SECTION 2:

INTRODUCTION
Opioids are standard drugs used to manage severe pain and are the most commonly used psychoactive substances across the world. Their chronic use has been associated with the development of dependence in the treated subjects (Akil H and Lewis, 1987; Van Ree et al., 1999; Hardman et al., 2001). Abrupt opioid withdrawal in the dependent subjects is noted to cause the precipitation of a severe abstinence syndrome (Williams et al., 2001). This opioid withdrawal syndrome is noted to impair the ability of dependent subjects to discontinue the addictive substance. One of the approaches used to treat opioid dependence include the replacement of the opioid drug with other less addictive opioids followed by gradual dose reduction (Hardman et al., 2001; Krantz and Mehler, 2004). Other treatment approaches involve the usage of $\alpha_2$-adrenergic agonists like clonidine & non-pharmacological methods like acupuncture or transcutaneous electrical stimulation (Hardman et al., 2001). However, none of the available options promises to conclusively treat the condition of opioid dependence and its related abstinence syndrome.

Nuclear factor-ĸ-B (NF-ĸB) is an inducible transcription factor regulating a battery of inflammatory genes involved in the progression of various neurological disorders (Baeuerle, 1991). Reports have indicated the role of NF-ĸB in the N-methyl-D-aspartate (NMDA) receptor activation based precipitation of opioid withdrawal syndrome (Trujillo and Akil, 1995). Initial studies have documented that the inhibition of NF-ĸB suppresses opioid withdrawal contracture in morphine withdrawn isolated guinea pig ileum (Capasso, 2001). Thus, nuclear factor kappa B activation has been proposed to be an important target mediating the progression of opioid withdrawal syndrome. Recently, NF-ĸB activation has been reported to control the transcription and biochemical activation of chemokines and thus regulate inflammatory processes, which are, in turn, proposed to precipitate withdrawal syndrome (Palma-Nicolas et al., 2010). Ammonium pyrrolidine dithiocarbamate (APD) is a
relatively selective inhibitor of NF-κB (Schreck et al., 1992). RS 102895 is relatively selective CC chemokine receptor 2 antagonist (Mirzadegan et al., 2000; Onuffer et al., 2002).

Opioid receptor activation is known to inhibit adenylyl cyclase (AC) activity (Law et al., 2000). However, sustained opioid receptor activation in locus coeruleus neurons followed by a sudden withdrawal of the drug has been shown to cause a paradoxical super-activation of adenylyl cyclase mediated increase in the intracellular levels of cAMP. The increased intracellular cAMP has been reported to cause transmission of impulses leading to the withdrawal syndrome (Sharma et al., 1977; Law et al., 1982; Koob and Bloom, 1988; Pineyro and Archer-Lahlou, 2007). This observed change from opioid receptor-mediated AC inhibition to activation reflects possible receptor signal switching. Src tyrosine phosphorylation of µ-opioid receptor and generalized tyrosine phosphorylation of the µ receptor associated G-proteins has been shown to be responsible for this receptor switching from an inhibitory to a stimulatory signal (Hardman et al., 2001; Zhang et al., 2009). Moreover, a report has shown (O’Connor et al., 1995) that tyrosine phosphatase induced dephosphorylation is a prerequisite for the activation of opioid receptor-Gαi2-c-SRC-Src-kinase complex dependent AC super-activation based development of physiological dependence associated precipitation of opioid withdrawal syndrome. Further, a group has shown (Sato-Kusubata et al., 2000) that calpain, a calcium activated neutral cysteine endopeptidase, catalyses the proteolytic activation of Gαi proteins which mediate adenylyl cyclase super-activation linked causation of opioid withdrawal syndrome (Trujillo and Akil, 1991; Trujillo and Akil, 1995; Zang et al., 2000; Sweitzer et al., 2004; Esmaeili-Mahani et al., 2008; Drdla et al., 2009; Zadran et al., 2010). SU-6656, sodium orthovanadate and SJA 7019 are noted to be selective inhibitors of src-kinase, tyrosine phosphatase and calpains respectively (Blake et al., 2000; Liu et al., 2002; McLauchlan et al., 2010).
Histone deacetylase is a nuclear transcription factor that defines the course of chromatin remodelling. Evidence has shown that histone deacetylase positively modulates the activity of cAMP response element binding protein (CREB) (Shen et al., 2008). In turn, CREB participates in the feed-forward loop leading to the characteristic AC super-activation linked with opioid withdrawal syndrome. Additionally, pharmacological inhibition of histone deacetylase has been shown to enhance the transcription of opioid receptors in neurons (Hu et al., 2001; Hwang et al., 2007). Thus, histone deacetylase might be involved in mediating the precipitation of opioid dependence related withdrawal syndrome. Histone deacetylase inhibition is noted to modulate the activity of CREB by an interleukin 1-β converting enzyme (IL-1β) associated pathway (Suzuki et al., 2003). Further, it has been observed that an elevated level of hippocampal expression of IL-1β is associated with opioid withdrawal induced jumping behavior in mice (Liu et al., 2011). Thus, interleukin-1β converting enzyme over-activation might be involved in the potential histone deacetylase linked precipitation of opioid dependence related withdrawal syndrome. Tributyrin and trichostatin A are noted to possess a selective histone deacetylase potential (Chen and Breitman, 1994; Yoshida et al., 1995). N-Acetyl-Asp-Glu-Val-Asp-al is noted be a selective inhibitor of interleukin-1β converting enzyme (Margonin, 1997).