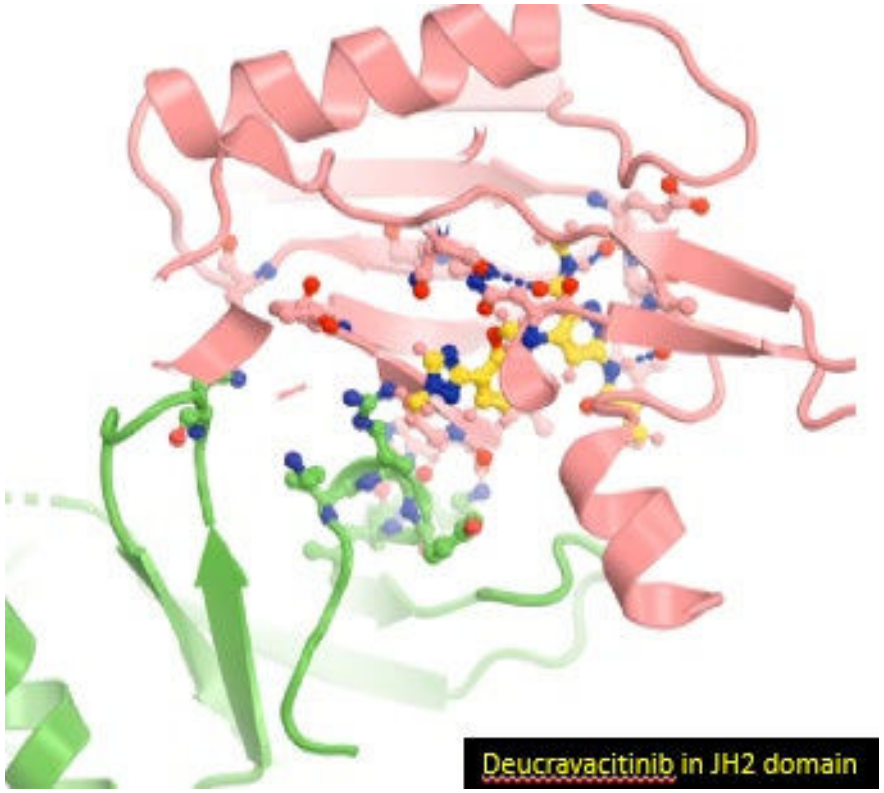
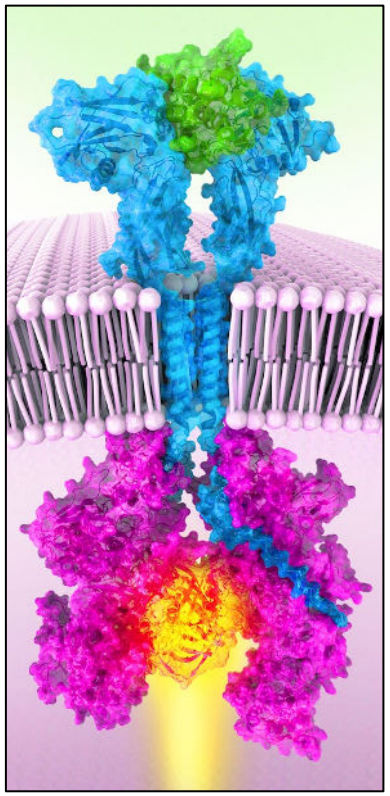
South Beach Symposium
medical + aesthetic dermatology

TYK2 in PsO + Beyond





Christopher G. Bunick, MD, PhD
Associate Professor of Dermatology & Program in Translational Biomedicine
Yale School of Medicine

South Beach Symposium
medical + aesthetic dermatology

TYK2 in PsO + Beyond

DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

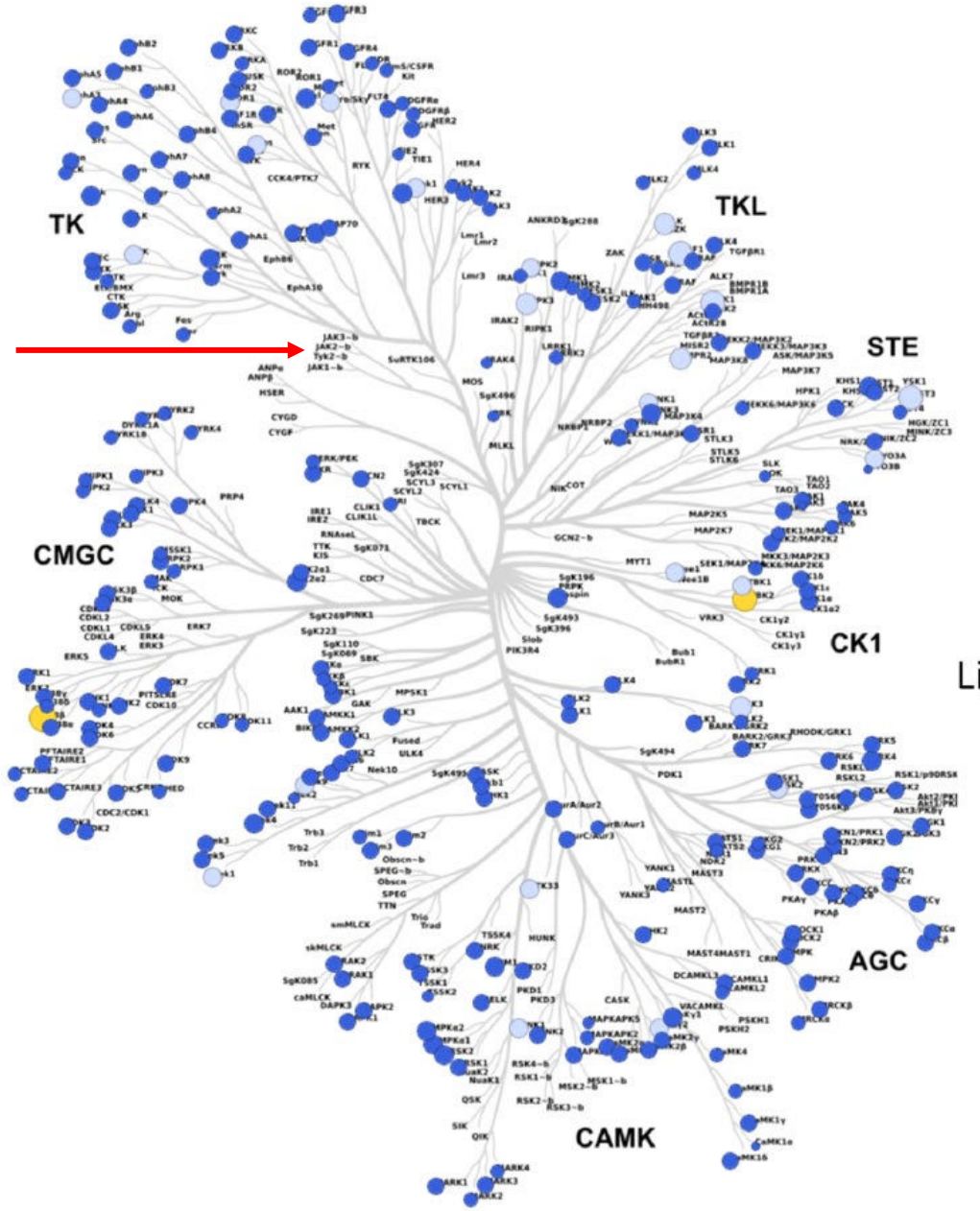
Abbvie: Investigator, Consultant
Almirall: Investigator, Consultant
Apogee: Investigator, Consultant
Arcutis: Consultant
Eli Lilly: Consultant
LEO Pharma: Investigator, Consultant
Novartis: Consultant

Ortho Dermatologics: Investigator, Consultant
Palvella: Investigator
Pfizer: Consultant
Sanofi-Regeneron: Consultant
Sun Pharma: Investigator, Consultant
Timber: Investigator
UCB Pharma: Consultant

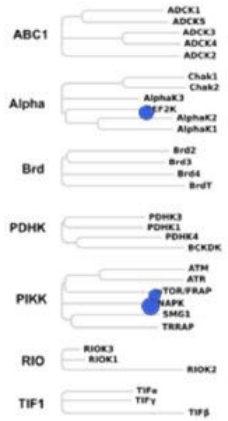
Christopher G. Bunick, MD, PhD
Associate Professor of Dermatology & Program in Translational Biomedicine
Yale School of Medicine

