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DISCOVERY OF POVORCITINIB (INCB054707), AN ISOFORM SELECTIVE JANUS KINASE 1 (JAK1) INHIBITOR THAT INCORPORATED INTRAMOLECULAR HYDROGEN-BONDING TO ACHIEVE EXCEPTIONAL ORAL BIOAVAILABILITY AND IS UNDER CLINICAL INVESTIGATION FOR THE TREATMENT OF AUTOIMMUNE AND INFLAMMATORY DISEASES

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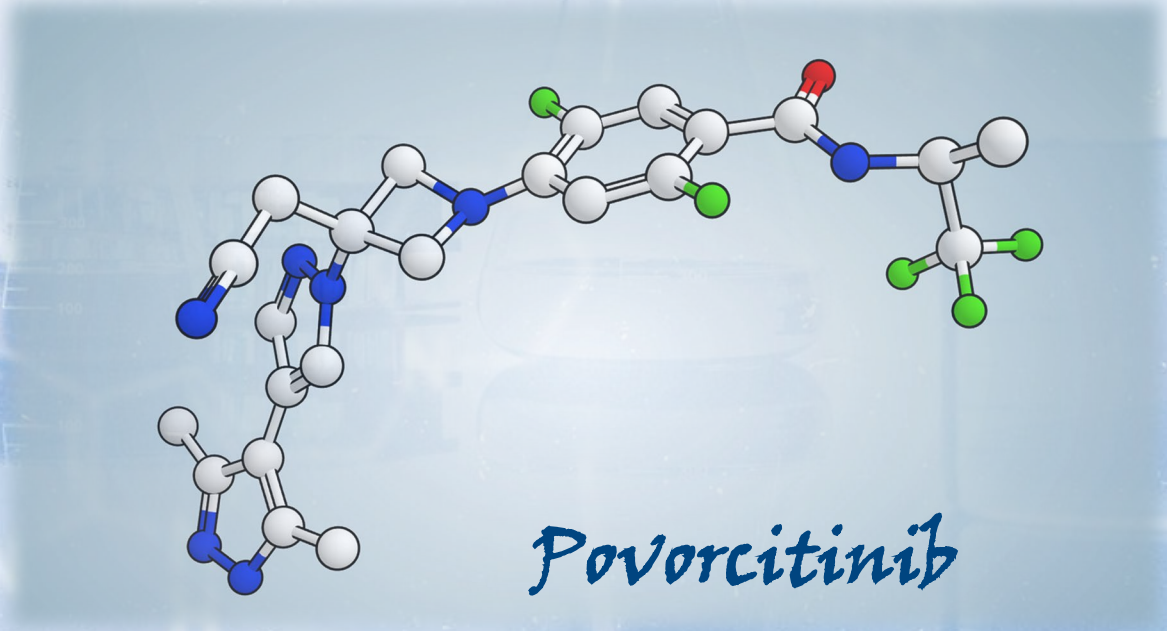
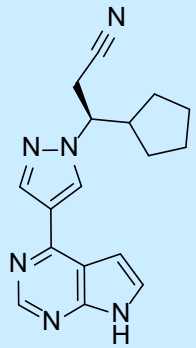
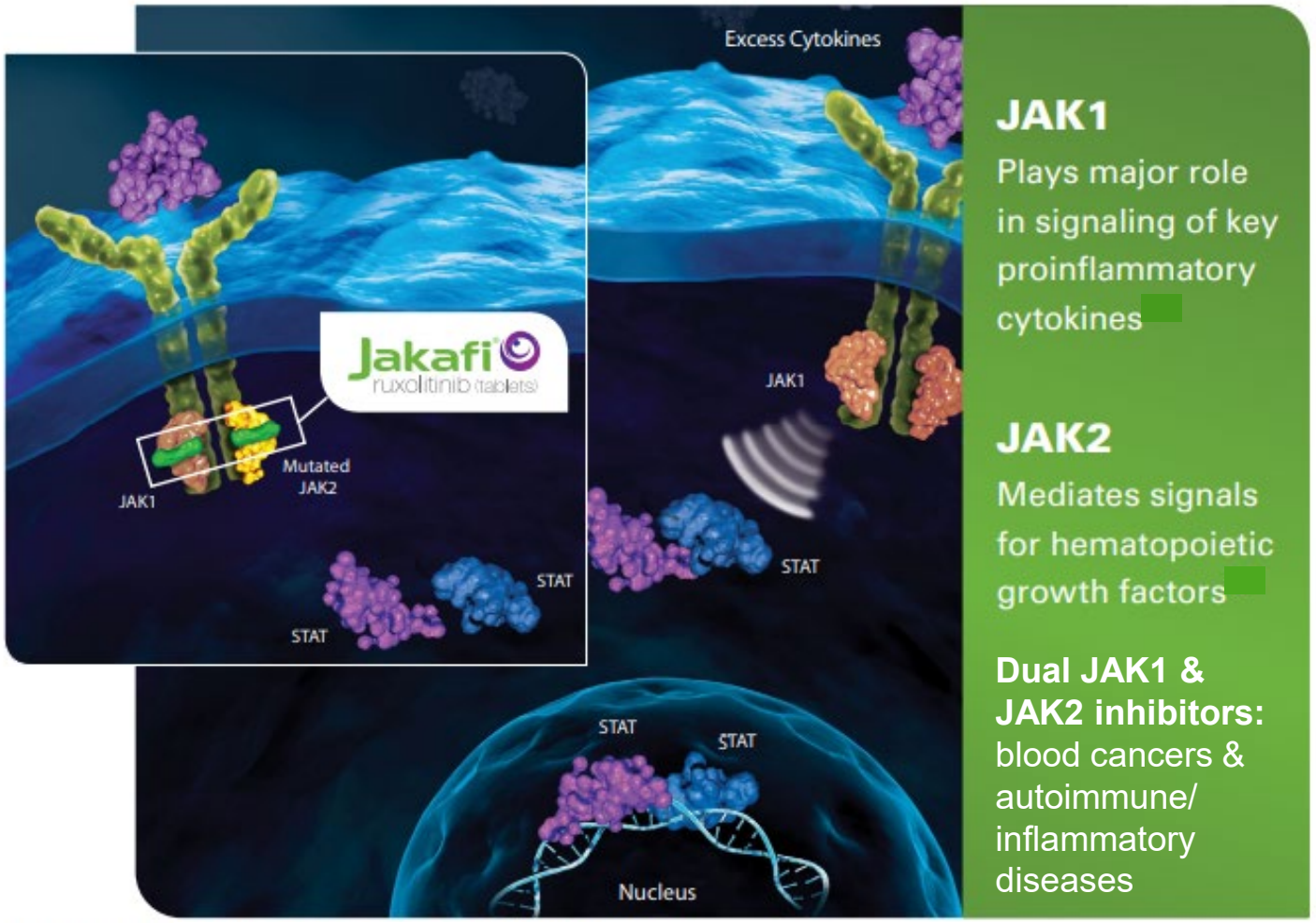


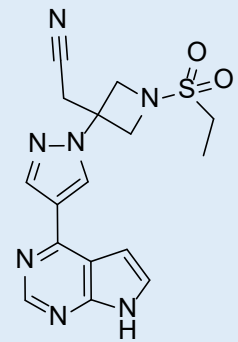
In the Early 2000's Incyte Discovered the First FDA Approved JAK Inhibitor



INCB018424
Stacey Shepard 2005
Ruxolitinib (Jakafi® 2011)



JAK- Janus Kinase; STAT- Signal Transducer and Activator of Transcription



INCB028050
Stacey Shepard 2007
Baricitinib (Olumiant® 2017)

