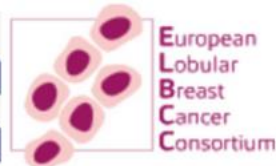


# ILC Symposium: highlights on translational research

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# Outline

- What is translational research?
- How can models be translated into the clinic?
- Prognostic tests for ILC
- Disease heterogeneity
- Towards new treatment targets
- Autopsy programs to enhance research



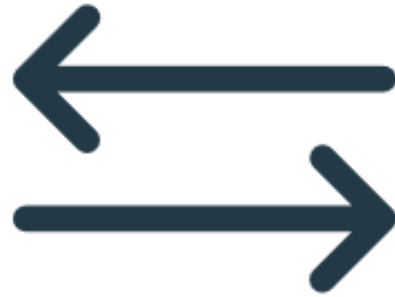
# What is translational research?



Fundamental research

=

Scientists using different models to understand the underlying mechanisms of a disease



Translational research

=

Researchers that bring the knowledge of the fundamental research into the clinic



Clinical research

=

Trials with patient data and trials with new types of medication



How can models be translated  
into the clinic?



# Differences in the animal kingdom

- Unique differences in the mammary gland of different species
  - Some species adapt their milk to the sex of the baby
  - Others adapt in to the age of the babies



Mammary Gland development  
by Renée van Amerongen

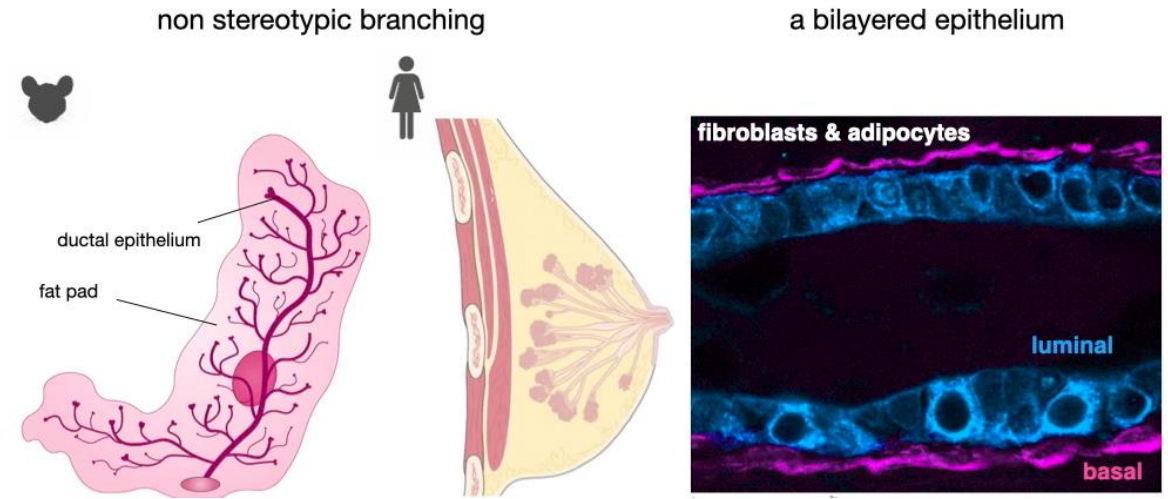




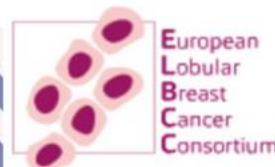
# Similarities with animal models

- The mammary gland of the mouse shows some similar features as compared to the human mammary gland
  - Branching pattern in the breast
  - The build-up of the cells of the branches in the breast
- Mouse models can help understand how human breast tumors grow and spread

## Similarities between mouse and humans



Mammary Gland development  
by Renée van Amerongen



# Prognostic tests for ILC



# What is a prognostic test?

- Tests of different mutations that can occur in the genes of the tumor to determine how aggressive the tumor is
  - Gene signatures of the tumors
- Determine which patient are at high risk of developing distant tumor growths (=metastases) in the future
- Used in the clinic to determine if additional treatment with chemotherapy is necessary in patients where it is not clear
- Mammaprint, OncotypeDx, Prosigna, ...





