CELSA
Central Europe Leuven Strategic Alliance

CELSA - Collaborative research project - Application form - COVER PAGE

1. Identification of the principal investigator of the CELSA application – co-ordinator of the CELSA research project (from partner university *OR* KU Leuven)
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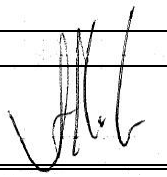
Signature[1]: 

2. Identification of the second investigator
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3. Identification of third and fourth co-investigator(s) (if applicable) Expand table if more than four research units are involved.	
Third co-investigator	**Fourth co-investigator**
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3. Non confidential and public friendly summary (max. 2000 characters)

Project title: Molecular mechanisms underlying Ca2+-signaling dysregulation in Wolfram Syndrome

Summary:

Wolfram syndrome (WS) is a genetic disorder characterized by diabetes insipidus, diabetes mellitus, optic atrophy, deafness, and brain atrophy. Brain abnormalities occur at the earliest stage of clinical symptoms, suggesting that Wolfram syndrome has also a pronounced impact on early brain development. The majority of Wolfram syndrome cases are caused by mutations in the gene Wolfram syndrome 1 (WFS1), which encodes for a protein localized to the endoplasmic reticulum (ER) membrane. However, the clinical symptoms of WS resemble mitochondrial disease symptoms, suggesting strong **mitochondrial involvement**. Furthermore, **Ca^{2+}-signaling dysregulation** has been implicated in WS involving a hyperactivity of the ryanodine receptor (RyR).

The **Estonian team** has recently demonstrated that deficiency of the gene WFS1 triggers an ER-stress cascade, which impairs the function of the IP_3-receptor calcium channel (IP_3R), leading to altered calcium homeostasis. The latter leads to dysregulation of mitochondrial dynamics and function that compromises cell survival. They are now searching for small molecular compounds that could be used to restore ER and IP3R function.

The **Belgian team** on the other hand has focused the last decade on the study of the regulation of Ca^{2+}-transport systems at the ER and mitochondria, including IP_3Rs and RyRs. In these studies, Bcl-2 proteins emerged as critical modulators of these channels in several cell models including neurons, enabling adequate Ca2+ flux through these channels. The team has discovered peptides with direct IP_3R- & RyR-modulatory properties function with therapeutic potential in neurons and in models of Wolfram Syndrome.

Thus, **in this application**, the Kaasik & Bultynck teams want to join forces to scrutinize (i) the molecular mechanisms underlying Ca^{2+}-signaling dysregulation in Wolfram Syndrome, (ii) the potential implication of Bcl-2 (or other Bcl-2-family member) dysregulation as an underlying cause and (iii) the application of BH4 domains as IP_3R/RyR inhibitors as a therapeutic strategy. Both teams have complementary expertise and access to a plethora of tools, methods and models to tackle the triadic interplay between Wolfram syndrome proteins, Bcl-2 proteins and Ca^{2+} signaling.

4. List 5 key words

Wolfram syndrome, Ca^{2+} signalling, mitochondria, neurodegeneration, Bcl-2