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

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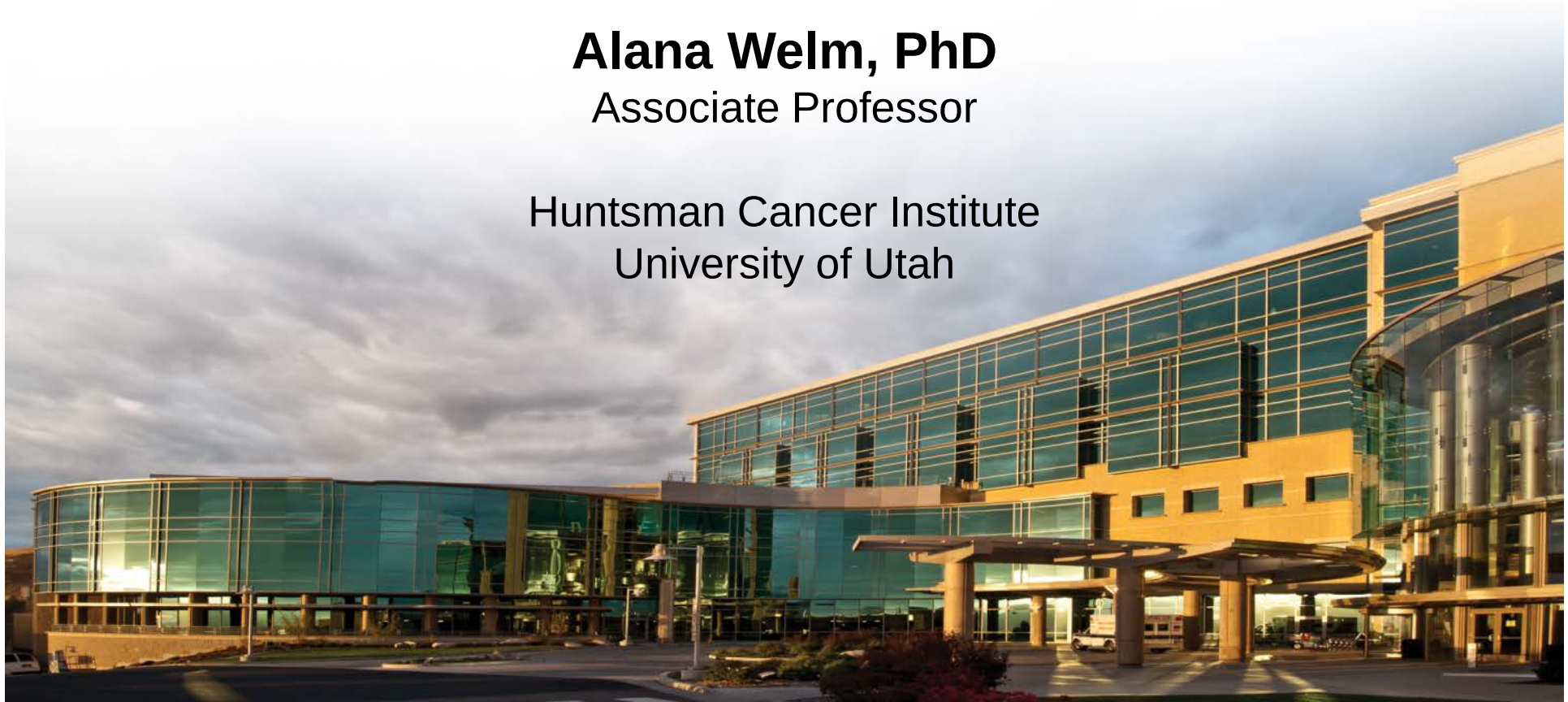
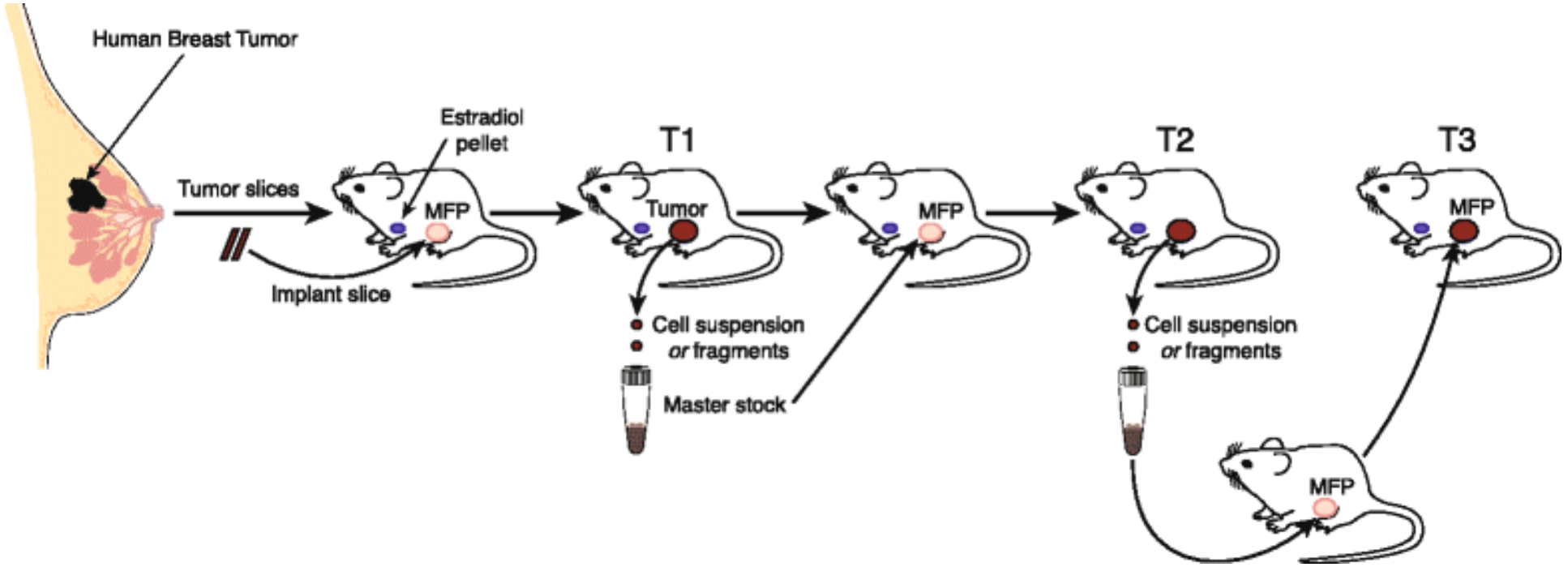


