LIST OF TEN BEST PAPERS (in chronological order, recent papers first)

1. Kumari, P., Kaul, G., Kumar, A., Akhil, A., Shukla, M., Sharma, S., **Kamat, S. S.***, Chopra, S.*, Chakrapani, H.* (2023) Heterocyclic diaryliodonium-based inhibitors of Carbapenem-resistant *Acinetobacter baumannii* (CRAB), ***Microbiology Spectrum*** 11 (2), e04773-22.

   [Please also refer to companion paper: Kulkarni, A., Soni, I., Kelkar D. S., Dharmaraja, A. T., Sankar, R. K., Beniwal, G., Rajendran, A., Tamhankar, S., Chopra, S.*, **Kamat, S. S.***, Chakrapani, H.* (2019) Chemoproteomics of an indole-based quinone-epoxide identifies druggable vulnerabilities in Vancomycin-resistant *Staphylococcus aureus*, ***J. Medicinal Chemistry*** 62, 6785-6795]

   Importance: With the emergence of antibiotic resistant clinical strains (e.g. VRSA, MTB, A. baumannii), and the lack of any new antibiotics emerging in the market, it is being increasingly important to identify new druggable hotspots in such resistant clinical pathogens. In collaboration with Harinath Chakrapani's lab (Chemistry Department, IISER Pune), and Sidharth Chopra's lab (CSIR-CDRI Lucknow), we have recently identified the metabolism regulating enzyme BetB (betaine aldehyde dehydrogenase) as a new drug target in the gram-negative pathogen and a common hospital infection *Acinetobacter baumannii*, for which no efficacious antibiotics currently exist (*Microbiology Spectrum 2023*). Using a similar strategy, we have previously identified critical transcription factors from the MarR family, that were thought be undruggable, as attractive drug targets in developing antibiotics against vancomycin resistant S. aureus (VRSA) (*J. Med. Chem. 2019*). Our lab's chemical proteomics technologies, and downstream biochemical characterization of the targets, were critical to the success of both these published studies.

2. Mehdiratta, K., Singh, S., Sharma, S., Bhosale, R. S., Choudhary, R., Masal, D. P., Manocha, A., Dhamale, B. D., Khan, N., Vivekanand, A., Sharma, P., Ikeh, M., Brown A. C., Parish, T., Ojha, A., Michael, J. S., Faruq, M., Medigeshi, G. R., Mohanty, D., Reddy, D. S., Natarajan, V. T., **Kamat, S. S.***, Gokhale, R. S.* (2022) Kupyaphores are zinc homeostatic metallophores required for colonization of *Mycobacterium tuberculosis*, ***PNAS*** 119(8), e2110293119.

   Importance: It has been known for many years that *Mycobacterium tuberculosis* (MTB) needs optimal concentrations of metals such as iron, zinc, for survival under stressful conditions. However, the pathways and/or secondary metabolites that regulate this, remained unknown till recently. Using a combination of genetic models and stress conditions developed by Rajesh Gokhale' lab, and leveraging advanced lipidomics/metabolomics technologies, our lab identified and elucidated the chemical structures of a set of secondary metabolites, we termed "kupyaphores", that are able to regulate zinc homeostasis in MTB. This study shows for the first time, a need for zinc by MTB, and uncovers a previously unknown zinc acquisition strategy by pathogenic microbes that can modulate host-pathogen interactions and disease outcomes.

3. Rajendran, A., Soory, A., Khandelwal, N., Ratnaparkhi, G. S., **Kamat, S. S.*** (2022) A multi-omics analysis reveals that the lysine deacetylase ABHD14B influences glucose metabolism in mammals, ***J. Biological Chemistry*** 298 (7), 102128, 1- 14.

