# Gene regulation network-based drug discovery in plexiform neurofibromas

Team: NF terminators

# NFhackathon2020

- *Team name:* NF Terminators
- *Project title:* Gene network based drug discovery in plexifiorm neurofibromas
- We take the "NF Data" challenge and do a datamining on plexiform neurofibromas drug screen data and related cell transcriptomes.
  https://github.com/sundaochun/NFhackathon2020
  https://hub.docker.com/repository/docker/sundaochun/daochunproject
- We want to compete for the GRANT prize
  https://github.com/sundaochun/NFhackathon2020/blob/main/Grant%20prize%20application.pdf
- *Team member names*: Daochun Sun (*Researcher, Data Scientist*)

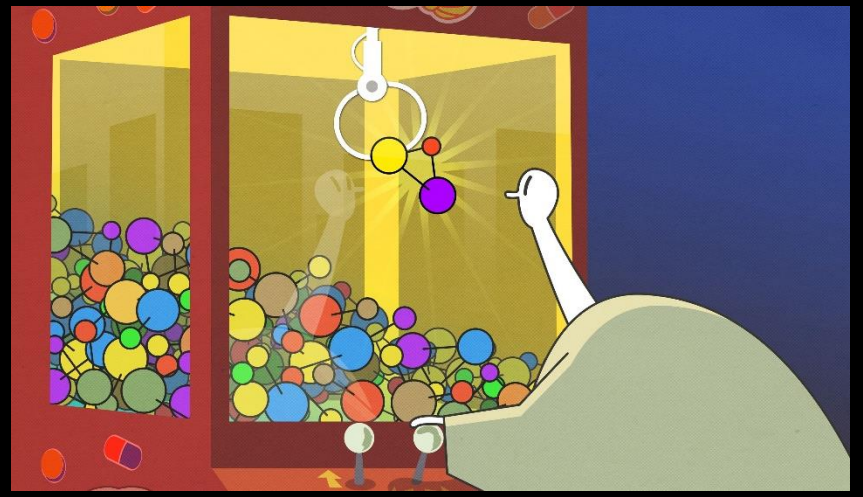

Rebecca Brown (*Health&Pharma, Researcher, Clinician*)

Sameer Farouk Sait (*Clinician, Researcher*)

Before drug screen


After drug screen


What we really want



## Challenges for patients, clinicians and researchers in a drug screen:

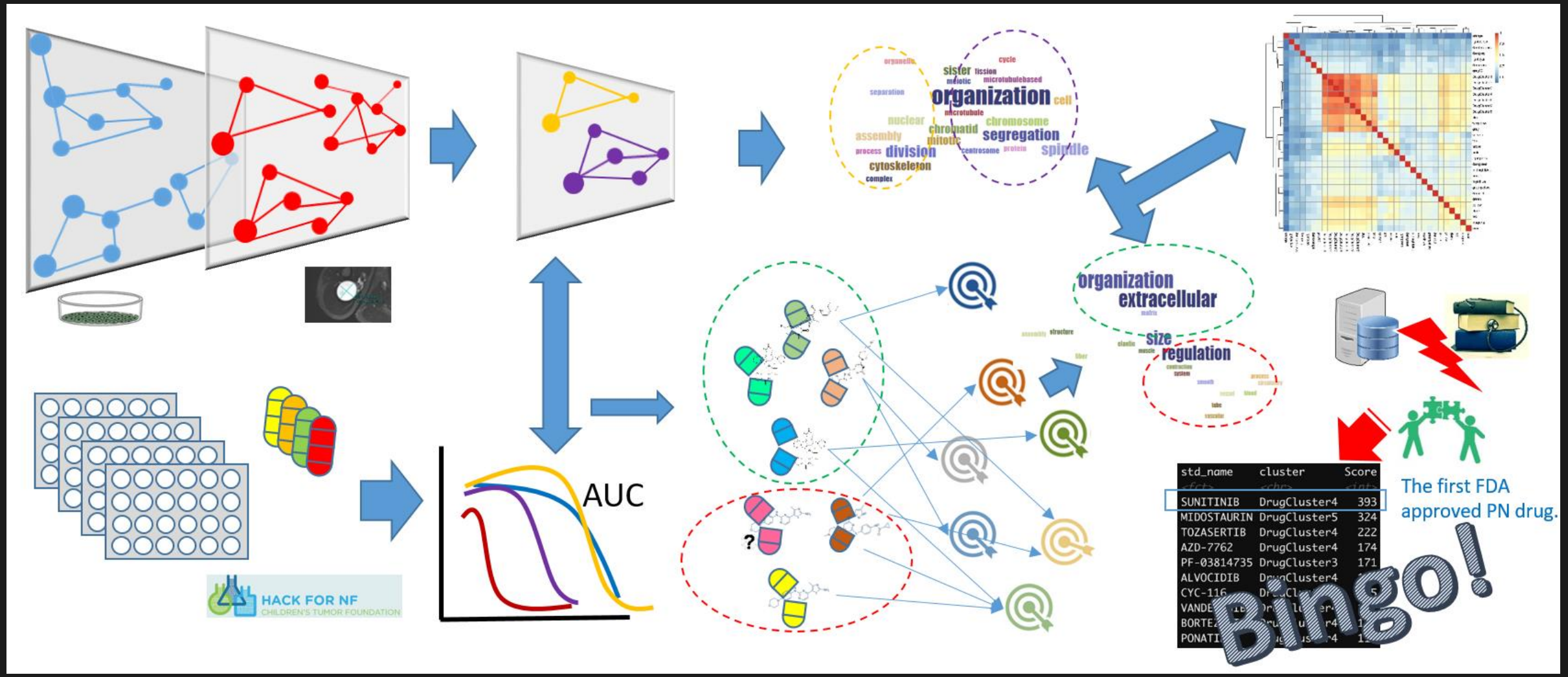
1. We need a ranked candidate list to prioritize.

