

## A Novel Molecule for the Systemic Imaging and Treatment of Rheumatoid Arthritis

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### Objectives:

A Tc-99m labeled mannosyl-dextran molecule (Tc-99m tilmanocept) has demonstrated specificity for targeting CD206 macrophages associated with sentinel nodes in breast cancer patients. The CD206 receptor is also expressed on inflammatory cells in the joints of patients with rheumatoid arthritis (RA) and in other inflammatory conditions (such as atherosclerosis) [1]. In patients with advanced RA, direct injections of radiocolloid into affected joints are used therapeutically to relieve pain and increase mobility. RA rarely effects a single joint, so multiple injections at multiple sites are required. If the radiocolloid could be administered systemically, it may be possible to treat multiple joints simultaneously. We combined a therapeutic isotope, Sn-117m ( $\gamma$  159 keV, 86% ;  $e^-$  ~140 keV, 112% ;  $t_{1/2}$  14d) with mannosyl-dextran to test the ability of the therapeutic tracer to localize in sites of inflammation in similar fashion to Tc-99m tilmanocept.

### Methods:

Sn-117m was chelated with aminobenzyl-DOTA. Mannose coupled dextran amine was combined with the Sn-117m chelate and the pH was adjusted and the final product purified with a size exclusion column. Yields ranged from 30 to 60%.

A sterile abscess (containing CD206 macrophages) was induced in eight BALB/c mice (injection of 20 uL of turpentine into the gastrocnemius muscle). Twenty-four hours later mice were each injected with 20  $\mu$ L (~200 kBq) of Sn-117m composition into the lateral tail vein. Four mice were sacrificed at 2 hours after and the other four at 24 hours after the injection. Identical parallel experiments were also performed with 8 additional mice using the commercial preparation of Tc-99m tilmanocept. Biodistribution analyses were performed of tissues and fluids.

### Results:

A comparison demonstrated similar elevated abscess to normal muscle uptake (Table 1) with both compounds. Biodistribution profiles were similar although an increase in liver uptake was observed for the Sn-117m molecule.

### Conclusions:

These studies suggest that systemic administration of a Sn-117m tilmanocept analogue localizes in inflamed RA tissue.

1. "The inextricable axis of targeted diagnostic imaging and therapy: An immunological natural history approach", F.O Cope *et al.*, Nuclear Medicine and Biology 43, (2016) 215-225

	Tc-99m	Sn-117m
2 hrs	3.5	5.5
24 hrs	4.4	4.5

Table 1: Ratio of uptake of Tc-99m tilmanocept in abscess compared to Sn-117m analogue.

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**Supporting Data: Biodistribution Results**

%ID	Sn-117m 2hr Biodistribution			
	Mouse #			
Tissue	A1	B1	C1	D1
Blood	1.1%	1.0%	1.5%	1.6%
Abscess	0.07%	0.06%	0.10%	0.1%
Heart	0.1%	0.1%	0.1%	0.1%
Lung	0.1%	0.1%	0.1%	0.1%
Bone	10.4%	13.3%	17.4%	13.2%
Muscle	1.7%	1.8%	1.8%	2.0%
Liver	57.0%	69.9%	70.0%	68.2%
Spleen	4.1%	4.8%	4.2%	4.5%
Kidney	1.0%	1.1%	1.0%	1.2%
Sm Int	5.2%	0.8%	1.0%	1.0%
Lg.Int	2.1%	2.1%	1.6%	2.7%
Stomach	0.1%	0.1%	0.1%	0.1%

Ratio Abscess/muscle (%ID/g)	
Mouse A1	4.21
Mouse B1	5.77
Mouse C1	6.29
Mouse D1	4.49
Avg:	5.52

Ratio Abscess/muscle (%ID/g)	
Mouse E1	3.78
Mouse F1	3.84
Mouse G1	6.55

Mouse H1	3.90
Avg:	4.52

%ID	Sn-117m 24hr Biodistribution		
	Mouse #		
Tissue	F1	G1	H1
Blood	0.2%	0.2%	0.2%
Abscess	0.1%	0.1%	0.1%
Heart	0.0%	0.0%	0.0%
Lung	0.0%	0.1%	0.1%
Bone	11.8%	14.8%	13.7%
Muscle	1.9%	1.5%	1.6%
Liver	71.4%	63.8%	70.6%
Spleen	5.3%	3.4%	4.0%
Kidney	0.8%	0.6%	0.9%
Sm Int	0.8%	0.6%	0.7%
Lg.Int	0.3%	0.3%	0.3%
Stomach	0.1%	0.1%	0.1%

%ID	Tc-99m 2hr Biodistribution		
	Mouse #		
Tissue	A2	B2	C2
Blood	6.0%	6.8%	7.5%
Abscess	0.4%	0.2%	0.1%
Heart	0.3%	0.2%	0.3%
Lung	0.3%	0.4%	0.4%
Bone	25.5%	23.0%	29.3%
Muscle	7.0%	7.1%	8.0%
Liver	27.2%	30.2%	23.2%
Spleen	4.0%	3.1%	3.5%
Kidney	5.8%	5.8%	6.9%
Sm Int	4.1%	5.2%	5.6%
Lg.Int	0.7%	0.7%	1.0%
Stomach	0.8%	1.3%	0.8%

Ratio Abscess/muscle (%ID/g)	
Mouse A2	4.29
Mouse B2	3.70
Mouse C2	2.15
Mouse D2	3.69
Avg:	3.46

%ID	Tc-99m 24hr Biodistribution	
	Mouse #	
Tissue	F2	G2
Blood	1.0%	1.0%
Abscess	0.05%	0.06%

Heart	0.1%	0.0%
Lung	0.1%	0.1%
Bone	11.2%	13.3%
Muscle	2.2%	2.8%
Liver	21.2%	21.5%
Spleen	1.2%	1.4%
Kidney	1.6%	1.5%
Sm Int	1.1%	0.7%
Lg.Int	0.8%	0.9%
Stomach	0.2%	1.0%

Ratio Abscess/muscle (%ID/g)	
Mouse F2	4.70
Mouse G2	4.73
Mouse H2	3.73
Avg:	4.39

Figure: Structure of Sn-117m labeled Manoccept.

