Kinases in immunology:

«A mini Review»

Immunopharmacology Meeting

Edinburgh 2018-10-02

Outline

- Introduction to Kinases
- Kinases & immunology: where are we ?
- Selected examples for immuno kinases: JAK, SYK, RIPK, IRAK.....

and

- PI3Kδ: Leniolisib from the bench to the bedside

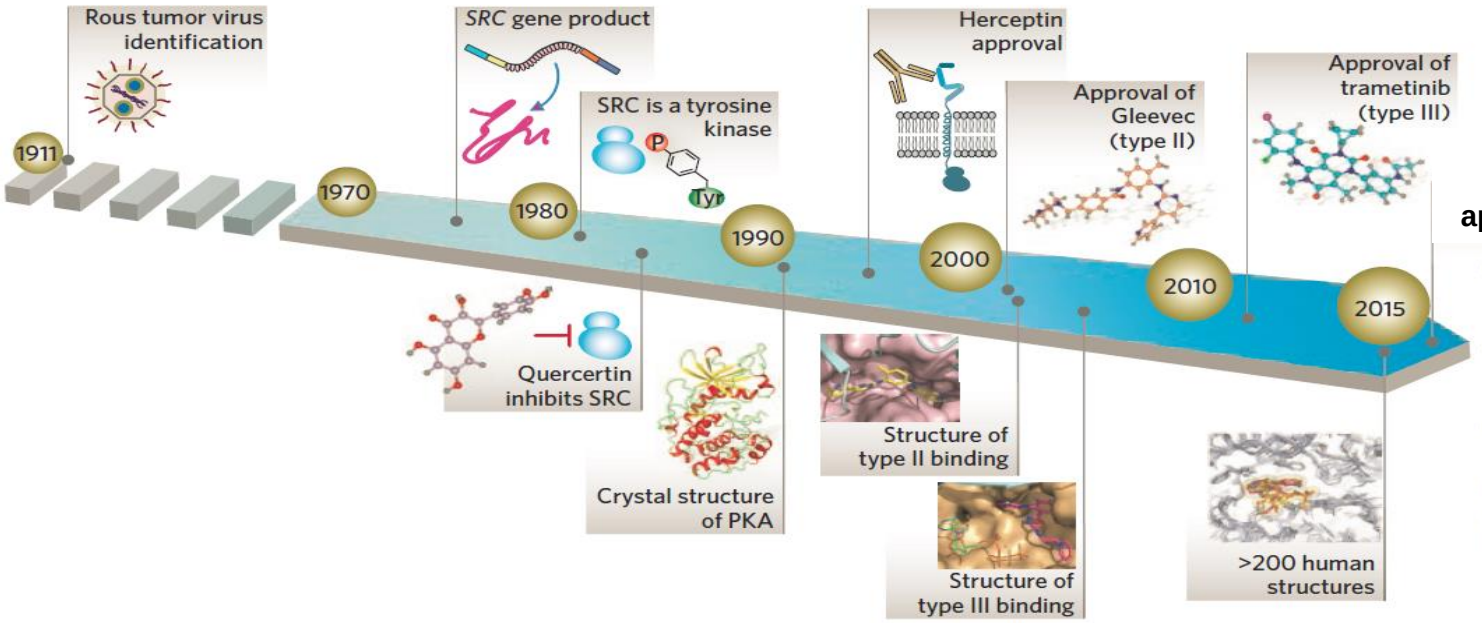
Why are kinase attractive drug targets ?

- Druggable by ATP (ITB) and/or non-ATP (OTB) inhibitors
- Large knowledge-base of structures and inhibitors
- Genetics, differential cytotox (synthetic lethal), host mechanisms
- Non-oncological indications ?

Disease	Kinase
LKB1 (LoF)	Peutz-Jegher Syndrome
ATM (LoF)	Ataxia Telangectasia
WNK1 (GoF)	Gordon Hypertension Syndrome
mTOR (GoF)	LoF of TSC1 and TSC2 (Tubersclerosis, Hamartomas)
B-raf (GoF)	Melanoma & other sporadic carcinomas
LRRK2 (GoF)	Hereditary early onset Parkinson
PI3Ka (GoF)	Sporadic carcinomas
BTK (LoF)	X-linked a-gamma-globulinaemia
Ret (GoF)	Men2A, Medullary Thyroid Cancer, Chrom. rearrang. In PTC
ZAP70 (LoF)	CD8 deficiency form of SCID
Jak2 (GoF)	V617F in PV, ET, IMF; Transl in Leukemia Muts im AML
Jak3 (LoF)	SCID (X-linked),
Alk (GoF)	Translocation in ALCL, IMF and NSCLC
ErbB1-4	Amplification & overex. in Carcinomas
PDGFR (GoF)	GIST, chrom. rearrang. in CML, CMML and HES
FGFR1 & 2 (GoF)	Craniosynostosis & Crouzon/Pfeiffer thanatophoric dysp.
FGFR3 (GoF)	Chrom. rearrang. & muts in leukemia, myeloma, dwarfism, bladder
VEGFR3 (LoF)	Hereditary lymphedema. Host mechanisms
Met (GoF)	Amplification & overex. in sporadic & hereditary Ca

KINASEPTAHIES

33 years of Kinase-DD → 50 approved KIs (26-09-2018)



1995 1999 2001 2003 2004 2005 2006 2007 2009 2011 2012 2013 2014 2015 2016 2017 2018

Fasudil Asahi
Sirolimus Wyeth
Imatinib Novartis
Gefitinib AZ
Erlotinib OSI
Sorafenib Bayer
Sunitinib Pfizer
Dasatinib BMS
Nilotinib Novartis
Lapatinib GSK
Temsirolimus Pfizer
Everolimus Novartis
Crizotinib Pfizer
Vemurafenib Roche
Ruxolitinib Novartis
Vandetanib AZ
Pazopanib GSK
Axitinib Pfizer
Regorafenib Bayer
Tofacitinb Pfizer
Cabozantinib Exelexis
Ponatinib Ariad
Bosutinib Pfizer
Radotinib Deawong
Dabrafenib GSK
Trametinib GSK
Afitinib BI
Ibrutinib Jansen
Ceritinib Novartis
Idelalisib Gilead
Nintedanib BI
Alectinib Roche
Palbociclib Pfizer
Levantinib Eisai
Cobibetinib Roche
Osimertinib AZD
Omultinib IB
Ribociclib Novartis
Brigatinib Arad
Midostaurin Novartis
Copanlisib Bayer
Abemaciclib Eli-Lilly
Acalabrutinib AZ
Baricitinib Eli-Lilly
Neratinib Puma
Fostamitinib Rigel
Simotinib Jangsu Simcere
Encorafenib & Binimetinib
Duvelisib Verastem
Dacomitinib Pfizer

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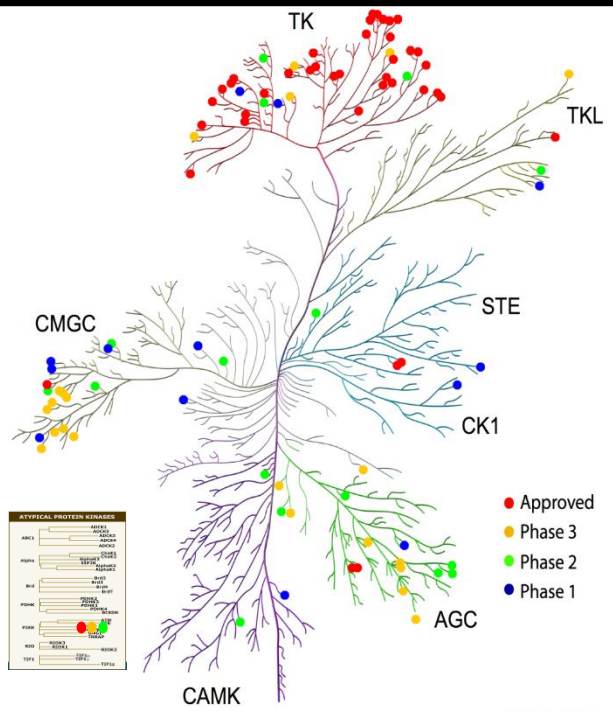
Table I: Registered kinase inhibitors updated 29-09-2018

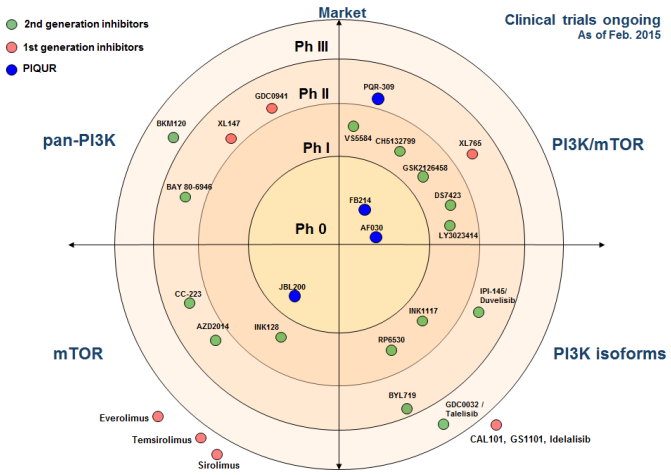
26.09.2018					
Year	Generic name (compound code, Trade names)	Kinase Target	Disease	Company (year, type)	Class
1995	Fasudil (HA-1077) [5181]	ROCK1/2	Cerebral vasospam, PAH	Asahi Kasei (1995, type-1)	
1999	Sirolimus (Rapamune) [6031]	mTOR	Kidney transplants	Pfizer, Wyeth (1999, type-3)	Rapa
2001	Imatinib (STI571, Glivec, Gleevec) [5687]	ABL, PDGFR, KIT	CML, Ph+ B-ALL, CMML, HES, GIST	Novartis (2001, type-2)	ABLinib
2003	Gefitinib (ZD1839, Iressa) [4941]	EGFR	NSCLC	AZ (2003, type-1)	HERinib
2004	Erlotinib (OSI-774,Tarceva) [4920]	EGFR	NSCLC, pancreatic cancer	Roche, OSI (2004, type-1)	HERinib
2005	Sorafenib (BAY 43-9006, Nexavar) [5711]	VEGFR2, PDGFR, KIT, FLT3, BRAF	RCC, HCC	Bayer, Onyx (2005, type-2)	Multi
2006	Sunitinib (SU11248, Sutent) [5713]	VEGFR, KIT, PDGFR, RET, CSF1R, FLT3	RCC, imatinib resistant GIST	Pfizer (2006, type-1)	Multi
2007	Lapatinib (GW2016, Tykerb) [5692]	EGFR, ERBB2	BC	GSK (2007, type-1.5)	HERinib
2007	Dasatinib (BM-354825,Sprycel) [5678]	ABL], PDGFR, KIT, SRC	CML	BMS (2007, type-1)	ABLinib
2007	Nilotinib (AMN107,Tasigna) [5697]	ABL, PDGFR, KIT	CML	Novartis (2007, type-2)	ABLinib
2009	Everolimus (Rad001, Certican, Zortress, Afinitor, Votubia) [5889]	mTOR	RCC, SEGA, Transplantation	Novartis (2009, type-3)	Rapa
2009	Temsirolimus (CCI-779, Torisel) [5892]	mTOR	RCC	Pfizer, Wyeth (2009, type-3)	Rapa
2011	Crizotinib (PF-02341066, Xalcori) [4903]	MET and ALK	NSCLC with ALK translocations	Pfizer (2011, type-1)	ALKinib
2011	Vandetanib (ZD6474, Caprelsa) [5717]	RET, VEGFR1-2, FGFR, EGFR	MTC	AZ (2011, type-1)	RETinib
2011	Ruxolitinib (INC424, Jakafi) [5688]	JAK2	IMF JAK2V617F	Novartis, Incyte (2011, type-1)	JAKinib
2011	Vemurafenib (PLX4032, RG7204, Zelboraf) [5893]	BRAF	Metastatic melanoma BRAFV600E	Roche, Plexxikon (2011, type-2)	RAFinib
2011	Axitinib (AG013736, Inlyta) [5659]	VEGFR, KIT, PDGFR, RET, CSF1R, FLT3	RCC	Pfizer (2012, type-1)	Multi
2012	Regorafenib (BAY 73-4506, Stivarga) [5891]	VEGFR2, Tie2	CRC, GIST and HCC (2017)	Bayer (2012, type-2)	Multi
2009	Pazopanib (GW-786034, Votrient) [5698]	VEGFR, PDGFR, KIT	RCC	GSK (2012, type-1)	Multi
2012	Tofacitinib (CP-690550, Xeljanz Tasocitinib) [5677]	JAK3	RA	Pfizer (2012, type-1)	JAKinib
2012	Cabozantinib (XL184, BMS907351, Cometriq) [5887]	VEGFR2, PDGFR, KIT, FLT3	MTC	Exelexis (2012, type-1)	Multi
2012	Ponatinib (AP24534, Iclusig) [5890]	ABL	Imatinib resistant CML ABL-T315I mutations	Ariad (2012, type-1)	ABLinib
2012	Bosutinib (SKI-606, Bosulif) [5710]	ABL	CML resistant/ intolerant to therapy	Pfizer (2012, type-1)	ABLinib
2013	Dabrafenib (Tafinlar) [6494]	BRAF	Metastatic melanoma with BRAFV600E	GSK (2013, type-1.5)	RAFinib
2013	Trametinib (Mekinist) [6495]	MEK	Met melanoma with BRAFV600E mutations	GSK (2013, type-3)	MEKinib
2013	Afatinib (Gilotrif, Tomtovok, Tovok) [5667]	EGFR	NSCLC with EGFR activating mutations	BI (2013, covalent)	HERinib
2013	Ibrutinib (PCI-32765, Imbruvica) [6912]	BTK	MCL, CLL	Janssen, Pharmacyclic (2013, covalent)	BTKinib
2014	Ceritinib (LDK378, Zykadia) [7397]	ALK	NSCLC with ALK translocations	Novartis (2014, type-1)	ALKinib
2014	Idelalisib (CAL101, GS1101, Zydelig) [6741]	PI3Kdelta	CLL, FL and SLL	Gilead, Calistoga, ICOS (2014, type-1)	PIKlisib
2014	Nintedanib (BIBF 1120, Vargatef, Intedanib) [5936]	VEGFR, PDGFR, FGFR	Idiopathic Pulmonary Fibrosis	BI (2014, type-1)	Multi
2014	Alectinib (AF802, Alecensa) [7739]	ALK	ALK-transloctaed NSCLC (brain mets)	Roche, Chugai (2014, type-1) appr. in japan	ALKinib
2015	Palbociclib (PD-0332991, Ibrance) [7380]	CDK4/6	Advanced (metastatic) BC	Pfizer (2015, type-1)	CYClib
2015	Lenvatinib (E7080, Lenvima) [7426]	VEGFRs multikinase	Thyroid cancer (DTC); Kindney cancer	Eisai Co (2015, type-1)	Multi
2015	Cobimetinib (GDC-0973, XL-518, Cotellic)	MEK	Melanoma in combination with vemurafenib	Roche, Exelexis (2105, type-3)	MEKinib
2012	Radotinib (Supect, IY5511)	BCR-ABL, PDGFR	CML	Daewoong Pharmaceutical (2015, type-2) appr. SK	ABLinib
2015	Osimertinib (Mereletinib, AZD9291; Tagrisso)	EGFR (T790M)	NSCLC with EGFR-T790M	AZ (2015, covalent)	HERinib
2016	Olmutinib (HM-61713, BI-1482694	EGFR (T790M)	NSCLC with EGFR-T790M	Boehringer Ingelheim/Hanmi)	HERinib
2017	Ribociclib (LEE011; Kisqali)	CDK4/6	1st-line HR+/HER2- metastatic BC in combo with any AI	Novartis (2017, type-1)	CYClib
2017	Brigatinib (AP26113, Alunbrig)	ALK and EGFR	ALK-rearranged and EGFR-T790M NSCLC	Ariad (2017, type-1)	ALKinib
2017	Midostaurin (PKC412, CGP41251, Rydapt)	FLT3, KIT	AML, Mastocytosis	Novartis, (2017, type-1)	Multi
2017	Neratinib (HKI-272, Nerlynx)	EGFR	BC-HER2 overexpressed after trastuzumab	Wyeth, Pfizer -> Puma (2017, covalent)	HERinib
2017	Baricitinib (Olumiant, INCB28050, LY3009104)	JAK1/JAK2	RA	Incyte/Eli Lilly	JAKinib
2017	Abemaciclib (LY2835219, Verzenio)	CDK4/6	1st-line HR+/HER2- metastatic BC in combo with any AI	Eli Lilly (2017, type-1)	CYClib
2017	Copanlisib (BAY 80-6946, Aliqopa)	dual PI3K/mTOR	FL	Bayer (2017, type-1)	PIKlisib
2017	Acalbrutinib (ACP-196, Calquence)	BTK	MCL	AZ, Acerta Pharma (2017, covalent)	BTKinib
2818	Fostamatinib (R-406, Tavalisse)	SYK	Idiopathic Thrombocytopenic Purpura	Rigel (2018, Type-1)	SYKinib
2018	Simotinib	EGFR	NSCLC patients with EGFR	Jiangsu Simcere Pharmaceutical (China only)	HERinib
2018	Binimetinib (MEK162, Mektovi) with Encorafenib (LGX818, Braftovi)	MEK/RAF combo	Melanoma	ARRAY (2018, type-3) with Novartis (2018, type-2)	MEKinib
2018	Duvelisib (IPI-145, Copiktra)	PI3Kdelta/gamma	CLL and SLL	Verastem (2018, type-1)	PIKlisib
2018	Dacomitinib (PF-00299804, Vizimpro)	EGFR	NSLSC with EGFRmut	Pfizer (2018 covalent)	HERinib

