

TRANSLATIONAL SCIENCE

# JAK selectivity and the implications for clinical inhibition of pharmacodynamic cytokine signalling by filgotinib, upadacitinib, tofacitinib and baricitinib

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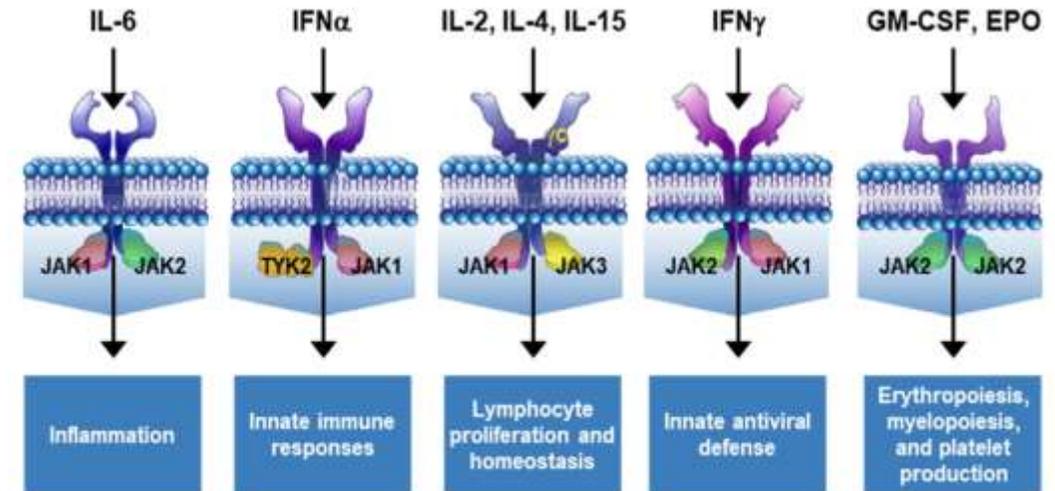
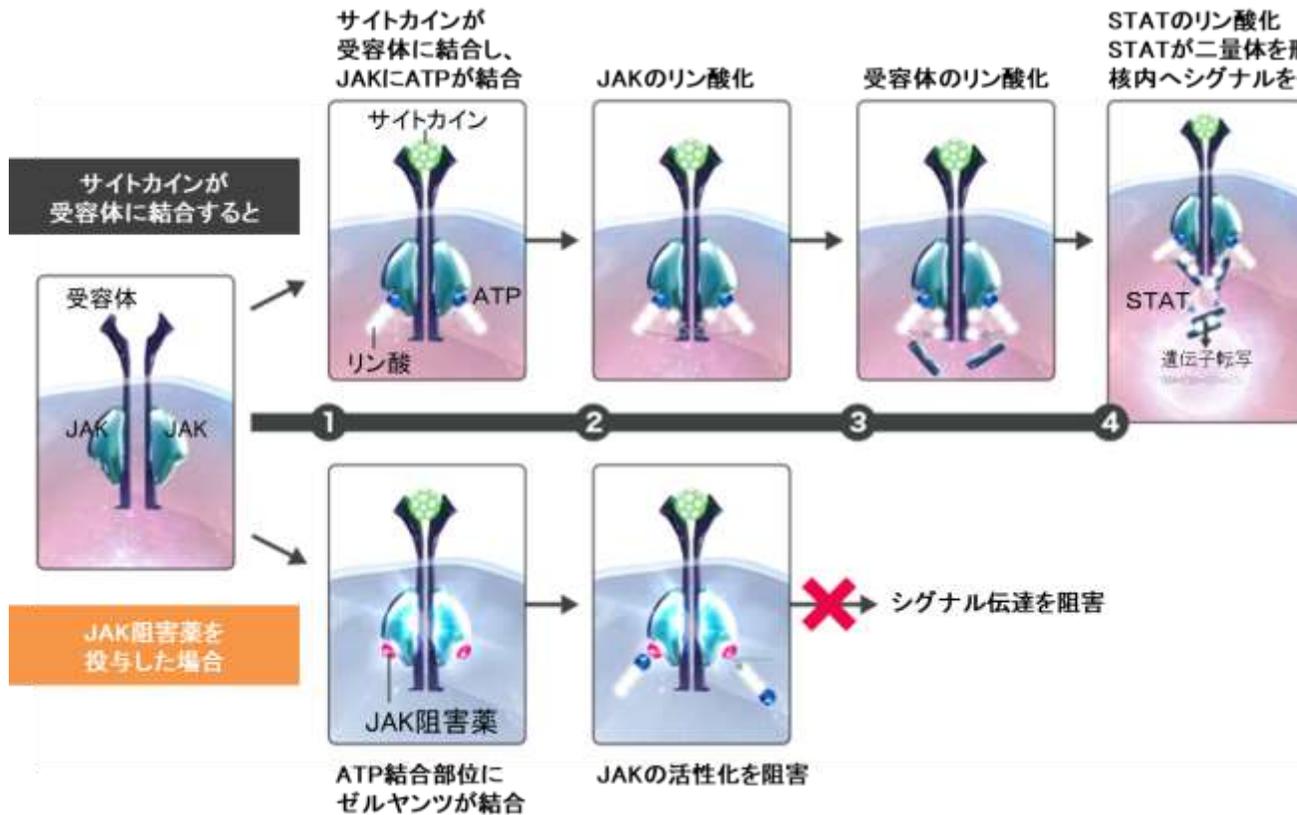
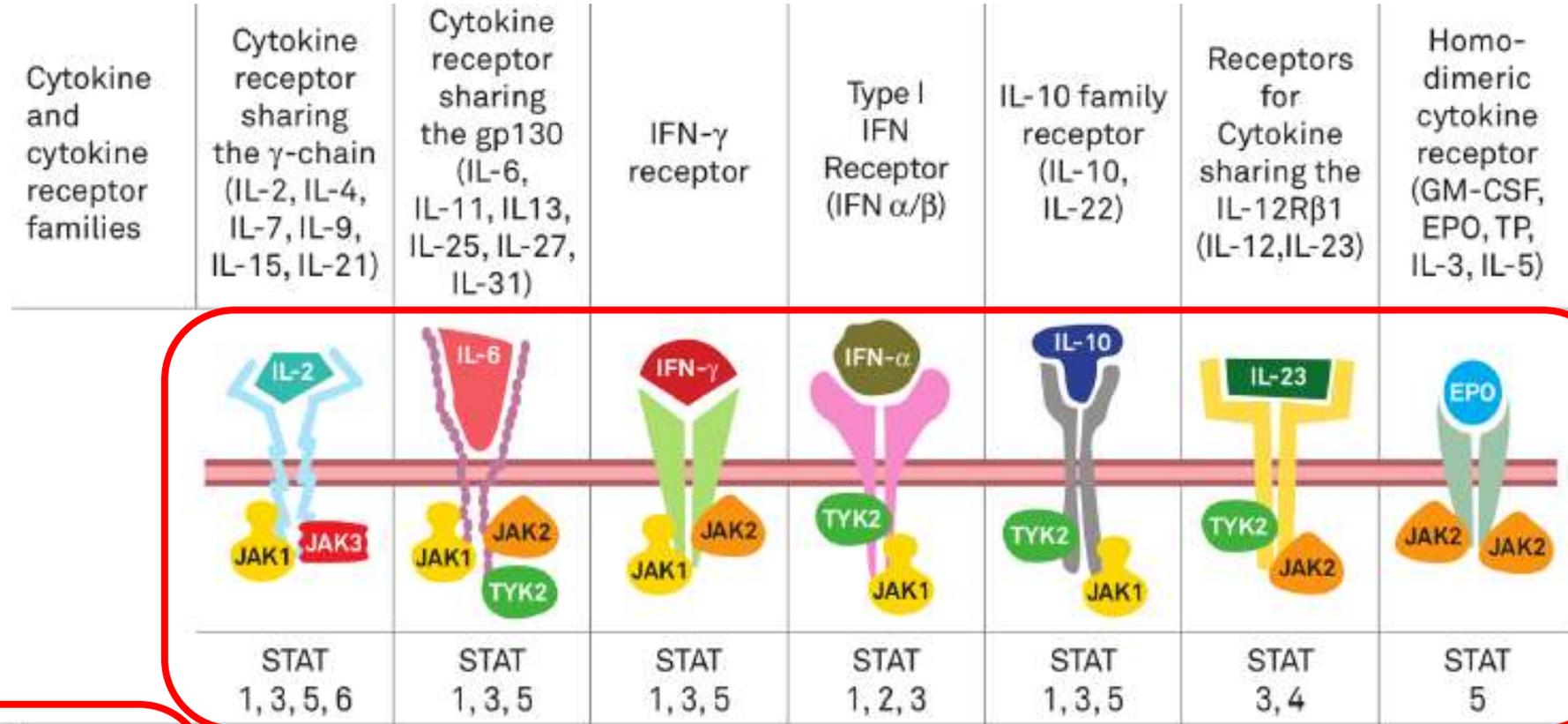


Figure 1 Cytokine receptors are associated with distinct JAK pairing patterns. The JAK isoforms involved in each pathway vary according to the specific cytokine receptor and dictate downstream outcomes. Figure adapted from Winthrop.<sup>40</sup> EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; TYK2, tyrosine kinase 2.

