EAPC

4th Research Forum of the European Association for Palliative Care (ONLUS)

"Collaborate to Catalyse Research"

Venezia Lido (Italy), Palazzo del Casinò 25-27 May 2006

www.eapcnet.org/research2006

PARALLEL SESSIONS: Themed Research Sessions (ALPHABETICAL ORDER)

Themed Session 105 Min	**Bone metastasis. New aspects.**	Chairs: Peter Hoskin, Jean-Philippe Vuillez,	UK F
20 min	Pathophysiology of bone metastasis	Jean-Philippe Vuillez	F
20 min	Bisphosphonates: effects and side effects	Carla Ripamonti	I
20 min	Scientific Evidence of Radionucleotides in Palliative Care.	Pierre Olivier	F
20 min	Comprehensive treatment for metastatic bone pain	Peter Hoskin	UK
25 min	Discussion		

Pathophysiology of bone metastasis : how does it apply to pain treatment in palliative care ?

JP Vuillez, Grenoble, France

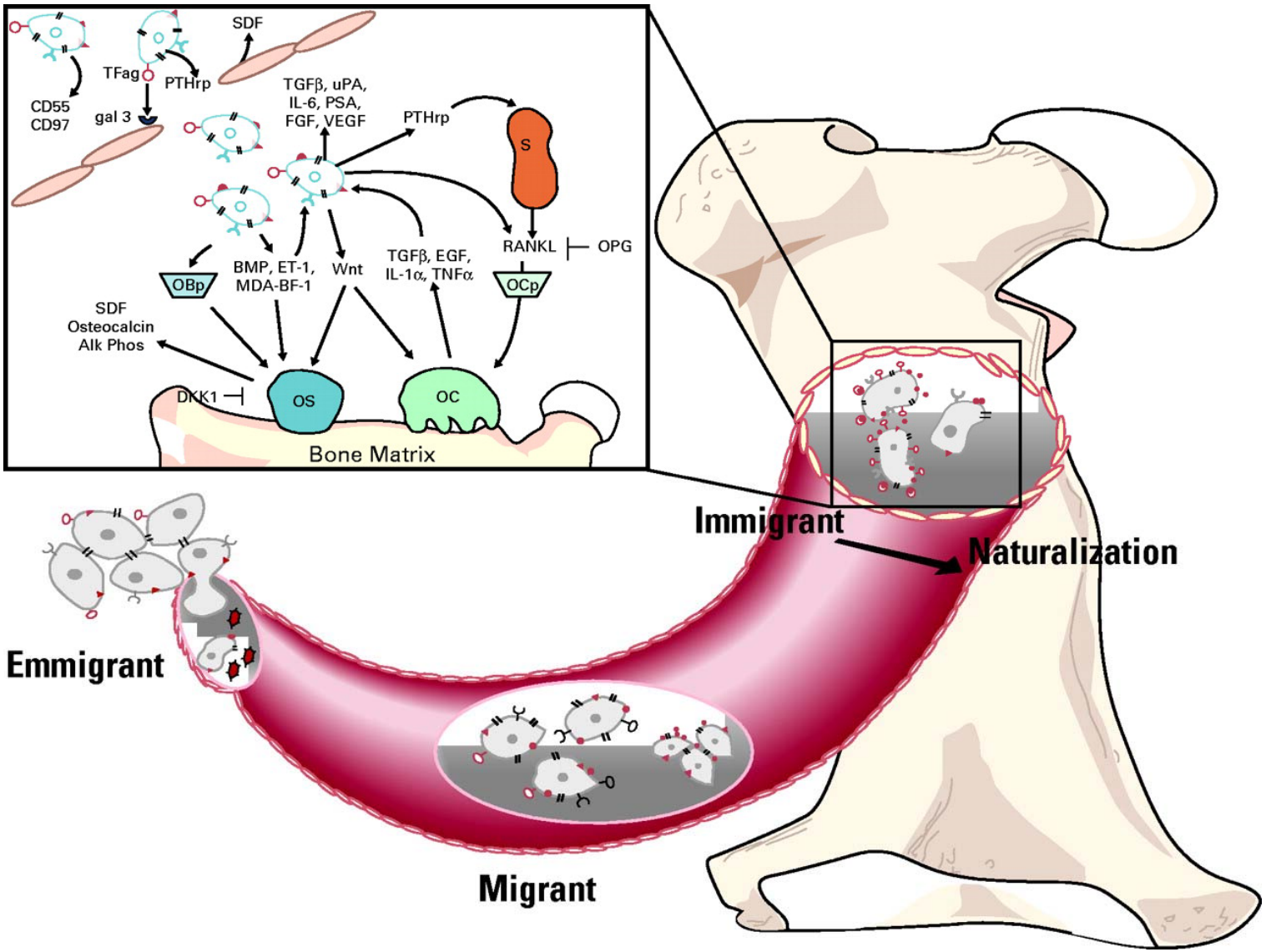
Bone metastases

- 70 % of prostate and breast cancers
- 30 % of lung, bladder and thyroid cancer
- Prostate + breast + lung = 45% of cancers…
- Bone metastases : 1 000 000 patients in the world

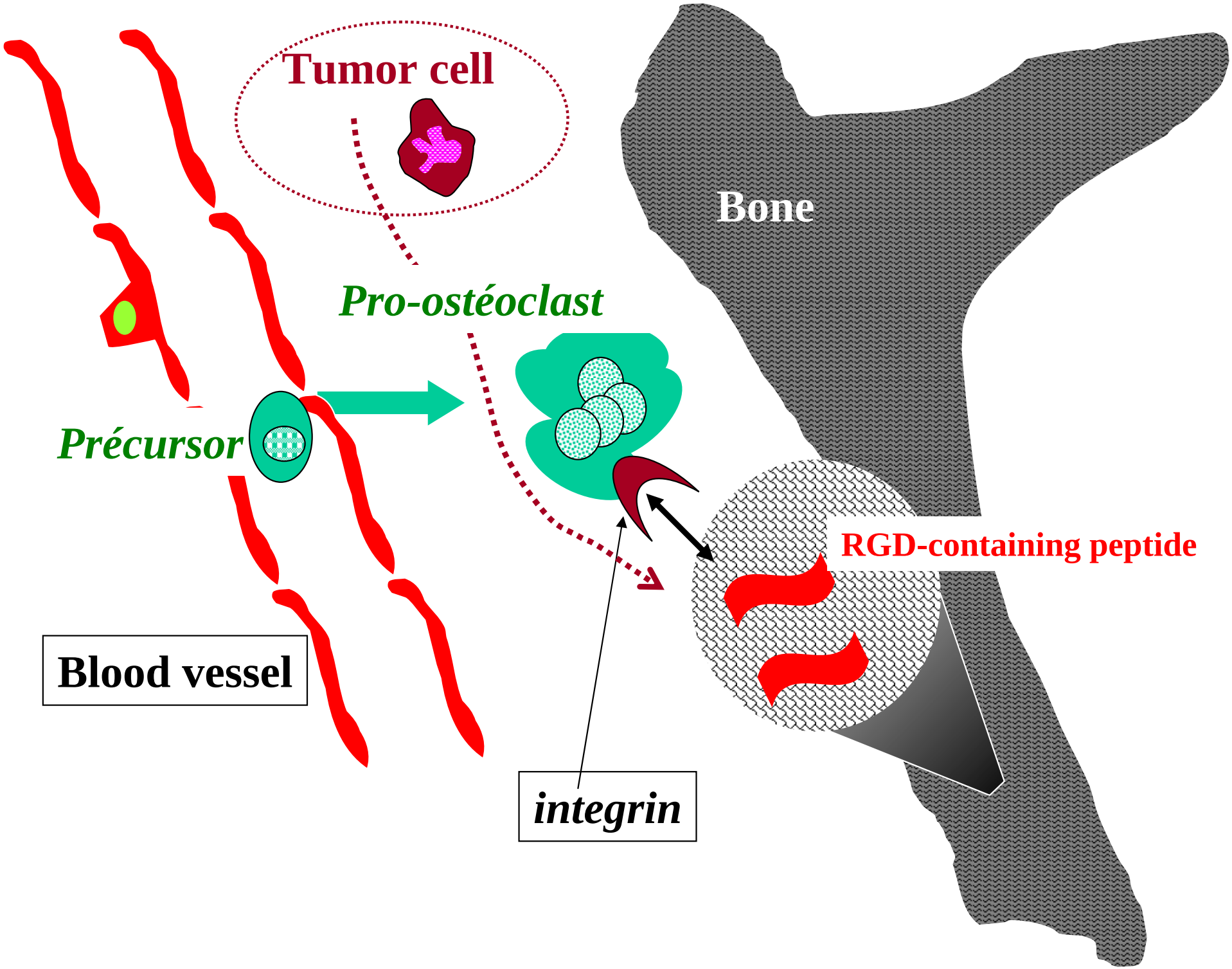
➔Thus treatments are desperately needed for deleterious effects of bone metastases, especially bone pain

➔Treatments could be optimized through a better understanding of pathophysiology

Fig 2. The migration of prostate cancer

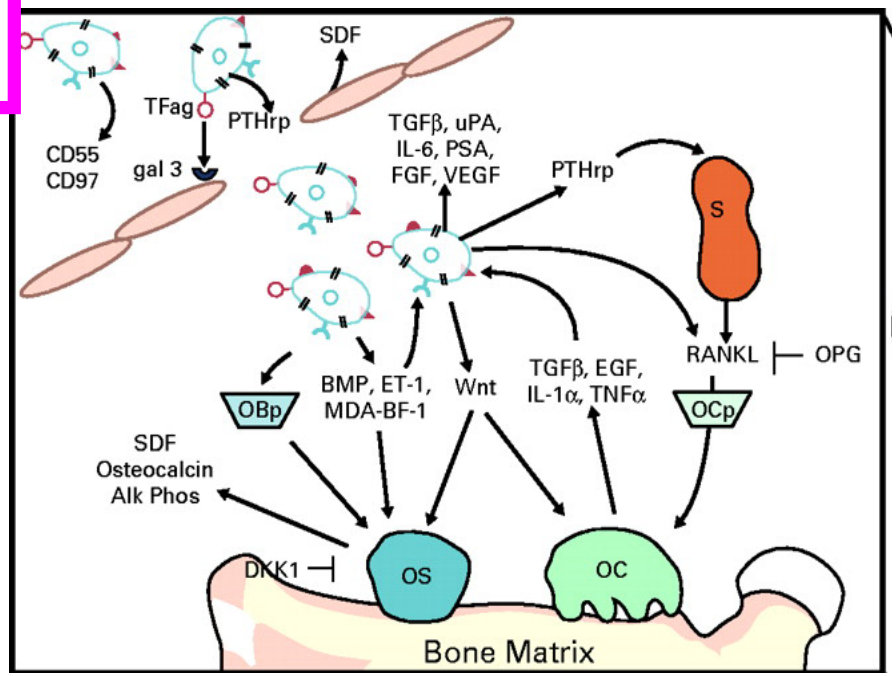


Loberg, R. D. et al. J Clin Oncol; 23:8232-8241 2005

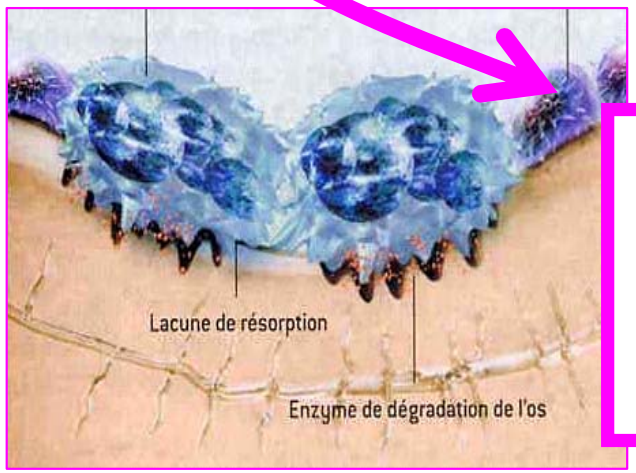

Tumor cell
Bone
Pro-ostéoclast
Précursor
RGD-containing peptide
Blood vessel
integrin

