Do you know JAK?: New Applications for Janus Kinase Inhibitors in Dermatology

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Dr. Bhatia's Disclosures:

- Affiliations with Aclaris, Almirall, Biofrontera, BiopharmX, Dermira, Encore, EPI Health, Ferndale, ISDIN, LaRoche Posay, Leo, Mayne, Menlo, Novartis, Ortho-Derm, Pierre-Fabre, Pfizer, Regeneron/Sanofi, and Sun Pharma
  Some slides from industry were borrowed for explanation of data and scientific background, not for promotion; Off-label discussion is likely
- Copies of pdf or questions: bhatiaharbor@gmail.com

Important References

REVIEWS

Topical Janus kinase inhibitors: A review of applications in dermatology

Anna-Marie Hosking, BS, Margit Juhasz, MD, and Natasha Atanaskova Mesinkovska, MD, PhD
Irvine, California

Janus kinase inhibitors in dermatology: A systematic review

Rony Shreberk-Hassidim, MD, Yuval Ramot, MD, MSc, and Abraham Zlotogorski, MD
Jerusalem, Israel

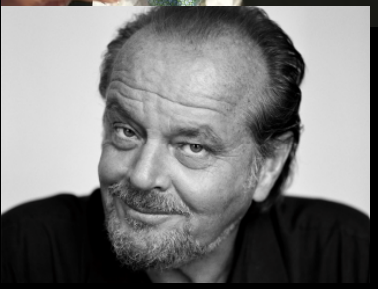
JAK inhibitors in dermatology: The promise of a new drug class

William Damsky, MD, PhD, and Brett A. King, MD, PhD
New Haven, Connecticut

Acknowledgments:
Jim Del Rosso, D.O.
Mark Lebwohl, M.D.
Brett King M.D. PhD

So exactly is this JAK guy?

Can they possibly be inhibited?










Janus Kinase…Signal Tranducer and Activator of Transcription (JAK-STAT)

- Pathway utilized to transmit extracellular signals to the nucleus.
  - Dysregulation of this pathway is responsible for immune deficiency syndromes and myeloproliferative neoplasms.
- Phosphorylation after ligand binding leads to translocation and gene expression regulation.
- JAK/STAT pathway suppresses:
  - dendritic cell activation, T-cell mediated inflammation

Starting Lineup:

- JAK 1
- JAK 2
- JAK 3
- TYK 2

- STAT 1
- STAT 2
- STAT 3
- STAT 4
- STAT 5a
- STAT 5b
- STAT 6

4 JAK (1,2,3, TYK 2) and 6 STAT (1-6) interact to send cytokine signals to nucleus

Cytokine receptor	JAKs	STATs
IFNα	JAK1/TYK2	STAT1/STAT2
IFNγ	JAK1/JAK2	STAT1/STAT1
IL-2	JAK1/JAK3	STAT5/STAT5
IL-4	JAK1/JAK3	STAT6/STAT6
IL-6	JAK1/JAK2	STAT3/STAT3
IL-12	JAK2/TYK2	STAT4/STAT4
IL-22	JAK1/TYK2	STAT3/STAT1/5
IL-23	JAK2/TYK2	STAT3/STAT4

IL-1β, TNF, and IL-17 do **not** signal through the JAK-STAT pathway

Yoshimura A et al, Arthr Res Ther 2005, 7, 100-110
Laurence A et al, The Open Rheumatology Journal, 2012, 6, 232-244
Vignali DAA & Kuchroo VK, Nature Immunology 2012, 13, 722-728
Tohyama M et al, J Invest Dermatol, 2012, 132, 1933–1935
Eyerich S et al, Trends Immunol 2010, 31, 354–361

How do these things work?
Janus Kinase Inhibitors

1 Cytokine binding to its cell surface receptor leads to receptor polymerization[1]

Courtesy Steven Hays, Pharm D, Pfizer Medical Information

How do these things work?
Janus Kinase Inhibitors

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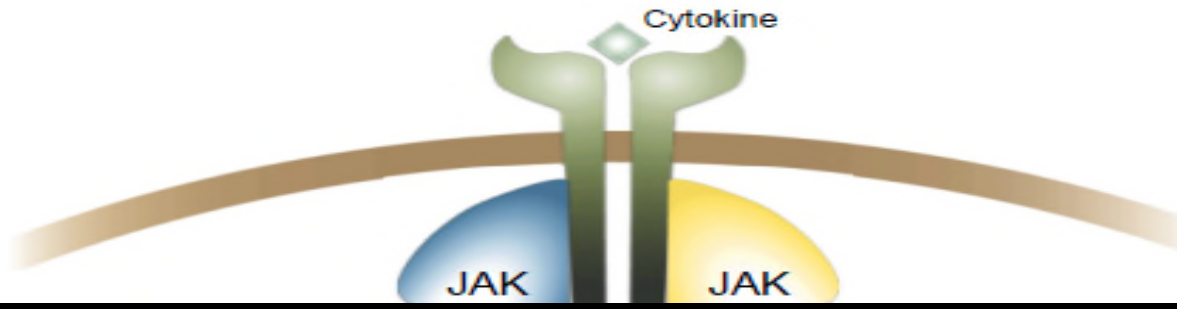
2 Tofacitinib inhibits the phosphorylation and activation of JAKs[2,3]



