


Atopic dermatitis

- strongly pruritic chronic or chronically relapsing non-infectious dermatitis with variable morphology and clinical course, usually starting during early childhood
- often associated with positive personal or family history of allergic rhinitis, conjunctivitis and bronchial asthma.
- genetic predisposition
- In about 80% associated with  IgE levels

Atopic dermatitis - epidemiology

Incidence in population: 0,5 - 5%
(higher incidence – scandinavian countries)

infants	20-30%
children under 2 y	15-20%
children under 14 y	15%
adults	2-10%

Atopic dermatitis usually starts early in life



Infancy¹

Onset usually between 3 and 6 months, 60% in the first year of life

Early onset form



Childhood^{2,3}

85% of childhood onset occurs before 5 years of age

70% of childhood AD does not persist by 8 years of age



Adolescence³⁻⁵

Risk factors for persistence: later onset, gender (female), severity, atopic comorbidities, family history of atopy

Sometimes AD occurs in adulthood

Late onset form

AD=atopic dermatitis

1. Eichenfeld LF, et al. J Am Acad Dermatol 2014;70(2):338-51; 2. Silverberg NB, Durán-McKinster C. Dermatol Clin 2017;35:351-63; 3. Kim JP, et al. J Am Acad Derm 2016;75:681-87 e11; 4. Wen HJ, et al. Br J Dermatol 2009;161(5):1166-72; 5. Mortz CG, et al. Allergy 2015;70(7):836-45

Atopic dermatitis

two forms, same clinical picture

extrinsic 80%

elevated IgE

sensitization to airborne
and/or food allergens (sIgE)

- **association with allergic
rhinoconjunctivitis and/or
allergic asthma**

intrinsic 20%

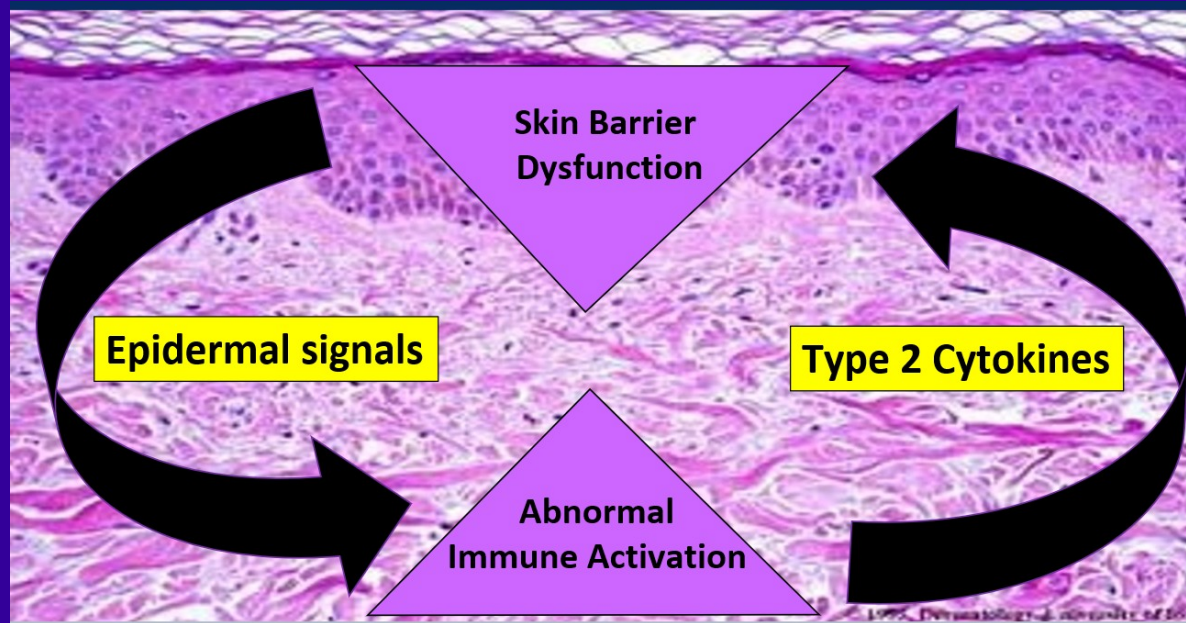
normal levels of IgE

skin barrier disturbance

Etiopathogenesis of AD:

genetic predisposition

- 1) skin barrier dysfunction
- 2) abnormal immune activation



environmental triggers:

- 1) irritant substances, allergens
- 2) stress
- 3) many others

-
-
-

I. skin barrier dysfunction

Genetically conditioned:

