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Targeted DART-AAVs as in vivo gene delivery platform for the specific transduction of TME cell subsets

In vivo gene delivery has emerged as powerful tool for novel therapeutic concepts. A major challenge is the development of vectors capable of mediating highly selective gene transfer specifically into therapy-relevant cells. For this purpose, we have developed the concept of rational-based receptor-targeting of AAV vectors harnessing designed ankyrin repeat proteins (DARPins) in order to specifically deliver therapeutic genes into particular cell types of the tumor microenvironment (TME) such as CD8+ T cells and tumor cells (DARPin Targeting AAV: DART-AAV).

In our recent work [1], we engineered AAV capsids displaying high-affinity DARPins specific for murine or human CD8 to specifically manipulate CD8+ cytotoxic T cells. The modified vectors exhibit high selectivity for both murine and human CD8+ T lymphocytes. Upon systemic injection, the targeted vectors achieved an impressive in vivo gene transfer rate of up to 80%, which represents a breakthrough in the in vivo modification of T cells with AAV vectors. Most remarkably, near absolute selectivity for CD8+ T cells while detargeted from liver was observed in immunocompetent mouse models.

Building on this platform, we engineered AAV9 for receptor-targeted delivery into tumor cells. Specifically, we developed HER2-AAV9 vectors displaying DARPins against the HER2/neu, resulting in significantly enhanced transduction of HER2+ tumor cells in vitro. These vectors conferred robust checkpoint-inhibitor or IL2 secretion. In mice bearing subcutaneous HER2+ SKOV-3 xenografts, HER2-AAV9 mediated tumor-targeted delivery of a luciferase reporter with minimal hepatic transduction.
Collectively, these receptor-targeted AAV vectors exhibit exceptional efficiency and specificity, opening new avenues for directly modifying therapy-relevant cell populations in vivo. This platform holds promise for basic research and the development of next-generation gene therapy strategies, particularly in the context of tumor-specific immunomodulation.

1- Demircan, Muhammed Burak, et al. "T-cell specific in vivo gene delivery with DART-AAVs targeted to CD8." Molecular Therapy 32.10 (2024): 3470-3484

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