

Sistema immunitario, microambiente osseo e cancro: nuovi target terapeutici

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PALAZZO ZACCO

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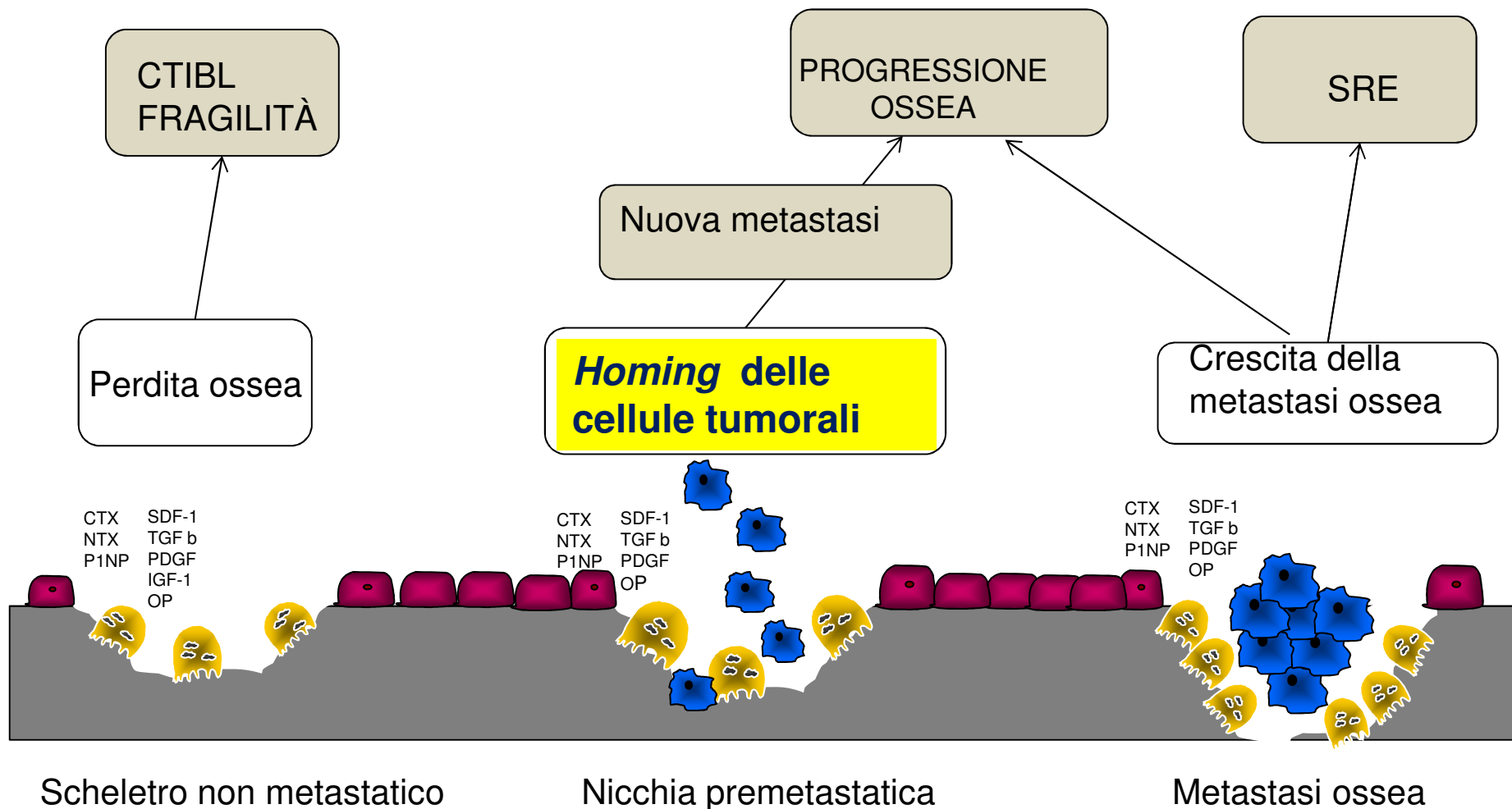


My disclosures

- Research grants from: Amgen, Janssen, Roche, Ipsen
- Advisory boards from: Amgen, Janssen, Merck-Serono, MSD, Roche, Bayer, Novartis, Bristol, Boeringher

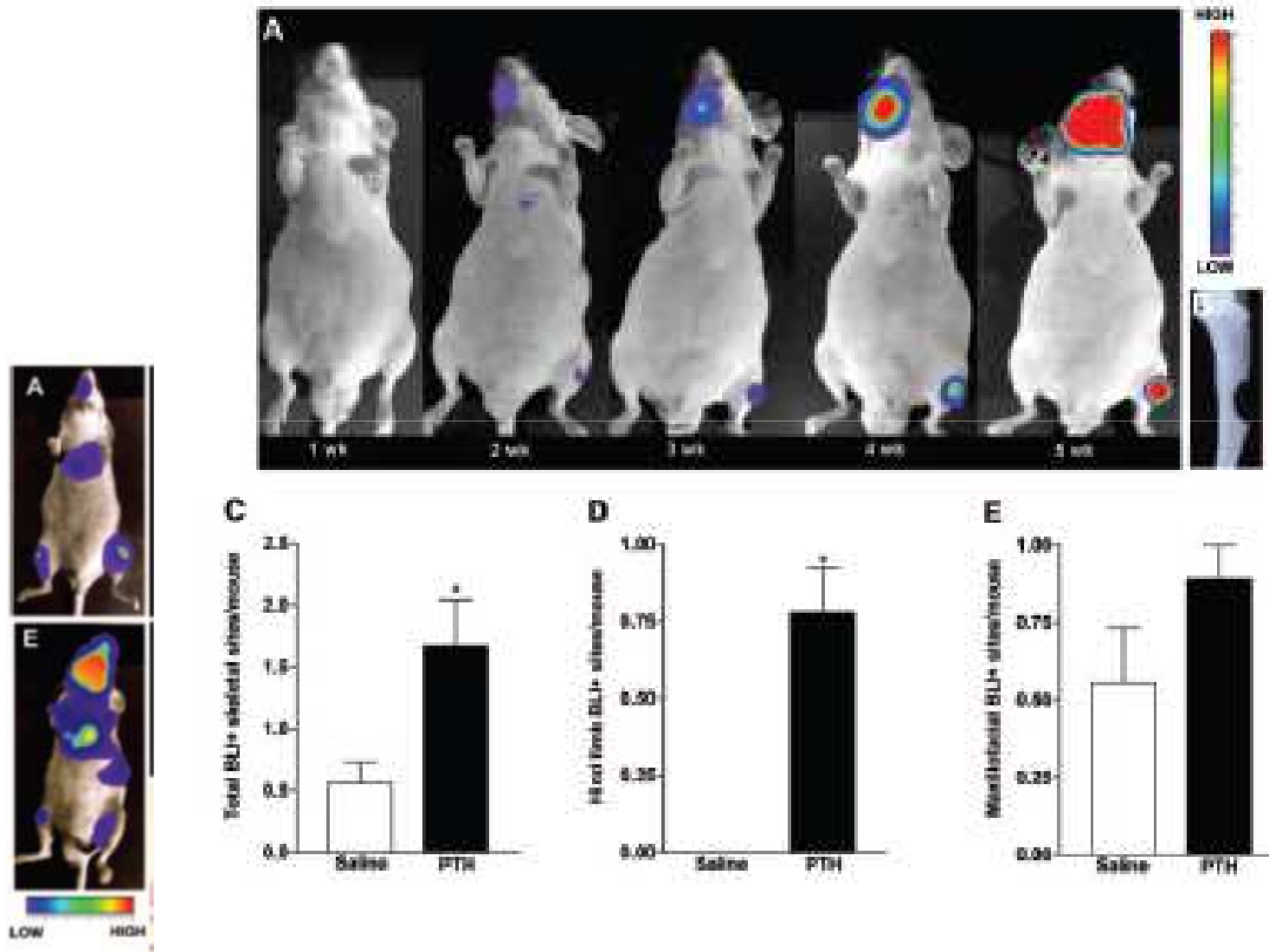
1. High bone turnover increases the risk of new bone metastases and of skeletal progression

ELEVATO TURNOVER OSSEO
(eta' –livelli vit D – Terapia ormonale adiuvante- metastasi)

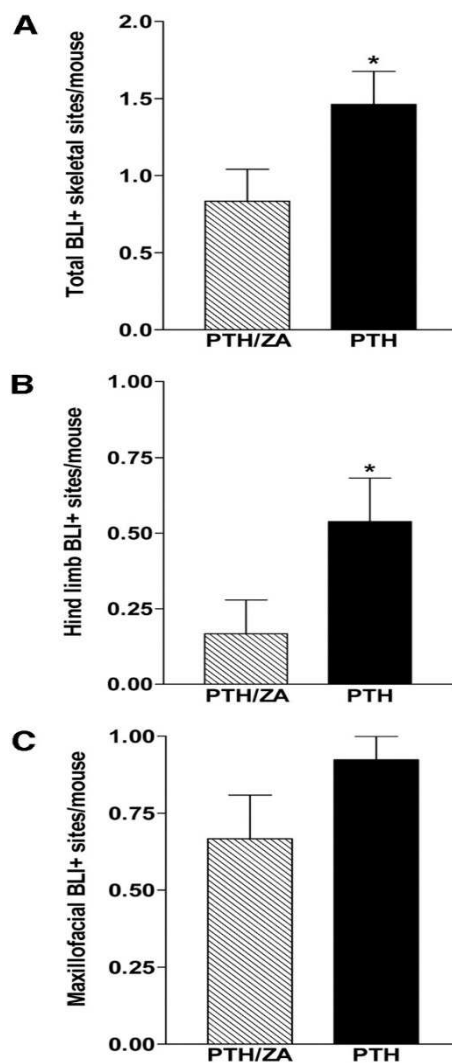
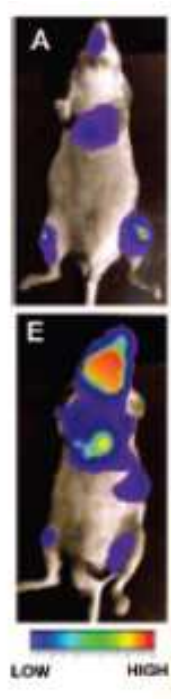


