Sistema Sanitario Regionale Piemonte
Azienda Ospedaliera Nazionale
SS. Antonio e Biagio e Cesare Arrigo
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rete oncologica

AIOM

SIPMO

SICMF
Società Italiana Chirurgia Maxillo-Facciale

Osteonecrosi dei Mascellari (ONJ): Prevenzione, Diagnosi, Trattamento UPDATE 2009

23 Giugno 2009

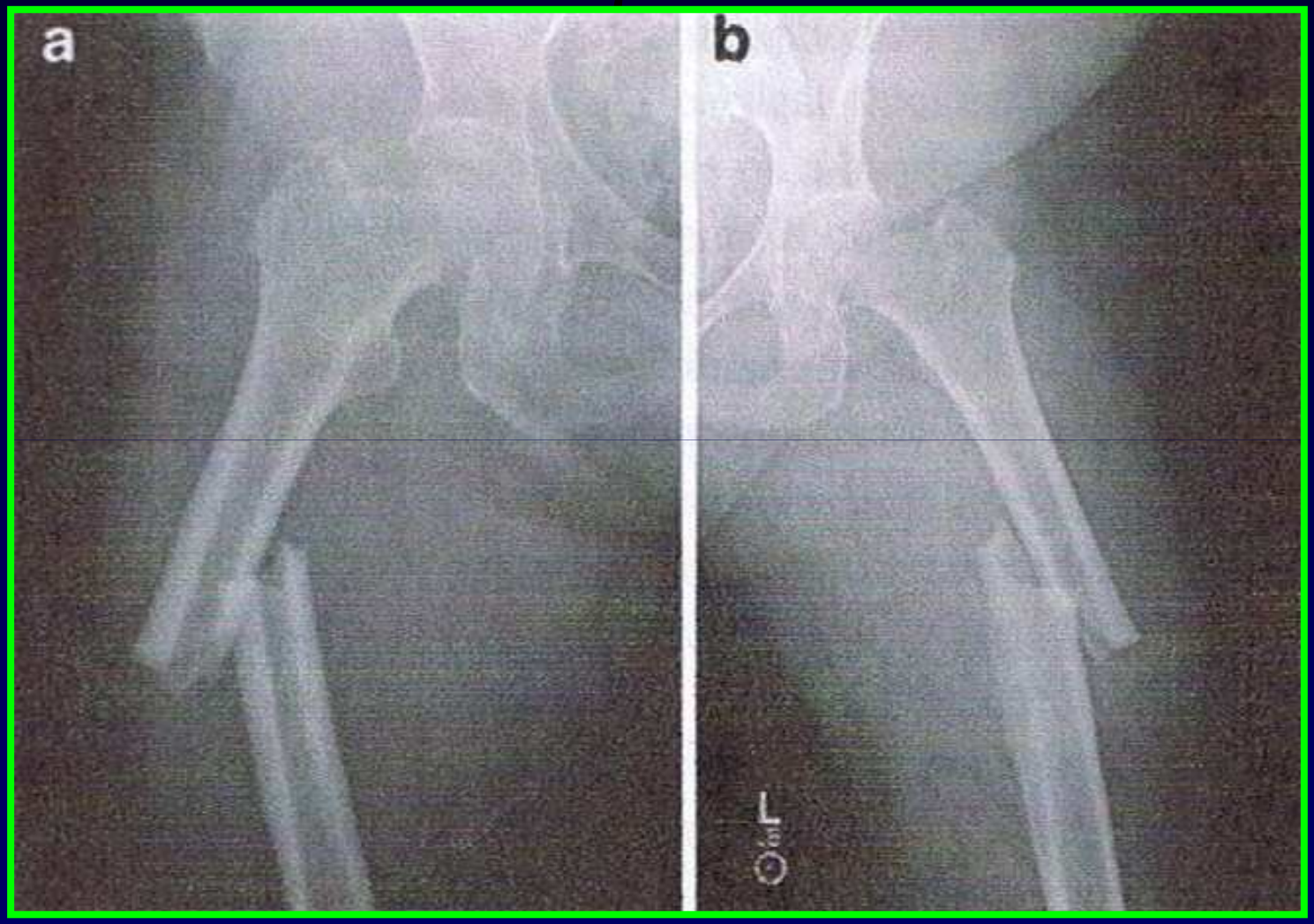
Associazione Cultura e Sviluppo
Piazza F. De Andrè 76 - Alessandria

Medicina Interna I
Dipartimento di Scienze Cliniche e Biologiche
Università degli Studi di Torino
AOU San Luigi, Orbassano

