Thesis Project Portfolio

eLiposomes as a Targeted Thrombolytic Drug Delivery Vehicle During Sonothrombolysis

(Technical Report)

An Actor-Network of the FDA Approval Process of Aduhelm

(STS Research Paper)

An Undergraduate Thesis

Presented to the Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Fulfillment of the Requirements for the Degree

Bachelor of Science, School of Engineering

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Department of Biomedical Engineering

Contents of Portfolio

Executive Synthesis

This thesis attempted to explore concepts related to the development of a sonothrombolytic agent from both the perspective of research and design as well as examining the overall process of FDA approval for a new biological agent. Sonothrombolytic agents are small particles injected into the bloodstream that can cavitate in response to ultrasound waves. They are experimentally used to mechanically break down blood clots with reduced amounts of thrombolytics, drugs that can catalyze the breakdown of blood clots but are also associated with risks of bleeding. Research is ongoing on the effectiveness of many different types of cavitation agents such as microbubbles, nanobubbles, or nanodroplets, with the intent to maximize the possible damage done to the clot by an agent but also minimize risks of tissue damage from inertial cavitation and tissue heating from absorbed ultrasound waves. Clinical trials for sonothrombolytic treatments, such as the Phase III CLOTBUST-ER program, are undergoing consideration for FDA approval as a treatment method for stroke. This has motivated both an investigation into the creation of a more optimal sonothrombolytic cavitation agent as well as the sociotechnical intricacies of the FDA approval process.

The technical research project focused on the devisement and synthesis of a targeted sonothrombolytic agent using an ultrasound sensitive liposome containing a perfluorocarbon emulsion droplet. Called an emulsion liposome or eLiposome, research on them has primarily focused on selective release of chemotherapeutics within tumors. The project had two aims. First, to develop a prep to create monodisperse eLiposomes and characterize their encapsulation efficiency, thermal stability, size distribution, and ultrasound release rates of calcein dye relative to control liposomes with no perfluorocarbon droplets. Second, to compare the relative rates of sonothrombolysis using conventional sonothrombolytic agents like microbubbles or nanodroplets paired with free rtPA and the novel eLiposome targeted to blood clots using fucoidan. We were able to demonstrate a statistically significant increase in calcein release in eLiposomes compared to control liposomes (78% vs 32%) after 90 seconds of ultrasound treatment with a 1MHz transducer. Additionally, we were able to demonstrate a monodisperse size distribution (PDI = 0.24), statistical indistinguishability in thermal release relative to

control in 4 °C, and an encapsulation efficiency of 1.5%. We were unfortunately not able to complete the second aim, which further research should aim to accomplish.

The sociotechnical project consisted of an analysis of the actor-network of the FDA approval process for the Alzheimer's drug Aduhelm in 2021 through a literature review. The underlying research question was: *What was the actor network for the FDA approval process of aducanumab (Aduhelm) and how does it reflect on the modern FDA approval process?* Evidence was collated to reconstruct the actor-network and steps of translation: problematization, interessement, enrollment, and mobilization, that the principal actor, Biogen, carried out. What was found was that the recruitment of the reviewers of the drug in the FDA's Office of Neuroscience in the Center for Drug Evaluation and Research during the phase of interessement and enrollment lead the reviewers themselves to participate in the interessement of the other actors. They eventually advocated for the accelerated approval of the drug despite the limited clinical evidence in favor of its effectiveness on clinical symptoms. Instead, accelerated approval was justified by shifting the criteria away from a clinical rating of dementia symptoms to a measure of reduced aggregated alpha-amyloid proteins, which may or may not be a cause of symptoms. This eventually led to controversy and betrayal by healthcare professionals in their role in the network to accept the legitimacy of FDA approved drugs. Ultimately, while the drug may have been genuinely effective in slowing cognitive decline in Alzheimer's patients, the highly unusual collaboration of the FDA and Biogen led to distrust in the entire network. The use of accelerated approval was also noted to be frequently abused, with the framework of Phase IV studies after approval being loosely demanded and enforced.

In summation, I have accomplished some, but not all that I have set out to do this year. My technical project has been partially successful, but I have not achieved my goal of creating an eLiposome sonothrombolysis agent and testing it. My STS project was more successful in

accomplishing its scope of picking up on the larger issues around the approval of Aduhelm and the FDA accelerated approval process.

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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