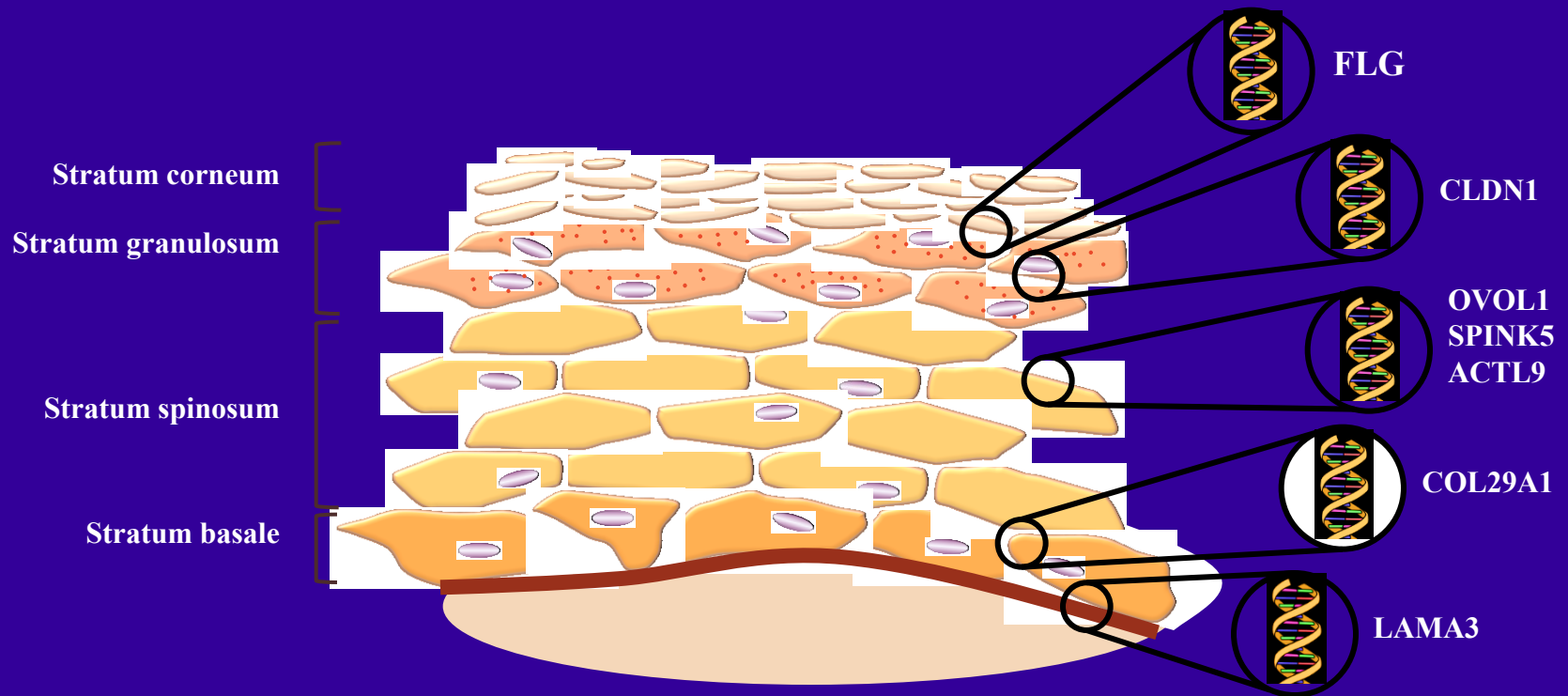
Filaggrin: null mutation of FLG R501X and 2282del4 alleles lead to increased permeability of skin barrier and they are associated with AD (in about 50% cases), as well as with ichthyosis vulgaris

Claudin - 1, corneodesmosin, loricrin, involucrin

Increased activity of serin proteases

-
-
-
-
-
-
-
-

Mutation of key genes for structural epidermal proteins



Adapted from © CFCF / https://commons.wikimedia.org/wiki/File:502_Layers_of_epidermis.jpg / CC BY 3.0

1. Hoffjan S & Stemmler S. *Arch Dermatol Res* 2015;307(8):659-70; 2. Esaki H et al. *J Allergy Clin Immunol* 2015;135(1):153-63; 3. Stemmler S et al. *BMC Dermatol* 2014;14:17; 4. Söderhäll C et al. *PLoS Biol* 2007;5(9):e242; 5. Yang T et al. *Genes Dev* 2004;18(19):2354-8; Lee B et al. *Dev Cell* 2014;29(1):47-58

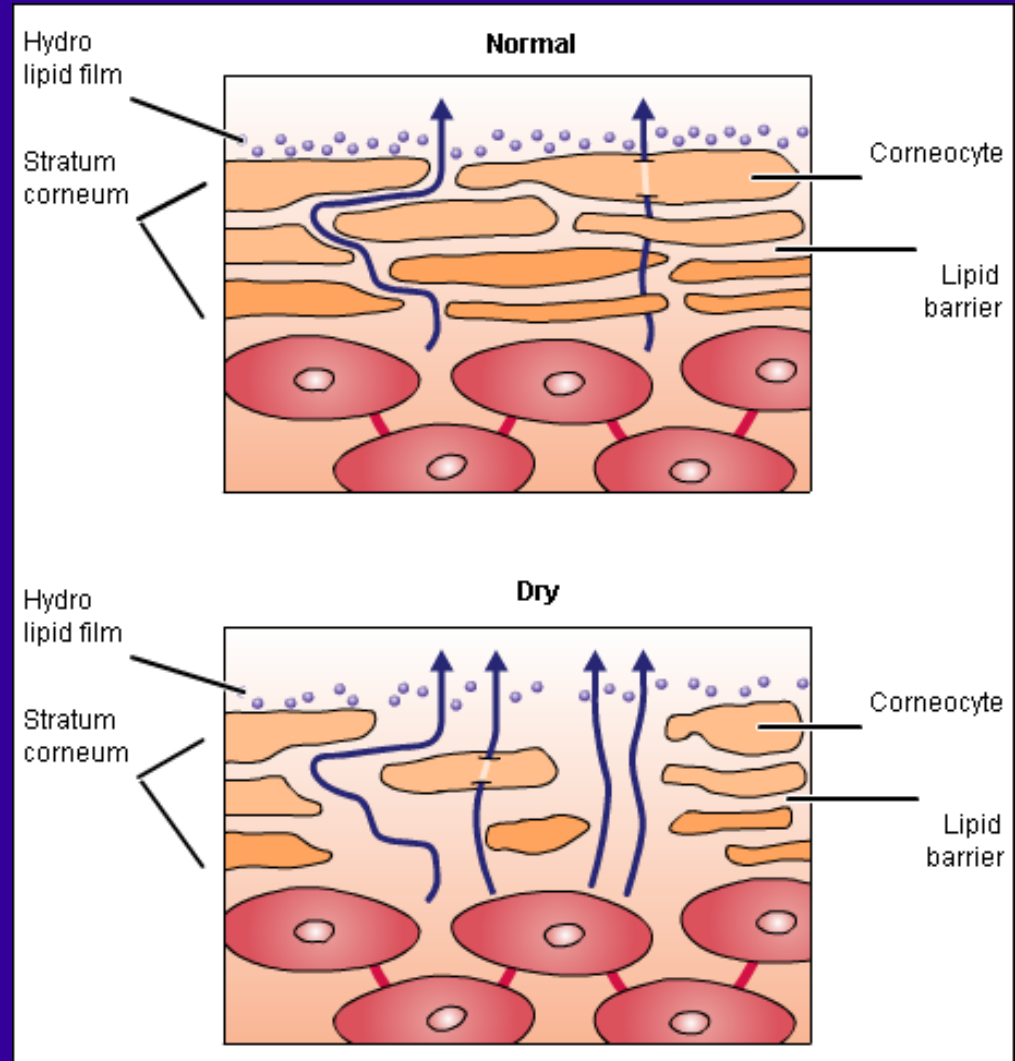
skin barrier disturbance

- defective synthesis of ceramides

(in lamellar bodies in granular layer of epidermis)



