Project Notes:
Project Title: Understanding Drug Resistance in the cancer kinase BCR-ABL
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Note Well: There are NO SHORT-cuts to reading journal articles and taking notes from them. Comprehension is paramount. You will most likely need to read it several times, so set aside enough time in your schedule.

Contents:

Knowledge Gaps:
This list provides a brief overview of the major knowledge gaps for this project, how they were resolved and where to find the information.

Knowledge Gap	Resolved By	Information is located	Date resolved
Drug Resistance in kinases	Literature reading	Articles	10/11/23
Role of BCR-ABL in CML	Literature reading	Articles	10/21/23
Common mutations in the BCR-ABL kinase domain, how do they affect TKI drug resistance?	Article given to me	Articles	11/18/23

Literature Search Parameters:
These searches were performed between 08/29/2023 and 12/15/2023.
List of keywords and databases used during this project.

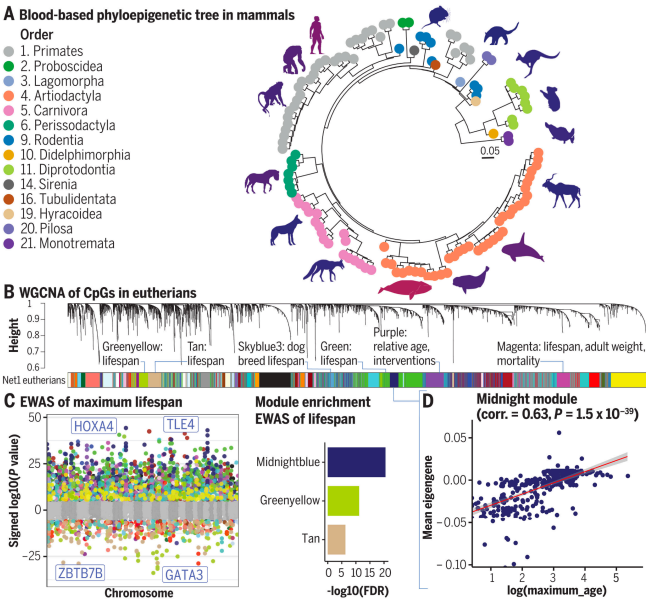
Database/search engine	Keywords	Summary of search
WPI Gordan library	Drug Resistance in kinases	Found articles pertaining to other instances of kinases, background information
Google.com	Chronic Myeloid Leukemia	Found lots of articles in regard the details of CML and why the BCR-ABL mutation is important
WPI Gordan library	BCR-ABL mutation	Found a few articles that detailed mutations of interest in the BCR-ABL kinase

Tags:

Tag Name	
#BCR-ABL	#Drug Resistance
#Inhibitor	#Protein
#CML	#Kinase
#PyMOL	#Imatinib

Article #1 Notes:

Source Title	DNA methylation networks underlying mammalian traits

Source citation (APA Format)	DNA methylation networks underlying mammalian traits. (2023). *Science*, *381*(6658). https://www.science.org/doi/10.1126/science.abq5693
Original URL	https://www.science.org/doi/10.1126/science.abq5693
Source type	Research Article
Keywords	DNA, Genes, evolutionary biology
#Tags	
Summary of key points + notes (include methodology)	DNA methylation installs a methyl group to cytosine, placing an epigenetic mark that regulates gene expression. Comparative epigenomics combines epigenetic signatures with phylogenetic relationships to understand species characteristics. Haghani *et al*. evaluated methylation levels in highly conserved DNA sequences, profiling ~15,000 samples across 348 mammalian species (see the Perspective by de Mendoza). Phylogenetic trees suggest that the divergence of DNA methylation profiles closely mirrors genetic evolution. Species with longer maximum life spans have developed tidier methylation patterns within the genome, characterized by unique peaks and troughs of methylation. Methylation patterns associated with maximum life spans generally differ from those connected to age or interventions that affect mortality risk in mice. These data provide a rich resource of information for fields including evolutionary biology and longevity research.
Research Question/Problem/ Need	How can we better understand species characteristics using comparative epigenomics
Important Figures	 **DNAm network relates to mammalian phylogeny and traits.**

	(**A**) Phyloepigenetic tree from the DNAm data generated from blood samples. (**B**) Unsupervised WGCNA networks identified 55 comethylation modules. (**C**) EWAS of log-transformed maximum life span. Each dot corresponds to the methylation levels of a highly conserved CpG. Shown is the log (base 10)–transformed *P* value (*y* axis) versus the human genome coordinate Hg19 (*x* axis). (**D**) Comethylation module correlated with maximum life span of mammals. Eigengene (first principal component of scaled CpGs in the midnight blue module) versus log (base e) transformed maximum life span. Each dot corresponds to a different species.
VOCAB: (w/definition)	Methylation: mix or impregnate with methanol or methylated spirit phyloepigenetic:relating to the evolutionary development and diversification of a species or group of organisms, or of a particular feature of an organism epigenome:multitude of chemical compounds that can tell the *genome* what to do
Cited references to follow up on	D. Villar, C. Berthelot, S. Aldridge, T. F. Rayner, M. Lukk, M. Pignatelli, T. J. Park, R. Deaville, J. T. Erichsen, A. J. Jasinska, J. M. A. Turner, M. F. Bertelsen, E. P. Murchison, P. Flicek, D. T. Odom, Enhancer evolution across 20 mammalian species. *Cell***160**, 554–566 (2015).
Follow up Questions	

Article #2 Notes:

Source Title	Bacteria's Immune Sensors Reveal a Novel Way to Detect Viruses
Source citation (APA Format)	Melchor, A. (2022, August 29). *Bacteria's Immune Sensors Reveal a Novel Way to Detect Viruses*. Quanta Magazine. Retrieved October 15, 2023, from https://www.quantamagazine.org/bacterias-immune-sensors-reveal-a-novel-way-to-detect-viruses-20220829/
Original URL	https://www.quantamagazine.org/bacterias-immune-sensors-reveal-a-novel-way-to-detect-viruses-20220829/
Source type	article
Keywords	Bacteria, proteins
#Tags	
Summary of key points + notes (include methodology)	A study published in *Science* tells us of a discovery that a family of proteins in bacteria and archaea can detect viruses in a way never seen before. Many

	antiviral defenses that bacteria use either recognize specific sequences in the DNA that a virus injects into its host or respond to the evidence of the harm the virus causes. However Bacterial immune sensors called Avs proteins don't do either, they detect viral proteins made by cells hijacked machinery. Protein surveillance can be a risky strategy for microbes since it only takes a few mutations to let a pathogen escape detection, however, Avs proteins aren't bothered by changes in amino acid sequences. The targeted proteins in different viral families had different amino acid sequences, all performing the same job by spooling up strands of viral DNA and packing them into newly formed particles. The Avs proteins take advantage of this molecular resemblance by recognizing three-dimensional folds & shapes. The wraparound recognition skills of the proteins can spot viruses that infect bacteria as well as detect animal herpesviruses. When they detect viral proteins they can get rid of the virus in multiple ways with some ending in self-destruction, which lets infected cells protect neighbors. Researchers have also discovered that immune defenses in bacteria have striking parallels to ones in eukaryotic cells, it's not certain if humans inherited anything from the Avs proteins however since protein-shape recognition works well for bacteria and the like, it could be expected for something similar to show up in humans and other eukaryotes.
Research Question/Problem/ Need	How are bacteria's immune sensors able to Detect Viruses?
Important Figures	N/A
VOCAB: (w/definition)	
Cited references to follow up on	
Follow up Questions	

Article #3 Notes:

Source Title	Underground Cells Make 'Dark Oxygen' Without Light
Source citation (APA Format)	Bolakhe, S. (2023, July 17). *Underground Cells Make 'Dark Oxygen' Without Light*. Quanta Magazine. Retrieved October 15, 2023, from https://www.quantamagazine.org/underground-cells-make-dark-oxygen-without-light-20230717/
Original URL	https://www.quantamagazine.org/underground-cells-make-dark-oxygen-without-light-20230717/

Source type	Article
Keywords	Cells, Oxygen, Microbes
#Tags	
Summary of key points + notes (include methodology)	In *Nature Communications*, evidence that challenged the assumption that subterranean realms are oxygen-deficient zones where only primitive microbes live was presented. In groundwater reservoirs below Alberta, microbes were discovered that produce large amounts of "dark oxygen" even in the absence of light, creating conditions for oxygen-dependent life. The study looked at deep aquifers in Alberta, the researchers collected groundwater, then started doing basic microscopy to count microbial cells. They were able to identify the ages of the groundwater aquifers, however, a pattern in the numbers puzzled them. Usually, the number of microbial cells decreases with depth, however, the older, deeper groundwaters held more cells than the fresher waters did. The researchers started identifying the microbes in the samples and were surprised that many of the bacteria found were aerobes – microbes that require oxygen – which didn't make sense in groundwaters. Further research led to the discovery that a type of methane-feeding bacteria created its oxygen by using enzymes to break down nitrites. The bacteria used self-generated oxygen to split methane for energy (dismutation). Oxygen produced this way can leak out of the cells and into the surrounding medium to the benefit of other oxygen-dependent organisms. This could be how these microbes survive in the groundwater and surrounding soils, and lets us understand more about how the subterranean biosphere has evolved, and how dismutation contributes to the cycle of compounds moving through the global environment.
Research Question/Problem/ Need	How do underground cells have the ability to make 'Dark Oxygen' without light?
Important Figures	N/A
VOCAB: (w/definition)	
Cited references to follow up on	
Follow up Questions	

Article #4 Notes:

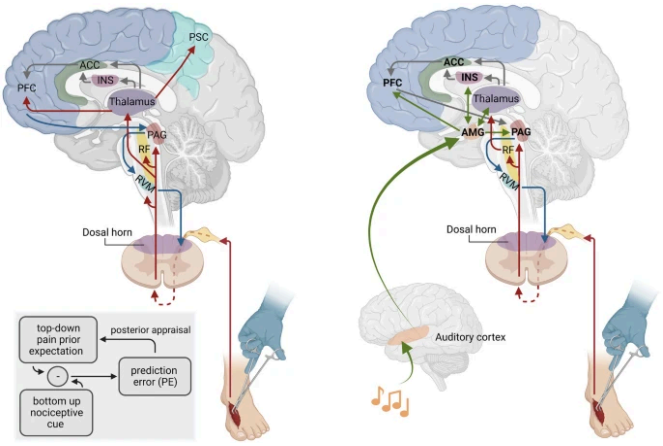
Source Title	Personalized anti-cancer vaccine combining mRNA and immunotherapy tested in melanoma trial
Source citation (APA Format)	Personalized anti-cancer vaccine combining mRNA and immunotherapy tested in melanoma trial. (2023). *naturemedicine*. https://www.nature.com/articles/d41591-023-00072-0
Original URL	https://www.nature.com/articles/d41591-023-00072-0
Source type	Article
Keywords	Anti-cancer, melanoma, RNA
#Tags	
Summary of key points + notes (include methodology)	On 26 July 2023, Moderna and Merck announced the launch of a phase 3 trial of their personalized vaccine against melanoma, mRNA-4157 , plus pembrolizumab , as combination therapy for high-risk patients who have undergone surgery. In the phase 2 KEYNOTE-942 trial, the minimal number of target epitopes per patient was 9, and 91% of patients received mRNA encoding the full 34 epitopes. This explanation is appealing and fits conventional immunological wisdom, however the tumor mutational burden is an unreliable marker for responsiveness to immunotherapy.
Research Question/Problem/ Need	How does the vaccine against melanoma, mRNA-4157 (also known as V940), plus pembrolizumab (Keytruda), work as combination therapy for high-risk patients?
Important Figures	N/A
VOCAB: (w/definition)	intramuscular:situated or taking place within, or administered into, a muscle
Cited references to follow up on	
Follow up Questions	How was it learnt that the combination of mRNA-4157 and pembrolizumab work as combination therapy? What did the phase 1 trial of the vaccine from Merck and Moderna consist of? What are the storage requirements and shelf life of the vaccine?

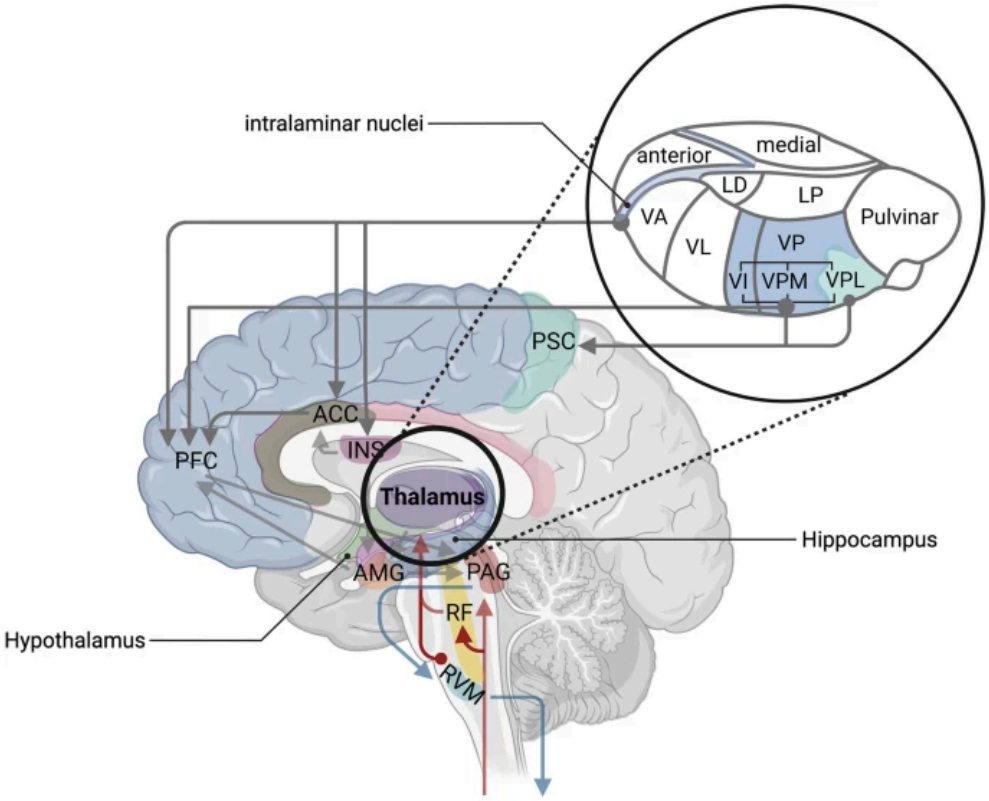
Article #5 Notes:

Source Title	Deadly olive tree pathogen came by road and rail
Source citation (APA Format)	Deadly olive tree pathogen came by road and rail. (2023). *natureitaly*. https://www.nature.com/articles/d43978-023-00118-4
Original URL	https://www.nature.com/articles/d43978-023-00118-4
Source type	Article
Keywords	
#Tags	
Summary of key points + notes (include methodology)	Scientists from Italy's Council for Agricultural Research and Agricultural Economics Analysis found that Xylella fastidiosa, a bacterium endemic in America, is more likely to be found near roads, railways, and urban settings. The study compared the spatial distribution of infected trees between 2015 and 2020 to land-use distribution, finding that Xylella is more likely to be found near these areas. The findings could inform containment strategies in the initial phase of the epidemic and be considered in regions where Xylella has not spread yet.
Research Question/Problem/ Need	Why is the bacterium *Xylella fastidiosa* more commonly found in urban settings than natural areas?
Important Figures	N/A
VOCAB: (w/definition)	anthropogenic:originating in human activity
Cited references to follow up on	
Follow up Questions	Could the spread of the bacterium be due to the materials used during rapid industrialisation to the detriment of the ecosystem? What information could be found by focusing research on land-use management and anthropic pressure? Could the bacterium be surviving on industrial waste due to pollution, urbanization, and deforestation?

