"Off-Target" Therapeutic Mechanisms of "Target-Based" Drugs
Rationality or Luckiness?

Supplementary Data 2

for

Biological Sciences and Physics Unified: Internal Evolution

and Urging the Second Scientific Revolution

Arash Sadri, PharmD student

Interdisciplinary Neuroscience Research Program, Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran.
Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
a-sadri@student.tums.ac.ir
arash4sadri@outlook.com
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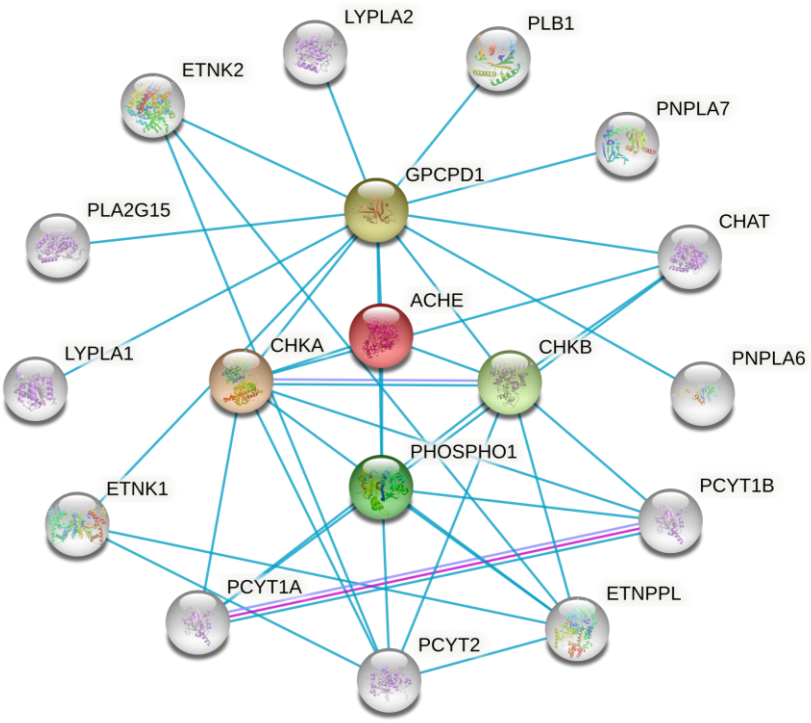
See the main article for the detailed method.

Below most target-tables, there is the STRING interaction network along with its permalink, from which the interactive network along with relevant data and files can be accessed; STRING png and svg image files, STRING interaction and annotation files and the downloaded and deduplicated citations are also available at doi.org/10.5281/zenodo.5732942.

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
DONEPEZIL	acetylcholinesterase	ACHE	P22303	41



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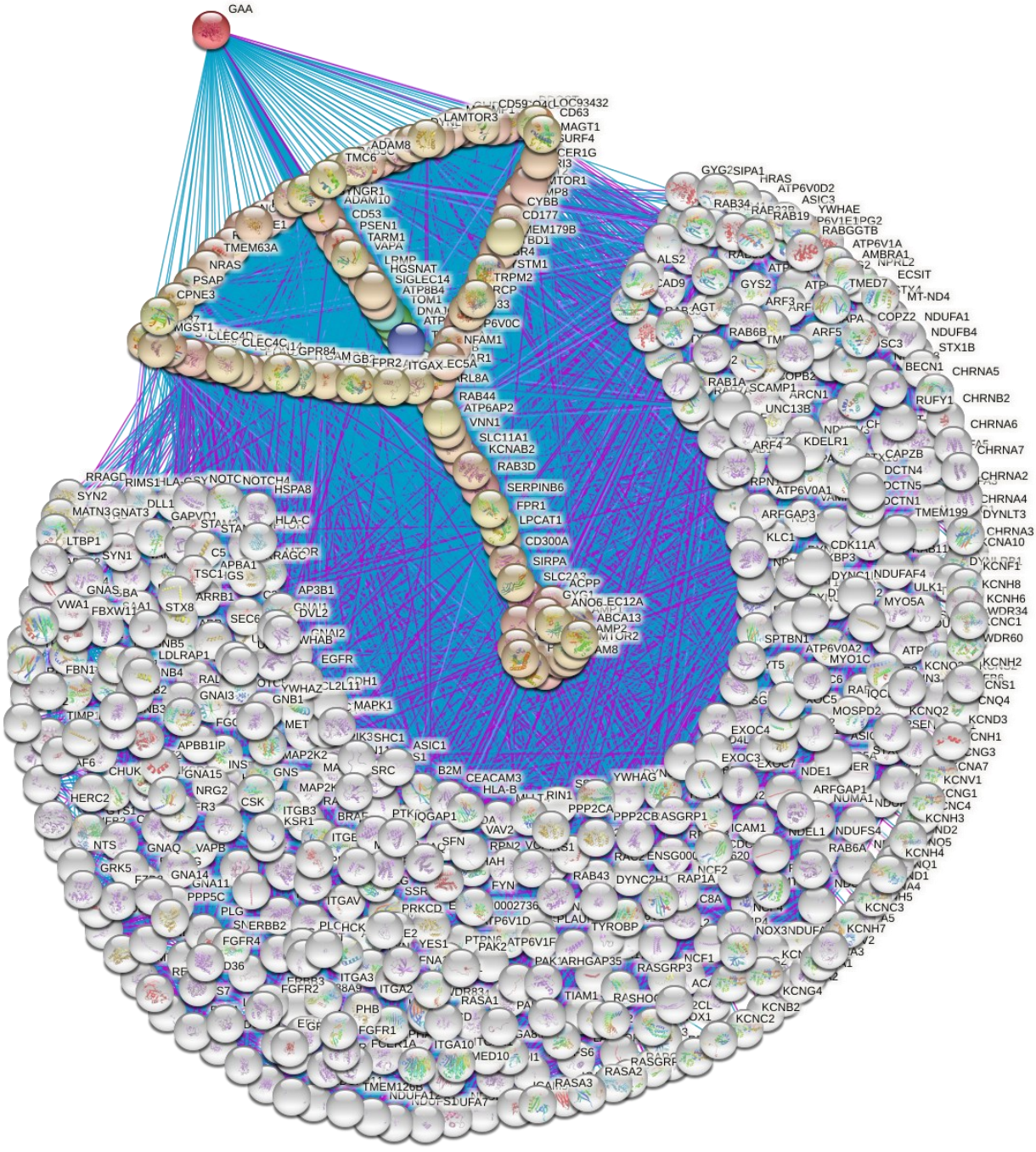
1. prevents glutamate neurotoxicity through α4- and α7-nicotinic acetylcholine receptors, followed by activation of PI3-Akt pathway and downregulation of NMDA receptors(*1-5*)
2. protective effect against oxygen–glucose deprivation-induced injury independent of muscarinic cholinergic system and nicotinic cholinergic system(*6*)
3. modulates the vasoconstrictive effects of Aβ peptides at the level of skin microvasculature, independent of a direct action on smooth muscle cell reactivity or on endothelial cell function in the absence of Aβ(*7*)
4. neuroprotective activity against depolarization-induced toxicity via inhibition of the rapid influx of sodium and calcium ions, and via decrease of glutamate and glycine release(*8*)
5. anti-inflammatory properties independent of its acetylcholinesterase inhibition(*9*)
6. directly inhibits microglial activation induced by Aβ through blocking MAPK and NF-κB signaling(*10*)
7. increases mitochondrial biogenesis through AMP-activated protein kinase in the hippocampus(*11*)

8. improves neuropathy through activation of AMPK pathway(*12*)
9. modulates a T helper 2 bias via α7-nAChR leading to increased expression of naturally occurring auto-antibodies against amyloid beta (Aβ)(*13*)
10. attenuates vascular reactivity dysfunction by decreasing reactive oxygen species generation and increasing NO bioavailability; possibly via increased endothelial NO synthase activity, and inhibition of NADPH oxidase activity(*14*)
11. direct non-competitive inhibition of nAChR(*15*)
12. increases the activity of α-secretase and decreases the activity of β-secretase(*16*)
13. inhibitory effects on the production of PGE2, TXB2, COX-1 and COX-2 mRNA and protein expression in macrophages(*17*)
14. antioxidant properties(*18, 19*)
15. inhibits microglial activation and release of proinflammatory cytokines(*20*)
16. enhances Aβ clearance across the blood-brain barrier and liver by upregulating the expression of Aβ major transport proteins(*21*)
17. promotes phagocytic activity of microglial cells through the PI3K pathway(*22*)
18. agonistic activity at sigma-1 receptor(*23-28*)
19. inhibits a canonical inflammatory NF-κB signaling and microglial activation independent of acetylcholine(*29*)
20. stimulates oligodendrocyte differentiation and myelin-related gene expression via nicotinic acetylcholine receptors in neural stem cell-derived oligodendrocyte progenitor cells(*30*)
21. attenuates vascular dementia through increasing BDNF by reducing HDAC6 nuclear translocation(*31*)
22. produces acute vasodilation induced by a selective activation of neuronal nitric oxide synthase in the cerebral parenchymal arterioles(*32*)
23. ameliorates Aβ impairments in hippocampal long-term potentiation(*33, 34*)
24. increases blood flow and reduces ischemia-induced cellular injury(*35-37*)
25. neuroprotective effects via reducing the efflux of lactate dehydrogenase which is induced by Aβ(1-42)(*38*)
26. enhances the survival of newborn neurons in the hippocampal dentate gyrus via CREB signaling(*39*)
27. neuroprotection by upregulation of BDNF(*40*)
28. inhibits neuronal apoptosis and regulates synaptic plasticity, through the upregulation of p-Akt, p-GSK-3β Bcl-2 and the downregulation of Bax, Caspase-3(*41*)
29. inhibits the inflammatory response and the increase of the intracellular reactive oxygen species induced by bradykinin via nAChR and PI3K-Akt pathway in astrocytes(*42*)
30. promotes neurogenesis via Src signaling pathway(*43*)
31. inhibits apoptosis of endothelial cells(*44*)
32. improves cognitive function by increasing the hippocampal production of IGF-I through sensory neuron stimulation(*45*)
33. inhibits acetylcholine esterase activity and increases the release of sAPPα not only through a muscarinic receptor pathway, but also by

directly enhancing trafficking and activity of both TACE and ADAM 10(*46*)

34. prevents Aβ42-induced neurotoxicity through the activation of PI3K/Akt and inhibition of GSK-3, as well as through the activation of nAChR(*47*)
35. increased neuronal viability with reduced p-tau by enhancing protein phosphatase 2A activity(*48*)
36. reverses the age-related downregulation of the growth hormone/insulin-like growth factor-1 axis(*49*)
37. potentiates neuronal differentiation by enhancing the activation of ERK(*50*)
38. promotes neurite outgrowth(*51*)
39. regulates serum adipokine level(*52*)
40. modulates monocyte chemotactic protein-1 and IL-4 production, which may reflect a general shift towards type Th0/Th2 cytokines which could be protective in Alzheimer(*53*)
41. inhibits microtubule affinity-regulating kinase (MARK4)(*54*)
42. neuroprotective effects via inhibiting voltage-gated calcium and potassium and sodium channels(*55, 56*)
43. upregulates and sensitizes α7-nAChR(*57*)
44. reduces Aβ by increasing the activity of phospholipase A2(*58*)
45. reduces the phosphorylation of tau protein by phosphorylating and inactivating GSK-3β(*58*)
46. decreases the expression of the pro-apoptotic protein, glyceraldehyde-3-phosphate dehydrogenase(*59*)
47. decreases the expression of miR-206-3p(*60*)
48. attenuates Aβ-associated mitochondrial dysfunction and reduces mitochondrial Aβ accumulation(*61*)
49. rescues spatial learning and memory deficits following traumatic brain injury independent of its effects on neurogenesis(*62*)
50. attenuates cell apoptosis induced by oxygen-glucose deprivation via blocking Kv2.1 potassium channels(*63*)
51. delays cellular senescence that is promoted under high glucose condition via activation of SIRT1 and inhibiting the generation of reactive oxygen species(*64*)
52. neuroprotective effects via PINK 1 that is related to mitophagy and cellular protection from mitochondrial dysfunction(*65*)
53. upregulates proteins relevant to axon guidance, cytoskeleton, and mitophagy, and modulates the proteins connected to mTOR and MAPK pathways(*65*)
54. decreases the level of Aβ by increasing SNX33 expression and APP cleavage by α-secretase(*66*)
55. neuroprotection via inhibition of sodium channels(*67*)
56. modulates the insulin and IGF-1 signaling pathways(*68*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
ACARBOSE	alpha glucosidase	GAA	P10253	14



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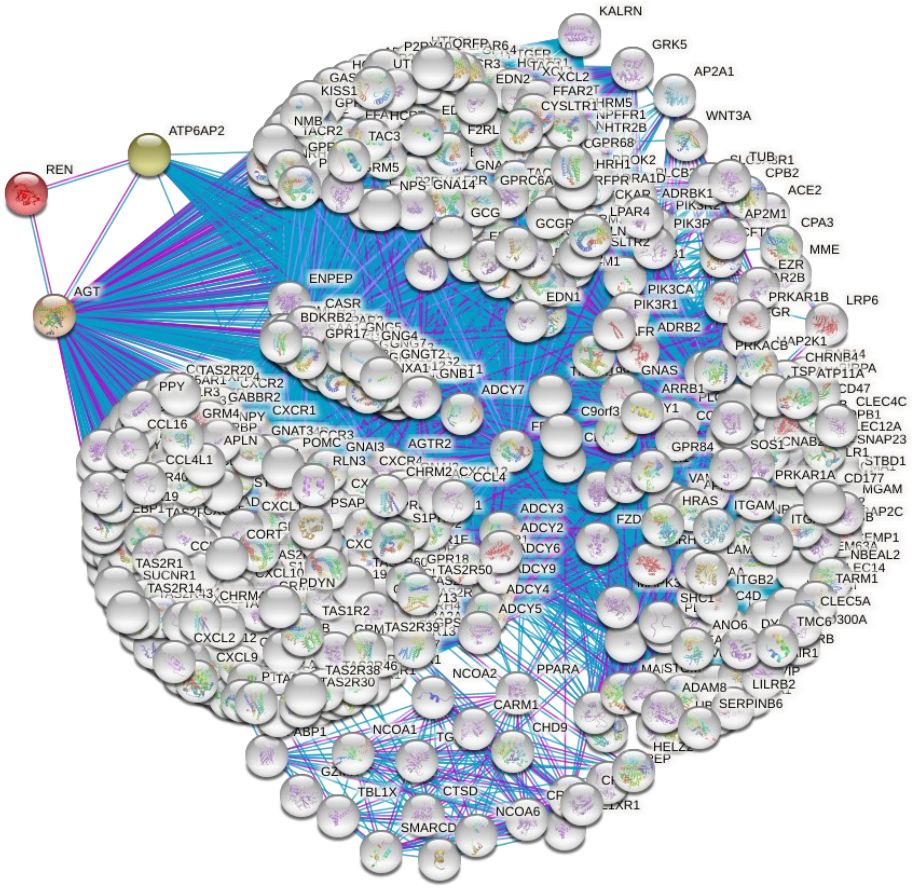
1. directly inhibits the absorption of free glucose and some other hexoses(*69, 70*)
2. prevents pancreatic islet hypertrophy and augments islet blood flow(*71*)
3. regulates lipid metabolism(*72*)
4. downregulates sucrase-isomaltase and sGLT1 gene expressions and upregulates GLUT4 mRNA and protein expressions(*73*)
5. ameliorates endothelial barrier dysfunction by directly inhibiting NLRP3 inflammasome(*74*)
6. inhibits glucose-6-phosphatase and hepatic glucose production(*75*)
7. regulates thyroid hormones(*76*)
8. delays gastric emptying(*77*)
9. regulates gut microbiome and their fermentation products(*78, 79*)
10. activates miR-10a-5p and miR-664 and regulates the MAPK pathway(*80*)
11. attenuates insulitis via anti-inflammatory actions(*81*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
ALISKIREN	renin	REN	P00797	12



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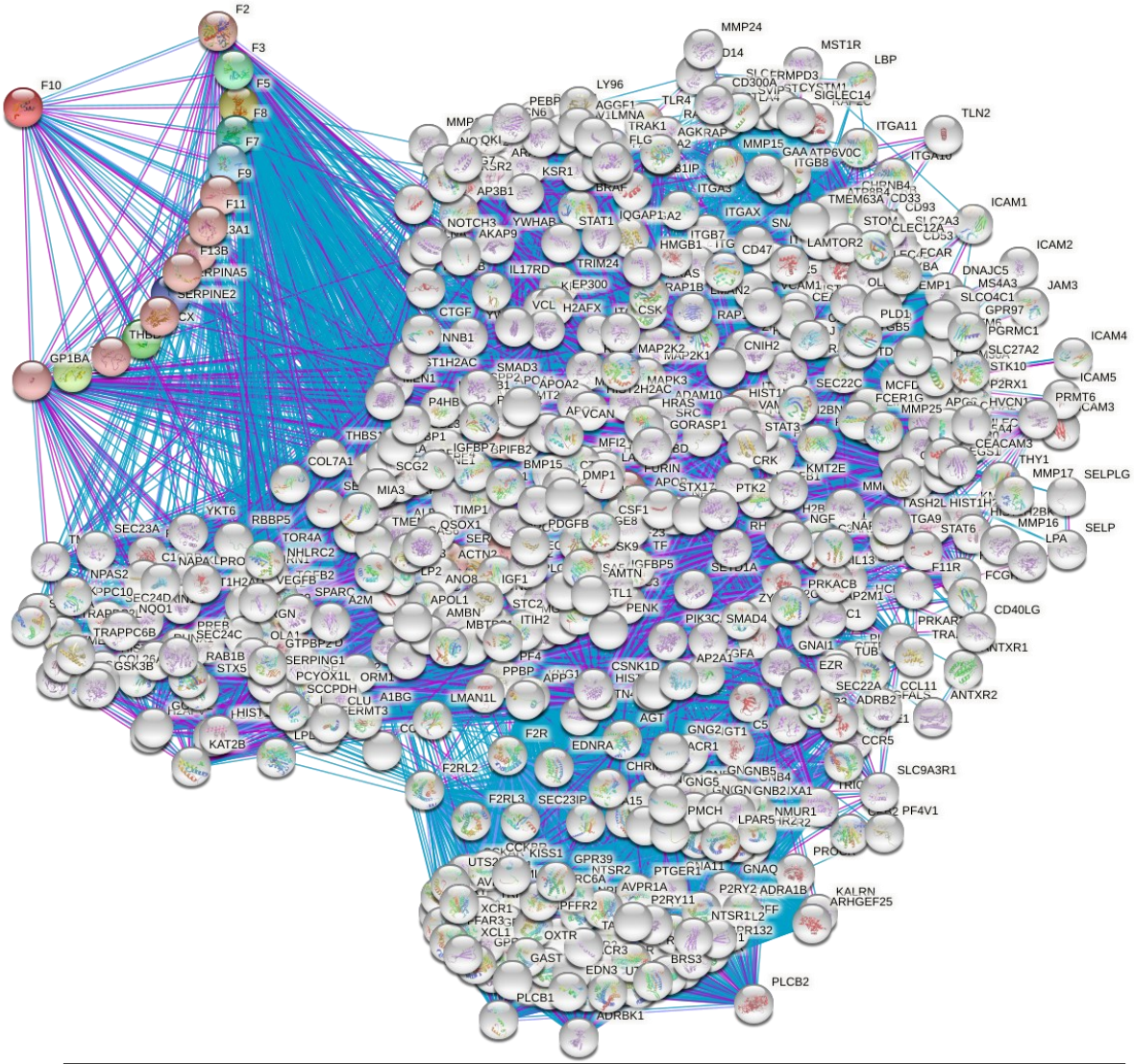
1. protects against myocardial I/R injury via eNOS dependent mechanisms(*82*)
2. increases cardiomyocyte survival via increasing autophagosomal formation and decreasing apoptosis and necrosis via modulating AMPK expression(*83*)
3. improves endothelium-dependent relaxation and oxidative stress by activating PI3K/Akt/eNOS pathway(*84*)
4. protects endothelial function and improves impaired nitric oxide bioavailability(*85*)
5. downregulates the expression of the (pro)renin and AT_1 receptors(*86*)
6. attenuates myocardial ischemia-reperfusion injury by a bradykinin B_2 receptor- and angiotensin AT_2 receptor-mediated mechanism(*87*)
7. improves vascular endothelial function and platelet-endothelium activation independent of antihypertensive effects(*88*)
8. cardioprotective properties and beneficial effects on oxidative stress biomarkers(*89*)
9. upregulates pro-angiogenic cells and reduces atherogenesis independent of blood pressure lowering(*90*)
10. favorable effects on endothelial function and epithelial progenitor cells, reduced arterial stiffness, and improved left ventricular twisting and untwisting, independent of blood pressure(*91*)
11. attenuates myocardial apoptosis and oxidative stress(*92*)
12. ameliorates aortic endothelial dysfunction and oxidative vascular remodeling via elevating plasma nitric oxide metabolite levels and reducing systolic hypertension, insulin resistance, dyslipidemia, aortic lipid peroxide levels and aortic wall hypertrophy(*93*)
13. positive effects on cardiac function via MMP-9(*94*)
14. inhibits intracellular angiotensin II levels without affecting (pro)renin receptor signals(*95*)
15. improves vascular remodeling partially via increasing vasculature NO production(*96*)
16. reduces pulmonary vein arrhythmogenic activity with a direct vasodilatory property(*97*)
17. positive inotropic effect on cardiomyocytes(*97*)
18. improves endothelium-dependent vasodilation and NO availability in the peripheral resistance arterioles probably because of antioxidant activities(*98*)
19. inhibits cardiac hypertrophy and fibrosis, independent of blood pressure reduction, by blocking Ang II-PKCβI-ERK1/2-regulated autophagy(*99*)
20. improves the endothelial repair capacity of endothelial progenitor cells via Tie2/PI3k/Akt/eNOS Pathway(*100*)
21. protects against myocardial ischemia/reperfusion injury by activating the PI3K-Akt-eNOS pathway
22. direct effects on myocardial matrix turnover and beneficial effects on diastolic function(*101*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
RIVAROXABAN	coagulation factor X	**F10**	P00742	7
APIXABAN				2
EDOXABAN				1
BETRIXABAN				



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Rivaroxaban

1. fibrinolytic effect(*102*)
2. protective, repairing and fibrinolytic effects on vascular endothelium(*103*)
3. directly affects endothelial cells and activates the NO-mediated vasorelaxant pathway(*104*)
4. ameliorates angiotensin II-induced cardiac remodeling by attenuating TXNIP/Trx2 interaction(*105*)
5. protects against atherosclerosis by increasing the anti-inflammatory cytokine IL-10(*106*)
6. improves blood flow recovery and increases neovascularization and promotes the functions of endothelial progenitor cells, including migration, tube formation, and senescence via NO-related pathways(*107*)
7. anti-atherosclerotic effects by regulating the expression of genes in the TLR4/NF-κB pathway(*108*)
8. reduces TRAP-induced platelet aggregation(*109*)
9. inhibited tissue factor-induced platelet aggregation(*110*)
10. reduces DNA oxidative changes and vascular endothelial damage via inhibiting reactive oxygen species production(*111*)

Apixaban

1. directly affects endothelial cells and activates the NO-mediated vasorelaxant pathway(*104*)
2. reduces TRAP-induced platelet aggregation(*109*)

Edoxaban

1. improves atrial fibrillation and thromboembolism through regulation of the Wnt-β-induced PI3K/ATK-activated protein C system(*112*)
2. improves venous thrombosis by decreasing hydrogen sulfide and homocysteine through the PI3K/AKT pathway(*113*)

Drugs			Discovery Target
ZANAMIVIR	**OSELTAMIVIR**	**PERAMIVIR**	Influenza Neuraminidase

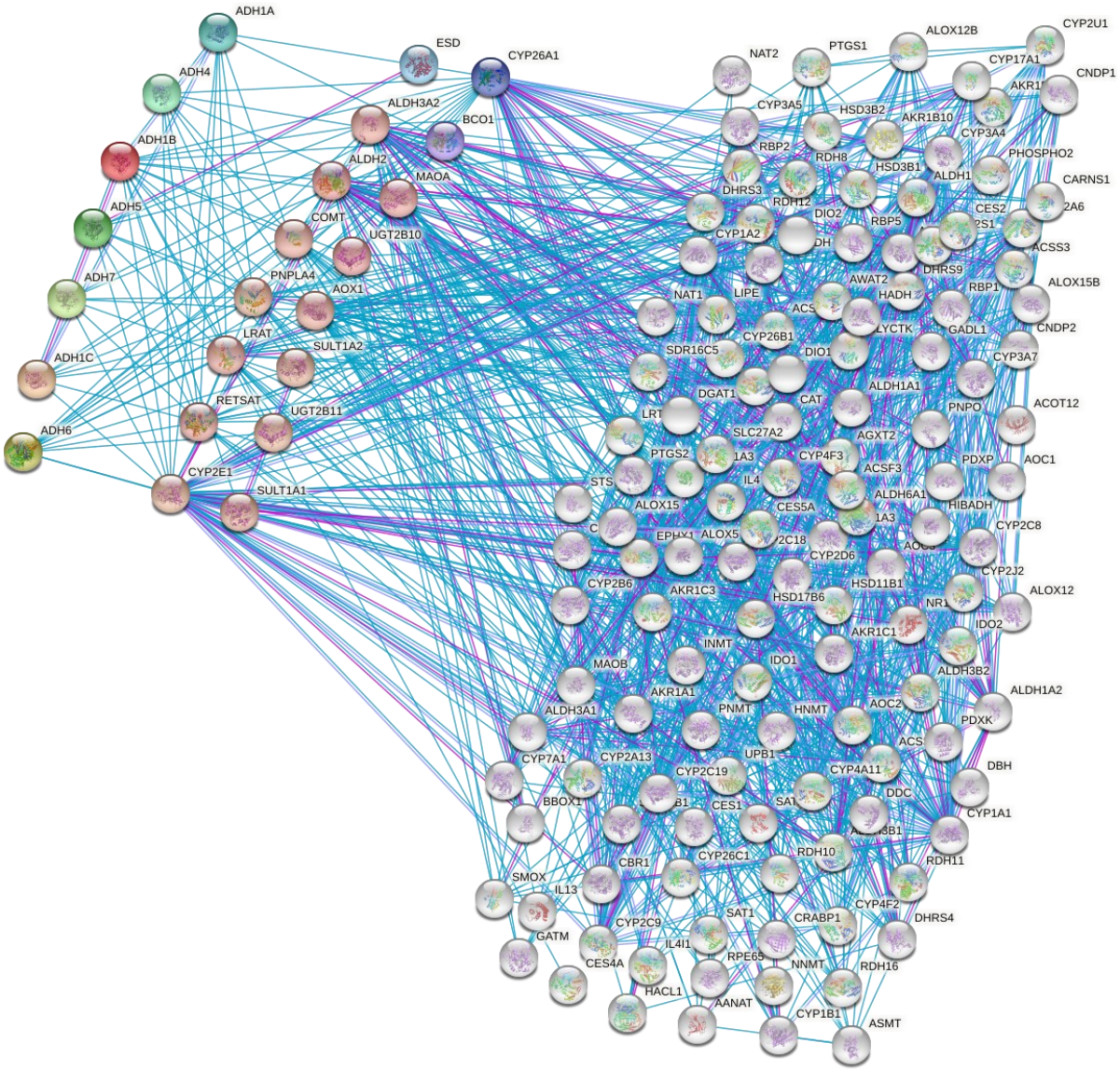
Zanamivir

1. reduces intense infiltration of pulmonary tissues by macrophages and consequent pulmonary inflammation by reducing nitric oxide production in influenza virus-infected and gamma interferon-activated RAW 264.7 macrophages(*114*)
2. reduces lung inflammation and damage by inhibiting nitric oxide production(*115*)

Oseltamivir

1. reduces intense infiltration of pulmonary tissues by macrophages and consequent pulmonary inflammation by reducing nitric oxide production in gamma interferon-activated RAW 264.7 macrophages(*114*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
FOMEPIZOLE	Alcohol dehydrogenase	ADH1A ADH4 ADH1B ADH5 ADH7 ADH1C ADH6	P07327 P08319 P00325 P11766 P40394 P00326 P28332	2



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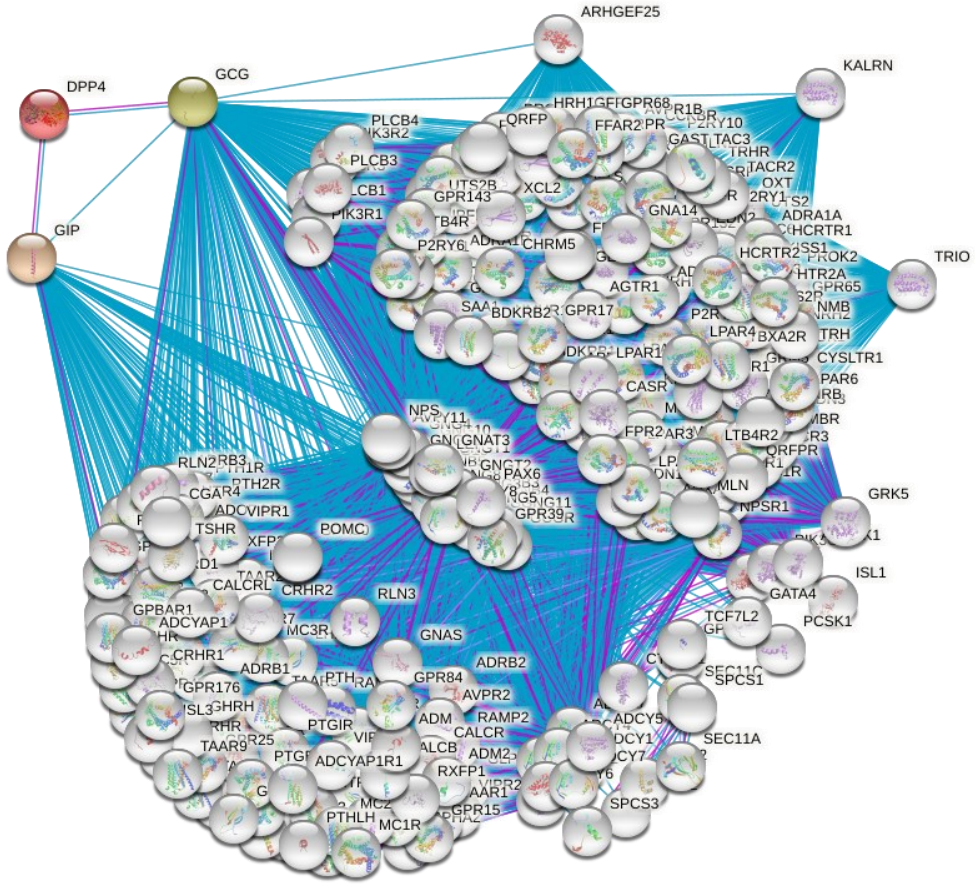
1. Protection of gastric mucosa independent of alcohol dehydrogenase inhibition and via prevention of acute vascular injury through endogenous sulfhydryls, prostaglandins(*116, 117*)
2. Gastroprotection via increasing adherent gastric mucus and reducing oxidative stress(*118, 119*)
3. Reduces catalase-H_2O_2 system activity by reducing H_2O_2 availability(*120*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
SITAGLIPTIN	dipeptidyl peptidase 4	DPP4	P27487	13
SAXAGLIPTIN				20
LINAGLIPTIN				1
ALOGLIPTIN				1



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Sitagliptin

1. in addition to its well-known hypoglycemic action, may also have beneficial effects on hyperglycemia-induced vascular changes in an endothelium-dependent manner(*121*)
2. direct influence on the diabetes-induced dysfunctional collagen metabolism(*122*)
3. prevents high glucose-induced apoptosis via activation of AMP-activated protein kinase in endothelial cells(*123*)
4. ameliorates oxidative stress in experimental diabetic nephropathy by diminishing the miR-200a/Keap-1/Nrf2 antioxidant pathway(*124*)
5. anti-inflammatory effects in adipose tissue and in pancreatic islets that accompany the insulinotropic effect(*125*)
6. prevents nitrosative stress, inflammation and apoptosis in retinal cells induced by diabetes and exerts beneficial effects on the blood-retinal barrier integrity(*126*)
7. protects against vascular inflammation via the SIRT6/ROS-dependent signaling pathway(*127*)
8. Modulation of the RBP4-GLUT4 system may be one of the mechanisms by which sitagliptin ameliorates the symptoms of type 2 diabetes mellitus(*128*).
9. reverses the diabetes-induced endothelial-mesenchymal transition of human aortic endothelial cells as well as the cardiac function through the SDF-1α/PKA pathway(*129*)
10. alleviates diabetes-induced cardiac injury by reducing nitroxidative stress and promoting autophagy(*130*)
11. improves glucose-lipid metabolism and protects kidney and vascular endothelial cells during diabetic nephropathy pathogenesis through inhibiting iNOS expression(*131*)
12. attenuates endothelial cell dysfunction and atherogenesis via attenuation of TNFα-mediated induction of NF-κB and orphan nuclear receptor NUR77 mRNA expression, inhibiting TNFα induction of PAI-1, ICAM-1 and VCAM-1 mRNA and protein expression(*132*)
13. ameliorates diabetes-induced renal injury via inhibiting the TGF-β/Smad pathway(*133*)
14. improves diabetes-induced endothelial impairment via mechanisms related to antiperoxynitrite and promoting autophagy(*134*)
15. ameliorates diabetic nephropathy fibrosis via MAPK/ERK pathway(*135*)
16. ameliorates renal tubular injury in diabetic kidney disease via STAT3-dependent mitochondrial homeostasis through SDF-1α/CXCR4 pathway(*136*)
17. ameliorates insulin resistance by inhibiting inflammatory responses and activating autophagy via AMPK/mTOR signaling pathway(*137*)

