Nammisomes: Preclinical validation of a platform for selective and synchronized delivery of novel immunotherapy prodrug combinations to tumors

1581

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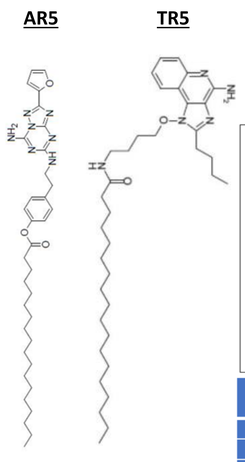
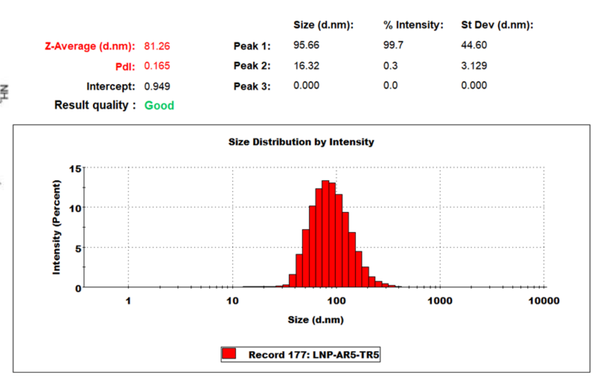
Abstract:

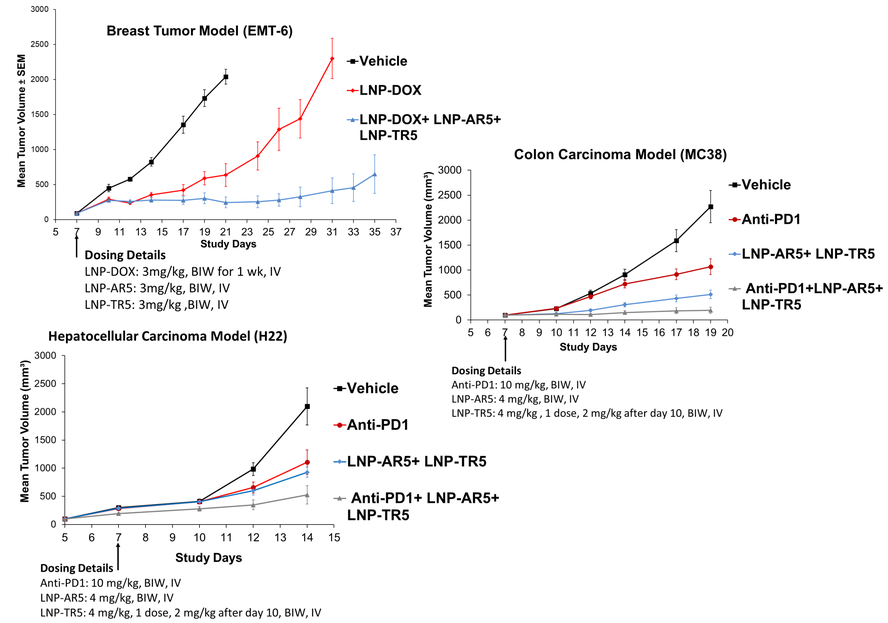
The approval of checkpoint inhibitors, CAR-T cell therapies, and other immunotherapies has led to a significant improvement in cancer patient survival rates over the past 7 years. However, the pace of improvement has slowed lately as the field moves beyond the minority of patients with immune primed or accessible cancers. It is generally expected that rational combinations of immunotherapies that provide mechanisms to both induce as well as maintain the immune responses in the face of tumor-derived immune checkpoint mediators, will be required to effectively treat these patients. Systemic exposure to such combinations often can give rise to severe toxicity profiles that limit their therapeutic efficacy. Nammisomes are an innovative and unique platform designed to deliver novel immune modulating prodrugs more selectively and synchronously to the tumor site. The immune active agents are conjugated to lipids to create prodrugs that self-assemble into a liposomal bilayer. By mixing multiple prodrugs at the desired ratio, co-formulations are produced with the optimum stoichiometry. These Nammisomes are iv injected and selectively enter tumors through the leaky vasculature within tumors, while remaining in circulation in normal tissues with intact blood vessels, The enriched phagocytic activity in tumor environments causes the release of the active agents within tumors relative to normal tissues limiting systemic exposure and toxicities. Preclinical efficacy and safety data of Nammisomes delivering combinations of a TLR agonist and a checkpoint inhibitor showing anti-tumor efficacy and tolerability in syngeneic mouse models will be presented. In summary, Nammisomes will be highlighted as a combination therapeutic modality to demonstrate the potential of this approach in anti-cancer therapy..