http://www.guidetopharmacology.org/GRAC/LigandListForward?type=Approved&database=all (D Fabbro)

The Clinical Kinome

http://www.guidetopharmacology.org/GRAC/LigandListForward?type=Approved&database=all





- **49approved KIs**
  - inib = TK-i -> JAKinibs, HERinibs, ALKinibs, ABLinibs, RAFinibs, MEKinibs....
  - rolimus = mTOR-i
  - rafenib = Raf-i
  - anib = VEGFR-i
  - metinib = MEK-i
  - dil = ROCK-i (Japan only)
  - lisib = PI3K-i or PIKlisibs
- **~ 400 Clinical trials (many, but most in the oncology arena)**
  - 40 Ph-3
  - 140 Ph-2
  - 200 Ph-1
- PPP to increase number of publically available KIs (~ 300)

the “non-onc kinome”: still a bonsai

- 556 protein kinases
- ~50 kinases “associated” with non-onc indications

- Activation of kinases in non-onc:
  - Overactivation (wt):
    TGFβ-R (pulmonary hypertension)
    GSK3β (Diabetes)
    PKC (TX)
    mTOR (TX, Toropathies)
    JNK (Diabetes, Ischemic reperfusion)
    PI3Kγ/dδ (Inflammation)
  - GOF or LOF:
    LRRK2 (GoF in Parkinson)
    WNK1 (GoF in Gordon Hypertension Syndrome)
    Jak3 (LoF in X-linked SCID)
    LIMK (LoF in Williams Syndrome)
    Zap70 (LoF in CD8 def. form of SCID)
    BTK (LoF in X-linked agamma-globulinemia)
    Syk (LoF in mast cells)
  - Ectopic expression of Cyto-/Chemokines etc.
    TNF-R/IL-1R/Toll-R-> p38, IRAK, etc.
  - Bacteria, parasites, fungi:
    PknB (TB), Waap (PA), Pfl kinases (PF) etc.

<u>non-ONC indications</u>

- Transplantation
- Inflammation
- Hpyertension
- Immun-disorders
- CV
- Metabolic disorders
- Muscle/bones
- Neglected diseases

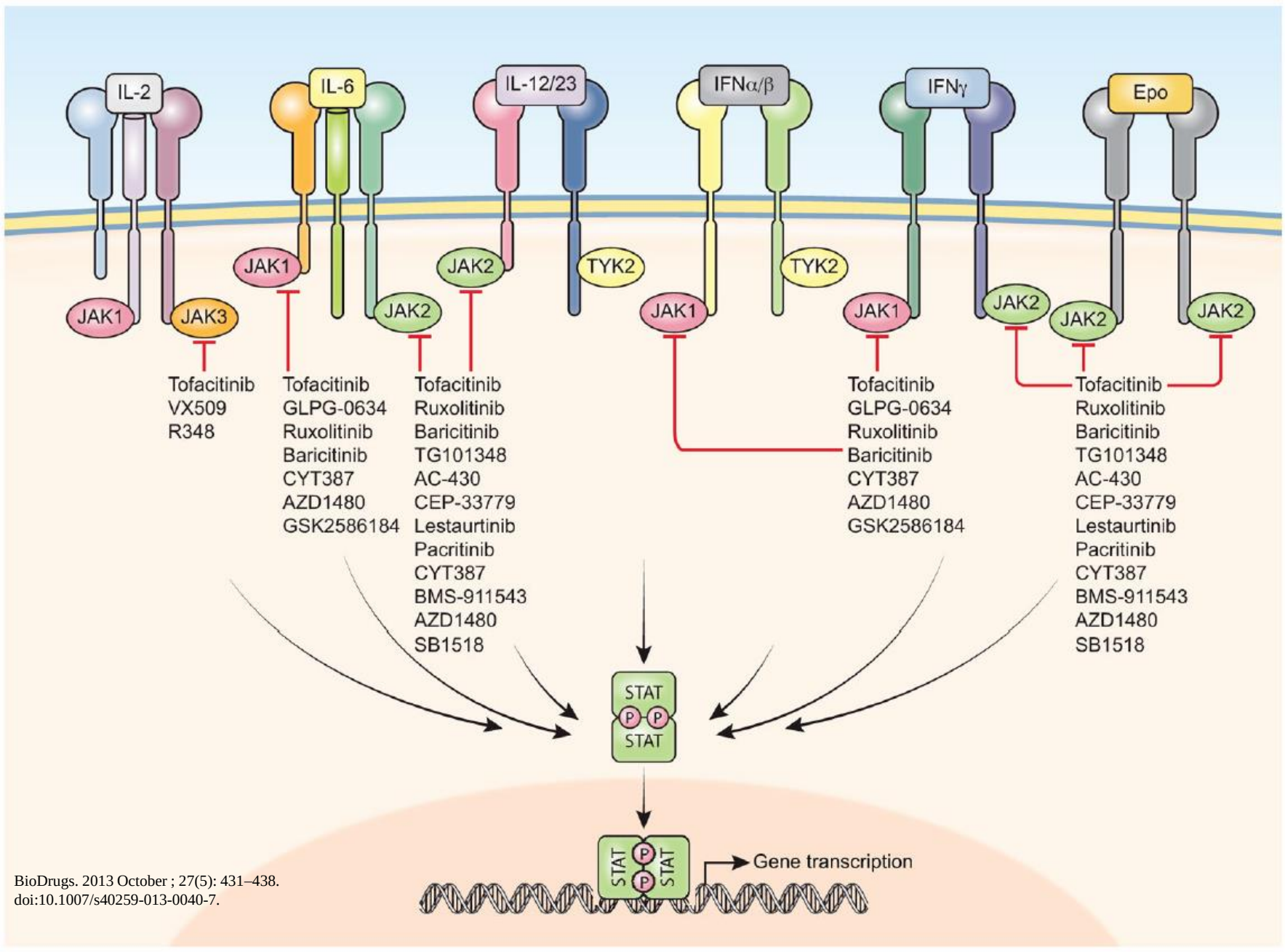
Drugging the Kinome: ImmPhar

Kinase family	Possible Kinase Targets
RTPKs	KIT, Ron, TAMs (Tyro, Axl, Mer), PDGFR, NTRKs
NRTPKs	JAKs, LCK, TECs, ZAP70, SYK
SerPKs	IRAK4, TAK1, TBK1, ROCK, LIMK, COT, ERK, PKC, MAP3Ks, MAP4Ks (HIPK1), IKK, JNK, p38, MK2, MNK, RIPKs, GSK3a
Dual specificity	MEK, MAP3Ks
PI3Ks & lipid mod. kinases	PI3Kδ, PI3Kγ, SPHK1

Drugging the Kinome: ImmPhar

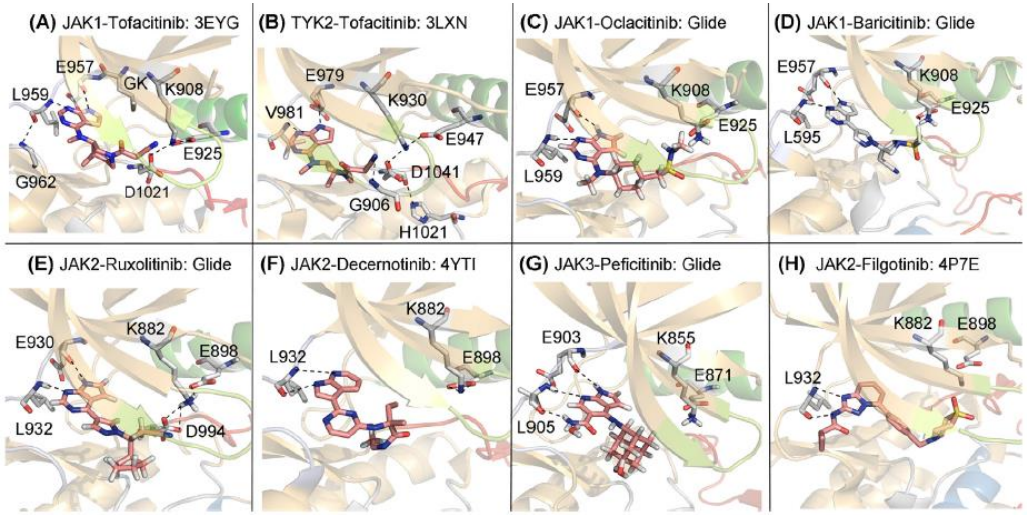
	Compound	Phase	Target	Indication	Status	Company
JAKs						
JAKinibs	AC430	1	JAK2	RA		Ambit
	baricitinib	approved	JAK1/2	RA	approved	E Lilly
	cerdulatinib	1/2	JAK/SYK	NHL		Portola
	decernotinib	3	JAK3	RA	stopped	Vertex
	delgocitinib	2	pan-JAK	Atopic D, Alopecia		Japan Tobacco
	filgotinib	3	JAK1	RA, UC, Crohns		Galapagos/Gilead
	peficitinib	3	JAK1/2, TYK2	RA		Astellas
	PF-04965842	3	JAK1/2	Atopic D	BreakThrough	Pfizer
	PF-06263276	1	pan-JAK	Inhaled/topical		Pfizer
	PF-06651600	1	JAK3	Alopecia Areata	BreakThrough	Pfizer
	solcitinib	2	JAK1	SL, Plaque psoriasis	stopped	GSK
	tofacitinib	approved	JAK3	RA	approved	Pfizer
	Upadacitinib	3	JAK1	UC, Ps. Arthritis		Abbvie
SYK						
	fostamatinib	approved	SYK	ITP, AI anemia, IgA	approved	Rigel
ZAP70						
	preclin					
RIPK1-3						
	GSK2982772	2	RIPK1	Ulcerative Colitis		GSK
IRAK1-4						
	preclin					
IKK						
	amlexanox	approved	TBK1 & IKKε	Aphtous ulcer	withdrawn in US	
PI3K						
	leniolisib	3	PI3Kδ	ADPS/PASLI	Orphan	Novartis

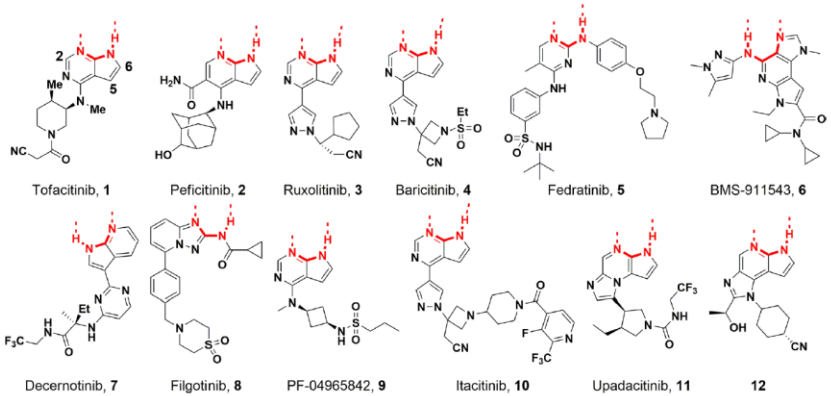
JAKinibs



BioDrugs. 2013 October ; 27(5): 431–438.
doi:10.1007/s40259-013-0040-7.

JAKinibs





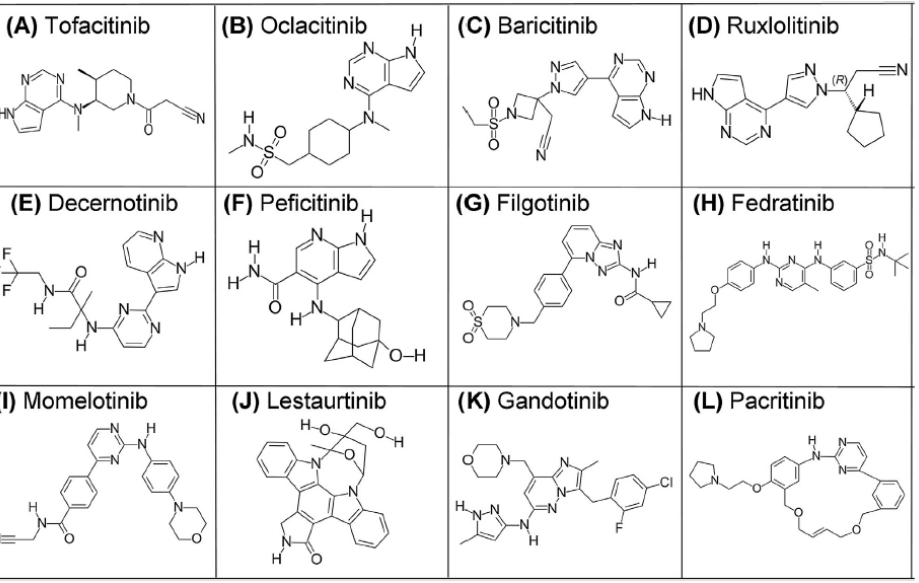


Table 5
Janus kinase inhibitor EC_{50} values (nM)[a].

