



The French National Research Agency

Projects for science

Innovation biomédicale (DS0404) 2014

Projet *NarConX*

An innovative therapeutic strategy to treat residual sleepiness in narcolepsy

Narcolepsy is an orphan disorder, characterized by severe, irresistible daytime sleepiness and sudden loss of muscle tone (cataplexy). As presented by the National Reference Center for Narcolepsy (Pr Yves Dauvilliers, Partner 4), this disease affects 500,000 people worldwide. Within the last years only modafinil and sodium oxybate have been recognized as useful therapy. Despite medication, the main problem in the vast majority of patients remains the persistence of daytime sleepiness (50 to 70% of narcoleptic populations). New promising compounds or combination of drugs are clearly required to reduce residual daytime sleepiness.

Theranexus Company (Partner 1/Coordinator) is a CEA spin-off created by two former CEA scientists which developed a unique platform for improving CNS drugs as answers to high unmet medical needs. Theranexus has developed, in collaboration with Institut de Recherche Biomédicale des Armées, Centre de Recherche en Neurosciences de Lyon (Dr Jian-Sheng's team, Partner 3), and Collège de France (Dr Christian Giaume, Partner 2), a combination called THN102. This combination, composed of modafinil and THN02 – as a connexin modulator – is positioned to treat the residual sleepiness in narcoleptic patients (50 to 70% of narcoleptic patients). Its effect on cataplexy, based on positive results in narcoleptic animals, will also be of high interest and evaluated in clinical phase.

Connexins (Cxs) are transmembrane proteins notably involved in sleep-wake rhythm, Theranexus firstly identified THN02 (a generic compound used in arrhythmias), as able to inhibit Cx function in the brain. This small blood-brain barrier permeable molecule, when used at a very low dosage, significantly potentiates the effects of modafinil in rodent models (on sleep/wake cycle, attention, cataplectic-like event). The modafinil/THN02 combination, further referred to as THN102, is a first-in-class candidate combination with a finished regulatory non-clinical phase, and is now covered by a two-patent portfolio (EP2344146 and EP13306074).

Development plan has been presented to the ANSM in July 2013. The French healthy authority accepted that the first in man could be reached just after a limited non-clinical cardiovascular study in dog (this study has finished in March with highly favorable results). A two-step PK/PD dose finding study in sleep deprived healthy subjects is currently ongoing before clinical phase in narcolepsy. The proof of concept in narcolepsy as well as the deciphering of the mechanism of action of THN102 is proposed in the framework of this ANR proposal. Hence, the present translational two-year project, NarConX, is designed to answer the two following objectives:

- To demonstrate the clinical efficacy of THN02 as an enhancer of modafinil in narcoleptic patients with residual sleepiness (Partners 1 and 4). Based on our preliminary data, we will also evaluate the efficacy of our combination on cataplexy.
- To continue the full characterization of the mechanism of potentiation of modafinil by THN02 using relevant *in vitro*, *ex vivo* and *in vivo* approaches (Partners 1, 2 and 3).

Those two objectives will provide high quality clinical, non-clinical and mechanistic knowledge on the implication of cerebral connexins in the pathophysiology of sleep disorders and in response to arousing drugs. Ultimately, this innovative therapeutic strategy and the choice of repositioned drug are a strong opportunities to offer fast and low-risk solutions for the narcoleptic patients.

Partners

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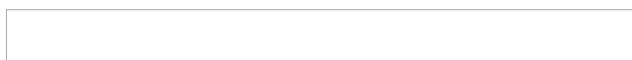
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The project coordinator is the author of this abstract and is therefore responsible for the content of the summary. The ANR disclaims all responsibility in connection with its content.

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