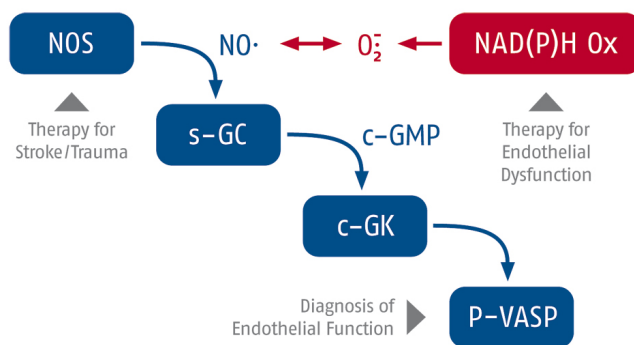


## :: Scientific Background

An important factor in the process of endothelial dysfunction is the functioning of nitric oxide (NO) as determined by the NO/cGMP pathway. Nitric oxide, in conjunction with its cellular signalling pathway, is a key factor in vascular protection by preserving vessel reactivity. Endothelial dysfunction is considered as the precursor of several cerebro- and cardiovascular diseases, e.g. stroke, hypertension, atherosclerosis, myocardial infarction, coronary artery disease, peripheral arterial occlusive diseases.



The vascular tone of arteries is primarily steered by the bioavailability of NO. Increasing concentrations of this molecule lead to a relaxation of the vessels. NO concentrations that are too low hamper the ability of the arteries to dilate and the ground for atherosclerotic changes is laid.

Excessive NO production is known to contribute to the damaging effects of closed head injury (CHI). A compound (VAS203) able to reduce the availability of NO by inhibition of its synthesizing enzyme, nitric oxide synthase (NOS), has been developed to control the deleterious consequences of CHI. This new drug will address the unmet medical need of more than 300.000 patients who suffer from persistent disabilities after closed head injury every year. Currently there is no pharmacological treatment available, and so far all previous drug development efforts have failed, most likely because the treatments were based exclusively on protecting the brain tissue. In contrast, VAS 203 intervenes on both vascular and intra-cranial pressure.

Chronically insufficient NO production has been proposed to underlie chronic cardiovascular diseases such as hypertension and atherosclerosis. Since reactive oxygen species (ROS) are the most important biological reactants which remove NO and therefore and substantially lower its availability, another approach of **vasopharm** is to discover compounds to inhibit enzymes which produce ROS. The most important source of ROS in vascular tissues, particularly under pathological conditions, is the NAD(P)H oxidases (NOX). **vasopharm** has discovered compounds which inhibit the entire NOX enzyme family. Such compounds should for the first time permit prophylactic treatment of hypertension, atherosclerosis and other cardiovascular diseases related to endothelial dysfunction.