**Grant prize application from team NF Terminators**

Our project for NFhackthon2020 is “Gene network-based drug discovery in plexiform neurofibromas.” We devise an algorithm to rank the candidates from the drug screen in plexiform neurofibromas cell lines.

Plexiform neurofibromas (PN) are embryonic tumors predisposed with loss of function of the NF1 gene in children and young people. Besides the recent FDA approved drug, SUNITINIB, treatment options are minimal. Drug screen using the immortalized PN cell lines provides an efficient way to obtain a pool of drug candidates. However, there are multiple challenges to scrutinize the candidates before clinical-related studies: 1) *in vitro* screen has a different tumor microenvironment from *in vivo* tests, which yields a low success rate in the latter, 2) a novel chemical will have an unknown mechanism and targets, 3) a “well-studied” drug commonly has numerous targets and side-effects, 4) it is hard to evaluate the possibility of the drug combination.

To tackle these issues, 1) we established the consensus gene regulation networks among cell lines and PN tissues by using the transcriptomes from Hackathon data and publicly available data set, 2) the drug response data were correlated to the preserved gene networks and then clustered to reveal the similar pattern among all drug candidates, 3) the known drug target genes within drug clusters and the genes within preserved networks were annotated using gene ontology (GO) analysis, respectively, and the similarities among the GO terms of a gene network and a drug cluster were computed using GO semantic analysis to confirm a biologically reliable drug-gene relationship, 4) drug candidates can be combined according to their drug clusters and correlated gene networks to reduce the toxicities or enhance the effects.

We ranked the drug candidates according to drug responses, potential mechanisms and targets, and biological consistency between cell lines and tumors. We surprisingly discovered SUNITINIB as the NO.1 candidate in our final actionable list, supporting our algorithm’s clinical value.

We found the NF hackathon recently released the drug combination data on three PN cell lines and drug screen data on malignant peripheral nerve sheath tumors (MPNST). One of the purposes of our algorithm is to identify potential drug candidates for combinations. We would like to further explore the drug combination data for verification and optimization of our algorithm. For the other data set, PN have an increased risk to progress into MPNST, a deadly tumor with 39% five-year survival. We want to integrate our current methodology and results with the MPNST drug screen data to identify potential drug candidates targeting both tumors, which provides practical strategies to inhibit PN and prevent PN malignant transformation.

We propose in the next three months, with the support of GRANT prize, 1) we will correlate the drug recombination data to our drug clusters and preserved gene regulation networks to verify or optimize our algorithm, 2) propose possible mechanisms explaining combination effects, 3) if the data set is big enough, we can generate a machine learning model to predict the combination effects according to our drug-network correlation, 4) define the preserved gene networks among PN and MPNST cell models and evaluate the shared candidates between the two drug screen to provide a new ranked drug candidate list actionable to both tumors.