KEY ISSUES IN BREAST TUMOR PROGRESSION & METASTASIS

- **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"



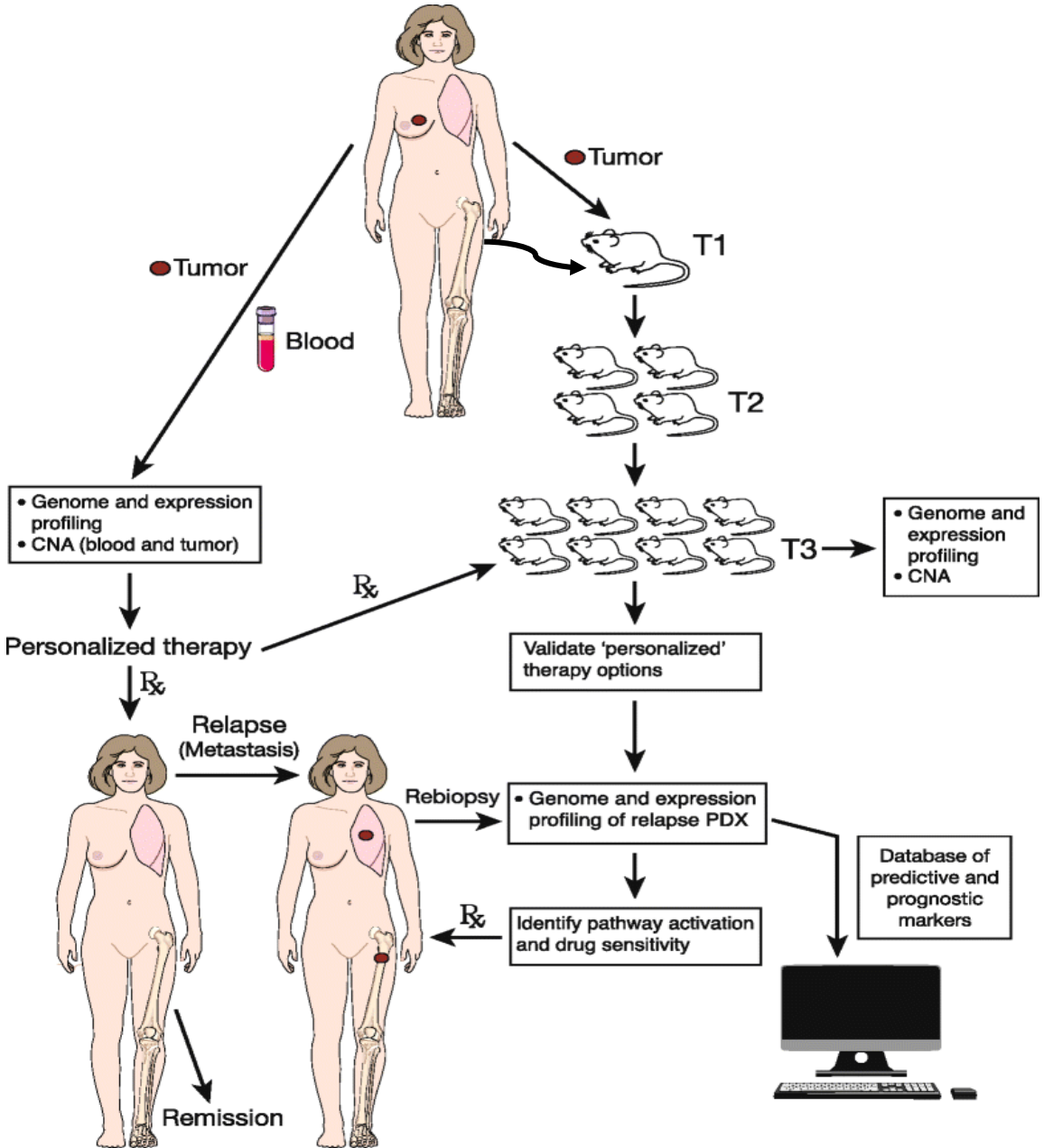
- **PDXs maintain tumor histology, genomics, and gene expression of the patient's tumor**
- **High concordance of therapy response between PDX and patient**
- **Clinically relevant chemotherapies can be tested in PDX concomitantly with patient care**
- **Genomically relevant targeted therapies (e.g. Foundation One) can be functionally evaluated**

