CHARITÉ

UNIVERSITÄTSMEDIZIN BERLIN

Mast Cell Activation Diseases

Marcus Maurer
Dermatological Allergology
Allergie-Centrum-Charité
Department of Dermatology and Allergy
Charité - Universitätsmedizin Berlin
Germany

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Mast Cell *Activation* Diseases

- Its is not always the activation

  of mast cells, that makes us sick

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- What is activation? Degranulation?

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- What is activation? Degranulation?

Mast Cell-mediated Diseases

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- **Mastocytosis**
- **Urticaria**
- **Mast Cell Activation Syndrome (MCAS)**

Mast Cell-mediated Diseases

- **Mastocytosis**
- **Urticaria**
- **Mast Cell Activation Syndrome (MCAS)**
- Allergies
- Autoimmune diseases
- Cancer
- …

Mast Cell Activation Syndrome

A **chronic** condition, in which **mast cells** inappropriately and excessively release **mediators**, resulting in a range of signs and symptoms affecting **multiple organs**.

Mast Cell Activation Syndrome

- Known cause or idiopathic
- …

Kown causes of MCAS

- KIT mutation (mMCAS)
- Allergy (Anaphylaxis)

Idiopathic MCAS (iMCAS)

- ‚Chronic Spontaneous Urticaria with systemic involvement‘ (CSU+)
- ‚Idiopathic Anaphylaxis‘
- ‚Horror autotoxicus‘

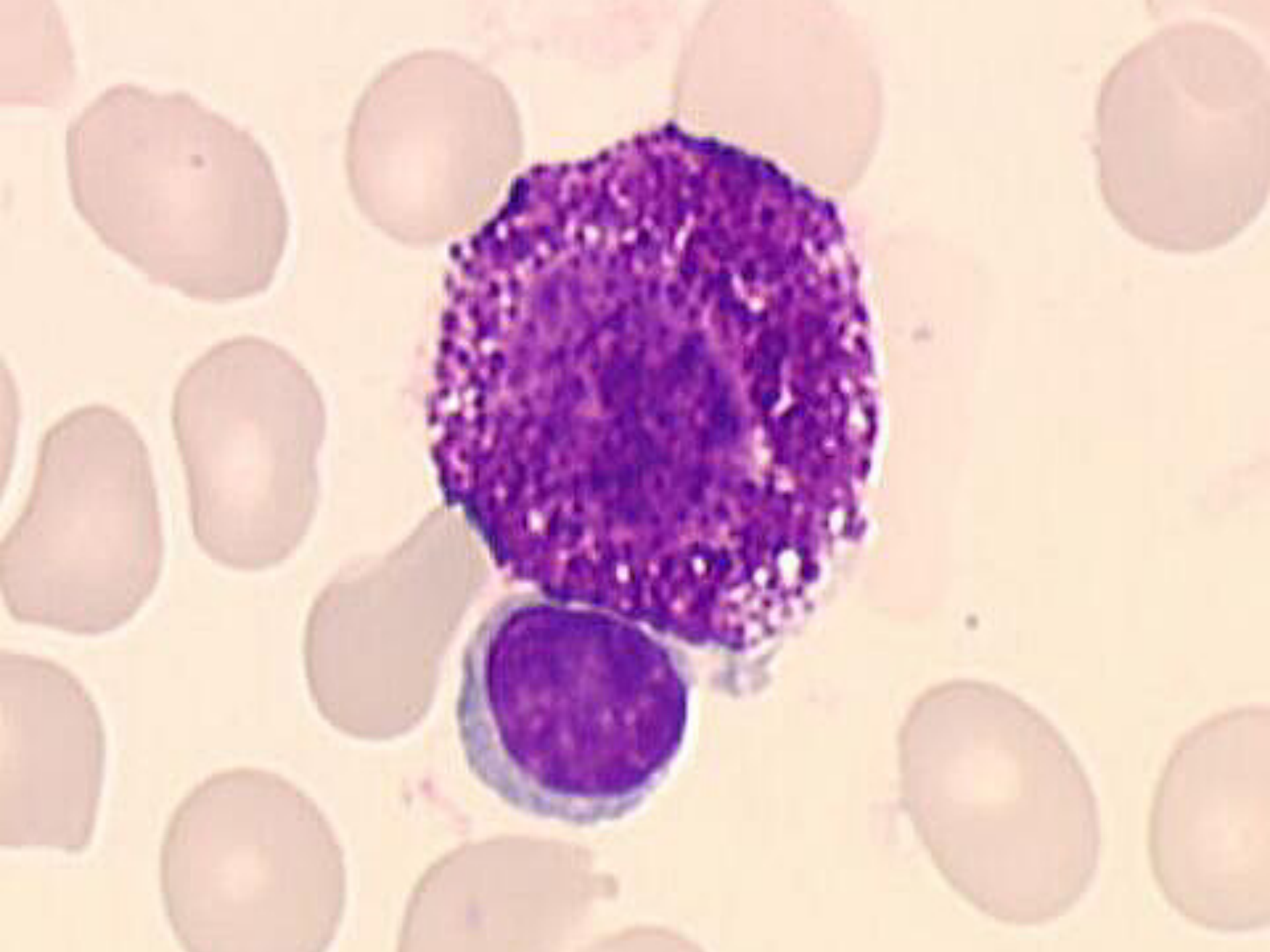
Mast Cell Activation Syndrome

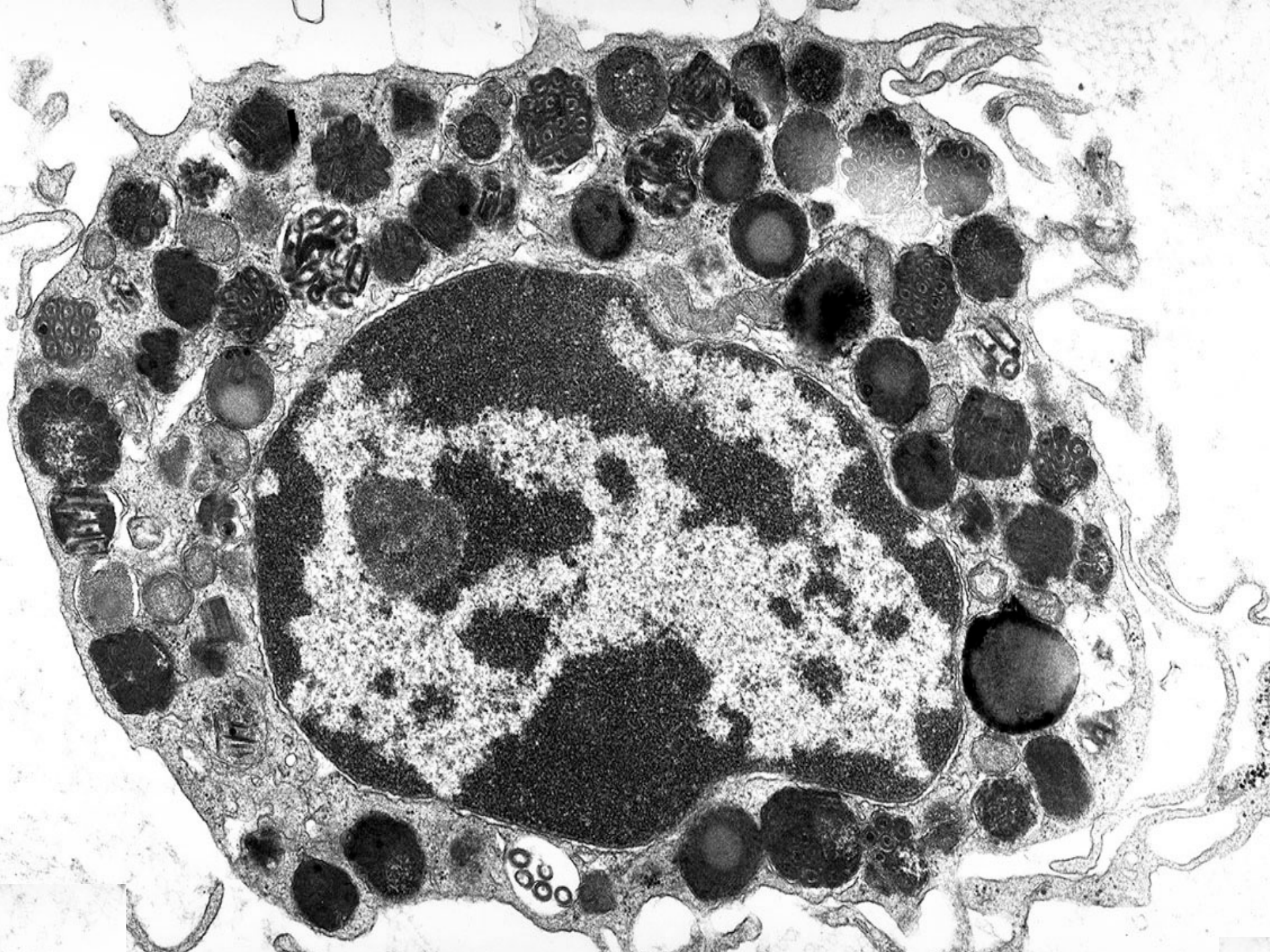
- Known cause or idiopathic
- …

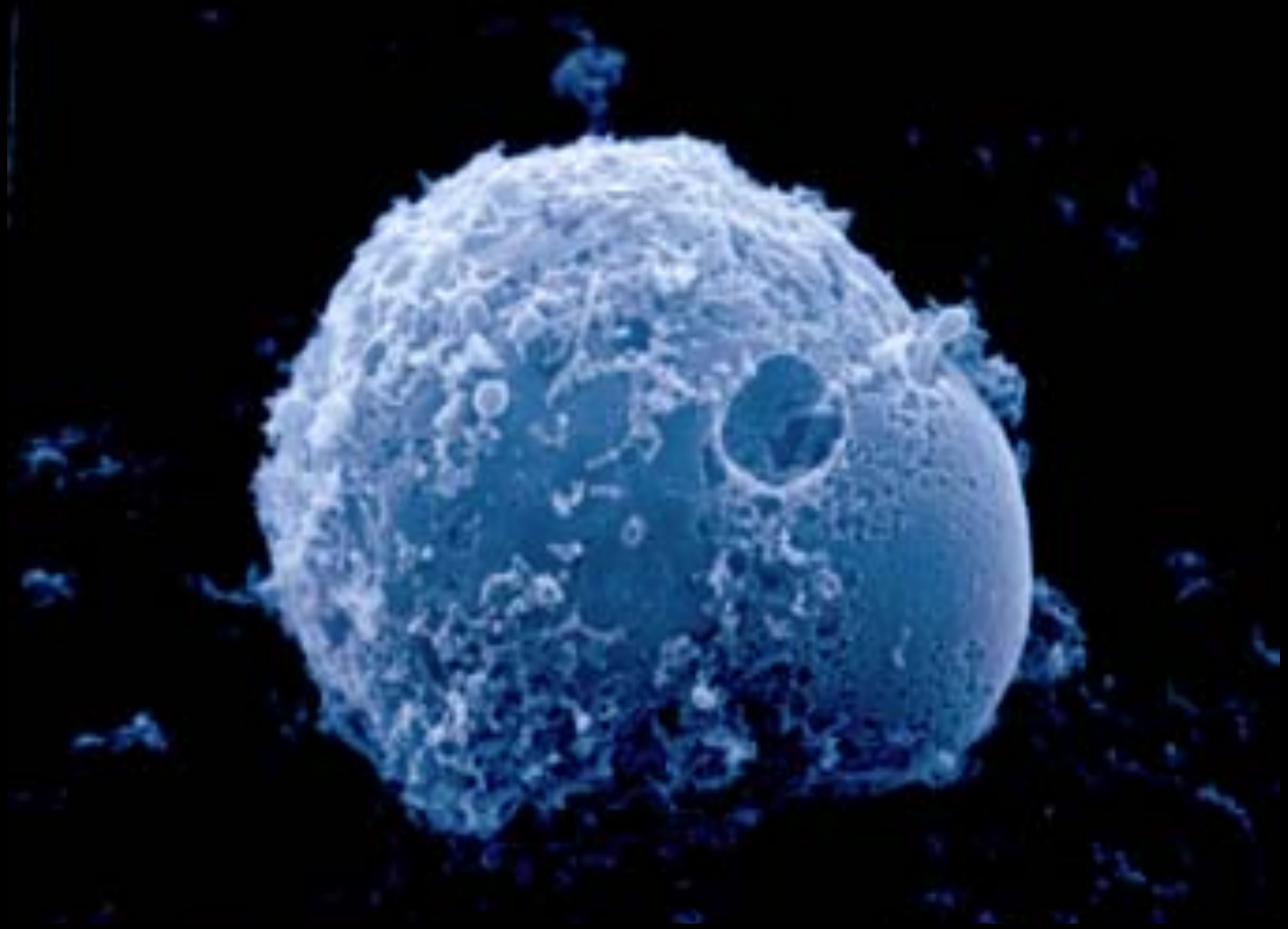
Mast Cell Activation Syndrome

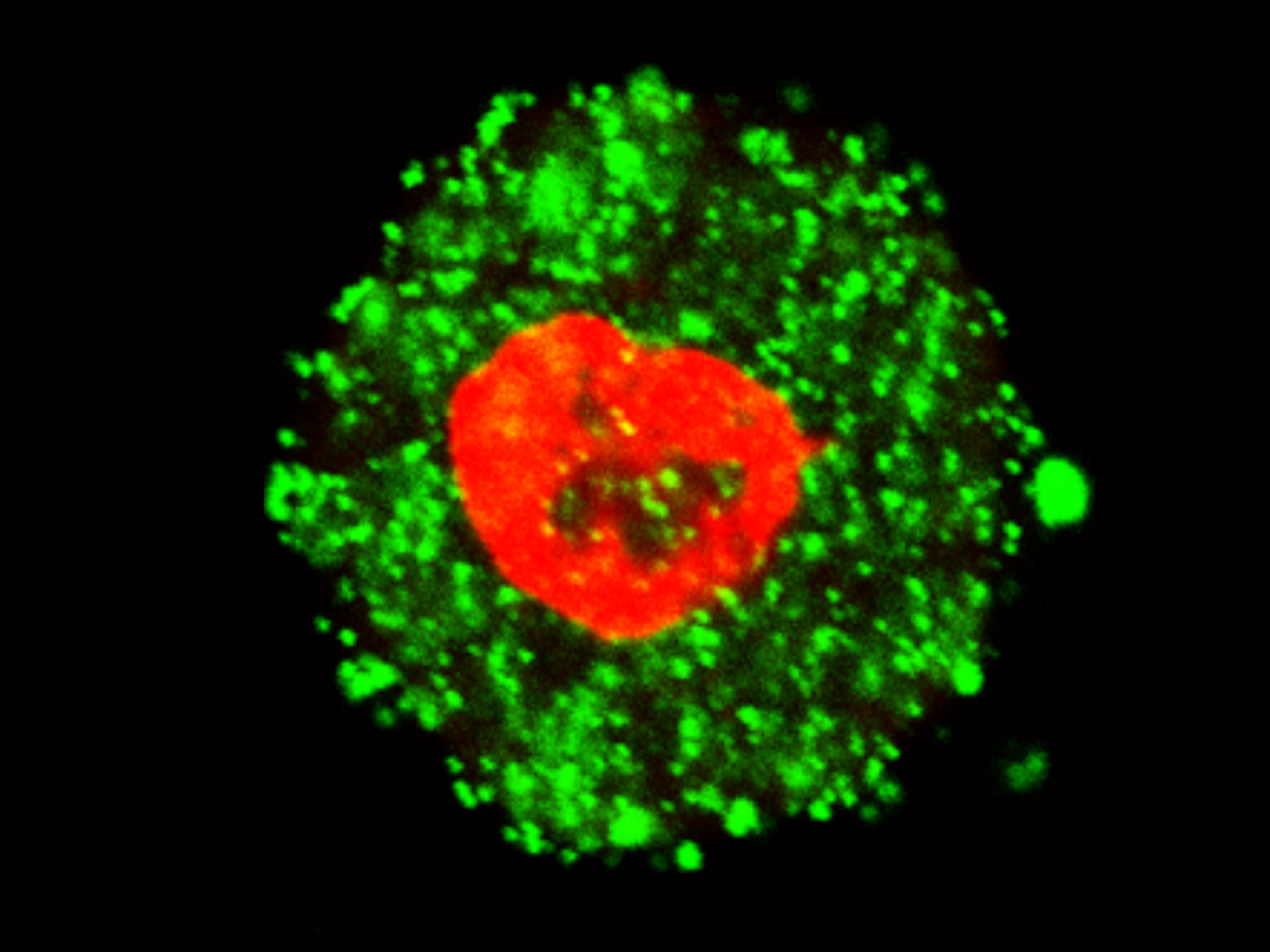
- Known cause or idiopathic
- Attacks, bouts, episodes
- …

