Chronic spontaneous urticaria: the edge of a new era

WSAAI 2025

02-13-2025

Aaron Ver Heul, MD, PhD

Objectives

- Discuss autoimmune mechanisms in CSU and how they impact response to treatment
- Discuss non-IgE-mediated pathways contributing to CSU
- Discuss latest clinical trial results for new therapies being developed for CSU

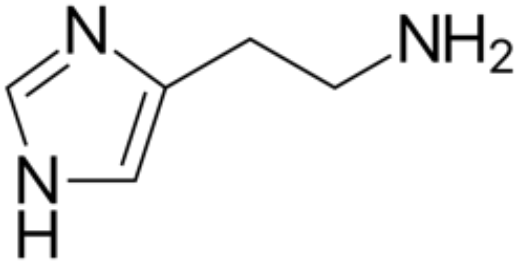
Urticaria

- Gets its name from stinging nettles (*Urtica dioica)*
- Wheal and flare
- Itch

https://www.google.com/

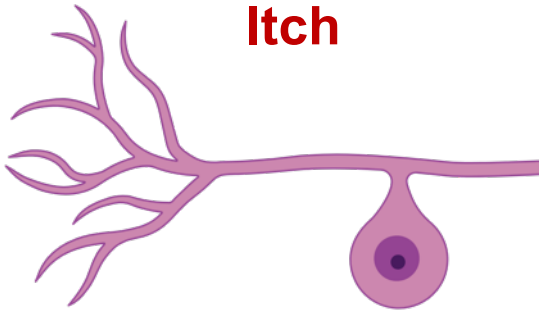
https://en.wikipedia.org

Acute Urticaria



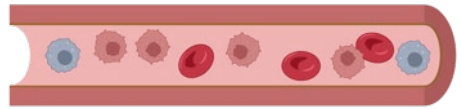
Histamine

Itch



Skin sensory neuron

Wheal and flare



Skin blood vessels

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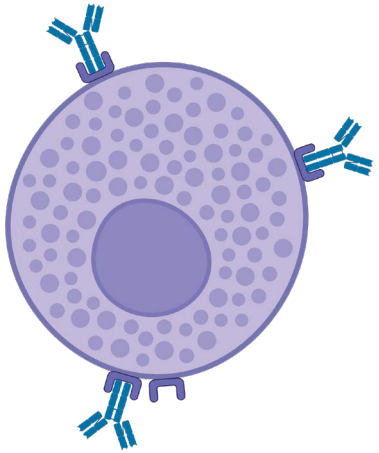
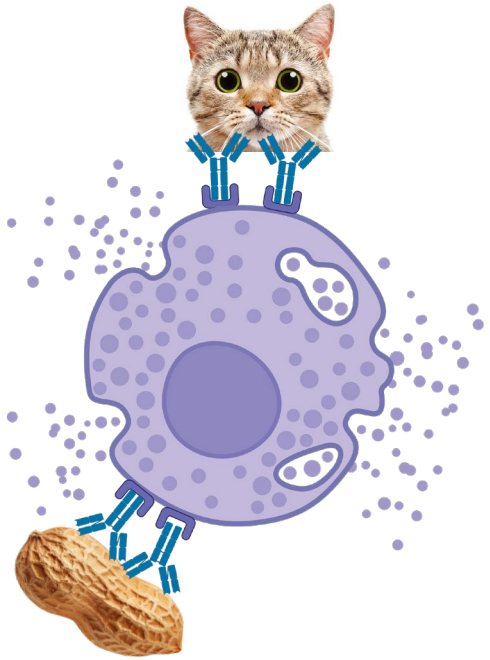
The pathophysiology of acute urticaria

Sensitized mast cell



Allergen-specific IgE

Exposure to allergen



Mediator release:

- histamine
- leukotrienes
- proteases
- etc.

Signs & Symptoms

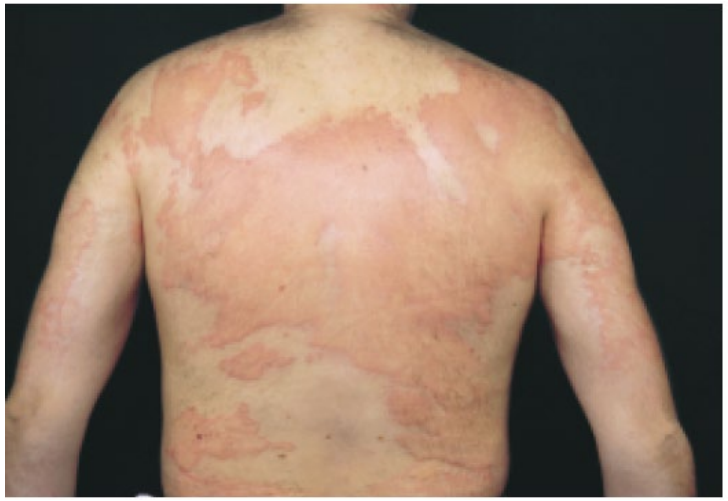
- **itch**
- **hives**
- watery eyes
- runny nose
- cough
- wheeze
- nausea/vomiting/diarrhea
- tachycardia
- hypotension

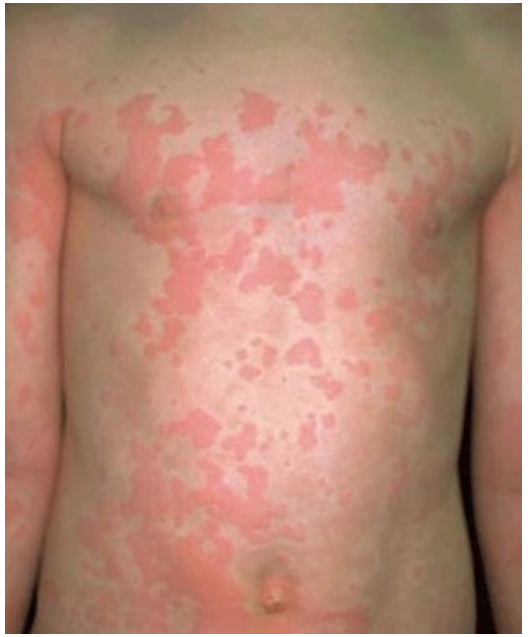
Created with Biorender

Classic urticarial lesions

Key features of urticarial lesions

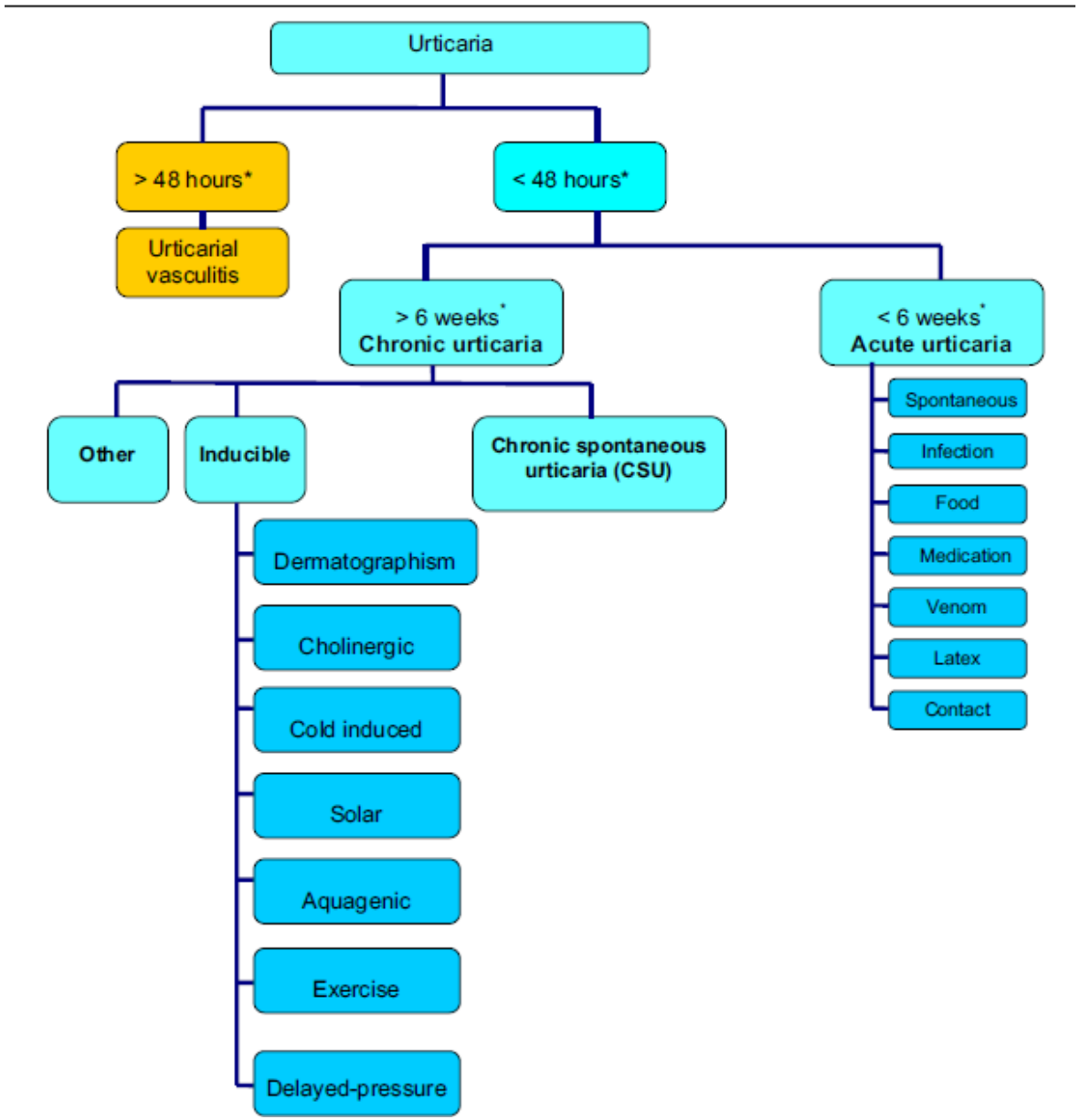
- Evanescence
  - Last less than 24 hours
  - “Wander”
  - No scars or discoloration (chronic excoriation can make this distinction difficult)
- Itch
  - Beware urticarial lesions that do not itch





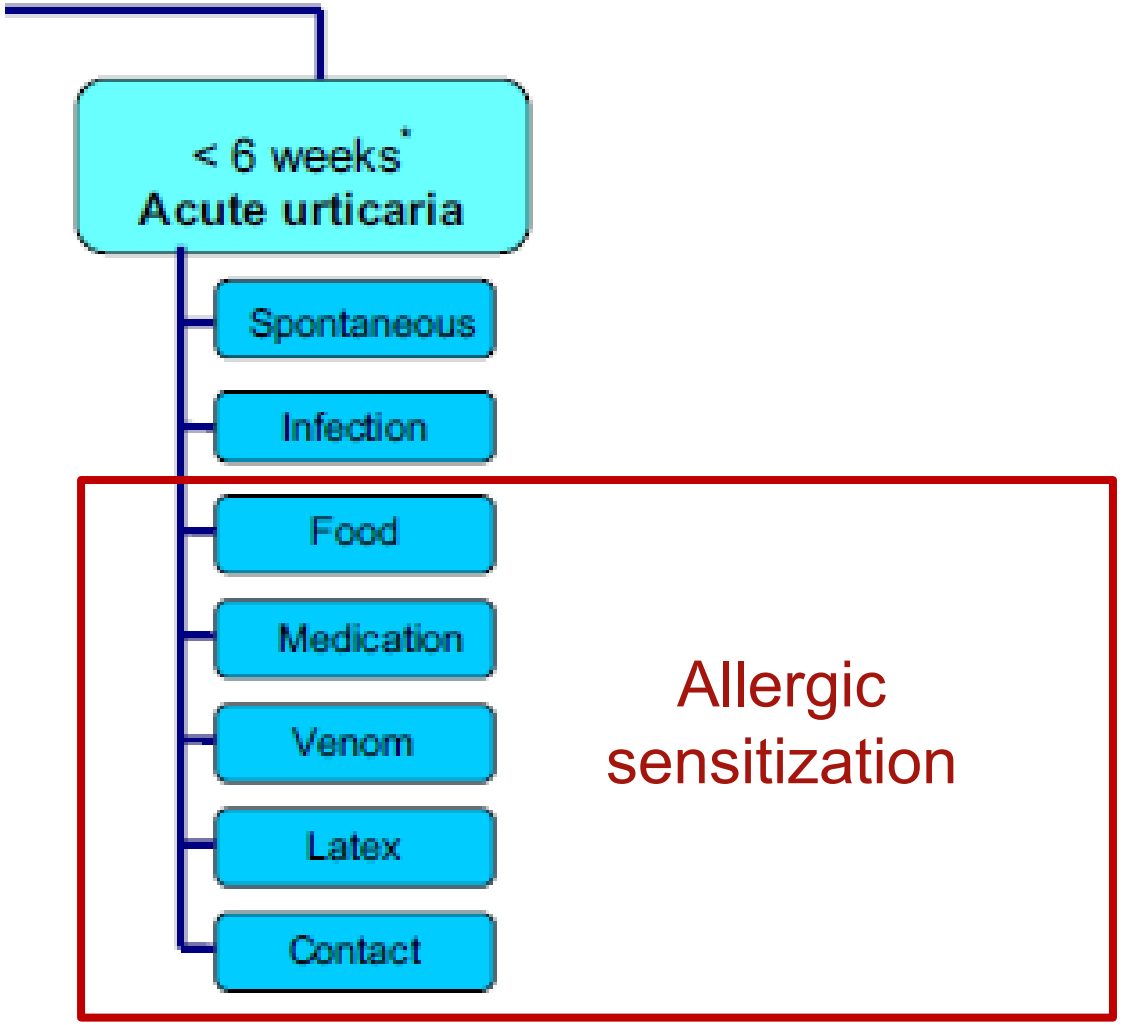
1. Greaves MW. NEJM. 1995
2. Kolkhir P. et al. Nat. Rev. Dis. Prim. 2022
3. Merck Manual

Classification of urticaria



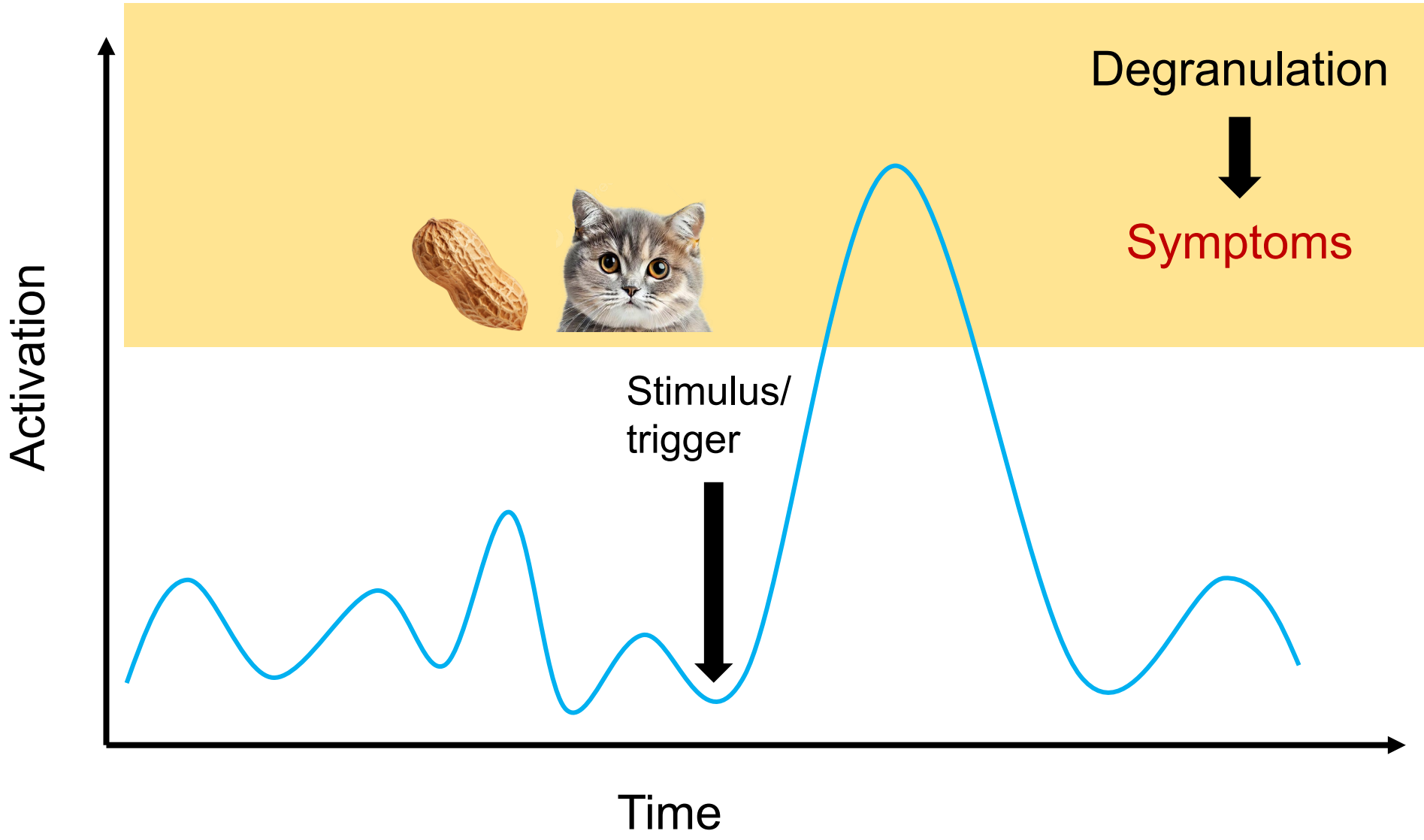
Kanani et al. Allergy Asthma Clin Immunol 2018

Acute urticaria



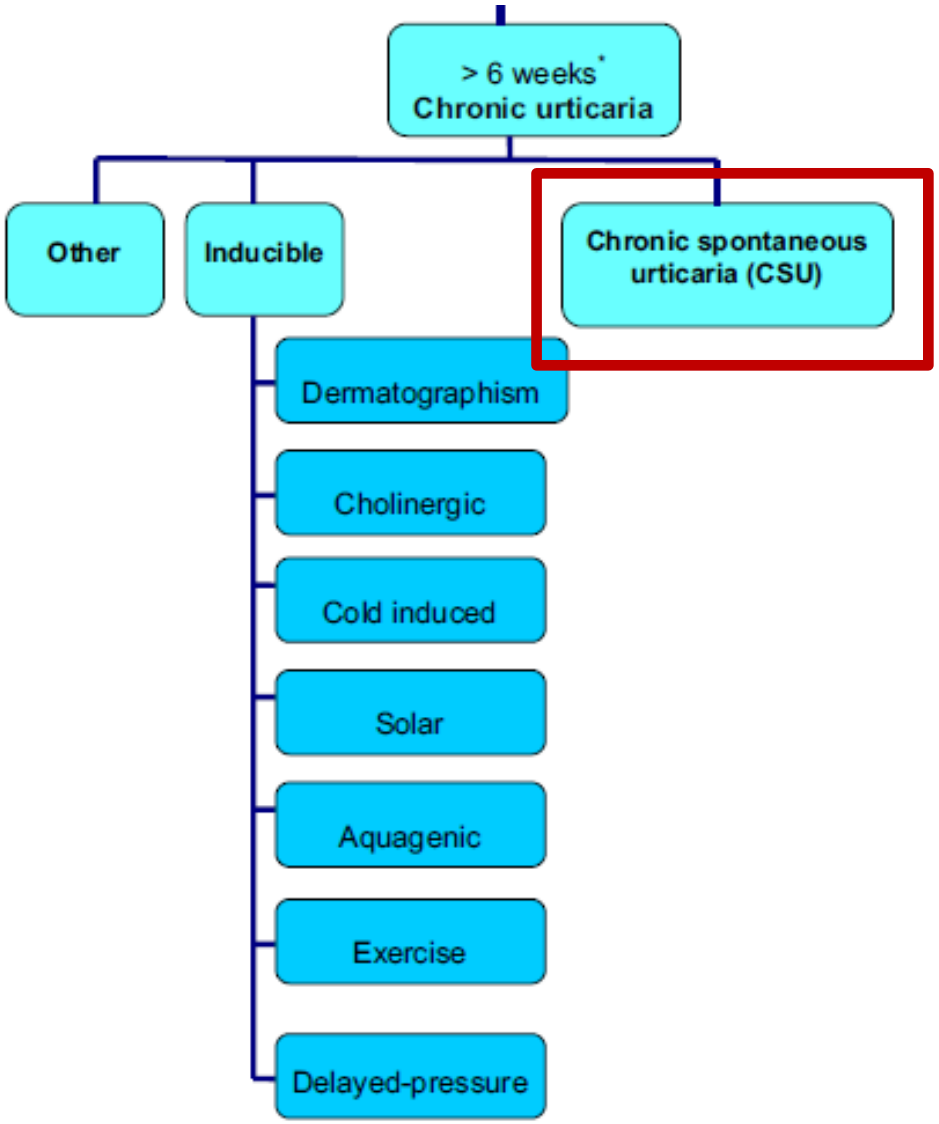
Kanani et al. Allergy Asthma Clin Immunol 2018

Mast cell activation in acute urticaria



Reactions correlate with exposures

Chronic urticaria

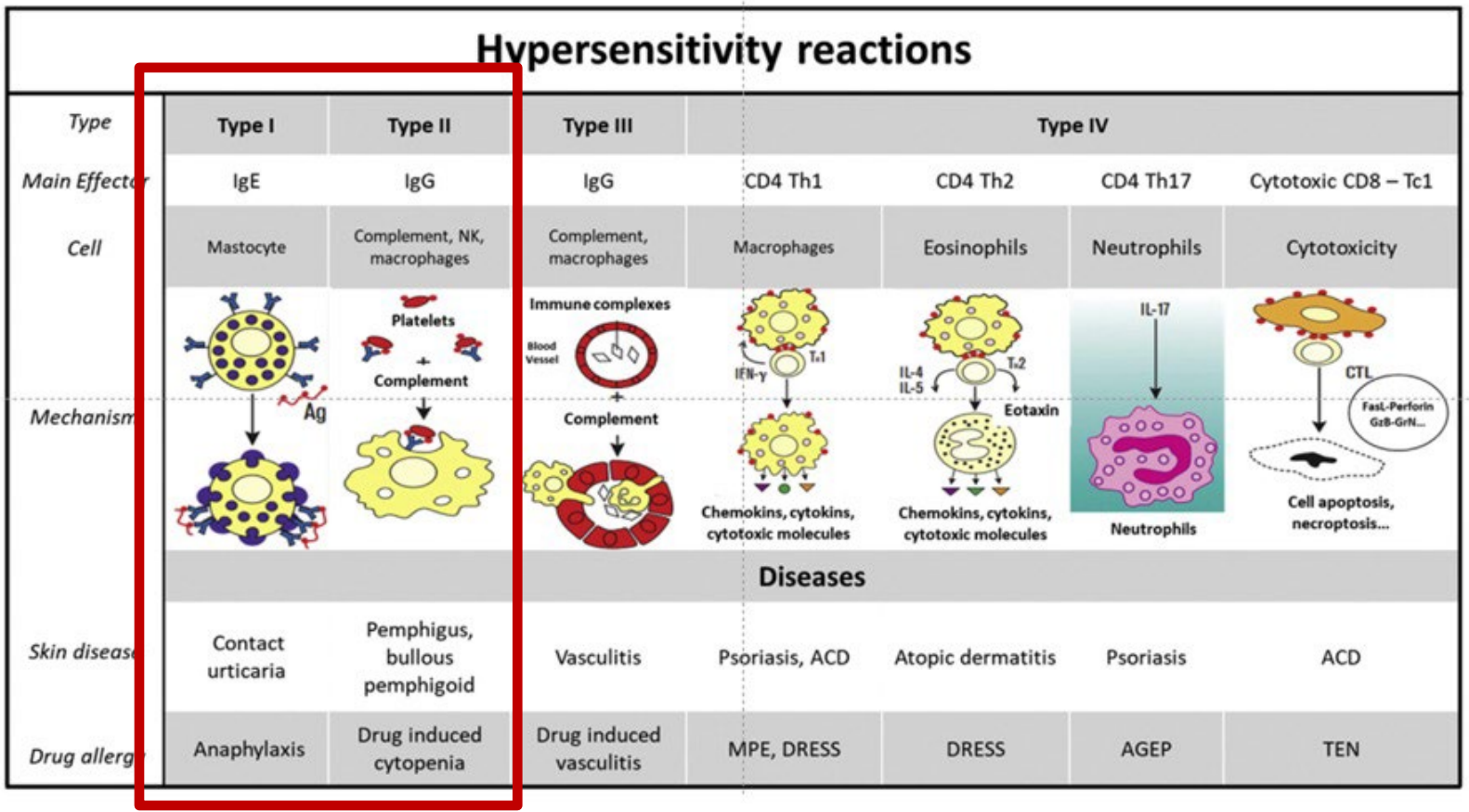


Kanani et al. Allergy Asthma Clin Immunol 2018

Immune mechanisms of CSU

Type I: “autoallergy”

Type IIb: “autoimmune”



Villani, AP et al Curr. Opin. Toxicol. 2018

How did we arrive at our current understanding?

