + 0	5 + 2 + 1	4 + 3 + 2

EXAMPLE 77**Peptide Variants**

[0463] This example illustrates the design of variant peptide sequences with increased stability, decreased regions of immunogenicity, and the substitution of a tyrosine for spectrophotometric reporting as compared to a parent peptide sequence. Potential mutations or corresponding substitutions to the parent peptide sequence, SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205), that may result in a peptide with increased stability, decreased immunogenicity, or increased absorbance at 270-280 nm (such as the substitution to a tyrosine or tryptophan residue for spectrophotometric reporting) were identified based on information from multiple sequence alignment from **EXAMPLE 75** and immunogenicity testing from **EXAMPLE 76**.

[0464] In SEQ ID NO: 149, residue N7 is at risk for deamidation. Based on the multiple sequence alignment of SEQ ID NO: 198 – SEQ ID NO: 215, the candidate residue mutations or corresponding substitutions to best reduce this risk were N7S and N7G. N7S was determined to be more likely to result in a peptide with desirable properties such as folding and stability as shown by matches in the alignment and conservationist presence in a peptide with high stability (SEQ ID NO: 206).

[0465] Residue D18 is at risk for cleavage. Based on the multiple sequence alignment, the candidate residue mutations or corresponding substitutions to best reduce cleavage at D18 are D18E and D18Q. D18E is the preferred choice based on retaining charge.

[0466] Residue M25 is at risk for oxidation. Based on the multiple sequence alignment, the candidate residue mutations or corresponding substitutions to best reduce oxidation were M25T and M25A. Based on the immunogenicity score of peptides with each mutation or corresponding substitutions, it was determined that M25T is the better mutation or corresponding substitutions, as it eliminates a significant source of immunogenicity as compared to SEQ ID NO: 108 as well as the variant with M25A, which did not eliminate the predicted immunogenicity of the parent peptide of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205).

[0467] Residue N32 is at risk for deamidation, at least in part due to the neighboring residue S33. However, N32 is conserved across Kv1. 3 binding cystine-dense peptides in the alignment of **EXAMPLE 75**, and implicated in receptor binding (Peigneur, S., *Biochemistry*, 55(32): 2927-35 (2016)). For certain applications, peptides are designed to maintain this binding interaction, and for other applications, peptides are designed to remove this binding interaction. To maintain functionality, one candidate residue mutation or corresponding substitution based on the multiple sequence alignment is S33R, which would impact deamidation. However, it resulted in a predicted increased immunogenicity score. Another candidate residue mutation or corresponding substitution is S33G, but this may result in higher deamidation rates. If N32 is mutated, the best candidate residue mutation or corresponding substitution based the multiple sequence alignment in combination with the immunogenicity score was N32Q despite it having a slight increase in immunogenicity. Other options are N32A, N32S, or N32T. Alternatively, to remove functionality, candidate mutations or corresponding substitutions based on the multiple sequence alignment are N32A and N32L, which are the preferred choices.

[0468] For the substitution to a tyrosine for spectrophotometric reporting, the best candidate locations were T38Y (which had the strongest precedence in the multiple sequence alignment and is found in several of the stable peptides (e.g., SEQ ID NO: 206, SEQ ID NO: 210, and SEQ ID NO: 211)), L17Y, and H36Y. However, T38Y may slightly increase immunogenicity with respect to the DR allele. Another option for spectrophotometric absorbance is to substitute Trp for the Leu at position 17.

[0469] Based on the above analysis, the following short list of potential mutations or corresponding substitutions for SEQ ID NO: 149 were compiled: N7S; D18E; M25T; N32Q, N32A, N32S, N32T, N32L, S33G, and S33R (variants both to retain function and to remove function of binding ion channel); and L17Y, H36Y, and T38Y.

[0470] **TABLE 7A** provides some exemplary sequences using various combinations of these mutations or corresponding substitutions with reference to SEQ ID NO: 149. Corresponding substitutions located at the corresponding location in another peptide relative to those amino acid residues (or with reference to those amino acid residues) as located within a sequence of the disclosure can be obtained, for example, using a sequence alignment or other methodology.

TABLE 7A – Exemplary Sequence Variants of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205)

SEQ ID NO:	Mutations	Sequence
149	Parent	GSGVPINVRCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
52	N7S, D18E, M25T, S33G	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCINGRCHCTP
53	N7S, D18E, M25T, N32Q	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
54	N7S, D18E, M25T, S33R	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCINRRCHCTP
55	D18E, M25T	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCINSRCHCTP
56	D18E, M25T, N32Q	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
57	D18E, M25T, N32Q, T38Y	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCYP
58	L17Y, D18E, M25T, N32Q	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
59	D18E, M25T, N32Q, H36Y	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
60	N7S, D18E, M25T, N32Q, T38Y	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCYP
61	N7S, L17Y, D18E, M25T, N32Q	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
62	N7S, D18E, M25T, N32Q, H36Y	GSGVPISVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP
63	D18E, M25T, N32A, T38Y	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCIASRCHCYP
64	D18E, M25T, N32S, T38Y	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCISSRCHCYP
65	D18E, M25T, N32T, T38Y	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCITSRCHCYP
66	D18E, M25T, T38Y	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCINSRCHCYP
241	D18E, M25T, N32L	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCILSRCHCTP
242	D18E, M25T, N32L, T38Y	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCILSRCHCYP
243	D18E, M25T, N32L, H36Y	GSGVPINVRCRGSRDCLDPCRRAGTRFGRCILSRCHCTP
244	N32Q,	GSGVPINVRCRGSRDCLDPCRRAGMRFGRCIQSRCHCTP
245	N32A,	GSGVPINVRCRGSRDCLDPCRRAGMRFGRCIASRCHCTP
246	N32S,	GSGVPINVRCRGSRDCLDPCRRAGMRFGRCISSRCHCTP
247	N32T,	GSGVPINVRCRGSRDCLDPCRRAGMRFGRCITSRCHCTP
248	N32L	GSGVPINVRCRGSRDCLDPCRRAGMRFGRCILSRCHCTP

[0471] **TABLE 7B** similarly provides some exemplary sequences using various combinations of these mutations or corresponding substitutions at corresponding locations but as applied to SEQ ID NO: 128 (GVPINVRCRGSRDCLDPCRRAGMRFGRCINSRCHCTP; also disclosed herein as SEQ ID NO: 205; GS versions of SEQ ID NO: 128 and SEQ ID NO: 205 are shown in SEQ ID NO: 46 and SEQ ID NO: 149).

TABLE 7B – Exemplary Sequence Variants of SEQ ID NO: 128 (also disclosed herein as SEQ ID NO: 205)

SEQ ID NO:	Mutations	Sequence
128	Parent	GVPINVRCRGSRDCLDPCRRAGMRFGRCINSRCHCTP
134	N5S, D16E, M23T, S31G	GVPIVRCRGSRDCLDPCRRAGTRFGRCINGRCHCTP
135	N5S, D16E, M23T, N30Q	GVPIVRCRGSRDCLDPCRRAGTRFGRCIQSRCHCTP

SEQ ID NO:	Mutations	Sequence
136	N5S, D16E, M23T, S31R	GVPISVRCRGSRDCLPCRRAGTRFGRCINRRCHCTP
137	D16E, M23T	GVPINVRCRGSRDCLPCRRAGTRFGRCINSRCHCTP
138	D16E, M23T, N30Q	GVPINVRCRGSRDCLPCRRAGTRFGRCIQSRCHCTP
139	D16E, M23T, N30Q, T36Y	GVPINVRCRGSRDCLPCRRAGTRFGRCIQSRCHCYP
140	L15Y, D16E, M23T, N30Q	GVPINVRCRGSRDCLPCRRAGTRFGRCIQSRCHCTP
141	D16E, M23T, N30Q, H34Y	GVPINVRCRGSRDCLPCRRAGTRFGRCIQSRCYCTP
142	N5S, D16E, M23T, N30Q, T36Y	GVPISVRCRGSRDCLPCRRAGTRFGRCIQSRCHCYP
143	N5S, L15Y, D16E, M23T, N30Q	GVPISVRCRGSRDCLPCRRAGTRFGRCIQSRCHCTP
144	N5S, D16E, M23T, N30Q, H34Y	GVPISVRCRGSRDCLPCRRAGTRFGRCIQSRCYCTP
145	D16E, M23T, N30A, T36Y	GVPINVRCRGSRDCLPCRRAGTRFGRCIASRCHCYP
146	D16E, M23T, N30S, T36Y	GVPINVRCRGSRDCLPCRRAGTRFGRCISSRCHCYP
147	D16E, M23T, N30T, T36Y	GVPINVRCRGSRDCLPCRRAGTRFGRCITSRCHCYP
148	D16E, M23T, T36Y	GVPINVRCRGSRDCLPCRRAGTRFGRCINSRCHCYP
249	D16E, M23T, N30L	GVPINVRCRGSRDCLPCRRAGTRFGRCILSRCHCTP
250	D16E, M23T, N30L, T36Y	GVPINVRCRGSRDCLPCRRAGTRFGRCILSRCHCYP
251	D16E, M23T, N30L, H34Y	GVPINVRCRGSRDCLPCRRAGTRFGRCILSRCYCTP
252	N30Q,	GVPINVRCRGSRDCLDPCRRAGMRFGRCIQSRCHCTP
253	N30A,	GVPINVRCRGSRDCLDPCRRAGMRFGRCIASRCHCTP
254	N30S,	GVPINVRCRGSRDCLDPCRRAGMRFGRCISSRCHCTP
255	N30T,	GVPINVRCRGSRDCLDPCRRAGMRFGRCITSRCHCTP
256	N30L	GVPINVRCRGSRDCLDPCRRAGMRFGRCILSRCHCTP

EXAMPLE 78

Peptide-Budesonide Complex

[0472] This example describes conjugation of a peptide of any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 to budesonide. Budesonide is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013) or by any of the methods described in **EXAMPLES 23-26**.

[0473] The peptide-budesonide conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage and/or kidneys. The subject is a human or animal and has inflammation in the cartilage or kidney tissues. Upon administration and homing of peptide-budesonide conjugates, the inflammation in the cartilage and/or kidney tissues is alleviated.

EXAMPLE 79**Peptide-Dexamethasone Complex**

[0474] This example describes conjugation of a peptide of any one SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 to dexamethasone.

Dexamethasone is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013) or by any of the methods described in

EXAMPLES 23-26.

[0475] The peptide-dexamethasone conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage and/or kidneys. The subject is a human or animal and has inflammation in the cartilage or kidney tissues. Upon administration and homing of peptide-dexamethasone conjugates, the inflammation in the cartilage and/or kidney tissues is alleviated.

EXAMPLE 80**Peptide-Triamcinalone Acetonide Complex**

[0476] This example describes conjugation of a peptide of any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 to triamcinalone acetonide.

Triamcinalone acetonide is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013) or by any of the methods described in **EXAMPLES 23-26.**

[0477] The peptide-triamcinalone acetonide conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage and/or kidneys. The subject is a human or animal and has inflammation in the cartilage or kidney tissues. Upon administration and homing of peptide-triamcinalone acetonide conjugates, the inflammation in the cartilage and/or kidney tissues is alleviated.

EXAMPLE 81**Peptide-Desciclesonide Complex**

[0478] This example describes conjugation of a peptide of any one of SEQ ID NO: 115, SEQ ID NO: 234, SEQ ID NO: 139, SEQ ID NO: 242, or SEQ ID NO: 110 to desciclesonide.

Desciclesonide is readily complexed, conjugated, or fused to any peptide disclosed herein via standard chemistries such as those described in, but not limited to, Bioconjugate Techniques by Greg Hermanson (Elsevier Inc., 3rd edition, 2013) or by any of the methods described in

EXAMPLES 23-26.

[0479] The peptide-desciclesonide conjugates are administered to a subject in need thereof and home, target, are directed to, are retained by, accumulate in, migrate to, and/or bind to cartilage and/or kidneys. The subject is a human or animal and has inflammation in the cartilage or kidney tissues. Upon administration and homing of peptide-desciclesonide conjugates, the inflammation in the cartilage and/or kidney tissues is alleviated.

[0480] The peptide can be any one of SEQ ID NO: 52 - SEQ ID NO: 66, SEQ ID NO: 241 - SEQ ID NO: 248, SEQ ID NO: 134 - SEQ ID NO: 148, SEQ ID NO: 249 - SEQ ID NO: 256, SEQ ID NO: 111 - SEQ ID NO: 126, or SEQ ID NO: 233 - SEQ ID NO: 240. The peptide can be any one of SEQ ID NO: 27 - SEQ ID NO: 45, SEQ ID NO: 47 - SEQ ID NO: 66, SEQ ID NO: 109 - SEQ ID NO: 126, SEQ ID NO: 129 - SEQ ID NO: 148, SEQ ID NO: 233 - SEQ ID NO: 256, or SEQ ID NO: 260 - SEQ ID NO: 263.

EXAMPLE 82**Method of Peptide Synthesis**

[0481] This example describes the synthesis of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205).

[0482] A peptide of SEQ ID NO: 149 was made using Solid Phase Peptide Synthesis (SPPS). After release of the peptide from the solid phase, the peptide was purified prior to folding by oxidation in solution. The folded peptide was further purified by reversed-phase chromatography and lyophilized as a TFA salt. The final SEQ ID NO: 149 peptide product had a purity of 96.1% and a mass of 4,301.7 Da, which confirmed its identity as a peptide of SEQ ID NO: 149.

EXAMPLE 83**Whole Body Autoradiography of Cartilage Homing Peptides**

[0483] This example illustrates peptide homing to cartilage mice 5 minutes to 48 hours after administration of a radiolabeled peptide. Signal from the radiolabeled peptides was found in all

types of cartilage at each time point examined. Each peptide was radiolabeled by methylating lysines at the N-terminus as described in **EXAMPLE 2**. As such, the peptide may contain methyl or dimethyl lysines and a methylated or dimethylated amino terminus. A dose of 100 nmol radiolabeled peptide was administered via tail vein injection in Female Harlan athymic nude mice, weighing 20-25 g. The experiment was done in duplicate (n=2 animals per group). Each radiolabeled peptide was allowed to freely circulate within the animal for the described time period before the animals were euthanized and sectioned.

