Topical Anti- Inflammatory Drugs

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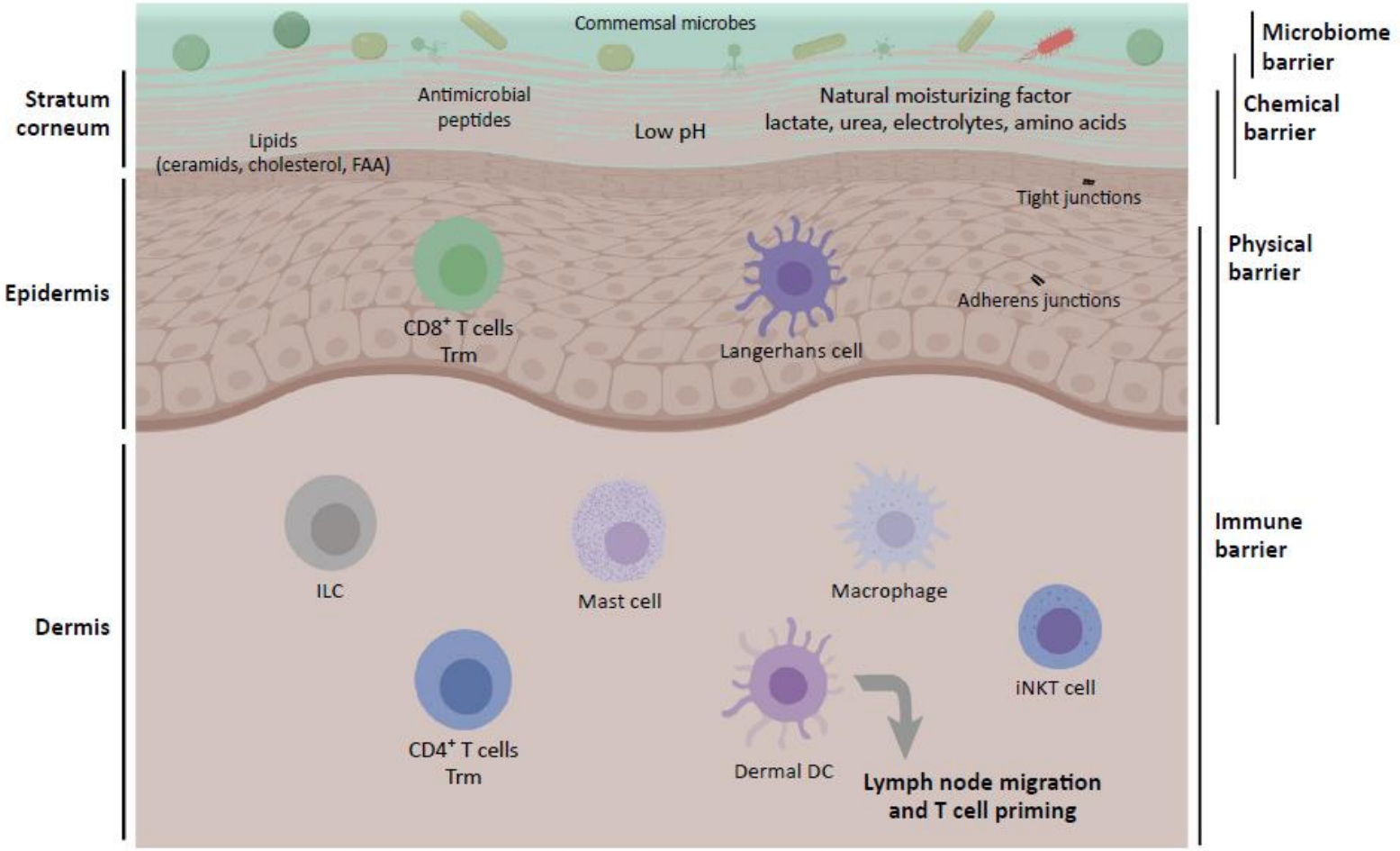
Tehran University of Medical Sciences (TUMS)

Skin barrier: A connected network



Barrier disruption

- Inflammation
- Allergy
- Infections
- Cancer

Gell & Coombs Hypersensitivity reactions

- Type 1: Ig E mediated
- Type II: Auto antibody
- Type III: Immune complex
- Type IV: Cell mediated