   [Please also refer to companion paper: Rajendran, A., Vaidya, K., Mendoza, J., Bridwell-Rabb, J., **Kamat, S. S.*** (2020) Functional annotation of ABHD14B, an orphan serine hydrolase enzyme, ***Biochemistry*** 59 (2), 183-196. Featured on the January 2020 issue front cover of Future of Biochemistry- Asia Pacific Issue]

Importance: Until recently, the lysine deacetylase (KDAC) family was thought to comprise only of the sirtuins and the histone deacetylases. Using elegant biochemical assays along with chemical proteomics and metabolomics approaches, we functionally annotate the orphan serine hydrolase enzyme ABHD14B as a novel KDAC, that is exclusively localized in mammalian liver, and plays an important role in central metabolism. Our annotation of ABHD14B has since expanded the repertoire of the KDAC family (*Biochemistry 2020*). Following up on this discovery, we have since shown that ABHD14B plays in systemic glucose metabolism during feeding-fasting cycles in animal and cell models. Further, we show that hepatic ABHD14B in particular is responsible for this systemic glucose metabolism, and it does so by regulating levels of key enzymes and transcriptional factors that as associated with central metabolism. Our studies designate ABHD14B as an important pharmacological target in the treatment of diabetes, metabolic syndrome and general obesity (*JBC 2022*).

4. Khandelwal, N., Shaikh, M., Mhetre, A., Singh, S., Sajeevan, T., Joshi, A., Balaji, K. N., Chakrapani, H., **Kamat, S. S.*** (2021) Fatty acid chain length drives lysophosphatidylserine dependent immunological outputs, ***Cell Chemical Biology*** 28, 1169-1179.
Featured on August 2021 issue front cover of Cell Chemical Biology

Importance: The lysophosphatidylserines (lyso-PSs) are immunomodulatory signaling lipids that regulate many facets of mammalian physiology. However, studying their biological effects has been relatively challenging given their commercial paucity and limited synthetic routes in making them. To overcome these challenges, in this paper, we report a facile synthetic method in making lyso-PS lipids, and assessed the biological pathways that they are known to regulate as a function of the lipid tail esterified to them. We found very-long chain lyso-PS are preferred substrates for the lyso-PS lipase ABHD12, and they robustly elicit pro-inflammatory responses via a TLR2 dependent pathway. Interestingly, we also found that long chain lyso-PSs signal through GPCRs, and modulate signaling events that are important for macrophage activation and mast cell degranulation. This is the first rigorous structure activity relationship study performed for this important lysophospholipid class, particularly in the context of important immunological processes. Our synthetic strategy has now paved the way for making biorthogonal multi-functional probes for the identification of the receptors and/or protein ligands for lyso-PS lipids.

5. Mehendale, N., Mallik, R. M., **Kamat, S. S.*** (2021) Mapping sphingolipid metabolism pathways during phagosomal maturation, ***ACS Chemical Biology*** 16(12), 2757-2765.
Featured on the December 2021 issue front cover of ACS Chemical Biology

Importance: Previously, we have shown that ceramides are important lipids during phagosomal maturation, and disruption in their metabolism can result in hampered phagocytosis. In this study, we specifically show that along with ceramide synthases, the various isoforms of ceramidases also have an important role to play in phagosomal maturation by regulating levels of ceramides during this process. Further, we discover that glucosylceramides, a kind of glycosylated ceramide, is also important during phagocytosis, and that its levels of this lipid are regulated by the enzyme glucosylceramide synthase during phagosomal maturation. Additionally, we show that all the ceramide biosynthetic pathways are “hot” targets for invading microbes, that have developed secondary metabolites to inhibit these enzymes, and by doing so, allows these microbes alternative strategies to evade our immune system.

6. Kumar, K., Mhetre, A., Ratnaparkhi, G. S., **Kamat, S. S.*** (2021) A superfamily-wide activity atlas of serine hydrolases in *Drosophila melanogaster*, ***Biochemistry*** 60 (16), 1312-1324.

   Importance: The serine hydrolases are an important enzyme class that regulate many important physiological processes in all organisms. Flies have served as an important model organism for studying numerous human diseases, and the serine hydrolase enzymes remain largely understudied in this model organism. To bridge this gap, in this paper, using the suite of our chemical proteomics technologies, we map the full complement of active serine hydrolases in flies during various stages of development, and in doing so, show the first time that there exists sexual dimorphism in their activities. Our findings also show that we detect and can track several serine hydrolase enzymes that are difficult to identify and map in higher mammalian organisms.

7. Singh, S., Joshi, A., **Kamat, S. S.*** (2020) Mapping the neuroanatomy of ABHD16A-ABHD12 & lysophosphatidylserines provides new insights into the pathophysiology of the human neurological disorder PHARC, ***Biochemistry*** 59 (24), 2299-2311.

