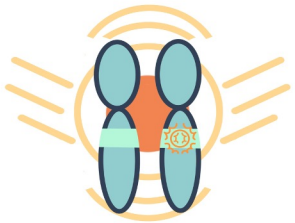
Reversing the detrimental gene expression in pNF by integrated drug screen mining

--Prediction and validation



Team: **NF-Buster**

2022 Hack for NF

- Team name: **NF-Buster**

- Project title: Reversing the detrimental gene expression in pNF by integrated drug screen mining

- We take on challenge #3 and do a datamining on plexiform neurofibromas drug screen data.
https://github.com/yunguangsun/hack4nf2022

- We want to compete for "**Best Use of Data**", "**Best project page**" and "**Challenge winner**"

- Team members: Kathy Sun (Researcher, High School Student)
Yunguang Sun (Researcher, Data Scientist)

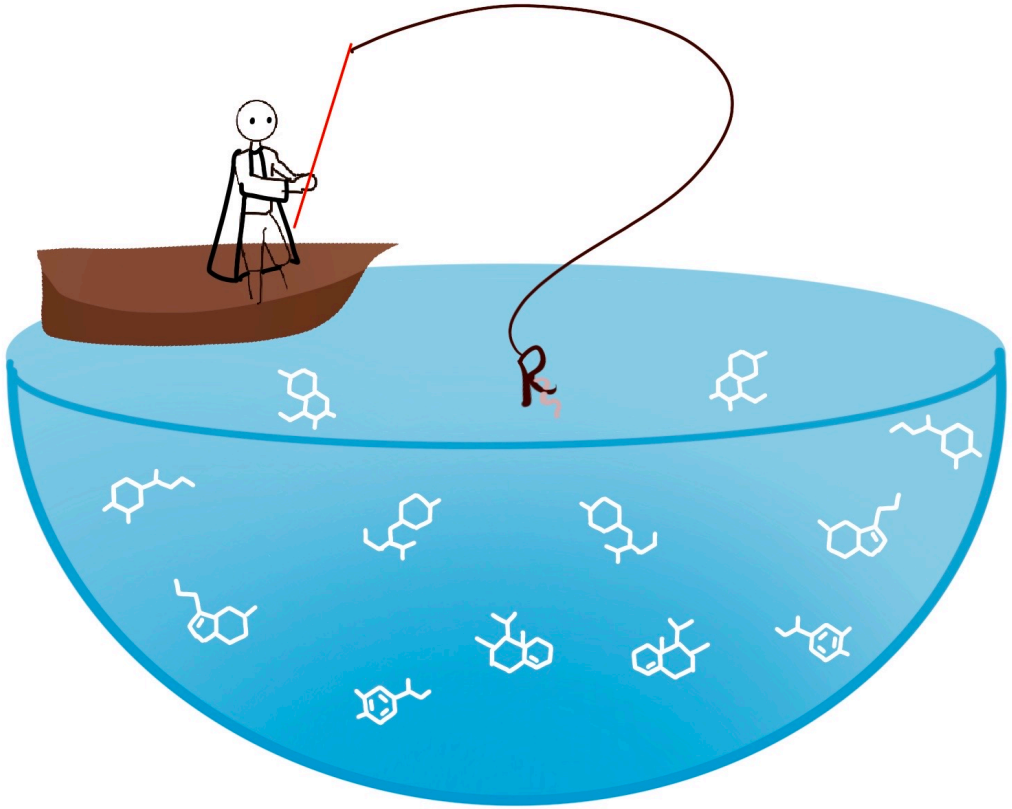
Our considerations in the drug screen challenge:

- Potential drug response bias from screening data
  - Genetic discrepancy in pNF cell lines with human *TERT* or mouse *CDK4*
  - Transcriptome drift between physiological condition and cell culture