Inflammatory Skin Diseases

DOI: 10.1111/jdv.14673 JEADV

REVIEW ARTICLE

Immune response patterns in non-communicable inflammatory skin diseases

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[2]ZAUM – Center of Allergy and Environment, Technical University and Helmholtz Center Munich, Munich, Germany
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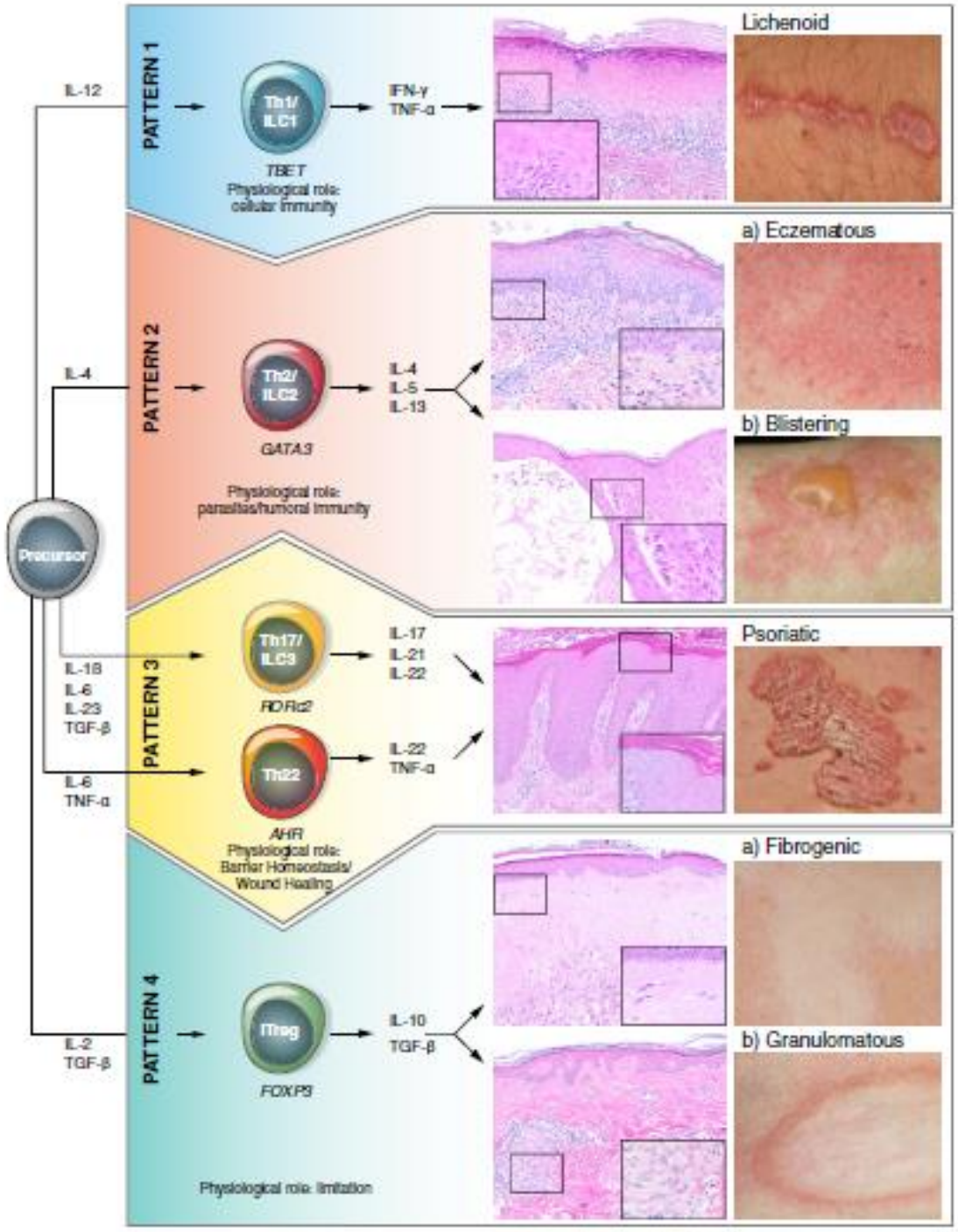
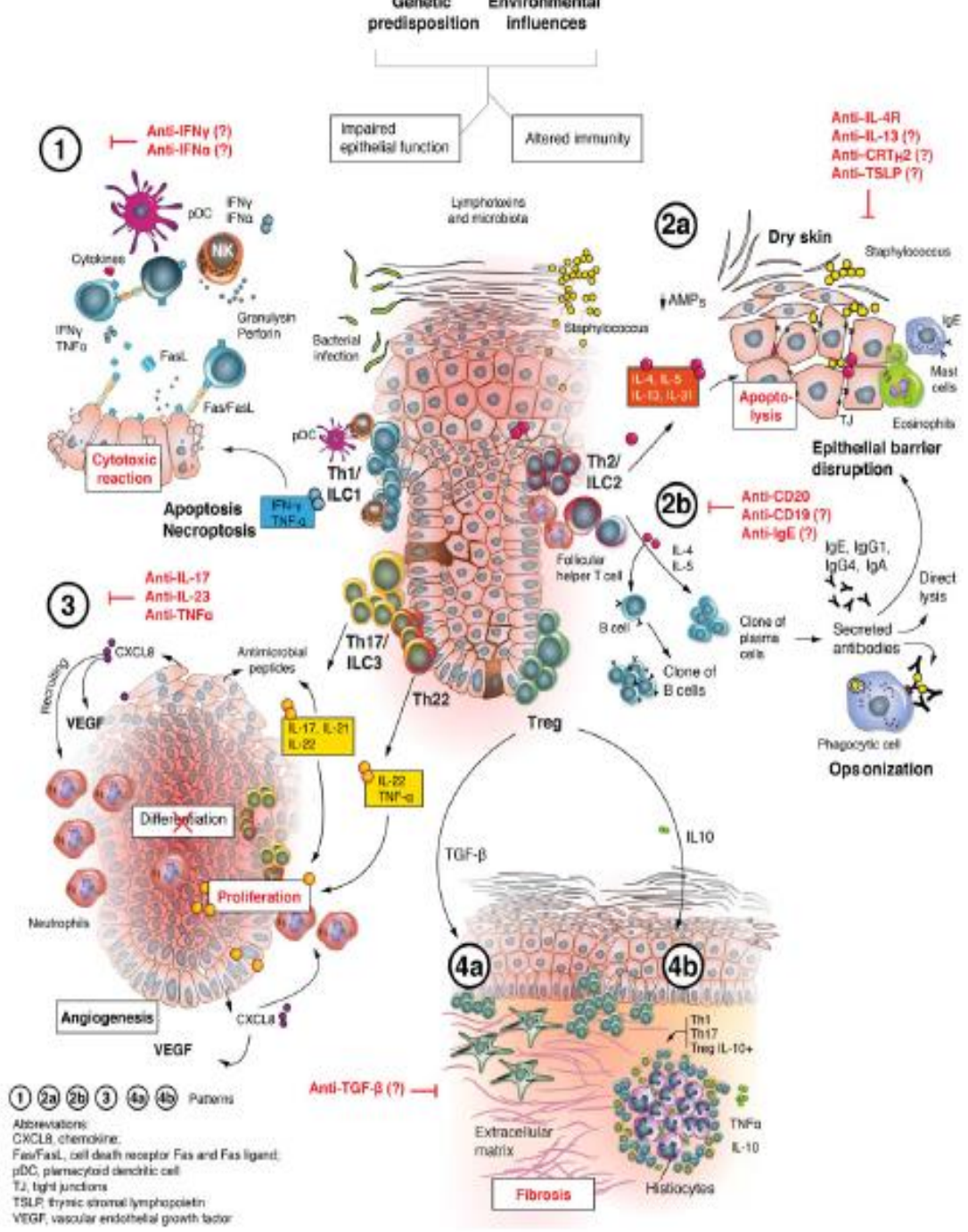

