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2nd European Conference on the Biology of Hydrogen Sulfide, Exeter, England 8th–11th September 2013

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This special issue of the *Nitric Oxide* journal presents recent proceedings and developments in the fields of hydrogen sulfide (H₂S) chemistry, physiology, biology and pharmacology that were discussed at the 2nd European Conference on the Biology of Hydrogen Sulfide held in Exeter, England on 8th–11th September 2013. This conference was the fourth dedicated international meeting on H₂S after Shanghai, PR China (June 2009) [1], Smolenice, Slovakia (June 2012) [2], Atlanta, USA (September 2012) [3] and strongly reflects the recent growing European [4] and international interest in this intriguing endogenously produced ‘gasomediator’. Indeed, subsequent meetings are planned for 2014 in Japan [5] and 2015 in Greece [6]. The aim of the meeting was to promote close international and multidisciplinary collaboration between researchers working on H₂S to address key problems in the research field (donors, inhibitors, real time probes, analytical techniques tools) and to identify new potential areas for exploiting H₂S in agriculture and medicine. Although the title of the meeting suggested a European focus, researchers and students from around the world attended the meeting with just under half of the 120 delegates coming from outside the European Union; from USA, Canada, Mexico, Argentina, PR China, Singapore and Australia reflecting the growing global interest in H₂S. There were 21 plenary lectures from leaders in the field, 32 short talks selected from submitted abstracts and 65 poster presentations presented over 3 ½ days.

The meeting was started on the evening of Day 1 with an excellent opening plenary by Hideo Kimura (Japan) illustrating the rapid rise of the H₂S field in the scientific literature over the last two decades. This was followed by a detailed historic overview of the evolution of H₂S field to date, focussing on cellular signalling events mediated by H₂S and persulfide intermediates in the brain. Day 2 started with a lecture from Ken Olson (USA) [7] on the analytical and methodological problems in quantifying H₂S/sulfides in biological fluids. This was followed by Andreas Papapetropoulos (Greece) [8] and advances and pitfalls with pharmacological tools used to investigate the physiology of H₂S presenting interesting data on the selectivity and potency of commonly used H₂S synthesis inhibitors. Both lectures provided a critical appraisal of the research methodology and pharmacological tools used in the H₂S research and highlighted the need for the field to refine the techniques and experimental tools, especially inhibitors. This session was followed by a lecture from Peter Radermacher (Germany) [9] on the central role of H₂S-synthesising enzymes in the development and maintenance of atherosclerosis and sepsis. Matt Whiteman (UK) then gave

a lecture on the on novel slow release donors to model endogenously produced H₂S and compounds such as AP39 which target mitochondria and regulate cell survival and pro-inflammatory signalling when used at low nM concentrations [10,11]. The role of H₂S signalling in plants were also presented with stimulating lectures from Stanislav Kopriva (UK) [12] and Lorenzo Lamattina (Argentina) [13] and four short talks from submitted abstracts. Many of the problems with H₂S measurement and enzyme activity assays, H₂S donors and synthesis inhibitors are also common in plant research and the conference provided an excellent opportunity for interdisciplinary discussion and collaboration to move the field forwards. Day 2 was expertly rounded off by evening plenary lectures by Rui Wang (Canada) and John Wallace (Canada) on the therapeutic potential for H₂S donating molecules in the treatment of metabolic disorders, atherosclerosis [14], colitis and enteropathy [15]. In particular, a H₂S-donor derivative of naproxen (ATB-346) offers an exciting prospect for the field in being the first H₂S donor to enter clinical trials for colitis.