Patogenesi e fisiopatologia della ONJ

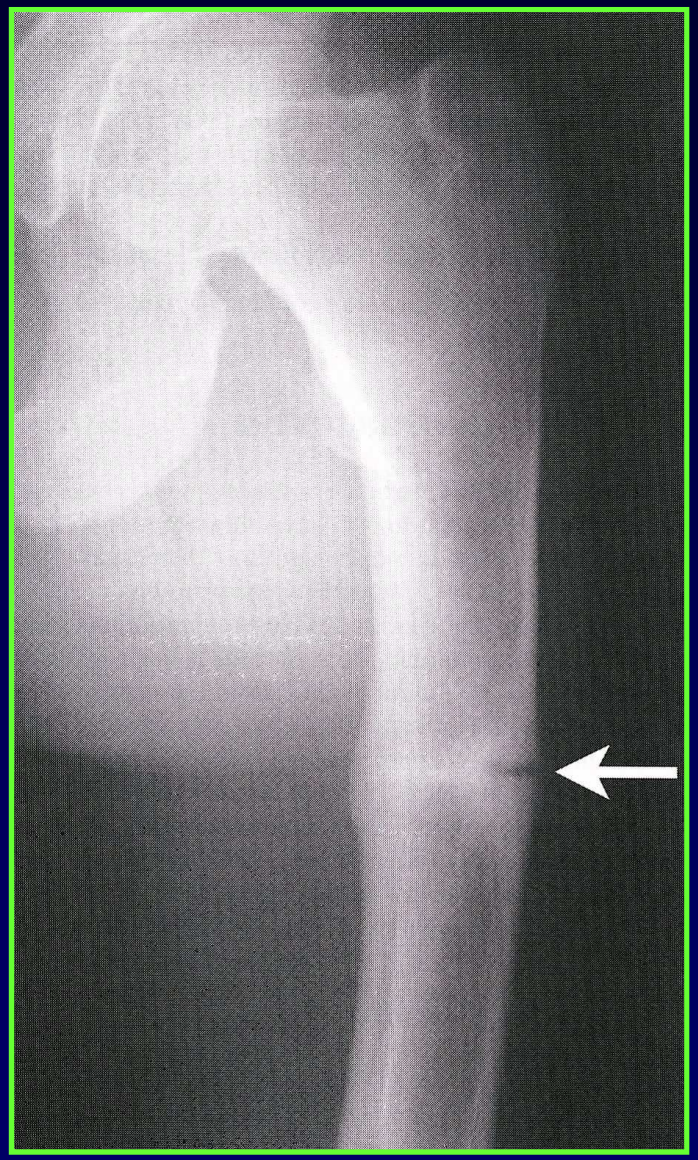
Alberto Angeli

Fratture femorali



Lenart BA. *et al.* Osteoporos Int 2008: DOI 10.007/s00198-008-08-05x

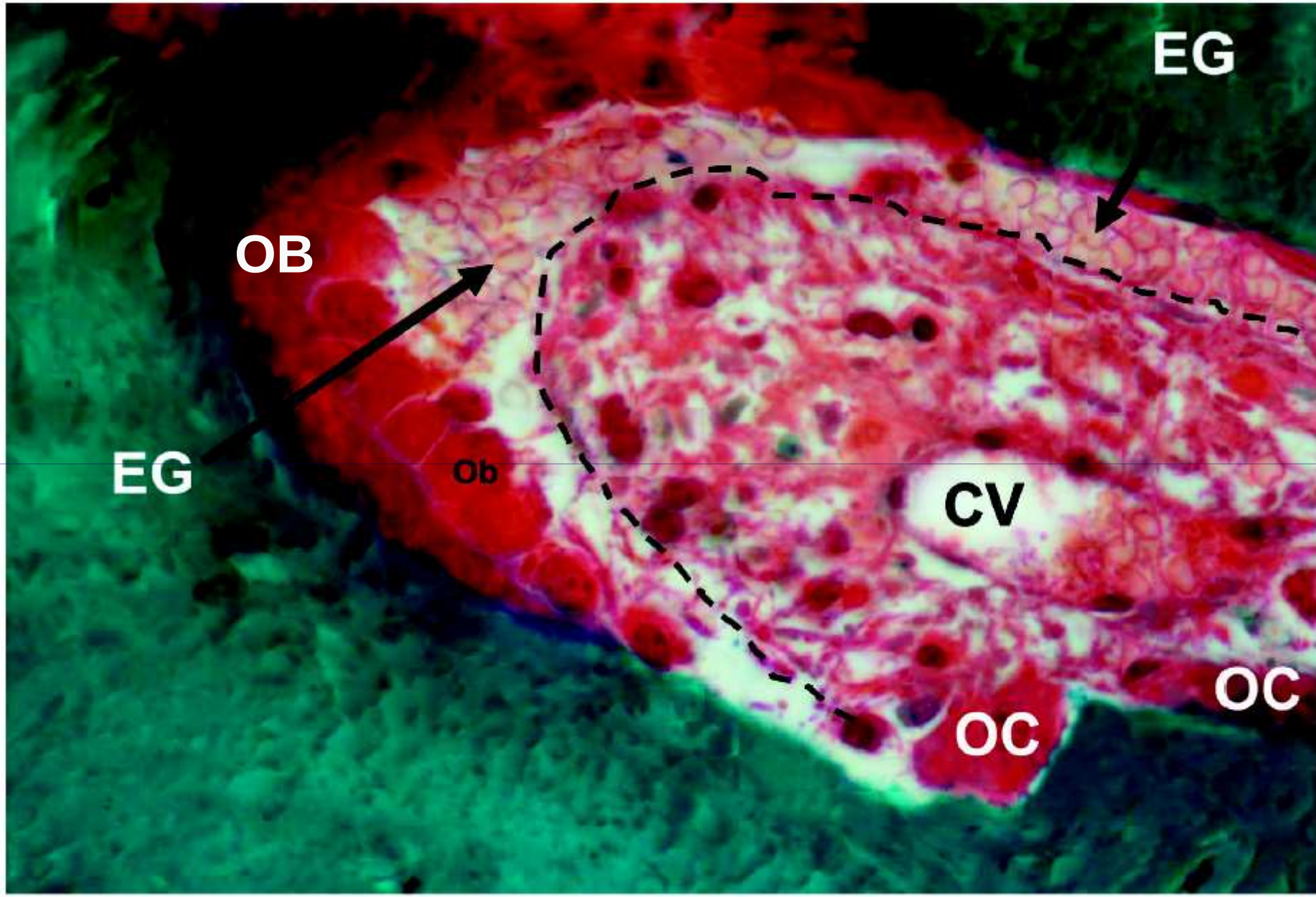
Fratture femorali



Whyte MP. *J Bone Min Res* 2009; 6: 1132-1133

HETEROGENEITY OF SKELETAL SITES

- Bone architecture and biomechanics (trabecular/cortical).
- Modeling/remodeling rate.
- BMU activation and control.
- Subpopulations of bone cells.
- Osteoimmunology.



Eriksen EF et al. J Bone Miner Res. 2007;22:1-6.

BISPHOSPHONATE-RELATED (BR) ONJ

Definitions given by some medical societies (AAOMS position paper, update 2009; ASBMR task force 2007; CAOMS 2008).

- A clinical diagnosis.
- A patient is considered to have BRONJ if all following 3 characteristics are present:

1. Current or previous treatment with a bisphophonate.
2. Area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider.
3. No history of radiation of the jaw.

Clin Oral Investig 2009 Jun 4. [Epub ahead of print]

Bisphosphonate-associated osteonecrosis of the jaw: what do we currently know? A survey of knowledge given in the recent literature.

Rustemeyer J, Bremerich A.

Generic name	Brand name	Formulation	Manufacturer	Nitrogen containing	FDA approval
Alendronate	Fosamax®	Oral	Merck & Co.	Yes	1995
Etidronate	Didronel®	Oral/IV	Procter & Gamble	No	1977
Ibandronate	Bonviva®	Oral	Roche	Yes	2005
Pamidronate	Aredia®	IV	Novartis	Yes	1991
Risedronate	Actonel®	Oral	Procter & Gamble	Yes	1998
Tiludronate	Skelid®	Oral	Sanofi	No	1997
Zoledronic Acid	Zometa®	IV	Novartis	Yes	2001

Rustemeyer J, 2009.

29th Annual Meeting of the ASBMR, Honolulu, September 16-19, 2007

Progression of osteonecrosis of the jaw in breast cancer patients even with discontinuation of intravenous bisphosphonate therapy.

