Undergraduate Thesis Prospectus

A Novel Genetic Therapy for Treatment of Acute Myeloid Leukemia

(technical research project in Biomedical Engineering)

How Advocacy Groups Fight Racism in Healthcare

(sociotechnical research project)

by

Colin Haws

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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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STS advisor: Peter Norton, Department of Engineering and Society

General Research Problem: Improving Personalized Medicines

How may the quality of and access to personalized medicines be improved?

Personalized medicines have become increasingly important in health care. Emerging research has identified an individual's genetic profile to be instrumental in disease prognosis. Certain biomarkers (genetic indicators of disease) have therefore become targets for tailored therapies. However, technical obstacles have impeded the development of effective gene-based, personalized treatments for cancers such as leukemias.

The equitable distribution of personalized medicines is also essential to their therapeutic efficacy. In the United States, access to these and other medicines is fraught with racial disparities at provider and institutional levels (Hoffman et al., 2016). Advocacies are striving to achieve more equitable access to medicine.

Nanotechnology for a Cure: A Novel Treatment for Acute Myeloid Leukemia

How can researchers decrease the production of proteins which propagate the development of leukemia?

Acute myeloid leukemia (AML) is a cancer originating in the bone marrow characterized by a rapid accumulation of diseased blood cells (Rushworth et al., 2012). The time and magnitude of this uncontrolled growth is characterized by a five-year survival rate of 26% (Vakiti & Mewawalla, 2021; ACS, 2021). Patients with AML are conventionally treated with chemotherapies which rely on an oxidative stress pathway to induce cell death. However, researchers have discovered AML propagation occurs through a cascade of genetic malfunctions which inhibits this pathway (Liu et al., 2021). New proposed therapies target upstream progenitors which regulate these diseased gene networks. This project aims to reduce the

production of the pathologically manipulated transcription factor NF-E2–related factor 2 (Nrf2) in AML cells. Knockdown of Nrf2 is hypothesized to decrease signaling of pathways responsible for this "chemoresistance" and increase chemotherapeutic efficiency. An effective treatment must therefore lead to significant knockdown in Nrf2 protein, increased cell death when used in combination with standard chemotherapeutic agents, and offer scalable manufacturing potential.

This technical problem will be addressed as a solo capstone research project under advisement from Dr. Anuradha Illendula of the Department of Pharmacology. The proposed project intends to intersect emergent technologies in lipid-based nanoparticles (LNPs) and ribonucleic acid interference (RNAi). LNP vectors demonstrate high encapsulation of nucleic acids due to favorable charge-charge interactions which improves the delivery of therapies *in vivo* (Carrasco et al., 2021). RNAi therapies lead to tunable decreases in Nrf2 protein levels and do not rely on an immune response which is desirable for treatment of an autoimmune disease such as AML. A combination of these platforms recently received FDA approval as a treatment for amyloidosis which emphasizes the potential for clinical translation in a similar therapy (Alnylam Pharmaceuticals, 2018).

Production of LNPs will concur with previous high-throughput research using microfluidics (Meel et al., 2020). Design of effective RNAi constructs will require consultation of my advisors and previous studies (Roces et al., 2020; Rushworth et al., 2012). Testing of the final combinatorial therapy will utilize cell culturing/microbiology techniques along with lipid and drug resources acquired by the lab. Each step of the design process will be paired with appropriate methods of characterization including particle analysis and cell viability assays to promote step-wise optimization.

A successful therapy will provide a novel treatment option for patients with AML. Furthermore, the design process will provide further insight into the development and implementation of nucleic acid-based nanomedicines for treatment of genetic based diseases.

How Advocacy Groups Fight Racism in U.S. Healthcare

In the U.S., how do advocates of equitable healthcare strive to reduce racial inequities in medicine?

Racism has existed in the U.S. healthcare system for centuries. Medical researchers have examined the case of Dr. Sims who conducted gynecological experiments on black American women in the 19th century (Wall, 2006). Similarly, from the 1930s to the 1970s, syphilitic black men were deceived into serving as experimental subjects. Researchers told them they were receiving free treatment in return for their participation, and instructed them to seek no other treatment. In fact, the researchers had lied. They were studying the effects of untreated syphilis, and the men received no treatment (Tuskegee University). Racial inequalities in treatment recommendations and pain assessments continue to pervade modern medicine (Hoffman et al., 2016). Racial equity advocacies publicize such injustices, past and present, and fight biases in medicine.

