Scientific Focus of the HAMLET Core

Breast cancer is a complex disorder comprised of a spectrum of cancer subtypes with distinct clinical phenotypes, genetic anomalies and therapeutic responsiveness. Preclinical testing of new anticancer drugs and cancer translational study requires model systems that recapitulate the breast cancer spectrum as accurately as possible. While cell line-derived human breast xenografts are frequently used for this purpose, the ability of these systems to predict drug efficacy is limited for the following reasons. First, fundamental issues arise from the fact that the clinical features of the tumors from which these cell lines were derived were not adequately documented, so that it is rarely possible to establish whether any given cell line is a truly valid model for the therapeutic hypothesis in question. Next, there are concerns regarding artifacts generated by long term *in vitro* culture. Also since the establishment of breast cancer cell lines has been a very rare event, we can be certain that the genetic diversity of human breast cancer is not fully represented in the one hundred or so breast cancer cell lines that are currently available.

With this in mind, Drs. Matthew Ellis and Shunqiang Li launched the HAMLET project in 2006 to establish xenograft models using patient-derived breast cancer tissue and to compare the similarities between the original tumors and their xenografts. In collaboration with others, Drs Ellis and Li have established over thirty WHIM (**W**ashington University **h**uman-**i**n-**m**ouse) tumor lines with major financial help from the Susan G. Komen Foundation (grants BCTR0707808 and KG090422).

The patient's clinical outcome, therapeutic history and responsiveness to treatment have been fully documented and are available to researchers. Patients provided documented consent for the use of their tumor tissues, DNA and RNA by researchers. The WHIM lines were propagated in NOD/SCID mice for at least three serial passages and have been characterized by global gene expression; by array CGH; and in some cases, by complete whole genome sequencing [featured in our Nature publication[1]], reverse phase protein array (RPPA), and testing for response to estrogen stimulation. Our study found that the WHIM models exhibit remarkable genetic and phenotypic similarities with the human tumor from which they were derived. In essence, they are "live" replicas of the human tumors.

WHIM tumor-related materials have been disseminated to over fifteen investigators for use in translational research. WHIM models have been successfully incorporated in multiple investigators' funded projects, including:

- The Cancer Proteomics Centers at Washington University in St. Louis; the University of North Carolina, Chapel Hill; and Boise State University (M. Ellis, *et al;* NIH grant 5U24A160035);
- Personalized Breast Cancer Vaccines Based on Genome Sequencing (W. Gillanders, T. Hansen; Komen Foundation grant KG111025);
- Cell Death Activation to Prevent Late Relapse in Breast Cancer (M. Ellis, P. Meier, E. Mardis; Komen Foundation grant PG12220321);
- Chk1- and PI3K- Pathways as Therapeutic Targets in Triple Negative Breast Cancers[2] (H. Piwinica; Komen Foundation grant KG081551).

References

1. Ding, L., Ellis, M.J., Li, S., Larson, D.E., Chen, K., Wallis, J.W., Harris, C.C., McLellan, M.D., Fulton, R.S., Fulton, L.L., et al. 2010. Genome remodelling in a basal-like breast cancer metastasis and xenograft. *Nature* 464:999-1005.
2. Ma, C.X., Cai, S., Li, S., Ryan, C.E., Guo, Z., Schaiff, W.T., Lin, L., Hoog, J., Goiffon, R.J., Prat, A., et al. 2012. Targeting Chk1 in p53-deficient triple-negative breast cancer is therapeutically beneficial in human-in-mouse tumor models. *J Clin Invest* 122:1541-1552.