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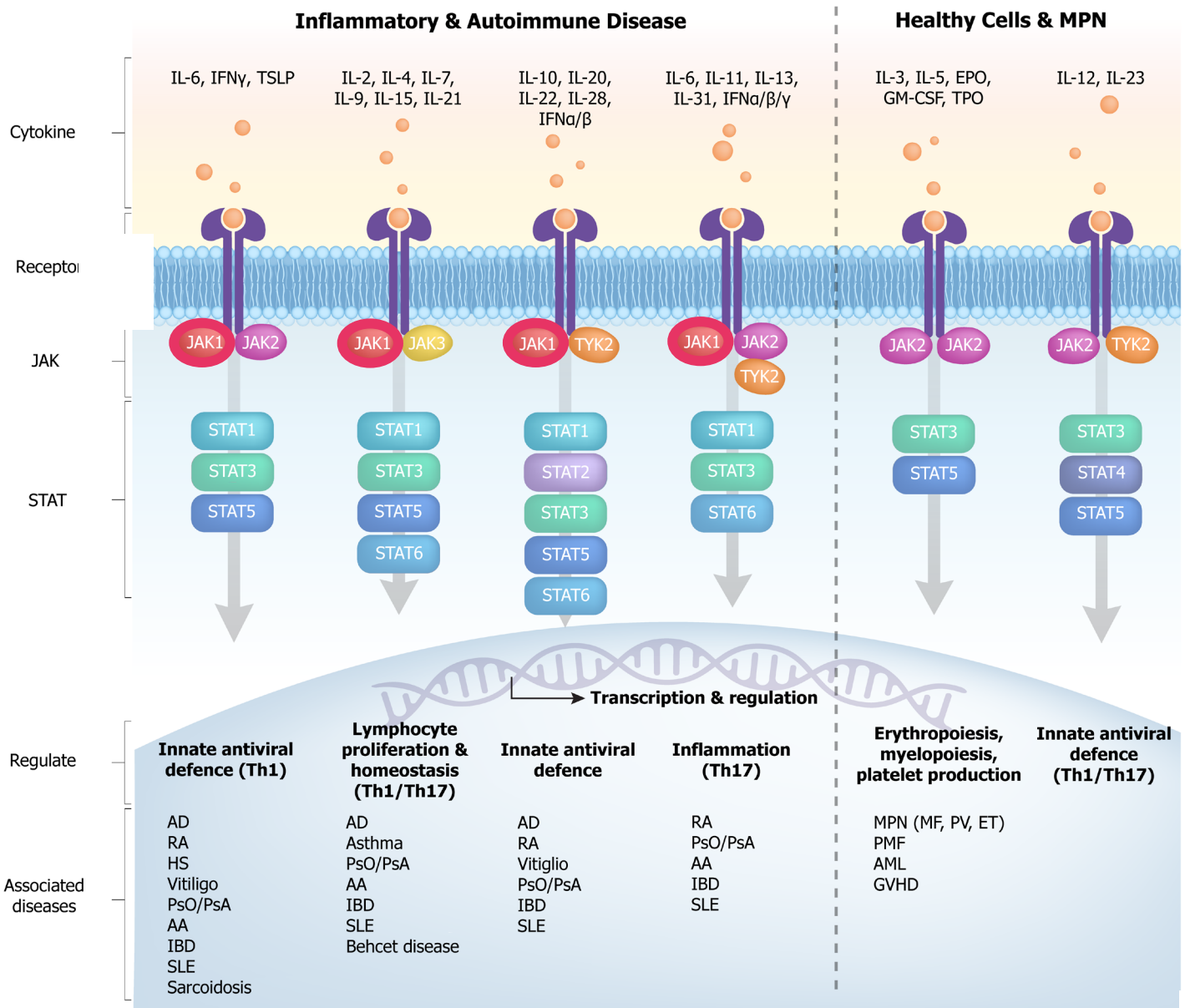
2007-2011 Pursuit of Selective JAK1 Inhibitors for Autoimmune Diseases



AD: atopic dermatitis; RA: rheumatoid arthritis; HS: hidradenitis suppurativa; PsO/PsA: psoriasis/ psoriatic arthritis; AA: alopecia areata; IBD: irritable bowel disease; SLE: systemic lupus erythematosus; MPN: myeloproliferative neoplasm; MF: myelofibrosis; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis; AML: acute myeloid leukemia; GVHD: graft-vs-host disease

Potential advantages of JAK1 selective inhibitors:

- JAK1 is implicated in a variety of autoimmune & inflammatory diseases beyond JAK2
- Normal JAK2-STAT signaling can occur to ensure proper hematopoietic processes
- Avoid side effects, particularly JAK2 associated toxicities such as anemia, thrombocytopenia, neutropenia, *etc.*

Image generated by DrawImpacts

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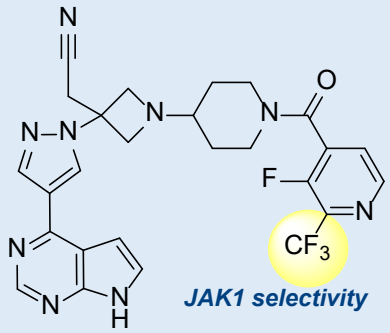
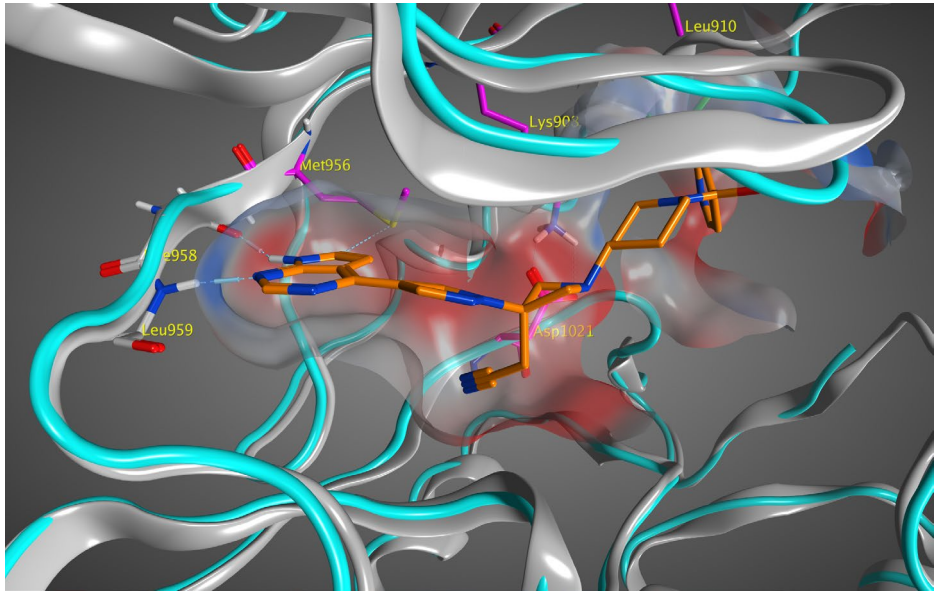
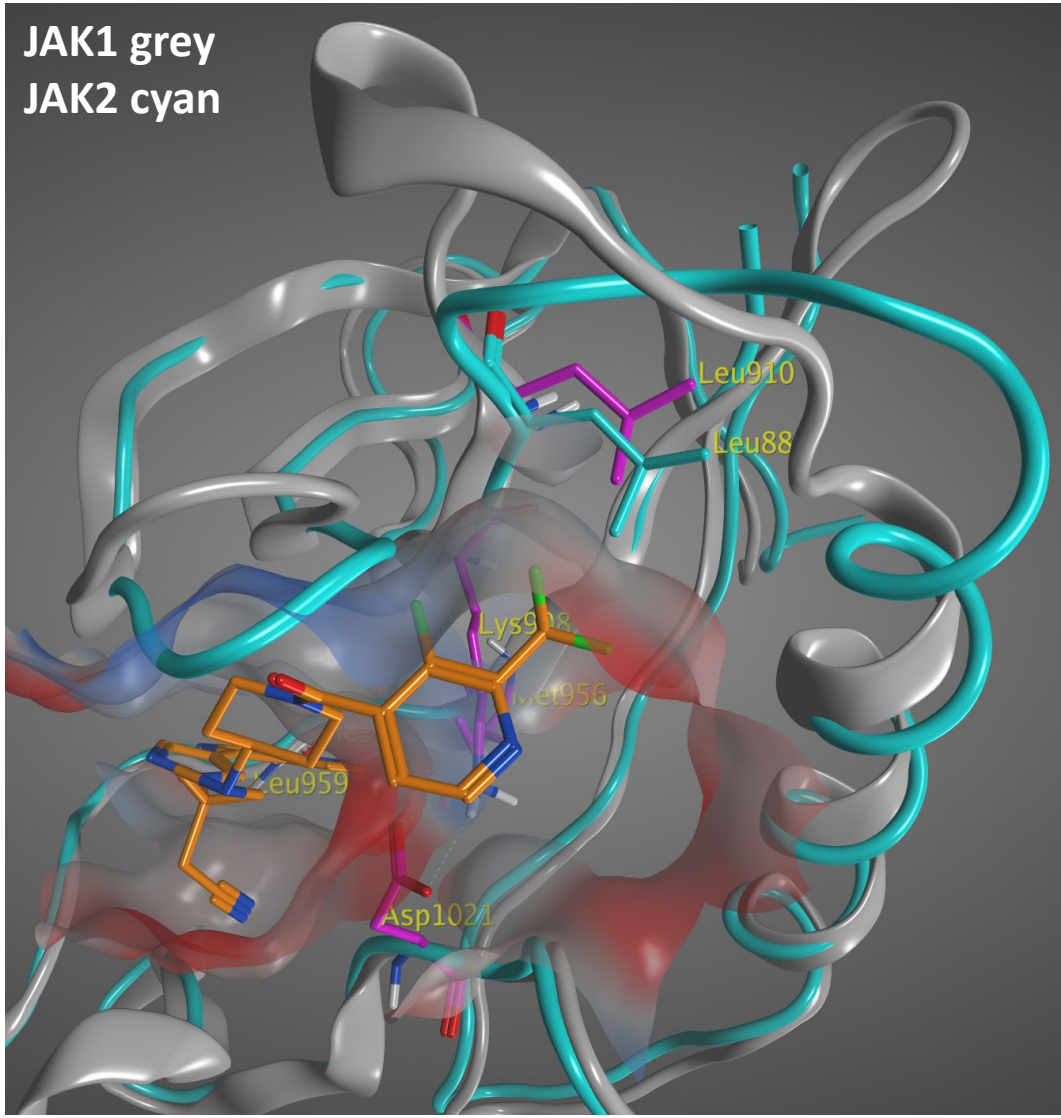
In 2009 We Discovered Our First Internal JAK1 Selective Clinical Candidate Itacitinib



JAK1 selectivity

INCB039110 (Itacitinib)
Taisheng Huang (2009)
JAK1 IC_{50} (nM) 3.6
JAK2 IC_{50} (nM) 75
JAK1/JAK2 selectivity 21x





High level of homology between JAK1 and JAK2 in the ATP-binding pocket; however there are subtle differences:

- JAK1 P-loop is retracted more than JAK2 to create a small pocket
- JAK1 connection point between β3 and αC-helix is extended by one amino acid creating a small pocket that can accommodate CF_3

Modeling performed by Ravi Jalluri

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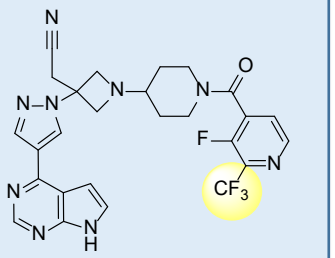
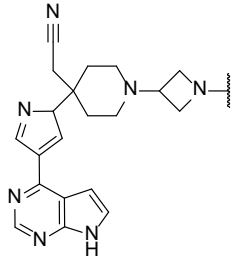
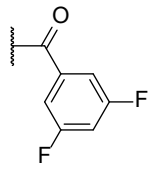
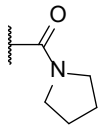
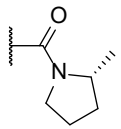
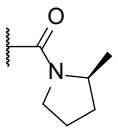
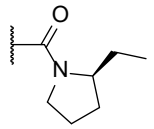
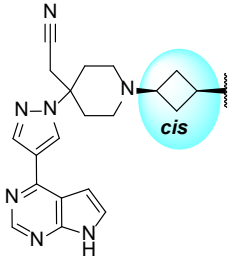
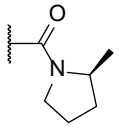
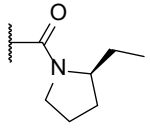
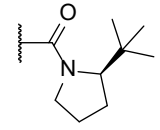
Further SAR Investigations Led to the Discovery of Low Molecular Weight Analogs



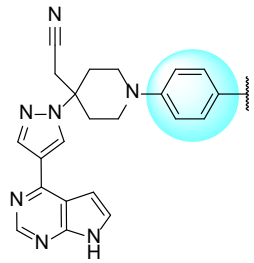
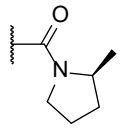
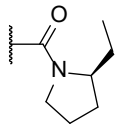
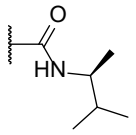
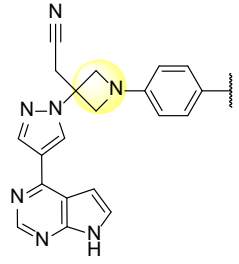
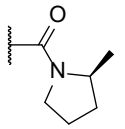
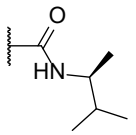
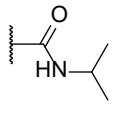
INCB039110 (Itacitinib)
JAK1 IC_{50} (nM) 3.6
JAK2 IC_{50} (nM) 75 *(21)*
Poor rat PK

Good rat PK
Poor cyno PK

INCB0	39523	40524	44335	44339	44459		43522	44458	44571
JAK1 IC_{50} (nM)	1.5	20	1000	6.3	2.3		7.5	4.9	15
JAK2 IC_{50} (nM)	13 *(9)*	170 *(9)*	1000	135 *(21)*	127 *(55)*		178 *(24)*	242 *(49)*	>1000 *(67)*
INA6 IC_{50} (nM)	180			1600	741		2000	882	2900
WB IL-6 IC_{50} (nM)	200			406	311		1051	391	3500
WB TPO IC_{50} (nM)	413 *(2)*			2800 *(7)*	5275 *(17)*		6350 *(6)*	4625 *(12)*	10K *(3)*
Caco-2 (x10^{-6} cm/s)	1.2	0.1		0.3	0.7		1.3	1.7	
Proj. h-CL (L/h/kg) (%F)	0.9 *(26)*			>1.1 *(7)*	>1.1 *(<10)*		>1.1 *(<10)*	>1.1 *(<10)*	

INCB0	45704	45816	46088		46307	46439	46308
JAK1 IC_{50} (nM)	3.3	4.4	2.8		1.3	3.9	1.6
JAK2 IC_{50} (nM)	48 *(15)*	51 *(12)*	30 *(11)*		16 *(12)*	64 *(16)*	31 *(19)*
INA6 IC_{50} (nM)	612	485	266		226	411	306
WB IL-6 IC_{50} (nM)	736	625	758		321	1300	331
WB TPO IC_{50} (nM)	1550 *(2)*	1600 *(3)*	1600 *(2)*		1600 *(5)*	2200 *(2)*	4050 *(12)*
Caco-2 (x10^{-6} cm/s)	2.1	6.4	1.5		2.3		0.9
Proj. h-CL (L/h/kg) (%F)	>1.1 *(<10)*	>1.1 *(<10)*	>1.1 *(<10)*		>1.1 *(11)*	>1.1 *(<10)*	0.7 *(42)*

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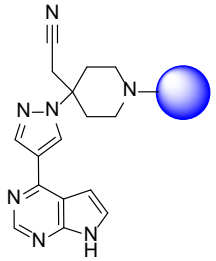
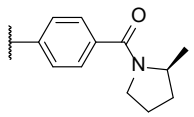
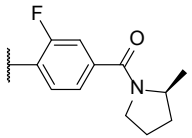
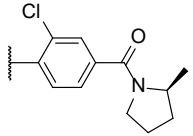
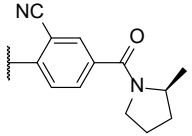
Potency Increased by Small Substituent Meta to the Amide Moiety

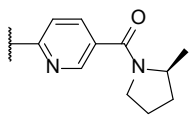


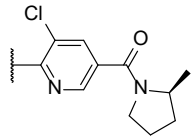


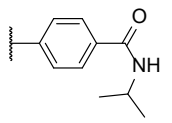


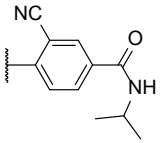




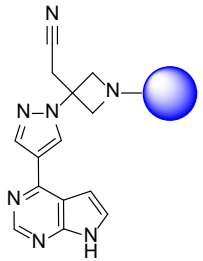


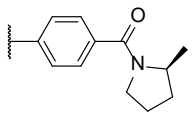


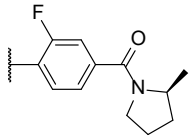


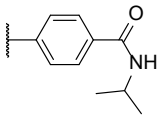


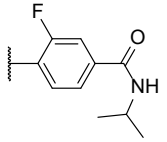
INCB0	45704	46087	46089	46085	45838	45839	45599	46369
JAK1 IC_{50} (nM)	3.3	3.9	0.2	0.5	7.6	0.2	3.6	0.38
JAK2 IC_{50} (nM)	48 *(15)*	22 *(6)*	0.7 *(4)*	3.1 *(6)*	78 *(10)*	1.0 *(5)*	24 *(7)*	2.5 *(7)*
INA6 IC_{50} (nM)	612	734	147	214	1300	142	507	---
WB IL-6 IC_{50} (nM)	736	515	215	183	661	250	1004	---
WB TPO IC_{50} (nM)	1550 *(2)*	642	108	94	2550 *(4)*	124	2150 *(2)*	---

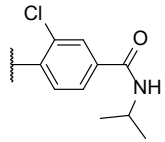


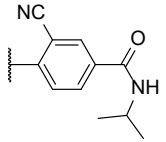


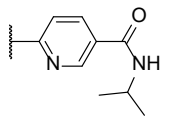


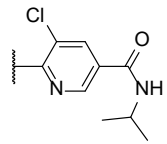






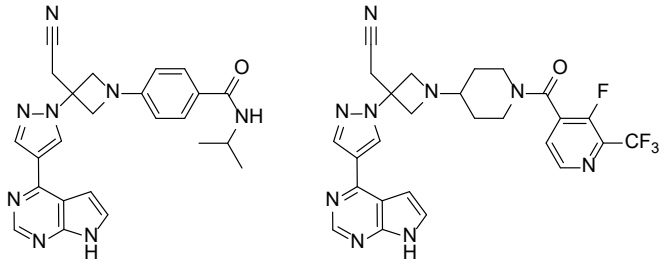






INCB0	46307	47818	46308	46534	47088	46184	46180	48131
JAK1 IC_{50} (nM)	1.3	0.52	1.6	0.29	0.1	0.8	7.4	2.5
JAK2 IC_{50} (nM)	16 *(12)*	7.4 *(14)*	31 *(19)*	4.1 *(14)*	1.1 *(11)*	12 *(15)*	102 *(14)*	23 *(9)*
INA6 IC_{50} (nM)	226	107	306	61	48	240	1081	---
WB IL-6 IC_{50} (nM)	321	103	331	133	101	478	742	---
WB TPO IC_{50} (nM)	1600 *(5)*	490 *(5)*	4050 *(12)*	299 *(2)*	203 *(2)*	1100 *(2)*	7500 *(10)*	---

PK Profile of New Low Molecular Weight Scaffold 46308 *vs.*39110

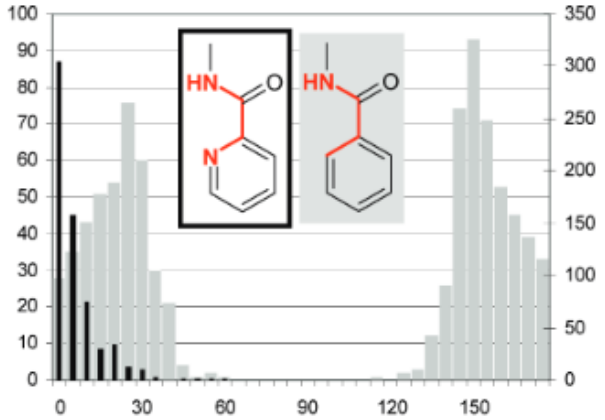


Species	Parameters	INCB 46308	INCB 39110
Rat IV	CL (% HBF)	**29**	100
	Vdss (L/kg)	0.87	2.9
	t½ (h)	**5.3**	1.1
Rat PO	AUC (nM*h)	**3793**	532
	%F	31	19
Cyno IV	CL (% HBF)	25	26
	Vdss (L/kg)	0.57	0.76
	t½ (h)	1.9 (3)	1.2
Cyno PO	AUC (nM*h)	1549	2610
	%F	**9**	19
Dog IV	CL (% HBF)	49	37
	Vdss (L/kg)	0.54	0.82
	t½ (h)	2.8	1.2
Dog PO	AUC (nM*h)	**610**	5630
	%F	**6**	43

Phosphate salt of 46308 was used in dog study; TFA salt was used in cyno and rat studies.

