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Translational approach to develop novel medications on alcohol addiction: Focus on neuropeptides

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Abstract

Research on alcohol and drug dependence has shown that the development of addiction depends on a complex interplay of psychological factors, genetic or epigenetic predisposing factors, and neurobiological adaptations induced by drug consumption. A greater understanding of the mechanisms leading to alcohol abuse will allow researchers to identify genetic variation that corresponds to a specific biological vulnerability to addiction, thus defining robust endophenotypes that might help deconstruct these complex syndromes into more tractable components. To this end, it is critical to develop a translational framework that links alterations at the molecular level, to changes in neuronal function, and ultimately to changes at the behavioral and clinical levels. Translational phenotypes can be identified by the combination of animal and human studies designed to elucidate the neurofunctional, anatomical and pharmacological mechanisms underlying the etiology of alcohol addiction. The present article offers an overview of medication development in alcoholism with a focus on the critical aspect of translational research. Moreover, significant examples of promising targets from neuropeptidergic systems, namely nociceptin/orphanin FQ and neuropeptide S are given.

Keywords

Alcoholism; Drug abuse; Addiction; Translational Medicine; Brain Imaging

Introduction

Alcoholism is one of the most widespread form of addiction and has one of the highest negative social, medical and economical impact on our societies In recent years several approaches have been investigated to help alcohol abusers to not only control alcohol drinking but also alcohol cravings and relapse. Medications such as disulfiram, naltrexone (injectable or oral), and acamprosate have been developed and approved for the treatment of alcoholism [1]. While all of these medications have demonstrated effectiveness in reducing alcohol abuse, there are limitations associated with each option, such as limited efficacy, occurrence of side effects and high dropout rates Clearly, the continued development of

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effective pharmacotherapies for alcohol dependence is needed. Drug development, which is classically carried out by the pharmaceutical industry is a complex process that requires a multilevel approach, is extremely expensive and takes several years. Compared to other disease areas the pharmaceutical industry has historically invested limited resources in drug development programs for alcoholism, which may explain, at least in part, the paucity of approved medication so far available. Several factors may explain the lack of interest in developing medication for alcoholism by private industry. First is the stigma that is still associated with alcoholism and addiction in general. There are problems associated with the coverage of the medication costs by the private insurance or the public health systems and, differently from other diseases, little desire to treatment by a substantial proportion of patients that is unable to recognize alcoholism as a medical condition.

A second important limitation is the complexity of the disease which dramatically reduce the expectation of the industry to successfully develop a medication from lab to marketplace. Over the years, preclinical research has identified a large number of promising biological targets for alcoholism and several promising molecules are available. However, the limited number of medication successfully developed so far, as well as the lack of a well validated development path severely limit the interest of the pharmaceutical industry in this area. The development of a clear and well structured translational approach for medication development is a major challenge in alcohol addiction research (Fig.1). The present article offers an overview of the-state-of-art in medication development in alcoholism focusing on critical aspect of translational research. Moreover, significant examples of promising targets from neuropeptidergic systems, namely nociceptin/orphanin FQ (N/OFQ) and neuropetide S will be presented.

Brain Imaging Technologies a Bridge Between Preclinal and Clinical Research

Neuroimaging methods have been extensively applied to study the human brain and its structural and functional organization in healthy and disease states. Imaging techniques enable the researcher to explore endophenotypes that are more proximal to the biological mechanisms underlying the risk for the development of alcohol use disorders. An important advantage of the neuroimaging approach is that the output does not rely on subjective reports of an effect, but rather measure a biologically-based expression of the phenotype. Recent developments have extended this approach to animal models, thus paving the way to a translational use of neuroimaging techniques to bridge clinical and preclinical research.

Among the various imaging modalities, two have emerged as particularly impactful in addressing psychiatric disorders like addiction and alcohol dependence, and amenable to application in both humans and laboratory animals: Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET).

