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Ellisen Laboratory

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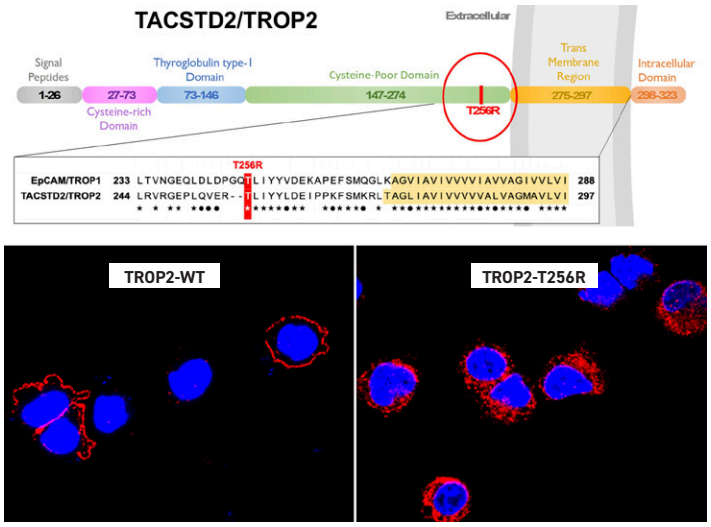
Our laboratory specializes in work at the interface between basic tumor biology and therapeutic application. Understanding how key genes and pathways trigger the early, stepwise progression of cancer will be essential to moving beyond incremental steps and toward revolutionary advances in cancer treatment 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 that 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 has a broad interest 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 therapeutic resistance. 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 For more details please see our website, Ellisenlab.com.

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 triple-negative breast cancer (TNBC), extensive intratumoral heterogeneity is itself a driver that we have characterized through single-cell genomic and transcriptomic analysis, leading to our discovery of unanticipated drug resistance mechanisms with immediate therapeutic implications. 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.



TROP2 is a cell-surface protein selectively expressed on tumor cells and targeted by emerging therapeutics including the antibody-drug conjugate sacituzumab govitecan (SG). Immunofluorescence (bottom) for TROP2 (red) in TNBC cells shows that the novel resistance mutation T256R results in TROP2 cytoplasmic mislocalization, which prevents SG binding.

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 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.

The p53 family network in cancer biology and therapy

The p53 tumor suppressor is inactivated in more than 50% of sporadic human cancers, and heterozygous germline p53 mutation confers striking tumor predisposition. As a transcription factor and key nodal point for integrating cellular responses to DNA damage, p53 controls 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 reprograms the transcriptome and thereby promotes proliferation, inhibits differentiation, and contributes to immune evasion. These findings likely explain the observation that p63 is over-expressed in a large 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.

Selected Publications:

Coates JT, Sun S, Leshchiner I, Thimmiah N, Martin EE, McLoughlin D, Danysh BP, Slowik K, Jacobs RA, Rhrissorrakrai K, Utro F, Levovitz C, Denault E, Walmsley CS, Kambadakone A, Stone JR, Isakoff SJ, Parida L, Juric D, Getz G, Bardia A, and **Ellisen LW**. Parallel genomic alterations of antigen and payload targets mediate polyclonal acquired clinical resistance to sacituzumab govitecan in triple-negative breast cancer. *Cancer Discovery.* 2021 11:1-10.

Qiao S, Koh SB, Vivekanandan V, Salunke D, Patra KC, Zaganjor E, Ross K, Mizukami Y, Jeanfavre S, Chen A, Mino-Kenudson M, Ramaswamy S, Clish C, Haigis M, Bardeesy N, and **Ellisen LW**. REDD1 loss reprograms lipid metabolism to drive progression of RAS-mutant tumors. *Genes & Development.* 2020 Jun 1;34(11-12):751-766.

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Karaayvaz M, Cristea S, Gillespie SM, Patel AP, Mylvaganam R, Luo CC, Specht MC, Bernstein BE, Michor F, and **Ellisen LW**. Unravelling subclonal heterogeneity and aggressive disease states in TNBC through single-cell RNA-seq. *Nature Communications.* 2018 9:3588-97.

Matissek KJ, Onozato ML, Sun S, Zheng Z, Schultz A, Lee J, Patel K, Jerevall PL, Saladi SV,...Finkelstein DM, Le LP, Bardia A, Goss PE, Sgroi DC, Iafrate AJ, **Ellisen LW**. Expressed Gene Fusions as Frequent Drivers of Poor Outcomes in Hormone Receptor-Positive Breast Cancer. *Cancer Discovery*. 2018; 8:336-353.

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