Co-funded by the Erasmus+ Programme of the European Union

Pathophysiology of cancer pain

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Lecture October 17 th 2019
IORS, Belgrade, Serbia

Project number: 585927-EPP-1-2017-1-RS-EPPKA2-CBHE-JP (2017 – 3109 / 001 – 001)

THE HISTORY OF MEDICINE IS THE HISTORY OF PAIN

- Asclepius, the god of medicine attending to a patient in pain

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Representations of Lancet or Phlebotome in Serbian Medieval Art

Sanja Pajić[1], Vladimir Jurišić[2]
[1]University of Kragujevac, Faculty of Philology and Arts, Department of Applied and Fine Arts, Kragujevac, Serbia;
[2]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

Srp Arh Celok Lek. 2015 Sep-Oct;143(9-10):639-643 DOI: 10.2298/SARH1510639P
ИСТОРИЈА МЕДИЦИНЕ / HISTORY OF MEDICINE UDC: 75.052.046.3(497.11)"04/14"

St. Cosmas with a lancet and a medical box (late 13th century)
Church of the Holy Apostles Peter and Paul near Novi Pazar, (photo by Sanja Pajić)

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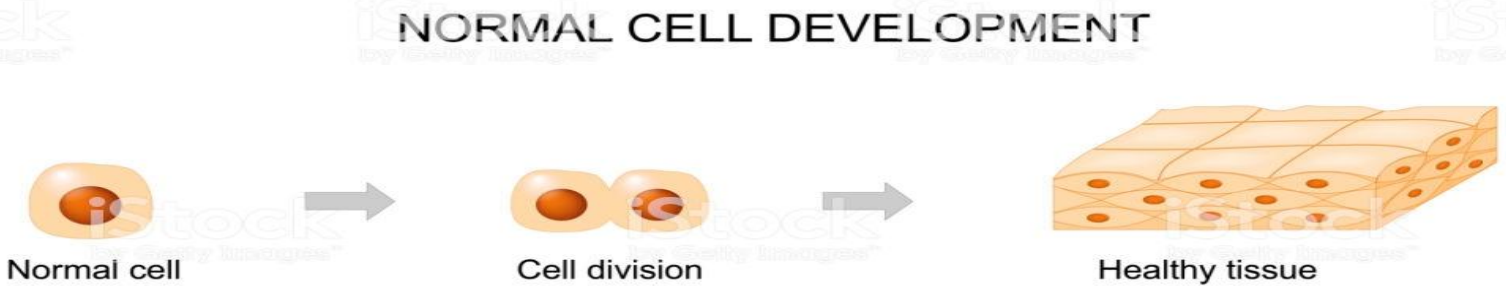

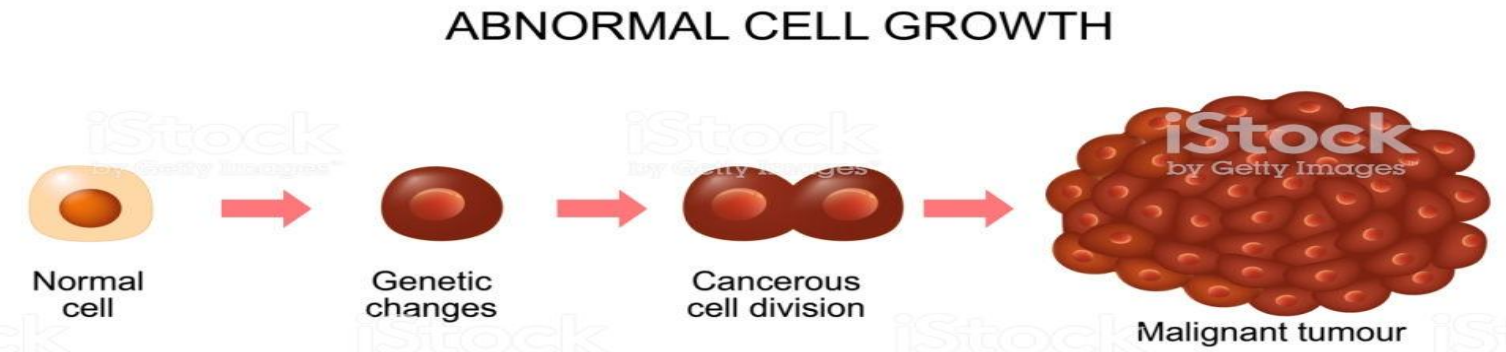

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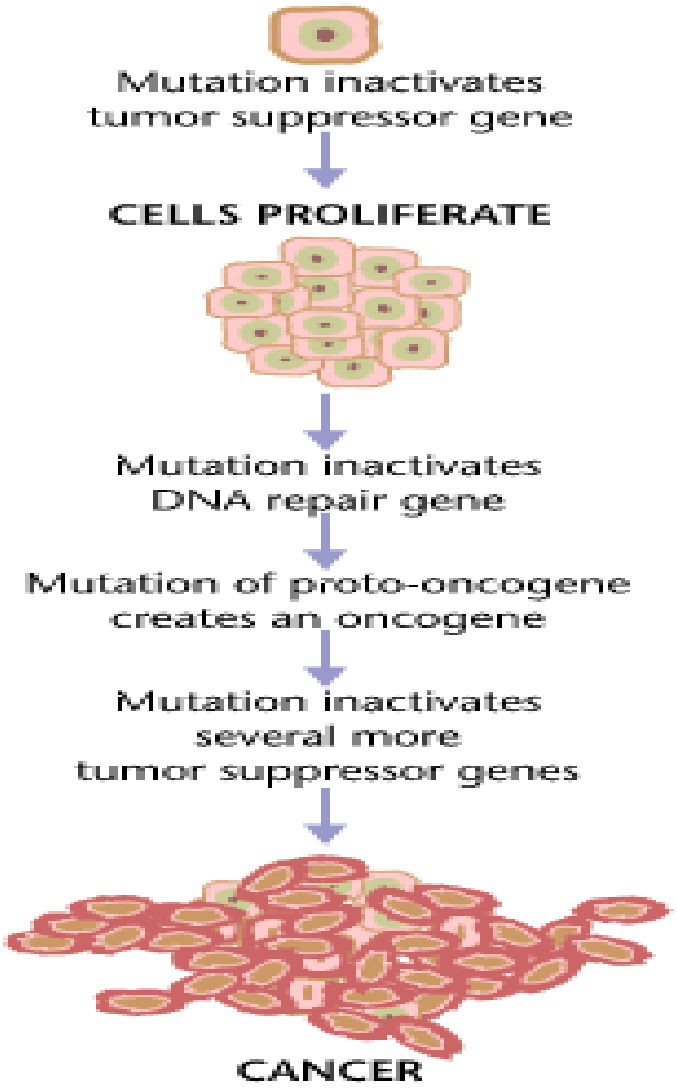

Cancerogenesis

Jurišić V et al, Anal Cell Pathol (Amst). 2018 Oct 14;2018:6192187
Jurisic V, Radenkovic S, Konjevic G. Adv Exp Med Biol. 2015;867:115
Jurisic V et al, Pathol Res Pract. 2012
Jurisic V, Blood. 2003 , 1;101(7)

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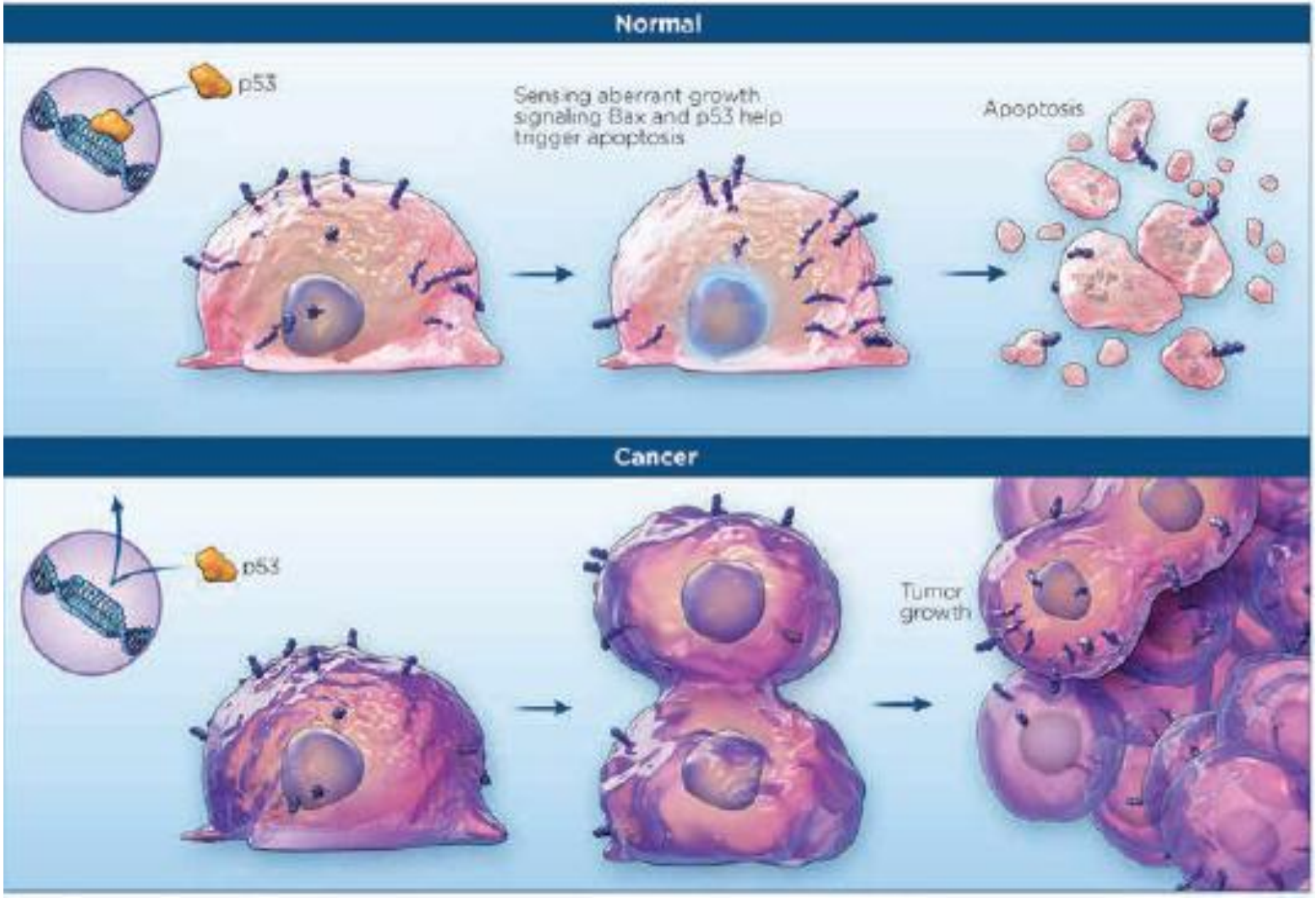

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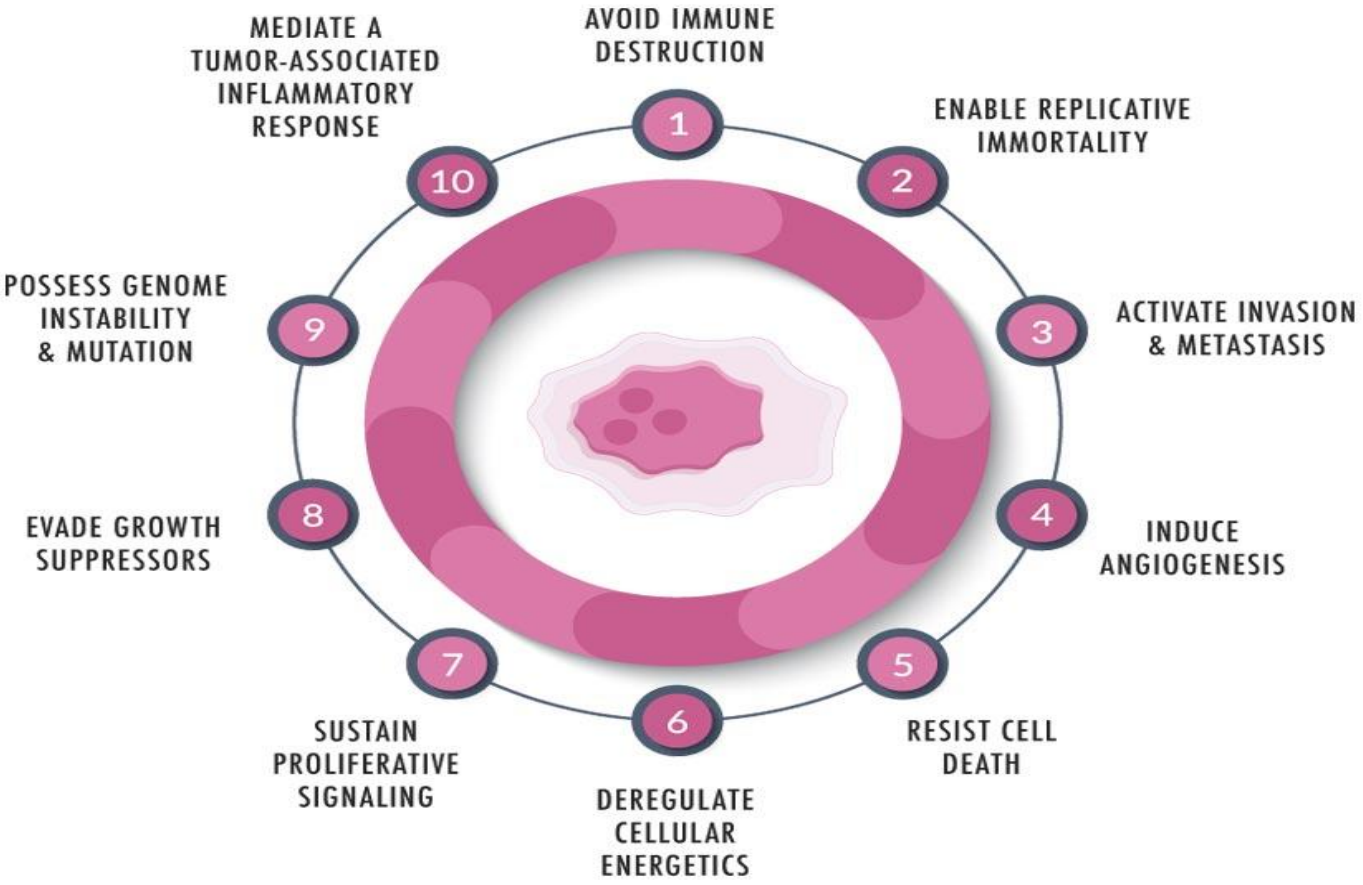
Characteristics of cancer cells