decreased ability to bind water in the skin



AD and skin barrier

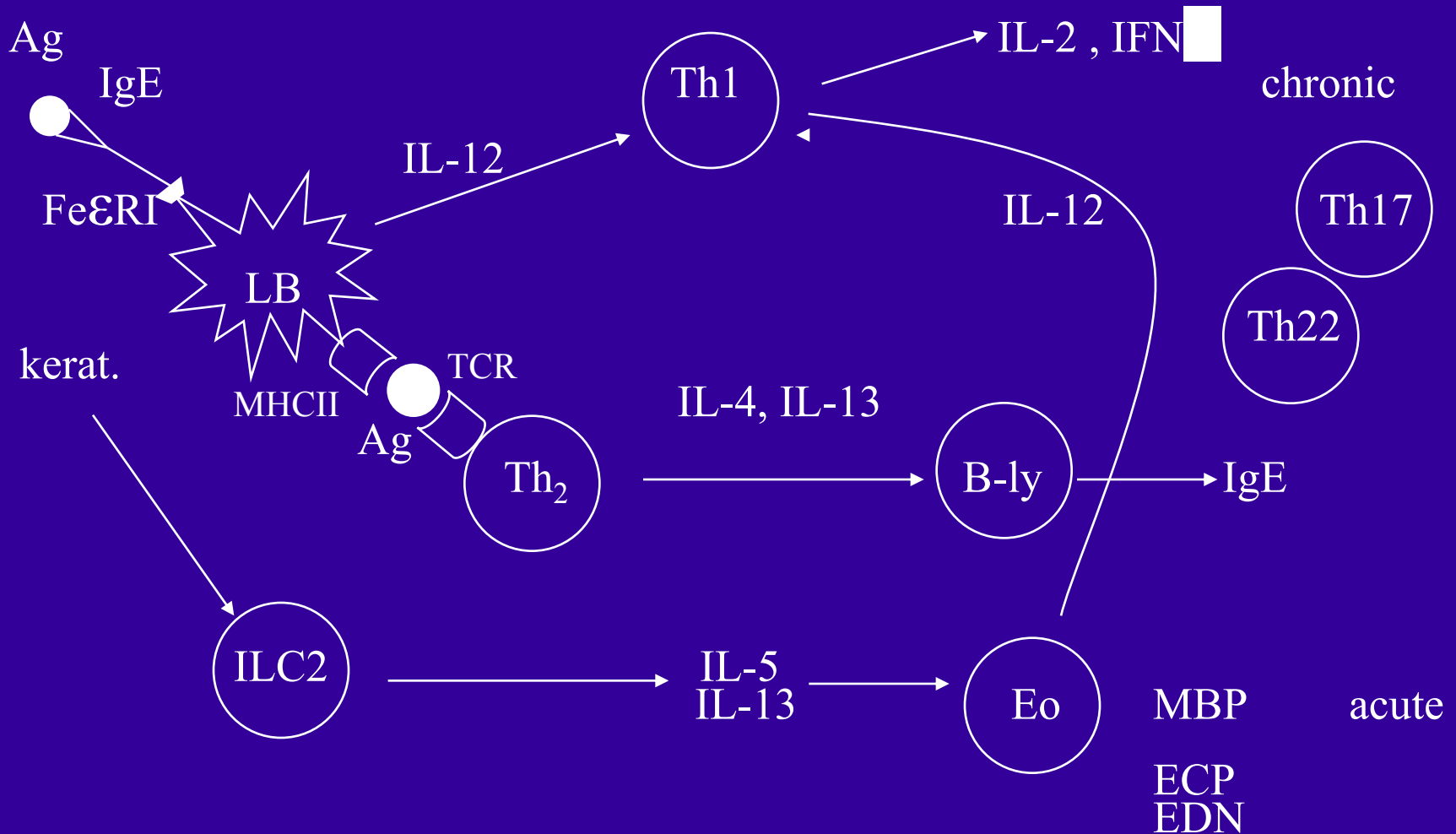
Defective structure and function of skin barrier

insufficient hydration (TEWL ↑)

dryness - xerosis

increased irritability of the skin
possibility of contact sensitization

II. Immune dysregulation



Phenotypes of AD

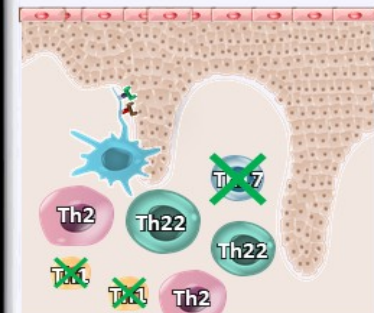
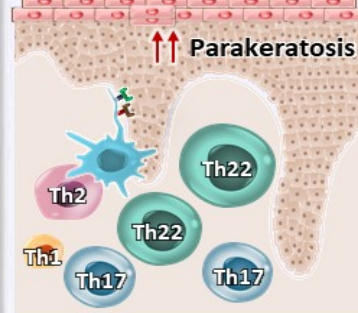
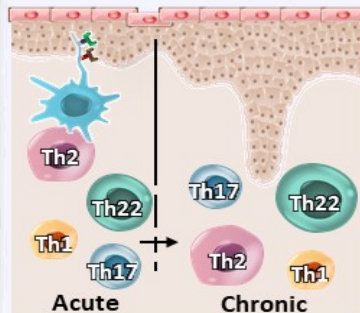
according to the activation of Th cell populations

European American AD

Asian AD

African American AD

Clinical phenotype



Th2 (Int>Ext, C>A)	↑↑↑
Th22 (Int>>Ext, C>A)	↑↑↑
Th17 (Int>>Ext, C=A)	↑
Th1 (C>>A)	↑↑

Th2	↑↑↑
Th22	↑↑↑↑
Th17	↑↑↑
Th1	↑↔

Th2	↑↑↑
Th22	↑↑
Th17	X (Absent)
Th1	X (Absent)