Courtesy by Bertoldo F

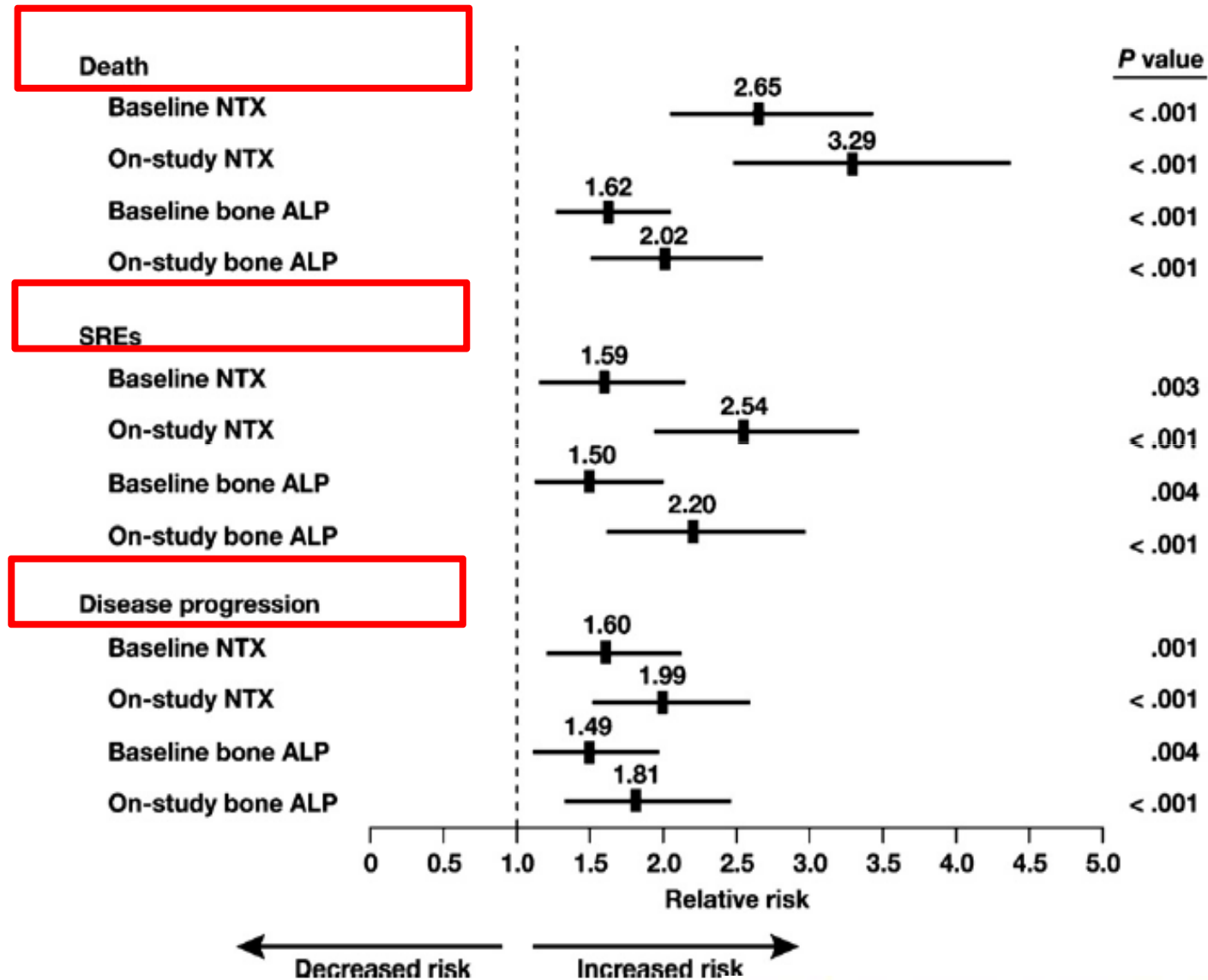
Bone Turnover Mediates Preferential Localization of Prostate Cancer in the Skeleton



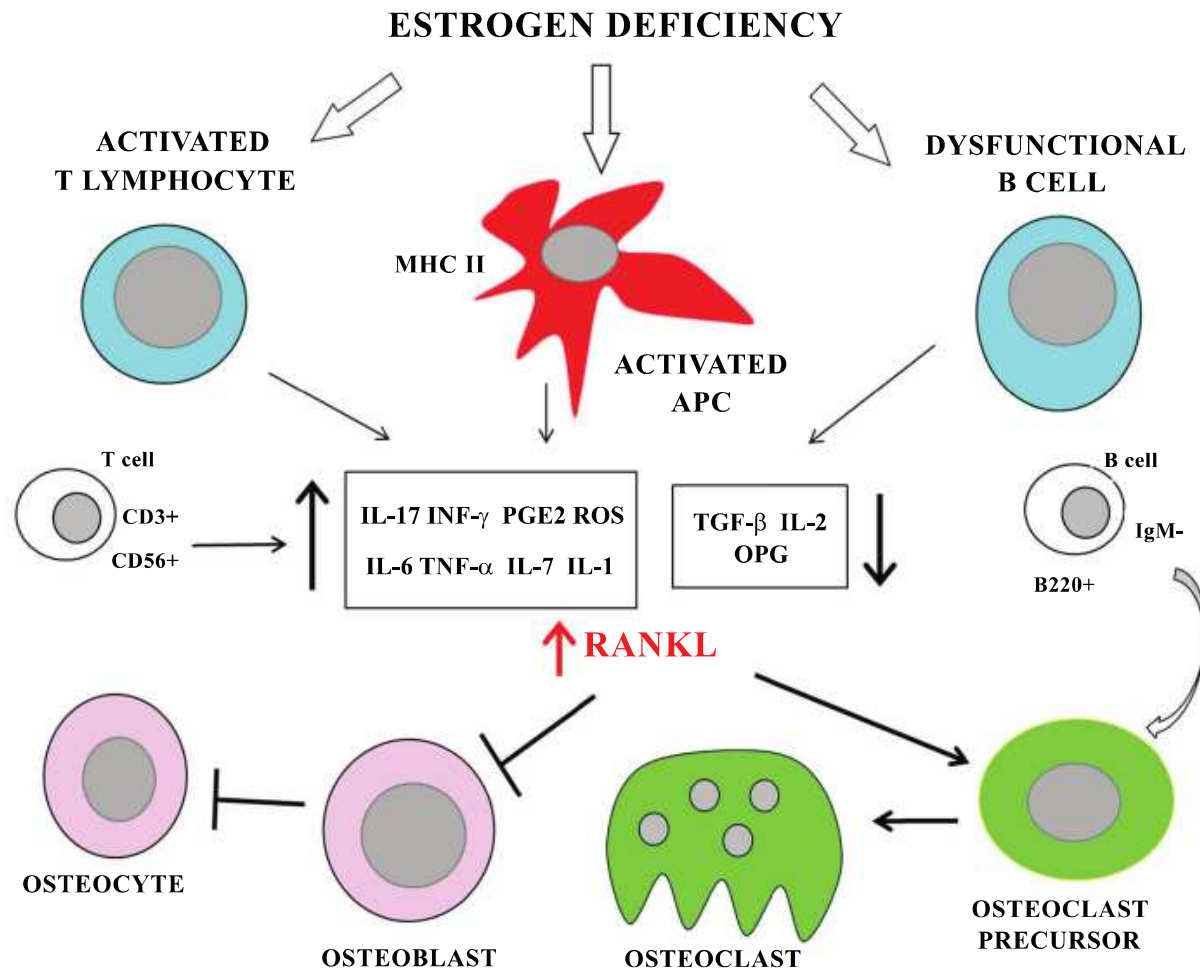
Bone Turnover Mediates Preferential Localization of Prostate Cancer in the Skeleton



CORRELATIONS BETWEEN BONE TURNOVER AND CLINICAL OUTCOME IN PATIENTS WITH BONE METASTASES FROM SOLID TUMORS (NO BPs)



