

## Genetically encoded chemical tools for GPCR studies

We apply non-canonical amino acids (ncAAs) to address general questions about functioning of G protein-coupled receptors (GPCRs) directly from the natural environment of the live mammalian cell. On one hand, we use ncAAs bearing chemical and photo-chemical crosslinking groups to define the topology of GPCR interactions with ligands (especially peptide ligands) at the extracellular side, and intracellular partners (especially arrestins) at the intracellular side. On the other hand, we have engineered enhanced tRNAs that have enabled efficient incorporation of last generation ncAAs for bioorthogonal chemistry into challenging protein targets. In this way, we could achieve single-residue labeling of sensitive GPCR regions, such as the loops, with small organic fluorescent probes in quantitative yields. While further experiments are ongoing, we have put the basis for the development of small-size fluorescent sensors for in-cell studies of GPCR dynamics.