METHOD FOR DIAGNOSING AMYLOID DISEASES

CROSS-REFERNECE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/575,473, filed April 5, 2024 and U.S. Provisional Application No. 63/657,718, filed June 7, 2024, each of which are hereby incorporated by reference in their entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0002] This present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 165992001540SeqList.xml, created April 2, 2025, which is 48,564 bytes in size. The information in the electronic format of the Sequence Listing is incorporated by reference in its entirety.

FIELD

[0003] The present invention relates to methods of labeling a detection reagent and uses thereof for detecting and diagnosing types of amyloid-related diseases.

BACKGROUND

[0004] Systemic amyloidosis is a progressive protein misfolding disorder characterized by the extracellular deposition of proteinaceous fibrils, extracellular matrix components, and serum proteins. Accumulation of amyloid, notably within the heart and kidneys, the most affected organs in all types of amyloidosis, leads to organ dysfunction, poor quality of life, and ultimately death. Approximately 20 different proteins have been identified as fibrillar components in systemic amyloidosis (Aimo A, Merlo M, Porcari A, *et al. Eur J Heart Fail.* 2022); however, patients with variant or wild type transthyretin- (ATTRv and ATTRwt), immunoglobulin light chain- (AL), and leukocyte chemotactic factor 2- (ALECT2) associated amyloidosis comprise more than 90% of the cases diagnosed in the US (Edwards CV, Rao N, Bhutani D, *et al. Blood.* 2021;138:2632–2641).

[0005] Cardiac amyloidosis is an ominous manifestation in both AL and ATTR-associated amyloidosis causing restrictive hypertrophic cardiomyopathy, notably of the left ventricular wall and interventricular septum, accompanied by abnormalities of electrical conduction and strain (Garcia-Pavia P, Aus Dem Siepen F, Donal E, *et al. N Engl J Med.* 2023:NEJMoa2303765). However, any organ or tissue may be involved, resulting in

heterogeneous clinical presentation and rendering accurate and rapid diagnosis challenging (Dorbala S, Cuddy S, Falk RH. *JACC Cardiovasc Imaging*. 2020;13:1368–1383).

[0006] Non-invasive imaging is particularly useful in the diagnostic algorithm for cardiac amyloidosis (Dorbala S, Park M-A, Cuddy S, *et al. J Nucl Med*. 2021;62:716–722). Echocardiography and cardiac magnetic resonance imaging (CMR) can reveal structural abnormalities and functional sequelae associated with amyloidosis10; however, these techniques are not amyloid specific. Nuclear imaging with ^{99m}Tc-pyrophosphate (^{99m}Tc-PyP) or ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) is routinely used for diagnosing cardiac ATTR amyloidosis. These bone-seeking agents bind cardiac microcalcifications associated with cardiac amyloid and preferentially detect only ATTR-associated cardiac amyloidosis (Antoni G, Lubberink M, Estrada S, *et al. J Nucl Med*. 2013;54:213–220). In some aspects, existing methods are limited by the unavailability of amyloid specific measures to monitor change in amyloid load over time. Thus, a non-invasive and quantitative measure to detect and monitor cardiac, as well as extracardiac, amyloid deposits would be clinically beneficial. Provided herein are methods and compositions that address such and other needs.

SUMMARY

[0007] Provided herein are methods for the diagnosis and treatment of amyloid disease. In some embodiments, the methods comprise the administration of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the methods further comprise detecting the label in one or more organs or tissues. In some embodiments, the methods provided herein are able to differentiate between different types of systemic amyloidosis such as AL and ATTR, based upon the organ distribution pattern of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the method comprises providing a prognosis for a type of amyloid disease based upon the organ distribution pattern of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the method comprises providing a diagnosis of a type of amyloid disease based upon the organ distribution pattern of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the method further comprises selecting a therapy based upon the type of amyloid disease. In some embodiments, the method comprise estimating a cardiac amyloid burden. Cardiac amyloid burden may be based on a ratio of technetium^{99m} detectable label in the heart and blood (signal to background ratio) of an

individual following administration of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. Provided herein are methods of producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual. Using technetium^{99m} detectable labels in the method disclosed herein provide for increased diagnostic, prognostic, and treatment power compared to conventional methods.

[0008] Provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease, the method comprising, administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual, wherein the individual has previously tested negative using an alternative detection method; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label in one or more organs or tissues of the individual; wherein detecting the amyloid-reactive peptide in the one or more organs or tissues indicates that the individual has the amyloid disease.

[0009] In some aspects, the alternative detection method is selected from a group consisting of ^{99m}Tc-labeled pyrophosphate (PYP), ^{124}I-labelled amyloid-reactive peptide detection, 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), Aβ amyloid imaging agents, ^{18}F-Florbetapir (Amyvid), ^{18}F-Flutemetamol (Vizamyl), ^{18}F-Florbetaben (Neuraceq) transthoracic echocardiography and cardiac magnetic resonance imaging.

[0010] In some aspects, provided herein is a method of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, the method comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more tissues.

[0011] In some aspects, detecting the amyloid-reactive peptide in the organ or tissue indicates that the individual has an amyloid disease. In some aspects, detection of the amyloid-reactive peptide in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis.

[0012] In some aspects, provided herein is a method of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising

administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues the individual between about 0.1 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease.

[0013] In some aspects, the individual is determined to be at risk for an amyloid-related disease based upon the presence of a genetic mutation, having multiple myeloma, having amyloid positive laminectomy tissue, having an amyloid positive tissue from carpal tunnel release surgery, having a monoclonal gammopathy of unknown significance (MGUS), having heart failure with preserved ejection fraction (HFpEF), having heart failure with reduced ejection fraction (HFrEF), being from susceptible ethnic populations, or being elderly. In some aspects, the genetic mutation is in the transthyretin gene. In some aspects, the genetic mutation is in the transthyretin gene.

[0014] In some aspects, provided herein is a method of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual.

[0015] In some aspects, the prognosis of an individual having an amyloid-related disease is based on detecting amyloid-reactive peptide in the heart alone. In some aspects, the

prognosis of an individual having an amyloid-related disease is based on detecting amyloid-reactive peptide in the heart.

[0016] In some aspects, provided herein is a method of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual between about 0.1 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected.

[0017] In some aspects, a method of managing the treatment of an amyloid-related disease in an individual comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and adjusting the treatment for the amyloid-related disease.

[0018] In some aspects, the methods further comprise estimating a cardiac amyloid burden in the individual. In some aspects, the cardiac amyloid burden is based on a ratio of the technetium^{99m} detectable label the heart and blood of the individual.

[0019] Also provided herein are methods of estimating cardiac amyloid burden in an individual with an amyloid-related disease, the method comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label in images of heart and blood of the

individual between about 0.1 hours and about 3 hours after administering the amyloid-reactive peptide; and estimating a cardiac amyloid burden based on the ratio of the technetium^{99m} detectable label detected in the heart and the blood of the individual. In some aspects, the cardiac amyloid burden correlates with one or more biomarkers associated with the amyloid-related disease.

[0020] In some aspects, the method further comprises administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at a tissue or organ of the individual to detect amyloid in the individual a second time, optionally a third time a fourth time, and/or a fifth time. In some aspects, the first time and the second time are at least six weeks apart. In some aspects, if the amyloid disease is stable between the first and second times treatment is be modified. In some aspects, the amyloid burden increases treatment is reinitiated.

[0021] In some aspects, the detecting takes place about 0.5 and about 3 hours after administration of the amyloid-reactive peptide. In some aspects, the detecting takes place about 0.5, about 1, about 1.5, about 2, about 2.5, or about 3 hours after administration of the amyloid-reactive peptide.

[0022] In some aspects, the tissue or organ of the individual is selected from the group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand. In some aspects, the tissue or organ of the individual is selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue. In some aspects, the tissue or organ of the individual is selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland.

[0023] In some aspects, the detecting comprises imaging by single photon emission computed tomography (SPECT), SPECT with x-ray computed tomography (SPECT/CT), or Planar gamma imaging. In some aspects, the detecting comprises imaging by single photon emission computed tomography with x-ray computed tomography (SPECT/CT).

[0024] In some aspects, the detecting comprises quantifying the amount of detectable label to quantify the amount of amyloid-reactive peptide. In some aspects, an amount of amyloid-reactive peptide above a threshold indicates presence of amyloid deposits in the one or more organs or tissues. In some aspects, amyloid deposits detected in one or more organs or tissues indicates the individual has an amyloid related disease. In some aspects, detection of an amount of amyloid-reactive peptide in the heart is about 1.96 times the SD of the heart of a healthy individual, indicating the individual has ATTR.

[0025] In some aspects, the amyloid-reactive peptide comprises or consists of the amino acid sequence set forth in SEQ ID NO:13. In some aspects, a dose of about 10 to about 25 mCi of Tc-99m is administered to the individual. In some aspects, a dose of about less than 20 mCi of Tc-99m is administered to the individual. In some aspects, a dose of about 0.3 mg, 1 mg, 1.5 mg, or about 2 mg of amyloid-reactive peptide is administered to the individual. In some aspects, a dose of about 20 mCi of Tc-99m is administered to the individual. In some aspects, a dose of about comprising about less than 0.1 mg amyloid-reactive peptide is administered to the individual. In some aspects, the amyloid-reactive peptide is administered intravenously.

[0026] In some aspects, the methods further comprise determining an organ-specific standard uptake value ratio (SUVR) for the tissue or organ of the individual. In some aspects, the organ-specific SUVR for the individual is selected from the group consisting of SUVR mean, SUVR max, and SUVR peak. In some aspects, the methods comprise determining an organ-specific SUV for the individual. In some aspects, the organ-specific SUV for the individual is selected from the group consisting of SUV mean, SUV max, and SUV peak. In some aspects, the amyloid-reactive peptide has a sensitivity of at least 90%. In some aspects, the sensitivity is about 95%, about 99% or about 100%.

[0027] In some aspects, the methods comprise determining one or more health related quality of life measures for the individual. In some aspects, the methods comprise detecting one or more biomarkers associated with the amyloid-related disease. In some aspects, the biomarker associated with amyloid-related disease is selected from the group consisting of Troponin T, NTproBNP, urine protein levels, UACR, EGFR, interventricular septal wall thickness (IVS), left ventricular (LV) wall thickness, global longitudinal strain (GLS), and alkaline phosphatase levels.

[0028] In some aspects, the methods comprise performing a cardiac biopsy if amyloid is detected in the heart. In some aspects, the methods comprise performing additional amyloid imaging on the individual. In some aspects, the additional amyloid imaging on the individual comprises ECHO, CMR, bone scintigraphy or positron emission tomography imaging. In some aspects, the additional amyloid imaging on the individual further comprises a tracer selected from the group consisting of ^{99m}Tc-PyP, ^{99m}Tc-DPD, ^{99m}Tc-HMDP, ^{99m}Tc-MDP other bone scintigraphy tracers, ^{124}I-evuzamatide, and ^{18}F-florbetapir, ^{18}F-flutemetamol, and ^{18}F-florbetaben.

[0029] In some aspects, the individual is diagnosed with amyloid cardiomyopathy. In some aspects, the individual is suspected of having amyloid cardiomyopathy. In some aspects, the amyloid-related disease is systemic or localized amyloidosis.

[0030] In some aspects, the amyloid-reactive peptide has pan-amyloid specificity. In some aspects, the amyloid-reactive peptide binds to amyloid of immunoglobulin light chain (AL), immunoglobulin heavy chain (AH), β2-microglobulin (Aβ2M), transthyretin (ATTR wild type; ATTR variant), apolipoprotein AI (AApoAI), apolipoprotein AII (AApoAII), apolipoprotein AIV (AApoAIV), gelsolin (AGel), apolipoprotein C-II (AApoCII), apolipoprotein C-II (AApoCIII), lysozyme (ALys), leukocyte chemotactic factor (ALECT2), fibrinogen a variants (AFib), cystatin variants (ACys), calcitonin (ACal), lactadherin (AMed), islet amyloid polypeptide (AIAPP), prolactin (APro), insulin (AIns), prior protein (APrP); α-synuclein (AαSyn), tau (ATau), atrial natriuretic factor (AANF), IAAP, ALβ4, or ALβ1.

[0031] In some aspects, the individual has a genetic predisposition to an amyloid-related disease. In some aspects, the individual has a family history of an amyloid-related disease. In some aspects, the individual is elderly. In some aspects, the individual has an early stage of an amyloid-related disease. In some aspects, the individual has an early stage of AL amyloidosis. In some aspects, the early stage of AL amyloidosis is diagnosed according to the Mayo Clinic system. In some aspects, the early stage of AL amyloidosis is stage 1 AL amyloidosis.

[0032] In some aspects, the individual has an early stage of ATTR amyloidosis. In some aspects, the early stage of ATTR amyloidosis comprises stage 1 ATTR amyloidosis.

[0033] In some aspects, the methods further comprise administering a therapy for the amyloid-related disease. In some aspects, the therapy for the amyloid-related disease is selected

from the group consisting of transthyretin stabilizers (e.g. tafamidis, acoramidis), transthyretin silencers (e.g. Patisiran, Inotersen, Vutrisiran, Eploetersen), gene editing approaches, anti-amyloid approaches utilizing monoclonal antibodies, treatments targeting plasma cell clones (e.g. Daratumumab, Bortezomib), and an antibody-peptide fusion comprising an antibody-peptide fusion protein comprising a second amyloid-reactive peptide and an antibody that does or does not binds to amyloid fibrils. In some aspects, the second amyloid-reactive peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-14 comprising 0, 1, 2, 3, or 4 amino acid substitutions, insertions, or deletions. In some aspects, the antibody-peptide fusion protein comprises a heavy chain and a light chain and wherein the amyloid-reactive peptide is linked to at the C-terminal end of the light chain of the antibody via a spacer. In some aspects, the antibody-peptide fusion protein comprises: (i) an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:2; and (ii) an antibody that binds to a human amyloid fibrils, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain of the antibody comprises a heavy chain variable region (VH) and the light chain of the antibody comprises a light chain variable region (VL), wherein the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:106, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:107, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:108, and the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:103, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:104, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:105; wherein the amyloid-reactive peptide and antibody are linked at the C-terminal end of the light chain, and wherein the amyloid-reactive peptide is linked to the antibody via a spacer comprising an amino acid sequence set forth in SEQ ID NO:83.

[0034] In some aspects, provided herein is a method of producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual, the method comprising (a) combining a solution comprising 10-30 μg of the amyloid-reactive peptide and a solution comprising 1.0-3.5 mg of $SnCl_2$ with a solution comprising technetium^{99m} to produce a labeling composition; (b) incubating the labeling composition to produce a labeled amyloid reactive peptide; and (c) adding a quencher to the labeling composition within five minutes of

the combining to produce a quenched composition comprising a labeled amyloid-reactive peptide with technetium^{99m}.

[0035] In some aspects, the methods comprise diluting the quenching composition after step (c).

[0036] In some aspects, the solution comprising 10-30 μg of the amyloid-reactive peptide further comprises sterile phosphate buffered saline.

[0037] In some aspects, the methods comprise preparing the solution comprising 1.0-3.5 mg of $SnCl_2$ before step (a). In some aspects, the preparing the solution comprising 1.0-3.5 mg of $SnCl_2$ comprises combining 1N HCl and $SnCl_2$ to create a tin solution. In some aspects, the tin solution is diluted with pure water to create a stock solution. In some aspects, the stock solution is diluted with HCl. In some aspects, the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m}. In some aspects, the solution comprising technetium^{99m} comprises saline. In some aspects, the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m} and about 100 to about 300 μL saline. In some aspects, the technetium^{99m} is in the form of pertechnetate.

[0038] In some aspects, the methods comprise measuring radiopurity of the labeled amyloid-reactive peptide after step (c) by reverse phase high performance liquid chromatography (HPLC). In some aspects, wherein the radiopurity of the labeled amyloid-reactive peptide is greater than about 90%, greater than about 95% or greater than about 99%.

[0039] In some aspects, the integrity of the amyloid-reactive peptide before adding the radio label is the same as the integrity of the labeled amyloid-reactive peptide. In some aspects, the integrity of the amyloid-reactive peptide labeled and the amyloid-reactive peptide relates to the proportion of degraded peptide. In some aspects, the labeled amyloid-reactive peptide is not significant degraded. In some aspects, the labeled amyloid-reactive peptide does not cause an adverse reaction when administered to an individual.

[0040] In some aspects, a peptide comprising the amyloid-reactive peptide and an N-terminal leader sequence is administered to the individual. In some aspects, the peptide comprising the amyloid reactive peptide comprises the amino acid sequence set forth in SEQ ID NO: 100. In some aspects, the technetium^{99m} detectable label is bound to one or more amino acids at positions 1 to 6 of the amino acid sequence set forth in SEQ ID NO: 100.

[0041] Also provided herein is a peptide comprising the amino acid set forth in SEQ ID NO: 100, wherein the peptide comprises a technetium^{99m} detectable label bound to one or more amino acids at positions 1 to 6.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] The drawings illustrate certain features and advantages of this disclosure. These embodiments are not intended to limit the scope of the appended claims in any manner.

[0043] **FIG. 1** depicts exemplary structure of a radio labeled peptide.

[0044] **FIGs. 2A-2B** depicts exemplary whole body planar scintigraphic images of a healthy participant (**FIG. 2A**) and a patient with ATTR amyloidosis (**FIG. 2B**).

[0045] **FIGs. 3A-3C** depicts exemplary SPECT/CT of a healthy participant, **FIG. 3A** (axial view), **FIG. 3B** (coronal view), **FIG. 3C** (sagittal view).

[0046] **FIGs. 4A-4C** depicts exemplary SPECT/CT of a patient with ATTR amyloidosis, **FIG. 4A** (axial view), **FIG. 4B** (coronal view), **FIG. 4C** (sagittal view).

[0047] **FIG. 5** depicts^{99m}Tc-p5+14 uptake in representative regions of the heart on SPECT/CT axial images in healthy subjects, subjects with ATTRwt and subjects with ATTRv amyloidosis.

[0048] **FIG. 6** depicts representative ^{99m}Tc-p5+14 uptake in CT, SPECT/CT and SPECT images of a pulmonary lesion of a patient with ATTR amyloidosis.

[0049] **FIG. 7** depicts representative ^{99m}Tc-p5+14 and ^{99m}Tc-PYP uptake in SPECT/CT images in a patient with ATTR.

[0050] **FIG. 8** depicts representative ^{99m}Tc-p5+14 uptake in SPECT/CT images of the myocardium of a patient with biopsy-proven cardiac ATTR amyloidosis.

[0051] **FIGs. 9A-9C** depict uptake of ^{99m}Tc-p5+14 and ^{99m}Tc-PYP Heart (H):Right Atrium(RA) (max units), H:Aorta (mean units), H:RA (max units), and H:Aorta (max units) measured using SPECT/CT images for subjects with ATTRv (**FIG. 9A**), ATTRwt **(FIG. 9B),** and AL **(FIG. 9C)**.

[0052] **FIG. 10** depicts uptake of radio tracer uptake for ^{99m}Tc-p5+14 and ^{99m}Tc-PYP in subjects with amyloidosis.

[0053] **FIGs. 11A-11C** depict correlations between radio tracer uptake calculated from whole body (WB) planar images of subjects with cardiac amyloidosis. **FIG. 11A** depicts a correlation between of ^{99m}Tc-p5+14 uptake (Y axis) in the heart and ^{99m}Tc-PYP (X axis) in the heart. **FIG. 11B** depicts a correlation between of ^{99m}Tc-p5+14 uptake in the lung and muscles (Y axis) and ^{99m}Tc-p5+14 in the heart (X axis). **FIG. 11C** depicts a correlation between of ^{99m}Tc-PYP uptake in the lung and muscles (Y axis) and ^{99m}Tc-PYP in the heart (X axis).

[0054] **FIG. 12** depicts representative ^{99m}Tc-p5+14 uptake in whole body planar gamma scintigraphy (PGS)of a patient with AL amyloidosis.

[0055] **FIG. 13** depicts representative ^{99m}Tc-p5+14 uptake in SPECT, SPECT/CT and CT images of the heart, liver, and spleen of a patient with AL amyloidosis.

[0056] **FIG. 14** depicts representative ^{99m}Tc-p5+14 uptake in SPECT/CT, SPECT, and CT images of the heart of a patient with AL amyloidosis.

[0057] **FIGs. 15A-15D** depict representative ^{99m}Tc-p5+14 uptake in multiple patients with AL amyloidosis. **FIG. 15A, FIG. 15B**, and **FIG. 15C** depict anterior and posterior whole body PGS imaging for three patients with AL amyloidosis. **FIG. 15D** depicts head and neck PGS imaging for the three patients with AL amyloidosis.

[0058] **FIG. 16** depicts representative ^{99m}Tc-p5+14 uptake in SPECT/CT and CT images of the heart and a lung lesion of a patient with AL amyloidosis.

[0059] **FIG. 17** depicts cardiac ^{99m}Tc-p5+14 uptake in patients with ATTR amyloidosis 1 hour and 3 hours after injection. The error bars represent mean and standard deviation and the ns indicates no significant difference between the uptake ratio for patients 1 hour and 3 hours after injection of ^{99m}Tc-p5+14.

[0060] **FIGs. 18A-18B** depict cardiac uptake of ^{99m}Tc-p5+14 in healthy volunteers (HV) and uptake of ^{99m}Tc-p5+14 and ^{99m}Tc-PYP in patients with ATTR amyloidosis (**FIG. 18A**) and with AL amyloidosis (**FIG. 18B**). The error bars represent mean and standard deviation and the ns indicates no significant difference between the distributions, ** indicates $p<0.005$ and_*** indicates $p<0.0005$.

[0061] **FIGs. 19A-19D** depict ^{99m}Tc-p5+14 uptake in heart (**FIG. 19A**), liver (**FIG. 19B**), spleen (**FIG. 19C**), an kidney (**FIG. 19D**) in healthy volunteers, and patients with AL

amyloidosis or ATTR amyloidosis. AL amyloidosis patients denoted in black, healthy volunteers and ATTR amyloidosis patients are denoted in gray in all panels. Dotted lines in all panels depict interim diagnostic cutoffs based on mean (± 1.96*SD) organ uptake in healthy volunteers.

DETAILED DESCRIPTION

[0062] All publications, comprising patent documents, scientific articles and databases, referred to in this application are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication were individually incorporated by reference. If a definition set forth herein is contrary to or otherwise inconsistent with a definition set forth in the patents, applications, published applications and other publications that are herein incorporated by reference, the definition set forth herein prevails over the definition that is incorporated herein by reference.

[0063] As used herein, an "amino acid" or "amino acid residue" refers to any naturally occurring amino acid, any non-naturally occurring amino acid, any modified including derivatized amino acid, or any amino acid mimetic known in the art. The amino acid may be referred by both their common three letter abbreviation and single letter abbreviation.