One theater, 3 characters …

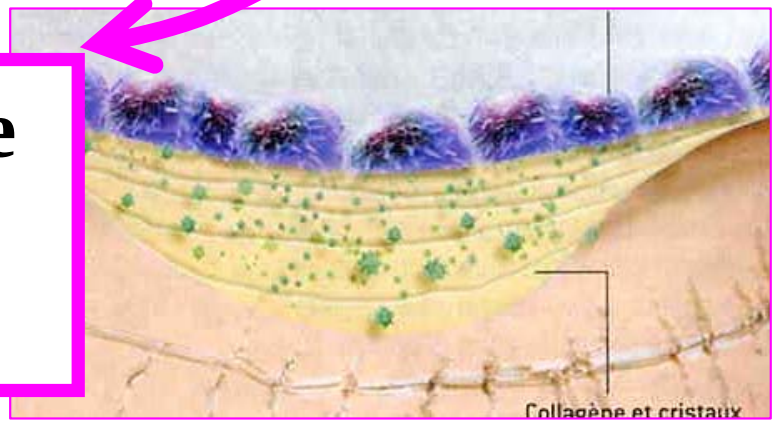
Tumor proliferation



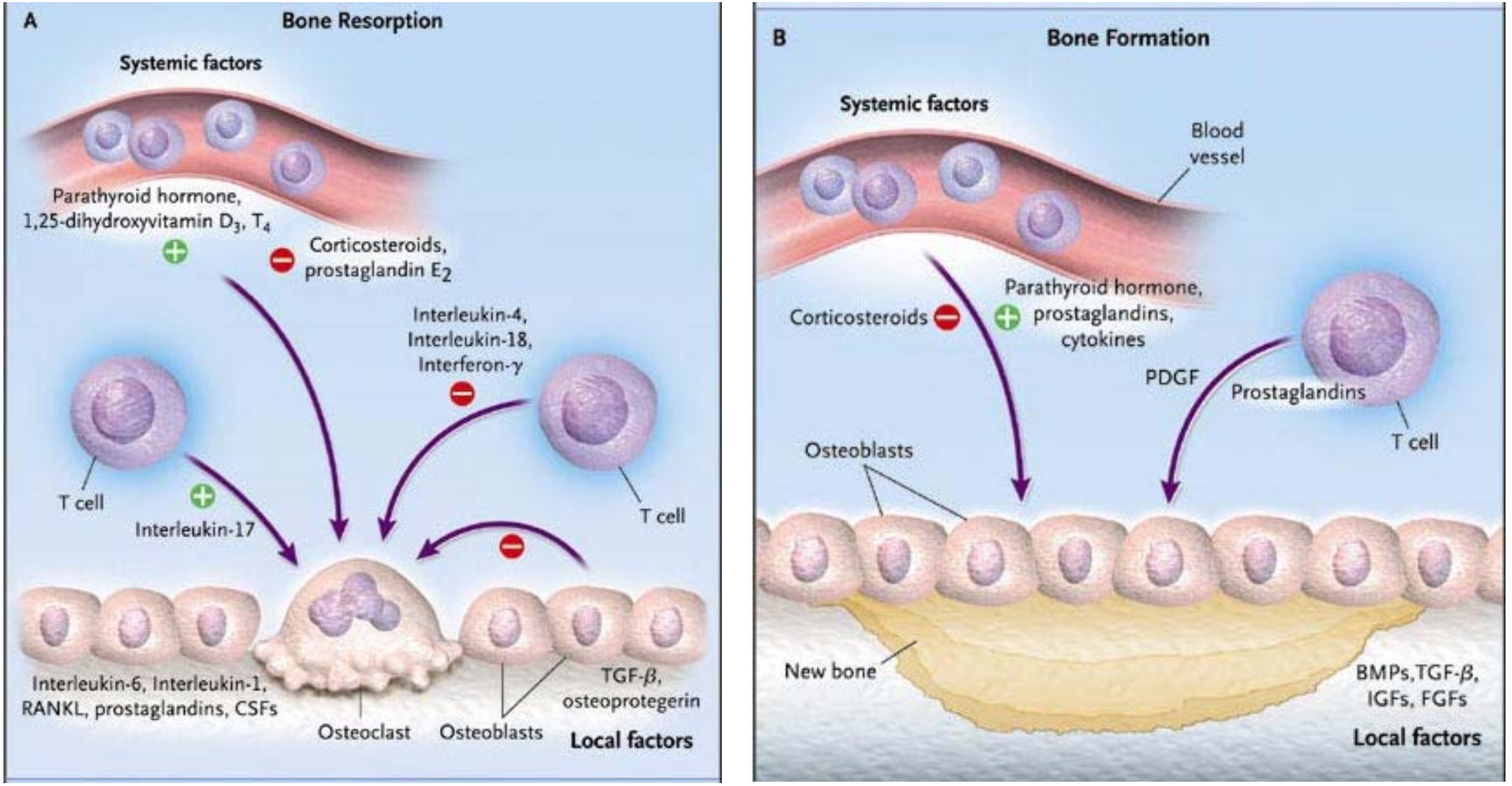
Inflammation



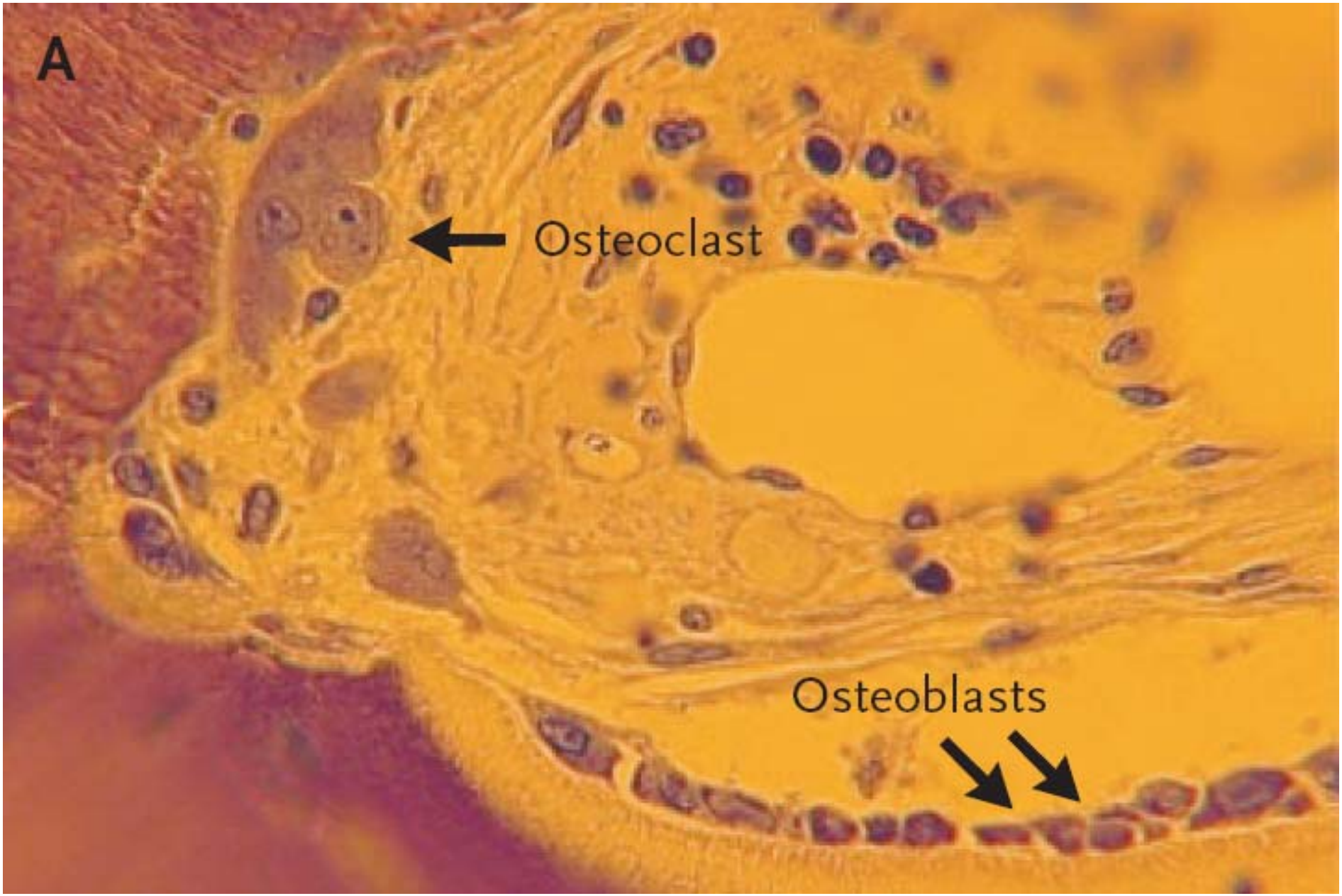
Normal bone remodeling disruption



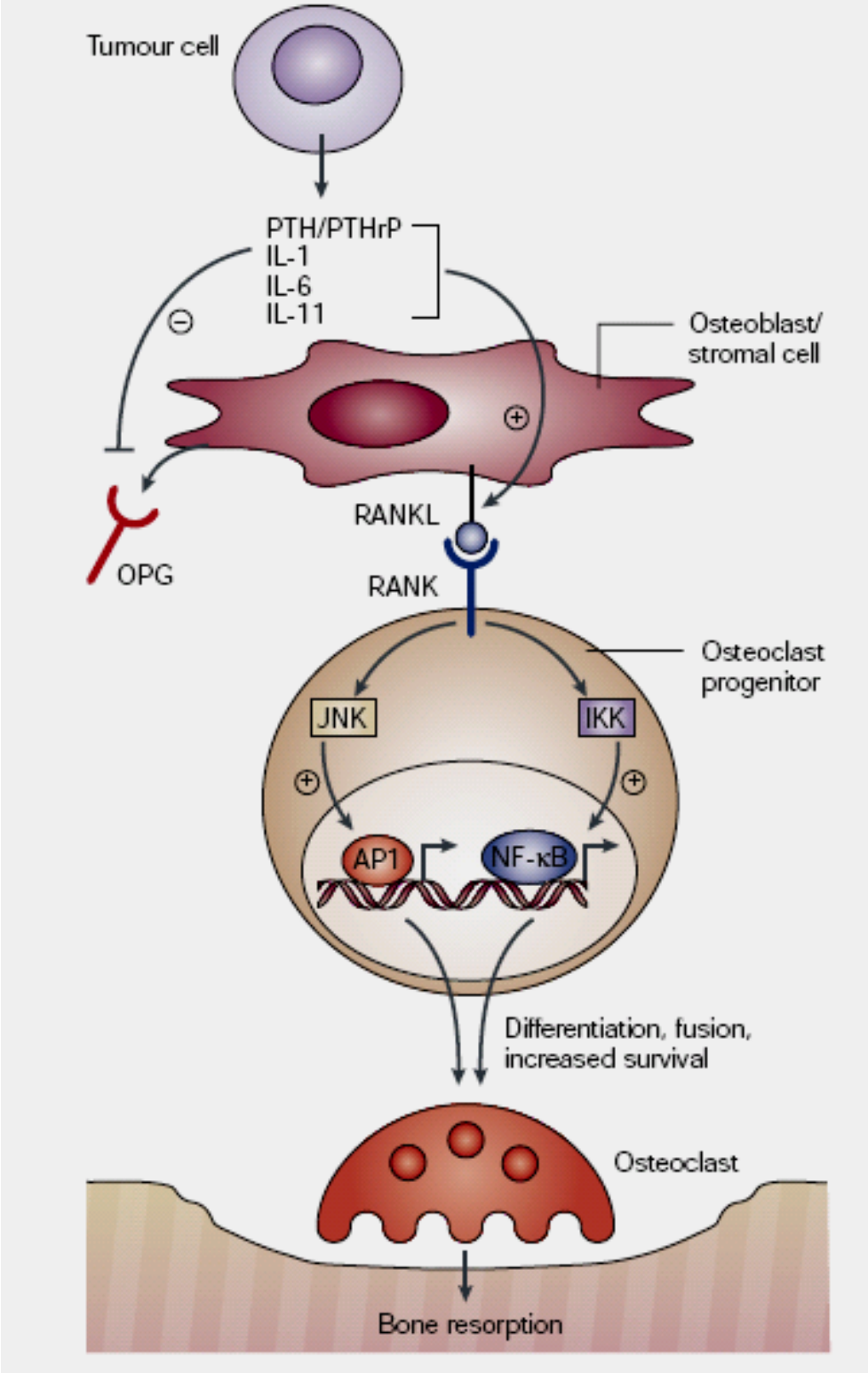
Roodman GD N Engl J Med 2004 ; 350 (16) :1655-1664



Roodman GD N Engl J Med 2004 ; 350 (16) :1655-1664



(toluidine blue, x100).



