Zdeněk Sofer

TEIGER

Cancer immunotherapy: rejuvenation of anti-cancer response by immune checkpoint blockade using novel multifunctional nanoparticle to block CTLA-4 and eliminate ICER

Coordinator:

Zdeněk Sofer, University of Chemistry and Technology, Prague, Czech Republic

Contact:

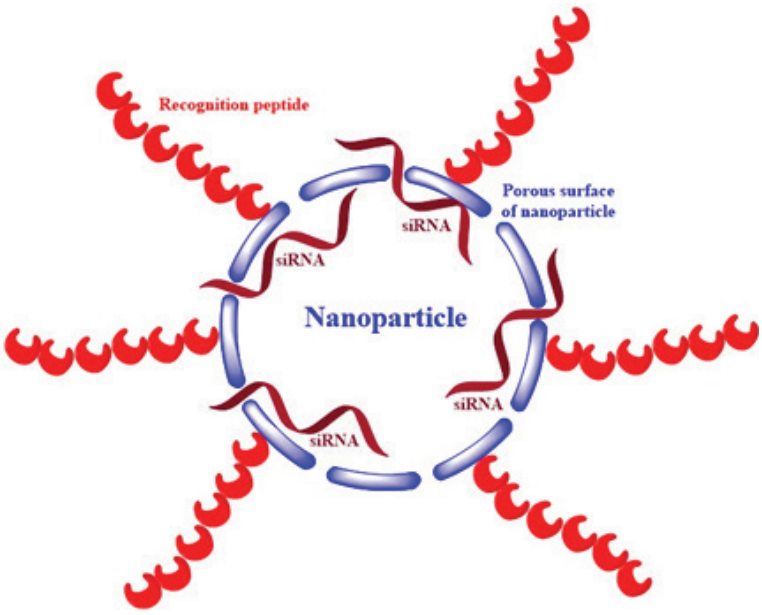
zdenek.sofer@vscht.cz

Partners:

Josef Bodor, NanoSYS Biologics

Franck Pavan, V-Nano

Oscar Lee, National Yang-Ming University and Yi-Shiuan Liu, Chang Gung University



Checkpoint blockade immunotherapies work by inhibiting pathways that keep duration and strength of immune system in check. To treat cancer by targeting immune system instead of tumour itself is an attractive approach, since fighting tumour directly requires depletion of all malignant cells. Even a small number of surviving tumour cells can induce recurrence, thus a traditional anticancer drug needs to reach billions of cells. On the contrary for cancer immunotherapy it is more realistic to achieve the activation of several thousands of leukocytes sufficient to induce potent anticancer response. Our strategy for removal of immune tolerance is to elicit antitumor immunity in several thousands of T cells using mesoporous silica nanoparticle (MSN) targeting potent immune checkpoint inhibitors irrespective of their cellular localization; such as - inducible cAMP early repressor (ICER) in the nucleus and cytotoxic T lymphocyte associated antigen 4 (CTLA-4) on T cells surface. Thus, aim of our proposal is to elicit antitumor immunity against melanoma via targeting ICER in CTLA-4 positive T cells using MSNs loaded with anti-ICER small interfering (si)RNA decorated with oligopeptides spanning specific paratopes trapping CTLA-4. Importantly, these peptides are meant not only to guide ICER RNAi delivery into CTLA-4 positive T cells but also to serve as functional CTLA-4 blockade replacing ipilimumab - clinically proven monoclonal antibody against melanoma blocking CTLA-4. It is expected that targeting ICER in CTLA-4 positive T cells will primarily circumvent regulatory T (Treg) cells ability to affect the potency of antigen presenting cells (APCs) to activate tumour-specific T cells.