[0064] The terms amyloids, amyloid deposits, amyloid fibrils, and amyloid fibers refer to insoluble fibrous protein aggregates sharing specific structural traits. The protein aggregates have a tertiary structure, for example, that is formed by aggregation of any of several different proteins and that consists of an ordered arrangement of β sheets stacked perpendicular to a fiber axis. See Sunde *et al.*, J. Mol. Biol. (1997) 273:729-39. Abnormal accumulation of amyloids in organs may lead to amyloidosis. Although they are diverse in their occurrence, all amyloids have common morphologic properties in that they stain with specific dyes such as Congo red and have a characteristic red-green birefringent appearance in polarized light after staining. Amyloids also share common ultrastructural features and common x-ray diffraction and infrared spectra.

[0065] Amyloidosis refers to a pathological condition or disease characterized by the presence of amyloids, such as the presence of amyloid deposits. "Amyloid diseases" or "amyloidosis" are diseases associated with the formation, deposition, accumulation or persistence of amyloid fibrils. Such diseases include, but are not limited to, Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, and cerebral beta-amyloid angiopathy. Other amyloid diseases such as systemic AA amyloidosis, AL

amyloidosis, ATTR amyloidosis, ALECT2 amyloidosis, and IAPP amyloidosis of type II diabetes are also amyloid diseases.

[0066] As used herein, the term "carriers" includes pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell, tissue, mammal, or subject being exposed thereto at the dosages and concentrations employed. Often the pharmaceutically acceptable carrier is an aqueous pH buffered solution. Examples of pharmaceutically acceptable carriers include without limitation buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween®, polyethylene glycol (PEG), and Pluronics®.

[0067] As used herein, the term "effective amount" or "suitable amount" is an amount sufficient to effect beneficial or desired clinical or biochemical results. An effective amount can be administered one or more times. For purposes of this invention, an effective amount of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label or detection is an amount that is sufficient to bind to and allow detection of amyloids.

[0068] As used herein, the term "imaging agent" or "contrast agent" which terms may be used interchangeably, refers to any agent which may be used in connection with methods for imaging an internal region of a subject and/or diagnosing the presence or absence of a disease in a subject by the application and/or detection of an energy source. Exemplary imaging agents include contrast agents for use in connection with ultrasound, magnetic resonance imaging, radionuclide imaging, or x-ray (including computed tomography) imaging of a patient, and the compositions described herein.

[0069] As used herein, the term "mammal" for purposes of the present invention refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, and so on. In some embodiments, the mammal is human.

[0070] As used herein, the term "peptide" refers to any peptide or peptidomimetic structure comprising or consisting of two or more amino acids, including chemical modifications and derivatives of amino acids.

[0071] As used herein, the term "purified" or "isolated" molecule refers to biological or synthetic molecules that are removed from their natural environment and are isolated or separated and are free from other components with which they are naturally associated.

[0072] As used herein, the term "specifically binds" refers to a non-random binding reaction between two molecules, for example between an amyloid-reactive peptide and an amyloid. The term "specifically binds" may be used interchangeably with "selectively targets" or "selectively associates."

[0073] As used herein, the term "selectively targets" or "selectively associates" with reference to amyloids, refers to, for example, the selective localization or binding between an amyloid-reactive peptide and an amyloid compared to a non-amyloid protein. An amyloid-reactive peptide can selectively target multiple types of amyloid.

[0074] As used herein, the term "subject" refers to a vertebrate. The vertebrate may be a mammal, for example, a human. The subject may be a human patient.

[0075] As used here, the term "amyloid-reactive peptide" is a peptide that reacts with or binds to amyloid.

[0076] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

I. OVERVIEW

[0077] The rates of early mortality in newly diagnosed amyloid-related diseases suggest there continue to be significant delays in diagnosis (Muchtar E, Gertz MA, Kumar SK, *et al. Blood.* 2017;129(15):2111-2119). For example, nearly 20% of patients succumb to AL amyloidosis within 6 months of diagnosis, and this statistic has shown no improvement in 40 years, suggesting, that patients who are diagnosed at an advanced state cannot be helped despite major advances in therapy for this disease (Hasib Sidiqi, M, and Morie A Gertz. Blood cancer journal vol. 11,5 90. 15 May. 2021). Current anatomic imaging methods, including echocardiography and cardiac magnetic resonance imaging, provide valuable structural and functional information once a diagnosis of amyloidosis has been established. ^{99m}Tc-PyP and similar bone-seeking agents are used for detecting cardiac amyloid; however, their relationship

with amyloid fibrils is not well understood. Therefore, a non-invasive imaging method using a reagent that directly binds amyloid deposits, is quantifiable, and can detect cardiac amyloidosis before the onset of overt anatomic changes and organ dysfunction would be of significant clinical benefit.

[0078] Provided herein are methods for diagnosing, estimating cardiac burden, and treating amyloid disease comprising the administration of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. The methods provide a non-invasive imaging method using a reagent that binds directly to amyloid deposits with numerous significant clinical and technical advances compared to previous methods. Detection of the amyloid-reactive peptide conjugated to a technetium^{99m} detectable label allows for diagnosis and treatment of patients who have previously tested negative for an amyloid related disease. For example a patient who received a false negative test for an amyloid related disease with imaging of the ^{99m}Tc-PyP agent may receive a true positive using the methods described herein. The patients may also receive false negative tests for an amyloid related disease because the pharmaceutical agent use to detect amyloid is not detectable in certain organs. For example, an amyloid-reactive peptide conjugated to technetium^{99m} may outperform an amyloid-reactive peptide conjugated to ^{124}I in detecting amyloid in organs such as the esophagus, stomach, thyroid gland, and salivary gland. Detection of amyloid in the thyroid and salivary gland are of particular clinical significant because detection of amyloid in these organs has been used to differentiate between different amyloid-related diseases. Thus, the methods provided herein provide increased diagnostic precision as compared to other methods.

[0079] Earlier detection of amyloid related diseases is also a benefit of the methods described herein. Detection of the amyloid-reactive peptide conjugated to a technetium^{99m} detectable label with noninvasive imaging is possible within 3 hours of injecting the peptide. Early detection allows for increased clinical efficiency because a patient can receive the injection and the imaging in a single visit.

[0080] Provided herein are methods for the diagnosis, estimating cardiac burden, and treatment of amyloid disease. In some embodiments, the methods comprise the administration of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the methods further comprise detecting the label in one or more organs or tissues. In some embodiments, the methods provided herein are able to differentiate between different

types of systemic amyloidosis such as AL and ATTR, based upon the organ distribution pattern of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the method comprises providing a prognosis for a type of amyloid disease based upon the organ distribution pattern of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the method comprises providing a diagnosis of a type of amyloid disease based upon the organ distribution pattern of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the method further comprises selecting a therapy based upon the type of amyloid disease. Provided herein are methods of producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual.

[0081] Provided herein are methods for the diagnosis, estimating cardiac burden, and treatment of amyloid disease. In some embodiments, the methods comprise the administration of an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the methods further comprise detecting the label in heart and blood between about 0.1 hours and about 3 hours after administration of the amyloid-reactive peptide. The methods may comprise estimating cardiac amyloid burden based on the ratio of the technetium^{99m} detectable label in the heart and blood. The cardiac amyloid burden may be correlated with one or more biomarkers associated with amyloid-related disease. Cardiac amyloid burden is the amount of amyloid in the heart based on the uptake of the technetium^{99m} labeled amyloid-reactive peptide in the amyloid. A higher cardiac amyloid burden may indicate more extensive amyloid and later stage amyloid disease. Cardiac amyloid burden estimated using the methods described herein can be used in diagnosing an amyloid related disease, staging the disease, selecting treatment for an individual diagnosed with an amyloid related disorder, and in providing a prognosis for an individual with an amyloid related disease.

II. METHODS OF LABELING

[0082] In some embodiments, provided herein are methods of producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual, the method comprising (a) combining a solution comprising 10-30 µg of the amyloid-reactive peptide and a solution comprising 1.0-3.5 mg of $SnCl_2$ with a solution comprising technetium^{99m} to produce a labeling composition; (b) incubating the labeling composition to produce a labeled amyloid reactive peptide; and (c) adding a quencher to the labeling composition within five

minutes of the combining to produce a quenched composition comprising a labeled amyloid-reactive peptide with technetium^{99m}.

[0083] In some embodiments, provided herein are methods of producing a labeled amyloid-reactive peptide comprising an amino acid sequence set forth as any one of SEQ ID NOs: 1-14, with technetium^{99m} suitable for administration to an individual, the method comprising (a) combining a solution comprising 10-30 μg of the amyloid-reactive peptide and a solution comprising 1.0-3.5 mg of $SnCl_2$ with a solution comprising technetium^{99m} to produce a labeling composition; (b) incubating the labeling composition to produce a labeled amyloid reactive peptide; and (c) adding a quencher to the labeling composition within five minutes of the combining to produce a quenched composition comprising a labeled amyloid-reactive peptide with technetium^{99m}.

[0084] In some embodiments, provided herein are methods of producing a labeled amyloid-reactive peptide comprising SEQ ID NO:13, with technetium^{99m} suitable for administration to an individual, the method comprising (a) combining a solution comprising 10-30 μg of the amyloid-reactive peptide and a solution comprising 1.0-3.5 mg of $SnCl_2$ with a solution comprising technetium^{99m} to produce a labeling composition; (b) incubating the labeling composition to produce a labeled amyloid reactive peptide; and (c) adding a quencher to the labeling composition within five minutes of the combining to produce a quenched composition comprising a labeled amyloid-reactive peptide with technetium^{99m}.

[0085] In some embodiments, the labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual is any of the labeled amyloid-reactive peptides described herein. In some embodiments, the labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual is SEQ ID NO: 13 labeled with ^{99m}Tc.

[0086] In some embodiments, the method of producing a labeled amyloid-reactive peptide with technetium^{99m} comprises labeling an amino acid that is at least 80%, 85%, 90% or more identical to the amino acid sequence set forth as any one of SEQ ID NOs: 1-14, such as at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence set forth as any one of SEQ ID NOs: 1-14. In some embodiments, the a labeled amyloid-reactive peptide comprises SEQ ID NO:13.

[0087] In some embodiments, the method of producing a labeled amyloid-reactive peptide with technetium^{99m} comprises preparing a $SnCl_2$ solution. In some embodiments,

preparing a $SnCl_2$ solution comprises combining 1N HCl and $SnCl_2$ to create a tin solution. In some embodiments, preparing a $SnCl_2$ solution comprises combining about 30 1N HCl and about 3 mg $SnCl_2$ to create a tin solution. In some embodiments, preparing a $SnCl_2$ solution comprises combining about 15-35 1N HCl and about 2-6 mg $SnCl_2$ to create a tin solution.

[0088] In some embodiments, the tin solution is diluted with pure water to create a stock solution. In some embodiments, between about 2 mL and about 4 mL of pure water is used. In some embodiments, between about 2 mL and about 3 mL, about 2.5 mL and about 3 mL or about 2 mL and about 2.5 mL of pure water is used. In some embodiments, about 2.97 mL of pure water is used. In some embodiments, the stock solution is diluted with HCl. In some embodiments, the stock solution has a concentration of about 1 mg/mL $SnCl_2.2H_2O$ in 0.01 N HCl.

[0089] In some embodiments, the $SnCl_2$ solution comprises about 1.0-3.5 mg of $SnCl_2$. In some embodiments, the $SnCl_2$ solution comprises about 1.0 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg or about 3.5 mg of $SnCl_2$. In some embodiments, the $SnCl_2$ solution comprises between about 1.0 mg and about 3.5 mg, between about 1.5 mg and about 3.0 mg, or between about 2.0 and about 2.5 mg $SnCl_2$.

[0090] In some embodiments, the method of producing a labeled amyloid-reactive peptide with technetium^{99m} comprises combining a solution comprising 10-30 µg of the amyloid-reactive peptide and a solution comprising 1.0-3.5 mg of $SnCl_2$ with a solution comprising technetium^{99m} to produce a labeling composition. In some embodiments, the solution comprising the amyloid-reactive peptide comprises 10-30 µg of the amyloid-reactive peptide or 15-25 µg of the amyloid-reactive peptide. In some embodiments, the solution comprising the amyloid-reactive peptide comprises about 10 µg, about 15 µg, about 20 µg, or about 25 µg of the amyloid-reactive peptide or about 10 µg to about 20 µg, about 15 µg to about 20 µg, or about 10 µg to about 25 µg.

[0091] In some embodiments, provided herein is a method of producing a labeled amyloid-reactive peptide with technetium^{99m} comprises combining a solution comprising 10-30 µg of the amyloid-reactive peptide and a solution comprising 1.0-3.5 mg of $SnCl_2$ with a solution comprising technetium^{99m} to produce a labeling composition, wherein the amyloid-reactive peptide comprises the amino acid sequence set forth in SEQ ID NO:13. In some embodiments, the solution comprising the amyloid-reactive peptide comprises 10-30 µg of the amyloid-reactive

peptide or 15-25 μg of the amyloid-reactive peptide. The amyloid-reactive peptide comprises an amino acid that is at least 80%, 85%, 90% or more identical to the amino acid sequence set forth as any one of SEQ ID NOs:1-14, such as at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence set forth as any one of SEQ ID NOs: 1-14. In some embodiments, the a amyloid-reactive peptide comprises SEQ ID NO:13.

[0092] In some embodiments, the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m}. In some embodiments, the solution comprising technetium^{99m} comprises about 1, about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45 or about 50 mCi technetium^{99m}. In some embodiments, the solution comprising technetium^{99m} comprises between about 1 and about 50, between about 5 and about 50, between about 10 and about 50, between about 15 and about 50, between about 20 and about 50, between about 25 and about 50, between about 30 and about 50, between about 35 and about 50, or between about 40 and about 50 mCi technetium^{99m}. In some embodiments, the solution comprising technetium^{99m} comprises between about 1 and about 50, between about 1 and about 45, between about 1 and about 40, between about 1 and about 35, between about 1 and about 30, between about 1 and about 25, between about 1 and about 20, between about 1 and about 15, or between about 1 and about 10 mCi technetium^{99m}.

[0093] In some embodiments, the solution comprising technetium^{99m} comprises saline. In some embodiments, the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m} and about 100 to about 300 μL saline. In some embodiments, the solution comprising technetium^{99m} comprises about 100, about 150, about 200, about 250, or about 300 μL saline. In some embodiments, the solution comprising technetium^{99m} comprises between about 100 and about 300, about 100 and about 250, about 100 and about 200, about 100 and about 150, about 150 and about 300, about 200 and about 300, or about 250 and about 300 μL saline. In some embodiments, the saline is phosphate buffered saline. In some embodiments, the phosphate buffered saline is basic. In some embodiments, the phosphate buffered saline has a pH of between 7 and 8. In some embodiments, the phosphate buffered saline has a pH of about 7.9, such as 7.96.

[0094] In some embodiments, the technetium^{99m} is in the form of pertechnetate. In some embodiments, the technetium^{99m} is in the form of ^{99m}TcO4-.

[0095] In some embodiments, the method of producing a labeled amyloid-reactive peptide with technetium^{99m} comprises incubating the labeling composition to produce a labeled amyloid reactive peptide. In some embodiments, the method comprises incubating a labeling composition comprising an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 for less than about five minutes. In some embodiments, the labeling composition is incubated for about less than five minutes, about less than four minutes, about less than 3 minutes, or about less than two minutes. In some embodiments, the labeling composition is incubated for about 2 minutes. In some embodiments, the labeling composition is incubated for between about 1 and about 5, about 2 and about 5, about 3 and about 5, about 4 and about 5, about 1 and about 4, about 1 and about 3, or about 1 and about 2 minutes.

[0096] In some embodiments, the method of producing a labeled amyloid-reactive peptide with technetium^{99m} comprises adding a quencher to the labeling composition within five minutes of combining to produce a quenched composition comprising a labeled amyloid-reactive peptide with technetium^{99m}. In some embodiments, the method comprises adding a quencher to a labeling composition comprising an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 for within about five minutes. In some embodiments, the method comprises adding a quencher within about 5 minutes, about 4 minutes, about 3 minutes, or about 2 minutes. In some embodiments, the method comprises adding a quencher within between about 1 and about 5, about 2 and about 5, about 3 and about 5, about 4 and about 5, about 1 and about 4, about 1 and about 3, or about 1 and about 2 minutes.

[0097] In some embodiments, the quencher is of 0.5 M sodium dibasic phosphate. In some embodiments, the quencher is a solution with strong buffering capacity. In some embodiments, the quencher can be used to achieve a reaction pH of about 7, about 6, or about 8. In some embodiments, the quencher can be used to achieve a reaction pH of between about 7 and about 8, about 6 and about 7, or about 6 and about 8.

[0098] In some embodiments, the method of producing a labeled amyloid-reactive peptide with technetium^{99m} comprises diluting the quenching composition. In some embodiments, diluting takes place immediately. In some embodiments, the quenching composition is diluted with phosphate buffered saline. In some embodiments, the quenching composition in sterile filtered.In some embodiments, the method further comprises purifying the labeled amyloid-reactive peptide from the quenched composition. In some embodiments,

purifying the labeled amyloid-reactive peptide comprises purifying the labeled amyloid-reactive peptide from the free technetium^{99m} label. In some embodiments, purifying Is performed with any size-exclusion chromatography known in the art, including but not limited to columns or spin columns.

[0099] In some embodiments, the labeled peptide is suitable for administration to an individual. In some embodiments, suitable for administration to an individual relates to the ability to inject the labeled amyloid-reactive peptide into the individual for use in diagnosing an amyloid-related disease. In some embodiments, suitable for administration to an individual relates to the ability to inject the labeled amyloid-reactive peptide into the individual for use in diagnosing and treating an amyloid-related disease. In some embodiments, the labeled amyloid-reactive peptide does not cause an adverse reaction when administered to an individual. In some embodiments, the labeled amyloid-reactive peptide has a sufficient amount of label for detection using SPECT/CT. In some embodiments, the labeled amyloid-reactive peptide does not undergo degradation during the labeling.

[0100] In some embodiments, provided herein are methods of producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual comprises measuring the radiopurity of the labeled amyloid-reactive peptide. In some embodiments, measuring the radiopurity is performed by reverse phase high performance liquid chromatography (HPLC). In some embodiments, measuring the radiopurity is performed by instant thin layer chromatography.

[0101] In some embodiments, the radiopurity of the labeled amyloid-reactive peptide is greater than about 90%, greater than about 95% or greater than about 99%. In some embodiments, the radiopurity of the labeled amyloid-reactive peptide is between than about 90% and about 100%, between about 95% and 100%, between about 99% and about 100%. In some embodiments, the radio purity of the labeled amyloid-reactive peptide is greater than about 90%, wherein the amyloid-reactive peptide comprises the amino acid sequence set forth in SEQ ID NO:13.

[0102] In some embodiments, provided herein are methods of producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual comprises measuring the integrity of the amyloid-reactive peptide before adding the radio label and of the labeled amyloid-reactive peptide. of the In some embodiments, the integrity of the

amyloid-reactive peptide before adding the radio label is the same as the integrity of the labeled amyloid-reactive peptide. In some embodiments, integrity of the amyloid-reactive peptide labeled and the amyloid-reactive peptide relates to the proportion of degraded peptide. In some embodiments, labeled amyloid-reactive peptide is not significant degraded. In some embodiments, the amyloid-reactive peptide is not less than about 75%, not less than about 80%, not less than about 85%, not less than about 90% or not less than about 100% degraded. In some embodiments, the amyloid-reactive peptide between about 75% and about 100%, about 80% and about 100%, about 855 and about 100%, about 90% and about 100%, or about 95% and about 100% degraded.

[0103] In some embodiments, the level of the amyloid-reactive peptide and the labeled amyloid-reactive peptide degraded is measured HPLC. In some embodiments, the level of the amyloid-reactive peptide and the labeled amyloid-reactive peptide degraded is measured by mass spectrometry.

III. METHODS OF DIAGNOSIS

[0104] Provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease.

[0105] In some embodiments, provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease.

[0106] In some embodiments, provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual between about 0.1 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease.

[0107] In some embodiments, provided herein are methods for estimating cardiac amyloid burden in an individual with an amyloid-related disease. In some embodiments, the methods comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label in heart and blood of the individual between about 0.1 and about 3 hours after administering the amyloid-reactive peptide; and estimating a cardiac amyloid burden based on the ratio of the technetium^{99m} detectable label detected in the heart and the blood of the individual. In some embodiments, the cardiac amyloid burden is the ratio of the technetium^{99m} detectable label detected in the heart and the blood of the individual.

[0108] In some embodiments, cardiac amyloid burden may indicate disease progression and may be used for diagnosis, prognosis, staging the disease and treatment selection. Increased cardiac burden may indicate more extensive amyloid an later stage disease. In some embodiments, the cardiac amyloid burden correlates with one or more biomarkers associated with the amyloid-related disease. The biomarkers associated with amyloid-related disease may comprise Troponin T, NTproBNP, urine protein levels, UACR, EGFR, interventricular septal wall thickness (IVS), left ventricular (LV) wall thickness, global longitudinal strain (GLS), and/or alkaline phosphatase levels.

[0109] Provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more

organs or tissues selected from a group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand in the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0110] Provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in an SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues selected from a group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand in the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0111] Provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue in the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the

individual has the amyloid disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0112] Provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in an SEQ ID NOs 13 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue in the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0113] Provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland in the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0114] Provided herein are methods of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in an SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland in the individual between about 0.5 and about 3 hours after administering the amyloid-reactive

peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0115] In some embodiments, the methods comprise detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual can occurs about 0.5, about 1, about 1.5, about 2, about 2.5 or about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual can occurs between about 0.5 and about 3 hours, between about 1 and about 3 hours, between about 1.5 and about 3 hours, between about 2 and about 3 hours, or between about 2.5 and about 3 hours. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual can occurs between about 0.5 and about 2.5 hours, between about 0.5 and about 2 hours, between about 0.5 and about 1.5 hours, or between about 0.5 and about 1 hours.

[0116] In some embodiments, the methods comprise detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual between about 0.1 and about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the methods comprise detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual can occurs about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 1, about 1.5, about 2, about 2.5 or about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the method comprise detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual can occurs between about 0.1 and about 3 hours, between about 0.2 and about 3 hours, between about 0.3 and about 3 hours, between about 0.4 and about 3 hours, between about 0.5 and about 3 hours, between about 1 and about 3 hours, between about 1.5 and about 3 hours, between about 2 and about 3 hours, or between about 2.5 and about 3 hours. In some embodiments, the methods comprise detecting amyloid-reactive

peptide by detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual can occurs between about 0.1 and about 2.5 hours, between about 0.1 and about 2 hours, between about 0.1 and about 1.5 hours, between about 0.1 and about 1 hour, between about 0.1 and about 0.5 hours, between about 0.1 and about 0.4 hours, between about 0.1 and about 0.3 hours or between about 0.1 and about 0.2 hours.

A. Amyloid-reactive peptides

[0117] In some embodiments, the methods for diagnosing a type of amyloid disease comprise administering an amyloid-reactive peptide conjugated to a detectable label.

