Technology Offer

Ref.-No. M15/20

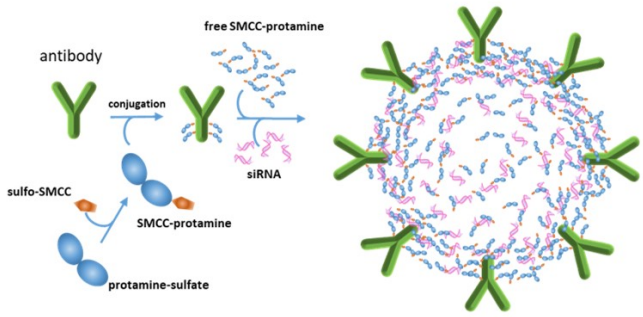
Nanoparticle for cell-type specific therapeutic delivery of siRNA and other effector drugs

Introduction

In the last years, high expectations were raised concerning the use of small interfering RNAs (siRNA) against gain-of-function gene products such as oncogenes in malignant neoplasia. However, therapeutic use of siRNAs was always compromised by their instability and missing cell specific carrier systems. Thus, the development of an efficient siRNA nano-carrier is a major goal to make use of RNAi as a molecular therapeutic modality.

Invention

We applied the high RNA binding capacity of the small arginine-rich protein protamine for spontaneous electrostatic assembly of therapeutic nanoparticles decorated with tumor cell-specific antibodies for efficiently targeting siRNA. Fluorescence microscopy and DLS measurements of these nano-carriers revealed the formation of a vesicular architecture that requires presence of antibody-protamine, defined excess of free SMCC (succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate)-protamine, and anionic siRNA to form. These complex nanoparticles were efficient in the treatment of non-small-cell lung cancer (NSCLC) xenograft models, when the oncogene KRAS was targeted via EGFR-mediated delivery. To show general applicability, we used the modular platform for IGF1R-positive Ewing sarcomas. We conclude that these antibody-protamine-siRNA nano-carriers provide a novel platform technology to specifically target different cell types and yet undruggable targets in cancer therapy by RNAi.



mAB-protamine/siRNA nanoparticle

Illustration of a cross section through an idealized nanoparticle structure fulfilling the conditions for an effective antibody-protamine-siRNA-SMCC-protamine nano-carrier complex deduced from our experiments. Electrostatic binding bridges are formed between mAB, with some protamines (cationic) coupled to the targeting antibody, siRNA (anionic), and free SMCC-protamine (cationic). The nanostructures assemble spontaneously into the optimal and most stable electrostatic status and function as nano-carriers for siRNA.

Advantages of the invention

- modular and quite easily applicable
- efficient therapeutic option in malignant disease
- potential side effects of nanostructures may be limited

Patent situation

Patent application filed.

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