New tools to (hopefully) shift the paradigm for metastatic breast cancer

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• Primary tumors can usually be resected, yet up to 30% of patients will eventually develop metastatic disease
  • “The horse has left the barn” – adjuvant tx
  • How disseminated tumor cells remain (clinically) dormant and then “reawaken” *years later* is poorly understood
  • Once detected, metastasis is considered incurable
  • 40,000 deaths per year in U.S. alone
  • Every tumor is different!
• PDXs maintain tumor histology, genomics, and gene expression of the patient’s tumor
• High concordance of therapy response between PDX and patient
• Clinically relevant chemotherapies can be tested in PDX concomitantly with patient care
• Genomically relevant targeted therapies (e.g. Foundation One) can be functionally evaluated

Issues:
- Time
- Accuracy
- Cost
- Feasibility on large scale
- Immune component not taken into account

Remove Tumor

Isolate Tumor Fragments

Transplantation of Tumor Cells

Culture in 3D

Identify New Anti-Cancer Drugs

Cell Death

Human breast cancers

COMBINED USE OF PDX AND 3D MODELS FOR DRUG SCREENING
Bone metastases are a significant cause of morbidity for breast cancer patients.

• Bone is the most common site for breast cancer metastasis in all subtypes except basal-like (Kennecke et al., JCO, 2010)

• Approximately 70% of metastatic breast cancer patients are affected by bone metastasis

• Bone metastases are associated with:
  • Pain
  • Fracture
  • Nerve compression
  • Hypercalcemia

http://www.nationalbreastcancer.org/metastatic-breast-cancer

Primary Sites of Breast Cancer Metastasis

- Brain
- Lungs
- Liver
- Bones

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X-ray of 75-year-old breast cancer patient

http://breast-cancer.ca/prog-untreated/
THE “VICIOUS CYCLE” OF BREAST CANCER BONE METASTASIS

Guise and Mundy Endocr Rev 1998
Weilbaecher et al Nat Rev Cancer 2011
Kretschmann and Welm, Cancer Metastasis Rev. 2012

Tumor cells

Osteoclast

Activated osteoclasts

Bone-derived growth factors
IGFs
FGFs
TGFβ

Bone-derived growth factors
MSP
FGFs
TGFβ

Bone metabolism

pSMAD2

Vicious Cycle

RANKL

Osteoblasts

Bone

Acted osteoclasts

Metastatic tumor cells

denosumab

PTHrP

IL-11

Kang Lab, Princeton
DISCOVERY OF A NEW PATHWAY THAT IS IMPORTANT FOR BREAST CANCER-MEDIATED METASTATIC BONE DESTRUCTION

Andrade et al, Sci Transl Med, 2017
OSTEOLYTIC BONE DESTRUCTION IS SIGNIFICANTLY REDUCED BY RON KINASE INHIBITOR TREATMENT

MOUSE MODEL

HUMAN XENOGRAFT

Andrade et al, Sci Transl Med, 2017
Compound published but not in clinic....
Contacted company, no response....

1 year later, compound licensed by another company, started Phase I
Contacted CMO, no response....
Contacted CSO, quick response!!!

Developed collaboration

But how??
Next steps?

“The” last figure?

Maybe this could be useful...
FIRST-IN-MAN PHASE I CLINICAL TRIAL WITH BMS-777607/ASLAN002: EFFECT ON BONE TURNOVER MARKERS

Various cancers; no bone involvement
All subjects except one > age 50 (V)
28 days treatment or longer (*)

CLEAVED COLLAGEN:
OSTEOCLAST ACTIVITY

BONE SPECIFIC ALKALINE PHOSPHATASE:
OSTEOBLAST ACTIVITY

Andrade et al, Sci Transl Med, 2017
But how??
Next steps?

Collaboration with Aslan Pharma and Dr. Adam Cohen (HCI) to write a trial for breast cancer patients

Prepared IND with Aslan (1 year)

DRUG BOUGHT BACK by big pharma

... killed
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**Continuously learning from many people!**

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