Article #6 Notes:

Source Title	The effect of Perioperative auditory simulation with music on procedural pain: A narrative review
Source citation (APA Format)	The effect of Perioperative auditory simulation with music on procedural pain: A narrative review. (2023). *Current Pain and Headache Reports*, *27*(10). https://link.springer.com/article/10.1007/s11916-023-01138-x
Original URL	https://link.springer.com/article/10.1007/s11916-023-01138-x
Source type	Journal article
Keywords	Music
#Tags	
Summary of key points + notes (include methodology)	Music therapy is becoming increasingly popular in various medical fields, including perioperative pain management. However, its physiological underpinnings are not fully understood. This article provides concepts for the use of music in perioperative pain management. The article shows that the pain matrix and neuronal networks of pleasure triggered by music overlap significantly. These functions seem to antagonize each other, which can be utilized in pain therapy. Although fMRI and EEG studies have shown encouraging results, this top-down modulating mechanism has not yet been fully translated into clinical practice. The review embeds the current clinical literature in a neurobiological framework, touching on Bayesian "predictive coding" pain theories and outlining functional units in nociception and the pain matrix. This helps to understand the clinical findings summarized in the second part of the review. Overall, music therapy is a promising approach to perioperative pain management. It can be used to relieve pain and anxiety in emergency and perioperative situations.
Research Question/Problem/ Need	What are some possible uses of music in perioperative pain management?

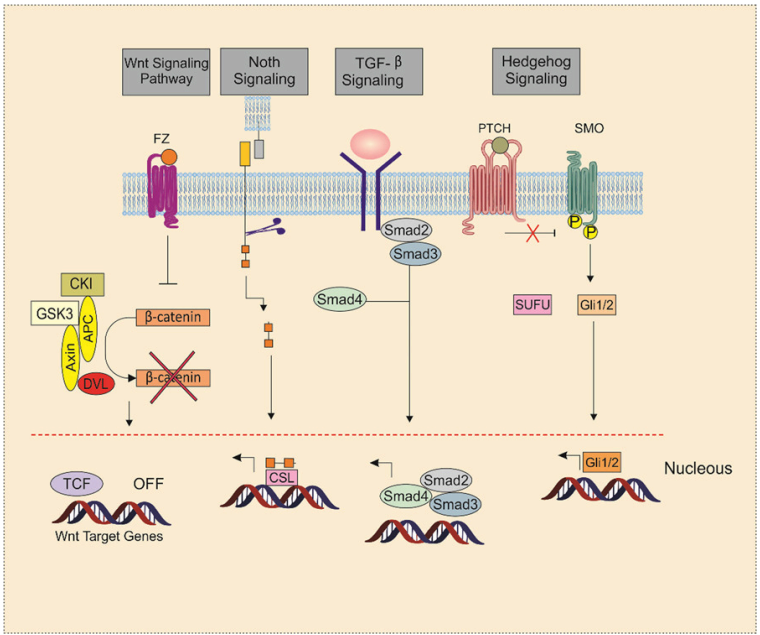
Important Figures	 The pain matrix (left) and musical pain modulation (right). Sensory informations about a noxious stimulus travel on ascending pathways (red arrows) via relay stations (RF = reticular formation, PAG = periaqueductal grey, RVM = rostral ventromedial medulla, INS = insular cortex, ACC = anterior cingulate cortex, PFC = prefrontal cortex, PSC = primary somatosensory cortex). The assessment of the stimulus is modulated through subcortical and cortical connections (grey arrows) and regulatory descending pathways (blue arrows). Musical sounds stimulate the auditory cortex, which has connections to the amygdala (AMG). AMG interconnections are indicated with green arrows. Top-down reactions to a simultaneously occurring noxious stimulus are modulated through emotional and attentional changes caused by the musical sounds. The prediction model for pain perception (bottom left). Created with BioRender.com

	 Detailed schematic representation of thalamic nuclei and structures of the limbic system involved in the pain processes (anterior = anterior nucleus, medial = medial nucleus, LD = laterodorsal nucleus, LP = lateral posterior nucleus, ventral anterior nucleus, VA = ventral anterior nucleus, VL = ventral lateral nucleus, VP = ventral posterior complex, VI = ventral intermediate nucleus, VPM = ventral posteromedial nucleus, VPL = ventral posterolateral nucleus). Connections to subcortical and cortical pain regions marked with grey arrows (RF = reticular formation, PAG = periaqueductal grey, RVM = rostral ventromedial medulla, INS = insular cortex, ACC = anterior cingulate cortex, PFC = prefrontal cortex, PSC = primary somatosensory cortex, AMG = amygdala). Created with BioRender.com
VOCAB: (w/definition)	Noxious: harmful, poisonous, or very unpleasant: reticular formation: a diffuse network of nerve pathways in the brainstem connecting the spinal cord, cerebrum, and cerebellum, and mediating the overall level of consciousness. Mesencephalon: a small central part of the brainstem, developing from the middle of the primitive or embryonic brain. Also called midbrain rostral ventromedial medulla: The rostral ventromedial medulla (RVM) is a group of neurons located close to the midline on the floor of the medulla oblongata

	Norepinephrine: a hormone that is released by the adrenal medulla and by the sympathetic nerves and functions as a neurotransmitter. It is also used as a drug to raise blood pressure.
Cited references to follow up on	Yam MF, Loh YC, Tan CS, Adam SK, Manan NA, Basir R. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci. 2018;19(8):2164. https://doi.org/10.3390/IJMS19082164.
Follow up Questions	

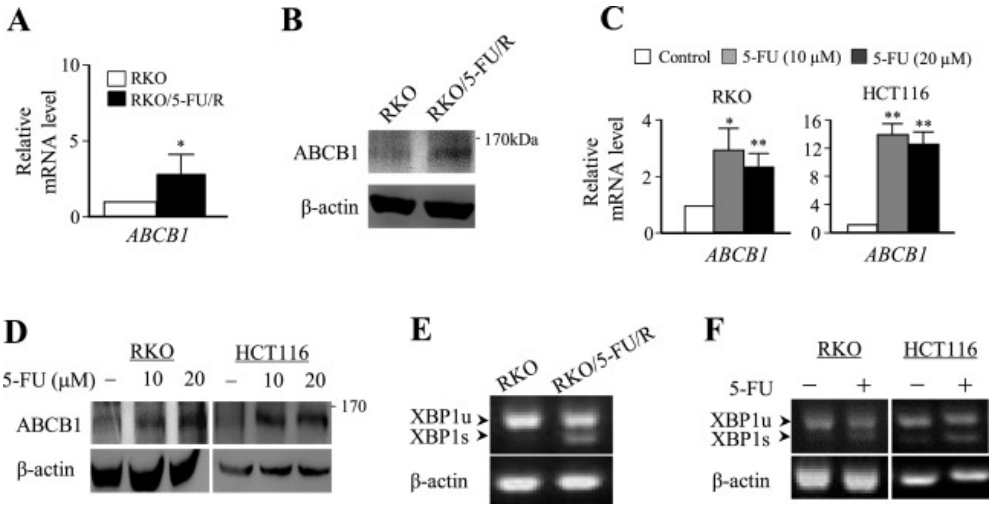
Article #7 Notes:

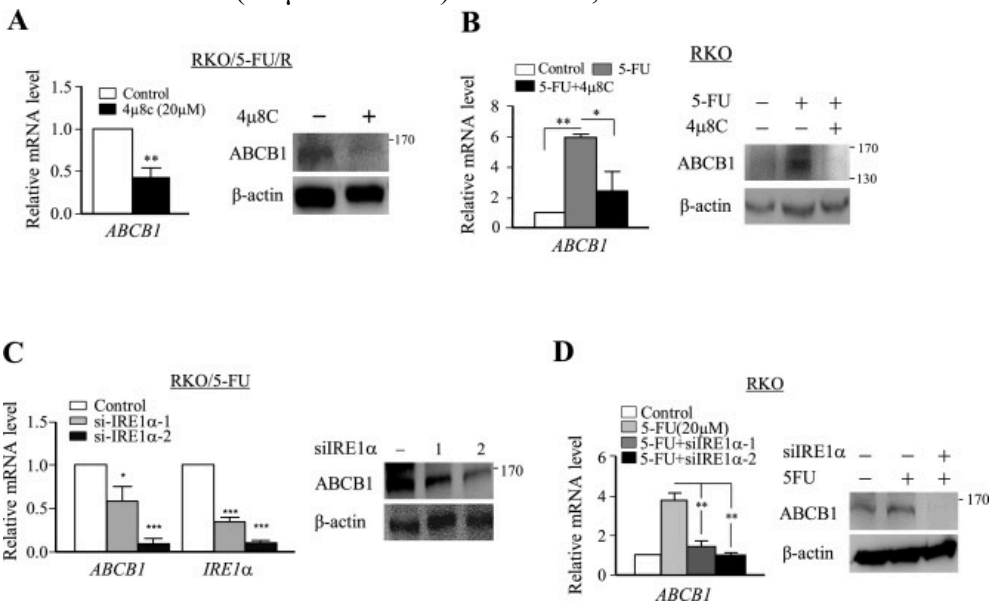
Source Title	Colon cancer therapy by focusing on colon cancer stem cells and their tumor microenvironment
Source citation (APA Format)	Colon cancer therapy by focusing on colon cancer stem cells and their tumor microenvironment. (2019). *Journal of Cellular Physiology*, *235*(5). https://onlinelibrary.wiley.com/doi/10.1002/jcp.29337
Original URL	https://onlinelibrary.wiley.com/doi/10.1002/jcp.29337
Source type	Journal article
Keywords	Drug resistance, colon cancer
#Tags	
Summary of key points + notes (include methodology)	The article talks about the role of Colon Cancer Stem Cells (CCSCs) in colon cancer initiation and underscores the possibility of eradicating these cells in cancer therapy. The article highlights the significance of the Wnt, TGF-β, Notch, and Hedgehog signaling pathways in CCSCs and suggests targeting components of these pathways for effective colon cancer treatment. It also stresses the influence of the tumor microenvironment (TME) on CCSC behavior, cancer progression, and therapy responses, advocating for its consideration in treatment strategies. The article proposes a multi-pronged approach to target both CCSCs and the TME for more effective cancer eradication and discusses the potential of microRNAs as therapeutic targets as well as the need for personalized approaches to colon cancer therapy.

Research Question/Problem/ Need	What are some possible ways to eradicate colon cancer stem cells in order to effectively curb the cancer's initiation and resurgence?
Important Figures	 Some misregulated signaling pathways in CCSCs. Wnt, Notch, and Hedgehog signaling pathways are mostly upregulated and involved in survival, proliferation, and stemness maintenance; however, TGF-β signaling is mostly involved in stemness maintenance and differentiation of CCSCs. CCSC, colon cancer stem cell; TCF, T-cell factor; TGF-β, transforming growth factor-β
VOCAB: (w/definition)	epithelial:elating to or denoting the thin tissue forming the outer layer of a body's surface and lining the alimentary canal and other hollow structures
Cited references to follow up on	Basu, S., Haase, G., & Ben-Ze'ev, A. (2016). Wnt signaling in cancer stem cells and colon cancer metastasis. *F1000Research*, 5, 699.
Follow up Questions	

Article #8 Notes:

Source Title	IRE1α-targeting downregulates ABC transporters and overcomes drug resistance of colon cancer cells
Source citation (APA Format)	IRE1α-targeting downregulates ABC transporters and overcomes drug resistance of colon cancer cells. (2020). *Cancer Letters*, *476*, 67-74. https://www.sciencedirect.com/science/article/pii/S0304383520300690?ref=pdf_download&fr=RR-2&rr=80ab945fff154cf8

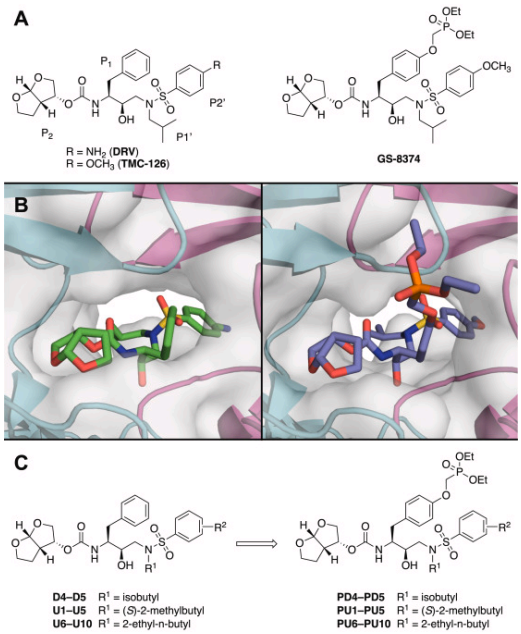
Original URL	https://www.sciencedirect.com/science/article/pii/S0304383520300690?ref=pdf_download&fr=RR-2&rr=80ab945fff154cf8
Source type	Journal Article
Keywords	Drug resistance, colon cancer
#Tags	
Summary of key points + notes (include methodology)	Drug resistance is a major challenge in cancer treatment. One common way that cancer cells become resistant to drugs is by overproducing proteins called ABC transporters, which can pump drugs out of the cells. Researchers have found that a protein called IRE1α can play a role in drug resistance by turning on genes for ABC transporters. IRE1α is part of a cellular stress response called the unfolded protein response (UPR). In this study, researchers found that cancer drugs such as 5-FU can activate IRE1α, which leads to increased expression of ABC transporters and drug resistance. The researchers also found that blocking IRE1α with a small molecule called 4μ8C could prevent cancer cells from developing drug resistance. In a mouse model of colon cancer, they found that combining 4μ8C with 5-FU chemotherapy was more effective at shrinking tumors than 5-FU alone. These findings suggest that targeting IRE1α could be a new way to overcome drug resistance and improve cancer treatment.
Research Question/Problem/ Need	
Important Figures	 **(A)** Determination of the relative *ABCB1* mRNA levels in 5-FU-resistant RKO cells. **(B)** Determination of ABCB1 protein in 5-FU-resistant RKO cells. **(C)** Determination of relative *ABCB1* mRNA levels in RKO and HCT116 cells treated with 5-FU (0, 10, 20 μM) for 48 h. **(D)** Determination

	of ABCB1 protein levels in RKO and HCT116 cells treated with 5-FU (0, 10, 20 μM) for 48 h. **(E)** Determination of XBP1 splicing in RKO and RKO/5-FU-R cells by regular PCR. **(F)** RKO and HCT116 cells were treated with 5-FU (10 μM for 48 h). *P < 0.05; **P < 0.01.  **(A)** RKO/5-FU-R cells were treated with 4μ8C (20 μM) for 24 h followed by determination of mRNA (left panel) and protein (right panel) of ABCB1. **(B)** RKO cells were treated with 5-FU (20 μM) or 5-FU (20 μM) plus 4μ8C (20 μM) for 48 h, followed by determination of mRNA (left panel) and protein (right panel) of ABCB1. **(C)** RKO/5-FU-R cells were transfected with control or siIRE1α oligos as indicated. After 48 h, the cells were harvested for determination of mRNA (left panel) and protein (right panel) of ABCB1. **(D)** RKO cells were transfected with control or siIRE1α oligos as indicated. After 24 h, the cells were treated with 5-FU (20 μM) for 48 h, followed by qPCR (left panel) and westernblot (right panel). *, P < 0.05; **, P < 0.01; ***, P < 0.001.
VOCAB: (w/definition)	Apoptosis:the death of cells which occurs as a normal and controlled part of an organism's growth or development. (programmed cell death) Autophagy:consumption of the body's own tissue as a metabolic process occurring in starvation and certain diseases ATP-binding cassette (ABC) transporters: efflux pumps that transport various structurally unrelated and potentially dangerous substances out of the cells
Cited references to follow up on	G. Szakacs, J.K. Paterson, J.A. Ludwig, C. Booth-Genthe, M.M. Gottesman Targeting multidrug resistance in cancer

	ABC transporters as mediators of drug resistance and contributors to cancer cell biology
Follow up Questions	

Article #9 Notes:

Source Title	HIV-1 protease inhibitors with a P1 phosphonate modification maintain potency against drug-resistant variants by increased interactions with flap residues
Source citation (APA Format)	HIV-1 protease inhibitors with a P1 phosphonate modification maintain potency against drug-resistant variants by increased interactions with flap residues. (2023). *European Journal of Medicinal Chemistry*, *257*. https://www.sciencedirect.com/science/article/pii/S0223523423004671?via=ihub
Original URL	https://www.sciencedirect.com/science/article/pii/S0223523423004671?via=ihub
Source type	Research paper
Keywords	Drug resistance
#Tags	
Summary of key points + notes (include methodology)	The article discusses the challenges posed by HIV/AIDS, emphasizing the need for improved treatments due to the absence of an HIV vaccine. It highlights the effectiveness of direct-acting antiviral drugs, particularly protease inhibitors, in suppressing HIV replication. However, long-term use of these drugs can lead to issues like pill burden and drug resistance. The study focuses on enhancing protease inhibitors by modifying their chemical structures. Researchers introduced a phosphonate modification at a specific position (P1) and tested various combinations of modifications at P1', P2', and P2 positions. These modified inhibitors demonstrated increased potency against drug-resistant HIV variants while maintaining low cellular toxicity. The study also provides insights into the molecular interactions between these inhibitors and the HIV protease enzyme. The phosphonate modification was found to interact with key protease residues, suggesting its role in improving drug effectiveness against resistant variants.