PATTERN 1
IL-12
Th1/
ILC1
TBET
Physiological role:
cellular Immunity
IFN-γ
TNF-α
Lichenoid
PATTERN 2
IL-4
Th2/
ILC2
GATA3
Physiological role:
parasitic/humoral Immunity
IL-4
IL-5
IL-13
a) Eczematous
b) Blistering
Precursor
PATTERN 3
IL-1β
IL-6
IL-23
TGF-β
Th17/
ILC3
RORc2
IL-17
IL-21
IL-22
Psoriatic
IL-6
TNF-α
Th22
AHR
Physiological role:
Barrier Homeostasis/
Wound Healing
IL-22
TNF-α
PATTERN 4
IL-2
TGF-β
iTreg
FOXP3
IL-10
TGF-β
a) Fibrogenic
b) Granulomatous
Physiological role: limitation

Targeted immunotherapy



Topical Anti- Inflammatory Drugs

- Corticosteroids
- Calcineurin inhibitors
- JAK inhibitors
- PDE inhibitors
- Opioids
- Traditional medicine

CS Potency

- Corticosteroid molecule
- Salt
- Concentration
- Vehicle

Potency	Class	Topical corticosteroid	Formulation
Ultra high	I	Clobetasol propionate	Cream, 0.05%
		Halobetasol	Cream, 0.05%
High	II	Betamethasone dipropionate	Ointment, 0.05%
		Desoximetasone	Cream or ointment, 0.025%
		Fluocinonide	Cream, ointment or gel, 0.05%
		Halcinonide	Cream, 0.1%
		Mometasone furoate	Ointment, 0.1%
	III	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Fluticasone propionate	Ointment, 0.005%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	IV	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	V	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Hydrocortisone butyrate	Cream, 0.1%
		Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Clobetasol butyrate	Cream 0,05%
		Fluocinolone acetonide	Solution, 0.01%
	VII	Hydrocortisone acetate	Cream, 1%

WHO Model Prescribing Information: Drugs Used in Skin Diseases. Classification of Topical Corticosteroids. Geneva: World Health Organization; 1997. p. 117-8. Available from: http://www.apps.who.int/medicinedocs/en/d/Jh2918e/32.html#Jh2918e. 32.1. [Last accessed on 2016 May 25]

Topical Anti- Inflammatory Drugs

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- Topical calcineurin inhibitors (TCI) are a relatively new class of drugs used in dermatology.
- There are two drug forms available - tacrolimus 0.03% or 0.1% ointment and 1.0% pimecrolimus cream.
- Tacrolimus and pimecrolimus, were approved by the US Food and Drug Administration (FDA) for the treatment of Atopic Dermatitis in 2001 and 2002.
- The drugs act by inhibiting synthesis of proinflammatory cytokines.
- Topical calcineurin inhibitors do not cause skin atrophy and the drug absorption through the skin is minimal.
- The anti-inflammatory potency of tacrolimus ointment is similar to a corticosteroid with moderate activity, while the latter is clearly more active than pimecrolimus cream.

Safety of TCI

- Long term safety is much better than CS
- Most common side effect is local irritation
- US Food and Drug Administration black box warning for risk of cancers in 2006

Research

JAMA Dermatology | Original Investigation

Association Between Topical Calcineurin Inhibitor Use and Keratinocyte Carcinoma Risk Among Adults With Atopic Dermatitis

Maryam M. Asgari, MD, MPH; Ai-Lin Tsai, MA; Lyndsay Avalos, PhD, MPH; Monica Sokil, BS; Charles P. Quesenberry Jr, PhD

- The results of this postmarketing surveillance study of adult health plan members with AD revealed no apparent association between TCI exposure and overall KC, BCC, or SCC risk.
- Secondary analyses examining dose, frequency, and duration of TCI exposure revealed no associations.
- These findings suggest that use of TCIs may be safe with respect to KC risk among adults with AD

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Janus Kinases (JAKs)

- Tyrosine kinase of the Janus family, better known as JAKs, were shown to be a critical step in several immune functions.
- This family comprises four molecules, namely JAK1, JAK2, JAK3, and TYK2.

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Journal of Dermatological Treatment

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Janus kinase (JAK) inhibitors for the treatment of skin and hair disorders: a review of literature

Aniseh Samadi, Saman Ahmad Nasrollahi, Ashkan Hashemi, Mansour Nassiri Kashani & Alireza Firooz

