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SNMMI Abstract

**A Novel Molecule for the Systemic Treatment of Rheumatoid Arthritis**

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**Objectives:** A Tc-99m labeled mannosyl-dextran molecule (Tc-99m tilmanocept) has demonstrated specificity for targeting systemic RA (CD206 macrophages). An analogue molecule containing a therapeutic isotope might provide the opportunity to treat the disease. Sn-117m ( $t_{1/2}$  14d) is being evaluated to treat RA locally (radiosynoviorthesis) since it has ideal characteristics with therapeutic conversion electrons (~140 keV, 112%) that have a maximum range of about 300  $\mu$ m in tissue. Its photon emission ( $\gamma$  159 keV, 86%) also allow for simultaneous imaging. A Sn-117m analogue of the Tc-99m tilmanocept molecule has been produced and its specificity in targeting systemic RA evaluated.

**Methods:**

Tilmanocept uses DTPA as the chelant for Tc-99m. However, DTPA is known to be unstable for Sn-117m in-vivo so an alternative linking molecule is needed. High specific activity Sn-117m was chelated with the bifunctional chelating agent aminobenzyl-DOTA which has demonstrated in-vivo stability when linked to other molecules. Mannose coupled dextran amine was then combined in a 5:1 molar excess over the Sn-117m chelate and the pH was adjusted from 9 to 9.2 for 90 minutes at 37 °C. Purification was accomplished using a 6,000 molecular weight gravity fed size exclusion column. Yields using this process typically ranged from 30 to 60%. The final molecule is shown in Figure 1.

Eight male BALB/c mice were each injected with 20  $\mu$ L of turpentine into the gastrocnemius muscle of the right hind leg. This produces a sterile abscess containing the CD206 macrophage associated with RA. After 24 hours, the mice were each injected with 20  $\mu$ L of the 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. Tissues and samples collected were: blood, heart, lung, left femur, left thigh muscle, liver, spleen, kidneys, small intestine, large intestine, stomach, tail, abscess, remainder of carcass and bladder along with all collected absorbent paper containing accumulated feces and urine. The samples were then counted in a NaI detector. Identical parallel experiments were also performed with 8 additional mice using the commercial preparation of Tc-99m tilmanocept.

**Results:**

The biodistribution of Sn-117m labeled mannosyl-dextran was compared to that of similar Tc-99m labeled product. In both cases the elevated abscess to normal muscle uptake was about the same (see table 1) showing that both constructs have similar biological specificity. Biodistribution profiles were also similar although a difference in liver uptake was noted.

**Conclusions:**

Recent success with employing Tc-99m tilmanocept to selectively target and image CD206 macrophages associated with RA is very encouraging. A similarly labeled molecule employing Sn-117m has been constructed and tested in a rat model. The very similar uptake of both labeled molecules suggests the possibility of a systemic therapy for RA. Future work includes efficacy and toxicology studies.

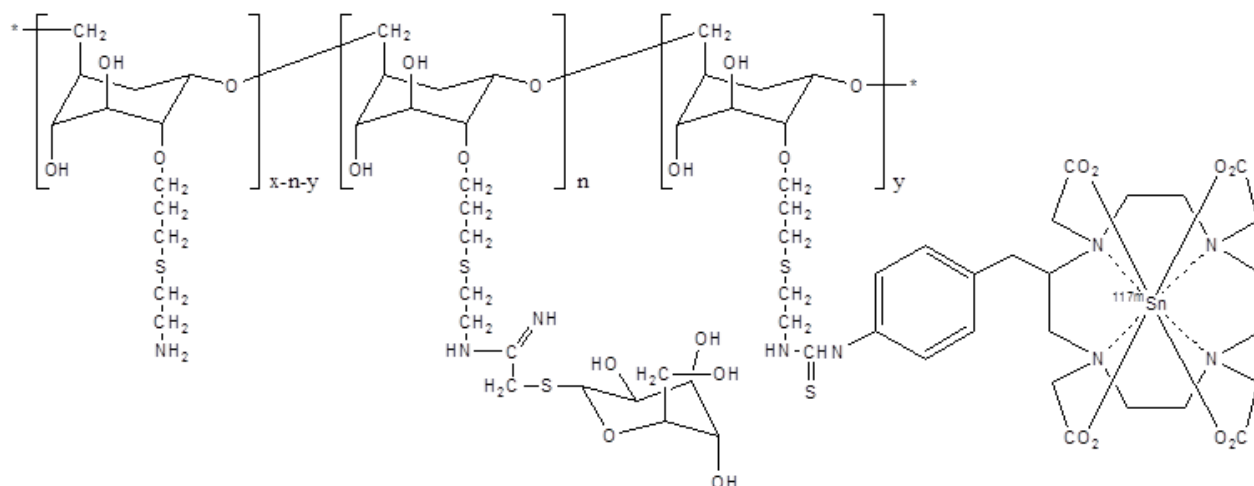


Figure 1: Structure of Sn-117m labeled Mancept.

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

Table 1: Uptake of product in abscess compared to Tc-99m analogue. Numbers represent the ratio of uptake in abscess (CD206 sites) to normal tissue.

**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 |

| %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%  |

| 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     | 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 |