Daniel Wong

Annotated Bibliography for Mini Qual

Generally speaking, I’ll be working on a project that looks at the protein aggregates of alpha synuclein in neurodegeneration and discovering the pathway mechanisms of disease. We will be approaching aggregation and how to inhibit it from a large data screen. This will require usage and building off of previous work done in the Keiser lab, particularly the similarity ensemble approach (SEA) to find drugs and their corresponding targets that may be of use in ameliorating protein aggregation. After in silico hits, we can then validate in vitro and then build phenotypic profiles in vivo and analyze them.

**References:**

**1. Large-scale prediction and testing of drug activity on side-effect targets**

SEA was used to identify new drug-off target pairs. A drug of interest is compared to the drug set defined by the target. If the SEA score is relevant (below a specific threshold), it can be tested in vitro or confirmed in external databases that SEA did not view. 26% of newly discovered off targets had no sequence similarity to the drug’s known target. So similar targets don’t necessarily bind similar drugs, and a shift to a ligand based approach in which we think similar drugs behave similarly and bind to similar targets is more appropriate. Off target-ADR pairs were constructed from databases (getting counts and checking significance, also have info on drug-ADR pairs, pg 363-associating in vitro targets with ADRs). Drug-off target-ADR links were then formed (we have the drug-off target pairs from SEA). Links showed new connections of drug to ADR, which is interesting because known targets of drug are not associated with the ADR. SEA needs work, and it cannot yet replace traditional compound-target testing. The open question remains as to what would happen if we apply this method specifically to a subset of drugs and targets in neurodegeneration?

**2. Leveraging Large-scale Behavioral Profiling in Zebrafish to Explore Neuroactive Polypharmacology**

In vitro testing for discovering new drugs has its limitations, mainly because they merely confirm or deny target candidates. Phenotypic profiling and predictive multi-target enrichment from the Similarity Ensemble Approach (SEA) can help identify new compounds with complex polypharmacology in vivo. Especially for psychiatric drugs, therapeutic effects are often the result of multi-target actions. There are multiple ways of telling if two drugs yield similar phenotypic effect, like through comparing plots of motion vs time in zebrafish, clustering drugs on axes with specific pheontypes, and manual inspection (figure 2). From phenotypically similar drugs, we can look at their targets through SEA, and map phenotype to the set of targets (pathway). Joint enrichment factors are calculated to predict multiple targets potentially required for phenotype. This approach can help discover the complex pathways of neurodegeneration for my project.

**3. Propagation of prions causing synucleinopathies in cultured cells**

Many neurodegenerative diseases exhibit prion like behavior, including diseases like supranuclear palsy and multiple system atrophy. MSA prions exists in more than one strain. However, this does not currently hold for all neurodegenerative diseases, as attempts to demonstrate alpha synuclein prions in brain homogenates from Parkinson’s were unsuccessful. In mouse models, the researchers are able to induce prion like propagation of alpha synuclein, yet the mice do not exhibit neurological disease. This paper is useful in showing the type of protein aggregate screen data that is available and what we will be working on next quarter. Investigating the exact mechanism and why prions can propagate without inducing disease is still a mystery. Finding drugs that prevent aggregation can be a future direction, and discovering the underlying mechanism from effective drugs will be crucial to our understanding of neurodegenerative diseases.

**4. Zebrafish behavioral profiling identifies multitarget antipsychotic-like compounds**

Zebrafish phenotypic profiling when treated with different antipsychotic drugs can provide readouts that cluster by drug class (PhenoBlast). New unknown drugs can be screened phenotypically, and we can take this new phenotypic profile and check which class it is closest to. SEA can then take a drug class (of both known and unconfirmed drugs) and look at the targets of those drugs through a ‘guilt by association’ measure similar to the 2012 nature paper (first reference). We now have a drug class that induces a phenotype, and a set of corresponding targets that these drugs reach, which underscores the mechanism of action. A drug that they named finazine had similarities to the reference haloperidol, and was further investigated in *in vitro* tests and in mouse models. It showed similar target binding, and showed antipsychotic properties in mice given PCP. Open questions remain as to how reliable these results will be in humans since zebra fish are different. Also, further investigation into finazine remains a future direction.

**5. Evidence for α-synuclein prions causing multiple system atrophy in humans with parkinsonism**

Similar to the prion paper mentioned before (reference 3). It seems that alpha synuclein deposits from patients who had MSA are infectious and can induce propagation and central nervous system degeneration. It is odd though how alpha synuclein from Parkinson’s does not induce CNS damage or prion like propagation. Alpha synuclein prions can exists in different strains that have different biochemical implications. The prions are able to replicate to the same levels as the source (prions taken from human brain given to mouse generation 1-> mouse generation 1 prions given to mouse generation 2-> reached same levels as human brain level!). When attempting transfection of A53T mutant alpha synuclein into mice expressing human alpha synuclein or WT mouse alpha synuclein, transfection and CNS dysregulation did not occur (the A53T point mutation seems to be causal for infection). Future directions into how the strains are different and how these implications can carry over to humans remain. MSA as a prion disease in humans as opposed to mice is also a question to be answered.

1. Lounkine, E. et al. (2012) *Nature.* **486**, 361-367.
2. McCarrol, M. et al. (2016) *ACS Chem Biol*. **11**, 842-849.
3. Woerman, A. et al. (2015). *PNAS*. **35**, 4949-4958.
4. Bruni, G. et al (2016). Nat Chem Biol. **12(7)**, 559-566.
5. Prusiner, S. et al (2015). *PNAS*. 38, 5308-5317.