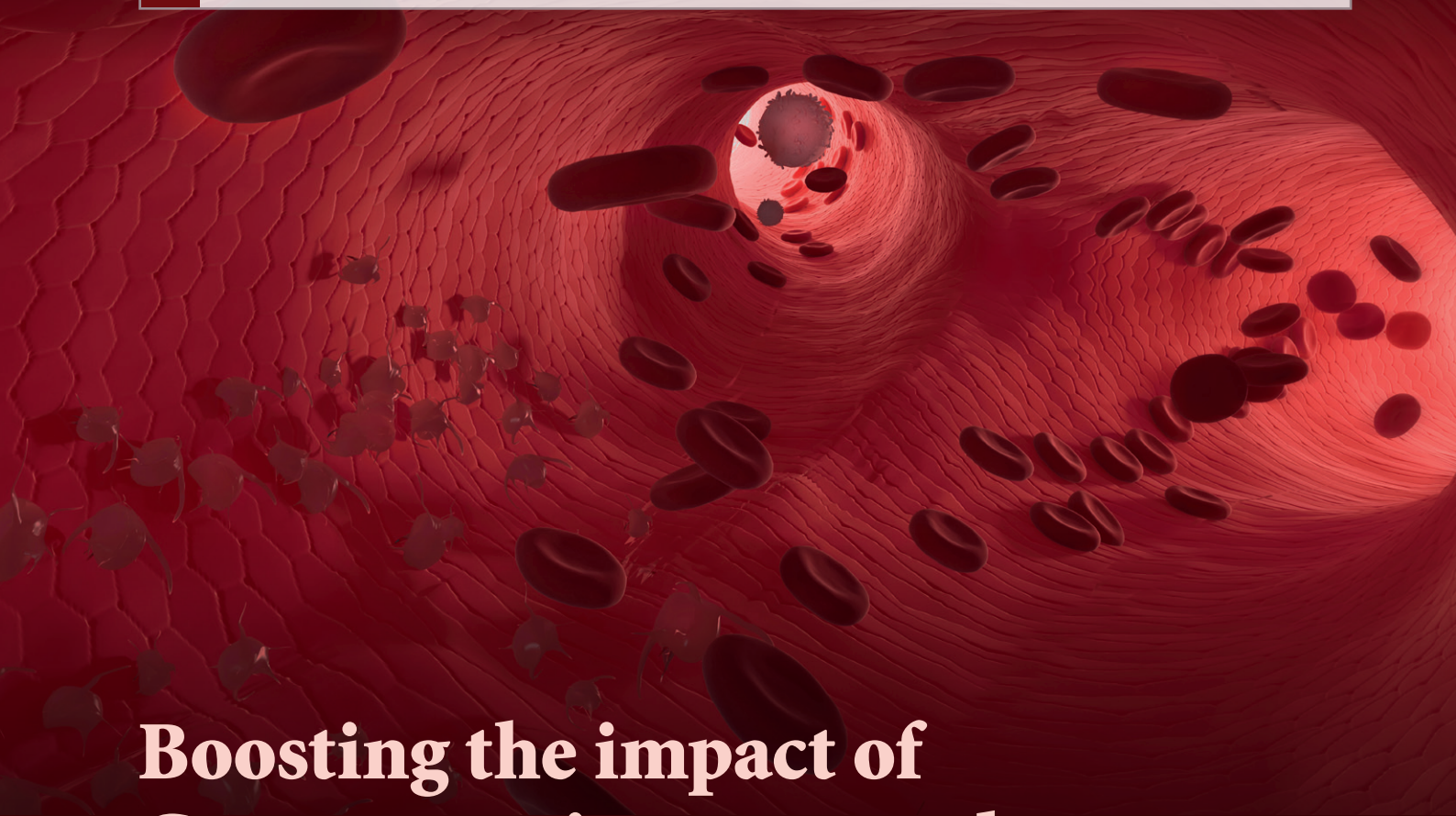
A family of endogenously produced gaseous molecules, 'gasotransmitters', are associated with a number of beneficial biological properties, but they can have adverse effects on health in excess amounts. The European Network on Gasotransmitters aims to boost the impact of European research in this field, as **Professor Andreas Papapetropoulos** explains