Barracan-Adjenian C et al.

- Discontinuation of the intravenous BPs in breast cancer patients does not prevent further evolution of the lesions as detected using cone-beam computerized tomography (CBCT).
- After cessation of BP-therapy, a 2-yr follow-up specifically addressed to ONJ is recommended.

ONJ. Site specific complication
Why the jaw?

- Jaw bone: unique-blood supply, structure, function & microbiology
- Thin t mucosa & periosteum barrier between jaw bone & microorganism-rich & trauma-intense external environment
- Bone turnover higer in jaw related to masticatory forces & presence of teeth
- Teeth separed from bone by thin connective tissue & allowing bacteria easy access
- Jaw subjected to dental procedures & dental disease requiring bone repair
- Concentration of bisphosphonates may be higher in the jaw

Adamo V. *et al.* Expert Opin Pharmacoter 2008; 9: 1351-1361
Marx RE. *et al.* J Oral Maxillfac Surg 2005; 63: 1351-1361

Expert Meeting on ONJ, *EMEA*, London 2009

J Oral Pathol Med (2006) 35: 155–60

www.blackwellmunksgaard.com/jopm

Osteonecrosis of the jaws in patients treated with bisphosphonates – histomorphologic analysis in comparison with infected osteoradionecrosis

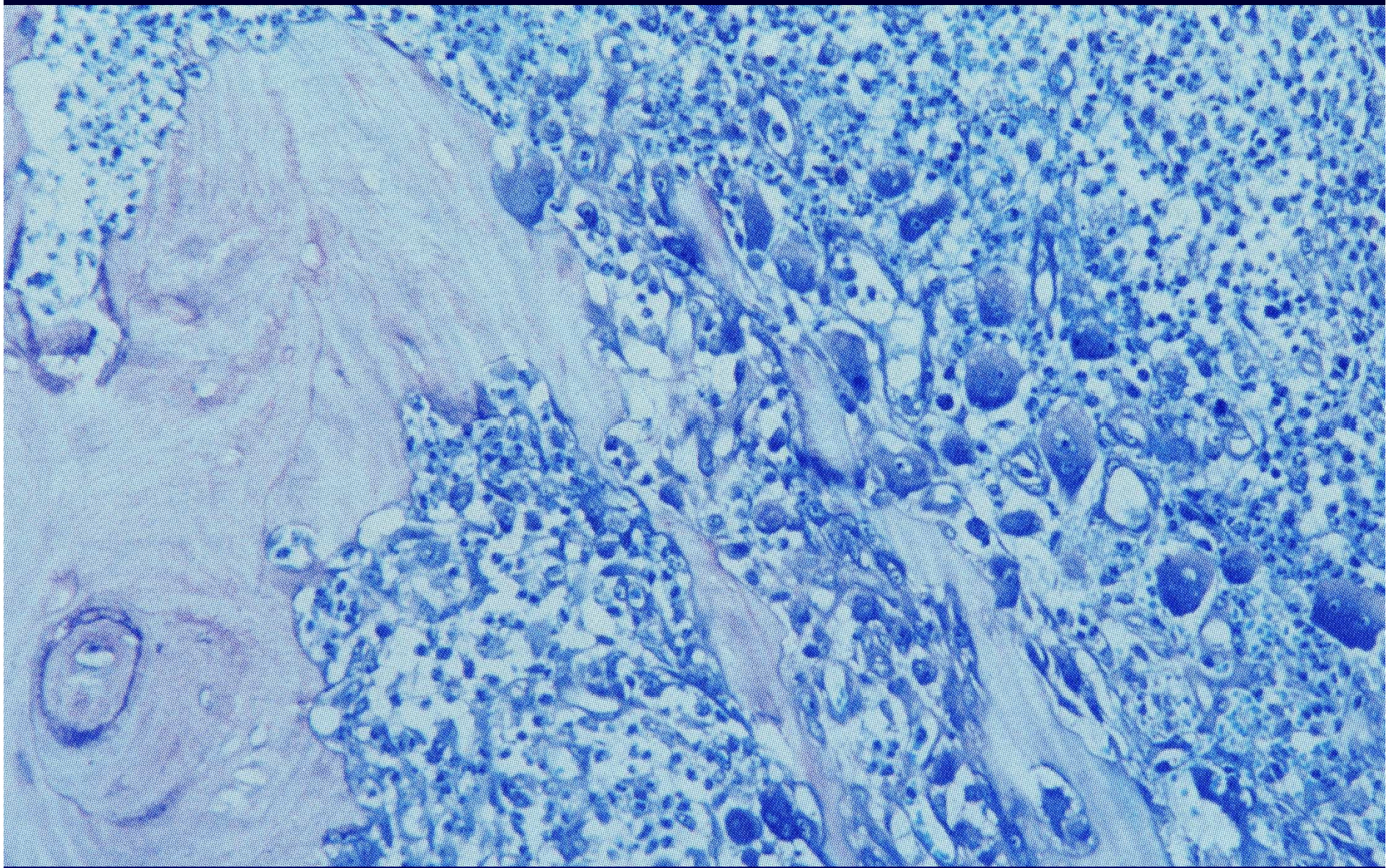
Torsten Hansen[1]*, Martin Kunkel[2]*, Achim Weber[1], C. James Kirkpatrick[1]

[1]Institute of Pathology, Johannes Gutenberg University, Mainz; [2]Clinic of Maxillofacial Surgery, Johannes Gutenberg University, Mainz, Germany

- *Actinomyces* colonies were found in all cases studied. These bacteria typically formed numerous sulfur granules. The colonies were most commonly detected at the site of necrotic bone exhibiting remarkable signs of erosion. Osseous tissue was not clearly demarcated but showed numerous irregularly shaped contours.
- In all cases, we found *Actinomyces* colonies in close contact with the necrotic bone tissue, rendering it likely that these organisms are involved in the chronic, non-healing inflammatory processes.

Actinomicosi cervico-facciale (infezione da *Actinomyces Israelii*)

- *A. Israelii* è un normale costituente della flora batterica orale. E' reperibile nel solco gengivale, in prossimità di denti cariati. Spesso microorganismo prevalente nelle lesioni periapicali.
- Penetra facilmente attraverso la mucosa danneggiata.
- Meccanismi di difesa locali non chiari. Progressione dell'actinomicosi associata all'assenza di reazioni immunitarie efficaci.
- Facile co-infezione con anaerobi Gram+ e Gram- (*B. actinomycetes comitans*).



