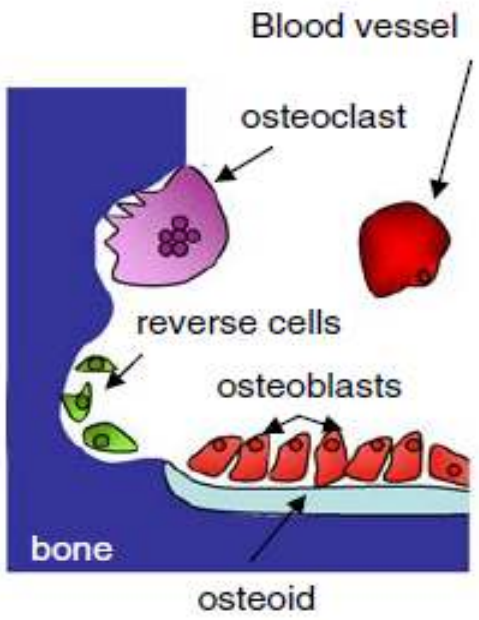
FISIOPATOLOGIA DELLE METASTASI OSSEE

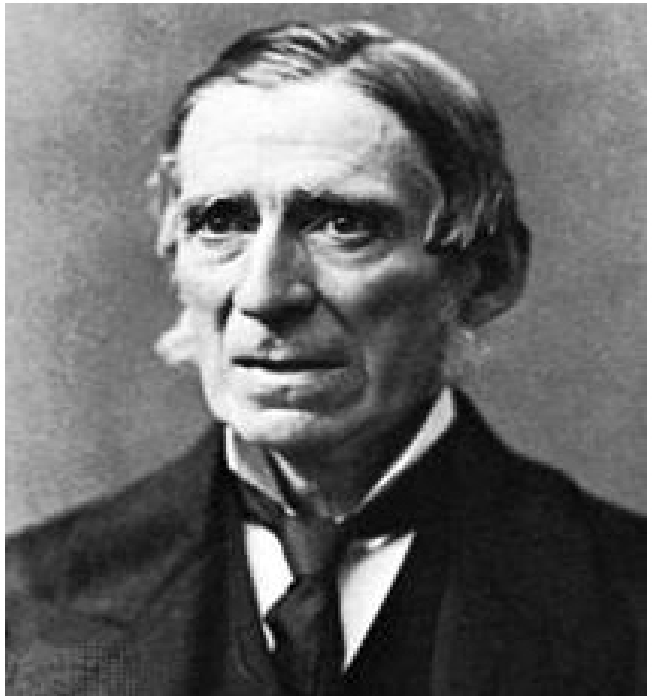
AIRO-LAM 23 OTTOBRE 2012

Alessio G. Morganti

classification of bone metastases

Clezardin P &Teti A – Clin Exp Metastasis 2007;24:599.