Mundy GR
Nature reviews-Cancer
2002;2:584-593

Roodman GD N Engl J Med 2004 ; 350 (16) :1655-1664

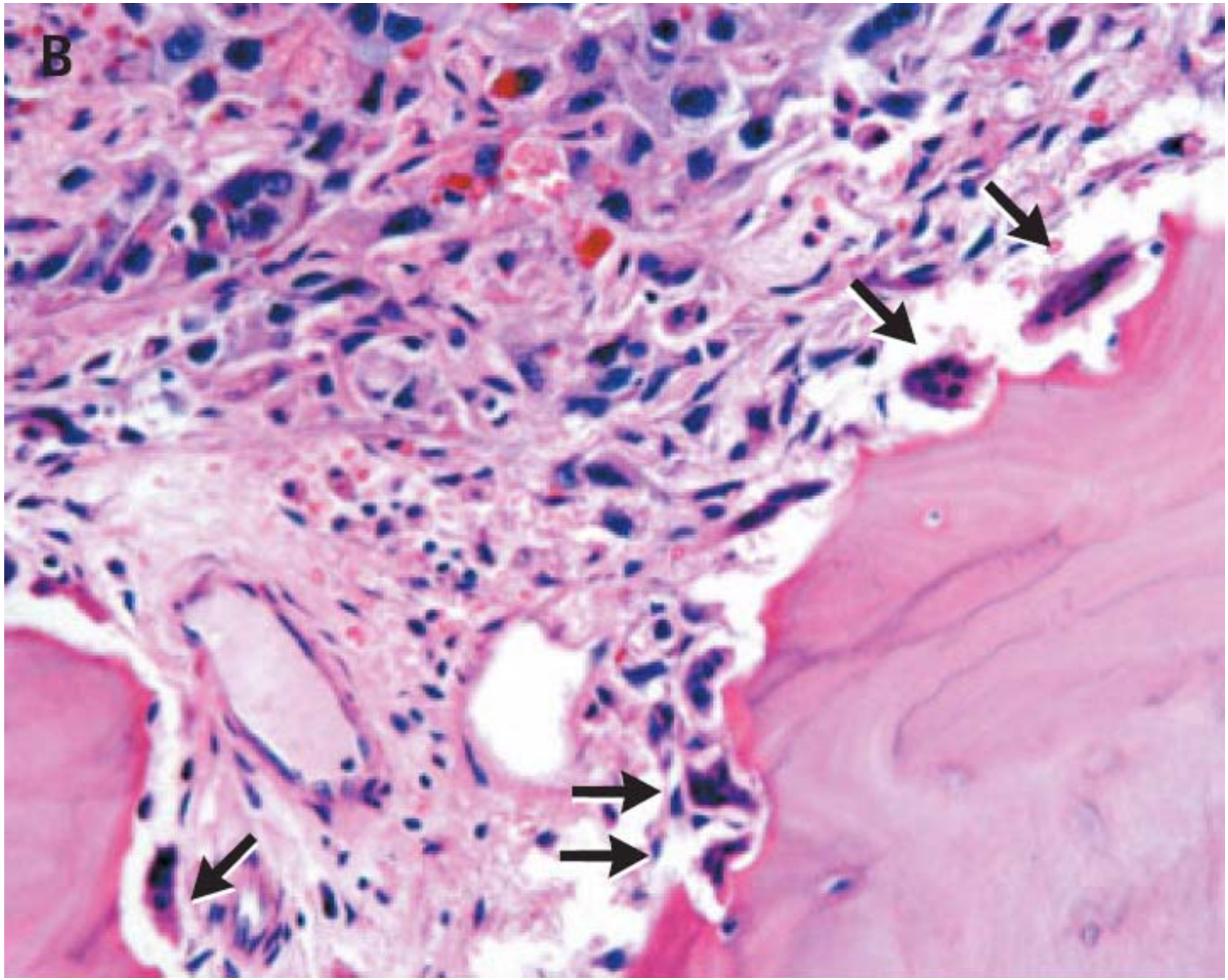
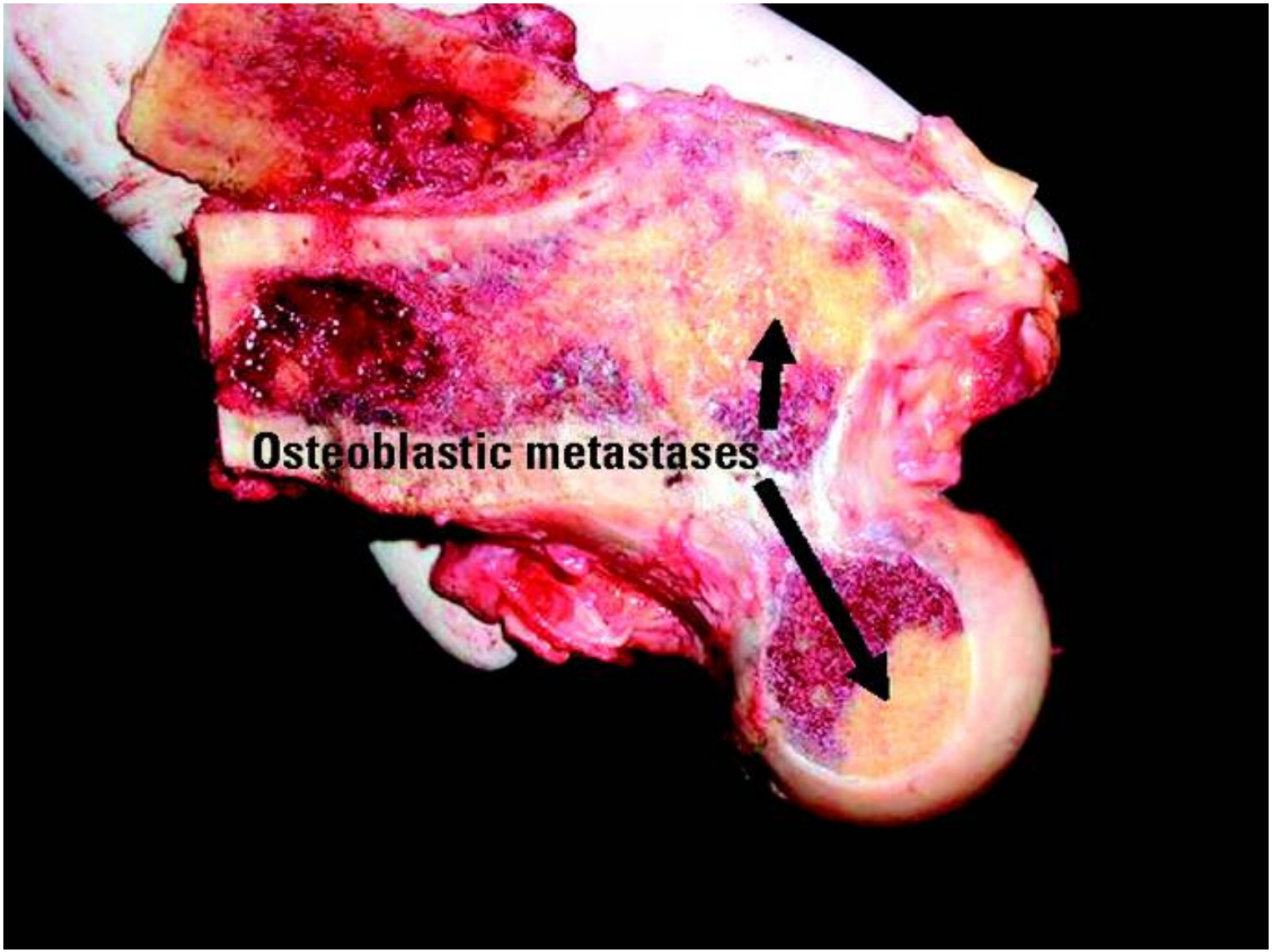
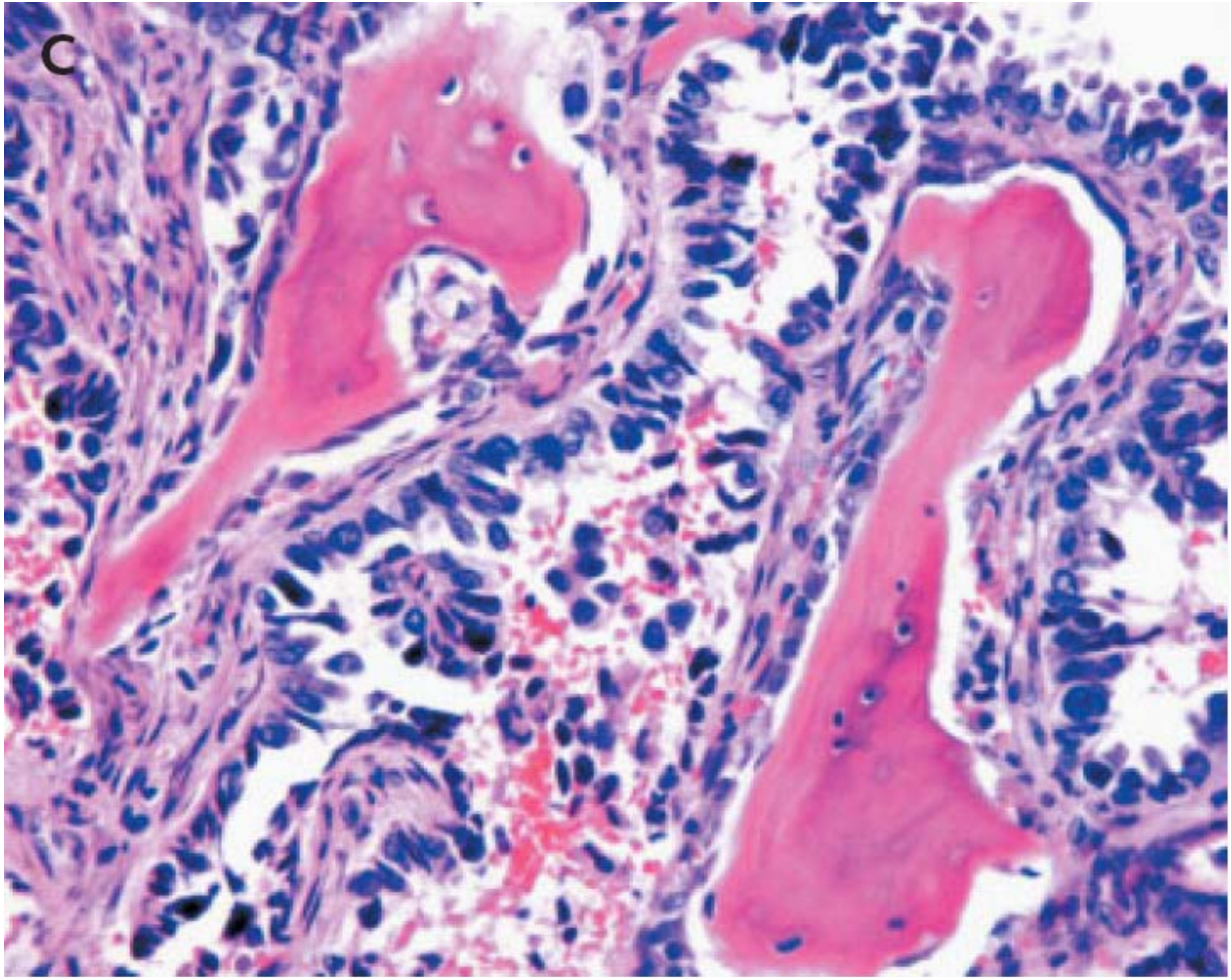


