Indian Institute of Technology Delhi

School of Interdisciplinary Research (SIRe)

SIRe Project Number

2025-02-19

(will be assigned by SIRe)

Project Proposal for Ph.D.

Project Details	
Project Title	**Inducing T-cell-mediated anti-tumor immune responses using nanoparticles displaying immune stimulatory molecules.**
Project Summary (Minimum 500 and maximum 2000 characters)	Cancer remains one of the most challenging diseases to treat because tumors have evolved diverse mechanisms to evade and suppress the immune surveillance. One effective way to address this challenge is to empower CD8+ T cells to recognise and destroy cancer cells. CD8+ T-cells get activated through the molecular engagement of T cell receptor (TCR) and peptide-major histocompatibility (peptide-MHC) complexes on professional antigen-presenting cells, along with signals from co-stimulatory molecules such as CD28. These activated CD8+ T-cells can produce cytolytic molecules such as granzyme B and perforin to execute the killing of tumor cells. Based on this natural mechanism, researchers have developed nano- and micro-scale artificial antigen-presenting cells (aAPCs) that display tumor-specific peptide-MHC complexes together with co-stimulatory signals, so they can effectively activate CD8+ T-cells in a cancer situation. Artificial antigen-presenting cells (aAPCs) can efficiently activate and expand tumor-specific T cells that are capable of recognizing and killing tumor cells. However, these two initial signals can trigger an immune response, but they fail to sustain the expansion and persistence of T cells over time. This limitation emphasizes the critical role of a third signal. For a durable and effective immune response, T cells also require a third signal in the form of cytokines. These cytokines, such as IL-2, IL-12, IL-15, and IL-21, promote T cell proliferation and survival, enhance effector function, and promote the development of long-lived memory cells. Further, tumors worsen the situation by upregulating PD-L1, which binds to PD-1 on activated T cells, leading to exhaustion. This is one of the major barriers to persistent anti-tumor immunity. Thus, an effective immunotherapy platform should integrate all three signals; along with this, it also includes strategies that prevent checkpoint-mediated T cell exhaustion. To address this problem, we will develop nano-formulations that will provide all the signals necessary to provide an effective and sustained immune response. 1. We will formulate aAPCs displaying tumor-specific peptide–MHC complexes with a co-stimulatory molecule. Hence, this nanoparticle will provide signals 1 and 2 required for antigen-specific T cell activation. 2. The second platform is an immunomodulatory nanoparticle that will be developed to sustain and enhance an effective CD8+ T-cell response. So, this nanoparticle will be conjugated with interleukins such as IL-2, IL-12, IL-21, and IL-15, which promote the proliferation, enhance effector function, inhibit activation, induce death, and memory differentiation of CD8+ T cells. In addition, co-stimulatory molecules and anti-PD-L1 antibodies are functionalized on its surface to enhance the T cell activation and block the inhibitory checkpoint pathways within the TME. 3. MicroRNA profiling of activated T cells will be conducted under three distinct conditions: a) Activation by artificial Antigen Presenting Cells (aAPCs) displaying tumor-specific peptide-MHC complexes along with co-stimulatory molecules. b) Activation by aAPCs functionalized with additional interleukins to enhance cytokine signaling. c) Activation by aAPCs further conjugated with anti-PD-L1 antibodies to block immune checkpoint inhibition. This comparative analysis aims to uncover the differential microRNA expression patterns associated with each activation strategy, providing insights into the molecular regulation of T cell activation, proliferation, and anti-tumor response under various immunomodulatory environments. Collectively, by integrating interdisciplinary approaches to dissect T-cell activation and expansion dynamics in the tumor situation using various types of nanoformulations, including aAPC displaying different immune-stimulatory signals, and nanoparticles with dual functions to block the immune-inhibitory signals but to provide immune activation signals, would enhance the durability of T-cell-mediated anti-tumor immune responses.

	Hence, these nano-formulations are expected to generate powerful T cell responses, establish long-lasting immune memory, and more effectively inhibit tumor growth.

Ph.D. Supervisors

Role	Name of Faculty	Academic Unit in IITD/Institute/University	Email ID (Official)
Supervisor 1	Dr. Tanmay Dutta	Chemistry-IIT-D	dtanmay@chemistry.iitd.ac.in
Supervisor 2	Dr. Santiswarup Singha	Nano-Biotechnology Lab National Institute of Immunology, New Delhi	santiswarup@nii.ac.in

Project requirements (Student qualifications, experience required, etc.)
***The candidate will be shortlisted based on common shortlisting criteria decided by ScRC (SIRe)**

- MSc in Chemistry, Biochemistry, Biotechnology or any branch of Life Sciences, B. Tech. / M. Tech. In Biotechnology or Biochemical Engineering, or related areas.
- The student should have prior training in some of these aspects: Protein production and purification, Nanotechnology, Molecular biology, Cancer cell culture, and Immunology.
- The student should have a NET JRF qualification or a valid GATE score

Source of fellowship/~~funding~~

Candidate with his/her own fellowship.

Role of Faculty Members involved:

Supervisor-1	Dr. Dutta's lab will conduct experiments to examine the microRNA profiles of activated T-cells induced by different nanoformulations. The outcomes of these studies will provide valuable feedback for refining the design of nanoformulations optimized to trigger T-cell-mediated anti-tumor immune responses.
Supervisor-2	Dr. Singha's lab will formulate various types of nanoparticles displaying immunostimulatory signals, produce required proteins, and conduct in vitro and in vivo experiments for evaluating the anti-tumor immune responses against cancer.