

Pan-amyloid reactivity of radioiodinated peptide ^{124}I -AT-01 in patients with systemic amyloidosis demonstrated by PET/CT imaging

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Disclosure Information

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Emily Martin, UTGSM

I have the following financial relationships to disclose:

Founder:

Solex, LLC

Shareholder:

Attralus Inc.

I will not discuss off-label use in my presentation.

Polybasic Peptide for Targeting Amyloidosis



GGGYS KAQKA QAKQA KQAQK AQKAQ AKQAK QAQKA QKAQA KQAKQ



Iodination (I-124) site



Amyloid-binding domain

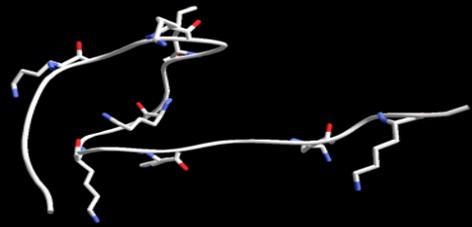
45 all L-amino acids

Synthetic peptide

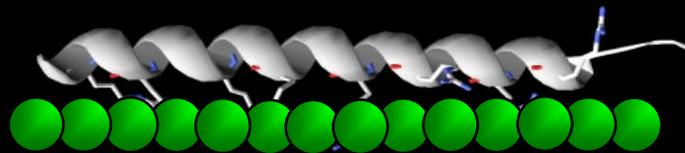
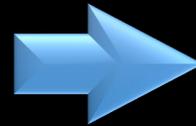
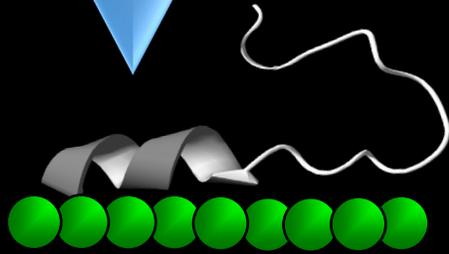
Net charge = +12

Binds hypersulfated heparan sulfate and fibrils

Target-induced helix formation results in high affinity binding

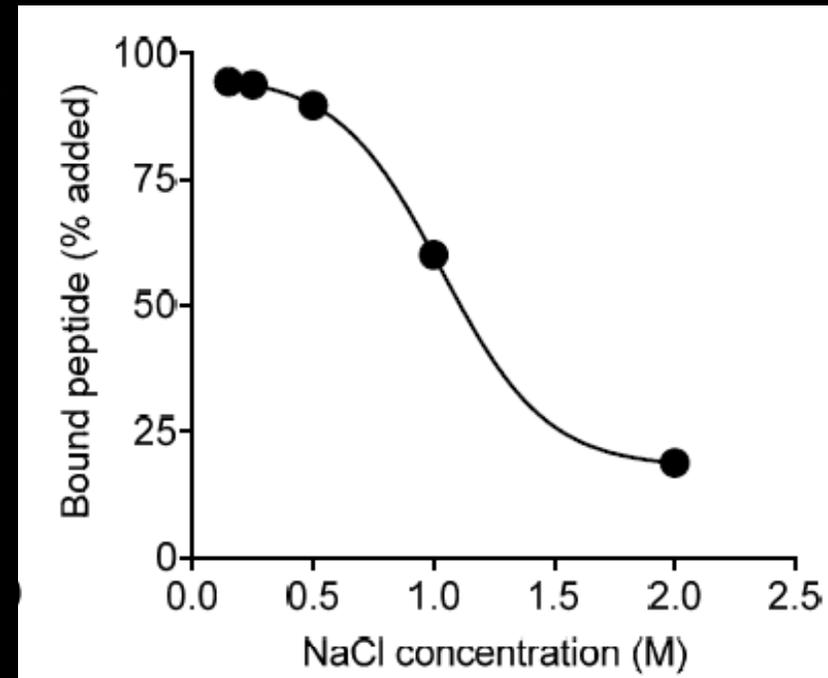
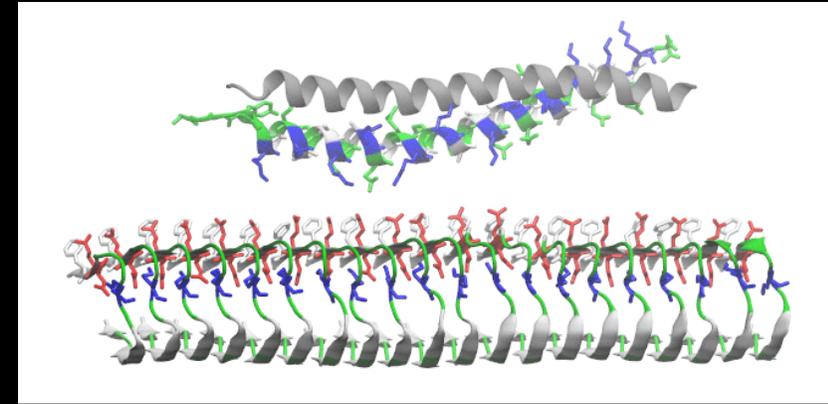


Random coil in PBS
(in the absence of fibrils or heparin)

