Hormones and breast cancer: why models matter
The challenges:

- **90% of potential drugs in oncology fail**
  - preclinical models used to test them are inadequate.

- **breast cancer**
  - lack of in vivo models for the estrogen receptor positive (ER+) subtypes, which represent more than 75% of all cases
    - **genetically engineered mouse models**
      - almost all ER- (exception: Stat1⁻/⁻ 50% at 1.5 years)
    - **xenografted breast cancer cell lines**
      - few ER+ cell lines grow in vivo, require exogenous estrogen
        => estrogen levels do not correspond to what is seen in women
    - **patient-derived-xenografts (PDXs)**
      - selection for high grade cancers
      - 2.5% engraftment rate for 423 ER+ tumors (Cottu et al., 2012)
The many dimensions of ER+ breast cancer

Hormone receptor expression changes

Systemic/endocrine environment

Microenvironment

Progesterone/Oestrogens

Amphiregulin

RANKL

WNT4?

Cyclin D1

ID4

The individual patient

Metastasis

Dormancy

The individual patient

genetic background
mutations
clonal evolution

Normal breast epithelium

Initiated cell

Carcinoma in situ

Invasive carcinoma

Time

Modified Brisken 2013 Nature Rev Cancer
Fat pad versus intraductal engraftment of tumor cells

1,000,000 cells

50,000 cells

Breast cancer cells

Lentivirus GFP-luciferase

Intraductal Injection

Bioluminescence

in vivo imaging

behbehod et al. BCR 2009

Courtesy: Valentina Scabia
MCF7 xenografts

fat pad (FP) versus intraductal (MIND)

CD31

Ki67

Collagen Type 1&3

=> MCF7-MIND recapitulates biological features of ER+ breast cancer

George Sflomos
Intraductal MFC7 xenografts show microcalcifications

Intraductal MFC7 xenografts become invasive
Intraductal MCF-7 xenografts metastasize to clinically relevant organs

Alu ISH  ER IHC

=> MFC7 intraductal xenograft model recapitulates disease development
PAM50
MIND vs FP and patient samples (C. Theillet)

=> MCF7-MIND resembles patient tumors at the molecular level

George Sflomos
Intraductal patient-derived xenografts (PDXs)
# 21 ER+ intraductal PDXs

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ER+ intraductal PDXs recapitulate human histopathology

\[ \Rightarrow \text{histopathology is tumor cell-intrinsic} \]

Maryse Fiche, Valentina Scabia
## 21 ER+ intraductal PDXs

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<th>Case</th>
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=> tumor cells are pushed back in their history

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ER+ intraductal PDXs reflect prognosis of the patient tumor they are derived from

**Tumor extent**

Maryse Fiche, Valentina Scabia

**Micrometastasis**

=> metastatic seeding occurs while disease is still in situ
ER+ intraductal PDXs and hormone receptor status

=> Hormone receptor expression fluctuates
ER+ intraductal PDXs and endocrine therapy

=> ER+ PDX-MINDs are predictive

George Sflomos
Human-Mouse Clinic:

Choosing the right treatment with humanized mouse mammary glands

**Patient-derived material**
- Tumorectomies
- Tumor biopsies
- Mammoctomies
- Pleural and peritoneal effusions
- Metastases

Cell transduction with lentiviral vectors

Injection of human cells to mouse milk ducts

Treatments. A, B, C…

-luciferase-based in vivo imaging
-cellular, molecular analyses

Feedback
The many dimensions of ER+ breast cancer

Hormone receptor expression changes

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Modified Brisken 2013 Nature Rev Cancer
Conclusions:

Intraductal engraftment

- allows to preserve luminal characteristics
- preserves hormone receptor expression and hormone response
- increases take rates for cell lines and PDX (from 2.5% to > 90%)
- pushes tumor cells back in their history
- shows early seeding to distant sites
- suggests that hormone receptor expression is dynamic
- Preserves tumor heterogeneity
- Reflects tumor response to therapy
- Allows to study the disease under physiological hormone levels
- Drawback: immuno compromised host: hence abnormal immune system
Acknowledgements:

George Sflomos, Valentina Scabia, Céline Constantin, Fabio DeMartino, Patrik Aouad, Ayyakannu Ayyannan, Laura Battista, Dalya Ataca, former: Marie Shamsheddin, Rachel Jeitziner, Csaba Laslo, Valerian Dormoy