Il riassorbimento osseo è anche mediato dal sistema immunitario



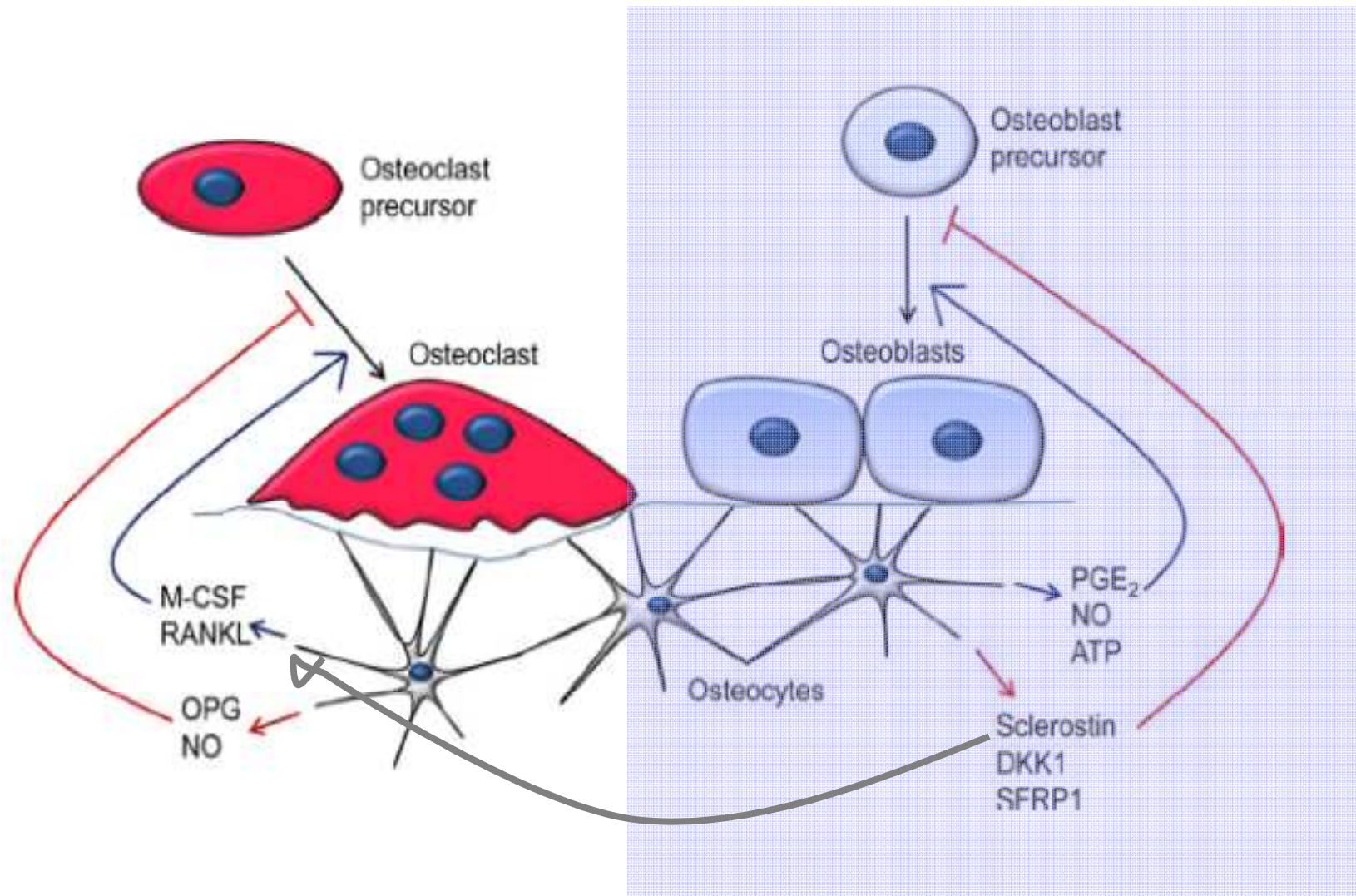
Linee Guida AIOM 2017

Bisfosfonati e denosumab in setting adiuvante

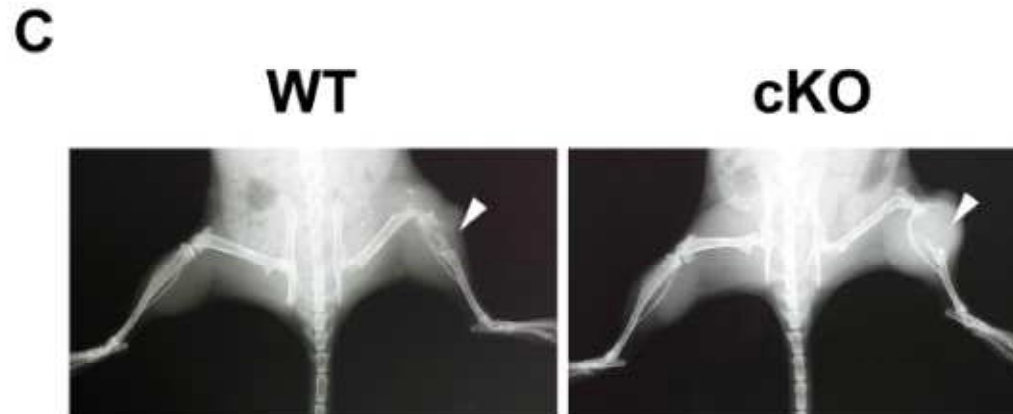
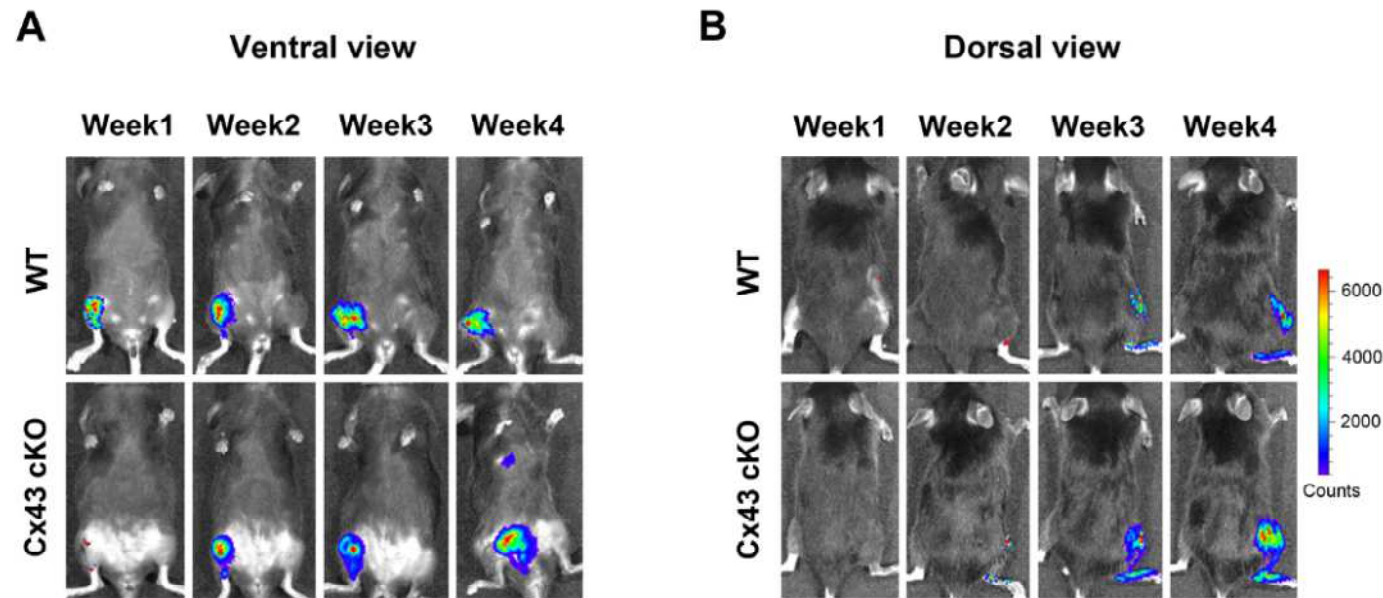
Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
B	Nei pazienti affetti da tumore prostatico e tumore polmonare, i bisfosfonati e il denosumab non devono essere utilizzati con l'obiettivo terapeutico di aumentare la sopravvivenza libera da malattia nel setting adiuvante	Negativa Forte
A	Nelle pazienti affetti da tumore mammario in fase post-menopausale, l'acido zoledronico o il clodronato dovrebbero essere considerati con l'obiettivo terapeutico di aumentare la sopravvivenza libera da malattia e di ridurre la mortalità nel setting adiuvante [13]	Positiva Forte

2. Osteocytes have an important role in bone turnover regulation and in the metastatization process

Functions of osteocytes



Osteocytic Connexin hemichannel suppress breast cancer growth and bone metastases



