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Hydrogen sulfide as a therapeutic gas: challenges and opportunities in precision medicine

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Hydrogen sulfide (H_2S) was once considered a toxic environmental pollutant, but scientific thinking has shifted, and it is now recognized as the third endogenous gasotransmitter, alongside nitric oxide and carbon monoxide.[1] This transition to a central signaling molecule was catalyzed by the discovery of key endogenous enzymes, cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase, producing H_2S at physiological concentrations.[2] Since then, biomedical research has discovered that H_2S in physiological concentrations within the nanomolar to low micromolar range is a key regulator of vascular tone, mitochondrial respiration, redox balance, and inflammatory response.[3] The expanding preclinical evidence base supports the therapeutic potential of H_2S in an expansive range of pathological conditions, e.g., cardiovascular and neurodegenerative diseases, metabolic disorders, and inflammatory disorders.[4] However, there is little clinical use of H_2S-based therapy. This perspective presents a concise summary of the recent development in the therapeutic discovery of H_2S, the translational issues, and the tools to progress clinical application, in particular in the era of precision medicine, as illustrated in **Table 1** and **Figure 1**.

Endogenous H_2S signaling: Endogenous H_2S is enzymatically synthesized in mammalian tissues through three key enzymes: CBS, which is predominantly expressed in the brain; CSE, which is abundant in cardiovascular and hepatic tissues; and 3-mercaptopyruvate sulfurtransferase, which is distributed in both cytosol and mitochondria.[5] These enzymes metabolize sulfur-containing amino acids, mainly L-cysteine and homocysteine, to generate H_2S.[6] Expression and activity of these enzymes are tissue-specific and dynamically regulated by physiological stressors such as hypoxia, inflammation, and oxidative stress.[3]

H_2S mediates its biological functions via multiple, tightly regulated signaling mechanisms:

Protein persulfidation and redox signaling: One of the central mechanisms of H_2S signaling is persulfidation (also known as S-sulfhydration), wherein H_2S modifies the reactive cysteine residues of target proteins. This redox-sensitive modification alters protein conformation and activity, impacting critical signaling pathways, including nuclear factor-κB, Keap1-Nrf2, GAPDH (glyceraldehyde-3-phosphate dehydrogenase), and Akt.[6] Through these interactions, H_2S contributes to cytoprotection, antioxidant defense, and metabolic regulation.[5]

Mitochondrial function and energy metabolism: H_2S supports mitochondrial bioenergetics by stimulating adenosine triphosphate production, enhancing complex IV activity under hypoxic conditions, and reducing reactive oxygen species generation within mitochondria.[6] These effects underscore its role in maintaining cellular energy homeostasis and mitigating oxidative damage, particularly in metabolically active and stress-prone tissues.

Anti-inflammatory and immunomodulatory effects: H_2S exhibits potent anti-inflammatory properties by inhibiting leukocyte adhesion, reducing pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β, and IL-6, and suppressing the activation of the NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) inflammasome.[5] These actions position H_2S as a modulator of innate immune responses and a potential therapeutic agent in chronic inflammatory conditions.

Angiogenesis and hypoxia response: In conditions of low oxygen, H_2S promotes angiogenesis through upregulation of vascular endothelial growth factor and modulation of hypoxia-inducible factor-1α.[6] These actions are vital in tissue repair, wound healing, and adaptation to ischemic stress.

Taken together, these diverse signaling routes highlight H_2S as a multifaceted mediator of cellular homeostasis. However, its dose- and context-dependent effects necessitate careful regulation in therapeutic applications to avoid deleterious outcomes. Targeted delivery systems that preserve physiological concentrations are essential to harness the full therapeutic potential of H_2S.[6]

Therapeutic potential, disease models and experimental evidence: H_2S donors have shown promising effects in various disease models. For instance, the application of H_2S donors significantly reduces myocardial infarct size while improving endothelial function and lowering blood pressure in cardiovascular conditions.[7] The administration of sodium hydrosulfide (NaHS) and mitochondria-targeted H_2S donor AP39 to mice has resulted in enhanced cardiac output and decreased oxidative damage during reperfusion injury.[8] In neurodegenerative diseases, H_2S improves outcomes by attenuating neural cell death and mitigating dementia-like symptoms, primarily through modulating microglial activation and mitochondrial function.[9] In models of type 2 diabetes, exogenous H_2S improves insulin sensitivity, protects pancreatic β-cells, and decreases systemic inflammation.[10] Interestingly, the role of H_2S in cancer remains dualistic: while it promotes tumor growth and angiogenesis in some cancers, it induces apoptosis and redox imbalance in others. These divergent effects emphasize the need for context-dependent delivery strategies and precise dosing, as inappropriate administration could exacerbate disease progression. Current laboratory findings reinforce this duality, stressing that future therapeutic delivery should consider tissue sensitivity, molecular environment, and concentration thresholds.

