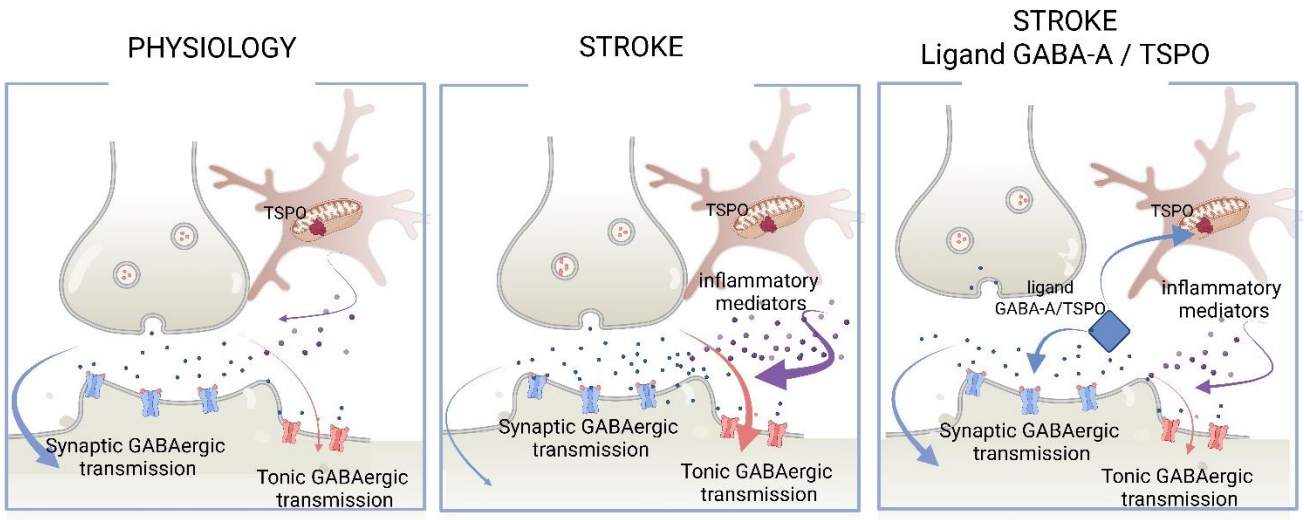
SCIENTIFIC SUMMARY

Ischemic stroke remains one of the leading causes of mortality and long-term disability in the adult population worldwide. Despite substantial advances in drug discovery, **effective pharmacological interventions are still lacking**. Current therapeutic options are limited to a very narrow time window immediately after stroke onset, which markedly reduces the proportion of patients eligible for treatment. To date, most research efforts have focused on neuroprotection during the acute phase of stroke. Although numerous compounds have demonstrated promising effects in experimental models, none have produced clinically meaningful improvements in patient outcomes. One explanation is that stroke induces damage not only to neurons but also to glial elements such as astrocytes and microglia, whose chronic dysfunction significantly impairs the brain's endogenous repair mechanisms.

In recent years, increasing attention has been directed toward the GABAergic system, a key regulator of neuronal excitability. Stroke disrupts the delicate balance between synaptic and tonic GABA signalling. Excessively enhanced tonic inhibition contributes to profound neuronal suppression and limits the capacity for synaptic remodelling and network reorganization. Concurrently, clinical evidence suggests that **pharmacological enhancement of synaptic GABAergic transmission may improve neurological function** in a subset of patients, indicating that precise and targeted modulation of GABAergic pathways could facilitate post-stroke recovery. In parallel, accumulating data indicate that prolonged neuroinflammation constitutes a major barrier to regeneration. The translocator protein **TSPO**-upregulated in activated glial cells-**plays a pivotal role in regulating inflammatory responses**, making it a particularly compelling target for therapeutic intervention (Scheme 1).



Scheme 1. Mechanism of action of GABA-A/TSPO dual ligands.

The project aims to **develop a library of innovative ligands acting as dual modulators of GABA-A receptors and the TSPO protein,** followed by an in-depth characterization of their molecular properties and safety profiles. The synthesized compounds will undergo comprehensive physicochemical analyses and an extensive panel of biological assays, including in vitro tests. Their neuroprotective activity will be evaluated in a cellular model of ischemic stroke, alongside their anti-inflammatory potential, assessed by monitoring changes in cytokine and chemokine levels. The results of these studies will enable the identification of the most promising compound, which will subsequently undergo detailed pharmacokinetic evaluation and assessment of its therapeutic efficacy in an animal model of ischemic stroke. This will allow verification of its potential as a novel therapeutic agent.

The overarching goal of the project is to establish an **innovative therapeutic strategy** that moves beyond classical approaches focused solely on limiting damage in the acute phase of stroke. Instead, the project emphasizes modulation of mechanisms underlying long-term regeneration and the recovery of neurological functions. Such a research direction may provide the foundation for future therapeutic interventions aimed at supporting sustained improvement in motor function and enhancing neuroplasticity processes that are essential for functional recovery after stroke.