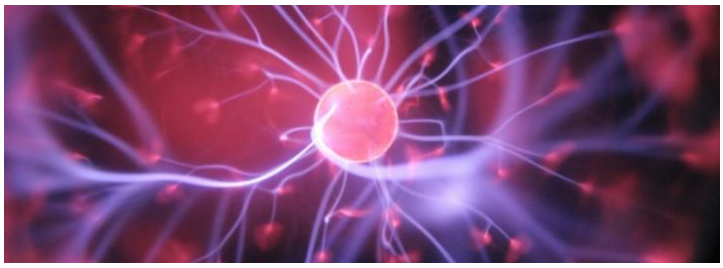
LIÈGE université
Interface Entreprises
Recherche & Innovation

GESVAL s.a.

TARGETING UNFOLDED PROTEIN RESPONSE TO PREVENT NEURODEVELOPMENTAL DISORDERS



KEY ACHIEVEMENTS

- Demonstration that **inhibitors of the UPR activation pathway stand as potential therapeutic molecules to treat or prevent neurodevelopmental disorders**

KEY COMPETITIVE ADVANTAGES

- Set up and validation of an **integrated set of biological models** to study cerebral cortex development or neurodegeneration: **mouse** (Laguesse *et al.*, Dev Cell, **(**2015), 35(5): 553-567; Gladwyn-Ng *et al.*, Nature Neurosci, (2018), 21(1):63-71), **iPSC** (Borgs *et al.*, Sci Rep (2016), Sep 19; 6:33377. doi: 10.1038/srep33377), **human brain and cell cultures** (Gladwyn-Ng, 2018) and **drosophila** (Ryoo, (2015) BMB Rep., Aug;48(8):445-53).

UPCOMING CHALLENGES

- Research and development: mode of administration of UPR inhibitors for treating/preventing neurodevelopmental disorders
- Research and development: validation of the relevance c UPR targeting in neurodegenerative diseases
- Research and development: validation of the relevance c UPR targeting in other virus-dependant congenital microcephaly

INTELLECTUAL PROPERTY

Patent application covering UPR pathway inhibitors for use in the prevention or treatment of neurodevelopmental disorders (WO2018/138358)

The "Molecular regulation of neurogenesis" Lab of the GIGA (University of Liège, Belgium), directed by Dr. Laurent Nguyen, aims at identifying fundamental mechanisms that regulate cerebral neurogenesis.

Based on its expertise in cortical development and Unfolded Protein Response (UPR), the group showed that Zika virus (ZIKV) infects cortical neuronal progenitors during development. This infection dramatically decreases the total neuronal outcome leading to a microcephalic cerebral cortex. The group investigated Zika virus-induced impairments in infected postmortem human fetal brains as well as in cultures of infected human neural stem cells. By intracerebral and intraplacental inoculation of ZIKV in mouse embryos they revealed that ZIKV triggers endoplasmic reticulum stress in cerebral cortex precursor cells in vivo. This perturbs a physiological unfolded protein response within cortical progenitors that control neurogenesis. Thus, ZIKV-infected progenitors have an imbalanced neurogenesis that finally leads to a decrease in the production of projection neurons, the main constituents of the cerebral cortex. Moreover, the sustained endoplasmic reticulum stress in the neurons leads to apoptosis at late stages of cortical development, and this further depletes the number of neurons in infected cortices. Interestingly, administration of pharmacological inhibitors of unfolded protein response counteracts the pathological mechanisms and prevents microcephaly in ZIKV-infected mouse embryos (Gladwyn-Ng *et al.*, Nature Neurosci, (2018), 21(1):63-71).

PARTNERSHIP SOUGHT

- Companies developing therapies/vaccines related to neurodevelopmental disorders
- Companies developing therapies/vaccines related to cortex pathologies
- Companies developing therapies/vaccines linked to ZIKV infection

CONTACT

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