# Prognostic tests for ILC

- Breast Cancer Index
  - Can be used in patients with ILC
  - Determines which patients are at risk for early and late distant recurrences (= metastases)
- Lobsig
  - Prognostic tests specifically developed for patients with ILC
  - Promising results for determining which patients are at high risk for recurrences ⇒ needs validation







npj | Breast Cancer

[www.nature.com/npjbcancer](http://www.nature.com/npjbcancer)

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ARTICLE OPEN

LobSig is a multigene predictor of outcome in invasive lobular carcinoma

Amy E. McCart Reed <sup>1</sup>, Samir Lal<sup>1,5</sup>, Jamie R. Kutasovic <sup>1</sup>, Leesa Wöckner<sup>2</sup>, Alan Robertson<sup>3</sup>, Xavier M. de Luca <sup>1</sup>, Priyakshi Kalita-de Croft <sup>1</sup>, Andrew J. Dalley <sup>1</sup>, Craig P. Coorey<sup>1</sup>, Luyu Kuo<sup>1</sup>, Kaitin Ferguson<sup>1</sup>, Colleen Niland<sup>1</sup>, Gregory Miller<sup>1,4</sup>, Julie Johnson<sup>1</sup>, Lynne E. Reid<sup>1</sup>, Renique Males<sup>1</sup>, Jodi M. Saunus<sup>1</sup>, Georgia Chenevix-Trench<sup>2</sup>, Lachlan Coin<sup>3</sup>, Sunil R. Lakhani<sup>1,4</sup> and Peter T. Simpson <sup>1</sup>

Keynote

Steffi Oestenreich



# Disease heterogeneity



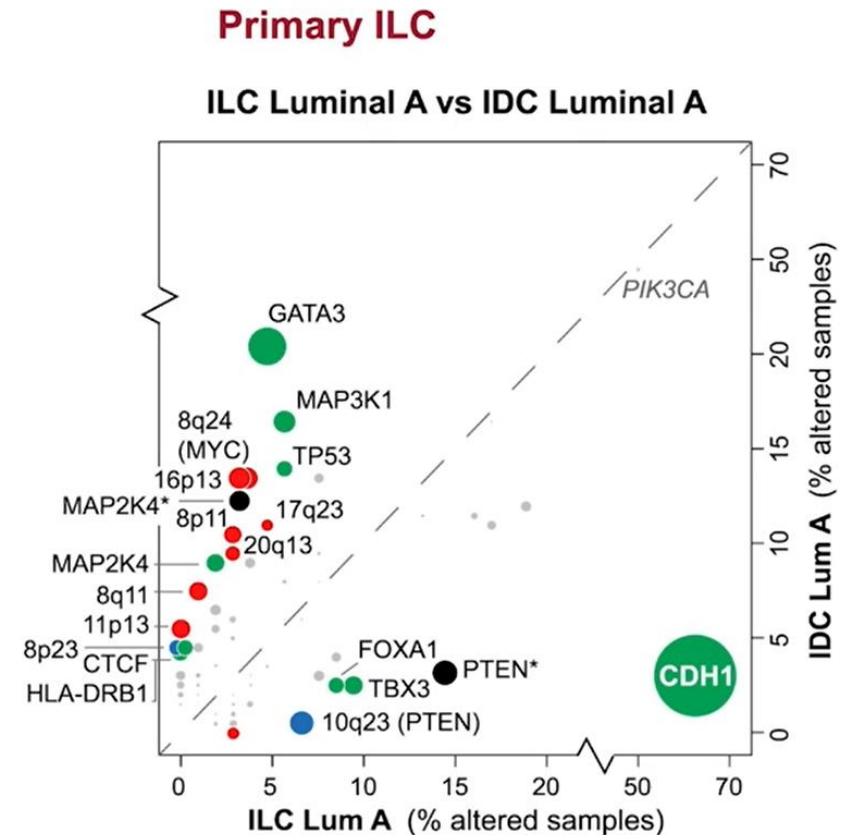
# What is disease heterogeneity?

- Variations in different aspects of the tumor
  - Expression of receptors
    - e.g. hormone sensitive or not
  - Mistakes in the genes of the tumor cells (= mutations)
  - Other cells that close to the tumor and that can influence the tumor (= tumor microenvironment)
  - ...
- Large differences in these aspects between ILC and non-special breast cancer underpin the need to see ILC as a separate disease



# Differences in mutations

- Comparison between ILC and NST
  - Luminal A = hormone sensitive, HER2 negative
  - Double scale
    - Percentage of ILC with those specific mutations = horizontal
      - The more to the right a gene is put, the more mutations in that gene in ILC
    - Percentage of NST with those specific mutations = vertical
      - The higher a gene is put, the more mutations in that gene in NST



Ciriello G et al. Cell (2015)