DeRose et al. Nat. Med. 2011; Whittle et al. Br. Can. Res. 2015

PDX AS “AVATAR” MODELS FOR DRUG TESTING

Issues:

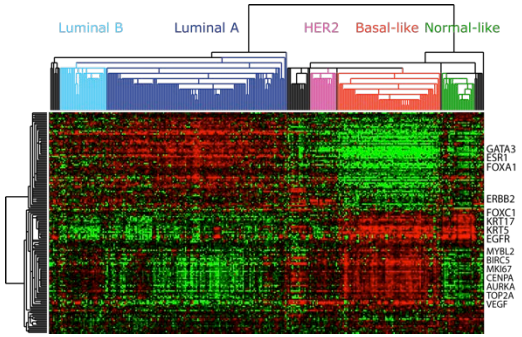
- **Time**
- **Accuracy**
- **Cost**
- **Feasibility on large scale**
- **Immune component not taken into account**

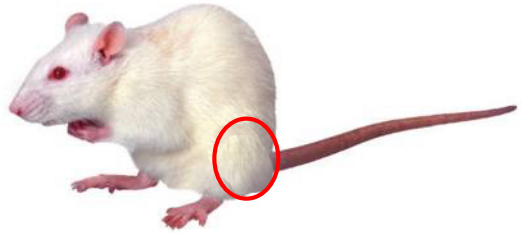


Whittle et al. Br. Can. Res. 2015

COMBINED USE OF PDX AND 3D MODELS FOR DRUG SCREENING

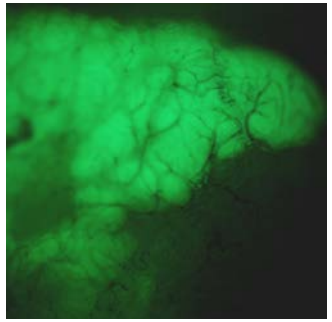
Human breast cancers

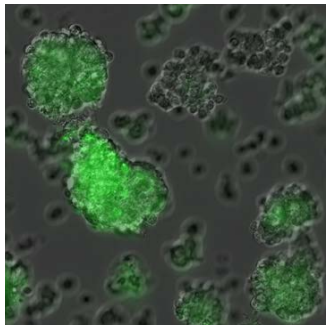




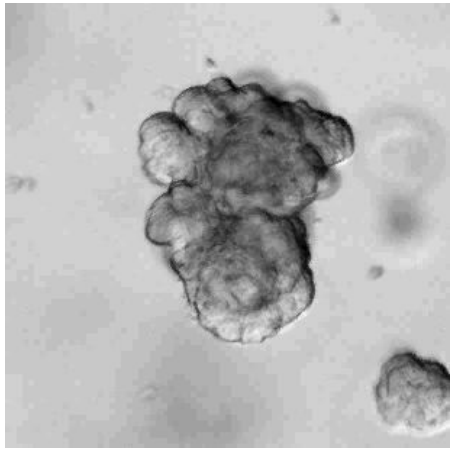
Transplantation of Tumor Cells

Remove Tumor

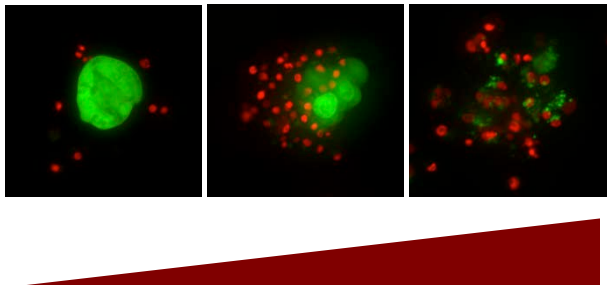




Isolate Tumor Fragments



Culture in 3D



Cell Death

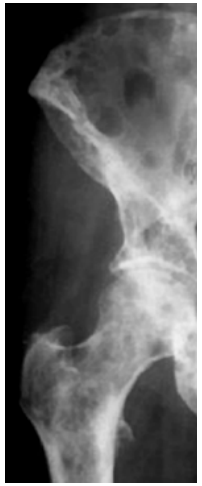
Identify New Anti-Cancer Drugs

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**

X-ray of 75-ye



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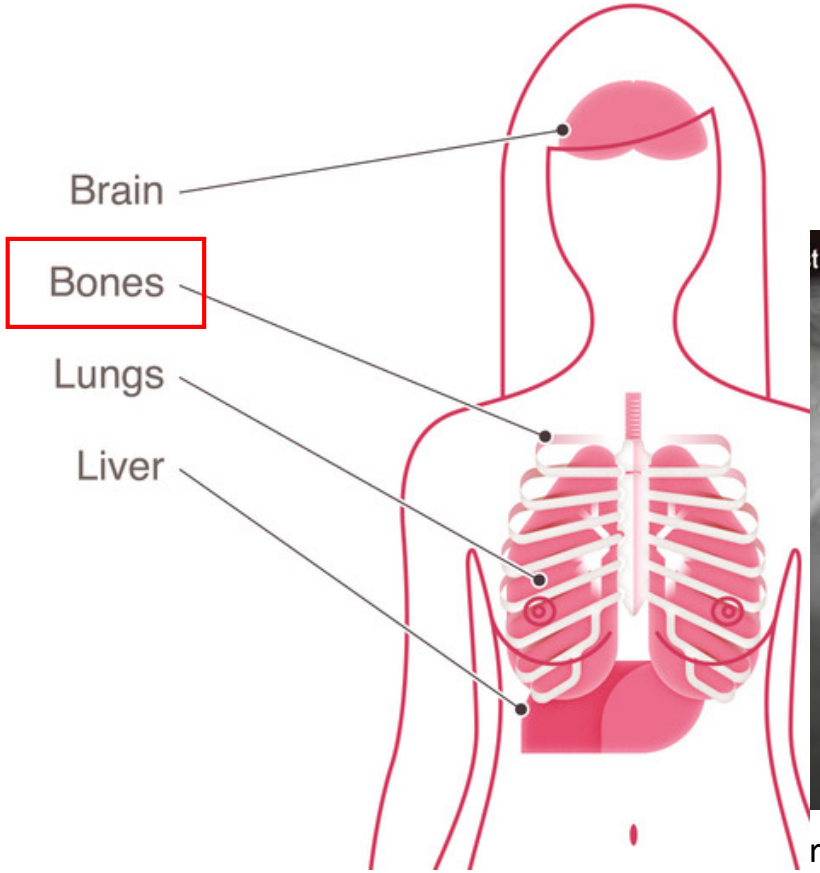
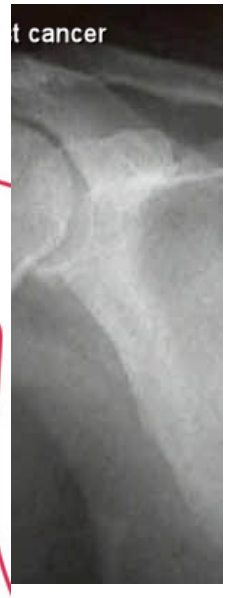
Primary Sites of Breast Cancer Metastasis

