Welcome to Cara Therapeutics 2022 R&D Day

MARCH 11, 2022

CARA™ THERAPEUTICS

Forward Looking Statements

Statements contained in this presentation regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include statements concerning the expected timing of the initiation, enrollment and data readouts from the Company's planned and ongoing clinical trials, the potential results of ongoing clinical trials, timing of future regulatory and development milestones for the Company's product candidates, the potential for the Company's product candidates to be alternatives in the therapeutic areas investigated, the Company's expected cash reach, and the potential impact of COVID-19 on the Company's commercial launch, clinical development and regulatory timelines and plans. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Risks are described more fully in Cara Therapeutics' filings with the Securities and Exchange Commission, including the "Risk Factors" section of the Company's Annual Report on Form 10-K for the year ending December 31, 2021 and its other documents subsequently filed with or furnished to the Securities and Exchange Commission. All forward-looking statements contained in this presentation speak only as of the date on which they were made.

Cara Therapeutics undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

Today's Speakers

Christopher A. Posner
President & CEO

Dr. Joana Goncalves, M.D.
Chief Medical Officer

Dr. Brian Kim, MD, MTR

Sol and Clara Kest Professor | Vice Chair of Research | Site Chair, Mount Sinai West and Morningside | Director, Mark Lebwohl Center for Neuroinflammation and Sensation | The Kimberly and Eric J. Waldman Department of Dermatology | Precision Immunology Institute | Friedman Brain

Dr. Jonathan Silverberg, MD, PHD, MPH

Director, Clinical Research | Director, Patch Testing | Associate Professor, Department of Dermatology | The George Washington University School of Medicine and Health Sciences, Washington, DC

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Agenda

01 **Introductory Remarks**

Christopher Posner, CEO, President and Director, Cara Therapeutics

02 **Review of Oral Difelikefalin Phase 3 Clinical Programs in Patients with Advanced CKD and AD-associated Pruritus**

Dr. Joana Goncalves, MD, CMO, Cara Therapeutics

03 **Difelikefalin Potential Mechanism of Action in Atopic Dermatitis**

Dr. Brian Kim, MD, MTR

04 **Heterogeneity and Novel Phenotypes of Atopic Dermatitis**

Dr. Jonathan Silverberg, MD, PHD, MPH

05 **Live Q&A Session**

Oral difelikefalin is an investigational agent that has not been approved by the FDA. The efficacy and safety of oral difelikefalin has not been established.

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Introductory Remarks

CHRISTOPHER POSNER

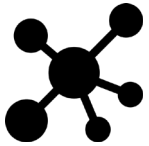
CEO, PRESIDENT AND DIRECTOR, CARA THERAPEUTICS

OUR MISSION:

Transform the way pruritus is treated to bring quality to the lives of those who suffer.

Commercializing & Developing First-in-Class Pruritus Treatments

Executing second strategic priority with category-defining Phase 3 trials



Strong scientific rationale in pruritus with advanced CKD & atopic dermatitis

Clear clinical rationale and market opportunity for pruritus-focused treatments

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Oral Difelikefalin Phase 3 Clinical Programs in Patients with Advanced CKD and AD-associated Pruritus

DR. JOANA GONCALVES, MD

CMO, CARA THERAPEUTICS

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“KICK”

Advanced Chronic Kidney Disease

Phase 3 Program

Difelikefalin for Pruritus in Advanced Chronic Kidney Disease

- ✓ KALM Phase 3 program with Korsuva injection and Phase 2 study with oral difelikefalin support use as antipruritic treatment in advanced chronic kidney disease (CKD).
- ✓ Phase 2 Study with oral difelikefalin met primary endpoint with 1mg dose in stage 3-5 CKD-associated pruritus.
- ✓ Alignment with FDA reached on Phase 3 Program in advanced CKD.

Initiation of Phase 3 program for oral difelikefalin in advanced CKD with moderate-to-severe pruritus.

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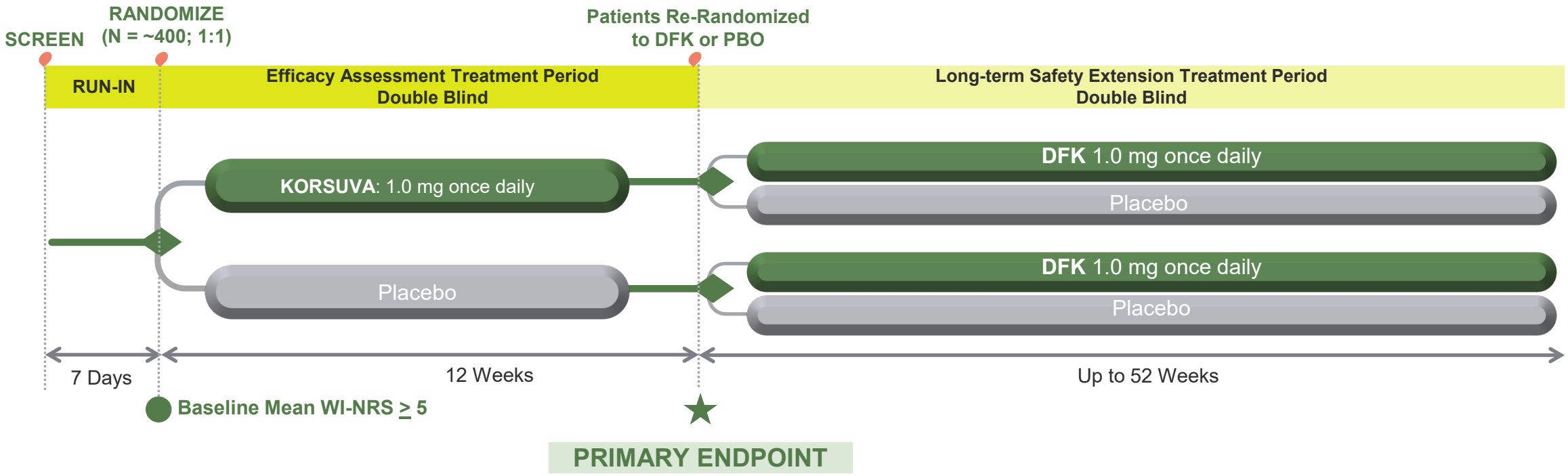
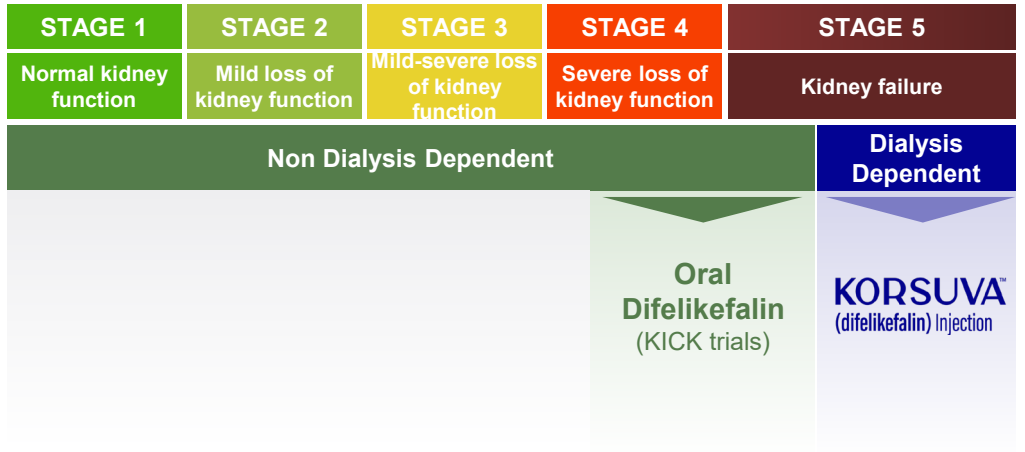
KICK 1 & KICK 2: Phase 3 Development Program with Oral DFK in Advanced CKD



KICK 1 & KICK 2: Patient Population

STUDY PATIENT POPULATION

- Adults with advanced stage 4 and 5 CKD
- Chronic Pruritus for at least 6 months prior to screening
- Moderate to Severe Pruritus at Baseline (WI-NRS ≥ 5)
- Allowed to be on stable treatment for itch including antihistamines and gabapentinoids



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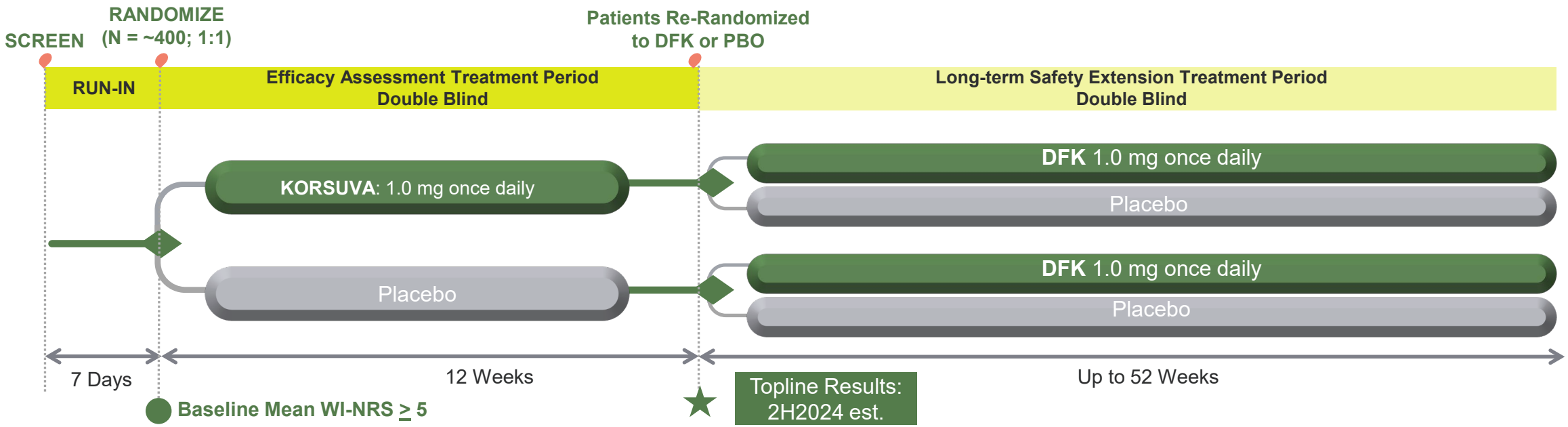
KICK 1 & KICK 2: Study Design



PRIMARY ENDPOINT

- **% of subjects with ≥4-point improvement from baseline in WI-NRS score at Week 12**

ADDITIONAL ENDPOINTS

- Quality of life including sleep
- Safety assessments

 KICK1 US sites only, KICK 2 US and ex-US sites

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“KIND”

Atopic Dermatitis Phase 3 Program

Difelikefalin for Pruritus in Atopic Dermatitis

- ✓ KARE phase 2 data support antipruritic efficacy of oral difelikefalin in atopic dermatitis (AD) with moderate-to-severe pruritus especially patients with a BSA <10%.
- ✓ Pre-clinical and clinical data support that difelikefalin has a predominant neuromodulatory action in AD.
- ✓ Alignment with FDA reached on Phase 3 Program as adjunctive therapy to topical corticosteroids (TCS).

Initiation of Phase 3 program for oral difelikefalin as adjunct therapy to TCS in AD with moderate-to-severe pruritus.