Boosting the impact of Gasotransmitter research

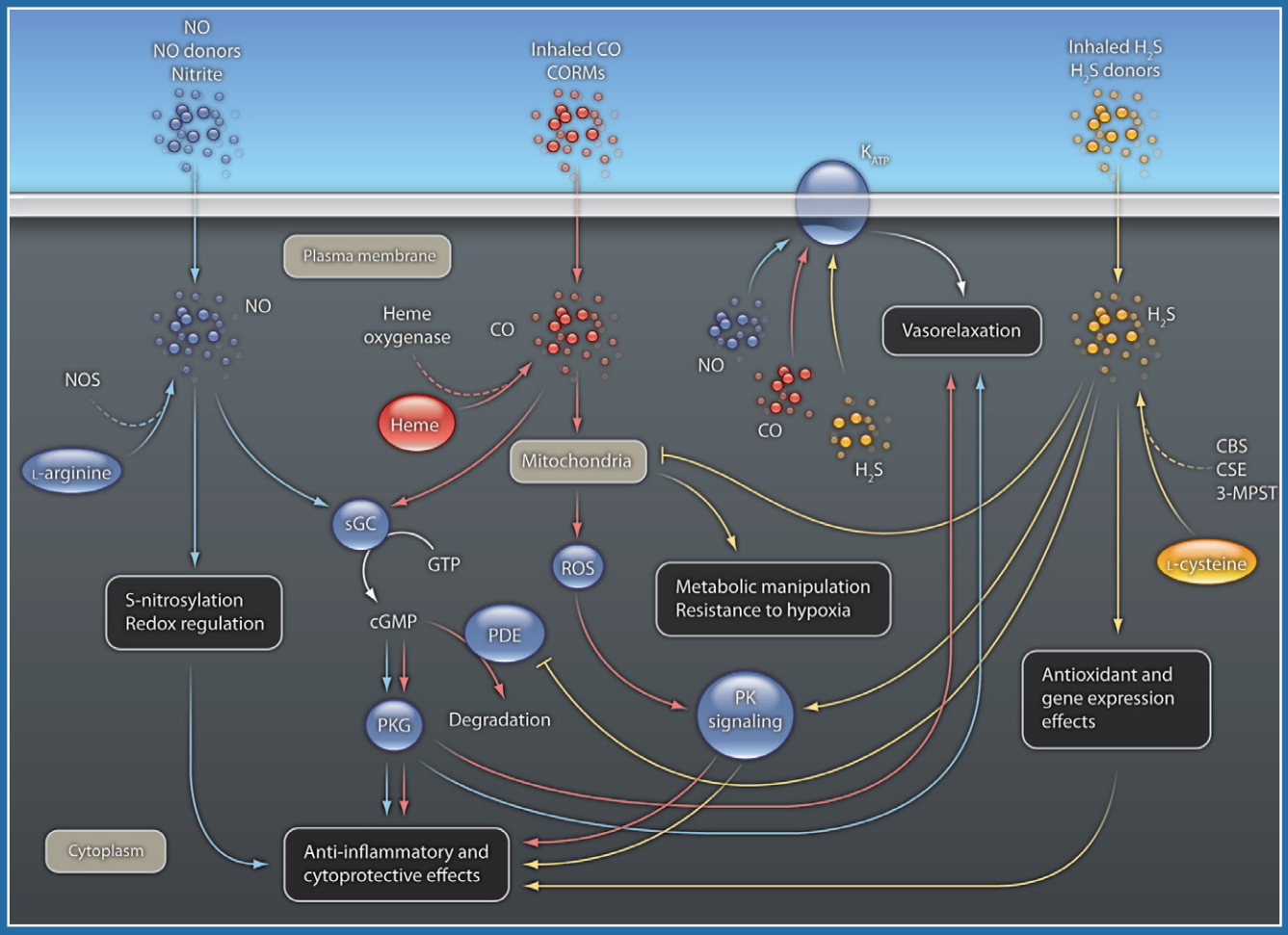
A family of endogenously produced gaseous molecules, 'gasotransmitters', play important roles in many human organs and tissues, including the heart and the blood vessels, the immune system and the nervous system. The three principal gasotransmitters are nitric oxide (NO), carbon monoxide (CO) and hydrogen sulphide (H_2S). "A common feature linking NO, CO and H_2S is that they are produced by human cells in small amounts, but are associated with considerable toxicity when present in high concentrations. High concentrations might be the result of uncontrolled endogenous production or exposure to high exogenous levels," explains Professor Andreas Papapetropoulos, the coordinator of the European Network on Gasotransmitters (ENOG).

