

XVII^{èmes} Journées de Sénologie

Lyon, 18 Septembre 2014

Les Mécanismes de Formation des Métastases Osseuses

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Skeletal-Related Events (SREs)

- SREs are defined as:



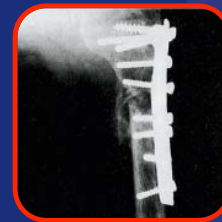
Radiation to
bone



Pathological
fracture



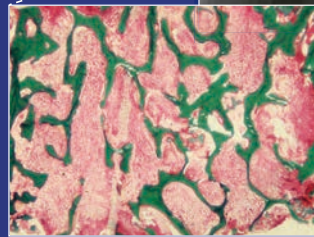
Spinal cord
compression



Surgery to
bone

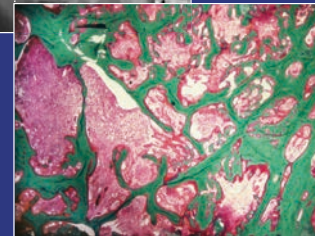
1. Saad F, et al. J Natl Cancer Inst 2004;96:879–82;
2. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf (Accessed 2 March 2011).

Bone Metastasis Phenotypes



Osteolytic lesion

Breast cancer

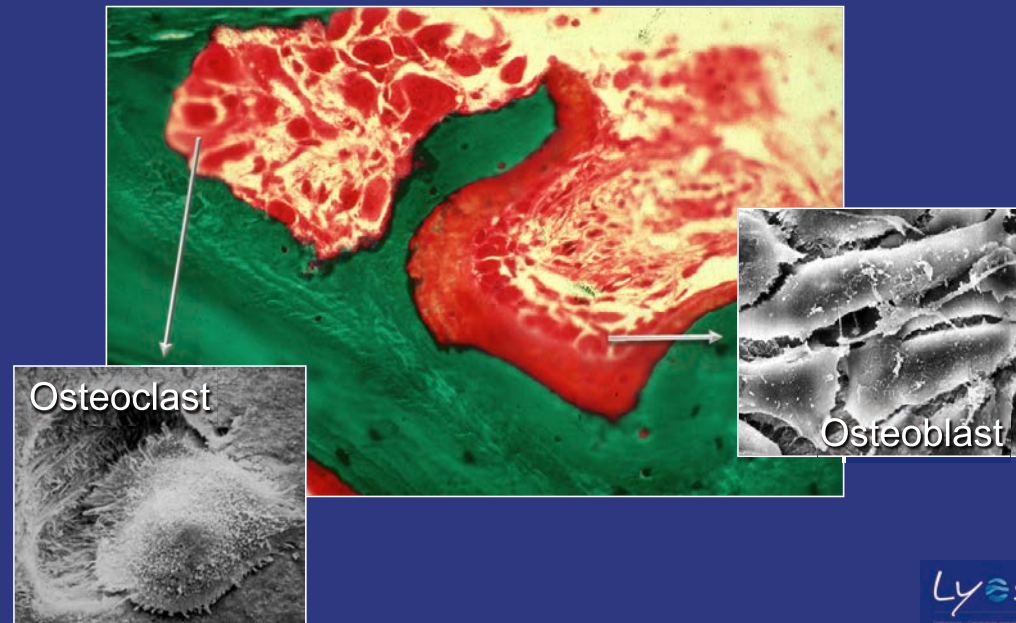


Osteoblastic lesion

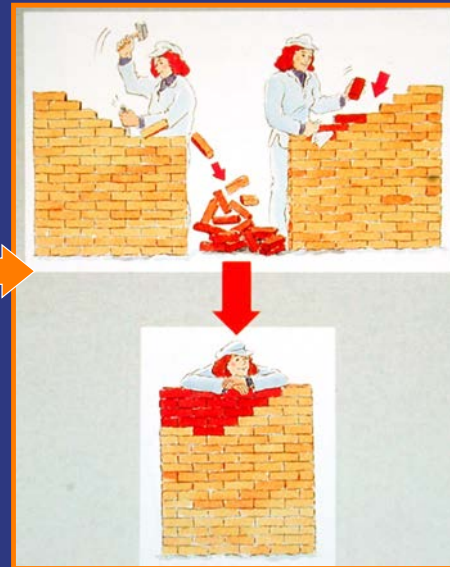
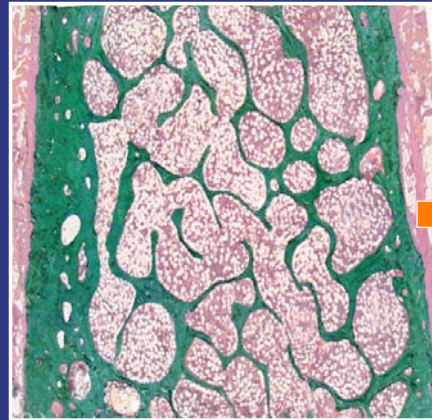
Prostate cancer



