Technology Offer

Trimannose-Functionalized Human Serum Albumin Nanocarriers for Targeted Immunotherapy

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Abstract

This technology introduces a novel nanocarrier system based on human serum albumin (HSA) functionalized with multiple trimannose (TM) ligands for precision delivery of immunomodulatory drugs. The TM groups enable high-affinity targeting to mannose receptors such as MMR and DC-SIGN, abundant on immune cells and liver tissue. By dynamic-covalently attaching active agents – such as Toll-like receptor 7/8 (TLR7/8) agonists or STAT3 inhibitors – to HSA, the system ensures rapid localization, selective uptake, and controlled drug release. With sizes of < 40 nm, these biopolymer carriers penetrate tissues effectively while minimizing off-target exposure. The approach offers high drug loading, biodegradability, and biocompatibility, enabling safer and more effective treatment of liver diseases and cancer, and immune disorders through targeted immune modulation.

Background

Immunotherapy is increasingly essential for treating cancer, chronic liver diseases, and autoimmune disorders. However, conventional small-molecule drugs often suffer from low response rates, systemic toxicity, and poor tissue selectivity. Current nanoparticle formulations, such as liposomes, provide some improvement but still face limitations in biodistribution, stability, and targeted delivery. Mannose receptor-targeting strategies have shown potential for enhancing drug uptake by antigen-presenting cells, but the chemical synthesis of highly branched mannose structures is complex. Trimannose offers an optimal balance of binding strength and synthetic accessibility. Human serum albumin, a natural plasma protein, is an attractive carrier due to its small size, non-immunogenicity, and modifiable surface. Combining TM-targeting with HSA-based nanocarriers enables a new class of delivery systems with superior organ and cell specificity.

Technology

The invention utilizes human serum albumin (HSA) as a nanoscale drug carrier (< 40 nm), chemically modified with multiple covalently bound trimannose (TM) moieties via PEG-based linkers. TM ligands selectively bind mannose-specific receptors such

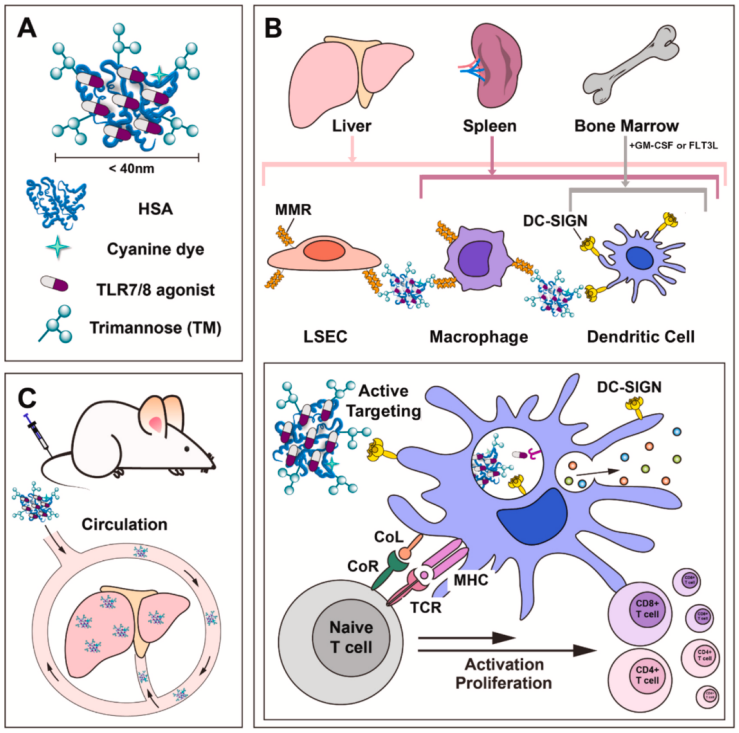

Figure 1: Trimannose-functionalized HSA nanocarriers for targeted immune activation. (A) Design of < 40 nm nanocarrier with HSA core, multiple trimannose ligands, covalently bound TLR7/8 agonist, and optional fluorescent dye. **(B)** Investigated target cell population expressing MMR- and DC-SIGN including LSECs, macrophages, and dendritic cells. Bottom: Schematic illustration of OVA-peptide-specific $CD8^+$ cytotoxic and $CD4^+$ helper T cells in OVA-preincubated BMDCs after TM-HSA-TLR7/8a incubation. **(C)** Following administration of TM-HSA with maximum TM modification rate, nanocarriers accumulate rapidly in the target organ liver and are taken up by all liver NPCs.

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as MMR and DC-SIGN, prevalent on macrophages, dendritic cells, and liver sinusoidal endothelial cells. The number of TM groups can be tailored (typically 1–59 per HSA molecule) to optimize receptor binding uptake efficiency and in vivo biodistribution.

In addition to targeting moieties, the HSA is conjugated with one or more immunomodulatory drugs—preferably TLR agonists (e.g., TLR7/8a) or STAT3 inhibitors—using thiol-reactive linkers. This allows high drug payloads (up to 30 molecules per carrier) with controlled and traceless release, triggered intracellularly after receptor-mediated endocytosis. The HSA may be denatured during drug conjugation and subsequently refolded to maintain stability.

Fluorescent dyes can also be incorporated for imaging and biodistribution studies. The glycogen-inspired architecture with tunable avidity ensures selective accumulation in target organs (the liver for high-TM nanocarriers) and immune cells, minimizing systemic circulation time and off-target toxicity. The system's fully biopolymer composition guarantees biodegradability, long-term stability, and adaptability to various therapeutic agents, making it a versatile platform for precision nano-immunotherapy.

Advantages

- Highly specific targeting to immune cells via multivalent trimannose–lectin binding.
- Adjustable ligand density for optimizing cellular uptake and biodistribution.
- High drug loading capacity with adjustable, thiol-reactive linker chemistry, ensuring versatile drug compatibility.
- Fully biopolymer-based for excellent biocompatibility and biodegradability.
- Potential integration of imaging agents for theranostic applications.

Potential applications

- Targeted immunotherapy for liver cancer, fibrosis, and chronic hepatitis.
- Delivery of TLR agonists for enhancing immunochemotherapy.
- Selective STAT3 inhibitor transport for modulating immune suppression in tumors or hepatitis.
- Precision drug delivery to dendritic cells for vaccine development.
- Combined therapeutic–diagnostic (theranostic) applications in oncology and hepatology.

Publications

Lantzberg, B., Zeyn, Y., Forster, R., Jian, L., Schauenburg, D., Hieber, C., Weil, T. et al (2025): "Glycogen-inspired trimannosylated serum albumin nanocarriers for targeted delivery of toll-like receptor 7/8 agonists to immune cells and liver", Journal of Controlled Release, 382, 113705.

R. Forster, B. Lantzberg, S. Ling Kuan, M. Bros, T. Weil, T. Opatz et al: "Surface Density of Mono- and Trivalent High-Mannan-Derived Targeting Structures with Different Affinities Impacts Cellular Uptake of Human Serum Albumin-Derived Nanocarriers", Biomacromolecules 2025, 26, 8087−8102.

Patent information

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