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MINIMALLY INVASIVE IN-SITU PERFUSION METHOD FOR TARGETED AAV DELIVERY IN THE NATIVE KIDNEY: PROOF OF CONCEPT IN PIGS

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Currently, there is not any method for efficient and targeted delivery of gene therapies using viral vectors to the native kidneys. Adeno-associated viruses (AAV) are limited by hepatotoxicity and poor kidney tropism. This study aimed to develop a minimally invasive approach that overcomes both challenges. We evaluated in pigs a technique leveraging external perfusion systems to transiently isolate native kidney vascularization. Using a percutaneous femoral approach, fluoroscopy-guided catheterization of the kidney artery and vein enabled the establishment of a temporary isolated kidney perfusion circuit permitting native kidney in-situ perfusion. AAV delivery was then assessed by detecting construct encoding Td-Tomato protein, its mRNA and fluorescence 6 days after the perfusion. The method was achieved with two different external perfusion systems and was not associated with procedure related mortality or any major complication. Td-Tomato was detected in the perfused kidney without a significant detection in the liver which showed no inflammatory infiltrates. We developed, in pigs, a minimally invasive method permitting in-situ native kidney perfusion that enables kidney-targeted AAV delivery. Besides, it limits liver off-target transduction, potentially reducing its main side effect, hepatotoxicity, when AAV is systemically injected. It offers fast-track translational possibilities for developing kidney-targeted gene therapies. Finally, it may permit additional non-AAV therapeutics for patients with kidney diseases.