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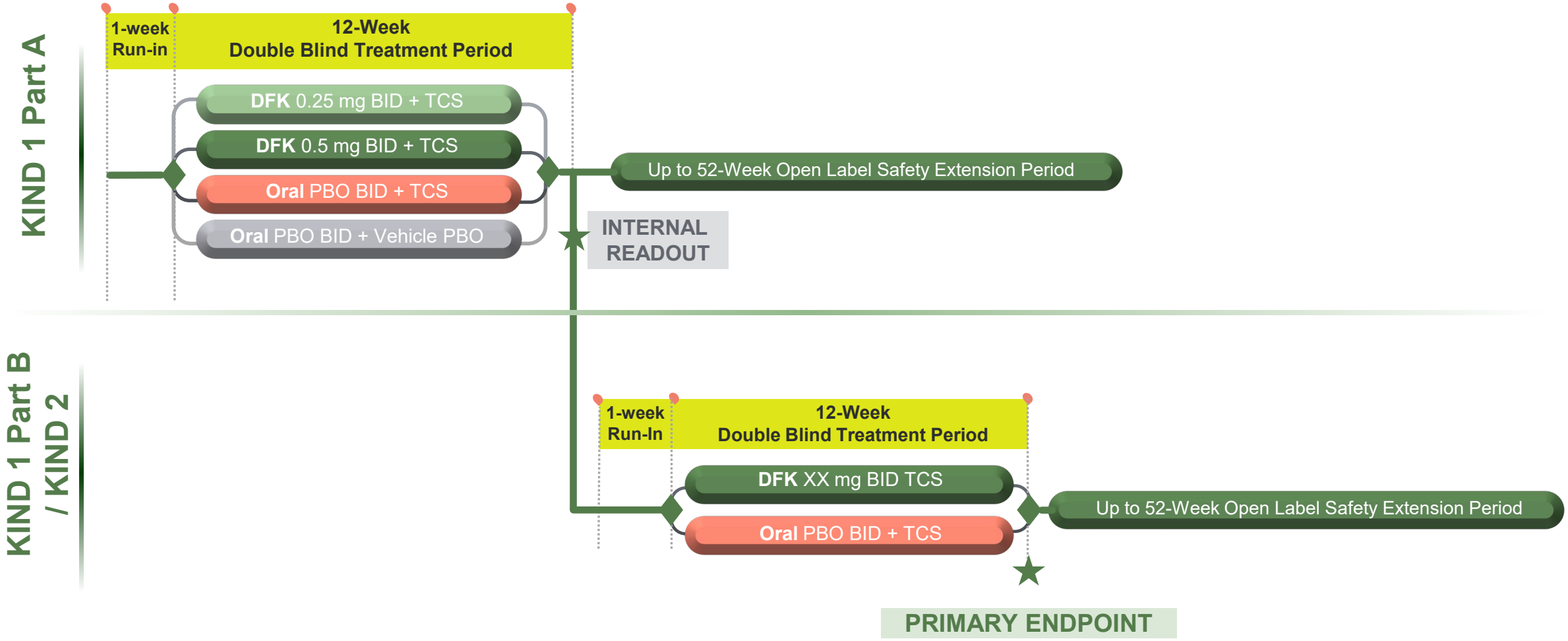
KIND 1 & KIND 2:
Phase 3 Development Program with Oral Difelikefalin in AD



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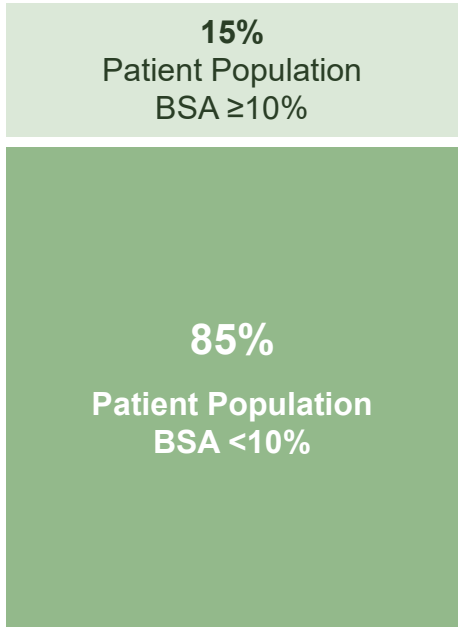
KIND 1 & KIND 2: Patient Population

STUDY PATIENT POPULATION

- Adults with AD-related pruritus not adequately controlled by topical therapy alone
- Chronic AD-related Pruritus ≥6 weeks
- Moderate to Severe Pruritus at Baseline (I-NRS ≥ 5)
- Mild to severe Atopic Dermatitis:
  - IGA ≥ 2, BSA ≤20%
- Patients need to be washed out of any medication that may impact itch and/or AD prior to screening
- Stratification to BSA <10% and ≥10%

Target Enrollment



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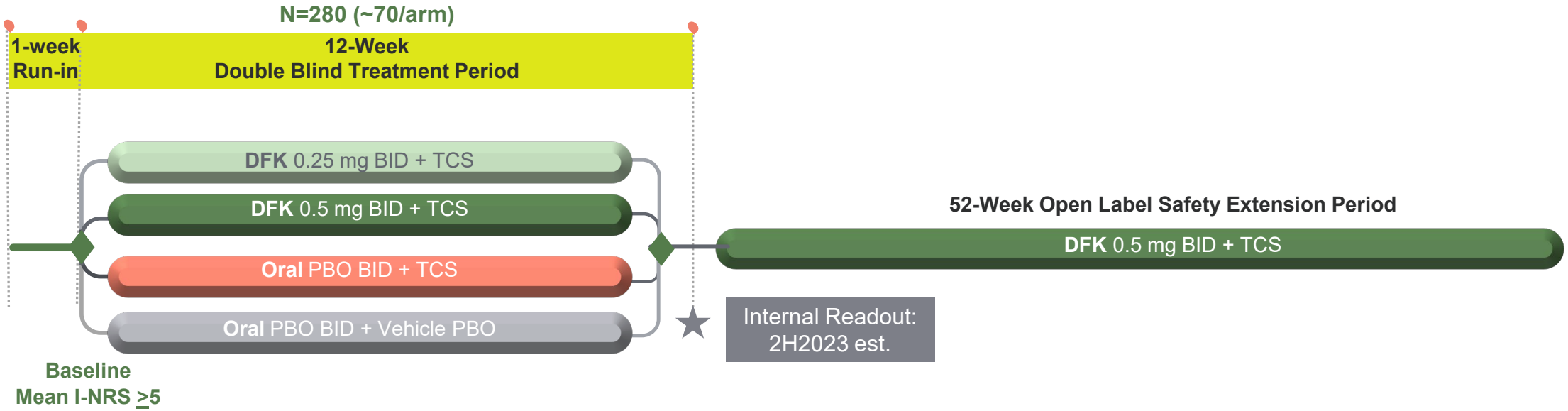
KIND 1 Part A: Study Design



CRITERIA

- % of subjects with ≥4-point improvement from baseline in WI-NRS score at Week 12
- Safety assessments

INFORMATION

- Dose
- Sample size

 KIND 1 Part A will include sites in North America only

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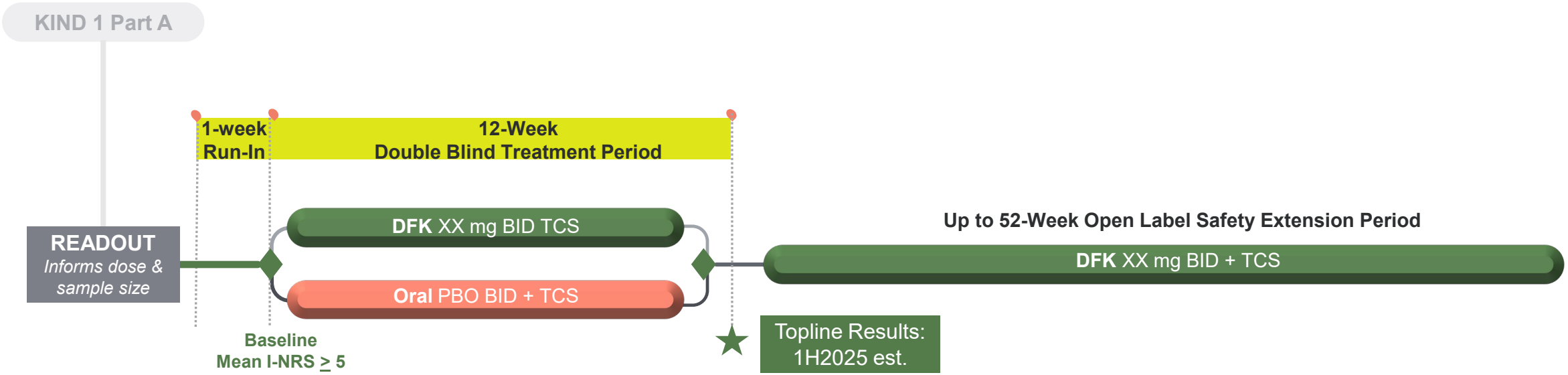
KIND 1 Part B & KIND 2: Study Design



PRIMARY ENDPOINT

- **% of subjects with ≥4-point improvement from baseline in WI-NRS score at Week 12**

ADDITIONAL ENDPOINTS

- Quality of life including sleep
- Skin assessment
- Safety assessments

KIND 1 Part B will include sites in North America only, while KIND 2 will include sites in North America and outside of North America

KICK advanced CKD & KIND AD Phase 3 Programs designed to accomplish 3 Things

- ❑ **Address the unmet need** which is not sufficiently addressed with current treatment options.
- ❑ Focus on the **most appropriate patient populations** for difelikefalin considering current clinical practice.
- ❑ Execute on the most appropriate **study designs with the greatest likelihood of success.**

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Difelikefalin Potential MOA in Atopic Dermatitis

BRIAN S. KIM, MD, MTR

SOL AND CLARA KEST PROFESSOR

VICE CHAIR OF RESEARCH ,

SITE CHAIR, MOUNT SINAI WEST AND MORNINGSIDE

DIRECTOR, MARK LEBWOHL CENTER FOR NEUROINFLAMMATION AND SENSATION

THE KIMBERLY AND ERIC J. WALDMAN DEPARTMENT OF DERMATOLOGY

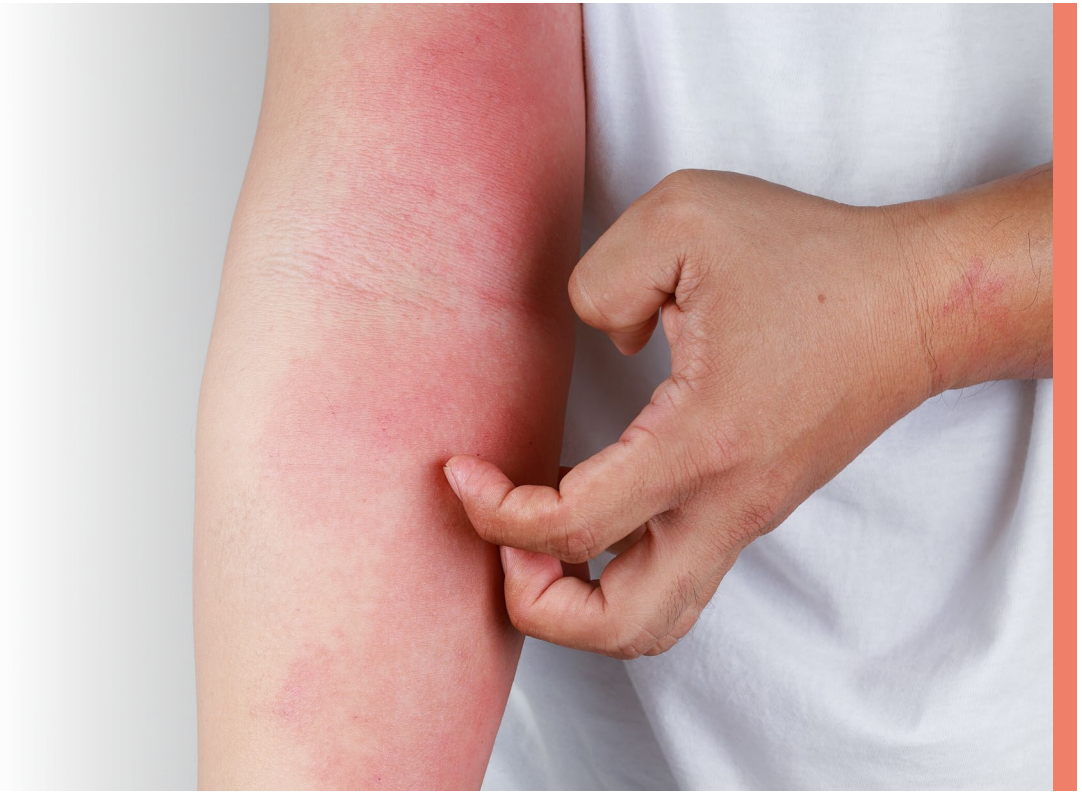
PRECISION IMMUNOLOGY INSTITUTE

FRIEDMAN BRAIN INSTITUTE

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI, NEW YORK

Atopic Dermatitis (AD) is a Classic Chronic Itch Disorder

- High incidence, costly
- Itch is the central symptom
- Negative impact on quality of life
- Therapeutic options specifically targeting pruritus are limited
- Increasing number of patients treated for rash left with residual itch