- Autologous serum skin testing (1986)
- Inspired by experiment showing induction of local vasculitis by ASST in patient with cryoglobulinemia
- Most patients with improved disease were not positive on follow up

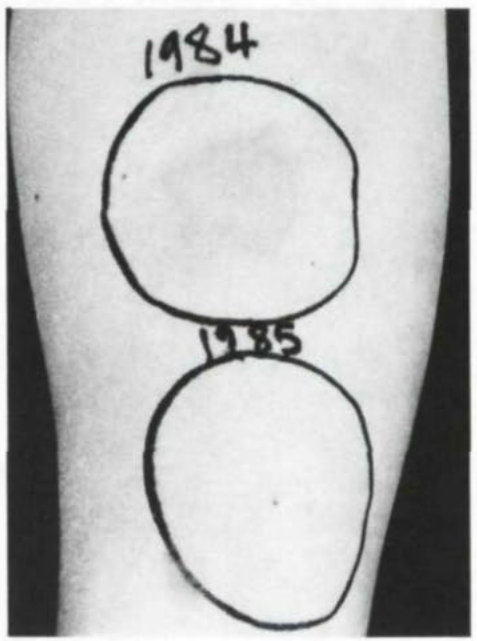


FIGURE 1. Reaction to re-injection of stored (1984) and fresh (1985) autologous serum.

TABLE 2. Characteristics of skin test response in serum-positive patients

			Initial assessment			Follow-up at one year		
			State of urticaria when serum drawn				Re-injection of serum	
Patient	Sex	Age	Erupting	Stable	Clear	Activity of urticaria	Original	Fresh
1	F	31	+	N/R	+	Almost clear No treatment	–	–
2	F	30	N/R	+	+	Sporadic anti-H_1 p.r.n.	+	–
3	F	32	+	+	N/R	Active Regular anti-H_1	+	+
4	M	78	+	+	N/R	Clear No treatment	+	–
5	F	64	N/R	+	+	Sporadic anti-H_1 p.r.n.	+	+
6	F	32	N/R	N/R	+	Clear No treatment	+	–
7	F	23	N/R	+	N/R	Lost to follow-up		

+ = serum-positive skin test.
– = serum-negative skin test.
N/R = not recorded.
anti-H_1 = antihistamines.

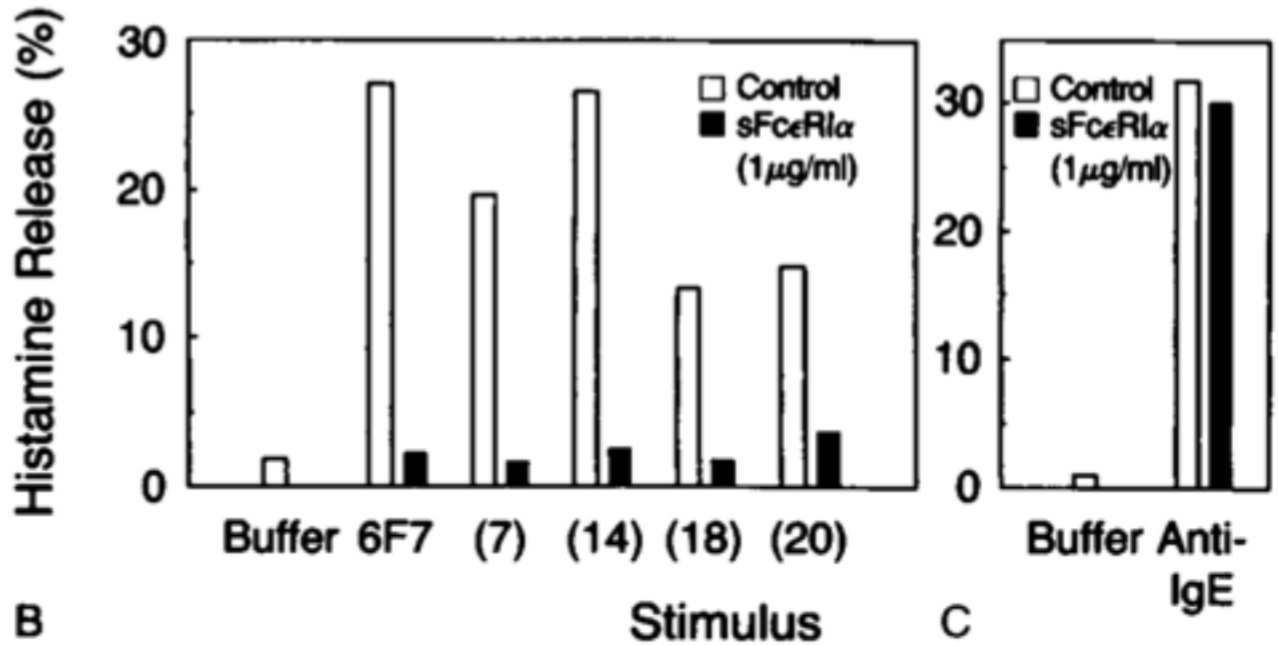
GRATTAN, C. E. H., et al. *Br. J. Dermatol.* 1986

Definition of first autoantibody antigen in CSU

AUTOANTIBODIES AGAINST THE HIGH-AFFINITY IgE RECEPTOR AS A CAUSE OF HISTAMINE RELEASE IN CHRONIC URTICARIA

MICHIHIRO HIDE, M.D., PH.D., DAVID M. FRANCIS, B.SC., CLIVE E.H. GRATTAN, M.R.C.P., JOHN HAKIMI, PH.D., JAREMA P. KOCHAN, PH.D., AND MALCOLM W. GREAVES, M.D., PH.D., F.R.C.P.

Adding soluble Fcer1a inhibited basophil histamine release



Hide, M. *et al. New Engl J Medicine* 1993
Fiebiger, E. *et al. J. Clin. Investig.* 1995

Increasing recognition of auto-IgE in CSU

- IgE against TPO already identified*

Anaphylaxis, drug allergy, urticaria, and angioedema

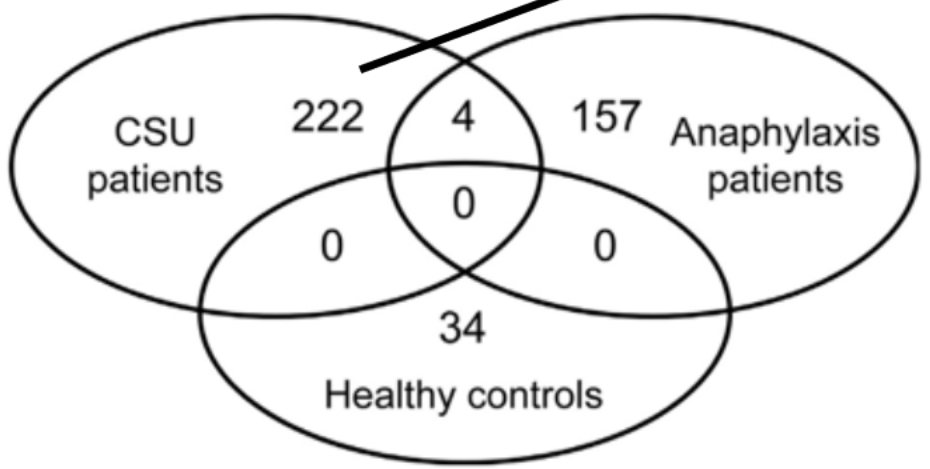
IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria

Oliver Schmetzer, MD, PhD, Elisa Lakin, Fatih A. Topal, Patricia Preusse, Denise Freier, Martin K. Church, PhD, DSc, and Marcus Maurer, MD *Berlin, Germany*

*Maurer, M. *et al. J. Allergy Clin. Immunol.* 2011
*Altrichter, S. *et al. PLoS ONE* 2011
Schmetzer, O. *et al. J Allergy Clin Immun.* 2018

Screening to find IL-24 auto-IgE

We analyzed **1062 patients (!!)** with CSU (73% female), 7 patients with Idiopathic anaphylaxis (IdA) (57% female), and **482 healthy control subjects** (61% female). There was no significant difference between the ages of patients with CSU (mean ± SD, 44.0 ± 14.7 years), patients with IdA (44.4 ± 13 years), and healthy control subjects (46.9 ± 16.7 years).



9,374 human proteins screened for IgE reactivity in CSU patients, patients with anaphylaxis, and normal controls

→ 8,957 are not detected by IgE

417 human proteins are autoantigens (AAs) detected by IgE

→ 34 / 161 AAs detected by IgE of normal controls / anaphylaxis patients

222 AAs are detected by IgE of CSU patients, but not control subjects

→ 191 AAs are detected by IgE in < 70% of CSU patients

31 AAs are detected by IgE of >70% of CSU patients

→ 23 AAs are not accessible or expressed in the skin

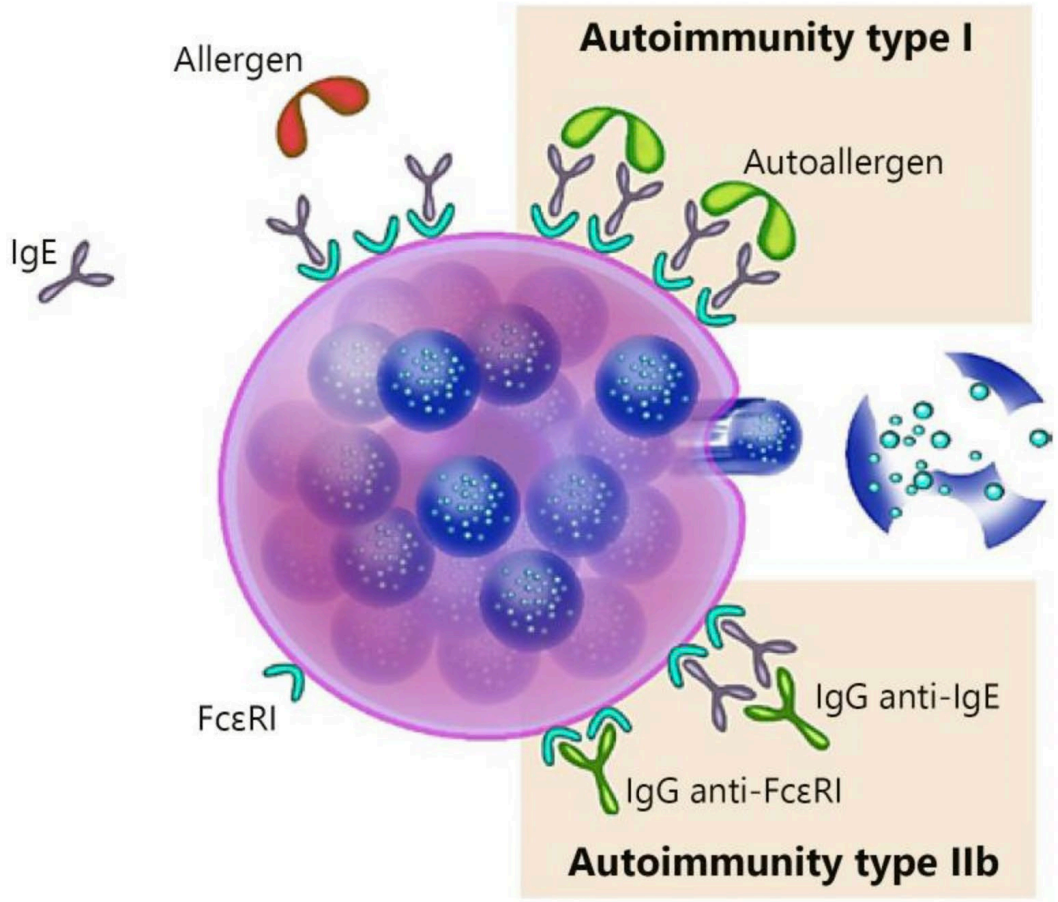
8 AAs are accessible and expressed in the skin

→ 7 AAs are not detected by IgE in all CSU patients

Interleukin 24 (IL-24)

Schmetzer, O. *et al. J Allergy Clin Immun.* 2018

Autoimmune activation of mast cells in CSU



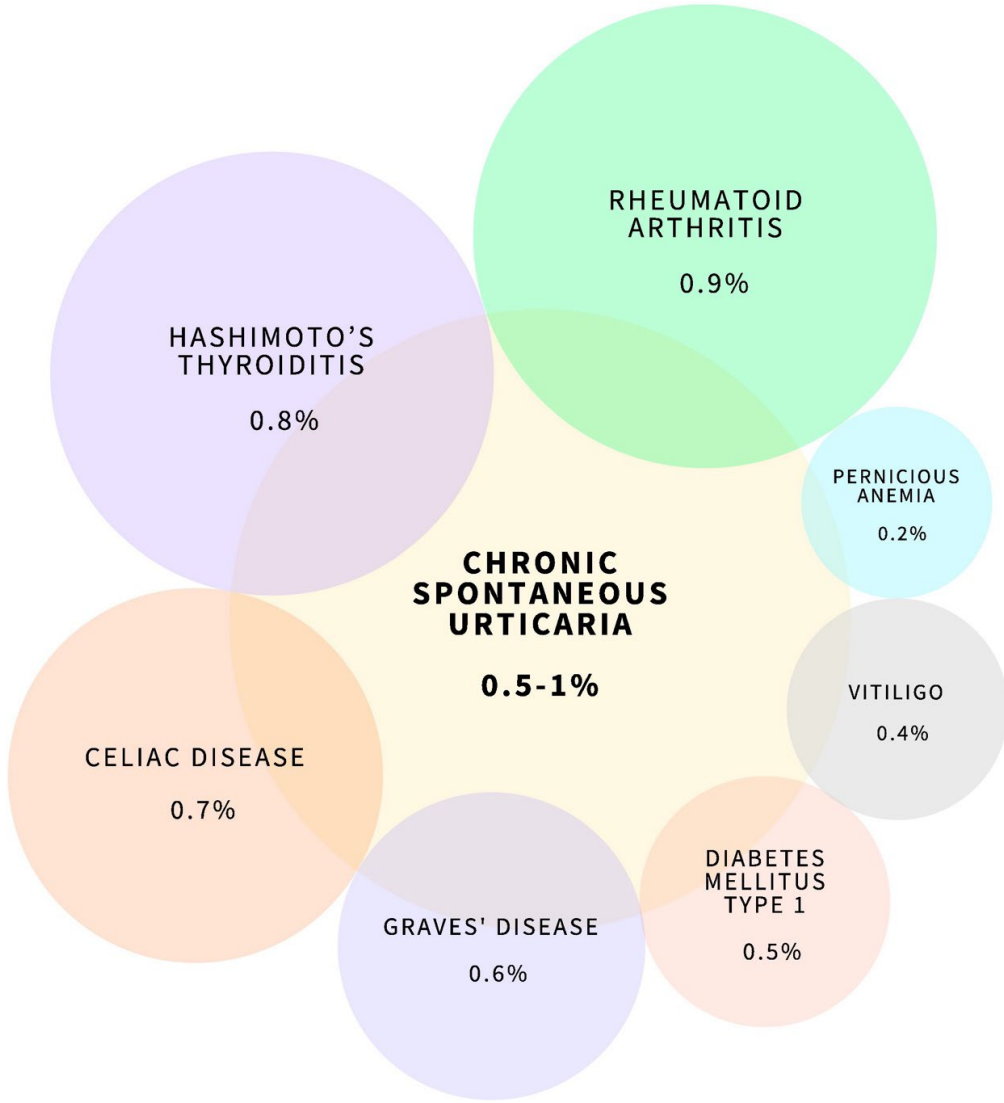
Features of type I and type IIb autoimmune CSU

Features	Type I versus type IIb autoimmunity
Autoantibodies	auto-IgE (e.g., against TPO, TG, TF, IL-24, dsDNA) in type I [12, 13, 15, 111], auto-IgG (against IgE, FcεRI) in type IIb [112, 113, 114]
Diagnosis	total auto-IgE and specific IgE to autoallergens[1] in type I [115], triple positivity: BHRA/BAT+ASST+WB/ELISA+ in type IIb [24, 25]
Disease activity/severity	tends to be higher in type IIb [12, 14, 25, 111][2]
Disease duration	tends to be longer in type IIb as shown in some [116, 117] but not all [25] studies
Rates of concomitant autoimmune diseases	tend to be higher in type IIb [25, 118, 119, 120, 121]
Rates of concomitant allergic diseases	might be higher in type I [119]
Total IgE levels	low in type IIb and normal or high in type I [14, 25]

Maurer, M. et al *Int Arch Allergy Imm* 2020

CSU and other autoimmune disorders (AIDs)

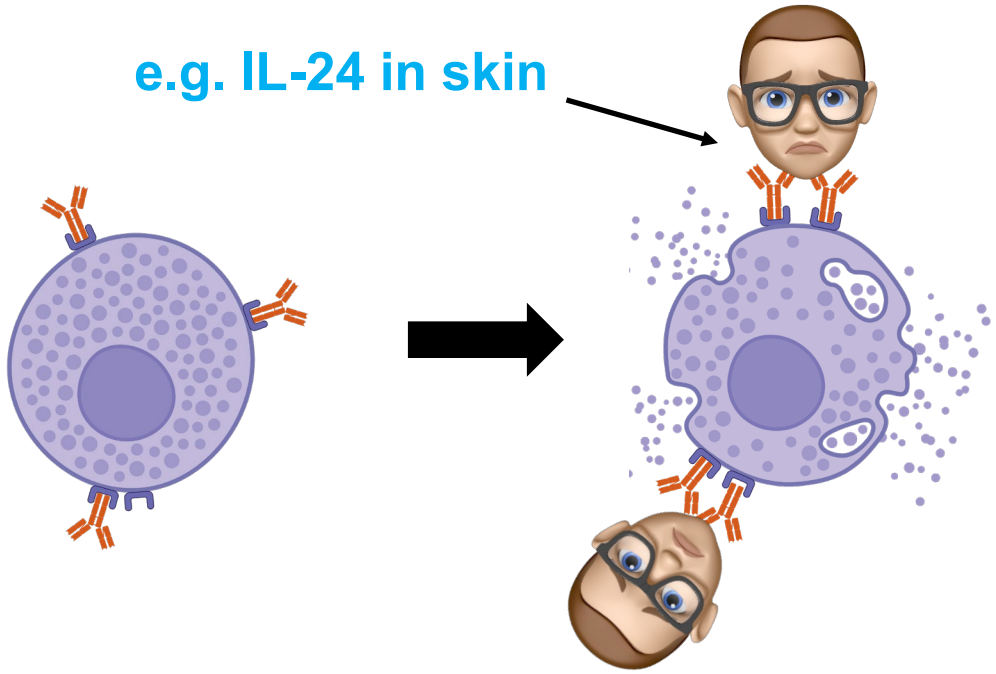
- Overlap is likely due to a shared mechanism – a propensity to lose self tolerance
- The prevalence of individual AIDs ≥1% in CSU vs ≤1% in the general population
- The prevalence of AIDs in patients with CSU increases over time, suggesting CSU might precede development of other AIDs



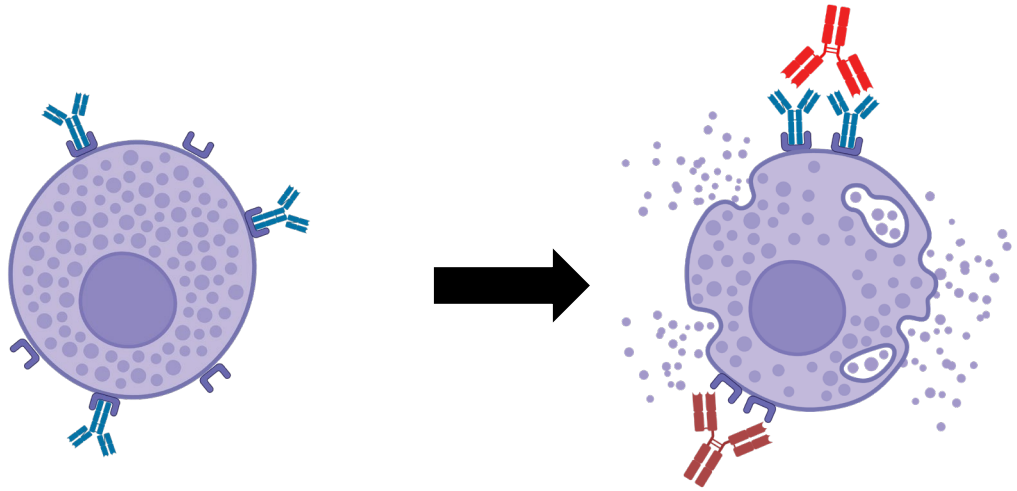
Kolkhir, P. et al. Autoimmun Rev 2017

The pathophysiology of CSU

Auto-sensitized mast cell (type I)



ANY mast cell (type IIb)



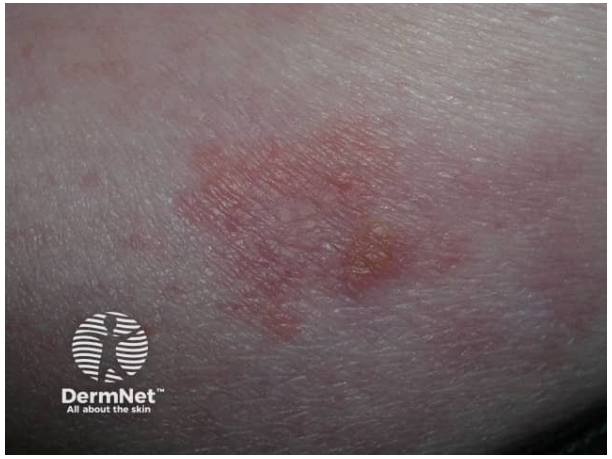
CSU symptoms

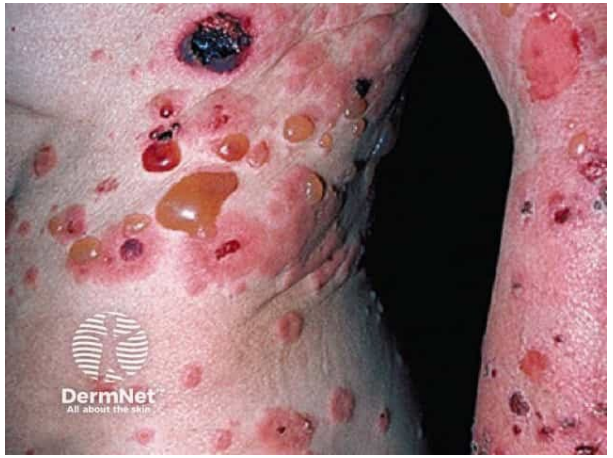
- **itch**
- **hives**
- watery eyes
- runny nose
- cough
- wheeze
- nausea/vomiting/diarrhea
- tachycardia
- hypotension

