# SFB Guest Lecture Series

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## Novel insights into targeting therapy-resistant cancer through functional multiomics

Cell-fate decisions are influenced by changes in lipid metabolism that play crucial roles in both health and disease. Beyond their essential roles in compartmentalization and energy storage, certain low-abundance lipid species function as signaling molecules – acting as second messengers or lipokines – that critically regulate processes such as programmed cell death [1, 2]. Exploiting the mechanistic diversity of cytotoxic natural products, we employ functional multiomics to dissect lipid-driven regulatory mechanisms. This approach has proven particularly valuable in studying metabolically regulated cell death pathways like ferroptosis, characterized by excessive membrane peroxidation leading to membrane disruption. Ferroptosis induction holds promise as an anti-cancer strategy, particularly for targeting EMT-driven metastatic and therapy-resistant cancers, with mesenchymal-type persister cells displaying heightened sensitivity [3]. This presentation will illustrate how we identified the lipid metabolic mechanisms underlying this enhanced ferroptosis sensitivity [4] and will reveal a mechanism through which various cytotoxic stressors amplify membrane peroxidation – a process intrinsic to most cell death programs. Lastly, we will share initial findings from our drug discovery pipeline, which aims to harness this sensitizing mechanism for anti-cancer combination therapies.

[1] T. Harayama, Nat. Rev. Mol. Cell Biol. 2018, 19, 281.
[2] M. Thürmer 2022, Nat. Commun. 13, 2982.
[3] S. Koeberle 2023, Med. Res. Rev. 43, 614.
[4] A. Schwab, Nat. Cell Biol. 2024, 26, 1470.