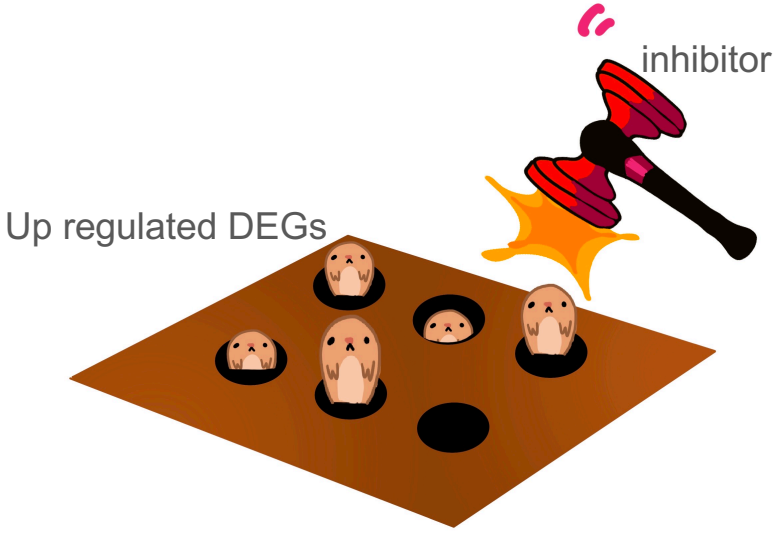
- Library of Integrated Network-Based Cellular Signatures (LINCS) database
  - Integrated the gene expression and drug response data
  - More than 54,000 small compounds in tumor drug screening
  - 431 Datasets and 353 Cell Lines
  - 4082 Gene over-expressions, 1113059 Signatures

- Reverse the highly expressed gene expression in pNF to inhibit tumor growth
  - Prioritize the drug candidates in LINCS by determine scores of Reversal of Gene Expression Signatures (sRGES)
  - Use pNF cell line drug screen as experimental validations for the predicted drug candidates

Let’s go fishing



We hypothesize that decreasing the highly expressed genes in tumors will inhibit the pNF growth



Microarray data
Plexiform neurofibromas primary tissue
Dataset: GSE14038 (syn5950004)

library(Biobase)
library(edgeR)

Generate the differentially expressed genes between Plexiform neurofibromas and normal human Schwann cell

library(OCTAD)

Predicted drug targets
Reversal Gene Expression Score
sRGES.pNF

Drug screening datasets
Syn20700260
Hack4NF2022 dataset

Prioritize Drug Candidates — Seven plexiform neurofibroma related cells

Select data for plexiform neurofibroma related cells in the drug screen database

Prioritize Drug Candidates — Select pchembl > 6 from pchembl

Select pchembl > 6 from pchembl database annotation (syn17091507)

Overlapping two drug lists
sRGES score less than -0.2

Top drug Candidates specific for NF1

Top drug Candidates for NF1 from Team NF-Buster: We have 22 distinct drugs and 169 targets