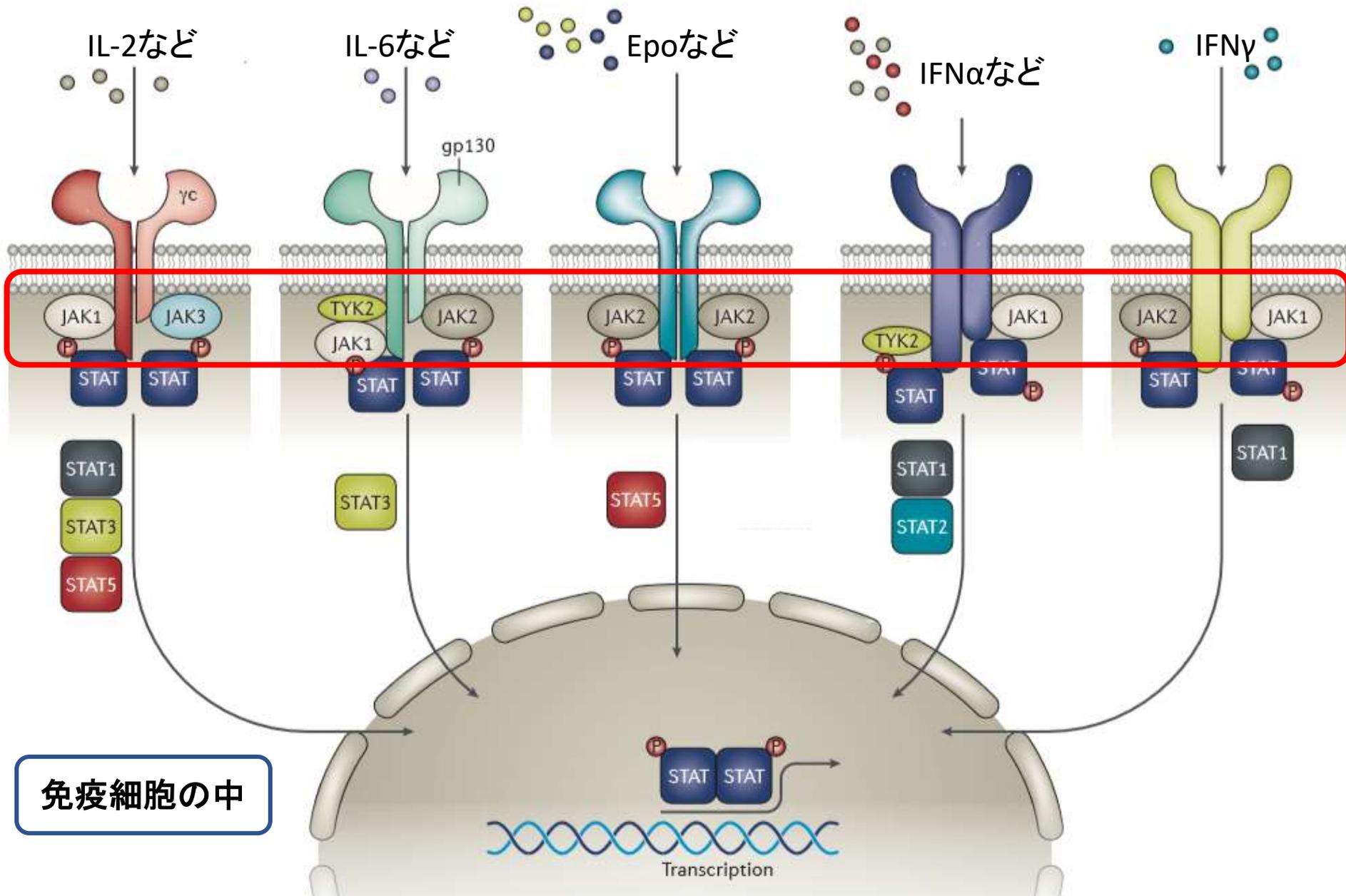
# JAKとSTAT の関係と JAK阻害薬 の選択性



Drug	Selectivity*
Baricitinib	JAK1, 2
Filgotinib	JAK1
Peficitinib	JAK1, 2, 3
Tofacitinib	JAK1, 2, 3
Upadacitinib	JAK1, (2)


\* also taking the clinical perspective into account

# JAKとSTATの関係（もう少し単純化したもの）



# JAK選択性の判断の仕方

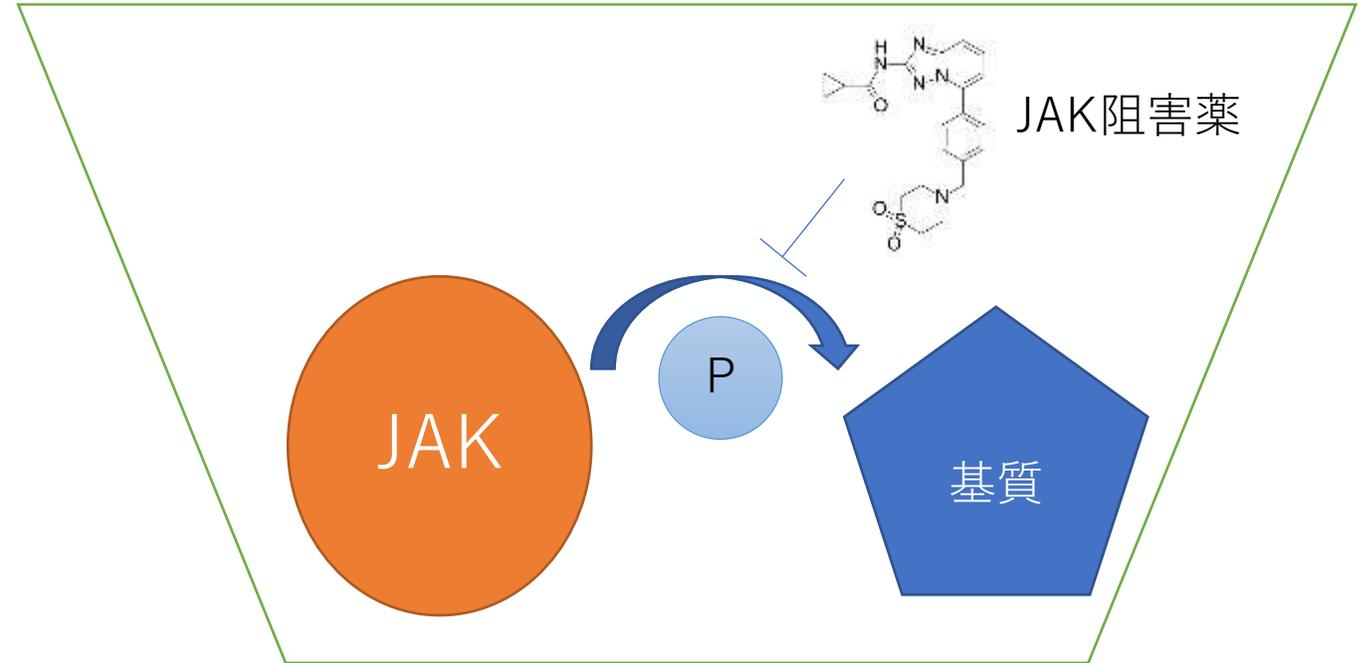
例)