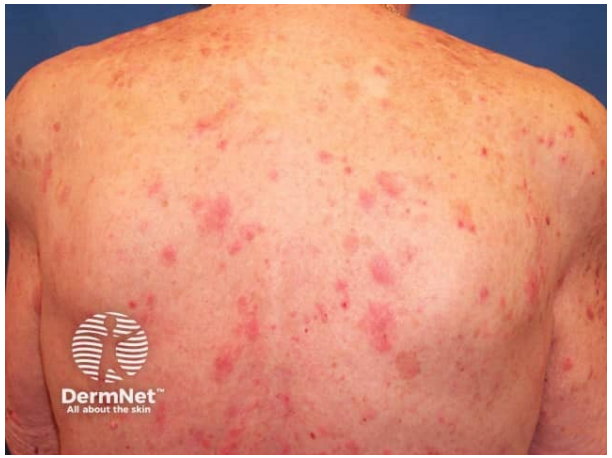
Created with Biorender

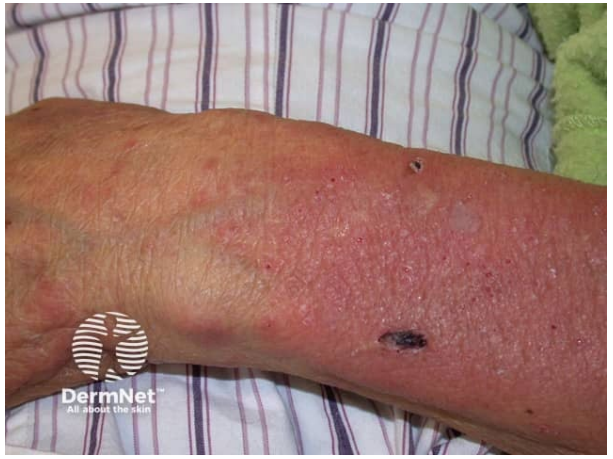
Bullous pemphigoid (BP)

- Pathophysiology: autoantibodies against subepidermal structural proteins (hemidesmosomes)
  - Linear IgG/C3 seen by immunofluorescence on biopsy
  - IgE correlates to severity and itch in some studies
- The challenge with BP is the highly variable presentation
  - Classic blistering
  - Urticarial
  - Eczematous
  - Pruritic without skin lesions
- Lesions typically last >24 hours, *very itchy*





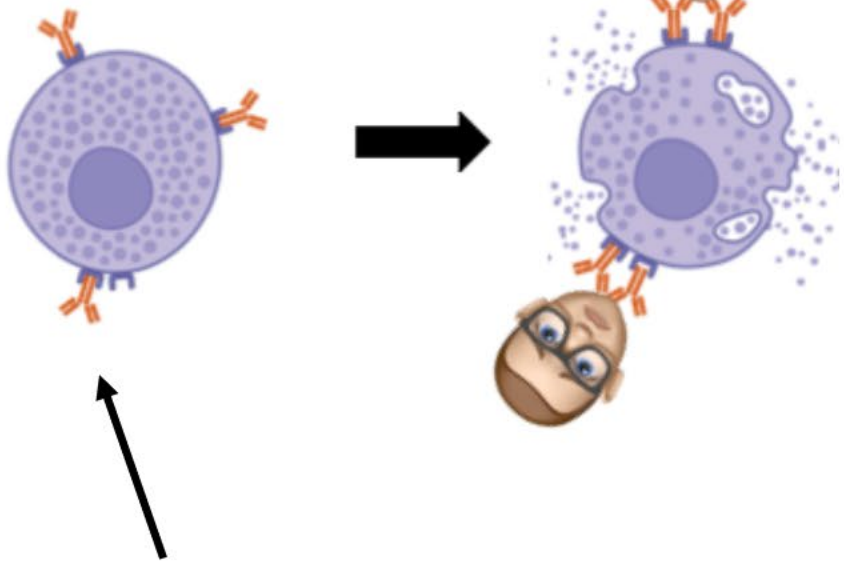




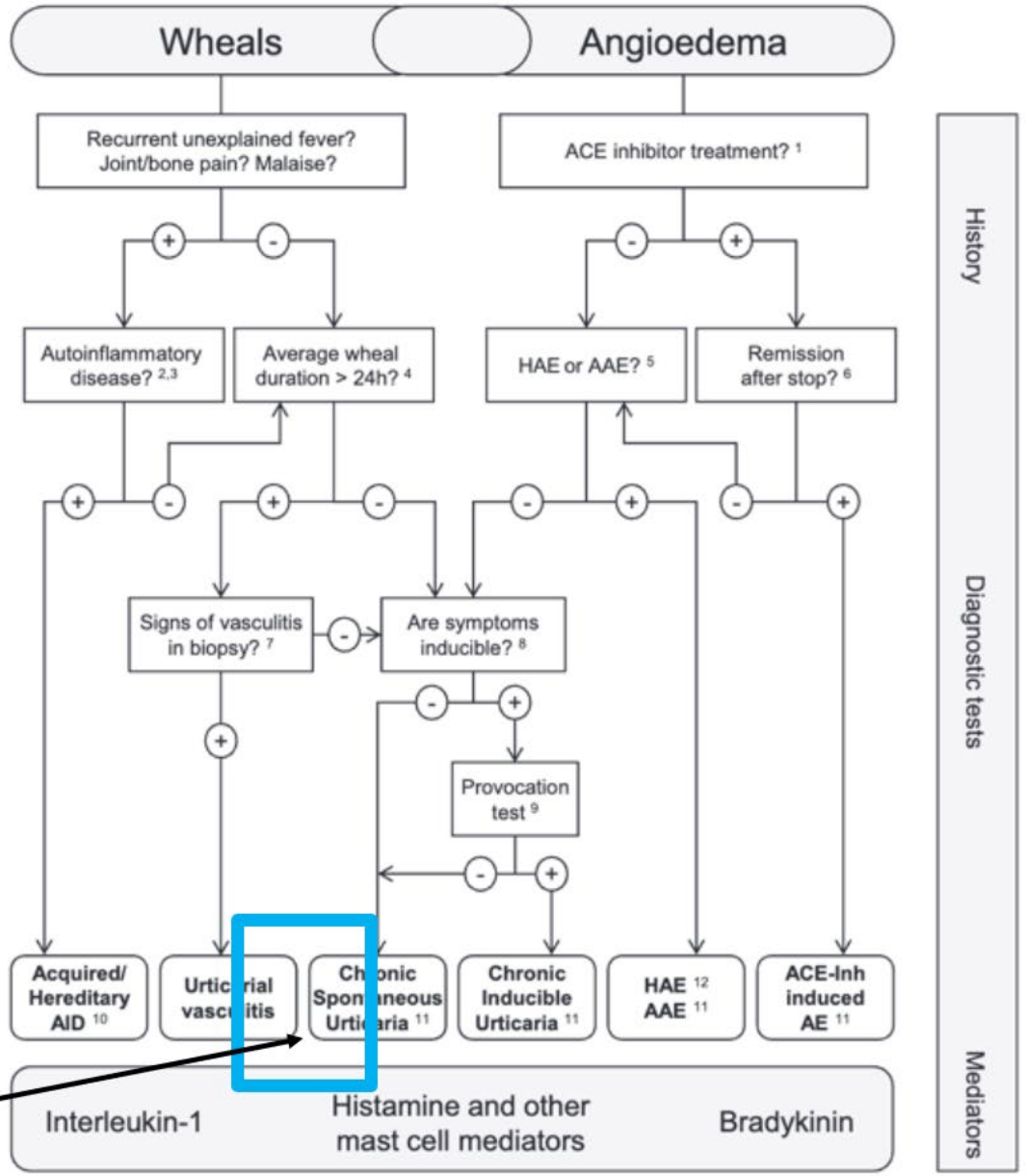
1. Bernard, P & Antonicelli, F. *Am. J. Clin. Dermatol.* 2017
2. https://dermnetnz.org

Does BP belong in the urticaria algorithm?

Auto-sensitized mast cell (type I)



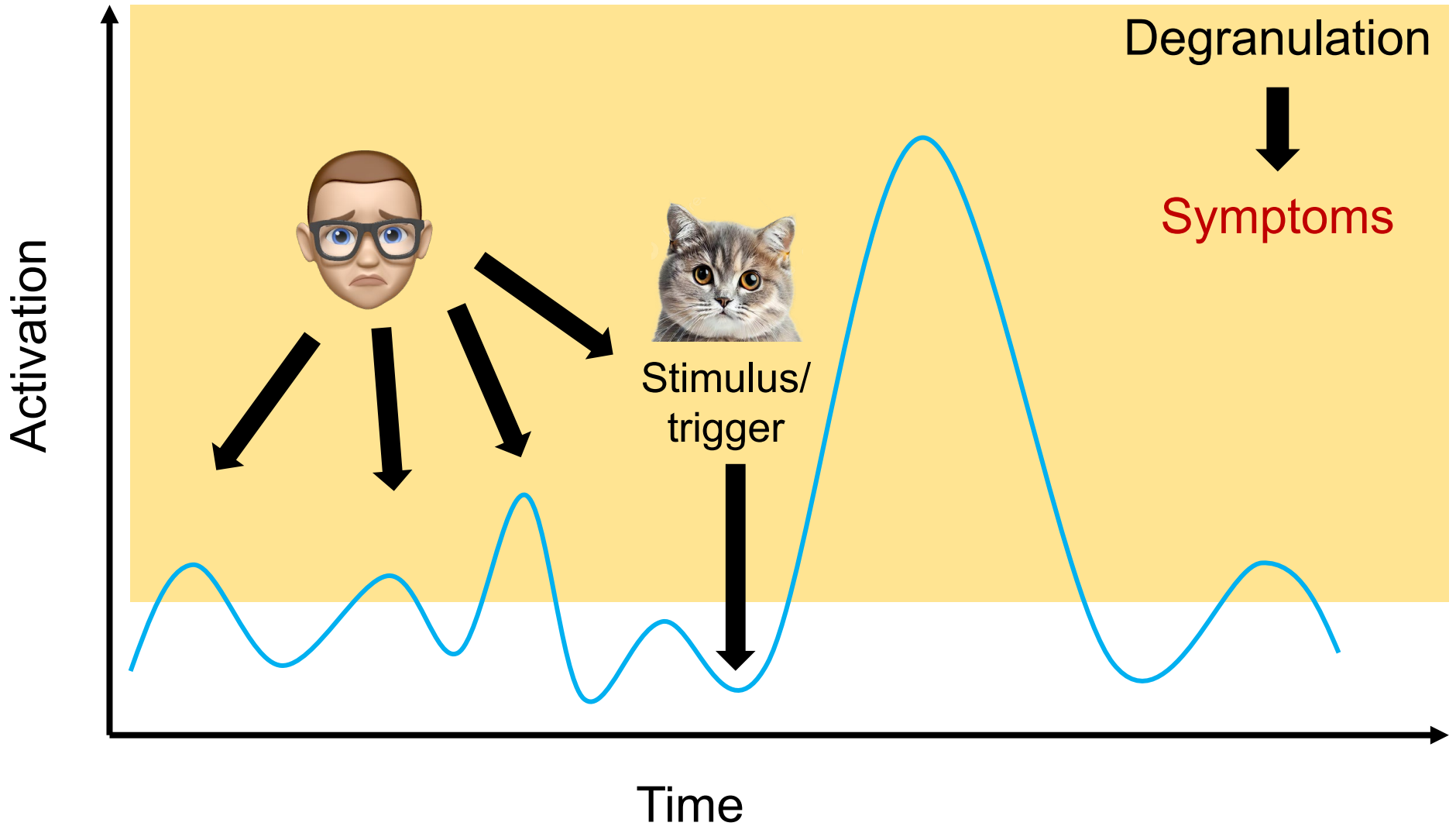
anti-BP180 IgE and/or anti-BP230 IgE



Bullous pemphigoid??

Zuberbier, T. *et al. Allergy* 2022

Mast cell activation in chronic urticaria



Reactions do not always correlate with exposures

“twitchy mast cells”

Therapeutic landscape for CSU in 2025

FDA-approved drugs for CSU

- Loratidine (des-) – 1993 (2001)
- Cetirizine (levo-) – 1995 (2007)
- Fexofenadine – 2000

4x dosing off label!

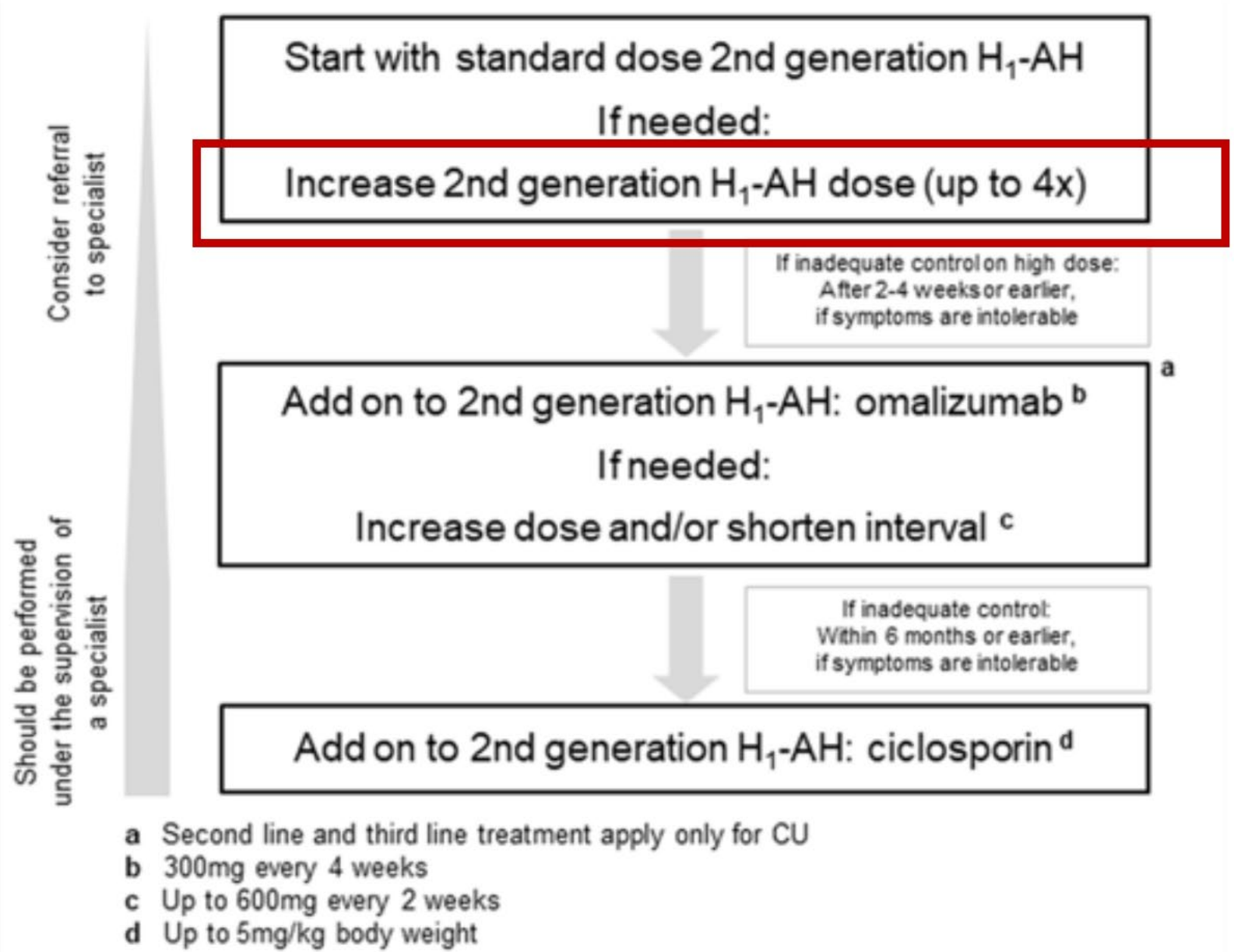
- **Omalizumab – 2014**

- **Dupilumab??**
- **Remibrutinib??**
- **Barzolvolimab??**

entering or completed phase 3

Through the itch/neuroimmune lens

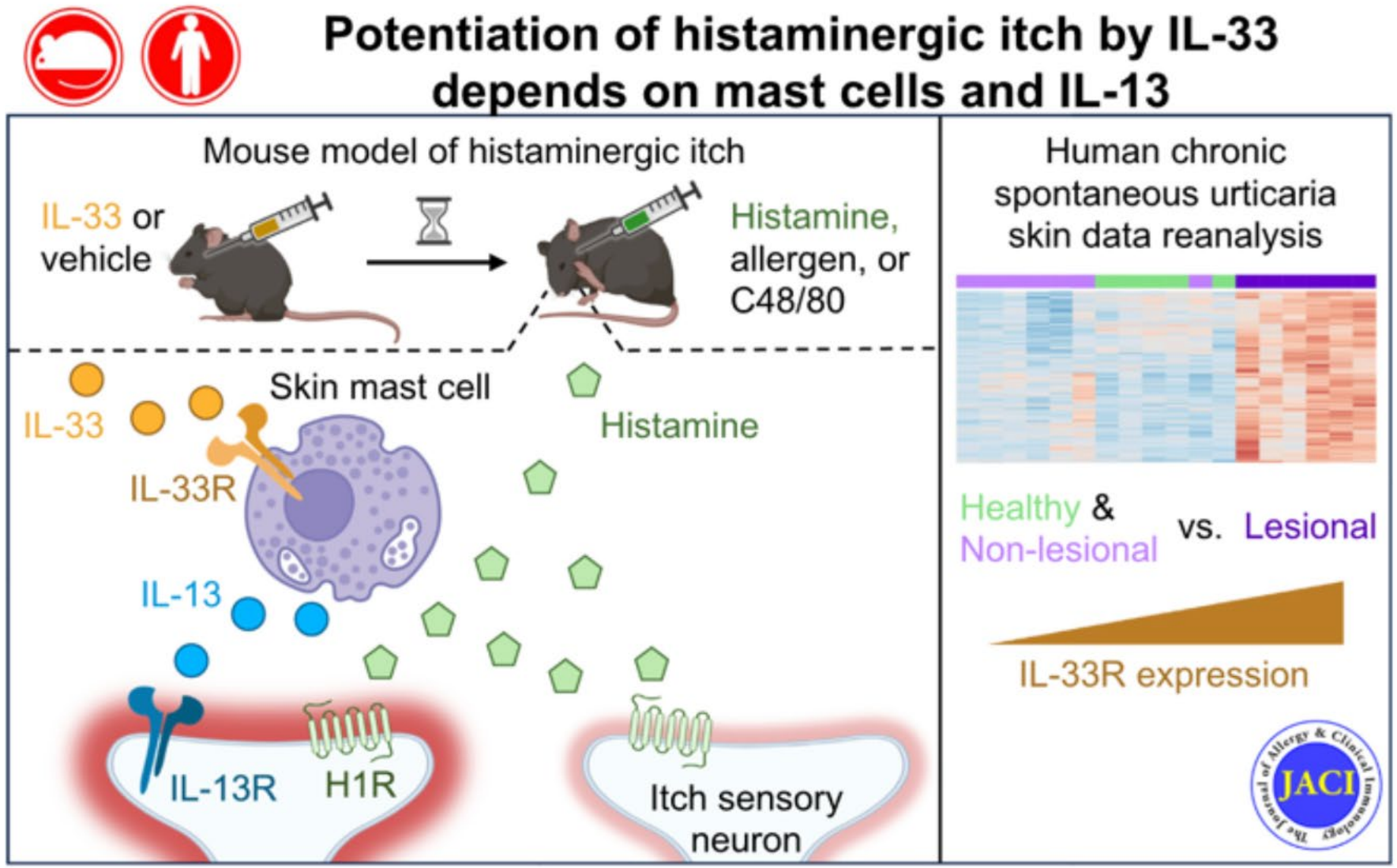
The most recent EAACI guidelines for CSU



Why are standard doses of antihistamines frequently inadequate in CSU?

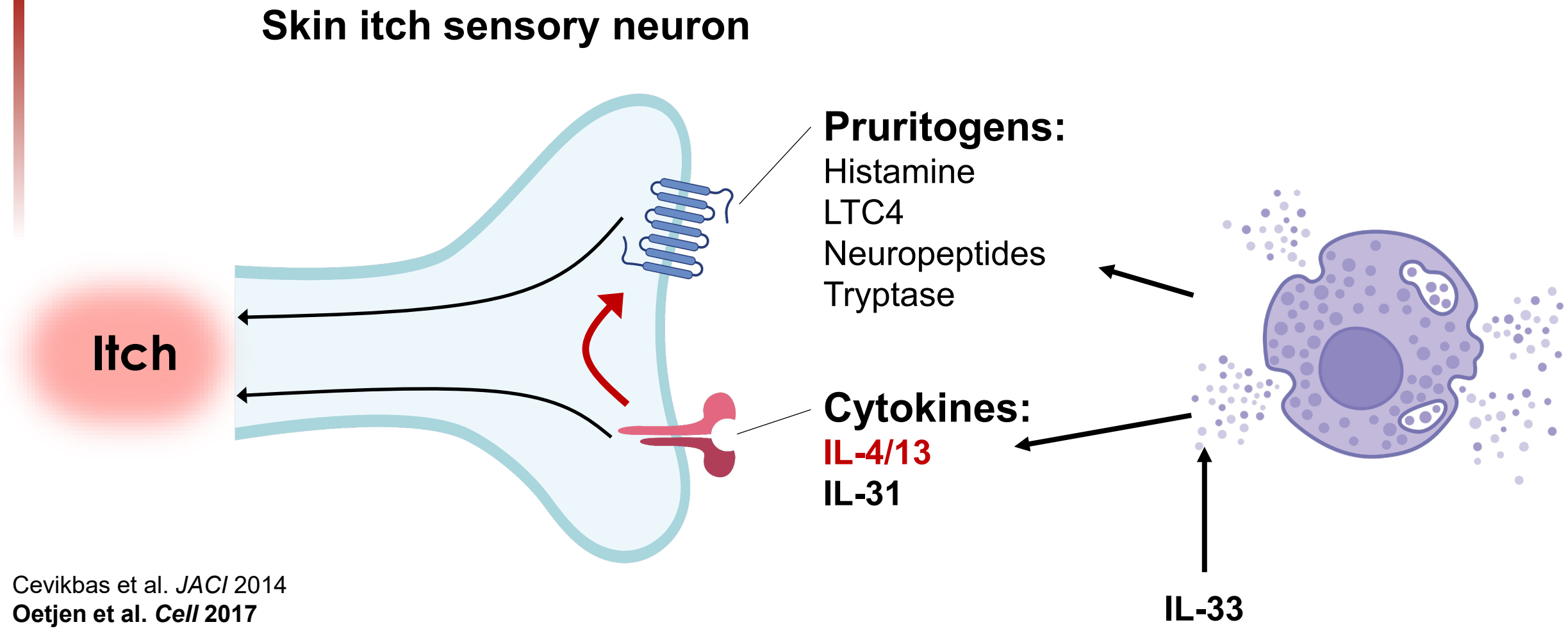
Zuberbier, T. *et al*. *Allergy.* 2022

IL-33 potentiates histaminergic itch in mice



Trier, A. M. *et al. J. Allergy Clin. Immunol.* 2024

Type 2 cytokines can sensitize neurons to pruritogens

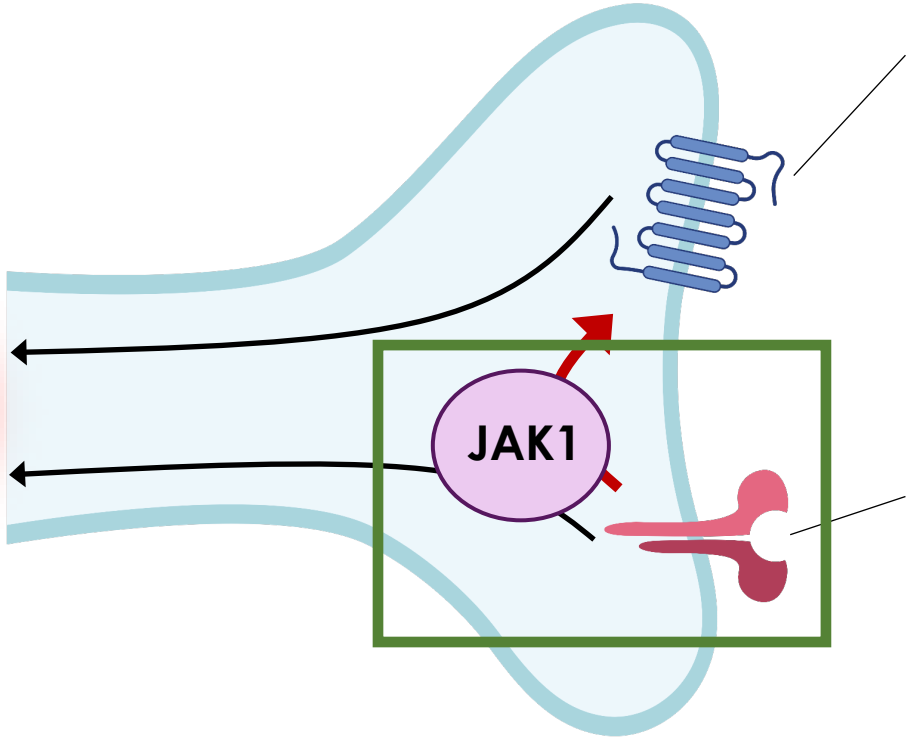


Cevikbas et al. *JACI* 2014
Oetjen et al. *Cell* 2017
Trier and Ver Heul et al. JACI 2024