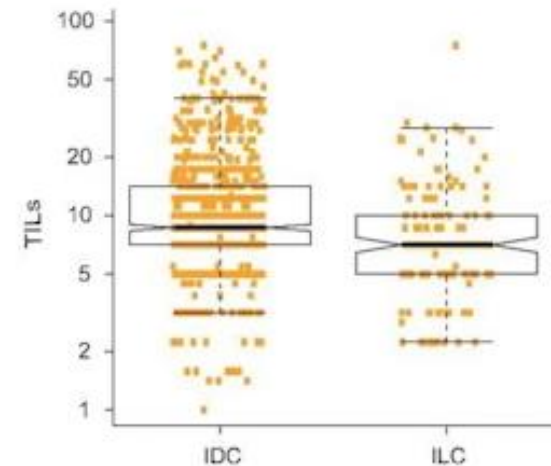
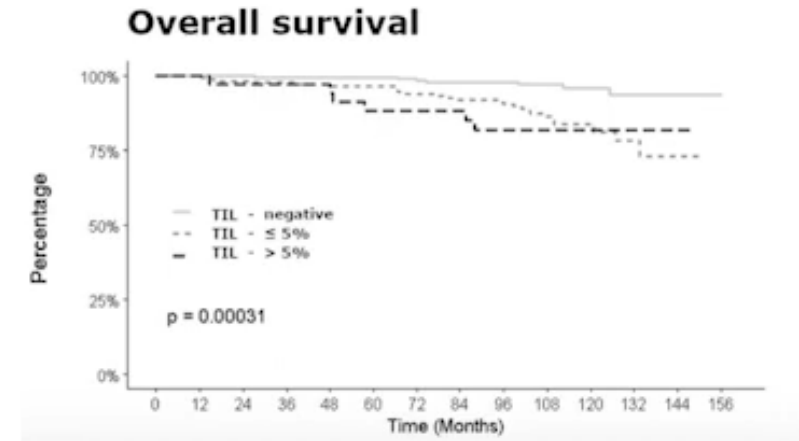
Heterogeneity of E-cadherin and the immune microenvironment in ILC

Rachel Natrajan



# Differences in immune cells in the tumor microenvironment

- Lymphocytes = type of white blood cells
  - Involved in the immune respons
  - TILs = Tumor infiltrating lymphocytes
    - Lymphocytes nearby the tumor cells
    - Although normally defence system of the body, cancer cells can inactivate and exhaust the immune cells  
=> higher TILs in hormone sensitive tumors is a sign of more aggressive tumors
    - TILs are lower in ILC



