EMBARGOED FOR RELEASE **Monday October 7, 2013, 12.50 (CET)**

This press release is in support of a presentation by Dr Benoit Delatour on Monday 7 October at the 26th ECNP Congress in Barcelona, Spain.

GABA inverse agonist restores cognitive function in Down's syndrome

Promising new evidence in mice trials presented at the 26th ECNP Congress suggests GABA inverse agonist could reverse cognitive impairment and improve learning in people born with Down's syndrome.

BARCELONA, SPAIN (7 October 2013) – A selective GABA inverse agonist has restored cognitive function in a mouse model of Down's syndrome (DS) and has the potential to benefit humans, French researchers have revealed.

"The drug we used is a specific GABA-A α5 inverse agonist (α5IA) that hypothetically could combat the abnormal neuronal excitation/inhibition balance associated with DS", explained lead researcher Dr Benoit Delatour from the Research Centre of the Institute of Brain and Spinal Cord (Centre de Recherche de l'Institut du Cerveau et de Moelle Epinière) at the University Pierre and Marie Curie, Paris.

"We observed that repeated and even single administrations of the α5IA molecule can potentiate learning and memory performances in cognitively-impaired DS mice, underlying the potency of this therapeutic approach," he added.

An imbalance between inhibitory and excitatory neurotransmission has recently been proposed as a factor in the altered brain function of individuals with DS. While several studies have suggested GABA-A antagonists for restoring learning and memory performances in DS mouse models, many tend to cause seizures in animal models as well as in humans.

To investigate safer agents, the researchers used a GABA-A inverse agonist (α5IA) to specifically target the α5 subunit of GABA-A receptors in Ts65Dn mice, a classical animal model of DS.

They found that the drug had no convulsant effects and did not promote any side effects on sensory-motor and anxiety-related behaviours. They also found no evidence of histological changes in various organ tissues following chronic administration.

To investigate what impact α5IA had on learning and memory function, the team trained the mice in a spatial navigation (Morris water maze) task. They found that Ts65Dn mice showed a clear learning impairment that was reversed following daily treatment with α5IA. Furthermore, an acute injection of α5IA before acquisition was enough to alleviate recognition memory impairments in the Ts65Dn mice.

"α5IA enhanced behaviourally-evoked immediate early gene products (as markers of neuronal activation) in specific brain regions and also restored normal levels of gene expression in several disregulated pathways", explained Dr Delatour.

"Such stimulation of neuronal activity and normalisation of gene expression combined with the known effects of α5IA on synaptic plasticity, might support the promnestic [memory enhancing] and therapeutic effects of the drug," he added.

With future human trials planned, Dr Delatour is optimistic about the impact his research could have on cognitive impairment in individuals with DS. "The results obtained by us and by others are very encouraging ... it appears that several targets in DS have been identified and can be the source of new pharmaceutical interventions. It is very likely that the combination of different emerging therapies will provide significant clinical outcomes for people with DS."

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About ECNP

The European College of Neuropsychopharmacology (ECNP) is an independent scientific association dedicated to translating advances in the understanding of brain function and human behaviour into better treatments and enhanced public health. ECNP organises a wide range of scientific and educational activities, programmes and events across Europe, promoting exchange of high-quality experimental and clinical research and fostering young scientists and clinicians in the field. The annual ECNP Congress attracts around 4,000-7,000 scientists and clinicians from across the world to discuss the latest advances in brain research in Europe's largest meeting on brain science.

Further information

- Down syndrome (DS) is the most common genetic cause of intellectual disability (affecting around 1 in 800 live births).
- DS is caused by the presence of all or part of a third copy of chromosome 21, causing delays in the way a child develops, both mentally and physically.
- Cognitive impairments in DS include deficits in attention and in memory and learning capacities.
- DS represents about one third of the mental retarded school-aged children and is also associated with a large panel of clinical features beside mental retardation.
- Throughout like DS patients have difficulties learning and memorizing and any treatment that would ameliorate this condition is expected to have a profound impact on their autonomy and on their quality of life.
- The main results of this study have been communicated through peer-reviewed journals and oral and poster communications in international congresses.
- The researchers have filled a patent application (WO2011024115 : COMPOSITION AND METHOD FOR TREATING COGNITIVE IMPAIRMENTS IN DOWN SYNDROM SUBJECTS) which is available at : http://patentscope.wipo.int/search/en/detail.jsf?docId=WO2011024115&recNum=65&docAn=IB2010053796&queryString=FP:%28EN_ALL:NMR%20AND%20PA:%28Centre%20national%20de%20la%20recherche%20scientifique%29%29&maxRec=296