

# Research Poster Awards 2023

## Network-based drug repurposing for schizophrenia

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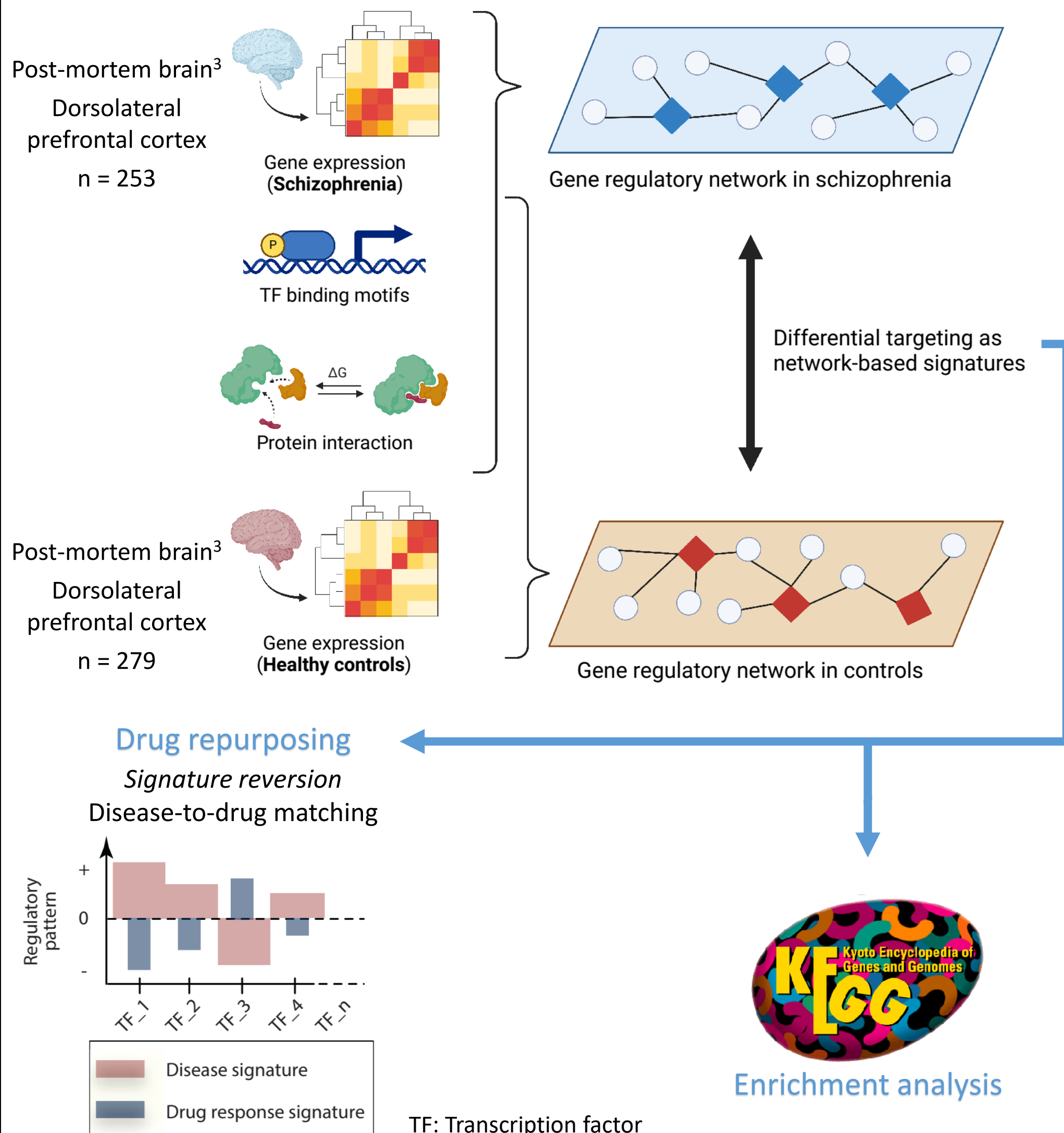
### INTRODUCTION

Despite recent advances, drug discovery for schizophrenia remains challenging. Computational drug repurposing is a promising new methodology utilising expanding biomedical databases. Network analyses allow the comprehensive assessment of transcription factor (TF) regulatory effects via gene regulatory networks, reflecting TF and target gene interactions by incorporating multiple lines of evidence<sup>1,2</sup>.

