PROFILE

Researchers at **CIB Margarita Salas** study the structure and organization of living matter and its processes, seek to understand the bases of disease and discover experimental treatments. Translational Medicinal and Biological chemistry group is focused on the design, synthesis, biological evaluation, study and further optimization of structurally diverse chemical entities as innovative drugs with novel mechanism of action Our group applies medicinal chemistry programs combining classical and computational medicinal chemistry to discover and develop new candidates for unmet severe pathologies such as neurodegenerative and infectious diseases.

SPEAKER

Prof **Ana Martinez**'s research is focused on drug discovery and development for neurodegenerative and infectious diseases since more than 30 years ago, caring the close contact with biopharmaceutical companies for technology transfer. She has been NeuroPharma's R&D Director for six years and more recently, founder of ANKAR PHARMA. She is author of more than 275 scientific publications and thirty active patents in the field. She is the head of Translational Medicinal and Biological Chemistry group..

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PRODUCT

CDC7 inhibitors for ALS and FTD therapy

MECHANISM OF ACTION

Our candidates are CDC7 inhibitors, a conserved ser/thr kinase involved in cell cycle, and recently identified to be involved in in vivo TDP-43 phosphorylation. Candidates have IC50 values in submicromolar range and are AT-competitive but selective in a panel of 40 structural related kinases. They are able to cross the blood brain barrier.

Brain permeates small molecules able to recover TDP-43 homeostasis (phosphorylation decrease and nuclear localization) in celular models, including human lymphoblast from ALS and FTD patients.

TARGET INDICATIONS

Neurodegenerative diseases, mainly amyotrophic lateral sclerosis and frontotemporal dementia, but also CDC7 inhibitors can play an important therapeutic role in other diseases where homeostasis of TDP-43 is lost. These may include rare disease such as Alexander' and Perry' diseases but also the prevalent limbic-predominant age-related TDP-43 encephalopathy (LATE)

CURRENT STATUS

The following are last tasks already done and main achieved goals:

- Reverse chemical genetic approach to identify hits able to inhibit CDC7
- Med Chem program to optimize the hit. Focus on increase biological potency and blood brain barrier penetration. More than 50 different heterocyclic related small molecules with submicromolar potency.

- Recovery of TDP-43 homeostasis (reduction of hyperphosphorylation and recovery of nuclear localization) both in neuroblastoma cell lines and lymphoblasts from ALS and FTD patients.
- Decrease of TDP-43 phosphorylation in vivo (C. elegans model)
- Confirmed in vivo penetration into CNS and spinal cord TDP-43 phosphorylation reduction after chronic administration in a transgenic TDP-43 murine model.

INNOVATIVE ASPECTS

- Up to now, only some antibodies targeting TDP-43 are under clinical evaluation as a strategy to alleviate TDP-43 pathology. In preclinical stage, CK1 inhibitors have shown also important biochemical changes in a TDP-43 transgenic ALS model but no modification of phenotypic behaviour. By the moment, phenotypic differences among these two different families of compounds are unknown. We are studying muscle changes looking for these differences.
- The advanced candidate is able to decrease TDP-43 phosphorylation in two different TDP43 transgenic animal models: C. Elegans and mice. Chronic administration for 21 days of our candidate in the PrTDP43 A315T mice ameliorates phenotypic behaviour and decrease TDP-43 phosphorylation in spinal cord.

IPR

Compounds are protected by two independent patents. The first one (ES20170322) is now granted in Spain (ES2686909 (B1)) and under study in national phases (AU2018240527(A1); US2020093828 (A1) and EP3604310(A1)). The second one (ES20180921) is also granted in Spain (ES2749743(B2) and just published in international phases (WO2020058558 (A1)).

PARTNERING OPPORTUNITIES

We are looking for a partner to work in co-development (private-public collaboration) or some company interested in licencing the patent and develop the technology.