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## Ellisen Laboratory

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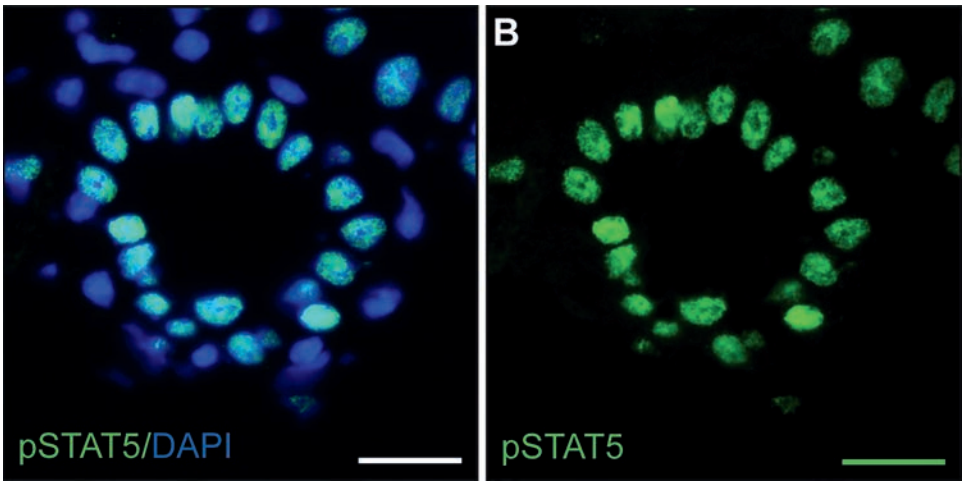
Recent progress in cancer treatment has been made possible through new insights into the key genes and pathways that underlie most malignancies. Understanding how these central players trigger the early, stepwise progression of cancer will be essential to moving beyond incremental steps and toward revolutionary advances in cancer treatment and prevention. **The Ellisen laboratory** is broadly interested in identifying such genetic abnormalities, understanding how they influence the biology of cancer cells, and discovering how biology can inform the selection of the most effective therapy for each patient. We address these questions through basic research studies of key tumor-cell signaling pathways, and through molecular analysis of patient tumor samples conducted in partnership with collaborators in the fields of molecular diagnostics and computational biology. Our discoveries in the basic laboratory and through tumor analysis have already been translated to clinical trials that seek to identify new predictive markers, and new prevention and therapeutic strategies for breast and other cancers.

Our group is broadly interested in how genetic abnormalities in breast cancer and related malignancies influence tumor biology, and how that biology can, in turn, be exploited to therapeutic advantage. We address these questions through basic research studies of key cancer drivers including DNA repair defects through BRCA1/2 and related pathways, and transcriptional reprogramming through the p53 gene family. Supporting and complementing these studies are sophisticated analyses of patient-derived precancerous and cancerous tissues. Recent innovative tissue-based studies have led to our discovery of novel cancer drivers, and have provided a unique window on early cancer pathogenesis, intratumoral heterogeneity and tumor progression. Our discoveries in the basic laboratory and through human tumor analysis are being applied in ongoing clinical trials that seek to identify predictive markers of response to specific therapeutics for breast and other cancers. Our ability to work at the interface of basic tumor biology and therapeutic application is strongly supported by our network of collaborators and by the research and clinical infrastructure of the Mass General Cancer Center.