## ■ 酵素活性阻害

パラメータ	IC <sub>50</sub> (nmol/L)
JAK1	3.2
JAK2	4.1
JAK3	1.6
TyK2	34.0

Tofacitinib資料より

## In vitro kinase assay



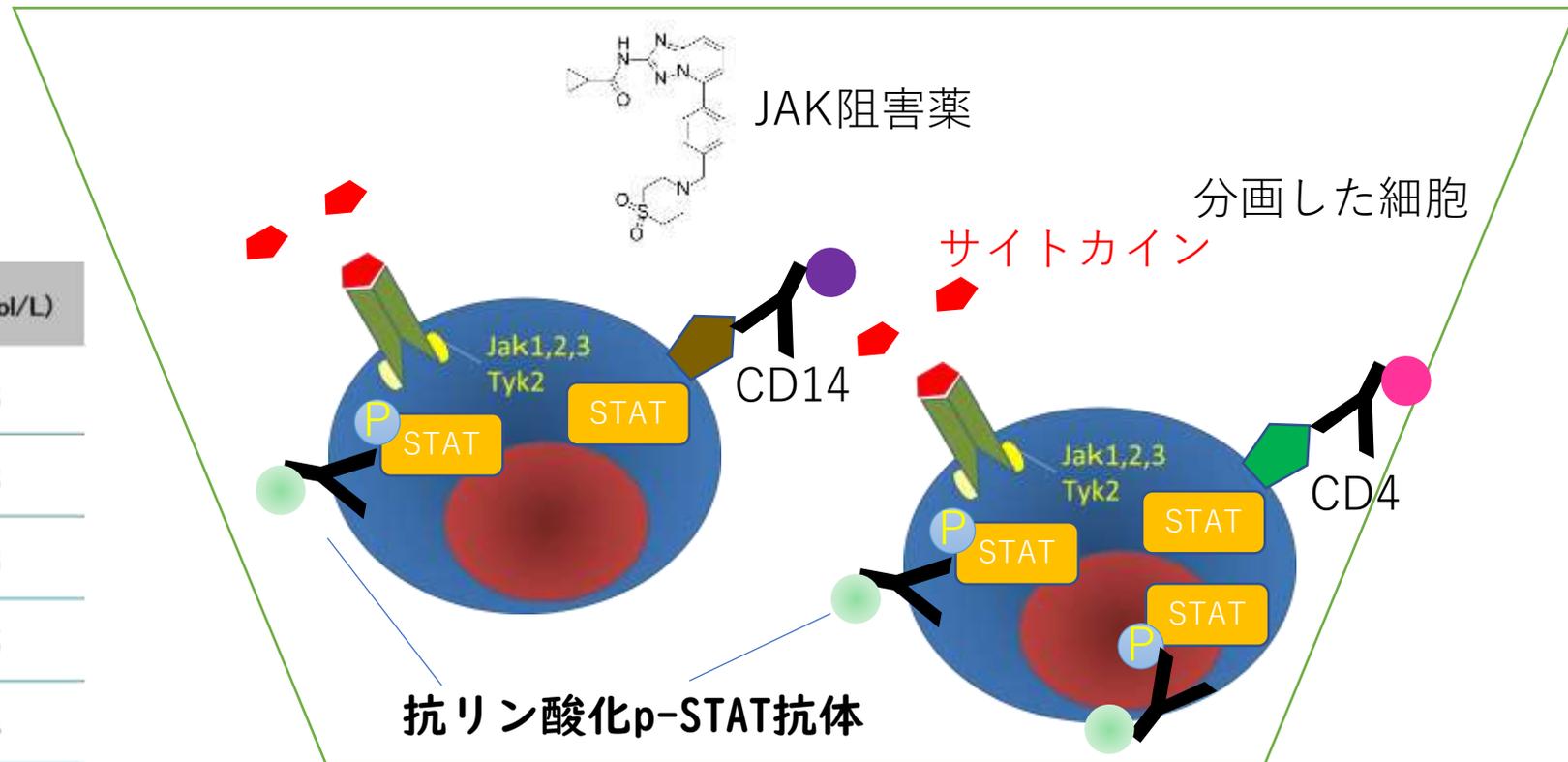
JAK阻害薬の濃度を変えて、リン酸化基質の量を測定  
リン酸化基質の量が50%になる濃度がIC<sub>50</sub>

# 細胞とサイトカインを用いたSTATリン酸化阻害実験

## In vitro whole blood STATリン酸化アッセイ

### ■ STATリン酸化に対する阻害作用

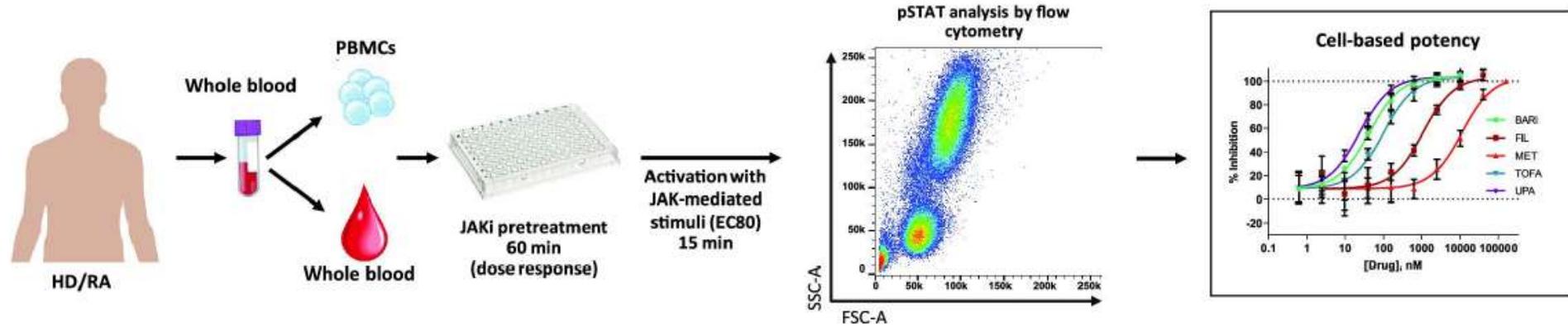
パラメータ	サイトカイン	リン酸化されるSTAT	細胞	IC <sub>50</sub> (nmol/L)
JAK1/3	IL-2	STAT5	CD3 <sup>+</sup> Tリンパ球	28
	IL-7	STAT5	CD3 <sup>+</sup> Tリンパ球	38
	IL-15	STAT5	CD8 <sup>+</sup> Tリンパ球	56
	IL-21	STAT3	CD3 <sup>+</sup> Tリンパ球	25
JAK1/2	IL-6	STAT1	CD3 <sup>+</sup> Tリンパ球	54
	IL-6	STAT3	CD3 <sup>+</sup> Tリンパ球	367
JAK2	GM-CSF	STAT5	CD14 <sup>+</sup> 単球	1377



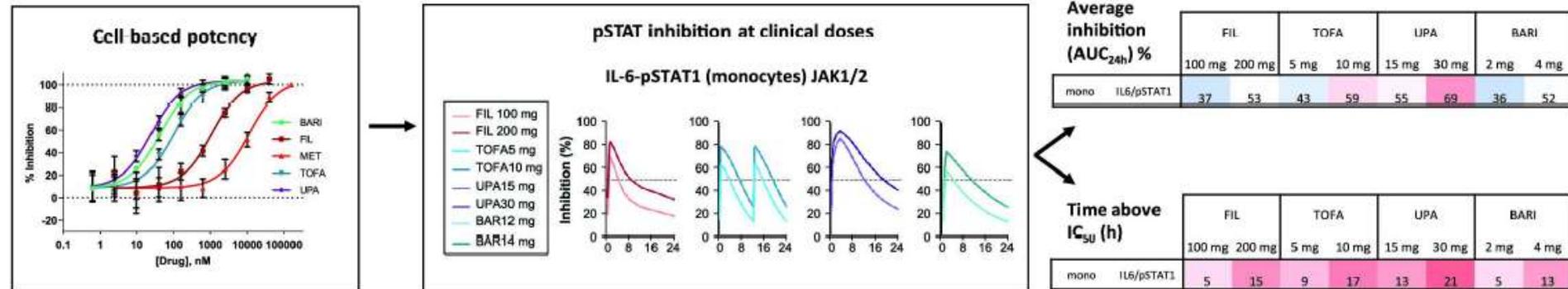
各細胞分画の細胞内のp-STATの量をFACSで測定  
 JAK阻害薬を濃度を変えて投与し、pSTATが50%減る  
 JAK阻害薬濃度がIC<sub>50</sub>

# 実験方法の概略

## A. Experimental procedure



## B. Data analysis procedure



**Figure 2** (A) Experimental design and (B) data analysis procedures. Detailed methods are included in online supplemental materials. AUC-24h, area under the curve 0–24 hours; BARI, baricitinib; FIL, filgotinib; FSC-A, forward scatter area; HD, healthy donors; IC<sub>50</sub>, half maximum inhibitory concentration; IL, interleukin; JAK, Janus kinase; JAKi, JAK inhibitor; MET, major metabolite of filgotinib (GS-829845); mono, monocytes; PBMCs, peripheral blood mononuclear cells; pSTAT, phosphorylated signal transducer and activator of transcription; RA, rheumatoid arthritis; SSC-A, side scatter area; TOFA, tofacitinib; UPA, upadacitinib.

# JAK阻害薬による効果と副作用発現率の比較

Supplemental Table 1. Clinical Efficacy and Safety Findings From Phase 3 Studies of JAKinibs.

