soluble molecules while providing significant benefits in terms of ease of administration to affected individuals. If these results can be duplicated in humans, then the resulting products will have a much greater dosing interval than that required for current products. Considering the recent explosion in the number of antibody-drug conjugates in development, this work presents an alternative strategy by demonstrating that a relatively simple carbohydrate ligand is sufficient to achieve effective, targeted delivery of multiple components. Considering nature's predominant use of carbohydrates in recognition and trafficking, advances in the field of glycobiology should pave the way for future drug delivery research.

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Cell programming to protect the ischemic heart and limb

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New strategies for myocardial protection and regeneration after myocardial infarction are urgently needed to counter the heart failure pandemic. To address this unmet medical need, Kaur and colleagues (in this issue of *Molecular Therapy*)[1] have identified in a preclinical proof-of-concept study a cocktail of modified RNA (modRNA) to endow stromal cells with angiogenic growth factor releasing activity (Figure 1). Sustained angiogenic programming was realized by lipid-nanoparticle (LNP) delivery, using formulations that have been employed safely and efficaciously in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations.

Reprogramming cell fate by transient expression of transcription factors has been explored for decades. A prominent, if not the most prominent example, is the overexpression of the skeletal muscle master regulator MyoD1 to reprogram fibroblasts into skeletal myoblasts.[2] More recently, reprogramming of somatic cells into pluripotent stem cells by the so called four Yamanaka factors (Oct3/4, Klf4, Sox 2, and c-*myc* [OKSM]) has revolutionized biomedical research.[3] To bypass the programming to an embryonic-cell-like state, direct cardiac reprogramming of myofibroblasts by overexpression of GATA4, Mef2c, Tbx5 (GMT) has been introduced[4] with demonstrated therapeutic activity in mice with myocardial infarction.[5,6] The original protocol employed retroviral delivery and was further refined to also convert human cells into cardiomyocyte-like cells, with, however, limited efficiency in adult human fibroblast reprogramming.[7]

Because of the inherent limitations of retroviral delivery of DNA, modRNA has been investigated by many labs as an alternative means for cell type conversion. Transient expression via RNA versus stable expression of DNA after genome insertion is considered advantageous from a translational point of view. Key for transient but efficacious delivery of RNA were specific chemical modifications to prevent premature degradation and activation of the innate immune system.[8,9] In an earlier study, Zangi and co-workers administered VEGF-A encoding modRNA by intramyocardial injection and observed vascular regeneration by enhanced epithelial-to-mesenchymal transition of WT-1^{+} epicardium-derived cells in mice with myocardial infarction.[10] In the present study, the protocol was extended by the application of 7G-modRNA, i.e., modRNA encoding for GMT + Hand2 + dominant negative (DN)-transforming growth factor β (TGF-β) + DN-Wnt8a + acid ceramidase (AC), to turn myofibroblasts into cardiac-like cells. Although direct injection of modRNA, despite its chemical stabilization, resulted in a near-complete loss of transcripts within 72 h,[10] LNP delivery of 7G-modRNA enhanced angiogenic growth factor expression for the whole study duration of 4 weeks, which resulted in a clear attenuation of disease progression with

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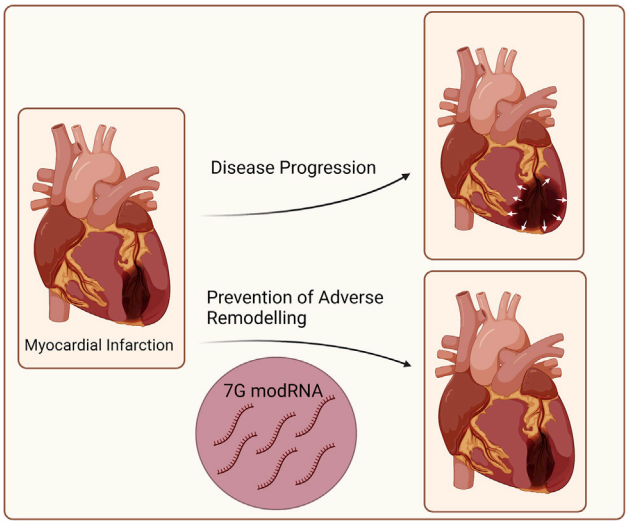

Figure 1. LNP delivery of 7G at the time of myocardial infarction attenuates disease progression
7G comprises modified RNA encoding for GATA4, Mef2c, Tbx5, Hand2, DN-TGF-β, DN-Wnt8a, and AC. After intramyocardial injection into acutely infarcted mouse hearts, expression of transcripts encoding for a broad spectrum of angiogenic growth factors (e.g., VEGF-A/B/C/D) remained enhanced for at least 4 weeks compared to controls.

markedly reduced mortality in mice with myocardial infarction. Similarly, administration of LNP-7G to the ischemic limb stabilized blood perfusion to pre-injury levels after 21 days, demonstrating a common biological activity in ischemic muscle, i.e., enhanced angiogenesis by paracrine factors.

The use of LNP for 7G delivery is particularly interesting for several reasons: (1) LNP delivery shields modRNA from degradation and thus allows for extended activity in the target tissue; (2) LNP delivery has been demonstrated to be safe and efficacious in the delivery of SARS-CoV-2 spike protein encoding RNA via the BioNTech and Moderna vaccines; and (3) further modifications of LNP are conceivable to enhance organ or cell type targeting by, for example, insertion of specific biological motifs or chemical moieties into its lipid bilayer.

Collectively, the study by Kaur and colleagues provides important proof of concept in a small animal model for modRNA delivery to ischemic heart and limb muscle. Although the precise molecular mechanisms for angiogenic programming remain to be clarified and further optimization will be required, we anticipate an increasing body of literature reporting on LNP delivery of RNA not only to the heart but also skeletal muscle with high translational potential. It is important to note that LNP delivery of RNA encoding CRISPR-Cas9 and a single guide RNA has recently been demonstrated to be safe and efficacious in patients with transthyretin amyloidosis.[11] Although the goal to reprogram scar into muscle remains challenging, in particular in human models, it is exciting to see that, after many years of development, modRNA delivery is becoming increasingly attractive not only for *in vitro* manipulations but also therapeutic applications *in vivo*. Sufficiently long on-target activity will be key to clinical utility.

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