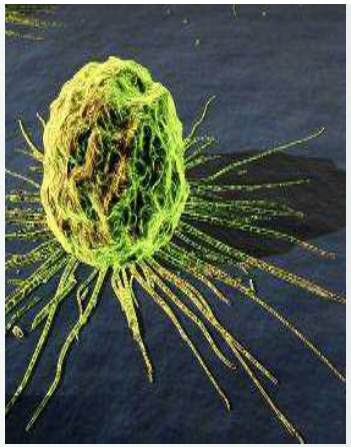
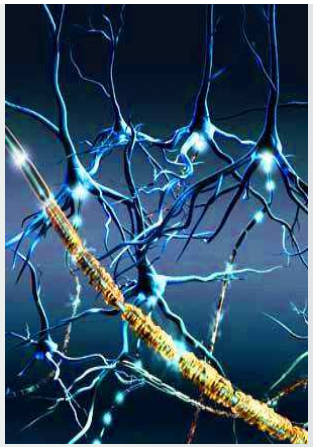
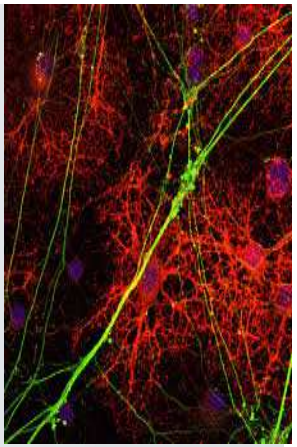






Gaetano Lanzetta
Oncologia Medica
I.N.I. - Grottaferrata (RM)

CURE SIMULTANEE ED OUTCOME ONCOLOGICI

DOLORE DA METASTASI OSSEE : UN DOLORE DIFFICILE

Aiom
Associazione Italiana di Oncologia Medica

INI

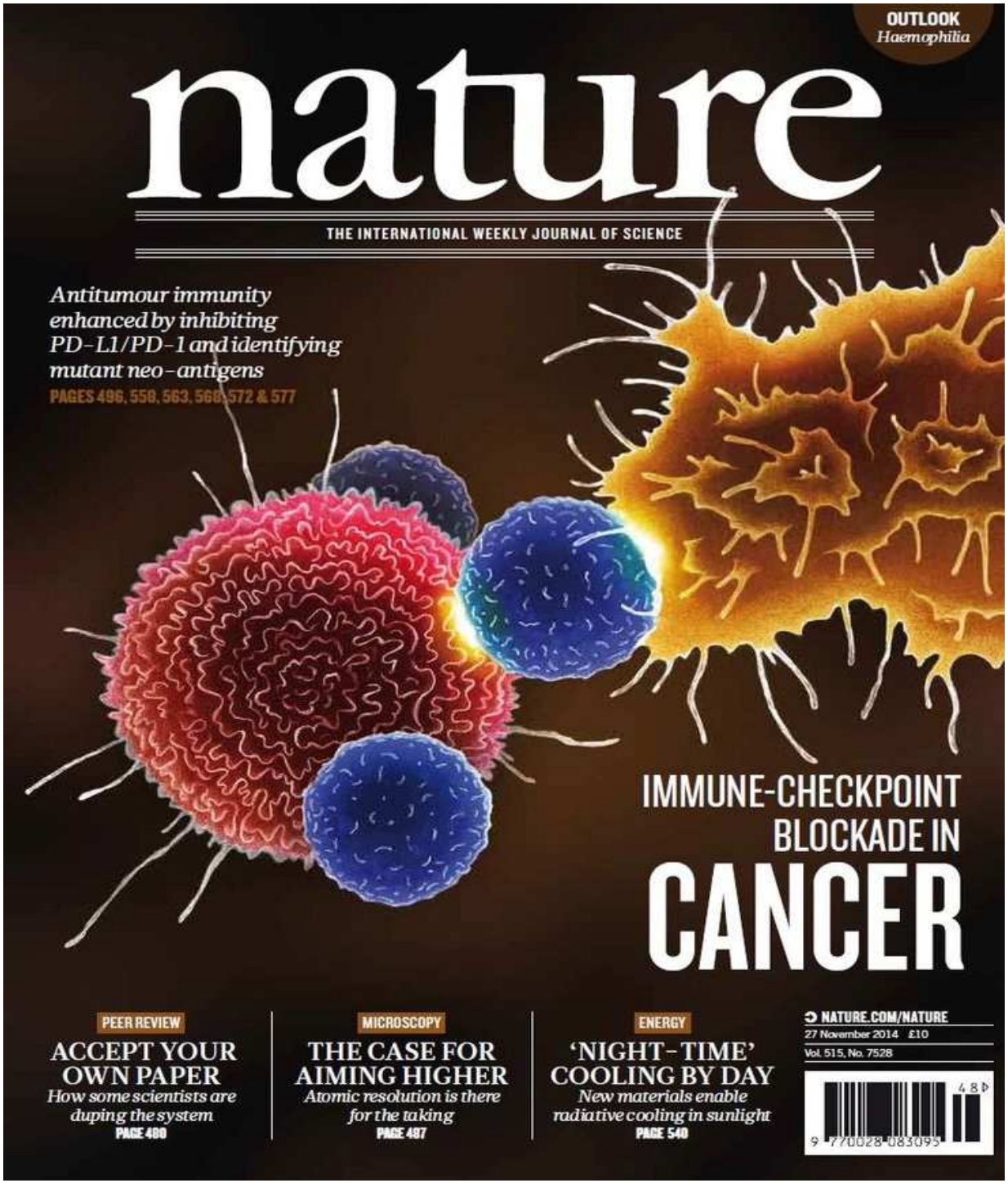
Italian Society of Osteoncology
Società Italiana di Osteoncologia
ISO

ESMO
Designated Centers of Integrated Oncology and Palliative Care

DISCLOSURES

Advisory Boards / Honoraria / Speakers' fee / Consultant for:

- **ITALFARMACO**
- **KIOWA KIRIN**
- **PFIZER**
- **JANSSEN**
- **ASTELLAS**
- **NOVARTIS**


OUTLOOK
Haemophilia
nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
Antitumour immunity enhanced by inhibiting PD-L1/PD-1 and identifying mutant neo-antigens
PAGES 496, 558, 563, 568, 572 & 577
IMMUNE-CHECKPOINT BLOCKADE IN
CANCER
PEER REVIEW
ACCEPT YOUR OWN PAPER
How some scientists are duping the system
PAGE 480
MICROSCOPY
THE CASE FOR AIMING HIGHER
Atomic resolution is there for the taking
PAGE 487
ENERGY
'NIGHT-TIME' COOLING BY DAY
New materials enable radiative cooling in sunlight
PAGE 540
NATURE.COM/NATURE
27 November 2014 £10
Vol. 515, No. 7528

FACING AVDVANCED CANCER IS....

Remission or death !!!

Only two options?

A third way should always exist:

living with disease

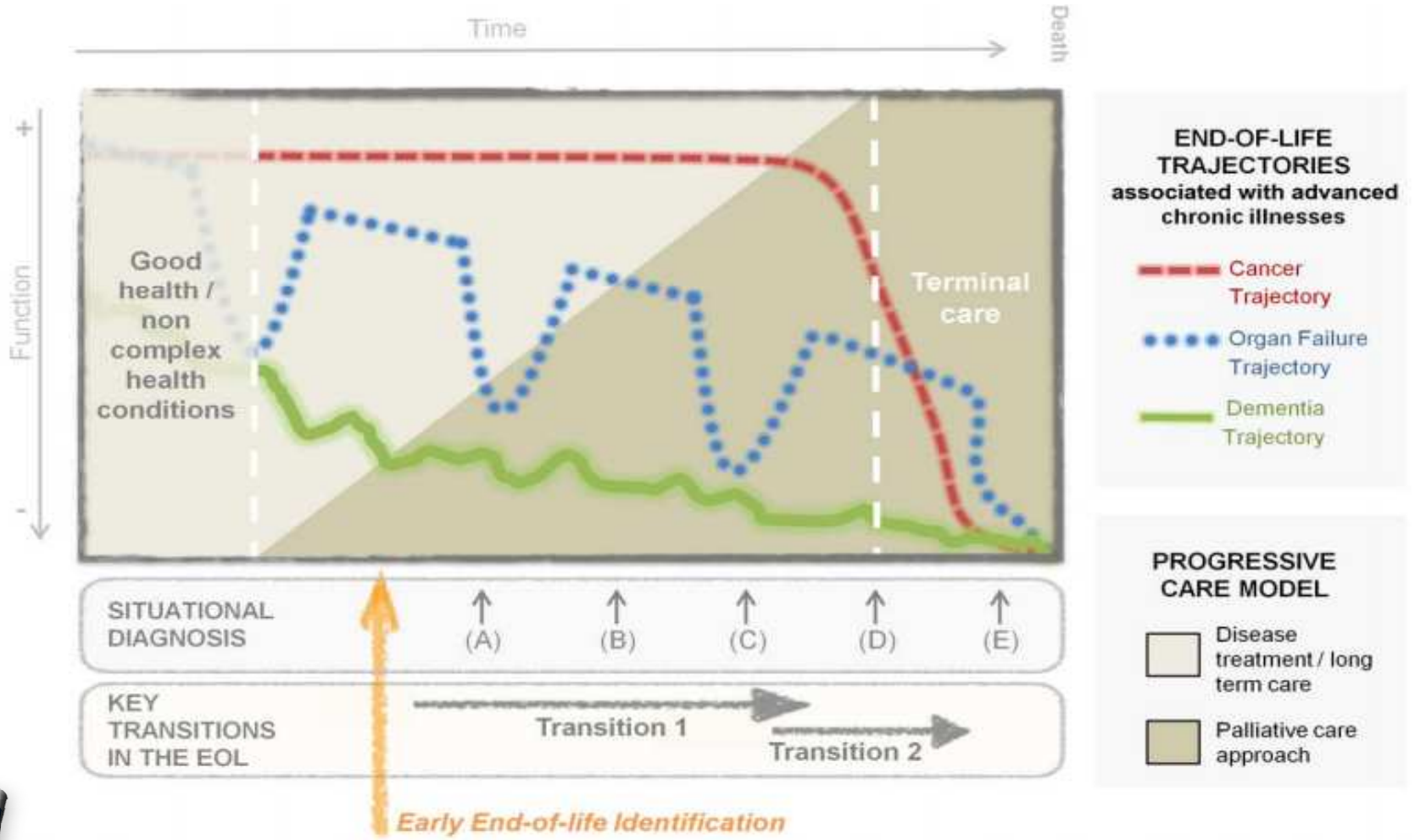
«..cancer isn't a war, there are no winners or losers..»

«..I can't cure you but I can help you control it..»

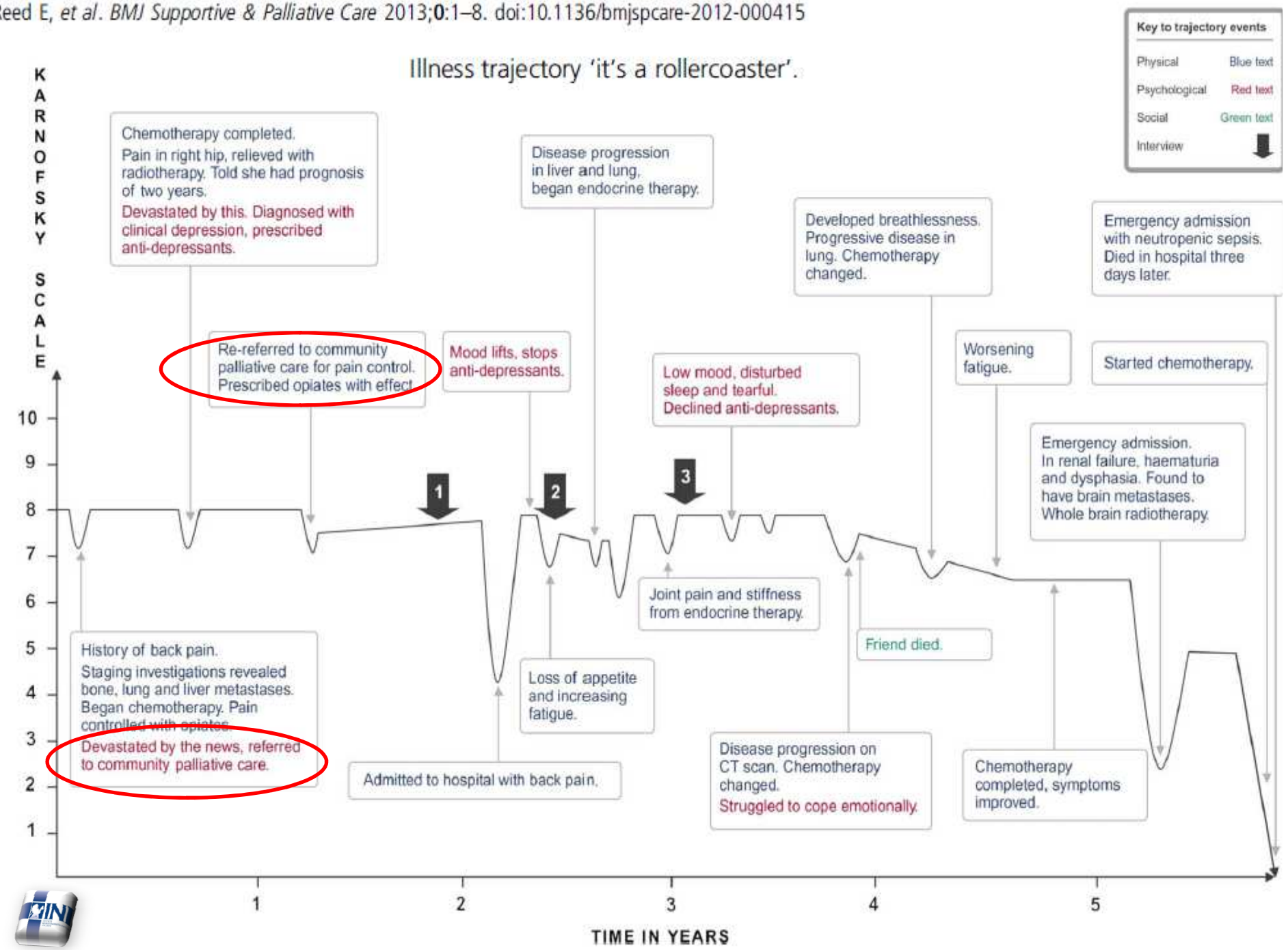
BMJ
October 21, 2016

Identifying patients with advanced chronic conditions for a progressive palliative care approach: a cross-sectional study of prognostic indicators related to end-of-life trajectories

J Amblàs-Novellas,[1,2] S A Murray,[3] J Espaulella,[1,2] J C Martori,[4] R Oller,[4] M Martinez-Muñoz,[5] N Molist,[1,2] C Blay,[2,6] X Gómez-Batiste[2,7]



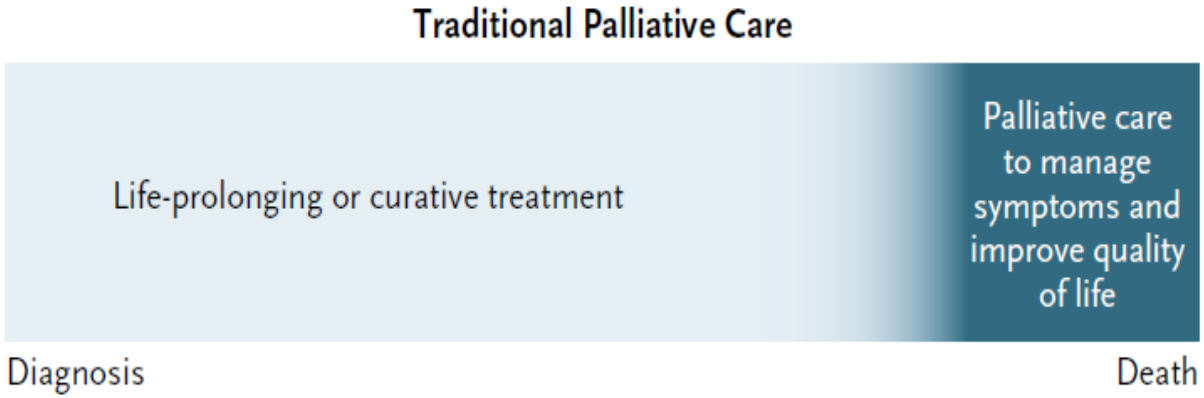
Reed E, *et al*. *BMJ Supportive & Palliative Care* 2013;**0**:1–8. doi:10.1136/bmjspcare-2012-000415

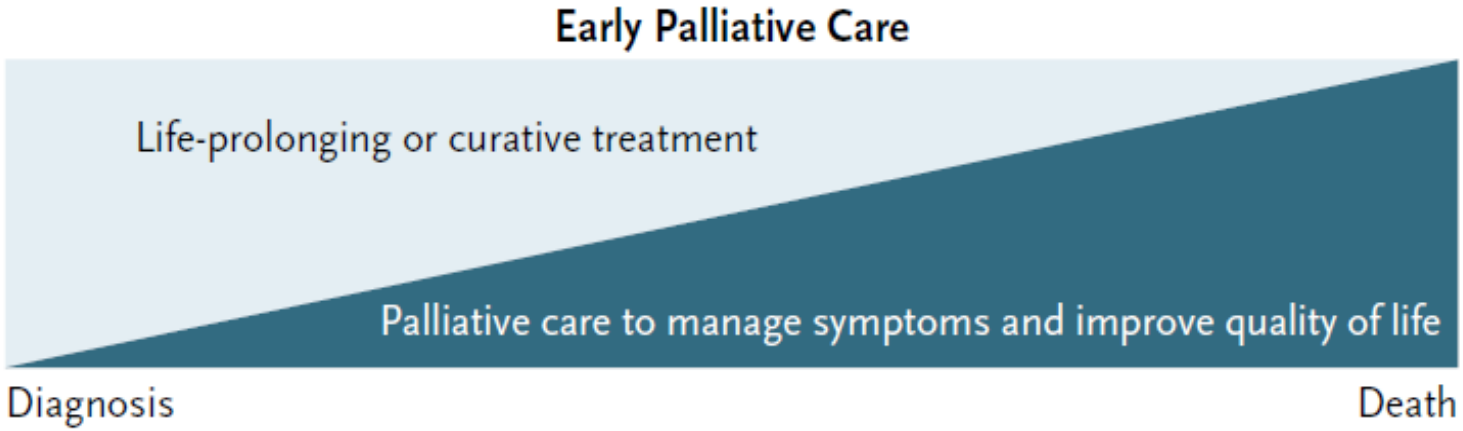


SOUNDING BOARD

Early Specialty Palliative Care — Translating Data in Oncology into Practice

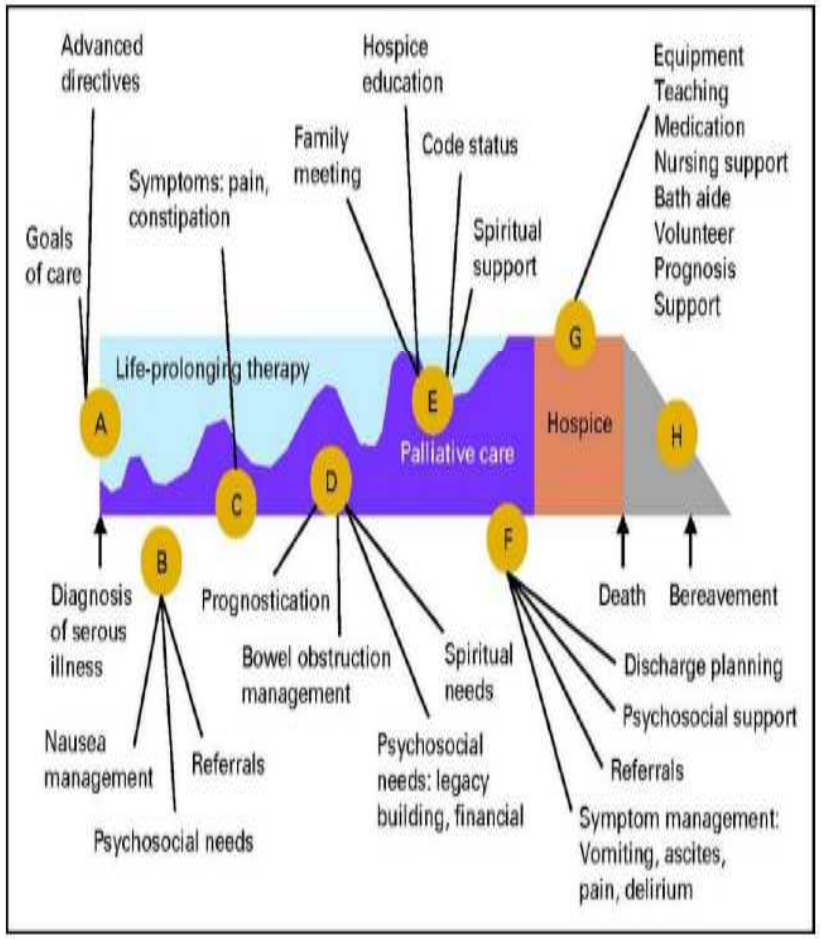
Ravi B. Parikh, A.B., Rebecca A. Kirch, J.D., Thomas J. Smith, M.D., and Jennifer S. Temel, M.D.






LA FINE E' NOTA.
EMBE'?! E' IL RESTO DEL ROMANZO CHE DEVE AVVINCERE, MICA LE ULTIME PAGINE.
LA MIA VITA
PV

Potenziali interventi palliativi per paziente durante il percorso di cura



Hennessy JE et al. JOP 2013;9:78-80

CURE SIMULTANEE

Integrazione tra le terapie oncologiche attive e le cure palliative*
dal momento della presa in carico del malato oncologico.

*Prevenzione, identificazione, valutazione e trattamento dei sintomi fisici, funzionali e dei problemi psicosociali ed esistenziali del malato oncologico nella fase avanzata di malattia, quando l'outcome non è più la sopravvivenza.

Tumori 95:652-654, 2009.

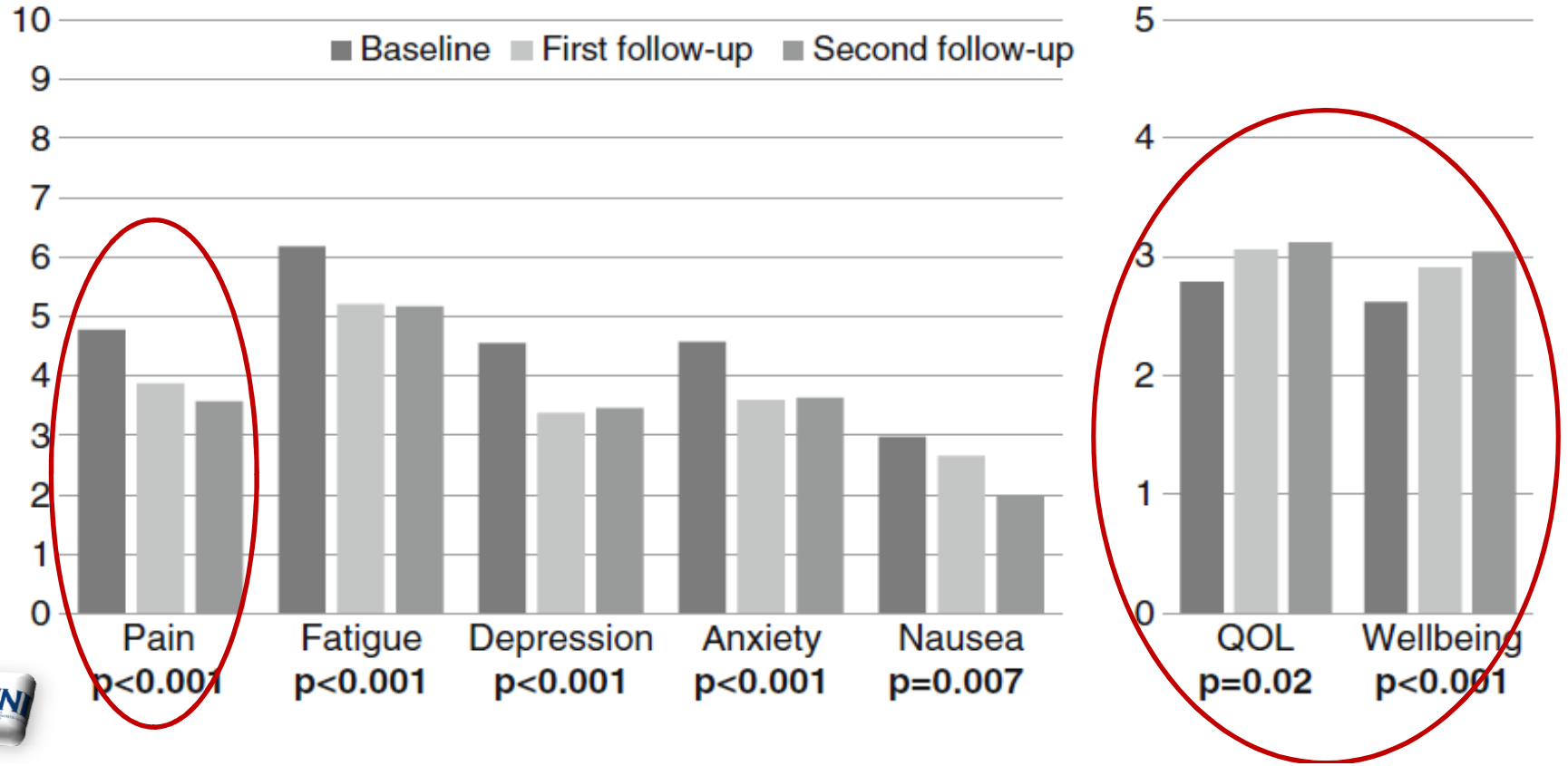
Support Care Cancer (2013) 21:3031–3037
DOI 10.1007/s00520-013-1838-z

ORIGINAL ARTICLE

Palliative and oncologic co-management: symptom management for outpatients with cancer

Kara Bischoff · Vivian Weinberg · Michael W. Rabow

In conclusion, our study demonstrated that outpatient palliative and oncologic co-management was associated with significant improvement in nearly all the symptoms evaluated. Symptomatic improvement was observed regardless of patients' gender, disease stage, concurrent oncologic treatment, and disease progression. To control for the impact of time and non-palliative treatments, as well as for referral bias, randomized controlled studies of outpatient palliative care are indicated for patients with a variety of diagnoses, stages of disease, and prognoses.



VOLUME 35 · NUMBER 1 · JANUARY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update

Betty R. Ferrell, Jennifer S. Temel, Sarah Temin, Erin R. Alesi, Tracy A. Balboni, Ethan M. Basch, Janice I. Firn, Judith A. Paice, Jeffrey M. Peppercorn, Tanyanika Phillips, Ellen L. Stovall,† Camilla Zimmermann, and Thomas J. Smith

Key Recommendation

Patients with advanced cancer, whether patient or outpatient, should receive dedicated palliative care services, early in the disease course, concurrent with active treatment. Referring patients to interdisciplinary palliative care teams is optimal, and services may complement existing programs. Providers may refer caregivers of patients with early or advanced cancer to palliative care services.

