Molecular Imaging of the Kidney

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MOLECULAR IMAGING CENTER

Molecular Imaging of the Kidney

Clinical Collaborators

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UCSD

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Molecular Imaging of Mesangial Cells

My reason for attending this meeting.

Radiology manuscript review
Reviewer #3

"In truth, tight glucose control is about all that can be offered as a preventative for DN so the diagnosis of early disease (if possible) is probably not a top development priority."

Molecular Imaging

Bimolecular Reaction

$$[S] + [R] \underset{k_{-b}}{\overset{k_b}{\rightleftarrows}} [C]$$

$[S]$	Substrate Concentration
$[R]$	Receptor Concentration
$[C]$	Substrate-Receptor Complex Concentration
k_b	Forward Binding Rate Constant
k_{-b}	Reverse Binding Rate Constant

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Molecular Imaging

Bimolecular Reaction

$$[L^*] + [R] \underset{k_{-b}}{\overset{k_b}{\rightleftharpoons}} [C^*]$$

$[L^*]$	Radiopharmaceutical Concentration
$[R]$	Receptor Concentration
$[C^*]$	RP-Receptor Complex Concentration
k_b	Forward Binding Rate Constant
k_{-b}	Reverse Binding Rate Constant

Molecular Imaging

Image formation governed by bimolecular rate law

$$uptake\ rate = k_b[L^*][R]$$

k_b Forward Binding Rate Constant (affinity)

$[R]$ Receptor Concentration

$[L^*]$ Radiopharmaceutical Concentration

Molecular Imaging

Hypothesis:
A receptor-binding radiopharmaceutical can measure tissue reserve

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Molecular Imaging

A receptor-binding radiopharmaceutical can measure tissue reserve

- Demonstrate with a current radiopharmaceutical
- Introduce a RP for mesangial cell functional imaging

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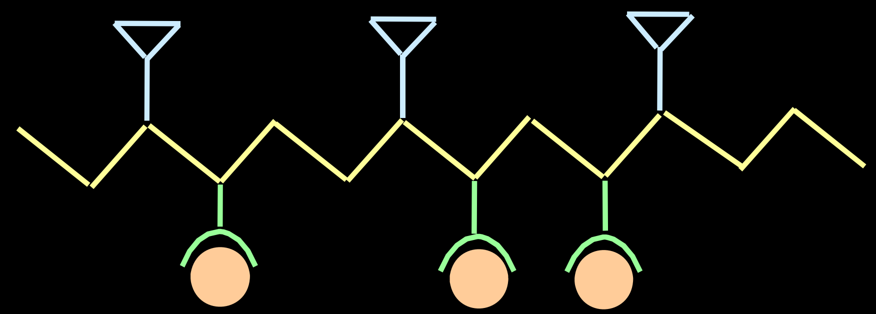
Nihon MediPhysics

AsialoSciniti

Binds to the Asialoglycoprotein Receptor in the Liver

Galactosyl-Neoglycoalbumin: GSA

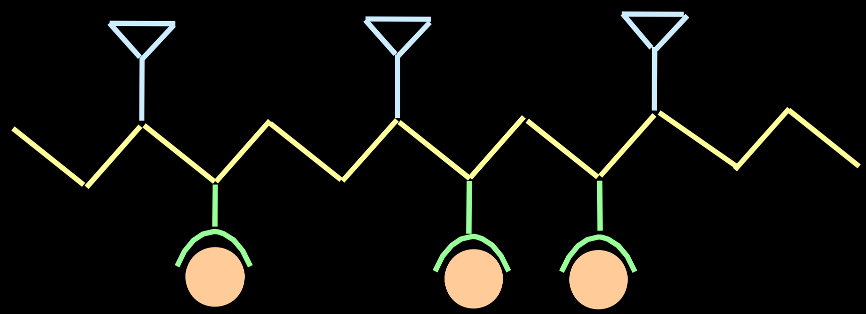


Receptor Substrate: galactose
Backbone: HSA
Chelator: DTPA
Radioactive Atom: Tc-99m

Galactosyl-Neoglycoalbumin: GSA

Chemically Control

- receptor affinity
- mass dose



Receptor Substrate: galactose

Backbone: HSA

Chelator: DTPA

Radioactive Atom: Tc-99m

Kinetic Model
with a Bimolecular Reaction

$$\frac{d[L]_e}{dx} = \frac{F}{V_e}[L]_h - \frac{F}{V_e}[L]_e$$

$$\frac{d[L]_h}{dx} = \frac{F}{V_h}[L]_e - \frac{F}{V_h}[L]_h - k_b[L]_h[R] + k_{-b}[C]$$