[0484] Whole body autoradiography (WBA) sagittal sectioning was performed as follows. At the end of the dosing period, mice were frozen in a hexane/dry ice bath and then embedded in a frozen block of carboxymethylcellulose. Whole animal sagittal slices were prepared that resulted in thin frozen sections for imaging. Sections were allowed to dessicate in a freezer prior to imaging. For the autoradiography imaging, tape mounted thin sections were freeze dried and radioactive samples were exposed to phosphorimager plates. These plates were developed and the signal (densitometry) from each organ was normalized to the signal found in the cardiac blood of each animal. A signal in tissue darker than the signal expected from blood in that tissue indicates accumulation in a region, tissue, structure, or cell.

[0485] **FIG. 9** illustrates autoradiography image of frozen sections from a mouse, 3 hours after administration of 100 nmol of a radiolabeled peptide of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205). **FIG. 9A** illustrates the ^{14}C signal in a frozen section of a mouse, 3 hours after administration of 100 nmol of a radiolabeled peptide of SEQ ID NO: 149. The ^{14}C signal identifies the radiolabeled peptide distribution in the cartilage of the mouse. **FIG. 9B** illustrates the ^{14}C signal in a different frozen section of a mouse, 3 hours after administration of 100 nmol of a radiolabeled peptide of SEQ ID NO: 149. The ^{14}C signal identifies the radiolabeled peptide distribution in the cartilage of the mouse.

[0486] **TABLE 8** shows the signal of radiolabeled peptides of SEQ ID NO: 150 and SEQ ID NO: 149 in intervertebral discs (IVD) and knee joints as a percentage of the blood. Because the peptides may arrive at the joint within five minutes, a therapeutic effect from the peptide or a complexed, conjugated, or fused active agent may begin quickly. A therapeutic effect could be long lasting, due to continued presence of detected agents at 48 hours and/or due to long lasting pharmacodynamics effects.

TABLE 8 – Signal of Radiolabeled Peptides of SEQ ID NO: 150 and SEQ ID NO: 149 in IVD and Knee Joints as a Percentage of Blood

Hours	SEQ ID NO: 150 IVD	SEQ ID NO: 149 IVD	SEQ ID NO: 149 Knee
0.08		164	404
0.5		369	510
1		961	1114
3	1779	3213	4059
8		3777	4990
24	833	5391	2137
48		3320	843

[0487] This data illustrates peptides of SEQ ID NO: 150 and SEQ ID NO: 149 homed to and accumulated in the cartilage of the animals. The peptide of SEQ ID NO: 149 is a K to R variant of a peptide of SEQ ID NO: 150. These data show that K to R variants of cartilage homing peptides retained their cartilage homing properties.

[0488] SEQ ID NO: 218 (GSGVPINVRSRGSRDSLDPSSRRAGMRFGRSINRSRSHSTP) is a linearized version of SEQ ID NO: 149, where the knotted scaffold of the peptide was removed by mutating out the cysteine residues that form the disulfide bonds of the peptide to serine residues, but retaining the rest of the sequence. **TABLE 9** shows quantification of signal as a percentage of signal in blood from a linearized radiolabeled SEQ ID NO: 218 peptide in intervertebral discs (IVD).

TABLE 9 – Signal of Radiolabeled Peptides of SEQ ID NO: 218 in IVD as a Percentage of Blood

	3 hr Ligated Kidneys	3 hr Intact Kidneys	24 hr Intact Kidneys
IVD	117	177	104

[0489] The peptide of SEQ ID NO: 218, a linearized version of the peptide of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205), homed to cartilage to a much lesser extent than the folded knotted peptide (SEQ ID NO: 149). The signal of the folded knotted peptide of SEQ ID NO: 149 was ~20-fold greater at 3 hours and ~50-fold greater at 24 hours (**TABLE 8**) as compared to the linearized peptide of SEQ ID NO: 218 (**TABLE 9**). These results indicate that in addition to changes in primary sequence or peptide charge, homing to cartilage can also be related to changes in conformation, or tertiary structure. Namely, in some cases, folded cysteine-dense peptides can be exemplary cartilage homers in comparison to unfolded, linearized peptides of the same primary sequence (except for the mutated cysteine residues).

EXAMPLE 84**Fluorescence of Cartilage Homing Peptides**

[0490] This example illustrates peptide homing to cartilage mice after administration of a peptide-fluorophore complex. A peptide of SEQ ID NO: 149 was chemically conjugated to one molecule of Cyanine 5.5, and then imaged using the methods of **EXAMPLE 11**.

[0491] **FIG. 5** shows white light images and corresponding whole body fluorescence images of a mouse administered 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A) at 24 hours post-administration. **FIG. 5A** illustrates an image of a frozen section of a mouse, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A). **FIG. 5B** illustrates the fluorescence signal in the mouse, corresponding to the section shown in **FIG. 5A**, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A). **FIG. 5C** illustrates an image of a different frozen section of the mouse, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 46 (also disclosed herein as SEQ ID NO: 149) conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A). **FIG. 5D** illustrates the fluorescence signal in the mouse, corresponding to the section shown in **FIG. 5C**, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A). **FIG. 5E** illustrates an image of a different frozen section of the mouse, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A). **FIG. 5F** illustrates a fluorescence signal in the mouse, corresponding to the section shown in **FIG. 5E**, 24 hours after administration of 10 nmol of a peptide of SEQ ID NO: 149 conjugated to a Cy5. 5 fluorophore (SEQ ID NO: 149A).

[0492] **FIG. 8** shows IVIS fluorescence imaging of an isolated hind limb from a first mouse and an isolated hind limb from a second mouse after administration of 10 nmol SEQ ID NO: 108 peptide conjugated to a Cy5.5 fluorophore (SEQ ID NO: 149A). **FIG. 8A** shows the right hind limb with skin removed from a first mouse and from a second mouse 3 hours after peptide administration. **FIG. 8B** shows the right hind limb with muscle removed from a first mouse and from a second mouse 3 hours after peptide administration. **FIG. 8C** shows the right hind limb with skin removed from a first mouse and from a second mouse 24 hours after peptide administration. **FIG. 8D** shows the right hind limb with muscle removed from a first mouse and from a second mouse 24 hours after peptide administration. **FIG. 8E** shows the right hind limb with skin removed from a first mouse and from a second mouse 48 hours after peptide

administration. **FIG. 8F** shows the right hind limb with muscle removed from a first mouse and from a second mouse 48 hours after peptide administration. **FIG. 8G** shows the right hind limb with skin removed from a first mouse and from a second mouse 72 hours after peptide administration. **FIG. 8H** shows the right hind limb with muscle removed from a first mouse and from a second mouse 72 hours after peptide administration. Peptide fluorescence was observed in the knee joints of isolated right hind limbs at all time points tested. The peptides of this disclosure can be complexed, conjugated, or fused to one or more Cy5.5 fluorophores.

EXAMPLE 85

Peptide Resistance Under Various Conditions

[0493] This example illustrates peptide stability under various stress conditions such as high temperature, low pH, reducing agents, and proteases. To determine resistance to high temperatures, cystine-dense peptides (CDPs) were incubated at 0.5 mM in PBS at 75 °C or 100 °C for 1 h and pelleted, and the supernatant was analyzed with reversed-phase chromatography (RPC). To determine resistance to proteolytic digestion, CDPs were mixed with 50 U of porcine pepsin, in simulated gastric fluid at pH 1.0, or 50 U of porcine trypsin in PBS, incubated for 30 minutes at 37 °C and analyzed with RPC. Oxidized and reduced forms (prepared through addition 10 mM DTT) were compared. Circular Dichroism spectroscopy was used in order to measure the secondary structure of peptides with a Jasco J-720W spectropolarimeter in a cell with a 1.0-mm path length, and CDPs were diluted into 20 mM phosphate buffer, pH 7.4, at a concentration of 15–25 µM. These conditions were expected to denature or degrade conventional globular proteins and many peptides. In **TABLE 10**, “high” resistance indicated a high amount of the peptide remained or was retained as unmodified under the given experimental conditions and “low” resistance indicated a low amount of the peptide remained or was retained unmodified under the given experimental conditions. Notably, the experimental conditions described in this example were more extreme stress conditions than to many standard in vivo or physiologic conditions, in vitro conditions, conditions during manufacturing, and handling conditions. As such, even “low” resistance can indicate meaningful resistance to these stress conditions that may have applicability for a number of uses described herein. The data from these studies are shown in **TABLE 10**. The peptide tested, SEQ ID NO: 150, showed high resistance to one or more of the conditions tested.

TABLE 10 – Resistance of SEQ ID NO: 150 to Various Conditions

SEQ ID NO:	Resistance to Reduction	Resistance to 75° C	Resistance to 100° C	Resistance to Pepsin	Resistance to Trypsin
150	High	High	High	High	High

EXAMPLE 86**Truncated Peptide Variant Synthesis**

[0494] This example illustrates the synthesis of truncated peptide variants of a parent peptide. SEQ ID NO: 149 (39 amino acids) (SEQ ID NO: 149 is also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) was synthesized using Solid Phase Peptide Synthesis (SPPS). After release of the peptide from the solid phase, the peptide was purified prior to folding by oxidation in solution. The folded peptide was further purified by reversed-phase chromatography and lyophilized as a TFA salt. The final product had a purity of 96.1 % and a mass of 4,301.7 Da, which confirmed its identity as a peptide of SEQ ID NO: 149.

[0495] A truncated form of SEQ ID NO: 149, which is only 31 amino acids and is SEQ ID NO: 110, was synthesized using SPPS. After release of the peptide from the solid phase, the peptide was folded by oxidation in solution. The folded peptide was further purified by reversed-phase chromatography and lyophilized as a TFA salt. The truncation consisted of omitting the last eight amino acids from the N-terminus of SEQ ID NO: 149 to produce SEQ ID NO: 110.

[0496] The truncation was designed to remove a section of the peptide as to not disturb the tertiary structure and retain all disulfide bridges and charges. The synthesis was successful and the final product had a purity of 96.8% and a mass of 3,578.0 Da, which confirmed its identity as a peptide of SEQ ID NO: 110

[0497] A major cost of manufacturing peptides occurs during the solid phase synthesis. The cost of raw materials used in SPPS (i.e., Fmoc amino acids and organic solvents) along with labor costs and manufacturing time (e.g., 1-2 days per amino acid addition step) are major contributors to the overall cost of the peptide. Therefore, reducing the length of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) by eight amino acids (~20%) to create the SEQ ID NO: 110 lowers both the time (labor, facility time) and the amount of raw materials required and thus lowers the cost and time needed to produce the final product.

[0498] The same manufacturing advantages can also apply to any one of the peptides comprising SEQ ID NO: 24 – SEQ ID NO: 44, SEQ ID NO: 47 – SEQ ID NO: 51, SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 106 – SEQ ID NO: 108, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 221 – 224, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 260-263.

EXAMPLE 87**Truncated Peptide Conjugation**

[0499] This example tests whether a truncated peptide of this disclosure has accessible N-terminal primary amines for conjugation. The full length peptide of SEQ ID NO: 149 and truncated variant peptide of SEQ ID NO: 110 each contain a single primary amine in their sequence located at the N-terminus of the peptide chain. To determine whether the N-terminal primary amines are accessible for conjugation, a small-scale reaction was performed using the amine specific reactive dye Cy5.5-NHS ester on both the full length peptide of SEQ ID NO: 149 and the truncated variant peptide of SEQ ID NO: 110. The reactions were monitored by reversed-phase HPLC. The area of the peaks corresponding to the retention times of the unmodified full length peptide of SEQ ID NO: 149 was observed before initiation and after completion of the reaction. The peak corresponding to the full length peptide of SEQ ID NO: 149 showed a decrease in peak area after initiation of the reaction, and a new peak appeared with a different retention time, indicating the N-terminal primary amine of the full length peptide of SEQ ID NO: 149 was available and accessible for conjugation. Likewise, the area of the peak corresponding to the unmodified truncated variant peptide of SEQ ID NO: 110 showed a decrease in peak area after initiation of the reaction and a new peak appeared with a different retention time, indicating that the N-terminal primary amine of the truncated variant peptide of SEQ ID NO: 110 was available and accessible to conjugation.

EXAMPLE 88**Truncated Peptide Variants**

[0500] This example illustrates the design of variant peptide sequences with increased stability, decreased regions of immunogenicity, and the substitution of a tyrosine for spectrophotometric reporting as compared to a parent peptide sequence. Potential mutations to the parent peptide sequence, SEQ ID NO: 110, may result in a peptide with increased stability, decreased immunogenicity, or increased absorbance at 270-280 nm (such as the substitution to a tyrosine or tryptophan residue for spectrophotometric reporting) were identified based on information from multiple sequence alignment from **EXAMPLE 75** and immunogenicity testing from **EXAMPLE 76**.

[0501] In SEQ ID NO: 110, residue D10 is at risk for cleavage. Based on the multiple sequence alignment, the candidate residue mutations to best reduce cleavage at D10 are D10E and D10Q. D10E is the preferred choice based on retaining charge.

[0502] Residue M17 is at risk for oxidation. Based on the multiple sequence alignment, the candidate residue mutations to best reduce oxidation were M17T and M17A. Based on the immunogenicity score of peptides with each mutation, it was determined that M17T is the better mutation, as it eliminates a significant source of immunogenicity as compared to SEQ ID NO: 110 as well as the variant with M17A, which did not eliminate the predicted immunogenicity of the parent peptide of SEQ ID NO: 110.

[0503] Residue N24 is at risk for deamidation, at least in part due to the neighboring residue S25. However, N24 is conserved across Kv1.3 binding cystine-dense peptides in the alignment of **EXAMPLE 77**, and implicated in receptor binding (Peigneur, S., *Biochemistry*, 55(32): 2927-35 (2016)). For certain applications, peptides are designed to maintain this binding interaction, and for other applications, peptides are designed to remove this binding interaction. To maintain functionality, one candidate residue mutation based on the multiple sequence alignment is S25R, which would impact deamidation. However, it resulted in a predicted increased immunogenicity score. Another candidate residue mutation is S25G, but this may result in higher deamidation rates. If N24 is mutated, the best candidate residue mutation based the multiple sequence alignment in combination with the immunogenicity score was N24Q despite it having a slight increase in immunogenicity. Other options are N24A, N24S, or N24T. Alternatively, to remove functionality, candidate mutations based on the multiple sequence alignment are N24A and N24L, which are the preferred choices.

