Drug blending as a mechanism to overcome drug resistance in cancer therapy.

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http://marciuslab.org
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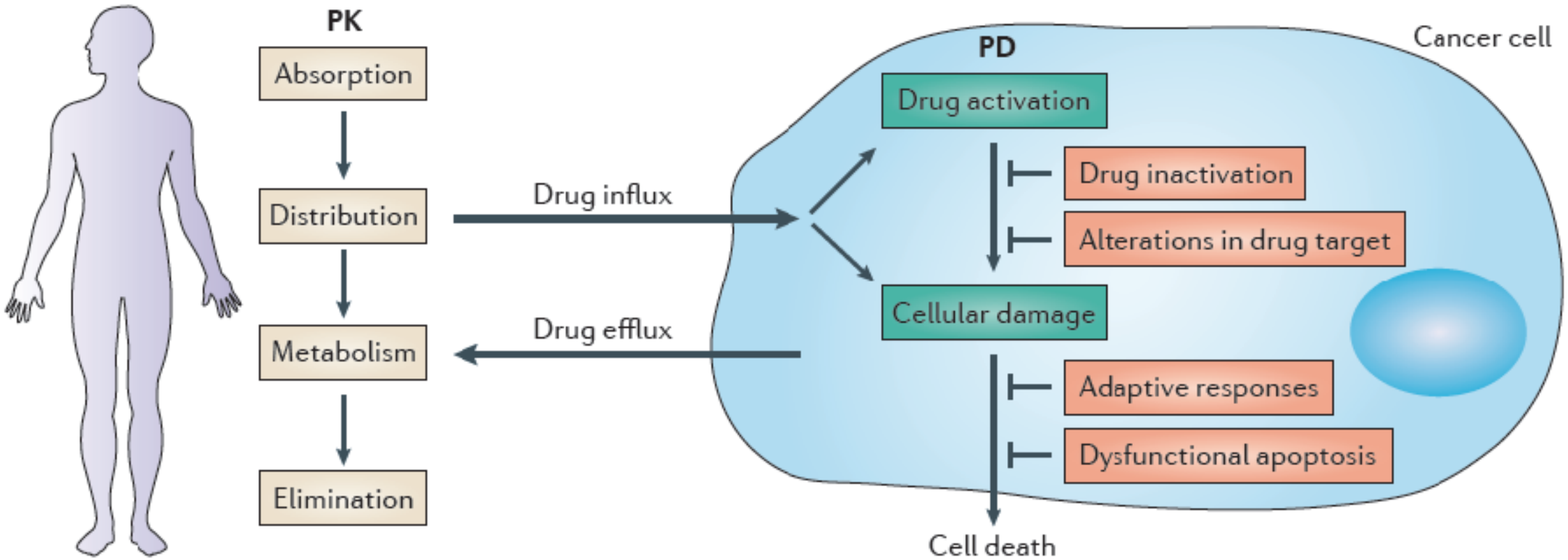
Francisco Martínez-Jiménez

Bissan Al-Lazikani
(ICR)

Francisco Martínez-Jiménez et al. (2017) Scientific Reports. Under revision.

Drug resistance is a major problem in cancer treatment



Holohan, C.et al. Cancer drug resistance: an evolving paradigm. Nature Reviews. Cancer.

Mutations in drug targets is a high-frequent mechanism resistance

PNAS

The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP

Cai-Hong Yun*†, Kristen E. Mengwasser†, Angela V. Toms*†, Michele S. Woo‡, Heidi Greulich‡§, Kwok-Kin Wong‡¶, Matthew Meyerson‡§‖, and Michael J. Eck*†**

Departments of *Biological Chemistry and Molecular Pharmacology and ‖Pathology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115; Departments of †Cancer Biology and **Medical Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115; ¶Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115; and §The Broad Institute of Harvard and Massachusetts Institute of Technology, 320 Charles Street, Cambridge, MA 02141

Edited by Harold E. Varmus, Memorial Sloan–Kettering Cancer Center, New York, NY, and approved December 18, 2007 (received for review October 11, 2007)

Clinical Resistance to STI-571 Cancer Therapy Caused by BCR-ABL Gene Mutation or Amplification

Mercedes E. Gorre,[1,3] Mansoor Mohammed,[2] Katharine Ellwood,[1] Nicholas Hsu,[1] Ron Paquette,[1] P. Nagesh Rao,[2] Charles L. Sawyers[1,3]*

Clinical studies with the Abl tyrosine kinase inhibitor STI-571 in chronic myeloid leukemia demonstrate that many patients with advanced stage disease respond initially but then relapse. Through biochemical and molecular analysis of clinical material, we find that drug resistance is associated with the reactivation of BCR-ABL signal transduction in all cases examined. In six of nine patients, resistance was associated with a single amino acid substitution in a threonine residue of the Abl kinase domain known to form a critical hydrogen bond with the drug. This substitution of threonine with isoleucine was sufficient to confer STI-571 resistance in a reconstitution experiment. In three patients, resistance was associated with progressive *BCR-ABL* gene amplification. These studies provide evidence that genetically complex cancers retain dependence on an initial oncogenic event and suggest a strategy for identifying inhibitors of STI-571 resistance.

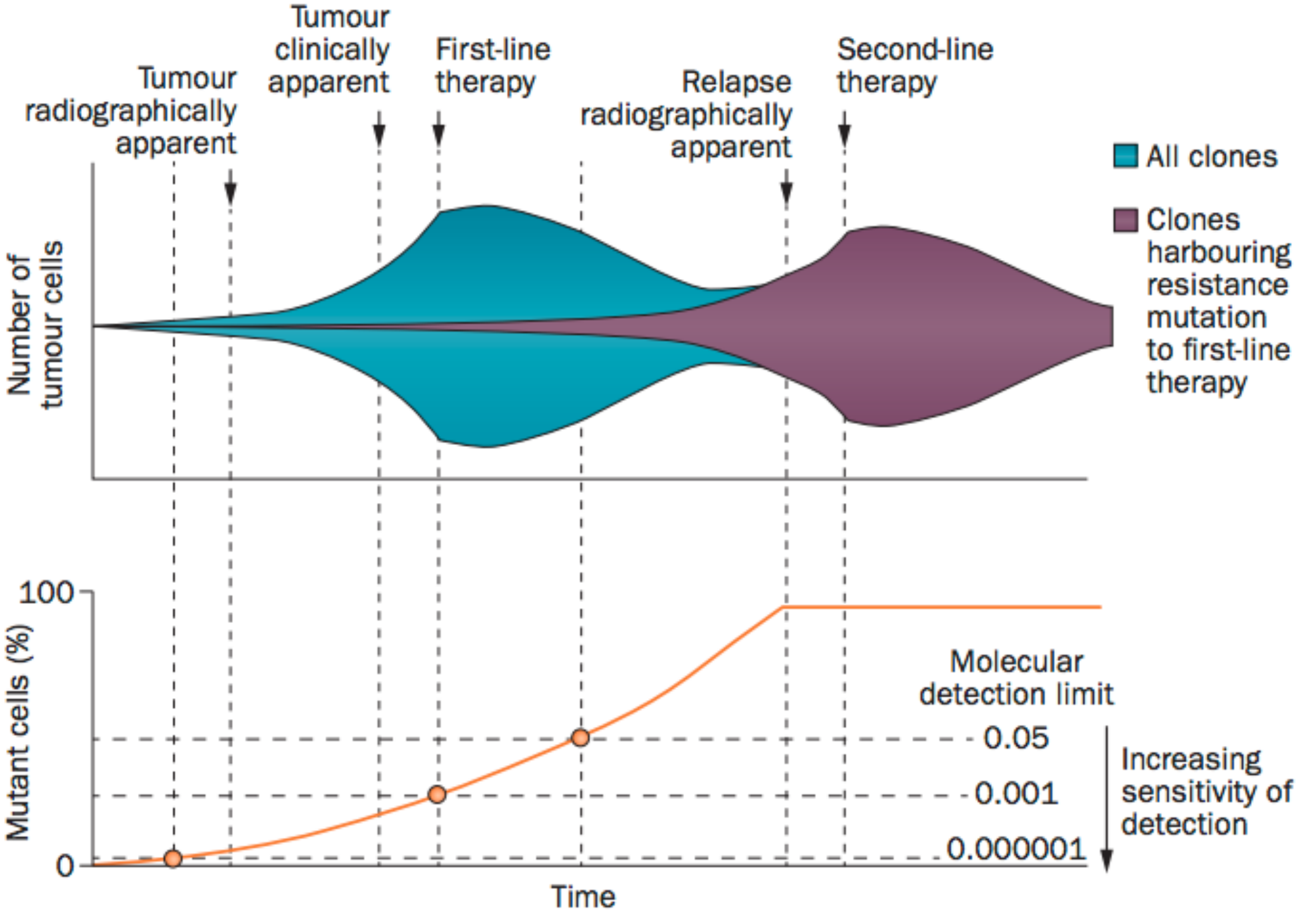
So… can we…

Predict of the cancer-associated likelihood of a mutation?

Predict the resistance-impact of the mutation?.

Propose alternative treatment to the resistance?

Low-frequency mutations can drive drug resistance

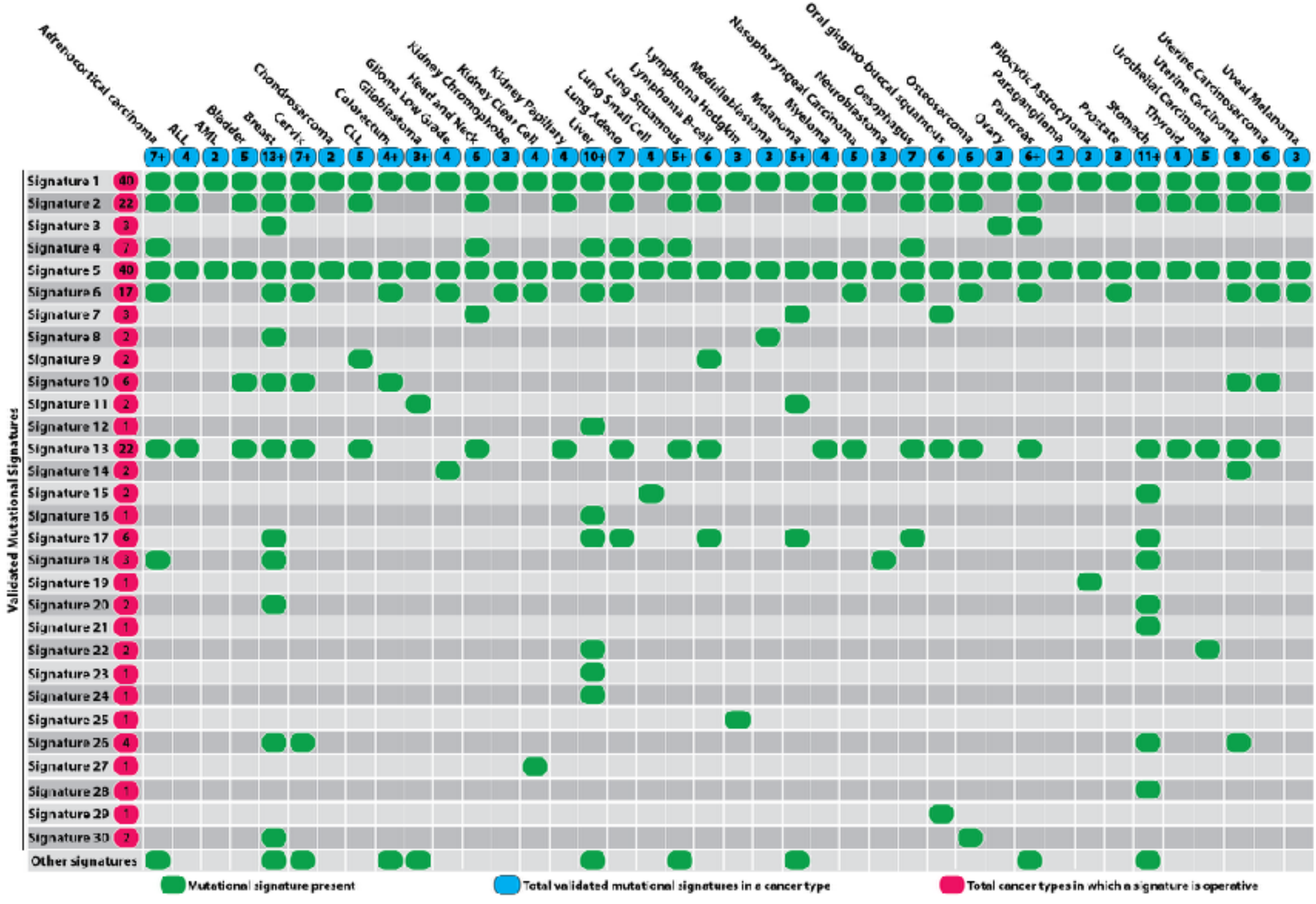


Schmitt, M., et al. (2015). The influence of subclonal resistance mutations on targeted cancer therapy. Nature Reviews. Clinical Oncology.