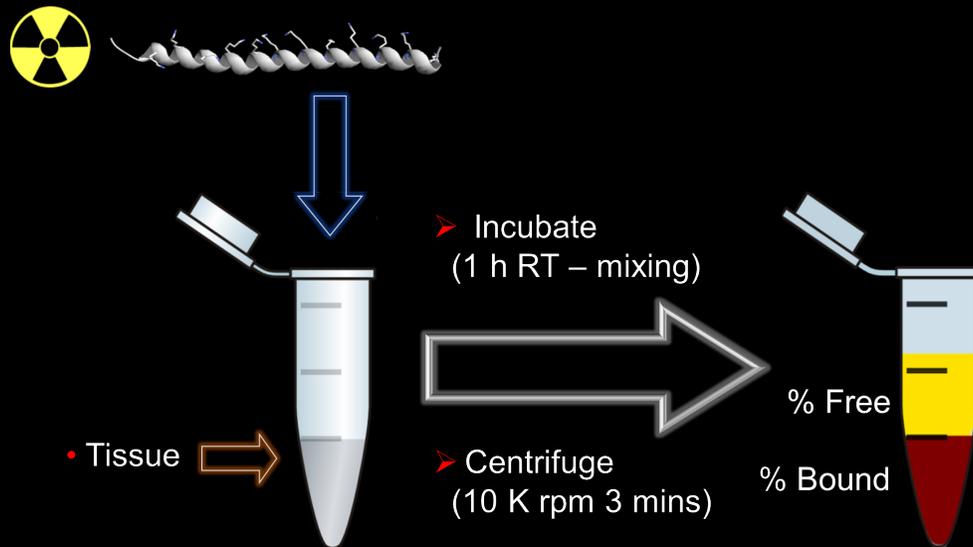


Helicity is induced in the presence of a dense electronegative surface: Heparin, heparan sulfate (on amyloid), or fibrils

High affinity electrostatic binding requires multivalent interactions involving at least 6 side chains



In vitro binding of ^{125}I -AT-01 to Human Amyloid Extracts



Human Amyloid Extracts	% Bound (mean \pm SD)
ATTR heart	79.93 \pm 1.23
κ 4 AL01 spleen	97.00 \pm 0.11
λ 2 AL02 liver	92.95 \pm 0.31
λ 2 AL02 spleen	96.76 \pm 3.65
λ 1 AL03 liver	91.16 \pm 0.87
λ 3 AL04 spleen	92.29 \pm 0.30
λ 3 AL04 liver	88.44 \pm 0.25
λ 4 AL05 spleen	95.44 \pm 0.03
λ 2 AL06 liver	89.66 \pm 0.91
λ 2 AL06 spleen	97.11 \pm 0.05
λ 1 AL07 liver	51.81 \pm 0.25
κ 1 AL08 liver	96.35 \pm 0.47
λ 2 AL09 liver	84.99 \pm 0.14
λ 2 AL10 spleen	12.25 \pm 1.08

% bound represents the amount of peptide bound to the substrate after a 1 h incubation. N = 2 for each assay.

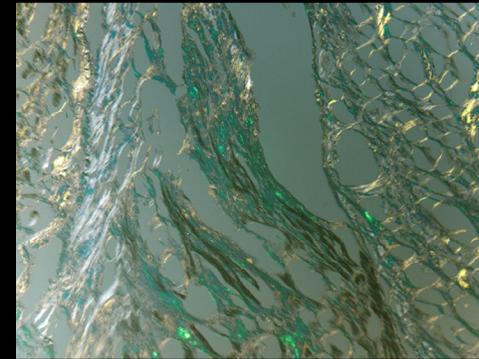
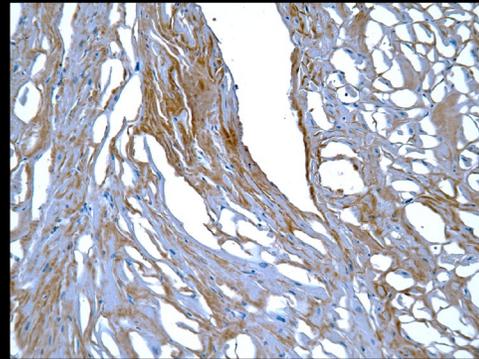
Peptide AT-01 Binds Various Tissue Amyloid Types

Cardiac Amyloid

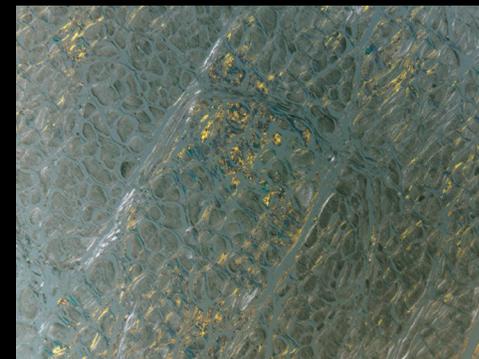
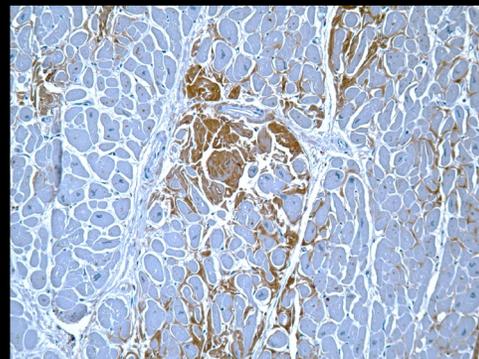
Biotinyl-AT-01

Congo red

AL κ



ATTR ν



Peptide AT-01 Binds Various Tissue Amyloid Types

Renal Amyloid

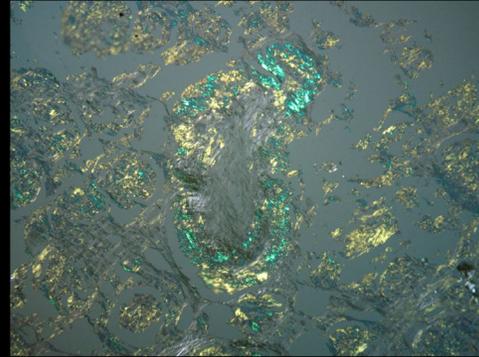
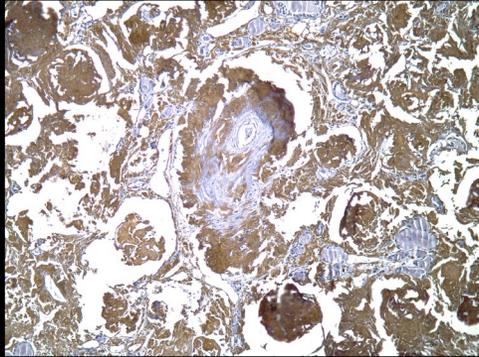
Biotinyl-AT-01