[0504] For the substitution to a tyrosine for spectrophotometric reporting, the best candidate locations were T30Y (which had the strongest precedence in the multiple sequence alignment and is found in several of the stable peptides (e.g., SEQ ID NO: 206, SEQ ID NO: 210, and SEQ ID NO: 211)), and L9Y, and H28Y. However, T30Y may slightly increase immunogenicity with respect to the DR allele. Another option for spectrophotometric absorbance is to substitute Trp for the Leu at position 9.

[0505] Additionally, variant peptide sequences with residues R1, R13, R21, and R26 mutated to K maintain similar stability and immunogenicity as the SEQ ID NO: 110.

[0506] Based on the above analysis, the following short list of potential mutations for SEQ ID NO: 110 were compiled: D10E; M17T; N24Q, N24A, N24S, N24T, N24L, S25G, and S25R (variants both to retain function and to remove function of binding ion channel); and L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K and R26K.

[0507] Furthermore, mutations denoted above and in **TABLE 11** below at the corresponding positions in SEQ ID NO: 27, SEQ ID NO: 28, and SEQ ID NO: 47 – SEQ ID NO: 51, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 127 - SEQ ID NO: 133, SEQ ID NO: 149, SEQ ID

NO: 150, SEQ ID NO: 199, and SEQ ID NO: 260 - SEQ ID NO: 263 can create variant peptide sequences which similarly can reduce immunogenicity, increase stability, increase manufacturability, or otherwise improve the properties of the peptides.

TABLE 11 – Exemplary Sequence Variants of SEQ ID NO: 110

SEQ ID NO:	Mutations	Sequence
110	Parent	RCRGSRDCLDPCRRAGMRFGRCSNSRCHCTP
111	D10E, M17T, S25G	RCRGSRDCLDPCRRAGTRFGRCSNGRCHCTP
112	D10E, M17T, S25R	RCRGSRDCLDPCRRAGTRFGRCSNRRCHCTP
113	D10E, M17T	RCRGSRDCLDPCRRAGTRFGRCSNSRCHCTP
114	D10E, M17T, N24Q	RCRGSRDCLDPCRRAGTRFGRCSIQSRCHCTP
115	D10E, M17T, N24Q, T30Y	RCRGSRDCLDPCRRAGTRFGRCSIQSRCHCYP
116	L9Y, D10E, M17T, N24Q	RCRGSRDCLDPCRRAGTRFGRCSIQSRCHCTP
117	D10E, M17T, N24Q, H28Y	RCRGSRDCLDPCRRAGTRFGRCSIQSRCHCTP
118	D10E, M17T, N24A, T30Y	RCRGSRDCLDPCRRAGTRFGRCSIASRCHCYP
119	D10E, M17T, N24S, T30Y	RCRGSRDCLDPCRRAGTRFGRCSISSRCHCYP
120	D10E, M17T, N24T, T30Y	RCRGSRDCLDPCRRAGTRFGRCSITSRCHCYP
121	R1K	KCRGSRDCLDPCRRAGMRFGRCSNSRCHCTP
122	R13K	RCRGSRDCLDPCRRAGMRFGRCSNSRCHCTP
123	R14K	RCRGSRDCLDPCRRAGMRFGRCSNSRCHCTP
124	R21K	RCRGSRDCLDPCRRAGMRFGRCSNSRCHCTP
125	R26K	RCRGSRDCLDPCRRAGMRFGRCSNSRCHCTP
126	D10E, M17T, T30Y	RCRGSRDCLDPCRRAGTRFGRCSNSRCHCYP
233	D10E, M17T, N24L	RCRGSRDCLDPCRRAGTRFGRCSILSRCHCTP
234	D10E, M17T, N24L, T30Y	RCRGSRDCLDPCRRAGTRFGRCSILSRCHCYP
235	D10E, M17T, N24L, H28Y	RCRGSRDCLDPCRRAGTRFGRCSILSRCHCTP
236	N24Q	RCRGSRDCLDPCRRAGMRFGRCSIQSRCHCTP
237	N24A	RCRGSRDCLDPCRRAGMRFGRCSIASRCHCTP
238	N24S	RCRGSRDCLDPCRRAGMRFGRCSISSRCHCTP
239	N24T	RCRGSRDCLDPCRRAGMRFGRCSITSRCHCTP
240	N24L	RCRGSRDCLDPCRRAGMRFGRCSILSRCHCTP

EXAMPLE 89

Peptide-Active Agent Use in Rodent Arthritis Models

[0508] This example illustrates peptide-active agent use in rodent arthritis models. A peptide of SEQ ID NO: 115, SEQ ID NO: 234, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 126, or SEQ ID NO: 109 or any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 is complexed, conjugated, or fused to an active agent. Optionally the active agent is a glucocorticoid such as dexamethasone and optionally the linker is a cleavable linker. The peptide-active agent conjugate is administered to animals in one or more rodent arthritis models.

[0509] Exemplary models include the streptococcal cell wall–induced arthritis (SCW) model. Streptococcal cell wall peptidoglycan polysaccharide (PGPS) is administered intra-articularly into the knee or ankle of a rodent such as a Lewis rat and inflammation and joint swelling is induced. After the initial administration subsides, such as after 14 days or 1 month post-administration, the arthritis is reactivated by administering PGPS intravenously, which causes another reaction in the same joint that was originally injected. The peptide-active agent conjugate is administered to the animal intravenously, subcutaneously, or intra-articularly into the joint that has been activated with PGPS, 1 hour, 3 hour, 8 hours, 24 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, or more prior to the joint reactivation, concurrent with, or after joint reactivation.

[0510] Exemplary models also include collagen-induced arthritis (CIA) model, a rodent such as a Lewis rat is immunized with intradermal injection of collagen in incomplete Freund's adjuvant (day 0). A challenge dose is optionally performed 7 days later. Arthritis develops in one or more paws. The peptide-active agent is administered to the animal intravenously or subcutaneously once every 1, 2, 3, 4, 7, or 14 days, starting 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days after day 0.

[0511] In another model, inflammation is induced in a joint by injecting IL-1beta intra-articularly into the joint. The peptide-active agent is administered to the animal intravenously or subcutaneously 1 hour, 2 hour, 3 hours, 4 hours, 6 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 7 days, or 14 days before IL-1beta administration, concurrent with, or after IL-1beta administration.

[0512] Other optional models include adjuvant-induced or antigen-induced arthritis, adjuvant arthritis, or administration of anti-collagen or other antibodies.

[0513] By administering the peptide-active agent conjugate comprising a peptide of any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 in any of the above arthritis models, the arthritic reaction in the animal is blocked, slowed, mitigated, or reduced, as measured by readouts such as joint swelling (such as by diameter or volume), cytokine protein or mRNA levels (such as IL-1beta, IL-6, TNFalpha) in the joint or in the blood, histopathology, or pain measures such as gait.

EXAMPLE 90**Peptide-Active Agent Use in Rodent Lupus Models**

[0514] This example illustrates peptide-active agent use in rodent lupus models. Lupus is modeled in rodents using the spontaneous NZB/W or MRL/lpr or BXSB mice, or is induced in rodents using pristine or accelerated in rodents by administering IFNalpha in NZB/W mice, such as described by Celhar 2017 (Rheumatology (Oxford). 2017 Apr 1;56(suppl_1):i88-i99.

Modelling clinical systemic lupus erythematosus: similarities, differences and success stories. Celhar T, Fairhurst AM). Symptoms of systemic lupus erythematosus are, optionally, present, such as autoantibodies, anti-dsNA, immune complex glomerulonephritis, ANA, synovitis arthritis, skin rash. Optionally, the animals develop lupus nephritis.

[0515] A peptide of SEQ ID NO: 115, SEQ ID NO: 234, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 126, or SEQ ID NO: 109 or any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 is complexed, conjugated, or fused to an active agent. Optionally the active agent is a glucocorticoid such as dexamethasone and optionally the linker is a cleavable linker. The peptide-active agent is administered to the animals intravenously or subcutaneously once every 1, 2, 3, 4, 7, or 14 or more days. By administering the test agent, the symptoms of lupus or nephritis are improved.

[0516] By administering the peptide-active agent conjugate comprising a peptide of any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 in any of the above lupus models, the lupus effects in the animal are blocked, slowed, mitigated or reduced.

EXAMPLE 91**Immunogenicity Testing of Peptides**

[0517] This example illustrates immunogenicity testing of peptides, including a peptide of SEQ ID NO: 115, SEQ ID NO: 234, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 126, or SEQ ID NO: 109 or any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

[0518] Dendritic cells and/or CD4⁺ T cells and/or peripheral blood mononuclear cells are isolated from healthy or diseased, such as affected by rheumatoid arthritis, human donors. Multiple donors are tested. Any peptide of SEQ ID NO: 115, SEQ ID NO: 234, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 126, or SEQ ID NO: 109 or any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 is applied in separate wells to the cells. The cells are assessed for proliferation and for secretion of cytokines such as IL-2 or IFN-gamma. Control peptides, such as those known to be immunogenic, non-immunogenic, or of known immunogenic potential are also incubated with the cells. Peptides that are less immunogenic by inducing less cell activation are identified.

[0519] Separately, one or more peptides of SEQ ID NO: 115, SEQ ID NO: 234, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 126, or SEQ ID NO: 109 or any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 are injected into a mouse or rat or non-human primate one to four times, intravenously or subcutaneously. The serum from the animal is collected at various time points and tested for the presence of antibodies that bind or neutralize the peptide that was dosed. Control proteins or peptides, such as those known to be immunogenic, non-immunogenic, or of known immunogenic potential are also separately tested in the animals. Peptides that are less immunogenic by inducing less antibody formation are identified.

[0520] By administering the peptide-active agent conjugate comprising a peptide of any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 in any of the above models, the immunogenic effects in the animal are blocked, slowed, mitigated, or reduced.

EXAMPLE 92

Accelerated Stability Testing of Peptides

[0521] This example illustrates accelerated stability testing of peptides. A peptide of any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263, or

an active-agent conjugate thereof, is subjected to accelerated stability testing. The peptide or peptide-conjugate is formulated in a buffer and, optionally, lyophilized. This formulated material is incubated at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ relative humidity (RH)} \pm 5\% \text{ RH}$ or $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$ or $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ and analyzed. The peptide or peptide-conjugate stays within acceptance criteria, optionally $\geq 90\%$ purity or $\geq 95\%$ purity, for at least 1 week, 2 weeks, 1 month, 3 months, 6 months, 1 year, 2 years, or more.

EXAMPLE 93

Cleavage Rate of Peptide-Conjugates

[0522] This example illustrates the cleavage rate of peptide-conjugates. A peptide of SEQ ID NO: 115, SEQ ID NO: 234, SEQ ID NO: 114, SEQ ID NO: 118, SEQ ID NO: 126, or SEQ ID NO: 109 or any of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 is complexed, conjugated, or fused to a drug such as desciclesonide by a cleavable linker. Optionally, the linker is an ester. The peptide-conjugate is incubated in buffer, rat plasma, human plasma, or synovial fluid of an animal species at 37°C and analyzed at various time points for cleavage. The sample is processed and analyzed by liquid chromatography-mass spectrometry (LC-MS). The peptide-conjugate cleavage half-life is found to be greater than 1 h, 2 h, 4 h, 8 h, 12 h, 24 h, or more.

EXAMPLE 94

Cartilage Binding of Peptides

[0523] This example illustrates cartilage binding of peptides of this disclosure. One or more peptides of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263 are either radiolabeled, such as with C^{14} using the methods of **EXAMPLE 2**, or labeled with a fluorophore, such as using the methods of **EXAMPLE 3**. The peptides are administered to a normal or diseased mouse or rat or other animal intravenously such as by the methods of **EXAMPLES 6, 7 or 11**. The peptides are allowed to circulate for 5 min, 1 h, 3 h, 8 h, 24 h, 48 h, or 96 h. The tissues are harvested and analyzed for signal. The labeled peptides are seen to accumulate in the cartilage of the treated animals, including the knee and intervertebral discs.

EXAMPLE 95**Stability testing of Peptide**

[0524] This example describes stability testing of peptides of the present disclosure. A 5 mg/mL solution of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205) was prepared in 50 mM Tris, 5% Mannitol, pH 7.6. The stability of SEQ ID NO: 149 in solution was assessed by stressing the sample at 40 °C for 10 days and analyzed by RP-HPLC side-by-side with an unstressed sample prepared under the same conditions and stored at -20 °C. The purity of SEQ ID NO: 149 when stressed decreased slightly compared to the non-stressed sample from an initial purity of 96.4% to 93.5% when analyzed by RP-HPLC. This change was predominantly the result of an increase in area of one predominant impurity peak eluting after the main peak in the sample that was exposed to the higher temperature. No other impurities present in the initial sample increased substantially and no substantial new impurities were seen. Visual inspection of the samples showed no change in solubility and no visible appearance of a pellet due to precipitation following centrifugation.

[0525] The samples were further analyzed by LC-MS to characterize two major impurities eluting before and after the main peak as well as the main peak. The predominant ions (m/z) observed in the main peak were 1076.2 and 1104.7; representing a +4 charge state resulting in an average mass of 4300.8 Da and 4415.0 Da respectively. The theoretical average mass of SEQ ID NO: 149 is 4300.1; thus this close match to 4300.8 Da confirming its identity. The 4415 Da mass differs by +114 amu and is consistent with the presence of bound trifluoroacetic acid TFA (TFA adduct).

[0526] A peak that was observed immediately preceding to the main peak, in both the non-stressed and the stressed sample, was also analyzed. The main ion observed in this preceding peak was 1080.5 (m/z); a +4 charge state resulting in an average mass of 4316.9. The difference of +16 amu is consistent with an oxidized species of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205), which was present in the non-stressed and the stressed sample, indicating it may have been formed during manufacturing of the peptide.