Brain imaging techniques have been extensively used to investigate morphological, metabolic and functional changes associated with alcohol abuse in humans. Morpho-anatomical studies have revealed reduced grey matter (GM) volume in alcoholic patients, in the frontal lobes, the cerebellum and the limbic system showing the most pronounced abnormalities [2–6]. Such alterations have been recently demonstrated to be predictive of relapse risk, suggesting a significant role for grey matter shrinkage in clinical outcomes in alcoholism [•5]. White matter abnormalities as well as numerous functional and neuro-metabolic deficits (reviewed by [2]) have also been reported in heavy consumers of alcohol [7,8]. Reduced resting-state metabolism in frontal-parietal, orbitofrontal cortex and striatal areas in active and abstinent alcohol-abusers has also been reported [9–11].

An unanswered question in alcohol research is whether these alterations are the sole consequence of chronic alcohol use, or also represent an innate factor contributing to biological propensity toward ethanol addiction. Recent neuorimaging studies have begun to address this question. Individuals at high-risk for alcohol dependence have been shown to have altered sensitivity of the reward circuitry [12–14], and reductions in cortical and thalamic grey matter volumes [15], two features commonly observed in abstinent alcoholic patients. Importantly, the presence of shared fronto-striatal abnormalities has also been recently reported in drug-naïve siblings of psycho- stimulant drug abusers [16]. These preliminary findings highlight a putative role for inborn morpho-functional brain abnormalities in the aetiology of alcohol-dependence.

Neuroimaging studies in preclinical species exploring the role of heritable brain abnormalities as a vulnerability factor for alcoholism have only very recently started appearing in the literature [••17]. The genetically selected alcohol preferring msP rat was chosen as an established selection-based model for the investigation of the neurobiology of alcoholism closely mimicking several fundamental aspects of human disease such as the occurrence of binge-like ethanol drinking [18], psychological withdrawal symptoms escalating alcohol intake upon abstinence and highvulnerability to stress-mediated relapse [19]. Importantly, the model also reproduces important comorbid states pervasively associated with alcoholism, such as increased sensitivity to stress, anxious phenotype and depressive-like symptoms [18,19].

Structural and functional MRI was applied to study alterations in brain morphometry and basal metabolism in this model. msP rats exhibited reduced grey matter volume in the thalamus, ventral tegmental area, insular and cingulate cortex, consistent with observations in abstinent alcoholics and in individuals at high risk of alcohol dependence [••17]. As the animals imaged in this study were alcohol-naïve, this work suggests that some of the morpho-functional alterations documented in alcoholics may reflect a pre-existing endophenotype predisposing to alcohol addiction. Recent clinical data lends preliminary evidence to this hypothesis.

While MRI approaches will give information about the morphoanatomical alterations related to alcohol dependence, and can help establish a link between behavior and brain circuits, they do not provide specific information about its neurochemical determinants. To this end, molecular PET-imaging represents a powerful means to explore the neurochemistry of addiction, and the specific receptor and neurotransmitter systems involved. However, PET imaging relies on the availability of selective radiotracer ligands. Currently, no more than 25 targets can be quantified in the human brain, and dopamine is the only system for which transmitter-sensitive radioligands have been extensively used. With regard to peptidergic neurotransmission the only PET ligand available until recently was [11C]carfentanil which allowed the exploration of mu opioid receptor (MOP) receptor function in brain diseases including addiction [20].

A new advancement in the study of opioid peptide neutrasmission is the very recent development of PET radioligands for the kappa opioid receptor (KOP) and the N/OFQ receptor (NOP) [••21,••22]. The availability of these new tools will allow investigators to better determine the role of these receptors in psychiatric research. For example, referring to alcoholism, they could be used to investigate if KOP and NOP receptors may have an abnormal distribution in alcoholic patients, thus providing evidence of the involvement of abnormal peptidergic neurotransmission in the aetiology of alcohol dependence; but avalibility to these ligands will also facilitate the development of drugs targeting this system.