Saxagliptin

1. ameliorates insulin resistance by reducing endoplasmic reticulum stress(*138*)
2. induces β-cell proliferation through increasing stromal cell-derived factor-1α(*139*)
3. additional metabolic benefits via increased serum bile acid(*140*)

4. vascular benefits via regulating AP-1 and NF-κB(*141*)
5. prevents cell death via extrinsic and intrinsic apoptotic pathways in pancreas by insulin resistance(*142*)
6. anti-inflammatory effects via upregulation of IL-10(*143*)
7. induces insulin secretion(*144*)
8. can dose-dependently upregulate proliferator-activated receptor γ coactivator-1α and irisin, potentially improving insulin resistance and glycolipid metabolism and inhibiting inflammation(*145*)
9. ameliorates diabetes-induced renal injury via inhibiting TGF-β/Smad pathway(*146*)
10. protects β-cells in the pancreas by elongating the telomere length(*147*)
11. modulates immune-relevant pathways in beta cells which may protect them from inflammation, for example, downregulates HLA Class I and II expression and upregulates the immune-regulatory molecules PD-L1 and CTLA4(*148*)
12. improves cardiac function and glucose homeostasis and ameliorates β-Cell dysfunction via reducing S6K1 activation and IRS-1 and IRS-2 degradation(*149*)
13. attenuates high glucose-induced alterations in migration, proliferation, calcification and apoptosis of vascular smooth muscle cells via ERK1/2 pathway(*150*)
14. inhibits the tubulointerstitial Wnt/β-catenin pathway in diabetic nephropathy and provides renal protection by alleviating renal tubulointerstitial transdifferentiation and fibrosis(*151*)
15. upregulates nesfatin-1 secretion(*152*)
16. improves function of circulating proangiogenic cells(*153*)
17. delays diabetic nephropathy progression, possibly via inhibiting ERK1/2 signaling and promotion of the interaction between GLP-1 and the GLP-1 receptor(*154*)
18. accelerates endothelial regeneration through SDF-1/CXCR4 in a GLP1R-independent manner(*155*)
19. exerts direct, DPP-IV independent effects on intestinal L cells, activating cAMP and ERK1/2 signaling and stimulating total GLP-1 secretion(*156*)
20. reduces inflammatory cytokines and improves unfavorable M1/M2-like phenotypes of peripheral blood monocytes(*157*)
21. reduces insulin resistance via downregulating RBP-4
22. exerts favorable effects on the vascular endothelium by inhibiting ET-1 via suppressing the NF-κB/IκBα system through the activation of AMPK pathway(*158*)

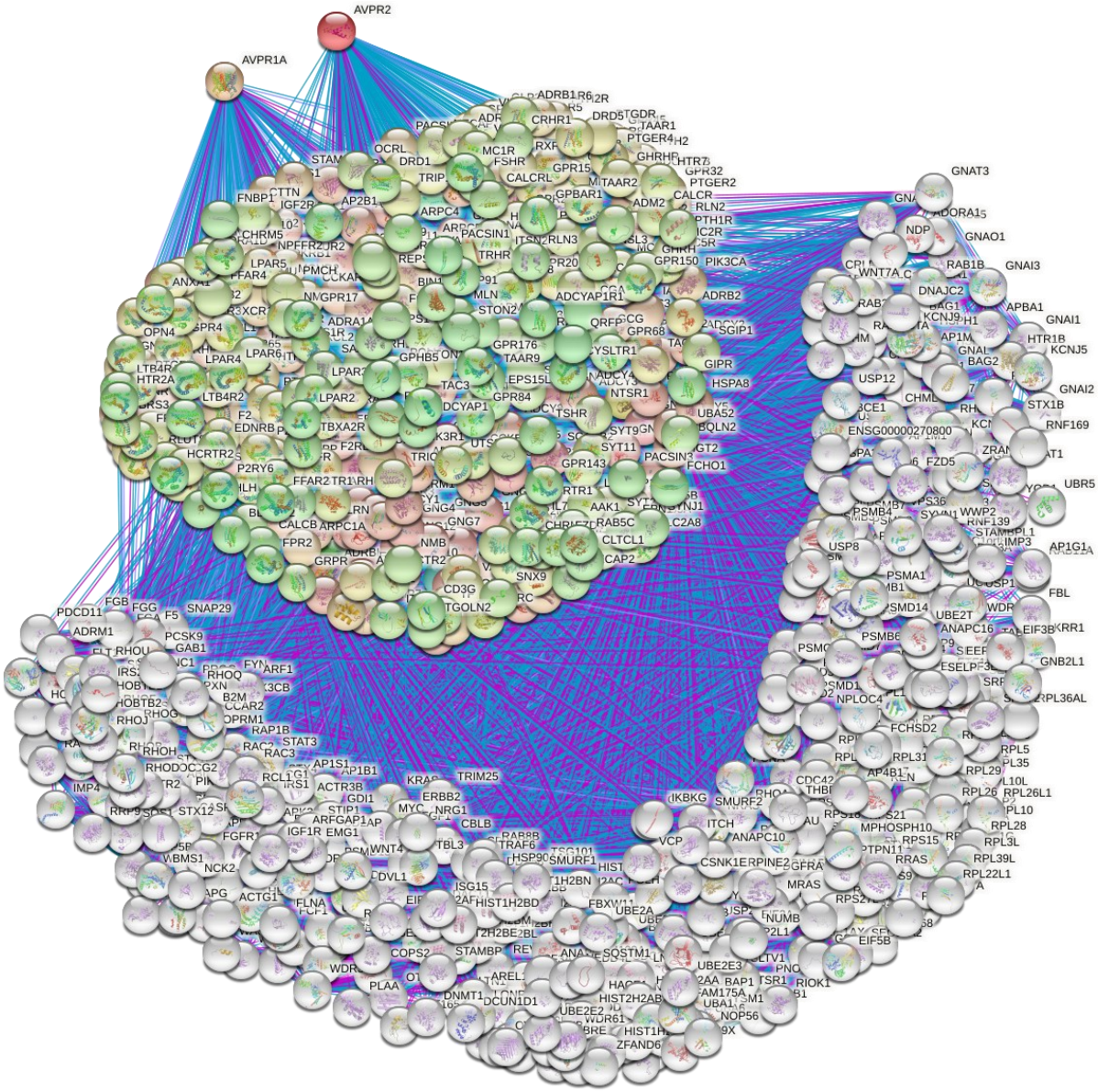
Linagliptin

1. direct protective effect on β-cell function and survival(*159*)

Alogliptin

1. alleviates diabetes-induced ventricular hypertrophy, interstitial fibrosis, atrial remodeling and diastolic dysfunction via decreasing the production of reactive oxygen species, mitochondrial membrane depolarization and improving mitochondrial swelling and biogenesis via PGC-1α/NRF1/Tfam pathway(*160, 161*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
CONIVAPTAN	V1A receptor	AVPR1A	P37288	6
TOLVAPTAN	V2 receptor	AVPR2	P30518	



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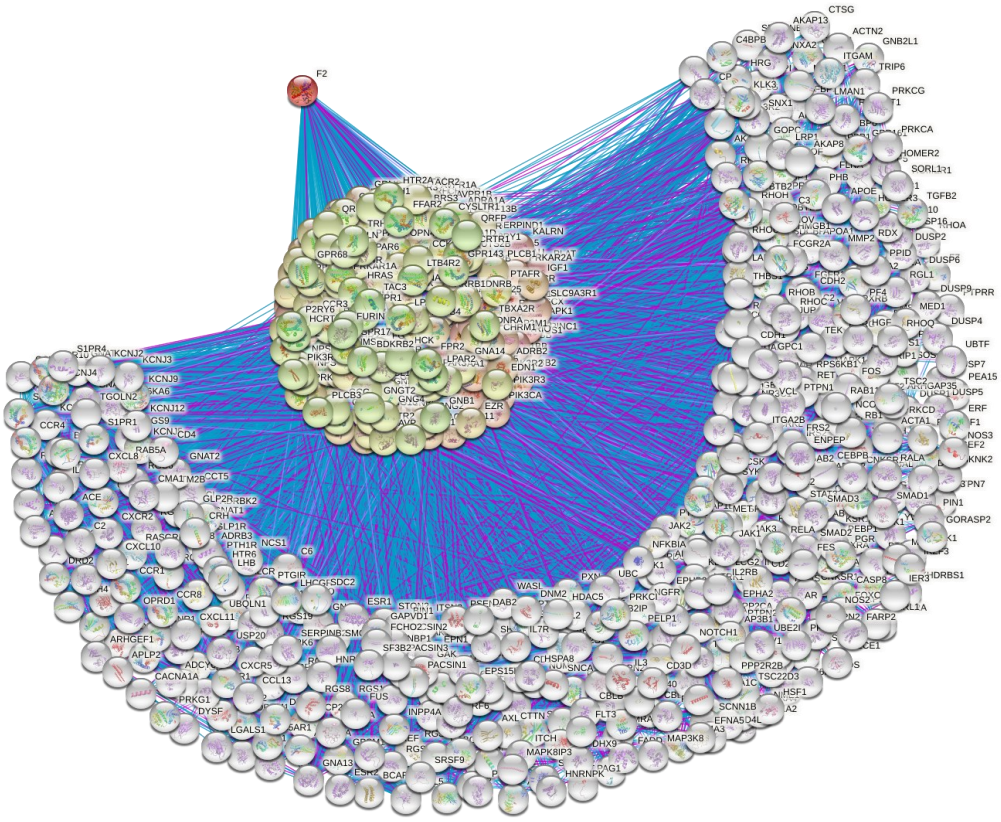
Tolvaptan

1. inhibits adrenal aldosterone synthesis via V_2 receptor-independent pathway(*162*)
2. improves renal functions via activating the Nrf2/HO-1 antioxidant pathway through PERK phosphorylation(*163*)
3. renoprotective via inhibiting TNFα and monocyte chemoattractant protein-1 expression and NFκB phosphorylation(*164*)
4. attenuates MI-induced mRNA expressions of atrial and brain natriuretic peptides, monocyte chemotactic protein-1, transforming growth factor-β1, arginine vasopressin V(1a) receptor, and endothelin-1 in the marginal infarct region(*165*)
5. beneficial effects on atrial remodeling via miR-21/Spry1/ERK/MMP-9, miR-21/PTEN/PI3K/AKT, and NF-κB pathways(*166*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
ARGATROBAN	coagulation factor II, thrombin	**F2**	P00734	1
DABIGATRAN				2



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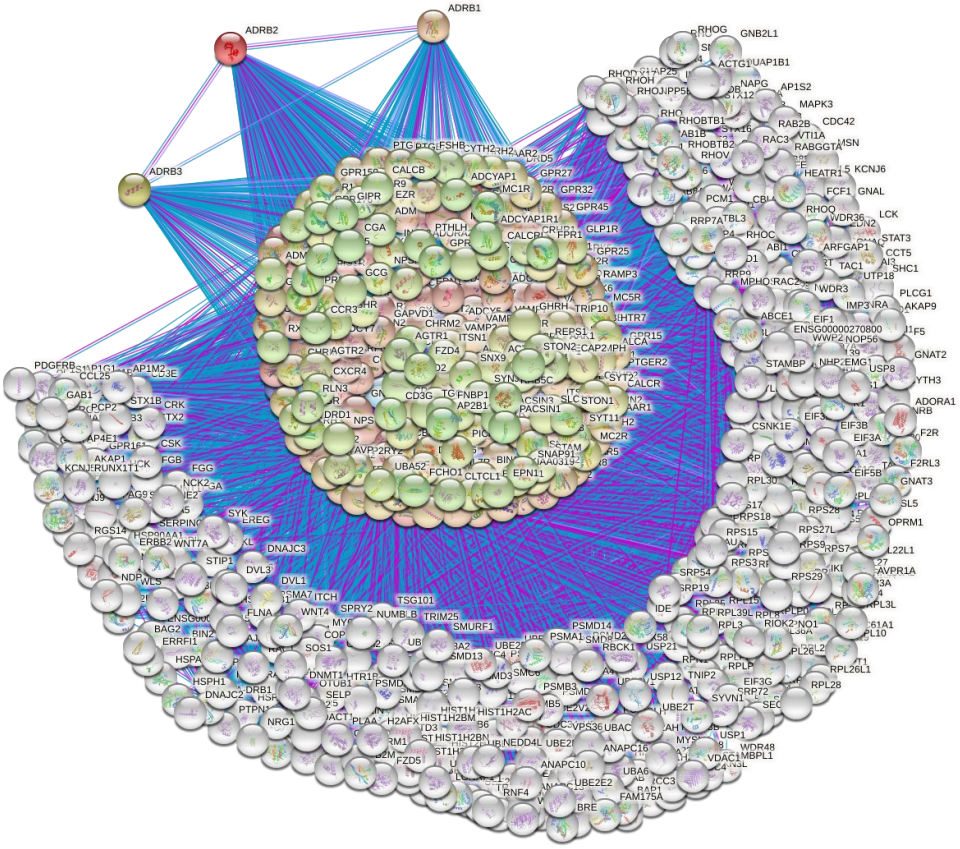
Argatroban

1. anti-inflammatory effects via nitric oxide pathway(*167*)
2. improves microcirculation through increasing plasma NO(*168*)

Dabigatran

1. reduces proinflammatory M1 macrophages in atherosclerotic lesions, thereby contributing to plaque stabilizing and atheroprotective effects(*169*)
2. reduces proinflammatory stimuli via reduced expression of cytokines and chemokines(*170*)
3. reduces DNA oxidative changes and vascular endothelial damage via inhibiting reactive oxygen species production(*111*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
MIRABEGRON **VIBEGRON**	β1-adrenoceptor β2-adrenoceptor β3-adrenoceptor	ADRB1 ADRB2 ADRB3	P08588 P07550 P13945	2



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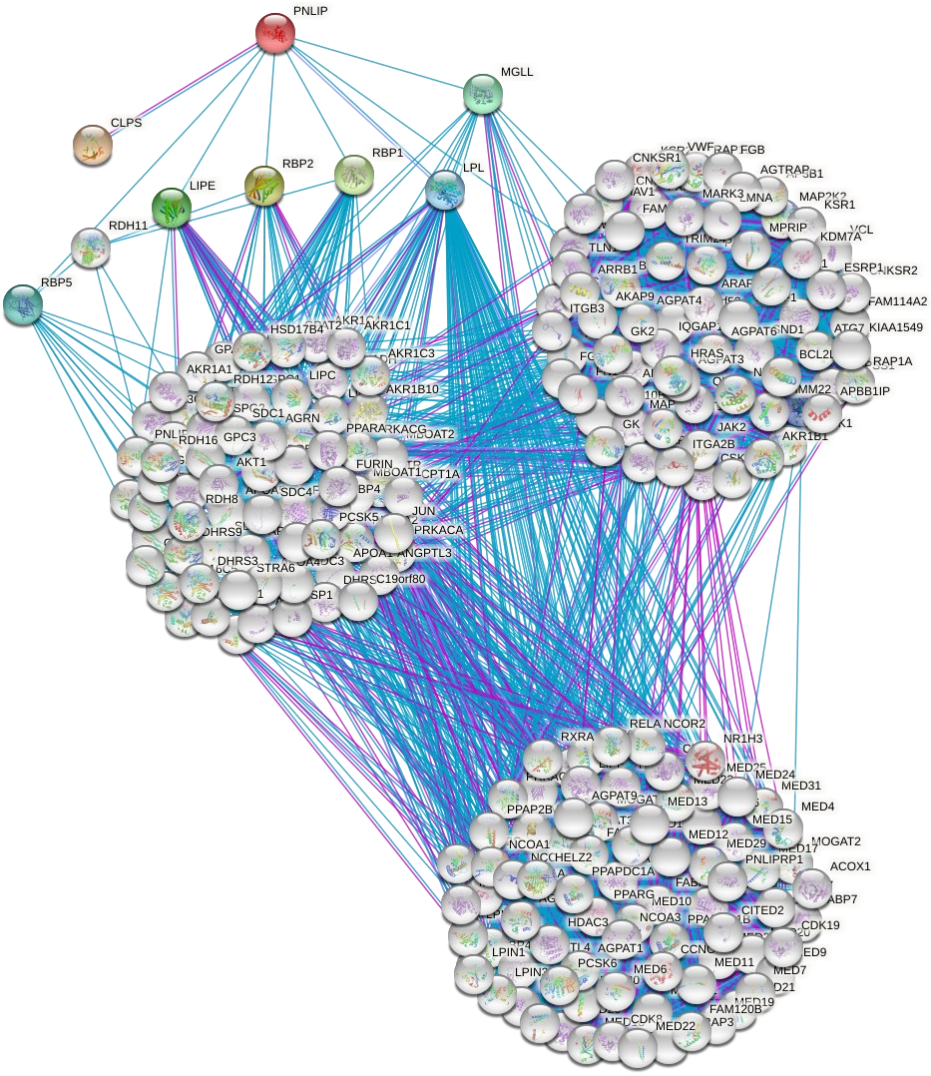
Mirabegron

1. relaxes smooth muscle also through α_{1A} and α_{1D}-adrenoceptor antagonism(*171*)
2. relaxes smooth muscle via both β3-adrenoceptor/cAMP-dependent and -independent pathways(*172*)
3. with the participation of endogenous adenosine may exert inhibitory effects on bladder functions increasing the storage capacity and prolonging the micturition interval, without affecting the voiding pressure or postvoid residual volume(*173*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
ORLISTAT	pancreatic lipase	PNLIP	P16233	10



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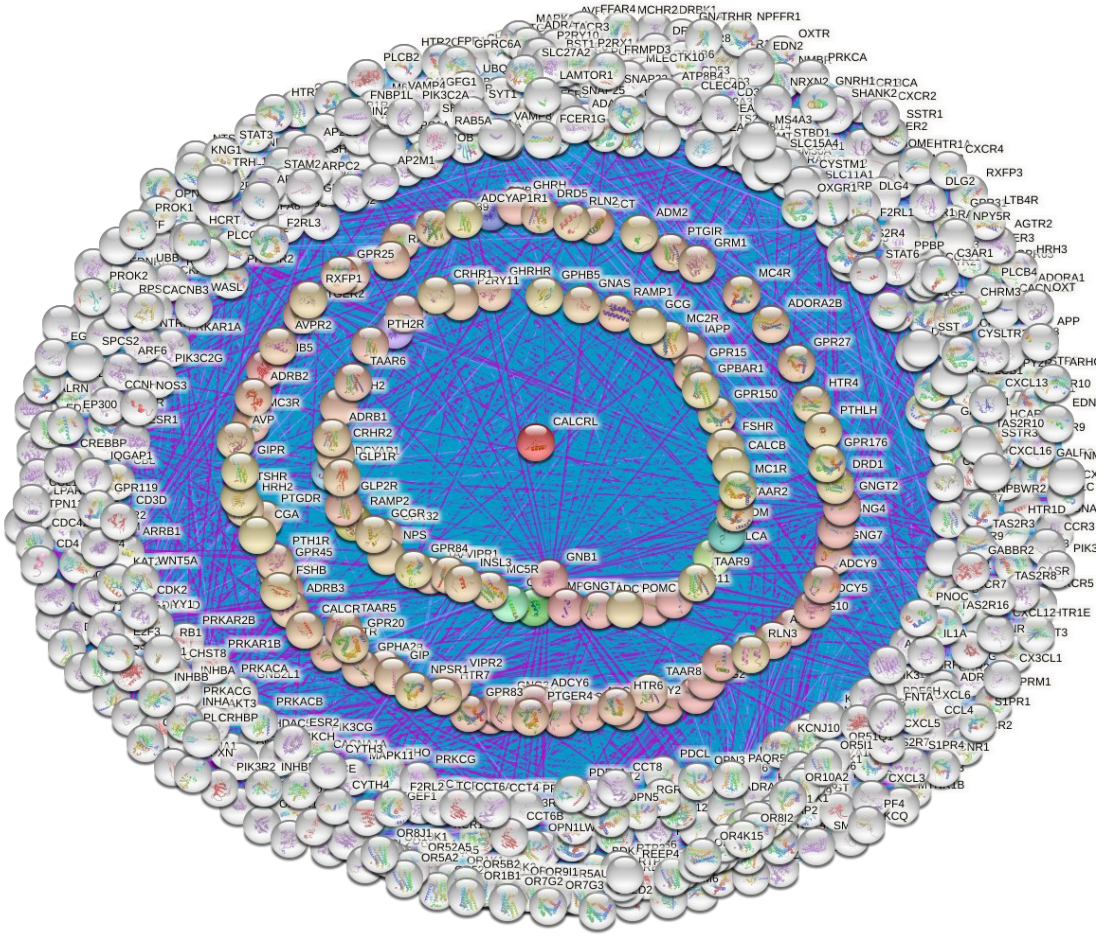
1. increases postprandial GLP-1 levels, thereby enhances insulin secretion and thus may lead to decreased food intake(*174*), also see(*175, 176*)
2. induces a weight-independent reduction in post-prandial NEFA levels along with increase in stimulated GH response, IGF-I levels, and IGF-I/IGFBP-3 ratio(*177*)
3. limits cholesterol absorption by the inhibition of Niemann-Pick C1-like 1 transport protein(*178*)
4. other targets identified by activity-based proteome profiling which have functions related to biogenesis, glycolysis, protein biosynthesis and GTPase activity: Hsp90AB1, RPL14, RPS9, GAPDH, ANXA2, β-tubulin, RPL7a(*179*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
UBROGEPANT **RIMEGEPANT**	Calcitonin receptor-like receptor	CALCRL	Q16602	1



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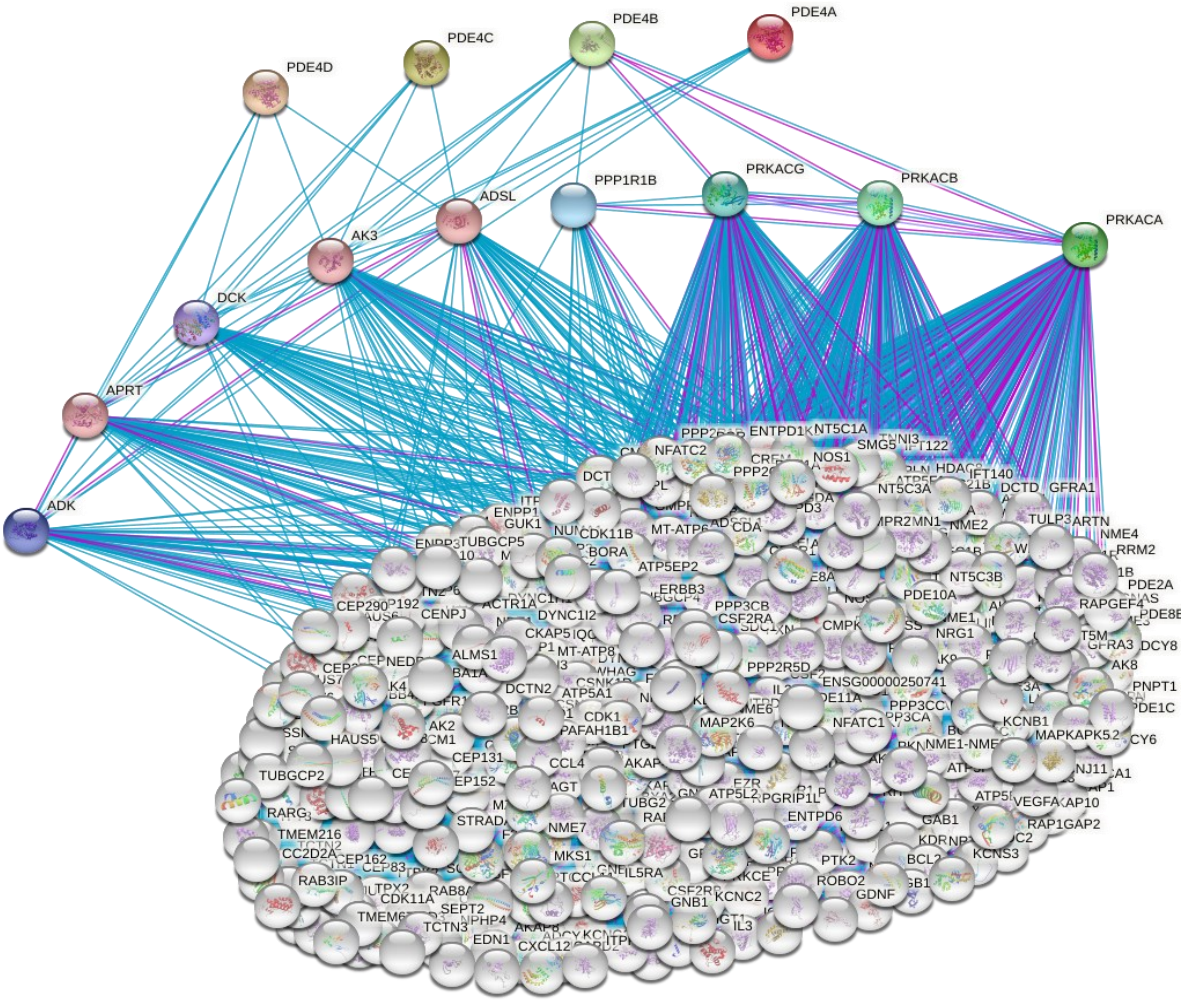
Rimegepant

1. effectively antagonizes αCGRP-mediated signaling through the AMY_1 receptor, in addition to the CGRP receptor(*180*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
ROFLUMILAST	phosphodiesterase 4A/4B/4C/4D	PDE4A PDE4B PDE4C PDE4D	P27815 Q07343 Q08493 Q08499	9



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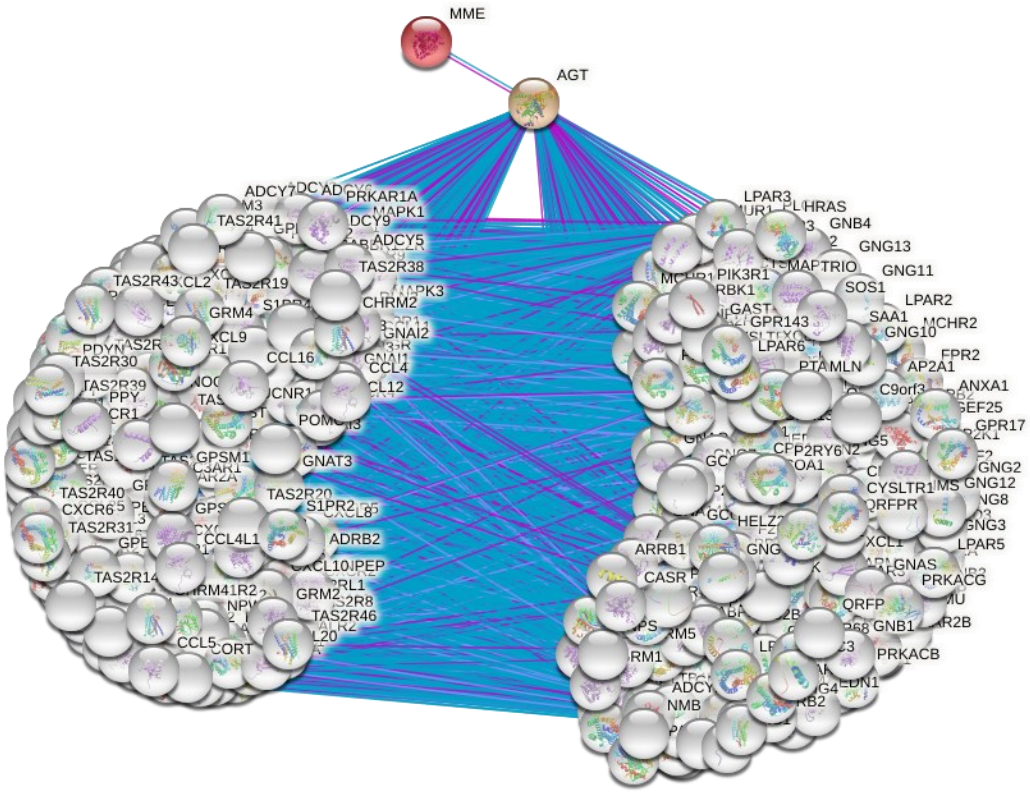
1. inhibits inflammatory mediators via suppression of NFκB, p38 mitogen-activated protein kinase, and c-jun NH2-terminal kinase activation(*181*)
2. may modulate the SCF/c-kit pathway(*182*)
3. suppresses T cell proliferation by interfering with IP3-IP3R binding to inhibit calcium emission, blocking pathway activation from this phase onward, eventually decreasing the level of a growth factor for T cell proliferation, IL-2(*183*)
4. modulates heme oxygenase-1 and its product carbon monoxide(*184*)
5. activates cystic fibrosis transmembrane conductance regulator (CFTR)(*185*)
6. upregulates glucocorticoid receptor (GRα) transcript levels(*186*)
7. inhibits leukocyte-endothelial cell interactions, expression of adhesion molecules and microvascular permeability(*187*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
SACUBITRILAT	Neutral endopeptidase	MME	P08473	2



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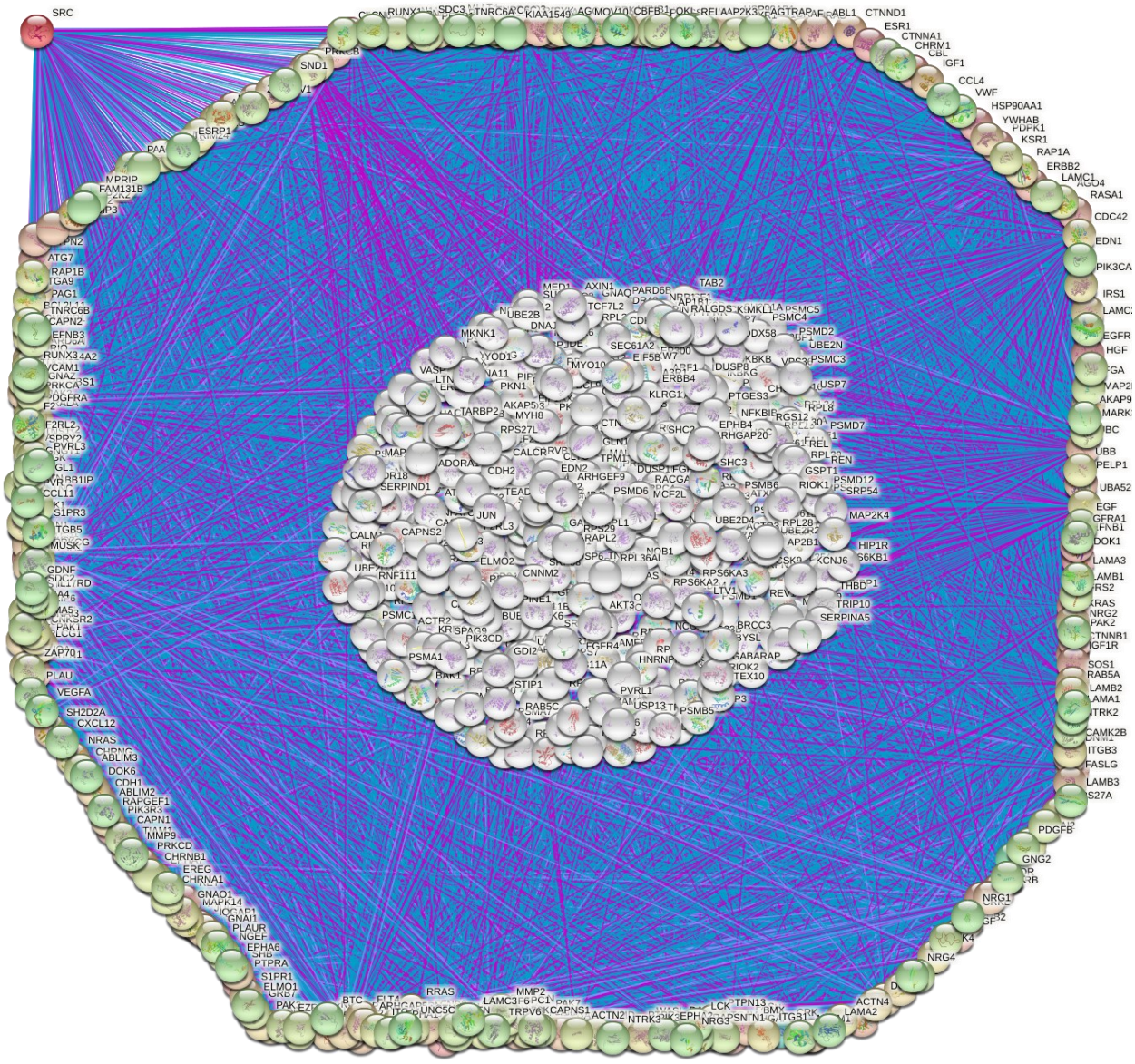
1. directly improves Ca^{2+} homeostasis by reducing proarrhythmogenic sarcoplasmic reticulum Ca^{2+} leak without acutely affecting systolic Ca^{2+} release and inotropy. These effects might contribute to its mortality benefits(*188*).
2. antioxidant properties(*189*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
TIRBANIBULIN	SRC proto-oncogene, non-receptor tyrosine kinase	SRC	P12931	2