	drug_name	median_response	hugo_gene	std_name	pert_iname	sRGES
1	NCGC00250406-01	43.98139723	FNTA	TIPIFARNIB	tipifarnib	-0.245848822
3	NCGC00262603-01	44.75736189	PIK3CB	IDELALISIB	idelalisib	-0.229061682
8	NCGC00168110-01	46.94346416	AAK1	TOZASERTIB	tozasertib	-0.238526074
82	NCGC00346508-01	46.9546487	DCK	TG100-115	TG100-115	-0.523947529
83	NCGC00346877-01	48.10236892	ADAM17	BATIMASTAT	batimastat	-0.215815757
90	NCGC00263539-03	48.35751978	ADRA1A	ZIPRASIDONE	ziprasidone	-0.207924917
112	NCGC00016759-03	48.87592645	AKR1C3	NAPROXEN	naproxen	-0.284358613
114	NCGC00094818-08	49.86684411	TDP1	HEXESTROL	hexestrol	-0.20074983
115	NCGC00159453-06	50.23976884	EPHX2	ZILEUTON	zileuton	-0.24721922
117	NCGC00016311-16	50.55306749	ADRA1A	PHENTOLAMINE	phentolamine	-0.225438256
124	NCGC00159509-02	50.74462695	ACE	PERINDOPRIL	perindopril	-0.209761043
125	NCGC00016268-09	51.19216213	HCAR2	NIACIN	niacin	-0.213302736
126	NCGC00015439-06	51.3509198	GABRA1	FLUMAZENIL	flumazenil	-0.216771654
131	NCGC00164619-04	51.62238074	CYP19A1	ANASTROZOLE	anastrozole	-0.602553876
132	NCGC00021146-06	51.63304745	ADORA3	KETANSERIN	ketanserin	-0.222011256
135	NCGC00168781-01	51.65878703	PDE11A	TADALAFIL	tadalafil	-0.223077039
137	NCGC00167781-07	51.71523734	HRH1	CETIRIZINE	cetirizine	-0.255861124
138	NCGC00164549-01	52.47023255	KCNH2	DOFETILIDE	dofetilide	-0.542226678
139	NCGC00096077-05	52.90058534	ADRA1A	OLANZAPINE	olanzapine	-0.382206228
166	NCGC00167531-03	53.01633198	BCHE	RIVASTIGMINE	rivastigmine	-0.349656807
167	NCGC00014670-16	53.40765291	DRD3	DOMPERIDONE	domperidone	-0.239881158
169	NCGC00178734-03	55.72963108	DPP4	SITAGLIPTIN	sitagliptin	-0.432513651

Top 5 winners:

1. Protein farnesyltransferase/geranylgeranyltransferase
2. Pi3K kinase
3. AP2 Kinase 1
4. DeoxycytiAssociateddine kinase
5. A disintegrin and metalloprotease 17

Future Directions

- Collect and accumulate more relevant gene expression datasets from pNF1 in vivo progression specimen to establish more biological relevant gene expression changes
- Collection of experimental drug test data from various sources related to pNF1 especially *in vivo*
- Ranking and prioritizing promising drug candidates using more relevant differentially expressed genes in more biological screening data
- Validate top 5 drug candidates in pNF1 cell lines and further validate 1 to 2 more effective drugs *in vivo*

References:

•Zeng, B., Glicksberg, B.S., Newbury, P. *et al*. OCTAD: an open workspace for virtually screening therapeutics targeting precise cancer patient groups using gene expression features. *Nat Protoc* **16**, 728–753 (2021). https://doi.org/10.1038/s41596-020-00430-z

•Brown, R.M.; Farouk Sait, S.; Dunn, G.; Sullivan, A.; Bruckert, B.; Sun, D. Integrated Drug Mining Reveals Actionable Strategies Inhibiting Plexiform Neurofibromas. *Brain Sci*. **2022**, *12*, 720. https://doi.org/10.3390/brainsci12060720

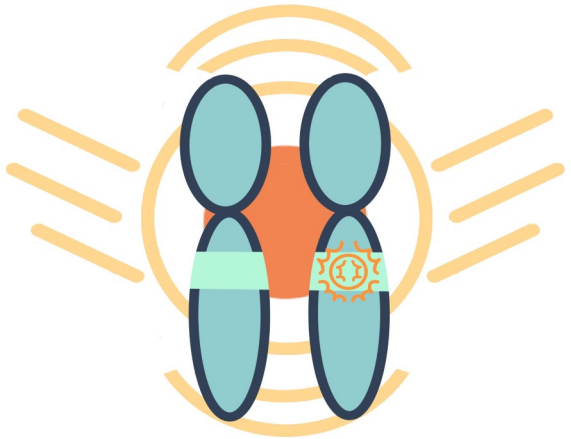
•The slack discussions in the general and scientific channels

• The R codes provided by the NFhackathon organizers

Acknowledgements

- Public datasets:
  - GSE14038 (syn5950004)
  - Syn20700260
  - LINCS
  - syn17091507
  - GTEx (Genotype-Tissue Expression)
  - TARGET (Therapeutically Applicable Research to Generate Effective Treatments)
  - TCGA (The Cancer Genome Atlas)
- The teamwork among the NFhackathon community
- Promote awareness of pNF in our new generations

Thank you for listening!



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