Courtesy Steven Hays, Pharm D, Pfizer Medical Information

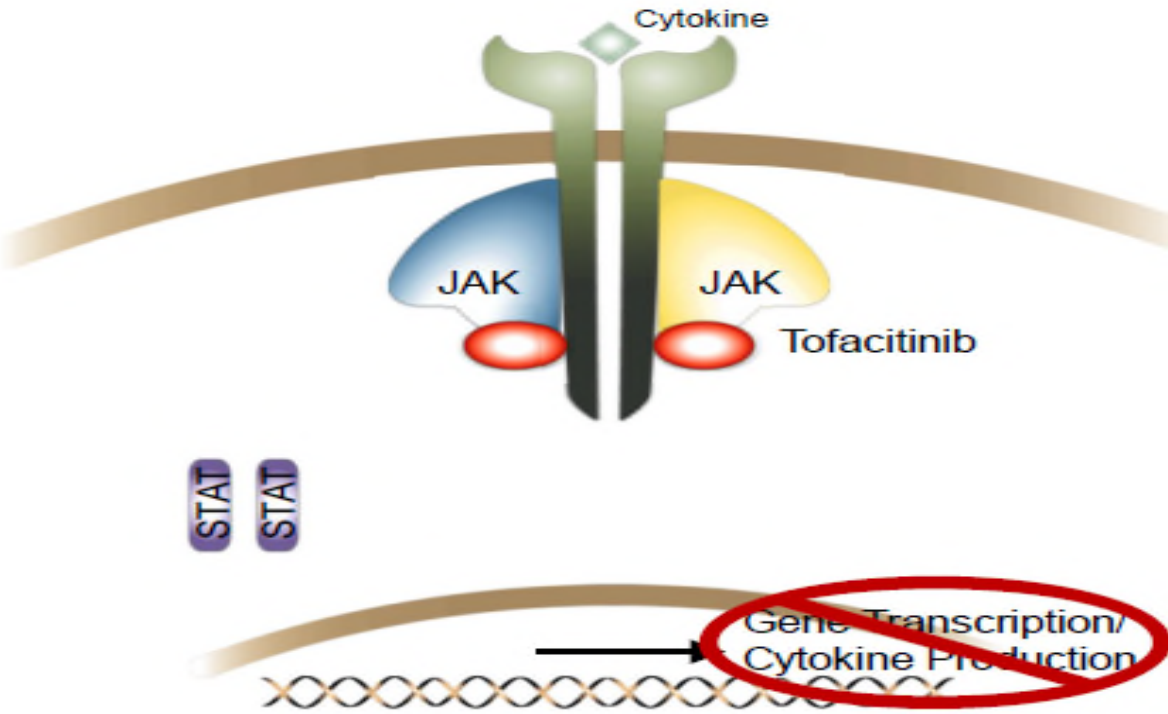
How do these things work?
Janus Kinase Inhibitors

1. Cytokine binding to its cell surface receptor leads to receptor polymerization[1]

2. Tofacitinib inhibits the phosphorylation and activation of JAKs[2,3]

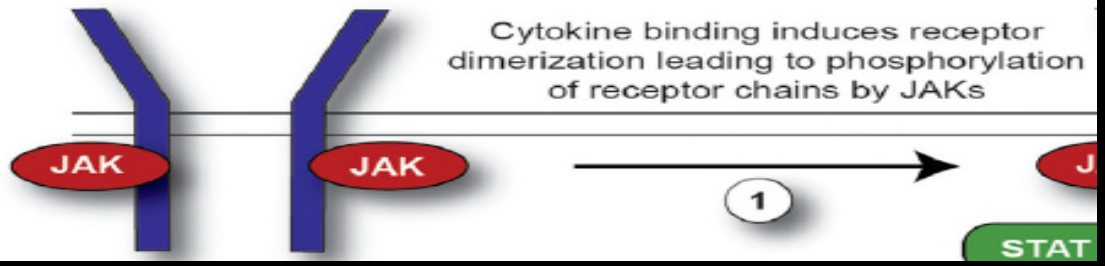
3. JAKs cannot phosphorylate the cytokine receptors. Therefore, the receptors cannot dock STATs[2,3]

4. Since the STATs cannot dock, they are not phosphorylated or activated. Gene transcription and cytokine production is thereby inhibited[2,3]

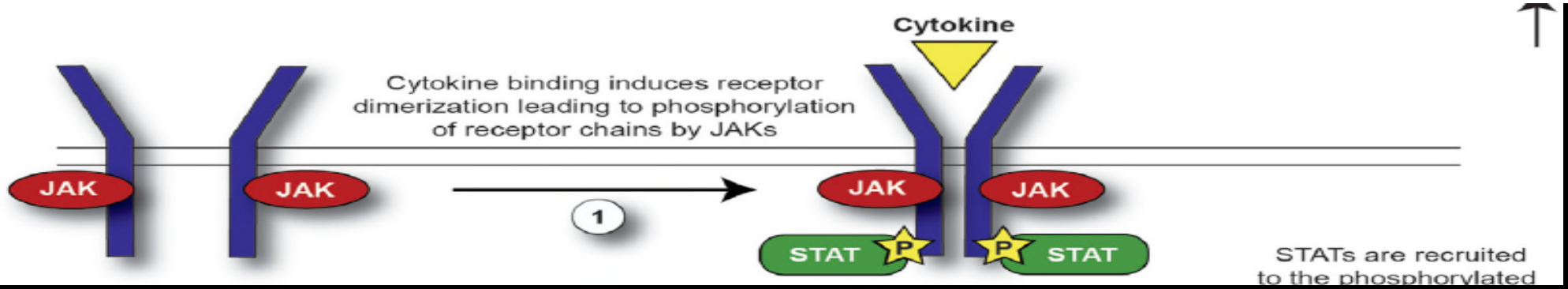


1. Shuai K et al. *Nat Rev Immunol*. 2003;3(11):900-911; 2. Jiang J et al. *J Med Chem*. 2008;51(24):8012-8018; 3. XELJANZ. [prescribing information]. New York, NY: Pfizer Inc.; 2012.

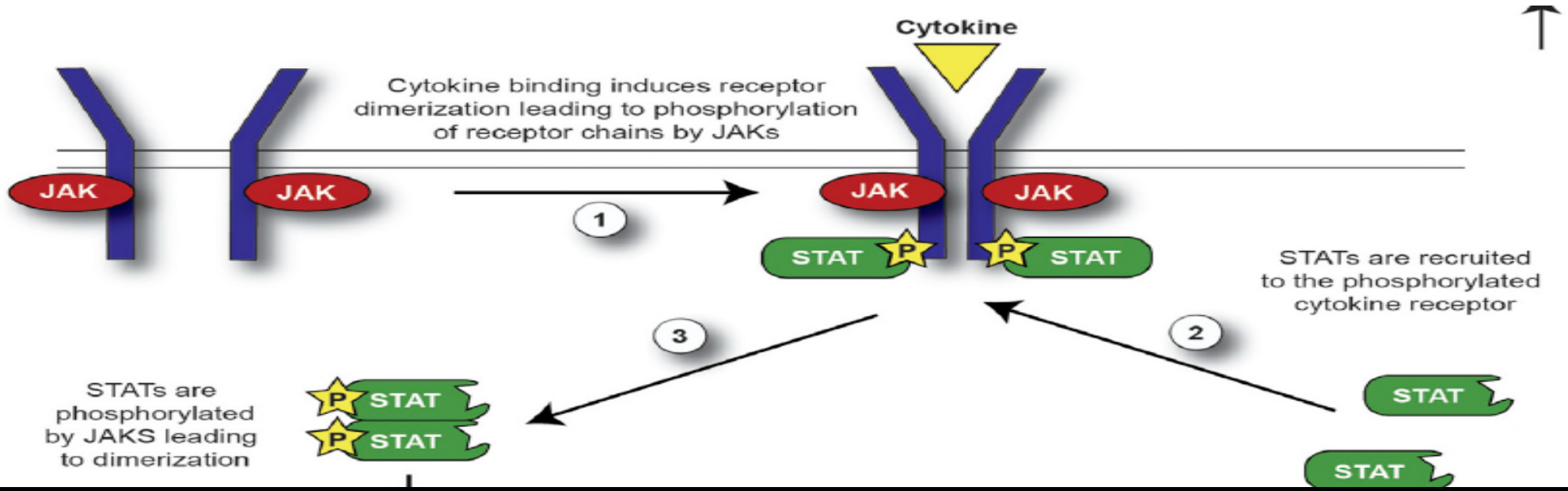
Courtesy Steven Hays, Pharm D, Pfizer Medical Information



