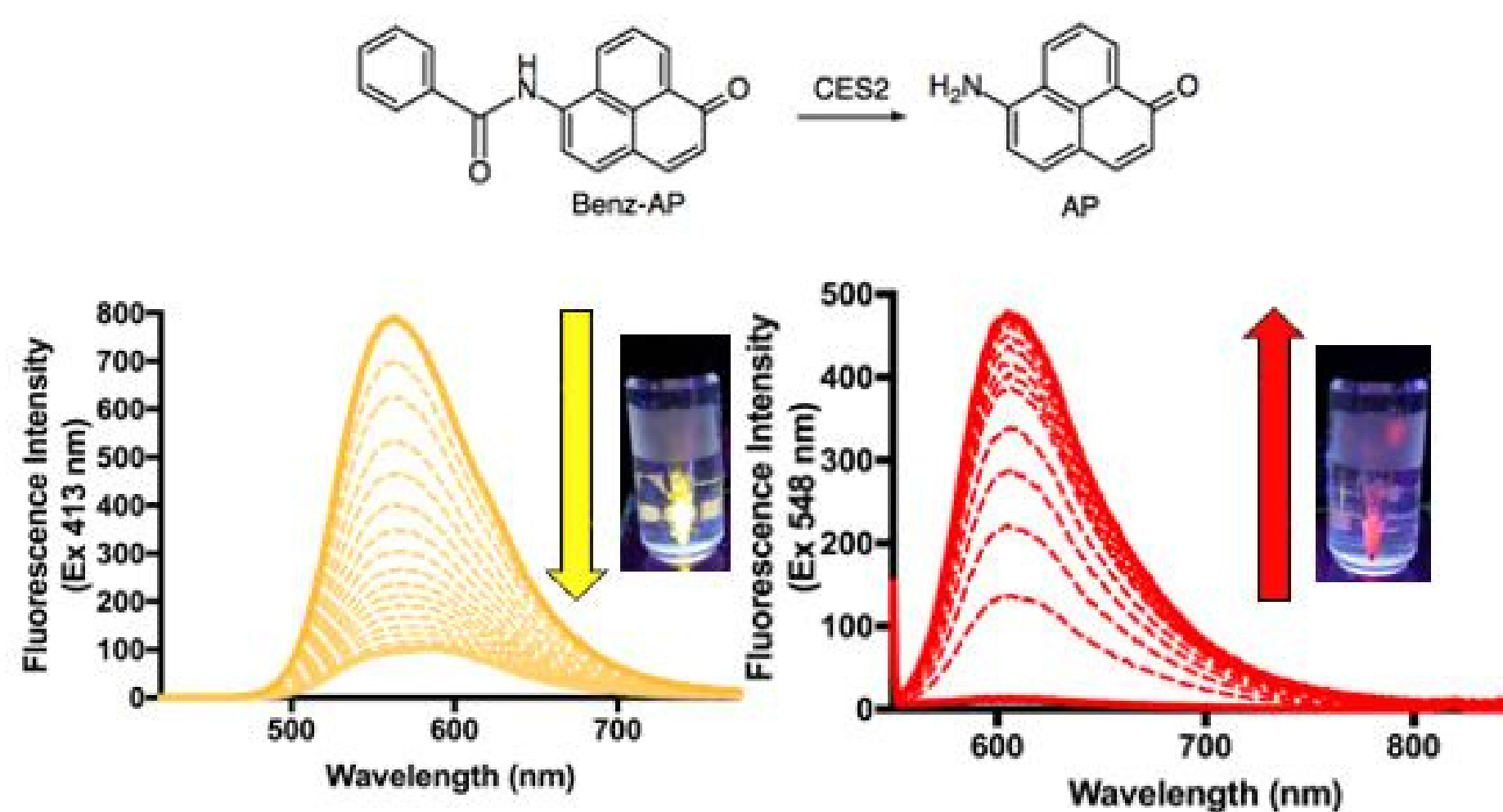




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Pancreatic ductal adenocarcinoma (PDAC) is an aggressive form of cancer, with low patient 5-year survival rates of approximately 5%. Irinotecan, a commonly administered chemotherapeutic prodrug, is activated by the enzyme carboxylesterase 2 (CES2), which is established as a predictive and prognostic biomarker of patient response to irinotecan, whereby low activity of the enzyme confers resistance. CES2 serves as a suitable target given its indicated role and interindividual variability in activity. To this regard, my research explores applications towards predicting and improving resistance to irinotecan-based therapies. To measure CES2 activity, a fluorescent chemosensor, Benz-AP, was developed. Initially yellow-fluorescent, CES2-mediated hydrolysis of the benzoyl amide linkage releases a red-fluorescent amine fluorophore, enabling ratiometric determination of CES2 activity. Measurements in panels of commercial and primary patient pancreatic cancer cell lines show significant non-linear correlations to irinotecan-based drug response. Collectively, these results form the basis for clinical translation towards ex vivo measurements of CES2 in biopsy assessment settings. Benz-AP further serves as a photosensitizer, in which two-photon photodynamic therapy may be used to cause death in low-activity CES2 environments through production of cytotoxic singlet oxygen and reactive oxygen species, including pancreatic cancer tumour spheroids, for therapeutic alternatives to samples otherwise deemed resistant to irinotecan-based treatments. To improve irinotecan-based therapy, Benz-AP was engaged in a high-throughput screen in collaboration with the Novartis Institutes of Biomedical Research against CES2 to find small molecule modulators capable of inhibition or activation, the latter of which provides the first record of allostery in CES2. In all, this presentation describes a diverse set of applications for targeting CES2 towards the goal of improving patient survival in PDAC.