Quinoline and steroidal nitrones with neuroprotective activity for the treatment of ictus
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1. The Institution

Hospital Universitario Ramón y Cajal (Ctra Colmenar, km 9,1 – Madrid)
- The Ramón y Cajal University Hospital is a public owned center, under the Local Government of Health of the Community of Madrid and integrated into the Madrid Health Service (SERMAS).
- Since the beginning of its activities in 1977, the difference of this center is that has a Research Department. This peculiarity us to be recognized in our facet biomedical research both nationally and internationally.

- The **Neuroproteins and Ischemia Laboratory** is located in the **Protein Unit** of the Department.

- In collaboration with:
  Prof. Dr. José Marco-Contelles
  Medical Chemistry Laboratory
  Organic Chemistry Institute, CSIC (Juan de la Cierva, 3 - Madrid)
2. The Product

a) Target Indications

- The nitrone derivates presented here are new potential drugs for treatment of stroke.

- Stroke, or cerebrovascular disease (CVD), is classified into ischemic and hemorrhagic according to their etiology, with a rate of 85% and 15%, respectively.

- Cerebral ischemia is caused by decreased blood flow which can affect an area (focal ischemia) or whole brain (global ischemia).

- In Spain, CVD is the second cause of death and the first in women; besides is the first cause of permanent disability and the second of dementia. Generates between 90,000 and 110,000 new cases each year and over half of patients become disabled or die.

- In addition, it has high economic impact since it consumes 3-4% of health spending.
2. The Product  
   a) Target Indications  

- The nitrone derivates presented here are new potential drugs for treatment of stroke.

- Globally, CVD is the second most common cause of death after heart disease and ahead of cancer. Produces about of 6 million deaths per year, and about 30 million people have had the disease and are still alive.

- Among them, 30% of patients CVD has permanent disability and most of the survivors have functional deficit.

- In despite its great social impact, there is a lack of effective treatment.
2. The Product

b) Innovative mechanisms of action
2. The Product

b) Innovative mechanisms of action

- The use of nitrone derivates represents a new and interesting approach for the treatment of diseases like ictus or ischemia, related with the oxidative stress-induced injury after reoxygenation.

- The nitrone group acts as a radical scavenger and reduces oxidative stress. Known nitrones like phenyl-t-butyl nitrone (PBN) and NXY-059, had shown a high activity as antioxidant agents, however, their in vivo efficacy was limited, due to low cell permeability.
2. The Product

c) Differential features facing the market

The presence of a quinoline group in the structure of the molecules increases their lipophilicity and can improve their cell permeability.

![Chemical structure of a quinoline molecule]

In addition, it is well known the neuroprotective capacity of steroids, specifically in inflammatory processes affecting the central nervous system.

![Chemical structure of a steroid molecule]
2. The Product

c) Differential features facing the market

- *In vitro* assays in neuronal cultures show that these compounds have high neuroprotective activity against ischemia-reoxygenation.

Neuroprotective effect in ischemia *in vitro*: oxygen-glucose deprivation (OGD) on neuronal cultures and cell viability after 24h recovery (R24h).
2. The Product

c) Differential features facing the market

- These compounds have shown a high neuroprotective effect on primary neuronal cell cultures exposed to ischemia *in vitro* (76.9 % of neuroprotection at 10 μM) for quinolin-nitrones (RP19).
2. The Product

c) Differential features facing the market

- The compounds shown a high neuroprotective effect on primary neuronal cell cultures exposed to ischemia *in vitro* (80.7% of neuroprotection at 5 μM) for S2 steroidal-nitrone.
2. The Product

c) Differential features facing the market

- The drugs shown higher neuroprotective effect on neuronal cultures exposed to ischemia in vitro than other known nitrones like PBN or NXY-059.

- The neuroprotective effect was in micro-molar range compared to mili-molar range of the known compounds. More specificity.

- Furthermore, the compounds are able to cross the blood-brain barrier, which, together with their antioxidant activity, make them especially useful as drugs for the treatment of CNS diseases.
2. The Product

d) Current status of development

- *In vivo* assays in global cerebral ischemia animal model.
2. The Product

d) Current status of development

- Neuronal death in the cerebral ischemia animal model.

Fluoro Jade B (FJB)  

TUNEL
2. The Product

d) Current status of development

- *In vivo* assays in cerebral ischemia animal model show that these compounds are able to significantly decrease neuronal death.
2. The Product

d) Current status of development

- *In vivo* assays in cerebral ischemia animal model show that these compounds are able to significantly decrease neuronal death.
2. The Product

e) IPR protection

Quinoline nitrones: Pat nº P201131338 from 01/08/2011; PCT from 24/07/2012

Steroidal nitrones: Pat nº P201330738 from 22/05/2013
2. The Product

f) Pitfalls & Risks to be considered

- Is necessary performing a large scale proof of concept in global and focal cerebral ischemia animal models.

- There is no financial support for this phase.

- Next expiration PCT quinoline nitrones.
3. Partnering Opportunities

- We have an approach to a new therapy for stroke.
- Only less than 3% of patients with cerebral ischemia receiving treatment with current therapies.
- There is a lack of effective treatments for cerebral ischemic stroke.
- The use of nitrone derivatives represents a promising therapeutic approach for the treatment of stroke, and other neurodegenerative diseases, as Alzheimer, Parkinson and Amyotrophic Lateral Sclerosis (ALS), where oxygen-radical scavengers and reduction of oxidative stress have an important therapeutic role.