ISCHEMIC MICROENVIRONMENT PREDISPOSES PROGRESSION OF ONJ

- Excess fat within critical areas of bone medullary space (aging; glucocorticoids; alcohol abuse; diabetes; impaired osteoblast differentiation; drugs).
- Prothrombotic conditions (genetics; immune mediated; smoking; atheroschlerosis; glucocorticoids; cancer related thrombophilia and coagulopathies; DIC).
- Anti-angiogenetic medication.

Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents

Jeanny B. Aragon-Ching[1], Yang-Min Ning[1], Clara C. Chen[2], Lea Latham[1], Jean-Pierre Guadagnini[3], James L. Gulley[1], Philip M. Arlen[1], John J. Wright[4], Howard Parnes[5], William D. Figg[6], and William L. Dahut[1,*]

Cancer Invest.;27(2):221-6.

Combination of Bisphosphonates and Antiangiogenic Factors Induces Osteonecrosis of the Jaw More Frequently than Bisphosphonates Alone

C. Christodoulou[a, b] A. Pervena[a] G. Klouvas[a] E. Galani[a] M.E. Falagas[b]
G. Tsakalos[a] A. Visvikis[a] A. Nikolakopoulou[a] V. Acholos[a] G. Karapanagiotidis[a]
E. Batziou[a] D.V. Skarlos[a]

Oncology 2009; 76: 209-211

Associazione Nazionale Dentisti Italiani

Società Italiana dell'Osteoporosi del Metabolismo Minerale e delle Malattie dello Scheletro

RACCOMANDAZIONI RELATIVE ALL'OSTEONECROSI DELLA MASCELLA/MANDIBOLA ASSOCIATA A TERAPIA CON BISFOSFONATI IN PAZIENTI CON OSTEOPOROSI: DOCUMENTO DI CONSENSO

Associazione Nazionale Dentisti Italiani – ANDI
Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro – SIOMMMS

Le raccomandazioni sono state condivise dalle seguenti Società Scientifiche, che si sono impegnate a partecipare alla futura revisione delle stesse:

Collegio dei Reumatologi Ospedalieri Italiani – CROI
Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti – FADOI
Società Italiana di Medicina Fisica e Riabilitativa – SIMFER
Società Italiana di Reumatologia – SIR
Società Italiana di Radiologia Medica - SIRM

Fattori di rischio per ONJ legati al paziente in trattamento per osteoporosi

- patologia bucco-dentale
- diabete non controllato
- terapia corticosteroidea cronica
- malattie ematologiche
- alcool, fumo
- trattamento immunosoppressivo
- sindrome da immunodeficienza acquisita

~60-80% of ONJ following recent dental or oral surgical procedures

(Ruggiero, *J Maxillofac Surg* 2004; Mavrokokki, *J Maxillofac Surg* 2007)

Local risk factors for ONJ (AAOMS position paper):

- Dentoalveolar surgery, icluding:
  - Extractions
  - Dental implant placemet
  - Periapical surgery
  - Periodontal surgery involving osseous injury
- Local anatomy
  - Mandible vs maxilla: 2:1, areas with thin mucosa overlying bony prominences
- Concomitant oral disease
  - Inflammatory dental disease; e. g. periodontal and dental abscesses

Expert Meeting on ONJ, *EMEA*, London 2009

Actinomicosi cervico-facciale Caratteristiche cliniche

- Cute sovrastante di colorito rosso cupo o porpora; infiltrati duri, irregolari; tragitti fistolosi con essudato purulento color giallo-zolfo contenenti granuli.
- Dolore scarso o assente all'inizio; di crescente intensità con il sopravvenire di co-infezioni.
- Febbre scarsa o assente. Condizioni generali non compromesse.
- Autentico processo osteomielitico, con distruzione ossea o con rarefazione ossea (pseudocitsi osteonecrotica)

OSTEONECROSIS OF THE JAW: MULTIPLE ETIOLOGIES

- Idiopathic
- Post-traumatic
- Dysbaric
- Ischemic: → primary: reduced local bone's blood supply

  →secondary: associated with sistemic disease
- Osteomyelitic (infectiuos agents)
- Radiation-induced (osteoradionecrosis)
- Drug-induced → Bisphosphonates

  → Anti-angiogenetic agents

Expert Meeting on ONJ, *EMEA*, London 2009

BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAW: CLINICAL STAGING

STAGE 1 — Exposed necrotic bone that is asimptomatic.

STAGE 2 — Exposed necrotic bone associated with pain and infection.

STAGE 3 — Exposed necrotic bone with pain, infection, and one or more of the following:

- Pathological fractures
- Extraoral fistula
- Osteolysis extending to the inferior border