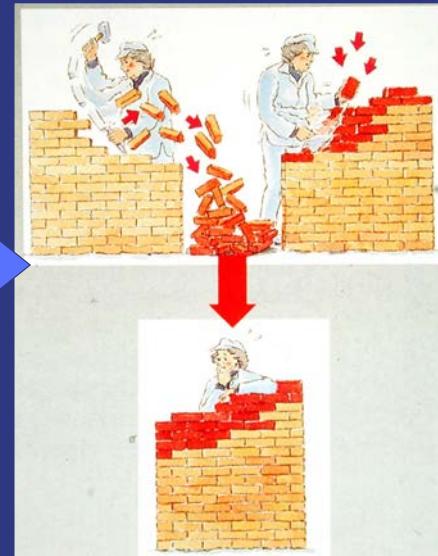
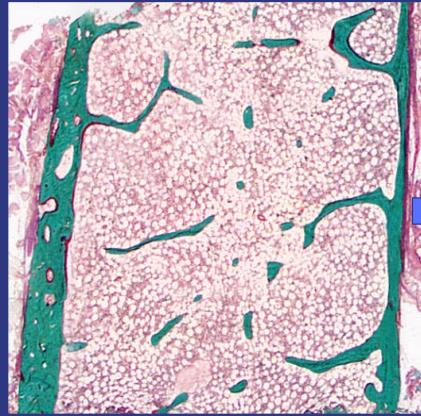
Bone remodeling