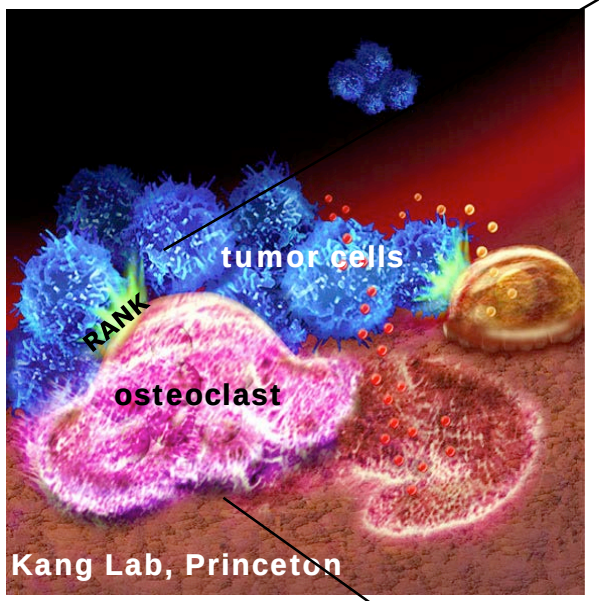


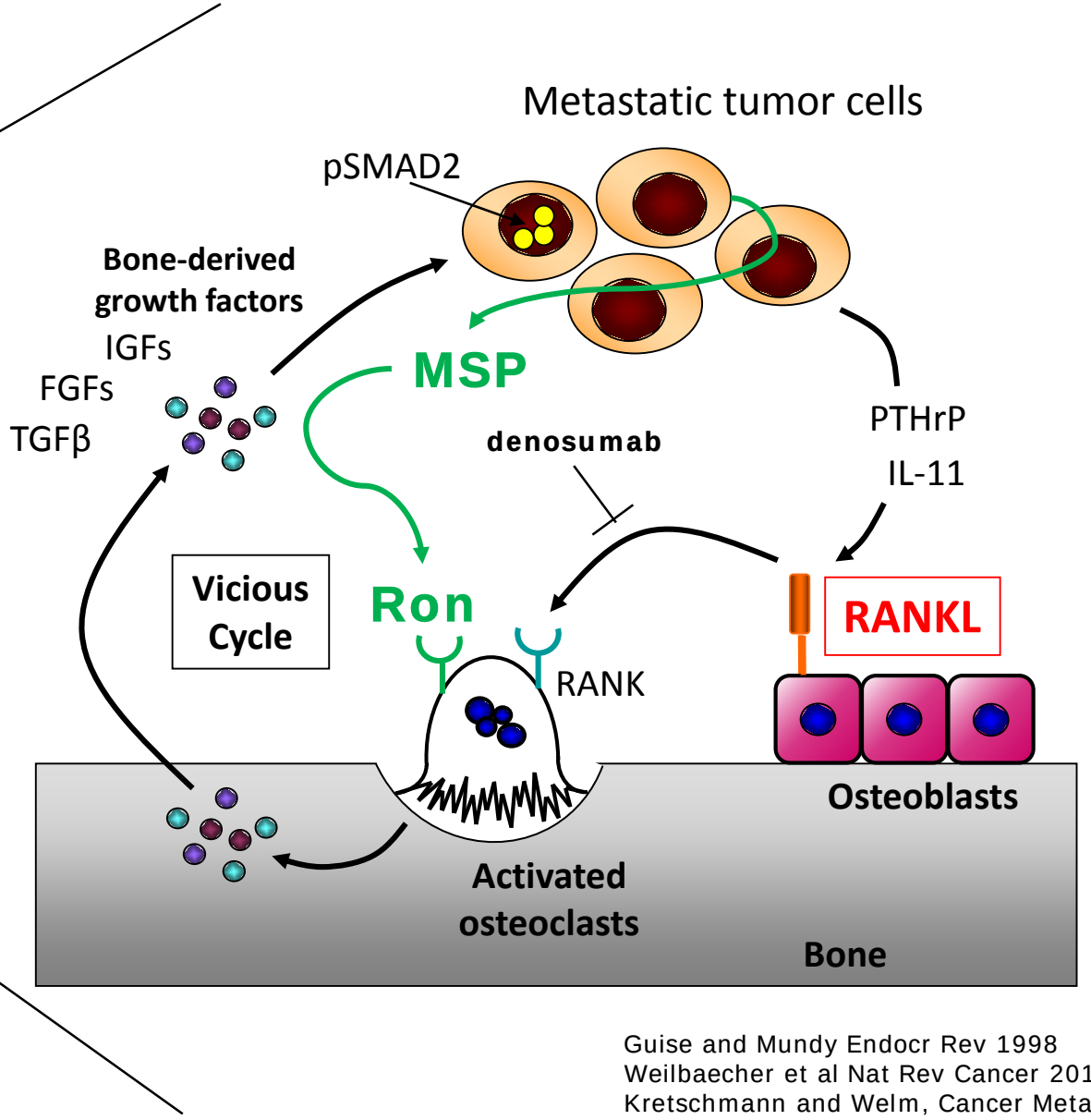


r.ca/prog-untreated/

