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Bone Mets: Introduction

- Bone Mets are **common feature** of advanced cancer
- Are associated with significant **morbidity** and **mortality**
- About **90%** and **70%** of pts die of **prostate** and **breast Ca**, respectively, show bone mets at autopsy

Papachristou, personal files

Coleman RE, Clin Cancer Res 2006

Frequency of skeletal metastases at autopsy

Garcia et al, 2007

Tumour	Bone metastases (%)
Breast	**50-85**
Prostate	**60-85**
Lung	**32-64**
Kidney	33-60
Thyroid	28-60
Oesophagus	6
GI tract/colon	3-10
Rectum	8-60
Bladder	42
Uterine/cervix	50
Ovaries	9
Liver	16
Melanoma	7

Table 1. Molecular subtypes of breast cancer and bone metastasis.

Subtype	Pathological definition		Bone metastases rate (%)	
Luminal A	ER and /or PR positive; HER2 negative; Ki-67 low (<14%)		66.6	(2.2 yrs)
Luminal B	Luminal B1	ER and /or PR positive; HER2 negative Ki-67 high (>14%)	71.4	(1.6 yrs)
	Luminal B2	ER and/or PR positive; HER2 positive Any Ki-67	65	(1.3 yrs)
HER2(+)	HER2 overexpression (non-luminal); ER/PR absent		59.6	(0.7 yrs)
Basal-like	ER and/or PR negative; HER2 negative EGFR positive and/or CK5/6 positive		39	(0.5 yrs)
Triple-negative	ER and/or PR negative; HER2 negative EGFR positive and/or CK5/6 negative		43.1	(0.9 yrs)

Yang, 2019; Chen et al, 2018

What the heck is “wrong” with bone?
(or…the “seed and soil” theory revisited)

“Traveling” towards and “docking to” bone

- **1889: Stephen Paget: “Seed and Soil” Theory**
- 1940: Blood flow is increased to BM (Batson’s plexus)
- BM sinusoids?
- Focusing on the role of metastatic tumor cells
- **2000s: Seed and soil theory revisited**

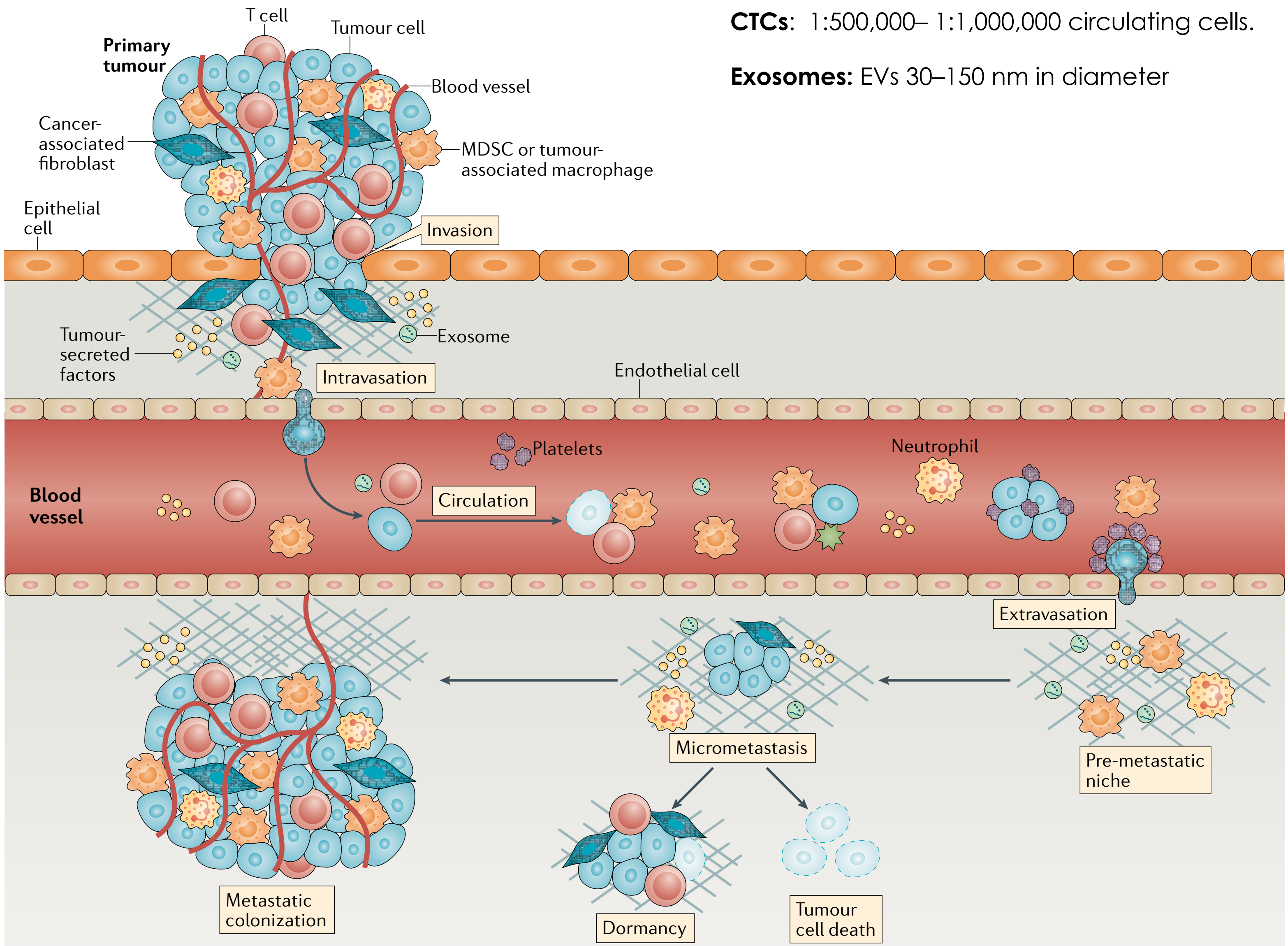
Papachristou et al, Med Res Rev 2012

"The best work in the pathology of cancer now is done by those who are studying the nature of the seed. They are like scientific botanists, and he who turns over the records of cases of cancer is only a ploughman, but his observations of the properties of the soil might also be helpful"

St. Paget, 1889

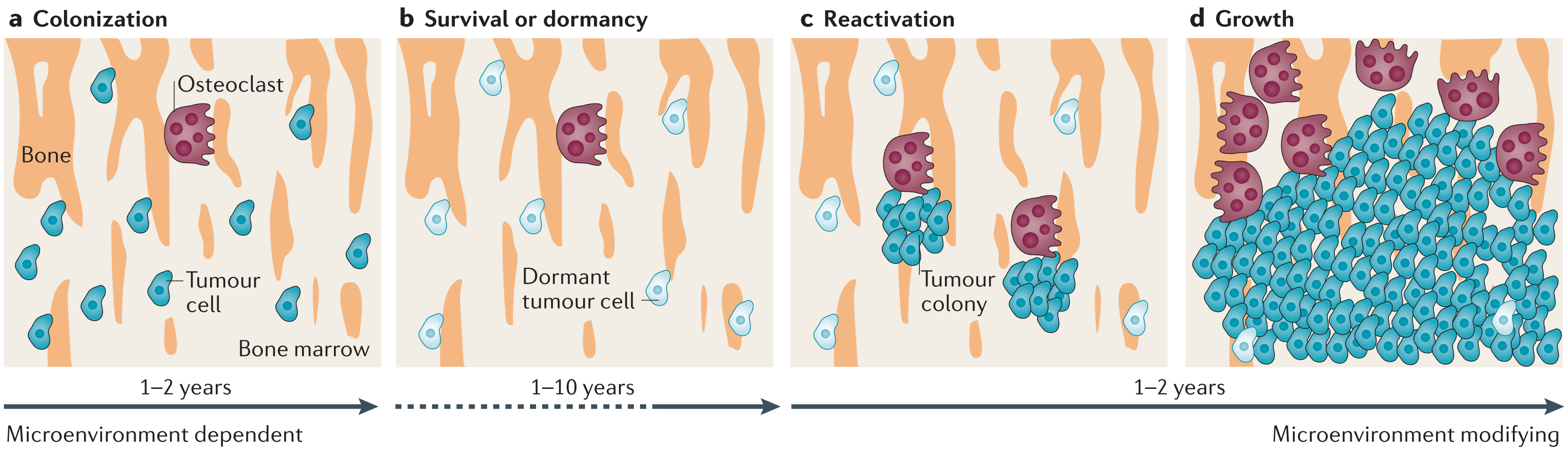
CTCs: 1:500,000– 1:1,000,000 circulating cells.

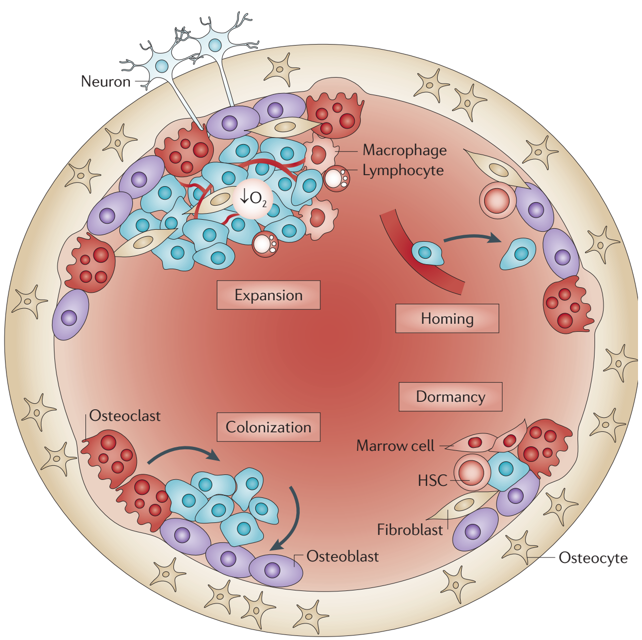
Exosomes: EVs 30–150 nm in diameter

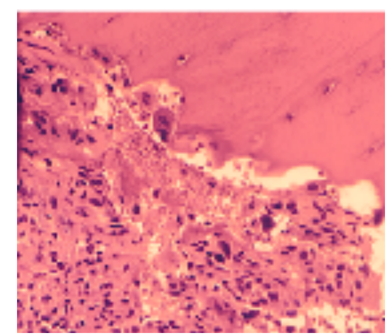


Anderson et al. Nat Rev Clin Oncol 2019

From BM Colonization to Overt Metastasis: a long-lasting road trip







Johnson & Suva, Calcf Tis Int, 2018

Croucher et al. Nat Rev Cancer 2016

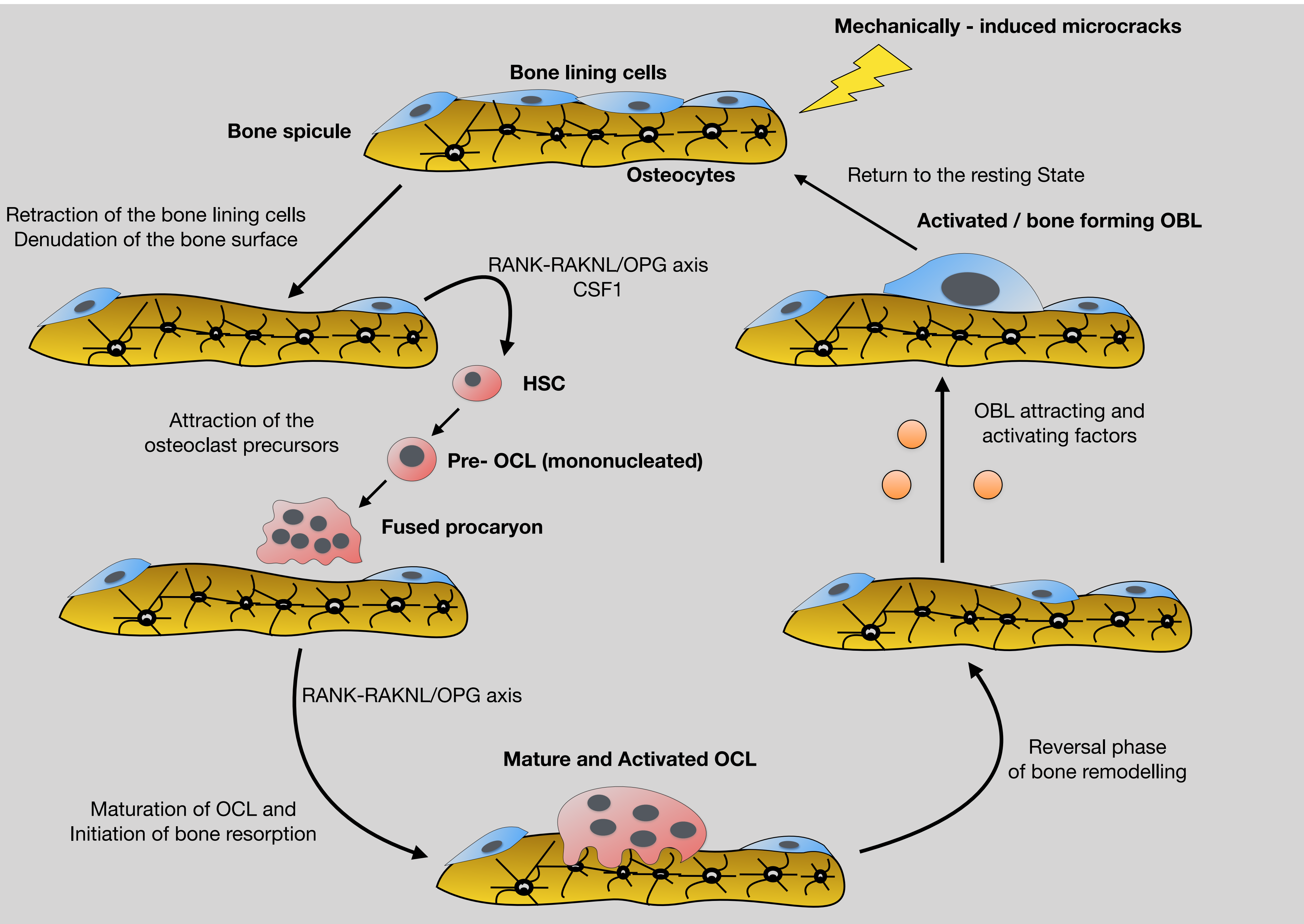
Molecular “Dissection” of Bone Metastases

Bone Remodeling

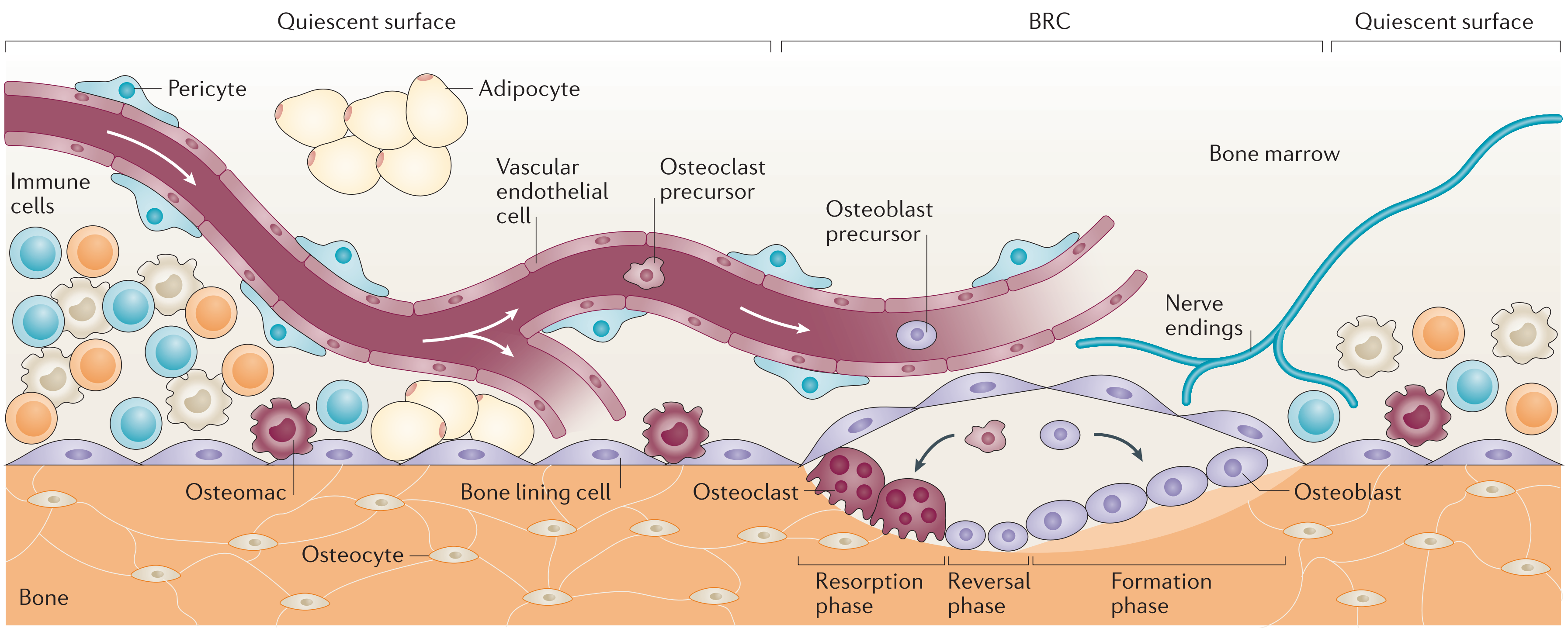
Cells of bone

- Osteoprogenitors
- **Osteoblasts**
- Osteocytes
- **Lining cells**
- **Osteoclasts**

Papachristou personal archive



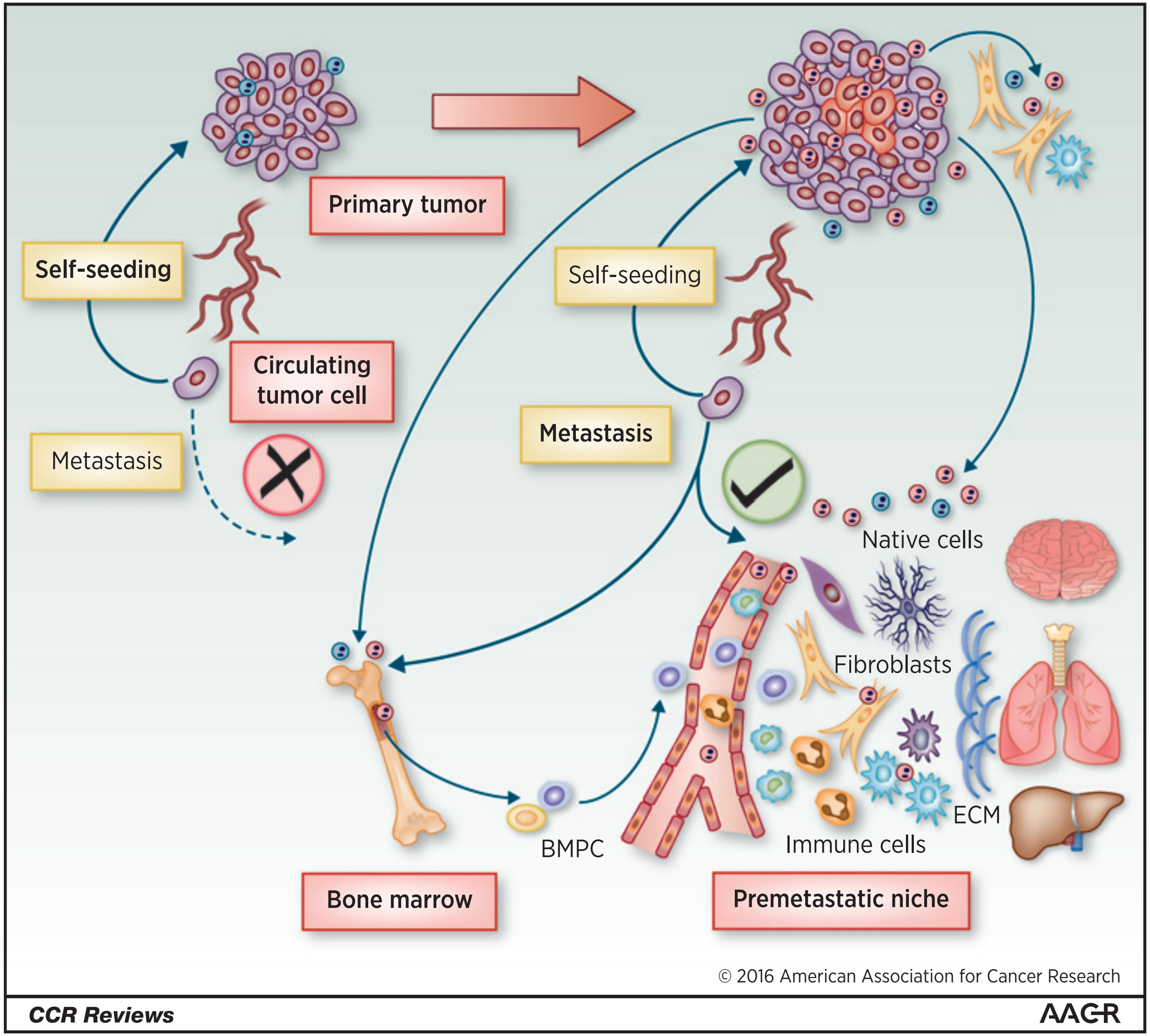
Papachristou et al, JCS 2021 (IN PRESS)