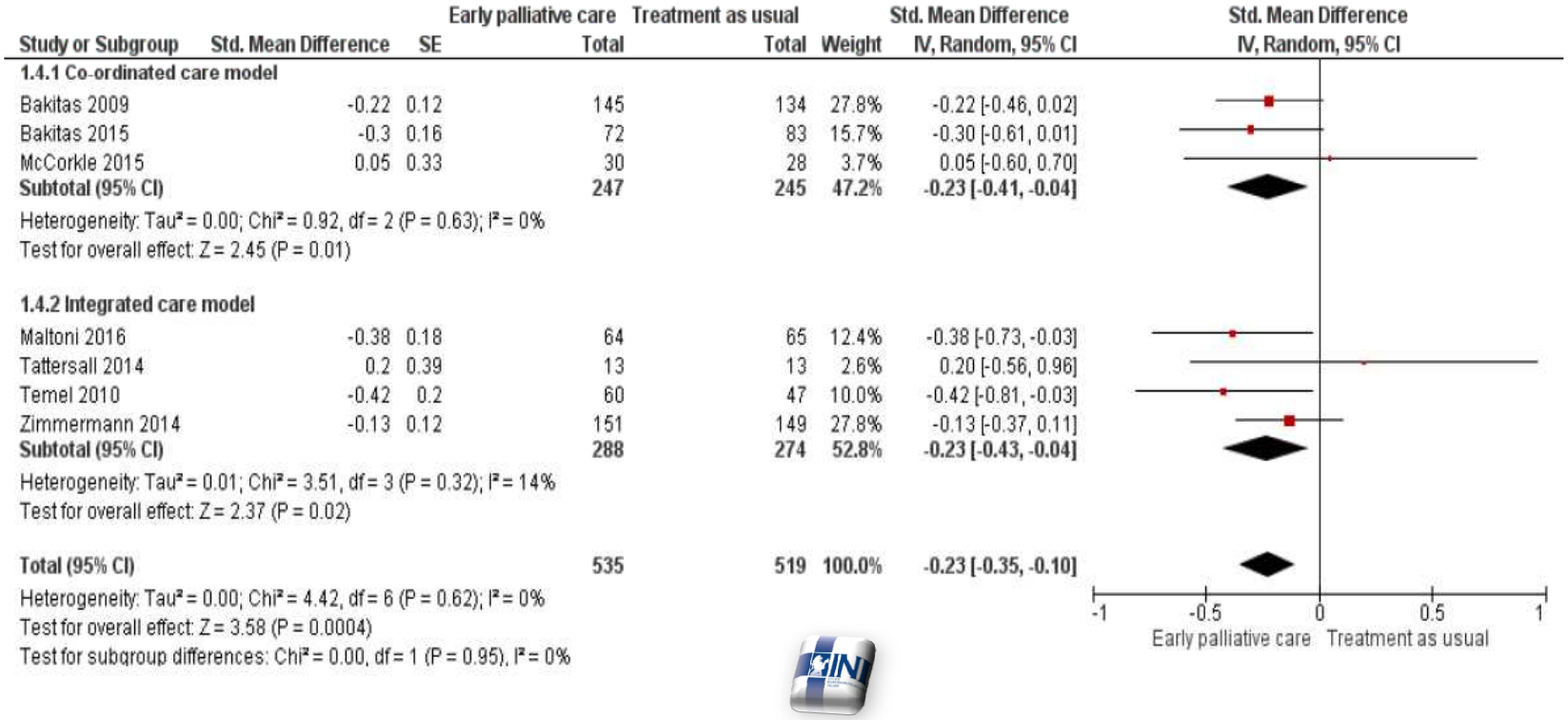
ASCO believes that cancer clinical trials are vital to informing medical decisions and improving cancer care and that all patients should have the opportunity to participate. Patients in clinical trials may benefit from the support of palliative care.

Cochrane Library
Cochrane Database of Systematic Reviews

el S, Rücker G, Friederich HC, Villalobos M, Thomas M, Hartmann M

Primary outcome: symptom intensity

Figure 7. Forest plot of comparison: 1 Early palliative care vs standard oncological care, outcome: 1.4 Symptom intensity.



Nat Rev Clin Oncol. 2016 March ; 13(3): 159–171. doi:10.1038/nrclinonc.2015.201.

Integrating palliative care into the trajectory of cancer care

David Hui and **Eduardo Bruera**

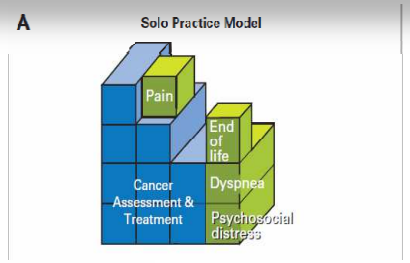
...alliative Care & Rehabilitation Medicine, Unit 1414, University of Texas MD ... Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA (D.H., E.B.)

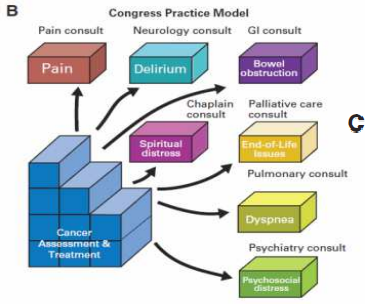
VOLUME 28 · NUMBER 25 · SEPTEMBER 1 2010

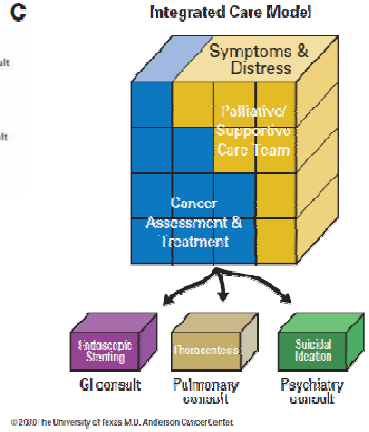
JOURNAL OF CLINICAL ONCOLOGY | THE ART OF ONCOLOGY

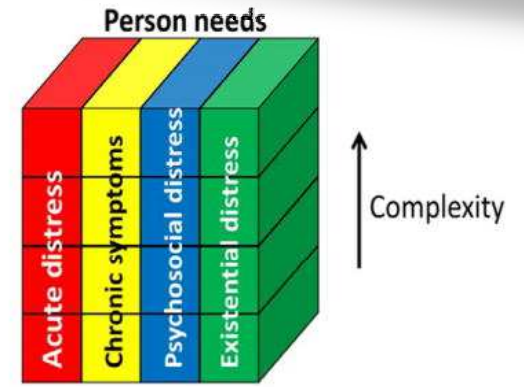
Integrating Supportive and Palliative Care in the Trajectory of Cancer: Establishing Goals and Models of Care

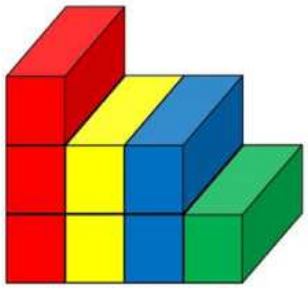
Eduardo Bruera and David Hui





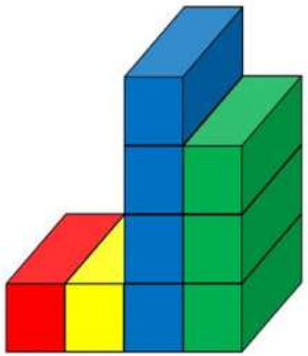






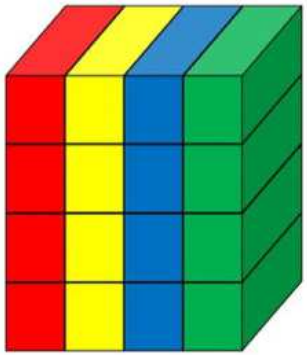
Oncology teams

Lack of time
Lack of screening
Lack of team members
Lack of specialized training



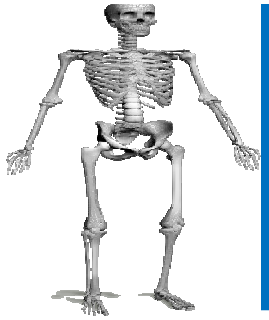
Psychosocial teams

Less emphasize on physical symptoms
Lack of comprehensive interdisciplinary team

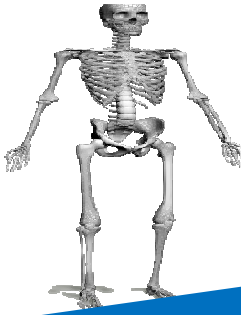


Palliative care teams

Expertise and resources to provide comprehensive symptom management and psychosocial care



BONE METASTASES HAVE DEBILITATING CONSEQUENCES



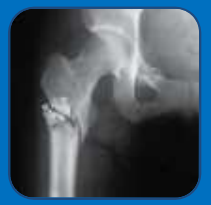
Disease

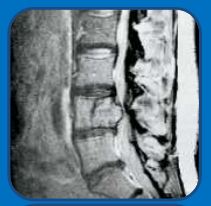
SRE

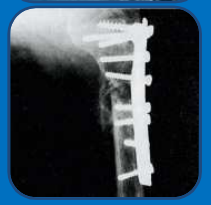
Consequences to functional independence and QOL

Bone metastases

- **Fracture**
- **Rx therapy to bone**
- **SCC or vertebral collapse**
- **Hypercalcemia**
- **Surgery to bone**

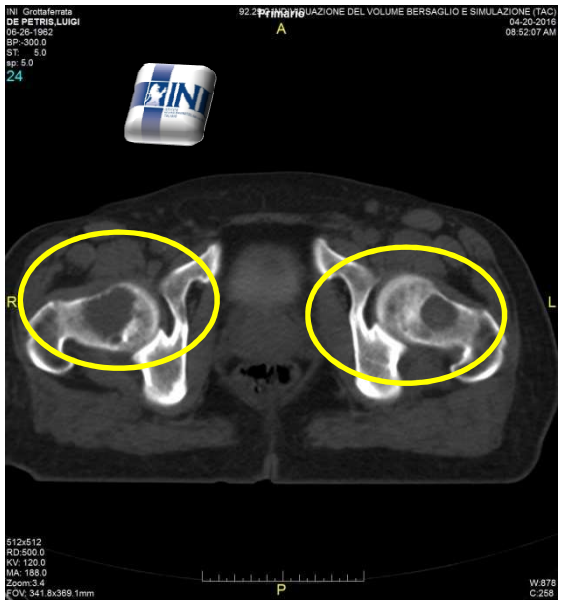






- **Loss of autonomy**
- **Bone pain**
- **Anxiety and depression**

1. Gainor, Buchert. Clin Orthopaed Rel Res 1983;178:297–302; 2. Saad F et al. Cancer 2007;110:1860–7; 3. Poor et al. Osteoporos Int 1995;5:419–26; 4. Loblaw et al. Supp Care Cancer 2007;15:451–5; 5. Hellman, Krasnow. J Palliat Med 1998;1:277–83; 6. Maranzano et al. Tumori 2003;89:469–75; 7. Katzer et al. Arch Orthopaed Trauma Surg 2002;122:251–8; 8. Loblaw et al. J Clin Oncol 2005;23:2028–3.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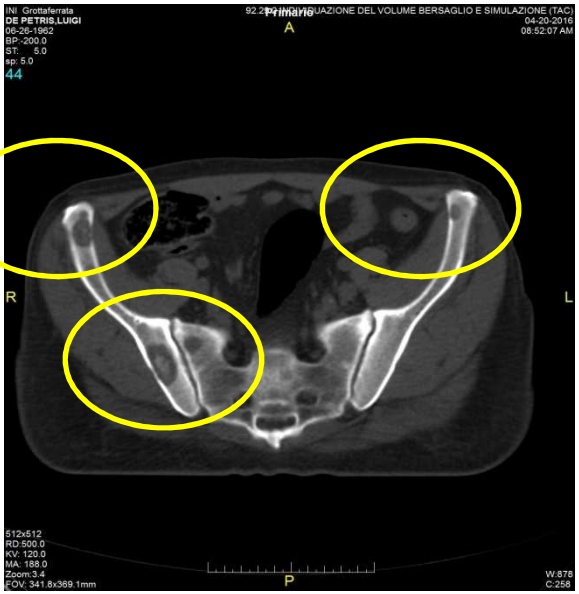
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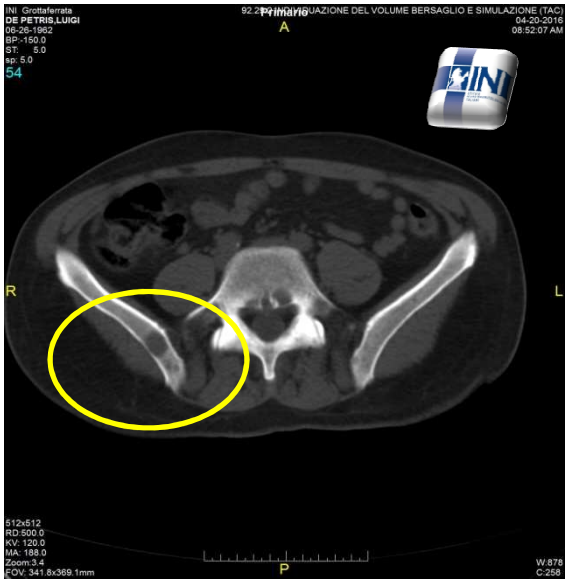
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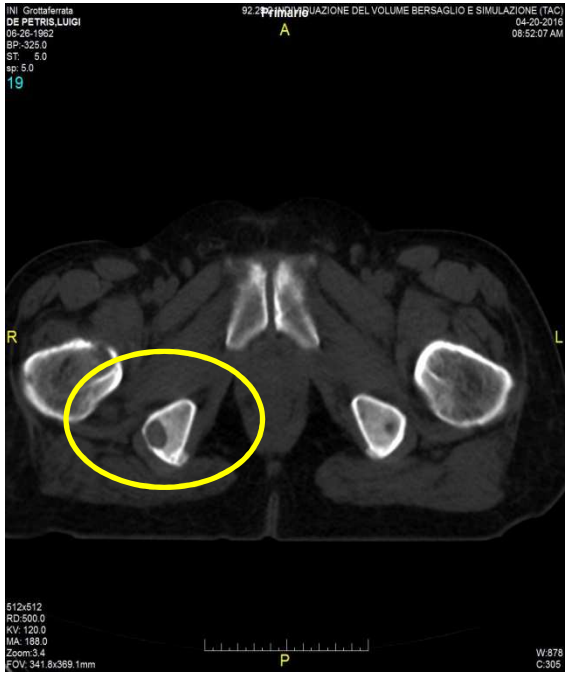
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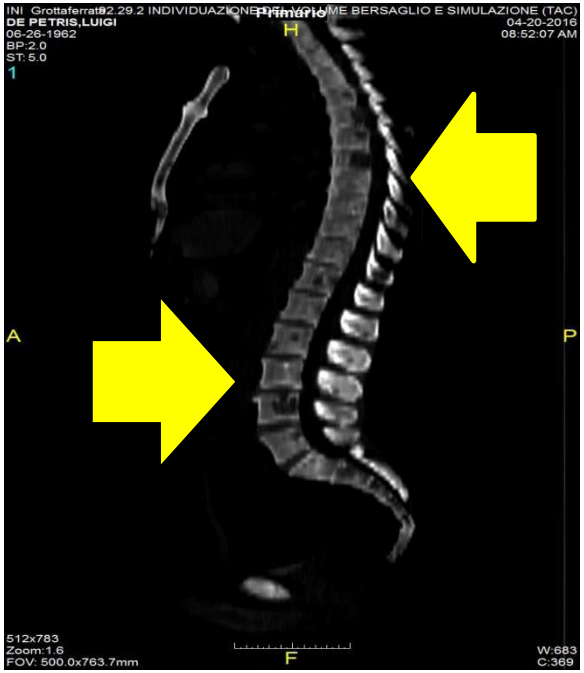
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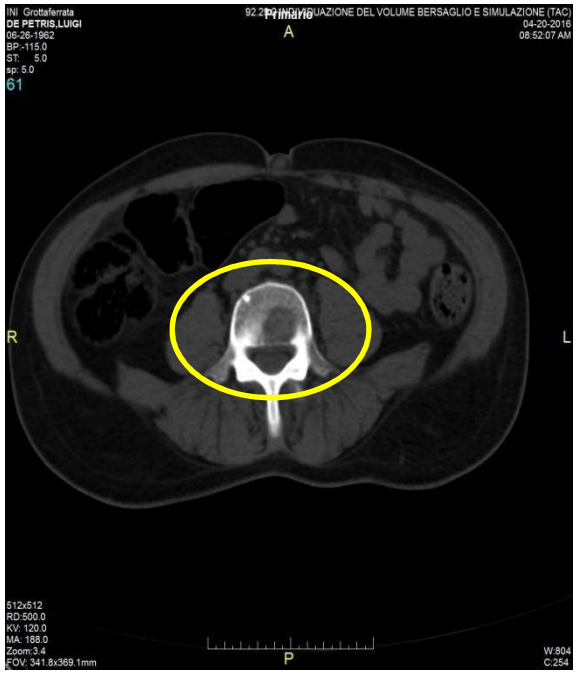
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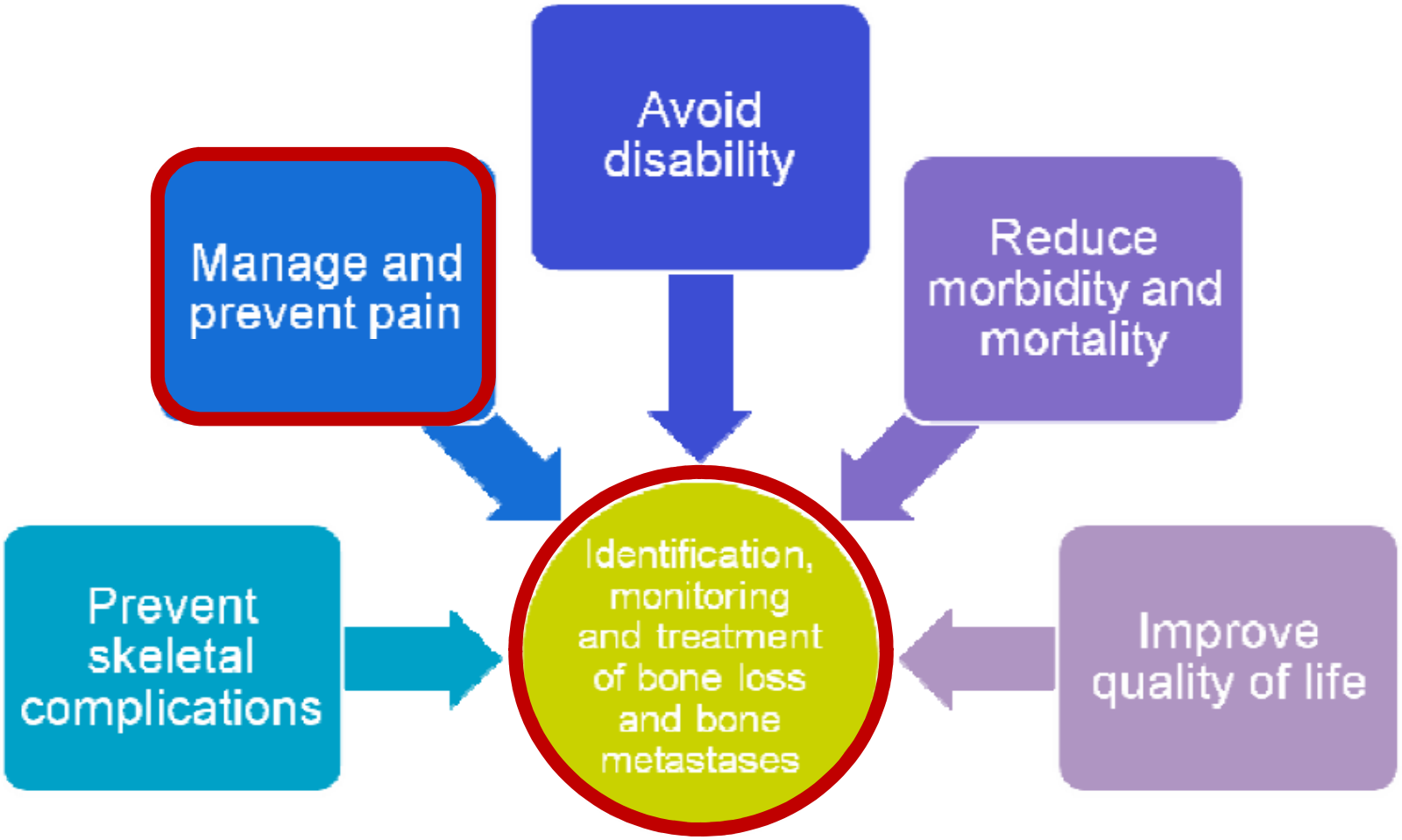
Why is awareness of bone health in cancer so important?



Costelloe CM, et al. Lancet Oncol 2009;10:606-14.

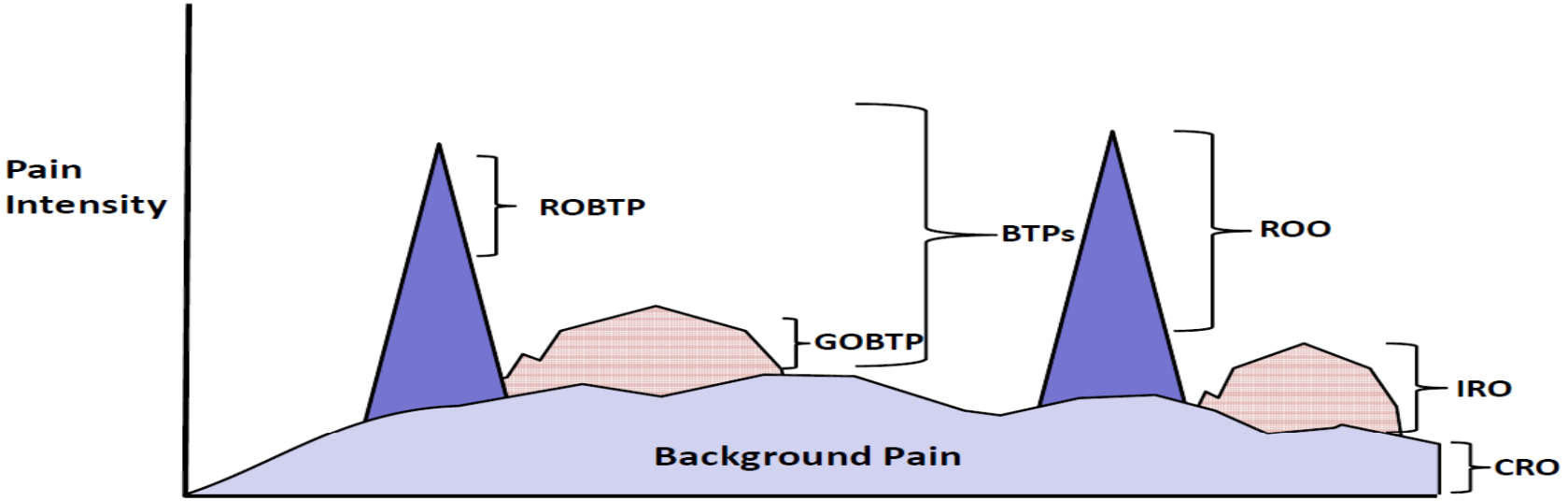
Annals of Palliative Medicine, Vol 1, No 1 April 2012

REVIEW ARTICLE

Painful boney metastases

Howard S. Smith

Department of Anesthesiology, Albany Medical College, New York, USA



frontiers in Physiology

REVIEW
published: 26 April 2016
doi: 10.3389/fphys.2016.00157

CrossMark

The Physiology of Bone Pain. How Much Do We Really Know?

*Sara Nencini and Jason J. Ivanusic **

Department of Anatomy and Neuroscience, University of Melbourne, Melbourne, VIC, Australia

British Journal of Anaesthesia 101 (1): 87–94 (2008)
doi:10.1093/bja/aen100 Advance Access publication May 19, 2008
BJA

Translational medicine: cancer pain mechanisms and management

A. Delaney[1], S. M. Fleetwood-Walker[1], L. A. Colvin[2] and M. Fallon[3]*

CANCER GROWTH AND METASTASIS 2015:8(S1)

Use of Animal Models in Understanding Cancer-Induced Bone Pain

Supplementary Issue: Animal Models of Cancer Biology

Lauren M. Slosky, Tally M. Largent-Milnes and Todd W. Vanderah
Department of Medical Pharmacology, University of Arizona College of Medicine, Tucson, AZ, USA.

- Metastatic cancer induced bone pain **(CIBP)** is a severe clinical problem that is often inadequately treated by current analgesic.

- **CIBP** is a **complex pain syndrome** involving **background pain** (typically opiod responsive), which can be describe as a dull ache that increase in intensity with progression of the disease

- **CIBP** involves spontaneous **breakthrough pain** and movement-related pain, which are generally difficult to treat with opioids without intolerable side-effects.

- While the etiology of **CIBP** remains to be fully elucidated, increasing evidence suggest that **CIBP is uniquely complex and is accompained by neurochemical changes distinct from other chronic pain pathologies (neuropathic pain, inflammatory pain**).