Unlocking and targeting the Kinome: only a fraction has been therapeutically explored

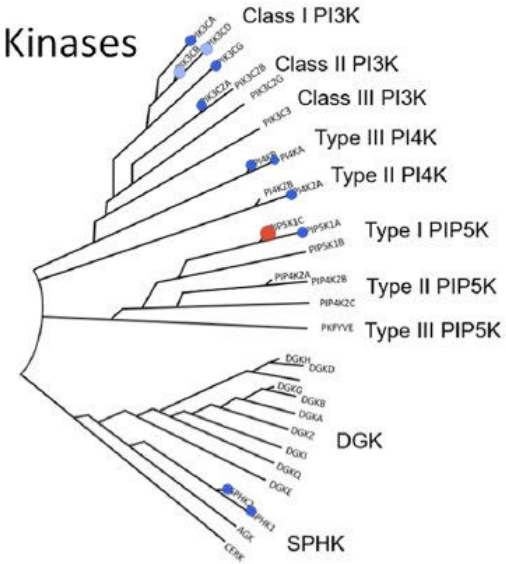
4 Derm JAKs



Atypical Kinases

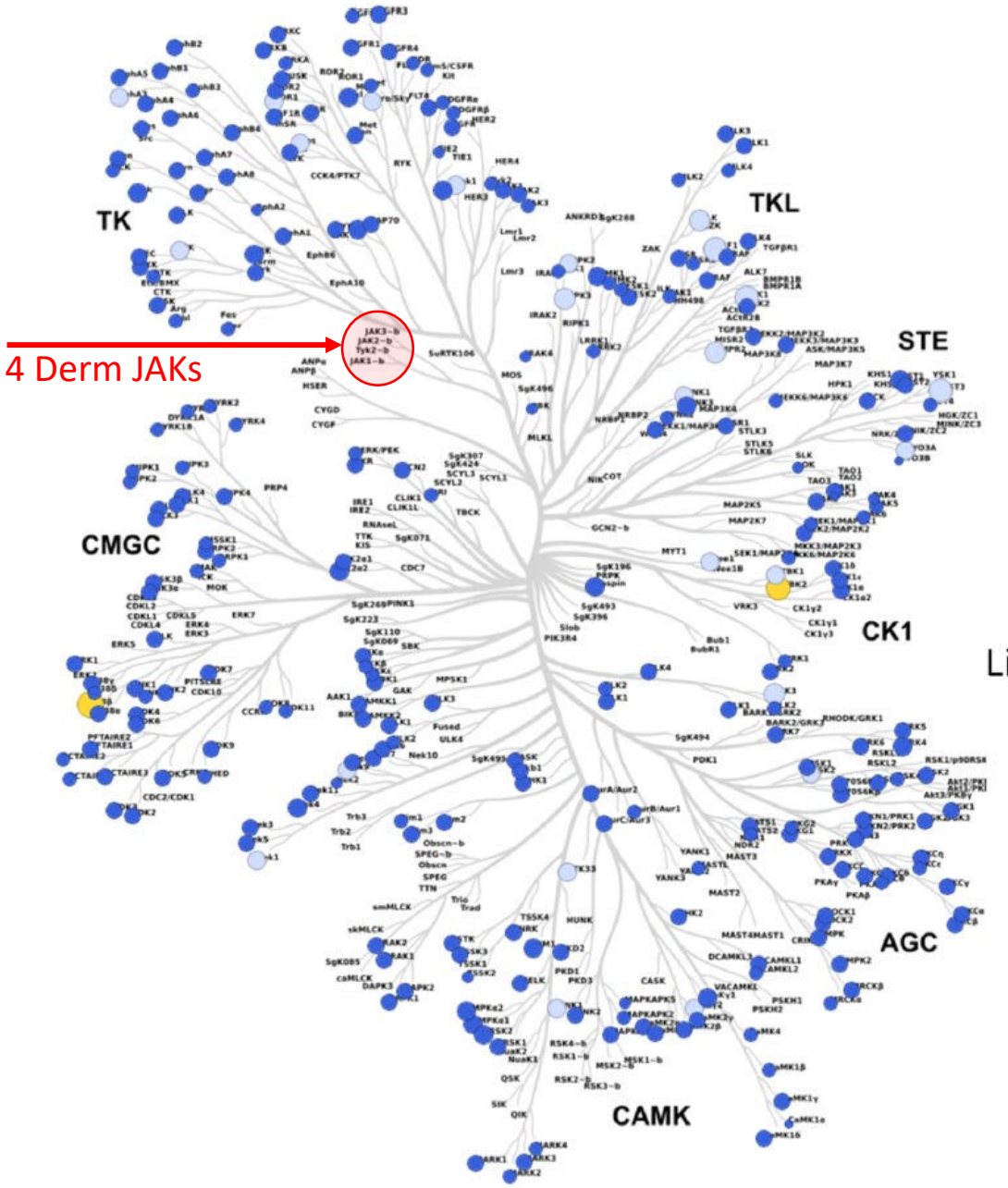


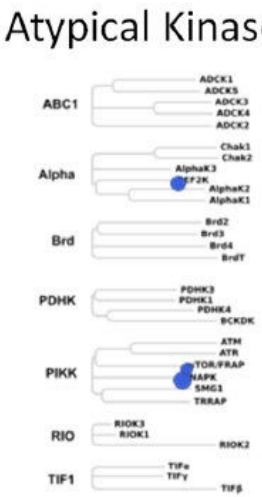
Lipid Kinases

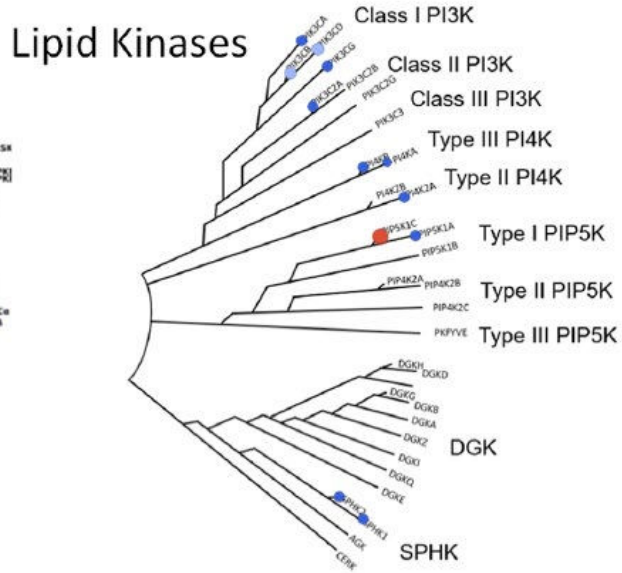


Leit S, et al. Discovery of a Potent and Selective Tyrosine Kinase 2 Inhibitor: TAK-279. J Med Chem. 2023 Aug 10;66(15):10473-10496.

Unlocking and targeting the Kinome: only a fraction has been therapeutically explored

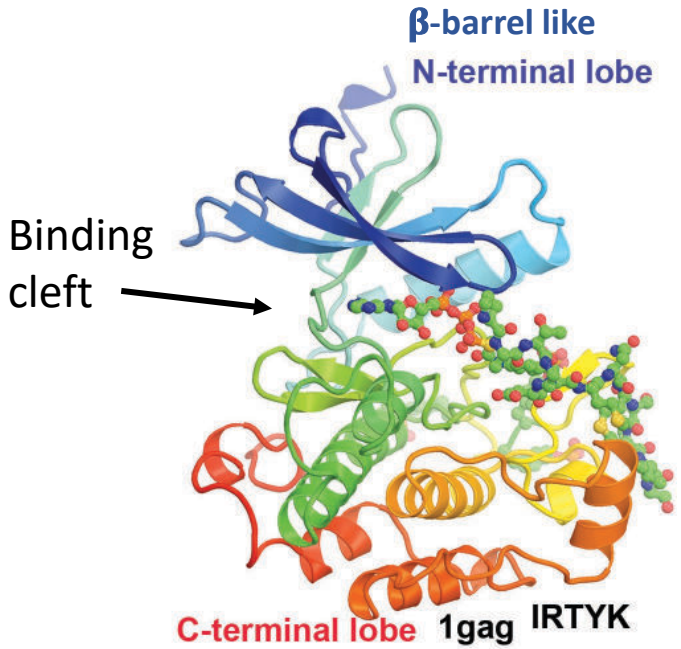






JAK protein organization

Leonard & O'Shea



Leit S, et al. Discovery of a Potent and Selective Tyrosine Kinase 2 Inhibitor: TAK-279. J Med Chem. 2023 Aug 10;66(15):10473-10496.

