# Generation of mouse models for the identification of new driver pathways of drug resistance in human breast cancer
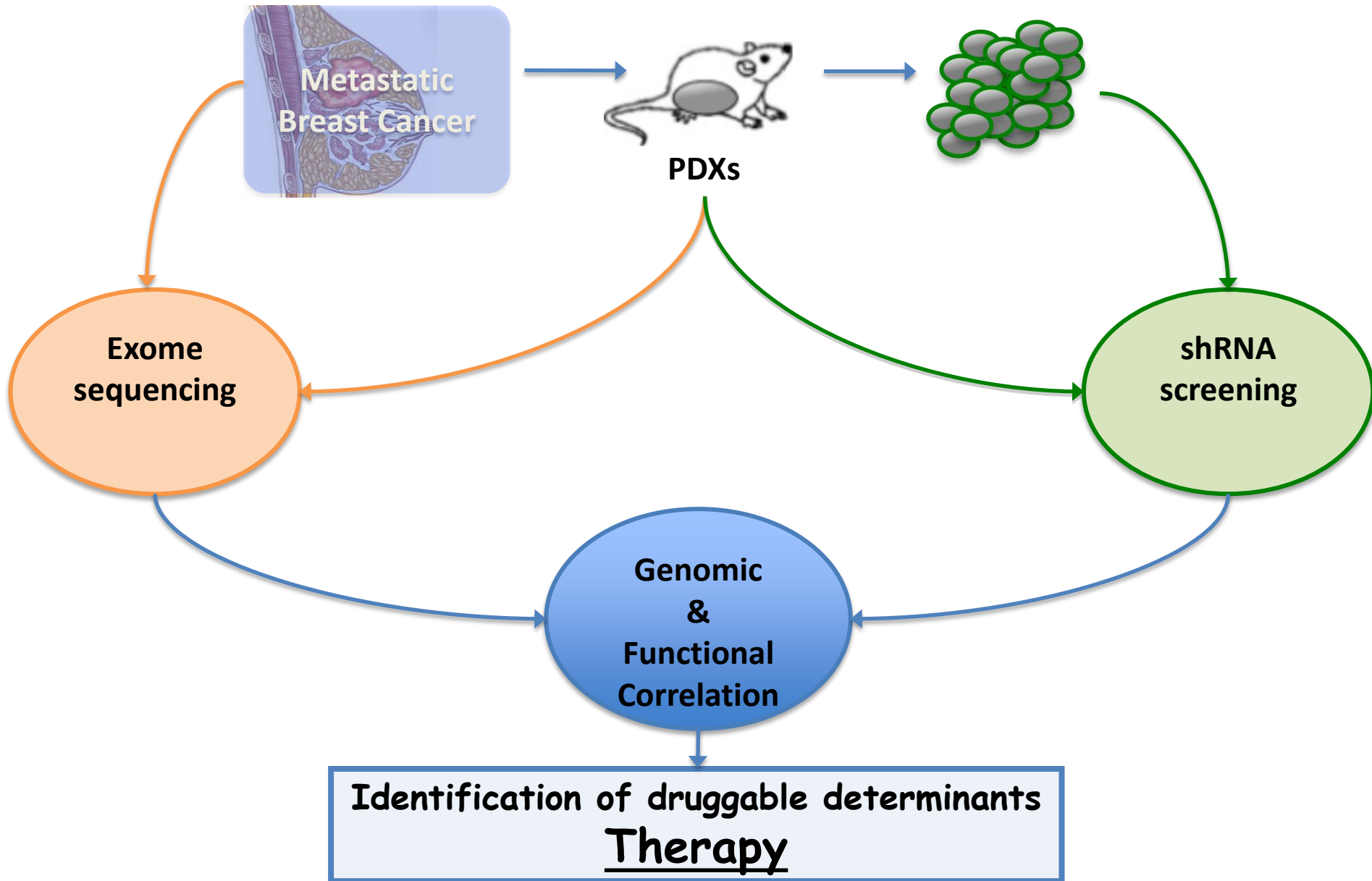
Carmen Criscitiello, Angelo Cicalese, Daniela Bossi, Giancarlo Pruneri, Franco Orsi, Monica Casiraghi, Simona Punzi, Lorenzo Spaggiari, Giuseppe Curigliano, Luisa Lanfrancone

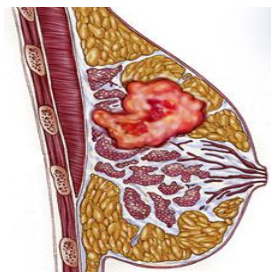European Institute of Oncology, Milano Italy

