IEO
Istituto Europeo di Oncologia

Histone demethylases inhibitors to ameliorate cognitive-behavioral deficits in rare subtype of Autism Spectrum Disorders

Introduction

Autism Spectrum Disorders (ASD) is a group of incurable, developmental disabilities which affect the brain and are usually diagnosed between the ages of 18–24 months. ASD encompasses a **broad spectrum of disorders** whose core symptoms vary among the affected individuals that have often impairments in the language and social communication and display anxiety and mental retardation. **Prof**. **Giuseppe Testa's** research program is aimed at identifying the molecular mechanisms and potential therapeutic intervention of certain subtypes of ASD, in particular the **7dup-Autism Spectrum Disorder** (**7dup- ASD**), where the **abnormal duplication** of the genomic region of the **chromosome 7q11.23** has been recognized as the cause. 7Dup syndrome has a prevalence between 1:12.000-20.000, thus qualifying it as a **rare disease** (ORPHA96121). Individuals affected by 7dup-ASD show language impairment and hyposociality along with other characterizing aspects of ASD.

Medical Need

There are currently no effective pharmacological therapies for autistic patients, and only very partial improvements by the extremely costly intensive behavioral therapies. To date, the main challenges for the development of efficacious treatments of ASD have been both the **lack of reliable models** to study cognitive functions and human social interaction and the **inadequateness of high-throughput screenings** for the identification of drugs. Therefore, there is a strong unmet medical need for **effective products modulating specific neuronal pathways** implicated in the onset of such diseases.

Solution

For the first time, Prof. Testa's lab has generated **7-Dup patient-specific dysfunctional neurons**, from pluripotent stem cells reprogrammed from patients' skin fibroblasts, representing a relevant **model** exploitable for the identification of **druggable targets** and for the **discovery of new drugs**. Indeed, the interaction between the transcription factor GTF2I and the **histone demethylase LSD1** (Lysine-specific demethylase 1) has been identified as a **new potential therapeutic target** playing a critical role in the cognitive profile of 7Dup-ASD patients. These findings allowed to identify **IEO proprietary anti-LSD1 compounds as potential novel 7dup-ASD treatment** whose efficacy **in reverting the disease phenotype** has been proved both in ***in vivo*** and **3D-organoid models.**

Advantages

- **First-in-class** therapeutic molecule for 7Dup-ASD
- Availability of **patient-derived *in vitro* 3D models and genetic mouse models** for 7Dup-ASD
- Drug discovery **platform** for other subtypes of ASD
- **Patent application** (PCT/EP2015/077659)
- **Leadership** in modeling diseases through cell reprogramming
- **Proof of concept** validation completed with the support of **ERC PoC grant.**

Opportunity

IEO is seeking industrial partners interested in the **preclinical** and **clinical development** of IEO proprietary **LSD1 inhibitors** for the treatment of **ASD**.

Group Leader

Giuseppe Testa is Professor of Molecular Biology at the University of Milan and Principal Investigator at IEO. His laboratory focuses on the exploitation of the potential of cell reprogramming to develop physiopathologically meaningful models of both neurodevelopmental disorders and cancer. He was awarded with the European Research Council (ERC) Consolidator grant and ERC Proof of Concept grant. He has published in leading peer reviewed journals and he serves on the advisory boards of several research networks and academic societies.

References

Adamo et al. Nature Genetics 2015

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