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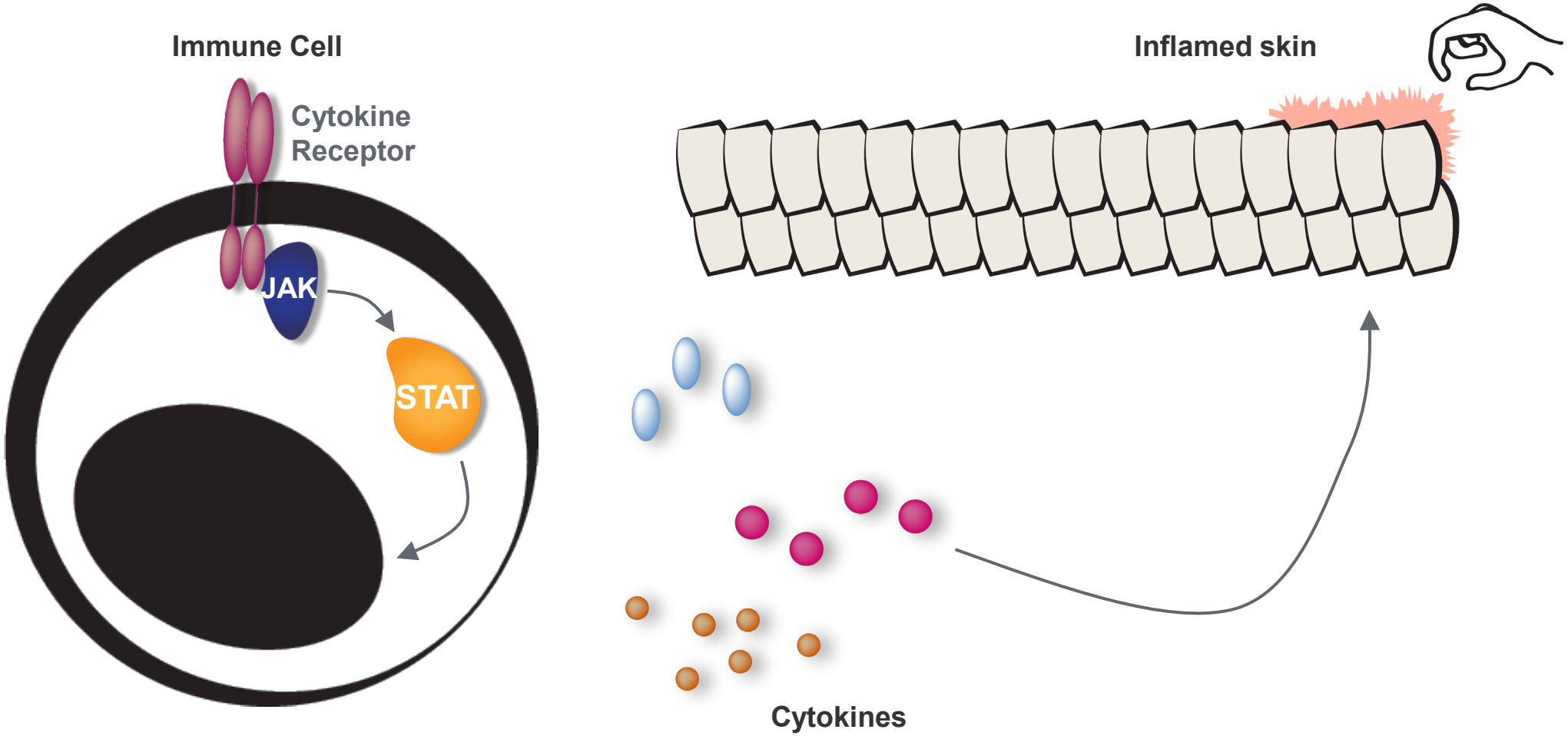
Conventional Paradigm of Atopic Dermatitis Pathogenesis



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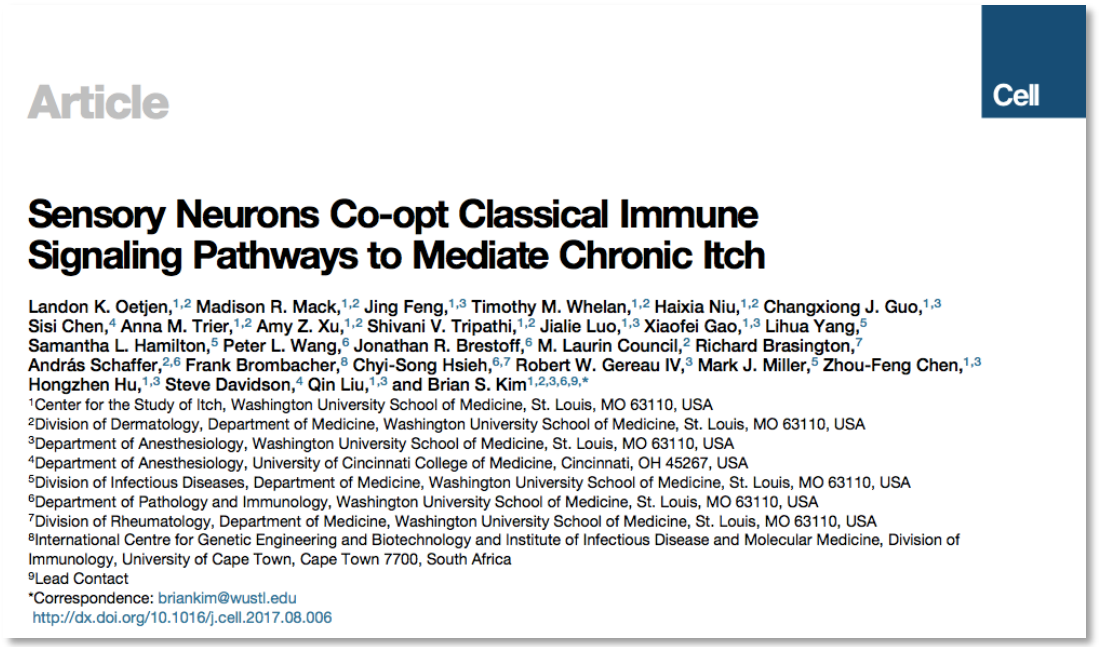
Discovery of Novel Itch Targets in the Nervous System



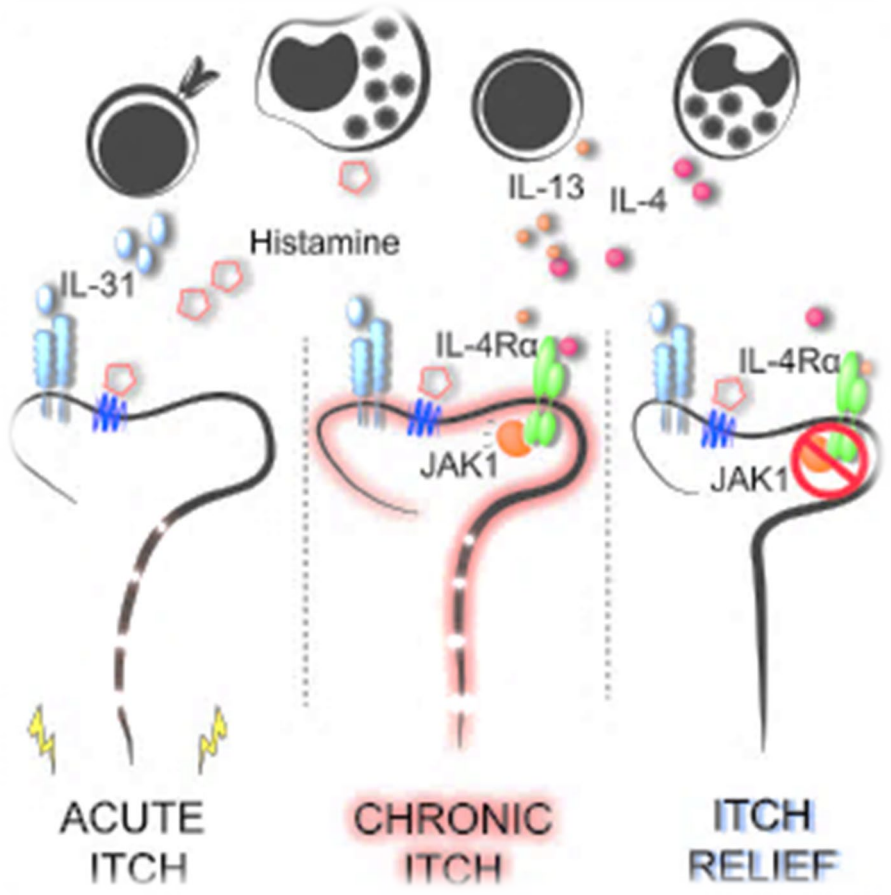
Article

Cell

Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch

Landon K. Oetjen,[1,2] Madison R. Mack,[1,2] Jing Feng,[1,3] Timothy M. Whelan,[1,2] Haixia Niu,[1,2] Changxiong J. Guo,[1,3] Sisi Chen,[4] Anna M. Trier,[1,2] Amy Z. Xu,[1,2] Shivani V. Tripathi,[1,2] Jialie Luo,[1,3] Xiaofei Gao,[1,3] Lihua Yang,[5] Samantha L. Hamilton,[5] Peter L. Wang,[6] Jonathan R. Brestoff,[6] M. Laurin Council,[2] Richard Brasington,[7] András Schaffer,[2,6] Frank Brombacher,[8] Chyi-Song Hsieh,[6,7] Robert W. Gereau IV,[3] Mark J. Miller,[5] Zhou-Feng Chen,[1,3] Hongzhen Hu,[1,3] Steve Davidson,[4] Qin Liu,[1,3] and Brian S. Kim[1,2,3,6,9,*]

[1]Center for the Study of Itch, Washington University School of Medicine, St. Louis, MO 63110, USA
[2]Division of Dermatology, Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA
[3]Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO 63110, USA
[4]Department of Anesthesiology, University of Cincinnati College of Medicine, Cincinnati, OH 45267, USA
[5]Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA
[6]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO 63110, USA
[7]Division of Rheumatology, Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA
[8]International Centre for Genetic Engineering and Biotechnology and Institute of Infectious Disease and Molecular Medicine, Division of Immunology, University of Cape Town, Cape Town 7700, South Africa
[9]Lead Contact
*Correspondence: briankim@wustl.edu
http://dx.doi.org/10.1016/j.cell.2017.08.006