[0118] In some embodiments, the methods for diagnosing a type of amyloid disease comprise administering an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the amyloid-reactive peptide comprises an amino acid sequence that is at least 80%, 85%, 90% or more identical to the amino acid sequence set forth as any one of SEQ ID NOs: 1-14, such as at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to the amino acid sequence set forth as any one of SEQ ID NOs: 1-14. In some embodiments, amyloid-reactive peptides used with the methods described herein comprise or consist of from about 10 to 55 amino acids. The amyloid-reactive peptides of the present invention may, for example, comprise or consist of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, or 55 amino acids. Such peptides are described, for example, in international patent application WO2016032949, which is hereby incorporated herein in its entirety. In some embodiments, the methods for diagnosing an amyloid disease comprise an amyloid-reactive peptide with an amino acid sequence as set forth in SEQ ID NO:13. In some embodiments, the methods for diagnosing an amyloid disease comprise an amyloid-reactive peptide with an amino acid sequence as set forth in SEQ ID NO:13, conjugated to a technetium^{99m} detectable label.

Table 1. Example Amyloid-Reactive Peptide Sequences

PEPTIDE	PRIMARY SEQUENCE:	SEQ ID NO
P5	KAQKA QAKQA KQAQK AQKAQ AKQAK Q	SEQ ID NO: 1
P5R	RAQRA QARQA RQAQR AQRAQ ARQAR Q	SEQ ID NO: 2
P5G	GAQGA QAGQA GQAQG AQGAQ AGQAG Q	SEQ ID NO: 3

P8	KAKAK AKAKA KAKAK	SEQ ID NO: 4
P9	KAQAK AQAKA QAKAQ AKAQA KAQAK AQAK	SEQ ID NO: 5
P19	KAQQA QAKQA QQAQK AQQAQ AKQAQ Q	SEQ ID NO: 6
P20	QAQKA QAQQA KQAQQ AQKAQ AQQAK Q	SEQ ID NO: 7
P31	KAQKA QAKQA KQAQK AQKAQ AKQAK Q	SEQ ID NO: 8
P37	KTVKT VTKVT KVTVK TVKTV TKVTK V	SEQ ID NO: 9
P42	VYKVK TKVKT KVKTK VKT	SEQ ID NO: 10
P43	AQAYS KAQKA QAKQA KQAQK AQKAQ AKAK Q	SEQ ID NO: 11
P44	AQAYA RAQRA QARQA RQAQR AQRAQ ARQAR Q	SEQ ID NO: 12
P5+14	KAQKA QAKQA KQAQK AQKAQ AKQAK QAQKA QKAQA KQAKQ	SEQ ID NO: 13
P5R+14	RAQRA QARQA RQAQR AQRAQ ARQAR QAQRA QRAQA RQARQ	SEQ ID NO: 14

[0119] The amino acids forming all or a part of the amyloid-reactive peptides used with the present methods may be stereoisomers and modifications of naturally occurring amino acids, non-naturally occurring amino acids, post-translationally modified amino acids, enzymatically synthesized amino acids, derivatized amino acids, constructs or structures designed to mimic amino acids, and the like. The amino acids forming the peptides of the present invention may be one or more of the 20 common amino acids found in naturally occurring proteins, or one or more of the modified and unusual amino acids. The amyloid-reactive peptides used with the methods described herein may be made by any technique known to those of skill in the art, including chemical synthesis or recombinant means using standard molecular biological techniques.

[0120] The peptides of the present invention may also comprise one or more modified amino acids. The modified amino acid may be a derivatized amino acid or a modified and unusual amino acid. Examples of modified and unusual amino acids include but are not limited to, 2-Aminoadipic acid (Aad), 3-Aminoadipic acid (Baad), β-Amino-propionic acid (Bala, β-alanine), 2-Aminobutyric acid (Abu, piperidinic acid), 4-Aminobutyric acid (4Abu), 6-

Aminocaproic acid (Acp), 2-Aminoheptanoic acid (Ahe), 2-Aminoisobutyric acid (Aib), 3-Aminoisobutyric acid (Baib), 2-Aminopimelic acid (Apm), 2,4-Diaminobutyric acid (Dbu), Desmosine (Des), 2,2′-Diaminopimelic acid (Dpm), 2,3-Diaminopropionic acid (Dpr), N-Ethylglycine (EtGly), N-Ethylasparagine (EtAsn), Hydroxylysine (Hyl), allo-Hydroxylysine (AHyl), 3-Hydroxyproline (3Hyp), 4-Hydroxyproline (4Hyp), Isodesmosine (Ide), allo-Isoleucine (Alle), N-Methylglycine (MeGly, sarcosine), N-Methylisoleucine (Melle), 6-N-Methyllysine (MeLys), N-Methylvaline (MeVal), Norvaline (Nva), Norleucine (Nle), and Ornithine (Orn).

[0121] Other examples of modified and unusual amino acids are described generally in Synthetic Peptides: A User's Guide, Second Edition, April 2002, Edited Gregory A. Grant, Oxford University Press; Hruby V J, Al-obeidi F and Kazmierski W: Biochem J 268:249-262, 1990; and Toniolo C: Int J Peptide Protein Res 35:287-300, 1990; the teachings of all of which are incorporated herein by reference.

[0122] In certain embodiments, the peptides of the present invention may comprise or consist of the following amino acid sequence: SRAQRAQARQARQAQRAQRAQARQARQ. (SEQ ID NO: 17).

[0123] The peptides of the present invention may be a fusion protein comprising a second peptide as a leader sequence at the amino terminus, such as CGGY (SEQ ID NO: 18) or GGGYS (SEQ ID NO: 19) for labeling with an agent for detection. Accordingly, in some embodiments, the amyloid-reactive peptide may have at most 55 amino acids and comprise an amino acid sequence as set forth in SEQ ID NO: 17.
CGGYSRAQRAQARQARQAQRAQRAQARQARQ. (SEQ ID NO: 20)

[0124] In some embodiments, provided herein is a peptide comprising an amyloid reactive peptide fused to an N-terminal leader sequence. In some embodiments, the leader sequence comprises the amino acid sequence GGGYS (SEQ ID NO: 19). In some embodiments, provided herein is a peptide comprising an amyloid reactive peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1-14 and the N-terminal leader sequence GGGYS. In some embodiments, provided herein is a peptide comprising the amino acid sequence GGGYS KAQKA QAKQA KQAQK AQKAQ AKQAK QAQKA QKAQA KQAKQ (SEQ ID NO: 100). In some embodiments, the peptide comprises the amino acid sequence set forth in SEQ ID NO: 100 and is conjugated to a detectable label. In some

embodiments, the detectable label is bound to one or more of amino acids 1-6 of SEQ ID NO: 100. In some embodiments, the detectable label is bound to the N-terminal leader sequence. In some embodiments, the peptide comprises the amino acid sequence set forth in SEQ ID NO: 100 and is conjugated to a technetium^{99m} detectable label. In some embodiments, the technetium^{99m} detectable label is bound to one or more of amino acids 1-6 of SEQ ID NO: 100. In some embodiments, the detectable label is bound to the N-terminal leader sequence. The fusion protein may comprise other leader sequences such as a cell penetrating peptide (CPP) or a blood brain barrier (BBB) translocating peptide.

[0125] The present invention also provides other peptides and fusion proteins that are rich in positively charged amino acids for imaging amyloids.

[0126] The peptides of the present invention may be made by any technique known to those of skill in the art, including chemical synthesis, recombinant means using standard molecular biological techniques, or the isolation of peptides from natural sources. The peptides may be synthesized in solution or on a solid support in accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. (See, for example, Stewart and Young, Solid Phase Peptide Synthesis, 2d ed. Pierce Chemical Co., 1984; Tam et al., J. Am. Chem. Soc., 105:6442, 1983; Merrifield, Science, 232: 341-347, 1986; and Barany and Merrifield, The Peptides, Gross and Meienhofer, eds., Academic Press, New York, pp. 1-284, 1979, each is incorporated herein by reference in its entirety.)

[0127] Alternatively, recombinant DNA technology may be employed wherein a nucleotide sequence which encodes a peptide of the invention is inserted into an expression vector, transformed or transfected into an appropriate host cell, cultivated under conditions suitable for expression, and isolating the peptide.

[0128] In certain embodiments, amyloid-reactive peptide conjugated to a technetium^{99m} detectable label may be a naturally occurring peptide and may be obtained by isolation or purification from its natural sources. Protein purification techniques involve, at one level, the homogenization and crude fractionation of the cells, tissue or organ to peptide and non-peptide fractions. Other protein purification techniques include, for example, precipitation with ammonium sulfate, polyethylene glycol (PEG), antibodies and the like, or by heat denaturation, followed by: centrifugation; chromatography steps such as ion exchange, gel filtration, reverse

phase, hydroxylapatite and affinity chromatography; isoelectric focusing; gel electrophoresis, for example polyacrylamide gel electrophoresis; and combinations of these and other techniques

[0129] Various chromatographic techniques include but are not limited to ion-exchange chromatography, gel exclusion chromatography, affinity chromatography, immunoaffinity chromatography, and reverse phase chromatography. A particularly efficient method of purifying peptides is fast performance liquid chromatography (FPLC) or even high performance liquid chromatography (HPLC).

[0130] The order of conducting the various purification steps may be changed, or that certain steps may be omitted, and still result in a suitable method for the preparation of a substantially purified peptide. The peptides of the present invention may be a part of a polypeptide or protein and may be produced by biochemical or enzymatic fragmentation of the polypeptide or protein. Accordingly, the peptides of the present invention may be (a) naturally-occurring, (b) produced by chemical synthesis, (c) produced by recombinant DNA technology, (d) produced by biochemical or enzymatic fragmentation of larger molecules, (e) produced by methods resulting from a combination of methods a through d listed above, or (f) produced by any other means for producing peptides.

[0131] During chemical synthesis, the peptides may be modified at its N- or C-terminus, thereby providing for improved stability and formulation, resistance to protease degradation, and the like. Examples of modifications of amino acids include pegylation, acetylation, alkylation, formylation, amidation. Moreover, various amino acids which do not naturally occur along the chain may be introduced to improve the stability of the peptides.

[0132] Cysteine is also useful for facilitating the labeling of peptides of the present invention with biotin, fluorophores, or other ligands via conjugation. Moreover, a cysteine on the leader peptide allows the generation of covalently bound dimer molecules that might increase the relative affinity of the peptides for their targets.

B. Tc^{99m} detectable label

[0133] In some embodiments, the method for diagnosing a type of amyloid disease comprises administering an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. As used herein, conjugation may be covalent and/or non-covalent binding. In some embodiments, the method comprise administering an amyloid-reactive peptide conjugated to a

technetium^{99m} detectable label, wherein the technetium^{99m} detectable label is either covalently or non-covalently bound to the peptide.

[0134] In some embodiments, the methods for diagnosing a type of amyloid disease comprise administering an amyloid-reactive peptide comprising a radiolabel. In some embodiments, the radiolabel is ^{99m}Tc

[0135] In some embodiments, the radiolabeled amyloid-reactive peptide is a ^{99m}Tc -labelled amyloid-reactive peptide. In other embodiments, the method for diagnosing a type of amyloid disease comprise administering ^{99m}Tc -p5+14. In some embodiments the amyloid-reactive peptide comprises an amino acid sequence set forth in SEQ ID NO:13. In some embodiments, the amyloid-reactive peptide is conjugated to ^{99m}Tc. In some embodiments, method for diagnosing a type of amyloid disease comprises administering an the amyloid-reactive peptide comprising SEQ ID NO:13 conjugated to ^{99m}Tc.

[0136] In some embodiments, the method for diagnosing a type of amyloid disease comprises administering an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label at a dose of about 10 to about 25 mCi of Tc-99m. In some embodiments, the dose of Tc-99m is about 10, about 15, about 20, or about 25 mCi. In some embodiments, the dose of Tc-99m is between about 10 and about 20, about 10 and about 15, about 15 and about 25, about 20 and about 25 or about 15 and about 25 mCi. In some embodiments, the dose of Tc-99m is about less than 20 mCi, about less than 15 mCi, about less than 10 mCi, or about less than 5 mCi of Tc-99m. In some embodiments, the dose of Tc-99m is about 20 mCi.

[0137] In some embodiments, the method for diagnosing a type of amyloid disease comprises administering an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label at a dose of about 0.3 mg, 1 mg, 1.5 mg, or about 2 mg of amyloid-reactive peptide. In some embodiments, the dose of the amyloid-reactive peptide administered to the individual is about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, or about 2.0 mg of amyloid-reactive peptide. In some embodiments, the dose of the amyloid-reactive peptide administered to the individual is between about 0.3 and about 1.5, about 0.3 and about 0.5, about 0.3 and about 1, about 0.3 and 1.5, about 0.3 and 2, about 0.5 and about 1.0, about 1.0 and about 1.5, or about 1.5 and about 2 mg amyloid-reactive peptide. In some embodiments, the dose of the amyloid-reactive peptide administered to the individual is about less than 0.1, about less than

0.09, about less than 0.08, about less than 0.07, about less than 0.06, about less than 0.05 mg amyloid-reactive peptide.

[0138] In some embodiments, the amyloid-reactive peptide specifically binds to amyloid deposits. In some embodiments, the amyloid-reactive peptide is able to detect the presence, absence, or amount of amyloid in the subject. In some embodiments, the amyloid-reactive peptide cross-reacts to amyloid deposits formed by a number of different proteins. In some embodiments, the amyloid-reactive peptide binds to amyloid deposits formed by a variety of proteins and/or peptides. In some embodiments, the amyloid-reactive peptide binds to amyloid deposits formed by amyloid light chain (AL). In some embodiments, the amyloid-reactive peptide binds to amyloid formed by transthyretin (TTR) fibrils. In some embodiments, the amyloid-reactive peptide binds to amyloid formed by serum amyloid protein A (sAA). In some embodiments, the amyloid-reactive peptide binds to amyloidogenic forms of immunoglobulin light chain (AL), immunoglobulin heavy chain (AH), β_2-microglobulin ($A\beta_2M$), transthyretin variants (ATTR), apolipoprotein AI (AApoAI), apolipoprotein AII variants (AApoAII), apolipoprotein AIII variants (AApoAIII), gelsolin (AGel), lysozyme (ALys), leukocyte chemotactic factor (ALECT2), fibrinogen a variants (AFib), cystatin variants (ACys), calcitonin ((ACal), lactadherin (AMed), islet amyloid polypeptide (AIAPP), prolactin (APro), insulin (AIns), prior protein (APrP); α-synuclein (AαSyn), tau (ATau), atrial natriuretic factor (AANF), or IAAP, ALβ4, ALβ1 other amyloidogenic peptides.

[0139] In some embodiments, the amyloid-reactive peptide binds to heperan sulfate glycosaminoglycans (GAGs). In some embodiments GAGs are associated with amyloid deposits. Binding of GAGs to amyloid fibrils occurs mainly through electrostatic interactions involving the negative polyelectrolyte charges and positively charged side chains residues of aggregating protein. Similarly to catalyst for reactions, GAGs favor aggregation, nucleation and amyloid fibril formation functioning as a structural templates for the self-assembly of highly cytotoxic oligomeric precursors, rich in β-sheets, into amyloid fibrils. Moreover, the GAGs amyloid promoting activity can be facilitated through specific interactions via consensus binding sites between amyloid polypeptide and GAG molecules.

[0140] In some embodiments, the method comprises administering an amyloid-reactive peptide to an individual. In some embodiments, the amyloid-reactive peptide is administered in a pharmaceutical composition. In some embodiments, the composition

comprises an aqueous buffer. The compositions may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. The ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0141] The compositions may further comprise a carrier. The present invention also provides pharmaceutical compositions comprising one or more peptides and/or fusion peptides of the present invention. Such pharmaceutical compositions comprise an effective amount of the peptide or fusion peptide for binding to and detection of amyloids and a pharmaceutically acceptable carrier.

[0142] Pharmaceutically acceptable carriers include solid or liquid carriers or components which may be added to enhance or stabilize the composition, or to facilitate preparation of the composition include, without limitation, syrup, water, isotonic saline solution, 5% dextrose in water or buffered sodium or ammonium acetate solution, oils, glycerin, alcohols, among others. Examples of oils include those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, and sesame oil. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. Other suitable pharmaceutical carriers include but are not limited to include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, propylene, glycol, water, ethanol, flavoring agents, preservatives, coloring agents diluents, granulating agents, lubricants, binders, and the like.

[0143] Water may be the preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. Such compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The compositions can be

formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of other suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

[0144] Methods for imaging amyloids include but are not limited to magnetic resonance imaging (MRI), computed axial tomography (CAT) scanning, positron emission tomography (PET), ultrasonic imaging, x-rays, radionuclide imaging, single photon emission computed tomography (SPECT), and multiphoton microscopy.

[0145] The present invention provides a method for detecting amyloids in a subject. The method comprises administering a pharmaceutical composition comprising an effective amount of one or more peptides or fusion peptides of the present invention to a subject and detecting the peptides or fusion peptides bound to the amyloids. The peptides may be labeled with an imaging agent, such as a radioisotope. The peptide has specific binding affinity for the deposits and the binding is detectable. The binding of the peptides or fusion peptides to the amyloids may be detected by MRI, CAT scan, PET imaging, ultrasound imaging, SPECT imaging, X-ray imaging, fluorescence imaging, or radionuclide imaging.

[0146] In some instances, the methods for diagnosing a type of amyloid disease comprise administering to an individual a detectable amount of an amyloid-reactive reagent conjugated to technetium^{99m}. The detectable amount to be administered may be based on the type of detection to be performed. For example, in some embodiments, a detectable amount of an amyloid-reactive reagent or dye may be an amount sufficient to be detectable by imaging when administered to a subject. The detectable amount of the amyloid-reactive peptide to be administered to an individual may vary depending upon such factors as the age, sex and weight of the individual, the specific response of the individual, the dosimetry, the formulation, and instrument-related factors. Optimization of such factors is well within the level of skill in the art. The detectable amount of the amyloid-reactive peptide may also vary with the mode of administration of the amyloid-reactive peptide conjugated to technetium^{99m}.

[0147] In some instances, the amyloid-reactive agent is administered parenterally, paracancerally, transmucosally, tansdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitonealy, intraventricularly, or intracranially. In some instances, the

amyloid-reactive peptide is administered intravenously. In other instances, the amyloid-reactive peptide is administered intraperitonealy.

[0148] One of ordinary skill in the art will further appreciate that an effective amount of the amyloid-reactive peptide can be administered in a single dose, or can be achieved by administering multiple doses. In some instances, the administration of the amyloid-reactive peptide may further comprise administering a flushing solution. For example, a flushing solution, e.g. saline, may be administered after immediately after administration of the amyloid-reactive peptide, or after a set period of time after administration of the amyloid-reactive peptide. In other instances, the amyloid-reactive peptide may be metabolized and excreted a certain period of time after administration.

C. Detection of amyloid in organs and tissues

[0149] Provided herein are methods of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, the method comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more tissues. In some embodiments, detecting the amyloid-reactive peptide in the organ or tissue indicates that the individual has an amyloid disease. In some embodiments, detection of the amyloid-reactive peptide in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis.

[0150] In some embodiments, provided herein are methods of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, the method comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:13 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more tissues. In some embodiments, detecting the amyloid-reactive peptide in the organ or tissue indicates that the individual has an amyloid disease. In some embodiments, detection of the amyloid-reactive peptide in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis.

[0151] In some embodiments, provided herein are methods of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of thyroid gland and salivary gland, the method comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more tissues. In some embodiments, detecting the amyloid-reactive peptide in the organ or tissue indicates that the individual has an amyloid disease. In some embodiments, detection of the amyloid-reactive peptide in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis.

[0152] In some embodiments, provided herein are methods of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of thyroid gland and salivary gland, the method comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more tissues. In some embodiments, provided herein are methods of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of thyroid gland and salivary gland, the method comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label in the thyroid or salivary gland.

[0153] In some embodiments, provided herein are methods of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of thyroid gland and salivary gland, the method comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual; and detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more tissues. In some embodiments, detecting the amyloid-reactive peptide in the organ or tissue indicates that the individual has an amyloid disease. In some embodiments, detection of the amyloid-reactive peptide in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis.

[0154] In some embodiments, the methods of diagnosing an amyloid-related disease comprise detecting amyloids with an amyloid-reactive peptide. Examples of amyloids that can be

detected as part of the present methods include, but are not limited to, amyloidogenic forms of immunoglobulin heavy chain (AH), β2-microglobulin (Aβ2M), transthyretin variants (ATTR), amyloid beta (Aβ), apolipoprotein AI (AApoAI), apolipoprotein AII (AApoAII), gelsolin (AGel), lysozyme (ALys), leukocyte chemotactic factor (ALect2), fibrinogen a variants (AFib), cystatin variants (ACys), calcitonin (ACal), lactadherin (AMed), islet amyloid polypeptide (AIAPP), prolactin (APro), insulin (AIns), prior protein (APrP); α-synuclein (AαSyn), tau (ATau), atrial natriuretic factor (AANF), or IAAP, and other amyloidogenic peptides. In some embodiments of the present disclosure, the method for diagnosing a type of amyloid disease comprises detecting ATTR, AL and/or ALECT2 amyloids. In other embodiments, the method for diagnosing a type of amyloid disease comprises distinguishing between ATTR, AL and ALECT2 amyloids.

[0155] In some embodiments, detecting the amyloid-reactive peptide in one or more organs or tissues comprises detecting the presence of amyloid-reactive peptide in one or more tissues or organs. In some embodiments, the detecting amyloid-reactive peptide in one or more tissues or organs comprises detecting the location of amyloid-reactive peptide in one or more tissues or organs.

[0156] In some embodiments, detecting the amyloid-reactive peptide in one or more organs or tissues as in the present methods comprises determining an organ uptake value for each organ. Organ uptake may be determined by methods known to those skilled in the art. For example, the organ uptake value may indicate the relative or absolute levels of the amyloid-reactive peptide detected in each organ in an individual. In some embodiments, the organ uptake value ratio is a relative uptake value. In some embodiments, the organ uptake value is a standard uptake value (SUV) for each organ. In some embodiments, As would be appreciated by those skilled in the art, the standard uptake value may be determined by measuring the amount of amyloid-reactive peptide detected in a reactive organ, e.g. heart, relative to the amount of amyloid-reactive peptide detected in a non-reactive tissue or sample, e.g. blood. The amount of amyloid-reactive agent in an organ may be determined, for example, by quantifying the detectable signal from the amyloid-reactive peptide in an organ, e.g. by computing pixel values in an image. In some embodiments, the standard uptake value is determined as the ratio of the amount of amyloid-reactive peptide detected in an organ, and the amount of amyloid-reactive peptide detected in blood. In some embodiments, the organ uptake value is indicative of the

organ distribution pattern of the amyloid-reactive peptide. In some embodiments, the method comprises determining an organ-specific SUV for the individual. In some embodiments, the organ-specific SUV for the individual is selected from the group consisting of SUV mean, SUV max, and SUV peak.