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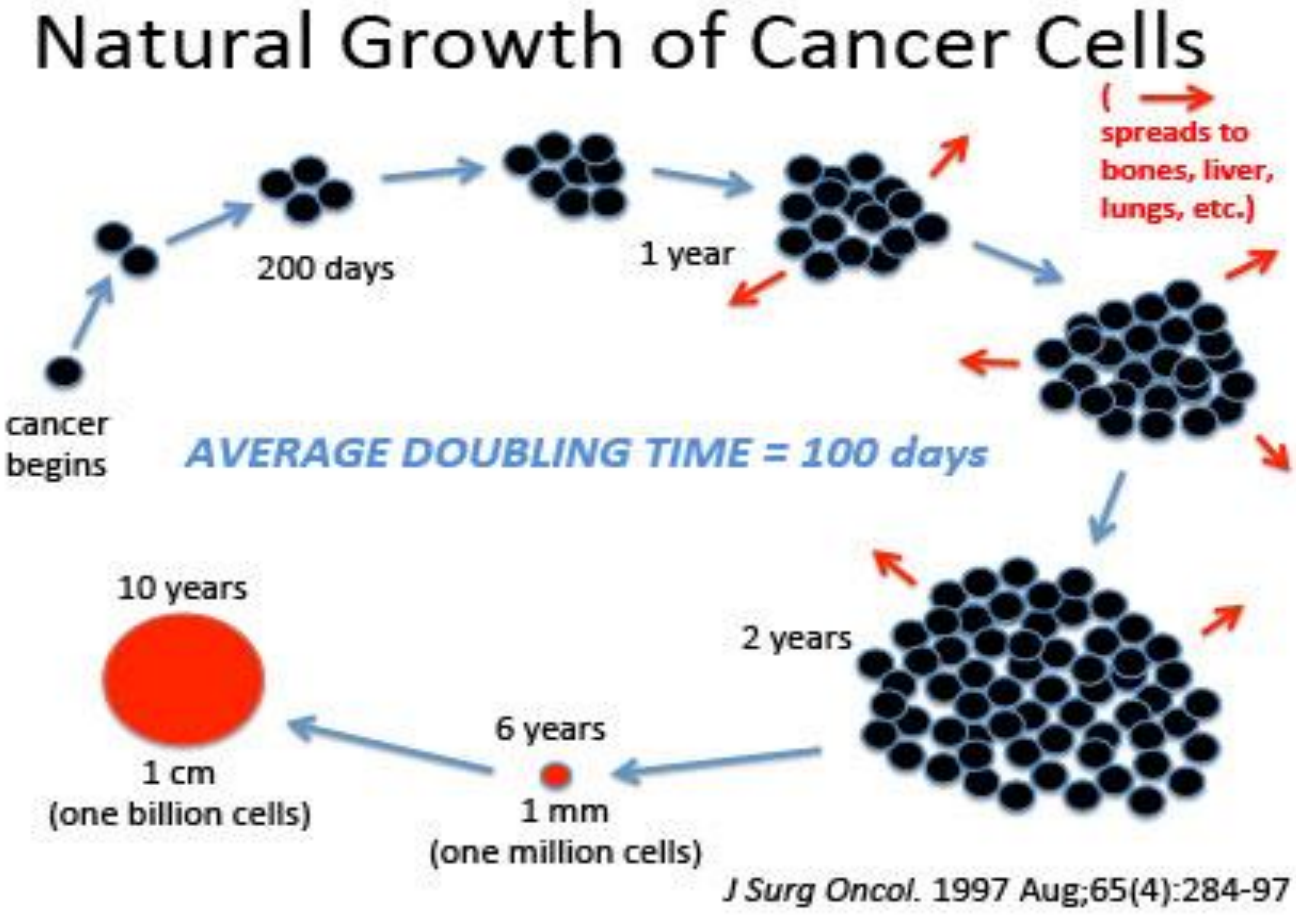

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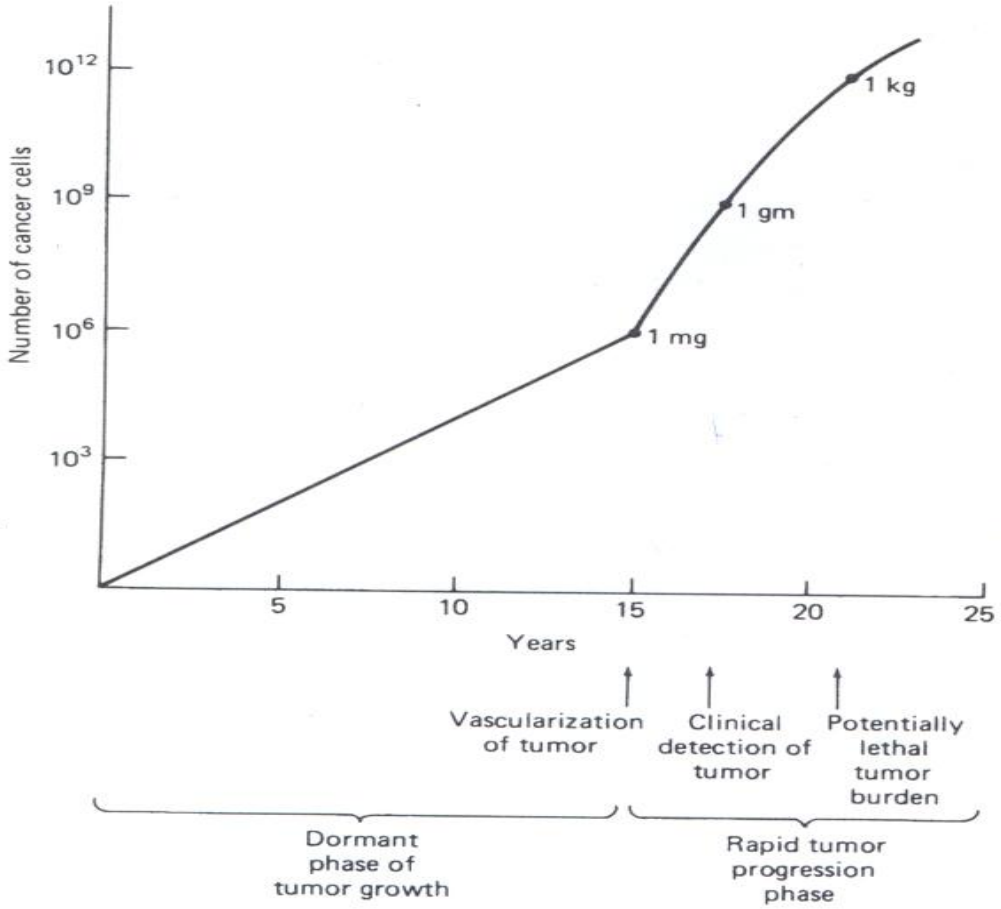
Cell growth



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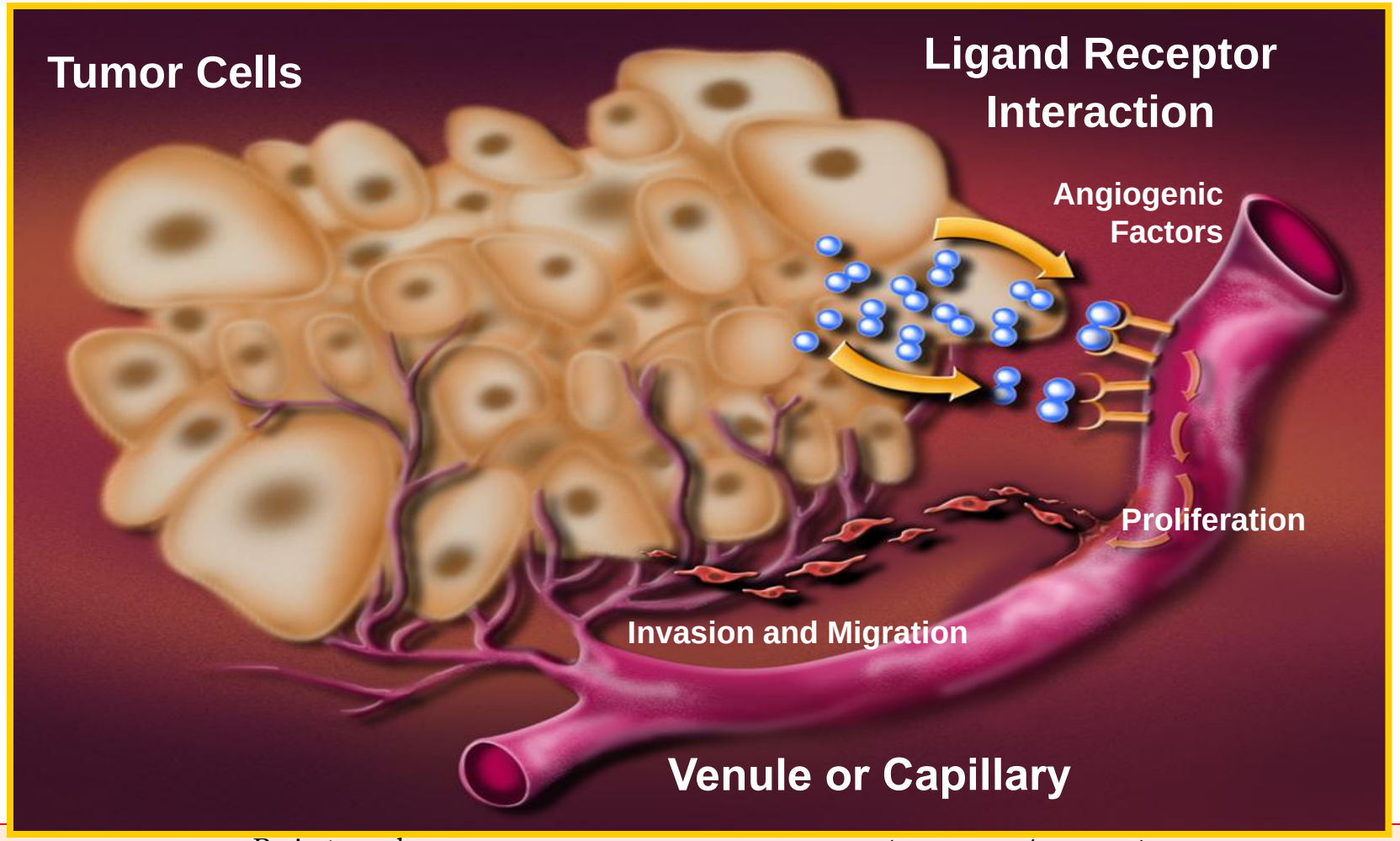
Neovascularisation



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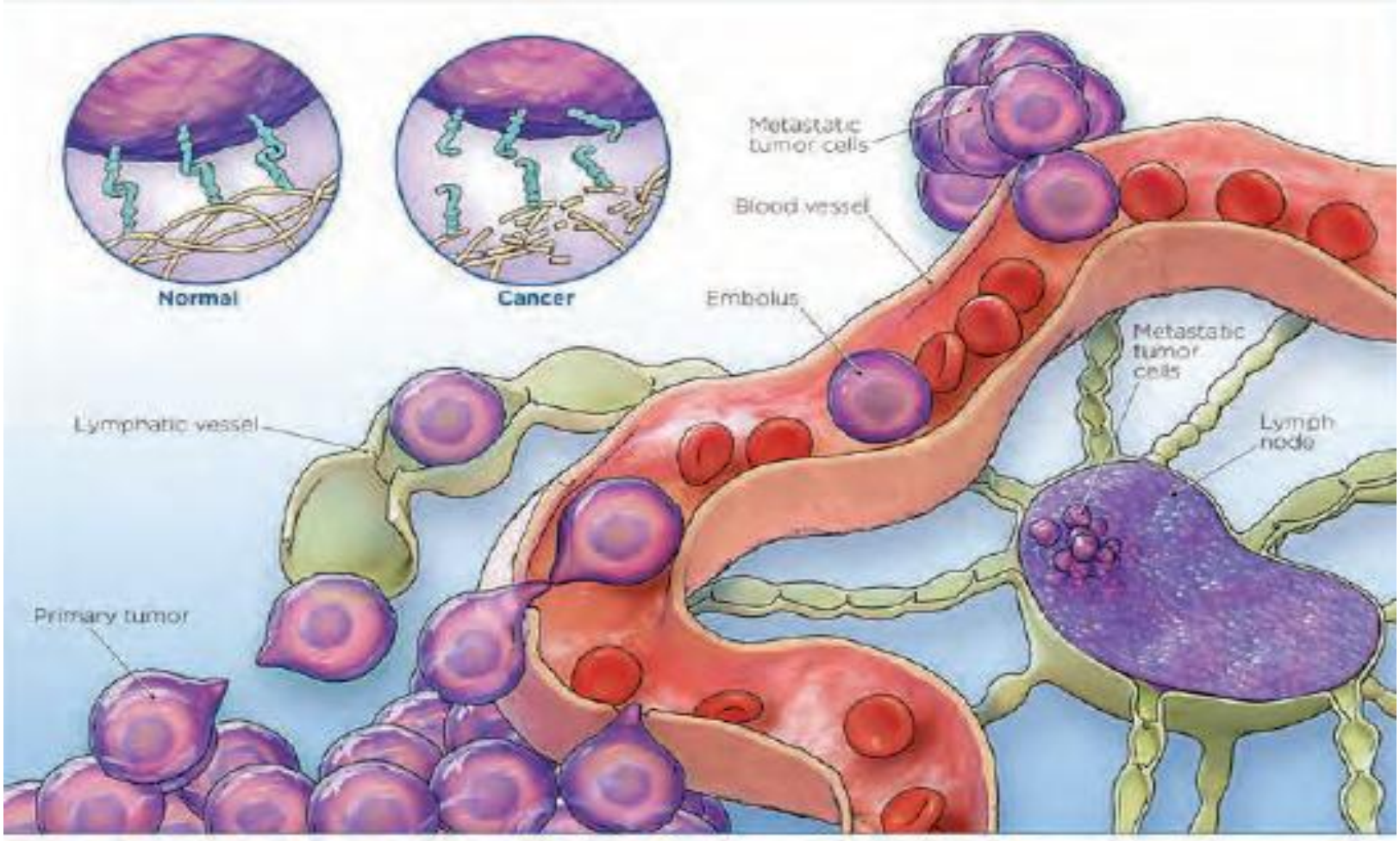
Metastases