Research Question/Problem/ Need	Protease inhibitors as an antiviral for HIV can still lose efficiency when faced with drug resistant variants of the virus.
Important Figures	 Structures of HIV-1 protease inhibitors. (A) Darunavir (DRV), TMC-126, and the corresponding P1 phosphonate analog GS-8374. (B) DRV and GS-8374 bound to wild-type HIV-1 protease (PDB: 6DGX and 2I4W, respectively). The protease is depicted as a gray surface and a cartoon representation, with chain A in teal and chain B in magenta. (C) DRV analogs with variations at the P1′ and P2′ positions and the corresponding P1 phosphonate analogs analyzed in this study.
VOCAB: (w/definition)	cocrystal structures: a crystalline structure composed of at least two components, where the components may be atoms, ions or molecules. moiety:a distinct part of a large molecule
Cited references to follow up on	A.K. Ghosh *et al.* Beyond darunavir: recent development of next generation HIV-1 protease inhibitors to combat drug resistance Chem. Commun. (2022)
Follow up Questions	

Article #10 Notes:

Source Title	Epigenetic enzyme mutations as mediators of anti-cancer drug resistance
Source citation (APA Format)	Epigenetic enzyme mutations as mediators of anti-cancer drug resistance. (2022). *Drug Resistance Updates*, *61*. https://www.sciencedirect.com/science/article/pii/S1368764622000206
Original URL	https://www.sciencedirect.com/science/article/pii/S1368764622000206
Source type	Journal article
Keywords	Drug resistance
#Tags	
Summary of key points + notes (include methodology)	Drug resistance is a major challenge in cancer treatment. Genetic mutations are thought to be important drivers of drug resistance, but epigenetic alterations can also play a role. Epigenetic enzymes are proteins that modify DNA and histones, which can affect gene expression. Mutations in epigenetic enzymes can lead to changes in gene expression that make cancer cells resistant to drugs. Researchers have identified a number of epigenetic enzyme mutations that are associated with drug resistance in different types of cancer. For example, mutations in the DOT1L gene have been linked to lung cancer drug resistance. Researchers are developing small molecule inhibitors that target various functional domains of epigenetic enzymes. These inhibitors have the potential to overcome drug resistance and improve the outcomes of cancer patients. In addition to targeting epigenetic enzymes, researchers are also developing other therapeutic strategies to reverse or overcome drug resistance. These strategies include combination therapy with multiple drugs and targeted therapy that targets specific signaling pathways involved in drug resistance. The goal of this research is to develop new and effective ways to treat cancer patients who have developed drug resistance.
Research Question/Problem/ Need	What are strategies that target mutations in epigenetic enzymes in order to offset drug resistance?

Important Figures

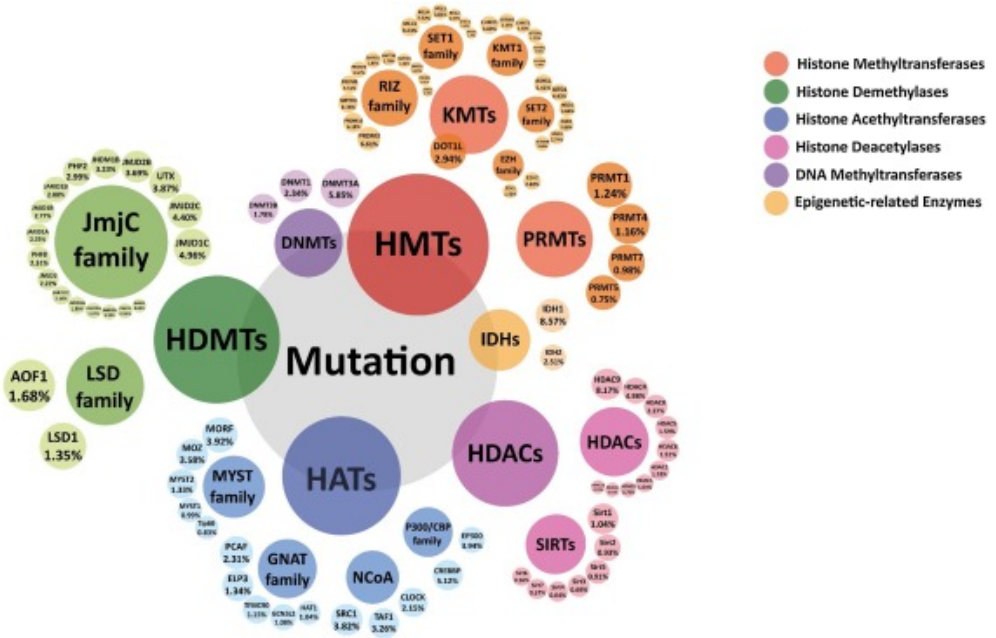


Fig. 1 The mutation rate of epigenetic regulatory enzymes in cancers according to the COSMIC database.

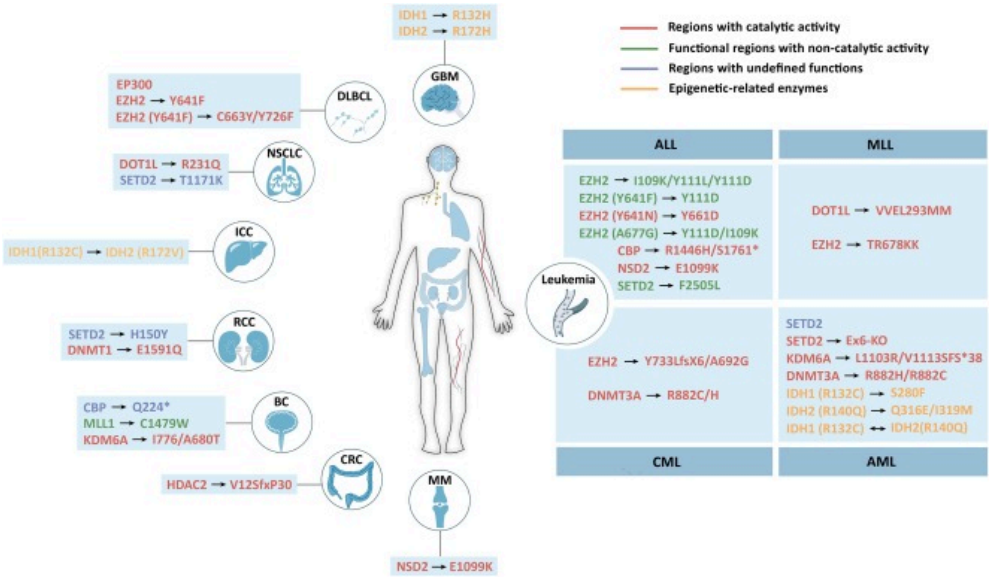
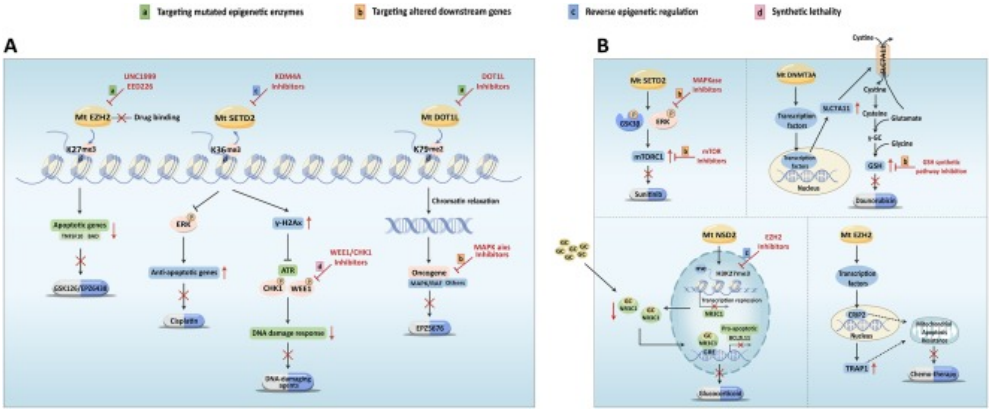


Fig. 2

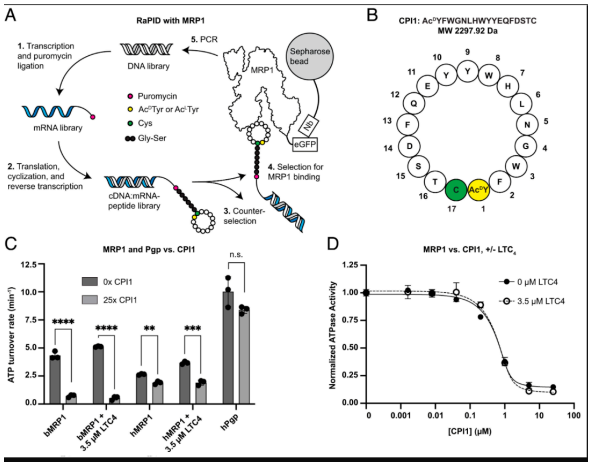
Distribution of epigenetic enzyme mutations associated with anti-cancer drug resistance in various types of cancer. The location of epigenetic enzyme mutations is classified into regions with catalytic activity (including the SET domain, SAM-dependent MTase C5-type domain, JmjC domain, CBP/p300-type HAT domain, histone deacetylase domain, and DOT1 domain), functional regions with non-catalytic activity (including the PHD zinc finger domain, protein interaction region/D1 domain and SRI domain) and regions with undefined functions (including low-complexity domains

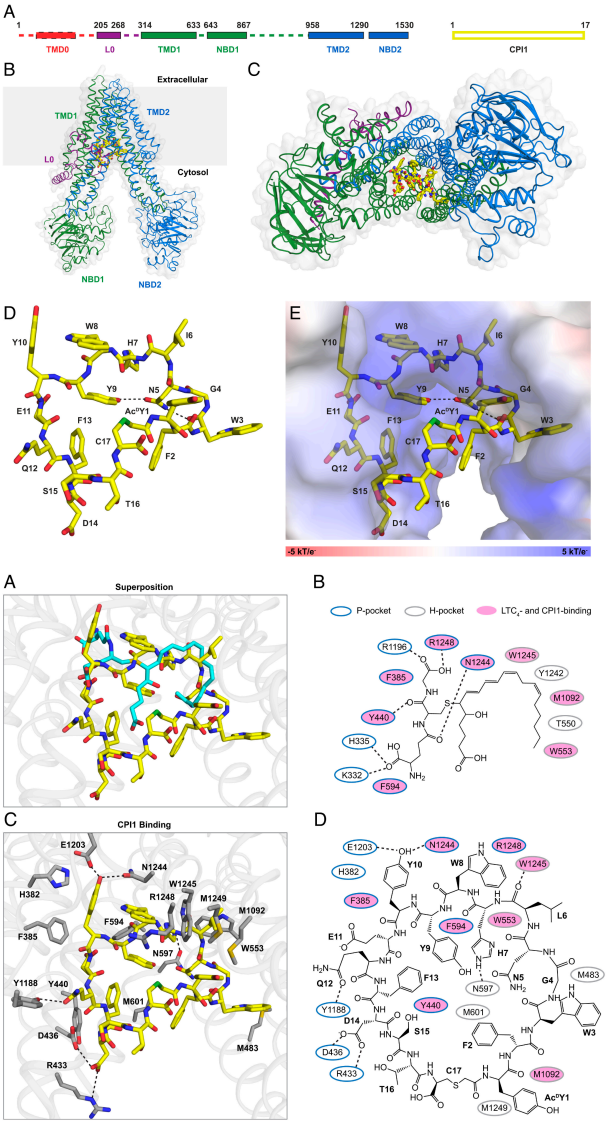
	and disordered domains). Some hotspot mutations in epigenetic-related enzyme IDHs are shown as well. GBM, glioblastoma; DLBCL, diffuse large B cell lymphoma; NSCLC, non-small cell lung cancer; ICC, intrahepatic cholangiocarcinoma; RCC, renal cell carcinoma; BC, bladder cancer; CRC, colorectal cancer; MM, multiple myeloma; ALL, acute lymphocytic leukemia; MLL, mixed lineage leukemia; CML, chronic myelogenous leukemia; AML, acute myeloid leukemia.  Fig. 3. Overview of mechanisms of antitumor drug resistance mediated by epigenetic enzyme mutations, and representative strategies to overcome drug resistance. (A) Mutated epigenetic enzymes possess altered enzyme activity which directly affects the level of histone modification and changes the compaction status of chromatin. Aberrant transcriptional activation or inhibition of target genes eventually leads to the occurrence of drug resistance. (B) Mutant epigenetic enzymes can activate signaling pathways which regulate cell survival through diverse downstream transcriptional elements, thereby contributing to the occurrence of drug resistance. The strategies to overcome drug-resistant phenotypes caused by epigenetic enzyme mutations include: (a) targeting mutated epigenetic enzymes, (b) targeting altered downstream genes, (c) reverse epigenetic regulation, and (d) synthetic lethality. Mt, mutation; GC, glucocorticoids.
VOCAB: (w/definition)	epigenetic: study of how gene activity can change without altering the DNA sequence. chemoresistance: quality or state of being resistant to a chemical, such as a drug histone methyltransferases:histone-modifying enzymes that catalyze the transfer of one, two, or three methyl groups to lysine and arginine residues of histone proteins.
Cited references to follow up on	Aleksakhina et al., 2019 S.N. Aleksakhina, A. Kashyap, E.N. Imyanitov Mechanisms of acquired tumor drug resistance

	Bouwman and Jonkers, 2012 P. Bouwman, J. Jonkers The effects of deregulated DNA damage signaling on cancer chemotherapy response and resistance
Follow up Questions	

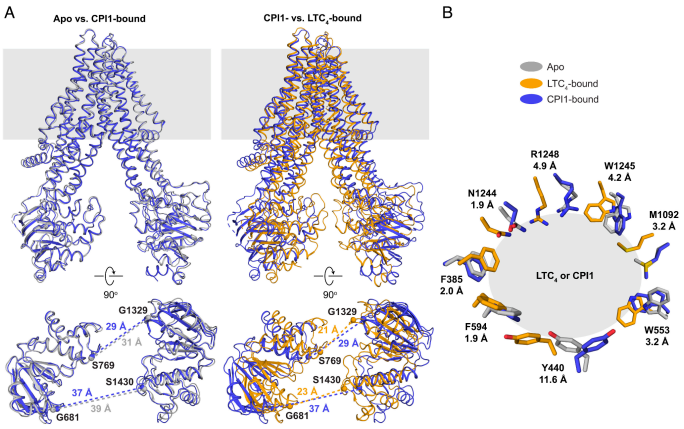
Article #11 Notes:

Source Title	A macrocyclic peptide inhibitor traps MRP1 in a catalytically incompetent conformation
Source citation (APA Format)	Pietz, H. L., Abbas, A., Johnson, Z. L., Oldham, M. L., Suga, H., & Chen, J. (2023). A macrocyclic peptide inhibitor traps MRP1 in a catalytically incompetent conformation. *Proceedings of the National Academy of Sciences of the United States of America*, *120*(11). https://doi.org/10.1073/pnas.2220012120
Original URL	https://www.pnas.org/doi/10.1073/pnas.2220012120
Source type	Journal article
Keywords	Inhibitor, ABC transporters, MRP1
#Tags	Drug resistance, inhibitor
Summary of key points + notes (include methodology)	Adenosine triphosphate-binding cassette (ABC) transporters, like multidrug resistance protein 1 (MRP1), help protect cells from harmful substances by moving them out of the cell. However, when MRP1 is always active, it can make it difficult for certain drugs to reach the brain, and in some cancers, too much MRP1 can make treatments less effective. Scientists have found a tiny molecule called CPI1 that can stop MRP1 from working effectively, but it doesn't interfere much with another similar transporter called P-glycoprotein. They used a special imaging technique to see that CPI1 attaches to MRP1 in the same place as a natural substance the body uses. The way CPI1 sticks to MRP1 stops the normal changes needed for the cell to use energy (ATP) and move substances, suggesting it could be a possible new treatment.
Research Question/Problem/ Need	Can CPI1, a molecule inhibiting MRP1 without affecting P-glycoprotein, serve as an effective treatment to overcome drug resistance in certain cancers by disrupting normal ATP-driven substance transport?