Fig 1. Osteoblastic metastases in bone

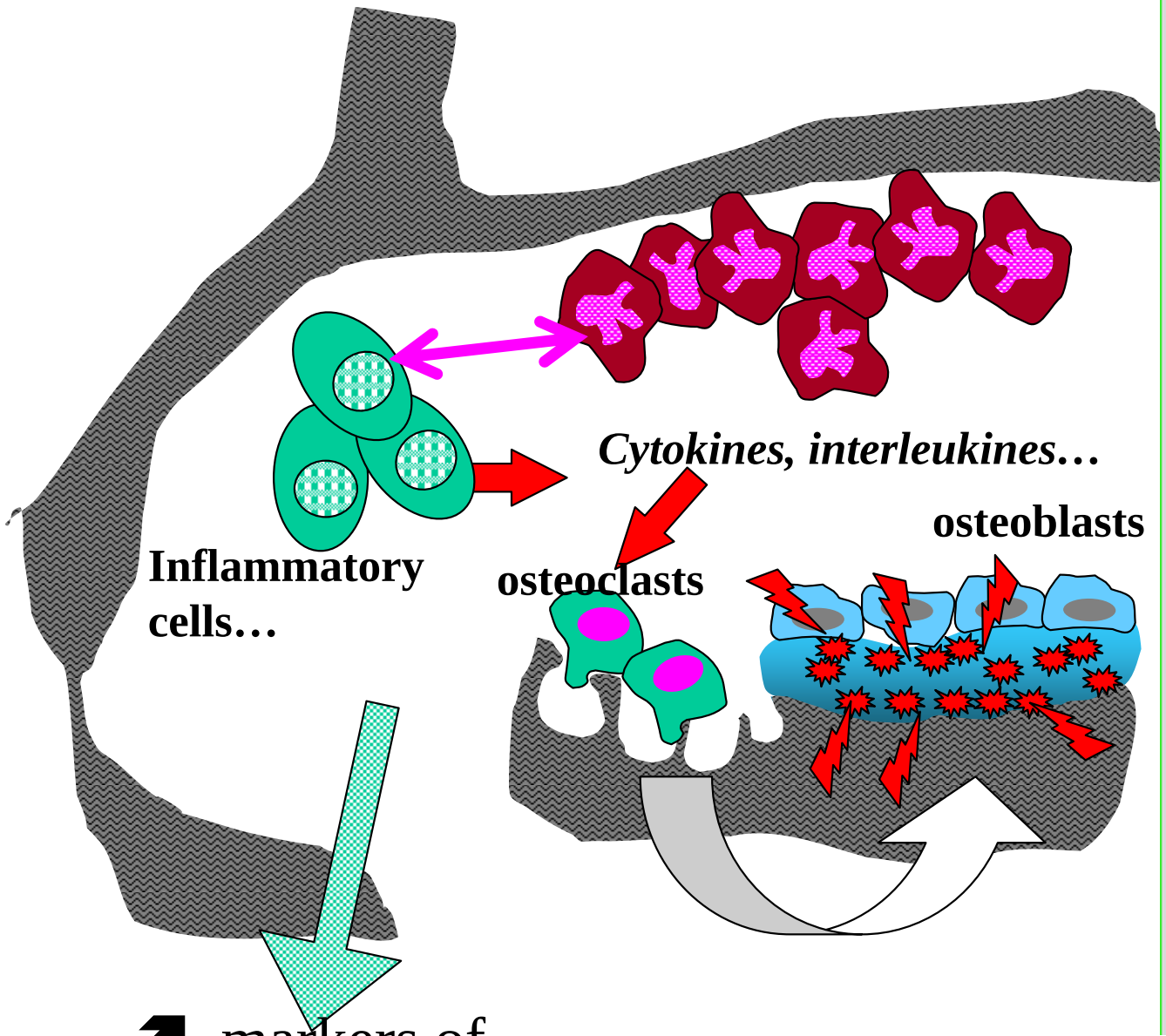


Loberg, R. D. et al. J Clin Oncol; 23:8232-8241 2005

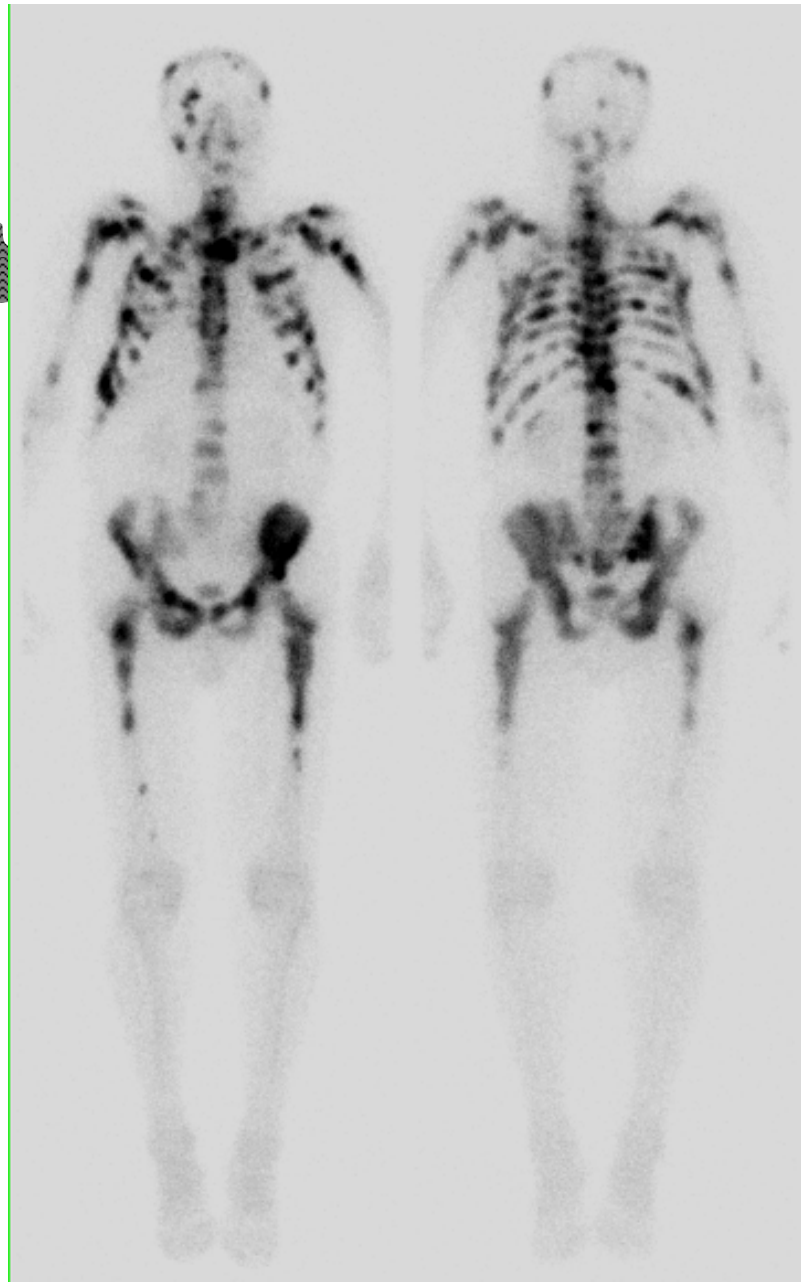
Roodman GD N Engl J Med 2004 ; 350 (16) :1655-1664



Bone resorption/remodeling



↗ markers of bone resorption



Concordance between histology and bone scintigraphy in prostate cancer bone metastases
Roudier et al. ***Clinical & Experimental Metastasis* 20: 171–180, 2003.**

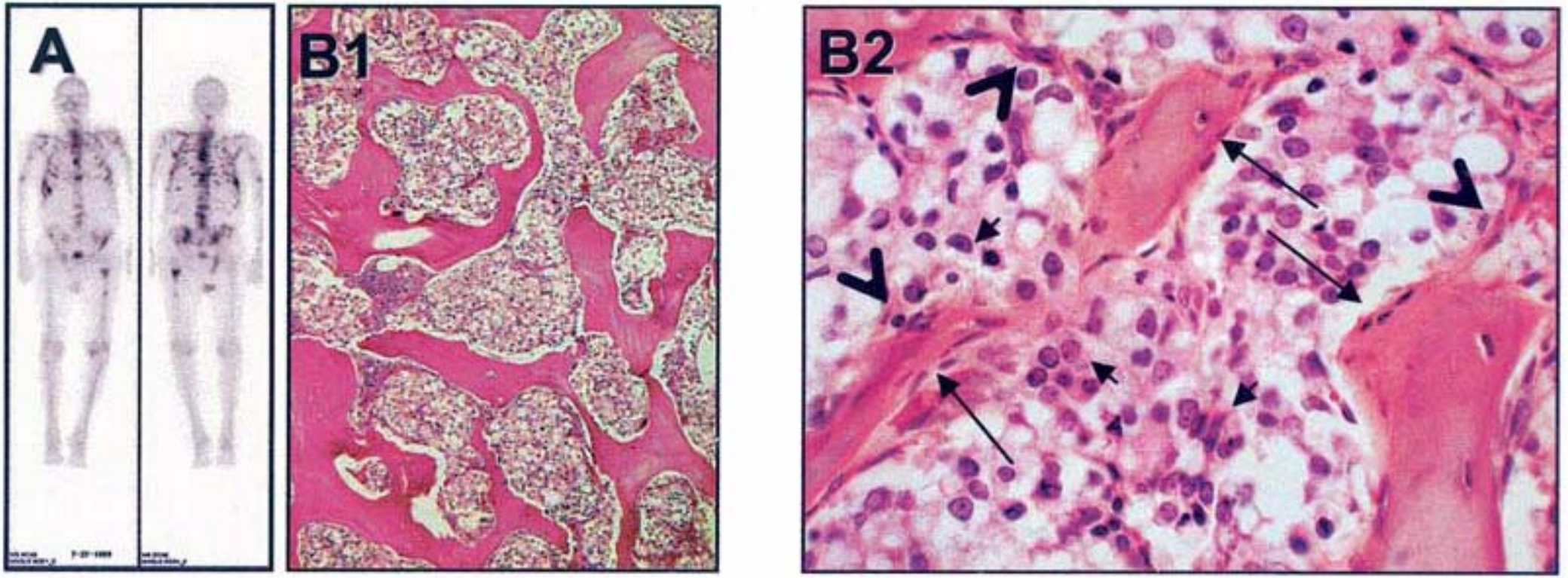


Figure 2. (A) Bone scintigraphy of patient #2 with multiple bone metastases of prostate cancer. The scintigraphy is presented as an anterior and posterior view. (B1) Histology section of an osteoblastic prostate cancer bone metastasis from patient #2. The typical osteoblastic response consists of numerous and irregular bone trabeculae that are highly anastomotic 10×. (B2) Higher magnification of B1 metastasis, showing spindle cells laying down on *de novo* bone trabeculae (long arrows), *de novo* new bone formation arising from the tumor stroma (empty arrowheads) and tumor cells filling the space between bone trabeculae (short arrows) 40×.