2. Candidates in a drug screen have low success rate on real tumors.

3. Does the efficacy has a reliable biology (clear targets or mechanisms)?

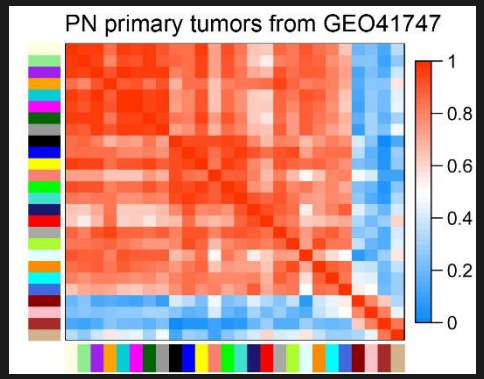
4. Can we combine different candidates to enhance the response and reduce the toxicity?

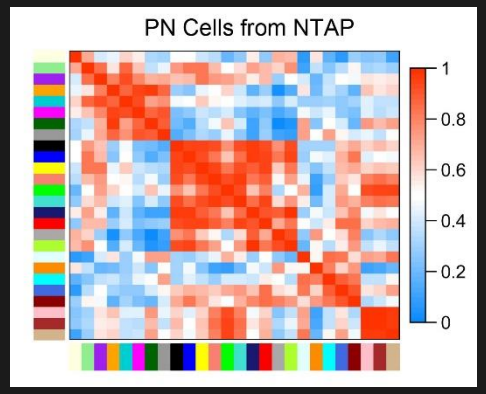
# A magic strategy using R

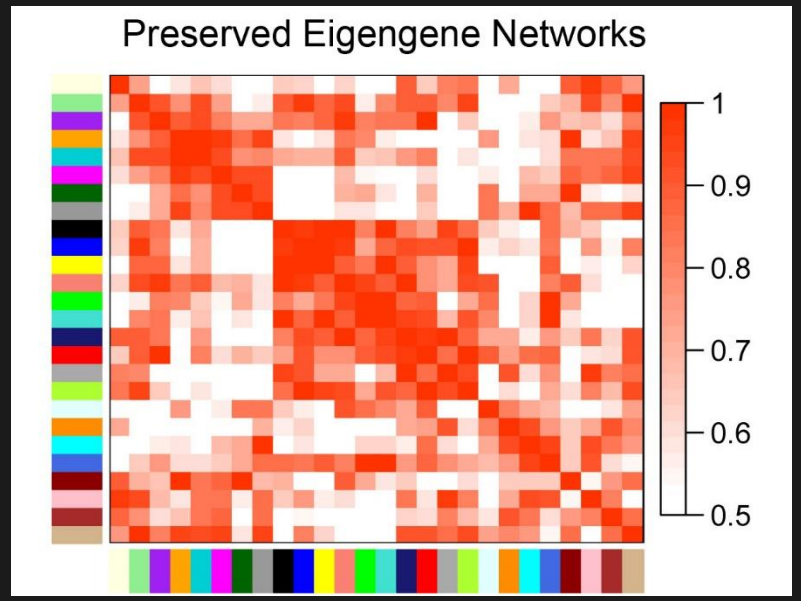


# Use preserved gene networks to bridge the gap between models

- Gene expression of PN from GSE41747 study
- Gene expression of immortalized PN cell lines used in drug screen
- WGCNA package in R

