DR. MICHAEL WENDT (2015 AWARD)

Targeting Growth-Factor Receptor Discordant Metastatic Breast Cancer

The purpose of our METavivor proposal was to define and target potential mechanisms that contribute to metastatic discordance following acquisition of epithelial-mesenchymal transition (EMT)-associated anti-Her2 drug resistance. We have determined that another receptor tyrosine kinase called fibroblast growth receptor (FGFR1) is upregulated during the process of EMT. Importantly, we determined that cell surface expression of FGFR1 interferes with the binding of Her2 targeted antibodies. Therefore, not only does FGFR1 expression constitute an alternative growth factor signaling pathway, but is also physically disrupts the ability to Her2-targeting therapies to detect these tumor cells. Using the optimized 3D culture approach from Aim2 of our proposal we also found that a novel covalent kinase inhibitor to targeting FGFR is capable of inhibiting metastatic cells impart by leading to the degradation of Her2. We are now moving forward with this compound to conduct investigational new drug (IND) enabling studies as we move forward toward its clinical application.

Publications resulting from the METAvivor work:

1. Brown WS, Akhand SS, Wendt MK. FGFR signaling maintains a drug persistent state following induction of epithelial-mesenchymal transition. Oncotarget. DOI: 10.18632/oncotarget.13117. Epub Nov 4 2016.
2. Ali RA, Wendt MK. The paradoxical functions of EGFR during breast cancer progression. Signal transduction and targeted therapy. 2017. Signal Transduction and Targeted Therapy. doi:10.1038/sigtrans.2016.42. Epub Jan 20 2017.
3. Hardy S, Shinde A, Wang WH, Wendt MK†, Geahlen R†. Regulation of epithelial-mesenchymal transition and metastasis by TGF-b, P-bodies, and autophagy. Oncotarget, DOI:10.18632/oncotarget.21871. Epub Oct 17 2017
4. Ali RA, Akhand SS, Wendt MK. Targeting FGFR for the treatment of breast cancer. 2017 Editor: Jenifer Prosperi. https://link.springer.com/chapter/10.1007/978-3-319-70142-4_5 - enumeration
5. Akhand SS, Purdy SC, Doctor NB, Wendt MK. FGFR facilitates recurrence of minimal residual disease post trastuzumab emtansine therapy. (To be submitted March 2018).

Funding: Data obtained with METAvivor funding was used to generate an NCI R01 grant and a research scholar grant from the American Cancer Society