[0527] The predominant increasing peak on stress (eluting after the main peak) was also analyzed. One ion observed in this peak eluting after but not found in the main peak was 1076.4 m/z; representing a +4 charge state corresponding to an average mass of 4301.6 Da. The difference of +1 amu is consistent with the possible deamidation of asparagine. This

deamidation may have occurred during manufacture and may have increased during stress. In addition, it is possible that isomerization events occurred (such as Asp isomerization), as those would not have a mass shift from the original species.

[0528] These results indicate that oxidation of the Met residue at position M25 could have occurred during the manufacture of the peptide of SEQ ID NO: 149 (also disclosed as SEQ ID NO: 46; non-GS version of SEQ ID NO: 149/SEQ ID NO: 46 are shown in SEQ ID NO: 128 and SEQ ID NO: 205). They also indicate that deamidation of the Asn residue(s) at position N7 or N32 could have occurred during the manufacture of and increased during the stressing of the peptide of SEQ ID NO: 149.

[0529] These results indicate that one or more of the M25, N7 and N32 residues in SEQ ID NO: 149 can be less stable and hence by making modifications or substitutions at one or more of these residues in the peptide (or in corresponding positions in variant or shorter peptides), the peptide can be stabilized and its properties improved. Consequently, modifying or substituting one or more of the M25, N7, and/or N32 residues in corresponding peptides of the present disclosure, for example, can result in a more stable structure such as shown in or can be applied to the exemplary peptides of SEQ ID NO: 23, SEQ ID NO: 89, SEQ ID NO: 24, SEQ ID NO: 106, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226 which are peptides with such improved properties. For example, many of the peptides as shown in in TABLE 7A and TABLE 7B, and TABLE 11 one or more of these of these changes. Further exemplary peptides comprising these modifications includes the peptides of SEQ ID NO: 52 – SEQ ID NO: 66, SEQ ID NO: 241 – SEQ ID NO: 248, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 249 – SEQ ID NO: 256, SEQ ID NO: 111 – SEQ ID NO: 126, and SEQ ID NO: 233 – SEQ ID NO: 240. Such improved properties are also shown in can be applied to any one of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, SEQ ID NO: 198, SEQ ID NO: 200 – SEQ ID NO: 215, SEQ ID NO: 233 – SEQ ID NO: 256, or SEQ ID NO: 260 – SEQ ID NO: 263.

[0530] While certain embodiments of the present disclosure have been exemplified or shown and described herein, it will be apparent to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the disclosure be limited by the specific examples provided within the specification. While the disclosure has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. Furthermore, it shall be understood that all embodiments of the disclosure are not

limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure. It is therefore contemplated that the disclosure shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED:

1. A peptide comprising:
 - a) any one of SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 219, SEQ ID NO: 223, SEQ ID NO: 225, or a functional fragment thereof; or
 - b) any one of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221, or a functional fragment thereof and further comprising at least one amino acid in each of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221 is selected from the group consisting of:
 - i) for SEQ ID NO: 89, wherein X^1 is selected from N, S, or G, wherein X^2 is selected from L or Y, wherein X^3 is selected from D or E, wherein X^4 is selected from M or T, wherein X^5 is selected from N, Q, A, S, T, or L, wherein X^6 is selected from S, G, or R, wherein X^7 is selected from H or Y, and wherein X^8 is selected from T or Y;
 - ii) for SEQ ID NO: 106, wherein X^1 is selected from L or Y, wherein X^2 is selected from D or E, wherein X^3 is selected from M or T, wherein X^4 is selected from N, Q, A, S, T, or L, wherein X^5 is selected from S, G, or R, wherein X^6 is selected from H or Y, and wherein X^7 is selected from T or Y;
 - iii) for SEQ ID NO: 221, wherein each X and X_{1-13} are individually any amino acid or no amino acid and at least one of the following residues at the denoted position, more than one of the following residues at the denoted position, or all of the following residues at the denoted position is included in SEQ ID NO: 221: X_1 is K, X_2 is Q, X_3 is Y, X_4 is E, X_5 is K, X_6 is T, X_7 is K, X_8 is M, X_9 is Q, A, S, T, or L, X_{10} is G, X_{11} is K, X_{12} is Y, or X_{13} is Y;
 - iv) a corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

2. The peptide of claim 1, wherein the peptide comprises a sequence of any one of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221 and further comprises at least one of KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); or GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N, Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null.

3. The peptide of any one of claims 1-2, wherein the peptide comprises a sequence of any one of SEQ ID NO: 89, SEQ ID NO: 106, and SEQ ID NO: 221 and the peptide further comprises at least one of RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N, Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); or RFGRCI (SEQ ID NO: 259).

4. The peptide of any one of claims 1-3, wherein the peptide has a sequence selected from the group consisting of any one of SEQ ID NO: 106, and SEQ ID NO: 221.

5. The peptide of any one of claims 1-4, wherein the peptide comprises SEQ ID NO: 89 and wherein the peptide comprises one or more of the following characteristics:

- a) X¹ is selected from S, or G;
- b) X² is selected from Y;
- c) X³ is selected from E;
- d) X⁴ is selected from T;
- e) X⁵ is selected from Q, A, S, T, or L;
- f) X⁶ is selected from G, or R;
- g) X⁷ is selected from Y; or
- h) X⁸ is selected from Y.

6. The peptide of claim 5, wherein the peptide comprises two, three, four, five, six, seven or more of the characteristics, or wherein the peptide comprises all of the characteristics.

7. The peptide of any one of claims 1-6, wherein

- a) the peptide comprises at least 70%, at least at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100%

sequence identity with a sequence selected from the group SEQ ID NO: 111 – SEQ ID NO: 126 or SEQ ID NO: 233 – SEQ ID NO: 240; or

b) the peptide comprises at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with a sequence selected from the group SEQ ID NO: 134 – SEQ ID NO: 148 and SEQ ID NO: 249 – SEQ ID NO: 256.

8. The peptide of any one of claims 1-7, wherein

a) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with any one of SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H

b) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 129 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

c) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 130 and wherein the peptide further comprises

a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- d) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 131 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- e) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 132 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- f) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 133 and wherein the peptide further comprises

a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

g) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 260 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or
- ii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; or

h) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

9. The peptide of claim 8, wherein the joining sequence is at the N-terminus or a C-terminus of the peptide, or both the N-terminus and the C-terminus of the peptide.

10. The peptide of any one of claims 8-9, wherein the joining sequence comprises from 1 to 100 amino acid residues.

11. The peptide of any one of claims 1-10, wherein the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of SEQ ID NO: 109 - SEQ ID NO:

110, SEQ ID NO: 260, or SEQ ID NO: 262 and further comprising no more than 5 additional amino acids at the N-terminus.

12. The peptide of any one of claims 1-11, wherein the peptide consists of a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of the peptides selected from the group consisting of SEQ ID NO: 109 - SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, or SEQ ID NO: 262.

13. The peptide of claim 12, wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein:

- a) for any one of SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262:
 - i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
 - ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
 - iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
 - iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
 - v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- b) for SEQ ID NO: 129, N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- c) for SEQ ID NO: 130:
 - i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- d) for SEQ ID NO: 131:
 - i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;

- ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- e) for SEQ ID NO: 132:
 - i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
 - ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
 - iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- f) for SEQ ID NO: 133:
 - i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
 - ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
 - iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
 - iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- g) for SEQ ID NO: 260:
 - i) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or
 - ii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; or
- h) for SEQ ID NO: 262, C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

14. The peptide of any one of claims 1-13, wherein the peptide is selected from the group consisting of SEQ ID NO: 109 - SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, and SEQ ID NO: 262.

15. The peptide of any one of claims 1-14, wherein the peptide consists of a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of the peptides selected from the group consisting of SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256.

16. The peptide of any one of claims 1-15, wherein the peptide is selected from the group consisting of SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256.

17. A peptide, wherein

a) the peptide comprises at least 70%, at least at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with a sequence selected from the group SEQ ID NO: 111 – SEQ ID NO: 126 or SEQ ID NO: 233 – SEQ ID NO: 240; or

b) the peptide comprises at least 70%, at least at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, at least 99%, or 100% sequence identity with a sequence selected from the group SEQ ID NO: 134 – SEQ ID NO: 148 and SEQ ID NO: 249 – SEQ ID NO: 256.

18. A peptide, wherein

a) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with any one of SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or

- vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H
- b) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 129 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- c) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 130 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein
 - i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- d) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 131 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein
 - i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
 - ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- e) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 132 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
 - ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
 - iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- f) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 133 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein
- i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
 - ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
 - iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
 - iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
 - v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- g) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least 100% sequence identity with SEQ ID NO: 260 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein
- i) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or
 - ii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; or
- h) the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, or at least

100% sequence identity with SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

19. The peptide of claim 17, wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide.

20. The peptide of any one of claims 18-19, wherein the joining sequence is at an N-terminus or a C-terminus of the peptide, or both the N-terminus and the C-terminus of the peptide.

21. The peptide of any one of claims 18-20, wherein the joining sequence comprises from 1 to 100 amino acid residues.

22. The peptide of any one of claims 18-21, wherein the peptide comprises a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of SEQ ID NO: 109 - SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262 and further comprising no more than 5 additional amino acids at the N-terminus.

23. The peptide of any one of claims 18-22, wherein the peptide consists of a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of the peptides selected from the group consisting of SEQ ID NO: 109 - SEQ ID NO: 110, SEQ ID NO: 129 - SEQ ID NO: 133, SEQ ID NO: 260, or SEQ ID NO: 262.

24. The peptide of claim 23, wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein:

a) for any one of SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 260, or SEQ ID NO: 262:

- i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

- iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- b) for SEQ ID NO: 129, N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- c) for SEQ ID NO: 130:
 - i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- d) for SEQ ID NO: 131:
 - i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
 - ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- e) for SEQ ID NO: 132:
 - i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
 - ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
 - iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
 - iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- f) for SEQ ID NO: 133:
 - i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
 - ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

- iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- g) for SEQ ID NO: 260:
 - i) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or
 - ii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; or
- h) for SEQ ID NO: 262, C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

25. The peptide of any one of claims 18-24, wherein the peptide is selected from the group consisting of SEQ ID NO: 109 - SEQ ID NO: 110, SEQ ID NO: 129 – SEQ ID NO: 133, SEQ ID NO: 260, and SEQ ID NO: 262.

26. The peptide of any one of claims 17 or 19-25, wherein the peptide consists of a sequence that has at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% sequence identity with any one of the peptides selected from the group consisting of SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256.

27. The peptide of any one of claims 17 or 19-26, wherein the peptide is selected from the group consisting of SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 240, SEQ ID NO: 249 - SEQ ID NO: 256.

28. The peptide of any one of claims 1-27, wherein the peptide comprises SEQ ID NO: 28, SEQ ID NO: 45 - SEQ ID NO: 51, SEQ ID NO: 109, SEQ ID NO: 150, SEQ ID NO: 199, SEQ ID NO: 110, SEQ ID NO: 127 - SEQ ID NO: 133, SEQ ID NO: 149, or SEQ ID NO: 260 - SEQ ID NO: 263 and further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null.

29. The peptide of any one of claims 1-28, wherein the peptide comprises SEQ ID NO: 27, SEQ ID NO: 29 – SEQ ID NO: 44, SEQ ID NO: 52 – SEQ ID NO: 66, SEQ ID NO: 109, SEQ ID NO: 150, SEQ ID NO: 199, SEQ ID NO: 111 – SEQ ID NO: 126, SEQ ID NO: 134 – SEQ ID NO: 148, SEQ ID NO: 233 – SEQ ID NO: 256, and SEQ ID NO: 21 – SEQ ID NO: 26, SEQ ID NO: 87 – SEQ ID NO: 89, SEQ ID NO: 106 – SEQ ID NO: 108, SEQ ID NO: 219 – SEQ ID NO: 226 and further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259).

30. The peptide of any one of claims 1-29, wherein the peptide comprises one or more of the following peptide fragments within its sequence: GKCINKKCKC (SEQ ID NO: 90); KCIN (SEQ ID NO: 91); KKCK (SEQ ID NO: 92); PCKR (SEQ ID NO: 93); KRCSRR (SEQ ID NO: 94); KQC (SEQ ID NO: 95); GRCINRRRC (SEQ ID NO: 96); RCIN (SEQ ID NO: 97); RRCR (SEQ ID NO: 98); PCRR (SEQ ID NO: 99); RRCSSR (SEQ ID NO: 100); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); KKCSKK (SEQ ID NO: 103); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null, GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R (SEQ ID NO: 229), PCR (SEQ ID NO: 230), CLDPCRR (SEQ ID NO: 231), CLDPCRR (SEQ ID NO: 232), RCRGSRDC (SEQ ID NO: 257), PCRRAG (SEQ ID NO: 258), and RFGRCI (SEQ ID NO: 259).

31. The peptide of any one of claims 1-30, wherein the peptide comprises an N-terminal sequence comprising GG, SS, GS, SG, S, or G.

32. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 219.

33. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 220.

34. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 221 and wherein:

a) the peptide further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228)

wherein each X can independently be any amino acid or amino acid analogue or null;

GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R

wherein each X can independently be any amino acid or amino acid analogue or null; or

b) the peptide further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRRA (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259)

c) and the peptide further comprises at least one corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

35. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 222.

36. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 223.

37. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 224.

38. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 225.

39. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 226.

40. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 87.

41. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 89 and

wherein:

a) the peptide further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null; or

b) the peptide further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230);

CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259)

c) and the peptide further comprises at least one corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

42. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 106 and wherein:

a) the peptide further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null; or

b) the peptide further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259)

c) and the peptide further comprises at least one corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

43. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 110 and further comprising no more than 5 additional amino acids at the N-terminus.

44. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 219.

45. The peptide of any one of claims 1-31, wherein the peptide is SEQ ID NO: 221

a) the peptide further comprises one or more of the following peptide fragments within its sequence: KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCIXXRC (SEQ ID NO: 228)

wherein each X can independently be any amino acid or amino acid analogue or null;

GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R

wherein each X can independently be any amino acid or amino acid analogue or null; or

b) the peptide further comprises one or more of the following peptide fragments within its sequence: RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); and RFGRCI (SEQ ID NO: 259)

c) and the peptide further comprises at least one corresponding substitution selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

46. A peptide comprising at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 92%, at least 95%, at least 97%, at least 99%, or 100% sequence identity with any one of SEQ ID NO: 209 – SEQ ID NO: 215, wherein the peptide further comprises an active agent and wherein the active agent is complexed with the peptide to form a peptide active agent complex.

