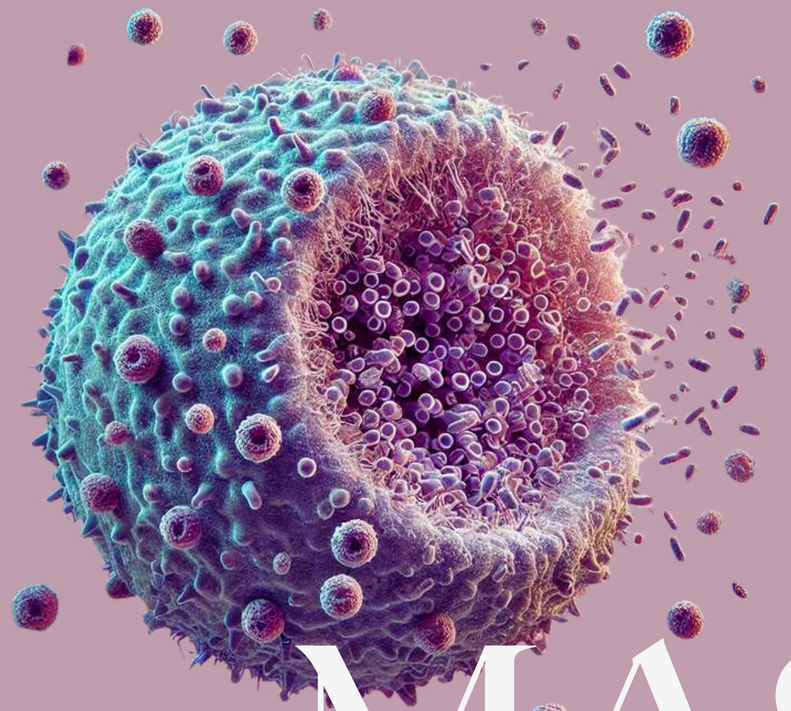
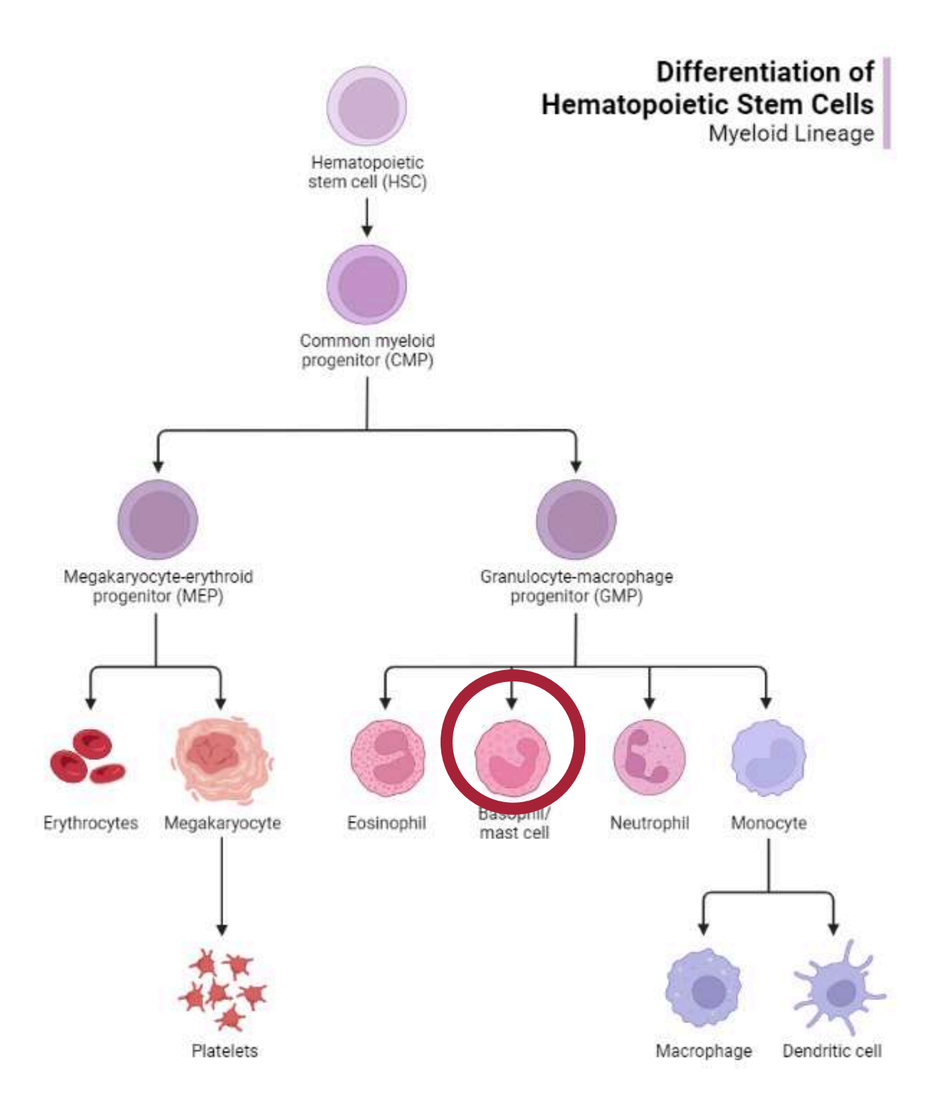


MASTOCITOSI

IX Matí Al·lèrgia Bellvitge: Malalties al·lèrgiques de risc vital

Helena Valero Castañer- A1
hvalero@bellvitgehospital.cat

EL MASTÒCIT



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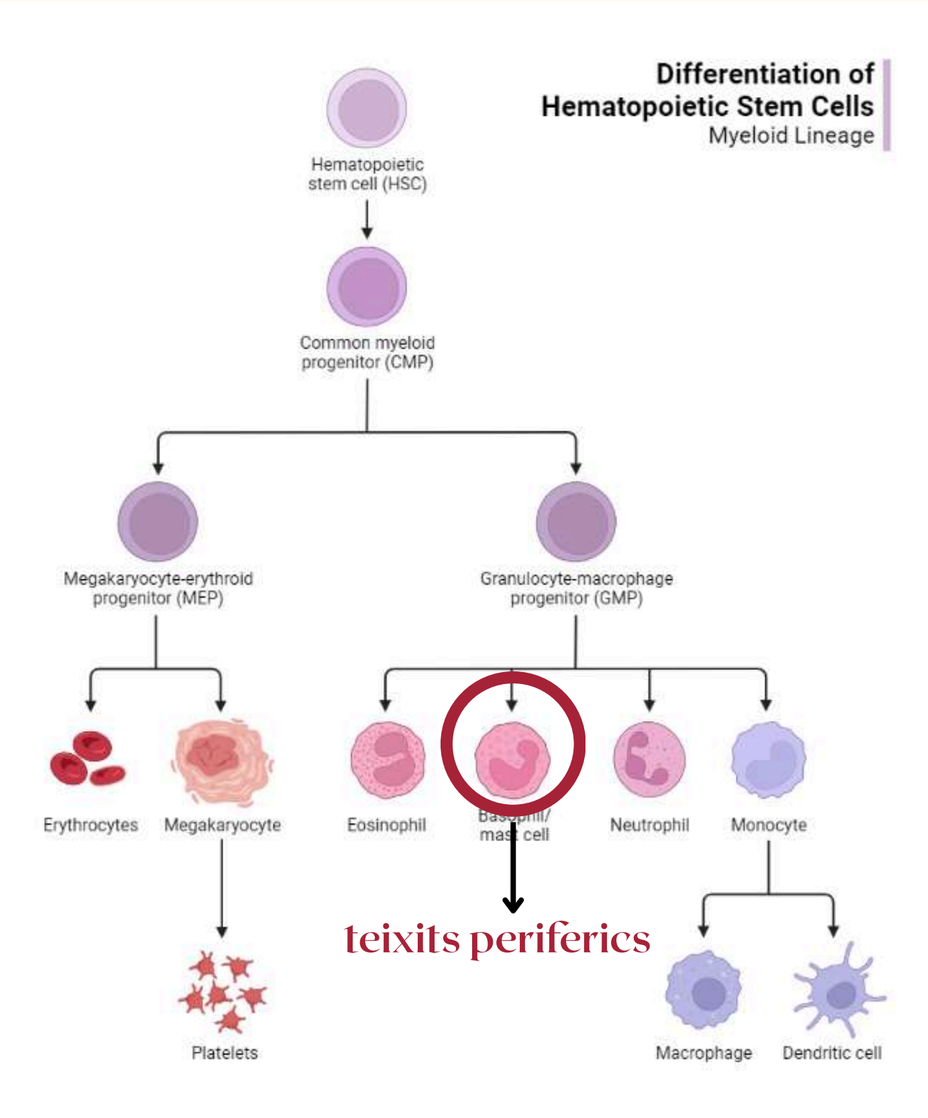

Es formen a la medul·la òssia i **maduren** als teixits perifèrics.

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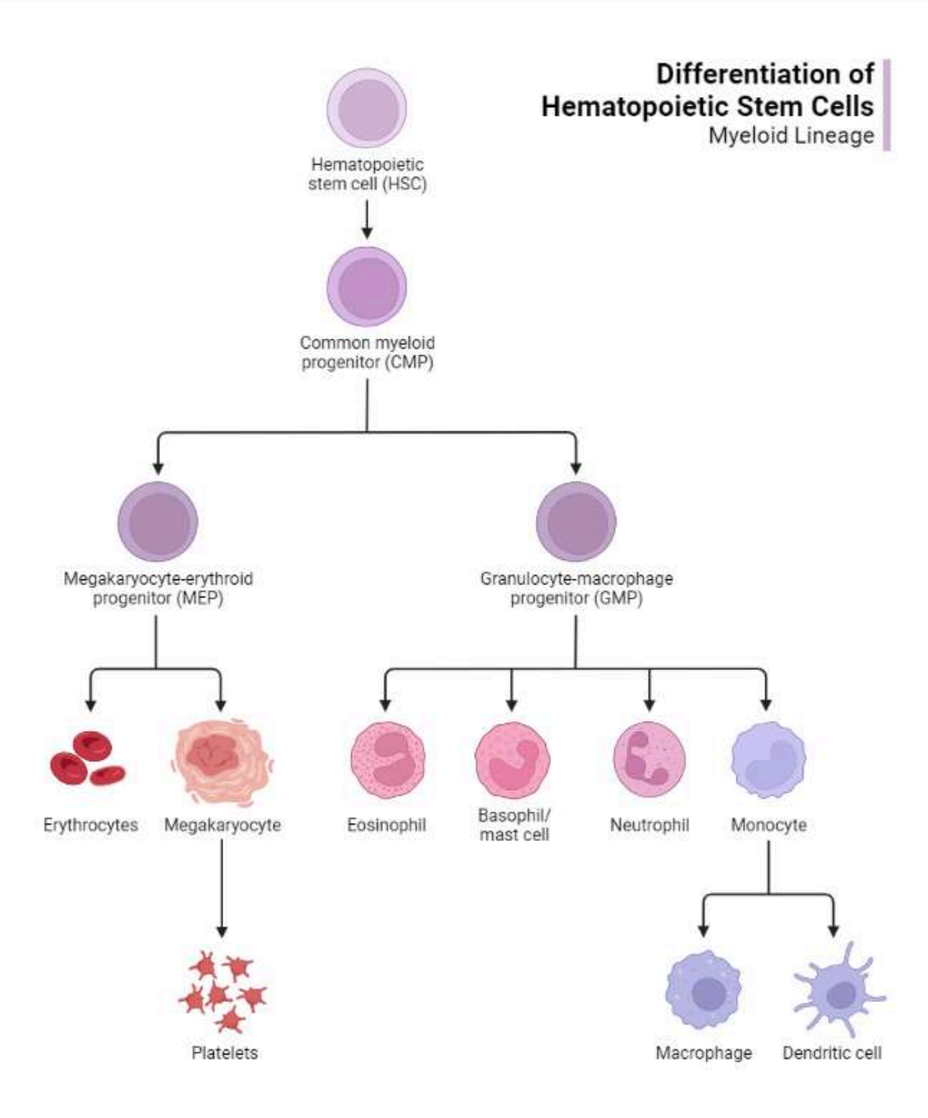

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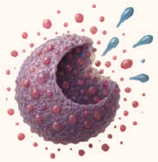

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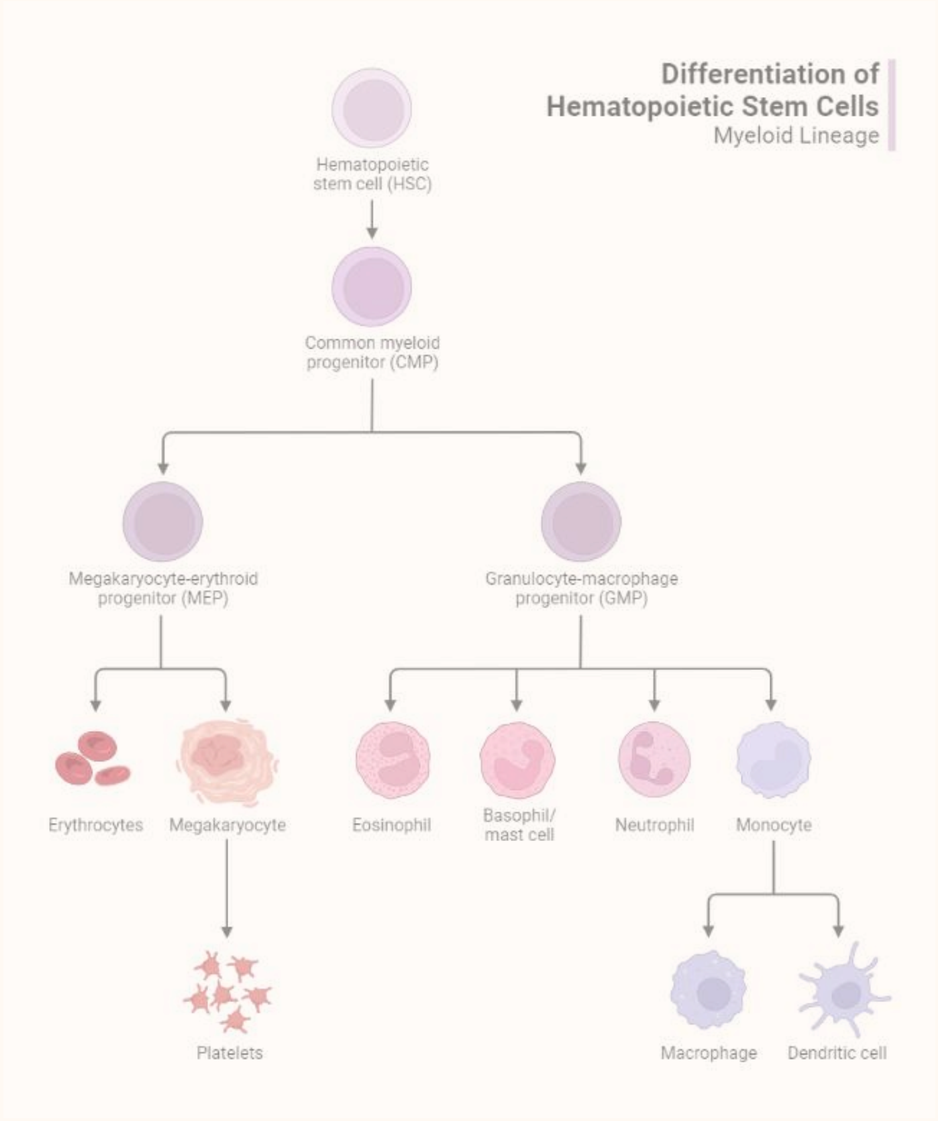

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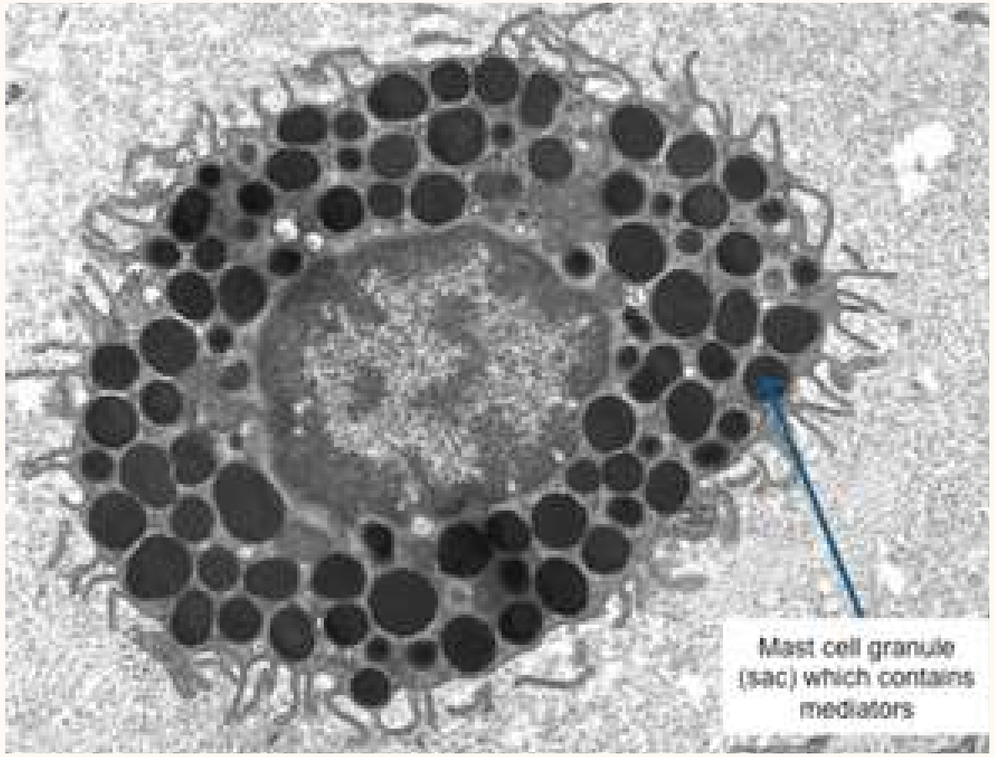
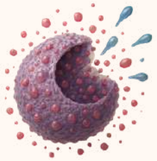


essencials per la seva funció immunológica



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Resposta al·lèrgica

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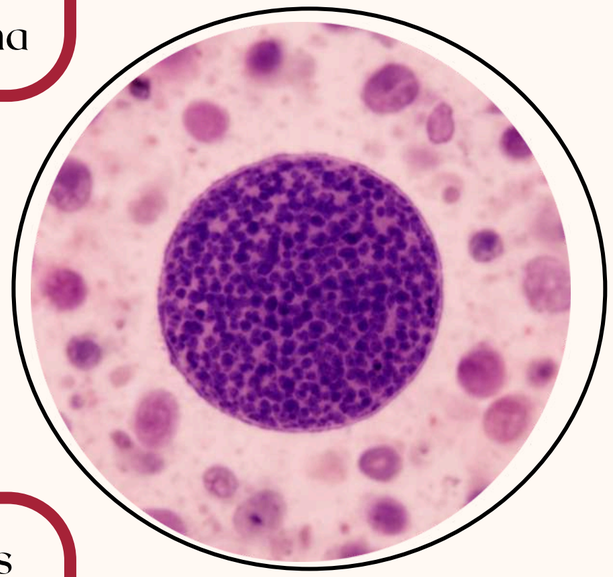

Control de l'homeòstasi

Funcions endotelial

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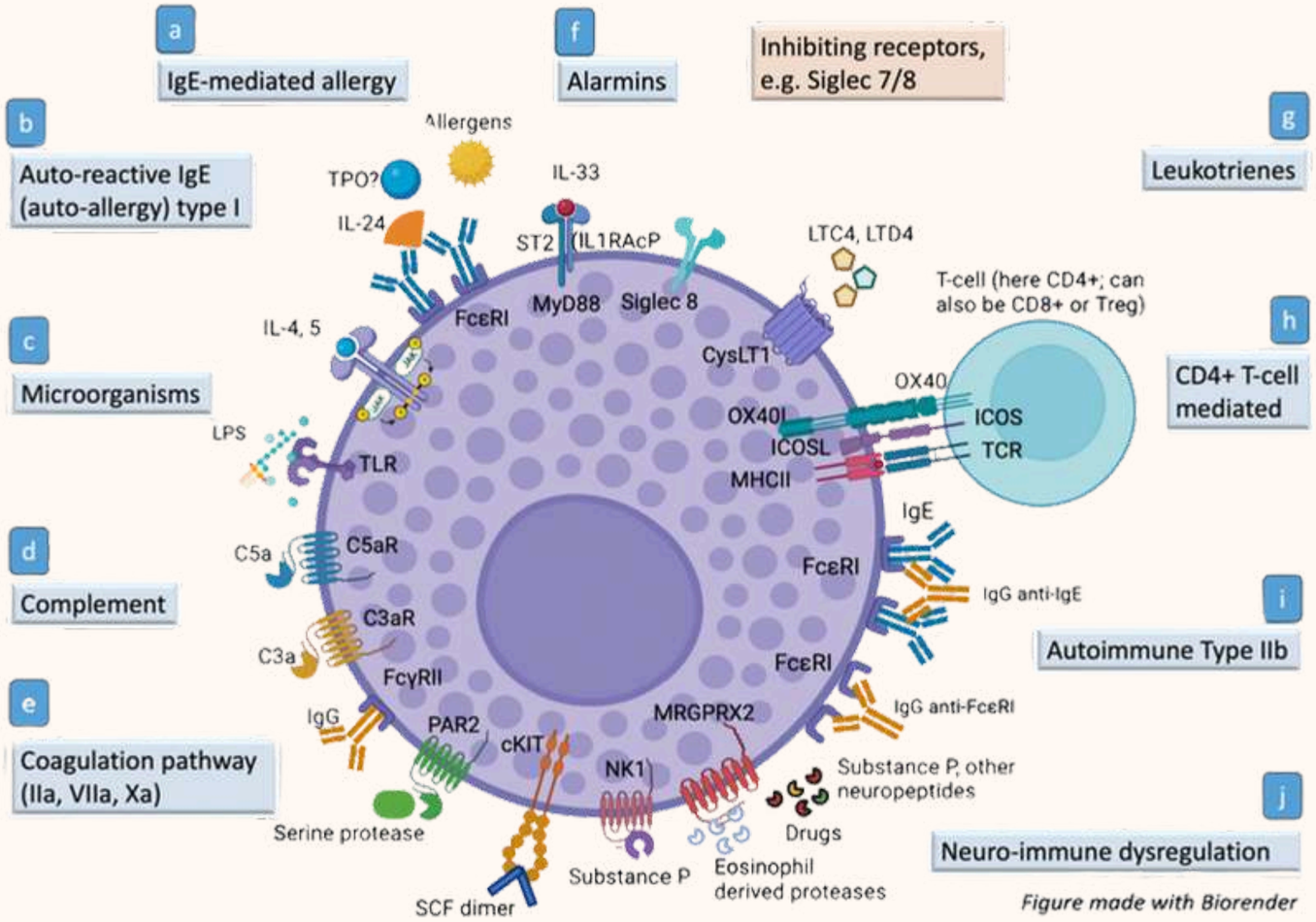

Larenas-Linnemann D. Biomarkers of Autoimmune Chronic Spontaneous Urticaria. Curr Allergy Asthma Rep. 2023 Dec;23(12):655-664. doi: 10.1007/s11882-023-01117-7.