[0157] In some embodiments, the organ uptake is based upon an organ-specific standard uptake value ratio (SUVR). In some embodiments, a SUVR is calculated using a blood pool as a reference tissue. In some embodiments, the SUVR is calculated for each organ by dividing the amount of amyloid detection agent or dye in the organ by the blood pool ratio. In some embodiments, the blood pool is a vein or artery. In some embodiments, the blood pool is the lumen of the thoracic aorta. In some embodiments, the organ-specific SUVR for the individual is selected from the group consisting of SUVR mean, SUVR max, and SUVR peak. In some embodiments, the organ-specific SUVR for the individual is an SUVR mean. In some embodiments, an organ-specific SUVR is utilized to control for differences in radiotracer clearance rates.

[0158] In some embodiments, and the steps of measuring the organ uptake value or organ uptake value ratio of the amyloid-reactive peptide in one or more organs or tissues comprises analyzing imaging data. The imaging data may be generated by any procedure known in the art that may allow the imaging of the amyloid-reactive reagent or dye. For example, the amyloid-reactive peptide may be detected by positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), gamma imaging, or single-photon emission computed tomography (SPECT). In certain embodiments, the amyloid-reactive peptide may be detected by combined imaging methods such as PET/CT (PET with concurrent computed tomography imaging) or PET/MRI (PET with concurrent magnetic resonance imaging). The imaging procedure may result in one or more images of the region of observation of the individual. In certain embodiments, the imaging results in more than one image, these multiple images may be combined, overlaid, added, subtracted, color coded or otherwise fused and mathematically manipulated by any method known in the art. The image produced may be a digital or analog image that may be displayed as a "hard" image on, for example, printer paper, photographic paper or film, or as an image on a screen, such as for example, a video or LCD screen.

[0159] In some embodiments, the threshold value for diagnosing a particular type of amyloid disease is selected based upon a desired sensitivity. In some embodiments, the cutoff is selected to provide a sensitivity of at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95%. In some embodiments, the sensitivity of cardiac uptake of the amyloid-reactive peptide conjugated to a detectable label is between about 80% and about 100%. In some embodiments, the sensitivity of cardiac uptake of the amyloid-reactive peptide conjugated to a detectable label is about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%. In some embodiments, the sensitivity of cardiac uptake of the amyloid-reactive peptide conjugated to a detectable label is about 96%.

[0160] In some embodiments, the sensitivity of cardiac uptake in patients with AL amyloidosis is between about 80% and about 100%. In some embodiments, the sensitivity of cardiac uptake in patients with AL amyloidosis is about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%. In some embodiments, the sensitivity of cardiac uptake in patients with AL amyloidosis is about 93%.

[0161] In some embodiments, the sensitivity of cardiac uptake in patients with ATTR amyloidosis is between about 80% and about 100%. In some embodiments, the sensitivity of cardiac uptake in patients with ATTR amyloidosis is about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100%. In some embodiments, the sensitivity of cardiac uptake in patients with ATTR amyloidosis is about 100%.

[0162] In some embodiments, the threshold value is selected based upon a desired specificity (i.e. the ability to exclude individuals who do not have an amyloid-related disease). In some embodiments, the cutoff is selected to provide a specificity of at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95%.

[0163] In some embodiments, the threshold value is selected to obtain the optimal relationship between sensitivity and specificity based on organ-specific SUV or SUVR values. In some embodiments, the threshold value is selected that provides the highest Youden's index. In some embodiments, the Youden's index is determined by the following formula: sensitivity +

specificity – 1. In some embodiments, if several SUV or SUVR provide the same Youden's index, the SUV or SUVR that results in the highest specificity is selected.

[0164] In some embodiments, the heart $SUVR_{mean}$ threshold value for AL amyloidosis is between about 0.6 and about 4. In some embodiments, the heart $SUVR_{mean}$ threshold for AL amyloidosis is about 1.0, about 1.1, about 1.2, about 1.4, about 1.6, about 1.8, about 2.0, about 2.2, about 2.4, about 2.6, about 2.8, about 3, about 3.5, or about 4.0.

[0165] In some embodiments, the heart $SUVR_{mean}$ threshold value for ATTR amyloidosis is between about 0.6 and about 4. In some embodiments, the heart $SUVR_{mean}$ threshold for ATTR amyloidosis is about 1.0, about 1.1, about 1.2, about 1.4, about 1.6, about 1.8, about 2.0, about 2.2, about 2.4, about 2.6, about 2.8, about 3, about 3.5, or about 4.0.

[0166] In some embodiments, the sensitivity and specificity of the amyloid-reactive peptide conjugated to a detectable label are defined relative to clinically approved methods to diagnose an amyloid-related disease. In some embodiments, the clinically approved method is selected from the group consisting of a measure of the health related quality of life of the individual, the presence or amount of one or more biomarkers associated with the amyloid-related disease, a cardiac biopsy, and additional amyloid imaging of the individual. In some embodiments, the biomarker associated with amyloid-related disease is selected from the group consisting of Troponin T, NTproBNP, urine protein levels, UACR, EGFR, interventricular septal wall thickness (IVS), left ventricular (LV) wall thickness, global longitudinal strain (GLS), and alkaline phosphatase levels. In some embodiments, the sensitivity and specificity of the amyloid-reactive peptide conjugated to a detectable label are defined relative a diagnosis derived from an individual's medical record.

[0167] In some embodiments, the step of detecting the amyloid-reactive peptide is performed in more than one organ in an individual. In some embodiments, detecting comprises quantifying the amount of detectable label to quantify the amount of amyloid-reactive peptide. In some embodiments, an amount of amyloid-reactive peptide above a threshold indicates presence of amyloid deposits in the one or more organs or tissues. In some embodiments, amyloid deposits detected in one or more organs or tissues indicates the individual has an amyloid related disease. The type of amyloid disease may be a sporadic amyloidosis, or have a genetic component, e.g. hereditary amyloidosis. Some non-limiting examples of amyloid diseases are AA amyloidosis, AL amyloidosis, AH amyloidosis, Aβ amyloidosis, ATTR amyloidosis, ALect2

amyloidosis, and IAPP amyloidosis of type II diabetes, Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, cerebral beta-amyloid angiopathy, spongiform encelohalopathy, thyroid tumors, Parkinson's disease, dementia with Lewis bodies, a tauopathy, Huntington's disease, senile systemic amyloidosis, familial hemodialysis, senile systemic aging, aging pituitary disorder, iatrogenic syndrome, spongiform encephalopathies, reactive chronic inflammation, thyroid tumors, myeloma or other forms of cancer. In some embodiments, the type of amyloid disease is a systemic amyloid disease. In some embodiments, the type of amyloid disease is AL amyloidosis, ATTR amyloidosis, or ALECT2 amyloidosis.

[0168] In some embodiments, the methods for diagnosing an amyloid-related disease comprise detecting amyloid-reactive peptide in one or more tissues or organs. Without being bound by theory, it is thought that the anatomic distribution of amyloid in each of form of the disease may have a specific pattern. For example, the amyloid deposits in ATTR amyloidosis are prevalent in the heart and peripheral nerves, while AL amyloidosis, another common amyloidosis, exhibits a variable pattern of amyloid deposition, with amyloids observed in, for example, the heart, spleen, liver, kidneys, peripheral nerves, gastrointestinal tract, muscle, lung, and lymph nodes. In some embodiments, the methods for diagnosing the type of amyloid disease comprise detecting the amyloid-reactive peptide in one or more of tissues or organs of the individual is selected from the group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand. In some embodiments, the one or more tissues or organs of the individual is selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue. In some embodiments, the one or more tissues or organs is selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland. In some embodiments, the one or more organs are abdominothoracic organs. In some embodiments, the one or more organs are heart, spleen, liver, or kidney.

[0169] In some embodiments, detection of an amount of amyloid-reactive peptide in an organ can be used to determining positivity of amyloid in an organ. In some embodiments, detection of an amount of amyloid-reactive peptide in the heart is about 2, about 3, or about 4, or

about 5 or more times the standard deviation (SD) of the mean technetium^{99m} detectable label in the heart, of healthy subjects, indicating the individual has cardiac amyloid. In some embodiments, detection of an amount of amyloid-reactive peptide in the heart, is about 1.96 times the SD of the mean technetium^{99m} detectable label in the in the heart of healthy individuals, indicating the individual has cardiac amyloid. In some embodiments, detection of an amount of amyloid-reactive peptide in the heart is between about 2 and about 5, about 2 and about 4, or about 2 and about 3 times the SD of the mean technetium^{99m} detectable label in the heart, of healthy individuals, indicating the individual has cardiac amyloid.

[0170] In some embodiments, detection of an amount of amyloid-reactive peptide in an organ can be used to determining positivity of amyloid in an organ. In some embodiments, detection of an amount of amyloid-reactive peptide in the liver is about 2, about 3, or about 4, or about 5 or more times the standard deviation (SD) of the mean technetium^{99m} detectable label in the liver of healthy subjects, indicating the individual has liver amyloid. In some embodiments, detection of an amount of amyloid-reactive peptide in the liver, is about 1.96 times the SD of the mean technetium^{99m} detectable label in the in the liver of healthy individuals, indicating the individual has liver amyloid. In some embodiments, detection of an amount of amyloid-reactive peptide in the liver is between about 2 and about 5, about 2 and about 4, or about 2 and about 3 times the SD of the mean technetium^{99m} detectable label in the liver of healthy individuals, indicating the individual has liver amyloid.

[0171] In some embodiments, detection of an amount of amyloid-reactive peptide in an organ can be used to determining positivity of amyloid in an organ. In some embodiments, detection of an amount of amyloid-reactive peptide in the spleen is about 2, about 3, or about 4, or about 5 or more times the standard deviation (SD) of the mean technetium^{99m} detectable label in the spleen of healthy subjects, indicating the individual has spleen amyloid. In some embodiments, detection of an amount of amyloid-reactive peptide in the spleen, is about 1.96 times the SD of the mean technetium^{99m} detectable label in the in the spleen of healthy individuals, indicating the individual has spleen amyloid. In some embodiments, detection of an amount of amyloid-reactive peptide in the spleen is between about 2 and about 5, about 2 and about 4, or about 2 and about 3 times the SD of the mean technetium^{99m} detectable label in the spleen of healthy individuals, indicating the individual has spleen amyloid.

[0172] Preferably, the organ uptake values or the organ-to-organ uptake ratio cut-off or threshold values for diagnosing the type of amyloid disease is determined using a receiver operator characteristic curve. As is understood in the art, the receiver operating characteristic curve, or, ROC curve, is a plot of the performance of a particular feature for distinguishing two populations, patients with an amyloid disease, and controls, e.g., those without an amyloid disease. Data across the entire population (namely, the patients and controls) are sorted in ascending order based on the value of a single feature (e.g. organ uptake value). Then, for each value for that feature, the true positive and false positive rates for the data are determined. The true positive rate (sensitivity) is determined by counting the number of cases above the value for that feature under consideration and then dividing by the total number of patients. The false positive rate (specificity) is determined by counting the number of controls above the value for that feature under consideration and then dividing by the total number of controls.

[0173] ROC curves can be produced for a single feature as well as for other single outputs, for example, combinations of two or more features are mathematically added together (added, drawn, multiplied, etc.) to provide a single total value, which can be plotted in the ROC curve. Furthermore, any combination of multiple features by which the combination leads to a single output value can be plotted in the ROC curve. These combinations of features may include testing. The ROC curve is a plot of the true positive rate (sensitivity) of the test against the false positive rate (1-specificity) of the test. The area under the ROC curve can be a figure of merit for a given sample population, with the test ranging from 1 to 0 for a complete test that gives a completely random response in classifying the test subjects. As with any diagnostic application, the area under the ROC curve is indicative of the predictive power of the model, and can be used to compare the predictive power of one model against another. Using the ROC curve a cut-off value can be selected for diagnosing an amyloid disease and/or amyloid type in an individual with high confidence.

[0174] In some embodiments, the method comprises obtaining organ distribution data for an amyloid-reactive peptide. In some embodiments, organ distribution data are images. The images produced using the imaging procedure embodied in the present invention may be analyzed by any method known in the art. For example, in some embodiments, imaging data derived from a PET or SPECT scan can be inputted into a processor that identifies individual pixels or groups of pixels whose brightness is greater than a predetermined threshold or an

average background, and identified pixels may be characterized as indicating the presence of the amyloid-reactive reagent or dye. In another embodiment, the image data may be derived from images scanned and inputted into a processor. In such embodiments, a similar process that identifies bright spots on the image may be used to locate the amyloid-reactive reagent or dye in the image. In certain embodiments, the analysis of the image may further include determining the intensity, concentration, strength or combination thereof of the output brightness, which may be correlated to the amount of radiolabeled protein in the image, an area or region of the image, or a particular spot on the image. Without wishing to be bound by theory, an area or spot on an image having a greater intensity than other areas or spots may hold a higher concentration of radiolabeled protein targeted to, for example, an amyloid deposit, and thus may have a higher concentration of the radiolabeled-amyloid-reactive reagent or dye attached to the region where the amyloid-reactive reagent or dye localizes.

[0175] In some embodiments, the method for diagnosing a type of amyloid disease comprises analyzing images by the spatial location of regions of interest to which the administered amyloid-reactive peptide are targeted. In other embodiments, analysis of the pharmacokinetics of the administered amyloid-reactive reagent or dye may provide information on the appropriate timing of injection of the amyloid-reactive reagent or dye. By identifying areas, regions, or spots on an image that correlate to the presence of a radiolabeled protein, the presence or absence of amyloids may be determined. For example, in some embodiments, identifying regions or spots where the amyloid-reactive peptide concentrates indicates the presence of amyloids. In some embodiments, images that correlate to the presence of an amyloid-reactive peptide are used to diagnose an amyloid disease in an individual.

[0176] In some embodiments, the method further comprises providing a diagnosis of a type of amyloid disease based upon the organ distribution pattern. In some embodiments, a particular organ distribution pattern is indicative of a particular type of amyloid disease. In some embodiments, detection of the amyloid-reactive peptide in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis

[0177] In some embodiments, the cutoff value for diagnosing a particular type of amyloid disease is selected based upon a certain p value. In some embodiments, the cutoff is selected to provide a p-value of less than 0.1, less than 0.05, less than 0.01, less than 0.005, or less than 0.001.

[0178] One of ordinary skill in the art will appreciate that each of the ratios discussed herein can easily converted to its inverse. For example, a heart to spleen ratio of 2:1 (2) is the same as a spleen to heart ratio of 1:2 (0.5).

[0179] In some embodiments, the diagnosis is confirmed by a measure of the health related quality of life of the individual. In some embodiments, the diagnosis is confirmed by the presence or amount of one or more biomarkers associated with the amyloid-related disease. In some embodiments, the biomarker associated with amyloid-related disease is selected from the group consisting of Troponin T, NTproBNP, urine protein levels, UACR, EGFR, interventricular septal wall thickness (IVS), left ventricular (LV) wall thickness, global longitudinal strain (GLS), and alkaline phosphatase levels. In some embodiments, the diagnosis is confirmed by a cardiac biopsy. In some embodiments, the diagnosis is confirmed by additional amyloid imaging of the individual.

D. Patient populations

[0180] In some embodiments, the methods of diagnosing a type of amyloid disease are particularly useful in individuals at risk of developing an amyloid-related disease. In some embodiments, the methods of diagnosing a type of amyloid disease are particularly useful subject where there is high clinical suspicion of the disease. In some embodiments, the individuals at risk of developing an amyloid-related disease have a family history of amyloid-related disease. In some embodiments, the individuals are at risk of developing a hereditary form of an amyloid-related disease. In some embodiments, the hereditary form of an amyloid-related disease comprises hereditary transthyretin amyloidosis (hATTR).

[0181] In some embodiment, individuals are determined to be at risk for an amyloid-related disease based upon the presence of a genetic mutation, having multiple myeloma, having amyloid positive laminectomy tissue, having an amyloid positive tissue from carpal tunnel release surgery, having a monoclonal gammopathy of unknown significance (MGUS), having heart failure with preserved ejection fraction (HFpEF), having heart failure with reduced ejection fraction (HfrEF), being from susceptible ethnic populations, or being elderly. In some embodiments, an individual is determined to be at risk for an amyloid related diseased where there is high clinical suspicion of disease.

[0182] In some embodiments, the individual is determined to be at risk for an amyloid-related disease based upon the presence of a genetic mutation. In some embodiments,

the genetic mutation is an ATTR genetic mutation. In some embodiments, the genetic mutation is within the *TTR* gene. In some embodiments, the genetic mutation comprises a point mutation resulting in an amino acid substitution e.g., of valine by methionine at position 30 (Val30Met).

[0183] In some embodiments, the individual is determined to be at risk for an amyloid-related disease based upon having multiple myeloma. In some embodiments, the individual at risk for developing an amyloid-related disease has smoldering multiple myeloma. In some embodiments, the individual is at risk for developing Immunoglobulin light chain amyloidosis (AL) based upon having multiple myeloma.

[0184] In some embodiments, the individual is determined to be at risk for an amyloid-related disease based upon having monoclonal gammopathy of undetermined significance (MGUS).

[0185] In some embodiments, the individual is determined to be at risk for an amyloid-related disease based upon having amyloid positive laminectomy tissue. In some embodiments, the individual is determined to be at risk for an amyloid-related disease based upon having amyloid positive carpal tunnel release tissue. In some embodiments, the individual is determined to be at risk for an amyloid-related disease based upon being elderly. In some embodiments, the individual is at least about 60, 65, 70, 75, 80, 85, or 90 years old. In some embodiments, the individual is at least 80 years old.

[0186] In some embodiments, the individual at risk of developing an amyloid-related disease displays symptoms of an amyloid-related disease. In some embodiments, the symptom of an amyloid-related disease is selected from the group consisting of swollen ankles and legs, severe fatigue, shortness of breath, significant weight loss, difficulty in swallowing, tingling, numbness or pain in the hands, wrist or feet, enlarged tongue, irregular heartbeat, diarrhea, and easy bruising, thickening, or purplish patches on the skin.

[0187] Alternatively, in some embodiments, the individual at risk of developing an amyloid-related disease does not display symptoms of an amyloid-related disease.

E. Prognosis

[0188] Also provided herein are methods of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label

at one or more organs or tissues of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0189] In some embodiments, provided herein are methods of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0190] In some embodiments, provided herein are methods of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence p5+14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues of the individual to detect amyloid in the individual a first time, wherein the detecting

occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence p5+14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0191] In some embodiments, provided herein are methods of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues, selected from the group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual.

[0192] In some embodiments, provided herein are methods of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label

at one or more organs or tissues, selected from the group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0193] In some embodiments, provided herein are methods of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues, selected from the group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual.

[0194] In some embodiments, provided herein are methods of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues, selected from the group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual.

[0195] In some embodiments, provided herein are methods of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues, selected from the group consisting of esophagus, stomach, thyroid gland and salivary gland, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual. In some embodiments, the technetium^{99m} detectable

label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0196] In some embodiments, provided herein are methods of determining prognosis of an individual having an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues, selected from the group consisting of esophagus, stomach, thyroid gland and salivary gland, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0197] In some embodiments, the prognosis of an individual having an amyloid-related disease is based on detecting amyloid-reactive peptide in the heart alone. In some embodiments, the prognosis of an individual having an amyloid-related disease is based on detecting amyloid-reactive peptide in the heart.

[0198] In some embodiments, the individual has an amyloid disorder selected from the group consisting of AL, AH, Aβ2M, ATTRv, ATTRwt, AA, AapoAI, AApoAII, Agel, Alys, ALECT2, Afib, Acys, Acal, Amed, AIAPP, Apro, Ains, AprP, or Aβ amyloidosis. In some embodiments, the individual has an early stage of an amyloid-related disease.

[0199] In some embodiments, the first time the amyloid-reactive peptide conjugated to a detectable label is administered and the second time the amyloid-reactive peptide conjugated to a detectable label is administered are between at least one week, two weeks, three weeks, one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, one year, two years, three years, four years, or

five years apart. In some embodiments, the first time and the second time are at least two weeks apart. In some embodiments, the first time and the second time are at least one month apart. In some embodiments, the first time and the second time are at least three months apart.

[0200] In some embodiments, the prognosis of the individual with an amyloid-related disease has worsened. In some embodiments, the prognosis of the individual with an amyloid-related disease has improved.

[0201] In some embodiments, the prognosis is confirmed by a measure of the health related quality of life of the individual. In some embodiments, the prognosis is confirmed by the presence or amount of one or more biomarkers associated with the amyloid-related disease. In some embodiments, the biomarker associated with amyloid-related disease is selected from the group consisting of Troponin T, NTproBNP, urine protein levels, UACR, EGFR, interventricular septal wall thickness (IVS), left ventricular (LV) wall thickness, global longitudinal strain (GLS), and alkaline phosphatase levels. In some embodiments, the prognosis is confirmed by a cardiac biopsy. In some embodiments, the prognosis is confirmed by additional amyloid imaging of the individual.

IV. METHODS OF TREATMENT

[0202] Also provided herein are methods of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0203] In some embodiments, provided herein are methods of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:13 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-

related disease if the amyloid-reactive peptide is detected. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0204] In some embodiments, provided herein are methods of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid p5+14 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0205] In some embodiments, provided herein are methods of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs, selected from a group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand, of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0206] In some embodiments, provided herein are methods of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs, selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-related disease if the amyloid-reactive

peptide is detected. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0207] In some embodiments, provided herein are methods of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs, selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland, of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected.

[0208] In some embodiments, provided herein are methods of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:13 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs, selected from a group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand, of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0209] In some embodiments, provided herein are methods of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs, selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is

detected. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0210] In some embodiments, provided herein are methods of treating an amyloid-related disease comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual; detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs, selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland, of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

A. Administering an amyloid-reactive peptide

[0211] Some aspects of the present invention provide methods of treating an amyloid disease based upon detecting amyloids with an amyloid-reactive peptide. In some embodiments, provided herein is a method of treating an amyloid disease comprising administering an amyloid-reactive peptide, measuring the organ distribution of the amyloid-reactive peptide, and selecting a treatment based upon the type of disease.

[0212] In some embodiments, the methods of treating an amyloid disease comprising administering an amyloid-reactive peptide, and measuring the organ-specific SUV and/or SUVR of the amyloid-reactive peptide for one or more organs or tissues. In some embodiments, the organ distribution pattern of the amyloid-reactive peptide indicates a type of amyloid disease. In some embodiments, the methods further comprise selecting a treatment based upon the type of amyloid disease.

[0213] In some embodiments, the method comprises obtaining an organ distribution pattern of an amyloid-reactive peptide, wherein the organ distribution pattern indicates a particular type of amyloid disease, and administering a treatment based upon the amyloid disease.

[0214] In some embodiments, the methods of treating an amyloid disease comprise administering amyloid-reactive peptide conjugated to a technitium^{99m} detectable label. In some

embodiments, the amyloid-reactive peptide comprises a peptide, a fusion protein, a small molecule compound, or an antibody or fragment.

