Molecular Therapy
Commentary

cSMRTS for cancer therapeutics

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COVID-19 vaccines brought mRNA lipid nanoparticles (LNPs) into the global spotlight, and this technology is now extending into cancer therapies.[1–3] Although many improvements have been made to deliver LNPs to specific organs, tissues, and cells, off-target delivery remains evident. In LNP-based cancer therapies, delivering the mRNA-encoding proteins and expressing them only in target cancer cells is crucial to minimize off-target toxicity and improve clinical translation.

In this issue of *Molecular Therapy*, Żak et al.[4] demonstrated that, rather than modifying the LNP formulation, the mRNA can be modified and selectively translated into therapies in cancer cells. Their cell-selective modified RNA translation system (cSMRTS) uses LNPs to encapsulate two modified mRNAs (modRNAs). One modRNA, which encodes for Cas6 endoribonuclease, has an added microRNA (miRNA) recognition sequence specific to miRNAs expressed in cancer cells. The other modRNA, which encodes a therapeutic protein, is modified with a Cas6 hairpin recognition element. When these two modRNAs reach the tumor cells, the specific miRNAs expressed in the cancer cell bind to the miRNA recognition sequence on the Cas6 modRNA and block its translation, resulting in translation of the therapeutic protein encoded by the other modRNA. When the modRNAs reach other, non-cancer cells, the absence of the cancer-specific miRNAs leads to the translation of Cas6, which then cleaves the other modRNA at the hairpin recognition element, blocking the translation of the therapeutic protein (Figure 1).