Key research gaps and limitations: Despite progress, several critical research gaps continue to hinder the clinical translation of H_2S-based therapeutics. One major challenge is the lack of standardized techniques to measure free versus bound H_2S in biological samples. Current methodologies such as colorimetric assays, gas chromatography, and electrochemical sensors vary greatly in sensitivity, specificity, and reproducibility, leading to inconsistent results.[8,9] Moreover, many existing H_2S donors display uncontrolled or burst-release pharmacokinetics, limiting their therapeutic reliability. Species-specific metabolic differences further complicate extrapolation from animal models to human physiology. A major barrier is the absence of clinically validated biomarkers for monitoring treatment efficacy or predicting patient response. Though protein sulfhydration patterns and H_2S-metabolite ratios hold potential as biomarkers, they require rigorous clinical validation.[9] Additionally, the long-term safety profile of H_2S therapy remains unclear due to a lack of comprehensive studies on immunogenicity, toxicity, and interference with endogenous redox systems.

Recent innovations in H_2S delivery systems: Several next-generation H_2S delivery platforms have emerged to address the challenges of dose precision, tissue targeting, and timed release. Slow-releasing donors such as GYY4137 and SG-1002 demonstrate extended half-lives, reducing systemic toxicity and improving in vivo tolerance.[2] Notably, SG-1002 has advanced into Phase I/II clinical trials for heart failure therapy. The mitochondria-targeted donor AP39 selectively accumulates in energy-demanding tissues such as the heart and brain, enhancing oxidative protection.[2] Recent developments include stimuli-responsive prodrugs, which release H_2S only under specific pathological triggers like acidic pH or elevated thiol levels.[3] Mesoporous silica nanoparticles, thiobenzamide-based carriers, and enzyme-activated nanogels represent innovative systems that enable site-specific, on-demand H_2S delivery. Additionally, biomaterial scaffolds functionalized with H_2S-releasing nanoparticles are being tested in tissue engineering applications such as wound healing and post-ischemic regeneration.[2,3] These novel systems demonstrate substantial potential, but require further optimization to improve release kinetics, ensure biocompatibility, and enable scalable manufacturing.[4]

Biomarker development and systems integration: The development of clinically viable diagnostic tools and biomarkers is vital for translating H_2S therapy. Multi-omics approaches integrating transcriptomics, redox proteomics, and metabolomics have provided insights into systemic H_2S signaling.[10] Protein sulfhydration can now be profiled using mass spectrometry coupled with modified biotin-switch techniques, revealing key regulatory mechanisms.[2] Additionally, gold nanoparticle-based electrochemical sensors have improved the real-time detection of H_2S in blood and tissue samples, while fluorescent probes (e.g., HSip-1 and AzMC) enable subcellular visualization of H_2S distribution and effects.[1] However, the translation of these experimental tools into approved clinical diagnostics is hindered by several unresolved issues. These include the absence of universal calibration standards, inter-platform variability, and the need for longitudinal validation studies. To overcome these challenges, future efforts should focus on: Standardizing detection protocols across platforms and laboratories. Developing reference ranges and diagnostic thresholds. Implementing long-term studies for biomarker validation in diverse patient populations. Regulatory framework development for approval and clinical adoption.[2] Addressing these aspects will be key to ensuring reliable therapeutic monitoring, patient stratification, and safety evaluation in H_2S-based medicine.

Precision medicine applications of H_2S: Medical precision frameworks that incorporate H_2S therapeutics provide an effective solution for managing drug symptoms among different patients.[5] The production of H_2S through CBS and CSE enzymes depends on genetic variants, which lead to hypertension and hyperhomocysteinemia and cognitive impairment.[6] The screening process of these variants enables doctors to determine, which patients should receive H_2S-targeted therapy.[9] Research shows H_2S metabolism operates at different levels between male and female patients and across different age groups so therapeutic dosing should be adjusted for each demographic.[10] The epigenetic regulation of H_2S synthesis pathways through DNA methylation to CSE and microRNA-mediated regulation to CBS indicates that H_2S acts as a gene expression-modulating factor to enable new epigenetic treatment possibilities.[6] The combination of H_2S-based treatments with

Table 1 | Biochemical properties, signaling mechanisms, and therapeutic roles of hydrogen sulfide (H_2S)