$$\frac{d[C]}{dx} = k_b[L]_h[R] - k_m[C] - k_{-b}[C]$$

$$\frac{d[D]}{dx} = k_m[C]$$

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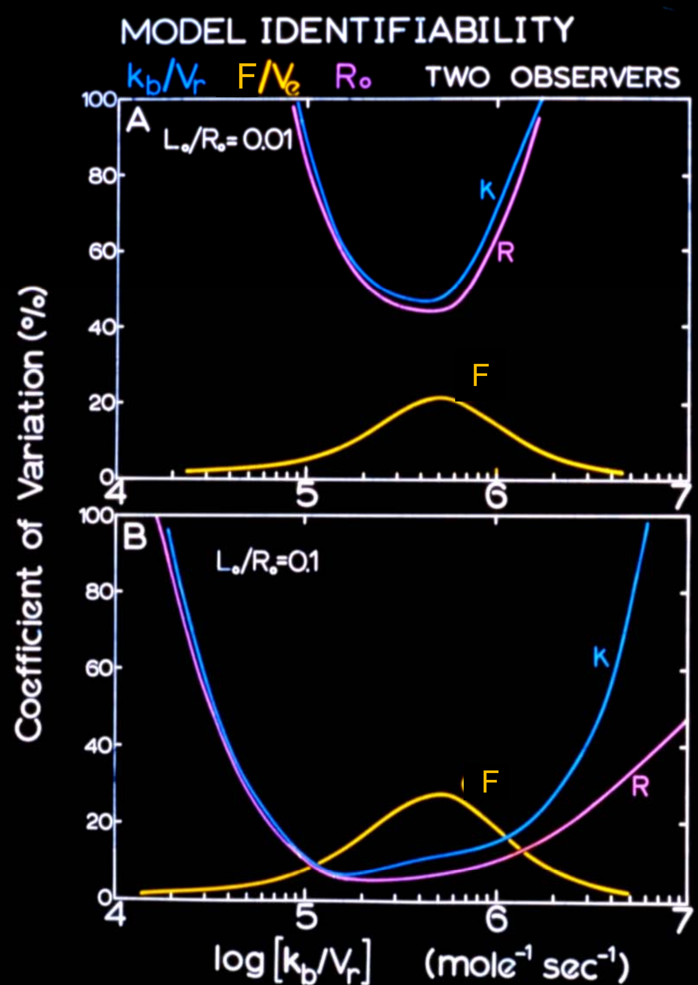

Use Engineering Methods to Optimize Performance

- moderate receptor affinity
- non-tracer mass dose

Vera et al *IEEE BME* 1983; 13: 311

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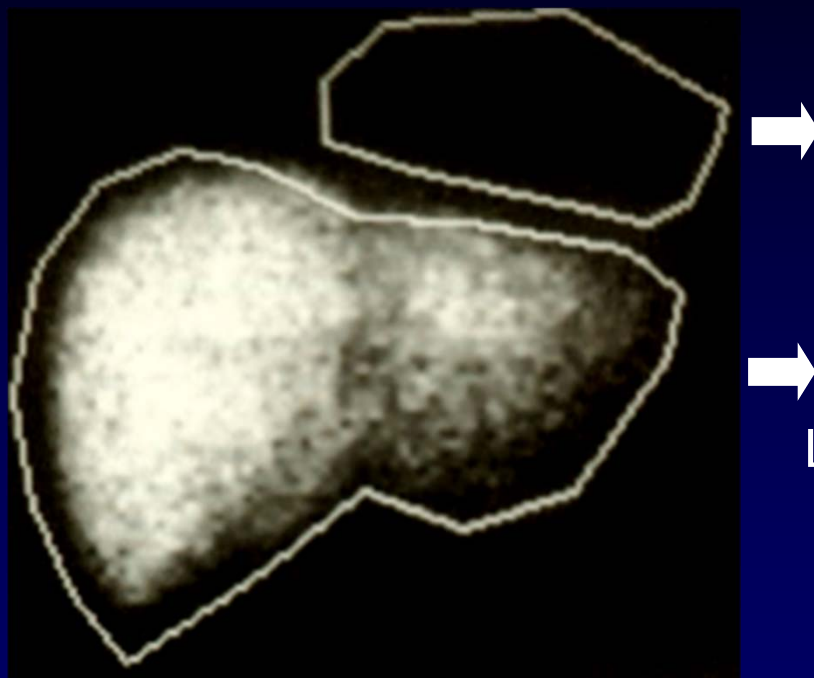
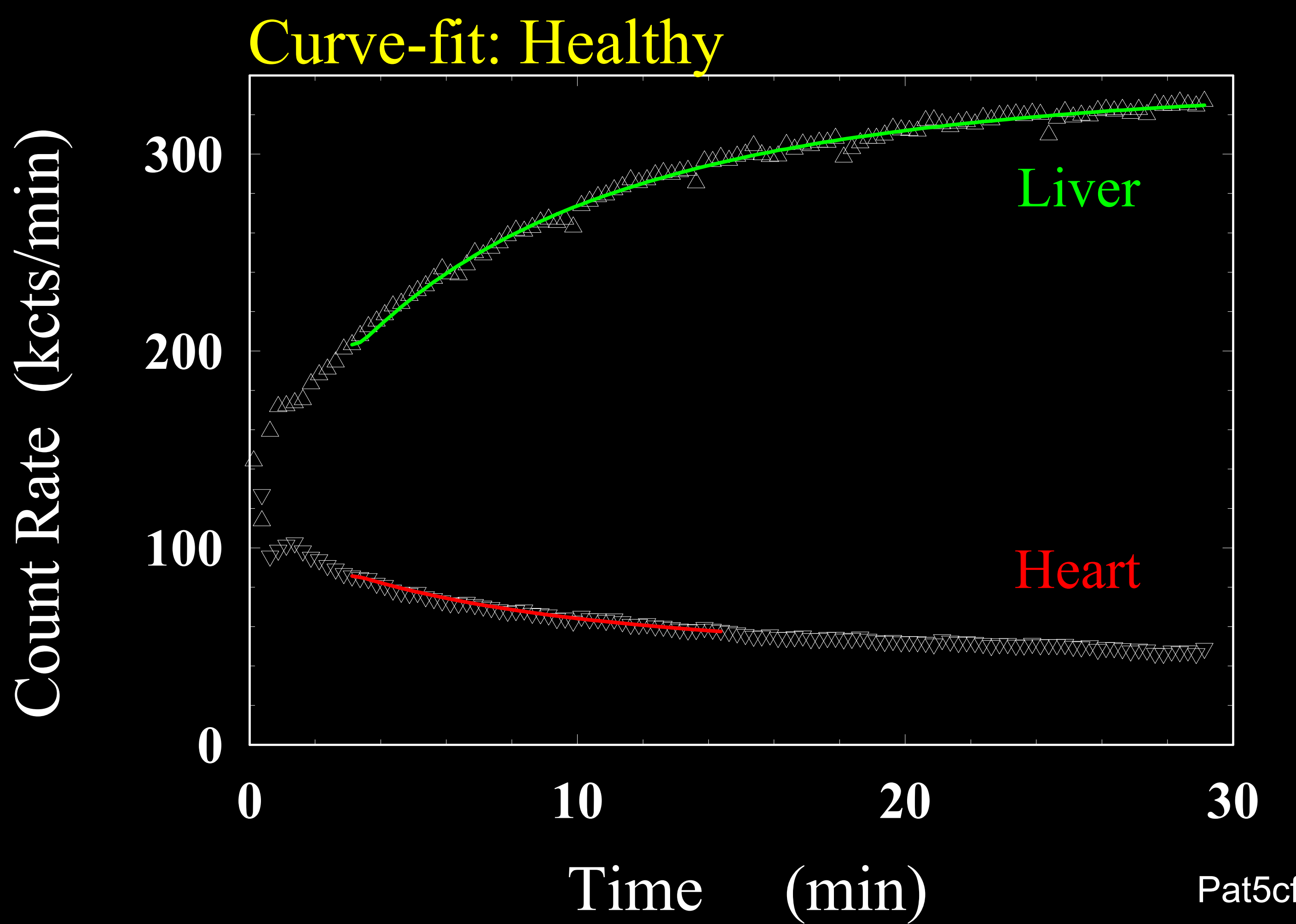
Generate Time-Activity Curves



