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Targeting Adeno-Associated Virus to Osteosarcoma Tumor-Initiating Cells

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Recombinant adeno-associated virus (rAAV) is used as a promising vector for human gene therapy including cancer. Insufficient gene expression and inability to use systemic administration remain major limitations to AAV mediated cancer gene therapy. In this study, based on the advancement of AAV vector technology and the understanding of osteosarcoma (OS), a pediatric bone cancer, we aimed to make designer AAV vector that can specifically target OS following systemic injection. An OS mouse model generated from tumor-initiating cells (TICs) from OS patient biopsies was used to isolate novel AAV mutants that are capable of transducing OS TICs following IV injection. The sequence alignment of the resulting AAVs allowed us to identify OS specific motifs that determine the specific interaction between OS cells and AAV. In addition, the AAVs were abolished the uptake into normal tissues for further lowing the off-targeting. These engineering enables hundreds of fold higher OS transduction while the off-targeting in normal tissues is limited. This novel targeting platform holds great potential for further translational studies for the treatment of OS. The strategic exploitation of these technologies can serve as a template for the development of novel AAV vector for targeting other solid tumors as well.