Cancer mutational landscape is complex and heterogeneous

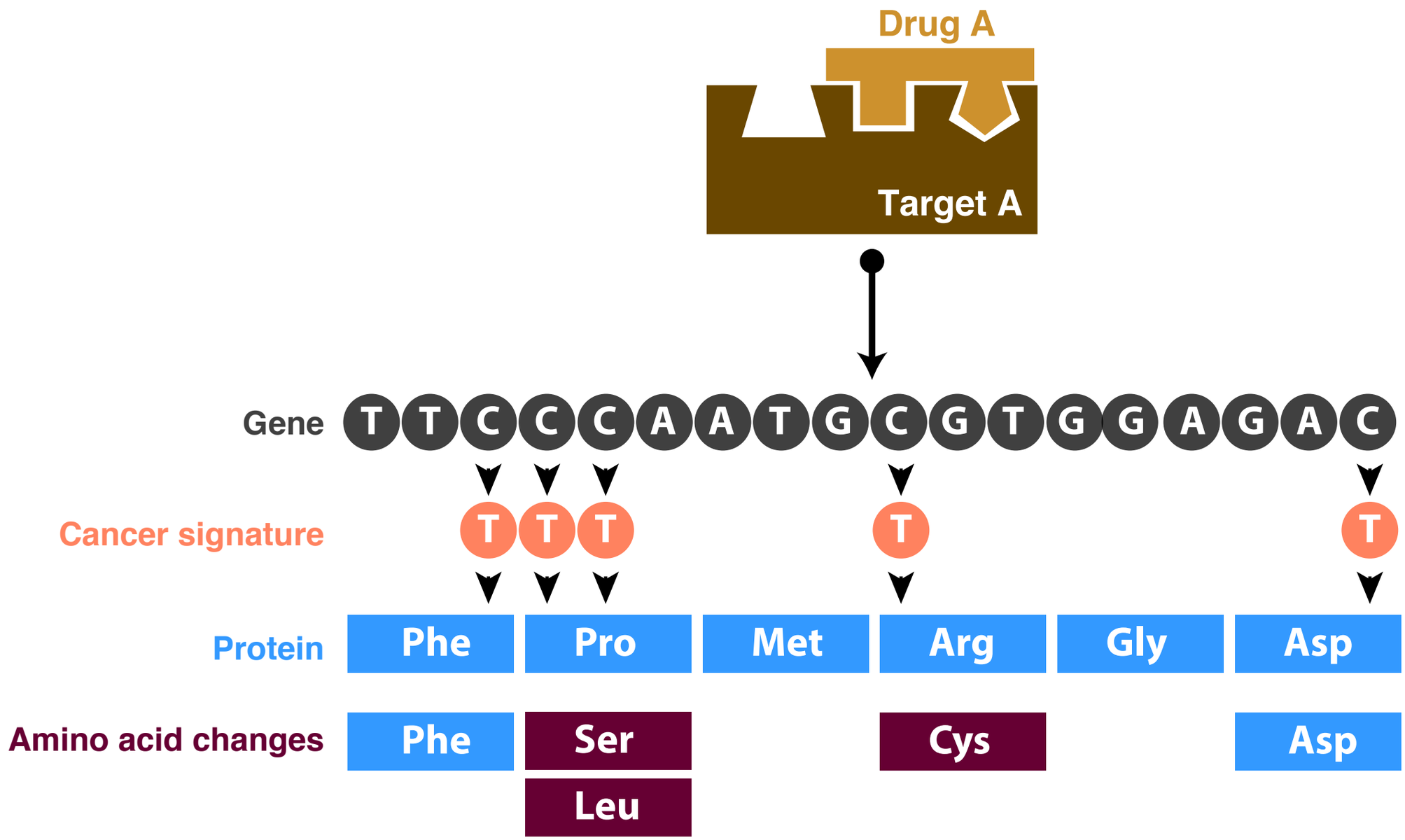
Alexandrov, L. B.et al. (2013). Signatures of mutational processes in human cancer. Nature, 500(7463), 415–21

Mutational signatures of ~30 types of cancer

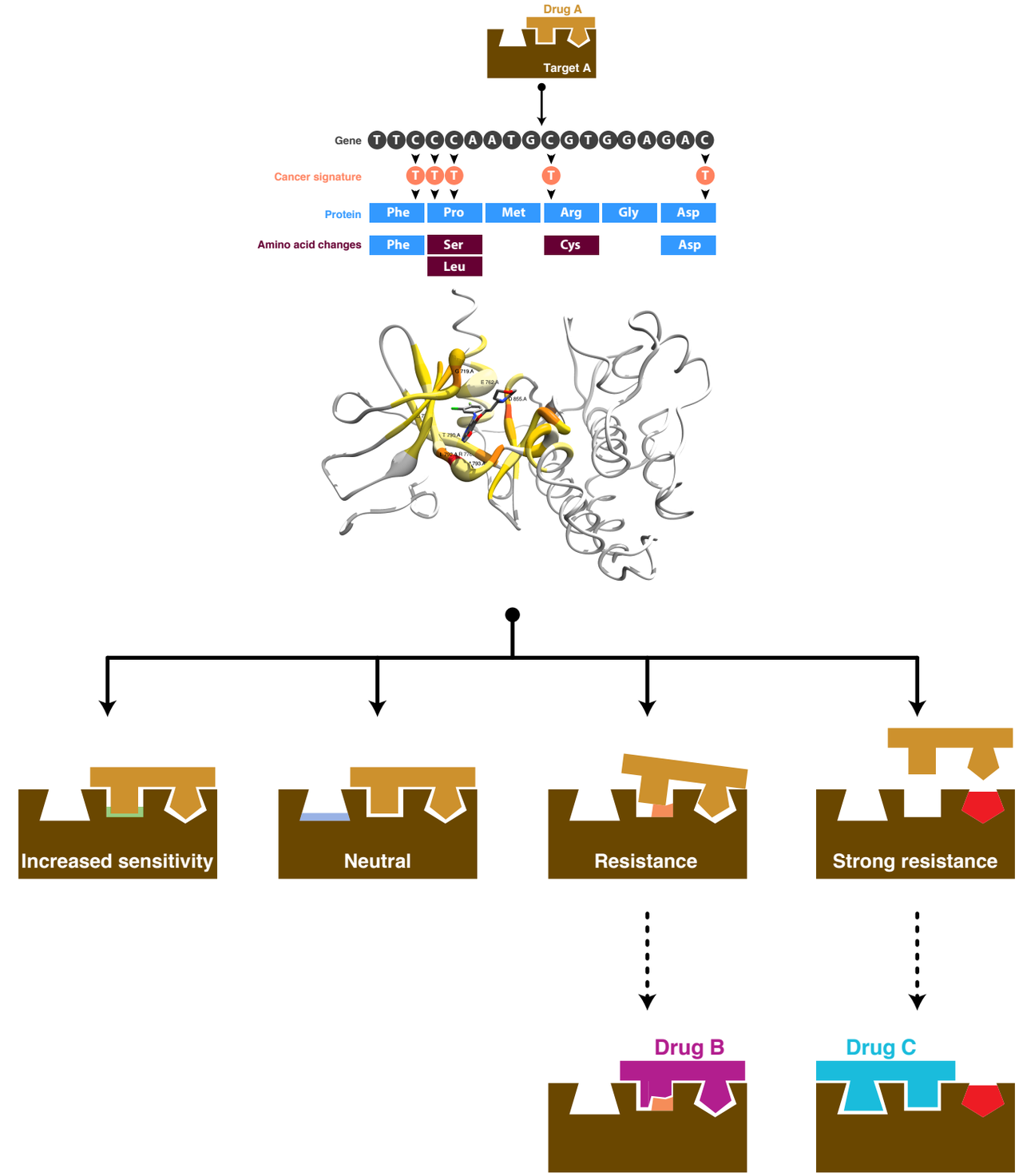


Alexandrov, L. B.et al. (2013). Signatures of mutational processes in human cancer. Nature, 500(7463), 415–21

Drug Blending concept



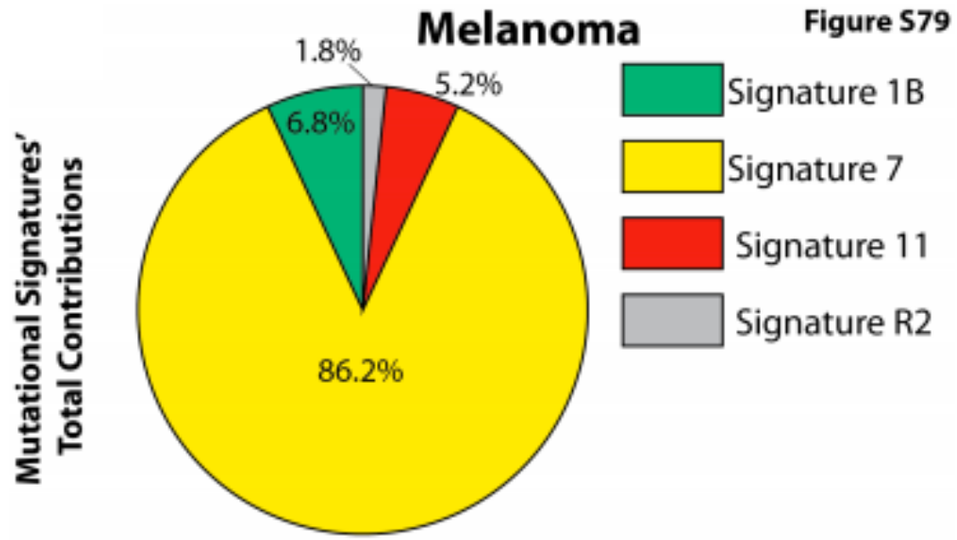
Drug Blending concept

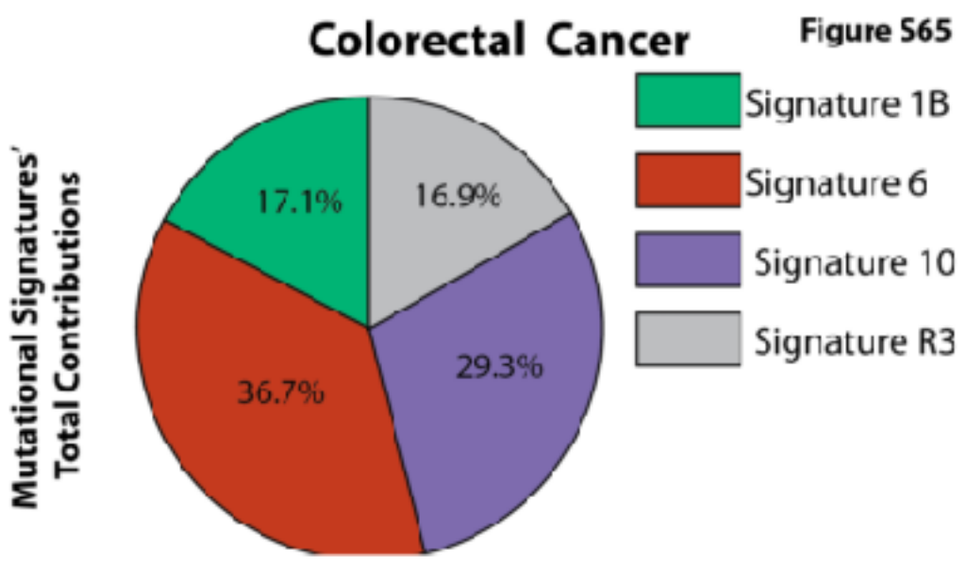


Mutational probability in melanoma and colorectal cancer

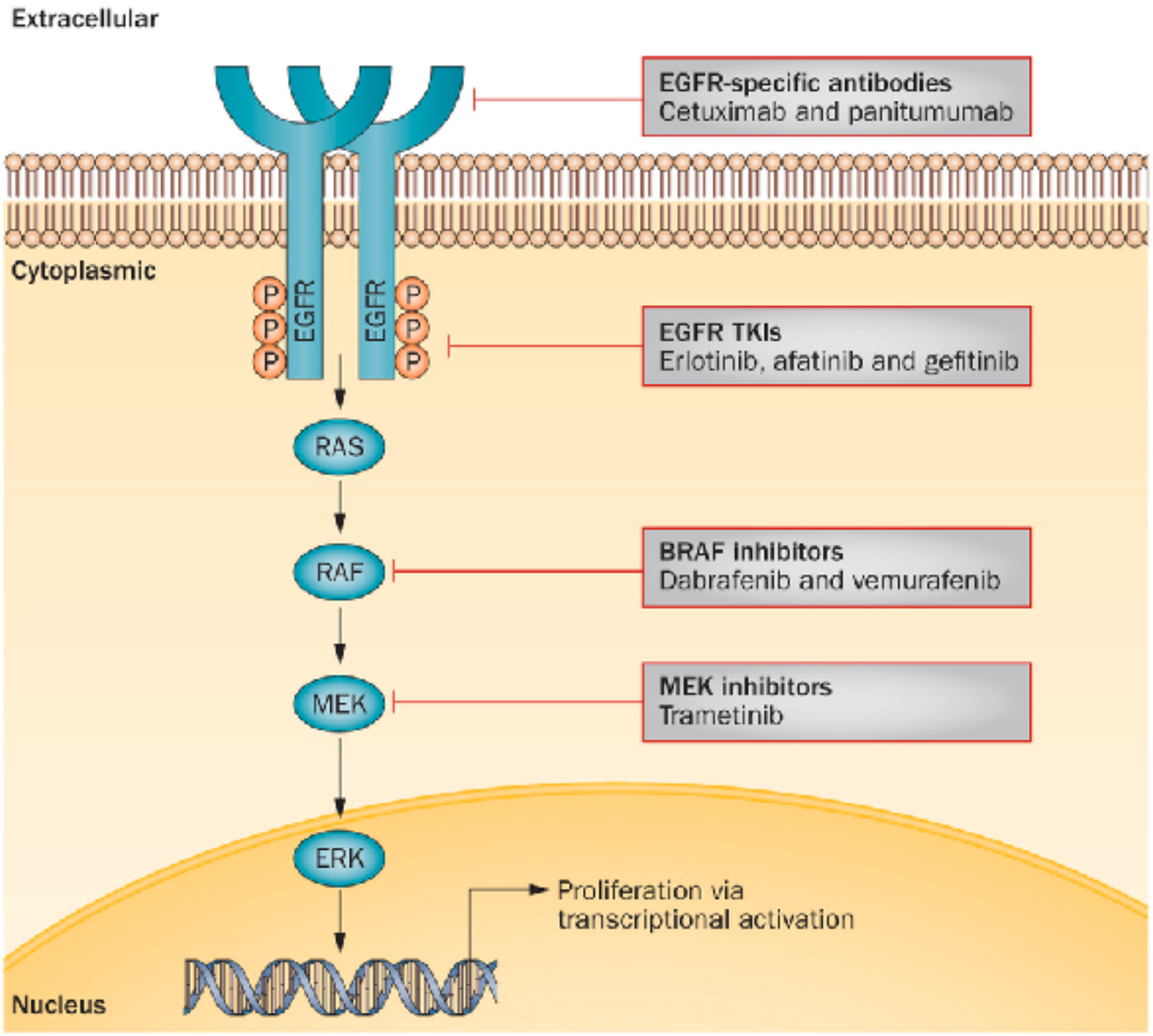
$$Likelihood_{\text{mutationAA}} = \sum_{i=0}^{M} \sum_{j=0}^{S} W_{jk} * P_{nj}$$

M = Posible nt. changes for the mutation
S = Signatures associated with the cancer class.
W_{jk} = Contribution of signature j to cancer class k.
P_{nj} = Probability of mutation n in signature j