Damsky W, and King, B, “The Promise of a New Drug Class,” J Amer Acad Dermatol, 2017; 76; 736-44



Damsky W, and King, B, “The Promise of a New Drug Class,” J Amer Acad Dermatol, 2017; 76; 736-44



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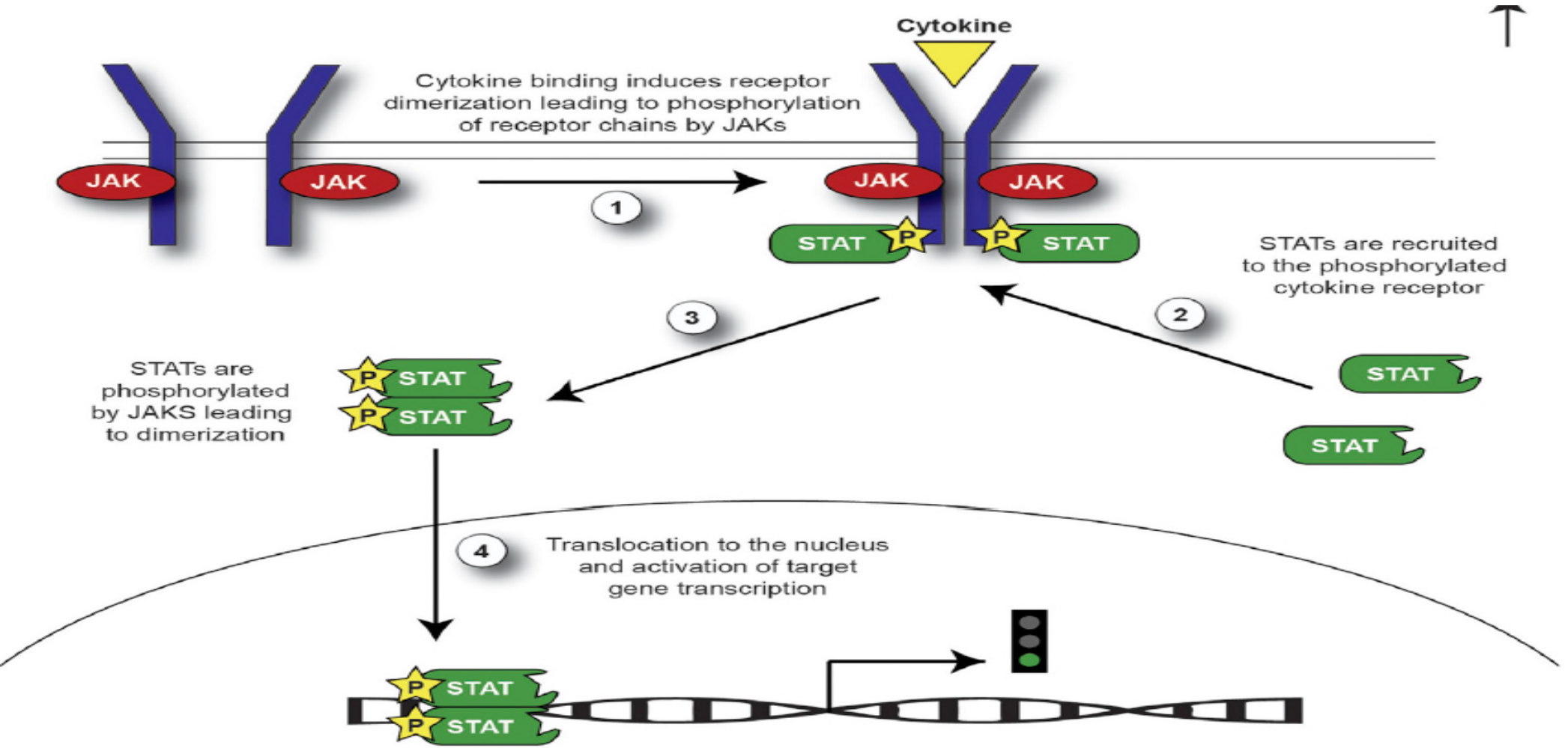
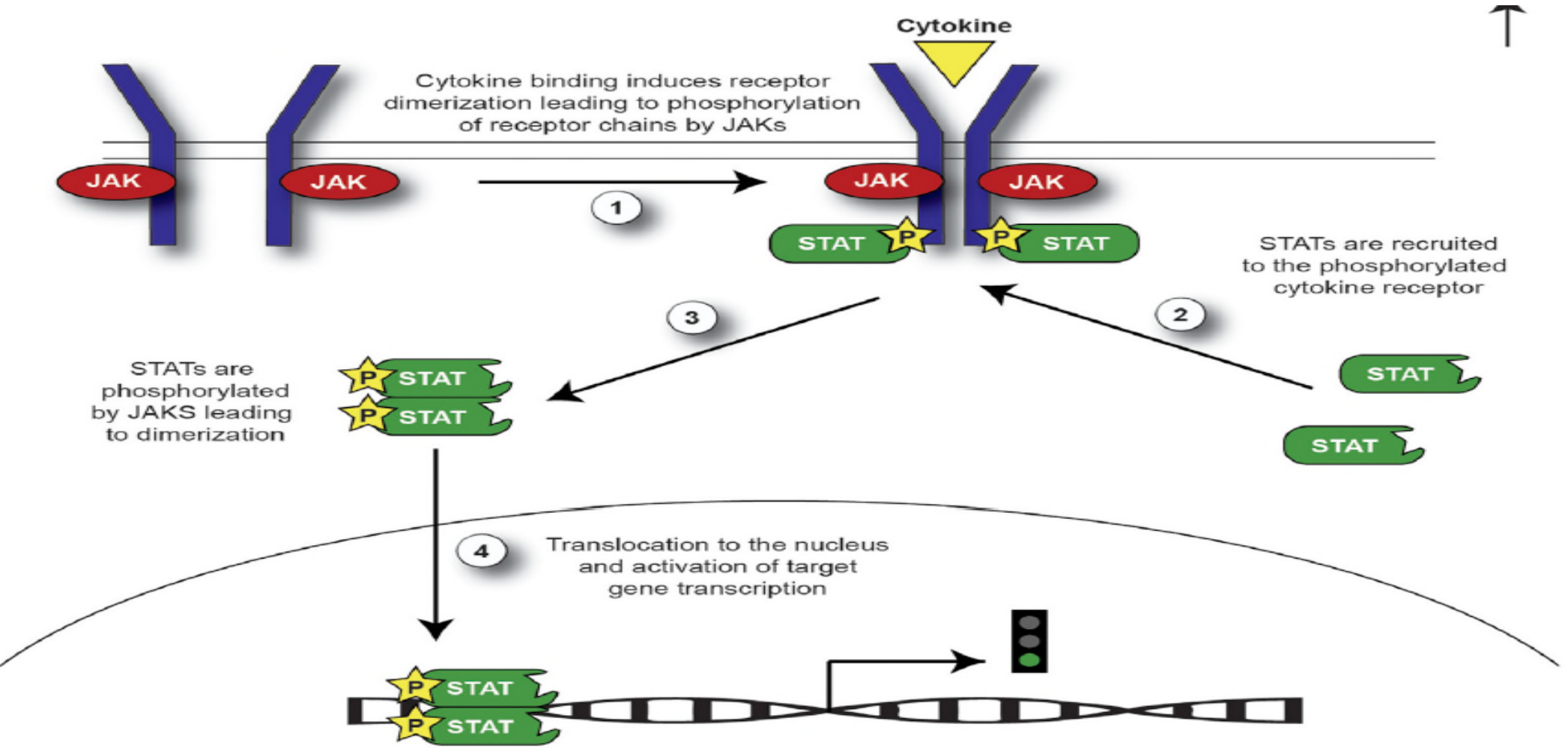