Bone remodeling



Osteoporosis

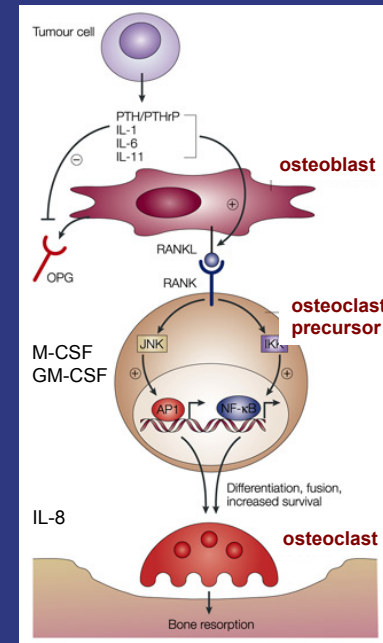


Molecular mechanisms associated with the formation of osteolytic lesions



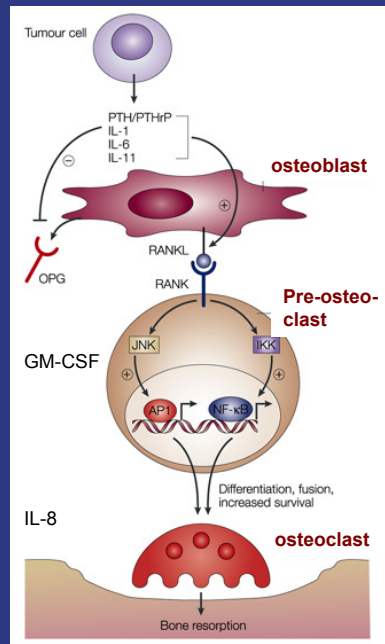
Bone resorption stimulators

PTH-rP,
prostaglandins,
cytokines

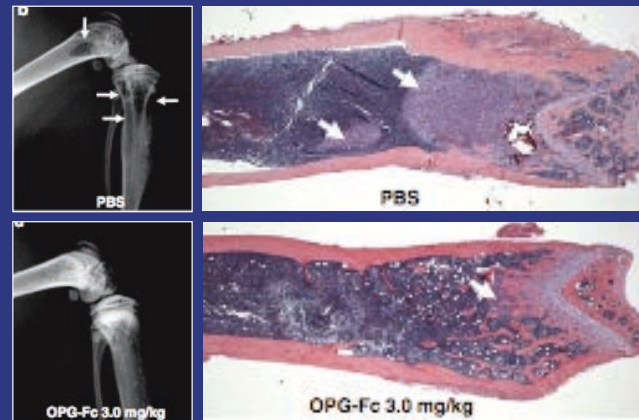


Adapted from Mundy, Nat. Rev. Cancer, 2002

OPG/RANK/RANKL



Adapted from Mundy, Nat. Rev. Cancer, 2002



Canon *et al.*, Clin Exp Metastasis., 2008

Molecular mechanisms associated with the formation of osteolytic lesions

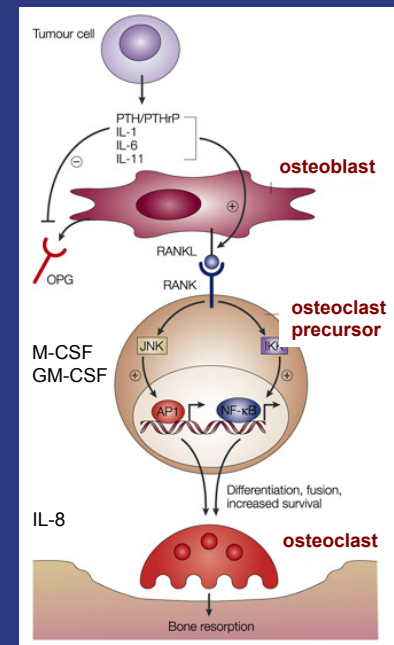


Inhibitors of bone formation

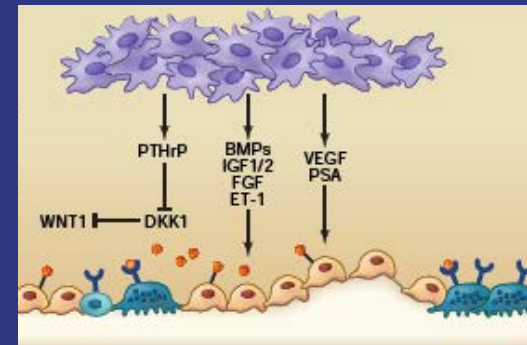
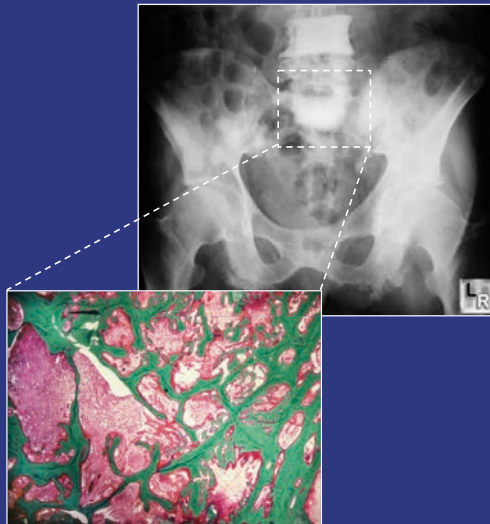
DKK-1, Sclerostin
(inhibitor of the Wnt signaling pathway),

Noggin (inhibitor of the BMP signaling pathway),

Activin A (a member of the TGF- β superfamily of growth factors)



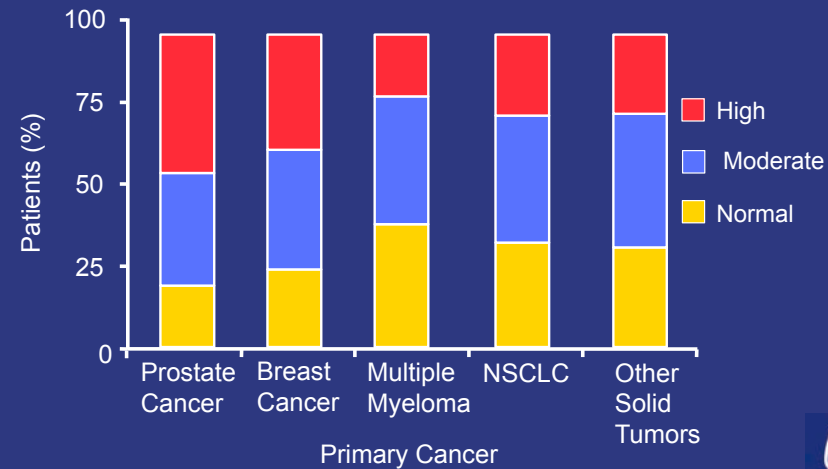
Molecular mechanisms associated with the formation of osteoblastic lesions