# Aims of the study

- To generate patient derived xenograft (PDX) from metastatic breast cancer

- To perform exome sequencing in PDX model in order to identify potential driver pathways of resistance

- To set up an in vivo shRNA screening in PDX in order to identify druggable targets involved in tumor growth and drug resistance.
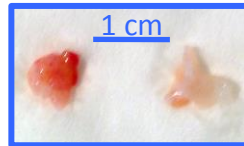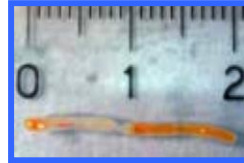
# Experimental strategy

# Feasibility of transplantation



**Lum B HER2+ TN**

*Metastatic in Liver, nodes, lung*

1 cm

**PDX 1**

**PDX2**

**PDX3**

*Criteria of Tumor Selection:*
  *-Therapy-resistant*
  *-Biologically aggressive*
  *-Paucity of available therapies*

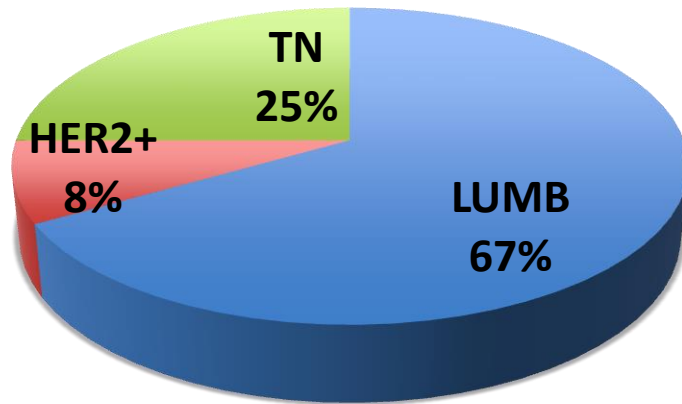# Patients' characteristics

Patients included in the study: 21
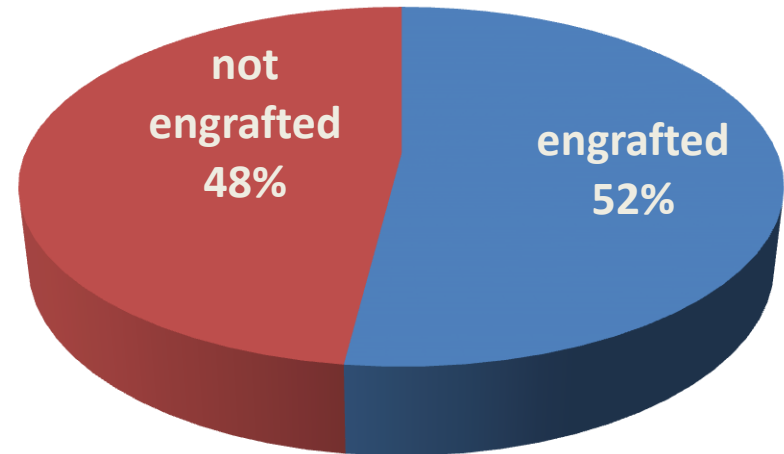- ✓ 14 Luminal B
- ✓ 3 HER2+
- ✓ 4 Triple-negative