Day 2 started with a focus on H₂S and vascular disease. David Lefer (USA) demonstrated the efficacy of the *Allium* derived organosulfur H₂S donor diallyl disulfide in heart failure by promoting the expression of pro-angiogenic factors and enhancing eNOS-derived *NO bioavailability, highlighting *in vivo* cross-talk between H₂S / *NO (see below) and as a 'natural product' offers exciting therapeutic potential [16]. Suresh Tyagi (USA) followed up with a talk describing the intimate relationship between homocysteine and H₂S in renal complications associated with hyperhomocysteinaemia [17]. In addition, Jin-Song Bian (Singapore) presented an intriguing study to at least partly explain the depressive effect of exogenous H₂S on mitochondrial oxidant production; sulfhydration of redox enzyme p66Shc and inhibition of PKC signalling [18]. The contradictory effects of H₂S in angiogenesis and cellular bioenergetics in relation to carcinogenesis were also discussed; Csaba Szabo (USA) and Ciro Coletta (USA) provided compelling evidence that the H₂S synthesising enzyme CBS is upregulated in colorectal carcinoma where CBS-derived H₂S promoted vigorous cell proliferation and showed data strongly suggesting inhibitors of CBS would be useful therapeutic agents in cancer treatment [19–21]. In sharp contrast, similarly compelling evidence for an anti-cancer effect of H₂S donors, notably by GYY4137, was provided in a short talk by Li-Wen Deng (Singapore) [22,23] and poster presentations by her group [24] highlighting the complex and at present ambiguous role H₂S and its synthesising enzymes has in carcinogenesis. The direct metabolic effects of H₂S on mitochondria were further discussed by Frederic Bouillaud (France) [25,26], specifically the central role of mitochondrial sulfide quinone reductase (SQR) in regulating the mitochondrial effects of sulfide, where at low (nM) concentrations H₂S acts as a hydrogen donor and respiratory substrate and at high (μM) concentrations, sulfide inhibits respiration and exerts detrimental effects on cellular bioenergetics. Mitochondria appear to act as a sink for sulfide and understanding how they regulate intracellular sulfide levels is crucial to unravelling the biological role and agricultural and therapeutic potential of H₂S. Lily Wu (Canada) then examined the role of H₂S in diabetes, cellular uptake of glucose and inhibition hyperglycaemia driven production of toxic intermediates such as methylglyoxal [27] suggesting H₂S supplementation may be beneficial in the treatment of diabetes and / or diabetic complications. Day 3 was rounded off with an evening plenary by Yi-Zhun Zhu (PR China) giving an overview of the development of a novel CSE 'activator' and H₂S donor S-

propargylcysteine (SPRC); from its discovery in the laboratory through to its effects in animal models of vascular and neurodegenerative disease, drug delivery and formulation as well as its progress from pre-clinical testing to phase I trials in humans [28].

The final day focussed on the chemical cross-talk between $\cdot\text{NO}$ and H_2S and future directions for the field. Milos Fillipovic (Germany) [29,30] and Martin Feelisch (UK) [31] dissected the chemical interactions between $\cdot\text{NO}$, H_2S and nitrosothiols and the analytical challenges in precisely defining this interaction and identifying, then physiologically characterising the likely products and/or intermediates formed *in vivo* such as HSNO [30] and SSNO⁻ [31]. Chris Kevil (USA) showed *in vivo* data on H_2S and $\cdot\text{NO}$ bioavailability in a variety of models which clearly highlighted the complex nature of the relationship between these gaseous cousins, as well as how to tackle the analytical problems associated with measuring both in biological fluids. The short talks from this session included Jose A. Olabe (Argentina), Sebastiaan Wesseling (Netherlands) and Eliana D'Ario (UK) who discussed the chemical reactions and interactions of H_2S with nitroprusside, carbon monoxide/Heme oxygenase. This session was finished with a short talk from Paul Winyard (UK) presenting data which suggested H_2S may be involved in mediating the functional effects of dietary nitrate ingestion. The precise nature of the direct chemical interaction of H_2S , $\cdot\text{NO}$, HO/CO and their intermediates is highly complex and is likely to create animated debate for years to come. The final two talks by Pauline M. Snijder (Netherlands) and Christopher J Kelsall (UK) provided an intriguing insight into future directions the field may take; using the power of fly genetics (*Drosophila Melanogaster*) to examine the role of H_2S and H_2S synthesising enzymes in spinocerebellar ataxia and using metal organic frameworks as a means for selective vascular delivery of H_2S .

In Summary, results from this meeting provided in important and unique insights into the emerging importance of H_2S in biology, agriculture and medicine. In particular, the analytical challenges, the need for better pharmacological tools (donors and inhibitors) and advances with animal knock-outs. Methodological advances for the measurement of H_2S in biological systems (plants, animals and humans) were provided as well as several presentations highlighting novel tools for the real time detection of H_2S (e.g. fluorescent probes). Excitingly, at least two H_2S donor compounds ATB-346 and SPRC are being evaluated in early clinical testing and if successful, will propel the field forward. Together, the presentations and discussion at this conference has answered many questions but as the field progresses very rapidly, it has also created many more to be answered in future, setting the tone for future meetings such as Japan [5] and Athens [6].

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2. First European Conference on Hydrogen Sulfide Biology, Smolenice, Slovakia, 15th–18th June 2012. (<http://www.h2s.sk>), organised by Prof. Karol Ondrias, Slovak Academy of Science, Slovakia.
3. Second International Conference on Hydrogen Sulfide in Biology and Medicine. (<http://h2s2012.wordpress.com/>) organised by Prof. David Lefer, Emory University, USA.
4. European Network on Gasotransmitters. (<http://gasotransmitters.eu/>).

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