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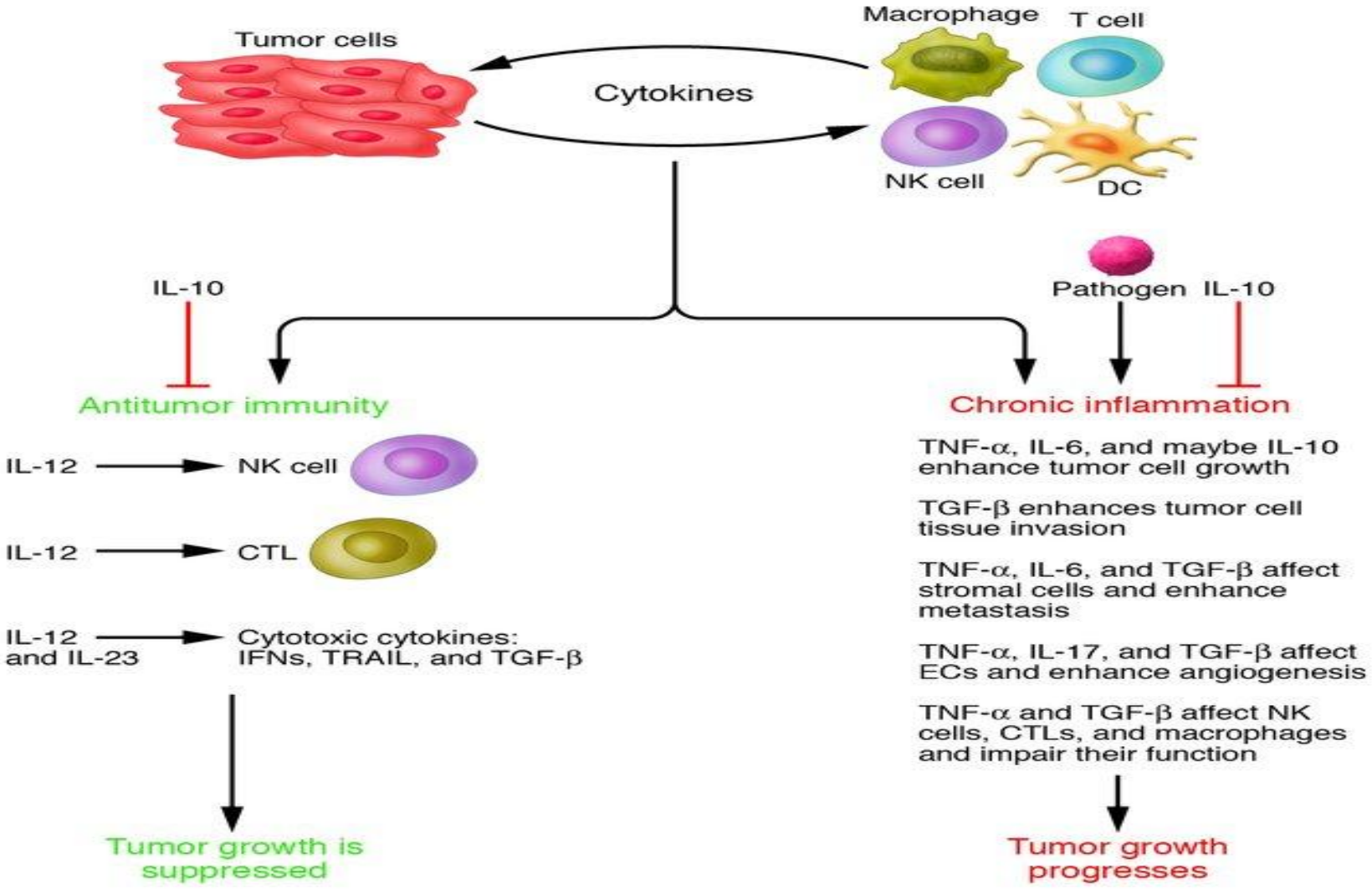

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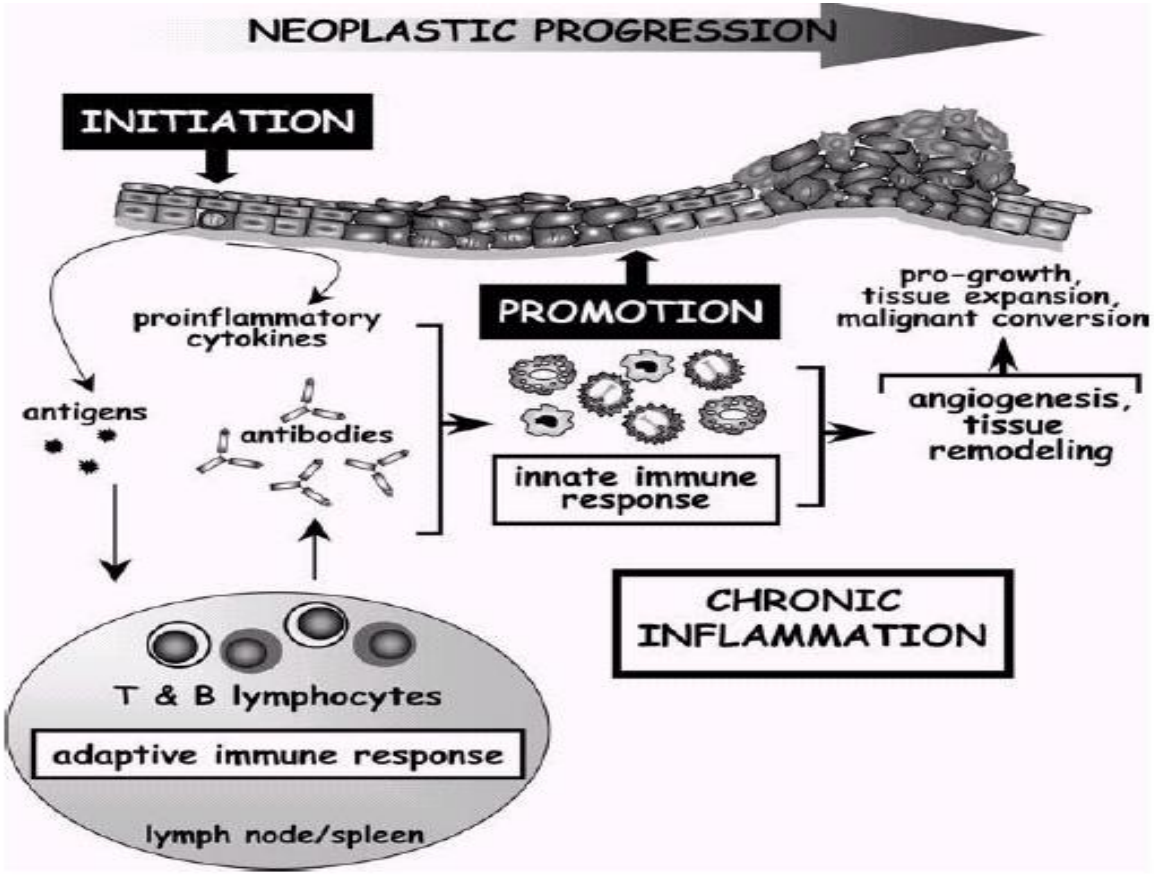
Cancer and inflamation



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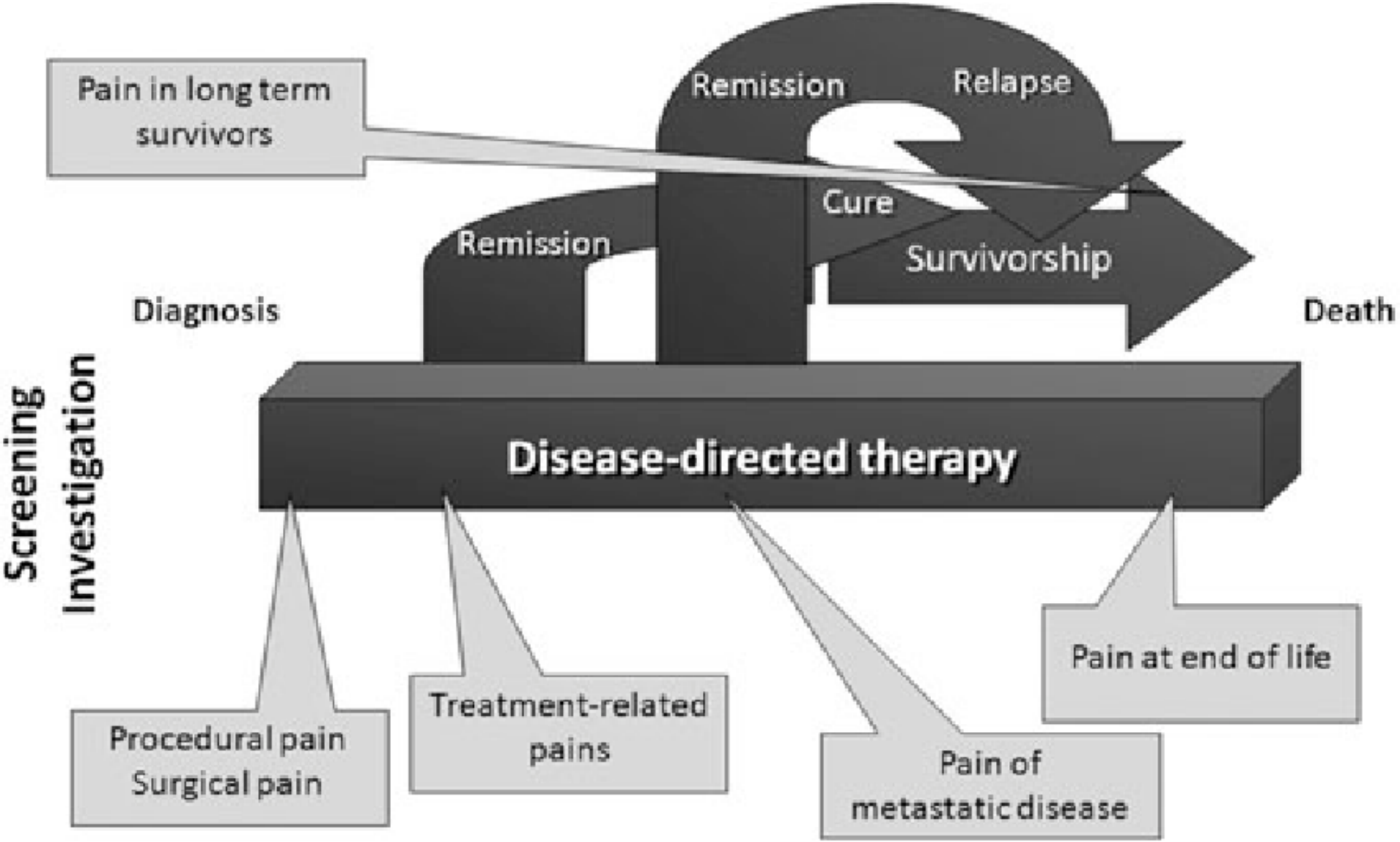
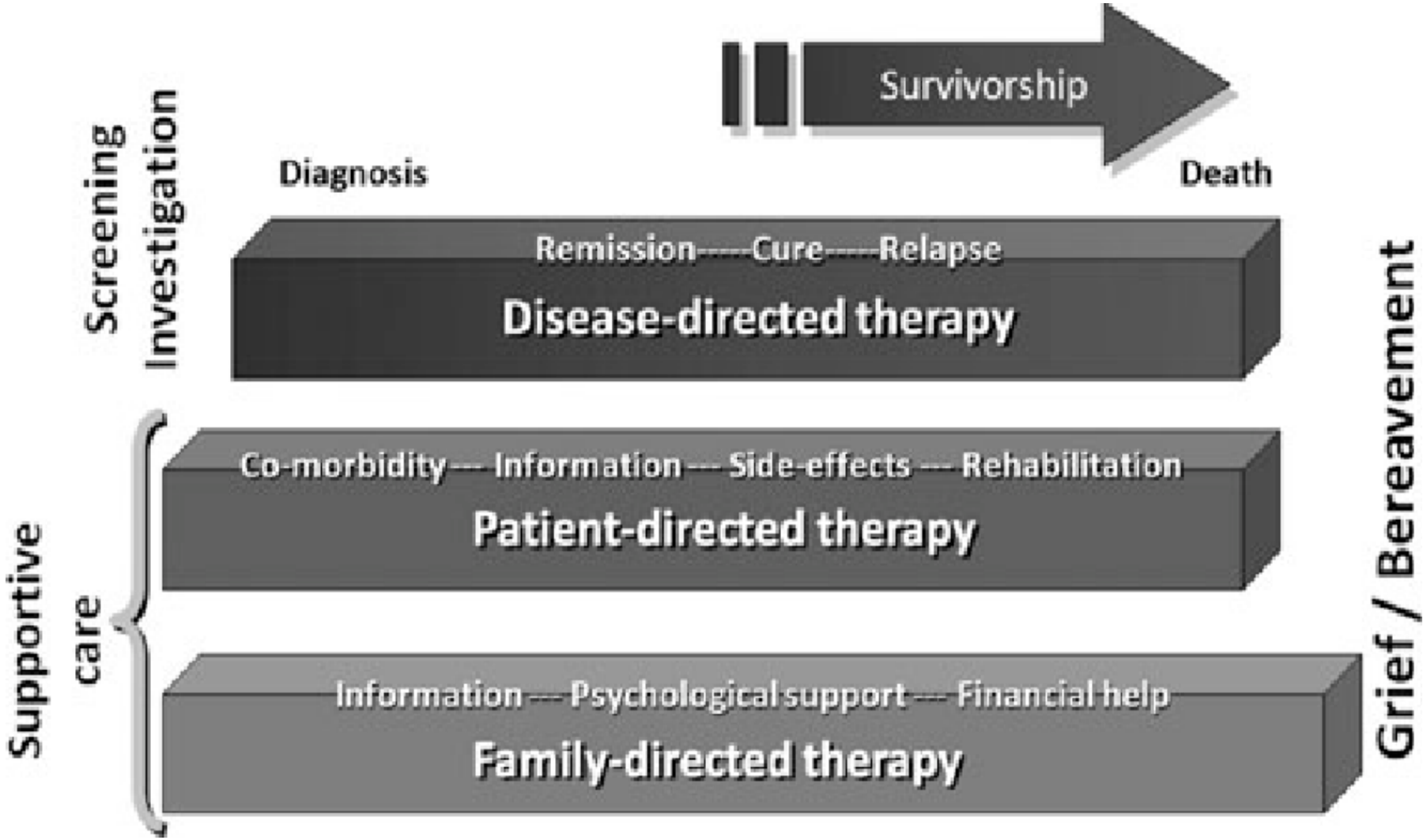
Complexity of cancer pain





