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# *Systems Approach to Rational Combination Therapy*

### Abstract:

One of the key lessons of the last century of cancer therapy is that combination therapy is, in most cases, necessary, particularly in advanced disease and complex epithelial tumors, to increase tumor control. However, as we have matured in the era of precision oncology which includes small molecule targeted therapeutics and immuno-oncology agents, while response to targeted therapies are relatively frequent, durable responses are rare and in contrast response to immuno-oncology agents are less frequent but are commonly durable and can approximate cures. It is thus clear that rational combination therapy approaches not only within a single modality but across different therapy approaches such as targeted and immunotherapy will be necessary to fulfill the promise of precision medicine.

Indeed, in terms of the emerging fields of target therapy and immuno-oncology, we are at the end of the beginning. A number of monotherapies have demonstrated remarkable activity. However, only a portion of patients with our best biomarkers respond and responses are in general short for monotherapy with targeted therapies. Responses to immuno-oncology monotherapy and even initial attempts at combination therapy are extremely exciting in that although only subpopulations of patients still benefit, responses can be remarkably durable approximating cures. Given the intrinsic heterogeneity of tumors as well as the many mechanisms underlying resistance to targeted and immuno therapy, the limited benefit from monotherapy is to be expected.

The short term of response to therapy for most patients is due to a major degree to the almost inevitable emergence of resistance. We have used PARP inhibitors as an effective emerging therapy to explore genomic and adaptive mechanisms of resistance. Importantly, the tumor as well as the tumor ecosystem adapts to the stress induced by targeted or immunotherapy agents. These adaptive responses, which can be observed in tissue culture, animal models, and patient samples, offer therapeutic opportunities which can be targeted to increase the fraction of patients who will benefit as well as the depth and duration of responses. Based on this paradigm, we have identified a series of unexpected mechanisms of resistance to PARP inhibitors and have developed rational combination therapies to interdict emerging resistance. Based on these preclinical studies, we have promoted a number of therapies to clinical trials and have demonstrated exciting preliminary responses.

**Keck Seminar**

**Friday, February 23, 4pm**

**BioScience Research Collaborative**

**Room 280 (2<sup>nd</sup> Floor)**

**Gulf Coast Consortia**  
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