Targeting of siRNA to tumors and their stroma (Ramot)

code: 2-2011-139

Ronit SATCHI-FAINARO, T.A.U Tel Aviv University, Medicine-Sackler Faculty, Physiology and Pharmacology
Rainer Haag, Freie University, Berlin

Technology

Tumor-directed in vivo delivery of miRNA and siRNA by novel dendritic nanocarriers was developed. The invention is based on a novel polyglycerols (PG)-based dendrimer core–shell structure that delivers miRNA/siRNA in vivo to tumors and their vasculature. This water-soluble macromolecular carrier accumulates in the tumor environment due to the enhanced permeability and retention (EPR) effect, and, therefore, represents an ideal delivery vehicle for antitumor biological agents.

The Need

RNA interference (RNAi) is making great progress as an indispensable strategy for target-specific knockdown of gene expression. New targets for RNAi-based cancer therapy are constantly emerging. Promising second-generation technologies represent advances in RNAi design, efficiency, and efficacy. Yet, in vivo delivery of miRNA/siRNA remains a crucial issue for its therapeutic success, as well as hurdles such as exposure to the right organ, cytoplasmic uptake and stability of the RNAi compound itself.

Our novel PG-based dendrimer was demonstrated to deliver miRNA/siRNA in vivo, while strongly improving siRNA stability, cellular uptake, and silencing efficacy. We predict that in vivo silencing of important cell growth and angiogenesis regulators in a selective manner will warrant this approach as a successful anticancer therapy in the future.

Potential Application

Treatment of cancer, inflammation and other angiogenesis-dependent diseases (AMD, arthritis, diabetes, etc).

Stage of Development

The PG based dendrimer was characterized by dynamic light scattering, atomic force microscopy, and electrophoretic mobility shift assay. It was demonstrated to form a neutral complex with miRNA and/or siRNA, mediating its intracellular uptake and endosomal release in the cytoplasm.

The PG-based dendrimer polyplex effectively silences a reporter gene in vitro and in vivo when administered both intratumorally and intravenously. It exhibited the optimal silencing efficiency and safety profile in biocompatibility and efficacy tests performed in vitro, in comparison to other dendritic nanocarriers tested.

A significant gene silencing effect was accomplished in vivo in both human glioblastoma and murine mammary adenocarcinoma mouse models: Within 24 hours, 85% and 68% silencing was achieved following intratumoral and intravenous treatment, respectively.

Ongoing work includes specific silencing of a key regulator of growth and angiogenesis in vitro and in vivo in glioblastoma and neuroblastoma animal models.

Patents

Granted patents

Supporting Selected Publications

1. Ofek P, Fischer W, Calderon M, Haag R and Satchi-Fainaro R, In Vivo delivery of siRNA to tumors and their vasculature by novel dendritic nanocarriers, FASEB Journal, 24(9), 3122-34 (2010).

2. Ofek P, Miller K, Eldar-Boock A, Polyak D, Segal E and Satchi-Fainaro R, Rational design of multifunctional polymer therapeutics for cancer theranostics, Special Theme issue: Polymer Therapeutics as novel nanomedicines, Israel Journal of Chemistry, 50 (2), 185-203 (2010).

3. Segal E and Satchi-Fainaro R, Design and Development of polymer conjugates as anti-angiogenic agents, Special Theme issue: Polymer Therapeutics: Clinical Applications and Challenges for Development, Advanced Drug Delivery Reviews 61(13), 1159-1176 (2009).

4. Markovsky E, Baabur-Cohen H, Eldar-Boock A, Omer L, Tiram G, Ferber S, Ofek P, Polyak D, Scomparin A and Satchi-Fainaro R, Administration, distribution, metabolism and elimination of polymer therapeutics, Theme issue: Drug Delivery Research in Europe, Journal of Controlled Release, 161, 446–460 (2012).

Watch related video: http://www.ramot.org/media-center/video-gallery/ramot/media/24853

Contact for more information:
Ariela Markel , VP Business Development, Healthcare , 02-6586608

Ramot at Tel Aviv University Ltd. P.O. Box 39296, Tel Aviv 61392 ISRAEL
Phone: +972-3-6406608
Fax: +972-3-6406675