X-TREME-OMICS: A Novel Systems Biology Framework for Probing Genetically Complex Multisystem Disorders

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Genetically complex multisystem disorders (CMDs) affecting neonatal populations arise from coordinated regulatory interactions across genes, tissues, and organ systems, yet their underlying architecture remains inadequately characterized. Existing approaches identify disease-associated genes and local interactions but struggle to explain how these signals organize into coherent mechanisms across gene-phenotype relationships, tissues and model systems. While animal models capture key aspects of disease biology, they only partly reflect the heterogeneity and complexity of traits in human patients, limiting translational impact. To address this, I developed X-TREME-OMICS, a cross-species multi-omics framework for delineating genetic architecture underlying complex disease aetiology, aligned with systems biology perspectives. At its core, X-TREME (X-Species Transformer for Regulatory Embedding and Manifold Extraction) is a novel deep learning architecture that integrates single-cell RNA sequencing data from multiple model organisms, while accounting for species-specific functional divergence, to generate a unified cross-species embedding.The model learns biologically consistent representations and enables identification of key elements. Benchmarking analyses indicate that X-TREME outperforms existing methods in cross-species alignment and consistency. Finally, applying the XTREME-OMICS to complex congenital heart diseases identified master regulators and revealed coordinated patterns that suggest a shared systems-level organization. Altogether, X-TREME-OMICS enables a comprehensive understanding of the transcriptomic architecture of CMDs by dissecting their heterogeneity and complexity, while identifying high-confidence targets for preclinical therapeutic development.

Awards Won:

Zydus Pharmaceuticals USA Inc.: Third Place Computational Biology and Bioinformatics