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Genetic mechanisms of aldosterone related disorders – towards integrative precision medicine

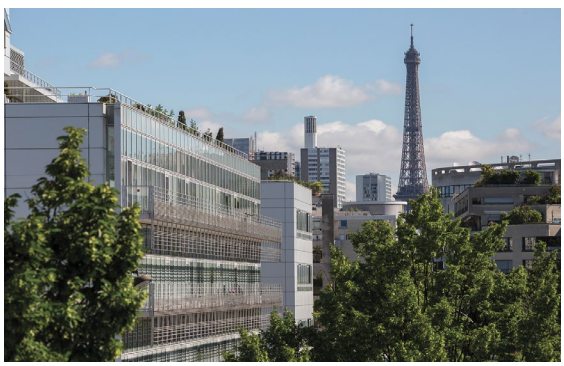
Maria-Christina Zennaro[1,2,3] Paris Cardiovascular Research Center – PARCC Team 12
[1]*INSERM, UMRS_970, Paris Cardiovascular Research Center, Paris, France*
[2]*Université Paris Descartes, Sorbonne Paris Cité, Paris, France*
[3]*Assistance Publique-Hôpitaux de Paris,*
Hôpital Européen Georges Pompidou, Service de Génétique, Paris, France

The Paris Cardiovascular Research Center (PARCC), INSERM-UMR-970, is built upon the substantial strengths and excellence in basic, translational and clinical cardiovascular research of 13 teams, which have been approved by the French National Institute of Health and Medical Research (INSERM) and Université Paris Descartes (now Université de Paris). The center is located at the Georges-Pompidou European Hospital (HEGP), in a single location equipped with laboratories, office space and core facilities, occupying a surface of 4,200 m^2. Teams of the PARCC are conducting projects spanning basic molecular and cellular biology to integrated physiology and pathophysiology, biomarkers, genetics and epidemiology, with the goal of furthering the understanding of major cardiovascular disease, including atherosclerosis, hypertension, heart failure and sudden cardiac death (http://parcc.inserm.fr/).

Translational research is an integral part of the mission of the PARCC, in close connection with clinical laboratories and departments of the HEGP. The HEGP is a new and leading hospital opened in 2000, which comprises 39 services dispatched within 7 health poles and offers 710 beds and 120 daily places. The hospital develops three major areas of activity: cardiovascular diseases, oncology and emergencies.

PARCC team "Genetic mechanisms of aldosterone related disorders – towards integrative precision medicine" is directed by Maria-Christina ZENNARO, MD, PhD, Inserm Research Director, and is composed of three full-time INSERM researchers, two associated clinicians, one engineer, one post-doc, and three PhD students. Our team also hosts 3-4 undergraduate students per year. The team has been appointed FRM team by the "Fondation pour la recherché médicale" in 2014 and 2019.

The overarching aim of our program is to unravel the genetic architecture of blood pressure regulation in relation to aldosterone in order to generate knowledge translatable to clinics. To achieve this goal, we apply the most recent genomic technologies on unique cohorts of patients with primary aldosteronism with access to standardized clinical and biological information, tumor and DNA samples, integrated within national and international networks and programs (COMETE, ENS@T, COST-Admire, ENSAT-HT). An original interdisciplinary approach combines complementary expertise in genetic and clinical investigation with high throughput genomic approaches, molecular, cellular and animal experiments.



This strategy is particularly applied to the development and evaluation of an omics-based stratified health promotion programme for patients with endocrine forms of hypertension in the context of the EU-funded Horizon 2020 research and innovation project ENSAT-HT, which is coordinated by MC Zennaro (www.ensat-ht.eu). The goal of ENSAT-HT is to improve the identification of endocrine causes of hypertension for curative treatment and prevention of cardiovascular and metabolic complications as well as to stratify primary forms of hypertension for effective and cost efficient therapy.

