THESIS PROJECT PORTFOLIO

The Design of Lipid Nanoparticles for Delivery of RNA Therapeutics as a Treatment for Acute Myeloid Leukemia

(Technical Report)

Scientific Integrity: Performing Pre-Clinical Research the Right Way

(STS Research Paper)

An Undergraduate Thesis

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Biomedical research is one of humanity's most powerful tools. When used correctly, novel pre-clinical findings may lead to the development of life-saving therapies. Transformational medicines such as nanoparticle mediated drug delivery have the potential to provide improved treatments for patients with serious illnesses such as Acute Myeloid Leukemia (AML). The technical portion of the proposed work examines a lipid nanoparticle based combinatorial approach with chemotherapies as a novel treatment for AML patients. Unfortunately, some researchers have misused this "scientific power" to reap short-term social and economic benefits through publication of research which is fabricated, falsified, or plagiarized. As of the year 2022, more than 32,000 publications have been removed from journals due to this detrimental practice of research misconduct (Oransky, 2021). This propagation of misinformation causes public distrust of scientific research while delaying the clinical progress of patient-saving therapies. The social portion of the proposed thesis examines past instances of research misconduct while identifying organizations which encourage research responsibility. The discovery of effective medicines of the future requires technical advancements and a commitment to scientific integrity. The proposed thesis serves to highlight the significance of both principles.

Acute myeloid leukemia (AML) is a rare disease characterized by the overproduction of white blood cells which leads to a five-year survival rate of 26% (Vakiti & Mewawalla, 2021). Unfortunately, the current standard of care, chemotherapies, suffer from genome-specific mechanisms of resistance and revolutionizing treatments such as CAR-T cell therapies remain in early stages of clinical trials. AML patients need better short-term treatment options. The proposed design directly addresses this issue of 'chemoresistance' through the formulation of lipid nanoparticles (LNPs) encapsulating small interfering ribonucleic acids (siRNAs).

Exploration of this method is justified by its scalability and clinical translation as portrayed by the success of similar medicines including the coronavirus-19 vaccine (Carrasco et al., 2021) and Patisiran, an siRNA-based treatment vector for amyloidosis (Adams et al., 2018). An effective combinatorial treatment pairing the standard of care, chemotherapies, with an siRNA-LNP vector has the potential to extend the life expectancy for patients suffering from AML. Furthermore, the design process will provide further insight into the scalable development and implementation of nucleic acid-based nanomedicines for treatment of genetic based diseases.

Scientists exist as the public's ambassadors to the unknown. However, with this power comes an extreme responsibility to produce research results which are clear and truthful. Past researchers engaged in scientific malpractice have glorified false discoveries and distracted the public from truly viable breakthroughs in medicine. These perpetrators include large, obvious cases surrounding findings of Dr. Gregg Semenza and Haruko Obokata but also more miniscule incidences which introduce a cascading effect upon an entire field of research. However, these transgressors are not met without opposition. Retraction Watch has reinforced the adoption of ethical research practices by policing past perpetrators of research misconduct. Organizations including the Center for Open Science stemming from the University of Virginia grant researchers additional opportunities to receive feedback to correct both conscious and unconscious biases in their work. By identifying past events of research misconduct and developing action items intended to encourage research responsibility, clinically translatable science is able to persist.

The technical progress of the proposed thesis has provided a promising new avenue for in vitro transfection of difficult cell lines and enumerates a novel methodology for high-throughput production of versatile nanoparticle vectors. The social portion of the project raises awareness

towards conscious and unconscious examples of research misconduct while offering substantiative measures to promote research responsibility through motivated organizations. Science presents humanities only chance at learning more about the world and each other. We must therefore push its limits while also treating it with deserved respect.

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