Heterogeneity of E-cadherin and the immune microenvironment in ILC

Rachel Natrajan



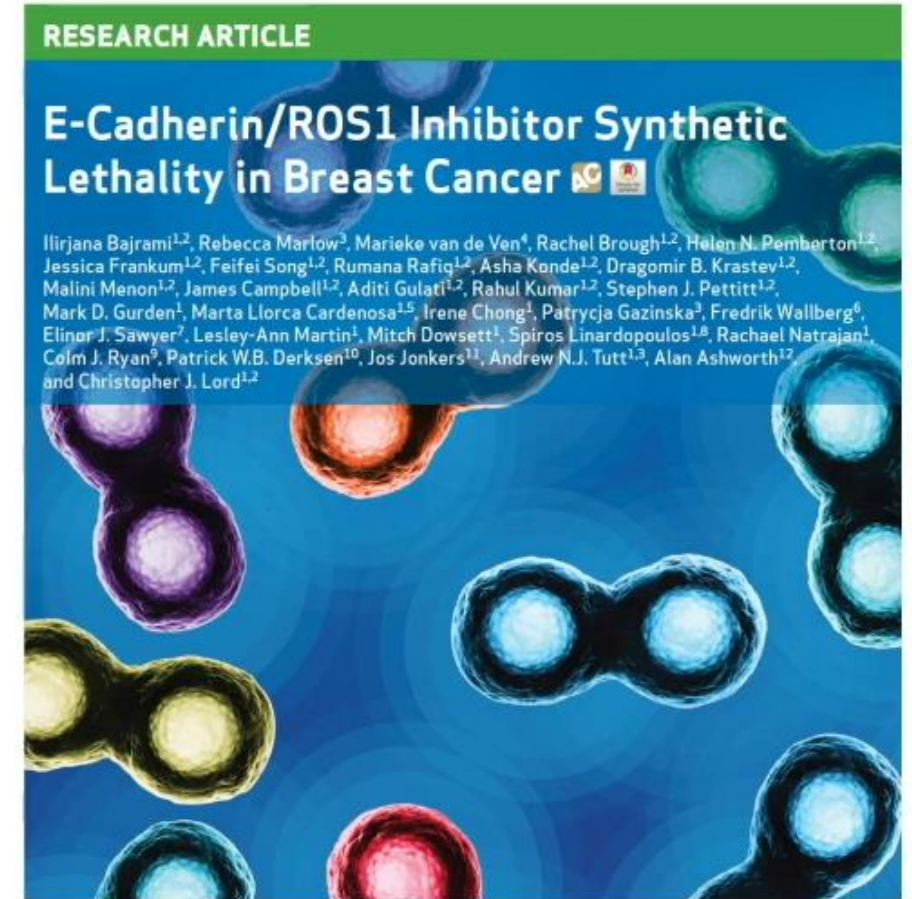
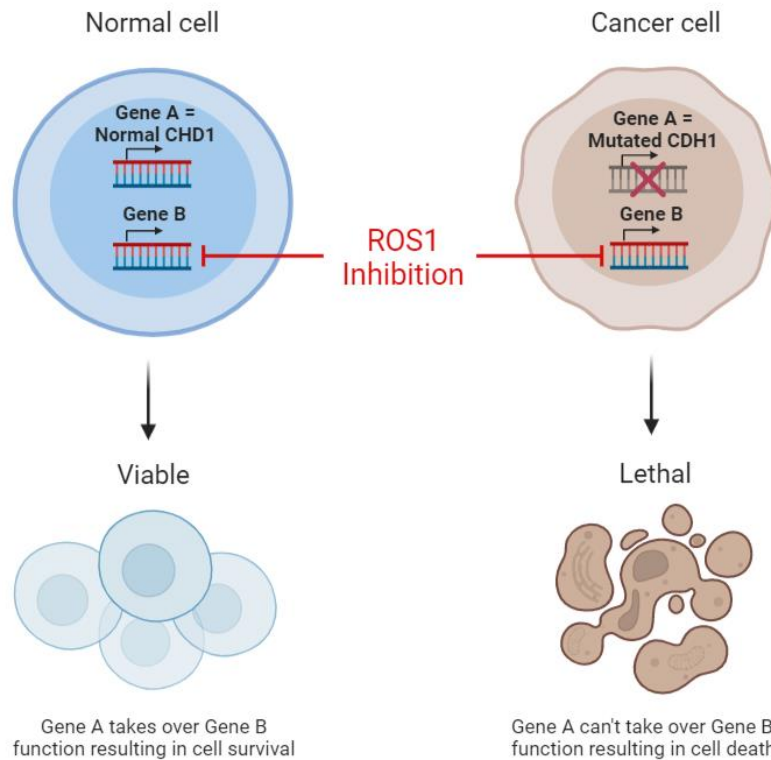


# Towards new treatment targets



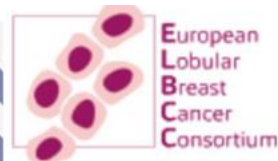
# ROS1-inhibitors

- Most ILC have a mutation in *CDH1*-gene



*Cancer Discovery*. 2018 Apr;8(4):498-515.

Keynote  
Steffi Oestenreich



# HER2 mutations

- HER2 is a protein that can be overly expressed on a tumor cell (=amplification)
- The underlying gene can also be mutated (even without amplification)
- More often in metastatic breast cancer
- More common in ILC than NST
- Those mutations can be targeted by new drugs like neratinib

Keynote

Steffi Oestenreich



# Autopsy programs to enhance research





# Autopsy programs to enhance research

- Currently 2 autopsy projects that are including also ILC

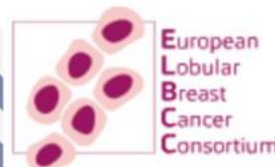
Pittsburgh: Hopes for Others	Leuven: UPTIDER
24 autopsies performed	16 autopsies performed
21 more consented	5 more consented
1 ILC, 1 mixed ILC/IDC	3 ILC, 3 mixed ILC/IDC
6-27 biospecimens/patient	45-303 samples/patient + liquid samples
Duration of 4,2 hours on average	Duration of 6,3 hours on average
Creation of new models	