Congo red

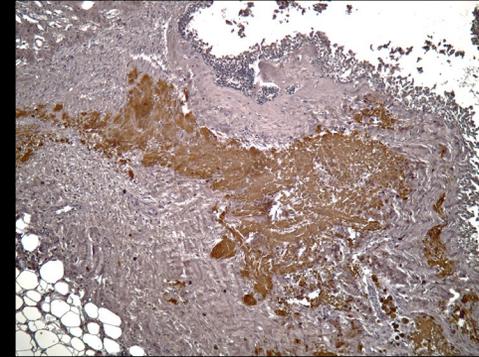
Biotinyl-AT-01

Congo red

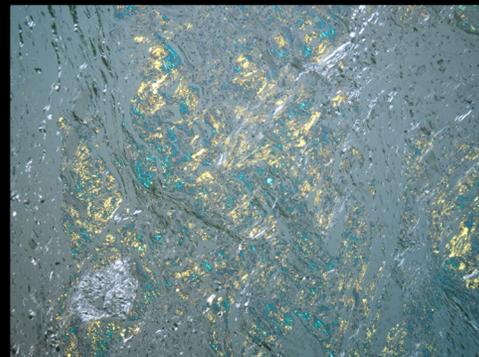
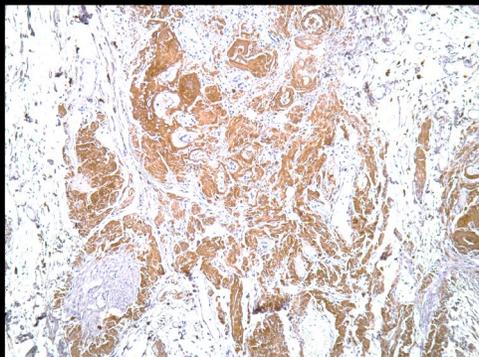
AL κ



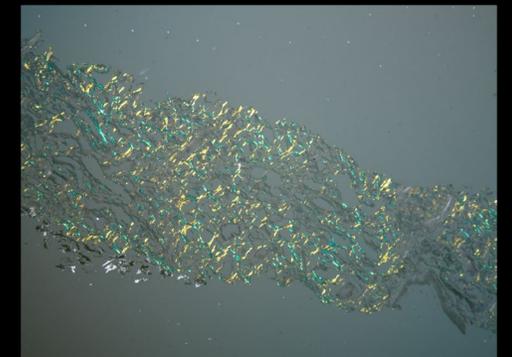
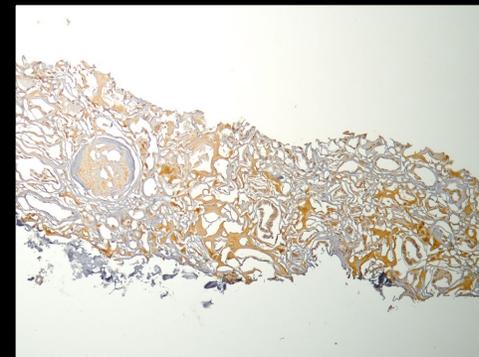
ATTR ν



AL λ



ALECT2



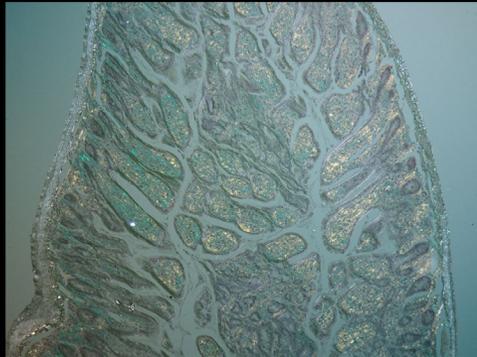
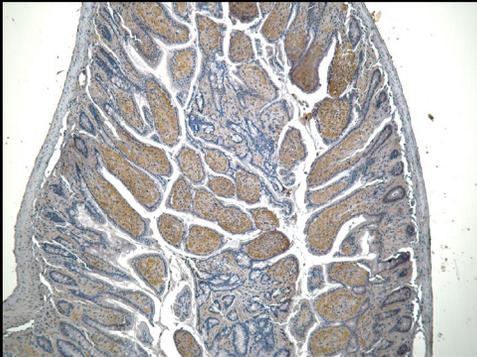
Peptide AT-01 Binds Various Tissue Amyloid Types

Non-Human Tissue Amyloid

ApoA2c Mouse GI

Biotinyl-AT-01

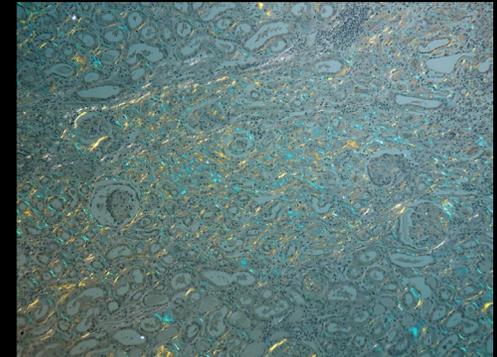
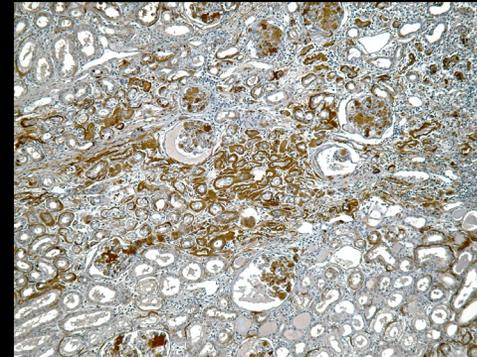
Congo red



