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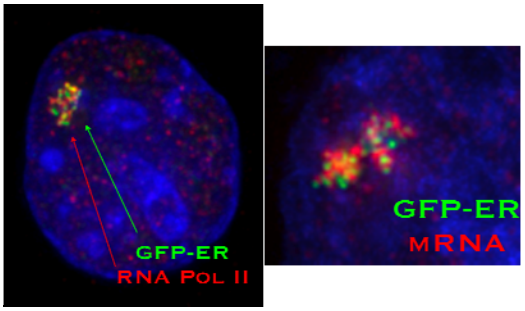
ER Project: Combined over-stimulation of estrogen receptor-α (ER) and the EGF receptor (EGFR) may provide a strong stimulus for breast tumor growth and may contribute to the resistance of tumor cells to antagonist therapy. A PRL-HeLa cell line (See Figure) is a novel tool quantitative studies of ER function at the single-cell level. (Sharp et al., 2006). Our systems-biology level approach will integrate functional data from multiple readouts at a single cell level for ERα and coregulators including 1) nuclear targeting, 2) promoter array occupancy, 3) large scale chromatin modeling, 4) histone modifications, and 5) mRNA synthesis. Data obtained will be crucial to understanding the temporal ER responses to two physiological and breast cancer related agonists and antagonists, and will point the way toward development of new therapies (Berno, et al., 2008).



HeLa PRL Biosenor Line. PRL chromosomal array decorated by GFP-ER (green), which co-localizes with reporter mRNA (by FISH, right image) and RNA polymerase II (immunofluorescence, left image). Blue is DAPI stained nuclear DNA.

mTOR Project: The mTOR kinase is a key node in cell autonomous signaling pathways that integrate growth factor and nutrient signaling for regulated cell growth (mass) and division. Inhibitors of mTOR (e.g., rapamycin) are postulated to mimic food (FR) and growth factor restriction (GFR) both of which extend lifespan. An interim report on lifespan studies of mice (20 months of age at start of treatment) eating rapamycin-containing food showed significant extension of lifespan in both males and females. We posit that one of benefits of derived by chronic rapamycin treatment will be a delay in cancer development and/or a reduction in severity.

Recent Publications:

Sharp, Z. D., Mancini, M. G., Hinojos, C. A., Dai, F., Berno, V., Szafran, A. T., Smith, K. P., Lele, T. P., Ingber, D. E., and Mancini, M. A. (2006). Estrogen-receptor-α exchange and chromatin dynamics are ligand- and domain-dependent. J Cell Sci *119*, 4101-4116.

Berno, V., Amazit, L., Hinojos, C., Zhong, J., Mancini, M.G., Sharp, Z.D., and Mancini, M.A. (2008) Activation of Estrogen Receptor-α by E2 or EGF Induces Temporally Distinct Patterns of Large-Scale Chromatin Modification and mRNA Transcription. PLoS One (In production).