Pathway inhibitor for preventing NF2 tumor growth

Team: Paranoid Androids

Why we chose this track

Sheer **curiosity**

Offering a potentially **actionable solution** to NF2 Patients

The Basic Idea

To find a correlation, if any, between **PTK2 expression** and **NF2 disease**

Formulate a **new computational approach** to arrive at PTK2 inhibitor molecule/drug

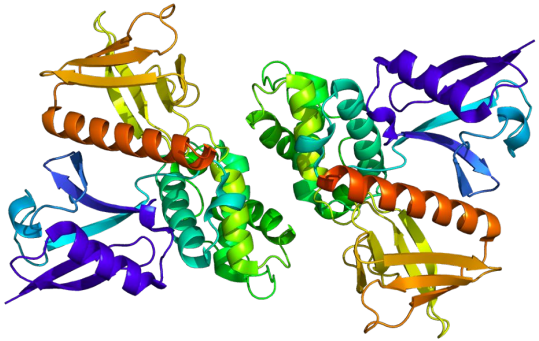
The hypothesis

Can we intercept PTK2 and HSP90 pathways to slow down or stop NF2 tumor growth?

Background

Typically the NF2 gene creates a protein called *Merlin* that acts as a tumor inhibitor

Mutations cause the *Merlin* protein in NF2 patients to be shortened or absent, leading to benign tumors



Connection between *NF2* and cancer

It has been observed in studies [1,2,3] that mutations in *NF2* and hence absence or suppression of *Merlin* are found across various types of cancer, which include:

Mesothelioma, meningioma, ependymoma, glioblastoma

Out of these, mesothelioma has the maximum occurrence of *NF2* mutations. We thus decided to explore if the mutations had anything in common with that in the *NF2* disease and it's therapeutic consequences.

In addition, the patient's *NF2* mutation has been observed to be somatic in nature whereas typical *NF2* cases are autosomal dominant further pointing to possible connections with cancer pathways (possibly atypical for *NF2* disorder).

Target Proteins

Two candidates for target proteins that could potentially be involved in growth of NF2 tumors (schwannomas, acoustic neuroma etc.) were:

- HSP90 (Heat shock protein 90; HSP90AA1, HSP90AA2, HSP90AB1, HSP90B1, TRAP1)

- PTK2/FAK (Protein tyrosine kinase 2; PTK2)

After analysis of patient's genomic data, no mutations were found in HSP90 genes and the involvement of the Src/Fak pathway has been confirmed in other cases[4], which is why we decided to target PTK2.

Our approach

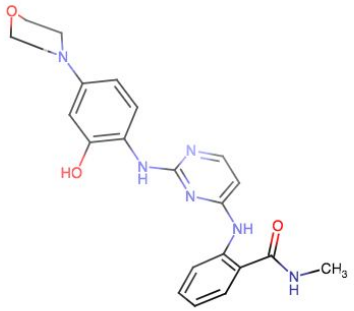
- Perform a **substructure search** for inhibitor molecule by modelling target molecule as a graph
- Extend DeepChem to work with GGT-NN[5] model for efficient, stepwise search (WIP)

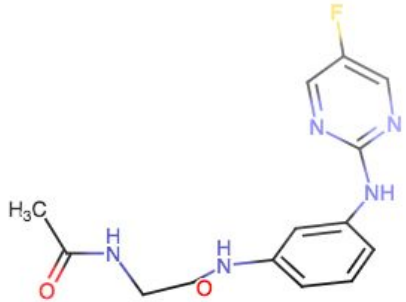
Progress so far

- We extended DeepChem's Graph Convolution method with a dilated/atrous convolution receptive field which gave better results on our dataset (gathered from PubChem) containing inhibitory drugs and targets, possibly because of better long-range interaction modelling (0.52 validation v/s 0.67 validation)
- We found preliminary FAK inhibitor drug candidates that could potentially prevent or slow *NF2* tumor growth

Preliminary Results

1. Preliminary results from the algorithm generated the following FAK inhibitor molecules that could prevent growth of the NF2 tumor
2. The action of the molecules was verified with pyMol small molecule docking





Conclusion

It is possible, or even probably that tumors caused by somatic *NF2* mutations have similar molecular pathways for growth as cancers such as mesothelioma.

The molecular pathways can be selectively inhibited to slow down the growth of *NF2* caused tumors as a potential treatment

What should we do next

Verify the efficacy of the discovered drugs and find similar pathway inhibition mechanisms to stop tumor growth