Neuropeptide systems as a target of novel medication for alcoholism

Neuropeptides have always received much attention in the alcohol field, the main reason being the early discovery of the key role of opioid neurotransmission in mediating alcohol reward, withdrawal-induced dysphoria and relapse [23,24]. Over the years, in addition to opioids, the involvement of several other neuropetidergic systems in the physiophathology of alcoholism has been documented. Some of these neurotransmitter systems are now under deep scrutiny because they are considered as highly promising targets for medication development. For some of these neuropeptide targets (i.e., Corticotrophin Releasing Factor receptor 1 and Neurokinin receptor 1), clinical stage molecules are already available and initial studies in humans have been already carried out or are underway. Medication development programs and translational approaches related to these targets have been recently covered by comprehensive studies and will not be the focus in the present review (for review see: [25,26]. Here, we will focus instead on two less explored but highly promising peptidergic systems, the nociceptin/orphanin FQ and the neuropeptide S, that are currently being subjected to intense exploration and are considered highly promising targets for medication development in alcohol addiction.

Nociceptin/Orphanin FQ System

Nociceptin/orphanin FQ is a 17 amino acid neuropeptide, structurally related to the opioid peptide dynorphin A and binds to its cognate receptor opioid receptor-like1 (ORL1) now named NOP receptor.

N/OFQ and NOP receptors are widely distributed in the brain, where they are largely co-expressed .. Despite being opioid-like, N/OFQ acts in the brain to produce functional anti-opioid effects. For instance, it blocks opioid-induced supraspinal analgesia [27], morphine-induced conditioned place preference [28,29] and morphine induced increases in extracellular dopamine levels in the nucleus accumbens [30].

Moreover, activation of NOP receptors by N/OFQ or by synthetic agonists produces anxiolytic-like effects [31,32] that appear to be particularly robust under stressful conditions, such as e.g. during alcohol withdrawal [•33]. This may depend upon the ability of N/OFQ to act as a functional antagonist for extrahypothalamic actions of Corticotrophin Releasing Factor (CRF) and CRF1R receptor activation [34,35].

Consistent with the anti-opioid nature of N/OFQ it has been shown that activation of the NOP receptors blunts the reinforcing and motivational effects of alcohol across a range of behavioral measures, including alcohol intake [36], conditioned place preference [37] and relapse to alcohol seeking triggered by alcohol associated cues [38]. Whereas, in agreement with its antiCRF properties it has been shown that N/OFQ administration prevents foot-shock stress-induced reinstatement of alcohol seeking in the rat [39].

Studies in msP rats have shown that they are particularly sensitive to suppression of alcohol drinking and relapse by N/OFQ and N/OFQ analogues [36,38,40]. msP rats exhibit high innate sensitivity to stress, and high measures of both anxiety- and depression-like behaviors that are ameliorated by alcohol consumption [18]. Hence, N/OFQ effects in msP rats are in part likely due to its ability to alleviate a negative emotional state that otherwise provides an incentive for negatively reinforced alcohol consumption. If this hypothesis is correct, one could predict that a NOP agonist might be particularly efficacious in alcoholic patient that drink to self-medicate from a negative affective state or for tension reduction purposes.

From the translational point of view, an exciting recent development was the discovery that buprenorphine, a drug currently employed for pain management and heroin addiction

treatment, in addition to its ability to activate MOP and to block KOP receptors at higher dose it also activates NOP receptors [41,42]. Interestingly, similar to prototypical MOP agonists, buprenorphine at low doses increased ethanol consumption in the rat, an effect that was blocked by co-administration of the MOP preferential antagonist naltrexone [43–45]. At higher doses, buprenorphine markedly reduced alcohol intake and this effect was blocked by the selective NOP antagonist UFP 101 but not by naltrexone. These findings indicate that at low doses buprenorphine increases alcohol intake via stimulation of classic opioid receptors, while at higher doses reduces it via activation of NOP receptors [•46]. An intriguing finding from studies on heroin addicts was that treatment with buprenorphine also attenuates alcohol consumption in these patients [47,48] whereas methadone, the other opioid agonist used to treat heroin addiction, appears to be less efficacious on alcohol and in some studies was even shown to increase drinking [47,49]. Although these findings point to the possibility that NOP receptor activation by buprenorphine is responsible for these effects on alcohol in the absence of clinically available N/OFQ antagonists this hypothesis hard to demonstrate.