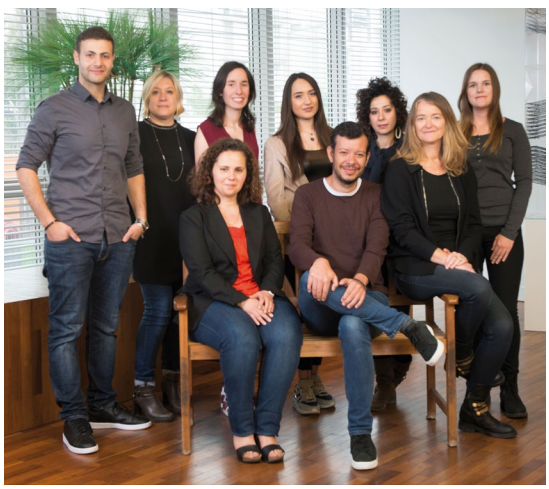
Translational research is performed in close connection with clinical laboratories and departments of the HEGP, where MC Zennaro is associated investigator at the Genetics Department and member of the European Society of Hypertension Centre of Excellence (www.centre-hypertension.org).

The ESH-Centre of Excellence at the HEGP-Paris houses an expert centre for the care of primary and secondary forms of hypertension, and includes the hypertension unit (M. Azizi, L. Amar, G. Bobrie), the clinical investigation center (M. Azizi), the Pharmacology Department (S. Laurent, P. Boutouyrie), and the Genetics department (X. Jeunemaitre), which performs genetic testing and/or genetic counselling. The Centre of Excellence is acknowledged by the French Ministry of Health as a reference clinical centre for rare adrenal diseases. The genetics laboratory of the HEGP (with a ISO 15180 accredited molecular genetics laboratory and a genetics clinic) is reference center for the genetic diagnosis of rare arterial disorders, distal tubulopathies (within the national reference center for rare inherited renal disorders of the child and the adult (MARHEA), adrenal tumors, and for the genetic diagnosis of primary aldosteronism.

Research activities

Detection of secondary forms of hypertension is key to targeted management of the underlying disease and prevention of cardiovascular complications. Primary aldosteronism (PA) is the most common and curable form of secondary arterial hypertension, with an estimated prevalence of ~10% in referred patients and 4% in primary care, but as high as 20% in patients with resistant hypertension [1]. Increased aldosterone levels in PA are associated with increased cardiovascular risk compared to essential hypertension [2]. PA results from autonomous aldosterone production from the adrenal cortex. It is caused in the majority of cases by a unilateral aldosterone producing adenoma (APA) or bilateral adrenal hyperplasia (BAH). Recurrent mutations in genes coding for ion channels (*KCNJ5*, *CACNA1D*, *CACNA1H*, *CLCN2*) and ATPases (*ATP1A1* and *ATP2B3*) regulating intracellular ionic homeostasis and cell membrane potential have been identified in aldosterone producing adenoma and familial forms of PA [3-6]. The current pathophysiological model of APA development involves modifications in intracellular ionic homeostasis and membrane potential, leading to the activation of calcium signaling, the major trigger for aldosterone production. Over the past five years, our team has made major contributions to the identification of genetic abnormalities in PA and the understanding of the mechanistic determinants of increased aldosterone production and nodule formation in the adrenal cortex. In particular, we have identified two new genes involved in inherited forms of PA and deciphered the molecular mechanisms responsible for increased aldosterone production [5, 7]. Our laboratory has also coordinated the largest multicenter study published so far, exploring the genetic, clinical and molecular correlates of somatic mutations in aldosterone producing adenoma [8]. Our laboratory is currently coordinating the EU-funded Horizon 2020 research and innovation project ENSAT-HT (www.ensat-ht.eu). This project will develop and evaluate an omics-based stratified health promotion program for patients with endocrine forms of hypertension. Specific omics profiles will be defined for patients with PA and other forms of endocrine hypertension (pheochromocytoma/functional paraganglioma and Cushing syndrome) by integrating high throughput genetics, genomics and metabolomics data with phenome annotations through bioinformatics modelling

