Using Hsp90 inhibitors to treat triple negative breast cancer

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This is an exciting time in breast cancer biology research, as we are beginning to identify targetable proteins that drive triple-negative breast cancer (TNBC) growth. For example, while TNBCs don’t express estrogen, progesterone or HER2 receptor proteins, a subset of them do express significant glucocorticoid receptor (GR), androgen receptor (AR) and Janus Kinase (JAK) proteins. High GR-expressing TNBC is associated with earlier relapse after chemotherapy, while high AR expression promotes tumor cell proliferation. Janus Kinase (JAK) proteins play a role in both TNBC proliferation and chemo-resistance.

In addition to GR, AR and JAK proteins, TNBCs activate interconnected pro-cancer “signaling” pathways; therefore the need for simultaneous targeting of these pathways is of great importance. One approach for targeting multiple key proteins at once is to inactivate their common “chaperone” protein These proteins associate with “client proteins” and shepherd them around the cell so that they fold properly and are functional. Hsp90 is an important chaperone protein that escorts cancer-promoting client proteins, thereby allowing tumor growth. When Hsp90 activity is blocked by a specific Hsp90 inhibitor, these cancer causing client proteins are misfolded and subsequently degraded. While previous Hsp90 inhibitors were quite toxic, new safer small molecule drugs are now available. In Phase 1 Hsp90 inhibitor clinical trials, there have been some dramatic responses of TNBC growth inhibition, but the specific characteristics of the responding tumors that allow them to be sensitized and shrink are not known. The goal of our
studies is to discover which cancer-promoting client proteins are targeted by Hsp90 inhibitor treatment in TNBC, and use them to potentially identify which TNBCs are likely to respond.

We will study known TNBC oncogenic Hsp90 client proteins GR, AR and JAK, as well as examine “global” protein changes in the pre-clinical setting in response to Hsp90 inhibitors. Degraded Hsp90 client proteins will be present in significantly lower amounts after treatment with an Hsp90 inhibitor. This pre-clinical data will then be confirmed in TNBC patient biopsies taken before and after Hsp90 inhibitor neoadjuvant treatment. We will also perform global protein analysis in patient biopsies and compare to our pre-clinical results so that we can parse out a few biologically relevant client proteins. Our studies will provide new insights into TNBC biology while developing a much needed treatment for TNBC.