Concordance between histology and bone scintigraphy in prostate cancer bone metastases
***Roudier et al. Clinical & Experimental Metastasis* 20: 171–180, 2003.**

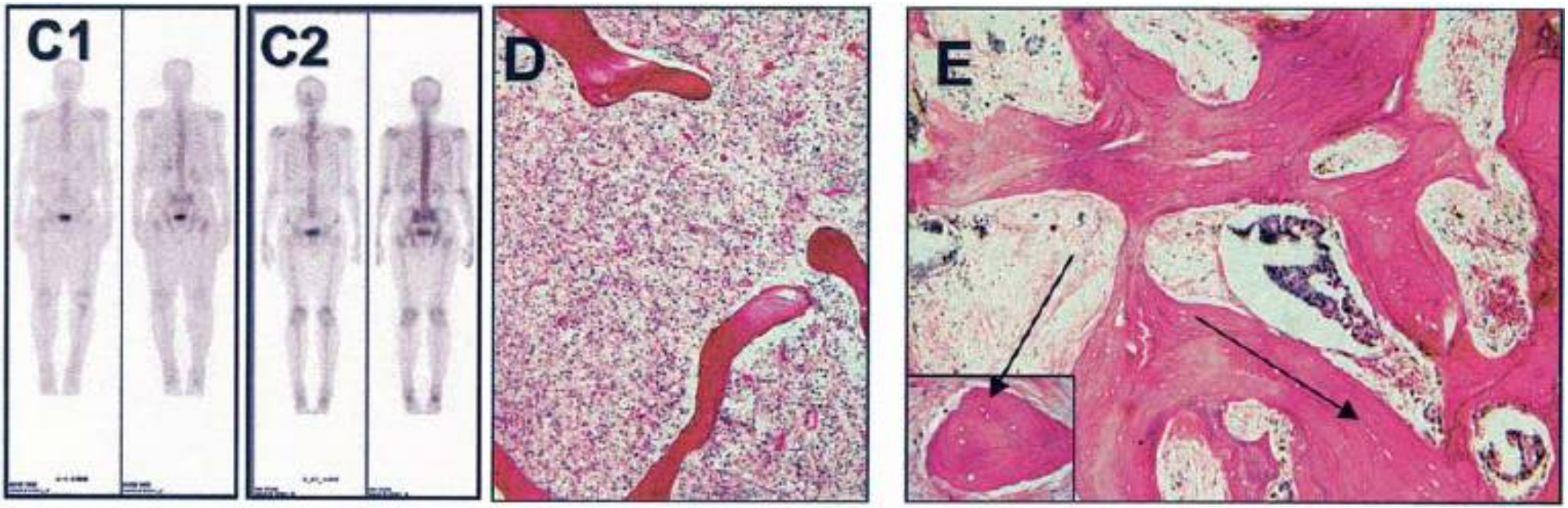
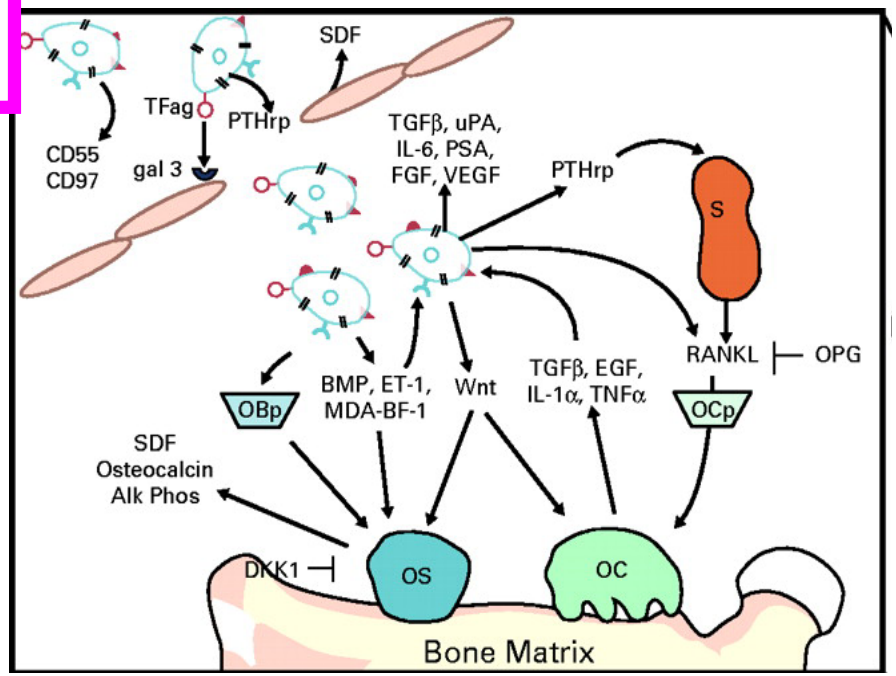


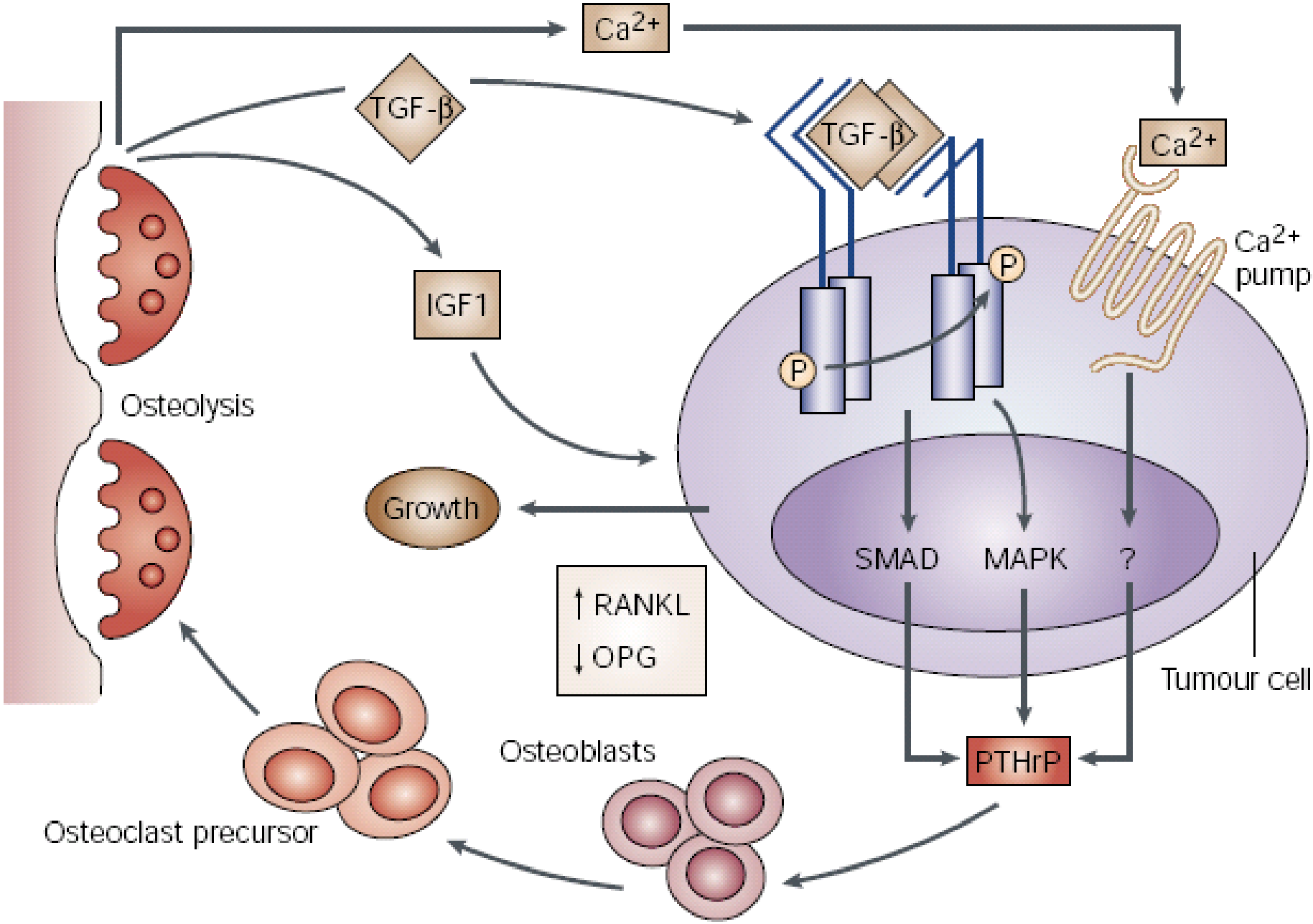
Figure 2. (C1 and C2) Last two bone scintigraphies of patient #3, performed one year apart. (C1) No obvious increased uptake was observed. (C2) This scintigraphy was performed less than one month before the autopsy and did not show any increased uptake although 12 bone metastases were found histologically at autopsy (pelvis, L5 to L1, T12-T11 and T8, sternum); (D): A H&E histology section of one of the 12 bone metastases found in patient #3. Bone marrow is totally replaced by prostate cancer cells. Note the absence of reactive bone changes: the number of trabeculae is normal; trabeculae are thin, long, regular without scalloped area H&E 10×. (E) Prostate cancer metastasis with osteonecrosis observed in areas treated with palliative radiation. Insert shows necrotic bone trabeculae with empty enlarged osteocyte lacunae (long arrows) H&E 10×.

2)

Tumor proliferation



… the vicious circle of bone metastases.