Annals of Palliative Medicine, Vol 1, No 1 April 2012

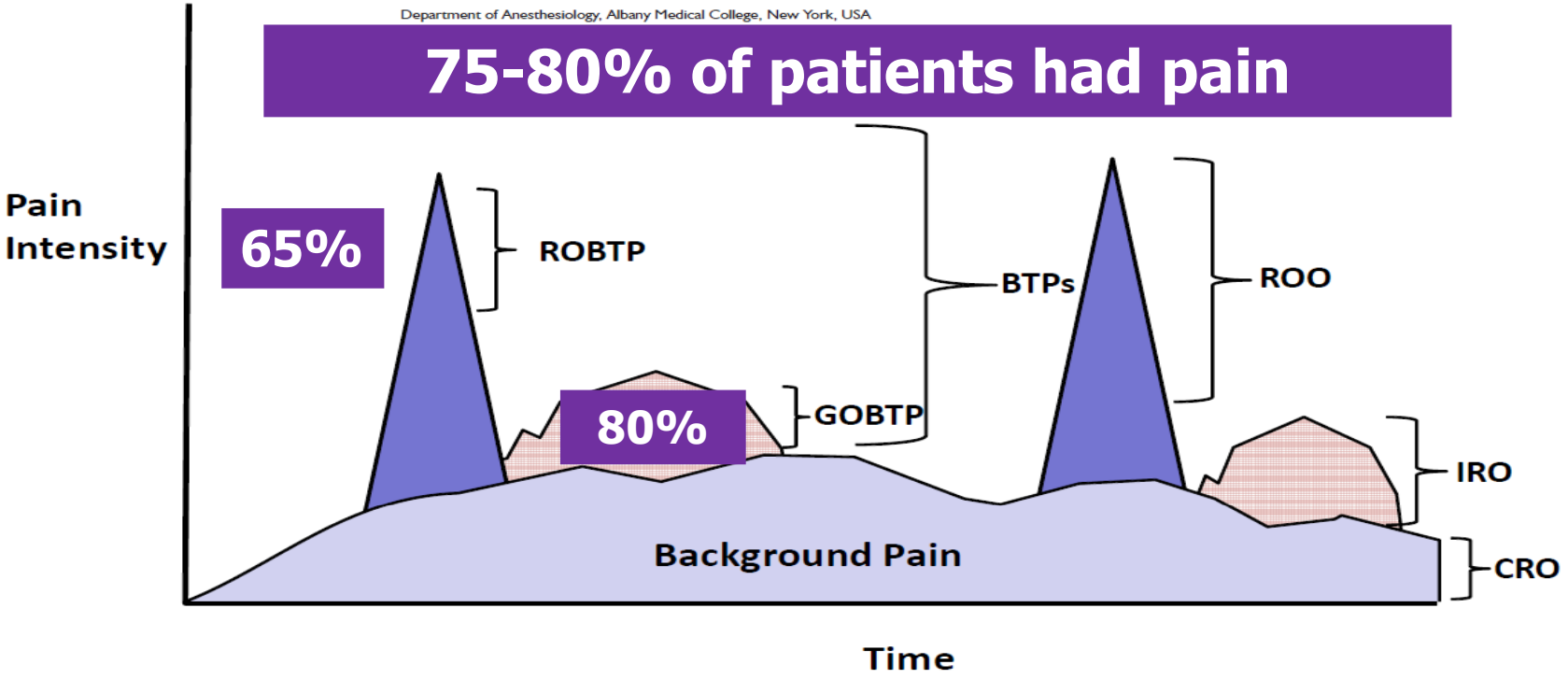
REVIEW ARTICLE

Painful boney metastases

Howard S. Smith

Department of Anesthesiology, Albany Medical College, New York, USA

75-80% of patients had pain



CRO – Controlled Release Opioid
GOBTP – Gradual onset breakthrough Pain
IRO – Immediate Release Opioid
ROBTP – Rapid onset breakthrough pain
ROO – Rapid Onset Opioid

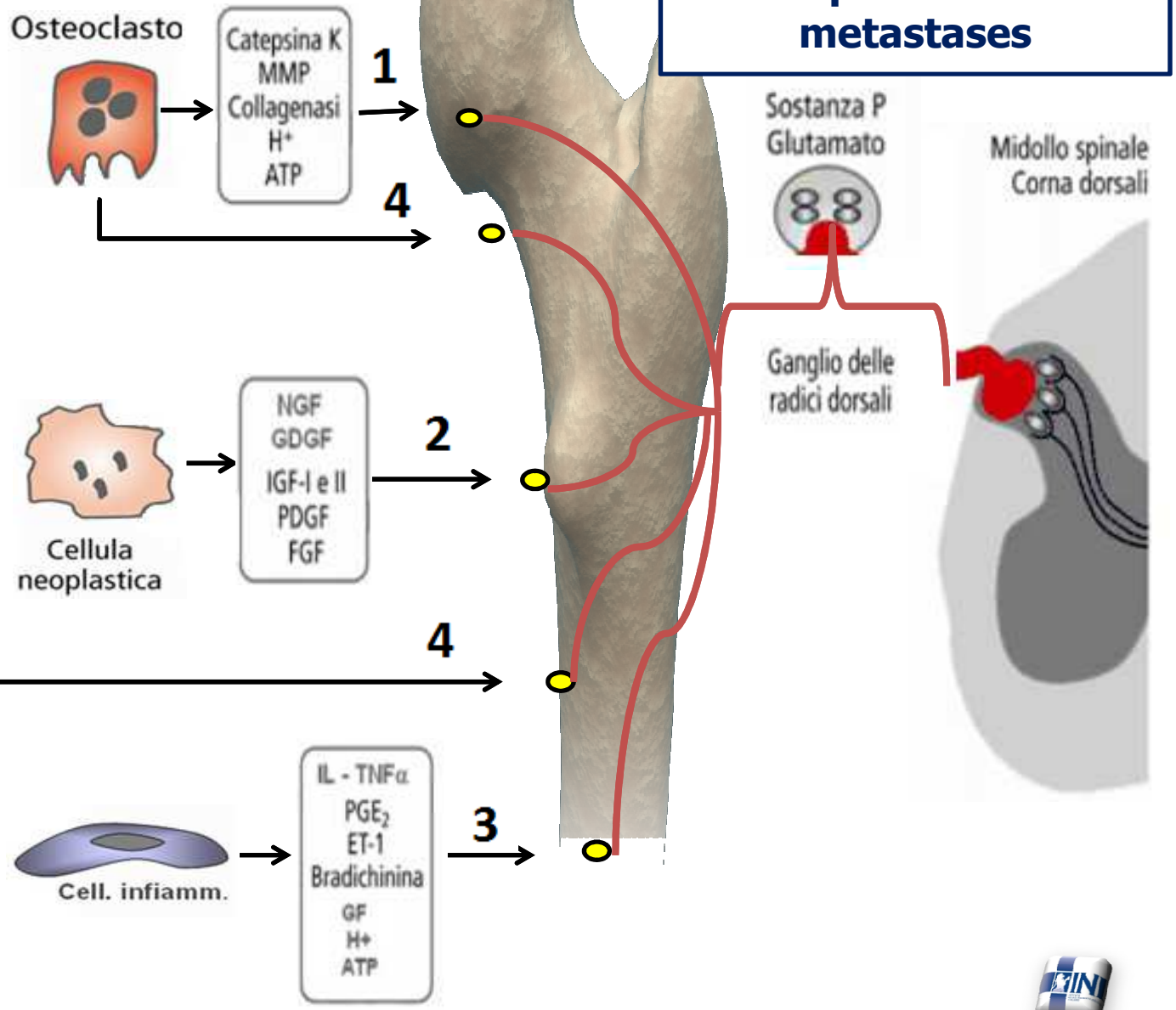
Only about 40% of patients reported adequate relief of pain from bone metastases

PATHOPHYSIOLOGY OF CANCER INDUCED BONE PAIN

Role of the nervous system in mantaninig the pain in bone metastases

Osteoclast activity source of algogenic stimulations

Neoplasia source of algogenic stimulations



NIH Public Access
Author Manuscript
Nat Rev Cancer. Author manuscript; available in PMC 2013 May 29.

Published in final edited form as:
Nat Rev Cancer. 2011 June ; 11(6): 411–425. doi:10.1038/nrc3055.

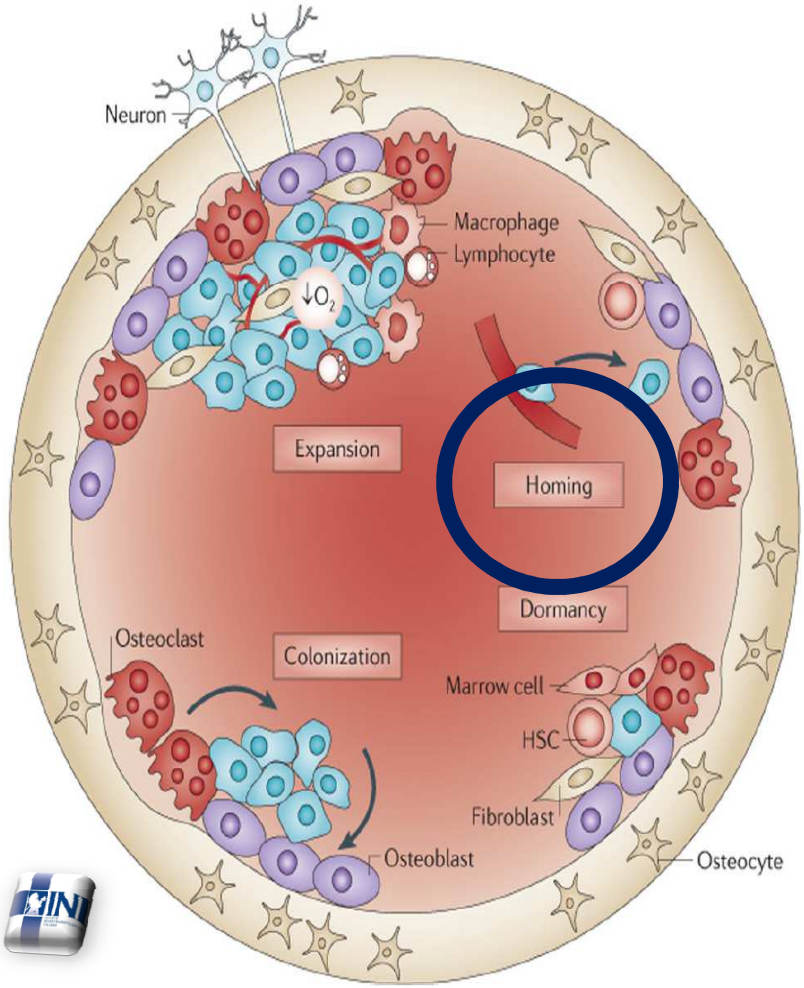
Cancer to bone: a fatal attraction

Katherine N. Weilbaecher*, Theresa A. Guise‡, and Laurie K. McCauley§

*Department of Medicine, Division of Molecular Oncology, Washington University School of Medicine, St. Louis, Missouri 63110, USA

‡Department of Medicine, Division of Endocrinology, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA

§Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, and Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.



Cancer Microenvironment (2011) 4:221–235
DOI 10.1007/s12307-011-0083-6

ORIGINAL PAPER

Homing of Cancer Cells to the Bone

Anjali Mishra · Yusuke Shiozawa · Kenneth J. Pienta · Russell S. Taichman

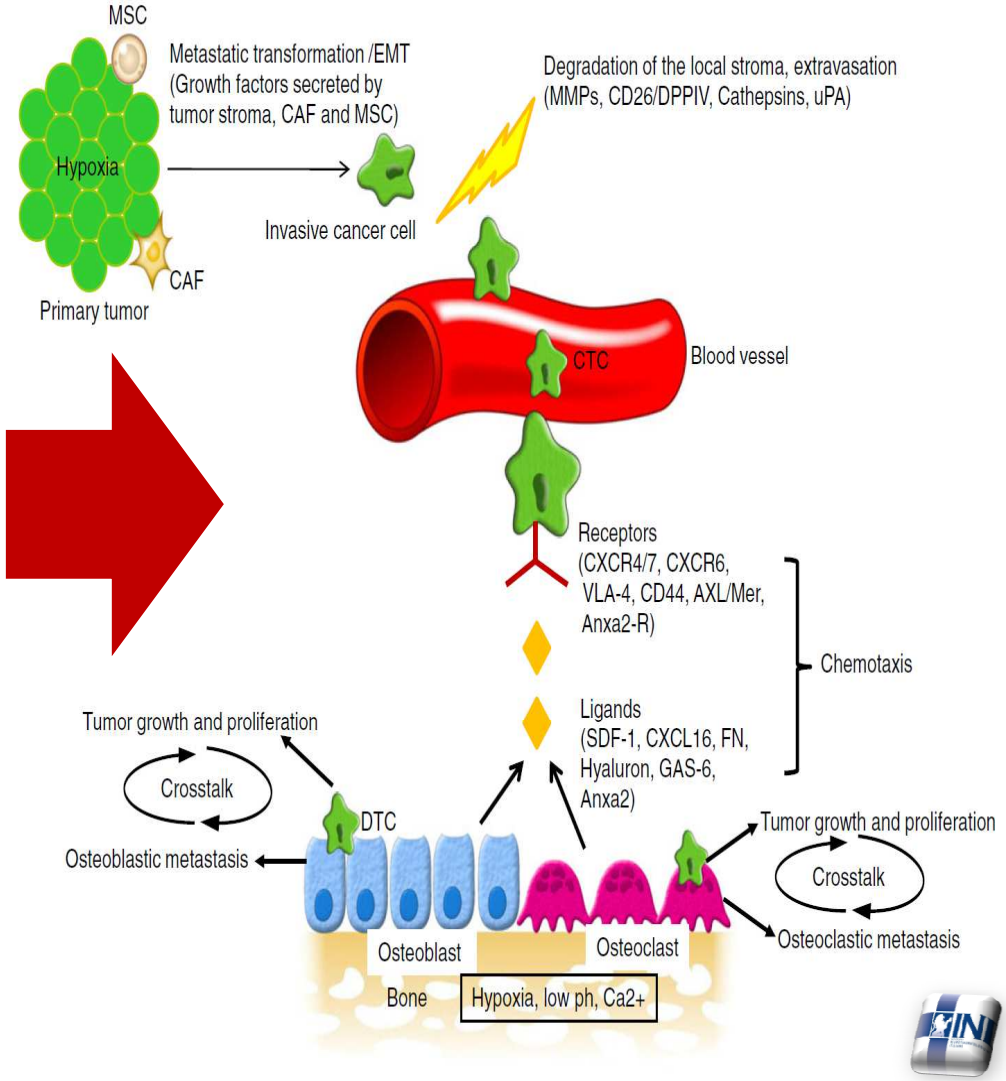
Yang *et al. Journal of Neuroinflammation* (2015) 12:219
DOI 10.1186/s12974-015-0441-2

Journal of Neuroinflammation

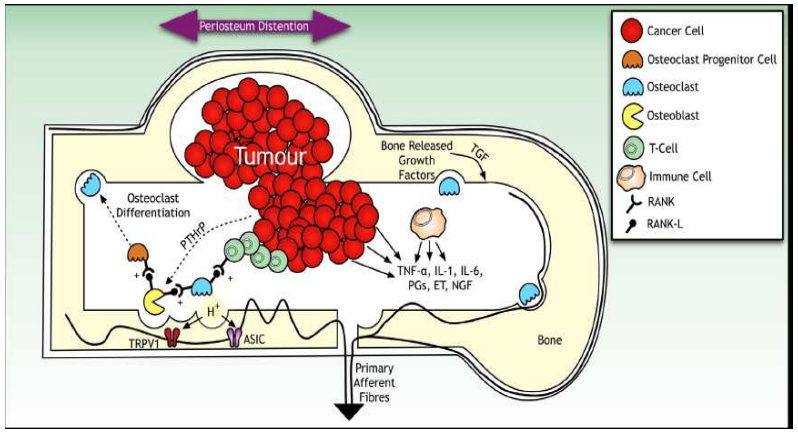
RESEARCH Open Access

SDF1–CXCR4 signaling contributes to persistent pain and hypersensitivity via regulating excitability of primary nociceptive neurons: involvement of ERK-dependent Nav1.8 up-regulation

Fei Yang[1†], Wei Sun[1,2†], Yan Yang[3], Yan Wang[1,2], Chun-Li Li[1,2], Han Fu[1,2], Xiao-Liang Wang[1,2], Fan Yang[3], Ting He[1,2] and Jun Chen[1,2,3*]



PATHOPHYSIOLOGY OF CANCER INDUCED BONE PAIN



Neoplasia source of algogenic stimulations

Cellula neoplastica

Cell. infiamm.

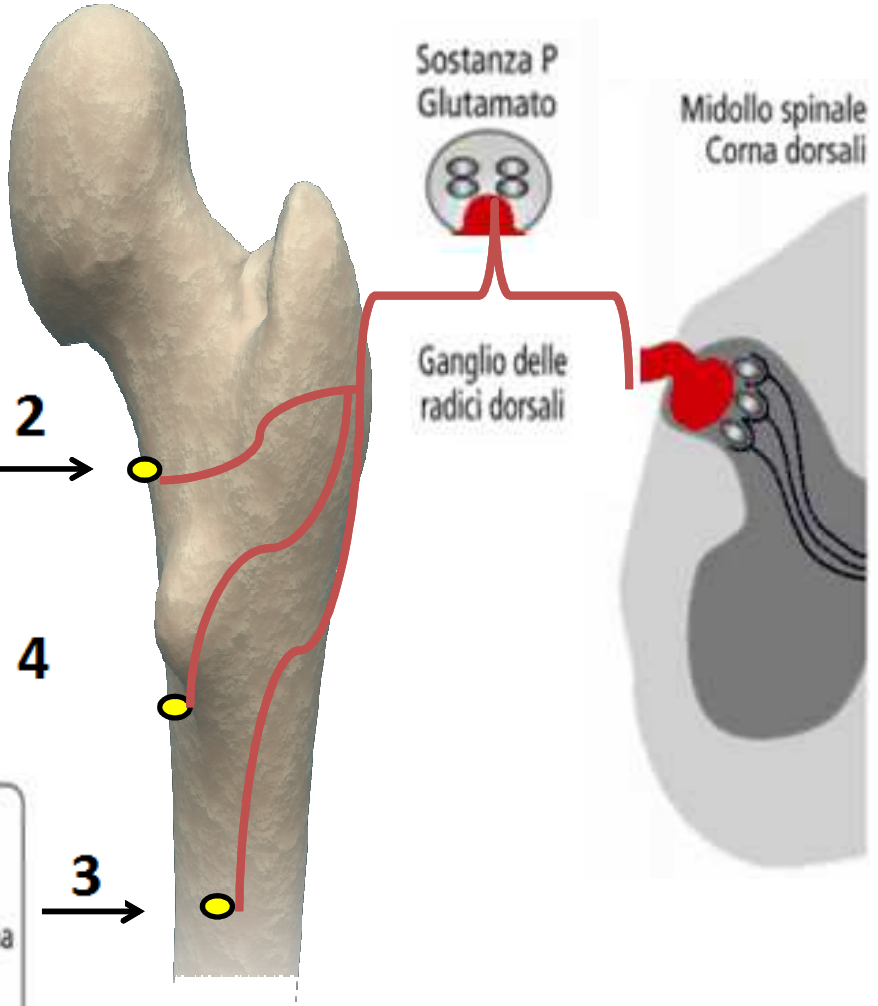
NGF
GDGF
IGF-I e II
PDGF
FGF

2

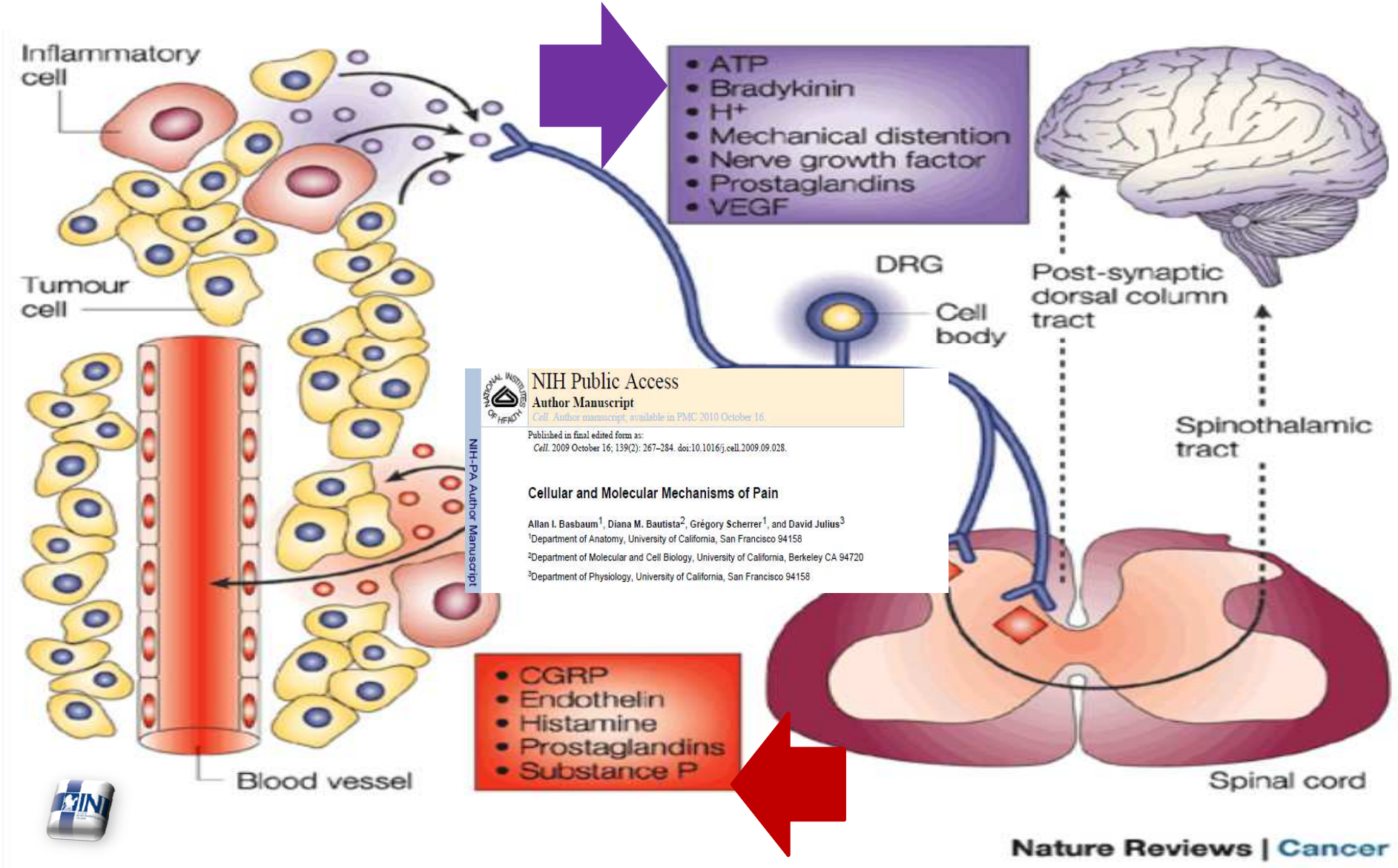
4

IL - TNFα
PGE_2
ET-1
Bradichinina
GF
H+
ATP

3



"CANCER MICROENVIRONMENT"



Published in final edited form as:
Cell. 2009 October 16; 139(2): 267–284. doi:10.1016/j.cell.2009.09.028.

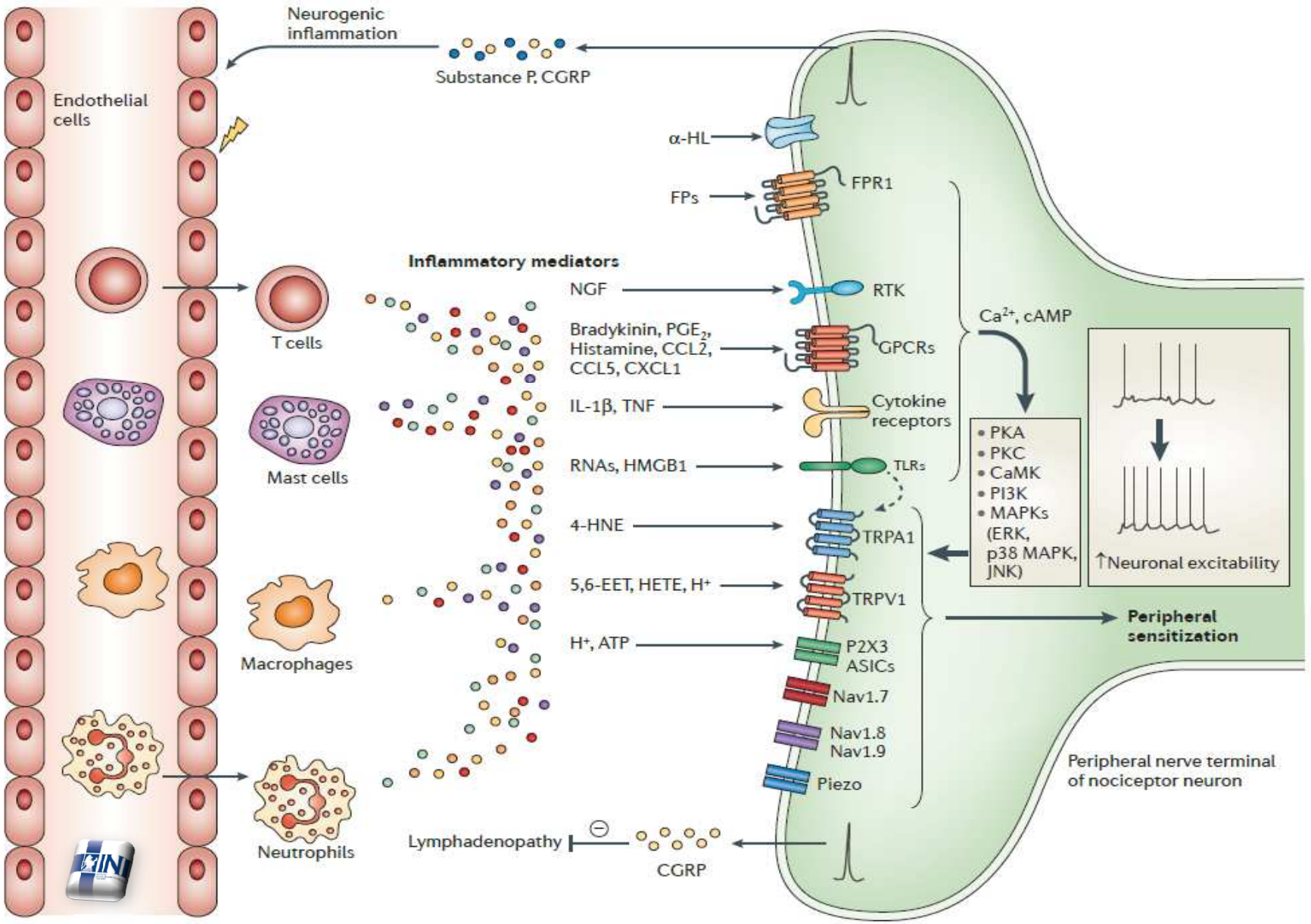
Cellular and Molecular Mechanisms of Pain

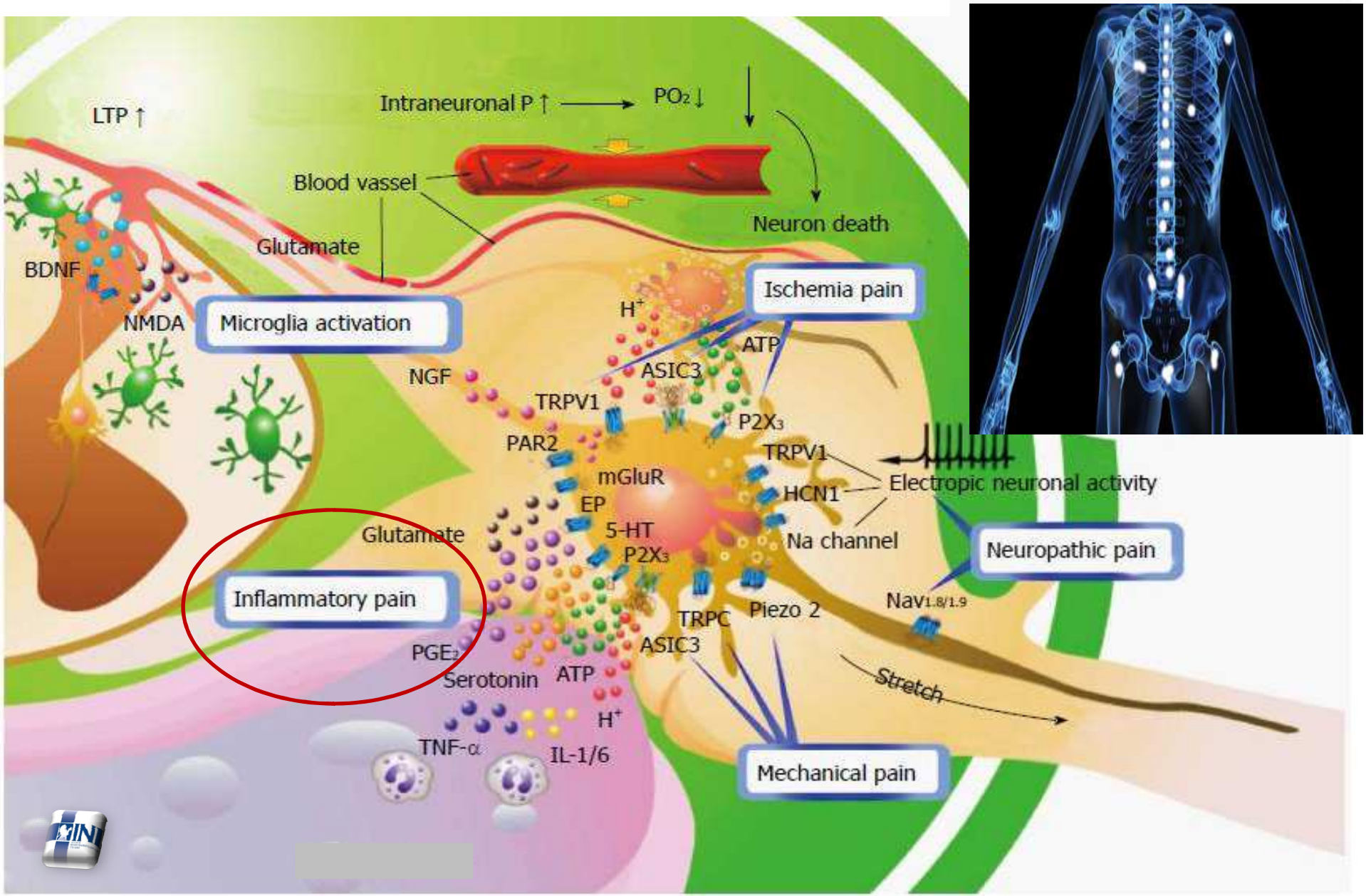
Allan I. Basbaum[1], Diana M. Bautista[2], Grégory Scherrer[1], and David Julius[3]
[1]Department of Anatomy, University of California, San Francisco 94158
[2]Department of Molecular and Cell Biology, University of California, Berkeley CA 94720
[3]Department of Physiology, University of California, San Francisco 94158