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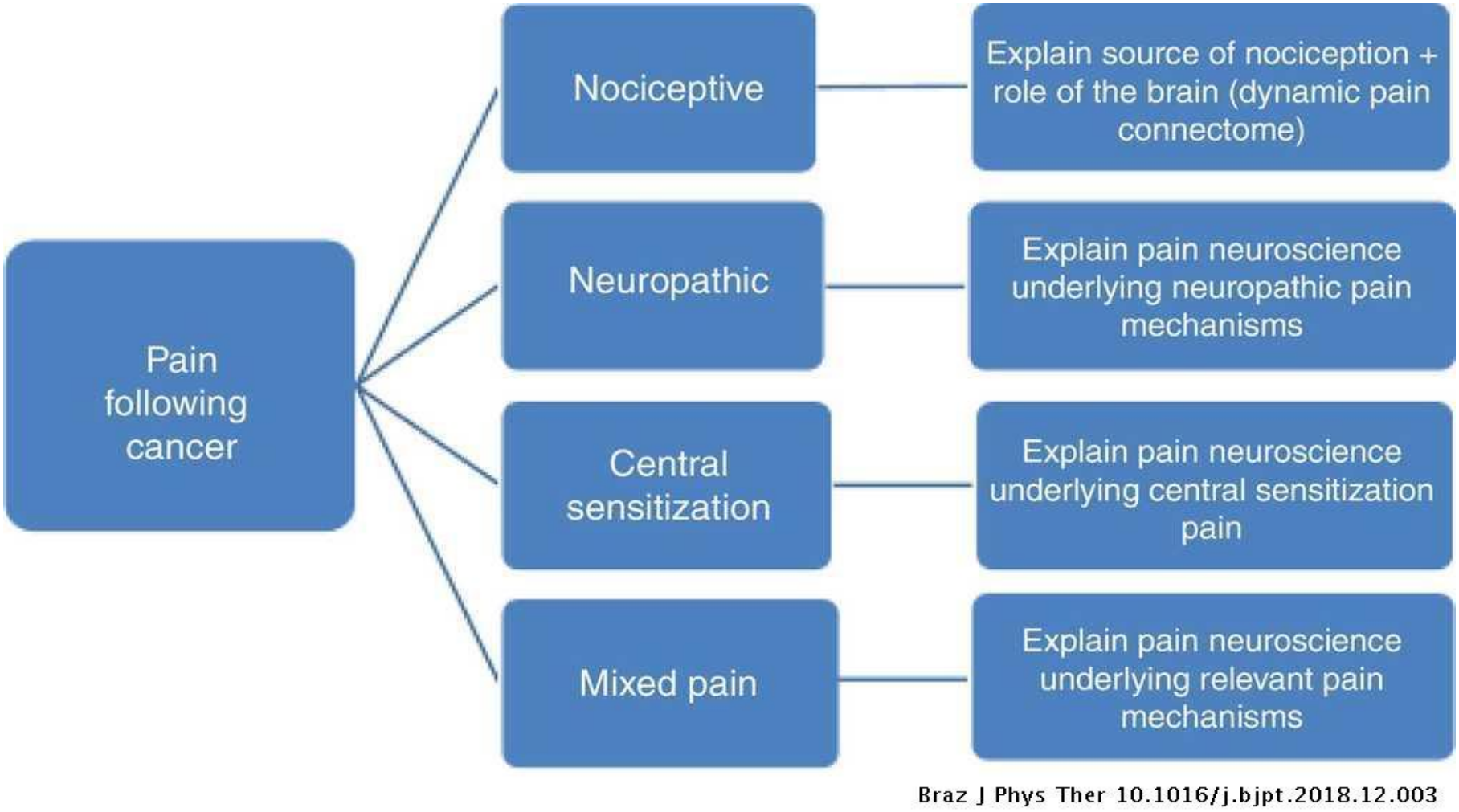

Braz J Phys Ther 10.1016/j.bjpt.2018.12.003

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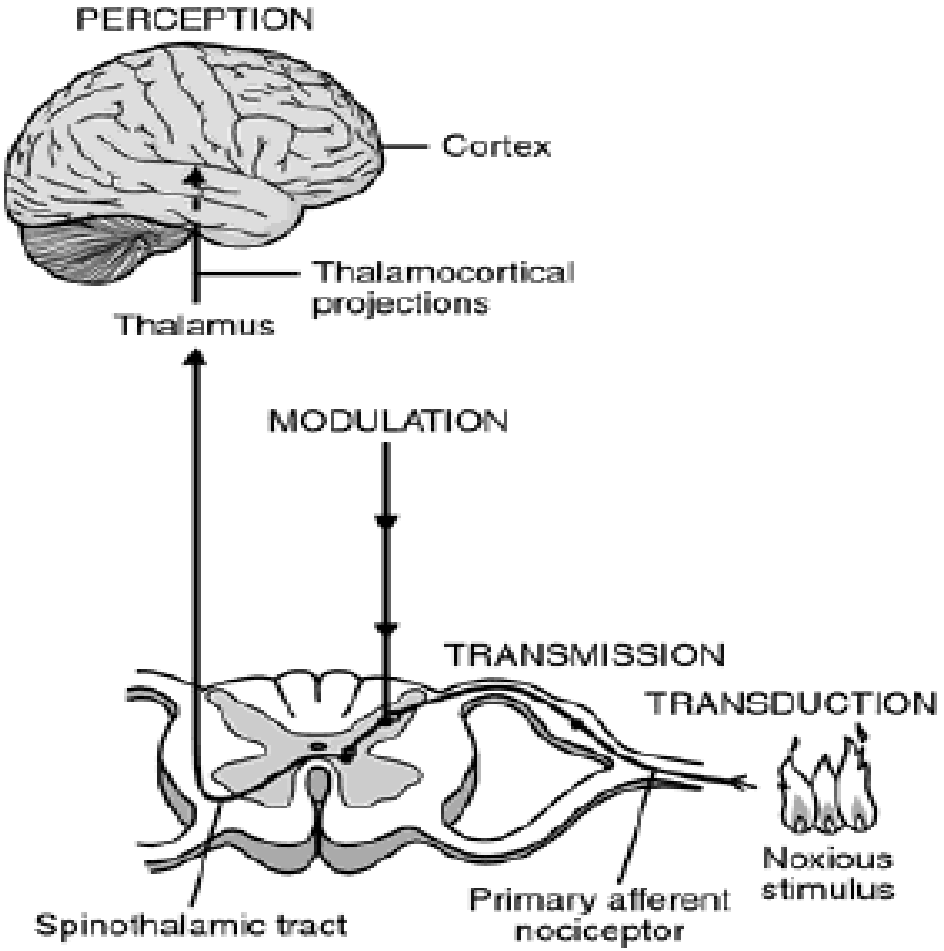

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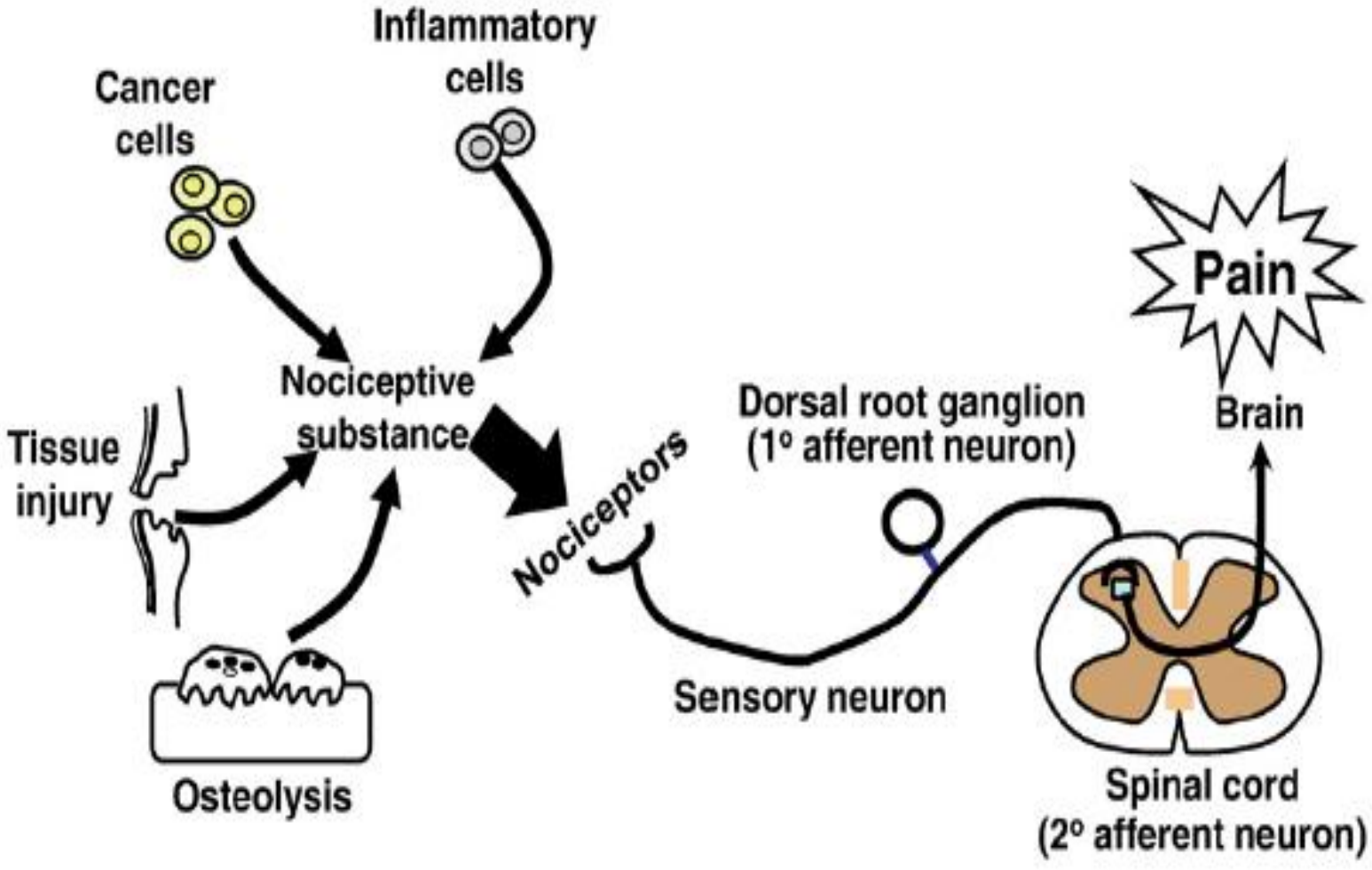

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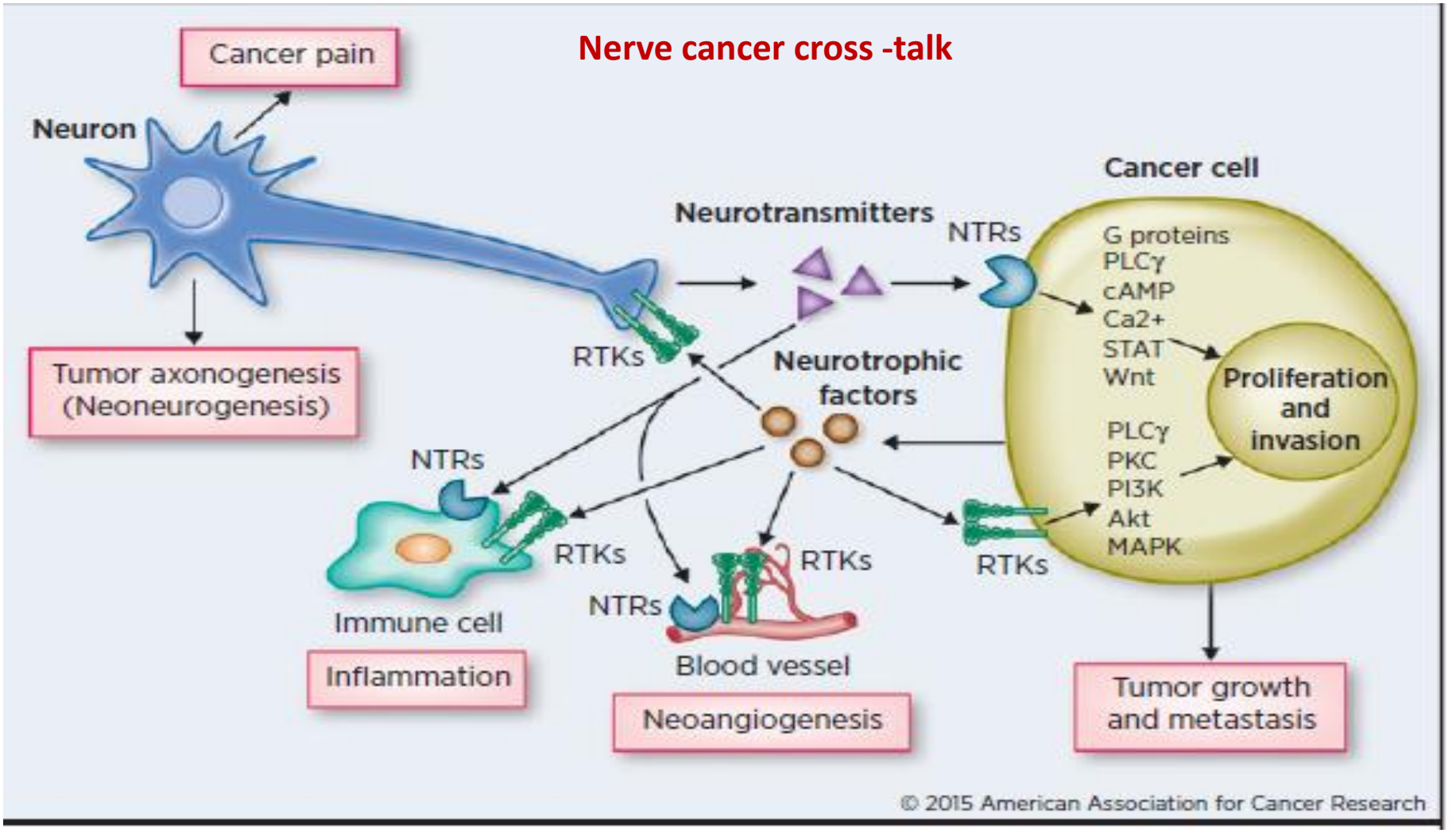