AA Dog Kidney

Biotinyl-AT-01

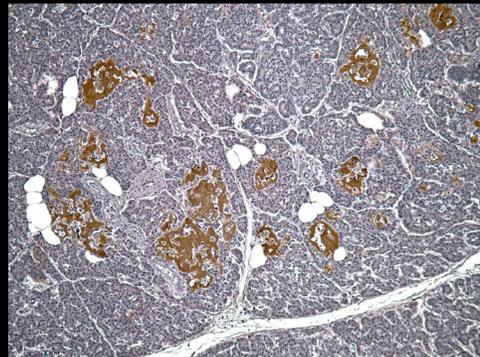
Congo red



AIAPP Cat Pancreas

Biotinyl-AT-01

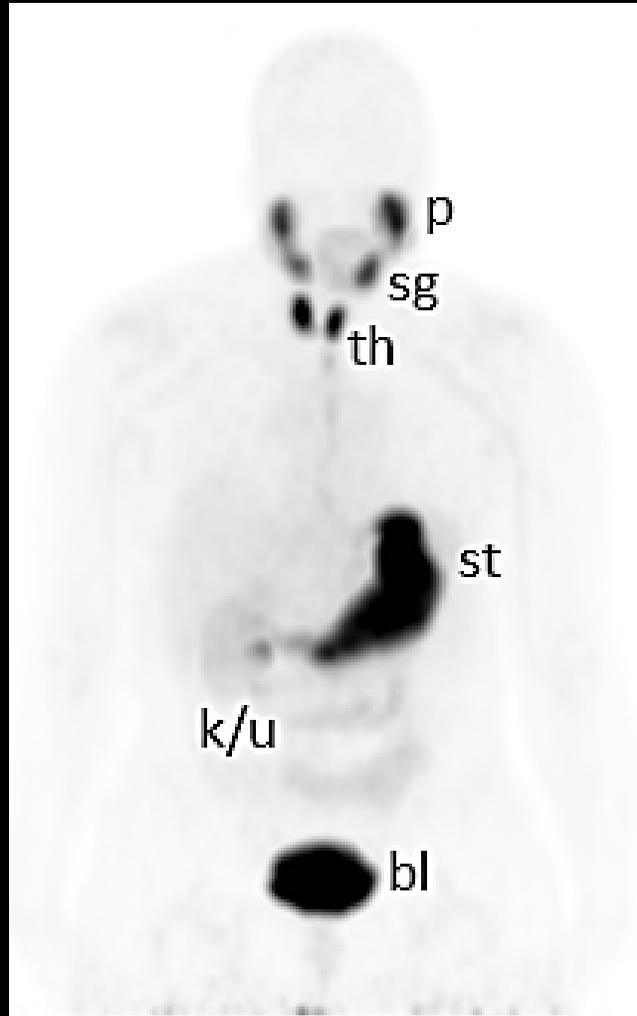
Congo red



^{124}I -AT-01 Distribution in Healthy Subjects



Healthy Subject 1



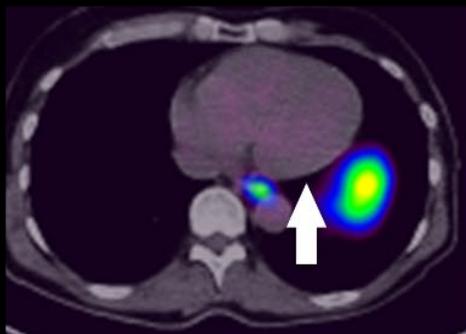
Healthy Subject 2

Physiological Distribution

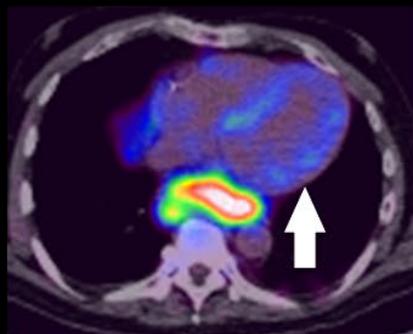
- Kidney (renal pelvis)
- Ureter
- Urinary bladder
- Stomach lumen
- Thyroid gland
- Parotid gland
- Salivary gland
- Saliva