Epidermal thickness	↑↑
KRT16	↑↑ Int=Ext, C>A
Ki67	↑↑
FLG, LOR, PPL	↓↓↓

Epidermal thickness	↑↑↑
KRT16	↑↑↑
Ki67	↑↑↑
FLG	↓
LOR	↔

Epidermal thickness	↑↑
KRT16	↑↑
Ki67	↑↑
FLG	↔
LOR	↓↓↓

Immune polarisation

Epidermal barrier

•
•
•

III. Staphylococcus aureus and AD

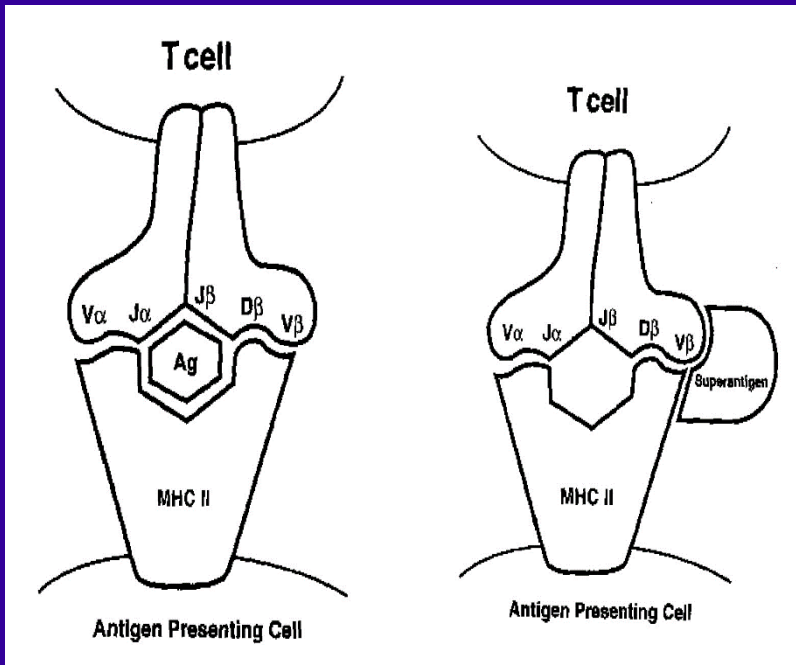
- colonization of AD lesions in 74 - 96% atopic patients, 30 - 56% even on „healthy“ skin

Mechanisms:

- Defective skin barrier with „naked“ laminin and fibronectin enables SA binding the skin
- Decreased defensive mechanisms: defective signalling via TLR 2
 - defensins and cathelicidins
 - production of IFN γ

Staphylococcus aureus and AD

- 1) Toxic effect: staphylococcal exfoliatine
- 2) Stimulation of sIgE production (sIgE → stimulation of basophils → histamine)
- 3) **superantigens**: SEA- SEE a TSST-1



- without previous processing by LC
- able to bridge V chain of TC Receptor,
- not necessary exact conformity of all 5 subunits of the receptor
- 1000x stimulation
- non-specific but huge stimulation of Tly (1 SA even 20% of circulating lymph.)

Triggering and mainaining factors of AD

Allergy (house dust mites, pollen, pets, molds, foods — milk, eggs, wheat, soya, nutts, fish)

Microbes — Staphylococcus aureus

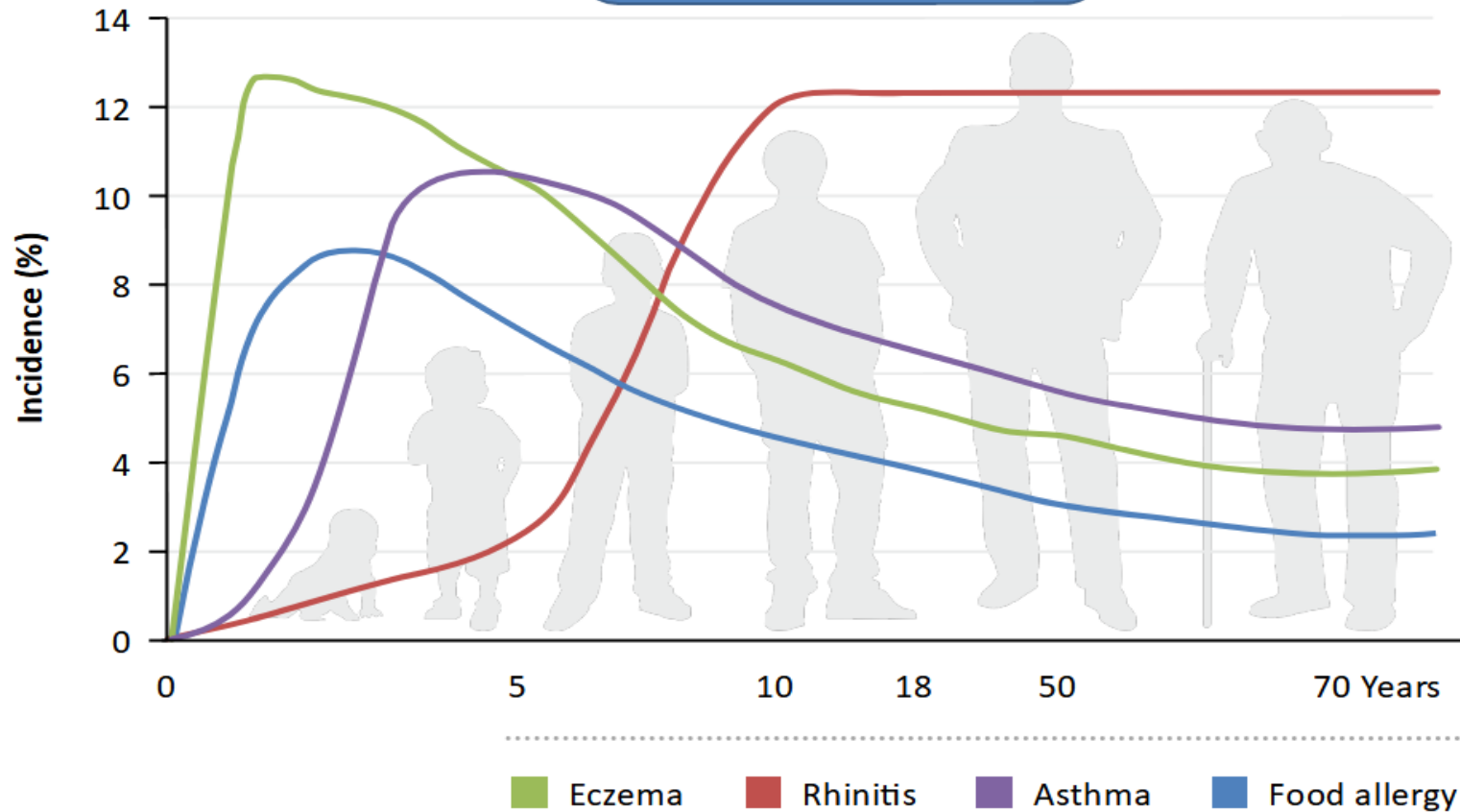
Irritant substances (water,detergents etc.)