Conceptual framework for JAK and TYK2 Inhibition

JAK family of kinases

TYK2
JAK1
JAK2
JAK3

4 phylogenetically related proteins

Shared structural homology

Regulatory or allosteric domain

Active phosphorylation domain

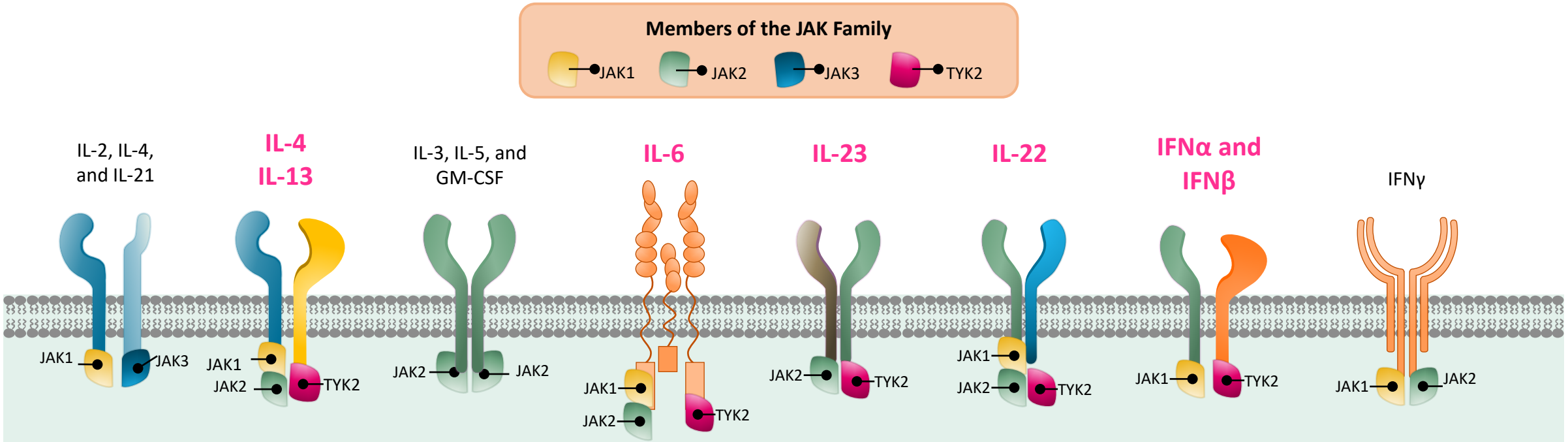
"TYK2 inhibitors"

"JAK inhibitors"

Regulatory Domain Inhibitors or Allosteric Domain Inhibitors

Kinase Domain Inhibitors

Extracellular cytokine signaling is linked to intracellular JAK/STAT signaling



Different combinations of JAKs and TYK2 associate with different cytokine receptors, thereby mediating distinct immunomodulatory and inflammatory signals

*The **JAK-STAT pathway** is implicated in the activation of keratinocytes and immune cells. This may lead to increased cytokine secretion, which in turn **promotes further inflammation** and amplifies the immune response.*[2,7,8]

GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; JAK, Janus kinase; TYK, tyrosine kinase.

Adapted from Schwartz DM et al. Nat Rev Drug Discov. 2017;16:843–62.

1. Schwartz DM et al. Nat Rev Drug Discov. 2017;16:843–62. 2. Lee GR, et al. *Dermatol Ther* 2019;e12840:1–12; 3. Tanimoto A, et al. *Inflamm Res* 2015;64:41–51; 4. Dubin C, et al. *Ther Clin Risk Manag* 2020;16:1319–1332. Erratum in: *Ther Clin Risk Manag* 2021;17:233; 5. Virtanen AT, et al. *BioDrugs* 2019;33:15–32. 6. Junttila, S Iikka. Frontiers in Immunology 2018(9);1-6, 7. Weidinger S, et al. *Nat Rev Dis Primers* 2018;4:1; 8. Gittler JK, et al. *J Allergy Clin Immunol* 2013;131:300–313.

Table 1 Jaks and STATs that are activated by cytokines

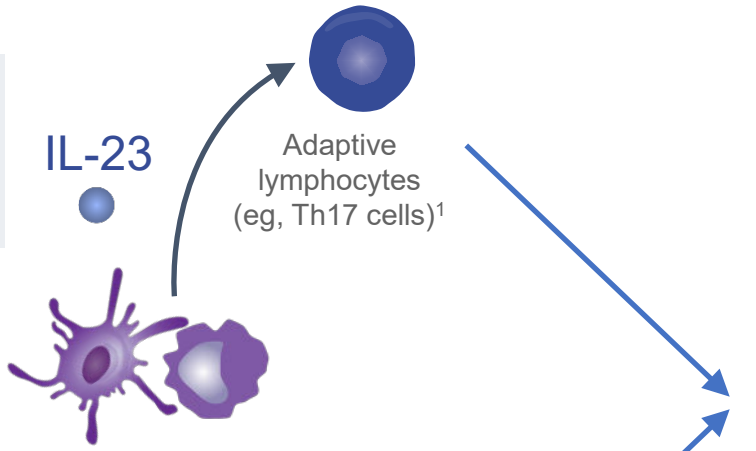
Type I Cytokines	Jaks	STATs
Cytokines whose receptors share γ_c		
IL-2, IL-7, IL-9, IL-15	Jak1, Jak3	Stat5a, Stat5b, Stat3
IL-4	Jak1, Jak3	Stat6
IL-13*	Jak1, Jak2, Tyk2	Stat6
Cytokines whose receptors share β_c		
IL-3, IL-5, GM-CSF	Jak2	Stat5a, Stat5b
Cytokines whose receptors share gp130		
IL-6, IL-11, OSM, CNTF, LIF, CT-1	Jak1, Jak2, Tyk2	Stat3
IL-12$^+$	Jak2, Tyk2	Stat4
Leptin$^+$		Stat3
Cytokines with homodimeric receptors		
Growth hormone	Jak2	Stat5a, Stat5b, Stat3
Prolactin	Jak2	Stat5a, Stat5b
Erythropoietin	Jak2	Stat5a, Stat5b
Thrombopoietin	Jak2	Stat5a, Stat5b
Type II Cytokines		
Interferons		
IFNα, IFNβ	Jak1, Tyk2	Stat1, Stat2
IFNγ	Jak1, Jak2	Stat1
IL-10‡	Jak1, Tyk2	Stat3

*IL-13 does not share γ_c but uses IL-4Rα.
$^+$IL-12 and leptin do not share gp130, but their receptors are related to gp130.
‡IL-10 is not an interferon, but its receptor is a type II cytokine receptor.

The IL-23/IL-17 Axis: A Central Part of the Pathophysiology of Psoriasis

TYK2 is involved in IL-23 dependent and independent pathways in PsO

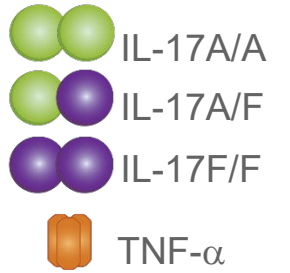
IL-23–dependent IL-17A/F production via adaptive immune cells



IL-23–independent IL-17A/F production via innate-like immune cells

Innate lymphocytes (eg, MAIT / γδ T cell)[1,2]

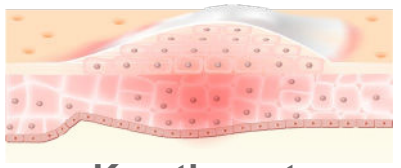
Innate cells are slightly more biased to IL-17F production[3]



Inflammation

IL-17F Has Overlapping Biology With IL-17A and Forms Hetero- and Homodimers Secreted by Adaptive and Innate Immune Cells

