The majority of western societies face an epidemic of substance abuse as a public health emergency. Abuse of amphetamines (methamphetamine or ecstasy) presents an emerging problem worldwide, because these compounds can be synthesized relatively easy from commonly available ingredients, making them more affordable than other abused drugs. Indeed, methamphetamine is being used by approximately 37 million people worldwide and it is favored by young people. Unfortunately, methamphetamine has high dependency potential and is characterized by high toxicity.

It is now accepted that immature neural progenitor cells are present in the adult brain and they produce neurons throughout the life span. These new neurons can then be incorporated into the existing neuronal networks. Altered differentiation of neural progenitor cells into neurons may result in impaired memory and cognition. We discovered that methamphetamine can inhibit the transition of immature neural progenitor cells to mature neurons and that this process is responsible for cognitive decline. In the present research application, we will evaluate the mechanisms of this process.

We will focus on inflammatory processes that are induced by so called “inflammasomes”. The main product of inflammasome activation is interleukin-1β (IL1β), which affects the transition (i.e., differentiation) of neural progenitor cells to mature neurons. Our studies revealed that neural progenitor cells are very sensitive to IL1β; however, IL1β is not produced by these cells but rather by astrocytes, one of the main cell types in the brain. Consistent with these results, we formulated the **central hypothesis of this proposal is that methamphetamine activates inflammasomes in astrocytes, followed by the release of IL1β, which then diminishes differentiation of neural progenitor cells into mature neurons, contributing to cognitive decline.**

This grant application is based on cell culture studies and animal experimentation and will implement a model of exposure to methamphetamine. The experimental models will closely mimic the doses and the pattern of methamphetamine intake by addicted people. Interdisciplinary analyses will include the assessment of inflammatory reactions, oxidative stress, functions of mitochondria, analysis of metabolites produced by mitochondria, and the transition of immature neural progenitor cells to mature neurons. We will use a variety of state-of-the-art molecular methods and visualization after staining for specific cell markers.

While there is currently no effective strategy to treat methamphetamine dependency, our project that is focused on protection against methamphetamine-induced neurotoxicity and neuroinflammation constitutes an alternative therapeutic strategy to alleviate long-term consequences of exposure to this drug. Therefore, the completion of the proposed study promises to establish new therapeutic targets to protect against neurotoxicity of methamphetamine, making this proposal highly significant for the improvement of public health.