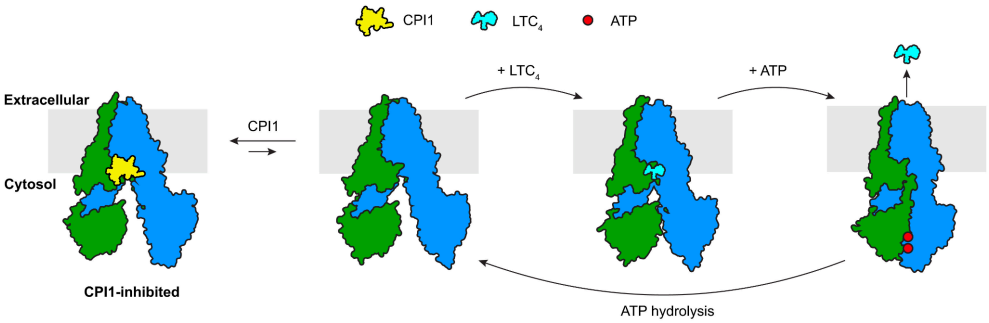
Important Figures	 Identification of an MRP1-specific inhibitor. (A) Selection strategy for novel cyclic peptide MRP1 ligands. eGFP: enhanced green fluorescent protein; Nb: anti-eGFP nanobody. (B) CPI1 composition. The first residue in the sequence (AcDY1, yellow) is covalently bonded to the 17th residue (C17, green) via a thioether linkage. (C) ATPase activity of detergent-solubilized hMRP1 (1 µM), bMRP1 (1 µM), and Pgp (0.5 µM) at 4 mM ATP in the presence or absence of CPI1 (25-fold molar excess). All values reported as the mean ± standard error (SE) of three separate measurements. The statistical significance was calculated using unpaired, parametric, two-sided t tests. Labels: not significant (n.s.), $P < 0.05$ (*), $P < 0.01$ (**), $P < 0.001$ (***) $P < 0.0001$ (****). P-values: bMRP1, 0.000065; bMRP1 + 3.5 µM LTC4, 0.000002; hMRP1, 0.001153; hMRP1 + LTC4, 0.000277; hPgp, 0.107. (D) Dose–response curves of the basal and LTC4-stimulated ATPase activity of bMRP1. Rates of ATP hydrolysis were normalized to maximal activity. Data were fit to a modified version of the quadratic binding equation to account for free ligand depletion (Materials and Methods).



CPI1 binds at the same site as LTC4. (A) Local superposition of the CPI1- (yellow) and LTC4- (cyan) bound structures based on TM helices 6, 7, 8, 11, 15, and 16. MRP1 is shown as grey ribbons. (B) Diagram of MRP1 interactions with LTC4. Dashed lines represent hydrogen bonds and salt bridges. Residues forming the P-pocket are circled in blue and the H-pocket residues are in grey. Residues that also interact with CPI1 are indicated in pink. (C) Zoomed-in view of the CPI1-binding site with interacting side chains shown as sticks. Hydrogen bonds and salt bridges are indicated by dashed lines. Residues that form van der Waals contacts with CPI1 are also indicated. (D) Diagram of the CPI1 interactions with MRP1, annotated as in panel B.



Binding of CPI1 and LTC4 stabilize MRP1 in different conformations. (A) Superposition of CPI1-bound structure (blue) with the apo (grey, Left) and LTC4-bound (orange, Right) structures. (Top) The overall structures. (Bottom) The NBD dimer. The distances between the Cα atoms of the Walker A glycine and signature motif serine on opposing NBDs are indicated. (B) Eight residues interact with both CPI1 and LTC4. Distances indicate the largest displacement of each side chain between LTC4-bound and CPI1-bound conformations.



CPI1 arrests MRP1 in the inward-facing conformation while competing with LTC4. CPI1 is a competitive inhibitor of LTC4 that stabilizes MRP1 in the inward-facing conformation (left diagram), preventing ATP-dependent LTC4 export (transport cycle depicted on the right).

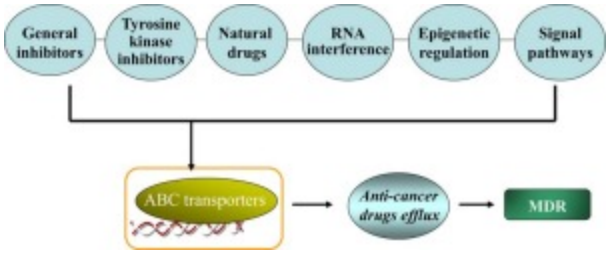
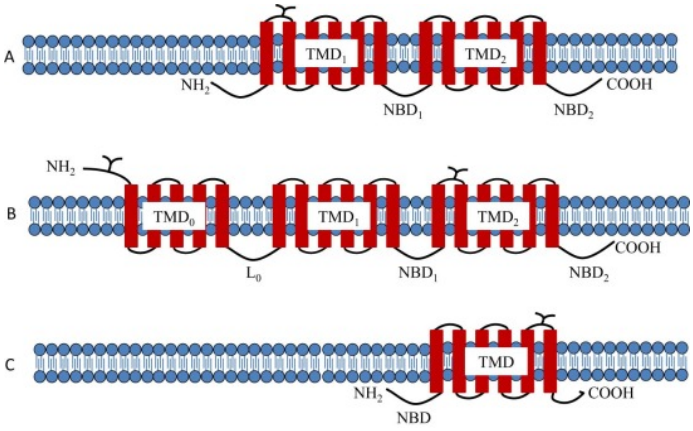
VOCAB: (w/definition)

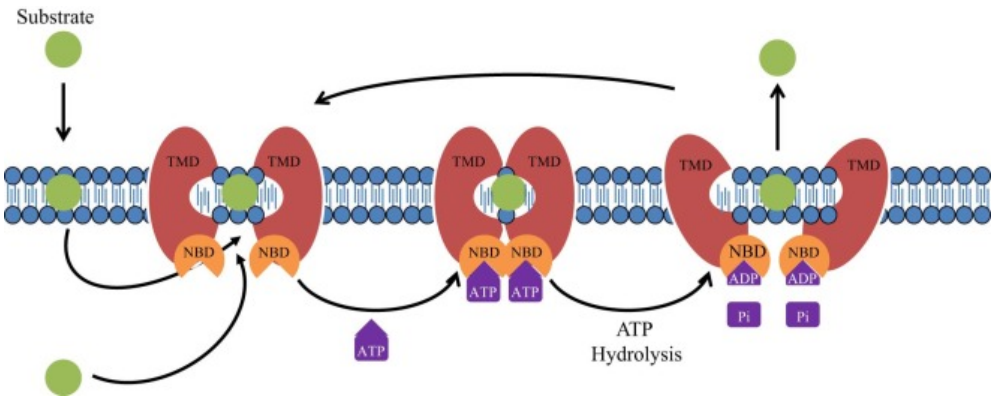
Macrocyclic: containing or being a chemical ring that consists usually of 15 or more atoms
Xenobiotic: a chemical compound (such as a drug, pesticide, or carcinogen) that is foreign to a living organism
Thioether: a compound analogous to ether in which the oxygen has been replaced by sulfur
Puromycin: an antibiotic C22H29N7O5 that is obtained from an actinomycete (Streptomyces alboniger) and is a potent inhibitor of protein

	synthesis
Cited references to follow up on	Flens, M. J., Zaman, R., Paul, Izquierdo, M., Schroeijers, A. B., Scheffer, G. L., Van Der Groep, Marcel de Haas, Meijer, C., & Scheper, R. J. (1996). Tissue distribution of the multidrug resistance protein. *PubMed*, *148*(4), 1237–1247.
Follow up Questions	How specific is CPI1 in targeting MRP1, and why is it more selective compared to P-glycoprotein? How does the mechanism of action of CPI1 compare with existing strategies to overcome drug resistance in cancer?

Article #12 Notes:

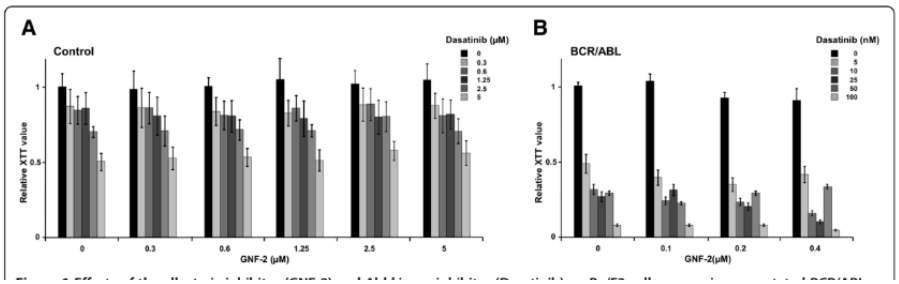
Source Title	Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: A review of the past decade
Source citation (APA Format)	Chen, Z., Shi, T., Zhang, L., Zhu, P., Deng, M., Huang, C., Hu, T., Jiang, L., & Li, J. (2016). Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: A review of the past decade. *Cancer Letters*, *370*(1), 153–164. https://doi.org/10.1016/j.canlet.2015.10.010
Original URL	https://www.sciencedirect.com/science/article/pii/S0304383515006278#bbib0015
Source type	Journal article
Keywords	MDR, transporters, ABC transporters
#Tags	Drug resistance
Summary of key points + notes (include methodology)	Multidrug resistance (MDR) is a problem in cancer treatment because some cancer cells have a way to resist the effects of drugs. One common reason for this resistance is the overproduction of certain proteins, like P-glycoprotein, in cancer cells. These proteins push out the drugs, making them less effective. Scientists are trying to create substances that can block these proteins and make the drugs work better. However, many of these

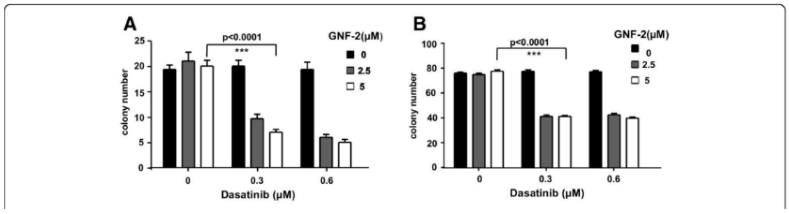
	substances tested in clinical trials have been found to be harmful and don't help patients much. So, researchers are now looking for new substances that can inhibit these proteins without causing harm. Additionally, recent studies suggest that these proteins can be controlled by certain genetic factors. This review summarizes recent discoveries about how these proteins contribute to drug resistance in cancer.
Research Question/Problem/ Need	How can we overcome multidrug resistance in cancer by finding substances that effectively inhibit proteins like P-glycoprotein without causing harm, and what role do genetic factors play in controlling these proteins and influencing drug resistance?
Important Figures	 Graphical Abstract  Secondary structure models of drug efflux transporters of the ATP-binding cassette family. (A) P-gp/ABCB1, (B) MRP2/ABCC2, (C) BCRP/ABCG2. TMD – transmembrane domain; NBD – nucleotide-binding domain; L0 – loop 0.

	 Function of ABC transporters. ABC transporters are energy-dependent transporters; they exhibit a conformational change upon substrate binding and ATP hydrolysis which drives the transport process of the substrate.
VOCAB: (w/definition)	Antineoplastic: inhibiting or preventing the growth and spread of tumors or malignant cells Homodimer: a protein composed of two polypeptide chains that are identical in the order, number, and kind of their amino acid residues Extruding: to force, press, or push out
Cited references to follow up on	A.K. Tiwari, K. Sodani, C.L. Dai, C.R. Ashby Jr., Z.S. Chen Revisiting the ABCs of multidrug resistance in cancer chemotherapy Curr. Pharm. Biotechnol, 12 (2011), pp. 570-594 P-glycoprotein inhibition as a therapeutic approach for overcoming multidrug resistance in cancer: current status and future perspectives
Follow up Questions	How do the substances under investigation work to inhibit proteins like P-glycoprotein, and what makes them potentially more effective and safer than previous candidates? What specific genetic factors are believed to influence the control of proteins like P-glycoprotein?

Article #13 Notes:

Source Title	Allosteric inhibition enhances the efficacy of ABL kinase inhibitors to target unmutated BCR-ABL and BCR-ABL-T3151

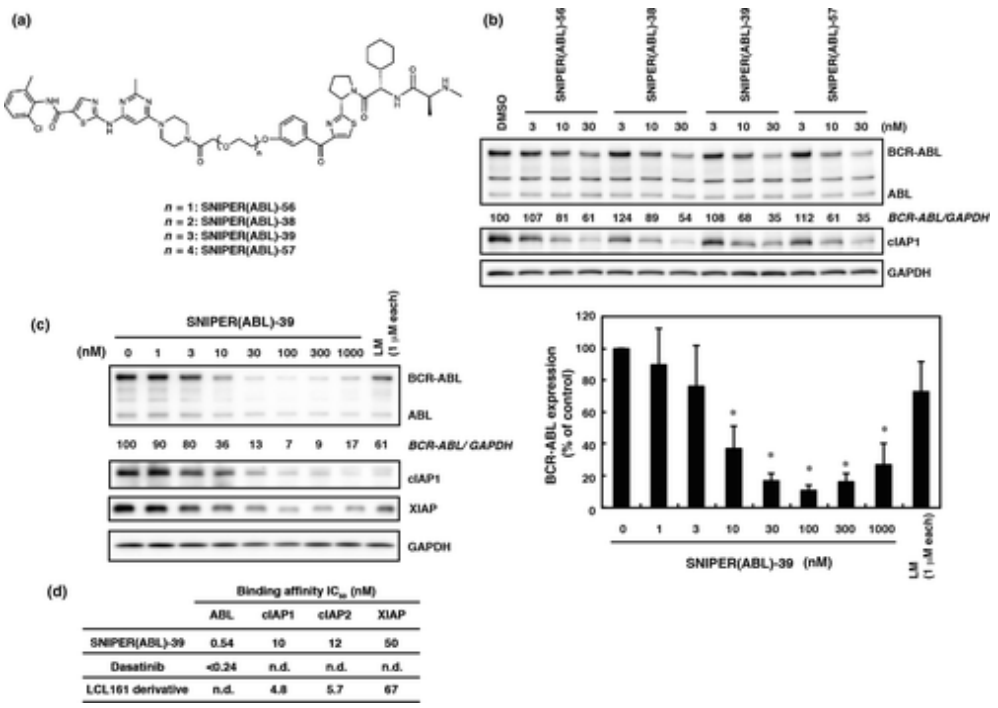
Source citation (APA Format)	Mian, A. A., Metodieva, A., Badura, S., Khateb, M., Ruimi, N., Najajreh, Y., Ottmann, O. G., Mahajna, J., & Ruthardt, M. (2012). Allosteric inhibition enhances the efficacy of ABL kinase inhibitors to target unmutated BCR-ABL and BCR-ABL-T315I. *BMC Cancer*, *12*(1). https://doi.org/10.1186/1471-2407-12-411
Original URL	https://www.proquest.com/docview/1125603510?accountid=29120&pq-origsite=primo&parentSessionId=SDheg%2B4hODUgYDOojBHp2ocMbQ4W%2Fqn7IOpHPkQjIdU%3D&sourcetype=Scholarly%20Journals
Source type	Journal article
Keywords	ABL kinase inhibitors, BCR-ABL-T3151
#Tags	Inhibitors, BCR-ABL
Summary of key points + notes (include methodology)	This study explores a new way to treat certain types of leukemia, specifically chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphatic leukemia (Ph+ ALL). These cancers are caused by a genetic change called t(9;22), resulting in a fusion of BCR and ABL genes and causing abnormal ABL-tyrosine kinase activity. Current treatments using ABL-kinase inhibitors (AKIs) like Imatinib, Nilotinib, or Dasatinib are effective but struggle against a specific mutation called T315I. The researchers investigated a combination of AKIs with another inhibitor called GNF-2 that targets a different aspect of the cancer-causing protein. They found that this combination was more effective, even against the resistant T315I mutation, providing a new potential strategy for treating these types of leukemia.
Research Question/Problem/ Need	Can combining ABL-kinase inhibitors (AKIs) like Imatinib, Nilotinib, or Dasatinib with the inhibitor GNF-2 provide a more effective treatment strategy for chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphatic leukemia (Ph+ ALL), including cases with the challenging T315I mutation?
Important Figures	 Effects of the allosteric inhibitor (GNF-2) and Abl kinase inhibitor (Dasatinib) on Ba/F3 cells expressing unmutated BCR/ABL. (A) XTT assay

