DrugCell: A visible neural network to guide precision medicine

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Abstract

Many potential cancer therapies fail during clinical trials, in part due to difficulty in predicting how different cancers will respond to a given drug. Here we develop DrugCell, a "visible" neural network (VNN) that predicts anti-cancer drug responses by modeling the hierarchical organization of a human cancer cell. Using 509,294 examples of different cancer cell drug treatments, we trained a novel branched neural network (NN). The first branch is a VNN which represents the human cancer cell by structurally mirroring the hierarchical organization of cellular subsystems with collections of neurons representing protein complexes, signaling pathways, and cellular functions. During training, this VNN learns which cellular subsystems contribute to therapeutic responses based on the mutational profile of the genome. The second NN is fully connected and models the chemical structure of each drug. These two NNs connect to a series of fully connected layers that simulate a cellular drug treatment. DrugCell outperformed Elastic-Net as well as a matched structure random model. Analysis of the top layer of the VNN showed that DrugCell learned cancer cell states that explain well described chemogenetic relationships and in some cases learned tissue types from the underlying mutational profiles.

When running simulations with DrugCell, genotypes and chemical structures induce differential patterns of subsystem activity, allowing for in silico investigations into the molecular mechanisms underlying cancer drug responses. For example, we found that the pathways mediating sensitivity to etoposide included MAPK signaling, PI3K/AKT signaling and regulation of histone deacetylation. Consistent with these inferences, combinations of etoposide with an AKT, MEK or HDAC inhibitor were highly synergistic across multiple cell lines. Similar results were observed upon CRISPR/Cas9-mediated knockdown of key genes in these pathways. We also tested the generalizability of DrugCell to more patient-relevant contexts by evaluating its ability to predict effective mono- and combination therapies. For example, DrugCell was able to accurately predict monotherapy response in leukemia patient samples across a panel of drugs. DrugCell suggested combinations of sorafenib and DNA damaging agents or tandutinib and PI3K/MTOR inhibitors to be effective combination therapies in this leukemia cohort. Subsequent validation showed that these combinations were highly synergistic across multiple leukemia cell lines. Lastly, DrugCell was able to accurately suggest effective and ineffective drug combinations in a pan-cancer PDX tumor cohort and significantly improve progression-free survival compared to monotherapy. DrugCell serves as an important step towards next generation intelligent systems in drug discovery and personalized medicine.

Conclusions

- DrugCell is the first AI system that simulates a cancer cell in response to therapy
- DrugCell makes highly accurate predictions for dozens of drugs across hundreds of cancer cell lines
- Pathway predictions made by DrugCell represent potential drug combinations
- DrugCell predictions can be applied to patient samples to design effective combination therapies

References

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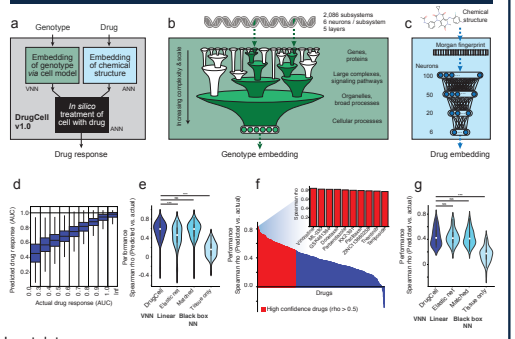
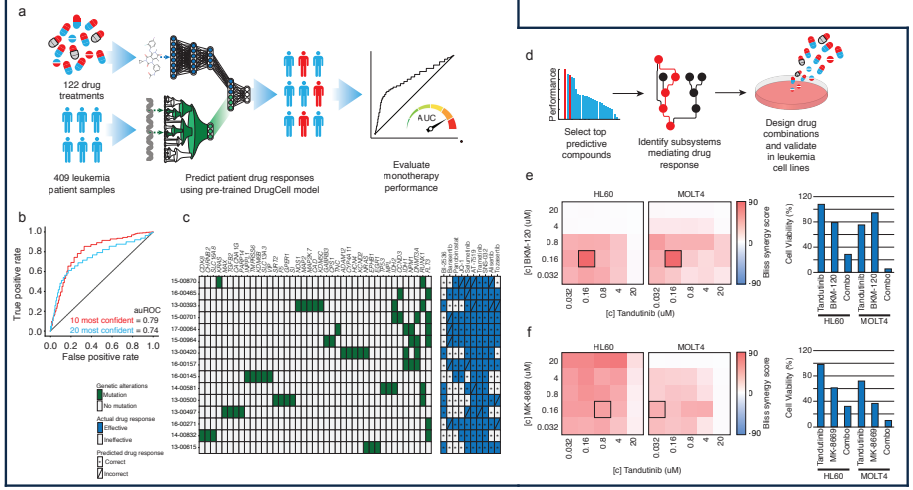
DrugCell Design & Performance



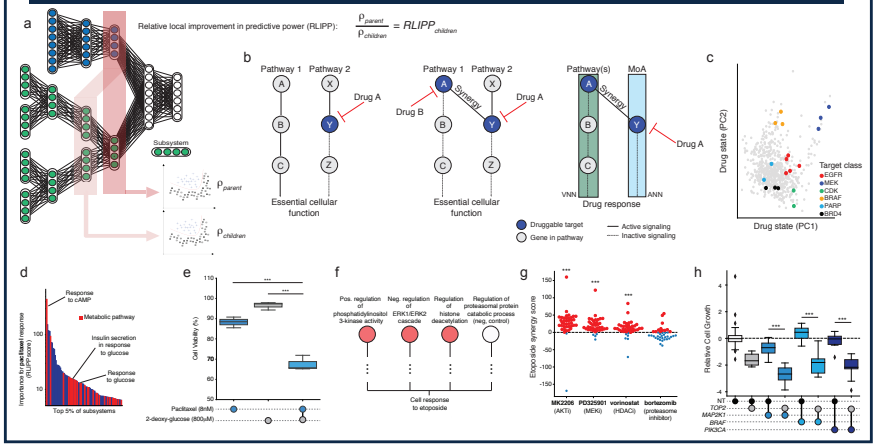
Input data sources:

CCLE Cancer Cell Line Encyclopedia GDSC & CTRPv2

Guiding therapy in leukemia patients



Interpretation of DrugCell Predictions



Guiding combination therapy in vivo