Drug	JAK1	JAK2	JAK3	TYK2
First generation				
Tofacitinib[b]	0.16	0.58	1.6	4.8
Oclacitinib[c]	10	18	99	84
Baricitinib[d]	4	6.6	259	21.1
Ruxolitinib[d]	0.09	0.036	2	0.4
Second generation				
Decernotinib[e]	11	13	2	11
Peficitinib[f]	3.9	5.0	0.71	4.8
Filgotinib[g]	10	2.8	81	11.6
Fedratinib[b]	18	1.1	?	?
Momelotinib[d]	11	18	155	17
Lestaurtinib[d]	8.8	3.7	2.3	15
Gandotinib[h]	25	3	60	?
Pacritinib[i]	1280	23	520	50

R. Roskoski Jr. / Pharmacological Research 111 (2016) 784–803

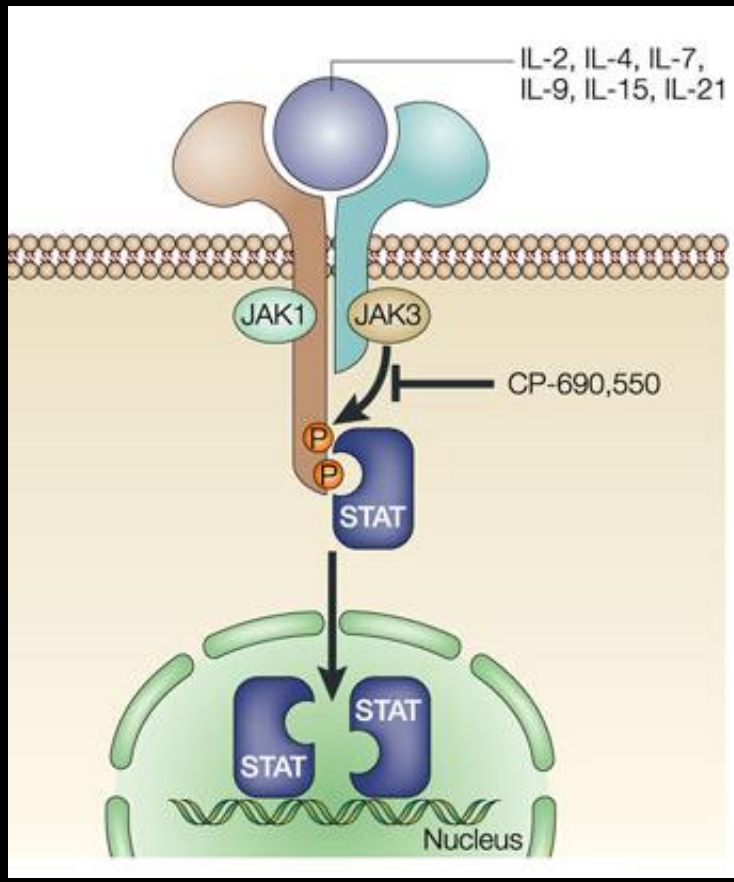
Properties of JAKinibs in clinical trials

Table 6
Properties of small molecule Janus kinase inhibitors in clinical trials[a,b].

Name, code, trade name®	Targets	PubChem CID	Formula	MW	D/A[c]	cLogP[d]	Indications and clinical trials
First generation							
Tofacitinib, CP690550, Xeljanz®	JAK1/2/3	9926791	$C_{16}H_{20}N_6O$	312.37	1/7	1.076	RA[e], psoriasis, alopacia areata, atopic eczema, spondyloarthritis, systemic lupus, ulcerative colitis, acute host-vs.-graft disease
Oclacitinib, OF03394197, Apoquel®	JAK1/2	44631938	$C_{15}H_{23}N_5O_2S$	337.44	2/6	1.528	Canine allergic dermatitis[f]
Baricitinib, INCB28050, LY3009104	JAK1/2	44205240	$C_{16}H_{17}N_7O_2S$	371.42	1/7	0.330	RA, psoriasis, autoinflammatory disease
Ruxolitinib, INC424, Jakafi®	JAK1/2	25126798	$C_{17}H_{18}N_6$	306.37	1/6	1.967	Myelofibrosis[g], polycythemia vera[g], ALL, AML, CLL, CML, NSCLC, breast, colorectal, head and neck, prostate, and pancreatic cancers, RA, psoriasis
Second generation							
Decernotinib, VX509	JAK3	59422203	$C_{18}H_{19}F_3N_6O$	392.38	3/8	2.021	RA
Peficitinib, ASP015 K	JAK3	57928403	$C_{18}H_{22}N_4O_2$	326.39	4/4	2.046	Psoriasis, RA, ulcerative colitis
Filgotinib, GLPG0634	JAK1/2	49831257	$C_{21}H_{23}N_5O_3S$	425.50	1/6	1.958	RA, Crohn disease
Fedratinib, SAR302503, TG101348	JAK2	16722836	$C_{27}H_{36}N_6O_3S$	524.68	3/9	4.934	Myelofibrosis, polycythemia vera, primary thrombocythemia
Momelitinib, Cyt387	JAK1/2	25062766	$C_{23}H_{22}N_6O_2$	414.46	2/7	2.352	Myelofibrosis, polycythemia vera, NSCLC, pancreatic carcinoma
Lestaurtinib, CEP-701	JAK2, FLT3, TRKA/B/C	126565	$C_{26}H_{21}N_3O_4$	439.36	3/4	2.816	Myelofibrosis, psoriasis, polycythemia vera, ALL, AML, prostate cancer, multiple myeloma, neuroblastoma, Hodgkin lymphoma
Gandotinib, LY2784544	JAK2	46213929	$C_{23}H_{25}ClFN_7O$	469.94	2/7	3.661	Myeloproliferative disorders
Pacritinib, SB1518	JAK2	46216796	$C_{28}H_{32}N_4O_3$	472.58	1/7	4.499	Myelodysplastic syndromes, myelofibrosis, AML, CLL, NSCLC, colorectal cancer

Why do we need JAK3 selectivity?

- LOF of JAK3 lead to immunodeficiency in human (lack of T and NK cells)
- LOF of JAK3 in mice -> SCID mice
- GOF of JAK3 kinase lead to lymphoproliferative disorders (T-ALL, T-PLL) and leukemias (A572V)
- JAK1 and JAK3 are always companioms at the γ_c cytokine receptors
- Still not known if isolated JAK3 inhibition is sufficient to shut down γ_c-signalling completely



O'Shea, J et. al. *Nat Rev Drug Discov* **2004**, 555-564
Haan, C et al., *Chem. Biol*. **2011** 314-323

→to clarify this issue molecular probes with high selectivity towards JAK3 are needed

→Exploit Cys 909 in JAK3 (covalent inhibitors)

PF-06651600: JAK3 covalent inhibitor (Ph1, Alopecia)

Table 1. PF-06651600 Inhibition of JAK Isoforms in Biochemical Assays[a]

JAK isoform	ATP [μM]	IC_{50} [nM]	SEM (*n*)	ATP [μM]	IC_{50} [nM]	SEM (*n*)
JAK1	40*	1638	43 (7)	1000	>10 000	(16)
JAK2	4*	1507	88 (7)	1000	>10 000	(15)
JAK3	4*	0.346	0.025 (7)	1000	33.1	3.1 (16)
TYK2	12*	3779	464 (7)	1000	>10 000	(16)

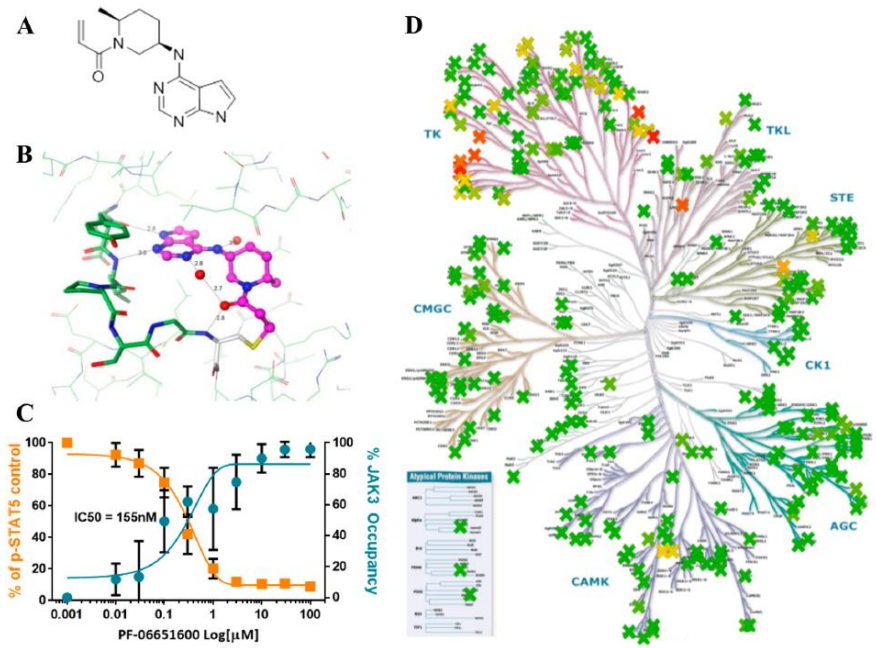


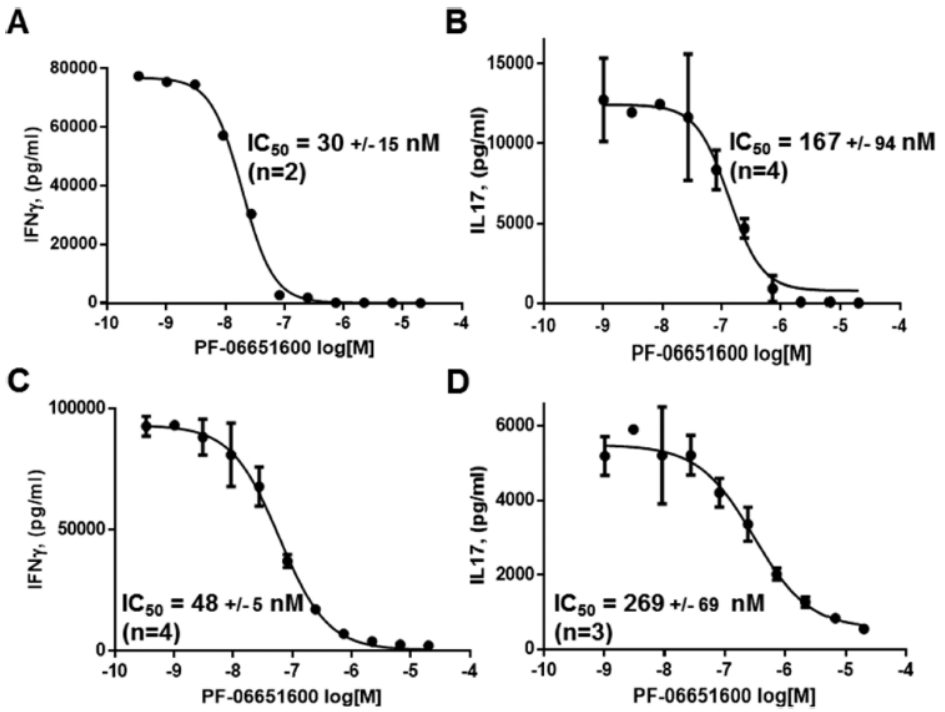
Table 2. Cellular Potency of PF-06651600 in Total Lymphocytes in Human Whole Blood[a]

cytokine	JAK pairing	p-STAT measured	IC_{50} [nM]	SEM (*n*)
IL-2	JAK1/JAK3	p-STAT5	244	16 (6)
IL-4	JAK1/JAK3	p-STAT6	340	49 (6)
IL-7	JAK1/JAK3	p-STAT5	407	24 (6)
IL-15	JAK1/JAK3	p-STAT5	266	24 (21)
IL-21	JAK1/JAK3	p-STAT3	355	38 (12)
IL-6	JAK1/JAK2	p-STAT1	>20 000	(3)
IL-6	JAK1/JAK2	p-STAT3	>20 000	(3)
IL-12	JAK2/TYK2	p-STAT4	>20 000	(2)
IL-10	JAK1/TYK2	p-STAT3	>60 000	(6)
IL-27	JAK1/JAK2	p-STAT3	>60 000	(6)
IFNγ	JAK1/JAK2	p-STAT1	>20 000	(2)
IFNα	JAK1/TYK2	p-STAT3	>60 000	(3)
IL-23	JAK2/TYK2	p-STAT3	>20 000	(1)
G-CSF	JAK1/JAK2	p-STAT3	>20 000	(1)
EPO[b]	JAK2/JAK2	p-STAT5	>20 000	(1)

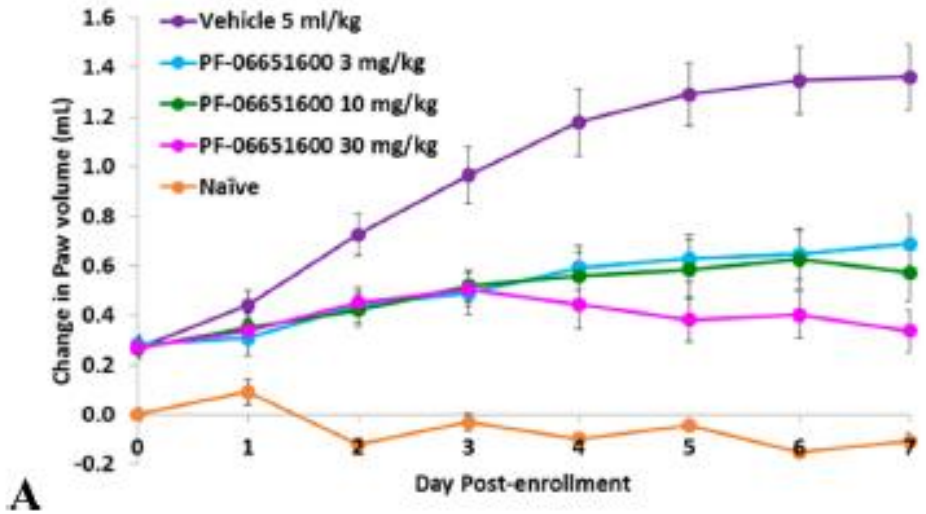
DOI: 10.1021/acschembio.6b00677
ACS Chem. Biol. XXXX, XXX, XXX−XXX