	using Ba/F3 cells expressing empty vector upon exposure to 0.3, 0.6, 1.25, 2.5 and 5 μM GNF-2 and 0.3, 0.6, 1.25, 2.5 and 5 μM Dasatinib. (B) XTT assay using Ba/F3 cells expressing BCR/ABL upon exposure to 0.1, 0.2 and 0.4 μM GNF-2 and 5, 10, 25, 50 and 100 nM Dasatinib. Proliferation status was determined by the metabolic activity of cells given by the reduction rate of XTT to formazan. The means +/- SD of triplicates from one representative experiment out of three performed are given.  Effects of GNF-2 and Dasatinib on HSPCs expressing BCR/ABL-T315I. Sca1+ BM cells were retrovirally infected with BCR/ABL-T315. Infected cells were then plated in semi-solid medium in the presence of 2.5 or 5 μM GNF-2 and 0.3 or 0.6 μM Dasatinib (A) without cytokines and (B) with cytokines (mIL-3, mIL-6 and mSCF) to determine the effect of the drugs on HSPC colony formation in semi-solid medium. Colonies were counted after 10 days. The means +/- SD of triplicates from one representative experiment out of two performed are given.
VOCAB: (w/definition)	Allosteric: of, relating to, undergoing, or being a change in the shape and activity of a protein (such as an enzyme) that results from combination with another substance at a point other than the chemically active site Leukemogenic: induction or production of leukemia Murine: of, relating to, or involving these rodents and especially the house mouse
Cited references to follow up on	Daley GQ, Van Etten RA, Baltimore D: Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. Science 1990, 247(4944):824–830. Haeno H, Levine RL, Gilliland DG, Michor F: A progenitor cell origin of myeloid malignancies. Proc Natl Acad Sci U S A 2009, 106(39):16616–16621. Beissert T, Hundertmark A, Kaburova V, Travaglini L, Mian AA, Nervi C, Ruthardt M: Targeting of the N-terminal coiled coil oligomerization interface by a helix-2 peptide inhibits unmutated and imatinib-resistant

	BCR/ABL. Int J Cancer 2008, 122(12):2744–2752.
Follow up Questions	How effective are ABL-kinase inhibitors (Imatinib, Nilotinib, Dasatinib) in treating chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphatic leukemia (Ph+ ALL) before the emergence of the T315I mutation? What specific aspect of the cancer-causing protein does the GNF-2 inhibitor target, and how does it differ from ABL-kinase inhibitors?

Article #14 Notes:

Source Title	Development of protein degradation inducers of oncogenic BCR-ABL protein by conjugation of ABL kinase inhibitors and IAP ligands
Source citation (APA Format)	Shibata, N., Miyamoto, N., Nagai, K., Shimokawa, K., Sameshima, T., Nobumichi Ohoka, Hattori, T., Yasuhiro Imaeda, Nara, H., Cho, N., & Naito, M. (2017). Development of protein degradation inducers of oncogenic BCR‐ABL protein by conjugation of ABL kinase inhibitors and IAP ligands. *Cancer Science*, *108*(8), 1657–1666. https://doi.org/10.1111/cas.13284
Original URL	https://onlinelibrary.wiley.com/doi/full/10.1111/cas.13284
Source type	Journal article
Keywords	BCR-ABL, kinase, ligands
#Tags	Inhibitors, BCR-ABL
Summary of key points + notes (include methodology)	In some types of cancer, like chronic myelogenous leukemia (CML), there's a genetic change that creates abnormal proteins, such as BCR-ABL. Medicines like imatinib and dasatinib work well against these proteins, but over time, the cancer can become resistant to them. This study explores a different approach to treat CML by making the cancer-causing protein disappear. Scientists used a method called Specific and Non-genetic inhibitor of apoptosis protein [IAP]-dependent Protein Erasers (SNIPER) to create a molecule called SNIPER(ABL)-39. This molecule, made by combining dasatinib with another compound, was successful in breaking down the BCR-ABL protein, inhibiting the cancer's growth, and could be a promising new treatment for this type of leukemia.

Research Question/Problem/ Need	Can the molecule SNIPER(ABL)-39, created through the SNIPER method, effectively eliminate the cancer-causing BCR-ABL protein in chronic myelogenous leukemia (CML), providing a promising new treatment approach?
Important Figures	 SNIPER(ABL)-39 shows potent protein knockdown activity. (a) Chemical structures of SNIPER(ABL) with different linker length. (b) Effect of linker length on the protein knockdown activity of the SNIPER(ABL). K562 cells were incubated with the indicated concentration of SNIPER(ABL) for 6 h. (c) Dose response of the protein knockdown activity of SNIPER(ABL)-39. K562 cells were incubated with the indicated concentration of SNIPER(ABL)-39 or ligands mix (LM; dasatinib and the LCL161 derivative) for 24 h. Numbers below the ABL panel represent the BCR-ABL/GAPDH ratio normalized by vehicle control as 100. Data in the bar graph (c) are means ± SD ($n = 4$). *$P < 0.01$ compared with vehicle control. (d) Binding affinities of SNIPER(ABL)-39 to ABL and IAP. IC50 values (concentrations of SNIPER(ABL)-39 required to inhibit the probe binding to each protein by 50%) are presented. n.d., not determined.

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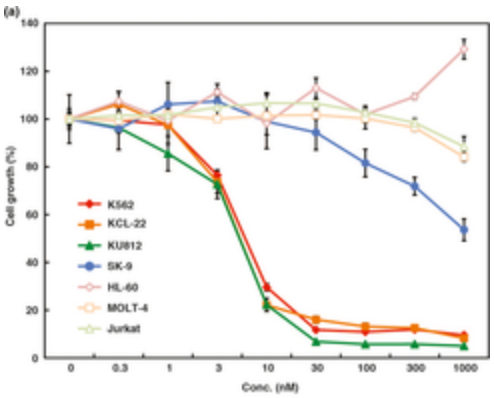

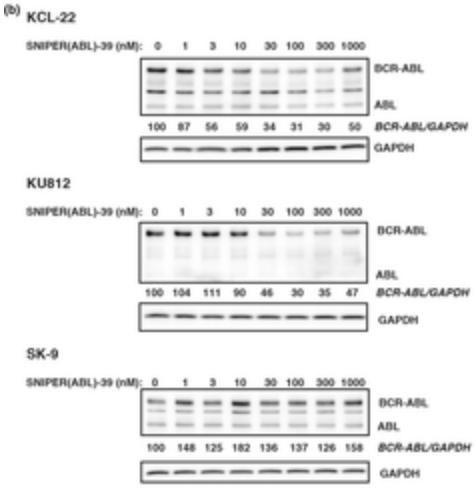

(c)

	Cell growth inhibition IC_{50} (nM)		
	K562	KCL22	KU812
SNIPER(ABL)-39	8.92 ± 0.18	8.06 ± 0.63	6.72 ± 0.98
Dasatinib	0.207 ± 0.007	0.0497 ± 0.0067	0.0395 ± 0.0040

SNIPER(ABL)-39 inhibits proliferation of chronic myelogenous leukemia (CML) cells expressing native BCR-ABL. (a) Effect of SNIPER(ABL)-39 on cell growth in various CML and leukemia cells. Cells were incubated with the indicated concentration of SNIPER(ABL)-39 for 48 h and subjected for WST assay. Data in the graphs are means ± SD (n = 3). (b) Degradation of BCR-ABL protein in various CML cells. Cells were incubated with the indicated concentration of SNIPER(ABL)-39 for 6 h, and the cell lysates were analyzed by western blot. (c) Growth inhibitory effect of SNIPER(ABL)-39 and dasatinib in various CML cells. Cells were incubated with the SNIPER(ABL)-39 and dasatinib for 48 h and subjected for WST assay. IC50 values (half-maximal inhibitory concentration of cell growth) are presented as means ± SD (n = 3).
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<td>VOCAB: (w/definition)</td>
<td>Oncogenic: relating to tumor formation
Ubiquitin: a chiefly eukaryotic protein that when covalently bound to other</td>
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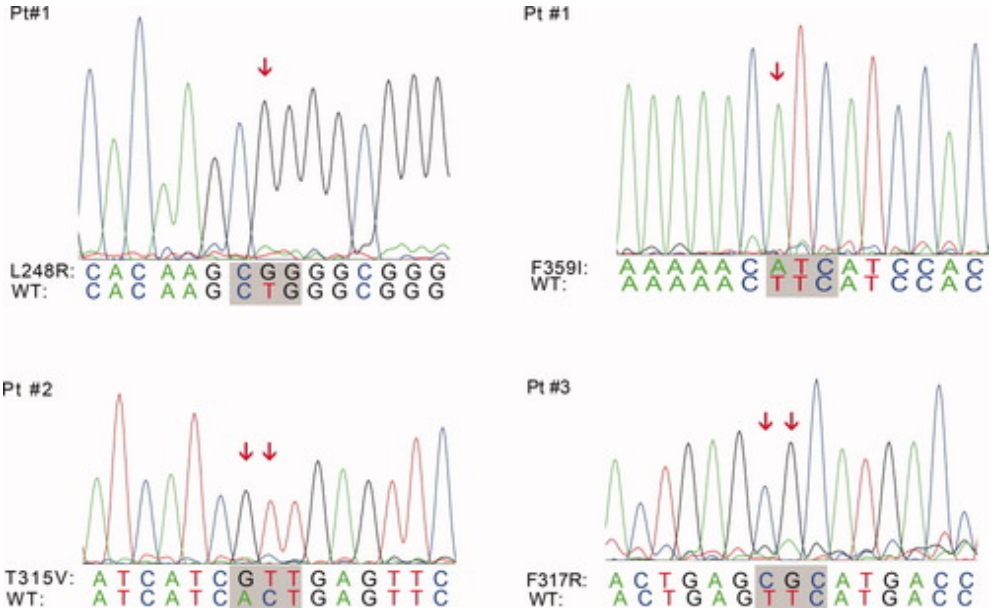
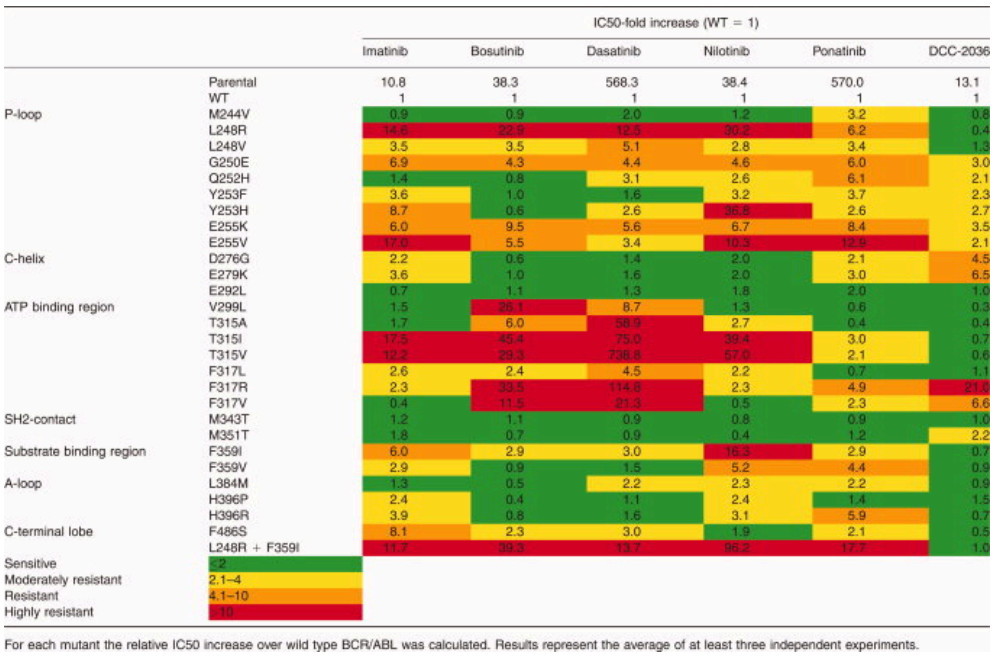
	cellular proteins marks them for proteolytic degradation especially by a proteasome
Cited references to follow up on	Rudkin CT, Hungerford DA, Nowell PC. DNA contents of chromosome Ph1 and chromosome 21 in human chronic granulocytic leukemia. *Science* 1964; 144: 1229–31. Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. *Nature* 1973; 243: 290–3.
Follow up Questions	Can you provide more details on how the SNIPER(ABL)-39 molecule, created by combining dasatinib with another compound, works to break down the BCR-ABL protein? What specific mechanisms are involved in the disappearance of the cancer-causing protein?