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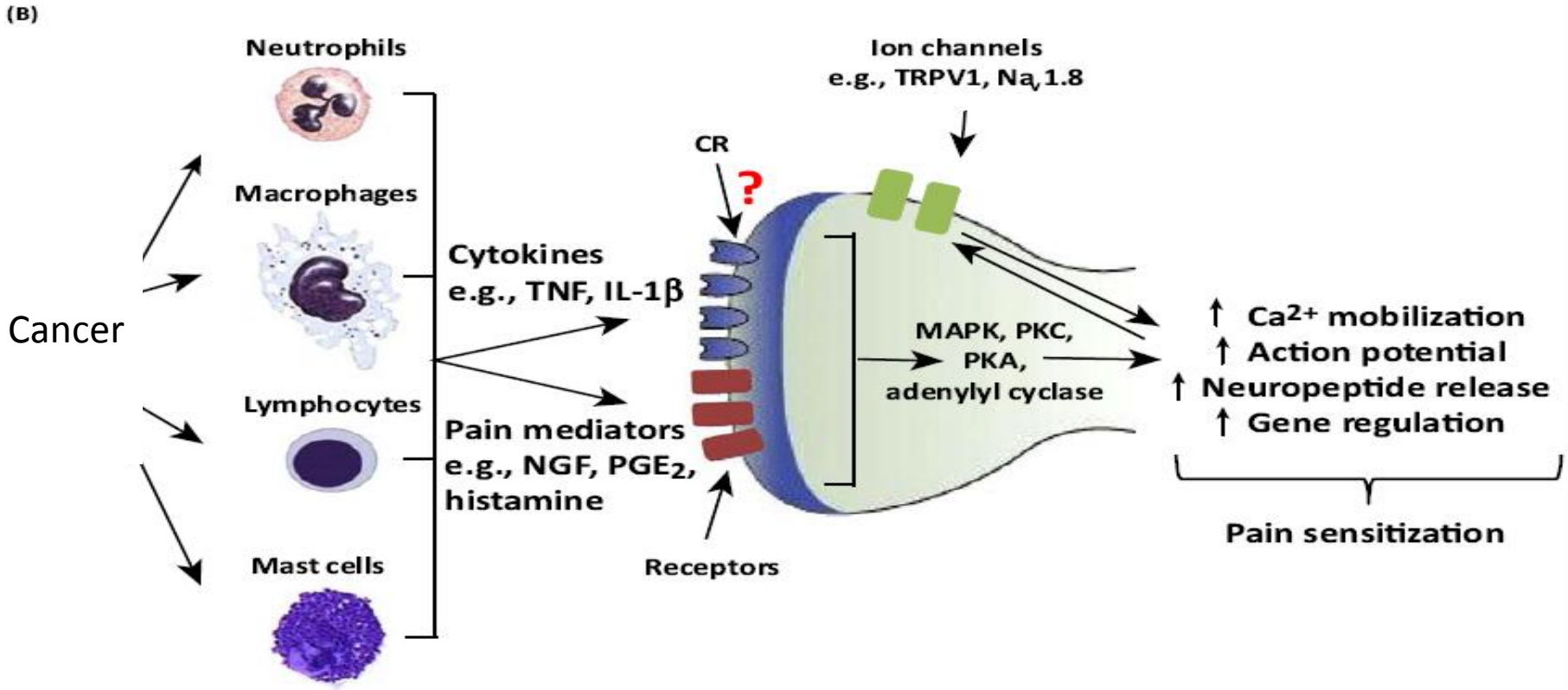
Cancer inflammation and pain



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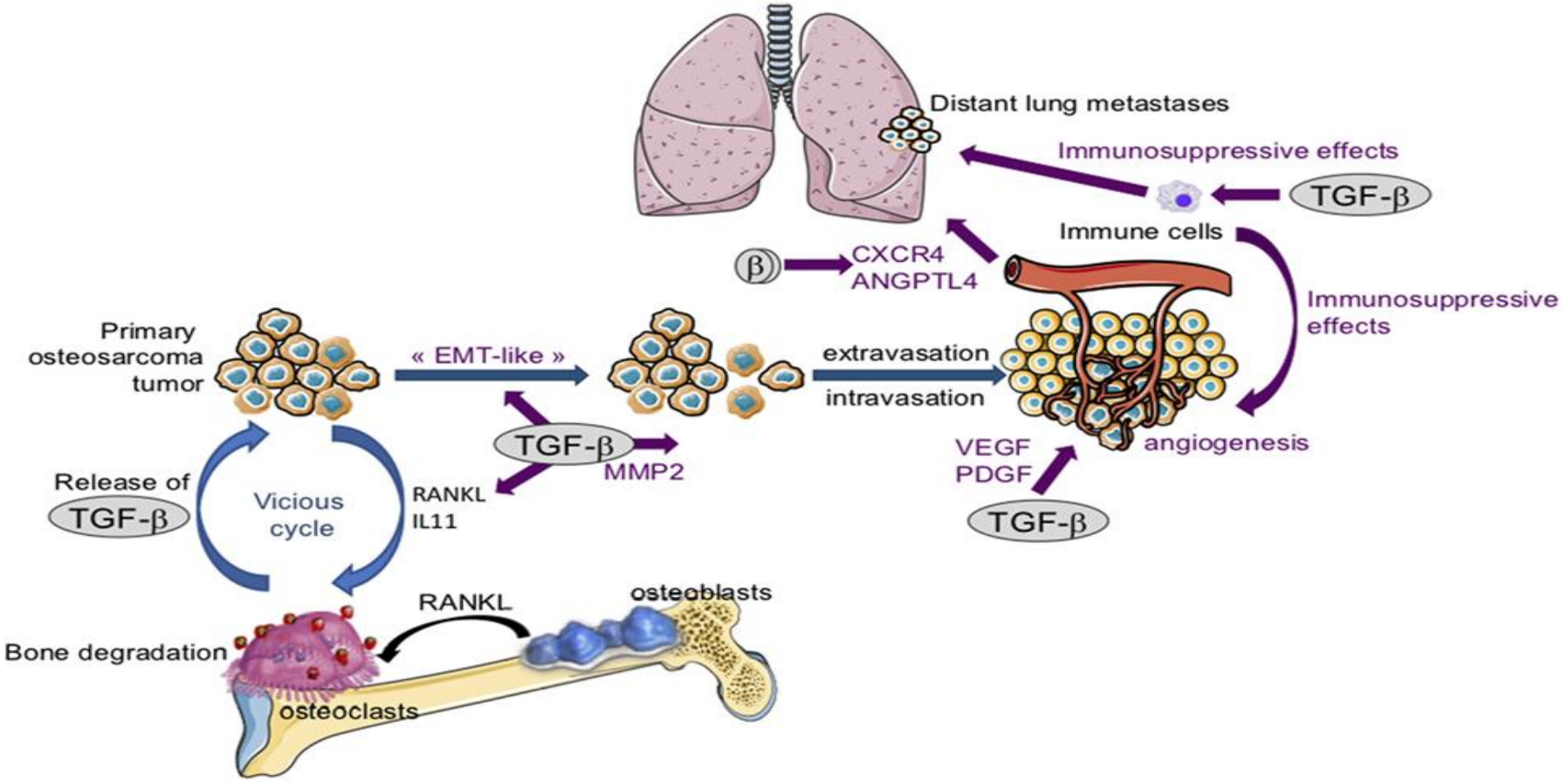
Pain and cancer metastases



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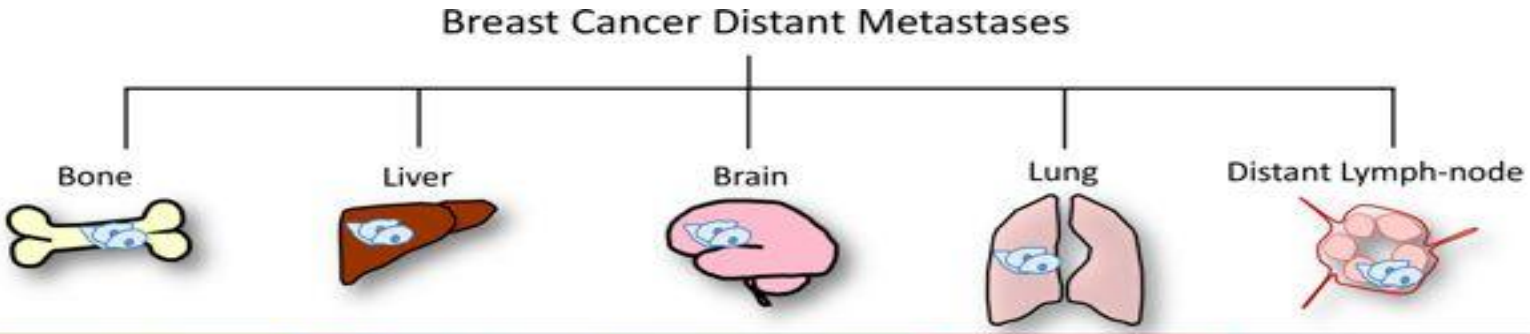
Localisation of cancer metastases



	Bone	Liver	Brain	Lung	Distant Lymph-node
Associated subtypes	Luminal-HER2	HER2-enriched ER-positive Luminal B Luminal-HER2	HER2-enriched Luminal-HER2 TN-nonbasal Basal-like	TN-nonbasal Basal-like Luminal B HER2+, HR-, p53-	Luminal type HER2-enriched
Molecular features	Growth factors: IGF1, PGE2, TGFβ, PDGF and FGF2 Interleukins: IL-11, IL-1, IL-6 PTHrP OPN Heparanase RANKL-RANK pathway Src-dependent pathway	Chemokines and receptors: CXCR4/CXCL12 Interleukins: IL-6 Integrin complexes: α2β1, α5β1 N-cadherin HIF-regulated genes: LOX, OPN, VEGF, TWIST β-catenin-independent WNT signaling Downregulation of ECM (stromal) genes	ST6GALNAC5 CSC markers: Nestin, CD133, and CD44 Growth factors: VEGF and HBEGF Chemokines and receptors: CXCR4 Cytokines: CK5 MMP-1 and MMP-9 IL-8 Ang-2 COX2 L1CAM	Growth factors and their receptors: TGFβ, EGFR, EREG, VEGF Matrix metalloproteinases: MMP-1 and MMP-2 COX2 LOX BMP inhibitors: GALNTs and Coco	Kallikreins: KLK10, KLK11, KLK12, and KLK13 Downregulation of BCR signal pathway

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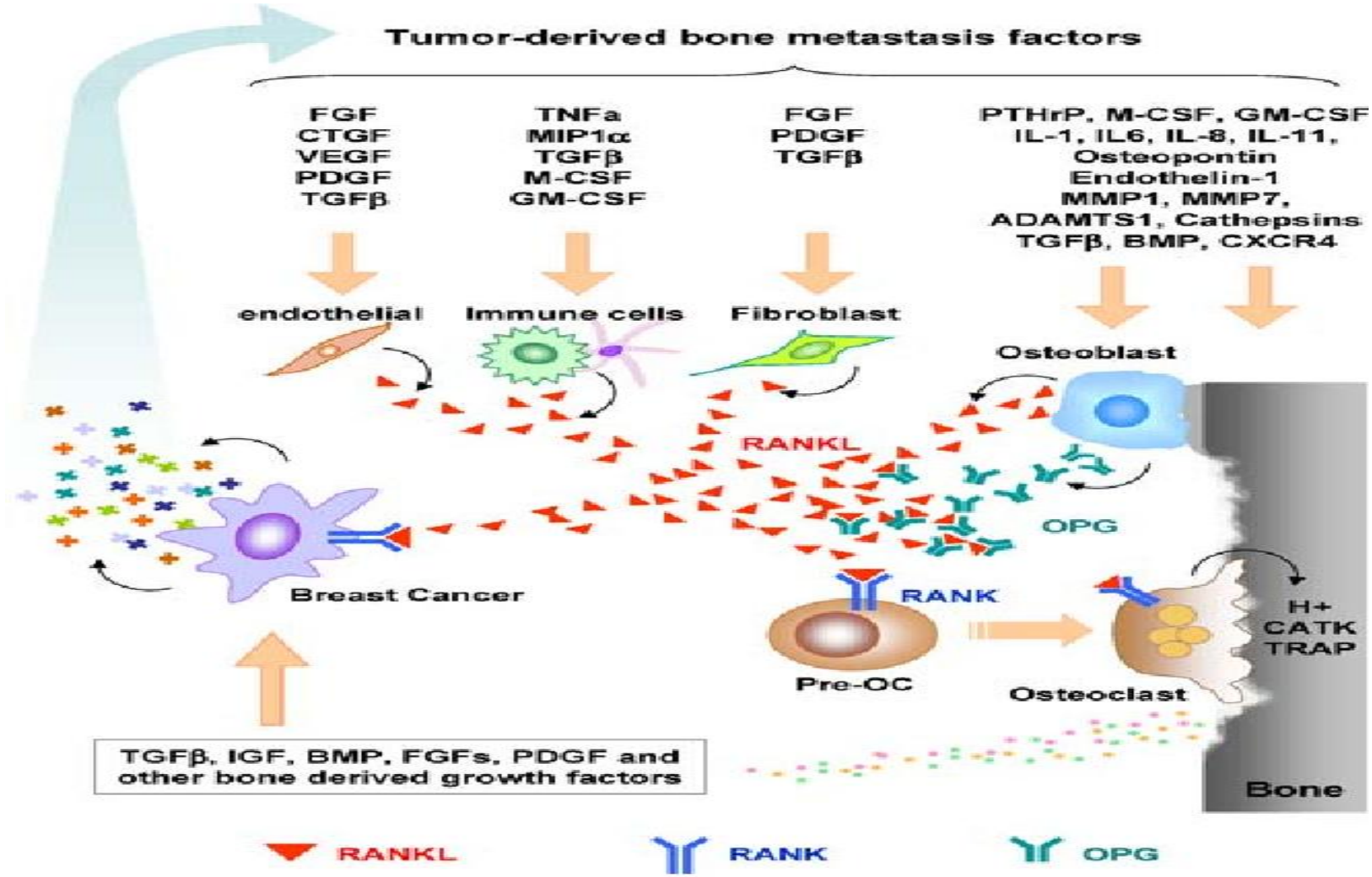

Figure 3 Tumor-stroma interactions in osteolytic bone metastasis.