[0215] In some embodiments, the methods of treating an amyloid disease comprise administering an amyloid-reactive peptide comprising an amyloid-reactive peptide conjugated to a technetium^{99m} detectable label. In some embodiments, the amyloid-reactive peptide is a peptide with amino acid sequence set forth as any one of SEQ ID NOs: 1-14. In some embodiments, the methods of treating an amyloid disease comprise an amyloid-reactive peptide with an amino acid sequence as set forth in SEQ ID NO:13. In some embodiments, the methods of treating an amyloid disease comprise an amyloid-reactive peptide with an amino acid sequence comprising p5+14.

[0216] In some embodiments, the methods of treating an amyloid disease comprising administering an amyloid-reactive peptide, and measuring the organ-specific SUV and/or SUVR of the amyloid-reactive peptide for one or more organs or tissues. In some embodiments, the methods of treating an amyloid disease comprise administering an amyloid-reactive peptide comprising a technetium^{99m} detectable label to determine an organ distribution pattern. In some embodiments, the radiolabeled amyloid-reactive peptide is ^{99m}Tc -p5+14. In some embodiments, the methods of treating an amyloid disease comprise p5+14. In some embodiments, the amyloid-reactive peptide.is radiolabeled. In some embodiments, the radiolabel is ^{99m}Tc. In some embodiments, the radiolabeled amyloid-reactive peptide is a ^{99m}Tc -labelled amyloid-reactive peptide. In other embodiments, the method for diagnosing a type of amyloid disease comprise administering ^{99m}Tc -p5+14.

[0217] In some embodiments, the amyloid-reactive peptide is administered parenterally, paracancerally, transmucosally, tansdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitoneally, intraventricularly, or intracranially. In some instances, the amyloid-reactive peptide is administered intravenously or intraperitoneally.

B. Detecting amyloid

[0218] In some embodiments, the methods comprise detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual occurs about

0.5, about 1, about 1.5, about 2, about 2.5 or about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual occurs between about 0.5 and about 3 hours, between about 1 and about 3 hours, between about 1.5 and about 3 hours, between about 2 and about 3 hours, or between about 2.5 and about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual occurs between about 0.5 and about 2.5 hours, between about 0.5 and about 2 hours, between about 0.5 and about 1.5 hours, or between about 0.5 and about 1 hours after administering the amyloid-reactive peptide. In some embodiments, detecting comprises detecting the location of detectable label to detect the organs with update of the amyloid-reactive peptide. In some embodiments, detecting comprises quantifying the amount of detectable label to quantify the amount of amyloid-reactive peptide.

[0219] In some aspects, the present method allows for rapid detection following administration of the Tc^{99m} labeled amyloid reactive peptide that shorten hospital visit duration compared to existing imagining methods. Advantageously, in some embodiments, the imaging can be carried out within one hour of administering the Tc^{99m} labeled amyloid reactive peptide. In some embodiments, the methods comprise detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual between about 0.1 hours and about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual occurs about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 1, about 1.5, about 2, about 2.5 or about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual occurs between about 0.1 and about 3 hours, between about 0.2 and about 3 hours, between about 0.3 and about 3 hours, between about 0.4 and about 3 hours, between about 0.5 and about 3 hours, between about 1 and about 3 hours, between about 1.5 and about 3 hours, between about 2 and about 3 hours, or between about 2.5 and about 3 hours after administering the amyloid-reactive peptide. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or

organs of the individual occurs between about 0.1 and about 2.5 hours, between about 0.1 and about 2 hours, between about 0.1 and about 1.5 hours, between about 0.1 and about 1 hour, between about 0.1 and about 0.5 hours, between about 0.1 and about 0.4 hours, between about 0.1 and about 0.3 hours or between about 0.1 and about 0.2 hours after administering the amyloid-reactive peptide. In some embodiments, the of the detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual occurs between about 0.5 and about 2.5 hours, between about 0.5 and about 2 hours, between about 0.5 and about 1.5 hours, or between about 0.5 and about 1 hours after administering the amyloid-reactive peptide. In some embodiments, detecting comprises detecting the location of detectable label to detect the organs with update of the amyloid-reactive peptide. In some embodiments, detecting comprises quantifying the amount of detectable label to quantify the amount of amyloid-reactive peptide.

[0220] In some embodiments, the methods comprise detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in one or more of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand. In some embodiments, the one or more organs or tissues are esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue. In some embodiments, the methods comprise detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in the esophagus, stomach, thyroid gland and salivary gland. In some embodiments, the methods comprise detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in the thyroid gland and salivary gland.

[0221] In some embodiments, the methods of treating an amyloid disease comprise administering an amyloid-reactive peptide and determining the organ-specific SUV and/or SUVR of the amyloid-reactive peptide for one or more organs or tissues. In some embodiments, the methods of treating an amyloid disease comprise determining the organ distribution pattern of the amyloid-reactive peptide for one or more organs or tissues. In some embodiments, the methods for treating the type of amyloid disease comprise determining the organ-specific SUV and/or SUVR of the amyloid-reactive peptide in one or more of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine,

spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand. In some embodiments, the one or more organs or tissues are esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue. In some embodiments, the tissue or organ of the individual is selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland.

[0222] In some embodiments, the detecting amyloid-reactive peptide in one or more tissues or organs comprises detecting the presence of amyloid-reactive peptide in one or more tissues or organs. In some embodiments, the detecting amyloid-reactive peptide in one or more tissues or organs comprises detecting the location of amyloid-reactive peptide in one or more tissues or organs.

[0223] In some embodiments, the detecting amyloid-reactive peptide in one or more tissues or organs comprise determining an organ uptake value for each organ or tissue. In some embodiments, the organ uptake value is a standard uptake value for each organ or tissue. In some embodiments, the standard uptake value is determined as the ratio of the amount of amyloid-reactive peptide detected in an organ or tissue, and the amount of amyloid-reactive peptide detected in blood. In some embodiments, the organ uptake value is indicative of the organ distribution pattern of the amyloid-reactive peptide.

[0224] In some embodiments, the step of determining the organ distribution pattern of the amyloid-reactive peptide in one or more organs or tissues comprise determining an organ uptake value for each organ or tissue. In some embodiments, the organ uptake value is a standard uptake value for each organ or tissue. In some embodiments, the standard uptake value is determined as the ratio of the amount of amyloid-reactive peptide detected in an organ, and the amount of amyloid-reactive peptide detected in blood. In some embodiments, the organ uptake value is indicative of the organ distribution pattern of the amyloid-reactive peptide or detection dye.

[0225] In some embodiments, the determining the organ-specific SUV and/or SUVR of the amyloid-reactive peptide comprises the analysis of imaging data generated by PET, CT, MRI, SPECT, PET/CT, PET/MRI, SPECT with x-ray computed tomography (SPECT/CT), or Planar gamma imaging or other imaging techniques. In some embodiments, the determining the organ-specific SUV and/or SUVR of the amyloid-reactive peptide comprises the analysis of

imaging data generated by SPECT, SPECT/CT or CT or other imaging techniques. In some embodiments, the step of determining the organ-specific SUV and/or SUVR of the amyloid-reactive peptide comprises analysis of images by the spatial location of regions of interest.

[0226] In other embodiments, the step of measuring the organ distribution pattern of the amyloid-reactive peptide in one or more organs or tissues comprises calculating an organ-to-organ ratio for two or more organs or tissues. In some embodiments, the step of calculating an organ-to-organ ratio for two or more organs or tissues comprises calculating the ratio between the organ uptake value for a first organ and the organ uptake value for a second organ.

[0227] In some embodiments, the organ or tissue distribution pattern indicates a type of amyloid disease. In some embodiments, the organ or tissue distribution pattern is used to select a particular treatment based upon a type of amyloid disease. In some embodiments, the method further comprises providing a diagnosis of a type of amyloid disease based upon the organ or tissue distribution pattern. In some embodiments, a particular organ or tissue distribution pattern is indicative of a particular type of amyloid disease. For example, an organ or tissue distribution wherein amyloid is detected in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis.

C. Administering a treatment

[0228] In some embodiments, the method comprises treating or selecting a treatment for an amyloid-related disease. Some example amyloid diseases that can be diagnosed and/or treated with the methods disclosed herein include, but are not limited to, AA amyloidosis, AL amyloidosis, AH amyloidosis, Aβ amyloidosis, ATTR amyloidosis, ALECT2 amyloidosis, and IAPP amyloidosis of type II diabetes, Alzheimer's disease, thyroid tumors, Parkinson's disease, a tauopathy, senile systemic amyloidosis, familial hemodialysis, senile systemic aging, aging pituitary disorder, iatrogenic syndrome, reactive chronic inflammation, thyroid tumors, myeloma or other forms of cancer. In some embodiments, the methods of treating an amyloid disease comprise selecting a treatment for a systemic amyloidosis. In some embodiments, the methods of treating an amyloid disease comprise selecting a treatment for AL amyloidosis, ATTR amyloidosis, or ALECT2 amyloidosis. In some embodiments, the treatment is a targeted therapy for an ATTR amyloidosis, an AL amyloidosis, or an ALECT2 amyloidosis.

[0229] In some embodiments, the treatment is a small molecule, an antibody, a peptide, a protein, a nucleic acid, and/or a gene therapy. In some embodiments the treatment is a targeted treatment that is specific a particular type of amyloid disease.

[0230] In some embodiments, the treatment is a targeted therapy for an ATTR amyloidosis, an AL amyloidosis, or an ALECT2 amyloidosis. In some embodiments, the treatment is a targeted therapy for ATTR amyloidosis. In some embodiments, the treatment comprises a TTR tetramer stabilizer. In some embodiments, the TTR tetramer stabilizer is epigallocatechin-3-gallate (EGCG), AG-10, CHF5074, tafadimis, or diflunisal. In some embodiments, the treatment comprises an antibody or fragment that binds misfolded TTR. In some embodiments, the antibody is PRX004. In some embodiments, the treatment comprises an oligonucleotide. In some embodiments, the oligonucleotide is a TTR silencer. In some embodiments, the TTR silencer is patisiran (ALN-TTR02), vutrisiran, inotersen, or AKCEA-TTR-LRx. In some embodiments, the treatment comprises an ATTR amyloid disruptor. In some embodiments, the treatment comprises doxycycline, tauroursodeoxycholic acid, or serum amyloid P (SAP). In some embodiments, the treatment comprises an organ transplant. In some embodiments, the treatment comprises a liver transplant.

[0231] In other embodiments, the treatment is a targeted therapy for AL amyloidosis. In some embodiments, the treatment comprises bortemozib, ixazomib, or cazilfomib. In some embodiments, the treatment comprises an antibody or fragment. In some embodiments, the treatment comprises daratumab, CAEL-101, elotuzumab, or belantamab mafodotin. In some embodiments, the treatment comprises a stem cell therapy. In some embodiments, the treatment comprises a corticosteroid. In some embodiments, the corticosteroid is dexamethasone.

[0232] In some embodiments, the method is used to eliminate a potential therapy for a patient having amyloidosis. In some embodiments, the method is used to diagnose one type of amyloidosis and eliminate therapies for other types of amyloidosis. In some embodiments, the method is used to diagnose ALECT2 and eliminate therapies for AL or ATTR amyloidosis. In some embodiments, the method is used to differentiate types of amyloidosis in order to develop therapies specific for a specific type of amyloidosis. For example in some embodiments, the method is used to identify individuals with ALECT2 amyloidosis and develop a therapy specific to ALECT2 amyloidosis.

[0233] In some embodiments, the method is used to eliminate a potential therapy for a patient having amyloidosis. In some embodiments, the method is used to diagnose one type of amyloidosis and eliminate therapies for other types of amyloidosis. In some embodiments, the method is used to diagnose AL and eliminate therapies for ALECT2 or ATTR amyloidosis.

[0234] In some embodiments, the method is used to differentiate types of amyloidosis in order to develop therapies specific for a specific type of amyloidosis. For example in some embodiments, the method is used to identify individuals with AL amyloidosis and develop a therapy specific to AL amyloidosis.

[0235] In some embodiments, provided herein, are methods of managing the treatment of an amyloid-related disease in an individual comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and adjusting the treatment for the amyloid-related disease.

[0236] In some embodiments, provided herein, are methods of managing the treatment of an amyloid-related disease in an individual comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NOs: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ

ID NOs: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and adjusting the treatment for the amyloid-related disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0237] In some embodiments, provided herein, are methods of managing the treatment of an amyloid-related disease in an individual comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs, selected from a group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and adjusting the treatment for the amyloid-related disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0238] In some embodiments, provided herein, are methods of managing the treatment of an amyloid-related disease in an individual comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NOs: 13 conjugated to

a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs, selected from a group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NOs: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and adjusting the treatment for the amyloid-related disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0239] In some embodiments, provided herein, are methods of managing the treatment of an amyloid-related disease in an individual comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs, selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in a tissue

or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and adjusting the treatment for the amyloid-related disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0240] In some embodiments, provided herein, are methods of managing the treatment of an amyloid-related disease in an individual comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NOs: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs, selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NOs: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and adjusting the treatment for the amyloid-related disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0241] In some embodiments, provided herein, are methods of managing the treatment of an amyloid-related disease in an individual comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs, selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease; administering an amyloid-reactive peptide comprising the amino acid sequence set forth

in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and adjusting the treatment for the amyloid-related disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0242] In some embodiments, provided herein, are methods of managing the treatment of an amyloid-related disease in an individual comprising: administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs, selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland, of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and adjusting the treatment for the amyloid-related disease. In some embodiments, the technetium^{99m} detectable label is detectable between about 0.1 and about 3 hours after administering the amyloid-reactive peptide.

[0243] In some embodiments, the first time the amyloid-reactive peptide is administered and the second time the amyloid-reactive peptide is administered are between at least one week, two weeks, three weeks, one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months, one year, two years, three years, four years, or five years apart. In some embodiments, the first time and the second time are at least two weeks apart. In some embodiments, the first time and the

second time are at least one month apart. In some embodiments, the first time and the second time are at least three months apart.

[0244] In some embodiments, provided herein, are methods of selecting a treatment for an amyloid-related disease in an individual comprising; administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual to detect amyloid in the individual, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide; administering a treatment for an amyloid-related disease, wherein if amyloid is detected in the heart a treatment for the amyloid-related disease is administered and wherein if amyloid is not detected in the heart, an alternative therapy is administered.

[0245] In some embodiments, the treatment is a small molecule, an antibody, a peptide, a protein, a nucleic acid, and/or a gene therapy. In some embodiments the treatment is a targeted treatment that is specific for a particular type of amyloid disease.

[0246] In some embodiments, the therapy for the amyloid-related disease is selected from the group consisting of transthyretin stabilizers (e.g. tafamidis, acoramidis), transthyretin silencers (e.g. Patisiran, Inotersen, Vutrisiran, Eploetersen), gene editing approaches, anti-amyloid approaches utilizing monoclonal antibodies, treatments targeting plasma cell clones (e.g. Daratumumab, Bortezomib), and an antibody-peptide fusion comprising an antibody-peptide fusion protein comprising a second amyloid-reactive peptide and an antibody that does or does not binds to amyloid fibrils. In some embodiments, the second amyloid-reactive peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-14 comprising 0, 1, 2, 3, or 4 amino acid substitutions, insertions, or deletions.

[0247] In some embodiments, the antibody-peptide fusion protein comprises a heavy chain and a light chain and wherein the amyloid-reactive peptide is linked to at the C-terminal end of the light chain of the antibody via a spacer.

[0248] In some embodiments, the antibody that binds to a human amyloid fibril comprises a heavy chain and a light chain. In some embodiments, the antibody that binds to a human amyloid fibril comprises a heavy chain variable region (VH) and the light chain of the antibody comprises a light chain variable region (VL) according to **Table 2.** In some

embodiments, the VH comprises the amino acid set for in SEQ ID NO: 102. In some embodiments, the VL comprises the amino acid set for in SEQ ID NO: 101.

Table 2: Exemplary Antibody VH and VL

	Primary Sequence	**SEQ ID NO**
VL4-N33S	DVVMTQSPLSLPVTLGQPASISCRSSQSLVHRSGNTYLHWF QQRPGQSPR*L*LIYKVSNRFSGVPDRFSGSGSGTDFTLKISRV EAEDVGVYFCFQTTYVPNTFGGGTKLEIK	SEQ ID NO: 101
VH9-D54E	QVQLQESGPGLVKPSETLSLTCTVSGFSLSSYGVSWIRQPPG KGLEW*L*GVIWGEGSTNYHPNLMSRVTISVDTSK*S*Q*VLF*KLS SVTAADTAVYYCA*T*LDYWGQGTSVTVSS	SEQ ID NO: 102

[0249] In some embodiments, the antibody-peptide fusion protein comprises: (i) an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:2; and (ii) an antibody that binds to a human amyloid fibrils, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain of the antibody comprises a heavy chain variable region (VH) and the light chain of the antibody comprises a light chain variable region (VL). In some embodiments, the heavy chain variable region (VH) of the antibody and the light chain of the antibody comprises a light chain variable region (VL) according to **Table 2**.

[0250] In some embodiments, the heavy chain of the antibody comprises a heavy chain variable region (VH) and the light chain of the antibody comprises a light chain variable region (VL), wherein the VH and HV comprise the CDR according to **Table 3**. In some embodiments, the heavy chain of the antibody comprises a heavy chain variable region (VH) and the light chain of the antibody comprises a light chain variable region (VL), wherein the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:106, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:107, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:108, and the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:103, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:104, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:105.

Table 3:Exemplary Antibody CDRs

	Primary Sequence	**SEQ ID NO**
CDR-L1	RSSQSLVHRSGNTYLH	SEQ ID NO: 103
CDR-L2	KVSNRFS	SEQ ID NO: 104
CDR-L3	FQTTYVPNT	SEQ ID NO: 105
CDR-H1	GFSLSSYGVS	SEQ ID NO: 106

CDR-H2	VIWGEGSTNYHPNLMS	SEQ ID NO: 107
CDR-H3	LDY	SEQ ID NO: 108

[0251] In some embodiments, the antibody-protein fusion peptides comprises (i) an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:2; and (ii) an antibody that binds to a human amyloid fibrils, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain of the antibody comprises a heavy chain variable region (VH) and the light chain of the antibody comprises a light chain variable region (VL), wherein the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:106, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:107, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:108, and the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:103, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:104, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:105; wherein the amyloid-reactive peptide and antibody are linked at the C-terminal end of the light chain, and wherein the amyloid-reactive peptide is linked to the antibody via a spacer comprising an amino acid sequence set forth in SEQ ID NO:83.

[0252] In some embodiments, the amyloid-reactive peptide and antibody are linked at the C-terminal end of the light chain, and wherein the amyloid-reactive peptide is linked to the antibody via a spacer comprising an amino acid sequence: VSPSV (SEQ ID NO:83). In some embodiments, the antibody-peptide fusion may be any of the modified immunoglobulins described in U.S. Patent Publication 12,030,934B2.

V. KITS

[0253] Some aspects of the invention provide kits for diagnosing or detecting a type of amyloid disease in an individual with the methods described herein.

[0254] In some embodiments, the kit comprises an amyloid-reactive peptide and instructions for use. In some embodiments, the amyloid-reactive peptide comprising a technetium^{99m} detectable label. In some embodiments, the amyloid-reactive agent is ^{99m}Tc-p5+14. In some embodiments the amyloid-reactive peptide conjugated to a technetium^{99m} detectable label comprises an amino acid sequence comprising SEQ ID NO:13.

[0255] In some embodiments, the amyloid-reactive peptide is a ^{99m}Tc -labelled amyloid-reactive peptide. In other embodiments, the method for diagnosing a type of amyloid disease comprise administering ^{99m}Tc-p5+14.

[0256] In some embodiments, the instructions comprises instructions for detecting the amyloid-reactive peptide conjugated to a technetium^{99m} detectable label in one or more organs or tissues. In some embodiments the amyloid-reactive peptide conjugated to a technetium^{99m} detectable label is detected in lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand.

[0257] In some embodiments, the kit comprises instructions for calculating an organ-specific SUV. In some embodiments, the kit comprises instructions for calculating an organ-specific SUVR. In some embodiments, the kit comprises instructions for calculating a SUVR ratio for one or more organs or tissues. In some embodiments, a SUVR is calculated using a blood pool as a reference tissue. In some embodiments, the SUVR is calculated for each organ by dividing the amount of amyloid detection agent or dye in the organ by the blood pool ratio. In some embodiments, the blood pool is a vein or artery. In some embodiments, the blood pool is the lumen of the thoracic aorta.

[0258] In some embodiments, the kit further comprises instructions for providing a diagnosis based upon the organ-specific SUV or SUVR. In some embodiments, the kit comprises instructions for providing a diagnosis based upon the organ to organ ratio.

[0259] In some embodiments, the kit comprises a therapeutic agent for treating an amyloid disease.

[0260] Some aspects of the invention provide kits for producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual. In some embodiments, the kit comprises reagents for producing labeled amyloid-reactive peptide with technetium^{99m} suitable for administration and instructions for use. In some embodiments, the labeled amyloid-reactive peptide is ^{99m}Tc-p5+14. In some embodiments the labeled amyloid-reactive peptide comprises an amino acid sequence comprising SEQ ID NO:13.

EXEMPLARY EMBODIMENT

[0261] Various embodiments provided herein are included in the following non-limiting list of embodiments.

[0262] Embodiment 1. A method of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease, the method comprising

administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual, wherein the individual has previously tested negative using an alternative detection method; and

detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label in one or more organs or tissues of the individual;

wherein detecting the amyloid-reactive peptide in the one or more organs or tissues indicates that the individual has the amyloid disease.

[0263] Embodiment 2. The method of embodiment 1, wherein the alternative detection method is selected from a group consisting of ^{99m}Tc-labeled pyrophosphate (PYP), ^{124}I-labelled amyloid-reactive peptide detection, 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), Aβ amyloid imaging agents, ^{18}F-Florbetapir (Amyvid), ^{18}F-Flutemetamol (Vizamyl), ^{18}F-Florbetaben (Neuraceq) transthoracic echocardiography and cardiac magnetic resonance imaging.

[0264] Embodiment 3. A method of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, the method comprising

administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and

detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more tissues.

[0265] Embodiment 4. The method of embodiment 3, wherein detecting the amyloid-reactive peptide in the organ or tissue indicates that the individual has an amyloid disease.

[0266] Embodiment 5. The method of embodiment 3, wherein detection of the amyloid-reactive peptide in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis.

[0267] Embodiment 6. A method of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising

administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and

detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide,

wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease.

[0268] Embodiment 7. The method of any of embodiments 1- 2 and 6, wherein the individual is determined to be at risk for an amyloid-related disease based upon the presence of a genetic mutation, having multiple myeloma, having amyloid positive laminectomy tissue, having an amyloid positive tissue from carpal tunnel release surgery, having a monoclonal gammopathy of unknown significance (MGUS), having heart failure with preserved ejection fraction (HFpEF), having heart failure with reduced ejection fraction (HFrEF), being from susceptible ethnic populations, or being elderly.

