NEW PROSPECTS FOR RESTORING BRAIN DEVELOPMENT IN DOWN SYNDROME

RESEARCH GROUP:

Coordination

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Assicurazioni Generali

ABSTRACT

Down syndrome (DS) is a genetic condition (incidence: 1 out of 800/1000) caused by triplication of chromosome 21. The consequence of this chromosomal alteration is a form of disability marked by a variable degree of cognitive, physical and motor impairment.
In a recent study, the group from the University of Bologna coordinated by Prof. Renata Bartesaghi came up with the idea of exploiting the embryonic period and the immediately post-natal period to attempt to correct the neurogenesis defect of DS right from the outset.
Through clinical trials and laboratory tests, the project aims to demonstrate the validity of this hypothesis on young pediatric patients.

The international research project involves the cooperation of several research groups:

1) Group coordinated by Prof. Renata Bartesaghi from Alma Mater Studiorum – University of Bologna;
2) Group coordinated by Prof. Mariagrazia Grilli of the University of Eastern Piedmont;
3) Group coordinated by Prof. Pietro Strisciuglio, Prof. Carmela Bravaccio and Prof. Iris Scala of the University of Naples Federico II;
4) Group coordinated by Prof. Marie-Claude Potier of the Institut du Cerveau et de la Moelle épinière, Paris;
5) Group coordinated by Prof. Carmen Martinez Cué of the University of Cantabria, Santander, Spain.

The project, which began in March 2015 and which will run for three years, was made possible thanks to a grant of 1.5 million EUR from the Fondazione Assicurazioni Generali.

THE PROJECT

WHY THIS PROJECT IS IMPORTANT

Can cognitive disability in Down Syndrome patients be prevented?

Down syndrome (DS) is a genetic condition (incidence*: 1 out of 800/1000)* caused by triplication of chromosome 21.
Cognitive disability is the inevitable hallmark and the most invalidating aspect of Down Syndrome. Cognitive disability is caused by a severe reduction in neurogenesis (generation of nerve cells) leading to cerebral hypotrophy. This defect begins during the embryonic period, a critical time during which most of the neurons in the brain are formed.

Currently there is no treatment for this disability: the proposed project aims to identify therapies that are able to **restore brain development and cognitive performance in DS.**

THE IDEA

In a recent study, the group from the University of Bologna, coordinated by Prof. Renata Bartesaghi, came up with the idea of exploiting the embryonic period and the immediately post-natal period to attempt to correct the neurogenetic defect of DS right from the outset.

A consolidated model of DS was used for this purpose, presenting many analogies with the human condition. Exploiting the trisomic model, the group from the Alma Mater discovered that prenatal or immediately post-natal therapy with **Fluoxetine**, a widely used antidepressant, can fully restore neurogenesis and cognitive performance. This discovery aroused great interest among the scientific community as it offers **the first demonstration that brain defects caused by the trisomic condition are reversible.**
Considering the time span of cerebral development, we can hope to restore brain development in DS through **early therapy.** Therapy at adult stages of life may improve the brain, though to a much more limited extent.

THE WORK GROUP

This international project will be conducted by the following research groups:

- Group coordinated by Prof. Renata Bartesaghi, University of Bologna, Bologna, Italy;
- Group coordinated by Prof. Mariagrazia Grilli of the

University of Eastern Piedmont, Novara, Italy;

- Group coordinated by Prof. Pietro Strisciuglio, Prof. Carmela Bravaccio and Prof. Iris Scala, University of Naples Federico II, Naples, Italy;
- Group coordinated by Prof. Marie-Claude Potier, Institut du Cerveau et de la Moelle épinière (ICM), Paris, France;
- Group coordinated by Prof. Carmen Martinez Cué, University of Cantabria, Santander, Spain.

The scientific qualification of the participants and the involvement of scientists with consolidated experience in the field of neuroscience and in DS constitute a strong point of the project.

OBJECTIVES

This research has two objectives:

1. To establish whether Fluoxetine is effective in children with DS

Fluoxetine is an antidepressant prescribed to adults and also to children. We do not know, however, whether this drug, which is so effective in the model, is equally effective in children with DS. Only clinical trials will be able to establish its effectiveness on pediatric patients.

Planned activities:
Having obtained a positive response from the ethics committee, a pilot study will be conducted at the University of Naples Federico II, with children with DS aged between 5 and 10 years. Although the process of neurogenesis has ended, this is a critical period for neuronal maturation and the formation of neuronal synaptic connections. In order to establish the effectiveness of this treatment on brain development we will compare children treated with fluoxetine and children in the same age group treated with a placebo.

2. To identify alternative drugs to fluoxetine that are equally effective

Given that we now know that it is possible to act pharmacologically on brain development in DS, it is crucial to identify other molecules that can promote neurogenesis. The identification of a series of drugs that are able to correct alterations in brain development will allow us to select the most

effective and safest drugs for treating cognitive disability in children with DS.

Planned activities:

1. Verify whether drugs that can improve cerebral neurogenesis are able to improve/restore neurogenesis in the trisomic model;
2. Perform in-vitro screening of a range of approved drugs to identify those which are able to increase neurogenesis. The most promising drugs will then be tested in the trisomic model, as potential new stimulators of neurogenesis in DS.

EXPECTED RESULTS

We expect to demonstrate that cognitive disability in DS can be prevented pharmacologically.

There are over 500,000 DS patients in Europe and over 5 million around the world who may have difficulty in enjoying an independent life. Demonstration that cognitive disability can be prevented through early pharmacological therapy

1. may **lead to clinical trials** using the drugs we have identified;
2. may offer DS patients greater **autonomy**.

THE ROLE OF THE FONDAZIONE ASSICURAZIONI GENERALI

The project would not have been possible without the generosity of the Assicurazioni Generali Group Foundation which is supporting this project with a 1.5 million EUR grant.