47. The peptide of any one of claims 1-46, further comprising an active agent, wherein the active agent is complexed with the peptide to form a peptide active agent complex.

48. The peptide active agent complex of claim 47, wherein the active agent is selected from TABLE 3, TABLE 4, or TABLE 5.

49. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-48, wherein the peptide comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or 100% sequence identity to:

SEQ ID NO: 27;

SEQ ID NO: 28;

SEQ ID NO: 29;

SEQ ID NO: 30;

SEQ ID NO: 31;

SEQ ID NO: 32;

SEQ ID NO: 33;

SEQ ID NO: 34;

SEQ ID NO: 35;
SEQ ID NO: 36;
SEQ ID NO: 37;
SEQ ID NO: 38;
SEQ ID NO: 39;
SEQ ID NO: 40;
SEQ ID NO: 41;
SEQ ID NO: 42;
SEQ ID NO: 43;
SEQ ID NO: 44;
SEQ ID NO: 45;
SEQ ID NO: 234;
SEQ ID NO: 47;
SEQ ID NO: 48;
SEQ ID NO: 49;
SEQ ID NO: 50;
SEQ ID NO: 51;

SEQ ID NO: 109 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

SEQ ID NO: 110 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

SEQ ID NO: 111;

SEQ ID NO: 112;

SEQ ID NO: 113;

SEQ ID NO: 114;

SEQ ID NO: 115;

SEQ ID NO: 116;

SEQ ID NO: 117;

SEQ ID NO: 118;

SEQ ID NO: 119;

SEQ ID NO: 120;

SEQ ID NO: 121;

SEQ ID NO: 122;

SEQ ID NO: 123;

SEQ ID NO: 124;

SEQ ID NO: 125;

SEQ ID NO: 126;

SEQ ID NO: 87;

SEQ ID NO: 129 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus

or a C-terminus of the peptide and wherein N-1 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

SEQ ID NO: 130 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or

ii) N-2 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

SEQ ID NO: 131 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;

ii) N-2 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or

iii) N-3 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

SEQ ID NO: 132 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

i) N-1 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;

iii) N-3 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or

iv) N-4 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

SEQ ID NO: 133 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

i) N-1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;

- ii) N-2 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- iv) N-4 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- v) N-5 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;

SEQ ID NO: 89;

SEQ ID NO: 106;

SEQ ID NO: 219;

SEQ ID NO: 221;

SEQ ID NO: 260 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- vii) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, C, Y, N, Q, D, E, K, R, and H; or
- viii) C+2 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H; or

SEQ ID NO: 262 and wherein the peptide further comprises a joining sequence of one or more amino acid residues located immediately adjacent to an N-terminus or a C-terminus of the peptide and wherein

- i) N-1 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- ii) N-2 is selected from the group consisting of G, A, V, L, I, M, F, W, P, S, T, C, Y, Q, D, E, K, R, and H;
- iii) N-3 is selected from the group consisting of G, A, V, L, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- iv) N-4 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H;
- v) N-5 is selected from the group consisting of G, A, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H;
- vi) N-6 is selected from the group consisting of A, V, L, I, M, F, W, P, S, T, C, Y, N, Q, D, E, K, R, and H; or
- vii) C+1 is selected from the group consisting of G, A, V, L, I, M, F, W, S, T, C, Y, N, Q, D, E, K, R, and H.

50. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-49, wherein the peptide comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to:

SEQ ID NO: 52;

SEQ ID NO: 53;

SEQ ID NO: 54;

SEQ ID NO: 55;

SEQ ID NO: 56;

SEQ ID NO: 57;

SEQ ID NO: 58;

SEQ ID NO: 59;

SEQ ID NO: 60;

SEQ ID NO: 61;

SEQ ID NO: 62;

SEQ ID NO: 63;

SEQ ID NO: 64;

SEQ ID NO: 65;

SEQ ID NO: 66;

SEQ ID NO: 134;

SEQ ID NO: 135;

SEQ ID NO: 136;
SEQ ID NO: 137;
SEQ ID NO: 138;
SEQ ID NO: 139;
SEQ ID NO: 140;
SEQ ID NO: 141;
SEQ ID NO: 142;
SEQ ID NO: 143;
SEQ ID NO: 144;
SEQ ID NO: 145;
SEQ ID NO: 146;
SEQ ID NO: 147; or
SEQ ID NO: 148.

51. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-50, wherein the peptide homes, targets, migrates to, accumulates in, binds to, is retained by, or is directed to cartilage, to kidney, or to cartilage and kidney.

52. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-51, wherein the peptide homes, targets, migrates to, accumulates in, binds to, is retained by, or is directed to proximal tubules of the kidney.

53. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-52, wherein the peptide is covalently complexed to the active agent.

54. The peptide active agent complex of any one of claims 47-53, wherein the peptide active agent complex homes, targets, migrates to, accumulates in, binds to, is retained by, or is directed to a cartilage or a kidney of the subject.

55. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-54, wherein the peptide comprises 4 or more cysteine residues.

56. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-55, wherein the peptide comprises three or more disulfide bridges formed between cysteine residues, wherein one of the disulfide bridges passes through a loop formed by two other disulfide bridges.

57. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-56, wherein the peptide comprises a plurality of disulfide bridges formed between cysteine residues.

58. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-57, wherein the peptide comprises a disulfide through a disulfide knot.

59. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-58, wherein at least one amino acid residue of the peptide is in an L configuration or, wherein at least one amino acid residue of the peptide is in a D configuration.

60. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-59, wherein the sequence comprises at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58 residues, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, at least 80, or at least 81 residues.

61. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-60, wherein any one or more K residues are replaced by an R residue or wherein any one or more R residues are replaced by for a K residue.

62. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-61, wherein any one or more M residues are replaced by any one of the I, L, or V residues.

63. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-62, wherein any one or more L residues are replaced by any one of the V, I, or M residues.

64. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-63, wherein any one or more I residues are replaced by any of the M, L, or V residues.

65. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-64, wherein any one or more V residues are replaced by any of the M, I, or L residues.

66. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-65, wherein any one or more G residues are replaced by an A residue or wherein any one or more A residues are replaced by a G residue.

67. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-66, wherein any one or more S residues are replaced by a T residue or wherein any one or more T residues are replaced by for an S residue.

68. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-67, wherein any one or more Q residues are replaced by an N residue or wherein any one or more N residues are replaced by a Q residue.

69. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-68, wherein any one or more D residues are replaced by an E residue or wherein any one or more E residues are replaced by a D residue.

70. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-69, wherein the peptide has a charge distribution comprising an acidic region and a basic region.

71. The peptide of claim 70, wherein the acidic region is a nub.

72. The peptide of claim 70, wherein the basic region is a patch.

73. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-72, wherein the peptide comprises 5-12 basic residues.

74. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-73, wherein the peptide comprises 0-5 acidic residues.

75. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-74, wherein the peptide comprises 6 or more basic residues and 2 or fewer acidic residues.

76. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-75, wherein the peptide comprises a 4-19 amino acid residue fragment containing at least 2 cysteine residues, and at least 2 positively charged amino acid residues.

77. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-76, wherein the peptide comprises a 20-70 amino acid residue fragment containing at least 2 cysteine residues, no more than 2 basic residues and at least 2 positively charged amino acid residues.

78. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-77, wherein the peptide comprises at least 3 positively charged amino acid residues.

79. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-78, wherein the positively charged amino acid residues are selected from K, R, or a combination thereof.

80. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-79, wherein the peptide has a charge greater than 2 at physiological pH.

81. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-80, wherein the peptide has a charge greater than 3.5 at physiological pH.

82. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-81, wherein the peptide has a charge greater than 4.5 at physiological pH.

83. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-82, wherein the peptide has a charge greater than 5.5 at physiological pH.

84. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-83, wherein the peptide has a charge greater than 6.5 at physiological pH.

85. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-84, wherein the peptide has a charge greater than 7.5 at physiological pH.

86. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-85, wherein the peptide has a charge greater than 8.5 at physiological pH.

87. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-86, wherein the peptide has a charge greater than 9.5 at physiological pH.

88. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-87, wherein the peptide is selected from a potassium channel agonist, a potassium channel antagonist, a portion of a potassium channel, a sodium channel agonist, a sodium channel antagonist, a calcium channel agonist, a calcium channel antagonist, a hadrucalcin, a theraphotoxin, a huwentoxin, a kaliotoxin, a cobatoxin or a lectin.

89. The peptide active agent complex of claim 88 or peptide of claim 88, wherein the lectin is SHL-Ib2.

90. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-89, wherein the peptide is arranged in a multimeric structure with at least one other peptide.

91. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-90, wherein at least one residue of the peptide comprises a chemical modification.

92. The peptide active agent complex of claim 91 or the peptide of claim 91, wherein the chemical modification is blocking the N-terminus of the peptide.

93. The peptide active agent complex of claim 91 or the peptide of claim 91, wherein the chemical modification is methylation, acetylation, or acylation.

94. The peptide active agent complex of claim 91 or the peptide of claim 91, wherein the chemical modification is:

methylation of one or more lysine residues or analogue thereof;

methylation of the N-terminus; or

methylation of one or more lysine residue or analogue thereof and methylation of the N-terminus.

95. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-94, wherein the peptide is linked to an acyl adduct.

96. The peptide active agent complex of any one of claims 47-95, wherein the active agent is fused with the peptide at an N-terminus or a C-terminus of the peptide.

97. The peptide active agent complex of any one of claims 47-96, wherein the active agent is another peptide.

98. The peptide active agent complex of any one of claims 47-96, wherein the active agent is an antibody.

99. The peptide active agent complex of any one of claims 47-96, wherein the active agent is an Fc domain, Fab domain, scFv, or Fv fragment.

100. The peptide active agent complex of any one of claims 47-96, wherein the active agent is a glucocorticoid.

101. The peptide active agent complex of any one of claims 47-96, wherein the active agent is dexamethasone.

102. The peptide active agent complex of claim 99, wherein the peptide fused with the Fc domain comprises a contiguous sequence.

103. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-102, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 active agents are linked to the peptide.

104. The peptide active agent complex of any one of claims 47-103, wherein the peptide is linked to the active agent at an N-terminus, at the epsilon amine of a lysine residue, at the carboxylic acid of an aspartic acid or glutamic acid residue, or a C-terminus of the peptide by a linker.

105. The peptide active agent complex of any one of claims 47-104, wherein the peptide is linked to the active agent via a cleavable linker.

106. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-105 further comprising a non-natural amino acid, wherein the non-natural amino acid is an insertion, appendage, or substitution for another amino acid.

107. The peptide active agent complex of claim 106 or peptide of claim 106, wherein the peptide is linked to the active agent at the non-natural amino acid by a linker.

108. The peptide active agent complex of any one of claims 47-107, wherein the linker comprises an amide bond, an ester bond, a carbamate bond, a carbonate bond, a hydrazone bond, an oxime bond, a disulfide bond, a thioester bond, a thioether bond, a triazole, a carbon-carbon bond, or a carbon-nitrogen bond.

109. The peptide active agent complex of any one of claims 47-108, wherein the linker comprises an ester bond.

110. The peptide active agent complex of claim 105, wherein the cleavable linker comprises a cleavage site for matrix metalloproteinases, thrombin, cathepsins, or beta-glucuronidase.

111. The peptide active agent complex of any one of claims 104-110, wherein the linker is a hydrolytically labile linker.

112. The peptide active agent complex of any one of claims 104-111, wherein the linker is pH sensitive, reducible, glutathione-sensitive, or protease cleavable.

113. The peptide active agent complex of any one of claims 47-112, wherein the peptide is linked to the active agent via a stable linker.

114. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-113, wherein the peptide has an isoelectric point of about 9.

115. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-114, wherein the peptide is linked to a detectable agent.

116. The peptide active agent complex or peptide of claim 115, wherein the detectable agent is fused with the peptide at an N-terminus or a C-terminus of the peptide.

117. The peptide active agent complex or peptide any one of claims 115-116, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 detectable agents are linked to the peptide.

118. The peptide active agent complex or peptide of any one of claims 115-117, wherein the peptide is linked to the detectable agent via a cleavable linker.

119. The peptide active agent complex or peptide of any one of claims 115-118, wherein the peptide is linked to the detectable agent at an N-terminus, at the epsilon amine of an internal lysine residue, or a C-terminus of the peptide by a linker.

120. The peptide active agent complex or peptide of any one of claims 115-119, further comprising a non-natural amino acid, wherein the non-natural amino acid is an insertion, appendage, or substitution for another amino acid.

121. The peptide active agent complex or peptide of claim 120, wherein the peptide is linked to the detectable agent at the non-natural amino acid by a linker.

122. The peptide active agent complex or peptide of any one of claims 115-121, wherein the linker comprises an amide bond, an ester bond, a carbamate bond, a hydrazone bond, an oxime bond, or a carbon-nitrogen bond.

123. The peptide active agent complex or peptide of claim 118, wherein the cleavable linker comprises a cleavage site for matrix metalloproteinases, thrombin, cathepsins, or beta-glucuronidase.

124. The peptide active agent complex or peptide of any one of claims 115-118, wherein the peptide is linked to the detectable agent via a stable linker.

125. The peptide active agent complex or peptide of any one of claims 115-124, wherein the detectable agent is a fluorophore, a near-infrared dye, a contrast agent, a nanoparticle, a metal-containing nanoparticle, a metal chelate, an X-ray contrast agent, a PET agent, a radioisotope, or a radionuclide chelator.

126. The peptide active agent complex or peptide of any one of claims 115-125, wherein the detectable agent is a fluorescent dye.

127. The peptide of any one of claims 1-46 or the peptide active agent complex of any one of claims 47-126, wherein the peptide further comprises a joining sequence.