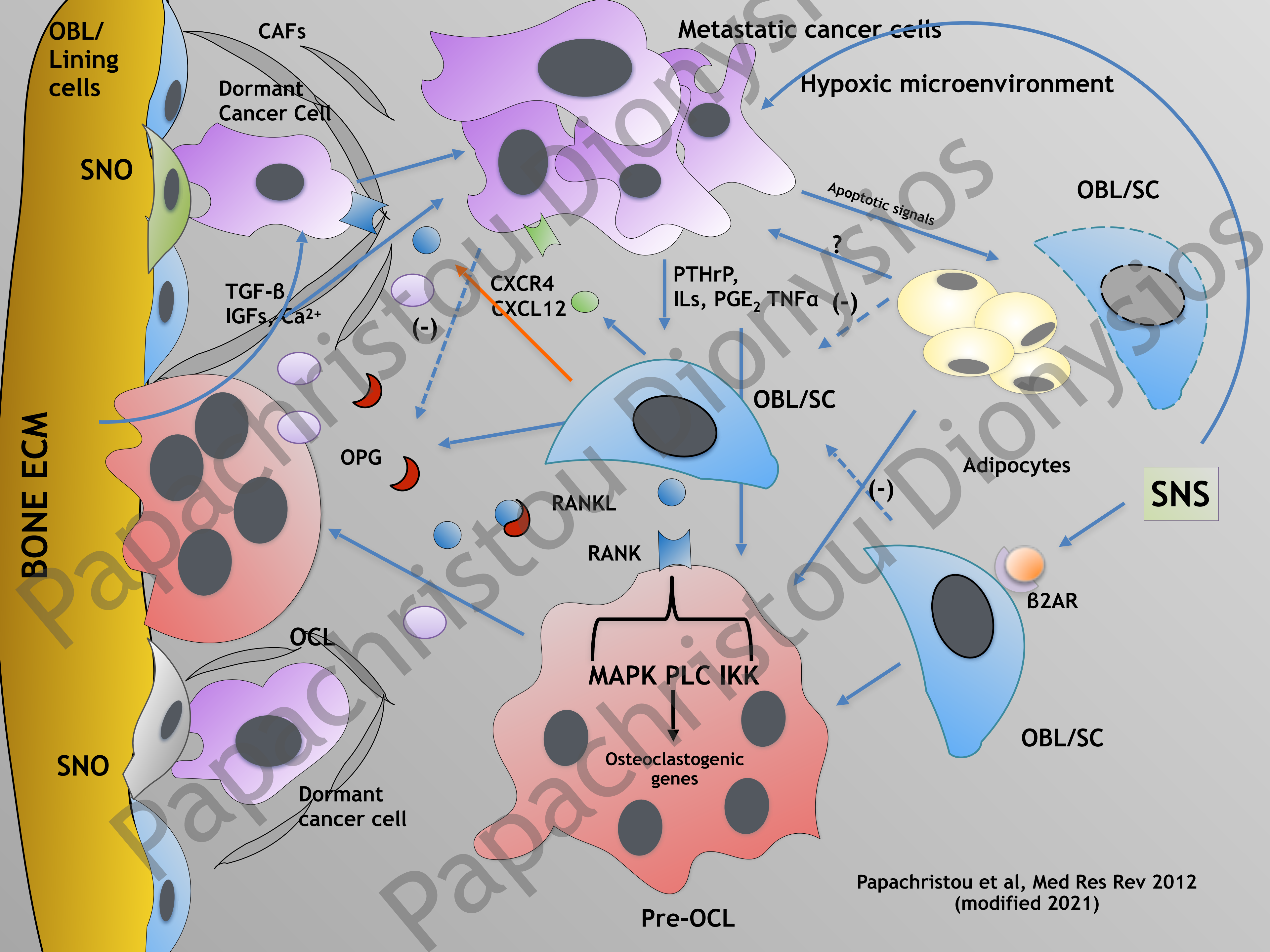
Croucher, Nat Rev Ca, 2016

Pathobiology of Osteolytic Bone Metastases

Kontogeorgakos V, Korompilias A and Papachristou D.J, Hand Microsurg 2011

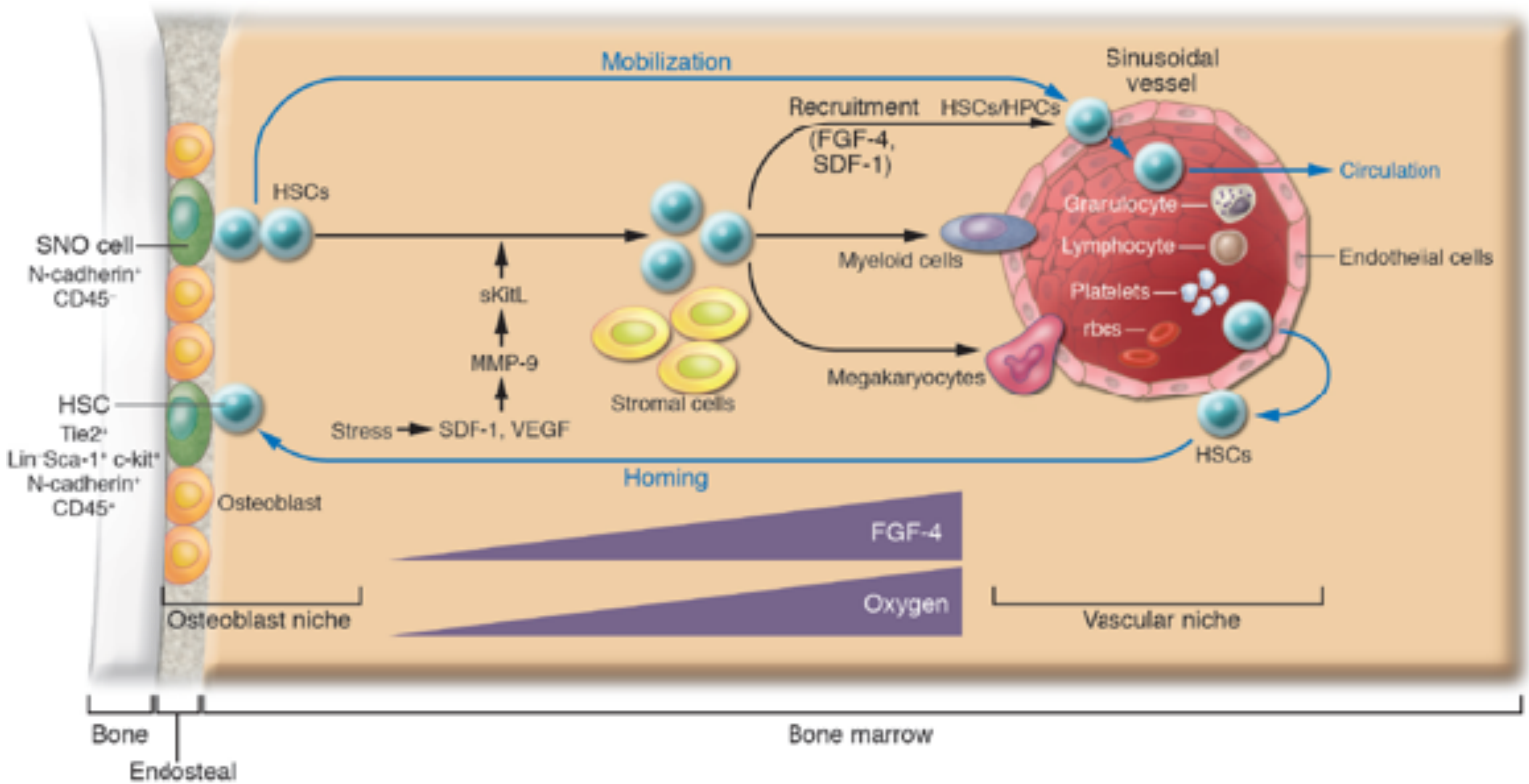


Chin and Wang, Clin Cancer Res 2017



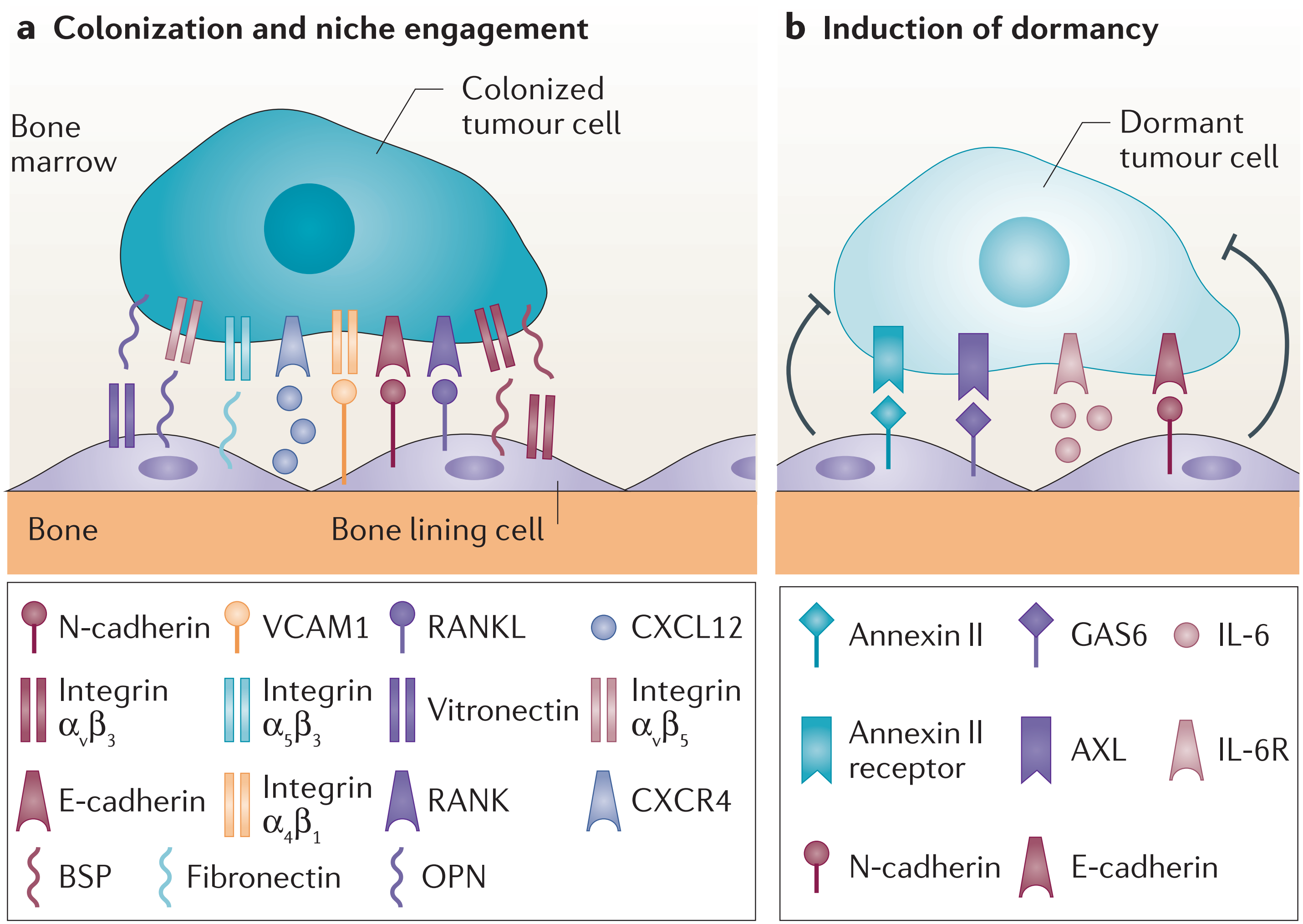
OBL/ Lining cells
CAFs
Metastatic cancer cells
Hypoxic microenvironment
Dormant Cancer Cell
SNO
Apoptotic signals
OBL/SC
?
TGF-β IGFs, Ca^{2+}
CXCR4 CXCL12
PTHrP, ILs, PGE_2 TNFα
(-)
(-)
OBL/SC
BONE ECM
OPG
Adipocytes
(-)
SNS
RANKL
RANK
β2AR
OCL
MAPK PLC IKK
Osteoclastogenic genes
OBL/SC
SNO
Dormant cancer cell
Pre-OCL
Papachristou et al, Med Res Rev 2012 (modified 2021)

Bone Marrow: A "love nest" where bone and HSCs meet



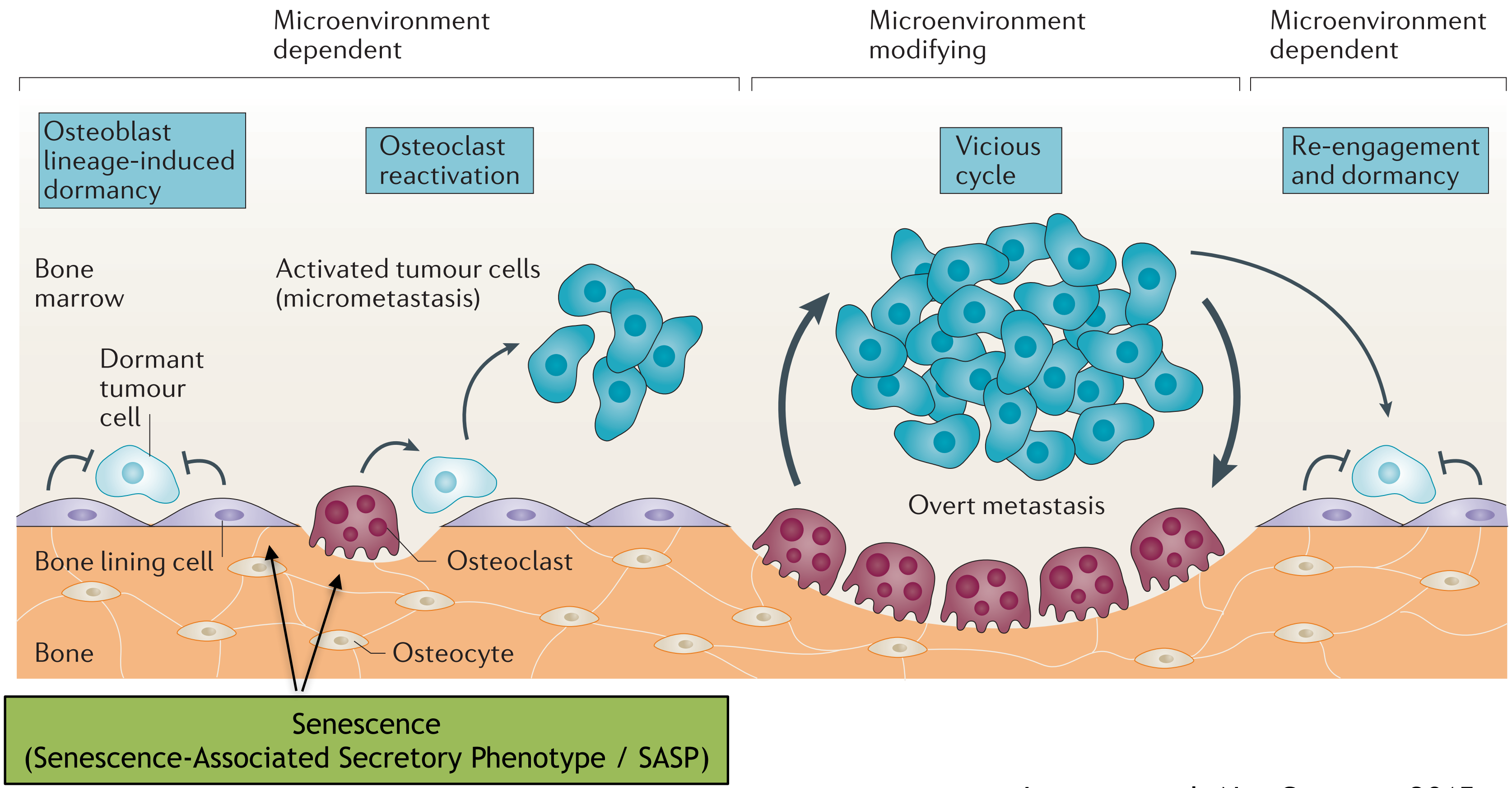
Yin and Li, 2006, Pantel Davos CIBD meeting 2010

Niche Engagement and Induction of Dormancy



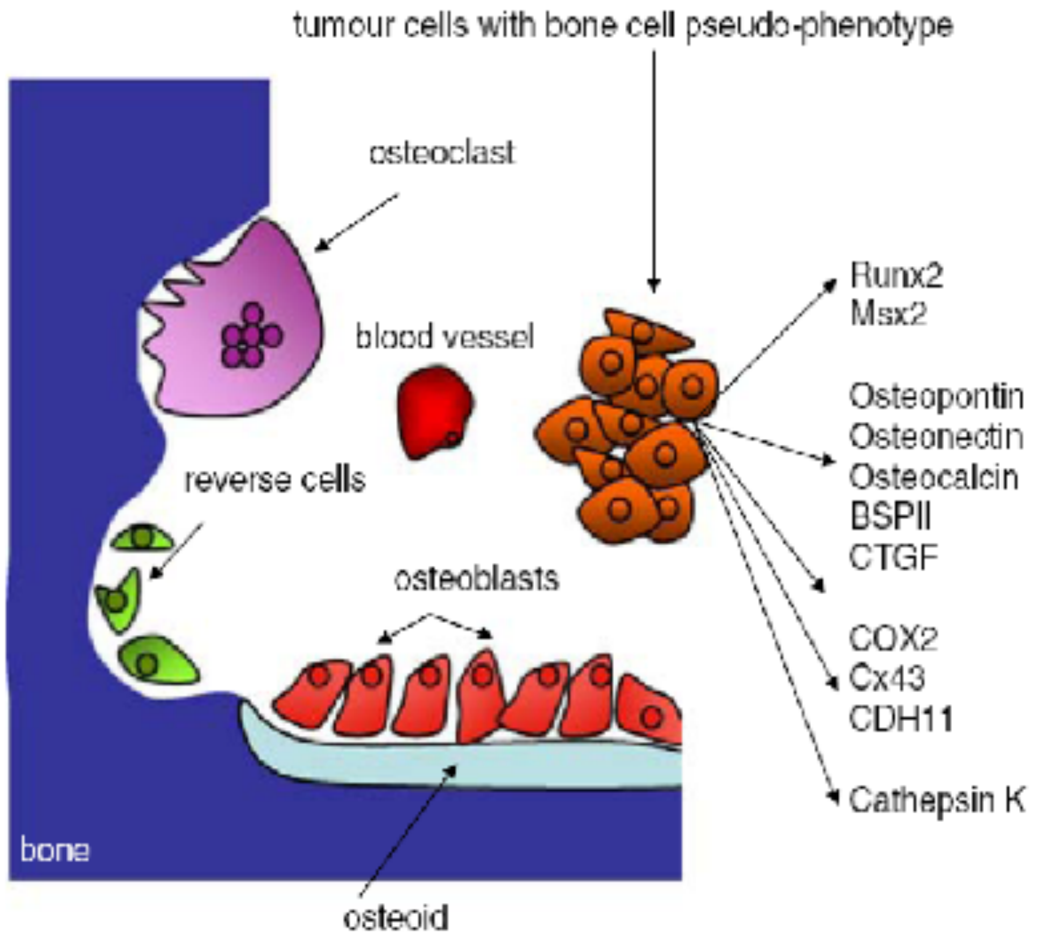
Wang et al, Cancer Cell 2015
Croucher et al. Nat Rev Cancer 2016

Emerge of Tumor Cells from Dormancy and Metastasis Overgrowth:
The Dual Role of OCL