- Improved rat PK profile
- Comparable IV PK profile in cynomolgus monkey and dog
- Poor oral bioavailability and low exposure following PO dosing in both monkeys and dogs may be due to low absorption.

Intramolecular Hydrogen Bonding (IMHB) Imparts Chameleonicity



Kuhn B. *et al. J. Med. Chem.* **2010**, *53*, 2601.

IMHB-Mediated Chameleonicity in Drug Design: A Focus on Structurally Related PROTACs

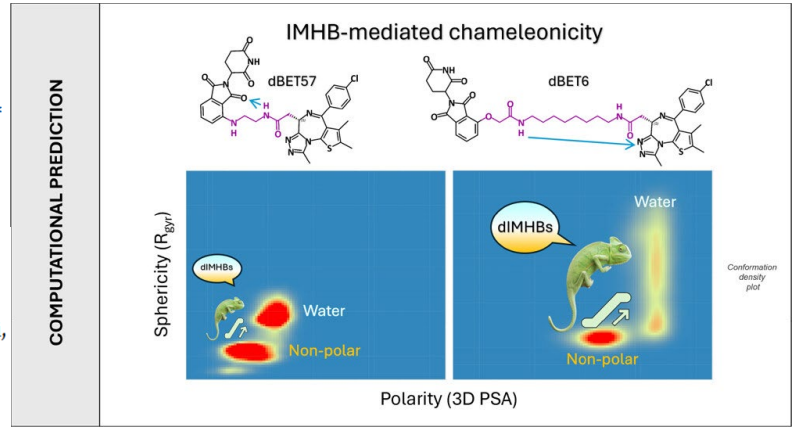
Diego Garcia Jimenez, Matteo Rossi Sebastiano, Maura Vallaro, Giuseppe Ermondi, and Giulia Caron*

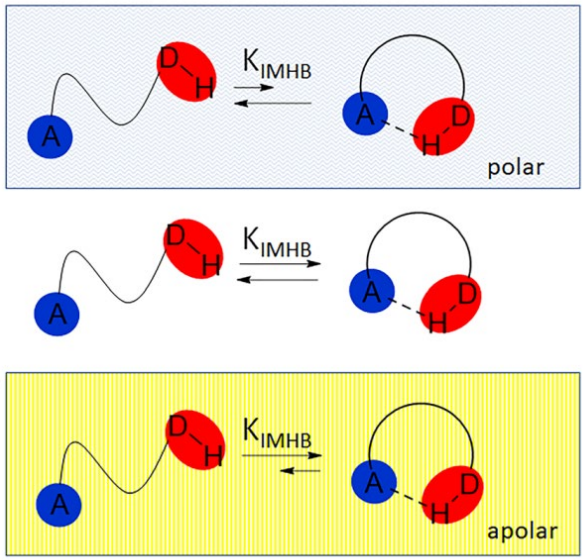
Cite This: *J. Med. Chem.* 2024, 67, 11421−11434 | Read Online

Chamelogk: A Chromatographic Chameleonicity Quantifier to Design Orally Bioavailable Beyond-Rule-of-5 Drugs

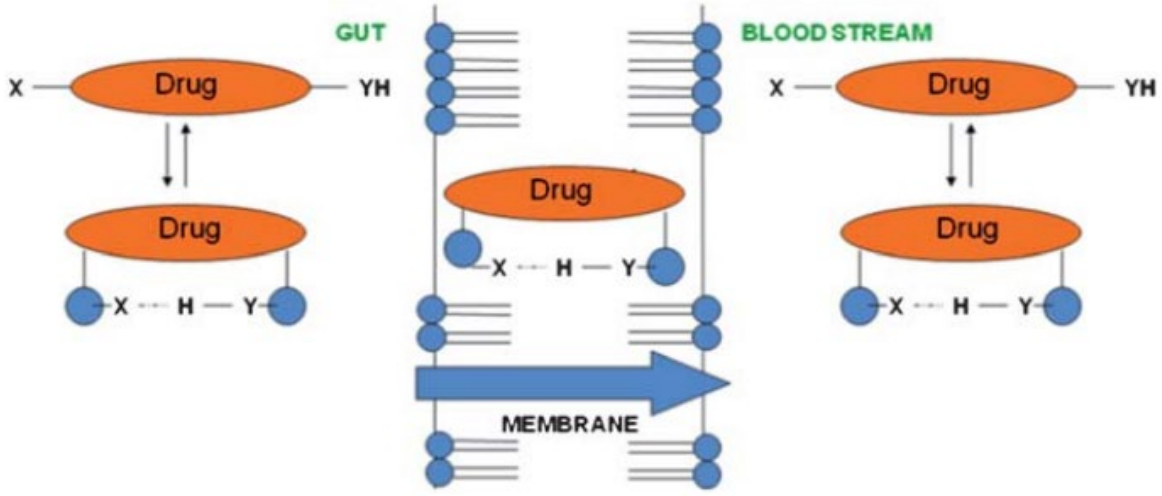
Diego Garcia Jimenez, Maura Vallaro, Matteo Rossi Sebastiano, Giulia Apprato, Giulia D'Agostini, Paolo Rossetti, Giuseppe Ermondi, and Giulia Caron*

Cite This: *J. Med. Chem.* 2023, 66, 10681−10693 | Read Online





Caron, G.; *et al. Med. Res. Rev.* **2019**, *39*, 1707.



Alex, A.; *et al. Med. Chem. Comm.* **2011**, *2*, 669.

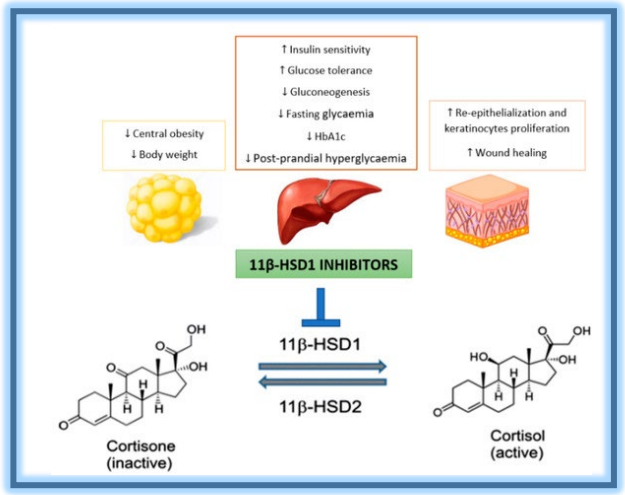
IMHB can convey:

- Conformational constraints
- Increase potency
  - (enzyme, cell, WB)
- Diminishment of HBD/ HBA count
- Polarity & lipophilicity simultaneously
- Improvement in ADME properties
  - Increase permeability/ absorption
  - Decrease efflux ratio

Incyte Research Institute

Internal Success Exploiting IMHB to Improve Permeability & PK Profile

2004-2005 11-β-HSD1



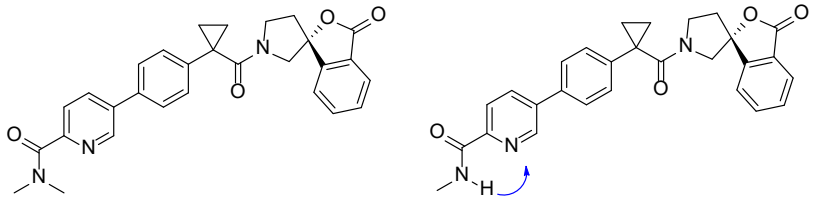
2006-2007 c-Met

For people taking **TABRECTA®** as their first treatment

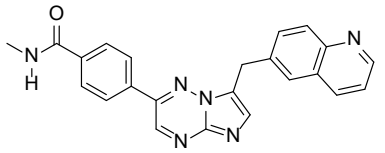
Overall response rate

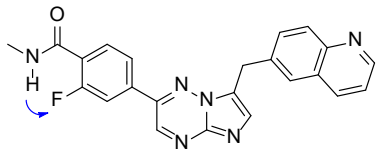
Nearly **7 in 10 people** had their tumors **shrink or disappear** **68%**

2020 FDA approved INCB028060 (capmatinib) as the first and only therapy for adult patients with metastatic NSCLC whose tumors have a MET exon 14 skipping mutation.