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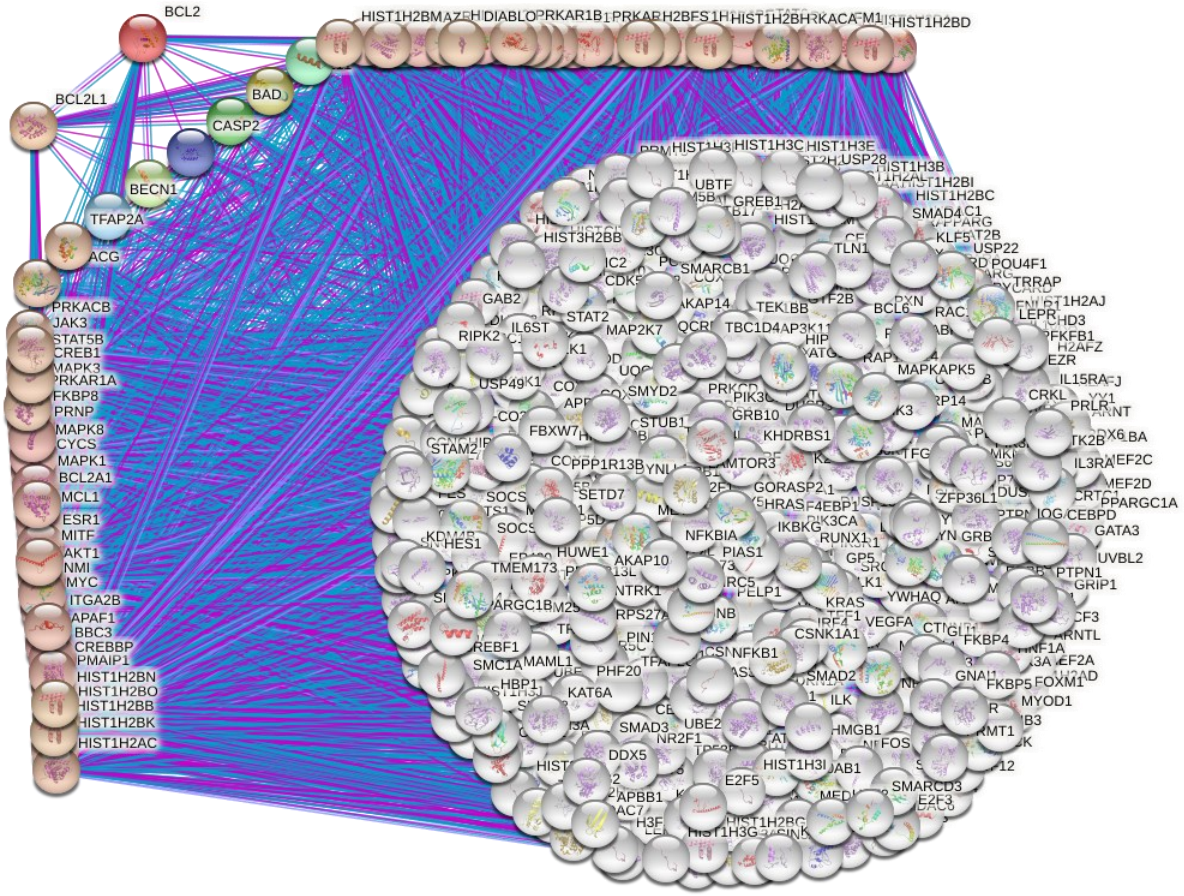
1. inhibits pre-tubulin and tubulin polymerization(*190*)

2. also inhibits additional key proteins involved in cell proliferation and fatty acid metabolism(*190*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
VENETOCLAX	Bcl-xL Bcl-2	BCL2L1 BCL2	Q07817 P10415	2



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1. modulates the mitochondrial signaling pathway and ATP production(320, 321)

2. inhibits Nrf2 antioxidant pathway activation induced by hypomethylating agents(322)

Drugs			Discovery Target
SAQUINAVIR: 11	**NELFINAVIR: 8**	**DARUNAVIR**	HIV Protease
RITONAVIR: 8	**LOPINAVIR: 2**	**AMPRENAVIR**	
INDINAVIR: 7	**ATAZANAVIR: 1**	**TIPRANAVIR**	

Saquinavir

1. immunomodulation via upregulation of telomerase activity and interferon-gamma release in activated nonadherent mononuclear cells(*191*)
2. direct immunomodulatory effects(*192*)
3. enhances the humoral immune response, possibly through modulating T cell functions(*193*)
4. It reduces the release of interleukin 2 probably via direct interaction with one or more of the transport or regulatory drug binding sites of P-glycoprotein. Given that activated lymphocytes preferentially replicate HIV-1, this inhibitory effect may be beneficial(*194*). Also see (*195*)
5. inhibits apoptosis by mitigating oxidative stress(*196*)
6. increases interferon gamma production from stimulated splenocytes(*195*)
7. inhibits pathological inflammation by targeting the interaction of cathepsin V with TLR4/MyD88(*197*)
8. protective effect on ventilation-induced lung injury via inhibition of NF-κB activation and high-mobility group box 1 expression(*198*)
9. inhibits HIV replication not only by inhibiting the HIV protease but also by blocking microbial antigen-induced endothelial cell activation via blocking the TLR-and TNF-α-mediated NF-κB activation and proinflammatory cytokine production(*199*)
10. modulates antigen presentation, and T cell responses via inhibiting the chymotrypsin-like activity of the 20S proteasome(*200*)
11. immunomodulation via regulating the maturation of dendritic cells(*201*)
12. strong inhibitory effect on the T cell stimulatory capacity of mature dendritic cells(*201*)
13. inhibits TNF-alpha induced cell death(*202*)

Ritonavir

1. regulates T cell receptor excisional circles(*203*)
2. modulates antigen presentation, and T cell responses via inhibiting the chymotrypsin-like activity of the 20S proteasome(*200, 204, 205*)
3. inhibits apoptosis via inhibiting calpain(*206*)

4. induces cell-cycle arrest at G1-phase and apoptosis through downregulation of cell-cycle gene cyclin D2 and antiapoptotic gene survivin. Also, it suppressse transcriptional activation of NF-κB in these cells. Thus, it may prevent EBV-associated lympho-proliferative diseases that occur in immunocompromised patients(*207*).

5. inhibits HIV replication not only by inhibiting the HIV protease but also by blocking microbial antigen-induced endothelial cell activation via blocking the TLR-and TNF-α-mediated NF-κB activation and proinflammatory cytokine production(*199*)

6. It reduces the release of interleukin 2 probably via direct interaction with one or more of the transport or regulatory drug binding sites of P-glycoprotein. Given that activated lymphocytes preferentially replicate HIV-1, this inhibitory effect may be beneficial(*194*).

7. modulates activation of peripheral blood CD4(+) T cells and decreases their susceptibility to apoptosis(*208*)

8. stimulates hematopoiesis and decreases apoptosis and ICE expression in CD34(+) cells(*209*)

9. is an immune modulator that may affect leukocyte activation and apoptosis as an important part of its therapeutic benefit(*210*)

10. immunomodulation via regulating the maturation of dendritic cells(*201*)

11. inhibits TNF-alpha induced cell death(*202*)

12. direct immunomodulatory effects(*192*)

Indinavir

1. inhibits HIV replication not only by inhibiting the HIV protease but also by blocking microbial antigen-induced endothelial cell activation via blocking the TLR-and TNF-α-mediated NF-κB activation and proinflammatory cytokine production(*199*)

2. inhibits apoptosis via inhibiting calpain(*206, 211*)

3. It reduces the release of IL-2 probably via direct interaction with one or more of the transport or regulatory drug binding sites of P-glycoprotein. Given that activated lymphocytes preferentially replicate HIV-1, this inhibitory effect may be beneficial(*194*).

4. independent of its antiviral activity, may modulate immunologic responses by prolonging cell survival via inhibiting their entry into cell cycle(*212*)

5. immunomodulation via regulating the maturation of dendritic cells(*201*)

6. slightly affects the dendritic cell induced proliferation of T cells(*201*)

7. induces restoration of both memory and naive CD8 T cells and improves T cell function, as assessed by enhanced lymphoproliferative capacity and diminished propensity to undergo apoptosis(*213*)

8. immunoregulation by regulating dendritic cells' functions and antifungal activity(*214*)

9. inhibits the trypsin-like and mostly chymotrypsin-like activities of purified 26S proteasome(*215*)

10. inhibits TNF-alpha induced cell death(*202*)

Nelfinavir

1. inhibits HIV replication not only by inhibiting the HIV protease but also by blocking microbial antigen-induced endothelial cell activation via blocking the TLR-and TNF-α-mediated NF-κB activation and proinflammatory cytokine production(*199*)
2. modulates activation of peripheral blood CD4(+) T cells and decreases their susceptibility to apoptosis(*208*)
3. protects against apoptosis via inhibiting the adenine nucleotide translocator pore function(*216*)
4. immunomodulation via regulating the maturation of dendritic cells(*201*)
5. inhibits host proteases and reduces immature dendritic cell transendothelial migration(*217*)
6. activates PP2 and inhibits MAPK signaling in macrophages and may offer beneficial effects independent of antiviral activity by reducing severity of chronic innate immune activation in HIV-1 infection(*218*)
7. It triggers inflammasome formation and elicits an IL-1R-dependent inflammation. Inflammasomes are critical sensors that convey cellular stress and pathogen presence to the immune system(*219*).
8. inhibits HIV gp41-induced mitochondrial depolarization, unlike other HIV protease inhibitors or inhibitors of calpain and cathepsin(*220*)
9. augments thymic output independent of HIV(*221*)
10. increases CD4 T cells through a non-viral effect(*222*)
11. may exert some beneficial effects counteracting the increased mitochondrially driven apoptosis present in HIV-infected people(*223*)

Lopinavir

1. increases IL-8 mRNA expression(*224*)
2. upregulates expression of the antiviral protein ribonuclease L(*225*)

Atazanavir

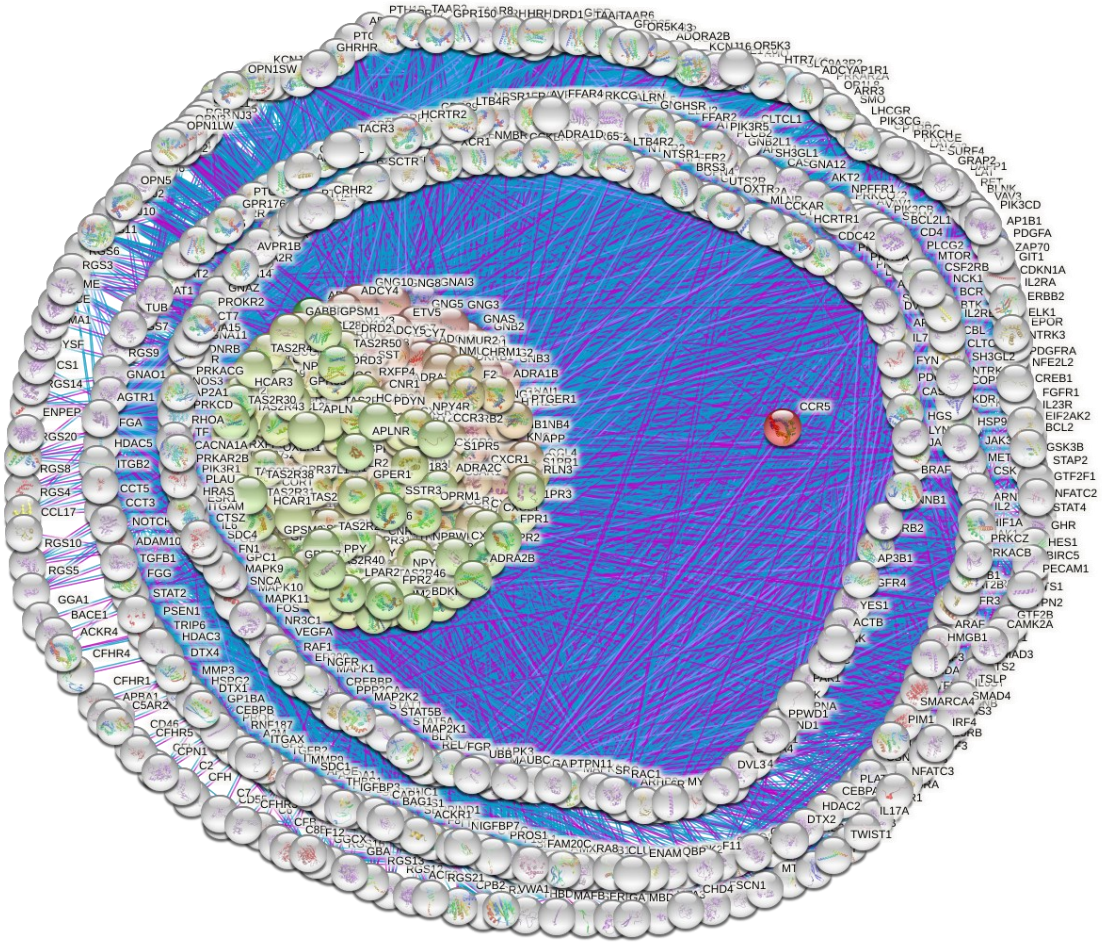
1. increases IL-8 mRNA expression(*224*)

Drugs		Discovery Target
RALTEGRAVIR	**ELVITEGRAVIR**	HIV Protease
DOLUTEGRAVIR	**BICTEGRAVIR**	

Raltegravir

has profound and specific effects on the host transcription profile that may contribute to the overall antiviral activity of the drug(*226*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
MARAVIROC	CCR5	CCR5	P51681	3



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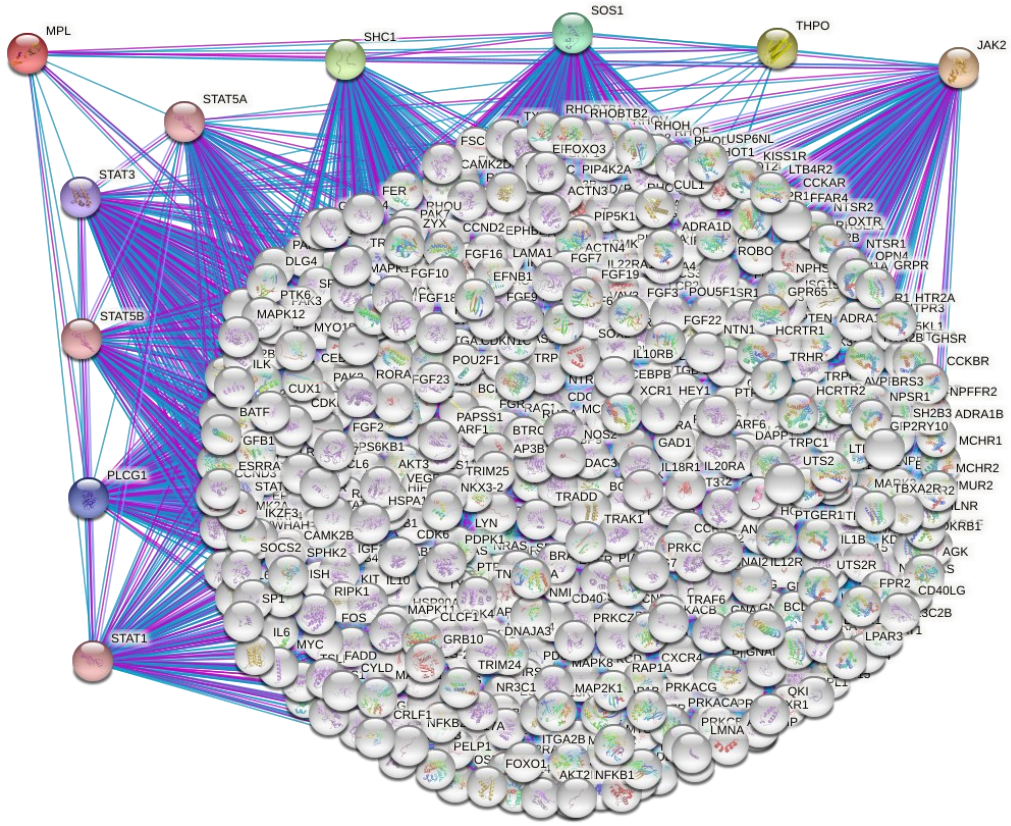
1. It has additional immunological effects via decreasing some activation expression markers on T lymphocytes and also migration towards chemoattractants that might have potential capacity to inhibit HIV-associated chronic inflammation and activation, both by directly affecting T cell activation and by reducing entrapment of lymphocytes in lymph nodes(*227*).
2. may prevent neurologic disorders in HIV-infected individuals by also reducing inflammation in the brain(*228*)
3. contributes to the restoration of the homeostasis of regulatory T cell subsets(*229*)
4. downregulates HIV-associated chronic inflammation by blocking the recirculation and trafficking of macrophages and monocyte-derived dendritic cells(*230*)

5. reduces chronic inflammation via reducing activation and cytokine secretion of CD8+ T cells via a CCR5-independent pathway(*231*)
6. increases T cell activation(*232*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
ELTROMBOPAG **LUSUTROMBOPAG** **AVATROMBOPAG**	Thrombopoietin receptor	MPL	P40238	1



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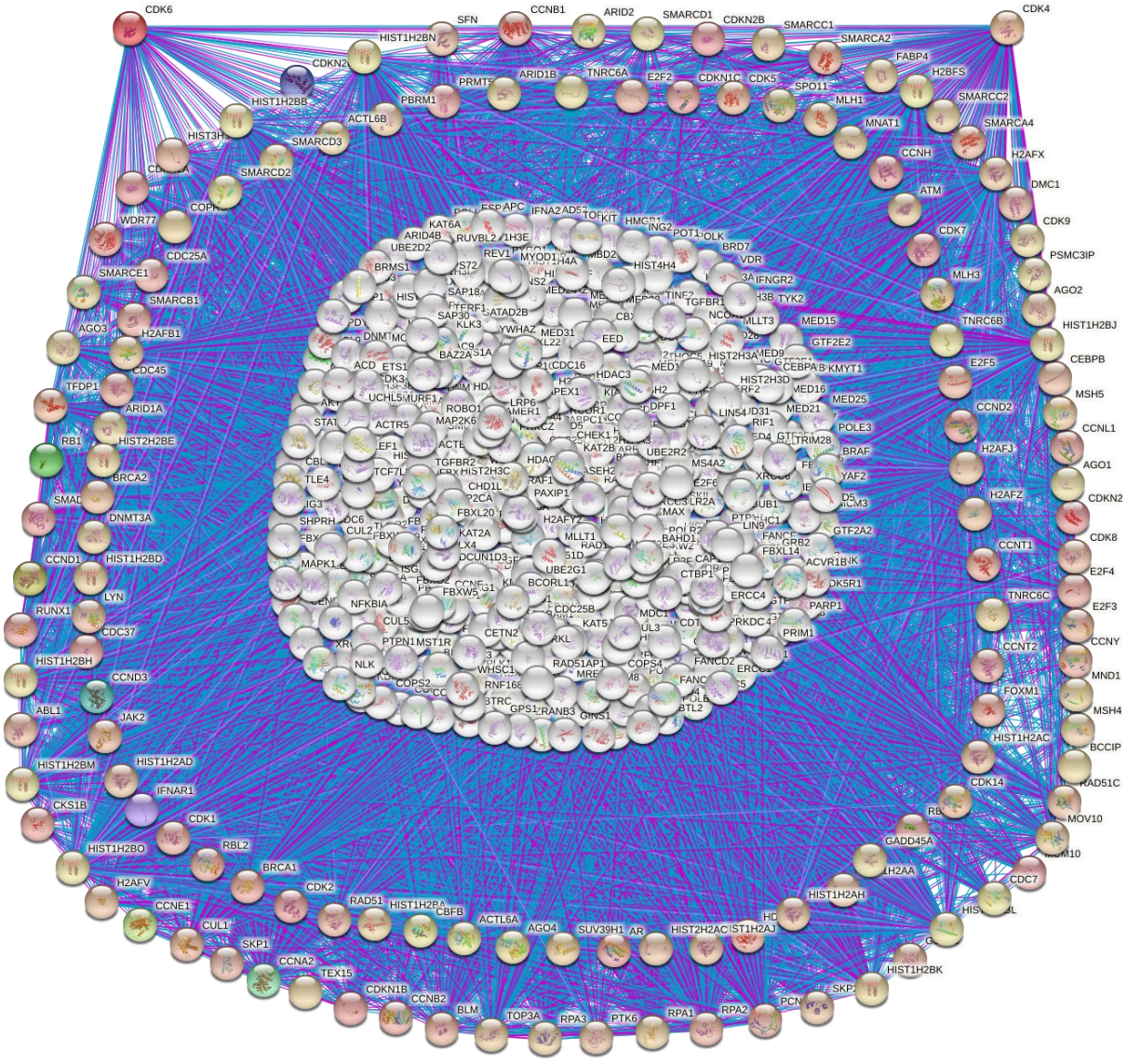
Eltrombopag: stimulates hematopoiesis at the stem cell level through iron chelation–mediated molecular reprogramming, independent of thrombopoietin receptor(*233*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
PALBOCICLIB	CDK4 CDK6	CDK4	P11802 Q00534	38
RIBOCICLIB				14
ABEMACICLIB		CDK6		17



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Palbociclib

1. induces senescence via activating proteasome(*234*)
2. activates p53 via inhibition of the PRMT5-MDM4 axis(*235*)
3. inhibits other kinases(*236*):
    1) AAK1
    2) AMPKα1
    3) BMP2K
    4) CAMK2D
    5) CAMK2G
    6) CDK9
    7) CSNK2α1
    8) CSNK2α2
    9) DAPK3
    10) ERK2
    11) FAK
    12) FER
    13) GSK3β
    14) JNK1
    15) JNK2
    16) PIP4K2A
    17) PIP4K2B
    18) PIP4K2C
    19) PRKD2
    20) PRKD3
    21) RSK1
    22) TNK1
    23) AXL
    24) CDK11B
    25) CDK17
    26) IRAK1
    27) PIK3C3
    28) PIK3CD
    29) PIK3R4
    30) MSK2
    31) ATM
    32) TBK1
    33) TTK
    34) PYK2
    35) TAOK3
4. induces apoptosis via activating CDK2(*237*)
5. inhibits metastasis via downregulating the c-Jun/COX-2 pathway(*238*)
6. induces apoptosis via the PP5/AMPK axis(*239*)
7. inhibits other kinases(*240*):
    1) CAMK2D (CaMKII δ)
    2) TTK
    3) CLK1
    4) CLK2

Ribociclib

1. induces senescence through downregulation of the transcriptional expression of MYBL2(*241*)
2. inhibits other kinases(*240*):
    1) CDK9/cyclin T1

2) CAMK2D (CaMKII δ)
3) TTK
4) CAMK2A (CaMKIIα)

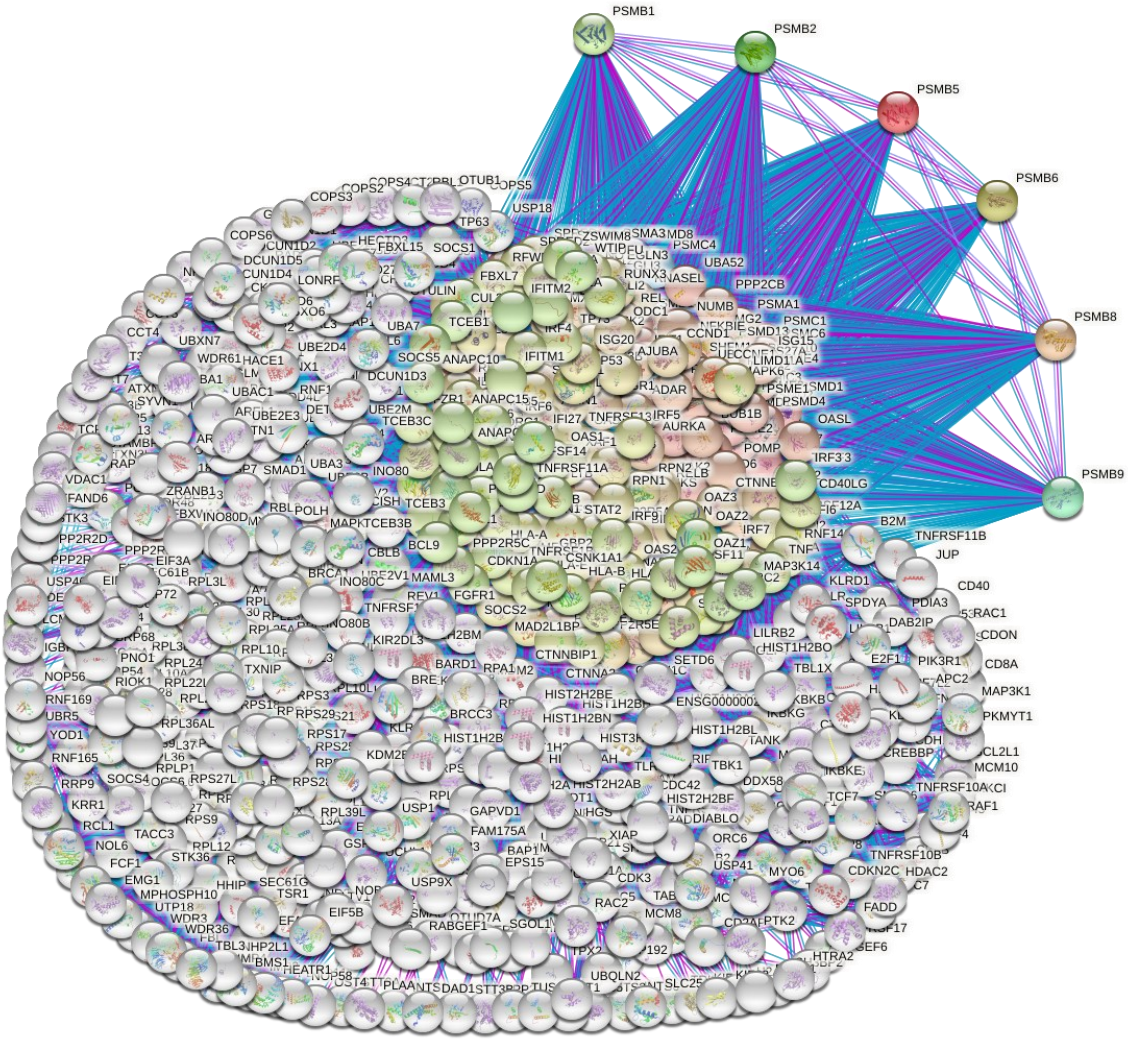
3. inhibits other kinases(*236*):
   1) CAMK2D
   2) CAMK2G
   3) CDK9
   4) GAK
   5) AURKA
   6) PRKD2
   7) FER
   8) TNK1
   9) FAK

Abemaciclib

1. upregulates antigen processing and presentation on tumor cells(*242, 243*)
2. elevates secreted proinflammatory cytokines(*243*)
3. markedly upregulates the canonical interferon signaling pathway(*243*)
4. activates T cells(*242*)
5. inhibits other kinases(*240*):
   1) CDK9/cyclin T1
   2) CDK9/cyclin K
   3) CDK1/cyclin B
   4) CDK2/cyclin A1
   5) CDK2/cyclin E1
   6) GSK3B (GSK3β)
   7) CAMK2D (CaMKII δ)
   8) TTK
   9) PRKCG (PKC γ)
   10) GSK3A (GSK3 α)
   11) PRKCA (PKC α)
   12) PRKCB1 (PKC β1)
   13) DYRK1A AAK1
   14) CAMK2G (CaMKII γ)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
BORTEZOMIB	Proteasome	PSMB1	P20618	69
		PSMB2	P49721	
CARFILZOMIB		PSMB5	P28074	2
		PSMB6	P28072	
IXAZOMIB		PSMB8	P28062	
		PSMB9	P28065	

Note: Here, because of the central role of proteasome in various downstream processes, to identify the downstream effects of inhibiting proteasome, I also took benefit from the results of the study "Genome-wide siRNA screen for modulators of cell death induced by proteasome inhibitor bortezomib(*244*)," in addition to using the interactors reported by STRING.