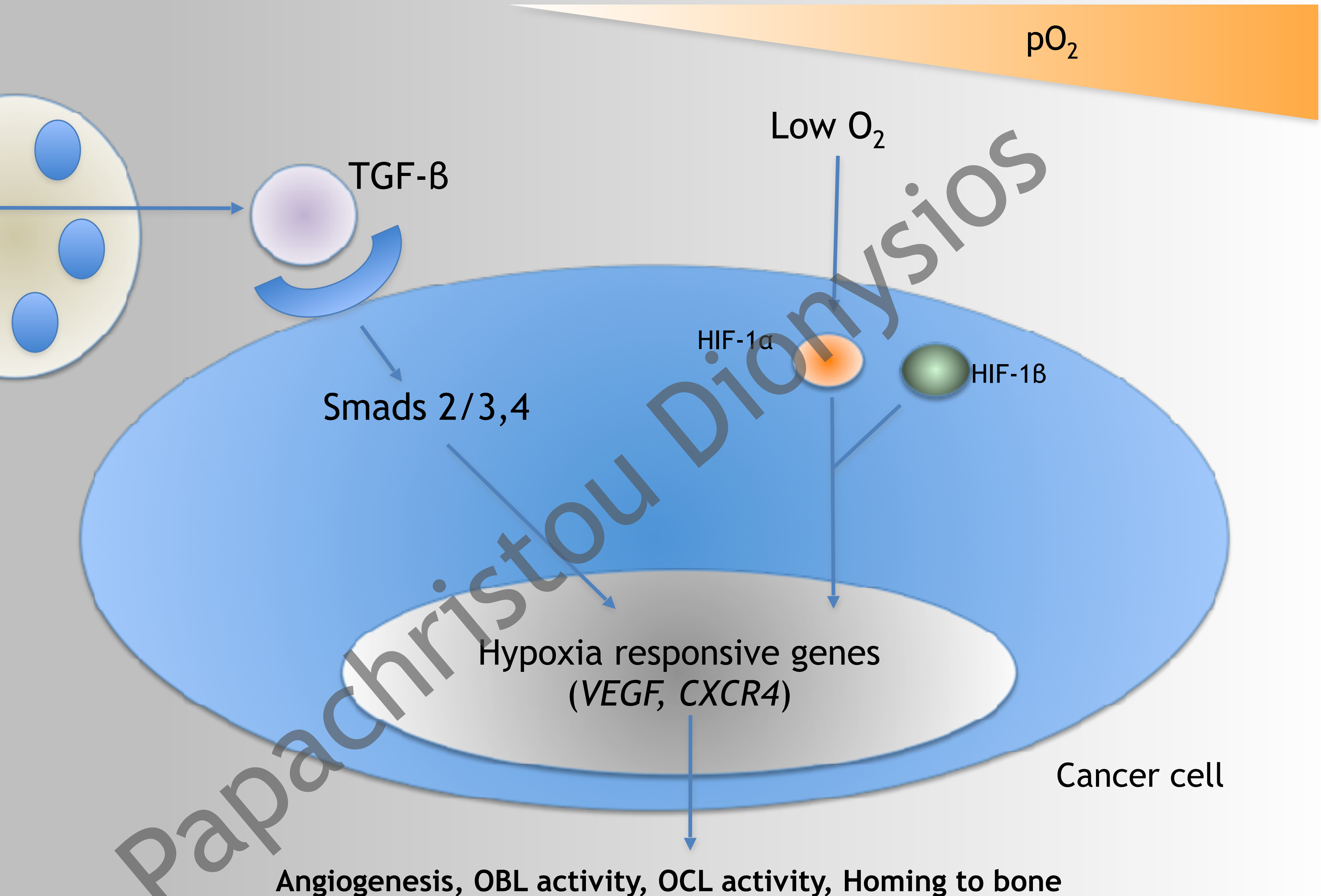


Lawson et al, Nat Commun 2015
Croucher et al. Nat Rev Cancer 2016

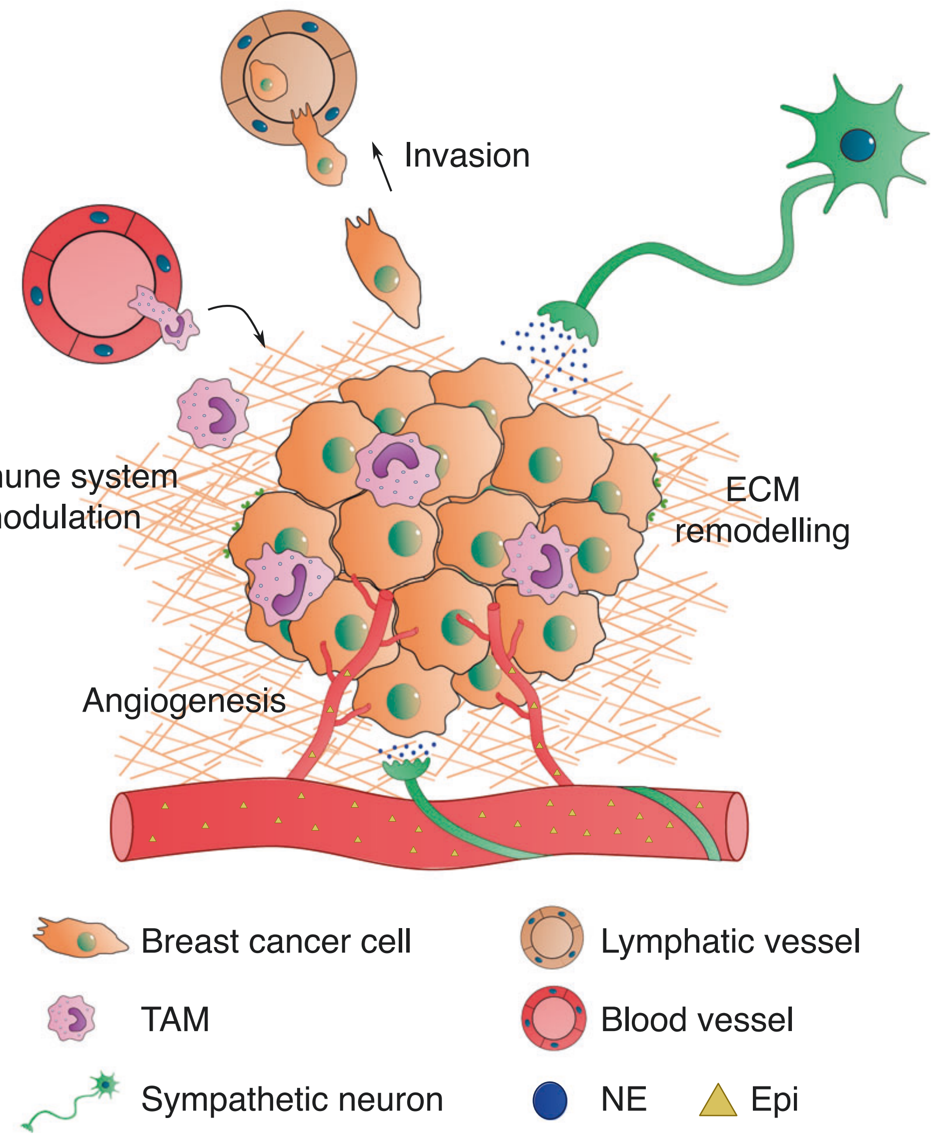
The Concept of Osteomimicry



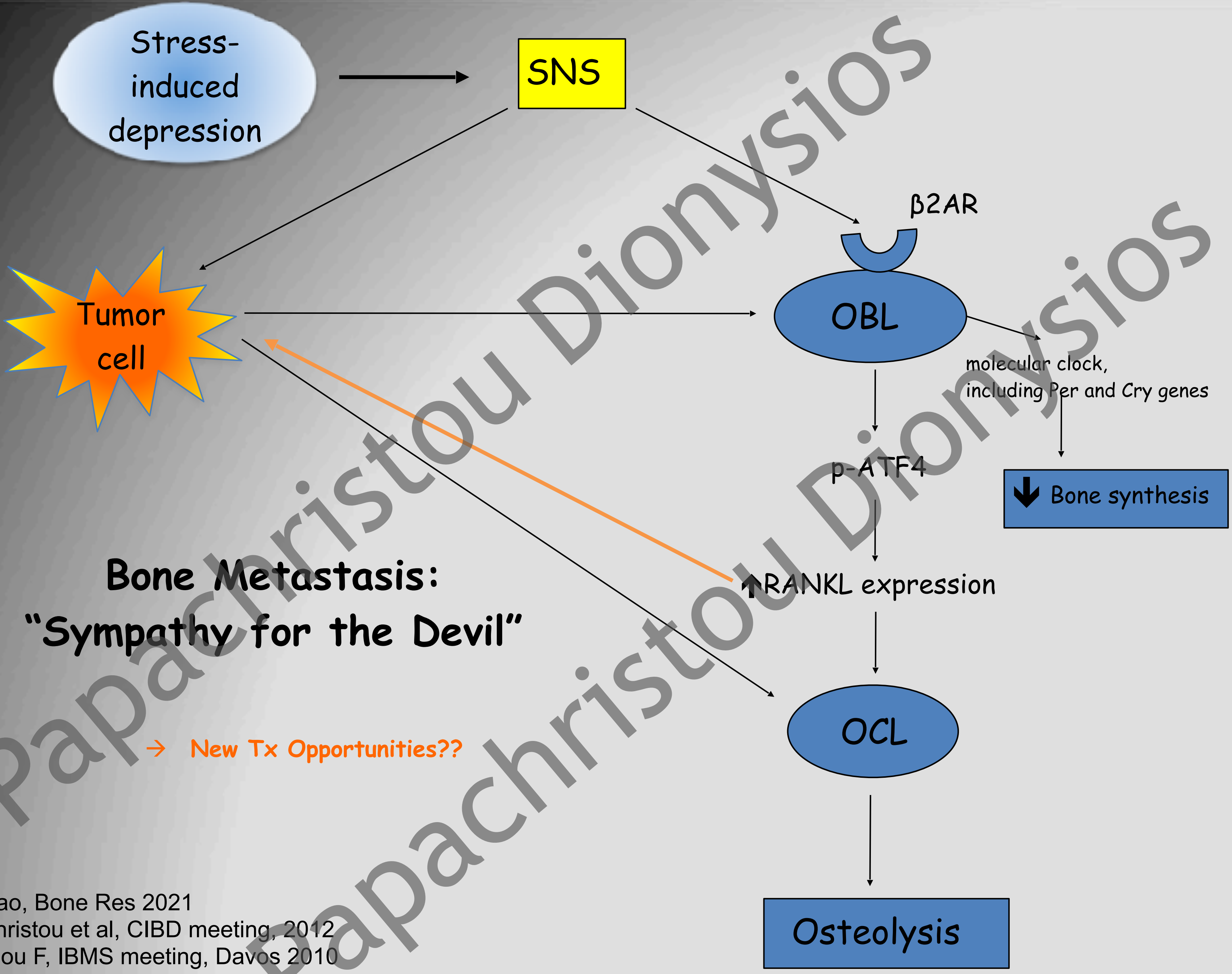
Clezardin and Teti, 2008



Papachristou, 2010; Knowls et al, Abstract Davos 2010



Conceicao, Bone Res 2021



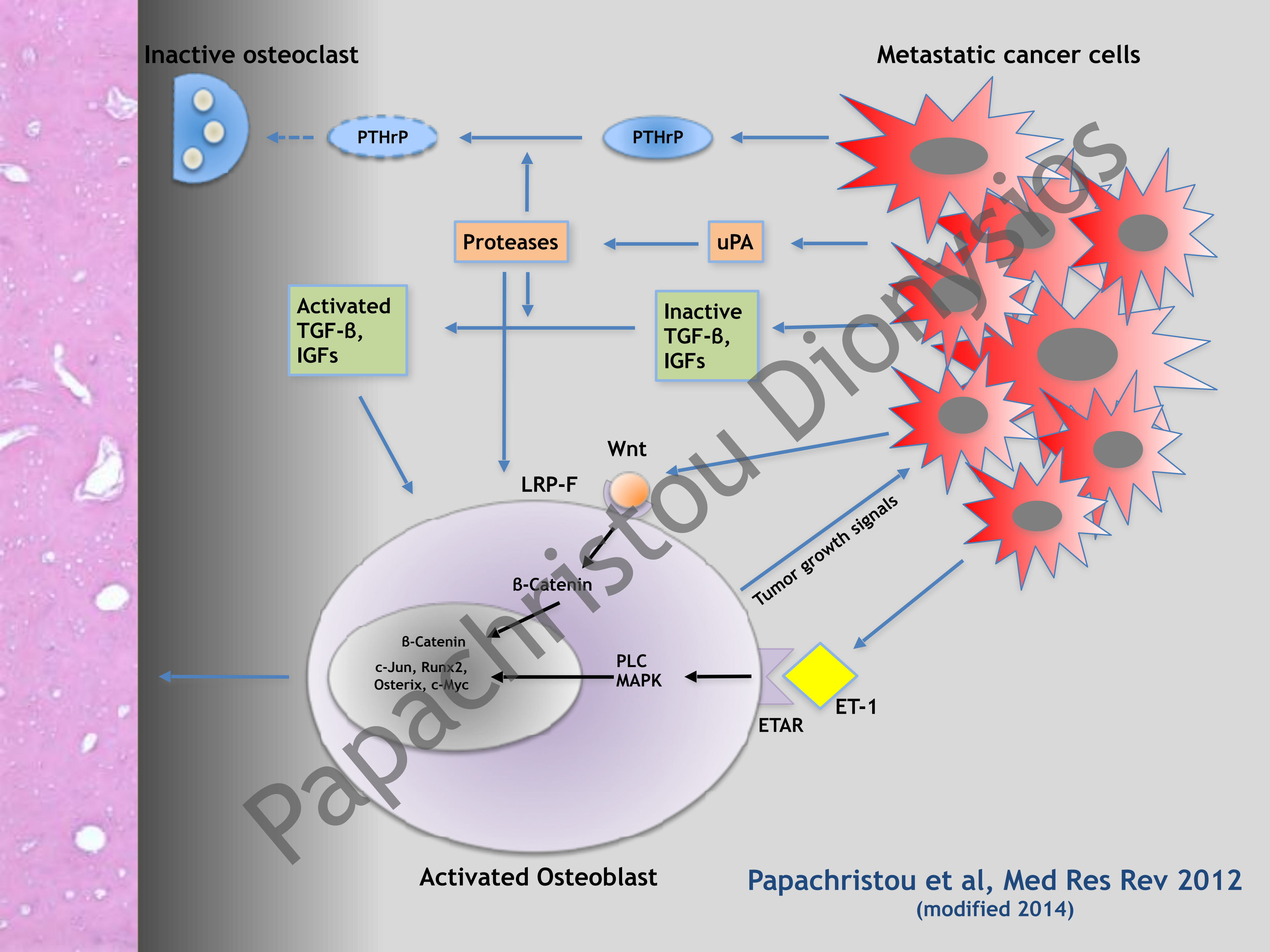
Bone Metastasis:
"Sympathy for the Devil"

→ New Tx Opportunities??

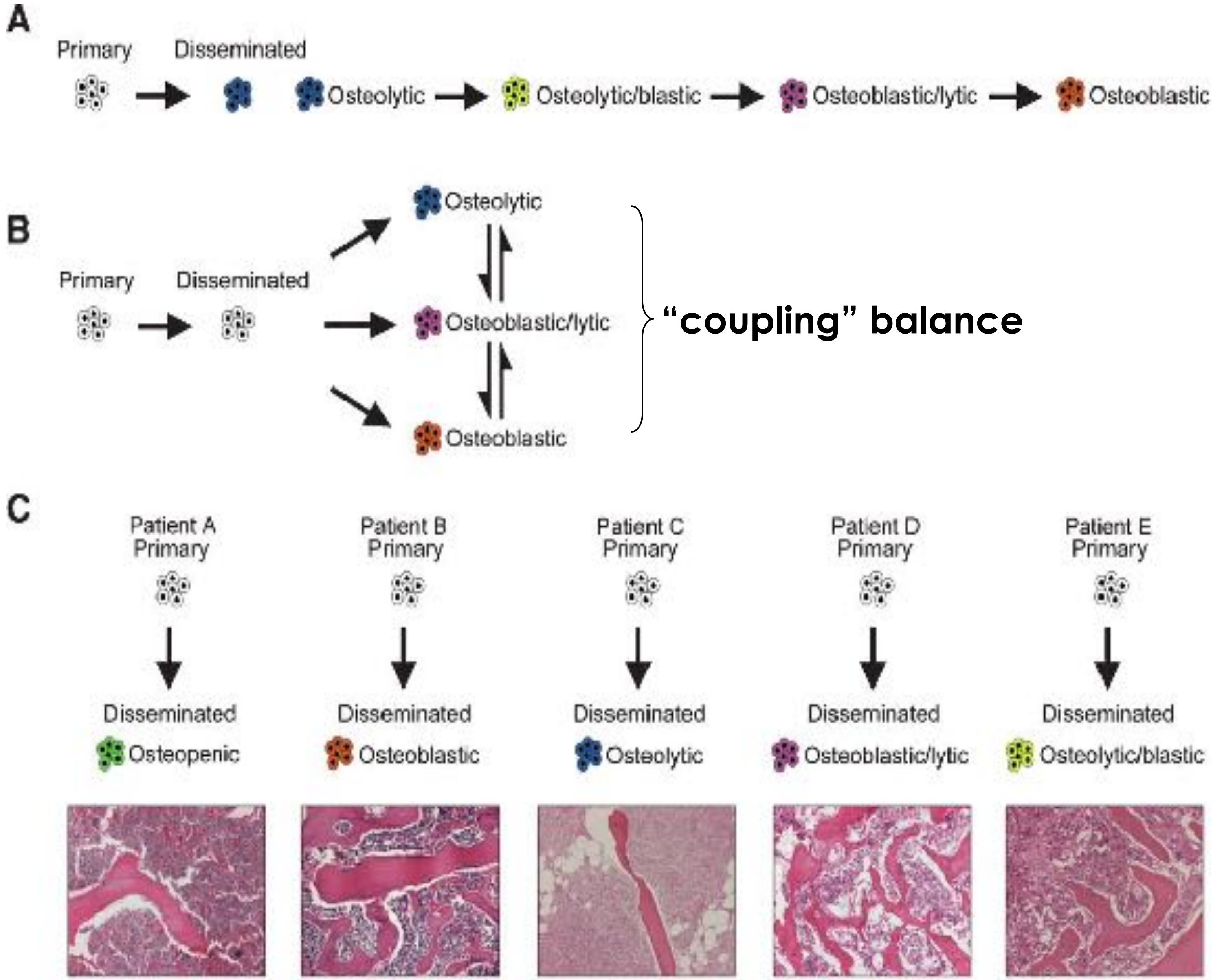
Conceao, Bone Res 2021
Papachristou et al, CIBD meeting, 2012
Elefteriou F, IBMS meeting, Davos 2010
Campbell et al, PLOSBiol 2012

Molecules implicated in osteoblastic bone mets

- **Endothelin-1:** ↑ expression in the circulation of pts w/ OBL mets, prostate Ca and breast Ca cell cultures
- **TGF-β Family**: stimulates OBL proliferation and bone formation in vitro (is expressed in high levels in prostate Ca cells) and in vivo
- **BMPs** (2, 3, 4, 6, 7), **FGFs** (1, 2), **PDGF** (esp PDGF-BB isoform)
- **Wnt/β-catenin** signal transduction pathway
- **Proteases** (e.g. PSA), their **activators** (urokinase-type Plasminogen Activator-{**uPA**} from tumor cells) and their **inhibitors** (PAIs)

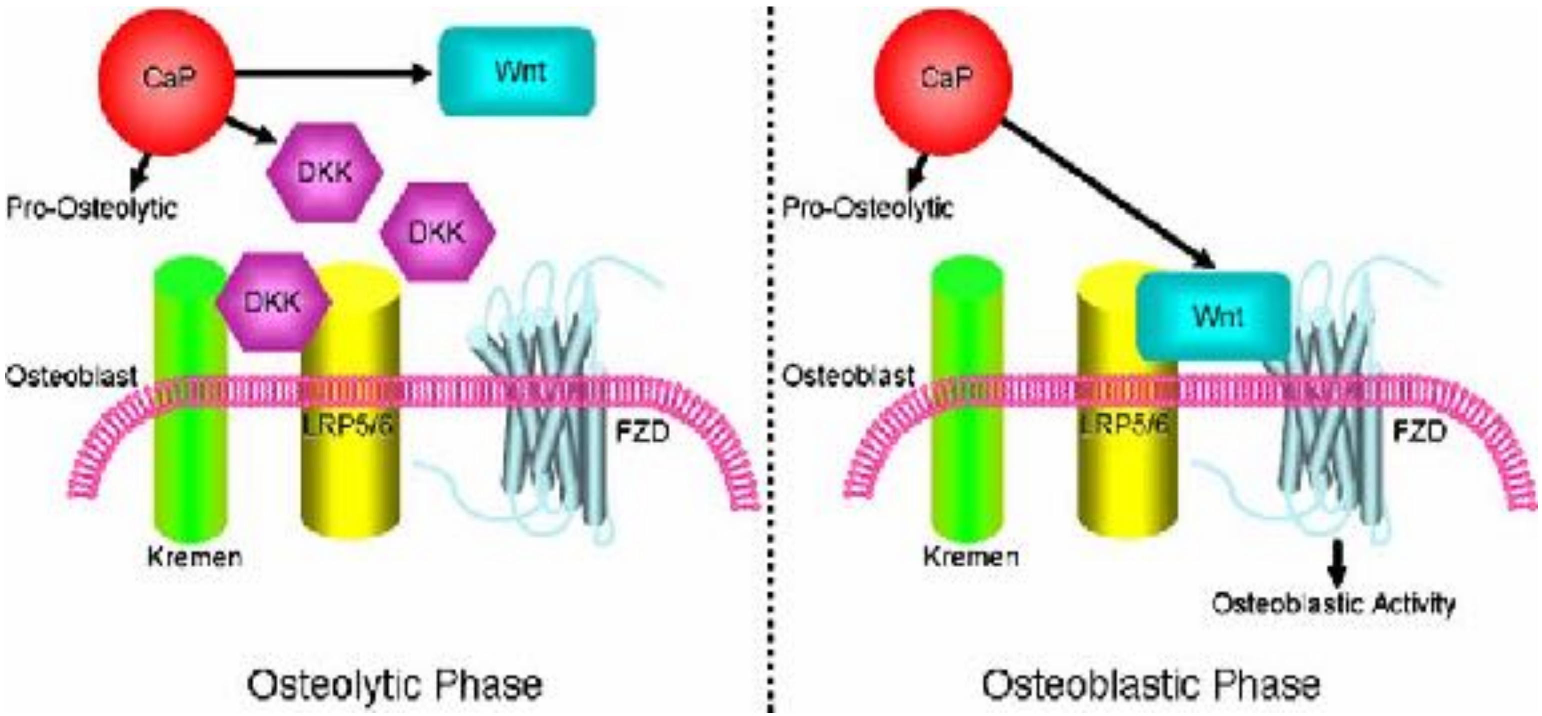


Papachristou et al, Med Res Rev 2012
(modified 2014)



Morrissey and Vessella, 2007; Suva et al, 2011

Wnt Signalling in PCa Bone Mets



DKK: Dickkopf: Wnt antagonist

Hall et al, JCB 2006

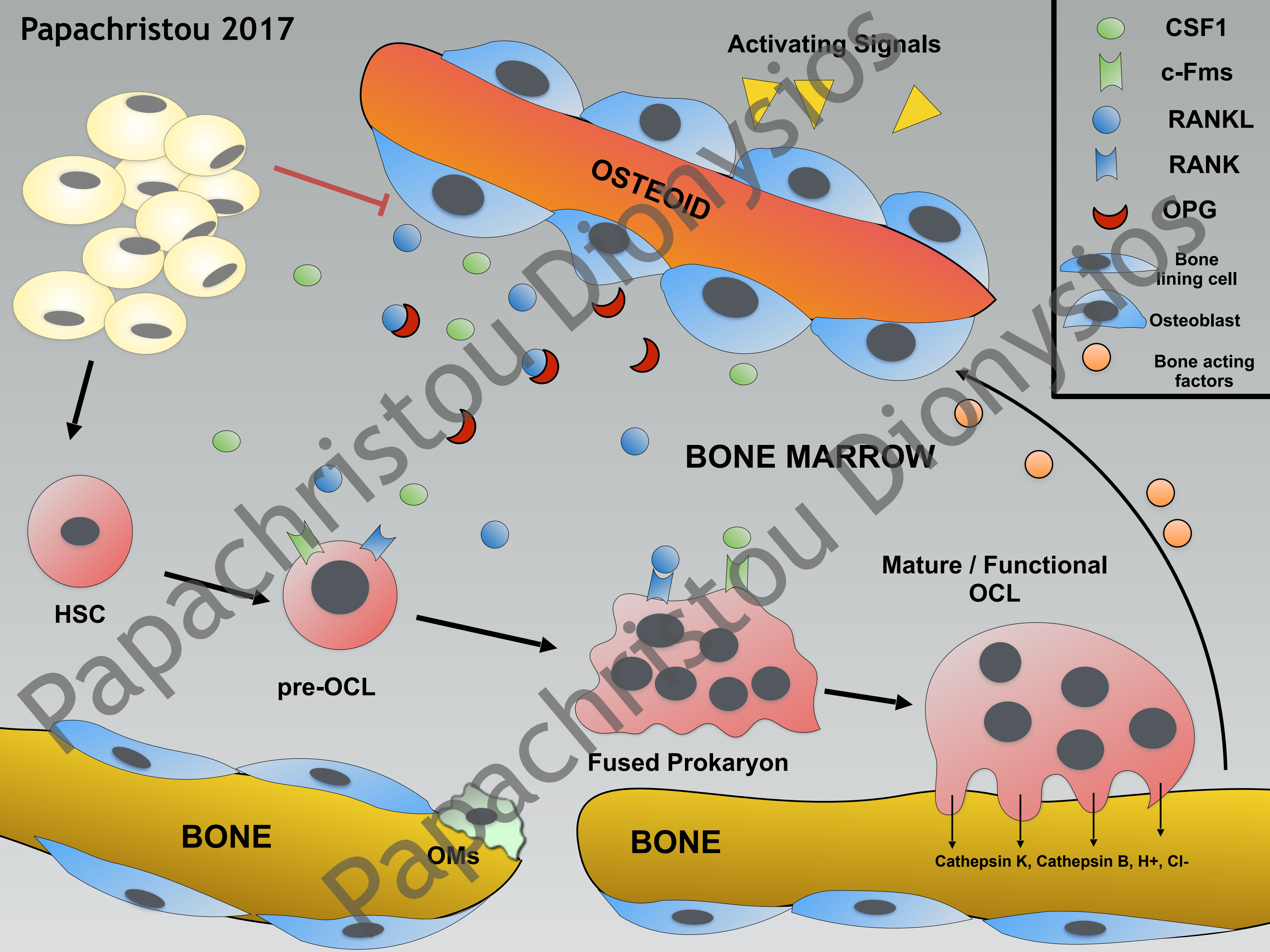
Bone Morrow Fat and Bone Metastases

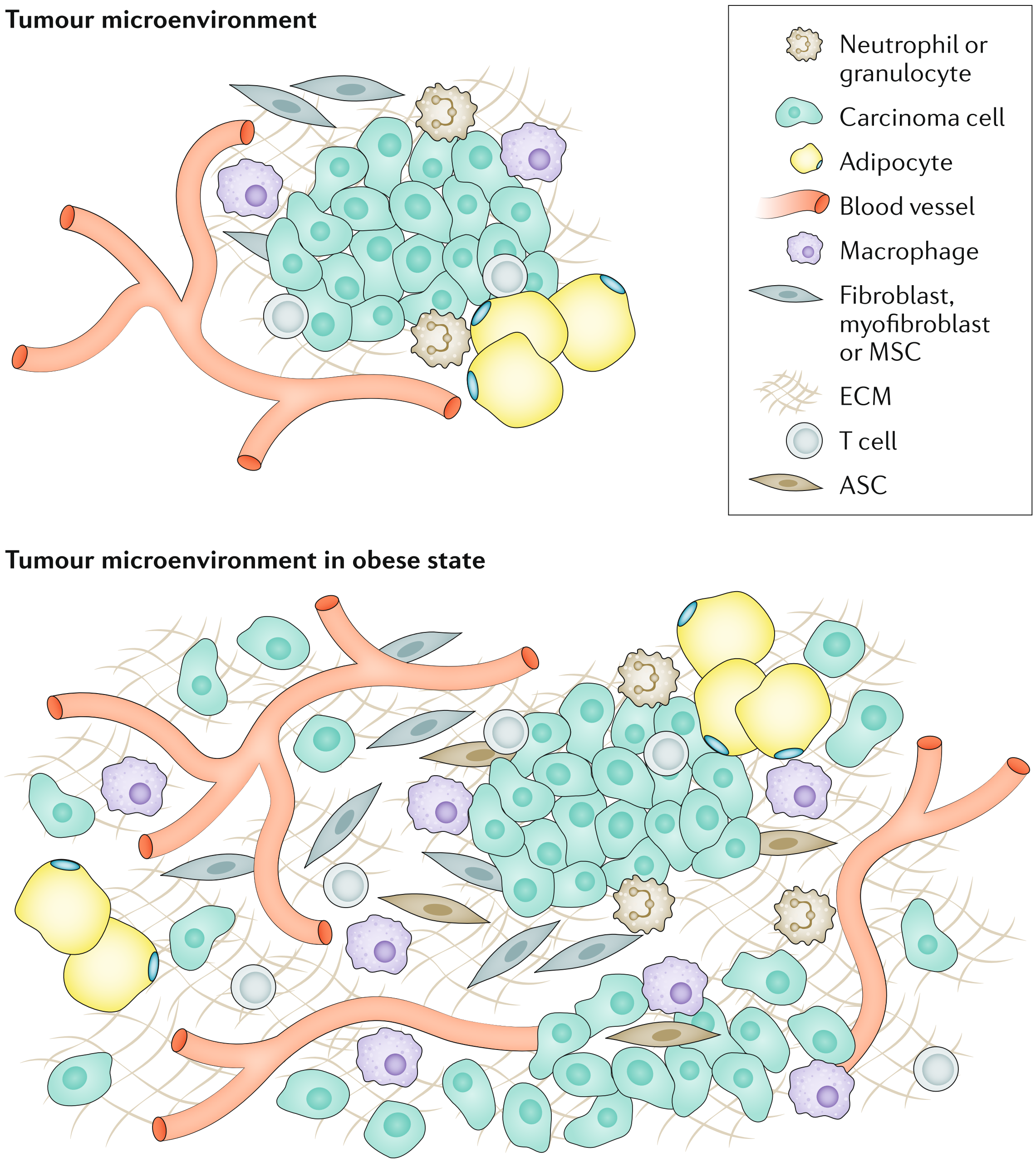
ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ

