18 APRIL
at 2 p.m.
Room A110, *Povo 1*

UNIVERSITÀ DI TRENTO
Dipartimento di
Biologia Cellulare, Computazionale e Integrata - CIBIO

CIBIO EXTERNAL seminar

IDENTIFICATION OF NEUROPROTECTIVE GENES AND DRUGS USING A C. ELEGANS MODEL FOR SPINAL MUSCULAR ATROPHY

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Spinal muscular atrophy (SMA) is a neurodegenerative disease caused by mutations in the survival motor neuron gene (Smn1). **Smn1 is involved in mRNA splicing**, but motor neurons seem highly sensitive to perturbations in this disease. Why motor neurons are more affected to splicing alterations in SMA is still debated. Importantly, in the last years three different drugs have been approved by FDA for SMA treatment, nevertheless they resulted to be not efficacious for all the conditions or all types of SMA patients. So, to 1) understand the specific role of Smn1 in mRNA splicing in motor neurons and 2) identify new potential therapeutic molecules to be used in combination with actual treatments, we took advantage of our C. elegans SMA model. In this model smn-1, the Smn1 ortholog, is specifically silenced in motoneurons (MNs), causing an age-dependent neurodegeneration.
Through the RNA-sequencing of induced pluripotent cell-derived motoneurons (iPSC-MNs) from SMA patients we identified differentially spliced genes, enriched in RNA motif 7. This motif is specifically bound by SYNCRIP, a spliceosomal component. We demonstrated that **hrpr-1/SYNCRIP and smn-1 genetically interact in MNs in C.elegans** and that they regulate the expression and the splicing pattern of ret-1/RTN in C. elegans, in SMA mice and iPSC-MN. Then, we successfully used the same model for an unbiased semi-automated drug screening of an FDA-approved library, that allowed us to analyse 384 compounds/week in triplicate. **By using this approach, we identified four new exciting leading compounds counteracting smn-1 related neurodegeneration in C. elegans**. Our results demonstrate that we are **able to isolate genetic and pharmacological hits that suppress MNs degeneration** with an unbiased approach, delivering major progresses in defining new treatments for preventing the neuronal death caused by Smn1/smn-1 loss in motoneurons.

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