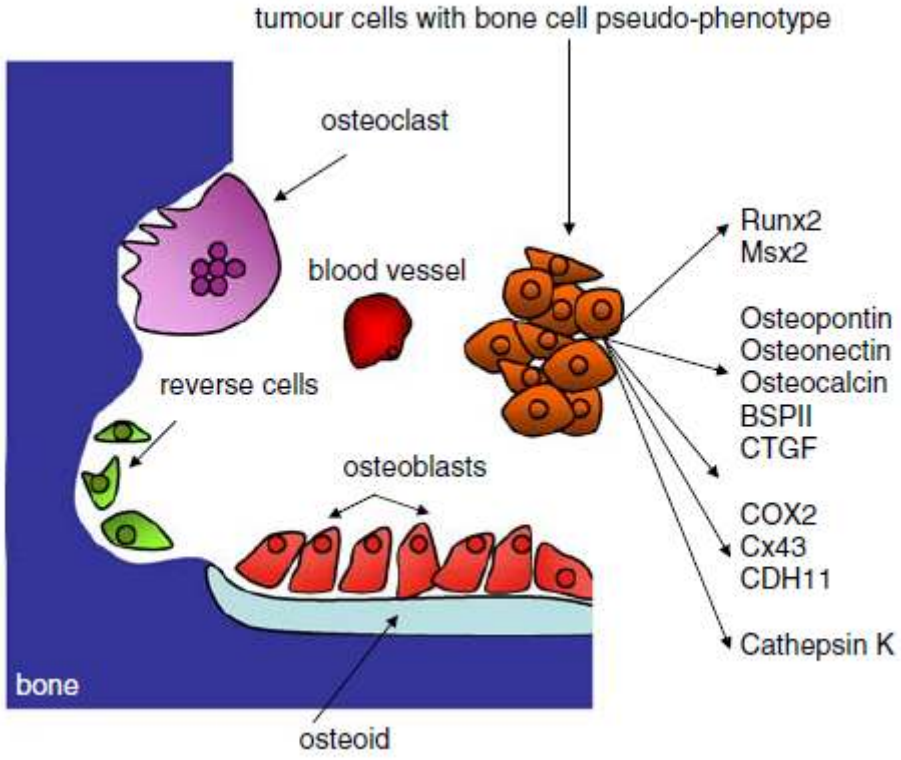




Stephen Paget, 1855-1926.
Ha elaborato alla fine del XIX secolo la teoria detta "seed and soil" (seme e terreno) per spiegare il processo di metastatizzazione. Questa teoria è tutt'ora attuale.

osteomimicry

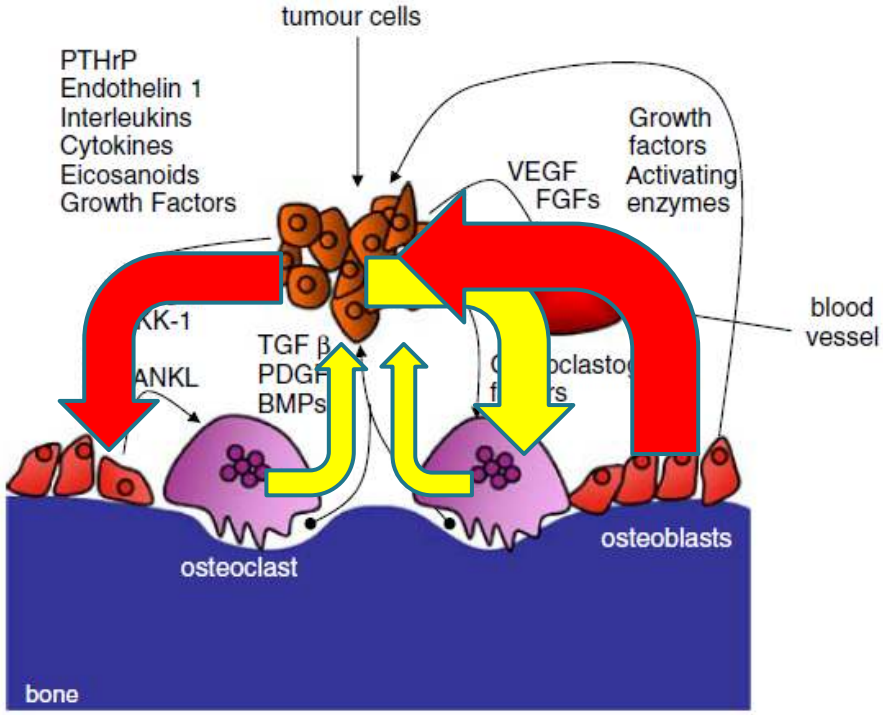
Clezardin P &Teti A – Clin Exp Metastasis 2007;24:599

