

 <p>UniSR Università Vita-Salute San Raffaele</p>	<p>APPLICATION TO ACT AS SUPERVISOR AND RESEARCH PROJECT PROPOSAL</p>	<p>MO 20-5 ed. 01 del 21/02/2025 PO 20 Page 4 of 11</p>
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PROJECT

Supervisor: MANUNTA PAOLO

Title: **A Translational Multidisciplinary Approach leading to Molecular Biomarkers of Sodium-Sensitive Hypertension**

Curriculum: Cell and Molecular Biology

Link to the personal page of the University or relevant hospital site website:

<https://www.unisr.it/docenti/m/manunta-paolo>

<https://research.hsr.it/en/divisions/genetics-and-cell-biology/genomics-of-renal-diseases-and-hypertension/paolo-manunta.html>

Description of the Project (max 3,000 characters including spaces).

Background/gap of knowledge

The relationship between hypertension (HT) and sodium-sensitive blood pressure (BP) remains unexplored. HT, a major contributor to cardiovascular and renal diseases, yet remains an unmet clinical need. Our lab investigates BP variation with high-sodium diet (HSD), named salt-sensitive hypertension (SS-HT), a pathologic condition caused by genetic predisposition that may evolve in kidney failure. The human genetic variant (rs2254524) in Lanosterol Synthase (*LSS*), involved in steroids/cholesterol synthesis (1), is associated with SS-HT and response to Rostafuroxin (2, 3), and acute kidney injury (4).

Rationale and hypothesis

Our team developed a knock-in mouse model carrying the human *LSS* variant (*Lss* KI) that exhibits HT on HSD (5). The *Lss* KI and wild type mice (WT) at middle-age were characterized for BP, sodium regulation, and renal function with biological samples collection. Data from renal metabolomics and plasma/renal proteomics are available. These datasets represent an informative source to investigate the role of the *Lss* V643L variant in inducing hypertensive organ damage (HMOD). The detected molecular signatures in our model will correlate with age-



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dependent exacerbation of HT and tissue pathology, elucidating mechanisms by which the *LSS* variant drives HMOD.

Objectives and specific aims

We aim at deepening our knowledge on HT onset and the effect of HSD. We will employ a multidisciplinary approach that will rely on the *Lss* murine model and some well-characterized HT patient cohorts.

1) To investigate the physiological and molecular responses to HSD in *Lss* model.

This objective involves assessing the impact of HSD (4% NaCl) versus normal-sodium diet (0.3% NaCl) in early-age *Lss* KI and WT C57BL/6 mice. We aim to detect early HT markers and molecular mechanisms with emphasis on inflammation as a contributing factor to HMOD during aging.

2) To evaluate the therapeutic potential of Rostafuroxin.

This aim assesses the efficacy of Rostafuroxin, a potent Na^+/K^+ -ATPase antagonist, in counteracting the HMOD in *Lss* KI mice underwent HSD. We will determine whether treatment can restore BP and limit the progression of chronic organ damage.

3) To assess the translational relevance of molecular pathways.

To bridge preclinical and clinical findings, targeted genetic analyses will be conducted in the MILANO cohort (1200 treatment-naïve HT individuals and 600 normotensive controls). We will validate biomarkers and pathways in HYPERGENES European cohort (1600 HT cases and 1700 controls), which includes comprehensive BP, dietary sodium intake, and anthropometric characteristics.

Expected outcomes

This study will deepen our understanding of the molecular mechanisms driving SS-HT onset and the impact of salt on BP. Pharmacological treatments will allow to understand whether it is possible to prevent the development of HT and progression of HMOD. We expect that the therapy will normalize BP in hypertensive mice and improve renal outcome.

Skills that the student should acquire (max. 600 characters including spaces):

Handling and management of mice colonies, treatment with different salt diets, and pharmacological drugs:



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- BP measurement with tail-cuff method using the BP-2000 instrument
- Use of metabolic cages for urine collections
- Nucleic acids/proteins extraction, expression quantification
- Identification of inflammation markers in plasma, urine and tissues
- Genetic analysis on human cohorts and validation on biological samples already collected
- Statistical analysis of the results
- Problem solving and possible resetting of the project
- Results dissemination (written/oral communications)

References (max. 15)

- 1 Lanzani C, et al. Adducin- and Ouabain-related gene variants predict the antihypertensive activity of rostaduroxin, part 2: clinical studies. *Sci Transl Med* 2010 Nov 24;2(59):59ra87
2. Lanzani C, et al. Lanosterol Synthase Gene Polymorphisms and Changes in Endogenous Ouabain in the Response to Low Sodium Intake. *Hypertension*. 2016 Feb;67(2):342-8.
3. Citterio L, et al. Antihypertensive treatment guided by genetics: PEARL-HT, the randomized proof-of-concept trial comparing rostaduroxin with losartan. *Pharmacogenomics J*. 2021 Jun;21(3):346-358.
4. Iatrino R, et al. Lanosterol Synthase Genetic Variants, Endogenous Ouabain, and Both Acute and Chronic Kidney Injury. *Am J Kidney Dis*. 2019 Apr;73(4):504-512
5. Faienza S, et al. A novel mouse model recapitulates the effects of rs2254524 variant in the lanosterol synthase gene on salt sensitivity and organ damage. *J Hypertens*. 2025 Jan 1;43(1):80-89. doi: 10.1097/HJH.0000000000003843.