UNIVERSITY OF PITTSBURGH

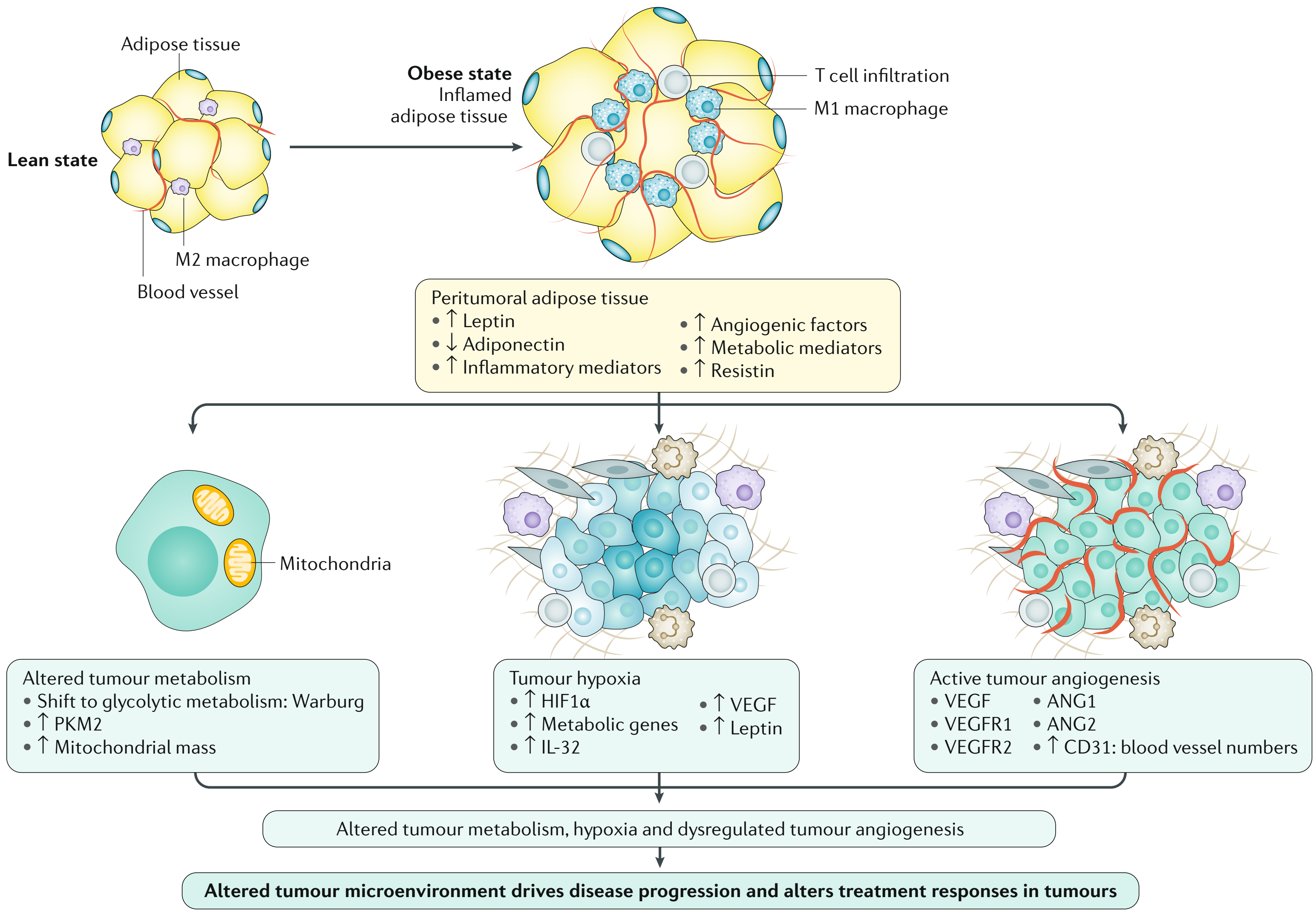
ΕΛΛΗΝΙΚΗ ΟΜΑΔΑ ΣΑΡΚΩΜΑΤΩΝ ΚΑΙ ΣΠΑΝΙΩΝ ΟΓΚΩΝ
ΕΟΣΣΟ

OsteoNet


Papachristou 2017
Activating Signals
OSTEOID
CSF1
c-Fms
RANKL
RANK
OPG
Bone lining cell
Osteoblast
Bone acting factors
BONE MARROW
HSC
pre-OCL
Fused Prokaryon
Mature / Functional OCL
BONE
OMs
BONE
Cathepsin K, Cathepsin B, H+, Cl-
Papachristou Dionysios
Papachristou Dionysios



Sullivan et al, Nat Rev Gast Hepatol 2018



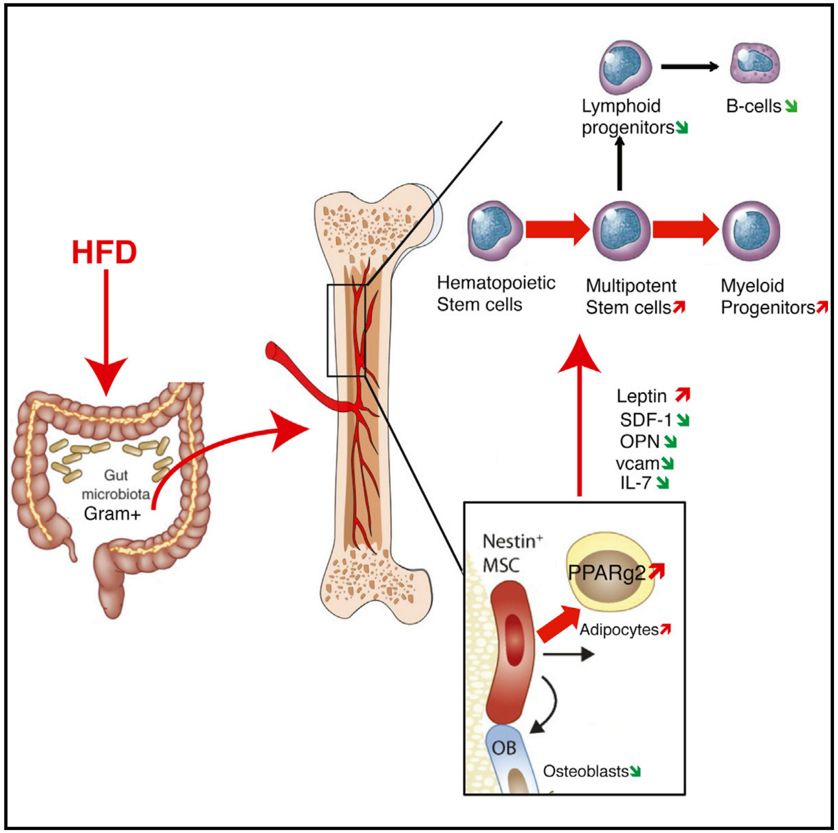
Sullivan et al, Nat Rev Gast Hepatol 2018

Short Article

Cell Metabolism

Microbiota from Obese Mice Regulate Hematopoietic Stem Cell Differentiation by Altering the Bone Niche

Graphical Abstract



Authors

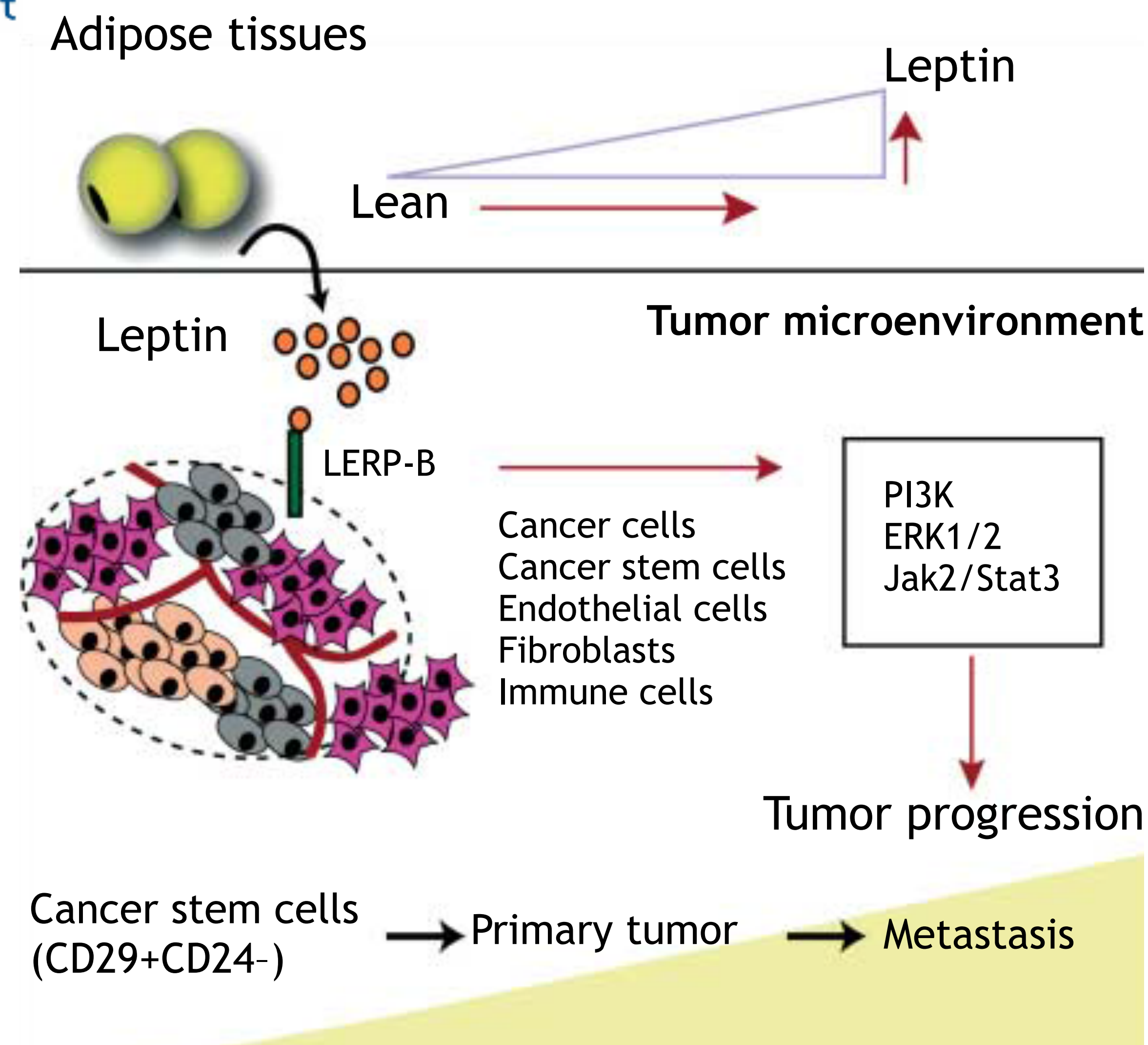
Yubin Luo, Guang-Liang Chen, Nicole Hannemann, ..., Stefan Wirtz, Georg Schett, Aline Bozec

Correspondence

georg.schett@uk-erlangen.de (G.S.), aline.bozec@uk-erlangen.de (A.B.)

In Brief

Luo et al. reveal how high-fat diet (HFD) shapes the gut microbiota to impact the bone microenvironment and regulate hematopoiesis. HFD alters the hematopoietic stem cell niche by increasing bone marrow adiposity via activation of PPARγ2, effects that can be recapitulated via microbiota transfer from obese mice.



Park and Scherer, 2011

The “Fat-Bone” Connection:
Old Foes Meet Again at the Site of B-Mets

- Obesity and adipokines (leptin and adiponectin) are associated w/ **increased risk for PCa B-Mets development**
- PCa cells at Bone Mets exhibit **adipomimetic** properties

Hardaway et al, Cancer Metastasis Rev 2014
Cheng et al, CIBD, 2012
Podggorski et al, CIBD Lyon 2012

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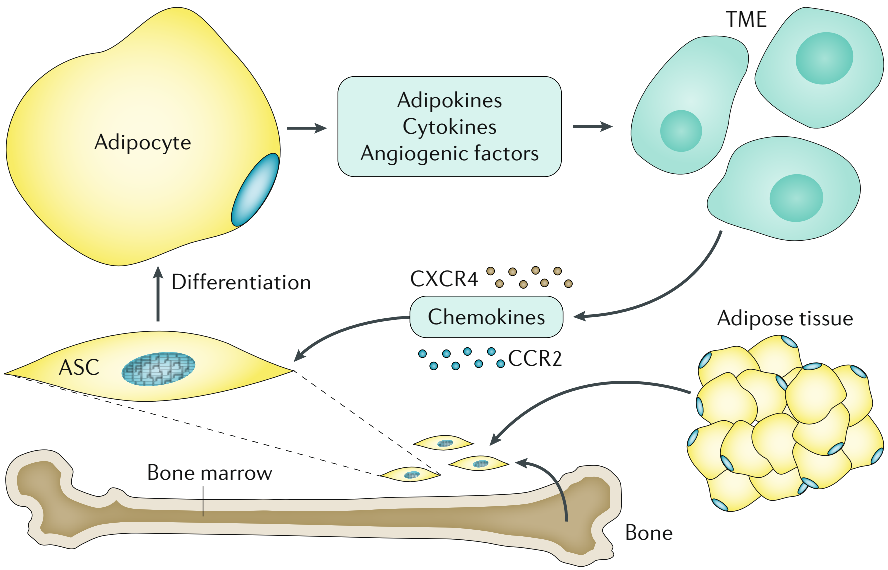
- PCa cells at Bone Mets exhibit **adipomimetic** properties

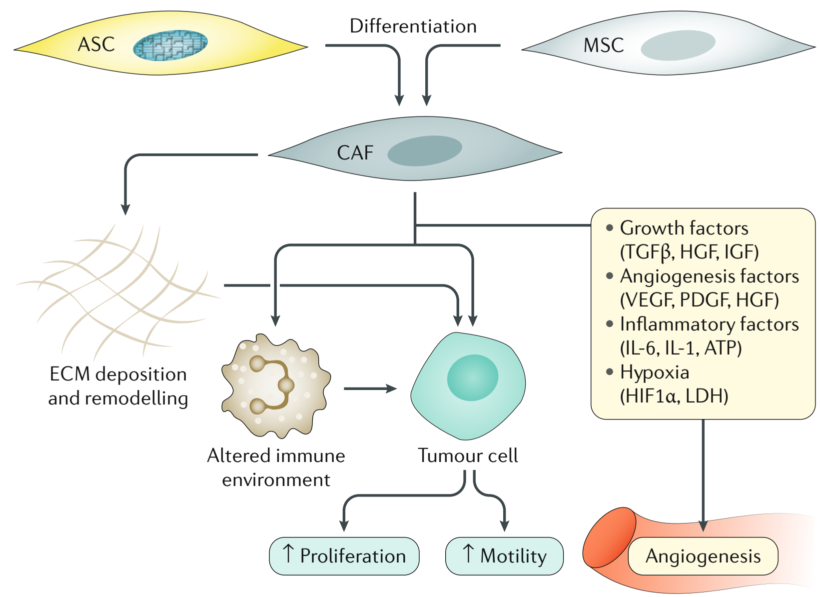
Introducing "**Lipoblastic Niche**"!!

Hardaway et al, Cancer Metastasis Rev 2014
Cheng et al, CIBD, 2012
Podggorski et al, CIBD Lyon 2012
Blair and Papachristou, WJO 2016

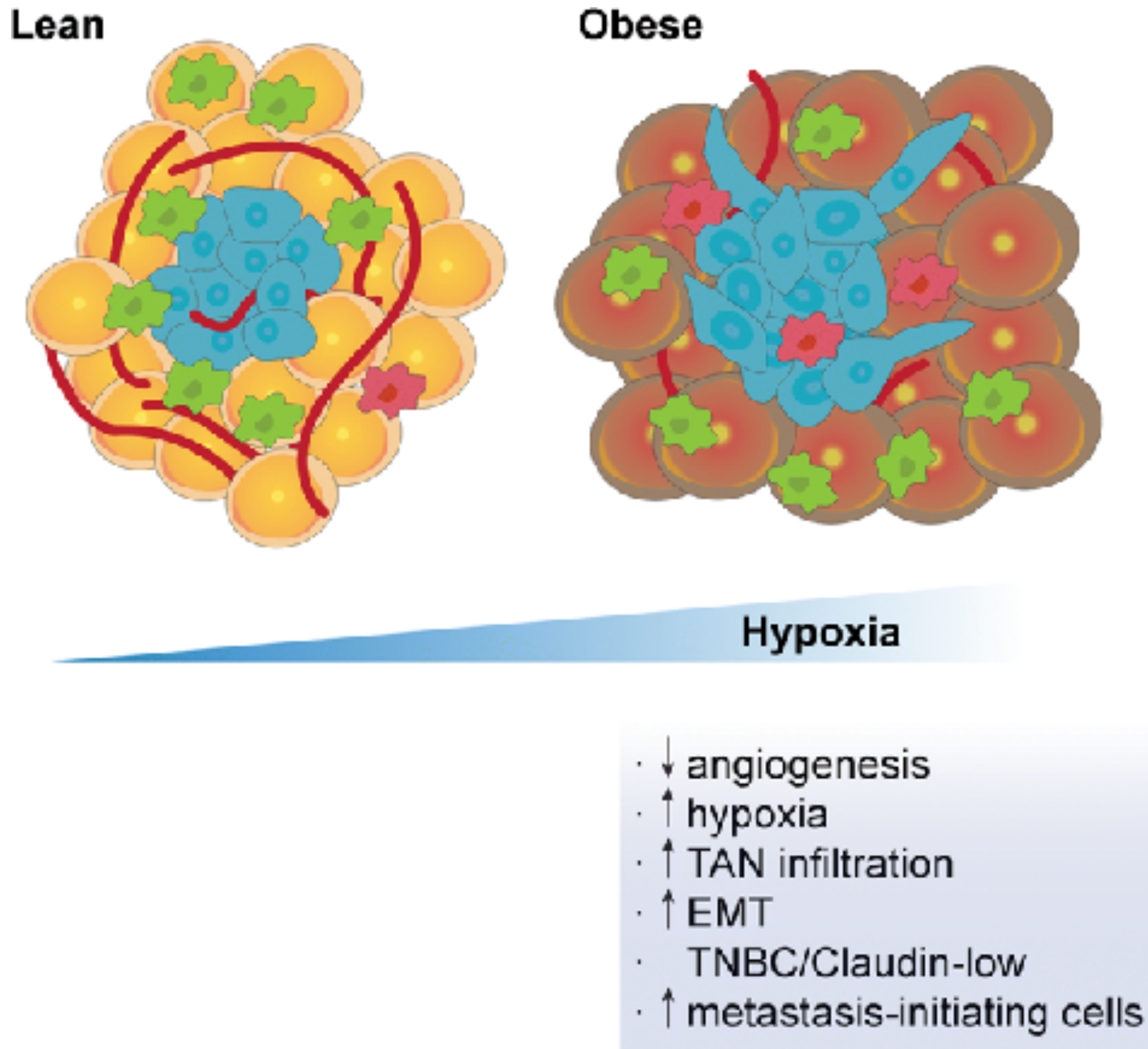
Highlights

- Alterations of hematopoietic stem cell differentiation after exposure to HFD
- HFD shifts MSC differentiation into adipocytes, altering the bone marrow HSC niche
- PPARγ inhibition blocks HFD-induced changes on the bone marrow niche
- Microbiota mediate the effects of HFD on the hematopoietic stem cells