Skin inflammation



Keratinocyte proliferation

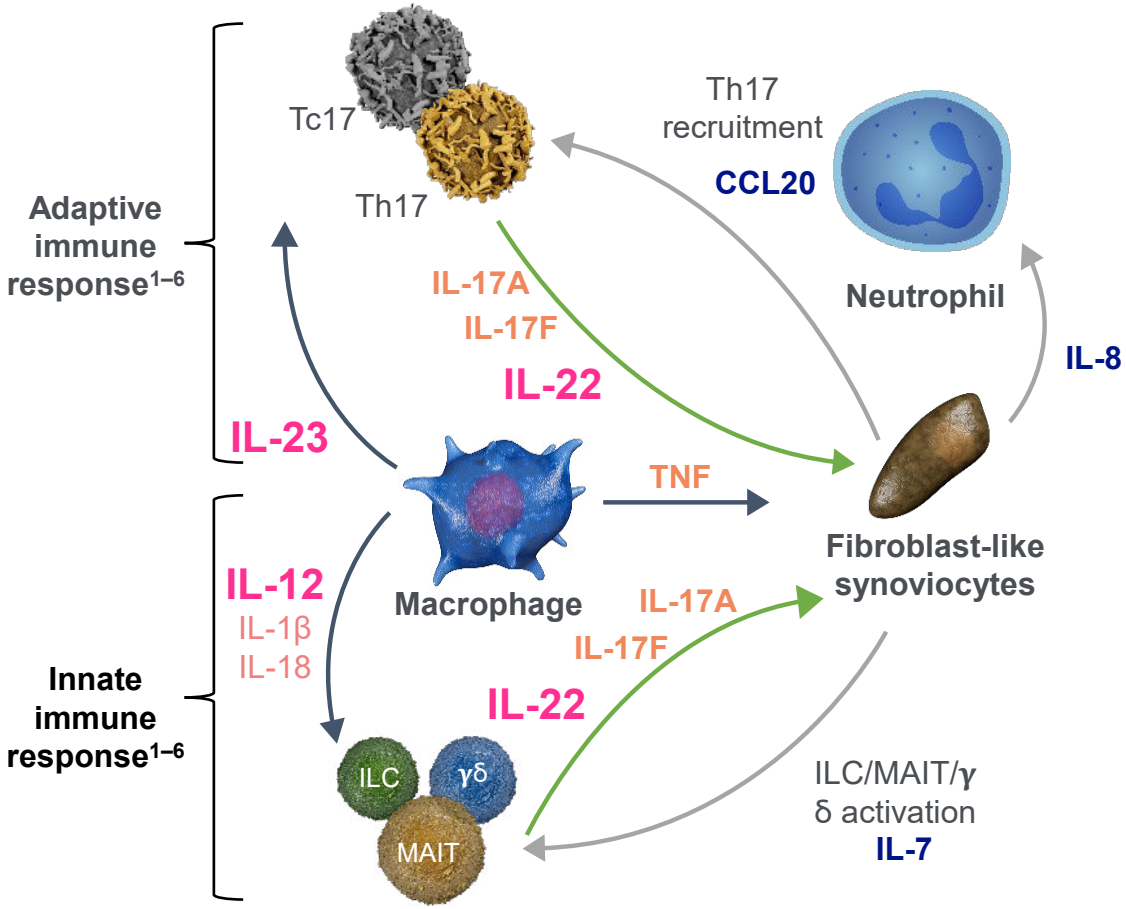
Keratinocytes, in turn, produce cytokines and chemokines, driving an inflammatory feedback loop

APC, antigen-presenting cell; γδ, gamma delta; IL, interleukin; ILC, innate lymphoid cell; MAIT, mucosal-associated invariant T cell; Th, T helper; TNF, tumor necrosis factor.

1. Tsukazaki H, Kaito T. *Int J Mol Sci*. 2020;21(17):6401. **2.** Rosine N, Miceli-Richard C. *Front Immunol.* 2021;11:553742. **3.** Cole S, et al. *Front Immunol*. 2020;11:585134. **4.** Blanco P, et al. *Cytokine Growth Factor Rev*. 2008;19(1):41-52. **5.** Lynde CW, et al. *J Am Acad Dermatol.* 2014;71(1):141-150. **6.** Oliver R, et al. *Br J Dermatol.* 2021;10.1111/bjd.20827.

Key Inflammatory Pathways Are Involved In the Pathobiology of Psoriatic Arthritis

TYK2 is involved in adaptive and innate immune pathways in PsA

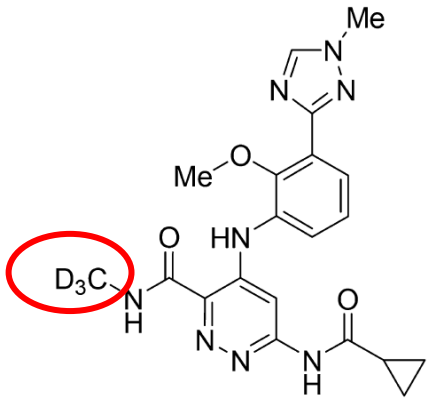


Pathobiology figure adapted from Smith J and Colbert R. *Arthritis Rheumatol*. 2014;66:231–241. *Image reproduced from Soldati E, et al. *PLoS One*. 2021;16(5):e0251788 under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/); †Image used with permission of the author from Nicolaes J, et al. ACR Convergence 2021. Poster 0157. ‡Image reproduced from Laloo F, et al. *Insights Imaging*. 2019;10(1):67 under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/). §Reproduced from Gottlieb A, et al. *PLoS One*. 2015;10:e0134703 under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

axSpA, axial spondyloarthritis; CCL, C-C motif chemokine ligand; IL, interleukin; ILC, innate lymphoid cell; MAIT, mucosal-associated invariant T cells; PsA, psoriatic arthritis; SI, sacroiliac; Tc, CD8+ T cell; Th, T helper; TNF, tumor necrosis factor

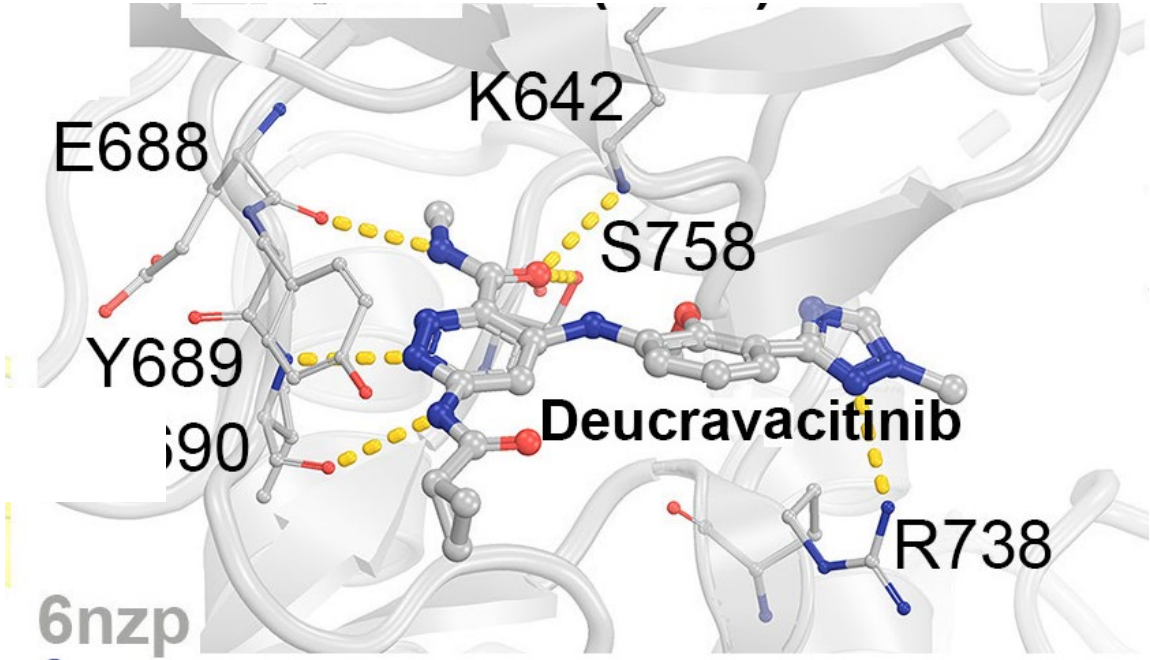
1. Tsukazaki H and Kaito T. Int *J Mol Sci*. 2020;21:6401. 2. Smith JA and Colbert RA. *Arthritis Rheumatol*. 2014;66(2):231–241. 3. Blanco P, et al. *Cytokine Growth Factor Rev*. 2008;19:41–52. 4. Rosine N and Miceli-Richard C. *Front Immunol*. 2021;11:553742. 5. Cole S, et al. *Front Immunol*. 2020;11:585134. 6. Taams L, et al. *Nat Rev Rheum*. 2018;14:453–466. 7. Shah M, et al. *RMD Open*. 2020;6(2):e001306. 8. Fassio A, et al. *Int J Mol Sci*. 2023;24(19):14924. 9. Soldati E, et al. *PLoS One*. 2021;16(5):e0251788. 10. Nicolaes J, et al. ACR Convergence 2021. Poster 0157. 11. Laloo F, et al. *Insights Imaging*. 2019;10(1):67. 12. Gottlieb A, et al. *PLoS One*. 2015;10:e0134703.