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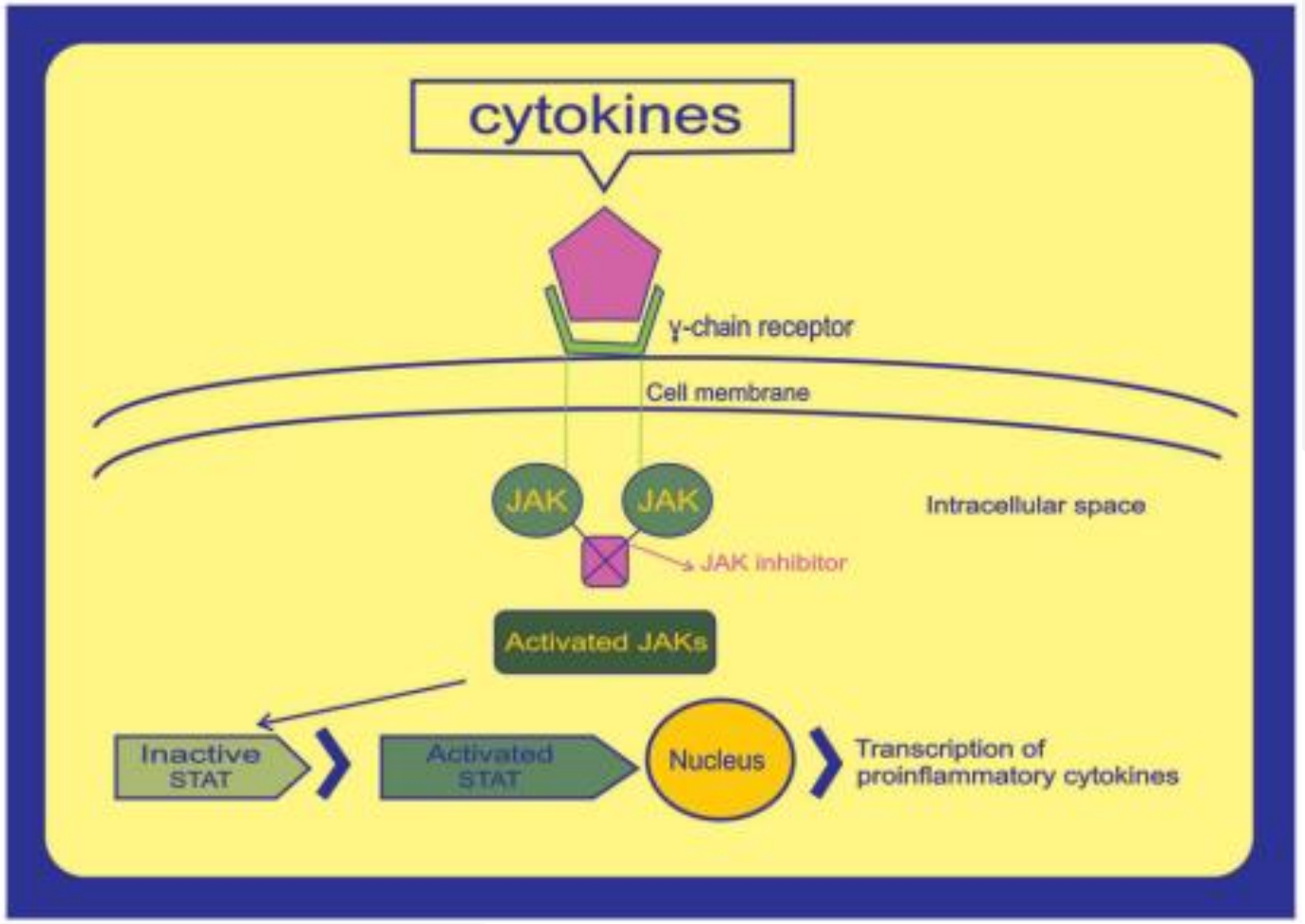
cytokines
γ-chain receptor
Cell membrane
JAK
JAK
Intracellular space
JAK inhibitor
Activated JAKs
Inactive STAT
Activated STAT
Nucleus
Transcription of proinflammatory cytokines

JAK inhibitors

- Baricitinib: selective JAK1 and JAK2 inhibitor
- Abrocitinib: selective JAK1 inhibitor
- Upadacitinib: selective JAK1 inhibitor
- Tofacitinib: JAk1/3 inhibitor
- Ruxolitinib: JAK 1 and 2 inhibitor

Indications of topical JAKi

- The FDA's September 21, 2021 approval of ruxolitinib gave the dermatology community the first and only topical Janus kinase [JAK] inhibitor in the United States for short-term, non-continuous treatment of mild to moderate atopic dermatitis (AD).
- It is approved for use by non-immunocompromised patients 12 years and older whose disease is not adequately controlled with topical prescription therapies or if those therapies are not advisable