Biopsied site:
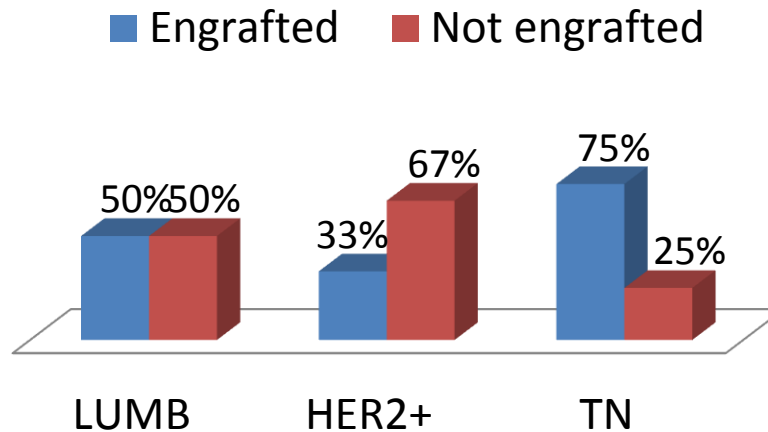- ✓ 14 liver
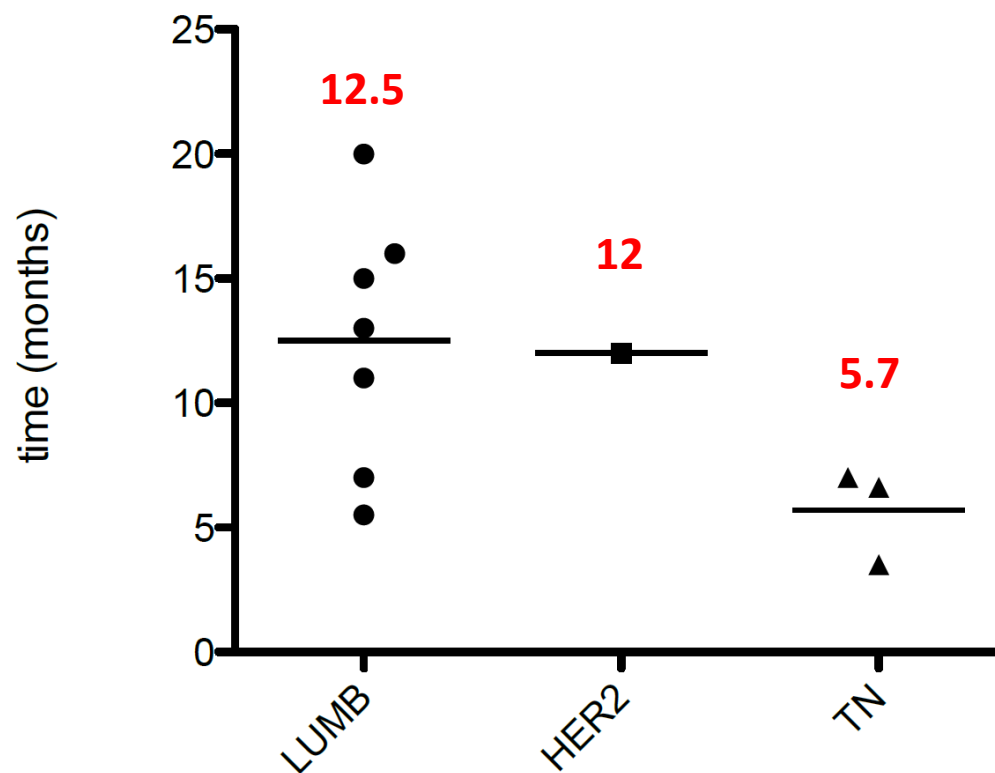- ✓ 1 lymph-node
- ✓ 6 lung

# Engraftment

## Subtypes engrafted



TN 25%

HER2+ 8%

LUMB 67%

## Take rate



not engrafted 48%

engrafted 52%

## Take rate for each subtype

■ Engrafted    ■ Not engrafted



50% 50%    33% 67%    75% 25%

LUMB        HER2+       TN

# Median time to xenograft generation

# PDXs recapitulate human tumors

## Luminal B
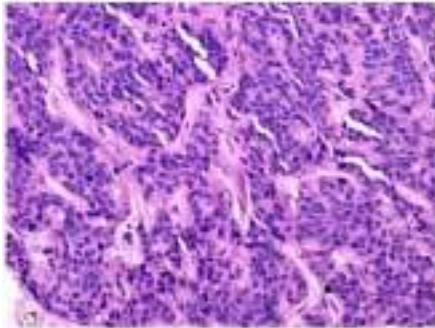


|  | H&E | ER | PgR | HER2 |
|---|---|---|---|---|
| Human | | 95% | 95% | 0% |
| PDX1 | | 90% | 80% | 0% |
| PDX2 | | 90% | 80% | 0% |

# PDXs recapitulate human tumors

## HER2$^+$

# PDXs recapitulate human tumors

## Triple Negative



|  | H&E | ER | PgR | HER2 |
|---|---|---|---|---|
| Human | | 1% | <1% | 0% |
| PDX1 | | 1% | 3% | 0% |
| PDX2 | | 3% | 3% | 1+(40%) |