Emerging targets in neuroinflammation-driven chronic pain

Ru-Rong Ji[1], Zhen-Zhong Xu[1], and Yong-Jing Gao[2]

Nature Reviews Drug Discovery | AOP, published online 20 June 2014; doi:10.1038/nrd4334




LTP ↑
Intraneuronal P ↑
PO2 ↓
Blood vessel
Neuron death
Glutamate
BDNF
NMDA
Microglia activation
Ischemia pain
H+
ATP
ASIC3
NGF
TRPV1
P2X3
PAR2
TRPV1
mGluR
HCN1
Electropic neuronal activity
EP
5-HT
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Nav1.8/1.9
TRPC
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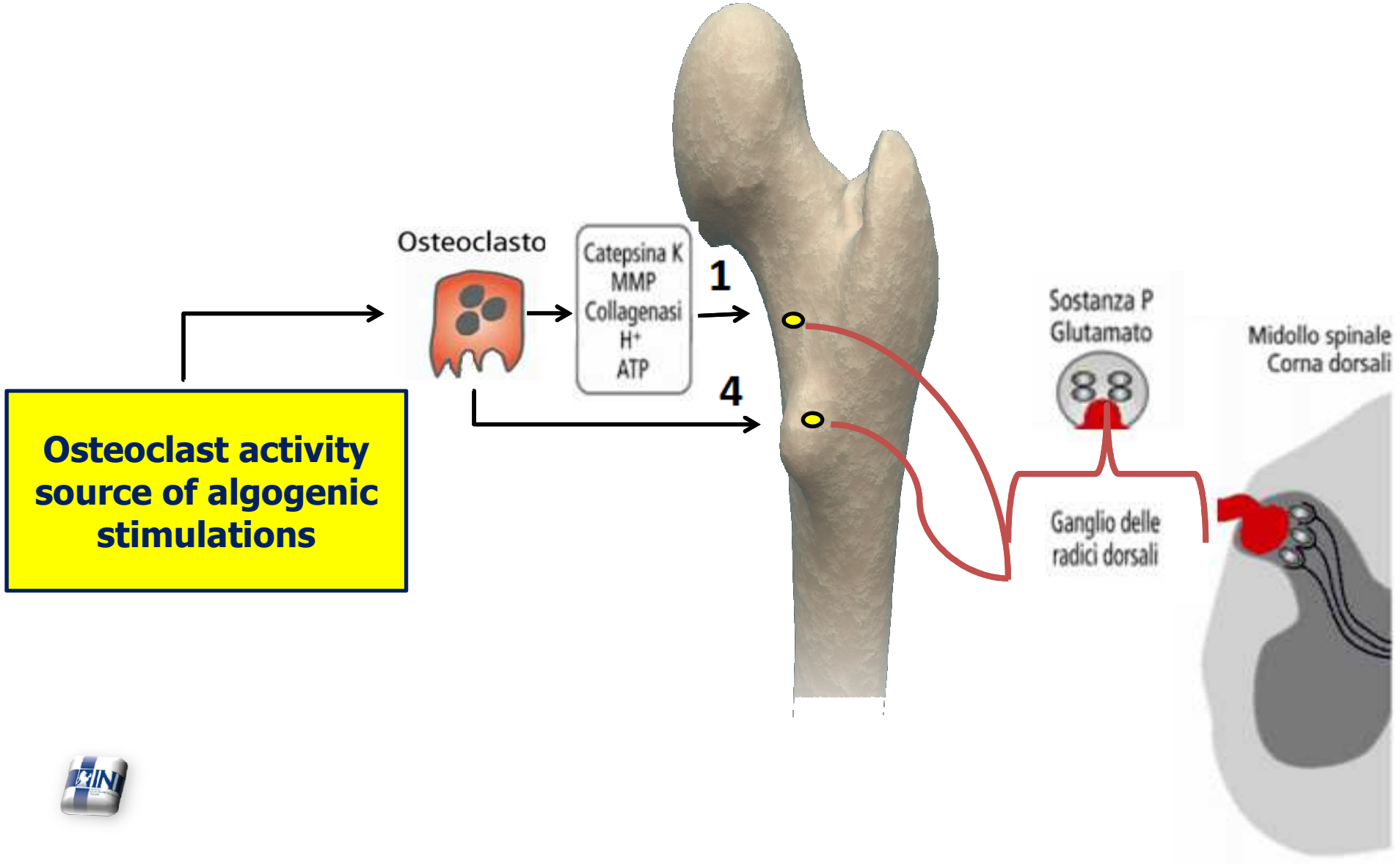
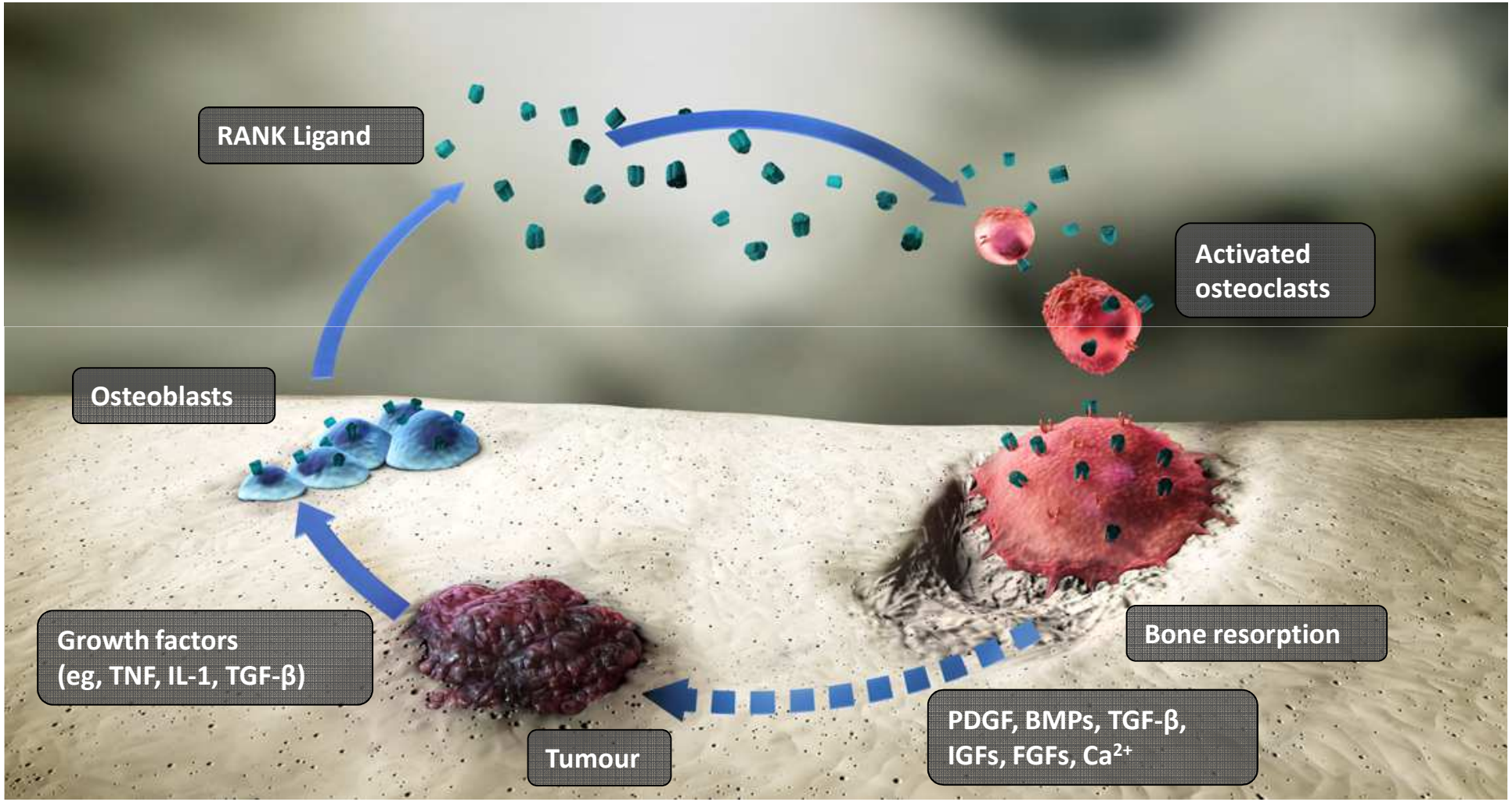
ASIC3
Serotonin
ATP
H+
Stretch
TNF-α
IL-1/6
Mechanical pain

PATHOPHYSIOLOGY OF CANCER INDUCED BONE PAIN



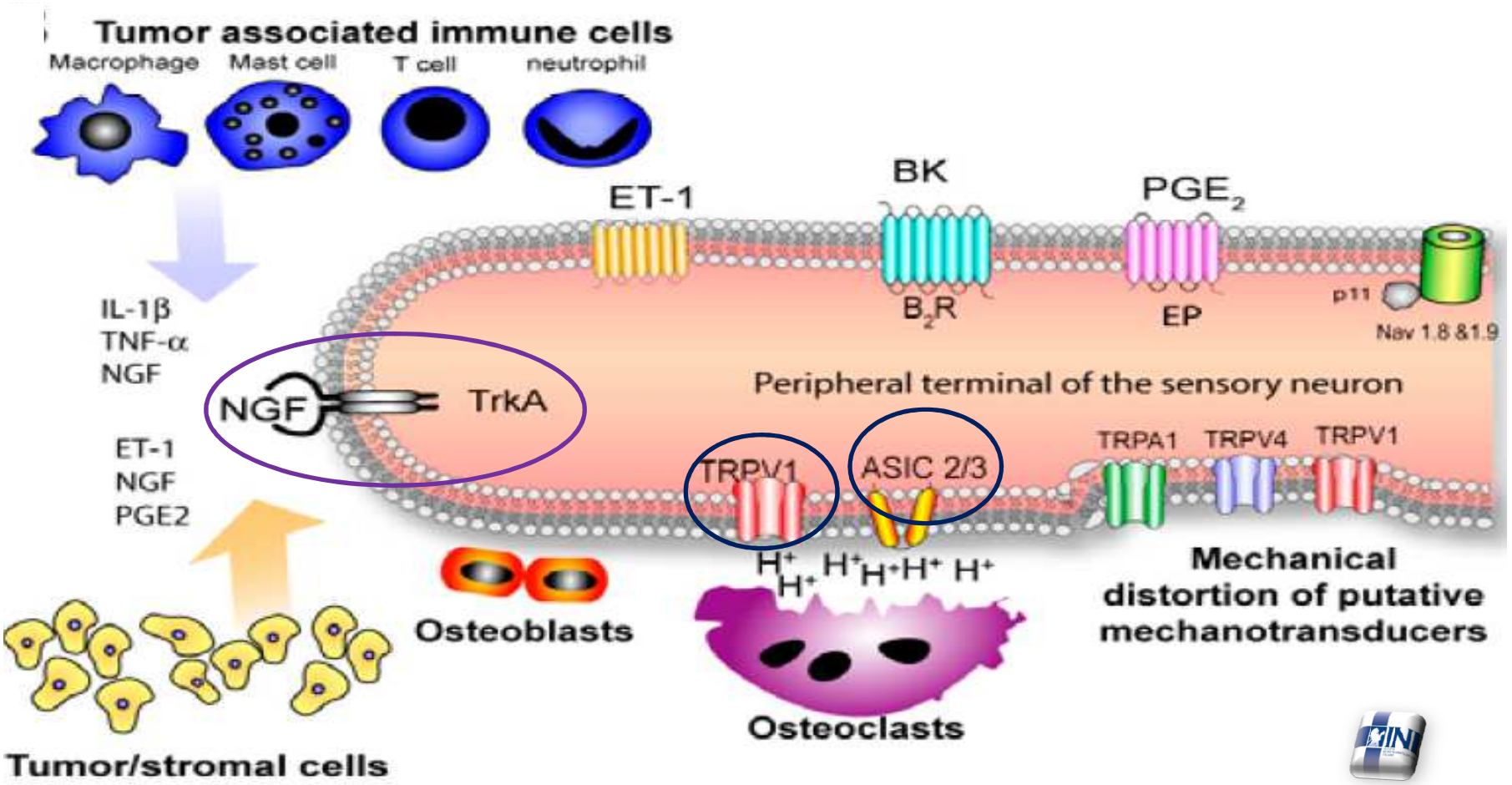
Osteoclast activity source of algogenic stimulations

RANK Ligand is an essential mediator of the vicious cycle of bone destruction



1. Adapted from: Boyle WJ, et al. Nature 2003;423:337–42;
2. Roodman GD. N Engl J Med 2004;350:1655–64.

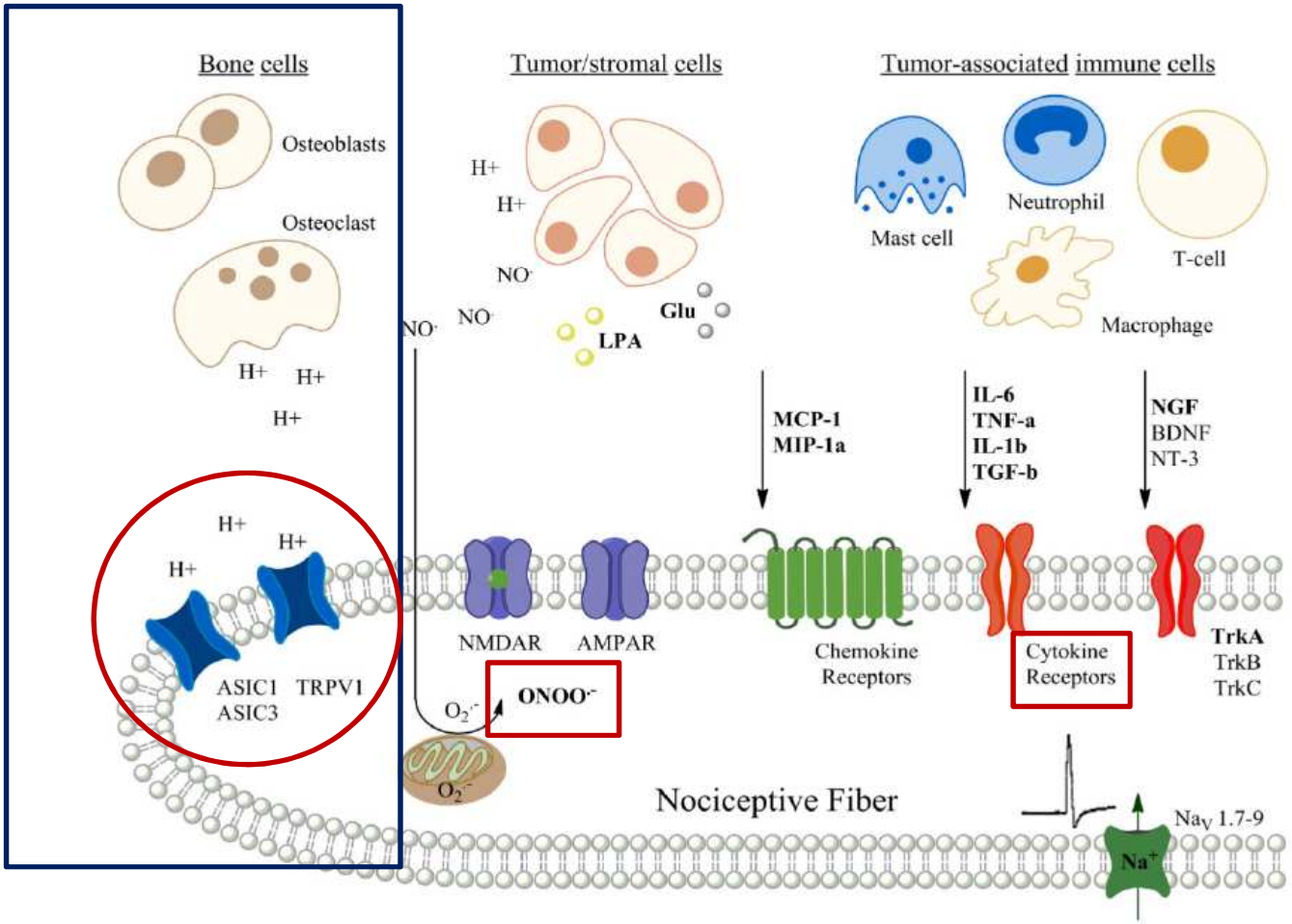
International Association for the Study of Pain
IASP
Working together for pain relief
PAIN
CLINICAL
UPDATES



Published in final edited form as:
Neurosci Lett. 2013 December 17; 557(0 0): 52–59. doi:10.1016/j.neulet.2013.08.003.

Mechanisms of cancer-induced bone pain

AN Lozano-Ondoua[1], **AM Symons-Liguori**[1], and **TW Vanderah**[1]
[1]Department of Pharmacology, College of Medicine, University of Arizona, Tucson, AZ, USA



REVIEW

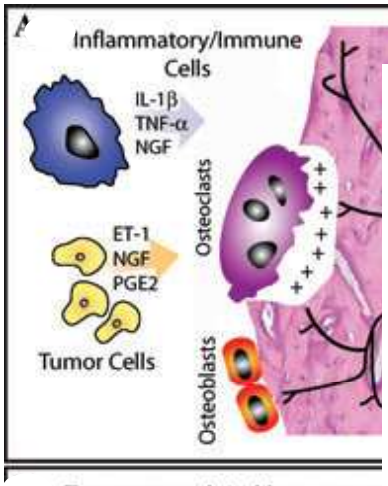
Acidic microenviro
cancer-colonized b

Toshiyuki Yoneda[1], Masahiro Hiasa
[1]Department of Medicine, Hematology/Onco
[2]Department of Anesthesia, Paul and Carole
IN, USA.

Published in final edited form as:
Curr Opin Support Palliat Care. 2014 June ; 8(2): 83–90. doi:10.1097/SPC.0000000000000048.

Bone Cancer Pain: From Mechanism to Therapy

Patrick W. Mantyh[*,♦]
[*]Department of Pharmacology, University of Arizona, Tucson, AZ 85716
[♦]Arizona Cancer Center, University of Arizona, Tucson, AZ 85716



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Mechanisms of cancer-induced bone pain

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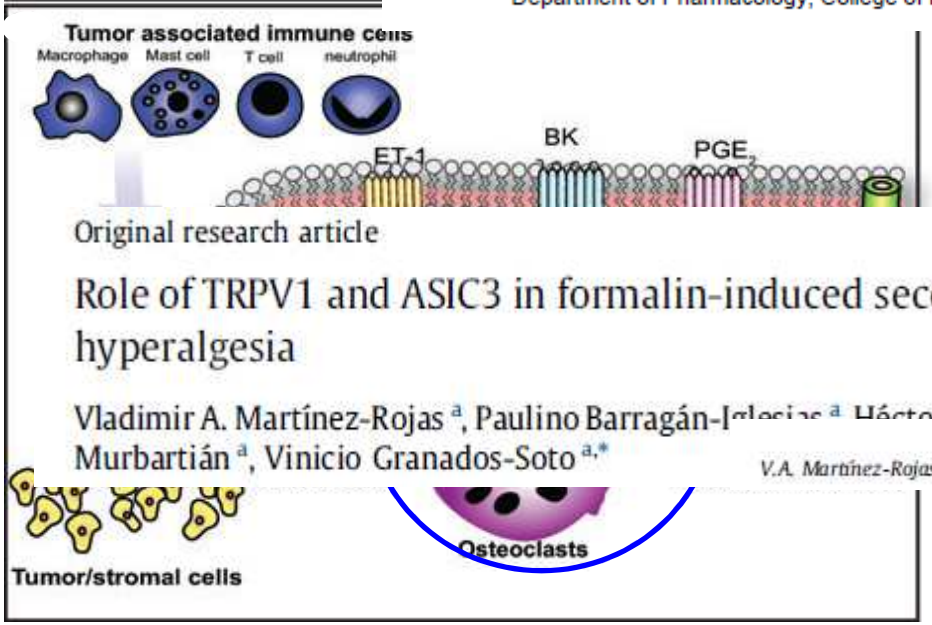
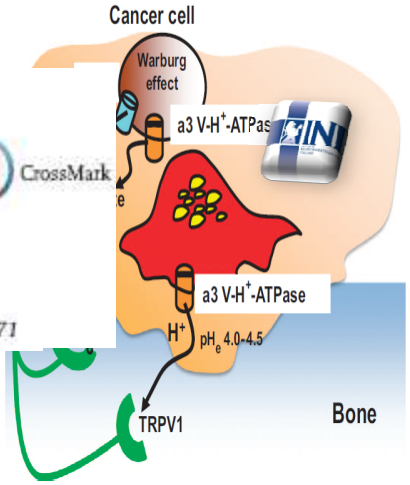


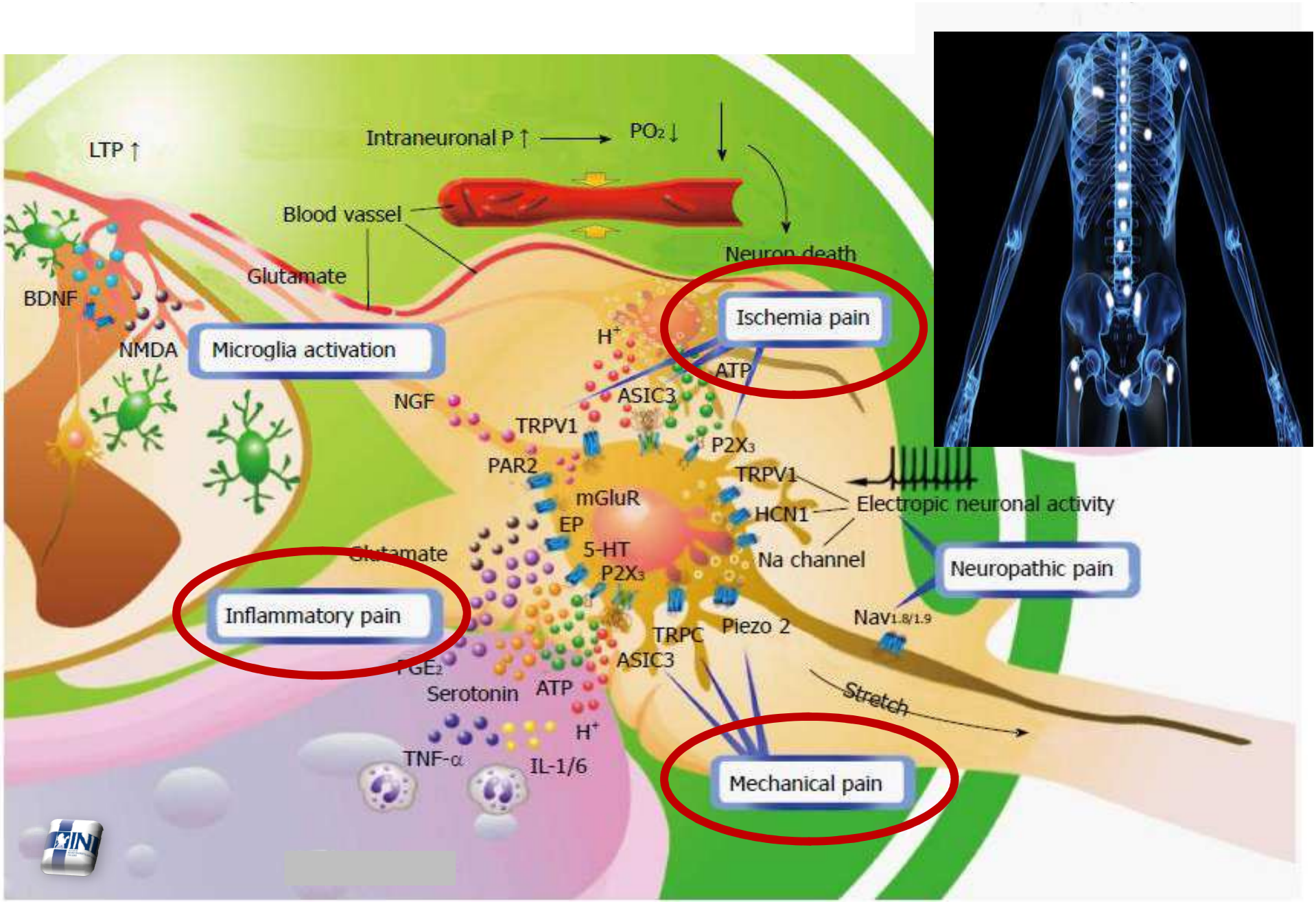
Original research article

Role of TRPV1 and ASIC3 in formalin-induced secondary allodynia and hyperalgesia

Vladimir A. Martínez-Rojas [a], Paulino Barragán-Iglesias [a], Héctor I. Rocha-González [b], Janet Murbartián [a], Vinicio Granados-Soto [a,*]

V.A. Martínez-Rojas et al. / Pharmacological Reports 66 (2014) 964–971




LTP ↑
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PO2 ↓
Blood vessel
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PGE2
Serotonin
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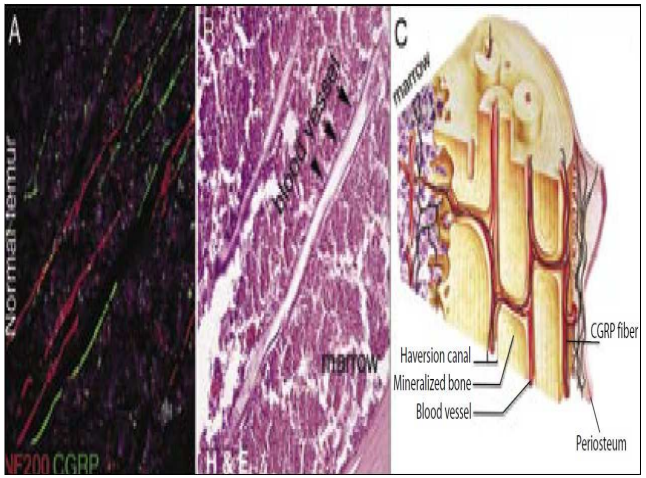
H+
Stretch
TNF-α
IL-1/6
Mechanical pain

PATHOPHYSIOLOGY OF CANCER INDUCED BONE PAIN

Role of the nervous system in mantaninig the pain in bone metastases



Osteoclasto

Cellula neoplastica

Cell. infiamm.