- climatic (temperature, wind, low humidity ..)

Psychological stress

Atopic march

“Atopický pochod”



Clinical picture of AD

AD in infants

**Exudative form – acute eczema
(oozing, crusting)**

■ Location - periorally
 - periorbitally

■ Possibility of spreading - erythroderma



**Atopic dermatitis –
Infant AD**



Infant AD

Clinical picture of AD

AD in children and adolescents

Decrease of exudation - lichenification

■ most often – flexural eczema

- facial eczema

■ less often - erythroderma



**Atopic dermatitis – flexural
eczema**



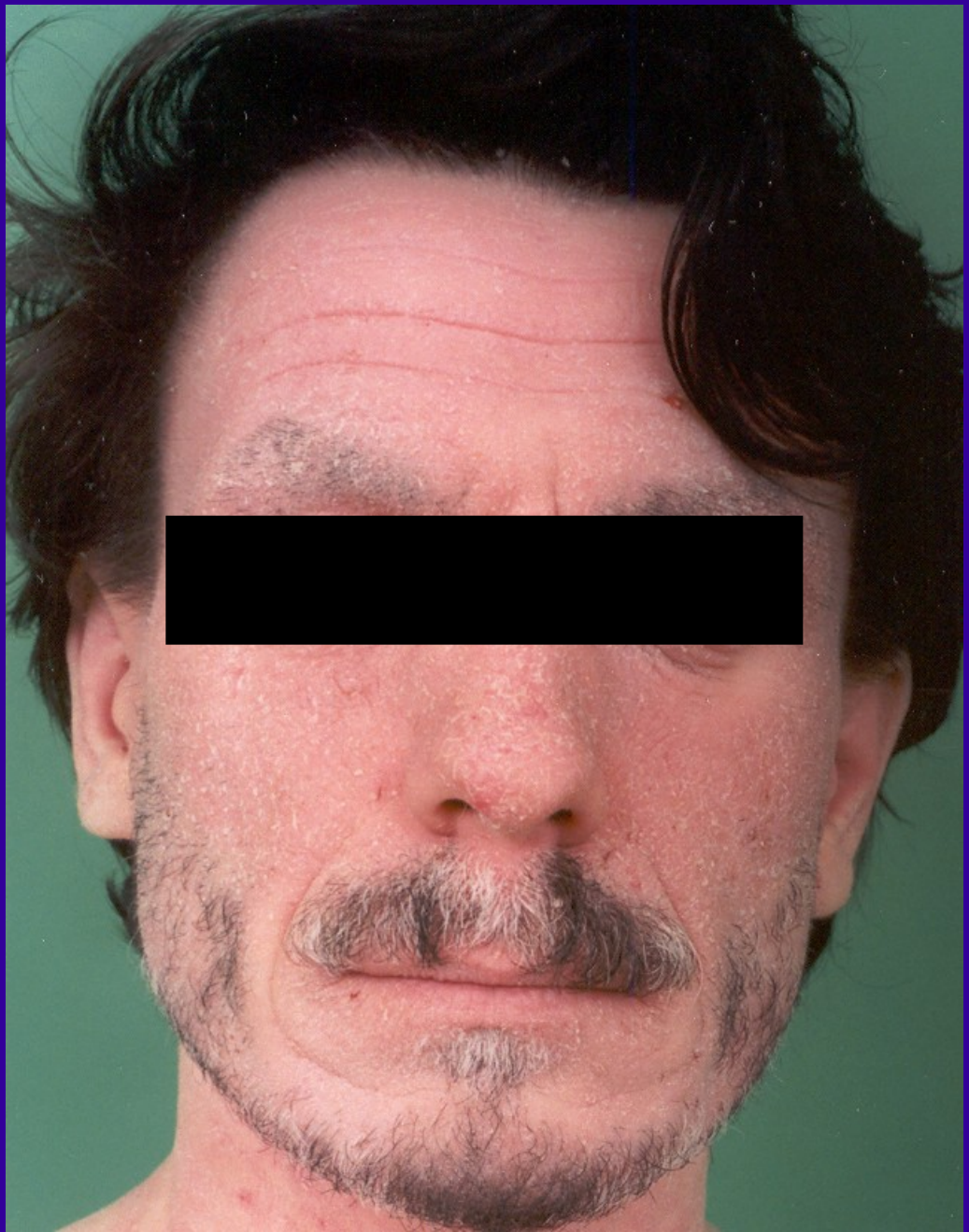
**Atopic dermatitis –
erythrodermic form**

Clinical picture of AD

AD in adults

(about 15% of cases appear after puberty)

- **head& neck**
 - **flexural**
 - **prurigininous**
 - **neurodermitic**
 - **erythrodermic**
- chronic course
- acute flares possible





Adult AD – pruriginous form



Adult AD – neurodermitic form



**Adult AD – erythrodermic
form**

AD in adults

atypical forms - nummular, dyshidrotic,
hyperkeratotic forms

minimal forms - cheilitis sicca, stomatitis
angularis, pulpitis sicca,
intertrigo retroauricularis, aj.



Adult AD - dyshidrotic form



Eczema atopicum hyperkeratoticum



AD eyelid dermatitis, lip dermatitis





AD retroauricular dermatitis

Diagnosis according to Hanifin and Rajka (1980)

Atopic dermatitis diagnosis =
≥3 basic features + ≥3 minor features

Requires the presence of
at least 3 basic features:

- **Pruritus**
- **Typical morphology and distribution**
 - Flexural lichenification or linearity in adults
 - Facial and extensor involvement in children
- **Chronic or chronically relapsing course**
- **Personal or family history of atopy** (asthma, allergic rhinitis, atopic dermatitis)

Requires the presence of **at least 3 minor features:**

- Xerosis
- Ichthyosis/palmar hyperlinearity/keratosis pilaris
- Immediate (type 1) skin test reactivity
- Elevated serum IgE
- Early age of onset
- Tendency towards cutaneous infections (especially *Staphylococcus aureus* or herpes simplex)
- Nonspecific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie–Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course from environmental/emotional factors
- White dermographism/delayed blanching

