Itch: the neuroimmune perspective

WSAAI 2025

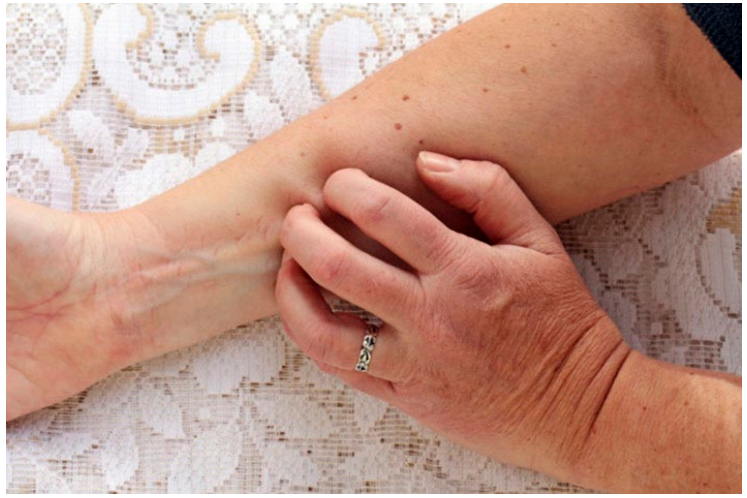
02-11-2025

Aaron Ver Heul, MD, PhD

Objectives

- Discuss the role of type 2 cytokines in modulating itch
- Discuss emerging treatment options for neuropathic itch
- Discuss mechanisms of neurogenic inflammation contributing to skin homeostasis

Why do we itch?



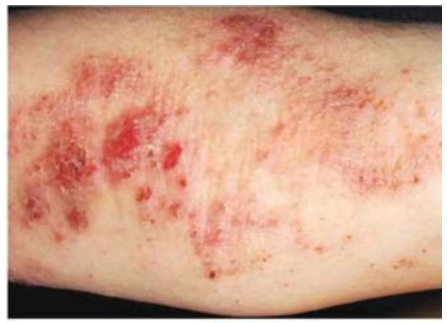
Itch (and pain) are reflex danger signals

		Reflex response	Adaptive Function
Itch	*Sarcoptes scabiei* 	→ Scratch	Remove noxious exposure
Pain		→ Withdraw	Avoid noxious exposure

https://en.wikipedia.org

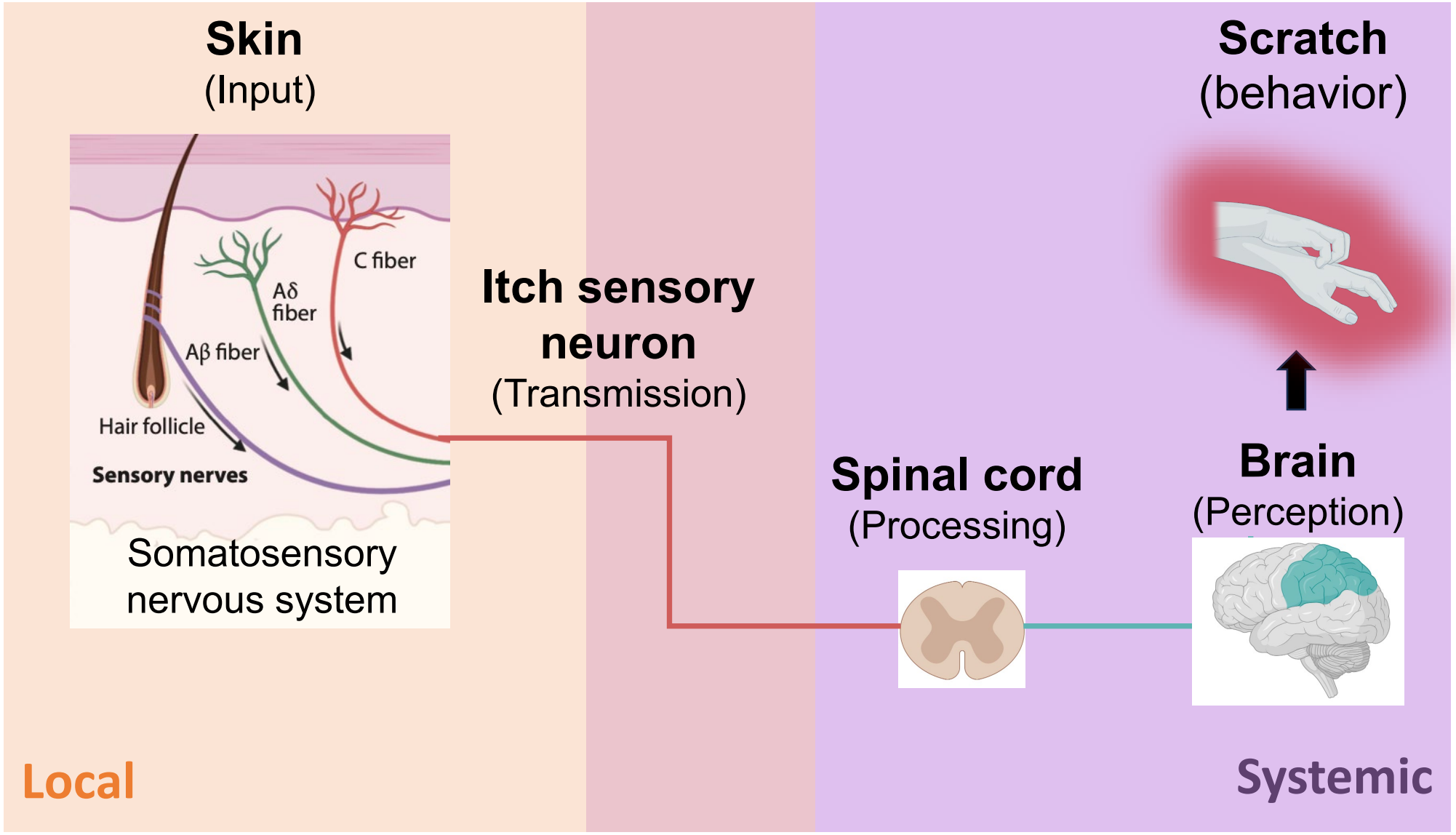
Acute vs chronic itch

	Reflex response	Maldaptive effect
Itch →	Scratch	Itch-Scratch cycle
Pain →	Withdraw	Immobility



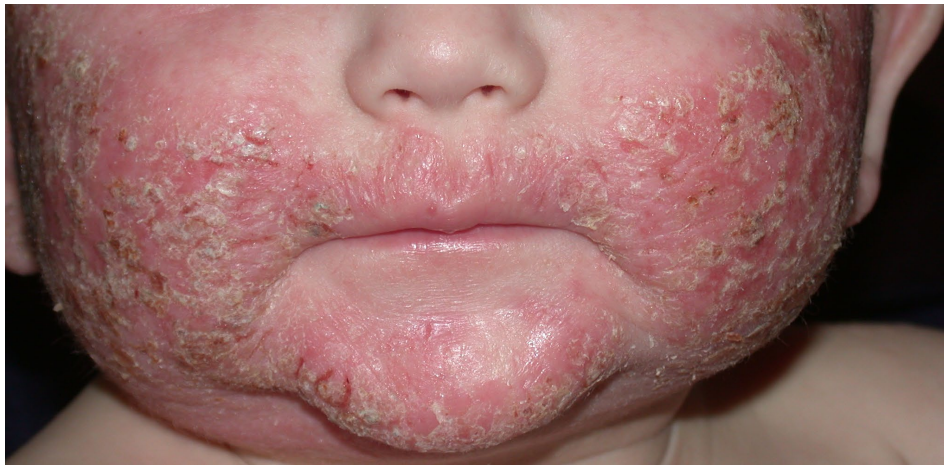
https://en.wikipedia.org

Perception of itch involves multiple steps



Atopic dermatitis as a model inflammatory pruritic disease

- Chronic, relapsing skin disease
- High incidence, costly
- Historically, therapeutic options limited
- Itch is the central symptom



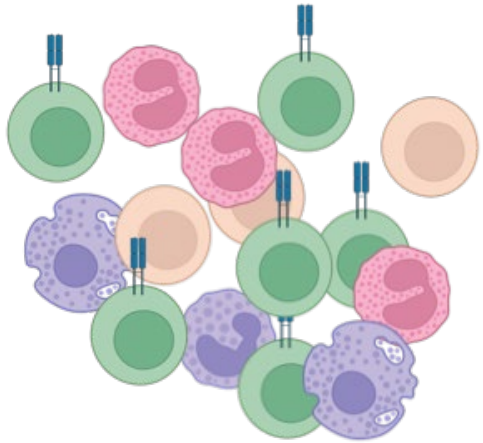
Andrews' Disease of the Skin Atlas 2018

Classical view of inflammatory itch

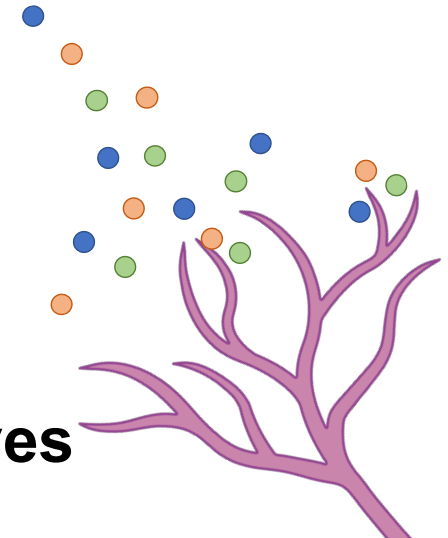
Noxious skin stimuli

Barrier defects
Allergens
Irritants
Pathogens
Scratching

Skin inflammation

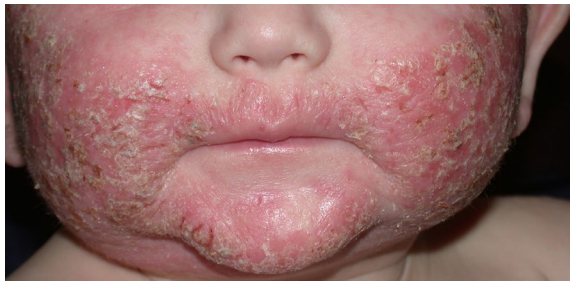


Th2 cells
Basophils
Eosinophils
Mast cells
IgE

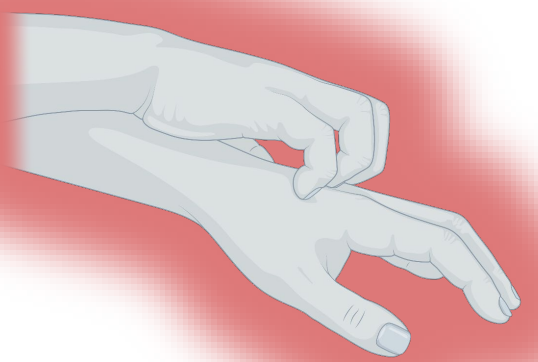


Skin sensory nerves

Rash



Itch



Classical treatment of inflammatory itch

Immune suppression

Topical and/or systemic steroids

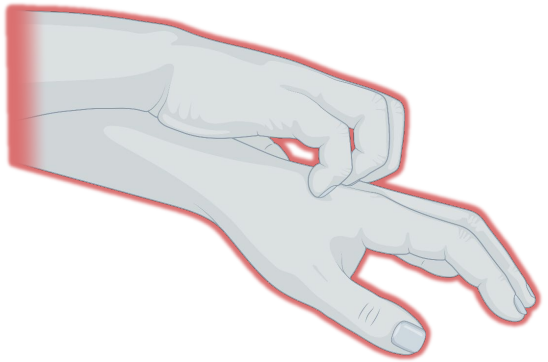
Off label immune suppressants:

- Cyclosporine
- MTX
- Azathioprine

Skin sensory nerves

Rash

Itch

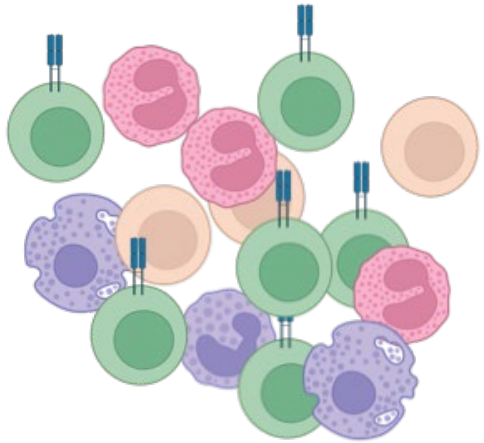


Evolving molecular understanding of atopic itch

Noxious skin stimuli

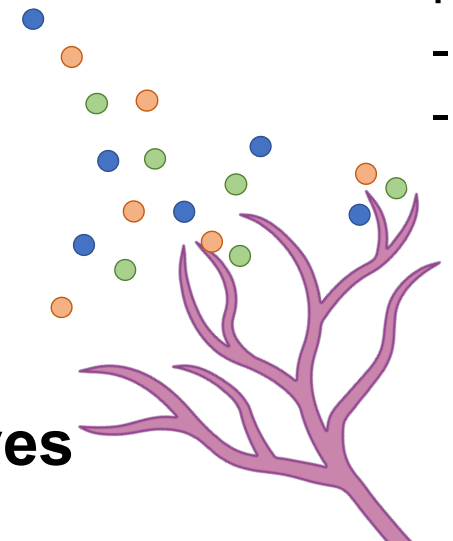
Alarmins:
- TSLP
- IL-33

Skin inflammation



Type 2 cytokines:
- IL-4
- IL-5
- IL-13
- IL-31

Pruritogens:
- Histamine
- Leukotrienes



Skin sensory nerves

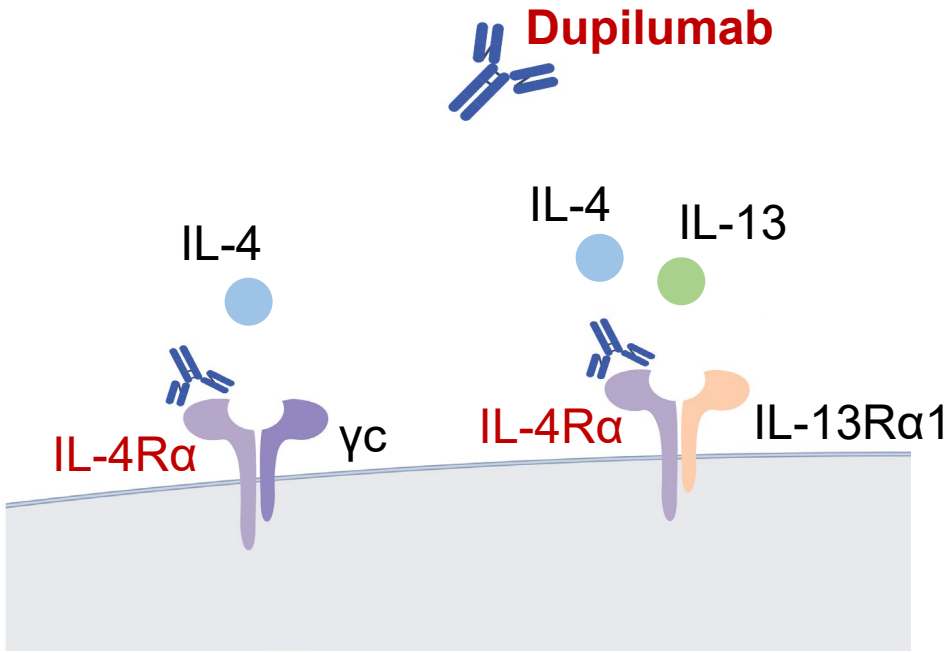
Dupilumab revolutionized treatment of atopic dermatitis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis

E.L. Simpson, T. Bieber, E. Guttman-Yassky, L.A. Beck, A. Blauvelt, M.J. Cork, J.I. Silverberg, M. Deleuran, Y. Kataoka, J.-P. Lacour, K. Kingo, M. Worm, Y. Poulin, A. Wollenberg, Y. Soo, N.M.H. Graham, G. Pirozzi, B. Akinlade, H. Staudinger, V. Mastey, L. Eckert, A. Gadkari, N. Stahl, G.D. Yancopoulos, and M. Ardeleanu, for the SOLO 1 and SOLO 2 Investigators*



Type 2 cytokines:

- **IL-4**
- IL-5
- **IL-13**
- IL-31

Simpson et al. NEJM 2016

Therapeutic landscape for AD in 2025

FDA-approved drugs for AD

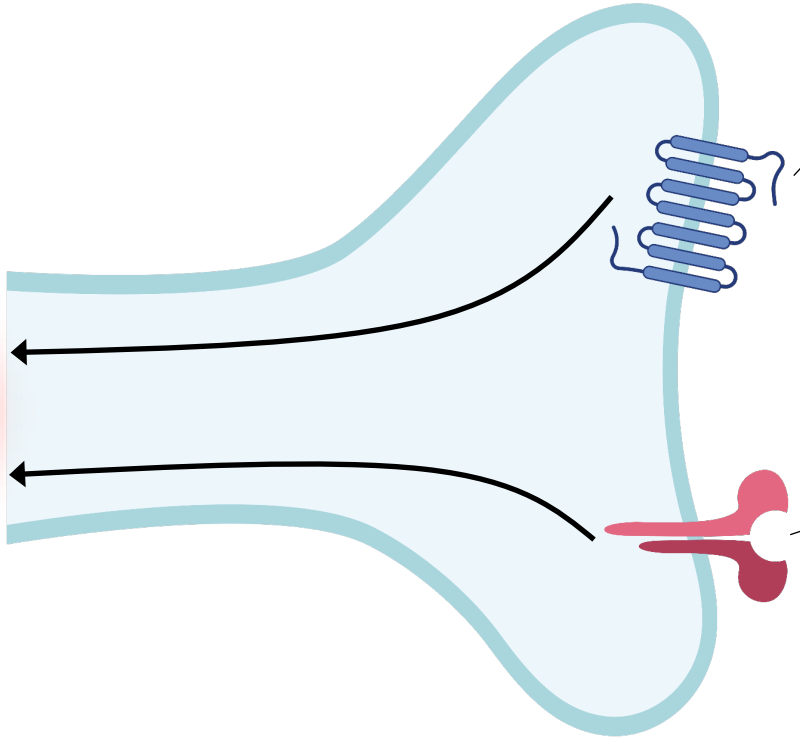
- Tacrolimus - 2000
- Pimecrolimus - 2001
- Desonide - 2006
- Crisaborole - 2016
- **Dupilumab - 2017**
- **Ruxolitinib - 2021**
- **Tralokinumab - 2021**
- **Abrocitinib - 2022**
- **Upadacitinib - 2022**
- **Lebrikizumb - 2024**
- **Nemolizumab - 2024**
- **Tapinarof - 2024**

Through the itch lens

Immune signaling pathways in sensory neurons

Skin itch sensory neuron

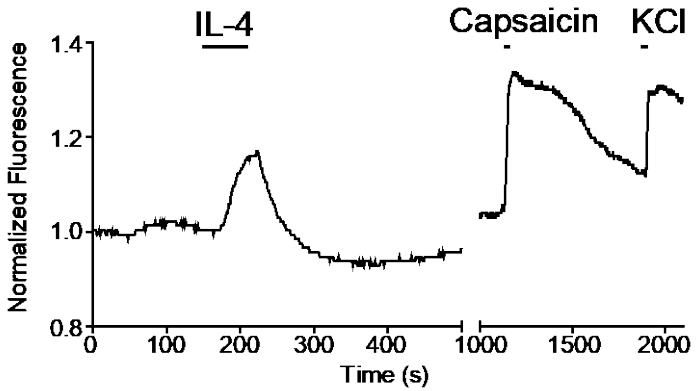
Itch

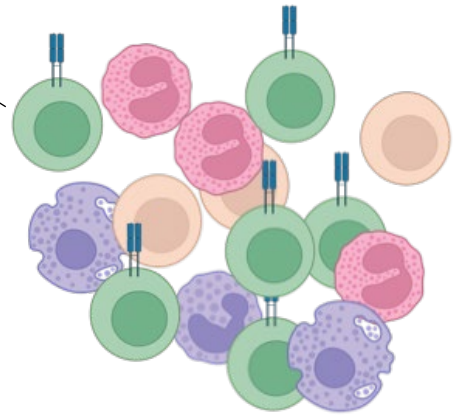


Pruritogens:
Histamine
LTC4
Neuropeptides
Tryptase

Cytokines:
IL-4/13
IL-31
IL-33
TSLP

Human sensory neurons

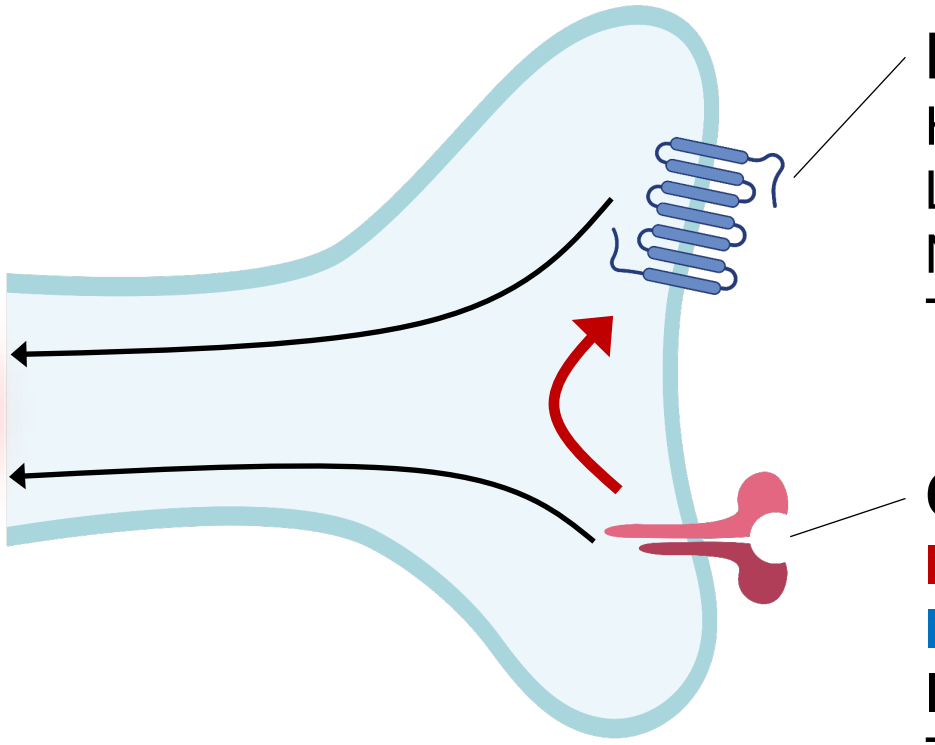




Wilson et al. *Cell* 2013
Cevikbas et al. *JACI* 2014
Oetjen et al. *Cell* 2017
Campion et al. *Exp. Derm*. 2019
Tamari and Ver Heul. *Ann Rev Immunol* 2021
Wang et al. *Cell* 2021
Miron et al. *JACI* 2022
Jung et al. *Nat Commun* 2023