NGF
GDGF
IGF-I e II
PDGF
FGF

IL - TNFα
PGE_2
ET-1
Bradichinina
GF
H+
ATP

1
2
3
4
4

Sostanza P
Glutamato

Midollo spinale
Corna dorsali

Ganglio delle radici dorsali

PAIN® 154 (2013) S54–S62

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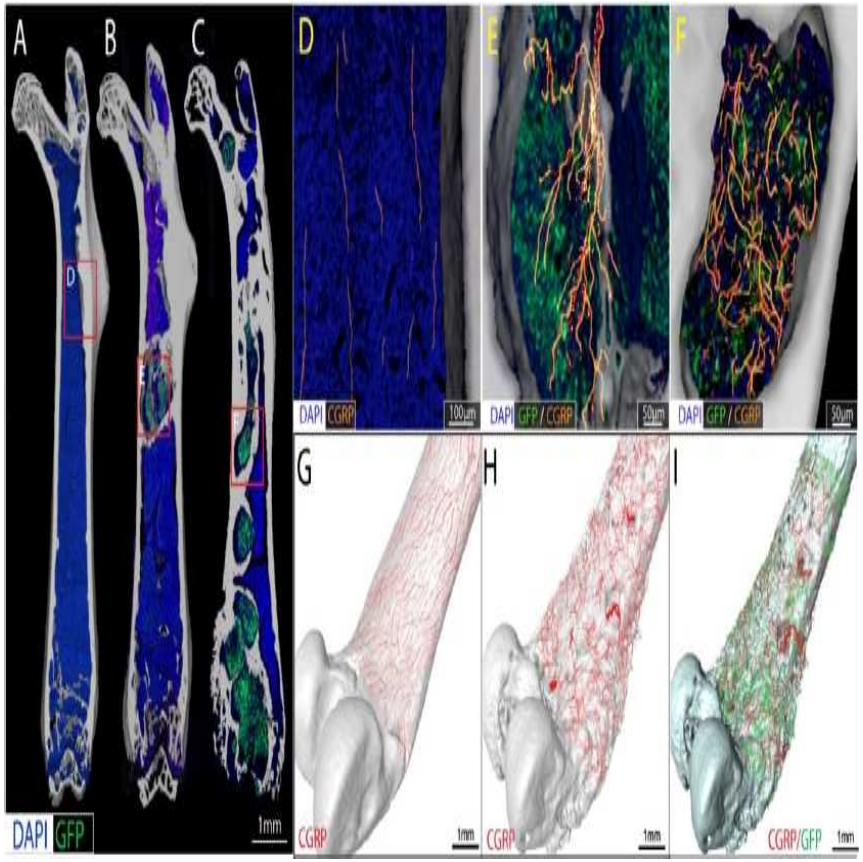
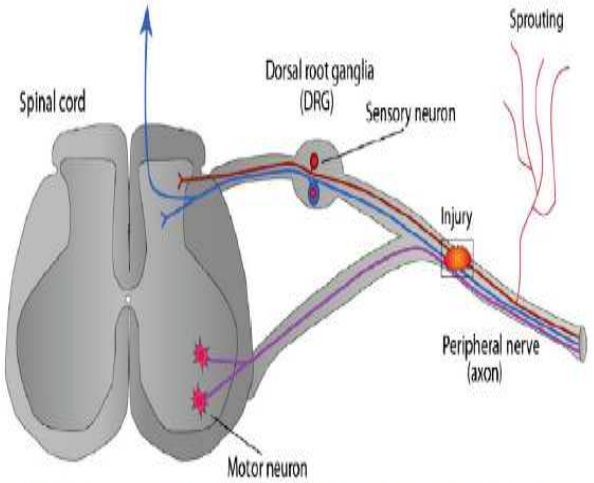
Review

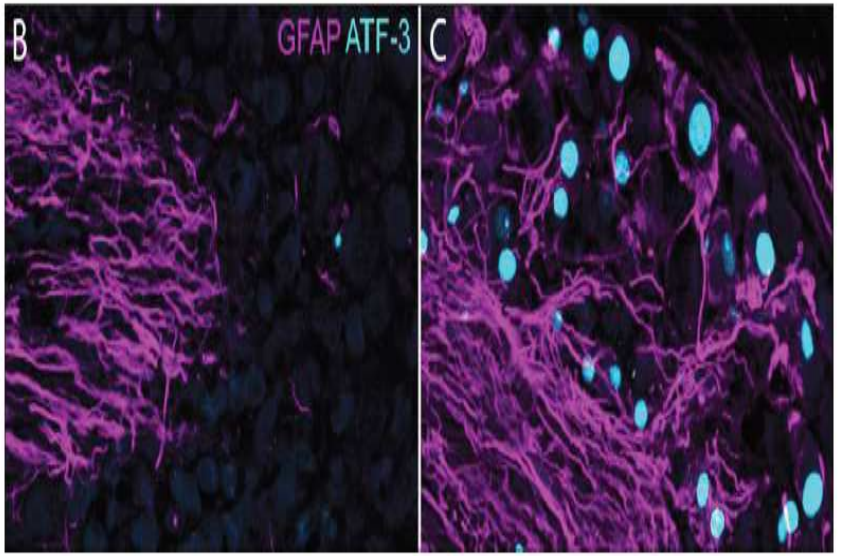
Bone cancer pain: Causes, consequences, and therapeutic opportunities

Patrick Mantyh*

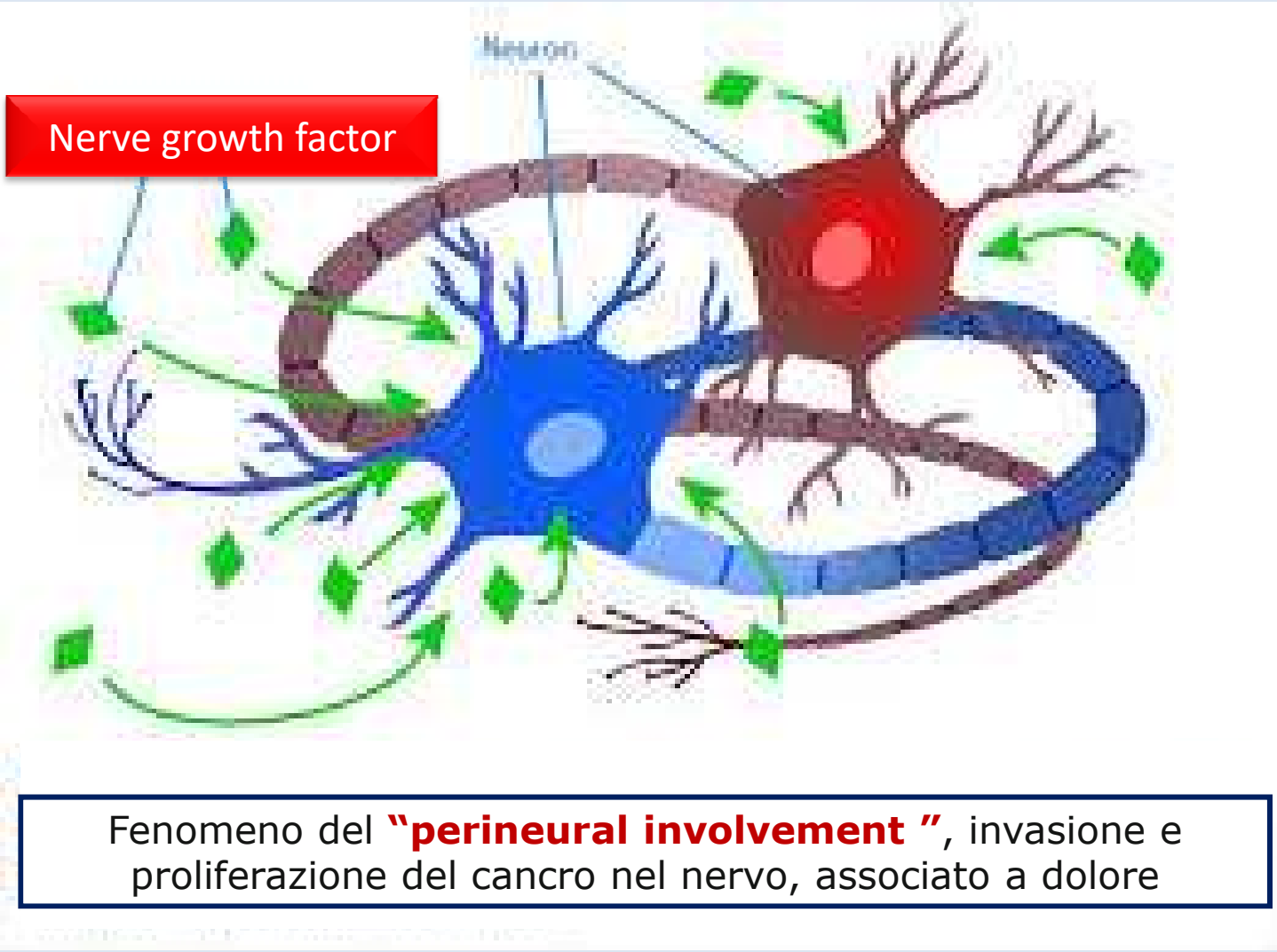
Department of Pharmacology, University of Arizona, 1501 North Campbell Avenue, LSN 560, PO Box 245050, Tucson, AZ 85724, USA





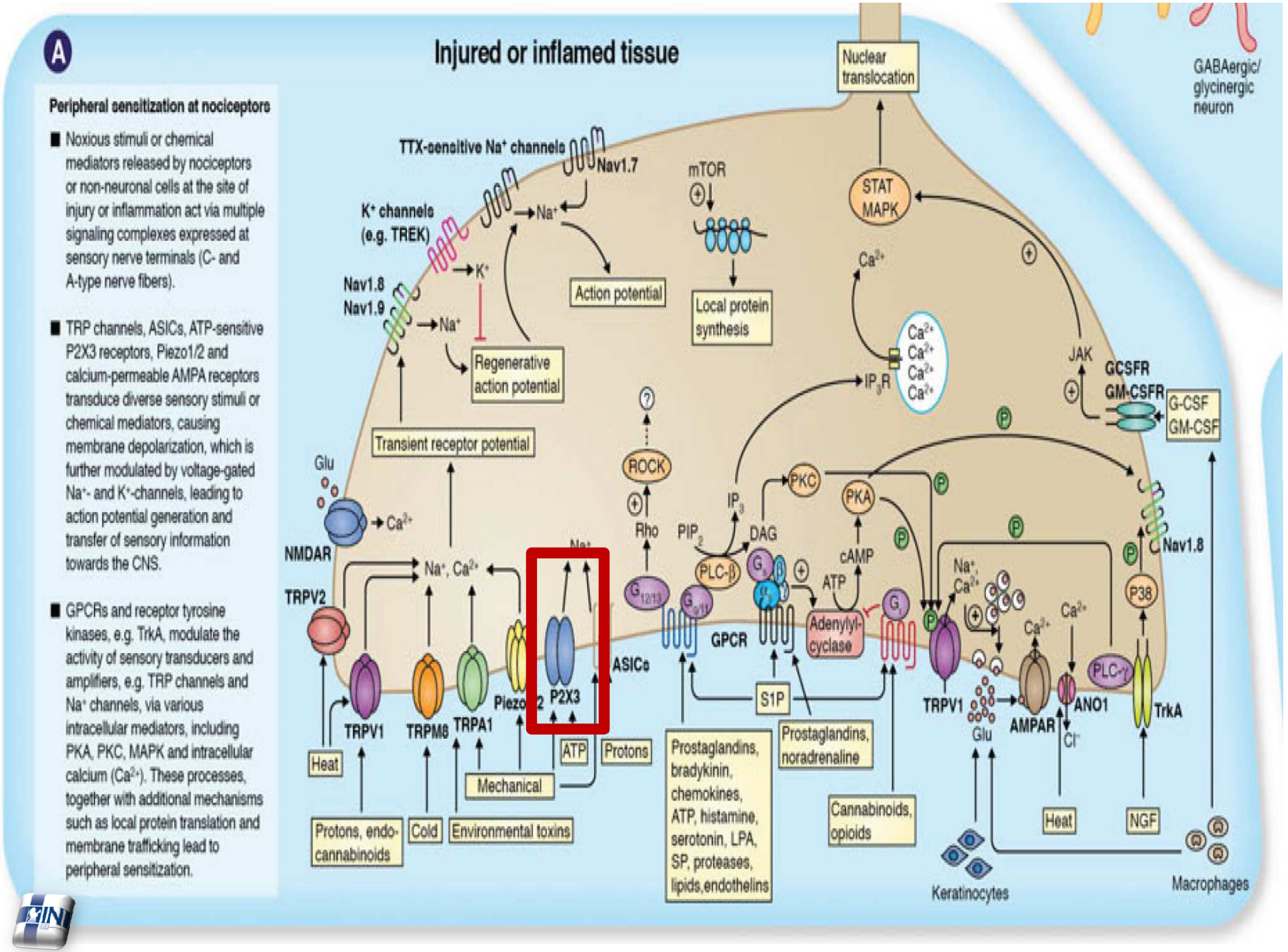


Nerve growth factor

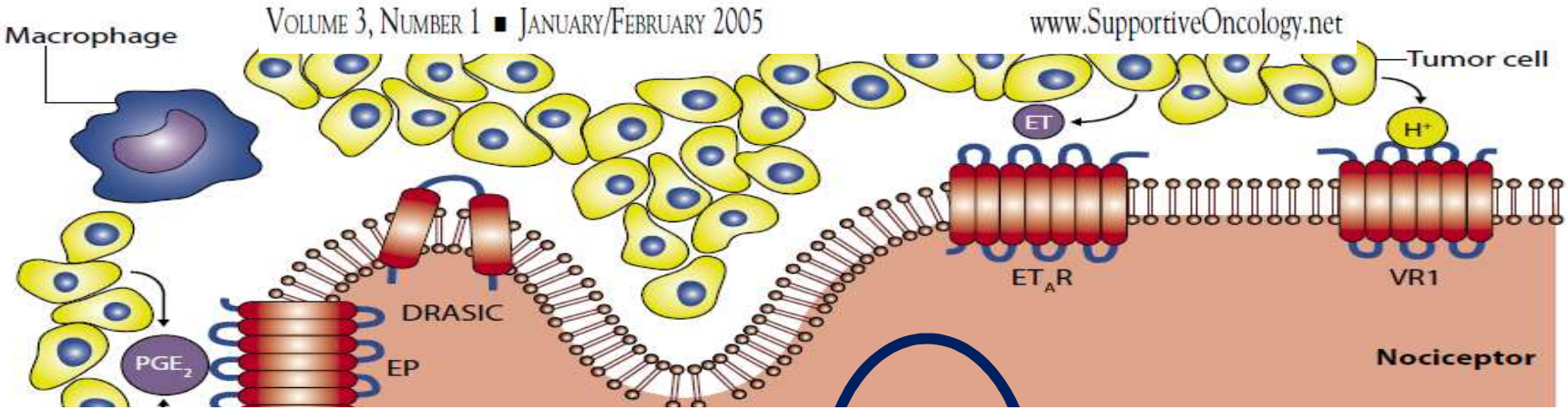


Fenomeno del **"perineural involvement "**, invasione e proliferazione del cancro nel nervo, associato a dolore

*Arizona Cancer Center, University of Arizona, Tucson, AZ 85724, USA


A
Injured or inflamed tissue
Peripheral sensitization at nociceptors
Noxious stimuli or chemical mediators released by nociceptors or non-neuronal cells at the site of injury or inflammation act via multiple signaling complexes expressed at sensory nerve terminals (C- and A-type nerve fibers).
TRP channels, ASICs, ATP-sensitive P2X3 receptors, Piezo1/2 and calcium-permeable AMPA receptors transduce diverse sensory stimuli or chemical mediators, causing membrane depolarization, which is further modulated by voltage-gated Na+- and K+-channels, leading to action potential generation and transfer of sensory information towards the CNS.
GPCRs and receptor tyrosine kinases, e.g. TrkA, modulate the activity of sensory transducers and amplifiers, e.g. TRP channels and Na+ channels, via various intracellular mediators, including PKA, PKC, MAPK and intracellular calcium (Ca2+). These processes, together with additional mechanisms such as local protein translation and membrane trafficking lead to peripheral sensitization.
TTX-sensitive Na+ channels
Nav1.7
K+ channels (e.g. TREK)
Nav1.8
Nav1.9
Action potential
Regenerative action potential
Transient receptor potential
mTOR
Local protein synthesis
Nuclear translocation
STAT MAPK
JAK
GCSFR
GM-CSFR
G-CSF
GM-CSF
GABAergic/ glycinergic neuron
Glu
NMDAR
TRPV2
TRPV1
TRPM8
TRPA1
Piezo2
P2X3
ASICs
Heat
Protons, endo-cannabinoids
Cold
Environmental toxins
Mechanical
ATP
Protons
ROCK
Rho
PIP2
IP3
DAG
PKC
PKA
PLC-β
cAMP
ATP
Adenylyl-cyclase
GPCR
S1P
Prostaglandins, bradykinin, chemokines, ATP, histamine, serotonin, LPA, SP, proteases, lipids,endothelins
Prostaglandins, noradrenaline
Cannabinoids, opioids
IP3R
Nav1.8
P38
PLC-γ
TrkA
NGF
TRPV1
Glu
AMPAR
ANO1
Heat
Keratinocytes
Macrophages

Tumor and Inflammatory By-products Involved in the Sensitization of a Nociceptor



Review Article

The Role of Purinergic Receptors in Cancer-Induced Bone Pain

Sarah Falk, Maria Uldall, and Anne-Marie Heegaard

doi:10.1155/2012/758181

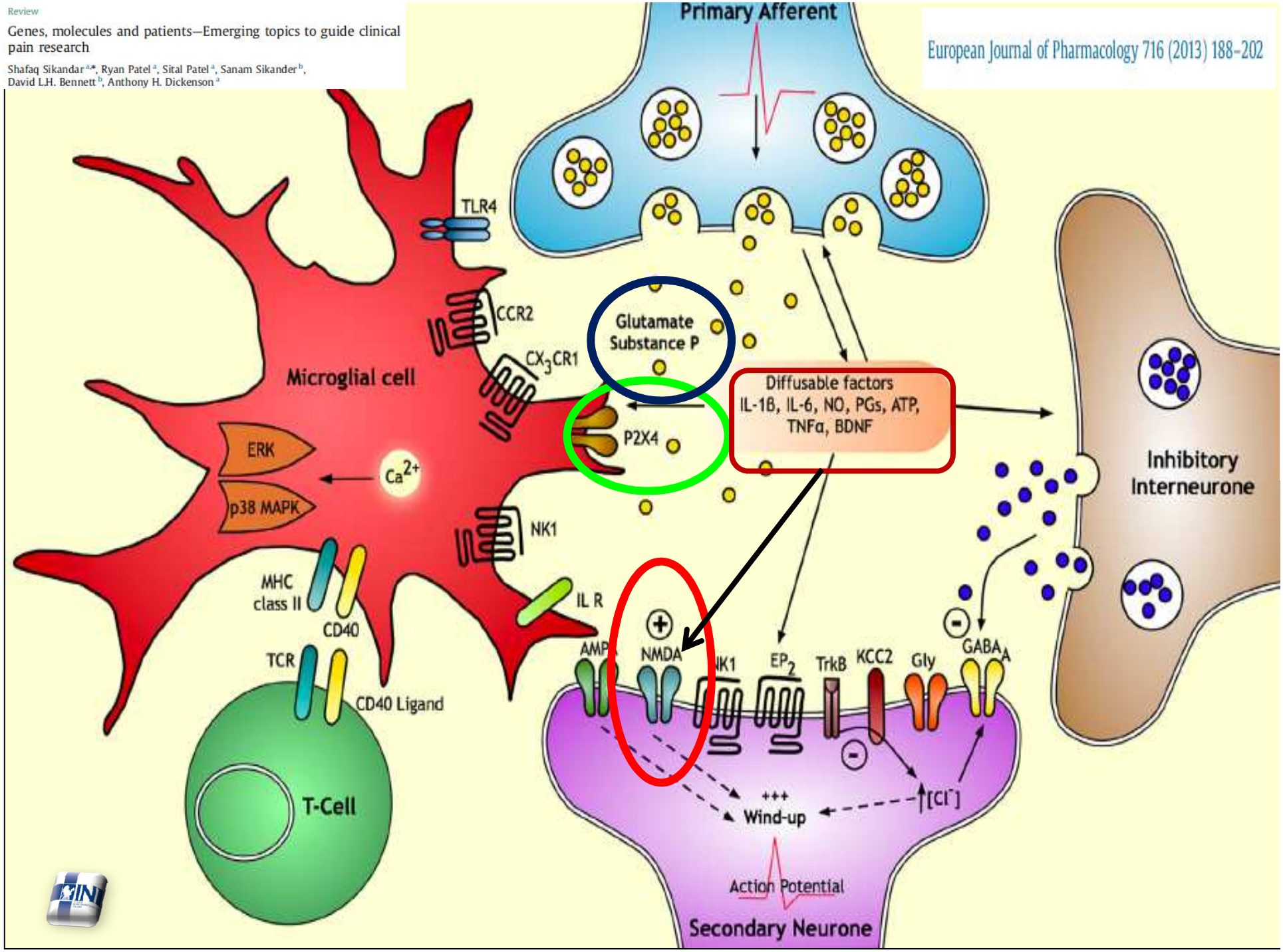
Cancer-induced bone pain severely compromises the quality of life of many patients suffering from bone metastasis, as current therapies leave some patients with inadequate pain relief. The recent development of specific animal models has increased the understanding of the molecular and cellular mechanisms underlying cancer-induced bone pain including the involvement of ATP and the purinergic receptors in the progression of the pain state. In nociception, ATP acts as an extracellular messenger to transmit sensory information both at the peripheral site of tissue damage and in the spinal cord. Several of the purinergic receptors have been shown to be important for the development and maintenance of neuropathic and inflammatory pain, and studies have demonstrated the importance of both peripheral and central mechanisms. We here provide an overview of the current literature on the role of purinergic receptors in cancer-induced bone pain with emphasis on some of the difficulties related to studying this complex pain state.

Review

Genes, molecules and patients—Emerging topics to guide clinical pain research

Shafaq Sikandar [a,*], Ryan Patel [a], Sital Patel [a], Sanam Sikander [b], David L.H. Bennett [b], Anthony H. Dickenson [a]

European Journal of Pharmacology 716 (2013) 188–202

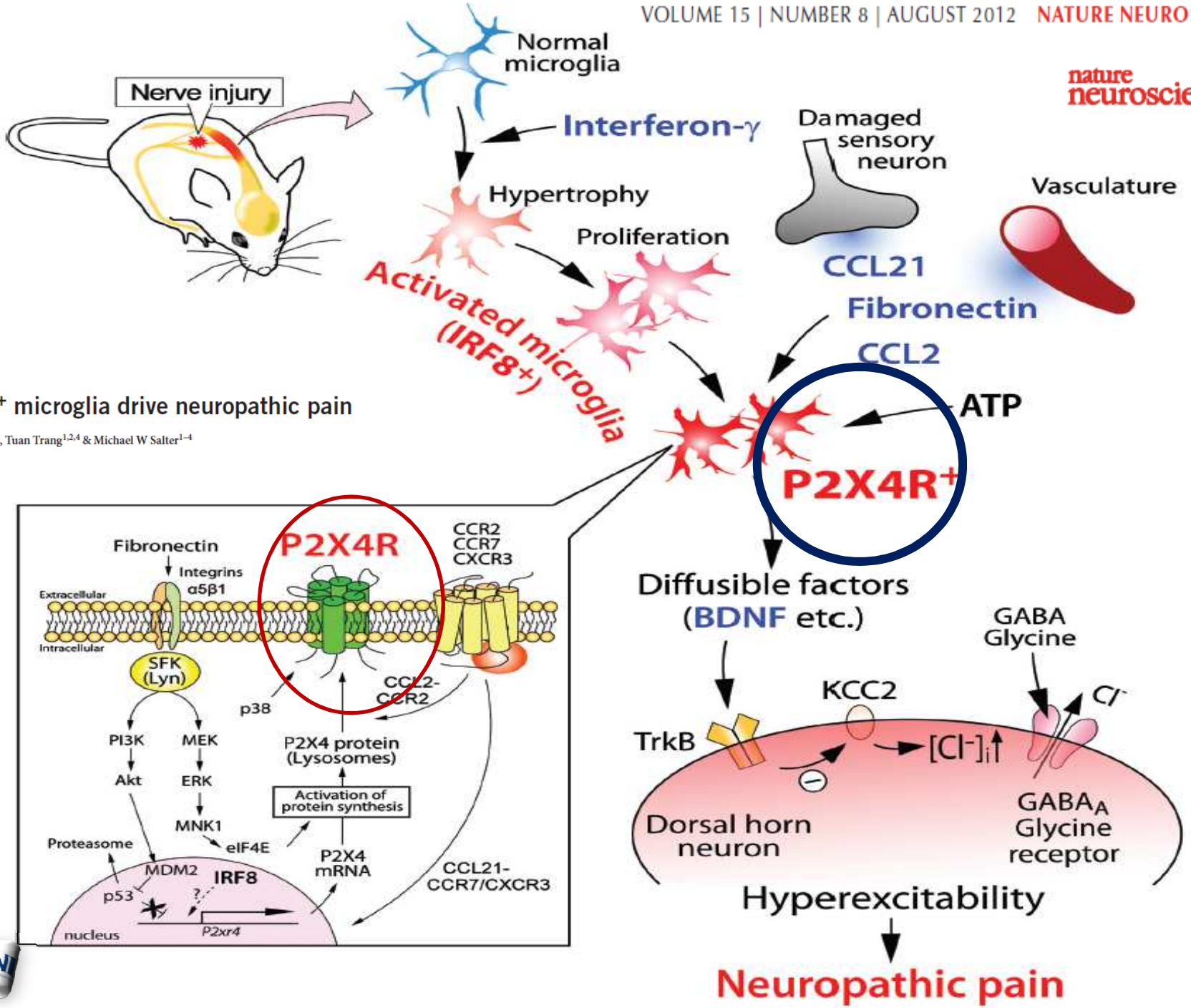


VOLUME 15 | NUMBER 8 | AUGUST 2012 NATURE NEUROSCIENCE

nature neuroscience

P2X4R+ microglia drive neuropathic pain

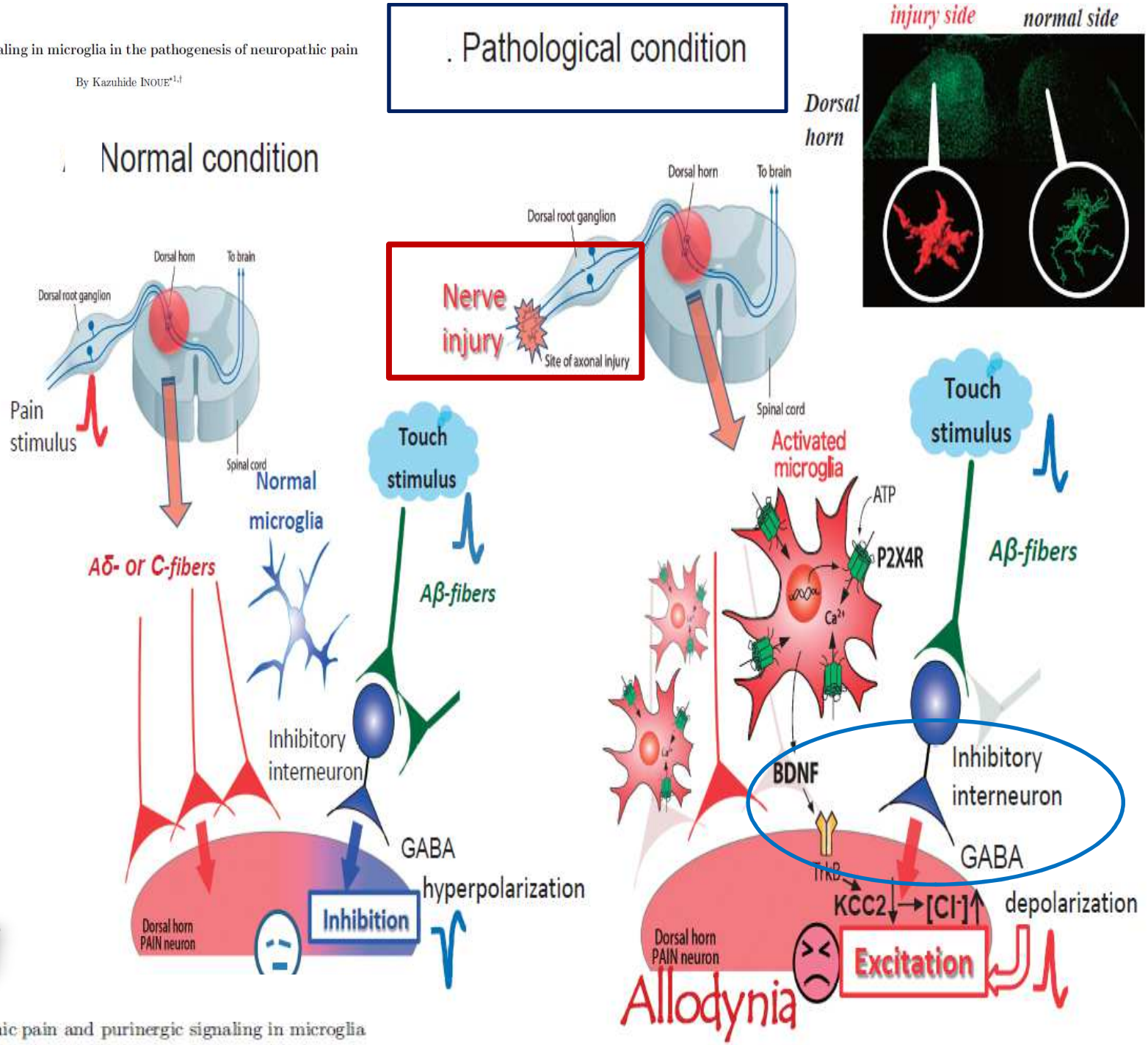
Simon Beggs[1–3], Tuan Trang[1,2,4] & Michael W Salter[1–4]



