Discovery of polymeric toll-like receptor-4 (TLR-4) agonists to design a pathogen mimicking vaccine delivery system (PMVDS)

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A new generation of vaccine adjuvants is aimed to specifically target pathogen recognition receptors of innate immunity, such as Toll-like receptors (TLRs) and Nod-like receptors (NLRs). Polysaccharides provide an exciting new platform to interact with the innate immune system due to their abundance in pathogens, and their relative non-toxic properties. By integrating the knowledge from recent advancements in immune-signaling, material science, and drug delivery, our laboratory had discovered a novel polysaccharide polymer-based TLR-4 agonists; Inulin, inulin acetate (InAc) and inulin benzoate (InBz). Hydrophobic polymers InAc and InBz were synthesized from water-soluble inulin using acetylation and benzoylation, respectively. The TLR-4 agonistic activity of these polymers was established in multiple immune cells (microglials, dendritic cells, and PBMCs) by various genetic and pharmacological approaches. By using these immune-active polymers as biomaterials, we have rationally engineered "Pathogen Mimicking Vaccine Delivery System" (PMVDS) that could potentially encapsulate multiple antigens. The uniqueness of PMVDS is that it is both an efficient vaccine delivery system similar to nanoparticles and a vaccine adjuvant. The polymers and PMVDS particles were thoroughly characterized by a myriad of physicochemical techniques. The effect of the size of the particles, dose of an antigen and adjuvant on immune-activation was studied in mice. The adjuvanticity of PMVDS was established in multiple animal species (mice, pigs, sheep, and dogs), multiple routes of administration (intradermal, subcutaneous, and nasal) and with multiple antigens (peptides and proteins). The safety of PMVDS was assessed using cytotoxicity, skin histochemistry and in-vivo imaging techniques. The robustness of PMVDS in preventing/treating the diseases was investigated on influenza and melanoma mouse models. In conclusion, using an interdisciplinary approach we have engineered PMVDS as a unique platform vaccine delivery and adjuvant technology, which will have broader applications in designing the next generation vaccines against challenging disease where both humoral and cell-mediated immunity is desired.

Speaker Biography

Hemachand Tummala had extensive training and expertise on formulation development (Pharmaceutics), immunology and biochemistry. This unique combination has enabled him to focus on interdisciplinary research to address challenges related to human and animal health. A large emphasis of his research program is focused on discovering functional biomaterials that interact with the biological system to overcome therapeutic challenges in various diseases including cancer, inflammatory diseases, and infectious diseases (vaccines). This approach had led to the discovery of novel polymer based TLR agonists and antagonists with applications in vaccines and inflammatory diseases, skin penetration peptides for transdermal delivery and functional nanoformulations to improve the pharmacokinetics of nanomedicine in cancer treatment. His discoveries led to six patent applications and are at various stages of commercialization both in animal and human health sectors. He also serves as a research consultant for several small biotech and pharma industries.

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