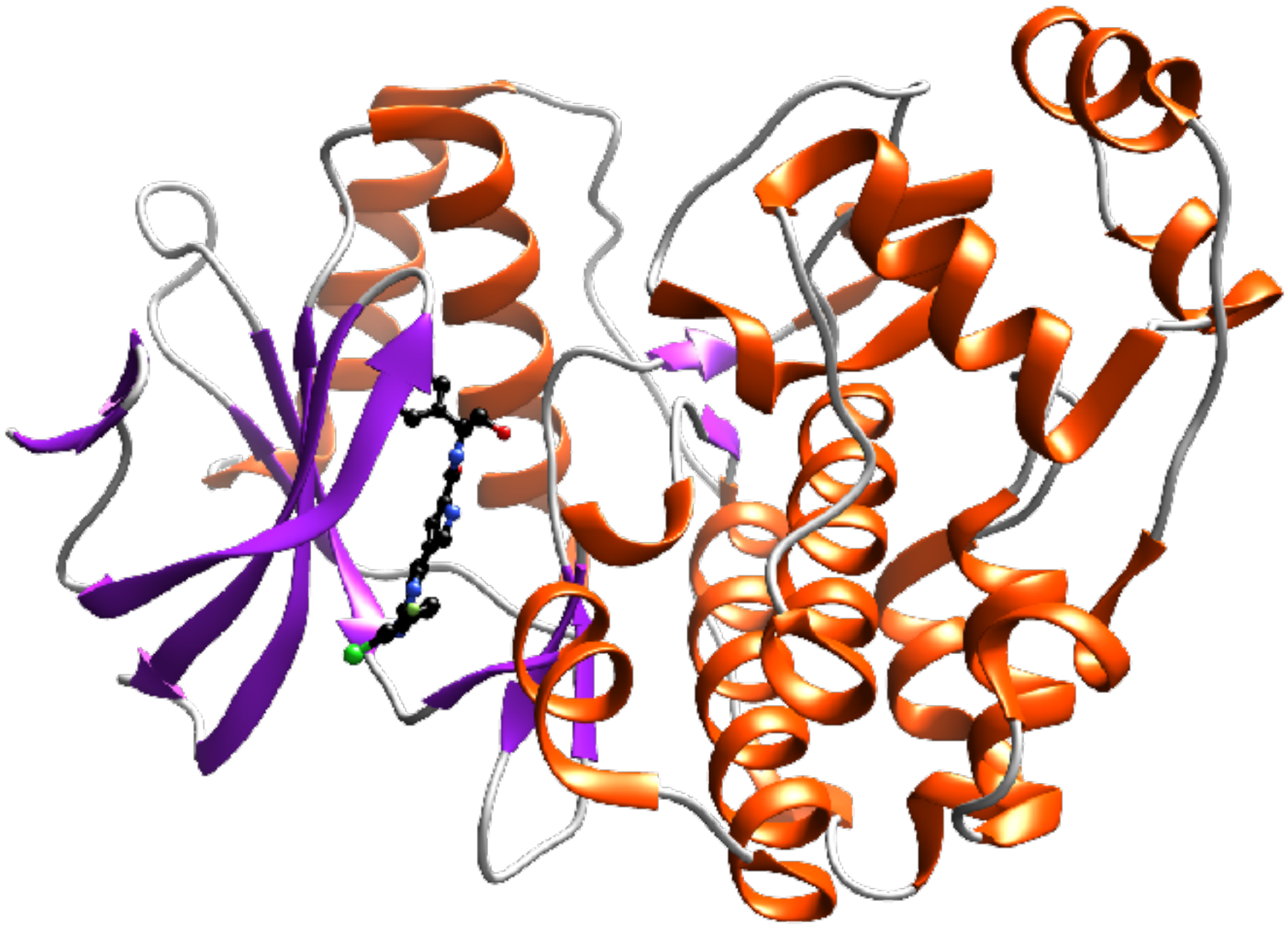


ERK1/2 are promising targets for the treatment of melanoma and colon cancer



Schmitt, M., et al. (2015). The influence of subclonal resistance mutations on targeted cancer therapy. Nature Reviews. Clinical Oncology.

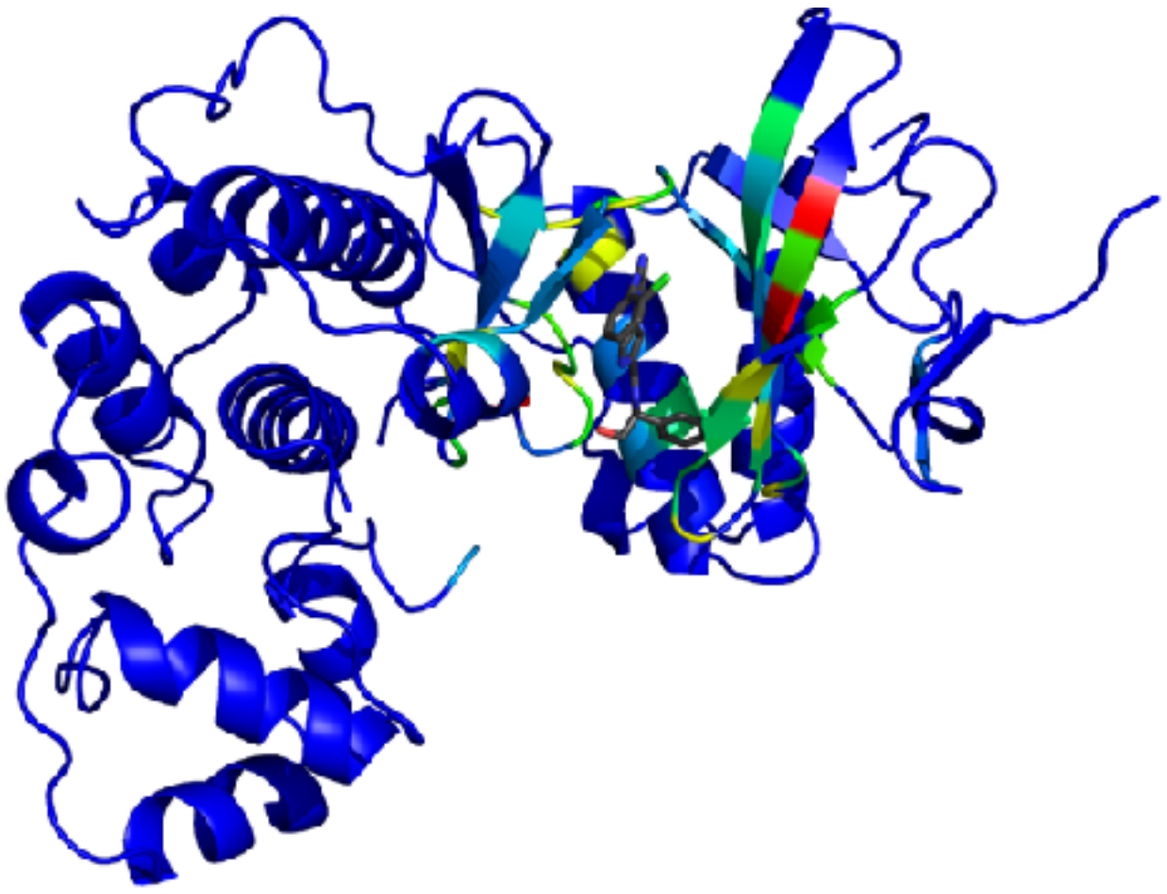
Probability of spontaneous mutation of ERK2 VTX-11e binding-site



