Using Adeno-Associated Virus (AAV) Mediated Sustained Expression of an Anti-methamphetamine Antibody Fragment to Alter Methamphetamine Disposition in Mice
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Purpose
Methamphetamine (METH) abuse is a global health issue with no FDA approved medications for treatment. METH specific monoclonal antibodies and their fragments (scFvs) are promising medications that could help protect users from METH overdose and/or relapse. Toward this end, we have designed and performed initial preclinical testing of an AAV based medication intended to achieve sustained therapeutically relevant serum concentrations of our high affinity anti-METH scFv6H4.

Methods
Plasmids containing scFv6H4 DNA were tested for their ability to transiently induce expression in male BALB/c mice using a hydrodynamic plasmid delivery method. Ex-vivo METH binding of expressed scFv in serum samples was determined using equilibrium dialysis. For AAV mediated gene delivery, vectors were packaged into AAV8 particles and mice were injected with either 1x10^{12} vector genome copies of AAV-scFv6H4 or saline as a negative control (n=10/group). Serum samples collected throughout the study were tested using functional ELISA for AAV-scFv6H4 expression. To test the extended functionality of AAV-scFv6H4, 1 mg/kg METH was administered sc 50 days after the initial AAV dose. Serum samples taken at 30 and 60 min after METH dosing were analyzed by LC-MS/MS.

Results
Hydrodynamic gene delivery in mice resulted in short term expression of functional scFv6H4, demonstrated the validity of the vector design, and justified further packaging of the vectors into AAV8 particles. After AAV dosing, the serum concentrations of AAV-scFv6H4 were 19 µg/ml on days 10-20 and increased to 55 µg/ml through day 90. METH studies on day 50 indicated that the AAVscFv6H4 expressing mice exhibited a significantly higher serum concentration of METH at both 30 and 60 min, suggesting METH sequestration in the serum by the circulating anti-METH scFv6H4.

Conclusion
In this proof of concept study, we provide in vivo evidence that AAV gene delivery can result in sustained serum concentrations (≥ 3 months) of functional anti-METH scFv6H4 in BALB/c mice. Funding NIDA R01 DA026423.