		INCB013740*	INCB013739*
Potency	11β-HSD1 IC_{50} (nM)	7	5
	11β-HSD1 PBMC IC_{50} (nM)	2.2	1
ADME	Caco-2 ($x10^{-6}$ cm/s)	15	**38**
	Proj. h-CL (L/h/kg) (%F)	<0.5 (*60*)	<0.5 (*60*)
Rat PK	Dose (mg/kg)	9.0	9.0
PO	C_{max} (nM)	552	**2,173**
	AUC (nM*h)	1,321	**10,235**
Distribution	Fat: Plasma @ 1h	0.8	**2.8**





Tabrecta® (capmatinib)

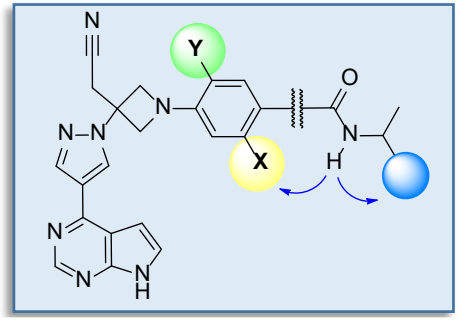
		INCB034049*	INCB028060*
Potency	C-Met IC_{50} (nM)	0.15	0.14
	C-Met SNU5 IC_{50} (nM)	3.1	1.3
ADME	Caco-2 ($x10^{-6}$ cm/s)	4.7	**22**
Rat PK	Dose (mg/kg)	5	5
PO	C_{max} (nM)	281	**8,400**
	AUC (nM*h)	428	**35,200**

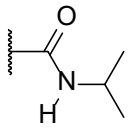
compounds prepared by Chunhong He

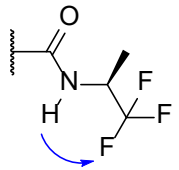
Zhang, C. *et al Bioorg. Med. Chem. Lett.* **2022**, *69*,128782. Burns, D. M. *et al Bioorg. Med. Chem. Lett.* **2022**, *69*,128884. Discovery of INCB028060 manuscript in preparation.

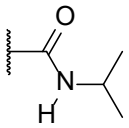
Incyte Research Institute

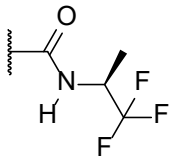
Exploration of Incorporation of IMHB to Secondary Amide INCB046308

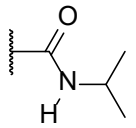


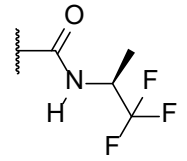


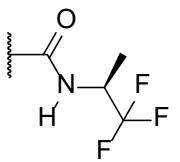


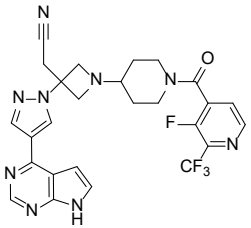










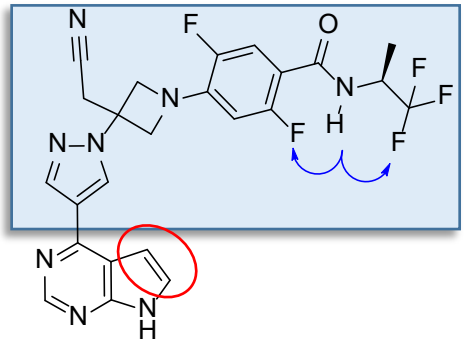


	INCB0	46308	47727	46599	48067	Ding-Quan Qian 46786	Ding-Quan Qian 47986	Ding-Quan Qian 47809	Taisheng Huang 39110
	X:	H	H	F	F	F	F	H	itacitinib
	Y:	H	H	H	H	F	F	F	
Enzyme, Cellular, & WB Potency (*Selectivity*)	JAK1 IC_{50} (nM)	1.5	0. 8	1.7	0.56	0.46	0.25	0.25	3.3
	JAK2 IC_{50} (nM)	31 *(21)*	24 *(30)*	19 *(11)*	11 *(19)*	5.5 *(12)*	6.1 *(25)*	7.8 *(25)*	67 *(20)*
	INA6 IC_{50} (nM)	308	150	192	126	60	70	83	366
	WB IL-6 IC_{50} (nM)	310	374	258	175	135	207	243	305
	WB TPO IC_{50} (nM)	3400 *(11)*	3182 *(9)*	860 *(3)*	782 *(5)*	417 *(3)*	1167 *(6)*	1161 *(5)*	2408 (8)
ADME	Caco-2 ($x10^{-6}$ cm/s)	0.9	1.1	3.1	4.7	4.6	8.5	1.4	2.7
	Proj. h-CL (L/h/kg) (%F)	0.7 *(42)*	0.6 *(53)*	0.8 *(34)*	0.6 *(49)*	0.8 *(35)*	0.7 *(42)*	<0.5 *(>60)*	0.8 *(38)*
Rat PO	Dose (mg/kg)	5	4	5	5	4	5	5	5
	AUC (nM*h)	3,793	2,501	14,954	28,766	28,559	11,884	5,606	532
	t½ (h)	5.7	4.8	4.2	4.3	2.5	4.6	2.2	1.3
	% F	31	31	61	60	70	54	21	19
Cyno PO	Dose (mg/kg)	4		4	5 (dose adj.)	4	5	5	5
	AUC (nM*h)	1,549		2,169	80,964	5,275	74,984	14,445	2,610
	t½ (h)			3.9	7.0	4.0	16	6.0	1.2
	% F	9		11	38	NA	54	28	19

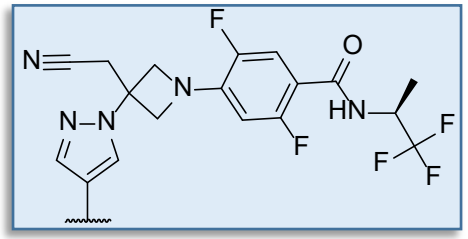
Dog IV	Dose (mg/kg)	2.5
	Clr %HBF	82
Dog PO	Dose (mg/kg)	5
	AUC (nM*h)	65
	% F	1

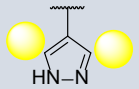
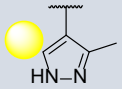
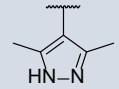
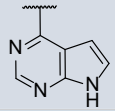
Incyte Research Institute