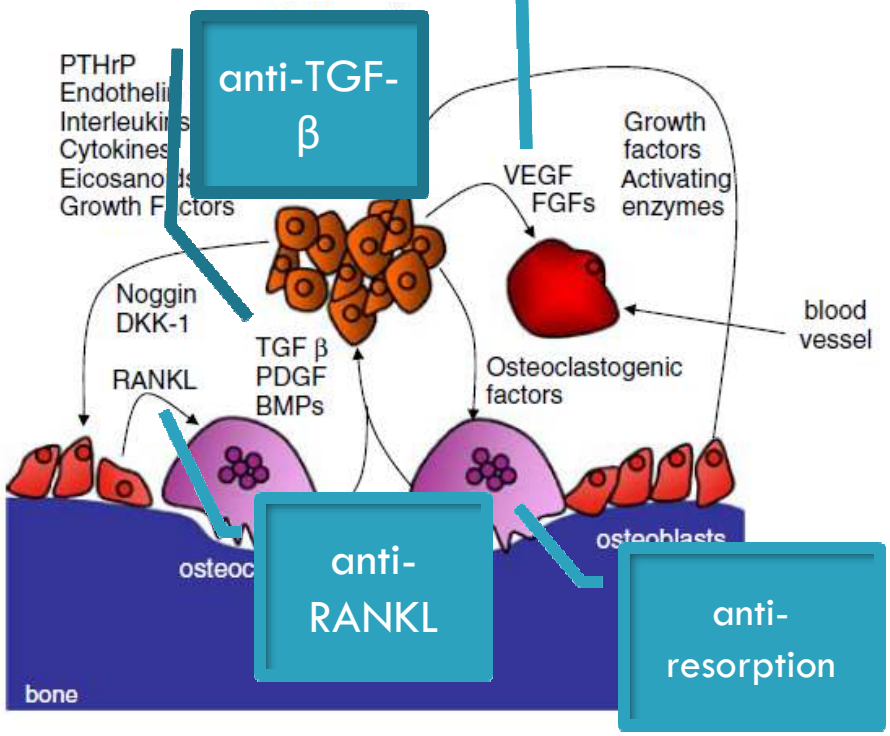


- transcription factors
- extracellular matrix proteins
- other bone related factors
- proteases

the vicious cycle

Clezardin P &Teti A – Clin Exp Metastasis 2007;24:599





therapeutic agents

Clezardin P &Teti A – Clin Exp Metastasis 2007;24:599

Agents	Application	Role
Anti-resorptive	Clinical	Inhibit osteoclast formation and/or bone resorption. Active in osteolytic metastases
Anti-TGFβ	Preclinical	Inhibit TGFβ family members or their receptors. Active in osteolytic metastases in which they block the vicious cycle. Active in osteoblastic metastases in which they inhibit osteoblast recruitment and differentiation
Anti-inflammatory	Chemoprevention study	Reduce tumour cell activity, reduces bone resorption. Active in osteolytic metastases
Anti-angiogenesis	Clinical	Blocks development of new vessels. Potentially active in any type of metastases
Anti-CXCL-12	Preclinical	Blocks metastatic destination of cancer cells
Anti-αVβ3 integrin	Clinical Phase I	Blocks bone colonization by cancer cells. Blocks angiogenesis
Anti-c-Src tyrosine kinase	Preclinical	Reduced proliferation, motility and responses to growth factors in cancer cells. Blocks bone resorption
Anti-Runx2	Preclinical	Blocks formation of bone metastasis