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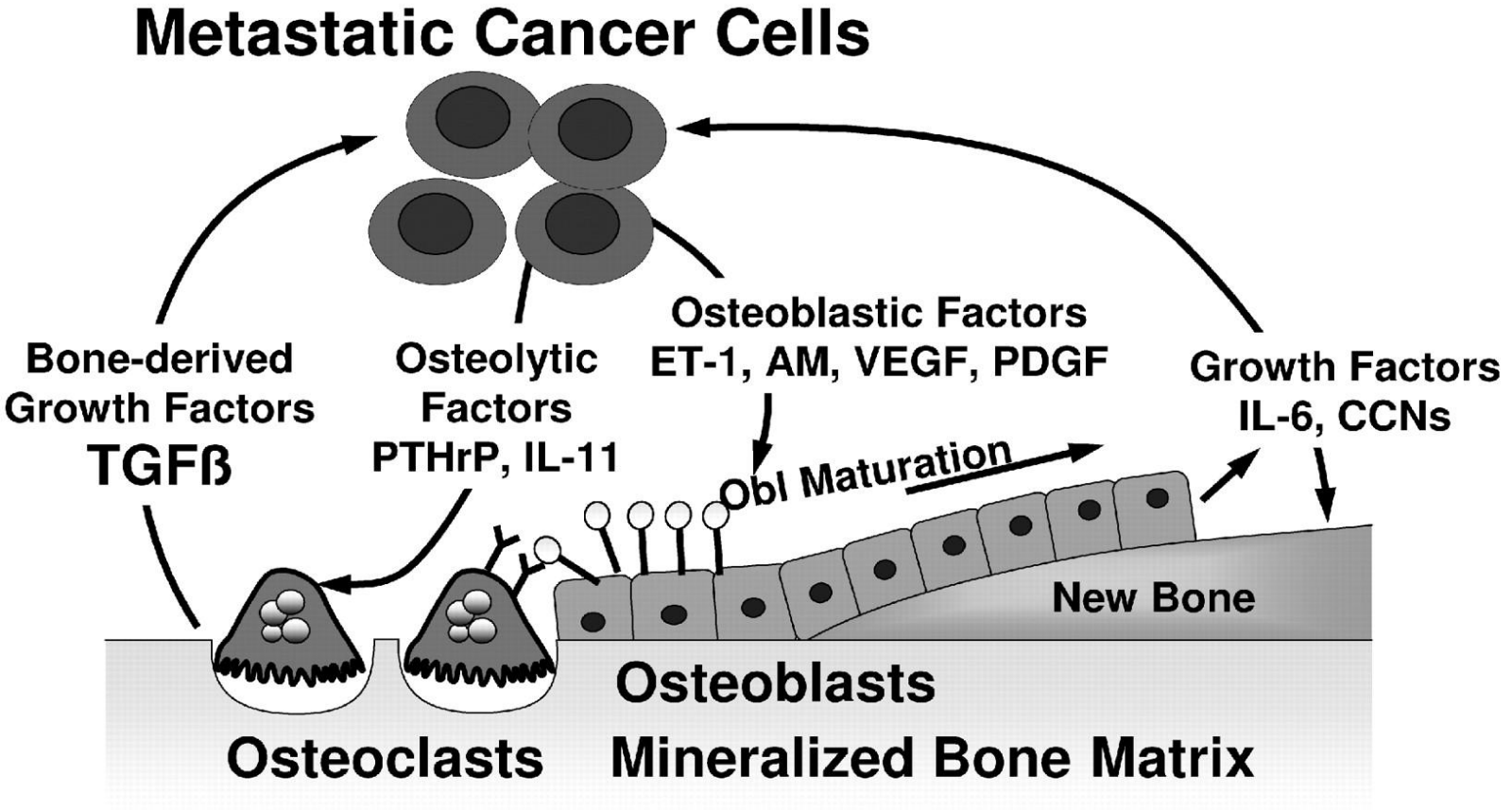

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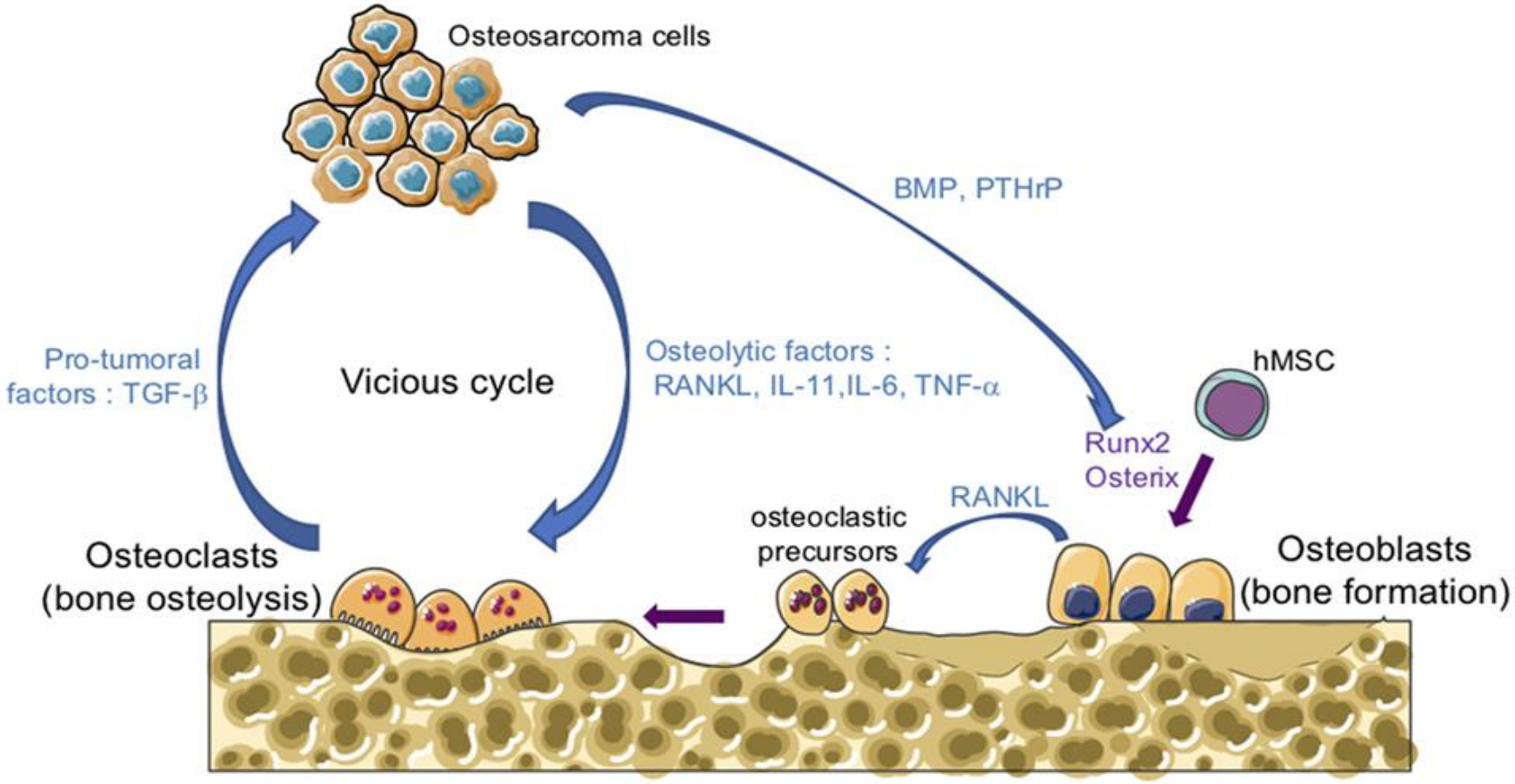
Primary bone cancer



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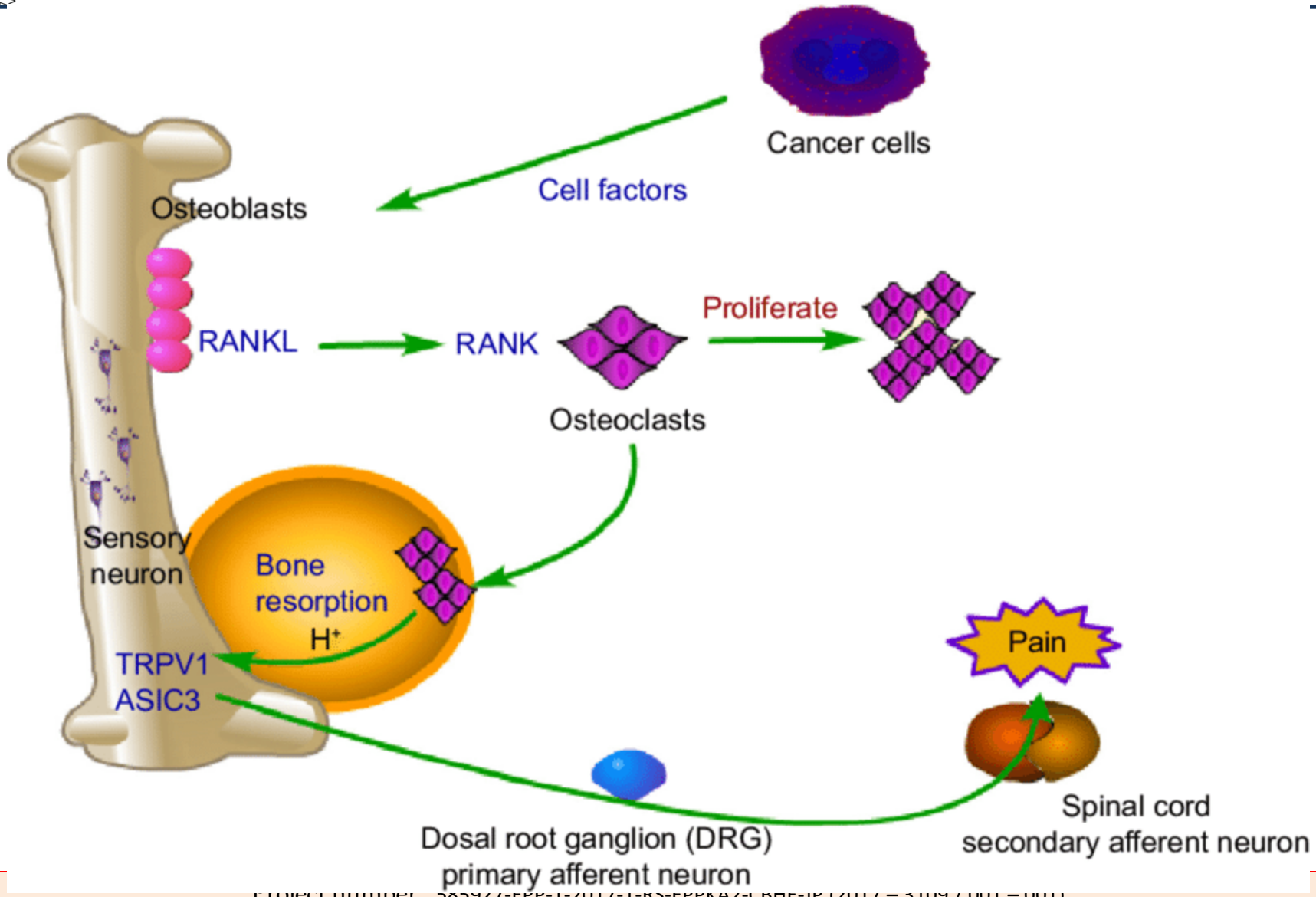

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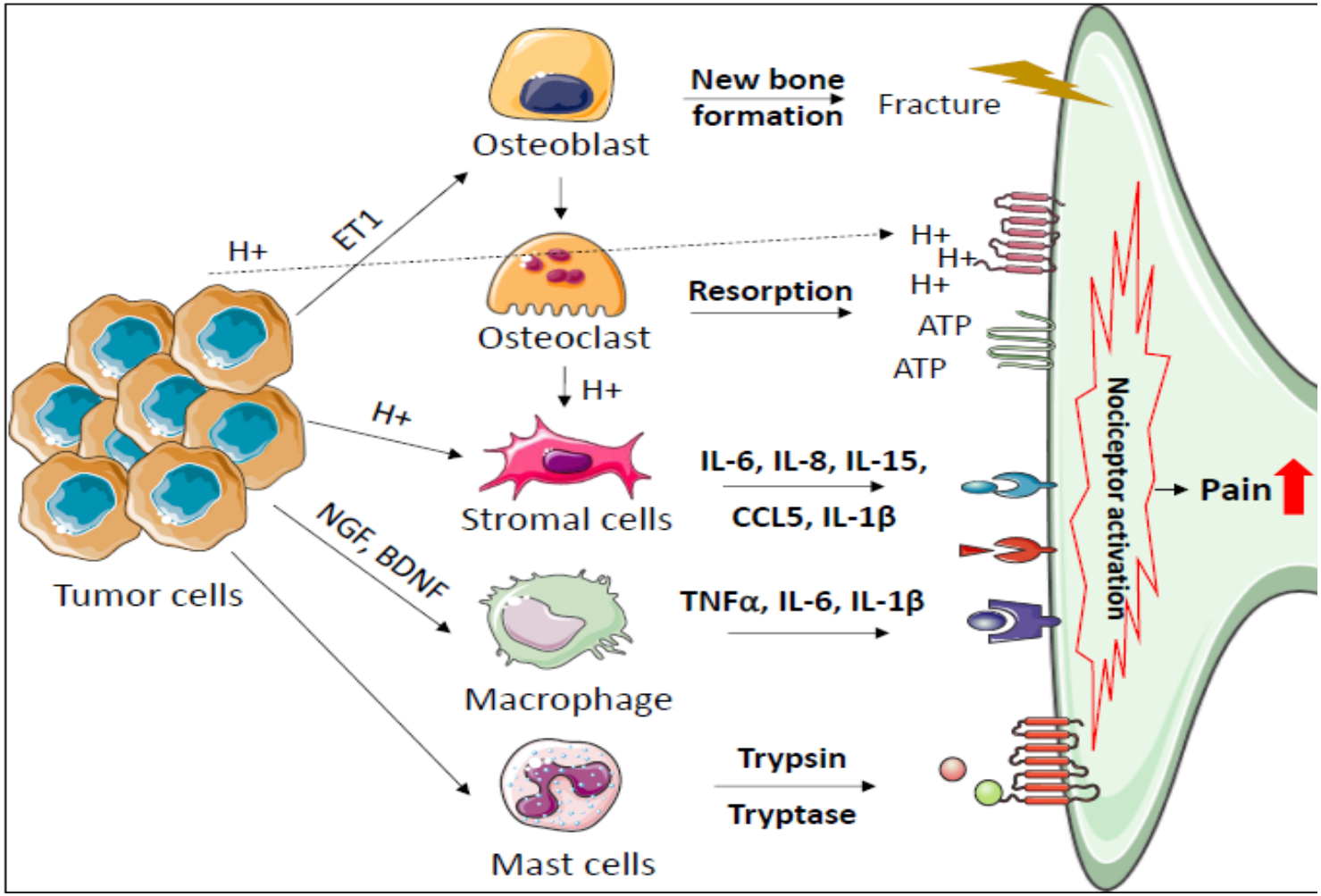
Cancer pain in bone metastasis



