Slide 3 ##Epigenetics – Swathy & Banerjee

Here we have a portrayal of epigenetic modifications associated with pharmacology. It shows cellular activities from histone modifications, microRNAs and DNA methylation. There is crosstalk between the different mechanisms, and all have an important role in the etiology of major psychosis and medication response. DNA methylation, for our study, is covalent binding of a methyl group to the 5th carbon of a cytosines that sit adjacent to guanines. It is associated with alterations in gene regulation – and the aim of these studies is to understand the interface between antipsychotic treatment and genetic regulation.

Slide 4 ##Background - Psychosis

1. Symptoms:

* Hallucinations, delusions, loss of contact with reality
* Loss of insight into their condition – tough to accept treatment
* May manifest at different states of SCZ, BPD and MDD

1. Treatment:

* Antipsychotics first line of treatment and alleviate or reduce symptoms
* Long-term use associated with side effects

1. Biomarkers:

* Lack of knowledge about pathophysiology and mechanisms of drug action make this difficult.

Slide 5 ## Background Antisychotics

\* Mechanism: alterations in multiple neurotransmitter systems & genes <br> <br>

- GABA/Glutamate <br>

- Voltage-gated Calcium channels <br>

- Dopamine <br>

- Serotonin <br> <br>

\* Recent work suggests implications beyond synaptic biology [1,2]

- Efficient for hallucinations but less so for cognitive

Slide 6 ##EWAS findings for antipsychotics

1. Drug response-related DNAm remains poorly understood
2. Variety of methods, tissues assayed, study designs, sample sizes
3. Lack of consistency in reporting medication in Candidate gene & Genome-wide studies
4. Integration of genomic data and genome-wide DNAm data may be more effective – towards discovery of underlying drug response

Slide 7 ##GWAS findings

## Hypothesize

Common and specific

We hypothesize that differential DNA methylation associated with

AP drugs identified in the peripheral blood of individuals taking these drugs, independent of diagnosis

The focus of SCZ research has been on the dysfunction thought to underlie changes in network activity across the brain – in particular, the balance between excitatory and inhibitory signaling. Glutamate (excitatory). GABA (inhibitory)

Neuropsychiatric drugs are grouped into various classes with slightly different mechanisms of action.

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## Factors that influence the efficacy of AP

Age: Significant impact on drug concentrationmost studies show increased concentration above age 60, but some, like Olanzapine and Quetiapine show changes every 5 to 10 years.

Sex: Women generally have dose-adjusted concentrations 20-30% higher than men (Castberg et all, 2017)

- Age, gender, smoking <br> <br />

- Genotype - i.e. metabolic enzymes <br> <br />

- Polypharmacy <br> <br />

- Time of day of administration <br> <br />

- Dose & Compliance - as monitored by serum values

Regulation of drug responses occurs at various levels including genetics, epigenetics, transcriptional, and protein modification, and also involves many functional pathways ([Amare et al., 2017](https://www.frontiersin.org/articles/10.3389/fnins.2021.674273/full#B6))

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## TOP Cohort

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## Study/model design

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### Models selected for Quetiapine n=92

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### Results for CpGs at Genome-wide significance

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## Manhatten plots comparing the two models

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### Glycosylation

Regulates nearly all cellular processes

Glycans are necessary for proper protein folding, protein trafficking, cell-cell recognition, cell migration, etc. Gysosulation enzymes often function in a single pathway with only one or occasional a few enzymes capable of completing each step.

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### Disregulated glycosylation in SCZ

Presynaptic neuron in green, postsynapitic neuron in blue

In addition to genes involved in synaptic transmission and the immune system, several glycosulation enzymes are directly implicated in the pathogenesis of the disorder (Mealer, 2020)

Glycosulation may contribute to abnormal neuronal signaling and connectivity observed in SCZ. However, such changes may also results from exposures associated with the disease ((Williams, 2020)

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Glycosylation changes observed in SCZ span several brain regions, cellular pathways, classes of proteins, and steps of the synthetic pathway. This suggests a general dysregulation of glycosylation as a feature of the disease state and does not implicated a specific synthetic step or cell type as being uniquely vulnerable.

Articles in psychiatry. Williams and Mealer

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### GLT8D1 <br> - transcripts associated with SCZ and BPD

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Differentially Methylated Regions (DMRs) <br/>

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### Future prospects

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##Acknowledgements