Article #15 Notes:

Source Title	Three novel patient-derived BCR/ABL mutants show different sensitivity to second and third generation tyrosine kinase inhibitors.
Source citation (APA Format)	Redaelli, S., Mologni, L., Rostagno, R., Piazza, R., Magistroni, V., Ceccon, M., Viltadi, M., Flynn, D., & Gambacorti-Passerini, C. (2012). Three novel patient-derived BCR/ABL mutants show different sensitivity to second and third generation tyrosine kinase inhibitors. *American Journal of Hematology*, *87*(11), E125–E128. https://doi.org/10.1002/ajh.23338
Original URL	https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.23338
Source type	Journal article
Keywords	BCR-ABL, kinase inhibitors, mutants
#Tags	BCR-ABL kinase
Summary of key points + notes (include methodology)	This study looks at changes in a gene called BCR-ABL in patients with chronic myeloid leukemia (CML). Some patients develop resistance to certain drugs used to treat CML because of mutations in this gene. The study

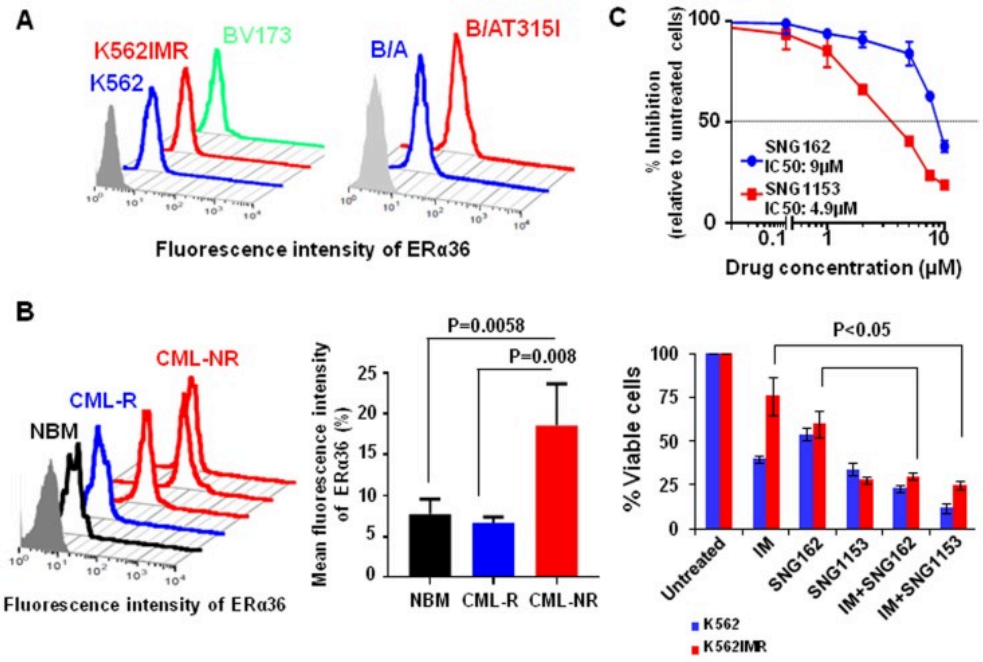
	found three new mutations, L248R, T315V, and F317R, in patients with CML. These mutations make the gene less responsive to common treatments. The researchers tested different drugs and found that a combination of two, called ponatinib and DCC-2036, was effective against these mutations in the lab. They also checked how well the drugs worked against other mutations in BCR-ABL. This information could help doctors choose the best treatment for CML patients with specific gene mutations, improving their chances of responding to therapy.
Research Question/Problem/ Need	How do new mutations in the BCR-ABL gene, like L248R, T315V, and F317R, affect the response to common treatments in chronic myeloid leukemia (CML)? Can a combination of drugs, ponatinib and DCC-2036, effectively target these mutations, informing personalized treatment strategies for CML patients?
Important Figures	 Sequencing chromatograms for the three patients analyzed. For all the mutations the WT sequence is reported as reference and the codon affected by the nucleotide change is shaded. The red arrows correspond to the mutation site. Chromatograms for Patient no. 1 refer to the same sequencing reaction and have been divided in two parts to allow visualization of both mutations.

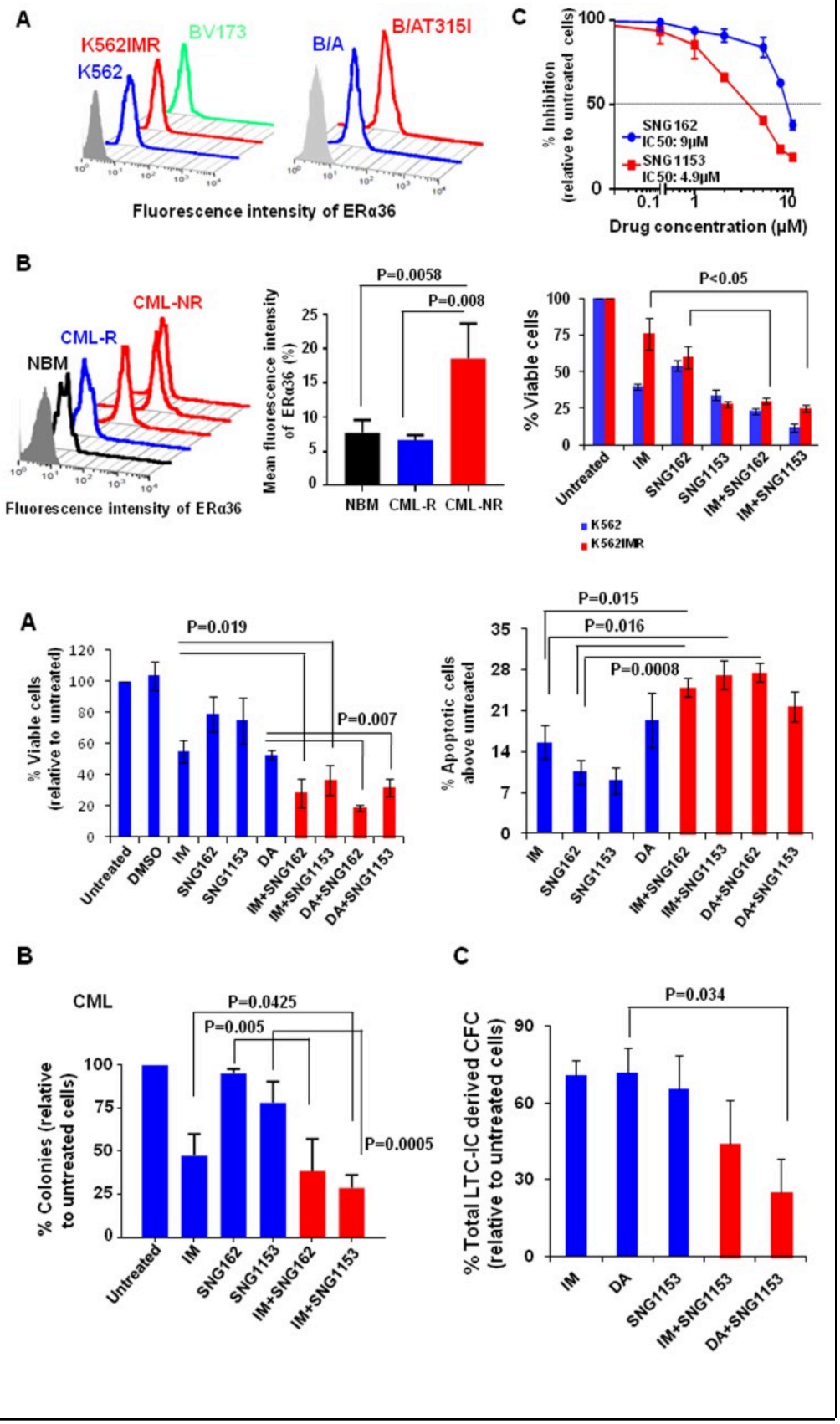
	
VOCAB: (w/definition)	Lymphoblastic: a lymphocyte that has enlarged following stimulation by an antigen, has the capacity to recognize the stimulating antigen, and is undergoing proliferation and differentiation either to an effector state in which it functions to eliminate the antigen or to a memory state in which it functions to recognize the future reappearance of the antigen Lymphocyte: any of the colorless weakly motile cells originating from stem cells and differentiating in lymphoid tissue (as of the thymus or bone marrow) that are the typical cellular elements of lymph, include the cellular mediators of immunity, and constitute 20 to 30 percent of the white blood cells of normal human blood Paradigm: a philosophical and theoretical framework of a scientific school or discipline within which theories, laws, and generalizations and the experiments performed in support of them are formulated
Cited references to follow up on	Kantarjian H,Shah N,Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Eng J Med*, in press. Saglio G,Kim D,Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Eng J Med*, in press. Puttini M,Coluccia AML,Boschelli F, et al. In vitro and in vivo activity of SKI-606, a novel Src-Abl inhibitor, against imatinib-resistant Bcr-Abl+ neoplastic cells. *Cancer Res* 2006; 66: 11314–11322.

Follow up Questions	Besides the three new mutations (L248R, T315V, and F317R), what other mutations in the BCR-ABL gene were investigated, and were any of them found to be responsive to the tested drug combination? Are there specific criteria or characteristics that could guide doctors in determining which CML patients with BCR-ABL mutations would be most likely to benefit from the identified drug combination?

Article #16 Notes:

Source Title	Targeting BCR-ABL+ stem/progenitor cells and BCR-ABL-T315I mutant cells by effective inhibition of the BCR-ABL-Tyr177-GRB2 complex
Source citation (APA Format)	Chen, M., Turhan, A. G., Ding, H., Lin, Q., Meng, K., & Jiang, X. (2017). Targeting BCR-ABL+ stem/progenitor cells and BCR-ABL-T315I mutant cells by effective inhibition of the BCR-ABL-Tyr177-GRB2 complex. *Oncotarget*, *8*(27). https://doi.org/10.18632/oncotarget.18216
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5546432/
Source type	Journal article
Keywords	BCR-ABL, inhibition, leukemia
#Tags	BCR-ABL, drug resistance
Summary of key points + notes (include methodology)	The treatment of a type of leukemia called BCR-ABL+ human leukemia has improved with drugs called ABL tyrosine kinase inhibitors (TKIs). However, these drugs don't cure everyone, and some patients relapse due to mutations in the leukemia-causing gene BCR-ABL. In this study, scientists found that a protein called estrogen receptor alpha 36 (ERα36) is increased in leukemia cells that don't respond well to TKIs. They also discovered that new drugs, SNG162 and SNG1153, which target abnormal ERα36 activity, can stop the growth and cause the death of these leukemia cells, especially those with a specific mutation called BCR-ABL-T315I. Combining these drugs with TKIs was effective in eliminating resistant cells while sparing healthy ones. The combination therapy, particularly using the drug dasatinib with SNG1153, was successful in mice, showing promise for more effective leukemia treatment, especially in patients with a high risk of drug resistance and disease progression.
Research Question/Problem/	How can the increased expression of estrogen receptor alpha 36 (ERα36) be

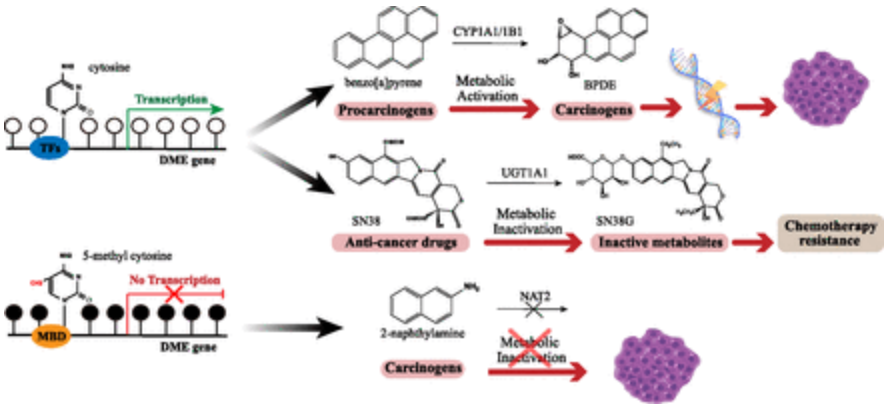
Need	targeted to improve the treatment of BCR-ABL+ human leukemia, especially in cases of TKI resistance, and what is the effectiveness of combining drugs SNG162 and SNG1153 with dasatinib for eliminating resistant leukemia cells while sparing healthy ones?
Important Figures	 Increased surface expression of ERα36 in TKI-resistant cells and CD34 + IM-nonresponder cells. A. Detection of surface expression of ERα36 in parental K562 and K562 IM-resistant cells (K562IMR), BV173 cells and human UT7 cells expressing either wild-type BCR-ABL (B/A) or BCR-ABL-T315 mutant (B/AT315I) cells using a specific anti-ERα36 antibody. B. Expression of ERα36 in CD34+ cells isolated from IM-nonresponders (n = 5), IM-responders (n = 3) and normal donors (n = 4). The differences detected were shown in mean fluorescence intensity of ERα36 in these samples. Values shown are the mean ± SEM of measurement from normal and CML patients. C. IC50 curves for K562 cells after 48 hours treatment with SNG162 and SNG1153 (from 0.1μM to 10 μM range). K562 and K562IMR cells were treated with IM (0.5 μM for K562 and 2.5 μM for K562IMR), SNG162 (5 μM) or SNG1153 (2.5 μM) alone or in combination for 48 hours. Viable cells were analyzed by counting trypan blue excluding cells. The percentage of viable cells relative to untreated cells was expressed. Data shown are mean ± SEM of measurements from three independent experiments.


A
K562IMR
K562
BV173
B/A
B/AT315I
Fluorescence intensity of ERα36
C
% Inhibition (relative to untreated cells)
SNG162 IC50: 9μM
SNG1153 IC50: 4.9μM
Drug concentration (μM)
B
NBM
CML-R
CML-NR
Fluorescence intensity of ERα36
Mean fluorescence intensity of ERα36 (%)
P=0.0058
P=0.008
NBM CML-R CML-NR
% Viable cells
P<0.05
Untreated IM SNG162 SNG1153 IM+SNG162 IM+SNG1153
K562
K562IMR
A
% Viable cells (relative to untreated)
P=0.019
P=0.007
Untreated DMSO IM SNG162 SNG1153 DA IM+SNG162 IM+SNG1153 DA+SNG162 DA+SNG1153
% Apoptotic cells above untreated
P=0.015
P=0.016
P=0.0008
IM SNG162 SNG1153 DA IM+SNG162 IM+SNG1153 DA+SNG162 DA+SNG1153
B
CML
% Colonies (relative to untreated cells)
P=0.0425
P=0.005
P=0.0005
Untreated IM SNG162 SNG1153 IM+SNG162 IM+SNG1153
C
% Total LTC-IC derived CFC (relative to untreated cells)
P=0.034
IM DA SNG1153 IM+SNG1153 DA+SNG1153

	A combination of SNG inhibitors and TKI is more effective in inducing apoptosis and suppressing the phosphorylation of tyrosine 177 of BCR-ABL in K562 and K562IMR cells A. K562 and K562IMR cells were treated with IM (0.5 μM for K562 and 2.5 μM for K562IMR), SNG162 (5 μM) or SNG1153 (2.5 μM) alone or in combination for 48 hours. Apoptotic cells were determined by Annexin V+ staining. Values are presented as mean ± SEM of three different experiments. B. Western blot analysis of protein expression of K562 or K562IMR cells treated with IM or SNG inhibitors, alone or in combination, for 48 hours. Specific antibodies used are indicated. The densitometry values of protein expression changes are indicated as compared to untreated control. C. GRB2 was immunoprecipitated from K562IMR cell lysates with the same treatment as indicated in B. The immunoprecipitates were then probed with either BCR-ABL or GRB2 antibodies.
VOCAB: (w/definition)	Myeloproliferative: of, relating to, or being a disorder (such as leukemia) marked by excessive proliferation of bone marrow elements and especially blood cell precursors Oncoprotein:a protein that is coded for by a viral oncogene which has been integrated into the genome of a eukaryotic cell and that is involved in the regulation or synthesis of proteins linked to tumorigenic cell growth Oncogene: a gene having the potential to cause a normal cell to become cancerous
Cited references to follow up on	Sawyers CL. Chronic myeloid leukemia. *N Engl J Med.* 1999;340:1330–40. doi: 10.1056/NEJM199904293401706. Goldman JM, Melo JV. Targeting the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344:1084–6. doi: 10.1056/NEJM200104053441409. Lee HJ, Thompson JE, Wang ES, Wetzler M. Philadelphia chromosome-positive acute lymphoblastic leukemia: current treatment and future perspectives. *Cancer.* 2011;117:1583–94. doi: 10.1002/cncr.25690.
Follow up Questions	What specific mechanisms or pathways does estrogen receptor alpha 36 (ERα36) activate that contribute to resistance in leukemia cells treated with ABL tyrosine kinase inhibitors (TKIs)? How specific are SNG162 and SNG1153 in targeting abnormal ERα36 activity, and what safety considerations or potential side effects are associated with these drugs?