Cardiac Uptake of ^{124}I -AT-01

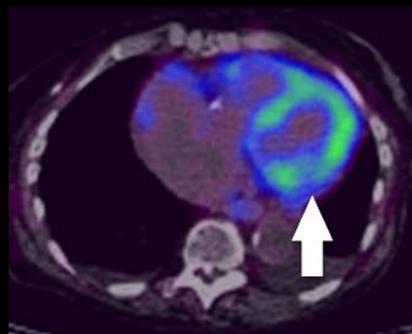
Healthy



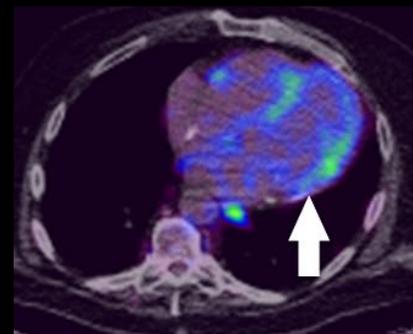
ALκ



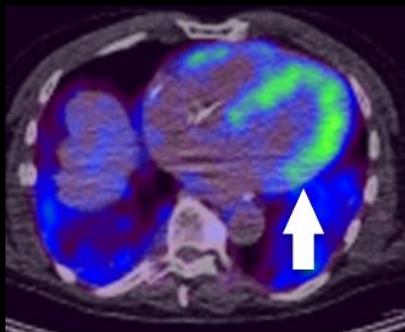
ALλ



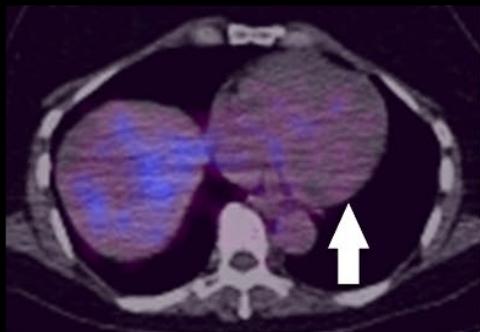
ATTRwt



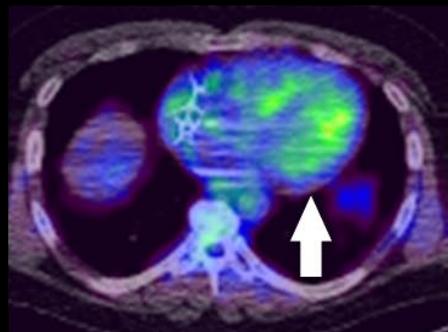
ATTRv



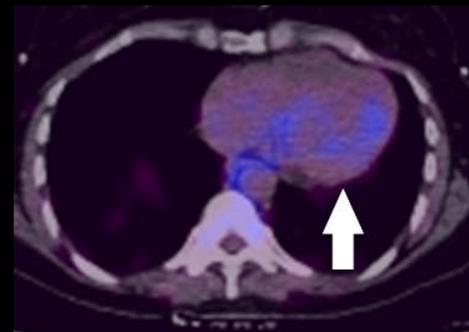
ALECT2



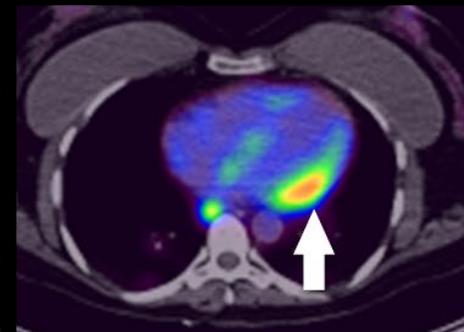