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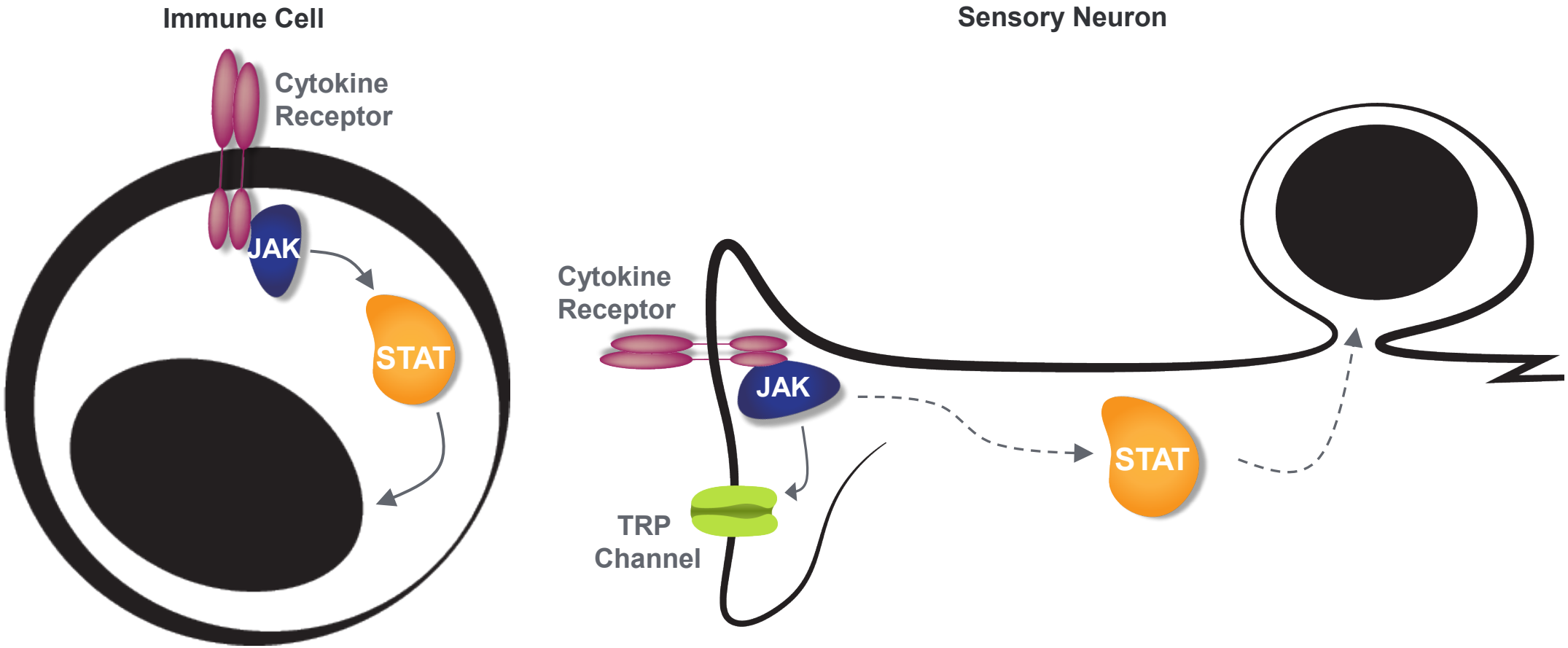
New Itch-Centric Paradigm of Atopic Dermatitis



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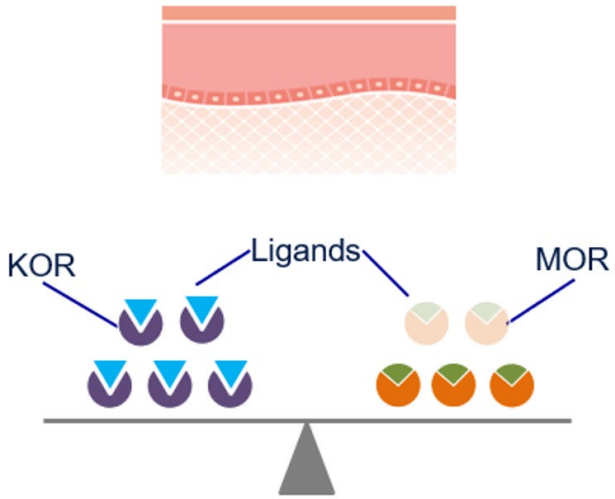
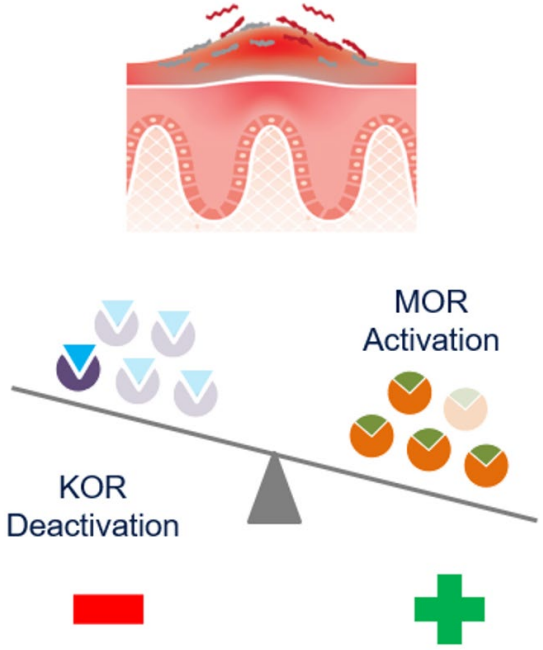
Kappa agonism and mu antagonism are desired in treating itch

Normal Skin



Pruritic Skin

Too much MOR activation
and/or too little KOR activation



Induction of Itch

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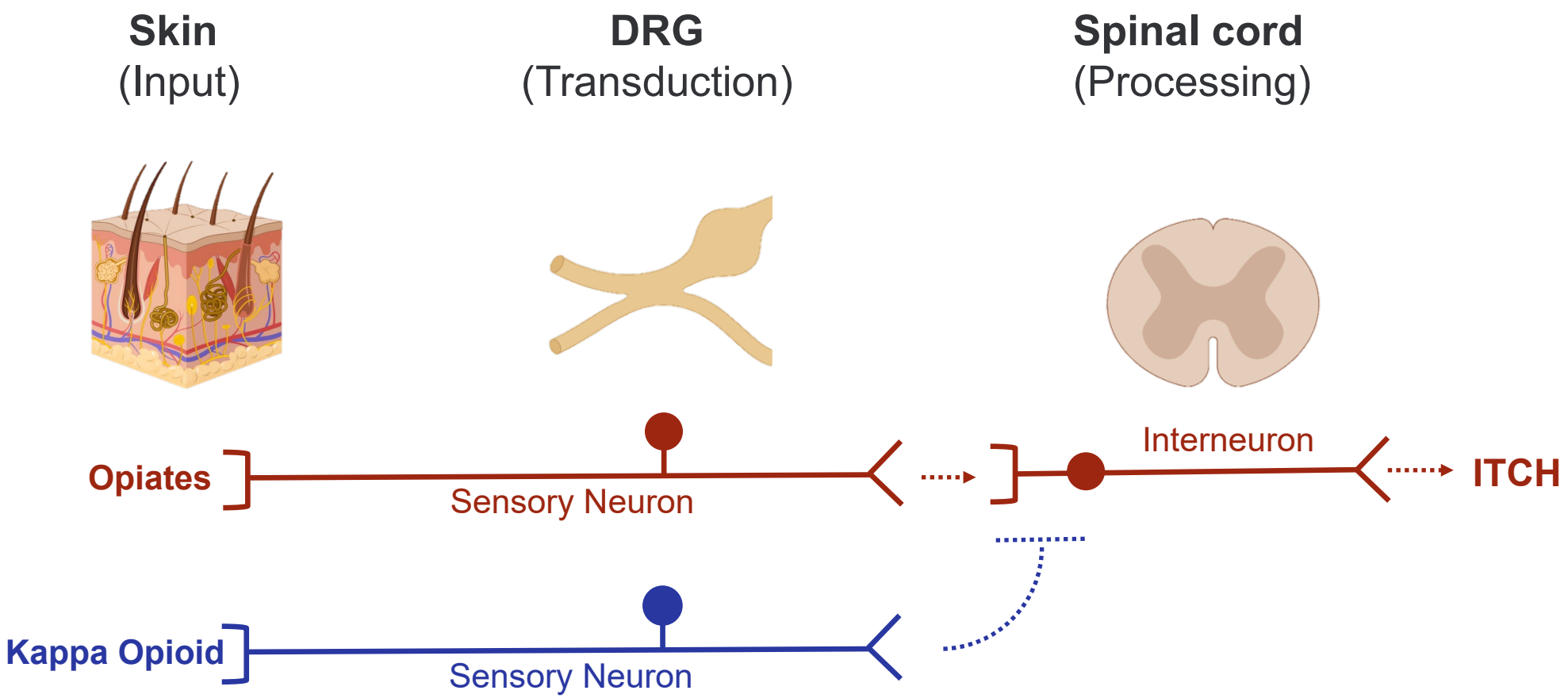
Kappa opioid signaling represents an itch-suppressive pathway



Kardon et al. *Neuron* 2014
Snyder et al. *Neuron* 2019

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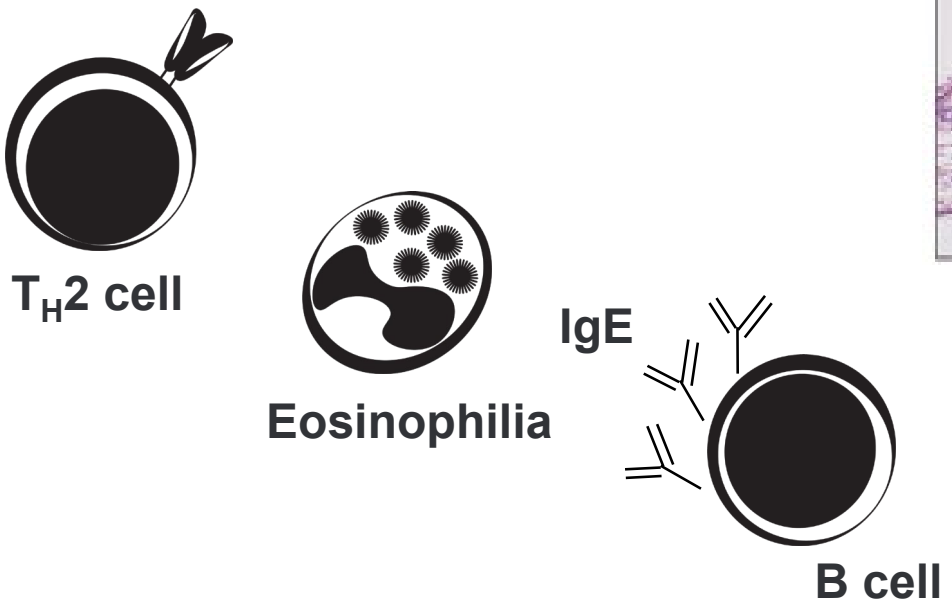
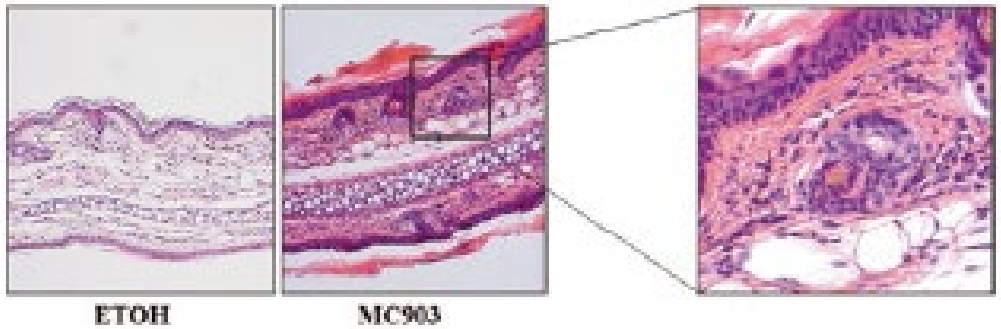
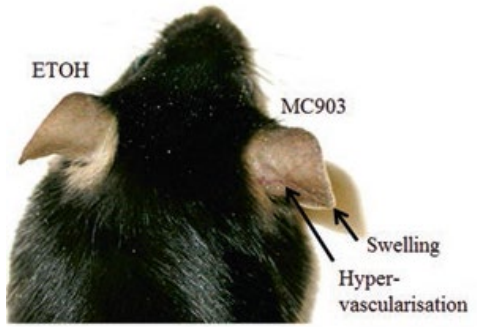
Difelikefalin Rapidly Reduces Pruritus in Preclinical AD

Mouse Study Methods and Results

Topical vehicle (EtOH) or MC903 → WT → AD-like disease







MC903, calcipotriol; IgE, immunoglobulin E; TH2, T helper 2; WT, wild type.

Moosbrugger-Martinz V, et al. Methods Mol Biol. 2017;1559:91-106.

