TITLE

Reactivation of the dormant wild-type allele of MECP2 as a therapy for Rett syndrome: screening of epigenetic compounds

DESCRIPTION

Rett Syndrome (RTT) is an X-linked neurodevelopmental disorder caused by mutation in the MECP2 gene. Heterozygous female patients are a somatic mosaic of two populations of cells due to X chromosome inactivation (XCI), that silences one of the two X chromosomes in female mammals [1]. In so, females tolerate X-linked mutations better than males, having a WT allele expressed in a proportion of cells that equals to 50%, if XCI occurs randomly and the mutant cells do not present any advantage or disadvantage in survival. The severity of RTT varies with the proportion of cells expressing the WT or the mutant MECP2, depending on XCI patterns in heterozygous females [2]. Reversibility of XCI has been recently shown in somatic cells. Therefore, it is theoretically possible to re-activate the WT XCI-silenced allele of a mutant gene to counteract the pathological phenotype. Re-expression of the protein in Mecp2-null mice with symptoms of Rett can reverse the neurological defects [3]. Accordingly, approaches to reactivate the endogenous WT copy of the MECP2 gene in heterozygous human patients with RTT might provide a potential avenue to treat this disease.
Our experimental strategy consists in cell-based screening of epidrugs for MECP2 reactivation. We propose to develop (i) a dual color Xi-reporter system of double knock-in mouse embryonic fibroblasts and (ii) an autofluorescence-based cell assay as tools for (iii) automated molecular screening aimed to the identification of molecules that specifically reactivate the silent-Mecp2 allele. More generally, we propose that the inactive X might be used as a backup to replace expression of the disease(s) allele on the active X chromosome. We believe that this research would open mid-term perspectives for new pharmacological treatments of neurological symptoms and brain damages in RTT. We are confident that our experimental design would be useful for other X-linked and/or imprinted diseases.

SELECTION CRITERIA

Eligibility Criteria

- Academic degree: Applicants shall have a master degree in **Life** or **Natural sciences** (e.g. Biology, Biochemistry, Biotechnology, Molecular Biology, or related fields), corresponding to the second level of studies.
- Mobility rule: There will be no nationality restrictions. Applicants can be from any Country. However, according to the mobility rule, at the time of the application deadline researchers should not have resided or carried out their main activity (work, studies, etc.) in Italy for more than 12 months in the 3 years immediately prior to the reference date. Compulsory national service and/or short stays such as holidays will not be taken into account.
- Research experience: Applicants shall, at the time of the application deadline, be in the first four years (full-time equivalent research experience) of their research careers and not yet awarded a doctoral degree.

Full-Time Equivalent (FTE) Research Experience will be determined from the date when a researcher obtained the degree which would formally entitle him or her to embark on a doctorate, either in the country in which the degree was obtained or in Italy, irrespective of whether or not a doctorate is or was ever envisaged.

Evaluation Criteria

Step 1 -Evaluation of documentation provided by the candidate: a) Academic record and training b) Research activities c) CV/motivation letter; d) Level of English; e) Reference letters.

Step 2 - Interview: a) Scientific knowledge in the field of interest; b) Research experience in the field of interest c), Motivation; d) English proficiency.

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