Heart Time-Activity Curve

Liver Time-Activity Curve

Last of 120 frames from zero to 30 minutes


Curve-fit: Healthy
Count Rate (kcts/min)
300
200
100
0
0
10
20
30
Time (min)
Liver
Heart
Pat5cf

Healthy Subject

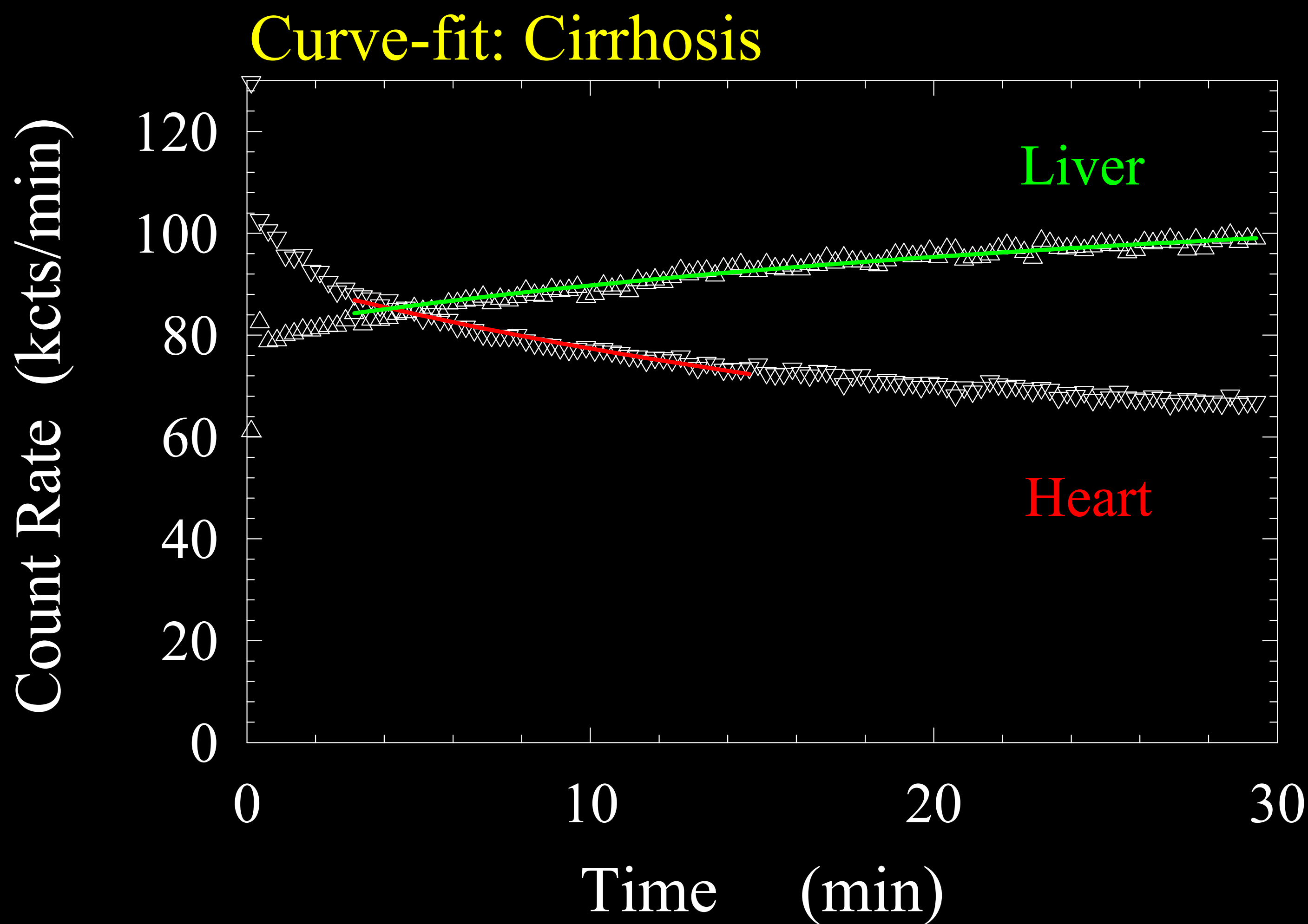
$$[R]_o = 0.914 \pm 0.099\ \mu M$$

$$k_b = 2.23 \pm 0.73\ \mu M^{-1}\ \mathrm{min}^{-1}$$

$$V_e = 1.99 \pm 0.02\ L$$

$$V_h = 0.274 \pm 0.001\ L$$

$$F = 0.685 \pm 0.384\ L\ \mathrm{min}^{-1}$$


Curve-fit: Cirrhosis
Liver
Heart
Count Rate (kcts/min)
Time (min)
0
20
40
60
80
100
120
0
10
20
30