128. The peptide of claim 127, wherein the joining sequence is at an N-terminus or a C-terminus of the peptide.

129. The peptide of any one of claims 127-128, wherein the joining sequence comprises from 1 to 100 amino acid residues.

130. A pharmaceutical composition comprising the peptide of any one of claims 1-46 or a salt thereof, or the peptide active agent complex of any of claims 47-129 or a salt thereof, and a pharmaceutically acceptable carrier.

131. The pharmaceutical composition of claim 130, wherein the pharmaceutical composition is formulated for administration to a subject.

132. The pharmaceutical composition of any of claims 130-131, wherein the pharmaceutical composition is formulated for inhalation, intranasal administration, oral administration, topical administration, parenteral administration, intravenous administration, subcutaneous administration, intra-articular administration, intramuscular administration, intraperitoneal administration, dermal administration, transdermal administration, or a combination thereof.

133. A method of treating a condition in a subject in need thereof, the method comprising administering to the subject the peptide of any one of claims 1-46, the peptide active agent complex of any of claims 47-129, or a pharmaceutical composition of any one of claims 130-132.

134. The method of claim 133, wherein the peptide active agent complex, peptide, or pharmaceutical composition is administered by inhalation, intranasally, orally, topically, parenterally, intravenously, subcutaneously, intra-articularly, intramuscularly administration, intraperitoneally, dermally, transdermally, or a combination thereof.

135. The method any one of claims 133-134, wherein the peptide active agent complex or the peptide homes, targets, or migrates to cartilage of the subject following administration.

136. The method of any of claims 133-135, wherein the condition is associated with cartilage.

137. The method of any one of claims 133-135, wherein the condition is associated with a joint.

138. The method of any of claims 133-135, wherein the condition is an inflammation, a cancer, a degradation, a growth disturbance, genetic, a tear, an infection, a disease, or an injury.

139. The method of any of claims 133-135, wherein the condition is a chondrodystrophy.

140. The method of any of claims 133-135, wherein the condition is a traumatic rupture or detachment.

141. The method of any of claims 133-135, wherein the condition is a costochondritis.

142. The method of any of claims 133-135, wherein the condition is a herniation.

143. The method of any of claims 133-135, wherein the condition is a polychondritis.

144. The method of any of claims 133-135, wherein the condition is a chordoma.

145. The method of any of claims 133-135, wherein the condition is a type of arthritis.

146. The method of claim 145, wherein the type of arthritis is rheumatoid arthritis.

147. The method of claim 145, wherein the type of arthritis is osteoarthritis.

148. The method of claim 145, wherein the type of arthritis is lupus arthritis.

149. The method of any one of claims 133-135, wherein the condition is Systemic lupus erythematosus.

150. The method of any of claims 133-135, wherein the condition is achondroplasia.

151. The method of any of claims 133-135, wherein the condition is benign chondroma or malignant chondrosarcoma.

152. The method of any of claims 133-135, wherein the condition is bursitis, tendinitis, gout, pseudogout, an arthropathy, psoriatic arthritis, ankylosing spondylitis, or an infection.

153. The method of claim 138, wherein the peptide active agent complex, peptide, or pharmaceutical composition is administered to treat the injury, to repair a tissue damaged by the injury, or to treat a pain caused by the injury.

154. The method of claim 138, wherein the peptide active agent complex, peptide, or pharmaceutical composition is administered to treat the tear or to repair a tissue damaged by the tear.

155. The method of any one of claims 133-134, wherein the peptide active agent complex, peptide, or pharmaceutical composition homes, targets, or migrates to a kidney of the subject following administration.

156. The method of any one of claims 133-134 or 155, wherein the condition is associated with a kidney.

157. The method of claim 156, wherein the condition is lupus nephritis, acute kidney injury (AKI), chronic kidney disease (CKD), hypertensive kidney damage, diabetic nephropathy, lupus nephritis, or renal fibrosis.

158. A method of imaging an organ or body region of a subject, the method comprising:

administering to the subject the peptide of any one of claims 1-46, the peptide active agent complex of any of claims 47-129, or a pharmaceutical composition of any one of claims 130-132; and

imaging the subject.

159. The method of claim 158, wherein further comprising detecting a cancer or diseased region, tissue, structure or cell.

160. The method of any one of claims 158-159, further comprising performing surgery on the subject.

161. The method of any one of claims 158-160, further comprising treating the cancer.

162. The method of any one of claims 158-161, wherein the surgery comprises removing the cancer or the diseased region, tissue, structure or cell of the subject.

163. The method of claim 160, further comprising imaging the cancer or diseased region, tissue, structure, or cell of the subject after surgical removal.

164. The peptide active agent complex of any one of claims 47-129, wherein the peptide active agent complex is expressed as a fusion protein.

165. A method of treating or delivering a peptide or peptide agent complex to a subject in need thereof according to any one of claims 133-164, the method further comprising administering a companion diagnostic, therapeutic, or imaging agent, wherein the companion diagnostic or imaging agent comprises

- a) the peptide active agent complex of any of claims 42-124,
- b) the peptide of any of claims 1-41; or
- c) a peptide of SEQ ID NO: 27 – SEQ ID NO: 45, SEQ ID NO: 47 – SEQ ID NO: 66, SEQ ID NO: 109 – SEQ ID NO: 126, SEQ ID NO: 129 – SEQ ID NO: 148, or SEQ ID NO: 233 – SEQ ID NO: 256 further comprising a diagnostic, therapeutic, or imaging agent, wherein the diagnostic or imaging agent comprises a chemical agent, a radiolabel agent, radiosensitizing agent, fluorophore, an imaging agent, a diagnostic agent, a protein, a peptide, or a small molecule.

166. The method of claim 165, wherein the companion diagnostic, therapeutic, or imaging agent is detected by a device.

167. The method of claim 166, wherein the device is used to detect the companion diagnostic, therapeutic, or imaging agent or to assess an agent's safety and physiologic effect.

168. The method of claim 167, wherein the agent's safety and physiologic effect is bioavailability, uptake, distribution and clearance, metabolism, pharmacokinetics, localization, measurement of concentrations in blood and tissues, assessing therapeutic window, range and optimization.

169. The method of any one of claims 165-168, wherein the method is combined with or integrated into a surgical microscope, confocal microscope, fluorescence scope, exoscope, endoscope, or a surgical robot comprising a KINEVO 900, QEVO, CONVIVO, OMPI PENTERO 900, OMPI PENTERO 800, INFRARED 800, FLOW 800, OMPI LUMERIA, OMPI Vario, OMPI VARIO 700, OMPI Pico, TREMON 3DHD, a PROVido, ARvido, GLOW 800, Leica M530 OHX, Leica M530 OH6, Leica M720 OHX5, Leica M525 F50, Leica M525 F40, Leica M525 F20, Leica M525 OH4, Leica HD C100, Leica FL560, Leica FL400 Leica FL800, Leica DI C500, Leica ULT500, Leica Rotatable Beam Splitter, Leica M651 MSD, LIGHTENING, Leica TCS SP8, SP8 FALCON, SP8 DIVE, Leica TCS SP8 STED, Leica TCS SP8 DLS, Leica TCS SP8 X, Leica TCS SP8 CARS, Leica TCS SPE), Leica HyD, Leica HCS A, Leica DCM8, Haag-Streit 5-1000, Haag-Streit 3-1000, and Intuitive Surgical da Vinci surgical robot.

170. The method of any one of claims 166-169, wherein the device incorporates radiology or fluorescence, including the X-ray radiography, magnetic resonance imaging (MRI), ultrasound, endoscopy, elastography, tactile imaging, thermography, flow cytometry, medical photography, nuclear medicine functional imaging techniques, positron emission tomography (PET), single-photon emission computed tomography (SPECT), surgical instrument, operating microscope, confocal microscope, fluorescence scope, exoscope, or a surgical robot.

171. The peptide of any one of claims 2, 28, 34, 41, 42, or 45, wherein the peptide comprises at least two of, at least three of, at least four of, at least five of, at least six of, at least seven of, at least eight of, or all of KCIN (SEQ ID NO: 91); PCKR (SEQ ID NO: 93); KQC (SEQ ID NO: 95); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); or GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R wherein each X can independently be any amino acid or amino acid analogue or null.

172. The peptide of any one of claims 3, 29, 34, 41, 42, or 45, wherein the peptide comprises at least two of, at least three of, at least four of, at least five of, at least six of, at least seven of, at least eight of, at least nine of, at least ten of, or all of RCIN (SEQ ID NO: 97); PCRR (SEQ ID NO: 99); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null; GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R; PCR (SEQ ID NO: 230); CLDPCRR (SEQ ID NO: 231); CLDPCRR (SEQ ID NO: 232); RCRGSRDC (SEQ ID NO: 257); PCRRAG (SEQ ID NO: 258); or RFGRCI (SEQ ID NO: 259).

173. The peptide of claim 30, wherein the peptide comprises at least two of, at least three of, at least four of, at least five of, at least six of, at least seven of, at least eight of, at least nine of, at least ten of, at least 11 of, at least 12 of, at least 13 of, at least 14 of, at least 15 of, at least 16 of, at least 17 of, at least 18 of, at least 19 of, at least 20 of, at least 21 of, at least 22 of, at least 23 of, at least 24 of, at least 25 of, or all of GKCINKKCKC (SEQ ID NO: 90); KCIN (SEQ ID NO: 91); KKCK (SEQ ID NO: 92); PCKR (SEQ ID NO: 93); KRCSRR (SEQ ID NO: 94); KQC (SEQ ID NO: 95); GRCINRRRC (SEQ ID NO: 96); RCIN (SEQ ID NO: 97); RRRCR (SEQ ID NO: 98); PCRR (SEQ ID NO: 99); RRCSRR (SEQ ID NO: 100); RQC (SEQ ID NO: 101); PCKK (SEQ ID NO: 102); KKCSKK (SEQ ID NO: 103); GKCMNGKC (SEQ ID NO: 104); GRCMNGRC (SEQ ID NO: 105); GRCINSRC (SEQ ID NO: 227); GRCIXXRC (SEQ ID NO: 228) wherein each X can independently be any amino acid or amino acid analogue or null, GRCIX¹X²RC (SEQ ID NO: 229), wherein X¹=N,Q, A, S, T or L and X²=S, G, or R

(SEQ ID NO: 229), PCR (SEQ ID NO: 230), CLDPCRR (SEQ ID NO: 231), CLDPCRR (SEQ ID NO: 232), RCRGSRDC (SEQ ID NO: 257), PCRRAG (SEQ ID NO: 258), and RFGRCI (SEQ ID NO: 259).

174. The peptide of any one of claims 1, 34, 41, 42, or 45, wherein the peptide further comprises at least two of, at least three of, at least four of, at least five of, at least six of, at least seven of, at least eight of, at least nine of, at least ten of, at least 11 of, at least 12 of, at least 13 of, at least 14 of, at least 15 of, at least 16 of, at least 17 of, at least 18 of, at least 19 of, at least 20 of, at least 21 of, at least 22 of, at least 23 of, at least 24 of, at least 25 of, at least 26 of, at least 27 of, at least 28 of, at least 29, of or all of the corresponding substitutions selected from the group consisting of N5S, D16E, M23T, N30Q, N30A, N30S, N30T, N30L, S31G, S31R, L15Y, H34Y, T36Y, D10E, M17T, N24Q, N24A, N24S, N24T, N24L, S25G, S25R, L9Y, H28Y, T30Y, R1K, R13K, R14K, R21K, and R26K.