$2,045 for a supply of 60 grams

NIMAD research grant

- Clinical study of **topical** nanoliposome formulation of **ruxolitinib** 1.5% in treatment of mild to moderate atopic dermatitis
- Study aim: Evaluation of clinical efficacy of **topical** formulation of **ruxolitinib** 1.5% in treatment (...) group: **Topical** use of emulgel of nanoliposomes contain **ruxolitinib** 1.5 percent produced by lipid film (...) participate in the study and complete the consent form are entered in the study.
- IRCTID: IRCT20161207031288N9

Papp *et al. BMC Dermatology* (2016) 16:15
DOI 10.1186/s12895-016-0051-4

BMC Dermatology

RESEARCH ARTICLE Open Access

Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor, tofacitinib: a Phase 2b randomized clinical trial

Kim A. Papp[1], Robert Bissonnette[2], Melinda Gooderham[3], Steven R. Feldman[4], Lars Iversen[5], Jennifer Soung[6], Zoe Draelos[7], Carla Mamolo[8], Vivek Purohit[8], Cunshan Wang[8] and William C. Ports[8*]

CLINICAL TRIALS

BJD
British Journal of Dermatology

Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial

R. Bissonnette,[1] K.A. Papp,[2] Y. Poulin,[3] M. Gooderham,[4] M. Raman,[5] L. Mallbris,[6] C. Wang,[7] V. Purohit,[7] C. Mamolo,[7] J. Papacharalambous[7] and W.C. Ports[7]

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[5]The Centre for Dermatology and Probity Medical Research Inc., Richmond Hill, ON, Canada
[6]Pfizer Inc., Collegeville, PA, U.S.A.
[7]Pfizer Inc., Groton, CT, U.S.A.

Linked Comments: Damsky and King. *Br J Dermatol* 2016; 175:861–862

Preliminary clinical activity of a topical JAK1/2 inhibitor in the treatment of psoriasis

Naresh Punwani, PhD,[a] Peggy Scherle, PhD,[a] Robert Flores, BSN,[a] Jack Shi, PhD,[a] Jinjin Liang, PhD,[a] Swamy Yeleswaram, PhD,[a] Richard Levy, MD,[a] William Williams, MD,[a] and Alice Gottlieb, MD, PhD[b]
Wilmington, Delaware, and Boston, Massachusetts

Background: Janus-associated kinases (JAKs) are involved in signal transduction from a variety of cytokines implicated in the pathogenesis of psoriasis, including interleukin (IL)-12, IL-23, and interferon-γ. INCB018424, a small molecule inhibitor of JAK1 and JAK2, inhibits cytokine-induced JAK/signal transducers and activators of transcription signaling and the resultant production of inflammatory proteins (eg, IL-17).

Objective: We sought to demonstrate proof of concept in patients with stable plaque psoriasis.

Methods: Patients were dosed with vehicle, 0.5% or 1.0% INCB018424 phosphate cream once a day or 1.5% twice a day for 28 days. Additional groups included two active comparators (calcipotriene 0.005% cream or betamethasone dipropionate 0.05% cream).

Results: Both the 1% and the 1.5% cream improved lesion thickness, erythema, and scaling and reduced lesion area compared with placebo. A composite lesion score decreased by greater than 50% with the efficacious doses of INCB018424 compared with 32% for vehicle controls. Topical application of INCB018424 was well tolerated with few mild adverse events noted. Mean plasma concentrations of INCB018424 after topical application of 0.5% to 1.5% cream were in the low nanomolar range, representing a fraction (<1%) of the half maximal inhibitory concentration (IC_{50}) in whole blood for inhibition of cytokine-stimulated signal transducers and activators of transcription-3 phosphorylation.

Limitations: This study was limited by the relatively short study duration and small sample size.

Conclusion: Topical INCB018424 is safe, is well tolerated, and exhibits clinical activity in the topical treatment of psoriasis. (J Am Acad Dermatol 2012;67:658-64.)

Key words: INCB018424; Janus-associated kinase inhibitor; psoriasis.

