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PARTNER SEARCH HEALTH-EU-SMCP-14

01 dicembre 2017

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Richiesta di un'università francese alla ricerca di partner da includere in un loro progetto da presentare nel programma COOPERATION tematica SALUTE.
Per maggiori informazioni sulla Ricerca Partner e per conoscere i contatti del proponente, potete consultare il seguente indirizzo web: http://www.apre.it/formaAssist/scheda.asp?id=1077

------- PARTNER SEARCH HEALTH-EU-SMCP-14 --------

<Reference n.: HEALTH-EU-SMCP-14>
<Deadline: 31/01/2009>
<Programme: COOPERATION- HEALTH>
<Project Title: Orphan drug labelled for Charcot-Marie-Tooth type 1A disease>
<Financial Scheme: Progetti in collaborazione - Small or Medium>
<Description: . HEALTH- 2009-2.4.4-2: Preclinical development of substances with a clear potential as orphan drugs. FP7-HEALTH-2009-single-stage.

We recently suggested that the use of high doses of ascorbic acid (AA) could be a treatment for Charcot-Marie-Tooth type 1A disease. The rationale of this proposition was based on the reversion of a CMT mouse model obtained after treatment by high doses of AA (Passage et al, 2004). This reversal does not appear to be due to the antioxidant properties of AA, but to its presently unknown capacity to modulate the intracellular pool of cAMP (Kaya et al, 2007, 2008). These data made possible the first clinical trial on adult CMT patients, launched in 2006. This discovery has been patented (EP1526850) and AA has been designated by EMEA as an orphan drug for CMT1A in April 2008 (EU/3/08/53).
These data open new insights into AA functions and roles in different biological situations. Once the efficiency confirmed, the next step is to precise the effects of the use in the long-term of high doses of ascorbic acid in different situations; hence the need for new preclinical studies of this drug in peculiar cases (especially high dose prescription, long-term use, prescription for children and during pregnancy).

Objectives and Work Plan:
We would like to improve our preclinical knowledge of recurrent treatment of CMT1A patient by high doses of AA in order to provide data to answer the following questions:
- What is the exact mechanism and nature of AA action?
- What is the bioaccumulation and metabolism of AA in Schwann cells and peripheral nerves?
- Is there situation were high doses of AA could be toxic?
In order to answer these questions, we plan to perform the following experiments and thus to put the following competences together:

I - Mode of action of AA on PMP22 expression and CMT1A.
1 - Is it AA or an intermediate of AA degradation that is active on PMP22 expression? We will characterize the metabolism of AA in peripheral nerve. We will isolate or synthesize these molecules and we will test their action on PMP22 expression, using system available in the laboratory.
2 - Is the mechanism of AA due to a structural similarity between AA and ATP? To answer this question we will synthesize structural intermediates between AA and ATP, and test their action on PMP22 expression.
For this part of the work we require a collaboration between researcher from the metabolomic field (to be found), chemist our lab.

II - Phamacodynamics, cell localisation and metabolomic of AA in Schwann cells and peripheral nerves.
This will be evaluated through a collaboration between a lab involved in a lab with competences in pharmacodynamics (to be found) performent in cell and tissues imaging (to be found) and our lab.

III - Impact of AA treatment on embryogenesis and growth of mammalians.
A - Embryogenesis.
Pregnant mouse or rats, will be fed with high doses of AA. Morphogenesis, expression of developmental genes ..., will be analyzed at different stages. This step requires competences into rodents embryogenesis, specially in terms of embryos morphology (to be found).
B - Growth.
Due to the inhibitory effect of AA on cell proliferation, two parameters will be evaluated:
1 - Growth performance of young mouse/rats, after treatment with a placebo or with increasing doses of AA
2 - Analysis of cognitive performances (Morris water maze? others?) of rats after treatment with a placebo or with increasing doses of AA
These two questions will be treated in collaboration with two labs (to be found) and our lab.

<Organisation Type: Università>
<Partner Sought: Several expertises are still required. Partner search is not restricted to SMEs, academia are welcome:
- Metabolomic analysis. An EU designed metabolomic platform will be preferred. The task will be to define the metabolism of AA in sciatic nerves.
- Organic Chemist. They will be in charge of synthesizing intermediates and analogues of these molecules.
- Pharmacodynamics. This structure will analyze the distribution of AA and intermediates in Schwann cells, sciatic nerves, and more generally peripheric nervous system.
- Mouse/rat embryologist. This structure will analyze morphology of embryos treated with high doses of AA. Teratogenesis and toxicity will be determined.
- Neonatal and growth period. This group will analyze the impact of AA on growth.
- Behavioral analysis. This group will analysis cognitive function in AA treated rats vs placebo>