Improving efficacy of therapeutics by enhancing delivery using chemical engineering

by

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Technical Summary

In the past decades, many new and interesting modalities for therapeutics have been discovered, including nucleic acid therapeutics such as siRNA and mRNA. However, one of the limiting challenges in developing these technologies into medicines is delivering the therapeutics to the correct location in the body or in the cell. Furthermore, many older modalities for therapeutics, such as vaccines and chemotherapeutics, could become more efficacious with optimization of delivery. By using chemical engineering principles, we can develop better delivery methods, materials, and formulations to improve the treatment of a wide range of diseases. In this thesis, I report on applications to vaccines and cancer.

Vaccines are currently the vanguard of public health efforts; unfortunately, a wide range of diseases have no effective vaccine. This includes devastating diseases such as HIV, malaria, and others. One area of vaccination that few people have considered optimizing is the kinetics by which the vaccine is delivered. We found that using an exponential increasing dosing profile, we could produce over 7 times more antibodies compared to the current prime-boost profile using the same amount and type of vaccine. The antibodies generated were also of higher affinity. By improving antibody affinity and titer, this work may make existing vaccines for diseases such as HIV sufficiently efficacious to use in humans.

Cancer is one of the leading causes of death in both developed and developing countries, and is extremely difficult to cure due to its high variability. Furthermore, current cancer therapeutics cause severe toxicity. By delivering more of the cancer therapeutics to the tumor, we can reduce the side effects. Some tumors, because of their location, are even harder to access: brain tumors, such as glioblastoma, are protected from most drugs by the blood-brain barrier or blood-brain-tumor barrier. Circumventing these challenges allow us to develop safer and more efficacious therapies. We found that conjugates of siRNA with chlorotoxin could knock down levels of a housekeeping gene *in vitro* and *in vivo* in a mouse brain tumor model. Furthermore, we developed prostate-cancer targeting ligands that demonstrate *in vitro* efficacy and tested them *in vivo*.

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