ENGINEERING PHYSIOLOGICAL MODELS OF ARTERIAL BIFURCATIONS TO EXPEDITE TREATMENTS

Jordi Martorell[1,2,*], Pablo Santomá[1,2], José J. Molins[2], Andrés A. García-Granada[2], José A. Bea[3], Elazer R. Edelman[1,4], Mercedes Balcells[1,2]

[1]Massachusetts Institute of Technology, Cambridge, MA, USA , [2]Institut Químic de Sarrià, URL, Barcelona, Spain, [3] Universidad de Zaragoza, Zaragoza, Spain, [4]Brigham and Women's Hospital, Boston, MA, USA

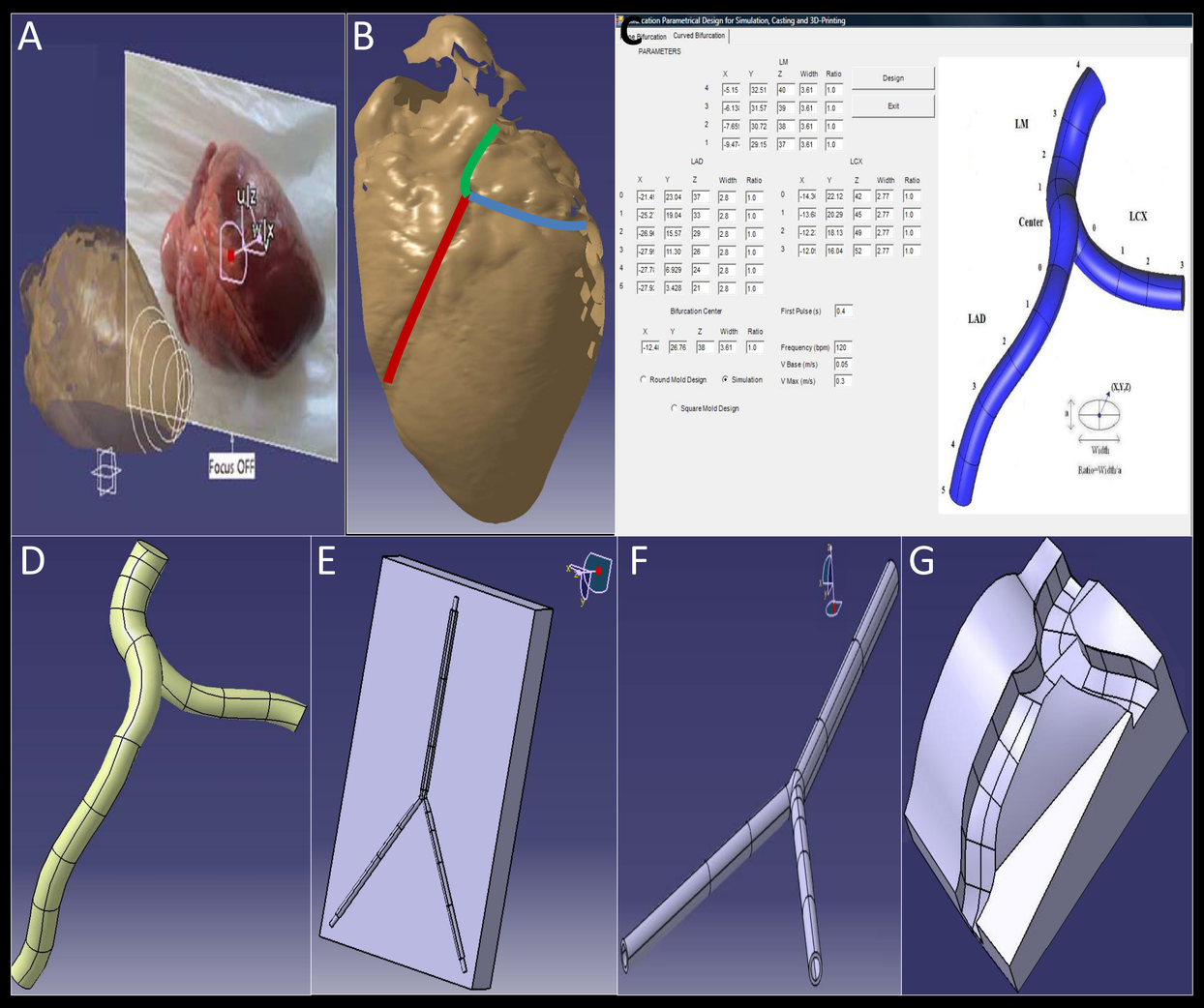


Figure 1. Computational Platform for Bifurcations Design
(A) A swine heart is scanned using a 3D scanner. (B) A physician or pathologist determines the bifurcation and points of interest based on the 3D CATIA® Image which are introduced into the Visual Basic® Interface (C), that creates up to four different macro files for CATIA®. The macros generate an IGS file (D), a CAM file (E) and two STL files (F)(G). The