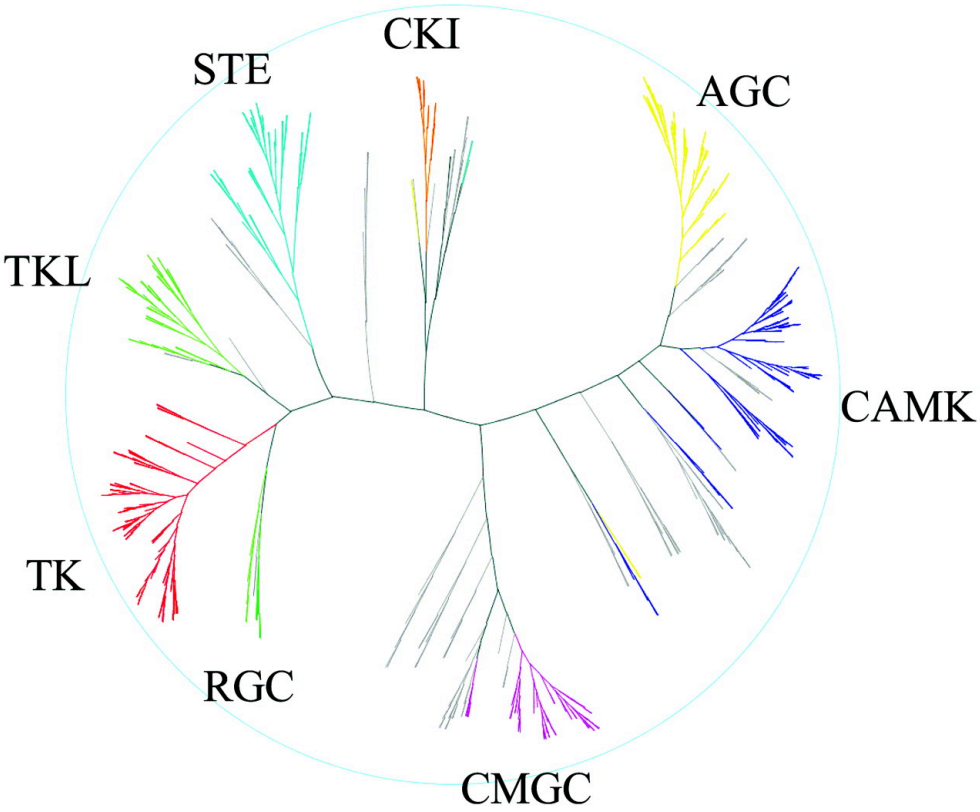
Article #17 Notes:

Source Title	Epigenetic Regulation of Differentially Expressed Drug-Metabolizing Enzymes in Cancer
Source citation (APA Format)	Wang, J., Yu, L., Jiang, H., Zheng, X., & Zeng, S. (2020). Epigenetic Regulation of Differentially Expressed Drug-Metabolizing Enzymes in Cancer. *Drug Metabolism and Disposition*, *48*(9), 759–768. https://doi.org/10.1124/dmd.120.000008
Original URL	https://dmd.aspetjournals.org/content/48/9/759
Source type	Journal article
Keywords	Enzymes, DMEs, CML
#Tags	Proteins, drug resistance
Summary of key points + notes (include methodology)	Drug-metabolizing enzymes (DMEs), divided into phase I and phase II DMEs, play a crucial role in how drugs affect individuals. In cancer, the normal expression of these enzymes can be disrupted at various stages, impacting cancer development and affecting how individuals respond to cancer drugs. This review discusses how, beyond known genetic differences, epigenetic factors like DNA methylation, histone modification, and noncoding RNAs influence the expression of DMEs in cancer. Understanding these epigenetic regulations can help create personalized and rationalized medication plans for cancer patients. Additionally, it opens avenues for identifying new markers and targets for diagnosing, treating, and predicting the outcomes of cancer. In essence, exploring how these enzymes are regulated in cancer provides valuable insights into cancer progression and resistance to chemotherapy.
Research Question/Problem/ Need	How do epigenetic factors impact the expression of drug-metabolizing enzymes in cancer, and how can this knowledge be used for personalized cancer medication plans, marker identification, and improved diagnosis and treatment outcomes?

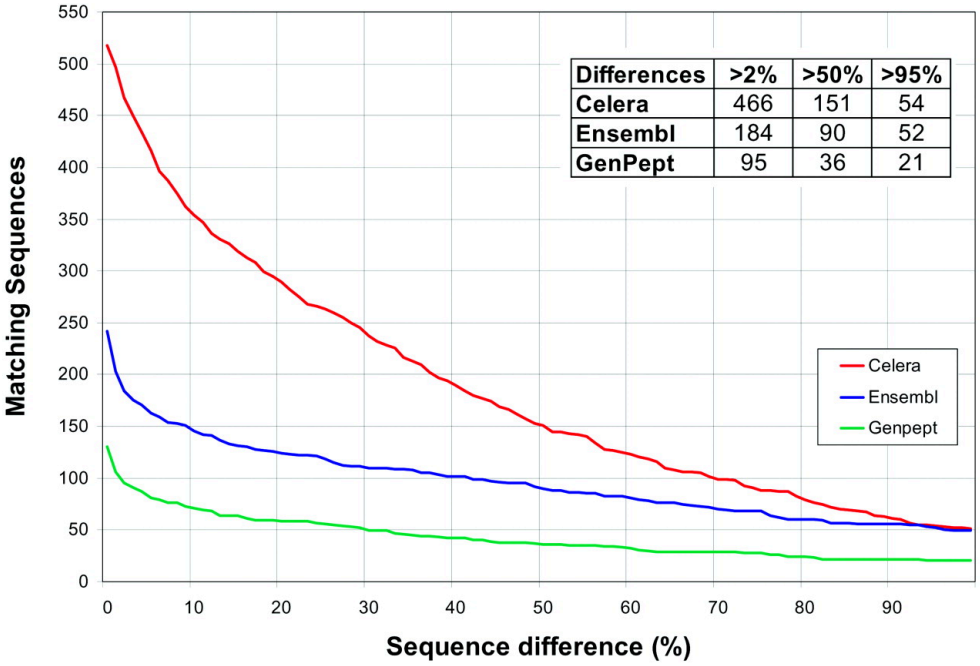
Important Figures	 The methylation status of DME genes contributes to cancer progression and chemoresistance. White dots represent cytosine, and black dots represent 5-methyl cytosine.
VOCAB: (w/definition)	Monooxygenases: any of several oxygenases that bring about the incorporation of one atom of molecular oxygen into a substrate Aldehyde : any of a class of highly reactive organic compounds that are analogous to acetaldehyde and characterized by a carbonyl group attached to a hydrogen atom Dehydrogenases: an enzyme that accelerates the removal of hydrogen from metabolites and its transfer to other substances
Cited references to follow up on	Almazrooa, Miah MK, and Venkataramanan R2017) Drug metabolism in the liver. *Clin Liver Dis* **21**:1–20. Alzahrani AM and Rajendran P(2020) The Multifarious Link between cytochrome P450s and cancer. *Oxid Med Cell Longev* **2020**:3028387. Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z, Wei G, Chepelev I, and Zhao K(2007) High-resolution profiling of histone methylations in the human genome. *Cell* **129**:823–837.
Follow up Questions	How can the understanding of epigenetic regulations of DMEs be applied to create personalized medication plans for cancer patients? What are the potential markers and targets identified through these epigenetic regulations, and how could they be used in the diagnosis of cancer outcomes?

Article #18 Notes:

Source Title	The Protein Kinase Complement of the Human Genome
Source citation (APA Format)	Manning, G. (2002). The Protein Kinase Complement of the Human Genome. *Science*, *298*(5600), 1912–1934. https://doi.org/10.1126/science.1075762
Original URL	https://www.science.org/doi/10.1126/science.1075762
Source type	Journal article
Keywords	Kinase, kinone, phosphorylation
#Tags	Protein Kinase
Summary of key points + notes (include methodology)	Scientists have compiled a comprehensive list of protein kinases in the human genome, known as the "kinome," by examining various genetic sequences. This catalog serves as a foundation for studying protein phosphorylation in both normal and diseased conditions, offering insights into the human genome's current status by focusing on a major gene family. The researchers identified 518 potential protein kinase genes, uncovering 71 new ones not previously known as kinases and refining the protein sequences of 56 others. These newly discovered genes belong to both well-known and unfamiliar families, some shared with model organisms. By classifying and comparing with other species, the study identified similar groups and highlighted expansions unique to humans and other lineages. The researchers also found 106 non-functional protein kinase genes, known as pseudogenes. Mapping these genes on chromosomes revealed clusters and showed that 244 kinases are associated with disease locations or cancer-related gene amplifications.
Research Question/Problem/ Need	How is the human protein kinome structured, including the identification of new genes, their classification, comparison with other species, and associations with diseases?
Important Figures	



Dendrogram of 491 ePK domains from 478 genes. Major groups (Table 1) are labeled and colored. For group-specific and comparative genomic trees, seewww.kinase.com/human/kinome.

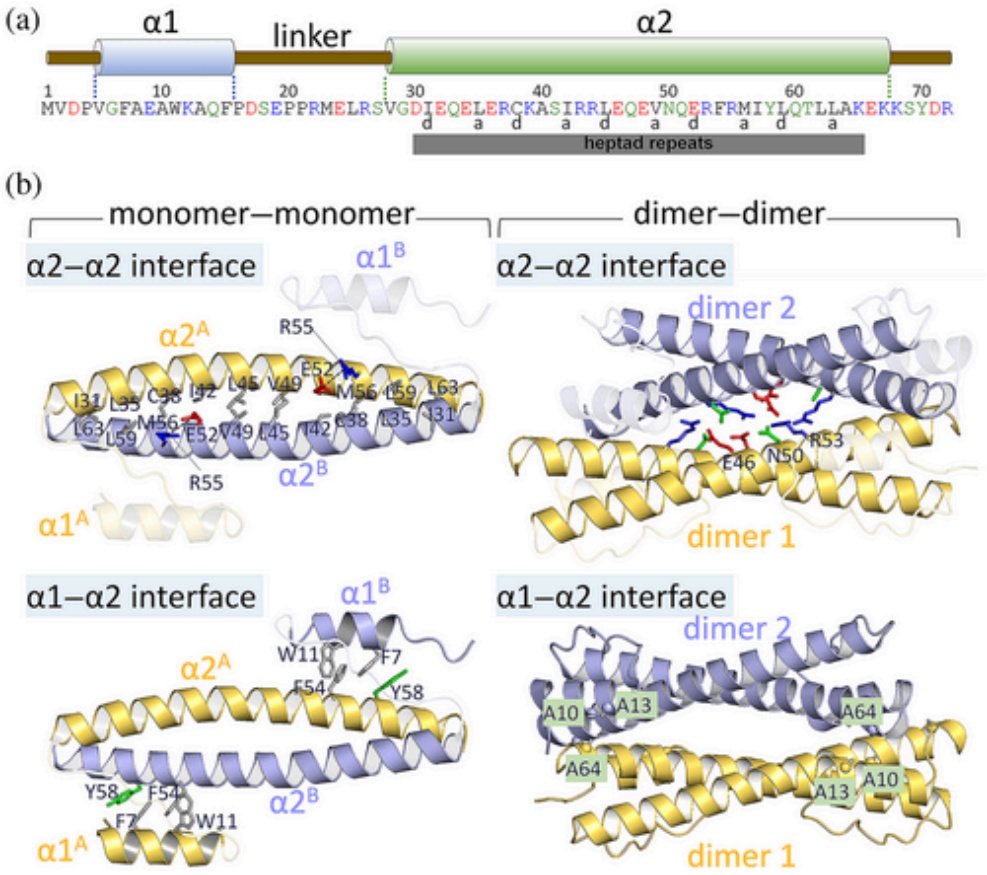


Comparison of the kinase protein sequences with the best matches in Celera,

	Ensembl, and GenPept databases. Each point shows the number of genes for which the percentage difference between the sequence and the database is greater than the value indicated. Insert table indicates number of sequences where differences between the sequence and closest database match is >2%, >50%, or >95%.
VOCAB: (w/definition)	Putative: commonly accepted or supposed Glycogen: a white amorphous tasteless polysaccharide (C6H10O5)x that is the principal form in which glucose is stored in animal tissues and especially muscle and liver tissue Burgeoning: growing, expanding, or developing rapidly
Cited references to follow up on	Hunter T. (1987). A thousand and one protein kinases. *Cell*, *50*(6), 823–829. https://doi.org/10.1016/0092-8674(87)90509-5 Lander, E. S., Linton, L. M., Birren, B., Nusbaum, C., Zody, M. C., Baldwin, J., Devon, K., Dewar, K., Doyle, M., FitzHugh, W., Funke, R., Gage, D., Harris, K., Heaford, A., Howland, J., Kann, L., Lehoczky, J., LeVine, R., McEwan, P., McKernan, K., … International Human Genome Sequencing Consortium (2001). Initial sequencing and analysis of the human genome. *Nature*, *409*(6822), 860–921. https://doi.org/10.1038/35057062 Manning, G., Plowman, G. D., Hunter, T., & Sudarsanam, S. (2002). Evolution of protein kinase signaling from yeast to man. *Trends in biochemical sciences*, *27*(10), 514–520. https://doi.org/10.1016/s0968-0004(02)02179-5
Follow up Questions	What functions or roles do the 71 newly discovered protein kinase genes play? How do they contribute to our understanding of protein phosphorylation in normal and diseased conditions?

Article #19 Notes:

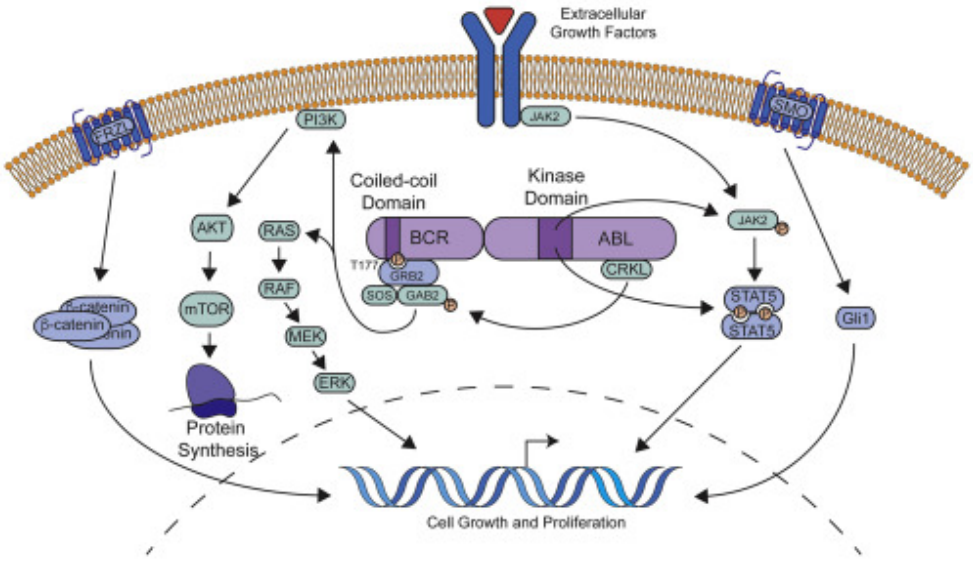
Source Title	Higher-order interactions of Bcr-Abl can broaden chronic myeloid leukemia (CML) drug repertoire
Source citation (APA Format)	Liu, Y., Zhang, M., Jang, H., & Nussinov, R. (2022). Higher‐order interactions of Bcr‐Abl can broaden chronic myeloid leukemia (CML) drug repertoire. *Protein|Science*, *32*(1). https://doi.org/10.1002/pro.4504
Original URL	https://onlinelibrary.wiley.com/doi/10.1002/pro.4504
Source type	Journal article
Keywords	BCR-ABL, CML, inase
#Tags	BCR-ABL, drug resistance
Summary of key points + notes (include methodology)	The Bcr-Abl oncoprotein, linked to certain types of leukemia, particularly chronic myeloid leukemia (CML), is a nonreceptor tyrosine kinase. When the N-terminal region of Abl, which is connected to myristoyl, is deleted, Bcr-Abl becomes continuously active. This fusion oncoprotein's ability to oligomerize, or group together, is crucial for potent signaling and cell growth. The study delves into the step-by-step process of Bcr-Abl oligomerization, identifying a specific surface and essential elements. The N-terminal coiled coil (CC) domain of Bcr controls this oligomerization, validated through crystallography, which reveals dimerization and tetramerization. Molecular dynamics simulations show that the Bcr CC domain's binary complex serves as a basic unit in the quaternary complex, providing a specific surface for oligomerization. The study discovers that a small α1-helix is key to this process. Understanding these mechanisms could aid in drug discovery, potentially using Bcr CC-derived peptides or targeting specific residues to disrupt oligomerization, supplementing other types of kinase inhibitors in leukemia treatment.
Research Question/Problem/ Need	How does the N-terminal coiled coil (CC) domain of the Bcr-Abl oncoprotein control its oligomerization, and how can this insight guide drug discovery for leukemia treatment, potentially through Bcr CC-derived peptides or targeted disruption of oligomerization?"