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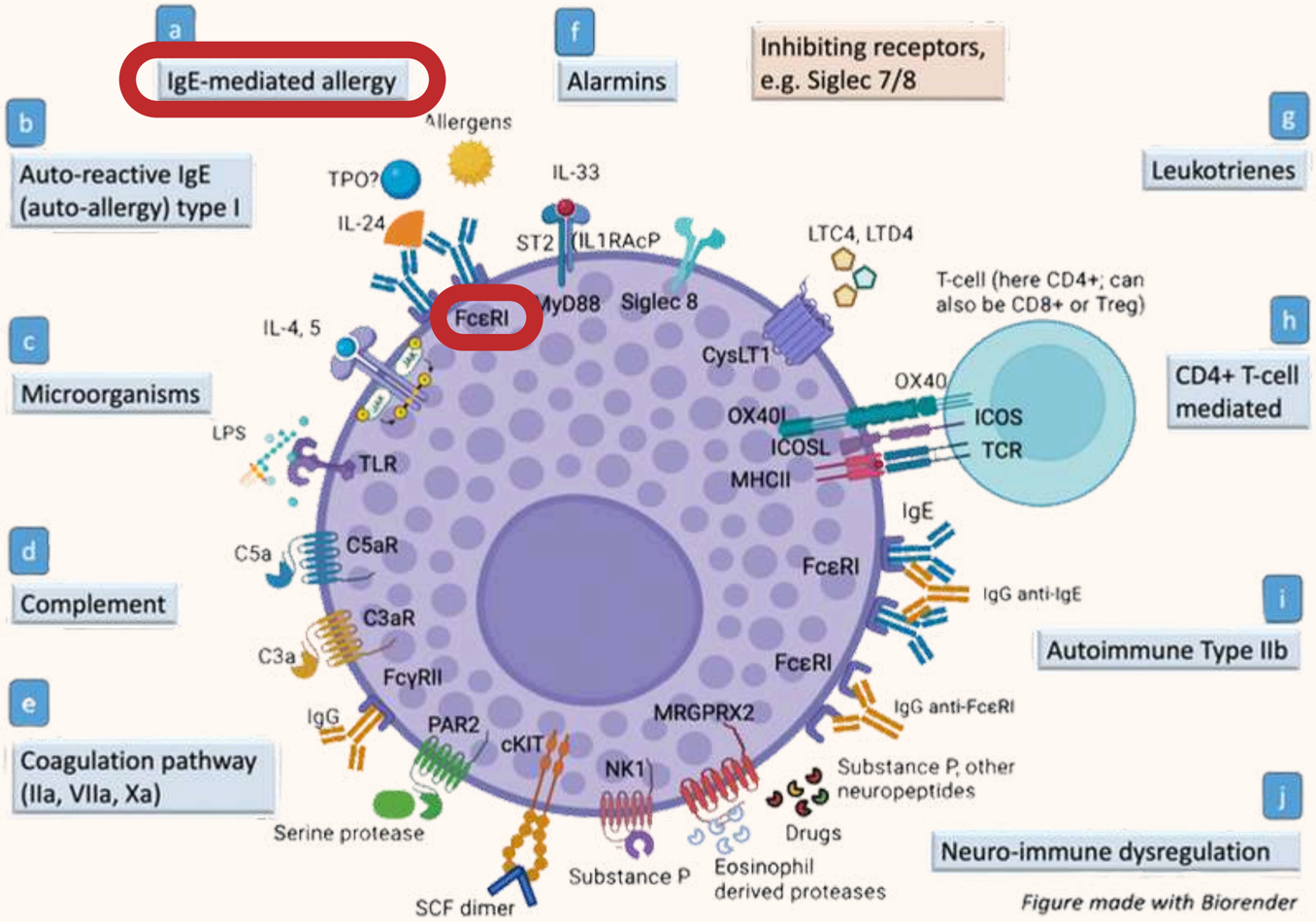

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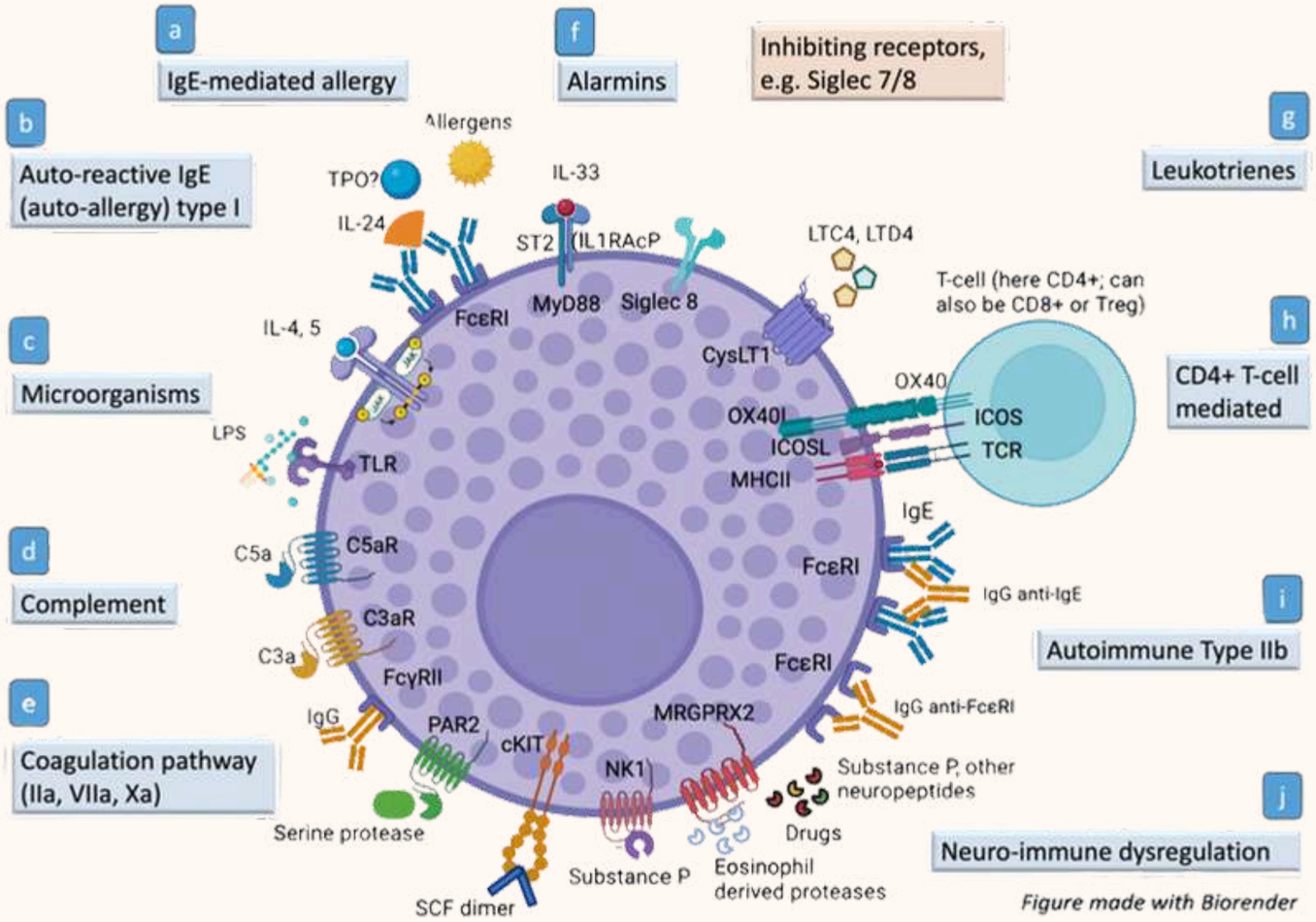

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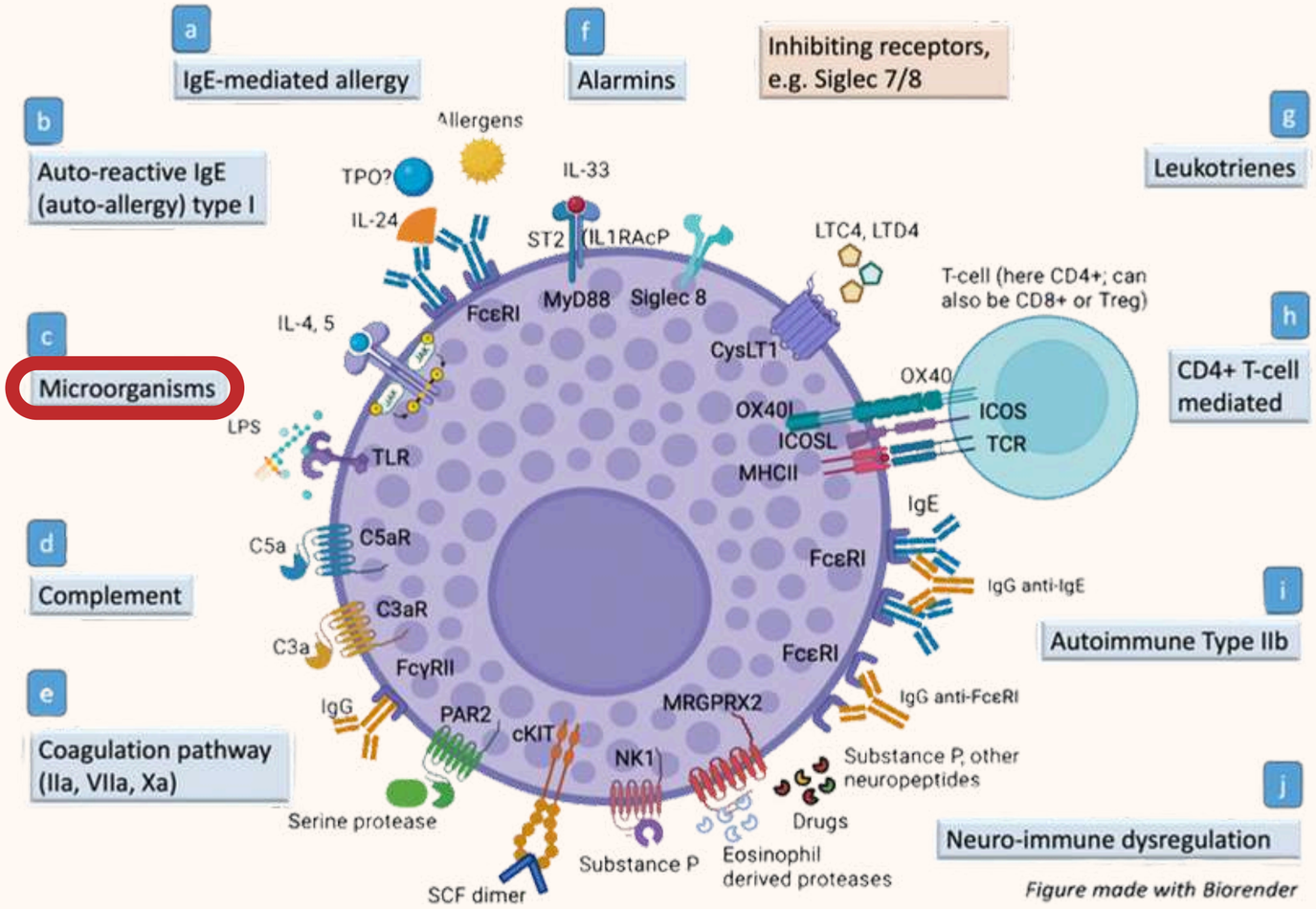

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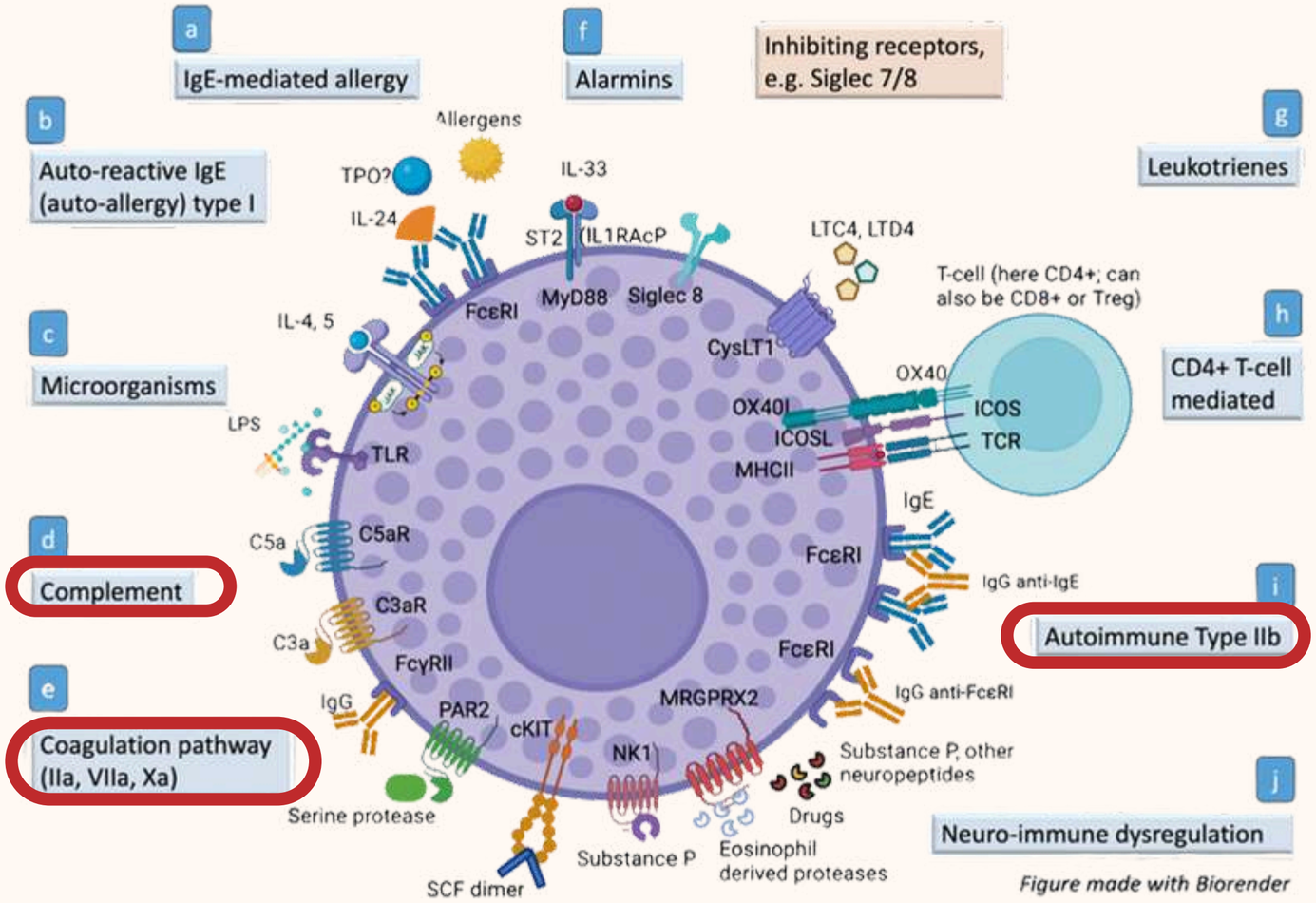

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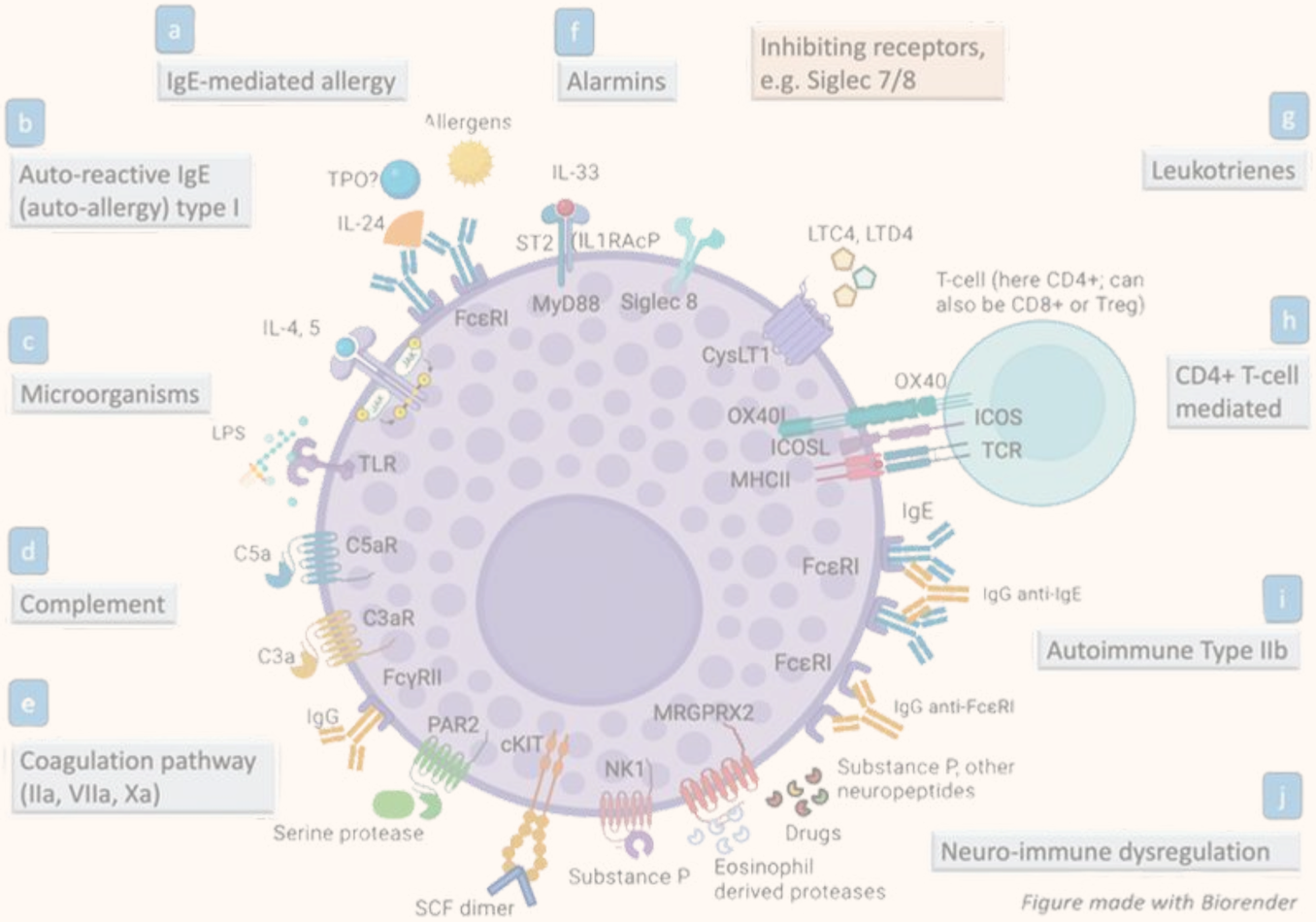
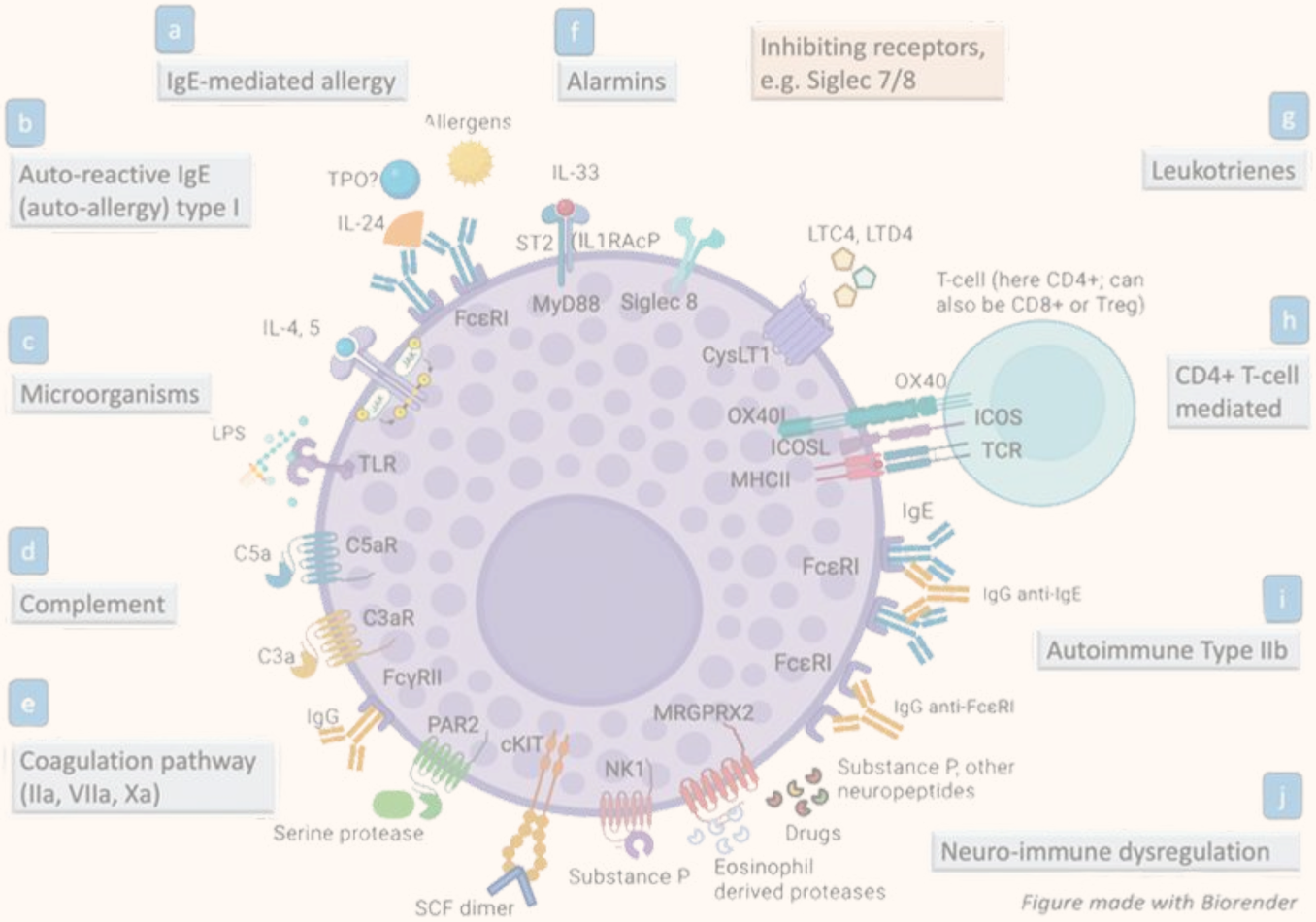


DESENCADENANTS [1,2]

- picades d'himenòpters
- alcohol
- fàrmacs (AINES, relaxants musculars, anestèsics, contrastos iodats)
- infeccions
- estímuls físics (pressió, fricció..)