IGS file (D) is used for computational fluid dynamics simulation in TDyn®, the CAM file (E) is used to mechanize Teflon® molds to build the PDMS scaffold. The STL file (F) allows for direct 3D printing of the selected bifurcation in a flexible polymer. The STL file (G) is used to 3D print a curved support to fold the artery into the exact shape of the scanned heart.

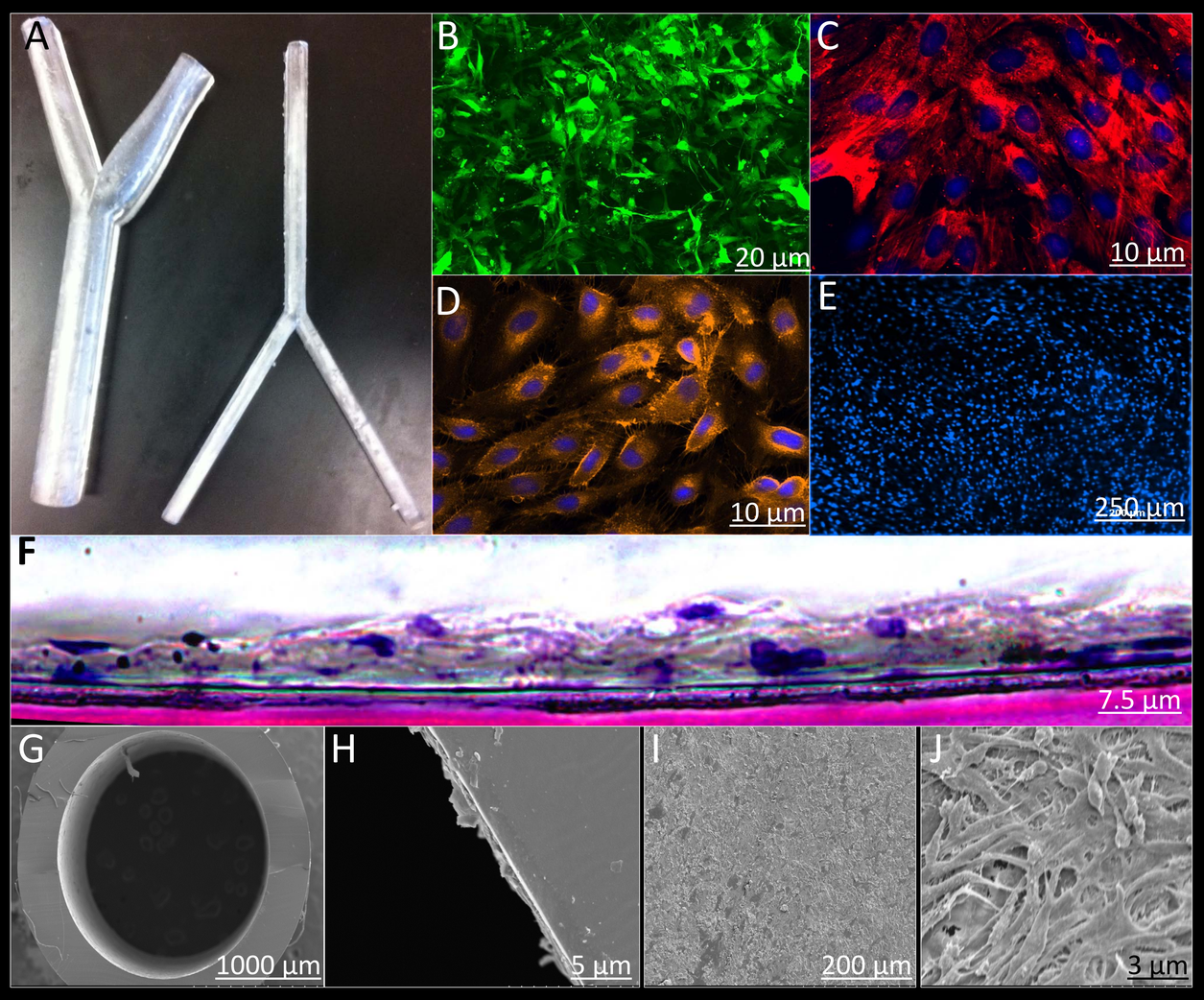
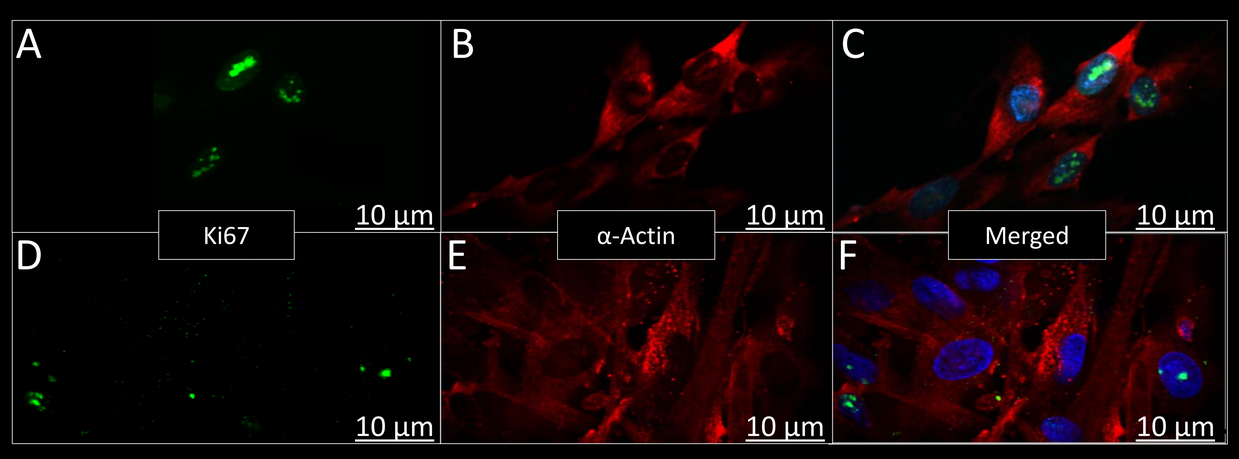