Type 2 cytokines can sensitize neurons to pruritogens

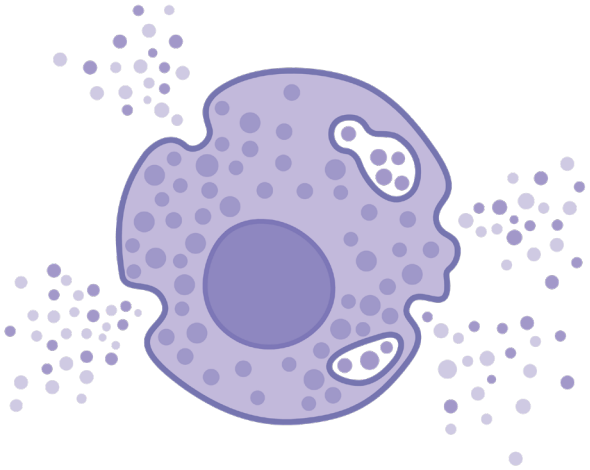
Skin itch sensory neuron

Itch



Pruritogens:
Histamine
LTC4
Neuropeptides
Tryptase

Cytokines:
IL-4/13
IL-31

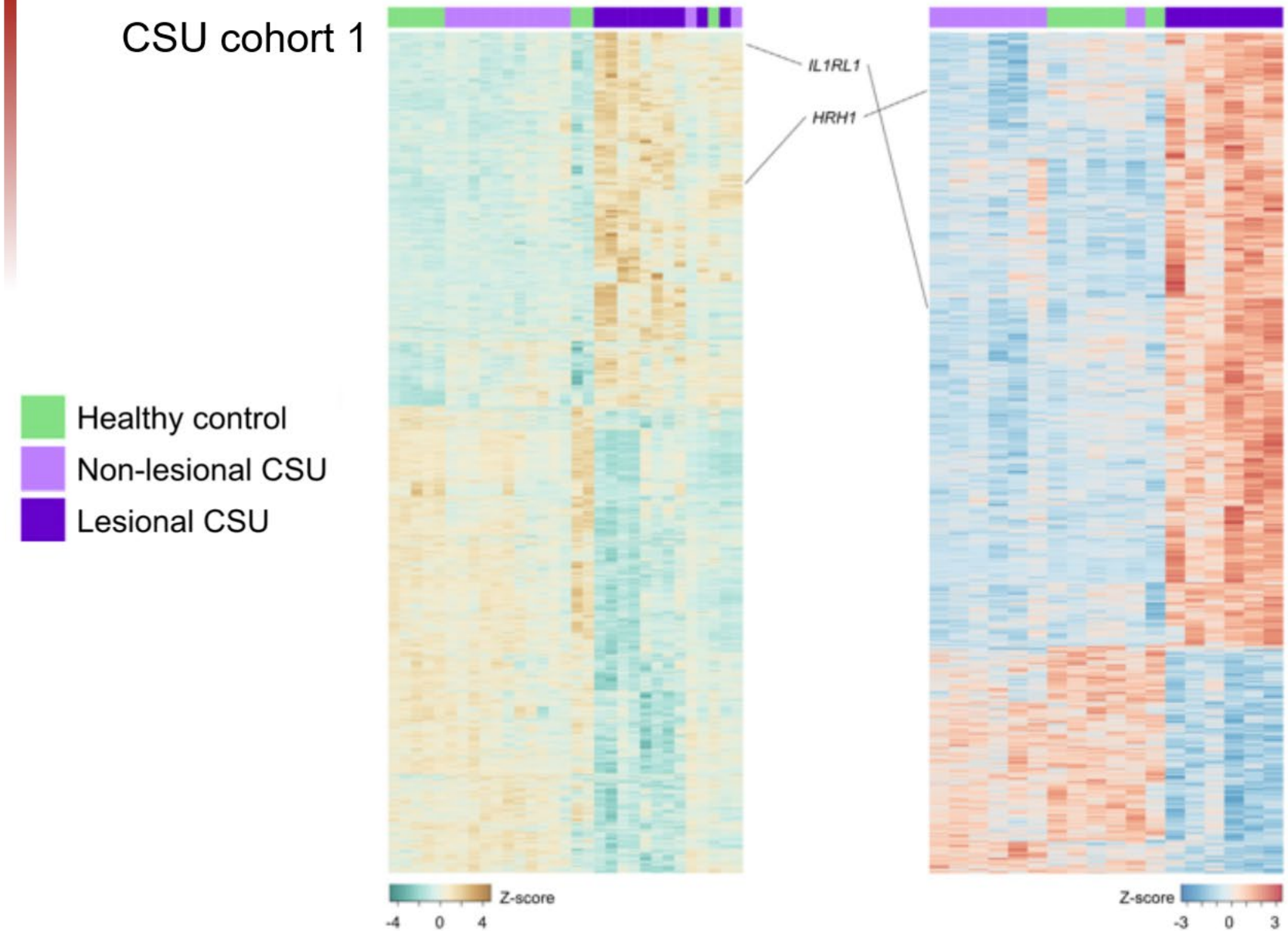


Cevikbas et al. *JACI* 2014
Oetjen et al. *Cell* 2017
Trier and Ver Heul et al. JACI 2024

Potential role for IL-4/13 and JAK1 blockade in CSU itch independent of effects on mast cells

Human skin is primed to respond to IL-33 and histamine in CSU

CSU cohort 1



CSU cohort 2

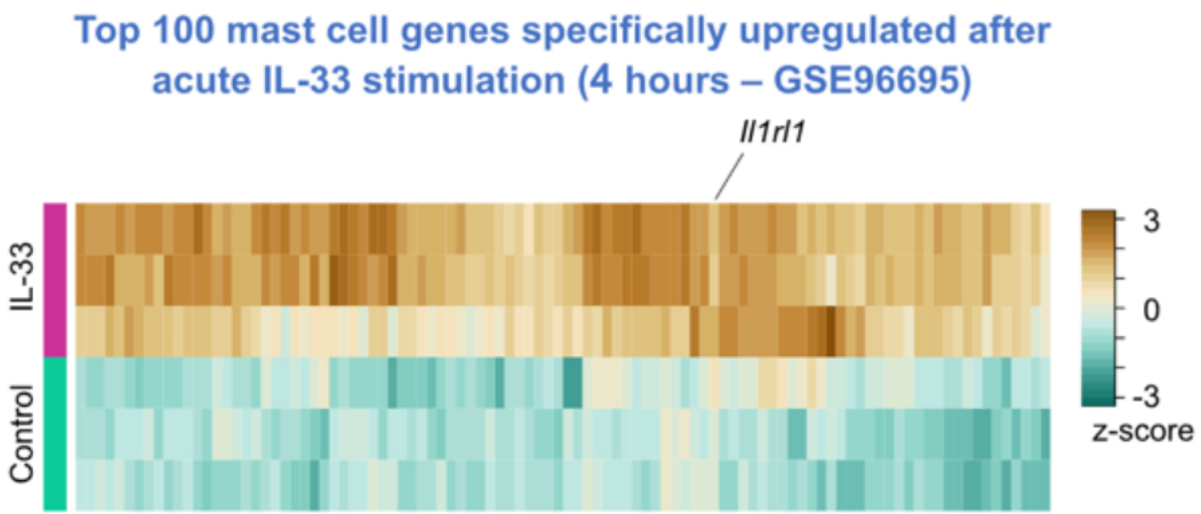
IL1RL1 = IL-33 receptor
HRH1 = histamine receptor

Trier, A. M. *et al. J. Allergy Clin. Immunol.* 2024

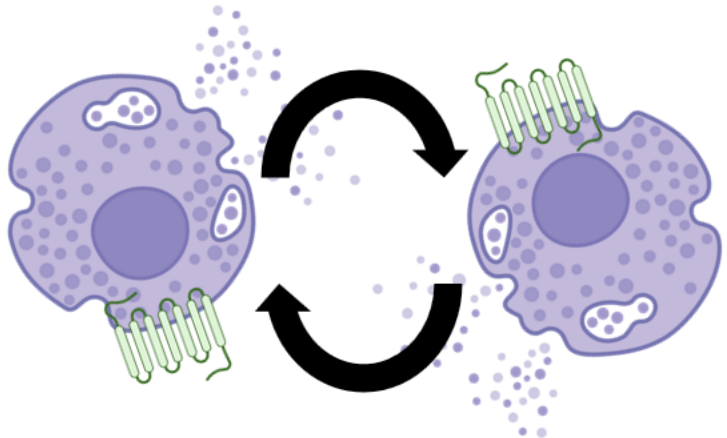
Mast cells have autocrine and paracrine activities

IgE-activated mast cells secrete IL-33*

IL-33 modulates mast cell responses

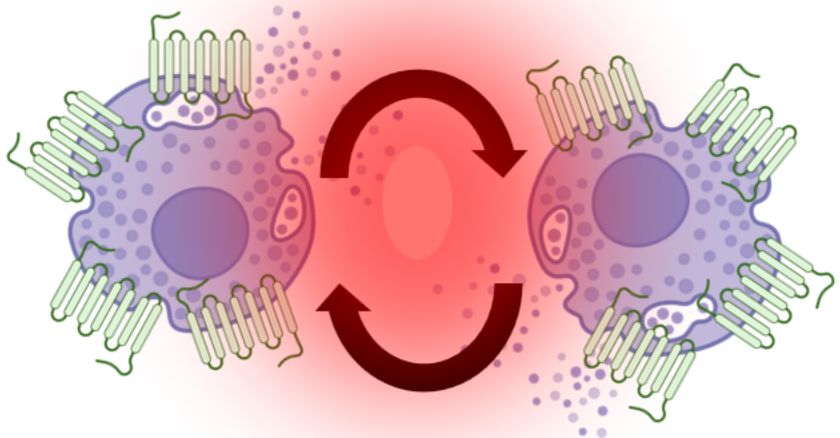


Steady state



IL-33

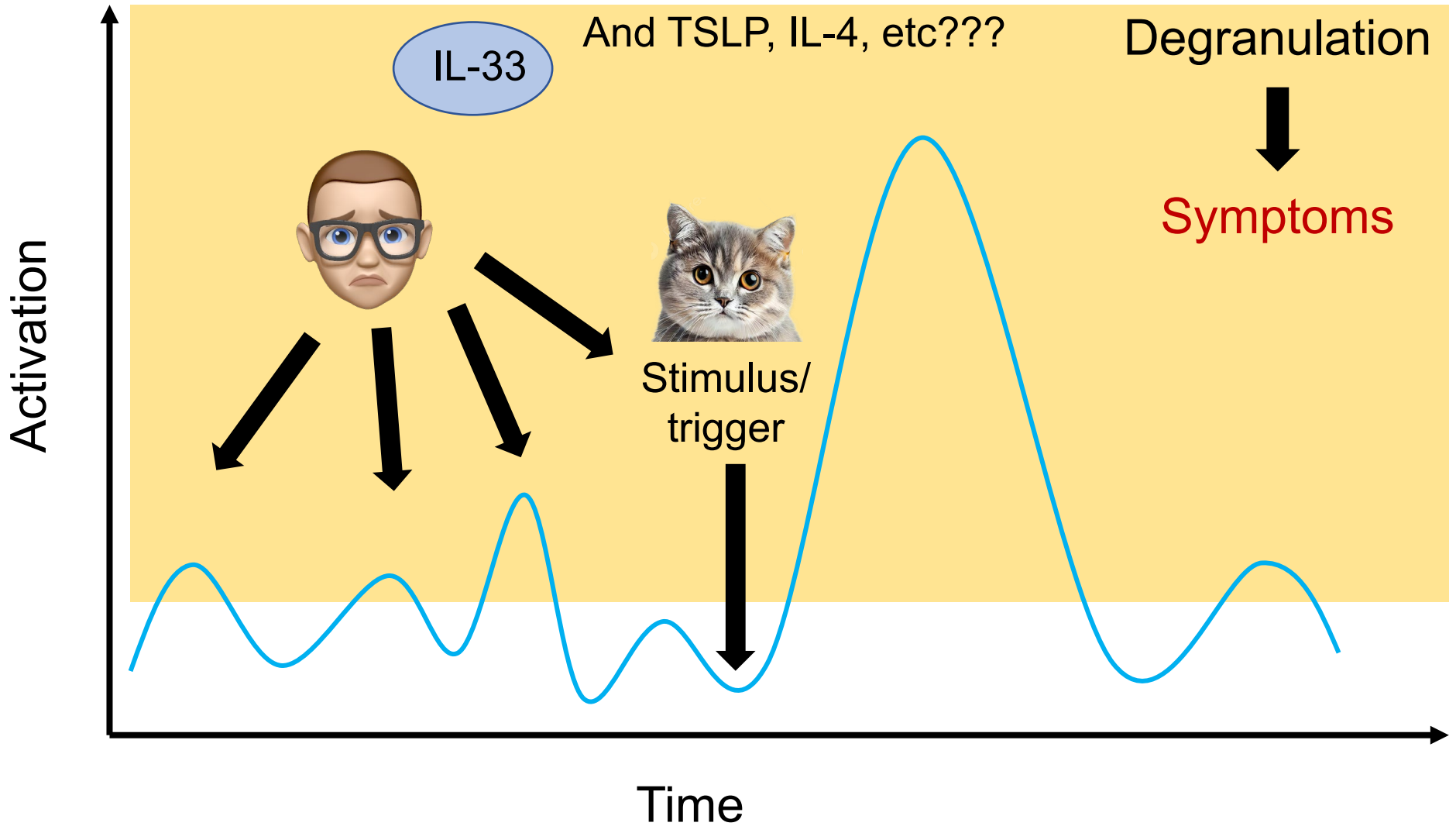
CSU



*Hsu, C.-L. *Plos One* 2010)

Trier, A. M. *et al. J. Allergy Clin. Immunol.* 2024

Mast cell activation in chronic urticaria

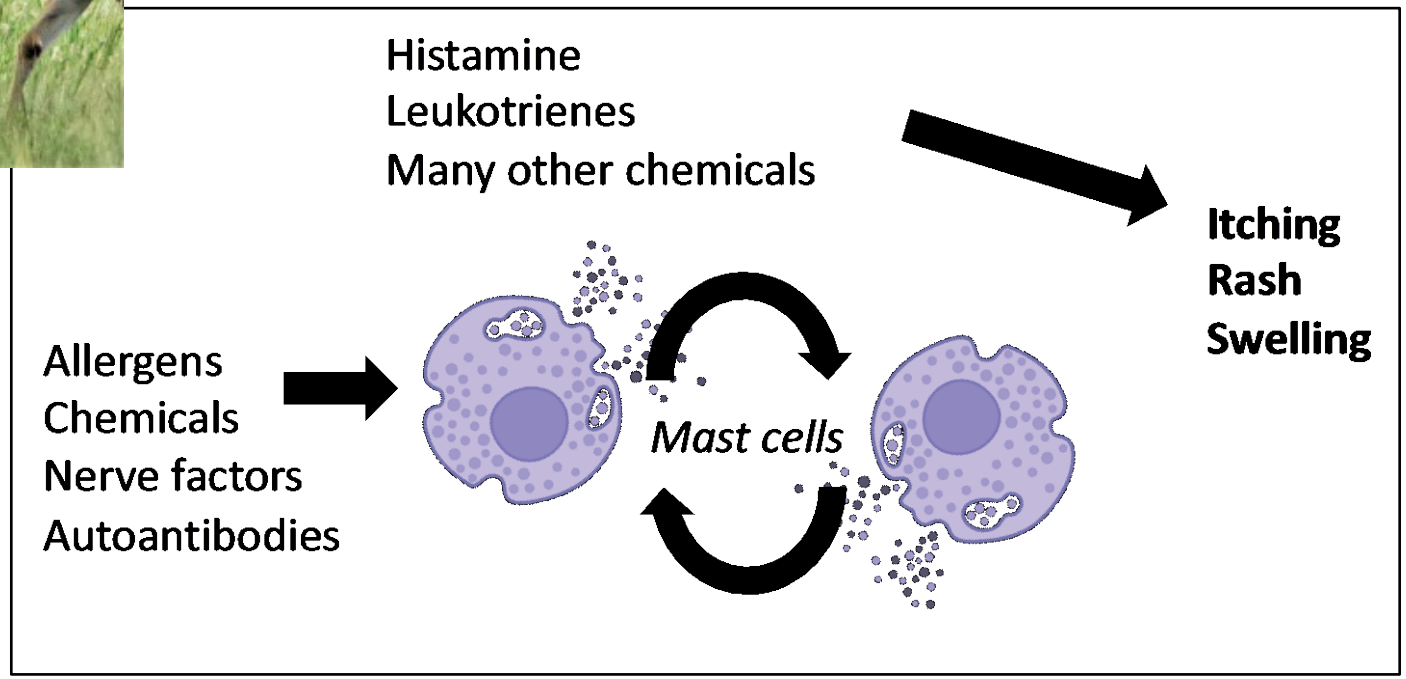


Reactions do not always correlate with exposures

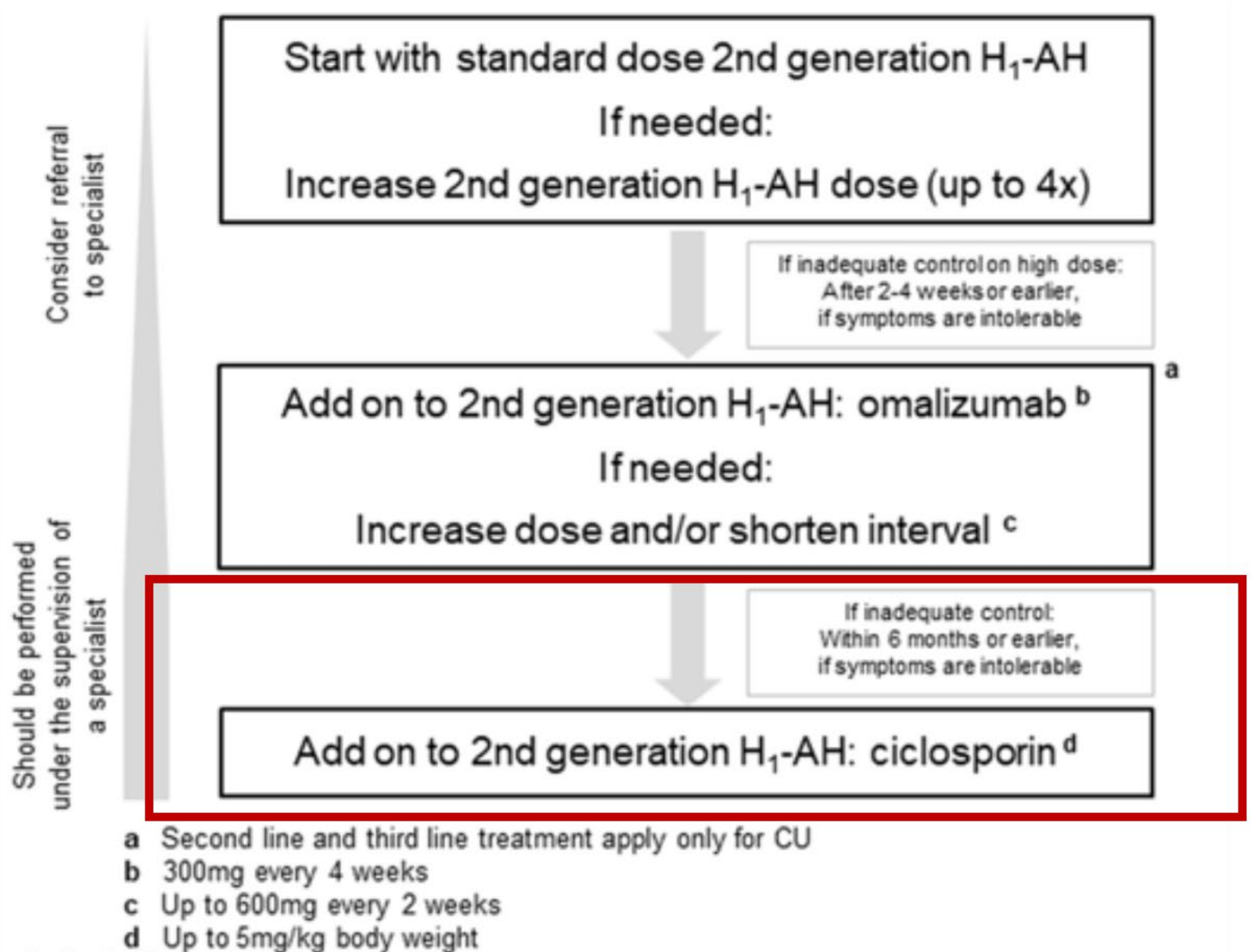
“twitchy mast cells”

Important to maintain consistent control of CSU activity

From my patient handout:



The most recent EAACI guidelines for CSU



a Second line and third line treatment apply only for CU
b 300mg every 4 weeks
c Up to 600mg every 2 weeks
d Up to 5mg/kg body weight

What are the reasons for inadequate responses to omalizumab??