Review

Purinergic signaling in microglia in the pathogenesis of neuropathic pain

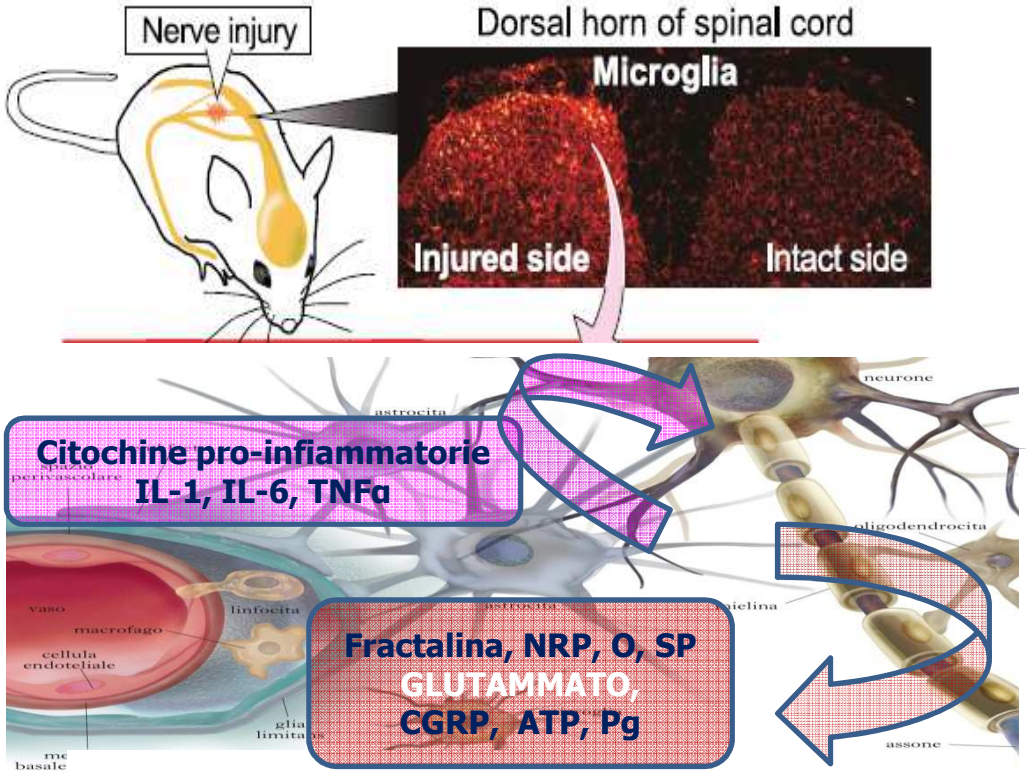
By Kazuhide INOUE[*1,†]

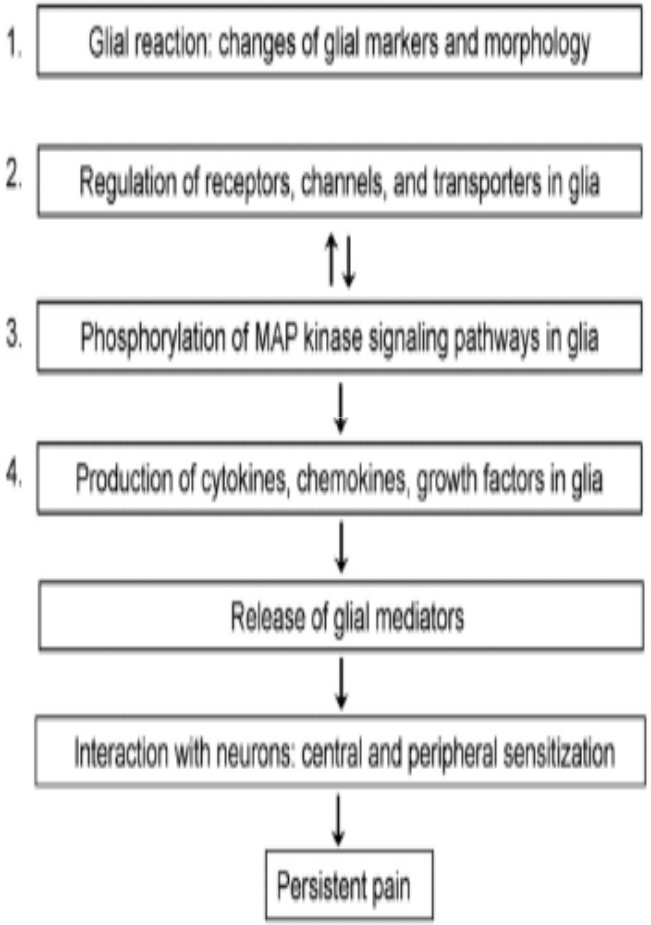


Neuropathic pain and purinergic signaling in microglia

ROLE OF GLIA: MICROGLIA - ASTROCYTES

STRENGTHENS THE PERCEPTION OF PAIN





IASP

PAIN® 154 (2013) S10–S28

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Review

Glia and pain: Is chronic pain a gliopathy?

Ru-Rong Ji [a,*], Temugin Berta [a], Maiken Nedergaard [b]

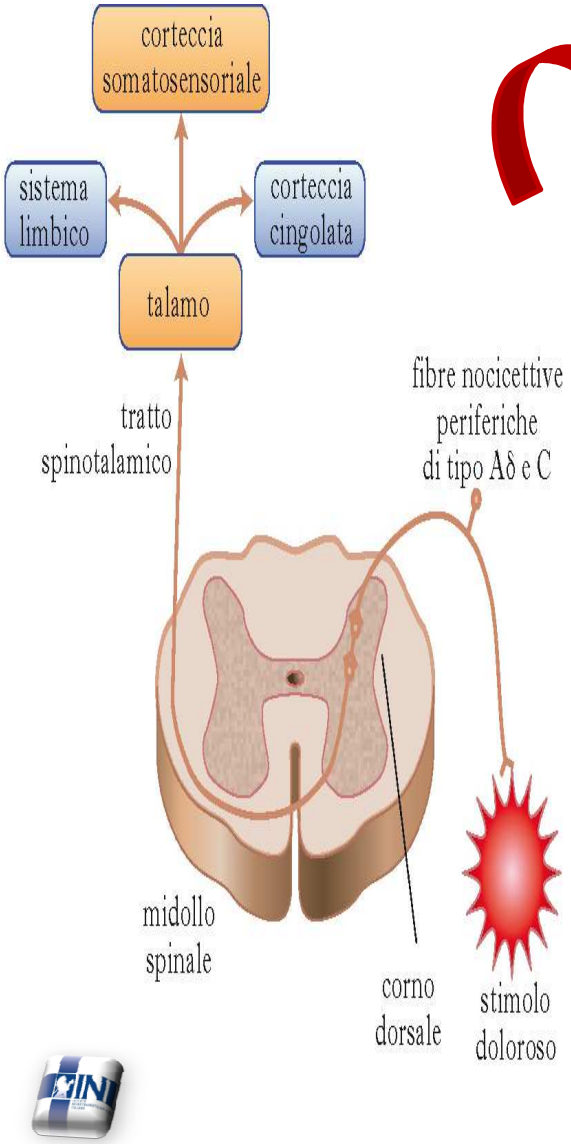
[a] Department of Anesthesiology and Neurobiology, Duke University Medical Center, Durham, NC, USA
[b] Division of Glial Disease and Therapeutics, Center for Translational Neuromedicine, University of Rochester, Rochester, NY, USA

epartment of Anesthesiology and Neurobiology, Duke University Medical Center, Durham, NC, SA

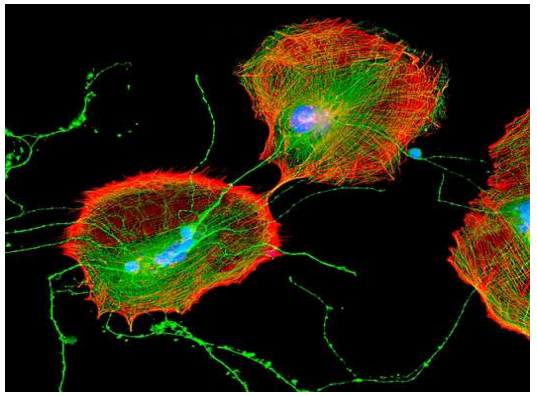
ivision of Glial Disease and Therapeutics, Center for Translational Neuromedicine, University Rochester, Rochester, NY, USA

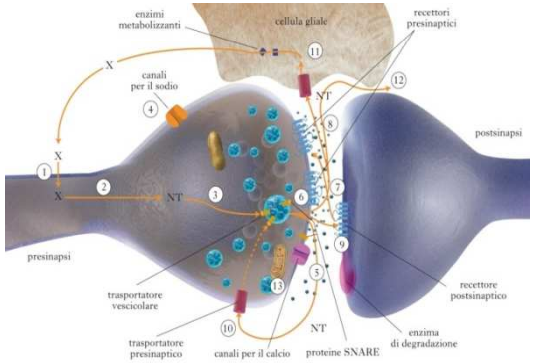
ROLE OF GLIA: MICROGLIA - ASTROCYTES

STRENGTHENS THE PERCEPTION OF PAIN

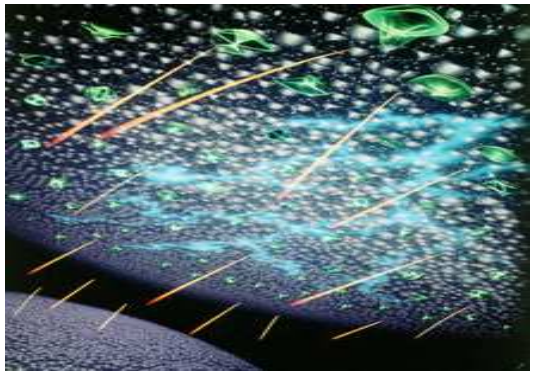


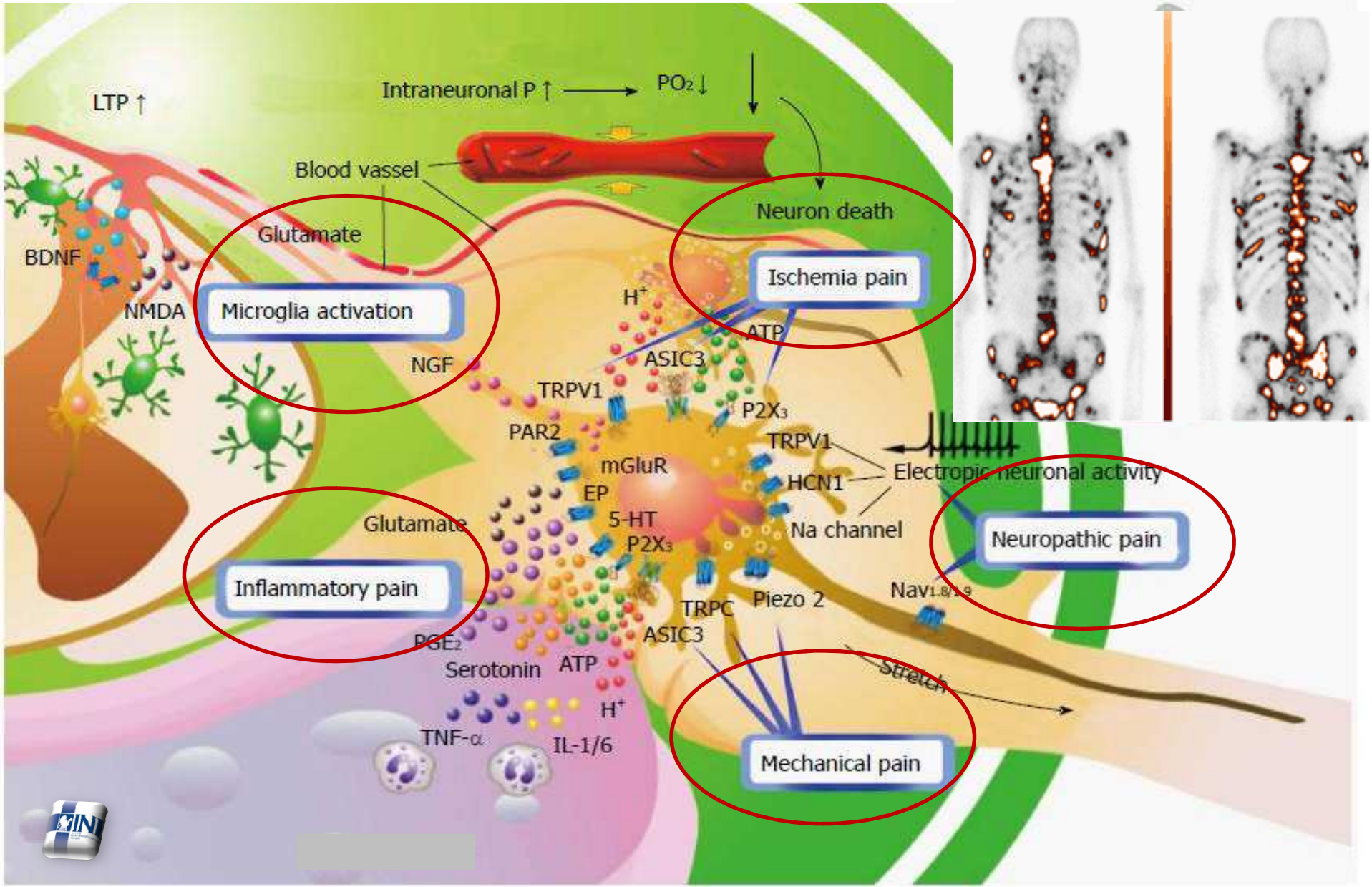
Fractalina, NRP, O, SP
Glutammato, CGRP, ATP, Pg





Citochine pro-infiammatorie
IL-1, IL-6, TNF

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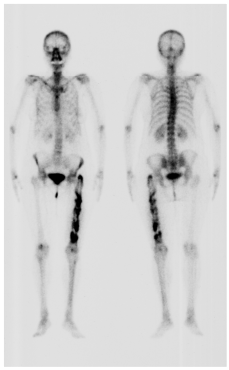
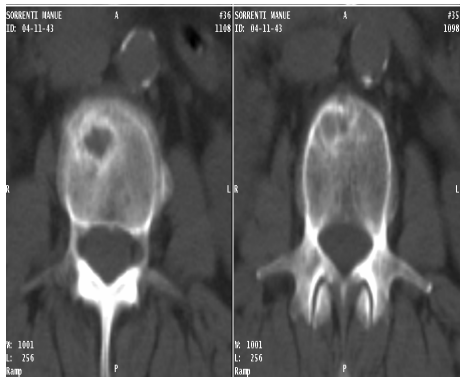
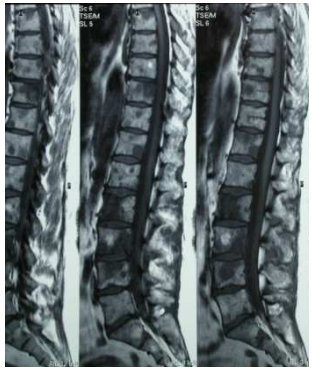
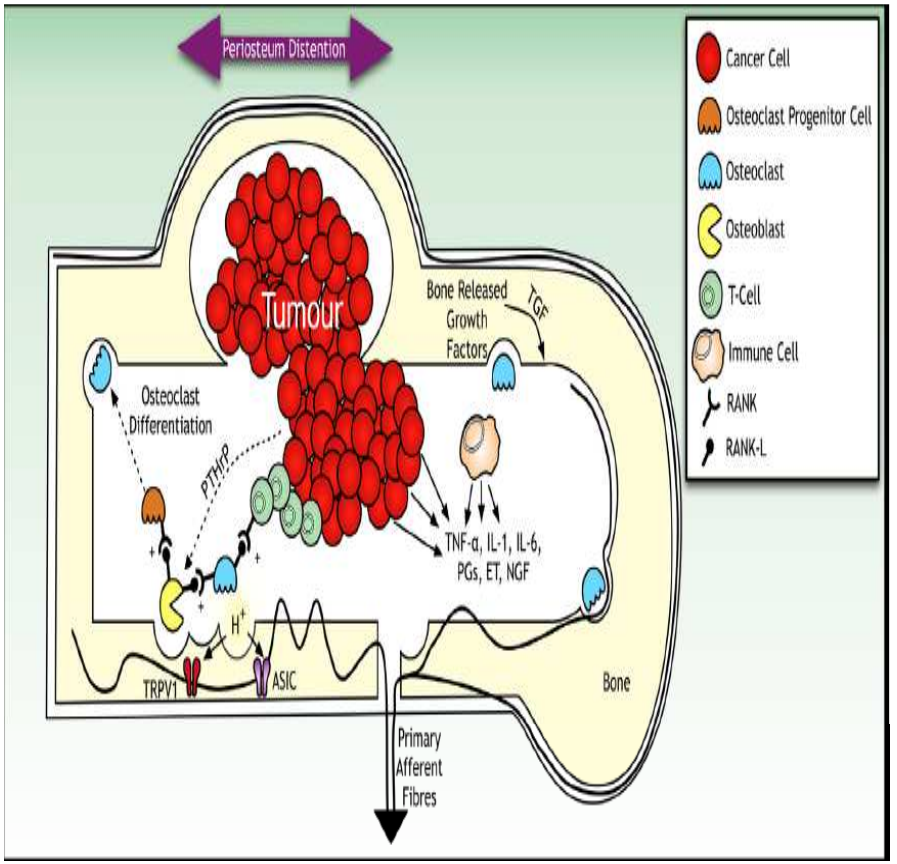
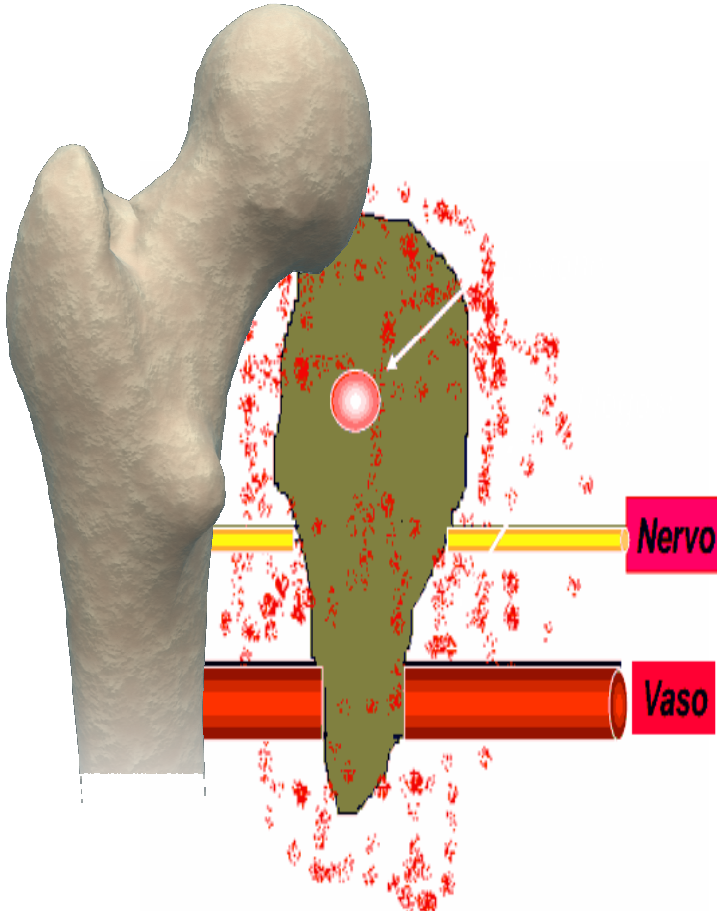










- **INVASIONE DIRETTA**
- **DISTORSIONE DELL'ARCHITETTURA OSSEA-IPERTENSIONE ENDOSTIALE**
- **COINVOLGIMENTO NERVOSO**
- **SPASMO DELLA MUSCOLATURA PERILESIONALE**

CIBP: A COMPLEX PAIN SYNDROME

INFLAMMATORY MECHANISM

- secretion of humoral mediators
- activation and excitation of primary afferent neurons

COMPRESSION MECHANISM

- rapid growth
  intratumoral hemorrhage
  invasion
  nerve entrapment
  osteolysis
  organ damage

COMPLEX PAIN SYNDROME

CHEMICAL MECHANISM

- low pH intra and extracellular

MECHANISM NEUROPATHIC

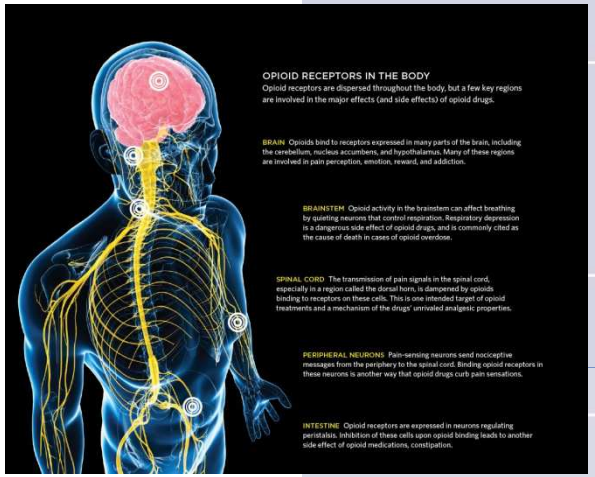
MECHANISM ISCHEMIC

It affects a large percentage of cancer patients
30-50% moderate to severe
25-40% very intense (Dickerson 2001)

↓ QoL
(Weinfurt KP 2002)