1. Adapted from National Comprehensive Cancer Network (NCCN ®) 2.Rama TA, Castells M. Curr Treat Options Allergy. 2023;10:442-457;

EL MASTÒCIT



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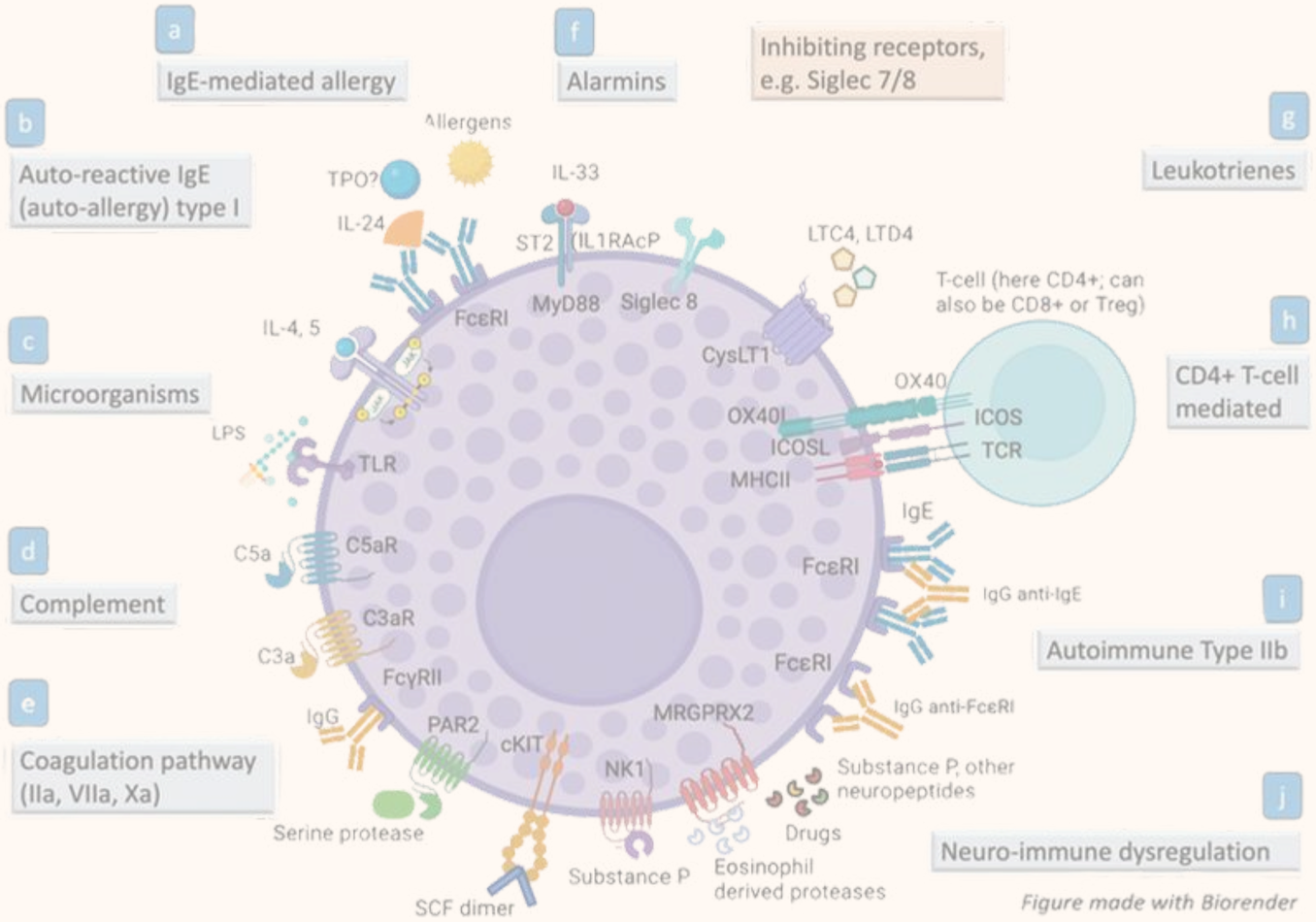

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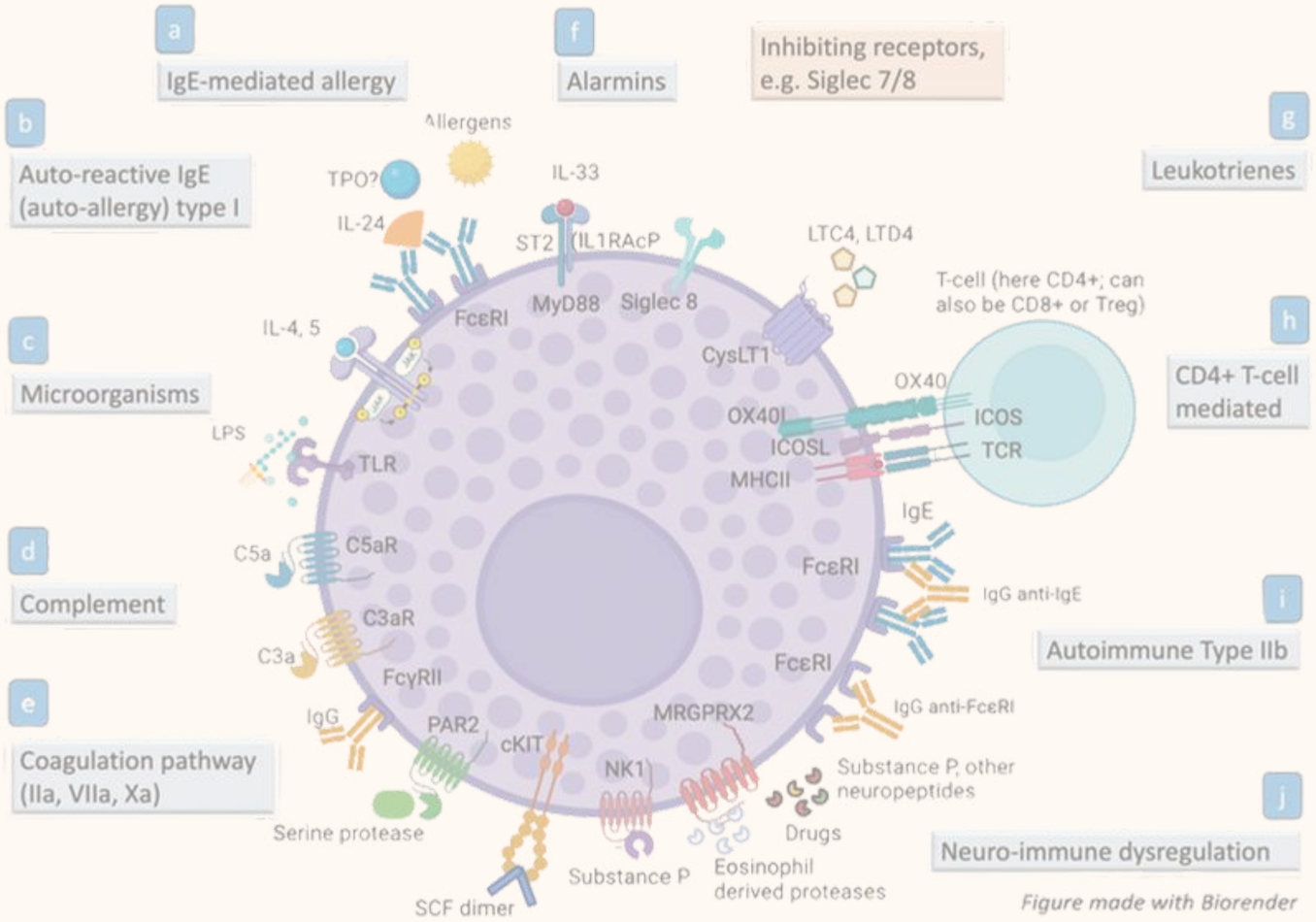

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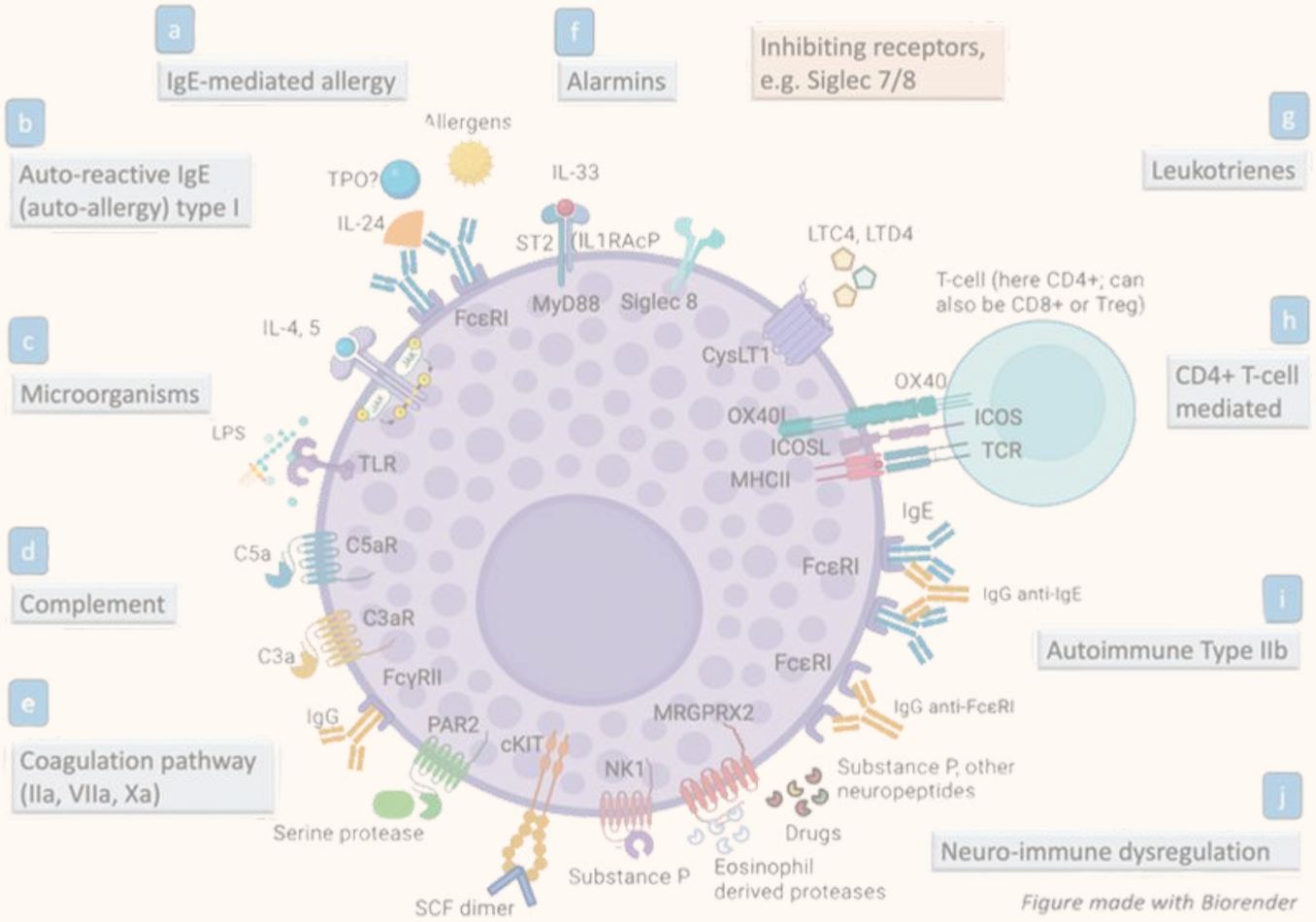

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EL MASTÒCIT

Cèl·lules del SI crucials en la resposta immunitària

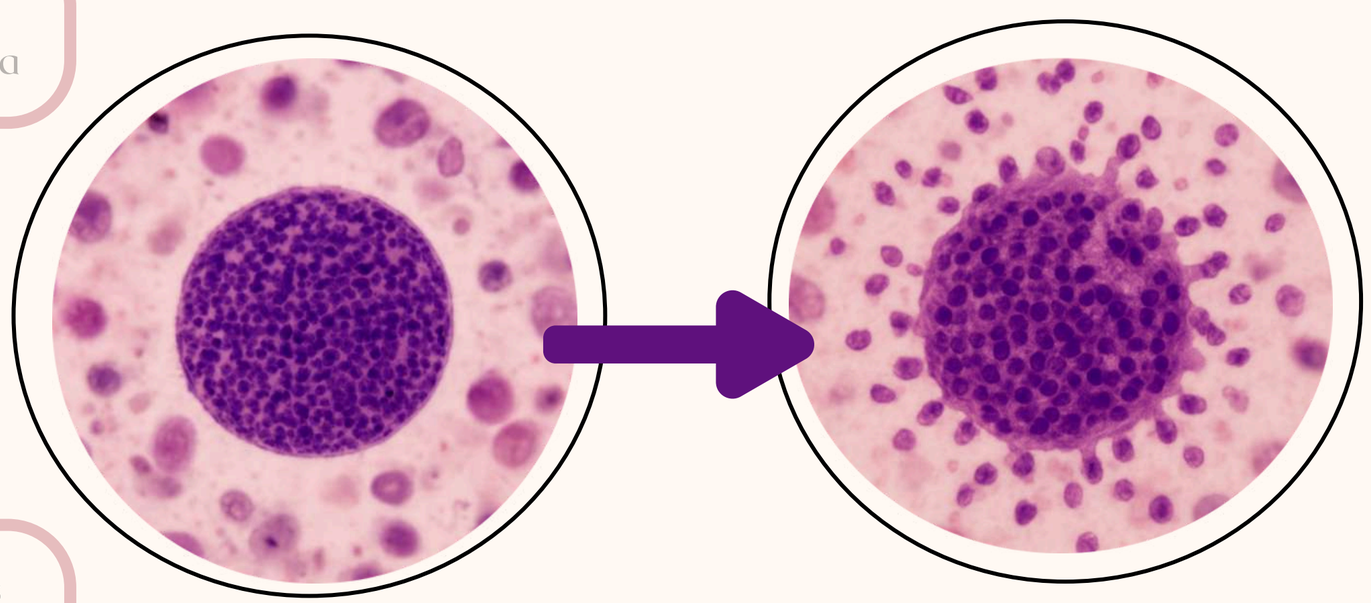
Resposta al·lèrgica

Defensa microbiana

Control de l'homeòstasi

Funcions endotelial

Reparació tissular



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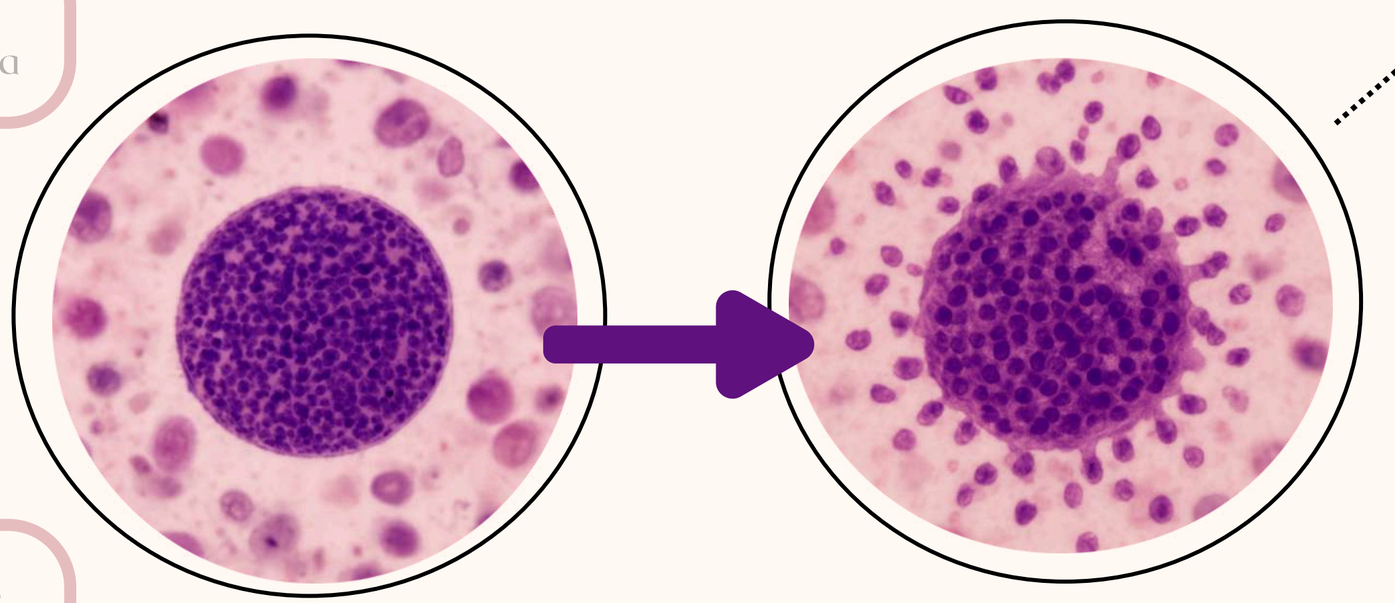

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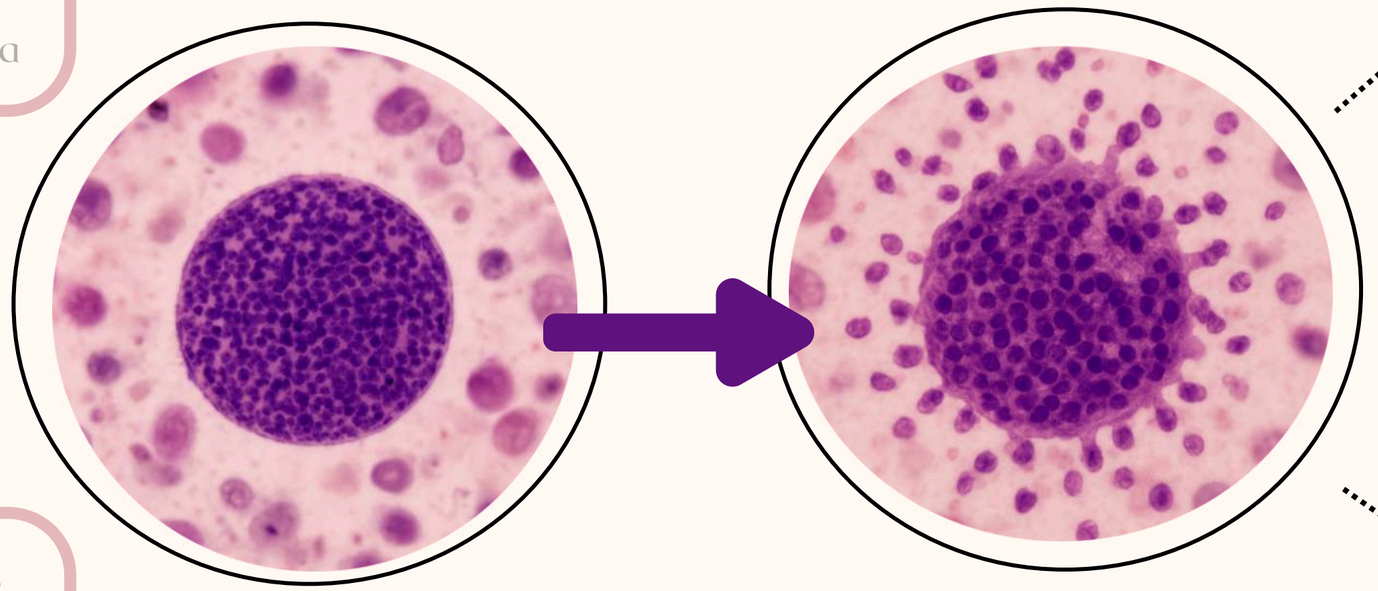

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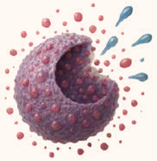
Síntesi de nous mediadors:
prostaglandines y leucotriens

Citocines induïbles:
IL-3, IL-4, IL-13..



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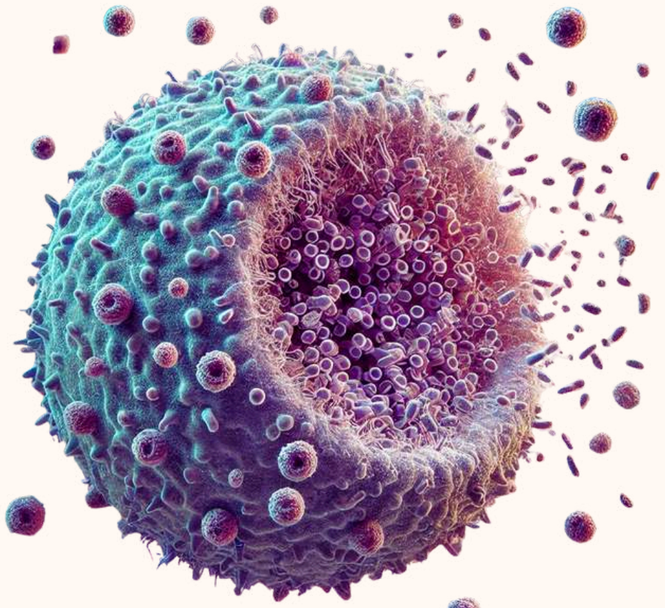


MASTOCITOSI

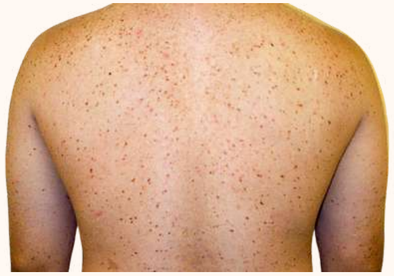
Bellvitge
Hospital Universitari

MASTOCITOSI

Grup de malalties hematològiques - mastòcits **CLONALS**

PROLIFERACIÓ

ACUMULACIÓ



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Brockow K. Immunol Clin North Am. 2014;34(2):283-295

MASTOCITOSI

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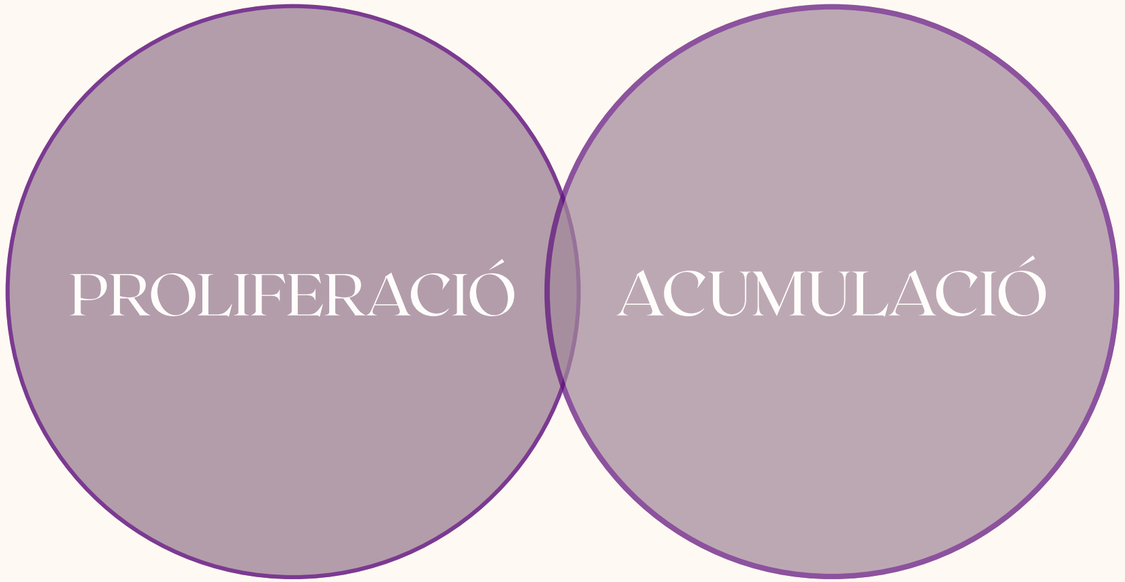
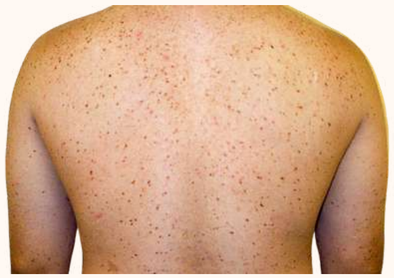


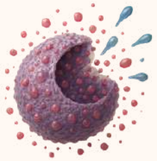


Epidemiologia

Prevalença: **27 casos/10.000 habitants** *(Incidencia de 0.89 per 100.000 adults/any)*

Caucàsics

H:M 1:1



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MASTOCITOSI

1) MASTOCITOSIS CUTÀNIA (MC)

2) MASTOCITOSI SISTÈMICA (MS)

TABLE 2 World Health Organization 5th Edition classification of mastocytosis (reproduced from Khoury et al.).[2,16]