Mundy GR Nature reviews-Cancer 2002;2:584-593

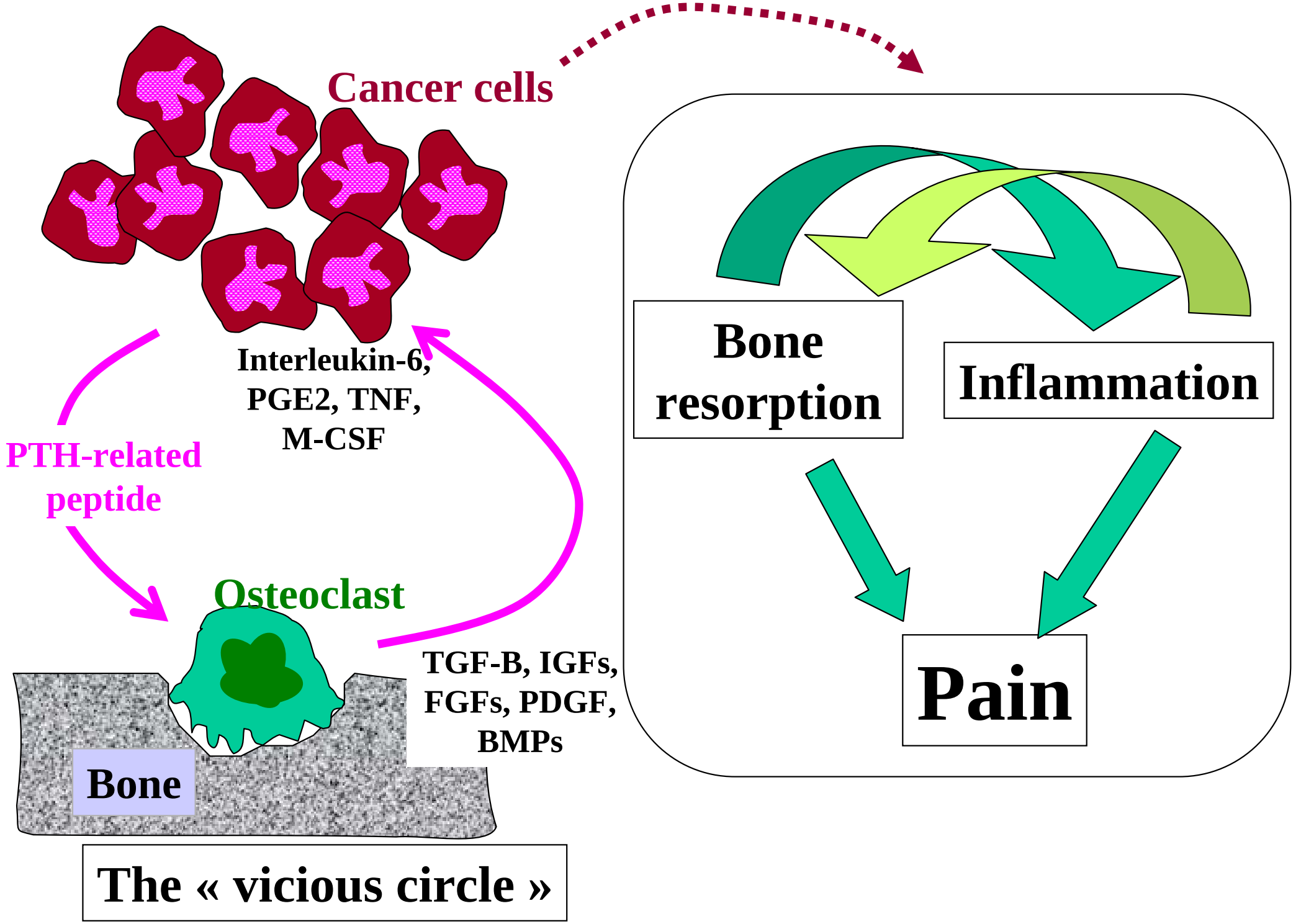
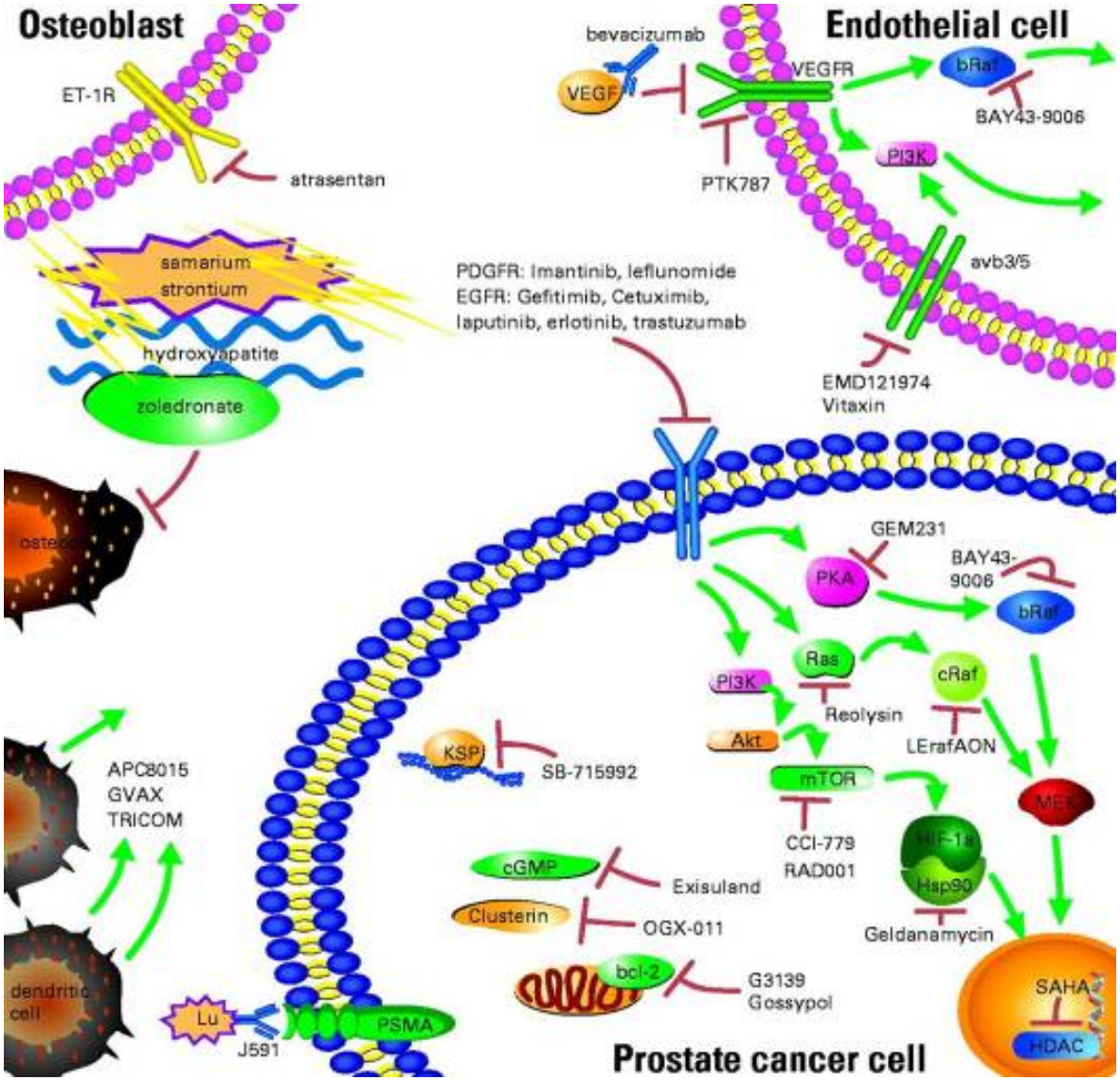
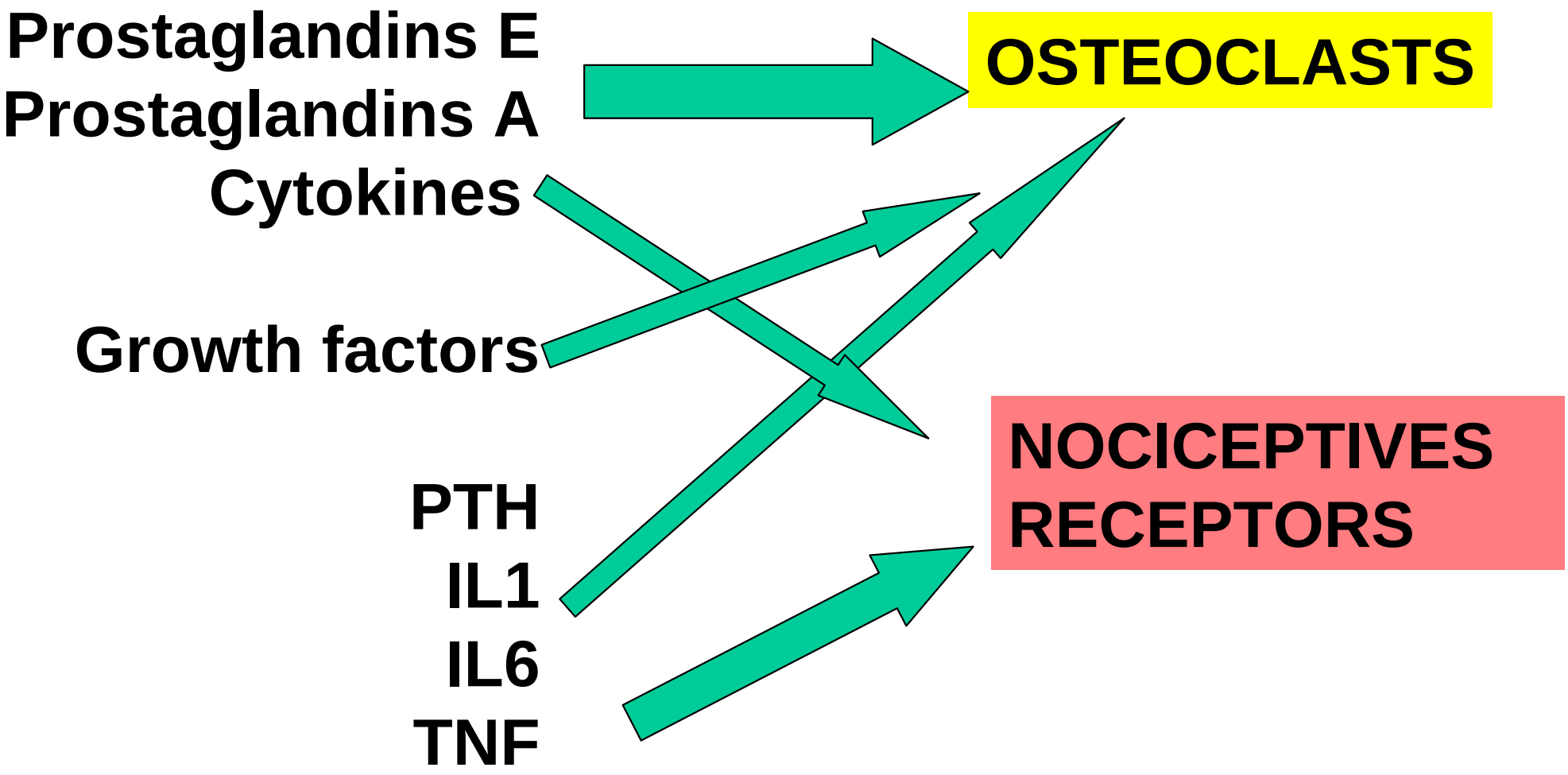

Cancer cells
Interleukin-6,
PGE2, TNF,
M-CSF
PTH-related
peptide
Osteoclast
TGF-B, IGFs,
FGFs, PDGF,
BMPs
Bone
Bone
resorption
Inflammation
Pain
The « vicious circle »

