PROJECT 2 (optional)

DoS: Dr.ssa Chiara Lanzani

Title: **A new paradigm for salt sensitive hypertension, inflammation, oxidative stress and ageing: from in vitro and in vivo models to human**

Curriculum: Experimental and Clinical Medicine

Residency Program: Nephrology

Link to OSR/UniSR personal page:

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):

The deleterious effect of a high salt diet on cardiovascular health is driven by arterial hypertension (HT).

In this project, we aim to dissect the complex relationship between salt sensitivity, BP regulation, inflammation, oxidative stress and understanding how these mechanisms act during ageing.

Blood pressure (BP) salt-sensitivity is at least in part under genetic control. Although the underlying mechanisms are largely unknown, our group showed that the Adducin-Endogenous Ouabain-Na^+-K^+-ATPase (ADD-EO-NKA) system is part of the regulatory genetic network triggering BP salt-sensitivity. EO, a stress hormone secreted by the adrenal gland with hemodynamic effect, activates renal NKA, leading to increased renal Na reabsorption and the gene encoding for lanosterol synthase (LSS), acting in one of the first steps of EO biosynthesis, was shown to be associated with BP decrease after low salt diet [1]. A second gene associated with HT and salt-sensitivity is *UMOD*, encoding uromodulin. Common variants in the *UMOD* gene were associated with increased risk of chronic kidney disease and HT [2].

Sodium concentration and the immune system co-ordinately impact on BP, exacerbating or decreasing the severity of HT. Interestingly, both LSS and UMOD have been shown to modulate not only Na reabsorption but also innate immunity. Also, ouabain activates proinflammatory cytokine. The paradigm linking salt accumulation and inflammation is further corroborated by recent data showing that Na can be stored in extrarenal districts, such as skin, and that immune cells from the mononuclear phagocyte system not only function as local on-site sensors of interstitial electrolyte concentration, but also, as systemic regulators of body fluid volume and BP.

The three main aims of this project are:

i) to improve our knowledge on the mechanisms of salt sensitivity of BP and on associated kidney damage and inflammation based on previously identified players (LSS-EO-UMOD) [3].

ii) to study the link between body Na accumulation and inflammation, oxidative stress, in HT and tissues fibrosis will be studied.

iii) to assess the relevance of the identified mechanisms in aged populations (HT follow-up and FRASNET cohorts).

We developed an acute sodium load test that allows estimation of the relationship between urinary sodium excretion and mean BP changes (PNat) during sodium load.

We will study three cohorts:

1) Pathophisiology of Salt sensitivity in Never treated essential hypertensive patients phenotyped by sodium load test (more than 500 patients already available).

2)Chronic kidney damage development in Follow-up cohort of essential hypertensives after Sodium load test (406 patients already available). Patients will undergo annual visit with evaluation of BP control, serum creatinine, microalbuminuria.
3) Relationsheep between kidney function, blood pressure, salt intake and fraility in healthy aged versus frail aged subjects are part of FRASNET Study (CARIPLO 2016-0980). This cross-sectional, observational cohort study includes at least 500 subjects (age >65 years) subdivided in 250 cases and 250 controls according to frailty.
Biological samples from these cohorts will be characterized for new biomarkers of inflammation and ageing. Similarly, genomic DNA will be collected for all patients for genotyping of genetic variants in UMOD, LSS and other genes related to sodium balance and inflammation.
The collected data derived from different patient protocols and genetic markers will be treated for statistical analyses.

Skills to be acquired by the student:
The PhD student will develop concrete scientific knowledge and in the field of clinical and experimental nephrology.
More specifically he/she will acquire proficient knowledge in pathophysiology of salt sensitivity. He/she will develop adequate skills in order to design of primary and alternative experimental strategies, to collect patient's data, to create database. He/she will also learn how to carefully analyze the results of the investigation perform specific statistical analysis and to appropriately discuss the strengths and the limits of his/her work. He/she will develops predisposition for critical presentation of data in internal seminars and at national and international meetings. Eventually the PhD student will acquire adequate skills in order to conceive and

design an independent investigation and to apply to a grant.

References (max. 3)
1.Lanzani C, Gatti G, Citterio L, et al. Lanosterol synthase gene polymorphisms and changes in Endogenous Ouabain in the response to low sodium intake. Hypertension. 2016;67:342–348.
2. Trudu M, Janas S, Lanzani C, et al. Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. Nat Med. 2013 Dec;19(12):1655-60.
3. Iatrino R*, Lanzani C*, Bignami E, Casamassima N, et al: Lanosterol Synthase Genetic Variants, Endogenous Ouabain, and Both Acute and Chronic Kidney Injury.Am J Kidney Dis. 2019 Jan 16