Depressive disorders constitute a major health challenge in developed countries, and over 300 million people are affected worldwide. Although many antidepressant drugs are commercially available, about 30% of patients fail to respond to treatment or show only partial treatment response. Furthermore, current antidepressants usually require several weeks of administration before clinical efficacy is observed. These observations have led to a major effort to discover new antidepressants that can overcome these drawbacks. A prototypical compound, ketamine, has attracted attention because it possesses rapid-acting antidepressant activity in depressed patients that lasts several days following a single intravenous administration. However, ketamine can also elicit a variety of side-effects which restrict its use to hospital-supervised patients. Nevertheless, recent studies have pointed towards an important role of brain proteins (known as serotonin 5-HT_{1A} receptors) in ketamine's pharmacological effects. 5-HT_{1A} receptors have a key role in the regulation of mood and targeting them with novel compounds may offer a promising strategy for improved treatment of depression.

The recent discovery of a novel 5-HT_{1A} receptor activator, NLX-101, offers a way forward in this respect. NLX-101 shows pronounced activation of 5-HT_{1A} receptors in a brain region (the frontal cortex) associated with antidepressant activity. Accordingly, in previous rodent studies, NLX-101 showed antidepressant-like effects which were more rapid and efficacious than that of comparator antidepressants, including ketamine. In addition, NLX-101 improved memory performance in depressed rats, suggesting that it could improve cognition in patients suffering from depression.

The present project aims to characterize the activity of NLX-101 in an established rodent model of depression, the chronic mild stress model. In this model, rats are subjected to mild disruption of their environment and, over time, this leads to behaviors associated with depression. A preliminary study found that NLX-101 was very active in reducing depressive behavior but its mechanism of action remains to be clarified. The project will therefore investigate the effects of NLX-101 at several levels: firstly, the biochemical effects of NLX-101 will be tested on enzymes and receptors that are known to be involved in antidepressant effects. Secondly, the role of serotonin 5-HT_{1A} receptors in the frontal cortex will be investigated by administering NLX-101 directly into this important brain region. Finally, the effects of NLX-101 will be compared directly with those of ketamine, tested under the same conditions, in order to determine the extent of similarity between these two novel compounds.

A notable feature of the project is its multidisciplinary and international structure: researchers at the Institute of Pharmacology in Krakow will collaborate with highly recognized teams at the University of Maastricht (The Netherlands) and at the university of Lyon (France) as well as with scientists at the biotechnology company, Neurolixis (USA and France) where NLX-101 originates. Overall, the present research project will generate novel information concerning the brain structures and neurological mechanisms that underlie depressive disorders. In addition, the project will break new ground in the characterization of novel antidepressant compounds. The information generated in this work will make a valuable input to advancement of knowledge in this field, contribute to the development of novel treatments for depression and, hopefully, alleviate the suffering of patients in this area of great medical need.