1

- **Cutaneous mastocytosis**
  - Urticaria pigmentosa/maculopapular cutaneous mastocytosis
    - Monomorphic
    - Polymorphic
  - Diffuse cutaneous mastocytosis
  - Cutaneous mastocytoma
    - Isolated mastocytoma
    - Multilocalized mastocytoma

2

- **Systemic mastocyosis**
  - Bone marrow mastocytosis
  - Indolent systemic mastocytosis
  - Smoldering systemic mastocytosis
  - Aggressive systemic mastocytosis
  - Systemic mastocytosis with an associated hematologic neoplasm
  - Mast cell leukemia

3

- **Mast cell sarcoma**

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limitada a la pell → **infància**, benigna + regressió espontània

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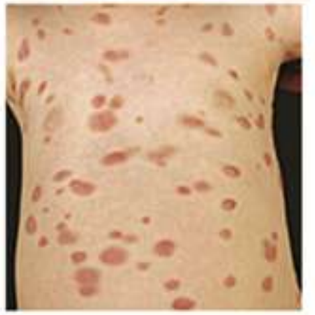

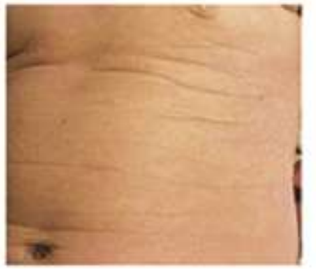

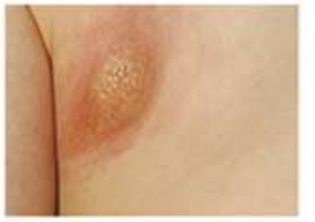

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afectació de ≥ 1 organ extracutàni → 90% adults, persistent

- **Non-Adv (~88%-95%)**
- Adv-SM (~5%-12%)

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- Mast cell sarcoma

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Brockow K. Immunol Clin North Am. 2014;34(2):283-295
Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. Am J Hematol. 2023 Jul;98(7):1097-1116

MASTOCITOSI

1) MASTOCITOSIS CUTÀNIA (MC)

limitada a la pell → **infància**, benigna + regressió espontània

2) MASTOCITOSI SISTÈMICA (MS)

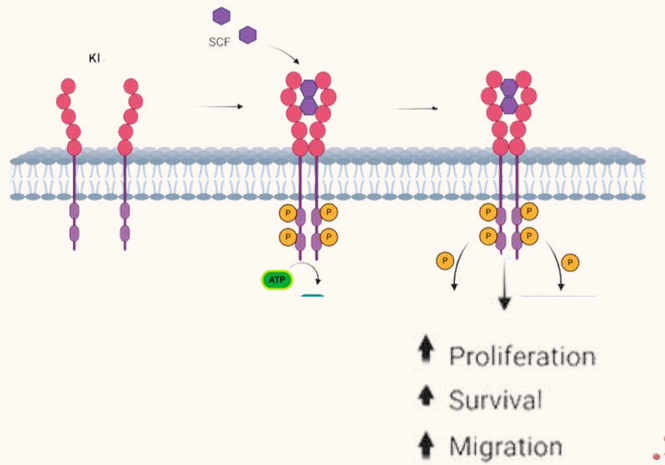
afectació de ≥ 1 organ extracutàni → 90% **adults**, persistent

- Non-Adv (~88%-95%)
- Adv-SM (~5%-12%)

TABLE 2 World Health Organization 5th Edition classification of mastocytosis (reproduced from Khoury et al.).[2,16]

Cutaneous mastocytosis
• Urticaria pigmentosa/maculopapular cutaneous mastocytosis
○ Monomorphic
○ Polymorphic
• Diffuse cutaneous mastocytosis
• Cutaneous mastocytoma
○ Isolated mastocytoma
○ Multilocalized mastocytoma
Systemic mastocyosis
• Bone marrow mastocytosis
• Indolent systemic mastocytosis
• Smoldering systemic mastocytosis
• Aggressive systemic mastocytosis
• Systemic mastocytosis with an associated hematologic neoplasm
• Mast cell leukemia
Mast cell sarcoma

- **Mutació somàtica de guany de funció al gen KIT**
  - Gen KIT: proliferació, maduració, adhesió i supervivència dels mastòcits
  - **Més freqüent (95%): D816V**
  - (<5%): V560G, D815K, D816Y, insVI815-816, D816F, D816H i D820G.



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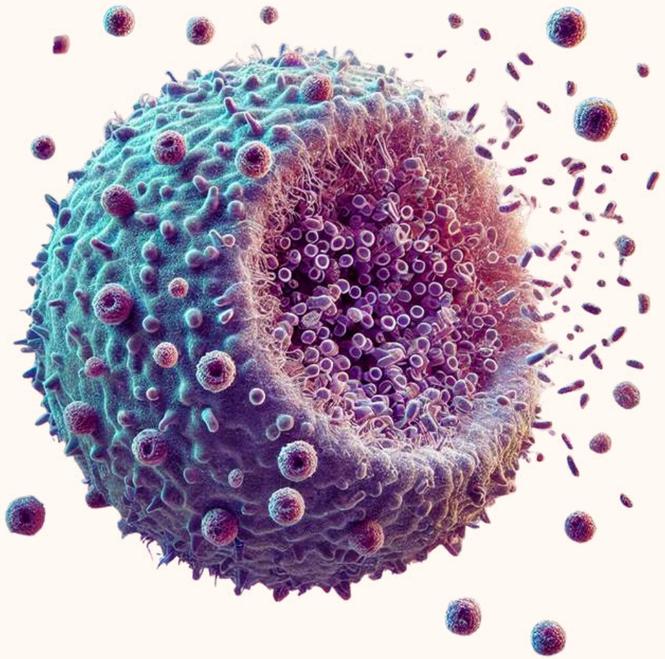

Clínica

Bellvitge
Hospital Universitari

MASTOCITOSI

Clínica[1]

Expressió fenotípica **HETEROGENIA** 2º als efectes locals o a distancia dels mediadors sobre els **DIFERENTS ÒRGANS**

Bellvitge Hospital Universitari

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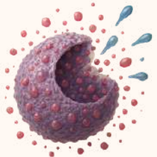

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Alliberació aguda

Bellvitge Hospital Universitari

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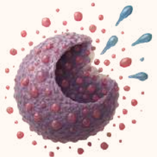

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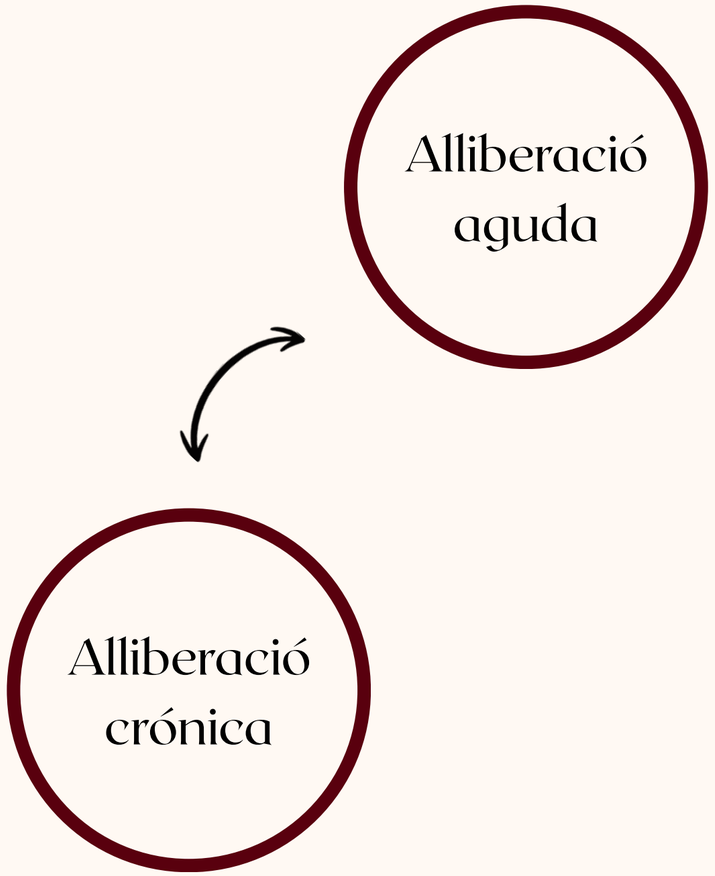

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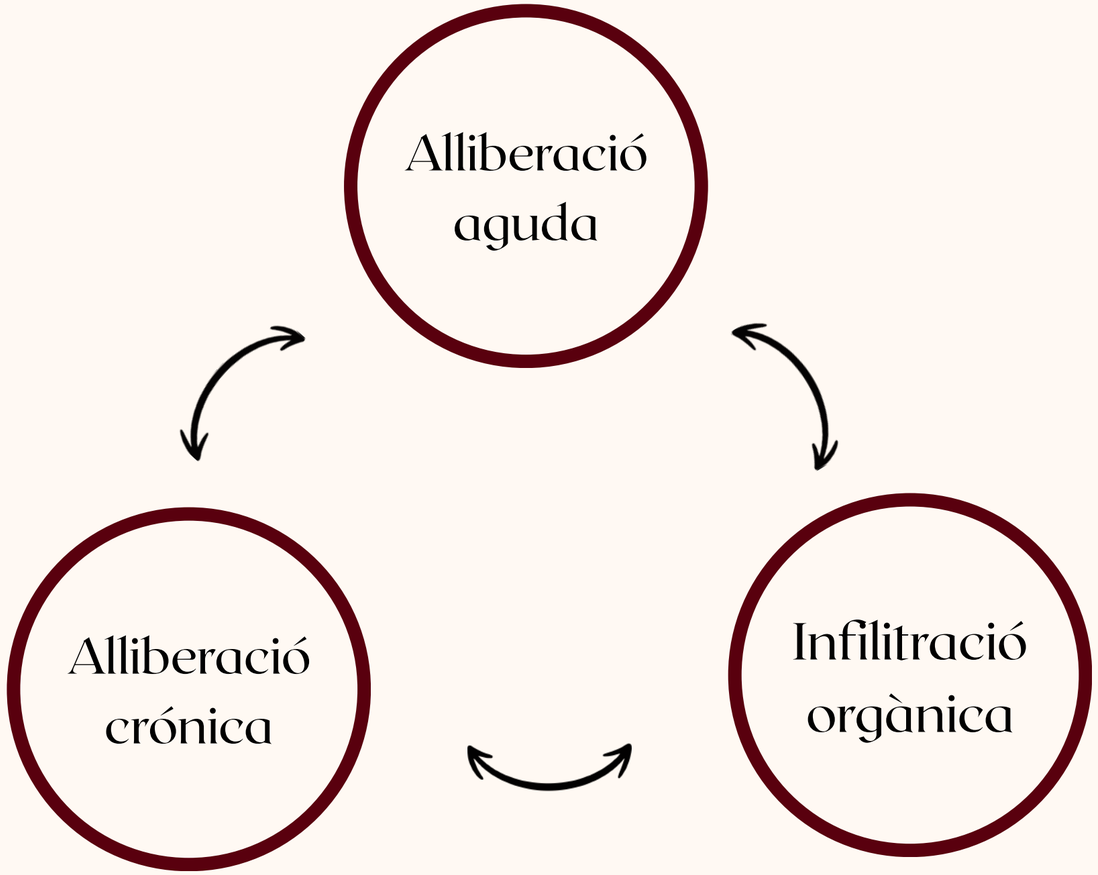

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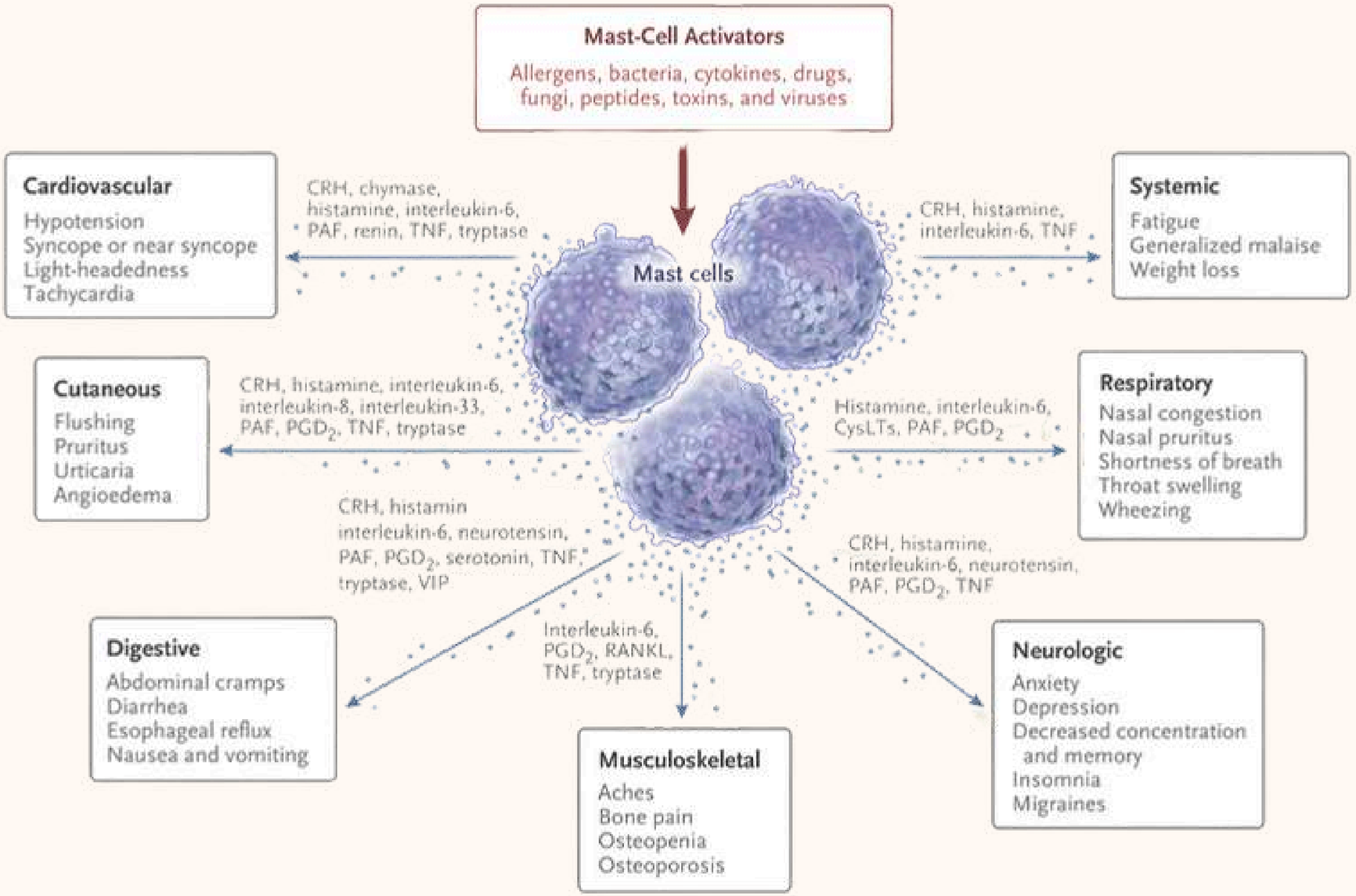

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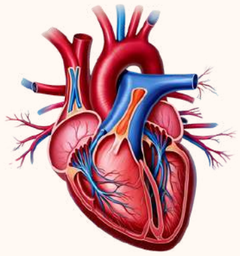

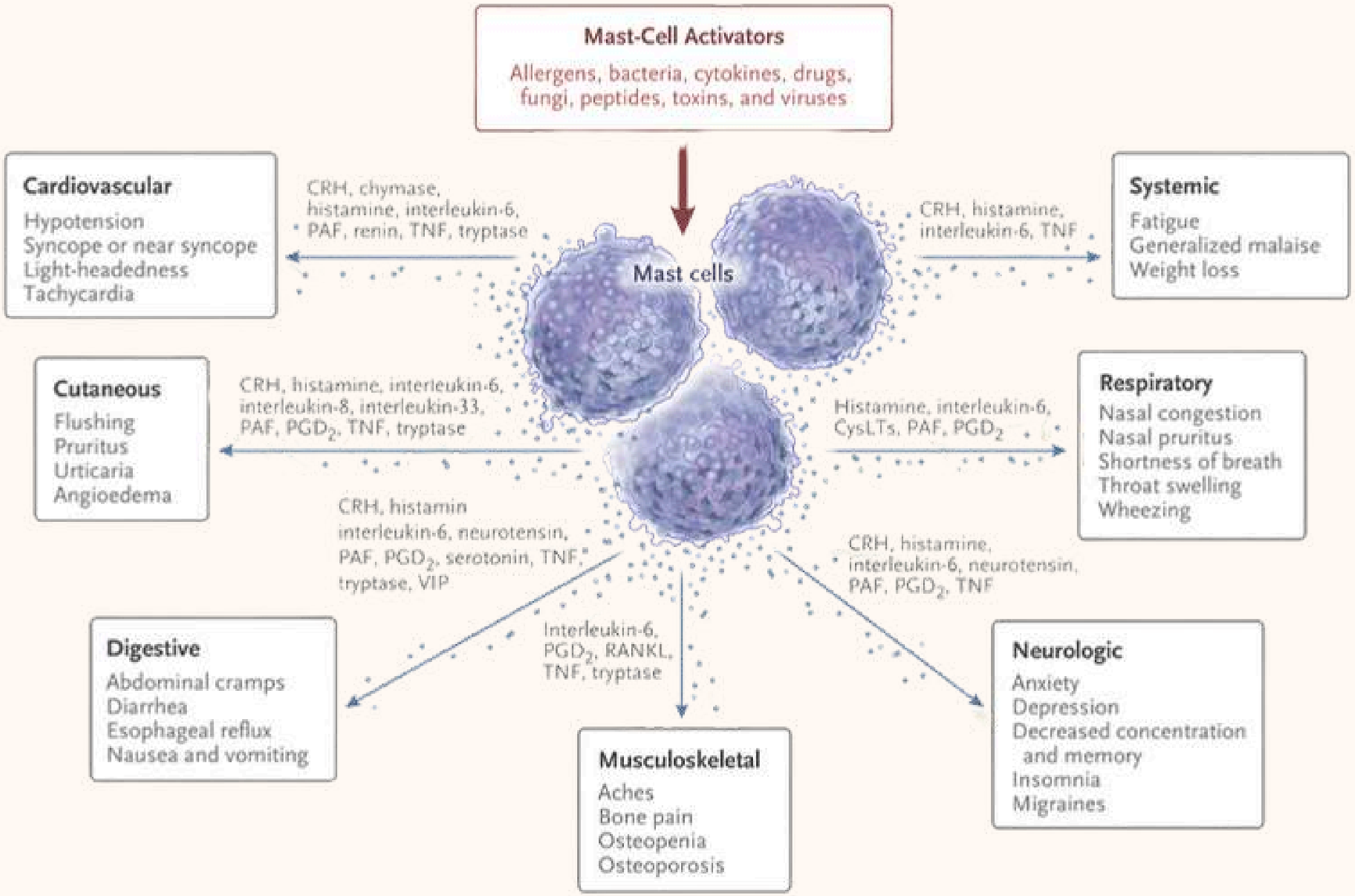

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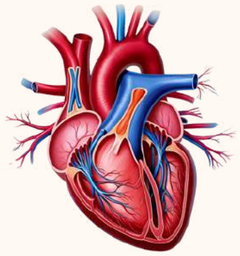

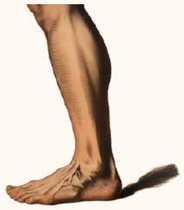

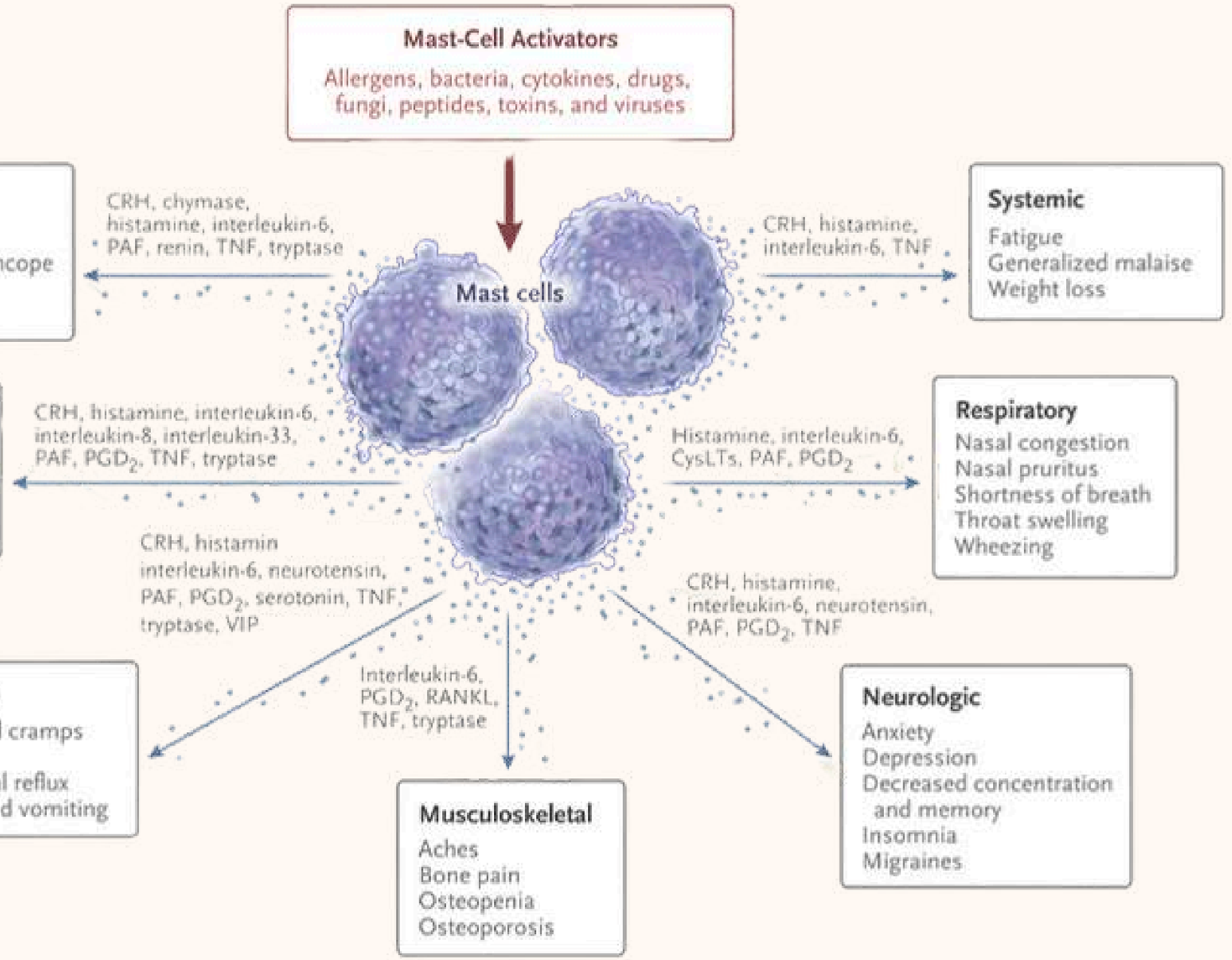

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MASTOCITOSI

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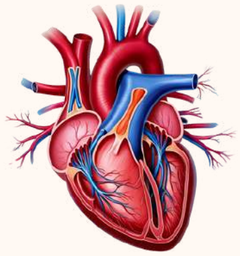