Figure 2. Trilaminate Structure on Polymeric Scaffold
(A) PDMS scaffolds of the carotid and left coronary artery bifurcations were manufactured, autoclaved and layer-by-layer seeded with fibroblasts (B), smooth muscle cells (C) and endothelial cells (D). Endothelial cells were marked with a rabbit anti-CD31 antibody and smooth muscle cells were characterized using a mouse anti α-smooth muscle cell actin antibody. Fibroblasts were infected with a retrovirus containing a GFP chain. Cells' nuclei were stained with DAPI and directly visualized non-destructively across the scaffold wall (E). (F) Scaffolds were fixed, embedded in Spurr's resin, microgrounded and H&E stained to confirm cells coverage, homogeneity and multilayer seeding. Scaffolds were fixed, sputter-coated and SEM imaged to confirm seeding homogeneity (G)(H), cells coverage (I) and morphology (J).



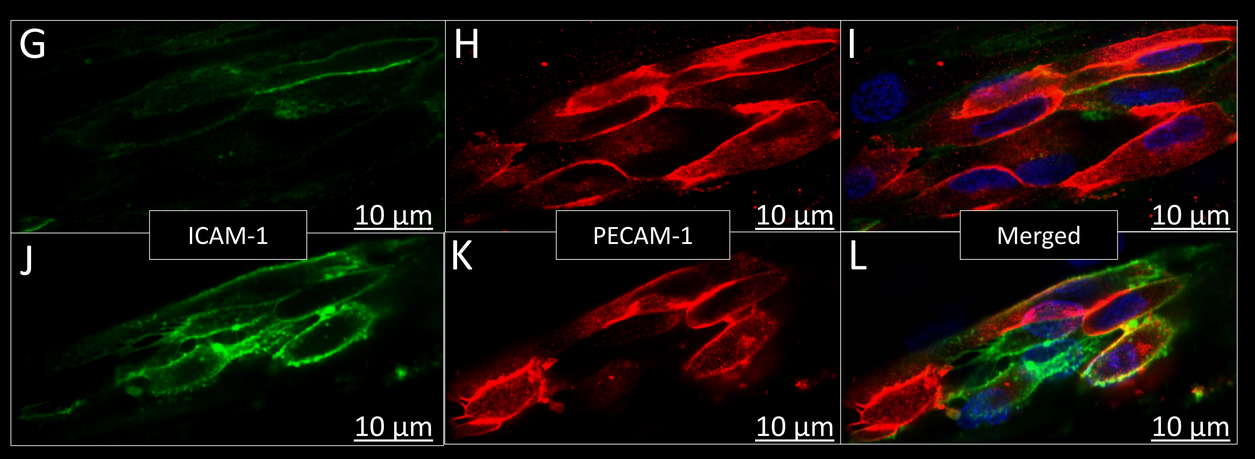


Figure 3. Cellular Functionality in the Scaffold
Cells in the trilaminate structure were tested for proper functionality. Smooth muscle cells (red) in mono-culture (A)(B)(C) exhibited high levels of Ki67 (green), a proliferation marker. Co-cultured smooth muscle cells (D)(E)(F) exhibited a 7-fold decrease in Ki67. Co-cultured endothelial cells (red) exposed to TNF-α (J)(K)(L) doubled the expression of ICAM-1 (green) versus non-exposed (G)(H)(I) co-cultured endothelial cells. Cytoglobin levels in fibroblasts were measured in single and co-culture, showing no significant differences (data not shown).