Differential diagnoses to consider in adult patients with suspected severe AD

Condition	Clinical features
Contact dermatitis	Atypical or localized distribution
Severe, suberythrodermic psoriasis	Less pruritus and lack of eczematous change such as oozing/crusting
Severe seborrheic dermatitis	Lack of pruritus with greasy scale in scalp
Scabies infestation	Inguinal, axillary, and genital papules
Widespread tinea corporis	Annular papulosquamous lesions without eczematous change
Cutaneous T-cell lymphoma	Lack of classic eczematous skin changes such as oozing and crusting

Complications of AD

bacterial - impetiginization (St. aureus)

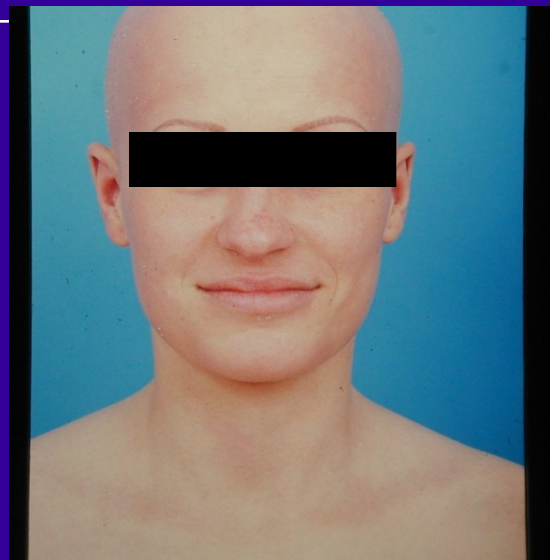
viral – herpetication-HSV, warts, mollusca

fungal (Tr. rubrum, Pityrosporum ovale)

contact sensitization (nickel, fragrances, KS...)

association:

- alopecia areata
- ichthyosis vulgaris
- vitiligo





Eczema atopicum impetiginisatum



Eczema atopicum herpeticatum



**Eczema atopicum –
verrucae vulgares –
warts**





Treatment of AD

mild form of AD (30-40% of patients):

education of patient (or parents)

identification of triggering factor

and their elimination

emollients and baths

topical corticosteroids

pimecrolimus

antihistamines during flares



Benefits vs. risks of topical corticosteroids in atopic dermatitis



BENEFIT

Large body of evidence on efficacy¹:

- Decreases acute and chronic signs of AD
- Decrease in pruritus



RISK

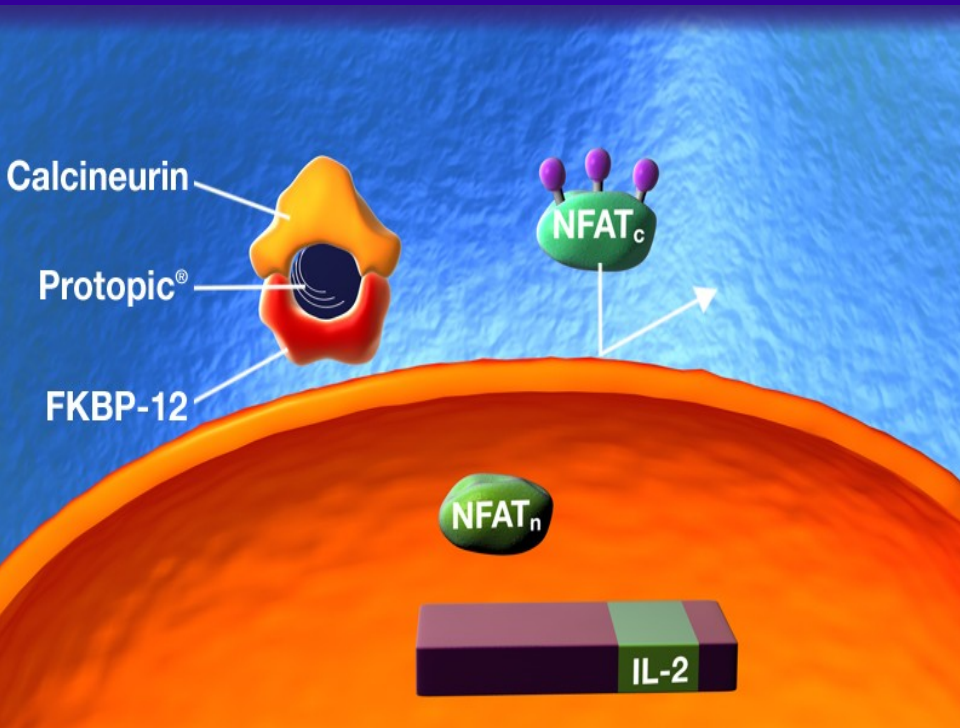
Adverse events:

- Skin atrophy
- Telangiectasias (spider veins)
- Ecchymosis (bruising)
- Stretch marks
- Hypertrichosis (excessive hair growth)
- Rosacea-like dermatitis
- Systemic effects (adrenal suppression)

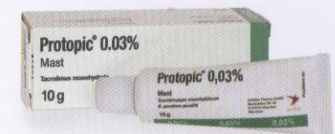
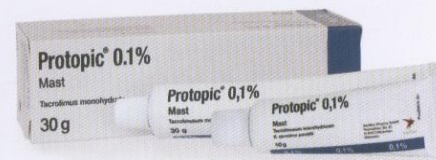
Treatment of AD

- mid-severe form of AD (40-50% of patients):
 - treatment similar as in mild form
 - + tacrolimus
 - or
 - hospitalization – lab. and clinical tests (triggers)
 - traditional topical treatment /tar/
 - or
 - phototherapy (UVB 311nm, UVA-1)

Tacrolimus (PROTOPIC oinment)



- Topical Immunomodulator
- Blocks calcineurin
- antiinflammatory
- antipruritic
- Long - term treatment
- No skin atrophy



Benefits vs. risks of topical calcineurin inhibitors in atopic dermatitis



BENEFIT

Demonstrated efficacy in short-term trials and up to 12 months:

- Decreases in physician's global evaluation scores
- Decrease in percentage BSA involved
- Decrease in patient-reported signs and symptoms of AD
- No risk of skin atrophy



RISK

Adverse events:

- Transient burning sensation at site of application
- Their onset of action is slower than in TCS
- Generalized cases of viral infections (eczema herpeticum and molluscum)
- Black box warning of rare case of malignancy (skin cancer and lymphoma – not proven later)

Treatment of AD

- severe form of AD (5-10% patients)
 - phototherapy (PUVA, UVA-1)
 - systemic corticosteroids (short courses)
 - immunosuppressives: cyclosporine A, MMF, AZT, MTX
 - new therapies:
 - i.v. Ig
 - JAK, PDE inhibitors
 - biologicals (dupilumab...)