Very recently, ^{11}C-NOP-1A, a new radioligand for the nociceptin/orphanin FQ peptide receptor, with high affinity (Ki, 0.15 nM) and adequate lipophilicity (measured logD, 3.4) for PET brain imaging has been developed [••21]. Using this ligand, it is possible to evaluate if the high doses of buprenorphine that attenuates alcohol and cocaine consumption will displace ^{11}C-NOP-1A from NOP receptors. This study will help to further clarify the potential of NOP receptors as a treatment target for alcoholism and possibly other forms of addiction opening new vistas for drug development programs on this peptidergic system. Non-peptide, orally available and brain penetrant NOP receptor agonists have been developed, and seem to have acceptable safety and tolerability. Some of these are in relatively advanced stages of development, and may soon become ready for clinical evaluation (Table 1).

Neuropeptide S system

A new interesting area of research in the field of neuropeptides is offered by the relatively recent deorphanization of the G-protein coupled receptor 154 (GPR 154), currently named the NPS receptor (NPSR), and that is activated by a 20 aa peptide named neuropeptide S (NPS) [50]]. NPS precursor mRNA is expressed in about 500 cells localized only in the brainstem [51,52]. Whereas NPSR is widely expressed in brain areas important in regulating affective responses, emotions and cognition such as the amygdala the hippocampus and the hypothalamus [51–53].

Recent preclinical findings suggest a strong role for the NPS system in drug abuse (see for review [54]). For example neurochemical studies have shown that central injection of NPS facilitates corticomesolimbic DA neurotransmission, a hallmark of reward [55,56]. But, ICV NPS administration induced neither place preference nor aversion [57], suggesting that NPS is devoid of direct rewarding properties. When given to rats trained to lever press for cocaine NPS did not influence drug self-administration [•58]. Cocaine self-administration was also unaffected by the selective NPSR antagonist SHA 68 [•58–60]. Central administration of NPS has also been found to leave alcohol self-administration unaffected in non-dependent Wistar rats. However, NPS decreased alcohol drinking in alcohol-preferring (P) rats but not in the non-preferring (NP) control line [61]. Similar results were found in msP alcohol preferring rats [54]. The P and the msP rat are both highly stress-reactive, and show increased measures of anxiety-like behavior. It has been hypothesized that their escalated alcohol drinking is in part negatively reinforced by alcohol's ability to relieve negative emotional states [18,19,62]. Hence it is possible that, in alcohol preferring rats, NPS decreases alcohol consumption through its anxiolytic-like properties.

One of the most striking features of NPS pharmacology in relation to addiction is its ability to promote relapse to drug seeking. For instance, it was shown that NPS, given ICV or into the LH potentiated relapse to alcohol seeking induced by cues; an effect apparently mediated by activation of the orexin-1 (OX1) receptor system [54].

Studies on cocaine have confirmed the permissive role of NPS in relapse to drug seeking. [•58,63]. Whereas administration of the NPSR antagonists reduced reinstatement of cocaine seeking [•58,60].

A link between the NPS system and alcohol withdrawal has been also described. Over-expression of NPSR transcript was observed at 12 hours and at one week after completion of a five day alcohol intoxication cycle [64]. Accordingly, anxiolytic-like effects of NPS were more pronounced in rats with a history of alcohol dependence than in controls [64]. This finding was confirmed in another study in which it was shown that the anxiolytic and anti-depressant effects of NPS are enhanced in abstinent previously alcohol exposed mice [•65]. Overall, these data suggest that elevation of NPSR expression following a history of alcohol dependence may represent a neuroadaptive mechanism that attempts to compensate for the increased anxiety in animals. This neuroadaptation may set up a dynamic in which increased NPS neurotransmission, initially induced to compensate for withdrawal anxiety persists and promotes relapse during later stages of abstinence.

Hence, of particular interest is the possibility that NPSR antagonists may be useful in the treatment of drug craving and relapse in dependent individuals. Development of selective heterocyclic brain penetrant small molecules are underway. At present NPSR antagonists that can be used as tools to probe the biology of the NPS system have been developed [59]. Hopefully, in the near future compounds for clinical evaluation will be available to be tested in addicted patients (Table 2).