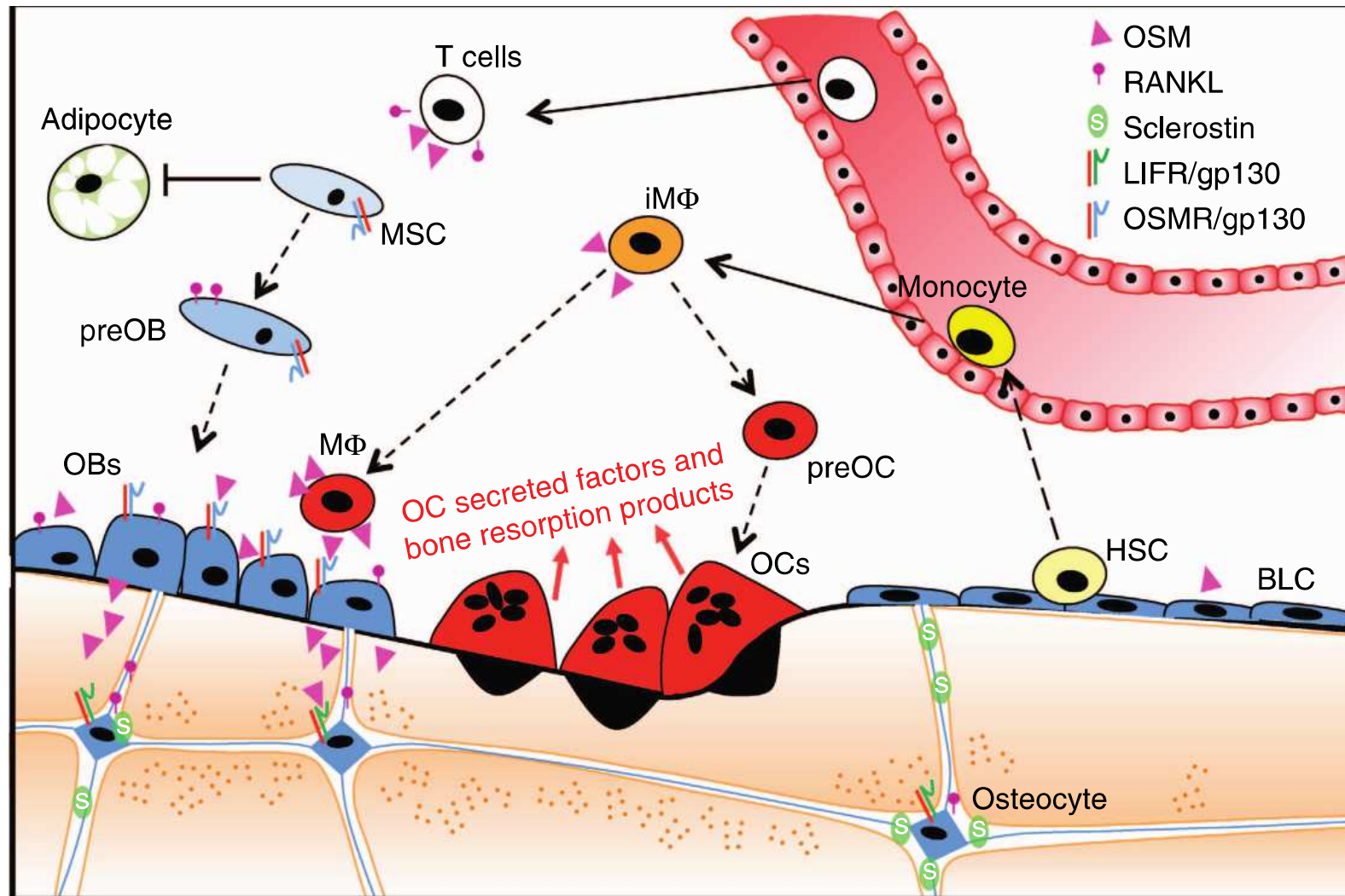
Osteocytes: take home messages

Connexin 43 (Cx43) is an endogenous bone anti-metastatic factor for cancer cells present in osteocytes.

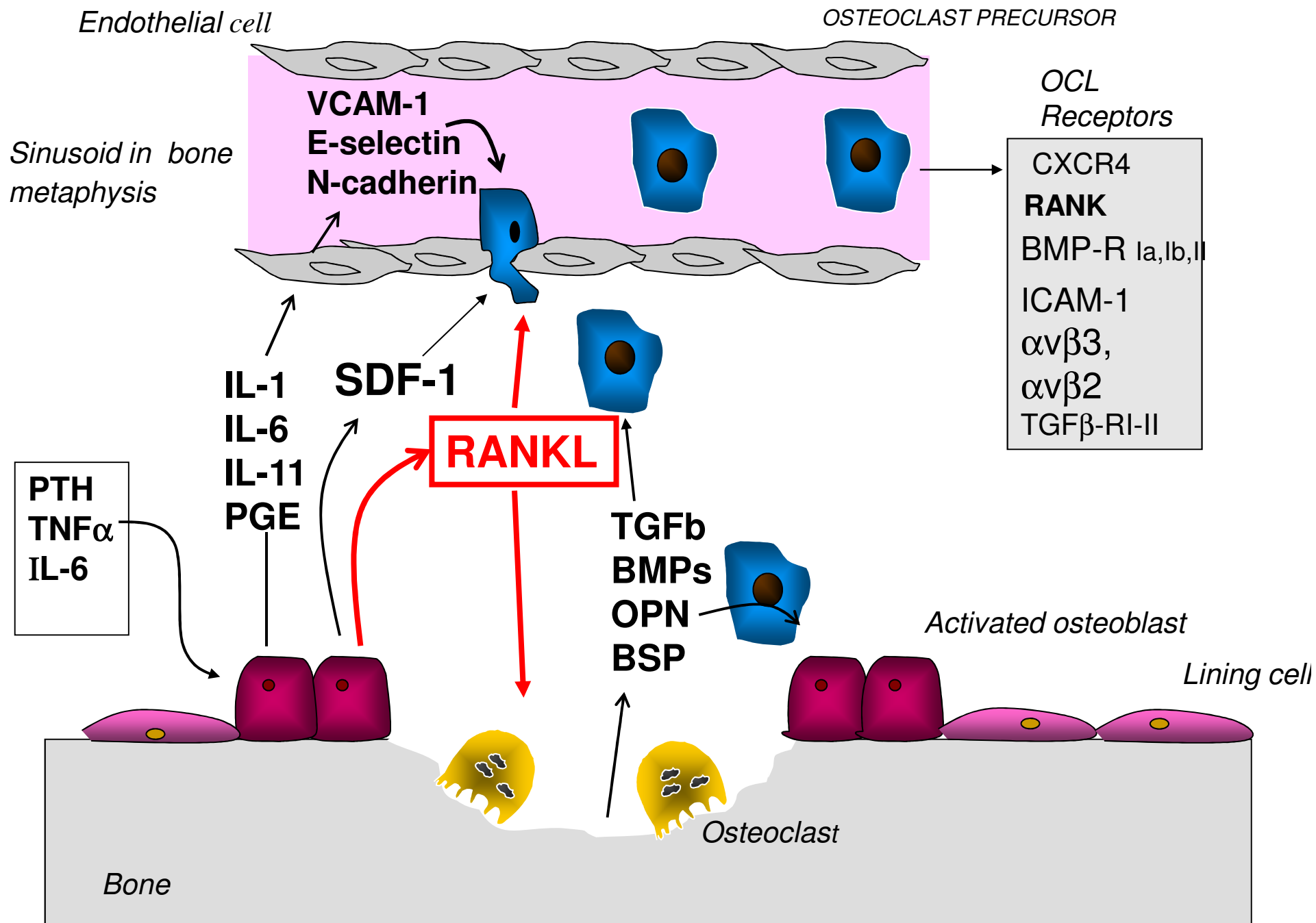
Osteocyte Cx43 proteins function as mechanosensitive hemichannels that release anti-metastatic molecules like ATP.

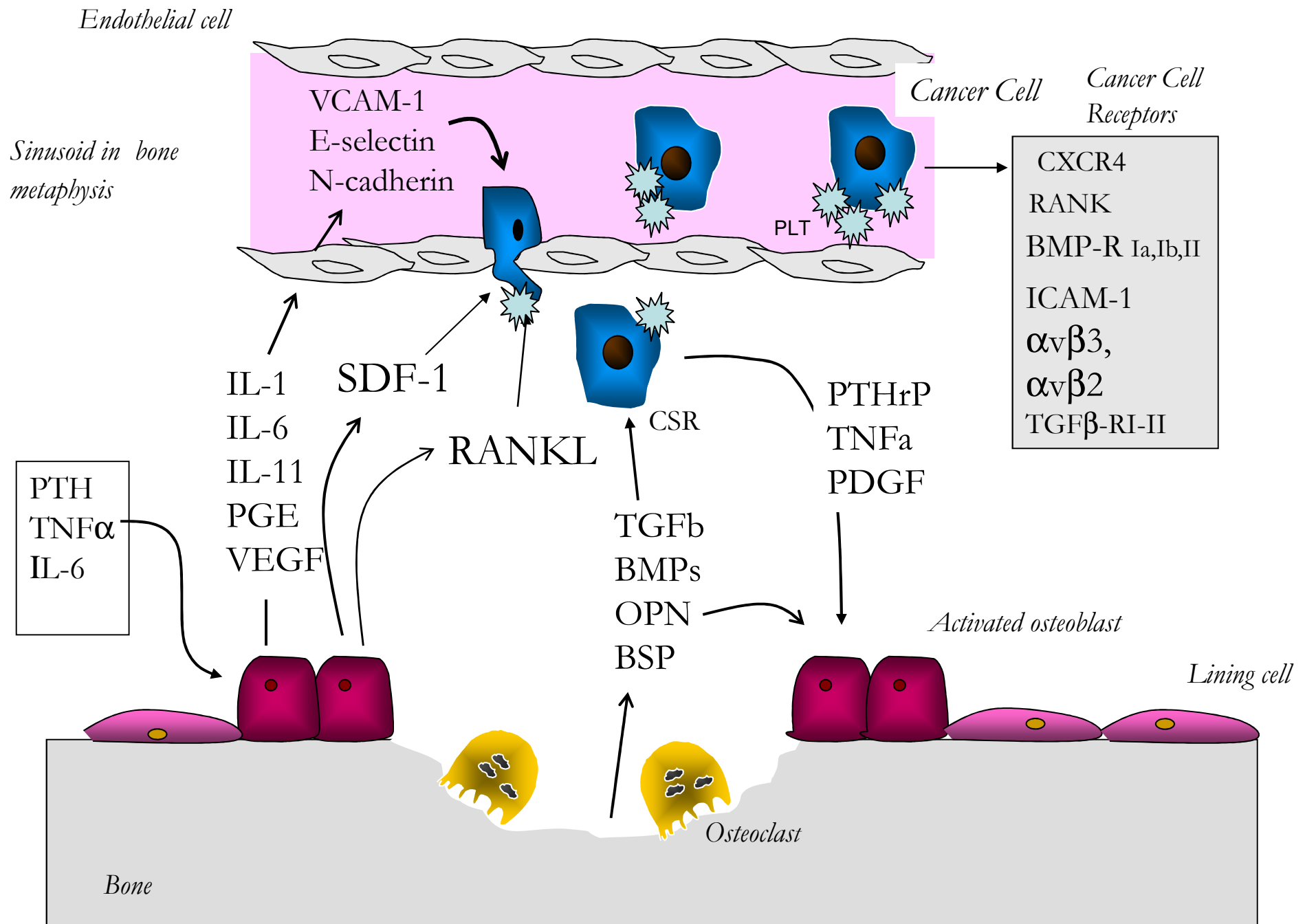
Activation of osteocyte Cx43 hemichannels by mechanical stimulation or bisphosphonate drugs suppresses bone metastases.

