

P004 PI3K-NOS3 pathway in shock
**Cauwels,A., Janssen,B*, Buys,E., Sips,P.,
Brouckaert,P.**

*Department for Molecular Biomedical Research,
Ghent University and VIB, Ghent, Belgium;*

**University of Maastricht, Maastricht, The Netherlands*

The PI3K/Akt pathway can phosphorylate Nitric Oxide Synthase-3 (NOS-3), thereby activating it independent of Ca^{++} and calmodulin, and allowing production of larger amounts of NO. NOS-3 or endothelial NOS is a constitutive NOS which is traditionally regarded as an isoform only involved in physiological vasorelaxation, activated by e.g. shear stress. In contrast, the inducible Ca^{++} independent NOS-2 is considered to be the source of the NO implicated in inflammatory shock conditions such as sepsis and anaphylaxis. We investigated the role of this PI3K-Akt-NOS-3 pathway in various shock models *in vivo* in non-anaesthetized mice. While we did not find any effect in TNF or LPS induced shock, we observed that this pathway is crucial in Platelet-Activating Factor (PAF)- induced and in anaphylactic shock. Anaphylaxis is an acute, systemic and potentially fatal systemic allergic reaction caused by e.g. bee stings, food, medications, and latex exposure. The use of knockout mice and/or chemical inhibitors allowed us to demonstrate that this critically depends on PI3K and NOS-3. We furthermore demonstrated that the Akt inhibitor perifosine could prevent development of shock in an anaphylactic shock model in ovalbumin-sensitized mice. We propose PI3K, Akt and NOS-3 as potential new targets in the prevention or treatment of anaphylaxis.