RATIONALLY DESIGNED DRUG BLENDING AS A MECHANISM TO OVERCOME DRUG RESISTANCE IN CANCER: AN APPLICATION IN EGFR.

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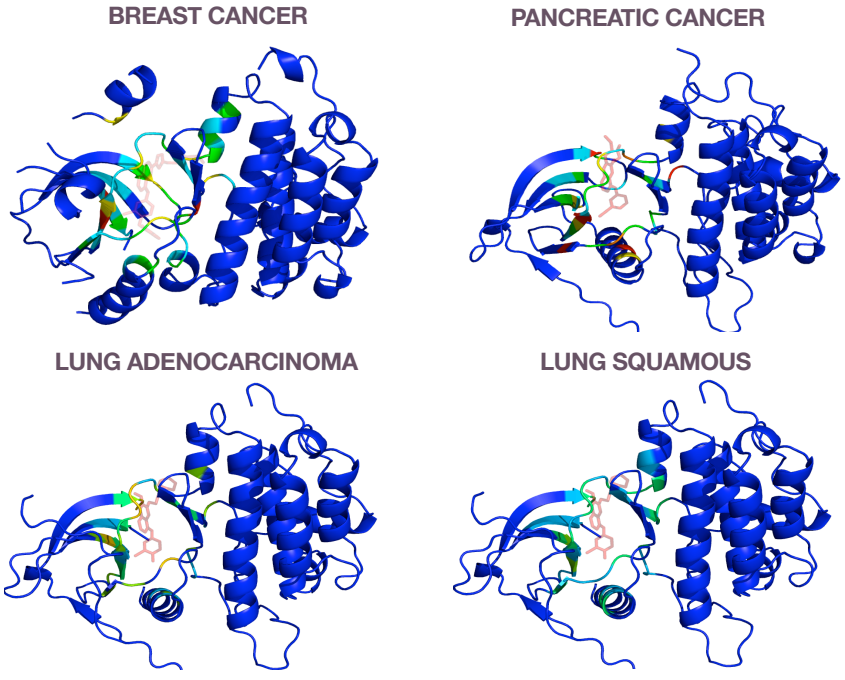
***Introduction**:* Drug resistance is one of the major problems in cancer treatment. Rapid mutation and selective pressure can efficiently select drug-resistant mutants, although there are many mechanisms for drug resistance, a classic mechanism is due to coding mutations in the drug-target binding site. Examples such as resistance to BRAF inhibitors in the BRAF (V600E) positive melanomas or resistance to gefitinib and erlotinib in non-small-cell lung cancers with mutated EGFR, highlight the importance of rational therapeutic drug combinations able to avoid drug resistance. We systematically analyse the mutational landscape of EGFR, predicting mutations that can potentially confer resistance and proposing blend of molecules able to defeat drug resistance for those mutants.



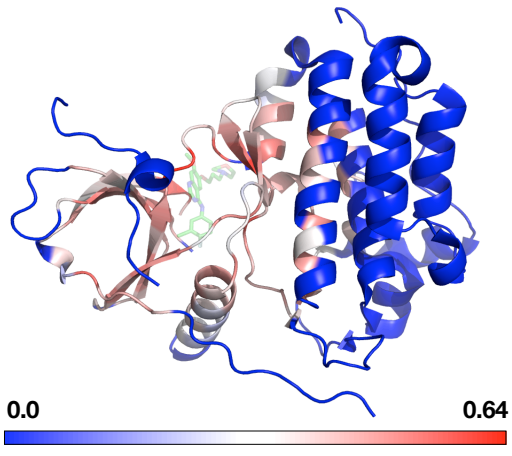
Mutational probabilities of EGFR in different cancer types

Methods: Using the mutational frequencies from Alexandrov et al (1), we have defined the likelihood of mutations in the binding site of FDA-approved drugs in four cancer types.
Results: The 3D-distribution of the mutations is heterogeneous across different cancer even in the same protein. The localization of regions prone to be mutated and the value of the likelihood of these mutations change substantially in different cancer types.

Predicting the resistance-likeness of the mutations

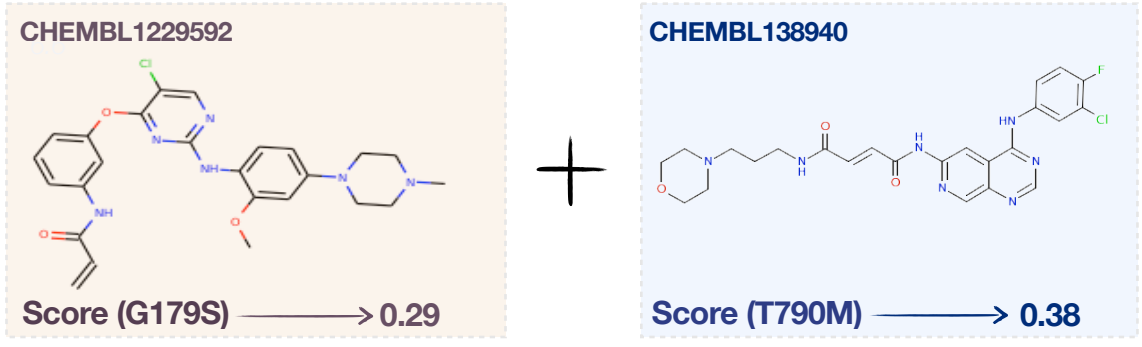
Methods: Using the Platinum database (2) as training set, we developed a RFC classifier that given structural information of the protein-drug complex predicts the effect of a mutation for the drug-target interaction.
Results: The loop ranging from T790 to C797 accumulates most of the top resistance-like mutations. Combination of likelihood and resistance score could help to detect the most dangerous mutations from a resistance perspective.

Mutation	Likelihood	Resistance Score
L792P	0.003	0.64
L792F	0.009	0.60
M793L	0.002	0.60
M793R	0.001	0.60
G719V	0.026	0.59
L844P	0.09	0.58
M793K	0.08	0.57
G796V	0.026	0.57
L792R	0.001	0.56
L718P	0.009	0.56



Blend of molecules overcoming resistance to T790M/G719S

We propose the following combination of molecules as a treatment to overcome EGFR carrying the T790M and G719S mutations.



Conclusion:

We propose a methodology to computationally study the most dangerous cancer related mutations from a resistance perspective. We also provide a framework to predict blend of molecules able to defeat these mutations.

Bibliography

1. *Alexandrov, L.B., Nik-Zainal, S., Wedge, D.C., Aparicio, S.A., Behjati, S., Biankin, A.V., Bignell, G.R., Bolli, N., Borg, A., Borresen-Dale, A.L. et al. (2013) Signatures of mutational processes in human cancer. Nature, 500, 415-421.*
2. *Pires, D.E., Blundell, T.L. and Ascher, D.B. (2015) Platinum: a database of experimentally measured effects of mutations on structurally defined protein-ligand complexes. Nucleic acids research, 43, D387-391.*

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