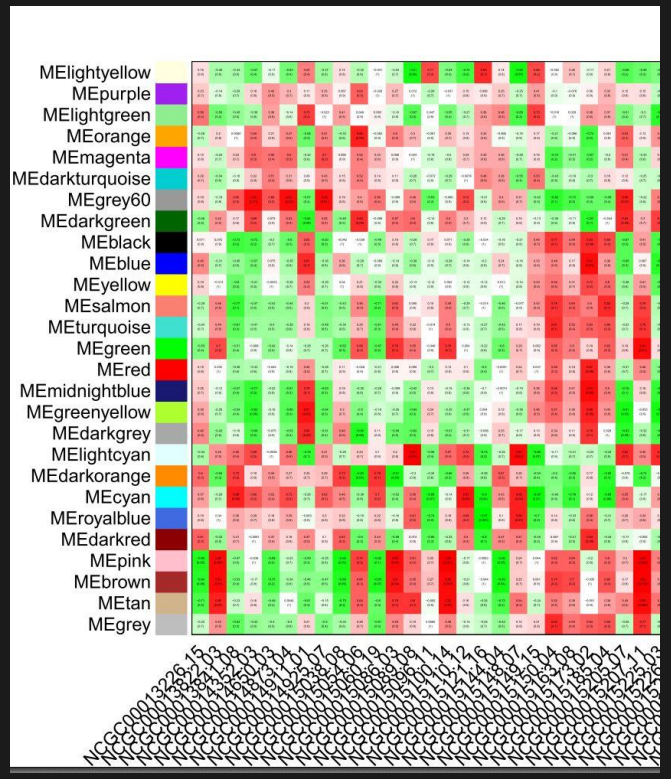



Color blocks represent different gene networks

# Correlate the drug responses to the preserved networks

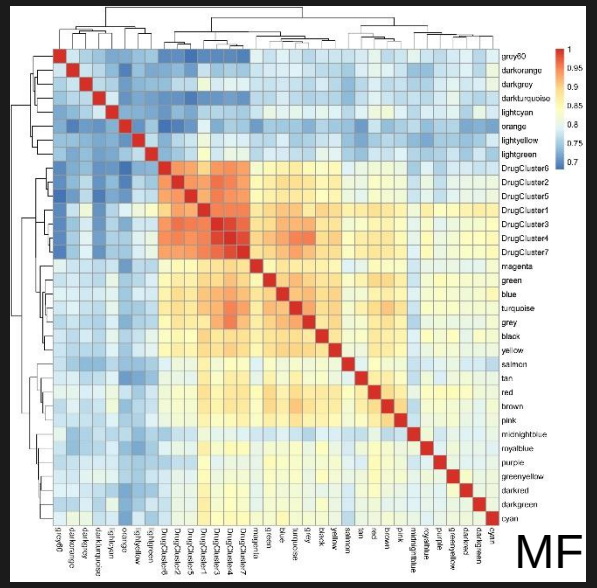


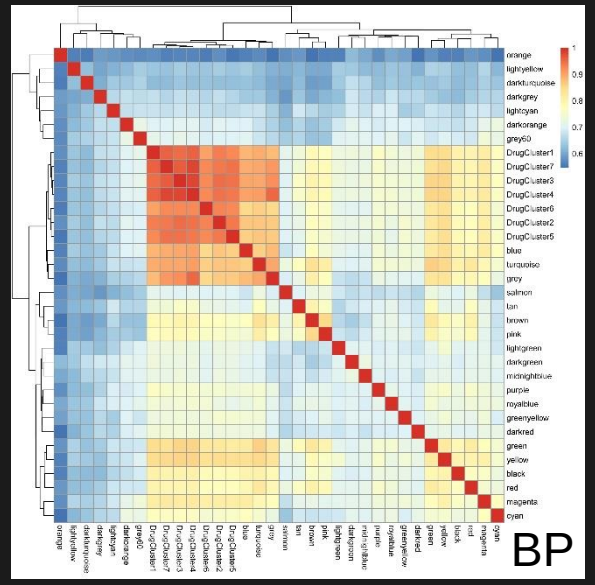

- In the heatmap, red indicates a positive correlation between drug efficacy and networks and green indicates a negative correlation.
- Color blocks on each row represent preserved networks
- Each column is a drug candidate
- This is a partial data without grouping the drugs

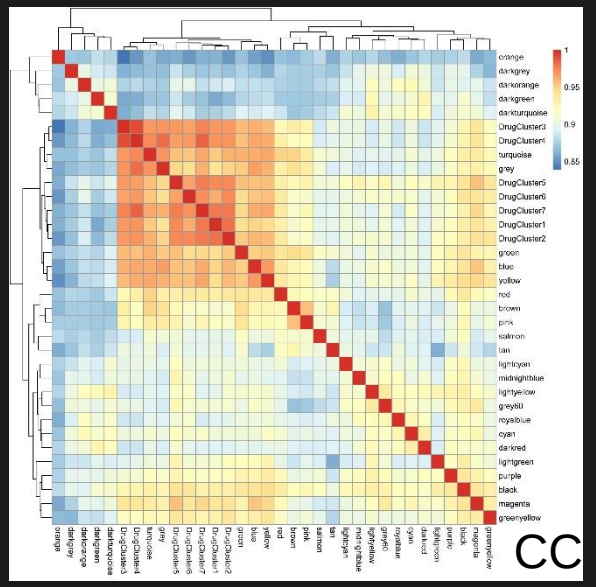
- Drugs can be clustered into unique groups based on correlation between their effects and various subcellular networks identified

# Gene ontology (GO) semantic analysis

- GO terms enriched in each gene networks were calculated (GOSemSim R package)
- According to the drug annotations, the known target genes in any drug cluster can be determined, and GO terms enrichment were calculated
- GO term similarity were determined by semantic analysis respectively in three GO branches: molecular function (MF), biological process (BP) and cell component (CC)




Assumption: High similarities indicate strong biology relevance, suggesting the drugs potentially target the networks

# Why our strategy is great?

- Using the preserved networks, we enrich candidates targeting both cells and tumors