Type 2 cytokines can sensitize neurons to pruritogens

Skin itch sensory neuron



Itch

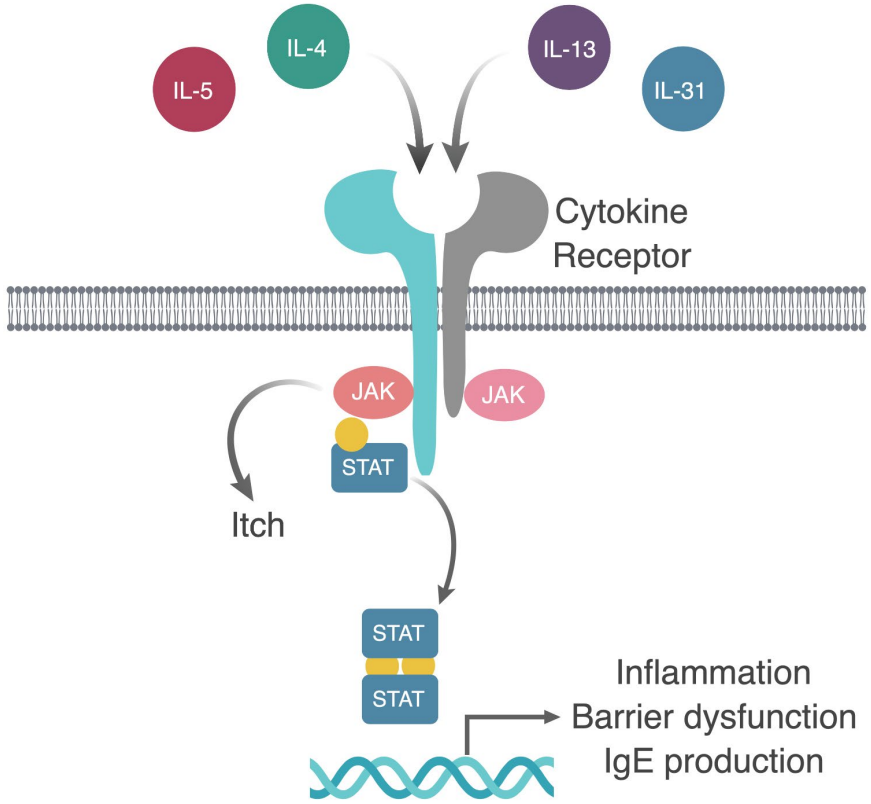
Pruritogens:
Histamine
LTC4
Neuropeptides
Tryptase

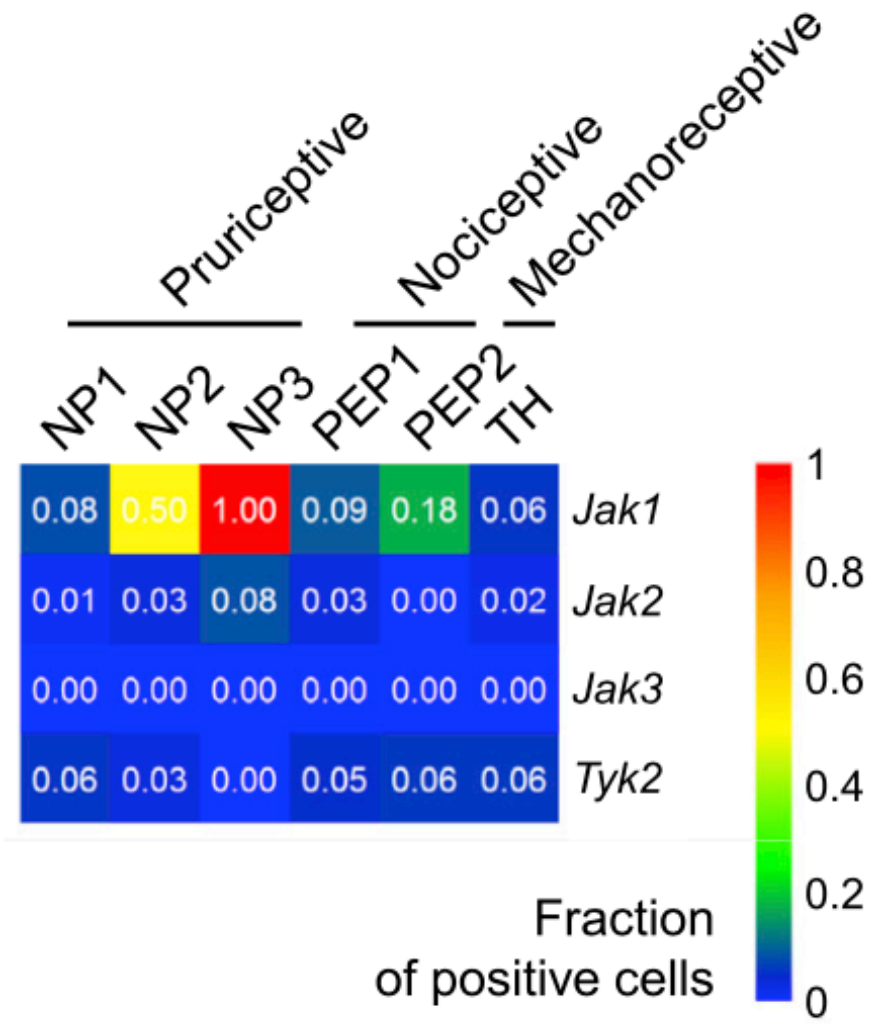
Cytokines:
IL-4/13
IL-31
IL-33
TSLP

Scratching

Wilson et al. *Cell* 2013
Cevikbas et al. *JACI* 2014
Oetjen et al. *Cell* 2017
Campion et al. *Exp. Derm*. 2019
Tamari and Ver Heul. *Ann Rev Immunol* 2021
Wang et al. *Cell* 2021
Miron et al. *JACI* 2022
Jung et al. *Nat Commun* 2023

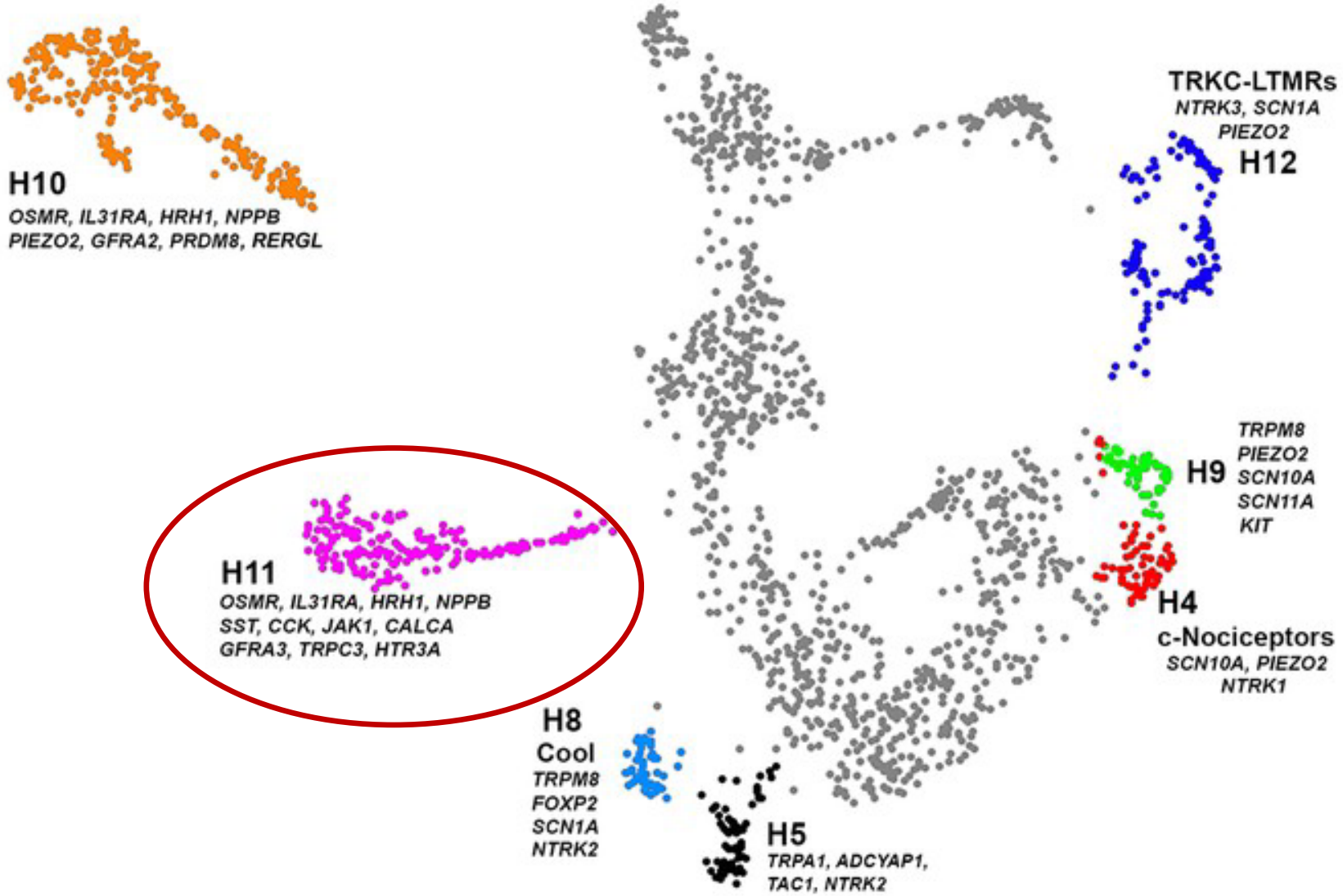
JAK1 is enriched in itch neurons in mice





Oetjen et al. Cell 2017
Usoskin et al. Nat Neurosci 2015

JAK1 is also enriched in human itch neurons

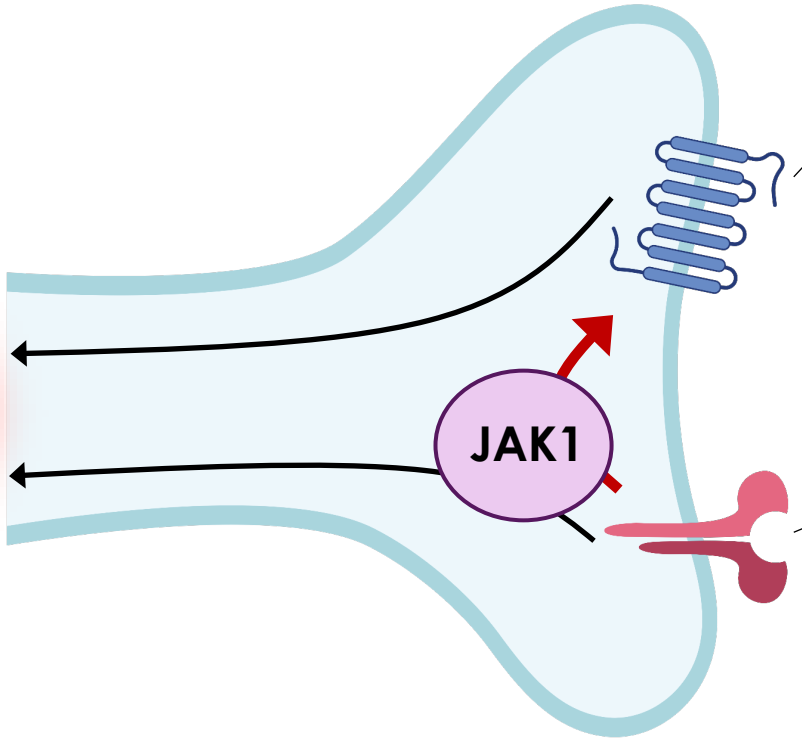


Nguyen et al. *eLife* 2021

JAK1 mediates inflammatory itch signaling in sensory neurons

Skin itch sensory neuron

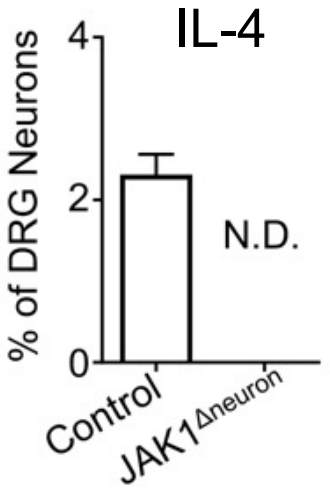
Itch



Pruritogens:
Histamine
LTC4
Neuropeptides
Tryptase

Cytokines:
IL-4/13
IL-31
IL-33
TSLP

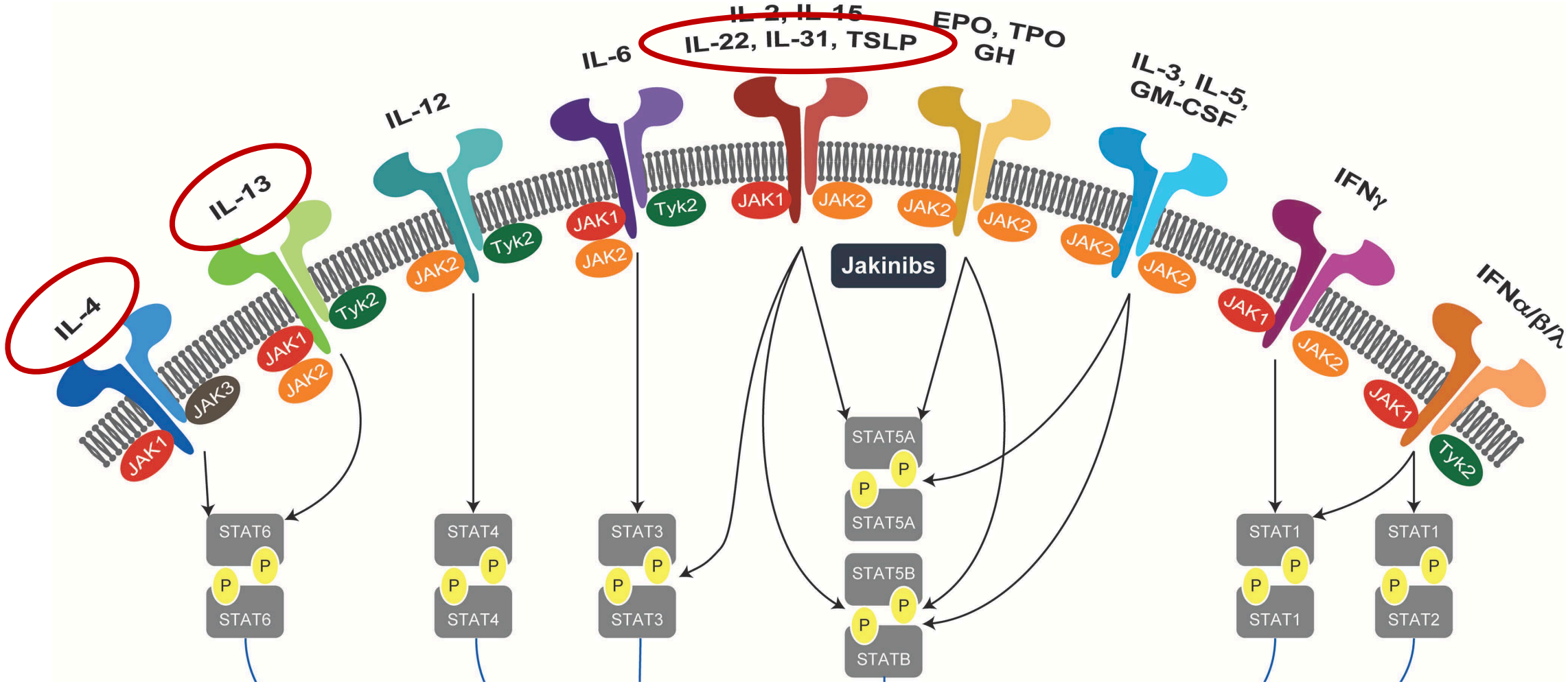
Mouse sensory neurons



Mouse scratching

Wilson et al. *Cell* 2013
Cevikbas et al. *JACI* 2014
Oetjen et al. *Cell* 2017
Campion et al. *Exp. Derm*. 2019
Tamari and Ver Heul. *Ann Rev Immunol* 2021
Wang et al. *Cell* 2021
Miron et al. *JACI* 2022
Jung et al. *Nat Commun* 2023

JAK inhibition should be broadly and rapidly anti-itch



Howell et al. *Front. Immun.* 2016

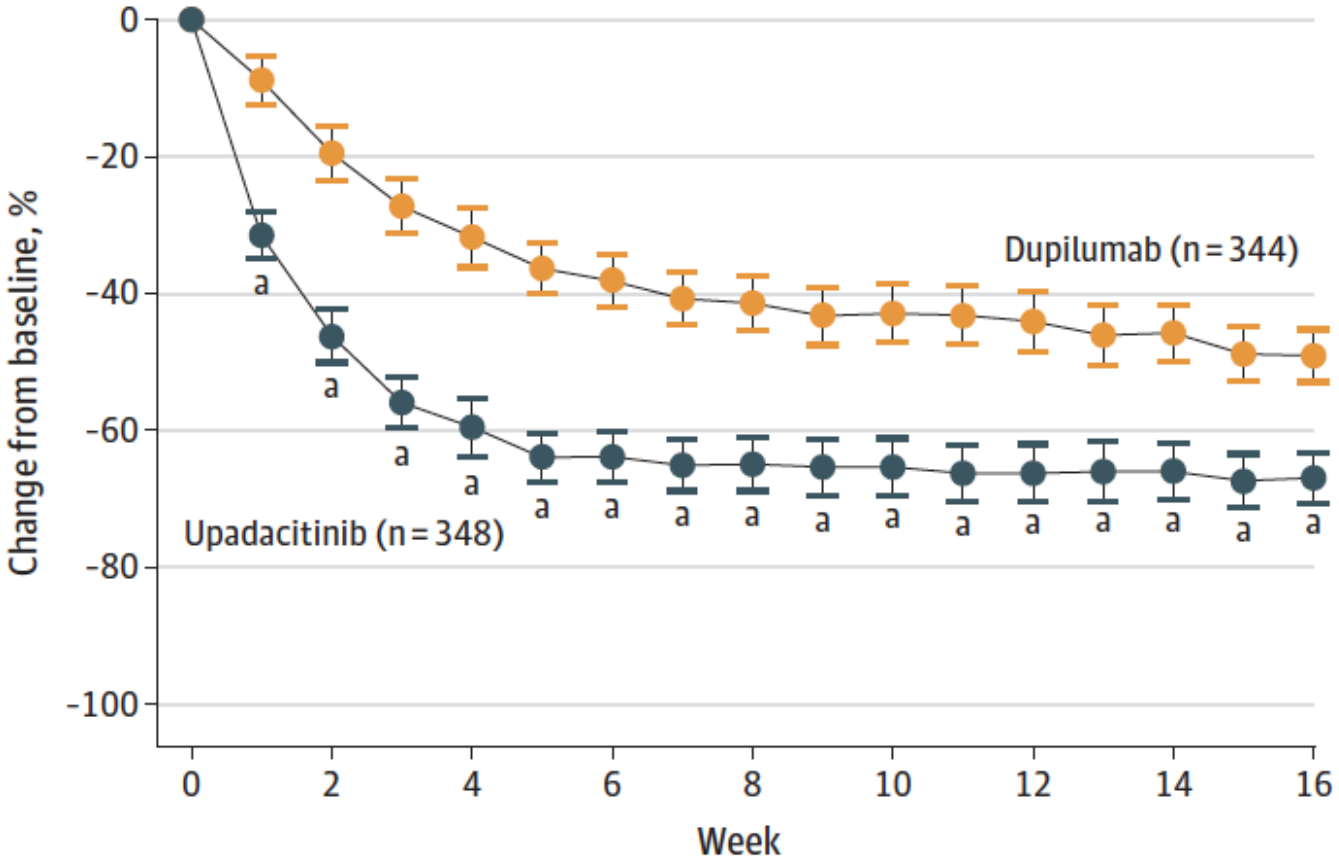
JAK1-selective inhibitors are potently anti-itch

JAMA Dermatology | Original Investigation

Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis
A Randomized Clinical Trial