How mast cells work

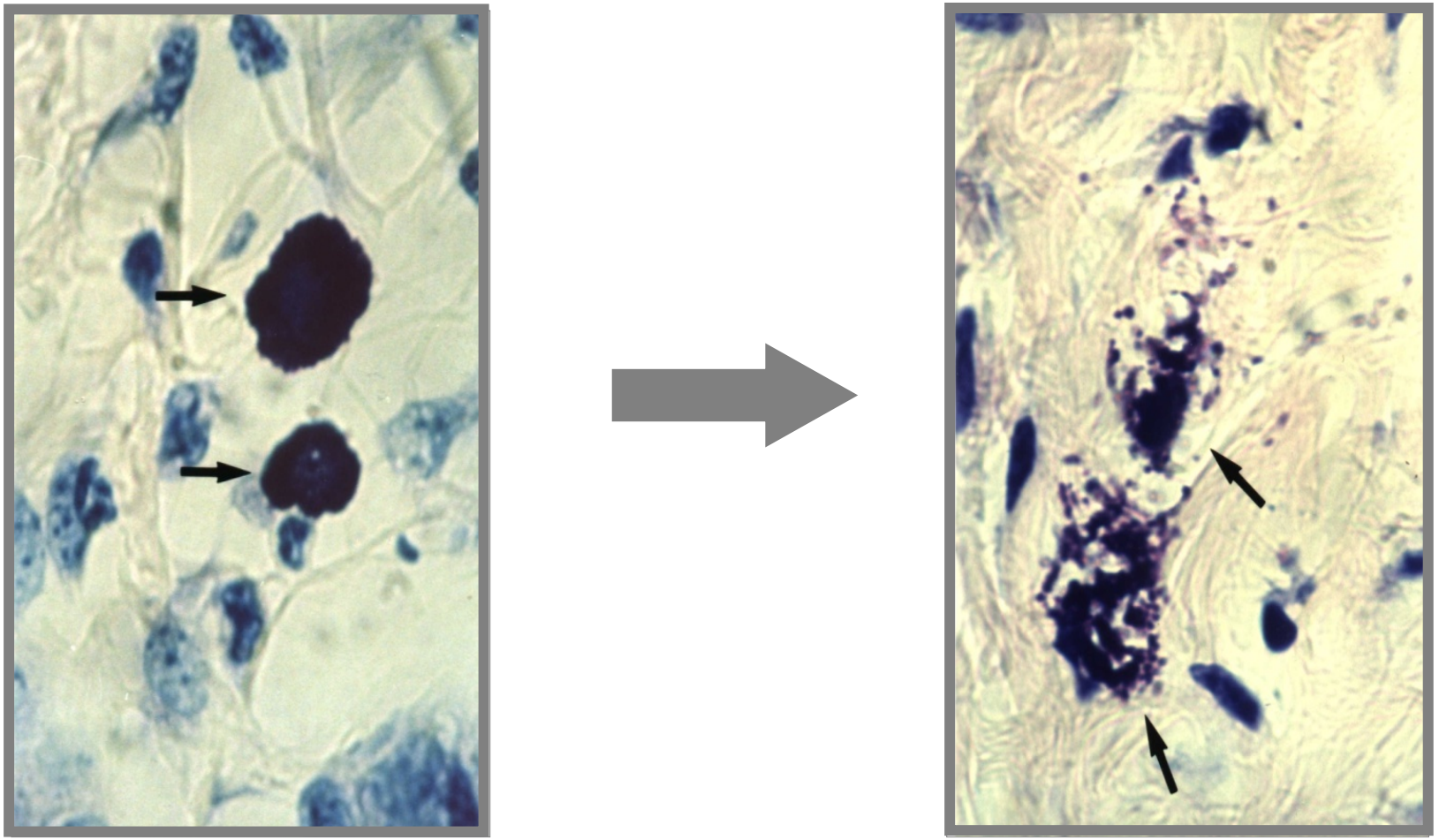






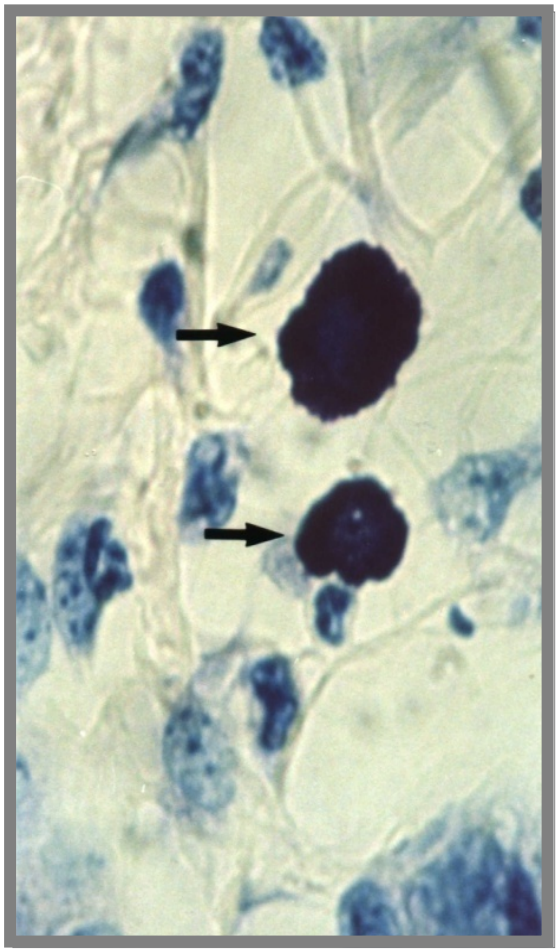


Mast cell degranulation



Church et al., *Immunol. Rev.* 2018: 282; 232-247

Mast cell degranulation



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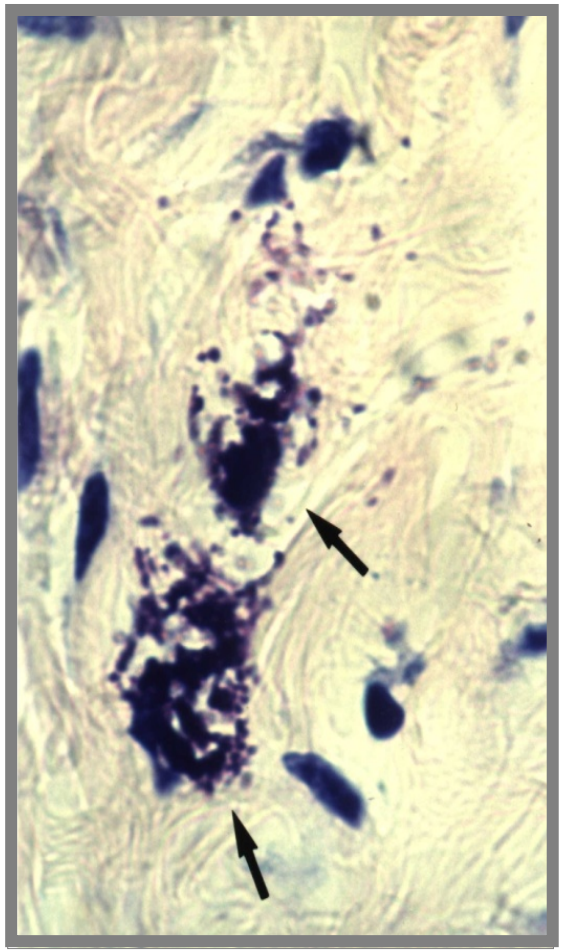
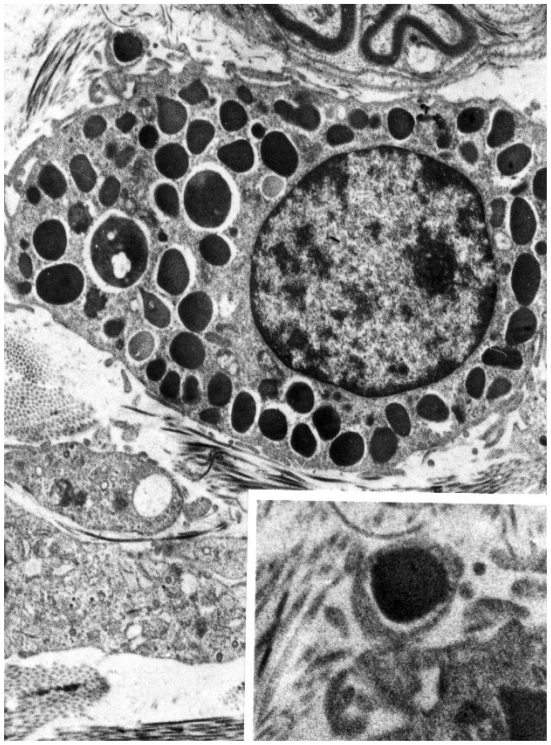
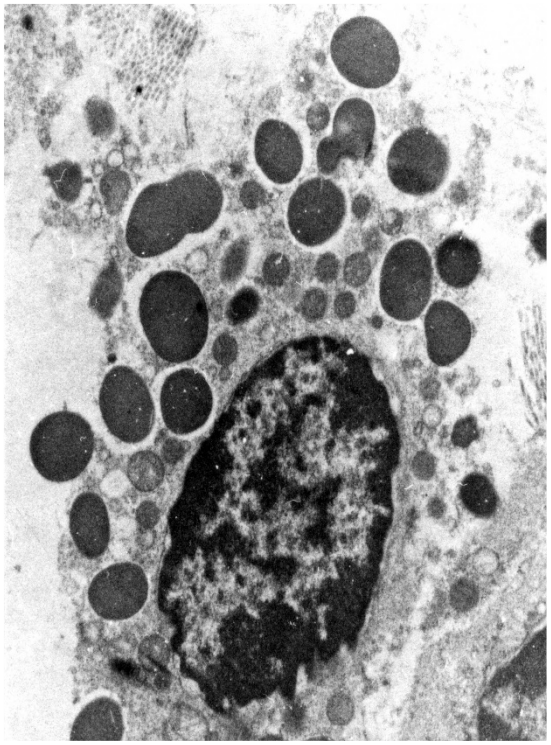


Church et al., *Immunol. Rev.* 2018: 282; 232-247

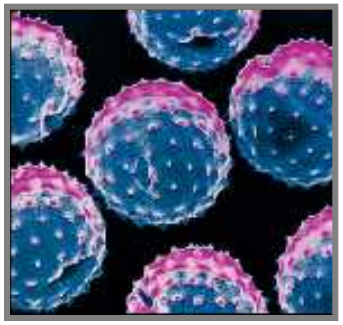
Anagen is linked to MC degranulation





Paus et al., Dev. Biol. 1994; 163: 230-40

Mast Cells are Allergy Cells

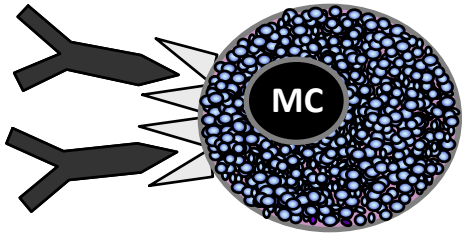


Allergen

Allergen

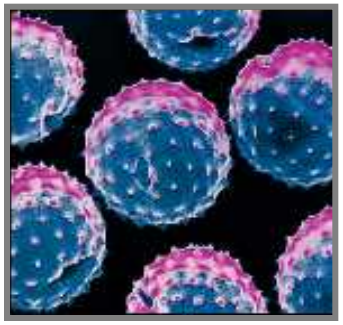
Allergen

IgE



$Fc_{\varepsilon}RI$

Mast Cells are Allergy Cells



IL-3R, IL-4R, IL-6R,IL-10R, IL-15R

C3aR, C5aR, CR1/2, CR3, CR4

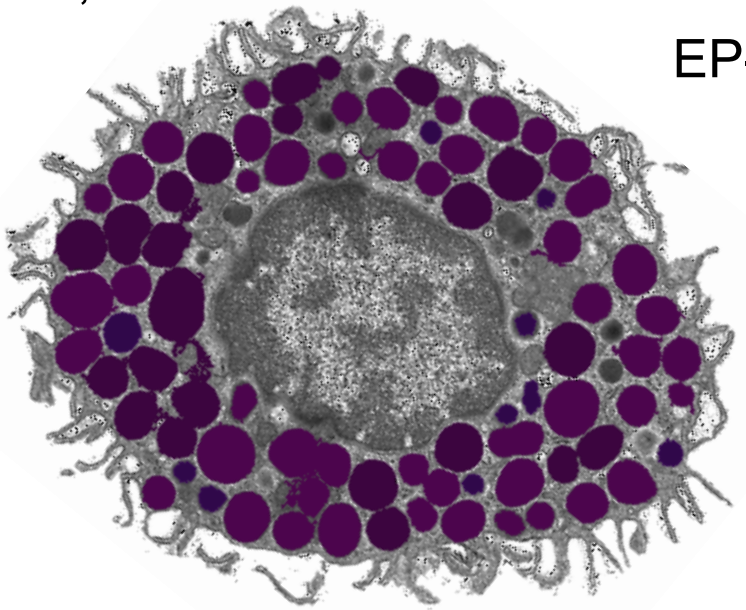
CXCR1, 2, 4, CCR3, 5

PAR2, OTRs, A_3R

TrkA, MC-1/MC-5

PIR-A/PIR-B

CD40L, OX40



FcεRI, FcγRIIb, FcγRIII

TLR1, 2, 3, 4, 6, 7, 8, 9

EP-1/EP-3, CysLT1R

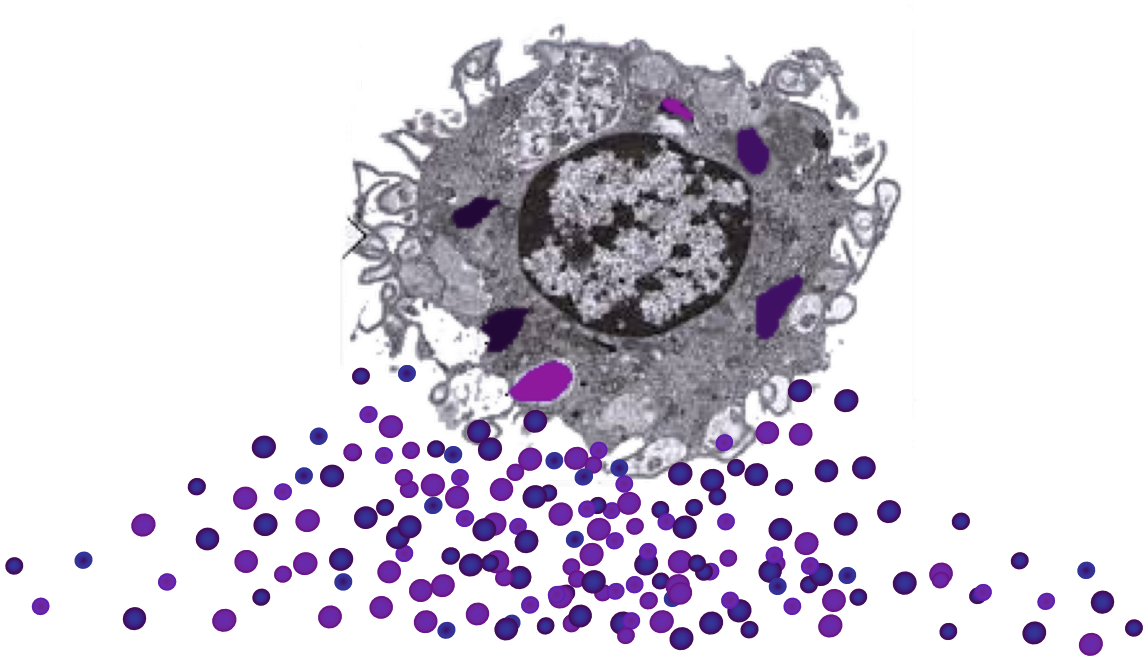
c-kit, CD48, LTβR

ET_A/ET_B, uPAR

CB1/CB2, VR

GITR, B7-1, -2

MRGPRX2

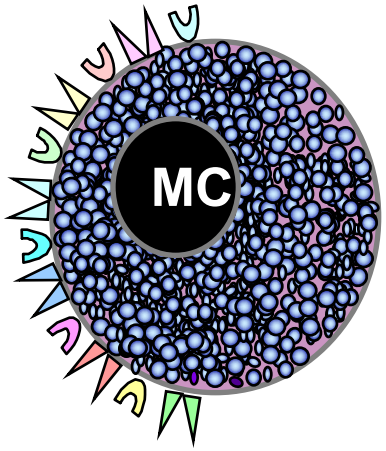


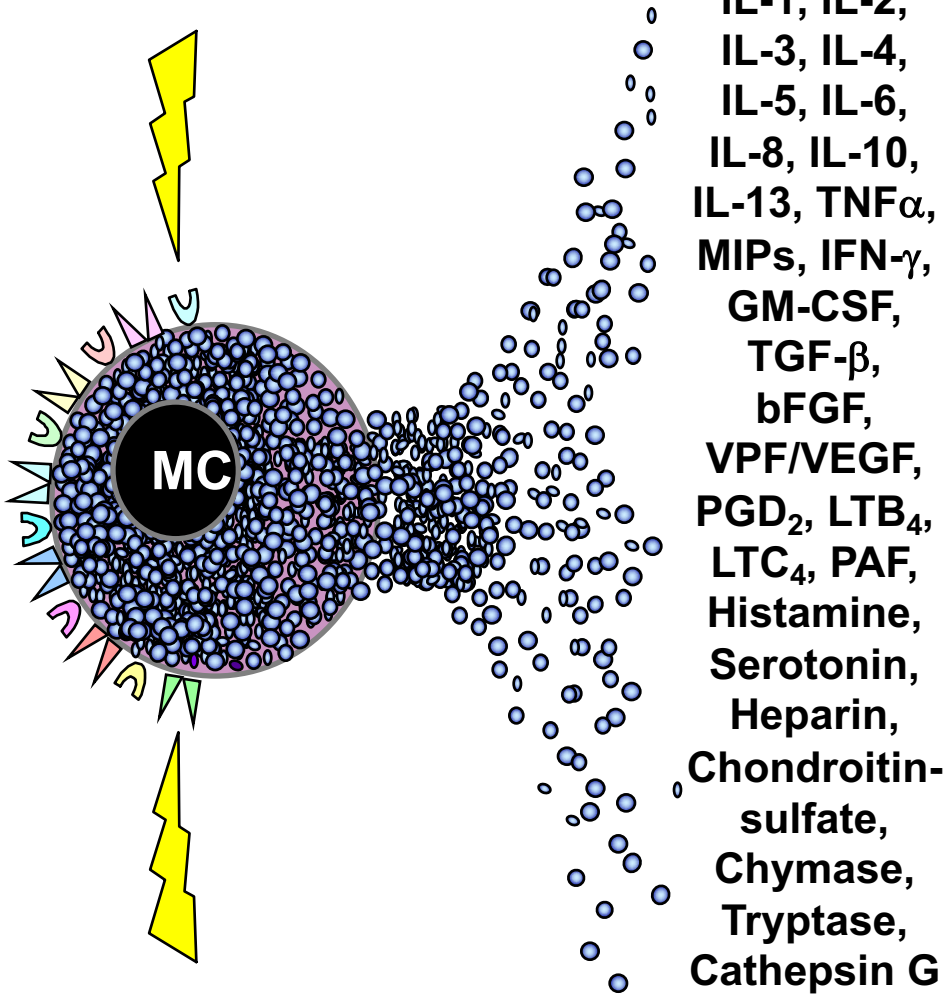
serotonin, heparine, histamine, chondroitinsulfate

chymase, tryptase, carboxypeptidase A, cathepsin G

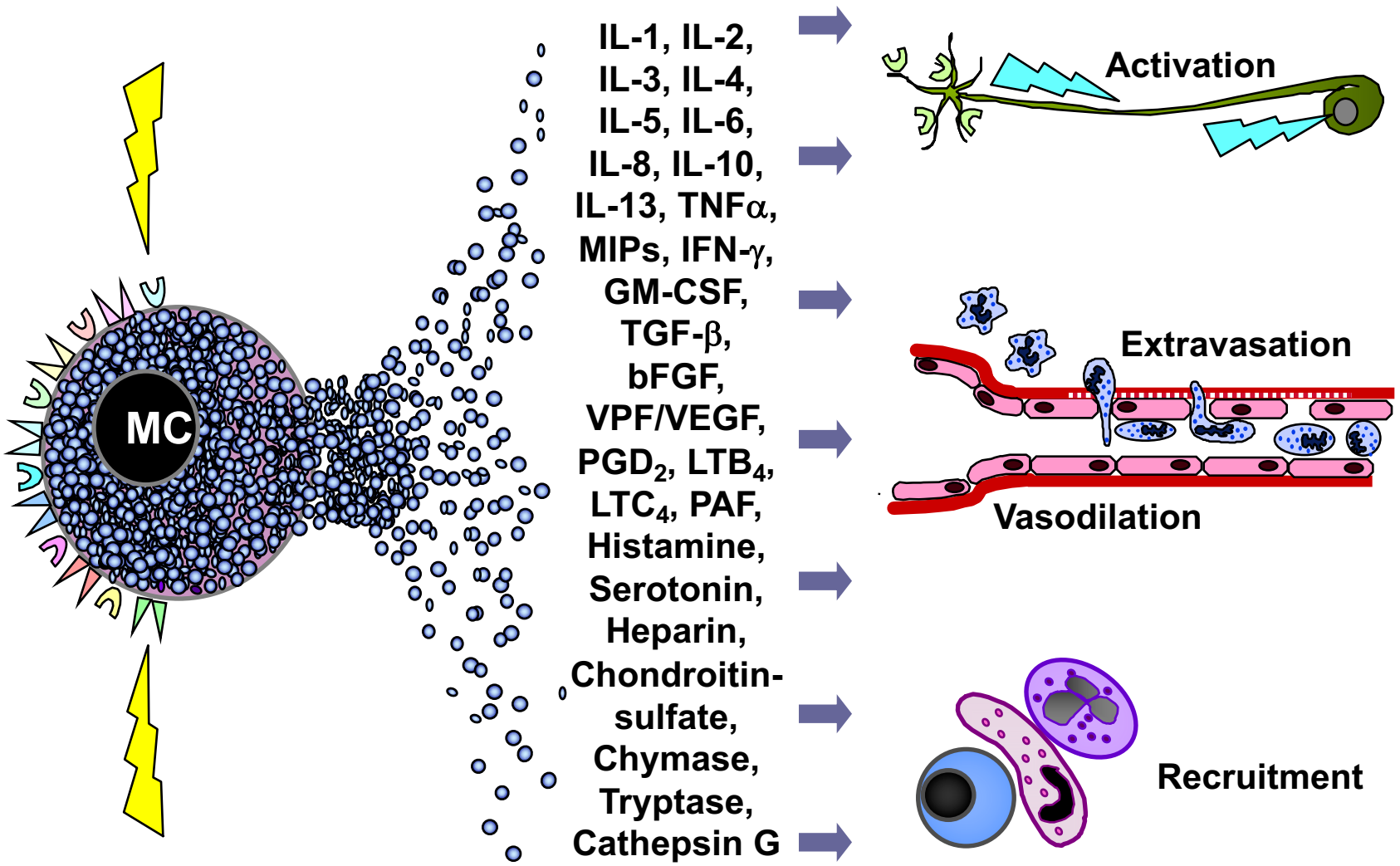
prostaglandins, leukotrienes, platelet-activating factor

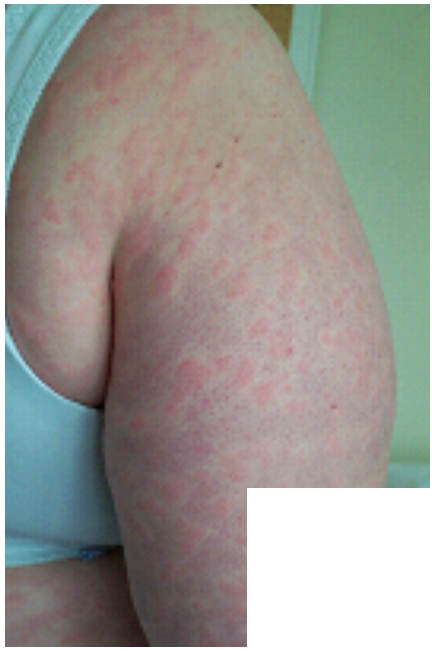
IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-21, TNF, IFNγ, GM-CSF, TGF-β, bFGF, VPF/VEGF, NGF, MIP-1α, MCP-1, RANTES, IP-10, …

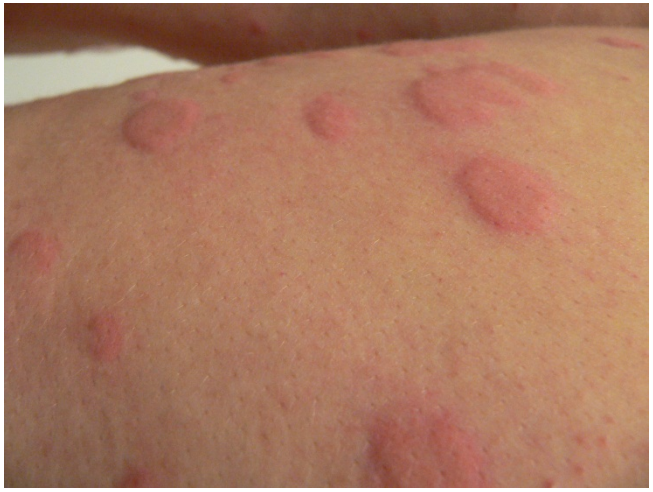

MC

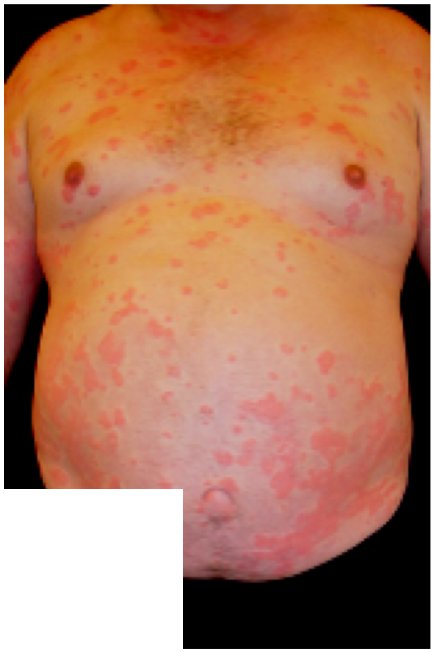


IL-1, IL-2,
IL-3, IL-4,
IL-5, IL-6,
IL-8, IL-10,
IL-13, TNFα,
MIPs, IFN-γ,
GM-CSF,
TGF-β,
bFGF,
VPF/VEGF,
PGD_2, LTB_4,
LTC_4, PAF,
Histamine,
Serotonin,
Heparin,
Chondroitin-
sulfate,
Chymase,
Tryptase,
Cathepsin G

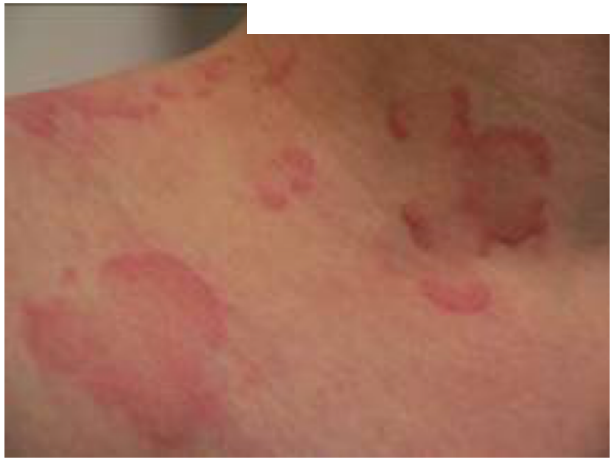

MC
IL-1, IL-2,
IL-3, IL-4,
IL-5, IL-6,
IL-8, IL-10,
IL-13, TNFα,
MIPs, IFN-γ,
GM-CSF,
TGF-β,
bFGF,
VPF/VEGF,
PGD2, LTB4,
LTC4, PAF,
Histamine,
Serotonin,
Heparin,
Chondroitin-
sulfate,
Chymase,
Tryptase,
Cathepsin G
Activation
Extravasation
Vasodilation
Recruitment

