LEUCEMIA LINFATICA CRONICA, OGGI... ED OLTRE

La selettività farmacologicamente parlando

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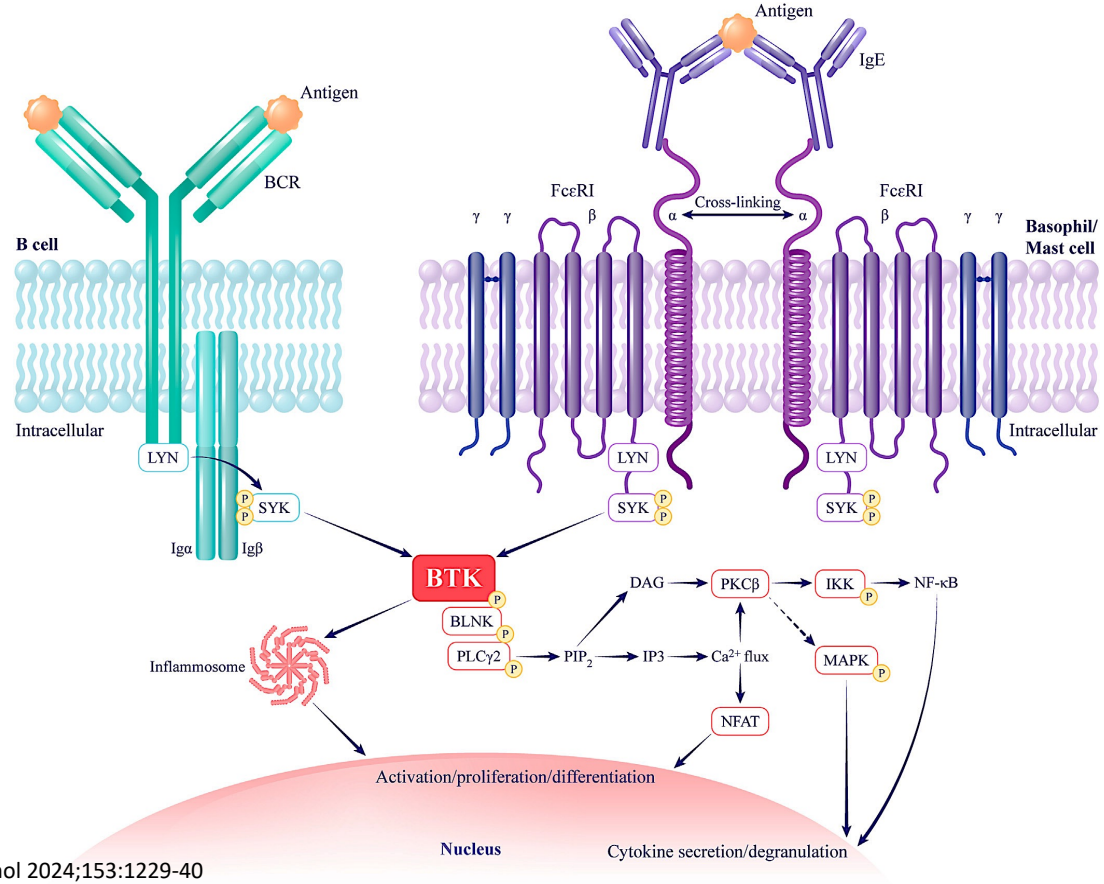
Università degli Studi di Milano

Napoli, Starhotels Terminus, 15 ottobre 2024

Declaration of interests

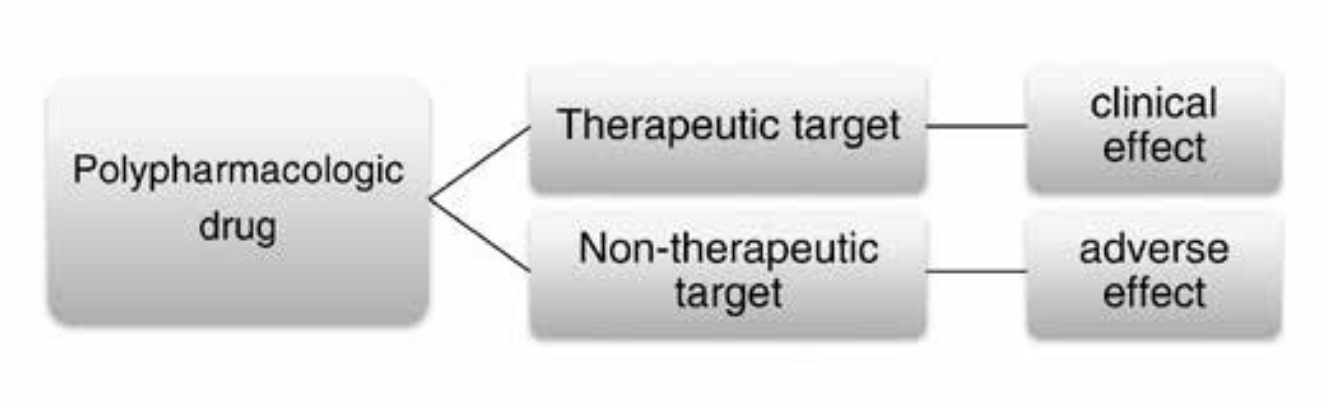
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
MSD			X		X		
Eisai			X		X	X	
AstraZeneca	X		X		X	X	
BeiGene					X		
Janssen	X		X		X		
Novartis			X		X		
Lilly			X		X		
Incyte			X		X		
AB Science			X				

BTK signal transduction



Bernstein JA et al. J Allergy Clin Immunol 2024;153:1229-40

The dual-face of multi-target compounds and relationship with master key drugs



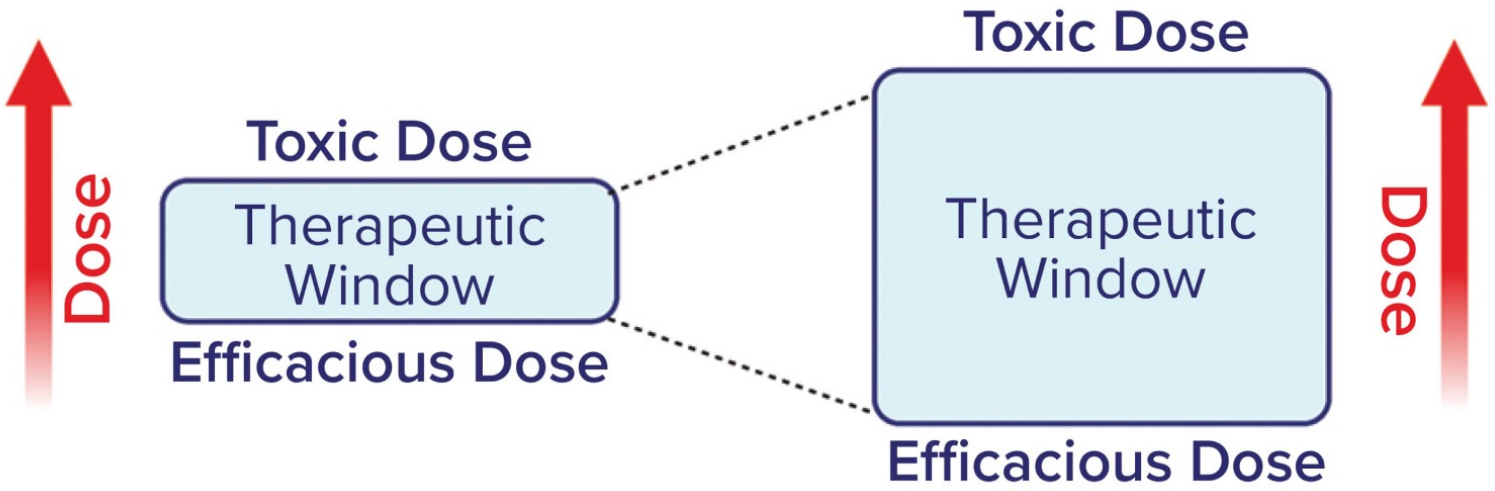
Oscar Méndez-Lucio et al. J. Mex. Chem. Soc. 2016, 60(3), 168-181

Classification of adverse drug reactions (ADRs)

- On-target: ADR depending on the inhibition of **primary target** expressed **also** in normal cells
- Off-target: ADR depending on the inhibition of **secondary targets** expressed in normal cells
- Off-tissue: ADR depending on the inhibition of **primary and secondary targets** expressed in normal cells