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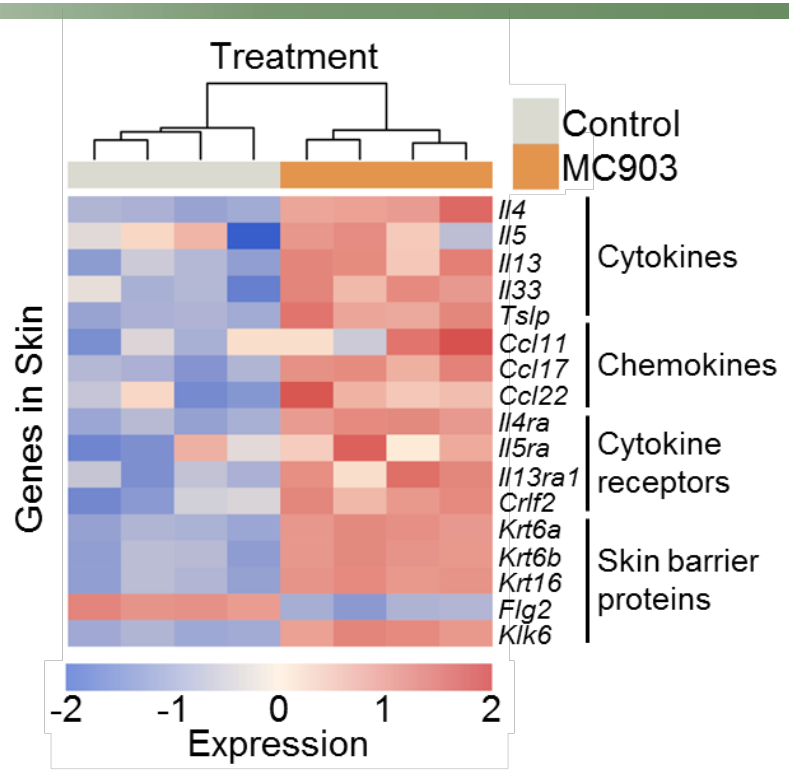
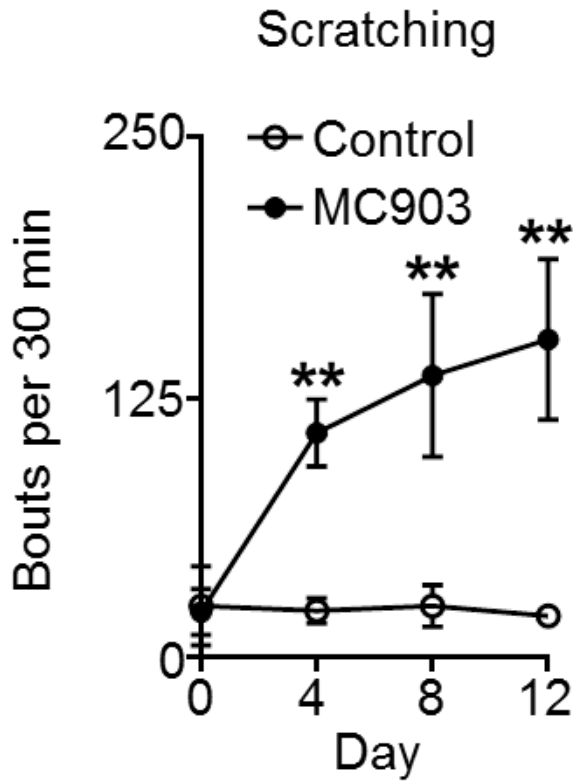
Mouse Study Methods and Results

Topical vehicle (EtOH) or MC903 → WT → AD-like disease





 | Oetjen LK, et al. Cell. 2017;171:217-228.

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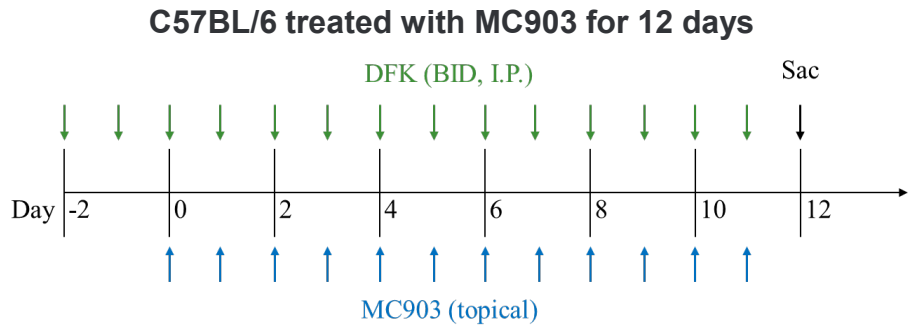
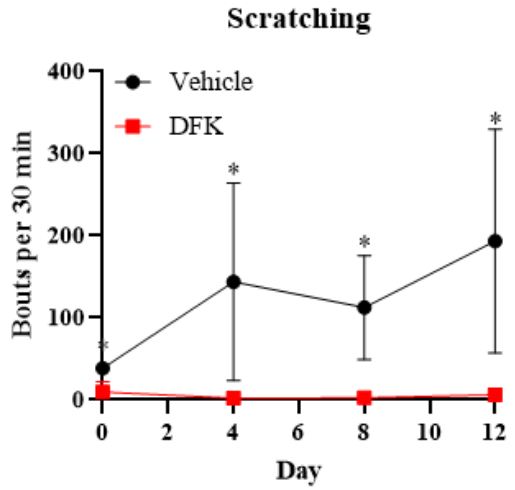
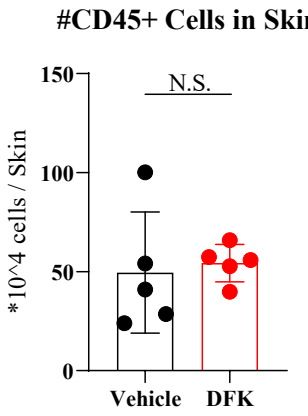
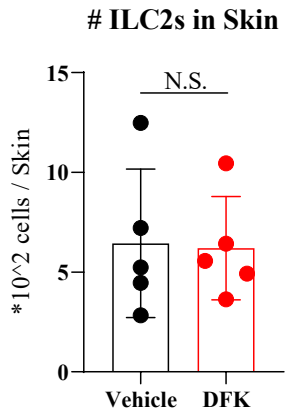
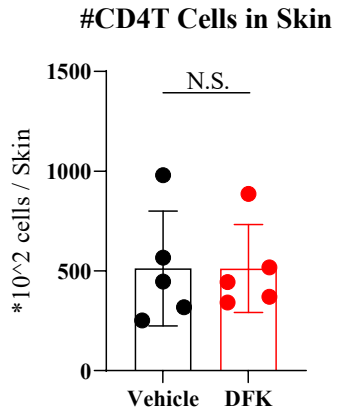
Mouse Study Methods and Results

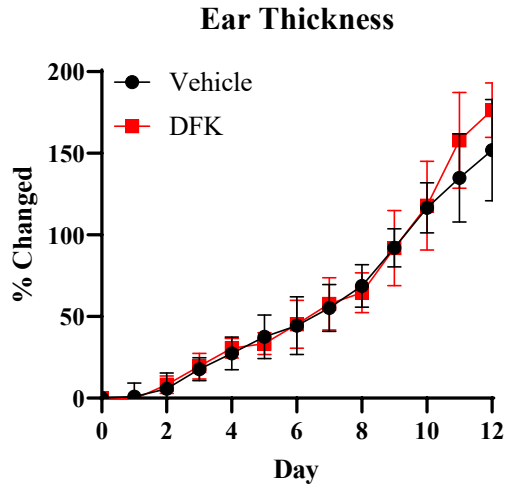












* p<0.05 vs. control (unpaired t-test)
BID, twice daily; I.P., intraperitoneal; ILC2, innate lymphoid type-2 cells

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Mouse Study Methods and Results

- Single cell RNA-sequencing datasets reveal expression of Oprk1 (gene encoding KOR) primarily on mechanosensory Aβ neurons

	A-LTMR (Touch)					C-fibers (Itch)					
Gene Symbol	**NF1**	**NF2**	**NF3**	**NF4**	**NF5**	**NP1**	**NP2**	**NP3**	**PEP1**	**PEP2**	**TH**
Oprk1	0	0.104	0.083	0	0	0	0	0	0	0	0
Oprm1	0	0	0	0.045	0	0.056	0.125	0.250	0.047	0.118	0.004
Nppb	0	0	0	0	0	0	0.031	0.833	0.031	0	0
Sst	0	0	0	0	0	0	0.031	0.833	0.016	0	0
Cysltr2	0	0	0	0	0	0.032	0	0.667	0	0	0
Hrh1	0	0	0.083	0	0	0	0.094	0.083	0	0	0
Mrgprd	0.032	0.021	0	0	0.038	0.840	0.219	0	0.016	0	0.013
Mrgpra3	0	0	0	0	0	0.008	0.625	0.083	0	0	0.004
Il4ra	0	0	0	0.045	0	0.208	0.281	0.167	0.109	0.059	0.039
Il13ra1	0	0.021	0	0	0	0.008	0.094	0.083	0.016	0	0
Il31ra	0	0	0.083	0	0	0	0.031	0.583	0.016	0	0

 | Usoskin D, et al. Nat Neurosci. 2015;18:145-153.

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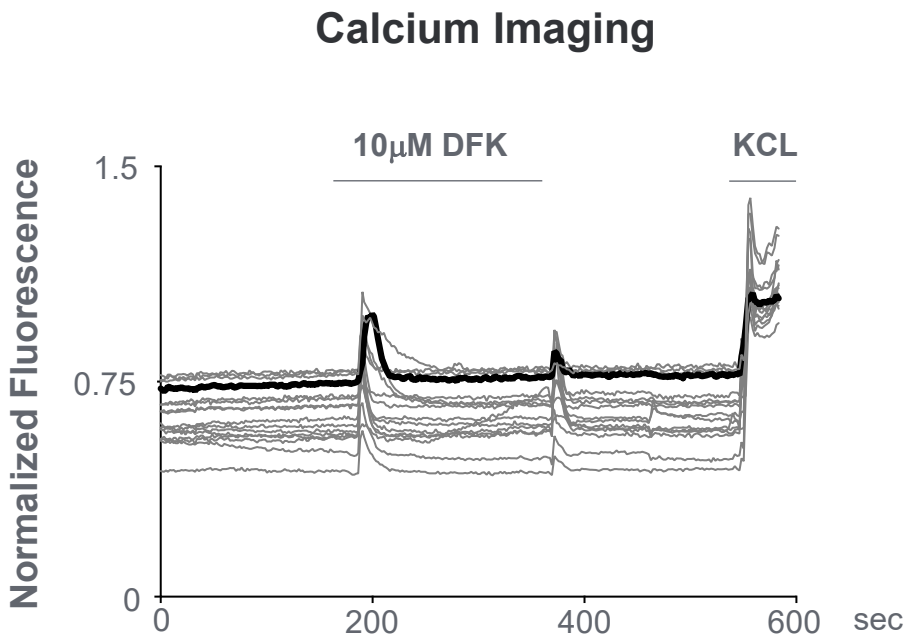
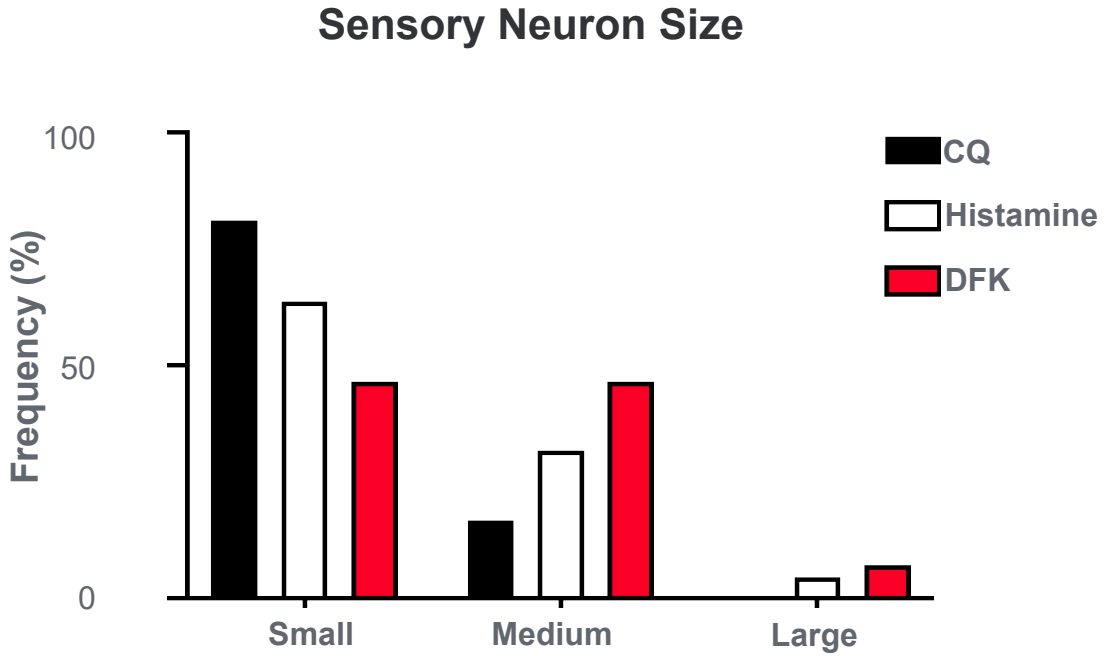
Mouse Study Results: DFK activates medium diameter (ie, Aβ) sensory neurons