Conclusions and Remarks

Processes involved in the development of alcoholism are thought to reside largely in the brain and they are the result of complex interactions between genetic and environmental determinants. To successfully move new drugs in alcoholism from lab to patient it is important to establish appropriate drug development strategies and to delineate a clear path for the development. Availability of well validated animal models and human laboratory paradigms with surrogate markers predictive of clinical efficacy are two important conditions. While neuroimaging methods can provide a novel and powerful tool to investigate and define a translational phenotype for alcohol dependence in preclinical species and in humans, a major excitement in the field of alcohol addiction is the preclinical characterization of a number of biological targets of potential interests; among those several neuropeptidergic systems, including N/OFQ and NPS. Novel imaging tracers selective for neuropeptide-sensitive receptors are currently being developed. Their availability will provide further possibilities to study the implication of these neuropeptides in the aetiology of alcohol addiction and will be of fundamental importance for the development of new compounds aimed at targeting these systems.

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Highlights

- Traslational medicine has a major significance in drug development on alcoholism.
- Brain imaging techniques are fundamental in bridging between preclinical and clinical research.
- Neuropeptidergic systems are promising for drug development in alcoholism.

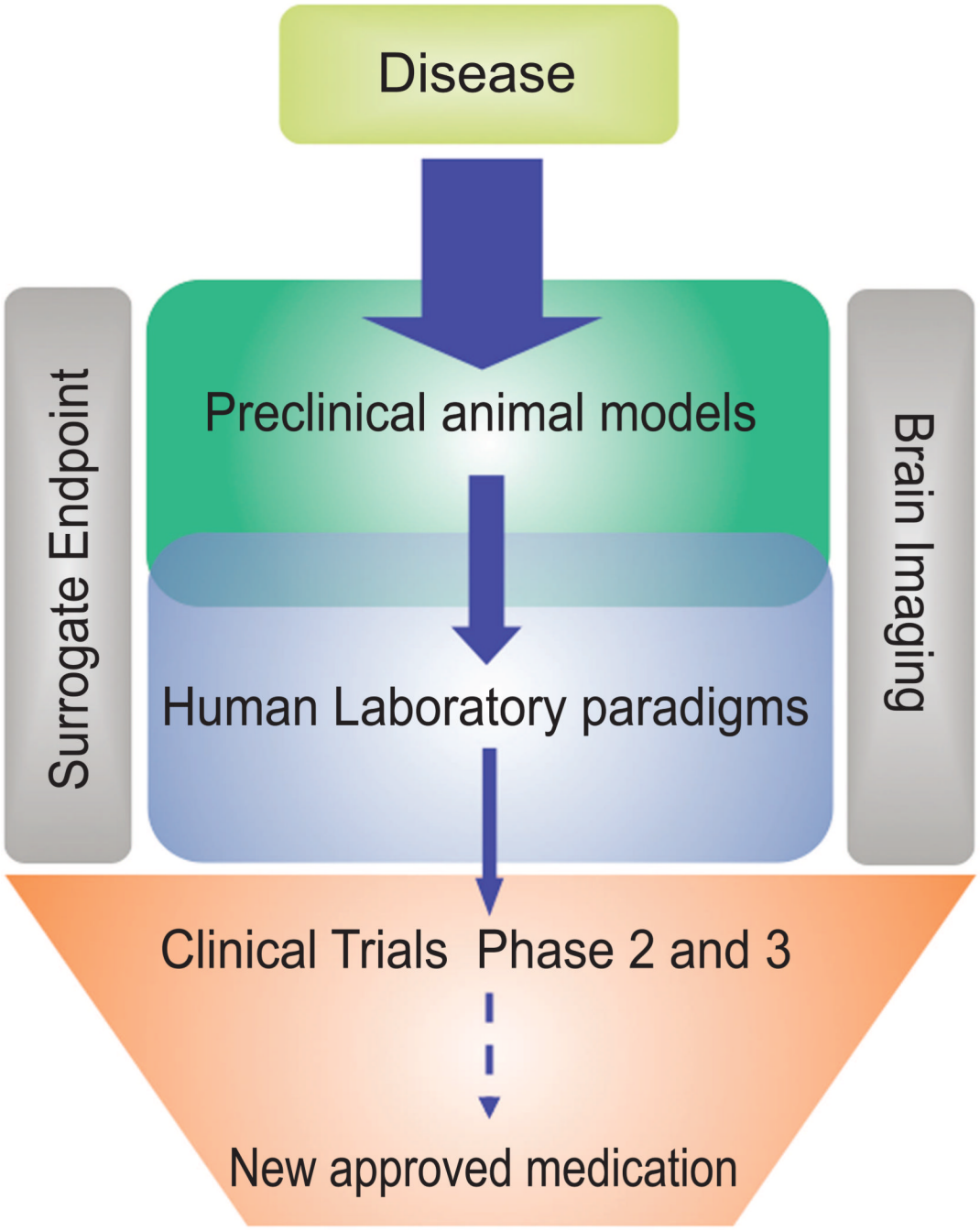

Figure 1.
Schematic representing the critical steps of translational research. A relatively large number of biological targets and promising chemical entities are available for preclinical investigation. The availability of well validated animal models is critical to screen these molecules. A limited number of molecules with satisfactory pharmacological and toxicological profile are moved into the clinic. Human laboratory paradigms can be used to provide initial evidence of efficacy in humans. The utilization of appropriate surrogate markers that possibly overlap preclinical endpoints (i.e, alcohol intake, cue- and stress-induced alcohol craving) is fundamental to translate preclinical findings into meaningful