Important Figures	 Sequence, structure, and interface. (a) Sequence and components, and (b) structures and interfaces for the binary and quaternary complexes, of the Bcr CC domain. The binary complex contains chains A and B (yellow and lightblue), and the quaternary complex contains two dimeric units, dimer 1 (chain A/B, yellow) and dimer 2 (chain C/D, lightblue). Each chain in the binary Bcr CC consists of an α1-helix (e.g., α1A for chain A and α1B for chain B) and an α2-helix (e.g., α2A for chain A and α2B for chain B), which are connected by a linker. Interfacial residues are showed as sticks. The positively charged, negatively charged, polar, and hydrophobic residues at the interfaces are colored in blue, red, green, and gray, respectively
VOCAB: (w/definition)	Proto-oncogene: a gene having the potential for change into an active oncogene Isoforms: any of two or more functionally similar proteins that have a similar but not an identical amino acid sequence Oligomerization: a polymer or polymer intermediate containing relatively few structural units

Cited references to follow up on	Alves R, Goncalves AC, Rutella S, Almeida AM, De Las Rivas J, Trougakos IP, et al. Resistance to tyrosine kinase inhibitors in chronic myeloid leukemia-from molecular mechanisms to clinical relevance. *Cancers (Basel)*. 2021; 13:4820. Apostolovic B, Danial M, Klok HA. Coiled coils: Attractive protein folding motifs for the fabrication of self-assembled, responsive and bioactive materials. *Chem Soc Rev*. 2010; 39: 3541–75. Astl L, Verkhivker GM. Atomistic modeling of the ABL kinase regulation by allosteric modulators using structural perturbation analysis and community-based network reconstruction of allosteric communications. *J Chem Theory Comput.* 2019; 15: 3362–80.
Follow up Questions	What are some potential advantages of using Bcr CC-derived peptides or targeting specific residues in drug discovery? What is the significance of the identified specific surface and essential elements in the oligomerization process of the Bcr-Abl oncoprotein?

Article #20 Notes:

Source Title	Response and Resistance to BCR-ABL1-Targeted Therapies
Source citation (APA Format)	Braun, T. P., Eide, C. A., & Druker, B. J. (2020). Response and Resistance to BCR-ABL1-Targeted Therapies. *Cancer Cell*, *37*(4), 530–542. https://doi.org/10.1016/j.ccell.2020.03.006
Original URL	https://www.sciencedirect.com/science/article/pii/S153561082030146X
Source type	Journal article
Keywords	BCR-ABL, drug resistance,
#Tags	BCR-ABL
Summary of key points + notes (include methodology)	Chronic myeloid leukemia (CML), caused by an overactive BCR-ABL1 fusion tyrosine kinase, has been a success story in molecularly targeted cancer therapy. The drug imatinib has been a game-changer, allowing CML patients to live nearly normal lives. However, some patients develop resistance to imatinib due to specific mutations, and newer drugs help overcome this challenge. While most patients with early-stage CML achieve

	long-term control, advanced stages or BCR-ABL1-positive acute lymphoblastic leukemia pose greater difficulties, and relapse can occur through various mechanisms. Second-generation drugs offer better results, pushing the disease burden to undetectable levels for many patients. Efforts now focus on finding strategies for even deeper responses, potentially allowing more patients to stop drug therapy altogether.
Research Question/Problem/ Need	How can we improve treatment for Chronic Myeloid Leukemia, especially in advanced stages, addressing issues like imatinib resistance, relapse mechanisms, and developing strategies for deeper responses to potentially allow some patients to stop drug therapy?
Important Figures	 Molecular Pathway Activation Downstream of BCR-ABL1 BCR-ABL1 dimerizes leading to autophosphorylation at tyrosine 177 of BCR. This serves as a docking point for the GRB2/GAB2/SOS complex which activates multiple signaling pathways, including PI3K/AKT and MAPK. Autophosphorylation of key residues in the BCR-ABL1 kinase domain also in turn activate the JAK/STAT pathway likely via activation of JAK2 and direct phosphorylation of STAT5. In the setting of BCR-ABL1 TKI resistance, extracellular growth factors can act via the JAK/STAT pathway to sustain cell growth. Leukemia stem cells may uniquely depend on WNT/β-catenin and SHH/SMO signaling for survival in the face of BCR-ABL1 kinase inhibition.

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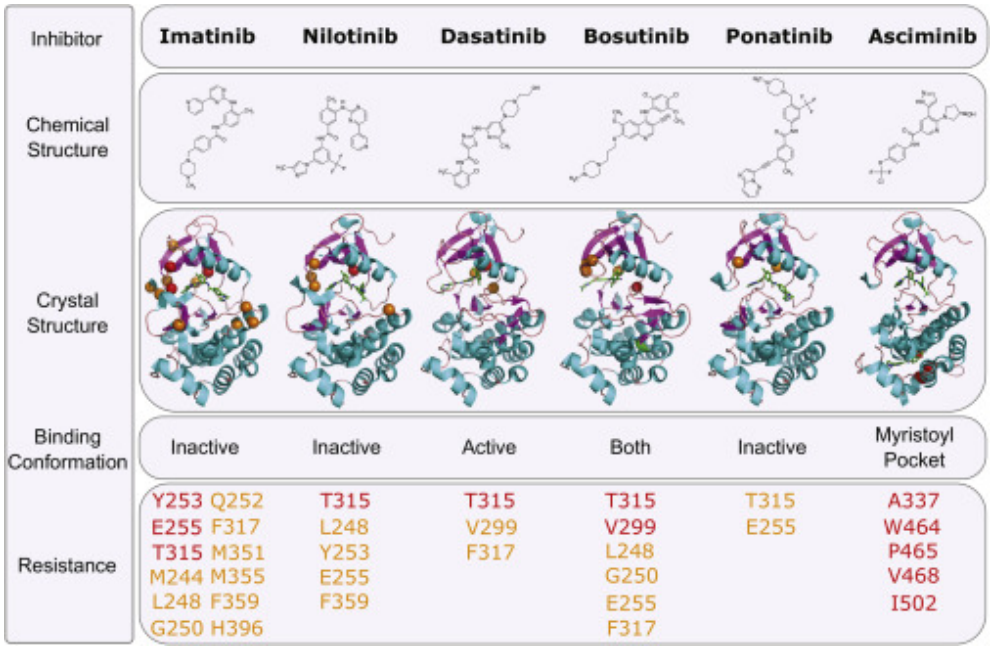

Figure 3. BCR-ABL1 Tyrosine Kinase Inhibitors and Resistance Mechanisms

Chemical structures and published X-ray crystallographic structures of ABL1 complexed with kinase inhibitors are shown. Residues at which mutations are associated with strong resistance to a given TKI are indicated in red, while those associated with lesser degrees of resistance are listed in orange. Both T315 and E255 mutations do lead to an increase in the IC50 for ponatinib; however, they do not typically lead to clinical resistance in isolation, but do as a compound mutation. The structure of ABL1 complexed with asciminib shows nilotinib in the ATP-binding site for reference. T315I is indicated in purple for visual reference
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<td>VOCAB: (w/definition)</td>
<td>Histocompatibility: a state of mutual tolerance that allows some tissues to be grafted effectively to others

Bioavailability: the degree and rate at which a substance (such as a drug) is absorbed into a living system or is made available at the site of physiological activity

Hematopoietic: the formation of blood or of blood cells in the living body</td>
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<td>Cited references to follow up on</td>
<td>Abbas et al., 2012, R. Abbas, B.A. Hug, C. Leister, M.E. Gaaloul, S. Chalon, D. Sonnichsen A phase I ascending single-dose study of the safety, tolerability, and pharmacokinetics of bosutinib (SKI-606) in healthy adult subjects,Cancer Chemother. Pharmacol., 69 (2012), pp. 221-227</td>
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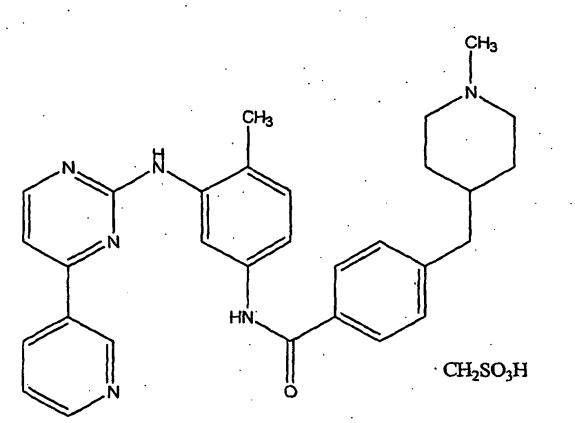
	Airiau et al., 2013, K. Airiau, F.-X. Mahon, M. Josselin, M. Jeanneteau, F. BellocPI3K/mTOR pathway inhibitors sensitize chronic myeloid leukemia stem cells to nilotinib and restore the response of progenitors to nilotinib in the presence of stem cell factorCell Death Dis., 4 (2013), p. e827 Awad et al., 2013, M.M. Awad, R. Katayama, M. McTigue, W. Liu, Y.-L. Deng, A. Brooun, L. Friboulet, D. Huang, M.D. Falk, S. Timofeevski, *et al.*Acquired resistance to crizotinib from a mutation in CD74–ROS1N. Engl. J. Med., 368 (2013), pp. 2395-2401
Follow up Questions	How do second-generation drugs differ from imatinib, and what makes them more effective in reducing the disease burden to undetectable levels? What research strategies are currently being explored to achieve even deeper responses in CML treatment?

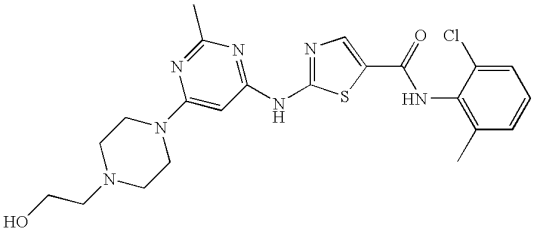
Patent # 1 Notes:

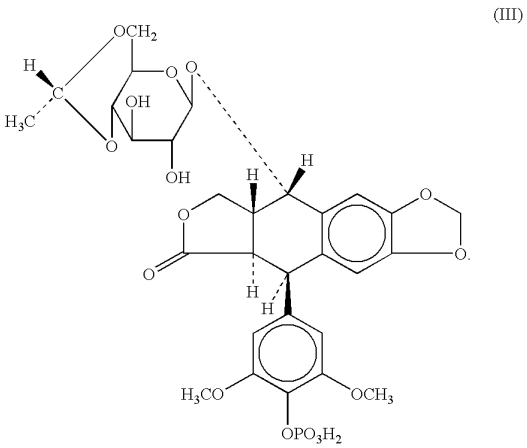
Source Title	Nanoparticulate imatinib mesylate formulations
Source citation (APA Format)	Jenkins, S. (2010). *Nanoparticulate imatinib mesylate formulations* (European Patent Office Patent) [Review of *Nanoparticulate imatinib mesylate formulations* https://patents.google.com/patent/EP1895984B1/en?q=(Imatinib)&oq=Imatinib
Original URL	https://patents.google.com/patent/EP1895984B1/en?q=(Imatinib)&oq=Imatinib
Source type	Patent
Summary of key points + notes (include methodology)	This patent focuses on nanoparticulate compositions of imatinib mesylate, along with its salts or derivatives, exhibiting enhanced pharmacokinetic profiles and diminished variability between fed and fasted states. The effective average particle size of the nanoparticulate imatinib mesylate in this composition is less than approximately 2000 nm. The application of this formulation extends to the treatment of chronic myeloid leukemia, gastrointestinal stromal tumors, and affiliated medical conditions.

Research Question/Problem/ Need	"How can we make imatinib mesylate work better for treating diseases like chronic myeloid leukemia and gastrointestinal stromal tumors by using tiny particles and improving how the body absorbs it, especially when taken with or without food?"
Important Figures	 Chemical structure of imatinib mesylate
VOCAB: (w/definition)	Mesylate: a salt or ester of an acid CH4O3S used especially in pharmaceutical preparations Hydroxyproline: an amino acid C5H9NO3 that occurs naturally as a constituent of collagen
Follow up Questions	Are there particular challenges in the pharmacokinetics of imatinib mesylate that this formulation aims to address? How does the effective average particle size of less than approximately 2000 nm contribute to the enhanced properties of the nanoparticulate imatinib mesylate formulation?

Patent # 2 Notes:

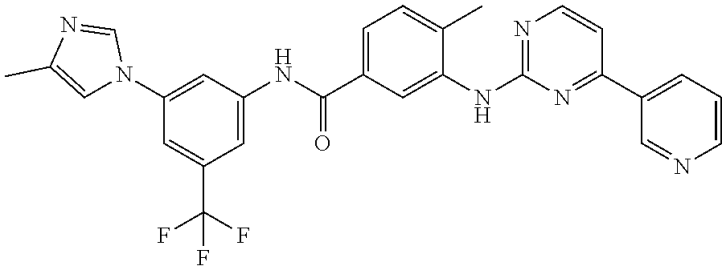
Source Title	Combination of anti-CTLA4 antibody with dasatinib for the treatment of proliferative diseases
Source citation (APA Format)	Jure-Kunkel, M. (2012). *Combination of anti-CTLA4 antibody with dasatinib for the treatment of proliferative diseases* (United States Patent) [Review of *Combination of anti-CTLA4 antibody with dasatinib for the treatment of proliferative diseases*]. https://patents.google.com/patent/US8119129B2/

	en?q=(Dasatinib)&oq=Dasatinib
Original URL	https://patents.google.com/patent/US8119129B2/en?q=(Dasatinib)&oq=Dasatinib
Source type	Patent
Summary of key points + notes (include methodology)	This patent is for a way to treat cancer by giving a mammal (like a human) a combination of treatements: (i) an anti-CTLA-4 antibody, which is a type of protein that fights against cancer, along with some other substances, and (ii) a chemotherapeutic agent called N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, or its approved forms like salts or hydrates, also mixed with some other substances.
Research Question/Problem/ Need	How can we make cancer treatment better by using a mix of a cancer-fighting protein (anti-CTLA-4 antibody) with other substances, and a chemotherapy drug (N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide or its approved forms) along with additional substances?
Important Figures	(I)  The structure of dasatinib

	 The structure of etoposide
VOCAB: (w/definition)	Alkylating: the act or process of introducing one or more alkyl groups into a compound (as to increase octane number in a motor fuel) Antineoplastic: inhibiting or preventing the growth and spread of tumors or malignant cells
Follow up Questions	What is the specific role of the other substances included with the anti-CTLA-4 antibody? Are there particular cancer types or stages for which this agent is most effective?

Patent # 3 Notes:

Source Title	Amorphous nilotinib microparticles and uses thereof
Source citation (APA Format)	Wertz, C. (2023). *Amorphous nilotinib microparticles and uses thereof* (United States Patent) [Review of *Amorphous nilotinib microparticles and uses thereof*]. https://patents.google.com/patent/US20230181585A1/en?q=(Nilotinib)&oq=Nilotinib
Original URL	https://patents.google.com/patent/US20230181585A1/en?q=(Nilotinib)&oq=Nilotinib
Source type	Patent

Summary of key points + notes (include methodology)	This research looks into a method of making medicine using a substance called nilotinib, specifically in a form called amorphous solid dispersions and pharmaceutical compositions. These medicines could be used to treat diseases that involve excessive cell growth, like cancer. It's also possible to take these medicines with or without food. Additionally, the study suggests that you might need less of this medicine compared to the regular nilotinib medicine, but it should still work just as well in treating the disease.
Research Question/Problem/ Need	How can we improve the treatment of cancer using nilotinib by creating new forms that allow easier administration without food restrictions and lower doses, while keeping the therapeutic effect similar to existing formulations?
Important Figures	 The structure of Nilotinib
VOCAB: (w/definition)	Amorphous: having no definite form Proliferative: to grow by rapid production of new parts, cells, buds, or offspring
Follow up Questions	What are some more details about the amorphous solid dispersions of nilotinib mentioned in the patent? Are there specific additives used in the composition?