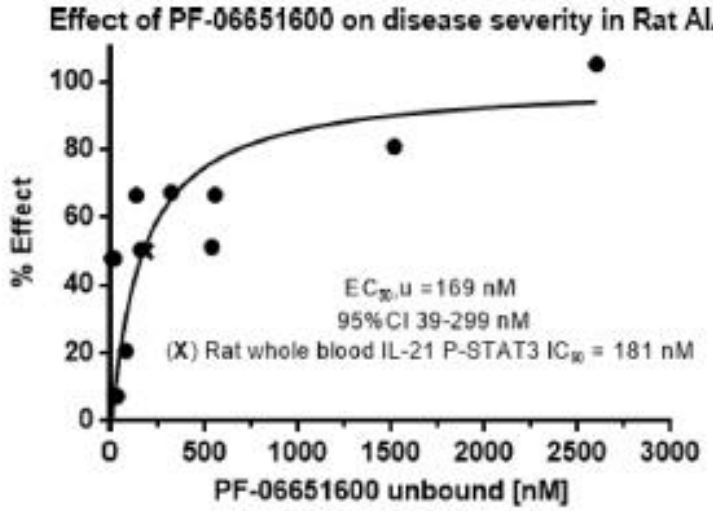
JAK3-selective inhibition

Inhibition of Th1 and Th17 differentiation and function

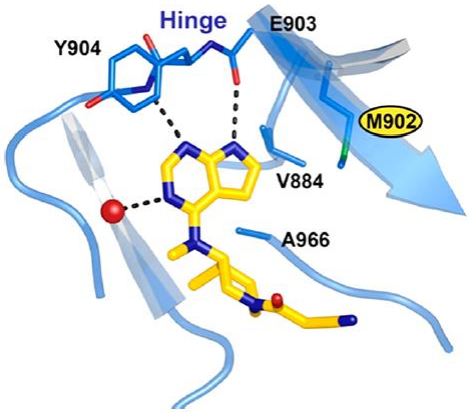


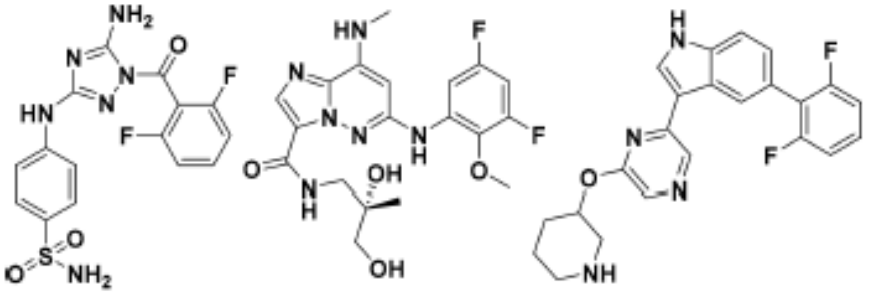
DOI: 10.1021/acschembio.6b00677, 2018



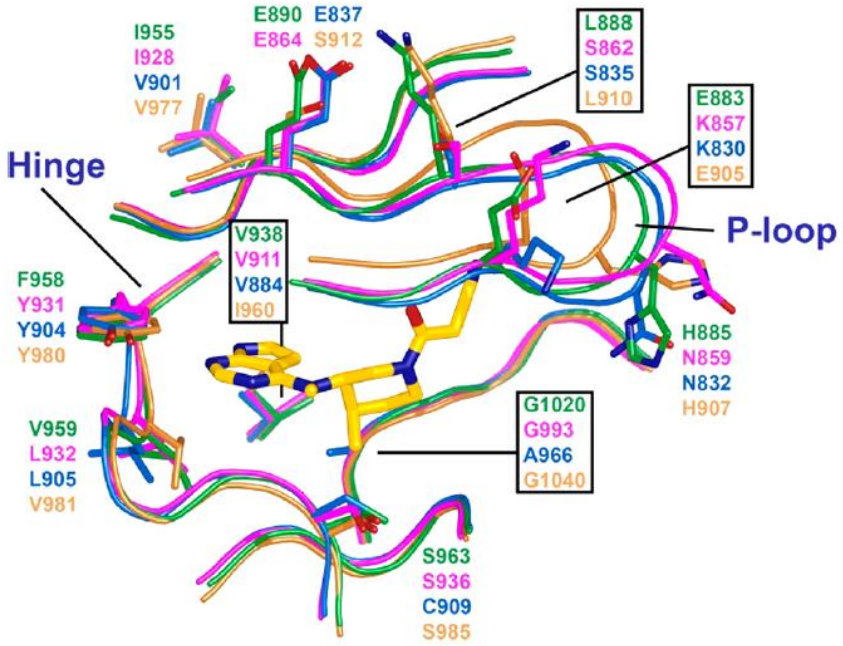


Summary of JAKinibs
X-ray cocrystal structures with sequence alignment



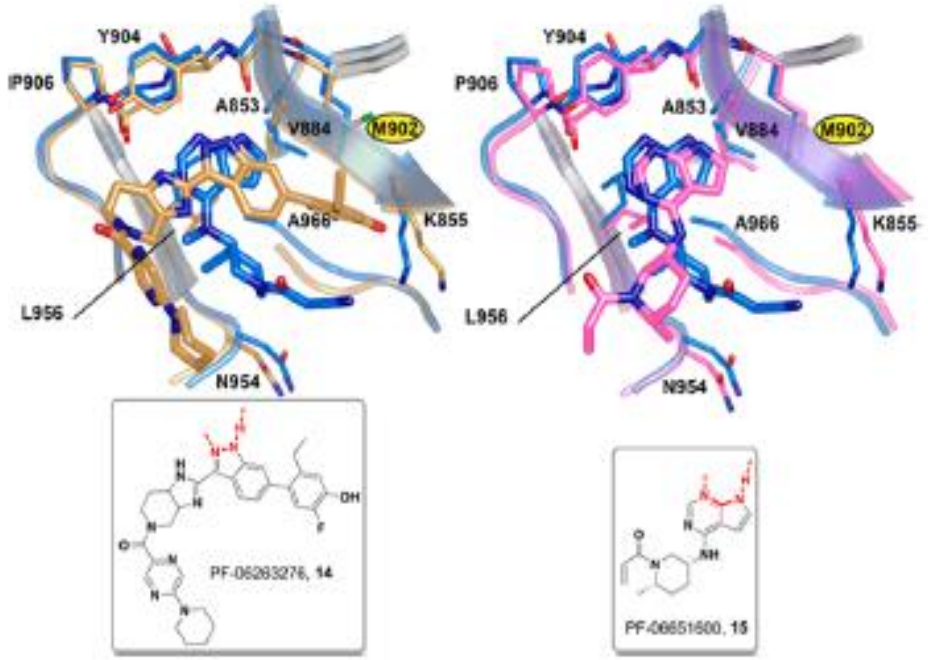


Tofacitinib in JAK1 JAK2 JAK3 and TYK2



DOI: 10.1021/acs.jmedchem.8b00667 J. Med. Chem. 2018

Reported pseudokinase inhibitors of JAK family members

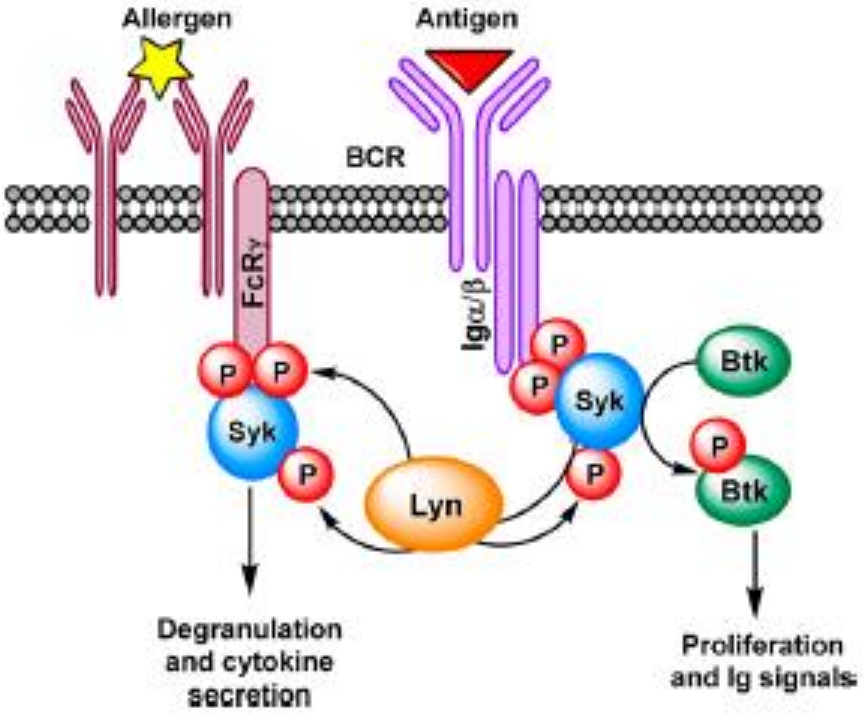


pan-JAK inhibitor PF-06263276 and JAK3 covalent inhibitor PF-06651600

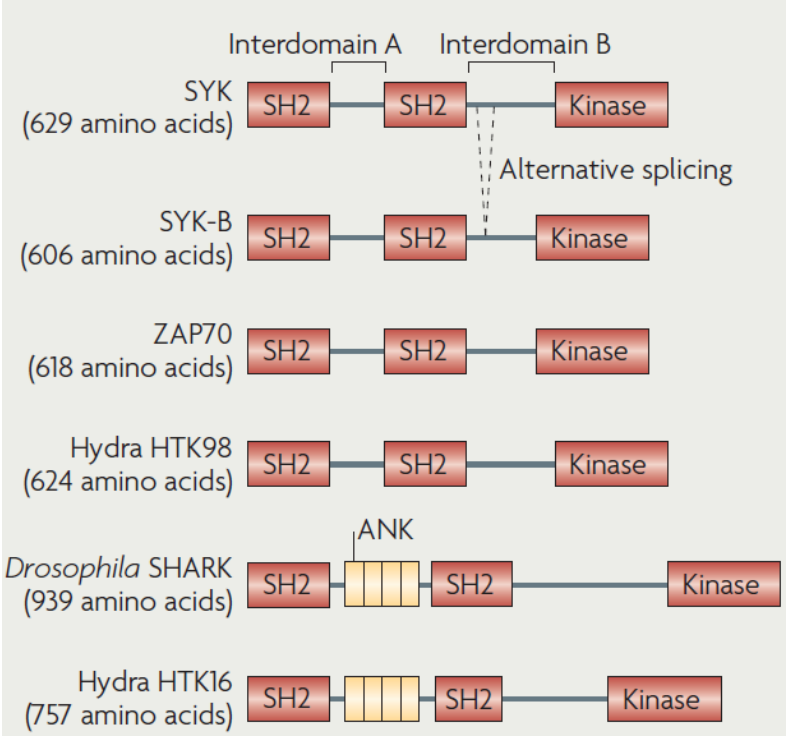
Drugging the Kinome: ImmPhar

	Compound	Phase	Target	Indication	Status	Company
JAKs						
JAKinibs	AC430	1	JAK2	RA		Ambit
	baricitinib	approved	JAK1/2	RA	approved	E Lilly
	cerdulatinib	1/2	JAK/SYK	NHL		Portola
	decernotinib	3	JAK3	RA	stopped	Vertex
	delgocitinib	2	pan-JAK	Atopic D, Alopecia		Japan Tobacco
	filgotinib	3	JAK1	RA, UC, Crohns		Galapagos/Gilead
	peficitinib	3	JAK1/2, TYK2	RA		Astellas
	PF-04965842	3	JAK1/2	Atopic D	BreakThrough	Pfizer
	PF-06263276	1	pan-JAK	Inhaled/topical		Pfizer
	PF-06651600	1	JAK3	Alopecia Areata	BreakThrough	Pfizer
	solcitinib	2	JAK1	SL, Plaque psoriasis	stopped	GSK
	tofacitinib	approved	JAK3	RA	approved	Pfizer
	Upadacitinib	3	JAK1	UC, Ps. Arthritis		Abbvie
SYK						
	fostamatinib	approved	SYK	ITP, AI anemia, IgA	approved	Rigel
ZAP70						
	preclin					
RIPK1-3						
	GSK2982772	2	RIPK1	Ulcerative Colitis		GSK
IRAK1-4						
	preclin					
IKK						
	amlexanox	approved	TBK1 & IKKε	Aphtous ulcer	withdrawn in US	
PI3K						
	leniolisib	3	PI3Kδ	ADPS/PASLI	Orphan	Novartis

SYK



DOI: 10.1021/acs.jmedchem.8b00667 J. Med. Chem.



NATuRe ReVIewS Immunology **10** , 2010

- SYK contains two tandem SH2 domains and a carboxy-terminal tyrosine kinase domain linked by two linker regions: interdomain A between the two SH2 domains and interdomain B between the C-terminal SH2 domain and the kinase domain.
- The major phenotypes displayed by SYK-deficient mice are perinatal lethality, a petechiated *in utero* appearance and the lack of mature B cells.

SYK expression & functions in different cell types

TABLE 1

Syk expression and functions in different cell types.

