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Commentary: A synthetic adeno-associated viral vector as a means of future precision treatment

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Treating acute myocardial infarction should not be like shooting flies with a cannon; the target is the ischemic heart only, and a specifically targeted local treatment decreases risks of systematic side effects. The key is to bring the treatment to the specific tissue area intended to heal without influencing unnecessarily the whole of the body.

Gene therapy could serve as an adjunct treatment of myocardial infarction. A healing gene molecule is incorporated within a transporting adeno-associated viral (AAV) 9 vector vehicle and specifically smuggled to a local area while minimizing overall viral infection and toxicity.¹ Unfortunately, delayed gene expression, poor sustainability, and any systematic immune response caused by the injection of AAV9 vector may restrict the wide adaption of gene therapy clinically.

A novel synthetic AAV vector, Anc80L65, enters the scene.² Anc80L65 was created using a reverse genetic approach and ancestral AAV sequence reconstruction; Anc80L65 may rule out some of the challenges presented by AAV vectors.^{3,4} The capsid structure of the Anc80L65 vector may ensure transduction capabilities. The aim of the experimental rat study by Katz and colleagues² was to investigate the efficacy of Anc80L65 as a vector vehicle for cardiac gene therapy. The transduction efficiency of Anc80L65 and AAV9 in neonatal rat cardiomyocytes in vitro and rat hearts in vivo after intramyocardial and

One needs to target the heart only with an AAV vector.

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Rather than like shooting flies with a cannon, gene therapy affords a targeted means of bringing a specific healing gene molecule to the exact site of treatment.

intracoronary administration were compared using fluorescence and bioluminescence techniques.

Three arguments were explored.² First, the efficacy of the delivery means to bring a molecule to the sick tissue area was investigated; the heart uptake of Anc80L65 was increased compared with AAV9 vector. As observed by fluorescence imaging, Anc80L65-mediated transgene expression increased in rat cardiomyocytes in vitro and in vivo in a time-dependent manner using intramyocardial or intracoronary rat heart administrations. Bioluminescence imaging confirmed the time-dependent increase of rat heart Anc80L65 vector. Second, Anc80L65 distribution adhered well to the heart, whereas AAV9 distribution was relatively dispersed in other organs as well, as detected by quantified polymerase analysis of the vectors. Finally, minimized systematic side effects could be anticipated as some pro- and anti-inflammatory cytokine responses were negligible after Anc80L65 administration.

The functional efficacy of a therapeutic molecule after the gene vector transport was not investigated and remains to be proven. Paradoxically, if the nonimmunogenic synthetic vector does not induce any systematic effect such as inflammation, is there a possibility that the synthetic vector has no meaningful auxiliary effect locally either? Rapid therapeutic gene induction may be important in treating the acute myocardial ischemia, but for chronic phases such as angiogenesis, could a constant foreign gene activation

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even be detrimental? Besides the cardiomyocytes, are other cardiac cells influenced by the induction of Anc80L65 vector?

The study by Katz and colleagues² includes empiric observations on a synthetic AAV gene transport; the rat hearts with Anc80L65 were aptly compared with another optional heart delivery means including AAV9 vector. The study reveals limitations of accepting the technology clinically, but it suggests that a sustainable gene therapy using Anc80L65 may replace the less precise AAV9 vector.

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Commentary: Can the new synthetic adeno-associated virus vector deliver the promise of cardiac gene therapy?

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Katz and colleagues¹ have reported the use of a synthetic adeno-associated virus (AAV) lineage clone, Anc80L65, and compared it with AAV9. They showed that transfer of reporter genes with Anc80L65 in rat cardiomyocytes and rat hearts was more efficient and robust than AAV9.¹ This was not associated with off-target transfection in other organs, lymphocyte or neutrophil activation, alteration in inflammatory cytokines, or disturbance of cardiac function. These findings are consistent with favorable reports of Anc80 in gene therapy in the retina and the central nervous system.^{2,3} However, the optimal route of administration, whether intramyocardial or intracoronary, needs to be

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The new synthetic adeno-associated virus vector Anc80L65 has superior gene transfer efficiency over the adeno-associated virus 9 vector in rat hearts, but other obstacles remain.

determined. Only a single vector dose was studied, and the optimal dosing and timing warrant further investigation.

In the past 5 years, several gene therapy products received approval for clinical use.⁴ However, the goal of therapeutic gene therapy in the heart remains elusive. Studies of cardiac gene therapy have focused mostly on 2 areas: therapeutic angiogenesis for coronary artery disease where conventional revascularization is not feasible and heart failure.

Notable examples of angiogenesis clinical trials include naked DNA plasmid encoding vascular endothelial growth factor A (VEGF-A) (EUROINJECT-1, NOGA Angiogenesis Revascularization Therapy: Assessment by Radioclide Imaging [NORTHERN trial], Kuopio Angiogenesis

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