Zuberbier, T. *et al*. *Allergy.* 2022

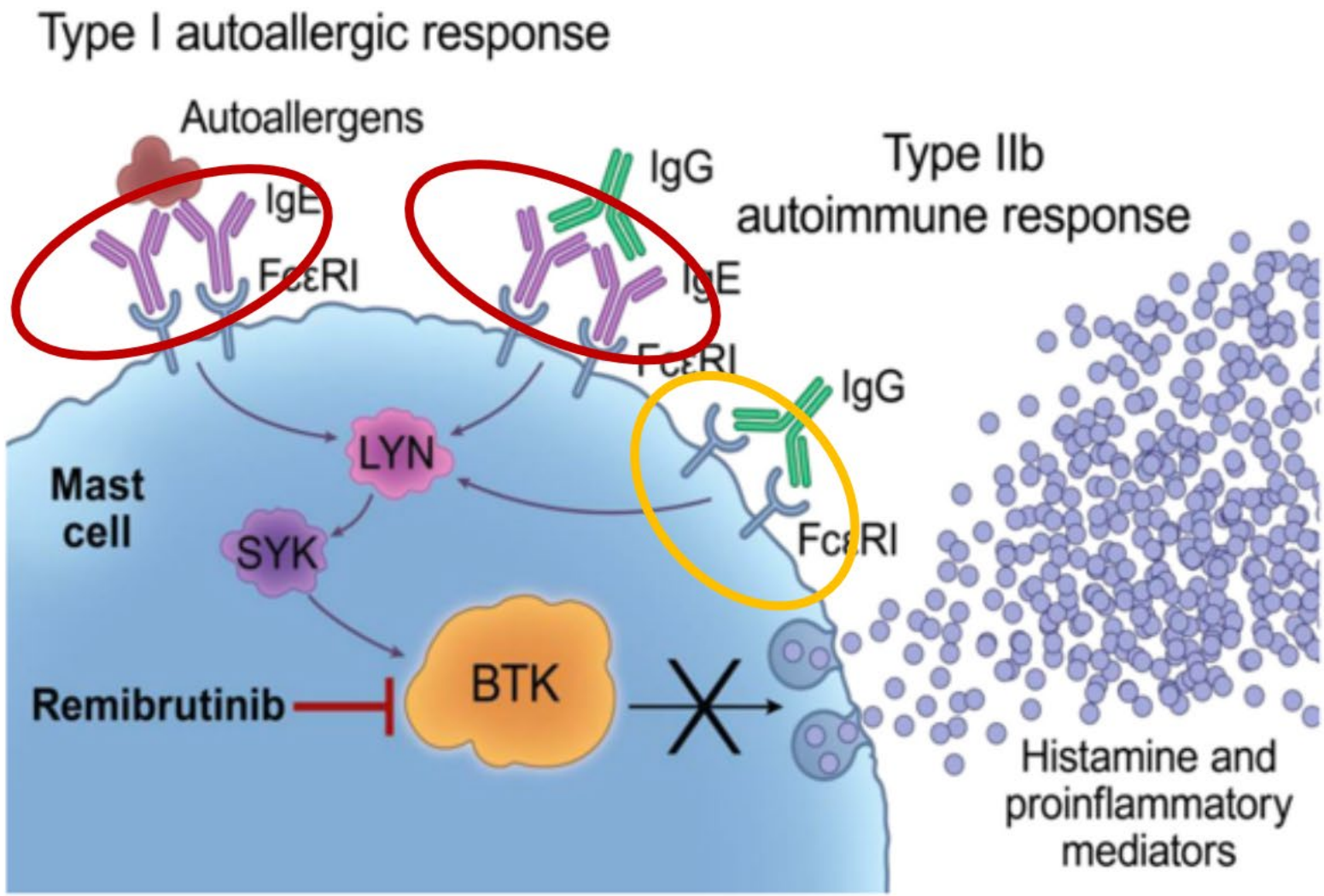
Prognostic markers for response to omalizumab in CSU

Poor prognosis	Good prognosis
Eosinopenia (<50 cells/mL)[41]	Normal or high IgE
Basopenia (<10 cells/mL)[41]	High d-dimer[49]
Low IgE[42] Positive basophil activation test[43]	Very high expression of FcεRI on basophils Negative ASST
Positive CD63[44]	Negative basophil activation test
IgG autoantibodies against FcεRI[44]	
Lower expression of FcεRI on basophils[45]	
Positive ASST[43,46]	
High CRP >3 mg/mL[47]	
Low ratio of 4th-week IgE to baseline IgE[48]	

Mustari, A. P. *Indian Dermatol. Online J.* 2022

How might targeting the IgE pathway be improved?

Targeted by omalizumab

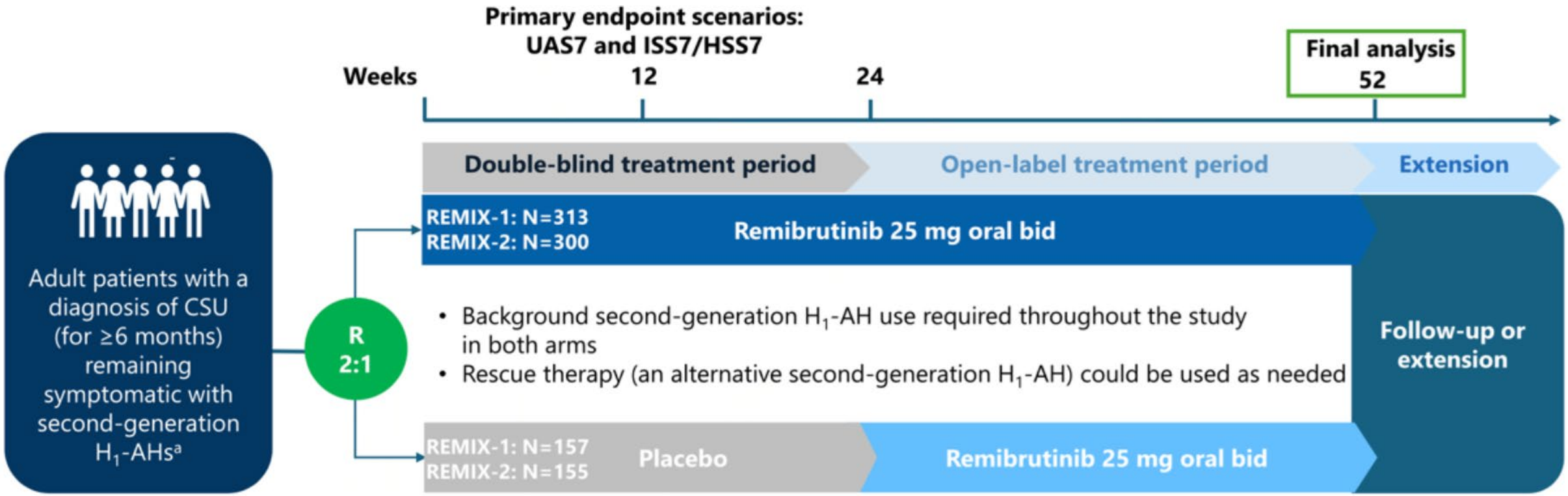


Saini et al. ACAAI. 2023

Remibrutinib for CSU

Remibrutinib is a highly selective BTK inhibitor

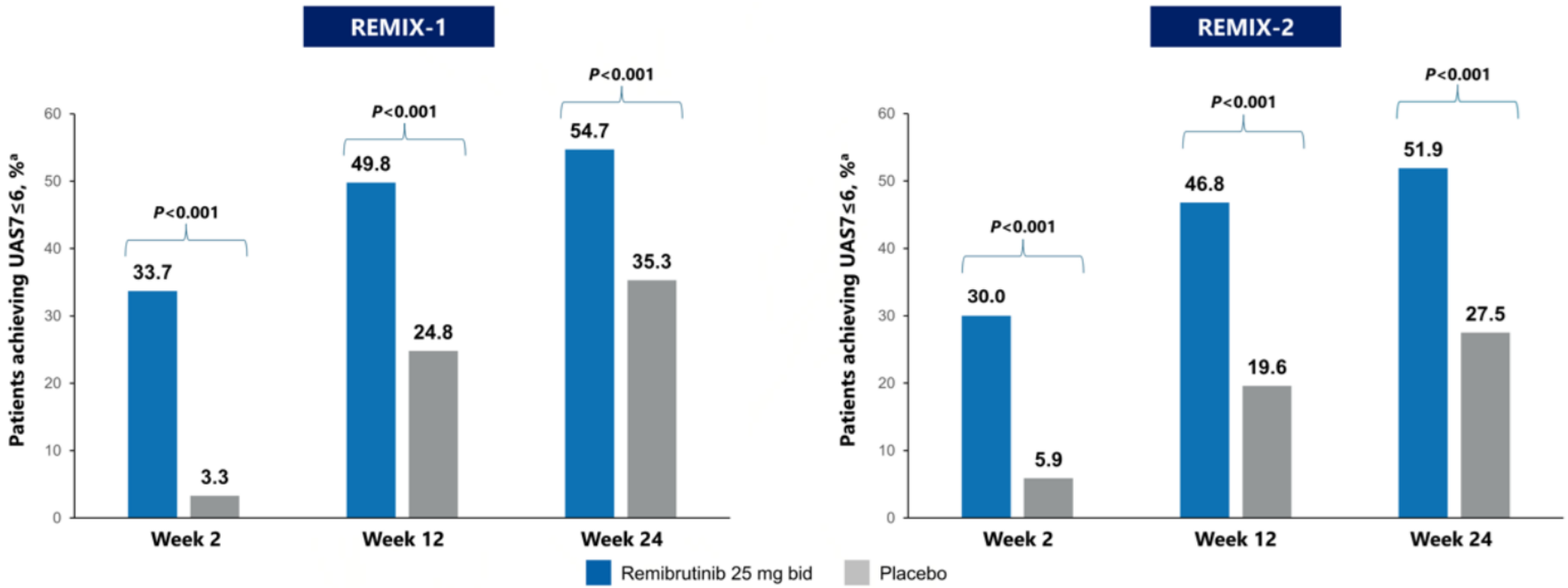
REMIX I and II phase 3 trials



Metz et al. EAACI. 2024

Remibrutinib for CSU

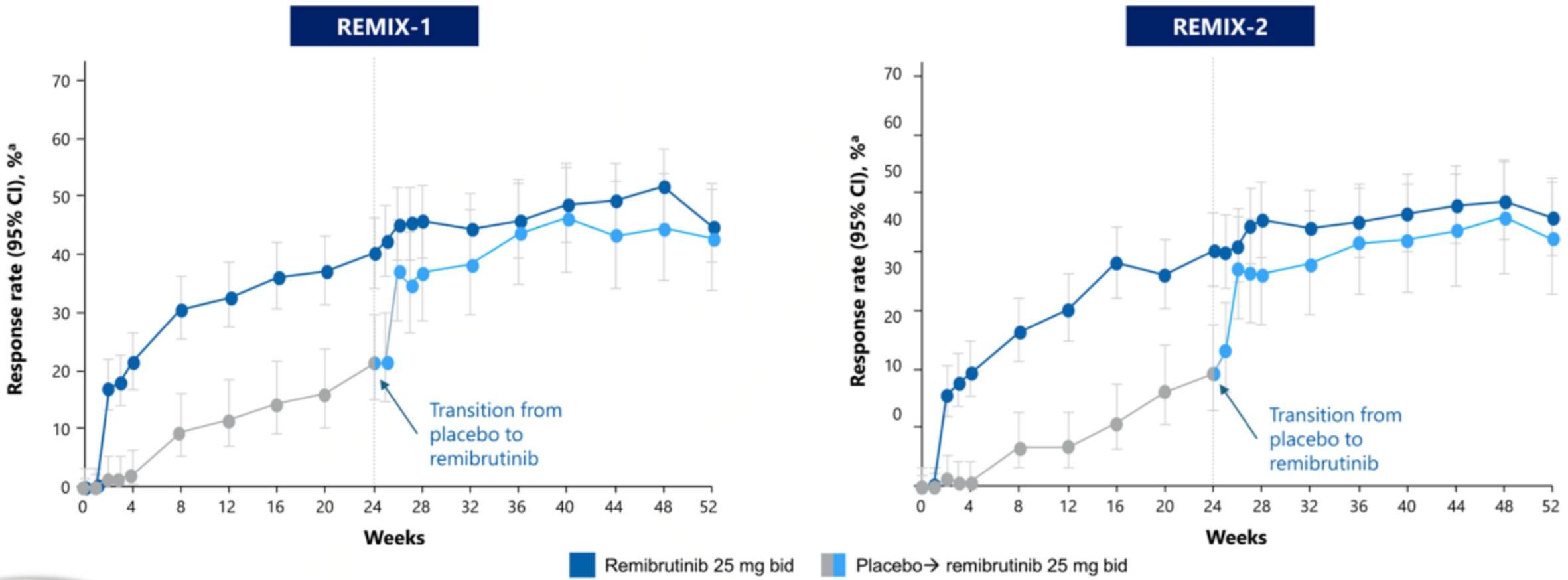
Rapid improvement in CSU based on UAS ≤ 6



Metz et al. EAACI. 2024

Remibrutinib for CSU

Significant proportion achieved complete response UAS = 0



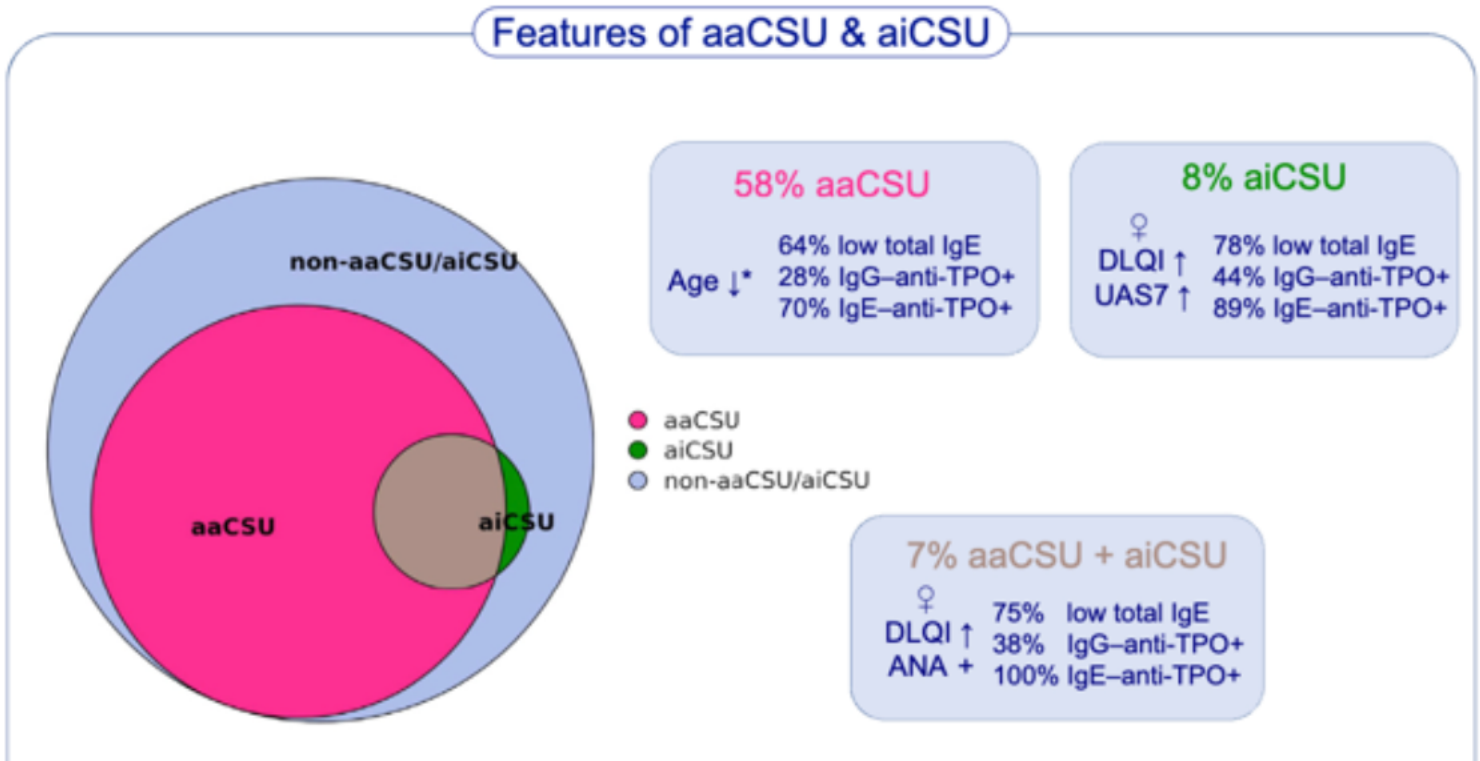
Metz et al. EAACI. 2024

Adverse events for remibrutinib

	Double-blind period[a]	
	Remibrutinib (n=606)	Placebo (n=306)
Median exposure, weeks	**24**	**24**
COVID-19, n (%), [EAIR]	65 (**10.7**), [26.0]	35 (**11.4**), [28.0]
Nasopharyngitis, n (%), [EAIR]	40 (**6.6**), [15.7]	14 (**4.6**), [10.9]
Headache, n (%), [EAIR]	38 (**6.3**), [15.0]	19 (**6.2**), [14.8]
Upper respiratory tract infection, n (%), [EAIR]	18 (**3.0**), [6.9]	6 (**2.0**), [4.6]
Urinary tract infection, n (%), [EAIR]	19 (**3.1**), [7.3]	8 (**2.6**), [6.1]
Petechiae, n (%), [EAIR]	23 (**3.8**), [8.9]	1 (**0.3**), [0.8]
Urticaria, n (%), [EAIR]	15 (**2.5**), [5.7]	15 (**4.9**), [11.7]

Metz et al. EAACI. 2024

CSU that falls outside the IgE pathway paradigm



aaCSU

- Autoallergic = auto-IgE
- Faster and better response to anti-IgE

aiCSU

- Autoimmune = anti-FcεR1a or anti-IgE
- Resistance to treatment with antihistamines and anti-IgE

Xiang, Y.-K. et al. JACI Pract. 2023

IgE-independent pathway to activate mast cells?

An alternative activation pathway to IgE in mast cells?

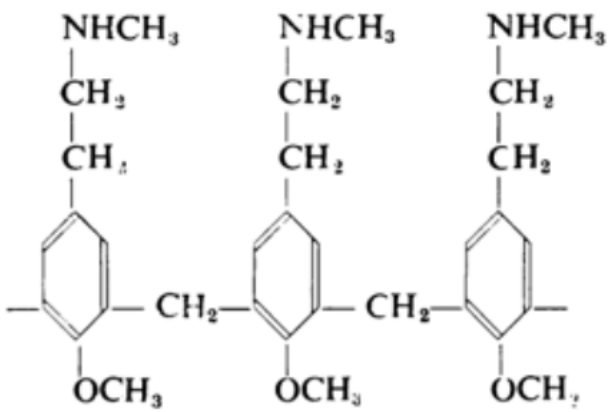
Brit. J. Pharmacol. (1951), **6**, 499.

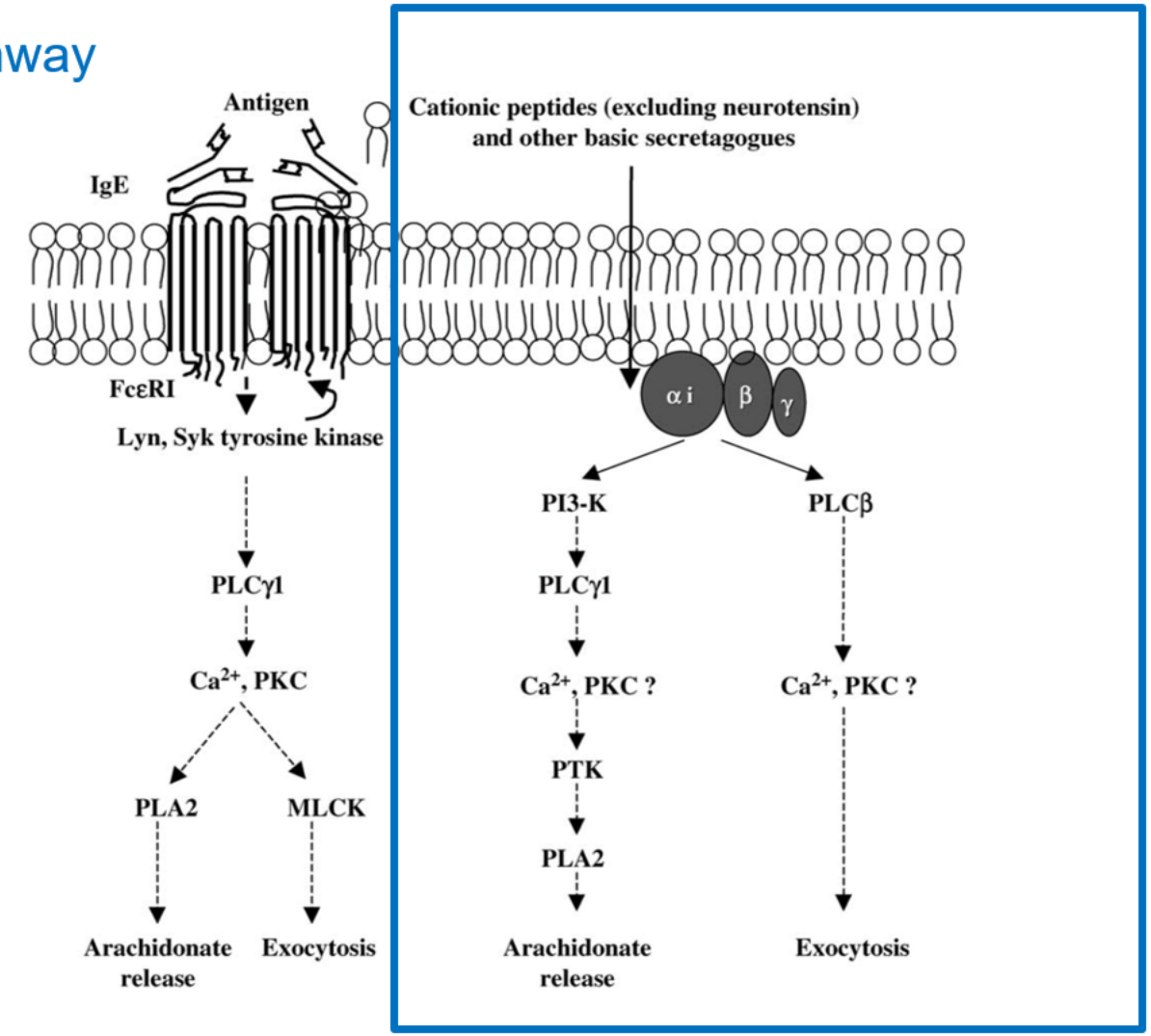
COMPOUND 48/80: A POTENT HISTAMINE LIBERATOR

BY

W. D. M. PATON

From the National Institute for Medical Research, Mill Hill, London, N.W.7





Ferry, X., Brehin, S., Kamel, R. & Landry, Y. G protein-dependent activation of mast cell by peptides and basic secretagogues. Peptides 23, 1507–1515 (2002).

