Towards understanding the mechanism of selective estrogen receptor degraders (SERDs)

Previous work by our laboratories demonstrated that proteins decorated with small molecules have different interactomes. The bound small molecules change the protein surface and trigger neo-morphic protein-protein interactions by bringing two proteins together that in the absence of the compound have little-to-no affinity (Kozicka *et al*., Nature Chem Biol *et al*., 2023; Tsai *et al*., Mol Cell 2023; Mark *et a*l., Cell 2023; Slabicki *et al*., Nature 2020; Sievers *et al*., Science 2018). These small proximity-inducing molecules hold tremendous therapeutic promise, as evidenced by the clinical successes of thalidomide and its derivatives in the treatment of hematological malignancies. Despite these clinical successes and recent, largely serendipitous findings with additional molecular glues, the forces and rules that govern protein-protein interactions in the presence of small molecules remain unclear.

Selective Estrogen Receptor Degraders (SERDs) including Fulvestrant, are important pillars of modern breast cancer therapy. We recently showed that the estrogen receptor (ER) is degraded in the presence of Fulvestrant by the ubiquitin E3 ligase RNF111 (Tsai et al., 2023). ER degradation is dependent on the solvent-exposed extension small molecule moiety. We will reconstitute the RNF111-ER-Fulvestrant complex to then structurally and functionally dissect RNF111-mediated degradation of ER in the presence of SERDs leveraging these learnings, we will explore whether other NRs such as the Glucocorticoid receptor (GR), Androgen receptor (AR), Progesterone can be degraded in a manner dependent on RNF111. The project will be done in close collaboration with Benjamin Ebert MD, Dana Farber Cancer Center, Boston, USA.