Adapted from Ell & Kang, Cell, 2012

Increased Bone Resorption Is the Organ-Specific Therapeutic Target

- Patients with each cancer type were categorized as low NTx (< 50 nmol/mmol creatinine), moderate NTx (50-100 nmol/mmol creatinine), or high NTx (> 100 nmol/mmol creatinine)



Coleman RE, et al. J Clin Oncol. 2005;23:4925-4935.

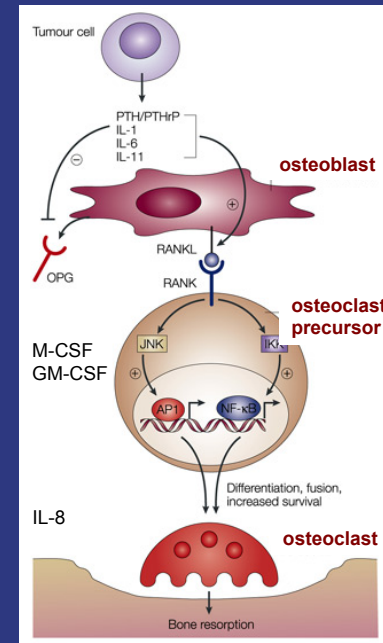


Molecular mechanisms associated with the formation of osteolytic lesions



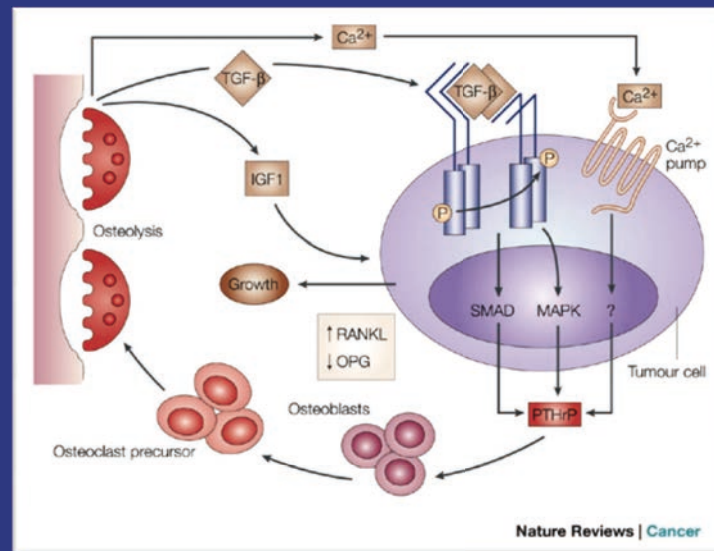
Bone tissue

TGF β , IGFs,
calcium, ...

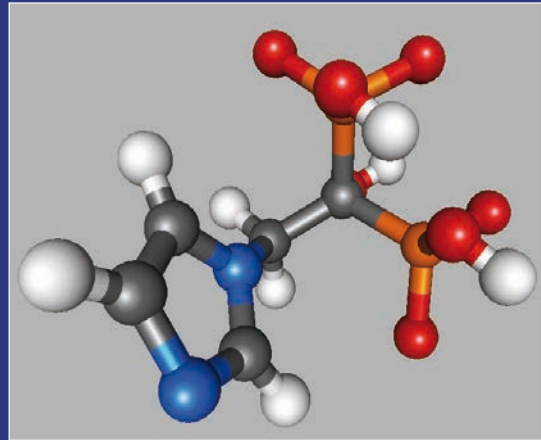


Adapted from Mundy, Nat. Rev. Cancer, 2002

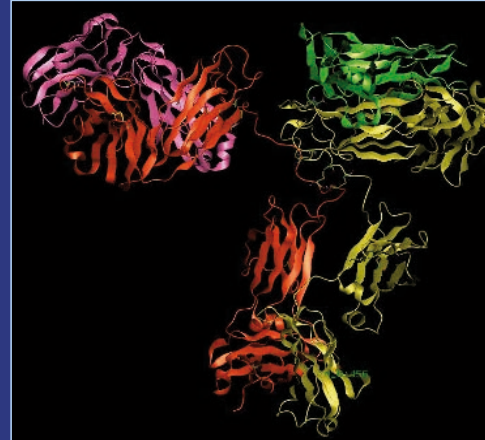
Bone metastasis: the « vicious cycle » theory