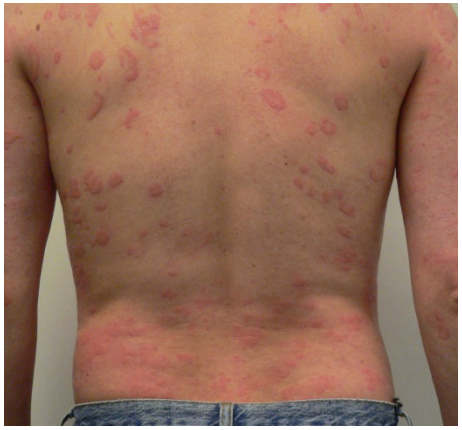


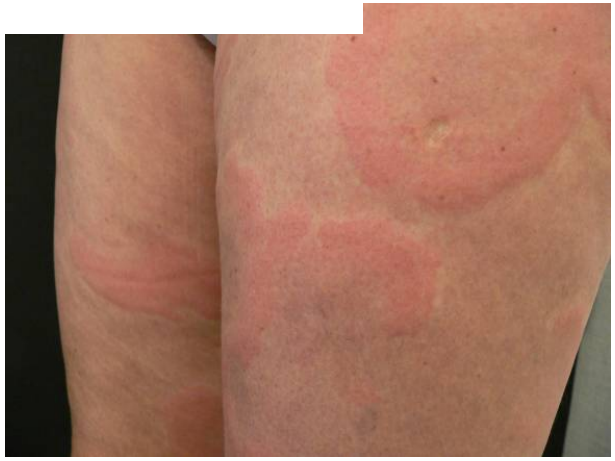


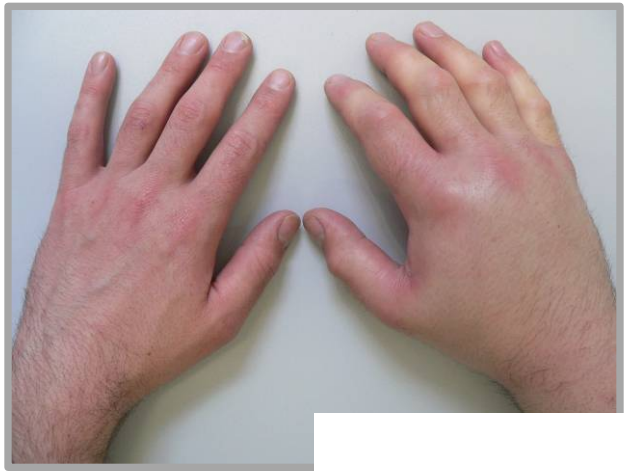
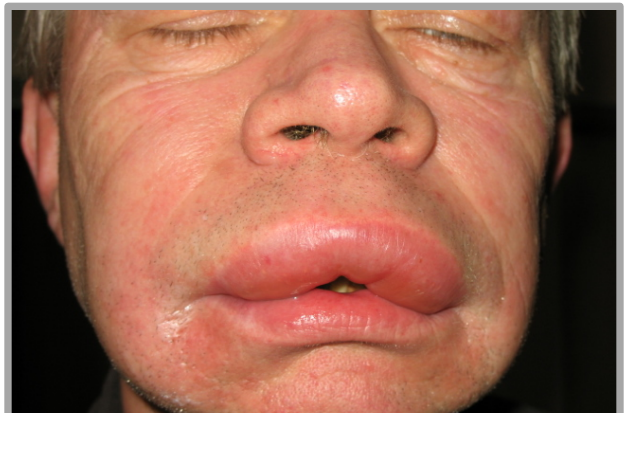
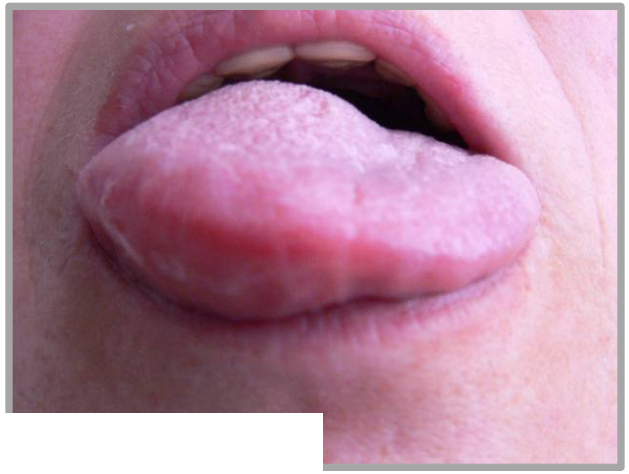


Wheals

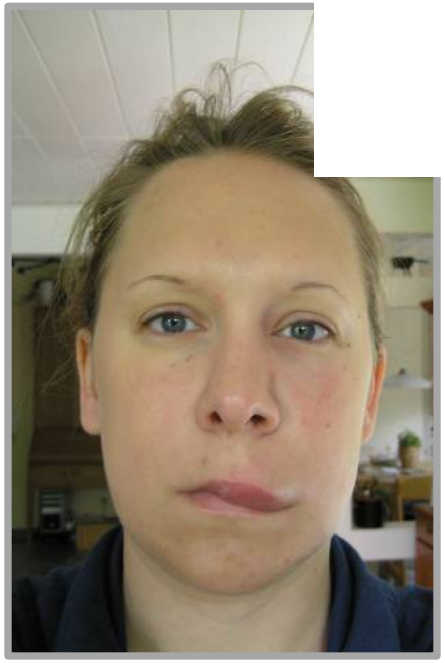
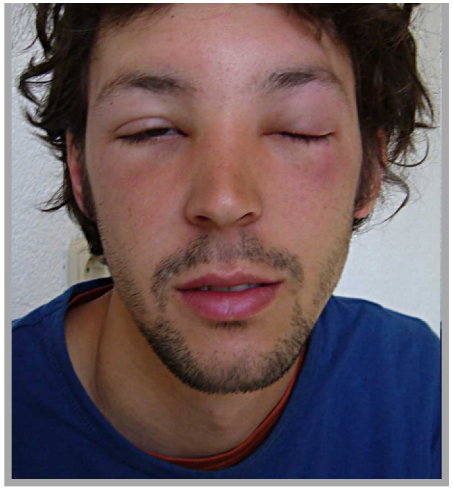
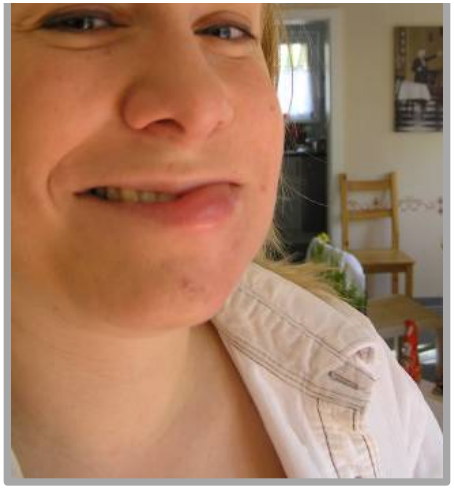
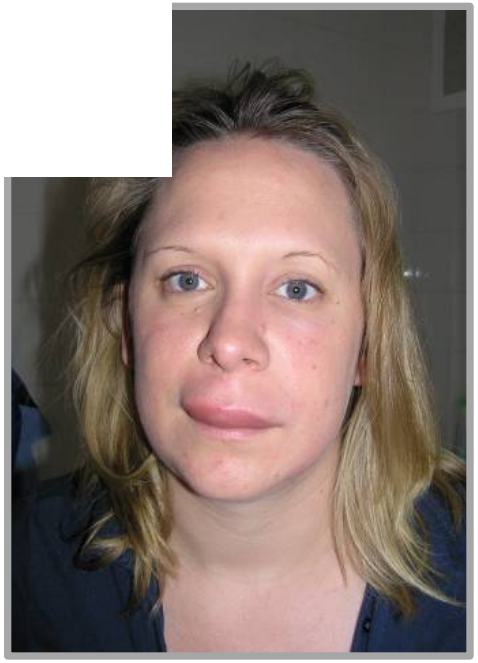




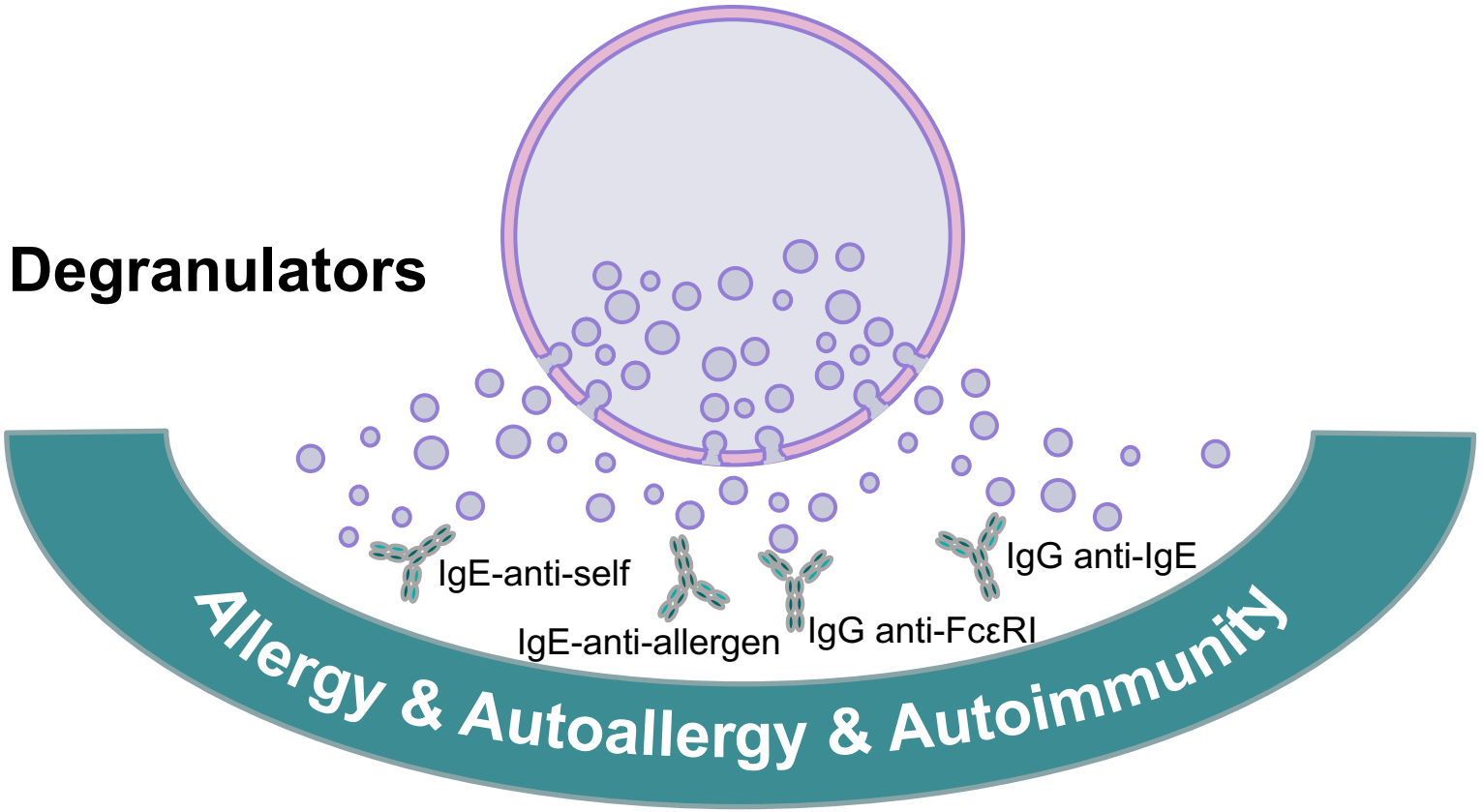


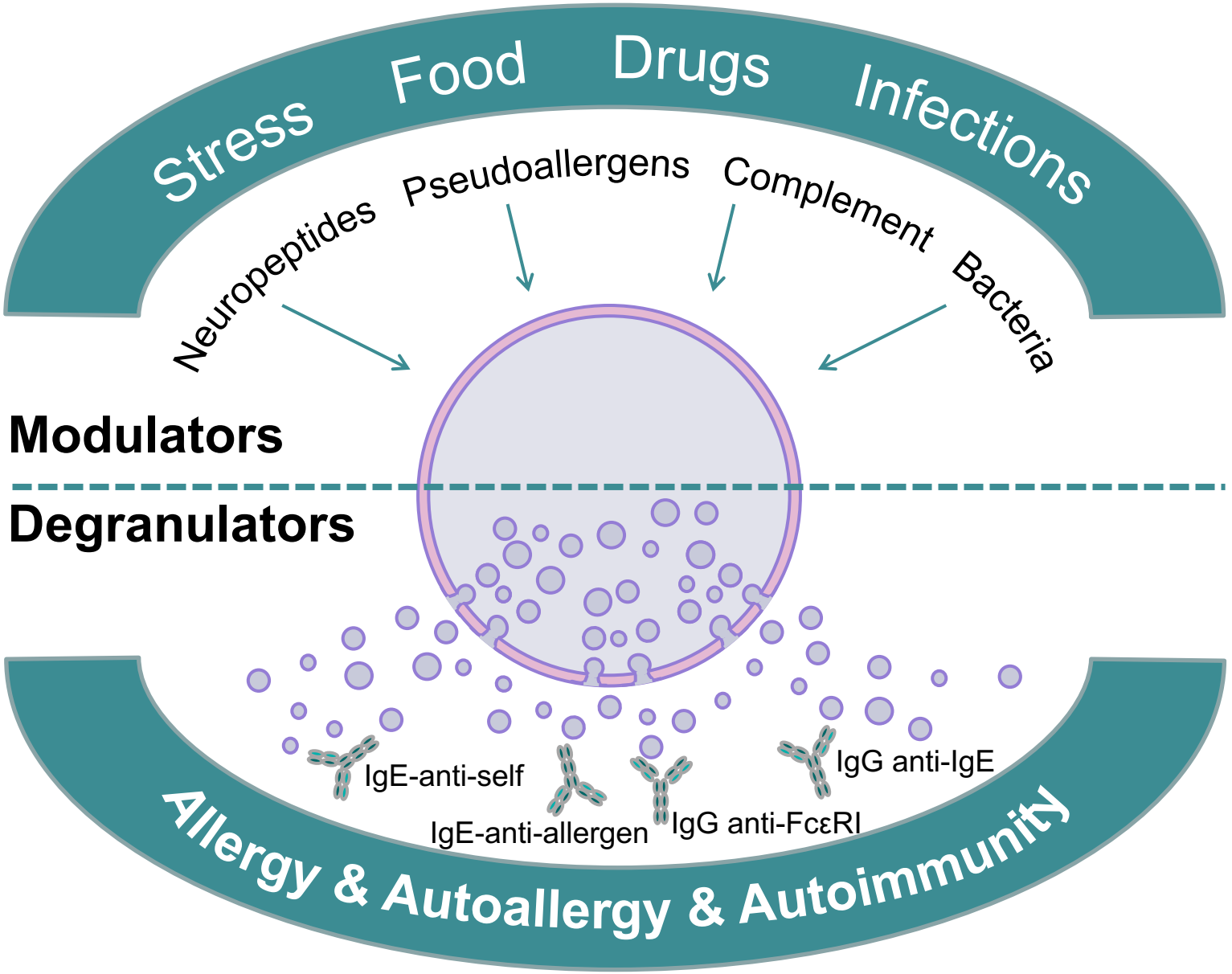




Angioedema

Degranulators




Stress
Food
Drugs
Infections
Neuropeptides
Pseudoallergens
Complement
Bacteria
Modulators
Degranulators
IgE-anti-self
IgE-anti-allergen
IgG anti-FcεRI
IgG anti-IgE
Allergy & Autoallergy & Autoimmunity

Mast Cell Activation Syndrome

- Known cause or idiopathic
- Attacks, bouts, episodes
- …

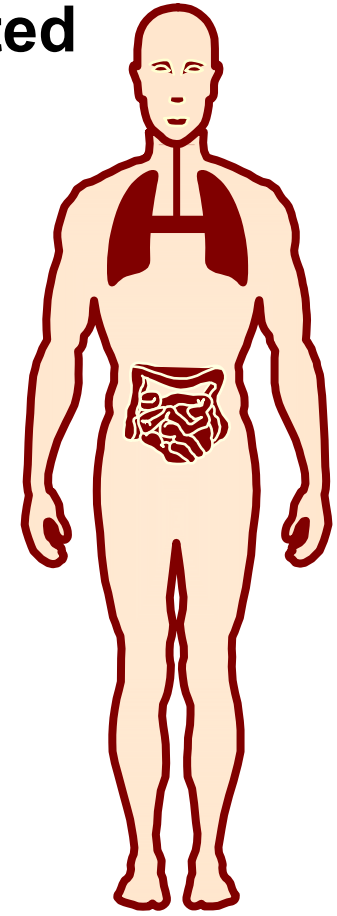
Mast Cell Activation Syndrome

- Known cause or idiopathic
- Attacks, bouts, episodes
- All organs can be affected, directly or indirectly
- ...

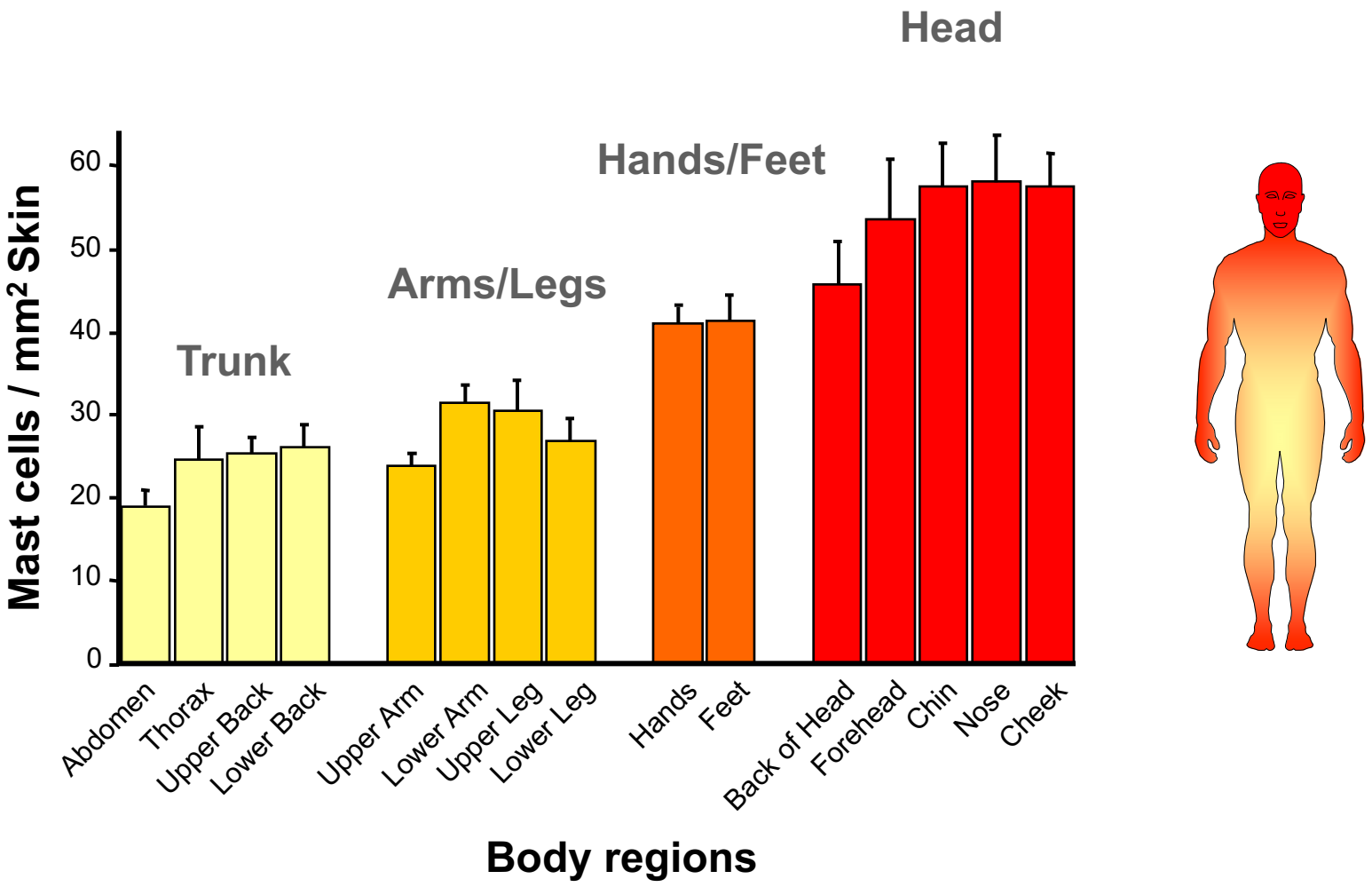
Where mast cells are

Mast cells are preferentially located at host-environment interfaces.