Category	Details	References
Molecular formula	H_2S – a small, lipophilic gaseous signaling molecule	1
Endogenous biosynthesis	Synthesized via enzymatic metabolism of L-cysteine and homocysteine by: • CBS (brain dominant) • CSE (liver, cardiovascular) • 3-MST (mitochondria, cytosol)	2, 5, 6
Physiological concentration	Nanomolar to low micromolar range under normal conditions	3
Key signaling mechanisms	• Protein persulfidation (S-sulfhydration): Alters cysteine residues on proteins like nuclear factor-κB, GAPDH, Akt, Keap1-Nrf2 • Mitochondrial modulation: Increases adenosine triphosphate production, enhances complex IV, reduces ROS • Anti-inflammatory action: Inhibits TNF-α, IL-1β, IL-6, suppresses NLRP3 inflammasome • Angiogenesis: Upregulates VEGF, modulates HIF-1α under hypoxia	5, 6
Major biological functions	• Regulation of redox homeostasis • Modulation of vascular tone • Promotion of angiogenesis • Inhibition of inflammatory signaling • Support of mitochondrial bioenergetics	3, 5, 6
Disease models	• Cardiovascular: Reduces infarct size, improves endothelial function • Neurodegenerative: Protects against neural cell death • Diabetes: Enhances insulin sensitivity, protects β-cells • Cancer: Dual roles – promotes or inhibits tumor growth depending on context	7–10
Therapeutic agents	• NaHS, GYY4137: Rapid and slow-releasing donors • AP39, SG-1002: Mitochondria-targeted or clinically tested donors • Stimuli-responsive nanocarriers: pH-, ROS-, or thiol-sensitive prodrugs; mesoporous silica nanoparticles; nanogels	2–4, 10
Biomarkers for monitoring	• Protein sulfhydration profiles • H_2S metabolite ratios • Detection via MS, biotin-switch, electrochemical and fluorescent probes (e.g., HSip-1 and AzMC)	10
Challenges and gaps	• Lack of standardized measurement techniques • Burst-release donor profiles • Poor biomarker validation • Inter-species metabolic variability • Incomplete toxicity/safety profiling	8–10
Precision medicine factors	• Influence of CBS/CSE gene variants • Sex- and age-dependent H_2S metabolism • Epigenetic regulation of H_2S pathways • Synergism with nitric oxide and antioxidant therapies	5, 6, 9, 10
Clinical translation needs	• Standardized pharmacokinetics • Multi-omics biomarker integration • Regulatory guidelines for delivery and safety • Computational modeling and stratified trial design	10

3-MST: 3-Mercaptopyruvate sulfurtransferase; CBS: cystathionine β-synthase; CSE: cystathionine γ-lyase; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; H_2S: hydrogen sulfide; HIF-1α: hypoxia-inducible factor-1α; IL: interleukin; NaHS: sodium hydrosulfide; NLRP3: NACHT, LRR, and PYD domains-containing protein 3; ROS: reactive oxygen species; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor.

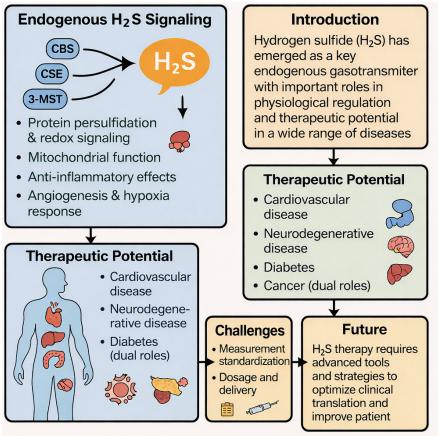


Figure 1 | H_2S therapy advances, clinical challenges, and future steps.
3-MST: 3-Mercaptopyruvate sulfurtransferase; CBS: cystathionine β-synthase; CSE: cystathionine γ-lyase; H_2S: hydrogen sulfide.

other medical gases such as nitric oxide donors or antioxidants, including N-acetylcysteine produces synergistic protective effects in preclinical models of ischemia and inflammation.[1] The current trends in personalized redox medicine match well with new opportunities to include H_2S as an individualized therapeutic compound in treatment protocols.[1]

Future directions and recommendations: The following actions need immediate attention to advance H_2S translation into medical treatments: The development of standardized pharmacokinetic/pharmacodynamic models should focus on new-generation H_2S donors. Research teams should unite computational models with systems biology approaches to create simulations of H_2S signaling pathways for discovering optimal drug combination protocols. Professional research efforts must expand their biomarker perception programs to conduct proteomic and volatile metabolite investigations for sulfur-bound and volatilized molecules. The clinical trials need to use genetic, metabolic, and sex-based stratification approaches in their design. The development of standard regulatory guidelines needs to establish specific thresholds, delivery standards along with pharmacovigilance monitoring procedures for H_2S-based medicine. The success of H_2S advanced therapeutic methods demands coordinated teamwork between chemists and pharmacologists and clinicians and systems biologists to bridge translational gaps.

Conclusion: Hydrogen sulfide appears as a signaling molecule that demonstrates diverse therapeutic applications throughout the body. The molecule participates in redox regulation, cellular survival mechanisms, inflammation control, and mitochondrial function. These capabilities make it intriguing for potential therapeutic uses.

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