COMPLEX PAIN SYNDROME

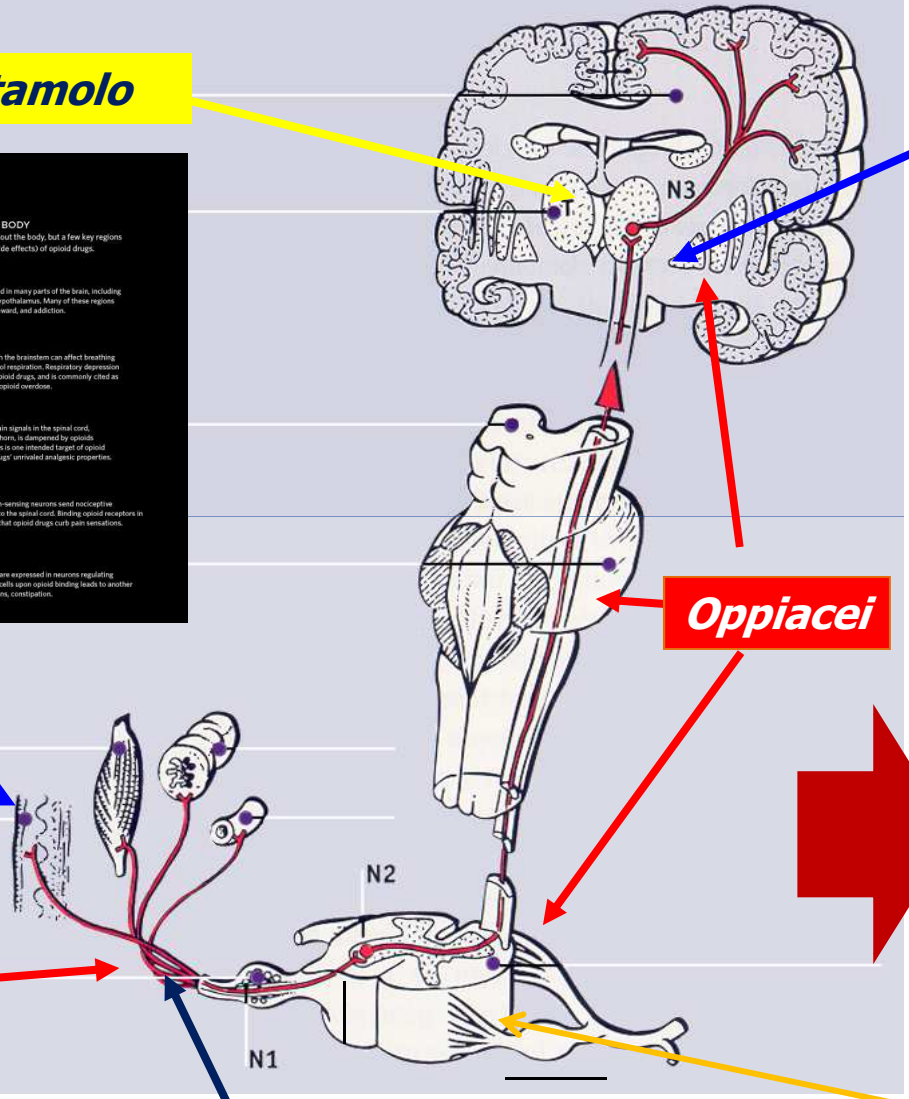
Paracetamolo



Cannabinoidi

Oppiacei

Oppiace



Cannabinoidi

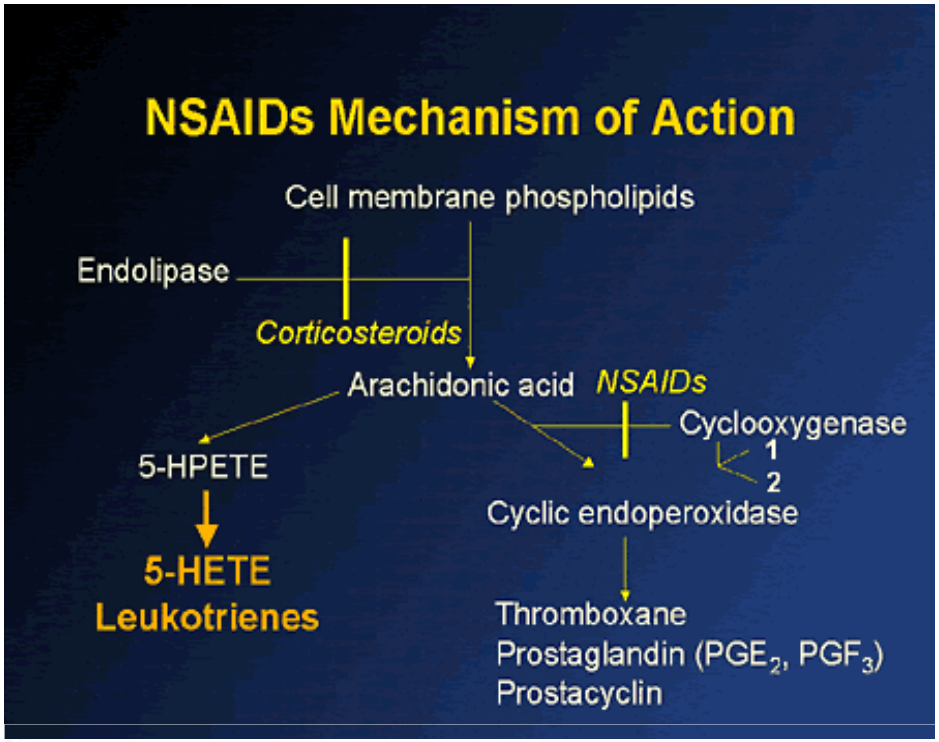
Oppiacei

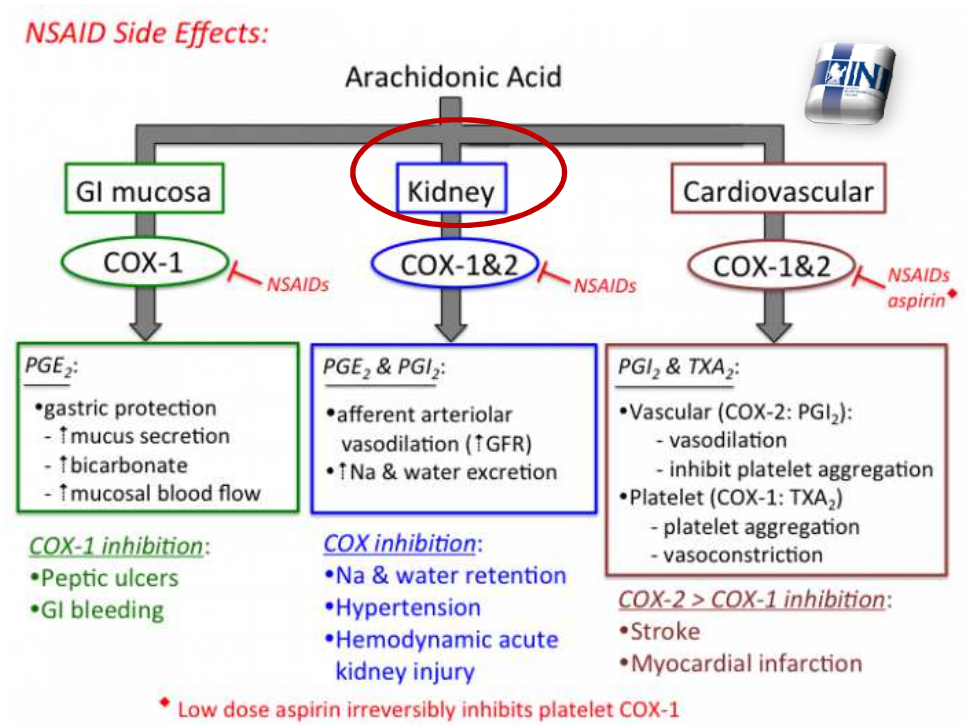
FANS

Gabapentinoidi

OPIOIDS

- Opioid analgesia – mainstay of management of moderate to severe cancer pain
- Opioids effective in background pain mainly!
- Malignant bone pain control without unwanted side-effects is impossible with opioids alone
- *Background/tonic pain*
- *Spontaneous pain*
- *Movement-related pain*





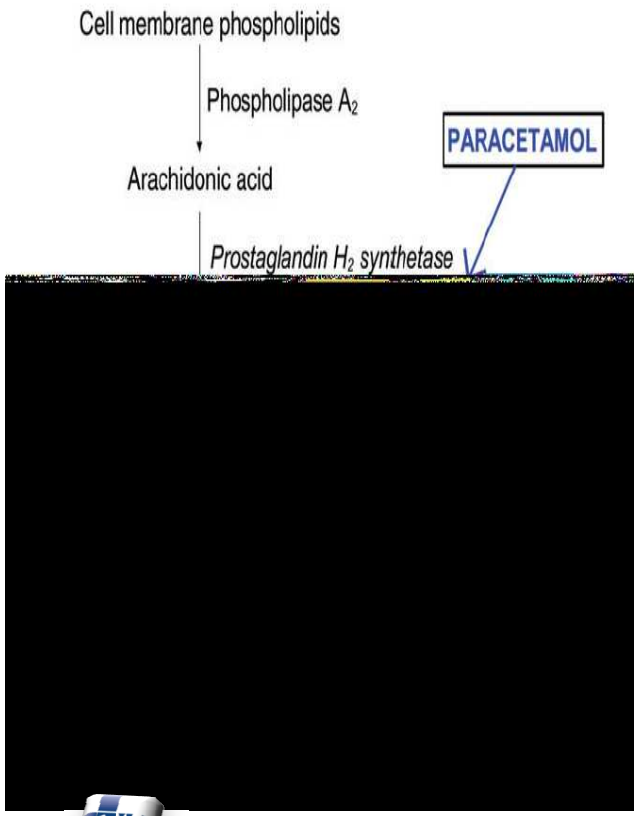
Substance	Caution	Maximal daily dose
Acetaminophen (paracetamol)	Hepatotoxicity	4 × 1000 mg
Acetylsalycic acid	GI toxicity, allergy, platelet inhibition	3 × 1000 mg
Ibuprofen	GI and renal toxicity	4 × 600 mg; 3 × 800 mg modified release
Ketoprofen	GI and renal toxicity	4 × 75 mg; 2 × 200 mg
Diclofenac	GI and renal toxicity	4 × 50 mg; 2 × 100 mg
Mefenamic acid	GI and renal toxicity	4 × 500 mg
Naproxen	GI and renal toxicity	2 x 500 mg

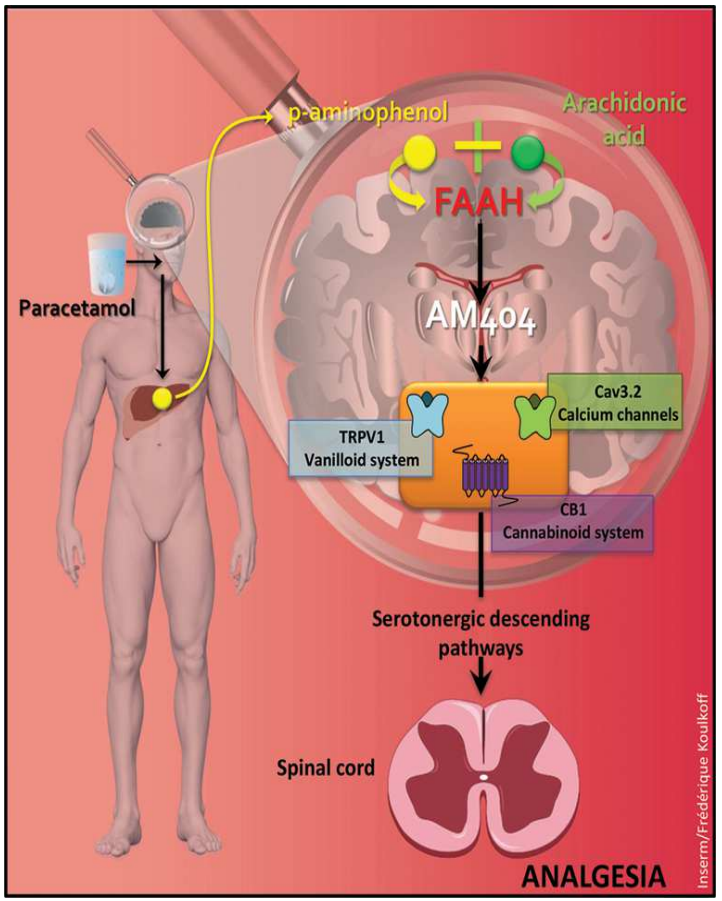
Review Article

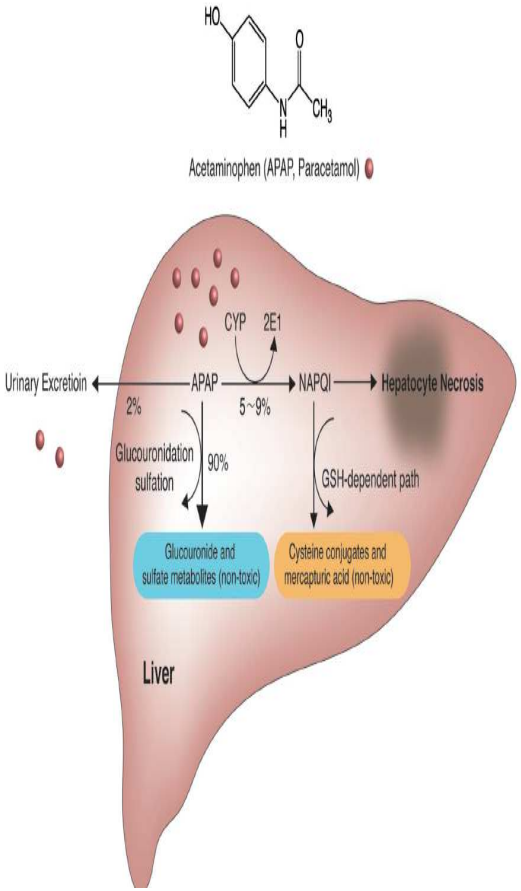
Acetaminophen-Induced Hepatotoxicity: a Comprehensive Update

Eric Yoon, Arooj Babar, Moaz Choudhary, Matthew Kutner and Nikolaos Pyrsopoulos*

Rutgers New Jersey Medical School, University Hospital, Newark, New Jersey, USA



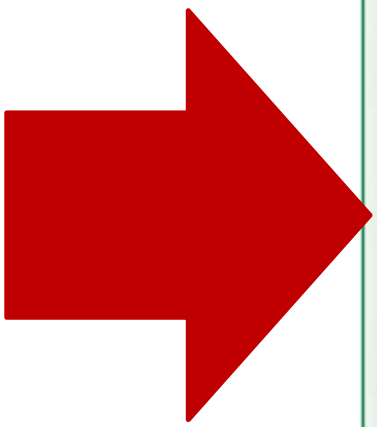




Journal of Clinical and Translational Hepatology **2016** vol. 4 | 131–142

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

Augusto Caraceni, Geoffrey Hanks*, Stein Kaasa*, Michael I Bennett, Cinzia Brunelli, Nathan Cherny, Ola Dale, Franco De Conno, Marie Fallon, Magdi Hanna, Dagny Faksvåg Haugen, Gitte Juhl, Samuel King, Pål Klepstad, Eivor A Laugsand, Marco Maltoni, Sebastiano Mercadante, Maria Nabal, Alessandra Pigni, Lukas Radbruch, Colette Reid, Per Sjogren, Patrick C Stone, Davide Tassinari, Giovambattista Zeppetella, for the European Palliative Care Research Collaborative (EPCRC), on behalf of the European Association for Palliative Care (EAPC)*



	Characteristics and comments
Codeine	Step II drug only: use alone or in combination with paracetamol; daily doses ≥360 mg not recommended
Tramadol	Step II drug only: use alone or in combination with paracetamol; daily doses ≥400 mg not recommended
Hydrocodone	Step II drug only: used as a substitute for codeine in some countries
Oxycodone	Step II opioid when used at low doses (eg, ≤20 mg per day) alone or in combination with paracetamol
Morphine	Step II opioid when used at low doses (eg, ≤30 mg per day)
Hydromorphone	Step II opioid when used at low doses (eg, ≤4 mg per day)

*Originally classified as weak opioids.

Table 1: **WHO step II opioids* for moderate cancer pain in opioid-naive patients**

The Lancet Oncology, Volume 13, Issue 2, Pages e58 - e68, February 2012

OPIOIDS AND BONE METASTASIS

CMRO
Current Medical Research & Opinion Vol. 27, No. 2, 2011, 439–448
0300-7995
Article FT-0163.R1/545379
doi:10.1185/03007995.2010.545379

Review

Opioids: a two-faced Janus

Peggioramento del dolore per esposizioni prolungate a morfina ed attivazione osteoclasti (King 2007)

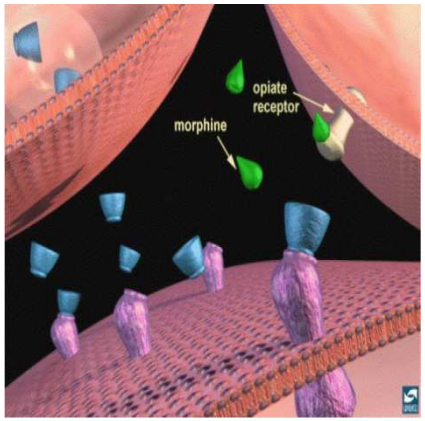
Incremento della glia (Honore 2000, Scholz 2007)

Downregulation delle popolazioni recettoriali per gli oppioidi (eg mu) Ridotta risposta a morfina (Yamamoto 2008)

Aumento dei dosaggi per analgesia (10 volte) (Luger 2002)

Incrementi di peptidi nocicettivi (dinorfina) (Vanderah 2001)

Sensibilizzazione dei neuroni WDR (Urch 2003)



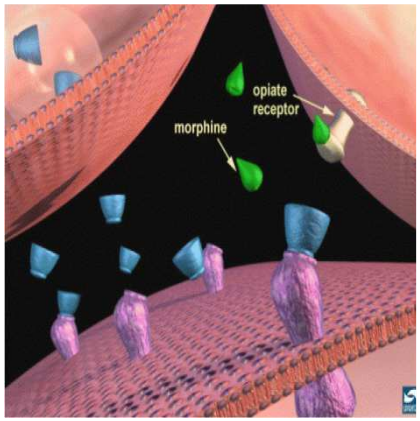
Inaugural Review Series
Translational Pain Research

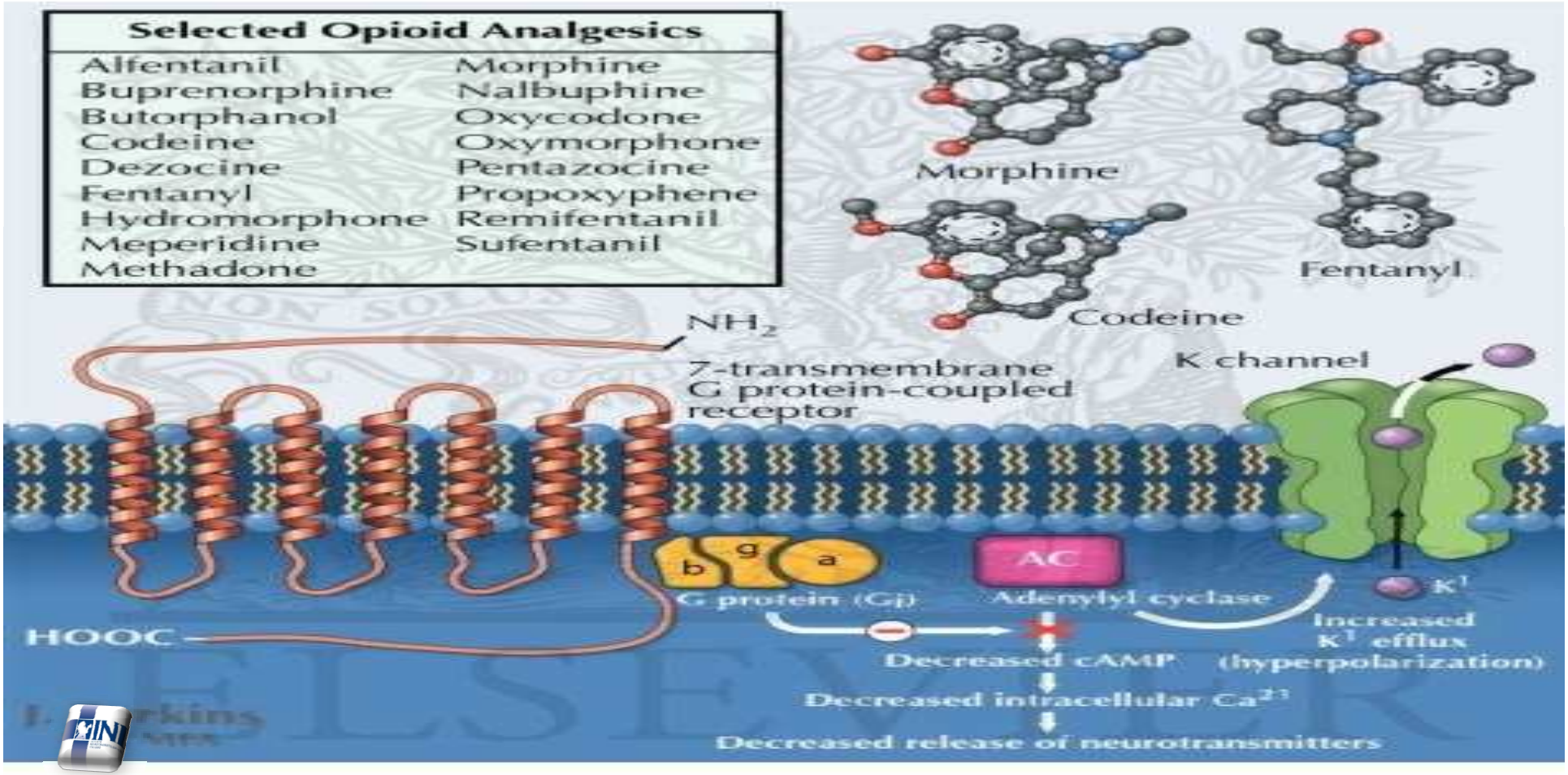
PAIN REPORTS

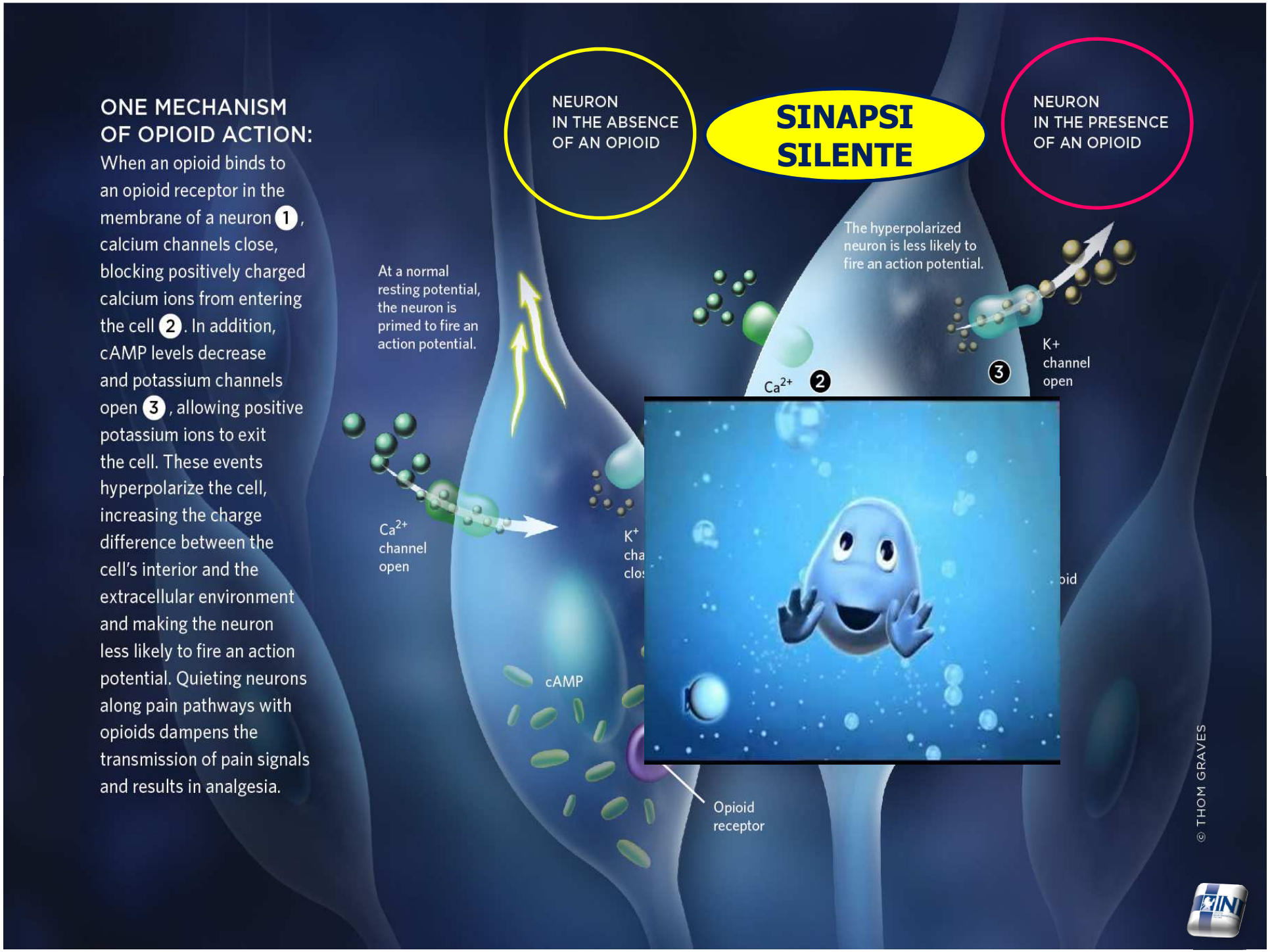
OPEN

The dark side of opioids in pain management: basic science explains clinical observation

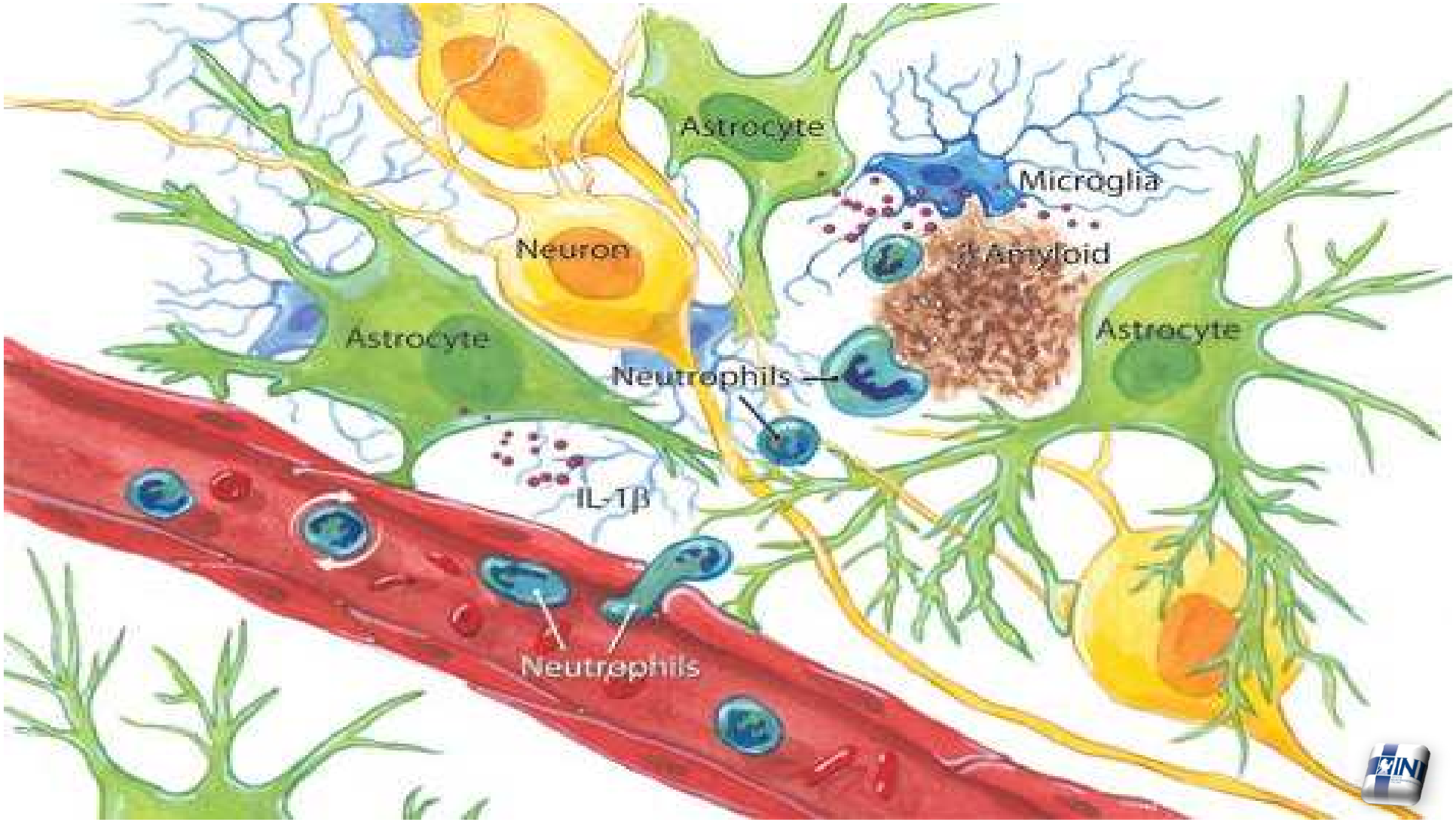
Cyril Rivat[a], Jane Ballantyne[b,*]