- Skin
- Airways
- Gut

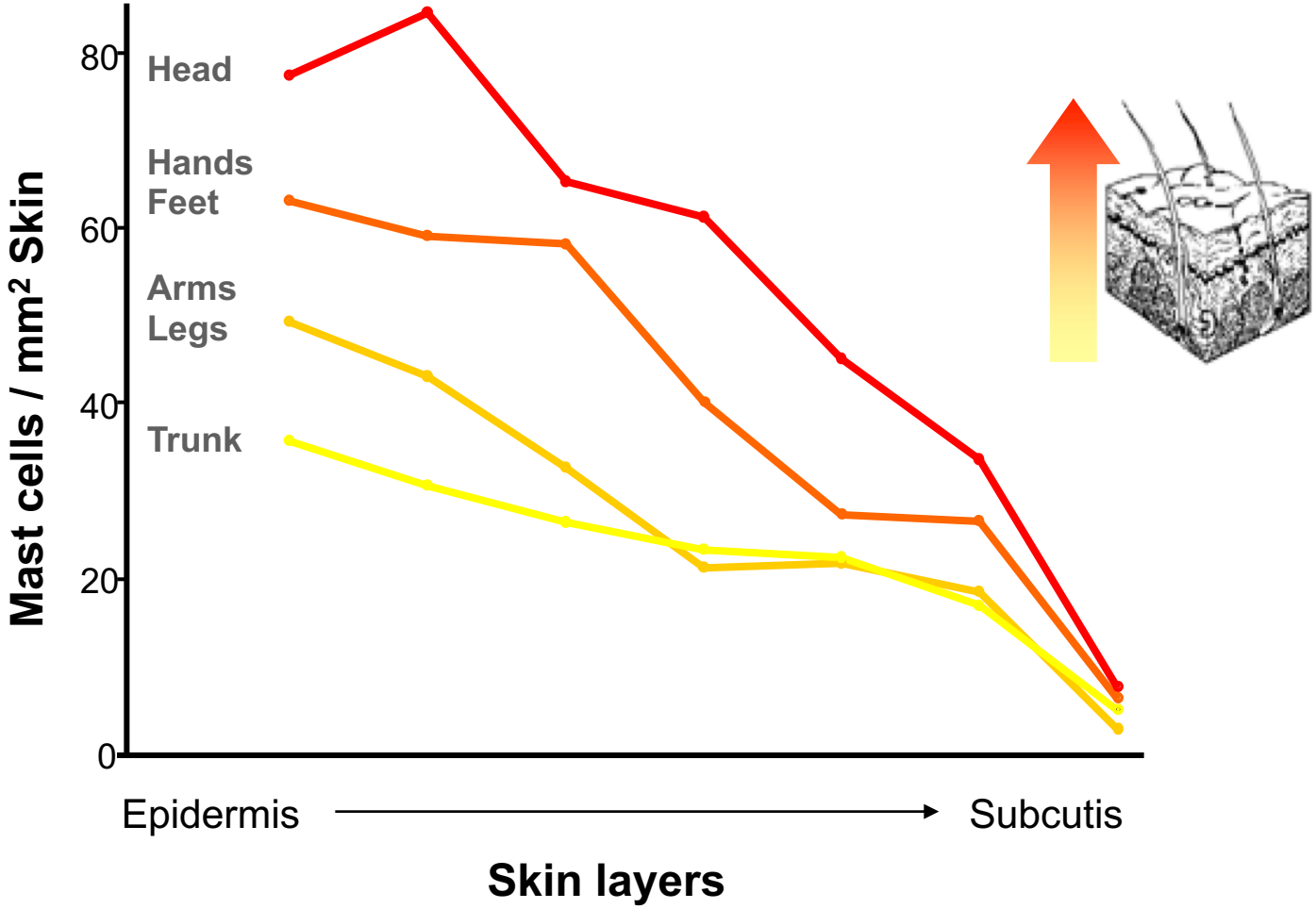


Distribution of mast cells in the skin



Weber et al., Br. J. Dermatol. 2003: 148; 224-225

Distribution of mast cells in the skin



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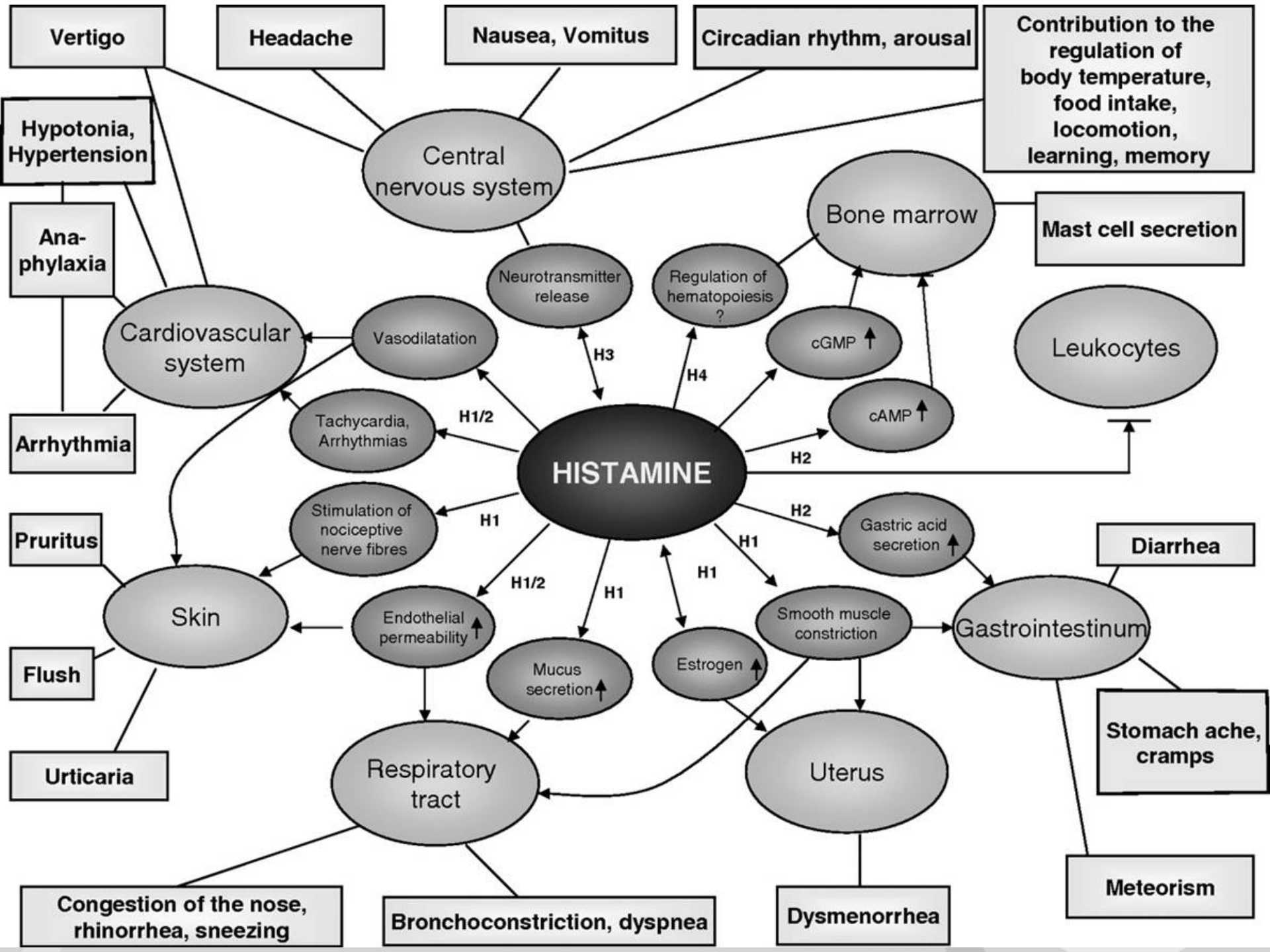
Vertigo
Headache
Nausea, Vomitus
Circadian rhythm, arousal
Contribution to the regulation of body temperature, food intake, locomotion, learning, memory
Hypotonia, Hypertension
Central nervous system
Bone marrow
Mast cell secretion
Ana-phylaxia
Neurotransmitter release
Regulation of hematopoiesis ?
Cardiovascular system
Vasodilatation
cGMP
Leukocytes
H3
H4
Tachycardia, Arrhythmias
H1/2
cAMP
Arrhythmia
HISTAMINE
H2
Stimulation of nociceptive nerve fibres
H1
H2
Gastric acid secretion
Pruritus
Diarrhea
H1
H1/2
H1
H1
Skin
Endothelial permeability
Smooth muscle constriction
Gastrointestinum
Flush
Mucus secretion
Estrogen
Stomach ache, cramps
Urticaria
Respiratory tract
Uterus
Meteorism
Congestion of the nose, rhinorrhea, sneezing
Bronchoconstriction, dyspnea
Dysmenorrhea

Mast Cell Activation Syndrome

- Known cause or idiopathic
- Attacks, bouts, episodes
- All organs can be affected, directly or indirectly

Mast Cell Activation Syndrome

- Known cause or idiopathic
- Attacks, bouts, episodes
- All organs can be affected,

  directly or indirectly
- What we think ≠ What patients think

The prevalence of iMCAS

1 - 20%

Diagnostic criteria of iMCAS

Episodic occurrence of typical MC-related clinical symptoms affecting 2 or more organ systems.

An increase in serum tryptase level by 20% over the individual baseline plus 2 ng/mL total within a 4-hour window after a reaction.

A clear response (improvement) of the symptoms to drugs targeting MC-derived mediators, MC-stabilizing agents, or both.

Valent et al., *J. Allergy Clin. Immunol.* 2018; 142: 1008-9

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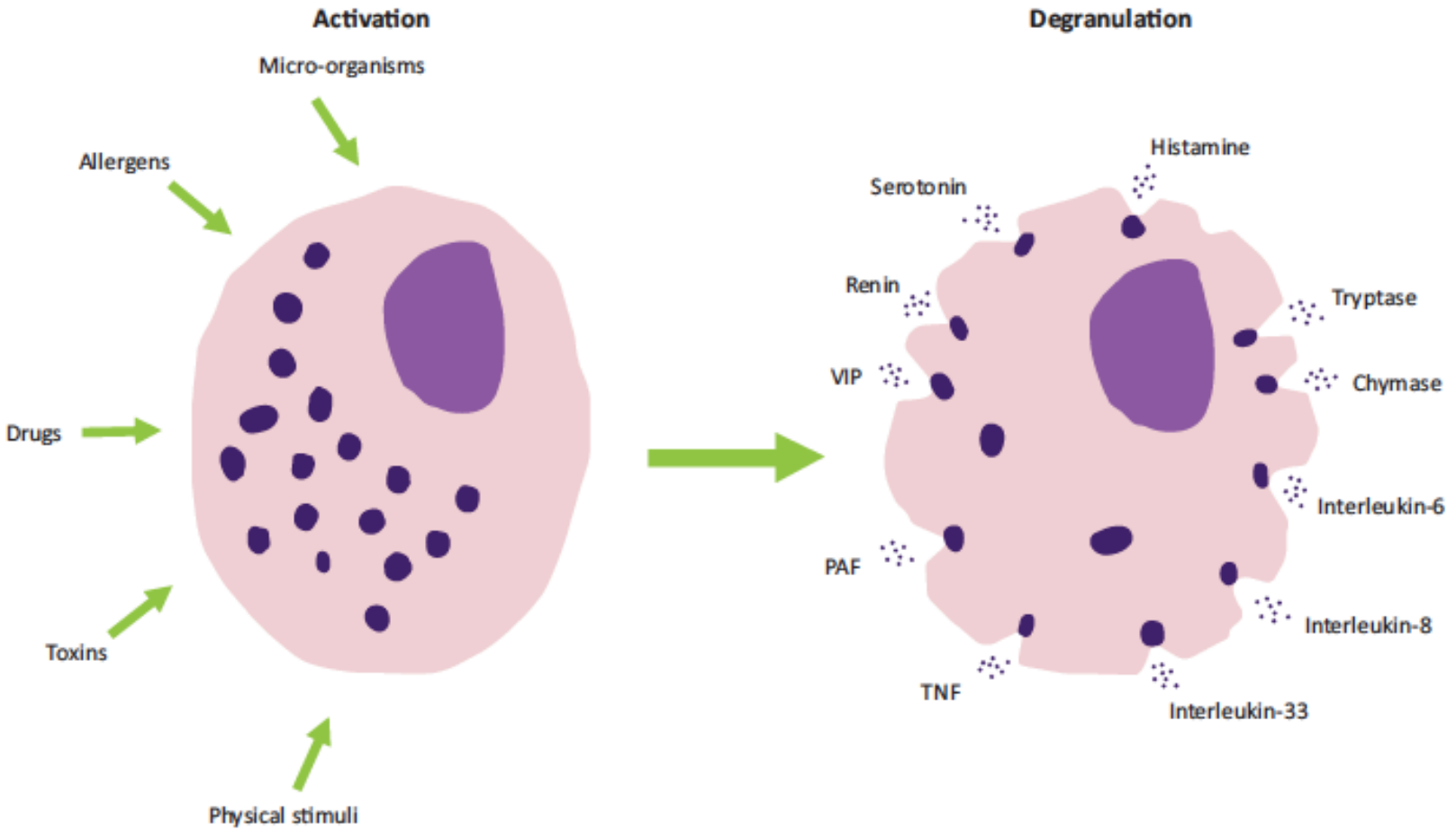
Valent et al., *J. Allergy Clin. Immunol.* 2018; 142: 1008-9

“Typical MC-related clinical symptoms“

„...such as urticaria, angioedema, flushing, pruritus, nausea, hoarseness, vomiting, diarrhea, abdominal cramping, hypotensive syncope, tachycardia, wheezing, conjunctival injection, nasal congestion, and headache.“

Valent et al., *J. Allergy Clin. Immunol.* 2018; 142: 1008-9

“Typical MC-related clinical symptoms“



Cardiovascular	Cutaneous	Gastrointestinal	Musculoskeletal	Naso-occular	Neurologic	Respiratory	Systemic
Hypotension	Flushing	Abdominal cramps	Aches	Conjunctival redness	Anxiety	Throat swelling	Fatigue
Syncope or pre syncope	Pruritus	Oesophageal reflux	Bone pain	Itch	Depression	Shortness of breath	Malaise
Light-headedness	Urticaria	Diarrhoea		Nasal stuffiness	Decreased concentration	Wheeze	Weight loss
Tachycardia	Angiooedema	Nausea and vomiting			Migraines		

Cookson and Grattan, *Clinical Medicine* 2016; 16: 580–3

The clinical picture of patients who think they have iMCAS

- Multiple variable signs and symptoms
- Often not episodic
- From mild to very severe
- Often hard to verify

Table 1. Clinical characteristics of 413 mast cell activation syndrome patients. The denominator for each frequency is the eligible portion of the study population (e.g., osteoarthritis: all patients (N = 413); miscarriage: only females (N = 287)).	
Comorbidities present in ≥10% of patients	Gastroesophageal reflux disease (35%), hypertension (29%), multiple/atypical drug reactions (23%), abdominal pain not otherwise specified (22%), hysterectomy/oophorectomy (21%), hyperlipidemia (20%), cholecystectomy (20%), environmental allergies (19%), tobacco abuse (18%), asthma (18%), diabetes mellitus type 2 (17%), hypothyroidism (17%), headaches (17%), depression (16%), sinusitis (16%), fibromyalgia (16%), anemia of chronic inflammation (15%), sleep apnea (15%), frequent upper respiratory tract infections (15%), miscarriage (15%), pharyngitis and/or tonsillitis (14%), dysmenorrhea (14%), thromboembolism (13%), frequent and/or atypical infections (13%), obesity (13%), osteoarthritis (13%), anxiety/panic (12%), vertebral disease (12%), cardiovascular malformations (12%), dermatitis (11%), presyncope and/or syncope (11%), interstitial cystitis (11%), chronic kidney disease (10%), postural orthostatic tachycardia syndrome (10%)
Symptoms present in ≥10% of patients	Fatigue (83%), fibromyalgia-type pain (75%), presyncope/syncope (71%), headache (63%), pruritus/urticaria (63%), paresthesias (58%), nausea ± vomiting (57%), chills (56%), migratory edema (56%), eye irritation (53%), dyspnea (53%), gastroesophageal reflux (50%), cognitive dysfunction (49%), rashes (49%), abdominal pain (48%), throat irritation (48%), palpitations/dysrhythmias (47%), sweats (47%), environmental allergies (40%), fever (40%), non-anginal chest pain (40%), easy bleeding/bruising (39%), alternating diarrhea/constipation (36%), proximal dysphagia (35%), insomnia (35%), flushing ± diaphoresis (31%), visual anomalies (30%), oral irritation/sores (30%), adenopathy/adenitis (28%), diarrhea (27%), urinary symptoms excluding interstitial cystitis (27%), frequent or atypical infections (27%), poor healing (23%), sinusitis (17%), weight gain/obesity (17%), dental deterioration (17%), weight loss (16%), cough (16%), anxiety/panic (16%), multiple/odd drug reactions (16%), dysmenorrhea (16%), asthma (15%), alopecia (15%), constipation (14%), depression (13%), tremor (13%), onychodystrophy (13%), heat and/or cold intolerance (13%)
Physical exam findings present in ≥10% of patients	Dermatographism (76%), tired appearance (47%), chronically ill appearance (42%), edema (any degree) (39%), obesity (any degree) (37%), edema (trace) (35%), rash (any type) (34%), mild systolic hypertension (140-159 mm Hg) (32%), abdominal pain (any location, any type, any severity) (32%), tachycardia (28%), achy appearance (28%), bruising (22%), deterioration of dentition (any type, any extent) (21%), paresthesia (20%), epigastric tenderness (19%), left upper quadrant abdominal tenderness (19%), edema (more than trace) (16%), soft tissue tenderness (16%), right upper quadrant abdominal tenderness (15%), mild diastolic hypertension (90-109 mm Hg) (14%), pallor (13%), moderate systolic hypertension (160-179 mm Hg) (12%), use of devices to assist mobility (12%), cognitive dysfunction ("brain fog") (12%), flushing (12%), weakness (global or focal) (12%), back tenderness (one or more points) (11%), anxiety (11%), depressed affect (11%), cardiac murmur (11%)
Problems occurring in the families of ≥5% of patients	Breast cancer (26%), atherosclerosis (21%), diabetes mellitus type 2 (19%), lung cancer (18%), hypertension (17%), osteoarthritis (16%), rheumatoid arthritis (15%), colon cancer (15%), prostate cancer (10%), lupus (10%), transient ischemic attacks or cerebrovascular accidents (8%), cancer not otherwise specified (8%), asthma (7%), environmental allergies (7%), leukemia or myelodysplastic syndrome (7%), sickle disease (5%), head and neck cancer (5%), non-Hodgkin lymphoma (5%), brain cancer (5%)

Afrin et al., *Blood* 2016; 128: 3683

Differential Diagnosis	Useful Test(s) in Investigation
Flushing	
Menopause	FSH, LH, estrogen
Carcinoid syndrome	24-Hour urine 5-hydroxyindoleacteic acid
Pheochromocytoma	24-Hour urine fractionated catecholamines and metanephrines
Medullary carcinoma of the thyroid	Serum calcitonin
Cardiovascular (presyncope/syncope, tachycardia, hypotension)	
Postural tachycardia syndrome (POTS)	Tilt table test
Autonomic dysfunction	Orthostatic drop in blood pressure
Cardiovascular diseases (arrhythmia)	ECG
Respiratory symptoms (throat tightness, stridor, wheezing)	
Asthma	Pulmonary function tests
Vocal cord dysfunction	Laryngoscopy, spirometry
Hereditary and acquired angioedema	C4, C1q, C1 inhibitor antigenic and functional levels
ACE inhibitor–associated angioedema	Plasma bradykinin*
Gastrointestinal symptoms (diarrhea, abdominal cramping)	
Primary bowel disease (irritable bowel syndrome, inflammatory bowel disease)	Endoscopy and biopsy
Neuroendocrine tumors	Serum vasoactive intestinal peptide
Other	
Panic attack	Psychiatric consultation

Picard et al., Clin. Ther. 2013; 35: 548 - 562

Diagnostic criteria of iMCAS

Episodic occurrence of typical MC-related clinical symptoms affecting 2 or more organ systems.

An increase in serum tryptase level by 20% over the individual baseline plus 2 ng/mL total within a 4-hour window after a reaction.

A clear response (improvement) of the symptoms to drugs targeting MC-derived mediators, MC-stabilizing agents, or both.

Valent et al., *J. Allergy Clin. Immunol.* 2018; 142: 1008-9

Marker	Comment
Tryptase	The most specific marker Almost always increased in patients with hypotensive mast cell activation episodes Must be measured within 4 h of an episode and compared with baseline values Increased baseline levels in the absence of renal disease or myeloid neoplasm might indicate mastocytosis or familial hypertryptasemia
Urinary histamine metabolites	Fairly specific for mast cell activation Might be influenced by diet or bacterial contamination Specific cutoffs for mast cell activation syndrome not established
Urinary prostaglandin D_2 or metabolites	Increased in patients with mast cell activation Not specific to mast cells Specific cutoffs for mast cell activation not established Not recommended as the single marker of mast cell activation Can guide the decision to initiate aspirin therapy if the patient is not allergic to nonsteroidal anti-inflammatory drugs
Urinary leukotriene E_4	Increased in patients with mast cell activation Less clinical experience than other markers Might guide the decision to initiate leukotriene-targeting therapy

Akin, J. Allergy Clin. Immunol. 2017; 140: 349-55

Diagnostic criteria of iMCAS

Episodic occurrence of typical MC-related clinical symptoms affecting 2 or more organ systems.

An increase in serum tryptase level by 20% over the individual baseline plus 2 ng/mL total within a 4-hour window after a reaction.

A clear response (improvement) of the symptoms to drugs targeting MC-derived mediators, MC-stabilizing agents, or both.

Valent et al., *J. Allergy Clin. Immunol.* 2018; 142: 1008-9

Treatment of iMCAS

- H1 Antihistamines
- H2 Blockers
- Leukotriene antagonists
- Comoglycate
- Omalizumab

Mast Cell Activation Syndrome

D89.40 Mast cell activation, unspecified
Mast cell activation disorder, unspecified
Mast cell activation syndrome, NOS

D89.41 Monoclonal mast cell activation syndrome

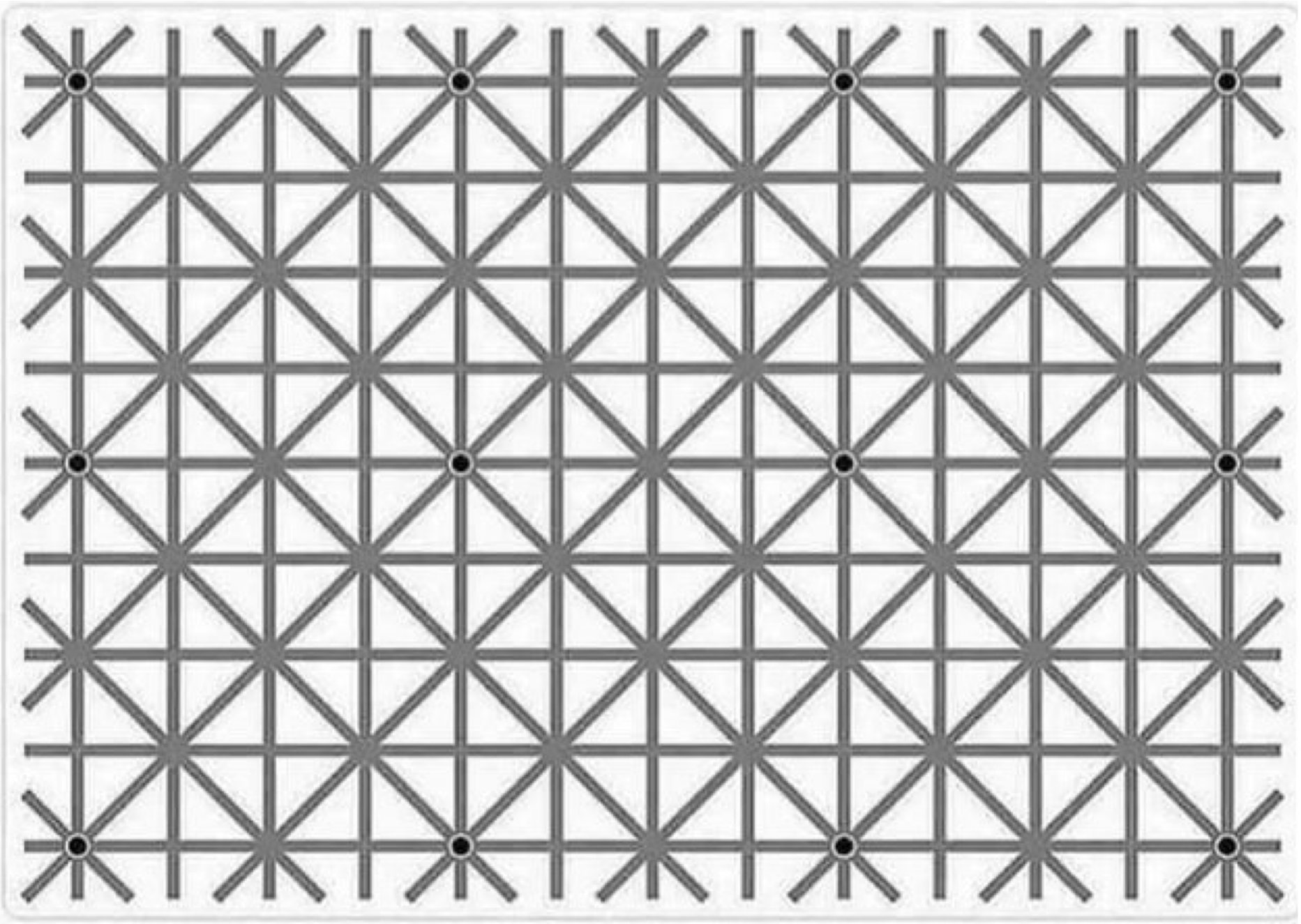
D89.42 Idiopathic mast cell activation syndrome

D89.43 Secondary mast cell activation
Secondary mast cell activation syndrome
Code also underlying etiology, if known

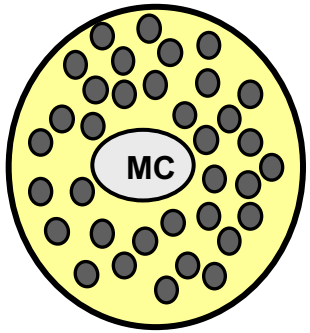
D89.49 Other mast cell activation disorder
Other mast cell activation syndrome

Idiopathic MCAS – Unmet needs

- What are the causes of iMCAS?



