A Radiolabeling Methodology to Monitor siRNA Nanodelivery by in vivo PET Imaging

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Substantial parts of this Master project are confidential, therefore this public poster has been kept very general.

Background

- Small interfering RNA (siRNA) are double-stranded nucleic acid molecules that can silence genes in a sequence-dependent manner. (Figure 1)
- SiRNA-mediated gene silencing occurs by RNA interference.¹
- The biggest challenge for siRNA therapeutics is delivery to target tissues and cells.
- The Mulder group has developed a robust and biocompatible lipoprotein-inspired platform that incorporates siRNA. (unpublished data)
- The goal of this technology is to deliver siRNA to innate immune cells.
- To develop effective siRNA immunotherapies, in vivo biodistribution studies are needed.
- To enable siRNA monitoring by in vivo PET imaging, siRNA requires radiolabeling before incorporation into nanobiologics and subsequent intravenous administration. (Figure 3)

Approach

We explored three siRNA radiolabeling strategies (Figure 4):
1. Covalent radiolabeling
2. Electrostatic radiolabeling
3. Chelator-based radiolabeling

Results

- Covalent radiolabeling with iodine-124 will result in PET images with low resolution and electrostatic radiolabeling was unsuccessful. (data not shown)
- Mass spectrometry of chelator-based radiolabeling looks promising. However, conditions need to be optimized as the chelator coupled to the passenger strand seems to interfere with MALDI-TOF analysis. (Figure 5)

Conclusions & Future experiments

- A new siRNA nanobiologic formulation was implemented and validated.
- I automated the nanobiologic formulation procedure such that it can be remotely controlled to minimize researchers’ exposure to ionizing radiation.
- To monitor siRNA biodistribution in vivo, three radiolabeling strategies were considered and we obtained promising results for chelator-based radiolabeling.
- As those experiments could not be repeated because of COVID-19-related supply chain disruptions, I designed a detailed plan for future experiments including biodistribution and pharmacokinetic studies, cellular specificity experiments as well as siRNA functionality assessment. (Figure 6)

References & Acknowledgements

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References: