Characterization of a Living Biobank of Patient-Derived Invasive Lobular Carcinoma Organoids that Retain Tumor Heterogeneity in 3D Culture and Tumorigenicity *In Vivo*.

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Invasive Lobular Carcinoma

Invasive Lobular Carcinoma (ILC) accounts for the 2nd most frequently diagnosed histological subtype of Breast Cancer (BC), constituting 10%-15% of all reported cases. ILC is hormonally driven (estrogen and progesterone receptors) with a hallmark characteristic of ILC being lack of *E-cadherin* (*CDH1*) or mutations in the *CDH1* gene reported in over 90% of cases. Mutations in the *CDH1* gene have also been associated with 39%–52% increased lifetime risk of developing breast cancer in women.

Patient-derived organoid (PDO) models have been shown to offer significant advantages in terms of better recapitulating the tumor/microenvironment niche, however such models have not been available to study ILC.

With a vision to establish 3D models to better understand ILC and to develop specific therapeutic targets, here, we describe a pipeline for establishment and comprehensive characterization of a diverse biobank of ILC PDOs.

Establishment of Invasive Lobular Carcinoma Biobank

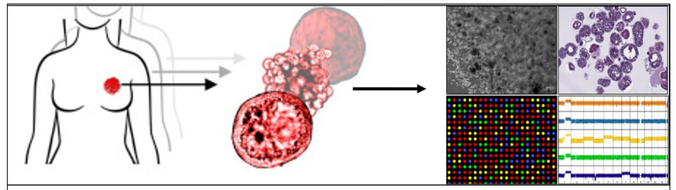

Fig.1a Diagrammatic representation of the pipeline for processing ILC PDOs from patient-derived tumor tissues. Right panel represents the characterization approaches (morphological, histological, transcriptomic and genomic) used for validating the PDOs.

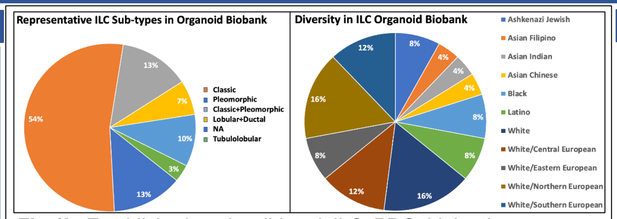

Fig.1b Established and validated ILC PDO biobank represents diverse ILC subtypes as well as diverse population groups.

ILC PDOs are morphologically distinct

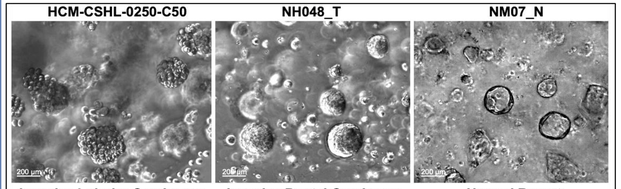

Fig. 2. Differences in PDO morphology based on histological origin of tissues . Left: Lobular, Middle: Ductal, Right: Normal

Genomic profiling of ILC PDOs

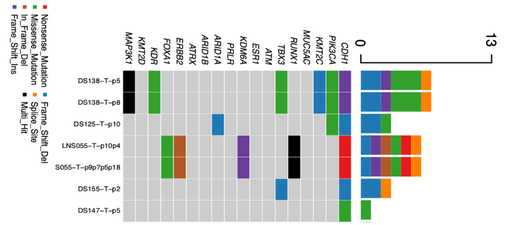

Fig. 3. Mutational profiling on ILC PDOs using targeted exome sequencing identifies ILC-associated mutations in ILC PDOs.

Copy Number Variants enriched in ILC PDOs

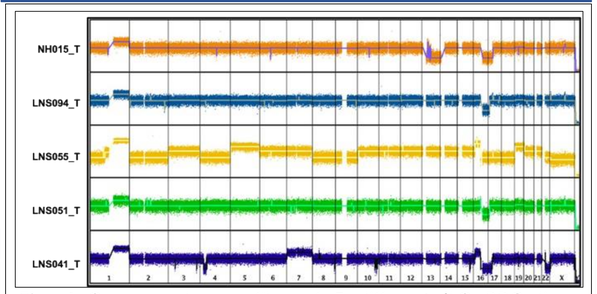

Fig. 4 Copy number profiles of 5 different ILC PDO lines confirming gains (Chr1q) and losses (Chr 16q, Chr 17p).

Transcriptome Profiling of ILC PDOs

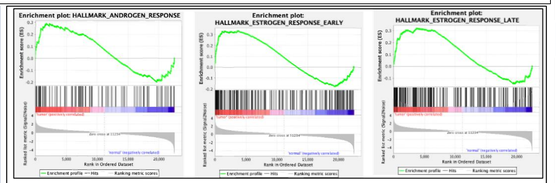

Fig. 5 GSEA profiles using transcriptome dataset of ILC PDOs reveal enrichment of genes involved in ER signalling.

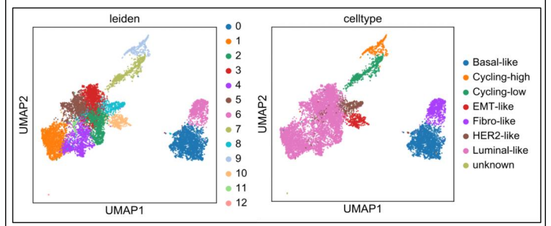

Fig. 6. Single-cell RNA sequencing of ILC PDOs reveal that PDOs retain complexity and heterogeneity of ILC tumors

ILC PDOs retain tumorigenicity when xenografted *in vivo*

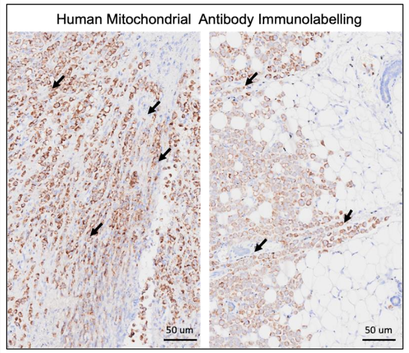

Fig. 7. ILC tumors developed in PDO-X models retain tumorigenicity in vivo and display single file growth pattern. Human tumor cells labelled with anti-human mitochondrial antibody.

ILC Biobank: Outlook

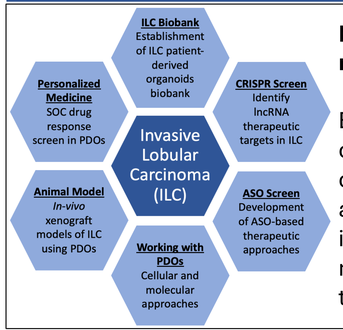

Fig.8 Overview of ILC research directions

Established and comprehensively characterized ILC PDOs are now being used to investigate and identify novel RNA-based therapeutic targets.

Conclusions

We have successfully established a pipeline and have now processed ~ 65 ILC derived patient tumor tissues with a ~ 50%-55% success rate in establishing organoid models.

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References

- Batra, H et al. Cancers (Basel) 2023 Nov 20;15(22):5491
- Sachs, N et al. Cell, 2018 Volume 172, Issue 1, 373 - 386.e10
- Bhatia, S et al, Cancer Res 2022 Apr 1;82(7):1174-1192

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