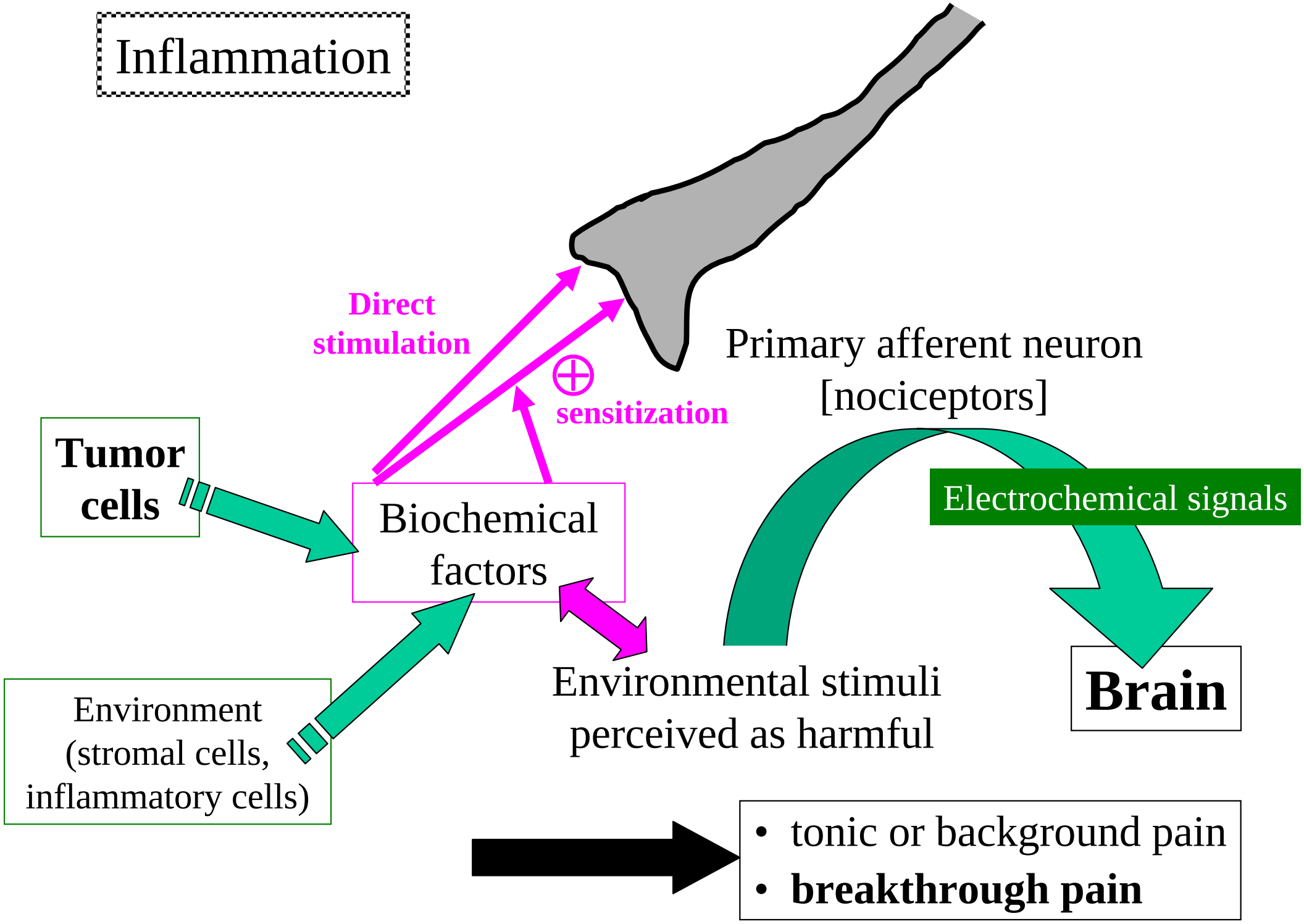
Fig 5. Targeted therapies in development for the lethal phenotype of prostate cancer metastasis



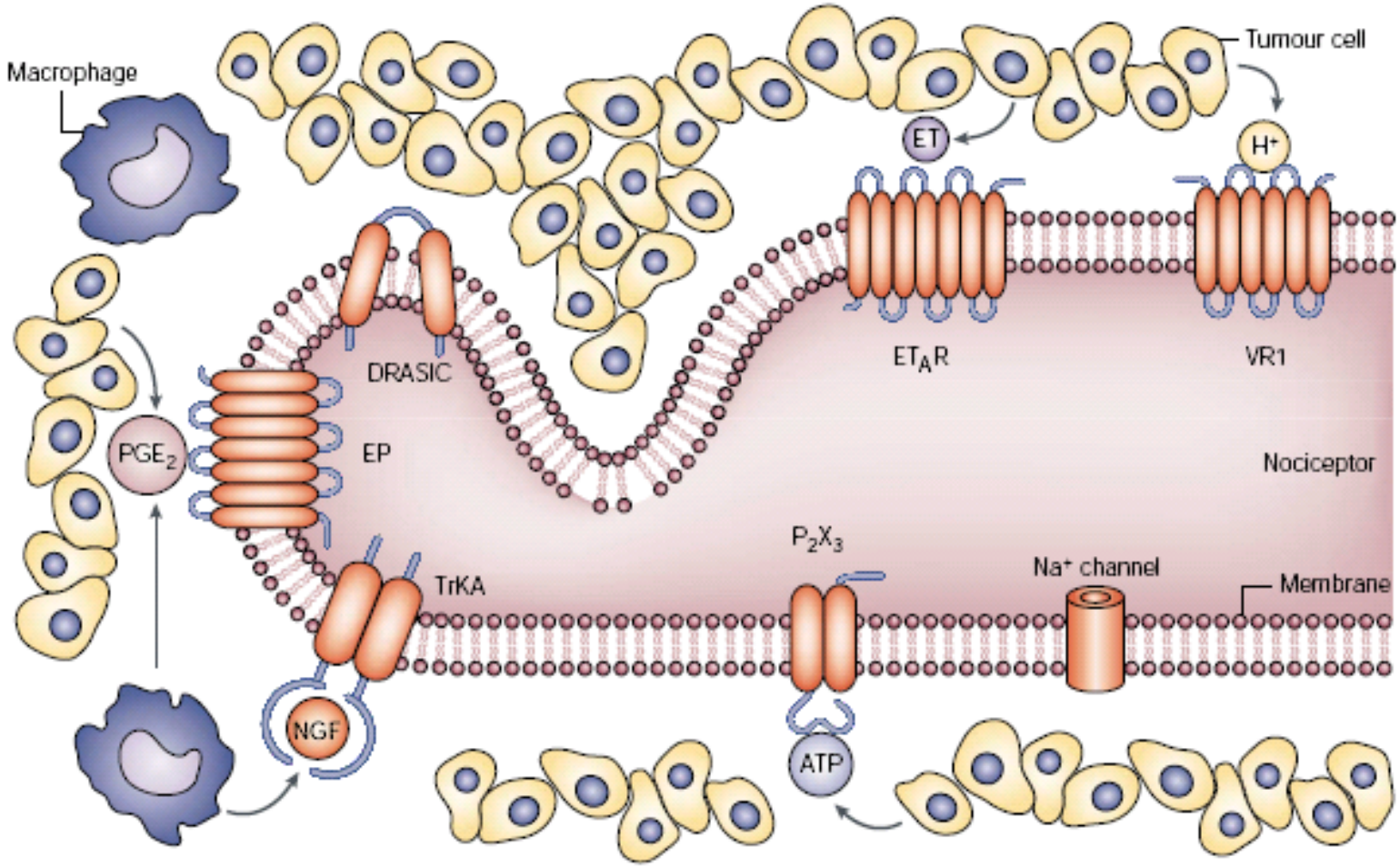
Loberg, R. D. et al. J Clin Oncol; 23:8232-8241 2005

3) « Inflammation »



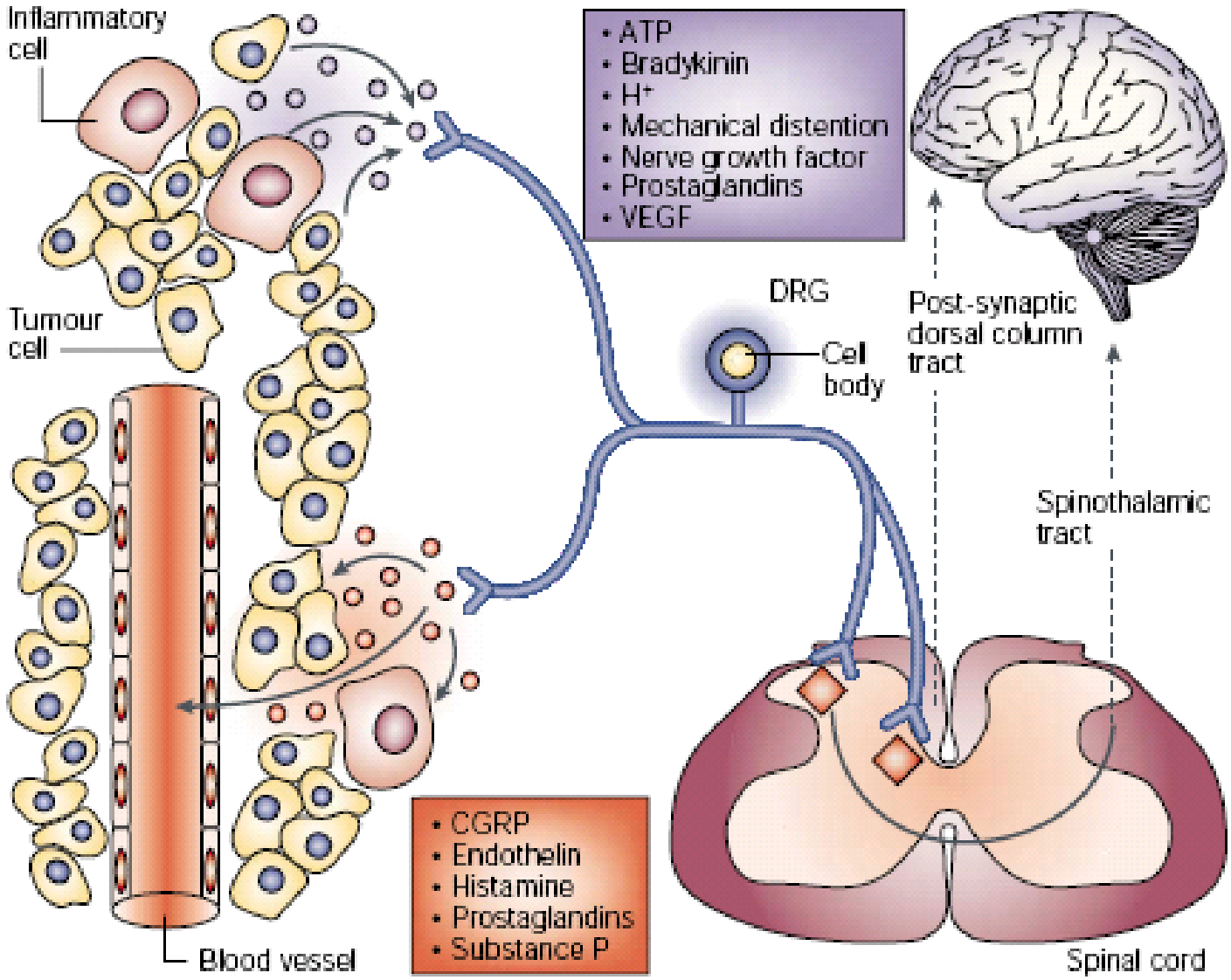

Inflammation
Direct stimulation
sensitization
Primary afferent neuron [nociceptors]
Tumor cells
Biochemical factors
Electrochemical signals
Environmental stimuli perceived as harmful
Brain
Environment (stromal cells, inflammatory cells)
• tonic or background pain
• breakthrough pain

Detection by sensory neurons of noxious stimuli produced by tumours.