The vicious cycle provides the rationale for the use of antiresorptive drugs

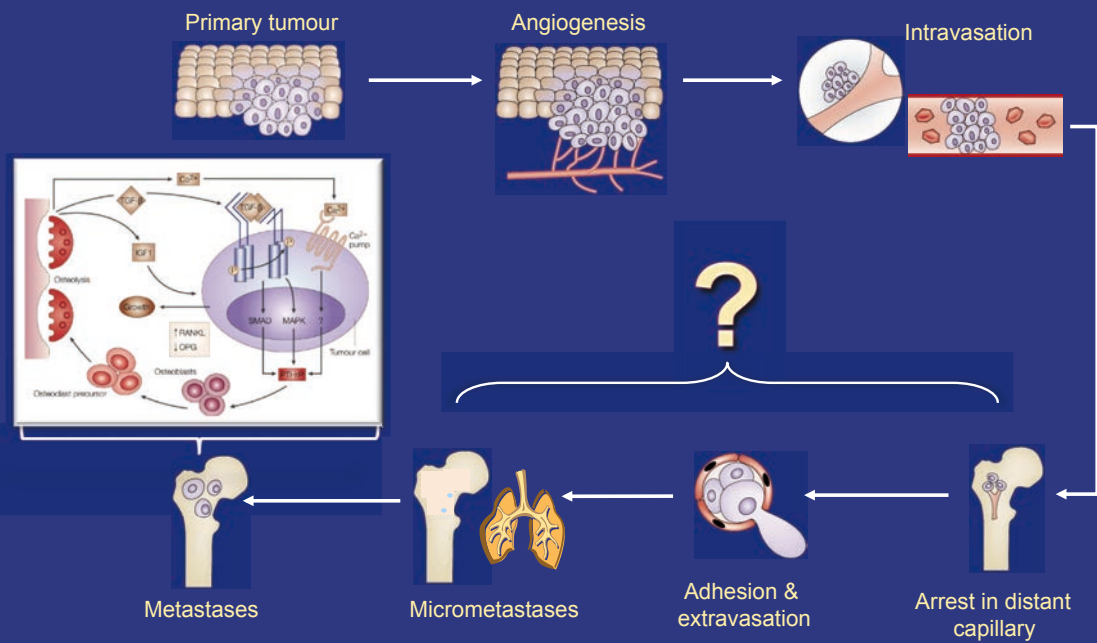


Bisphosphonate

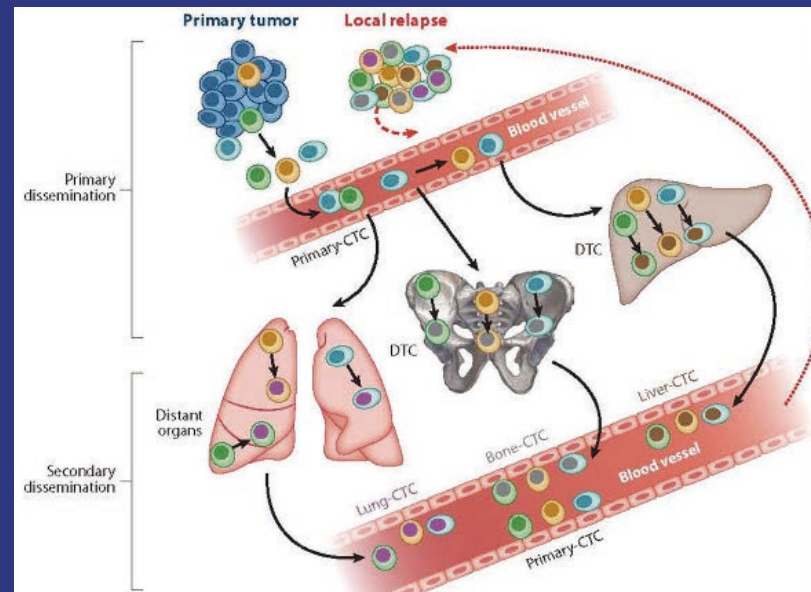


Anti-RANKL

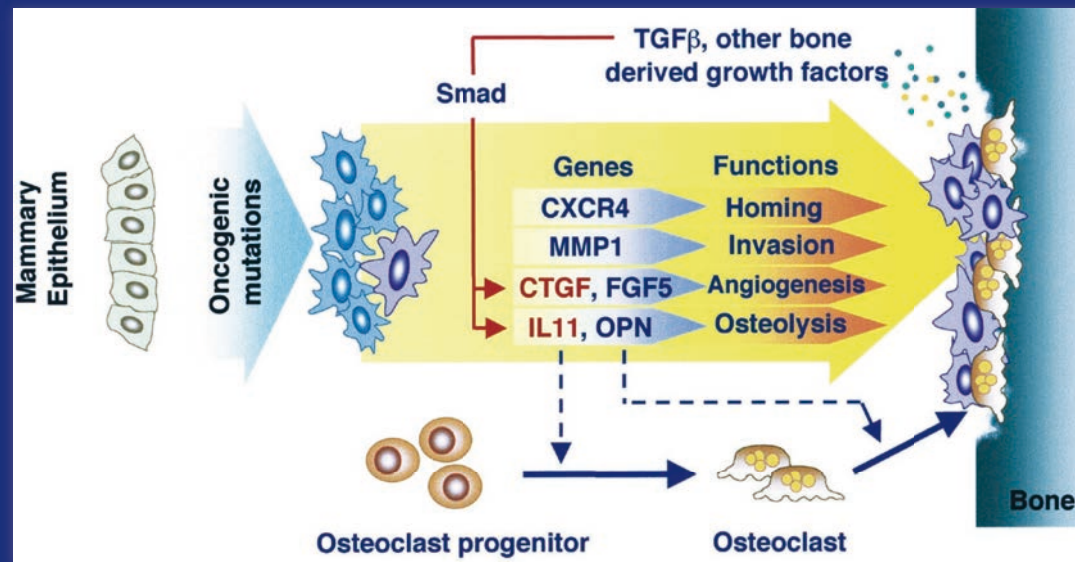
Metastatic cascade



Editing of the CTC pool by the micro-environment of secondary metastatic sites

