There is an unmet need for effective therapeutic strategies in Huntington's disease (HD) and drug abuse. 

**GluN3A** is a novel target that regulates synapse plasticity and neuronal connectivity.
- Its expression is reactivated in CNS pathologies including HD, cocaine and alcohol abuse.
- Proof of Concept: Knock-Out mice in HD and shRNA in drug abuse.
- Safety: lacking in healthy adult brain.

**Scope of the problem**
- HD is a rare disease: its average frequency ranges from estimated 4 to 10 individuals per 100,000 people, with symptoms usually occurring by late 40s. There is, at present, no cure and only one FDA-approved symptomatic treatment.
- Cocaine abuse is widespread and is becoming a major public health issue. The prevalence of cocaine use in the world is approximately 13 million people or 0.23% of the global population.

**New target**
- GluN3A subunits form part of NMDA receptors during early postnatal and juvenile stages, but are mostly absent in adult brain (human data).
- Adult reactivation of GluN3A is pathological: inhibits synaptic plasticity and triggers synapse loss (*Neuron*, 2009).

**Clinical Impact**
- Adult reactivation of GluN3A protein expression has been described:
  - in striatum of Huntington’s disease individuals (*Nat Med*, 2013)
  - after cocaine administration (*J Neuroscience*, 2013; *Neuron*, 2013)

**Proof of Concept**
- Suppressing aberrant reactivation blocks impaired plasticity (using shRNA in cocaine addiction), synapse loss and neurodegeneration (using GluN3A-KO mice in HD).

**Safety**
- Lacking in adult brain: lesser side-effects than previously failed approaches to target brain NMDA receptors.

**Reference**