Simplified Hinge Binding Motif Improves Selectivity & PK Profile

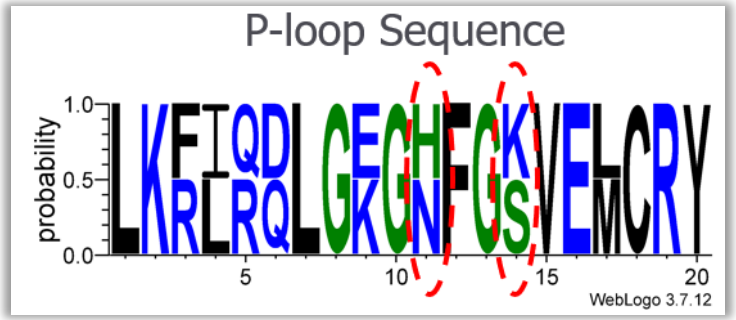


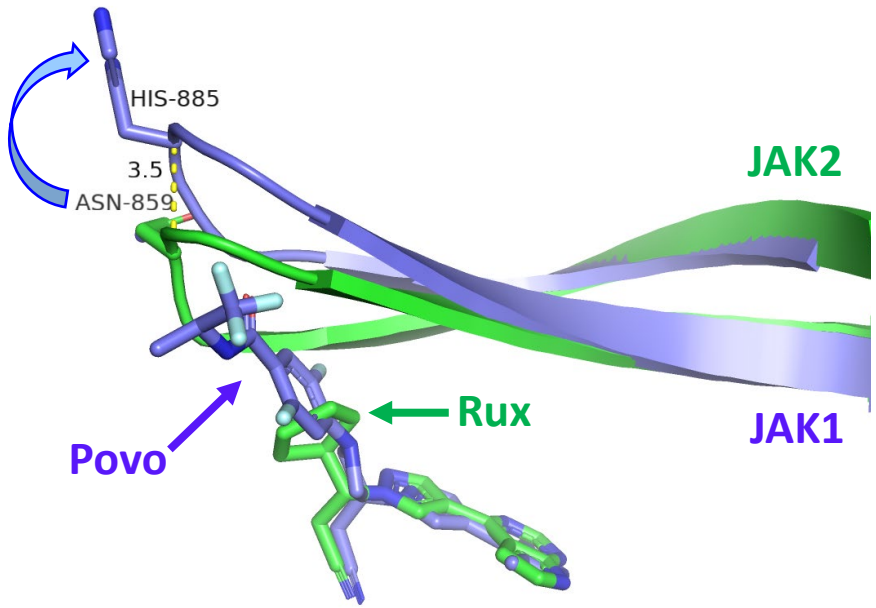
INCB047986

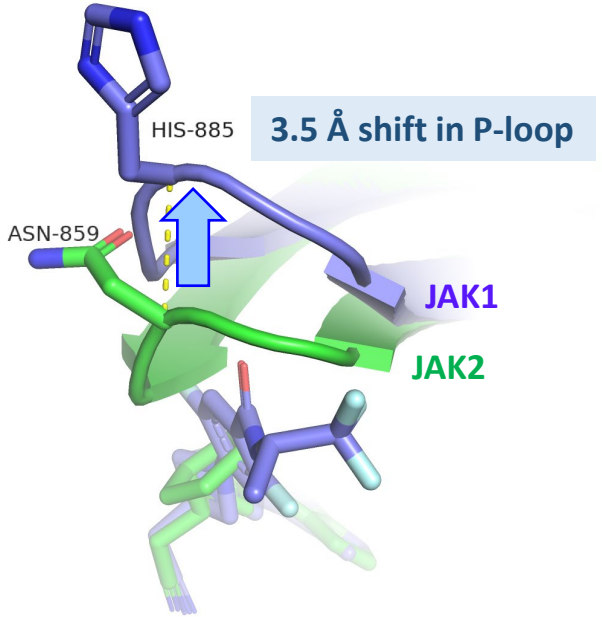


		INCB0	54361	54924	54707	47986
		Chemist	Ding-Quan Qian	Ding-Quan Qian	Song Mei	Ding-Quan Qian
		Hinge Binder:				
Enzyme Potency & (*Selectivity*)		JAK1 IC_{50} (nM)	314	19	11	0.25
		JAK2 IC_{50} (nM)	7319 (*23x*)	910 (*48x*)	505 (*46x*)	6.1 (*25x*)
Potency & (*Selectivity*)		INA6 IC_{50} (nM)	97	70		
		WB IL-6 IC_{50} (nM)	405	207		
		WB TPO IC_{50} (nM)	6389 (*16*)	1167 (*6*)		
ADME		Caco-2 ($x10^{-6}$ cm/s)	4.5	8.5		
		Proj. h-CL (L/h/kg) (%F)	0.7 (*48*)	0.7 (*42*)		
RAT		Dose (mg/kg)	5	5		
PO		AUC (nM*h)	45,210	11,884		
		% F	>100	54		
Cyno		Dose (mg/kg)	5	2.5		
PO		AUC (nM*h)	137,199	74,984		
		% F	100	54		
Dog IV		Dose (mg/kg)	2.5	2.5		
		Clr %HBF	4	82		
Dog PO		Dose (mg/kg)	5	5		
		AUC (nM*h)	165,386	65		
		% F	100	1		

Overlay of X-ray Crystal Structure of Povorcitinib with JAK1 & Ruxolitinib with JAK2

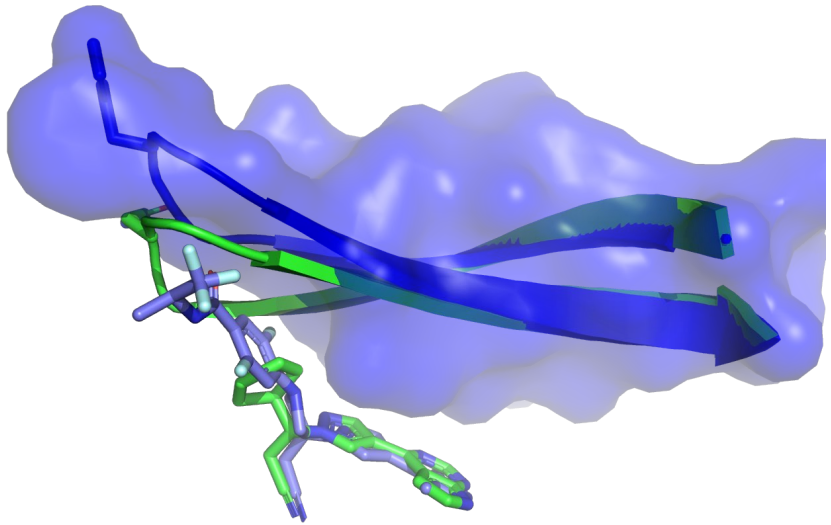


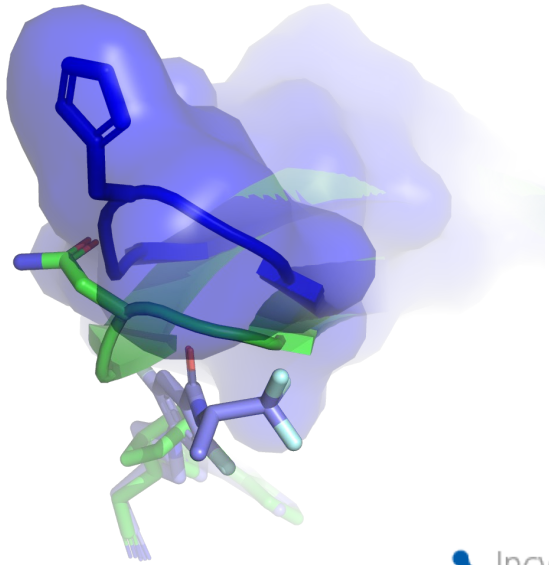




Subtle differences in the P-loop of JAK1 & -2

- JAK1 HIS-885 shifts the P-loop up ~3.5 Å compared to JAK2 ASN-859
- Ruxolitinib is truncated & does not extend into the P-loop of JAK1 or JAK2
- CF_3 of povorcitinib clashes with the P-loop of JAK2



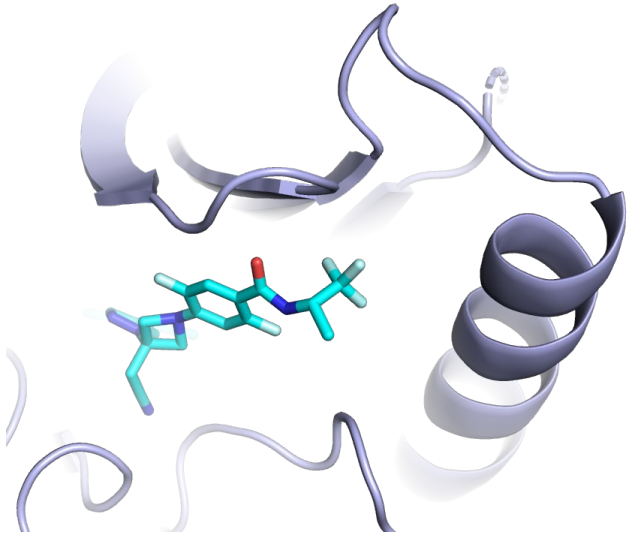


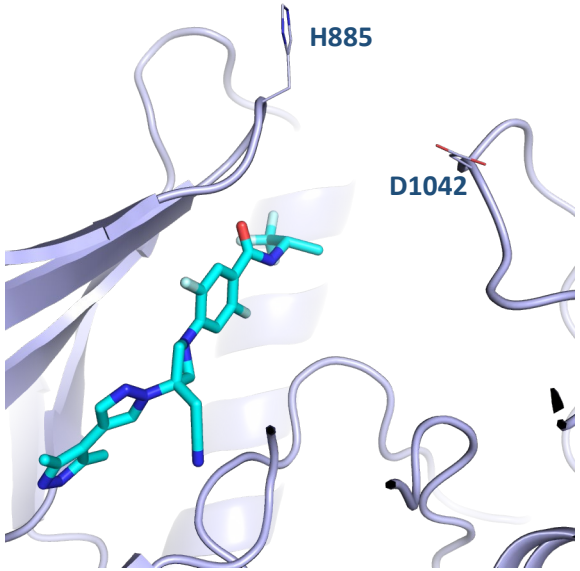
Crystallographic information & modeling performed by Marc C. Deller, Leslie B. Epling, Jessica Procak