- The algorithm weights higher on the “well-annotated” drug candidates
- The gene networks can help researchers to nail down the mechanisms
- The drug clusters can serve as a start point to explore the targets of a novel candidate
- Drugs can be combined according to their clusters
- ……

# More we can do given more time…

- Weighted toxicity scores (PMID: 29739789).
- The FDA drug label database to design a combination of candidates
- MPNST drug screen can be integrated for candidates to inhibit both
- ……

# References:


- MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors (J Clin Invest. 2013 Jan;123(1):340-7)
- Immortalization of Human Normal and NF1 Neurofibroma Schwann Cells (Lab Invest 96(10):1105-15, 2016)
- WGCNA package: https://horvath.genetics.ucla.edu/html/CoexpressionNetwork/Rpackages/WGCNA/Tutorials/
- GOSemSim: https://bioc.ism.ac.jp/packages/release/bioc/html/GOSemSim.html
- R Bioconductor project: https://www.bioconductor.org/
- Synapse NFhackathon2020: https://www.synapse.org/#!Synapse:syn22336443/wiki/605694
- CTF NFhackthon2020: https://www.ctf.org/news/hack-for-nf-2020
- The slack discussions in the general and scientific channels
- The R codes provided by the NFhackathon organizers

# Acknowledgements

- The teamwork among the NFhackathon community
- My 5-year-old daughter's strategy to end NF.