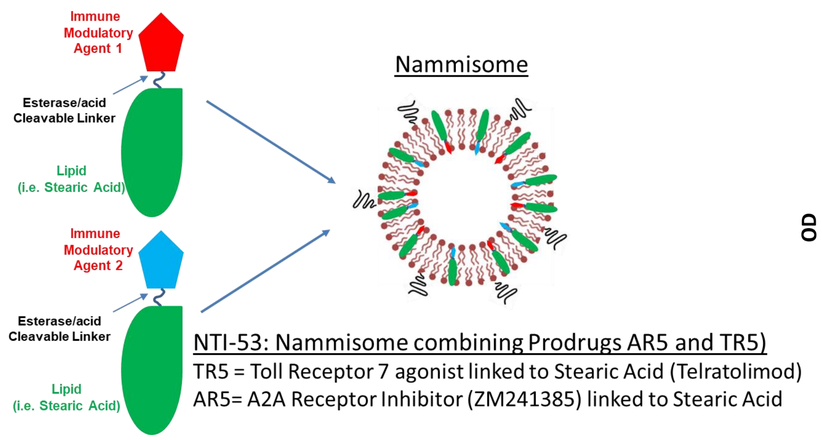


LNP-AR5-TR5(different Batches)	Size in nm diameter	PDI	Zeta potential (mV)
Batch 81120-1	81.26	0.165	-13.2
Batch 71120-2	79.23	0.146	-13.4
Batch 20121-4	78.07	0.143	-11.9

A lipid mixture of HSPC, CHOL, AR5, TR5 and DSPE-PEG at a molar ratio of 52:31:9:3:5 was prepared in ethanol and mixed with an aqueous solution of PBS using a NanoAssemblr Bench top microfluidics instrument (Precision Nanosytems). Size distribution and Zeta potential of LNP-AR5-TR5 was determined using a Malvern Zetasizer (Malvern Instrumentation Co., Westborough, MA, USA). The process provides consistent batch-to-batch formulation specifications.



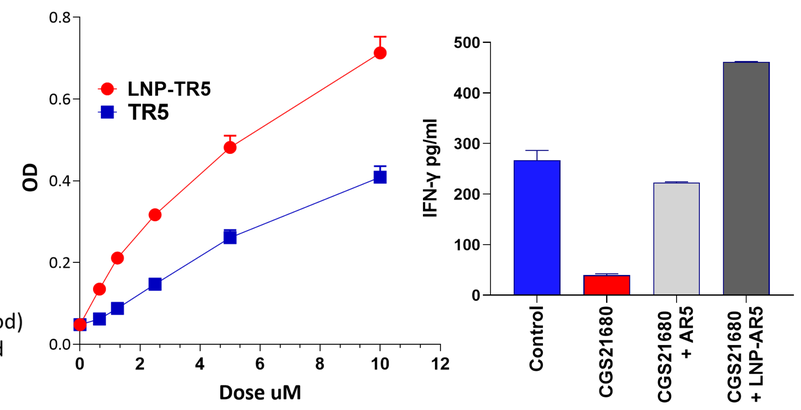
- NTI-53 efficacy in breast (EMT-6), Colon (MC-38), and Hepatocellular (H22) Carcinomas in combination with Doxil or anti-PD-1 antibody.



NTI-53: Nammisome combining Prodrugs AR5 and TR5)

TR5 = Toll Receptor 7 agonist linked to Stearic Acid (Telratolimod)

AR5= A2A Receptor Inhibitor (ZM241385) linked to Stearic Acid



- TLR7 agonist activity of Liposomal TR5 vs free 852A in RAW-Blue™ Cells (In vitrogen)
- A2A receptor inhibition by AR5 vs free ZM241385 in C57BL/6 mouse splenocytes activated with CD3/28 beads in the presence of A2A receptor agonist CGS21680.
- Both agents demonstrate enhanced cell activity as liposomal prodrugs than as free agents

Conclusions:

Formulation: Lipid particle with A2A receptor inhibitor prodrug (AR5) and Toll Receptor 7 agonist prodrug (TR5) incorporated. Robust and consistent production process.

AR5 rationale: A2A receptor has been clinically validated to be an important immune checkpoint. Inhibition of this receptor by the active component of AR5 and other inhibitors have demonstrated anti-tumor activity including in human patients

TR5 rationale: Toll receptor 7 agonists are clinically validated to have anti-tumor activity but are generally too potent to give systemically as free drugs. Incorporation of the prodrug in a Nammisome targets the activity to tumors while reducing systemic activity allowing for safe delivery of effective doses.

Target Indications: While the immune mechanisms targeted by AR5/TR5 are independent of cancer type, the mechanism of selective tumor delivery of Nammisomes is dependent on presence of a tumor mass (as opposed to dispersed cells). Therefore, solid tumors would be the potential market for this product. Initial development will be done in multiple indications to demonstrate efficacy in a large indication such as breast cancer and in an indication with Orphan Drug Potential such as bladder, pancreatic, and renal cancers

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