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Bortezomib

1. primes hepatoma cells for natural killer cell antitumor reactivity(*245*)
2. increases cellular ceramide production to promote cell apoptosis(*246*)
3. downregulates Stat3 activity(*247*)
4. in addition to the abolishment of the pro-survival NF-κB, directly induces apoptosis by activating proapoptotic endoplasmic reticulum stress-reactive oxygen species signaling cascades(*248*)
5. induces apoptosis and a decrease of both IL-6/IL-10 secretion and STAT3 phosphorylation(*249*)
6. disrupts tumor-dendritic cell interactions(*250, 251*)
7. stabilizes mitotic cyclins and prevents cell cycle progression via inhibition of UBE2C(*252*)
8. Microarray chips revealed multiple signaling pathways targeted by bortezomib, including endoplasmic reticulum, Wnt-β,

and calcium-mediated pathway, with possible targets including UBD, CUL3, HDAC6, and GADD45A(*253*)

9. sensitizes tumor cells to natural killer cells via endoplasmic reticulum-stress induced reduction of cell surface HLA-E which is exclusively controlled by the inhibitory receptor NKG2A(*254, 255*)
10. can render tumor cells immunogenic by upregulating the cell surface expression of heat shock protein 60 and heat shock protein 90(*256*)
11. improves the functions of dendritic cells and consequently exerts potent immune-mediated antitumor effects(*256*)
12. exerts numerous effects on the immune system(*257, 258*)
13. induces miRNAs that direct epigenetic silencing of locus genes and trigger apoptosis in leukemia, like miRNA/Ago2/YY1/PcG(*259*)
14. downregulates telomerase and disrupts telomere homeostasis and function(*260, 261*)
15. Dysregulation of unfolded protein response partially underlies its proapoptotic activity(*262*)
16. induces a quick increase in reactive oxygen species production and subsequently decreases the glutathione levels(*263*)
17. induces upregulation of the cell cycle inhibitor p21(WAF1) and the proapoptotic protein Noxa as well as cleavage of the anti-apoptotic protein Mcl-1(*264-270*)
18. It induces proteasome-independent degradation of the TRAF6 protein, but not mRNA. The reduction in TRAF6 protein coincides with bortezomib-induced autophagy, and subsequently with apoptosis(*271*).
19. inhibits the expression of SALL4 gene as well as C-mye and CCND1 downstream in the Wnt/β-catenin signaling pathway(*272*)
20. inhibits steroid receptor coactivator-3 degradation which leads to activated Akt(*273*)
21. Its apoptosis induction is dependent on caspase-2 activation, which is associated with ER stress and required for release of cytochrome c, breakdown of mitochondrial transmembrane potential, and its downstream caspase-9 activation(*274*).
22. abrogates IL-6 triggered signaling cascades via caspase-dependent downregulation of gp130(*275*)
23. induces G2-M arrest through reactive oxygen species-inducible phosphorylation of ATM-CHK1(*276*)
24. might inhibit cells migration and invasion function by downregulation of Tyr397 expression(*277*)
25. decreases ErbB family expression through lysosomal degradation pathway in a heat shock protein 90 (HSP90)-dependent manner(*278*)
26. induces growth arrest and apoptosis by blockade of the androgen receptor signaling pathway and downregulating the prostate-specific antigen (PSA)(*279, 280*)
27. sensitizes tumor cells to natural killer cell recognition by induction of NKG2D ligands(*281*)
28. induce FLT3-ITD degradation through autophagy(*282*)

29. inhibits angiogenesis(*283-286*)
30. relieves tumor immune tolerance via STAT1 suppression and indoleamine 2,3-dioxygenase downregulation(*287*)
31. induces the expression of gene products associated with the endoplasmic reticulum secretory pathway like(*288*):
    1) BCL2-associated athanogene 3 (BAG3)
    2) calreticulin, heat shock 70 kDa protein 1A (HSPA1A)
    3) VAMP-associated protein of 33 kDa mRNA
    4) heat shock 70 kDa protein 1B (HSPA1B)
    5) ATP-binding cassette
    6) subfamily F (GCN20)
    7) member 2 (ABCF2)
    8) EST pseudogene similar to UBL1 [ubiquitin-like 1 (sentrin)]
    9) Sec23-interacting protein p125
32. induces apoptosis via Bim and Bik upregulation(*289, 290*)
33. promotes the apoptosis potentially by downregulating the expression of HSP27(*291*)
34. It both inhibits VEGF-triggered caveolin-1 phosphorylation and markedly decreased caveolin-1 expression. Consequently, it inhibits VEGF-induced tumor cell migration. It also decreases VEGF secretion in the bone marrow microenvironment and inhibits VEGF-triggered tyrosine phosphorylation of caveolin-1, migration, and survival in human umbilical vascular endothelial cells(*292*).
35. It significantly affects the expression of these targets independent of p-53(*293*):
    1) Heat shock cognate 71 kDa protein (HSPA8)
    2) Heat shock protein HSP 90 alpha (HSP90AA1)
    3) Heat shock 70 kDa protein 1B (HSPA1B)
    4) Importin subunit alpha-2 (Kpna2)
    5) Hist1h3b
    6) Psmc3
    7) Psmd14
    8) Sqstm1
    9) Gnas
    10) Rps10
    11) Psma5
    12) PPlase B
    13) Psmb1
    14) ATP5F1
    15) RPS15a
    16) Psmb2
    17) Hadha
    18) Myo1c
    19) Hsd17b10
36. induces apoptosis through microRNA-17-5p by targeting p21(*294*)
37. reduces the RANKL expression, inhibits cell proliferation and activates caspase-3 activity to induce cell apoptosis(*295*)
38. induces apoptosis via inhibition of cancerous inhibitor of protein phosphatase

2A (CIP2A)-mediated PP2A dependent Akt activation, independent of proteasome inhibition(*296-299*)

39. triggers apoptosis by enhancing the caspase 3 activation(*300*)
40. reduces tumorigenicity via downregulation of upregulated targets in side population cells(*301*)
41. induces apoptosis via activation of the p38 mitogen-activated protein kinase pathway(*302*)
42. stabilizes NOXA and triggers reactive oxygen species-associated apoptosis(*303, 304*)
43. inhibits prosurvival autophagy, in addition to its known function in blocking the proteasome(*305*)
44. induces apoptosis via activation of sterile20-like kinase 1 (MST1)(*306*)
45. induces an inhibitory chromatin environment at a distal enhancer of the estrogen receptor-α gene(*307*)
46. inhibits cellular growth of vascular endothelial cells through suppression of G2/M transition(*308*)
47. inhibited the progression of tumor cells via upregulation of the expression of miR-198(*309*)
48. sensitizes tumor cells to induction of apoptosis by type I interferons through NOXA expression and Mcl-1 cleavage(*310*)
49. augments lymphocyte stimulatory cytokine signaling in the tumor microenvironment to sustain CD8+T cell antitumor function(*311*)
50. induces lysosomal cathepsin B release and a caspase-2-dependent mitochondrial permeabilization and apoptosis(*312*)

Carfilzomib

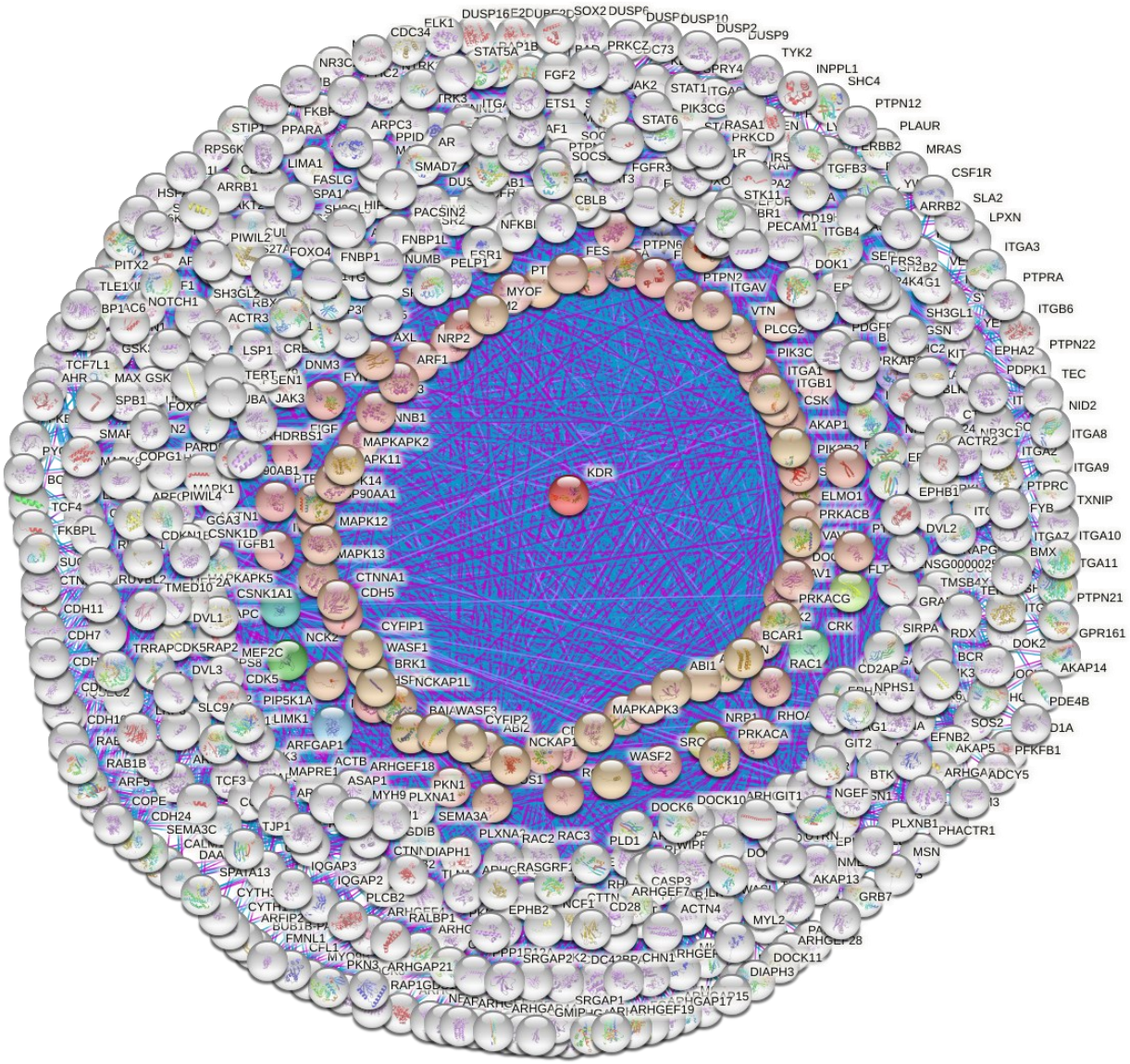
1. induces apoptosis via inhibiting ELK1/KIAA1524 (Elk-1/CIP2A) and activating PP2A not related to proteasome inhibition(*313*)
2. anti-tumor activity via the parathyroid hormone receptor pathway(*314*)

Drugs	Discovery Target
NEVIRAPINE **EFAVIRENZ: 2** **ETRAVIRINE** **RILPIVIRINE** **DORAVIRINE**	HIV Reverse Transcriptase

Efavirenz

1. inhibits the late stage of the HIV-1 replication and enhances the intracellular processing of Gag and Gag-Pol polyproteins. This is associated with a decrease in viral particle production from HIV-1-transfected cells(*315, 316*).
2. enhances Gag-Pol precursor dimerization after plasma membrane targeting but before complete particle assembly, resulting in an aberrant distribution of Gag/Gag-Pol processing products(*317*).

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
NINTEDANIB	VEGFR-2	KDR	P35968	229



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*As nintedanib was approved in approximately the same time for both idiopathic pulmonary fibrosis (US – 2014) and non-small-cell lung cancer (European Union – 2014), its "off-target" mechanisms in both these disorders were sought.

1. exhibits an anti-fibrosis effect via directly blocking Src and inhibiting the expression of genes downstream of Wnt signaling such as Cyclin D1, Wisp1, and S100a4(*318*)
2. inhibits several kinases in nanomolar range that are related to antitumor effects (IC_{50} (nmol/l))(*319*):

1) ABL1(12 ± 5)
2) BLK(42 ± 9)
3) BTK(34 ± 14)
4) CSF1R(5 ± 2)
5) DDR1(17 ± 7)
6) DDR2(16 ± 4)
7) FYN(74 ± 24)
8) JAK3(67 ± 27)
9) KIT(6 ± 3)
10) MAP3K3 (MEKK3)(58 ± 25)
11) MAP3K7(46 ± 31)
12) MELK(3 ± 2)
13) MST4(84 ± 9)
14) NTRK1 (TRKA)(30 ± 8)
15) NTRK3 (TRKC)(48 ± 25)
16) NUAK1(50 ± 8)
17) RET(2 ± 1)
18) SIK2(11 ± 4)
19) STK24(61 ± 12)
20) TGFBR1(77 ± 20)
21) YES1(14 ± 4)

3. induces TNBC apoptosis by acting as a SHP-1 agonist(*320*)
4. directly inhibits tumor cell growth and induces tumor shrinkage in addition to its antiangiogenic effect on the tumor stroma(*319*)
5. inhibits mast cell survival and activation and thus provides a novel additional mechanism by which this drug may exert anti-fibrotic effects(*321*)
6. independent of TGF-β signaling, downregulates protein and mRNA expression of extracellular matrix proteins, fibronectin, and collagen 1a1 and induces non-canonical autophagy(*322*)
7. reduces the expression of collagen I and V and inhibits collagen I fibril formation and causes a reduction in and an altered appearance of collagen fibril bundles(*323*)
8. Its derivate, which was used for binding-profiling of nintedanib itself, directly binds these kinases (K_d, nM) (NP: non-phosphorylated, P: phosphorylated)(*324*):

1) ZAP70: 3500
2) YSK4: 5.2
3) YES: 80
4) WEE1: 2900
5) TSSK1B: 6100
6) TTK: 22
7) TXK: 860
8) TYK2(JH1domain-catalytic): 37
   - ✓ TYK2(JH2domain-pseudokinase): 500
9) TYRO3: 4900
10) ULK1: 340

11) ULK2: 380
12) ULK3: 60
13) VEGFR2: 2.9
14) TRKA: 4.5
15) TRKB: 19
16) TRKC: 32
17) TNIK: 53
18) TNK1: 210
19) TNK2: 1600
20) TIE1: 2200
21) TIE2: 1400
22) TGFBR1: 4200
23) TBK1: 150
24) TAK1: 4.1
25) STK39: 520
26) SRPK1: 37
27) SRPK2: 36
28) SRPK3: 12
29) STK16: 18
30) STK33: 1100
31) STK35: 810
32) SRC: 580
33) SNARK: 21
34) S6K1: 190
35) SBK1: 110
36) SgK110: 2000
37) SGK3: 1000
38) SIK: 670
39) SIK2: 280
40) SLK: 51
41) RSK4(Kin.Dom.1-N-terminal): 230
42) RSK2(Kin.Dom.1-N-terminal): 65
43) RSK3(Kin.Dom.1-N-terminal): 58
44) RSK1(Kin.Dom.1-N-terminal): 180
45) RPS6KA5(Kin.Dom.1-N-terminal): 200
46) RPS6KA4(Kin.Dom.1-N-terminal): 620
47) ROS1: 3700
48) RIPK4: 440
49) RIOK3: 36
50) RIPK1: 240
51) RET: 31
    - ✓ RET(M918T): 30
    - ✓ RET(V804L): 9.8
    - ✓ RET(V804M): 9.6
52) RIOK1: 23
53) PRP4: 8.4
54) PYK2: 81
55) PRKCQ: 5500
56) PRKD1: 990
57) PRKD2: 720
58) PRKD3: 640
59) PRKG1: 14
60) PLK4: 53
61) PKN1: 740
62) PKN2: 1400
63) PKNB(*M. tuberculosis*): 3.6

64) PIP5K2B: 17

65) PIP5K1A: 49

66) PFTK1: 470

67) PHKG1: 140

68) PHKG2: 260

69) PAK7: 1300

70) PCTK1: 21

71) PCTK2: 93

72) PCTK3: 510

73) PDGFRA: 16

74) PDGFRB: 15

75) PDPK1: 2800

76) PFCDPK1(*P. falciparum*): 1200

77) PAK2: 3300

78) PAK3: 210

79) PAK4: 3000

80) OSR1: 1300

81) MYO3B: 2700

82) MUSK: 590

83) MYLK: 290

84) MYLK2: 4000

85) MYLK4: 440

86) MST2: 38

87) MST3: 110

88) MST4: 49

89) MST1: 9

90) MLCK: 110

91) MLK1: 220

92) MLK2: 2300

93) MLK3: 700

94) MELK: 4.9

95) MERTK: 8.5

96) MET: 200

- ✓ MET(M1250T): 340
- ✓ MET(Y1235D): 460

97) MINK: 82

98) MARK1: 1400

99) MARK2: 1400

100) MARK3: 770

101) MARK4: 2000

102) MAST1: 4600

103) MEK1: 10

104) MEK2: 42

105) MEK3: 2100

106) MEK4: 3700

107) MEK5: 1.8

108) MAP4K2: 290

109) MAP4K3: 290

110) MAP4K4: 150

111) MAP4K5: 390

112) MAP3K15: 1400

113) MAP3K2: 9.4

114) MAP3K3: 34

115) LKB1: 18

116) LOK: 87

117) LRRK2: 46

- ✓ LRRK2(G2019S): 37

118) LTK: 150

119) LYN: 940

120) LZK: 140

121) JNK3: 270

122) KIT: 5.7

- ✓ KIT(A829P): 87
- ✓ KIT(D816H): 310
- ✓ KIT(D816V): 47
- ✓ KIT(L576P): 2.7
- ✓ KIT(V559D): 6.3
- ✓ KIT(V559D,T670I): 2.9
- ✓ KIT(V559D,V654A): 29

123) LATS1: 420

124) LATS2: 380

125) LCK: 6.2

126) IKK-epsilon: 170

127) INSR: 24

128) INSRR: 21

129) IRAK1: 120

130) IRAK3: 5300

131) IRAK4: 810

132) ITK: 210

133) JNK1: 630

- ✓ JAK1(JH1domain-catalytic): 2500
- ✓ JAK1(JH2domain-pseudokinase): 4.8

134) JAK2(JH1domain-catalytic): 14

135) JAK3(JH1domain-catalytic): 8.2

136) ICK: 1700

137) IGF1R: 62

138) IKK-alpha: 4500

139) GCN2(Kin.Dom.2,S808G): 2000

140) GRK1: 100

141) GRK4: 17

142) GRK7: 1200

143) GSK3A: 430

144) GSK3B: 83

145) HCK: 5300

146) HIPK1: 1300

147) HIPK2: 790

148) HIPK3: 850

149) HIPK4: 1200

150) HPK1: 35

151) ERN1: 2000

152) FAK: 210

153) FER: 73

154) FES: 1200

155) FGFR1: 92

156) FGFR2: 350

157) FGFR3: 93

- ✓ FGFR3(G697C): 140

158) FGFR4: 1800

159) FGR: 300

160) FLT1: 63

161) FLT3: 3.8

- ✓ FLT3(D835H): 0.71

- ✓ FLT3(D835Y): 0.42
- ✓ FLT3(ITD): 0.7
- ✓ FLT3(K663Q): 4.5
- ✓ FLT3(N841I): 2.6
- ✓ FLT3(R834Q): 17

162) FLT4: 95
163) FRK: 2700
164) FYN: 630
165) ERK5: 2500
166) EPHB4: 1100
167) EPHB6: 140
168) EPHB1: 550
169) EPHA6: 940
170) DYRK1B: 1600
171) DRAK1: 110
172) DRAK2: 670
173) DCAMKL3: 770
174) DDR1: 12
175) DDR2: 42
176) DLK: 140
177) DAPK2: 3200
178) DAPK3: 2100
179) DCAMKL1: 540
180) CSNK2A1: 7500
181) CSNK2A2: 890
182) CSNK1D: 1300
183) CSNK1E: 230
184) CLK4: 18
185) CSF1R: 48
186) CLK1: 8.8
187) CLK2: 760
188) CHEK1: 290
189) CDKL2: 1300
190) CDK7: 300
191) CDK4-cyclinD1: 160
192) CDK4-cyclinD3: 720
193) CDK2: 1400
194) CAMK4: 3700
195) CAMKK1: 630
196) CAMKK2: 920
197) BTK: 310
198) CAMK1: 5900
199) CAMK1D: 2200
200) CAMK1G: 260
201) CAMK2A: 3600
202) BMPR2: 56
203) AURKB: 420
204) AURKC: 190
205) AXL: 12
206) BIKE: 2.2
207) BLK: 380
208) ARK5: 160
209) ALK: 31
210) AMPK-alpha1: 87
211) AMPK-alpha2: 84
212) ACVRL1: 4200

213) AAK1: 63

214) ABL1(E255K)-P: 63

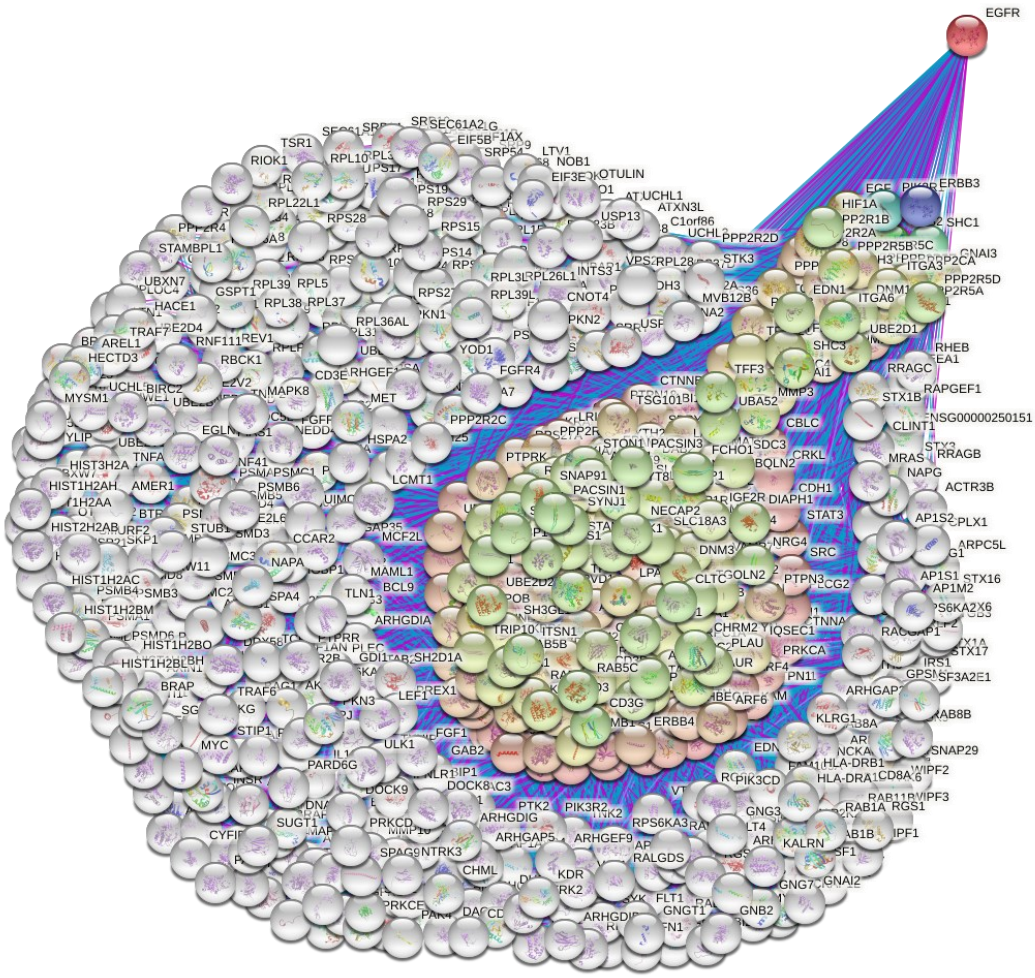
- ✓ ABL1(F317I)-NP: 6900
- ✓ ABL1(F317I)-P: 2600
- ✓ ABL1(F317L)-NP: 2300
- ✓ ABL1(F317L)-P: 640
- ✓ ABL1(H396P)-NP: 45
- ✓ ABL1(H396P)-P: 49
- ✓ ABL1(M351T)-P: 52
- ✓ ABL1(Q252H)-NP: 73
- ✓ ABL1(Q252H)-P: 28
- ✓ ABL1(T315I)-NP: 66
- ✓ ABL1(T315I)-P: 10
- ✓ ABL1(Y253F)-P: 37
- ✓ ABL1-NP: 230
- ✓ ABL1-P: 64

215) ABL2: 2000

216) ACVR1: 600

217) ACVR1B: 4900

Drugs		Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms	
GEFITINIB	**ERLOTINIB**	epidermal growth factor receptor	EGFR	P00533	111	109
LAPATINIB	**VANDETANIB**				16	114
AFATINIB	**DACOMITINIB**				41	
OSIMERTINIB	**NERATINIB**				8	4
AVAPRITINIB	**TUCATINIB**					



https://version-11-0b.string-db.org/cgi/network?networkId=bpVYSKoHpYlY

Gefitinib

1. induces apoptosis and antitumor effects via epidermal growth factor receptor (EGFR)-independent mechanisms as it also has activity in tumors lacking EGFR(*325, 326*)
2. induces apoptosis by inducing cytoplasmic translocation of the CDK inhibitor p27 and its binding to a cleaved intermediate of caspase 8(*327*)
3. induces apoptosis through activation of Bax(*328*)
4. directly inhibits other protein kinases(IC_{50} (μmol/L))(*329-331*):

1) Aurora A(60 ± 7)
2) Aurora B(11.1 ± 2.9)
3) BLK(3.1 ± 0.4)
4) BRK(0.82 ± 0.06)
5) CaMKII(13.5 ± 1.4)
6) CK1δ(61 ± 7)
7) CSK(41 ± 17)
8) EphB4(1.22 ± 0.49)
9) HCK(2.09 ± 0.35)
10) GAK(0.090 ± 0.018)
11) LYN(0.95 ± 0.46)
12) MET(3.2 ± 1.1)
13) p38α(1.19 ± 0.03)
14) RICK(0.049 ± 0.001)
15) YES(1.75 ± 0.13)
16) BTK(6.27)

5. induces apoptosis in human glioma cells by targeting Bad phosphorylation(*332*)
6. reduces the proliferation of glioma cells, presumably by autophagic mechanisms involving AMPK activation(*333*)
7. induces apoptosis probably via upregulation of Fas(*334*)
8. induces apoptosis through a p53-dependent upregulation of proapoptotic molecules and downregulation of antiapoptotic molecules(*335*)
9. increases the expression of both p27KIP1 and p21CIP1/WAF1 cyclin-dependent kinase (CDK) inhibitors(*336*)
10. Inhibition of angiogenesis by gefitinib seems to be independent of the EGFR genetic status of the tumors(*337*).
11. enhances natural killer cell cytotoxicity to lung cancer cells via upregulating the expression of NKG2D ligands ULBP1, ULBP2 or MICA on tumor cells and NKG2D on natural killer cells(*338*), also see (*339*)
12. inhibits retina angiogenesis by affecting VEGF signaling pathway(*340*)
13. Upregulation of YY1 and E-cadherin may account for the efficacy of gefitinib in bladder cancer(*341*).
14. apoptosis via translocating p53 from cytosol to nucleus and upregulating Fas(*342*)
15. inhibits EGF-independent angiogenesis, by acting through Fes as an inhibitor of fibroblast growth factor-2 (FGF-2)-driven angiogenesis, but not toward vascular endothelial growth factor-A (VEGF-A)(*343*)
16. cytotoxicity via phosphorylation of the eukaryotic initiation factor 2 alpha independent of EGFR(*344*)

17. may have an additional beneficiary effect on tumor cell proliferation and migration via decreasing the synthesis of hyaluronic acid by mesothelioma cells(*345*)

18. targets the transcription factor FOXO3a to mediate cell cycle arrest and cell death(*346, 347*)

19. directly binds these kinases (K_d (μM))(*348*):

1) CSNK1E: 2
2) EGFR: 0.0018
3) EPHA6: 1.4
4) EPHB1: 7.3
5) ERBB2: 1.1
6) GAK: 0.007
7) JNK2: 1.4
8) JNK3: 2.3
9) LCK: 1.1
10) MKNK2: 0.36
11) PHKG2: 6.4
12) RIPK2: 0.8
13) SLK: 1.1
14) SRC: 5
15) STK10: 0.87
16) STK17A: 2.9
17) STK17B: 6.5
18) ULK3_m: 1.4

20. exerts antimetastatic effects and reduces cell adhesion via downregulation of integrin α3, αv, β1, β4, β5, β6 and FAK phosphorylation independent of EGFR blockade(*349*)

21. modulates stress fibers and tubular-like structure formation and attenuates angiogenesis(*350*)

22. represses FOXM1 expression via FOXO3a activation and is mediated at the transcriptional level and gene promoter level(*347*)

23. induces apoptosis via downregulation of Bcl-2 and caspase-3 activation(*351*)

24. demonstrates amphiregulin-dependant activity, even in the absence of sensitizing EGFR mutations(*352*)

25. antitumor activity via downregulating the expression of cyclin-dependent kinase 2 (CDK2), CDK4, CDK6 and the antiapoptotic protein Bcl-2, upregulation of p27Kip1 and upregulation and activation of apoptosis related protein Bax(*353*)

26. induces cytostasis and primes the extrinsic (Fas) and intrinsic (mitochondrial and endoplasmic reticulum) apoptotic pathways(*354*)

27. accelerates Fas-mediated apoptosis by enhancing caspase-8 activation in cancer cells independent of EGFR(*355*)

28. reduces the expression of metastasis-related proteins(*356*):

1) basic fibroblast growth factor (bFGF)
2) matrix metalloproteinases-2 (MMP-2)
3) matrix metalloproteinases-9 (MMP-9)

29. causes cell arrest via inhibition of cyclin G-associated kinase and induction of miR-630(*357*)

30. antimetastatic activity via decreasing the synthesis of matrix metalloproteinase and adhesion of cancer cells to extracellular matrix proteins(*358*)

31. upregulates p27KIP1 and induces G1 arrest(*359*)
32. The antiproliferative effects of gefitinib may be, at least in part, due to the inhibition of E2F-1 expression and telomerase activity(*360*).
33. downregulates the expression of histone deacetylase(*361*)
34. downregulates the expression of VEGF(*361, 362*)
35. modulates cell growth and differentiation of acute myeloid leukemia cells via histamine receptors(*363*)
36. upregulates death receptor 5 expression to mediate apoptosis(*364*)
37. induces apoptosis through downregulating tumor necrosis factor-related apoptosis-inducing ligand expression levels(*365*)
38. inhibits cell growth via elevation of p21 levels (through inducing protein stability) and suppression of cdk2/4 and cyclinE/D1 activities(*366*)
39. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) ABL1-NP: 2200
   - ✓ ABL1-P: 480
   - ✓ ABL1(E255K)-P: 400
   - ✓ ABL1(F317I)-P: 4700
   - ✓ ABL1(F317L)-NP: 2700
   - ✓ ABL1(F317L)-P: 780
   - ✓ ABL1(H396P)-NP: 680
   - ✓ ABL1(H396P)-P: 460
   - ✓ ABL1(M351T)-P: 520
   - ✓ ABL1(Q252H)-NP: 1100
   - ✓ ABL1(Q252H)-P: 230
   - ✓ ABL1(Y253F)-P: 360
2) ABL2: 1600
3) AXL: 1800
4) BLK: 1200
5) CDK7: 610
6) CHEK2: 800
7) CIT: 1300
8) CSNK1D: 3200
9) CSNK1E: 430
10) DAPK3: 5700
11) DCAMKL3: 2900
12) DMPK: 6900
13) DRAK1: 2000
14) DRAK2: 3800
15) EGFR: 1
   - ✓ EGFR(E746-A750del): 0.54
   - ✓ EGFR(G719C): 2
   - ✓ EGFR(G719S): 1.1
   - ✓ EGFR(L747-E749del, A750P): 0.57
   - ✓ EGFR(L747-S752del, P753S): 0.57
   - ✓ EGFR(L747-T751del,Sins): 0.52
   - ✓ EGFR(L858R): 0.94
   - ✓ EGFR(L858R,T790M): 140
   - ✓ EGFR(L861Q): 1.4
   - ✓ EGFR(S752-I759del): 0.98

- ✓ EGFR(T790M): 40

16) EPHA1: 4000
17) EPHA3: 5500
18) EPHA5: 1500
19) EPHA6: 590
20) EPHA8: 1800
21) EPHB1: 1300
22) EPHB4: 2500
23) EPHB6: 3200
24) ERBB2: 3500
25) ERBB3: 790
26) ERBB4: 410
27) ERK3: 1600
28) ERK4: 3100
29) FGR: 2600
30) FLT3: 3100
    - ✓ FLT3(D835H): 1100
    - ✓ FLT3(D835Y): 1000
    - ✓ FLT3(ITD): 2900
    - ✓ FLT3(K663Q): 5100
    - ✓ FLT3(N841I): 3000
    - ✓ FLT3(R834Q): 3500
31) FRK: 2000
32) GAK: 13
33) HCK: 4400
34) HIPK4: 310
35) IRAK1: 69
36) IRAK3: 1500
37) IRAK4: 540
38) JNK2: 1700
39) JNK3: 3200
40) KIT(A829P): 1800
    - ✓ KIT(D816H): 5500
    - ✓ KIT(D816V): 4300
41) LCK: 630
42) LOK: 470
43) LTK: 5500
44) LYN: 990
45) MAP3K2: 3300
46) MAP3K3: 2100
47) MEK5: 600
48) MET(Y1235D): 3500
49) MINK: 1800
50) MKNK1: 290
51) MKNK2: 1200
52) MYLK2: 1900
53) NLK: 4200
54) PHKG1: 3700
55) PHKG2: 2700
56) PIM3: 5800
57) PIP5K2C: 7500
58) PRKD1: 3500
59) RIPK2: 530
60) RPS6KA4(Kin.Dom.2-C-terminal): 1200
61) SBK1: 560
62) SIK2: 2100

63) SLK: 920

64) SNARK: 4600

65) SRC: 3800

66) STK36: 5700

67) TNIK: 6900

68) TXK: 6000

69) YSK4: 240

Erlotinib

1. induces apoptosis and antitumor effects via EGFR-independent mechanisms as it also has activity in tumors lacking EGFR(*367-369*)
2. prevents epithelial-to-mesenchymal transition by acting on E-cadherin expression and displacing the ternary complex formed by integrin-linked kinase (ILK), α-parvin, and PINCH (IPP)(*370*)
3. directly binds these kinases (K_d (μM))(*348*):
   1) AAK1: 4.4
   2) ABL1: 0.77
      - ✓ ABL1(E255K): 2.4
      - ✓ ABL1(H396P): 0.69
      - ✓ ABL1(M351T): 0.73
      - ✓ ABL1(Q252H): 0.28
      - ✓ ABL1(T315I): 0.6
      - ✓ ABL1(Y253F): 0.54
   3) ABL2: 0.3
   4) Aurora2: 3.8
   5) BIKE: 1.8
   6) EGFR: 0.0014
   7) EPHA6: 0.93
   8) ERBB2: 5.1
   9) GAK: 0.04
   10) JNK2: 4
   11) LCK: 0.53
   12) MKNK2: 1.6
   13) RIPK2: 0.41
   14) SLK: 0.11
   15) SRC: 1.9
   16) STK10: 0.083
   17) ULK3_m: 0.63
4. sensitizes cancer cells to natural killer cell mediated cytotoxicity by increasing the levels of mRNA transcripts and surface protein of UL16-binding protein-1 (ULBP1) via inhibition of the PKC pathway(*371*)
5. activates mitochondrial death pathways related to the production of reactive oxygen species through inducing loss of mitochondrial membrane potential, the release of cytochrome c and apoptosis-inducing factor (AIF) and activation of JNK(*372, 373*)
6. exhibits antineoplastic off-target effects via JAK2 and nucleocytoplasmic translocation of nucleophosmin-1 (NPM-1) and p14ARF(*368*)
7. targets FLT3(*374*)
8. immunomodulation via increasing T cell mediated cytotoxicity on lung cancer through inhibiting the expression of PD-L1 and genes related to antigen presentation and inflammation(*375*)

9. decreases Rad51 protein levels by enhancing Rad51 mRNA and protein instability(*376*)
10. directly binds to six protein kinases with even higher affinity (K_d: ranging from 0.09 to 0.358 μM) compared to EGFR (K_d: 0.434 μM)(*330*):
    1) STK10
    2) MAP3K1
    3) ILK
    4) SLK
    5) Ripk2
    6) ABL2
11. prevents bone metastases by affecting host microenvironments irrespective of its direct effect on tumor cells and in cancers with no EGFR expression(*377*)
12. inhibits JAK2V617F activity, a mutant of tyrosine kinase JAK2(*378*)
13. directly binds(*331*):
    1) Lyn (IC_{50} = 1.46μm)
    2) Yes (IC_{50} = 3.99μm)
    3) Btk (IC_{50} = 5.62μm)
14. induces p27KIP1 upregulation and nuclear translocation in association with cell growth inhibition and G1/S phase arrest(*379*)
15. exerts antitumor effects via CIP2A(*380*)
16. increases the susceptibility of cancer cells to immune-cell-mediated cytotoxicity through PI3 and independent of EGFR(*381, 382*)
17. decrease VEGF expression also by hypoxia-inducible factor (HIF)-1-independent mechanisms(*383*)
18. directly inhibits HER2 kinase activation and downstream signaling(*384*)
19. induces apoptosis through inducing via p73 the transcription of PUMA(*385*)
20. triggers excessive mitochondrial fragmentation which promotes apoptosis via activating the mROS-HtrA2/Omi pathways(*386*)
21. suppresses the transcription of miR-9-1 and the consequent downregulation of FoxO1(*387*)
22. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):
    1) AAK1: 1200
    2) ABL1-NP: 330
        - ✓ ABL1-P: 76
        - ✓ ABL1(E255K)-P: 63
        - ✓ ABL1(F317I)-NP: 8200
        - ✓ ABL1(F317I)-P: 1100
        - ✓ ABL1(F317L)-NP: 640
        - ✓ ABL1(F317L)-P: 150
        - ✓ ABL1(H396P)-NP: 89
        - ✓ ABL1(H396P)-P: 58
        - ✓ ABL1(M351T)-P: 66
        - ✓ ABL1(Q252H)-NP: 230
        - ✓ ABL1(Q252H)-P: 61
        - ✓ ABL1(T315I)-NP: 620
        - ✓ ABL1(T315I)-P: 59

