PROFILE

The research group at **Rocasolano Institute** uses Crystallography together with Molecular, Biophysical and Biochemical approaches to understand the function of the Neuronal Calcium Sensor 1 (NCS-1) at molecular and atomic level to understand how the protein triggers distinct coordinated cellular responses based on the interaction and regulation of their target proteins.

IRYCIS (Hospital Ramón y Cajal) also participates in the project, where Dr. Alicia Mansilla works on the research as a Biologist.

SPEAKER

Dr **María José Sánchez** has a Master Degree in Chemistry (2000) and a PhD in Crystallography (2005). She has carried out a 3-year postdoc at the MRC-LMB (Cambridge, UK) working on cancer-related proteins combining structural, biochemical and cellular approaches to understand their function. In 2009, she moved back to Spain as a Ramón y Cajal Fellow. Since then, she lead projects at Institute Rocasolano (CSIC) on calcium signaling processes in mammals and in plants with biomedical and biotechnological interest.

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PRODUCT

Synapse modulators targeting the NCS-1/Ric8a complex for neurodegenerative disorders

MECHANISM OF ACTION

The product is a small molecule, 3b, that binds to the neuronal calcium sensor NCS-1 and strengthens the interaction between NCS-1 and its target protein Ric8a (a G-protein activator) has been found (Canal-Martín et al., Nat. Comms 2019). Tests performed in fly and mouse models of Alzheimer´s and Huntington´s diseases, have shown significant improvement in synapse number and cognitive characteristics associated with these neuronal disorders. Structural studies have shown at atomic level how 3b is recognized by NCS-1 and has allowed to propose a mechanism of action.

The NCS-1/Ric8a complex regulates in an antagonistic manner synapse number and probability of neurotransmitter release. The formation of this complex is essential to raise up synapse number in normal brain. Given that during neuronal degeneration there is a loss of synapses, a molecule able to enhance the protein complex, would increase synapse number to correct certain deficits associated with the loss of neuronal connections and therefore, improve cognitive abilities. We have demonstrated that this is the case of compound 3b, it targets NCS-1 and stabilizes a conformation that favours the interaction with Ric8a, enhancing complex formation. This is translated to an increase in synapse number, as shown with Alzheimer´s flies, and an improvement in cognitive characteristics both in Alzheimer´s (flies) and Huntington´s (mice) disease models.

TARGET INDICATIONS

Treatment of neurodegenerative disorders such as Alzheimer's, Huntington's or Parkinson's diseases characterized by a decrease in the number and efficacy of synapses that precedes neuronal death.

CURRENT STATUS

- Proof of concept in an animal model of Drosophila with pathology hallmarks reminiscent of Alzheimer's disease including defective locomotion, memory loss or reduced longevity.
- Compound 3b increases the number of synapses to normal levels, exclusively in the presence of a synaptic pathology, which is an essential requirement for any treatment directed to synapses.
- Proof of concept in Huntington's mice (HD). Promising preliminary experiments showed an improvement in locomotor activity in HD mice treated orally with compound 3b.
- Currently working on improving Blood Brain Barrier permeability of compound 3b. New compounds are currently being tested and will be validated in animal studies.

INNOVATIVE ASPECTS

- Despite the best efforts, neurodegenerative diseases do not have effective treatments. Research has focused on specific targets that are relevant for each pathology.
- This new approach is novel and general, as it focuses on the functional unit of a neuron, the synapse, which is altered in all these disorders. NCS-1/Ric8a is the first target known to control the probability of neurotransmitters release by each synapse, as well as the synapse number.
- This makes it the first strategy tackling both neuronal features at the same time.

IPR

This technology is protected by P201830933 "Acylhydrazones for the treatment of neurological diseases". Spanish priority granted on 03.12.2020 and published with reference ES 2 750 924 B2. Owned 80% CSIC and 20% FIBioHRC. The patent protects a group of compounds and their use for the treatment of neurological diseases.

PCT/ES2019/070649 requested on the 25th October 2019. Owned 70% CSIC and 30% FIBioHRC. The ISR issued is favourable. It enters phases on 03/27/2021. CSIC and FIBioHRC will enter on EU, USA, AUS, CA.

PARTNERING OPPORTUNITIES

In our commitment to develop this therapy we will seek funding and partnering with pharma and biotechs, to carry out the preclinical studies. Due to the contribution of Ramon y Cajal Research Institute we are able to manage and run clinical trials. We are also having conversations with international Venture Capital firms for funding.