Bone 2 – Metastatic Bone Cancer Responsible for Majority of Cancer Deaths

- **Luminal Epithelial cells** of the DUCT form the MAJORITY of breast cancer (~85% BUT RECALL THAT BC is HETEROGENEOUS therefore some Lobular acini carcinomas exist too) mutation DCIS = Ductal Carcinoma in Situ (increase in fibroblasts, angiogenesis, prolif of endothelial cells ALL BOUND BY BM) IDC = Invasive Ductal Carcinoma where breach of BM occurs BUT still bound to Organ Metastatic Breast Cancer is now where cancerous cells no longer bound in organ are now in blood stream.
- Mesenchymal Basal Luminal signatures. Subtypes of cancers exist from Bipotent stem cell mutation = Basal-Like (least chance of survival) all the way to differentiated epithelial cells or myoepithelial cells mutations = Luminal A or B (most chance of survival). There is also a preference for each subtype towards particular metastases. Eg. Luminal B accumulates in bone significantly more than Basal. Where Basal accumulates a lot more in Brain than luminal B.
- **Concept of Inter-Tumor heterogeneity** = patient to patient will have different tumors + Intra-Tumor heterogeneity where subtypes of various breast cancer populations exist = DIFFICULT TARGETS FOR CHEMO
- Breast Cancer Stages: 0 = Non-Invasive DCIS // I = High numbers indicate extensive disease // II= Breast tumor increase in size w/ lymph node help NO METASTASES // III Tumor, any size, spreads to ALL sites
- Metastatic Cascade: Challenges of Metastatic Tumor include leaving Primary site as malignant neoplasm inducing new vessel formation invasion embolism (multi-cell aggregate like platelets) Arrest in distant cap. bed adhering to endothelial cell EXTRAVASATION.
- **Microenvironment** response tumor-cell prolif bone metastases (micro-enviro IS RATE-LIMITING STEP as secondary site is foreign to tumor cell)
- **Linear Progression Model**: Prim. Tumor Prolif of Cell A Cell A disseminates to form Prim. Metastasis Cell B arises to form Sec. Metastasis. This model describes that DISSEMINATION ONLY OCCURS FROM FULLY MALIGNANT CANCER CELL HETEROGENOUS SUB POP AND HAVE ABILITY TO CREAT METASTASES. Arises **LATE** in development of Primary tumor
- **BETTER Hypothesis: Parallel Progression Model**: Eg **DTCs harbor fewer chromosomal aberrations** compared to primary tumor suggesting that tumor cells ARE getting out **EARLY** from prim. Tumor site @ a point where gene amplification or loss is not accumulated p **rolif, diff. and malignancy obtained once it has reached distal site**
- **Transgenic Mice to support alt. model** Before classification of invasive tumor before 18 weeks and despite the glands where prim. Tumor originated from being removed, metastases STILL formed there fore cells were still getting out far before it reached IDC.
- New Experiment Injected NORMAL Dox- mammary gland epithelial cells w/ oncogene into circulation despite not activating the oncogene with Dox, metastases formed!! This would essentially mimic the parallel progression

model where **early-disseminated cells DO NOT HAVE TO ACCUMULATE MUTATIONS AT PRIM. TUMOR in order to thrive/metastasize/extravasate into tissues**. When Dox was administered and the oncogene turned on, mutations occurred @ secondary site = PERSISTENCE and new tumors arising.