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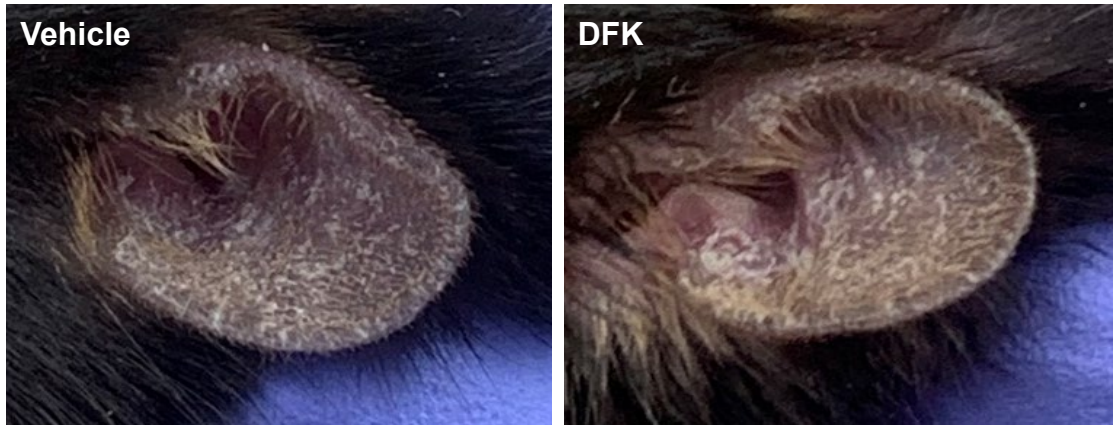
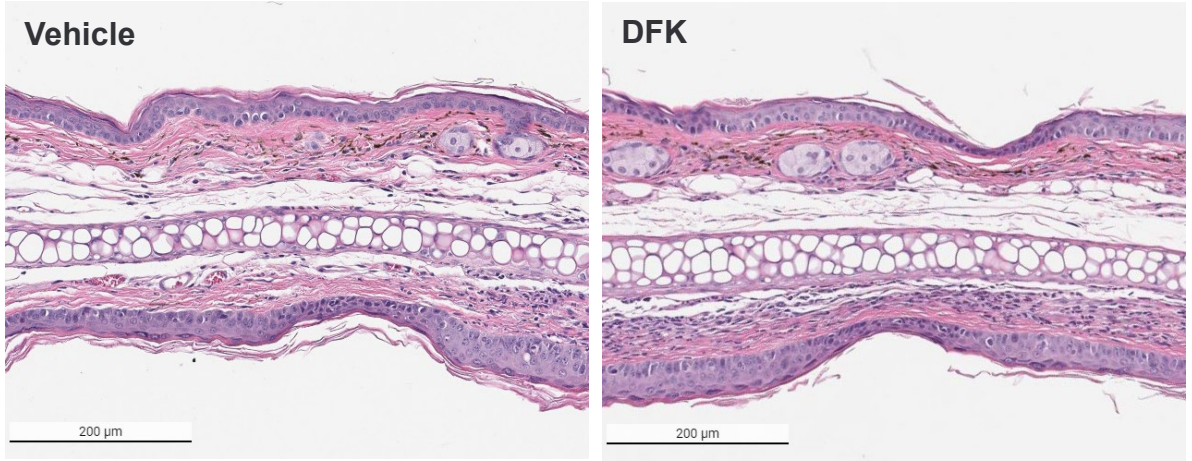
Mouse Study Results: DFK Reduces Scratching Independently of Skin Inflammation

- Calcium imaging demonstrated that DFK directly activated medium diameter (ie, Aβ) sensory neurons

AD-Like Skin Lesions



AD-Like Skin Histopathology



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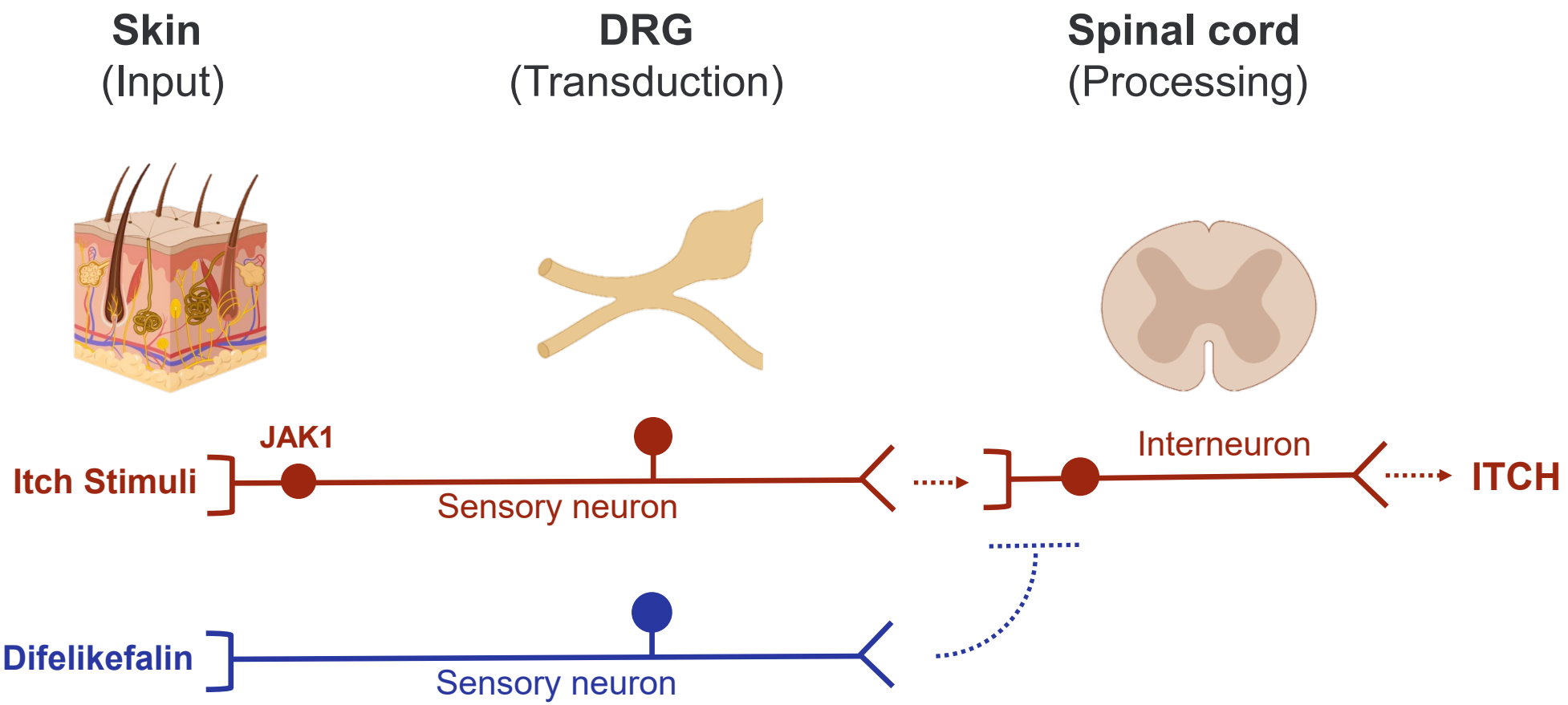
Kappa opioid signaling represents an itch-suppressive pathway



Kardon et al. Neuron 2014
Snyder et al. Neuron 2019

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How is Difelikefalin Different?

Anti-inflammatory Agents:

Abrocitinib
Baricitinib
Corticosteroids
Delgocitinib
Dupilumab
Lebrikizumab
Nemolizumab
Ruxolitinib
Tralokinumab
Upadacitinib

- **Scabetic Itch**
- **Brachioradial Pruritus**
- **Chronic Pruritus of Unknown Origin**
- **Postherpetic Itch**
- **Atopic Dermatitis Itch**
- **Prurigo Nodularis**
- **Dry Skin Itch**
- **Notalgia Paresthetica**
- **Uremic Pruritus**
- **Insect Bite Itch**
- **Scalp Pruritus**

Neuromodulatory Agents:

Gabapentin
Neurontin
Aprepitant
Nalfurafine (Japan)
Nalbuphine
Difelikefalin

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Heterogeneity & Novel Phenotypes of Atopic Dermatitis

JONATHAN I. SILVERBERG, M.D., PH.D., M.P.H.

DIRECTOR, CLINICAL RESEARCH

DIRECTOR, PATCH TESTING

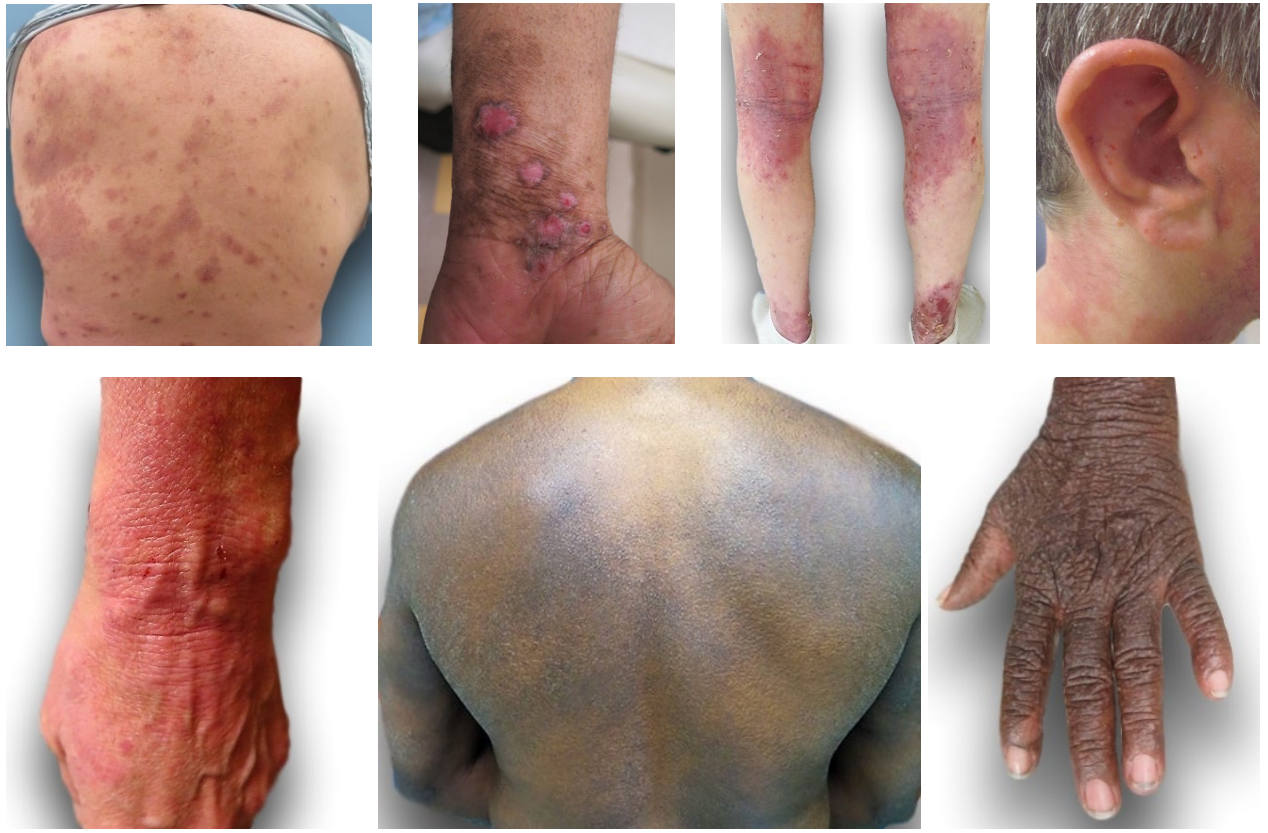
ASSOCIATE PROFESSOR, DEPARTMENT OF DERMATOLOGY

THE GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE AND HEALTH SCIENCES

WASHINGTON, DC USA

Heterogeneous signs of dermatitis

CLINICAL FEATURES	OVERALL (%)
Flexural involvement	58%
Head, face and neck involvement	42%
Hand and foot dermatitis	36%
Perifollicular accentuation	34%
Papular lichenoid lesions	22%
Nummular lesions	13%
Prurigo nodules	7%



Yew YW, Thyssen JP, Silverberg JI. A systematic review and meta-analysis of the regional and age-related differences of atopic dermatitis clinical characteristics. J Am Acad Dermatol. 2019;80(2):390-401.