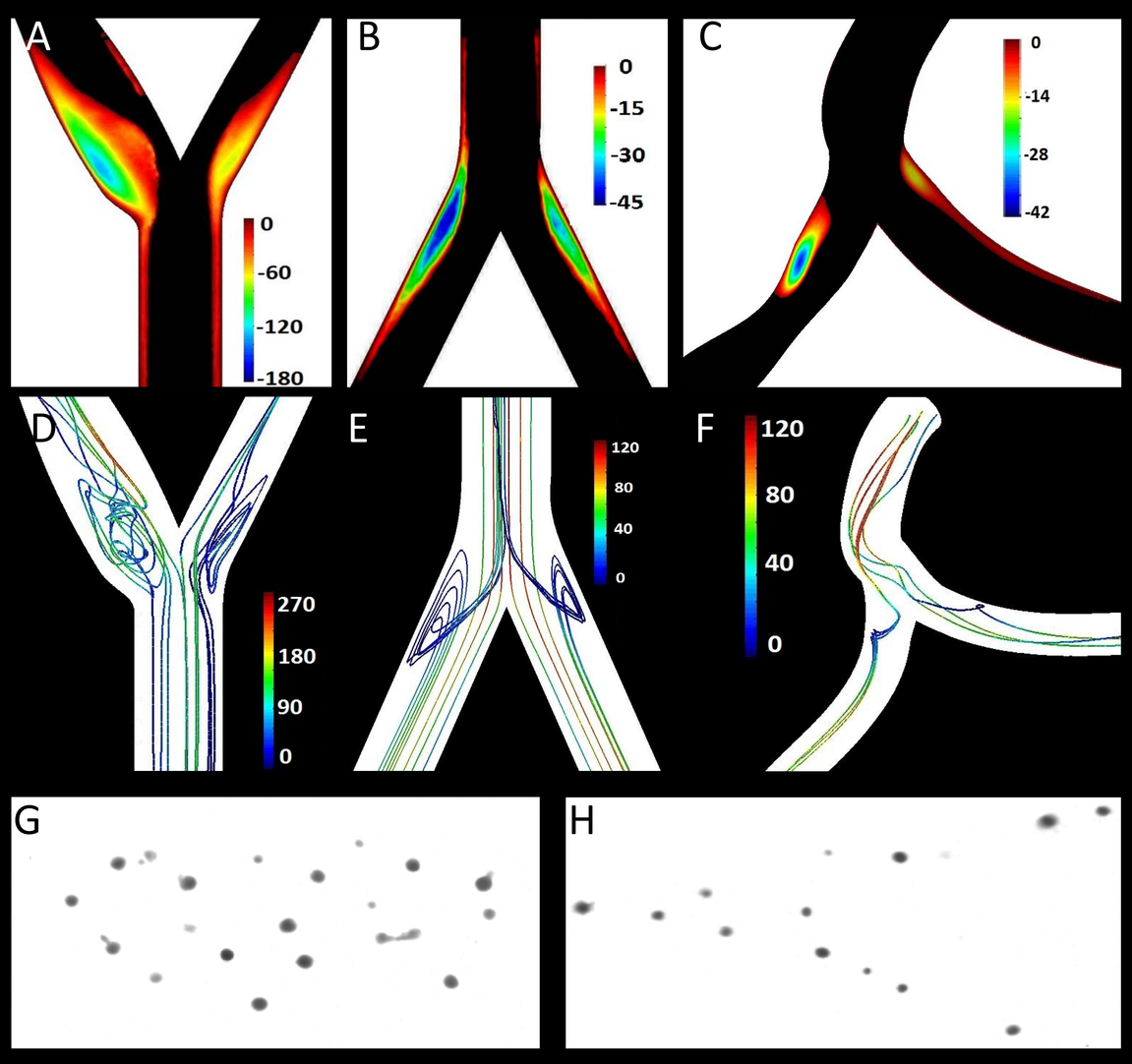


Figure 4. Computational Fluid Dynamics (CFD) Simulations and Microparticle Tracing
CFD simulations were performed to calculate blood flow profiles in a carotid bifurcation with a mild aneurysm (A)(D), a flat left main coronary artery bifurcation into LAD and LCX (B)(E) and the same bifurcation with the actual curvature of a scanned swine heart (C)(F). Results in (A)(B)(C) are velocity profiles in mm/s and results in (D)(E)(F) are absolute velocity stream lines in mm/s. We show patterns of flow stagnation and recirculation in the three bifurcations. Intense recirculation areas were observed after a pulse in both branches of each studied bifurcation, with minimal speed of -150mm/s for (A) the carotid bifurcation, -42mm/s for both (B) the ideal coronary bifurcation and (C) the curved coronary bifurcation. The stream lines (D)(E)(F) help visualizing the recirculation phenomena. Results were confirmed by tracing microparticles flowing through the PDMS bifurcated scaffolds, using a 295 fps camera connected to an optical microscope. We show microparticles at low velocity (G) and in a flow separation region(H).