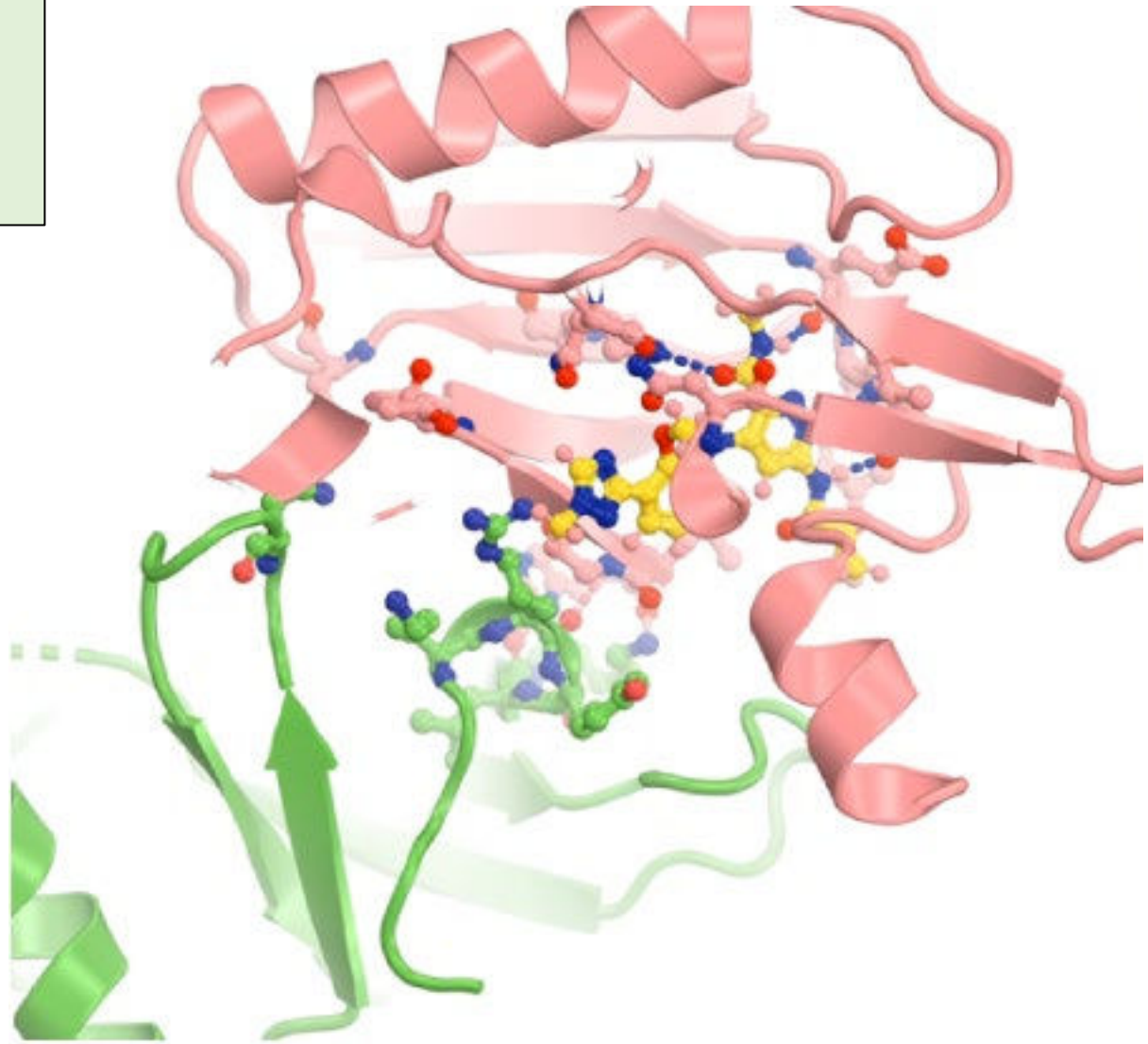
Deucravacitinib binding to TYK2 JH2



BMS-986165, **11**
TYK2-selective allosteric

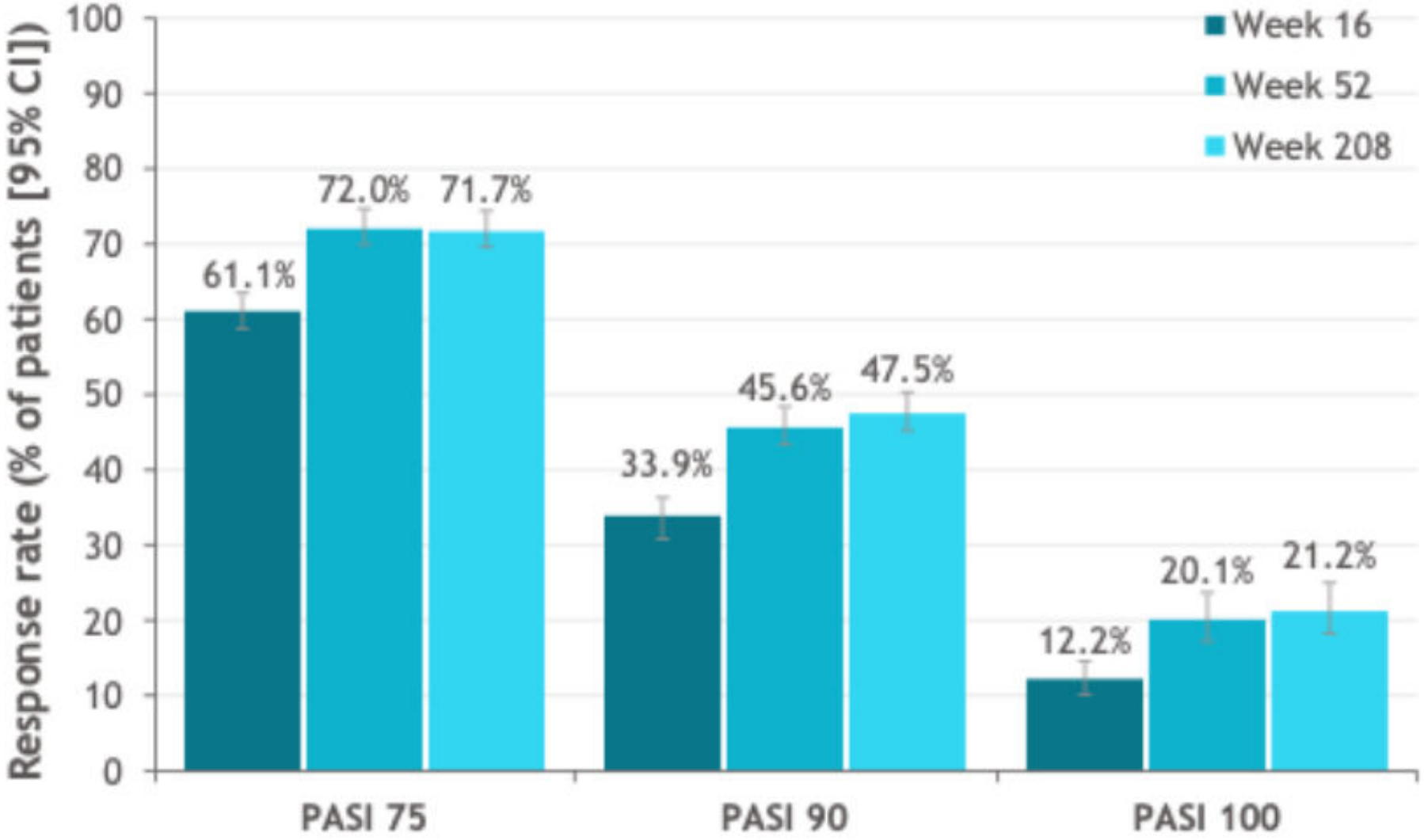
1) Deuterium incorporated into methyl group to block an N-demethylation metabolic pathway that generated a less selective metabolite.
2) Deuterium incorporated during de novo drug design to shunt an undesirable metabolic pathway in vivo.