MRGPRX2 (MrgprB2 in mice)

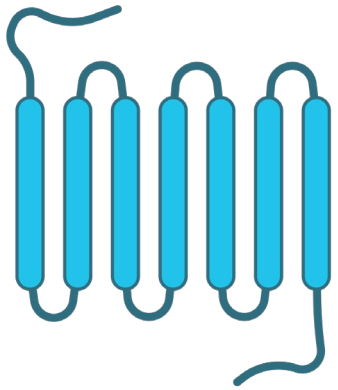
LETTER

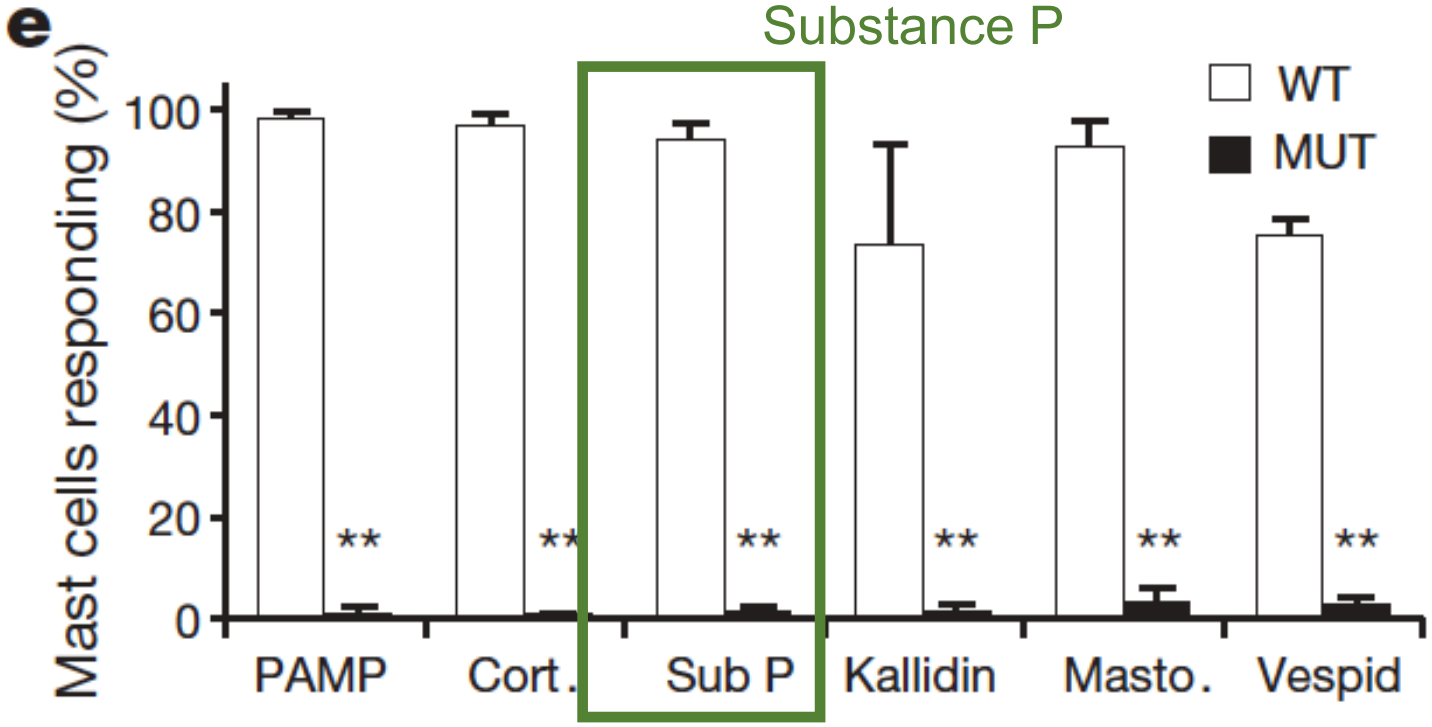
doi:10.1038/nature14022

Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions

Benjamin D. McNeil[1], Priyanka Pundir[2], Sonya Meeker[3], Liang Han[1], Bradley J. Undem[3], Marianna Kulka[2,4] & Xinzhong Dong[1,5]

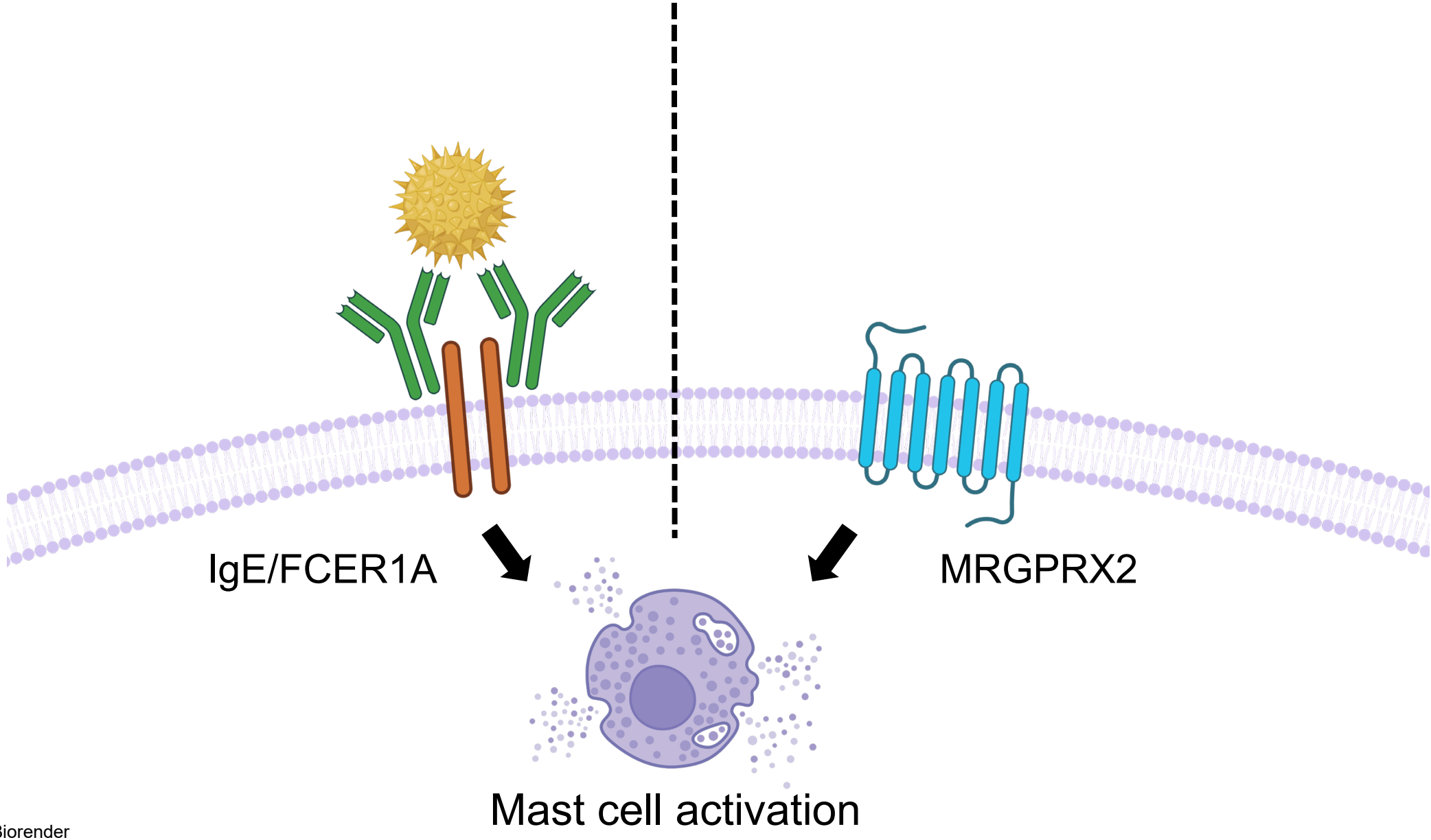
MrgprB2





Subramanian, H.*J Biol Chem.* 2011
Kashem, S. W. *et al. Eur J Pharmacol.* 2011
McNeil, B. D. *et al. Nature.* 2015

Two paths to degranulation. Is this a false dichotomy?

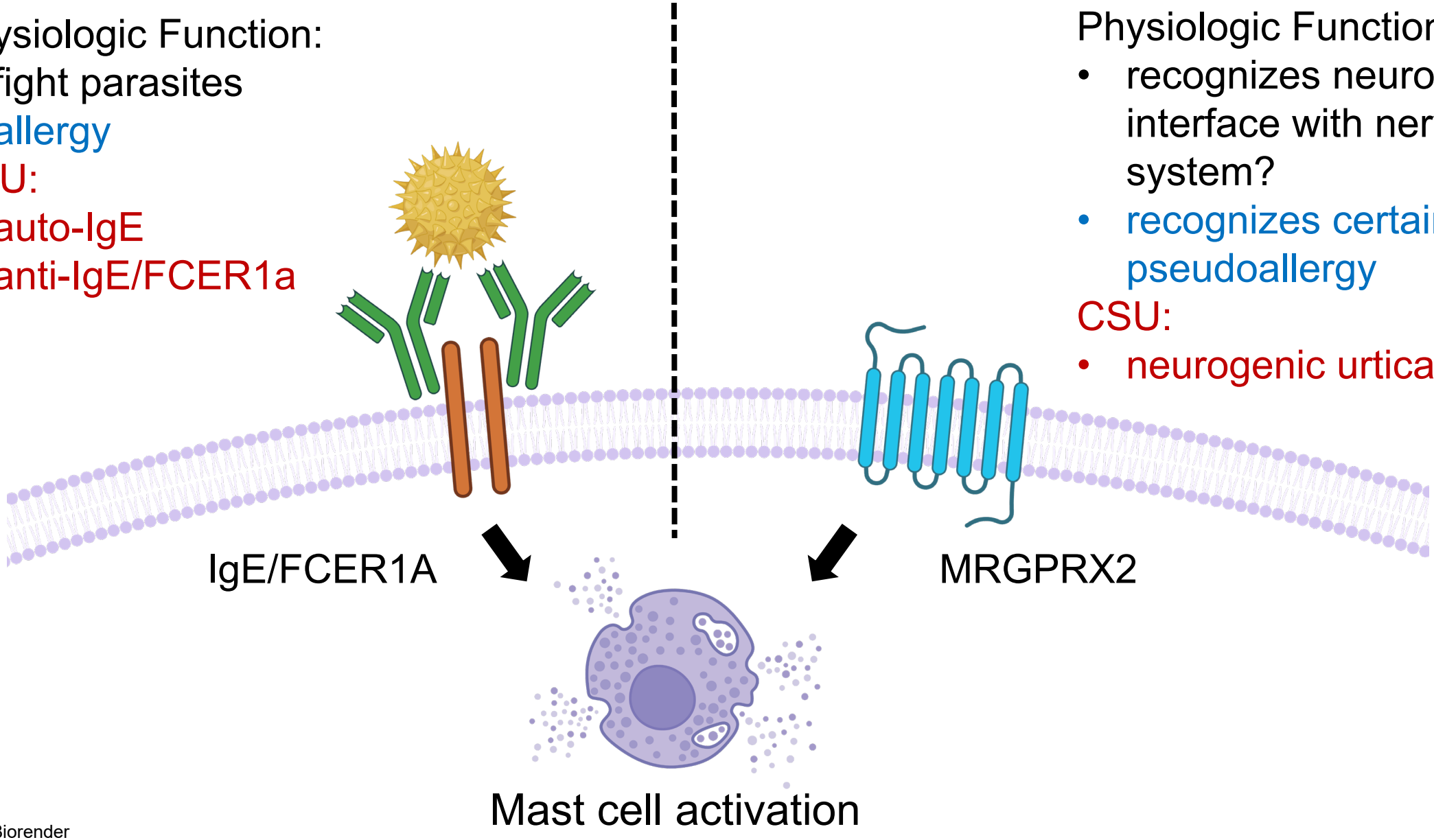


Created with Biorender

Two important paths to degranulation

Physiologic Function:
- fight parasites
- allergy

CSU:
- auto-IgE
- anti-IgE/FCER1a



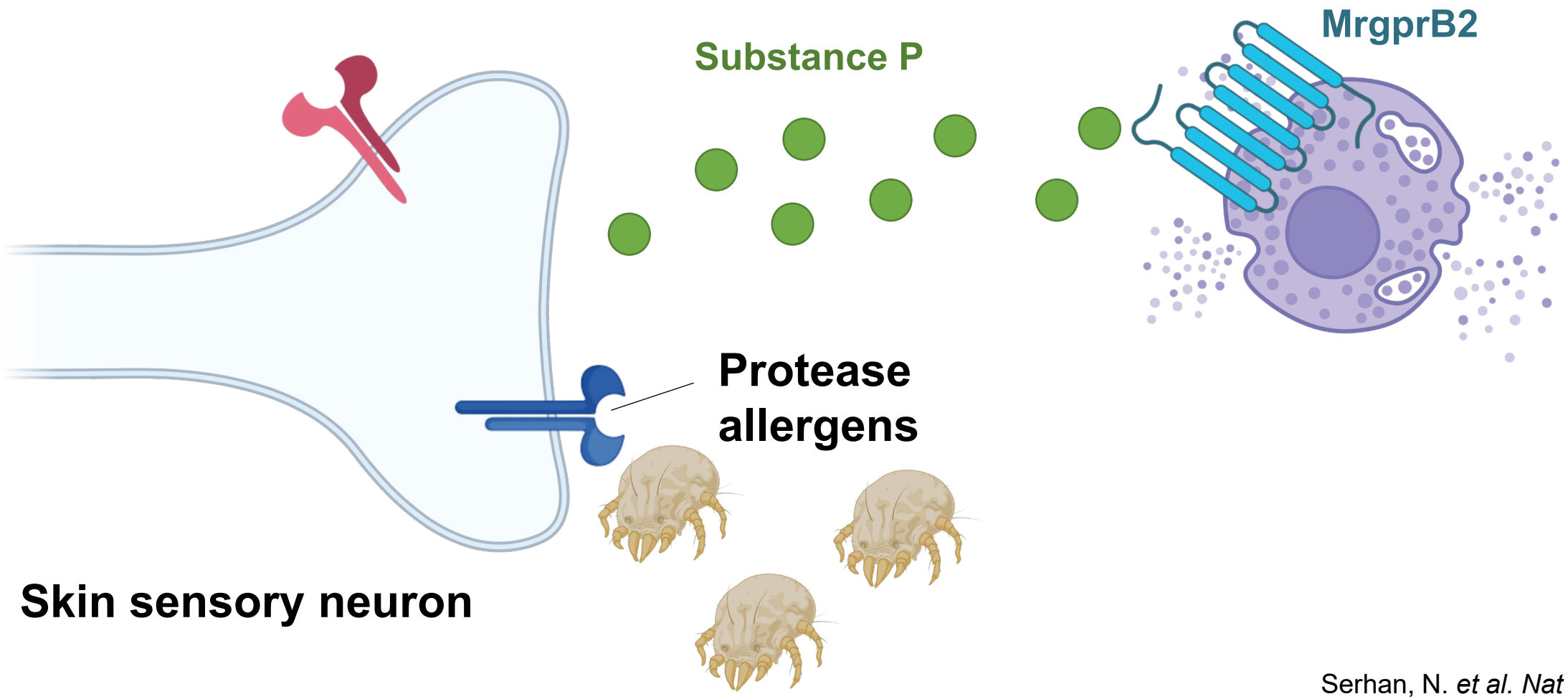
Physiologic Function:
- recognizes neuropeptides: interface with nervous system?
- recognizes certain drugs: pseudoallergy

CSU:
- neurogenic urticaria??

Created with Biorender

Allergens can drive mast cell inflammation via nerves in mice

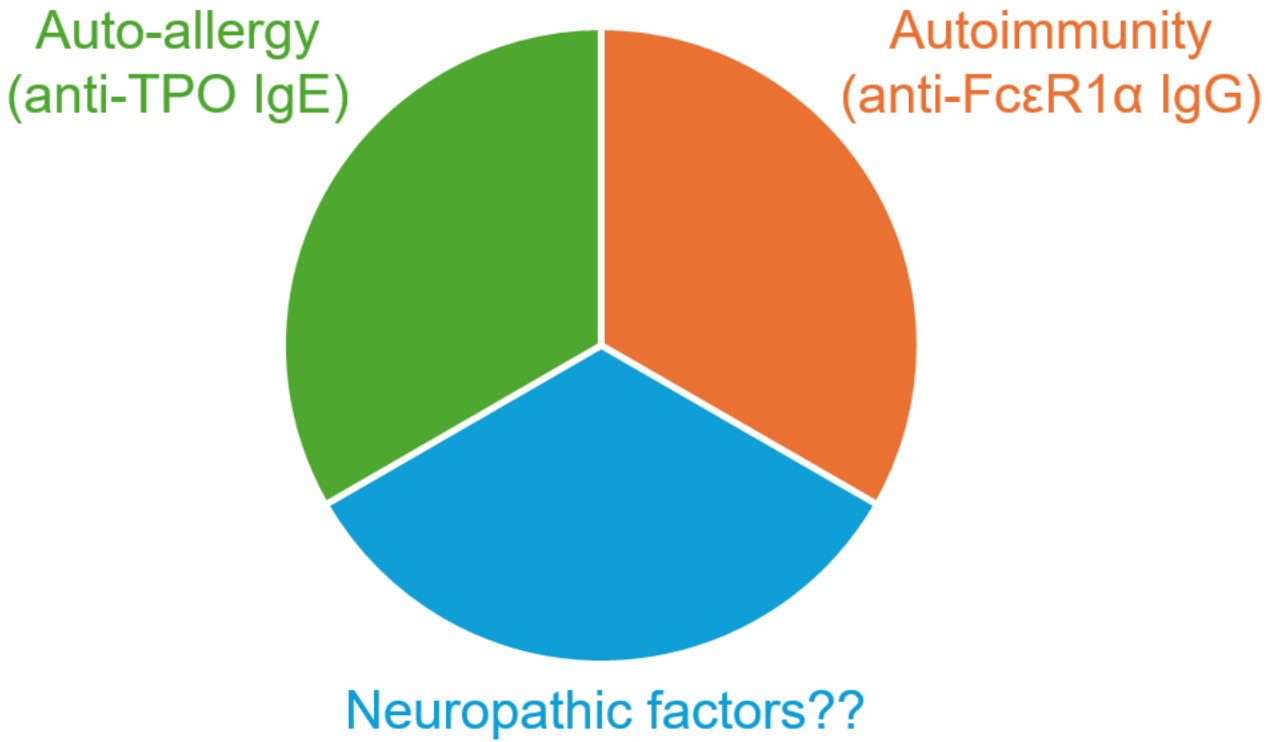
- Protease allergens activate sensory neurons
- Substance P released by neurons activates nearby mast cells via MrgprB2

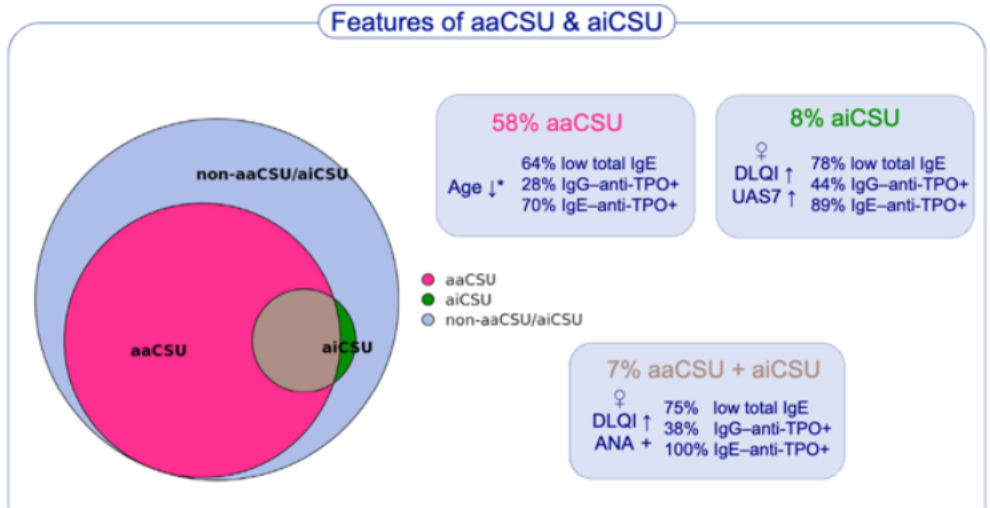


Serhan, N. *et al. Nat Immunol.* 2019

Neurogenic urticaria??

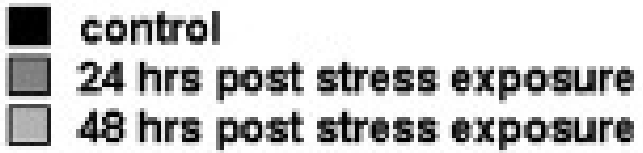
Etiology of CSU



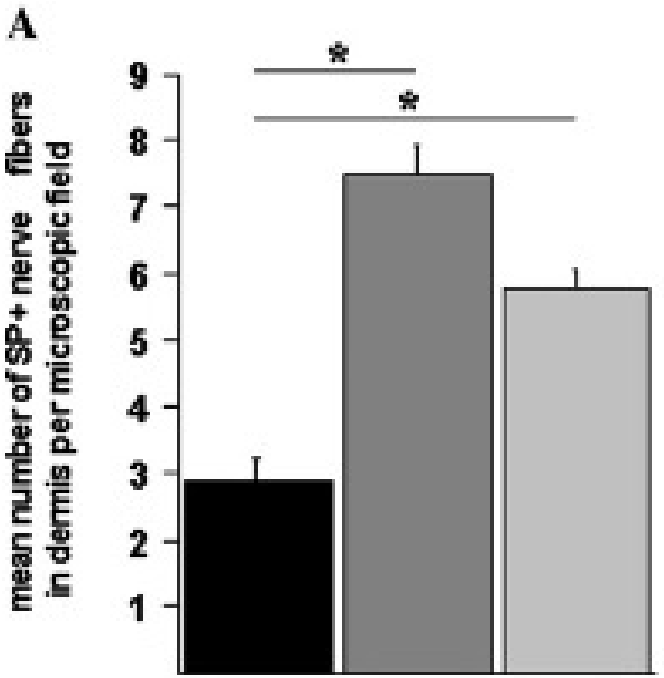


Neuron and mast cell crosstalk in CSU?

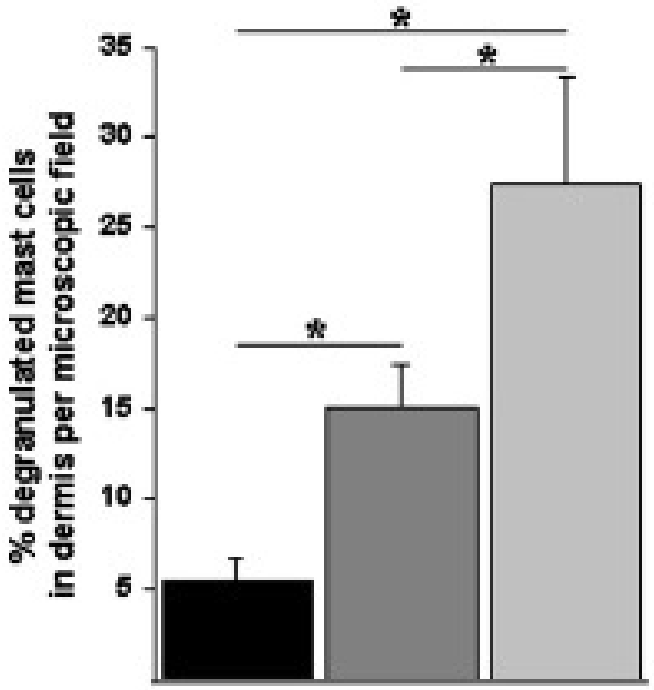
- Stress is a common trigger reported by patients with CSU[1]
- In mice, stress led to increased substance P in skin nerve fibers and increased mast cell activation in the skin[2]



Substance P+ nerves



% degranulated mast cells



1. Bernstein, J. A et al. *J Allergy Clin Immun* 2014
2. Peters, E. M. J. *et al. Brain Behav Immun* 2005

Passive transfer of fibromyalgia from patients to mice

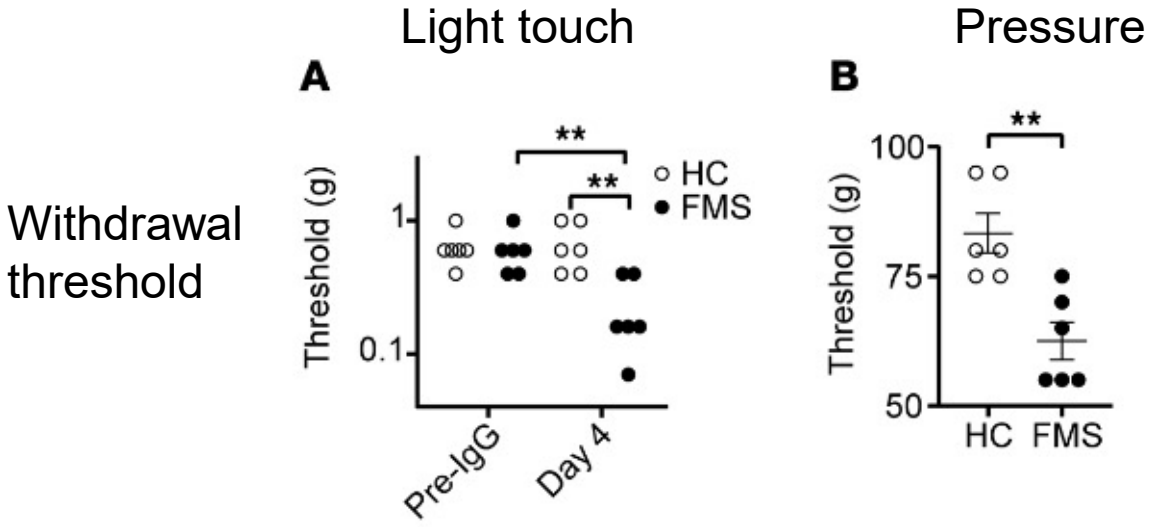
- Sera from fibromyalgia syndrome (FMS) patients decreased pain thresholds for mice
- If sera was depleted of IgG, this effect was lost

The Journal of Clinical Investigation RESEARCH ARTICLE

Passive transfer of fibromyalgia symptoms from patients to mice

Andreas Goebel,[1,2] Emerson Krock,[3] Clive Gentry,[4] Mathilde R. Israel,[4] Alexandra Jurczak,[3] Carlos Morado Urbina,[3] Katalin Sandor,[3] Nisha Vastani,[4] Margot Maurer,[4] Ulku Cuhadar,[4] Serena Sensi,[2] Yuki Nomura,[3] Joana Menezes,[3] Azar Baharpoor,[3] Louisa Brieskorn,[3] Angelica Sandström,[5] Jeanette Tour,[5] Diana Kadetoff,[5,6] Lisbet Haglund,[7] Eva Kosek,[5,8] Stuart Bevan,[4] Camilla I. Svensson,[3] and David A. Andersson[4]

[1]Walton Centre NHS Foundation Trust, Liverpool, United Kingdom. [2]Pain Research Institute, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, United Kingdom. [3]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden. [4]King's College London, Wolfson CARD, Institute of Psychiatry, Psychology & Neuroscience, Guy's Campus, London, United Kingdom. [5]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. [6]Stockholm Spine Center, Upplands Väsby, Sweden. [7]Department of Surgery, Division of Orthopaedic Surgery, McGill University, Montreal, Quebec, Canada. [8]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden.