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Heterogeneous symptoms of dermatitis

Itch*

Skin pain*

Sleep disturbance*

Anxiety*

Depression*

Dryness

Redness

Oozing / weeping

Frequency of symptoms

Intensity of symptoms

***Predictors of patient-reported global AD severity**

Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Simpson EL, Ong PY, Chiesa Fuxench ZC. Patient-burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Annals of Allergy, Asthma and Immunology. 2018. 121(3):340-347.
Silverberg JI, Chiesa Fuxench ZC, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Simpson EL, Ong PY. Content and construct validity, predictors, and distribution of self-reported atopic dermatitis severity in US adults. Annals of Allergy, Asthma and Immunology. 2018 Dec;121(6):729-734.

Heterogeneous Longitudinal course of AD

- Prospective real-world dermatology practice-based longitudinal study (n=463)
- Patients were assessed at baseline, 6, 12, 18, and 24 months by Numeric Rating Scale (NRS) worst and average-itch
- Among patients with baseline moderate (4-6) or severe (7-10) NRS average-itch scores, 21.2% and 16.3% continued to have moderate or severe scores at ≥1 follow-up visits

Hong MR, Lei D, Yousaf M, Chavda R, Gabriel S, Janmohamed SR, Silverberg JI. A real-world study of the longitudinal course of itch severity and frequency in adults with atopic dermatitis. Archives of Dermatological Research. 2022 Mar;314(2):141-149.

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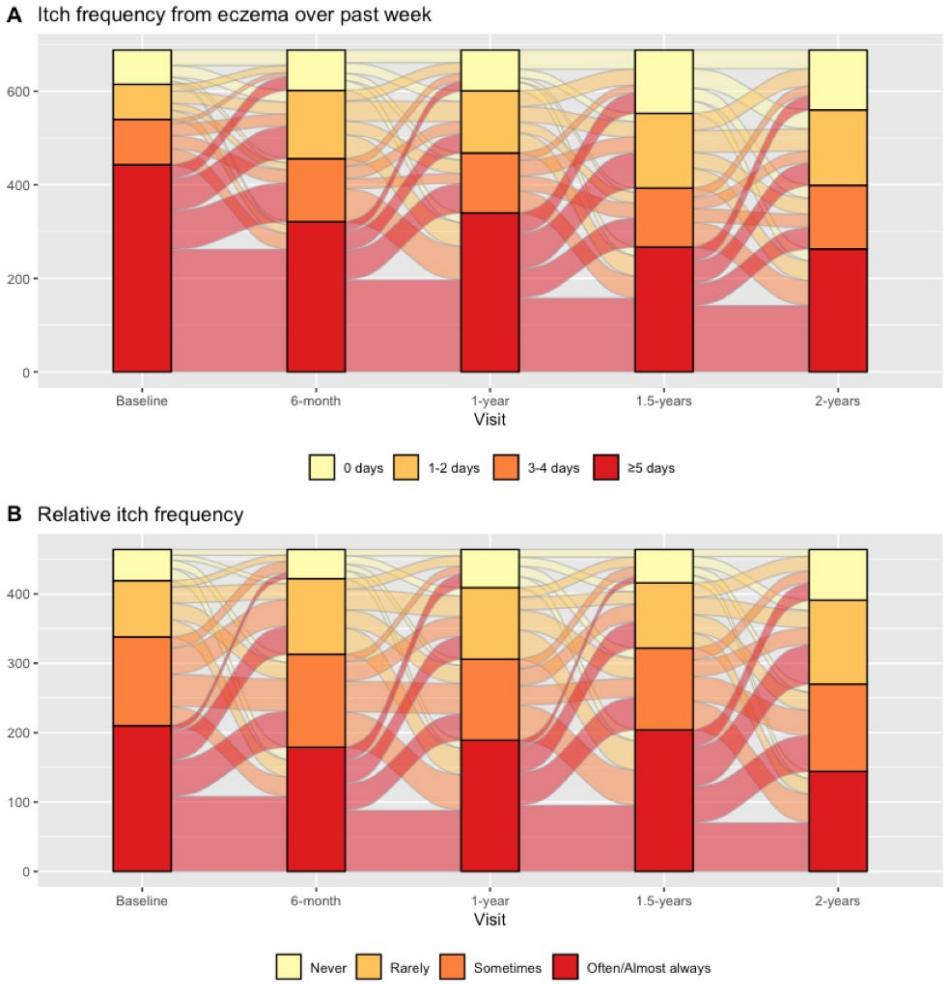
Heterogeneous Longitudinal course of AD

- 65.3% had persistent, 28.6% had fluctuating, and 6.1% had sustained improvement of NRS average-itch score categories at all follow-up visits
- Similarly, 73.5% had persistent, 22.4% had fluctuating, and 4.1% had sustained improvement of NRS worst-itch score categories at all follow-up visits



Hong MR, Lei D, Yousaf M, Chavda R, Gabriel S, Janmohamed SR, Silverberg JI. A real-world study of the longitudinal course of itch severity and frequency in adults with atopic dermatitis. Archives of Dermatological Research. 2022 Mar;314(2):141-149.

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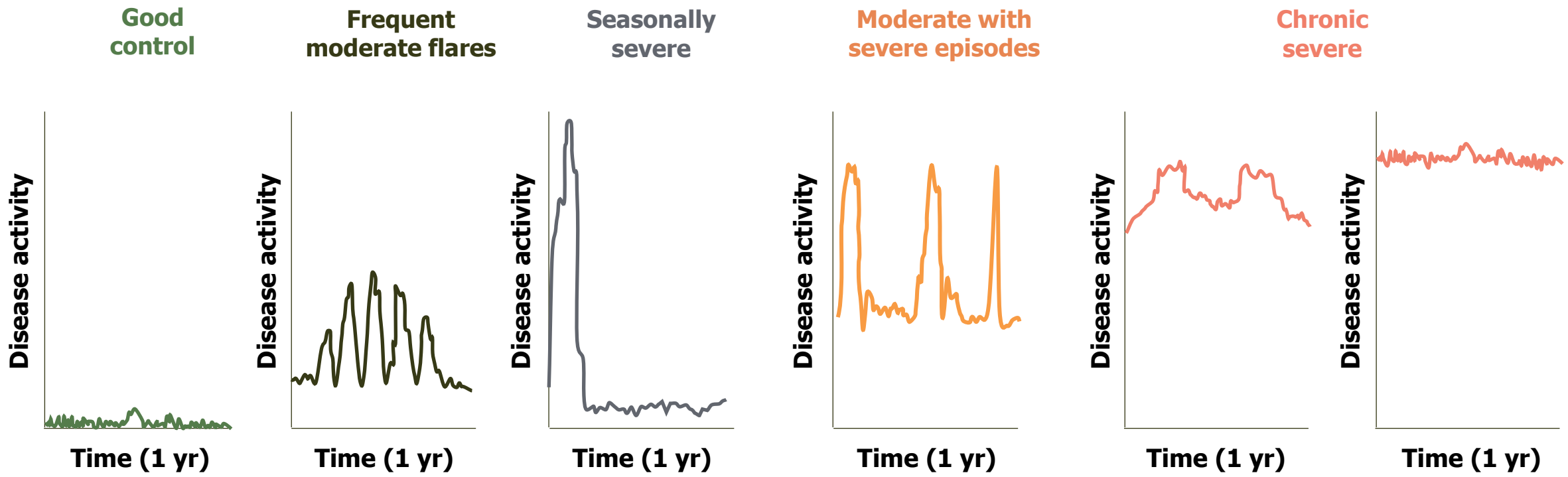
Heterogeneous Longitudinal course of AD

- Severity assessments are “snapshot” assessments
- They are fluid and can change at each visit



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Phenotyping AD by severity of itch and lesions

- Prospective Study (n=592 adult AD patients)
- Four AD subsets were defined using verbal rating scale for average-itch combined with either EASI, objective-SCORAD or vIGA-AD as follows:

1. Mild-moderate itch and lesions (MI/ML)
2. Mild-moderate itch and severe lesions (MI/SL)
3. Severe itch and mild-moderate lesions (SI/ML)
   a.k.a. itch-dominant
4. Severe itch and lesions (SI/SL)

Chovatiya R, Lei D, Ahmed A, Chavda R, Gabriel S, Silverberg JI. Clinical phenotyping of atopic dermatitis using combined itch and lesional severity: A prospective observational study. Annals of Allergy, Asthma and Immunology. 2021 Jul;127(1):83-90.

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Phenotyping AD by severity of itch and lesions

- Most patients had MI/ML (59.4-62.3%), followed by SI/ML (itch-dominant 21.3%-29.1%), SI/SL (6.0%-12.9%), and MI/SL (3.8%-6.4%)
- SI/ML (itch-dominant AD) was more common in females and blacks
- Patients with MI/SL or SI/ML (itch-dominant AD) described their AD as being more severe (PtGA) and had poor QOL scores; patients with SI/SL were most likely to describe their disease as severe and have poor QOL
- Patients with SI/ML (itch-dominant AD) had significantly more severe PGA scores; patients with MI/SL or SI/SL were far more likely to be rated with severe PGA scores

Chovatiya R, Lei D, Ahmed A, Chavda R, Gabriel S, Silverberg JI. Clinical phenotyping of atopic dermatitis using combined itch and lesional severity: A prospective observational study. Annals of Allergy, Asthma and Immunology. 2021 Jul;127(1):83-90.

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Phenotyping AD by severity of itch and lesions

- Baseline MI/SL, SI/ML (itch-dominant AD) and SI/SL were associated with similar:
  - Frequency of AD flares
  - Periods of AD clearance/remission
  - More itch-triggers
  - Longitudinal courses over time
- Most SI/SL (57.8%-66.7%) and MI/SL (53.9%-57.7%), but fewer MI/ML (36.7%-38.4%) and SI/ML (itch-dominant AD, 30.8%-32.0%) patients initiated systemic, biologic or phototherapy for their AD during follow-up

Chovatiya R, Lei D, Ahmed A, Chavda R, Gabriel S, Silverberg JI. Clinical phenotyping of atopic dermatitis using combined itch and lesional severity: A prospective observational study. Annals of Allergy, Asthma and Immunology. 2021 Jul;127(1):83-90.