[0269] Embodiment 8. The method of embodiment 7, wherein the genetic mutation is in the transthyretin gene.

[0270] Embodiment 9. The method of any one of embodiments 1-2 and 6-8, wherein the individual does not have symptoms of amyloidosis.

[0271] Embodiment 10. The method of any one of embodiments 1-2 and 6-8, wherein the individual has neuropathic symptoms of an amyloid disease.

[0272] Embodiment 11. A method of determining prognosis of an individual having an amyloid-related disease comprising

administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs

or tissues of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide;

administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide;

comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual.

[0273] Embodiment 12. The method of embodiment 11, wherein the prognosis of an individual having an amyloid-related disease is based on detecting amyloid-reactive peptide in the heart.

[0274] Embodiment 13. A method of treating an amyloid-related disease comprising

administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual;

detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual between about 0.5 and about 3 hours after administering the amyloid-reactive peptide, and

administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected.

[0275] Embodiment 14. A method of managing the treatment of an amyloid-related disease in an individual comprising:

administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual to detect amyloid in the individual a first time,

wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide;

administering a treatment for an amyloid-related disease;

administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.5 and about 3 hours of administering the amyloid-reactive peptide;

comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and

adjusting the treatment for the amyloid-related disease.

[0276] Embodiment 15. The method of any one of embodiments 1-14, further comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at a tissue or organ of the individual to detect amyloid in the individual a second time, optionally a third time a fourth time, and/or a fifth time.

[0277] Embodiment 16. The method embodiment 14 or 15, wherein the first time and the second time are at least six weeks apart.

[0278] Embodiment 17. The method of embodiment 16, wherein if the amyloid disease is stable between the first and second times treatment is be modified.

[0279] Embodiment 18. The method of embodiment 17, wherein if the amyloid burden increases treatment is reinitiated.

[0280] Embodiment 19. The method of any of embodiments 6-18, wherein the detecting takes place about 0.5, 1, 1.5, 2, 2.5, or 3 hours after administration of the amyloid-reactive peptide.

[0281] Embodiment 20. The method of any one of embodiments 1-2 and 6-19, wherein the tissue or organ of the individual is selected from the group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand.

[0282] Embodiment 21. The method of any one of embodiments 1-2 and 6-19, wherein the tissue or organ of the individual is selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue.

[0283] Embodiment 22. The method of any one of embodiments 1-2 and 6-19, wherein the tissue or organ of the individual is selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland.

[0284] Embodiment 23. The method of any of embodiments 1-22, wherein the detecting comprises imaging by single photon emission computed tomography (SPECT), SPECT with x-ray computed tomography (SPECT/CT), or Planar gamma imaging.

[0285] Embodiment 24. The method of embodiments 1-23, wherein the detecting comprises imaging by single photon emission computed tomography with x-ray computed tomography (SPECT/CT).

[0286] Embodiment 25. The method of any of embodiments 1-24, wherein the detecting comprises quantifying the amount of detectable label to quantify the amount of amyloid-reactive peptide.

[0287] Embodiment 26. The method of embodiment 25, wherein an amount of amyloid-reactive peptide above a threshold indicates presence of amyloid deposits in the one or more organs or tissues.

[0288] Embodiment 27. The method of embodiment 26, wherein amyloid deposits detected in one or more organs or tissues indicates the individual has an amyloid related disease.

[0289] Embodiment 28. The method of embodiments 1-27, wherein detection of an amount of amyloid-reactive peptide in the heart is between about 2 and about 5 times the SD of the heart of a healthy individual, indicating the individual has ATTR.

[0290] Embodiment 29. The method of embodiments 1-27, wherein detection of an amount of amyloid-reactive peptide in the heart is about 1.96 times the SD of the heart of a healthy individual, indicating the individual has ATTR.

[0291] Embodiment 30. The method of any one embodiments 1-29, wherein the amyloid-reactive peptide comprises or consists of the amino acid sequence set forth in SEQ ID NO:13.

[0292] Embodiment 31. The method of embodiment 30, wherein the amyloid-reactive peptide comprises of consists of the amino acid set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label.

[0293] Embodiment 32. The method of any one of embodiments 1-31, wherein the amyloid-reactive peptide comprises an N-terminal leader sequence that comprises the amino acid sequence set forth in SEQ ID NO: 100.

[0294] Embodiment 33. The method of any one of embodiments 1-32, wherein a dose of about 10 to about 25 mCi of Tc-99 is administered to the individual.

[0295] Embodiment 34. The method of embodiment 33, wherein a dose of about less than 20 mCi of Tc-99 is administered to the individual.

[0296] Embodiment 35. The method of any one of embodiments 1-34, wherein a dose of about 0.3 mg, 1 mg, 1.5 mg, or about 2 mg of amyloid-reactive peptide is administered to the individual.

[0297] Embodiment 36. The method of embodiment 35, wherein a dose of about comprising about less than 0.1 mg amyloid-reactive peptide is administered to the individual.

[0298] Embodiment 37. The method of any one of embodiments 1-36, wherein the amyloid-reactive peptide is administered intravenously.

[0299] Embodiment 38. The method of any one of embodiments 1-37, further comprising determining an organ-specific standard uptake value ratio for the tissue or organ of the individual.

[0300] Embodiment 39. The method of embodiment 38, wherein the organ-specific SUVR for the individual is selected from the group consisting of SUVR mean, SUVR max, and SUVR peak.

[0301] Embodiment 40. The method of any one of embodiments1-39, further comprising determining an organ-specific SUV for the individual.

[0302] Embodiment 41. The method of embodiment 40, wherein the organ-specific SUV for the individual is selected from the group consisting of SUV mean, SUV max, and SUV peak.

[0303] Embodiment 42. The method of any one of embodiments 1-41, wherein the amyloid-reactive peptide has a sensitivity of at least 90%.

[0304] Embodiment 43. The method of any one of embodiments 1-42, wherein the sensitivity is about 95%, about 99% or about 100%.

[0305] Embodiment 44. The method of any one of embodiments 1-43, further comprising determining one or more health related quality of life measures for the individual.

[0306] Embodiment 45.The method of any one of embodiments 1-44, further comprising detecting one or more biomarkers associated with the amyloid-related disease.

[0307] Embodiment 46. The method of embodiment 45, wherein the biomarker associated with amyloid-related disease is selected from the group consisting of Troponin T, NTproBNP, urine protein levels, UACR, EGFR, and alkaline phosphatase levels.

[0308] Embodiment 47. The method of any one of embodiments 1-46, further comprising performing a cardiac biopsy if amyloid is detected in the heart.

[0309] Embodiment 48. The method of any one of embodiments 1-47, further comprising performing additional amyloid imaging on the individual.

[0310] Embodiment 49. The method of embodiment 48, wherein the additional amyloid imaging on the individual comprises ECHO, CMR, bone scintigraphy or positron emission tomography imaging.

[0311] Embodiment 50. The method of embodiment 49, where in the additional amyloid imaging on the individual further comprises a tracer selected from the group consisting of ^{99m}Tc-PyP, ^{99m}Tc-DPD, ^{99m}Tc-HMDP, ^{99m}Tc-MDP other bone scintigraphy tracers, ^{124}I-evuzamatide, and ^{18}F-florbetapir, ^{18}F-flutemetamol, and ^{18}F-florbetaben.

[0312] Embodiment 51. The method of any one of embodiments 1-50, wherein the individual is diagnosed with amyloid cardiomyopathy.

[0313] Embodiment 52. The method of any one of embodiments 1-51, wherein the individual is suspected of having amyloid cardiomyopathy.

[0314] Embodiment 53. The method of any one of embodiments 1-52, wherein the amyloid-related disease is systemic or localized amyloidosis.

[0315] Embodiment 54. The method of any one of embodiments 1-53, wherein the amyloid-reactive peptide has pan-amyloid specificity.

[0316] Embodiment 55. The method of any one of embodiments 1-54, wherein the amyloid-reactive peptide binds to amyloid of immunoglobulin light chain (AL), immunoglobulin heavy chain (AH), β2-microglobulin (Aβ2M), transthyretin (ATTR wild type; ATTR variant), apolipoprotein AI (AApoAI), apolipoprotein AII (AApoAII), apolipoprotein AIV (AApoAIV), gelsolin (AGel), apolipoprotein C-II (AApoCII), apolipoprotein C-II (AApoCIII), lysozyme

(ALys), leukocyte chemotactic factor (ALECT2), fibrinogen a variants (AFib), cystatin variants (ACys), calcitonin (ACal), lactadherin (AMed), islet amyloid polypeptide (AIAPP), prolactin (APro), insulin (AIns), prior protein (APrP); α-synuclein (AαSyn), tau (ATau), atrial natriuretic factor (AANF), IAAP, ALβ4, or ALβ1.

[0317] Embodiment 56. The method of any one of embodiments 1-55, wherein the individual has a genetic predisposition to an amyloid-related disease.

[0318] Embodiment 57. The method of any one of embodiments 1-56, wherein the individual has a family history of an amyloid-related disease.

[0319] Embodiment 58. The method of any one of embodiments 1-57, wherein the individual is elderly.

[0320] Embodiment 59. The method of any one of embodiments 1-58, wherein the individual has an early stage of an amyloid-related disease.

[0321] Embodiment 60. The method of any one of embodiments 1-59, wherein the individual has an early stage of AL amyloidosis.

[0322] Embodiment 61. The method of embodiment 60, wherein the early stage of AL amyloidosis is diagnosed according to the Mayo Clinic system.

[0323] Embodiment 62. The method of embodiment 61, wherein the early stage of AL amyloidosis is stage 1 AL amyloidosis.

[0324] Embodiment 63. The method of any one of embodiments 1-4 and 6-62, wherein the individual has an early stage of ATTR amyloidosis.

[0325] Embodiment 64. The method of embodiment 63, wherein the early stage of ATTR amyloidosis comprises stage 1 ATTR amyloidosis.

[0326] Embodiment 65. The method of any one of embodiments 1-13, 21-64, further comprising administering a therapy for the amyloid-related disease.

[0327] Embodiment 66. The method of any one of embodiments 14-20 and 65, wherein the therapy for the amyloid-related disease is selected from the group consisting of transthyretin stabilizers (e.g. tafamidis, acoramidis), transthyretin silencers (e.g. Patisiran, Inotersen, Vutrisiran, Eploetersen), gene editing approaches, anti-amyloid approaches utilizing monoclonal antibodies, treatments targeting plasma cell clones (e.g. Daratumumab, Bortezomib), and an antibody-peptide fusion comprising an antibody-peptide fusion protein comprising a second amyloid-reactive peptide and an antibody that does or does not binds to amyloid fibrils.

[0328] Embodiment 67. The method of embodiment 66, wherein the second amyloid-reactive peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-14 comprising 0, 1, 2, 3, or 4 amino acid substitutions, insertions, or deletions.

[0329] Embodiment 68. The method of embodiment 66 or 67, wherein the antibody-peptide fusion protein comprises a heavy chain and a light chain and wherein the amyloid-reactive peptide is linked to at the C-terminal end of the light chain of the antibody via a spacer.

[0330] Embodiment 69. The method of any one of embodiments 66-68, wherein the antibody-peptide fusion protein comprises:

(i) an amyloid-reactive peptide comprising the amino acid sequence set forth in SEQ ID NO:2; and

(ii) an antibody that binds to a human amyloid fibrils, wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain of the antibody comprises a heavy chain variable region (VH) and the light chain of the antibody comprises a light chain variable region (VL), wherein the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:106, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:107, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:108, and the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:103, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:104, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:105; wherein the amyloid-reactive peptide and antibody are linked at the C-terminal end of the light chain, and wherein the amyloid-reactive peptide is linked to the antibody via a spacer comprising an amino acid sequence set forth in SEQ ID NO:83.

[0331] Embodiment 70. A method of producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual, the method comprising

(a) combining a solution comprising 10-30 μg of the amyloid-reactive peptide and a solution comprising 1.0-3.5 mg of $SnCl_2$ with a solution comprising technetium^{99m} to produce a labeling composition;

(b) incubating the labeling composition to produce a labeled amyloid reactive peptide; and

(c) adding a quencher to the labeling composition within five minutes of the combining to produce a quenched composition comprising a labeled amyloid-reactive peptide with technetium^{99m}.

[0332] Embodiment 71. The method of embodiment 70, further comprising diluting the quenching composition after step (c).

[0333] Embodiment 72. The method of any of embodiment 70 or 71, further comprising purifying the labeled amyloid peptide from the quenched composition.

[0334] Embodiment 73. The method of any of embodiments 70 -72 wherein the solution comprising 10-30 μg of the amyloid-reactive peptide further comprises sterile phosphate buffered saline.

[0335] Embodiment 74. The method of any of embodiments 70-73, comprising preparing the solution comprising 1.0-3.5 mg of $SnCl_2$ before step (a).

[0336] Embodiment 75. The method of claim 74, wherein the preparing the solution comprising 1.0-3.5 mg of $SnCl_2$ comprises combining 1N HCL and $SnCl_2$ to create a tin solution.

[0337] Embodiment 76. The method of embodiment 75, wherein the tin solution is diluted with pure water to create a stock solution.

[0338] Embodiment 77. The method of embodiment 76, wherein the stock solution is diluted with HCL.

[0339] Embodiment 78. The method of any of embodiments 70-77, wherein the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m}.

[0340] Embodiment 79. The method of any of embodiments 70 -78, wherein the solution comprising technetium^{99m} comprises saline.

[0341] Embodiment 80. The method of embodiment 79, wherein the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m} and about 100 to about 300 μL saline.

[0342] Embodiment 81. The method of any of embodiments 70-79, wherein the technetium^{99m} is in the form of pertechnetate.

[0343] Embodiment 82. The method of any of embodiments 70-80, further comprising measuring radiopurity of the labeled amyloid-reactive peptide after step (c) by reverse phase high performance liquid chromatography (HPLC).

[0344] Embodiment 83. The method of embodiment 82, wherein the radiopurity of the labeled amyloid-reactive peptide is greater than about 90%, greater than about 95% or greater than about 99%.

[0345] Embodiment 84. The method of any of embodiments 70-83, wherein the integrity of the amyloid-reactive peptide before adding the radio label is the same as the integrity of the labeled amyloid-reactive peptide.

[0346] Embodiment 85. The method of embodiment 84, wherein the integrity of the amyloid-reactive peptide labeled and the amyloid-reactive peptide relates to the proportion of degraded peptide.

[0347] Embodiment 86. The method of any of embodiments 70-85, wherein the labeled amyloid-reactive peptide is not significant degraded.

[0348] Embodiment 87. The method of any of embodiments 70-86, wherein the labeled amyloid-reactive peptide does not cause an adverse reaction when administered to an individual.

[0349] Embodiment 88. The method of any one of embodiments 1-87, wherein a peptide comprising the amyloid-reactive peptide and an N-terminal leader sequence is administered to the individual.

[0350] Embodiment 89. The method of embodiment 88, wherein the peptide comprising the amyloid reactive peptide comprises the amino acid sequence set forth in SEQ ID NO: 100.

[0351] Embodiment 90. The method of embodiment 89, wherein the technetium^{99m} detectable label is bound to one or more amino acids at positions 1 to 6 of the amino acid sequence set forth in SEQ ID NO: 100.

[0352] Embodiment 91. A peptide comprising the amino acid set forth in SEQ ID NO: 100, wherein the peptide comprises a technetium^{99m} detectable label bound to one or more amino acids at positions 1 to 6.

[0353] Embodiment 92. A method of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease, the method comprising, (a) administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual, wherein the individual has previously tested negative using an alternative detection method; and (b) detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label in one

or more organs or tissues of the individual; wherein detecting the amyloid-reactive peptide in the one or more organs or tissues indicates that the individual has the amyloid disease.

[0354] Embodiment 93. The method of embodiment 92, wherein the alternative detection method is selected from a group consisting of ^{99m}Tc-labeled pyrophosphate (PYP), ^{124}I-labelled amyloid-reactive peptide detection, 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), Aβ amyloid imaging agents, ^{18}F-Florbetapir (Amyvid), ^{18}F-Flutemetamol (Vizamyl), ^{18}F-Florbetaben (Neuraceq) transthoracic echocardiography and cardiac magnetic resonance imaging.

[0355] Embodiment 94. A method of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, the method comprising (a) administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and (b) detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more tissues.

[0356] Embodiment 95. The method of embodiment 94, wherein detecting the amyloid-reactive peptide in the organ or tissue indicates that the individual has an amyloid disease.

[0357] Embodiment 96. The method of embodiment 64, wherein detection of the amyloid-reactive peptide in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis.

[0358] Embodiment 97. A method of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising (a) administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and (b) detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues the individual between about 0.1 and about 3 hours after administering the amyloid-reactive peptide, wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease.

[0359] Embodiment 98. The method of any of embodiments 92- 93 and 97, wherein the individual is determined to be at risk for an amyloid-related disease based upon the presence of a genetic mutation, having multiple myeloma, having amyloid positive laminectomy tissue, having

an amyloid positive tissue from carpal tunnel release surgery, having a monoclonal gammopathy of unknown significance (MGUS), having heart failure with preserved ejection fraction (HFpEF), having heart failure with reduced ejection fraction (HFrEF), being from susceptible ethnic populations, or being elderly.

[0360] Embodiment 99. The method of embodiment 98, wherein the genetic mutation is in the transthyretin gene.

[0361] Embodiment 100. The method of any one of embodiments 92-93 and 97-99, wherein the individual does not have symptoms of amyloidosis.

[0362] Embodiment 101. The method of any one of embodiments 92-93 and 97-99, wherein the individual has neuropathic symptoms of an amyloid disease.

[0363] Embodiment 102. A method of determining prognosis of an individual having an amyloid-related disease comprising (a) administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide; (b) administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide; (c) comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual.

[0364] Embodiment 103. The method of embodiment 102, wherein the prognosis of an individual having an amyloid-related disease is based on detecting amyloid-reactive peptide in the heart.

[0365] Embodiment 104. A method of treating an amyloid-related disease comprising (a) administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; (b) detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or

more tissues or organs of the individual between about 0.1 and about 3 hours after administering the amyloid-reactive peptide, and (c) administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected.

[0366] Embodiment 105. A method of managing the treatment of an amyloid-related disease in an individual comprising: (a) administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide; (b) administering a treatment for an amyloid-related disease; (c) administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide; (d) comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and (e) adjusting the treatment for the amyloid-related disease.

[0367] Embodiment 106. The method of any of embodiments 92-105, further comprising estimating a cardiac amyloid burden in the individual.

[0368] Embodiment 107. The method of embodiment 106, wherein the cardiac amyloid burden is based on a ratio of the technetium^{99m} detectable label in heart and blood of the individual.

[0369] Embodiment 108. A method of estimating cardiac amyloid burden in an individual with an amyloid-related disease, the method comprising: (a) administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; (b) detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label in images of heart and blood of the individual between about 0.1 hours and about 3 hours after administering the amyloid-reactive peptide; and (c) estimating a cardiac amyloid burden based on the ratio of the technetium^{99m} detectable label detected in the heart and the blood of the individual.

[0370] Embodiment 109. The method of any of embodiments 106-108, wherein the cardiac amyloid burden correlates with one or more biomarkers associated with the amyloid-related disease.

[0371] Embodiment 110. The method of any one of embodiments 92-102 and 104, and 106-109, further comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at a tissue or organ of the individual to detect amyloid in the individual a second time, optionally a third time a fourth time, and/or a fifth time.

[0372] Embodiment 111. The method embodiments 102, 105 or 110, wherein the first time and the second time are at least six weeks apart.

[0373] Embodiment 112. The method of embodiment 111, wherein if the amyloid disease is stable between the first and second times treatment is be modified.

[0374] Embodiment 113. The method of embodiment 111, wherein if the amyloid burden increases treatment is reinitiated.

[0375] Embodiment 114. The method of any of embodiments 97-113, wherein the detecting takes place about 0.5 and about 3 hours after administration of the amyloid-reactive peptide.

[0376] Embodiment 115. The method of any of embodiments 97-113, wherein the detecting takes place about 0.01, about 0.2, about 0.3, about 0.4, about 0.5, about 1, about 1.5, about 2, about 2.5, or about 3 hours after administration of the amyloid-reactive peptide.

[0377] Embodiment 116. The method of any one of embodiments 92-93 and 97-113, wherein the tissue or organ of the individual is selected from the group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand.

[0378] Embodiment 117. The method of any one of embodiments 92-93 and 97-113, wherein the tissue or organ of the individual is selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue.

[0379] Embodiment 118. The method of any one of embodiments 92-93 and 97-113, wherein the tissue or organ of the individual is selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland.

[0380] Embodiment 119. The method of any one of embodiments 92-118, wherein the detecting comprises imaging by single photon emission computed tomography (SPECT), SPECT with x-ray computed tomography (SPECT/CT), or Planar gamma imaging.

[0381] Embodiment 120. The method of any one of embodiments 92-119, wherein the detecting comprises imaging by single photon emission computed tomography with x-ray computed tomography (SPECT/CT).

[0382] Embodiment 121. The method of any of embodiments 92-120, wherein the detecting comprises quantifying the amount of detectable label to quantify the amount of amyloid-reactive peptide.

[0383] Embodiment 122. The method of embodiment 121, wherein an amount of amyloid-reactive peptide above a threshold indicates presence of amyloid deposits in the one or more organs or tissues.

[0384] Embodiment 123. The method of any one of embodiments 92-122, wherein detection of an amount of amyloid-reactive peptide in the heart is between about 2 and about 5 times the SD of the heart of a healthy individual, indicating the individual has ATTR.

[0385] Embodiment 124. The method of any one of embodiments 92-123, wherein detection of an amount of amyloid-reactive peptide in the heart is about 1.96 times the SD of the heart of a healthy individual, indicating the individual has ATTR.

[0386] Embodiment 125. The method of any one of embodiments 92-124, wherein the amyloid-reactive peptide comprises or consists of the amino acid sequence set forth in SEQ ID NO:13.

[0387] Embodiment 126. The method of embodiment 125, wherein the amyloid-reactive peptide comprises of consists of the amino acid set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label.

[0388] Embodiment 127. The method of any one of embodiments 92-126, wherein the amyloid-reactive peptide comprises an N-terminal leader sequence that comprises the amino acid sequence set forth in SEQ ID NO: 100.

[0389] Embodiment 128. The method of any one of embodiments 92-127, wherein a dose of about 10 to about 25 mCi of Tc-99m is administered to the individual.

[0390] Embodiment 129. The method of any one of embodiments 92-128, wherein a dose of about 20 mCi of Tc-99m is administered to the individual.

[0391] Embodiment 130. The method of embodiment 128, wherein a dose of about less than 20 mCi of Tc-99m is administered to the individual.

[0392] Embodiment 131. The method of any one of embodiments 1-130, wherein a dose of about 0.3 mg, 1 mg, 1.5 mg, or about 2 mg of amyloid-reactive peptide is administered to the individual.