HETEROGEITY OF SKELETAL SITES

- Bone architecture and biomecanicy (trabecular/cortical).
- Modeling/remodeling rate.
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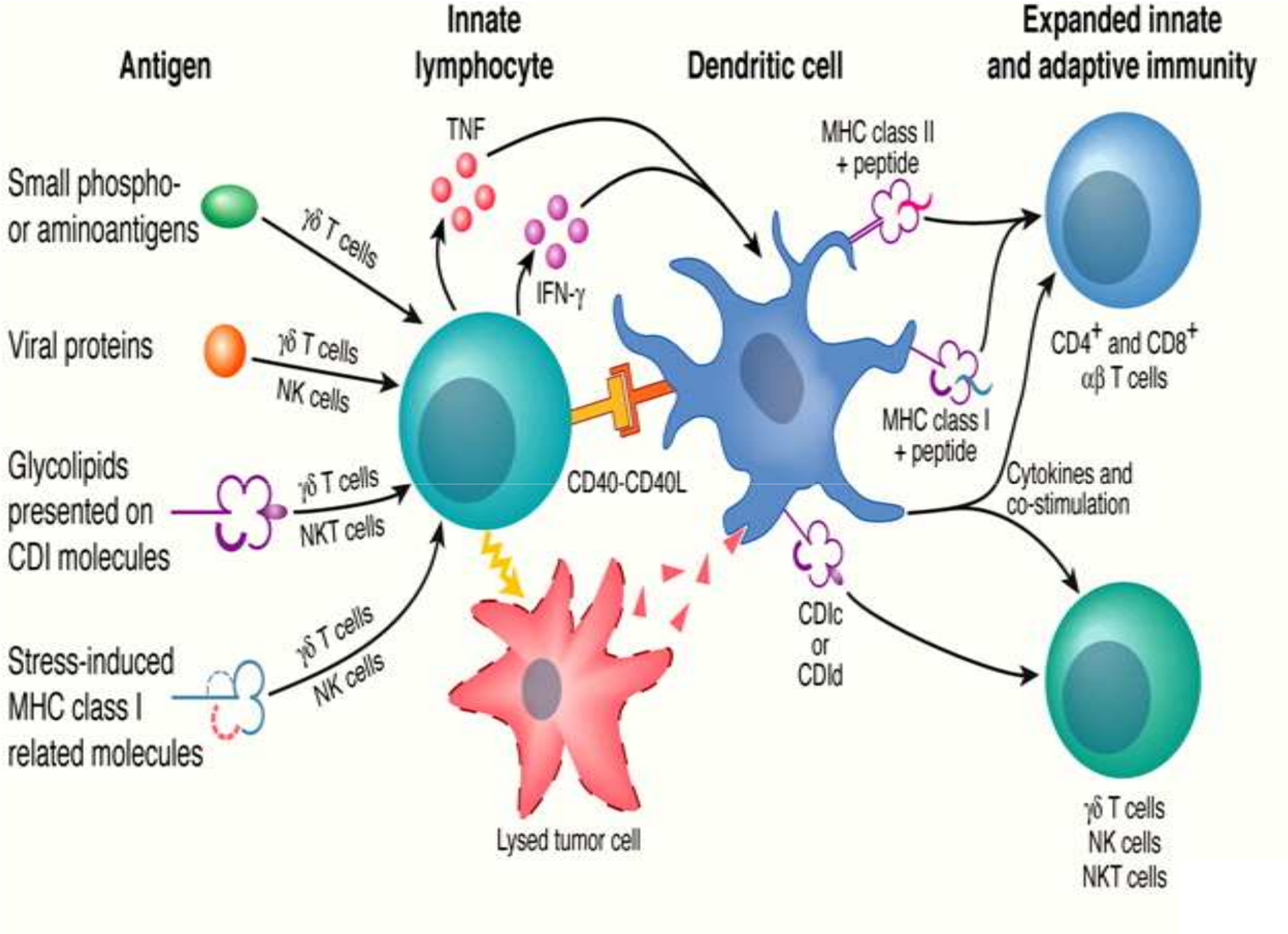
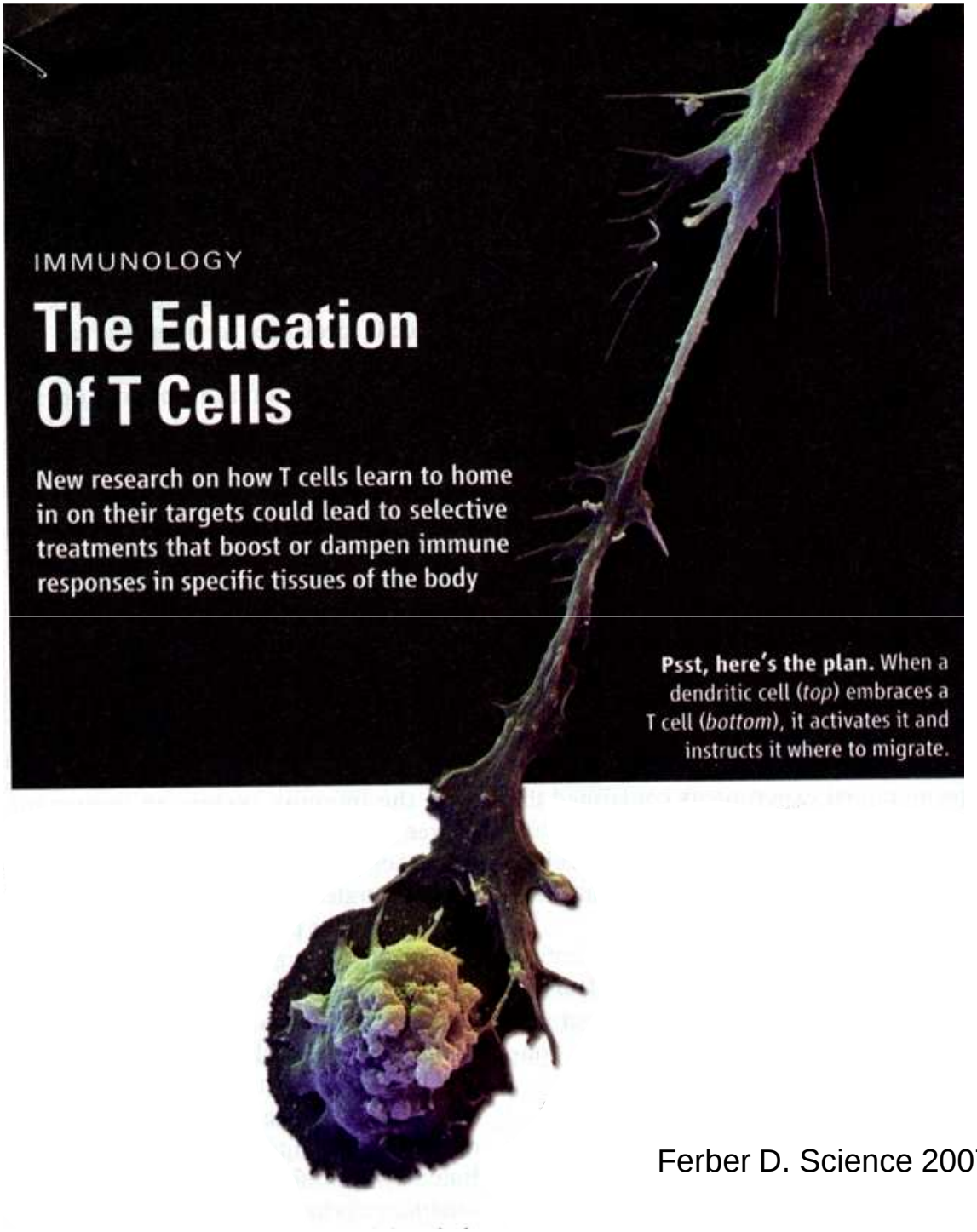
- Subpopulation of bone cells.
- Osteoimmunology.



Munz C et al. J Exp Med 2005;202:203-7.