- Collaboration between the programs

Keynote  
Steffi Oestenreich

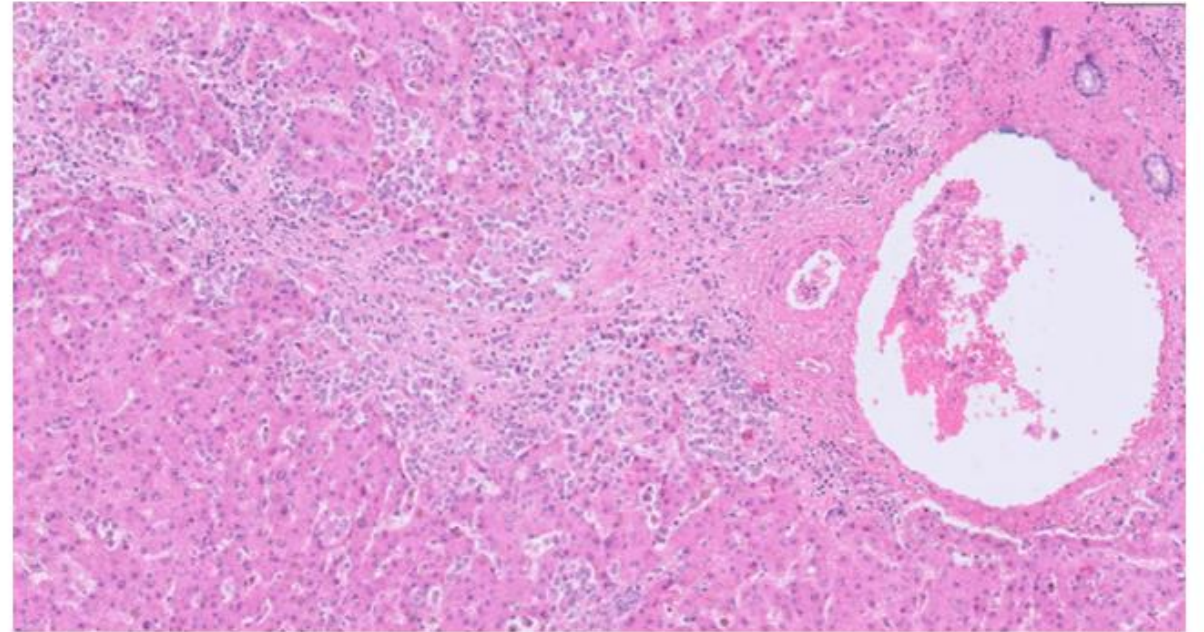
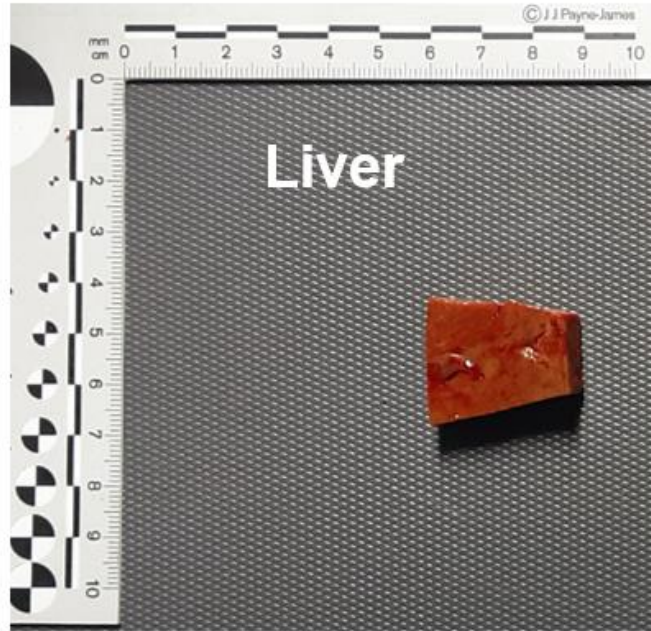
Enhancing research on metastatic lobular breast cancer through a post-mortem tissue donation study

Karen Van Baelen





# ILC can be underestimated by the naked eye



Enhancing research on metastatic lobular breast cancer through a post-mortem tissue donation study

Karen Van Baelen



# Take home messages



# Take home messages

- Translational research is bringing the knowledge of the fundamental research into the clinic
- Mouse models can help understand how human breast tumors grow and spread because of similarities in mouse and human mammary gland
- Prognostic tests are used to determine how high the risk of future metastases are to see if additional treatment is needed
  - New tests are being evaluated for ILC



# Take home messages

- New treatments are on their way
  - ROS1 inhibitors: specifically for ILC, since they more often have a CDH1 mutation and cells with this mutation can no longer survive if ROS1 is inactivated
  - HER2 mutations: more common in metastatic ILC, targeted with new drugs
- Autopsy programs can help to understand how ILC spreads and grows
  - 2 autopsy programs ongoing that have substudies on ILC





Thank you for your attention

