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Van Leeuwenhoek Award money Report

I've just finished my "grand tour" across several labs to explore possible future lines of research and collaborations with a number of investigators that are active in diverse fields of research, but in some way all related to my studies on the endothelial cell glycocalyx.

The major goal of this trip was for me to figure out what the best next step should be, i.e., where to take the glycocalyx research in the next several years.

I met with the following people:

Peter Butler (State College, PA, April 08/09 2003).
Peter Butler is very active within the field of mechanotransduction. More specific, he's interested in the mechanisms responsible for sensing and transducing fluid shear forces by the vascular endothelial surface and resulting in endothelial activation, enhanced NO synthesis and protection against atherosclerotic damage. Peter developed advanced fluorescence microscopic tools to monitor endothelial cell membrane fluidity. Using these tools he is able to demonstrate that fluid shear forces induce a spatially and temporally distributed increase in membrane fluidity. A common matter of interest is whether the biomechanical properties of the endothelial cell glycocalyx structures modulate the sensing and transduction of these fluid shear forces to the endothelial cell interior. We recently published 2 papers about visualization of the endothelial glycocalyx with EM (van den Berg & Vink, Circ.Res. 2003) and its role in sensing fluid shear forces in relation to endothelial NO production (Seiichi & Vink, AJP, 2003 in press). One possible question that we both would like to answer is whether glycocalyx damage via enzyme treatment or oxidative stress impairs endothelial NO production via attenuation of shear induced changes in membrane fluidity.

Peter Davies (Philadelphia, PA, April 102003).
Peter Davies is Director of the Biomedical Institute at the Vagalos labs in Philadelphia. He's also very much interested in the mechanisms for endothelial mechanotransduction of fluid shear forces in relation to development of atherosclerosis. Peter Davies is very well set up for genomics/proteomics type analyses, i.e., measurement of upregulation/downregulation of genes/proteins in (very small numbers of) endothelial cells in relation to endothelial cell activation by fluid shear stress. Peter developed special flow chambers in which cultured endothelial cells are exposed to a spatially and temporally well defined pattern of shear forces. Such an experimental setup can be used for both biochemical and morphological analysis of synthesis/breakdown of endothelial cell glycocalyx structures in relation to transients in fluid shear stress

Geert Schmid-Schoenbein (UCSD, La Jolla, April 11 2003)
Geert recently moved with the Department of Biomechanical Engineering to the new Biomedical Institute in La Jolla. Geert is interested in the role of the glycocalyx in protection against systemic inflammatory activation of the vasculature in response to

(intestinal) ischemia reperfusion damage. It is hypothesized that pancreatic enzymes find their way to the systemic circulation when intestinal wall integrity is compromised as a result of ischemia reperfusion challenge. It is expected that these (very aggressive) enzymes result in systemic breakdown of the endothelial glycocalyx arid associated loss of protective functions. It is of mutual interest to monitor glycocalyx dimension following exposure to pancreatic enzymes and to relate glycocalyx damage to an enhanced thrombogenic endothelial surface, leukocyte-endothelial adhesion and impaired flow dependent dilation.

Jeff Esko (UCSD, San Diego, April 15 2003).
Jeff is Director of the Glycobiology Core Center in San Diego, where advanced technologies have been developed for glycosarninoglycan analysis. More specifically, Jeff is able to analyze exact lengths and sulfation patterns on very short saccharide sequences (down to the monosaccharide level) and to relate these parameters to altered specificity of these saccharides for the binding of (plasma) proteins. Examples of specific Gag-protein interactions that can be studied now are heparan sulfate (HS) - antithrombin III (AT III), HS - FGF (fibroblast growth factor), and HS - LPL (lipoprotein lipase). We recently studied the effect of fluid shear stress on endothelial binding of LPL and are currently trying to relate enhanced LPL binding to shear stress exposed endothelial cells to enhanced synthesis / sulfation of endothelial heparan sulfates. Collaboration with Jeff would allow for detailed analysis of shear induced modulation of HS synthesis / sulfation levels / sulfation encoding patterns in relation to endothelial surface binding of anti-atherogenic proteins and enzymes.

Presentations have been given for Peter Butler, Peter Davies and Jeff Esko. Copies of the (rather large) power point presentations cannot be attached to this email because of size limitations in exporting files out of our Amsterdam Institute. Let me know if you need to have the presentations. In that case I can copy them to CD and send them to you by regular mail.

Hans Vink