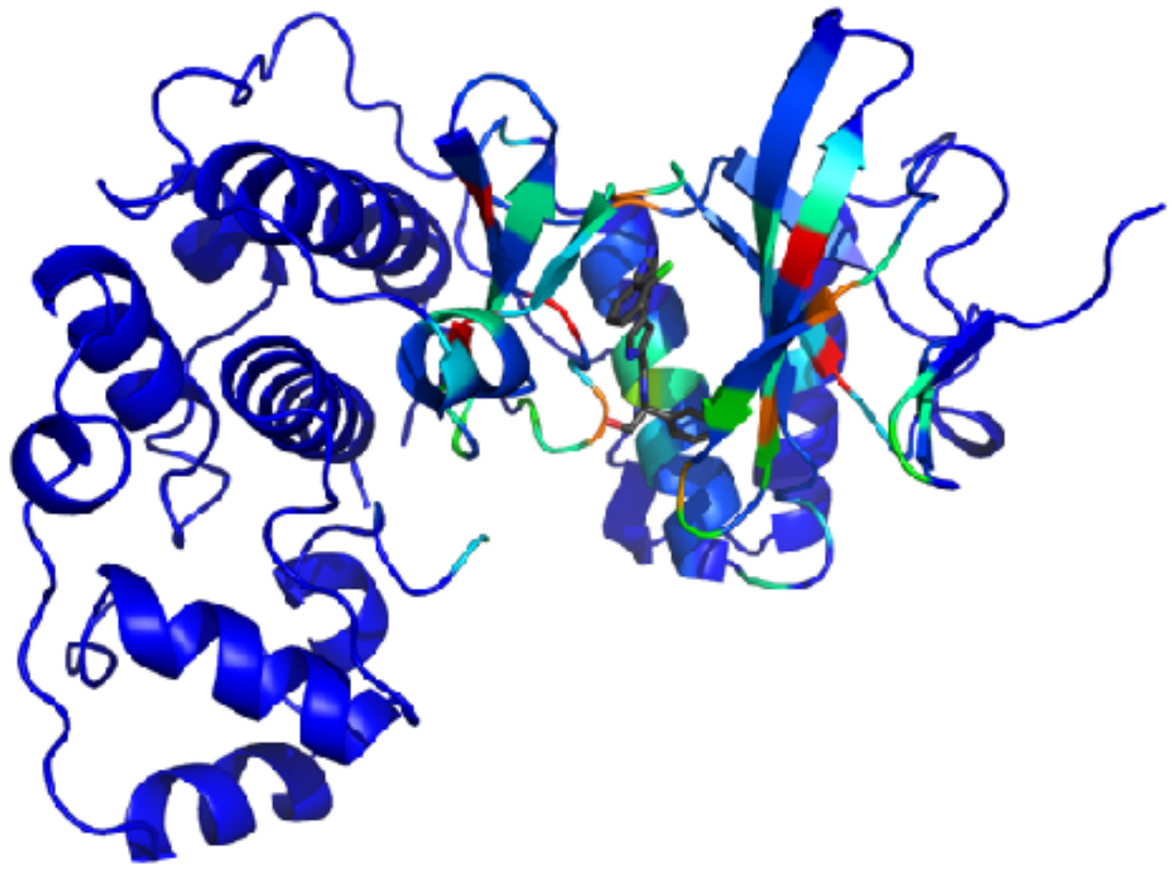
PDB: 4QTE

Probability of spontaneous mutation of ERK2 VTX-11e binding-site

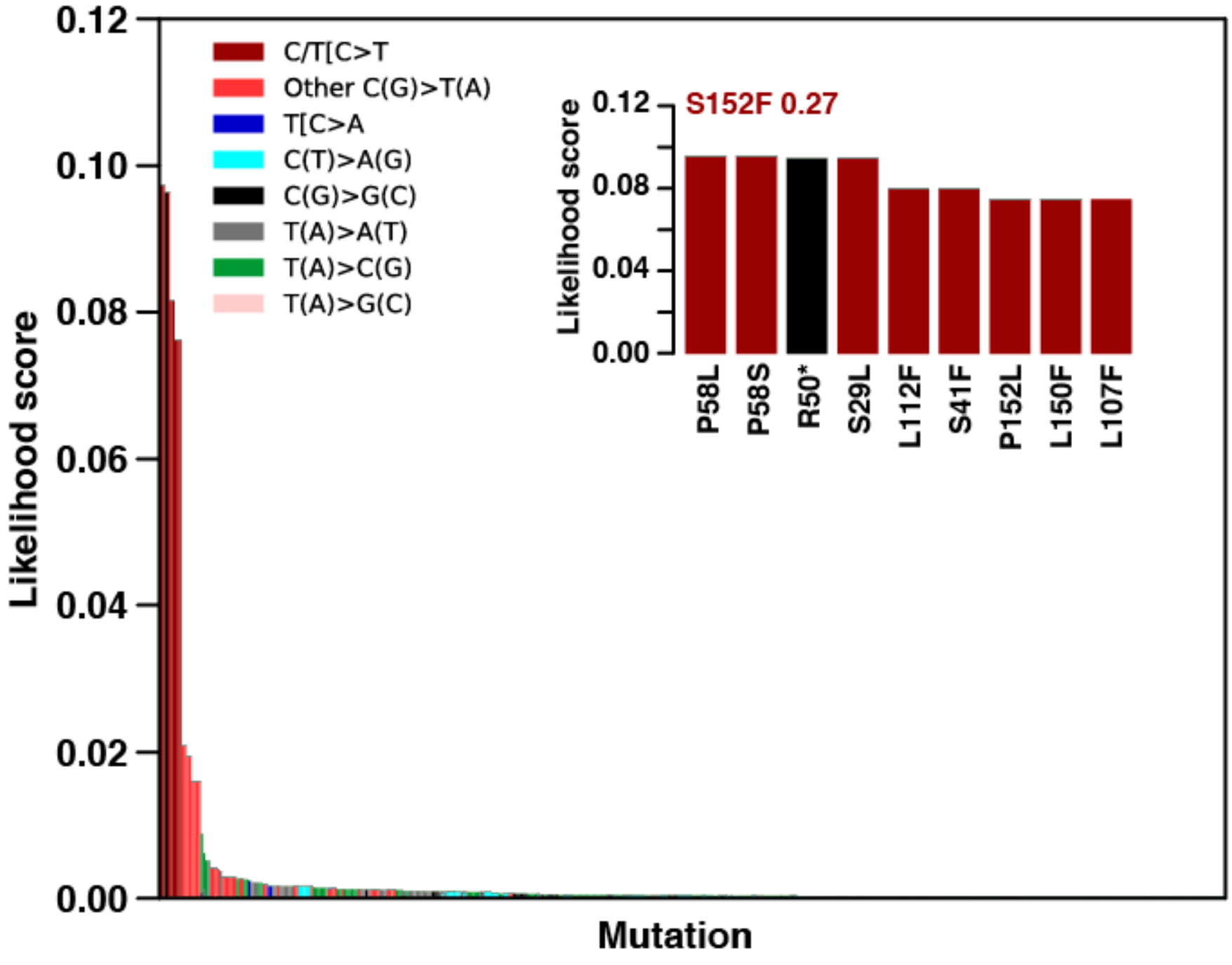
melanoma



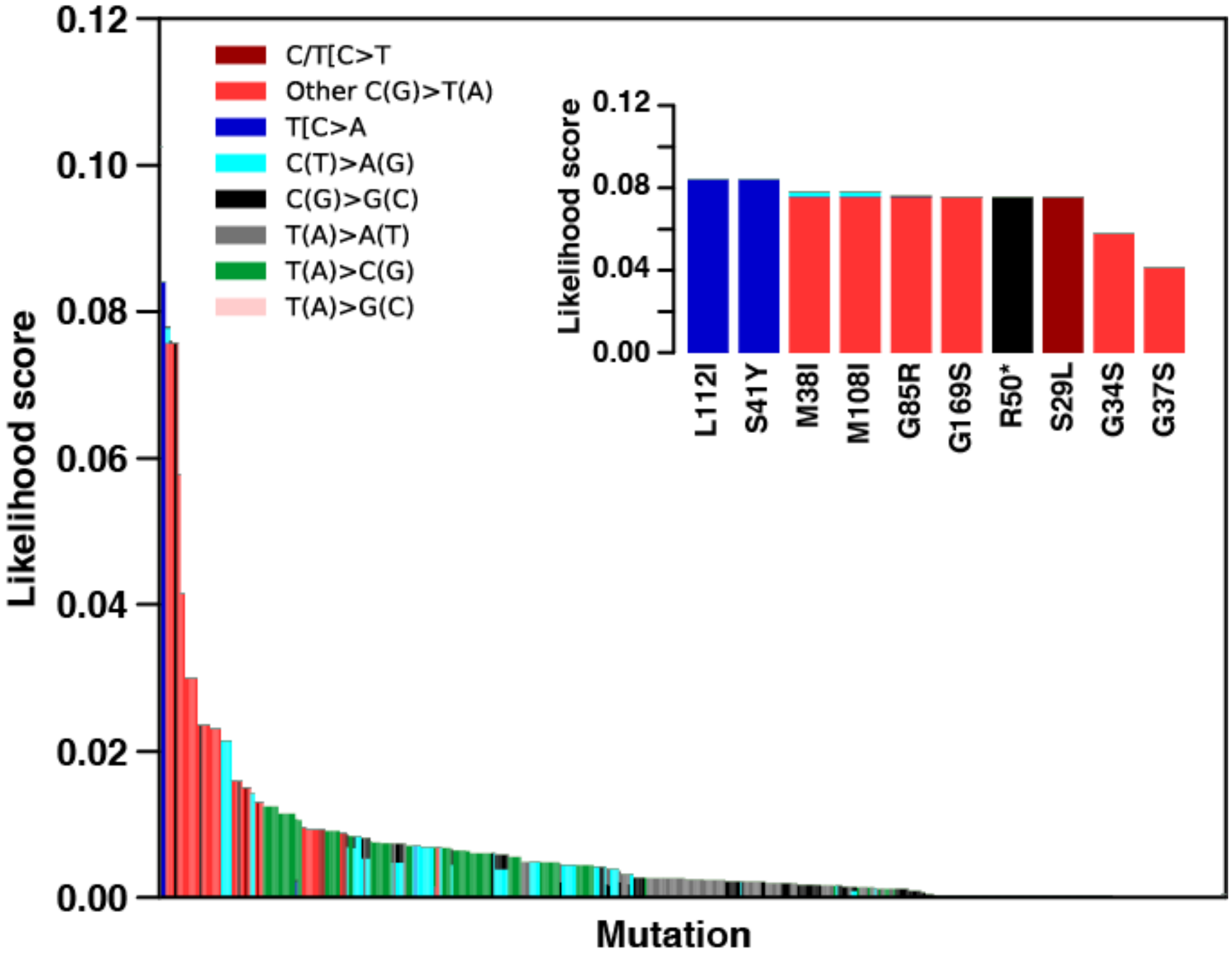
colorectal cancer



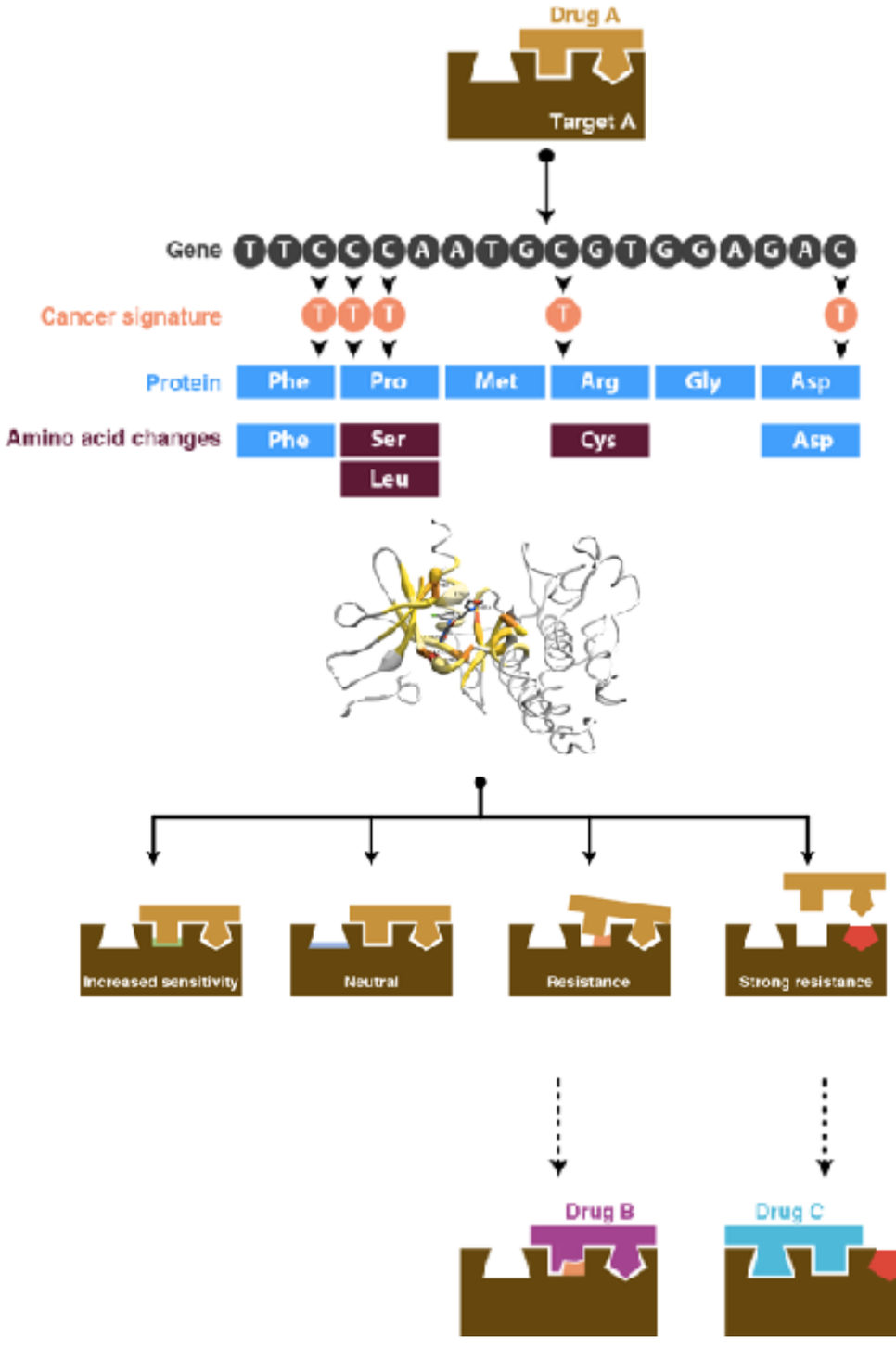
ERK2 melanoma mutational landscape reveals a long-tailed distribution enriched in C>T



Colorectal cancer distribution results in higher likelihood median values



what do we propose to overcome resistance?

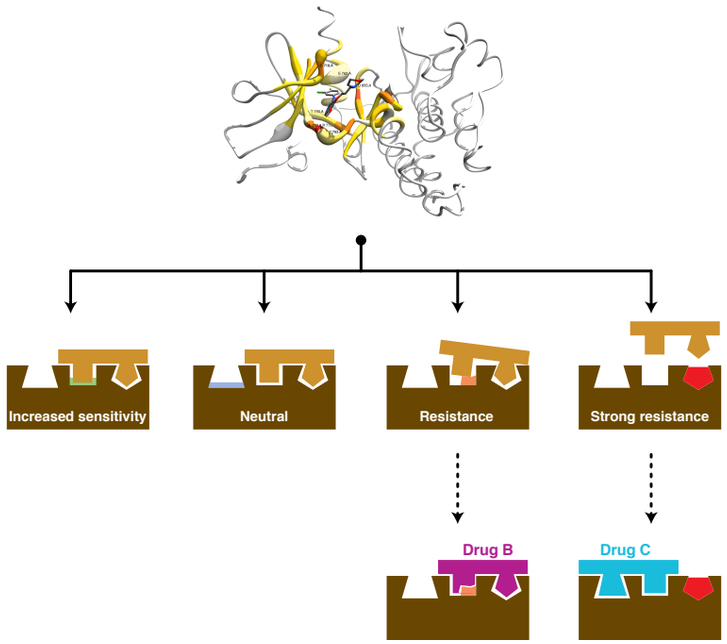


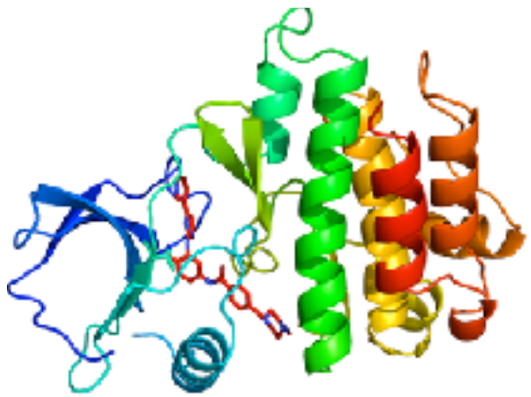
1.Prediction of the cancer-associated likelihood. ✓

2.Prediction of the resistance-impact.

3. Proposal of alternative non-resistant mutants

Predicting resistance using structural features and a Random Forest Classifier

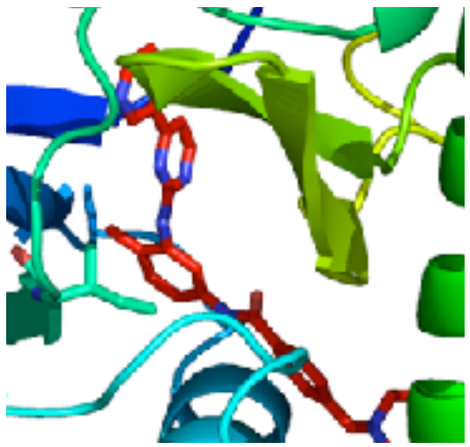




+

Residue Mutation

3D-Model of mutated protein

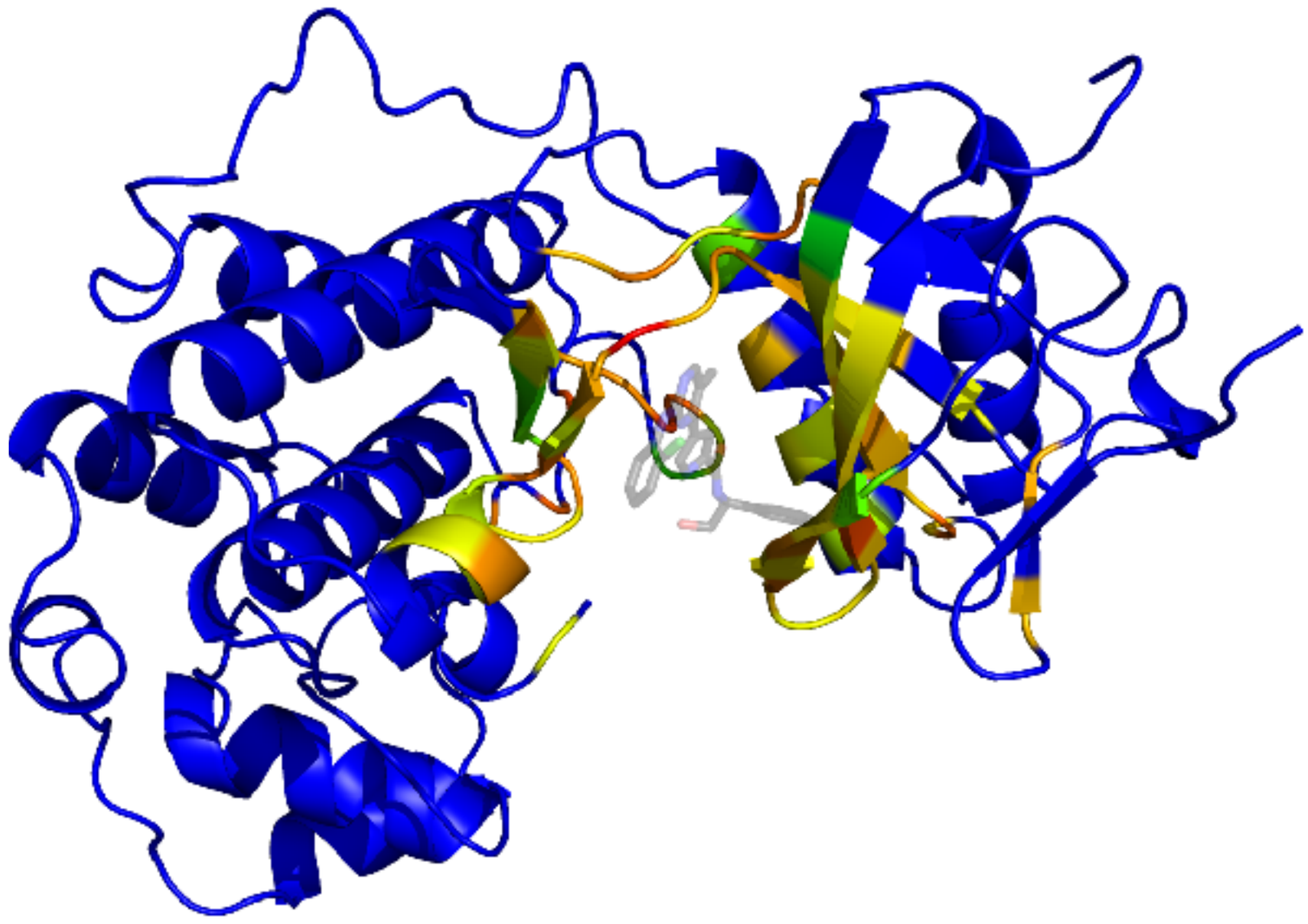


Structural features of wild type and mutated model

Trained Random Forest Classifier with Platinum database

Residue structural features

Mol. Surf. Diff.
Protein Stability Change
Mol. Surf. Area MT
Mol. Surf. Area WT
Avg. Dist. Ligand MT
Max. Dist. Ligand MT
Min. Dist. Ligand MT
Solvent RSA MT
Solvent Acc. MT
Solvent Acc. Diff
Avg. Dist. Ligand WT
Min. Dist. Ligand Diff.
Max. Dist. Ligand WT
Avg. Dist. Ligand Diff.
Min. Dist. Ligand WT.
RSA Diff.
Solvent Acc. WT
Half Sphere Exp. CA up Diff.
Max. Dist. Ligand Diff.
Kd nM WT
SS MT
Solvent RSA WT
SS WT
Half Sphere Exp. CA up MT
Half Sphere Exp. CN MT



Platinum database

http://bleoberis.bioc.cam.ac.uk/platinum/

Pires, D. E. V., Blundell, T. L., & Ascher, D. B. (2015). Nucleic Acids Research, 43(D1), D387–D391.