Cirrhotic Patient

$$[R]_o = 0.270 \pm 0.018 \ \mu M$$

$$k_b = 2.94 \pm 1.38 \ \mu M^{-1}\ \text{min}^{-1}$$

$$V_e = 2.44 \pm 0.09 \ L$$

$$V_h = 0.267 \pm 0.005 \ L$$

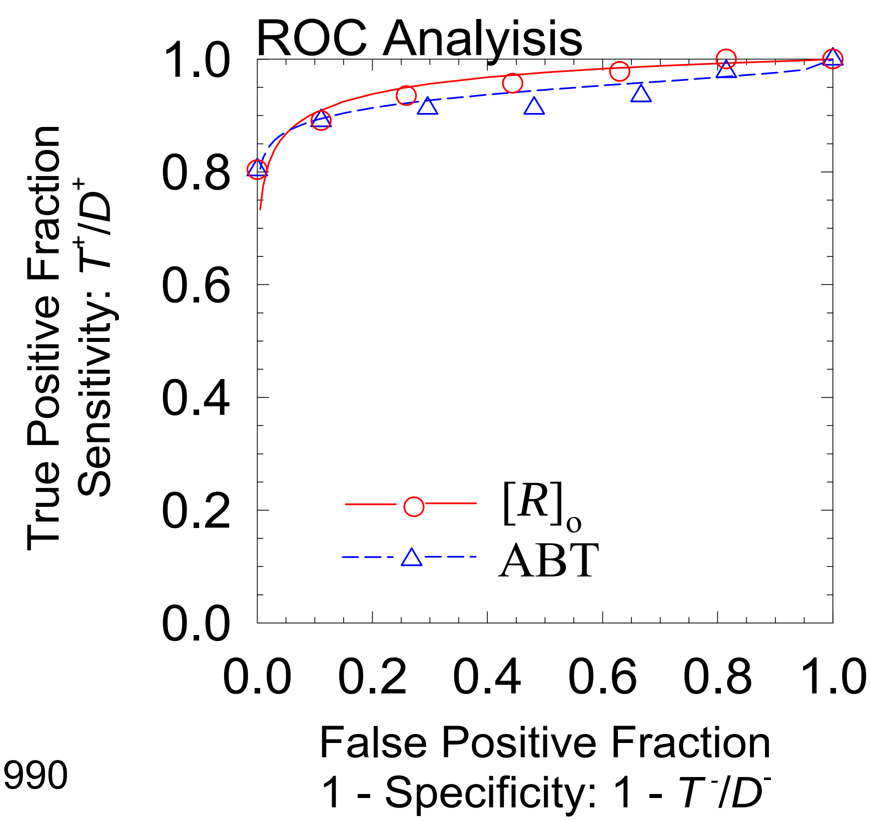
$$F = 0.454 \pm 0.858 \ L\ \text{min}^{-1}$$

patcfr

	Cirrhotic Patient	Healthy Subject
$[R]_o$ =	0.270	0.914 μM
k_b =	2.94	2.23 μM^{-1} min^{-1}
V_e =	2.44	1.99 L
V_h =	0.267	0.274 L
F =	0.454	0.685 L min^{-1}

patcfr

Diagnostic Performance



$A_z = 0.92 \pm 0.09$

$A_z = 0.90 \pm 0.06$

Vera et al. *J Nucl Med* 1990

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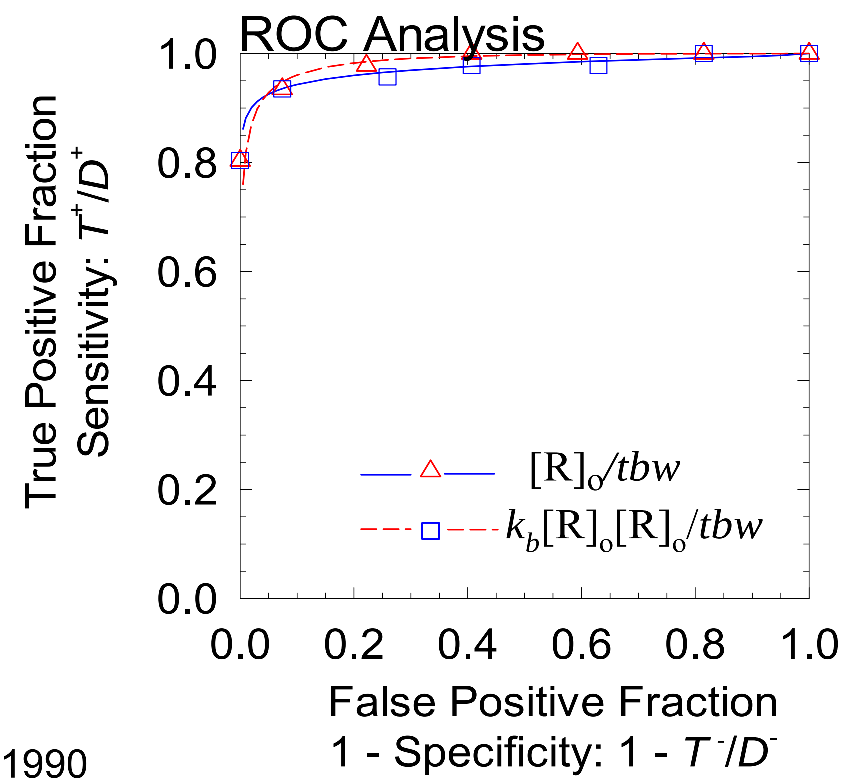
Diagnostic Performance