Andrew Blauvelt, MD, MBA; Henrique D. Teixeira, PhD, MBA; Eric L. Simpson, MD, MCR; Antonio Costanzo, MD; Marjolein De Bruin-Weller, MD; Sebastien Barbarot, MD, PhD; Vimal H. Prajapati, MD; Peter Lio, MD; Xiaofei Hu, PhD; Tianshuang Wu, PhD; John Liu, MD, MS; Barry Ladizinski, MD, MPH, MBA; Alvina D. Chu, MD; Kilian Eyerich, MD

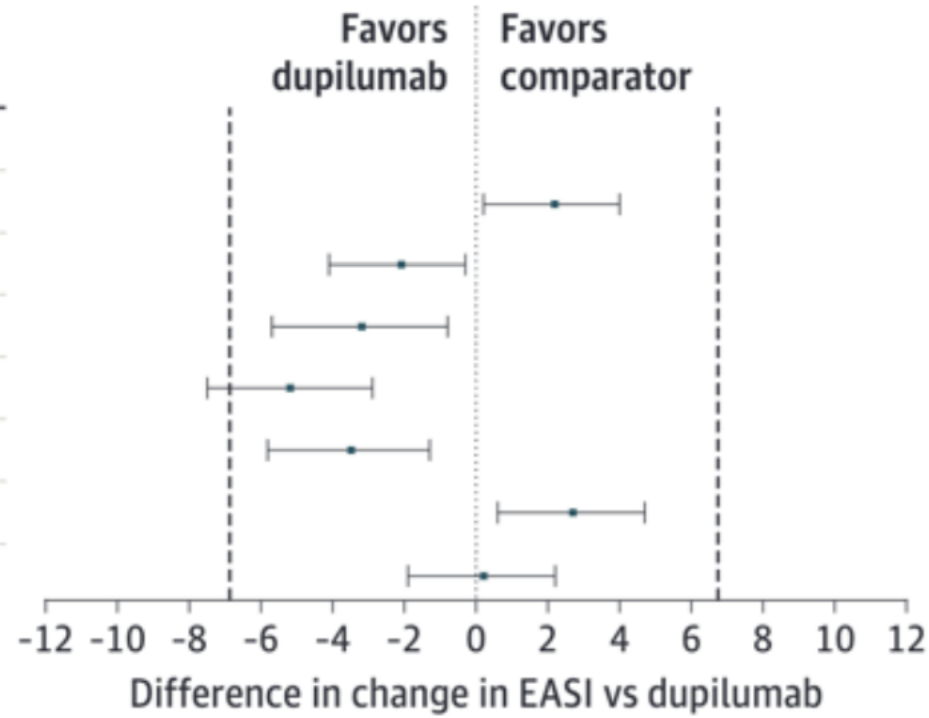
Worst pruritus NRS



JAK1-selective inhibitors in network meta-analyses

Comparison to Dupilumab for improvement in **skin inflammation - EASI**

Treatment	Point estimate (95% CI)
EASI	
Abrocitinib, 200 mg, once daily	2.2 (0.2 to 4.0)
Abrocitinib, 100 mg, once daily	-2.1 (-4.1 to -0.3)
Baricitinib, 4 mg, once daily	-3.2 (-5.7 to -0.8)
Baricitinib, 2 mg, once daily	-5.2 (-7.5 to -2.9)
Tralokinumab, 600 mg then 300 mg, every 2 wk	-3.5 (-5.8 to -1.3)
Upadacitinib, 30 mg, once daily	2.7 (0.6 to 4.7)
Upadacitinib, 15 mg, once daily	0.2 (-1.9 to 2.2)

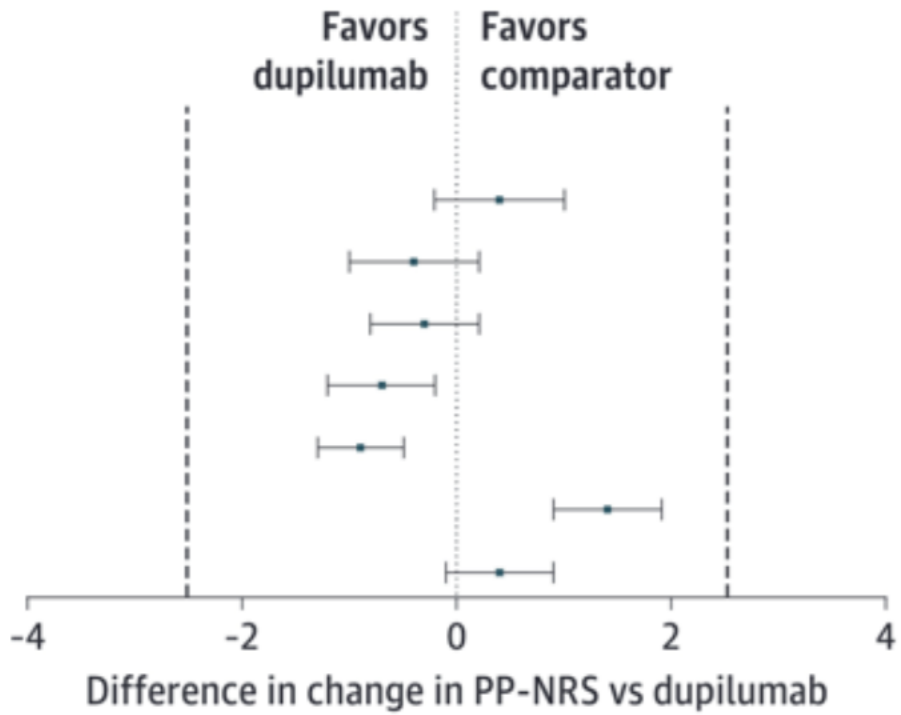


Drucker et al. *JAMA Der,* 2022

JAK1-selective inhibitors in network meta-analyses

Comparison to Dupilumab for improvement in **itch** - **Peak Pruritus NRS**

Treatment	Point estimate (95% CI)
PP-NRS	
Abrocitinib, 200 mg, once daily	0.4 (-0.2 to 1.0)
Abrocitinib, 100 mg, once daily	-0.4 (-1.0 to 0.2)
Baricitinib, 4 mg, once daily	-0.3 (-0.8 to 0.2)
Baricitinib, 2 mg, once daily	-0.7 (-1.2 to -0.2)
Tralokinumab, 600 mg then 300 mg, every 2 wk	-0.9 (-1.3 to -0.5)
Upadacitinib, 30 mg, once daily	1.4 (0.9 to 1.9)
Upadacitinib, 15 mg, once daily	0.4 (-0.1 to 0.9)

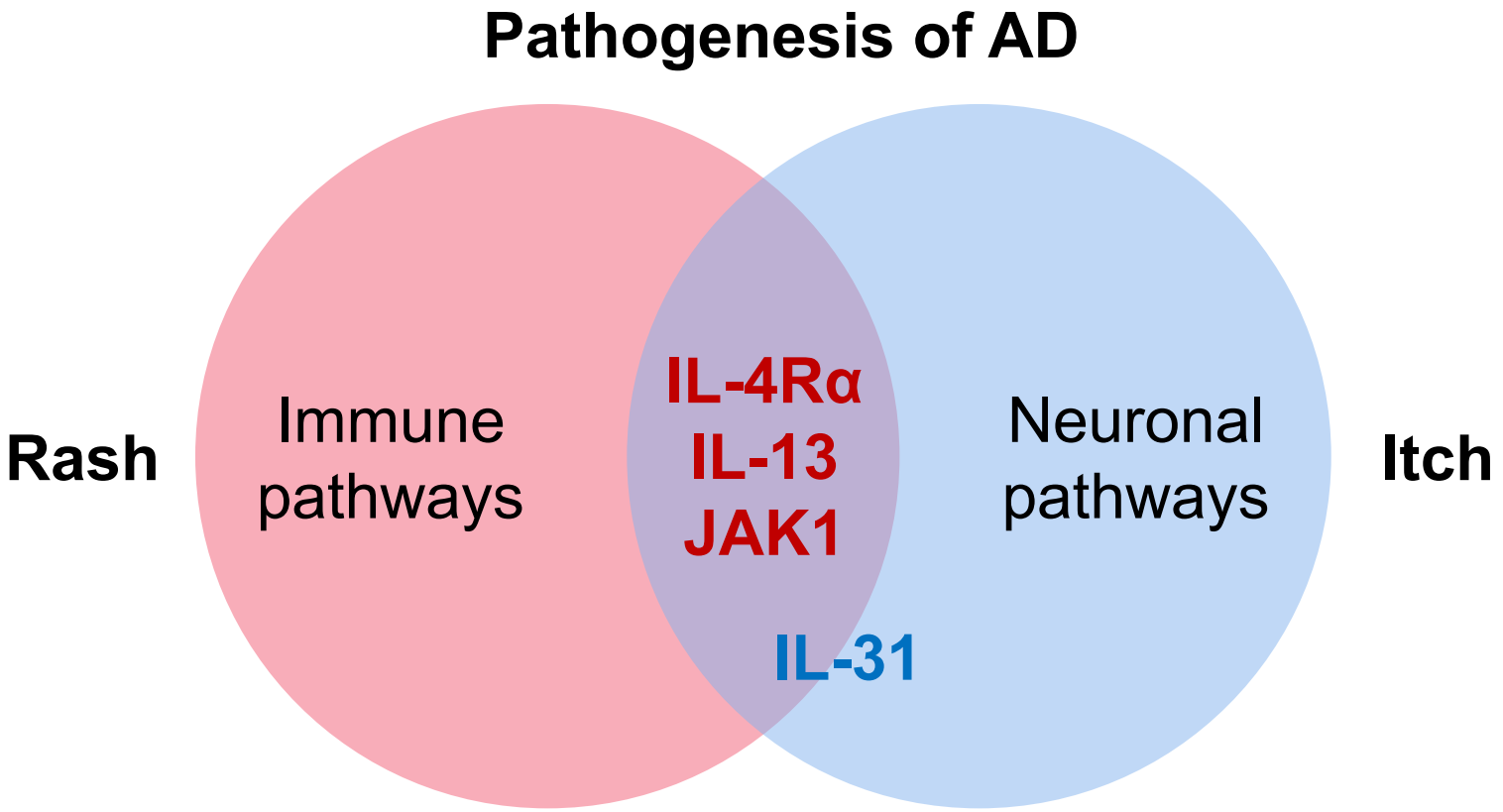


Drucker et al. *JAMA Der,* 2022

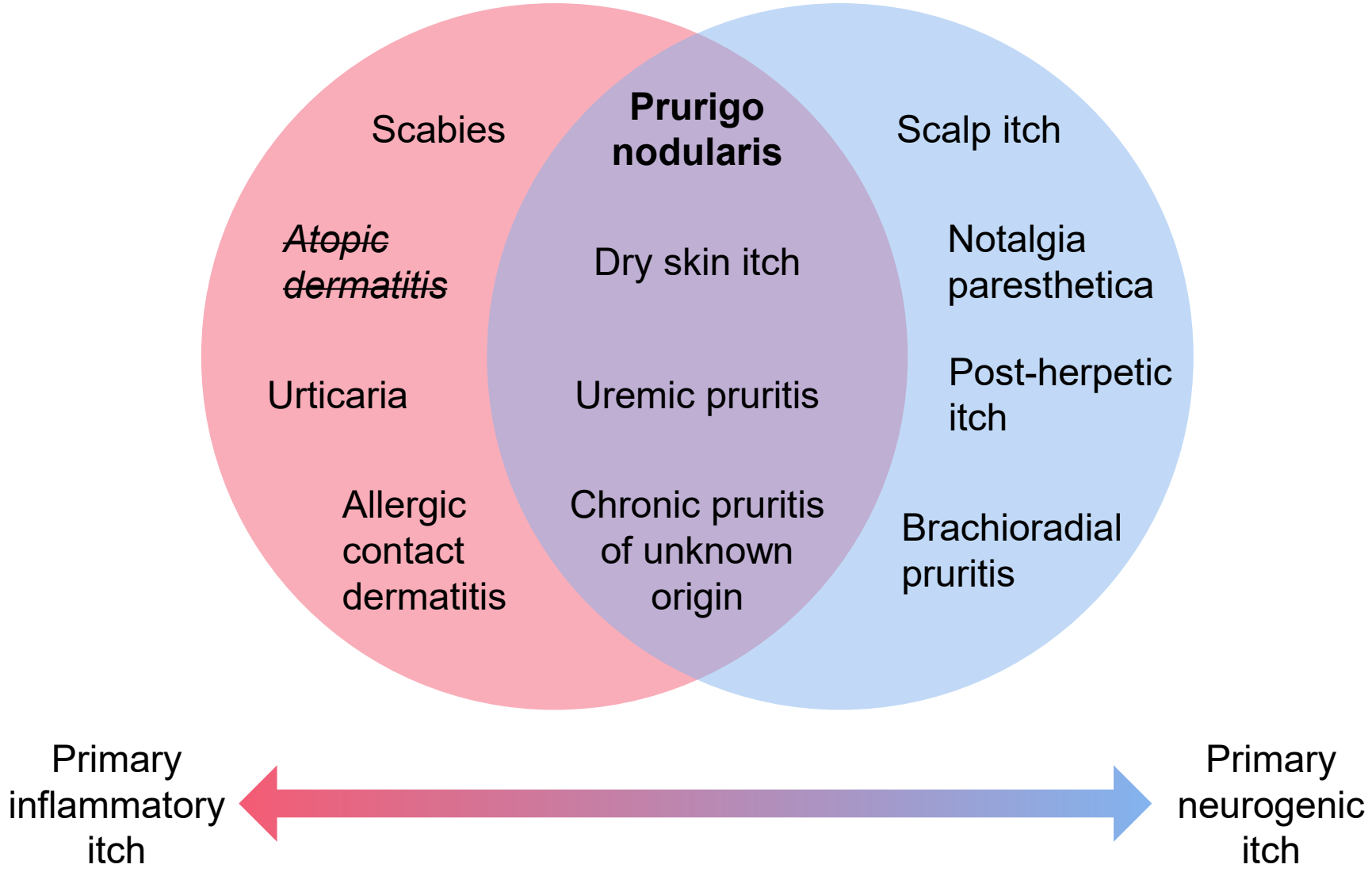
Newer drugs have dual action on inflammation and itch in AD

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**



Chronic itch conditions exist on a neuroimmune spectrum



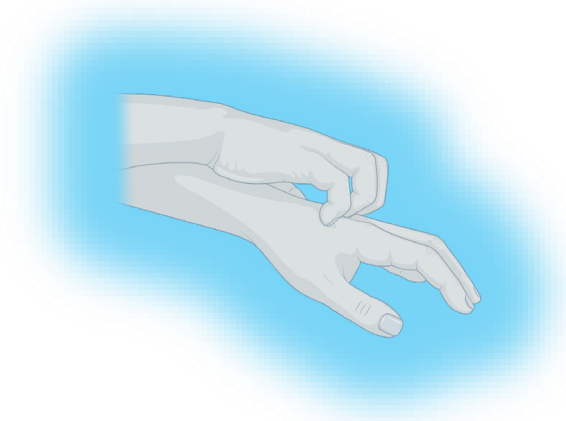
Classical view of neurogenic itch

Pruritogenic stimuli

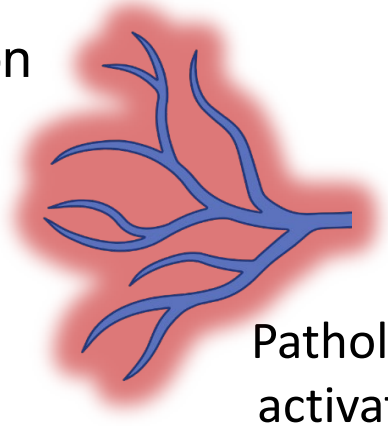
Skin sensory nerves

Physiologic activation

Acute Itch

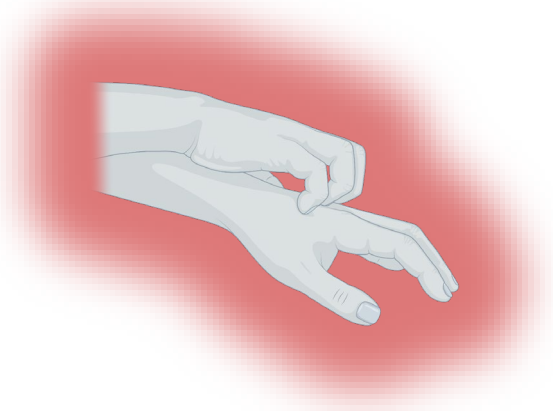


Trauma
Infection
Inflammation
??



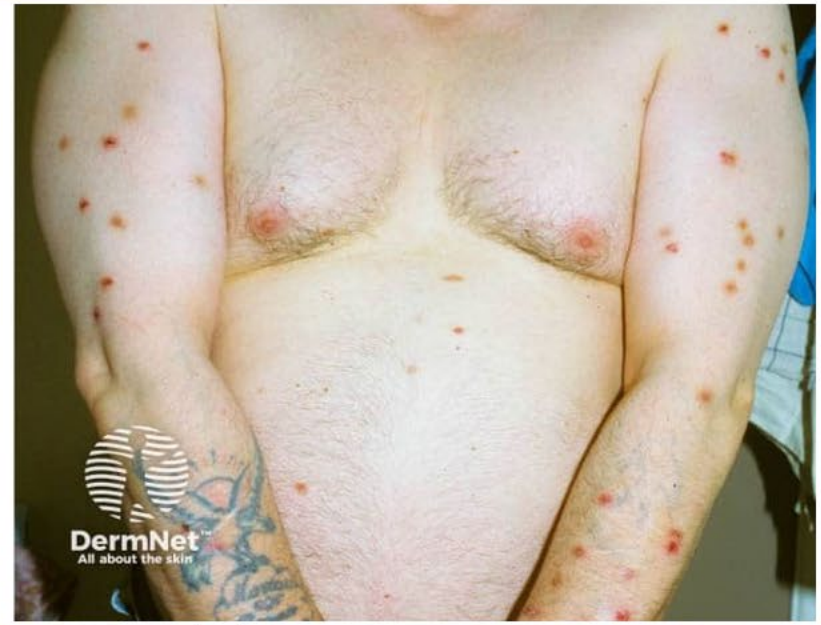
Pathologic activation

Pathologic Chronic Itch



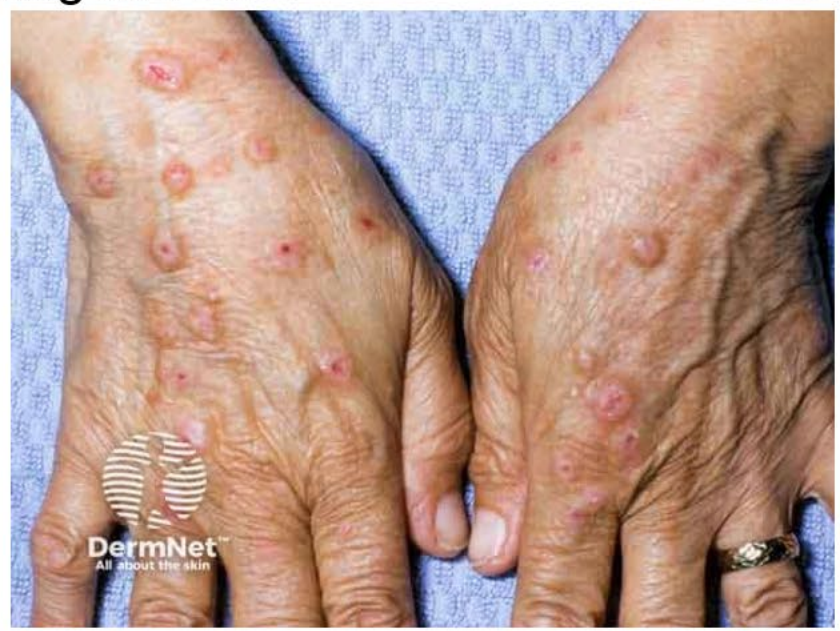
Prurigo nodularis

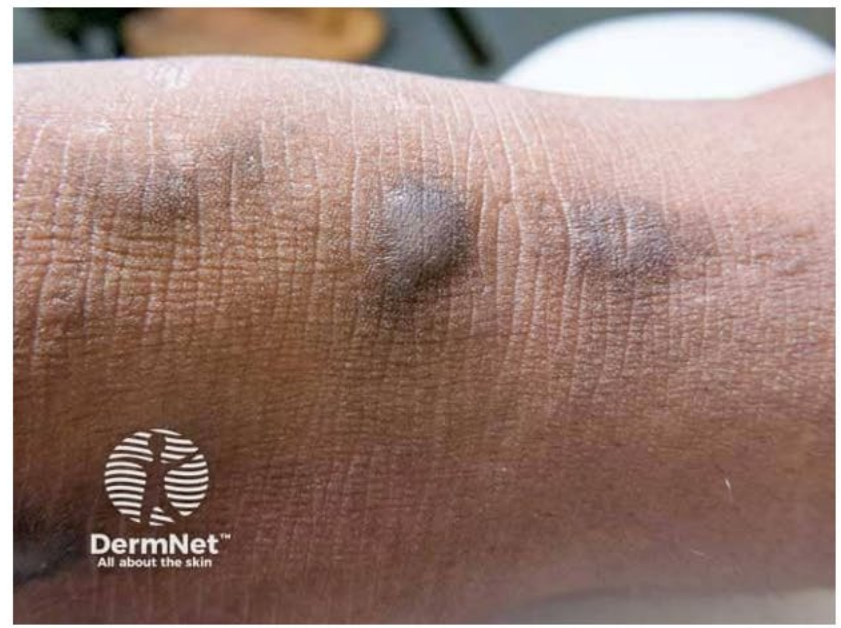
Subform of chronic prurigo, also known as chronic nodular prurigo.
Itching precedes lesions!
Neuropathic component!