Fig 1. Janus kinase—signal transducer and activator of transcription (JAK-STAT) signaling pathway. JAK inhibitors antagonize JAK protein function and prevent activation of the pathway.

Damsky W, and King, B, "The Promise of a New Drug Class," J Amer Acad Dermatol, 2017; 76; 736-44



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Are these safe?

- Perform all immunizations before starting
- Rare elevations of lipids (total, HDL, LDL)
  - no reported strokes or worse
- Pancytopenia worse ruxolitinib>tofacitnib
  - JAK2 signaling mediated by erythropoietin, thrombopoietin, and GCSF
- Low CA risk across specialties
  - Routine skin check for SCC
- Monitoring--TB test to start and annually
  - Lipids and LFTs—4-8 wks after start
  - CBC/diff at start and 4-8 wks then q 3 mo

Shreberk-Hassidim,R, *J Am Acad Dermatol,* 2017;76:745-53

Table V. Summary of dermatologic and nondermatologic adverse events and related data of Janus kinase inhibitors

Cutaneous	Noncutaneous
Infectious	
Herpes zoster*	Nasopharyngitis*
Reactivation of herpes simplex†[66]	Upper respiratory tract infection*
Disseminated molluscum contagiosum†[65]	Pulmonary cryptococcosis†[58]
Other	
Eruptive squamous cell carcinomas†[69]	Gastrointestinal complaints*
DRESS syndrome†[51]	Distal symmetric polyneuropathy†[62]
Drug eruption†[67]	Laboratory abnormalities
	Dose-dependent decrease in hemoglobin levels, RBCs, and neutrophil counts[61]
	Dose-dependent increase in CPK, HDL, LDL, and total cholesterol levels[64]

CPK, Creatine kinase; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *RBC*, red blood cell.
*In multiple randomized control trials, as described in Table II.
†In only 1 case report.

Curtis JR, Lee EB, Kaplan IV, *et al.,'*Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. " *Ann Rheum Dis.* 2016;75(5):831-841.

Lipid Levels in Patients with PsA reported elevations with Tofacitinib

- n=783 pts, pooled data from two phase 3 studies and an ongoing long-term extension study
  - Assessed fasting lipid levels, blood pressure, and MACE
  - Percentage increases of LDL and HDL ranged from 9% to 14% for 5 mg and 10 mg doses of tofacitinib at 3 and 6 mo
  - No meaningful changes in LDL/HDL or total cholesterol/HDL ratios. Blood pressure remained stable through 24 months
- *Conclusions: Serum lipid level increases at month 3 following tofacitinib treatment in PsA were consistent with observations in rheumatoid arthritis and psoriasis*

Gladman DD, Charles-Schoeman C, McInnes IB, *et al.* "Changes in lipid levels and incidence of cardiovascular events following tofacitinib treatment in patients with psoriatic arthritis: A pooled analysis across phase 3 and long-term extension studies" [published online May 21, 2019]. *Arthritis Care Res.* doi:10.1002/acr.23930

Risks more concerning in Transplant Patients?

- Concern with JAK inhibitors is a theoretical increased risk for malignancy-- dampen antitumor surveillance?
  - Initial studies of tofacitinib in renal transplantation:
    - 1% of patients treated with tofacitinib developed post-transplant lymphoproliferative disorder
  - Myelofibrosis and polycythemia vera treated with ruxolitinib
    - No increased risk for developing a second malignancy has been shown
- Topical JAK inhibitors
  - Monotherapy in less severe disease (Vitiligo, AD, patchy AA),
  - Potential maintenance therapy after oral treatment
  - Safer options for children (Vitiligo, AD, AA) would prefer to a topical if viable and avoid systemic side effects.