- Highly selective drugs have **less** off-target, off-tissue ADRs

The concept of therapeutic index/window



Drug with low selectivity

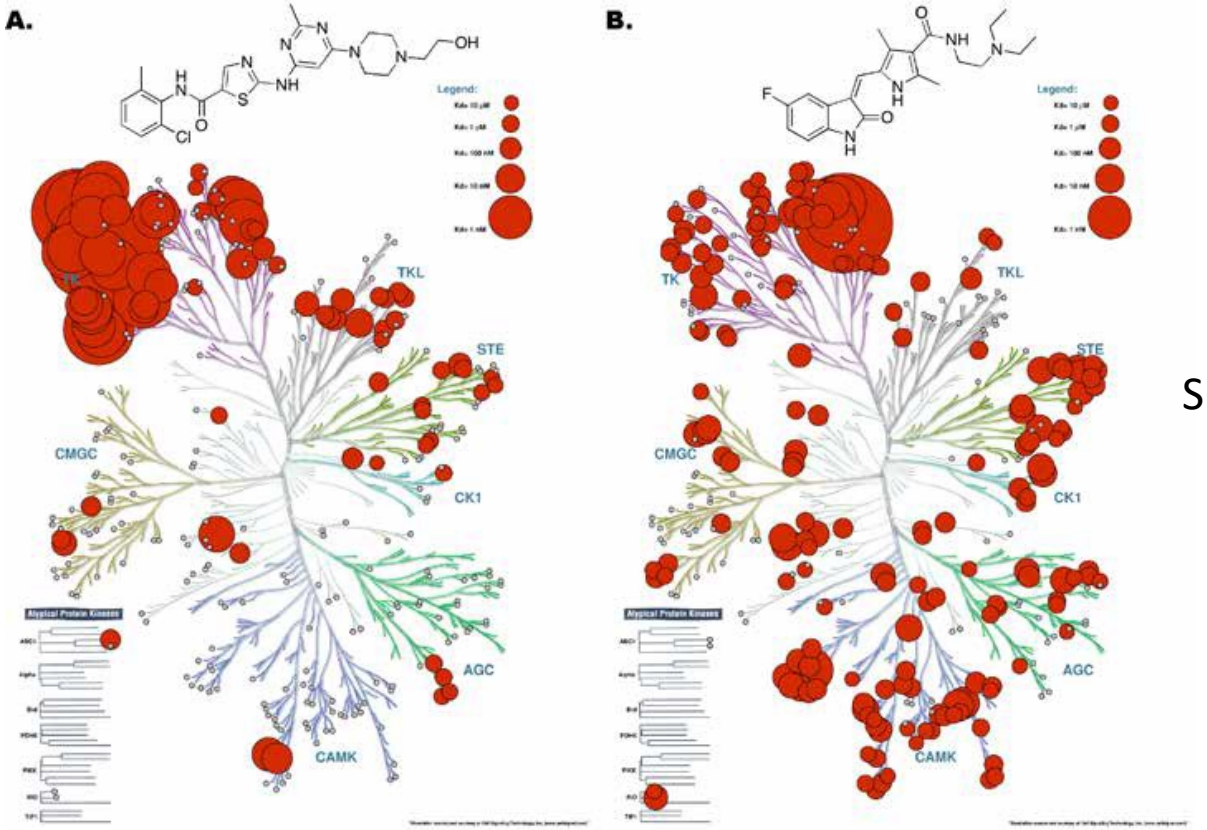
Drug with high selectivity

https://bioprocessintl.com/2023/september-2023-featured-report/manufacturing-challenges-of-therapeutic-antibody-drug-conjugates/ (modified)

Pharmacodynamics and selectivity of acalabrutinib

Examples of poor selectivity of kinase inhibitors

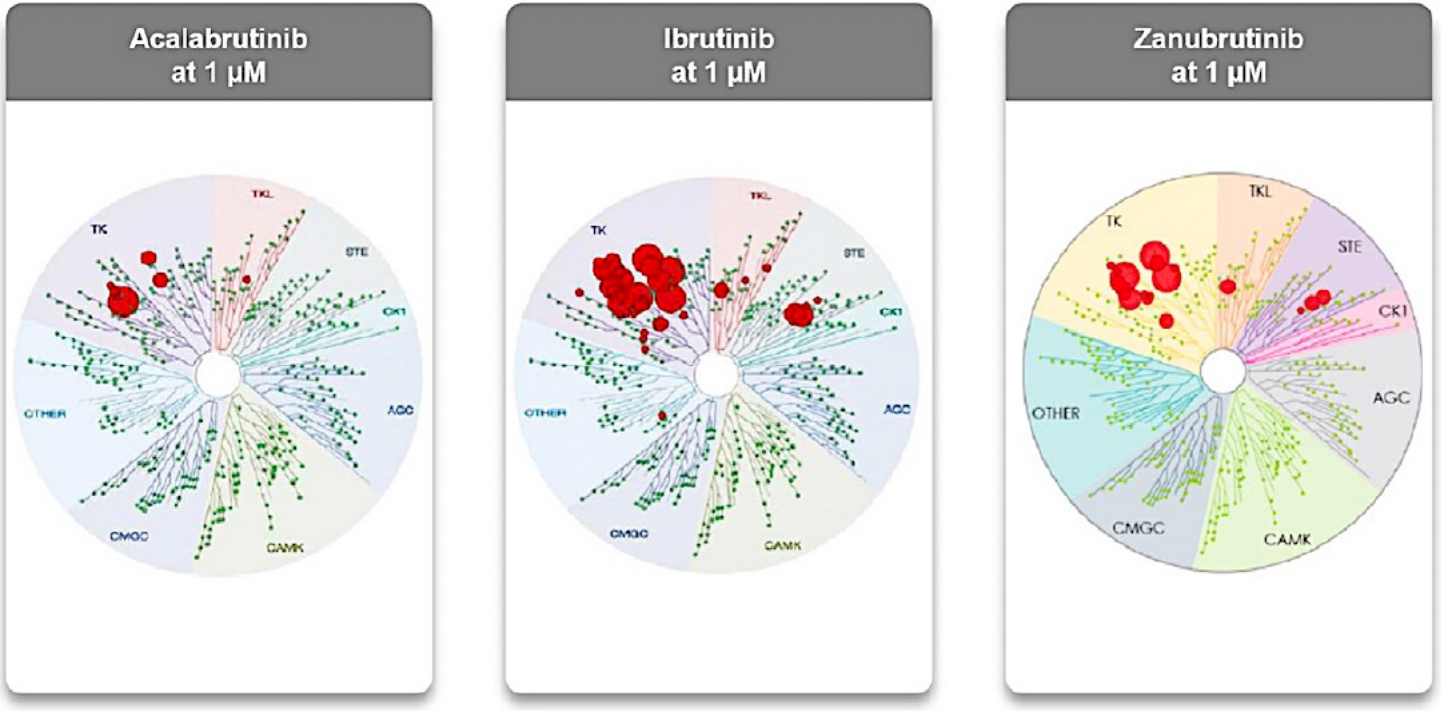
Dasatinib



Sunitinib

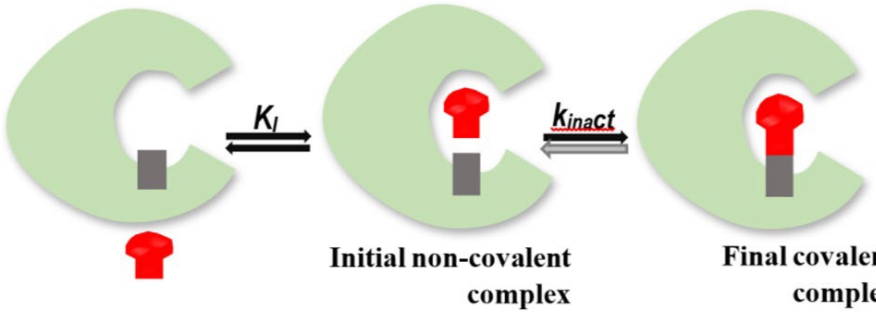
Oscar Méndez-Lucio et al. J. Mex. Chem. Soc. 2016, 60(3), 168-181