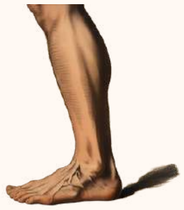

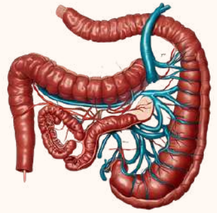

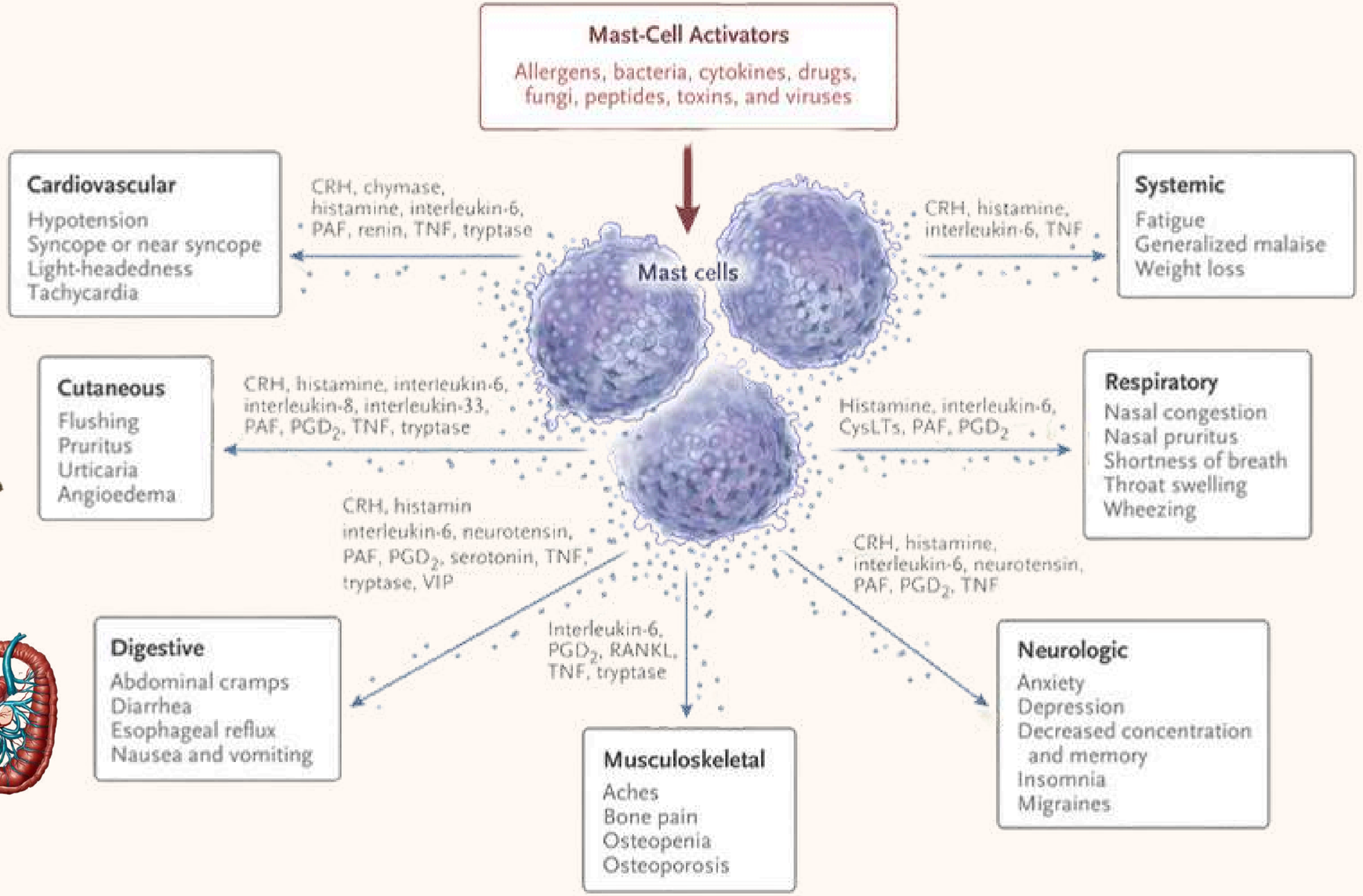

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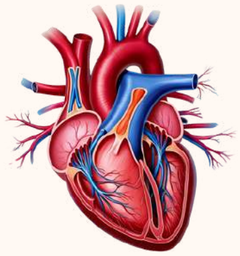

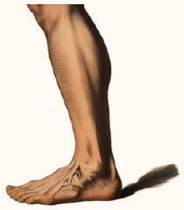

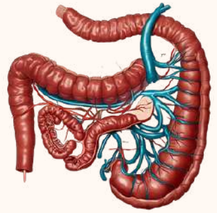

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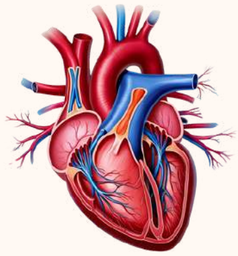

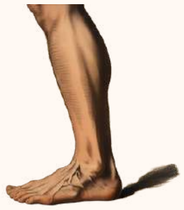

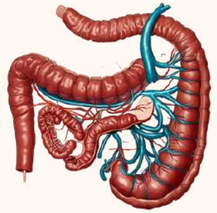

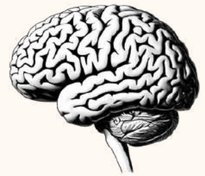

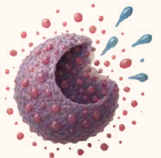

Mast-Cell Activators

Allergens, bacteria, cytokines, drugs, fungi, peptides, toxins, and viruses

Mast cells

Cardiovascular

Hypotension
Syncope or near syncope
Light-headedness
Tachycardia

CRH, chymase, histamine, interleukin-6, PAF, renin, TNF, tryptase

Systemic

Fatigue
Generalized malaise
Weight loss

CRH, histamine, interleukin-6, TNF

Cutaneous

Flushing
Pruritus
Urticaria
Angioedema

CRH, histamine, interleukin-6, interleukin-8, interleukin-33, PAF, PGD_2, TNF, tryptase

Respiratory

Nasal congestion
Nasal pruritus
Shortness of breath
Throat swelling
Wheezing

Histamine, interleukin-6, CysLTs, PAF, PGD_2

CRH, histamin interleukin-6, neurotensin, PAF, PGD_2, serotonin, TNF, tryptase, VIP

CRH, histamine, interleukin-6, neurotensin, PAF, PGD_2, TNF

Digestive

Abdominal cramps
Diarrhea
Esophageal reflux
Nausea and vomiting

Interleukin-6, PGD_2, RANKL, TNF, tryptase

Musculoskeletal

Aches
Bone pain
Osteopenia
Osteoporosis

Neurologic

Anxiety
Depression
Decreased concentration and memory
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MASTOCITOSI

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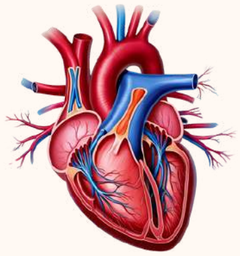

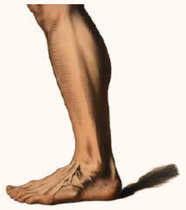

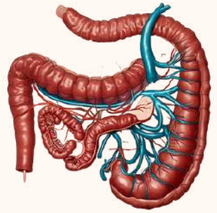

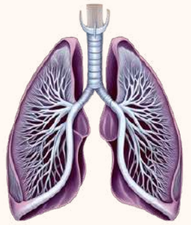

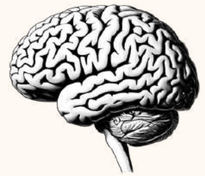

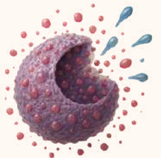

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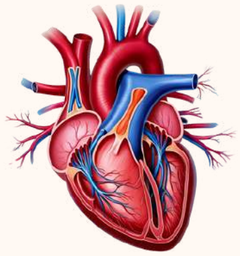

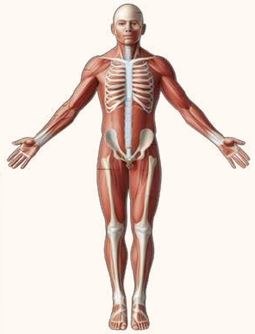

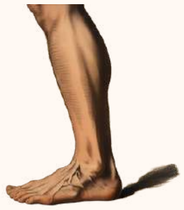

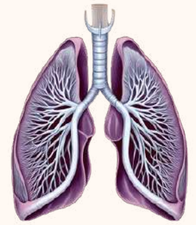

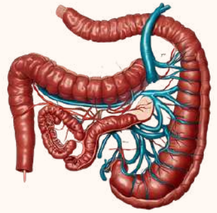

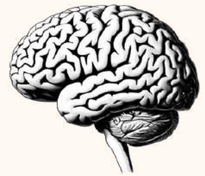

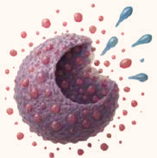

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Respiratory
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Nasal pruritus
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Throat swelling
Wheezing

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CRH, histamin interleukin-6, neurotensin, PAF, PGD_2, serotonin, TNF, tryptase, VIP

CRH, histamine, interleukin-6, neurotensin, PAF, PGD_2, TNF

Digestive
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Diarrhea
Esophageal reflux
Nausea and vomiting

Interleukin-6, PGD_2, RANKL, TNF, tryptase

Musculoskeletal
Aches
Bone pain
Osteopenia
Osteoporosis

Neurologic
Anxiety
Depression
Decreased concentration and memory
Insomnia
Migraines

MASTOCITOSI

Clínica

Símptomes mediadors mastocitaris

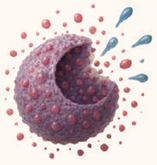
Pell: pruïja, flushing
GI: nàusees, vòmits, diarrea
CV: síncope, mareig, palpitacions
NRL: embotament, cefalea

Anafilaxia
Osteopènia +/-osteoporosis
Constitucional

INFILITRACIÓ ORGÀNICA (2º A MC):
-Osteòlisis amb **fx patològica**
-Linfadenopaties
-Esplenomegalia/hipersplenisme
-Hepatomegàlia/ascites
-Malabsorbció

Agressivitat

Pre-diagnosis SM
BMM / ISM
SMM
ASM + associat a malaltia hematològica
Leucèmia de MC



¿Quin símptoma NO es freqüent en pacients amb MS?

- FLUSHING
- PERDUA DE VISIÓ
- DIARREA
- DOLOR OSSI

¿Quin símptoma NO es freqüent en pacients amb MS?

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MASTOCITOSI

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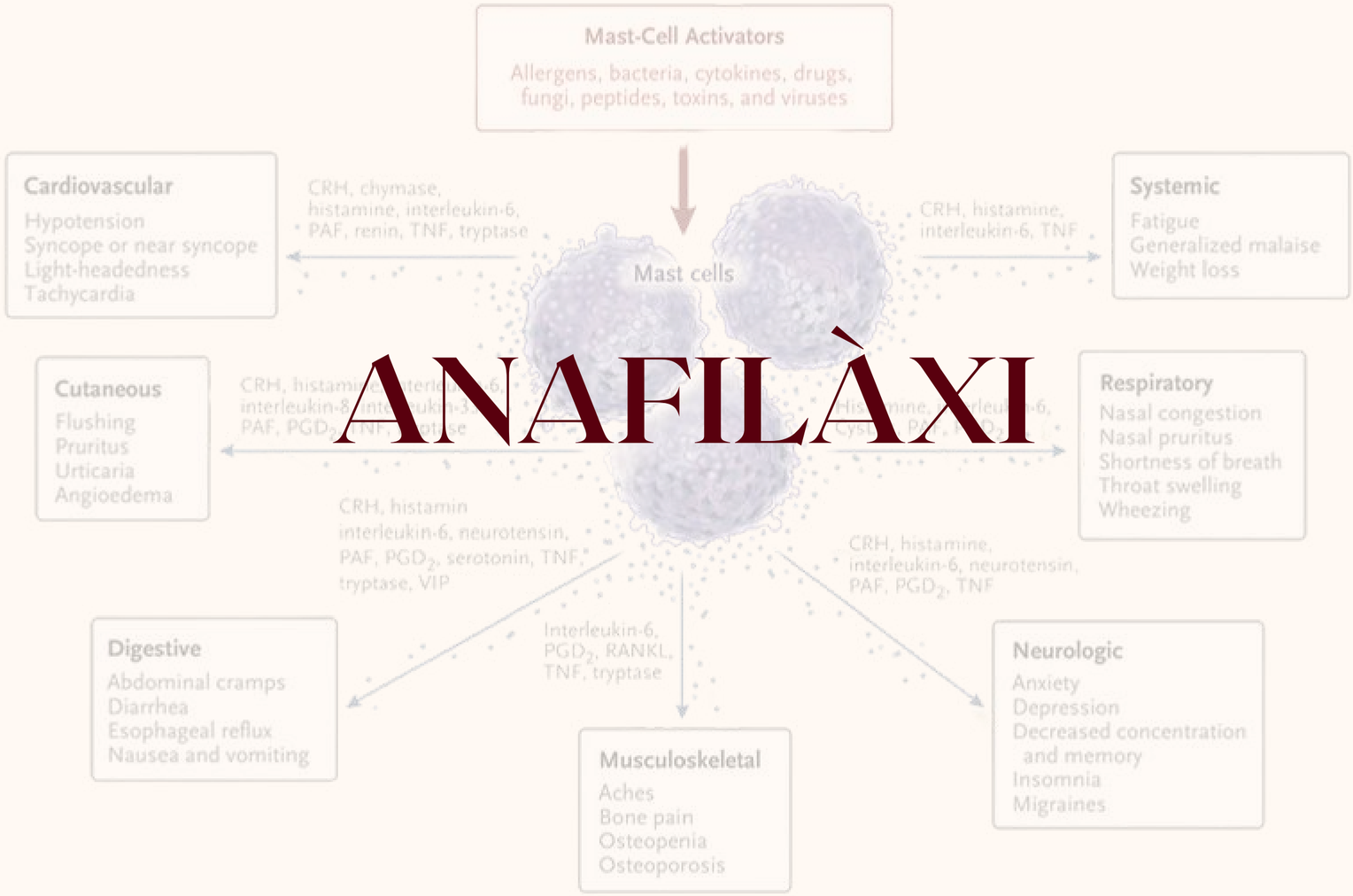

ANAFILÀXI

MASTOCITOSI

ANAFILÀXI

MS
20%- 49%

Sans
0,05-2%

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Hospital Universitari

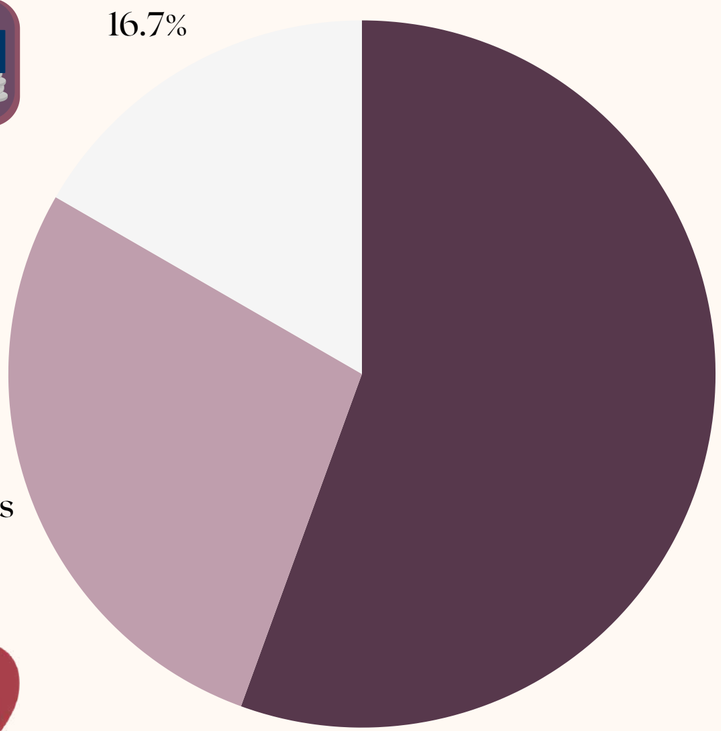
MASTOCITOSI

MS
20%- 49%

Sans
0,05–2%

ANAFILÀXI

Fàrmacs
16.7%



Himenòpters
55.6%

Aliments
27.8%

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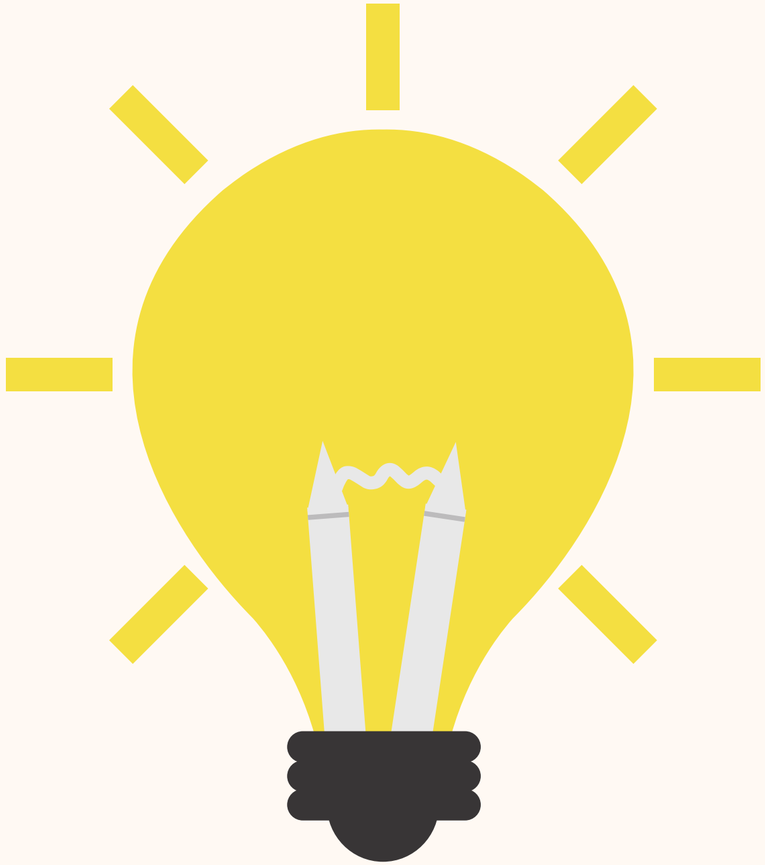
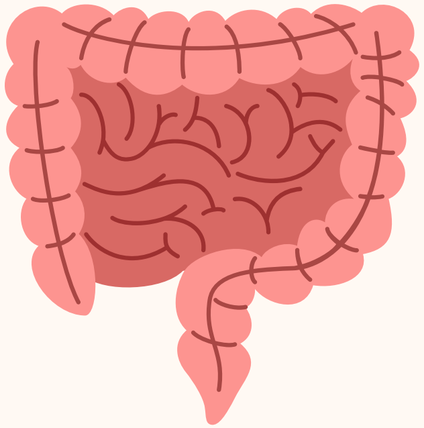
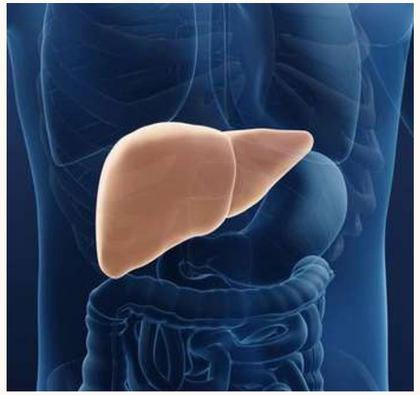


Símptomes GI: diarrea, náusees, reflux

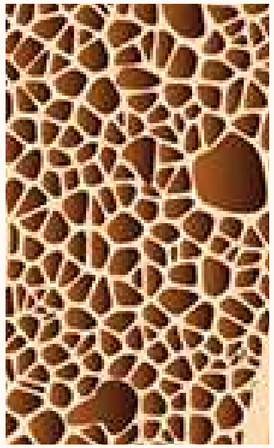


Podria ser MS!



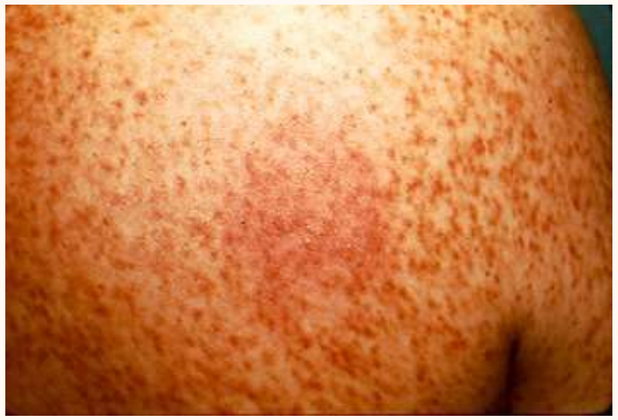
Hepato/esplenomegàlia
Citopènies

Osteoporosi en gent jove

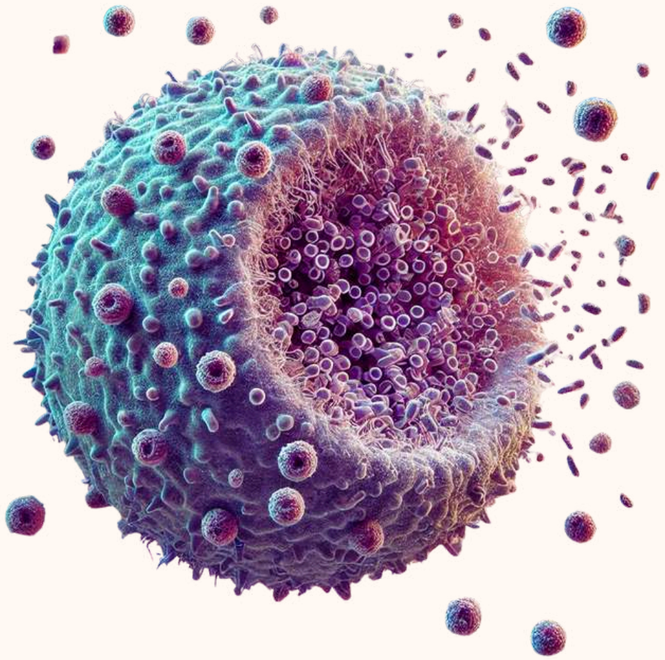


♂

Anafilaxi idiopàtica
Al·lèrgia a verí d'himenòpters



Lesions maculopapulars
Flushing



Diagnòstic

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MASTOCITOSI SISTÈMICA

CRITERIS DIAGNÒSTICS

WHO 2022

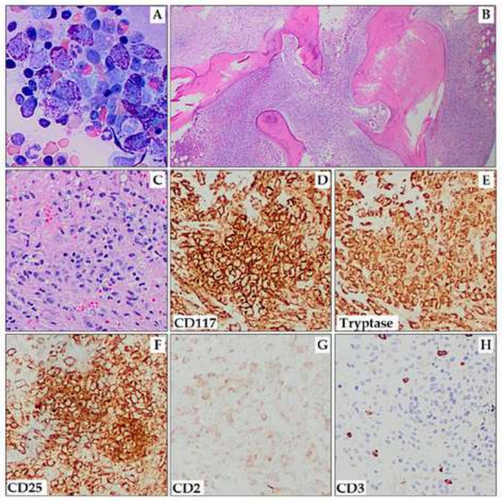
1 criteri **major** + 1 criteri **menor**

o

≥ 3 criteris **menors**

Criteri major

Infiltrats multifocals densos de mastòcits en BMO (≥**15 mastòcits en agregats**)



Criteris menors

- ≥25% de mastòcits **atípics**
- Mastòcits **CD25+, CD2+ i/o CD30+**
- Mutació de **KIT D816V** o altra mutació activadora de KIT
- Triptasa sèrica basal >**20 ng/ml**

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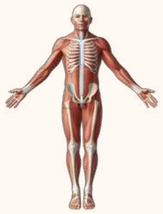
Valent P, Akin C, Hartmann K, Alvarez-Twose I, Brockow K, Hermine O, etal. Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal. Hemasphere. 2021 Oct 13;5(11):e646.

