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!
PATIENT-DERIVED XENOGRAFT (PDX) MODELS / AKA “AVATARS”

- 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

PDX AS “AVATAR” MODELS FOR DRUG TESTING

Issues:
- Time
- Accuracy
- Cost
- Feasibility on large scale
- Immune component not taken into account
COMBINED USE OF PDX AND 3D MODELS FOR DRUG SCREENING

Human breast cancers

Remove Tumor

Transplantation of Tumor Cells

Identify New Anti-Cancer Drugs

Cell Death

Culture in 3D

Isolate Tumor Fragments

Bryan Welm
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

For more information, visit:
- http://www.nationalbreastcancer.org/metastatic-breast-cancer
- http://breast-cancer.ca/prog-untreated/
THE “VICIOUS CYCLE” OF BREAST CANCER BONE METASTASIS

- Tumor cells
- Osteoclast
- Kretschmann and Welm, Cancer Metastasis Rev. 2012
- Kang Lab, Princeton
- TGFβ
- PTHrP
- IL-11
- Metastatic tumor cells
- pSMAD2
- Bone-derived growth factors
- IGFs
- FGFs
- MSP
- denosumab
- Vicious Cycle
- Ron
- RANK
- RANKL
- Osteoblasts
- Bone

Guise and Mundy Endocr Rev 1998
Weilbaecher et al Nat Rev Cancer 2011
Kretschmann and Welm, Cancer Metastasis Rev. 2012
DISCOVERY OF A NEW PATHWAY THAT IS IMPORTANT FOR BREAST CANCER-MEDIATED METASTATIC BONE DESTRUCTION

MSP-expressing tumor

MOUSE MODEL

HUMAN BREAST CANCER CELLS

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
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 (*)

Andrade et al, Sci Transl Med, 2017
Still "The last figure!"

But how??
Next steps?

Collaboration with Aslan Pharma and Dr. Adam Cohen (HCl) 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!**

**Collaborators:**
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