Interactions between osteocytes and immune cells



3. Osteoblasts have an important role in the bone homing of cancer cells

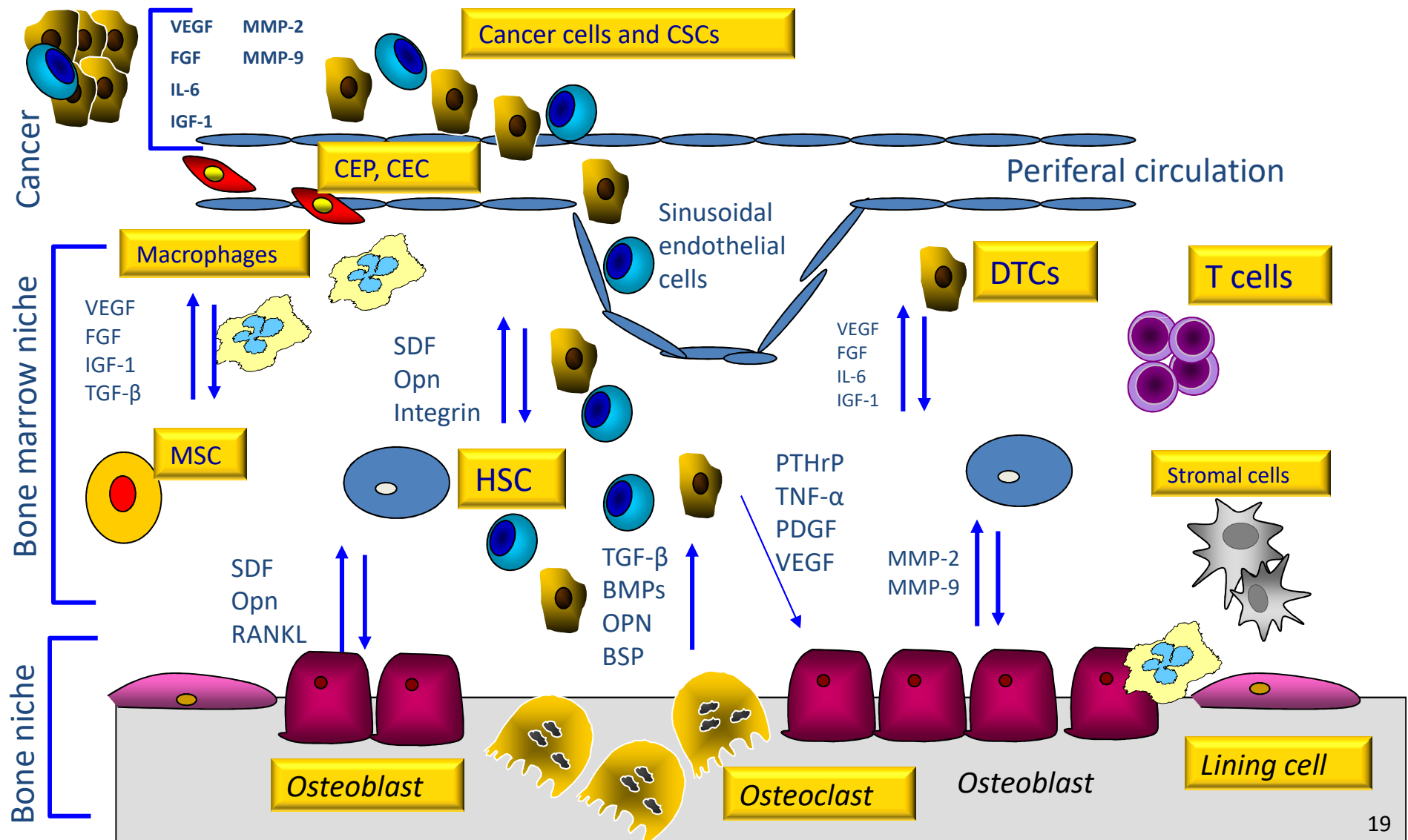




4. Role of bone microenvironment bone cells

Interactions between cancer cells and bone microenvironment cells

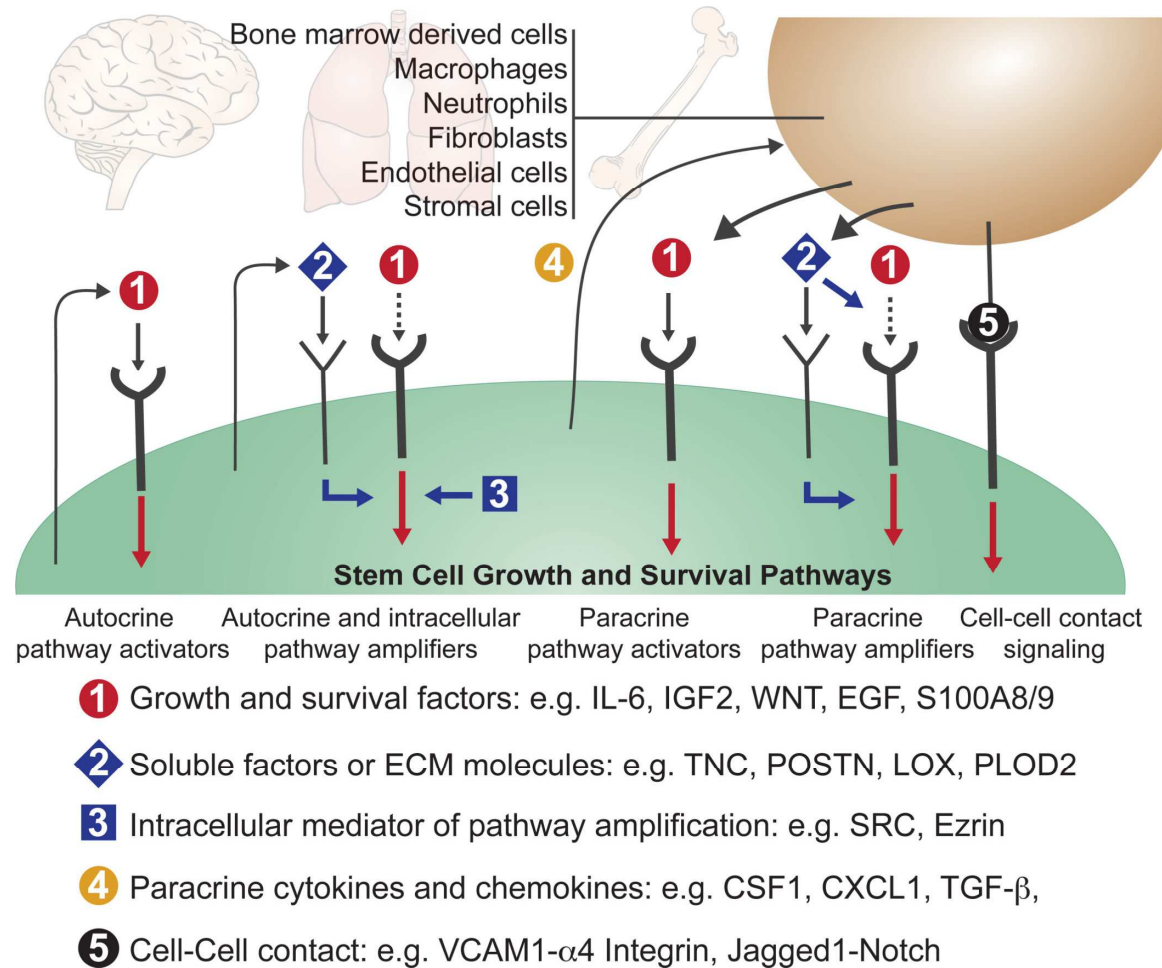
Modified from F. Bertoldo



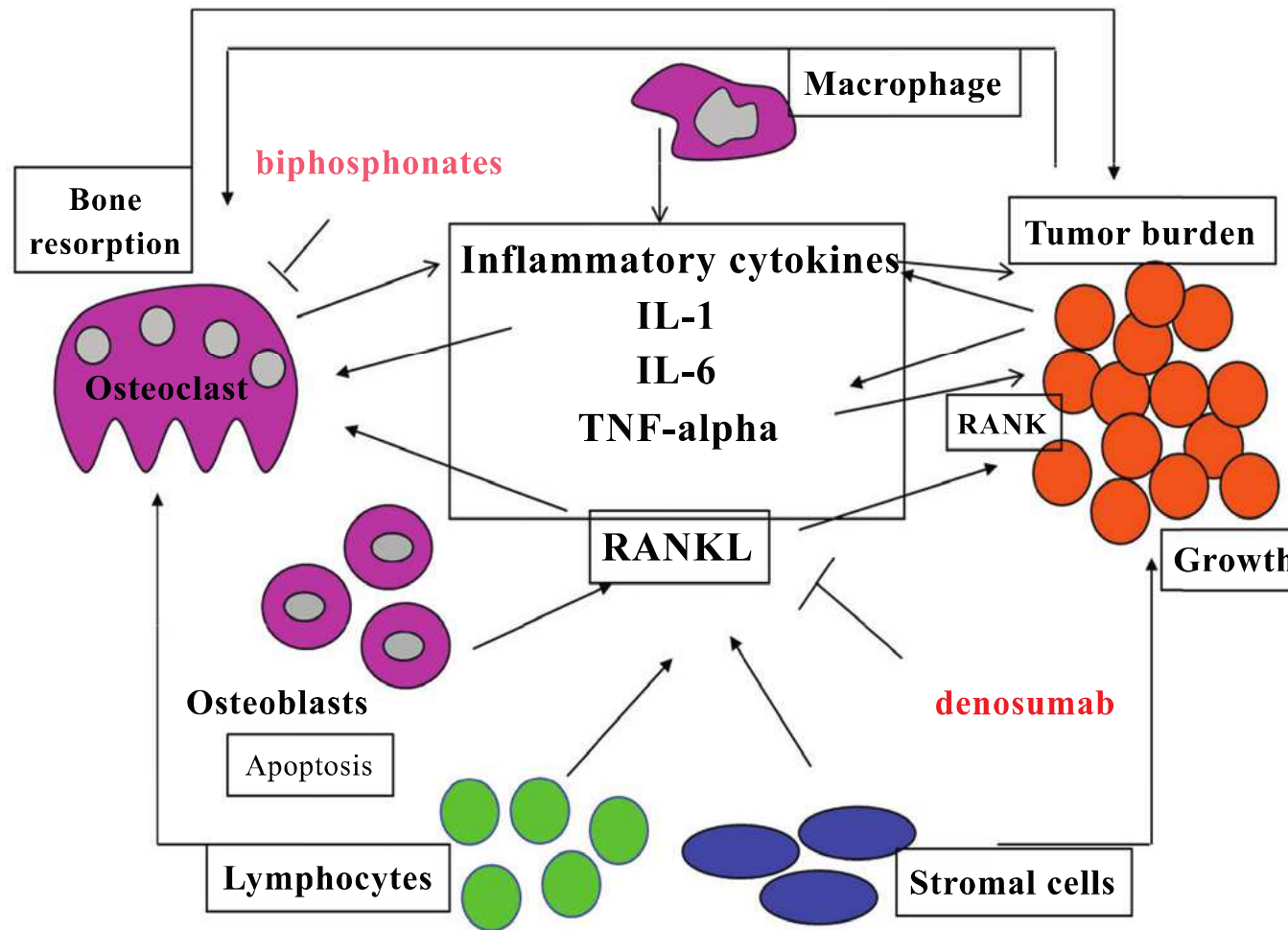
Molecular interactions between bone microenvironment and cancer cells

Massagué and Obenauf

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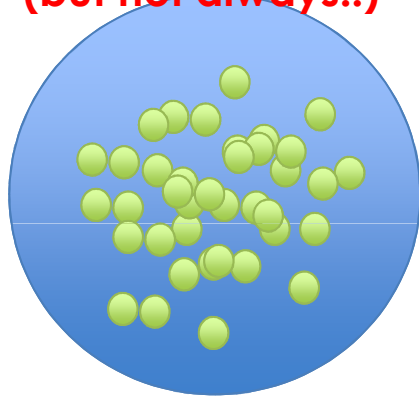


Le cellule del sistema immunitario interagiscono con osteoblasti, osteoclasti e cellule tumorali



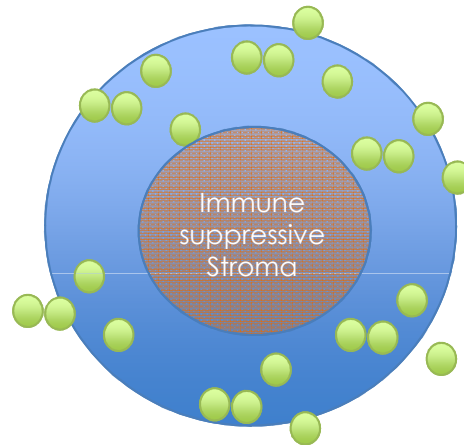
Ma non tutte le metastasi sono “calde

Immune-inflamed
more frequent response
(but not always!!)



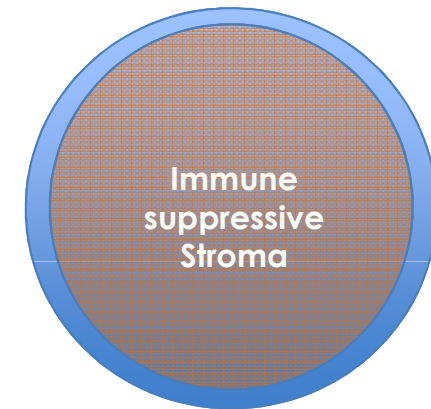
High tumor immogenicity