- ✓ ABL1(Y253F)-P: 76

3) ABL2: 200
4) ADCK3: 1900
5) ADCK4: 2500
6) ALK: 1200
7) AURKA: 2200
8) AURKB: 1400
9) AURKC: 600
10) AXL: 4000
11) BIKE: 1200
12) BLK: 190
13) CAMK2D: 6400
14) CIT: 680
15) CSK: 9600
16) CSNK1D: 3500
17) CSNK1E: 500
18) DAPK3: 6000
19) DDR1: 790
20) DMPK: 2900
21) DMPK2: 3400
22) DRAK1: 6300
23) DRAK2: 9400
24) DYRK2: 1300
25) EGFR: 0.67
    - ✓ EGFR(E746-A750del): 0.48
    - ✓ EGFR(G719C): 0.85
    - ✓ EGFR(G719S): 0.52
    - ✓ EGFR(L747-E749del, A750P): 0.52
    - ✓ EGFR(L747-S752del, P753S): 0.47
    - ✓ EGFR(L747-T751del,Sins): 0.35
    - ✓ EGFR(L858R): 0.97
    - ✓ EGFR(L858R,T790M): 190
    - ✓ EGFR(L861Q): 1.2
    - ✓ EGFR(S752-I759del): 1.6
    - ✓ EGFR(T790M): 140
26) EPHA3: 2400
27) EPHA5: 710
28) EPHA6: 440
29) EPHA7: 1400
30) EPHA8: 940
31) EPHB1: 1100
32) EPHB4: 2200
33) EPHB6: 1700
34) ERBB2: 2900
35) ERBB3: 1100
36) ERBB4: 230
37) ERK4: 2500
38) FGR: 1100
39) FLT1: 4400
40) FLT3: 1200
    - ✓ FLT3(D835H): 350
    - ✓ FLT3(D835Y): 130
    - ✓ FLT3(ITD): 820
    - ✓ FLT3(K663Q): 1300
    - ✓ FLT3(N841I): 500
41) FLT4: 2100

42) FRK: 2000

43) GAK: 3.1

44) GCN2(Kin.Dom.2,S808G): 4400

45) GRK4: 7300

46) HCK: 1800

47) HIPK4: 960

48) JAK2(JH1domain-catalytic): 3700

49) JAK3(JH1domain-catalytic): 700

50) JNK2: 2000

51) JNK3: 4300

52) KIT: 1700

- ✓ KIT(D816V): 1600
- ✓ KIT(L576P): 3500
- ✓ KIT(V559D): 3100
- ✓ KIT(V559D,T670I): 1300

53) LCK: 250

54) LOK: 19

55) LRRK2: 2900

- ✓ LRRK2(G2019S): 4800

56) LTK: 890

57) LYN: 530

58) MAP3K2: 2500

59) MAP3K3: 2300

60) MEK5: 96

61) MERTK: 980

62) MET: 3800

- ✓ MET(M1250T): 2800
- ✓ MET(Y1235D): 1100

63) MINK: 1300

64) MKNK1: 690

65) MKNK2: 1000

66) MYLK2: 970

67) PDGFRA: 1800

68) PDGFRB: 1400

69) PIP5K2C: 1000

70) PLK4: 1900

71) PRKR: 1300

72) RET: 1300

- ✓ RET(M918T): 330

73) RIPK2: 680

74) RIPK4: 4900

75) RPS6KA4(Kin.Dom.2-C-terminal): 7000

76) SBK1: 1200

77) SIK2: 2600

78) SLK: 26

79) SRC: 700

80) SRPK3: 8300

81) STK36: 4400

82) TBK1: 3100

83) TIE1: 850

84) TNIK: 4500

85) TNK1: 630

86) TNNI3K: 570

87) TTK: 3700

88) TXK: 3800

89) TYK2(JH2domain-pseudokinase): 2400

90) TYRO3: 3900

91) ULK3: 920

92) VEGFR2: 5700

93) YES: 2200

94) YSK4: 25

Lapatinib

1. negatively regulates general translation and induces stress granules formation through the kinase PERK(*388*)
2. induces G1 arrest via upregulation of p27 by targeting c-jun via miR-1470(*389*)
3. promotes apoptosis through mROS-HtrA2/Omi pathways(*390*)
4. Activity of lapatinib is independent of EGFR expression level in HER2-overexpressing(*391*)
5. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):
    1) EGFR: 2.4
    - ✓ EGFR(E746-A750del): 8.6
    - ✓ EGFR(G719C): 0.92
    - ✓ EGFR(G719S): 2.1
    - ✓ EGFR(L747-E749del, A750P): 2.2
    - ✓ EGFR(L747-S752del, P753S): 3.9
    - ✓ EGFR(L747-T751del,Sins): 3.5
    - ✓ EGFR(L858R): 2.8
    - ✓ EGFR(L861Q): 1.2
    - ✓ EGFR(S752-I759del): 4.2
    - ✓ EGFR(T790M): 860

    2) ERBB2: 7
    3) ERBB3: 5500
    4) ERBB4: 54
    5) LOK: 4400
    6) MEK5: 1100
    7) MKK7: 4400
    8) PIK3C2B: 670
    9) PIK3C2G: 7500
    10) PIK4CB: 940
    11) RIPK2: 3600
    12) SLK: 3300
6. induces p27 expression via both transcriptional and post-translational upregulations, leading to cell cycle arrest and cell proliferation inhibition(*392*)
7. directly binds these kinases (K_d (μM))(*348*):
    1) EGFR: 0.0055
    2) ERBB2: 0.011
    3) SLK: 9.3
    4) STK10: 2.6

Vandetanib

1. **Vandetanib, designed to inhibit VEGFR2 and EGFR signaling, had no clinical activity as monotherapy for recurrent ovarian cancer and no detectable modulation of VEGFR2. Proteomic analysis of paired biopsies detected both phosphorylated-EGFR and phosphorylated-VEGF receptor-2 in ovarian tumor tissue, but only phosphorylated-EGFR was measurably inhibited by vandetanib(463).

2. directly binds these kinases (K_d (μM))(*348*):

1) ABL1: 0.27
   - ✓ ABL1(E255K): 0.68
   - ✓ ABL1(H396P): 0.12
   - ✓ ABL1(M351T): 0.17
   - ✓ ABL1(Q252H): 0.18
   - ✓ ABL1(T315I): 0.12
   - ✓ ABL1(Y253F): 0.16
2) ABL2: 0.13
3) CSK: 3.7
4) CSNK1E: 1.5
5) EGFR: 0.017
6) EPHA2: 1.9
7) EPHA3: 1.8
8) EPHA4: 4.3
9) EPHA5: 0.31
10) EPHA6: 0.065
11) EPHA7: 3.4
12) EPHA8: 0.16
13) EPHB1: 0.54
14) EPHB4: 2.6
15) FGFR1: 5.3
16) FGFR2: 5.5
17) FGFR3: 0.24
18) FGR: 2.2
19) FLT3: 1.2
20) FLT4: 0.3
21) FRK: 0.48
22) FYN: 5.7
23) GAK: 0.33
24) HCK: 4.2
25) KIT: 1.1
26) LCK: 0.061
27) LYN: 0.71
28) MAP3K4: 4.8
29) MAP4K5: 0.51
30) MKNK2: 3.4
31) PDGFRB: 0.25
32) PHKG1: 7.1
33) PHKG2: 9.5
34) PRKAA1: 10
35) PTK6: 0.033
36) RIPK2: 0.031
37) SLK: 0.096
38) SRC: 0.17
39) STK10: 2.4
40) STK18: 1.5
41) TEK: 3.6
42) TNIK: 3.9
43) VEGFR2: 0.47
44) YES: 0.28

3. inhibits cancer cell migration and invasion via downregulating the SDF-1/CXCR4 axis and matrix metalloproteinase 14(*393*), also see (*394*)
4. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) ABL1-NP: 48
    - ✓ ABL1-P: 16
    - ✓ ABL1(E255K)-P: 13
    - ✓ ABL1(F317I)-NP: 770
    - ✓ ABL1(F317I)-P: 170
    - ✓ ABL1(F317L)-NP: 75
    - ✓ ABL1(F317L)-P: 33
    - ✓ ABL1(H396P)-NP: 9.8
    - ✓ ABL1(H396P)-P: 14
    - ✓ ABL1(M351T)-P: 15
    - ✓ ABL1(Q252H)-NP: 18
    - ✓ ABL1(Q252H)-P: 16
    - ✓ ABL1(T315I)-NP: 150
    - ✓ ABL1(T315I)-P: 20
    - ✓ ABL1(Y253F)-P: 9
2) ABL2: 69
3) ACVR1: 150
4) ACVRL1: 470
5) ADCK3: 4500
6) ADCK4: 1700
7) ALK: 2100
8) AMPK-alpha1: 3000
9) AURKC: 1500
10) AXL: 250
11) BLK: 66
12) BMPR1B: 240
13) BRK: 160
14) BTK: 1700
15) CDK7: 4100
16) CIT: 1800
17) CSF1R: 1200
18) CSK: 2500
19) CSNK1E: 3000
20) DDR1: 11
21) DDR2: 320
22) DMPK2: 2200
23) EGFR: 9.5
    - ✓ EGFR(E746-A750del): 4.8
    - ✓ EGFR(G719C): 9.6
    - ✓ EGFR(G719S): 5.9
    - ✓ EGFR(L747-E749del, A750P): 12
    - ✓ EGFR(L747-S752del, P753S): 7.9
    - ✓ EGFR(L747-T751del,Sins): 8.9
    - ✓ EGFR(L858R): 8.7
    - ✓ EGFR(L858R,T790M): 230
    - ✓ EGFR(L861Q): 11
    - ✓ EGFR(S752-I759del): 12
    - ✓ EGFR(T790M): 100
24) EPHA1: 230
25) EPHA2: 1100
26) EPHA3: 2000
27) EPHA4: 1600
28) EPHA5: 240
29) EPHA6: 50
30) EPHA7: 2400
31) EPHA8: 91

32) EPHB1: 290
33) EPHB2: 440
34) EPHB4: 520
35) EPHB6: 76
36) ERBB2: 2600
37) ERBB3: 160
38) ERBB4: 480
39) ERK3: 1500
40) FGFR1: 560
41) FGFR2: 1100
42) FGFR3: 1600
    - ✓ FGFR3(G697C): 6900
43) FGFR4: 2300
44) FGR: 270
45) FLT1: 260
46) FLT3: 850
    - ✓ FLT3(D835H): 560
    - ✓ FLT3(D835Y): 830
    - ✓ FLT3(ITD): 1800
    - ✓ FLT3(K663Q): 190
    - ✓ FLT3(N841I): 1200
    - ✓ FLT3(R834Q): 1300
47) FLT4: 1100
48) FRK: 170
49) FYN: 360
50) GAK: 86
51) HCK: 360
52) HPK1: 5500
53) HUNK: 4100
54) IRAK1: 1200
55) IRAK4: 75
56) KIT: 260
    - ✓ KIT(A829P): 34
    - ✓ KIT(D816H): 420
    - ✓ KIT(D816V): 290
    - ✓ KIT(L576P): 140
    - ✓ KIT(V559D): 180
    - ✓ KIT(V559D,T670I): 2000
    - ✓ KIT(V559D,V654A): 560
57) LCK: 17
58) LOK: 81
59) LTK: 550
60) LYN: 110
61) MAP3K4: 3000
62) MAP4K2: 1600
63) MAP4K3: 1500
64) MAP4K4: 1400
65) MAP4K5: 450
66) MEK1: 1800
67) MEK2: 1100
68) MEK5: 49
69) MERTK: 1400
70) MET: 5700
    - ✓ MET(Y1235D): 4100
71) MINK: 3400
72) MKNK1: 360

73) MKNK2: 1700

74) MRCKA: 2600

75) MRCKB: 2500

76) PDGFRA: 230

77) PDGFRB: 88

78) PHKG1: 1100

79) PHKG2: 7900

80) PLK4: 620

81) QSK: 3900

82) RET: 34

- ✓ RET(M918T): 14

83) RIPK2: 4.6

84) RIPK4: 620

85) ROCK2: 3600

86) RSK1(Kin.Dom.2-C-terminal): 400

87) RSK4(Kin.Dom.2-C-terminal): 240

88) S6K1: 1600

89) SIK: 1900

90) SIK2: 430

91) SLK: 95

92) SRC: 70

93) SRMS: 1900

94) STK33: 1400

95) STK35: 56

96) TESK1: 3700

97) TIE1: 1500

98) TIE2: 1000

99) TNIK: 2300

100) TNNI3K: 2800

101) TXK: 3700

102) TYRO3: 93

103) ULK3: 6400

104) VEGFR2: 820

105) YANK1: 5000

106) YES: 120

107) YSK4: 980

108) ZAK: 5100

Afatinib

1. induces apoptosis in cancer cells without EGFR mutation via suppressing CIP2A at the gene transcription level by reducing the promoter binding activity of Elk-1(*395*)
2. decreases epithelial-mesenchymal transition and tumorigenesis by regulating the ERK-VEGF/MMP9 signaling pathway(*396*)
3. hampers AKT-mTOR activation by stimulating PERK-eIF2α-ATF4 signaling pathway, giving rise to MCL-1 downregulation mediated apoptosis(*397*)
4. directly inhibits ErBB-4 with an EC_{50} of 1nM(*398*)
5. downregulates ribonucleotide reductase(*399*)
6. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) TXK: 3100

2) SRC: 2800

3) SLK: 3700

4) SBK1: 4800
5) RSK4(Kin.Dom.2-C-terminal): 3100
6) RIPK2: 2700
7) PHKG2: 470
8) PHKG1: 1300
9) p38-alpha: 1300
10) MKNK1: 1800
11) MKNK2: 1600
12) MET: 2200
    - ✓ MET(M1250T): 6000
    - ✓ MET(Y1235D): 2600
13) MEK5: 1300
14) LOK: 4300
15) LCK: 570
16) JNK2: 2100
17) JNK3: 2000
18) IRAK1: 240
19) HIPK4: 360
20) HCK: 2200
21) GAK: 79
22) FRK: 1400
23) FLT3(N841I): 6200
    - ✓ FLT3(D835H): 1800
    - ✓ FLT3(D835Y): 1400
24) EPHB6: 3100
25) ERBB2: 5
26) ERBB3: 4500
27) ERBB4: 6.3
28) EPHA6: 340
29) DYRK1A: 970
30) DYRK1B: 2800
31) DYRK2: 1800
32) DRAK1: 2300
33) CSNK1E: 1300
34) CIT: 2900
35) BLK: 220
36) AXL: 5300
37) ABL1-NP: 1300
    - ✓ ABL1-P: 570
    - ✓ ABL1(E255K)-P: 420
    - ✓ ABL1(F317I)-NP: 2900
    - ✓ ABL1(F317I)-P: 750
    - ✓ ABL1(F317L)-NP: 580
    - ✓ ABL1(F317L)-P: 230
    - ✓ ABL1(H396P)-NP: 500
    - ✓ ABL1(H396P)-P:500
    - ✓ ABL1(M351T)-P: 1200
    - ✓ ABL1(Q252H)-NP: 790
    - ✓ ABL1(Q252H)-P: 380
    - ✓ ABL1(T315I)-NP: 2600
    - ✓ ABL1(T315I)-P: 870
    - ✓ ABL1(Y253F)-P: 830

Osimertinib

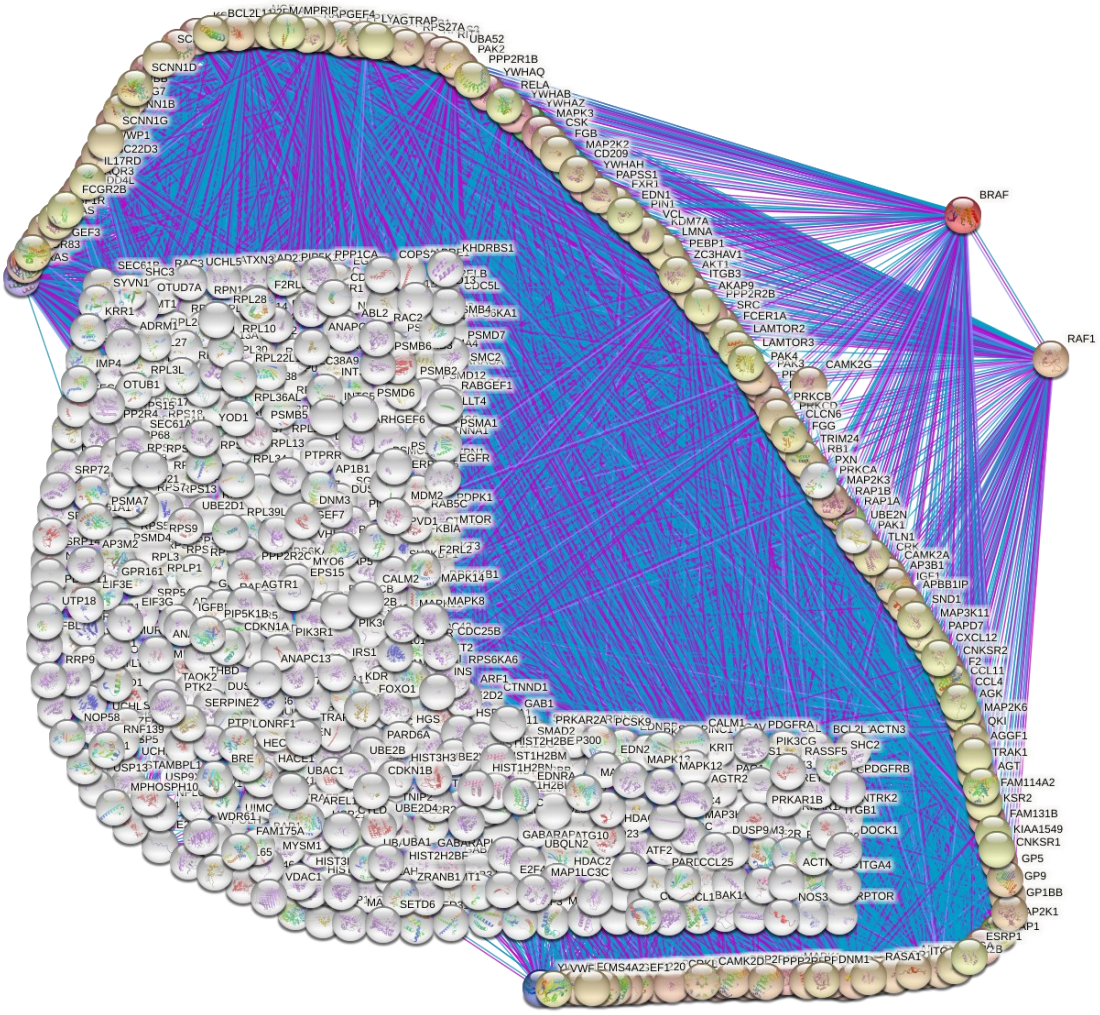
1. may reactivate immune activity of T cells in tumor microenvironment via reducing PD-L1 mRNA expression and inducing its protein degradation(*400*)

2. reduces EZH2 mRNA expression via up-regulating the expression of a tumor suppressor, miR-34a(*401*)
3. induces apoptosis via reactive oxygen species generation(*402*)
4. disrupts the interaction of EZH2–EED, leading to impairment of PRC2 activity and downregulation of EZH2 protein(*401*)
5. exerts antitumor effects via directly inhibiting MNK1 and MNK2 kinases with IC_{50} values of 324 nM and 48.6 nM, respectively, and subsequently suppressing the phosphorylation of eIF4E(*403*)
6. can trigger autophagy-mediated cell death by increasing the expression of phosphatidylethanolamine-modified microtubule-associated protein light-chain 3 (LC3) and decreasing the expression of p62(*404*)
7. directly inhibits LSD1 with an IC_{50} of 3.98 ± 0.3 μM(*405*)

Neratinib

1. It enhances LATS1/2 phosphorylation independently of RAP2A/MAP4K4 and that MST4 degradation and Ezrin dephosphorylation may represent a universal trigger for the biological actions of neratinib(*406*).
2. inhibits Hippo/YAP signaling, reduces mutant K-RAS expression, and kills pancreatic and blood cancer cells(*407*)
3. induces ubiquitylation-mediated endocytic degradation of ErbB2(*408*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
SORAFENIB	c-Raf	RAF1	P04049	140
PAZOPANIB				107
AXITINIB				102
REGORAFENIB	B-Raf	BRAF	P15056	20
LENVATINIB				10



https://version-11-0b.string-db.org/cgi/network?networkId=bkp1TxEsAQKB

Sorafenib

1. downregulates the respiratory chain complex I (NADH dehydrogenase) which is accompanied with the loss of mitochondrial transmembrane potential (ΔΨm) and complete impairment of complex I enzyme activity(*409*)
2. promotes immune responsiveness via selectively increasing effector T cell activation while blocking regulatory T cell function(*410*), also see (*411-417*)
3. enhances antitumor immunity via modulating immunosuppressive cell populations(*418*)
4. augments antitumor immunity via relieving cell-intrinsic and cell-extrinsic inhibitions of effector T cells in tumor microenvironment(*419*)
5. inhibits TGF-β signaling mainly by inducing caveolae/lipid raft-mediated internalization and degradation of cell-surface TβR-II in target cells(*420*)
6. dose-dependently induces the generation of ROS in tumor cells(*421*)
7. inhibits cell viability, migration, invasion, and STAT3 activation via ARHGAP24(*422*)
8. could potentially reverse the immunosuppressive cytokine profile of tumor-associated macrophages, rendering the tumor microenvironment more conducive to an anti-tumor immune response(*423*)
9. modulate the expression of a wide range of ncRNAs and specifically, GAS5 and miR-126-3p(*424*)
10. hinders oxidative phosphorylation, whereas at the same time stimulates aerobic glycolysis in glucose-grown cells, hence attenuating the cellular ATP depletion(*425*)
11. inhibits cell proliferation and induces apoptosis through the mitochondrial pathway, independent of MAPK and AKT and via AMPK-dependent inhibition of the mTORC1 pathway(*426*)
12. induces apoptosis and has antiproliferative properties via exerting free radical scavenging properties associated with the downregulation of nuclear factor E2-related factor 2 (Nrf2)-regulated thioredoxin 1 (Trx1) expression(*427*)
13. inhibits migration and invasion of cancer cells through suppression of matrix metalloproteinase expression(*428*)
14. induces apoptosis and exerts its effect – at least in part – by CSF1R inhibition(*429*)
15. directly binds these kinases (K_d (μM))(*348*):

1) ABL1: 0.13
   - ✓ ABL1(E255K): 4.4
   - ✓ ABL1(H396P): 1.2
   - ✓ ABL1(M351T): 0.23
   - ✓ ABL1(Q252H): 0.45
   - ✓ ABL1(T315I): 0.17
   - ✓ ABL1(Y253F): 0.58
2) ABL2: 1.3
3) CDK5: 6.2
4) EPHA2: 4.8
5) EPHA3: 6.4
6) EPHA4: 1.3
7) EPHA5: 0.36

8) EPHA6: 0.24
9) EPHA7: 0.67
10) EPHA8: 0.96
11) EPHB1: 1.7
12) EPHB4: 3.9
13) FGFR1: 2.5
14) FLT3: 0.02
15) FLT4: 0.016
16) FRK: 0.44
17) JNK2: 3.6
18) KIT: 0.74
19) LCK: 6.9
20) LIMK1: 2.2
21) MAP4K5: 1.7
22) MKNK2: 0.25
23) MYLK2: 1.3
24) NTRK1: 3.6
25) p38-alpha: 0.26
26) p38-beta: 0.2
27) p38-gamma: 9.9
28) PDGFRB: 0.041
29) RIPK2: 2.9
30) SLK: 1.6
31) STK10: 0.14
32) STK18: 3.4
33) STK36: 5.4
34) TEK: 3
35) VEGFR2: 0.093

16. induces ferroptosis, a novel form of programmed cell death(*430*) probably via the retinoblastoma protein(*431*)
17. sensitization of cancer cells to TRAIL- and Fas-induced apoptosis, dependent on FLIP and independent of Raf/MEK/ERK inhibition(*432, 433*)
18. promotes oxidative stress and mitochondrial dysfunction by inducing mitochondrial dysfunction via increasing reactive oxygen species formation and activating JNKs, leading to translocation of activated JNK to mitochondria(*434*)
19. Besides functioning as a multiple tyrosine kinase, sorafenib also acts via a kinase-independent mechanism to target STAT3 signaling in cancer cells. Sorafenib inactivates STAT3 and STAT3-related signaling by inducing a conformational change in and releasing the autoinhibition of Src homology region 2 domaincontaining phosphatase-1(*435*).
20. induces the formation of Atg5-deficient autophagosomes which promotes the interaction of p62 with RIPK, leading to caspase-independent cell death by necroptosis(*436*)
21. Sorafenib downregulates AIB1 protein expression by inhibiting AIB1 mRNA translation through simultaneously blocking eIF4E and mTOR/p70S6K/RP-S6 signaling. Downregulation of AIB1 contributes to sorafenib-induced cell death at least in part through upregulating the levels of reactive oxygen species(*437*).
22. can inhibit the proliferation of non-small cell lung cancer H460 and A549 cells, and block the cells in the G1 phase, which may be related to the regulation of Cyclin E1 and E2F1 protein(*438*)

23. Sorafenib suppresses ATP production, resulting in AMPK activation via phosphorylation. Further secondary effects include reduction of the levels of SREBP1, phosphorylation of mTOR, disruption of lipogenesis and liver cancer cell death(*439*).
24. Inhibits soluble epoxide hydrolase(*440*)
25. decreases proliferation and induces apoptosis of prostate cancer cells by inhibition of the androgen receptor and prostate-specific antigen expression(*441*)
26. induces cell death through a process involving induction of endoplasmic reticulum stress independent of MEK1/2-ERK1/2(*442*)
27. induces alteration of cell death receptor S-nitrosylation status which may have a relevant repercussion on cell death signaling(*443*)
28. may suppress mTOR signaling by direct inhibition of FLT3(*444*)
29. induces autophagic cell death through Akt inhibition in a RAF-MEK-ERK1/2 independent fashion(*445*)
30. inhibits macrophage-induced growth of cancer cells by interference with insulin-like growth factor-1 secretion(*417*)
31. exerts antitumor effects via a kinase-independent mechanism: SHP-1 dependent STAT3 inactivation(*446, 447*)
32. induces cell death via increasing the expression of extracellular vesicle long noncoding RNA (linc-VLDLR) in tumor cells(*448*)
33. inhibits invasion and metastasis by regulating the expression of MMP and TIMP gene families(*449*)
34. directly inhibits CSF-1R(*450*)
35. osteosarcoma cells respond to sorafenib chemotherapy by downregulation of the tumor progression factors S100A4, CXCR4 and the oncogene FOS(*451*)
36. induces apoptosis via upregulating ATF4
37. reduces infiltrated regulatory T cells by suppressing TGF-beta signaling(*452*)
38. suppresses growth and survival of cancer cells by accelerating degradation of EZH2(*453*)
39. Besides inhibition of the Raf-MAPK pathway, Sorafenib might also regulate hepatoma cell growth via alteration of receptor-mediated cytoskeletal rearrangement(*454*).
40. inhibits cancer cell proliferation and invasion by inhibiting MMP-2 and Ki-67 expression due to up-regulation of P53 and suppressing FoxM1(*455*)
41. inhibits tumor invasion and induces apoptosis via blocking the HIF-1α/VEGFA pathway(*456*)
42. These data indicate that the inhibition of STAT3 activity by sorafenib involves both the inhibition of upstream kinases (JAK1 and JAK2) of STAT3 and increased phosphatase activity. Phosphorylation of AKT was also reduced by sorafenib. In contrast, mitogen-activated protein kinases were not consistently inhibited by sorafenib in these cells(*457*).
43. inhibits STAT3 signaling associated with growth arrest and apoptosis(*458*)
44. inhibits AAA+ ATPase p97/VCP which leads to disruption of the secretory pathway, endoplasmic reticulum stress, and cancer cell death(*459*)

45. It inhibits ribonucleotide reductase regulatory subunit M2 (RRM2). This partially contributes to its anticancer activity(*460*).

46. directly binds MAPK14(*461*)

47. suppresses extrahepatic metastasis through inhibition of mesenchymal cancer stem cells characterized by the expression of CD90 and inhibiting the production of extracellular vesicles which contain TGF-β mRNA and regulate distant metastasis(*462*)

48. targets the mitochondrial electron transport chain complexes and ATP synthase to activate the PINK1-Parkin pathway and modulate cellular drug response(*463*)

49. In addition to its anticancer effects, it has an immunoregulatory property via inducing survival and differentiation of bone marrow cells that is apparent at low doses(*464*).

50. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) ABL1-NP: 130
   - ✓ ABL1-P: 1400
   - ✓ ABL1(E255K)-P: 3400
   - ✓ ABL1(F317I)-NP: 1700
   - ✓ ABL1(F317I)-P: 4900
   - ✓ ABL1(F317L)-NP: 770
   - ✓ ABL1(F317L)-P: 7100
   - ✓ ABL1(H396P)-NP: 520
   - ✓ ABL1(H396P)-P: 2400
   - ✓ ABL1(M351T)-P: 1200
   - ✓ ABL1(Q252H)-NP: 130
   - ✓ ABL1(Q252H)-P: 5500
   - ✓ ABL1(T315I)-NP: 590
   - ✓ ABL1(T315I)-P: 1500
   - ✓ ABL1(Y253F)-P: 660
2) ABL2: 2900
3) AURKB: 440
4) AURKC: 210
5) AXL: 4500
6) BRAF: 540
   - ✓ BRAF(V600E): 260
7) CDK11: 250
8) CDK2: 8700
9) CDK3: 3800
10) CDK5: 8300
11) CDK7: 140
12) CDK8: 310
13) CDKL2: 130
14) CDKL3: 490
15) CIT: 6200
16) CLK1: 7500
17) CSF1R: 28
18) DDR1: 1.5
19) DDR2: 6.6
20) EPHA1: 3100
21) EPHA2: 2000
22) EPHA3: 1900
23) EPHA4: 3000

24) EPHA5: 3500
25) EPHA6: 370
26) EPHA7: 5300
27) EPHA8: 2400
28) EPHB1: 3000
29) EPHB2: 1900
30) EPHB4: 1800
31) EPHB6: 240
32) ERK8: 46
33) FGFR1: 2800
34) FGFR2: 2700
35) FGFR3: 4200
    - ✓ FGFR3(G697C): 5900
36) FGR: 7800
37) FLT1: 31
38) FLT3: 13
    - ✓ FLT3(D835H): 30
    - ✓ FLT3(D835Y): 82
    - ✓ FLT3(ITD): 79
    - ✓ FLT3(K663Q): 4.5
    - ✓ FLT3(N841I): 11
    - ✓ FLT3(R834Q): 17
39) FLT4: 95
40) FRK: 510
41) FYN: 8400
42) HCK: 8500
43) HIPK1: 3300
44) HIPK2: 1700
45) HIPK3: 440
46) HIPK4: 3.3
47) HPK1: 4800
48) JAK3(JH1domain-catalytic): 7300
49) JNK2: 7400
50) KIT: 28
    - ✓ KIT(A829P): 20
    - ✓ KIT(D816H): 430
    - ✓ KIT(D816V): 310
    - ✓ KIT(L576P): 25
    - ✓ KIT(V559D): 16
    - ✓ KIT(V559D,T670I): 18
    - ✓ KIT(V559D,V654A): 240
51) LCK: 2700
52) LIMK1: 1600
53) LIMK2: 9600
54) LOK: 150
55) LYN: 3000
56) MAP4K4: 4800
57) MAP4K5: 1600
58) MEK5: 190
59) MERTK: 3600
60) MKNK1: 230
61) MKNK2: 130
62) MLCK: 9600
63) MUSK: 130
64) MYLK2: 5400
65) MYO3B: 7100

66) NLK: 640

67) p38-alpha: 370

68) p38-beta: 230

69) p38-delta: 6600

70) p38-gamma: 7600

71) PCTK2: 1600

72) PDGFRA: 62

73) PDGFRB: 37

74) PFCDPK1(*P. falciparum*): 220

75) PFTAIRE2: 2900

76) PFTK1: 2900

77) PLK4: 4500

78) RAF1: 230

79) RET: 13

- ✓ RET(M918T): 7.4
- ✓ RET(V804L): 39
- ✓ RET(V804M): 22

80) RIPK2: 1300

81) RSK4(Kin.Dom.2-C-terminal): 7500

82) SLK: 1000

83) SRMS: 9800

84) STK33: 2400

85) STK36: 3800

86) TAK1: 690

87) TAOK1: 3100

88) TAOK2: 540

89) TAOK3: 2700

90) TGFBR2: 6900

91) TIE1: 68

92) TIE2: 2100

93) TNIK: 7900

94) TNK1: 2300

95) TNNI3K: 280

96) TRKA: 6300

97) TRKB: 2100

98) TRKC: 600

99) TTK: 3500

100) VEGFR2: 59

101) YSK4: 99

102) ZAK: 6.3

51. triggers cell growth inhibition and apoptosis by directly targeting the mitochondria and inducing rapid mitochondrial fragmentation, which is associated with the deregulation of mitochondria fusion-related protein optic atrophy 1 (OPA1)(*465*)

52. ID1 might be a potential target for the antitumor activity of sorafenib by contributing to its antitumor activity by suppressing epithelial to mesenchymal transition(*466*).