[0393] Embodiment 132. The method of any one of embodiments 92-131, wherein the amyloid-reactive peptide is administered intravenously.

[0394] Embodiment 133. The method of any one of embodiments 92-132, further comprising determining an organ-specific standard uptake value ratio (SUVR) for the tissue or organ of the individual.

[0395] Embodiment 134. The method of embodiment 133, wherein the organ-specific SUVR for the individual is selected from the group consisting of SUVR mean, SUVR max, and SUVR peak.

[0396] Embodiment 135. The method of any one of embodiments 92-134, wherein the amyloid-reactive peptide has a sensitivity of at least 90%.

[0397] Embodiment 136. The method of any one of embodiments 92-135, wherein the sensitivity is about 95%, about 99% or about 100%.

[0398] Embodiment 137. The method of any one of embodiments 92-136, further comprising determining one or more health related quality of life measures for the individual.

[0399] Embodiment 138. The method of any one of embodiments 92-137, further comprising detecting one or more biomarkers associated with the amyloid-related disease.

[0400] Embodiment 139. The method of embodiment 138, wherein the biomarker associated with amyloid-related disease is selected from the group consisting of Troponin T, NTproBNP, urine protein levels, UACR, EGFR, interventricular septal wall thickness (IVS), left ventricular (LV) wall thickness, global longitudinal strain (GLS), and alkaline phosphatase levels.

[0401] Embodiment 140. The method of any one of embodiments 92-139, further comprising performing a cardiac biopsy if amyloid is detected in the heart.

[0402] Embodiment 141. The method of any one of embodiments 92-140, further comprising performing additional amyloid imaging on the individual.

[0403] Embodiment 142. The method of embodiment 141, wherein the additional amyloid imaging on the individual comprises ECHO, CMR, bone scintigraphy or positron emission tomography imaging.

[0404] Embodiment 143. The method of embodiment 142, where in the additional amyloid imaging on the individual further comprises a tracer selected from the group consisting of ^{99m}Tc-PyP, ^{99m}Tc-DPD, ^{99m}Tc-HMDP, ^{99m}Tc-MDP other bone scintigraphy tracers, ^{124}I-evuzamatide, and ^{18}F-florbetapir, ^{18}F-flutemetamol, and ^{18}F-florbetaben.

[0405] Embodiment 144. The method of any one of embodiments 92-143, wherein the individual is diagnosed with amyloid cardiomyopathy.

[0406] Embodiment 145. The method of any one of embodiments 92-144, wherein the individual is suspected of having amyloid cardiomyopathy.

[0407] Embodiment 146. The method of any one of embodiments 92-143, wherein the amyloid-related disease is systemic or localized amyloidosis.

[0408] Embodiment 147. The method of any one of embodiments 92-146, wherein the individual has a genetic predisposition to an amyloid-related disease.

[0409] Embodiment 148. The method of any one of embodiments 92-147, wherein the individual has a family history of an amyloid-related disease.

[0410] Embodiment 149. The method of any one of embodiments 92-148, wherein the individual is elderly.

[0411] Embodiment 150. The method of any one of embodiments 92-149, wherein the individual has an early stage of an amyloid-related disease.

[0412] Embodiment 151. The method of any one of embodiments 92-150, wherein the individual has an early stage of AL amyloidosis.

[0413] Embodiment 152. The method of embodiment 151, wherein the early stage of AL amyloidosis is diagnosed according to the Mayo Clinic system.

[0414] Embodiment 153. The method of embodiment 152, wherein the early stage of AL amyloidosis is stage 1 AL amyloidosis.

[0415] Embodiment 154. The method of any one of embodiments 92-95 and 6-97, wherein the individual has an early stage of ATTR amyloidosis.

[0416] Embodiment 155. The method of embodiment 154, wherein the early stage of ATTR amyloidosis comprises stage 1 ATTR amyloidosis.

[0417] Embodiment 156. The method of any one of embodiments 92-155, further comprising administering a therapy for the amyloid-related disease.

[0418] Embodiment 157. A method of producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual, the method comprising (a) combining a solution comprising 10-30 µg of the amyloid-reactive peptide and a solution comprising 1.0-3.5 mg of $SnCl_2$ with a solution comprising technetium^{99m} to produce a labeling composition; (b) incubating the labeling composition to produce a labeled amyloid reactive peptide; and (c) adding a quencher to the labeling composition within five minutes of the combining to produce a quenched composition comprising a labeled amyloid-reactive peptide with technetium^{99m}.

[0419] Embodiment 158. The method of embodiment 157, further comprising diluting the quenching composition after step (c).

[0420] Embodiment 159. The method of embodiment 157 or 158, further comprising purifying the labeled amyloid peptide from the quenched composition.

[0421] Embodiment 160. The method of any one of embodiments 157 - 159 wherein the solution comprising 10-30 µg of the amyloid-reactive peptide further comprises sterile phosphate buffered saline.

[0422] Embodiment 161. The method of any one of embodiments 157-160, comprising preparing the solution comprising 1.0-3.5 mg of $SnCl_2$ before step (a).

[0423] Embodiment 162. The method of embodiment 161, wherein the preparing the solution comprising 1.0-3.5 mg of $SnCl_2$ comprises combining 1N HCl and $SnCl_2$ to create a tin solution.

[0424] Embodiment 163. The method of embodiment 162, wherein the tin solution is diluted with pure water to create a stock solution.

[0425] Embodiment 164. The method of embodiment 163, wherein the stock solution is diluted with HCl.

[0426] Embodiment 165. The method of any one of embodiment157-164, wherein the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m}.

[0427] Embodiment 166. The method of any one of embodiments 157 - 165, wherein the solution comprising technetium^{99m} comprises saline.

[0428] Embodiment 167. The method of embodiment 166, wherein the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m} and about 100 µL to about 300 µL saline.

[0429] Embodiment 168. The method of any one of embodiments 157-167, wherein the technetium^{99m} is in the form of pertechnetate.

[0430] Embodiment 169. The method of any one of embodiments 157-168, further comprising measuring radiopurity of the labeled amyloid-reactive peptide after step (c) by reverse phase high performance liquid chromatography (HPLC).

[0431] Embodiment 170. The method of embodiment 169, wherein the radiopurity of the labeled amyloid-reactive peptide is greater than about 90%, greater than about 95% or greater than about 99%.

[0432] Embodiment 171. The method of any one of embodiments 157-170, wherein the integrity of the amyloid-reactive peptide before adding the radio label is the same as the integrity of the labeled amyloid-reactive peptide.

[0433] Embodiment 172. The method of embodiment 171, wherein the integrity of the amyloid-reactive peptide labeled and the amyloid-reactive peptide relates to the proportion of degraded peptide.

[0434] Embodiment 173. The method of any one of embodiments 157-172, wherein the labeled amyloid-reactive peptide is not significant degraded.

[0435] Embodiment 174. The method of any one of embodiments 157-173, wherein the labeled amyloid-reactive peptide does not cause an adverse reaction when administered to an individual.

[0436] Embodiment 175. The method of any one of embodiments 92-174, wherein a peptide comprising the amyloid-reactive peptide and an N-terminal leader sequence is administered to the individual.

[0437] Embodiment 176. The method of embodiment 175, wherein the peptide comprising the amyloid reactive peptide comprises the amino acid sequence set forth in SEQ ID NO: 100.

[0438] Embodiment 177. The method of embodiment 176, wherein the technetium^{99m} detectable label is bound to one or more amino acids at positions 1 to 6 of the amino acid sequence set forth in SEQ ID NO: 100.

[0439] Embodiment 178. A peptide comprising the amino acid set forth in SEQ ID NO: 100, wherein the peptide comprises a technetium^{99m} detectable label bound to one or more amino acids at positions 1 to 6.

EXAMPLES

[0440] The following examples are included for illustrative purposes only and are not intended to limit the scope of the present disclosure.

Example 1: Production of ^{99m}Tc labeled peptide suitable for administration to an individual

[0441] This example demonstrates the production of an amyloid-reactive peptide labeled with ^{99m}Tc suitable for administration to an individual.

[0442] An amyloid-reactive peptide comprising an amino acid sequence set forth in SEQ ID NO: 13 lacking a chelating moiety, was labeled with ^{99m}Tc. The amyloid-reactive peptide is a 45-amino acid synthetic reagent that has a predicted α-helical structure in the presence of its ligand. The amino sequence ensures that the 12 charged lysine side chains align on one face of the helix. The N-terminal of the peptide comprises three glycine residues at position one, two, and three. During radiolabeling of the peptide, we predict that, the ^{99m}Tc coordinates with the amyloid-reactive peptide through these three N-terminal glycine residues using a coordination pattern similar to that predicted for the ^{99m}Tc labeling of mercaptoacetyltriglycine (MAG-3) (**FIG. 1**).

Reaction

[0443] Prior to radiolabeling, a uniform suspension of tin chloride at 100 mg/ml was prepared by adding 30 µL of 1 N HCl to 3 mg of stannous chloride ($SnCl_2.2H_2O$) in a 1.5-mL microfuge tube. The suspension was added to 2.97 mL of water for injection to yield a stock solution of 1 mg/mL $SnCl_2.2H_2O$ in 0.01 N HCl.

[0444] For radiolabeling, 1 mg of the amyloid-reactive peptide p5+14 was dissolved in 0.8 mL of sterile phosphate buffered saline, pH 7.6 and the solution was allowed to stand for 10 minutes at room temperature. To the reaction vial, 0.2 mL of 0.15 N sodium hydroxide solution (15 µL of 10 N NaOH in 1 mL water for injection), 800 µL of peptide p5+14 solution

(1.25 mg/mL stock solution) and 45 mCi of ^{99m}TcO4- (Cardinal Health) in ~0.3 mL of saline were added. Lastly, 50 µL of the $SnCl_2.2H_2O$ solution (1 mg/mL) was added to the reaction and the mixture was allowed to stand for 2 minutes at room temperature. The reaction was quenched by addition of 65 µL of 0.5 M sodium dibasic phosphate. The solution was immediately diluted by addition to 14.5 mL of sterile phosphate buffered saline and sterile filtered. A volume of ~4.5 mL of the final product was used for quality control and quality assurance testing.

Example 2: Detection of Amyloid Cardiomyopathy in Patients with Systemic ATTR and AL Amyloidosis Using SPECT/CT and Planar Imaging of ^{99m}Tc-p5+14

[0445] This example demonstrates the utility of an amyloid-reactive peptide labeled with ^{99m}Tc to detect cardiac amyloid associated with AL and ATTR amyloidosis.

STUDY DESIGN

[0446] The clinical study (UTGSM-164388-101) is an ongoing four-part, open label, single site, Phase 1 study with the assessment of radiation dosimetry as the primary outcome.

[0447] Part 2-4 are completed or ongoing. In Part 3, which is complete, 5 healthy subjects underwent planar gamma scintigraphy (PGS) and SPECT/CT imaging following a single IV dose of 20 mCi^{99m}Tc-p5+14 to assess negative percent agreement in healthy subjects. Part 2 is ongoing. In Part 2, 10 ATTR patients and 5 AL patients with amyloid cardiomyopathy underwent PGS and SPECT/CT imaging following a single IV injection of 20 mCi^{99m}Tc-p5+14 to determine positive percent agreement in patients with cardiac amyloidosis and to compare with contemporaneous ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) imaging. Part 4 is ongoing. In Part 4, 10 patients with biopsy-confirmed ATTR cardiac amyloidosis who are ^{99m}Tc-PYP negative (or had non-diagnostic ^{99m}Tc-PYP imaging) undergo PGS and SPECT/CT imaging following a single IV dose of 20 mCi^{99m}Tc-+14 followed by PGS and SPECT/CT imaging of 20 mCi^{99m}Tc-PYP-PGS and SPECT/CT imaging to determine positive percent agreement with endomyocardial biopsy in a PYP-negative population

[0448] Part 1 has not begun. In Part 1, 5 AL patients undergo repeat planar gamma scintigraphy (PGS) and SPECT/CT imaging following a single intravenous (IV) administration of 20 mCi of the amyloid-reactive peptide comprising an amino acid sequence set forth in SEQ ID NO: 13 labeled with ^{99m}Tc (20 mCi ^{99m}Tc-p5+14) to assess safety and a whole body effective radioactivity dose measurements.

[0449] All parts are conducted in parallel, and subjects are enrolled at any time during the study. A total of 35 subjects are enrolled. The screening period is up to 24 weeks and the treatment/follow-up period (i.e., the time after consenting) was approximately 8 days; thus, the total participant duration was up to approximately 25 weeks.

[0450] In all parts, subjects are patients > 18 years of age with a diagnosis of cardiac amyloidosis within four years prior to imaging, or heathy subjects. Each subject is administered a singe IV injection of an amyloid-reactive peptide labeled with ^{99m}Tc (<22 mCi and <1 mg of peptide). Subjects are evaluated using PGS and SPECT/CT imaging acquired at 1 hour and 3 hours post injection (pi). Patient images are compared to those of the healthy subjects, both visually and by region of interest analysis, to assess differential cardiac uptake. Contemporaneous ^{99m}Tc-PYP imaging is performed for comparative purposes.

RESULTS

[0451] Image data collected in healthy subjects demonstrated that the physiological distribution of radiotracer was consistent with principally renal clearance of the peptide with some hepatic clearance. No cardiac uptake was observed in the images of healthy subjects. In contrast, specific cardiac uptake of ^{99m}Tc-p5+14 was seen in patients with ATTRwt, ATTRv, and amyloidosis. This was observed in both PGS and SPECT/CT images acquired at 1 hour and 3 hours post injection. Both the planar and SPECT/CT images using ^{99m}Tc-p5+14 were of high quality and readily interpretable at both 1 hour and 3 hours post-injection. The myocardium:blood ratio in the initial cohort was ~3:1 in patients and ~0.8:1 in healthy volunteers. The ~3:1 myocardium:blood ratio was 2-fold greater than the myocardium:blood ratio measured using ^{99m}Tc-PYP. Uptake of 99mTc-p5+14 in the lung of patients, particularly those with ATTRv, suggested the potential to image pulmonary amyloid also.

ATTR Amyloidosis Imaging

[0452] Biodistribution of ^{99m}Tc-p5+14 at 1 hour post injection in whole body planar scintigraphic images was assessed in each subject. In healthy participants, physiologic distribution of radioactivity was observed in the kidneys, liver, ureters, and urinary bladder, consistent with renal and hepatic clearance of the peptide. There was no evidence of radiotracer uptake in the heart (**FIG. 2A**). In patients with ATTRwt and ATTRv amyloidosis physiologic retention of radioactivity was observed in the kidneys, liver, and urinary bladder. In addition, radiotracer uptake was observed in the heart of the patients with cardiac ATTR amyloidosis.

Uptake in the joints of the hand were also observed in a patient with ATTR amyloidosis, a common feature in this patient population (**FIG. 2B).**

[0453] Biodistribution of ^{99m}Tc-p5+14 at 1 hour post injection was assessed with SPECT/CT in healthy subjects. **FIG. 3A** shows an exemplary axial view. **FIG. 3B** shows a coronal view. **FIG. 3C** shows a sagittal view. Physiologic retention of radioactivity was observed in the liver in one bed position view. There was no evidence of radiotracer uptake in the heart (in any view); rather, low level radioactivity associated with blood pool was observed.

[0454] Biodistribution of ^{99m}Tc-p5+14 at 1 hour post injection was assessed with SPECT/CT in a patient with ATTR amyloidosis. **FIG. 4A** shows an exemplary axial view. **FIG. 4B** shows a coronal view. **FIG. 4C** shows a sagittal view. Physiologic retention of radioactivity was observed in the liver (coronal view) and kidney (sagittal view). In contrast to healthy subjects, radiotracer uptake was observed in the heart – in the free left ventricular (LV) wall , interventricular septum (IVS), right ventricular (RV) wall and possibly right atrial (RA) wall.

[0455] These data demonstrate that SPECT/CT imaging of ^{99m}Tc-p5+14 (20 mCi) at 1 h post injection can generate high-resolution images that enable detection of cardiac amyloid (in the free LV wall, IVS, right ventricular wall and right atrium) in patients with ATTRv and ATTRwt amyloidosis.

[0456] A semi quantitative analysis of ^{99m}Tc-p5+14 uptake 1 hour post injection of a representative healthy subject and subjects with ATTRwt and ATTRv amyloidosis was performed. **FIG. 5** shows representative regions of interest drawn on SPECT/CT axial images of the heart to calculate SPECT activity per unit volume. **Table 4** shows semi-quantitative uptake of radiotracer in the heart (free left ventricular wall and interventricular septum [LV and IVS]), liver, spleen, stomach lumen, right (R)) and left (L) kidneys. The uptake in the heart was scaled (as a ratio) by blood pool radioactivity measured in the right atrial lumen (RA), LV lumen and in the thoracic aorta lumen or by the parenchyma of the lung. For all other organs the blood pool in the RA lumen was used as the reference tissue

Table 4:Semi-quantitiave uptake of ^{99m}Tc-p5+14

	Healthy Participant	**ATTRwt**	**ATTRv**
LV-IVS:right atrium (RA)	0.85	3.66	3.09
LV-IVS: LV lumen	0.82	2.43	2.35
LV-IVS:Aorta lumen	0.72	2.97	3.11

LV-IVS: Lung lumen	2.20	6.98	6.13
Liver:RA lumen	3.14	3.54	2.79
Spleen: RA lumen	1.77	1.73	1.29
Stomach: RA lumen	1.10	0.30	0.26
R. Kidney: RA lumen	23.40	22.52	15.53
L. Kidney: RA lumen	24.79	24.01	16.24

[0457] These preliminary data demonstrate that, regardless of the reference tissue used to calculate the relative uptake, uptake in the heart of patients with ATTR amyloidosis was 2.9 to 4.3 times greater than that seen in the healthy subject. The relative uptake in the liver, spleen, and kidneys was similar in healthy subjects and patients with ATTR amyloidosis, representing physiologic retention of radioactivity. Radioactivity in the stomach lumen was ~3 times less in the ATTR patients as compared to the healthy subjects.

[0458] Uptake of ^{99m}Tc-p5+14 was observed in a pulmonary lesion of a patient with ATTR amyloidosis at 1 hour post injection. In axial SPECT/CT images (CT, left; SPECT/CT, center; SPECT, right) a solitary pulmonary lesion was observed to take up the radiotracer (lung) (**FIG. 6**). Pulmonary uptake was not seen in ^{99m}Tc-PYP images. Although this lesion was not biopsied to demonstrate the presence of amyloid, pulmonary amyloidosis is a common manifestation in patient ATTR amyloidosis. Therefore, these data suggest that pulmonary amyloidosis may be detectable using ^{99m}Tc-p5+14 imaging.

Comparing imaging methods

[0459] Comparisons of ^{99m}Tc-p5+14 (20 mCi) and ^{99m}Tc-PYP (20 mCi) uptake in the patients with ATTR and AL amyloidosis was performed on all subjects enrolled in Parts 2 and 4 of the study. Exemplar SPECT/CT images of ^{99m} Tc-p5+14 (axial, left; coronal, right and ^{99m}Tc-PYP (acquired 72 h after the peptide imaging) in a patient with ATTR amyloidosis were compared (**FIG. 7**).

[0460] These data demonstrate that the uptake of ^{99m}Tc-p5+14 is visible in the heart of patients with ATTR who similarly image positively with ^{99m}Tc-PYP. In contrast to the ^{99m}Tc-PYP images, the blood pool radioactivity seen at 1 h post injection of ^{99m}Tc-p5+14 was significantly lower relative to uptake in the myocardium uptake based on visual evaluation of the images.

[0461] A comparison of ^{99m}Tc-p5+14 (20 mCi) and ^{99m}Tc-PYP(20 mCi) uptake in a patient with biopsy-proven cardiac ATTR amyloidosis but equivocal ^{99m}Tc-PYP imaging during the clinical evaluation was performed. Axial SPECT/CT imaging at 1 h and 3 h post injection, resulted in equivocal ^{99m}Tc-PYP imaging, with no apparent uptake of the radiotracer in the myocardium. In contrast, focal intense uptake of ^{99m}Tc-p5+14 was observed in the free left ventricular wall (circled and arrowed), at 1 h which persisted into the image acquired at 3 h (**FIG. 8**). These data suggest that SPECT/CT imaging with ^{99m}Tc-p5+14 can detect cardiac ATTR amyloid early in the disease, and potentially prior to imaging with ^{99m}Tc-PYP.

[0462] Semi-quantification of SPECT/CT image was used to compare uptake of ^{99m}Tc-p5+14 and ^{99m}Tc-PYP across all subjects with amyloidosis. ^{99m}Tc-p5+14 (20 mCi) and ^{99m}Tc-PYP (20 mCi) uptake measured by heart (H):Right atrium (RA) (mean units), H:Aorta (mean units), H:RA (max units) and H:Aorta (max units). According to all measurements, uptake of ^{99m}Tc-p5+14 was higher in ATTRv, ATTRwt, and AL patients (**FIG. 9A-9C).** For all subjects with amyloidosis, the difference in ratio tracer uptake was significantly higher between ^{99m}Tc-p5+14 H:RA (mean units) and PYP H:RNA (mean units) as well as between ^{99m}Tc-p5+14 H:Aorta (mean unites) and PYP H:Aotra (mean units) (**FIG. 10).**

[0463] Subjects with cardiac amyloidosis showed similar patterns of uptake patterns for ^{99m}Tc-p5+14 and ^{99m}Tc-PYP as measured with planar images. Specifically, uptake of ^{99m}Tc-p5+14 based on planar images showed a correlation with uptake of ^{99m}Tc-PYP ($r_p = 0.9852$, p-0.003) (**FIG. 11A**).Similar patterns between heart and lung uptake as well as heart and muscle uptake for ^{99m}Tc-p5+14 and ^{99m}Tc-PYP in planar images were seen (**FIG. 11B-11C.**).

AL Amyloidosis Imaging

[0464] Biodistribution of ^{99m}Tc-p5+14 at 1 hour post injection was assessed in whole body PGS images of a representative patient with AL amyloidosis **FIG. 12**. The images show an anterior and posterior view. Characteristic physiologic retention of radioactivity was observed in the kidneys and urinary bladder. In addition, radiotracer uptake was observed in the heart of the patients with cardiac AL amyloidosis. Uptake was also observed in salivary glands and spleen with increased uptake in the liver, common features of amyloid distribution in the AL patient population. These data suggest that gamma scintigraphic imaging with ^{99m}Tc-p5+14 can detect cardiac AL amyloid with characteristic uptake in the salivary gland, which has not been seen in

the five patients with ATTR amyloidosis. Uptake in the liver of the patient with AL was greater than the physiologic uptake seen in healthy subjects suggesting hepatic amyloidosis in this patient. Biodistribution of ^{99m}Tc-p5+14 at 1 hour post injection was assessed in SPECT/CT images of a patient with AL amyloidosis. **FIG 13** (showing axial [left], coronal [center], and sagittal [right] views of SPECT, SPECT/CT, and CT images). These data demonstrate that the uptake of ^{99m}Tc-p5+14 is visible in the heart, liver, and spleen of a patient with AL amyloidosis.

