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Aptamers enhance targeted gene therapy using viral vectors

Virus mediated gene therapy has emerged as a powerful and promising option for the treatment of various diseases such as metabolic, cardiovascular, muscular, hematologic, ophthalmologic, and infectious diseases and different types of cancer.

Among the viral vectors, adeno-associated virus (AAV) is particularly attractive because of its properties of low immunogenicity, high transfection efficiency and long-term transgene expression in vivo. However, due to the requirement of primary receptor heparin sulfate proteoglycan (HSPG) in AAV based gene transduction, AAV viral gene delivery is confronted with the

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developing safe and efficient targeted virus delivery systems.

Although antibodies exhibit receptor-binding specificities that can be genetically incorporated in the AAV2 capsid, the mutant viral capsid have sometimes resulted in failed production of AAV2 vectors or lower vector infectivity. Aptamers have come out to be the best alternatives to antibodies as they exhibit high affinity, excellent specificity, low toxicity or immunogenicity as well as additional merits of easy synthesis and modification, inherent stability with long term storage, high reproducibility at low cost, and design flexibility. Many aptamers have been selected for different types of tumor cells with high specificity, strong affinity, and rapid tissue penetration. All these advantages make aptamers ideal candidates for developing aptamer-mediated delivery vehicles.

In the view to enhance the viral gene delivery, Wu et al., 2018 demonstrated ApDC approach, which consisted of AAV2 vectors, conjugated with multiple sgc8 aptamers. The resulting sgc8-AAV2 construct significantly enhanced the delivery efficiency of AAV2, as demonstrated using a GFP gene as a model (Figure 1)

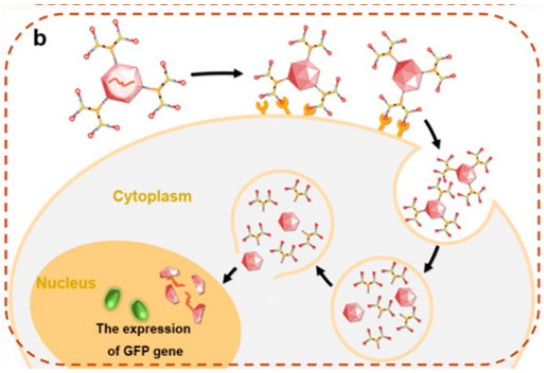

Figure 1. G-sgc8-AAV2 complexes generated by DSP cross-linkers (b) Intracellular GSH-responsive chemical modification of AAV2 vectors carrying GFP reporter gene with multiple aptamers to enhance cell-specific transduction of AAV2-based vectors.

Flow cytometry analysis showed a noticeable higher enhancement in the fluorescence signal for the target CEM cells treated with G-sgc8-AAV2, while no significant change in fluorescence intensity was observed for negative K562 cells, confirming the multivalent specific recognition capability of G-sgc8-AAV2 for the target CEM cell line (Figure 2). Moreover, efficient cellular uptake of AAV2 vectors was observed as indicated by rapid internalization into target cells within the first 30 min by PTK7 receptor-mediated endocytosis analysed by confocal microscopy and flow cytometry.

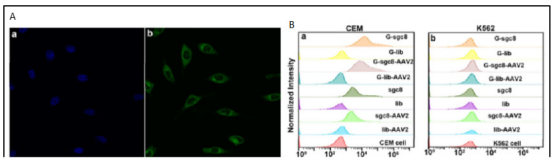

Figure 2. Subcellular distribution of Cy5-labeled G-sgc8-AAV2 vectors in target cells indicated that AAV2 vectors modified with G-sgc8 started to diffuse into lysosome within 30 min incubation as confirmed by confocal microscopy (A). Internalization test of Cy5- labeled G-sgc8-AAV2 vectors was confirmed by flow cytometry in CEM and K562 cells with different incubation time of 0, 0.5, 2, and 4 h (B).

Moreover, these specific vectors demonstrated several remarkable features such as wider application for AAV2 vectors to HSPG-negative cell lines because of conjugation with aptamers, enhanced gene transduction efficiency by incorporating multivalent aptamers and GSH-stimulated response and most importantly nontoxic in nature (refer paper for results).

Overall, AAV2 vectors carrying therapeutic genes can be conjugated to aptamers to achieve targeted gene therapy. At Aptamer Group Limited (AGL), we offer the advantage of designing aptamers to be optimized for the conditions you want to use them in. This way they are engineered to bind to their target with high specificity and affinity. Moreover, AGL continuously aims to conduct further research in prevention, diagnosis and treatment of various such diseases. If you would like to know more about aptamers and their

Reference: Wu Y, Zhang L, Cui C, et al. Enhanced Targeted Gene Transduction: AAV2 Vectors Conjugated to Multiple Aptamers via Reducible Disulfide Linkages. J Am Chem Soc. 2018;140(1):2–5. doi:10.1021/jacs.7b08518

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