Lyso-PCTP: A Reengineered Lipid Biosensor for Early PDAC Diagnosis and Monitoring

Ladegaonkar, Aksh (School: International Baccalaureate School at Bartow High)

Pancreatic ductal adenocarcinoma (PDAC) ranks 10th in US cancer incidence, yet it causes more deaths per year than breast cancer, ranked 1st, a disparity largely driven by complications regarding late diagnosis and a lack of effective early screening. Per recent studies by the NIH and others, lipid panels show significant potential for early diagnosis and monitoring, with sensitivity and specificity >95% across all stages, although current assays for lipid biomarkers remain too costly and impractical for clinical use. To fill this translational gap, I developed Lyso-PCTP, the first optical biosensor to leverage the extremely specific lipid-binding properties of phosphatidylcholine transfer protein (PCTP) for robust molecular quantification via Förster resonance energy transfer (FRET). Through 12 systematic mutations, PCTP binding was reengineered from its native ligand, phosphatidylcholine 16:0/18:2 (PLPC), to lysophosphatidylcholine (LPC) 18:2, the most significant lipid biomarker for PDAC risk, with selectivity then validated through multiple molecular dynamics simulation in GROMACS against PLPC, 4 common blood phospholipids, and 2 other LPC species. Following per atom fluctuation and distance analyses, residues A24 and K167 were identified as optimal labeling sites with the Cy2/Cy7 FRET donor-acceptor pair, yielding a change in FRET efficiency of 28%, a value readily detectable with clinical microplate technology, already present in virtually all modern hospitals to enable rapid lipid measurement at the point of care. Lyso-PCTP thus establishes the first example of transfer protein based lipid biosensing with broad implications beyond PDAC in diagnosis and monitoring for lipidome influencing diseases such as Alzheimer's, sepsis, diabetes and other aggressive cancers.

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