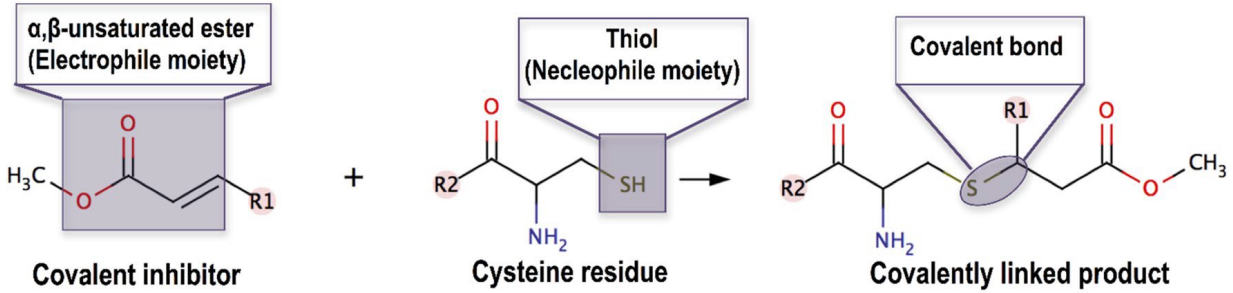
Kinome profiling at a single dose of 1 mM of BTK covalent inhibitors



Bernstein JA et al. J Allergy Clin Immunol 2024;153:1229-40

The generic mechanism of action of a target-specific covalent inhibitor



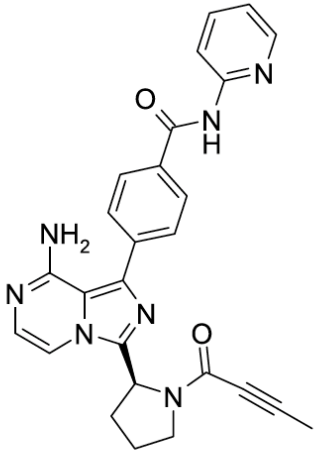


R1 = The non-covalent part of the inhibitor

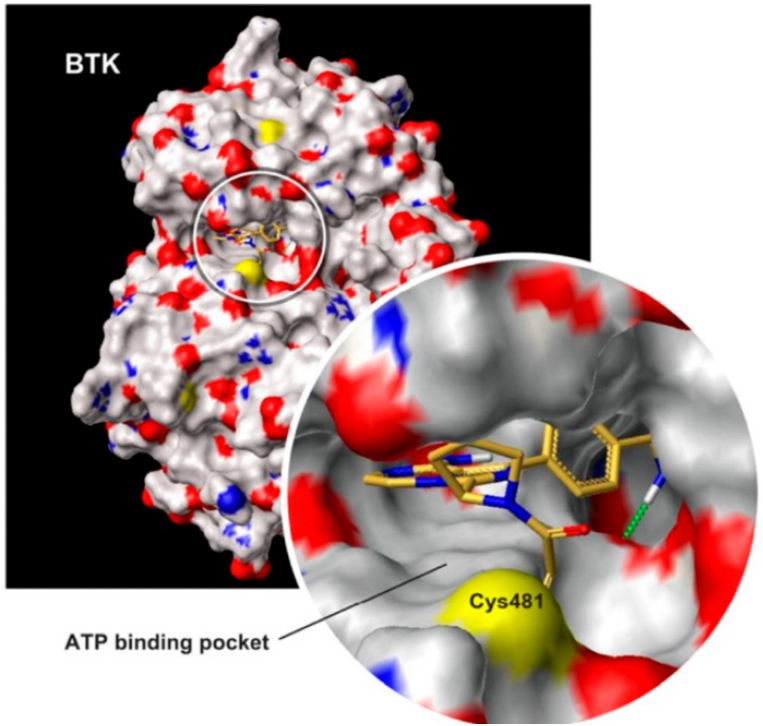
R2 = Protein residues

Aimen Aljoundi et al. The Protein Journal (2020) 39:97–105

Binding model of acalabrutinib in the ATP binding pocket of BTK

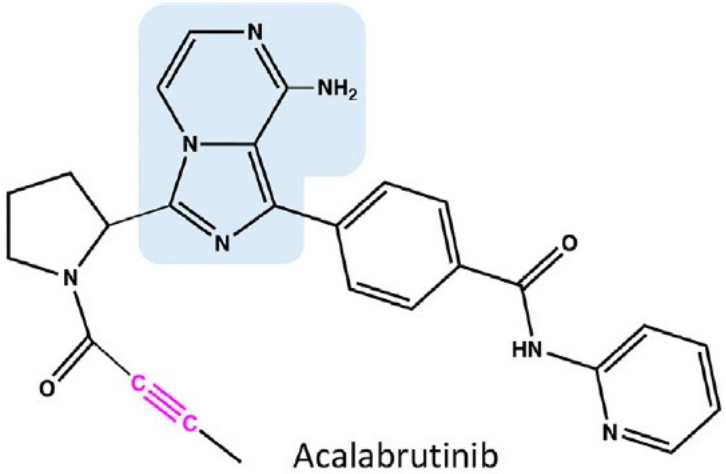


Acalabrutinib

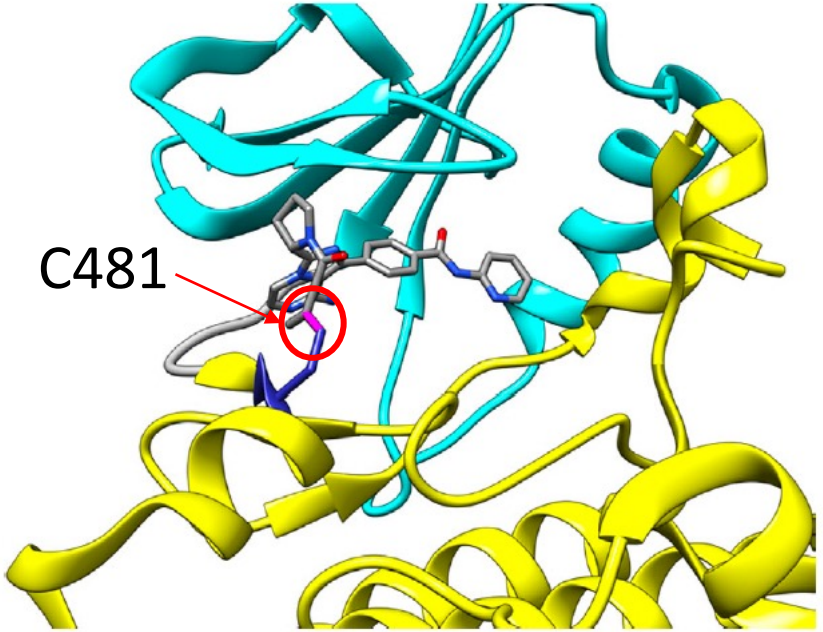


Barf T et al. J Pharmacol Exp Ther 363:240–252, 2017

Chemical structure of acalabrutinib and molecular model showing binding of the covalent inhibitor in BTK