FDA Black Box

- The US Food and Drug Administration (FDA) has announced additional box warnings for certain janus kinase (JAK) inhibitors following a study linking tofacitinib (Xeljanz and Xeljanz XR, respectively) to an increased risk of serious heart-related events such as heart attack, stroke, cancer, blood clots, and death.
- Risk factors: age > 50 y, personal or family history of malignancy, smoking, presence of > 1 cardiac risk factors (hypertension, hyperlipidemia, diabetes)

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(PDE) 4 inhibitors

- Blocking PDE4 increases intracellular adenosine monophosphate levels resulting in a downregulation of proinflammatory cytokines such as IL-2, IL-5, IL-13 and increased production of the regulatory cytokine IL-10.
  - Topical Crisaborole
  - Oral Apremilast

Crisaborole

- EUCRISA™ ointment (by Anacor), 2%, for topical use
- Initial U.S. FDA Approval: 2016
- A phosphodiesterase 4 inhibitor indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.
- Efficacy results were seen in some patients as early as day eight.
- The most common adverse reaction occurring in ≥1% in subjects is application site pain.
- However, the efficacy of crisaborole in comparison with TCI or TCS is difficult to determine.

Research

JAMA Dermatology | Original Investigation

Application of Topical Phosphodiesterase 4 Inhibitors in Mild to Moderate Atopic Dermatitis

A Systematic Review and Meta-analysis

Huan Yang, MD; Ji Wang, MD; Xin Zhang, MD, PhD; Yan Zhang, MD; Zi-li Qin, MD; Hua Wang, MD, PhD; Xiao-yan Luo, MD, PhD

- Seven studies were identified, which included 1869 patients with mild to moderate AD.
- Overall, compared with the topical vehicle control, topical application of PDE4 inhibitors was associated with a significant decrease in target lesion score and a higher response rate in investigators’ assessment of clear or almost clear skin
- There was no difference in treatment-related adverse events or in adverse events that required discontinuation of therapy.

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DOI: 10.1111/dth.15150

DERMATOLOGIC THERAPY WILEY

REVIEW ARTICLE

Topical opioid use in dermatologic disease: A systematic review

Yasmin Gutierrez[1] | Sarah P. Pourali[2] | Alison H. Kohn[3] |
Madison E. Jones[4] | Jeffrey R. Rajkumar[5] | April W. Armstrong[4]

Opioids

- Topical opioids are thought to provide a local analgesic effect by binding to peripheral opioid receptors induced by adjacent inflammation
- This study analyzed data from 14 articles and 263 patients on the use of topical opioids for pain related to chronic ulcers, burns, oral lichen planus, photodynamic therapy, and split-thickness skin grafts.
- Topical opioids included in this review were topical morphine and diamorphine. Common formulations consisted of 0.2–10 mg of opioid compounded with hydrogel or IntraSite gel.
- The use of topical opioids appears to be effective in the reduction of pain related to pressure ulcers.
- Topical opioids were generally well tolerated.
- Insufficient data exist to adequately evaluate the efficacy and safety of topical opioid use in the context of nonpressure ulcers, burns, oral lichen planus, photodynamic therapy, and split-thickness skin grafts.

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CED CLINICAL AND EXPERIMENTAL DERMATOLOGY
THE EDUCATIONAL JOURNAL OF THE BRITISH ASSOCIATION OF DERMATOLOGISTS

Review article

Dermatological effects of *Curcuma* species: a systematic review

S. M. Barbalho ✉, H. F. de Sousa Gonzaga, G. A. de Souza, R. de Alvares Goulart, M. L. de Sousa Gonzaga, B. de Alvarez Rezende

First published: 31 January 2021 | **https://doi.org/10.1111/ced.14584** | Citations: 2

Curcuma

- This search included papers published in the past 10 years in controlled clinical trials, double-blind and randomized controlled studies, and case studies.
- The search resulted in 12 studies published in the past 10 years.
- *Curcuma* species (*Curcuma longa* and *Curcuma aeruginosa*) and curcumin were found to produce various dermatological effects, including influencing antioxidant and anti-inflammatory processes in the production of hyaluronan, increasing skin moisture, and reducing axillary hair growth.

Curcuma

- Curcuma was also found to reduce thickness, erythema, pruritus, burning and pain in psoriasis lesions and to improve radiodermatitis lesions.
- Nevertheless, more clinical trials should be conducted with humans to establish the optimum delivery method and dosages for different dermatological conditions.


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