European treatment recommendations for adults with atopic dermatitis

Severe

SCORAD >50
or persistent AD

Hospitalization, PUVA,^a systemic immunosuppression: cyclosporine A,^b short course of oral corticosteroids,^b dupilumab,^{a,b} MTX,^c AZA,^c MMF^c; alitretinoin^{a,c}

Moderate

SCORAD 25–50
or recurrent AD

Proactive therapy with topical tacrolimus^b or TCS (class II or class III^c), wet wrap therapy, UV therapy (UVB 311 nm,^d medium-dose UVA1), psychosomatic counselling, climate therapy

Mild

SCORAD <25
or transient AD

Reactive therapy with TCS (class II^b) or TCI,^{b,e} antiseptics including silver^{b,e} and silver-coated textiles^{a,e}

Baseline

Basic therapy

Education, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

^aLicensed indication; ^bOff-label use; ^cNarrow-band UVB; ^dTreatments with particular restrictions on use

AD=atopic dermatitis; AZA=azathioprine; MMF=mycophenolate mofetil; MTX=methotrexate; PUVA=psoralen and ultraviolet A; SCORAD=SCORing Atopic Dermatitis; TCI=topical calcineurin inhibitor; TCS=topical corticosteroids; UV=ultraviolet
Wollenberg A, et al. J Eur Acad Dermatol Venereol 2018;32:657-82.

