Hsp90 is a molecular chaperone that is responsible for the conformational maturation of more than 200 known substrates, many of which are associated with signaling pathways that are hijacked by transformed cells. As a result, Hsp90 has evolved into a promising anti-cancer target as multiple signaling nodes can be targeted simultaneously through Hsp90 inhibition. More than 15 small molecules that bind to the Hsp90 N-terminal binding pocket have entered clinical trials for evaluation against a number of human malignancies, but unfortunately, a lack of efficacy and/or toxicity has been observed for many of these candidates.

In an effort to develop new strategies toward Hsp90 inhibition, we have focused on inhibition of the C-terminal binding site as well as the development of isoform-selective inhibitors. These methods have resulted in molecules that can segregate induction of the pro-survival heat shock response from client protein inhibition/degradation, and consequently have afforded new methods for the potential treatment of protein misfolding diseases and cancer, respectively.

In addition, the first isoform-selective inhibitor of Grp94 has been produced and biology associated with inhibition of this chaperone may provide new therapeutic strategies. This lecture will provide an overview of Hsp90 C-terminal and isoform-selective inhibitors for the treatment of various diseases.