On exam

- Pink-red papules, *evolve* to nodules
- Nodules typically small, but can get large
- Hyperpigmentation and scarring increase as nodules evolve
- Ulceration can be present
- Usually symmetrical
- Common in easy to reach places:
  - Arms
  - Legs
  - Chest
  - Buttocks



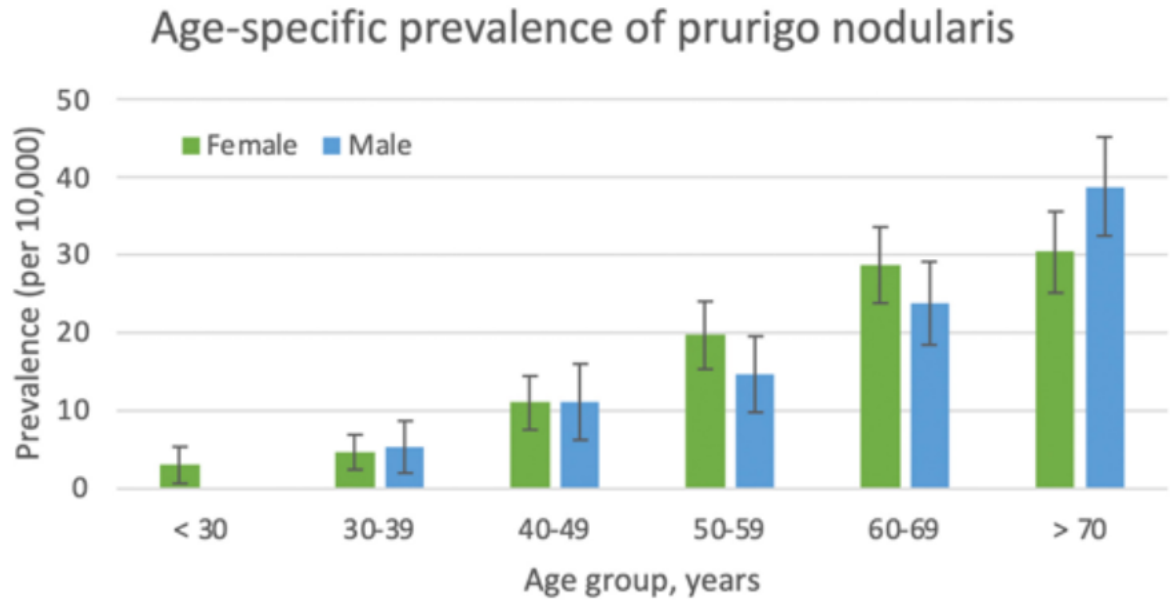


https://dermnetnz.org/

Prurigo nodularis

Demographics

- More common in older adults
- Association with atopy
- Association with systemic illness:
  - Cancer
  - HIV
  - Diabetes
  - Chronic kidney disease

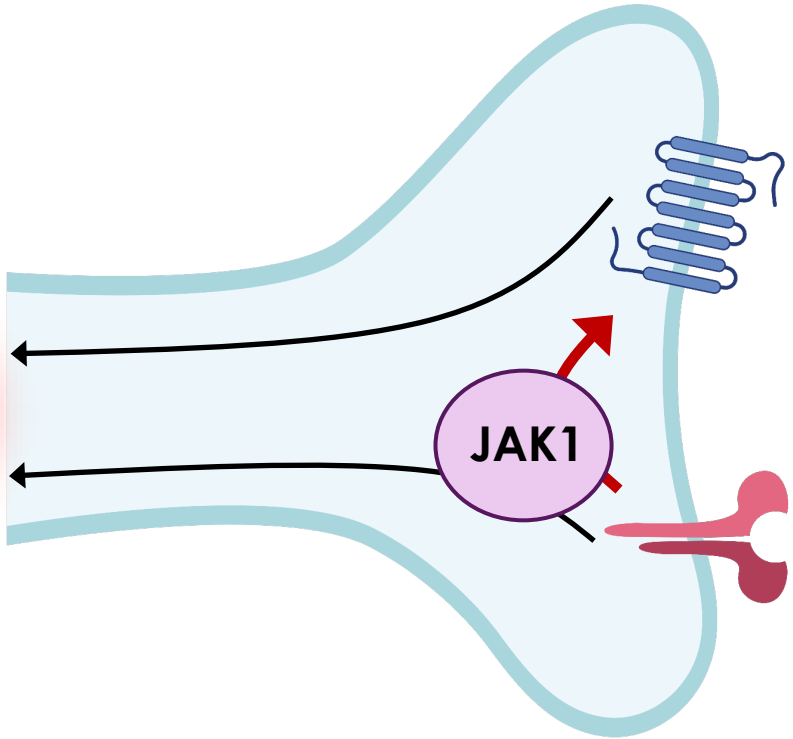


Characteristic	Participants, no. (%) Prurigo nodularis (*n* = 701)	Without prurigo nodularis (*n* = 368,281)	*P* value
Comorbidities			
Atopic dermatitis	109 (15.5)	5354 (1.5)	**<.001**
Chronic hepatitis C	45 (6.4)	5131 (1.4)	**<.001**
Chronic kidney disease	206 (29.4)	21,171 (5.7)	**<.001**
Congestive heart failure	142 (20.3)	12,387 (3.4)	**<.001**
COPD	163 (23.3)	19,117 (5.2)	**<.001**
Depression	381 (54.4)	66,459 (18.0)	**<.001**
HIV	52 (7.4)	4573 (1.2)	**<.001**
Type 2 diabetes mellitus	303 (43.2)	44,472 (12.1)	**<.001**

Joel, M. Z., et al. J Am. Acad. Dermatol. 2023

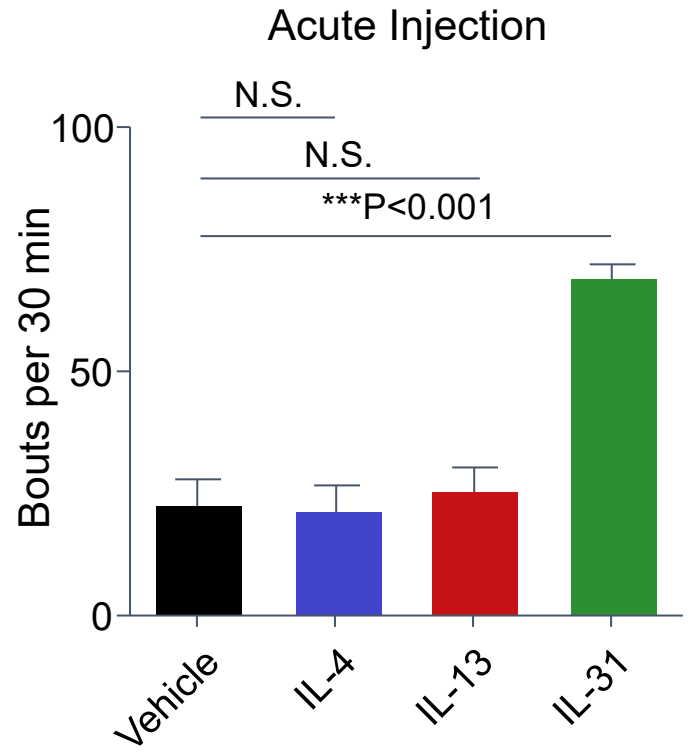
IL-31 is a key mediator of itch in PN

Skin itch sensory neuron



Itch

Cytokines:
IL-4/13
IL-31
IL-33
TSLP



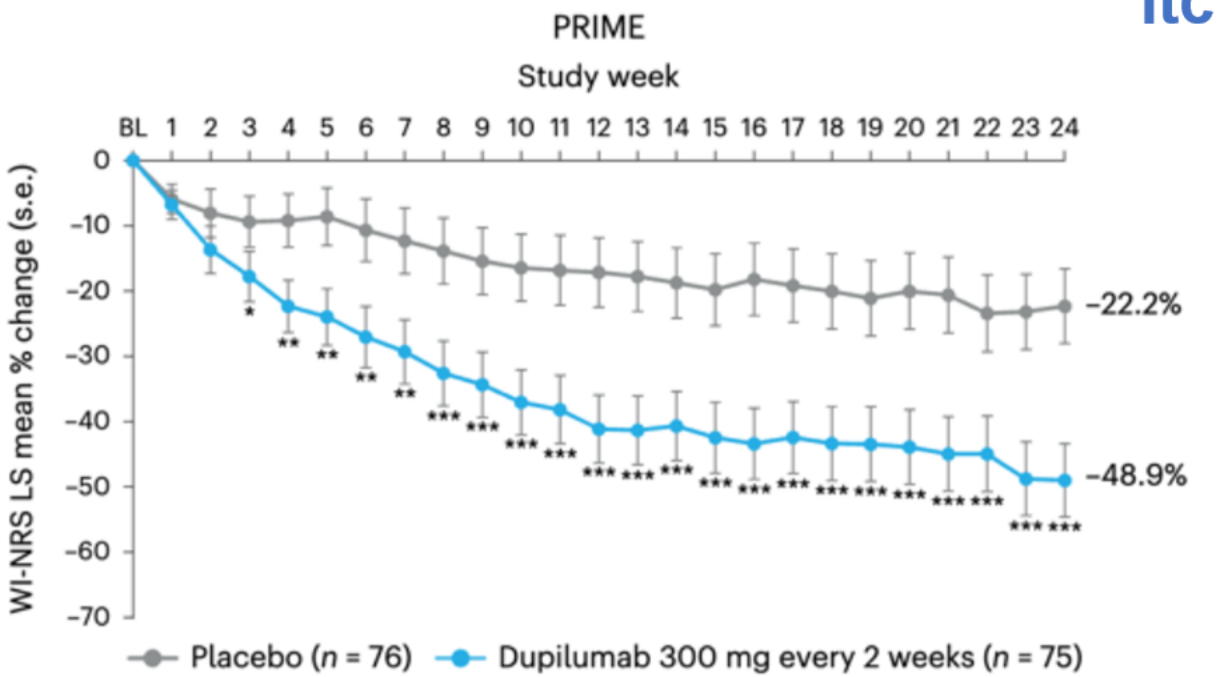
Wilson et al. *Cell* 2013
Cevikbas et al. *JACI* 2014
Oetjen et al. *Cell* 2017
Campion et al. *Exp. Derm*. 2019
Tamari and Ver Heul. *Ann Rev Immunol* 2021
Wang et al. *Cell* 2021
Miron et al. *JACI* 2022
Jung et al. *Nat Commun* 2023

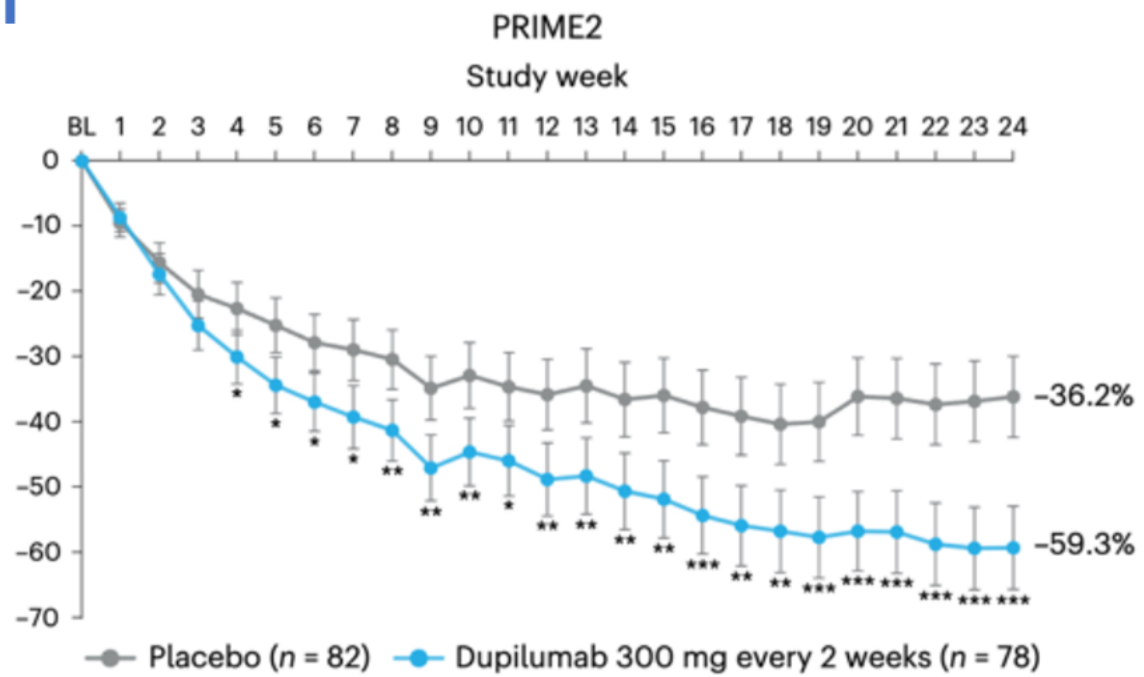
IL-31 is directly pruritogenic

Recent approvals are first drugs specifically for PN

- Dupilumab approved in 2022 based on LIBERTY-PN PRIME and PRIME2
- Nemolizumab (blocks IL-31RA) approved in 2024 based on OLYMPIA 1 and 2

itch

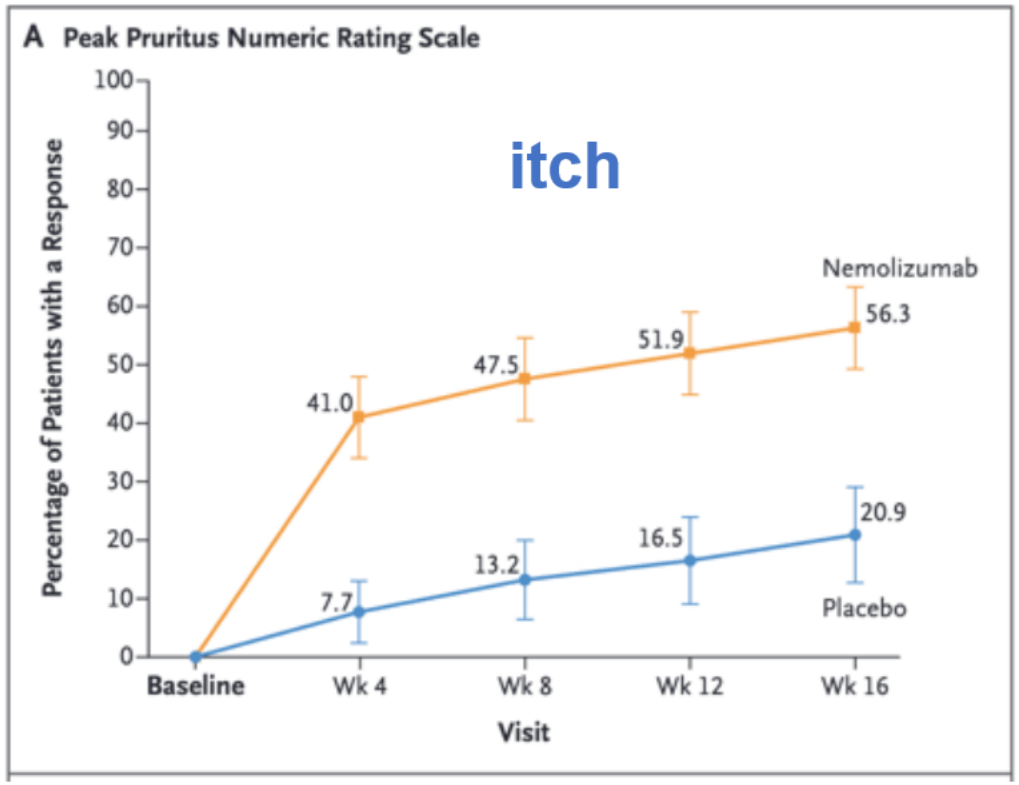


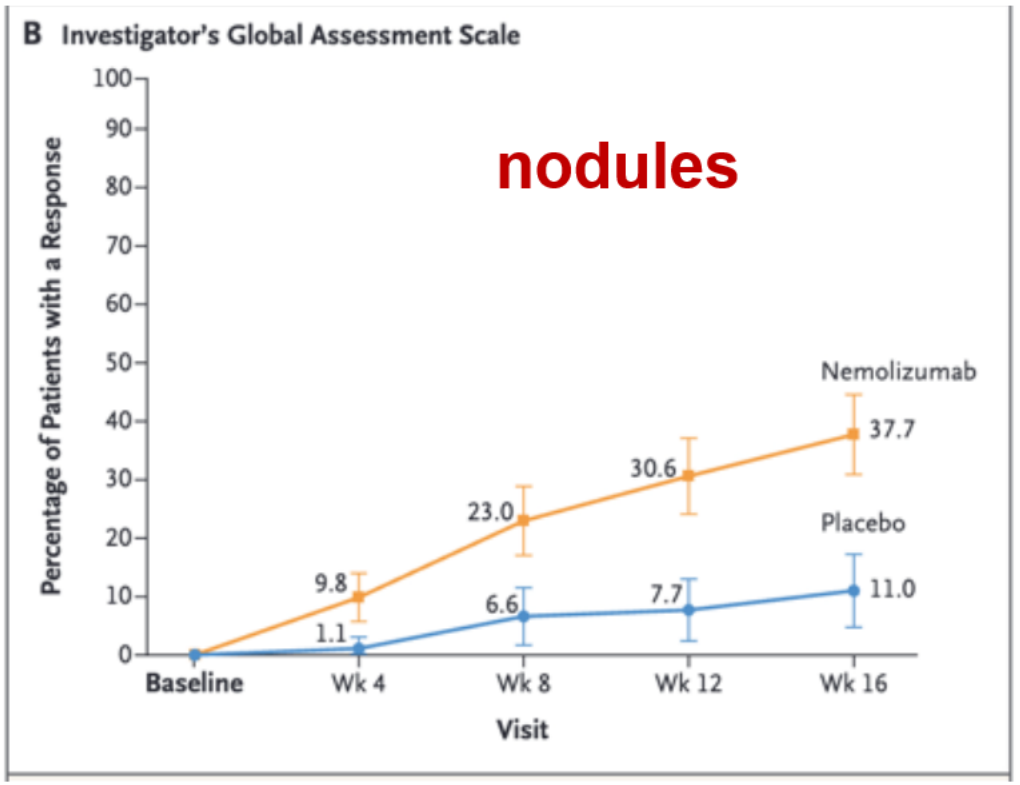


Kwatra, S. G. *et al. N. Engl. J. Med.* 2023
Yosipovitch, G. *et al. Nat Med* 2023
Ständer, S. *et al. JAMA Dermatol.* 2025

Recent approvals are first drugs specifically for PN

- Dupilumab approved in 2022 based on LIBERTY-PN PRIME and PRIME2
- Nemolizumab (blocks IL-31RA) approved in 2024 based on OLYMPIA 1 and 2