- Intravasation, Extravasation, Prolif in new site, persisting = metastasis is inefficient where efficiency is related to metastatic potential
- Right after extravasation, cell prolif is balanced b/w apoptotic and dormant arrest for single/micrometastatic until prolif occurs and clinically detectable tumor is seen Mechs that enforce tumor dormancy (not just genetic) = Angiogenesis, Cell-cycle (apoptosis vs arrested cell cycle balance), Immune system (aging decreases regulation). But cells can escape.
- **Microenvironment = crucial** cancer cells express GF, cytokines that influence behavior of host cells + modify EC @ site of metastasis to increase growth of metastases. (Also express cell-adhesion mol. In order to respond to cues offered by host micro env)
- **Organ specificity** of breast metastasis from Brain, liver, lungs and bone marrow (least to highest tumor mass size for luminal carcinoma). Unique enviro characterizes sites of breast cancer metastasis**: Fenestrated cap. in liver = easy for TC to pass vs. BBB of brain = difficult.**
- METASTATIC CANCER CELLS CAN OCCUPY PRE-EXISTING NICHE SITES = BONE ENDOSTEAL NICHE. TC compete w/ HSC: **Bone pre-matastatic niche + MTC metastatic niche**
- **Interplay b/w osteoblasts + osteoclasts control bone remodeling**: Pre-osteoblast w/ Rank-L secrete Rank-L bind to Rank on Pre-fusion Osteoclast Receptor Osteoclast differentiation. (Balance b/w Osteoblastic and Osteolytic metastases. Prostate vs. Breast Cancer vs. Multiple Myeloma)
- **Breast cancer cells favor OSTEOCLAST-GENESIS** by inducing Rank-L expression in osteoblasts increase resorption increase space for tumor cells to embed increase periosteal liberation of growth factors increase Rank-L expression via increasing tumor cell activity REPEAT: VICIOUS CYCLE OF BONE DESTRUCTION IN METASTATIC CANCER.
- **Osteolytic Metastasis Factors**: Multiple Myeloma TC
  A) "Seed" (Cancer cell) Factors: Indirect induction of Osteolytic factors via PTHrP, IL-11 = Increase Rank-L secretion from pre-osteoblast AND Direct via Osteolytic factors like IL-8 which induces Osteoclast differentiation
  B) **"Soil" Factors:** Liberated **TGF-Beta** from increase resorption + Rank-L increased all aim to provide micro-enviro for TC
- **Osteoblastic Metastasis Factors:** Prostate TC PSA which inhibits pTHrP therefore osteoblast do not release Rank-L therefore NO OSTEOCLAST DIFFERENTIATION
- **Osteomimicry observation** that cancer cells moving to bone from either prostate or breast display OSTEOBLAST PHENOTYPE tumor cells proliferate +survive in bone microenviro. Eg. TC coming from collagen rich to something that is collagen poor/mineralized therefore need to adapt/ promote host phenotype

there fore releases TF like Runx2, ECM, CD44 to mimic. Increase Bone Remodelling = increase bone/tumor metastasis

- Summary: Met. Cancer Comes from other sites spread to bone. Bone is preferred micro. Osteolytic vs Osteoblastic metastases. Seed and soil interactions = key for TC success. **CANCER CELLS COMMUNICATE W/ BOTH OSTEOBLASTS AND OSTEOCLASTS THE NET Result will determine whether it will be Osteolytic (eg. Breast cancer/Myeloma) or Osteoblastic (eg. Prostate)**
- Complications accompanied w/ metastatic cancers in bone: Increase osteolytic, increase Ca2+, increase bone pain, bone marrow suppression in Breast cancer as TC express inhibition over osteoblast activity
- TREATMENT FOR METASTATIC BONE**: BISPHOSPONATES** inhibit osteoclasts via inhibiting breast cancer cells from inducing micro-enviro that favors osteoclast-genesis. Since they have high affinity for bone Likely to affect bone-remodelling can be detrimental + osteoprenosis in jaw! (1st Gen = induce osteoclast apoptosis bone brittleness + severe adverse effects) 2 nd gen have nitrogen containing where they inhibit osteoclast function (Both interfere w/ osteoclast adhesion, recruitment, "sealing zone" prevention therefore no resoprtion = no GF liberated to initiate VICIOUS CYCLE.
- ALT. Treatment: DENUSAMAB = Human Ab impairs osteoclast differentiation via targeting Rank-L. BETTER THAN BIS cuz no bone brittleness + superior action in preventing fractures.
- New therapies include TARGETING micor-enviro and interactions b/w TC and other cells instead of just the tumor cell! Due to HETEROGENEITY conventional chemo = ineffective