ALys



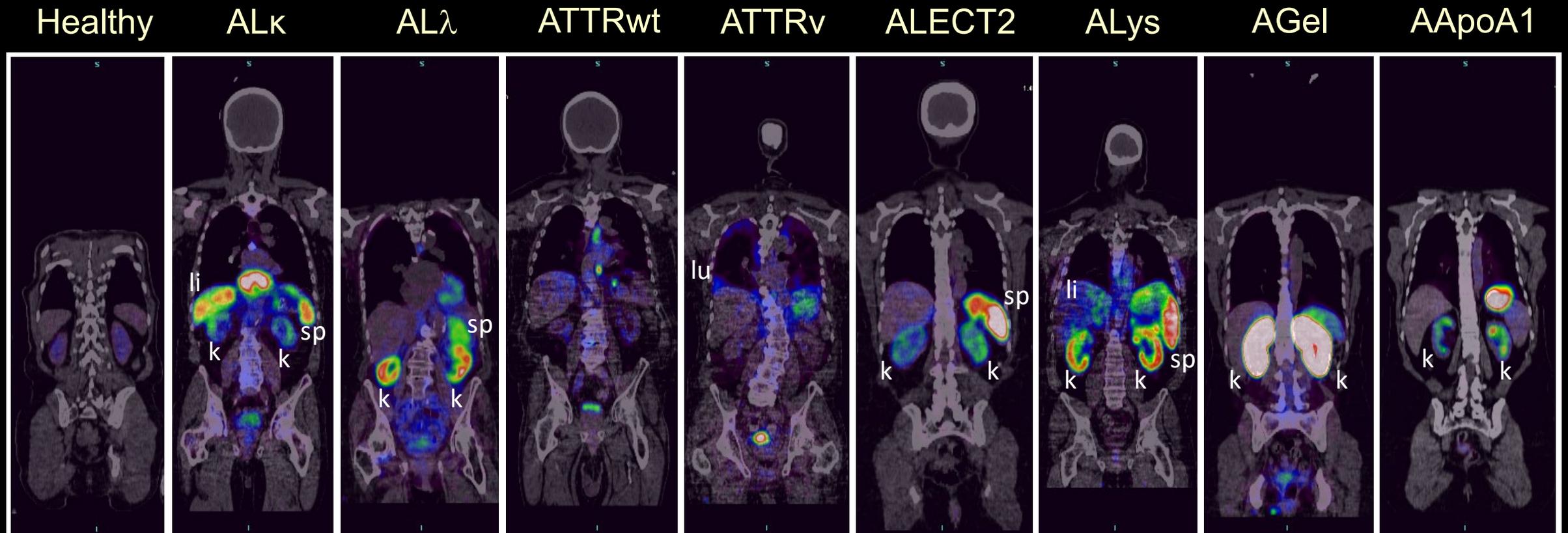
AGel



AApoA1



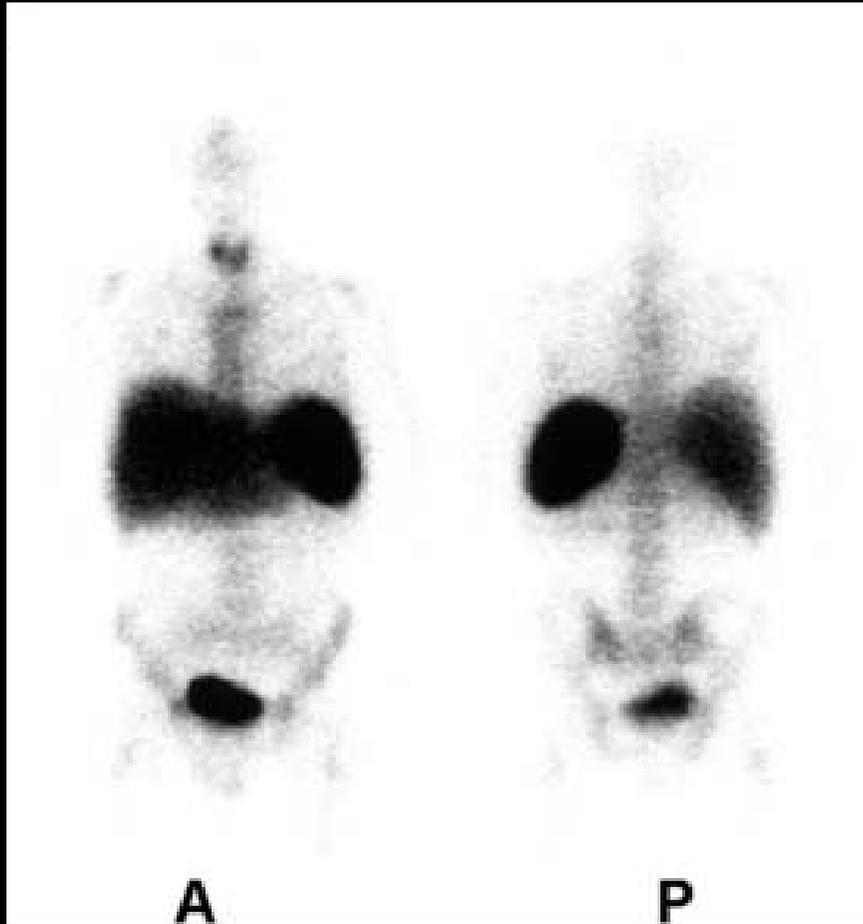
Extracardiac Uptake of ^{124}I -AT-01



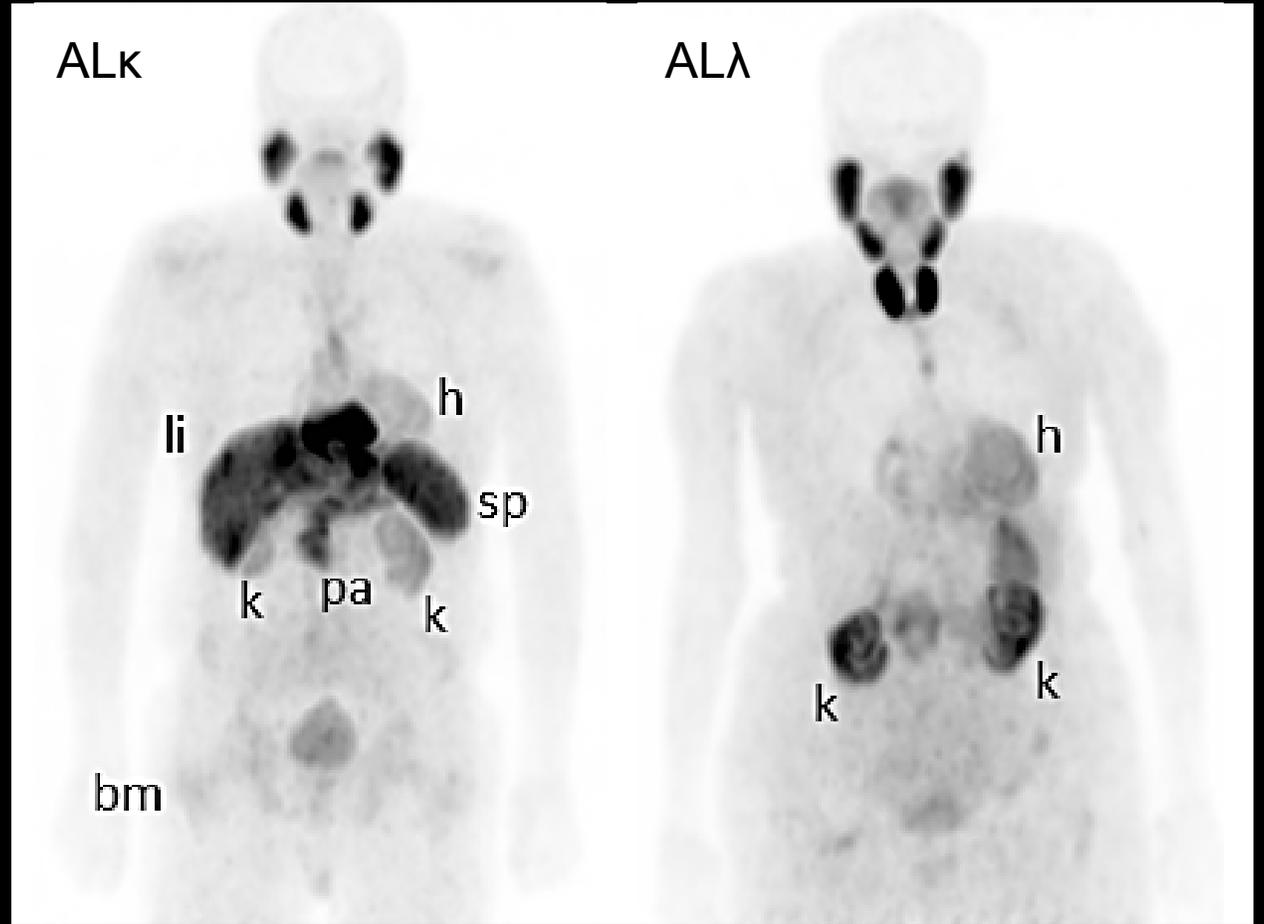
Visual comparisons of the distribution of
 ^{124}I -AT-01 vs the gold standard imaging
agent in representative patients with
diverse amyloid types