osteoblast niche

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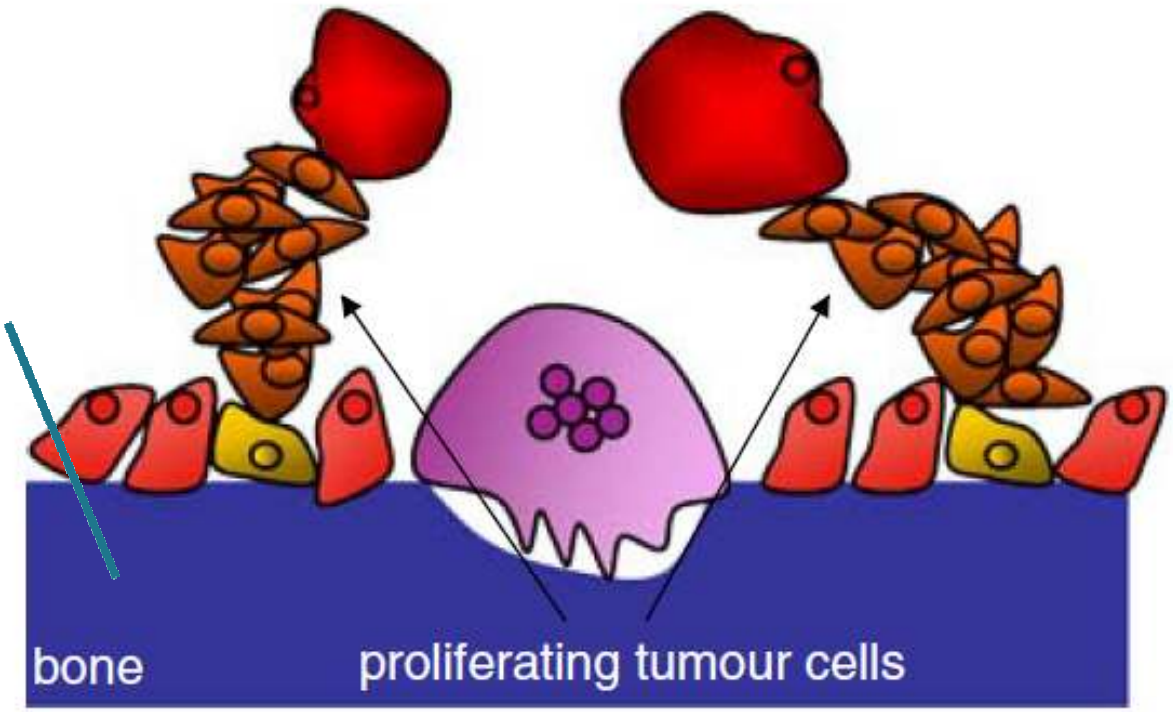
anti-inflammatory



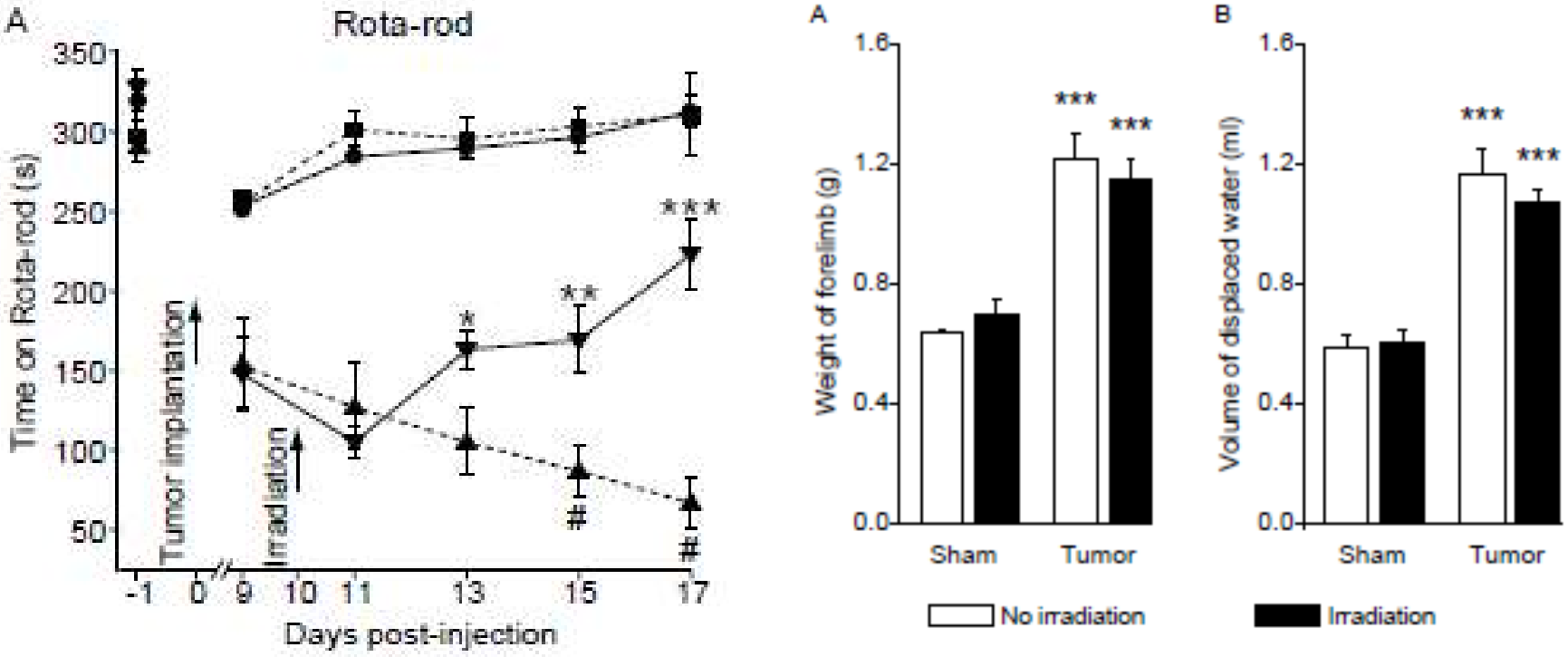
bone metastases:

