The Joint International ELBCC/LOBSTERPOT & LBCA Symposium

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The Joint International ELBCC/LOBSTERPOT & LBCA Symposium

- The LOBSTERPOT Summer School (7)
- Keynote Lectures (2)
- Scientific Talks (12)
- LBCA funded Researchers (3)
- Joint Session. Patient Advocates and Researchers
- Poster Session (15)

Thank you Leigh Pate
Countries Represented in Today’s Basic Research Highlights

USA
- Pittsburgh
- Dallas

Europe
- Switzerland
- UK
- Ireland
- Germany
- Scotland
- Netherlands
- Belgium

Presenter
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Basic Science Research Presented

- Lobular Carcinoma Research Models
- Lobular Tumor Microenvironment & Heterogeneity
- Lobular Carcinoma and Hormone Signaling
- Epigenetic Readers Inhibition in ILC
- Lobular Carcinoma Metastasis

Presenter
George SFLOMOS, Ph.D.
EPFL, Switzerland
Twitter Handle: @sflomos
ILC Preclinical Model Systems

Prof. Adrian V. Lee, PhD
Pittsburgh Foundation Chair in Precision Medicine
Director, Institute for Precision Medicine
Professor, Dept. Pharmacology & Chemical Biology UPMC Hillman Cancer Center

George Sflomos, PhD
Lab of Prof. Cathrin Brisken
Swiss Institute for Experimental Cancer Research
École Polytechnique Fédérale de Lausanne (EPFL) Switzerland
What is the definition of a Lobular Cell Line?

ILC is a diagnosis based upon histopathology and growth pattern – cell lines don’t have this so how do we identify them?

Molecular features?
Characterization of ILC models

Aim: to create a robust set of well-curated ILC models that are credentialed
Role of E-cadherin in ILC progression

Hypothesis: Unique growth and metastatic ILC patterns results from E-cadherin loss and that restoration in ILC will alter ILC phenotypes

• Inducible E-cadherin over-expression in 3 ILC cell lines (MM134, SUM44, BCK4).
• Restoration of E-cadherin leads to non-lobular like tumors.
• Restoration inhibits *in vitro* and *in vivo* tumor growth.
E-cadherin loss leads to ID-2 dependent cell cycle inhibition in ILC

Highlights

- Hypothesis: Loss of E-cadherin function is the leading factor of the indolent behavior of ILCs.
- Inhibitor of DNA binding 2 (Id2), a mediator of cell cycle progression, is essential for anchorage independent survival and metastasis.
- Does E-cadherin loss & Id2 expression stratification promising candidates for the use of clinical cell cycle intervention drugs, e.g CDK4/6 inhibitors?
ILC and Glucocorticoid Receptor

Does Glucocorticoid Receptor (GR) contribute to ILC biology?

- Increased GR in ILC.
- High GR expression correlates with better survival probability.
- Hypothesis: GR activation will slow ILC growth and decrease cell adhesion at the peritoneal surface.
- GR activation slows ILC proliferation in vitro and in cell adhesion assays and decreases cell adhesion to laminin and vitronectin.
ILC and Adipocytes (fat cells)

- To Investigate the Tumor Microenvironment Heterogeneity of ILC
ILC and Adipocytes (fat cells)

- To Investigate the Tumor Microenvironment Heterogeneity of ILC

Adapted from Sflomos & Brisken, Springer 2017
How to Effectively Study Lobular Tumor Microenvironment

Matteo Serra
Lab of Prof. Christos Sotiriou
Breast Cancer Translational Research Laboratory J.C. Heuson, Institut Bordet J.-C. Heuson Breast Cancer Translational Research Laboratory (BCTL)
ILC and Adipocytes (fat cells)

Highlights

- Spatial Transcriptome (ST) on frozen tumor samples from 43 primary hormone receptor-positive, HER2-negative ILC.
- Adipocytes-tumor contacts were enriched in samples from patients who relapsed.
- A gene expression signature of 27 genes was derived by performing differential gene expression analysis between relapse versus non-relapse disease on the selected spots.