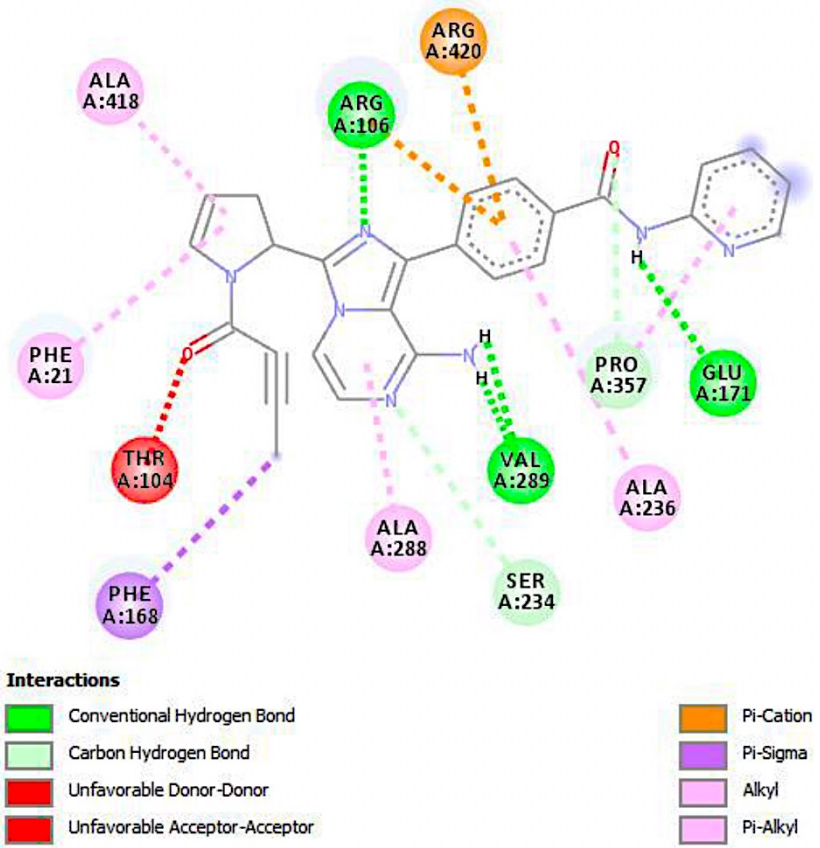


Acalabrutinib



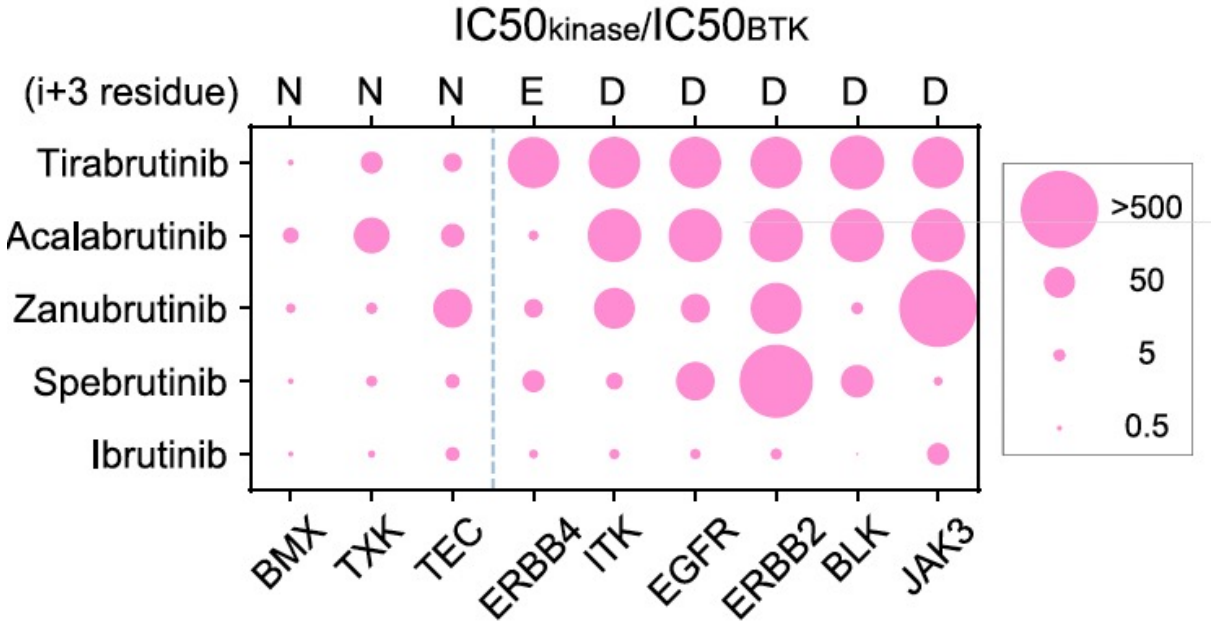
Rula Zain, Mauno Vihinen. Front. Immunol.2021;12:694853.

The 3D docked view of the most stable conformer of acalabrutinib in active site of α5β1 integrin



Celik S et al. Open Journal of Nano 2022;7:1

Relationship between the selectivity of various inhibitors relative to BTK



Mojgan Asadi et al. J. Am. Chem. Soc. 2022, 144, 16638−16646

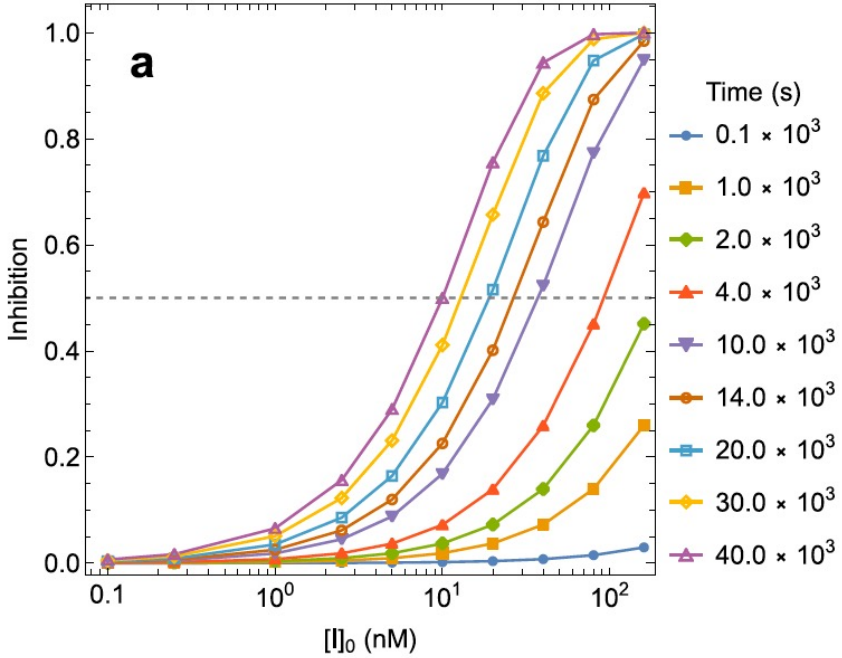
Comparison of inhibition potency of acalabrutinib and ibrutinib with BTK and ITK

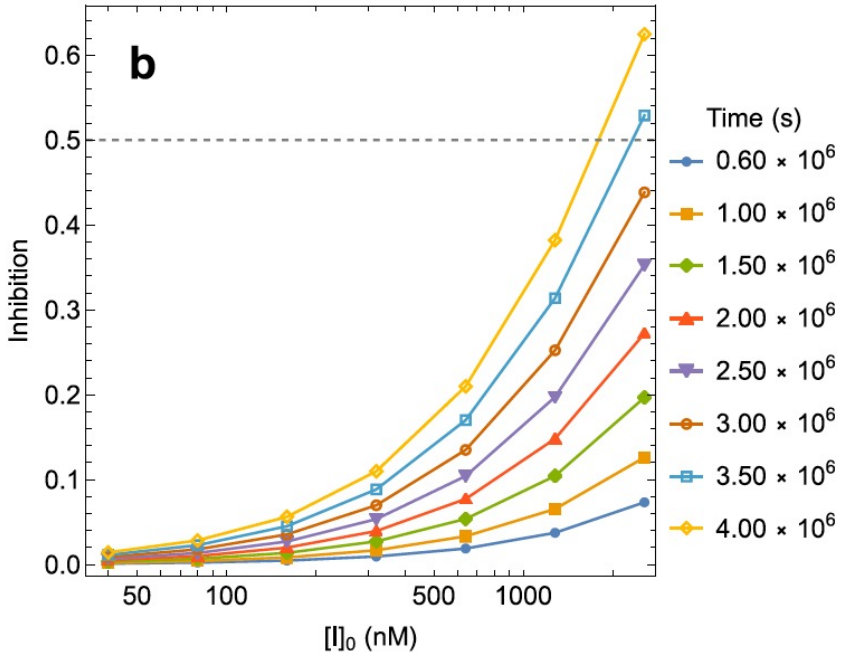
Acalabrutinib (Observed)			
Systems	IC50 (nM)	k_{inact}(kcal/mol)	k_{inact}/K_i (M^{-1} s^{-1})
BTK (ASN)	2.5	20.5	3.0×10^4
ITK (ASP)	>20,000		7
Ibrutinib (Observed)			
Systems	IC50 (nM)	k_{inact}(kcal/mol)	k_{inact}/K_i (M^{-1} s^{-1})
BTK (ASN)	0.47	19.6	1.0×10^6
ITK (ASP)	55		2.8×10^3

Mojgan Asadi et al. J. Am. Chem. Soc. 2022, 144, 16638−16646

Simulated inhibition progress vs initial acalabrutinib concentration at different time windows for both (a) BTK and (b) ITK

