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Preparation of Heat-Denatured Macroaggregated Albumin for Biomedical Applications using a Microfluidics Platform

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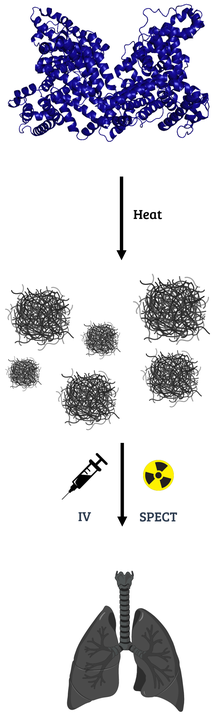
Background

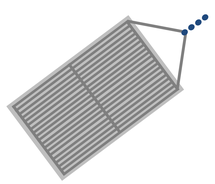
Clinical Use of Macroaggregated Albumin



- Macroaggregated Albumin (MAA) is easily synthesized by denaturing the free protein with heat [1].
- When labelled with the gamma-emitter ^{99m}Tc, macroaggregated albumin can be used for lung perfusion imaging with SPECT because it safely embolizes in the lung capillary beds [1].
- Batch preparation of MAA results in polydisperse and structurally heterogeneous samples [2].
- Because of the heterogeneity of MAA samples and variability between batches, there are concerns surrounding the reproducibility of imaging tests performed with ^{99m}Tc-MAA [2].

Microfluidics as a Promising Platform for the Synthesis of MAA

- Microfluidics is an attractive platform to synthesize homogeneous materials due to its ability to rapidly mix reagents, create a homogeneous reaction environment, and add reagents at precise times during reactions [3].
- Various microfluidics platforms have been reported to synthesize nanoparticles of all sorts, including protein nanoparticles [4].



Research Objectives

- Develop a microfluidics chip capable of synthesizing monodisperse MAA particles: microfluidic-MAA (M2A2)
- Radiolabel the M2A2 particles and assess their ability to be used for lung SPECT imaging

Methods

Microfluidics Chip Setup

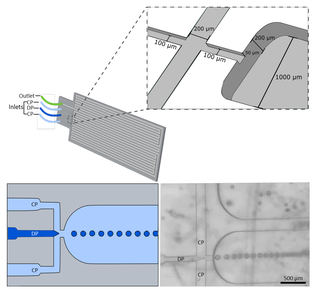


Figure 1. Schematic of the microfluidics chip. CP: continuous phase, DP: Dispersed phase.

Synthesis and Characterization of Radiolabeled MAA

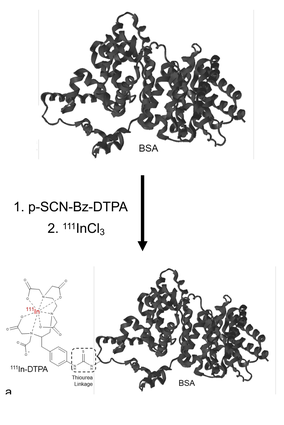


Figure 2. Synthesis scheme of radiolabeled albumin.

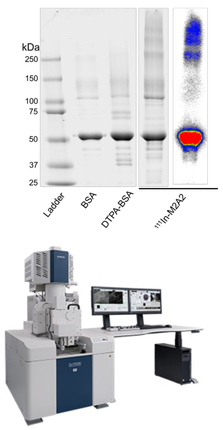


Figure 3. SDS-PAGE and SEM-based characterizations of M2A2.

Assessment of Lung Uptake and Biodistribution of M2A2

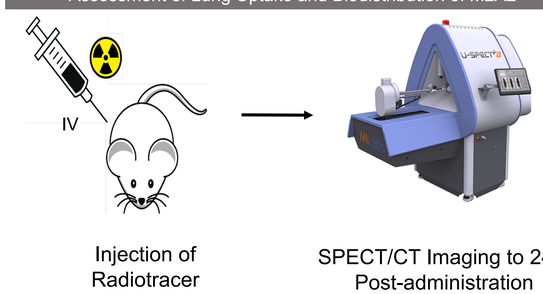


Figure 4. Scheme for assessing uptake of M2A2 into the lungs as well as its overall biodistribution using a VECTor SPECT system.