Deucravacitinib in JH2 domain

Proportions of patients achieving PASI thresholds over time with continuous DEUCRA treatment



South Beach Symposium
medical + aesthetic dermatology

Courtesy Bristol Myers Squibb

4-year Safety Summary of Deucravacitinib (as treated population)

	1 year		2 years		4 years	
	Cumulative through 1 year[1] (POETYK PSO-1 + PSO-2)		Cumulative through 2 years[1,2,a] (POETYK PSO-1 + PSO-2 + LTE)		Cumulative through 4 years[3,4,b] (POETYK PSO-1 + PSO-2 + LTE)	
	SOTYKTU 6 mg QD (N = 1364) Total PY = 969.0		SOTYKTU 6 mg QD (N = 1519) Total PY = 2482.0		SOTYKTU 6 mg QD (N = 1519) Total PY = 4392.8	
AE category	n	EAIR/100 PY	n	EAIR/100 PY	n	EAIR/100 PY
AEs	995	229.2	1214	154.4	1301	131.7
SAEs	55	5.7	145	6.1	205	5.0
Discontinued treatment due to AEs	43	4.4	69	2.8	97	2.2
Deaths[c]	2	0.2	10[c]	0.4	11[d]	0.3
Most common AEs (EAIR/100 PY ≥5)						
Nasopharyngitis	229	26.1	271	12.9	343	9.7
COVID-19[e]	5	0.5	124	5.1	321	8.3
Upper respiratory tract infection	124	13.4	150	6.5	240	6.1
Headache	80	8.5	99	4.2	117	2.8
Arthralgia	55	5.7	85	3.5	117	2.8
Diarrhea	69	7.3	84	3.5	99	2.4

South Beach Symposium
medical + aesthetic dermatology

Courtesy Bristol Myers Squibb

4-year Safety Summary of Deucravacitinib (AESI)

1 year 2 years 4 years

AE category	Cumulative through 1 year[1,2] (POETYK PSO-1 + PSO-2) SOTYKTU 6 mg QD (N = 1364) Total PY = 969.0		Cumulative through 2 years[1,3,a] (POETYK PSO-1 + PSO-2 + LTE) SOTYKTU 6 mg QD (N = 1519) Total PY = 2482.0		Cumulative through 4 years[4,5,b] (POETYK PSO-1 + PSO-2 + LTE) SOTYKTU 6 mg QD (N = 1519) Total PY = 4392.8	
	n	EAIR/100 PY	n	EAIR/100 PY	n	EAIR/100 PY
Serious infections	17	1.7	64	2.6	85	2.0
Serious COVID-19 infection	2	0.2	30	1.2	38	0.9
Serious COVID-19 pneumonia	0	0.0	13	0.5	16	0.4
Herpes zoster infection[c]	9	0.9	18	0.7	25	0.6
MACE[d]	3	0.3	9	0.4	14	0.3
VTE[e]	2	0.2	3	0.1	3	0.1
Total malignancies	10	1.0	22	0.9	39	0.9
NMSC[f]	7	0.7	11	0.4	18	0.4
Malignancies excluding NMSC	3	0.3	12	0.5	22[g]	0.5
Lymphoma	1	0.1	3	0.1	3	0.1
Acne[h]	30	3.1	38	1.6	45	1.0
Folliculitis	27	2.8	32	1.3	35	0.8
Mouth ulcers[i]	27	2.8	34	1.4	40	0.9

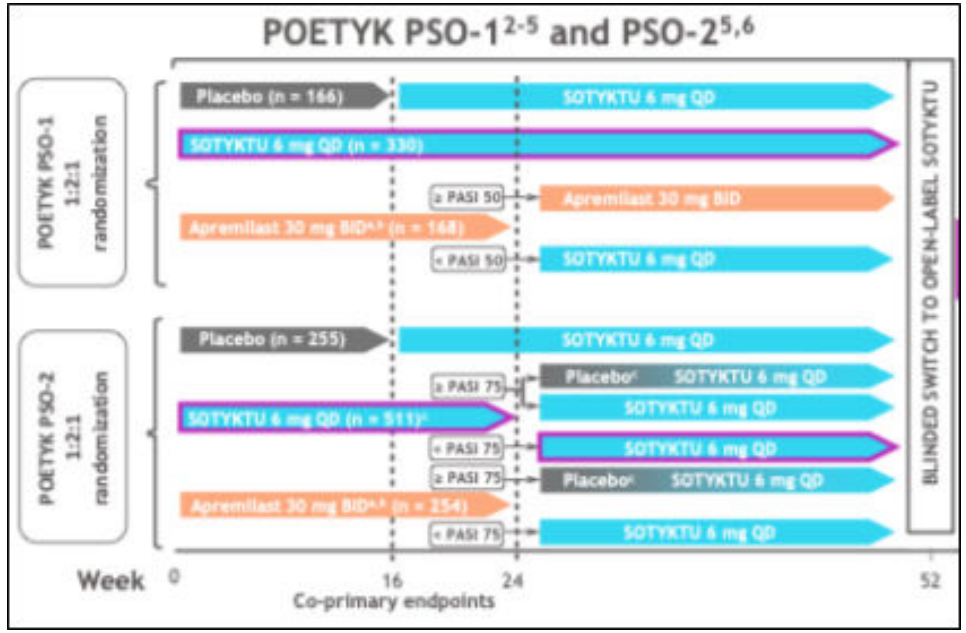
South Beach Symposium
medical + aesthetic dermatology

Courtesy Bristol Myers Squibb

Deucravacitinib superior to Apremilast in Head-to-Head Trial

Efficacy Results[1-5]

	Endpoints	POETYK PSO-1 SOTYKTU (n = 330)	POETYK PSO-1 Placebo (n= 166)	POETYK PSO-1 Apremilast (n= 168)	POETYK PSO-1 P value Vs PBO / Vs APR	POETYK PSO-2 SOTYKTU (n = 511)	POETYK PSO-2 Placebo (n= 255)	POETYK PSO-2 Apremilast (n= 254)	POETYK PSO-2 P value Vs PBO / Vs APR
Co-primary (vs placebo)	PASI 75 at week 16	58%	13%	–	<0.0001 / –	53%	9%	–	<0.0001 / –
	sPGA 0/1 response at week 16	54%	7%	–	<0.0001 / –	50%	9%	–	<0.0001 / –
Secondary	PASI 75 at week 16	58%	–	35%	– / <0.0001	53%	–	40%	– / 0.0004
	PASI 75 at week 24	69%	–	38%	– / <0.0001	58%	–	38%	– /<0.0001
	sPGA 0/1 response at week 16	54%	–	32%	– / <0.0001	50%	–	34%	– / <0.0001
	sPGA 0/1 response at week 24	59%	–	31%	– / <0.0001	49%	–	30%	– / <0.0001
	PASI 90 at week 16	36%	4%	20%	<0.0001 / 0.0002	27%	3%	18%	<0.0001 / 0.0046
	PASI 90 at week 24	42%	–	22%	– / <0.0001	32%	–	20%	– / 0.0002
	PASI 100 at week 16	14%	1%	–	<0.0001 / –	10%	1%	–	<0.0001 / –
	sPGA 0 at week 16	18%	1%	5%	<0.0001 / <0.0001	16%	1%	6%	<0.0001 / 0.0002
	ssPGA 0/1 with at least 2-grade improvement at week 16	70% (n=209)	17% (n=121)	39% (n=110)	<0.0001/ <0.0001	60% (n=305)	17% (n=173)	37% (n=166)	<0.0001/ <0.0001
	PSSD Symptom Score 0 (BL ≥ 1) at week 16	8%	1%	5%	0.0013 / NS	8%	1%	4%	0.0005 / NS
Additional	PASI 75 at week 52	65%	–	–	–	The same analysis at week 52 is not available because of the trial design and forced rerandomization			
	PASI 90 at week 52	44%	–	–	–				
	PASI 100 at week 52	19%							
	sPGA 0/1 response at week 52	53%	–	–	–				
	sPGA 0 at week 52	24%							



Courtesy Bristol Myers Squibb

Deucravacitinib superior to Apremilast in Head-to-Head Trial

Efficacy Results[1-5]

