Cytochrome P450 (CYP) metabolites are more frequently recognized as important regulators of cardiovascular and renal functions. CYP epoxygenases produce epoxyeicosatrienoic acids (EETs) that exhibit vasodilatory and natriuretic properties. EETs are degraded by the enzyme soluble epoxyde hydrolase (sEH). Inhibition of sEH reduces blood pressure (BP) and end organ damage in several models of hypertension.

The goal of this project was to define the role of EETs in BP regulation in the model of renovascular two kidney - one clip (2K1C) hypertension. We proposed to examine, whether sEH inhibition attenuates BP and improves renal autoregulation and pressure natriuresis in 2K1C hypertension. In addition, we will study the signaling of EETs in isolated renal arterioles to determine the changes in EETs - mediated signal transduction in hypertension. Overall, these studies were aimed to elucidate the role of EETs in the regulation of renal functions and BP under physiological conditions and in hypertension. In addition, these studies could provide new evidence supporting the role of sEH inhibitor as the new candidate for antihypertensive therapy.

To better understand the role of EETs, this project was based on both in vivo and in vitro experiments.

- The first part of this project involved radiotelemetrical recordings of BP in freely moving rats. We studied the effect of sEH inhibitor on BP and sodium excretion in both normotensive and 2K1C hypertensive rats.

- Second part of this project focused on renal functions in 2K1C hypertension and in sham rats. We studied the effect of sEH inhibition on functional characteristics of the kidney in anesthetized rats.

- Third part of this project focused on the vascular function of small renal arteries and how it might be altered in 2K1C hypertension, in terms of vascular responsiveness to EETs. Pressure myograph was employed to determine changes in functional responsiveness to EETs.

Data from this project deliver new knowledge about the role of epoxyeicosatrienoic acids (EETs), the metabolites of cytochrome P450, in the regulation of renal functions and blood pressure in 2K1C hypertension. In agreement with studies using other models of hypertension, hypertensive 2K1C rats express lower levels of EETs. Because EETs exhibit antihypertensive properties, we hypothesized that increasing the bioavailability of EETs may produce beneficial cardiovascular. Our data indicate that inhibition of the enzyme sEH that metabolizes EETs to biologically less active DHETEs results into enhanced bioavailability of EETs and decreased blood pressure (BP). In addition, this is the first study showing that inhibition of sEH improves renal hemodynamics and autoregulation in 2K1C hypertension and the improved renal functions contribute to the blood pressure lowering effect of the of sEH inhibitor cis-4-[4-(3-Adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid (c-AUCB).
Another important finding from the current study is that in addition to the decreased bioavailability of EETs, there occurs also an attenuation of functional responses to EETs in hypertension. Renal resistance arteries from hypertensive rats exhibited decreased vascular dilation to EETs compared to arteries from normotensive rats. These attenuated dilatory responses may further impair renal functions in hypertension, indicating that the inappropriately low EETs action in hypertension may be due to impaired signaling of EETs in addition to their lower bioavailability.

Overall, this study further contributed to our understanding of the role of cytochrome P450 metabolites in the regulation of renal functions and BP. Advancement in this field contributes to a better understanding of the mutli-factorial mechanisms that contribute to hypertension and therefore has the potential to improve the management of hypertension.