MASTOCITOSI SISTÈMICA

BMM: bone marrow mastocytosi
ISM: indolent systemic mastocytosi
SSM: smoldering systemic mastocytosi
ASM: aggressive systemic mastocytosi
SM-AMN: systemic mastocytosi with associated myeloid neoplasm
MCL: mast cell leukemia



- Es divideix en **6 subtipus**
- Requereix correlació amb els **B-findings** (“burden of disease”) i els **C-findings** (“cytoreduction-requiring”)

B-FINDINGS (“burden of disease”):

Càrrega mastocitaria alta
Signes de mieloproliferació o mielodisplàsia
Organomegàlia sense dany orgànic

C-FINDINGS (“cytoreduction-requiring”)

- **Citopènies**
- **Hepatopatia i esplenomegalia** amb afectació orgànica
- **Malabsorció intestinal**
- **Osteòlisi** (≥ 2cm) AMB fx patològiques ± dolor ossi

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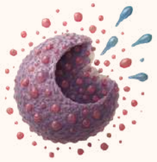
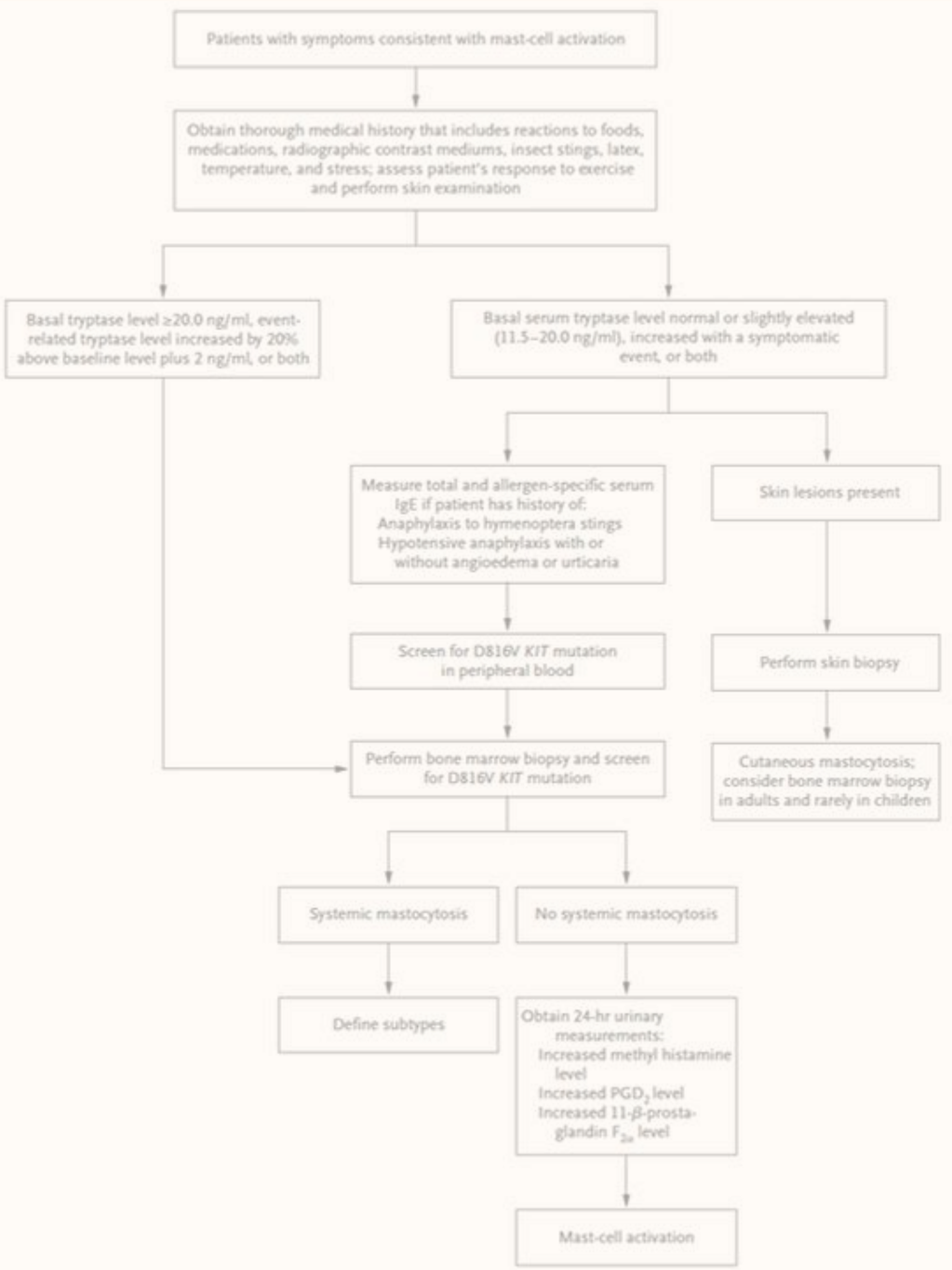


MASTOCITOSI SISTÈMICA

REMA score (2011)

Variable		Puntuación
Género	Hombre	+1
	Mujer	-1
Síntomas clínicos	No urticaria ni angioedema	+1
	Urticaria, prurito y/o angioedema	-2
	Presíncope o síncope	+3
Triptasa sérica basal	<15 ng/ml	-1
	>25 ng/ml	+2
Puntuación <2 = baja probabilidad de MS **Puntuación ≥2 = alta probabilidad de MS**		
Sensibilidad: 0.92 – VPP: 0.89 Especificidad: 0.81 – VPN: 0.87		



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Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. N Engl J Med. 2015 Nov 5;373(19):1885-6. doi: 10.1056

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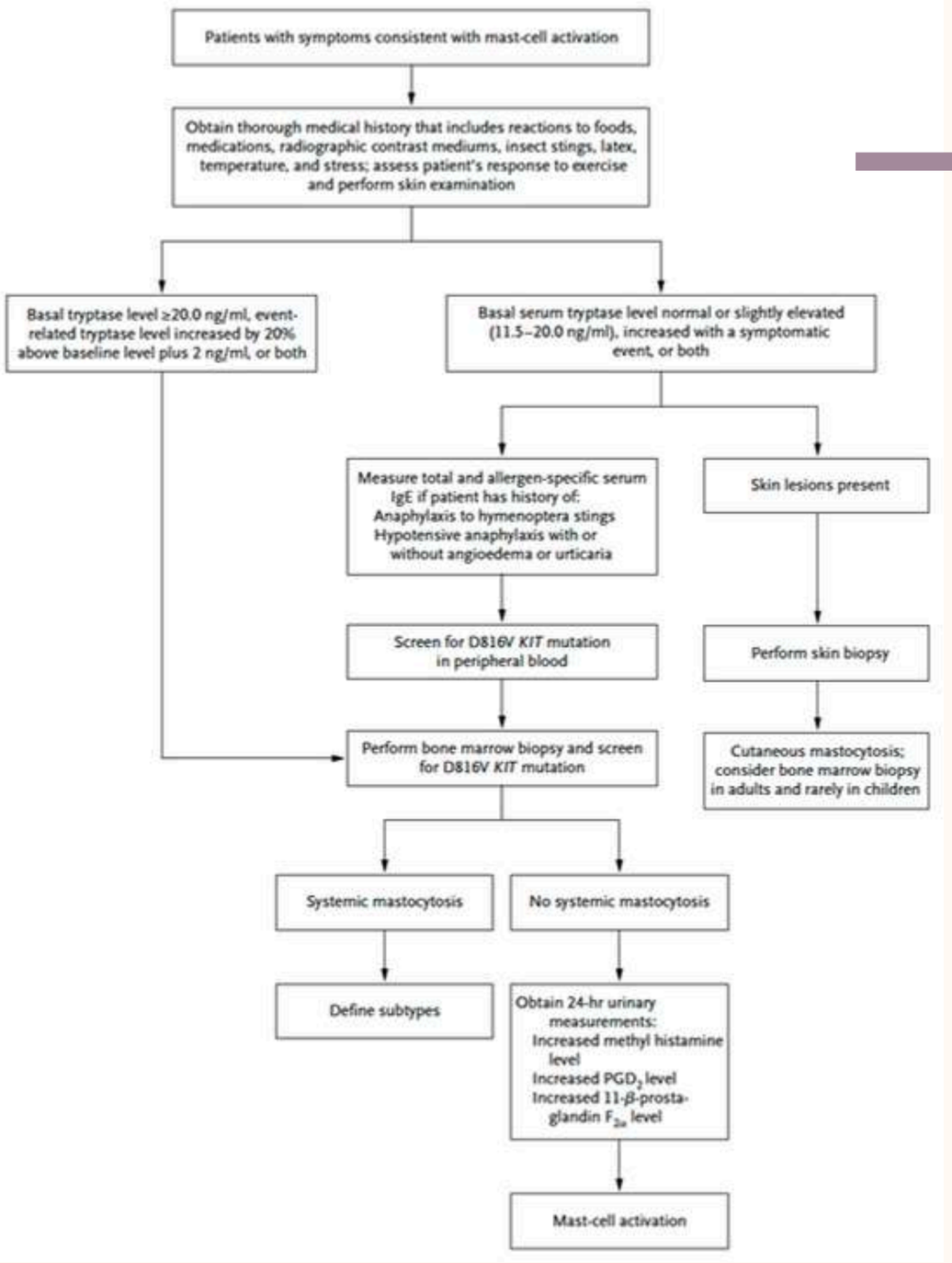

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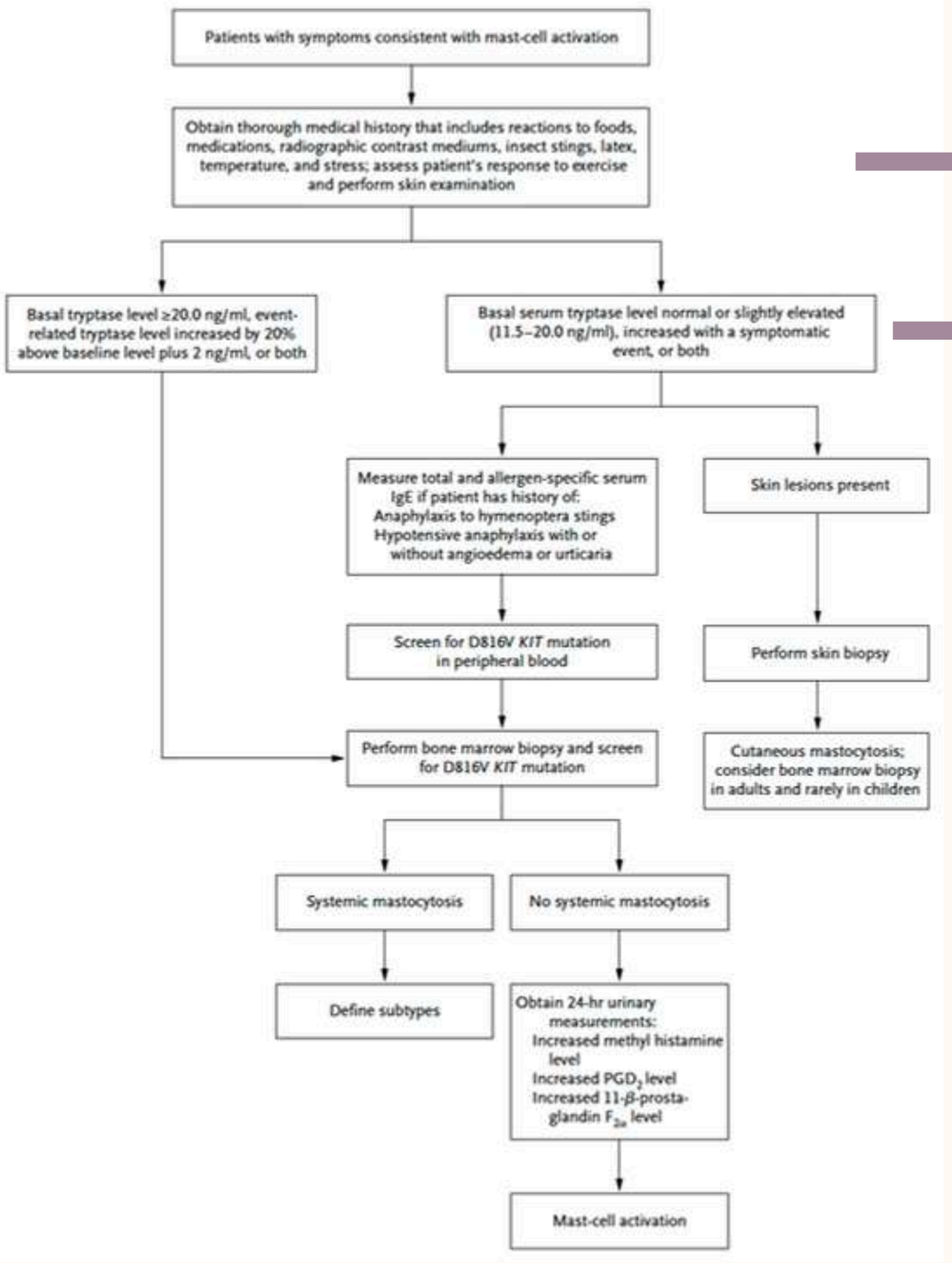

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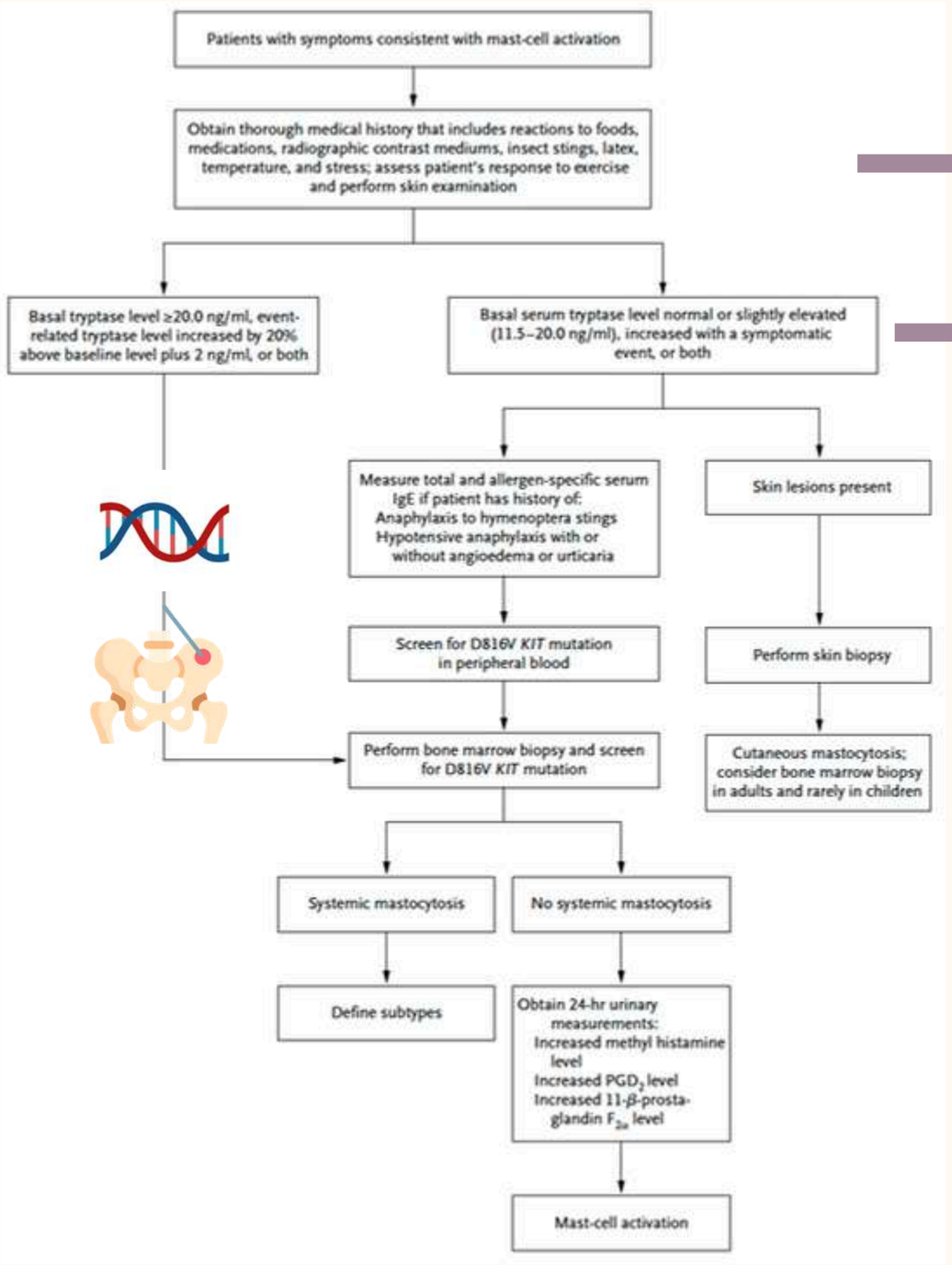

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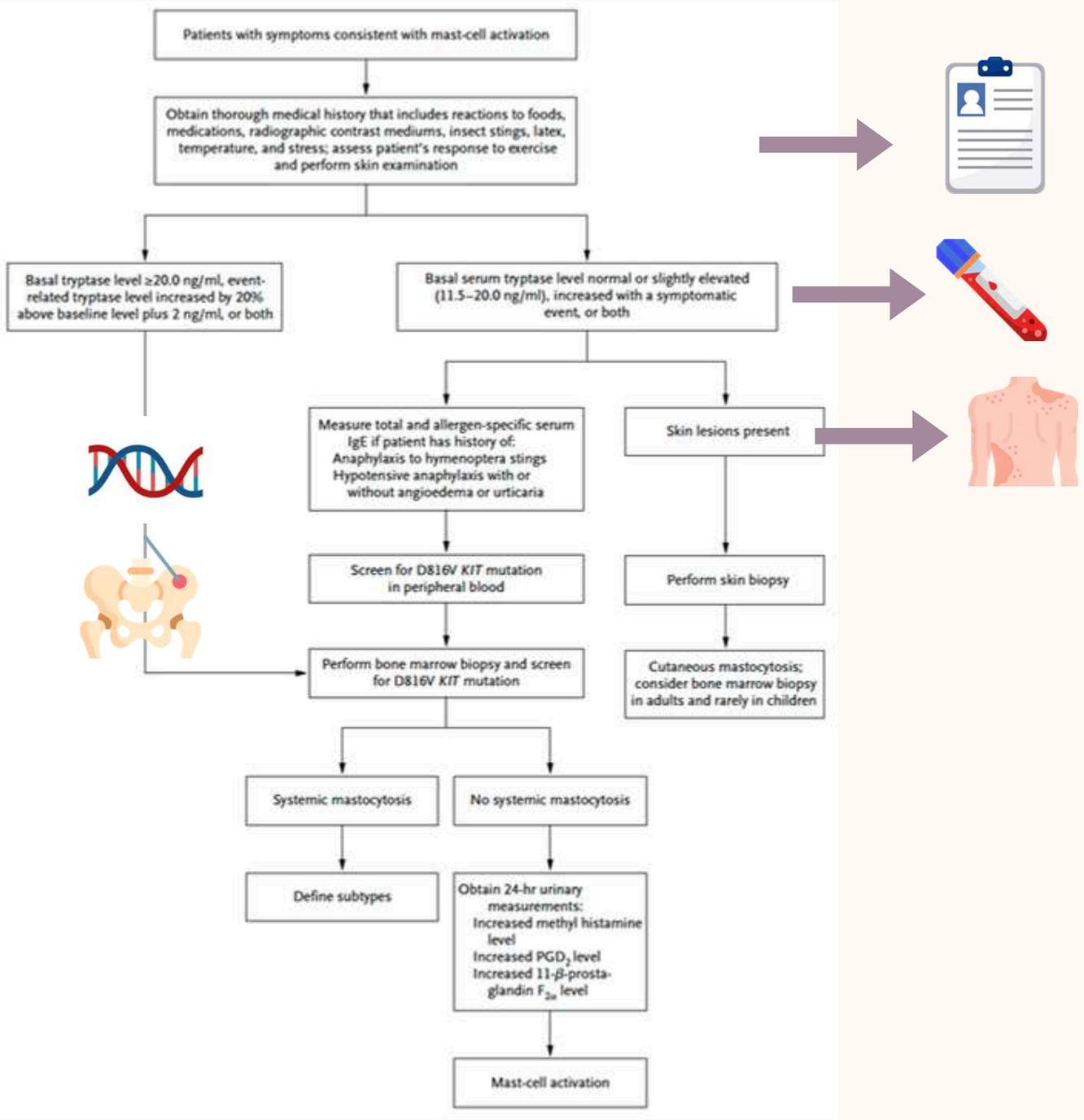

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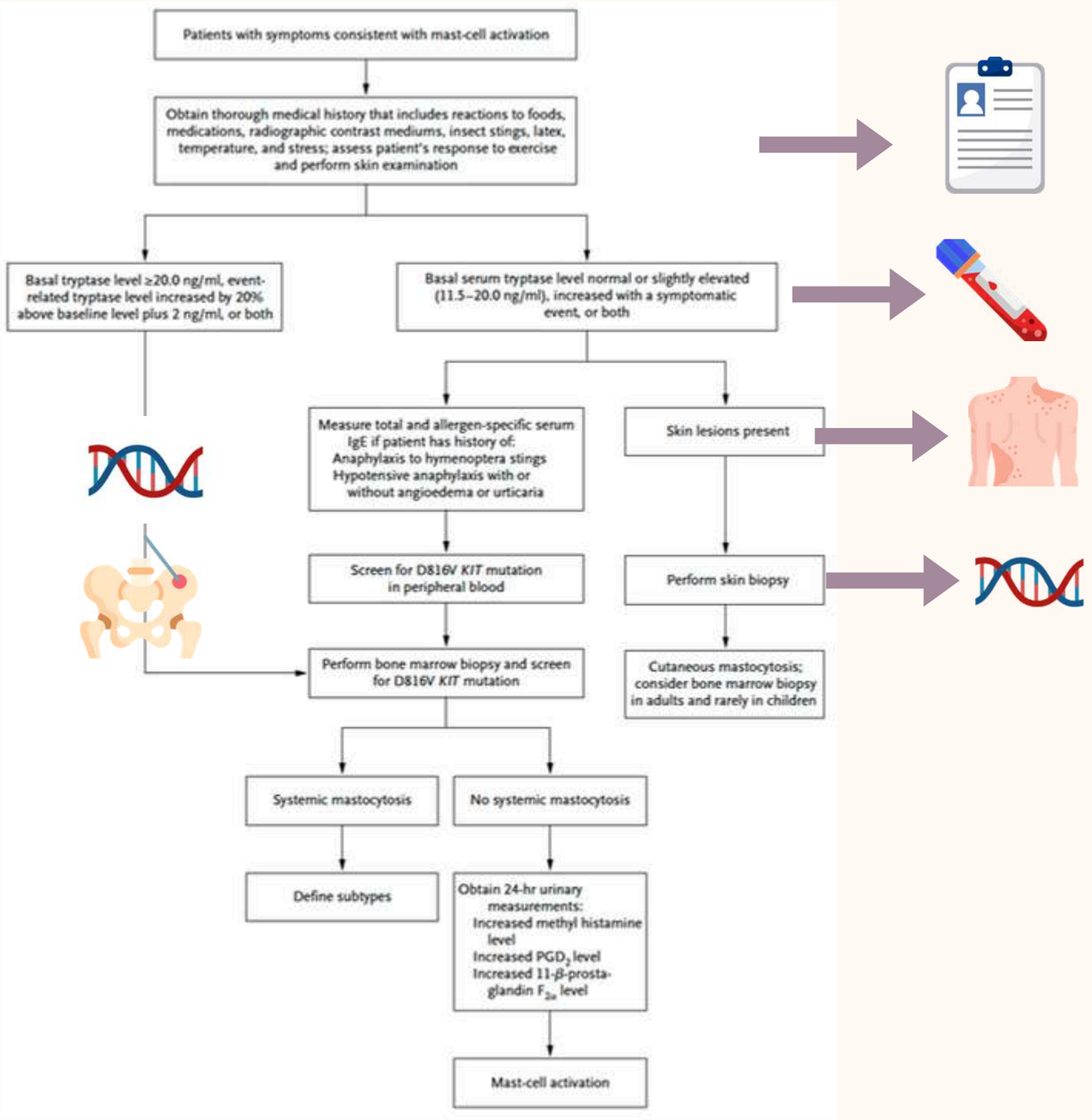