Imaging Light Chain Amyloidosis

^{123}I -SAP



^{124}I -AT-01



Imaging Transthyretin Amyloidosis

^{99m}Tc -DPD



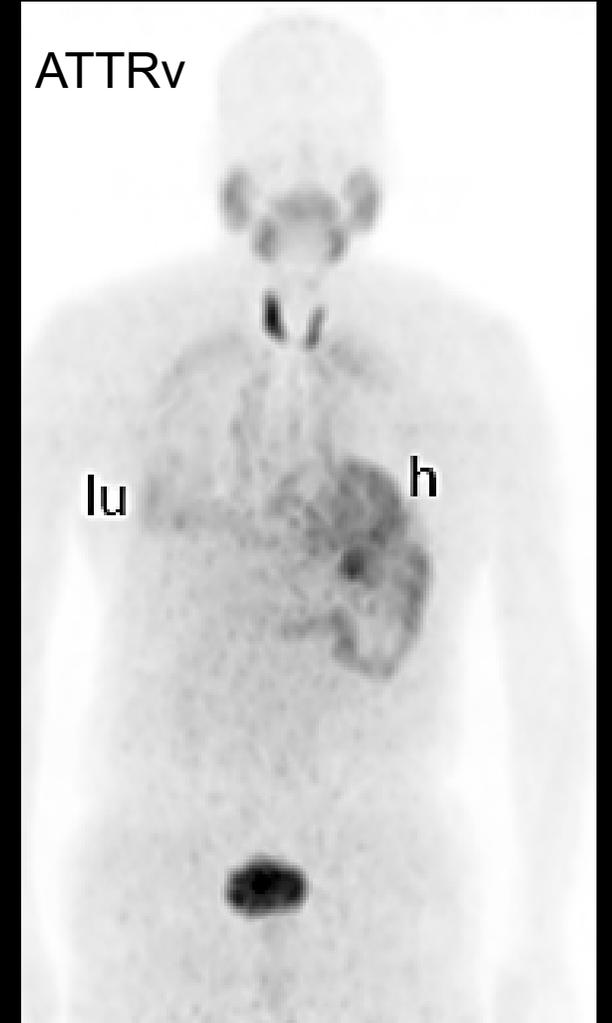
*Scully et al.,
JACC: Cardiovasc
Imaging, 2020*

^{99m}Tc -PYP



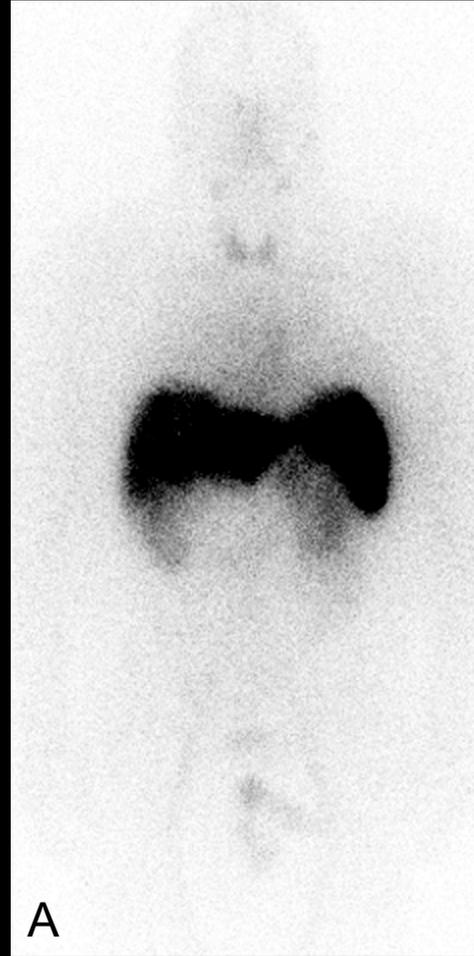
*Dorbala et al.
JACC: Cardiovasc
Imaging, 2020*

^{124}I -AT-01



Imaging Lysozyme Amyloidosis

^{123}I -SAP



^{124}I -AT-01

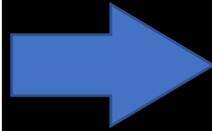


Images provided by Prof. Julian Gillmore and David Hutt.

Imaging ApoA1 Amyloidosis

Table 1. Continued

Organ involvement by amyloid	SAP scintigraphic findings	Organs not involved to date
Kidneys, liver	Large load: spleen and liver, small kidney	Heart, nerves
Kidneys, liver, GI tract	Large load: liver, spleen, kidneys	Heart, nerves
Kidneys, liver, testes, heart	Large or small load: liver, spleen, kidneys	Nerves
Kidneys, liver	Large load: liver, spleen, kidneys	Heart, nerves
Liver	Large load: liver, spleen	Heart, kidneys, nerves