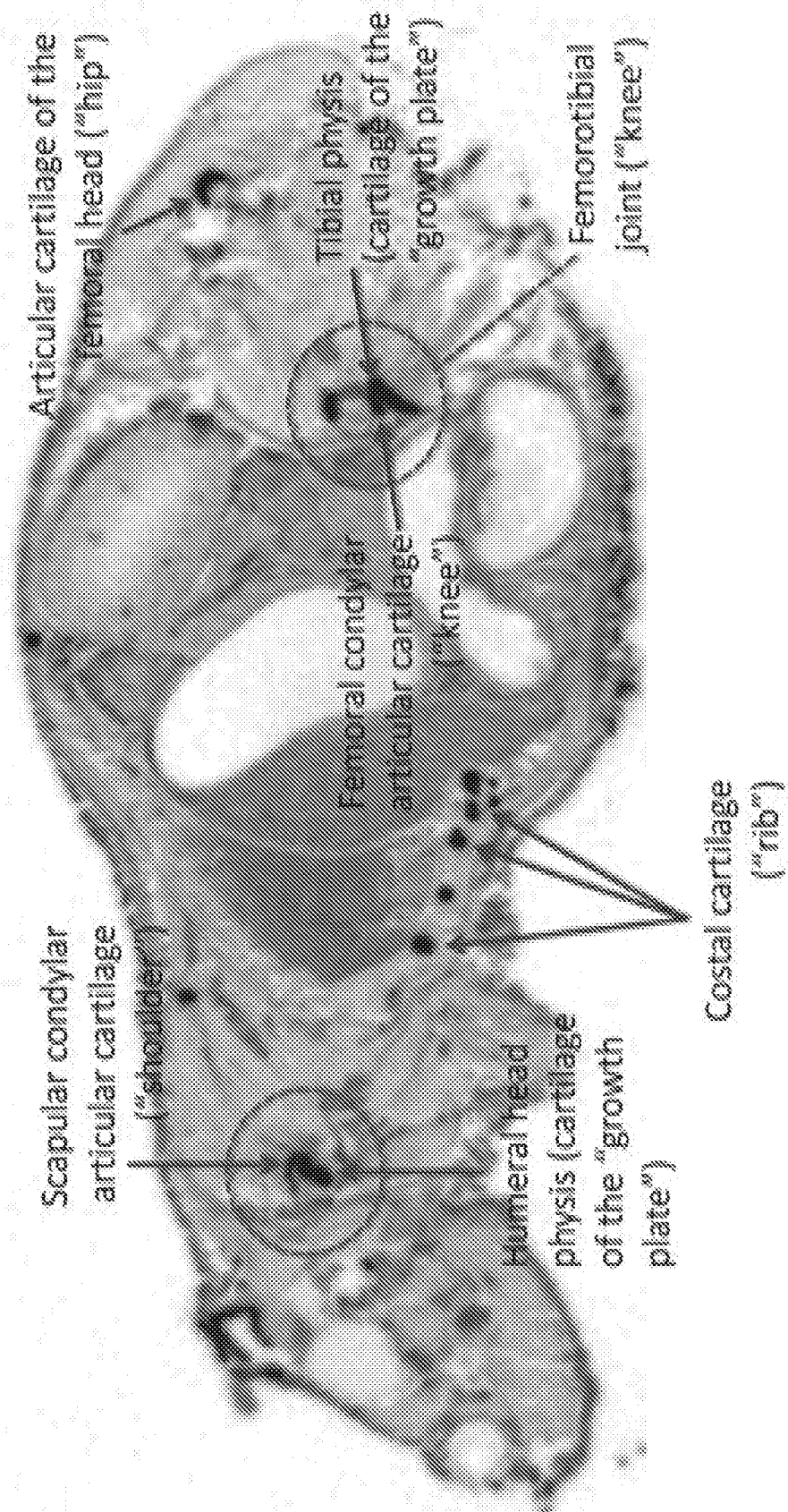


FIG. 1

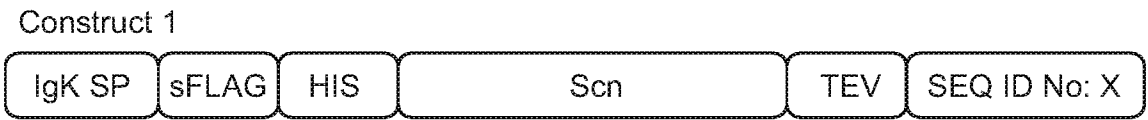


FIG. 2

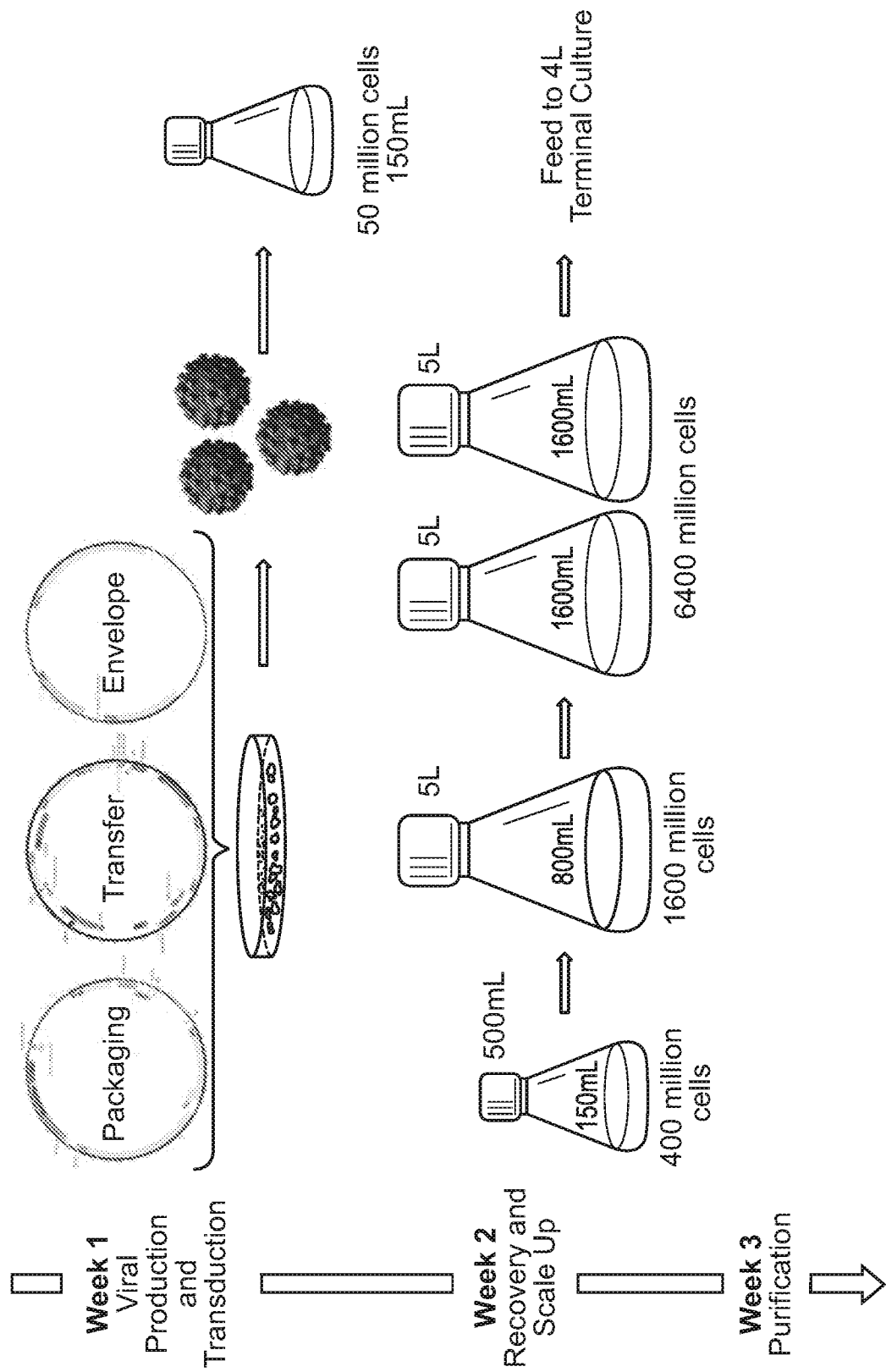


FIG. 3

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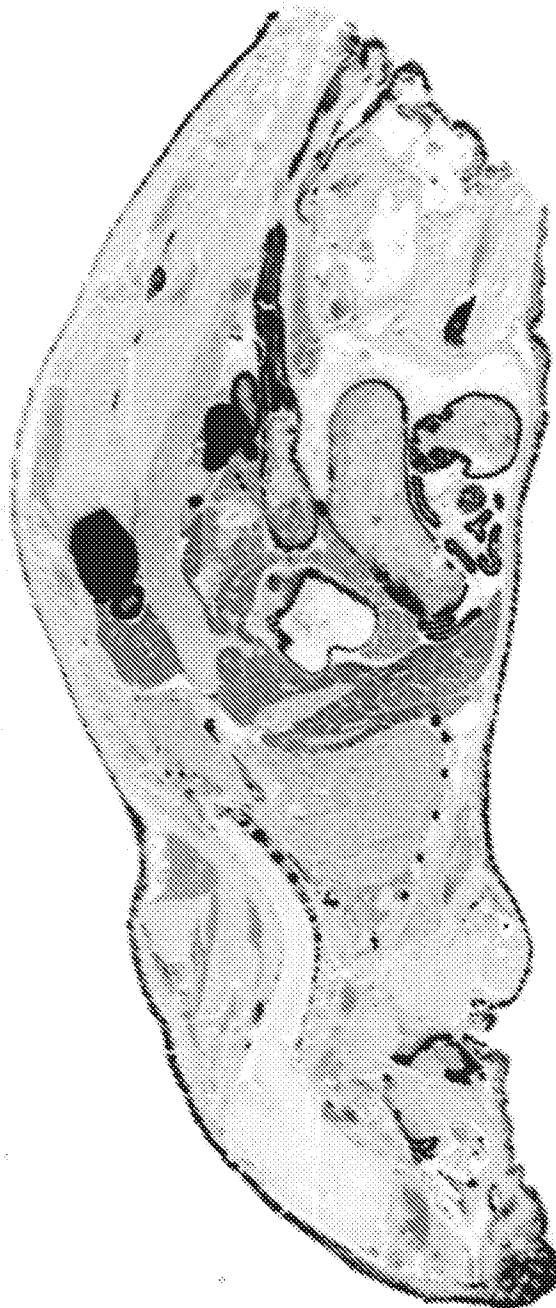


FIG. 4

5 / 10

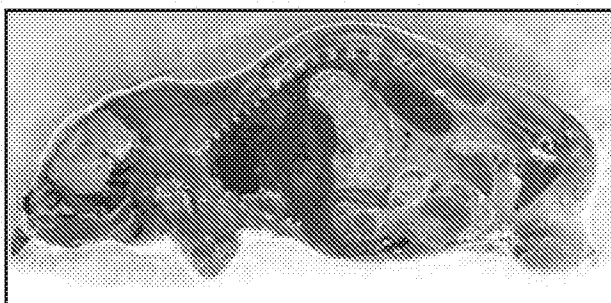


FIG. 5A

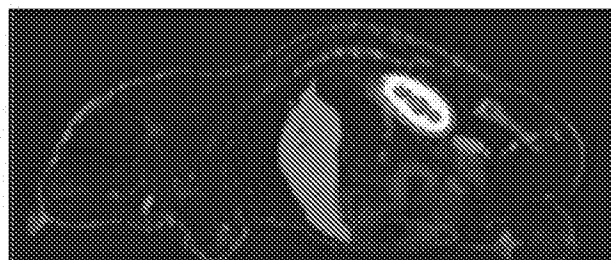


FIG. 5B

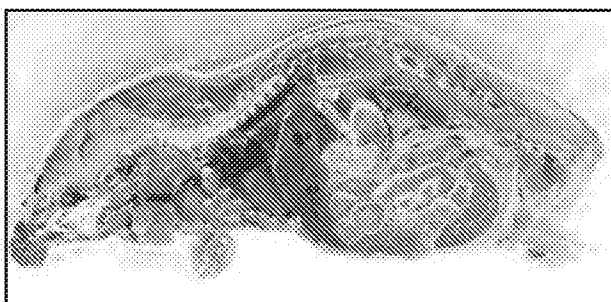


FIG. 5C

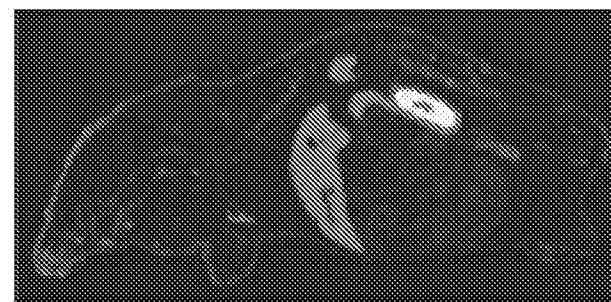


FIG. 5D



FIG. 5E



FIG. 5F

FIG. 5

6 / 10

SEQ ID NO:

		10	20	30	
321	...	EVIRCSGSKQCYGPCKQQTGCTNSKCMNKVCKCYGCG			
543	..AEI	IRCSGTRECYAPCQKLTGCLNAKCMNKACKCYGCV			
544	.RPTD	IKCSASYQCFPVCKSRFGKTNGRCVNGLCDCF...			
545	.QFTD	VKGTGSKQCPVCKQMF	GKPNGKCMNGKCR	CYS..	
317	GVPI	INVKCRGSRDCLDPCKKA.	GMRFGKCI	NSKCHCTP..	
398	GVPI	INVRCRGSRDCLDPCKRA.	GMRFGRCI	NSRCHCTP..	
340	.VG	INVCKHSGQCLPKCKDA.	GMRFGKCI	NGKCDCTPK.	
546	.VG	INVCKHSGRQCLPKCKDA.	GMRFGKCI	NGKCHCTPK.	
316	.VRIP	VSCKHSGQCLPKCKDA.	GMRFGKCM	NGKCDCTPK.	
333	GVI	INVCKKISRQCLEPKCKKA.	GMRFGKCM	NGKCHCTPK.	
337	GVPT	DVKCRGSPQCIQPKCKDA.	GMRFGKCM	NGKCHCTPK.	
486	.VPT	DVKCRGSPQCIQPKCKDA.	GMRFGKCM	NGKCHCTP..	
338	GVPI	INVSC	TGSPQCIKPKCKDA.	GMRFGKCMNRKCHCTPK.	
483	.VF	INVKCRGSP	ECLPKCKEAIGKSAGKCM	NGKCKCYP..	
547	.VV	IGQRCYRSPDCYSACKKLVGKATGKCTNGRCDC....			
548	..NFK	VEGACSKPCRKYCIDK.	GARNGKCI	NGRCHCYY..	
549	Q	IDTNVCKSGSSKCVKICIDRYNTRGAKCINGRC	CTCYP..		
474	QKI	LSNRCNNS	SECI	PHCIRIFGTAAKCI	NRKCYCYP..
295	.v.i.vkc.gs.qCl.pCk.a.g.r.gkCmNgkC.C.p..				

