PROJECT 1

DoS: Dr.ssa Chiara Livia Lanzani

Title: **Humoral and genetic determinants in the development of kidney complications in patients with hematological malignancies after chemotherapy and/or allogenic/autologous bone marrow transplant.**

Curriculum: Experimental and Clinical Medicine

Residency Program: Nephrology

Link to OSR/UniSR personal page:

Acute kidney injury (AKI), responsible for the chronic nephropathy (CKD) development, is a frequent complication in patients affected by hematological malignancies treated with chemotherapy and/or hematopoietic stem cell transplantation. The incidence ranges from 20 to 73%. It is noteworthy that some individuals are more predisposed than others to the development of renal amage, and this variability is likely to depend on the individual genetic background. Our group has recently proposed Endogenous Ouabain (EO), an adrenocortical cardiac glycoside, and well-known effector of the hypertension-mediated cardiovascular damage, as the first "predisposing" biomarker of AKI in humans [1].

Klotho has been evaluated as risk predictors of AKI development demonstrating a high predictive value. Soluble KL modulates ion-channel expression and growth factor sensitivity. In chronic kidney disease (CKD), impaired KL expression has been demonstrated. A linkage between KL depletion and RAS activation in aged kidneys and in CKD has been observed and our group recently demonstrate a link between Klotho and salt sensitivity and kidney damage [3].

The aim of our study is to evaluate the role of these new plasmatic/urinary biomarkers (EO and KL) and linked genetic polymorphisms in the development of renal complications in patients with hematological malignancies undergoing chemotherapy (CT) and/or hematopoietic stem cell transplantation. This role will be evaluated both as a marker of renal function and of possible renal damage during treatments and as a predictor of development of renal damage over time. This is an explorative observational prospective study. Patients affected by hematological malignancies, that are admitted in the Hematology and Bone Marrow Transplantation Unit (BMT), will be enrolled at the time of diagnosis, before chemotherapy conditioning and prior bone marrow transplantation. Blood and urine samples for the dosage of biomarkers will be collected before any chemotherapy cycle and/or bone marrow transplantation, then weekly in the phase of aplasia post-chemotherapy and every 2 months in the first year and subsequently every six month in the transplant follow-up phase. We will perform a longitudinal evaluation of EO and plasma KL together with genetic characterization of polymorphisms possibly involved in the development of renal damage in order to identify at risk subjects and to early recognize and potentially predict AKI development.

This study will be conducted in collaboration with the Hematology and Bone marrow Transplantation Unit of OSR. Patients will be treated with standard chemotherapy schemes and conditioning regimens according to current guidelines. A minimum of 15 patients/year with newly diagnosed hematological malignancies candidate to intensive chemotherapy/bone marrow transplantation is expected.

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 AKI and CKD in particular clinical settings and therapies.

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 anddesign an independent investigation and to apply to a grant.

References (max. 3)

1. Simonini M, Lanzani C, Bignami E, et al. A new clinical multivariable model that predicts postoperative acute kidney injury: impact of endogenous ouabain. Nephrol Dial Transplant. 2014;29: 1696–1701.
2. 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.
3. Citterio L, Delli Carpini S, Manunta P and Lanzani C: Klotho gene in human salt sensitive hypertension: a link between salt and renal ageing?".CJASN 2020; in press