- Tumor-adipocytes interaction has a role in defining prognosis in ILC.
Lobular Tumor Heterogeneity

Highlights
- Investigation of mixed lobular and non lobular - Heterogenous E-cadherin expression.
- Histology, Mutational and Methylation profiles show similarities between E-cadherin positive and negative compartments|tumors.
- Heterogeneity in druggable alterations in PIK3CA.
- APOBEC signatures more common in tumors with CDH1 mutations.
Fibroblasts in Lobular Cancer

The CAF cell of origin in breast cancer, in ILC?

- Tissue-resident fibroblast contributes almost entirely to the pool of Cancer Associated Fibroblasts (CAFs) in ILC
  1. iCAFS recruit myeloid cells and induce tumor cell invasion
  2. myCAFs produce excessive extracellular matrix
ILC and Tumor Microenvironment

Which genes are up in the ILC stroma?
Which genes are up in the ILC stroma?

- Laser-capture microdissection to separate tumor epithelium from stroma.
Which genes are up in the ILC stroma?

- Laser-capture microdissection to separate tumor epithelium from stroma.
- 23 ER+ ILC primary tumors.
- PAPP-A was the most enriched gene in the stroma compared to the tumor epithelial compartment in ILC.
- PAPP-A correlates with E-cadherin mutated tumors.
- Low expression of PAPP-A is associated with worse survival.
- PAPP-A needs to be active in order to cleave IGFBP-4 and liberate IGF-1.
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- Laser-capture microdissection to separate tumor epithelium from stroma.
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Matrisome signature is key characteristic of lobular tumors.
Lobular tumors overexpress the collagen crosslinking enzyme Lysyl Oxidase Like 1 (LOXL1).
In preclinical model pan-LOX inhibitors (e.g. BAPN) slowed tumor growth and reduced metastasis.
Ex vivo culture system (digested microstructures encapsulated in alginate) to test new potent LOX family inhibitors (e.g LOX-IN-3).
What Have we Learned About ILC and Their Immune Landscapes?

- Low number of tumor-infiltrating lymphocytes (TILs) infiltration in primary ILC (Lab of Prof. Christine Desmedt).
- Immune landscape dominated by T cells and M2 macrophages (alternatively activated macrophages) enrichment in ILC.
- Functionally diverse population of macrophages?
- Do macrophages migrate to ILC (promote ECM remodelling?) or does ILC differentially recruit macrophages?
Epigenetic Readers Inhibition in ILC

Investigating the use of BET inhibitors to treat anti-endocrine resistant invasive lobular carcinoma

- High expression of Bromodomain-Containing Protein 3 (BRD3) is associated with reduced disease-free survival.
- BET inhibitors JQ1 (Brander Lab - 2010) and Mivebresib (Abbvie - 2018).
- BET inhibition effectively inhibits tumor growth in vivo (JQ1 acts synergistically with tamoxifen).
- BET inhibition increases the gene expression of FGFR3 and decreases the gene expression of SUV39H1.
What have we learned from ILC histology/pathology?

- Samples derived from submucosa and mucosa
- E-cadherin to P-cadherin switching occurs in a subset of ILCs
- ILC switching: from a non-cohesive to a cohesive growth pattern
Mutations in Metastatic ILC

- 73 samples with E-cadherin mutations.

- Novel mutated genes
  - $KMT2C$, $RB1$, $ARID1A$, $CBFB$

- Novel amplified genes
  - $ZNF703$, $CCND1$, $ZNF217$, $FGFR1$

- Known (localized primary disease) and novel coding and non-coding mutations found in ILC versus non-ILC tumors.
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- Comprehensively credential ILC models
- Role of M2 Macrophages & Fibroblasts in ILC?
- Targeting of ECM components – LOXL1, PAPP-A?
- New RNA signatures to guide treatments based on ILC-Adipocytes interaction?
- What is the utility of modulating GR activity?
- Increased CDK4/6 inhibitors sensitivity in ILC?
- Epigenetic inhibitors JQ1 & Mivebresib?
- Role of E-cadherin to P-cadherin switching?
- Novel mutations of interest?
Thank you so much for your attention

EPFL Campus
Lausanne