$A_z = 0.97 \pm 0.09$

$A_z = 0.95 \pm 0.07$

Vera et al. *J Nucl Med* 1990

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Molecular Imaging

A receptor-binding radiopharmaceutical can measure tissue reserve

- Demonstrate with a current radiopharmaceutical
- <u>Introduce a RP for mesangial cell functional imaging</u>

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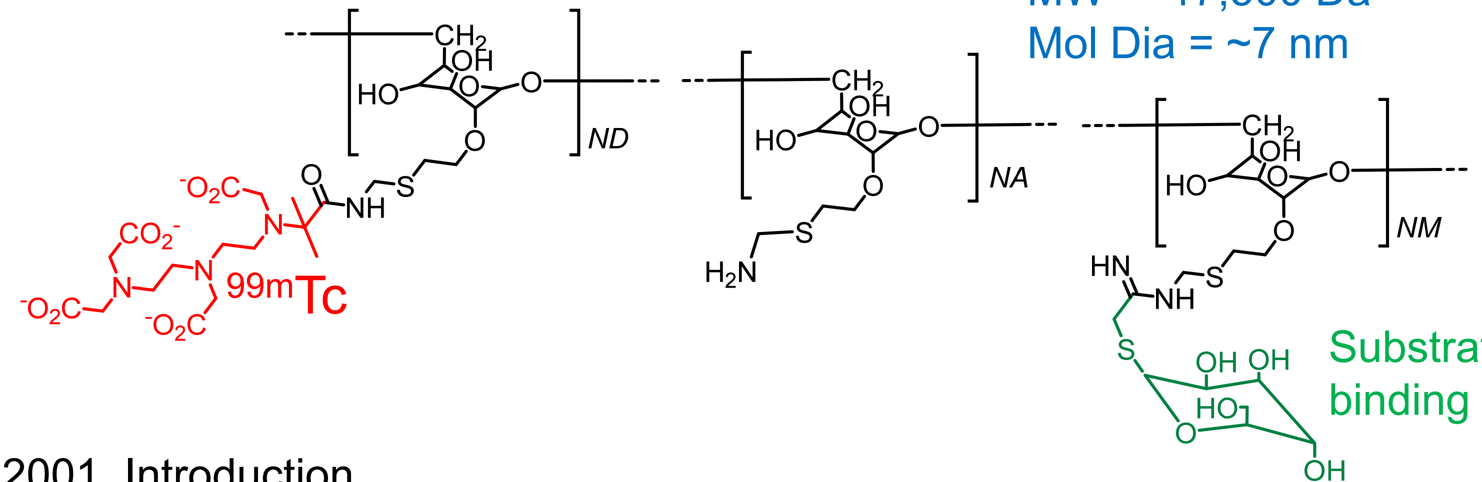
^{99m}Tc-labeled Tilmanocept

FDA & CMS approvals in 2013

Sentinel Lymph Node Mapping

MW= ~17,500 Da
Mol Dia = ~7 nm



Substrate for binding to **CD206**

Vera *JNM* 2001, Introduction
Wallace *Ann Surg Oncol* 2006, Phase 1, Breast Cancer
Wallace *Ann Surg Oncol* 2013, Phase 3, Breast Cancer
Marcinow *JAMA* 2013, Phase 3, H&N cancer

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^{99m}*Tc-labeled Tilmanocept*

Binds to the Receptor CD206

CD206 Cellular Distribution

- Fixed Macrophages
- M2 Macrophages
- Dendritic Cells
- Bacteria
- Microglial Cells
- Mesangial Cells

^{99m}Tc-labeled Tilmanocept

Phase 1 Clinical Trial of i.v. injection

NCT02865434

CD206 Cellular Distribution

- Fixed Macrophages
- M2 Macrophages
- Dendritic Cells
- Bacteria
- Microglial Cells
- Mesangial Cells

Imaging Rheumatoid Arthritis
Synovial Joint scan
30 mins PI
i.v. injection
10 mCi, 400 µg
Tc-99m-tilmanocept

Courtesy
Navidea Biopharmaceuticals

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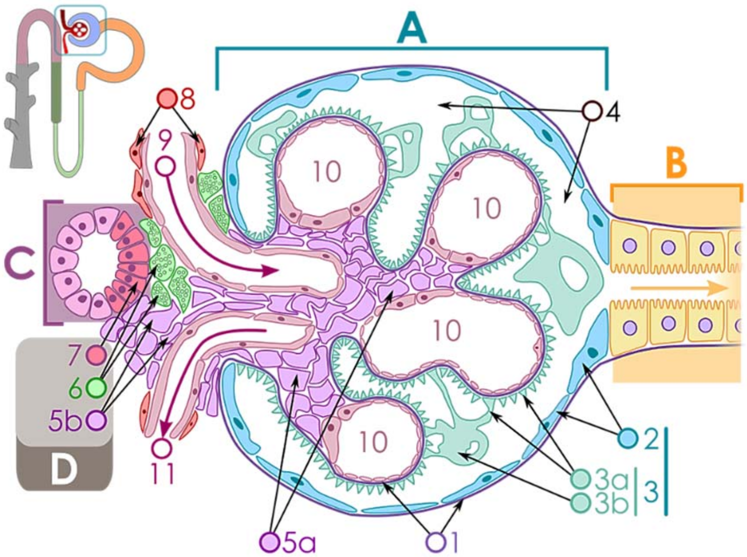
Mesangial Cell