PLATINUM

Platinum

Protein-ligand affinity change upon mutation database

Platinum: a structural database of experimentally measured effects of mutations on protein-ligand complexes

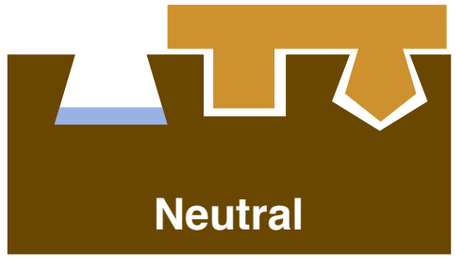
Douglas E. V. Pires, Tom L. Blundell, David B. Ascher

Nucleic Acids Research(Database Issue), v. 43 (D1), p. W387-W391, 2015.

High throughput sequencing initiatives are generating extensive data on non-synonymous single nucleotide polymorphisms (nsSNPs)in human and other genomes. The strong selective pressure imposed by small molecule drugs on many rapidly evolving systems, including viruses, bacteria and human cancer, can cause the rapid development of resistance to these therapies.

In order to study and understand the impacts of missense mutations on the interaction of ligands with the proteome, as well as to guide protein engineering, we have developed **Platinum**. This manually curated, literature-derived database comprising over 1,000 mutations for the first time associates experimental information on changes in protein-ligand affinity with the three-dimensional structures of the complex. To minimise differences arising from experimental techniques and to be able to compare directly binding affinities, Platinum considers only changes measured by the same group and with the same amino-acid sequence used for structure determination, providing a direct link between protein structure, how a

Fold change
> 1.2
180 entries

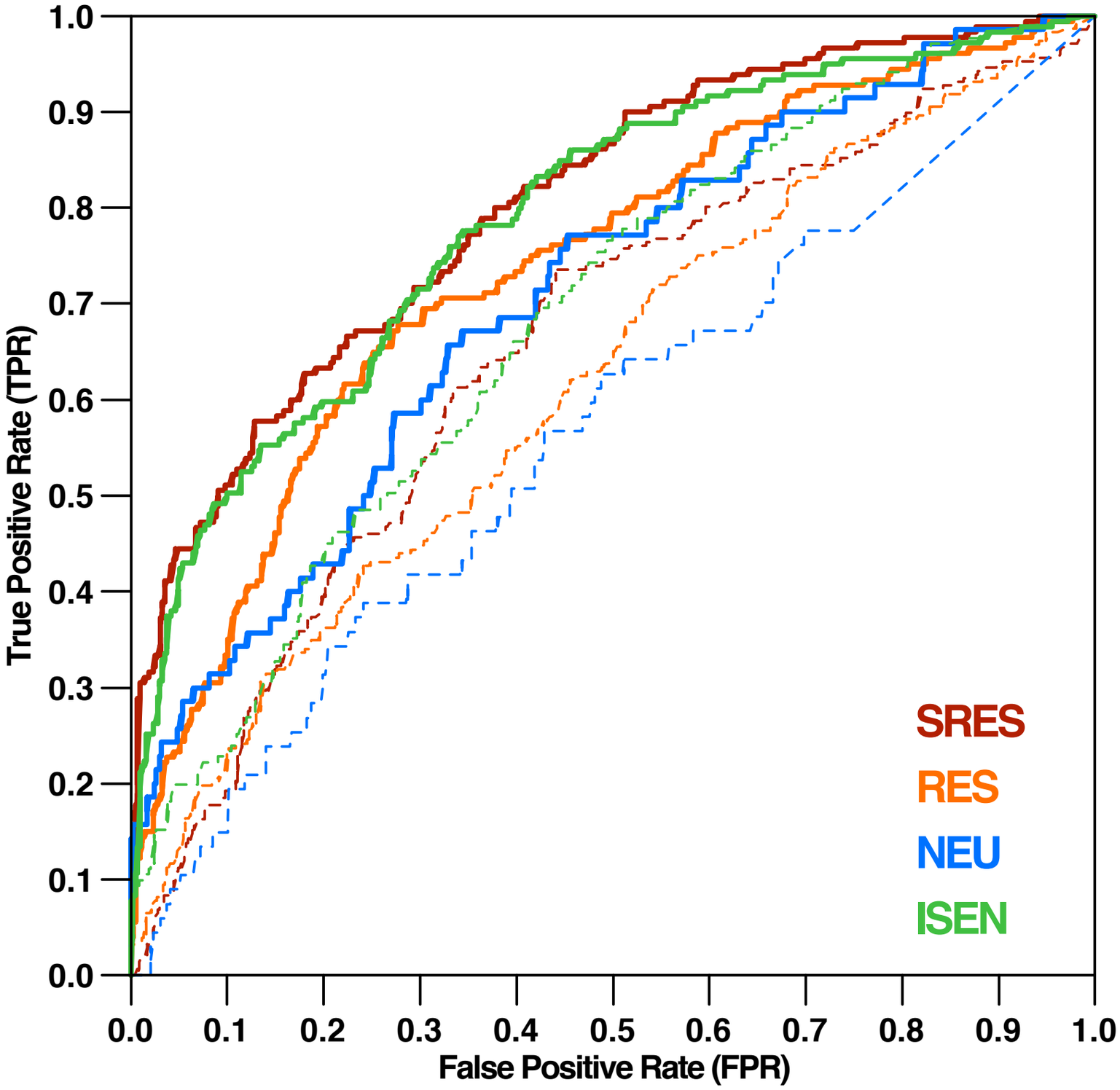


Fold change
<= 1.2 and > -1.2
71 entries

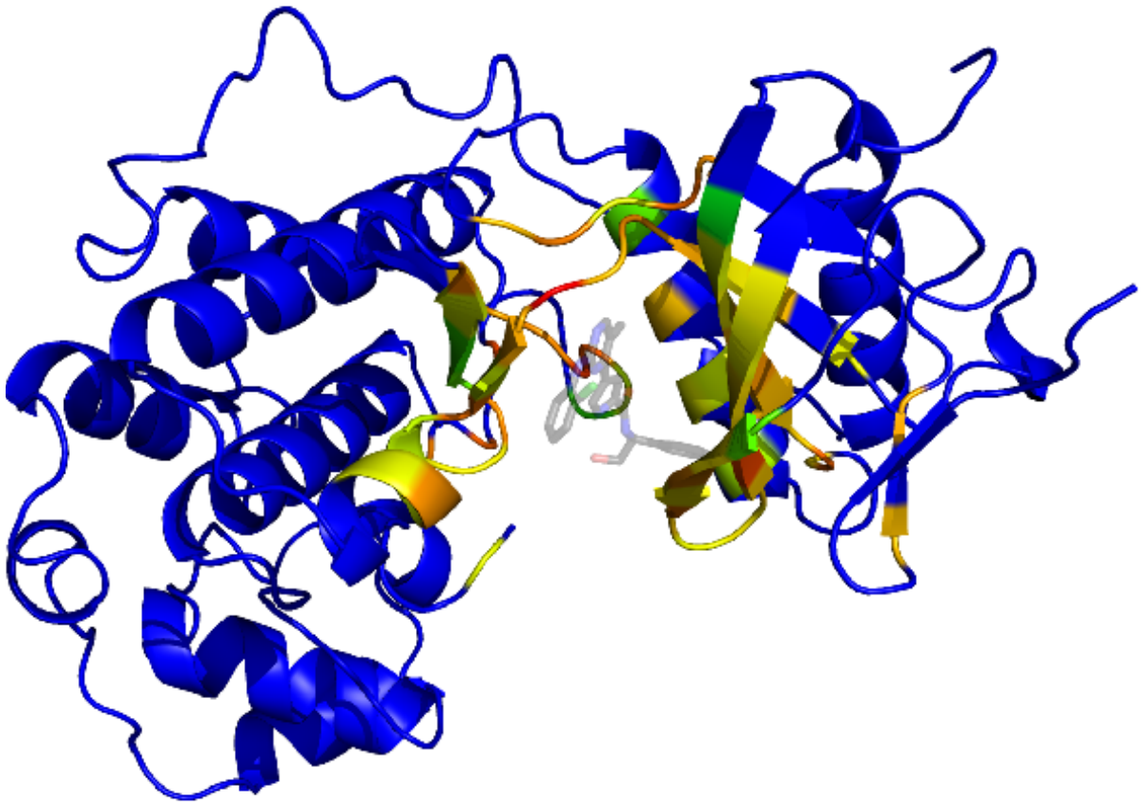
Fold change
<= -1.2 and >-5.0
180 entries