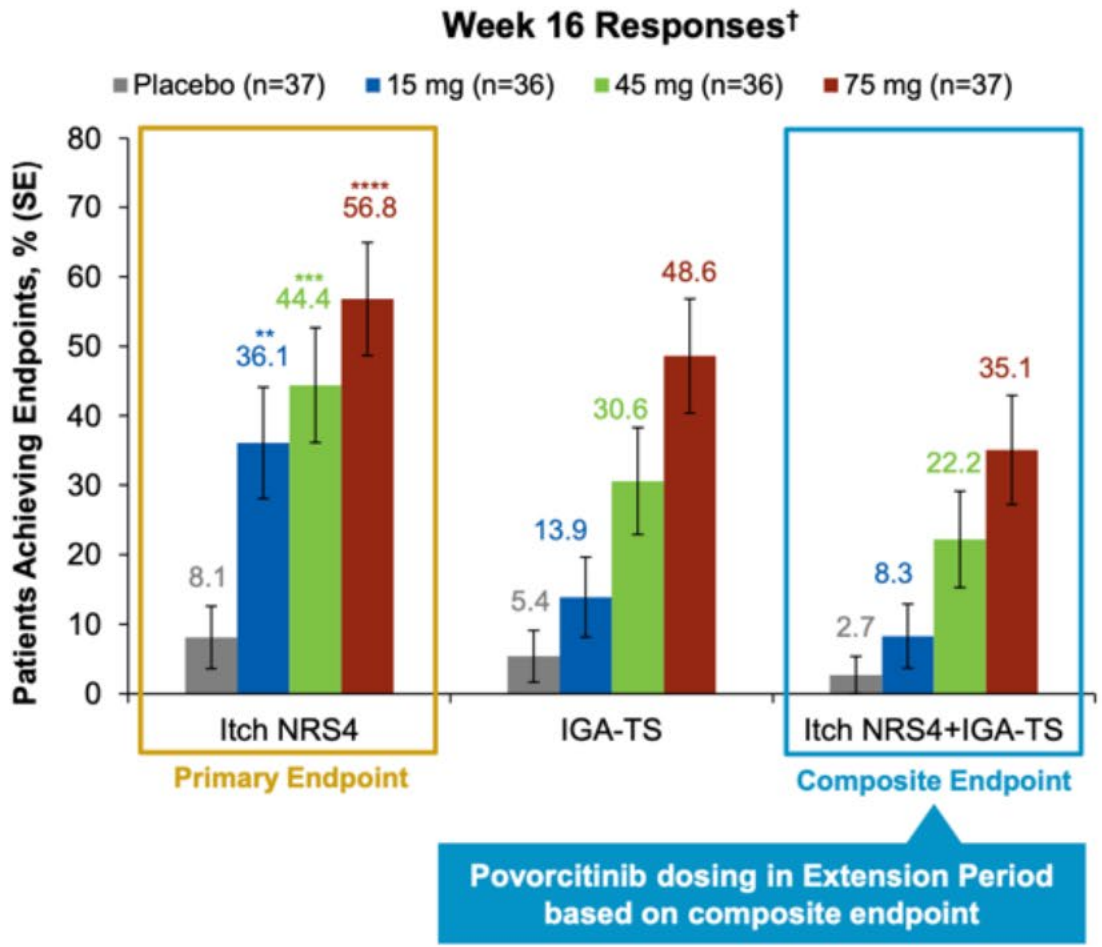


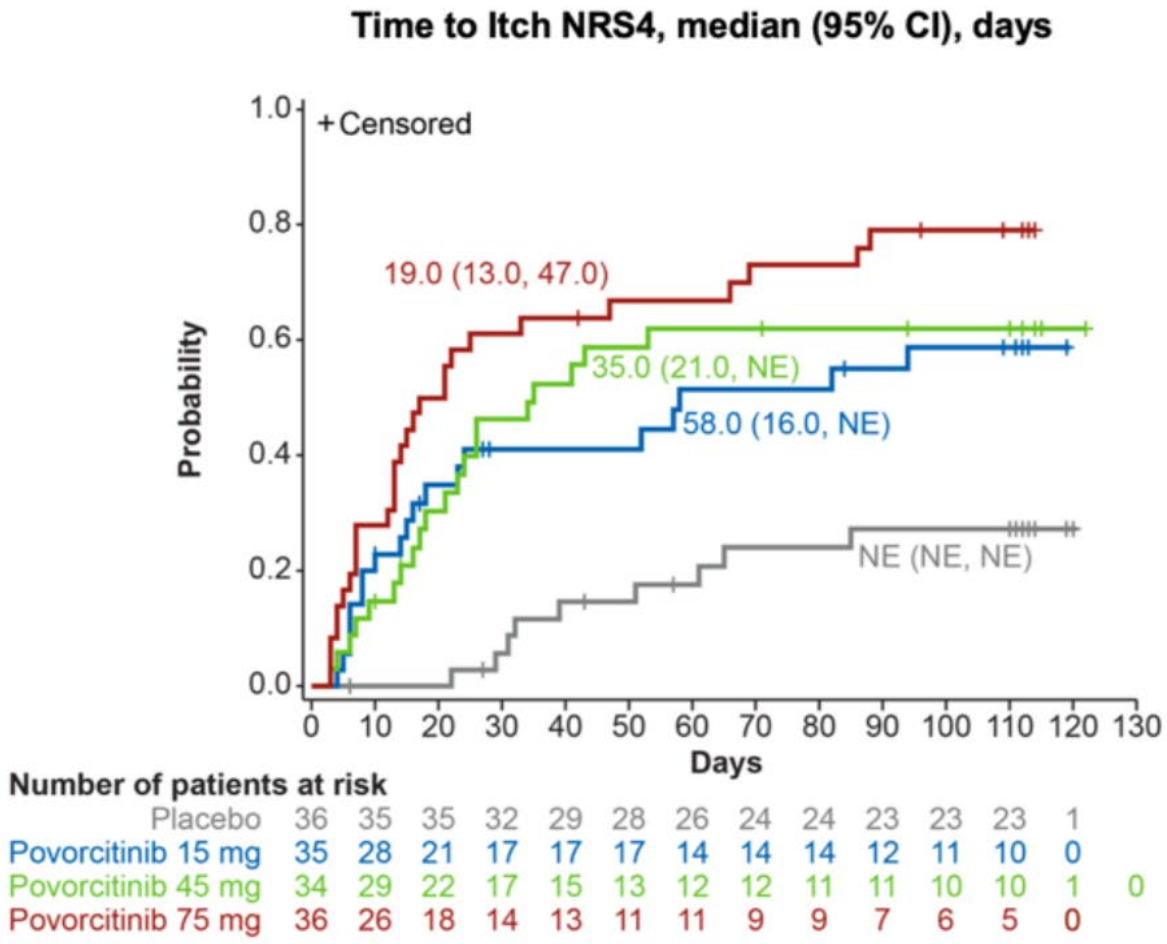


Kwatra, S. G. *et al. N. Engl. J. Med.* 2023
Yosipovitch, G. *et al. Nat Med* 2023
Ständer, S. *et al. JAMA Dermatol.* 2025

JAK inhibitors in PN

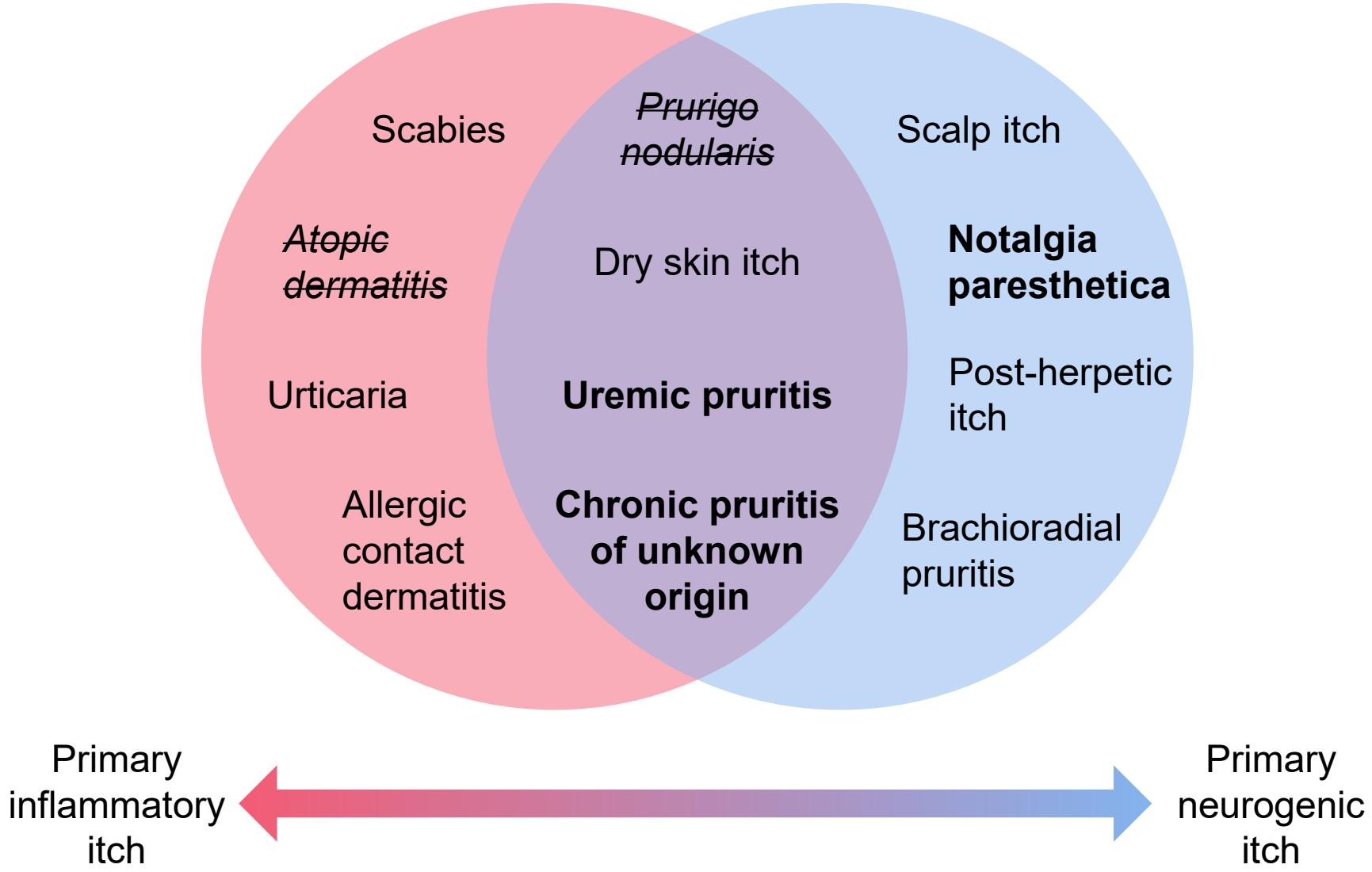
- JAK1 selective povorcitinib phase 2 data in PN





Kwatra S. EADV presentation. 2024

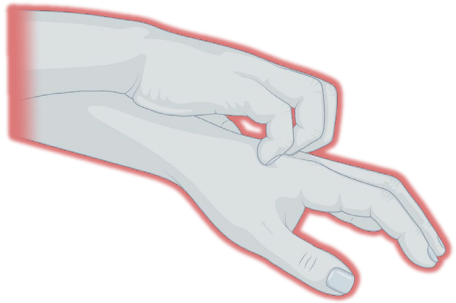
Chronic itch conditions exist on a neuroimmune spectrum



Classical treatment of neurogenic itch

Skin sensory nerves

Pathologic Chronic Itch



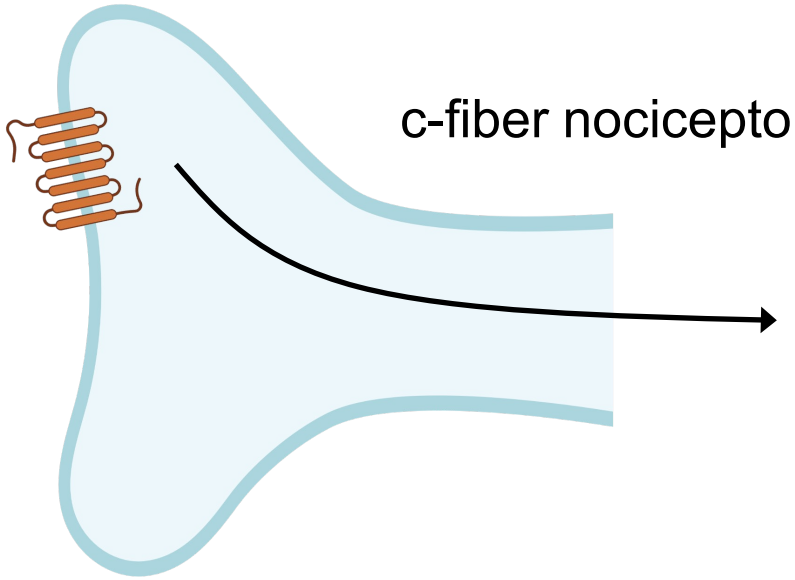
Off-label use:

- Topical capsaicin, menthol, lidocaine, TCAs
- Gabapentinoids
- Botox, paravertebral nerve block
- Systemic TCAs
- Opioids**

Where's the scalpel?

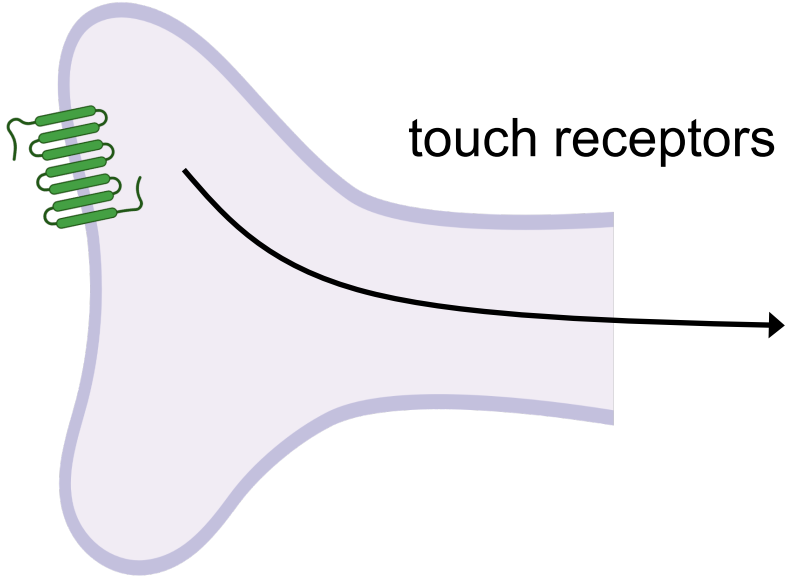
The peripheral opioid system in itch sensation

mu opioid receptor (MOR)



Inhibit pain
Activate itch (disinhibit)

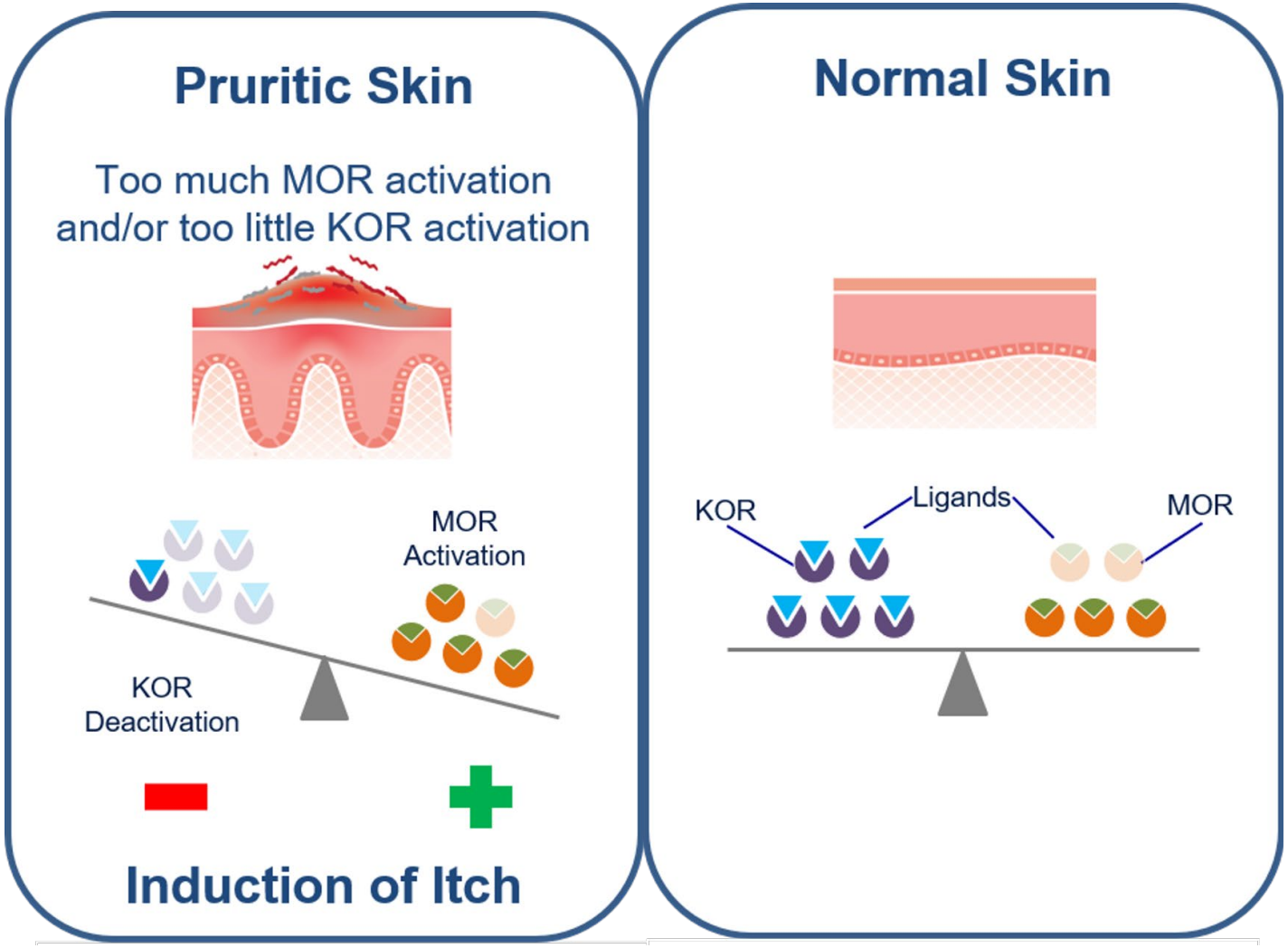
kappa opioid receptor (KOR)



Inhibit pain
Inhibit itch

Elmariah et al. *JAAD Int* 2022
Tamari et al. *JACI* 2023

Opioids in itchy skin



Drugs targeting the MOR/KOR pathways

MOR antagonist

Naltrexone (oral)

Mixed MOR antagonist/

KOR agonist

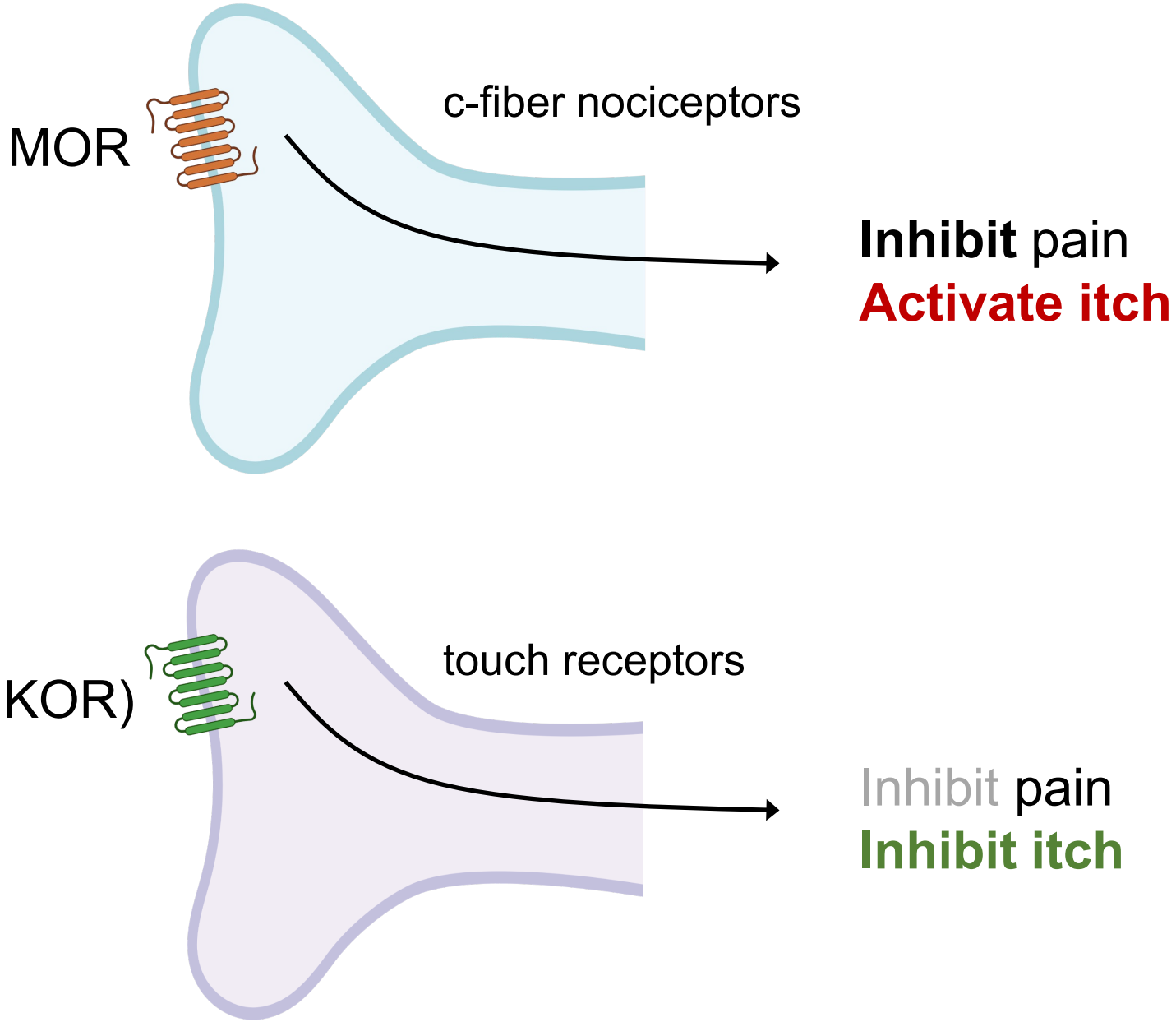
Butorphanol (intranasal)

Nalbuphine (oral)

KOR agonist

Nalfurafine

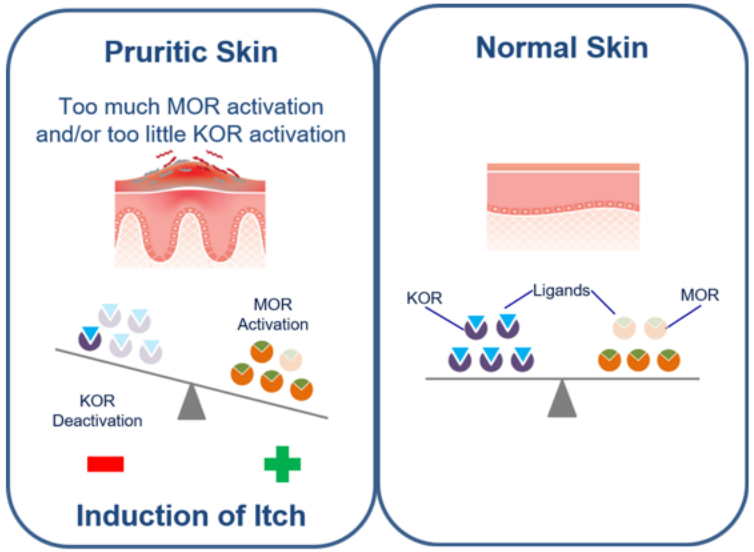
Difelikefalin (DFK)

