

DR. WILLIAM SCHIEMANN (2014 AWARD)

Implementing a Forward Genetic Screen to Identify Novel Proto-Oncogenes Operant in Overcoming Metastatic Dormancy

Summary

Metastasis remains the most significant predictor of clinical outcome and most lethal characteristic of breast cancer. In the majority of cases, the clinical manifestations of metastasis occurs years-to-decades after initial diagnosis and treatment. The delayed onset of clinical metastases reflects the ability of disseminated tumor cells to enter a state of quiescence and/or latency upon reaching their target destinations, namely residence in the lungs, bone, liver, or brain. The growth of these latent disseminated tumor cells is initially attenuated, but they preserve their tumor-initiating capacity. The propensity of these cells to form overt metastases is dictated by a host of cell-intrinsic genetic events, as well as by an array of cell-extrinsic signals derived from normal cells that surround the developing metastatic lesion. Our current understanding of how breast cancers become metastatic remains poor, as does our knowledge of how disseminated breast cancer cells escape clinical detection by remaining latent for years before reemerging as chemoresistant and incurable secondary tumors. Indeed, the mysteries of metastatic latency have been identified as 1 of the 10 most critical research gaps and translational priorities needed to be solved to alleviate metastatic breast cancers. To better understand this deadly pattern of metastatic recurrence, we performed a genetic screen that has provided a series of innovative insights into how disseminated breast cancer cells initially acquire and ultimately emerge from metastatic latency.

Our major findings include:

- The identification of a novel lncRNA, BORG, whose aberrant expression correlates with aggressive breast cancer phenotypes, particularly those belonging to the basal-like/TNBC subtype of breast cancers.
- BORG expression not only correlates with ability of breast cancers to metastasize and recur, but it also underlies the ability of latent metastatic lesions to reactivate proliferative programs and relapse.
- We defined the molecular mechanisms that enable BORG to drive metastatic recurrence and show that targeting these events dramatically impedes metastatic colonization in preclinical models.
- Aberrant BORG expression also fosters the survival of TNBC cells exposed to chemotherapies, rendering them resistant to the cytotoxic effects of doxorubicin in preclinical models.
- Thus, therapeutic targeting of BORG or its downstream effectors may provide a novel means to alleviate TNBC recurrence and chemoresistance.
- We established a novel role for telomere maintenance mechanisms in governing the metastatic progression and recurrence of human breast cancers.
- We discovered an inverse relationship between the aberrant expression of Pfkfb3 and autophagy that dictates whether disseminated breast cancer cells become dormant or recur.

Manuscripts: Published

- Gooding, A.J., Zhang, B., Jahanbani, F.K., Gilmore, H.L., Chang, J.C., Valadkhan, S. and Schieman, W.P. (2017) The lncRNA BORG drives breast cancer metastasis and disease recurrence. *Sci Rep.* 7:12698. DOI: 10.1038/s41598-017-12716-6. *Featured in "Mammary Cell News" volume 9.39, October 5, 2017. Full text: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5629202/>

- Gooding, A.J., Zhang, B., Gunawardane, L., Beard, A., Valadkhan, S. and Schiemann, W.P. (2018) The lncRNA BORG facilitates the survival and chemoresistance of triple-negative breast cancers. *Oncogene*. DOI: 10.1038/s41388-018-0586-4. Link to abstract: <https://www.nature.com/articles/s41388-018-0586-4>
- Flynn, A. Calhoun, B.C., Sharma, A., Chang, J.C., Almasan, A. and Schiemann, W.P. (2018) Inactivation of autophagy stimulates breast cancer emergence from dormancy by inducing Pfkfb3 expression.
- Robinson, N.J., Morrison-Smith, C.D. Gooding, A.J., Schiemann, B.J. Chang, J.C., Jackson, M.W., Taylor, D.J. and Schiemann, W.P. (2018) SLX4IP Coordinates telomere maintenance and Wnt signaling to control breast cancer metastasis. Funding Obtained with METAvivor Data: Active
- NIH/NCI R01 CA236273-01 (PI: Schiemann; MPI: Valadkhan) 12/18-11/23 Role of the lncRNA BORG in Breast Cancer Metastatic Progression and Recurrence The major goals are to determine the mechanisms whereby: (i) BORG:TRIM28 complexes form and drive TNBC metastasis and recurrence, and (ii) BORG:RPA1 complexes and NF-kB promote TNBC survival and chemoresistance. Pending
- NIH/NCI R01 CA236273-01A1 (PI: Schiemann; MPI: Taylor) 7/19-11/23 Role of the lncRNA BORG in Breast Cancer Metastatic Progression and Recurrence The major goals are to determine the mechanisms whereby: (i) BORG:TRIM28 complexes form and drive TNBC metastasis and recurrence, and (ii) BORG:RPA1 complexes and NF-kB promote TNBC survival and chemoresistance.
- NIH/NCI R01 CA228458-01A1 (PI: Schiemann; MPI: Taylor) 7/19-6/26 SLX4IP Directs Breast Cancer Telomere Homeostasis, Metastatic Progression, and Recurrence The major goals are to (i) determine the molecular mechanisms whereby SLX4IP suppresses Wnt/bcatenin signaling coupled to TERT expression and TMM plasticity; and (ii) determine the efficacy of targeting TMM plasticity to alleviate BC metastasis and disease recurrence.