[0465] The uptake of ^{99m}Tc-p5+14 in the heart of a patient with AL amyloidosis was assessed 1 hour post injection. **FIG. 14** shows axial SPECT/CT, SPECT, and CT transaxial images. Radiotracer uptake was observed in the free LV wall, IVS and RV wall.

[0466] ^{99m}Tc-p5+14 was determined to be a promising new reagent for detect of ATTR and AL cardiac amyloid using gamma imaging and may serve as a useful tool for early detection of amyloidosis by community cardiologists.

[0467] The present disclosure is not intended to be limited in scope to the particular disclosed embodiments, which are provided, for example, to illustrate various aspects of the present disclosure. Various modifications to the compositions and methods described will become apparent from the description and teachings herein. Such variations may be practiced without departing from the true scope and spirit of the disclosure and are intended to fall within the scope of the present disclosure.

Example 3: Detection of Amyloid Cardiomyopathy in Additional Patients with Systemic ATTR and AL Amyloidosis Using SPECT/CT and Planar Imaging of ^{99m}Tc-p5+14

[0468] This example provides further data collected from the clinical study presented in Example 2 and further demonstrates the utility of an amyloid-reactive peptide labeled with ^{99m}Tc to detect cardiac amyloid associated with AL and ATTR amyloidosis. These data were collected from 18 subjects, 5 healthy volunteers, 3 with AL and 10 with ATTR.

[0469] As described in example 2, each subject was administered a single IV injection of an amyloid-reactive peptide labeled with ^{99m}Tc (<22 mCi and <1 mg of p5+14 peptide (SEQ ID NO: 13). Subjects were evaluated using PGS and SPECT/CT imaging acquired at 1 hour and 3 hours post injection (pi). Patient images are compared to those of the healthy

subjects, both visually and by region of interest analysis, to assess differential cardiac uptake. Contemporaneous ^{99m}Tc-PYP imaging is performed for comparative purposes.

AL Amyloidosis Imaging

[0470] Biodistribution of 99mTc-p5+14 at 1 hour post injection was assessed in whole body PGS images of three patients with AL amyloidosis **FIG. 15A-15D**. **FIG 15A-15C** show anterior and posterior views of three patients and **FIG 15D** shows head and neck imaging of each patient. The patient represented in **FIG. 15C** is the same patient represented in F**IG. 12**. In patients with AL amyloidosis physiologic retention of radioactivity was observed in PGS images, in the kidneys, liver, and urinary bladder. In addition, radiotracer uptake was observed in the heart of the patients with cardiac AL amyloidosis. Uptake in the lungs, spleen, salivary glands, thyroid gland, and amyloid-associated (non-physiological) liver uptake was observed.

[0471] Uptake of ^{99m}Tc-p5+14 was observed in a pulmonary lesion of a patient with AL amyloidosis at 1 hour post injection. In SPECT/CT images (**FIG. 16**) (CT, upper; SPECT/CT, lower) pulmonary masses were observed in both lungs. Uptake of radiotracer in the lesions was intense (**FIG. 16**). Pulmonary uptake was not seen in ^{99m}Tc-PYP images. Although this lesion was not biopsied to demonstrate the presence of amyloid, pulmonary amyloidosis is a common manifestation in patients with AL amyloidosis. Therefore, these data suggest that pulmonary AL amyloid lesions may be detectable using ^{99m}Tc-p5+14 imaging.

ATTR Amyloidosis Imaging Stability

[0472] ^{99m}Tc-PYP is clinically performed at 3 hours post injection in part because the signal is typically not amyloid specific at 1 hour compared to 3 hours (data not shown). A comparison of ^{99m}Tc-p5+14 uptake in the heart of ATTR patients, based on heart:lung ratio measurements obtained from whole body PGS images acquired at 1 hour to 3 hour post injection was performed (**FIG. 17**). These data indicates that the uptake of ^{99m}Tc-p5+14 in the cardiac amyloid of patients with ATTR was equivalent and stable between 1 hour and 3 hours post injection. These data demonstrated that ^{99m}Tc-p5+14 imaging can be used detect cardiac amyloid shortly after injection, earlier than detection with other methods. This may advantageous because patient visits can be shorter, results can be obtained quicker, and patient image schedules with the Nuclear Medicine Departments can be more efficient.

Semi-quantitative analysis for ATTR

[0473] Although SPECT/CT imaging was not performed using a semi-quantitative protocol (i.e., with a calibrated reference source in each image and dedicated software) the heart:blood activity intensity ratio provided a semi-quantitative estimate of the "signal-to-background" reflecting the intensity of the uptake in the heart relative to the unbound circulating radiotracer. The ratios were compared to values obtained from the contemporaneous echocardiographic examination and bloodwork to assess linear correlations between uptake of ^{99m}Tc-p5+14 and the other marker of cardiac structure and function.

[0474] *Table 3* shows in patients with ATTR amyloidosis, significant, moderate to strong, linear correlations were seen between radiotracer uptake (heart:blood ratios) and serum NTproBNP levels (pg/mL), interventricular septal wall thickness (IVS; cm), left ventricular wall thickness (LV; cm), global longitudinal strain (GLS; %) and the uptake of ^{99m}Tc-PYP in the heart. These data indicated that the uptake of ^{99m}Tc-p5+14 in amyloid in the heart correlates linearly and can be a surrogate for the structural and functional measures that are used as indirect measures of cardiac amyloid burden.

Table 3*:Correlation between Semi-quantitative uptake of ^{99m}Tc-p5+14 cardiac measurements in patients with ATTR*

Measurement	*^{99m}Tc-p5+14 cardiac uptake*	
	Pearson *r*	*p* value
Serum NTproBNP	0.695	0.026
Troponin T	0.619	0.056
IVS thickness	0.790	0.007
LV wall thickness	0.904	3.29×10^{-4}
GLS (global longitudinal strain)	0.696	0.037
^{99m}Tc-PYP uptake	0.951	2.87×10^{-4}

Comparing imaging methods

[0475] As described in Example 2, ^{99m}Tc-p5+14 imaging and ^{99m}Tc-PYP imaging was compared. Cardiac update (SUVR) of ^{99m}Tc-p5+14 in patients with ATTR and AL amyloidosis and healthy volunteers (HV) and ^{99m}Tc-PYP in patients with ATTR and AL

amyloidosis was measured. As the Patients (AL and ATTR) were imaged with ^{99m}Tc-p5+14 and then three days thereafter with ^{99m}Tc-PYP. Repeat imaging was feasible after 3 days because the half-life of Tc-99m is about 6 hours, there was no radioactivity left from^{99m}Tc-p5+14 injection when the ^{99m}Tc-PYP was administered. Healthy volunteers were not imaged with ^{99m}Tc-PYP. There was significantly greater cardiac uptake of the ^{99m}Tc-p5+14 tracer in patients with ATTR as compared to HV (**FIG. 18A**). In addition, in the ATTR patients there was significantly greater cardiac uptake of the ^{99m}Tc-p5+14 tracer as compared to ^{99m}Tc-PYP uptake (**FIG. 18A**). In patients with AL amyloidosis, ^{99m}Tc-p5+14 cardiac uptake was greater than HV and ^{99m}Tc-PYP did not bind these three AL patients (**FIG. 18B**). These data suggested greater sensitivity in the uptake of ^{99m}Tc-p5+14 for AL and ATTR patients compared to ^{99m}Tc-PYP.

Interim Diagnostic results

[0476] Interim diagnostic cutoffs were determined based on the mean (± 1.96*SD) organ uptake in healthy volunteers (HV; n=5). **FIG. 19A-D** shows the interim diagnostic cutoffs and patient data. AL patients (n=3 in interim analysis) are colored in black, and the HV and ATTR patients are colored in gray. All patients had cardiac uptake of ^{99m}Tc-p5+14 that was greater than the cutoff values (dashed lines), although one patient (ATTR) was close to the upper limit (**FIG. 19A**). For the liver (**FIG. 19B**) and spleen (**FIG. 19C**), two patients, both AL were greater than the upper limit, indicating the presence of amyloid bound radiotracer. For the kidney (**FIG. 19D**), five patients (n=1 AL and n=4 ATTR) were below the lower cutoff value suggesting that these patients had compromised renal function (due to amyloid or other reasons) and therefore less radiolabeled peptide was seen in the kidney.

CLAIMS

1. A method of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease, the method comprising
    a. administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual, wherein the individual has previously tested negative using an alternative detection method; and
    b. detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label in one or more organs or tissues of the individual;
    wherein detecting the amyloid-reactive peptide in the one or more organs or tissues indicates that the individual has the amyloid disease.

2. The method of claim 1, wherein the alternative detection method is selected from a group consisting of ^{99m}Tc-labeled pyrophosphate (PYP), ^{124}I-labelled amyloid-reactive peptide detection, 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), Aβ amyloid imaging agents, ^{18}F-Florbetapir (Amyvid), ^{18}F-Flutemetamol (Vizamyl), ^{18}F-Florbetaben (Neuraceq) transthoracic echocardiography and cardiac magnetic resonance imaging.

3. A method of detecting an amyloid deposit in one or more organs or tissues selected from the group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue, the method comprising
    a. administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and
    b. detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more tissues.

4. The method of claim 3, wherein detecting the amyloid-reactive peptide in the organ or tissue indicates that the individual has an amyloid disease.

5. The method of claim 3, wherein detection of the amyloid-reactive peptide in the thyroid or salivary gland indicates that the individual does not have ATTR-associated amyloidosis.

6. A method of diagnosing an amyloid-related disease in an individual at risk for developing the amyloid-related disease comprising
    a. administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual; and
    b. detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label at the one or more organs or tissues the individual between about 0.1 and about 3 hours after administering the amyloid-reactive peptide,
    wherein detecting amyloid-reactive peptide at the one or more organs or tissues indicates that the individual has the amyloid disease.

7. The method of any of claims 1- 2 and 6, wherein the individual is determined to be at risk for an amyloid-related disease based upon the presence of a genetic mutation, having multiple myeloma, having amyloid positive laminectomy tissue, having an amyloid positive tissue from carpal tunnel release surgery, having a monoclonal gammopathy of unknown significance (MGUS), having heart failure with preserved ejection fraction (HFpEF), having heart failure with reduced ejection fraction (HFrEF), being from susceptible ethnic populations, or being elderly.

8. The method of claim 7, wherein the genetic mutation is in the transthyretin gene.

9. The method of any one of claims 1-2 and 6-8, wherein the individual does not have symptoms of amyloidosis.

10. The method of any one of claims 1-2 and 6-8, wherein the individual has neuropathic symptoms of an amyloid disease.

11. A method of determining prognosis of an individual having an amyloid-related disease comprising
    a. administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at one or more organs or tissues of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide;
    b. administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at the one or more organs or tissues of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide;
    c. comparing the amyloid detected in the one or more organs or tissues the first time with the amyloid detected in the tissue or organ the second time to determine the prognosis of the individual.

12. The method of claim 11, wherein the prognosis of an individual having an amyloid-related disease is based on detecting amyloid-reactive peptide in the heart.

13. A method of treating an amyloid-related disease comprising
    a. administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual;
    b. detecting amyloid-reactive peptide by detecting the technetium^{99m} detectable label in a one or more tissues or organs of the individual between about 0.1 and about 3 hours after administering the amyloid-reactive peptide, and
    c. administering a treatment for the amyloid-related disease if the amyloid-reactive peptide is detected.

14. A method of managing the treatment of an amyloid-related disease in an individual comprising:
    a. administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in one or more tissues or organs of the individual to detect amyloid in the individual a first time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide;
    b. administering a treatment for an amyloid-related disease;
    c. administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label in the one or more tissues or organs of the individual to detect amyloid in the individual a second time, wherein the detecting occurs within between about 0.1 and about 3 hours of administering the amyloid-reactive peptide;
    d. comparing the amyloid detected in a tissue or organ the first time with the amyloid detected in the one or more tissues or organs the second time; and
    e. adjusting the treatment for the amyloid-related disease.

15. The method of any of claims 1-14, further comprising estimating a cardiac amyloid burden in the individual.

16. The method of claim 15, wherein the cardiac amyloid burden is based on a ratio of the technetium^{99m} detectable label in heart and blood of the individual.

17. A method of estimating cardiac amyloid burden in an individual with an amyloid-related disease, the method comprising:
    a. administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual;

b. detecting the amyloid-reactive peptide by detecting the technetium^{99m} detectable label in images of heart and blood of the individual between about 0.1 hours and about 3 hours after administering the amyloid-reactive peptide; and
c. estimating a cardiac amyloid burden based on the ratio of the technetium^{99m} detectable label detected in the heart and the blood of the individual.

18. The method of any of claims 15-17, wherein the cardiac amyloid burden correlates with one or more biomarkers associated with the amyloid-related disease.

19. The method of any one of claims 1-10 and 13, and 15-18, further comprising administering an amyloid-reactive peptide comprising the amino acid sequence set forth in any one of SEQ ID NOs:1-14 conjugated to a technetium^{99m} detectable label to the individual and detecting the technetium^{99m} detectable label at a tissue or organ of the individual to detect amyloid in the individual a second time, optionally a third time a fourth time, and/or a fifth time.

20. The method claim 11, 14 or 19, wherein the first time and the second time are at least six weeks apart.

21. The method of claim 20, wherein if the amyloid disease is stable between the first and second times treatment is be modified.

22. The method of claim 20, wherein if the amyloid burden increases treatment is reinitiated.

23. The method of any of claims 6-22, wherein the detecting takes place about 0.5 and about 3 hours after administration of the amyloid-reactive peptide.

24. The method of any of claims 6-22, wherein the detecting takes place about 0.01, about 0.2, about 0.3, about 0.4, about 0.5, about 1, about 1.5, about 2, about 2.5, or about 3 hours after administration of the amyloid-reactive peptide.

25. The method of any one of claims 1-2 and 6-24, wherein the tissue or organ of the individual is selected from the group consisting of lung, fat, heart, free wall of the left ventricle, interventricular septum, right ventricular wall, right atrium, pancreas, joints, spine, spleen, adrenal gland, bone lesions, choroid plexus, pituitary gland, uterus, bone marrow, musculoskeletal tissue, gastrointestinal, prostate gland, and the joints of the hand.

26. The method of any one of claims 1-2 and 6-24, wherein the tissue or organ of the individual is selected from a group consisting of esophagus, stomach, small intestine, large intestine, urinary tract, thyroid gland, salivary gland, larynx, and tongue.

27. The method of any one of claims 1-2 and 6-24, wherein the tissue or organ of the individual is selected from a group consisting of esophagus, stomach, thyroid gland and salivary gland.

28. The method of any one of claims 1-27, wherein the detecting comprises imaging by single photon emission computed tomography (SPECT), SPECT with x-ray computed tomography (SPECT/CT), or Planar gamma imaging.

29. The method of any one of claims 1-28, wherein the detecting comprises imaging by single photon emission computed tomography with x-ray computed tomography (SPECT/CT).

30. The method of any of claims 1-29, wherein the detecting comprises quantifying the amount of detectable label to quantify the amount of amyloid-reactive peptide.

31. The method of claim 30, wherein an amount of amyloid-reactive peptide above a threshold indicates presence of amyloid deposits in the one or more organs or tissues.

32. The method of any one of claims 1-31, wherein detection of an amount of amyloid-reactive peptide in the heart is between about 2 and about 5 times the SD of the heart of a healthy individual, indicating the individual has ATTR.

33. The method of any one of claims 1-31, wherein detection of an amount of amyloid-reactive peptide in the heart is about 1.96 times the SD of the heart of a healthy individual, indicating the individual has ATTR.

34. The method of any one of claims 1-33, wherein the amyloid-reactive peptide comprises or consists of the amino acid sequence set forth in SEQ ID NO:13.

35. The method of claim 34, wherein the amyloid-reactive peptide comprises of consists of the amino acid set forth in SEQ ID NO: 13 conjugated to a technetium^{99m} detectable label.

36. The method of any one of claims 1-35, wherein the amyloid-reactive peptide comprises an N-terminal leader sequence that comprises the amino acid sequence set forth in SEQ ID NO: 100.

37. The method of any one of claims 1-36, wherein a dose of about 10 to about 25 mCi of Tc-99m is administered to the individual.

38. The method of any one of claims 1-37, wherein a dose of about 20 mCi of Tc-99m is administered to the individual.

39. The method of claim 37, wherein a dose of about less than 20 mCi of Tc-99m is administered to the individual.

40. The method of any one of claims 1-39, wherein a dose of about 0.3 mg, 1 mg, 1.5 mg, or about 2 mg of amyloid-reactive peptide is administered to the individual.

41. The method of any one of claims 1-40, wherein the amyloid-reactive peptide is administered intravenously.

42. The method of any one of claims 1-41, further comprising determining an organ-specific standard uptake value ratio (SUVR) for the tissue or organ of the individual.

43. The method of claim 42, wherein the organ-specific SUVR for the individual is selected from the group consisting of SUVR mean, SUVR max, and SUVR peak.

44. The method of any one of claims 1-43, wherein the amyloid-reactive peptide has a sensitivity of at least 90%.

45. The method of any one of claims 1-44, wherein the sensitivity is about 95%, about 99% or about 100%.

46. The method of any one of claims 1-45, further comprising determining one or more health related quality of life measures for the individual.

47. The method of any one of claims 1-46, further comprising detecting one or more biomarkers associated with the amyloid-related disease.

48. The method of claim 47, wherein the biomarker associated with amyloid-related disease is selected from the group consisting of Troponin T, NTproBNP, urine protein levels, UACR, EGFR, interventricular septal wall thickness (IVS), left ventricular (LV) wall thickness, global longitudinal strain (GLS), and alkaline phosphatase levels.

49. The method of any one of claims 1-48, further comprising performing a cardiac biopsy if amyloid is detected in the heart.

50. The method of any one of claims 1-49, further comprising performing additional amyloid imaging on the individual.

51. The method of claim 50, wherein the additional amyloid imaging on the individual comprises ECHO, CMR, bone scintigraphy or positron emission tomography imaging.

52. The method of claim 51, where in the additional amyloid imaging on the individual further comprises a tracer selected from the group consisting of ^{99m}Tc-PyP, ^{99m}Tc-DPD, ^{99m}Tc-HMDP, ^{99m}Tc-MDP other bone scintigraphy tracers, ^{124}I-evuzamatide, and ^{18}F-florbetapir, ^{18}F-flutemetamol, and ^{18}F-florbetaben.

53. The method of any one of claims 1-52, wherein the individual is diagnosed with amyloid cardiomyopathy.

54. The method of any one of claims 1-53, wherein the individual is suspected of having amyloid cardiomyopathy.

55. The method of any one of claims 1-52, wherein the amyloid-related disease is systemic or localized amyloidosis.

56. The method of any one of claims 1-55, wherein the individual has a genetic predisposition to an amyloid-related disease.

57. The method of any one of claims 1-56, wherein the individual has a family history of an amyloid-related disease.

58. The method of any one of claims 1-57, wherein the individual is elderly.

59. The method of any one of claims 1-58, wherein the individual has an early stage of an amyloid-related disease.

60. The method of any one of claims 1-59, wherein the individual has an early stage of AL amyloidosis.

61. The method of claim 60, wherein the early stage of AL amyloidosis is diagnosed according to the Mayo Clinic system.

62. The method of claim 61, wherein the early stage of AL amyloidosis is stage 1 AL amyloidosis.

63. The method of any one of claims 1-4 and 6-62, wherein the individual has an early stage of ATTR amyloidosis.

64. The method of claim 63, wherein the early stage of ATTR amyloidosis comprises stage 1 ATTR amyloidosis.

65. The method of any one of claims 1-64, further comprising administering a therapy for the amyloid-related disease.

66. A method of producing a labeled amyloid-reactive peptide with technetium^{99m} suitable for administration to an individual, the method comprising
    a. combining a solution comprising 10-30 μg of the amyloid-reactive peptide and a solution comprising 1.0-3.5 mg of $SnCl_2$ with a solution comprising technetium^{99m} to produce a labeling composition;
    b. incubating the labeling composition to produce a labeled amyloid reactive peptide; and
    c. adding a quencher to the labeling composition within five minutes of the combining to produce a quenched composition comprising a labeled amyloid-reactive peptide with technetium^{99m}.

67. The method of claim 66, further comprising diluting the quenching composition after step (c).

68. The method of claim 66 or 67, further comprising purifying the labeled amyloid peptide from the quenched composition.

69. The method of any one of claims 66 -68 wherein the solution comprising 10-30 μg of the amyloid-reactive peptide further comprises sterile phosphate buffered saline.

70. The method of any one of claims 66-69, comprising preparing the solution comprising 1.0-3.5 mg of $SnCl_2$ before step (a).

71. The method of claim 70, wherein the preparing the solution comprising 1.0-3.5 mg of $SnCl_2$ comprises combining 1N HCl and $SnCl_2$ to create a tin solution.

72. The method of claim 71, wherein the tin solution is diluted with pure water to create a stock solution.

73. The method of claim 72, wherein the stock solution is diluted with HCl.

74. The method of any one of claims 66-73, wherein the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m}.

75. The method of any of claims 66 -74, wherein the solution comprising technetium^{99m} comprises saline.

76. The method of claim 75, wherein the solution comprising technetium^{99m} comprises about 1 to about 50 mCi technetium^{99m} and about 100 μL to about 300 μL saline.

77. The method of any one of claims 66-75, wherein the technetium^{99m} is in the form of pertechnetate.

78. The method of any one of claims 66-76, further comprising measuring radiopurity of the labeled amyloid-reactive peptide after step (c) by reverse phase high performance liquid chromatography (HPLC).

79. The method of claim 78, wherein the radiopurity of the labeled amyloid-reactive peptide is greater than about 90%, greater than about 95% or greater than about 99%.

80. The method of any one of claims 66-79, wherein the integrity of the amyloid-reactive peptide before adding the radio label is the same as the integrity of the labeled amyloid-reactive peptide.

81. The method of claim 80, wherein the integrity of the amyloid-reactive peptide labeled and the amyloid-reactive peptide relates to the proportion of degraded peptide.

82. The method of any one of claims 66-81, wherein the labeled amyloid-reactive peptide is not significantly degraded.

83. The method of any one of claims 66-82, wherein the labeled amyloid-reactive peptide does not cause an adverse reaction when administered to an individual.

84. The method of any one of claims 1-83, wherein a peptide comprising the amyloid-reactive peptide and an N-terminal leader sequence is administered to the individual.

85. The method of claim 84, wherein the peptide comprising the amyloid reactive peptide comprises the amino acid sequence set forth in SEQ ID NO: 100.

86. The method of claim 85, wherein the technetium^{99m} detectable label is bound to one or more amino acids at positions 1 to 6 of the amino acid sequence set forth in SEQ ID NO: 100.

87. A peptide comprising the amino acid set forth in SEQ ID NO: 100, wherein the peptide comprises a technetium^{99m} detectable label bound to one or more amino acids at positions 1 to 6.