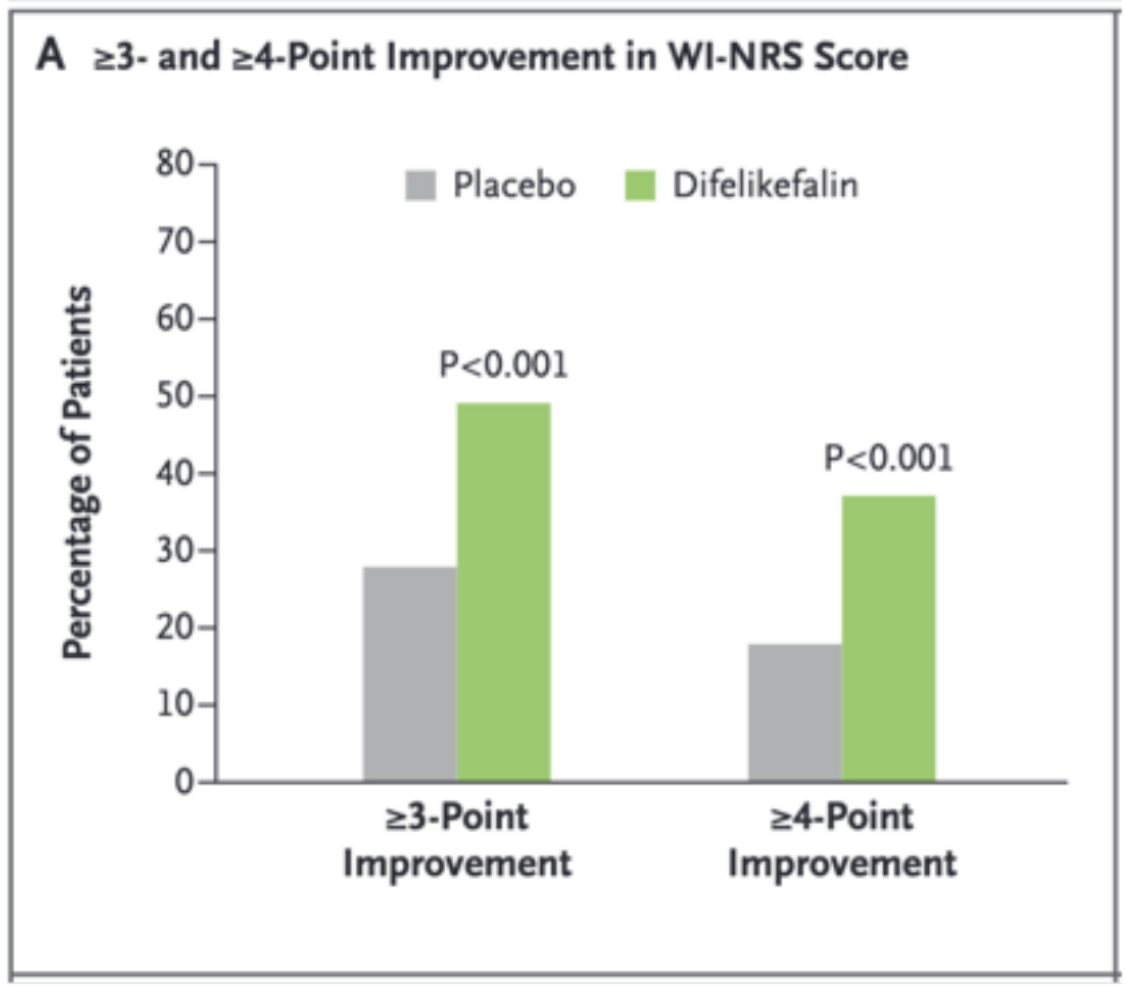


Activating KOR in uremic pruritus with DFK

- DFK first drug FDA-approved for pruritus in chronic kidney disease (IV formulation)
  - Nalfurafine approved in Japan for uremic pruritus

- One theory on why renal failure leads to itch is that buildup of endogenous opioids tips the balance

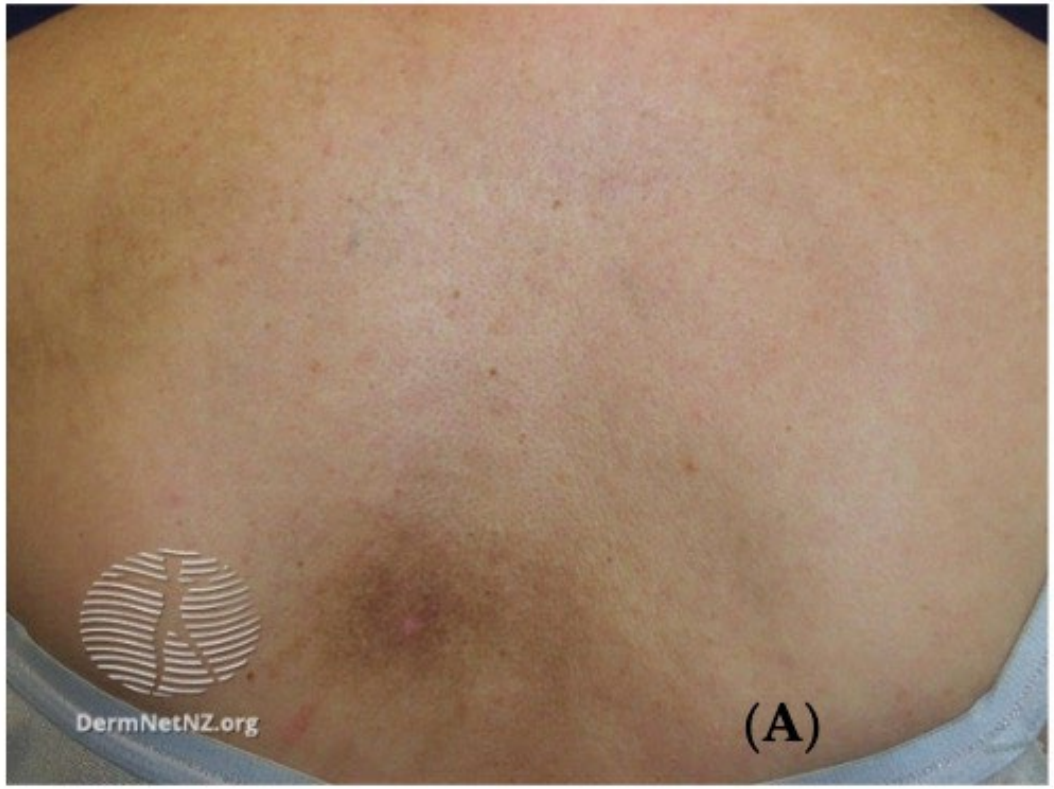




Fishbane et al. *NEJM* 2020

Notalgia paresthetica as a model neurogenic itch condition

- Chronic, cutaneous neuropathy
- Characterized by localized pruritus and associated dysesthesias
- It is typically unilateral and located medial or inferior to the scapula
- Thought to result from spinal nerve entrapment



Robinson et al. *Clin. Pr.* 2023

Oral DFK for notalgia paresthetica

- Newer oral formulation of DFK being developed
- DFK reduced itch in notalgia paresthetica

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Difelikefalin in Notalgia Paresthetica

Brian S. Kim, M.D., M.T.R., Robert Bissonnette, M.D., Kristine Nograles, M.D., Catherine Munera, Ph.D., Nilam Shah, Pharm.D., Alia Jebara, M.D., Joshua Cirulli, Pharm.D., Joana Goncalves, M.D., and Mark Lebwohl, M.D., for the KOMFORT Trial Investigators*

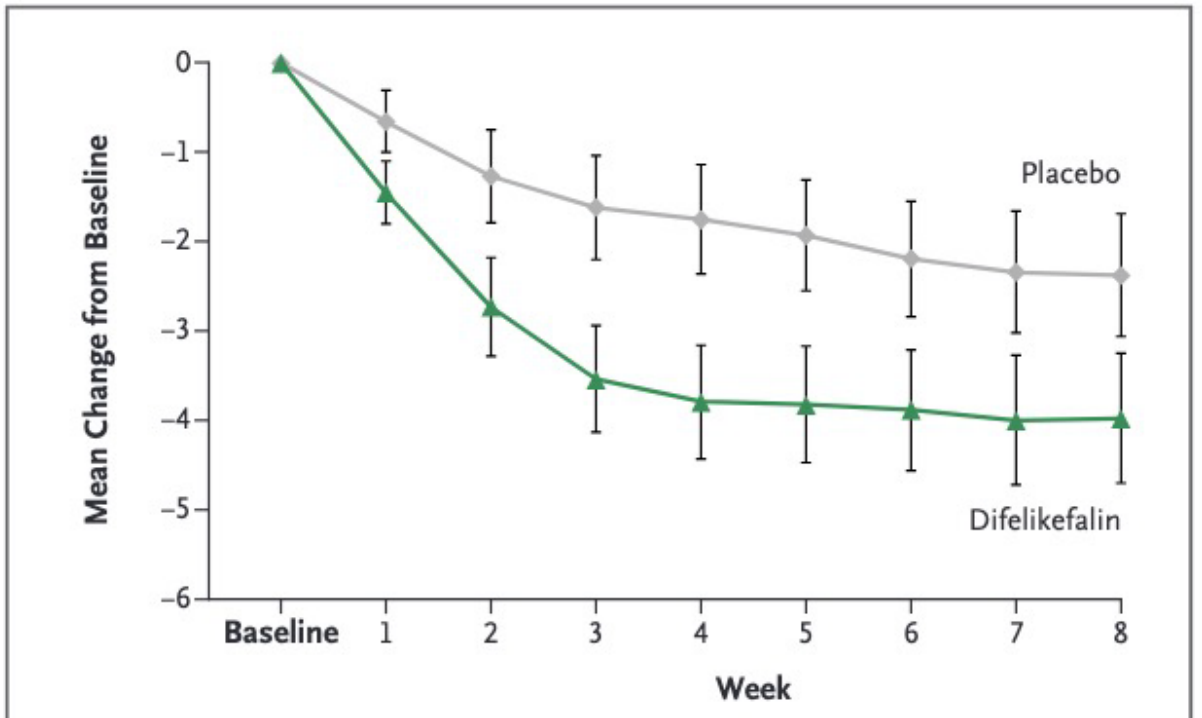


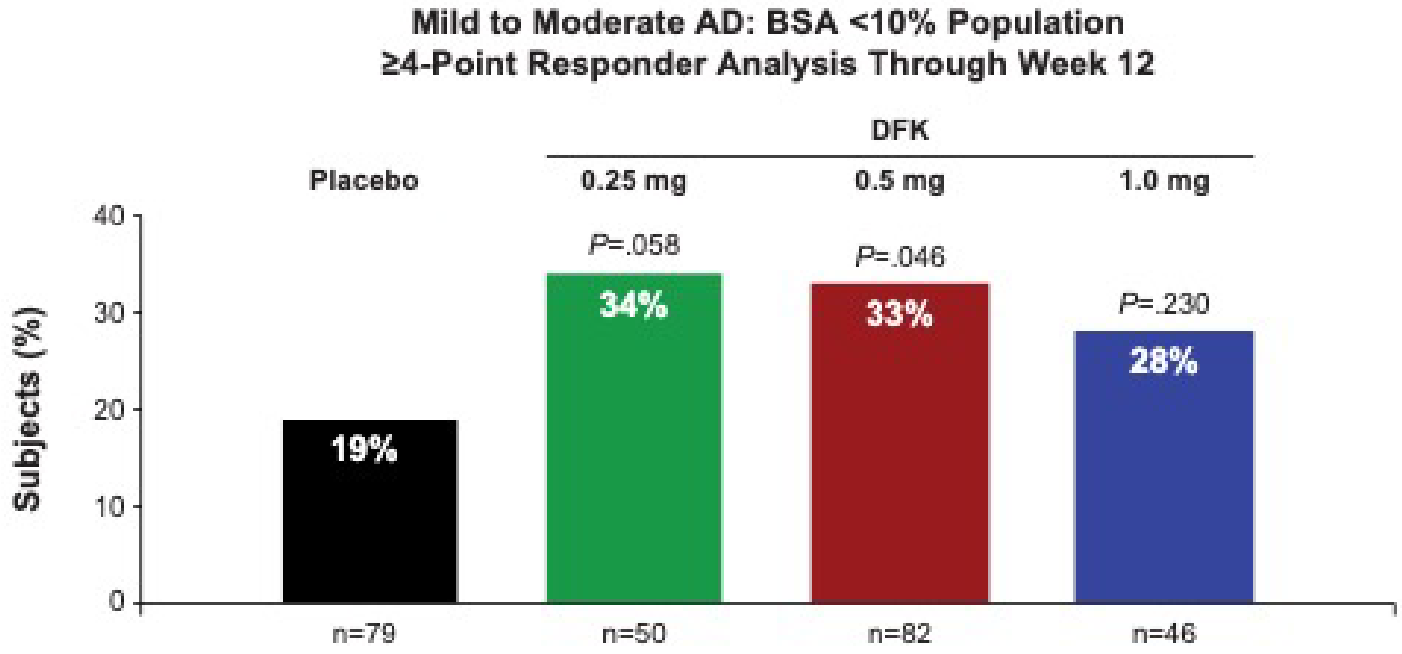
Figure 1. Mean Change in Score on the Worst Itch Numeric Rating Scale (WI-NRS).

Kim et al. *NEJM* 2023

DFK for AD – does it work in the setting of inflammation?

- Did not meet primary endpoint: no significant reduction in NRS itch at week 12

- *However*, subgroup analysis did show significant improvement:
  - mild to moderate skin inflammation
  - moderate to severe itch
  - “Itch-dominant” AD



Guttman-Yassky, et al. *JACI* 2023

Therapeutic landscape for neuropathic itch

FDA-approved

Difelikefalin (IV)

- Uremic pruritus

In clinical trials

Difelikefalin (oral)

- Notalgia paresthetica (phase 3 planned)
- AD (phase 2 completed)

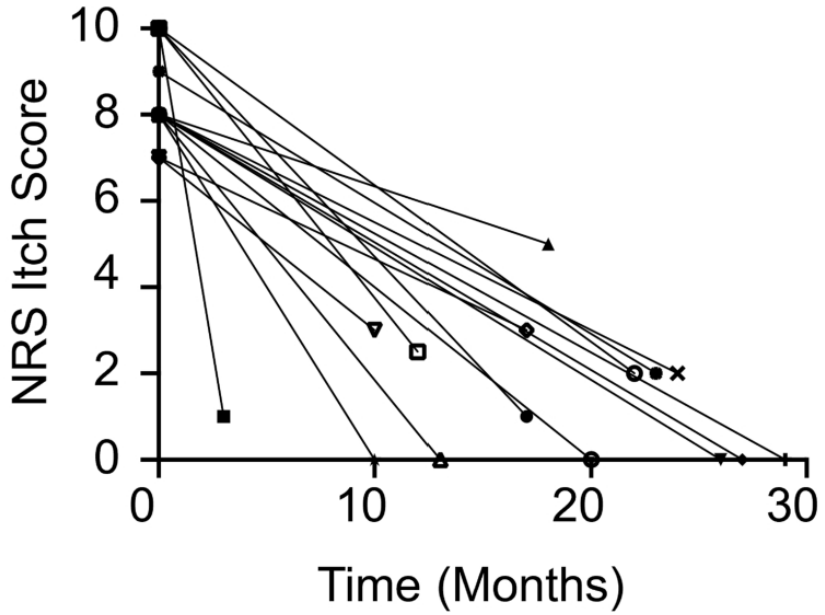
Nalfurafine (oral)

- Approved for uremic pruritus in Japan
- Uremic pruritus (phase 3 underway in US)

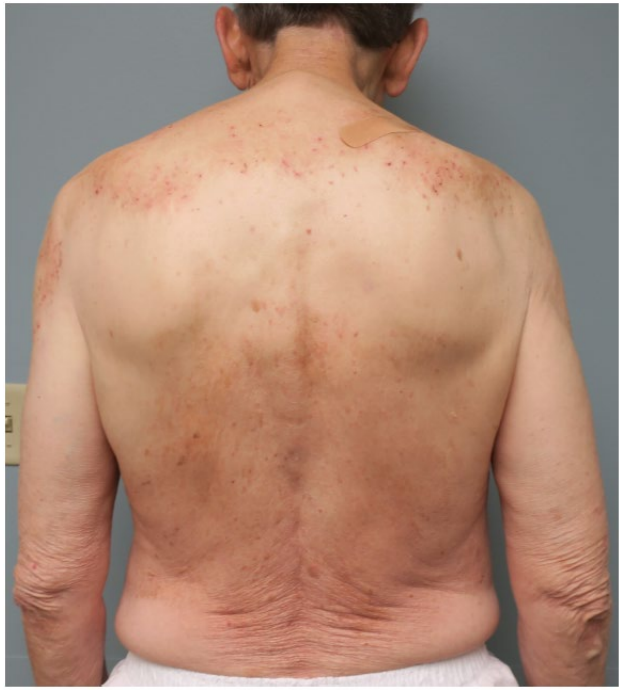
Itch in the absence of primary rash/inflammation

- Chronic pruritus of unknown origin (CPUO):
  - Itch lasting >6 weeks
  - Exclusion of all known chronic itch disorders
  - Exclusion of an etiologic agent (e.g. opioids)