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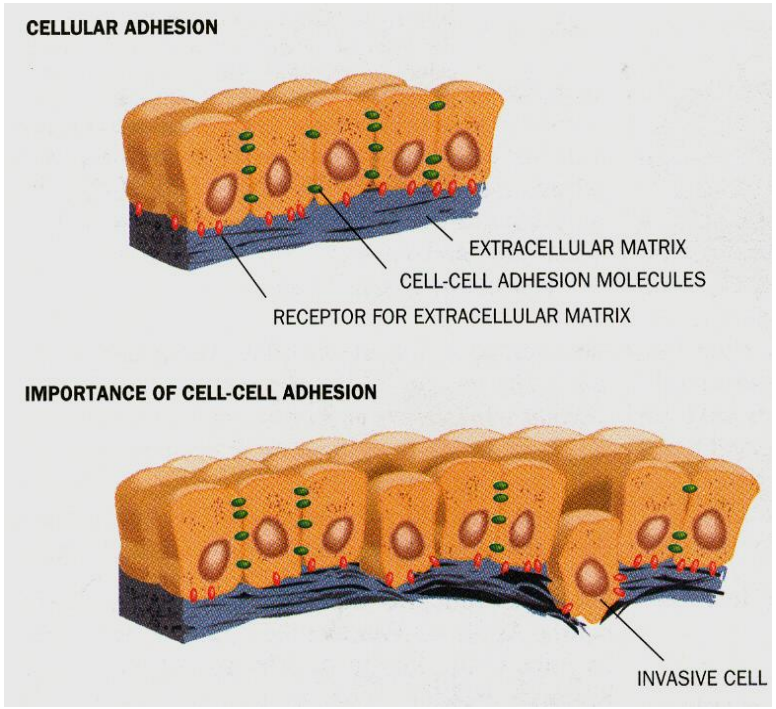
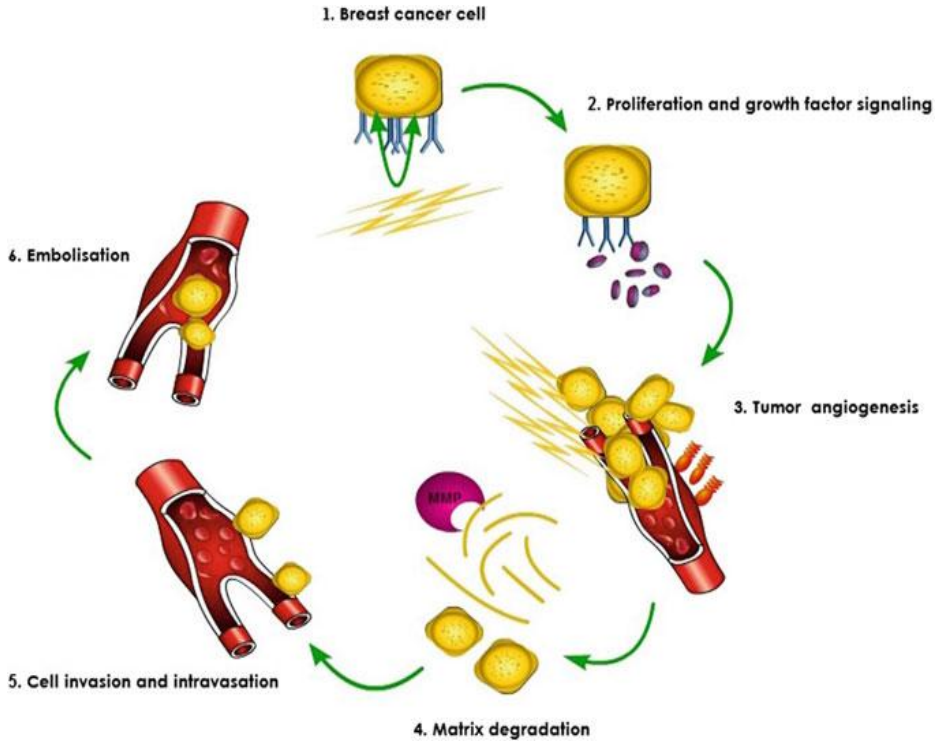
MMPs and cancer pain





Matrix metalloproteinases MMPs

Role of Proteases in Breast Cancer

Sandra Radenkovic, Kristina Gopcevic, Gordana Konjevic and Vladimir Jurisic

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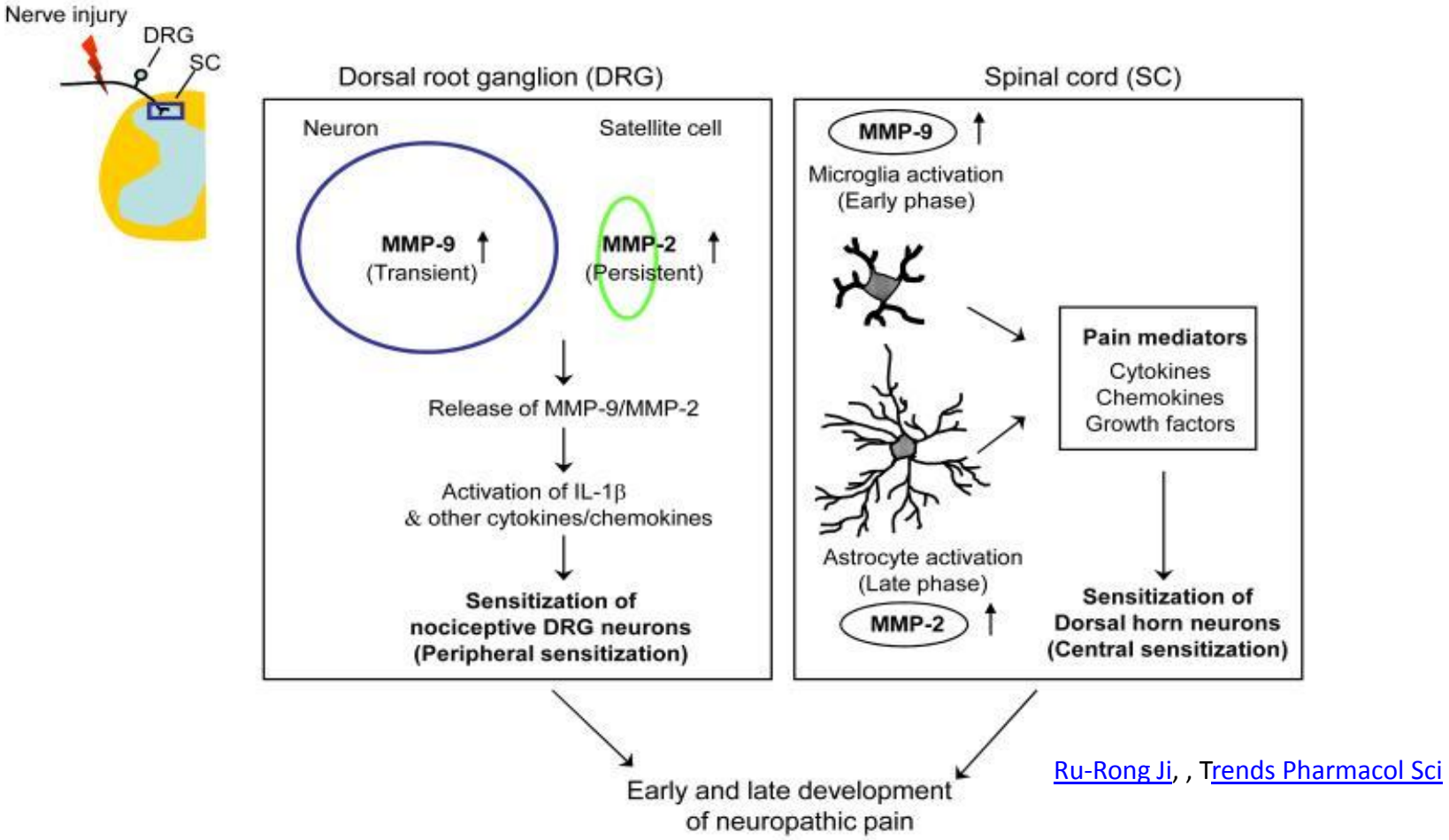
MMPs and nerve injury



Ru-Rong Ji, , Trends Pharmacol Sci

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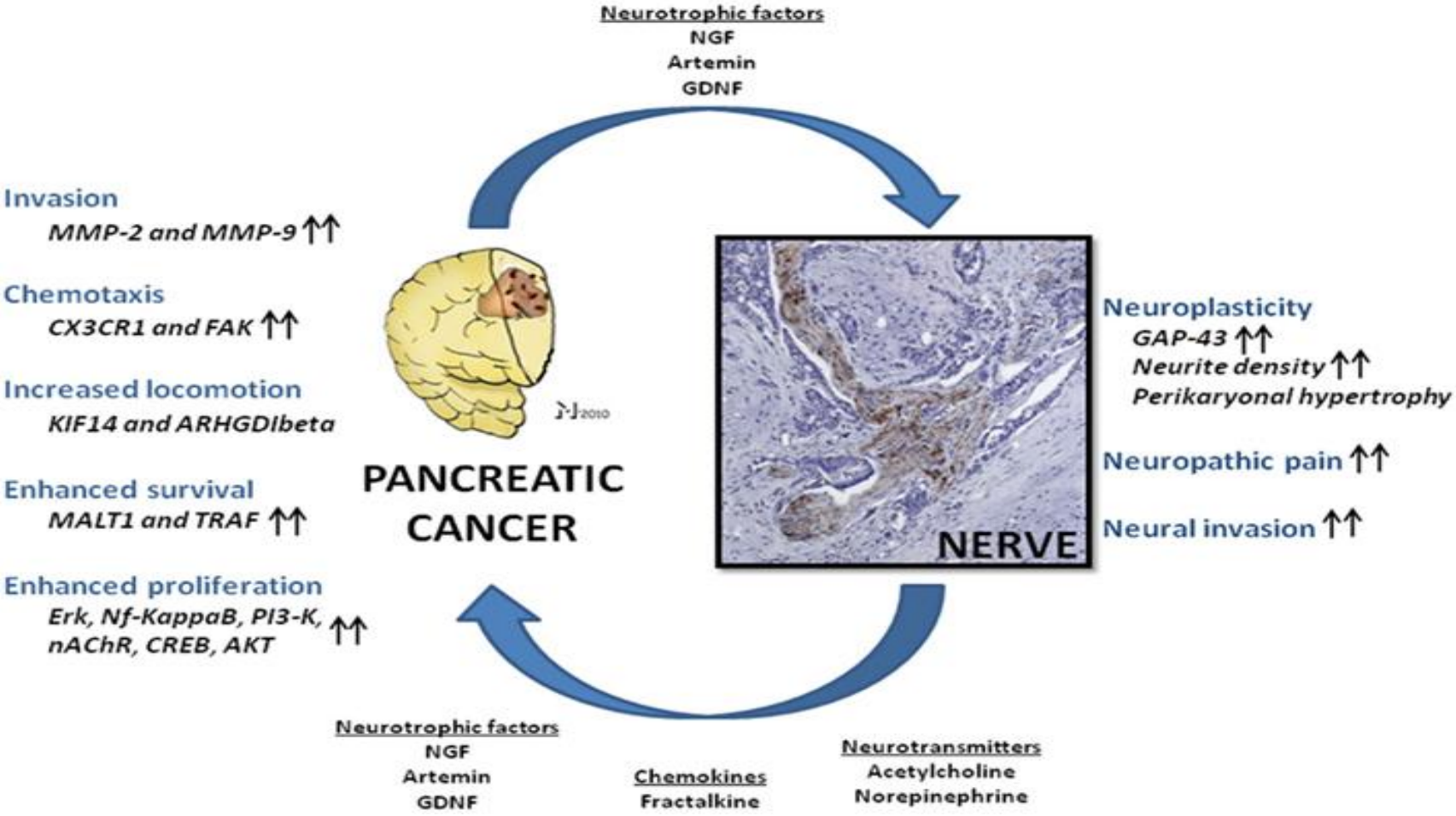
MMP and cancer pain



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Intensity of pain

COMPARATIVE PAIN SCALE CHART (Pain Assessment Tool)

0	1	2	3	4	5	6	7	8	9	10
Pain Free	Very Mild	Discomforting	Tolerable	Distressing	Very Distressing	Intense	Very Intense	Utterly Horrible	Excruciating Unbearable	Unimaginable Unspeakable
No Pain	**Minor Pain**			**Moderate Pain**			**Severe Pain**			
Feeling perfectly normal	Nagging, annoying, but doesn't interfere with most daily living activities. Patient able to adapt to pain psychologically and with medication or devices such as cushions.			Interferes significantly with daily living activities. Requires lifestyle changes but patient remains independent. Patient unable to adapt pain.			Disabling; unable to perform daily living activities. Unable to engage in normal activities. Patient is disabled and unable to function independently.			

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Commonly used pain terms.

Terminology	Definition/Description
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.
Nociception	The neural process of encoding noxious stimuli.
Pain threshold	The minimum intensity of a stimulus that is perceived as painful.
Pain tolerance level	The maximum intensity of a pain-producing stimulus that a subject is willing to accept in each situation.
Analgesia	Absence of pain in response to stimulation that would normally be painful.
Allodynia	Generation of pain by stimuli that were not previously painful.
Hyperalgesia	An increased sensitivity to pain; noxious stimuli evoke significantly more intense pain than normal.
Nociceptive pain	Pain that arises from actual or threatened damage to non-neural tissue and is caused by the activation of nociceptors.
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system.
Somatic pain	Pain resulting from the reduced irritability threshold in nociceptors located in superficial structures.
Visceral pain	Pain resulting from the reduced irritability threshold in nociceptor from organs located in body cavities.
Acute pain	Pain that has a quick onset and usually lasts less than 3 to 6 months.
Chronic pain	Pain that lasts more than 3 to 6 months and is persistent.
Breakthrough pain	A transient exacerbation of pain that occurs in conjunction with well-controlled background pain.
Refractory pain	Pain unrelieved by available therapeutic interventions.