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

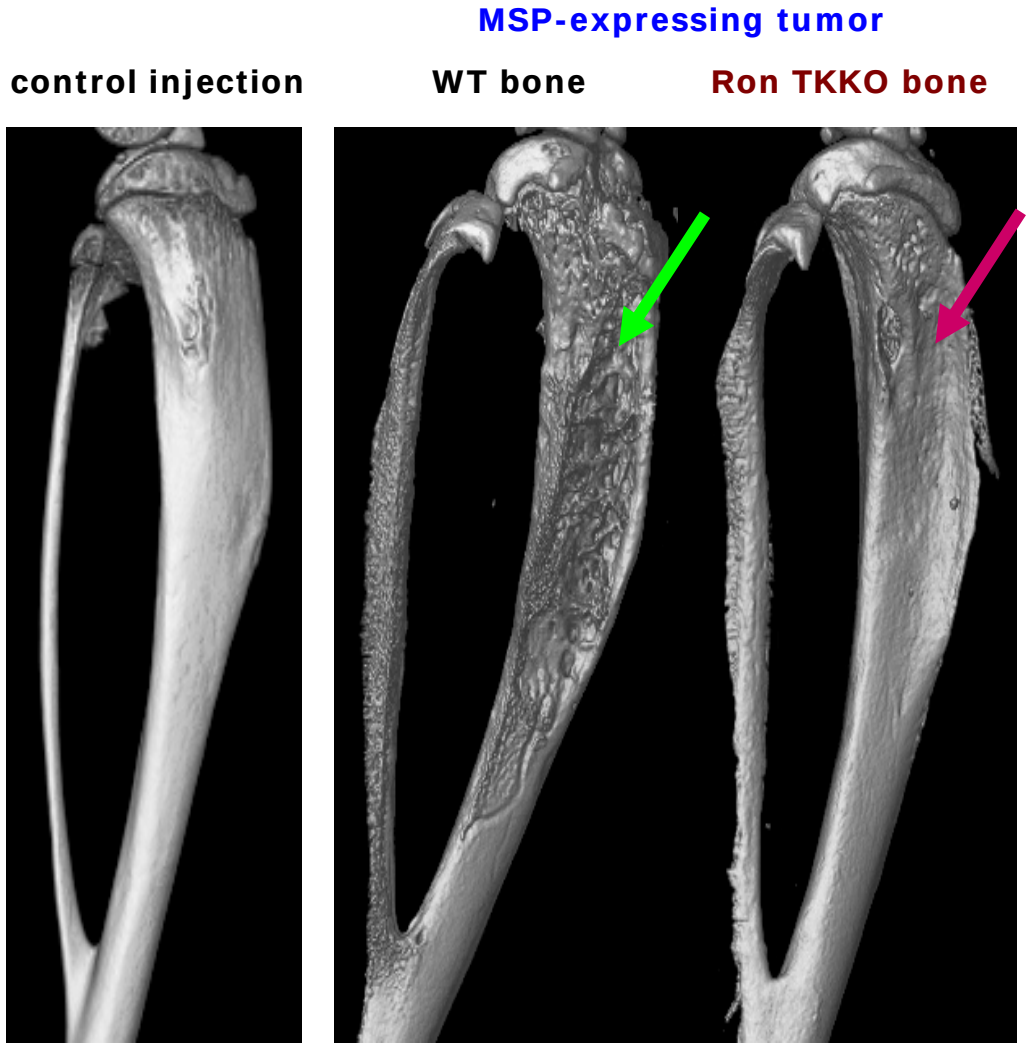
THE "VICIOUS CYCLE" OF BREAST CANCER BONE METASTASIS