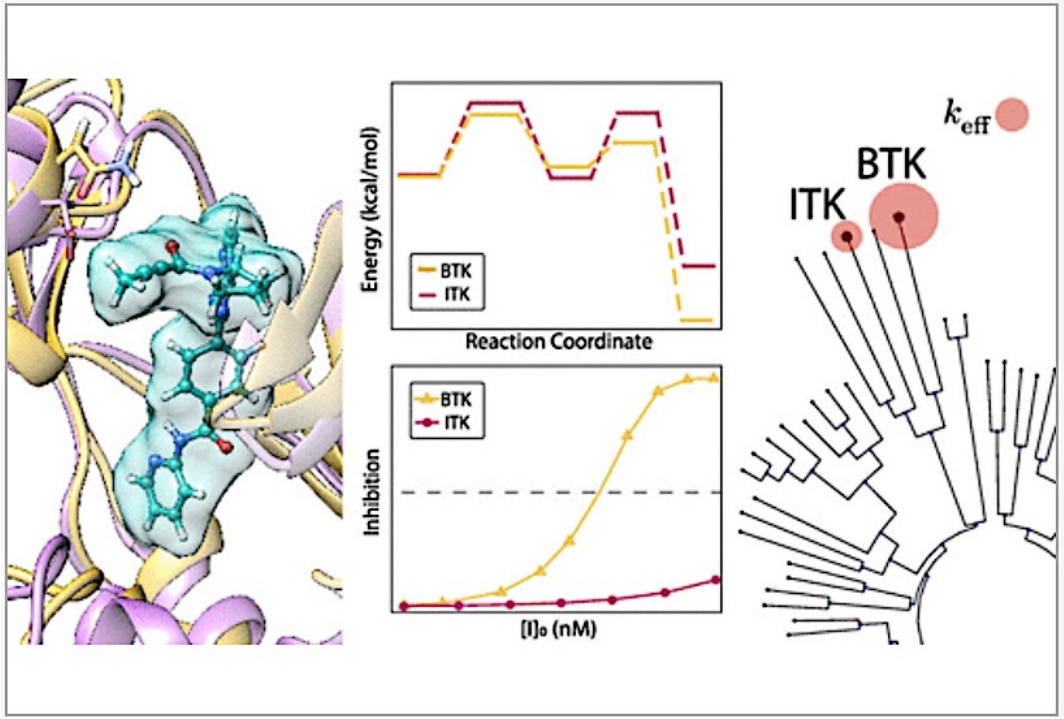
Unlike BTK, which may be half-inhibited with a dosage of 100 nM in about an hour, ITK can rarely be inhibited with the same dose in a clinically meaningful amount of time.





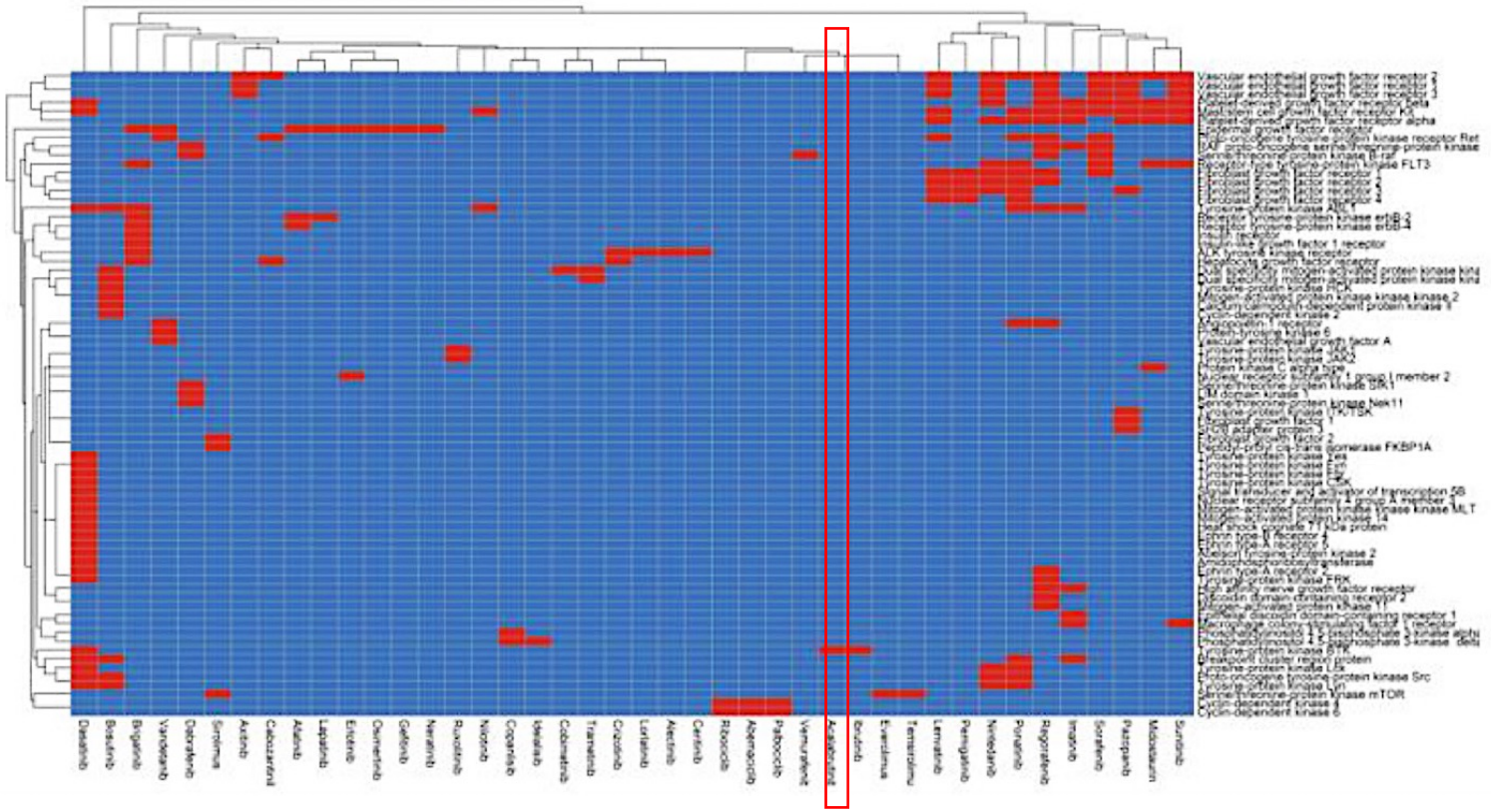
Mojgan Asadi et al. J. Am. Chem. Soc. 2022, 144, 16638−16646

Selectivity of acalabrutinib over the Bruton's tyrosine kinase (BTK) and the IL-2-inducible T-cell kinase (ITK)



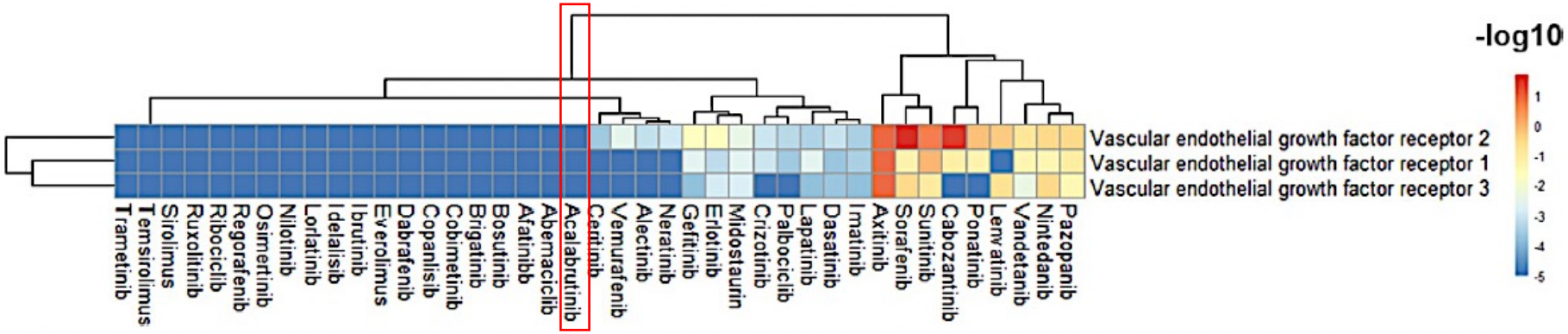
Mojgan Asadi et al. J. Am. Chem. Soc. 2022, 144, 16638−16646