(high neoantigen load)
Low immune suppression
High PD-1/PDL-1 expression

Immune-excluded
possible response



tumor immogenicity?
immune suppression?
IC expression?

Immune-desert
quite rare/no response



Need for CTLA4 blockade
or vaccines or “mutational” therapies?

Low tumor immogenicity?
High immune suppression?
Low IC expression?

REVIEW

doi:10.1038/nature21349

**Elements of cancer immunity and
the cancer-immune set point**

Daniel S. Chen¹ & Ira Mellman¹

Nature 2017

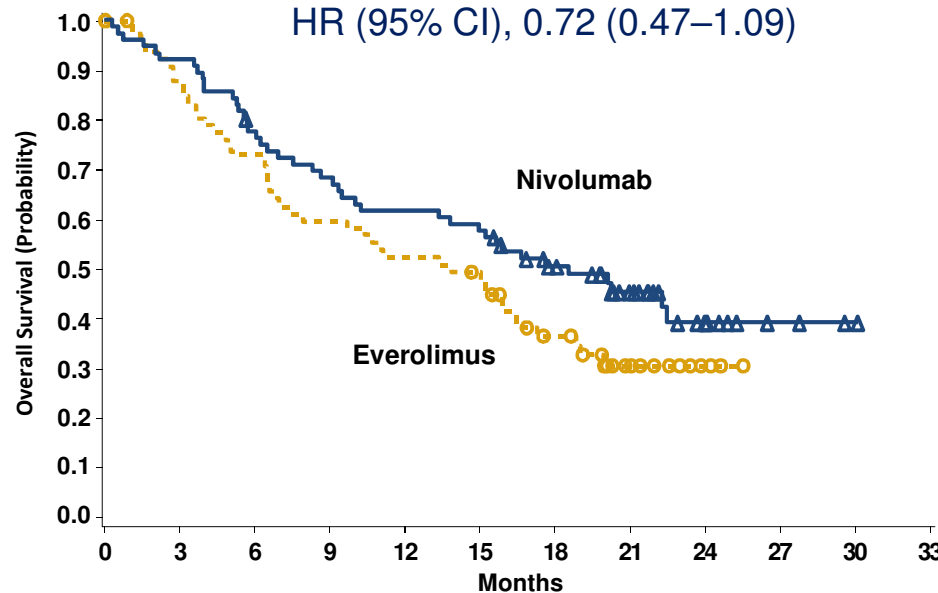
Courtesy of L. Rivoltini

OS: Bone and liver metastases

Bone

Median OS, months (95% CI)	
Nivolumab	18.5 (10.2–NE)
Everolimus	13.8 (7.0–16.4)

HR (95% CI), 0.72 (0.47–1.09)



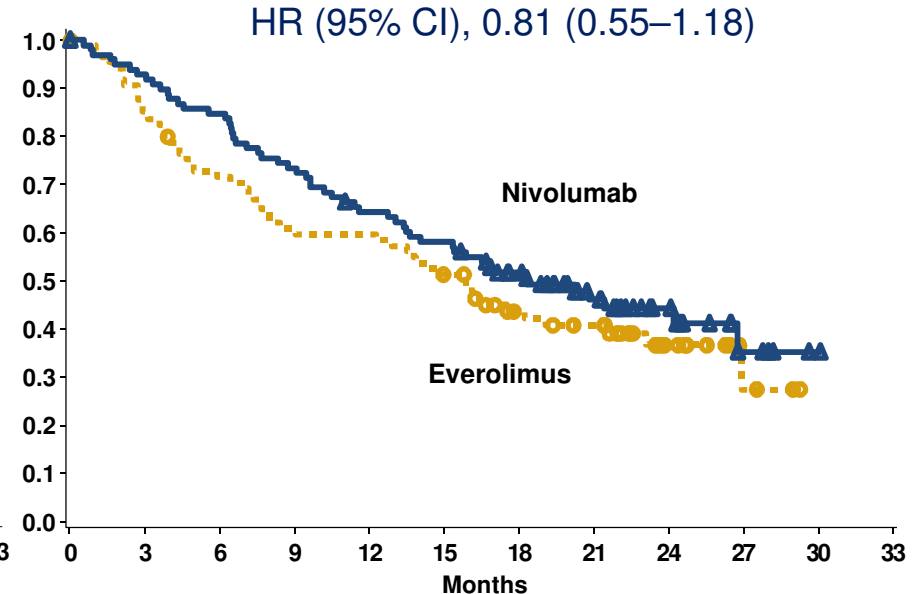
No. of patients at risk

Nivolumab	76	58	46	32	9	1
Everolimus	70	49	35	20	3	0

Liver

Median OS, months (95% CI)	
Nivolumab	18.3 (13.4–26.7)
Everolimus	16.0 (8.4–21.6)