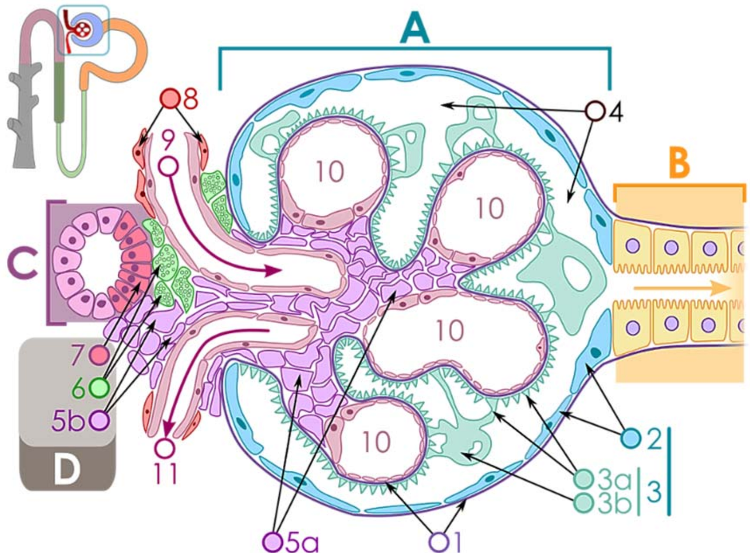
Mesangial Cell (5a & 5b) Functions

- Structural support
- Monitor glucose levels
- Immunologic surveillance

Wikipedia – mesangium

Mesangial Cell

Wikipedia – mesangium

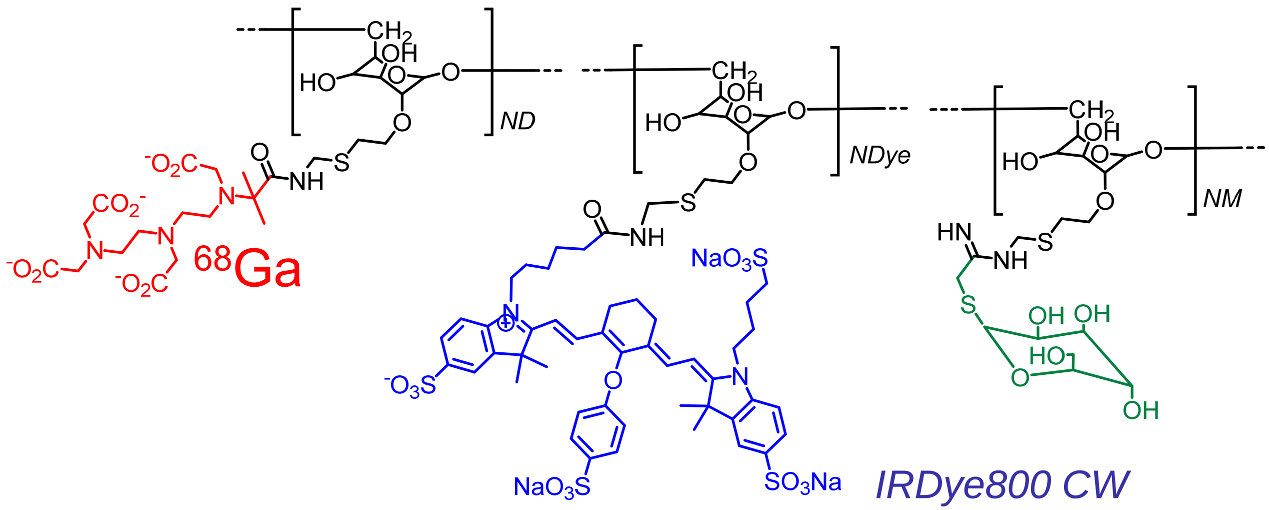


Motivation

- Mesangial cell expansion is an early indicator of DN
- Replace biopsy
- In Vivo measurement of MC expansion

Demonstration of Receptor-Binding

^{68}Ga-labeled *IRDye800CW-Tilmanocept*



IRDye800 CW
Excitation: 780 nm
Emission: 795 nm

Fluorescent-Tilmanocept

- K_A = 0.25 nM
  Emerson *Radiology* 2012
- Max brightness at 2 dyes per tilmanocept
  Qin *J Biomed Opt* 2013
  Liss *Urology* Epub

^{68}Ga-labeled Tilmanocept
CD206 Specificity

[^{68}Ga]DTPA-mannosyl-dextran

- Healthy Pig
- i.v. injection
- MW = 17 kDa
- 42 nmol
- 0.8 mCi
- MIP WB scan
- Start 20 min PI
- 5 bed positions
- 3 min/bed

^{68}Ga-labeled Tilmanocept CD206 Specificity

[^{68}Ga]DTPA-dextran

- Healthy Pig
- i.v. injection
- MW = 12 kDa
- 42 nmol
- 0.8 mCi
- MIP WB scan
- Start 20 min PI
- 5 bed positions
- 3 min/bed

[^{68}Ga]DTPA-mannosyl-dextran

- Healthy Pig
- i.v. injection
- MW = 17 kDa
- 42 nmol
- 0.8 mCi
- MIP WB scan
- Start 20 min PI
- 5 bed positions
- 3 min/bed