Sullivan et al, Nat Rev Gast Hepatol 2018



Bousquenaud_Br Ca Res 2018

ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ OsteoNet

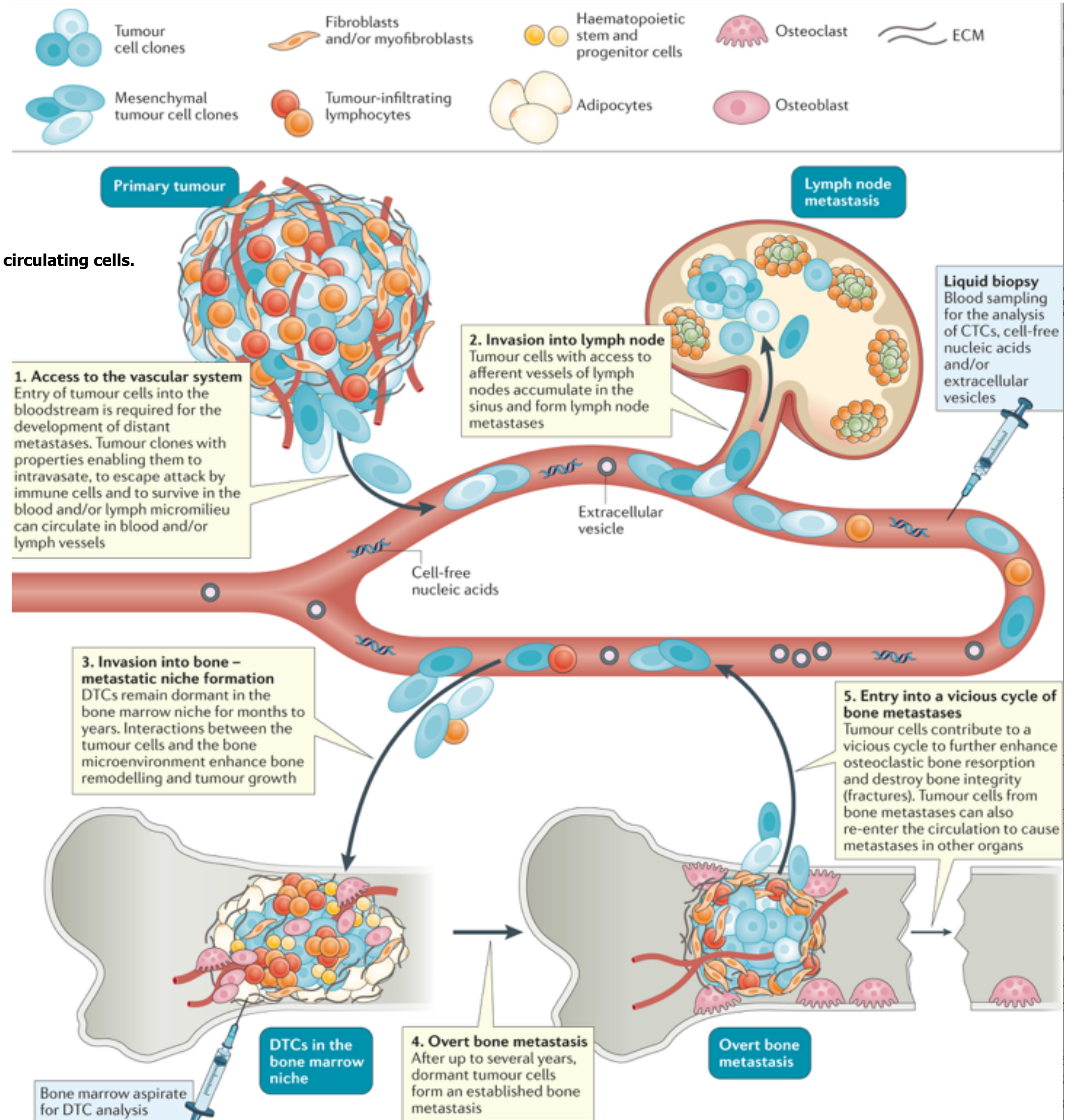
The role of OC, the orchestrators of bone remodelling in BMs

- Oc are numerous
- OC produce RANKL
- OC are the cardinal mechanoreceptors / mechanoregulators of the skeleton
- They can destroy bone (osteocytic osteolysis)

- OC may have a significant **role in B-Mets development**
- OC could serve as promising targets for **novel Tx**

Fornetti et al, JBMR_2018
Bonewald L, CIBD meeting, Lyon 2012

CTCs, 1:500,000– 1:1,000,000 circulating cells.



Current Therapies and Emerging Concepts

Table 1
Inhibitors of bone resorption for the management of BM.

Drug class	Mechanism of action	Experimental phase	Indication for BM treatment	References
BPs	N-BPs: ↓ mevalonate pathway, essential for osteoclast activity and survival; Non−N-BPs: ↑ osteoclast apoptosis	Phase III	Treatment of BM and SRE prevention in MM, BC, CRPC and other solid tumors (if clinically indicated)	[2, 46–55]
Denosumab	Anti-RANK-L mAb: ↓ osteoclast differentiation and activity	Phase III	Treatment of BM and SRE prevention in BC, CRPC and other solid tumors (if clinically indicated). Recently approved by FDA in MM setting.	[2, 46, 56–60]
Cathepsin-K inhibitors	↓ bone matrix degradation by osteoclasts	Discontinued	No indications	[28,62–64]
c-Src inhibitors	↓ RANK-L-induced osteoclast differentiation	Phase I/II	No indications	[28,67–71]
mTOR inhibitors	↓ osteoclast differentiation and activity; ↑ osteoclast apoptosis	Phase III in BC Phase II in other solid tumors Phase I in MM	Everolimus approved in association with exemestane in advanced HR + HER2-BC with bone-prevalent disease; BPs or Denosumab to be associated	[2, 74–82]
Proteasome inhibitors	↓ osteoclastogenesis; ↑ osteoblast differentiation; ↑ synthesis of collagen and BMP	Phase III in MM	Bortezomib and Carfilzomib + BPs (in association, or not, with cht, IMiDs and steroids) approved in MM	[83–87]
Abiraterone acetate	↓ osteoclastogenesis and osteoclast activity; ↑ osteoblast differentiation; ↑ bone matrix deposition; anti-tumor effect	Phase III in CRPC	Treatment of BM and SRE prevention in CRPC	[88,89,92,93]

D'Oronzo, J Bone Oncol 2019

Table 2
Modulators of osteoblast activity for the management of BM.

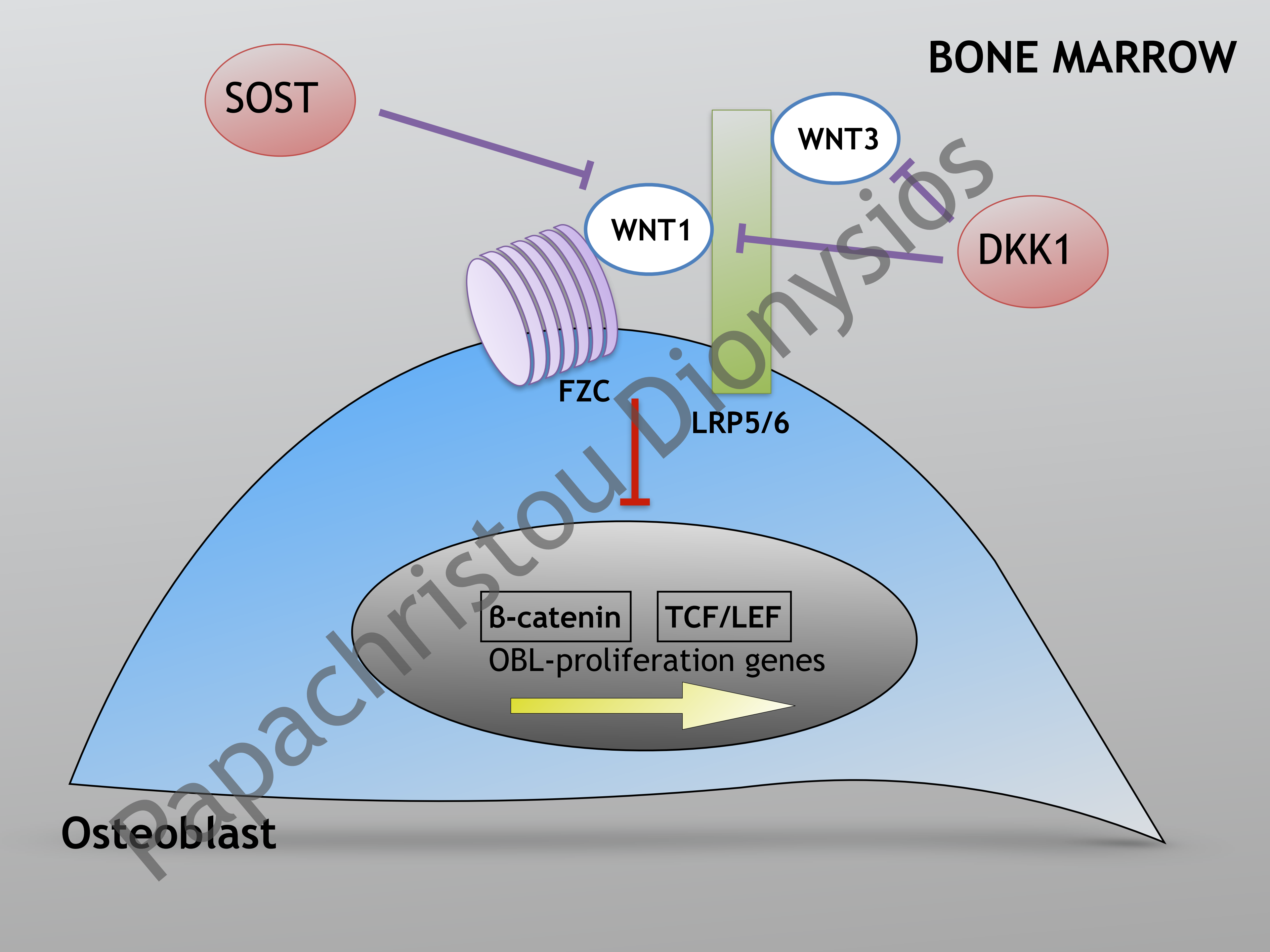
Drug class	Mechanism of action	Experimental phase	Indication for BM treatment	References
PTH	↑ Wnt pathway ↑ osteoblast differentiation ↓sclerostin and DKK-1 ↓ tumor cell migration towards bone	Pre-clinical	No indications	[94–98]
Anti-sclerostin antibodies	Sclerostin inhibition: ↑ Wnt pathway ↑ osteoblast differentiation	Pre-clinical	No indications	[99–105]
DKK-1 inhibitors	DKK-1 inhibition: ↑ Wnt pathway ↑ osteoblast differentiation	Phase I/II	No indications	[106–109]
Inhibitors of activin-A	↓ osteoclastogenesis ↑ osteoblast differentiation ↓ tumor cell migration towards bone	Phase I/II	No indications	[28,111–117]
ET-1 antagonists	↓ osteoblast inhibition of sclerotic BM	Phase II/III	No indications	[24,118,119]
Cabozantinib	TKI; Inhibition of VEGF/VEGFR pathway	Phase III	Metastatic renal cell carcinoma (with/without BM)	[121–124]

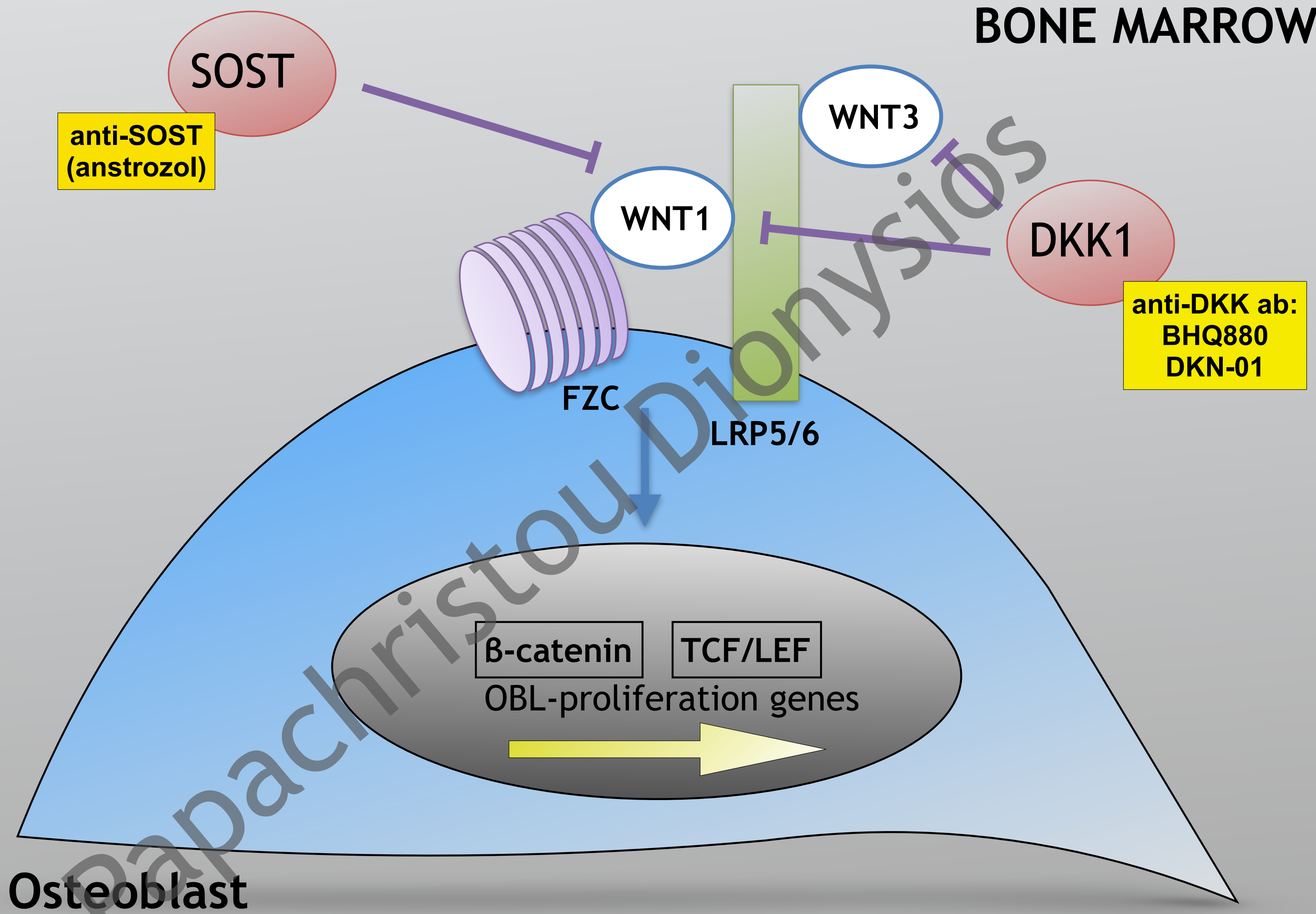
D'Oronzo, J Bone Oncol 2019

Table 1. Ongoing trials on breast cancer patients with bone metastases.

Study	Phase	Agent	Mechanism	Status
NCT03292536	Phase1B	Merestinib	c-met inhibitor	Recruiting
NCT01015560	Phase 2	MLN1202	Anti-CCR2(anti-CD192) monoclonal antibody	Completed
NCT02517918	Phase1	Sirolimus	mTOR inhibitor combined with metronomic CT	Recruiting
NCT00466102	Phase 2	Everolimus	mTOR inhibitor	Unknown
NCT00429507	Phase 2	Samarium	sm-EDTMP(Sm-153 lexidronam pentasodium)	Completed
NCT03239756	Phase 1	TK006	Full human monoklonal anti-RANKL antibody	Recruiting
NCT01070485	Phase 2	Alpharadin	Radium-223	Completed
NCT00051779	Phase 1	CAL	Humanized monoclonal antibody to the parathyroid hormone-related protein	Completed
NCT01644890	Phase 3	NK105	Nanoparticle drug delivery formulation	Completed
NCT00912639	Phase 4	Genexol-PM	Paclitaxel-loaded polymeric micelle	Unknown
NCT02646319	Phase 1	Nanoparticle	Nanoparticle albumin-bound rapamycin(mTOR)	Active, not recruiting
NCT00505271	Phase 2	Rexin-G	Nanoparticle bearing a dominant negative cyclin G1	Completed
NCT01441947	Phase 2	Cabozantinib	Tyrosine kinase inhibitor against met and VEGFR2	Active, not recruiting
NCT00692458	Phase 3	Odanacatib	Cathepsin K inhibitor	Withdrawn

Oruc et al. Exp Opion Pharmacol 2019


BONE MARROW
SOST
WNT3
WNT1
DKK1
FZC
LRP5/6
ß-catenin
TCF/LEF
OBL-proliferation genes
Osteoblast
Papachristou Dionysios



BONE MARROW
SOST
anti-SOST (anstrozol)
WNT3
WNT1
DKK1
anti-DKK ab: BHQ880 DKN-01
FZC
LRP5/6
ß-catenin
TCF/LEF
OBL-proliferation genes
Osteoblast

Calcif Tissue Int (2018) 102:227–250
https://doi.org/10.1007/s00223-017-0353-5

REVIEW

Bone-Targeted Therapies in Cancer-Induced Bone Disease

Sofia Sousa[1,2] · Philippe Clézardin[1,2,3]

Table 5 Currently ongoing clinical trials of bone-targeted agents for cancer-induced bone disease

Bone-targeted therapy	Patient population	Clinical trial acronym/number	Phase	Clinical trials.gov link
Denosumab	High-risk early breast cancer	D-CARE NCT01077154	3	https://clinicaltrials.gov/ct2/show/NCT01077154?term=NCT01077154&rank=1
Radium-223	Bone metastatic breast cancer with endocrine therapy	NCT02258464	2	https://clinicaltrials.gov/ct2/show/NCT02258464?term=NCT02258464&rank=1
Radium-223	Bone metastatic breast cancer treated with exemestane	NCT02258451	2	https://clinicaltrials.gov/ct2/show/NCT02258451?term=NCT02258451&rank=1
Radium-223	Osteosarcoma	NCT01833520	1–2	https://clinicaltrials.gov/ct2/show/NCT01833520?term=radium+223&cond=osteosarcoma&rank=1
Radium-223	Thyroid cancer refractory bone metastases	RAD-THYR NCT02390934	2	https://clinicaltrials.gov/ct2/show/NCT02390934?term=NCT02390934&rank=1
Bortezomib	Relapsed multiple myeloma (comparison carfilzomib and dexamethasone versus bortezomib)	NCT01568866	3	https://clinicaltrials.gov/ct2/show/NCT01568866?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=1
Bortezomib	Relapsed multiple myeloma (addition of daratumumab to bortezomib and dexamethasone)	NCT02136134	3	https://clinicaltrials.gov/ct2/show/NCT02136134?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=2
Bortezomib	Relapsed multiple myeloma (pomalidomide, bortezomib and low-dose dexamethasone)	OPTIMISMM NCT01734928	3	https://clinicaltrials.gov/ct2/show/NCT01734928?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=3
Bortezomib	Relapsed multiple myeloma (comparison carfilzomib, dexamethasose and once weekly bortezomib versus twice weekly bortezomib)	ARROW NCT02412878	3	https://clinicaltrials.gov/ct2/show/NCT02412878?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=4
Bortezomib	Relapsed multiple myeloma patients(pomalidomide, bortezomib and low-dose dexamethasone versus high-dose dexamethasone)	NIMBUS NCT01311687	3	https://clinicaltrials.gov/ct2/show/NCT01311687?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=5
Saracatinib	Cancer-induced bone pain	SarCaBon NCT02085603	2	https://clinicaltrials.gov/ct2/show/NCT02085603?term=NCT02085603&rank=1
Cabozantinib	Bone metastatic castration-resistant prostate cancer	NCT01599793	2	https://clinicaltrials.gov/ct2/show/NCT01599793?term=cabozantinib&cond=Bone+Metastases%2C+cancer&rank=1
Cabozantinib	Advanced solid (non-breast, non-prostate) malignancies and bony metastases	NCT01588821	2	https://clinicaltrials.gov/ct2/show/NCT01588821?term=cabozantinib&cond=Bone+Metastases%2C+cancer&rank=4
Cabozantinib	Non-metastatic and metastatic castration-resistant prostate cancer	NCT01703065	Pilot	https://clinicaltrials.gov/ct2/show/NCT01703065?term=cabozantinib&cond=Bone+Metastases%2C+cancer&rank=5
Cabozantinib	Metastatic colorectal cancer	CaboMAb NCT02008383	1	https://clinicaltrials.gov/ct2/show/NCT02008383?term=cabozantinib&recrs=abd&draw=1&rank=2
Cabozantinib	Multiple myeloma	NCT03201250	1-2	https://clinicaltrials.gov/ct2/show/NCT03201250?term=cabozantinib&recrs=abd&draw=3&rank=11
Cabozantinib	Androgen-dependent metastatic prostate cancer	NCT01630590	2	https://clinicaltrials.gov/ct2/show/NCT01630590?term=cabozantinib&recrs=abd&draw=3&rank=12
Cabozantinib	Metastatic hormone receptor-positive breast cancer	NCT01441947	2	https://clinicaltrials.gov/ct2/show/NCT01441947?term=cabozantinib&recrs=abd&draw=3&rank=15
Cabozantinib	Relapsed osteosarcoma or Ewing sarcoma	NCT02243605	2	https://clinicaltrials.gov/ct2/show/NCT02243605?term=cabozantinib&recrs=abd&draw=4&rank=22
Sotatercept	Refractory multiple myeloma treated with lenalidomide or pomalidomide and dexamethasone	NCT02406521	1	https://clinicaltrials.gov/ct2/show/NCT01562405?term=NCT01562405&recrs=abd&rank=1

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Current Opinion in Pharmacology

Emerging therapies in bone metastasis

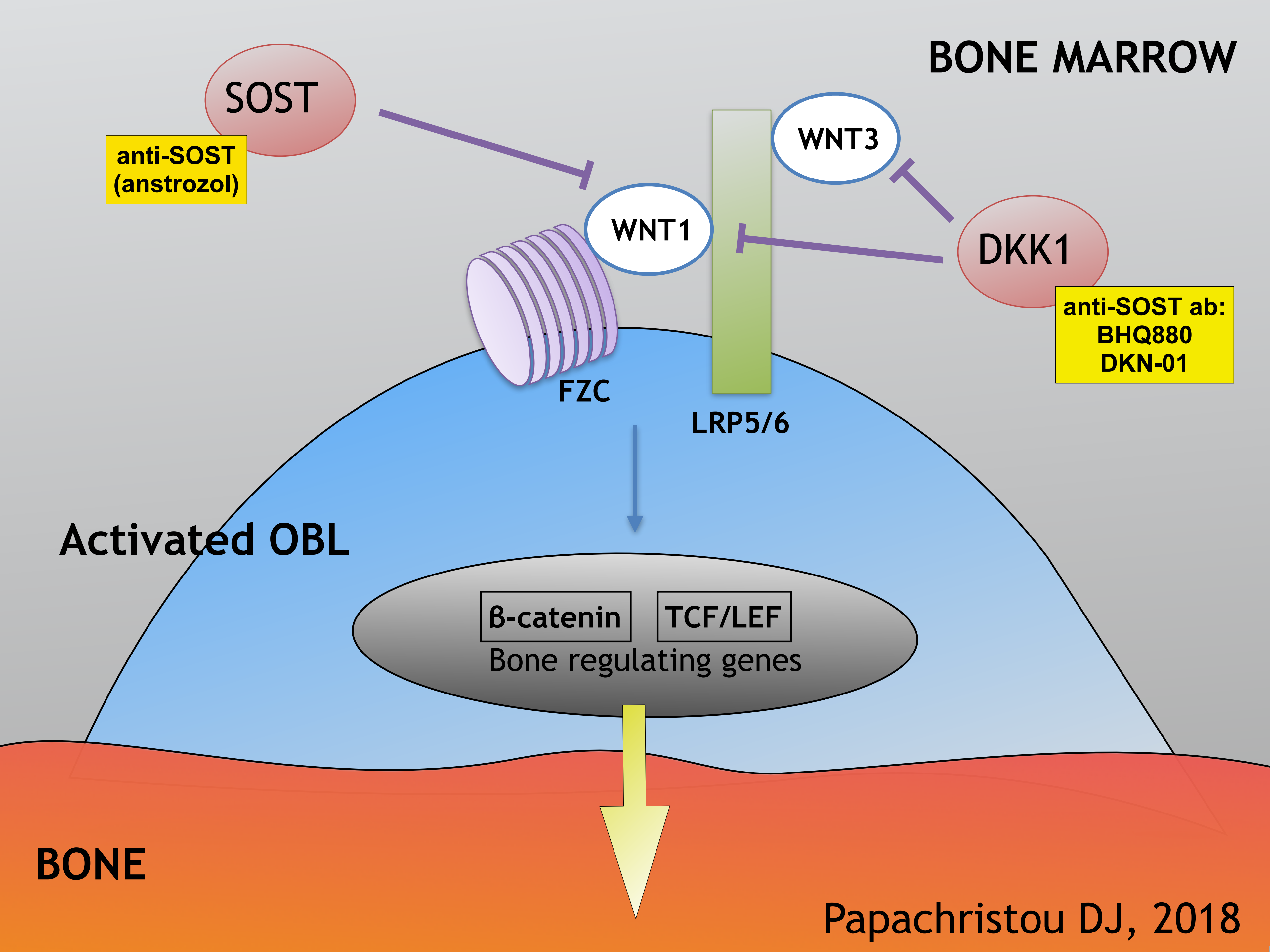
Lise Clément-Demange[1,2] and Philippe Clézardin[1,2]

