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Comparing the Effectiveness between Ivacaftor and GLPG 1837

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PDB File: 6O2P (CFTR), PDB file from Howard Hughes Medical Institute, (potentiator) Ivacaftor
6O1V (CFTR), PDB file from Howard Hughes Medical Institute (HHMI), (potentiator) GLPG 1837

Primary Citation: CFTR Ivacaftor: Liu, F., Zhang, Z., Levit, A., Levring, J., Touhara, K. K., Shoichet, B. K., & Chen, J. (2019). Structural identification of a hotspot on CFTR for potentiation. *Science (New York, N.Y.)*, *364*(6446), 1184–1188. https://doi.org/10.1126/science.aaw7611

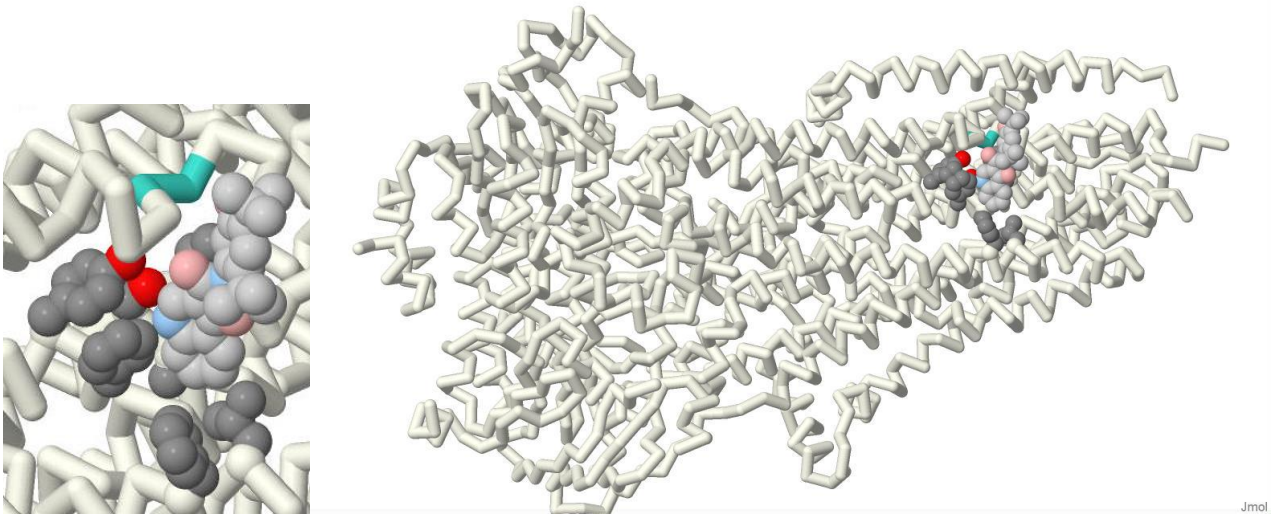
Description:

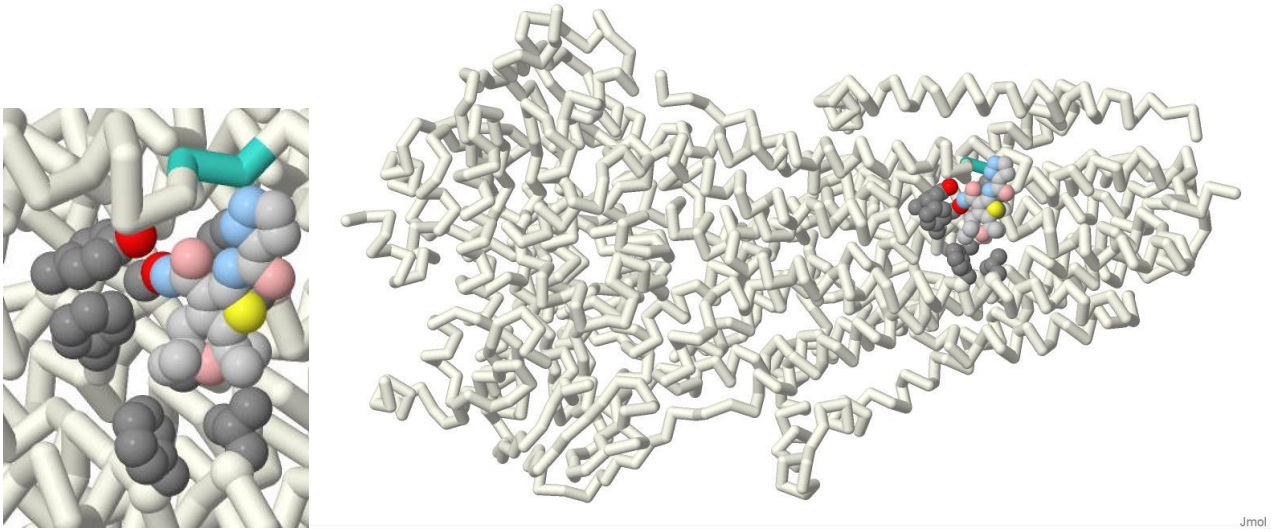
Cystic fibrosis is a fatal disease that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR). There have been many attempts to treat the disease, which have yielded two main categories of drugs that have been shown to be effective. There are correctors, which correct the misfolding of the CFTR protein causing an increase of the abundance of CFTR on the surface of the cell, and potentiators, which aid the recovery of the function of CFTR channels by increasing the ion influx of the mutant CFTR. Only one potentiator drug, Ivacaftor, has been approved by the U.S. Food and Drug Administration (FDA); there is another, GLPG1837, that is currently undergoing clinical trials to determine its safety. Although these two drugs are chemically different, it was shown that they bind at the same site and have majority of the same interactions with CFTR. Both drugs form hydrogen bonds with SER308 and TYR 304 and have hydrophobic interactions with LEU233, PHE236, PHE305, ALA309, and PHE312. It is being shown that GLPG1837 has a higher efficacy than Ivacaftor, which could be due to the fact that GLPG1837 could be used for a wider range of targets. Ivacaftor is approved to treat those with at least 1 G551D mutation in the CFTR. Contrastingly GLPG 1837 has been shown to be beneficial to those with class 3 mutations (e.g., G551D, G178R, and S549N), and to alleviate the CFTR defect caused by a class 4 mutation (R117H).