JAK Inhibitors for Psoriasis
JAK 1, 2, 3 and TYK 1

Ruxolitinib

- JAK 1,2
- phosphorylation due to IL-6, IL-12, or IL-23, resulting in suppression of Th17 differentiation
  - reduced lymphocytic infiltration
  - inhibited acanthosis,
  - reduces IFNγ expression

Tofacitinib

- JAK 1,3
- Suppression of IL-23 receptors, IL-15, IL-17A, 17F in mice models
- IL-22 suppressed when T cells were stimulated with IL-6 and IL-23
- Growth and Activation signals sent to nucleus

Amitava Mitra and Ercem Atillasoy (2012). Topical Therapies for Psoriasis, Psoriasis, Dr. Jennifer Soung (Ed.), ISBN: 978-953-307-878-6, InTech, Available from: http://www.intechopen.com/books/psoriasis/topicaltherapies-for-psoriasis

Ruxolitinib for Psoriasis
Topical JAK1/2 inhibitor against IL-12/23, IFN

- Two 28-day studies: BSA 2-7%, 8-13%, and 14-20%
- Double-blind, vehicle controlled
  - 1% cream QD: 53% plaque reduction vs. 32% vehicle (P =05);
  - 54% for 1.5% cream BID vs 27% for vehicle (P # .05);
  - 46% for 1.5% cream BID vs 40% for calcipotriene;
  - 58% for 1.5% cream BID vs 44% for betamethasone
- Open-label both for safety/tolerability/efficacy
  - Mean total area 59% for treated lesions, 3% untreated
  - Efficacy was seen as early as 1 week
  - Plasma concentrations did not correlate to the BSA treated

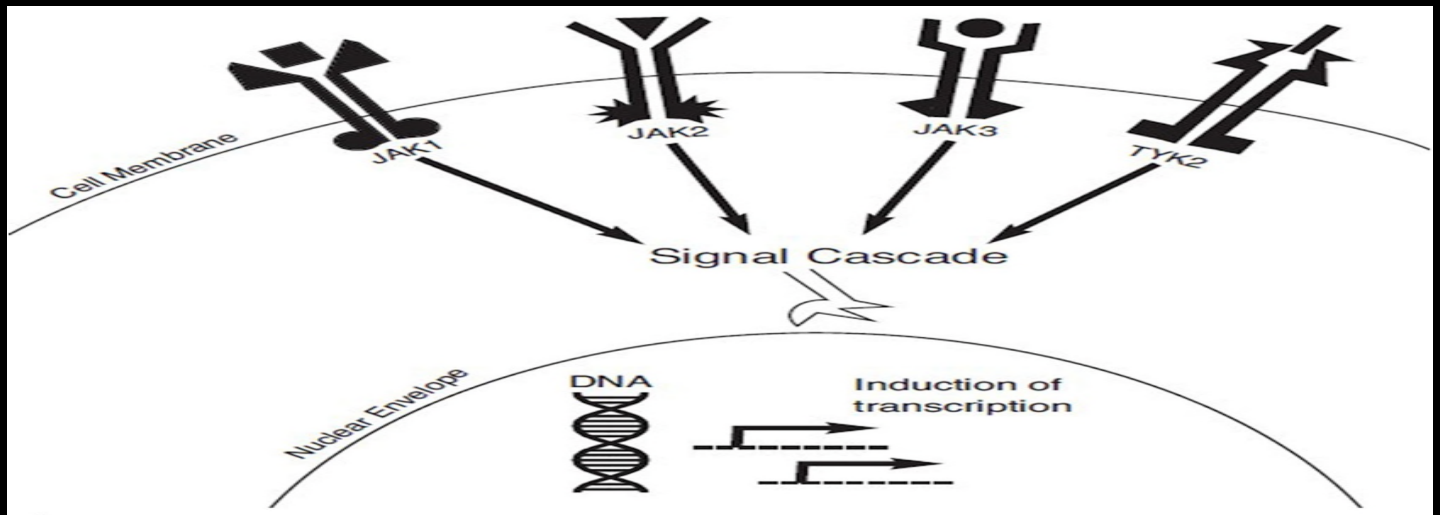
BMS-986165
Oral selective tyrosine kinase 2 (TYK2) inhibitor

- Highly selective for IL-23, IL-12, and interferon alpha.
- 12-week, double-blind, dose-ranging placebo-controlled
- PASI 75 rates: placebo 7%, 3 mg qod 9%, 3 mg daily 39%, 3 mg BID 69%, 6 mg BID 67%, 12 mg/day 75%
  - PASI 75 response and other clinical benefits were retained one month after last dose
  - biopsies obtained on study days 1, 15, and 85: 3 mg bid or higher:
  - reduced expression of IL-19 and IL-36A, markedly decreased expression of genes in the Th17 pathway and essentially normalized expression of the proinflammatory genes beta defensin and S100A9.

Papp K *et al. N Engl J Med.* 2018 Sep 11. doi: 10.1056/NEJMoa1806382.

Emerging therapies for atopic dermatitis: JAK inhibitors

David G. Cotter, MD, PhD, David Schairer, MD, Lawrence Eichenfield, MD



A

	JAK1	JAK2	JAK3	TYK2
γc family: IL-2, IL-4*, IL-7, IL-9, IL-15	✔		✔	
gp130 family: IL-6*, IL-11, OSM, LIF	✔	✔		✔
IL-12**/IL-23*		✔		✔
Others:	IFNα/β,IFNγ*, IL-10*	EPO, TPO, IFNγ* **βc family:** IL-3, IL-5*, GM-CSF*		IFNα/β

*Associated with acute lesions of atopic dermatitis
** Associated with chronic lesions of atopic dermatitis

B

Journal of the American Academy of Dermatology 2018 78, S53-S62DOI: (10.1016/j.jaad.2017.12.019)

JAK Inhibitors for Atopic Dermatitis

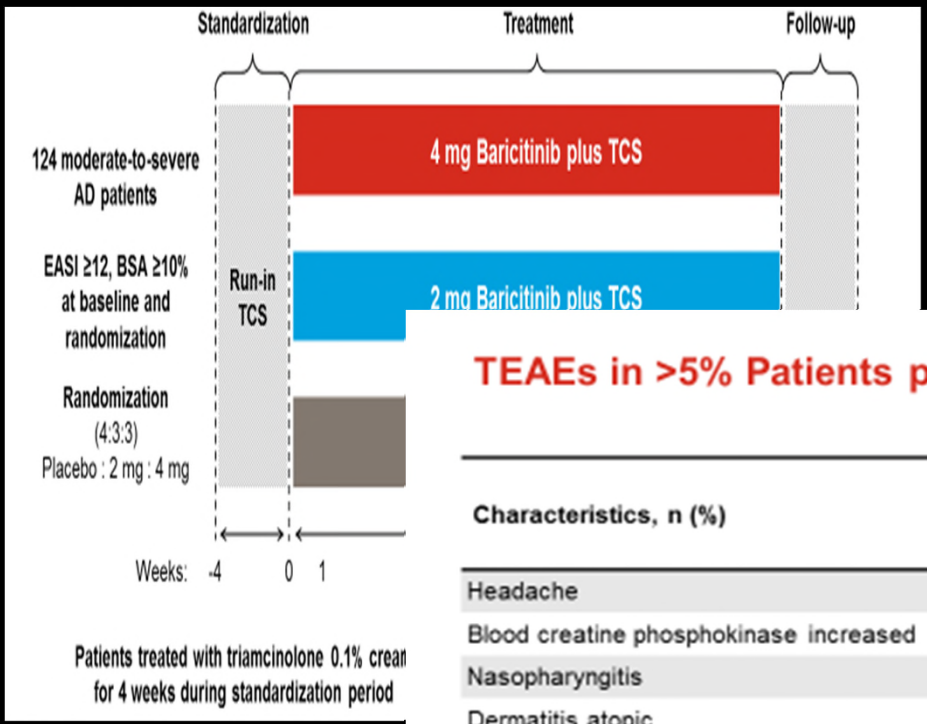
- Baricitinib: JAK 1-2 inhibitor: pro-inflammatory cytokine signaling, ph 3
- ASN002: JAK/SYK inhibitor: Reduce Th2/ Th22 cytokine signaling, ph 3
- Upadacitinib: JAK-1 inhibitor: ph 3
- Abrocitinib: JAK-1 inhibitor: ph 3, ages ≥ 12
- JTE-025 JAK-1 inhibitor: phase 2 studies in Japan