   Importance: The human neurological disorder PHARC is marked by cerebellar dystrophy, and the accumulation of lysophosphatidylserine (lyso-PS) lipids are thought to cause this pathology. In this paper, we map the anatomical localization of ABHD16A (major lyso-PS biosynthetic enzyme in the brain) and ABHD12 (major lyso-PS degradation enzyme in the brain), and show that both these enzymes along with lyso-PS lipids are significantly enriched in the mammalian brain. Further, we show that ABHD16A and ABHD12 are localized to distinct neurons in the brain, and that lyso-PS acts as a hormone like signaling molecule that likely coordinates various cerebellar functions. Together, this study provides the first evidence, as to why the cerebellum is the most susceptible anatomical region in the brain and why it undergoes atrophy in human PHARC subjects.

8. Kelkar, D. S., Ravikumar, G., Mehendale, N., Singh, S., Joshi, A., Sharma, A. K., Mhetre, A., Rajendan, A., Chakrapani, H., **Kamat, S. S.*** (2019) A chemical genetic screen identifies ABHD12 as an oxidized phosphatidylserine lipase, ***Nature Chemical Biology*** 15, 169-178.

   Importance: Oxidative stress is an imbalance between cellular oxidants and antioxidants in favor of the oxidants, resulting in increased cellular ROS levels, that disrupts redox signaling pathways, and is implicated in several human diseases. Phosphatidylserine (PS), an inner membrane leaflet localized phospholipid has several critical functions in mammalian biology, especially its role in ROS sensing and apoptosis. In response to elevated cellular ROS, PS flips its membrane orientation, and while a lot is known of the externalization of PS under oxidative stress, nothing was known of the chemical structure of oxidized PS lipids and enzymes that metabolize such lipids. In this paper, using pharmacological tools in conjunction with genetic mouse models, we report for the first time the chemical structures of oxidized PS lipids, and by performing a chemical genetic screen, showed that the enzyme ABHD12 is a major oxidized PS lipase that metabolizes these oxidatively damaged PS lipids under oxidative stress conditions. Following our findings, inhibitors to ABHD12 as clinical candidates for killing cancer cells by the ferroptosis pathway, and ABHD12's role in resolving (neuro)inflammation are being assessed.

9. Joshi, A., Shaikh, M., Singh, S., Rajendran, A., Mhetre, A., **Kamat, S. S.*** (2018) Biochemical characterization of the PHARC associated serine hydrolase ABHD12 reveals its preference for long chain lipids, ***J. Biological Chemistry*** 293, 16953-16963.
Featured on the November 2018 issue front cover of JBC

Importance: Deleterious (null) mutations to the ABHD12 gene results in the human neurological disorder PHARC, where very long chain (VLC) lipids, particularly lysophosphatidyserine lipids, accumulate in the brain. In this paper, we synthesize a library of mono-acyl-glycerol lipids with varying lipid tails, and show for the first time, that the lipase ABHD12 strongly prefers VLC lipids as substrates. Additionally, we also show that ABHD12 localizes to the endoplasmic reticulum membrane, where is regulates the secretion of VLC lipids, and that glycosylation of this lipase is important for its biochemical activities. Together our findings reported in this paper, provide the first explanation for why VLC lipids accumulate in the brains of human PHARC subjects, and result in the pathology observed in this neurodegenerative disease.

10. Pathak, D., Mehendale, N., Singh, S., Mallik, R. M., **Kamat, S. S.*** (2018) Lipidomics suggests a new role for ceramide synthase in phagocytosis, ***ACS Chemical Biology***, 13, 2280-2287.
Featured on the August 2018 issue front cover of ACS Chemical Biology

Importance: Phagocytosis is an evolutionary conserved innate immunological process, critical for clearing pathogens and fighting infections in higher organisms, including humans. While significant information is available on the proteomic content of the phagosomes as they mature, little remains known about their lipid composition. In this paper, using our in-house LC-MS based lipidomics platforms, we performed an exhaustive quantitative analysis of the different lipid classes during phagocytosis, and found that as phagosomes mature, they accumulate cholesterol and very-long chain (VLC) ceramides. We further showed that the accumulation of VLC ceramides is orchestrated by the enzyme ceramide synthase 2, and pharmacological inhibition of this enzyme hampers phagocytosis. This finding has tremendous physiological implications, as cholesterol and VLC ceramides form stable lipid rafts, that recruit dynein motors, which produce enough forces on these stable membranes to drive the unidirectional motion of maturing phagosomes to the lysosome for eventual degradation.