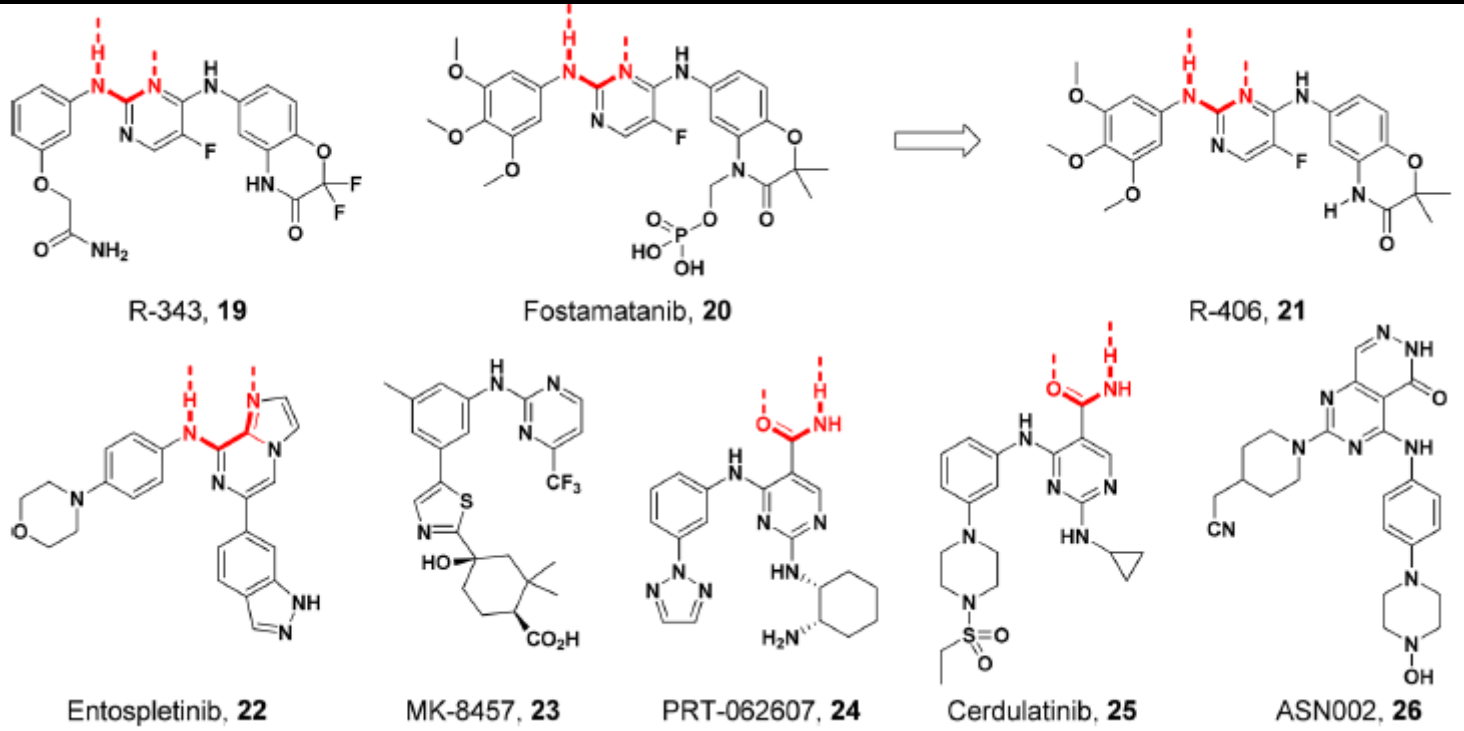
Cell type		Receptor	Ligand	Signal	Disease involvement	Syk functional role	Refs
T cells (TC)	Resting	TCR	MHC	CD3ζ	Autoimmunity	No involvement of Syk	[14]
	Effector	TCR	MHC	FcR-γ	Autoimmunity	Proliferation and differentiation?; releasing of mediators, self-antigen presentation to B cells	[14]
	Natural killer	FcγRIIIa; NKp30; NKp44; NKp46; KIR CD94/NKG2C	IgG; BAT3; HLA class I; HLA-E	DAP12	Autoimmunity	Elimination of antibody coated cells; surveillance of genotoxic stress/transformation; surveillance of mitotic cells	[15]
B cells		BCR	Membrane-bound antigen	Igα; Igβ	Autoimmunity	Pre-B cells development and activation	[12]
		FcgRIIB	Feedback		Autoimmunity	Inhibition of B cell activation	[13]
Red blood cell						Band 3 protein phosphorylation; cells removal from circulation, glycolysis, cell shape, membrane transport	[14]
Granulocytes	Neutrophil	FcγR1; FcγRII; FcεR1 FcγRIII; integrin	IgG; IgE	FcR-γ	Inflammation, autoimmunity	Releasing NO; reactive oxygen intermediates, adhesion, phagocytosis	[3]
	Basofil	FcεRI	IgE	FcR-β; FcR-γ	Allergy	Degranulation	[3]
	Eosinohil	FcγR; FcεR	IgG; IgE	FcR-γ	Allergy	Degranulation; reactive oxygen intermediates generation	[3]

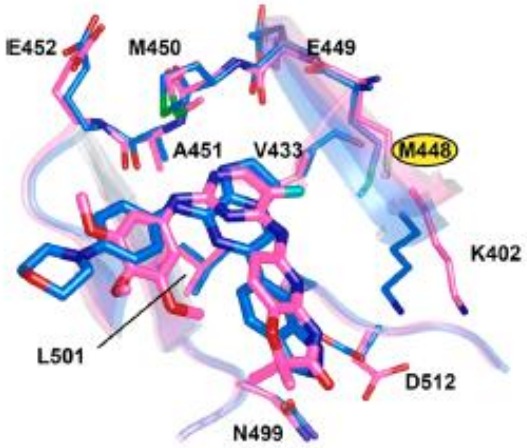
Summary of SYK studies in animal models

Table 1. Summary of intervention studies of Syk inhibitor in animal models

Animal model, reference	Resemblance of human disease	Intervention	Salient findings
EAG [16]	Anti-GBM disease	Syk inhibitor (R788)	Prevention of EAG (given before immunization) Reduced GN severity and prevention of pulmonary hemorrhage (given after established disease)
NTN [17, 18]	Anti-GBM disease	Syk inhibitor (R788) Conditional Syk gene deletion in myeloid cells	Reduced GN severity when treatment started after established disease Reduced GN severity
EAV [24]	ANCA-associated vasculitis/AAGN	Syk inhibitor (R788)	Reduced GN severity and pulmonary hemorrhage
Lupus prone NZB/NZW mice [31]	SLE and LN	Syk inhibitor (R788)	Delayed onset and reduced GN severity (given before disease onset) Reduced GN severity (given after disease onset)
MRL/lpr and BAK/BAX double-knockout mice [32]	SLE and skin disease	Syk inhibitor (R788)	Delayed onset and reduced severity of skin disease (given before disease onset) Reduced severity of skin disease (given after disease onset)
MRL/lpr mice [32]	SLE and lupus nephritis	Syk inhibitor (R788)	Prevention of GN (given before immunization) Reduced GN severity (given after established disease)
Experimental acute renal allograft rejection (Brown Norway to Lewis) [35, 36]	Acute renal allograft rejection	Syk inhibitor (R788)	Prevention of allograft infarction and reduced interstitial infiltrates Decreased donor-specific antibody
Experimental acute renal allograft rejection (Wistar to Dawley) [37]	Acute renal allograft rejection	Syk inhibitor (CC0482417)	Improved allograft function, reduced infiltration of macrophages and neutrophils, attenuated acute tubular injury and peritubular capillary thrombosis
UUO [41]	Renal fibrosis	Syk inhibitor (CC0417)	Reduced macrophage infiltration
NTN [40]	Renal fibrosis	Syk inhibitor (R788)	Late treatment (days 14–28) using Syk inhibitor reduced deposition of interstitial collagen, glomerular expression of α-smooth muscle actin and glomerular synthesis of transforming growth factor-β Reduced renal fibrosis Improved renal function

First generation SYK inhibitors

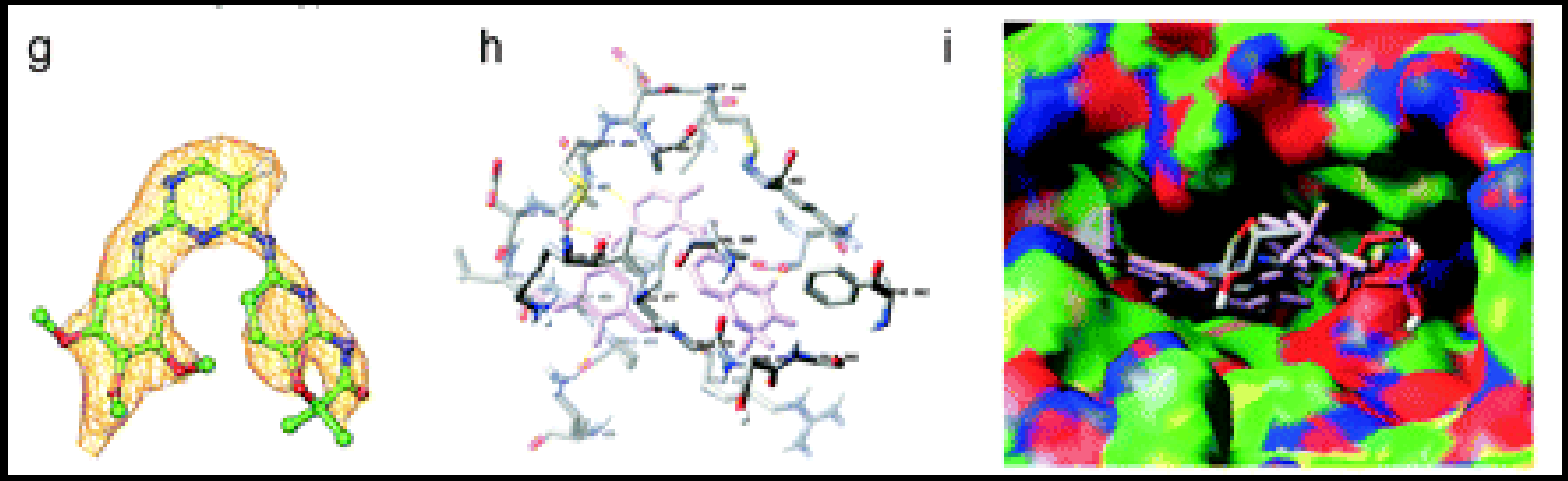




Overlay of first generation SYK inhibitor R406 (21, magenta, 3FQS) and entospletinib (22, blue, 4PUZ).,

DOI: 10.1021/acs.jmedchem.8b00667
J. Med. Chem. 2018

Fostamatinib: SYK inhibitor



- Fostamatinib (R788) is an oral prodrug
- R406 is the active metabolite which occupies the ATP binding pocket of Syk
- Selective for Syk with off targets on FLT3, KIT, LCK, JAK1 and JAK3 and Adenosine 3-R !!

Braselmann 2006 JPET 319:998-1008

Idiopathic Thrombocytopenia Purpura

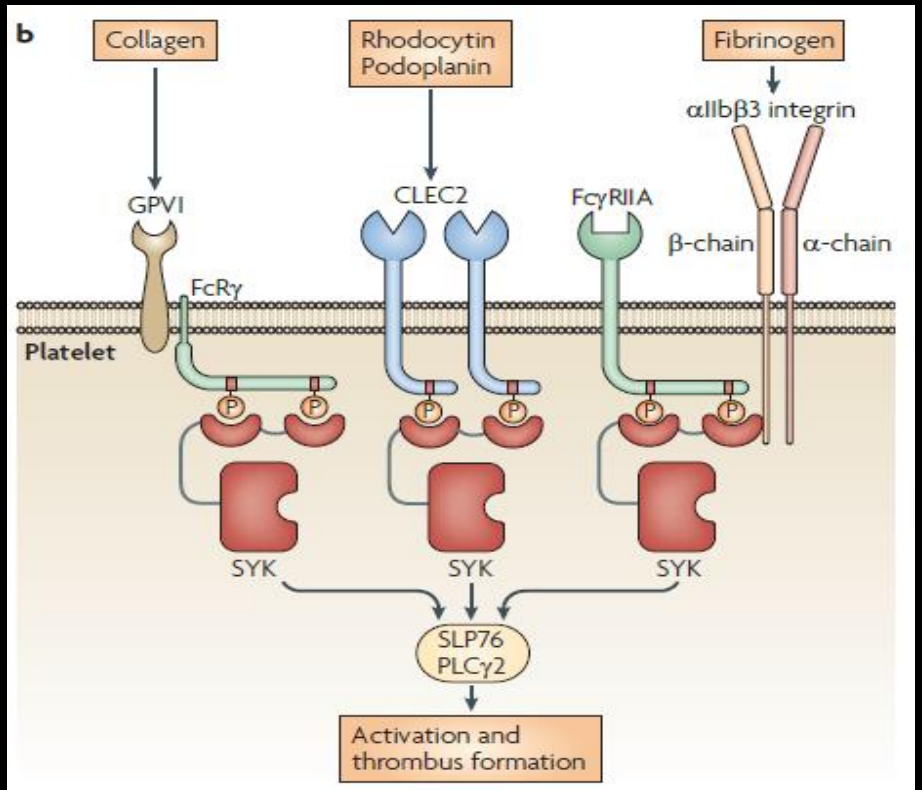
- Idiopathic thrombocytopenic purpura (ITP) occurs when the immune system destroys platelets (blood clotting).
- Few platelets in the blood causes bleeding
- Adults tend to get a chronic (long-term) form

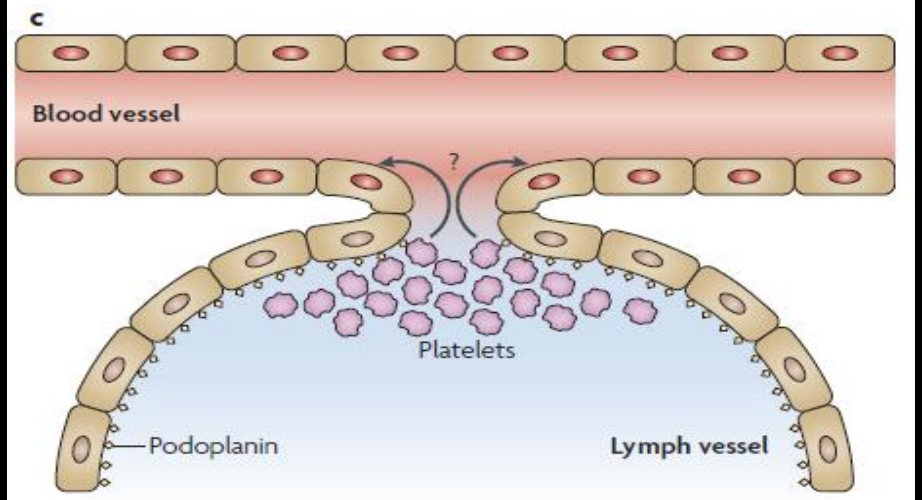
- Current Treatments

First line
- Corticosteroids
- Intravenous infusion of immunoglobulin (IV-Ig).
- Anti-D immunoglobulin (anti-D).