Results

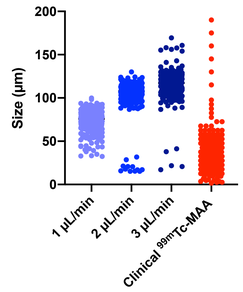


Figure 5. Altering the flow rate of the dispersed phase can lead to changes in the average particle diameter. The particle diameter of clinical ^{99m}Tc-MAA (adapted from Takagi *et al* is shown for comparison) [5]. Mean particle sizes were 72.0 ± 15.1, 105.6 ± 14.7, and 119.2 ± 12.5 µm for DP flow rates of 1, 2, and 3 µL/min, respectively. Clinical MAA had a mean particle size of 32.7 ± 17.8 µm.

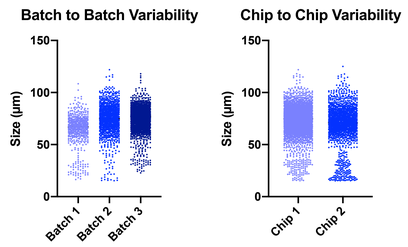


Figure 6. The microfluidic chips used to to synthesize M2A2 showed little variability between batches and between chips. Differences between chips and between batches are not statistically significant.

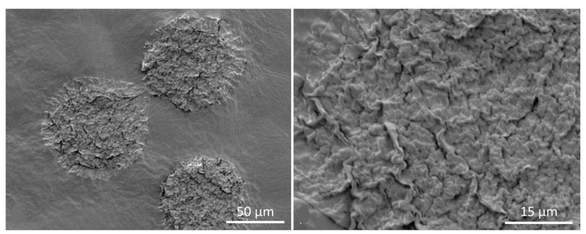
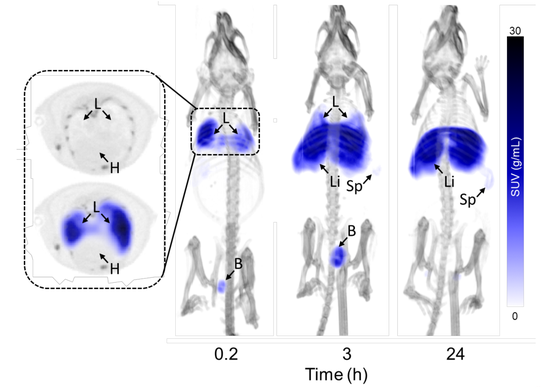


Figure 7. Scanning electron micrographs of M2A2 particles.



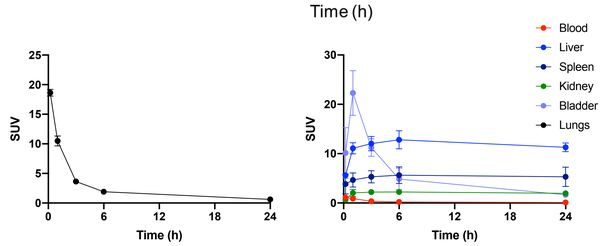


Figure 8. M2A2 was taken up into the lungs when administered intravenously and was eliminated from systemic circulation via the reticuloendothelial system (spleen and liver resident phagocytes) and renal system.

Conclusion and Future Directions

- Macroaggregated albumin was synthesized using a microfluidics ship, which resulted in less polydisperse samples than conventional synthesis methods.
- The microfluidic chips showed little variability between chips and between batches.
- SPECT imaging of a radiolabeled form of the particles showed that they behave similarly to conventional MAA particles and are suitable for lung imaging.
- Preliminary work shows that M2A2 particles can be loaded with various active compounds; M2A2 may see success as a non-toxic drug carrier for intravenous delivery of compounds to the lungs .

References

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