# Study Steps



**PDX generation**   **shRNA screening**   **PDX2 generation**

- What we did: Generation of PDXs
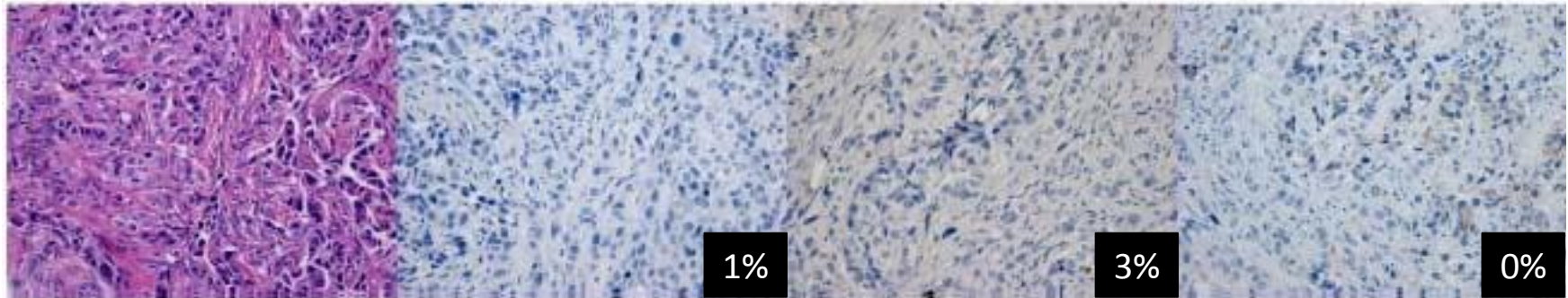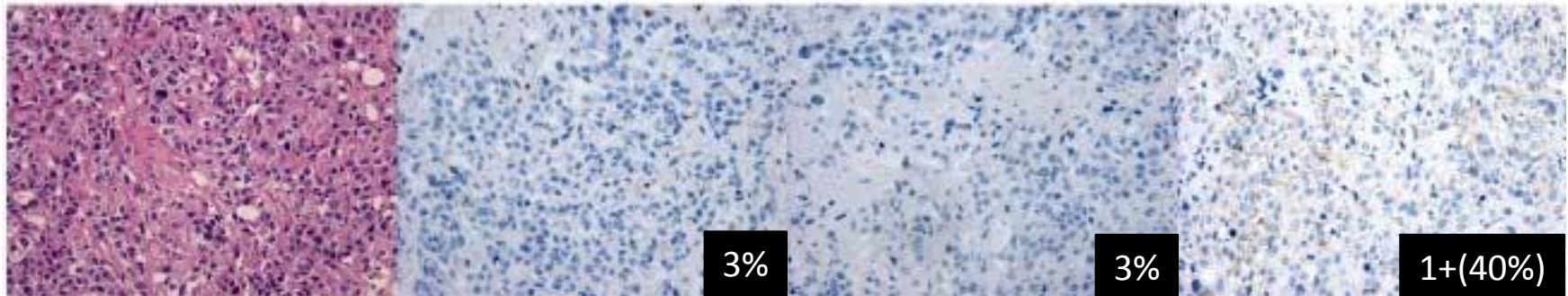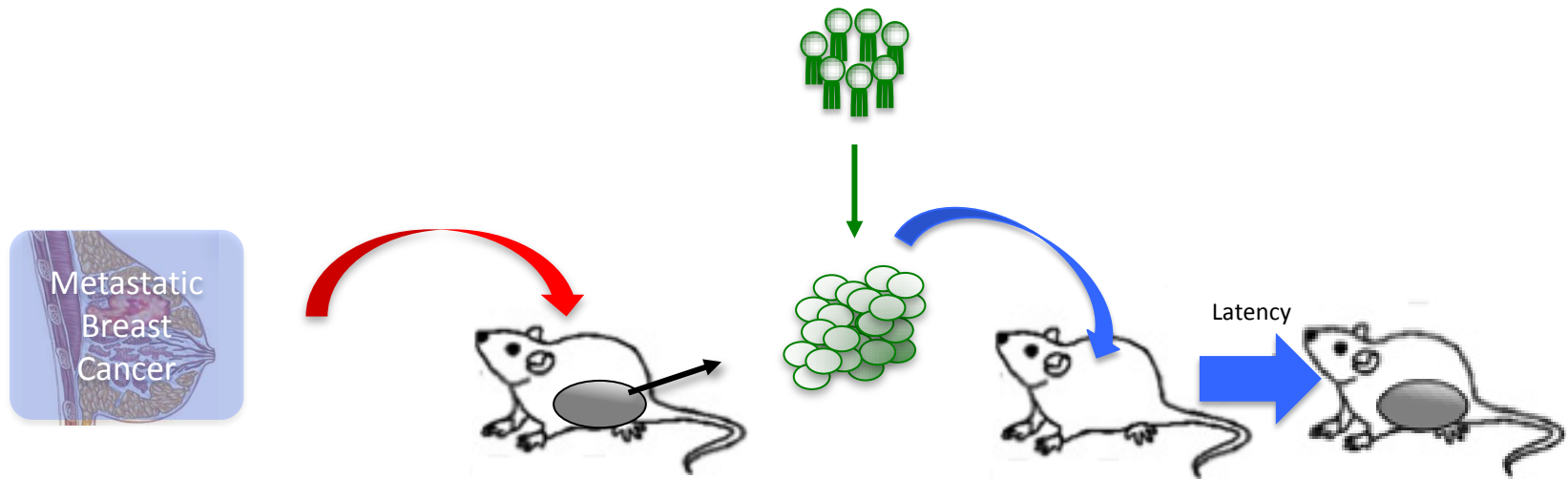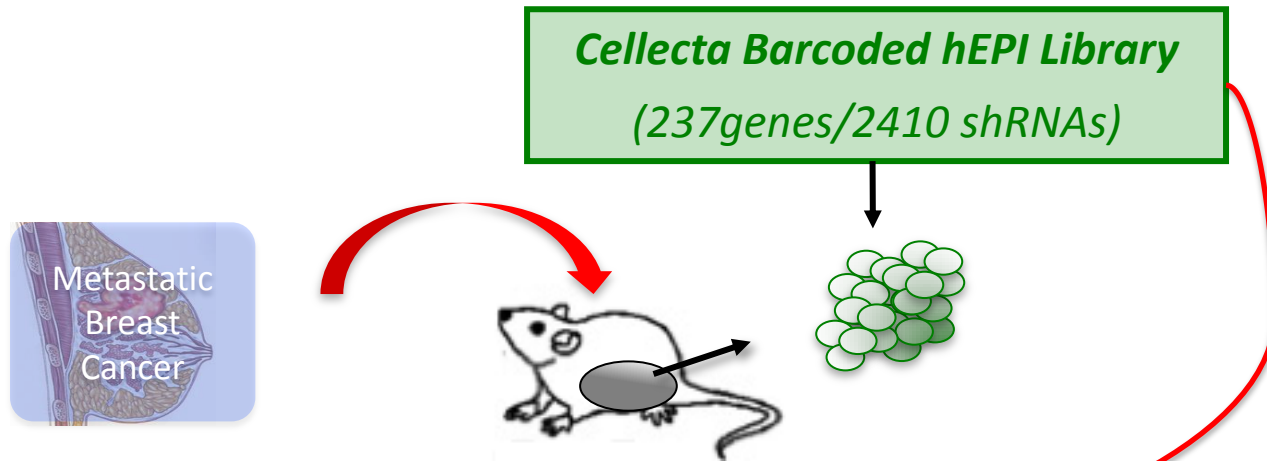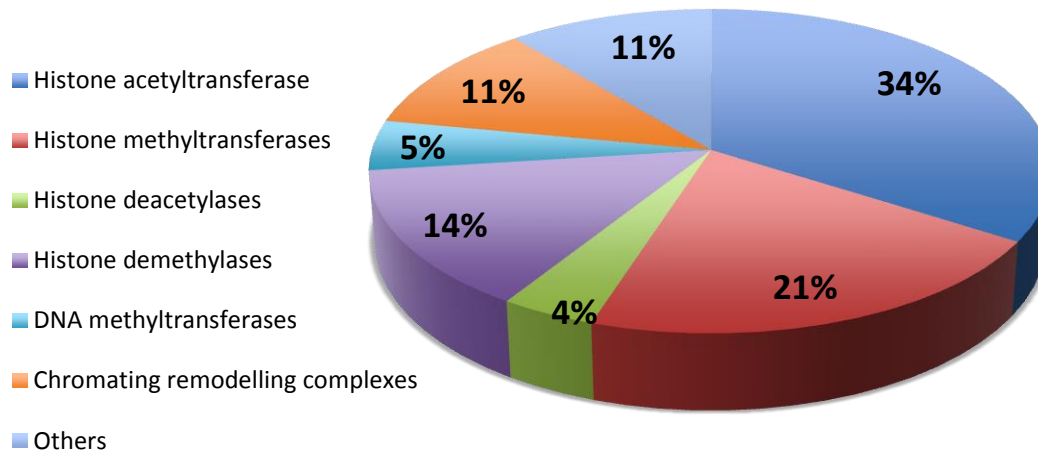
- What we're doing: Culture, Infection and Selection

- What we'll do: Transplantation of Transduced Cells

# shRNA screening- The way we do it

# Conclusions

- We generated human PDXs from patients with metastatic breast cancer progressing on standard of care.

- The xenograft model recapitulates the characteristics of the originating human tumor, maintaining the histologic and immunophenotipic features, thus confirming to be a reliable phenocopy.

- *In vivo* shRNA screening may allow to identify new determinants of tumor progression in a preclinical setting.

- The exome seq will integrate the *in vivo* functional analysis with the identification of activating mutations in breast cancer progression.

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Simona Punzi

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