

Determining the Effect of Liposomal Molecular Structure on Immune Response

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Specific problem being addressed: Although major emphasis in recent years has been on finding potent drug delivery systems like siRNA delivery vehicles, there is poor understanding of how delivery vehicles interface with and, subsequently, provoke the immune system. This is a critical knowledge gap that needs to be filled if we are to ever take advantage of the myriad chemistries available for incorporation into clinically viable delivery systems. The Prof. Purwar lab at IIT Bombay and Prof. Whitehead Lab at CMU are in a unique position to fill this knowledge gap through the identification of structure-immunogenicity relationships for liposomal delivery systems. The aim of this collaborative proposal is to investigate the relationship between the chemical structure of lipid drug delivery nanoparticles (lipidoids) generated at Whitehead Laboratory and the type and magnitude of the body's immune response. This will be done in conjunction with the expertise of Prof. Purwar's lab, an immunology specialist. If the proposed work is completed successfully, it will identify structure-immunogenicity relationships for lipid nanoparticle delivery systems.

Project Summary: The goal of this proposal is to ascertain how the type and strength of the body's immune response are influenced by the chemical structure of lipid drug delivery nanoparticles. Drug delivery is a field of great significance to human health, converting the promise of biomolecules into life-saving clinical therapies. Many contemporary medications, such as vaccinations, chemotherapy drugs, and nucleic acids, rely on delivery vehicles to make it easier for the drugs to enter the right cells and organs in the body.

One of the major hurdles preventing the translation of more drug delivery systems to the clinic is toxicity. While a typical drug has only one intended therapeutic effect (e.g. reduction of blood cholesterol levels), that same drug can cause many different types of toxicity. For example, a drug may damage one or more organs, such as the liver or the kidneys. Another very important type of toxicity, and the focus of the proposed work, is immunogenicity. The human immune system is remarkable in its ability to identify and destroy foreign entities, whether they are harmful things like viruses, or beneficial things like therapeutic drugs. The immune system presents a significant challenge to drug delivery researchers for two reasons:

- 1) the immune system eliminates delivery vehicles from the body before they reach their intended targets, which lowers efficacy; and
- 2) an immune response can result in potentially severe side effects in the patient, such as fever, inflammation, and anaphylaxis.

For these reasons, preventing an immune response is a major goal during the development of delivery materials. Unfortunately, little is now known about how delivery trucks interact with the immune system and subsequently trigger it. The Whitehead Lab at CMU is in a unique position to close this knowledge gap by determining the structure-immunogenicity correlations for liposomal delivery methods. Their area of expertise is high-throughput analysis of chemically varied libraries of molecules that resemble lipids, or "lipidoids." These lipidoids combine to create soft, liposomal nanoparticles (LNPs) that can transport medications to many different kinds of cells. Their preliminary findings demonstrate that, in vitro and in mice, distinct lipidoid chemical configurations elicit distinct innate and adaptive immune responses. They will be collaborating closely with the Purwar Lab at IIT Bombay whose expertise is in immunology and can help us with the design and interpretation of our research.

The objective of the collaborative proposal is to determine how the chemical structure of lipid drug delivery nanoparticles (lipidoids), which are generated by Prof. Whitehead's laboratory at CMU, influences the type and magnitude of the body's immune response. Following are the specific aims.

Objective 1: Determine the roles of humoral and cell mediated immune response upon repeat dosing of LNPs.

Objective 2: Determine the effect of lipidoid structure on the innate and adaptive immune response ex vivo.

Impact of this innovation: Over the past several decades, hundreds of promising drug delivery systems have been developed and introduced into human clinical trials. Unfortunately, however, very few drug delivery systems in the United States are ultimately approved by the FDA. The successful completion of the proposed work will identify structure--immunogenicity relationships for lipid nanoparticle delivery systems, which are currently used for the delivery of many types of drugs. Specifically, we will identify what chemical moieties present on lipidoid materials induce an innate, humoral, and/or adaptive immune response. This will enable us to avoid immunogenic structures when creating lipid nanoparticles for the delivery of proteins and nucleic acids; and take advantage on specific kinds of immunogenic reactions brought on by lipid nanoparticles when delivering medications which require an immune response (such as cancer immunotherapy and vaccines).