53. upregulates MiR-1274a which can repress the expression of ADAM9(*467*)

Pazopanib

1. triggers autophagic cell death via inducing cathepsin B activation, upregulating the glucosidase and downregulating the TP73 mRNA expression(*468*)

2. potently inhibits several mammalian carbonic anhydrases and in addition to its tyrosine kinase inhibitory action, it may

exert antitumor/antimetastatic effects also due to the potent inhibition of the tumor-associated, hypoxia-inducible enzymes carbonic anhydrase IX and XII(*469*)

3. immunomodulation through priming dendritic cells by downregulation of the β-catenin pathway(*470*)
4. directly binds and inhibits MEKK2 with an IC_{50} of 698 ± 163 nM(*471*)
5. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) AAK1: 2900
2) ABL1-NP: 620
   - ✓ ABL1-P: 650
   - ✓ ABL1(E255K)-P: 800
   - ✓ ABL1(F317L)-NP: 4400
   - ✓ ABL1(F317L)-P: 2700
   - ✓ ABL1(H396P)-NP: 380
   - ✓ ABL1(H396P)-P: 700
   - ✓ ABL1(M351T)-P: 560
   - ✓ ABL1(Q252H)-NP: 530
   - ✓ ABL1(Q252H)-P: 530
   - ✓ ABL1(T315I)-NP: 3800
   - ✓ ABL1(T315I)-P: 2100
   - ✓ ABL1(Y253F)-P: 480
3) ABL2: 3000
4) ACVR2B: 2400
5) ALK: 2200
6) AURKA: 7100
7) AURKC: 750
8) BIKE: 8800
9) BLK: 2600
10) BMPR1B: 1000
11) BRAF: 730
12) BRAF(V600E): 430
13) BRK: 2300
14) CAMK1: 2100
15) CAMK1G: 3700
16) CDC2L1: 2100
17) CDC2L2: 1300
18) CSF1R: 7.9
19) DDR1: 57
20) DDR2: 98
21) EPHB6: 81
22) FER: 2700
23) FES: 1400
24) FGFR1: 990
25) FGFR2: 210
26) FGFR3: 740
    - ✓ FGFR3(G697C): 620
27) FGFR4: 2800
28) FGR: 1600
29) FLT1: 14
30) FLT3: 1100
    - ✓ FLT3(D835H): 1100
    - ✓ FLT3(D835Y): 810
    - ✓ FLT3(ITD): 2500

- ✓ FLT3(K663Q): 740
- ✓ FLT3(N841I): 1600
- ✓ FLT3(R834Q): 9600

31) FLT4: 27

32) FRK: 750

33) FYN: 2700

34) GAK: 200

35) HCK: 5700

36) HPK1: 750

37) IRAK1: 5900

38) IRAK3: 800

39) JAK2(JH1domain-catalytic): 1700

40) JAK3(JH1domain-catalytic): 6900

41) JNK1: 2000

42) JNK3: 1900

43) KIT: 2.8

- ✓ KIT(A829P): 33
- ✓ KIT(D816H): 1000
- ✓ KIT(D816V): 500
- ✓ KIT(L576P): 1.8
- ✓ KIT(V559D): 2.3
- ✓ KIT(V559D,T670I): 6.5
- ✓ KIT(V559D,V654A): 30

44) LCK: 1200

45) LIMK1: 720

46) LIMK2: 390

47) LOK: 84

48) LTK: 6800

49) LYN: 1100

50) MAP3K1: 2900

51) MAP3K2: 290

52) MAP4K2: 2700

53) MAP4K3: 1600

54) MAP4K4: 2200

55) MAP4K5: 3000

56) MARK3: 4000

57) MEK4: 590

58) MEK5: 480

59) MEK6: 4100

60) MERTK: 3300

61) MET: 2000

- ✓ MET(M1250T): 3400
- ✓ MET(Y1235D): 2100

62) MLK1: 290

63) MLK2: 2100

64) MLK3: 740

65) MYLK2: 2000

66) NEK2: 980

67) NEK5: 7300

68) NLK: 4400

69) PCTK1: 1200

70) PDGFRA: 4.9

71) PDGFRB: 2

72) PFCDPK1(*P. falciparum*): 370

73) PIK4CB: 960

74) PIP5K1C: 1900

75) PIP5K2C: 280

76) PLK4: 290

77) PRKR: 1900

78) RAF1: 900

79) RET: 310

- ✓ RET(M918T): 270
- ✓ RET(V804L): 5900
- ✓ RET(V804M): 2300

80) RIOK2: 610

81) RIPK1: 260

82) RIPK2: 580

83) ROS1: 920

84) SIK: 2200

85) SIK2: 7300

86) SLK: 240

87) SRC: 2800

88) SRMS: 2500

89) STK16: 360

90) STK36: 470

91) SYK: 4700

92) TAOK1: 240

93) TAOK2: 1800

94) TAOK3: 45

95) TGFBR2: 3000

96) TIE1: 700

97) TIE2: 3300

98) TNIK: 310

99) TTK: 150

100) TXK: 2600

101) TYK2(JH1domain-catalytic): 3400

102) VEGFR2: 14

103) YES: 5000

104) YSK4: 940

Axitinib

1. induces DNA damage response characterized by γ-H2AX phosphorylation and Chk1 kinase activation leading to G2/M cell cycle arrest and mitotic catastrophe(*472*)
2. triggers senescence through ROS accumulation and ATM activation(*473*)
3. induces DNA damage response leading to senescence, mitotic catastrophe, and increased NK cell recognition through inducing a DNA damage response initially characterized by γ-H2AX phosphorylation and Chk1 kinase activation and at later time points by p21 overexpression(*474*)
4. blocks Wnt/β-catenin signaling and directs asymmetric cell division in cancer via directly stabilizing SHPRH and thereby increasing the ubiquitination and degradation of β-catenin(*475*)
5. induces the apoptosis of cancer cells possibly through decreasing the mitochondrial membrane potential(*476*)
6. has the potential to modulate antitumor immunity by downregulating STAT3 expression and reversing MDSC-mediated tumor-induced immunosuppression(*477*)
7. exerts an anticancer effect in melanoma through promoting antitumor immunity(*478*)

8. directly inhibits CSF-1R(*450*)
9. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) ZAK: 2600
2) YSK4: 270
3) YES: 2700
4) VEGFR2: 5.9
5) ULK3: 670
6) ULK2: 9900
7) TYK2(JH1domain-catalytic): 3600
8) TXK: 2400
9) TTK: 3900
10) TRKA: 1800
11) TNK2: 6000
12) TNK1: 160
13) TNIK: 180
14) TIE2: 310
15) TIE1: 97
16) TESK1: 4300
17) STK16: 370
18) SRPK3: 2300
19) SRPK1: 1800
20) SNARK: 1300
21) SLK: 1000
22) SIK: 2100
23) ROS1: 3200
24) RIPK4: 1400
25) RIPK2: 9900
26) RIPK1: 2500
27) RIOK3: 1000
28) RIOK1: 1200
29) RET: 120
    - ✓ RET(V804M): 1600
    - ✓ RET(V804L): 1300
    - ✓ RET(M918T): 100
30) PRKR: 7400
31) PLK4: 16
32) PKN2: 2700
33) PDGFRB: 0.57
34) PDGFRA: 0.51
35) PCTK1: 5300
36) PAK4: 4500
37) MYO3A: 1900
38) MYLK2: 1300
39) MST2: 2200
40) MST1: 1400
41) MRCKB: 4800
42) MLK1: 3000
43) MLCK: 1700
44) MINK: 560
45) MET: 820
    - ✓ MET(Y1235D): 990
    - ✓ MET(M1250T): 1100
46) MERTK: 3200
47) MEK5: 140
48) MEK2: 2600

49) MEK1: 2700

50) MAP4K5: 550

51) MAP4K4: 350

52) MAP4K3: 1200

53) MAP4K2: 1300

54) MAP3K4: 5600

55) MAP3K3: 2800

56) LRRK2: 920

- ✓ LRRK2(G2019S): 990

57) LOK: 1200

58) LCK: 2700

59) KIT: 3.2

- ✓ KIT(A829P): 1800
- ✓ KIT(D816H): 4200
- ✓ KIT(D816V): 1300
- ✓ KIT(L576P): 1.7
- ✓ KIT(V559D): 0.49
- ✓ KIT(V559D,T670I): 1.4
- ✓ KIT(V559D,V654A): 3.5

60) JNK1: 3900

61) JNK3: 1100

- ✓ JAK3(JH1domain-catalytic): 3100

62) JAK2(JH1domain-catalytic): 3300

63) ITK: 1200

64) IRAK1: 3100

65) HUNK: 1500

66) HPK1: 330

67) GRK4: 2300

68) GAK: 2700

69) FLT4: 170

70) FLT1: 5.8

71) FLT3: 42

- ✓ FLT3(D835H): 330
- ✓ FLT3(D835Y): 270
- ✓ FLT3(ITD): 250
- ✓ FLT3(K663Q): 31
- ✓ FLT3(N841I): 200
- ✓ FLT3(R834Q): 2400

72) FGR: 1800

73) FGFR1: 380

74) FGFR2: 110

75) FGFR3: 210

- ✓ FGFR3(G697C): 210

76) EPHB6: 360

77) EGFR(G719C): 2300

- ✓ EGFR(G719S): 6200

78) DDR1: 340

79) DDR2: 5300

80) DLK: 1700

81) CSNK2A2: 2800

82) CSK: 1100

83) CSF1R: 21

84) CDKL2: 530

85) CAMKK1: 1400

86) CAMKK2: 1500

87) BMPR1B: 2900

88) AURKA: 72

89) AURKB: 11

90) AURKC: 1.3

91) AXL: 420

92) BIKE: 1000

93) BLK: 3100

94) ANKK1: 3600

95) ACVR2B: 5200

96) AAK1: 1200

97) ABL1-NP: 84

- ✓ ABL1-P: 36
- ✓ ABL1(E255K)-P: 63
- ✓ ABL1(F317I)-NP: 2600
- ✓ ABL1(F317I)-P: 800
- ✓ ABL1(F317L)-NP: 830
- ✓ ABL1(F317L)-P: 330
- ✓ ABL1(H396P)-NP: 20
- ✓ ABL1(H396P)-P: 23
- ✓ ABL1(M351T)-P: 36
- ✓ ABL1(Q252H)-NP: 290
- ✓ ABL1(Q252H)-P: 200
- ✓ ABL1(T315I)-NP: 3.6
- ✓ ABL1(T315I)-P: 1.5
- ✓ ABL1(Y253F)-P: 230

98) ABL2: 70

Regorafenib

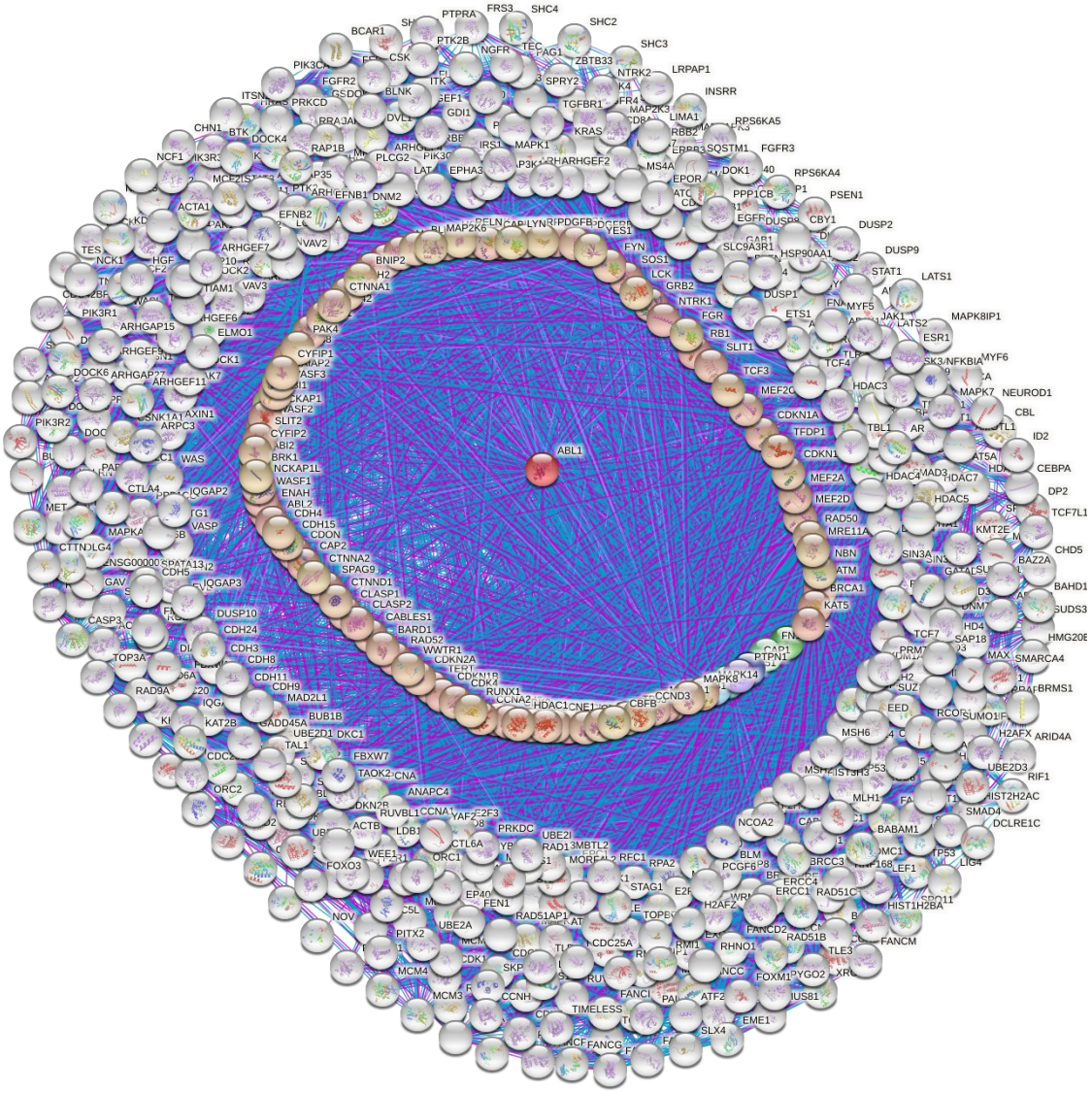
1. can exert antitumor effects via directly binding microRNA-21 pre-element(*479*)
2. exerts superior antitumor effects by enhancing SHP-1 activity that directly targets p-STAT3Tyr705(*480*)
3. Hippo signaling pathway is a mediator of regorafenib efficacy(*481*).
4. directly stabilizes PSAT1 to trigger PRKAA-dependent autophagy initiation and inhibit RAB11A-mediated autophagosome-lysosome fusion, resulting in lethal autophagy arrest(*482*)
5. abolishes epithelial-to-mesenchymal transition-related invasion/metastasis via enhancing SHP-1 activity which impedes TGF-β1-induced epithelial-to-mesenchymal transition/invasion through low p-STAT3Tyr705 level(*483*)
6. induces significant tumor inhibition by relieving the autoinhibited N-SH2 domain of SHP-1 directly and inhibiting p-STAT3 signals(*484*)
7. can efficiently block noncanonical Ang-2–driven angiogenesis by inhibiting the Ang-2/Tie2 axis(*485*)
8. inhibits invasion and metastasis by regulating the expression of MMP and TIMP gene families(*449*)
9. promotes antitumor immunity via inhibiting PD-L1 and IDO1 expression(*486, 487*)
10. inhibits Fos/Jun pathway(*488*)
11. inhibits cell proliferation and invasion of cancer cells via decreasing the expression of CXCR4 and further reducing the transcriptional activity of Wnt/β-Catenin pathway(*489*)
12. directly inhibits RIPK2(*490*)
13. inhibits these protein kinases(*491*):

1) VEGFR-1 (IC_{50}=13±0.4nm)
2) MURINE VEGFR-2(IC_{50}=4.2±1.6nm)
3) MURINE VEGFR-3 (IC_{50}=46±10nm)
4) TIE2 (IC_{50}=311±46nm)
5) FGFR1 (IC_{50}=202±18nm)
6) PDGFR-β (IC_{50}=22±3nm)
7) KIT (IC_{50}=7±2nm)
8) RET (IC_{50}=1.5±0.7nm)
9) RAF-1 (IC_{50}=2.5±0.6nm)

Lenvatinib

1. inhibits invasion and metastasis by regulating the expression of MMP and TIMP gene families(*449*)
2. has immunomodulatory activity that contributes to its antitumor activity(*492*)
3. directly inhibits these kinases(*493*):
    1) VEGFR1(K_i = 1.3nm)
    2) VEGFR2(K_i = 0.74nm)
    3) VEGFR3(K_i = 0.71nm)
    4) FGFR1(K_i = 22nm)
    5) FGFR2(K_i = 8.2nm)
    6) FGFR3(K_i = 15nm)
    7) RET(K_i = 1.5nm)
    8) KIT(K_i = 11nm)

Drugs		Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms	
IMATINIB		ABL1	ABL1	P00519	78	
DASATINIB	**NILOTINIB**				158	63
PONATINIB	**BOSUTINIB**				13	74
RIPRETINIB	**SELPERCATINIB**					



https://version-11-0b.string-db.org/cgi/network?networkId=bwgtq8WeUcGW

Imatinib

1. induces a significant increase in Type I (IFN-γ) cytokine-producing T cells(*494*)
2. potentiates antitumor T cell responses through the inhibition of IDO(*495*), see (*496*)
3. inhibition of topoisomerases may be a significant factor in imatinib-induced apoptosis(*497*)
4. induces apoptosis through Bim accumulation independently of cell cycle arrest(*498*)
5. increases apoptosis index through modulation of survivin subcellular localization in the blast phase of CML cells(*499*)
6. exerts natural killer cell-dependent antitumor effects via increasing the IFN-γ production by natural killer cells(*500*), see (*496*)
7. inhibits DDR1 and DDR2(*501, 502*)
8. induces apoptosis through production of reactive oxygen species(*503*)
9. reduces myeloid suppressor cells and releases effector lymphocyte responses(*504*)
10. inhibits the RET tyrosine kinase activity in a dose-dependent manner(*505, 506*)
11. Its anti-leukemic mechanism may involve not only the inhibition of BCR/ABL, but also DNA damage in the cells expressing this fusion protein(*507*).
12. induces downregulation of c-Kit by targeting the ATP pocket(*508*)
13. promotes apoptosis by targeting microRNA-30a-mediated runt-related transcription factor 2(*509*)
14. targets the macrophage colony-stimulating factor (M-CSF) receptor, c-FMS, and can inhibit cell proliferation and metastasis(*450, 510-513*)
15. reduces cancer stem cell ability and induces cell differentiation via continuous inhibition of PDGFR and c-Kit signaling through activation of MAPK signaling(*514*)
16. might act as an effective inhibitor of vacuolar H^+-ATPase function(*515*)
17. has an antifibrotic effect on human breast stromal fibroblasts that may inhibit desmoplastic reaction and thus tumor progression via downregulation of mRNA synthesis of collagen I and collagen III(*516*)
18. directly inhibits these kinases(*517*):
    1) PDGFRα
    2) PDFGFRβ
    3) Axl
    4) RYK
    5) EGFR
    6) EphA2
    7) EphA10
    8) IGF1R
    9) CSF-1R
19. Antiapoptotic proteins Bcl2 and BclX do not protect chronic myeloid leukemia cells from imatinib-mediated growth arrest. We conclude that, besides its apoptotic effect, imatinib acts through an apoptosis-independent mechanism to arrest cell growth(*518*).
20. directly binds MAPK14(*461*)

21. induces up-regulation of NM23, a metastasis suppressor gene(*519*)
22. It sensitizes T1 cells by directly downregulating c-FLIPL, with the use of an alternative pathway for antitumor activity, because PDGFRα is not activated in T1 cells and these cells do not express c-kit, c-ABL or PDGFRβ(*520*). See (*496*).
23. directly targets these proteins(*521, 522*):
    1) ARG(*523, 524*)
    2) KIT(*525, 526*)
    3) PDGFR(*526, 527*)
    4) DDR1
    5) NQO2
    6) CDC2
24. has antitumor effects on the GIST cells with respect to not only the inhibition of cell growth but also the suppression of VEGF at both the transcriptional and translational levels(*528*)
25. modulates the expression of various microRNAs(*529*):
26. immunomodulation via impairing the immunosuppressive function of regulatory T cells and enhancing antitumor immune responses to dendritic cell-based immunization(*530, 531*), see (*496*)
27. inhibits tumor angiogenesis by inhibiting c-Kit and consequently downregulating HIF-1α-mediated enhancement of VEGF expression(*532*)
28. causes a transcriptional shift toward alternative splicing in a large number of apoptotic genes(*533*)
29. exerts cytotoxic effects and modulates erythroid differentiation of CML cells by inducing endogenous Spred2 expression(*534, 535*)
30. binds DNA and causes conformational changes in DNA double helix(*536*)
31. triggers apoptosis in part through the upregulation of soluble histone H2AX(*537*)
32. induces a caspase-independent, necrosis-like programmed cell death via the serine protease activity of Omi/HtrA2(*538*), also see (*539*)
33. independent of its target, induces DNA damage which itself increases the activity of p53(*540*)
34. inhibits the expression of SCO2 and FRATAXIN genes that encode mitochondrial proteins(*541*)
35. can help to direct natural immunity toward an anti-leukemic reactivity by acting on the bone marrow microenvironment(*542*), see (*496*)
36. directly inhibits CSF-1R(*450*)
37. The mechanism for the apoptosis-inducing effects of imatinib may be associated with the upregulation of SHIP and caspase-9 genes(*543*).
38. not only has a direct cytotoxic effect on bcr-abl gene rearranged cells but also an indirect effect associated with increased anti-leukemic immunological function due to an intensified antigen presentation(*544*), see (*496*)
39. directly binds these kinases (K_d (μM))(*348*):
    1) ABL1: 0.0022
    2) ABL2: 0.013
    3) CLK1: 4.5

4) CLK4: 4.2
5) EPHA8: 2.1
6) FRK: 3.5
7) FYN: 5.5
8) GAK: 3.6
9) JNK1: 3.2
10) JNK2: 5.2
11) JNK3: 3.3
12) KIT: 0.83
13) LCK: 0.062
14) PDGFRB: 0.028
15) STK17A: 2.8
16) STK18: 9

40. prevents lung cancer metastasis by inhibiting M2-like polarization of macrophages via inhibiting STAT6 phosphorylation and nuclear translocation(*545*)
41. may modulate metastasis and exert anticancer activity via upregulating KAI1/CD82 gene expression(*546*)
42. enhances antigen-presenting cell function and overcomes tumor-induced CD4+ T-cell tolerance(*547*), see (*496*)
43. induces growth inhibition via production of spliced osteocalcin-mRNA(*548*)
44. modulates extracellular ATP catabolism and expression of NTPDases in a chronic myeloid leukemia cell line(*549*)
45. has the potential to exert its antileukemia effects by down-regulating hERG1 K+ channels in chronic myelogenous leukemia, independent of targeting tyrosine kinase(*550*)
46. inhibits glucose-6-phosphate dehydrogenase and glutathione reductase which are important for redox homeostasis and play key roles in many cellular processes and represent an attractive approach to the development of anticancer agents(*551*)
47. It downregulates telomerase activity and inhibits proliferation in telomerase-expressing cell lines. This study demonstrates an additional cellular target of imatinib, not necessarily mediated via known tyrosine kinases(*552*).
48. has antiangiogenic activities like downregulating VE cadherin, reducing the population of endothelial cell and reducing cell-to-cell cohesiveness, which possibly contribute to its therapeutic potential(*553*)
49. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) ABL1-NP: 1.1
✓ ABL1-P: 21
✓ ABL1(E255K)-P: 170
✓ ABL1(F317I)-NP: 8.3
✓ ABL1(F317I)-P: 580
✓ ABL1(F317L)-NP: 2.5
✓ ABL1(F317L)-P: 110
✓ ABL1(H396P)-NP: 5.9
✓ ABL1(H396P)-P: 65
✓ ABL1(M351T)-P: 44
✓ ABL1(Q252H)-NP: 1.8
✓ ABL1(Q252H)-P: 92

✓ ABL1(Y253F)-P: 130

2) ABL2: 10

3) BLK: 520

4) BRAF(V600E): 3300

5) CDK11: 5500

6) CLK1: 4500

7) CLK4: 2100

8) CSF1R: 11

9) DDR1: 0.7

10) DDR2: 15

11) DRAK1: 5300

12) EGFR(L747-E749del,A750P): 7600

13) EPHA8: 1400

14) FGR: 2400

15) FLT3(ITD): 6300

16) FRK: 1500

17) FYN: 3100

18) GAK: 1000

19) HIPK4: 960

20) IRAK1: 1200

21) JNK1: 5000

22) JNK3: 3100

23) KIT: 13

✓ KIT(A829P): 15

✓ KIT(D816H): 560

✓ KIT(D816V): 980

✓ KIT(L576P): 14

✓ KIT(V559D): 15

✓ KIT(V559D,T670I): 2500

✓ KIT(V559D,V654A): 91

24) LCK: 40

25) LYN: 890

26) MELK: 1900

27) PDGFRA: 31

28) PDGFRB: 14

29) PIP5K2C: 380

30) PLK4: 7800

31) RAF1: 1700

32) TNNI3K: 4300

33) TYK2(JH2domain-pseudokinase): 8700

34) ZAK: 2600

Dasatinib

1. directly targets these proteins(*521, 522, 554*):

1) ACK

2) ARG

3) BTK

4) KIT

5) PDGFR

6) SRC(*555, 556*)

7) YES

8) FYN

9) LYN(*557, 558*)

10) HCK

11) LCK

12) FGR

13) BLK

14) FRK

15) KHS2

16) CSK

17) RTK

18) TEC

19) BMX

20) TXK

21) DDR1(*502*)

22) DDR2(*502, 559*)

23) ACTR2B

24) ACVR2

25) BRAF

26) EGFR/ERBB1(*560*)

27) EPHA2(*561-563*)

28) EPHA3

29) EPHA4

30) EPHA5

31) EPHA8

32) EPHB1

33) EPHB2

34) EPHB4

35) EPHB6

36) ERBB2

37) ERBB4

38) FAK

39) GAK

40) GCK

41) HH498/TNNI3K

42) ILK

43) LIMK1

44) LIMK2

45) MAP2K5

46) MAP3K1

47) MAP3K2

48) MAP3K3

49) MAP3K4

50) MAP4K1

51) MAP4K5/KHS1

52) MAPK11/p38 beta

53) MAPK14/p38 alpha

54) MYT1(*564*)

55) NLK

56) PTK6/Brk

57) QIK

58) QSK

59) RAF1

60) RET

61) RIPK2

62) SLK

63) STK36/ULK

64) SYK

65) TAO3

66) TESK2

67) TYK2ZAK

68) ZAK

2. inhibits DDR1 and DDR2(*502, 559*)
3. reduces myeloid suppressor cells and releases effector lymphocyte responses(*504*)
4. transcriptional and post-translational inhibition of telomerase, independent of BRC/ABL(*565*)
5. Angiogenesis/blood vessel-related pathways and human vascular endothelial cell function (tube formation/viability) were adversely affected by dasatinib, ponatinib, and nilotinib but not by imatinib or bosutinib. These results correspond to the differences in vascular adverse event profiles of these tyrosine kinase inhibitors, imply a direct effect on vascular cells(*566*).
6. Btk tyrosine kinase is a major direct target of the Bcr-Abl inhibitor dasatinib(*554*)
7. reduces the expression of CDK8 probably independent of BCR/ABL(*567*)
8. induces apoptosis through downregulating expression levels of antiapoptotic SK-1 but not GCS, and upregulating expression levels of ceramide synthase (CerS) genes, especially CerS1(*568*)
9. inhibits FMS phosphorylation and cell proliferation(*513*)
10. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) ABL1-NP: 0.029
   - ✓ ABL1-P: 0.046
   - ✓ ABL1(E255K)-P: 0.047
   - ✓ ABL1(F317I)-NP: 0.1
   - ✓ ABL1(F317I)-P: 0.041
   - ✓ ABL1(F317L)-NP: 0.032
   - ✓ ABL1(F317L)-P: 0.019
   - ✓ ABL1(H396P)-NP: 0.025
   - ✓ ABL1(H396P)-P: 0.046
   - ✓ ABL1(M351T)-P: 0.016
   - ✓ ABL1(Q252H)-NP: 0.037
   - ✓ ABL1(Q252H)-P: 0.064
   - ✓ ABL1(T315I)-NP: 890
   - ✓ ABL1(T315I)-P: 120
   - ✓ ABL1(Y253F)-P: 0.058
2) ABL2: 0.17
3) ACVR1: 620
4) ACVR1B: 330
5) ACVR2A: 210
6) ACVR2B: 570
7) ACVRL1: 460
8) ADCK3: 190
9) AURKA: 9300
10) BLK: 0.21
11) BMPR1A: 7000
12) BMPR1B: 53
13) BMX: 1.4
14) BRAF: 500
   - ✓ BRAF(V600E): 570
15) BRK: 7.8
16) BTK: 1.4
17) CSF1R: 0.58

18) CSK: 1
19) CSNK1E: 1500
20) DDR1: 0.69
21) DDR2: 3.2
22) DMPK: 1300
23) DMPK2: 1200
24) EGFR: 120
    - ✓ EGFR(E746-A750del): 130
    - ✓ EGFR(G719C): 170
    - ✓ EGFR(G719S): 79
    - ✓ EGFR(L747-E749del, A750P): 110
    - ✓ EGFR(L747-S752del, P753S): 320
    - ✓ EGFR(L747-T751del,Sins): 160
    - ✓ EGFR(L858R): 120
    - ✓ EGFR(L858R,T790M): 2200
    - ✓ EGFR(L861Q): 110
    - ✓ EGFR(S752-I759del): 330
    - ✓ EGFR(T790M): 2300
25) EPHA1: 4.1
26) EPHA2: 0.85
27) EPHA3: 0.093
28) EPHA4: 1.2
29) EPHA5: 0.24
30) EPHA6: 2100
31) EPHA8: 0.24
32) EPHB1: 0.45
33) EPHB2: 0.39
34) EPHB3: 6.9
35) EPHB4: 0.34
36) EPHB6: 0.039
37) ERBB2: 1400
38) ERBB3: 18
39) ERBB4: 55
40) FGFR1: 3700
41) FGFR2: 1400
42) FGFR3: 3900
43) FGR: 0.5
44) FLT1: 5000
45) FLT3: 4800
    - ✓ FLT3(D835H): 8100
    - ✓ FLT3(D835Y): 4800
    - ✓ FLT3(ITD): 9900
    - ✓ FLT3(K663Q): 3200
    - ✓ FLT3(N841I): 7000
46) FRK: 0.31
47) FYN: 0.79
48) GAK: 2.6
49) GCN2(Kin.Dom.2,S808G): 1600
50) HCK: 0.35
51) HPK1: 980
52) JAK2(JH1domain-catalytic): 1000
53) JAK3(JH1domain-catalytic): 640
54) KIT: 0.81
    - ✓ KIT(A829P): 0.66
    - ✓ KIT(D816H): 1.6
    - ✓ KIT(D816V): 2.6