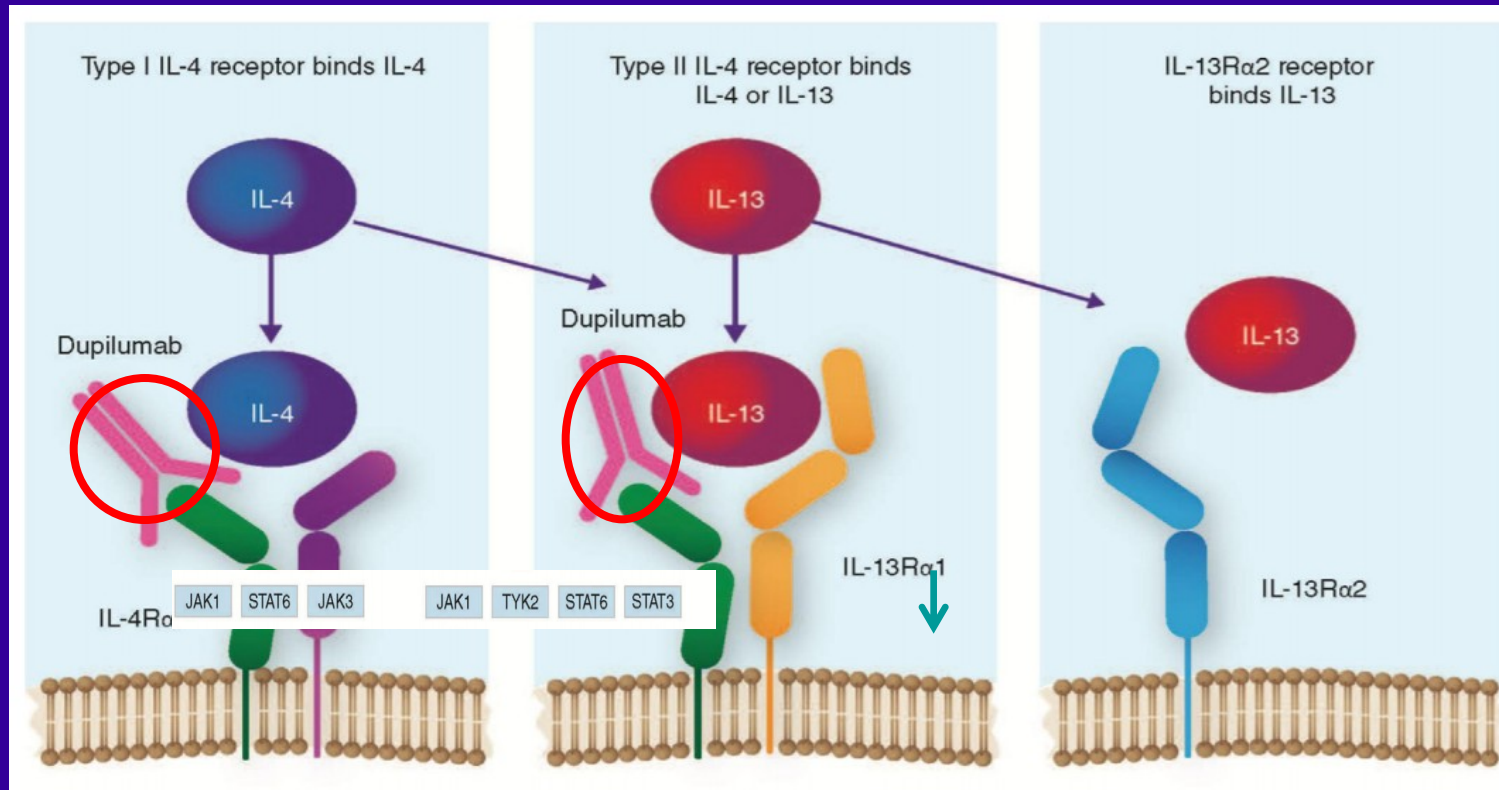
New treatments of AD

	PHASE 1	PHASE 2			PHASE 3	Approved
Interleukin Inhibitors	ARGX-1121-3 IL-22R1	Bermekimab ^{6,7} IL-1 α	Secukinumab ⁸ IL-17A	Risankizumab ^{9,10} IL-23	Tralokinumab ¹¹ IL-13	Dupilumab ¹² IL-4R α
	PF-06817024 ^{4,5} IL-33-related	Benralizumab ^{13,1} IL-5R α	MOR10615 IL-17C	REGN3500 ^{16,17} IL-33	Nemolizumab ¹⁸ IL-31RA	Dupilumab 300 mg q2w is licensed for treating moderate-to- severe AD in adult patients ¹²
		Lebrikizumab ¹⁹ IL-13	Fezakinumab ²⁰ IL-22	Etokimab ^{21,22} IL-33		
			Spesolimab ^{23,24} IL-36	LY3375880 ^{25,26} IL-33		
JAK/SYK Inhibitors			ASN00227 SYK/JAK		Upadacitinib ²⁸ JAK1	
					Abrocitinib ²⁹ JAK1	
					Baricitinib ³⁰ JAK1/JAK2	
Other Inhibitors	EDP106631 Undisclosed					
	EDP181531 Undisclosed	DS10732, ³³ CD40	Tezepelumab ^{34,35} TSLP	KY 100536 OX40L	Serlopitant ^{37,38} NK-1R <small>Refer</small>	
	LOU 06439-41 BTK	Adriforant ⁴¹ H4R	GBR 83042 OX40	KHK408343, ⁴⁴ OX40	Tradipitant ⁴⁵ NK-1R	

Dupilumab

- mechanism of action

human IgG4 class monoclonal antibody that specifically binds to the α subunit of the IL-4 and 13 receptors, thereby blocking the activation of protein kinases JAK 1 or 3 or TYK2



Effect of dupilumab treatment



JAK pathway in AD

CYTOKINES RELEVANT TO ATOPIC DERMATITIS

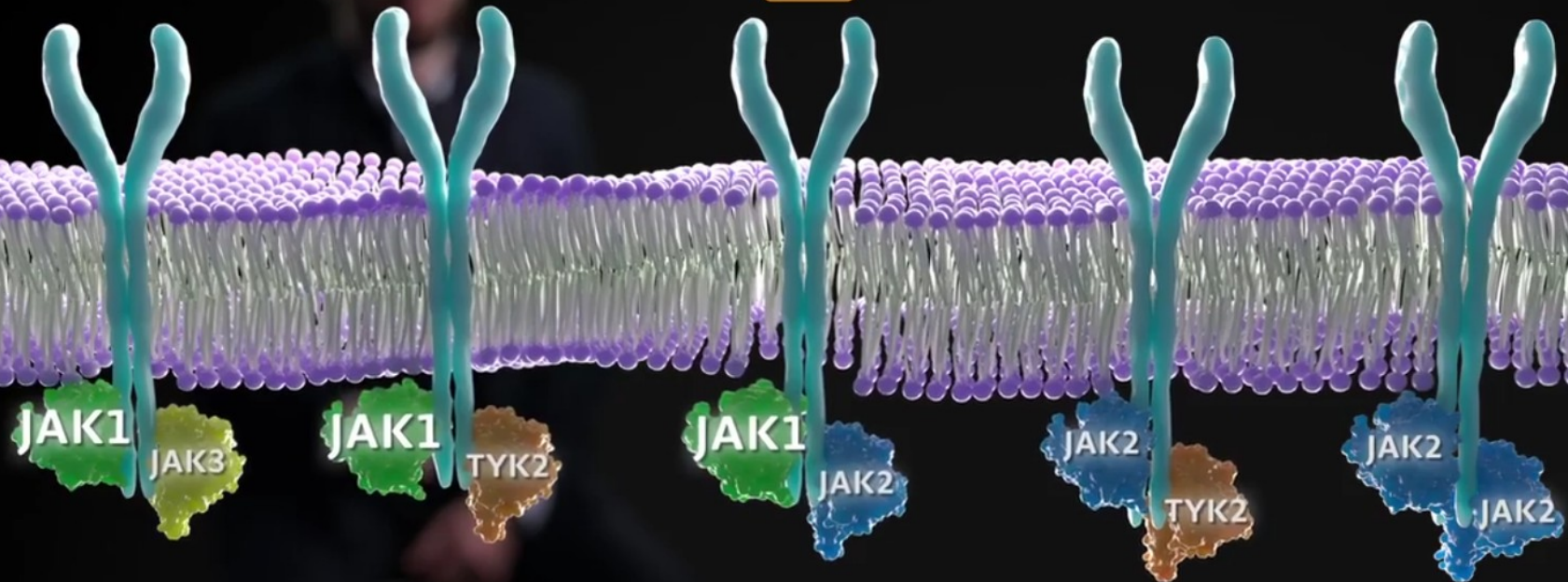
IL-2, IL-4, IL-7,
IL-9, IL-15, IL-21

IL-4, IL-13, IL-22,
IFN- α/β

IFN- γ
IL-31
TSLP

IL-12
IL-23

EPO
TPO
GM-CSF



Oral JAK Inhibitor Development in Atopic Dermatitis

DRUG	TARGET	PHASE 3 STUDIES COMPLETED	PHASE 3 STUDIES ONGOING
<i>Baricitinib (Lilly)</i>	JAK 1/2	<ul style="list-style-type: none"> • Monotherapy Ex-US (BREEZE AD1) • Monotherapy Ex-US (BREEZE AD2) • Monotherapy- US (BREEZE AD5) • Combo with TCS (BREEZE AD7) 	Pediatric studies Cyclosporine failures Long-term extension
<i>Abrocitinib (Pfizer)</i>	JAK 1	<ul style="list-style-type: none"> • Monotherapy Global (MONO-1) • Monotherapy Global (MONO-2) 	Abro vs Dupi (COMPARE) MOA study Combo with TCS Long-term extension
<i>Upadacitinib (Abbvie)</i>	JAK 1	None, but +P2 monotherapy	Monotherapy X 2 Combo with TCS Lon-term extension Upa vs. Dupi
<i>Gusacitinib (Asana)</i>	Pan JAK + SYK	None, but +P2b	None

JAK Inhibitors: Adverse Events of Interest



- Major adverse cardiac events (MACE)^{13,5}
- Venous thromboembolism (VTE)¹⁴
- Malignancy¹⁴
- Acne/folliculitis⁴
- Laboratory abnormalities^{5,15,16}
 - Anemia, neutropenia, lymphopenia
 - Elevated creatine phosphokinase (CPK)
 - Increased serum lipid levels

These adverse events appear to be a class effect of JAK inhibitors^{4,5,13-16}; however, long-term safety data on these are limited,¹⁷ and current studies in AD show low incidence of serious AEs¹⁸⁻²⁰