nitroTRKB: saying NO to neuronal plasticity

Tiny molecule, big responsibility: how Nitric Oxide decides who gets to dance with BDNF

WHO:

We are a recently established group at the Translational Neuropsychiatry Unit (TNU), Aarhus University. Our foundation reflects the contributions of many invaluable mentors, students, and collaborators, and the diverse academic environments that shaped our scientific perspective and approach. Our background spans pharmacology and neuroscience

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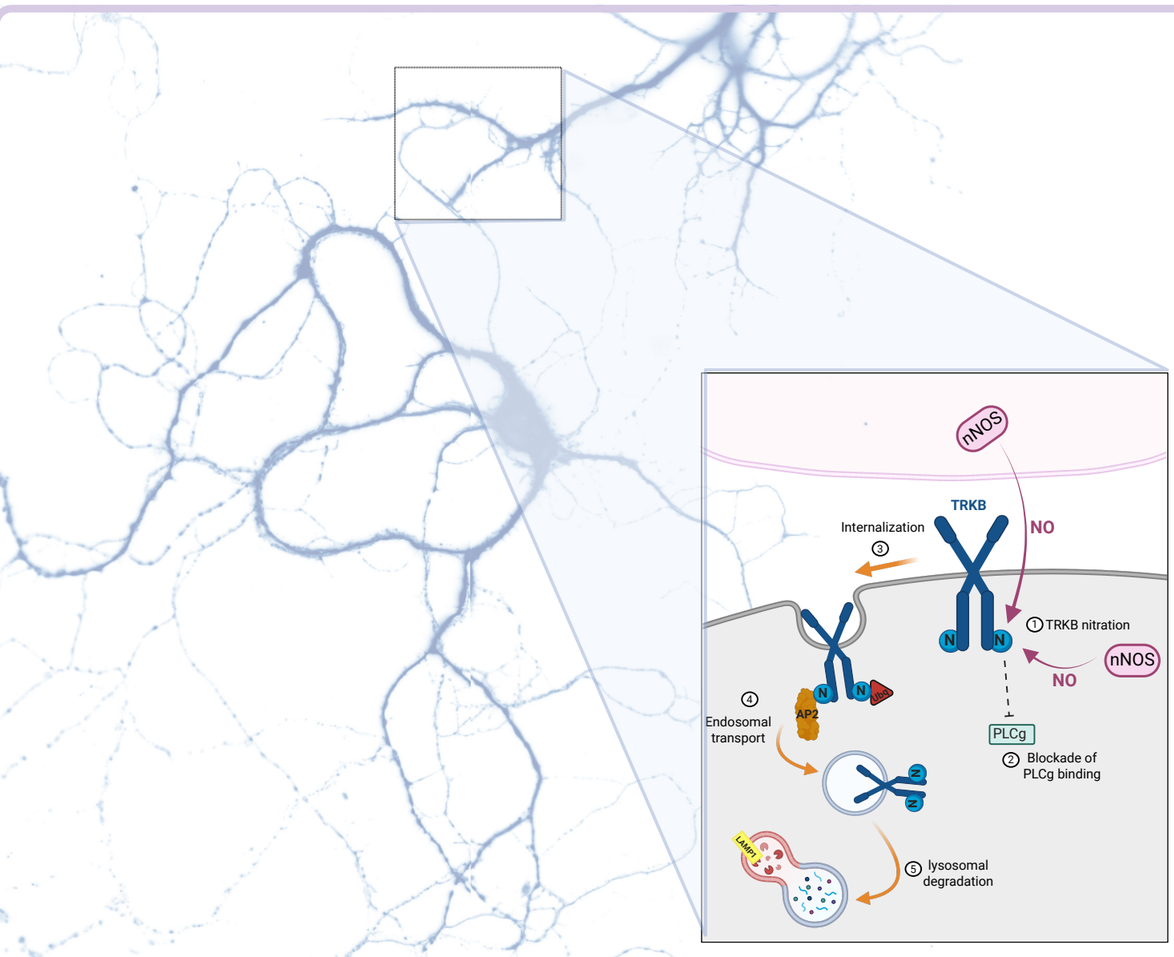
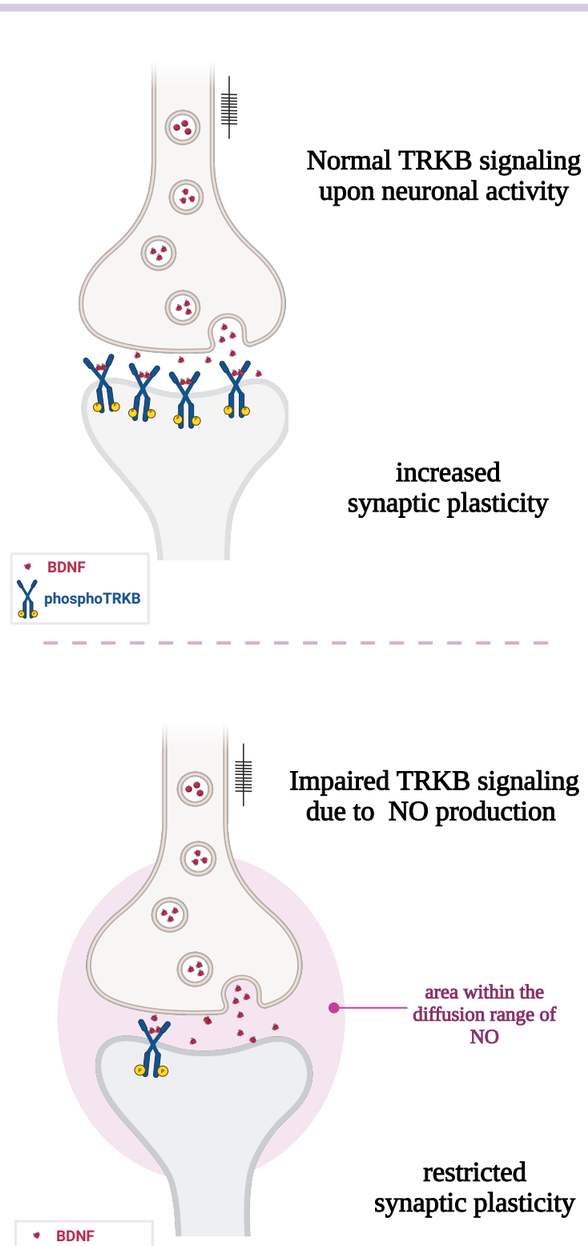
WHAT:
Our group investigates novel molecular mechanisms regulating neural plasticity and develops novel compounds for the pharmacological modulation of these targets. Our current focus is on characterizing the nitration of TRKB as a molecular brake on BDNF-induced plasticity and its role in psychiatric disorders.