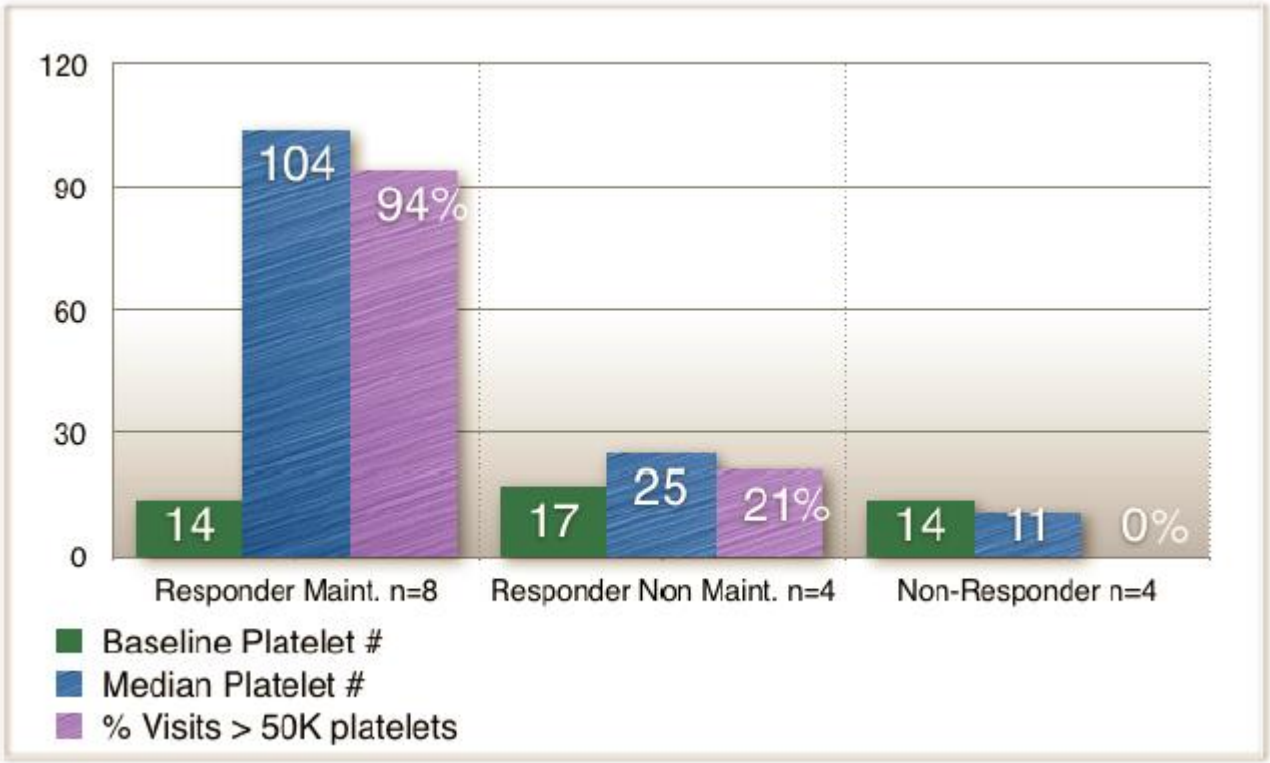
Second line
- Splenectomy
- Rituximab
- Thrombopoietin (TPO) receptor agonists
- Immunosuppressive agents - azathioprine, mycophenolate mofetil, and ciclosporin.
- Cytotoxic agents - cyclophosphamide and vinca alkaloids such as vincristine and vinblastine.

Treatment after failure of 1st and 2nd line
- Combination chemotherapy
- Haematopoietic stem cell transplantation (HSCT)





Fostamatinib ITP - P2 Study Results

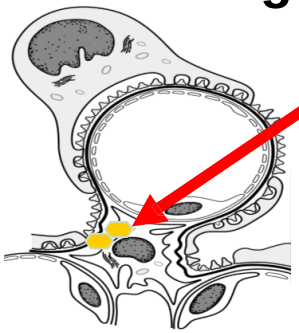


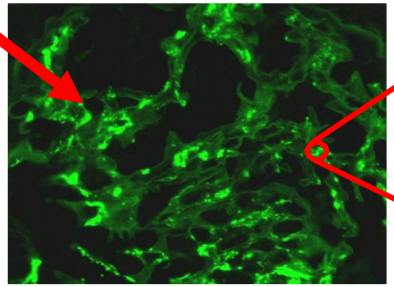
Clinically-significant response

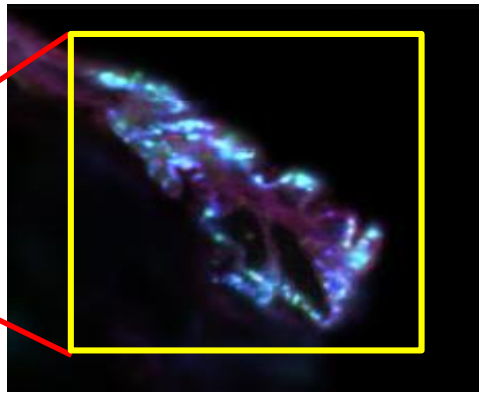
- **Increased platelet counts**
- **Reduced need for IV-Ig treatment**
- **Steroid tapering**

IgA Nephropathy

IgA1 deposition

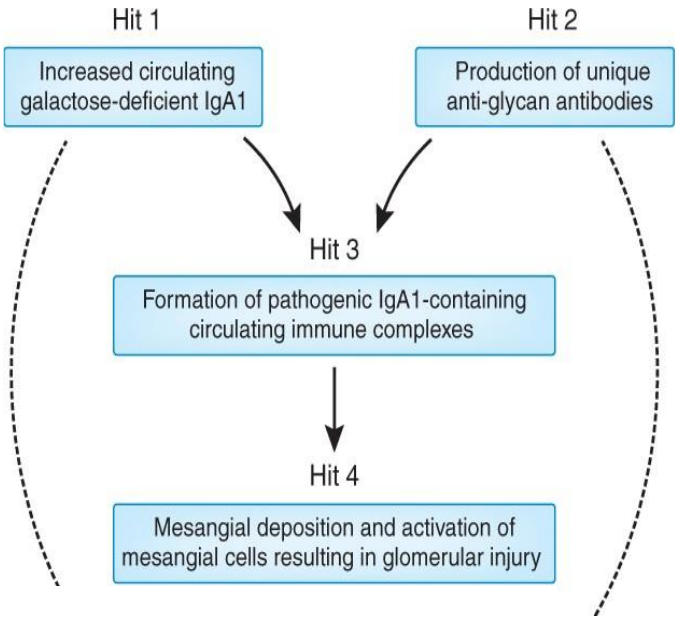


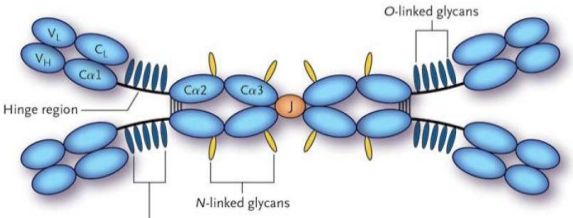




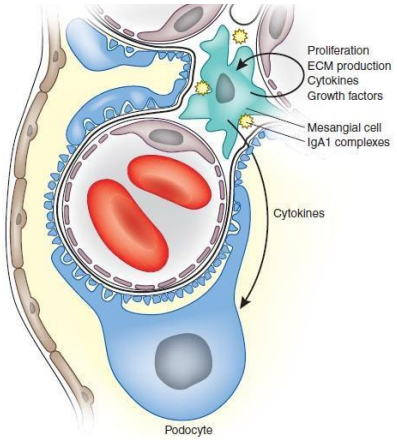
Co localization

IgG - red
IgA - blue
C3 - green





(IgG and IgA)

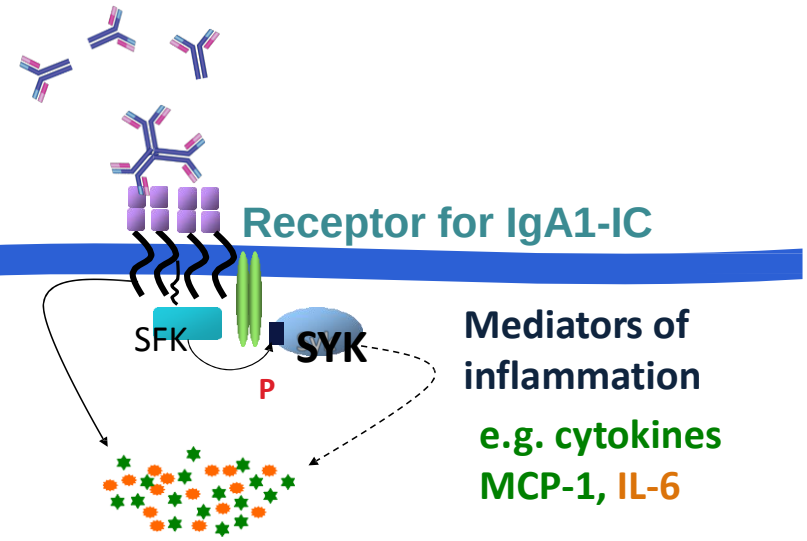


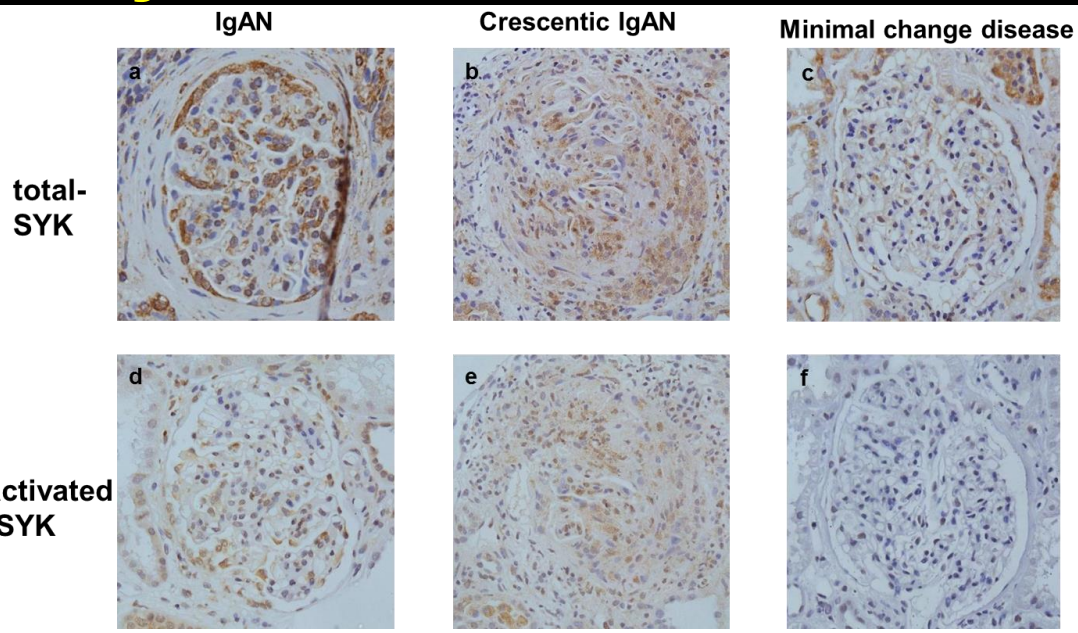
Jan Berger(1968): Berger's disease

Mesangial deposition of IgA and IgG/IgM (IgA>IgG).

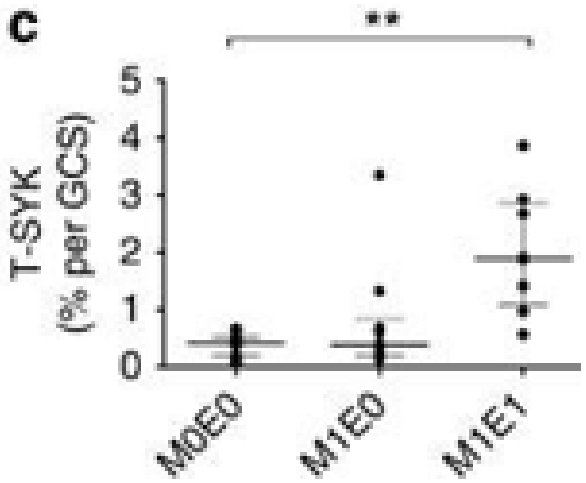
Suzuki H, et al: J Am Soc Nephrol 2011
Wyatt et al 2013 NEJM

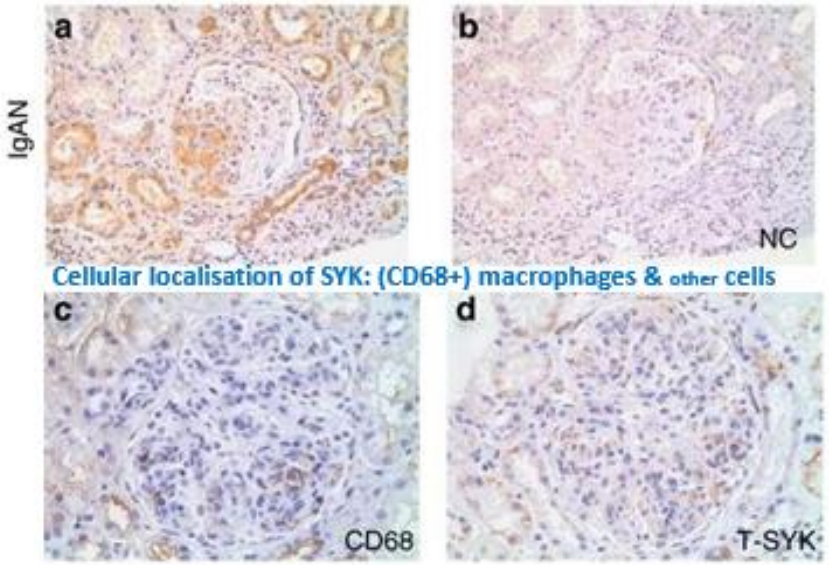
Hypothesis: IgA complex activates Syk and results in kidney inflammation



