Technology Offer CSIC/AH/048

Identification of therapeutic candidates for Congenital Central Hypoventilation Syndrome (CCHS)

An *in vitro* screening method by NMR spectroscopy of potential therapeutic compounds for Congenital Central Hypoventilation Syndrome (CCHS). The method is based in the identification of active agents that inhibit secondary structure changes in PHOX2B transcription factor.

Intellectual Property

PCT application filed

Intended Collaboration

Licensing and/or co-development

Stage of development

Proof of concept

Contact

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Market need

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder caused by heterozygous mutations in the PHOX2B gene, which results in life-threatening breathing difficulties. PHOX2B is a transcription factor essential for the development of the autonomic nervous system, particularly in brainstem respiratory centers. In CCHS, mutations in PHOX2B cause the protein to aggregate in the cytoplasm, impairing its ability to function as a transcriptional regulator. Currently, the only available treatment for CCHS is assisted mechanical ventilation. As a result, identifying molecules that can alleviate the breathing difficulties associated with PHOX2B loss of function in CCHS is of utmost importance.

CSIC solution

PolyAlanine mutations in PHOX2B are a major cause for CCHS, where triplet duplications, leading to an expansion of +4 to +13 additional residues of a 20-polyalanine (polyAla) stretch, account for approximately 90% of causative PHOX2B variants. It has been determined that polyAlanine expansions in PHOX2B cause the misfunction of PHOX2B by recruiting the protein into solid, irreversible macromolecular condensates.

To identify compounds with potential therapeutic effects on CCHS symptoms, an NMR-based method has been developed based on inhibition of PHOX2B changes in secondary structure therefore avoiding the formation of PHOX2B aggregates.

Competitive advantages

- Several constructs of PHOX2B were generated containing different protein regions to enhance solubility and minimize spectral complexity
- Structural changes in expanded PHOX2B triggering irreversible loss of function are monitored in a straight forward manner, enabling a mid-throughput screening of therapeutic compounds
- The combination of NMR and light scattering methods provide an unparalleled platform to determine the validity of potential therapeutic compounds