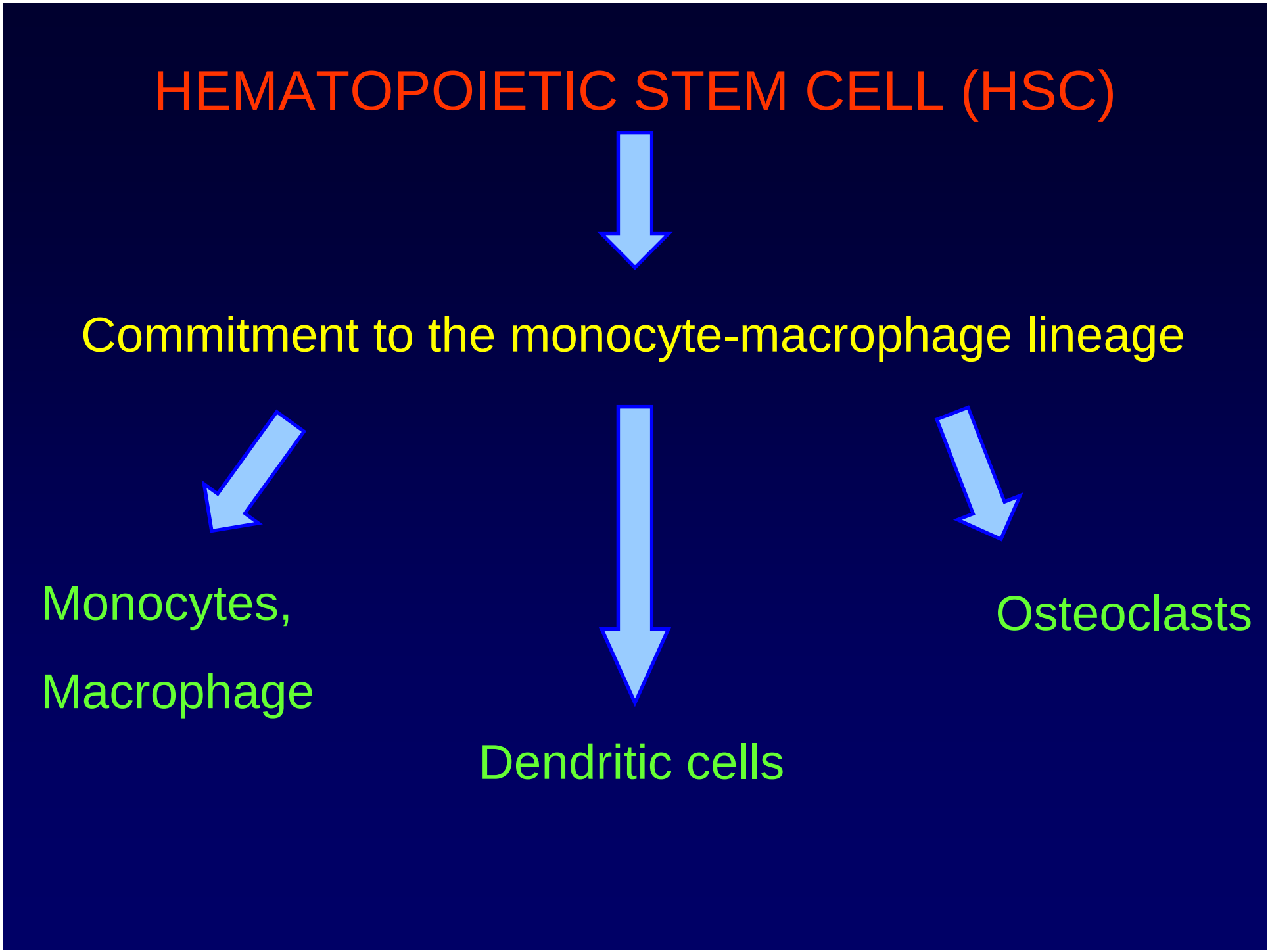
IMMUNOLOGY

The Education Of T Cells

New research on how T cells learn to home in on their targets could lead to selective treatments that boost or dampen immune responses in specific tissues of the body

Psst, here's the plan. When a dendritic cell (*top*) embraces a T cell (*bottom*), it activates it and instructs it where to migrate.

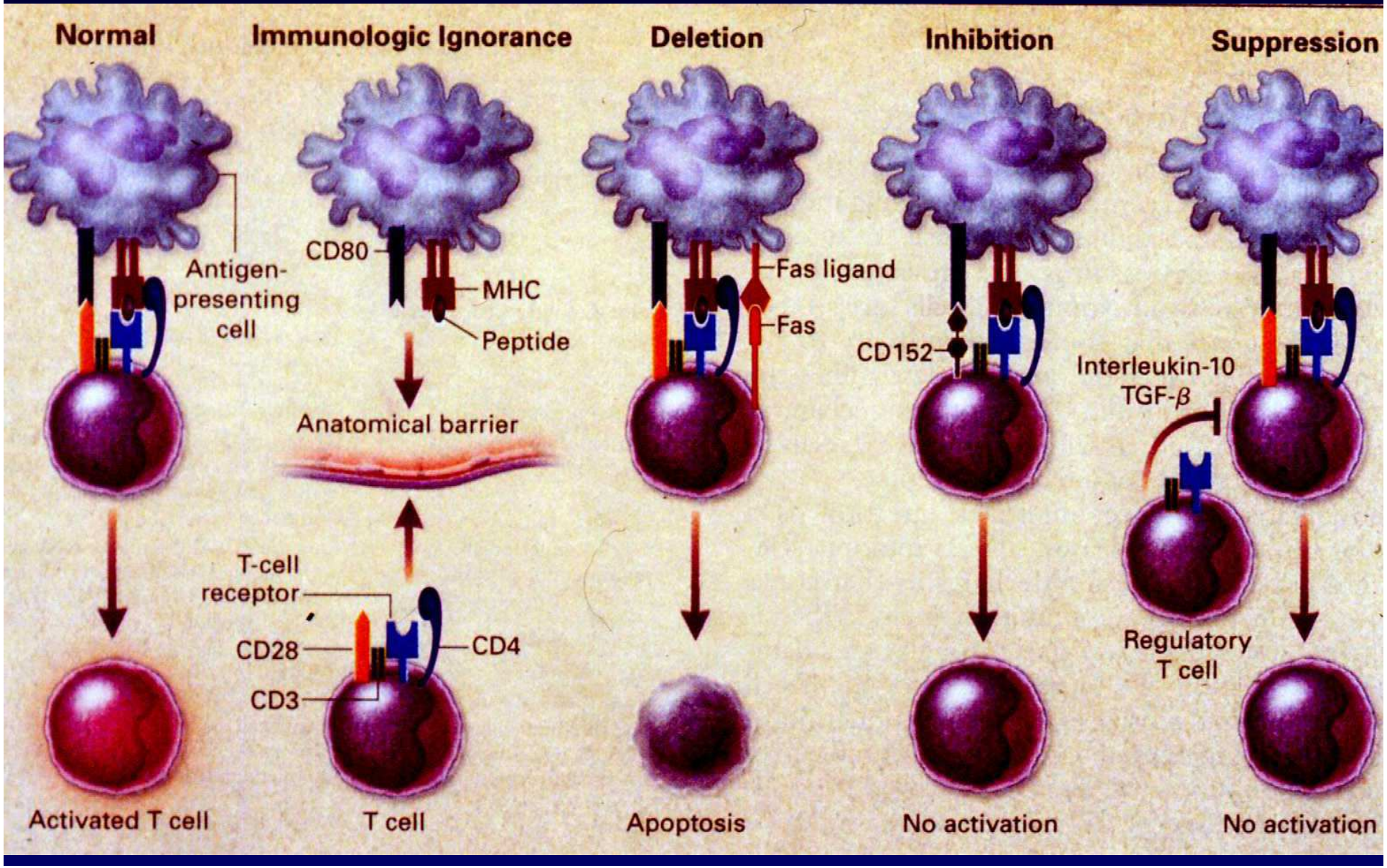
Ferber D. Science 2007:316;191-3.