FIG. 6

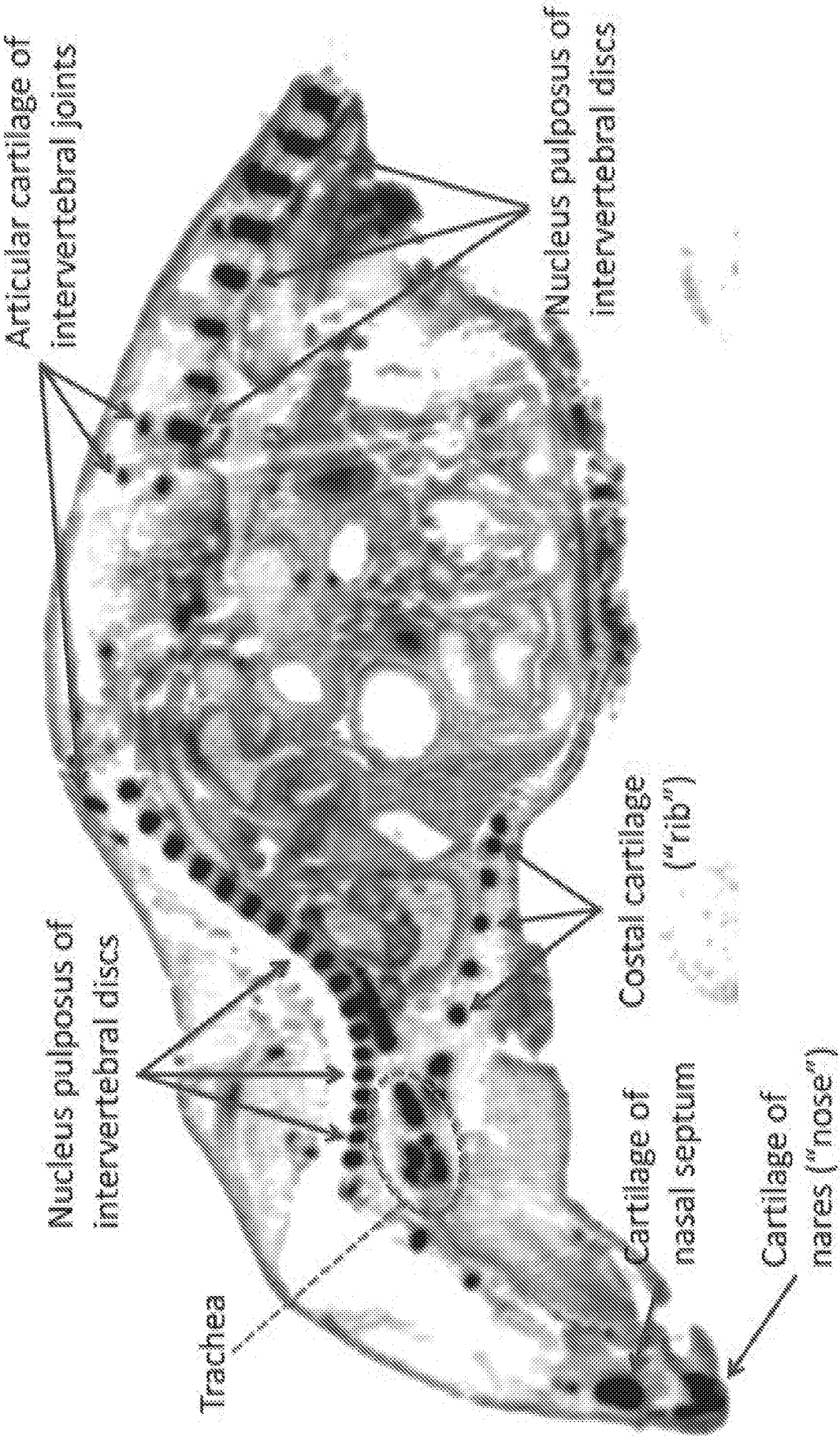


FIG. 7

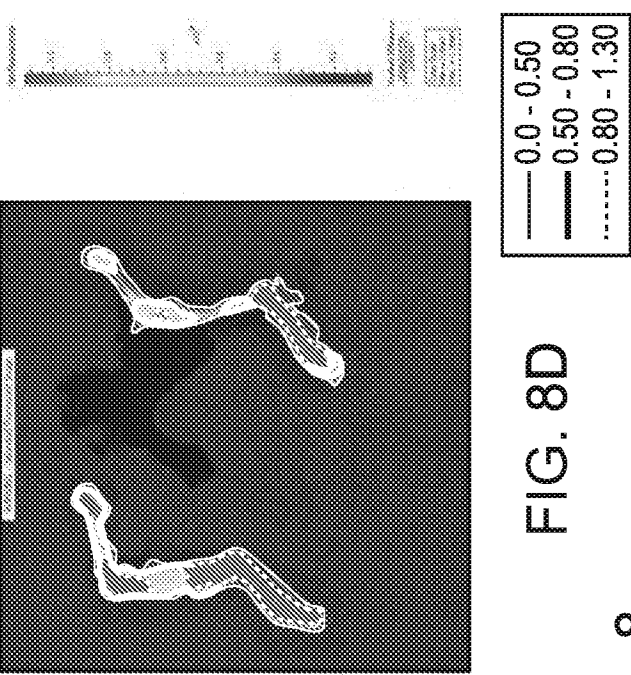
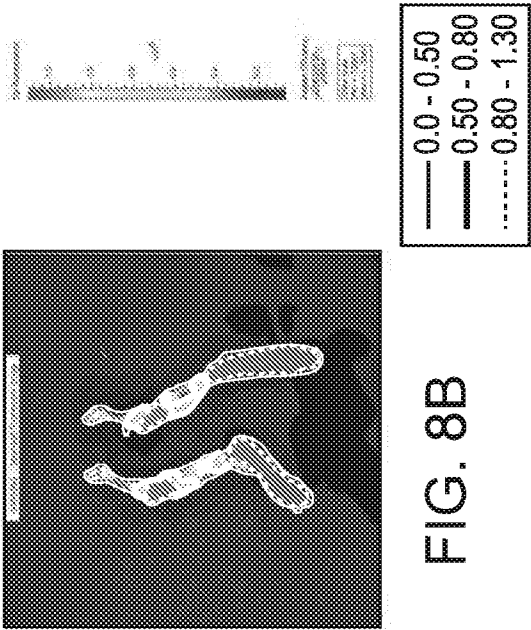
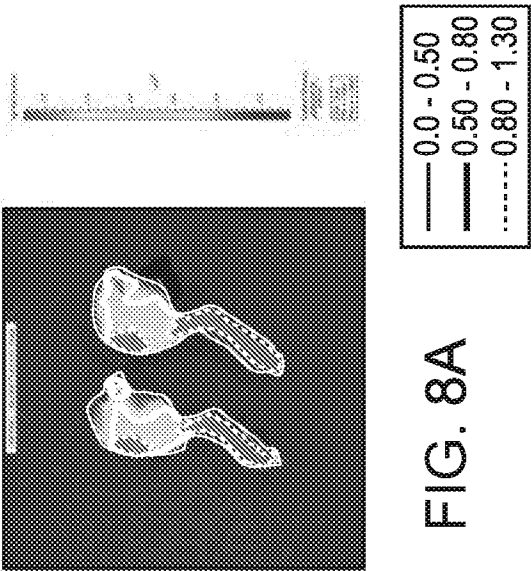
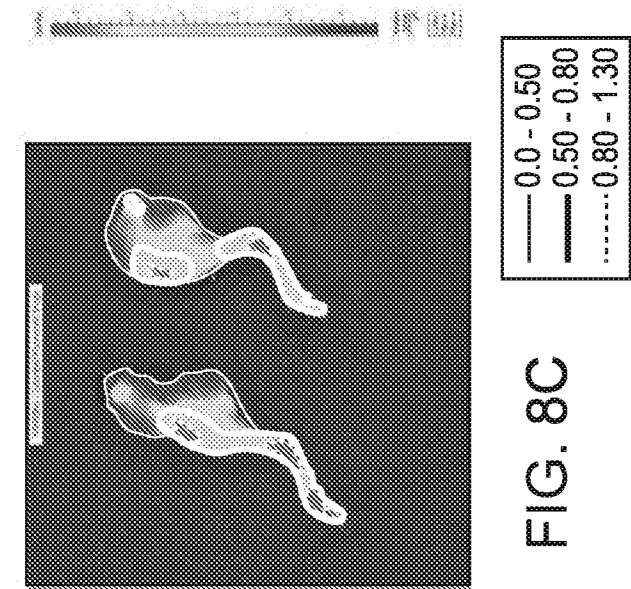


FIG. 8



3 hours



24 hours

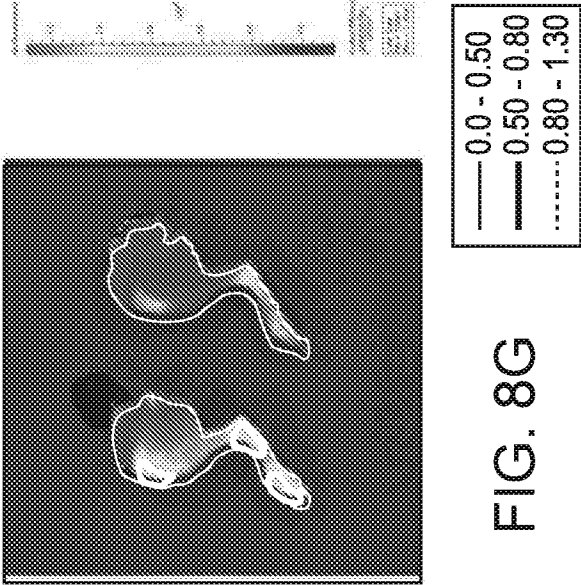
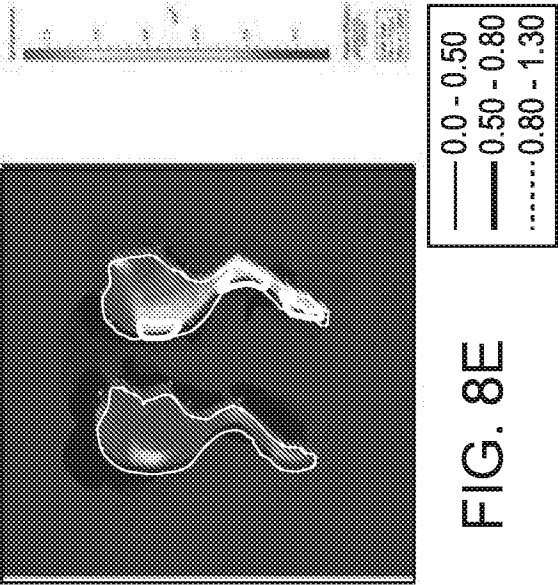
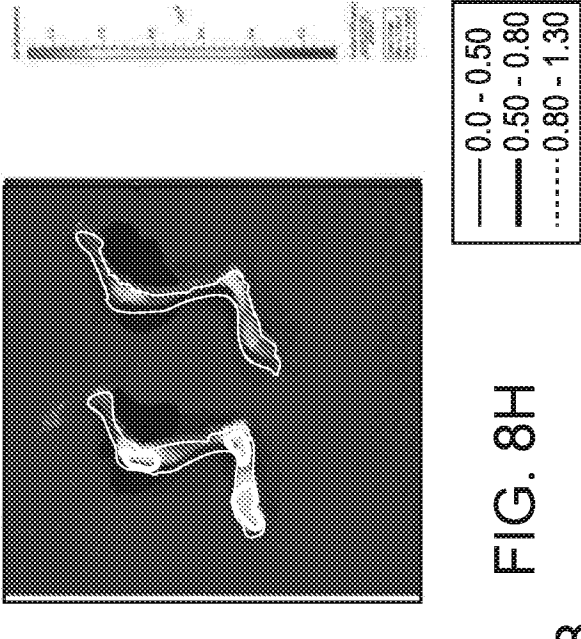
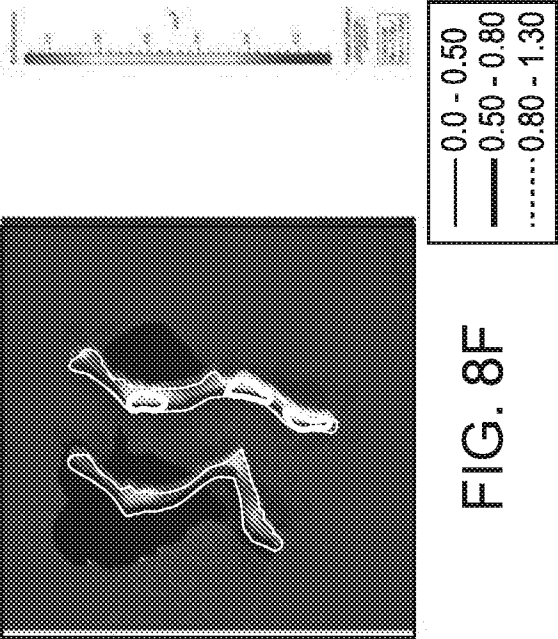


FIG. 8

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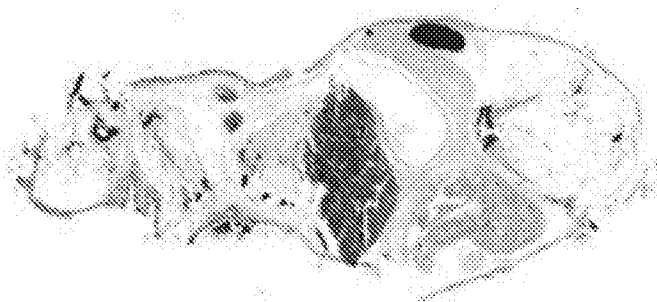


FIG. 9A

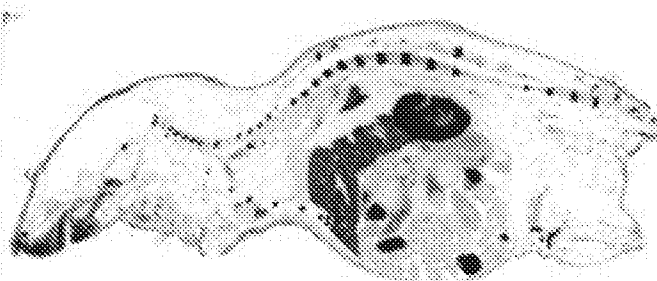


FIG. 9B

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/022630

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a. ☒ forming part of the international application as filed:

☒ in the form of an Annex C/ST.25 text file.

☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

SEQ ID NOs: 87-89, 106-129, 134, 135, 209-215, 219, 221, 223, and 225 were searched.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/022630

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-16, 21-45, 47-174
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/022630

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/16; A61K 38/17; C07K 14/435; C07K 19/00 (2019.01)

CPC - C07K 14/435; C07K 14/43513; C07K 14/43518; C07K 14/43522; C07K 2319/01; C07K 2319/33 (2019.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 530/324; 530/325; 530/326; 530/858 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/044894 A2 (FRED HUTCHINSON CANCER RESEARCH CENTER et al) 16 March 2017 (16.03.2017) entire document	1-3, 17-20
X	WO 2018/049285 A1 (FRED HUTCHINSON CANCER RESEARCH CENTER et al) 15 March 2018 (15.03.2018) entire document	46
P, X	WO 2018/170480 A1 (BLAZE BIOSCIENCE, INC.) 20 September 2018 (20.09.2018) entire document	1-3, 17-20, 46
A	-- CHEUNG et al. "Identification of Chondrocyte-Binding Peptides by Phage Display," J Orthop Res, 25 February 2013 (25.02.2013), Vol. 31, Iss. 7, Pgs. 1053-1058. entire document	1-3, 17-20, 46
A	WO 2008/063291 A2 (ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE et al) 29 May 2008 (29.05.2008) entire document	1-3, 17-20, 46
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Date of the actual completion of the international search

06 June 2019

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