clinical information. Brain imaging techniques play a critical role in bridging preclinical and clinical research: their use provides an unprecedented help in new medication development .

Table 1

Compounds targeting the N/OFQ system, relative developmental stage and effects on addiction.

Agonist	Chemical entity	Effects on drug taking and relapse	Dev. phase	Ref.
N/OFQ	peptidic	↓ Alcohol intake	Preclinic	36, 38
Ro 64-6198	small molecule	↓ ↑ Alcohol intake	Preclinic	70, 82
Ro 64-6570	small molecule	Not tested	Preclinic	71
W212393	small molecule	Not tested	Preclinic	72
GRT6005	small molecule	Not tested	Clinic	NCT01725087
SCH 655842	small molecule	Not tested	Preclinic	74
SCH 221510	small molecule	Not tested	Preclinic	75
UFP-112	peptidic	↓ Alcohol intake	Preclinic	70
UFP-102	peptidic	↓ Alcohol intake	Preclinic	70
OS-462	peptidic	↓ Alcohol intake	Preclinic	70
Buprenorphine *	small molecule	↓ Alcohol intake	Clinic	46
SCH 486757	small molecule	Not tested	Clinic	73 NCT00230230
Antagonist				
UFP-101	peptidic	— Alcohol intake	Preclinic	46
J113397	small molecule	Not tested	Preclinic	76
NiK-21273	small molecule	Not tested	Preclinic	77
Compound 24	small molecule	Not tested	Preclinic	78
SB-612111	small molecule	Not tested	Preclinic	79
Nphe	peptidic	— Alcohol intake	Preclinic	80
GF-4	peptidic	Not tested	Preclinic	81

* Buprenorphine-induced alcohol drinking reduction is mediated by NOP.

Table 2

Compounds targeting the NPS system, relative developmental stage and effects on addiction.

Agonist	Chemical entity	Effects on drug taking and relapse	Dev. Phase	Ref.
NPS	peptidic	— Alcohol intake	Preclinic	61
		↑ Alcohol cue-induce reinstatement		83
		↑Cocaine cue-induce reinstatement		63
Antagonist				
SHA68	small molecule	— Cocaine self-administration	Preclinic	58
		↓ Cocaine cue-induced reinstatement		
[^{t}Bu-D-Gly^{5}]NPS	peptidic	Not tested	Preclinic	66
[D-Cys(^{t}Bu)^{5}]NPS	peptidic	↓ Cocaine cue-induced reinstatement	Preclinic	60
[D-Val^{5}]NPS	peptidic	Not tested	Preclinic	66
PI1	small molecule	Not tested	Preclinic	67
QA1	small molecule	— Cocaine self-administration	Preclinic	60
		↓ Cocaine cue-induced reinstatement		
ML 154	small molecule	Not tested	Preclinic	68
RT-118	small molecule	↓ Cocaine self-administration and relapse	Preclinic	69