How are mast cells activated in CSU?



Maurer et al., *Front. Immunol.* 2018: 9; 689

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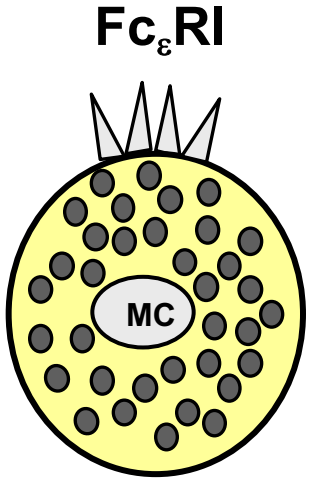

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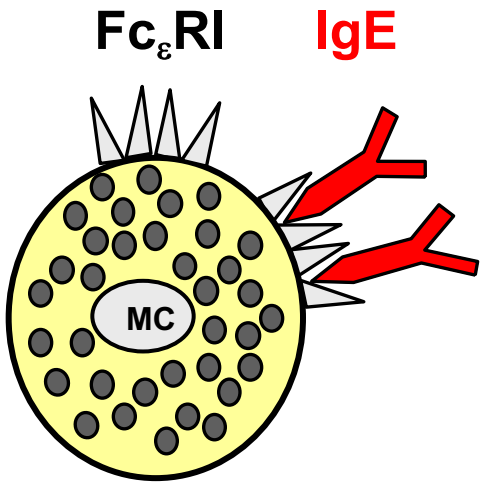

Maurer et al., *Front. Immunol.* 2018: 9; 689

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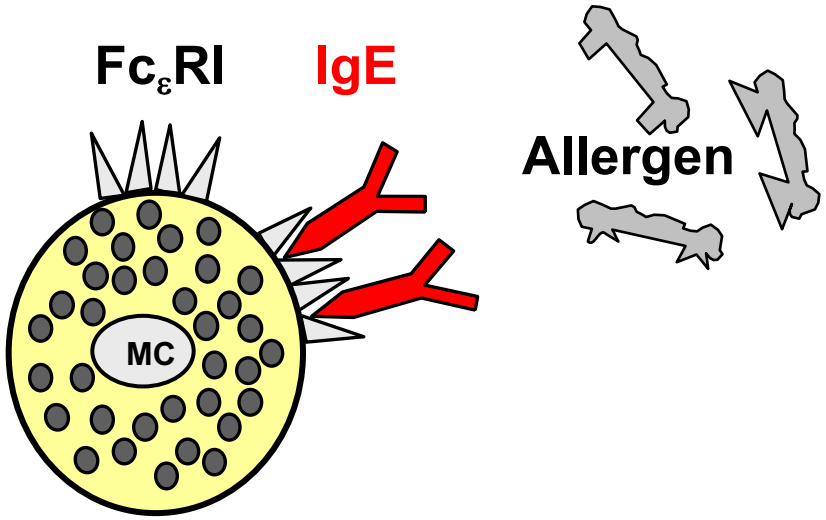
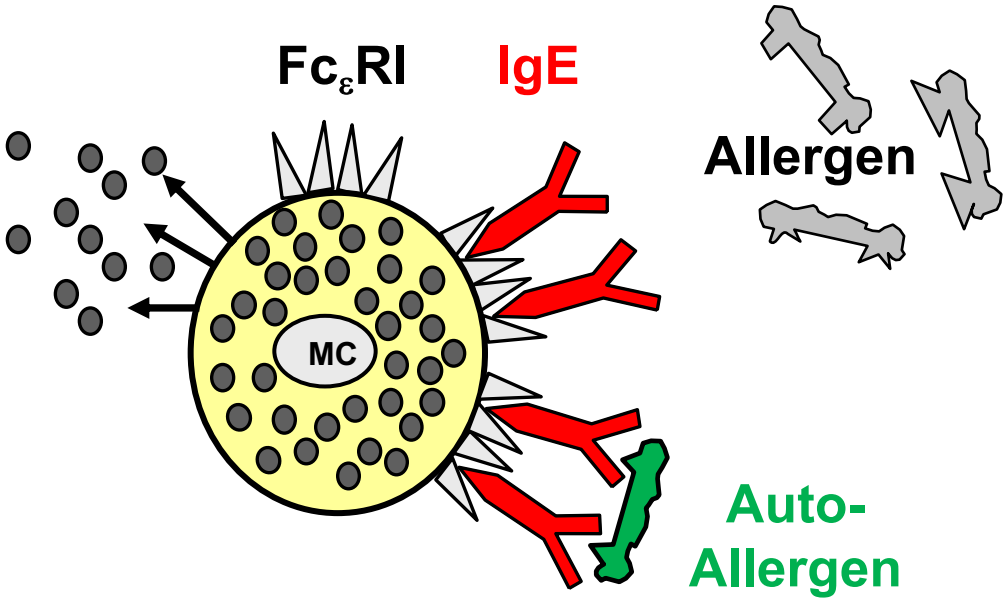


Maurer et al., *Front. Immunol.* 2018: 9; 689

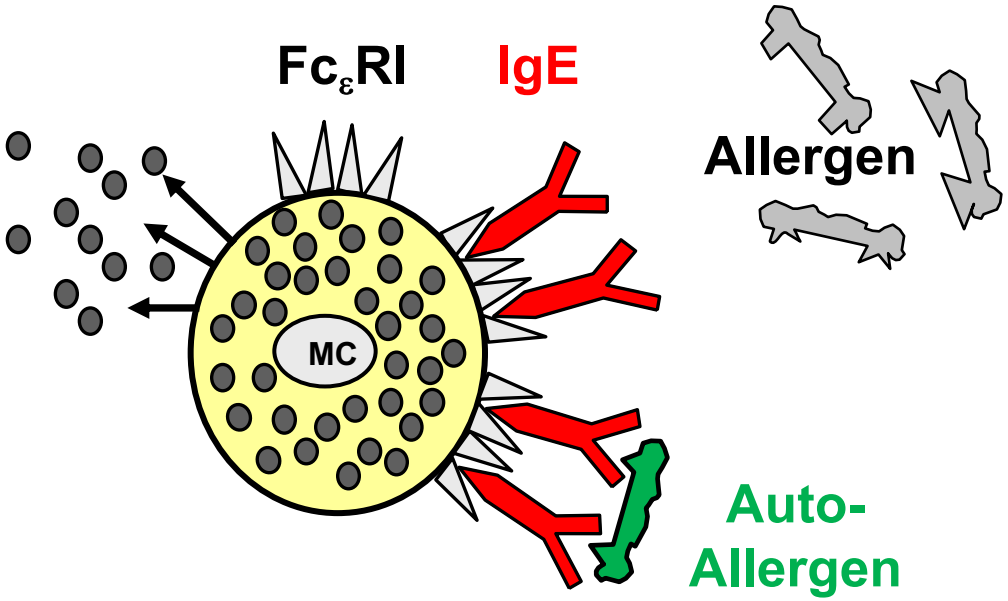
How are mast cells activated in CSU?



Autoallergy

Maurer et al., *Front. Immunol.* 2018: 9; 689

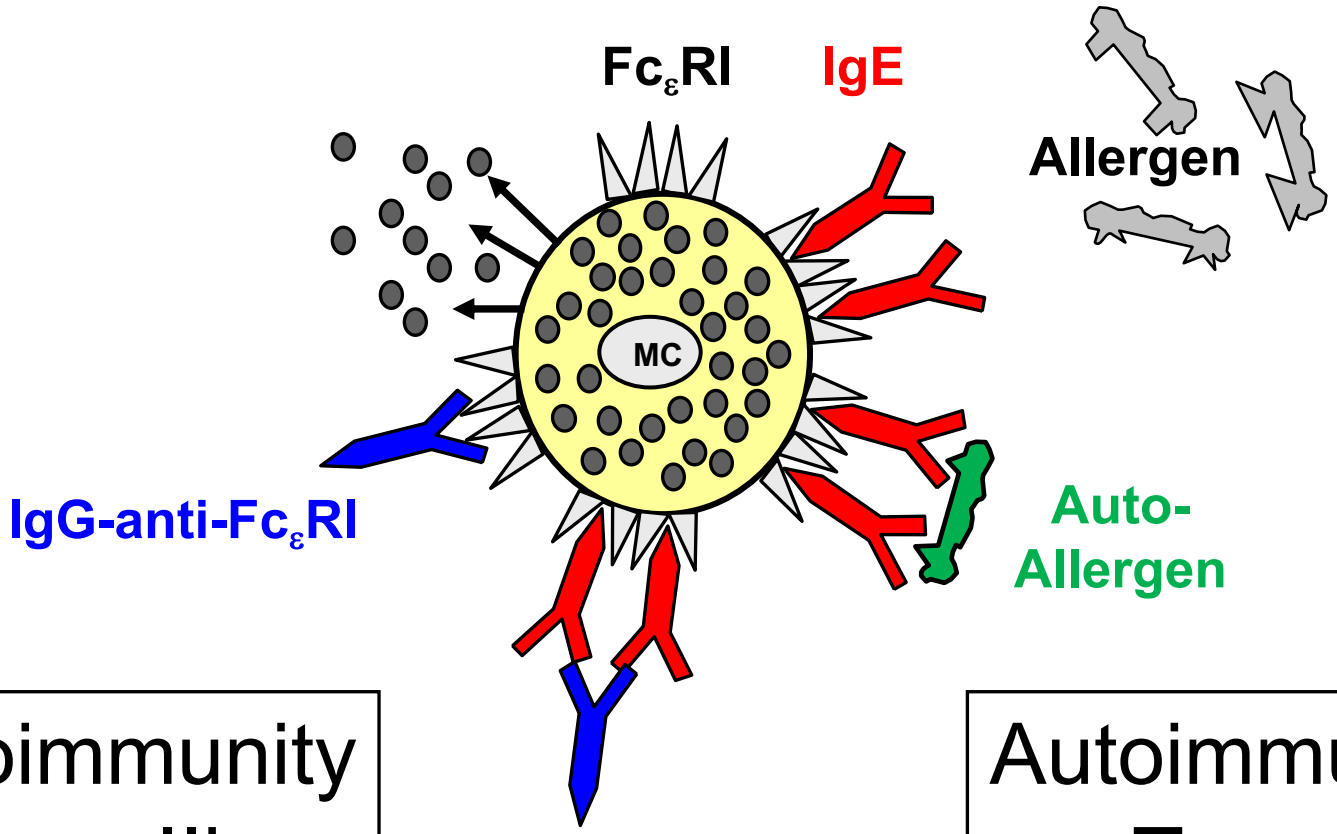
How are mast cells activated in CSU?



Autoimmunity
Type I

Maurer et al., *Front. Immunol.* 2018: 9; 689

How are mast cells activated in CSU?



Autoimmunity
Type IIb

Autoimmunity
Type I

Kolkhir et al., *J. Allergy Clin. Immunol*. 2017: 139; 1772

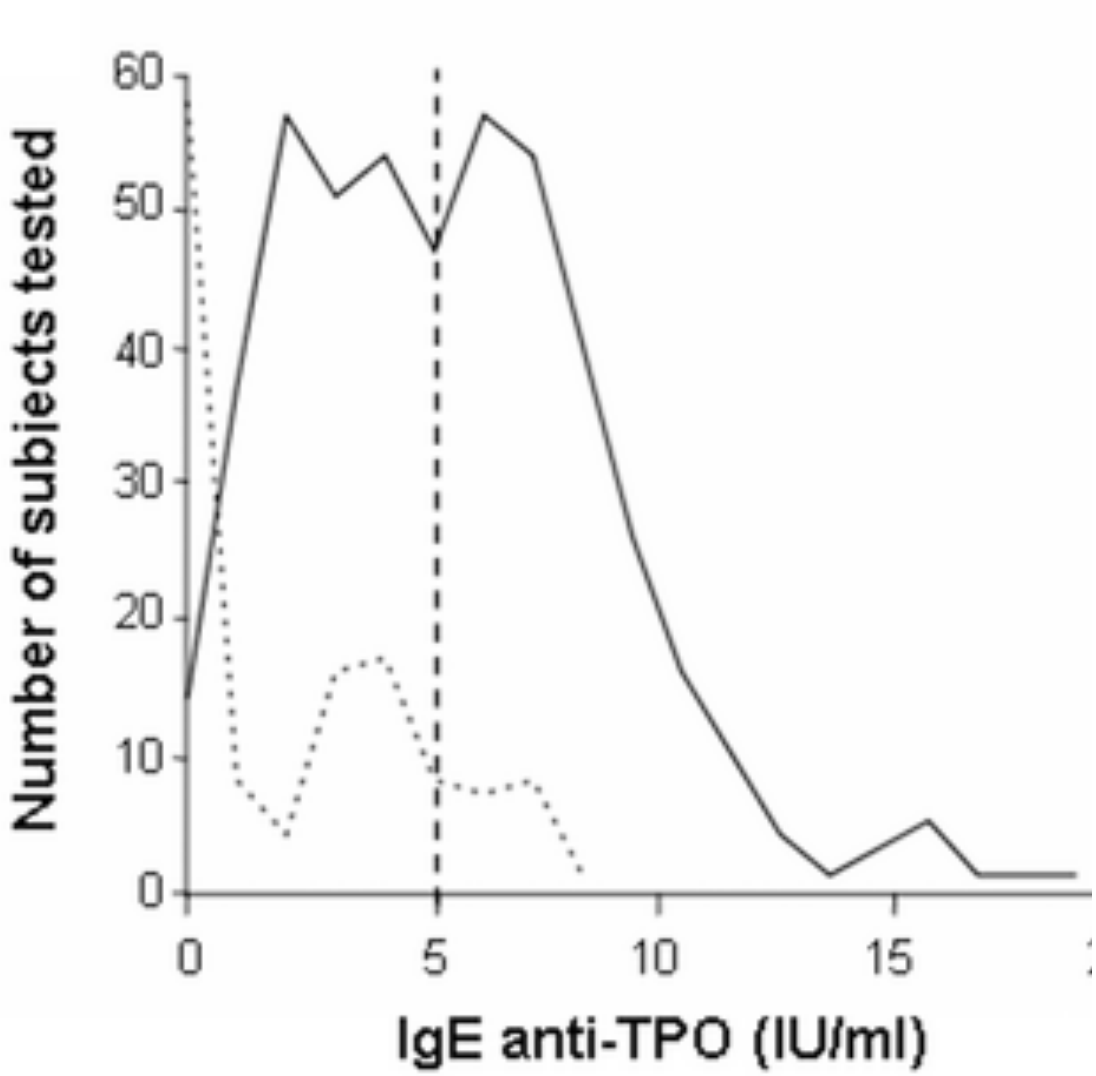
Type I autoimmune („autoallergic“) CSU

Type I autoimmune („autoallergic“) CSU

- CSU patients often have IgE-anti-thyreoperoxidase (TPO)

Altrichter et al., *PLoS ONE* 2011: 12; 6

IgE-anti-TPO in CSU



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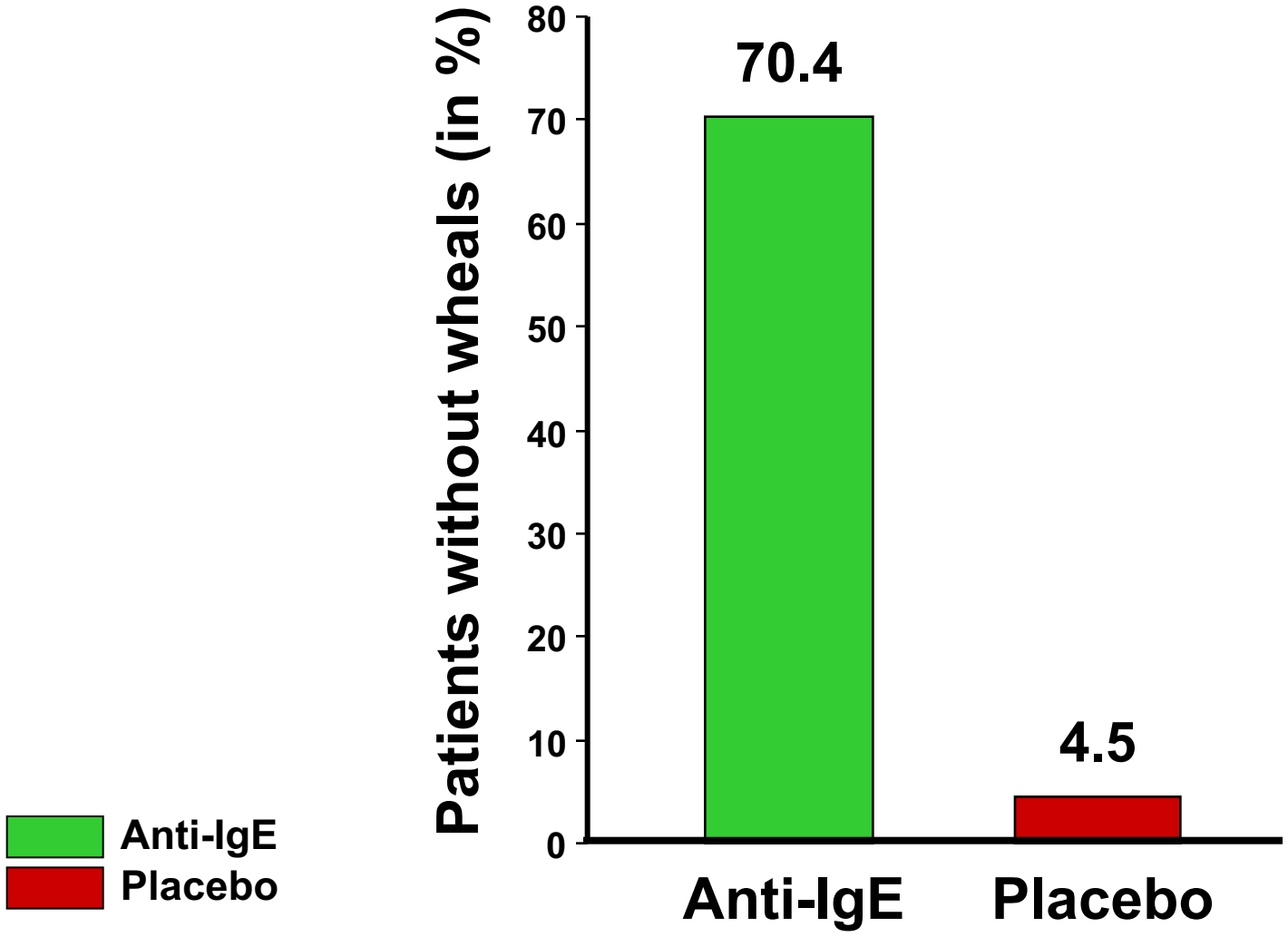
Type I autoimmune („autoallergic“) CSU

- CSU patients often have IgE-anti-thyreoperoxidase (TPO)
- IgE-anti-TPO+ CSU patients benefit from omalizumab

Maurer et al., *J Allergy Clin Immunol* 2011; 128: 202-209

Patients with Complete Disease Control (no more wheals …)