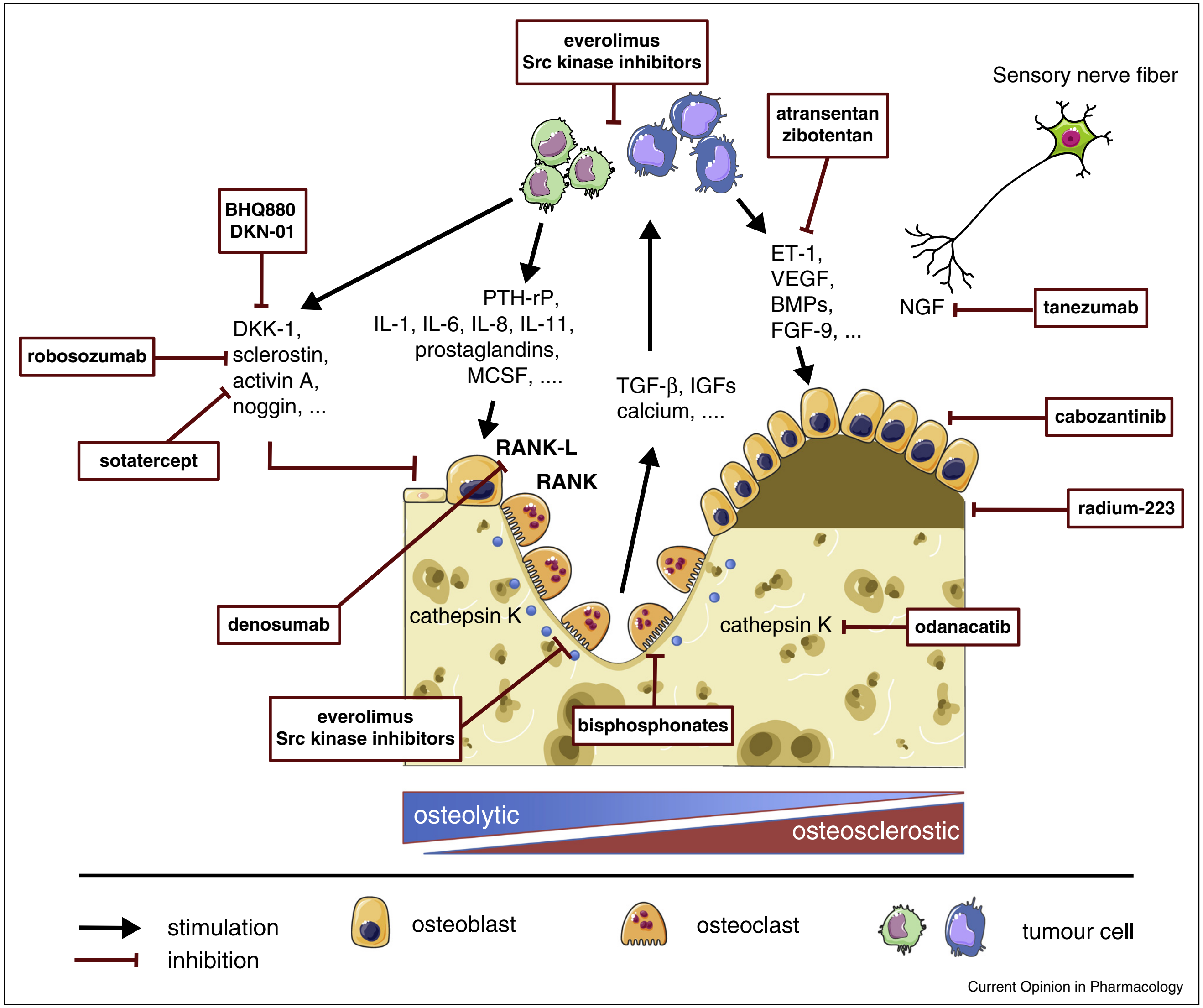
Table 1

Bone-targeted therapies in clinical development.

Target*	Compound	Cancer Type	Stage	Description/Comment*	Ref.
Cathepsin K	Odanacatib	Breast	Phase II	Safety and efficacy in comparison with ZOL.	[4]
Src	Dasatinib	Prostate	Phase III	Dasatinib + docetaxel versus placebo + docetaxel in men with CRPC (READY trial)/Negative trial. Dasatinib does not improve OS, nor time to first SRE.	[7]
	Saracatinib	Breast/prostate	Phase II	Safety and efficacy in comparison with ZOL (ClinicalTrials.gov identifier NCT00558272).	[4]
	Bosutinib	Breast	Phase II	Effect of bosutinib on PFS in pretreated patients with locally advanced and metastatic cancer/bosutinib prolongs PFS in chemotherapy-pretreated patients. No effect of bosutinib on circulating levels of bone turnover markers.	[8]
mTOR	Everolimus	Breast	Approved	Everolimus + exemestane versus placebo + exemestane in metastatic ER-positive breast cancer (BOLERO-2 trial)/It is reported an early reduction in bone turnover markers prior to clinical response and reduced bone complications in the everolimus arm.	[9,12]
		RCC	Phase II	Everolimus versus everolimus + ZOL in renal cell carcinoma patients with ≥ 1 bone metastasis (RAZOR trial)/Median time to first SRE was 9.6 months on everolimus plus zoledronic acid *vs* 5.2 months on everolimus ($P = 0.03$).	[13]
Endothelin-1	Atrasentan	Prostate	Phase III	Docetaxel/prednisone + atrasentan versus docetaxel/prednisone + placebo in men with metastatic CRPC (SWOG S0421)/Does not improve OS or PFS.	[14]
	Zibotentan	Prostate	Phase III	Docetaxel + zibotentan versus docetaxel + placebo in men with metastatic CRPC (ClinicalTrials.gov identifier NCT00617669)/Does not improve OS or PFS.	[14]
Activin A	Sotatercept	Myeloma	Phase IIa	Safety and tolerability in relapsed multiple myeloma patients/In patients without bisphosphonate use, anabolic improvements in bone mineral density and in bone formation relative to placebo occurred.	[18]
DKK-1	BHQ880	Myeloma	Phase Ib	Dose determination study.	[10]
MET/VEGFR2	Cabozantinib	Prostate	Phase III	Cabozantinib versus prednisone in men with metastatic CRPC (COMET-1 trial)/Despite striking results in phase II trials, this pivotal phase III trial did not meet the primary endpoint of demonstrating improved OS of patients treated with cabozantinib. However, the median PFS for the cabozantinib arm was 5.5 months versus 2.8 months for the prednisone arm ($P < 0.0001$).	[22]
NGF	Tanezumab	Prostate, breast, myeloma, RCC	Phase II	Safety and efficacy in cancer patients with pain due to bone metastasis/Study has been completed (ClinicalTrials.gov identifier NCT00830180). No data released.	–
Bone mineral	Radium-223	Prostate	Approved	Radium-223 + best standard of care versus placebo + best standard of care in men with CRPC and bone metastasis (ALSYMPCA trial)/the median time to first SRE in patients with bisphophosphonate use at entry is 19.6 months on radium-223 versus 10.2 months on placebo ($P = 0.00048$)	[25]
		Breast	Phase IIa	Safety and tolerability in women with breast cancer and bone metastasis.	[27]

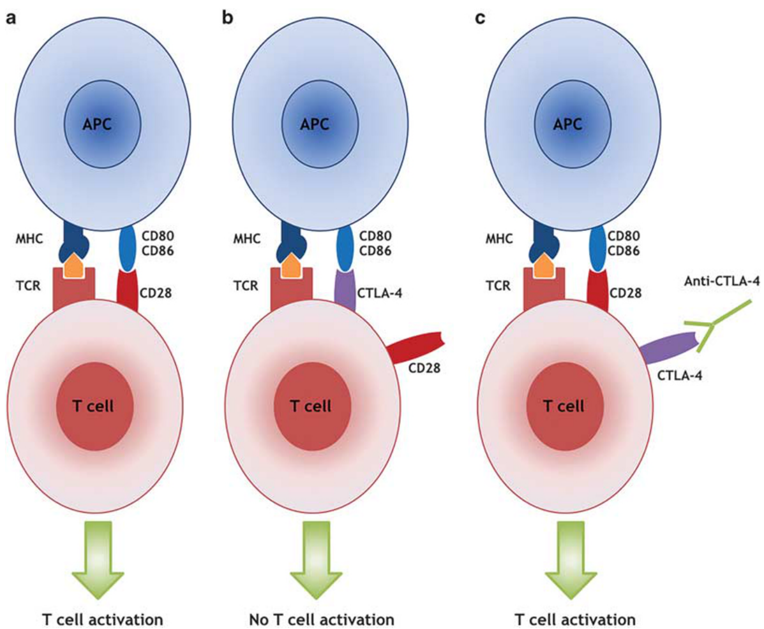
* CRPC: castration-resistant prostate cancer; DKK-1: dickkopf-1; mTOR: mammalian target of rapamycin; MET: hepatocyte growth factor receptor; NGF: nerve growth factor; OS: overall survival; PFS: progression-free survival; RCC: renal cell carcinoma; SRE: skeletal-related event; Src: proto-oncogene tyrosine-protein kinase; VEGFR2: vascular endothelial growth factor receptor 2; ZOL: zoledronic acid.

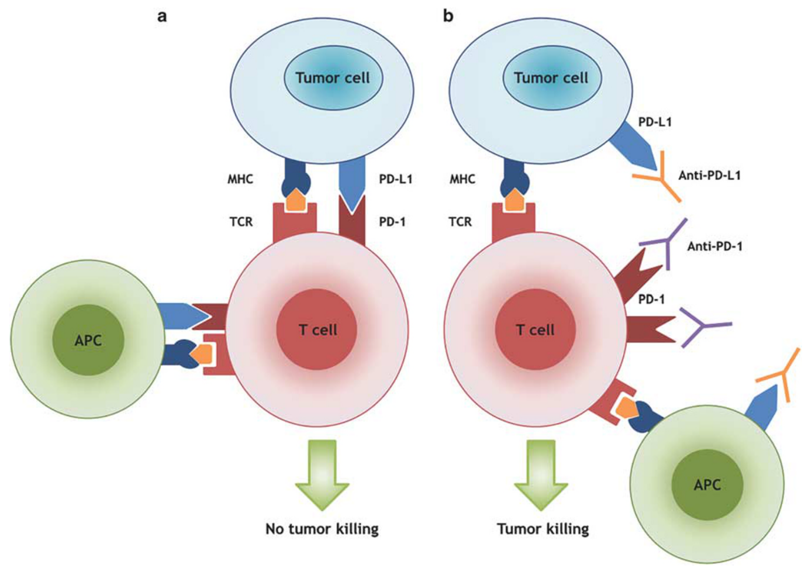

BONE MARROW
SOST
anti-SOST
(anstrozol)
WNT3
WNT1
DKK1
anti-SOST ab:
BHQ880
DKN-01
FZC
LRP5/6
Activated OBL
ß-catenin
TCF/LEF
Bone regulating genes
BONE
Papachristou DJ, 2018



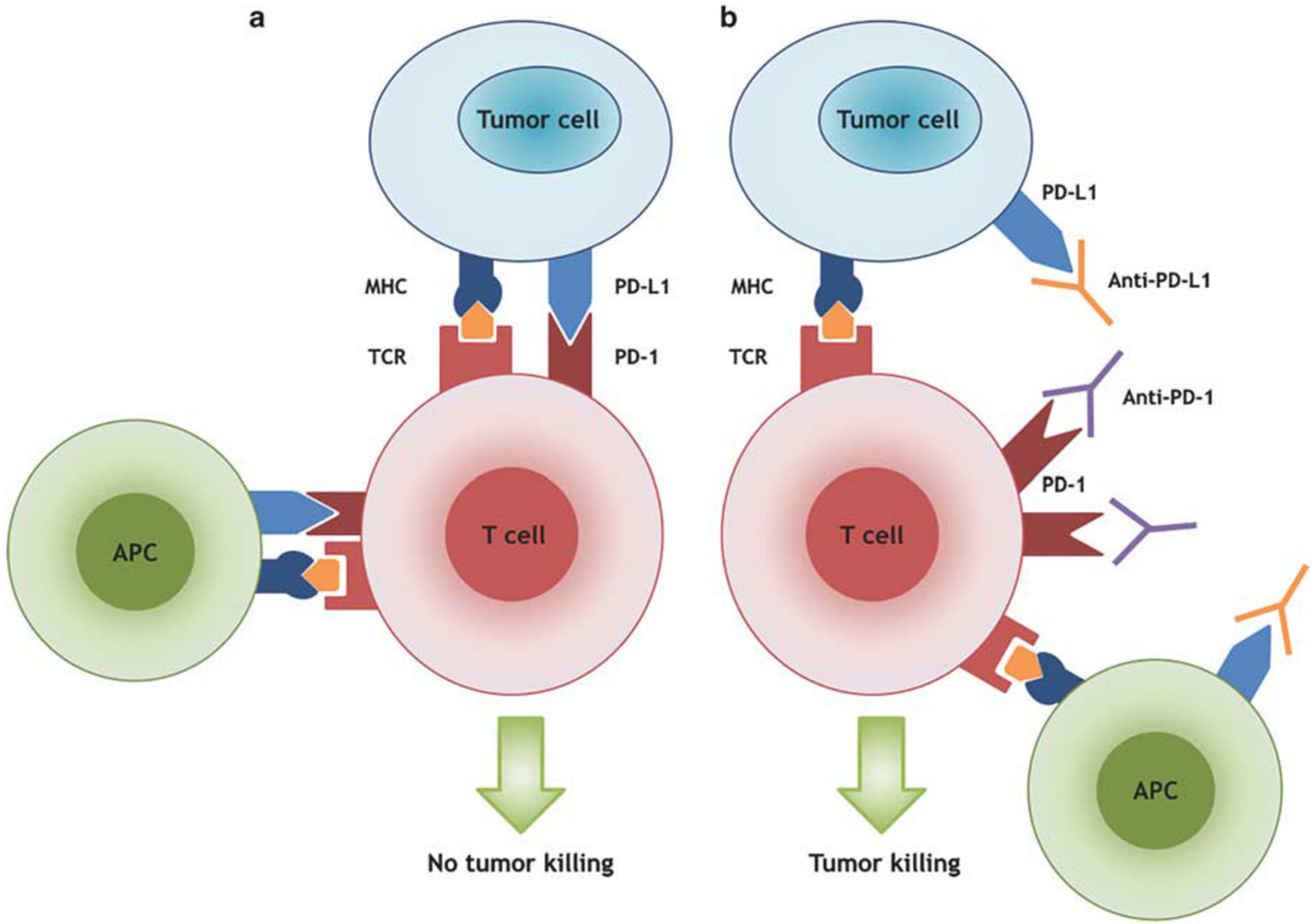
Clement-Demange L & Clezardin P, 2015
Hiraga T, 2016

Immune Check-Points and CIBD

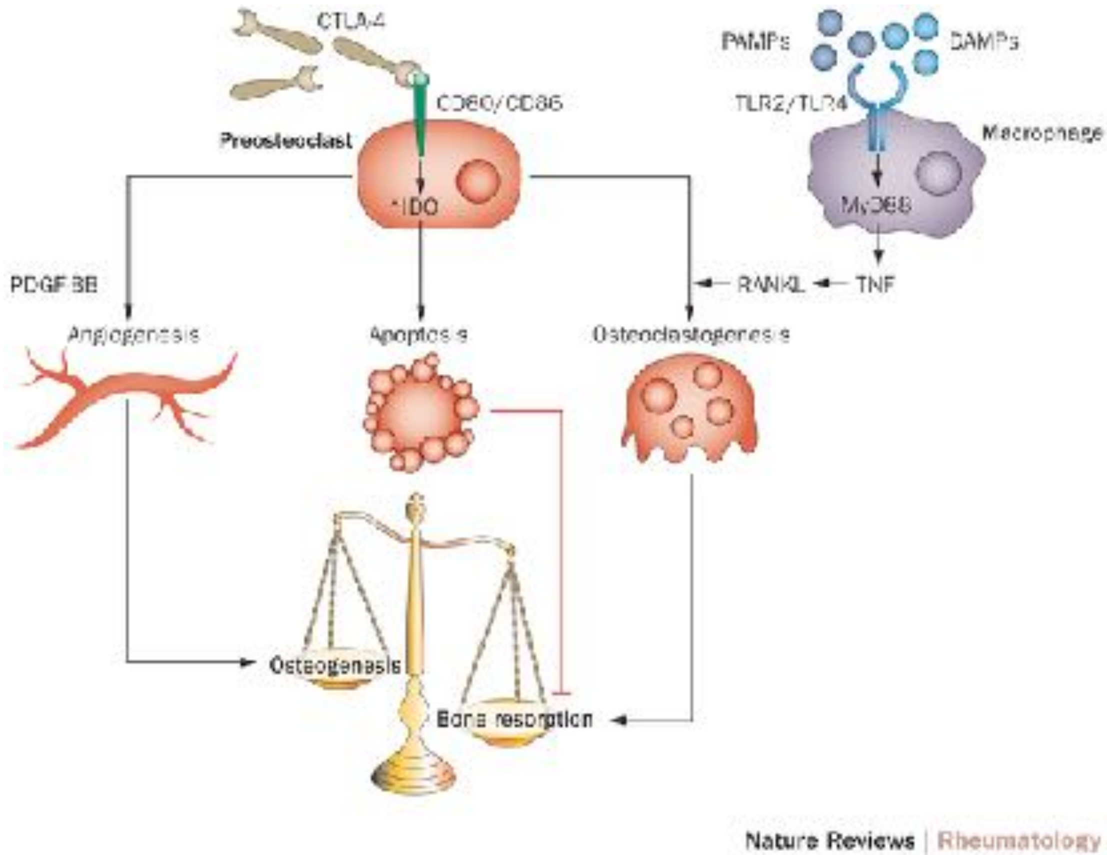


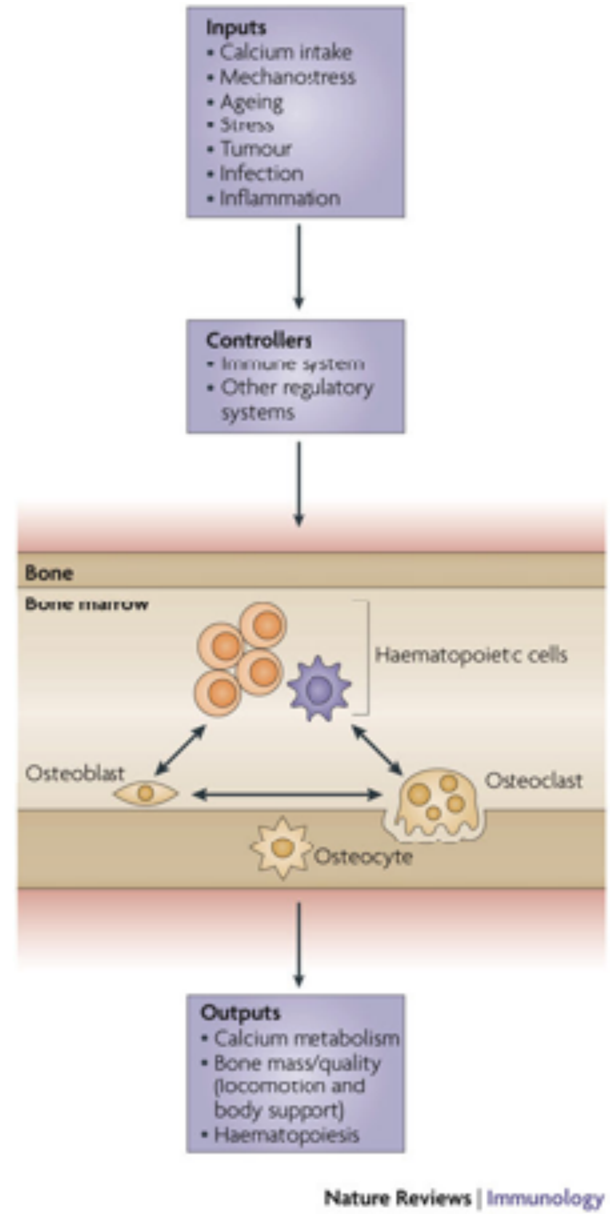


Veenstra et al, Lab Invest 2018


a
Tumor cell
MHC
PD-L1
TCR
PD-1
APC
T cell
No tumor killing
b
Tumor cell
PD-L1
Anti-PD-L1
MHC
TCR
Anti-PD-1
PD-1
T cell
APC
Tumor killing

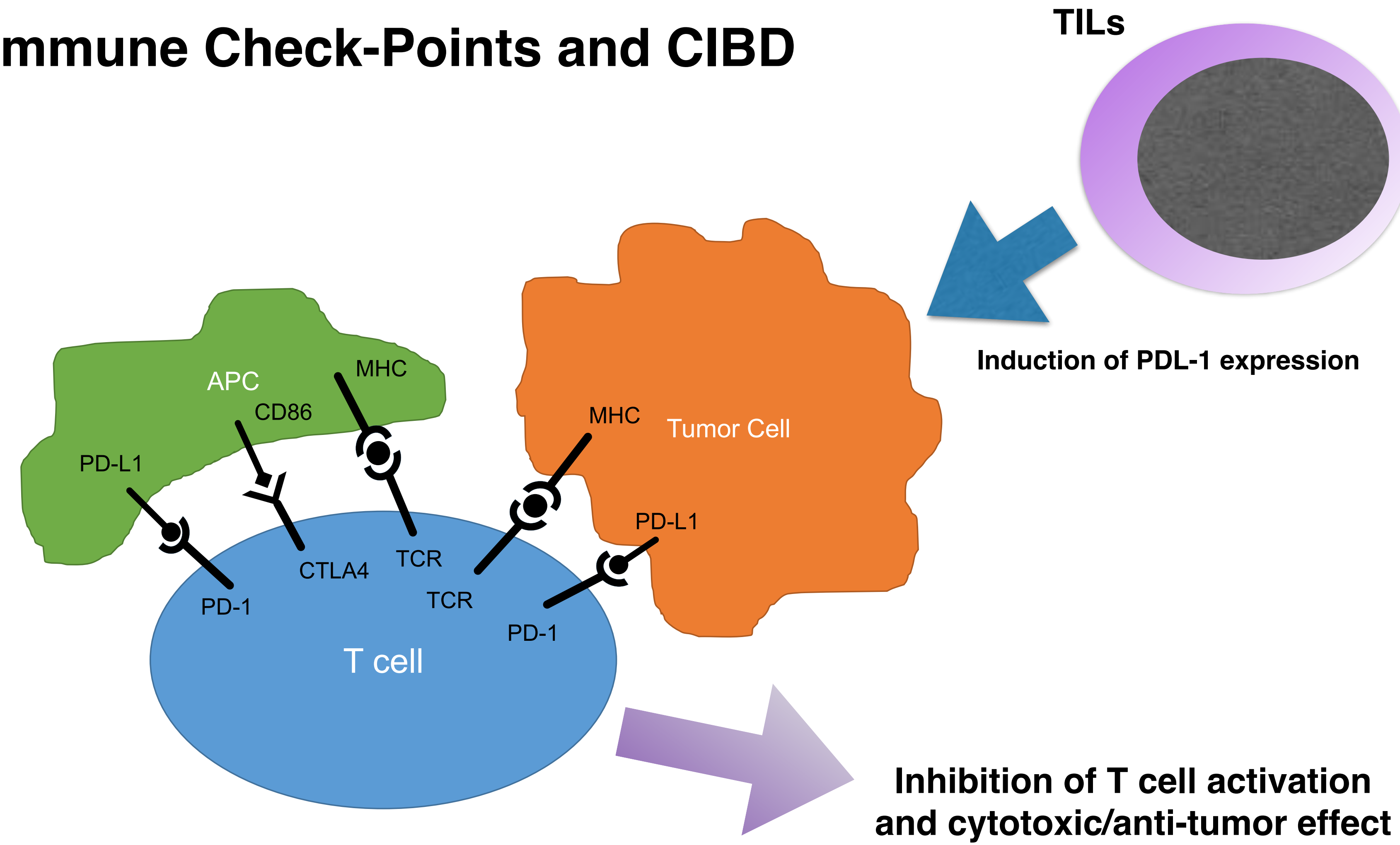
Osteoimmunology





Takayanagi, H. (2014) Two-faced immunology—from osteogenesis to bone resorption
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2014.219

Immune Check-Points and CIBD



CTLA-4: Cytotoxic T-Lymphocyte-Associated Protein 4
PD-1: Programmed cell Death 1

...but

Standard of care treatment of bone metastases.