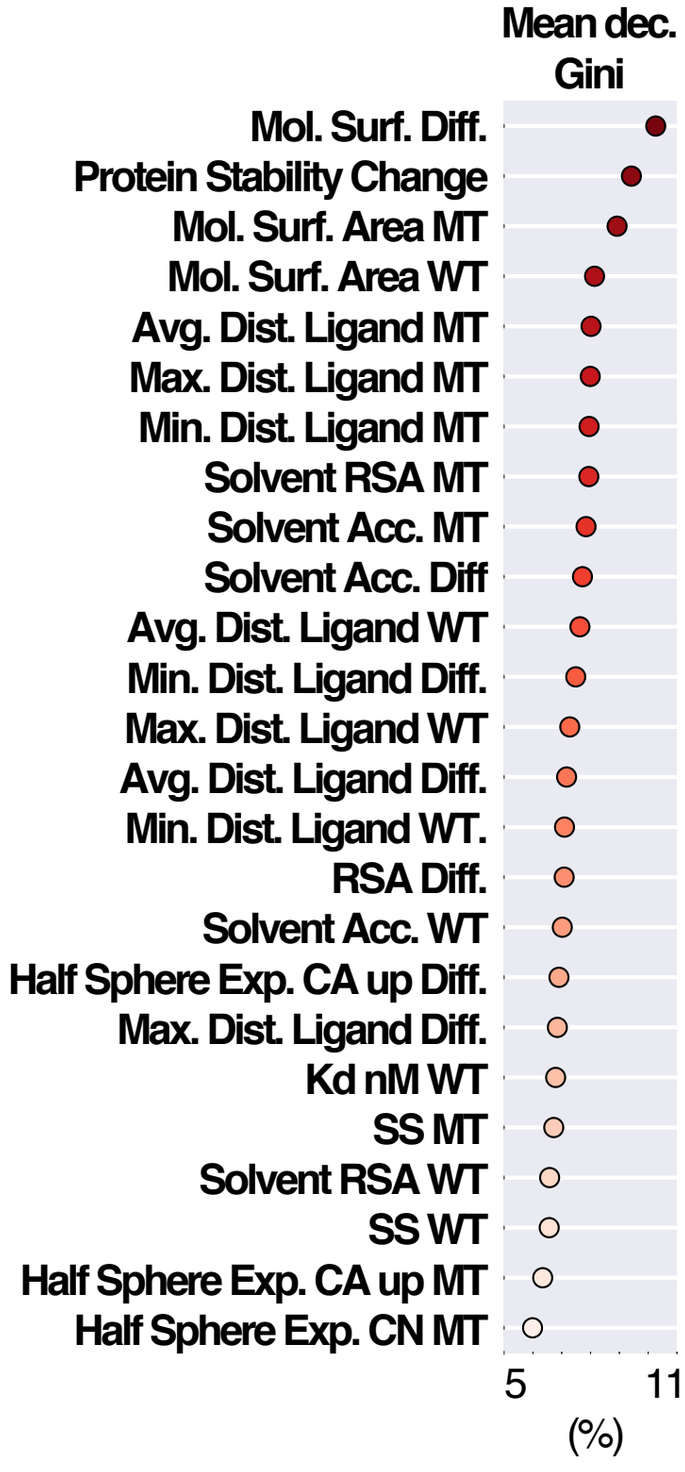
Fold change
<= -5.0
180 entries

10-fold cross validation

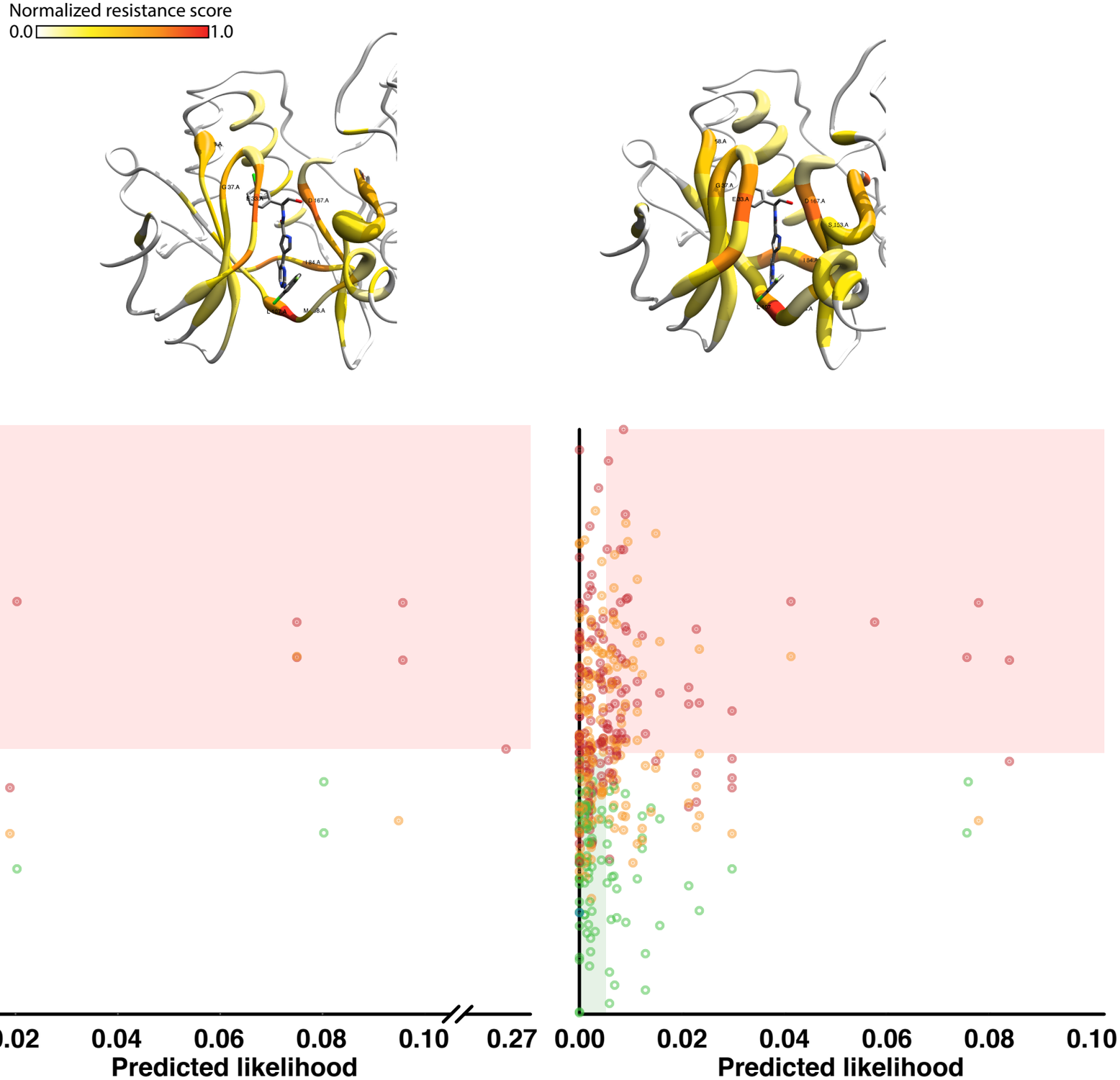


Residue structural features





Resistance-like mutations in ERK2 for melanoma and colorectal cancer



Validating some predictions

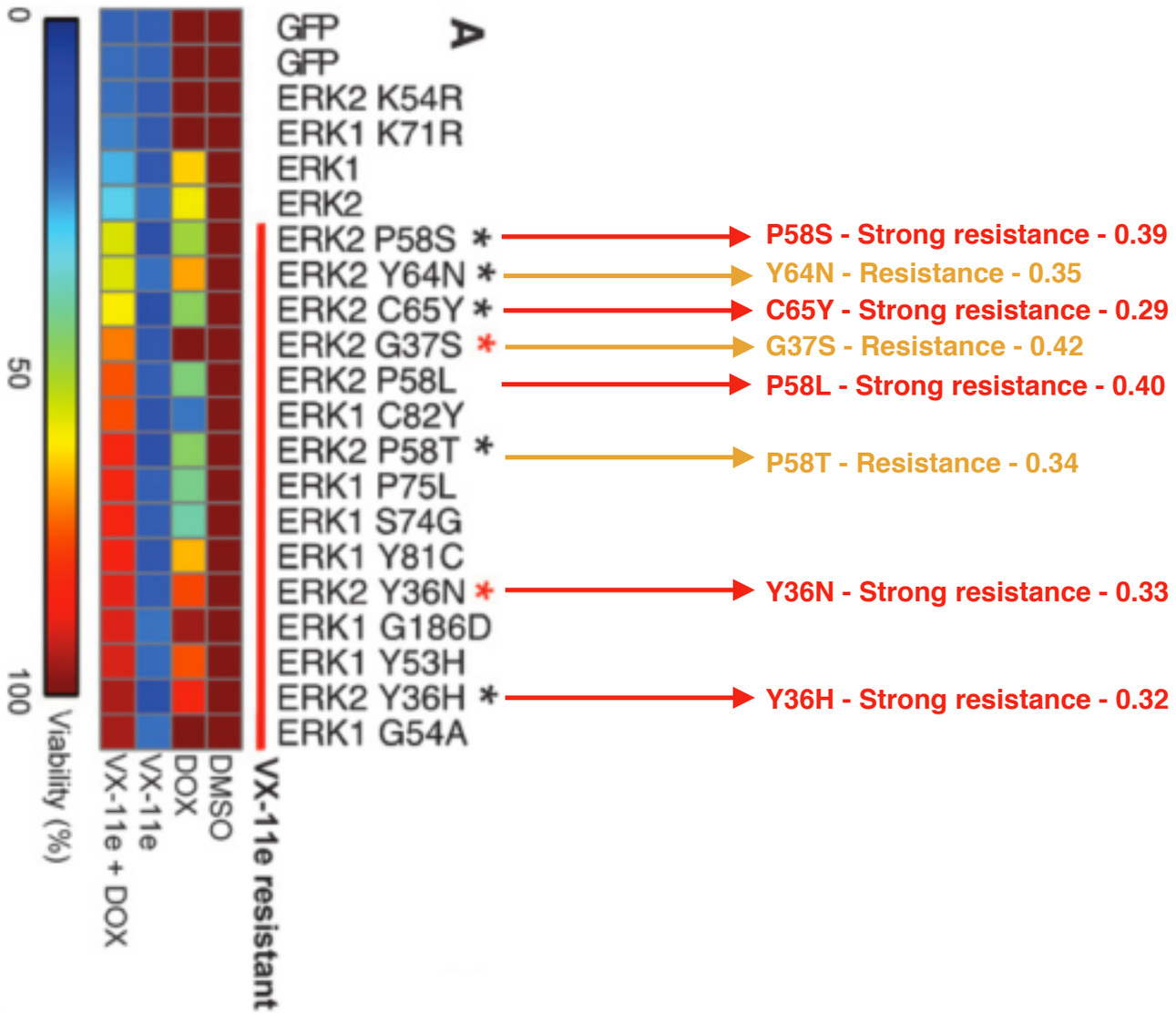
In-vitro identification of ERK2 VTX-11e mutants in A375 melanoma cell line

Therapeutics, Targets, and Chemical Biology

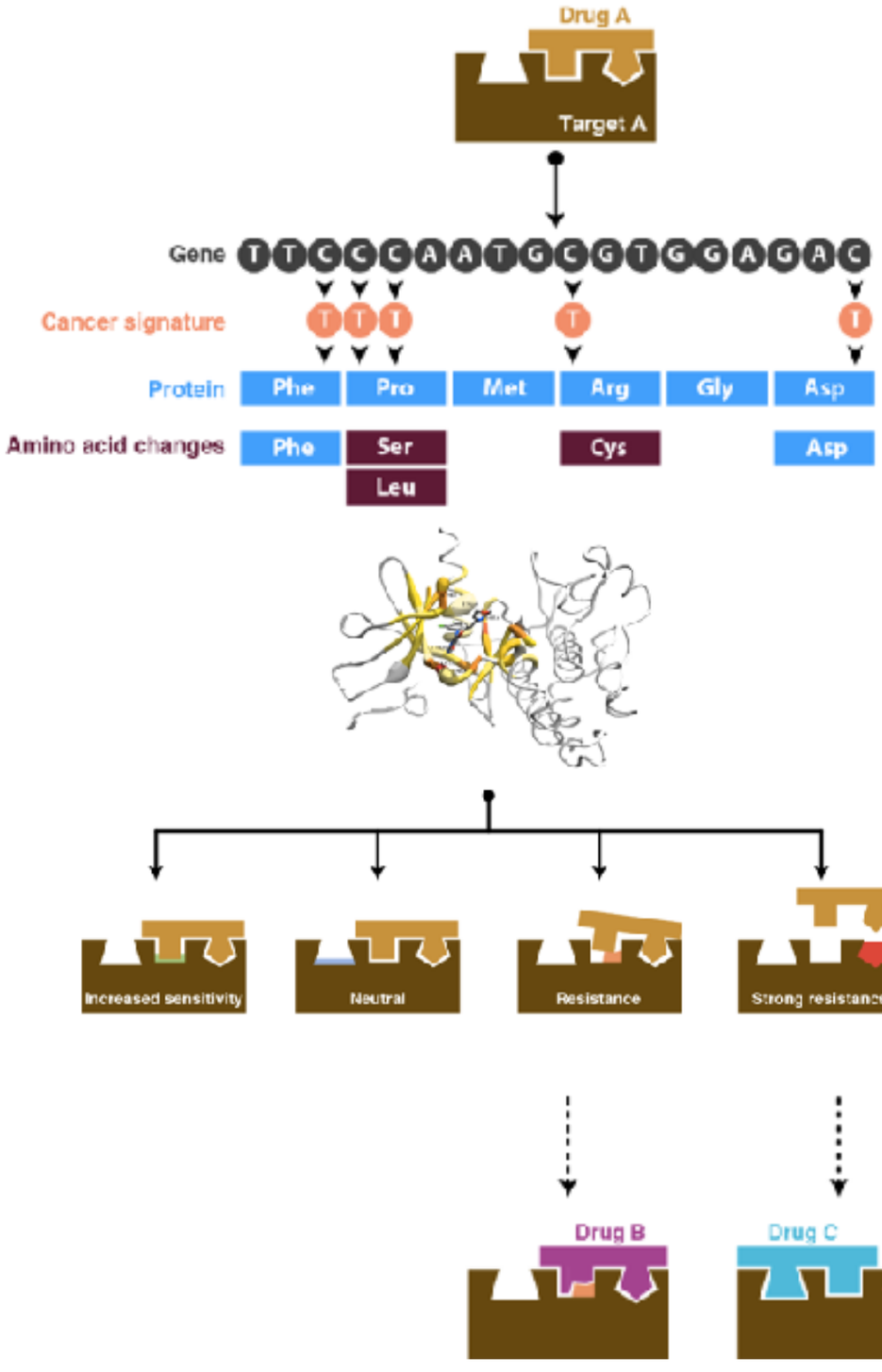
Cancer Research

ERK Mutations Confer Resistance to Mitogen-Activated Protein Kinase Pathway Inhibitors

Eva M. Goetz[1,2], Mahmoud Ghandi[2], Daniel J. Treacy[1], Nikhil Wagle[1,2], and Levi A. Garraway[1,2]



what do we propose to overcome resistance?