Heatmaps showing the targets of kinase inhibitors



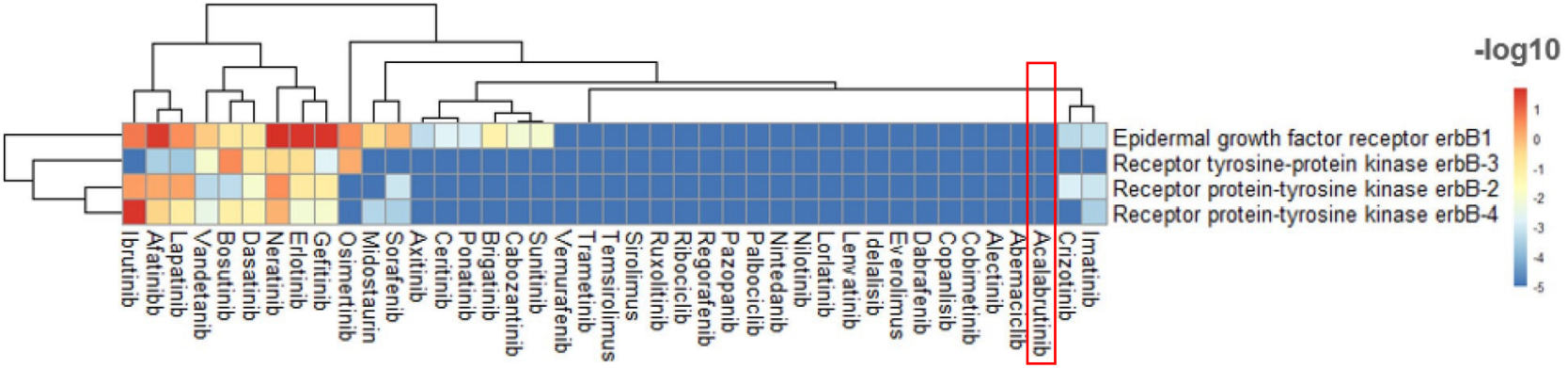
Omer Bayazeid, Taufiq Rahman. ChemistrySelect 2021, 6, 7799 –7814

Heatmap showing which KIs target VEGFR



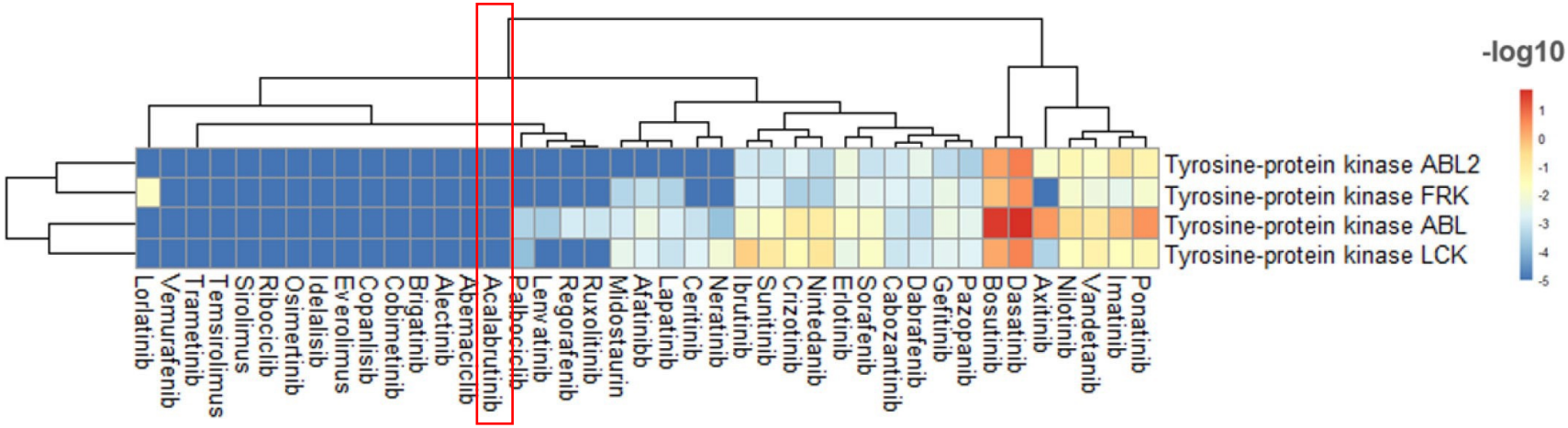
Omer Bayazeid, Taufiq Rahman. ChemistrySelect 2021, 6, 7799 –7814

Heatmap showing which KIs target EGFR



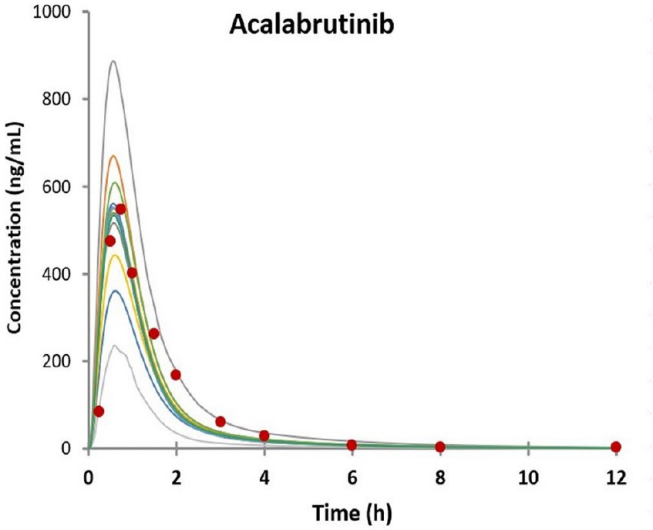
Omer Bayazeid, Taufiq Rahman. ChemistrySelect 2021, 6, 7799 –7814

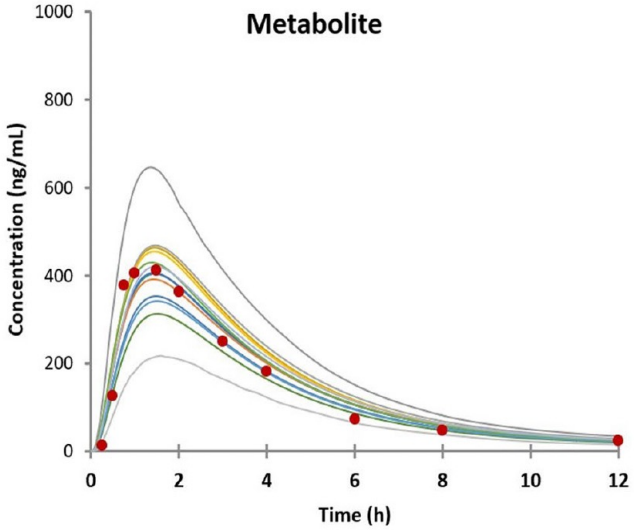
Heatmap showing which KIs target ABL family, LCK and FRK

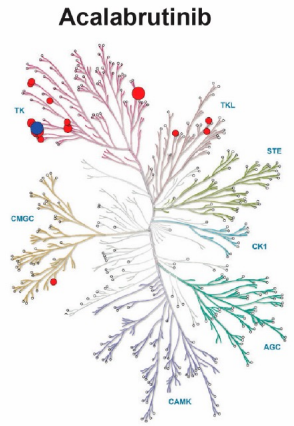


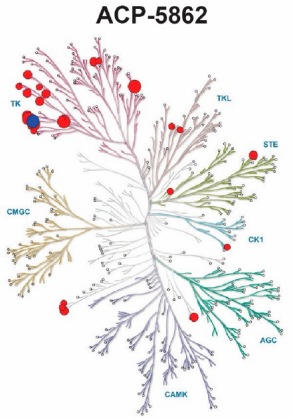
Omer Bayazeid, Taufiq Rahman. ChemistrySelect 2021, 6, 7799 –7814

Plasma levels of acalabrutinib and its metabolite ACP-5862 after 100 mg single oral dose









