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Title: Engineered AAVs for non-invasive gene delivery to rodent and non-human primate nervous systems

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Abstract: Gene therapy offers great promise in addressing neuropathologies associated with the central and peripheral nervous systems (CNS and PNS). However, genetic access remains difficult, reflecting the critical need for development of effective and non-invasive gene delivery vectors across species. To that end, we evolved the adeno-associated virus serotype 9 (AAV9) capsid in mice, and validated two capsids, AAV-MaCPNS1 and AAV-MaCPNS2, across rodent species (mice and rats) and non-human primate (NHP) species (marmosets and rhesus macaques). Intravenous administration of either AAV efficiently transduced the PNS in rodents, and both the PNS and CNS in NHPs. Furthermore, we used AAV-MaCPNS1 in mice to systemically deliver: (1) the neuronal sensor GCaMP8s to record calcium signal dynamics in nodose ganglia, and (2) the neuronal actuator DREADD to dorsal root ganglia to mediate pain. This conclusively demonstrates the translatability of these two systemic AAVs across four species, and their functional utility through proof-of-concept studies in mice.