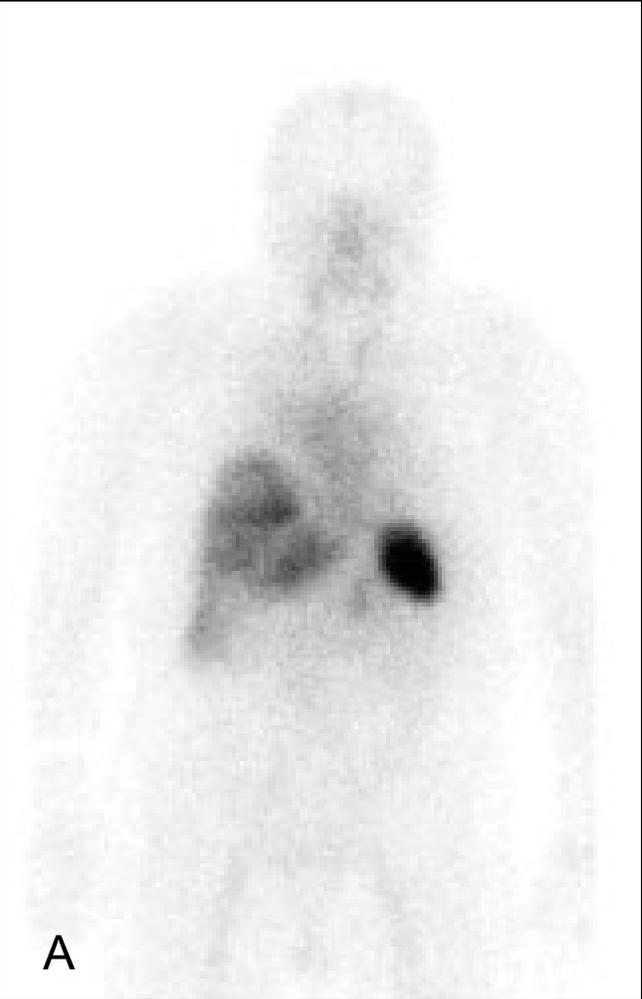
- Liver
- Spleen
- Kidneys

¹²⁴I-AT-01



Imaging Leukocyte chemotactic factor 2 Amyloidosis

^{123}I -SAP



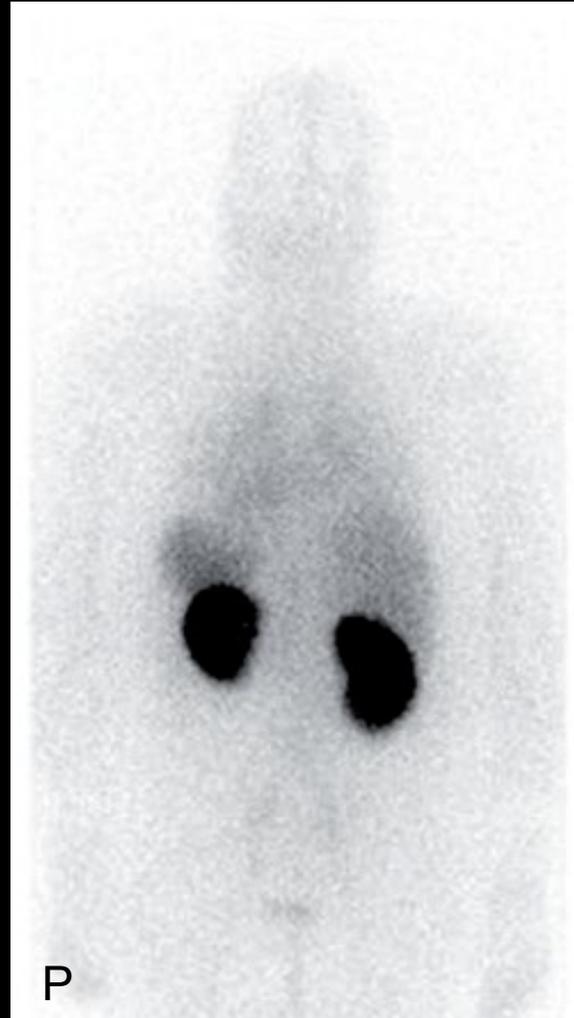
^{124}I -AT-01



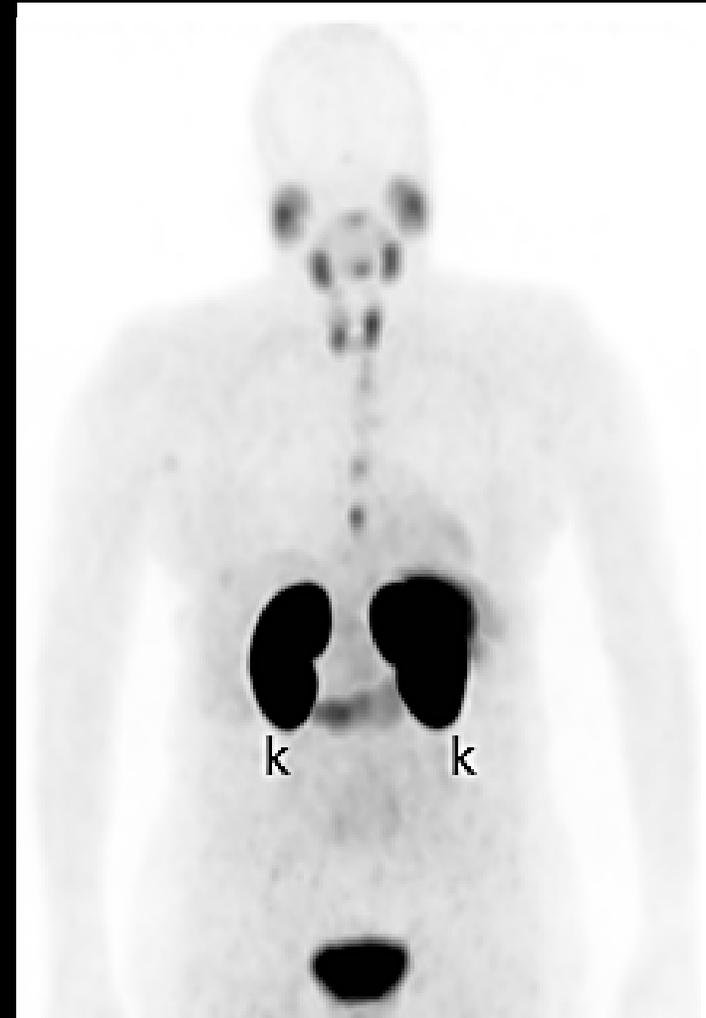
Rezk et al., *Nephrol. Dial. Transplant.* 2018

Imaging Gelsolin Amyloidosis

^{123}I -SAP



^{124}I -AT-01



Summary

- AT-01 is a pattern recognition peptide that binds the electronegative motif present on both fibrils and the highly sulfated heparan sulfate glycosaminoglycans – ubiquitous in amyloid deposits.
- Potent AT-01 binding to amyloid is independent of the fibril precursor protein
- PET/CT imaging with ^{124}I -AT-01 can be used to visualize amyloid in numerous abdominothoracic organs, including the heart and kidneys.
- The distribution of ^{124}I -AT-01 in patients with diverse types of amyloid is consistent with current gold standard imaging agents and provides quantitative tomographic data with uptake seen in all abdominothoracic organs including the heart.
- ^{124}I -AT-01 imaging can be used for the detection of diverse types of amyloid.

Amyloidosis and Cancer Theranostics Program



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