The prototype gasotransmitter is NO, which was described in 1980 as endothelium derived relaxing factor (EDRF). While a fair amount of information is available on NO, less is known about CO and H_2S, an issue that Professor Papapetropoulos and his colleagues are working to address. "We're trying to employ some of the paradigms used to understand the biological actions of NO in order to unravel the properties of the newer gasotransmitters (i.e. CO, H_2S)," he continues. "We have already learnt a lot about CO and H_2S over the past decade. The true challenge though is to harness the therapeutic potential of the newer gasotransmitters, once we understand more about how they work in our bodies."

The network is working to boost the quality, competitiveness and impact of European biomedical research in this area. Bringing together scientists from 24 European countries, the network aims to facilitate research on gasotransmitters by encouraging researchers to share their reagents, tools, knowledge and ideas. Another important aspect of the network is to provide financial support for mobility of young and early stage researchers between member laboratories. ENOG members have already published several joint publications as a result of their common work within the network.

Working groups

NO and H_2S are derived from amino acids and CO is produced through the breakdown of iron-containing structures



(C. Szabo, Gaseotransmitters: New Frontiers for Translational Science. Sci. Transl. Med. 2, 59ps54 (2010).)
Credit: C. Bickel/Science Translational Medicine.

called haem, while Professor Papapetropoulos says they are also quite different in their reactivity. "H_2S is more promiscuous – it reacts with more biological molecules than NO, and then CO has fewer targets than the other two," he explains. The project is investigating key issues around gasotransmitters, including their abundance in different cells of the body, how their production is controlled and what happens when their production becomes deregulated. A number of beneficial biological properties are associated with gasotransmitters, which researchers are trying to exploit. "Gasotransmitters inhibit programmed cell death (or apoptosis). They also dilate blood vessels, protect the heart, exert anti-inflammatory properties under most conditions and are neuro-protective," outlines Professor Papapetropoulos.

To answer the scientific questions on gasotransmitters, the action is divided into four working groups, covering different aspects of gasotransmitter chemistry and biology. This encompasses both fundamental research into their roles in the body, as well as more applied work. "One of the working groups is studying the production of the gasotransmitters and the signalling pathways they trigger, while another is looking at their role in physiology and in the initiation and progression of disease," says Professor Papapetropoulos. "A third group is looking at making new chemical entities, potentially new drugs (or lead compounds that will lead to drugs), that will either boost or inhibit the production or action of gasotransmitters, depending on whether they are in shortage or surplus in the disease studied. A fourth group employs these agents in different disease models, to see if they are effective."

Translational problems and opportunities

It has become apparent that gasotransmitters are found in almost every tissue in the body. "This widespread distribution tells us they are important for many functions, but also makes it difficult to selectively inhibit gasotransmitters in one part of the body without interfering with normal physiological processes in another," Professor Papapetropoulos points out.