- ✓ KIT(L576P): 0.57
- ✓ KIT(V559D): 0.68
- ✓ KIT(V559D,V654A): 2.7

55) LCK: 0.2

56) LIMK1: 570

57) LIMK2: 86

58) LOK: 1200

59) LYN: 0.57

60) LZK: 5300

61) MAP3K2: 140

62) MAP3K3: 280

63) MAP3K4: 310

64) MAP4K2: 1300

65) MAP4K3: 640

66) MAP4K4: 3100

67) MAP4K5: 45

68) MEK1: 1000

69) MEK2: 1400

70) MEK5: 3.3

71) MINK: 430

72) MRCKA: 2000

73) MRCKB: 2100

74) MST1: 3800

75) MST4: 1900

76) MYLK2: 3500

77) NEK11: 470

78) NEK2: 6500

79) NLK: 260

80) p38-alpha: 27

81) p38-beta: 410

82) PDGFRA: 0.47

83) PDGFRB: 0.63

84) PFCDPK1(*P. falciparum*): 640

85) PKMYT1: 130

86) QSK: 28

87) RAF1: 570

88) RET: 730

- ✓ RET(M918T): 390
- ✓ RET(V804L): 3200

89) RIPK2: 31

90) SBK1: 1200

91) SIK: 3.9

92) SIK2: 6.4

93) SLK: 720

94) SRC: 0.21

95) SRMS: 13

96) STK35: 770

97) STK36: 210

98) SYK: 2900

99) TAK1: 3700

100) TAOK2: 5400

101) TAOK3: 2300

102) TEC: 13

103) TESK1: 33

104) TGFBR1: 230

105) TGFBR2: 2900

106) TNIK: 2000

107) TNK2: 5.6

108) TNNI3K: 11

109) TXK: 2.1

110) TYK2(JH1domain-catalytic): 1800

- ✓ TYK2(JH2domain-pseudokinase): 110

111) ULK3: 4600

112) VEGFR2: 2900

113) VRK2: 3200

114) WEE1: 7000

115) WEE2: 200

116) YES: 0.3

117) YSK1: 3400

118) YSK4: 79

119) ZAK: 45

11. an immunological component of its anti-tumoral "off-target" effect is that it also influences non-conventional T-αβ cell subsets known for their potential anti-tumoral properties, namely iNKT cells and the distinct new innate CD8 T-cell subset(*569*)

12. targets several off-target proteins and peptide in tumor environment(*570*)

13. directly inhibits EphA2 in a dose-dependent manner and may exert anticancer effects due to EphA2 inhibition, besides its effects on Src(*561-563*)

14. increases the activation of allogenic T cells via modulating dendritic cell activity via confining c-Kit signaling and IDO-mediated tryptophan metabolism(*571*)

15. directly binds 40 different kinases (identified reproducibly in three human cell lines using affinity chromatography approach)(*572*):

1) ABL1

2) ABL2 isoform IB

- ✓ ABL2 isoform 4

3) ACVR1

4) ACVR1B

5) CSK

6) DDR1

7) EGFR(*560*)

8) EPHA1

9) EPHA2(*561-563*)

10) EPHA4

11) EPHA5

12) EPHA8

13) EPHB1

14) EPHB2

15) EPHB3

16) EPHB4

17) FRK

18) FYN

19) GAK

20) ILK

21) QSK

22) LCK

23) LIMK2

24) LYK5

25) LYN isoform A

- ✓ LYN isoform B(*557, 558*)

26) MAP2K5

27) MAP3K1

28) MAP3K2

29) MAP4K5

30) MAPK14 isoform1

- ✓ MAPK14 isoform2

31) PRO3078

32) BRK

33) RICK

34) SIK

35) QIK

36) SRC

37) TEC

38) TESK1

39) TGFBR1

40) TNK2(*573*)

41) TYK2

42) YES1

43) ZAK isoform 1

- ✓ ZAK isoform 2

16. has immunostimulatory effects in the form of persistent monoclonal/oligoclonal LGL lymphocytosis(*574-577*), at least partly through directly stimulating the proliferation of natural killer cells(*578*)

17. promotes cell death by targeting c-KIT(*579*)

18. is associated with a rapid mobilization of cytotoxic lymphocytes through direct effect on signal transduction pathways(*580, 581*)

19. exerts antitumor effects via directly inhibiting TNK2(*572, 573*)

20. induces apoptosis through degradation of EGFR(*582*)

21. can inhibit AR Tyr267 and AR Tyr 534 phosphorylation, and it may play a significant role in anti-prostate cancer cells by inhibiting Ack1-mediated AR Tyr-267 phosphorylation and the expression of PSA mRNA and hk2 mRNA induced by heregulin(*583*)

22. enhances the activity of immune system, particularly via natural killer cell differentiation through inhibition of regulatory T cells(*584*)

23. enhances T-cell responses and interleukin 12 (IL-12) production via enhancing the stimulatory activity of dendritic cells(*585*)

24. exerts antitumor effects via decreasing levels of T regulatory cells while specifically enhancing tumor antigen-specific T cell responses(*586*)

25. can induce pyroptosis in tumor cells and increase the protein levels of GSDMD and GSDME (gasdermin E) in a p53-independent manner(*587*)

26. directly binds and inhibits MEKK2(*324, 471*)

27. directly binds and targets these kinases(*588*):

1) AXL

2) c-KIT

- ✓ c-KIT(D816 V)
- ✓ c-KIT(D816 H)

3) c-RAF

4) EGFR
   - ✓ EGFR(T790M)

5) FES

6) IRAK4

7) LIMK1

8) PDGFRα

9) RIPK2

10) TIE2

11) TRKA

12) TRKB

13) TXK

Nilotinib

1. induces apoptosis through Bim accumulation independently of cell cycle arrest(*498*)
2. inhibits DDR1(*589*) and DDR2(*502*)
3. Angiogenesis/blood vessel-related pathways and human vascular endothelial cell function (tube formation/viability) were adversely affected by dasatinib, ponatinib, and nilotinib but not by imatinib or bosutinib. These results correspond to the differences in vascular adverse event profiles of these tyrosine kinase inhibitors, imply a direct effect on vascular cells(*566*).
4. Directly targets these proteins(*521, 522*):
   1) ARG
   2) KIT
   3) PDGFR(*590*)
   4) DDR1
   5) NQO2
5. transcriptional and post-translational inhibition of telomerase, independent of BRC/ABL(*565*)
6. induces apoptosis through upregulating ceramide synthase genes and downregulating SK-1 in CML cells in addition to inhibition of BCR/ABL(*591*)
7. in addition to its known activity against several tyrosine-kinase-mediated proliferative pathways, exerts antitumor effects via directly binding receptor Smoothened (SMO) and direct inhibition of the Hedgehog pathway(*592*)
8. induces autophagic cell death through deactivating phosphatase PP2A and subsequently increasing AMPK phosphorylation(*593*)
9. can exert antitumor effects in not only Philadelphia-positive but also Philadelphia-negative acute lymphoblastic leukemia via inhibiting MDM2 and inducing a p53-independent apoptosis pathway by downregulating XIAP(*594*)
10. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):
    1) ABL1-NP: 10
       - ✓ ABL1-P: 13
       - ✓ ABL1(E255K)-P: 36
       - ✓ ABL1(F317I)-NP: 18
       - ✓ ABL1(F317I)-P: 56
       - ✓ ABL1(F317L)-NP: 12

- ✓ ABL1(F317L)-P: 14
- ✓ ABL1(H396P)-NP: 4.9
- ✓ ABL1(H396P)-P: 21
- ✓ ABL1(M351T)-P: 15
- ✓ ABL1(Q252H)-NP: 10
- ✓ ABL1(Q252H)-P: 21
- ✓ ABL1(T315I)-NP: 660
- ✓ ABL1(Y253F)-P: 13

2) ABL2: 26
3) BLK: 500
4) BRAF: 1700
   - ✓ BRAF(V600E): 570
5) CLK1: 2100
6) CLK4: 7100
7) CSF1R: 45
8) CSK: 2400
9) DDR1: 1.1
10) DDR2: 33
11) EPHA1: 590
12) EPHA2: 230
13) EPHA3: 110
14) EPHA4: 330
15) EPHA5: 1900
16) EPHA6: 640
17) EPHA8: 37
18) EPHB1: 1300
19) EPHB2: 640
20) EPHB3: 1000
21) EPHB4: 730
22) EPHB6: 500
23) FGR: 320
24) FRK: 86
25) FYN: 1600
26) HCK: 390
27) HPK1: 890
28) JNK1: 450
29) JNK2: 5800
30) JNK3: 2000
31) KIT: 29
   - ✓ KIT(A829P): 46
   - ✓ KIT(D816H): 540
   - ✓ KIT(D816V): 770
   - ✓ KIT(L576P): 22
   - ✓ KIT(V559D): 46
   - ✓ KIT(V559D,T670I): 150
   - ✓ KIT(V559D,V654A): 260
32) LCK: 47
33) LOK: 6800
34) LYN: 100
35) MEK5: 190
36) MRCKB: 910
37) p38-alpha: 460
38) p38-beta: 36
39) PDGFRA: 180
40) PDGFRB: 73
41) PFCDPK1(*P. falciparum*): 790

42) PIP5K2C: 8800

43) RAF1: 3900

44) RET: 870

- ✓ RET(M918T): 1100

45) SRC: 1900

46) TAOK1: 4700

47) TAOK3: 1700

48) TIE1: 1000

49) TIE2: 1000

50) TNNI3K: 360

51) TRKB: 490

52) TRKC: 600

53) YES: 1100

54) ZAK: 11

Ponatinib

1. inhibits DDR1 and DDR2(*501, 502*)
2. Angiogenesis/blood vessel-related pathways and human vascular endothelial cell function (tube formation/viability) were adversely affected by dasatinib, ponatinib, and nilotinib but not by imatinib or bosutinib. These differences in vascular adverse event profiles of these tyrosine kinase inhibitors, imply a direct effect on vascular cells(*566*).
3. modulates the expression of various microRNAs(*529*):
4. directly binds and inhibits MEKK2 with an IC_{50} of 16 ± 3(*595*)
5. exerts antiangiogenic effects via blocking VEGFR signaling at its receptor level and downstream pathways(*596*)
6. directly inhibits RIPK2(*490*)
7. exerts antitumor effects via inhibiting various FGFRs(*597*)
8. inhibits the phosphorylation of(*598*):
    1) RYK
    2) CSF1R
    3) ALK
    4) TEK
9. Reduces endothelial survival and angiogenesis and induces their senescence and apoptosis via Notch-1 pathway(*599*)
10. has microtubule stabilizing activity(*600*)

Bosutinib

1. targets about 30 proteins in tumor environments(*570*)
2. directly binds and inhibits MEKK2 with an IC_{50} of 59 nM(*471, 595*)
3. directly inhibits these proteins(*521*):
    1) ACK
    2) ALK4
    3) ARG
    4) BCR-ABL
    5) BTK
    6) CaMKK2
    7) CK1d
    8) CK1e
    9) CLK2
    10) CSK
    11) DDR1
    12) EphB1

13) EphB4

14) FAK

15) FER

16) FRK

17) FYN

18) GAK

19) GCK

20) HCK

21) HRI

22) KHS2

23) LYN

24) MAP3K1

25) MAP3K2

26) MAP3K3

27) MAP3K4

28) MER

29) MYT1

30) NLK

31) PKCt

32) PYK2

33) QIK

34) QSK

35) RSK2

36) SLK

37) SRC

38) SYK

39) TBK1

40) TEC

41) Wee1

42) YES

43) ZAK

44) ZC2_TNIK

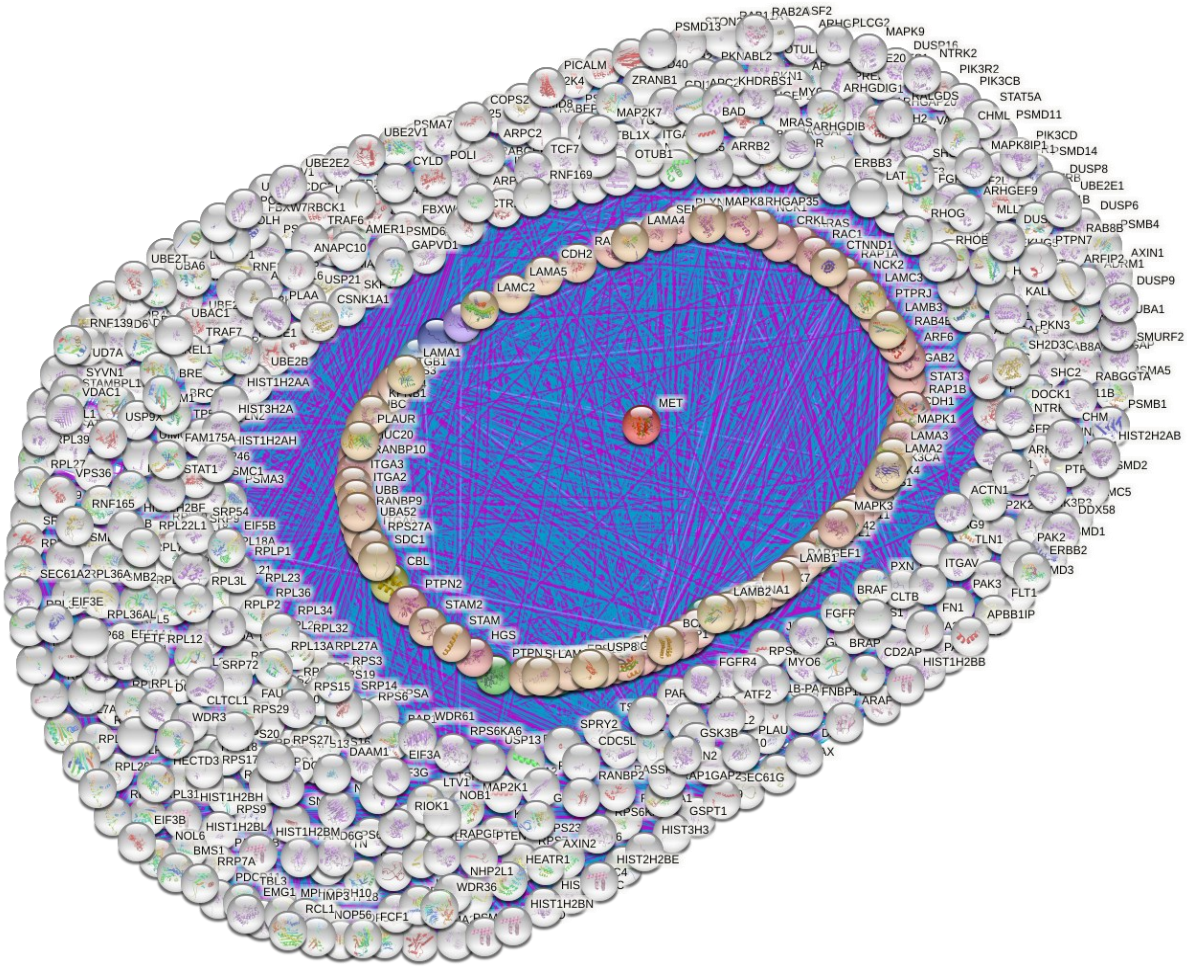
4. directly binds and prevents auto-phosphorylation of ACK1(*588*) and attenuates migration and invasion of tumors via inhibition of ACK1(*601*)

5. directly binds these kinases(*588*):

    1) MAP4K5 (KHS)
    2) YES1
    3) SRC
    4) FGR
    5) LCK
    6) FYN
    7) FRK (PTK5)
    8) BTK
    9) TNK2 (ACK1)
    10) HCK
    11) STK24 (MST3)
    12) EPHB4
    13) BMX
    14) LYN (A and B)
    15) MAP4K2 (GCK)
    16) MINK1
    17) STK10 (LOK)
    18) SYK
    19) CSK
    20) CAMK1D

21) PTK2B (FAK2, PYK2)
22) CAMK2G
23) STK4 (MST1)
24) TEC
25) TBK1
26) FER
27) PTK2 (FAK)
28) TAOK3 (JIK)
29) PRKAA1 (AMPK)
30) MAP2K1 (MEK1)
31) MST4 (MASK)
32) MAP2K2 (MEK2)
33) AAK1
34) MAP3K2
35) MAP3K3
36) ZAK (Isoforms 1 & 2)
37) STK35 (CLIK1)
38) MAPK14 (p38a)
39) BMP2K (BIKE)
40) ILK
41) STK25 (YSK1)
42) TNIK
43) SLK
44) MAP4K4 (HGK, NIK)
45) MAP3K1
46) GAK
47) MAP4K1 (HPK1)
48) PKMYT1
49) MAP2K5
50) MAP3K

Drugs	Discovery Target	Uniprot ID	"Off-Target" Therapeutic Mechanisms
CRIZOTINIB	MET	P08581	148
CABOZANTINIB			5
LAROTRECTINIB LORLATINIB			
CERITINIB BRIGATINIB			9
ENTRECTINIB CAPMATINIB			



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Crizotinib

1. "Shortly after in 2007, anaplastic lymphoma kinase (ALK) was fortuitously identified as a drug target in NSCLC. Initially, the industry researchers who developed crizotinib, the first-in-class oral ALK TKI, were searching for a mesenchymal–epithelial transition factor (MET) inhibitor.(*602*)"
2. directly binds and inhibits MEKK2 with an IC_{50} of 75 ± 35 nM(*471*)
3. reduces gastric cancer growth through oxidative DNA damage and triggers pro-survival Akt signal(*603*)
4. induces apoptosis via lethal endoplasmic reticulum stress response in cancer cells by increasing intracellular levels of reactive oxygen species, independent of MTH1 inhibition(*604, 605*)
5. induces apoptosis via downregulation of BCL-2 family proteins including MCL-1(*606*)
6. stimulates antitumor immune responses via inducing Immunogenic cell death(*607*)
7. Crizotinib-induced antitumor activity is not solely dependent on ALK and MET inhibition(*605*).
8. Exerts antitumor effects via directly inhibiting FAK1 (PTK2)(*608*)
9. suppresses the growth of aggressive thyroid cancer cells, and this potential therapeutic benefit results from their non-MET-targeting effects(*609*)
10. reduces tumor burden and metastasis via reducing the phosphorylation of Akt and the activity of matrix metalloproteinases and adhesion to various extracellular matrices(*610*)
11. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) AAK1: 2300
2) ABL1-NP: 78
   - ✓ ABL1-P: 110
   - ✓ ABL1(E255K)-P: 170
   - ✓ ABL1(F317I)-NP: 2700
   - ✓ ABL1(F317I)-P: 3200
   - ✓ ABL1(F317L)-NP: 610
   - ✓ ABL1(F317L)-P: 590
   - ✓ ABL1(H396P)-NP: 33
   - ✓ ABL1(H396P)-P: 87
   - ✓ ABL1(M351T)-P: 97
   - ✓ ABL1(Q252H)-NP: 97
   - ✓ ABL1(Q252H)-P: 100
   - ✓ ABL1(T315I)-NP: 12
   - ✓ ABL1(T315I)-P: 10
   - ✓ ABL1(Y253F)-P: 74
3) ABL2: 460
4) ACVR1: 440
5) ACVR1B: 860
6) ADCK4: 1100
7) ALK: 3.3
8) AMPK-alpha1: 2400
9) ANKK1: 780
10) AURKA: 260

11) AURKB: 76
12) AURKC: 4300
13) AXL: 7.8
14) BIKE: 740
15) BLK: 110
16) BMPR1B: 230
17) BMX: 3600
18) BTK: 7800
19) CAMKK2: 1500
20) CASK: 140
21) CDC2L1: 760
22) CDC2L2: 420
23) CDK7: 330
24) CDKL2: 2100
25) CSF1R: 210
26) DCAMKL1: 330
27) DCAMKL2: 370
28) DDR1: 510
29) DLK: 170
30) DMPK: 1400
31) DYRK2: 4000
32) EGFR(G719C): 2700
    - ✓ EGFR(L861Q): 2700
33) EPHA1: 140
34) EPHA2: 100
35) EPHA3: 700
36) EPHA4: 360
37) EPHA5: 1000
38) EPHA6: 65
39) EPHA7: 470
40) EPHA8: 280
41) EPHB1: 120
42) EPHB4: 570
43) EPHB6: 6
44) ERK5: 510
45) FAK: 310
46) FER: 270
47) FES: 450
48) FGFR3: 2700
    - ✓ FGFR3(G697C): 3500
49) FGR: 670
50) FLT1: 2300
51) FLT3: 850
    - ✓ FLT3(D835H): 500
    - ✓ FLT3(D835Y): 210
    - ✓ FLT3(ITD): 730
    - ✓ FLT3(K663Q): 900
    - ✓ FLT3(N841I): 860
    - ✓ FLT3(R834Q): 3000
52) FRK: 2900
53) FYN: 1300
54) GRK4: 4200
55) HIPK4: 3600
56) HPK1: 39
57) IGF1R: 780
58) IKK-beta: 5500

59) IKK-epsilon: 710
60) INSR: 340
61) INSRR: 600
62) IRAK1: 49
63) IRAK3: 31
64) IRAK4: 3600
65) ITK: 2000
66) JAK1(JH1domain-catalytic): 330
67) JAK2(JH1domain-catalytic): 290
68) JAK3(JH1domain-catalytic): 200
69) KIT(D816V): 3700
    - ✓ KIT(V559D,T670I): 800
70) LCK: 30
71) LIMK1: 830
72) LIMK2: 690
73) LOK: 44
74) LTK: 12
75) LYN: 940
76) LZK: 230
77) MAP3K1: 1100
78) MAP3K15: 2800
79) MAP3K2: 72
80) MAP3K3: 110
81) MAP4K2: 80
82) MAP4K3: 75
83) MAP4K5: 79
84) MEK3: 3300
85) MERTK: 3.6
86) MET: 2.1
    - ✓ MET(M1250T): 0.55
    - ✓ MET(Y1235D): 1.5
87) MINK: 4400
88) MST1: 580
89) MST1R: 25
90) MST2: 990
91) MST4: 2800
92) MUSK: 230
93) NEK7: 5700
94) NEK9: 790
95) NIM1: 4600
96) PIP5K1A: 3200
97) PLK4: 60
98) PRKD1: 990
99) PRKD3: 510
100) PRKR: 1100
101) PYK2: 190
102) RET(M918T): 1300
    - ✓ RET(V804L): 2100
103) RIOK1: 6100
104) RIOK3: 4000
105) RIPK1: 1600
106) RIPK2: 900
107) RIPK4: 2100
108) RIPK5: 450
109) ROCK1: 3700
110) ROCK2: 3300

111) ROS1: 4.1

112) S6K1: 640

113) SBK1: 1300

114) SgK110: 240

115) SIK2: 200

116) SLK: 18

117) SNARK: 120

118) SRC: 560

119) SRPK1: 1800

120) SRPK3: 8200

121) STK35: 610

122) SYK: 2500

123) TAK1: 1800

124) TAOK1: 1200

125) TAOK2: 900

126) TAOK3: 490

127) TBK1: 690

128) TESK1: 380

129) TGFBR1: 1000

130) TIE1: 110

131) TIE2: 270

132) TNK1: 320

133) TNK2: 760

134) TNNI3K: 110

135) TRKA: 95

136) TRKB: 37

137) TRKC: 82

138) TXK: 850

139) TYK2(JH1domain-catalytic): 210

✓ TYK2(JH2domain-pseudokinase): 2000

140) TYRO3: 800

141) ULK1: 1000

142) ULK2: 1600

143) ULK3: 6700

144) YES: 770

145) YSK4: 980

146) ZAP70: 4200

Cabozantinib

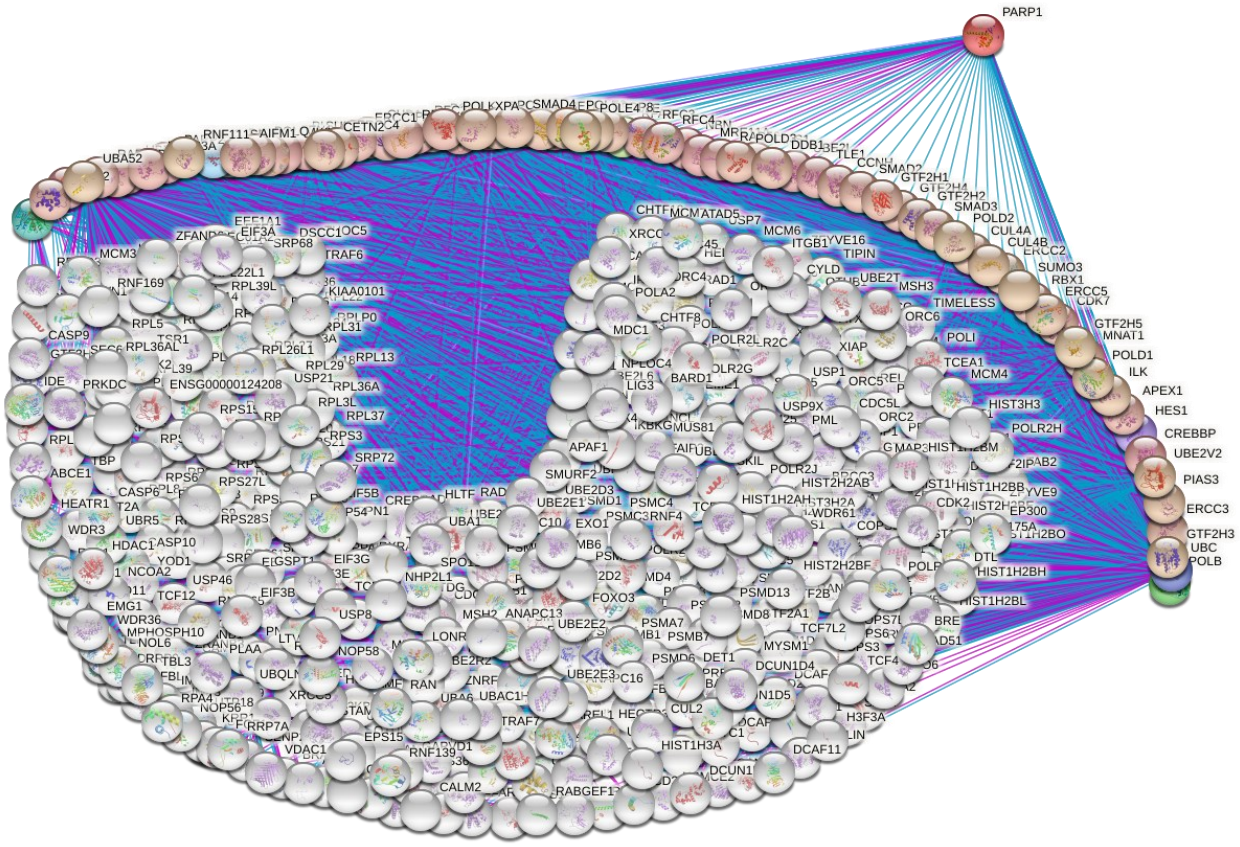
1. targets a broad range of targets, including(*611*):
    1) MET
    2) RET
    3) AXL
    4) VEGFR2
    5) FLT3
    6) c-KIT
2. inhibits cancer cell migration and invasion via inhibition of GAS6-AXL pathway independent of HGF-MET pathway(*612*)
3. exerts antitumoral and antimigratory effects which are most probably off-target effects, not mediated by c-Met(*613*)

Ceritinib

1. suppresses mTORC1 signaling in the presence of trametinib through direct inhibition of IGF1R and/or ACK1(*614*)
2. has activity even in ALK-negative cancer cell lines via off-targets like(*615*):

1) IGF1R
2) FAK1 (encoded by *PTK2*)
3) RSK1/2 (encoded by *RPS6KA1/3*)
4) ERK1/2
5) CAMKK2
6) FER
7) CAMKK2
8) AMPKα1

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
OLAPARIB	poly(ADP-ribose) polymerase 1	PARP1	P09874	4
RUCAPARIB				17
NIRAPARIB				2
TALAZOPARIB				3



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Olaparib

1. induces upregulation of death receptors in primary acute myeloid leukemia blasts by NF-κB activation(*616*)
2. inhibits the PI3K/AKT/mTOR signaling pathway(*617*)
3. induces cellular senescence through P16-RB/P53-RB signaling pathway(*618*)
4. traps PARP1 and PARP2 to the sites of DNA damage and prevents DNA repair, replication, and transcription, leading to cell death(*619*)

Rucaparib

1. micromolar affinities (IC_{50} values) for nine protein kinases(*620*):
    1) PIM1 (1.2 μM)
    2) PIM2 (7.7 μM)
    3) PRKD2 (9.7 μM)
    4) DYRK1A (1.4 μM)
    5) CDK1 (1.4 μM)
    6) CDK9 (2.7 μM)
    7) HIPK2 (4.4 μM)
    8) CK2 (7.8 μM)
    9) ALK (18 μM)
2. inhibits hexose-6-phosphate dehydrogenase(*621*)
3. induces vasodilation and potentiates response antitumor effects of other drugs through a complex process that involves myosin light chain kinase, P2 receptors, and PARP itself(*622*)
4. suppresses the lactate dehydrogenase pathway(*623*)
5. activates necrotic apoptosis via inducing the production of excessive reactive oxygen species and upregulating the expression of RIP1 and RIP3(*624*)
6. traps PARP1 and PARP2 to the sites of DNA damage and prevents DNA repair, replication, and transcription, leading to cell death(*619*)

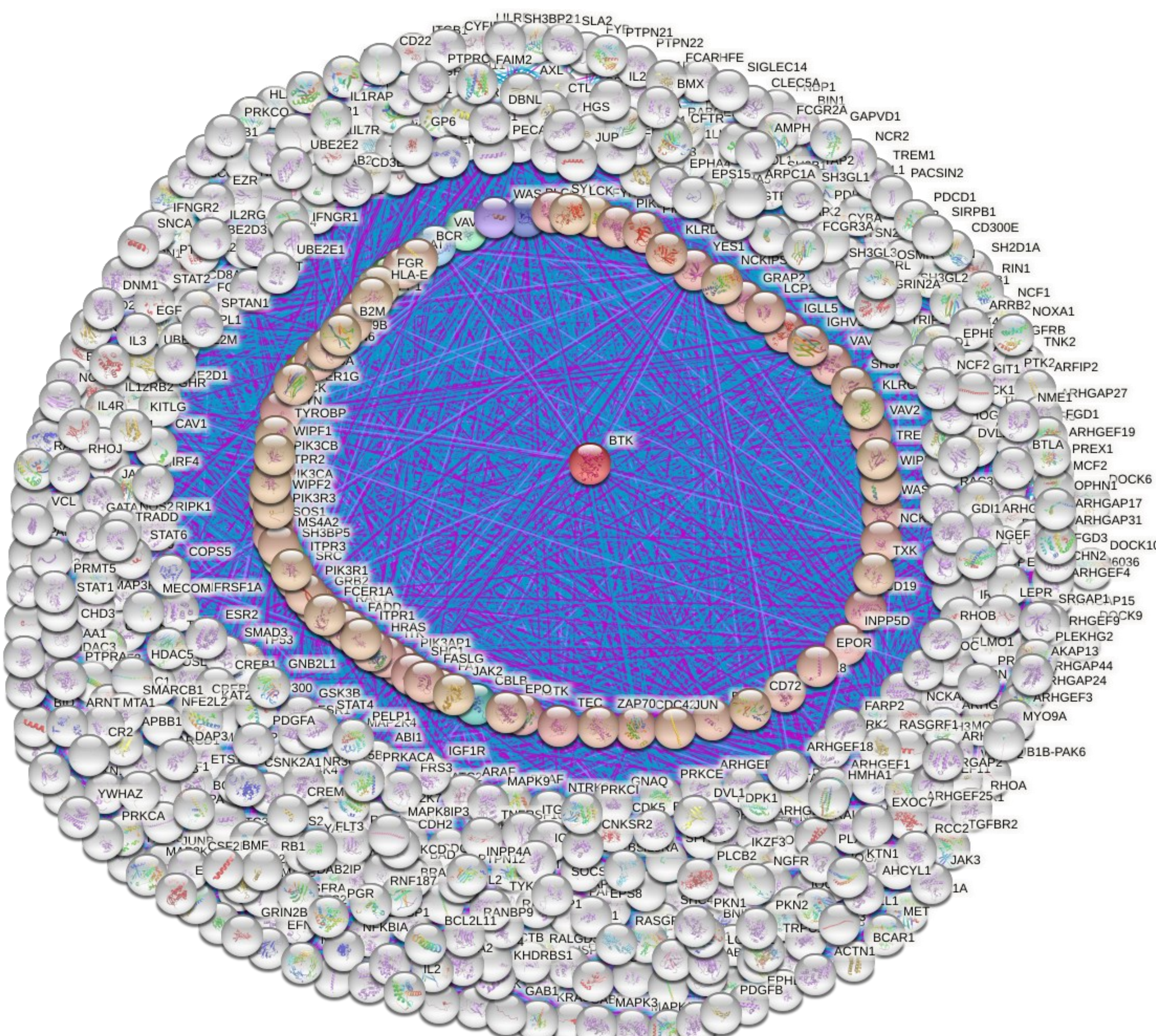
Niraparib

1. inhibits deoxycytidine kinase and reduces cytarabine activity(*621*)
2. traps PARP1 and PARP2 to the sites of DNA damage and prevents DNA repair, replication, and transcription, leading to cell death(*619*)

Talazoparib

1. induces not only cancer cell-intrinsic apoptosis but also cancer cell-extrinsic antitumor immune effects via increasing the number of peritoneal $CD8^+$ T cells and NK cells as well as their production of IFN-γ and TNF-α(*625*)
2. G2/M cell cycle arrest via the upregulation of p53(*626*)
3. traps PARP1 and PARP2 to the sites of DNA damage and prevents DNA repair, replication, and transcription, leading to cell death(*619*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
IBRUTINIB	Bruton tyrosine kinase	BTK	Q06187	40
ACALABRUTINIB				3
ZANUBRUTINIB				



