IEO
Istituto Europeo di Oncologia

Repositioning of histone deacetylase inhibitors to treat core symptoms of Autism Spectrum Disorder

Introduction

Autism Spectrum Disorder (ASD) comprises a **highly prevalent** group of **neurodevelopmental disorders** affecting almost 1% of children. Children diagnosed with ASD exhibit **core symptoms** being impairments in language and social interaction coupled to stereotyped behaviors and, in many cases, the co-occurrence of varying degrees of intellectual disability. ASD is phenotypically and genetically **highly heterogeneous** with over 400 identified causal **genetic alterations**. The convergence of core symptoms across the genetic spectrum of ASD suggests that few paradigmatic syndromes might make the understanding of ASD causes and therapeutic interventions feasible. **Drug repositioning** has the potential to provide new therapeutic alternatives through the "new" use of "old" drugs, reducing clinical development time compared to the development of new molecules. The team led by **Prof. Giuseppe Testa** aims at the identification of new therapeutic interventions for ASD core symptoms, in particular in the **7q11.23 microduplication syndrome** (7DupASD), a **rare autistic syndrome** characterized by duplication of the chromosomal region 7q11.23 and considered paradigmatic of the entire autistic spectrum.

Medical Need

There are **no medications** that can cure ASD or even treat the **core symptoms**. The most common prescribed pharmacological classes are anti-psychotic drugs, antidepressants, stimulants, and anticonvulsants.

Solution

The group of Prof. Testa conducted an **high-throughput drug screening** of 1500 compounds, including central nervous system compounds, epigenetic modulators and other experimental substances, on neurons of the cerebral cortex derived from reprogrammed stem cells of patients affected by 7DupASD, the so called **"Disease Avatars"**. Three **histone deacetylase inhibitors** (HDACi) have been identified that are able to reduce, at both transcriptional and protein levels, the **expression of the GTF2I gene** that is duplicated in 7DupASD patients and has a key pathogenetic role. HDACi are already used in various types of cancers, including brain tumors, and are considered potential treatment for neuropsychiatric disorders. ***Proof-of-Concept*** studies are underway to test whether these inhibitors are able to revert the main ASD core symptoms in mouse models characterized by the same genetic alterations as 7DupASD.

Advantages

- **Drugs** already approved in **oncology**;
- **First pharmacological treatment** for core symptoms of autistic syndromes including 7DupASD;
- **Reference hub** and unique **know-how** for **reprogrammin**g of pluripotent stem cells from autistic patients;
- Collaboration with international clinical centers for the recruitment of 7DupASD and other autistic patients;
- ***Proof-of-Concept*** studies funded by ERC PoC grant
- **Patent Application** file (EP20196503.5, co-owned by IEO, IFOM and University of Milan)

Opportunity

IEO is seeking industrial partners interested in the **preclinical** and **clinical development** of **HDAC inhibitors** for the treatment of **ASD**.

Group Leader

Giuseppe Testa is Professor of Molecular Biology at the University of Milan, Principal Investigator at IEO and Head of the Centre for Neurogenomics at the Human Technopole. His laboratory spearheads cell reprogramming, brain organoids and single-cell multi-omics to develop physio-pathologically meaningful models of both neurodevelopmental disorders and cancer. A three times awardee of the European Research Council (ERC), he has published in leading peer reviewed journals and serves on the advisory boards of several research networks and academic societies.

References

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