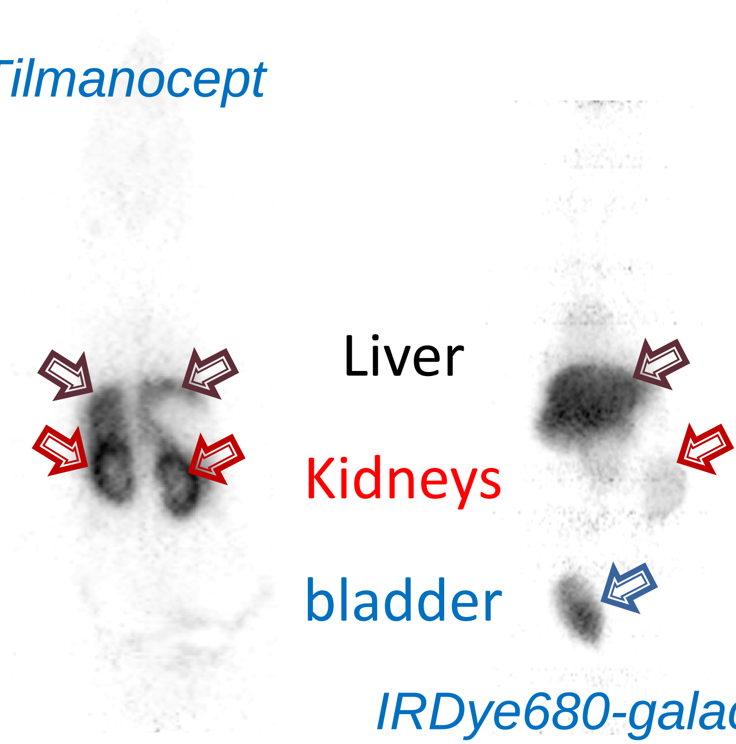
Demonstration of Receptor-Binding
^{68}Ga-labeled *IRDye800CW-Tilmanocept*

Experimental Design

- Radiolabel with gallium-68
  - *IRDye800CW-Tilmanocept*
  - *IRDye680-galactosyl-dextran*
- i.v. inject (0.1 nmol/g, ~0.2 mCi) healthy rats
- Perform 20-min dynamic PET imaging
- Wholebody imaging
- Excise, section & immunostain (CD206, *Alexa467*) kidneys
- View for co-localization of CD206 & tilmanocept

Ga-68 microPET Imaging

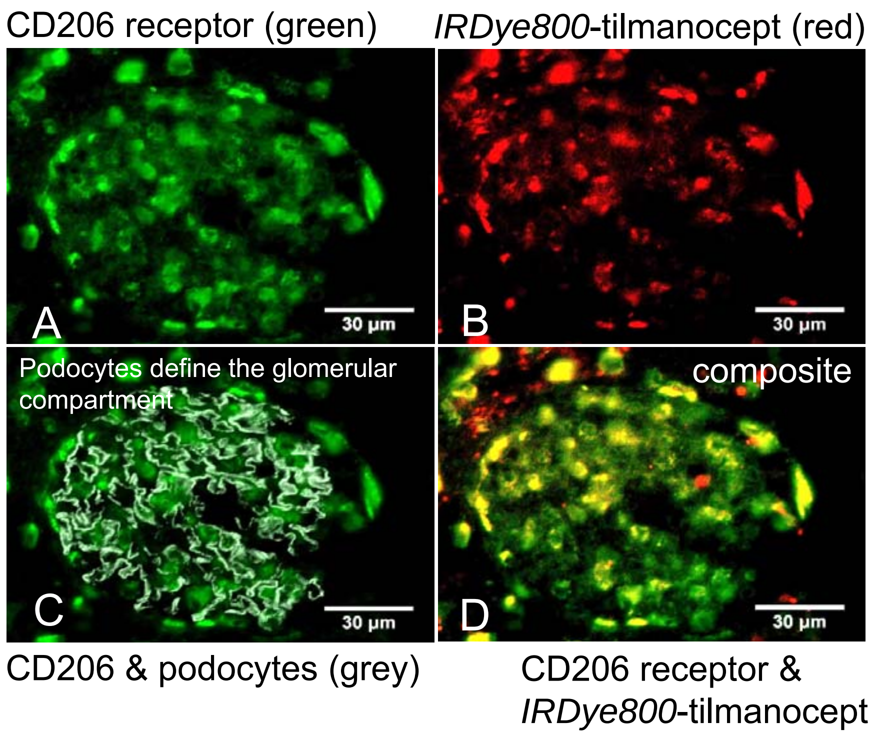
IRDye800CW-Tilmanocept



IRDye680-galactosyl-dextran

- Healthy Rats
- i.v. injection
- 42 nmol
- 0.8 mCi Ga-68
- 8 coronal sections
- Start 20 min PI
- 3 bed positions
- 5 min/bed