### The p53 family network in cancer biology and therapy

The p53 tumor suppressor is inactivated in more than 50% of sporadic human cancers, and patients carrying heterozygous germline p53 mutations show striking tumor predisposition. As a transcription factor and key nodal point for integrating cellular responses to DNA damage, p53 regulates genes involved in diverse cellular processes including cell cycle progression, apoptosis and angiogenesis. Through analysis of two p53-related genes, p63 and p73, we and others have defined a functional network through which these factors interact in human tumorigenesis. We have further defined a tissue-specific role for p63 as the enforcer of an epigenetically-controlled stem/progenitor state. Tumor-selective deregulation of p63 and its associated chromatin remodeling factors




*The lactating mammary alveolus (shown) requires activation of STAT5 (pSTAT5, green/aqua) in luminal cells, which is controlled by paracrine hormonal signaling from basal cells (blue). Loss of this signaling may block luminal differentiation and predispose to breast cancer.*

reprograms the transcriptome and thereby promotes proliferation, inhibits differentiation, and contributes to immune evasion. These findings are likely to explain the observation that p63 is over-expressed in a broad variety of epithelial tumors, particularly squamous cell and breast carcinomas. Collectively, this work serves as a paradigm for analysis of transcriptional reprogramming in cancer, while potentially providing new therapeutic possibilities for multiple treatment-refractory malignancies.

## BRCA1/2, hereditary cancer predisposition and prevention

Germline mutations in the DNA repair genes BRCA1 and BRCA2 confer dramatically elevated risk of cancers of the breast, ovary, and pancreas, yet the precise pathogenesis of BRCA1/2-associated cancer remains to be elucidated. Together with an international team of collaborators we are carrying out systematic studies of early events that give rise to these cancers, in part through detailed molecular analysis of normal and pre-cancerous tissues from BRCA1/2 mutation carriers. Defining the altered signaling and early cooperating events in this context is likely to reveal new markers of breast cancer predisposition and new targets for prevention. For example, our recently-published single-cell genome analysis has revealed extensive chromosomal damage in BRCA1/2-mutant breast tissues that precedes any histological abnormalities. This seminal finding implies the existence of early cellular defects and associated vulnerabilities that could be exploited for cancer prevention in this setting.

## Novel drivers of aggressive breast cancer subtypes

Our recent work employing advanced tumor molecular diagnostics has revealed gene fusions as novel drivers of an aggressive breast cancer subset. In a distinct aggressive breast cancer, triple-negative breast cancer (TNBC), extensive intratumoral heterogeneity is itself a driver that we have characterized through single-cell genomic and transcriptomic analysis. Our longstanding work on the biology of TNBC is supported by the institution-wide Triple-Negative Breast Cancer Program, which integrates basic research, translational and clinical studies together with human tumor propagation and high-throughput drug screening, all focused on overcoming drug resistance and improving outcomes for patients with TNBC.

## Selected Publications:

Koh S-B, Ross K, Isakoff SJ, He L, Matissek KJ, Schultz A, Mayer EL, Traina TA, Carey LA, Rugo HS, Liu MC, Stearns V, Langenbucher A, Saladi SV, Ramaswamy S, Lawrence MS and **Ellisen LW**. YAP activates RASAL2 to confer chemoresistance and MEK inhibitor vulnerability in triple-negative breast cancer. *Journal of Clinical Investigation.* 2019 (In Press)

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Saladi SV, Ross K, Karaayvaz M, Tata PR, Mou H, Rajagopal J, Ramaswamy S, and **Ellisen LW**. ACTL6A is co- Amplified with p63 in Squamous Cell Carcinoma to Drive YAP Activation, Regenerative Proliferation and Poor Prognosis. *Cancer Cell*. 2017 31:35-49.

Isakoff SJ, Mayer EL, He L, Traina TA, Carey LA, Krag K, Rugo H, Liu MC, Stearns V, Come SE, Timms K, Hartman A-R, Borger DR, Finkelstein DM, Garber JE, Ryan PE, Winer EP, Goss PE, **Ellisen LW**. TBCRC009: A multi-center Phase II clinical trial of platinum monotherapy with biomarker assessment in metastatic triple-negative breast cancer. *Journal of Clinical Oncology.* 2015; 33:1902.

Forster N, Saladi SV, Van Bragt M, Sfondouris ME, Jones FE, Li Z, and **Ellisen LW**. Basal cell signaling by p63 controls luminal progenitor function and lactation via NRG1. *Developmental Cell.* 2014; 28:147-60.