Goebel, A. *et al*. *J Clin Invest.* 2021

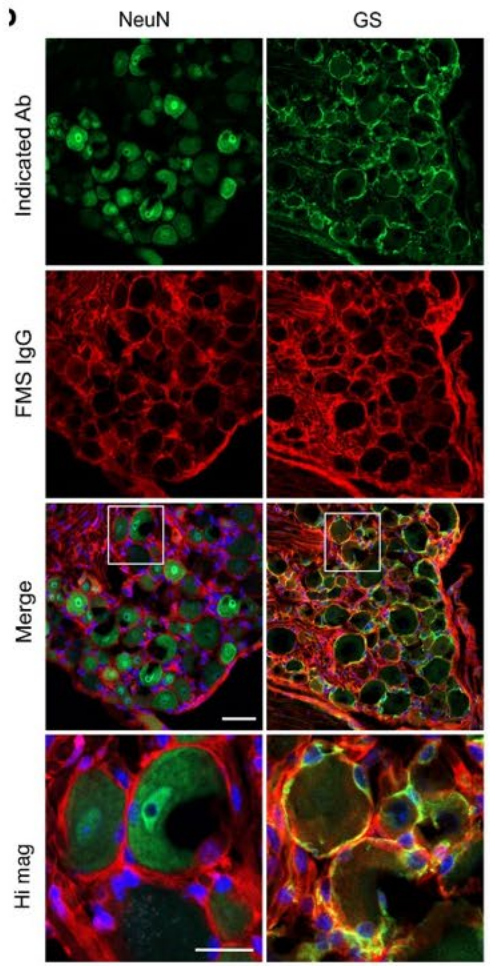
Passive transfer of fibromyalgia from patients to mice

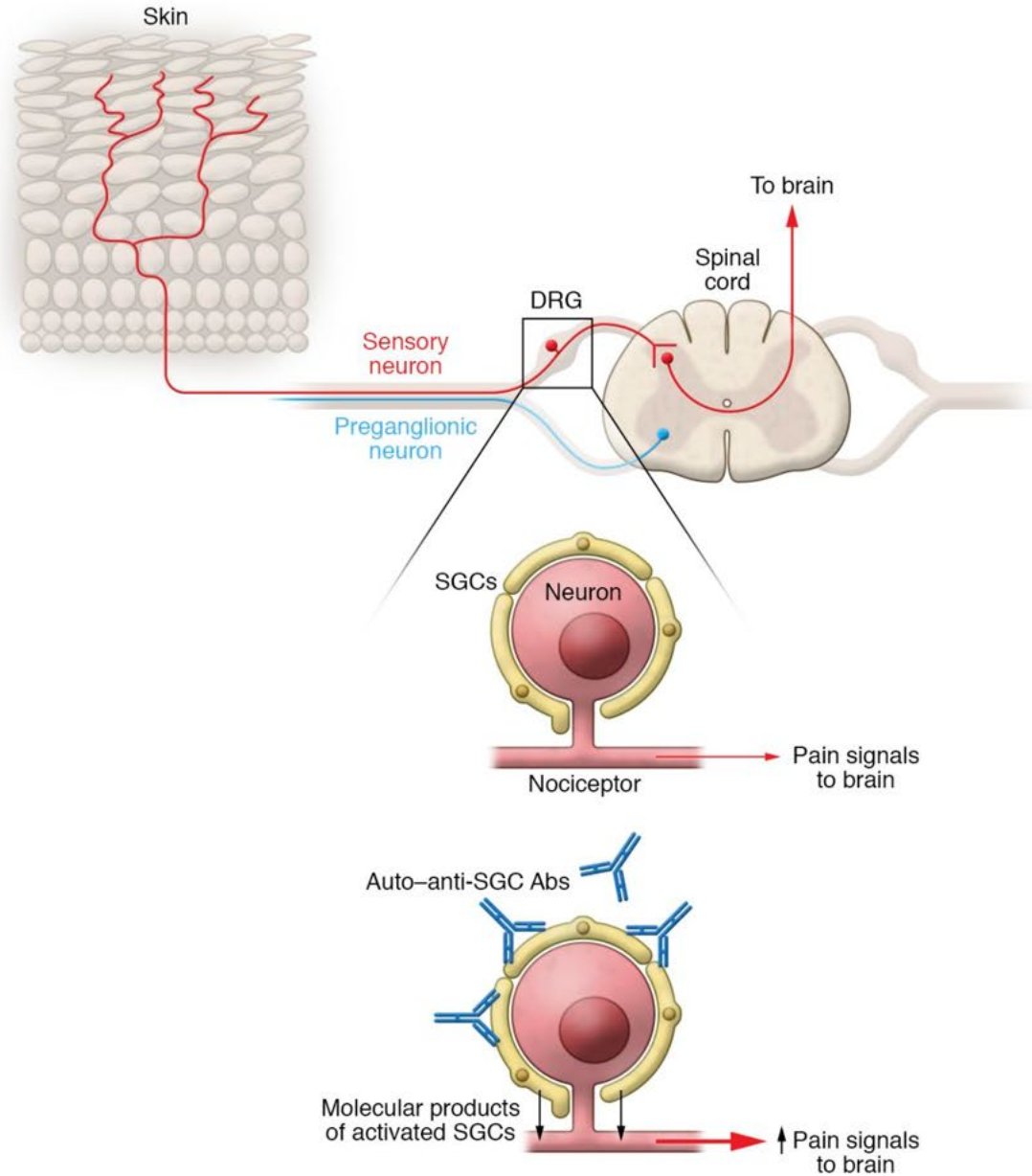
From human to mouse and back offers hope for patients with fibromyalgia

Kevin J. Tracey

Published July 1, 2021 - More info

View PDF

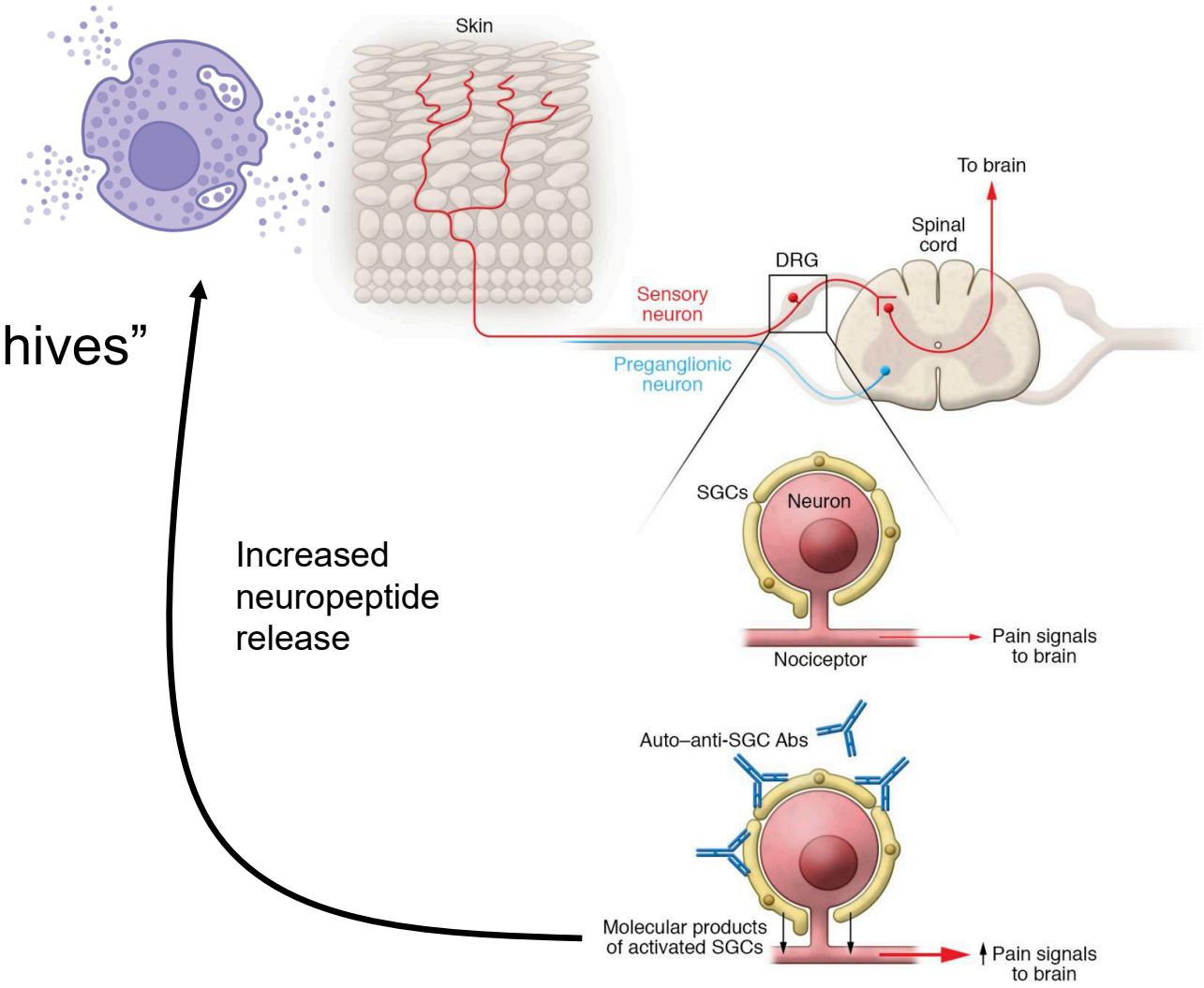




Tracey, K. J. *J. Clin. Investig*. 2021
Goebel, A. *et al*. *J Clin Invest*. 2021

Could autoantibodies against neurons contribute to CSU pathogenesis?

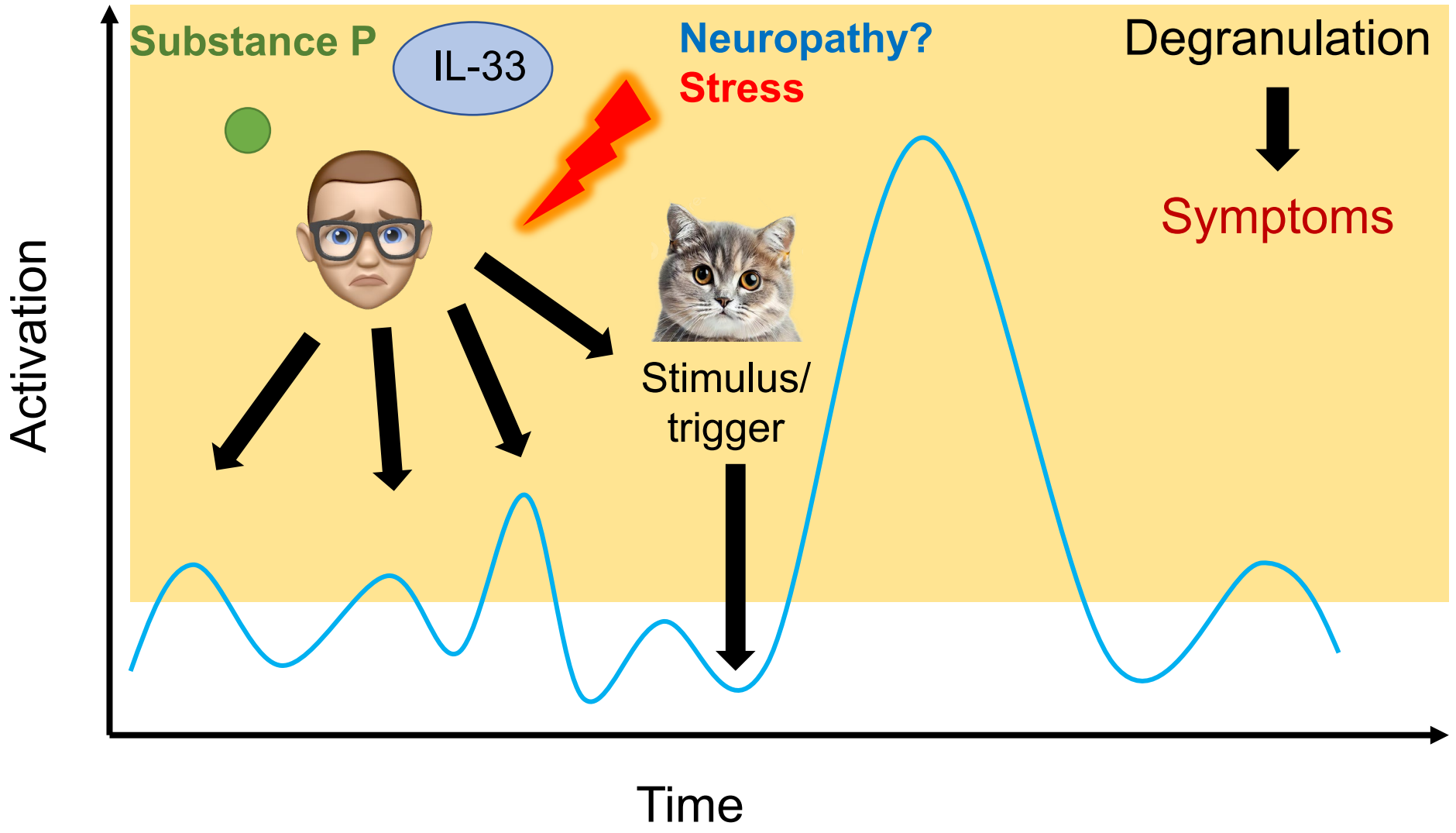
- Inducible
  - Dermatographism
  - Cholinergic
  - Cold induced
  - Solar
  - Aquagenic
  - Exercise
  - Delayed-pressure



"Neurogenic hives"

Increased neuropeptide release

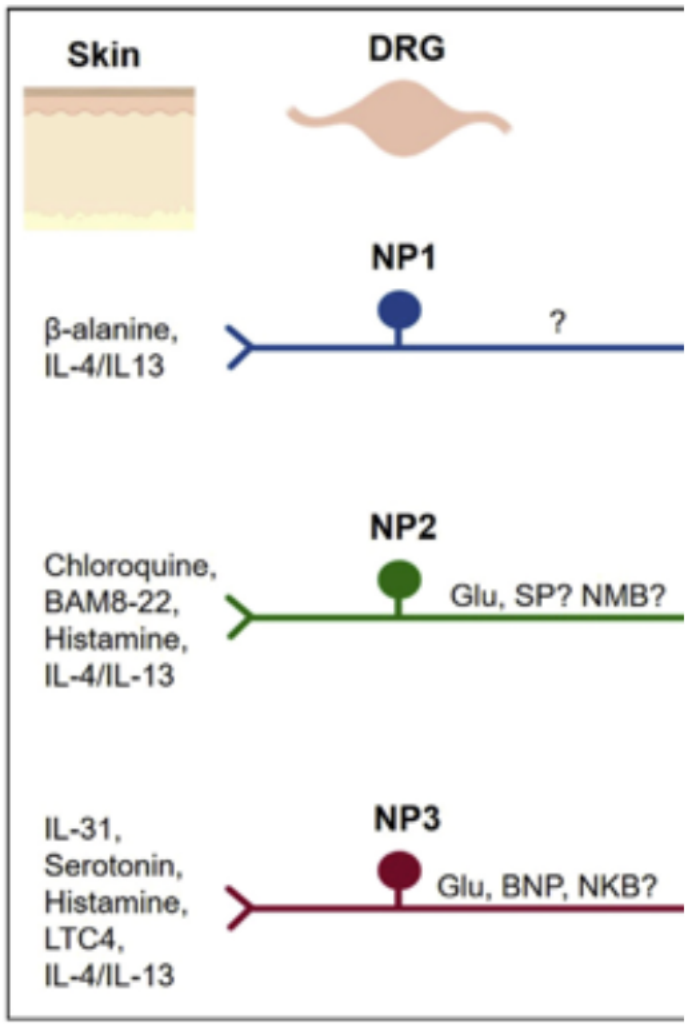
Mast cell activation in chronic urticaria



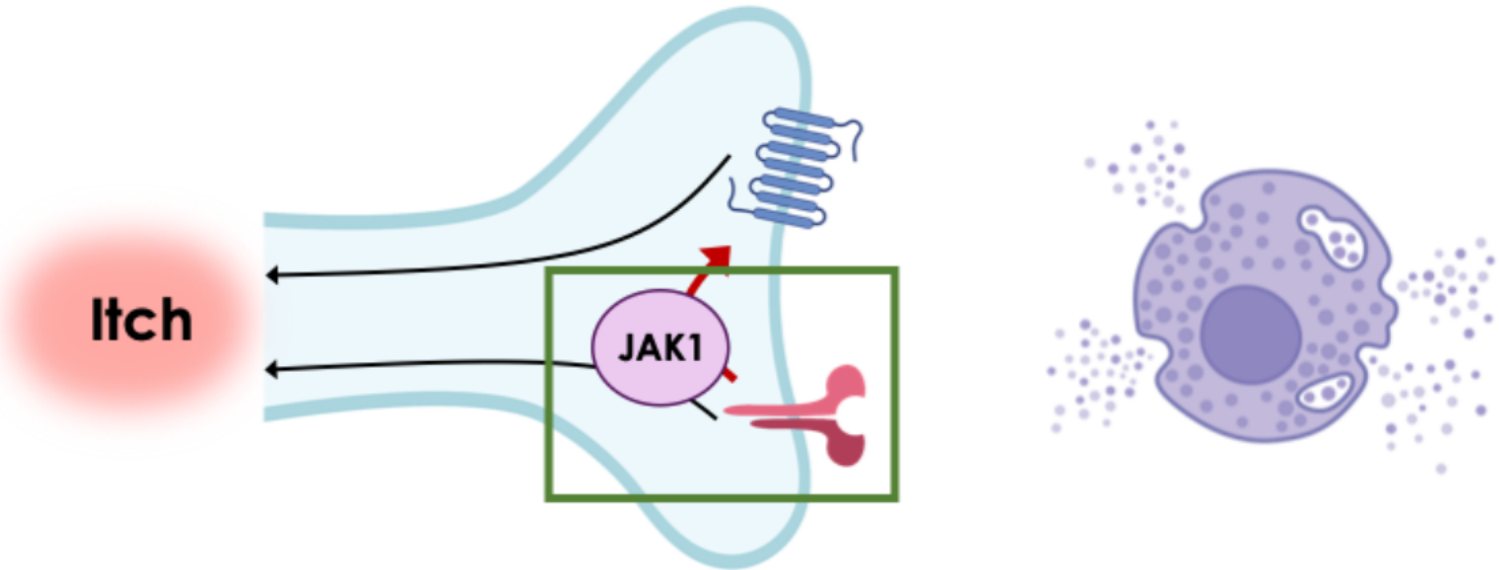
Reactions do not always correlate with exposures

“twitchy mast cells”

How might neurogenic inflammation in CSU be treated?