Demonstration of Disease Sensitivity
Co-Localization of CD206 and Tilmanocept



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^{99m}Tc-Cy5-Tilmanocept Disease Sensitivity

db/db mice
14 weeks old
0.1 nmol/g
0.1 mCi Tc-99m

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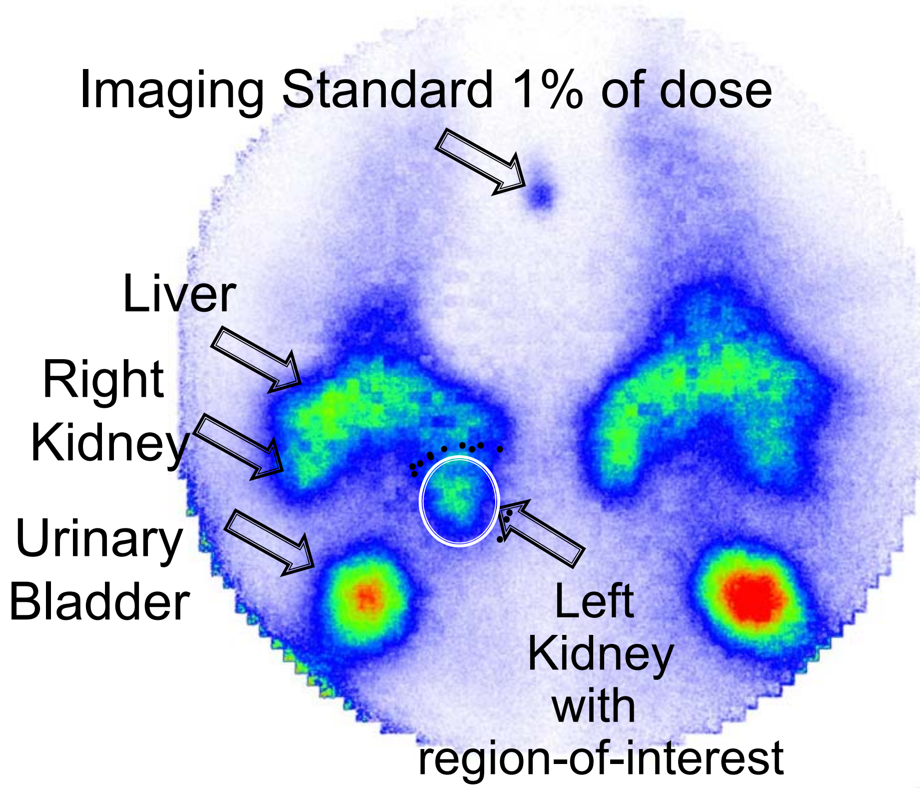
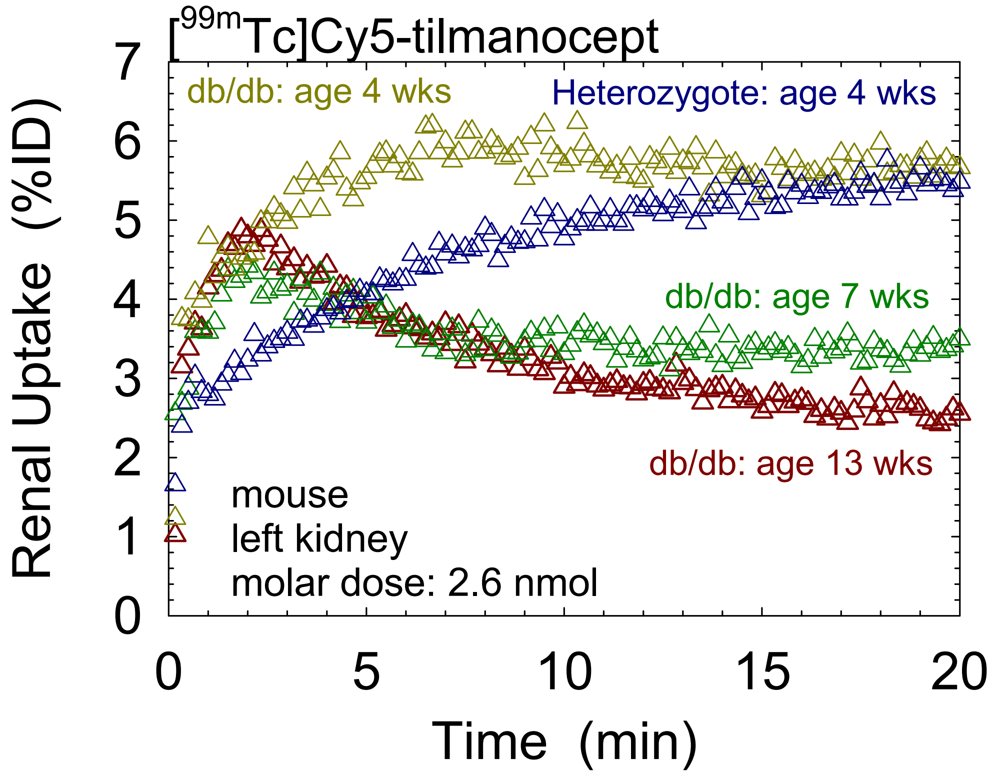
^{99m}Tc-*Cy5*-Tilmanocept Functional Imaging



db/db mice
14 weeks old
0.1 nmol/g
0.1 mCi Tc-99m

^{99m}Tc-*Cy5*-Tilmanocept Functional Imaging



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Conclusion

Demonstrated

- Tilmanocept binds to Mesangial Cells
- Kinetic sensitivity to diabetic nephropathy

Immediate Plans

- Phase 1 clinical trials
  - [^{99m}Tc]tilmanocept
  - [^{68}Ga]tilmanocept

Redesign

- Optimize chemical structure
  - Increase MW
  - Optimize affinity

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Molecular Imaging

Hypothesis:
A receptor-binding radiopharmaceutical can measure tissue reserve

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Molecular Imaging

Hypothesis (In Vivo Biopsy):
A radiopharmaceutical that binds to a mesangial cell receptor can measure intra-glomerular mesangial cell volume

Acknowledge

Molecular Imaging of the Liver

R23 AM34768

R01 AM34768

PET Imaging of the Kidney

In Vivo Cancer and Molecular Imaging Program

P50 CA128346

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