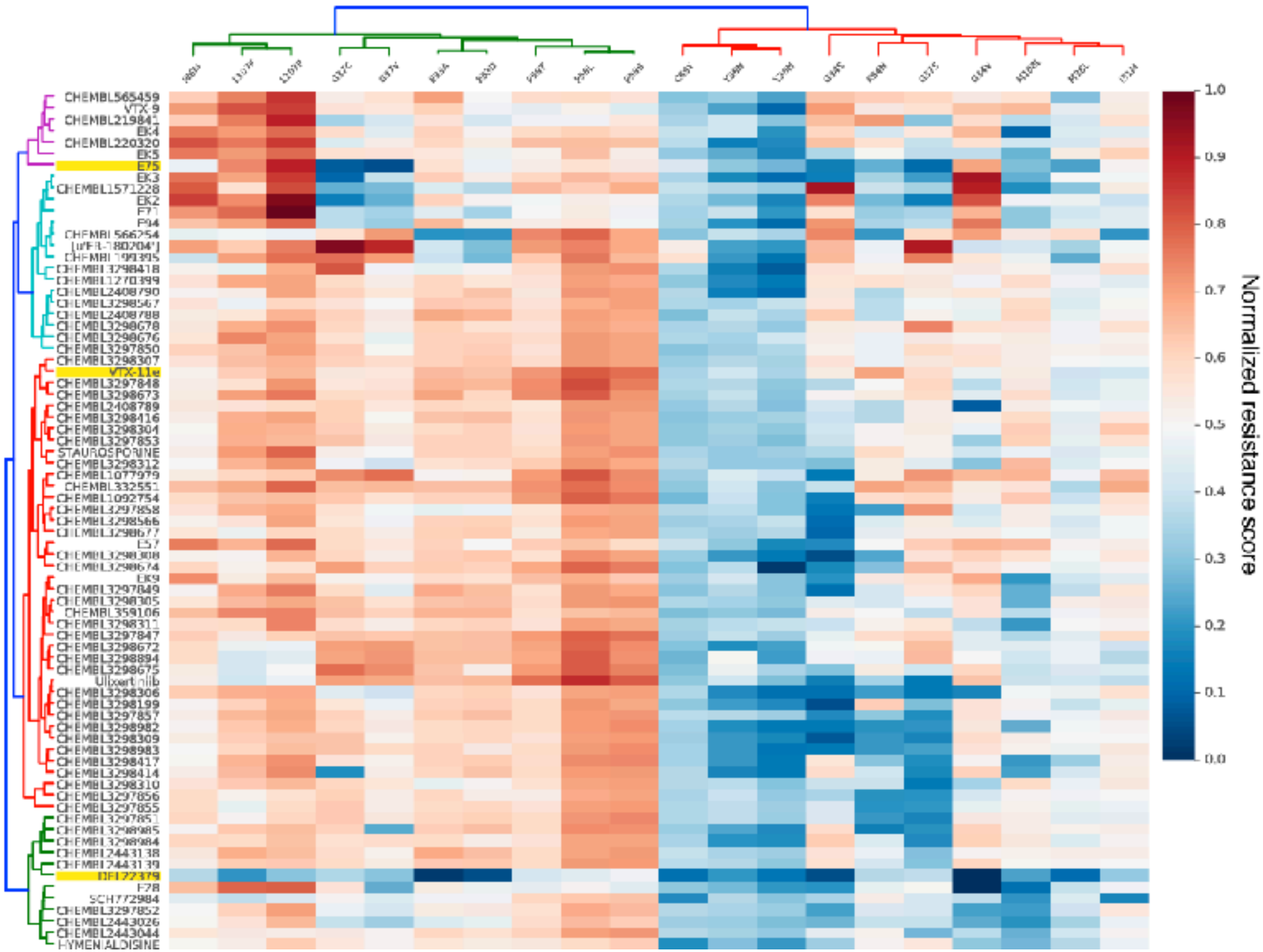


1.Prediction of the cancer-associated likelihood. ✓

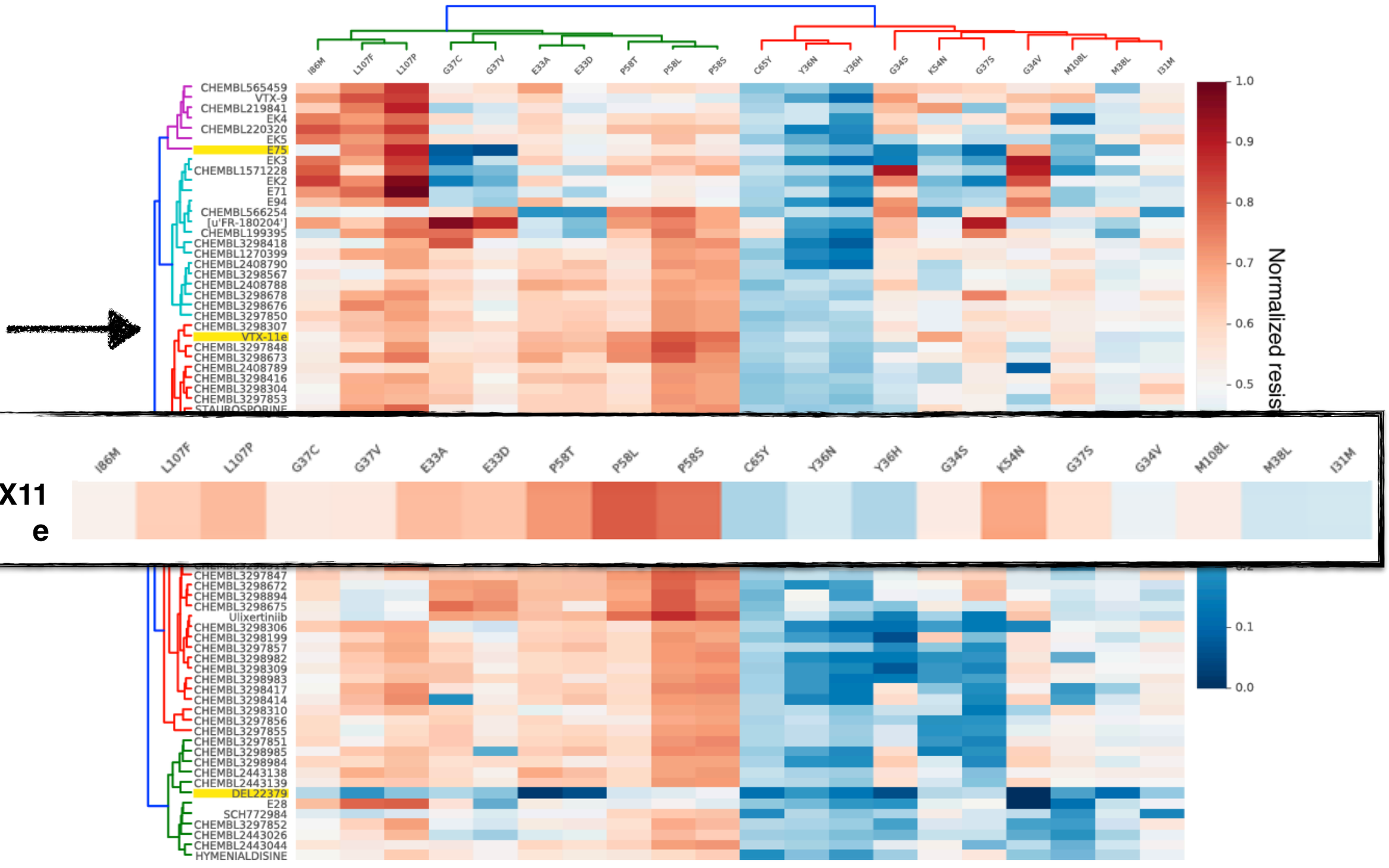
2.Prediction of the resistance-impact. ✓

3. Proposal of alternative non-resistant mutants

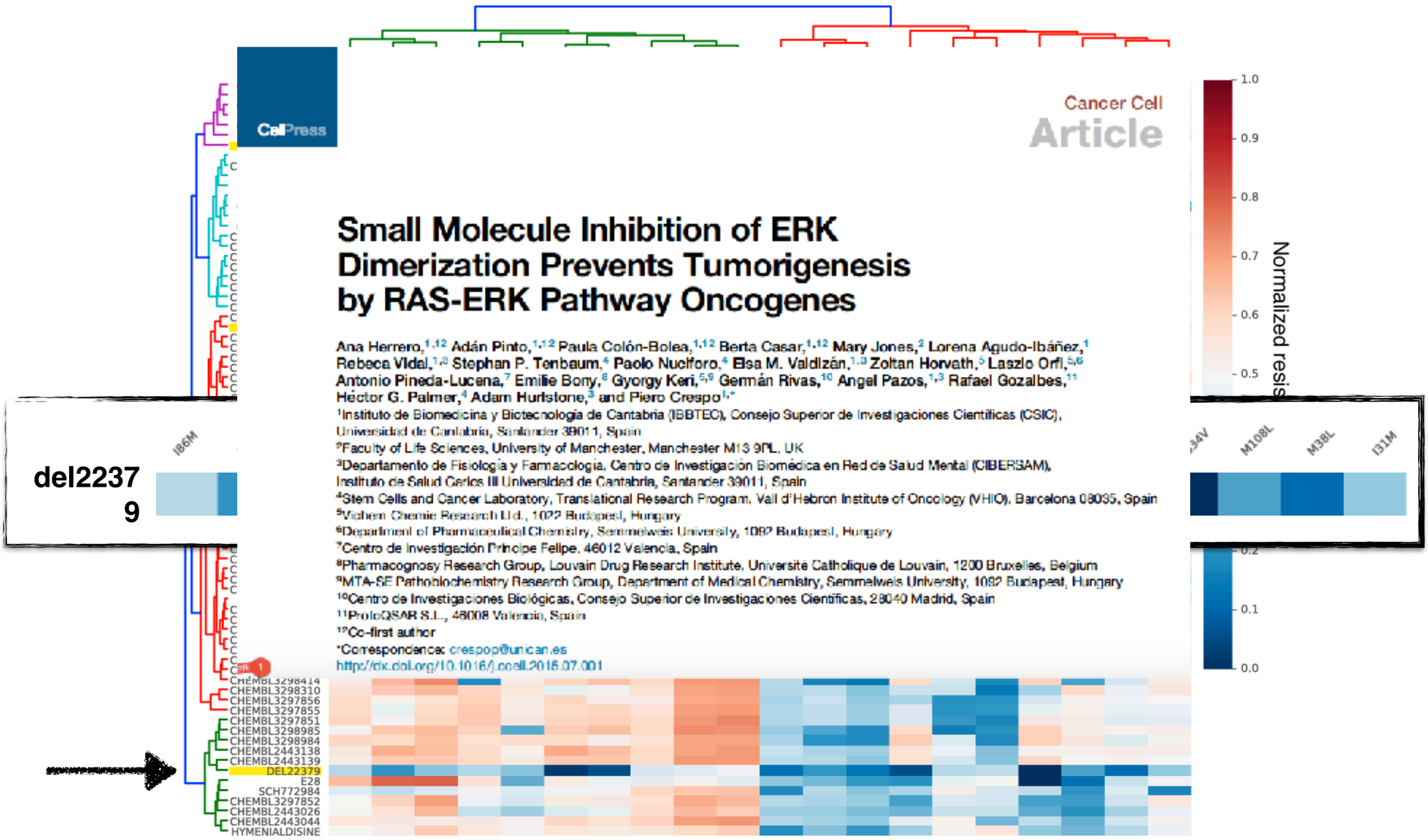
Predicted sensitivity map of ERK2 inhibitors to likely-and-resistant mutations



The control case, VTX11e, is predicted as sensitive to most of the screened mutations



del22379 seems to be unaffected by all of the screened mutations!



CellPress
Cancer Cell
Article

Small Molecule Inhibition of ERK Dimerization Prevents Tumorigenesis by RAS-ERK Pathway Oncogenes

Ana Herrero,[1,12] Adán Pinto,[1,12] Paula Colón-Bolea,[1,12] Berta Casar,[1,12] Mary Jones,[2] Lorena Agudo-Ibáñez,[1] Rebeca Vidal,[1,3] Stephan P. Tenbaum,[4] Paolo Nuciforo,[4] Elsa M. Valdizán,[1,3] Zoltan Horvath,[5] Laszlo Orfi,[5,6] Antonio Pineda-Lucena,[7] Emilie Bony,[8] Gyorgy Keri,[5,9] Germán Rivas,[10] Angel Pazos,[1,3] Rafael Gozalbes,[11] Héctor G. Palmer,[4] Adam Hurlstone,[3] and Piero Crespo[1,*]

[1]Instituto de Biomedicina y Biotecnología de Cantabria (IBBTEC), Consejo Superior de Investigaciones Científicas (CSIC), Universidad de Cantabria, Santander 39011, Spain
[2]Faculty of Life Sciences, University of Manchester, Manchester M13 9PL, UK
[3]Departamento de Fisiología y Farmacología, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III Universidad de Cantabria, Santander 39011, Spain
[4]Stem Cells and Cancer Laboratory, Translational Research Program, Vall d'Hebron Institute of Oncology (VHIO), Barcelona 08035, Spain
[5]Vichem Chemie Research Ltd., 1022 Budapest, Hungary
[6]Department of Pharmaceutical Chemistry, Semmelweis University, 1092 Budapest, Hungary
[7]Centro de Investigación Príncipe Felipe, 46012 Valencia, Spain
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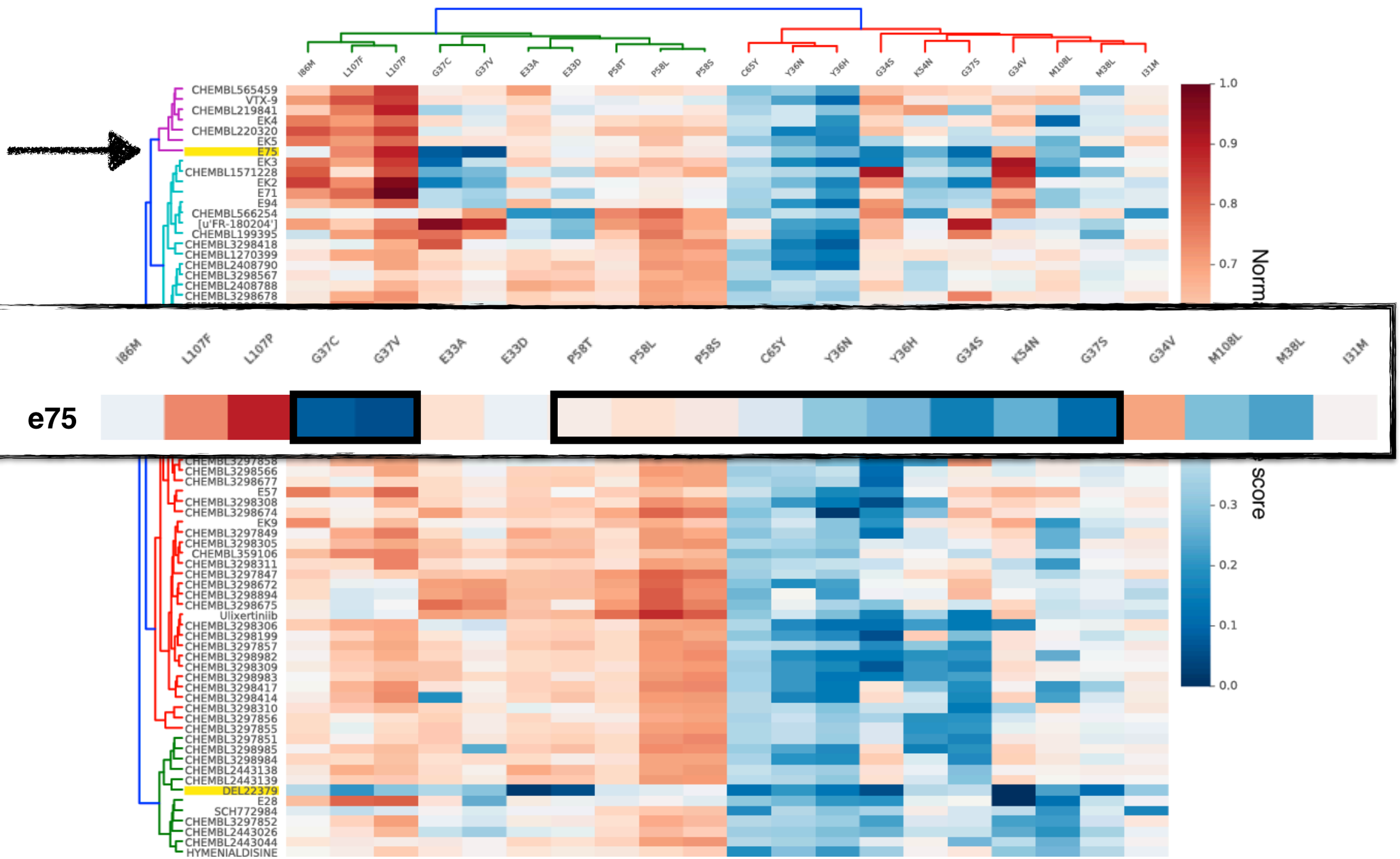
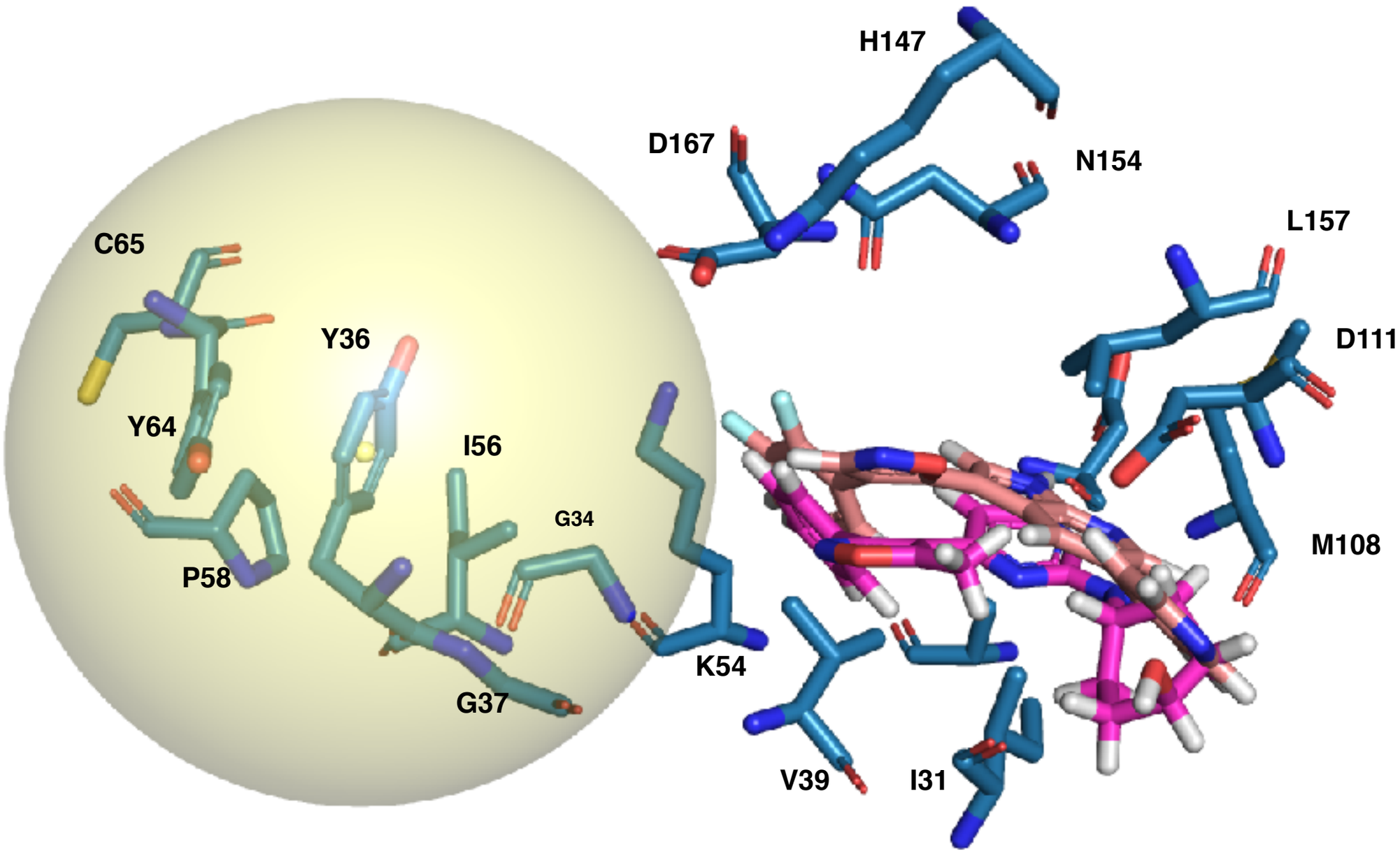
[9]MTA-SE Pathobiochemistry Research Group, Department of Medical Chemistry, Semmelweis University, 1092 Budapest, Hungary
[10]Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas, 28040 Madrid, Spain
[11]ProloQSAR S.L., 46008 Valencia, Spain
[12]Co-first author
*Correspondence: crespop@unican.es
http://dx.doi.org/10.1016/j.ccell.2015.07.001

