

Title	<b>“Synthetic high-density lipoprotein nanodiscs for personalized vaccination against glioblastoma multiforme”</b>
Keywords (up to 5)	neoantigen, glioblastoma, sHDL, immunotherapy, personalized
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Abstract	<p>Glioblastoma multiforme (GBM) continues to be the most deadly and untreatable brain malignancy. Cancer immunotherapy is an increasingly attractive treatment option for patients who have been through the trifecta of surgery, radiation, and chemotherapy only to experience tumor recurrence. A precise and sustainable approach to cancer immunotherapy is the delivery of tumor-specific antigens, also known as neoantigens. However, efficient delivery of neoantigens to immune activation sites remains a major challenge in this therapeutic approach.</p> <p>We have developed a synthetic high-density lipoprotein (sHDL) system for delivery of neo-antigens. sHDL’s small size (&lt; 30 nm) and high biocompatibility make sHDL an ideal candidate for lymphatic trafficking<sup>1,2</sup>. Additionally, sHDL readily binds to lipoprotein cell receptors, which are constitutively expressed on antigen-presenting cells, allowing for targeted delivery of sHDL nanodiscs to macrophages and dendritic cells<sup>3,4</sup>.</p> <p>Here, we developed antigen peptide-sHDL vaccine formulations for the treatment of GBM. Blank sHDL nanodiscs were made using DMPC and apo-A1 mimetic peptide 22A<sup>1</sup>. GBM neoantigen peptides<sup>5</sup> (RS Synthesis) were conjugated to DOPE and lyophilized. Lipid-peptide conjugates were rehydrated in DMSO and incorporated into sHDL nanodiscs by simple mixing. Reaction products were analyzed by LC/MS or HPLC. Cholesterol-modified CpG (TLR9 agonist) was added to GBM neoantigen peptide-sHDL and analyzed by GPC.</p> <p>To study therapeutic effect, C57BL/6 mice were inoculated with 1 x 10<sup>6</sup> GL261 cells in the right flank on day 0. When tumors were palpable, mice received prime vaccinations via s.c. injection at the tail base neoantigen peptide-sHDL/cho-CpG cocktail (n = 7). Boost vaccinations were given 7 days after prime. Tumor size was monitored over time, and blood samples were collected and processed for IFN-gamma ELISPOT. Mice vaccinated with antigen peptide-sHDL/cho-CpG cocktail exhibited significantly slowed tumor growth and stronger T cell responses against GBM neoantigens when compared to control tumor-bearing mice administered with either soluble neoantigens or PBS.</p>
References	<ol style="list-style-type: none"> <li>1. Kuai, Ochyl, Bahjat, Schwendeman, &amp; Moon. “Designer vaccine nanodiscs for personalized cancer immunotherapy.” <i>Nature Materials</i>. 2017.</li> <li>2. Huang, Cruz, Chen, &amp; Zheng. “Learning from biology: synthetic lipoproteins for drug delivery.” <i>Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology</i>. 2015.</li> <li>3. Dieudonné et al. “Scavenger receptors in human airway epithelial cells: role in response to double-stranded RNA.” <i>PLoS One</i>. 2012.</li> <li>4. Qian et al. “Targeting dendritic cells in lymph node with an antigen peptide-based</li> </ol>

nanovaccine for cancer immunotherapy." *Biomaterials*. 2016.

5. Johanns et al. "Endogenous neoantigen-specific CD8 T cells identified in two glioblastoma models using a cancer immunogenomics approach." *Cancer immunology research*. 2016.