JAK1選択的とされる薬剤

	Filgotinib	Tofacitinib	Upadacitinib	Baricitinib	
	200 mg	5 mg, bid	15 mg	2 mg	4 mg
MTX-IR ACR20/50/70/DAS28CR <sup>a</sup>	19/25/21/32 [1]	25/26/15/5 [2]	31/33/25/32 [3]	NR	37/32/22/33 <sup>b</sup> [4]
Biologic-IR ACR20/50/70/ DAS28CR <sup>c</sup>	35/28/15/14 [1]	17/18/12/4 [2]	37/22/5/20 [3]	22/12/11/9 <sup>d</sup> [4]	28/20/9/8 <sup>d</sup> [4]
Hemoglobin (g/dL)	+0.2 [5]	+0.08 [6]	-0.8 [7]	-0.28 [8]	-0.2 [8]
Herpes zoster (E/100PY)	0.1% (0.3% placebo) [1]	1-10% [2]	0.7% (0.2% placebo) [3]	1.4% (0.4% placebo) [4]	4.3% (1% placebo) [9]
Infections (E/100PY)	26.5 [1]	43.8 [2]	93.7 [3]	101 [4]	
Serious infection (E/100PY)	1.7 [1]	2.4 [2]	3.8 [3]	3.2 [4]	
Opportunistic infections (E/100PY)	0.1 [1]	<0.1 [2]	0.6 [3]	0 [9]	0.5 [9]
VTE (E/100PY)	0.2 [10]	0.27 [2]	0.5 [7]	0.6 [11]	0.8 [11]

UPAは本来（JAK1阻害なら）、貧血にならないはずなのに、なる

FILのみが帯状疱疹が少ない

一般の感染症もFILは少なくUPAは多い

UPAは本当にJAK1選択的？

# 目的

- Filgotinib (ジセレカ) のJAK選択性をBaricitinib (オルミエント)、Tofacitinib (ゼルヤンツ)、Upadacitinib (リンヴォック) と比較し、臨床効果や安全性に関連する薬理学的な根拠を明らかにする

# CD4+T細胞、単球での各JAK阻害薬のIC<sub>50</sub>

Table 1 JAKinib IC<sub>50</sub> values in CD4+ T-cells, monocytes and NK cells from whole blood assays

Stimulation/pSTAT	CD4+ T-cells					Monocytes				
	BARI	FIL	MET	TOFA	UPA	BARI	FIL	MET	TOFA	UPA
JAK2/JAK2 or JAK2/TYK2-dependent cytokines										
G-CSF/pSTAT3			NS			81	4977	50215	292	81
GM-CSF/pSTAT5			NS			127	9916	102910	510	74
IL-12/pSTAT4			NS			NS				
JAK1/JAK2/TYK2-dependent cytokines										
IFN $\alpha$ /pSTAT1	50	1096	17161	98	30	192	4560	91078	393	83
IFN $\alpha$ /pSTAT3	39	871	12644	80	24	40	991	15793	86	17
IFN $\alpha$ /pSTAT5	28	638	9587	49	17	25	613	9518	51	11
IFN $\gamma$ /pSTAT1			NS			74	4138	62374	228	58
IL-6/pSTAT1	29	783	5637	63	27	39	1011	10019	84	22
IL-6/pSTAT3	274	5435	62680	644	225	161	3527	49109	368	100
JAK1/JAK3-dependent cytokines										
IL-2/pSTAT5	40	988	14079	40	21			NS		
IL-4/pSTAT6	73	1458	39420	77	36	53	1337	36537	116	32
IL-15/pSTAT5	38	967	14326	39	21			NS		

数値の比較は薬剤間で比較しても意味なく、同じ薬剤で違う細胞や違うアイソフォームで比較するか、同じ細胞、同じ薬剤で異なるサイトカインJAK-STATで比較

この比がselectivityを表し Figure3につながる

①

# Table 1と同様です。細胞がB細胞、好中球、CD8+ T細胞でみた

**Table 2** JAKinib IC<sub>50</sub> values in B-cells, neutrophils and CD8+ T-cells from whole blood assays

Stimulation/pSTAT	B-cells					Neutrophils					CD8+ T-cells				
	BARI	FIL	MET	TOFA	UPA	BARI	FIL	MET	TOFA	UPA	BARI	FIL	MET	TOFA	UPA
IC <sub>50</sub> , nM															
JAK2/JAK2 or JAK2/TYK2-dependent cytokines															
G-CSF/pSTAT3			NS			404	16717	158111	1245	369			NS		
GM-CSF/pSTAT5			NS			66	3436	40925	143	21			NS		
IL-23/pSTAT3*			NS			NS					210	15040	138638	970	368
JAK1/JAK2/TYK2-dependent cytokines															
IFN $\alpha$ /pSTAT1	156	2957	54052	322	112			NS			80	1809	27730	163	56
IFN $\alpha$ /pSTAT3	28	588	9777	62	20	47	833	13438	66	18	35	795	10617	73	23
IFN $\alpha$ /pSTAT5	23	436	7524	44	16			NS			27	607	8231	46	17
IFN $\gamma$ /pSTAT1	22	900	12820	61	21	78	3137	42649	152	46			NS		
JAK1/JAK3-dependent cytokines															
IL-2/pSTAT5			NS					NS			32	809	11046	33	21
IL-4/pSTAT6	295	6426	164309	356	162	71	1200	37069	106	37	47	1022	25900	51	26
IL-15/pSTAT5			NS					NS			56	1459	19958	56	32

