PROFILE

The Research Group investigates, at **IIBB-CSIC** and **Hospital Sant Pau**, the cellular and molecular mechanisms involved in the onset, progression and complication of atherothrombotic diseases (ischemic heart disease and peripheral artery disease) and abdominal aortic aneurysm. His research is centered on the role of NR4A nuclear receptors, in particular NOR-1, and lysyl oxidases (LOX) in these pathologies. His ultimate goal is to identify novel therapeutic targets and biomarkers to better manage these highly prevalent diseases.

SPEAKER

Dr José Martínez González graduated and PhD in Pharmacy from the University of Barcelona. He leads the Atherosclerosis and Vascular Biology group at the IIBB-CSIC, and a multidisciplinary group which is one of the 40 Spanish research groups integrated in the Biomedical Research Networking Center on Cardiovascular Diseases (CIBERCV). He has been devoted to research in cardiovascular diseases for more than 25 years.

jose.martinez@iibb.csic.es

PRODUCT

Tyrosine hydroxylase inhibitors for the treatment of aortic aneurysm

MECHANISM OF ACTION

The formation of abdominal aortic aneurysm (AAA) is associated with the up-regulation of the enzyme tyrosine hydroxylase in the aortic vascular wall, while the systemic administration of a drug that competitively inhibits tyrosine hydroxylase activity attenuates the main pathophysiological mechanisms involved in AAA disease, including oxidative stress, inflammation and elastic fiber breakdown, thereby preserving vascular wall integrity and preventing the formation of aneurysms.

A therapeutic strategy for the medical management of abdominal aortic aneurysm, addressed to slow aneurysm progression and to prevent aneurysm dissection and rupture, based on the pharmacological inhibition of the vascular activity of the enzyme tyrosine hydroxylase by means of treatment with a-methyl-p-tyrosine (AMPT).

TARGET INDICATIONS

The product applies to abdominal aorta aneurysm (AAA), a life-threatening disorder characterized by a focal and permanent dilation of the abdominal aorta, whose diameter progressively grows increasing the risk of aortic rupture. AAA prevalence increases with age (up to 8% of men aged >65 years), and AAA rupture is a devastating condition with a high fatality rate that accounts for more than 16,000 deaths each year in the United States. Additionally, the treatment method could be useful for the clinical management of thoracic aneurysm.

CURRENT STATUS

- Microarray expression profiling shows the up-regulation of the rate limiting enzyme of catecholamine biosynthesis (tyrosine hydroxylase, TH) in an experimental model of AAA.
- TH is up-regulated in aneurysmal aorta from both AAA patients and preclinical animal models, mainly co-localizing with sympathetic nerve and inflammatory cells.
- The TH inhibitor a-methyl-p-tyrosine (AMPT) protects against the formation of AAA induced by angiotensin II infusion in two animal models of AAA.
- AMPT treatment significantly attenuates vascular oxidative stress and inflammation, reduces the activity of metalloproteinases that degrade extracellular matrix and preserves elastin integrity.
- AMPT treatment is well tolerated and improves the level of circulating markers of renal function.
- Studies to assess the effect of AMPT on pre-established aneurysms are ongoing.

INNOVATIVE ASPECTS

- There are no pharmacological treatments for abdominal aortic aneurysm (AAA) able to slow progression or to prevent aneurysm dissection and rupture.
- Elective surgical or endovascular repair of high-risk aneurysms is currently the only effective way to treat the disease.
- Guidelines recommend intensive risk factor modification in AAA patients, who are commonly treated with statins, β-blockers, antihypertensive or antithrombotic drugs, but no clinical trials have shown a significant effect of these treatments on AAA growth or rupture.

IPR

A patent application has been filed "Use of inhibitors of Tyrosine hydroxylase for the treatment of aortic aneurysm" (Appl. Nº ES201830607), owned by CSIC (80%) and FIRHSCSP (20%). International PCT extension published as WO2019243653. Currently, the patent is in National phases, filed in USA (App. Nº US17252677) and Europe (App. Nº EP19823676), not yet granted.

PARTNERING OPPORTUNITIES

CSIC and FIRHSCSP are seeking for out-licensing the technology to pharmaceutical companies interested in the development and commercialization of the product for treatment of aortic aneurysms. We are open to analyze different forms of collaboration