palliative effect of RT

- absent dose-response relationship
- absent radiosensitivity-response relationship
- early response (24 hours!)

effect of low dose irradiation

Vit J et al. Pain 2006;120:188



effect of low dose irradiation

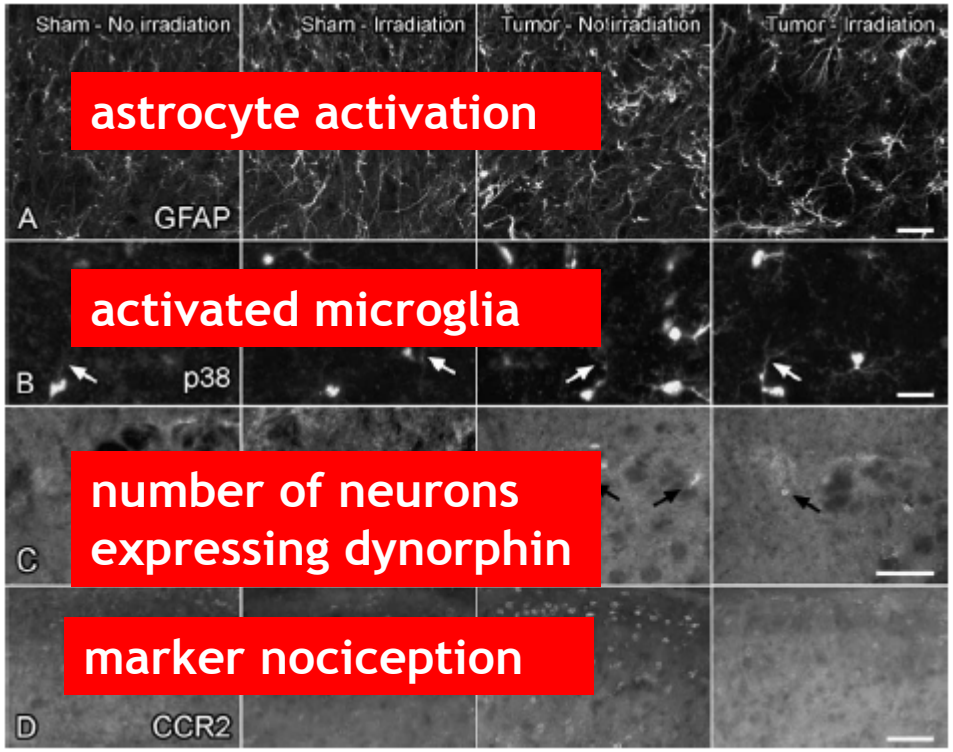
Vit J et al. Pain 2006;120:188

- **osteoblast activity** (alkaline phosphatase staining):
  - no difference ($p=0.086$)
- **osteoclast activity** (TRAP staining):
  - no difference ($p=0.166$)

- **markers of inflammation**
  - TNF-α:
    - increased ($p<0.05$)
  - MCP-1:
    - increased ($p<0.05$)
  - IL-6:
    - no difference ($p=0.752$)
  - IFN-γ:
    - no difference ($p=0.356$)

effect of low dose irradiation

Vit J et al. Pain 2006;120:188



altered nociceptive processing in the CNS!

summary

- bone metastases:
  - bone-like properties
  - bi-directional interactions
  - bone micro-environment: niche
- molecular mechanisms:
  - gradually unravelled
  - potential therapeutic targets

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