# JAK選択性をIFN $\alpha$ /JAK1-TYK2/pSTAT5の阻害に対する比として表示

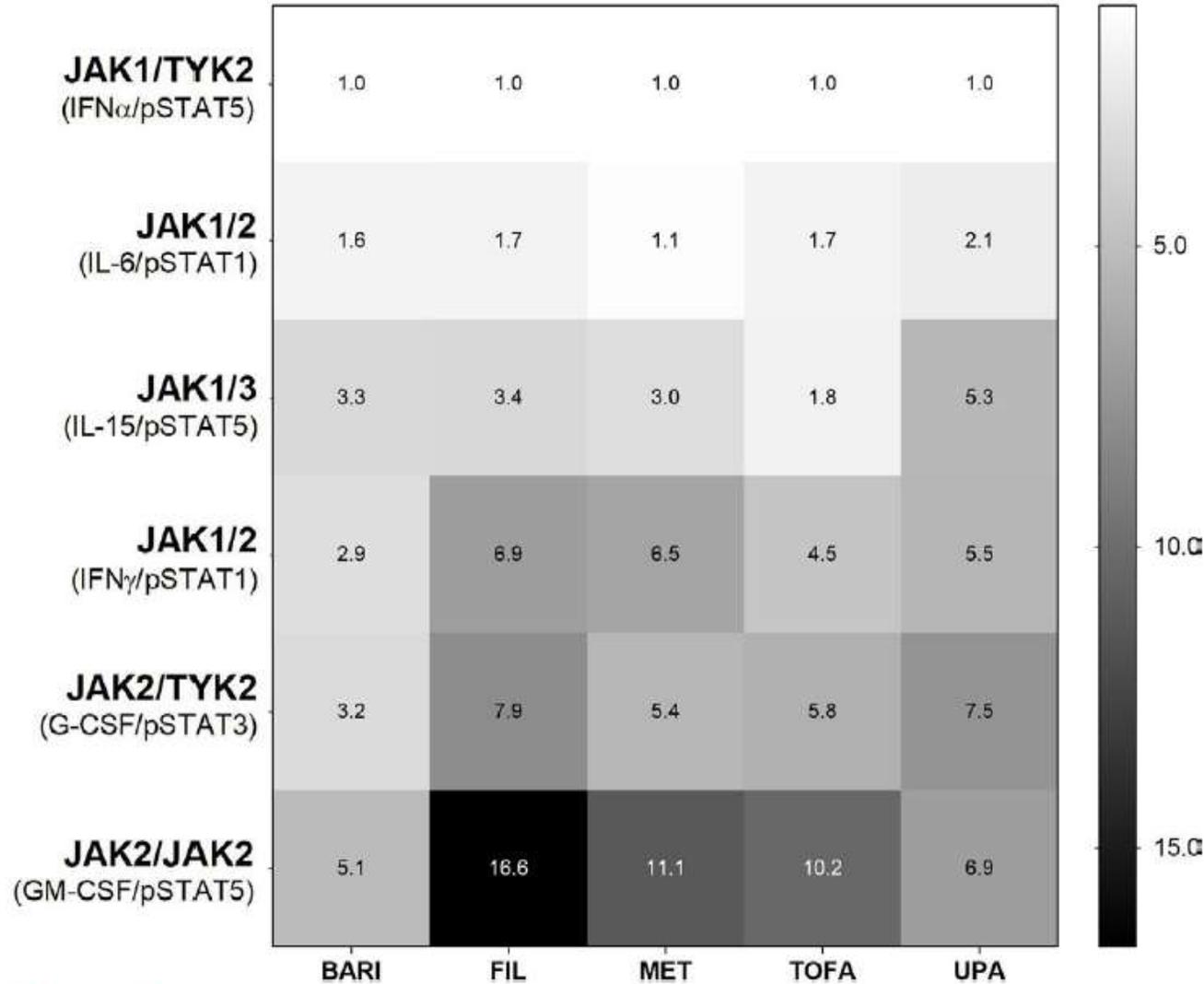
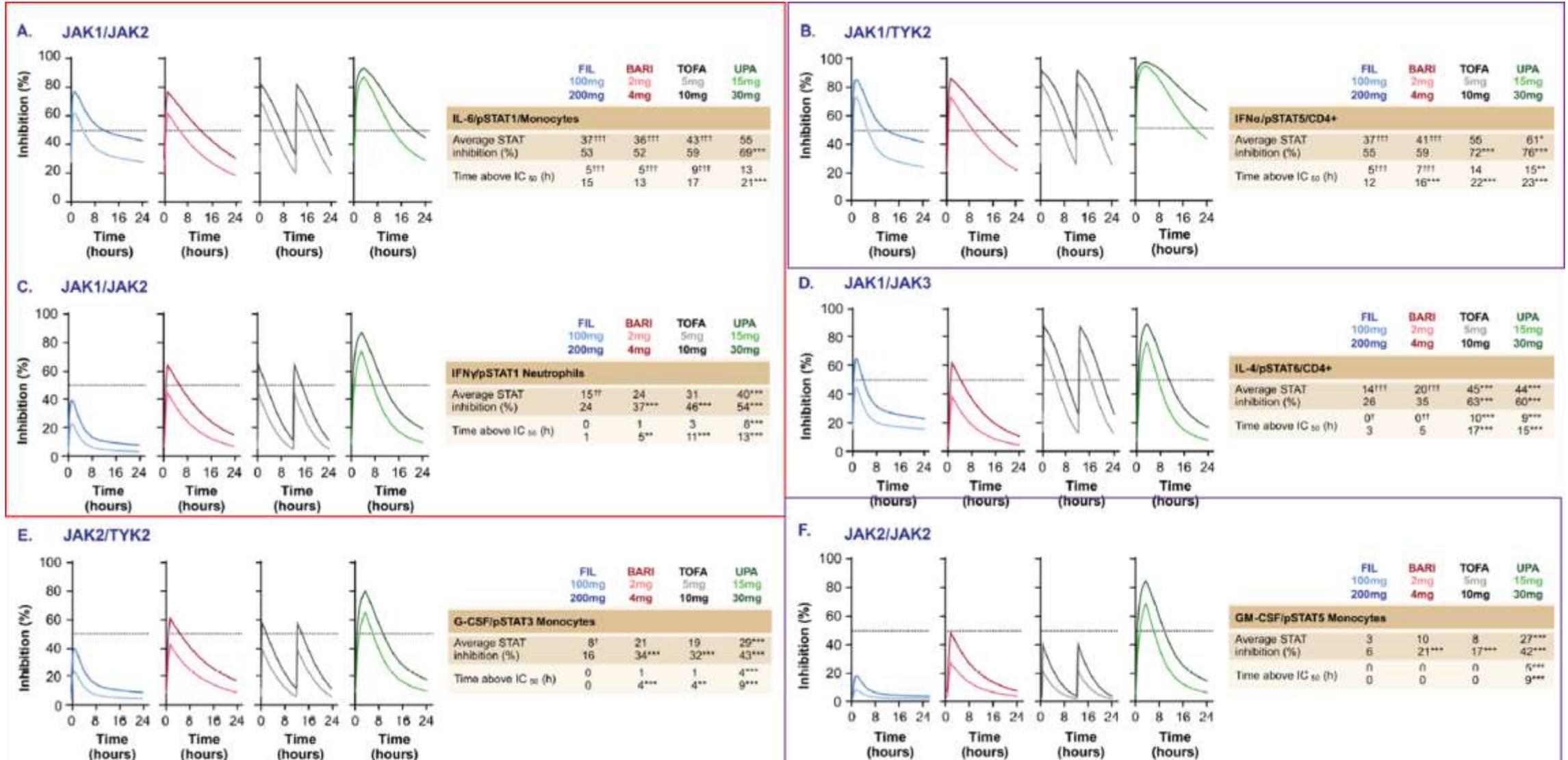


Table 1, 2から得られた数値 (IC50)をもとにこのFigureが得られる

FILが最も選択性が強そうではある

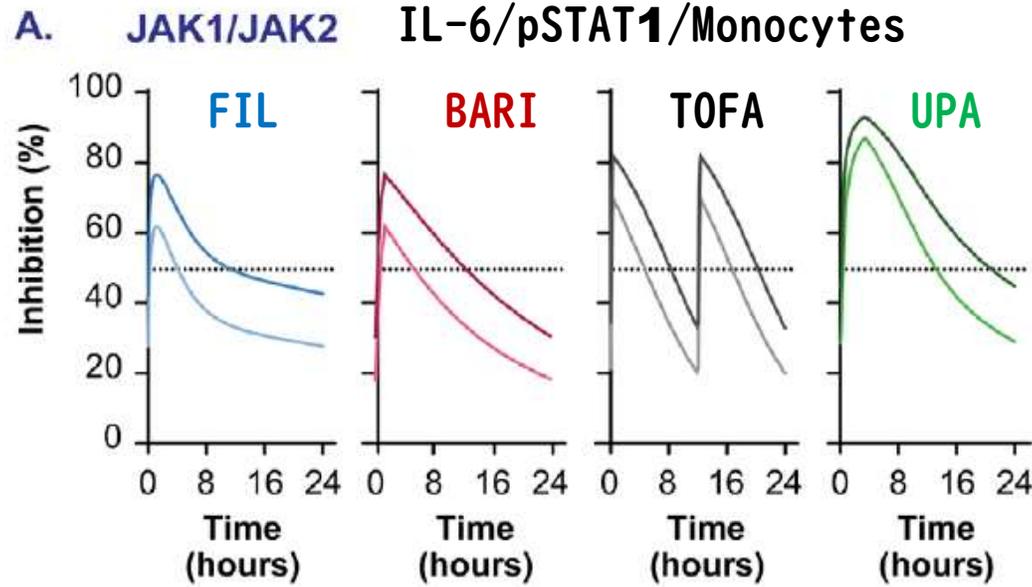
**Figure 3** Distinct JAKinib cellular selectivity for JAK heterodimeric cytokine signalling. Mean fold selectivity for each JAK-dimer pair

# 臨床用量のJAK阻害薬で、どの程度各サイトカインJAK-STATでpSTATを抑制できるかを時系列グラフで示した。

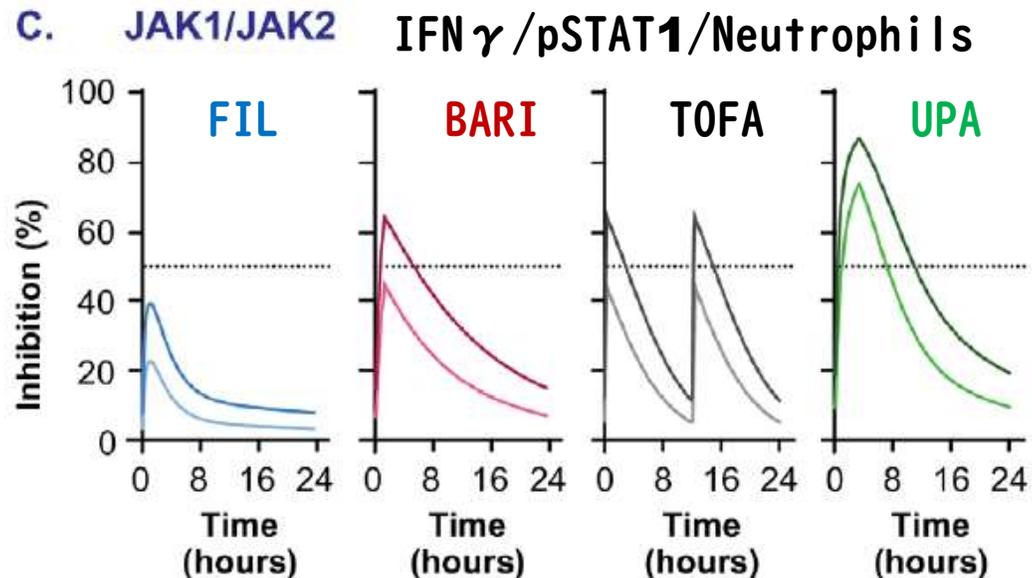


**Figure 4** Predicted cytokine inhibition profiles of JAKinibs at clinical doses. Pharmacodynamic pSTAT inhibition for JAKinibs at rheumatoid arthritis clinical doses over a 24-hour dose interval at steady state for selected cytokine stimulations based on in vitro blood measurements (n=7–10). (A) JAK1/JAK2 (IL-6/pSTAT1 in monocytes); (B) JAK1/TYK2 (IFN $\alpha$ /pSTAT5 in CD4+ T-cells); (C) JAK1/JAK2 (IFN $\gamma$ /