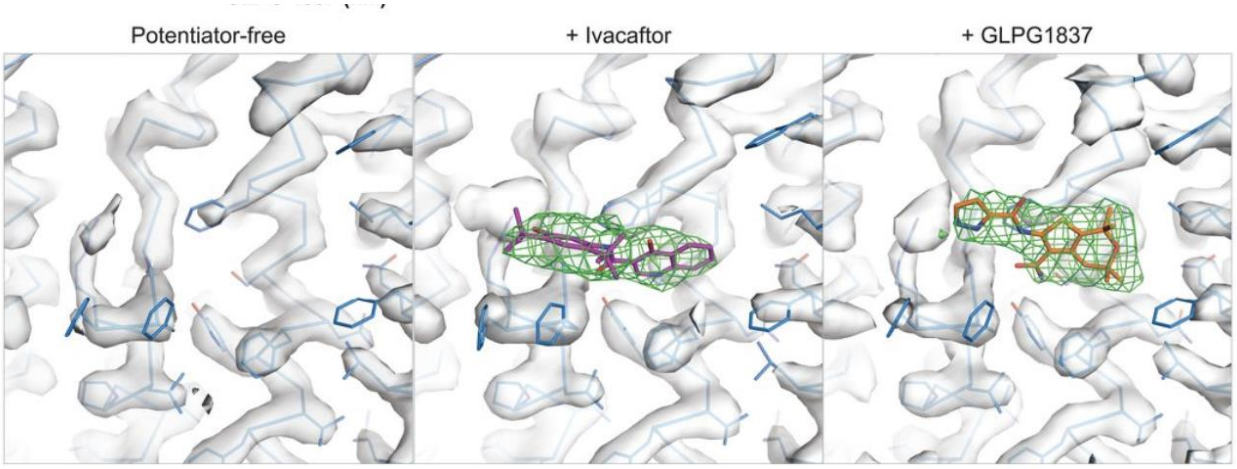
Specific Model Details:

- SER308 and TYR 304 (hydrogen bonds-red)
- LEU233, PHE236, PHE305, ALA309, and PHE312 (hydrophobic interactions-blue)
- Model depicts binding interactions between the CFTR protein channel and Ivacaftor, compared to GLPG1837.

Pictures/Additional Information for the Model:


Jmol


Jmol


Potentiator-free
+ Ivacaftor
+ GLPG1837

Additional References:

Haq, I. J., Parameswaran, M. C., Abidin, N. Z., Socas, A., Gonzalez-Ciscar, A., Gardner, A., & Brodlie, M. (2019, April 1). *Modulator therapies for cystic fibrosis*. Clinical Key. https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1751722219300113?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1751722219300113%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.paediatricsandchildhealthjournal.co.uk%2Farticle%2FS1751-7222(19)30011-3%2Freferences

Iyer, V. (2019, March 27). *Glpg1837*. Cystic Fibrosis News Today. https://cysticfibrosisnewstoday.com/glpg1837/

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