Permission for use granted from the International Association for the Study of Pain.[1]

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Cancer pain and localisation

Pain	Cause	Primary Tumor Types
Bone pain	Bone metastases	Myeloma Breast cancer Lung cancer (small and nonsmall cell)
Headache	Brain metastases	Germ cell tumors Lymphoma and leukemias [Breast cancer] [Small cell lung cancer]
Abdominal pain	Ascites Subacute obstruction	Ovary Colorectal Stomach
	Pancreatic pain	Pancreas
Pelvic pain	Local tumor infiltration	Colorectal ovary cervix
Chest pain	Local tumor infiltration	Lung cancer (small and nonsmall cell) Metastases from chemosensitive sites,

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Cancer-Related Pain: A Longitudinal Study of Time to Stable Pain Control and Its Clinicodemographic Predictors

Paulo Reis-Pina, MD, MSc, Elham Sabri, MSc, Nicholas J. Birkett, MD, MSc, BMath, Antonio Barbosa, MD, PhD, and Peter G. Lawlor, MB, FRCPI, MMedSc

Palliative Care Unit (P.R.-P.), Casa de Saúde da Idanha, Sintra, Portugal; Formerly Instituto Português de Oncologia de Lisboa (P.R.-P.), Lisbon, Portugal; The Ottawa Hospital Research Institute (E.S.), Ottawa, Ontario; School of Epidemiology and Public Health (N.J.B.), University of Ottawa, Ottawa, Ontario, Canada; Department of Psychiatry (A.B.), Centro Hospitalar Lisboa Norte, Centre of Bioethics & Palliative Care Studies Division, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal; Bruyère Research Institute (P.G.L.), Bruyère Continuing Care, The Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Canada; and Division of Palliative Care (P.G.L.), Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada

Pain mechanism	
No evidence of NPC	199 (62.4)
Evidence of NPC	120 (37.6)
Pain topographic level	
Visceral pain absent	218 (68.3)
Visceral pain present	101 (31.7)
Bone pain absent	183 (57.4)
Bone pain present	136 (42.6)
Soft tissue pain absent	126 (39.5)
Soft tissue pain present	193 (60.5)
Pain duration	
<1 month	56 (17.6)
≥1 month	263 (82.5)
Pain location	
Multiple sites	14 (4.4)
Upper or lower limb	74 (23.2)
Head and neck	83 (26)
Thorax or breast	27 (8.5)
Back	36 (11.3)
Abdomen	45 (14.1)
Pelvis and perineum	40 (12.5)

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Cancer therapy related pain

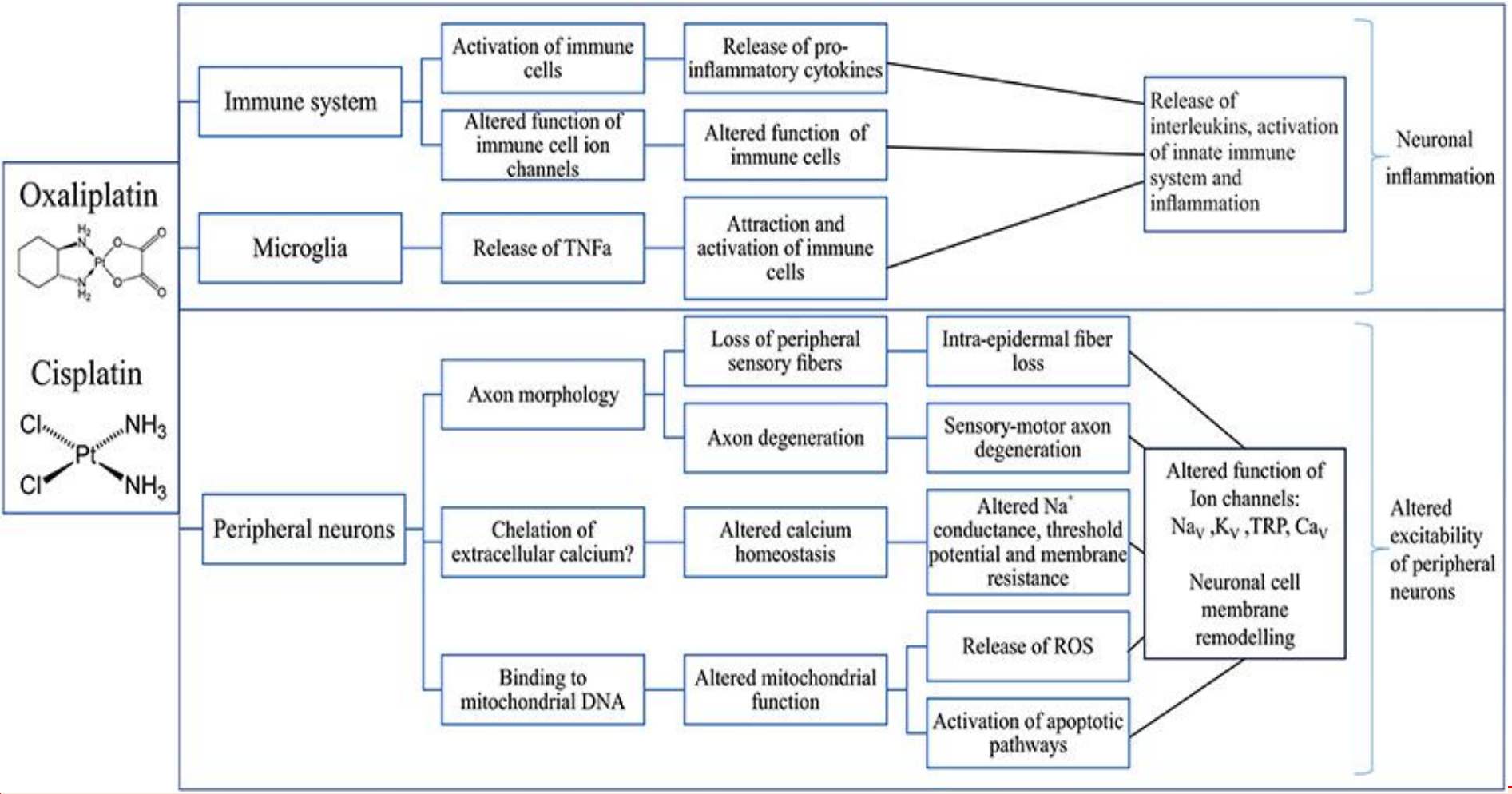

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Table 1
Acute pain syndromes associated with antineoplastic treatments

Pain Syndrome	Clinical Presentation
Chemotherapy-induced headaches	• Common after treatment with intrathecal methotrexate for leukemia, lymphoma, or leptomeningeal carcinomatosis, all-trans-retinoic acid for leukemia • May last for several days or longer
Diffuse bone pain	Common with trans-retinoic acid
Flare syndrome in advanced prostate cancer, after initiation of LHRH agonist	Characterized by increased bone pain, at times associated with added risk of cord compression, bladder outlet obstruction, and hypercoagulability
Palmar-plantar erythrodysesthesia (hand-foot syndrome)	Painful rash on the palms and soles after the administration of specific chemotherapies (particularly liposomal doxorubicin and capecitabine)
Myalgia and arthralgia	Pain in muscles and joints. Reported in 20% of patients treated with paclitaxel
Steroid-induced perineal burning	Perineal burning, reported with rapid administration of intravenous steroids

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Table 2
Acute pain syndromes associated with chemotherapy-induced neuropathy

Medication	Mechanism of Peripheral Neuropathy Toxicity
Platinum-based agents • Cisplatin • Oxaliplatin	Binding to DNA may inhibit the transcription of important proteins and impair axonal transport
Vinca Alkaloids • Vincristine • Vinblastine • Vinorelbine	Interference with axonal microtubule assembly, impairment of axonal transport Vinblastine is included for completeness, but the incidence of neuropathy is lower than others listed
Thalidomide	Unknown
Taxanes • Paclitaxel • Docetaxel	Toxic effect to the neuronal cell body, axon, or both

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Acute pain syndromes associated with cancer treatment.

Pain Syndrome	Clinical Presentation
Chemotherapy-induced headaches	Common after treatment with intrathecal methotrexate for leukemia, lymphoma, or leptomeningeal carcinomatosis, all-trans-retinoic acid for leukemia. May last for several days or longer.
Diffuse bone pain	Common with trans-retinoic acid.
Flare syndrome in advanced prostate cancer, after initiation of luteinizing hormone-releasing hormone agonist	Characterized by increased bone pain, at times associated with added risk of cord compression, bladder outlet obstruction, and hypercoagulability.
Palmar-plantar erythrodysesthesia (hand-foot syndrome)	Painful rash on the palms and soles after the administration of specific chemotherapies (particularly liposomal doxorubicin and capecitabine).
Myalgia and arthralgia	Pain in muscles and joints.
Steroid-induced perineal burning	Perineal burning, reported with rapid administration of intravenous steroids.

Chronic pain syndromes associated with cancer treatment	
Hormonal therapy-related pain syndromes	Arthralgias Dyspareunia Gynecomastia Myalgias Osteoporotic compression fractures
Radiation-related pain syndromes	Chest wall syndrome Cystitis Enteritis and proctitis Lymphedema Myelopathy Osteoporosis Osteoradionecrosis and fractures Painful secondary malignancies Peripheral mononeuropathies Plexopathies: Brachial, lumbosacral, sacral
Chemotherapy-related pain syndromes	Bony complications of long-term corticosteroids Avascular necrosis Vertebral compression fractures Carpal tunnel syndrome Chemotherapy-induced peripheral neuropathy
Surgical pain syndromes	Lymphedema Postamputation phantom pain Postmastectomy pain Postradical neck dissection pain Postsurgery pelvic floor pain Postthoractomy pain/frozen shoulder

Chemotherapy agents associated with mucositis

Medication

Platinum-based agents
- Cisplatin
- Oxaliplatin

Anthracyclines
- Daunorubicin
- Doxorubicin
- Epirubicin
- Idarubicin

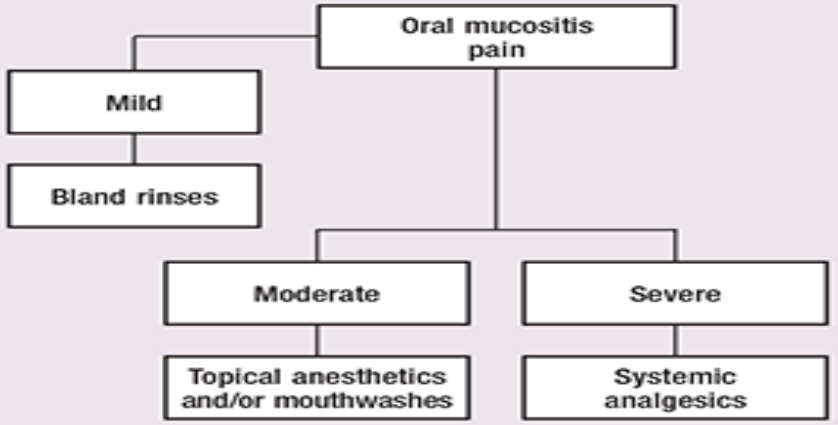
Alkylating agents
- Cyclophosphamide
- Ifosfamide
- Thiotepa
- Melphalan
- Cisplatin
- Busulfan

Antimetabolites
- 6-Mercaptopurine
- Cytarabine
- Fluorouracil
- Gemcitabine
- Hydroxyurea
- Methotrexate
- Docetaxel

Taxanes
- Docetaxel
- Paclitaxel

Targeted agents
- Erlotinib
- Everolimus
- Sorafenib
- Sunitinib
- Cetuximab

Figure 1. Stepwise Approach to Oral Mucositis Pain



Source: Reference 4.

Table 1. Oral Mucositis Grading Scales

Grade	WHO	NCI
1	Oral soreness, erythema	Asymptomatic or mild symptoms; intervention not indicated
2	Erythema, ulcers; patient can swallow solid food	Moderate pain; not interfering with oral intake; modified diet indicated
3	Ulcers with extensive erythema; patient cannot swallow food	Severe pain; interfering with oral intake
4	Mucositis to extent that alimentation not possible	Life-threatening consequences; urgent intervention indicated
5	NA	Death

NA: not applicable; NCI: National Cancer Institute; WHO: World Health Organization.
Source: References 6, 7.

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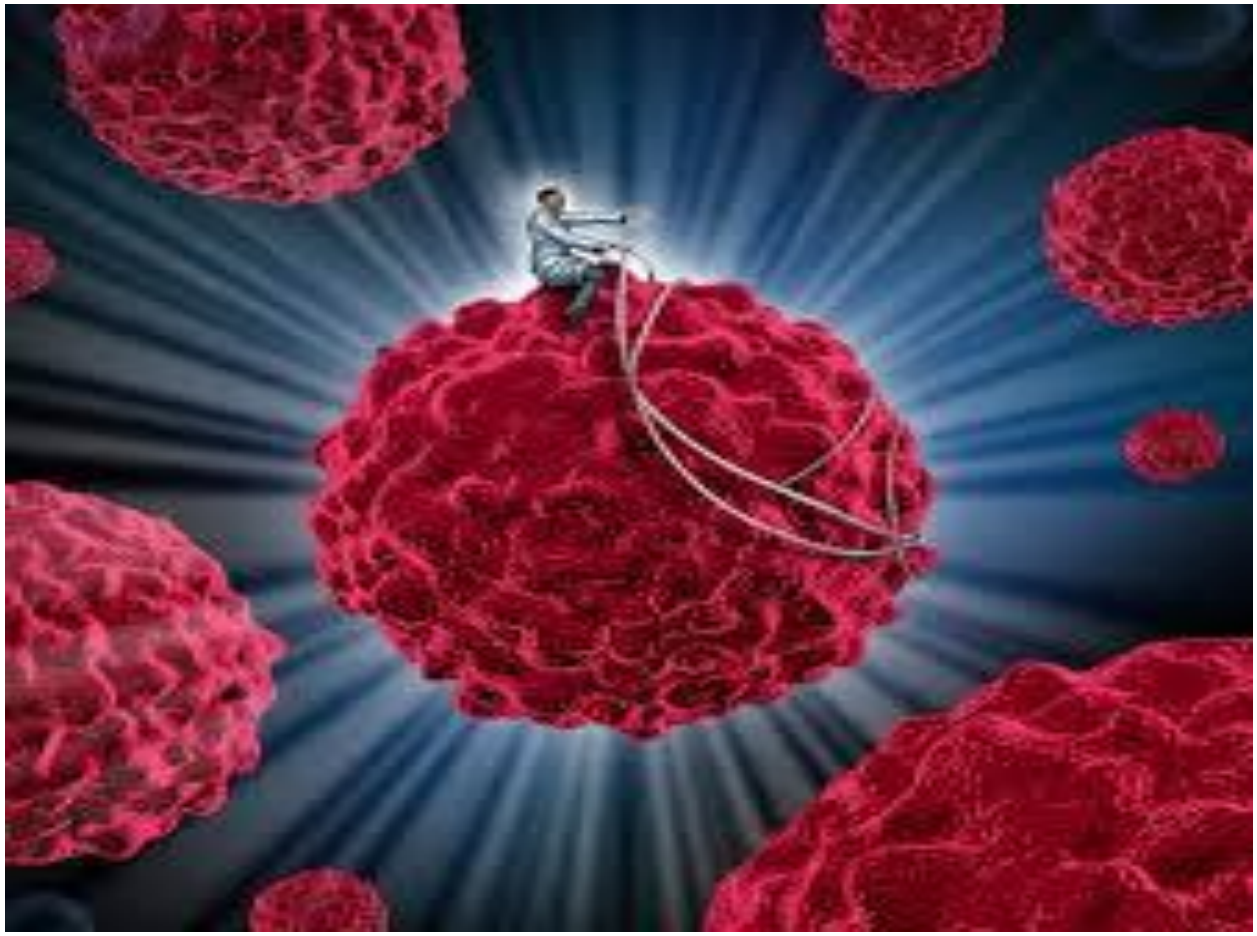
Questions?



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