

## **ABSTRACT**

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Title of Thesis: Immunochemical detection of PECAM-1 expression in hypertensive rats

Hypertension – abnormally high blood pressure - is a lifestyle disease, which belongs to the most frequent cardiovascular diseases. Hypertension seems to be a non-infectious epidemic with 25 to 30 % prevalence in adult population and presents a serious health problem.

PECAM-1 is an adhesive signal molecule expressed on hematopoietic and endothelial cells, creating the main component of the vascular tissue. Regarding its structure, it belongs to the immunoglobulin super-family of adhesive molecules.

Sunitinib is a biological treatment molecule of the group of tyrosine-kinase inhibitors used for treatment of generalised renal carcinoma and gastrointestinal stromal tumours. Pharmacologically, sunitinib is antineoplastic substance – protein-kinase inhibitor. The main adverse effect of sunitinib is hypertension.

The aim of this rigorous thesis was to define and to describe the expression of endothelial PECAM-1 in the aorta of spontaneously hypertensive rats (SHR) and their normotensive control group (Wistar - Kyoto rats - WKY) considering sunitinib treatment and using immunohistochemical methods and stereological evaluation.

Two strains of rats were used for the experiment – first inbred strain of spontaneously hypertensive rats (SHR) and second inbred strain of Wistar Kyoto normotensive rats. Both strains were divided into two groups – one was administered sunitinib and the other one water as a control.

Immunohistochemical staining was performed on 120 preparations, preparations were 5 random samples incisions from 6 animals of both groups. Immunohistochemical analysis showed PECAM-1 expression only on endothelial cells of vascular lumina. In addition, partial expression was detected on adventitia vessels. Positive reactions to PECAM-1 staining were observed in almost all tested vessels in all four groups of animals. Sunitinib administration led to increased expression of PECAM-1 (visual evaluation only) in SHR rats and WKY rats as well. Afterwards, these results underwent quantifying stereological analysis.

Stereological analysis of PECAM-1 expression in SHR group demonstrated statistically significant increase of PECAM-1 expression after sunitinib administration. Similar results were found in quantification of PECAM-1 expression in WKY group, which either showed significantly increased PECAM-1 expression after sunitinib expression.

Both immunohistochemical and stereological analysis of PECAM-1 expression demonstrated increased PECAM-1 expression after sunitinib administration in group of SHR rats and WKY rats and also suggested a significant trend in growing PECAM-1 expression in group of SHR rats when compared to WKY rats.

The results suggest that PECAM-1 expression in the aorta may induce hypertension.

Administration of sunitinib may lead to development or worsening of endothelial dysfunction which presents one of the mechanisms of sunitinib vascular toxicity.