Participants include patient support groups, racial equity advocacies, professional societies representing caregivers, and hospitals. Many black patients have publicized inequities in medicine. Patients who contend that they have experienced deficient care, such as Malaika Pedzayi-Ferguson (CBS News, 2020), are advocates for fairer healthcare. Some medical professionals hold implicit racial biases that impair their caregiving (Hoffman et al., 2016). Some healthcare professionals believe, for example, that “black people’s skin is thicker than white

people's skin," and black patients are less sensitive to pain (Hoffman et al., 2016). Physicians are represented by the American Medical Association (AMA) and by other professional societies. The AMA's Equity Strategy Plan condemns racism in medicine (AMA, 2020). White Coats for Black Lives (WC4BL) is an advocacy of medical students and professionals committed to fighting racial biases in medicine. It is a coalition of chapters at university hospitals that seek to "dismantle racism and accompanying systems of oppression in health" (WC4BL, 2021). WC4BL organizes demonstrations and publicizes racial inequities in medicine.

In a study of racial biases in physicians' recommendations for heart patients, Schulman et al. (1999) found a discrepancy in the recommendation for cardiac catheterization among patients of different race. Hoffman et al. (2016) found that many physicians suppose black people are less sensitive to pain than white people, impairing the care they offer black patients.

References

ACS (2021). American Cancer Society. *What Is Acute Myeloid Leukemia (AML)? | What Is AML?* https://www.cancer.org/cancer/acute-myeloid-leukemia/about/what-is-aml.html

Alnylam Pharmaceuticals. (2018). APOLLO: A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin (TTR)-Mediated Polyneuropathy (Familial Amyloidotic Polyneuropathy-FAP) (Clinical Trial Registration No. NCT01960348). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01960348

AMA (2020). American Medical Association. Organizational Strategic Plan to Embed Racial Justice and Advance Health Equity -equity-strategic-plan.pdf. American Medical Association

Carrasco, M. J., Alishetty, S., Alameh, M.-G., Said, H., Wright, L., Paige, M., Soliman, O., Weissman, D., Cleveland, T. E., Grishaev, A., & Buschmann, M. D. (2021). Ionization and structural properties of mRNA lipid nanoparticles influence expression in intramuscular and intravascular administration. *Communications Biology*, *4*(1), 1–15. https://doi.org/10.1038/s42003-021-02441-2

Hoffman, K. M., Trawalter, S., Axt, J. R., & Oliver, M. N. (2016). Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proceedings of the National Academy of Sciences*, *113*(16), 4296–4301. https://doi.org/10.1073/pnas.1516047113

Liu, P., Ma, D., Wang, P., Pan, C., Fang, Q., & Wang, J. (2021). Nrf2 overexpression increases risk of high tumor mutation burden in acute myeloid leukemia by inhibiting MSH2. *Cell Death & Disease*, *12*(1), 1–15. https://doi.org/10.1038/s41419-020-03331-x

Meel, R. van der, Chen, S., Zaifman, J., Kulkarni, J. A., Zhang, X. R. S., Tam, Y. K., Bally, M. B., Schiffelers, R. M., Ciufolini, M. A., Cullis, P. R., & Tam, Y. Y. C. (2020). Modular lipid nanoparticle platform technology for siRNA and lipophilic prodrug delivery (p. 2020.01.16.907394). *Small* 17(210): 1-12. https://doi.org/10.1101/2020.01.16.907394

Roces, C., Lou, G., Jain, N., Abraham, S., Thomas, A., Halbert, G., & Perrie, Y. (2020). Manufacturing Considerations for the Development of Lipid Nanoparticles Using Microfluidics. *Pharmaceutics*, *12*, 1095. https://doi.org/10.3390/pharmaceutics12111095

Rushworth, S. A., Zaitseva, L., Murray, M. Y., Shah, N. M., Bowles, K. M., & MacEwan, D. J. (2012). The high Nrf2 expression in human acute myeloid leukemia is driven by NF-κB and underlies its chemo-resistance. *Blood*, *120*(26), 5188–5198. https://doi.org/10.1182/blood-2012-04-422121

Schulman, K. A., Berlin, J. A., Harless, W., Kerner, J. F., Sistrunk, S., Gersh, B. J., Dubé, R., Taleghani, C. K., Burke, J. E., Williams, S., Eisenberg, J. M., Ayers, W., & Escarce, J. J. (1999). The Effect of Race and Sex on Physicians' Recommendations for Cardiac Catheterization. *New England Journal of Medicine*, *340*(8), 618–626. https://doi.org/10.1056/NEJM199902253400806

Tuskegee University. About the USPHS syphilis study https://www.tuskegee.edu/about-us/centers-of-excellence/bioethics-center/about-the-usphs-syphilis-study

Vakiti, A., & Mewawalla, P. (2021). Acute Myeloid Leukemia. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK507875/

Wall, L. L. (2006). The medical ethics of Dr J Marion Sims: A fresh look at the historical record. *Journal of Medical Ethics*, *32*(6), 346–350. https://doi.org/10.1136/jme.2005.012559

WC4BL (2021). https://whitecoats4blacklives.org/