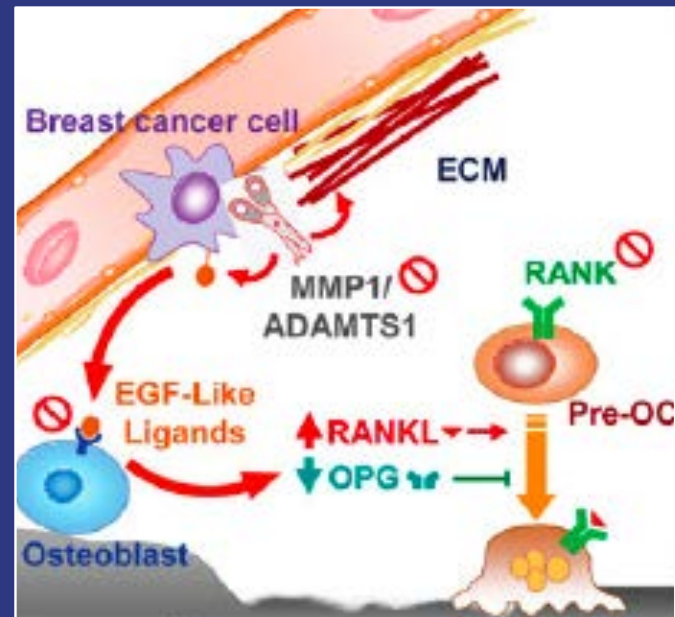


Bone-tropic metastasis is mediated by distinct classes of metastasis genes



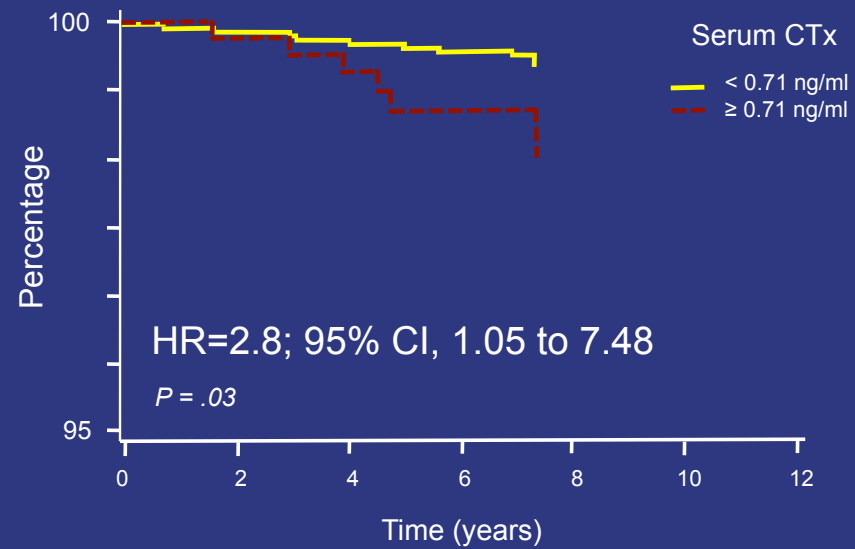
Role of MMPs in the early development of bone metastases

✓ MMP1/ADAMTS1



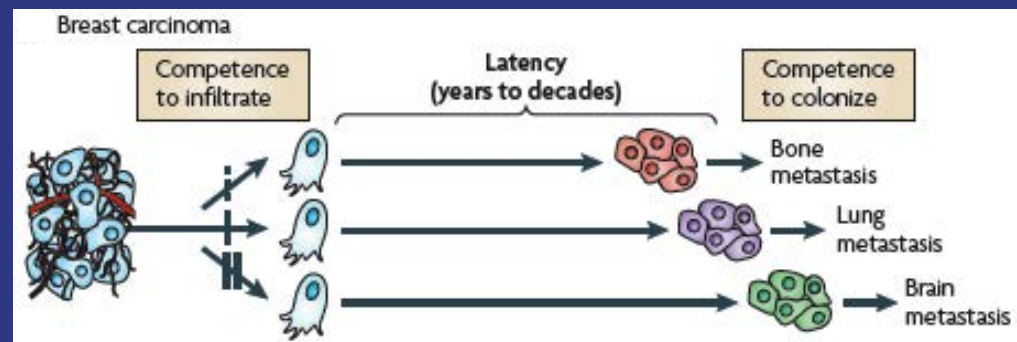
Lu et al., Gene Dev, 2009