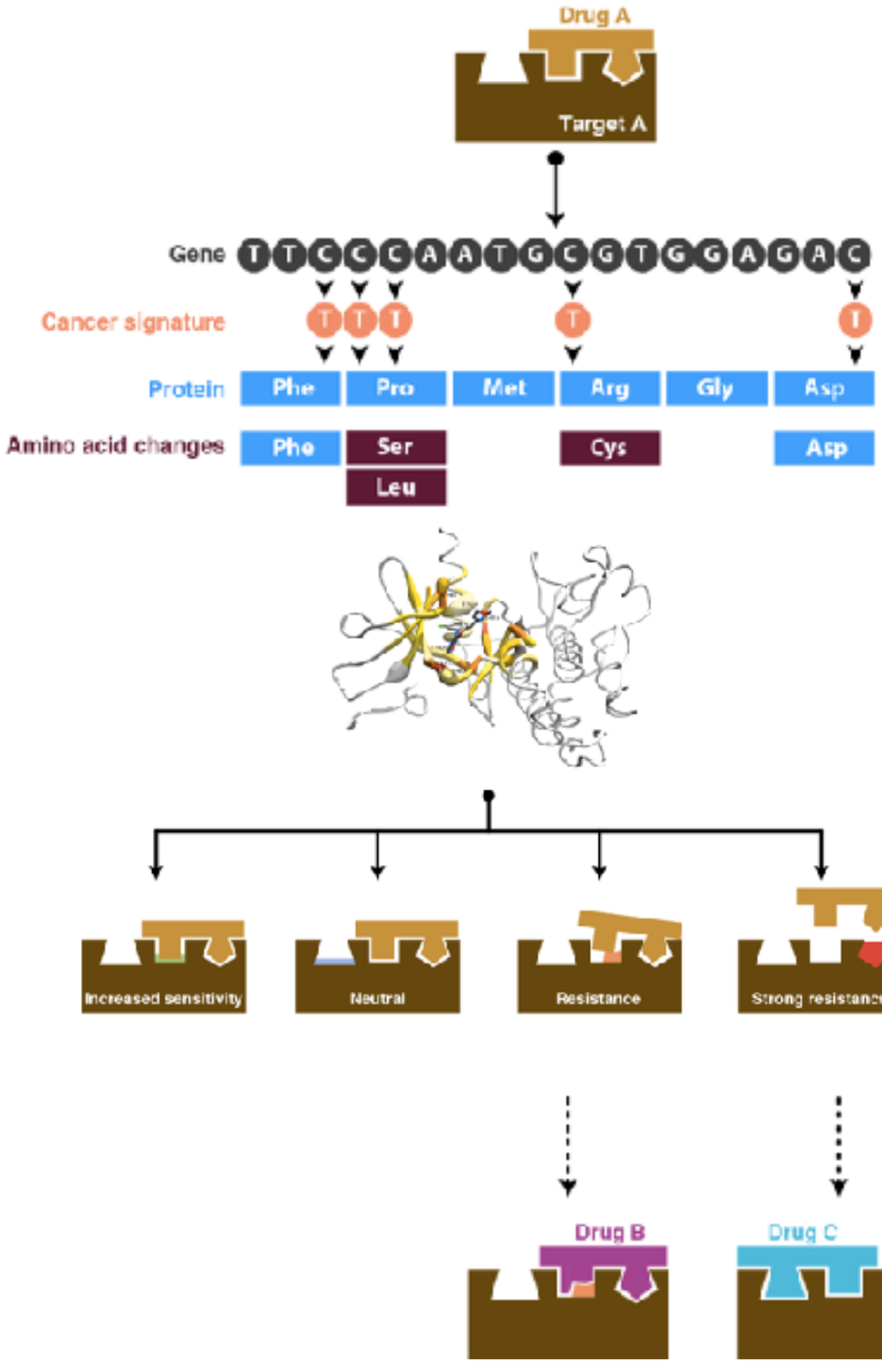
The e75 compound shows a low resistant profile against most of the VTX11e resistant mutations



E7X series does not occupy the "resistant region"



what do we propose to overcome resistance?

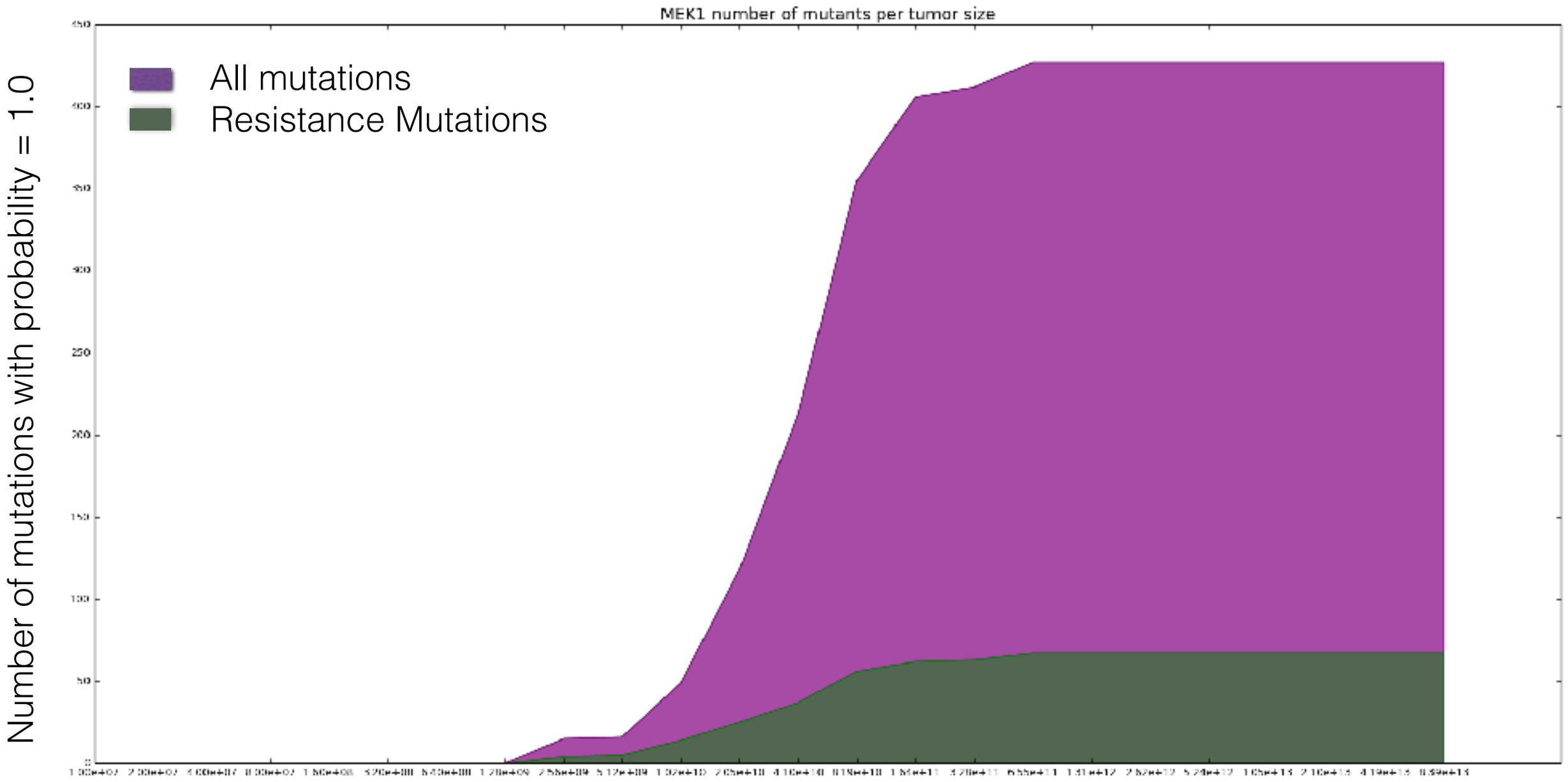


1.Prediction of the cancer-associated likelihood. ✓

2.Prediction of the resistance-impact. ✓

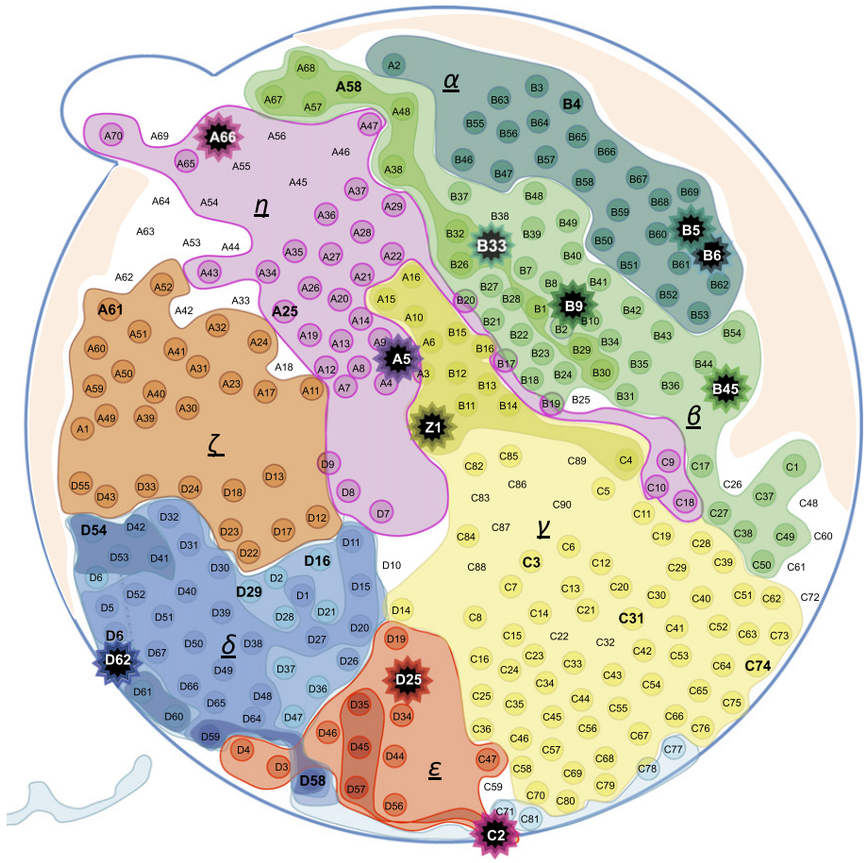
3. Proposal of alternative non-resistant mutants ✓

Resistant mutants per tumor size (MEK1 + Selumetinib)



All possible mutations will occur if a tumour is large enough

A tumor comprising many cells can be compared to a natural population with many individuals. The amount of genetic diversity reflects how it has evolved and can influence its future evolution. We evaluated a single tumor by sequencing or genotyping nearly 300 regions from the tumor. When the data were analyzed by modern population genetic theory, we estimated more than 100 million coding region mutations in this unexceptional tumor. The extreme genetic diversity implies evolution under the non-Darwinian mode. In contrast, under the prevailing view of Darwinian selection, the genetic diversity would be orders of magnitude lower. Because genetic diversity accrues rapidly, a high probability of drug resistance should be heeded, even in the treatment of microscopic tumors.



Ling, S., et al. (2015). Proc Natl Acad Sci U S A, 112(47), E6496–505.

Take home messages

We can use cancer signatures to predict the most likely mutations.
However, we need to move towards “personalized” signatures.

We can predict which of the likely mutations, are more prone to generate resistance to treatment.

We can propose alternative/parallel treatments to overcome future resistance.

All possible mutations will occur if a tumour is large enough

Francisco Martínez-Jiménez

Davide Baù
Gireesh K. Bogu
Yasmina Cuartero
David Dufour
Irene Farabella
Silvia Galan
Francesca di Giovanni
Mike Goodstadt
François Serra
Paula Soler
Yannick Spill
Marco di Stefano
Marie Trussart

in collaboration with John Overington (Stratified Medical) & Bissan Al-Lazikani (ICR)

http://marciuslab.org
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