- Sienna SNA-125: JAK 3 inhibitor proof of concept 2018
- Aclaris 502-AD-201 topical: completing ph 3

Guttman-Yassky E et al, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, de la Peña A, Nunes FP, Janes J, Gamalo M, Donley D, Paik J, DeLozier AM, Nickoloff BJ, Simpson EL, "Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study," *J Am Acad Dermatol,* 2018 Feb 1. pii: S0190-9622(18)30129-4. doi: 10.1016/j.jaad.2018.01.018. [Epub ahead of print]

Cotter, D, Schairer, D, Eichenfield, L, "Emerging therapies for atopic dermatitis: JAK inhibitors," *J Am Acad Dermatol,* 78(3): S53 - S62

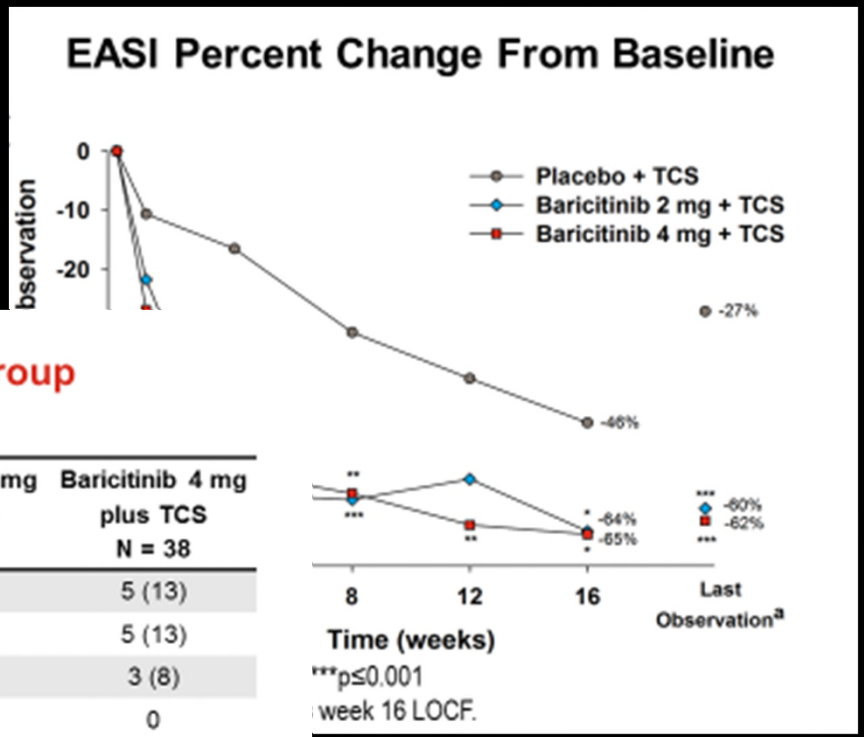
Baricitinib Phase 2 Trial



TEAEs in >5% Patients per Treatment Group

Characteristics, n (%)	Placebo plus TCS N = 49	Baricitinib 2 mg plus TCS N = 37	Baricitinib 4 mg plus TCS N = 38
Headache	0	2 (5)	5 (13)
Blood creatine phosphokinase increased	0	1 (3)	5 (13)
Nasopharyngitis	1 (2)	1 (3)	3 (8)
Dermatitis atopic	4 (8)	1 (3)	0
Cellulitis	3 (6)	1 (3)	0
Lymphopenia	3 (6)	0	0

TCS=topical corticosteroids; TEAE=treatment-emergent adverse event.



Guttman-Yassky E *et al*, *J Am Acad Dermatol* 2018; S0190-9622(18)30129-4.

Upadacitinib
Oral JAK1-selective inhibitor

- 59x more selective JAK1> JAK2; 133X for JAK1>JAK3; 194 X for JAK1> TYK2
  - No herpes zoster, malignancies, deaths or cases of thromboembolic dz
- Phase 2b dose-ranging study: upadacitinib 7.5 mg, 15 mg or 30 mg improvements overall
- Phase 2b study 32-week efficacy/safety patient-reported outcomes data evaluating upadacitinib once-daily
  - improved patient-reported itch and impact on sleep receiving upadacitinib 30 mg daily vs placebo at week 16.
- Phase 3 efficacy and safety n~2430 patients with moderate-to-severe AD (≥ 12 years old and ≤ 75 years old) ± topical TCS

Parmentier J *et al*, BMC Rheumatology

ASN002 oral JAK and SYK inhibitor

- n=36 moderate to severe AD
  - random 20 mg, 40 mg, 80 mg or placebo qd x 4 weeks.
  - EASI score ≥16, BSA ≥10%, and IGA of ≥3 at baseline.

- Dose-related declines in EASI75 (10%-55%) at 4 weeks
  - average decrease in EASI of 28%-68%
  - 19%-51% reducrion in Itch Numeric Rating Scale score
  - Most common AEs being mild headache and nausea, most of which were transient and occurred on day 1 of dosing

ClinicalTrials.gov Identifier: NCT03139981) were presented at the 2018 American Academy of Dermatology Annual Meeting, February 16-20, 2018 in San Diego, California.