Elevated Bone Turnover Predicts for Bone Metastasis in Postmenopausal Breast Cancer

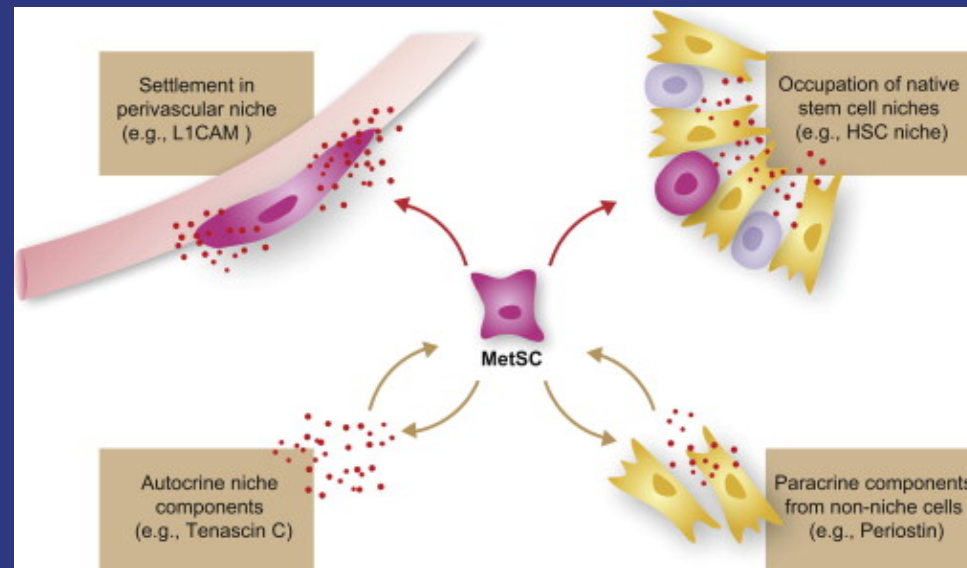


Lipton et al., JCO, 2011

The temporal course of metastasis



Possible sources of metastatic niche support for disseminated tumour cells



Conclusion



The perceptiveness (René Magritte)