Established profiles will then be validated as stratification biomarkers and applied to the screening of referred hypertensive patients for both stratifying primary forms of hypertension for effective and cost efficient therapy as well as improving identification of endocrine causes for curative treatment and prevention of cardiovascular and metabolic complications. Omics-based profiling should allow identification of patients with preclinical phenotypes along with those hypertensives that cluster into specific endocrine groups who may benefit from personalised treatment. In addition to our translational studies, our laboratory basic research in different model systems, with the aim of identifying molecular pathways of normal and pathological aldosterone production and investigating mechanisms of mineralocorticoid dysfunction in target organs. The results obtained through our program are expected to provide completely novel mechanistic principles on the pathogenesis of blood pressure regulation in relation to aldosterone. This knowledge should pave the way for the development of biomarkers and new and more efficient therapeutic approaches that could benefit a large proportion of the hypertensive population.



Front row (from left to right) : Sheerazed Boulkroun, Fabio Luiz Fernandes-Rosa, Maria-Christina Zennaro
Second row (from left to right) : Rami M El Zein, Isabelle Giscos-Douriez, Kelly de Sousa, Alaa B Abdellatif, Teresa Cosentino, Audrey Soria

Maria-Christina Zennaro - maria-christina.zennaro@inserm.fr

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COUNCIL'S CORNER

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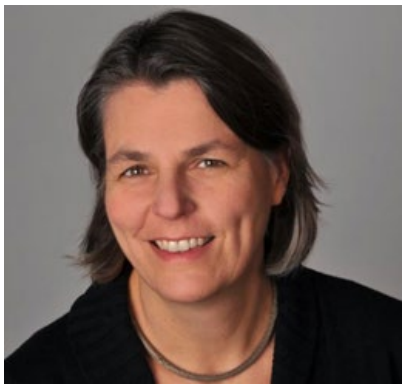
My views on Hypertension

Ulrike Muscha Steckelings, MD, PhD. IMM

Dept. of Cardiovascular & Renal Research, University of Southern Denmark, 5000 Odense, Denmark



Not surprisingly, my daily work as a pharmacologist and basic scientist has a major impact on my view on hypertension. As a pharmacologist, my interest is primarily the treatment of hypertension: the major advances in anti-hypertensive treatment over the last ~ 5 decades, the still insufficient treatment options for certain patient groups such as patients with resistant hypertension or women with preeclampsia and, consequently, the identification of novel drug targets. The focus of my own research is the angiotensin AT_2-receptor (AT_2R), which mediates tissue protective actions and which in many instances is a counter player of the AT_1-receptor [1].

Working with this receptor, which is stimulating endogenous protective mechanisms (including lowering of blood pressure), made me aware that the common approach for identifying new drug targets for the treatment of hypertension and other diseases is usually following a certain concept: In most cases, the starting point in drug discovery is the investigation of a pathomechanism, which the new drug is supposed to inhibit or interrupt. All currently approved drugs interfering with the renin-angiotensin-system (RAS) work according to this principle.

However, pharmacological interference in disease can also consist in strengthening endogenous mechanisms, which naturally counteract the disease mechanisms. For example, a new area in cancer therapy, immuno-oncology, is following this principle and has become one of the most promising and fruitful sources of new treatments – a fact that was recognised by the 2018 Nobel Prize in Medicine/Physiology [2].

In the treatment of systemic hypertension, the principle of reinforcing natural mechanisms is only rarely used. In contrast, in pulmonary hypertension, increasing the levels of the endogenous vasodilator nitric oxide (NO) is a common treatment approach, which is achieved by drugs such as phosphodiesterase-5 inhibitors (e.g. sildenafil), soluble guanylate cyclase stimulators or by direct application of NO [3].

Another example of a drug that stimulates an endogenous mechanism for therapeutic use are neprilysin-inhibitors, which are used in fixed combination with the ARB valsartan to prevent degradation and thereby increase levels of the protective natriuretic peptides [4]. These so-called ARNIs are approved for the treatment of chronic heart failure with reduced ejection fraction, but may also have potential for the treatment of hypertension [4]. Drugs for therapeutic use of what is now called "the protective arm of the RAS" are currently in preclinical and clinical development.