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NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

Study Design Abstract Results The comparison between the generated transcriptomic 2. Higher (the higher the better) cosine similarities were **Training Set** Animal studies are required for the evaluation of candidate drugs to TransorGAN profiles and the real profiles on the test set using three observed for the transcriptomic profiles inferred from male 63,504 pair-wised ensure patient and volunteer safety. Toxicogenomics is often samples (252 rats) to female (Figure 4). Similar results were observed for the methods (cosine similarity, RMSE, and UMAP) demonstrated applied in these studies to gain an understanding of the underlying 64,800 pair-wised the utility of TransOrGAN in inferring transcriptomic profiles transcriptomic profiles inferred from adolescent to younger samples (288 rats) mechanisms of toxicity, which is usually focused on critical organs • 9 Organs Transcriptomic profiles & conditions from one organ to another (Figure 3). and older ages (Figure 5). o 2 Sexes such as the liver or kidneys in young male rats. There is a strong 4 Development stages ethical reason to reduce, refine and replace animal use (the 3Rs), Generated Set Test Set \triangle Real \bigcirc Generated where the mapping of data between organs, sexes and ages could 1,296 pair-wised 1,296 pair-wised Lng ____ Compare p < 0.001 samples (36 rats) samples (36 rats) reduce the cost and time of drug development. Herein, we propose Spl 🖉 a generative adversarial network (GAN)-based framework entitled TransOrGAN study design. The 64,800 pairwise transcriptomic Figure 1 profiles between organs under different sex and developmental stage TransOrGAN that allows the molecular mapping of gene expression conditions were divided into training and test sets. The 63,504 pairwise profiles in different rodent organ systems and across sex and age transcriptomic profiles were used to develop TransOrGAN. TransOrGAN was groups. We carried out a proof-of-concept study based on rat RNAthen used to generate the 1,296 transcriptomic profiles in the test set. The ControlGenerated □ Control □ Generated seq data from 288 samples in 9 different organs of both sexes and generated transcriptomic profiles were then compared to the real Msc 4 developmental stages. First, we demonstrated that TransOrGAN Cross organ Within organ Within orgai Cross organ transcriptomic profiles to evaluate the model performance. p < 0.001 $M \rightarrow F$: Sex hormone-related genes M –> F: Full gene sets could infer transcriptomic profiles between any two of the 9 organs Figure 4 Translating transcriptomic profile from male to female with studied, yielding an average cosine similarity of 0.984 between Model update **TransOrGAN.** The cosine similarity distribution of the generated group synthetic transcriptomic profiles and their corresponding real NoiseTarget condition and control on two categories: within organ and cross organ. (A) Full gene profiles. Second, we found that TransOrGAN could infer Profile Generator Transcriptomic enhance sets (i.e., 40,064 genes); (B) Sex hormone-related genes (i.e., 19 genes). profile transcriptomic profiles observed in females from males, with an representation average cosine similarity of 0.991. Thirdly, we found that Figure Translating profile representation TransOrGAN could infer transcriptomic profiles in juvenile, adult, Top 5 and bottom 5 pathways profile transcriptomic and aged animals from adolescent animals with an average cosine Infectious disease Transcriptomi Generated eks to Organelle biogenesis and maintenance profile with transcriptomic similarity of 0.990, 0.991, and 0.991, respectively. Altogether, . 40064 features Cellular responses to stress older representation Gene Expression developmental stages TransOrGAN is an innovative approach to infer transcriptomic Transcriptional Regulation by TP53 Training se GPCR downstream signaling with TransOrGAN. The profiles between ages, sexes, and organ systems, offering the Real transcriptomic Neuronal System GPCR ligand binding similarity cosine opportunity to reduce animal usage and to provide an integrated Class A/1 (Rhodopsin–like receptors) distribution the Neuroactive ligand-receptor interaction Generated assessment of toxicity in the whole organism irrespective of sex or generated group and 🔲 Noise 6 -> 21 6 -> 104 Generated 6 -> 2 age. Target condition Franscriptomi

Introduction

Animal models are required for drug safety evaluation and risk assessment. Systemic toxicity considers toxicity on all organs that pose a risk. However, the multiple organ toxicological study is animal-consuming and labor-intensive. To advance the 3Rs principle, we propose TransOrGAN to infer transcriptomic profiles between different organs, ages, and sexes.



TransOrGAN: An Artificial Intelligence Mapping of Rat Transcriptomic Profiles Between Organs, Ages, and Sexes

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Figure 2 Overview of TransOrGAN Model. A transcriptomic profile with 40,064 genes was first fed into an encoder, and the output of the encoder (transcriptomic profile representation) combined with source organ condition (age, sex, organ, stage), target organ condition (age, sex, organ, stage), and noise as an input to the generator. The generated transcriptomic profile representation is compared with the transcriptomic profile representation of the target organ with the discriminator. The discriminator provided feedback to the generator for improvement. The process is iterative until no further updates are made, yielding the TransOrGAN model. In model validation, a transcriptomic profile with 40,064 genes was fed into the encoder, and the output of the encoder (i.e., transcriptomic profile representation) was combined with source organ condition (age, sex, organ, stage), target organ condition (age, sex, organ, stage), and noise as an input to the TransOrGAN model. The output (generated transcriptomic profile representation) was fed into the decoder to get the generated transcriptomic profile with a total 40,064 genes.

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Figure 3 The performance of TransOrGAN on the test set: (A) The root mean square error (RMSE) of the control (real transcriptomic profile vs. real transcriptomic profile) and generated group (generated transcriptomic profile) vs real transcriptomic profile); (B) The cosine similarity of the control and generated group; (C) The uniform manifold approximation and projection (UMAP) plot for the real and generated transcriptomic profiles; (D) The distribution of cosine similarity of the top 5 and bottom 5 among 87 toxicity pathway-related gene sets and one gene ontology term.

Conclusion

- TransOrGAN could infer transcriptomic profiles from one organ to other organs (except brain), from male to female, and from adolescent stage to younger and older ages.
- TransOrGAN offered a framework to gain understanding of toxicological mechanisms using toxicogenomics at the systemic level with testing only on a few organs and animals.

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control among group three categories: 6 -> 2 indicating from 6 weeks to 2 weeks; 6 -> 21 indicating from 6 weeks to 21 weeks; 6 -> 104 indicating from 6 weeks to 104 weeks. (A) Within organ (i.e., liver); (B) Cross organ (i.e., liver to kidney)

<u>Reference</u>: Li, Ting, Ruth Roberts, Zhichao Liu, and Weida Tong. "TransOrGAN: An Artificial Intelligence Mapping of Rat Transcriptomic Profiles between Organs, Ages, and Sexes." Chemical Research in Toxicology (2023).

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