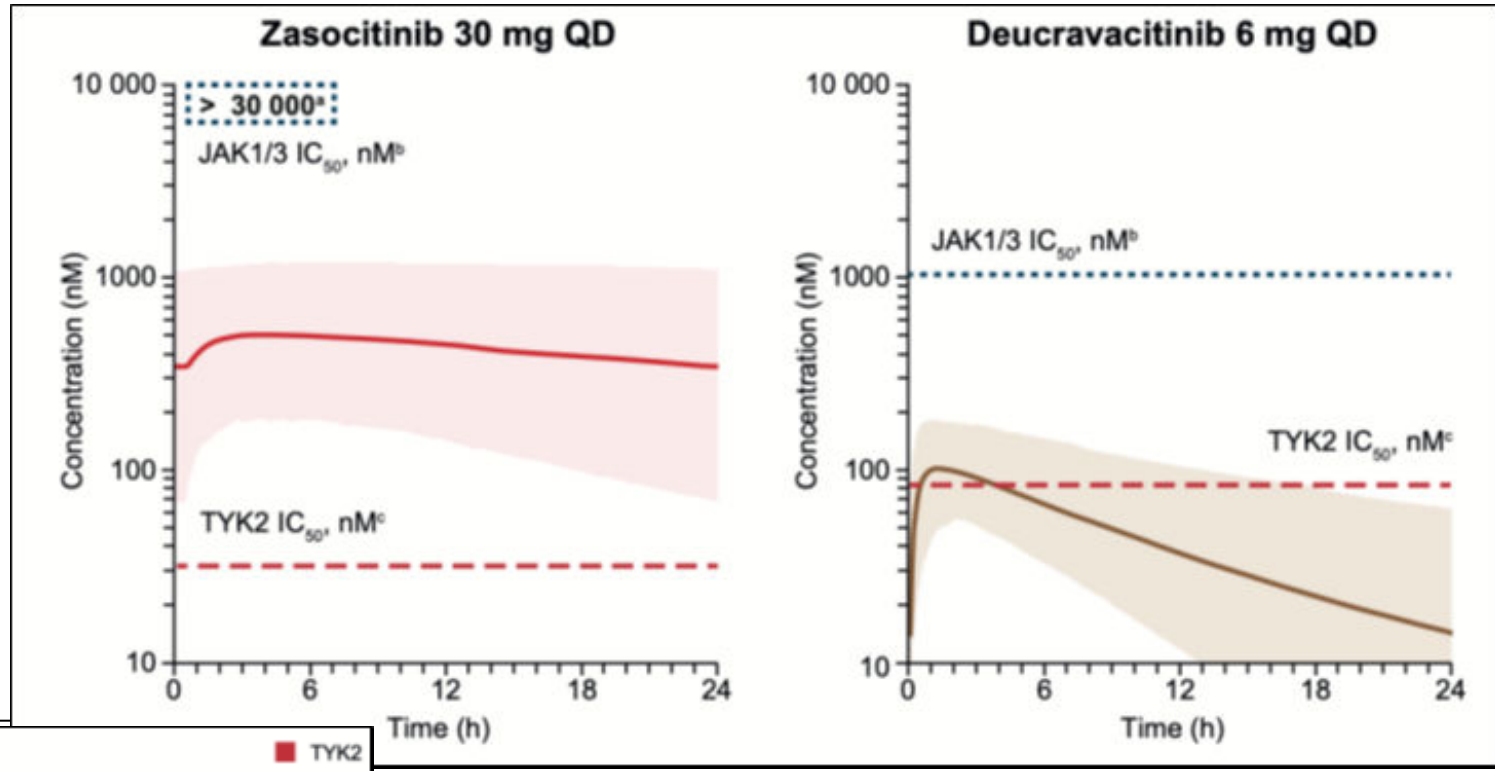
	Endpoints	POETYK PSO-1 SOTYKTU (n = 330)	POETYK PSO-1 Placebo (n= 166)	POETYK PSO-1 Apremilast (n= 168)	POETYK PSO-1 P value Vs PBO / Vs APR	POETYK PSO-2 SOTYKTU (n = 511)	POETYK PSO-2 Placebo (n= 255)	POETYK PSO-2 Apremilast (n= 254)	POETYK PSO-2 P value Vs PBO / Vs APR
Co-primary (vs placebo)	PASI 75 at week 16	58%	13%	–	<0.0001 / –	53%	9%	–	<0.0001 / –
	sPGA 0/1 response at week 16	54%	7%	–	<0.0001 / –	50%	9%	–	<0.0001 / –
Secondary	PASI 75 at week 16	58%	–	35%	– / <0.0001	53%	–	40%	– / 0.0004
	PASI 75 at week 24	69%	–	38%	– / <0.0001	58%	–	38%	– /<0.0001
	sPGA 0/1 response at week 16	54%	–	32%	– / <0.0001	50%	–	34%	– / <0.0001
	sPGA 0/1 response at week 24	59%	–	31%	– / <0.0001	49%	–	30%	– / <0.0001
	PASI 90 at week 16	36%	4%	20%	<0.0001 / 0.0002	27%	3%	18%	<0.0001 / 0.0046
	PASI 90 at week 24	42%	–	22%	– / <0.0001	32%	–	20%	– / 0.0002
	PASI 100 at week 16	14%	1%	–	<0.0001 / –	10%	1%	–	<0.0001 / –
	sPGA 0 at week 16	18%	1%	5%	<0.0001 / <0.0001	16%	1%	6%	<0.0001 / 0.0002
	ssPGA 0/1 with at least 2-grade improvement at week 16	70% (n=209)	17% (n=121)	39% (n=110)	<0.0001/ <0.0001	60% (n=305)	17% (n=173)	37% (n=166)	<0.0001/ <0.0001
	PSSD Symptom Score 0 (BL ≥ 1) at week 16	8%	1%	5%	0.0013 / NS	8%	1%	4%	0.0005 / NS
Additional	PASI 75 at week 52	65%	–	–	–	The same analysis at week 52 is not available because of the trial design and forced rerandomization			
	PASI 90 at week 52	44%	–	–	–				
	PASI 100 at week 52	19%							
	sPGA 0/1 response at week 52	53%	–	–	–				
	sPGA 0 at week 52	24%							

Courtesy Bristol Myers Squibb

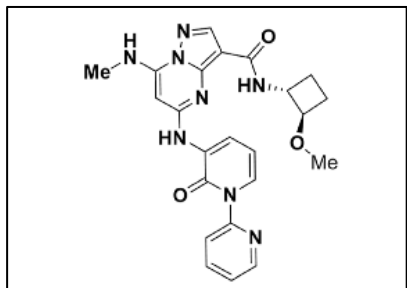
Zasocitinib: The next-generation TYK2 Inhibitor

	K_i from HTRF assay	
	Zasocitinib	Deucravacitinib
JAK1 JH2 (nM)[a]	> 15 000	1
TYK2 JH2 (pM)[b]	8.7	11.5
Biochemical selectivity (fold)	> 1.7×10^6	87

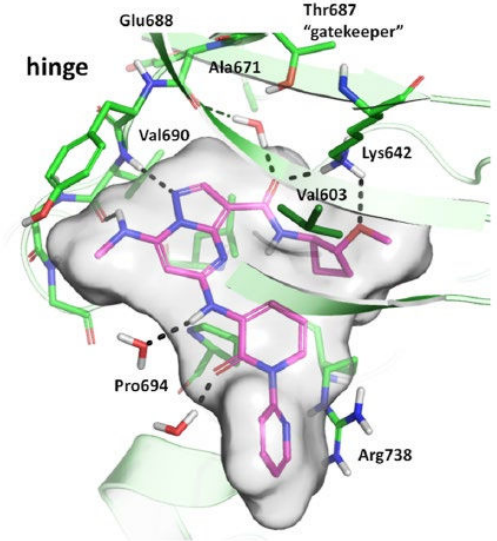
[a]Geometric mean of three samples; z-score ≥ 0.9, JAK1 JH2 (tracer) = 1 nM (K_D), JAK1 JH2 = 300 pM for both inhibitors.
[b]Geometric mean of three samples; z-score ≥ 0.8, TYK2 (tracer) = 225 nM (50 × K_D) for zasocitinib and 4.5 nM (K_D) for deucravacitinib, TYK2 = 200 pM for both inhibitors.