# IL-6/JAK1-JAK2/pSTAT1/Monocytes系はどのJAK阻害薬もよく抑制する IFN $\gamma$ /JAK1-JAK2/pSTAT1/Neutrophils系はほぼUPAのみが抑制する



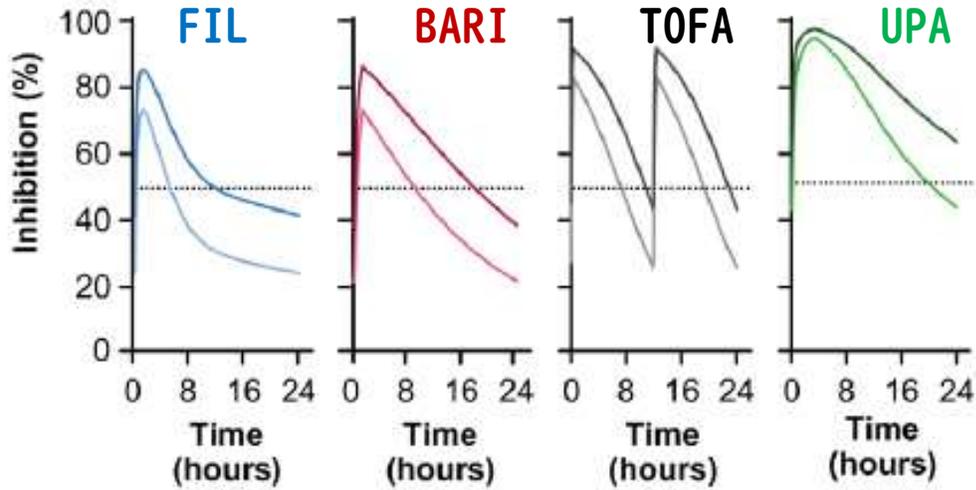
	FIL 100mg 200mg	BARI 2mg 4mg	TOFA 5mg 10mg	UPA 15mg 30mg
<b>IL-6/pSTAT1/Monocytes</b>				
Average STAT inhibition (%)	37 <sup>†††</sup> 53	36 <sup>†††</sup> 52	43 <sup>†††</sup> 59	55 69 <sup>***</sup>
Time above IC <sub>50</sub> (h)	5 <sup>†††</sup> 15	5 <sup>†††</sup> 13	9 <sup>†††</sup> 17	13 21 <sup>***</sup>



	FIL 100mg 200mg	BARI 2mg 4mg	TOFA 5mg 10mg	UPA 15mg 30mg
<b>IFN<math>\gamma</math>/pSTAT1 Neutrophils</b>				
Average STAT inhibition (%)	15 <sup>††</sup> 24	24 37 <sup>***</sup>	31 46 <sup>***</sup>	40 <sup>***</sup> 54 <sup>***</sup>
Time above IC <sub>50</sub> (h)	0 1	1 5 <sup>**</sup>	3 11 <sup>***</sup>	8 <sup>***</sup> 13 <sup>***</sup>

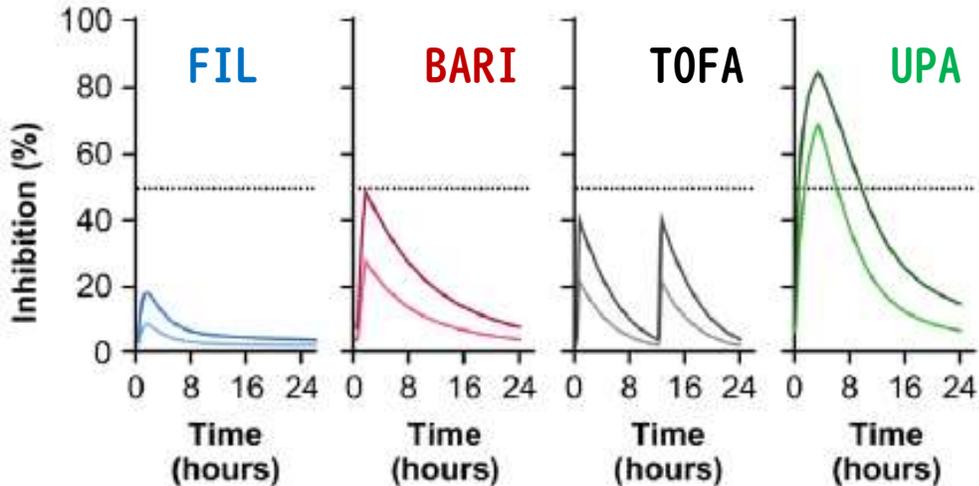
# IFN $\alpha$ / JAK1-TYK2 / pSTAT5 / CD4+T細胞系は選択性なし GM-CSF / JAK2-JAK2 / pSTAT5 / Monocytes系ではUPAのみが多少阻害する

## B. JAK1/TYK2 IFN $\alpha$ / pSTAT5 / CD4+T細胞



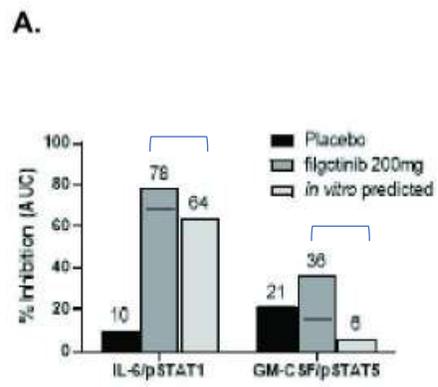
	FIL 100mg 200mg	BARI 2mg 4mg	TOFA 5mg 10mg	UPA 15mg 30mg
<b>IFN<math>\alpha</math>/pSTAT5/CD4+</b>				
Average STAT inhibition (%)	37 <sup>†††</sup> 55	41 <sup>†††</sup> 59	55 72 <sup>***</sup>	61* 76 <sup>***</sup>
Time above IC <sub>50</sub> (h)	5 <sup>†††</sup> 12	7 <sup>†††</sup> 16 <sup>***</sup>	14 22 <sup>***</sup>	15 <sup>**</sup> 23 <sup>***</sup>

## F. JAK2/JAK2 GM-CSF / pSTAT5 / Monocytes



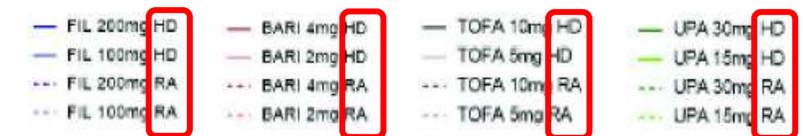
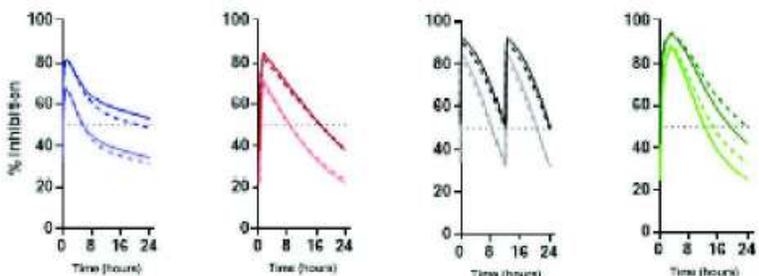
	FIL 100mg 200mg	BARI 2mg 4mg	TOFA 5mg 10mg	UPA 15mg 30mg
<b>GM-CSF/pSTAT5 Monocytes</b>				
Average STAT inhibition (%)	3 6	10 21 <sup>***</sup>	8 17 <sup>***</sup>	27 <sup>***</sup> 42 <sup>***</sup>
Time above IC <sub>50</sub> (h)	0 0	0 0	0 0	5 <sup>***</sup> 9 <sup>***</sup>

# In vitroでなく、ex vivoでも同様のselectivityを示すかどうか？



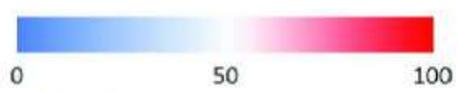
健常者orRA患者が  
FILもしくはplacebo  
をのんで、血液にIL-6  
or GM-CSFを加え、  
細胞中のpSTATを測定