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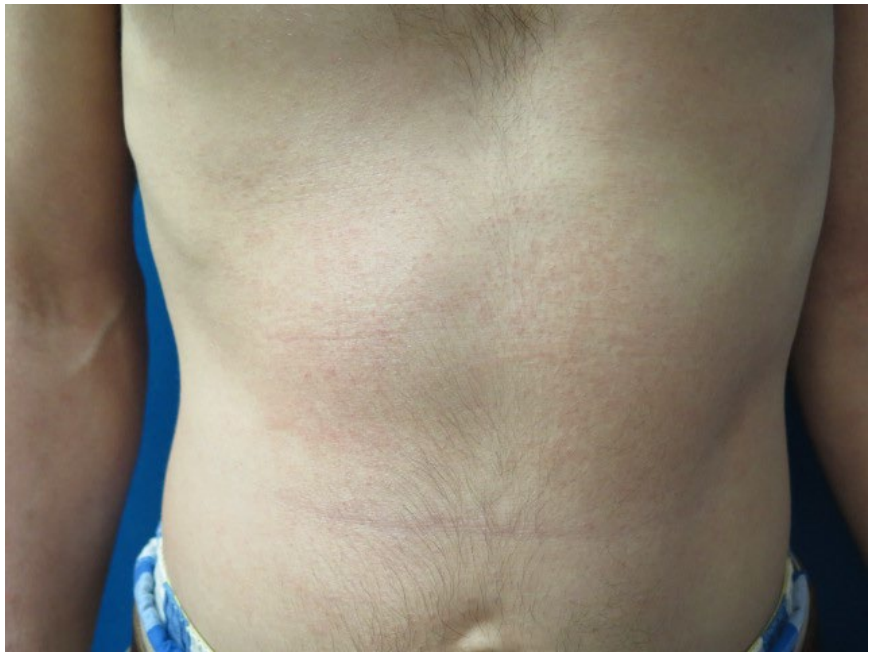
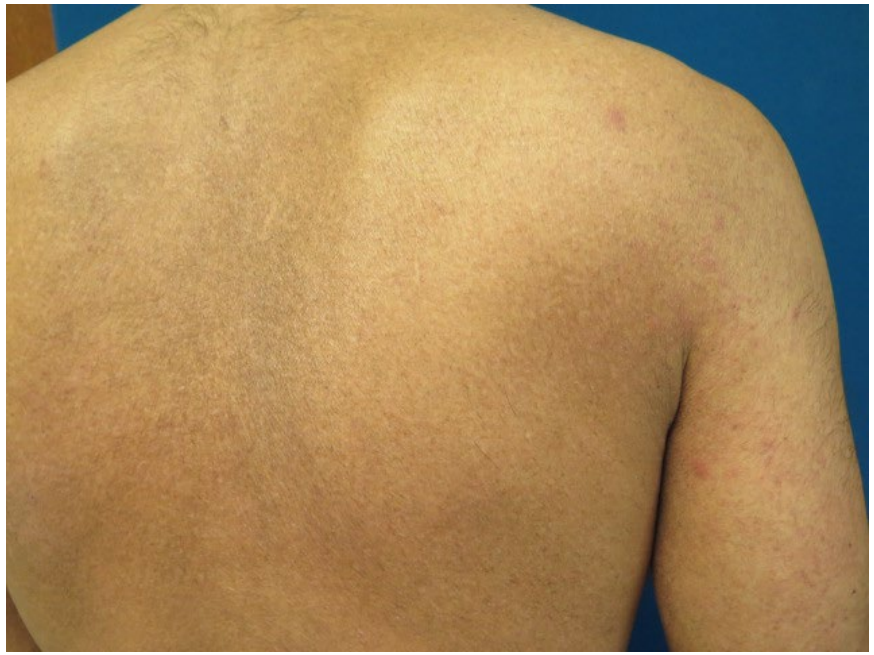
Examples





Why should we care about itch-dominant AD?

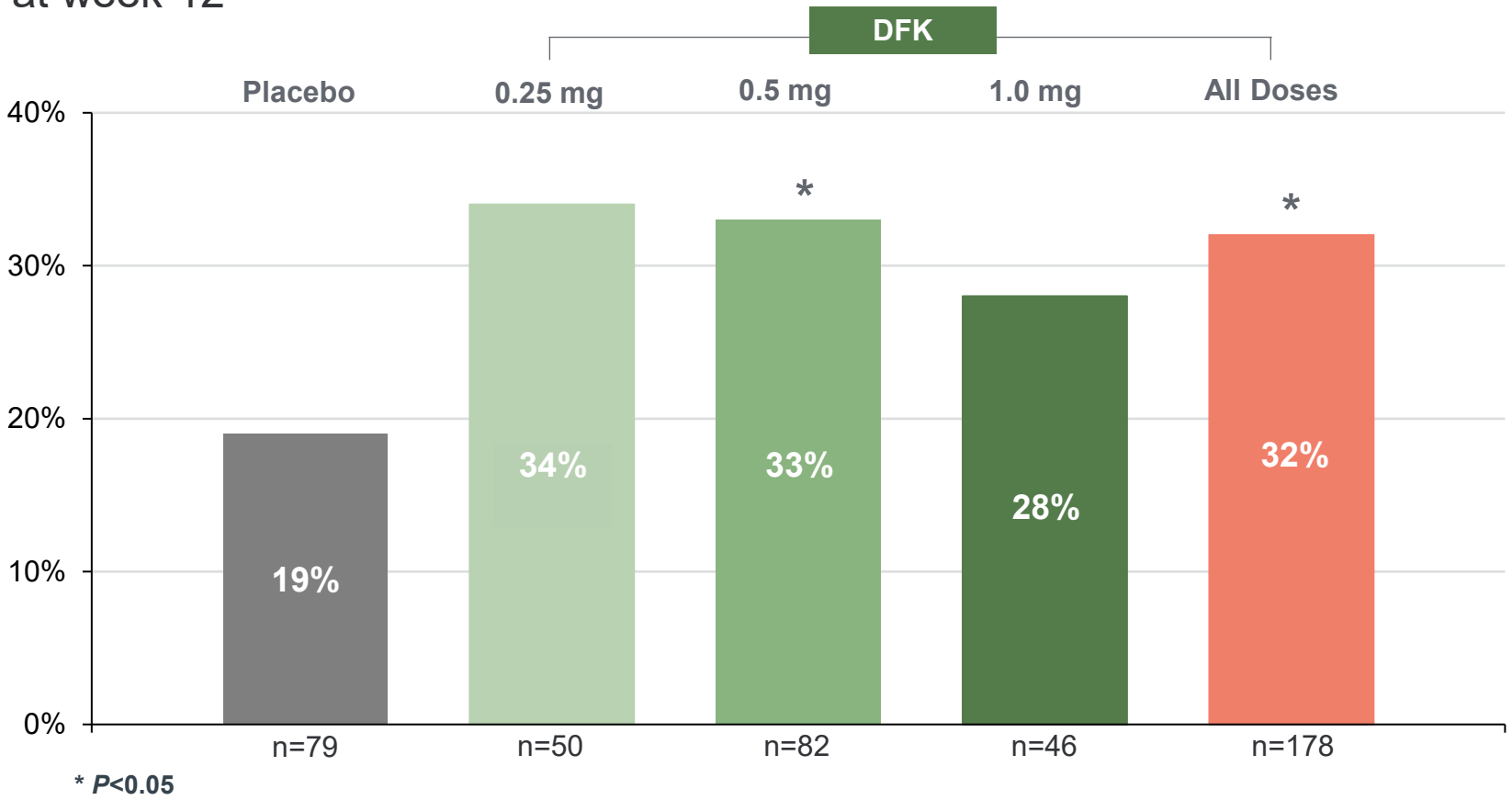
- Itch-dominant AD is a previously unrecognized subset of AD patients
- This subset would be almost entirely missed by physical examination alone
- It is essential to ask all patients about the severity of their itch in clinical practice
- Differences of itch-dominant AD by race may be due to limitations of ClinROMs at assessing lesional severity in skin of color

Why should we care about itch-dominant AD?

- This subset of patients has not been well-studied in clinical trials
- Regulatory definitions for disease subsets are mild-moderate or moderate-severe and defined by lesional severity
- These patients experience a high burden and poor disease control over time indicating unmet needs with respect to treatment
- Many unanswered questions about optimal management…
  - Topical?
  - Systemic anti-itch?
  - Systemic anti-inflammatory

BSA <10% Population (Itch-Dominant AD) 4-Point Responder Analysis at Week 12

- A significantly greater proportion of subjects achieved ≥4-point improvement in daily I-NRS with DFK vs placebo at week 12



 P values vs placebo. Estimated por percentage and P value based on a logistic regression model with terms for treatment group and baseline I-NRS score. Subjects who discontinued early or who took rescue medication or have missing data at week 12 are considered nonresponders.

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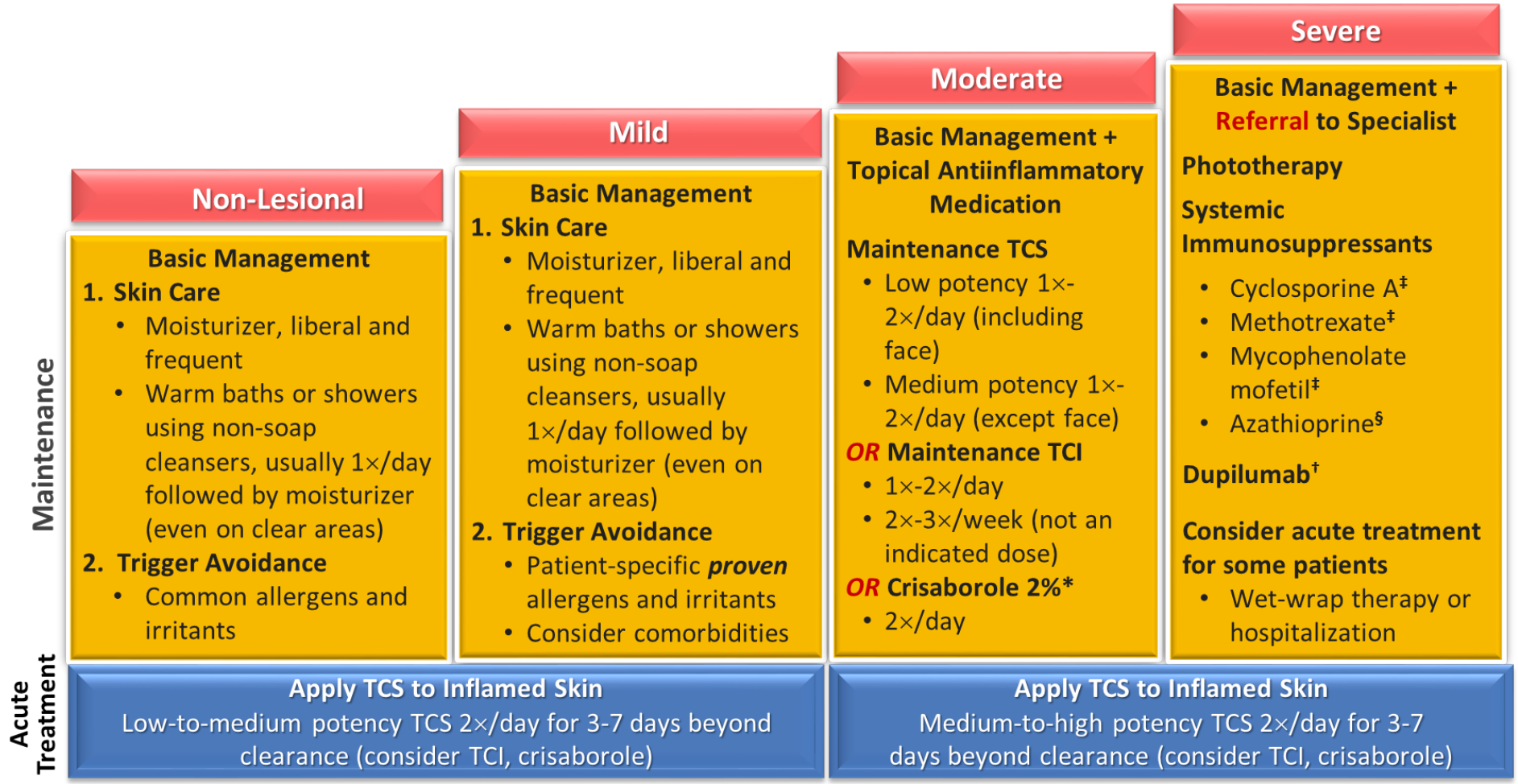
Step-up approach to management



Adapted from: Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg JI, Farrar JR. Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape. Ann Allergy Asthma Immunol. 2018. 120: 10–22.

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Thank you