# ESC first Contact Initiative Grant

# Report

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**Membership**: European Atherosclerosis Society

To:

European Society of Cardiology
The European Heart House
Councils Relations
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Dear ESC council members,

I would like to express my sincere gratitude to the council on the Basic Cardiovascular Science of the European Society of Cardiology for providing me with the First Contact Initiative grant of the European Society of Cardiology. This grant has given me the opportunity to visit Dr Jean-Sebastien Silvestre laboratory located at Paris Cardiovascular Research Center, 56 rue Leblanc 75737 Paris cedex 15, France.

## Activity in the area of cardiovascular sciences

I obtained my PhD in France where I studied the role of shear stress (SS) generated by flowing blood on regulating the selective expression of angiotensin receptors (AT1) by endothelial cells. I uncovered that laminar (athero protective) blood flow decreased the expression of AT1 receptors, which translated in the reduced expression of adhesion molecules responsible for the recruitment of pro-inflammation monocytes into the cholesterol-rich intima. In contrast, athero-prone blood patterns (oscillatory shear stress) unopposed the reduction in AT1 at the surface of endothelial cells creating a favorable microenvironment for lesion development. In parallel, I contributed in the set up a model of an arteriovenous (AV) fistula between the left carotid and the jugular vein in order to mimic flow-induced vascular remodeling. I studied the role of different SS patterns in the shedding of functional microparticles and designed a project investigating the micro RNA signatures harbored by these

microparticles. These projects were successfully terminated and provided insightful mechanisms of how SS patterns could impact vascular remodeling and atherosclerosis development.

Since, I am excited by the challenge of expanding my work into innovative and creative avenues, I pursued my training in New York in Dr Moore's laboratory to focus on the novel roles of neuronal cues that can additionally direct inflammation. I have successfully met those challenges as illustrated by my recent work published in Nature Medicine. I demonstrated that tissue macrophages populating the excessively inflamed obese adipose tissue express a neuronal cue, Netrin-1 where it thereby traps them within the tissue. This translates into the perpetuation of chronic inflammation and is accompanied by defective glucose metabolism and insensitiveness to insulin-characteristic features of type2 diabetes. Identifying signals that regulate egress is of paramount importance for better-adapted therapeutic strategies.

**Project**

Ongoing projects in view of establishing myself as an independent researcher include investigating additional roles of neuronal guidance cues in vascular remodeling more specifically in the setting of Abdominal Aortic Aneurysm (AAA) pathology. AAA is characterized by a focal dilatation of the aortic diameter >30 mm located in the infrarenal section of the aorta. Roughly 25 000 AAA repairs are performed each year, and despite progress in primary preventive measures, AAA still accounts for > 13000 deaths annually. Histological studies have revealed that transmural inflammation is manifested by the presence of macrophages (Mø). Since Mø have important roles in both the induction and resolution of inflammation, I hypothesize that in addition to signals directing their recruitment to the focal site of aortic dilation, other cues are expressed to orient the advanced avenues related the laminal destructive capacity of these cells.

Combined with my previous experience in various vascular models, I feel well prepared to tackle this area and begin the next phase of my career. Currently, there is no other alternative other than surgery to alleviate the drastic consequences of blood vessel rupture.

**Project: the host laboratory**

Dr Silvestre, who heads the laboratory (INSERM U970, Paris) focused on regenerative therapies for cardiac and vascular disease is an internationally recognized expert in cardiovascular pathologies. Current work in Dr Silvestre's laboratory aims to address the role of inflammatory-derived signaling molecules in blood vessels and peripheral nerves in the setting of critical limb ischemia and myocardial infarction. I have selected Dr JS Silvestre laboratory since he has an outstanding scientific knowledge but has also a solid mentoring background that will ensure my success in establishing myself in a unique niche for my independent research program. He has developed multiple cell specific knock down of Netrin-1 and its receptors DCC and Unc5b Cre/Lox systems. We have extensively discussed about how these mice could be beneficial in my research. Notably, Dr Silvestre has generously guided me on strategic experimental settings to adopt to delve the molecular mechanisms if ever I observe a role of netrin-1 and/or its receptors in aneurysm formation.

Dr Silvestre was also very hospitable with his time and provided me with seminal directions in my scientific career. We discussed about the potential avenues of applying for faculty grants such as ATIP-AVENIR, FRM in France and in Europe (ERC) to meet my long term view to settle myself as an independent researcher.

I would like to reiterate my gratitude to Dr Silvestre's time, scientific advice and mentorship guidance that has elaborated foundation results and seeded unique opportunities for our collaborative intentions.

Yours faithfully,

Bhama Ramkhelawon