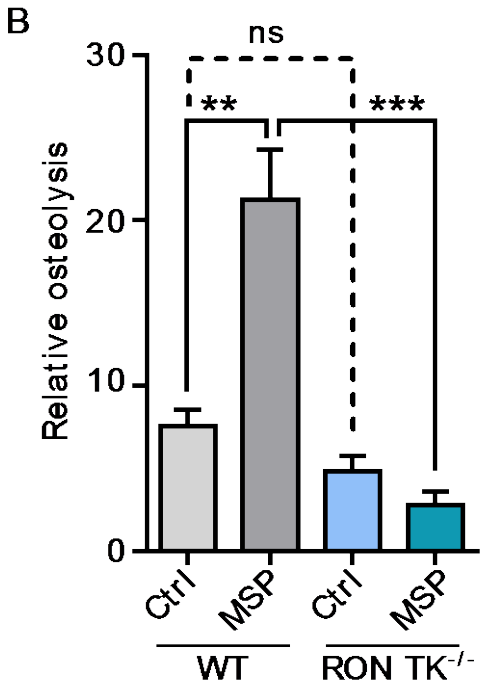




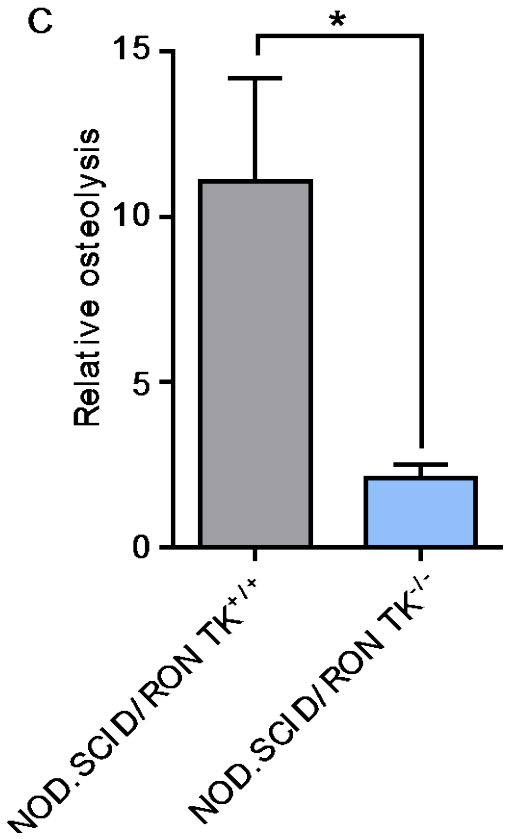
Guise and Mundy Endocr Rev 1998
Weilbaecher et al Nat Rev Cancer 2011
Kretschmann and Welm, Cancer Metastasis Rev. 2012