## B. JAK1/TYK2 IFN $\alpha$ /pSTAT5 CD4+ T cells



## C.

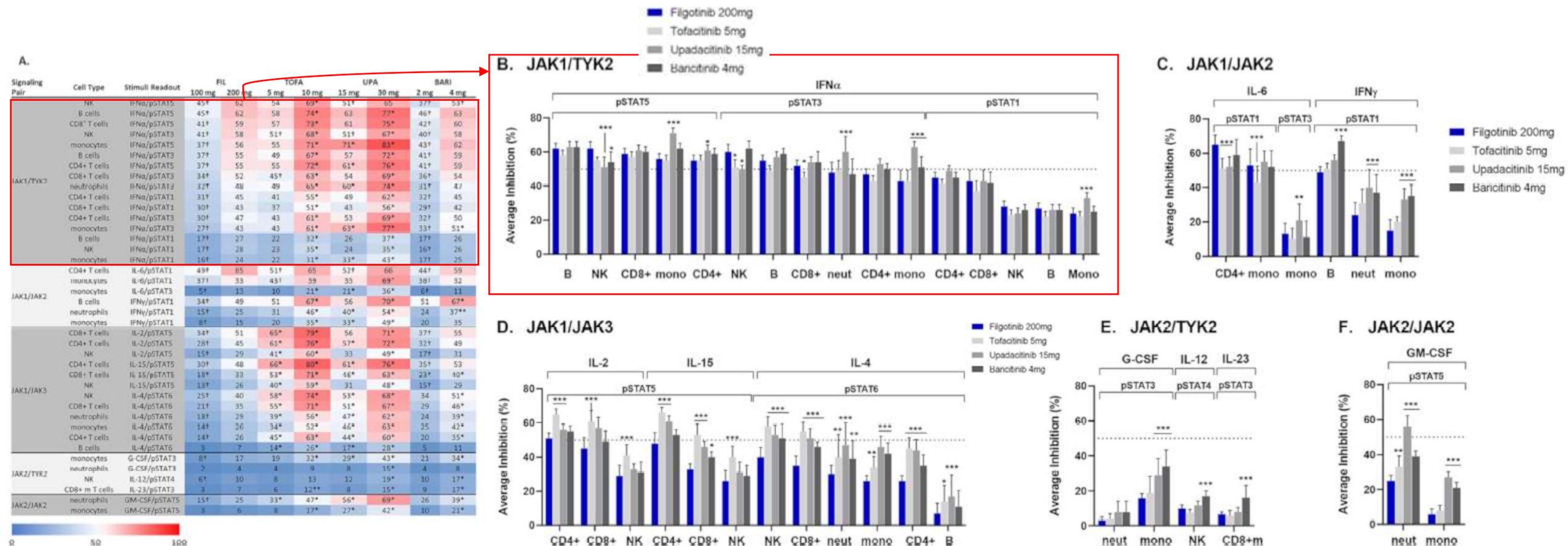
Cell type	Stimuli/Readout	RA donors								Matched HD							
		FIL		TOFA		UPA		BARI		FIL		TOFA		UPA		BARI	
		100mg	200mg	5mg	10mg	15mg	30mg	2mg	4mg	100mg	200mg	5mg	10mg	15mg	30mg	2mg	4mg
JAK1/TYK2	monocytes IFN $\alpha$ /pSTAT5	42	60	58	73	61	75	41	59	49	65	62	75	66	79	47	63
	CD8+ T cells IFN $\alpha$ /pSTAT5	40	57	58	73	55	69	39	58	49	68	64	78	55	89	44	60
	B cells IFN $\alpha$ /pSTAT5	45	63	59	74	60	74	46	63	47	66	61	76	56	72	48	66
	CD4+ T cells IFN $\alpha$ /pSTAT5	43	60	59	73	60	73	43	60	45	63	61	76	54	69	43	61
	CD8+ T cells IFN $\alpha$ /pSTAT3	44	61	55	70	55	70	44	61	44	61	58	72	50	65	43	59
	CD4+ T cells IFN $\alpha$ /pSTAT3	42	59	55	70	57	71	42	59	43	60	57	72	50	65	43	60
	NK IFN $\alpha$ /pSTAT3	46	63	54	69	49	64	40	58	43	60	57	71	51	68	46	63
	B cells IFN $\alpha$ /pSTAT3	38	57	52	68	54	69	41	58	38	58	58	75	47	64	42	61
	monocytes IFN $\alpha$ /pSTAT3	42	60	55	71	60	74	43	60	35	54	61	76	57	73	48	67
	CD4+ T cells IFN $\alpha$ /pSTAT1	38	51	44	58	48	61	35	48	34	48	48	60	40	53	34	47
	CD8+ T cells IFN $\alpha$ /pSTAT1	25	38	34	47	34	47	24	36	33	46	42	56	36	48	31	43
	B cells IFN $\alpha$ /pSTAT1	24	34	27	38	28	39	20	29	20	30	24	35	24	34	17	26
	NK IFN $\alpha$ /pSTAT1	18	30	25	39	21	33	15	26	19	32	32	48	29	43	19	32
	monocytes IFN $\alpha$ /pSTAT1	15	24	20	32	28	40	14	24	13	23	20	31	24	36	13	22
JAK1/JAK2	CD4+ T cells IL-6/pSTAT1	33	48	53	67	52	65	32	47	42	57	52	66	49	63	43	58
	CD4+ T cells IL-6/pSTAT3	28	46	33	50	39	54	27	44	13	26	25	42	23	38	14	28
	B cells IFN $\gamma$ /pSTAT1	28	44	42	59	44	60	39	56	30	48	46	63	47	62	46	64
	monocytes IFN $\gamma$ /pSTAT1	6	14	16	30	29	45	15	29	7	15	20	36	30	47	21	38
JAK1/JAK3	CD4+ T cells IL-15/pSTAT5	22	38	51	69	49	66	24	41	19	35	54	71	47	63	26	43
	CD8+ T cells IL-15/pSTAT5	15	30	45	64	40	58	18	34	14	27	44	63	38	54	18	33
	NK IL-15/pSTAT5	11	22	33	52	25	40	11	22	14	27	43	62	30	46	15	28
	CD8+ T cells IL-2/pSTAT5	31	47	59	74	57	72	35	52	29	46	60	78	52	68	32	49
	CD4+ T cells IL-2/pSTAT5	25	41	53	69	53	69	27	44	21	36	53	70	51	68	25	41
	NK IL-2/pSTAT5	16	31	45	64	36	53	17	32	17	32	49	68	39	56	19	35
	NK IL-4/pSTAT5	22	36	55	71	49	65	28	44	39	54	62	76	59	73	33	49
	CD8+ T cells IL-4/pSTAT6	18	30	53	70	48	64	26	43	26	41	60	75	56	71	31	47
monocytes IL-4/pSTAT6	19	34	44	63	56	73	33	52	25	41	50	68	56	72	37	56	
JAK2/TYK2	CD4+ T cells IL-4/pSTAT6	19	33	50	67	50	65	25	41	19	33	54	71	51	67	25	41
	B cells IL-4/pSTAT6	3	6	11	23	16	29	4	9	4	9	13	25	18	31	4	10
monocytes	G-CSF/pSTAT3	17	30	21	34	28	42	19	32	20	33	35	51	40	55	32	48



健常者血球を使ったデータとRA患者血球を使ったデータが  
同じとして用いてよいかの検証 (ex vivo)

Figure 5 Cytokine-induced pSTAT inhibition in the samples of patients with RA and in ex vivo stimulated blood from phase 1 studies of healthy volunteers. (A) Measured average inhibition of ex vivo stimulated pSTAT1 (IL-6/CD4+ T-cells) and pSTAT5 (GM-CSF/monocytes) over a 24-hour period in healthy volunteers receiving FIL (200 mg once daily) or placebo or from in vitro calculated values. The

# In vitroで健常人データを増やして解析。結論は同様。



**Figure 6** Calculated cytokine inhibition of JAK-STAT signalling pathways at clinical doses with similar efficacy. (A) Calculated average target inhibition (AUC-24h $\pm$ SD) over a 24-hour dose interval for selected JAKinibs for a given stimuli/cell type/pSTAT based on in vitro measurements in whole blood from healthy donors (n=7-10). \*P<0.05 higher vs FIL 200 mg; †P<0.05 lower vs FIL 200 mg.