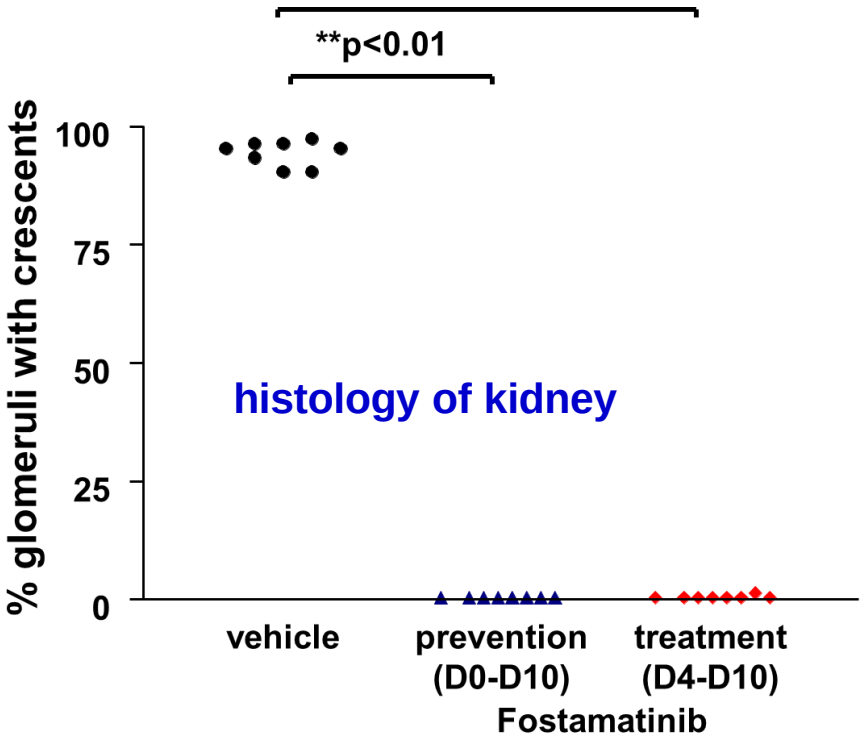


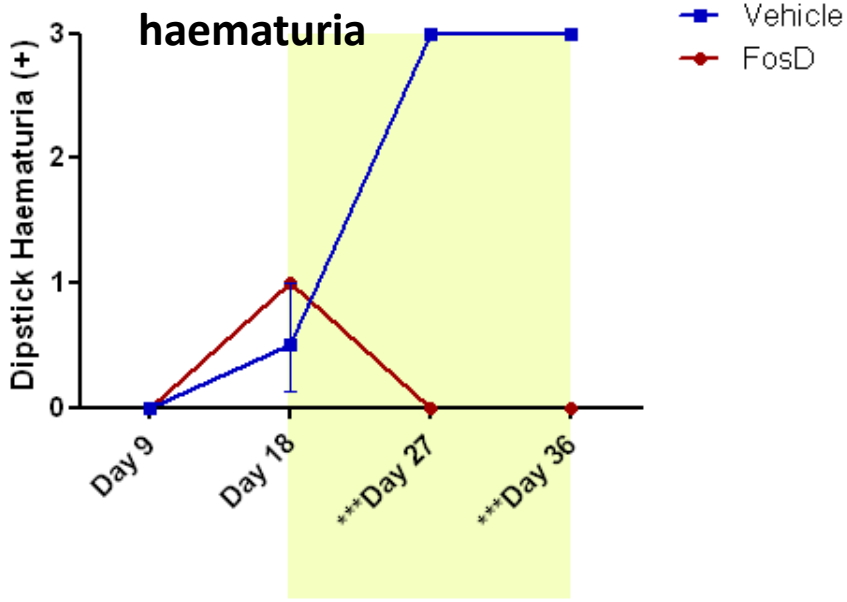
Kim MJ et al J Immunol 2012;189:3751-8

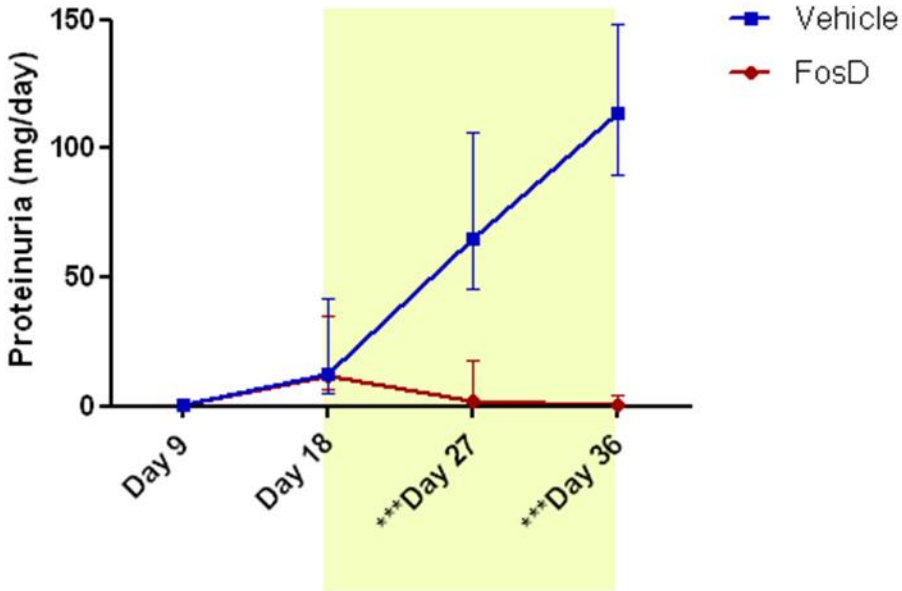




Experimental autoimmune GN (AEG)

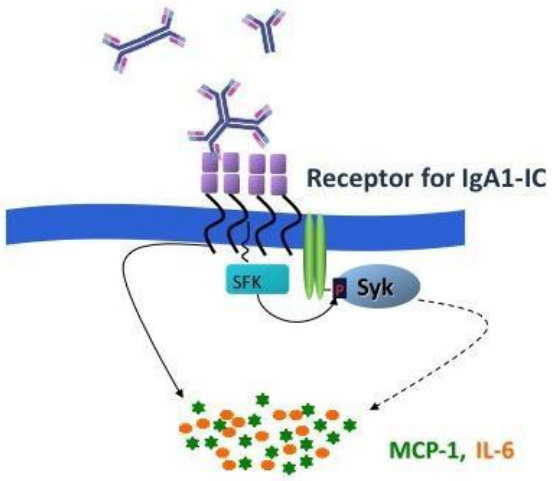






McAdoo et al, ***J Am Soc Nephrol.*** *25:2291-2014, 2014*

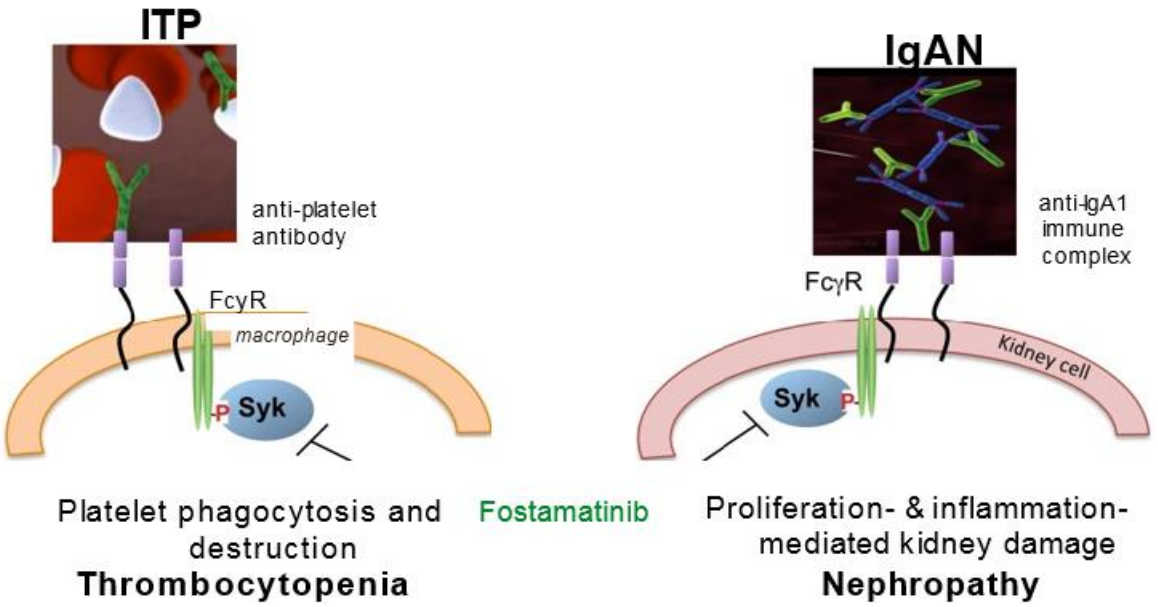
Conclusions (selective SYK inhibition)



- Increase p-SYK in the renal biopsies of patients with IgA nephropathy
- Both pharmacological inhibition of SYK and molecular knockout of SYK reduced production of inflammatory mediators from kidney cells in culture
- SYK inhibitor was shown to be effective in reducing autoantibody production and kidney damage in preclinical models of glomerulonephritis
- Developing a PoC clinical trials with fostamatinib for treatment patients with IgA nephropathy

Smith et al 2010, McAdoo et al, 2014

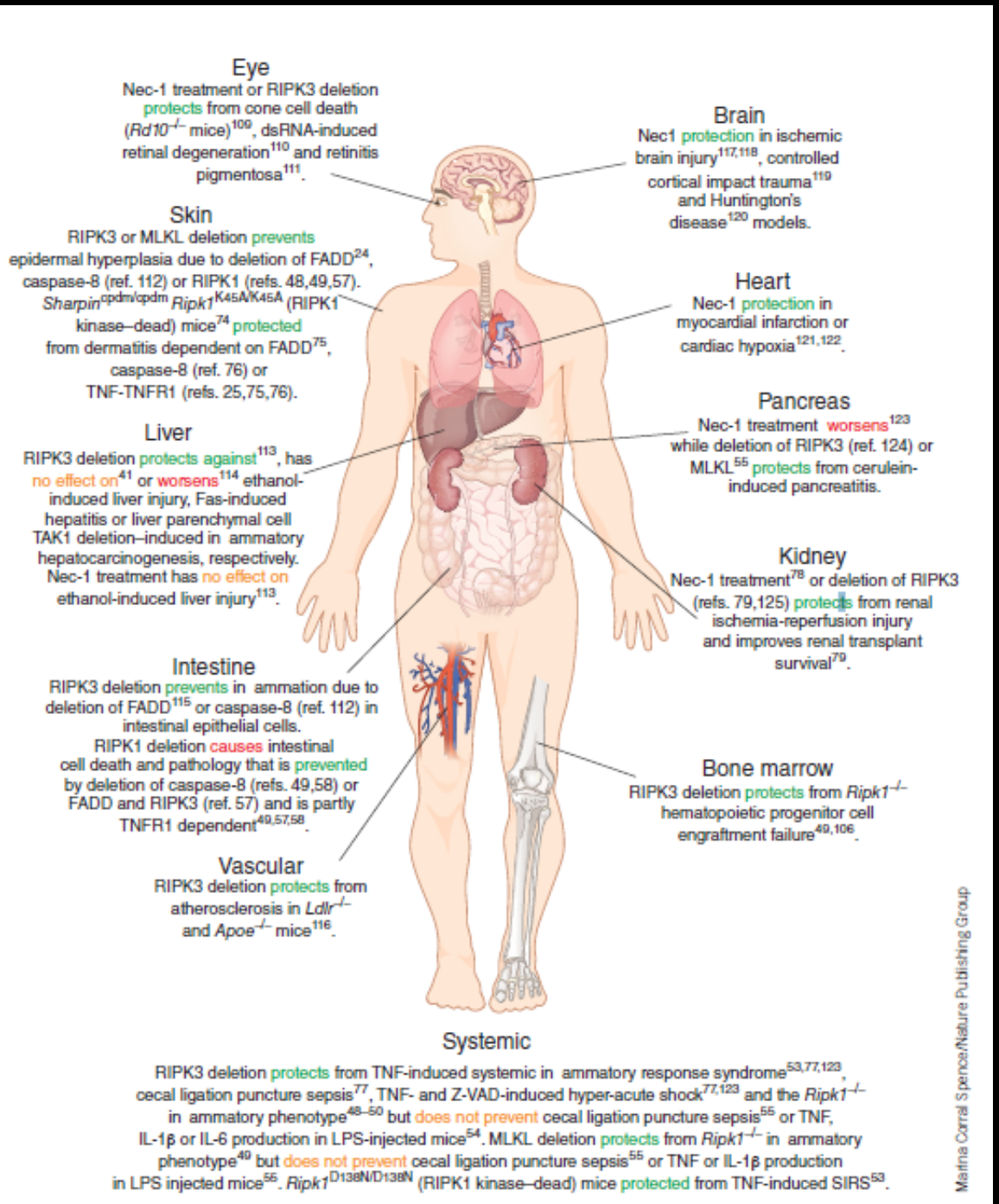
What is/are the mechanism(s) of action of SYK inhibitors in clinical use?



- SYK inhibitors have shown positive results in the treatment of allergy, autoimmune diseases and B cell lineage malignancies but the mechanism of their action is incompletely understood.
  - In part due to the diverse roles of SYK in immunological functions
  - In part due to R406 (ATP-competitive with limited specificity)

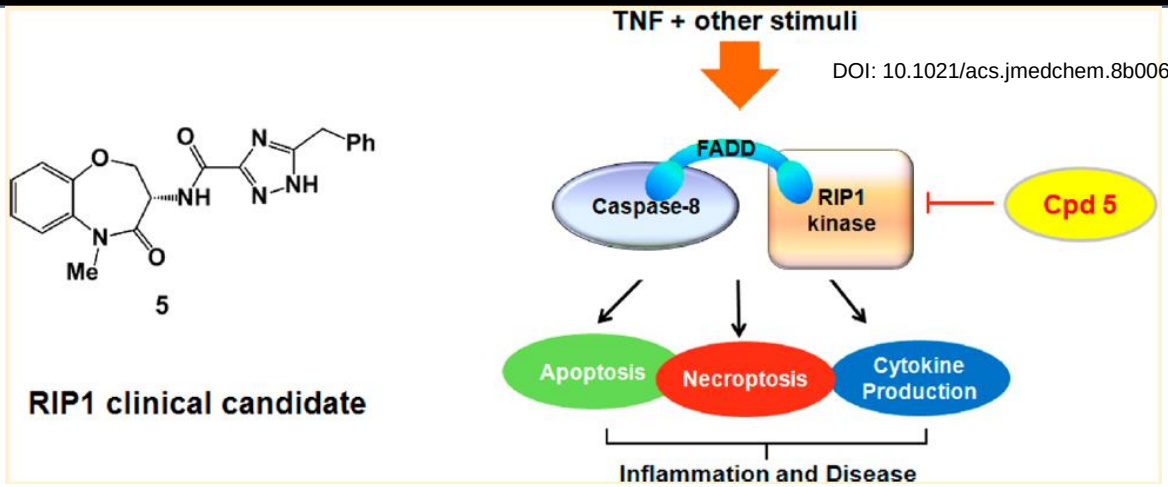
- **Taken together, the clinical effects of fostamatinib are probably mediated by inhibition of several SYK-dependent and SYK-independent immune signalling pathways.**

NATuRe ReVIewS **Immunology** VOluMe 10 , 2010

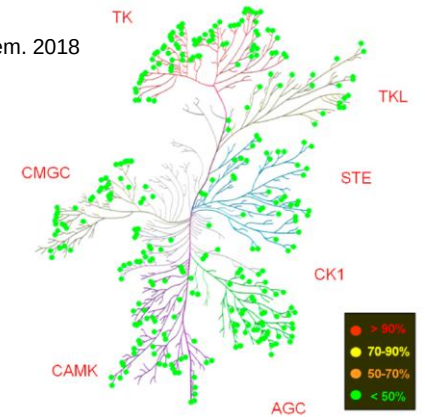


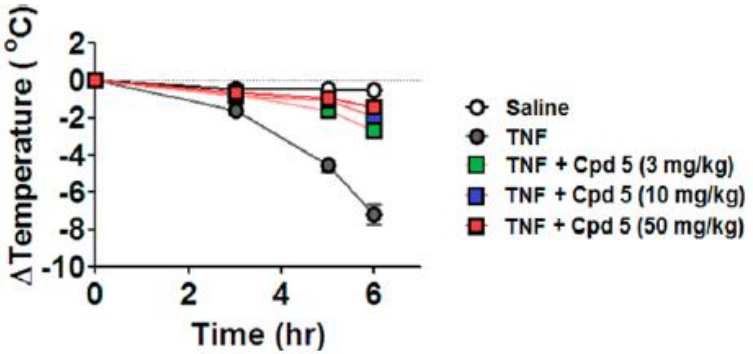
Evidence for the regulation of models of inflammation and tissue damage by RIPK1, RIPK3 and MLKL