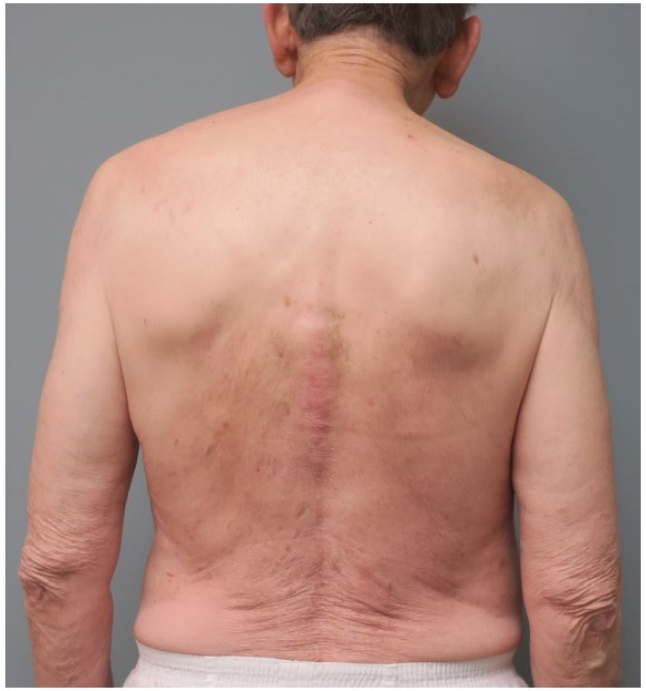
CPUO patients treated with dupilumab



Pre-treatment with dupilumab



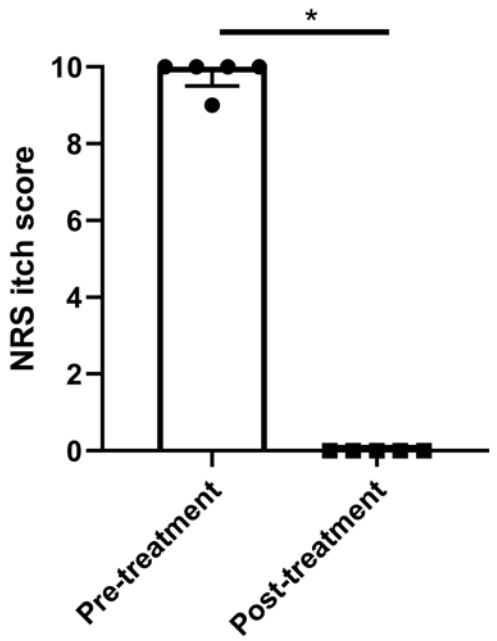
Post-treatment with dupilumab



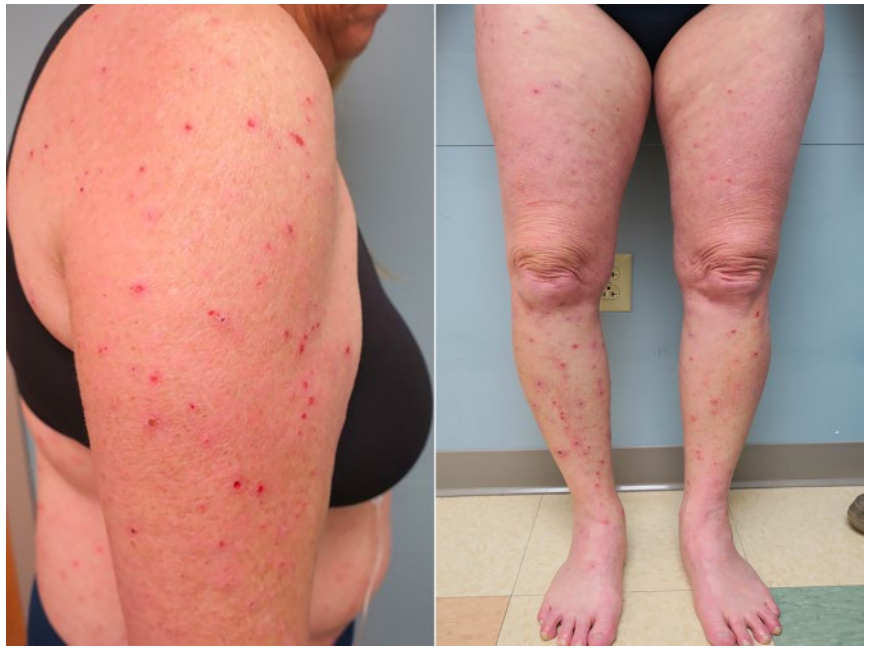
Jeon et al. *J Dermatol Treat* 2021

CPUO patients treated with tofacitinib

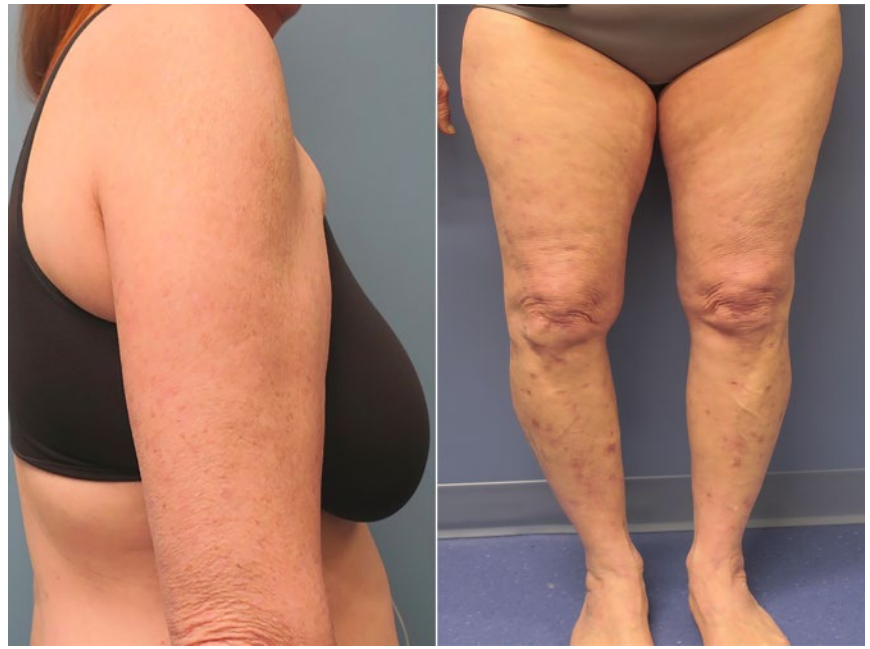
NRS Itch Score



Pre-treatment with tofacitinib



Post-treatment with tofacitinib



Wang et al. *JAMA Dermatol* 2019

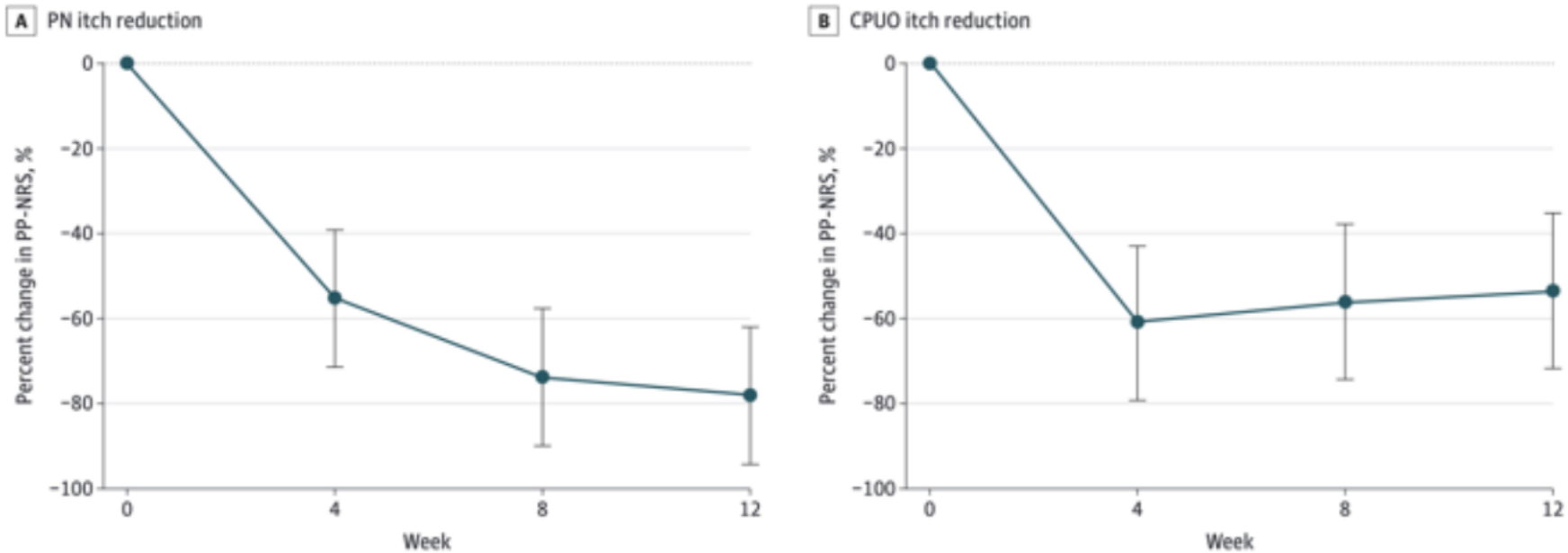
CPUO

Phase 3 clinical trial of dupilumab underway:

- Efficacy and Safety of Subcutaneous Dupilumab for the Treatment of Adult Participants With Chronic Pruritus of Unknown Origin (CPUO) (LIBERTY-CPUO-CHIC) – NCT05263206

Phase 2 clinical trial of abrocitinib completed:

- Efficacy of Abrocitinib for Reducing Pruritus in Adults With Prurigo Nodularis and Chronic Pruritus of Unknown Origin – NCT05038982



Kwatra, S. G. *et al*. *JAMA Dermatol.* 2024

New and emerging therapies for chronic itch

Scabies

Prurigo nodularis

Scalp itch

Atopic dermatitis

Dry skin itch

Notalgia paresthetica

Urticaria

Uremic pruritis

Post-herpetic itch

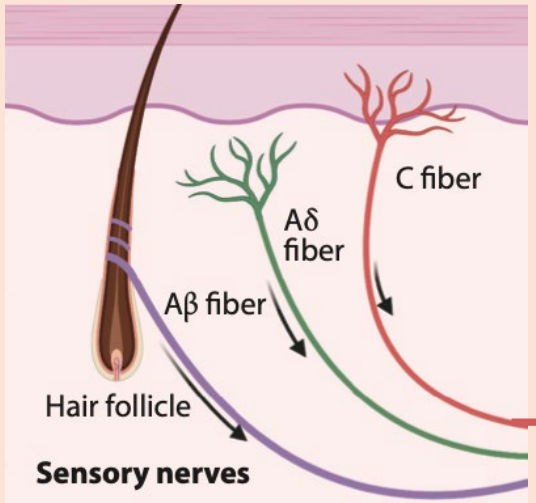
Allergic contact dermatitis

Chronic pruritis of unknown origin

Brachioradial pruritis

Focus up to now has been on local transmission from the skin

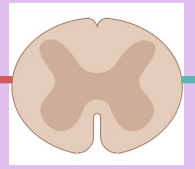
Skin
(Input)



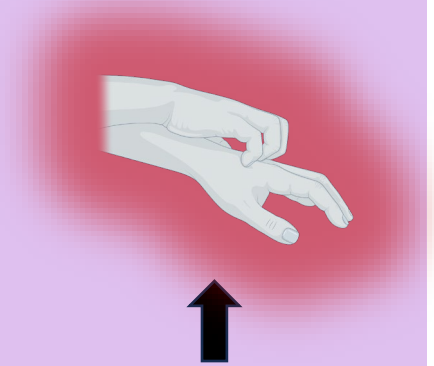
Somatosensory nervous system

Itch sensory neuron
(Transmission)

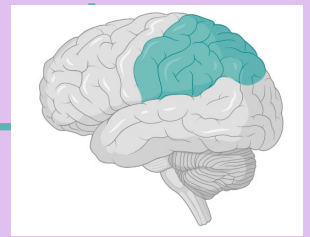
Spinal cord
(Processing)



Scratch
(behavior)



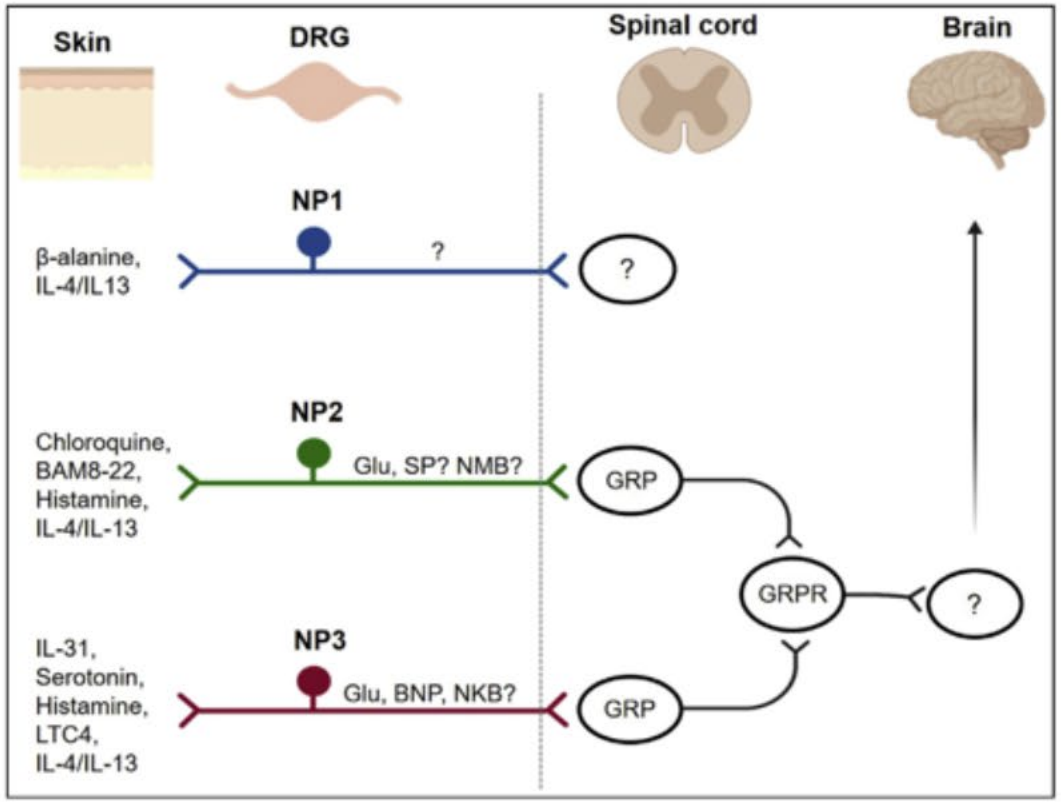
Brain
(Perception)

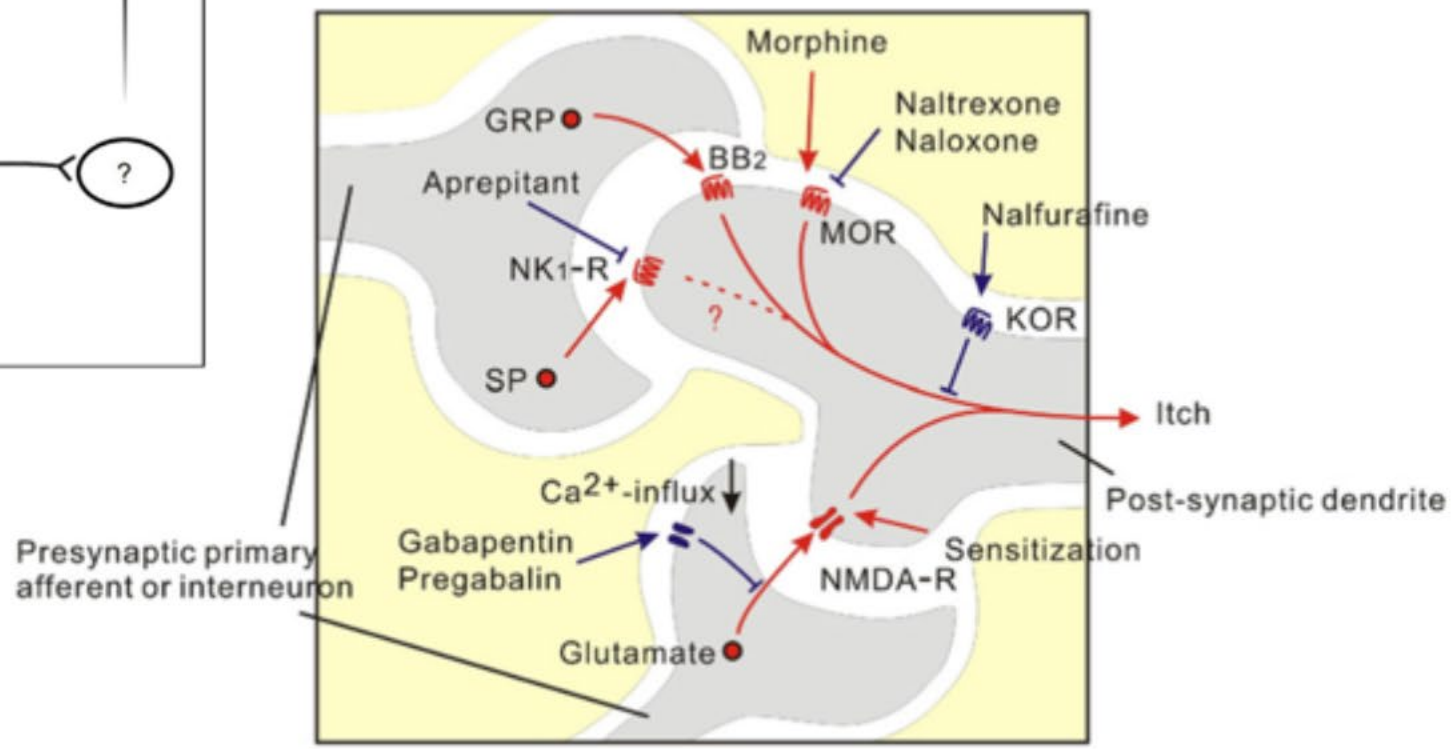


Local

Systemic

Processing in the spinal cord





Wang, F. *Immunity* 2020
Ikoma, A. *Semin. Cutan. Med. Surg.* 2011

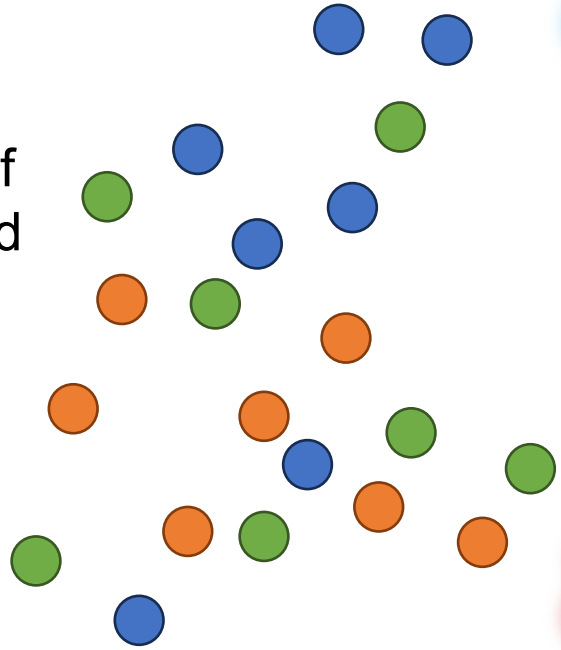
Let’s get back to immunology: neuroinflammation

Local neuroinflammation

Skin sensory nerves

Acute Itch

Efferent release of neuropeptides and neurotransmitters



Physiologic activation

Pathologic Chronic Itch

Pathologic activation

Classic example of neuroinflammation

Nerve injury noted to improve psoriatic lesions (reported 1990)

Subsequent studies showed:

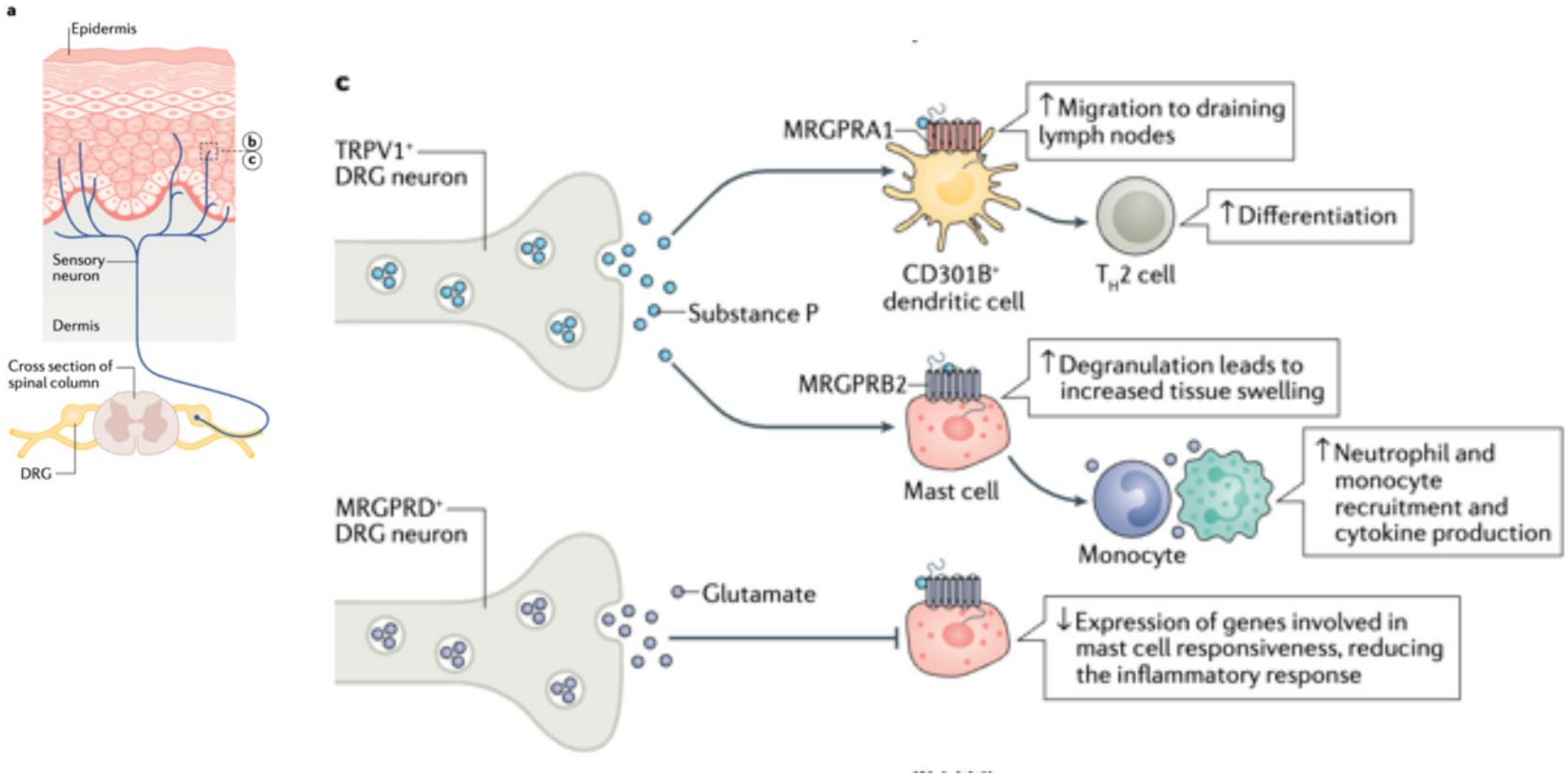
- Sensory neurons in skin release calcitonin gene-related peptide (CGRP)
- CGRP stimulates skin dendritic cells to secrete IL-23
- IL-23 stimulates skin γδ T cells to secrete IL-17