## まとめ

- IFN $\alpha$  と IL-6 シグナルはいずれの JAK も同様によく抑える
- IL-15 や IFN $\gamma$  シグナル、GM-CSF シグナルなどに差がみられる
- JAK-1 selective といえるのは Filgotinib のみかも
- UPA がいずれのシグナルも最も強く抑える傾向にある

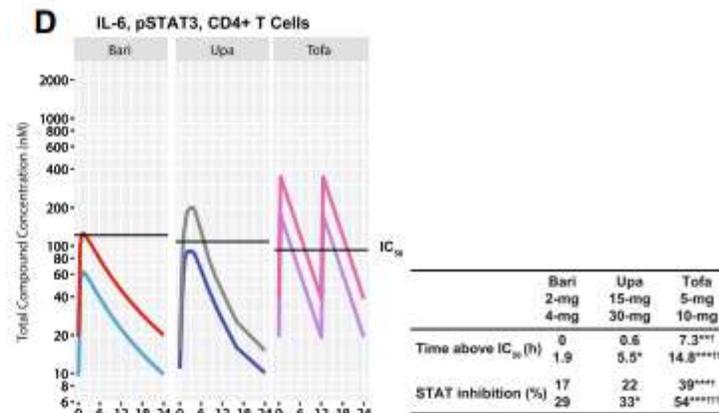
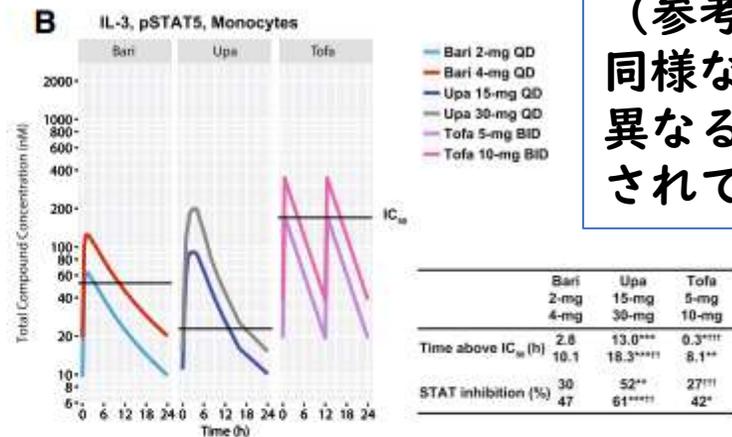
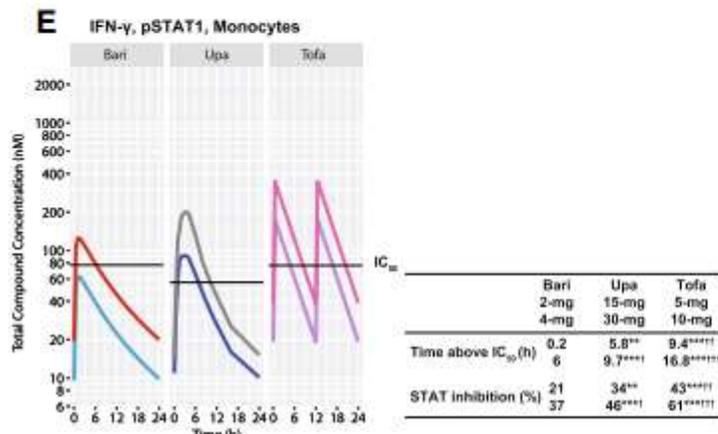
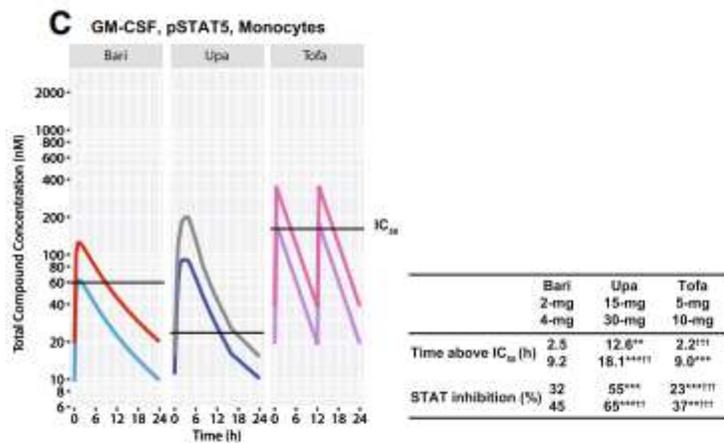
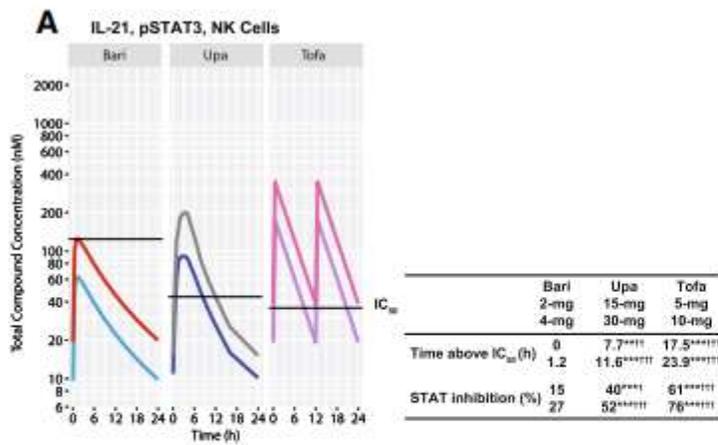
RESEARCH ARTICLE Open Access

# In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494)

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**Table 1** In vitro potency of upadacitinib

Recombinant Human Kinase	IC50 nM	Fold selectivity vs. JAK1		
in Biochemical Assays <sup>A</sup>				
JAK1	47 +/- 6.1	1		
JAK2	120 +/- 29.6	2.5		
JAK3	2304 +/- 380.3	49		
TYK2	4690	100		
Engineered Cellular Assays				
Ba/F3 Cellular	IC50 nM	Fold selectivity vs. JAK1		
JAK1	14	1		
JAK2	593 +/- 118.7	42		
JAK3	1860 +/- 207.2	133		
TYK2	2715 +/- 548.7	194		
Cytokine Signaling in Human Cells				
Cytokine	JAK	pSTAT	Cells	Human IC50 nM
IL-6	1	3	TF-1	11 +/- 1.3
IL-6	1	3	CD14+ whole blood	78 +/- 0.3
IL-6	1	3	CD3+ whole blood	207 +/- 9
OSM	1	3	TF-1	1.6 N=2
Epo	2	5	UT7	649 +/- 41.2
IL-2	1/3	5	T-blasts	10 +/- 1.1
IL-15	1/3	5	T-blasts	22 +/- 6.7
IFN $\gamma$	1/2	1	CD14+ monocytes	19
IL-4	1/3	6	HEKa <sup>B</sup>	2
IL-13	1/TYK2	6	HEKa	4
IL-31	1/2	3	HEKa	3



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(参考)  
 同様な実験手法で異なる結果も報告されています。

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

# Comparison of baricitinib, upadacitinib, and tofacitinib mediated regulation of cytokine signaling in human leukocyte subpopulations

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# 5種類のJAK阻害薬の比較

【関節リウマチに使用するJAK阻害薬：5製品】2020年12月現在

 新薬情報オンライン

製品名 (一般名)	ゼルヤンツ (トファシチニブ)	オルミエント (バリシチニブ)	スマイラフ (ペフィシチニブ)	リンヴォック (ウパダシチニブ)	ジセレカ (フィルゴチニブ)
販売開始年	2013年	2017年	2019年	2020年	2020年
効能・効果 (略)	<ul style="list-style-type: none"> <li>関節リウマチ</li> <li>潰瘍性大腸炎</li> </ul>	<ul style="list-style-type: none"> <li>関節リウマチ</li> <li>アトピー性皮膚炎</li> </ul>	<ul style="list-style-type: none"> <li>関節リウマチ</li> </ul>	<ul style="list-style-type: none"> <li>関節リウマチ</li> </ul>	<ul style="list-style-type: none"> <li>関節リウマチ</li> </ul>
用法・用量 (関節リウマチの 場合)	1日2回経口投与	1日1回経口投与			
作用機序	JAK1とJAK3を阻害	JAK1とJAK2を阻害	JAK1とJAK3を阻害	JAK1を阻害	JAK1を阻害
臓器機能に 関する <b>禁忌</b> 項目	<b>重度の 肝機能障害</b>	<b>重度の 腎機能障害</b>	<b>重度の 肝機能障害</b>	<b>重度の 肝機能障害</b>	<ul style="list-style-type: none"> <li><b>末期腎不全</b></li> <li><b>重度の肝機能 障害</b></li> </ul>
併用注意薬	<ul style="list-style-type: none"> <li>CYP3A4阻害剤</li> <li>グレープフルーツ</li> <li>フルコナゾール</li> <li>CYP3A4誘導剤</li> <li>セイヨウオトギリソウ(St. John's Wort、セント・ジョーンズ・ワート)含有食品</li> <li>肝機能障害を起こす可能性のある薬剤</li> </ul>	<ul style="list-style-type: none"> <li>プロベネシド</li> </ul>	なし	<ul style="list-style-type: none"> <li>CYP3Aを強く阻害する薬剤</li> <li>CYP3Aを強く誘導する薬剤</li> </ul>	なし