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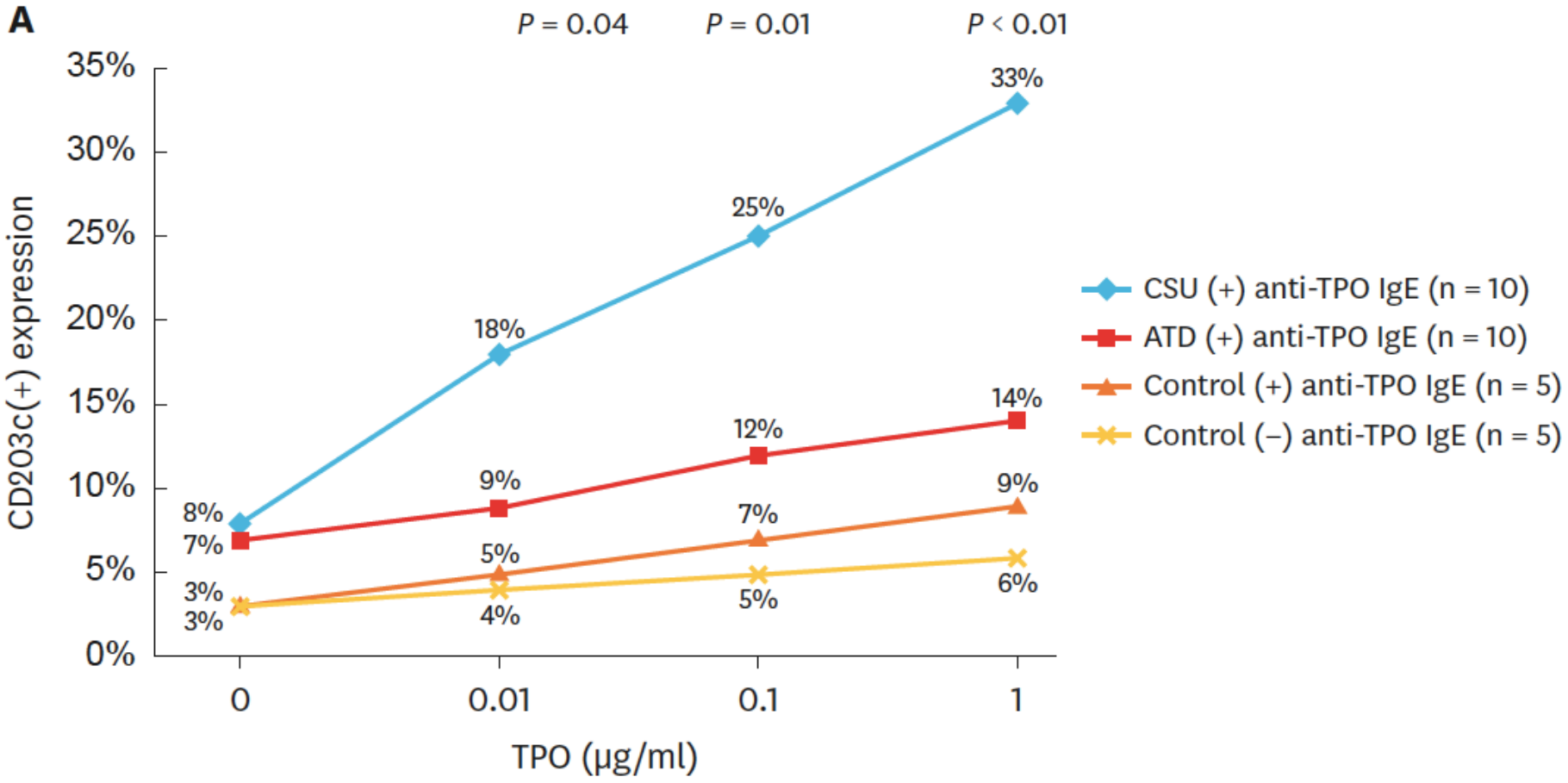
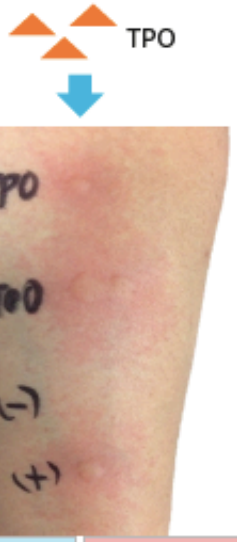
- CSU patients often have IgE-anti-thyreoperoxidase (TPO)
- IgE-anti-TPO+ CSU patients benefit from omalizumab
- IgE-anti-TPO & TPO degranulates mast cells

IgE-anti-TPO is functional

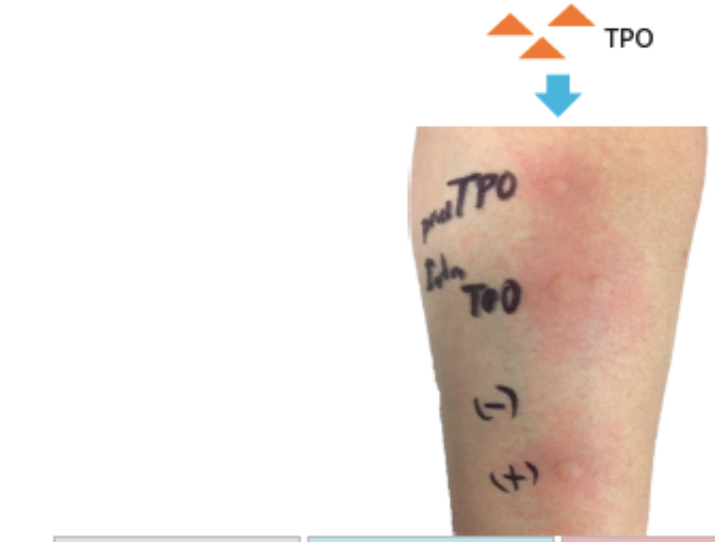


Sánchez et al., Allergy Asthma Immunol Res 2019; 11: 29-42



TPO SPT Intradermal	CSU (n = 50)	ATD (n = 30)	Control (n = 50)
	6 (12.0%)	0	0
	9 (18.0%)	1 (3.0%)	4 (8.0%)

Sánchez et al., Allergy Asthma Immunol Res 2019; 11: 29-42



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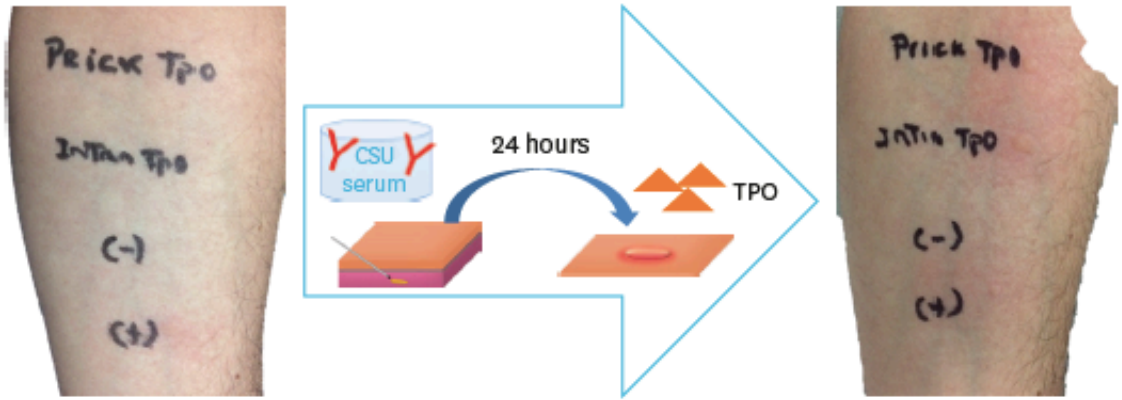
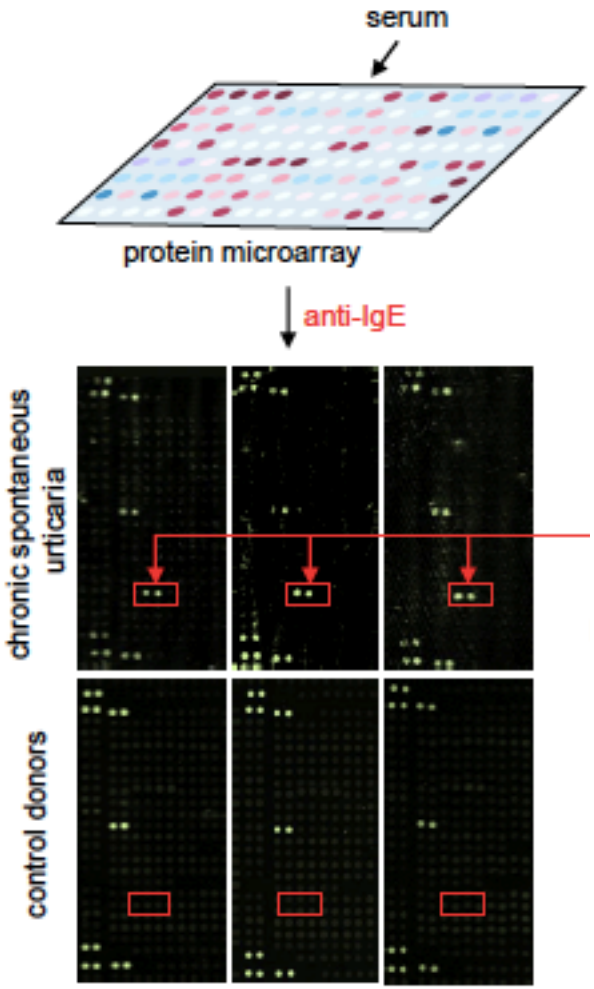


Control (–)

Control (with CSU serum)

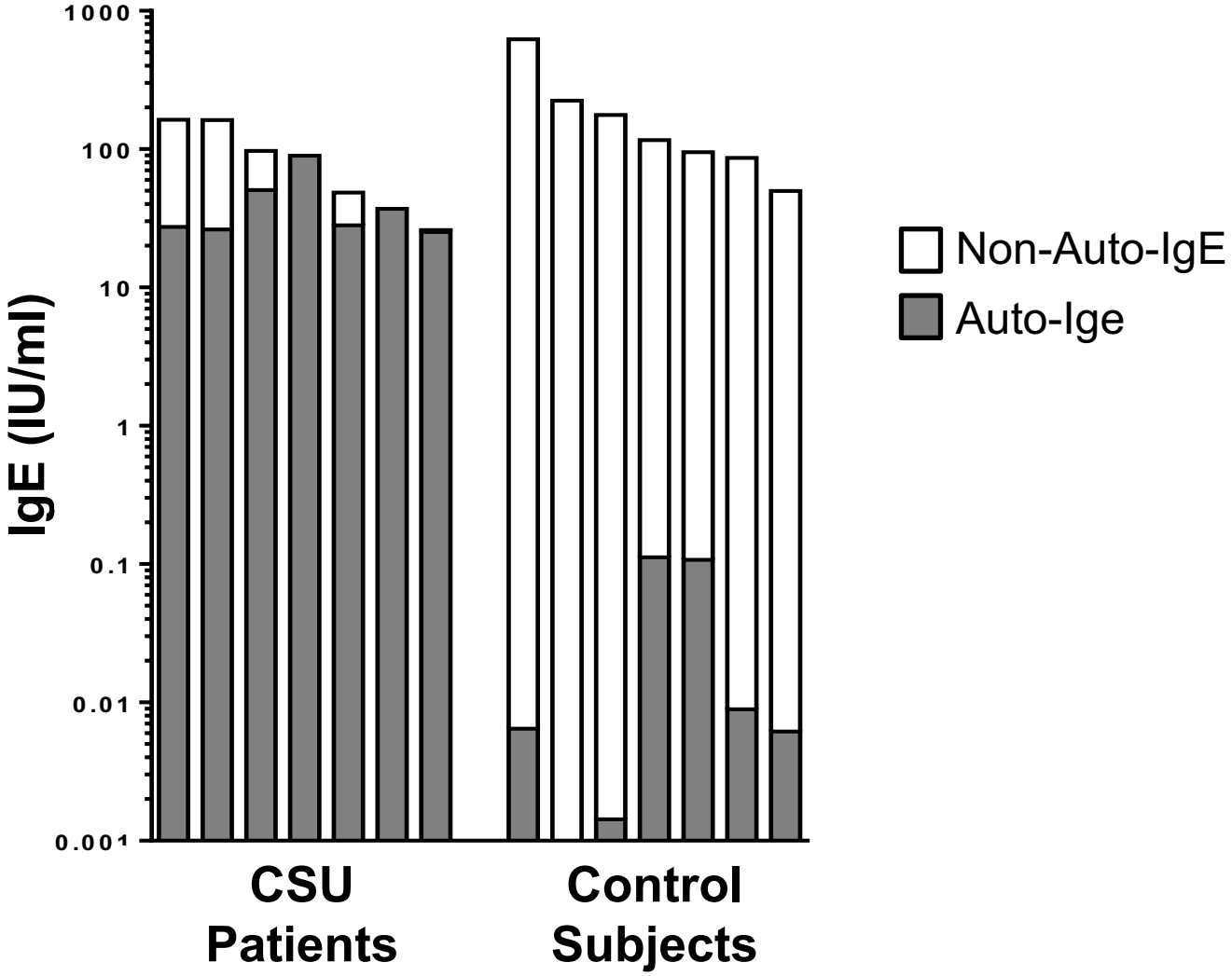
Sánchez et al., Allergy Asthma Immunol Res 2019; 11: 29-42



How much of the total IgE is auto-IgE?

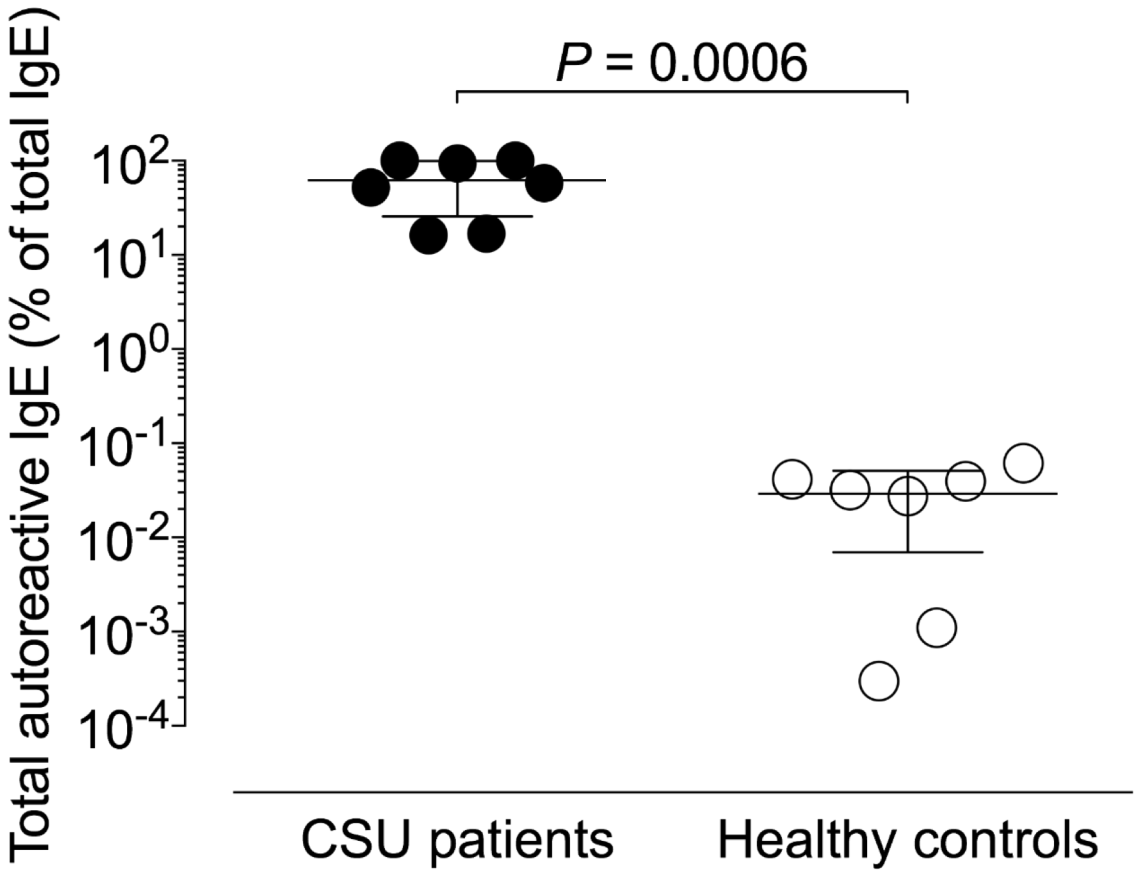
Lakin et al., Theranostics 2018; in press

Most of the IgE reactivity in CSU patients is directed against self



Lakin et al., Theranostics 2018; in press

CSU patients have much more auto-IgE



Lakin et al., Theranostics 2018; in press

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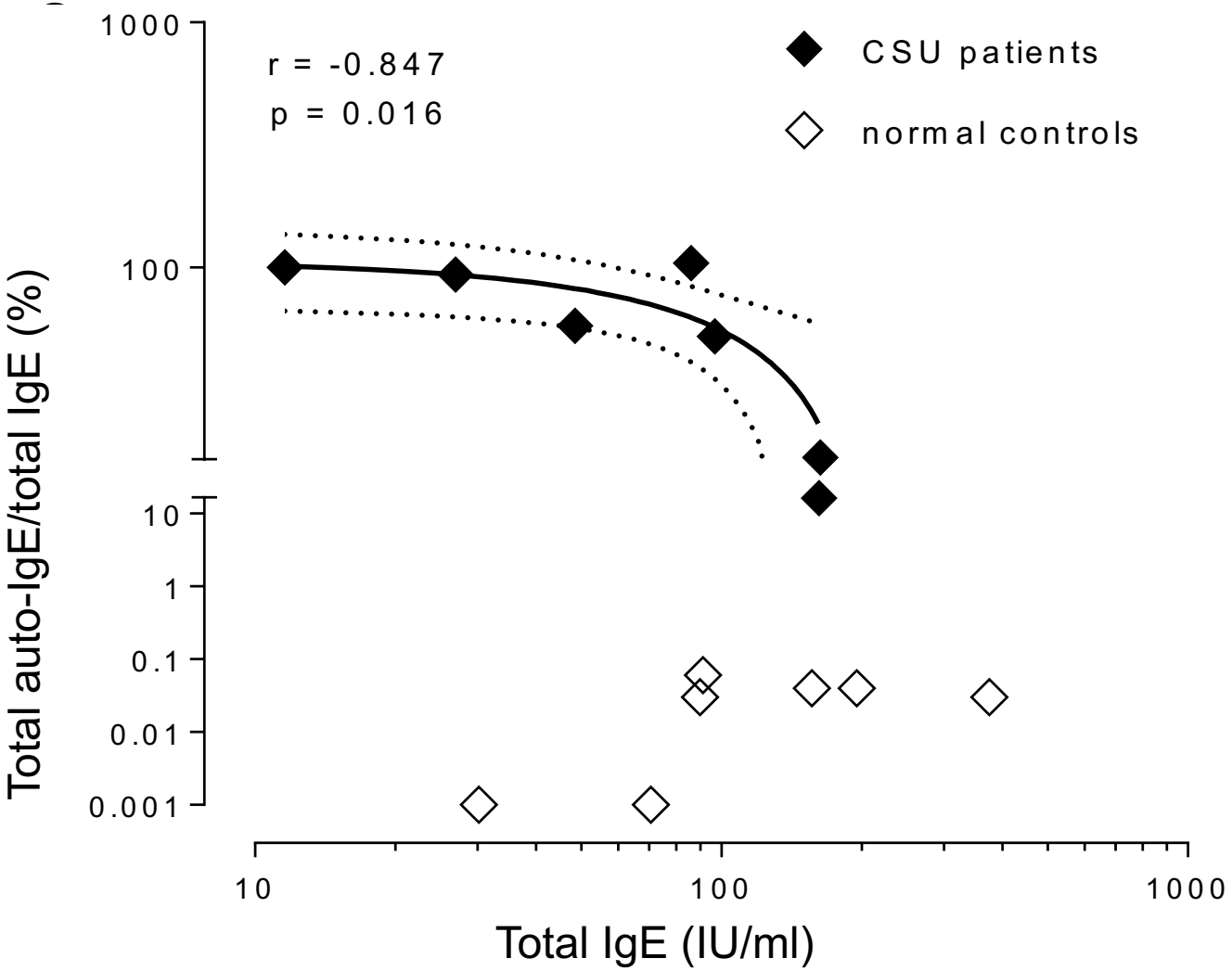
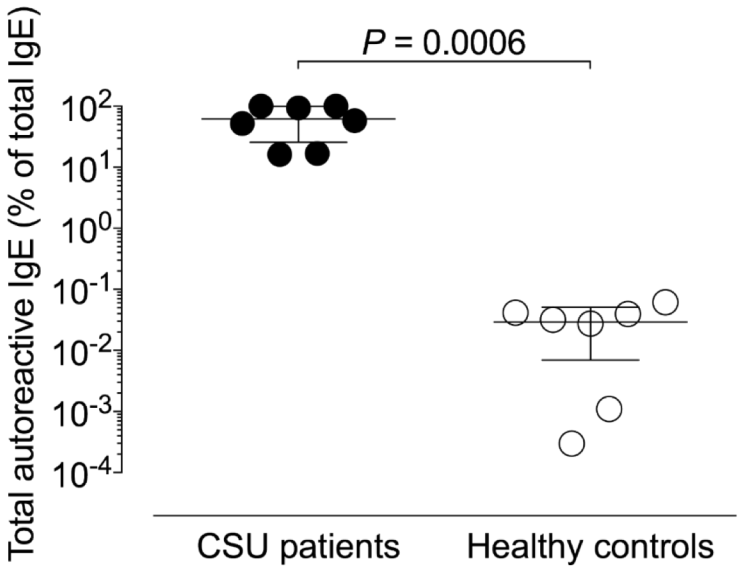


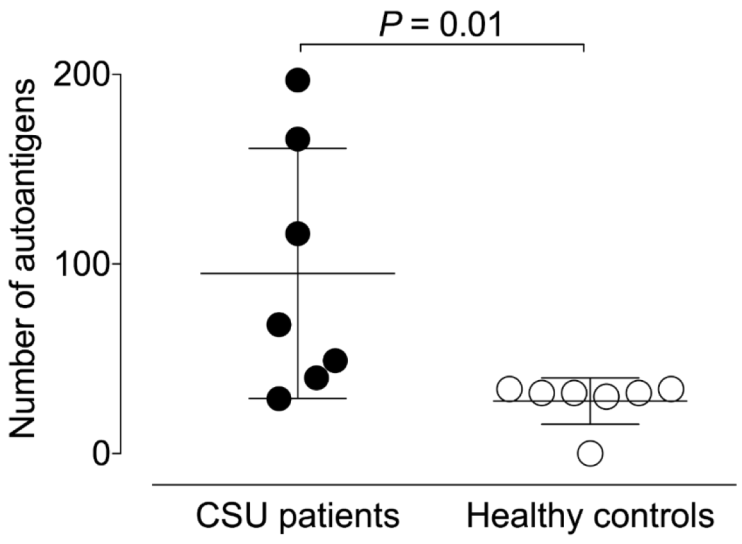
Lakin et al., Theranostics 2018; in press

