ARNA **Seminar Series**

Friday, May 23 at 10:30 am (BBS Amphitheatre)

Harnessing Biocatalysis to Promote Antioxidant Response

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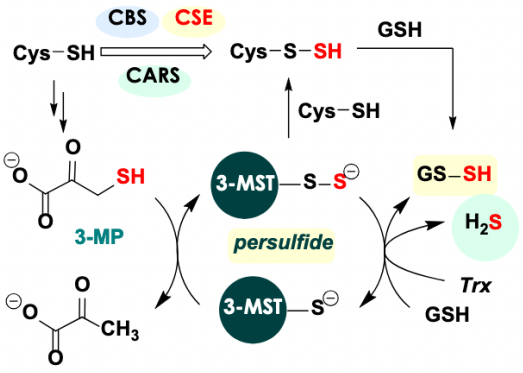
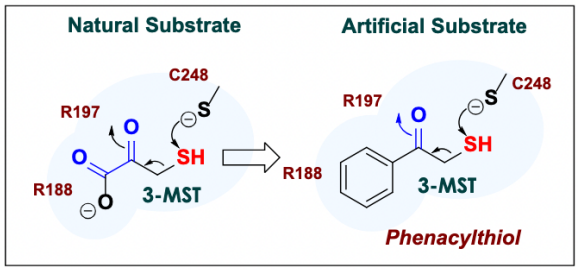
Hydrogen sulfide (H_2S), persulfides (RS-SH), and related sulfur species are produced in nearly all cells and have diverse roles, including as antioxidants.[1] Cysteine is the primary source of such sulfur species in cells, and enzymes that generate H_2S include cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), cysteinyl-tRNA synthetase (CARS) as well as 3-mercaptopyruvate sulfurtransferase (3-MST).[2] With a goal of promoting endogenous antioxidant response, our lab designed and developed artificial substrates for 3-MST.[3] The natural substrate for 3-MST is 3-mercaptopyruvate (3-MP), and its turnover produces a persulfide, which can either transfer sulfur to low molecular weight thiols such as glutathione or is cleaved by thioredoxin (Trx) to generate H_2S. The first generation of artificial substrates enhanced endogenous persulfides, and protected cells from oxidative stress-induced cell death as well as showed excellent anti-inflammatory properties in animal models.[3,4] Using a computational structure-guided approach, we designed and developed a new series of artificial substrates for 3-MST, and we describe results of this approach.[4] Together, we provide evidence that supports a new therapeutic paradigm of using small molecules to promote cells' own antioxidant response.





1. D. Giovinazzo, B. Bursac, J. I. Sbodio, S. Nalluru, T. Vignane, A. M. Snowman, L. M. Albacarys, T. W. Sedlak, R. Torregrossa, M. Whiteman, M. R. Filipovic, S. H. Snyder and B. D. Paul, Proc. Natl. Acad. Sci. U. S. A., 2021, 118, e2017225118.
2. Pedre, B.; Talwar, D.; Barayeu, U.; Schilling, D.; Luzarowski, M.; Sokolowski, M.; Glatt, S.; Dick, T. P. Nat. Chem. Biol. 2023, 19 (4), 507–517.
3. (a) Bora, P.; Manna, S.; Nair, M.; Sathe, R.M.S.; Singh, S.; Adury, V.S.S.; Gupta, K.; Mukherjee, A.; Saini, D. K.; Kamat, S.S.; Hazra, A. B.; Chakrapani, H. "Leveraging an Enzyme/ Artificial Substrate System to Enhance Cellular Persulfides and Mitigate Neuroinflammation" Chem. Sci., 2021, 12, 12939-12949. (b) Manna, S.; Agrawal, R.; Yadav, T. Anand Kumar, T.; Kumari, P. Dalai, A.; Kanade, S. Balasubramanian, N. Singh, A.; Chakrapani, H. "Orthogonal Persulfide Generation through Precision Tools Provides Insights into Mitochondrial Sulfane Sulfur" Angew. Chem. Intl. Ed., 2024, 63, e202411133 (c) Gupta, S. M.; Mohite, P. S. Chakrapani, H. "Mercapto-NSAIDs Generate a Non-Steroidal Anti-Inflammatory Drug (NSAID) and Hydrogen Sulfide" Chem. Sci., 2025, in press
4. (a) Manna, S.; Gupta, S.M; and coworkers, manuscript under review. (b) Gupta, S. M.; and coworkers, manuscript under preparation

Host: Valérie Desvergnes, ARNA laboratory