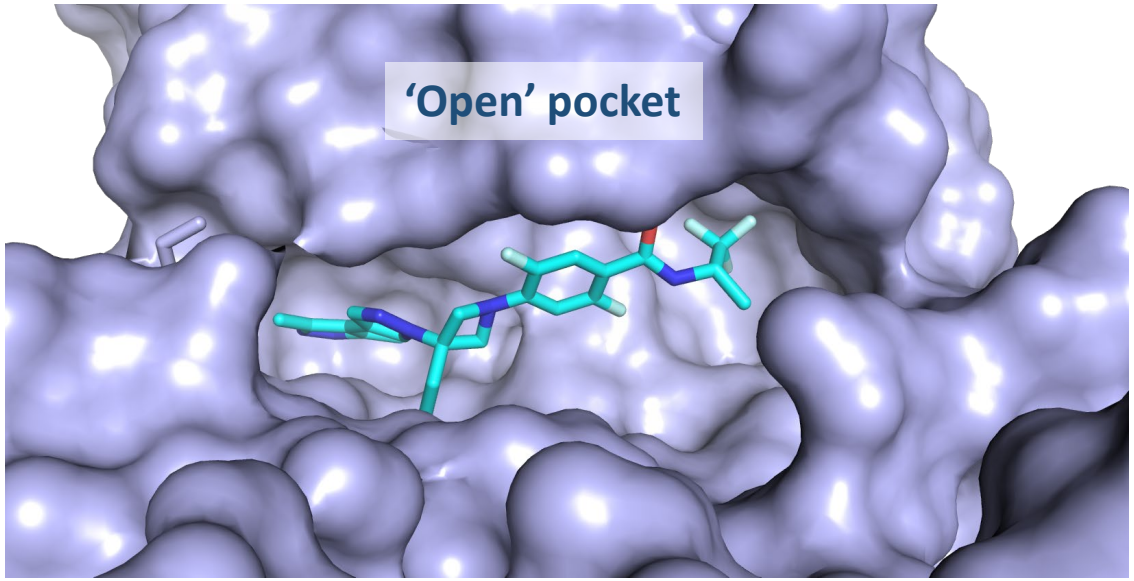
Incyte Research Institute

Overlay of X-ray Crystal Structure of Povorcitinib with JAK1 & JAK2

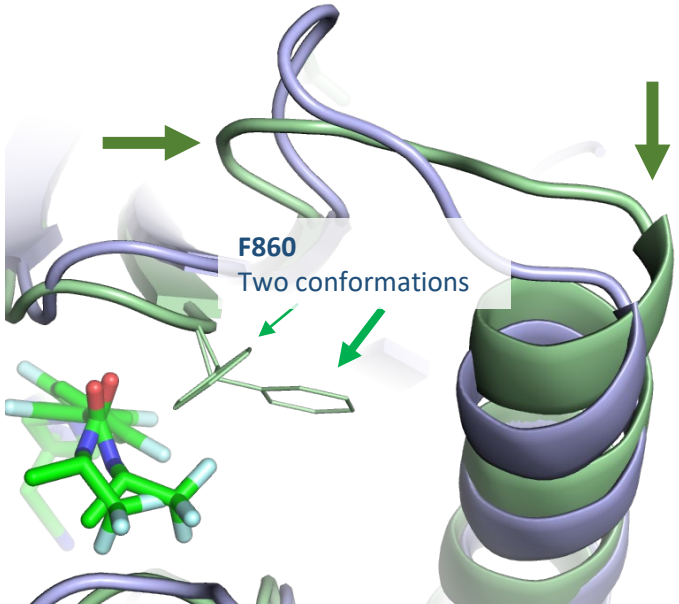
Povorcitinib with JAK1 (Purple)

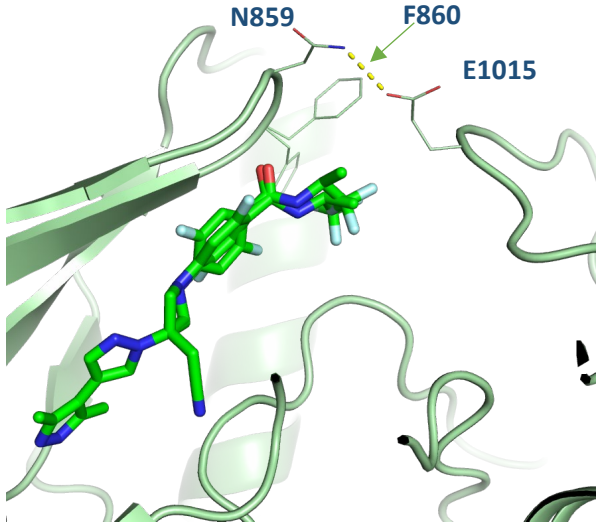


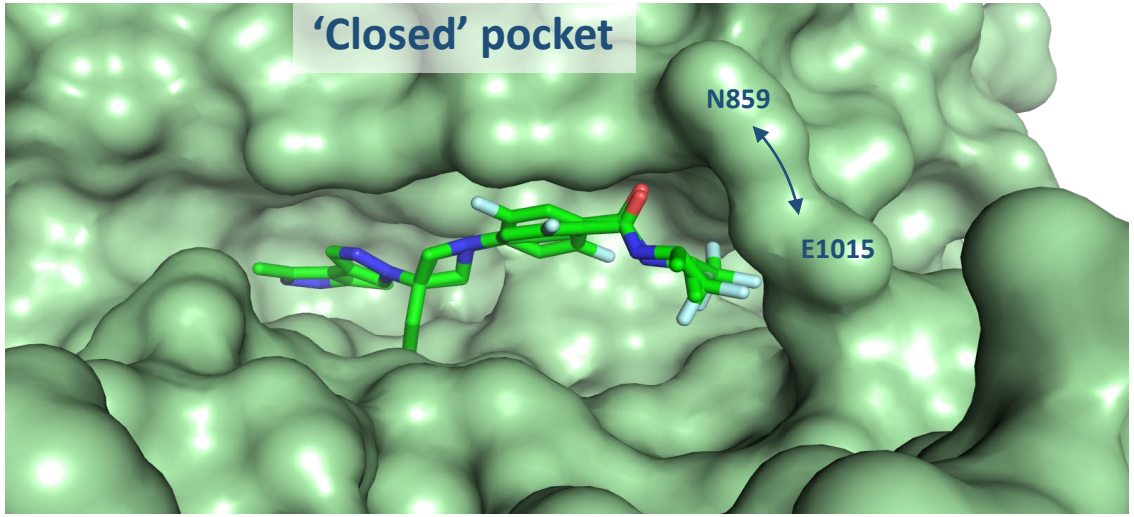




Povorcitinib with JAK2 (Green) & JAK1 (Purple)

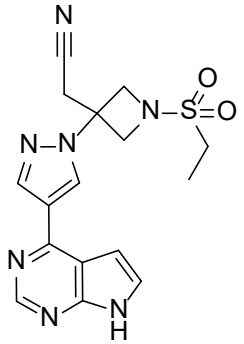






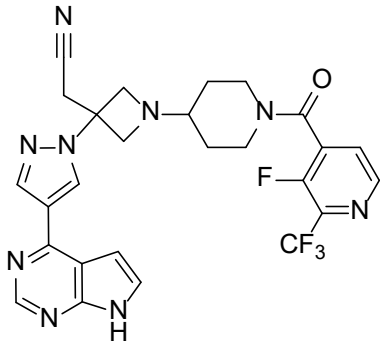
Crystallographic information & modeling performed by Gustavo Fenalti, Marc C. Deller, Leslie B. Epling, Jessica Procak

The Evolution of Baricitinib to Povorcitinib (Timeline & Effort)



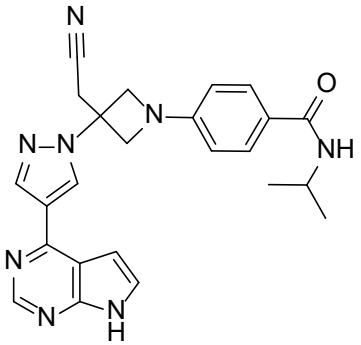
INCB028050 (Baricitinib)
Stacey Shepard
JAK1 IC_{50} (nM) 5.9
JAK2 IC_{50} (nM) 5.7
JAK1/JAK2 selectivity none

2007
Compound 4,454



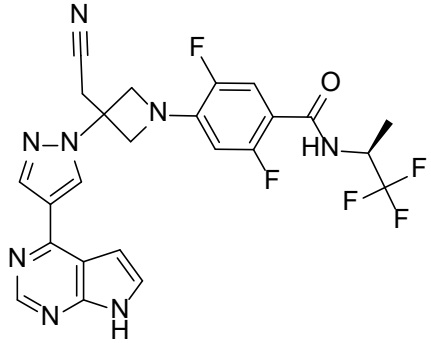
INCB039110 (Itacitinib)
Taisheng Huang
JAK1 IC_{50} (nM) 3.6
JAK2 IC_{50} (nM) 75
JAK1/JAK2 selectivity 21x

2009
Compound 9,789



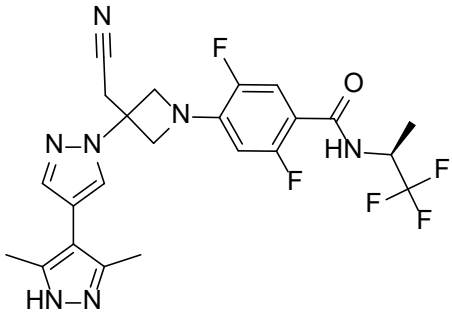
INCB046308
David Burns
JAK1 IC_{50} (nM) 1.5
JAK2 IC_{50} (nM) 31
JAK1/JAK2 selectivity 21x

2011
Compound 13,757



INCB047986
Ding-Quan Qian (Jincong Zhuo)
JAK1 IC_{50} (nM) 0.25
JAK2 IC_{50} (nM) 6.1
JAK1/JAK2 selectivity 25x

3 months later 2011
Compound 14,644



INCB054707 (Povorcitinib)
Song Mei (Yun-Long Li)
JAK1 IC_{50} (nM) 9.1
JAK2 IC_{50} (nM) 446
JAK1/JAK2 selectivity 49x