Type I autoimmune („autoallergic“) CSU

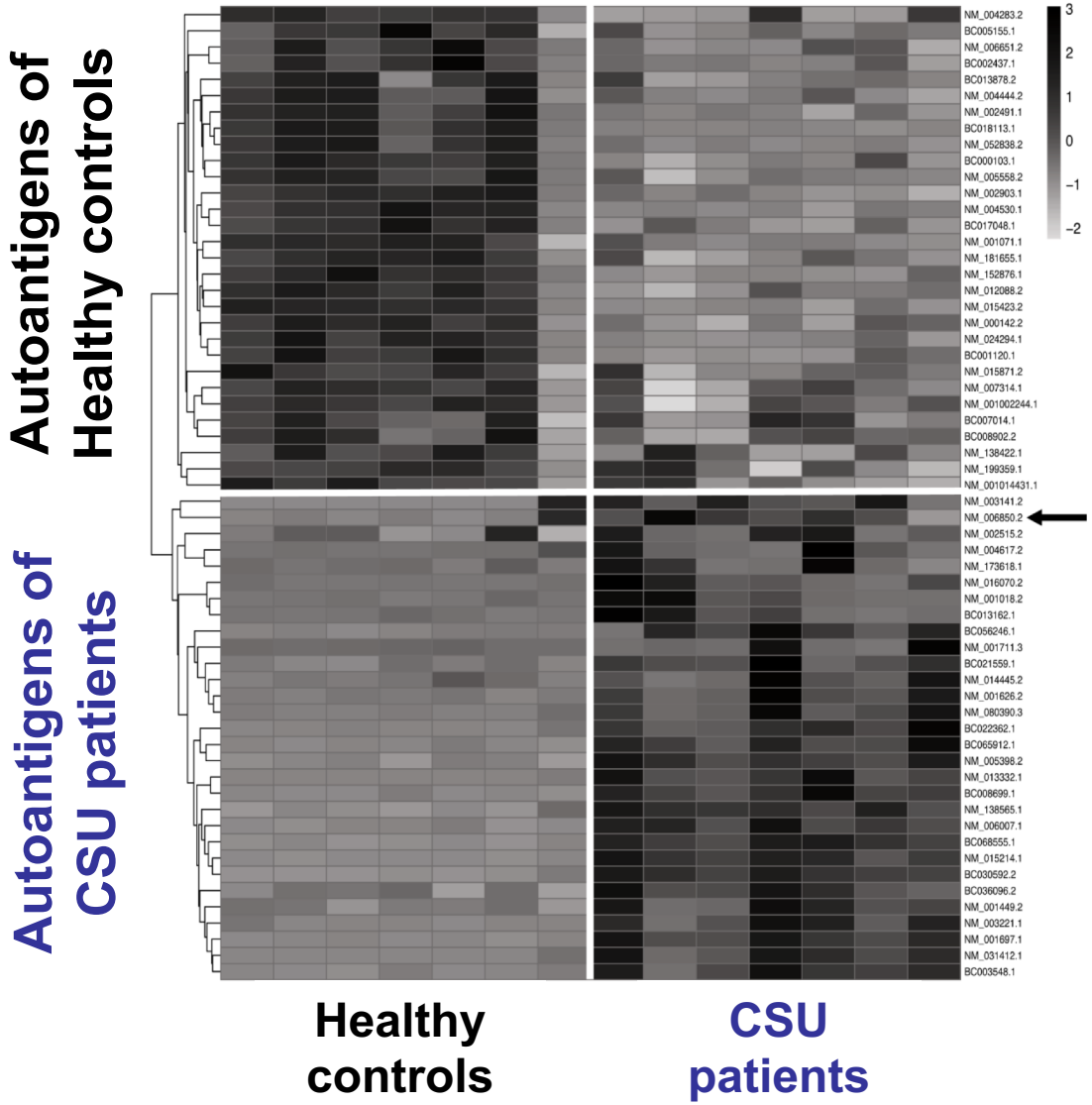
- CSU patients often have IgE-anti-thyreoperoxidase (TPO)
- IgE-anti-TPO+ CSU patients benefit from omalizumab
- IgE-anti-TPO & TPO degranulates mast cells
- Most of the IgE reactivity in CSU patients is against self

CSU patients have much more auto-IgE against many more autoantigens





Lakin et al., Theranostics 2018; in press



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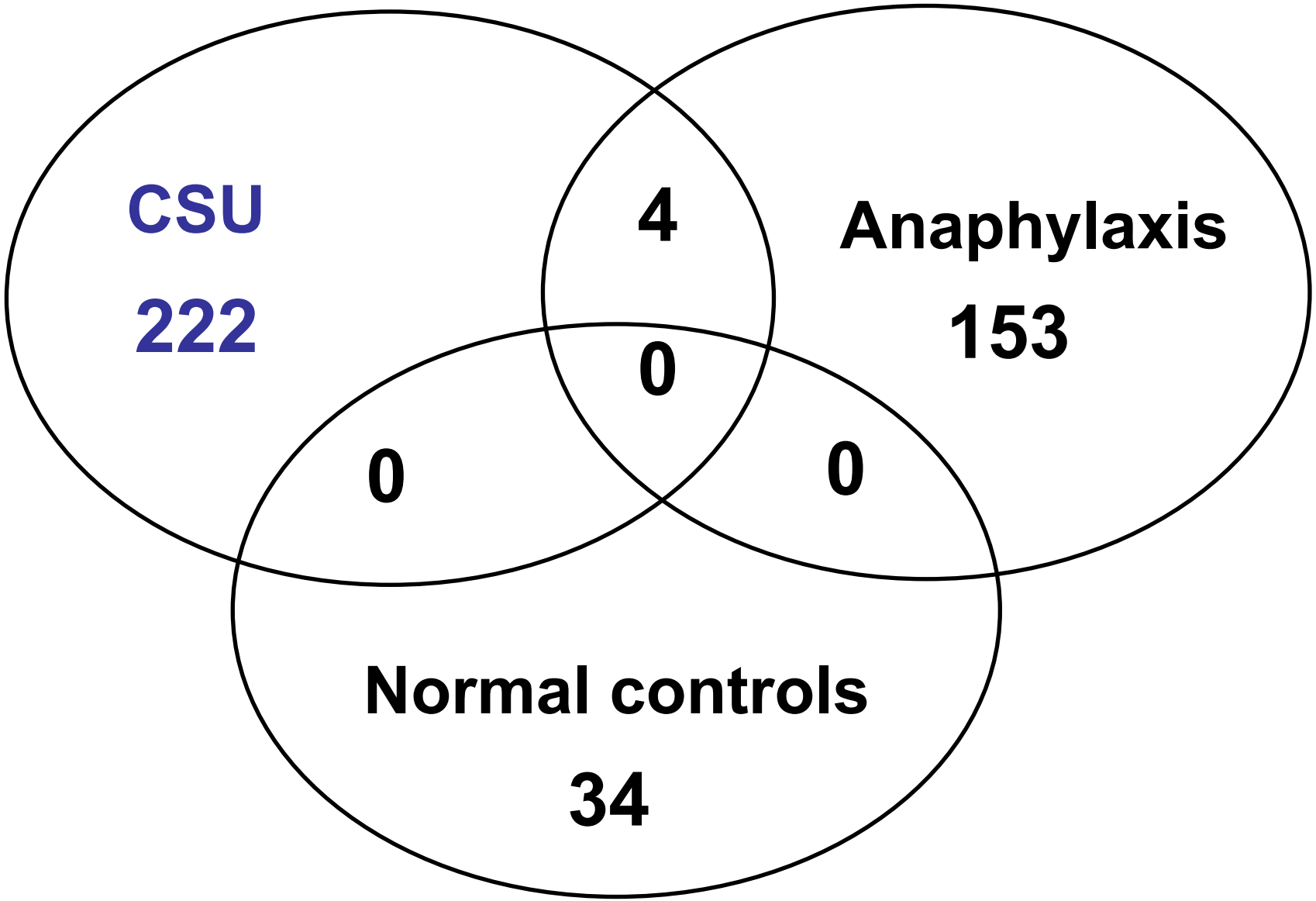
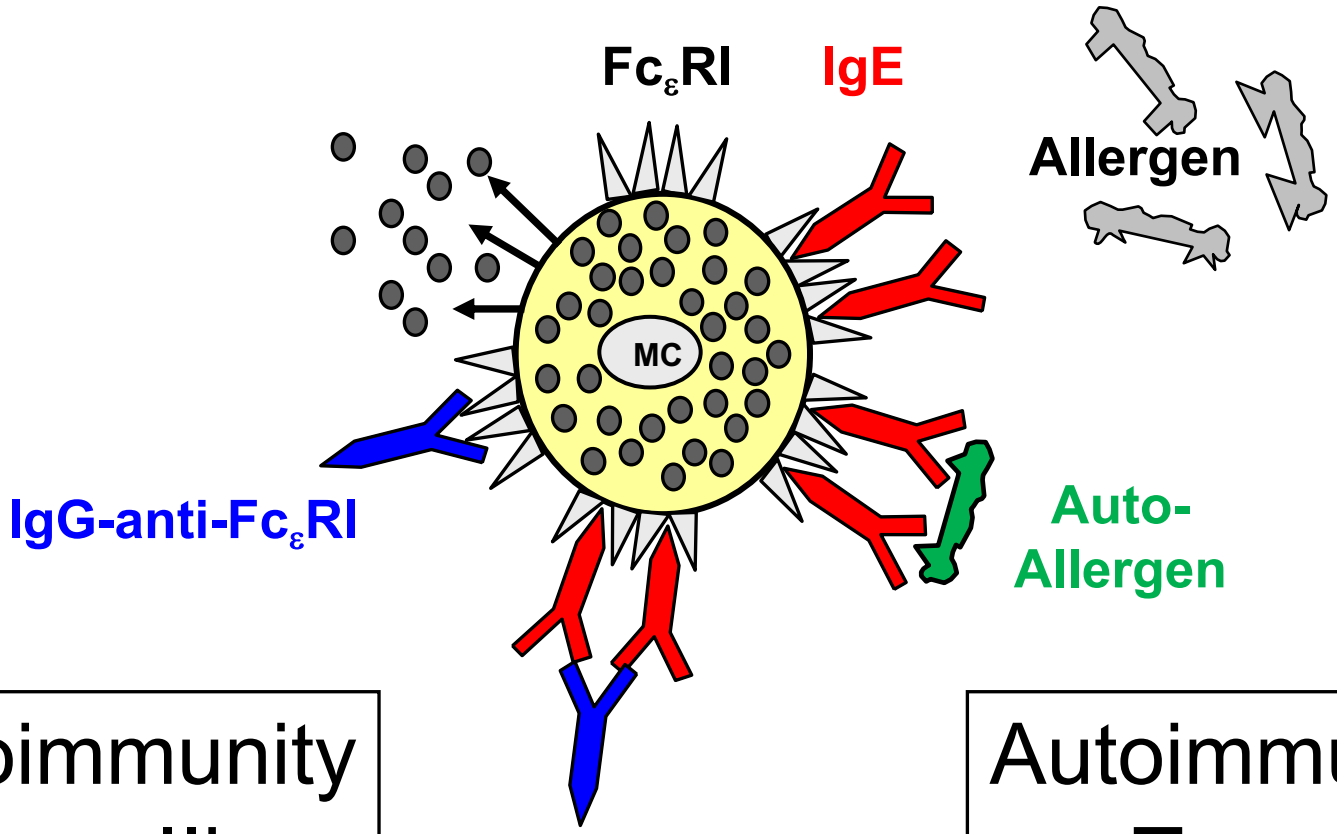


Lakin et al., Theranostics 2018; in press

What is the role of Type I and Type IIb autoimmunity in iMCAS?



Autoimmunity Type IIb

Autoimmunity Type I

Idiopathic MCAS – Unmet needs

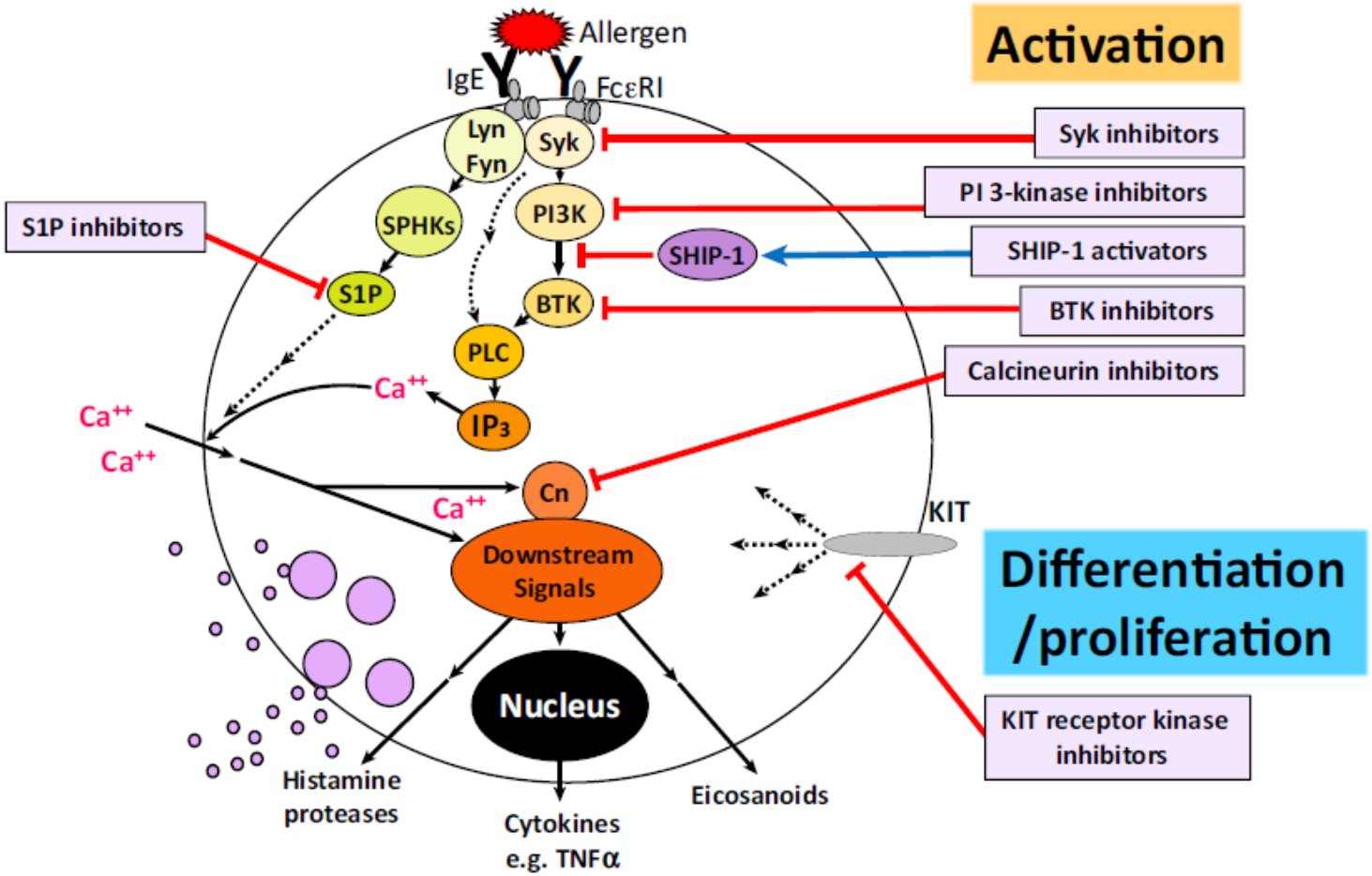
- What are the causes of iMCAS?

Idiopathic MCAS – Unmet needs

- What are the causes of iMCAS?
- Better diagnostic criteria / tests

Idiopathic MCAS – Unmet needs

- What are the causes of iMCAS?
- Better diagnostic criteria / tests
- Targeted treatment



Trends in Immunology

Figure 1. Simplified Overview of Therapeutic Strategies Targeting Signaling in Order to Prevent Activation (in Terms of Subsequent Mediator Release to Allergen Provocation), Chemotaxis, or Differentiation of Mast Cells. ⊣ Denotes inhibition, arrows activation (dotted arrows indirect activation). Abbreviations: Syk, spleen tyrosine kinase; PI3K, phosphatidylinositol 3-kinase; BTK, Bruton's tyrosine kinase; CN, calcineurin; IP3, inositol trisphosphate; PLC, phospholipase C; S1P, sphingosine-1-phosphate; SHIP-1, Src homology 2 (SH2) domain-containing inositol 5′ phosphatase 1; SPHKs, sphingosine kinases.

Siebenhaar et al., *Trends Immunol.* 2018: 39; 151-162

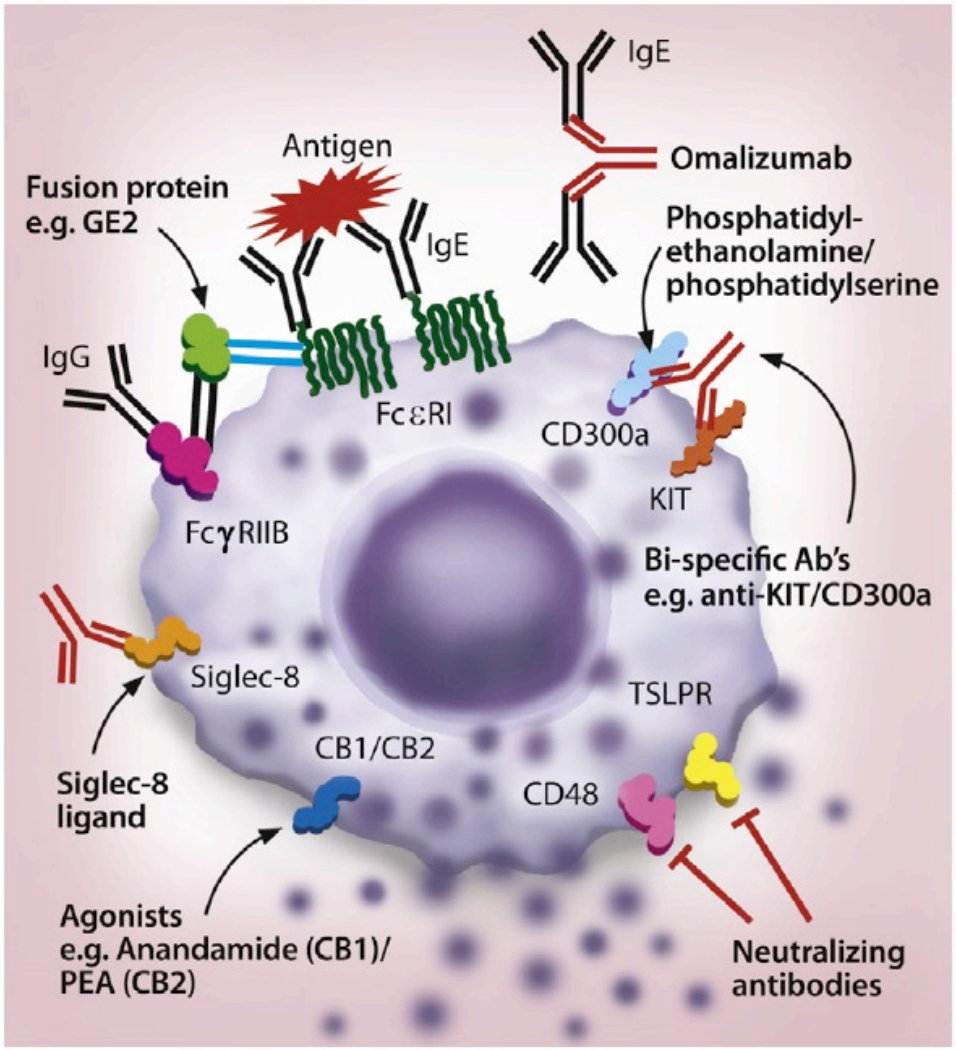


FIG 3. Novel surface receptors that alter IgE-dependent mediator release in MCs, Bs, or both. Stimulation of inhibitory receptors, such as CB1, CD300a, FcγRIIB, and Siglec-8, or blockade of surface activating receptors, such as CD48 and TSLPR, could potentially serve as targets for future allergy therapy. *PEA*, Palmitoylethanolamide.