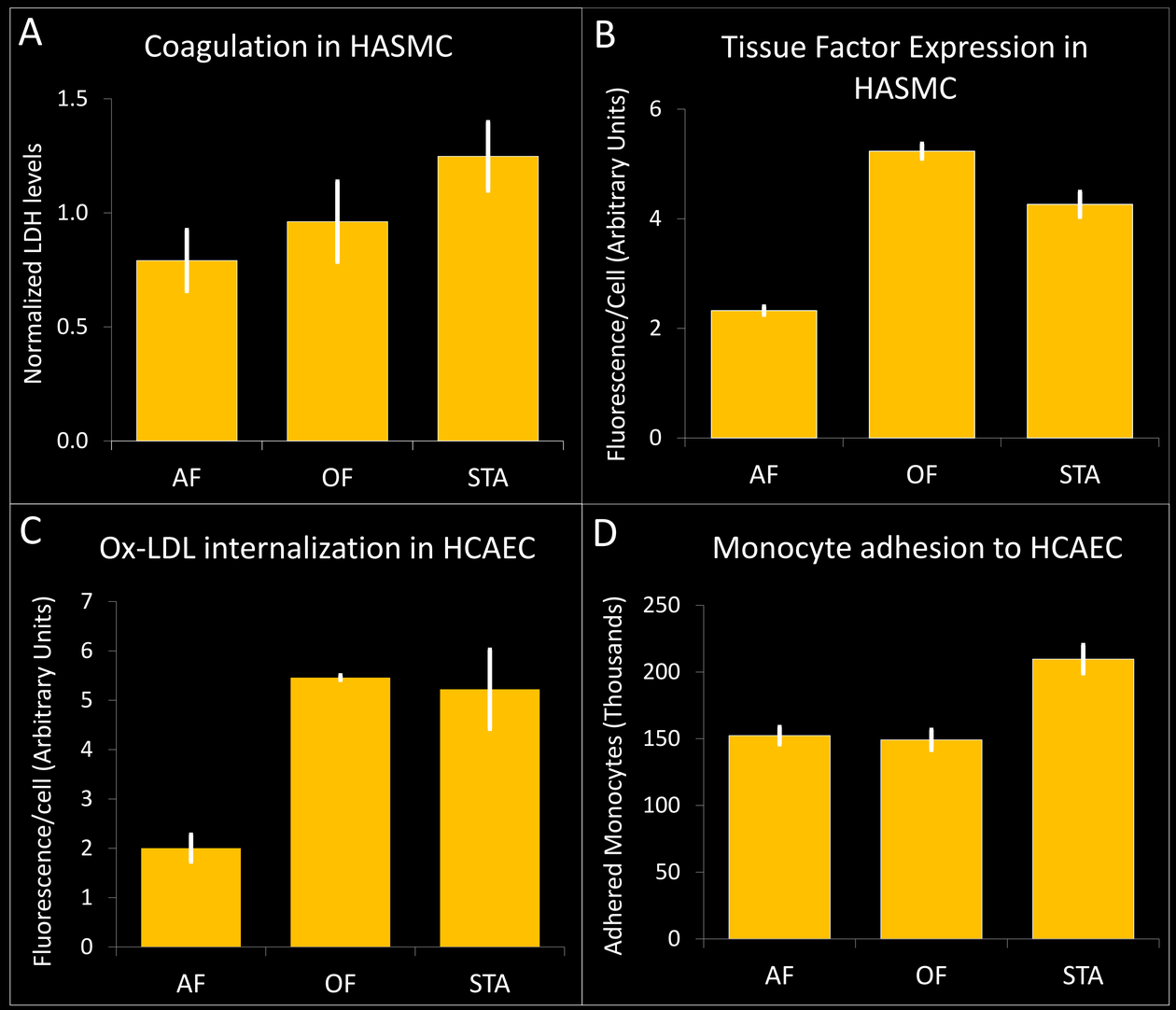


Figure 5. Biological Response to Disrupted Flow Regimes
Endothelial and smooth muscle cells were exposed to different flow regimes characteristic of the studied arterial bifurcations: steady arterial flow (AF) at 18dyn/cm^2, oscillatory flow (OF) at 1 Hz and 18dyn/cm^2, and static condition (STA). (A) The LDH content of coagulated tubes seeded with HASMC decreased a 60% in samples exposed to steady arterial flow compared to the static control. (B) Oscillatory flow caused a 2.5-fold increase while the static control had a 2-fold higher Tissue Factor expression in HASMC when compared to steady arterial flow. (C) The Ox-LDL absorption by HCAEC was 2.5 times higher in oscillatory and static compared to steady arterial flow. (D) Monocytes adhered a significant 25% more when HCAEC were not exposed to flow, compared to steady arterial and oscillatory flow regimes.

Funding Sources
This work has been supported by Ministerio de Innovacion Plan Nacional BFU2009-09804, NIH grant NIH/NIGMS RO1/GM049039, Generalitat de Catalunya FI-DGR-2011, Barcelona Chamber of Commerce, Fundació Empreses IQS, and POSIMAT.