Two forms of constitutive (expressed at all times) NO synthase (the enzyme that produces NO in the body) have been identified – one that is known to be primarily expressed in the endothelium, which lines all our blood vessels, and one in nerves. "We don't currently have good

Gasotransmitters **inhibit programmed cell death (or apoptosis). They also dilate blood vessels, protect the heart, exert anti-inflammatory properties** under most conditions and are **neuro-protective**

selective inhibitors that can differentiate between the two types of NOS. If one could come up with novel drugs that can inhibit only the neuronal NO, we might have a new candidate drug to use in strokes," says Professor Papapetropoulos.

Inhibiting neuronal NOS has been shown to be advantageous in treating strokes. However, whilst the NO that comes from the endothelial NO synthase is beneficial, you clearly need a compound to selectively inhibit one form of NOS and not the other. "It is equally difficult to selectively target an organ with a deficiency in a gasotransmitter without affecting the function of other tissues," says Professor Papapetropoulos.

In spite of these difficulties, there are clinically used drugs that work by modifying gasotransmitter levels. For example, nitroglycerin (NTG) has been used since 1867 to treat angina pectoris: it is effective against this condition because of the NO it generates. Physicians had used NTG for over 100 years, without knowing exactly how it worked.

It is thus not surprising that the scientists that described the mode of action of NTG were awarded the Nobel Prize for Physiology/Medicine in 1998. More recently, drugs that target the 'receptor' for NO (soluble guanylyl cyclase) received marketing authorisation approval for pulmonary hypertension; interestingly they activate the 'NO-receptor' without releasing NO.

The research performed within the ENOG is currently pre-clinical in nature, with researchers aiming to identify diseases which could be treated by either supplementing or inhibiting gasotransmitter production. "H_2S for example shows great promise for cardioprotection and gastrointestinal protection. Ultimately the hope is to translate these findings into therapeutic gain," explains Professor Papapetropoulos. "Interestingly, we have found some drugs, for example zofenopril, that are currently in clinical use and produce H_2S. It remains to be determined what percentage of the beneficial effects of the drug are gasotransmitter-related."

Effective collaboration is essential to building on this kind of fundamental knowledge and developing new drugs, a complex process that calls for a wide range of expertise. "You need biochemists to produce and characterize the enzymes that generate or respond to gasotransmittrers, structural biologists to define the 3 dimensional structures of the enzymes, and medicinal chemists to design the chemicals that would affect the function of the enzymes by targeting their active sites."

"Then, once the novel chemicals have been synthesized, you need pharmacologists to test the compounds for their efficacy. If need be, compounds undergo several rounds of optimisation," outlines Professor Papapetropoulos. "On the other hand, molecular biologists and geneticists make crucial contributions by generating model organisms that lack the expression of gasotransmitter-related enzymes, or overexpress them. Then physiologists characterize the phenotype of these animals generated. This latter approach can give valuable information about the types of diseases that would benefit from gasotransmitter treatments, so you can study which diseases they are involved in. It is exactly this multidisciplinary approach we are trying to take to get answers within our network."

There is great scope for further research, so while the current COST action will end in 2015, Professor Papapetropoulos and his colleagues are looking to continue their work in this area. Plans are already in place to apply for further funding (particularly to procure Horizon 2020 funding from the EU) and establish wider collaborative projects. "We are already in contact with other societies and scientists throughout the world that work with NO and H_2S. European scientists will have a very prominent position in the new networks formed," says Professor Papapetropoulos. "We also aim to establish partnerships with SMEs and biotech companies that are interested in developing chemicals, therapeutic agents and detection reagents for gasotrasnmitters."

The true challenge though is to harness the therapeutic potential of the newer gasotransmitters, once we understand more about how they work in our bodies

At a glance

Full Project Title
Gasotransmitters

Project Objectives
The objective of our network is to collate scattered knowledge, resources and expertise on NO, CO and H_2S in Europe and to drive research in order to better understand gasotransmitter biology so that the therapeutic potential of gasotransmitters can be harnessed. We aim to disseminate innovation, boost collaborations and increase the European competitiveness in this field of research.

Project Funding
European Science Foundation

Project Partners
170 members from 24 European countries.
http://www.cost.eu/domains_actions/bmbs/Actions/BM1005

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