Too much signaling = psoriasis

Not enough = susceptible to cutaneous fungal infections

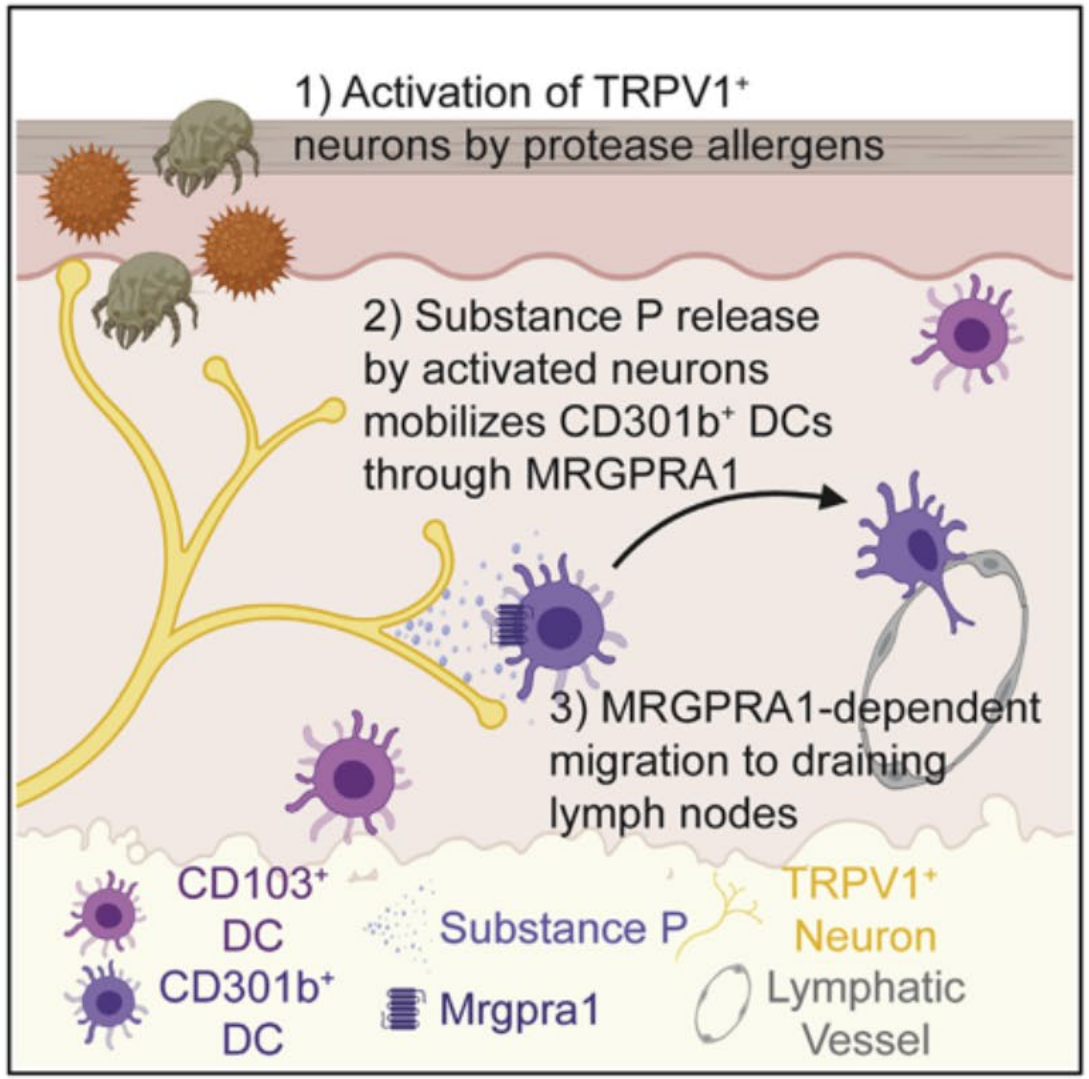
Farber, E. M. *Int J Dermatol.* 1990
Riol-Blanco, L. *et al. Nature.* 2014
Cohen, J. A. *et al. Cell.* 2019
Kashem, S. W. *et al*. *Immunity.* 2015

Review of established neuroinflammatory skin circuits



Udit, S. *Nat. Rev. Neurosci.* 2022

Allergens drive neuronal activation of DCs to induce IgE in mice



Article

Substance P Release by Sensory Neurons Triggers Dendritic Cell Migration and Initiates the Type-2 Immune Response to Allergens

Caroline Perner,[1,3] Cameron H. Flayer,[1,3] Xueping Zhu,[1,3] Pamela A. Aderhold,[1,4] Zaynah N.A. Dewan,[1,4] Tiphaine Voisin,[2] Ryan B. Camire,[1,2] Ohn A. Chow,[1] Isaac M. Chiu,[2] and Caroline L. Sokol[1,5,*]

[1]Center for Immunology and Inflammatory Diseases, Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

[2]Department of Immunology, Harvard Medical School, Boston, MA 02115, USA

[3]These authors contributed equally

[4]These authors contributed equally

[5]Lead Contact

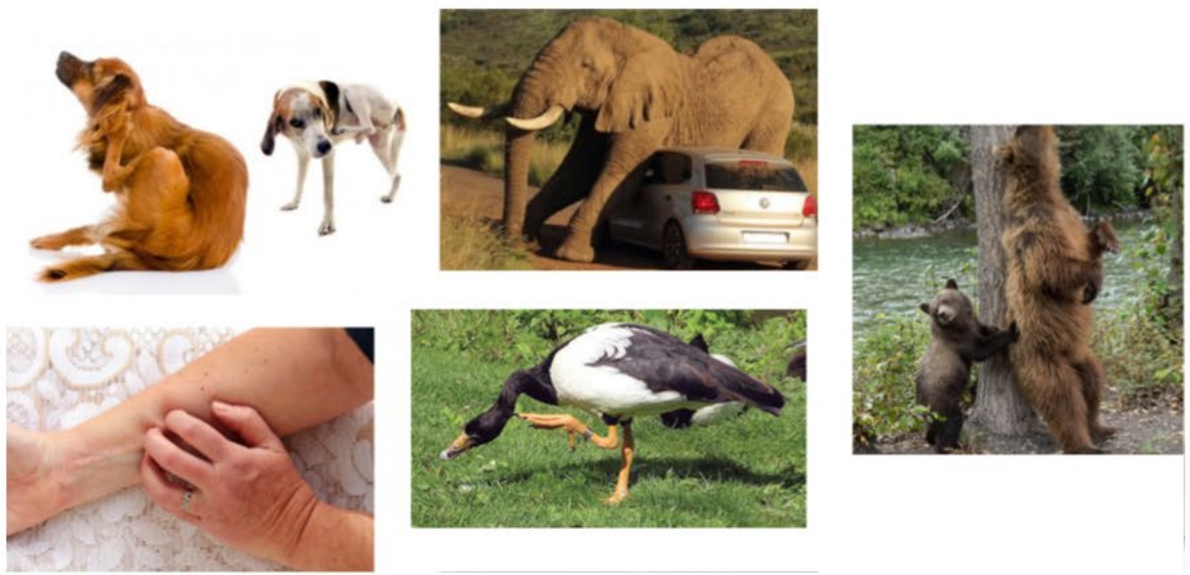
*Correspondence: clsokol@mgh.harvard.edu

https://doi.org/10.1016/j.immuni.2020.10.001

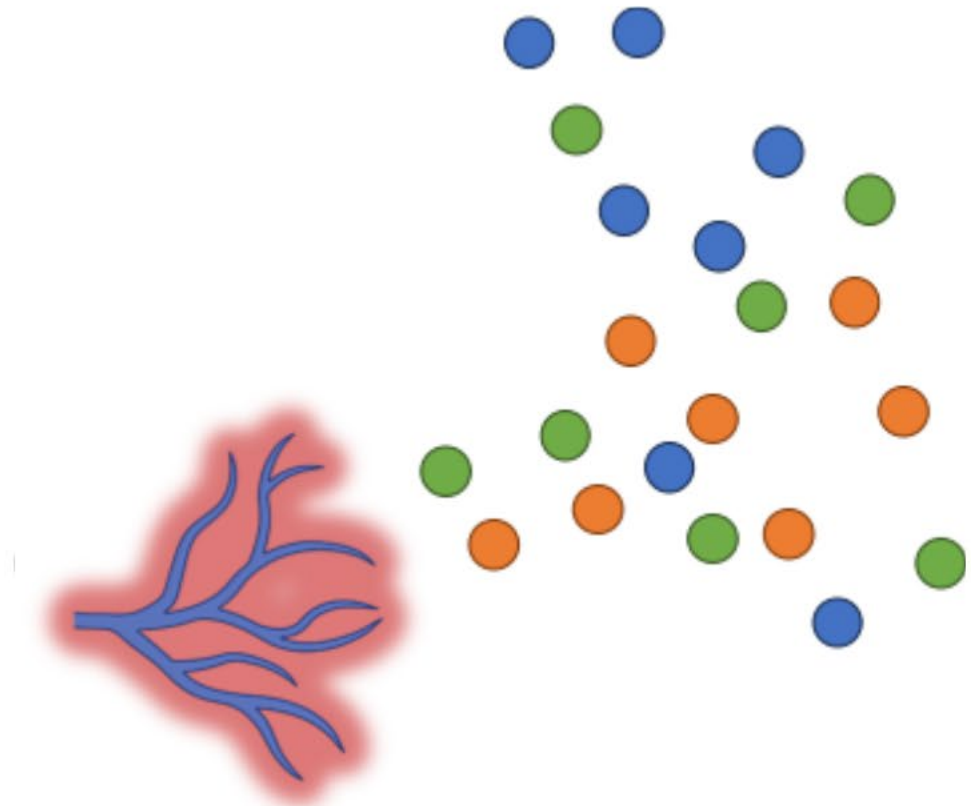
Perner, C. *et al*. *Immunity* 2020

What is itch?

Itch is a **sensation**

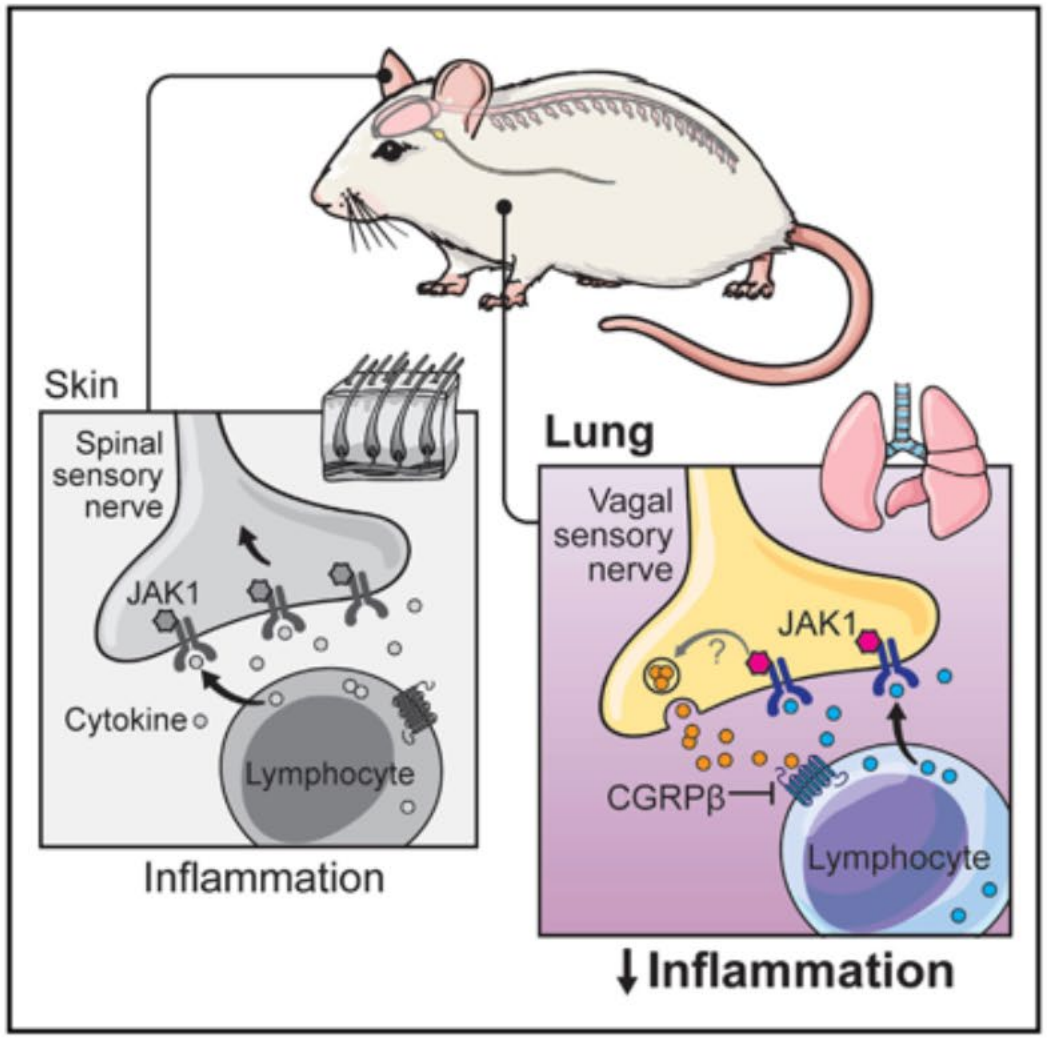


Itch is a **physiologic response**



Bringing mouse studies back to human

Sensory neurons promote immune homeostasis in the lung



Authors

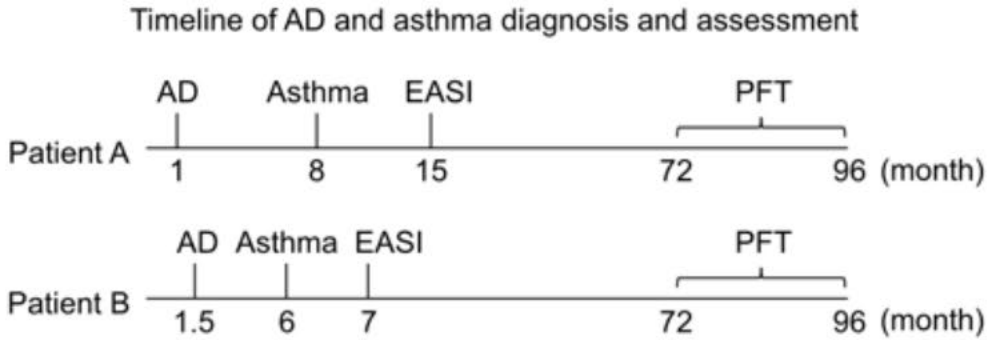
Masato Tamari, Kate L. Del Bel, Aaron M. Ver Heul, ..., David Artis, Stuart E. Turvey, Brian S. Kim

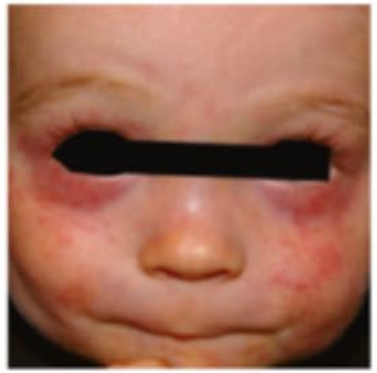
JAK1 inhibition

Skin	Immune cells:	protective
	Neurons:	protective
Lung	Immune cells:	protective
	Neurons:	pathogenic

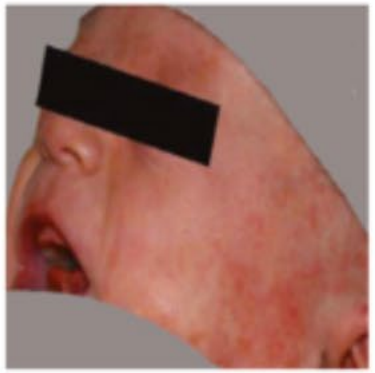
Tamari, M. *et al. Cell.* 2024

JAK1 GOF patients

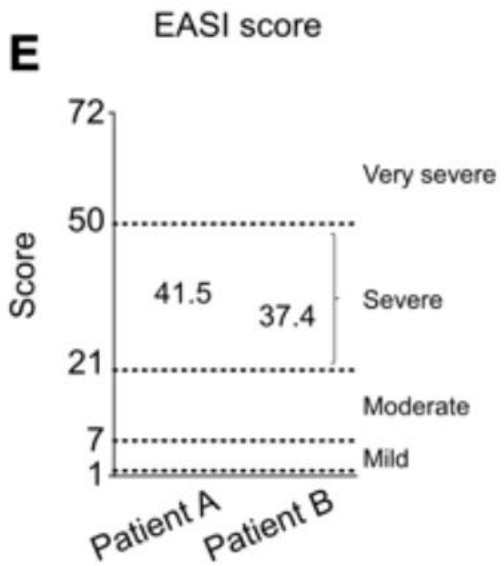


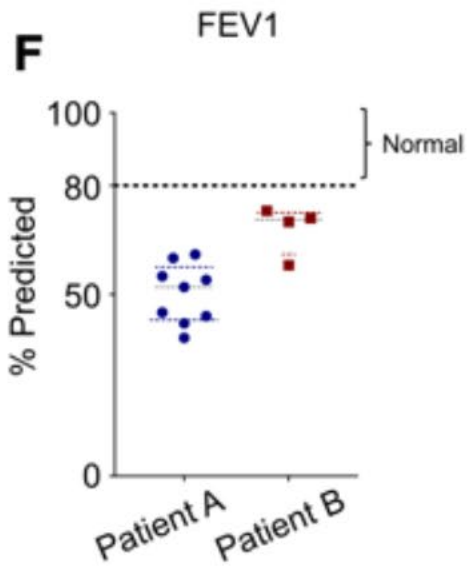


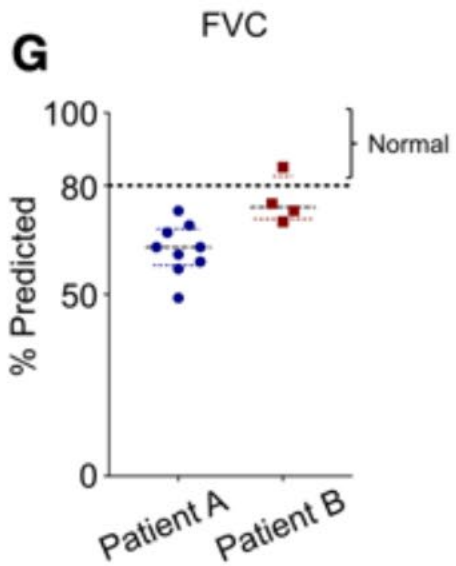
Patient A



Patient B







Tissue-specific JAK inhibition

Will the mechanistic preclinical neuroimmune studies predict outcomes for inhaled JAK inhibitors?

Skin	Immune cells:	protective
	Neurons:	protective

Lung	Immune cells:	protective
	Neurons:	pathogenic

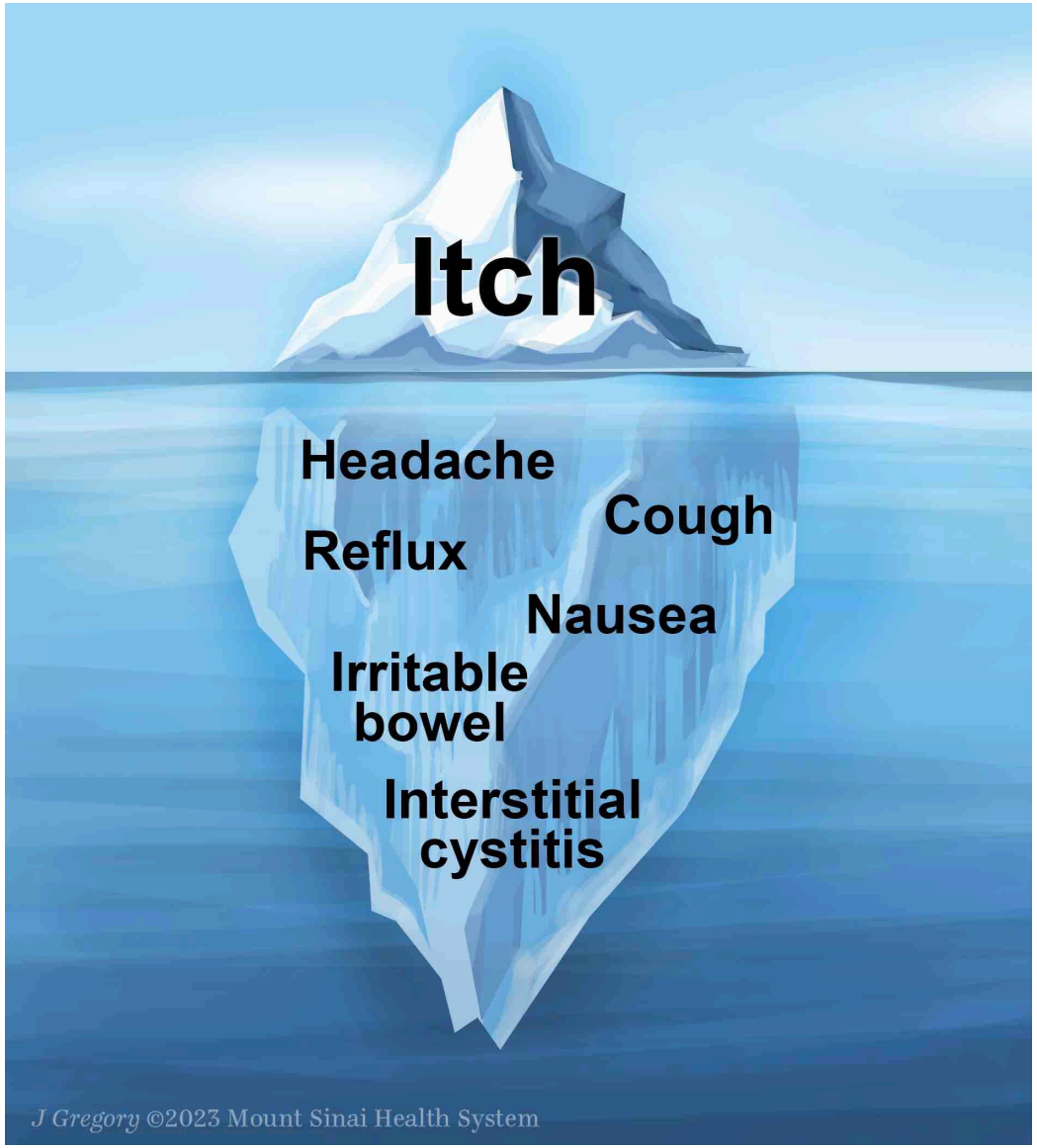
Topical ruxolitinib (JAK1/2):
FDA-approved 2021 for AD

Inhaled JAK inhibitor

Phase 1: AZD0449 not advanced (NCT03766399)
TD-8236 not advanced (NCT04150341)

Phase 2: AZD4604 recruiting (NCT06020014, NCT06435273)

Itch is more than just the skin deep



Conclusions

- Type 2 immune cytokines sensitize and activate itch-specific neurons, i.e. type 2 inflammation encodes itch

- New therapeutics for neuropathic itch will take advantage of neuronal gating, such as touch or pain inhibiting itch through pathways such as kappa opioids

- Itch is more than just an electrical signal transmitted to the brain as a “sensation.” Activation of itch leads to local changes in tissue physiology due to release of neuropeptides from the activated itch neurons.

Questions?