### OBJECTIVES

- To elucidate gene expression regulation driven by TFs in schizophrenia
- To repurpose drugs potentially targeting the TF-regulated aberrances in schizophrenia

### METHOD



### RESULTS

#### Significantly enriched KEGG pathways regulated by TF differential targeting

Enriched KEGG pathways are in blue at the bottom, grouped into 4 main functions at the top of the chord diagram. Pathways are ordered clockwise by p-value significance. Green links indicate increased targeting in schizophrenia, while red links show decreased targeting.



#### Top 5 repurposing candidates

Drug	Conditions	Known targets	Preclinical/clinical support
Alendronic acid	Approved: Osteoporosis, Paget's disease	Inhibitor: Farnesyl diphosphate synthase, Geranylgeranyl pyrophosphate synthetase	
Khellin	Phase II trial: Vitiligo Approved: Angina pectoris, Asthma	Inhibitor: Ca <sup>2+</sup> influx, Cytochrome P450 1A1 Activator: Aryl hydrocarbon receptor	
Rimonabant	Approved: Obesity Phase III trial: Arteriosclerosis, Fatty liver disease	Inverse Agonist: Cannabinoid CB1 receptor, Cannabinoid CB2 receptor	A 16-week double-blind randomized placebo-controlled trial in schizophrenia patients found an improvement in specific learning deficits, particularly in response to positive feedback <sup>4</sup>
Kaempferol	Preclinical: Cancer, Depression Phase II trial: Osteoarthritis	Inhibitor: Ribosomal protein S6 kinase alpha 5, DNA topoisomerase II, Monoamine oxidase A, Ribosomal protein S6 kinase alpha 3	Antipsychotic evidence on rat models of hippocampal damage and memory deficits via the activation of SIRT1 – a neuroprotective gene in schizophrenia <sup>5</sup>
Alizapride	Approved: Nausea and vomiting	Antagonist: Dopamine D2 receptor	

### DISCUSSION & CONCLUSION

Energy metabolism, immune response, cell adhesion, and thyroid hormone signalling are key pathways differentially regulated by TFs in schizophrenia cases compared to unaffected controls. Promising drug repurposing candidates, especially ones with preclinical/clinical evidence like rimonabant and kaempferol, show potential through these TF-targeted pathways. Further preclinical and clinical investigations are needed to explore their mechanisms of action and efficacy in alleviating schizophrenia symptoms.

### REFERENCES

1. Truong, T.T.; Panizzutti, B.; Kim, J.H.; Walder, K. Repurposing Drugs via Network Analysis: Opportunities for Psychiatric Disorders. *Pharmaceutics* 2022
2. Ben Guebila, M.; Lopes-Ramos, C.M.; Weighill, D.; Sonawane, Abhijeet R.; Burkholz, R.; Shamsaei, B.; Platig, J.; Glass, K.; Kuijjer, Marieke L.; Quackenbush, J. GRAND: a database of gene regulatory network models across human conditions. *Nucleic Acids Research* 2022
3. Hoffman, G.E.; Bendl, J.; Voloudakis, G.; Montgomery, K.S.; Sloofman, L.; Wang, Y.-C.; Shah, H.R.; Hauberg, M.E.; Johnson, J.S.; Girdhar, K.; et al. CommonMind Consortium provides transcriptomic and epigenomic data for Schizophrenia and Bipolar Disorder. *Scientific Data* 2019
4. Boggs, D.L.; Kelly, D.L.; McMahon, R.P.; Gold, J.M.; Garellick, D.A.; Linthicum, J.; Conley, R.R.; Liu, F.; Waltz, J.; Huestis, M.A.; et al. Rimonabant for neurocognition in schizophrenia: A 16-week double blind randomized placebo controlled trial. *Schizophrenia Research* 2012
5. Kaempferol protects against cadmium chloride-induced hippocampal damage and memory deficits by activation of silent information regulator 1 and inhibition of poly (ADP-Ribose) polymerase-1. *Science of The Total Environment* 2020