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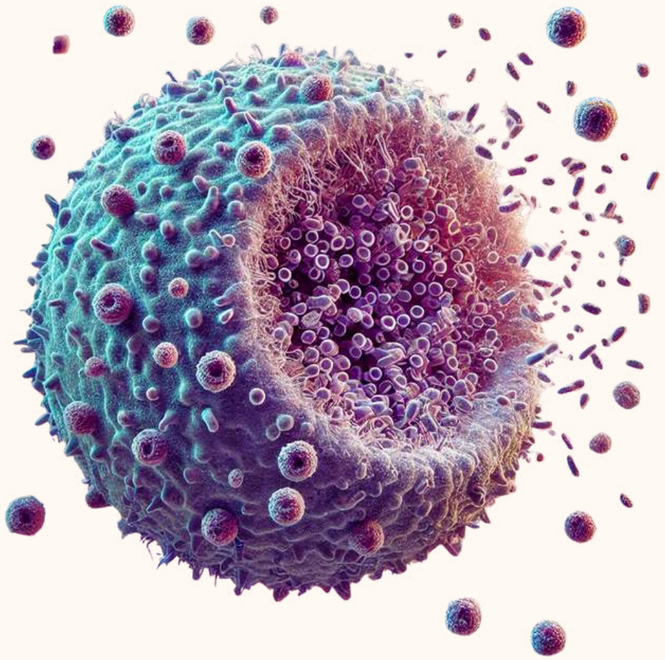
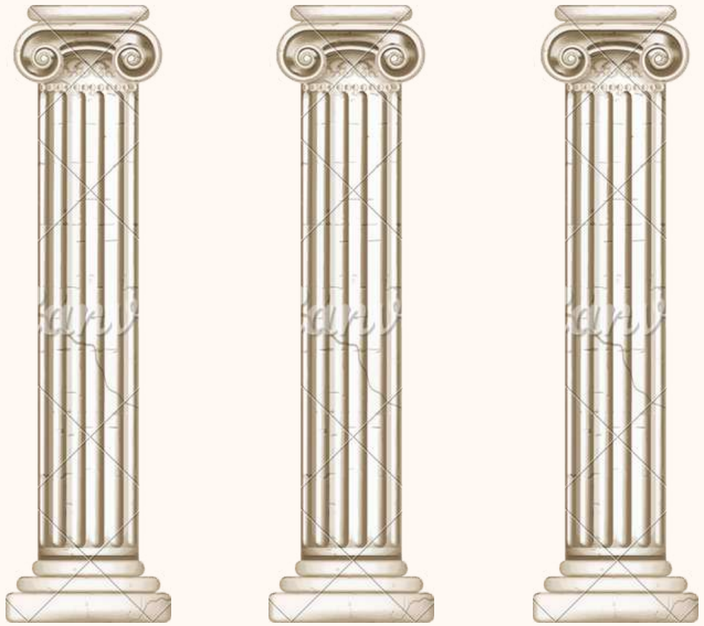


Maneig



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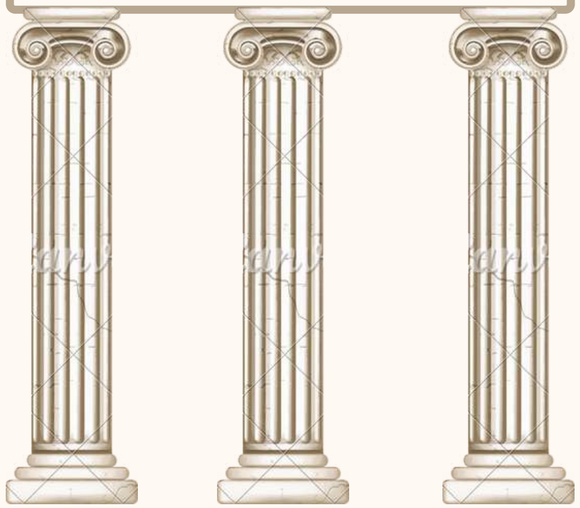
MANEIG GLOBAL

3 pilars fundamentals



Educació sanitaria

Tractament

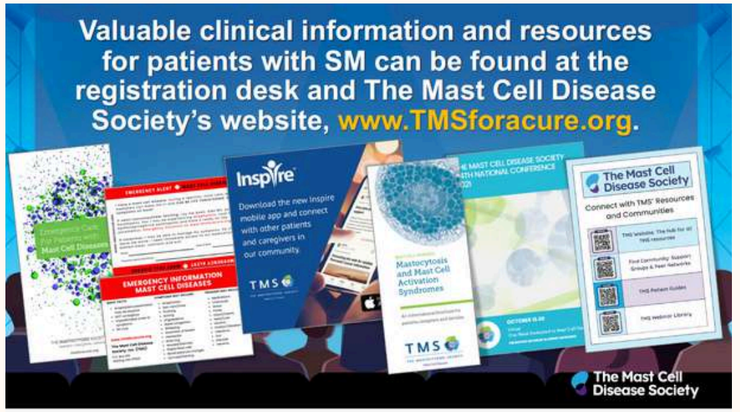
Evitació desencadenants

MANEIG GLOBAL

Educació sanitaria

- Coneixement sobre la malaltia
- Pronòstic
- Resoldre dubtes
- Recolzament psicològic i social
- Informació fiable
    - associacions, fòrums, webs...

mastocitosis
ASOCIACIÓN ESPAÑOLA DE MASTOCITOSIS
Y ENFERMEDADES RELACIONADAS



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Evitació desencadenants

- Identificar potencials triggers: himenòpters, fàrmacs, alcohol, estressos..
- Avaluació **individual** del risc: protocols **específics i individualitzats**
  - Premedicació si cal
  - No prohibir cap fàrmac empiricament: AINEs, ATB...

Medication Type	Avoid or Use With Caution		Medications That Are Typically Tolerated	
General Medications	• Alcohol • Amphotericin B • Dextran • Dextromethorphan • Polymyxin B	• Quinine • Vancomycin IV • Alpha-adrenergic blockers • Beta-adrenergic blockers	• Calcium channel blockers • Centrally-acting alpha 2 adrenergic stimulants • Aldosterone antagonists	
Pain Medications	• Opioid narcotics (may be tolerated by some individuals) • Ketorolac	• NSAIDs (unless the patient is already taking a drug from this class)	• Fentanyl (may require adjunctive treatment with ondansetron) • Tramadol	
General Anesthetics	• Atracurium • Doxacurium	• Rocuronium • Mivacurium	• Pancuronium • Vecuronium	
Local Anesthetics	• Benzocaine • Chloroprocaine	• Procaine • Tetracaine	• Bupivacaine • Lidocaine • Levobupivacaine	• Mepivacaine • Prilocaine • Ropivacaine
Intraoperative Induction Medications			• Ketamine • Midazolam • Propofol	
Inhaled Anesthetics			• Sevoflurane	

MANEIG GLOBAL

Tractament simptomàtic

Organ Involvement/Symptom	First Line	Additional Treatments
Skin: pruritus, flushing, urticaria, angioedema dermatographism	H_1R antagonist and H_2R antagonist	2. Leukotriene receptor antagonist 3. Aspirin 4. Ketotifen 5. Cromolyn sodium ointment
GI: abdominal pain, cramping, diarrhea, heartburn, nausea, vomiting	H_2R antagonist	2. Cromolyn sodium 3. Proton pump inhibitor 4. Leukotriene receptor antagonist 5. Ketotifen
Neurologic: headache, cognitive impairment (eg, brain fog, poor concentration and memory), depression	H_1R and H_2R antagonist	2. Cromolyn sodium 3. Aspirin 4. Ketotifen
Cardiovascular/Pulmonary: presyncope, tachycardia, wheezing, throat swelling	H_1R and H_2R antagonist	2. Corticosteroids 3. Omalizumab
Hypotensive episodes/anaphylaxis	Epinephrine IM (acutely), supine positioning	Prevention: VIT, Rush desensitization, omalizumab
Osteopenia/Osteoporosis	Supplemental calcium and vitamin D, bisphosphonate; bone mineral density assessment	Denosumab, interferon-α inhibitor, cytoreductive agent; vertebroplasty/kyphoplasty

1. NCCN. https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf; 2. Mesa RA, et al. Cancer. 2022;128(20):3691-3699.

MANEIG GLOBAL

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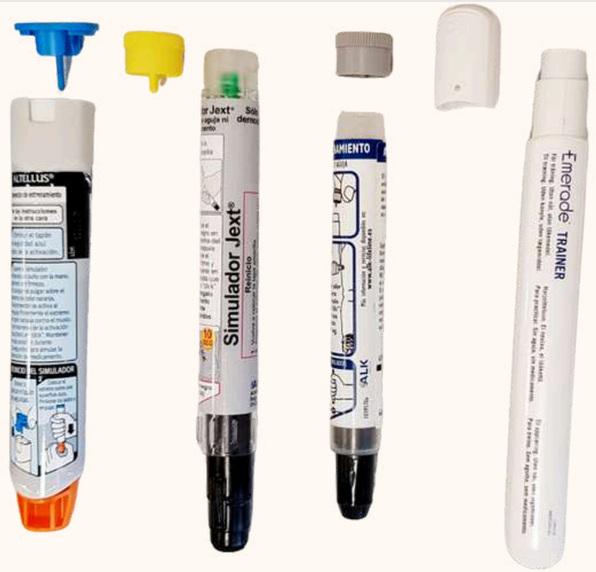
KIT D'EMERGÈNCIA:

-Adrenalina 0.5 mg IM x 2

-Cetirizina 10 mg 2 cp

-Prednisona 30 mg 2 cp (mg/kg/pes)



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MANEIG GLOBAL

Tractament dirigit

Organ Involvement/Symptom	First Line	Additional Treatments
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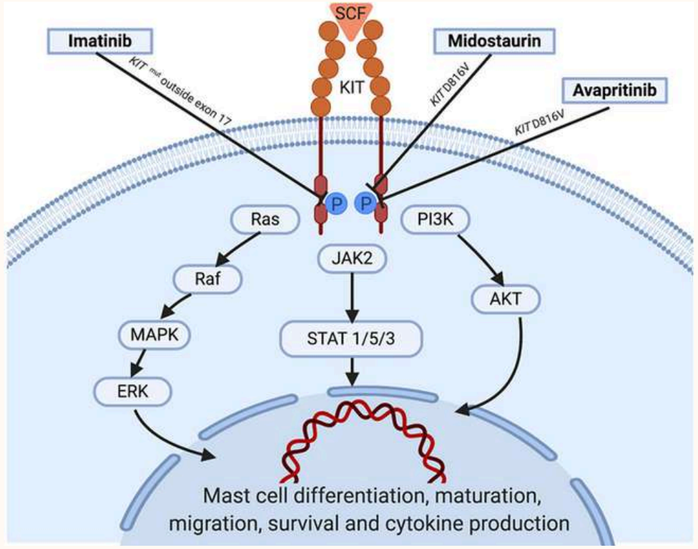

inhibició selectiva las mutacions activadores de KIT

¿Quin es el tractament de 1º linea en un pacient amb dispnea i urticaria en context d'una ANAFILAXI?

- PREDNISONA
- ADRENALINA SC
- FAMOTIDINA
- ADRENALINA IM

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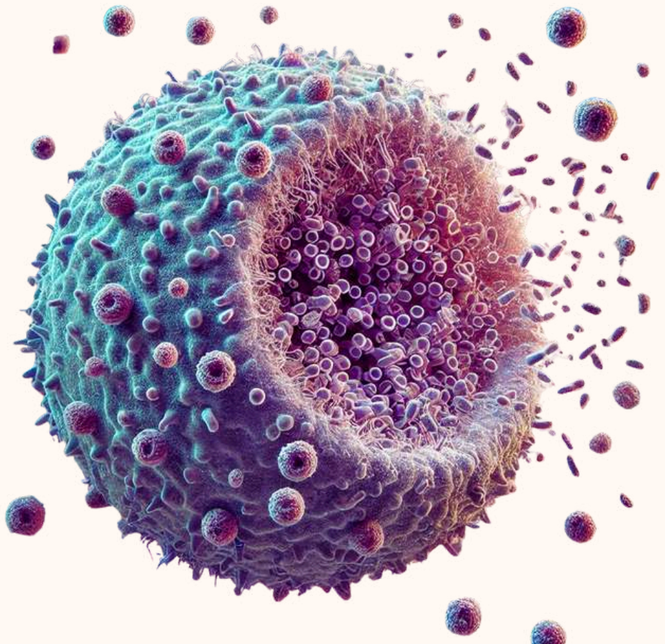

Càrrega de la malaltia

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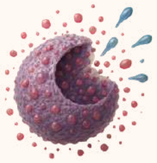
Hospital Universitari

Identificació insuficient i diagnòstic tardà: increment de la càrrega de la malaltia

Temps mig des de inici de símptomes fins al diagnòstic ~6-7 ANYS[1]

1. Ungerstedt J, et al. Cancers (Basel). 2022;14(16)3942; 2. Mikkelsen CS, et al. Dermatol Reports. 2014;6(1):5199; 3. Mesa RA, et al. Cancer. 2022;128(20):3691-3699; 4. Tse KY, et al. J Allergy Clin Immunol. 2024;3(4):100316



Identificació insuficient i diagnòstic tardà: increment de la càrrega de la malaltia

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Causes

Raresa de la malaltia

Espectre de S/S (ampli dx diferencial)

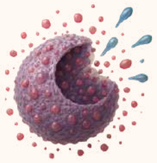
Riscos associats

Anafilaxies mortals

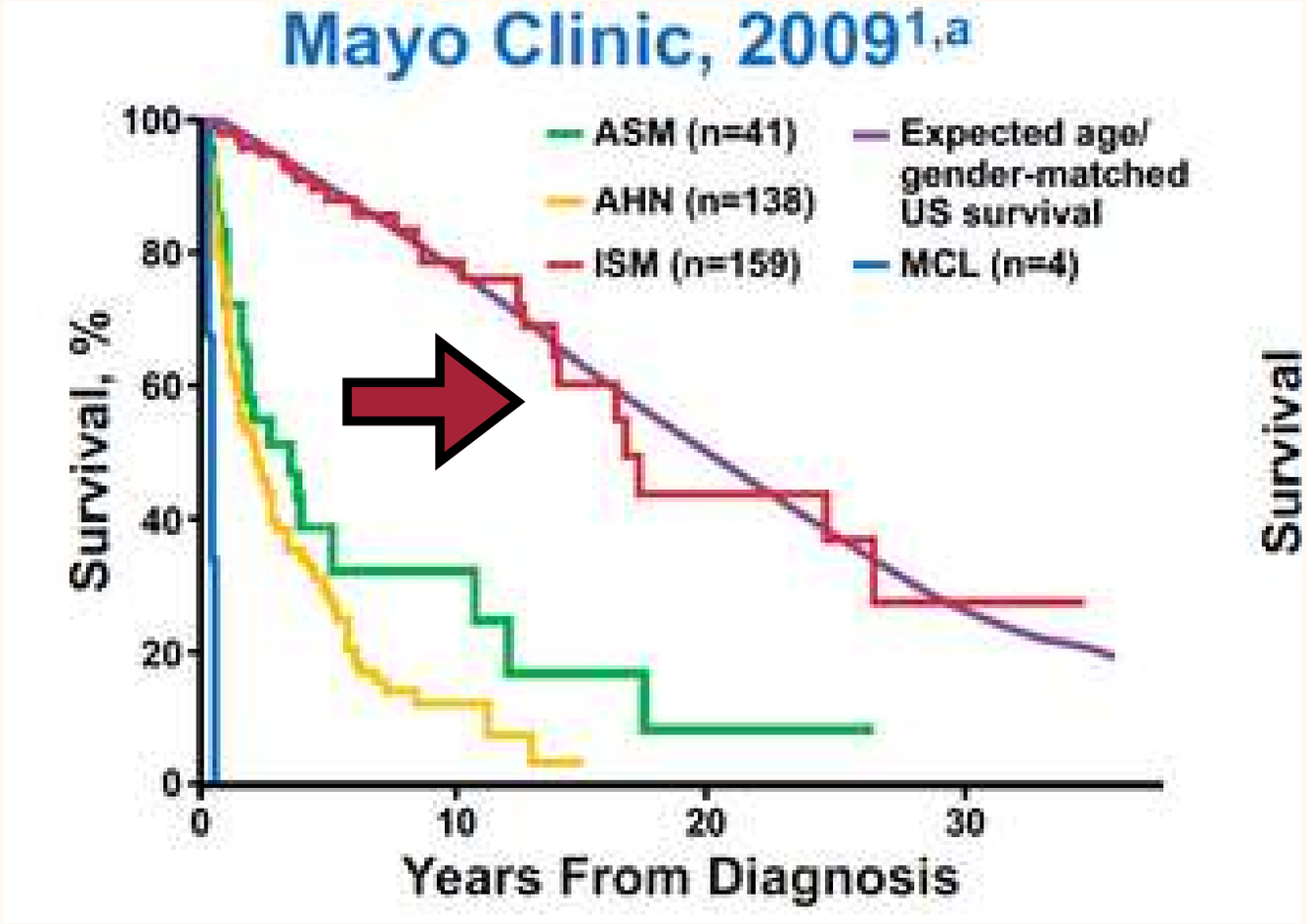
Disfunció orgànica

Osteoporosi

1. Ungerstedt J, et al. Cancers (Basel). 2022;14(16)3942; 2. Mikkelsen CS, et al. Dermatol Reports. 2014;6(1):5199; 3. Mesa RA, et al. Cancer. 2022;128(20):3691-3699; 4. Tse KY, et al. J Allergy Clin Immunol. 2024;3(4):100316



L'esperança de vida en pacients amb MS no avançada és equivalent a la de la població de control

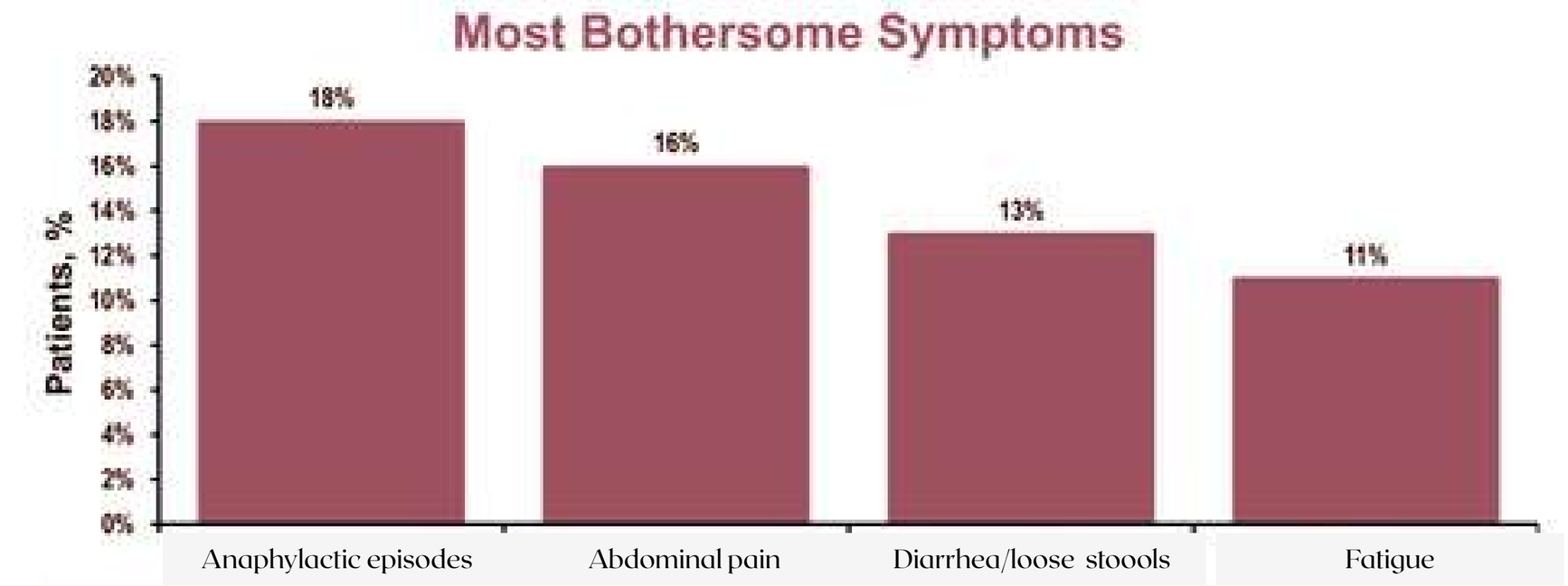


[a]N=342 patients with SM aged ≥18 years, median follow-up 1.7 years

1. Lim K , et al. Blood. 2009;113(23):5727-5736; 2. Cohen SS, et al. Br J Haematol. 2014;166(4):521-528.

1 Característiques cliniques de pacients amb ISM

Els pacients experimenten una mitjana de **14 símptomes** relacionats amb SM al llarg de la seva vida[2]



ISM-SAF[4]

ISM Symptom	Scoring
Abdominal pain	Symptoms scored daily over a 24-hour recall period 0 = no symptom 10 = worst imaginable symptom
Diarrhea[a]	
Nausea	
Spots	
Itching	
Flushing	
Brain fog	
Headache	
Dizziness	
Bone pain	
Fatigue	
TSS (0-110) ≥28 indicates moderate to severe symptoms	

Mesa RA, Sullivan EM, Dubinski D, eta Al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient Survey. Cancer. 2022 Oct;128(20):3691-3699.