HEMATOPOIETIC STEM CELL (HSC)
Commitment to the monocyte-macrophage lineage
Monocytes,
Macrophage
Dendritic cells
Osteoclasts

Dendritic cells

- Key component in bridging innate and adaptive immunity
- Activate naive T cells after presentation of Ag fragments bound to MHC-encoded molecules
- Maintain intracellular pools of undegraded Ags that can be recycled to the cell surface
- To detect invading pathogens, display an array of pattern-recognition receptors, including toll-like receptors
- Signaling by toll-like receptors, migration, secretion of cytokines, surface expression of class II MHC molecules and costimulatory molecules, all depend on rapid elevation of intracellular Ca^{2+} concentration

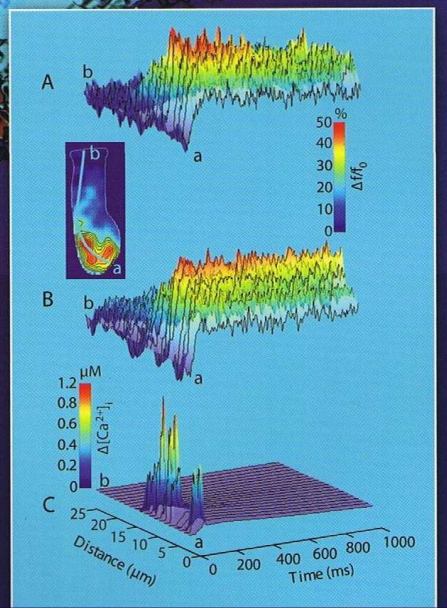
Possibili meccanismi interferenti con la funzione delle Dendritic Cells



Volume 45 Number 1 Pages 1–98 January 2009 ISSN 0143-416

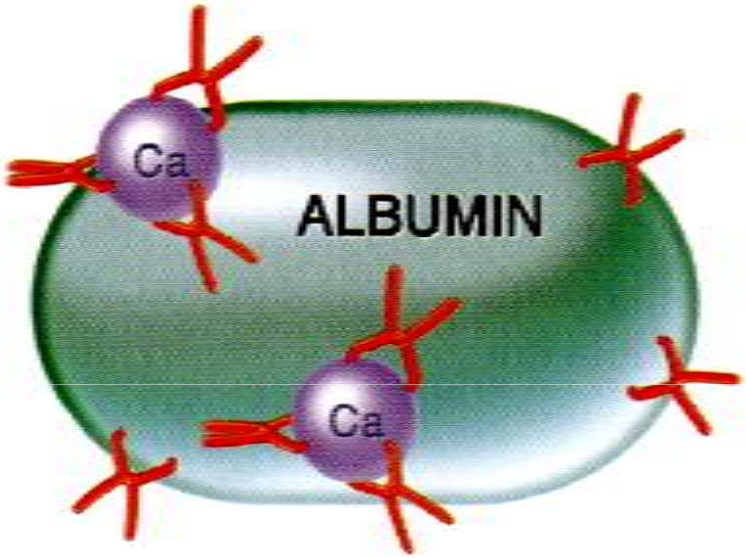
ELSEVIER

cell calcium

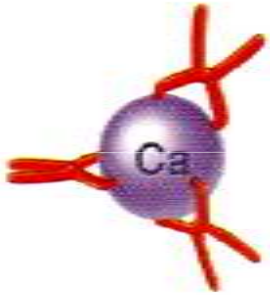


- Bivalent cations are essential for all living cells
- Tight control of the intracellular concentations of bivalent cations prevents the formation of unwanted complexes or chemical reactions that are toxic to the cell
- Storage, binding and transport are key to cellular homeostasis for Ca^{2+}, Mg^{2+}, Zn^{2+}, Fe^{2+}, Mn^{2+}, Cd^{2+}, Co^{2+}

Nies DH. Editorial. Science, September 21st, 2007



Bisphosphonate complex bound to albumin



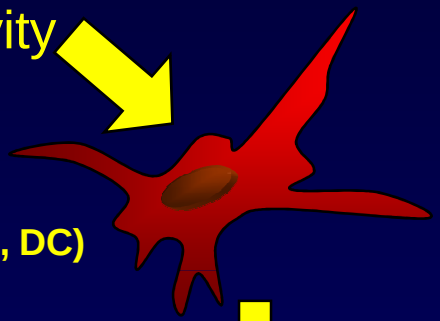
Bisphosphonate complex bound with a bivalent cation (e.g. Ca, Mg, Fe)

Unattatched bisphosphonate molecule

Aminobisphosphonate infusion *in vivo*

Uptake by cells with high endocytotic activity

Osteoclast



APC (Monocite, DC)

Inhibition of mevalonate pathway

Functional inactivation/apoptosis

Inhibition of bone resorption

Inhibition of mevalonate pathway

Accumulation of mevalonate metabolites

Stimulation of γδ T cells
Inhibition of APC funcion

KEY POINTS IN UNDERSTANDING LOCAL IMMUNOSOPPRESSIVE EFFECTS OF BISPHOSPHONATES IN THE JAW

- BP accumulation in the bone microenvironment (high bone turnover).
- BP recycling and internalization in cells of the monocyte-macrophage lineage including APC.
- Diphasic effect as a function of intracellular BP concentration (low stimulatory; high inhibitory). Role of accumulating IPP.
- BP electrical charge and complexing with Ca^{2+} and other bivalent cations essential for immune communication.
- Underlying disease. Comorbidities. Systemic immunological defects. Hypoxia. Additive/sinergic effects by concomitant drugs.

