Synthetic cathinones (SC) are one of the most prevalent groups of new psychoactive substances, which emerged on the market in the second half of 2000s. These compounds were synthesized by modification of cathinone, substance present in the leaves of plant growing in East Africa. Due to their ability to interact with monoamine neurotransmitters (chemical messengers responsible for the function of brain) SC produce psychostimulant effects, similar to those of old drugs of abuse, such as methamphetamine or cocaine. SC may induce strong addiction upon repeated intake.

3,4-methylenedioxypyrovalerone (MDPV) is one of the strongest and most addictive of all SC. Addictive properties of MDPV were documented in human abusers as well as in experiments using laboratory rodent, such as mice and rats.

Many studies showing the anti-addictive potential of two drugs used in the prevention of rejection of transplanted organs: rapamycin and tacrolimus (FK506) have been published in recent years. These compounds abolished addiction-related behaviors of cocaine- and methamphetamine-treated mice and rats. The direct mechanism of this phenomenon is not certain, because these drugs interact with multiple targets, such as mechanistic target of rapamycin (mTOR) and calcineurin via formation of ternary complexes with proteins belonging to immunophilins, i.e. FKBP12, FKBP51, FKBP52. Unfortunately, rapamycin and tacrolimus have immunosuppressant properties, meaning that they block the functions of the immune system, leading to increased risk of serious infections, which limits their use in the treatment of addictions. Therefore there is a strong need to identify a novel target for future anti-addictive treatments.

FKBP51 (FK506-binding protein 51) is mainly known as a regulator of glucocorticoid receptors (GR), with which it forms a negative-feedback loop to modify the physiological effects of hormones released from adrenal cortex, such as cortisol. Interestingly, FKBP51 interacts with rapamycin and tacrolimus with high affinity. Thus, it is involved in their mechanisms of action and mediates their effects. In addition, FKBP51 has many physiological functions independent of rapamycin and tacrolimus, through which it may interfere with mechanisms of development of addiction. Selective inhibitor of FKBP51, small molecule compound named SAFit2 has been recently developed and showed promising results in studies related to alcohol, cocaine or morphine addiction. However difficulties in reaching sufficient concentration of SAFit2 in blood and brain of living animals limit its value in research and future application in humans. Therefore it is crucial to first validate FKBP51 as a target for anti-addictive therapies in a proof-of-concept study.

Current project aims at understanding the role of FKBP51 in the addiction to psychostimulant MDPV. This will be achieved by thorough studies using mice lacking FKBP51 protein due to experimental intervention (FKBP51-knockout, FKBP51-KO) and their wild-type littermates (WT) having the normal levels of FKBP51 protein as controls. FKBP51-KO mice are viable, fertile and healthy, which makes them a useful tool in preclinical studies. The involvement of FKBP51 in addiction to MDPV will be studied by assessment of:

- Effects of single administration of MDPV on the activation of FKBP51-related signaling pathways and expression of markers of neuronal activation, synaptic plasticity and components of dopaminergic system in addiction-related brain structures of FKBP51-KO and WT mice.
- Susceptibility of FKBP51-KO mice to locomotor sensitization (stronger behavioral response after repeated treatment) to effects of MDPV, followed by analysis of activation of FKBP51-related pathways and expression of markers of synaptic plasticity and components of dopaminergic system in addiction-related brain structures.
- Susceptibility of FKBP51-KO mice to conditioned place preference induced by MDPV, followed by analysis of activation of FKBP51-related pathways and expression of markers of synaptic plasticity and components of dopaminergic system in addiction-related brain structures.

It is expected that FKBP51-related targets are activated in brains of animals treated with MDPV. Thus, it is expected that in mice lacking FKBP51, behavioral response to MDPV is blunted, because of reduced molecular changes in their brains in response to MDPV.

Proposed project will be one of the first studies on the involvement of FKBP51 in the addiction and the first study using FKBP51-KO mice as a model, instead of problematic inhibitors. Moreover, it will be the first study on exploring the link between FKBP51 and abuse of synthetic cathinones and one of the very few aiming at the identification of the potential target for treatment of addiction to SC.

Proposed project has a potential to form the foundation for the future development of novel therapies for treatment of addiction to psychostimulant SC in humans, which are currently lacking. Moreover, results of proposed project can be very likely generalized to other psychostimulant substances, such as cocaine or methamphetamine.