PHD IN Neuroscience, curriculum in Neuroscience & Neurotechnologies

TITLE: Pharmacological treatment of the newly identified CTNNB1 syndrome
TUTOR: Valter Tucci and Angelo Serani

BACKGROUND

CTNNB1 syndrome is a novel syndrome caused by the complete or partial alteration of one allele of CTNNB1. Clinical features of the syndrome include developmental delay, intellectual disability (ID), speech impairment, autistic behaviors, microcephaly, and reduced motor capabilities, as well as characteristic craniofacial features and ocular anomalies. Our group, together with the Clinical Proteomics Department of the "G. Gaslini Hospital" belongs to a multidisciplinary network focused on exploring all possible treatment strategies for this disease.

DESCRIPTION

We aim to explore novel potential treatments of CTNNB1 syndrome by investigating the effect of small molecules from a library that we designed in stabilizing the interaction between the two molecules β–catenin and N-cadherin, which we have previously shown to be decreased in the Batface (Bfc) mouse, a preclinical model of CTNNB1 syndrome. In collaboration with the Gaslini Hospital, we will use proteomic approaches, accompanied by the characterization of metabolites and lipids, which can generate insights and indications for drug discovery. We will also test a novel programmable epigenetic editing technology, designed in one of our labs, to modulate the expression of possible off-targets misregulated by the identified molecules.
The project includes three main parts:
1) Molecules in the library will be screened in neurons cultured in vitro to test their efficacy in correcting the structural and functional changes caused by impaired β-catenin interactions with N-cadherin, taking into account the crucial role of the β-catenin signalling and modulating any possible off-target with a target-specific epigenetic writer.
2) The molecules and the epigenetic writers that show modulatory effects in cultured Bfc neurons will be tested in neurons differentiated from iPSCs that are isolated from patients with CTNNB1 syndrome.
3) Then, we will select the treatment that shows the highest efficacy and most minor toxicity from the in vitro screening, and we will perform molecular analysis of proteins, metabolites, and lipids combined with a thorough functional study that will help define potential drug targets as well as monitoring of its efficacy by features critically associated with disease and treatment.

REFERENCES

- Italian CTNNB1 Syndrome Association (https://www.ctnnb1italia.it/)
- Tucci, V., et al., Dominant beta-catenin mutations cause intellectual disability with recognizable syndromic features. J Clin Invest, 2014. 124(4): p. 1468-82.

REQUIREMENTS

We are looking for highly motivated candidates with a degree in Biology-related fields that are keen to work in an interdisciplinary environment.
Experience in iPS/ES cells or primary cultures, molecular biology techniques, RNA/DNA handling and analysis and, microscopy are expected and knowledge or expertise in mouse models handling, FACS or, bioinformatics are considered a plus.
All candidates must be able to talk, listen and write in English at an academic level.

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