WHY:
Neuroplasticity promotes a permissive brain state that allows structural and functional circuit reorganization, thereby facilitating recovery from mental illness. By understanding how the molecular brakes on plasticity operate and how to release them, we aim to develop more effective psychiatric treatments.





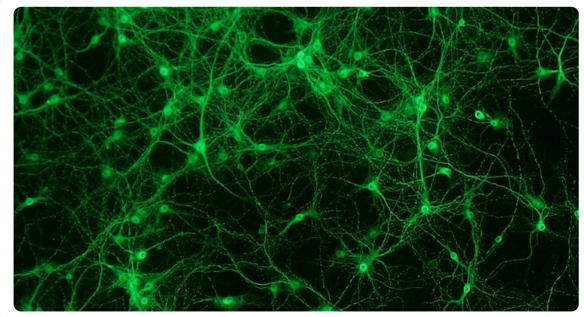
How NO Represse BDNF signaling: working model

nNOS-derived nitric oxide (NO) induces nitration of the TRKB receptor, decreasing its availability on the neuronal surface through endocytosis followed by degradation *(Biojone et al, 2023)*. We hypothesize that, in depressed patients and stress-based preclinical models, NO production restricts TRKB responsiveness even in the presence of normal levels of BDNF release, thereby impairing synaptic plasticity. This mechanism may restrain emotional and cognitive flexibility, thereby entrenching maladaptive patterns of behavior and emotion.

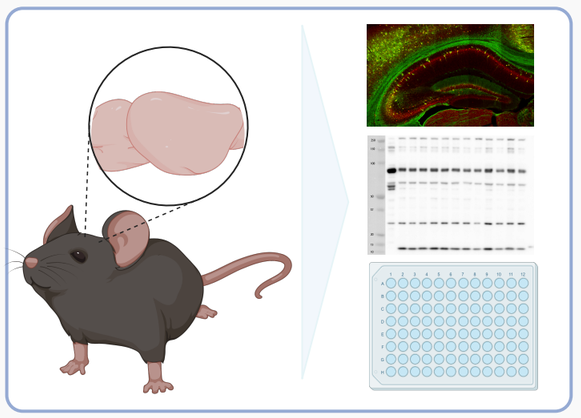
HOW:

To address scientific questions across multiple levels of analysis, we integrate complementary methodological branches:

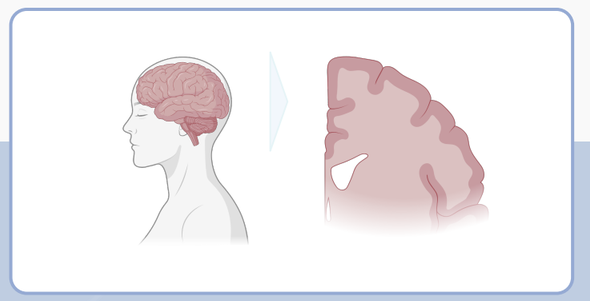
In vitro cellular and molecular approaches (primary **neuronal cultures**, immortalized cell lines) to investigate plasticity at cellular and molecular level.



In vivo preclinical models are used to study **emotional & cognitive flexibility**, and stress response (fear conditioning, reversal learning maze, CSDS, sucrose preference, FST, EPM, TST, ETM, NOR, etc).
We use **mutant mice with either *constitutive* or *conditional* genetic strategies** (e.g., activity-dependent expression of the target protein, or tamoxifen-inducible gene deletion in specific neuronal populations in adulthood), allowing temporal and cell-type-specific manipulation of gene expression.



Clinical samples to assess the relevance of such newly discovered mechanisms in **psychiatric conditions**, such as MDD.



Selected findings highlighting our group's research interests:

- Elucidation of the mechanism underlying PNN-mediated restriction of plasticity via PTPRS receptors. *Context: PNNs are increased by stress and regulate the stability and flexibility of acquired information, including the retention of fear memories.* — **PMID 34366821 & 33293360**
- Prediction and subsequent characterization of nNOS-induced nitration of TRKB as a novel molecular brake on plasticity. *Context: NO is an important regulator of emotional responses, extensively demonstrated in models of stress-related mental disorders.* — **PMID 26350341 & 36682419**
- Elucidation of the signaling pathways in the periaqueductal gray required for the anti-panic effect of nNOS inhibitors. — **PMID 30991078**
- Dissection of mechanisms underlying the plasticity-enhancing effects of classical antidepressants and psychedelics. — **PMID 37280397 & 33606976**

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