IL-4/13 receptor complex broadly expressed on skin sensory nerves



Potential role for IL-4/13 and JAK1 blockade in CSU itch independent of effects on mast cells

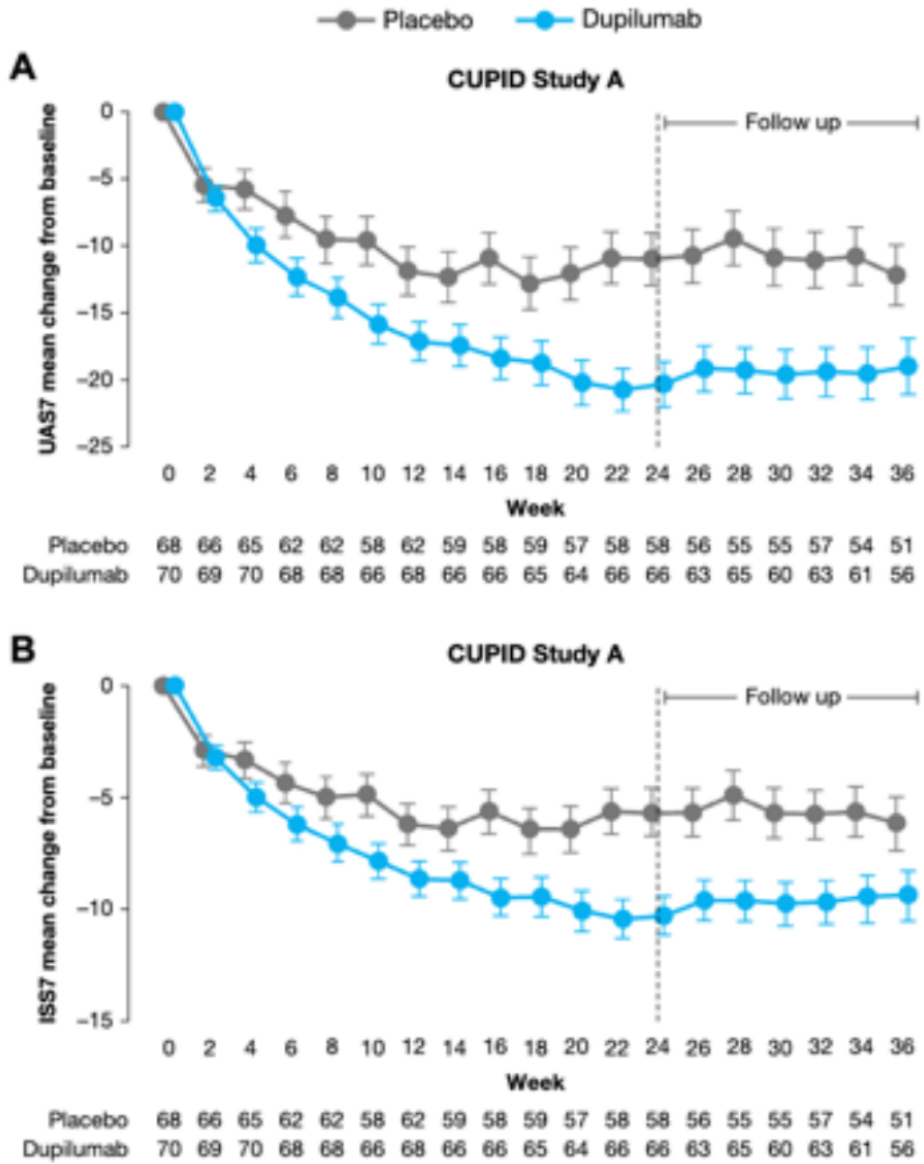
Wang, F. *Immunity* 2020

Dupilumab for CSU

LIBERTY-CSU CUPID Study A

- Children and adults (age ≥ 6 and ≤ 80) with CSU > 6 months with inadequate response to high dose antihistamines
- 24-week dupilumab vs placebo 1:1, with concurrent antihistamines
- Primary/secondary endpoints:
  - Non-EU (FDA-based guidelines): change from baseline in ISS7/UAS7
  - EU: change from baseline in UAS7/ISS7
- 138 total patients

**LIBERTY-CSU CUPID Study C companion to Study A recently completed. 151 patients enrolled, met primary end points

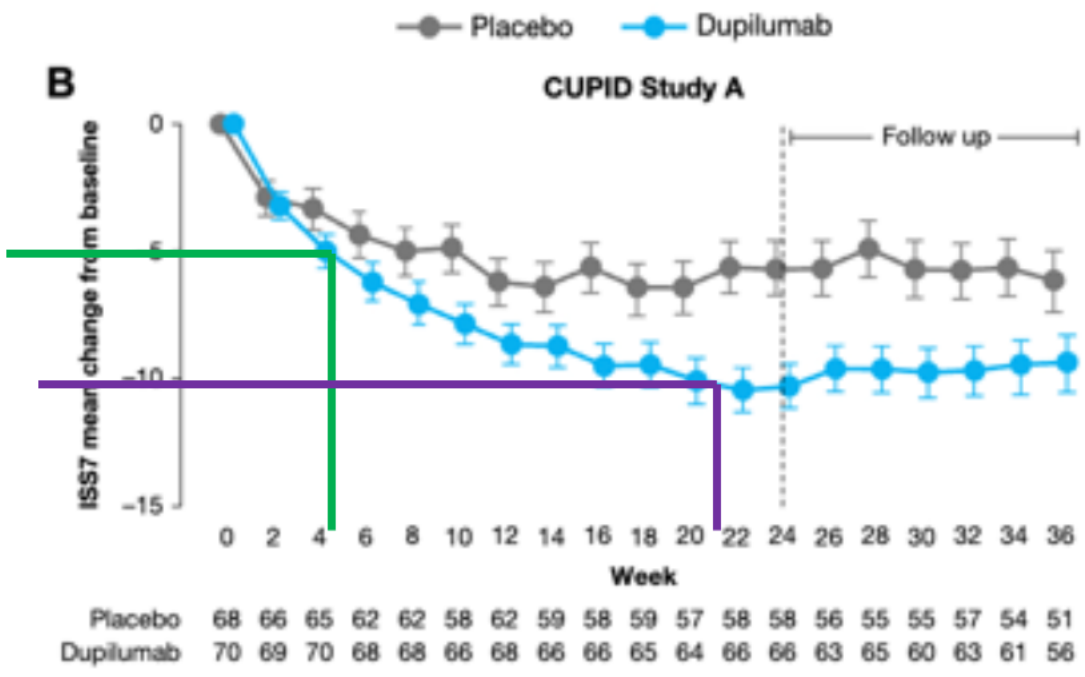


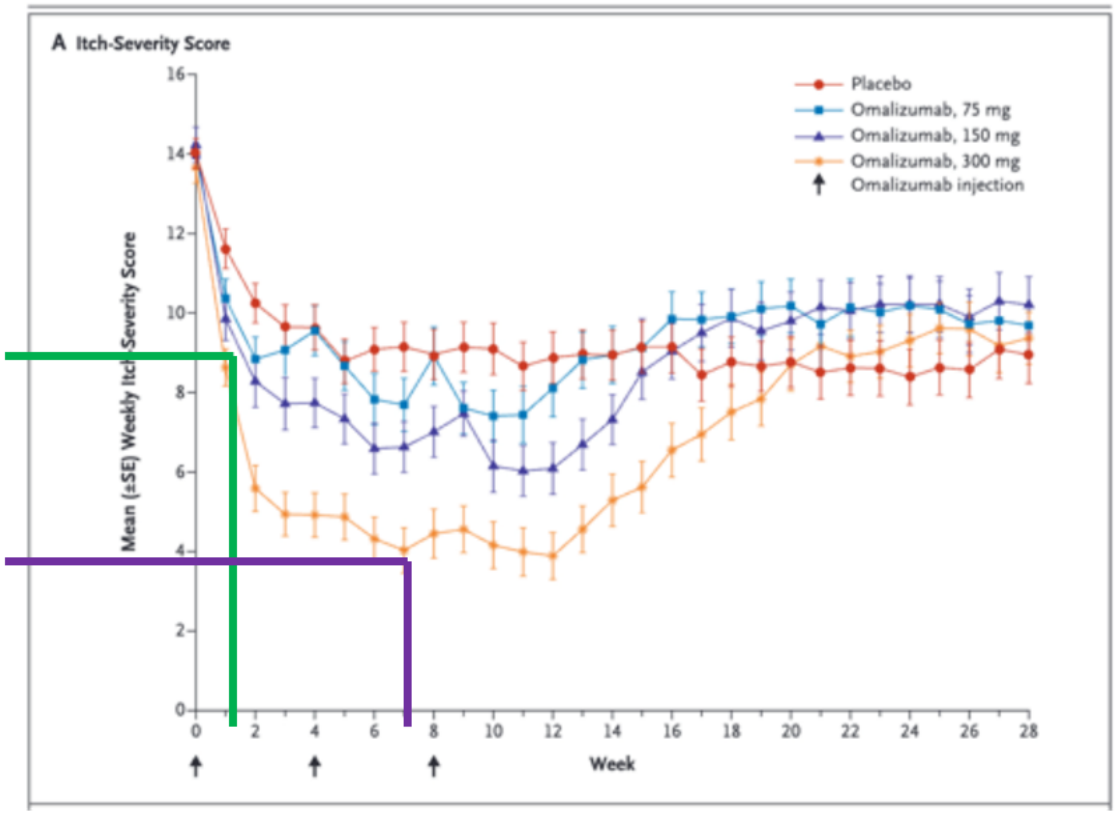
Maurer et al. JACI. 2024

Compare dupilumab to omalizumab

- Of course, these types of comparisons have caveats!!

Asteria II





Dupilumab 50% response >4 weeks vs <2 weeks for omalizumab

Dupilumab full response >20 weeks vs <8 weeks for omalizumab

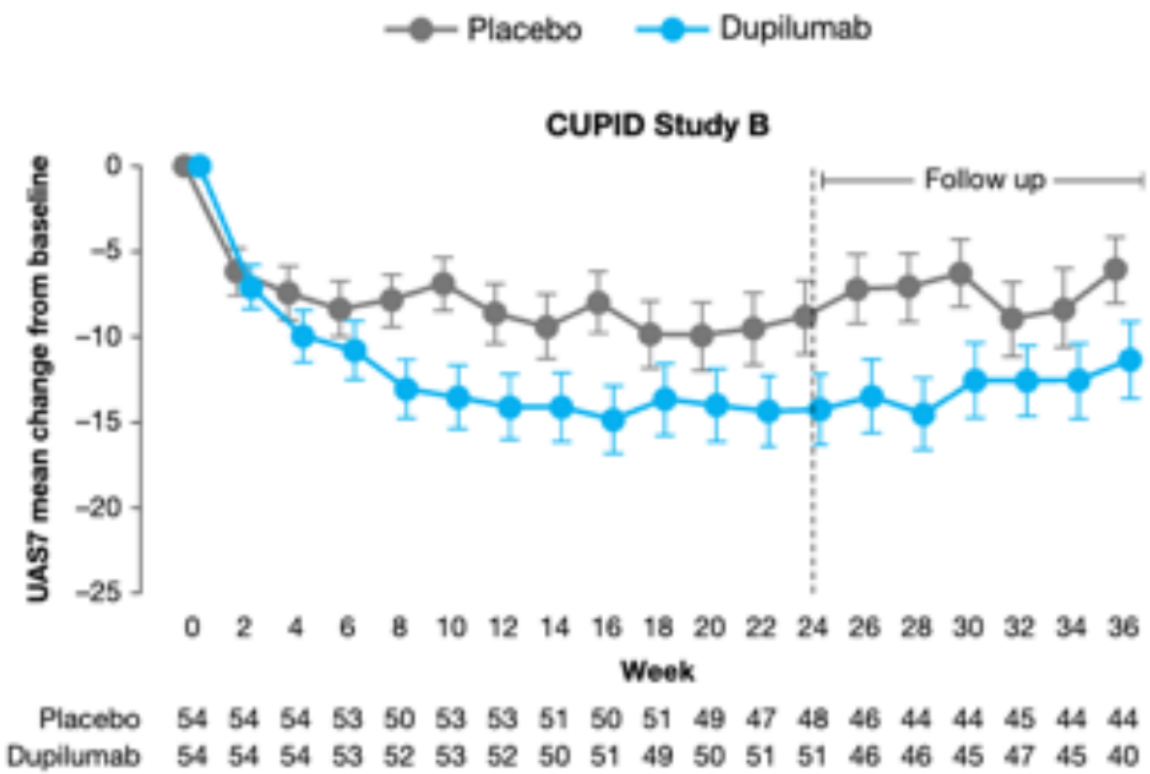
Maurer et al. JACI. 2024

Maurer et al. NEJM. 2013

Dupilumab in omalizumab non-responders

LIBERTY-CSU CUPID Study B

- Adolescents and adults (age ≥ 12 and ≤ 80)
- Inadequate response or intolerant to omalizumab



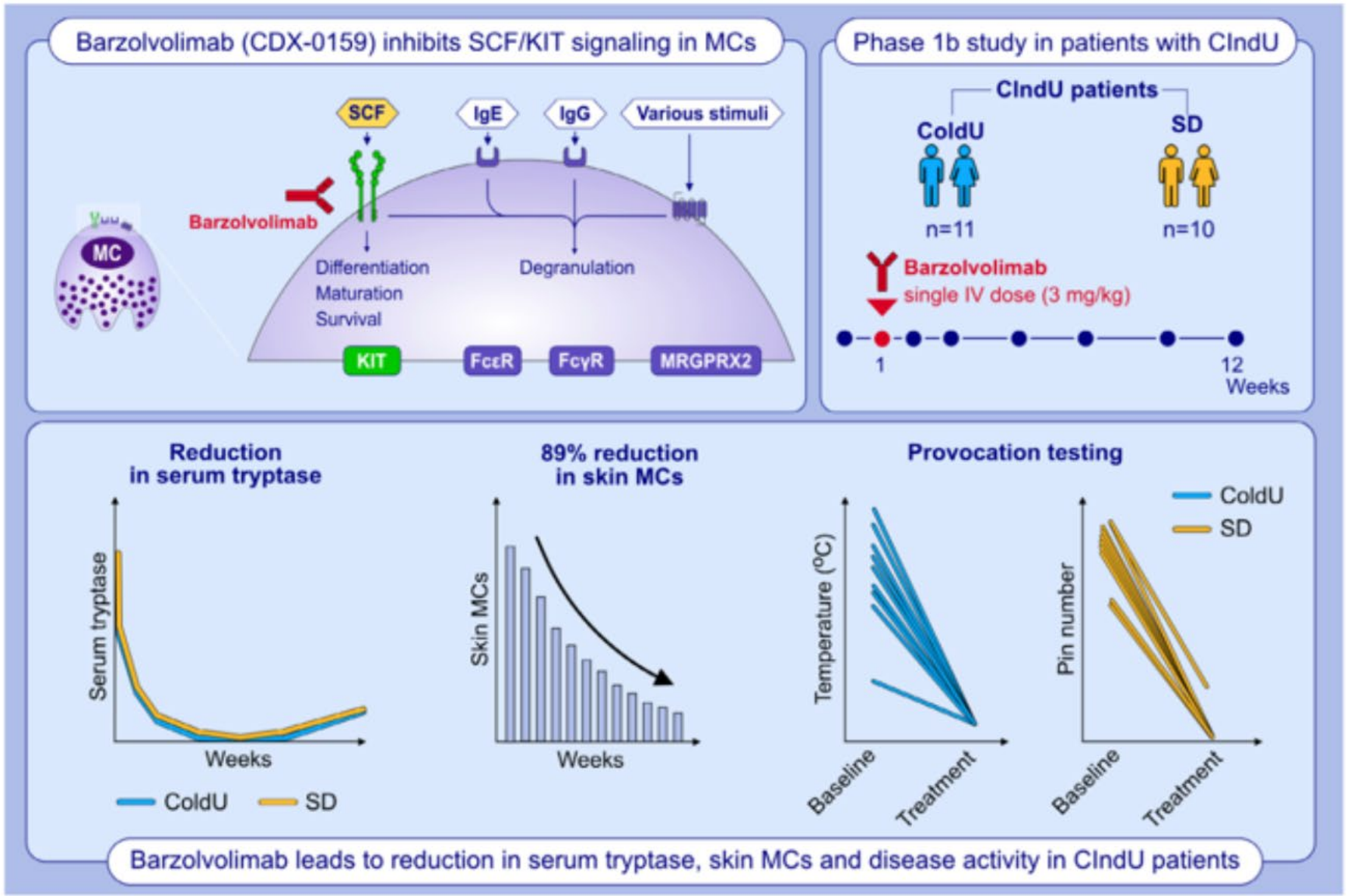
UAS marginally significant

ISS not significant

Maurer et al. JACI. 2024

Maybe the solution for CSU is simple…

Barzolvolimab for chronic urticarias



Phase 3 trials in CSU initiated in July 2024

Will include:

- biologic naïve
- biologic experienced

A new therapeutic era for CSU on the horizon

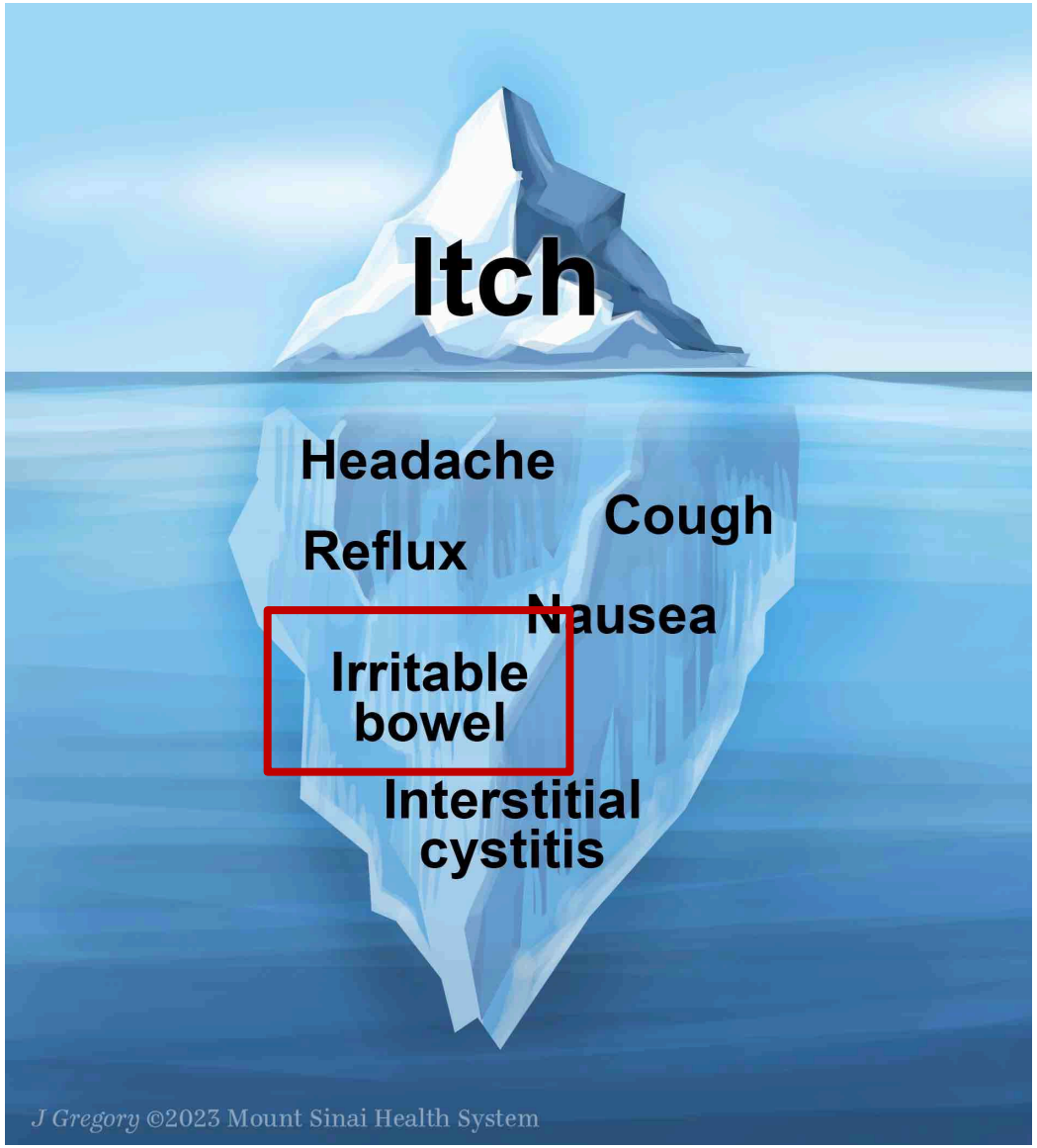
FDA-approved drugs for CSU

- Loratidine (des-) – 1993 (2001)
- Cetirizine (levo-) – 1995 (2007)
- Fexofenadine – 2000
- **Omalizumab – 2014**
- **Dupilumab??**
- **Remibrutinib??**
- **Barzolvolimab??**

FDA-approved drugs for AD

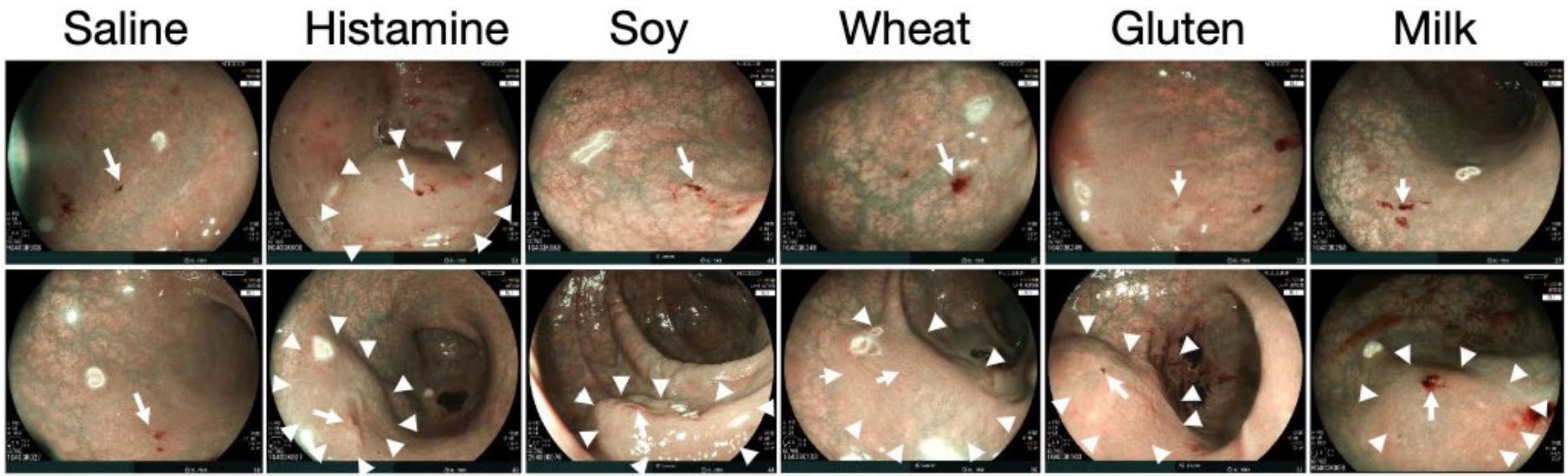
- Tacrolimus - 2000
- Pimecrolimus - 2001
- Desonide - 2006
- Crisaborole - 2016
- **Dupilumab - 2017**
- **Ruxolitinib - 2021**
- **Tralokinumab - 2021**
- **Abrocitinib - 2022**
- **Upadacitinib - 2022**
- **Lebrikizumb - 2024**
- **Nemolizumab - 2024**
- **Tapinarof - 2024**

CSU as a model disease to understand itch?



IgE-mediated irritable bowel syndrome symptoms

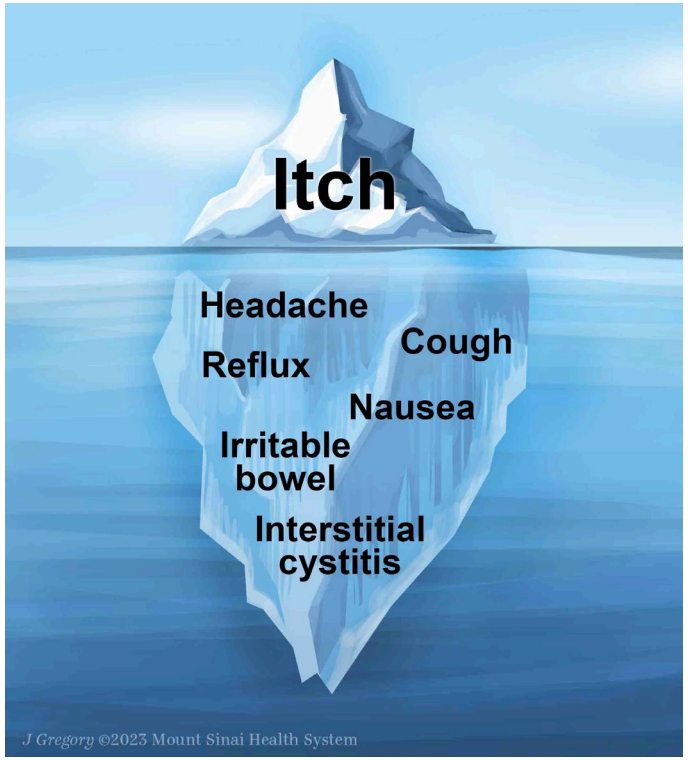
Intramucosal injection of food antigens = “colon tests”

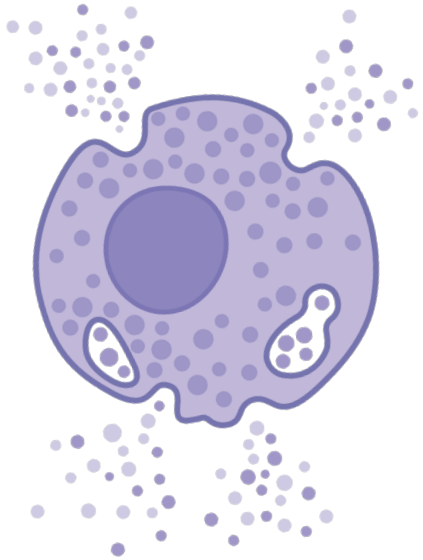


***All subjects had negative skin and serum testing to food allergens

Aguilera-Lizarraga, J. *et al*. *Nature.* 2021

CSU as a model disease to understand itch?





Pathogenic factor activating mast cells		Symptoms
Auto-IgE (IL-24 BP180) Neurogenic?	→	CSU
Local IgE to food Auto-IgE? Neurogenic?	→	IBS

Conclusions

- Both autoimmune (anti-IgE and anti-FcεRI) and auto-allergic (IgE to self) contribute to mast cell activation in CSU. Omalizumab appears to be more effective in cases driven by auto-IgE.

- Many stimuli can contribute to CSU through mast cell hypersensitization or activation including cytokines and neuropeptides.

- Many new therapies are in development for CSU. Dupilumab and remibrutinib have met primary endpoints for efficacy in phase 3 trials and are pending decisions by the FDA.

Questions?