Novel Alternative Method to Improve the Safety and Targeting of Nanotherapeutics

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Over 40% of chemotherapy patients suffer toxic side effects due to non-specific targeting, and most genetic therapies are prematurely degraded before they can reach target organs, limiting therapeutic efficacy. Nanocarrier (NC) based drug delivery offers promising solutions to such problems. However, the rational design and high-throughput development of breakthrough NCs are constrained by unpredictable cytotoxicity, biodistribution, and drug release. This project combines computational and wet-lab techniques to solve these problems. First, Machine Learning (ML) and Physiologically-Based Pharmacokinetic Models, trained on >14,000 previously unextracted data points, robustly predicted NC toxicity and organ/tumor delivery efficacy from physicochemistry (size, coating, etc.). ML effectively predicted the biofunctionality of >250 Lipid (created via lipid film hydration) and Silica (created via the Sol-Gel Process) NCs tested in vitro, suggesting these models could be used to avoid time-consuming experiments. Next, ML Explainability identified numerous novel NC rational design optimizations to improve targeting by avoiding reticuloendothelial sequestration and maximizing tumor accumulation. Similarly, an in situ technique was identified and validated in vitro to reduce toxicity while maintaining the therapeutic functionality of Cationic NCs by altering surface charge dispersion. Last, ML identified 11 novel NCs for the treatment of Ovarian Cancer and Genetic Kidney Diseases from a combinatorial library. These 11 NCs were loaded with chemotherapeutics or nucleic acids and showed optimal, preferential toxicity, uptake, and gene expression profiles in murine cells - proving this project’s potential to assist in the future creation of translatable, life-saving nanotherapeutics.

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