2013
Compound 15,950

~2 years
5,335 cmpds

<2 years
3,968 cmpds

3 months
887 cmpds

~2 years
1,306 cmpds

2018 FDA Approval

JAK1 Selective

Improved PK,
Potency & Selectivity*

*>50-fold selectivity observed for analogs

Improved PK
& Potency

Improved PK
& Selectivity

olumiant
(baricitinib) tablets

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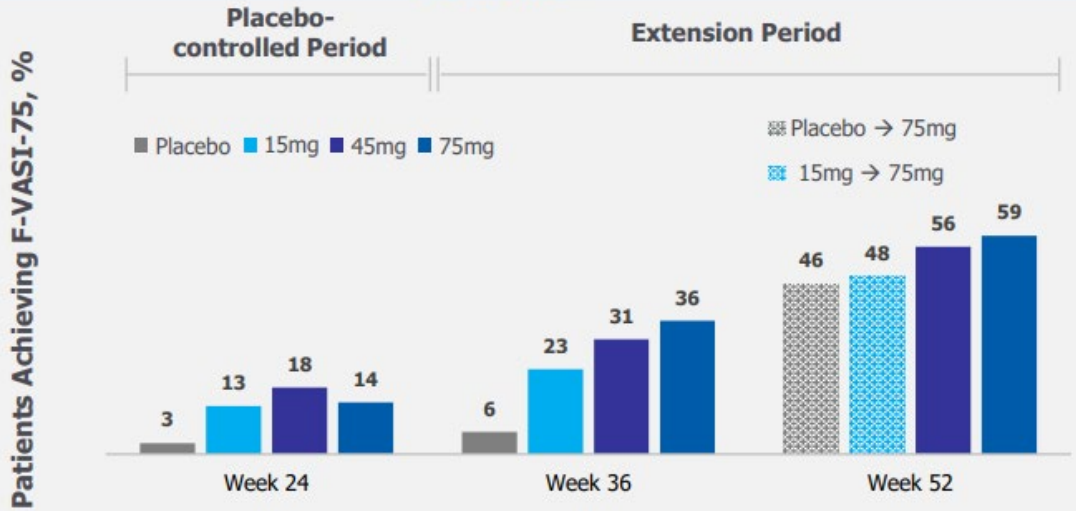
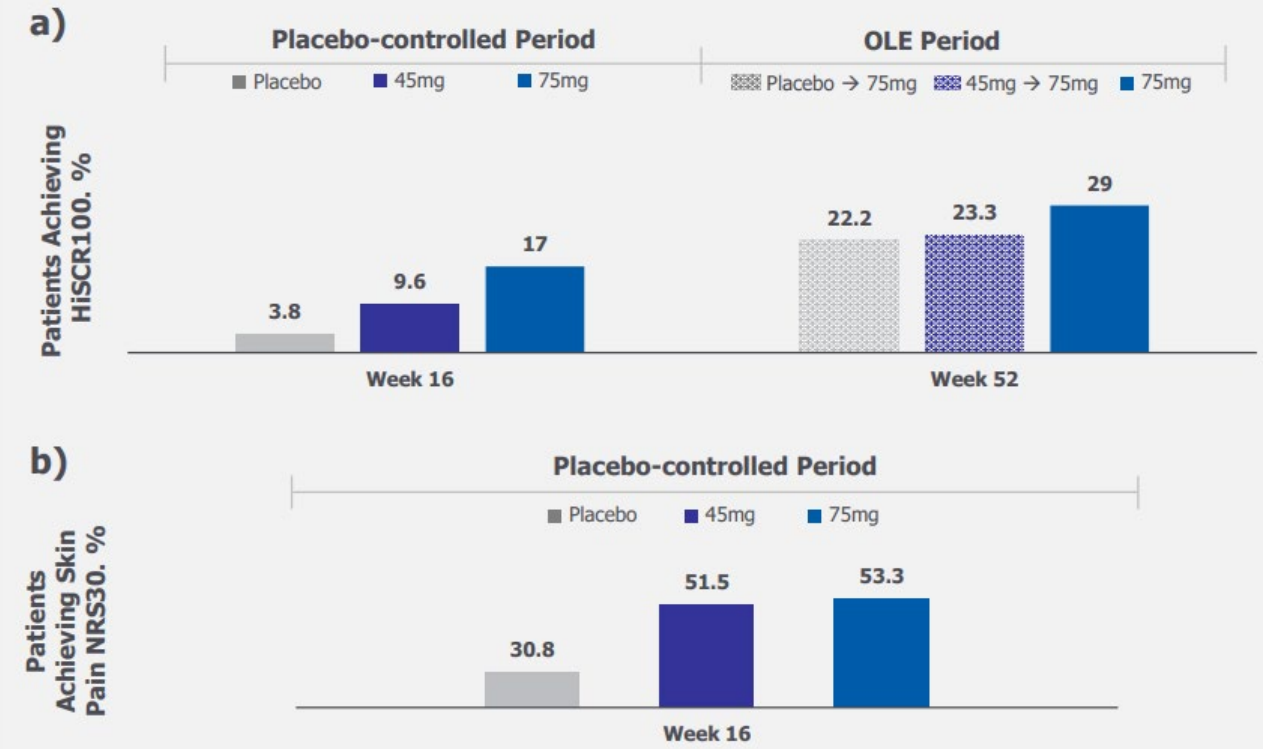
Why All the Time & Effort was Worth it!

Phase 2 Results in Extensive Nonsegmental Vitiligo



F-VASI75 = The proportion of participants achieving at least a 75% improvement in the facial vitiligo area scoring index
F-VASI = facial vitiligo area scoring index
Patient received povorcitinib 15 mg qd through Week 24 then switched to povorcitinib 75 mg qd through Week 52

Patients Achieving a) HiSCR100 and b) Skin Pain NRS30



OLE= open label extension

- Extensive Nonsegmental Vitiligo (>1.5M in US): Ph3 enrolling
- Moderate/ Severe Hidradenitis Suppurativa (HS) (>300K in US): Ph3 enrolled
- Prurigo Nodularis (PN) (>200K in US): Ph3 enrolling
- Povorcitinib has the potential to be first oral JAK drug in vitiligo, HS, & PN
- Clinical POC: Moderate/Severe Asthma & Chronic Spontaneous Urticaria (CSU)

Pandya, A. G., *et al.* presented @ AAD 2023, New Orleans

Kirby, J. S. *et al. J. Am. Acad. Dermatol.* **2024**, *90*, 521. Kirby, J.S. *et al.* Presented at EHSF **2023**, Florence, Italy

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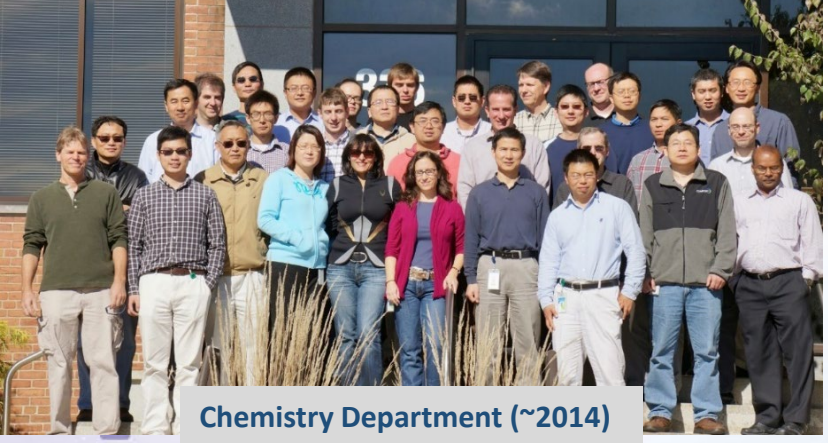

Chemistry Department (~2014)

15 Year Anniversary Discovery Team (~2018)

2023 Recipients of the ACS Heroes of Chemistry Award

Credit: EPNAC.com

Discovery Chemistry

Wenqing Yao
Jincong Zhuo
Yun-Long Li
Ding-Quan Qian
Maria Rafalski
Song Mei
Meizhong Xu
Gustavo Fenalti
Marc Deller
Leslie B. Epling
Jessica Procak
Stacey Shepard
Taisheng Huang
Jim Rodgers
Chubiao Xue
Chunhong He
Colin Zhang
Hai Fen
Ganfeng Cao
Yongchun Pan
Qun Li
Zhongjiang Jia
Amy Takvorian
Andy Combs
Anlai Wang
Ari Arvanitis
Beverly Folmer
Brent Douty
Brian Glass
Brian Metcalf
Brian Wayland
Costas Argyrios
Dan Levy
Dave Meloni
Dilip Modi
DJ Robinson
Eddy Yue
Emily Swain
Hai Fen Ye
Hao Feng
James Pruit
Jason Wang
Jiacheng Zhou
Joe Glenn
Ke Zhang
Laurine Galya
Lei Qiao
Lingkai Weng
Lingquan Kong
Lixin Shao
Lori Bostrom
Lou Storace
Matthew Crawley
Mei Li
Michael Bower
Michael Xia
Nikoo Falahatpisheh
Padmaja Polam
Qiyan Lin
Ravi Jalluri
Richard Sparks
Shaopei Cai
Tom Maduskie
Vaqar Sharief
Wenyu Zhu
Xiaohau He
Yongchun Pan
Yongzhong Wu
Zelda R. Wasserman

Discovery Biology

Kris Vaddi
Steve Friedman
Peggy Scherle
Swamy Yeleswaram
Sharon Diamond
Yan Zhang
Maryanne Covington
Bob Newton
Greg Hollis
Tim Burn
Bob Collins
Yanlong Li
Jun Li
Beth Thomas
Paul Collier
Paul Waeltz
Denise Hertel
Maggie Favata
Xiaoming Wen
Jack Shi
Ryan McGee
Pat Haley
Brian Sayers
Jason Boer
Jennifer Harris
Alex Margulis
Cindy Marando
Dale McCall
Dana Shuey
Ellham Behshad
Holly K. Koblish
Kamna Katiyar
Karen Gallagher
Katherine Drake
Leslie M. Hall
Lynn Leffet
Mark Rupar
Maxim Soloviev
Mike Hansbury
Nancy Contel
Nina Zolotarjova
Pat Feldmnan
Reid Huber
Richard Wynn
Xin He

Drug Development

Rich Levy
Bill Williams
Ed Bradley

Academic Collaborators

Ross Levine (MSKCC)
Srdan Verstovsek (MDACC)

Patients and their families for participating in clinical trials

Incyte