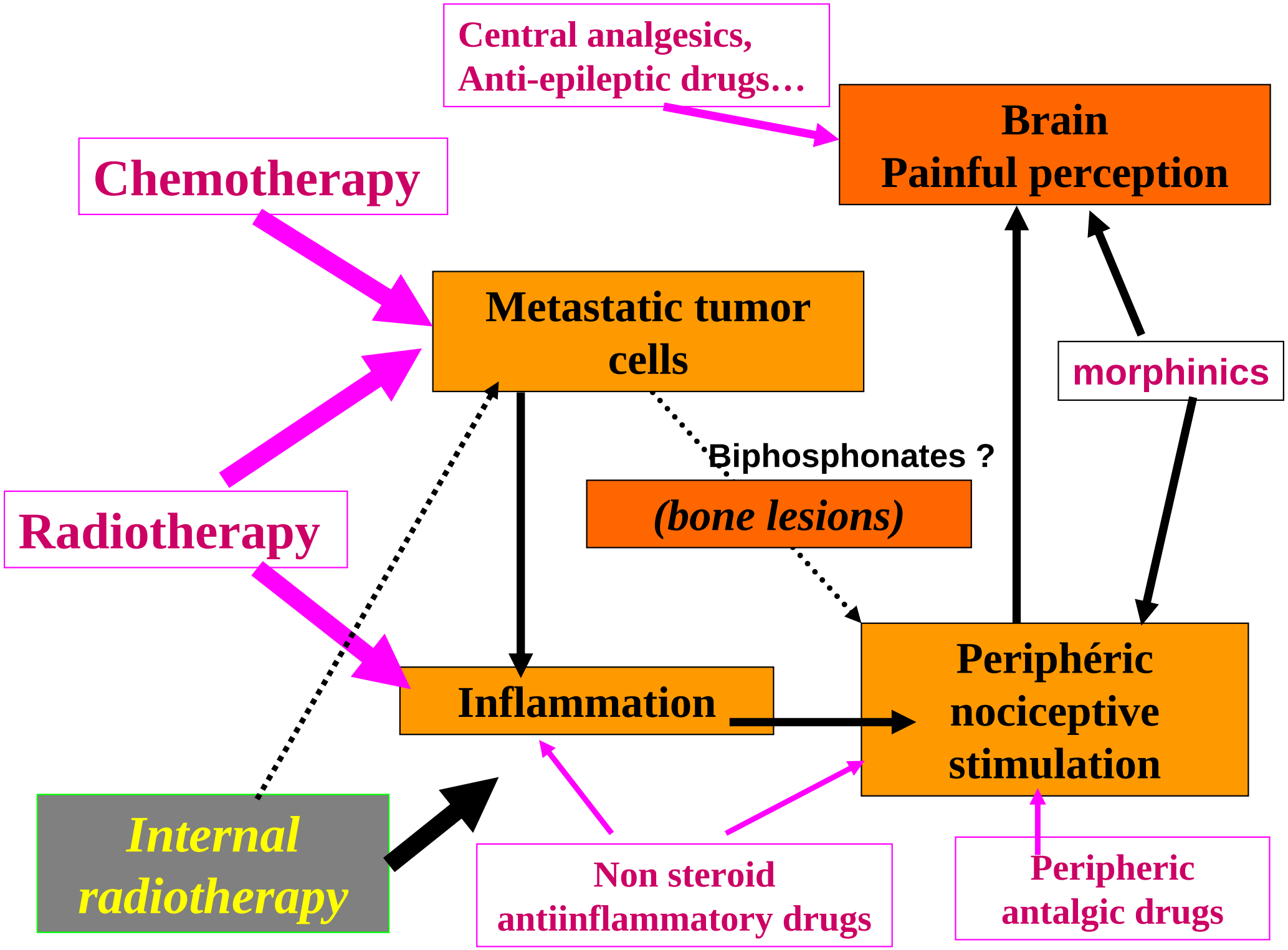


Mantyh PW et al. *Nature Reviews Cancer* 2002;2:201-209

The tumour –nociceptor interface.



Mantyh PW et al. *Nature Reviews Cancer* 2002;2:201-209


Central analgesics,
Anti-epileptic drugs…
Brain
Painful perception
Chemotherapy
Metastatic tumor cells
morphinics
Biphosphonates ?
(bone lesions)
Radiotherapy
Inflammation
Periphéric nociceptive stimulation
Internal radiotherapy
Non steroid antiinflammatory drugs
Peripheric antalgic drugs

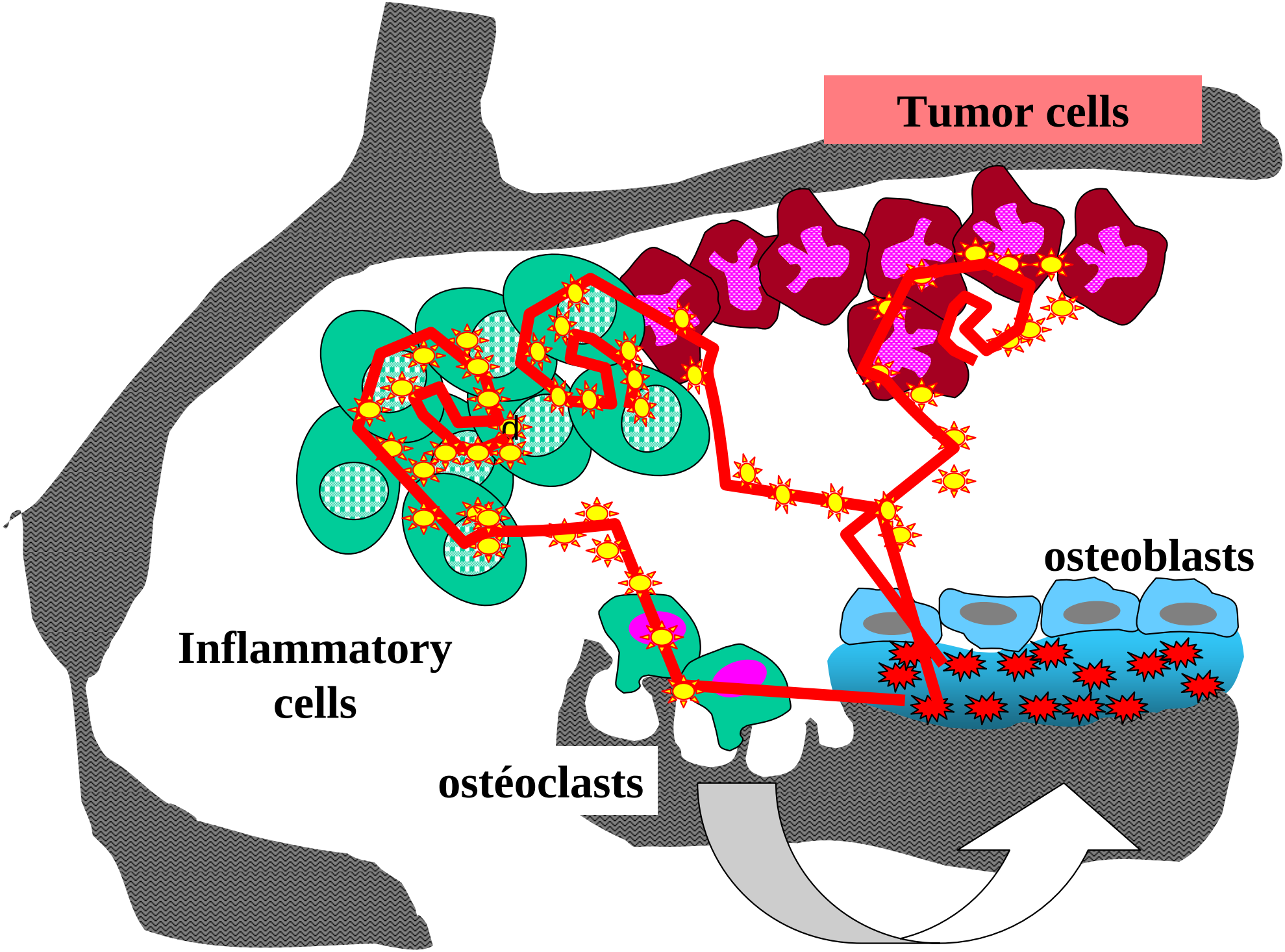
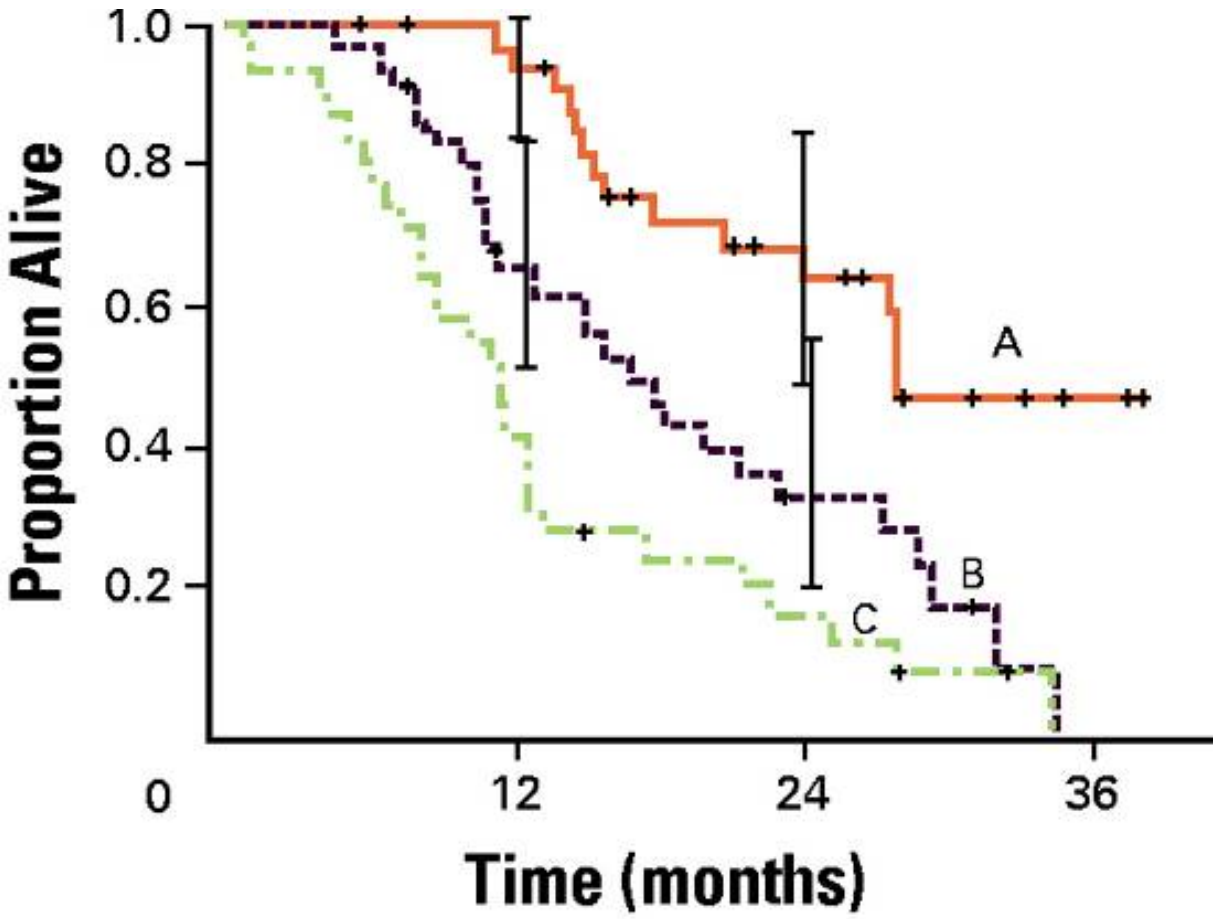

Tumor cells
osteoblasts
Inflammatory cells
ostéoclasts

Fig 3. Bone-targeted consolidation therapy in patients with stable or responding advanced androgen-independent carcinoma of the prostate may improve overall survival. **The addition of strontium-89 (Sr-89) plus doxorubicin to standard chemotherapy increased median survival to 27.7 months from 17.5 months in a study of 103 patients with androgen-independent prostate cancer.** ***Reprinted with permission from Tu et al.***[13]



A) Doxorubicin and Sr-89	36	35	34	26	21	15	5	3	0
B) Doxorubicin alone	36	35	27	18	7	7	3	0	0
C) Not randomly assigned	31	26	17	8	6	4	1	0	0

Loberg, R. D. et al. J Clin Oncol; 23:8232-8241 2005

Conclusions

- **Bone metastasis : role of the bone microenvironment**
- **« vicious circle » (osteoclasts-osteoblasts/tumour cells)**
- **Bone remodeling impairment leading to altered bone structure**
- **Inflammation**
- **Numerous and complex mechanisms of pain**
- **Numerous targets for treatments…**

thank you for your attention