Harvima et al., *J. Allergy Clin. Immunol*. 2014: 134; 530-544

Mast Cell Activation Diseases

Marcus Maurer
Dermatological Allergology
Allergie-Centrum-Charité
Department of Dermatology and Allergy
Charité - Universitätsmedizin Berlin
Germany

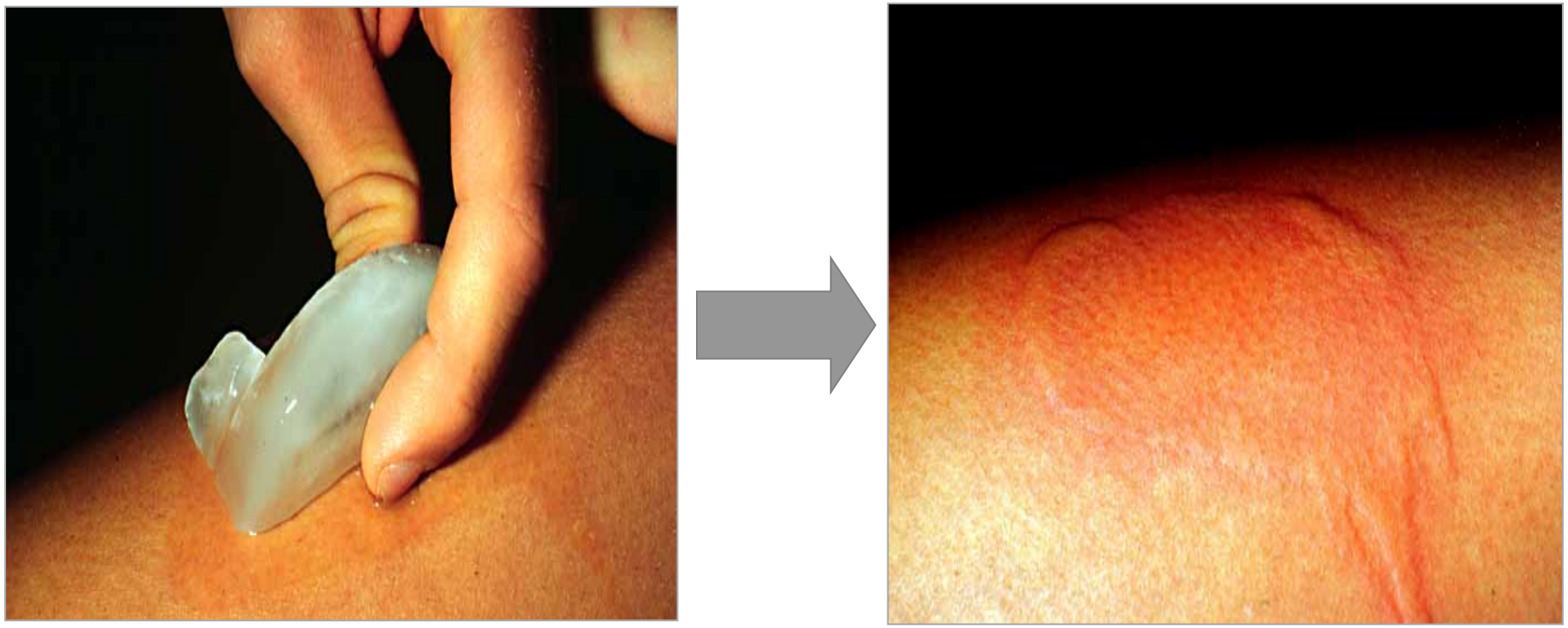
Dermatological Allergology

www.allergie-centrum-charite.de

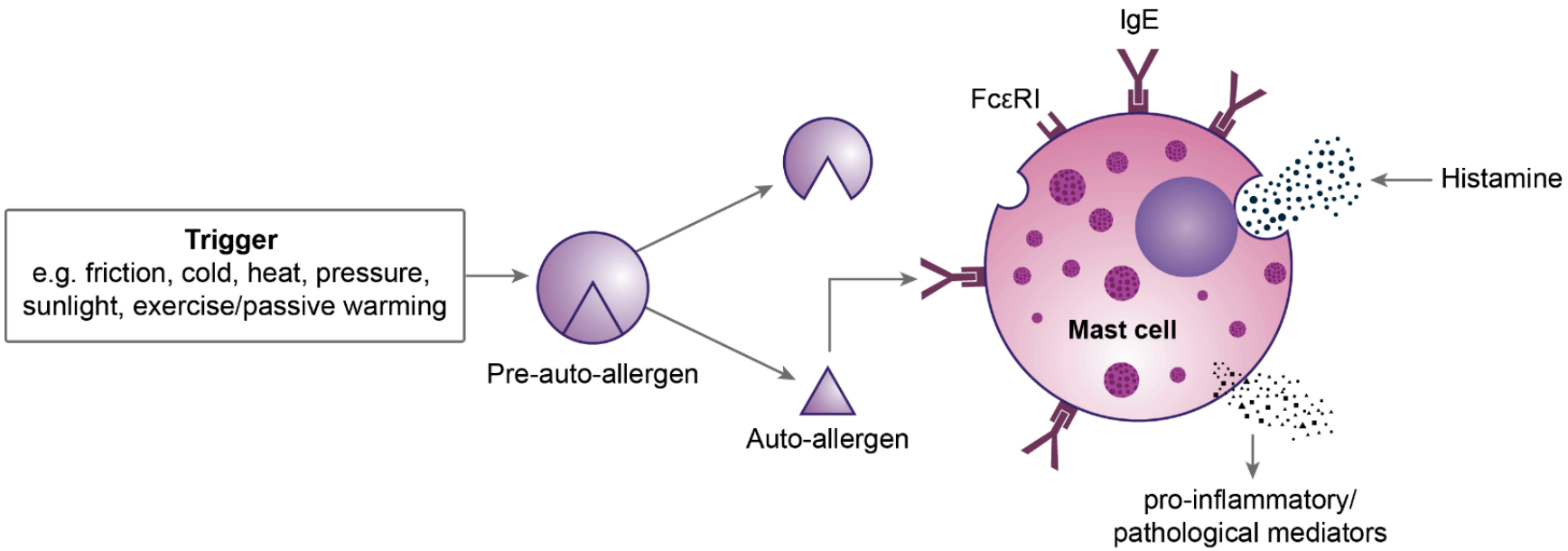
marcus.maurer@charite.de


CURE
CHRONIC
URTICARIA
REGISTRY

Cold Urticaria

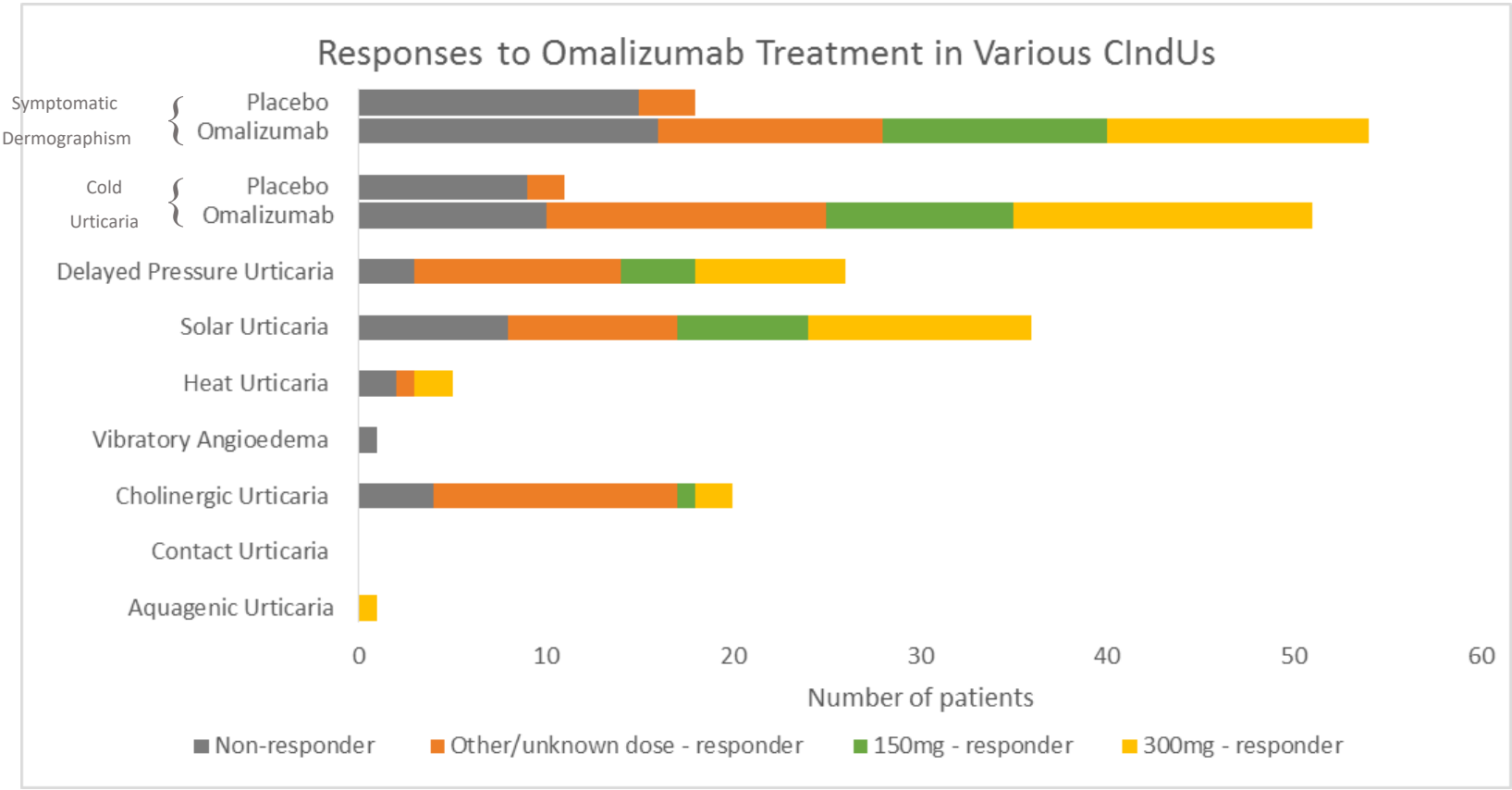


Chronic Inducible Urticaria



Maurer et al., J Allergy Clin Immunol 2018; 141: 638-649

Omalizumab Treatment in Chronic Inducible Urticaria: A Systematic Review of Published Evidence



Maurer et al., J Allergy Clin Immunol 2018; 141: 638-649

Division of Dermatological Allergology

www.allergie-centrum-charite.de

marcus.maurer@charite.de

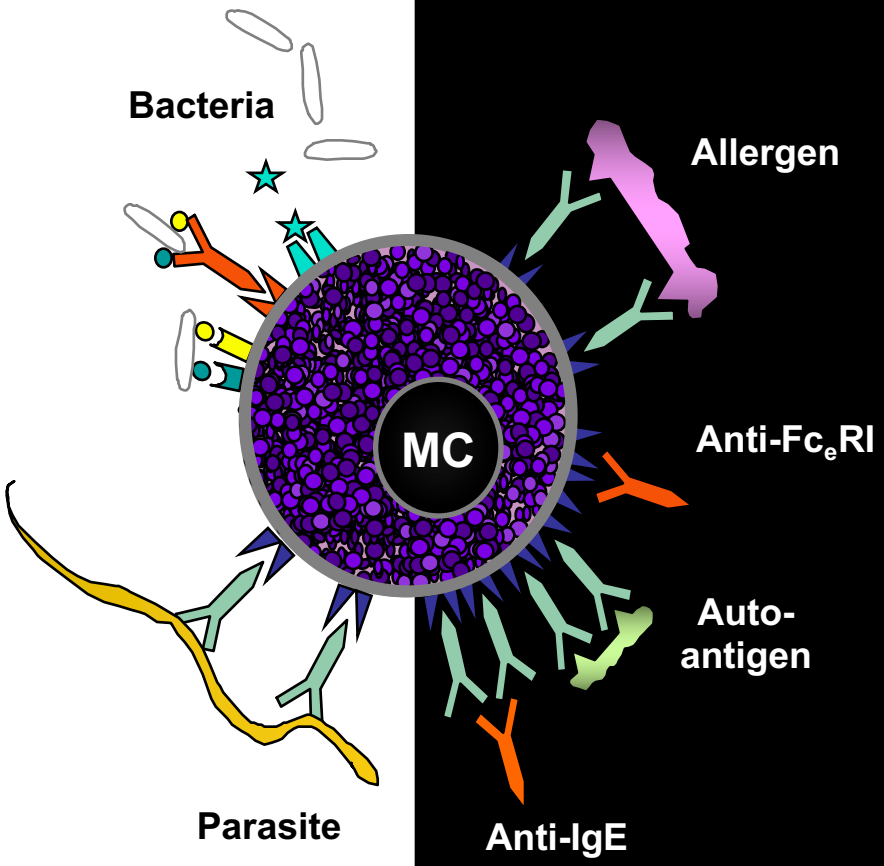
Mast cell activation disorders

Marcus Maurer
Dermatological Allergology
Allergie-Centrum-Charité
Department of Dermatology and Allergy
Charité - Universitätsmedizin Berlin
Germany

The role of mast cells

Innate Immunity

Adaptive Immunity



Allergy

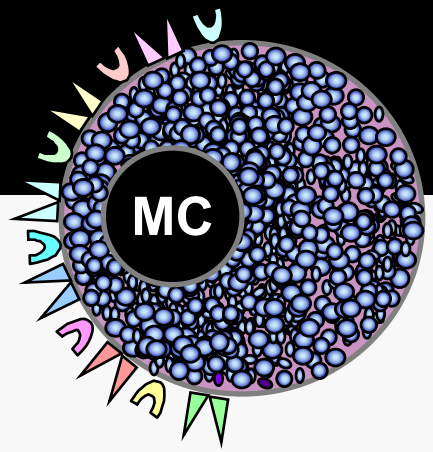
Autoimmunity

Autoallergy

Metz et al. *Science* 2006; 313: 526-30
Maurer et al. *Nature* 2004; 432: 512-6

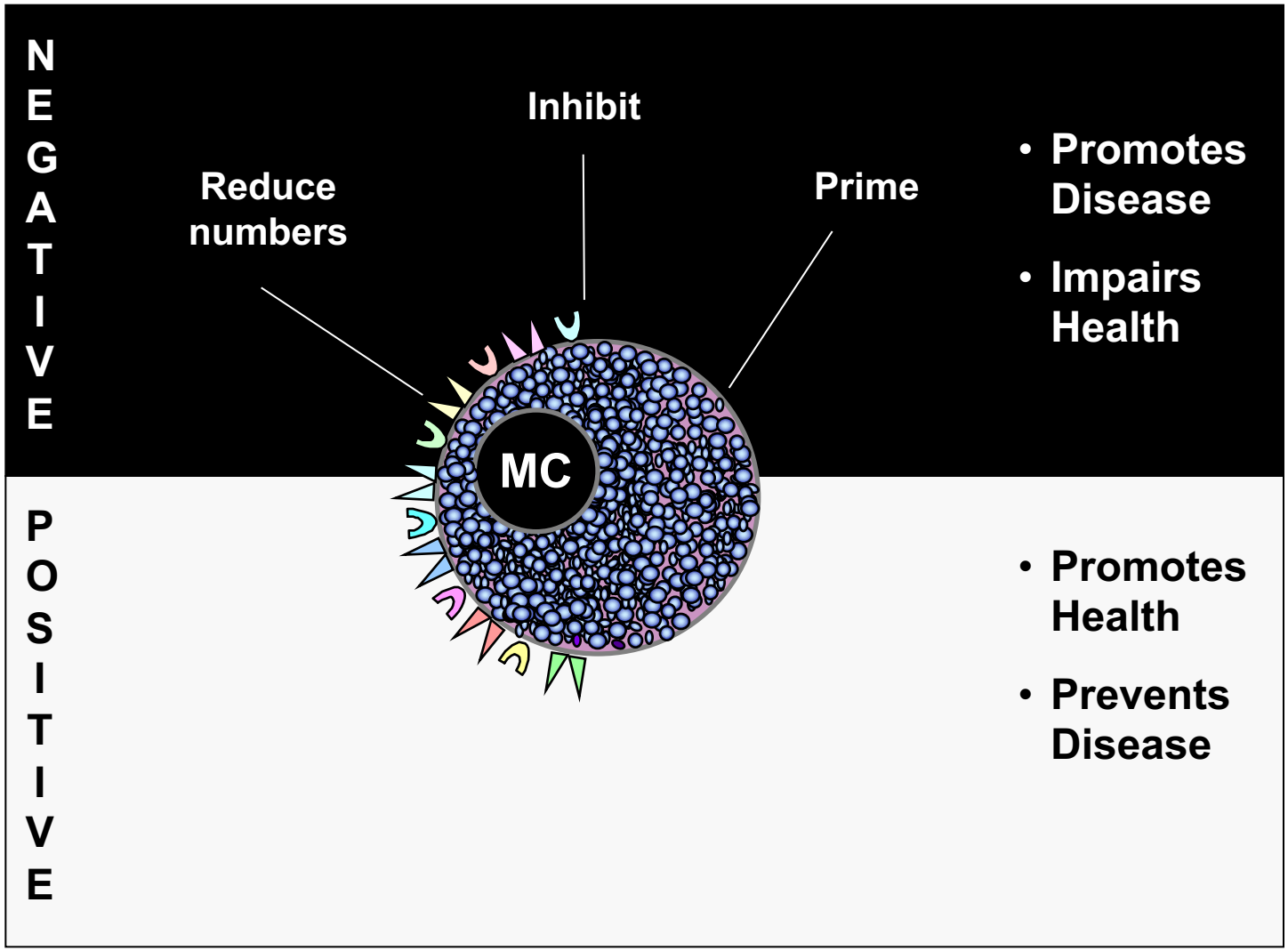
NEGATIVE

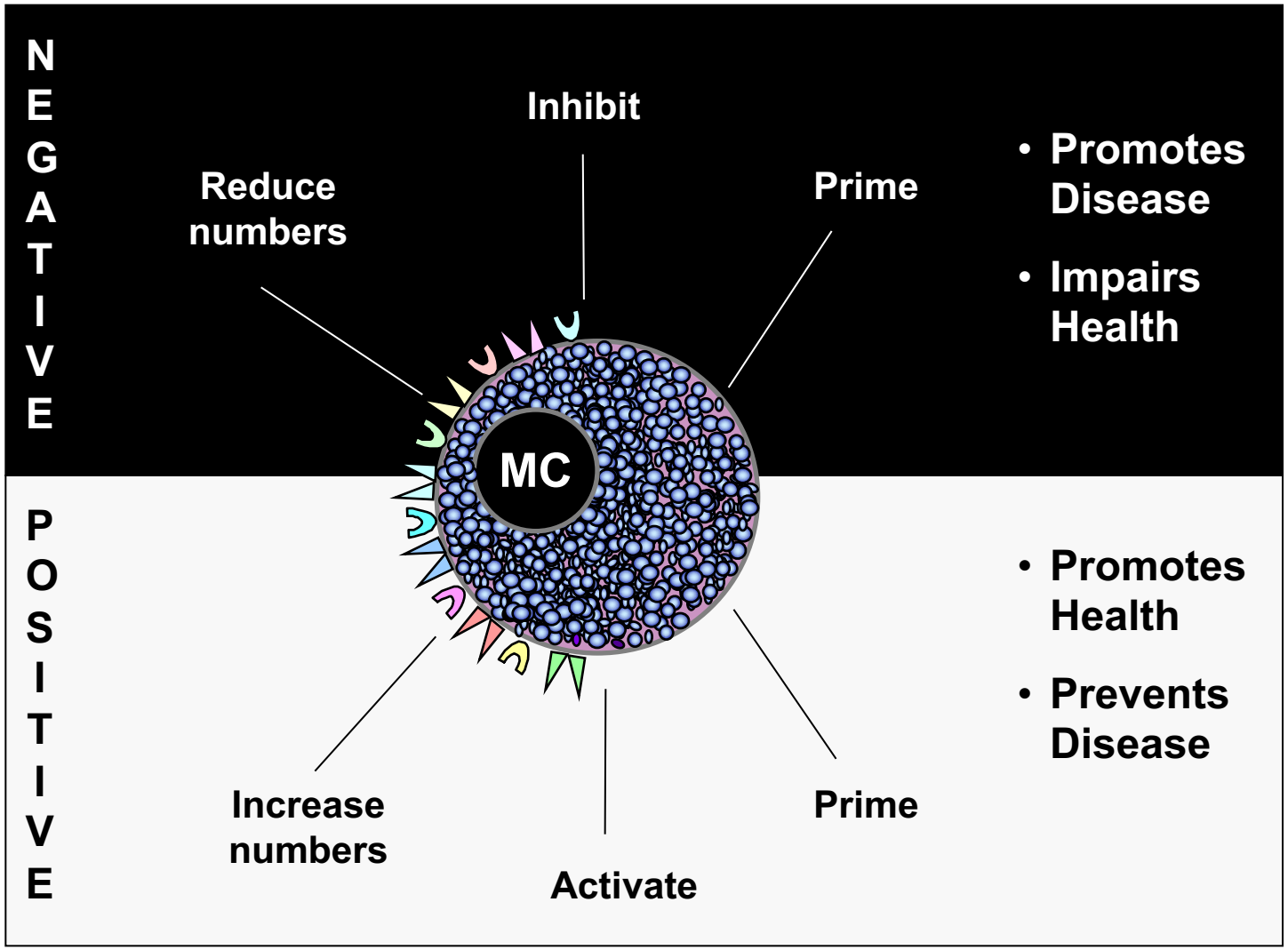
- Promotes Disease
- Impairs Health



POSITIVE

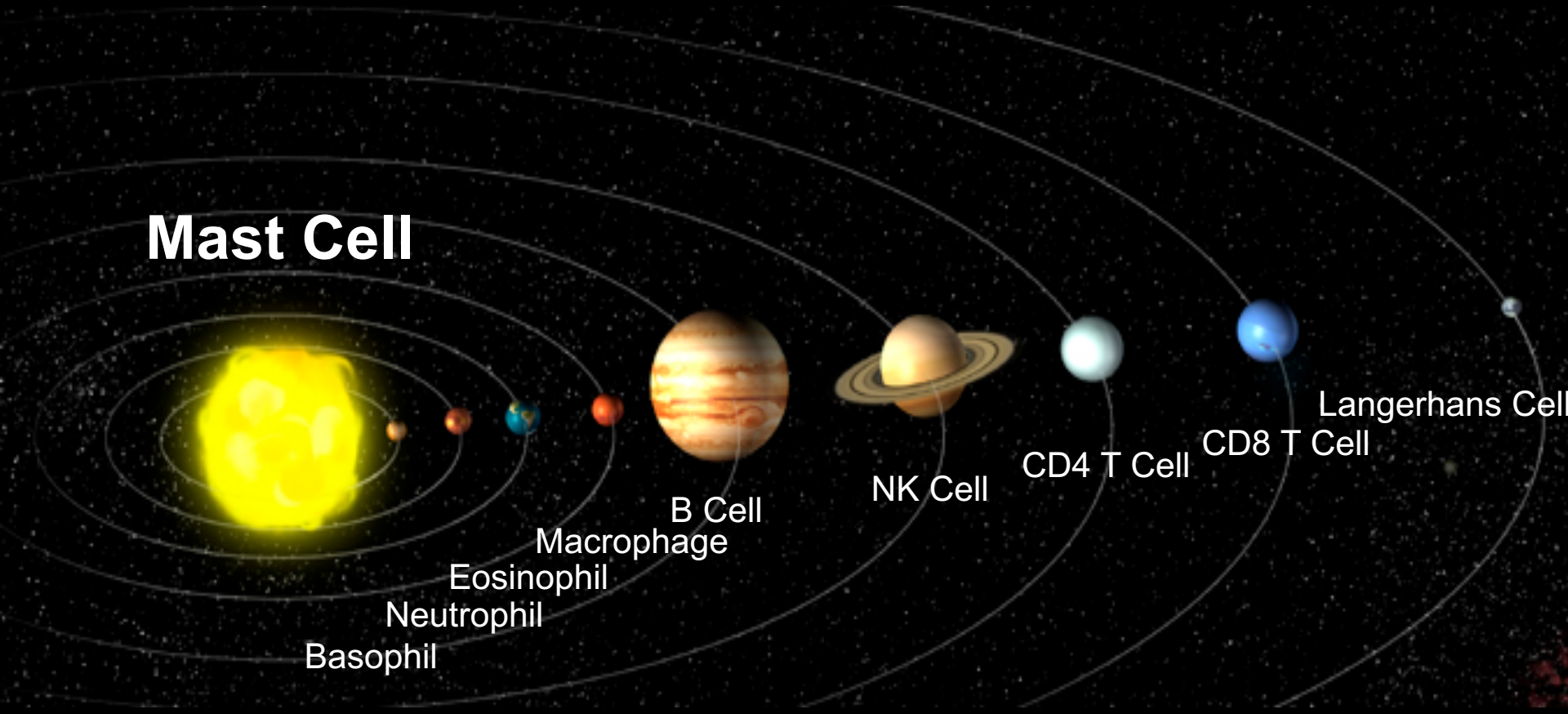
- Promotes Health
- Prevents Disease


NEGATIVE
Reduce numbers
Inhibit
Prime
MC
• Promotes Disease
• Impairs Health
POSITIVE
• Promotes Health
• Prevents Disease


NEGATIVE
Inhibit
Reduce numbers
Prime
• Promotes Disease
• Impairs Health
MC
POSITIVE
• Promotes Health
• Prevents Disease
Increase numbers
Activate
Prime

Mast Cell Research – Quo vadis?

- Mast cells can be modulated.
- “Bad effects” can be neutralized.
- “Good effects” can be used and promoted.
- The better we understand mast cells, the more our patients benefit.


Mast Cell
Basophil
Neutrophil
Eosinophil
Macrophage
B Cell
NK Cell
CD4 T Cell
CD8 T Cell
Langerhans Cell