Staphylococcus Dysbiosis Correlates of Success of Treatment of Atopic Dermatitis with the JAK/SYK Inhibitor ASN002

- Skin microbiome analyzed for effect on *S.aureus* dysbiosis and correlates of success of treatment
- Double-blind randomized phase-1b study
- ASN002 for 28 days in with doses: 20, 40 and 80mg daily and placebo (N=9 per arm). Skin microbiome from lesional (LS) and non-lesional (NL) skin swabs at days 1, 29 and 43 were sequenced (16S V1-3).

REFERENCES / Avidan U. Neumann, PhD, AAD 2018 Late Breaking Abstract presentation
A Phase 1b, Randomized, Double-Blind, Placebo-Controlled, Sequential, Multiple-Dose Escalation, Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of ASN002 in Subjects with Moderate-to-Severe Atopic Dermatitis

Higher *S.aureus* frequency associated with higher EASI score in lesional skin

- Lower *S.aureus* frequency at baseline predicts (p=0.03) higher probability for a sustained EASI response 14 days after end-of-treatment, and in consequence significantly (p<0.001) predicts lower EASI at day 43
- A significant (p=0.005) dose-dependent decline in *S.aureus* frequency in LS was exhibited at day 29 in 86% of patients, in comparison to placebo (33%), and correlated with EASI decline (R=0.7, p=0.003)

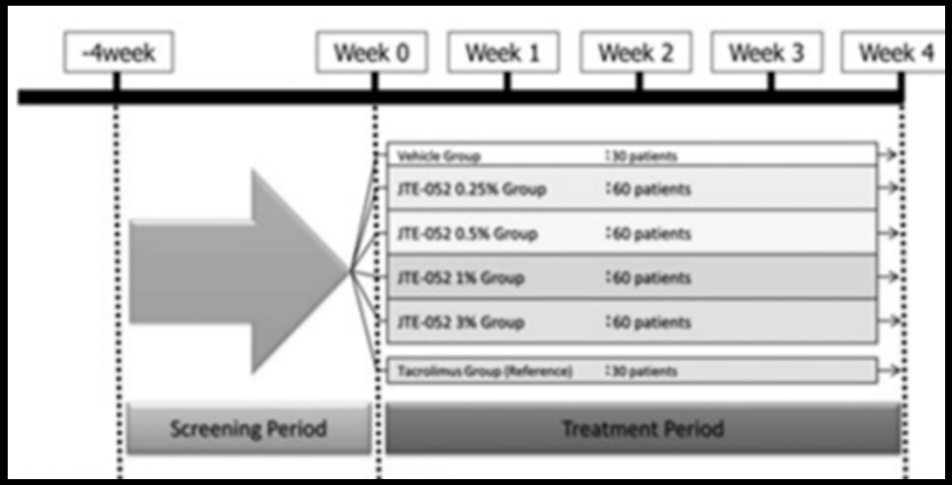
- Conclusions:
  - *JAK/SYK inhibition with ASN002 not only improves clinical scores and Th2/Th22 inflammation markers but also reduces S.aureus frequency in lesion.*
  - *Conversely, lower baseline S.aureus frequency in lesion correlated with ASN002 sustained efficacy post-treatment.*

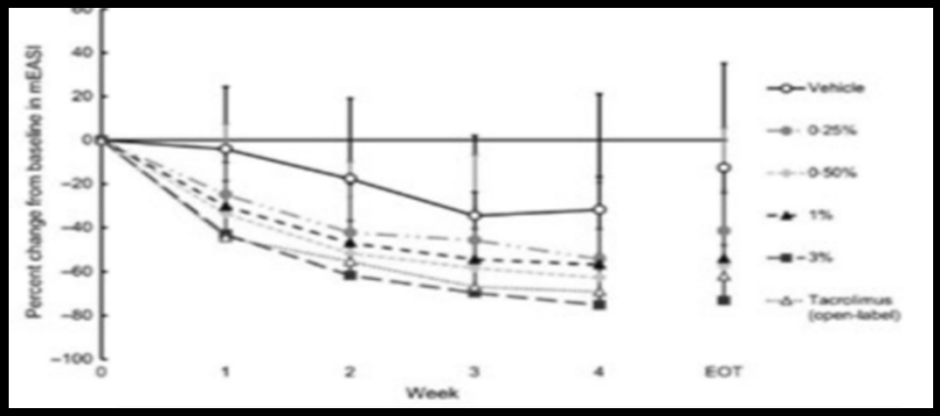
Abrocitinib
PF-04965842 JAK 1 selective inhibitor

(http://clinicaltrials.gov, NCT01835197).

- Abrocitinib received Breakthrough Therapy designation from the FDA for moderate to severe AD in February 2018
- Phase 1 study 79 healthy subjects single dose of placebo or 3, 10, 30, 100, 200, 400 or 800 mg (single ascending dose phase)
  - BID for 10 consecutive days (multiple ascending dose phase)
  - No deaths or serious AEs: headache, diarrhea, and nausea (n = 11)
  - mean t½ 2.8-5.2 h after 10 days of QD or BID administration in the multiple ascending dose phase
  - Less than 4.4% of the dose was recovered unchanged in urine.

JTE-052 Pan JAK Inhibitor





- Phase 2 study, n=327
- Well-tolerated with improvements even in one day
  - 0.025% less effective

Vitiligo

- CD81 T cells drive melanocyte destruction via IFN-ɣ
  - signaling utilizes the JAK-STAT pathway
- Activated CD8+ T cells produce IFN-ɣ and other inflammatory mediators to target melanocytes
- JAK inhibition allows melanocyte regeneration by blocking IFN-ɣ-mediated inflammation

Kim SR, *et al.* "Rapid repigmentation of vitiligo using tofacitinib plus low-dose, narrowband UV-B phototherapy," *JAMA Dermatol.* 2018;154(3):370-1;
Rothstein B, *et al., "*Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib," *J Am Acad Dermatol.* 2017; 76(6):1054-60.;
Joshipura D, *et al*. "Treatment of vitiligo with the topical Janus kinaseinhibitor ruxolitinib: A 32-week open-label extension study with optional narrow-band ultraviolet B," *J Am Acad Dermatol.* 2018; 78(6):1205-7.

