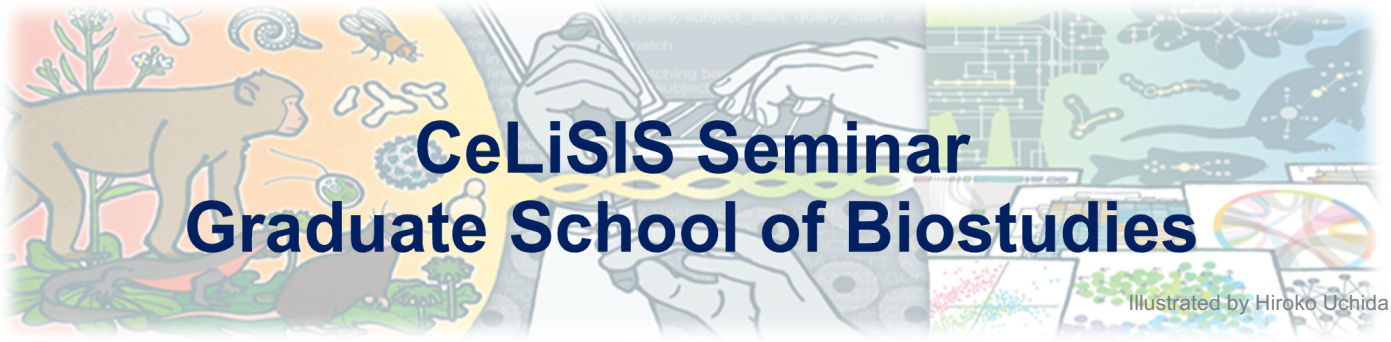

Seeing Microbial Function in Action: Chemical Imaging Reveals How Gut Microbes Respond to Drugs

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14:00-15:00, May 30, 2025
Seminar Room, 1st Floor of the Science Frontier Laboratory, Medical Campus
(Bldg. no. 16 in the campus map: https://www.kyoto-u.ac.jp/en/access/medicine-campus-map)

One of the biggest challenges in environmental and medical microbiome research is to better understand functional properties of microbial community members at a single-cell level. Single-cell isotope probing has become a key tool for this purpose, but the current detection methods for determination of isotope incorporation into single cells do not allow high-throughput analyses. Recently, we developed an imaging-based approach termed stimulated Raman scattering-two-photon fluorescence *in situ* hybridization (SRS-FISH) for high-throughput metabolism and identity analyses of microbial communities with single-cell resolution (Ge *et al.* 2022, PNAS). SRS-FISH offers an imaging speed of 10 to 100 ms per cell, which is two to three orders of magnitude faster than achievable by state-of-the-art methods. We applied SRS-FISH together with quantitative microbiome profiling and long-read metagenomics to investigate the impact of the nervous system targeted drugs entacapone and loxapine succinate on the human gut microbiome (Pereira *et al.* 2024, Nature Microbiology). Ex vivo supplementation of physiologically relevant concentrations of entacapone or loxapine succinate to faecal samples significantly impacted the abundance of up to one third of the microbial species present. Importantly, we demonstrate with SRS-FISH that the impact of these drugs on microbial metabolism is much more pronounced than their impact on abundances, with low concentrations of drugs reducing the activity, but not the abundance of key microbiome members like *Bacteroides*, *Ruminococcus* or *Clostridium* species. We further demonstrate that entacapone impacts the microbiome due to its ability to complex and deplete available ferric iron, and that microbial growth can be rescued by replenishing levels of microbiota-accessible iron. Remarkably, entacapone-induced iron starvation selected for iron-scavenging organisms carrying antimicrobial resistance and virulence genes. Collectively, these results unveil using next-generation chemical imaging the impact of two under-investigated drugs on whole microbiomes and identifies metal sequestration as a mechanism of drug-induced microbiome disturbance. In more general terms, SRS-FISH now provides a technology platform with which the activity of selected taxa in highly complex microbiomes can be determined precisely and in high throughput. This technology thus represents an important tool in our endeavors to decipher the functions and interactions of microbiomes and thus create the prerequisites for being able to manipulate them in a targeted manner.

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