Treatment	Mechanism	Effect on Bone metastases	Notes	Refs
SRE Treatments				
Zoledronic acid	inhibition of farnesyl pyrophosphate synthase	Inhibition of Osteolysis	Action against TAMs as well. Recommended for adjuvant use	(Vignani et al., 2016)
denosumab	mAb against RANKL	Reduces osteoclast activity		(Vignani et al., 2016)
Radium-223	Localizes to bone, releases alpha radiation	Cytotoxic to tumor cells by inducing dsDNA breaks	Offers less myelosuppression due to shorter range of alpha radiation	(Aragon-Ching and El-Amm, 2016)
Immunotherapies				
nivolumab	Anti-PD-1 mAb		Currently unstudied in bone metastases	
ipilimumab	Anti-CTLA-4 mAb		Currently unstudied in bone metastases	
pembrolizumab	Anti-PD-1 mAb		Currently unstudied in bone metastases	
atezolizumab	Anti-PD-L1 mAB		Currently unstudied in bone metastases	
Sipuleucel-T	Dendritic cells stimulated with GM-CSF and PAP	Unknown		(Vanneman and Dranoff, 2012)

Reinstein et al, CritRevOncol 2017

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Contents lists available at ScienceDirect

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Table 2
Emerging Targeted Therapies for Bone Metastases.

Treatment	Mechanism	Effect on Bone metastases	Outcomes	Notes	Refs
Tumor-targeted					
Osteoprotegerin	Natural inhibitor of RANKL	Inhibits osteoclastogenesis and subsequent bone reabsorption	Conflicting outcomes depending on dose and type of administration	New models have shown optimal dosages, need to be tested	(Morony et al., 2001; Ryser et al., 2012)
Cabozantinib	TKI, inhibits MET, VEGFR-2, RET, KIT, AXL, FLT3	inhibition of osteoblastic and osteolytic lesions in xenografts	PFS- 5.9 to 23.9 months, pain palliation in 57%, bone scan response in 63%	OS improvement not seen in phase III trial	(Basch et al., 2015; Choueiri et al., 2016; Escudier et al., 2016; Schimmoller et al., 2011; Smith et al., 2013; Smith et al., 2015, 2014; Yakes et al., 2011)
AP12009 (trabedersen)	Nucleotide-based, blocks production of TGF-β2	Reverses tumor-mediated immune suppression and prevented metastases	No bone metastases data reported		(Achyut and Yang, 2011; Hau et al., 2007)
galunisertib	Small molecule inhibitor of TGF-β	Inhibit the bone-tumor viscous cycle	Increased OS, especially in patients with low levels of TGF-β	No specific end points measured with bone metastases	(de Gramont et al., 2017; Melisi et al., 2016)
belagenpumatucel-L	Vaccine with four TGF-b2-antisense gene-modified, irradiated, allogeneic NSCLC cell lines	Target tumor cells in bone microenvironment that secrete TGF-β	OS benefits in patients with prior chemotherapy or radiotherapy	No specific end points measured with bone metastases	(de Gramont et al., 2017; Nemunaitis et al., 2006; Nemunaitis and Giaccone, 2014)
Abiraterone + prednisone	Androgen synthesis inhibitor via CYP17A1 inhibition	Shown to inhibit progression of prostatic lesions in the bone	significantly increase palliative benefit and decrease SREs	Only for use in mCRPC, SoC	(Logothetis et al., 2012)
P62 DNA Vaccine	P62 in plasmid administered created antibody response	Decreases tumor size, suppresses metastases, increased TIL, and decreases osteoclastogenesis	Suppression of osteoporosis	Currently only studied in animal models	(Durán et al., 2004; Gabai et al., 2014; Sabbieti et al., 2015; Zhang et al., 2016)
Stromal-targeted					
Zoledronic acid		Acts on TAMs, change from M2 to M1 phenotype			
PLX3397	Multi-targeted TKI, inhibits CSF-1	Prevents recruitment of M2 TAMs/MDSCs, improves immune response	Significantly decreased tumor volume with ACT	Preclinical data only	(Mok et al., 2014; Ngiow et al., 2016; Sluijter et al., 2014)
Bindarit	Inhibits CCL2	Prevents macrophage recruitment, Inhibits establishment of tumor-stromal niche	Reduced metastasis formation	Animal models only	(Steiner et al., 2014; Zollo et al., 2012)
Tasquinimod	Blocks S100A9	inhibits angiogenesis, immunomodulates through TAMs, prevents of the establishment of the bone-metastatic niche	patients with bone metastases 8.8 months vs 3.4 months (placebo) PFS, no OS benefit seen	No further research after failed phase III trial	(Pili et al., 2011; Sternberg et al., 2016)
Pirfenidone, and nintedanib	Target CAFs			No data published	(Antonia et al., 2016)
Ac-PhScN-NH2 inhibitor	α5β1 inhibition through a small peptide	prevents metastases and angiogenesis, due to vicious cycle of osteolytic lesions	reduced intratibial colony progression by almost 80% in mouse model	2nd generation is 100,000 x more potent. 1st gen saw 14 months PFS	(Jia et al., 2004; Yao et al., 2016)
Sunitinib	TKI, blocks STAT3 and IDO pathways	Decreases MDSCs, Tregs. Increased TIL	Reduced tumor volume, increased OS in mouse model, No change in tumor burden in RCC patients	Co-administered with CEA vaccine	(Farsaci et al., 2012; Ko et al., 2009)
Imatinib	TKI, blocks STAT3 and IDO pathways	activates CD8+ T cells, induces Treg apoptosis	Increased anti-tumor response with immunotherapies	In mouse models only	(Balachandran et al., 2011; Larmonier et al., 2008)
Bevacizumab	Anti-VEGF mAB	Prevents dysfunction of DC into MDSCs	Ex vivo DCs from MM patients functioned normally	At lower doses normalization of vasculature, increased TIL	(Huang et al., 2015; Yang et al., 2009)

Table 2 (*Continued*)

Treatment	Mechanism	Effect on Bone metastases	Outcomes	Notes	Refs
Temsirolimus	mTOR inhibitor, acts on IDO pathway	Activates CD8+ T cells, inhibits Tregs	Better PFS in RCC patients		(Chen and Kuo, 2016; Procaccini et al., 2010; Wang et al., 2011)
RG7386	Tetravalent FAP-DR5 Antibody	targets CAFs and defective apoptosis pathway on tumor cells	Stable disease and complete tumor regression with doxorubicin in vivo	Low toxicities	(Brünker et al., 2016)
Immune-targeted					
Chitosan thermogels	Specific targeting of ACT to solid tumor	More direct administration of ACT to bone metastases	Limited research in rat models		(Monette et al., 2016)
Vaccines via whole tumor lysates/fusions	DCs activated against a variety of TAAs	Better and more specific activation of DCs in bone microenvironment	Increased survival among patients with metastatic disease	Multiple trials done, see 97	(de Gruijl et al., 2008; Kajihara et al., 2015)
Carbon black nanoparticles & Antigens with mannosylated dendrimers	Increase antigen uptake and activate DCs	Significant increase of bone-marrow DC activation	Increased effectiveness of other vaccine-based therapies		(Koike et al., 2008; Sheng et al., 2008)
DC-derived exosomes	Endocytosis of exosomes for polyepitopic antigen presentation and response	Strong anti-tumoral T-cell response	High tolerability, with stable disease and partial responses in metastatic disease	Only one phase II trial done, may be more effective with different TAA	(Amigorena, 2000; Klippstein and Pozo, 2010; Zitvogel et al., 1998)
Sialidase	Exogenous sialic acid removal	Increased maturation and stimulation of autologous T-cells	Increased tumor cell apoptosis in murine model		(Silva et al., 2016)
Toll-like receptor agonists (resiquimod, imiquimod, poly ICLC)	Activation of macrophages DCs and other lymphocytes	Alone or in combination with vaccines, decrease immune suppression in tumor microenvironment, can directly induce apoptosis of tumor cells	Dramatic results seen specifically with poly ICLC with complete tumor regression	Considered adjuvants, Montanide also acts similarly	(Liu et al., 2005; Sabado et al., 2015; Salazar et al., 2014; Thapa et al., 2009; Valmori et al., 2007; Wang et al., 2008)
CRISPR-CaS9 edited CAR T-cells	PD-1 knockout	Increase CAR T-cell proliferation and cytotoxicity	No study results posted		NCT02793856
TRUCKs	IL-12 secreting CAR T-cells	Overcomes immunosuppression in tumor microenvironment	Increased efficacy of CAR T-cells, decreased immunosuppression of bone-derived stroma cells		(Chmielewski and Abken, 2012; Chmielewski et al., 2014; Kerkar et al., 2011)
CAR T-cells with chemokine receptors	CCR2 and CXCR4 receptors engineered into CAR T-cells	Better T-cell trafficking to tumor metastases, specifically prostatic metastases for CXCR4	Dramatic increase of TIL including in bone microenvironment	CXCR4 can also be therapeutic target, but inhibition increases osteoclastogenesis	(Asai et al., 2013; Bleul et al., 1996; Craddock et al., 2010; Hillerdal and Essand, 2015; Hirbe et al., 2010; Kantele et al., 2000; Moon et al., 2016)
Anti-FAP CAR T-cells	Targets CAFs	Reverses immunosuppression, activates T-cells against TAAs	Synergy with vaccination, decreasing tumor volume and OS in mouse model		(Gottschalk et al., 2013; Kakarla et al., 2013; Kraman et al., 2010; Wang et al., 2014; Y. Zhang and Ertl, 2016)
Bispecific T-cell Engagers	Target TAA and CD3 for T-cell activation	Increased T-cell cytotoxicity in metastatic disease, unaffected by tumor immunosuppression	Less efficacy compared to CARs due to inability to induce T-cell memory	Low toxicities, easily produced	(Fan et al., 2015; Hillerdal and Essand, 2015)
Cryoablation	Direct destruction of metastases through liquid-cooled probes	Rapid necrotic release of TAA induces immune response throughout body	With anti-ALCAM antibody, complete response in 100% of mouse models, significant pain palliation in patients	Use of Anti-CTLA antibody and adjuvants also improves response	(Brok, 2006; Brok et al., 2006; Gazzaniga et al., 2001; Kudo-Saito et al., 2016; Sabel, 2009; Ravindranath et al., 2002; Udagawa et al., 2006; Waitz et al., 2012)
Vesicular stomatitis virus	Oncolytic virus, highly sensitive to IFN-β response	Targets tumors with defective JAK1 pathway associated with immune resistance	Currently unstudied	Could be next-line treatment after failure of immunotherapies	(Cataldi et al., 2015; Escobar-Zarate et al., 2013; Felt et al., 2015; Greig, 2016; Zaretsky et al., 2016; Zhou et al., 2016)

Calcif Tissue Int (2018) 102:227–250
https://doi.org/10.1007/s00223-017-0353-5

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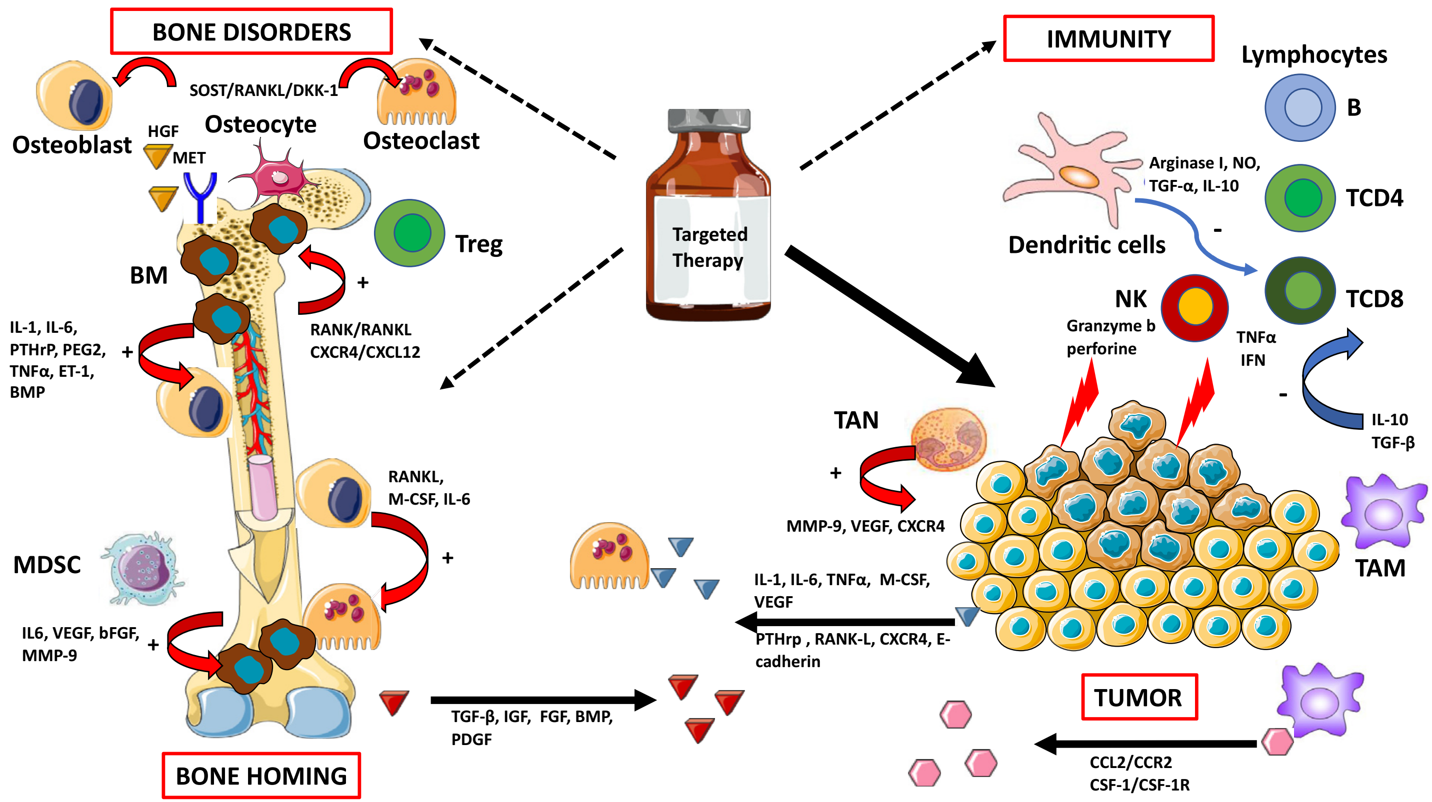
REVIEW

Bone-Targeted Therapies in Cancer-Induced Bone Disease

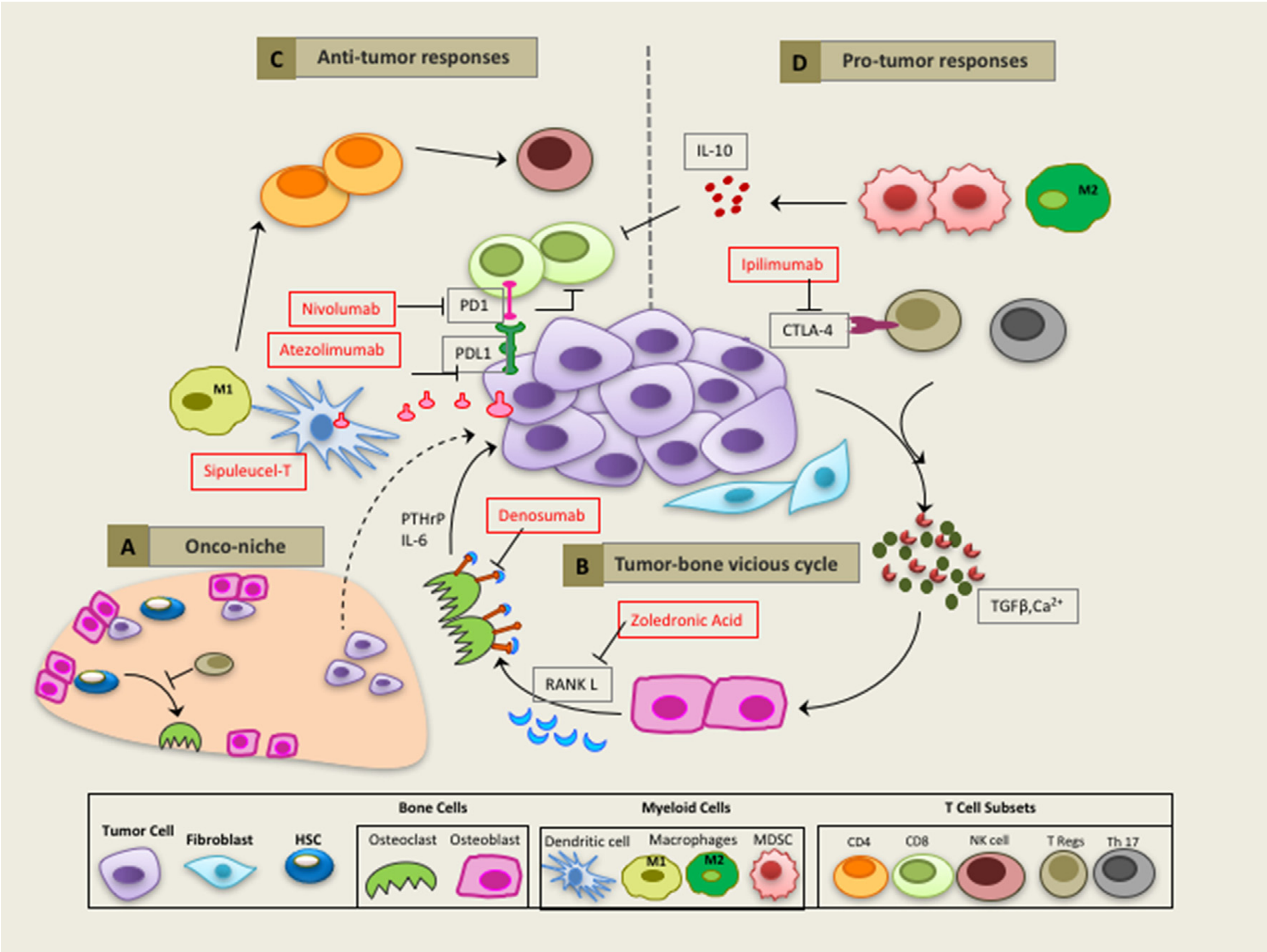
Sofia Sousa[1,2] · Philippe Clézardin[1,2,3]

Table 5 Currently ongoing clinical trials of bone-targeted agents for cancer-induced bone disease