Zhou D et al. Pharmaceutical Research (2023) 40:375–386

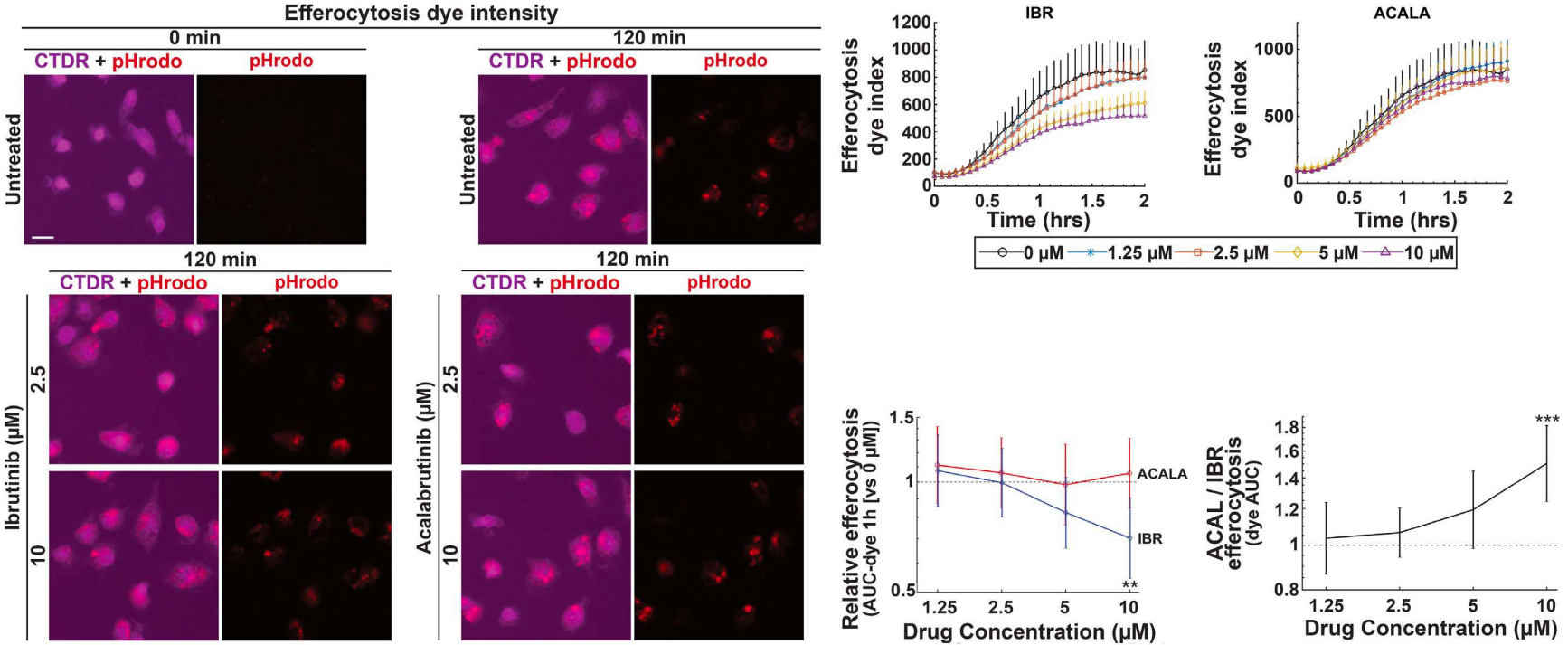
Effect of cBTKi on A431 cells, Jurkat cells, and human PBMCs

Compound	EC_{50}		
	EGF-Induced EGFR Phosphorylation in A431 Cells[a]	Anti-CD3/CD28–Induced IL-2 Production in Jurkat Cells[b]	Anti-CD3–Induced CD25 Expression in PBMCs[b]
		nM	
Acalabrutinib	>10,000	>10,000	>10,000
Ibrutinib	71 ± 14	99 ± 17	257 ± 71

[a]Results are the mean ± error of two independent experiments.
[b]Results are the mean ± S.D. of three independent experiments.

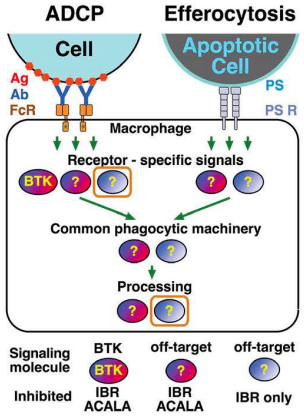
Barf T et al. J Pharmacol Exp Ther 363:240–252, 2017

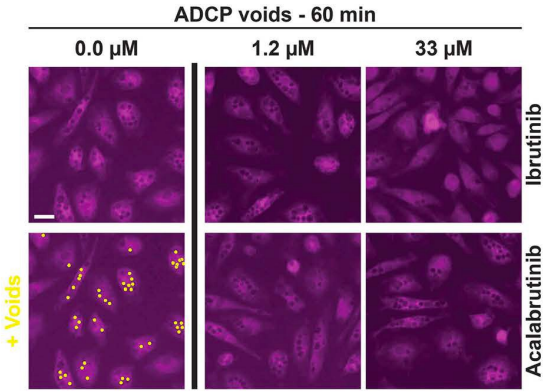
Phagolysosomal processing is inhibited by ibrutinib, but not by acalabrutinib

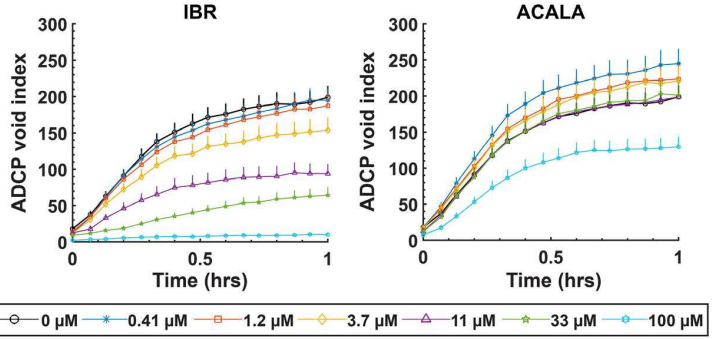


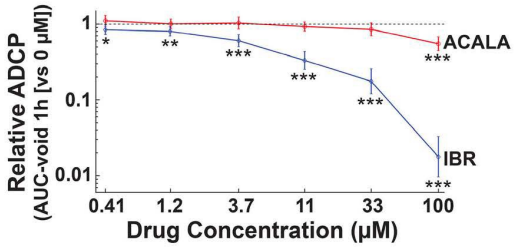
Charles C. Chu et al. Haematologica 107 - June 2022, 1460

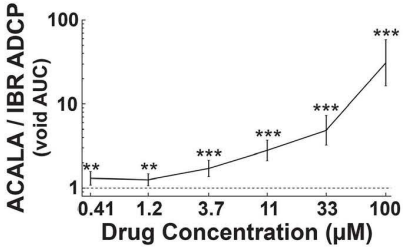
BTKi effects on phagocytosis and antibody-dependent cellular phagocytosis (ADCP) measurements











Charles C. Chu et al. Haematologica 107 - June 2022, 1460

BTKi effects on phagocytosis and antibody-dependent cellular phagocytosis (ADCP)

- These data show that short-term highly selective BTK inhibition in vitro by acalabrutinib does not alter macrophage functions of mAb mediated ADCP, antibody-independent efferocytosis, or phagolysosomal processing.
- In contrast, IBR significantly inhibited ADCP over a wide range of drug concentrations (0.41–100 mM).