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Ibrutinib

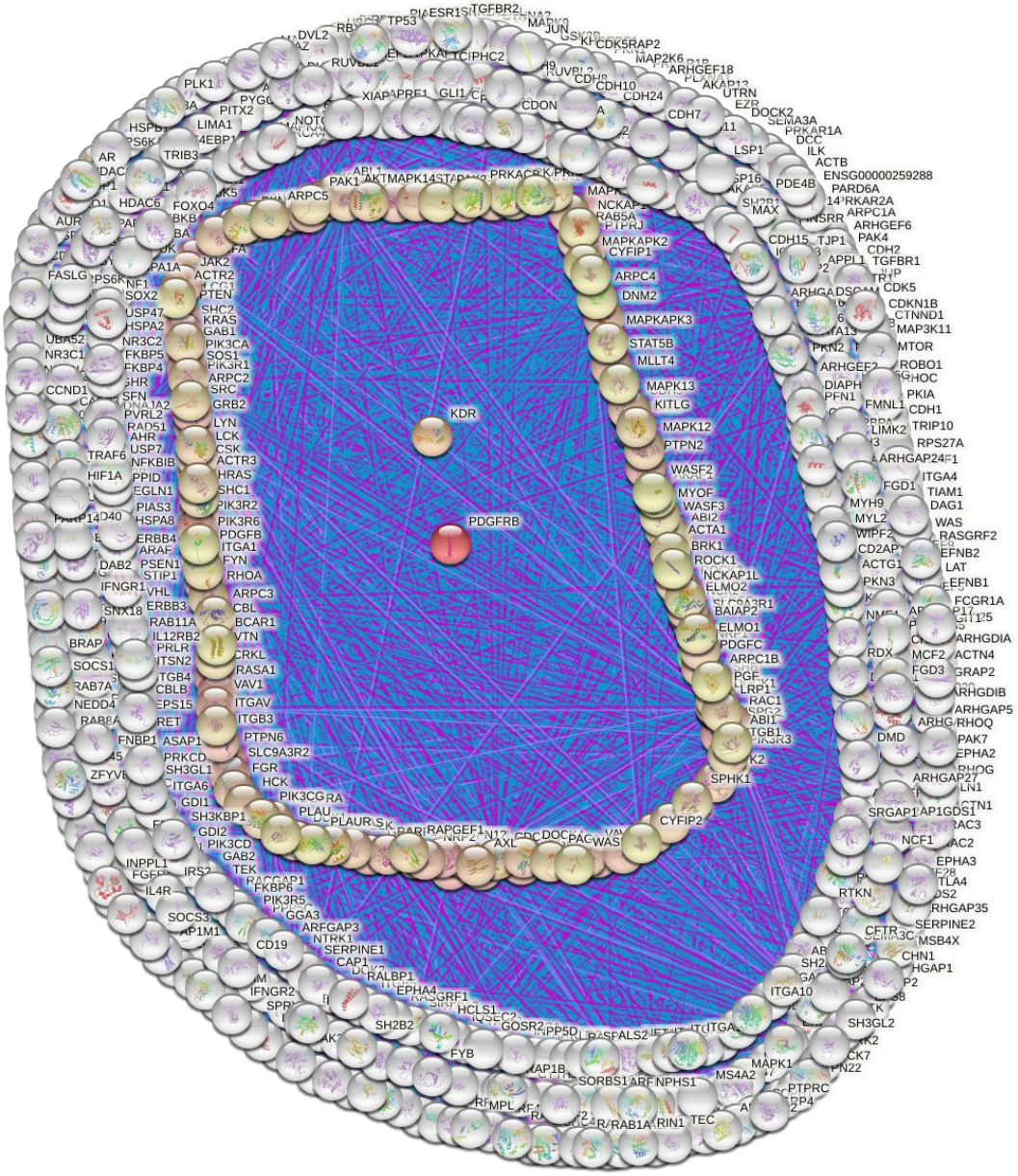
1. Inhibits VEGFR2(*627*)
2. Inhibits Janus Kinase 2 (JAK2)(*628*)
3. also binds other kinases that are relevant to antitumor effects (IC_{50} in nM)(*629*):
    1) TEC (78)
    2) ITK (10.7)
    3) BMX (0.8)
    4) BLK (0.5)
    5) EGFR (5.6)
    6) ErbB2/HER2 (9.4)
    7) JAK3 (16.1)
4. inhibits ERBB receptor tyrosine kinases and tumor growth(*630*)
5. inhibits IL-2-inducible kinase (ITK)(*630-632*)
6. immunomodulation via modifying the function of monocyte/macrophage populations(*633*)
7. causes cellular reactive oxygen species elevation and induces cancer cell apoptosis through irreversible inhibition of mammalian thioredoxin reductase enzymes, aside from its therapeutic mechanism through BTK inhibition(*634*)
8. both BTK and B lymphocyte kinase (BLK) are relevant targets of ibrutinib(*635*)
9. inhibits Wnt signaling pathway(*636*)
10. activates endoplasmic reticulum stress-induced cell death(*637*)
11. inhibits LCK and SRC phosphorylation in normal T cells(*638*)
12. increases the in vivo persistence of activated T cells, decreases the Treg/$CD4^+$ T cell ratio, and diminishes the immune-suppressive properties of CLL cells through BTK-dependent and -independent mechanisms(*639*)
13. targets microRNA-21 in multiple myeloma cells by inhibiting NF-κB and STAT3(*640*)
14. downregulates activation-induced cytidine deaminase (AID) enzyme and proliferative fractions in chronic lymphocytic leukemia(*641*)
15. induces rapid down-regulation of inflammatory markers and altered transcription of chronic lymphocytic leukemia-related genes in blood and lymph nodes(*642*)
16. exerts immunomodulatory effects through regulation of tumor infiltrating macrophages(*643*)
17. induces changes in nuclear morphology and causes apoptosis via caspase-dependent extrinsic apoptosis pathway with the activation of caspases-8, caspase-3, and cleavage of PARP1(*644*)
18. inhibits ERBB4 activity in the same nM range as its canonical target, BTK, and consequently reduces cell growth in a WNT5A-dependent manner(*645*)
19. inhibits free fatty acid metabolism in chronic lymphocytic leukemia(*646*)
20. inhibits wild and mutant-EGFR kinase(*647, 648*)
21. increases apoptosis and G1-S cell-cycle delay via inhibiting EGFR, HER2, ErbB3, and ErbB4 and consequently inhibiting AKT and ERK signaling pathways(*648*)

22. downregulates a subset of miRNAs leading to upregulation of tumor suppressors and inhibition of cell proliferation in chronic lymphocytic leukemia(*649*)
    1) miR-22
    2) miR-34a
    3) miR-146b
    4) miR-181b
23. blocks immunophenotypic changes associated with the adhesion and activation of CLL cells in the tumor microenvironment through changing the expression of these 11 antigens(*650*):
    1) CD23
    2) CD27
    3) CD53
    4) CD58
    5) CD71
    6) CD80
    7) CD84
    8) CD97
    9) CD126
    10) CD150
    11) FMC7
24. hematopoietic cell kinase (HCK) is a survival determinant transactivated by mutated MYD88, and a direct target of ibrutinib(*651*)
25. changes the quantity of about 1000 unique proteins, with nearly 400 significant changes (p-value < 0.05)(*652*)

Acalabrutinib

1. reduces expression of the immunosuppressive molecules CD200 and BTLA as well as IL-10 production by CLL cells(*639*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
SUNITINIB	kinase insert domain receptor	KDR	P35968	270
	platelet derived growth factor receptor beta	PDGFRβ	P09619	



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1. inhibits the autophosphorylation of the receptor tyrosine kinase fms-like tyrosine kinase 3 (FLT3) in a dose-dependent manner and reduces survival and migration of human meningioma cells(*653*)
2. Sunitinib but not VEGF blockade inhibits cancer stem cell endothelial differentiation, suggesting a VEGF-independent mechanism(*654*).
3. inhibits other tyrosine kinases including, KIT, FLT3, colony-stimulating factor 1 (CSF-1), and RET which are associated with neoplasms(*450, 655*)
4. inhibits autophagy independent of AMPK signaling and through SQSTM1/p62(*656*)
5. inhibits the migration and invasion of MCF-7 through downregulation of the interaction between furin and its substrates (pro-MT1-MMP, pro-VEGF-C)(*657*)
6. concentration-dependent induction of oxidative stress genes (heme oxygenase 1 and glutathione transferase A1) through the nuclear factor erythroid 2-related factor 2 pathway(*658*)
7. directly inhibits the activity of mammalian 5′-AMP-activated protein kinase (AMPK)(*659*)
8. directly induces cell death in renal cancer cells and simultaneously affect the expression levels of their apoptosis-related microRNAs, miR-145, miR-15a and miR-16, upon this process(*660*)
9. directly targets vascular endothelial-cadherin and inhibits phosphorylation which is induced by VEGF(*661*)
10. directly binds and inhibits MEKK2(*324, 471*)
11. induces apoptosis in colon cancer cells via PUMA(*662*)
12. inhibits hemangioma cell growth and migration by suppressing focal adhesion kinase signaling(*663*)
13. directly binds these kinases (K_d (μM))(*348*):
    1) AAK1: 0.13
    2) ABL1: 1
        - ✓ ABL1(H396P): 0.87
        - ✓ ABL1(M351T): 0.53
        - ✓ ABL1(Q252H): 2.3
        - ✓ ABL1(T315I): 0.21
        - ✓ ABL1(Y253F): 0.72
    3) ABL2: 1.2
    4) ACK1: 2.2
    5) Aurora2: 6.6
    6) Aurora3: 0.31
    7) BIKE: 0.038
    8) CAMK1: 2
    9) CAMK1D: 1.1
    10) CAMK1G: 0.99
    11) CAMK2A: 0.37
    12) CAMK2B: 3.2
    13) CAMK2D: 1.1
    14) CAMK2G: 0.76
    15) CAMKK1: 0.9
    16) CAMKK2: 5.8
    17) CLK1: 0.1
    18) CLK2: 0.19

19) CLK4: 0.08
20) DAPK2: 0.47
21) DAPK3: 0.3
22) EPHA5: 5.9
23) EPHA6: 2
24) EPHA7: 0.71
25) EPHB1: 0.96
26) EPHB4: 2.2
27) FER: 1.4
28) FGFR1: 1.8
29) FGFR2: 0.53
30) FGFR3: 0.3
31) FGR: 0.29
32) FLT3: 0.0008
33) FLT4: 0.035
34) FYN: 3.9
35) GAK: 0.12
36) HCK: 3.3
37) INSR: 0.18
38) JAK1 (Kin.Dom.1): 0.0092
39) JAK2 (Kin.Dom.2): 0.94
40) KIT: 0.00071
41) LCK: 1.2
42) LYN: 0.54
43) MAP3K4: 3.3
44) MAP4K5: 0.077
45) MARK2: 0.32
46) MYLK2: 0.057
47) NEK2: 0.5
48) NTRK1: 0.22
49) PCTK1: 0.13
50) PDGFRB: 0.00021
51) PHKG1: 0.07
52) PHKG2: 0.039
53) PIM2: 5
54) PRKAA1: 0.052
55) PRKACA: 6
56) PTK2: 0.61
57) RPS6KA2 (Kin.Dom.1): 0.058
58) RPS6KA3 (Kin.Dom.1): 0.055
59) RPS6KA5 (Kin.Dom.1): 0.25
60) SLK: 0.081
61) SRC: 3.1
62) STK10: 0.64
63) STK16: 0.36
64) STK17A: 0.021
65) STK17B: 0.22
66) STK18: 0.38
67) STK3_m: 0.16
68) STK38L: 1.5
69) STK4: 0.1
70) TNIK: 0.025
71) TTK: 0.23
72) ULK3_m: 0.11
73) VEGFR2: 0.00023
74) YES: 0.24

14. inhibits renal cancer cell migration and invasion via attenuating the expression of miR-452-5p(*664*)
15. indirectly enhances antitumor cytotoxicity of cytokine-induced killer cells and $CD3^{+}CD56^{+}$ subset through the coculturing dendritic cells(*665*)
16. immunomodulation via reversing MDSC-mediated tumor-induced immunosuppression(*666-668*)
17. triggers incomplete autophagy, impairs cathepsin B activation and stimulates a lysosomal-dependent necrosis(*468*)
18. directly inhibits FMS phosphorylation and cell proliferation(*513*)
19. may exert antitumor effects via direct inhibition of tumor growth as opposed to an antiangiogenic mechanism(*669*)
20. may contribute to immunologic recovery via inducing myeloid lineage redistribution(*670*)
21. directly binds these kinases (Kd, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):

1) AAK1: 11
2) ABL1-NP: 270
   - ✓ ABL1-P: 150
   - ✓ ABL1(E255K)-P: 180
   - ✓ ABL1(F317I)-NP: 3600
   - ✓ ABL1(F317I)-P: 890
   - ✓ ABL1(F317L)-NP: 730
   - ✓ ABL1(F317L)-P: 370
   - ✓ ABL1(H396P)-NP: 74
   - ✓ ABL1(H396P)-P: 140
   - ✓ ABL1(M351T)-P: 120
   - ✓ ABL1(Q252H)-NP: 240
   - ✓ ABL1(Q252H)-P: 76
   - ✓ ABL1(T315I)-NP: 150
   - ✓ ABL1(T315I)-P: 55
   - ✓ ABL1(Y253F)-P: 140
3) ABL2: 1000
4) AKT2: 2700
5) ALK: 170
6) AMPK-alpha1: 19
7) AMPK-alpha2: 89
8) ANKK1: 310
9) ARK5: 48
10) AURKA: 1700
11) AURKB: 380
12) AURKC: 220
13) AXL: 9
14) BIKE: 5.5
15) BLK: 65
16) BMPR1B: 2400
17) BMPR2: 570
18) BRK: 4600
19) BRSK1: 3500
20) BRSK2: 1100
21) BTK: 2100
22) CAMK1: 970
23) CAMK1D: 510
24) CAMK1G: 440

25) CAMK2A: 80
26) CAMK2B: 1400
27) CAMK2D: 420
28) CAMK2G: 690
29) CAMK4: 890
30) CAMKK1: 420
31) CAMKK2: 1500
32) CDK4-cyclinD1: 6200
33) CDK4-cyclinD3: 2000
34) CDK5: 6900
35) CDK7: 330
36) CDKL2: 1100
37) CHEK1: 300
38) CHEK2: 10
39) CIT: 3900
40) CLK1: 22
41) CLK2: 20
42) CLK4: 29
43) CSF1R: 2.5
44) CSNK1A1: 99
45) CSNK1A1L: 550
46) CSNK1D: 15
47) CSNK1E: 13
48) CSNK1G1: 930
49) CSNK1G2: 110
50) CSNK1G3: 240
51) CSNK2A1: 900
52) CSNK2A2: 160
53) CTK: 7700
54) DAPK1: 120
55) DAPK2: 150
56) DAPK3: 22
57) DCAMKL1: 370
58) DCAMKL2: 2700
59) DCAMKL3: 110
60) DDR1: 2000
61) DDR2: 2900
62) DLK: 100
63) DRAK1: 1
64) DRAK2: 110
65) DYRK1A: 200
66) DYRK1B: 2300
67) DYRK2: 680
68) EGFR(G719C): 6800
    - ✓ EGFR(L858R,T790M): 860
    - ✓ EGFR(T790M): 2400
69) EPHA3: 2100
70) EPHA5: 1200
71) EPHA6: 960
72) EPHA7: 2400
73) EPHB1: 480
74) EPHB4: 3100
75) EPHB6: 1000
76) ERK5: 9900
77) ERN1: 600
78) FAK: 440

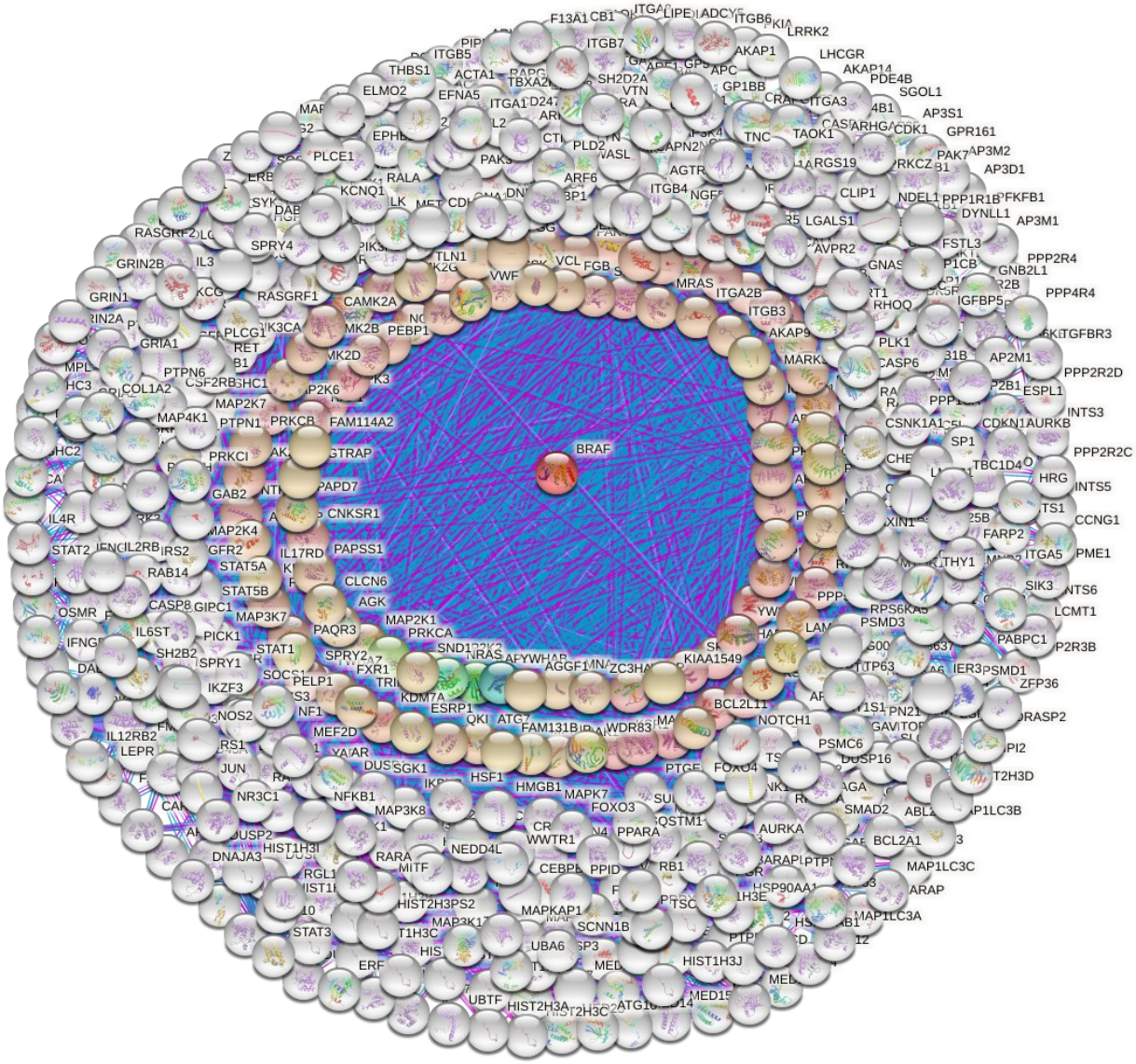
79) FER: 1100
80) FES: 960
81) FGFR1: 520
82) FGFR2: 570
83) FGFR3: 290
    - ✓ FGFR3(G697C): 1400
84) FGFR4: 2100
85) FGR: 270
86) FLT1: 1.8
87) FLT3: 0.41
    - ✓ FLT3(D835H): 4.3
    - ✓ FLT3(D835Y): 2.3
    - ✓ FLT3(ITD): 0.99
    - ✓ FLT3(K663Q): 0.22
    - ✓ FLT3(N841I): 2.4
    - ✓ FLT3(R834Q): 11
88) FLT4: 50
89) FRK: 530
90) FYN: 520
91) GAK: 20
92) GCN2(Kin.Dom.2,S808G): 180
93) GRK1: 290
94) GRK4: 140
95) GRK7: 180
96) HCK: 880
97) HIPK1: 55
98) HIPK2: 31
99) HIPK3: 41
100) HIPK4: 160
101) HPK1: 16
102) HUNK: 500
103) ICK: 470
104) IGF1R: 2600
105) IKK-alpha: 520
106) IKK-epsilon: 620
107) INSR: 500
108) INSRR: 430
109) IRAK1: 14
110) IRAK3: 940
111) IRAK4: 66
112) ITK: 13
113) JAK1(JH1domain-catalytic): 6000
    - ✓ JAK1(JH2domain-pseudokinase): 49
114) JAK2(JH1domain-catalytic): 410
115) JAK3(JH1domain-catalytic): 1200
116) JNK2: 2400
117) JNK3: 4300
118) KIT: 0.37
    - ✓ KIT(A829P): 43
    - ✓ KIT(D816H): 110
    - ✓ KIT(D816V): 380
    - ✓ KIT(L576P): 1.3
    - ✓ KIT(V559D): 0.41
    - ✓ KIT(V559D,T670I): 0.28
    - ✓ KIT(V559D,V654A): 0.21
119) LATS1: 630

120) LATS2: 460
121) LCK: 230
122) LKB1: 38
123) LOK: 19
124) LRRK2: 110
    - ✓ LRRK2(G2019S): 76
125) LTK: 1800
126) LYN: 270
127) LZK: 95
128) MAP3K15: 1300
129) MAP3K2: 57
130) MAP3K3: 220
131) MAP3K4: 4800
132) MAP4K2: 33
133) MAP4K3: 180
134) MAP4K4: 140
135) MAP4K5: 41
136) MARK1: 1200
137) MARK2: 310
138) MARK3: 410
139) MARK4: 3600
140) MAST1: 200
141) MEK1: 130
142) MEK2: 110
143) MEK3: 1700
144) MEK4: 700
145) MEK5: 46
146) MEK6: 5200
147) MELK: 350
148) MERTK: 26
149) MET: 7200
    - ✓ MET(M1250T): 1200
    - ✓ MET(Y1235D): 4700
150) MINK: 29
151) MKNK1: 3900
152) MKNK2: 5700
153) MLCK: 23
154) MLK1: 3400
155) MLK3: 1300
156) MST1: 19
157) MST2: 56
158) MST3: 63
159) MST4: 340
160) MUSK: 490
161) MYLK: 280
162) MYLK2: 49
163) MYLK4: 15
164) MYO3A: 3100
165) MYO3B: 4500
166) NDR1: 410
167) NDR2: 970
168) NEK2: 1400
169) NEK7: 4100
170) NIM1: 850
171) OSR1: 530
172) PAK3: 16

173) PAK4: 2300
174) PAK6: 2400
175) PAK7: 640
176) PCTK1: 150
177) PCTK2: 1200
178) PCTK3: 1700
179) PDGFRA: 0.79
180) PDGFRB: 0.075
181) PDPK1: 3500
182) PFCDPK1(P. falciparum): 1300
183) PFTK1: 270
184) PHKG1: 5.5
185) PHKG2: 5.9
186) PIM3: 2400
187) PIP5K1A: 5400
188) PIP5K2B: 39
189) PKN1: 710
190) PKN2: 1300
191) PKNB(*M. tuberculosis*): 87
192) PLK2: 4700
193) PLK4: 190
194) PRKCQ: 4300
195) PRKD1: 310
196) PRKD2: 380
197) PRKD3: 280
198) PRKR: 670
199) PRP4: 390
200) PYK2: 82
201) RET: 13
    - ✓ RET(M918T): 19
    - ✓ RET(V804L): 8.7
    - ✓ RET(V804M): 5.8
202) RIOK1: 35
203) RIOK2: 49
204) RIOK3: 3800
205) RIPK1: 370
206) RIPK4: 2100
207) RIPK5: 1300
208) ROCK1: 460
209) ROCK2: 140
210) RPS6KA4(Kin.Dom.1-N-terminal): 96
    - ✓ RPS6KA4(Kin.Dom.2-C-terminal): 2000
211) RPS6KA5(Kin.Dom.1-N-terminal): 28
    - ✓ RPS6KA5(Kin.Dom.2-C-terminal): 1700
212) RSK1(Kin.Dom.1-N-terminal): 140
    - ✓ RSK1(Kin.Dom.2-C-terminal): 5000
213) RSK2(Kin.Dom.1-N-terminal): 580
214) RSK3(Kin.Dom.1-N-terminal): 17
215) RSK3(Kin.Dom.2-C-terminal): 8400
216) RSK4(Kin.Dom.1-N-terminal): 2400
217) S6K1: 48
218) SBK1: 200
219) SgK110: 1900

220) SGK3: 220
221) SIK: 3200
222) SIK2: 580
223) SLK: 56
224) SNARK: 150
225) SNRK: 640
226) SRC: 2100
227) SRPK1: 250
228) SRPK2: 190
229) SRPK3: 59
230) STK16: 250
231) STK33: 17
232) STK35: 1300
233) STK39: 140
234) TAK1: 93
235) TAOK1: 890
236) TAOK3: 210
237) TBK1: 120
238) TIE1: 3900
239) TLK1: 740
240) TLK2: 330
241) TNIK: 25
242) TNK1: 680
243) TNK2: 8900
244) TRKA: 100
245) TRKB: 590
246) TRKC: 5100
247) TSSK1B: 6300
248) TTK: 63
249) TYK2(JH1domain-catalytic): 1600
    - ✓ TYK2(JH2domain-pseudokinase): 360
250) TYRO3: 49
251) ULK1: 23
252) ULK2: 13
253) ULK3: 42
254) VEGFR2: 1.5
255) WEE1: 1100
256) YES: 120
257) YSK1: 290
258) YSK4: 17

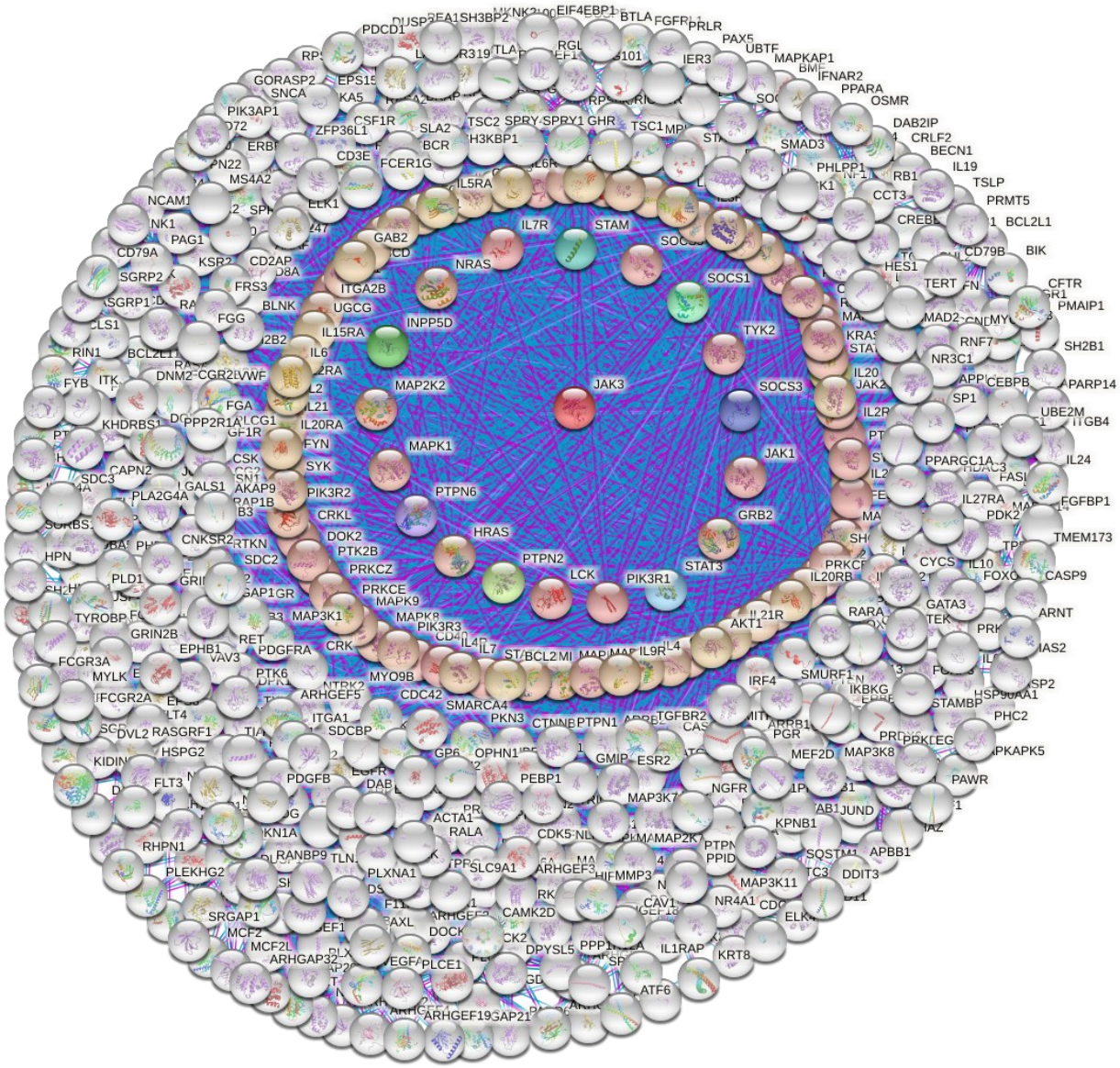
Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
VEMURAFENIB	B-Raf proto-oncogene, serine/threonine kinase	BRAF	P15056	18



https://version-11-0b.string-db.org/cgi/network?networkId=bhZ8HcCNoaIy

1. induces endoplasmic reticulum stress-mediated apoptosis(*671*)
2. downmodulates aggressiveness mediators of colorectal cancer: Low Molecular Weight Protein Tyrosine Phosphatase (LMWPTP)(*672*)
3. stimulate inflammasome activation and IL-1ß production in dendritic cells which may affect the dendritic cell-mediated course of anti-tumor immune responses(*673*)
4. compromise the ATP binding capacity of MAP2K5 and inhibit its kinase activity(*674*)
5. upregulates 58 kinases and downregulates 5 kinases(*674*)
6. reduces the ATP binding affinities of these kinases(*674*):
    1) ARAF
    2) ZAK
    3) SRC
    4) IP6K1
    5) MAP2K5
    6) FER
    7) PRPS1
    8) AK6
    9) ABR
    10) FGFR3
    11) CHUK
    12) PEAK1
7. increases TRAIL-induced apoptosis(*675*)
8. reverses immunosuppression by myeloid derived suppressor cells(*676*)
9. binds the active site of Protein tyrosine kinase 6 (PTK6, also called BRK) and inhibits its activation(*677*)
10. triggers production of superoxide and nitric oxide and the consequent depolarization of mitochondrial membranes, and potentially apoptosis and growth inhibition(*678*)

Drugs	Discovery Target		Uniprot ID	"Off-Target" Therapeutic Mechanisms
TOFACITINIB	Janus kinase 3	JAK3	P52333	34



https://version-11-0b.string-db.org/cgi/network?networkId=bD9gJDmjupjZ

1. restores the balance of γδTreg/γδT17 cells in rheumatoid arthritis by inhibiting the NLRP3 inflammasome(*679*)
2. modulates inflammation and exerts protective effects in endothelial cells via suppressing ox-LDL-mediated activation of NF-κB inhibitor α (IκB-α), accumulation of nuclear p65, activation of nuclear factor κB (NF-κB) promoter and adhesion of THP-1 monocytes to endothelial cells(*680*)
3. directly binds these kinases (K_d, nM) (NP: nonphosphorylated, P: phosphorylated)(*324*):
    1) ABL1(H396P)-NP: 4500
        - ✓ ABL1(H396P)-P: 6700
        - ✓ ABL1(T315I)-P: 2200
    2) BIKE: 7100
    3) CAMK1: 1200
    4) CAMK1D: 1600
    5) CAMK2A: 3500
    6) CAMK2D: 2700
    7) DCAMKL1: 6700
    8) DCAMKL3: 12
    9) DMPK: 1200
    10) FYN: 1100
    11) GRK7: 4300
    12) JAK1(JH1domain-catalytic): 1.6
    13) JAK2(JH1domain-catalytic): 0.58
    14) JAK3(JH1domain-catalytic): 0.16
    15) LCK: 460
    16) LRRK2: 1300
    17) LRRK2(G2019S): 550
    18) MAP4K2: 4800
    19) MKNK2: 1600
    20) PKN1: 170
    21) PKN2: 1200
    22) PKNB(*M. tuberculosis*): 2000
    23) PRKCD: 2000
    24) RET(M918T): 3300
    25) ROCK1: 470
    26) ROCK2: 420
    27) RSK1(Kin.Dom.2-C-terminal): 1400
    28) RSK3(Kin.Dom.2-C-terminal): 600
    29) RSK4(Kin.Dom.2-C-terminal): 540
    30) SNARK: 240
    31) TNK1: 120
    32) TYK2(JH1domain-catalytic): 4.8
    33) ULK3: 6400

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