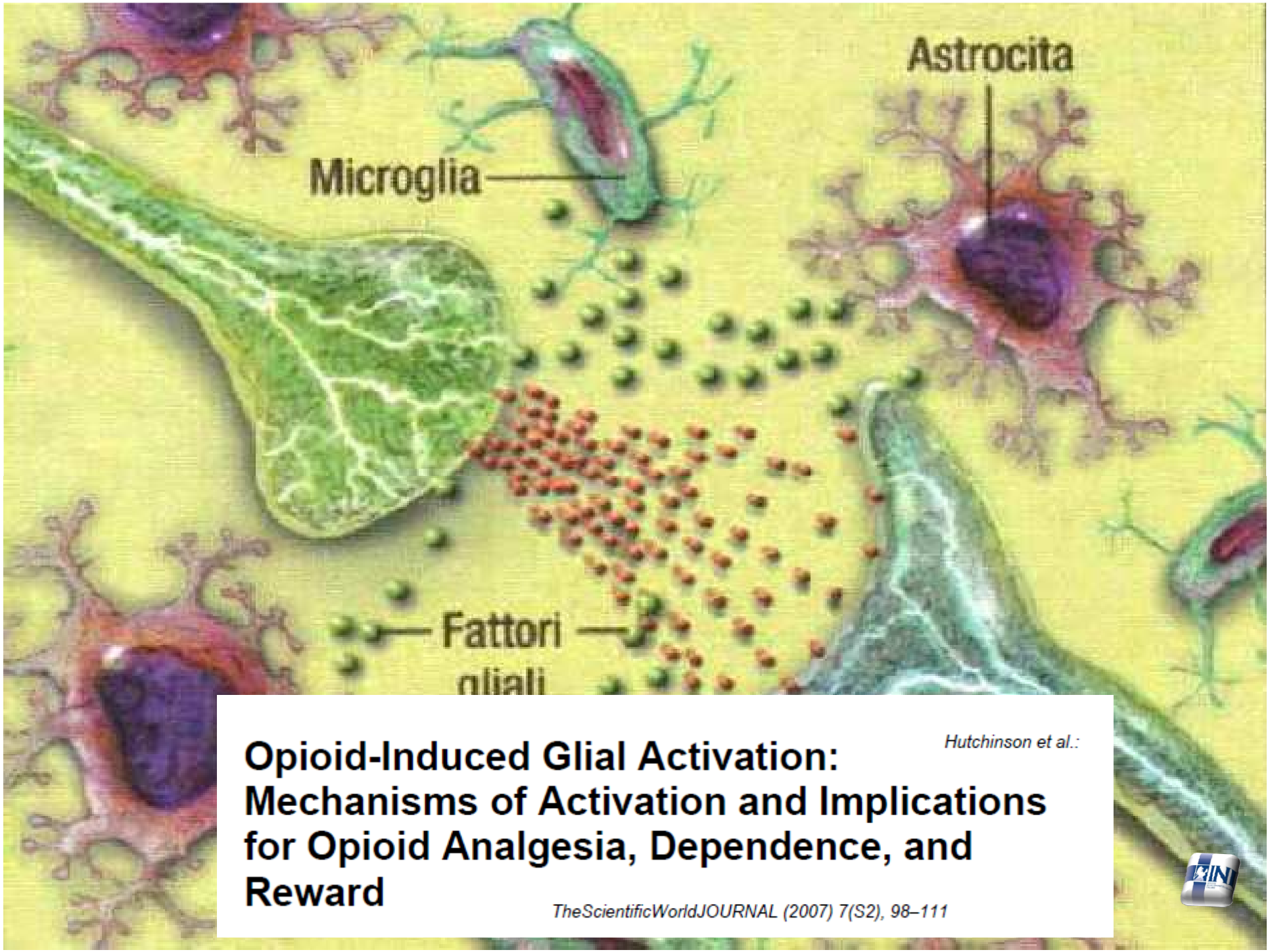





ONE MECHANISM OF OPIOID ACTION:
When an opioid binds to an opioid receptor in the membrane of a neuron 1, calcium channels close, blocking positively charged calcium ions from entering the cell 2. In addition, cAMP levels decrease and potassium channels open 3, allowing positive potassium ions to exit the cell. These events hyperpolarize the cell, increasing the charge difference between the cell's interior and the extracellular environment and making the neuron less likely to fire an action potential. Quieting neurons along pain pathways with opioids dampens the transmission of pain signals and results in analgesia.
NEURON IN THE ABSENCE OF AN OPIOID
SINAPSI SILENTE
NEURON IN THE PRESENCE OF AN OPIOID
At a normal resting potential, the neuron is primed to fire an action potential.
The hyperpolarized neuron is less likely to fire an action potential.
Ca2+ channel open
Ca2+
2
K+ channel open
3
cAMP
Opioid receptor
© THOM GRAVES

CELLS EAVESDROP AND MONITOR THE ACTIVITY OF SYNAPSES





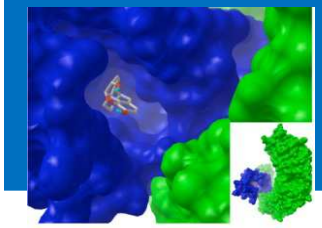
Hutchinson et al.:

Opioid-Induced Glial Activation: Mechanisms of Activation and Implications for Opioid Analgesia, Dependence, and Reward

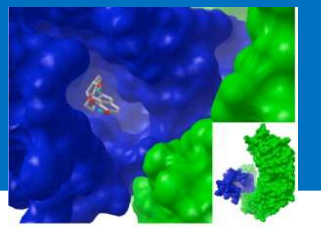
TheScientificWorldJOURNAL (2007) 7(S2), 98–111

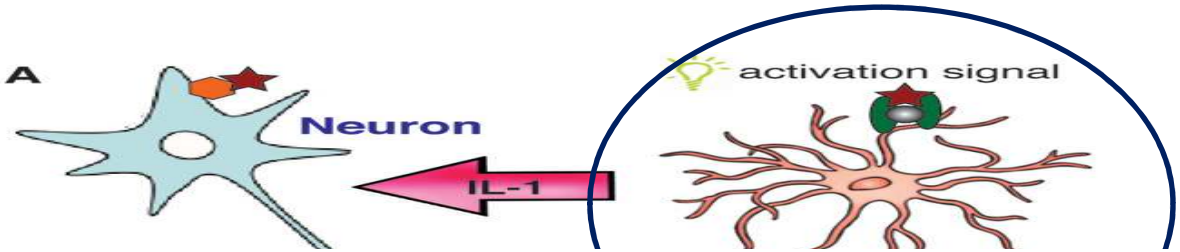
RECETTORI TLR4 : TOLL LIKE RECEPTOR

RECETTORI DI PEDAGGIO



Potenti attivatori della glia





VOLUME 25 · NUMBER 28 · OCTOBER 1 2007
JOURNAL OF CLINICAL ONCOLOGY
THE ART OF ONCOLOGY:
When the Tumor Is Not the Target

Systems/Circuits

May

Blockade of Toll-Like Receptor 4 Attenuates Morphine Tolerance and Facilitates the Pain Relieving Properties of Morphine

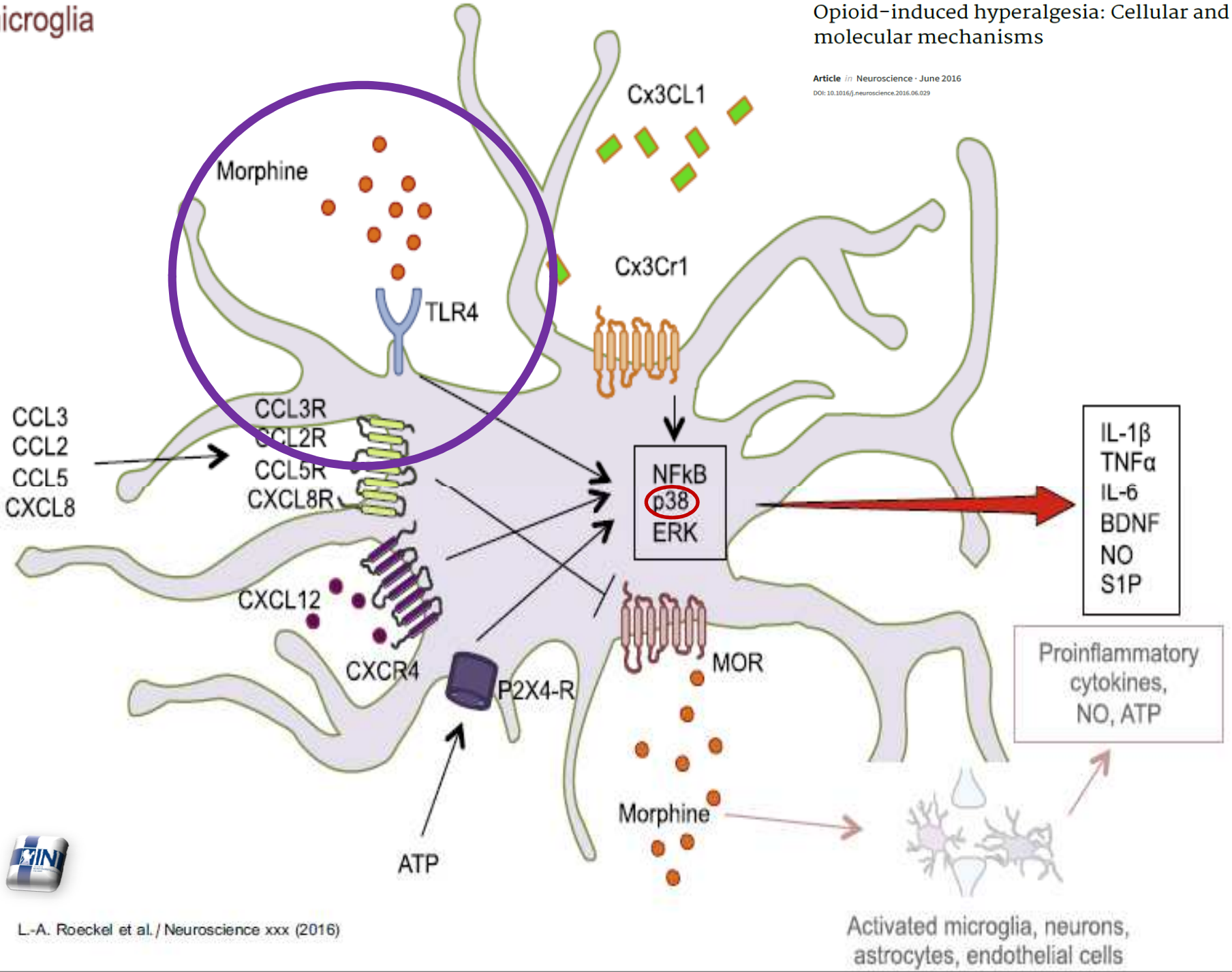
Lori N. Eidson and Anne Z. Murphy
Neuroscience Institute, Georgia State University, Atlanta, Georgia 30303

AL ONCOLOGY

microglia

Opioid-induced hyperalgesia: Cellular and molecular mechanisms

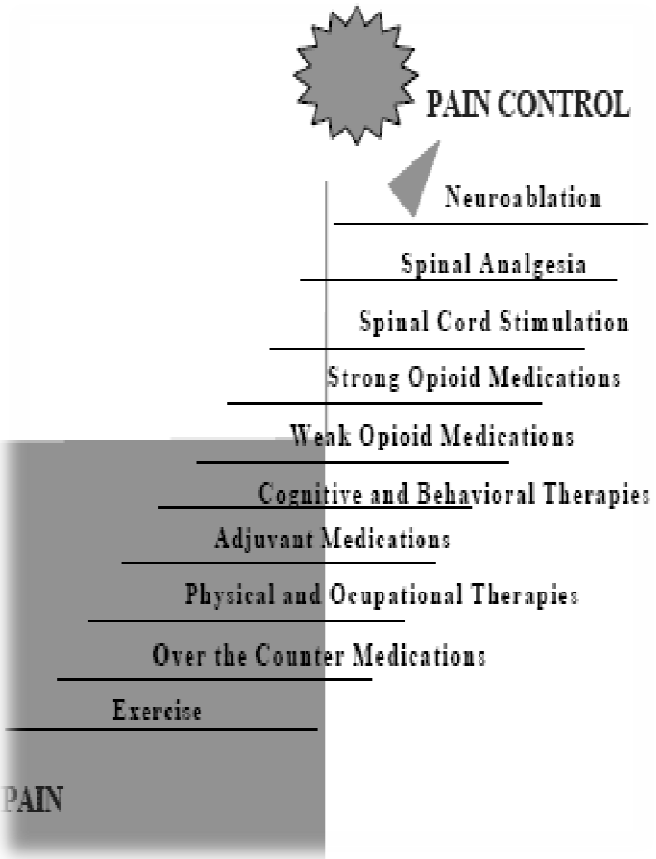
Article in Neuroscience · June 2016
DOI: 10.1016/j.neuroscience.2016.06.029



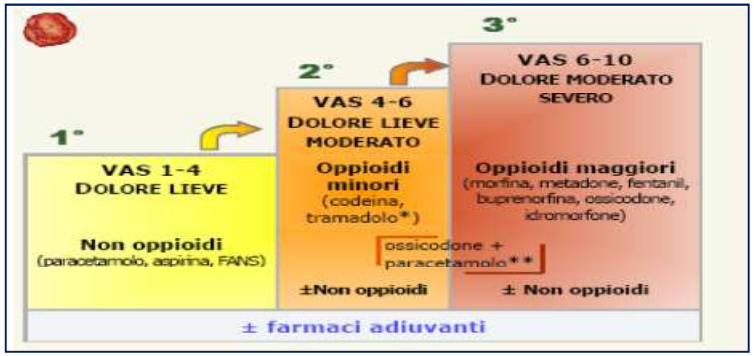
L.-A. Roeckel et al. / Neuroscience xxx (2016)

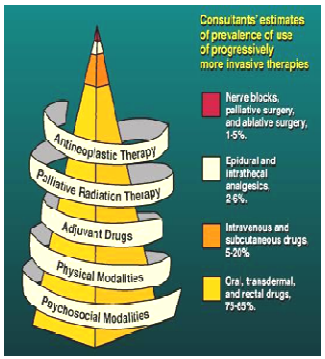
Scala antalgica OMS 1982…

Figure 4: Some of the 1982 WHO group at the Villa D' Este on Lake Como, Italy. L. to R: John Bonica, Mark Swerdlow, Robert Twycross, Kathleen Foley, Vittorio Ventafridda, and Jan Stjernswärd.



…nel 2017… ?!?





Drug Design, Development and Therapy

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REVIEW

Clinically significant drug–drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
16 September 2015
Number of times this article has been viewed

Aleksandra Kotlinska-Lemieszek[1]
Pål Klepstad[2,3,6]
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[1]Palliative Medicine Chair and Department, University Hospital of the Lord's Transfiguration, Karol Marcinkowski University of Medical Sciences, Poznan, Poland; [2]European Palliative Care Research Centre, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; [3]Department of Anaesthesiology and Intensive Care Medicine, St Olavs Hospital, Trondheim, Norway; [4]Regional Centre of Excellence for Palliative Care, Haukeland University Hospital, Bergen, Norway; [5]Department of Clinical Medicine K1, University of Bergen, Bergen, Norway; [6]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

Table 4 CYP3A4 enzyme inhibitors and inducers reported to have caused clinically significant drug–drug interactions with opioids metabolized by CYP3A4 (oxycodone, methadone, fentanyl) in papers included in the present review[24,27–33,37–39,44]

Drugs	Effect on CYP3A4 activity	Resulting effects when coadministered with opioid	Resulting effects after withdrawal of interacting drug
CYP3A4 inhibitors			
Voriconazole	Strong		
Itraconazole	Strong		
Fluconazole	Moderate	Decreased rate of opioid metabolism, increased opioid effect, increased risk of opioid toxicity	Increased opioid metabolism, decreased clinical effect of opioid
Clarithromycin	Strong		
Diltiazem	Moderate		
Cyclosporine	Weak		
Cimetidine	Weak		
CYP3A4 inducers			
Rifampin	Strong	Increased metabolism of opioid, requirement for higher opioid doses, deterioration of pain control	Decreased rate of opioid metabolism, increased risk of opioid overdose
Carbamazepine	Strong		

Conclusion

For obvious ethical reasons, there are no randomized controlled trials or other well-designed controlled studies exploring DDIs. Recommendations must therefore be based upon cases reporting serious adverse drug reactions and basic knowledge about drug mechanisms. The cases identified in this systematic review can give some suggestions for clinical practice:

- The combined use of an opioid and another drug with CNS depressant effect (eg, amitriptyline) increases the risk of acute opioid toxicity and respiratory depression. Such drugs should be carefully titrated according to effect.
- Opioids with antagonistic effects at the mu opioid receptor (eg, nalbuphine) should not be coadministered with another opioid analgesic.
- The concomitant use of an opioid and a drug, which affects the activity of cholinergic, dopaminergic, and/or serotonergic systems in the CNS (eg, selective serotonin inhibitors), can cause CNS-related complications (eg, delirium and serotonin syndrome) and should, therefore, be monitored carefully.
- Introduction of a CYP3A4 inhibitor in a patient treated with fentanyl, oxycodone, or methadone may result in opioid overdose and increased opioid toxicity (Table 4). Caution has to be undertaken when such drugs are implemented. The use of a major CYP450 inducer may impair pain treatment (Table 4). Opposite effects should be expected when these drugs are stopped (Table 4).
- Finally, the physician should recognize the risk for DDIs of opioids, monitor the patients carefully for interactions, and if possible avoid polypharmacy.

NSAIDS or paracetamol, alone or combined with opioids, for cancer pain (Review)

McNicol ED, Strassels S, Goudas L, Lau J, Carr DB

THE COCHRANE COLLABORATION®

EVIDENCE BASED MEDICINE: COMBINATION THER… TAILORED TH…

…un approccio **mul…** **…al…**
meccanismi …amenti

"Oppioid sparing effect"
riduzione del 30-50% delle dosi di morfina se associati FANS

Riduzione del 20% delle dosi di morfina se associato paracetamolo

Consente di …
nei m…
r…

Rappresenta l'opzione terapeutica per tutti i casi in cui non è stata sufficiente una monoterapia

…se as a result of both noci-
… mechanisms[114]. Therefore, tar-
… mechanisms of pain by combining
…erent mechanisms of action is a rational
…o management of chronic LBP.
…uidelines recommend combination therapy for the general management of neuropathic pain arising from a number of different causes as an option for patients in whom monotherapy has failed[15,41]. As well as improving analgesia, combination therapy has also been shown to reduce drug consumption of the single drug[60,101]. Fixed-dose combinations are likely to be associated with greater adherence than free combinations.

Aderen…

Consente una riduzione dei dosaggi dei farmaci rispetto alla monoterapia

EBioMedicine 5 (2016) 1

Contents lists available at ScienceDirect

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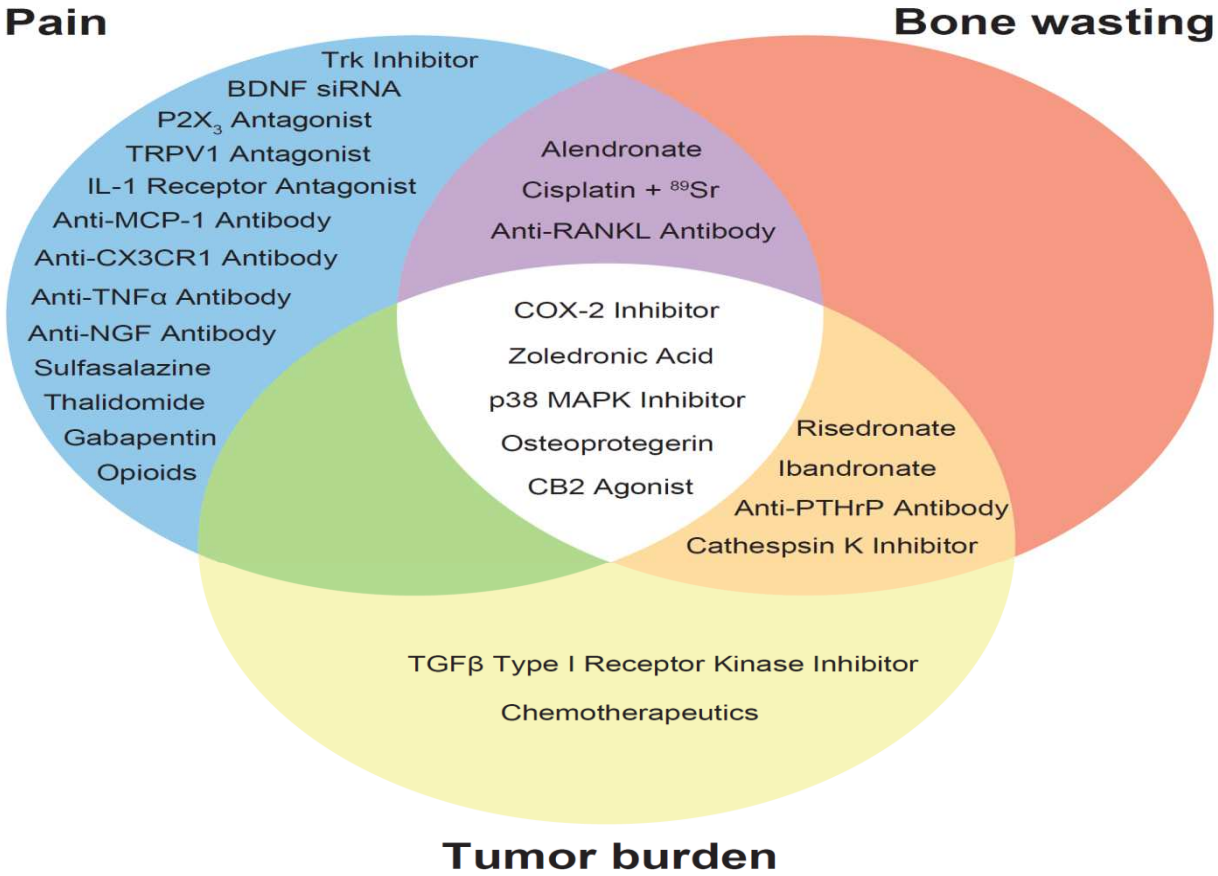
journal homepage: www.ebiomedicine.com

Editorial

Chronic Pain: The Need and Hope for Opioid Alternatives



Use of Animal Models in Understanding Cancer-induced Bone Pain

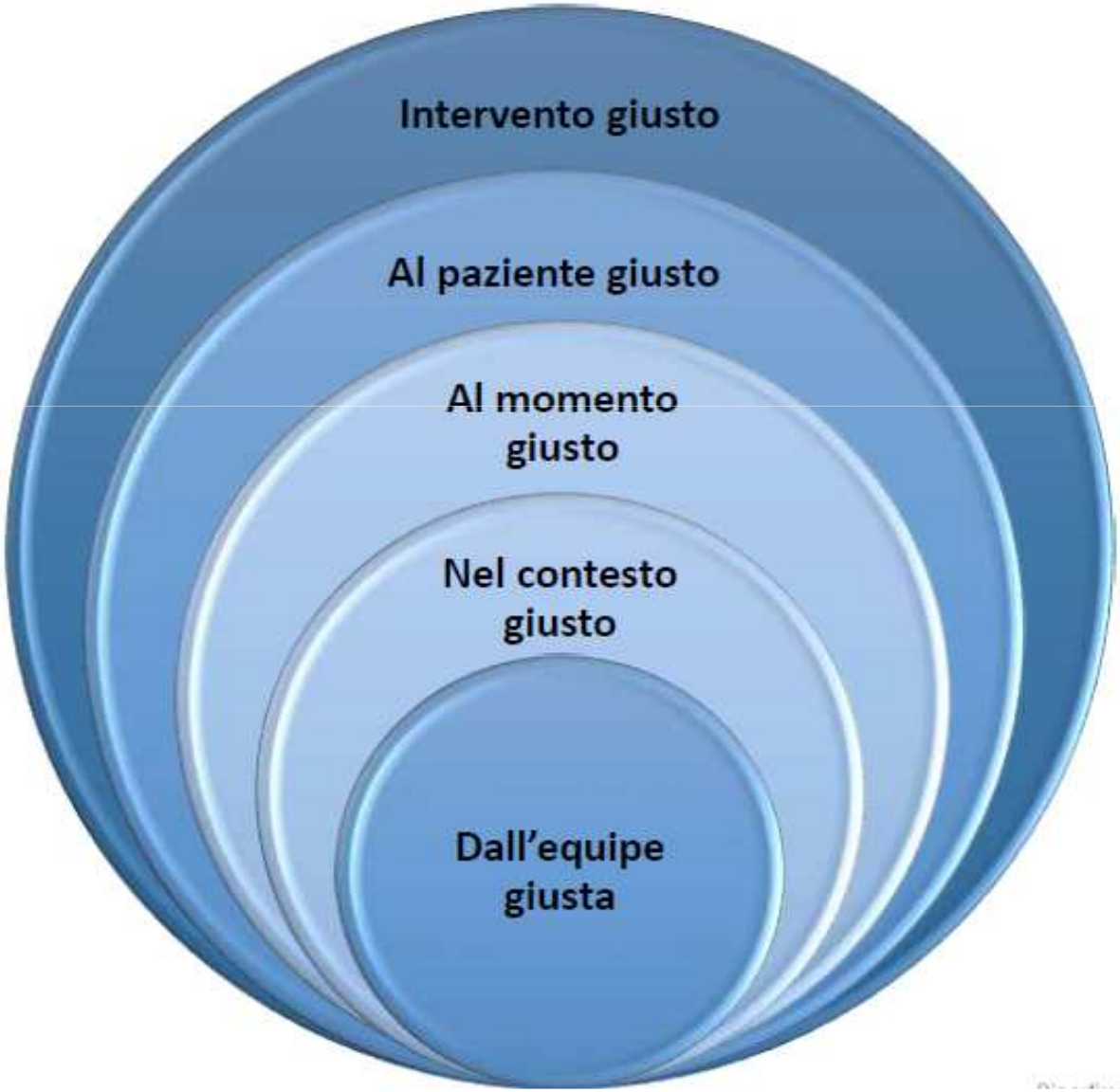
Supplementary Issue: Animal Models of Cancer Biology

Lauren M. Slosky, Tally M. Largent-Milnes and Todd W. Vanderah

Department of Medical Pharmacology, University of Arizona College of Medicine, Tucson, AZ, USA.

CANCER GROWTH AND METASTASIS 2015:8(S1)

PRESA IN CARICO



GRAZIE PER LA VOSTRA ATTENZIONE