Vitiligo

- Ruxolitinib1.5% cream applied bid, n=12
  - 4/11 → ↑ 76% facial VASI w. 20 (95% CI 53-99%; P = .001)
  - 3/8 patients responded on body, 1/8 patients on acral surfaces
    - With NB-UVB improved further
  - report phase 2 data in 2019, start phase 3 trial in 2019
- ATI-502 (topical): open label phase 2 study
  - Anticipated release of data early 2019.
- Oral Ruxolitinib 20 mg bid for over 20 weeks
  - Both vitiligo and AA
  - experienced significant facial repigmentation but depigmentation recurred after discontinuing ruxolitinib

Kim SR, *et al.* "Rapid repigmentation of vitiligo using tofacitinib plus low-dose, narrowband UV-B phototherapy," *JAMA Dermatol.* 2018;154(3):370-1;
Rothstein B, *et al., "*Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib," *J Am Acad Dermatol.* 2017; 76(6):1054-60.;
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Janus Kinase Inhibitors **for Vitiligo**

- Tofacitinib:
  - 53-year-old pt with vitiligo covering her face, hands and body
  - 5 mg every other day, increased to 5 mg daily after 3 weeks.
  - **2 months: partial repigmentation**
  - **5 months: “white patches nearly all gone”**
  - *Real world costs: $12,000/year*

Craiglow, BG and King, BA “Tofacitinib Citrate for the Treatment of Vitiligo, A Pathogenesis-Directed Therapy,” *JAMA Dermatol*, 2015;151(10):1110-1112

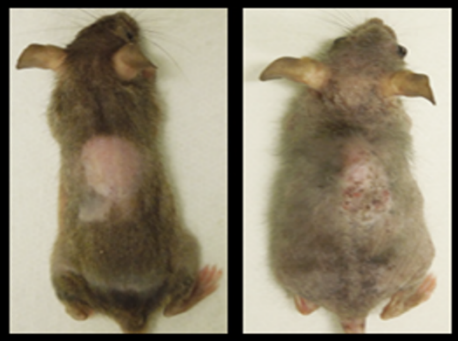
Tofacitinib and Alopecia Universalis

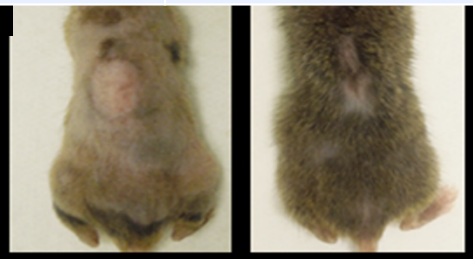
- IL-6 activates Janus kinase (JAK)→can reverse the IL-6-induced, STAT3-dependent profibrotic effects on TGF-β1 and collagen I expression
  - autoreactive CD81 T cells. JAK-STAT dependent cytokines, including IFN-g
  - IL-15, drive proliferation and activation of autoreactive T cells
- JAK Inhibitors induce restoration by:
  - anti-inflammatory effects
  - anagen initiation
  - promotion of the activation of hair follicles stem cells
- Phase 2 trials with both an oral JAK1/3 inhibitor (ATI-501) and a topical JAK1/3 inhibitor (ATI-502)

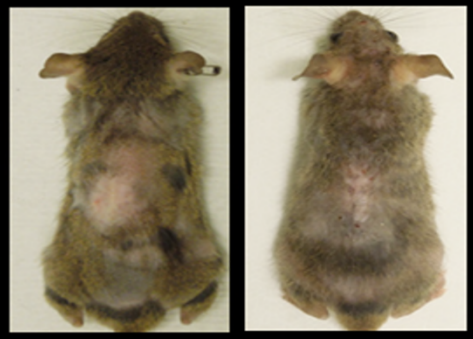
Mackay-Wiggan J, *et al.* "Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata" *JCI Insight.* 2016 1(15):e89790; Jabbari A, *et al* "Reversal of Alopecia Areata Following Treatment With the JAK1/2 Inhibitor Baricitinib" *EBioMedicine*. 2015 2(4):351-5

JAK2 inhibition is *not* required for efficacy in Alopecia Areata

Compound	JAK1/JAK 3 Enzyme IC_{50} (nM)	IL2 pSTAT5 (JAK1/JAK 3) IC_{50} (nM)	INFg pSTAT1 (JAK1/JAK 2) IC_{50} (nM)	GMCSF pSTAT5 (JAK2/JAK 2) IC_{50} (nM)
ATI-502	2/36	9	38	>20000
Ruxo	2/701	8	9	88
Bari	2/5	5	11	57
Tofa	3/1	12	55	241







Investigation of JAK1/3 selective compound, ATI-50001/50002

Courtesy Michael Tung, M.D., Aclaris Therapeutics, Inc.

JAK Inhibitors and Alopecia

- Open label phase 2 study n=66 tofacitinib 5 mg bid
  - 32% of patients with 50% Improvement
  - Relapse occurred after a median of 8.5 weeks after cessation.
- N=90 AA patients treated with tofacitinib 5mg bid reported 50% improvement in 42% of patients.
  - 9 of 13 adolescents treated showed significant hair regrowth.
  - AA>>universalis (81.9% vs 59.0%)
- Open-label study Ruxolitinib 20 mg bid n=12
  - ~92% was observed in 9 pts after 3 to 6 mo
  - 1 report topical ruxolitinib-- complete regrowth of eyebrows but only 10% regrowth of scalp hair
- Baricitinib—CANDLE Syndrome
  - chronic atypical neutrophilic dermatosis, lipodystrophy elevated temperature
  - exhibiting full scalp hair regrowth after 9 months

Liu LY, Craiglow BG, Dai F, King BA. "Tofacitinib for the treatment of severe alopecia areata and variants: a study of 90 patients," *J Am Acad Dermatol*. 2017;76:22-28.
Craiglow BG, Liu LY, King BA. "Tofacitinib for the treatment of alopecia areata and variants in adolescents. *J Am Acad Dermatol*. 2017;76:29-32.

Tofacitinib for Granuloma Annulare?

- Why?
- Control against Th-1 inflammation cascade
- TNF-α expression and release
- Potential use for disseminated variants

- Why not?
- Toxicity potential if above 5 mg
- Long-term issues of compliance when unsure of endpoint
- Costs

Where could JAK Inhibitors work in Derm?

- Tofacitinib: FDA approved for RA and PsA
- Ruxolitonib: Myelofibrosis and Polycythemia Vera
  - Oclacitinib: approved for atopic dermatitis…in dogs
- In trials:
  - Psoriasis
  - Atopic Dermatitis
  - Vitiligo
  - Alopecia Areata
- Anecdotal
  - CTCL
  - Mastocytosis
  - Granulomatous disorders
- Autoimmune disorders
  - Lupus/Dermatomyositis
- Where we haven’t had any luck:
  - Lichen Planus
  - GVHD
  - Erythema Multiforme
- Instead of Steroids? Biologics?

Don’t Be Afraid…

…To Think Outside the Box

Thank You