**VCAM1 modulation on endothelial cells**
**Implications for vasculopathy in sickle cell anemia**

Marisa Silva¹, Sofia Vargas¹, Andreia Coelho¹, João Lavinha¹,², Paula Faustino¹,³

¹Departamento de Genética Humana, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa; ²BioISI, Faculdade de Ciências, Universidade de Lisboa, Lisboa; ³ISAMB, Faculdade de Medicina, Universidade de Lisboa, Lisboa; Portugal.

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**Background**
- Sickle cell anemia (SCA) – chronic vascular disease caused by homozygous c.20A>T mutation in the HBB gene, resulting in abnormal hemoglobin S (HbS) accumulation in erythrocytes;
- Pediatric subphenotypes include cerebral vasculopathy (CVA), pain crisis, frequent infections and renal disease;
- Genetic modulation has been described to affect pathophysiology of SCA.

**Research Question**
Could genes involved in endothelial cell adhesion, like VCAM1, act as modulators in the onset and severity of vasculopathy, namely pediatric CVA?

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**Previous Results**

<table>
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<th>Variant</th>
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</table>

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**Experimental design**

**Take home messages**
- Functional studies show increased VCAM1 expression on cytokine-induced endothelial cells;
- Promoter haplotypes, previously associated with CVA, show different effects and confirm VCAM1 modulation of endothelial cell response;
- The results on different endothelial cell models enhance the possibility of this effect extending beyond cerebral to systemic vasculopathy.

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**Recent Results**
- Basal VCAM1 promoter activity is affected by all VCAM1 haplotypes tested, both in micro and macrovascular endothelial cells (Fig. 1, left);
- Stimulation with TNF-α leads to a ~2-fold increase in promoter activity in cells transfected with haplotypes 4 or 7, when compared with non-stimulated cells;
- In a pro-inflammatory milieu, haplotype 1 leads to a less active VCAM1 promoter in brain microvascular cells, suggestive of a protective effect;
- The presence of haplotype 7 results the highest promoter activity, especially in brain microvascular cells (Fig. 1, right);
- The inductive effect of haplotype 4 is more significant in macrovascular cells, despite ~2-fold increase, in stimulated cells.

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**References**

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**Contacts**
marisa.silva@insa.min-saude.pt
paula.faustino@insa.min-saude.pt

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**Figure 1.** VCAM1 Promoter activity ratios, as measured by luciferase assay, normalized to empty vector construct; Left: Ratios in non-stimulated cells; Right: fold change of promoter activity in cells after TNF-α (8h, 20 ng/mL) stimulus when compared with non-stimulated cells.