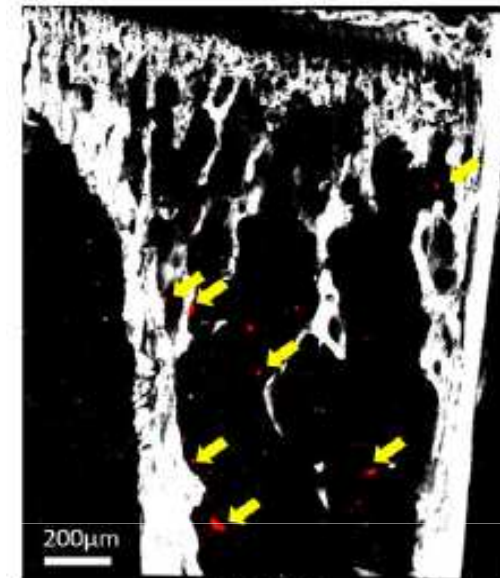
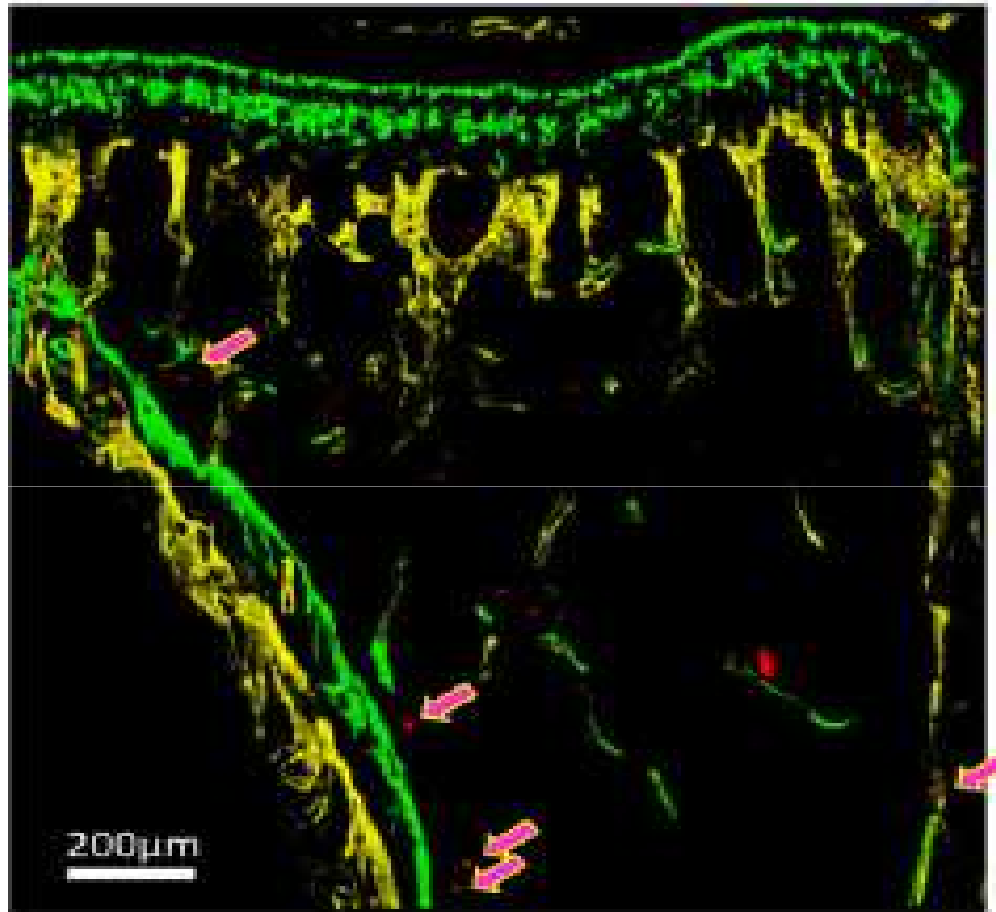
HR (95% CI), 0.81 (0.55–1.18)



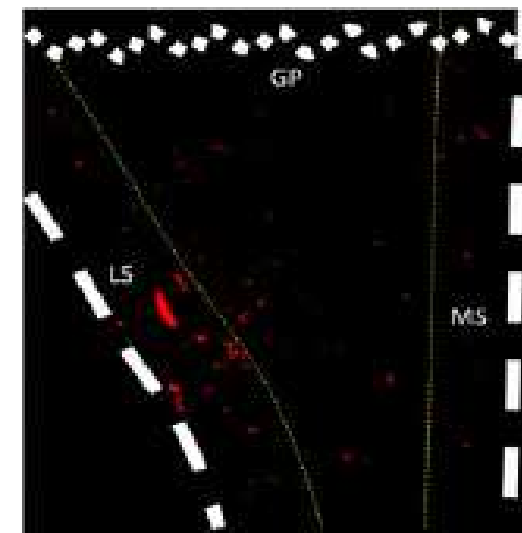
Nivolumab	100	83	62	43	15	1
Everolimus	87	60	50	30	11	0

5. Role of preneoplastic osteoblastic niche

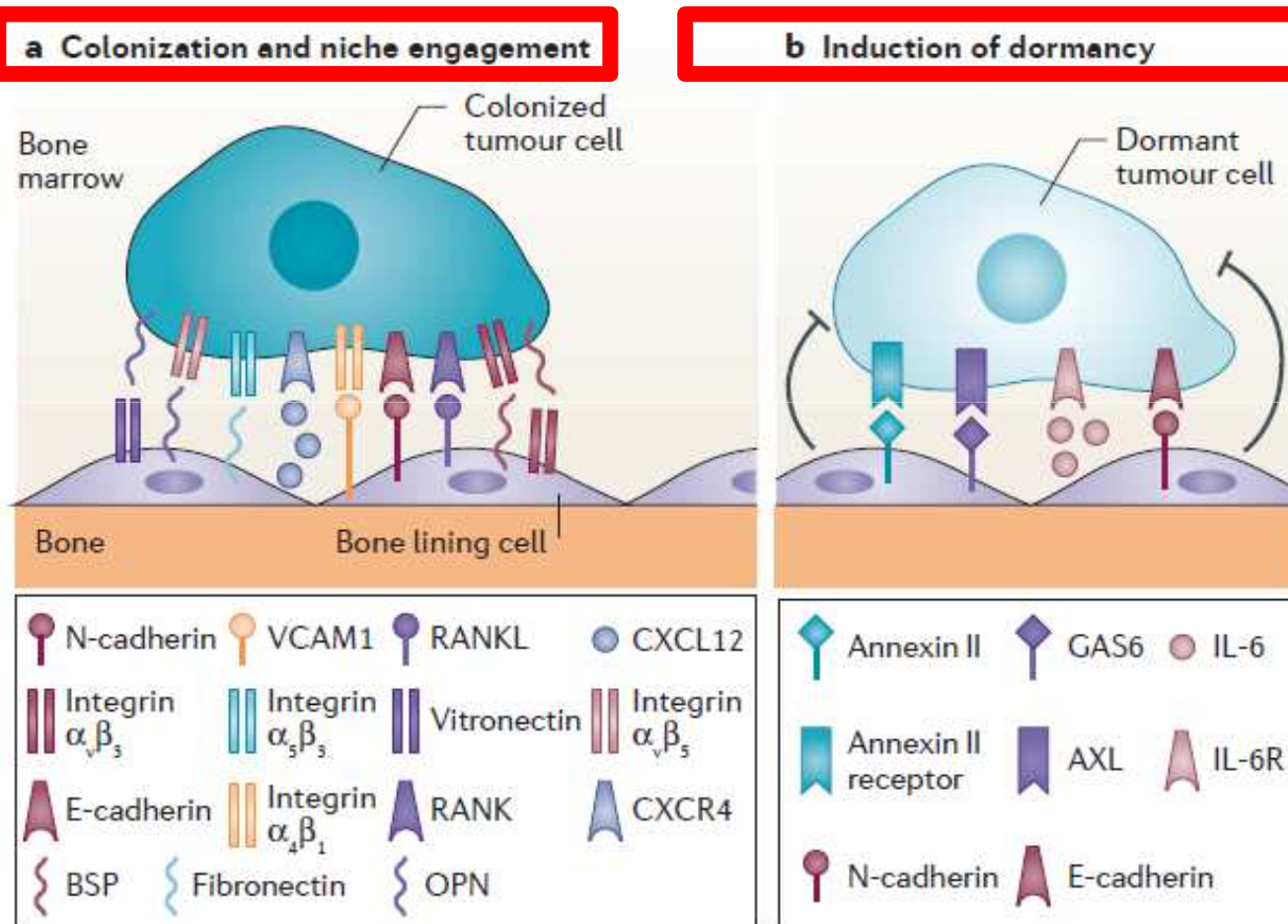
Prostate Cancer Cells Preferentially Home to Osteoblast-rich Areas in the Early Stages of Bone Metastasis: Evidence From In Vivo Models