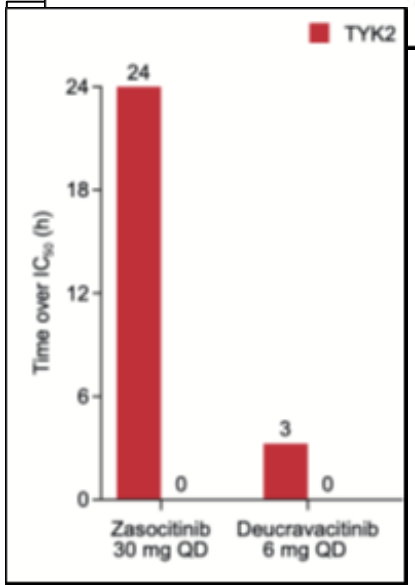
zasocitinib



Compound **30**
TAK-279 (formerly NDI-034858)



Compound **30**, TYK2 JH2 Kd = 0.0038 nM



Shailly Mehrotra,Yasuyo Sano, Petro Halkowycz, Elizabeth Wilson, Chandra Durairaj, Kok-Fai Kong, Guliang Xia, Faith Dunbar, Taylor Spector, Christopher Bunick, Iain B McInnes. Zasocitinib (TAK-279) displays high TYK2 inhibition and no inhibition of JAK1/3 versus licensed inhibitors. Poster presented at the European Society for Dermatological Research (ESDR) Conference 2024; 4–7 September 2024; Lisbon, Portugal.

South Beach Symposium
medical + aesthetic dermatology

Zasocitinib: The next-generation TYK2 Inhibitor

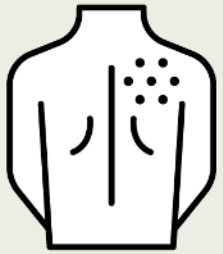
JAMA Dermatology

Phase 2b results

RCT: Tyrosine Kinase 2 Inhibition With Zasocitinib (TAK-279) in Psoriasis

POPULATION

177 Men, 82 Women



Adults with moderate to severe psoriasis for ≥6 mo covering ≥10% of total body surface area

Mean (SD [range]) age, 47 (13 [18-70]) y

INTERVENTION

259 Patients randomized and analyzed

52 Placebo
Matching oral placebo

50 Zasocitinib, 2 mg, daily

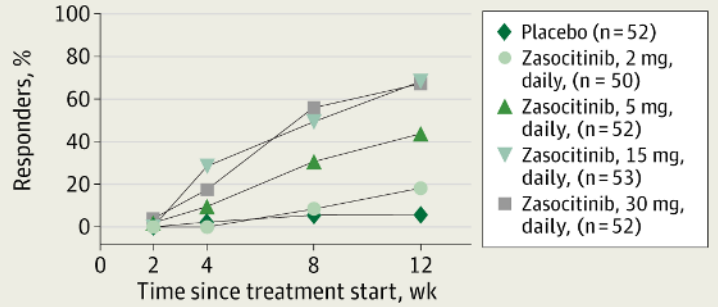
52 Zasocitinib, 5 mg, daily

53 Zasocitinib, 15 mg, daily

52 Zasocitinib, 30 mg, daily

FINDINGS

PASI 75 response rates were statistically significantly greater among patients receiving zasocitinib 5, 15, or 30 mg, daily, than receiving placebo (all $P < .001$)



PASI 75 response rate

Placebo: 6%

Zasocitinib, 2 mg: 18%, difference vs placebo: 12% (95% CI, 0-25; $P = .05$)

Zasocitinib, 5 mg: 44%, difference vs placebo: 39% (95% CI, 24-53; $P < .001$)

Zasocitinib, 15 mg: 68%, difference vs placebo: 62% (95% CI, 48-76; $P < .001$)

Zasocitinib, 30 mg: 67%, difference vs placebo: 62% (95% CI, 47-76; $P < .001$)

SETTINGS / LOCATIONS

55 Sites in North America

PRIMARY OUTCOME

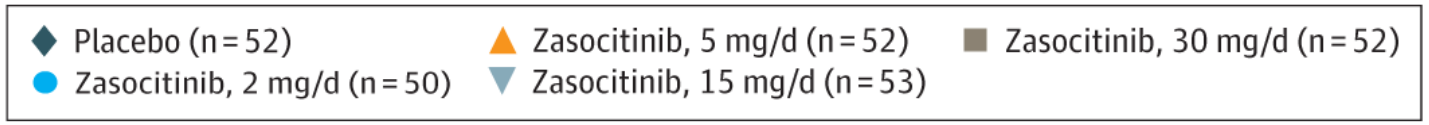
Proportion of patients achieving ≥75% improvement in Psoriasis Area and Severity Index (PASI) score from baseline (PASI 75) to wk 12

Armstrong AW, Gooderham M, Lynde C, et al. Tyrosine kinase 2 inhibition with zasocitinib in psoriasis: a randomized clinical trial. *JAMA Dermatol*. Published online August 21, 2024. doi:10.1001/jamadermatol.2024.2701

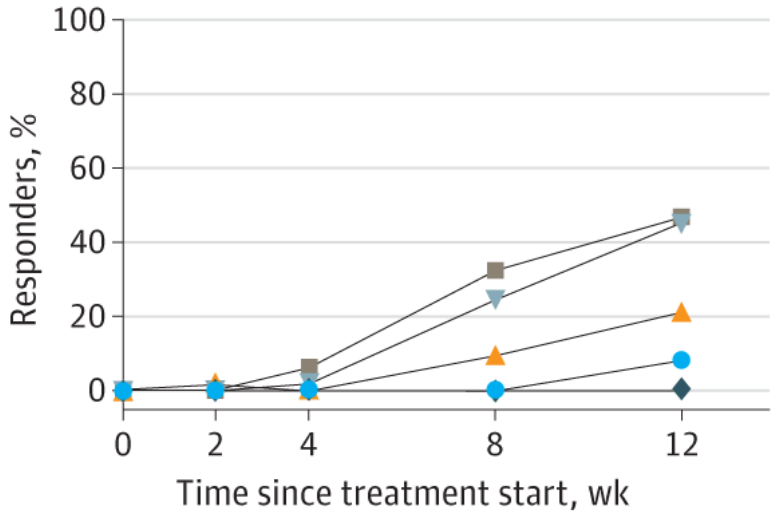
South Beach Symposium
medical + aesthetic dermatology

JAMA Dermatol. 2024;160(10):1066-1074. doi:10.1001/jamadermatol.2024.2701

Zasocitinib: The next-generation TYK2 Inhibitor

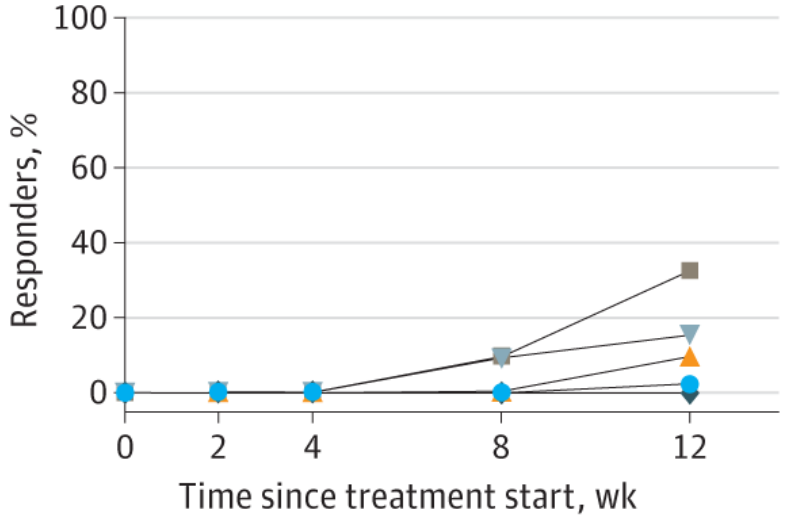


PASI 90



Response rate, No. (%)				
Placebo	0	0	0	0
Zasocitinib				
2 mg	0	0	0	4 (8)
5 mg	1 (2)	0	5 (10)	11 (21)
15 mg	0	1 (2)	13 (25)	24 (45)
30 mg	0	3 (6)	17 (33)	24 (46)

PASI 100



Response rate, No. (%)				
Placebo	0	0	0	0
Zasocitinib				
2 mg	0	0	0	1 (2)
5 mg	0	0	0	5 (10)
15 mg	0	0	5 (9)	8 (15)
30 mg	0	0	5 (10)	17 (33)

Deucra: PASI 100
wk 16 = 14%
wk 52 = 19%

JAMA Dermatol. 2024;160(10):1066-1074. doi:10.1001/jamadermatol.2024.2701