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Discovery and Cardioprotective Effects of the First Non-Peptide Agonists of Prokineticin Receptor-1 (PKR1)

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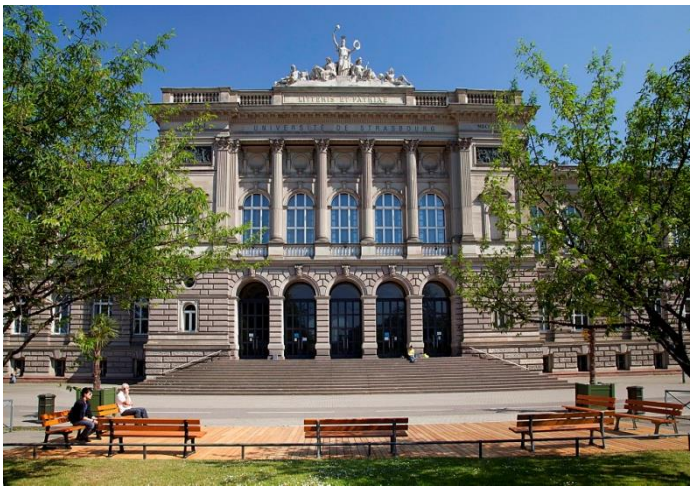
Abstract

Prokineticins are angiogenic hormones that activate two GPCR: PKR1 and PKR2. Through a combination of in silico studies, hit to lead optimization, and pharmacological profiling approaches, we designed, synthesized, and characterized the first PKR1 agonists, demonstrating their cardioprotective activity against myocardial infarction in mice. The most potent derivative, IS20, was confirmed for its selectivity and specificity through genetic gain- and loss-of-function of PKR1. Importantly, IS20 prevented cardiac lesion formation and improved cardiac function after myocardial infarction in mice, promoting proliferation of cardiac progenitor cells and neovasculogenesis. The preclinical investigation of the first PKR1 agonists provides a novel approach to promote cardiomyocyte survival and vascular stabilization after myocardial infarction. Recently we demonstrated that IS20 alleviates doxorubicin (DOX)-cardiotoxicity in cardiac cells and in mice models of acute and chronic DOX-cardiotoxicity. More importantly, IS20 did not alter the cytotoxic and anti-tumor effects of DOX in breast cancer lines or in mouse breast cancer models. Our study provides therapeutic strategies to combat cardiotoxicity in cancer and cardiomyopathy after myocardial infarction.



Biography:

Canan Nebigil is a Director of Research at CNRS. After her Pharm.D degree, she obtained her PhD at the University of Tennessee, USA and postdoctoral trainings, including at Duke University, NIH, Bethesda, and IGBMC, Strasbourg. Her team has been created with ATIP/Avenir CNRS, a young investigator award in Strasbourg. Her team has identified several fundamental mechanisms by which prokineticin signaling is involved in heart development and diseases associated with drug discovery. She obtained several scintific awards including, FRM, ESC, and CNRS. She is a coordinator of a EU project. She has 56 publications (H:28) and is editor of several journals. Her team was the first to explore the role of a new hormone, prokineticin, on cardiac physiopathology and metabolic disorders.

Speaker Publications:

1) Flavaglines as natural products targeting eIF4A and prohibitins: From traditional Chinese medicine to antiviral activity against coronaviruses; Eur J Med Chem, . 2020 Jul 15;203:112653
2) Prohibitin ligands: a growing armamentarium to tackle cancers, osteoporosis, inflammatory, cardiac and neurological diseases; Cell Mol Life Sci, 2020 Feb 15
3) Prokineticin Receptor-1 Signaling Inhibits Dose-and Time-Dependent Anthracycline-Induced Cardiovascular Toxicity Via Myocardial and Vascular Protection; JACC: CardioOncology
4) Volume 1, Issue 1, September 2019, Pages 84-102.
5) Targeting GPCRs Against Cardiotoxicity Induced by Anticancer Treatments; Front Cardiovasc Med. 2019; 6: 194. .Discovery of 3,3′-pyrrolidinyl-spirooxindoles as cardioprotectant prohibitin ligands; European Journal of Medicinal Chemistry,Volume 186, 15 January 2020, 111859.
6) 5th Pharmaceutical Chemistry Conference; Webinar, - April27-28, 2020.

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