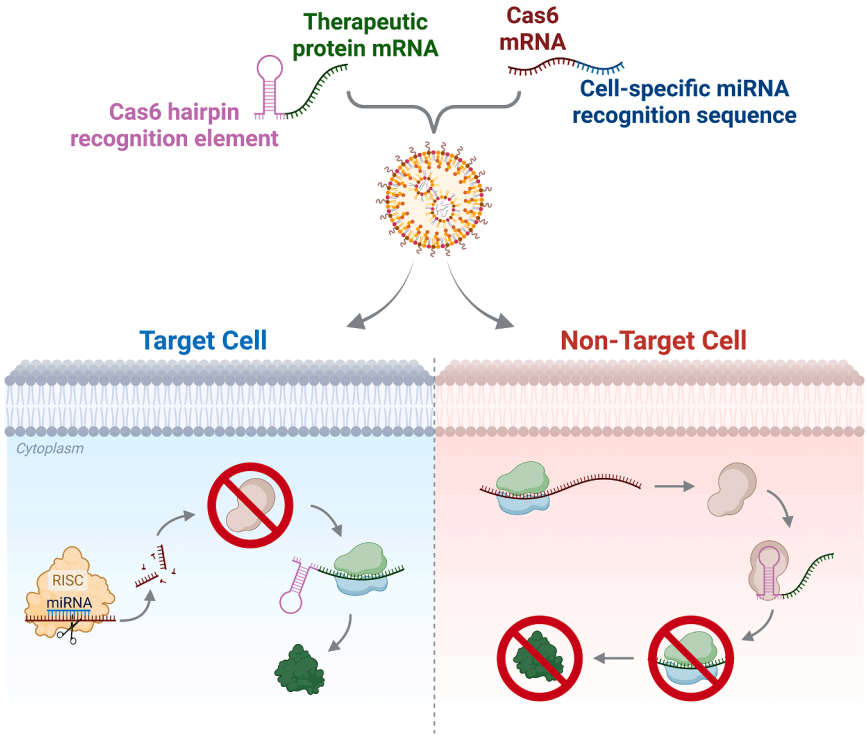

Figure 1. Mechanism of cell-specific mRNA translation of cSMRTS

Cas6 mRNA (red) is modified with a cell-specific miRNA recognition sequence (blue), while the therapeutic protein mRNA (green) is modified with a Cas6 hairpin recognition element (pink). Both modRNAs are co-encapsulated in an LNP. When the LNP reaches the target cell (blue), miRNA in the cell binds to the miRNA's complementary sequence on the Cas6 mRNA. This complex is recognized and degraded by the RNA-induced silencing complex (RISC), blocking the ribosome from translating the Cas6 protein. This enables the ribosome to translate the therapeutic protein. When the LNP reaches the non-target cell (red), the lack of the target-cell miRNA enables the Cas6 protein to be translated. Cas6 cleaves the therapeutic protein mRNA at the hairpin recognition element, blocking the ribosome from translating the therapeutic protein. Created in BioRender. Hazan-halevy, I. (2026), https://BioRender.com/tuzh6em.

As a proof of concept, the authors encapsulated the modRNAs in LNPs consisting of the same lipids as the Pfizer/BioNTech COVID-19 vaccine.[5] This LNP formulation, along with other LNP formulations such as the Moderna COVID-19 vaccine and Alnylam's Onpattro, has predominant protein expression in the liver when administered intravenously.[6] However, upon intravenous administration, their LNPs containing both modRNAs consistently had high activity in breast cancer and colon cancer and low activity in the liver, the spleen, the lungs, and other organs. The authors illustrated the modularity of this technology by swapping the Cas6 and the therapeutic protein modRNAs with modRNAs encoding for monoclonal antibodies commonly used as checkpoint inhibitors (modRNabs). Combining cSMRTS and modRNabs LNPs into one treatment resulted in a targeted cancer immunotherapy.

Although this work could improve the clinical translation of LNP cancer therapies, the

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technology still has a long and winding road to reach the clinic. Encapsulating two different mRNAs in LNPs for *in vitro* and *in vivo* studies might be simple, but ensuring that both mRNAs are encapsulated at a desired ratio in each LNP could be a difficult analytical and regulatory challenge. Additionally, because cells endocytose both modRNAs together when they are in the same LNP, some therapeutic protein might be expressed in non-target cells until the Cas6 endoribonuclease is expressed and cleaves the remaining therapeutic protein modRNA. Although this protein expression might be much lower than in the target cancer cells, it could still result in adverse, irreversible effects depending on the protein's function. Therefore, an alternative translational approach could be to encapsulate the two modRNAs in separate LNPs and administer the Cas6-modRNA-LNPs shortly before the therapeutic modRNA-LNPs, but this also needs to be calibrated, since one never knows if the same cancer cell will receive these two different payloads. It is also important to note that this technology does not improve LNP delivery but rather improves the activity of mRNA in the target cancer cells. LNP biodistribution will still need to be closely monitored in non-target cells and organs to prevent lipid-induced toxicities such as hepatotoxicity and inflammatory responses.

Even with these clinical barriers, the authors provide a novel approach to reduce off-target effects of mRNA: (1) identify intracellular characteristics unique to the target cell, (2) modify the mRNA to utilize these characteristics for translation, and (3) encapsulate the mRNA in LNPs for systemic administration. Having this strategy in mind early in the development of mRNA cancer therapies could significantly de-risk their clinical translation by reducing adverse cytotoxic effects. With rising concerns about the off-target effects of emerging RNA strategies such as editing approaches (with CRISPR-Cas9), this approach is extremely opportune and could address many concerns regarding off-target gene editing. Taken together, the work reported in this issue[4] demonstrates the tremendous, yet untapped, potential of leveraging unique intracellular characteristics in target cells to selectively express mRNA, bringing mRNA-LNPs for cancer therapeutics and other diseases one step closer to patients.

DECLARATION OF INTERESTS

D.P. receives licensing fees (to patents on which he was an inventor) from, invested in, consults (or is on the scientific advisory boards or boards of directors) for, lectured (and received a fee), or conducts sponsored research at Tel Aviv University for the following entities: ART Biosciences, BioNtech SE, Earli, Inc., Kernal Biologics, LAND Therapeutics, Merck KGaA, Newphase, Ltd., NeoVac, Ltd., RiboX Therapeutics, Roche, SirTLabs Corporation, and Teva Pharmaceuticals, Inc.

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