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





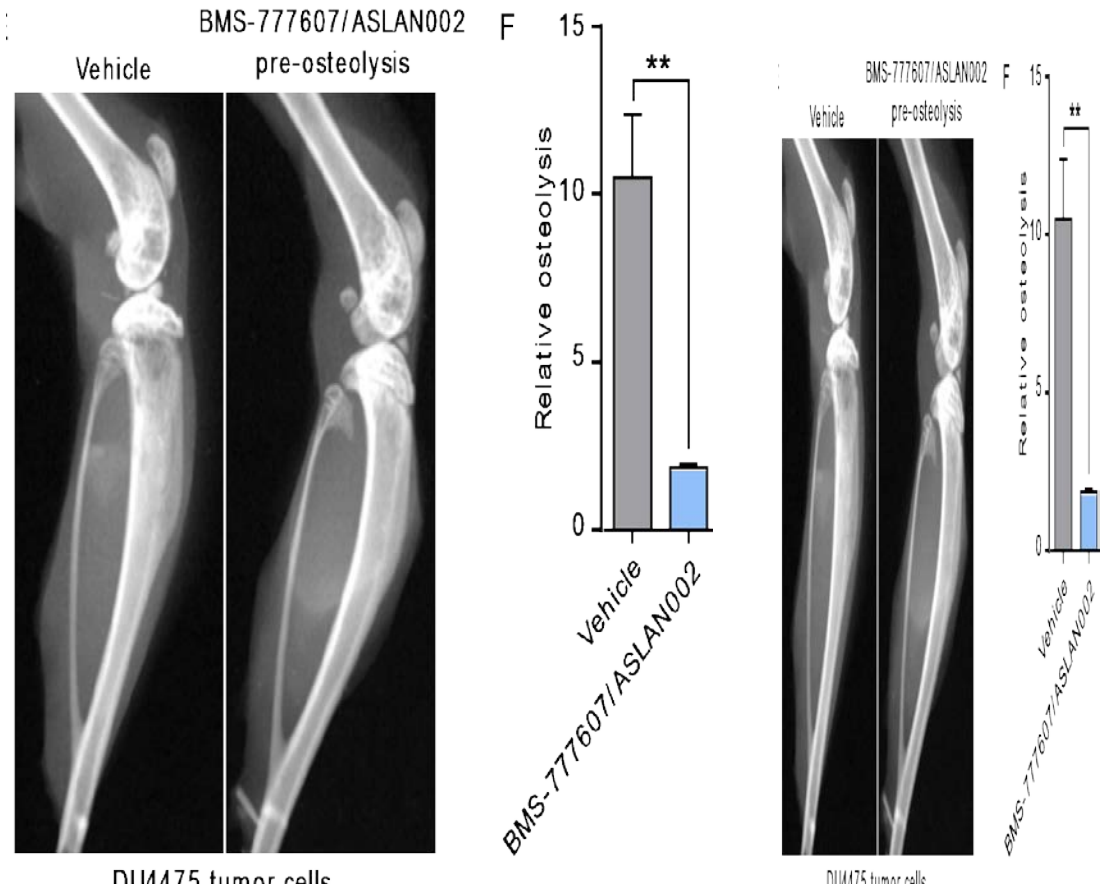
MOUSE MODEL



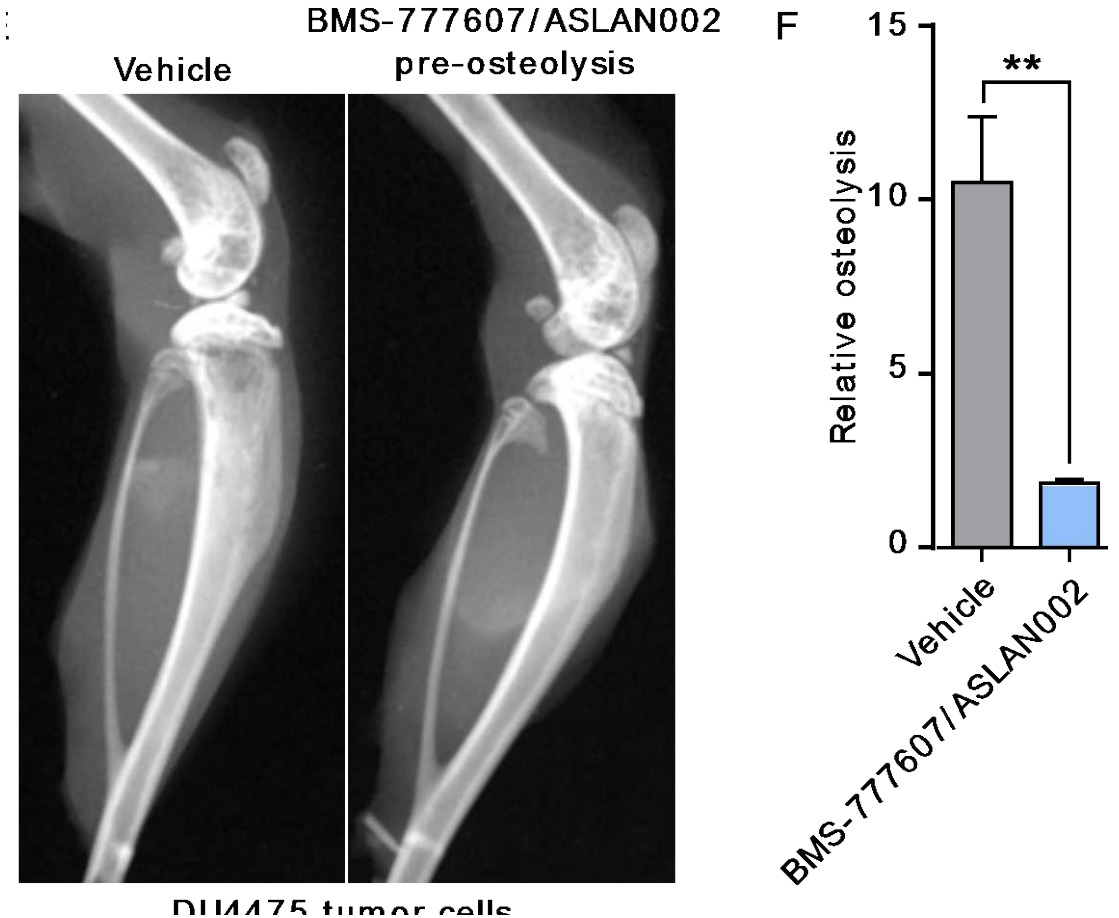
HUMAN BREAST CANCER CELLS

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....

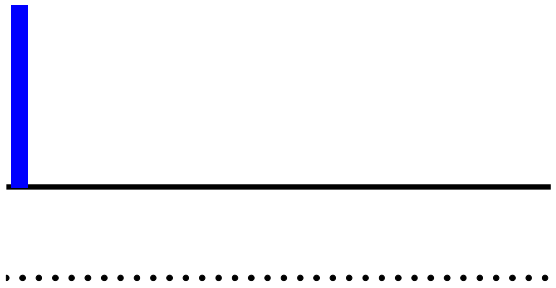
1 year later, compound licensed by another company, started Phase I
Contacted CMO, no response....
Contacted CSO, quick response!!!

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 (*)

A



CLEAVED COLLAGEN: OSTEOCLAST ACTIVITY

B

BONE SPECIFIC ALKALINE PHOSPHATASE: OSTEOBLAST ACTIVITY

Andrade et al, Sci Transl Med, 2017

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

A. Welm lab

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Atakan Ekiz
Najme Faham, PhD
Jaime Fornetti, PhD
Maihi Fujita
Harika Gundlapalli
Jeetendra Kumar, PhD
Alicia Lai, PhD
Matthew Strutz
Ling Zhao

Former lab members
(this project)
Kelsi Andrade, PhD

Continuously learning from many people!

Collaborators:

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Saundra Buys, MD (Med. Oncol.)
Adam Cohen, MD (Med. Oncol.)
Rachel Factor, MD (Pathology)
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Mark McHale, PhD (Aslan Pharm.)
Scott Miller, PhD (Radiology)
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