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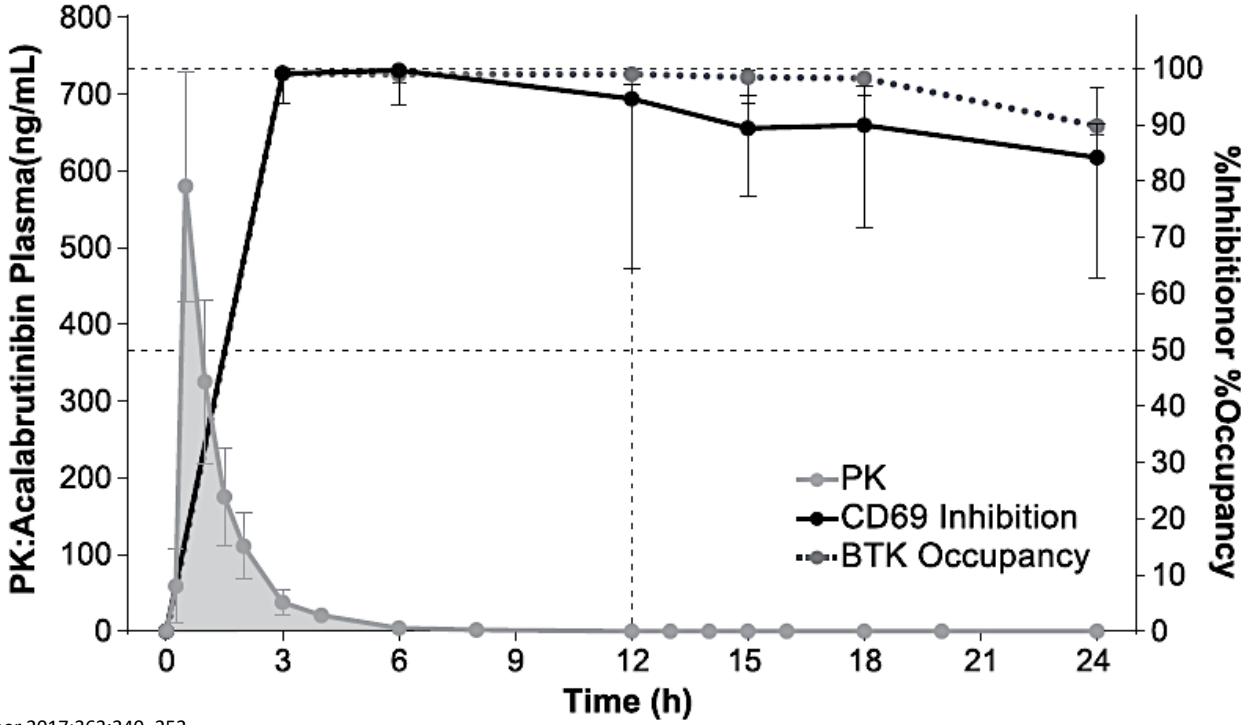
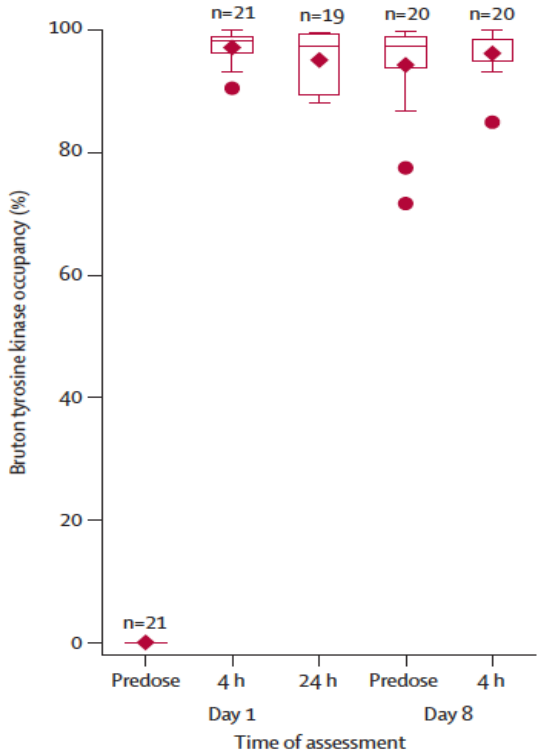
Acalabrutinib PK/PD in patients given a single 100-mg dose

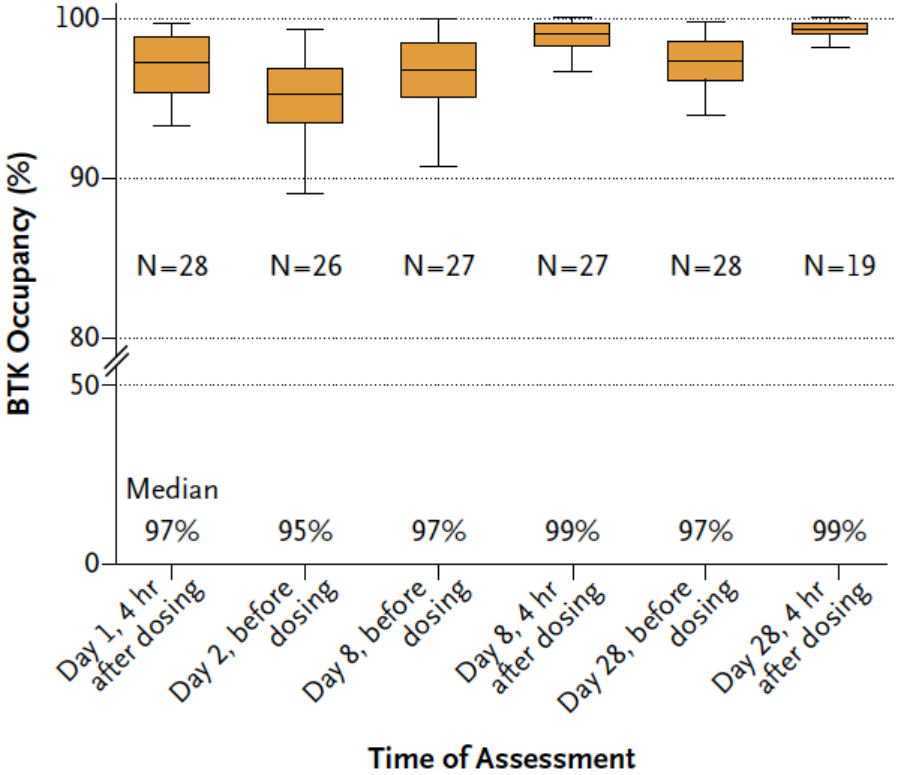


Barf T et al. J Pharmacol Exp Ther 2017;363:240–252

Ibrutinib (420 mg qd) and acalabrutinib (100 mg bid) BTK occupancy

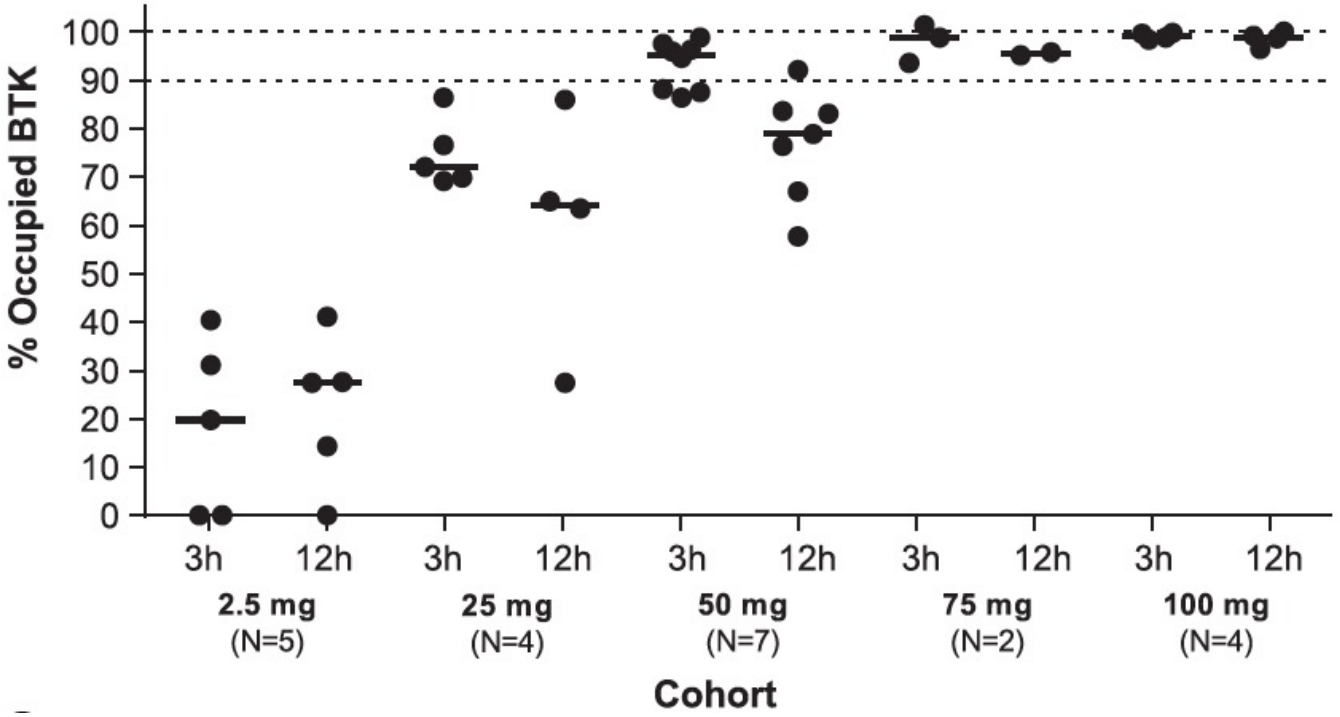


O'Brien S et al. Lancet Oncol 2014; 15: 48–58



Byrd JC et al. N Engl J Med 2016;374:323-32

Dose-dependent BTK occupancy derived from blood samples drawn 3 and 12 hours after acalabrutinib administration



Barf T et al. J Pharmacol Exp Ther 363:240–252, 2017

Conclusions

- Kinase deregulation in hematologic malignancies is very well established.
- The excellent progress in developing kinase inhibitors for the clinic has significantly improved the outcomes for patients.
- Acalabrutinib has favorable and improved pharmacokinetic and pharmacodynamic profile and represents an advanced-generation BTK inhibitor.