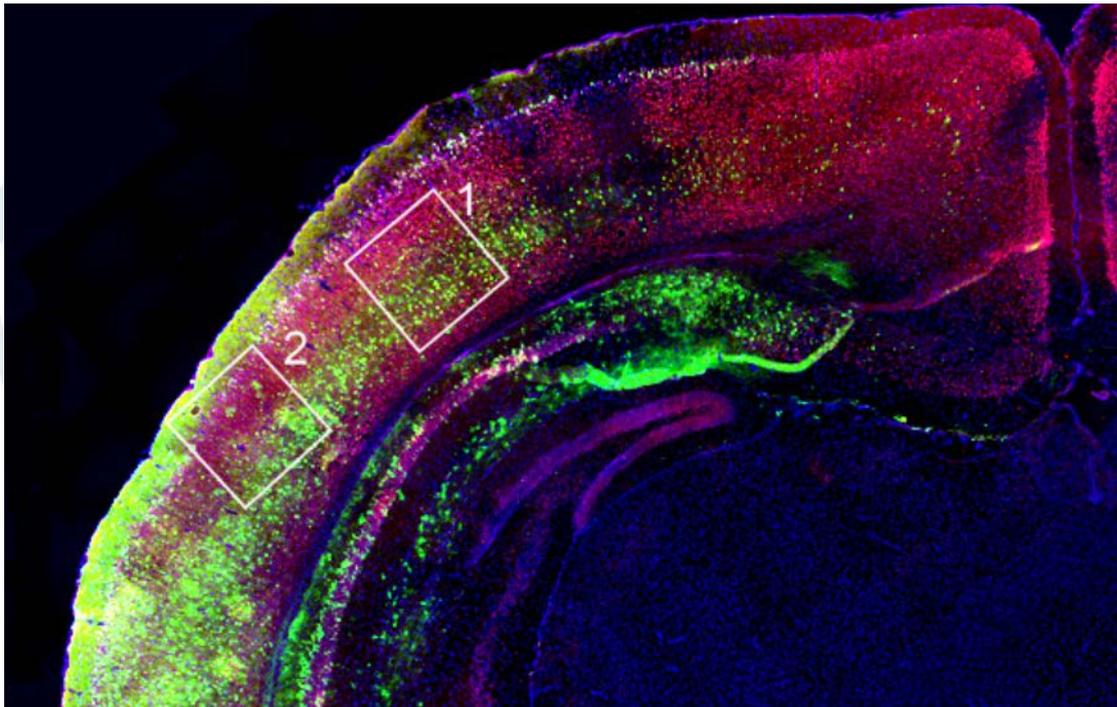




PRESS RELEASE

## Rett Syndrome: a new therapeutic project to grant a hope



**Significant funding for a SISSA research concerning innovative molecular technologies. The Cerebral Cortex Development Lab of Trieste's Institute is going to benefit from a two-year grant**

29 September 2017

A novel research path for a rare variant of Rett Syndrome might turn into the therapy for several other neurological pathologies. This is what is hoped for by the project of the Cerebral Cortex Development Lab of Trieste's SISSA, recent winner of a funding provided by the **Jerome Lejeune Foundation**, a French institution engaged, among other things, in supporting research on Rett Syndrome. A progressive pathology that strikes the nervous system, especially of girls, the disease is associated with the mutation of different genes.

In particular, in Italy a variant linked to the alteration of the **FOXP1** gene has been discovered. It is no coincidence that our country is extremely committed to the



search for a cure concerning this specific variant, which manifests more precociously, strikes males as well, and is even rarer than the classic form.

If an illness with such a low incidence hardly attracts the attention of pharmaceutical houses, the need to provide an answer to those affected by it has not eluded the French Jerome Lejeune Foundation. The body that funds the research dedicated to mental disorders of genetic origin has selected the "*RNAa therapy of Rett-syndrome-associated FOXP1 haploinsufficiency*" project as winner of a two-year grant. The research project has been proposed by **Cerebral Cortex Development Lab of Trieste's SISSA**, recent winner of a funding provided by the Jerome Lejeune Foundation, led by Antonello Mallamaci. The results of the funded research are going to yield key information for the targeted treatment of the Rett Syndrome variant associated with the haploinsufficiency of the FOXP1 gene, i.e. lack of a single copy of the gene, whereas there are normally two.

However, the protocol that will be put in place might be useful for the treatment of a broad spectrum of other rare neurological diseases. The aim of the project, in fact, is to develop a **new therapeutic design** capable of "repairing" the neuropathogenic haploinsufficiency for specific genes. It is a condition that links together a significant number of pathologies, inherently rare, yet very serious and especially bereft of any therapy whatsoever. The heterogeneity of the mechanisms lying at the root of this spectrum of diseases and their scarce individual prevalence make it hard to develop treatments. Because of this, it would be necessary to develop a general approach applicable in an "industrial" manner to all the cases. Unfortunately, not even the most modern genomic engineering tools, such as the popular enzymes of artificial restriction CRISPR, TALEN or ZF, or the programmable transcriptional factors based on the same platforms, are capable of furnishing an adequate response for this type of pathologies.

"In order to address that problem, we may proceed to delicately stimulate the allele of the gene spared by the mutation. That may be done through a **small molecule of RNA**, capable of stimulating its transcription and accordingly termed aRNA", suggests Mallamaci. To that end, a small specific RNA, capable of promoting the transcription of *Foxp1*, in vitro or in the brain of a living animal, has already been synthesized and validated.

Since the genic regulation of FOXP1 is based on a fine regulation mechanism, it will be essential to optimize the in vivo administration of the aRNA, in such a manner as to obtain a precise modulation of the magnitude of genic expression.

"Another step awaiting us is verification of the ability of the molecule to restore the normal morphological and functional properties in the neurons of mice that possess



a single copy of *FOXG1*”, added the SISSA professor. Moreover, relying on a technology developed in SISSA by the group of Prof. Gustincich, the Mallamaci laboratory is also **fine-tuning** a further gene stimulation system, based on a small RNA capable of **promoting the translation**. Hence, another method to increase the expression of *Foxg1* might be founded on the stimulation of its translation. “We think that the **combination of different techniques** might ensure effectiveness along with a low interference with other genes potentially sensitive to the stimulation”, explained the head of the Cerebral Cortex Development Lab.

“Of course, the implementation and adaptation of this strategy in patients must be studied accurately”, added Mallamaci. “We will need further analyses to establish whether the therapy is going to alter the behavioural or cognitive functions”.

From the proposed approach, we expect a robust proof of feasibility, molecular instruments for the realisation of a protocol suited to the patients, and a **general paradigm** that lends itself to being used as adequate response to several neuropathogenic haploinsufficiencies.

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#### PICTURE:

Credits: Mouse Cortex section stained in the Cerebral Cortex Development Lab of Trieste’s SISSA

#### CONTACTS:

Nico Pitrelli

[pitrelli@sissa.it](mailto:pitrelli@sissa.it)

Tel. +39 0403787462

Cell. +39 3391337950

Giulia Annovi

[gannovi@sissa.it](mailto:gannovi@sissa.it)

Tel. +39 0403787231

Cell. +39 3393132406



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