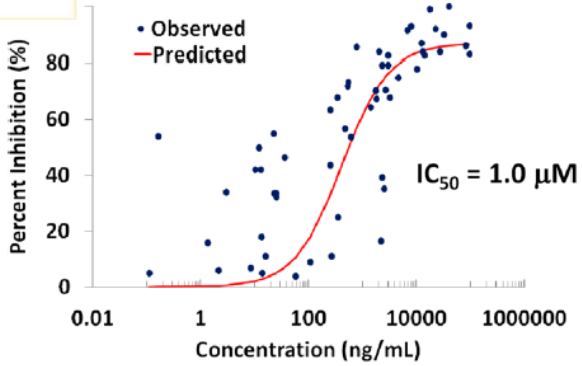
Discovery of a First-in-Class RIP1K (GSK2982772) for the Treatment of Inflammatory Diseases (Ph2, UC, RA, Psoriasis)

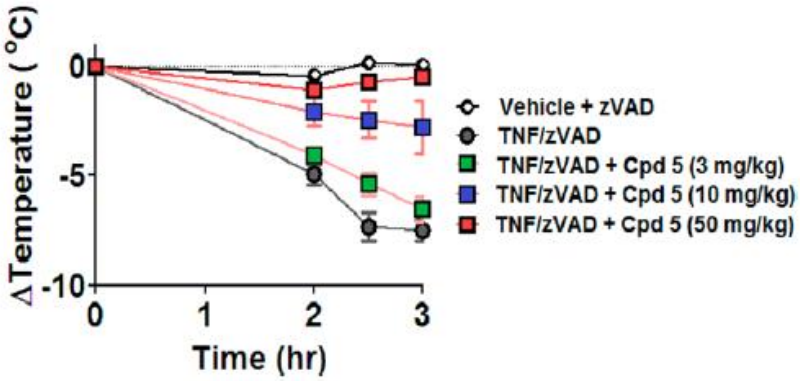


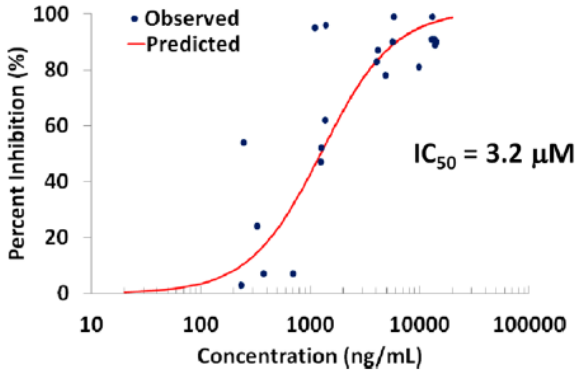
DOI: 10.1021/acs.jmedchem.8b00667 J. Med. Chem. 2018









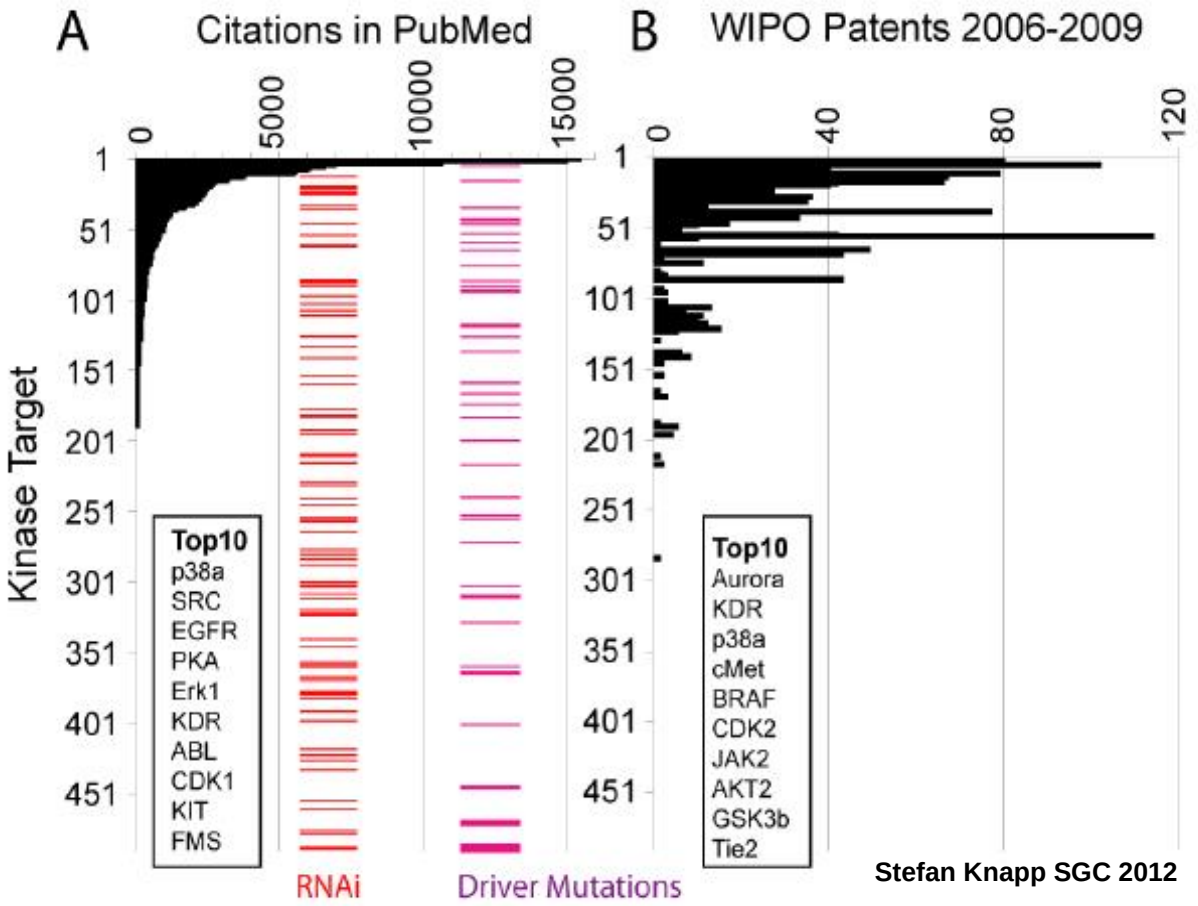


What do we know about protein kinases ?

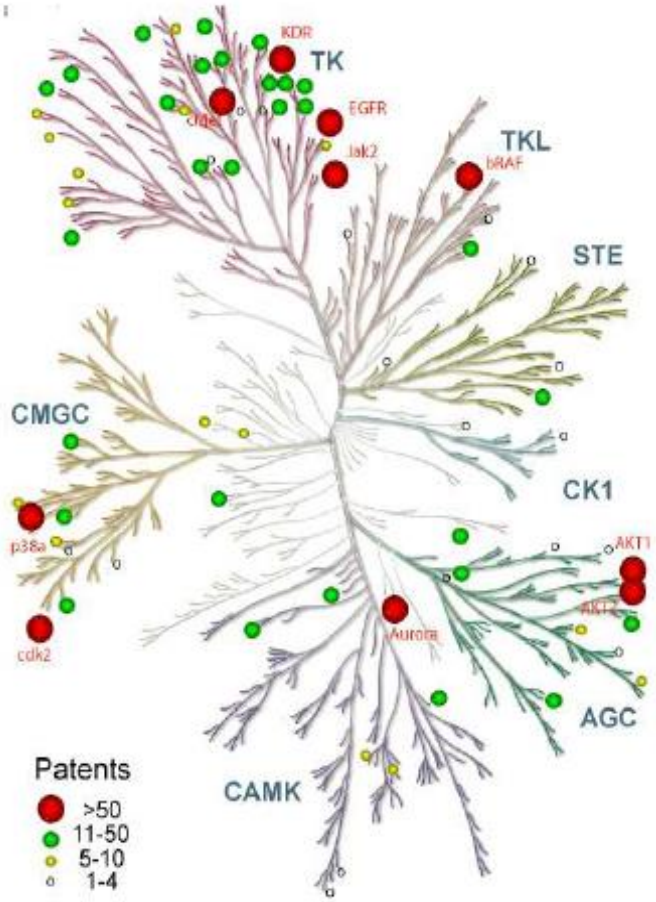
Kinases:

> 500 000 papers in PubMed
> 10 000 US patents

Publications covering ~10% Kinome
Patents follow public data

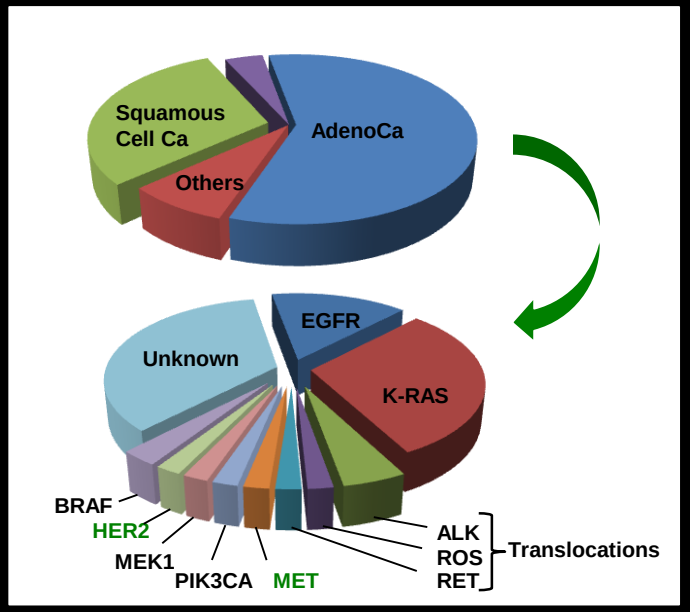


Stefan Knapp SGC 2012

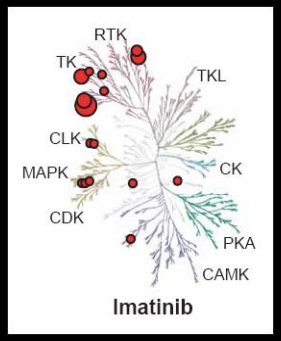


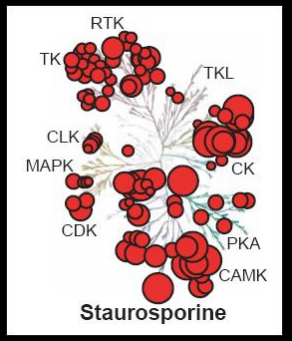
Major issues in kinase DD (Oncology)

- Targeted therapies
  - Small patient populations
  - Clinical benefit
  - Biomarkers:
    - Prediction, Prognosis, Stratification…

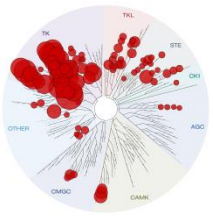


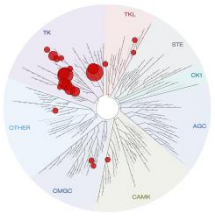
- On/off target pharmacology (selectivity)
- 538 kinase genes (30-50% of the kinome explored as target)
- New modes of inhibition (OOTB) & Novel scaffolds (IP)
- Drug resistance (mainly in Oncology)
  - Mutations in target kinase(s)
  - Pathway rectivation & bypass mechanisms
  - Pathway independent bypass (μenv, EMT etc.)

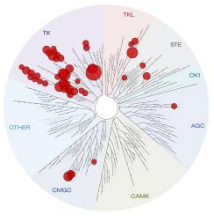


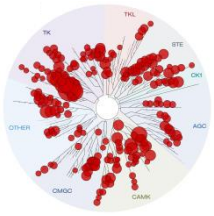


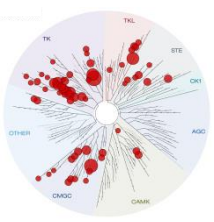
- Only a handful of kinase inhibitors in non-oncological indications

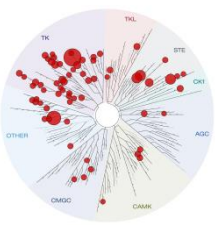

Dasatinib

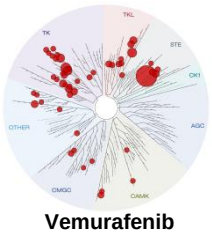

Imatinib

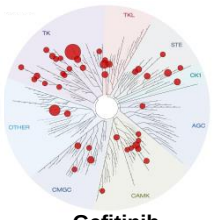

Nilotinib

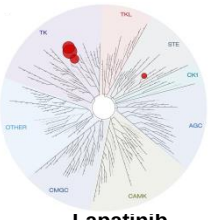

Sunitinib

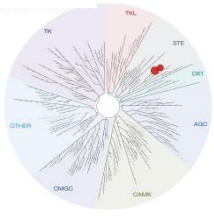

Sorafenib

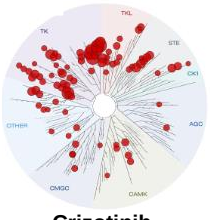

Erlotinib

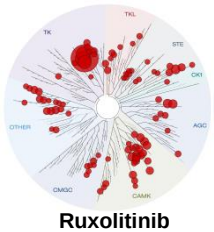

Vemurafenib

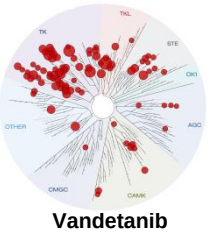

Gefitinib

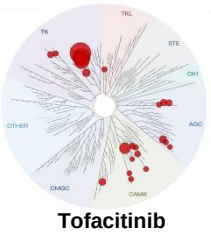

Lapatinib

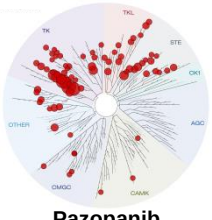

Trametinib


Crizotinib


Ruxolitinib


Vandetanib

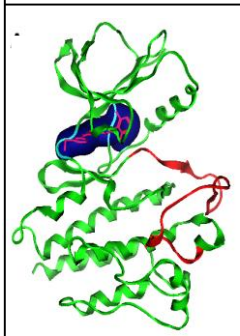

Tofacitinib

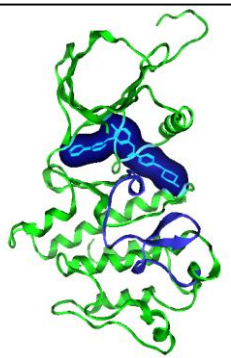

Pazopanib

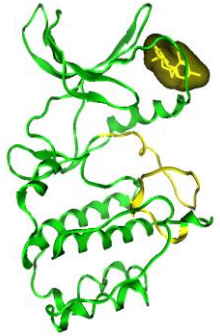
Afinitor

33 yrs of Kinase-DD

- 49 KIs approved
- Type 1-4 & covalent
- 5 non-oncology
- 30% kinome coverage
- many KIs in Ph-2/3
- various ABs


Type-1


Type-2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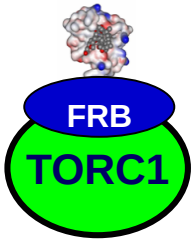

Type-4

Degrader approach for kinases

Destroy the kinase target rather inhibiting it