BISPHOSPHONATES-ASSOCIATED OSTEONECROSIS OF THE JAW: A MULTIFACTORIAL PATOGENESIS

Possible pathophysiological mechanism of osteonecrosis of the jaw

Five main mechanism are discussed in recent review aricles

- Excessive reduction of bone turnover
- Angiogenesis
- Bisphosphonate toxicity to soft tissue
- Bisphosphonate toxicity to bone
- Infection

Novince CM. et al.Cell Tissue Organs 2009; 189: 275-283
Reid IR. Bone 2009; 44: 4-10
Silverman SL. Et al. Am J Med 2009; 122: S33- S45

Identification of Microbial Biofilms in Osteonecrosis of the Jaws Secondary to Bisphosphonate Therapy

*Parish P. Sedghizadeh, DDS, MS,**
Satish K.S. Kumar, BDS, MDSc,† Amita Gorur, MS,‡
Christoph Schaudinn, PhD,§ Charles F. Shuler, DMD, PhD,¶
and J. William Costerton, PhD‖

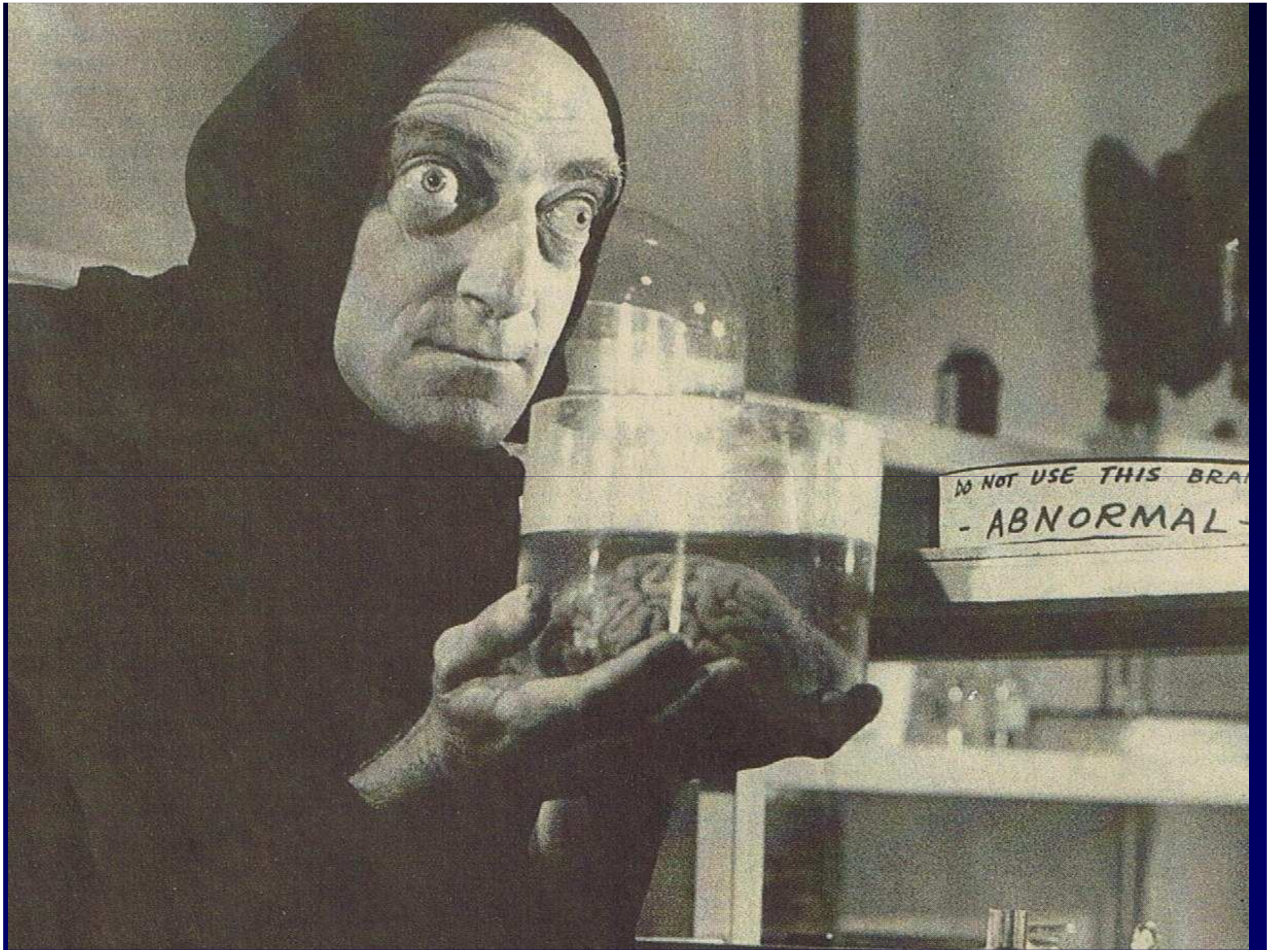
J Oral Maxillofac Surg 2008

Conclusions I

- ONJ is a severe, site-specific consequence of the accumulation of potent BPs in the local bone microenvironment
- Histology of chronic, non-healing osteomyelitis usually reveals inflammatory infiltrates and bacterial colonies at the site of necrotic bone
- Defective immunosurveillance against invading pathogens is conceivably important for the progression of necrosis
- Dendritic Ca^{2+}-dependent cells are essential to local homing and activation of T cells in periodontal tissues colonizable by the oral microflora

Conclusions II

- BPs notoriously form complexes with bivalent cations (Ca, Mg, Fe)
- The formation of BP-calcium complexes causes a drop of Ca^{2+} concentration in serum and extracellular fluid. BP-induced hypocalcemia associated with vitamin D deficiency induces secondary hyperparathyroidism especially in seriously ill and older patients
- Elevated serum PTH levels may be a marker of defective Ca^{2+} availability to crucial immune cells
- Studies are needed to explore the interactions between BPs and immune sentinels like dendritic cells in the jaw periodontal microenvironment and more generally the mechanisms of dampening local immune responses in ONJ


DO NOT USE THIS BRA
- ABNORMAL -

Who comprehends knowledge?

He who reflects.

Antico proverbio Tamil
Trad. J. Richardson, 1904