Bone-targeted therapy	Patient population	Clinical trial acronym/number	Phase	Clinical trials.gov link
Denosumab	High-risk early breast cancer	D-CARE NCT01077154	3	https://clinicaltrials.gov/ct2/show/NCT01077154?term=NCT01077154&rank=1
Radium-223	Bone metastatic breast cancer with endocrine therapy	NCT02258464	2	https://clinicaltrials.gov/ct2/show/NCT02258464?term=NCT02258464&rank=1
Radium-223	Bone metastatic breast cancer treated with exemestane	NCT02258451	2	https://clinicaltrials.gov/ct2/show/NCT02258451?term=NCT02258451&rank=1
Radium-223	Osteosarcoma	NCT01833520	1–2	https://clinicaltrials.gov/ct2/show/NCT01833520?term=radium+223&cond=osteosarcoma&rank=1
Radium-223	Thyroid cancer refractory bone metastases	RAD-THYR NCT02390934	2	https://clinicaltrials.gov/ct2/show/NCT02390934?term=NCT02390934&rank=1
Bortezomib	Relapsed multiple myeloma (comparison carfilzomib and dexamethasone versus bortezomib)	NCT01568866	3	https://clinicaltrials.gov/ct2/show/NCT01568866?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=1
Bortezomib	Relapsed multiple myeloma (addition of daratumumab to bortezomib and dexamethasone)	NCT02136134	3	https://clinicaltrials.gov/ct2/show/NCT02136134?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=2
Bortezomib	Relapsed multiple myeloma (pomalidomide, bortezomib and low-dose dexamethasone)	OPTIMISMM NCT01734928	3	https://clinicaltrials.gov/ct2/show/NCT01734928?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=3
Bortezomib	Relapsed multiple myeloma (comparison carfilzomib, dexamethasose and once weekly bortezomib versus twice weekly bortezomib)	ARROW NCT02412878	3	https://clinicaltrials.gov/ct2/show/NCT02412878?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=4
Bortezomib	Relapsed multiple myeloma patients(pomalidomide, bortezomib and low-dose dexamethasone versus high-dose dexamethasone)	NIMBUS NCT01311687	3	https://clinicaltrials.gov/ct2/show/NCT01311687?term=Bortezomib&recrs=d&cond=Multiple+Myeloma+in+Relapse&phase=2&rank=5
Saracatinib	Cancer-induced bone pain	SarCaBon NCT02085603	2	https://clinicaltrials.gov/ct2/show/NCT02085603?term=NCT02085603&rank=1
Cabozantinib	Bone metastatic castration-resistant prostate cancer	NCT01599793	2	https://clinicaltrials.gov/ct2/show/NCT01599793?term=cabozantinib&cond=Bone+Metastases%2C+cancer&rank=1
Cabozantinib	Advanced solid (non-breast, non-prostate) malignancies and bony metastases	NCT01588821	2	https://clinicaltrials.gov/ct2/show/NCT01588821?term=cabozantinib&cond=Bone+Metastases%2C+cancer&rank=4
Cabozantinib	Non-metastatic and metastatic castration-resistant prostate cancer	NCT01703065	Pilot	https://clinicaltrials.gov/ct2/show/NCT01703065?term=cabozantinib&cond=Bone+Metastases%2C+cancer&rank=5
Cabozantinib	Metastatic colorectal cancer	CaboMAb NCT02008383	1	https://clinicaltrials.gov/ct2/show/NCT02008383?term=cabozantinib&recrs=abd&draw=1&rank=2
Cabozantinib	Multiple myeloma	NCT03201250	1-2	https://clinicaltrials.gov/ct2/show/NCT03201250?term=cabozantinib&recrs=abd&draw=3&rank=11
Cabozantinib	Androgen-dependent metastatic prostate cancer	NCT01630590	2	https://clinicaltrials.gov/ct2/show/NCT01630590?term=cabozantinib&recrs=abd&draw=3&rank=12
Cabozantinib	Metastatic hormone receptor-positive breast cancer	NCT01441947	2	https://clinicaltrials.gov/ct2/show/NCT01441947?term=cabozantinib&recrs=abd&draw=3&rank=15
Cabozantinib	Relapsed osteosarcoma or Ewing sarcoma	NCT02243605	2	https://clinicaltrials.gov/ct2/show/NCT02243605?term=cabozantinib&recrs=abd&draw=4&rank=22
Sotatercept	Refractory multiple myeloma treated with lenalidomide or pomalidomide and dexamethasone	NCT02406521	1	https://clinicaltrials.gov/ct2/show/NCT01562405?term=NCT01562405&recrs=abd&rank=1

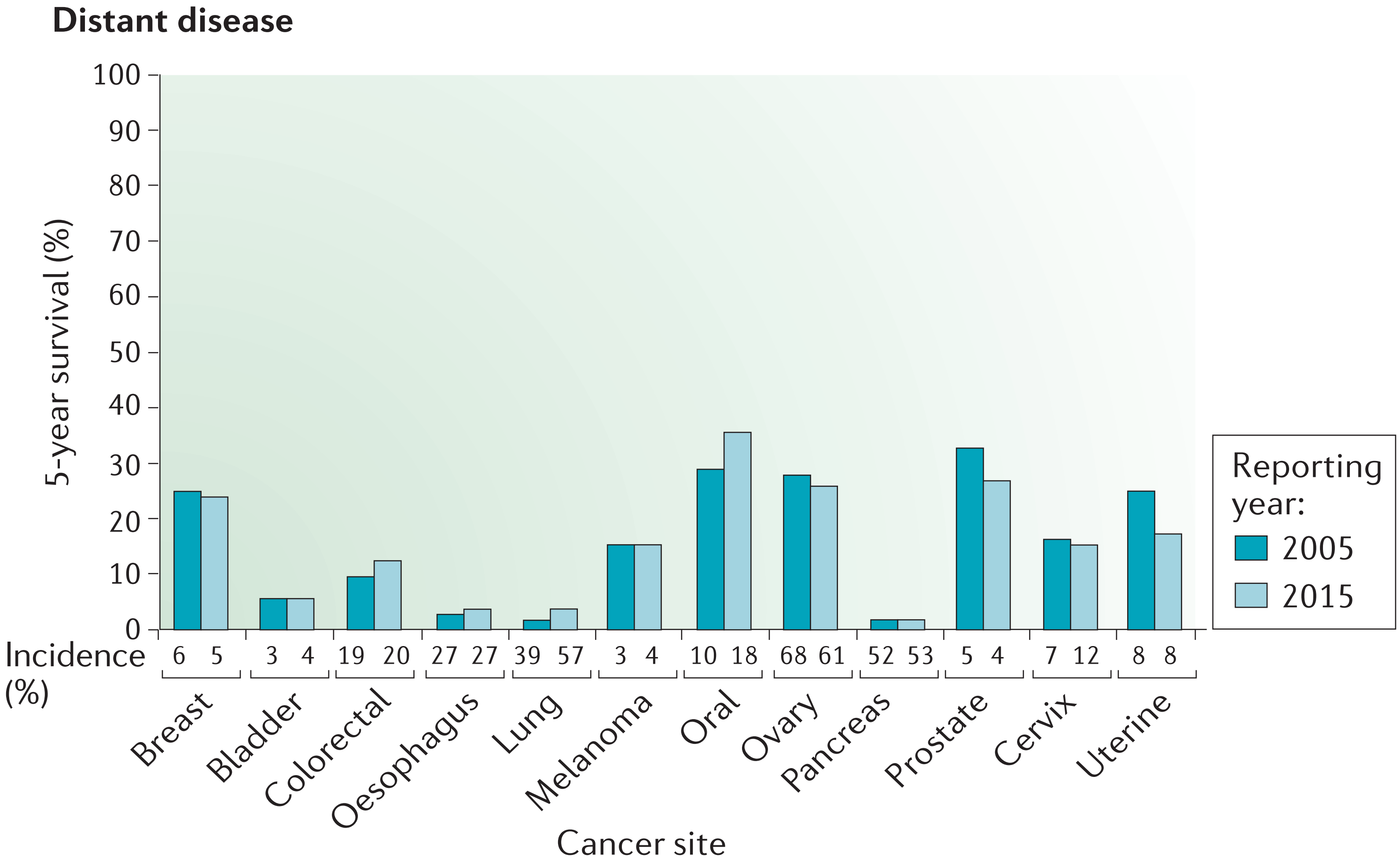

BONE DISORDERS
SOST/RANKL/DKK-1
Osteoblast
HGF
MET
Osteocyte
Osteoclast
Treg
BM
+
RANK/RANKL
CXCR4/CXCL12
IL-1, IL-6,
PTHrP, PEG2,
TNFα, ET-1,
BMP
+
RANKL,
M-CSF, IL-6
+
MDSC
IL6, VEGF, bFGF,
MMP-9
+
TGF-β, IGF, FGF, BMP,
PDGF
BONE HOMING
Targeted
Therapy
IMMUNITY
Lymphocytes
B
Arginase I, NO,
TGF-α, IL-10
TCD4
-
Dendritic cells
TCD8
NK
Granzyme b
perforine
TNFα
IFN
-
IL-10
TGF-β
TAN
+
MMP-9, VEGF, CXCR4
TAM
IL-1, IL-6, TNFα, M-CSF,
VEGF
PTHrp , RANK-L, CXCR4, E-
cadherin
TUMOR
CCL2/CCR2
CSF-1/CSF-1R

Osteoimmunology and Bone Metastasis



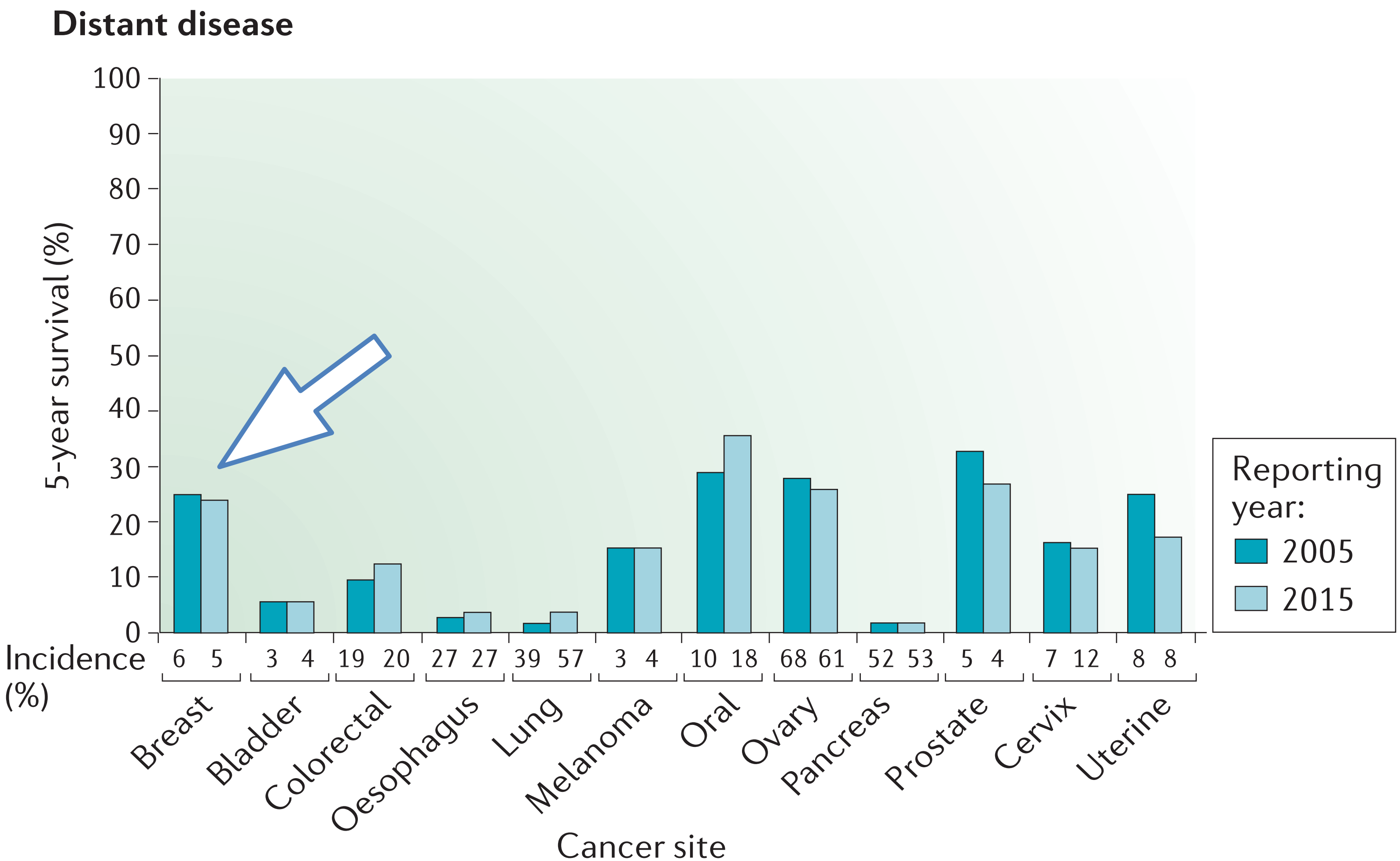
Z.Z. Reinstein et al. / Critical Reviews in Oncology/Hematology 117 (2017) 114–127

...alarmingly, however!



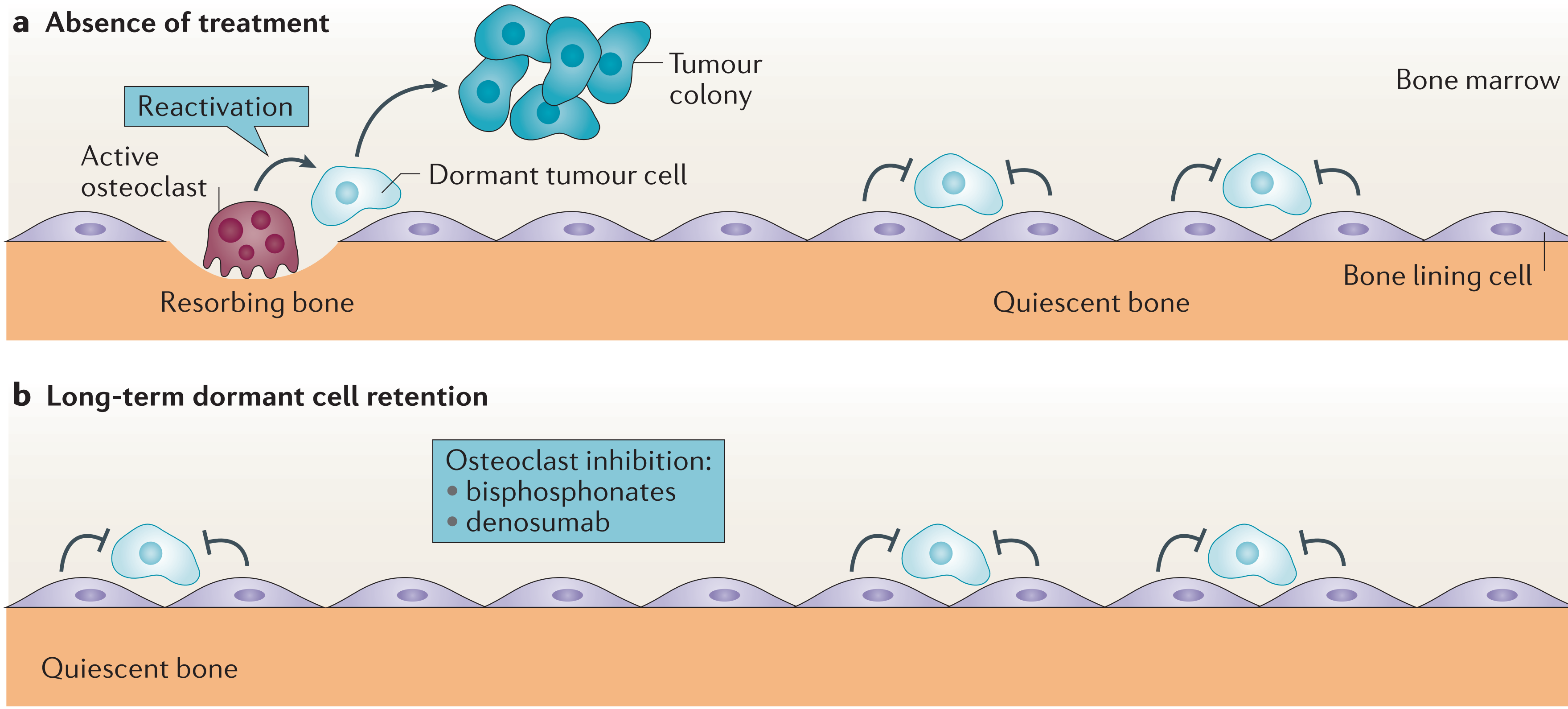
Steeg, Nat Rev Ca 2016

…alarmingly, however!



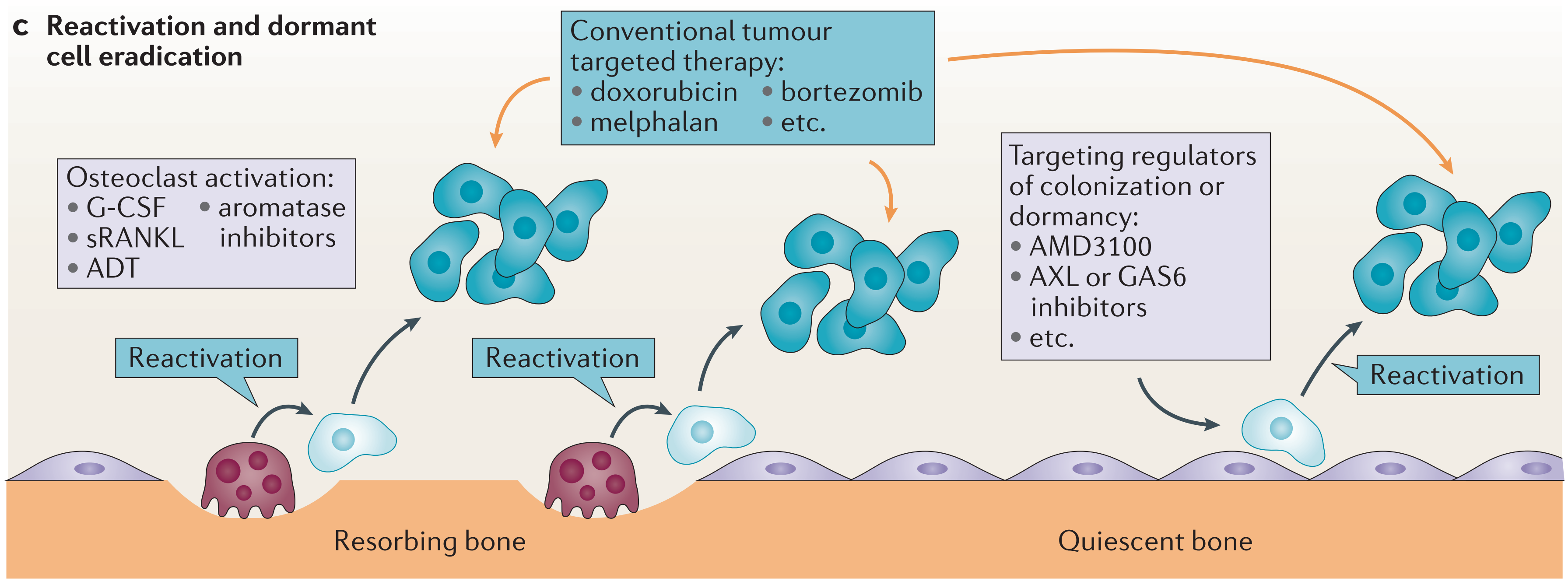
Steeg, Nat Rev Ca 2016

Targeting a Concept: Niche-Targeted Tx for Bone Mets



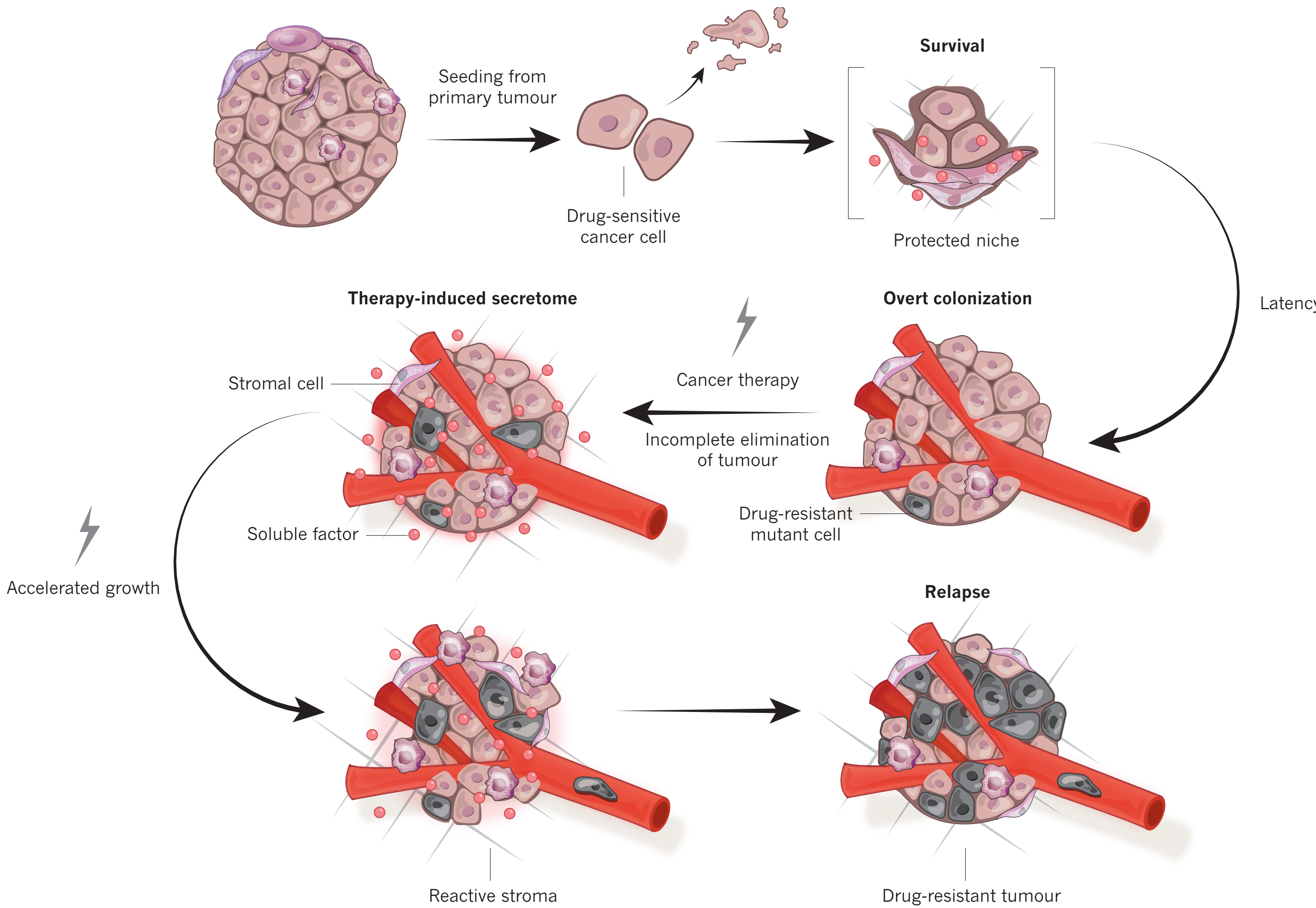
Chajar Nat Rev Cancer, 2015; Croucher et al. Nat Rev Cancer 2016

Targeting a Concept: Niche-Targeted Tx vs Bone Mets



Chajar Nat Rev Cancer, 2015; Croucher et al. Nat Rev Cancer 2016

REVIEW INSIGHT



Massague and Obenauf, Nature 2016

Future Directions

- Identification of metastasis mediators, **common** to different organs and tumor types that could serve as **potential Tx TARGETs** (e.g check-check-point ImmunoTx)
- **CT DNA, EV, CTC, DTC analysis** to monitor Tx response and early recurrence
- Therapeutic strategies towards **quiescent DTC/Ca stem cells** and not just growing cancer cells
- Better understanding of **CTC colonisation**
- Unveil **bone cell biology secrets**
- **Multidisciplinary** approach
- **Further clinical investigation** to confirm preclinical data
- Better priclinical models
- **Prevention** (…lifestyle)!

Thank you!