1 Característiques cliniques de pacients amb ISM

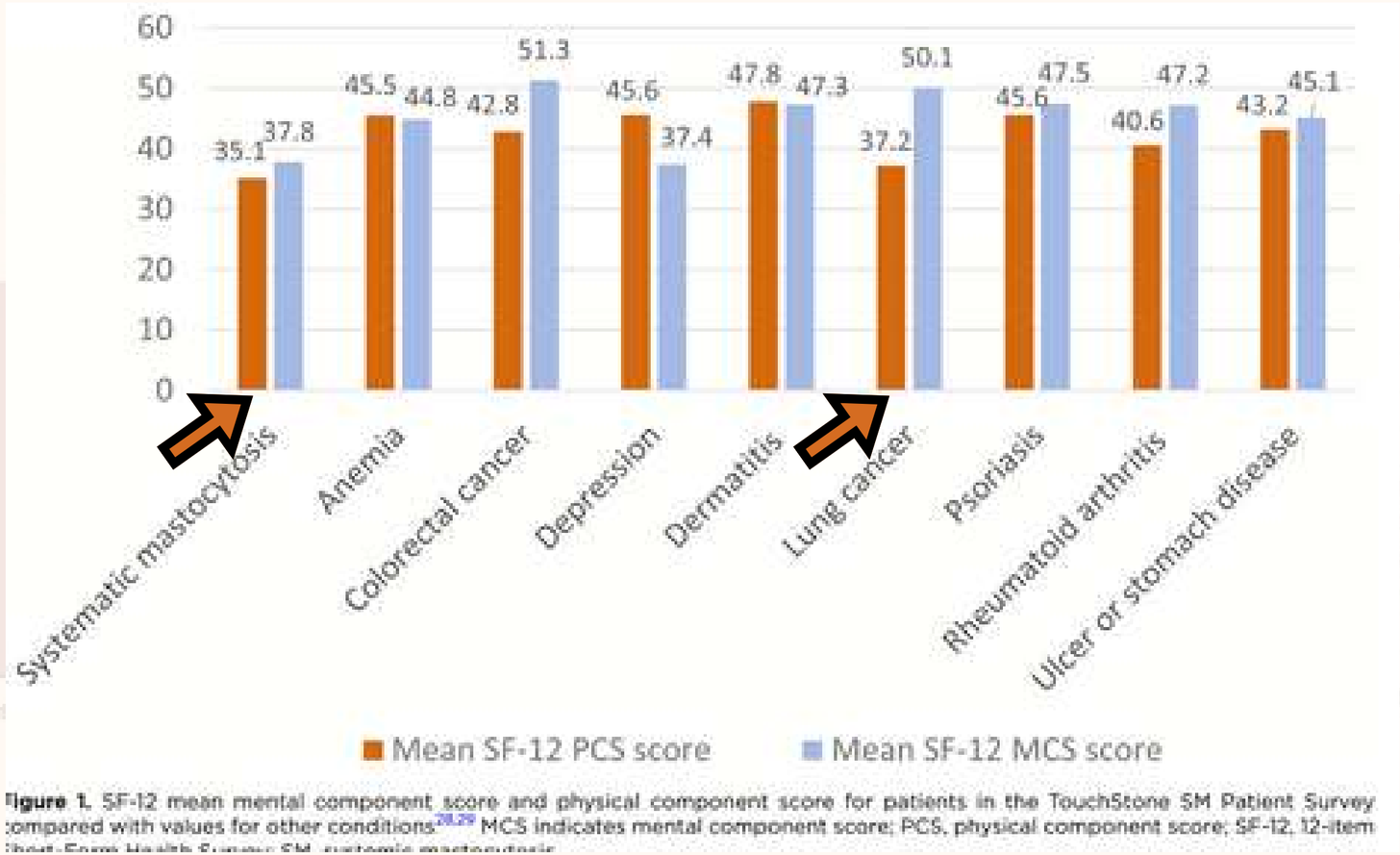


Figure 1. SF-12 mean mental component score and physical component score for patients in the TouchStone SM Patient Survey compared with values for other conditions[28,29] MCS indicates mental component score; PCS, physical component score; SF-12, 12-item

Mesa RA, Sullivan EM, Dubinski D, eta Al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient Survey. Cancer. 2022 Oct;128(20):3691-3699.

1 Característiques cliniques de pacients amb ISM

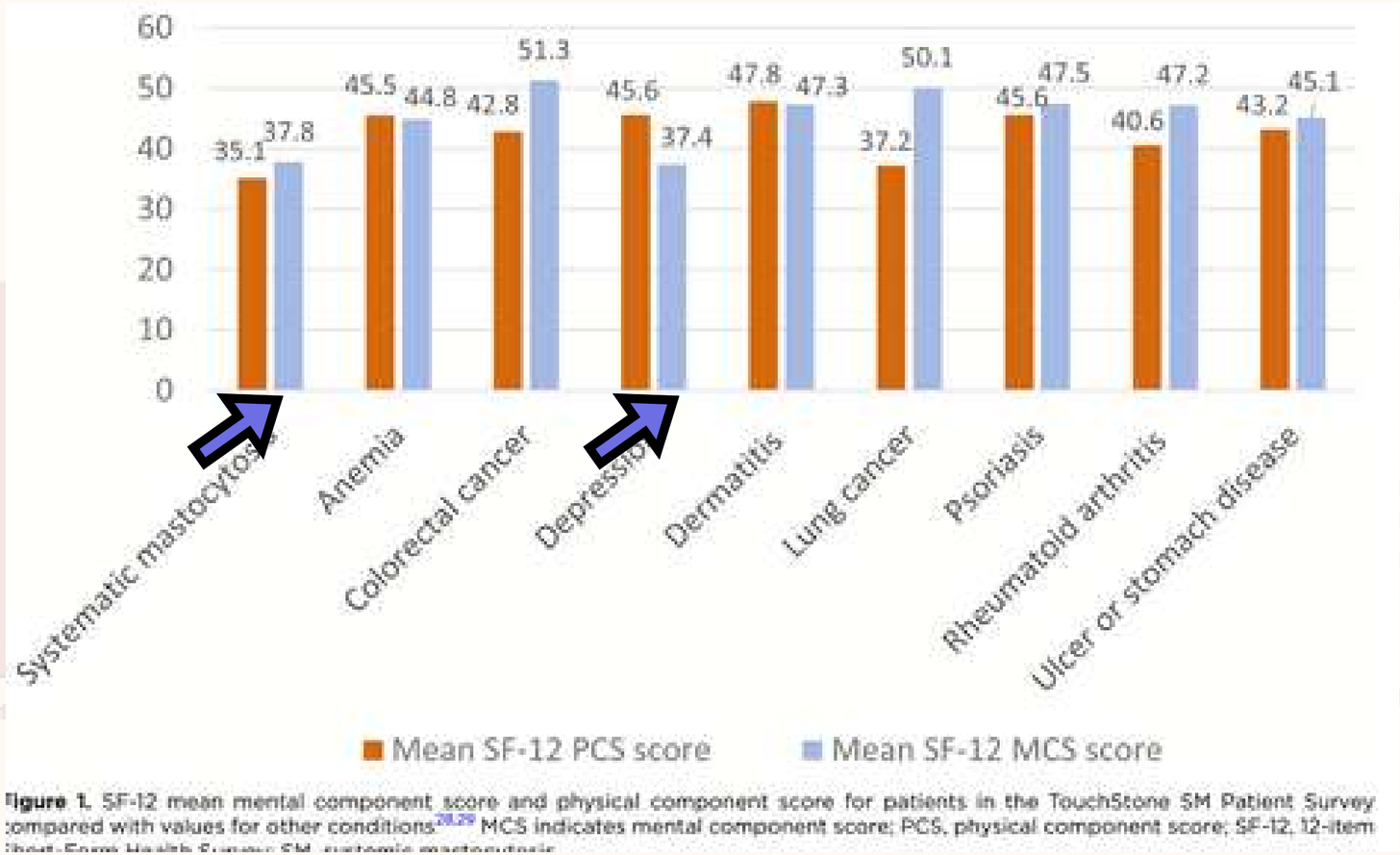


Figure 1. SF-12 mean mental component score and physical component score for patients in the TouchStone SM Patient Survey compared with values for other conditions[28,29] MCS indicates mental component score; PCS, physical component score; SF-12, 12-item

Mesa RA, Sullivan EM, Dubinski D, eta Al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient Survey. Cancer. 2022 Oct;128(20):3691-3699.

2 Pèrdua de productivitat i absentisme laboral

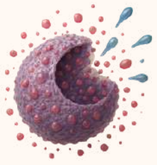
Canvis a la feina relacionat amb MS:

- 54% reducció d'hores de feina
- 27% van deixar la feina
- 16% acomiadats

66%

El **dolor** va **interferir** amb la **feina**

64% dels enquestats evitaven sortir de casa degut als símptomes de MS



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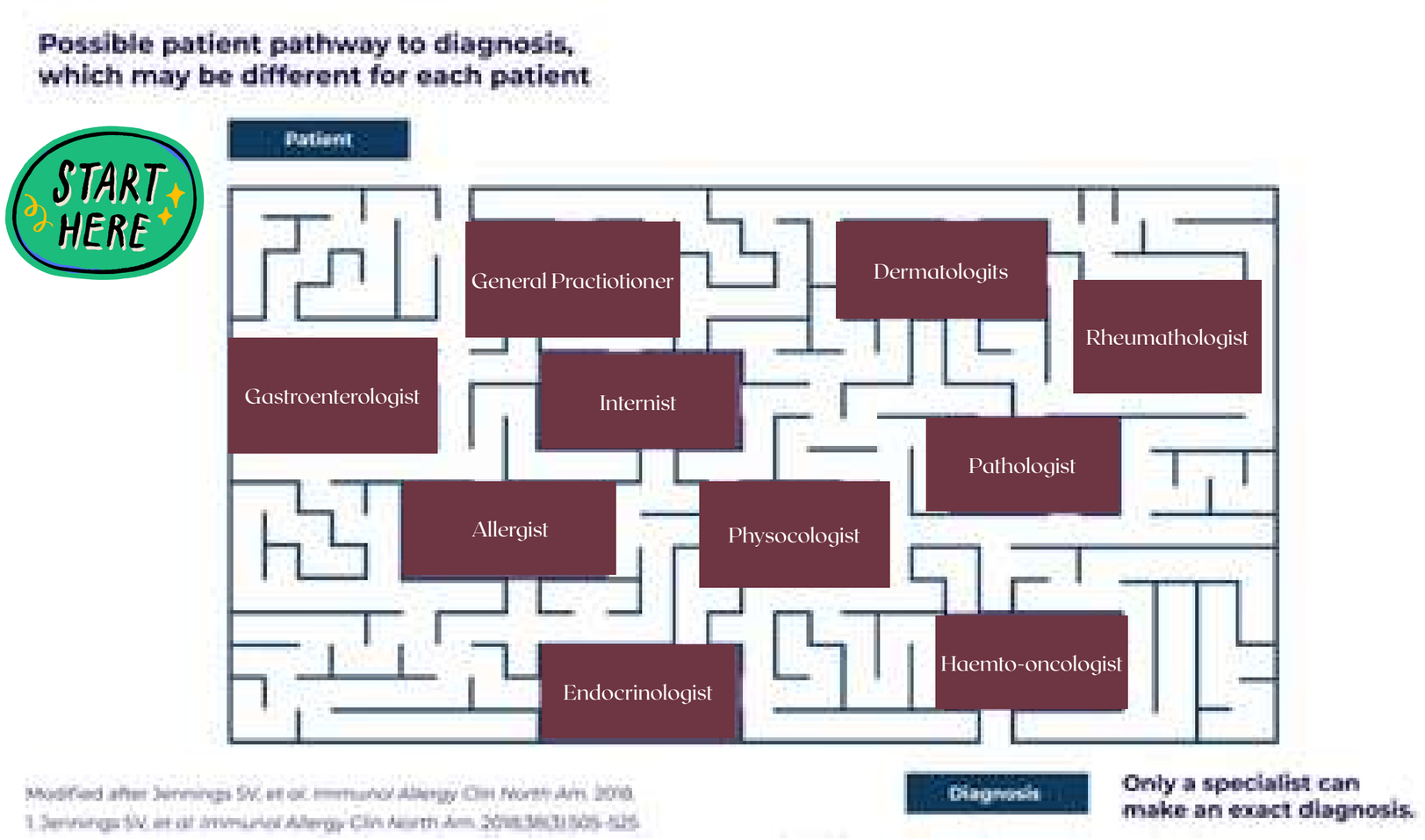
3 Càrrega sanitària i visites mèdiques

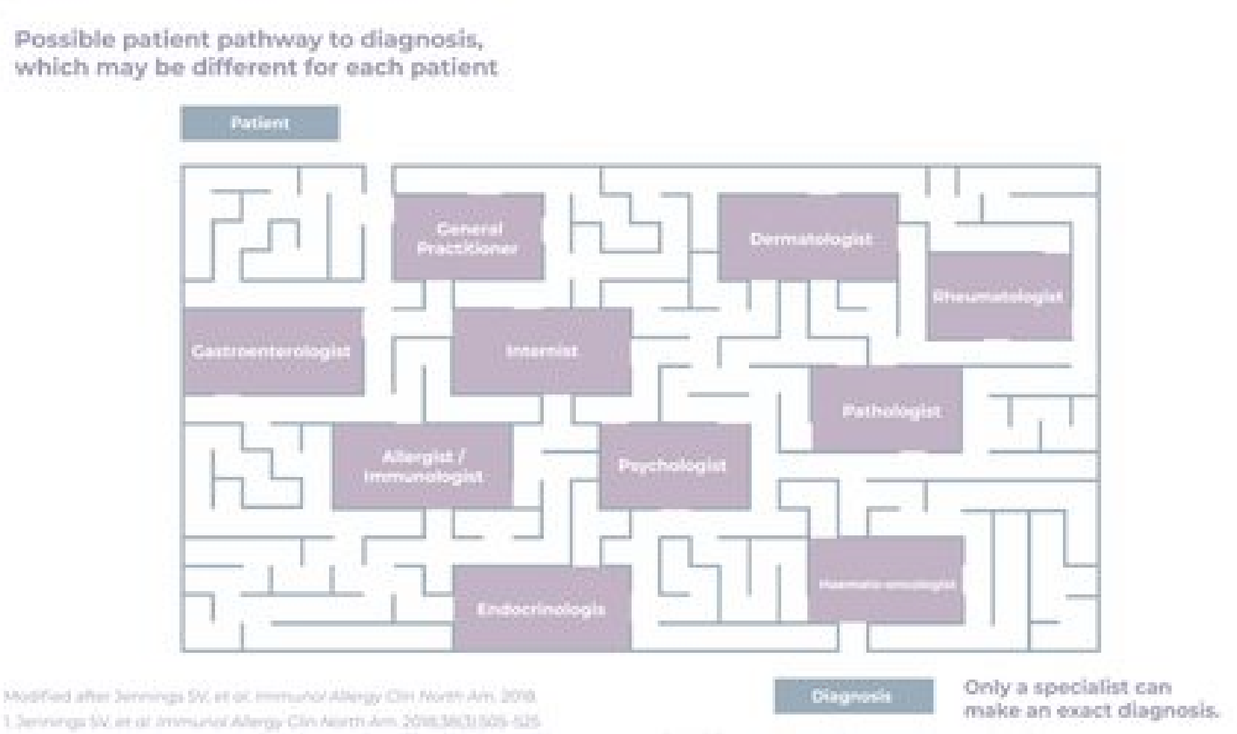
L'ODISSEA DIAGNÒSTICA



Modified after Jennings SV, et al. Immunol Allergy Clin North Am. 2018.
1 Jennings SV, et al. Immunol Allergy Clin North Am. 2018;38(3):505-525.

Immunol Allergy Clin N Am 38 (2018) 505–525 https://doi.org/10.1016/j.iac.2018.04.006

3 Càrrega sanitària i visites mèdiques



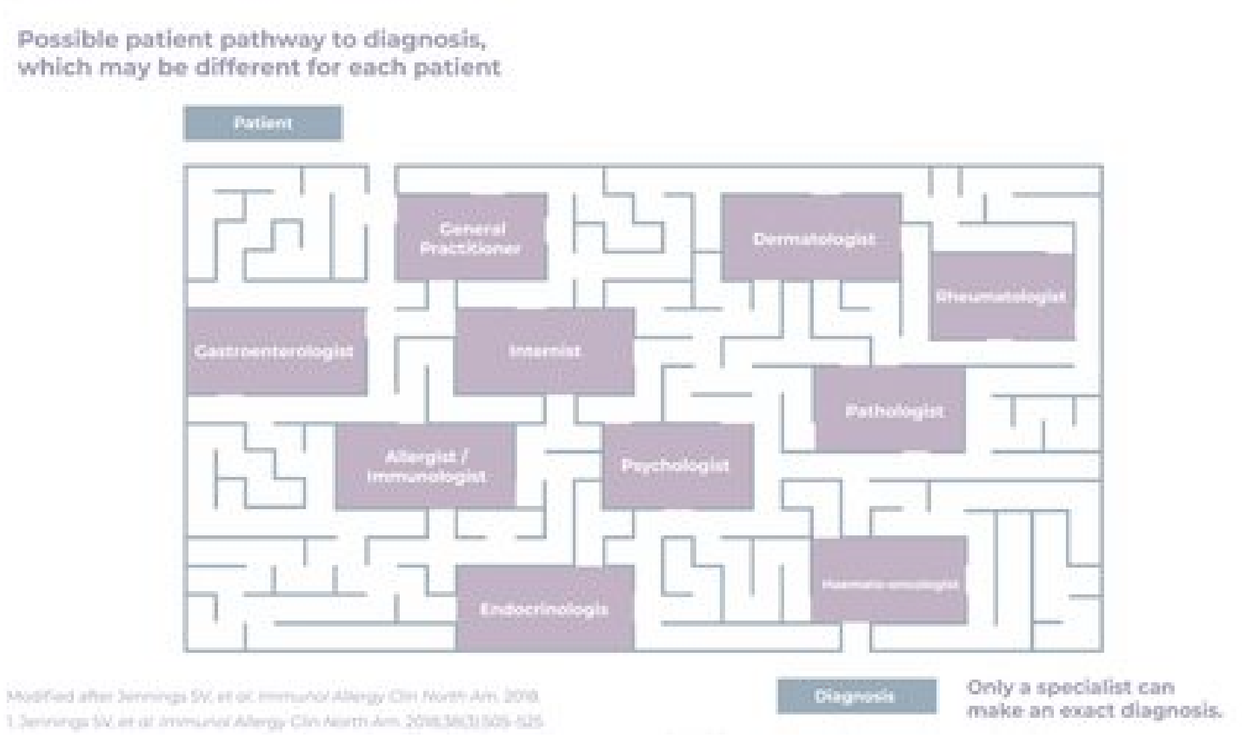
Modified after Jennings SV, et al. Immunol Allergy Clin North Am. 2018.
1. Jennings SV, et al. Immunol Allergy Clin North Am. 2018;38(3):505-525.

POLIFARMACIA[1]

≥ 3 fàrmacs prescrits per MS
EFECTES SECUNDARIS

aN=56 patients with nonadvanced SM.
1. Tse KY, et al. J Allergy Clin Immunol Glob. 2024;3(4):100316; 2. Mesa RA, et al. Cancer. 2022;128(20):3691-3699.

3 Càrrega sanitària i visites mèdiques



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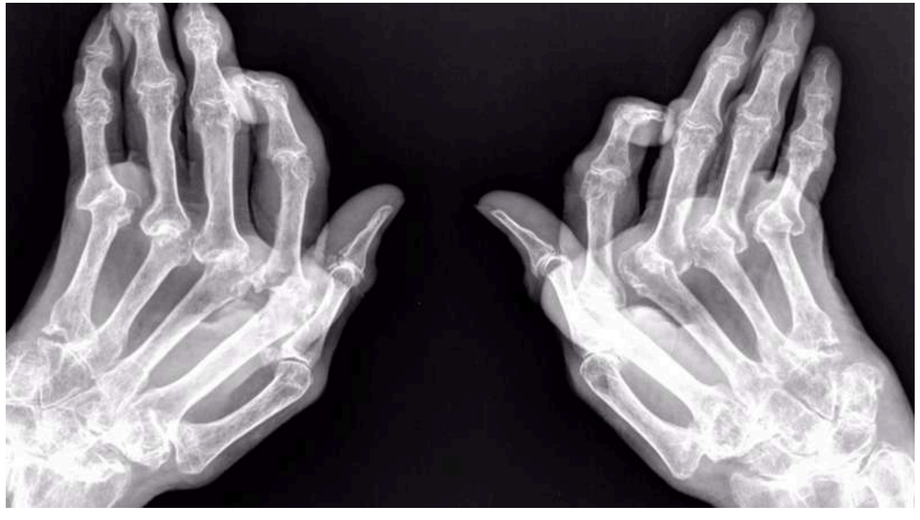
POLIFARMACIA[1]



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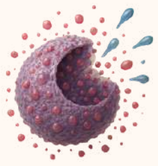
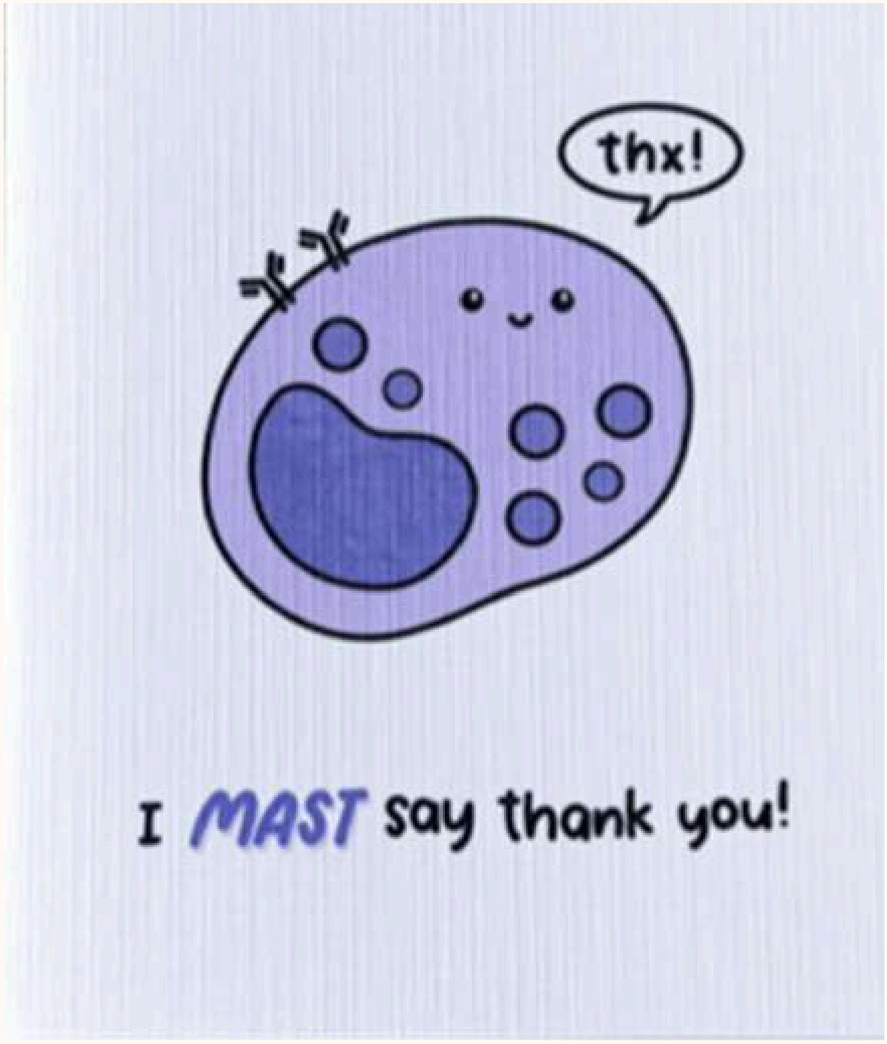
CONCLUSIONS

- Mastocitosi → **proliferació clonal** de mastòcits, que s'acumulen en organs amb presentació clínica **molt heterogènia**
- Es pot classificar en **mastocitosi cutània, mastocitosi sistèmica i sarcoma de mastòcits**
- Diagnòstic → **història clínica, triptasa basal, mutació de KIT D816V en SP o BMO i biòpsia de medul·la òssia**
- Tractament **simptomàtic → antihistamínics-H1 o H2 i estabilitzadors de la membrana del mastòcit. KIT D'EMERGENCIA (AIA) si cal.**
- **Complexitat i alta càrrega física i emocional** → necessari coneixement INTEGRAL i metges especialitzats.





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20 de maig de 2025