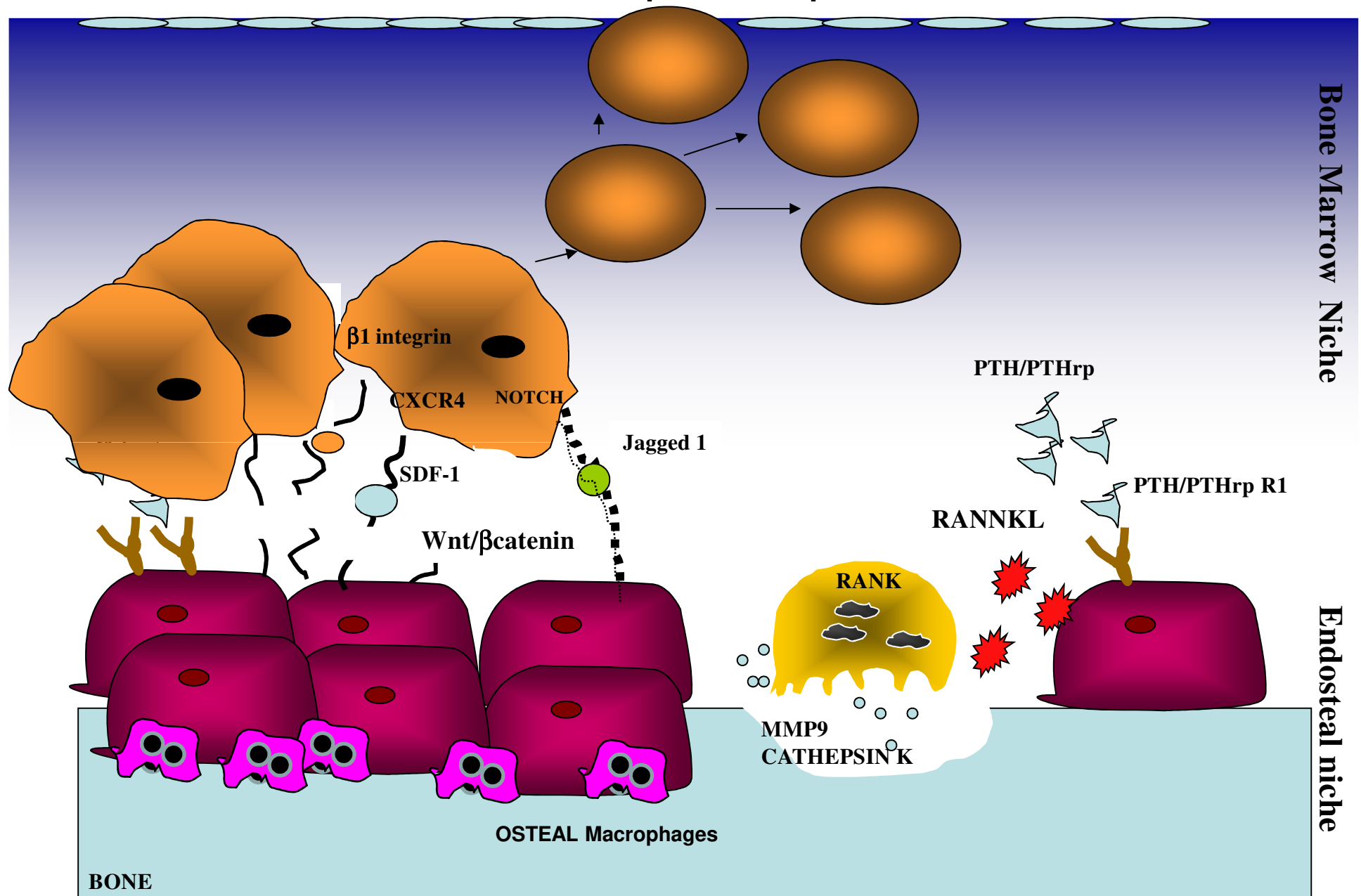
C4 2B4



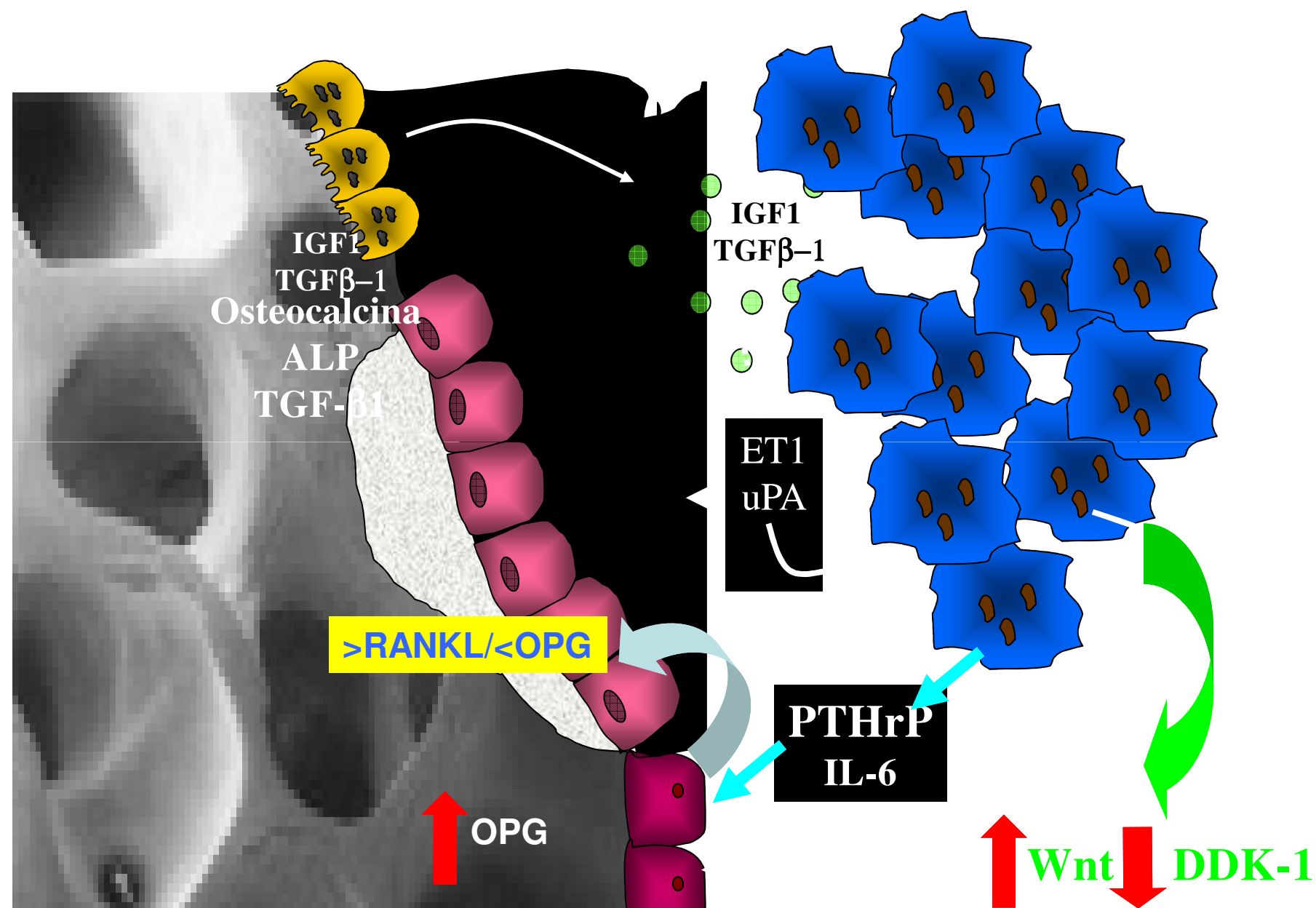
Osteoblasts regulate the cancer cell *fatus* in the preneoplastic niche



The osteoblastic preneoplastic niche



6. The vicious cycle in the “modern era”



Adapted from Bertoldo F, Santini D Textbook of Osteoncology 2010

....in summary

1. High bone turnover increases the risk of new bone metastases and of skeletal progression
2. The osteocytes have an important role in bone turnover regulation and in the metastatization process
3. The osteoblasts have an important role in the *bone homing* of cancer cells
4. The cells of bone microenvironment interact with the cancer cells (the new era of osteoimmunology)
5. The importance of preneoplastic osteoblastic niche
6. The vicious cycle in the “modern era”
7. Targeting immune system suppression can translate in targeting bone metastases

I believe in a “bone revolution”

- We moved from the “Seed and Soil” to the *preneoplastic niche* “era”: the cancer cells know where to go before homing bone and how to go away from the bone
- We moved from the osteoclast protagonist to multiple cells interactions in bone microenvironment: new cells, new targets, new drugs
- We moved from single molecular pathway to multiple molecular interactions in bone microenvironment: new pathways, new targets, new drugs

MAIN NATIONAL AND INTERNATIONAL RESEARCH COLLABORATIONS



Prof. Philippe Clézardin

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Prof. Robert E Coleman

- The University of Sheffield, Department of Oncology Sheffield, South Yorkshire, United Kingdom



Prof. Aleix Prat

- Vall D'HEBRON, Instituto de Oncologia, Barcelona



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Prof. Paolo Casali

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To our Translational Oncology Laboratory *Team*

Thank you for your Attention