Boehringer Ingelheim

# Advancing Toxicology in Drug Discovery using Generative Adversarial Networks – Part II

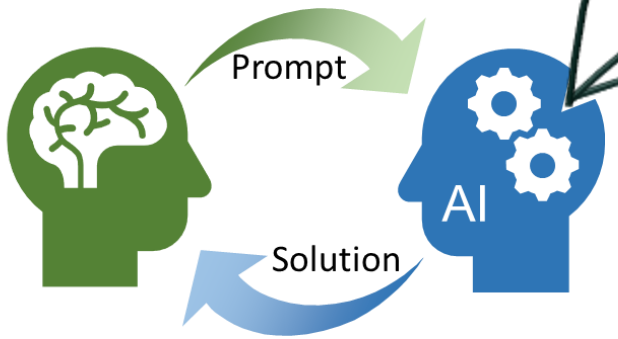
Zhichao Liu, Ph.D.

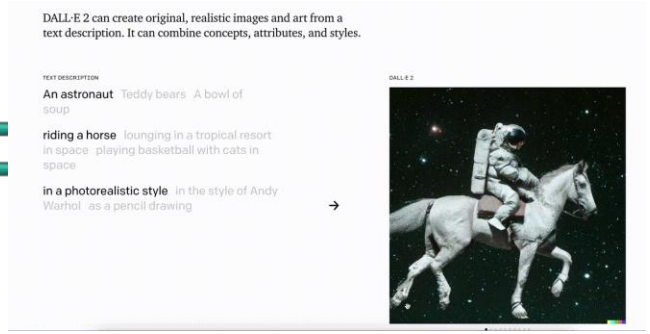
Nonclinical Drug Safety, Boehringer Ingelheim Pharmaceuticals, Inc.



*Life forward*

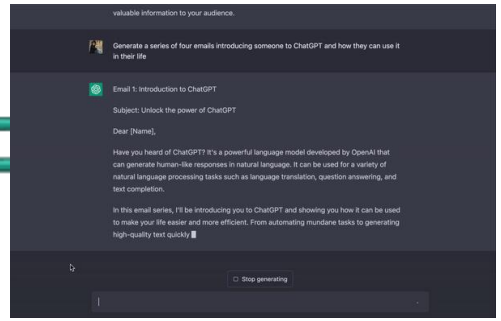
# Generative AI (GenAI)




**Heterogeneous data translation**

- DALL E3
- Stable Diffusion
- Midjourney
- **GANs**




**Large language models (LLMs)**

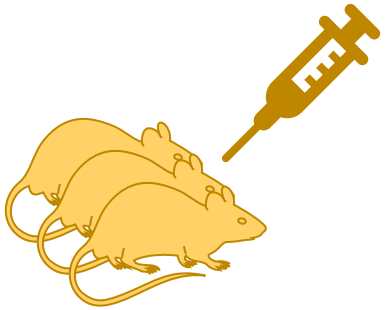
- GPT3/ChatGPT/GPT4
- BARD
- Claude 2
- LLaMA
- Llama 2
- …

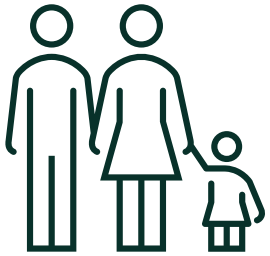
**Computer Vision**

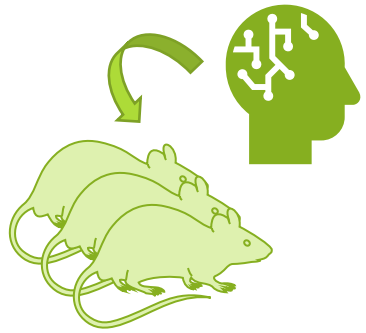
- Meta-AI Segment Anything Models (SAMs)

Boehringer Ingelheim

# Exploring the Use of GAN Models in Generating Animal Testing Results







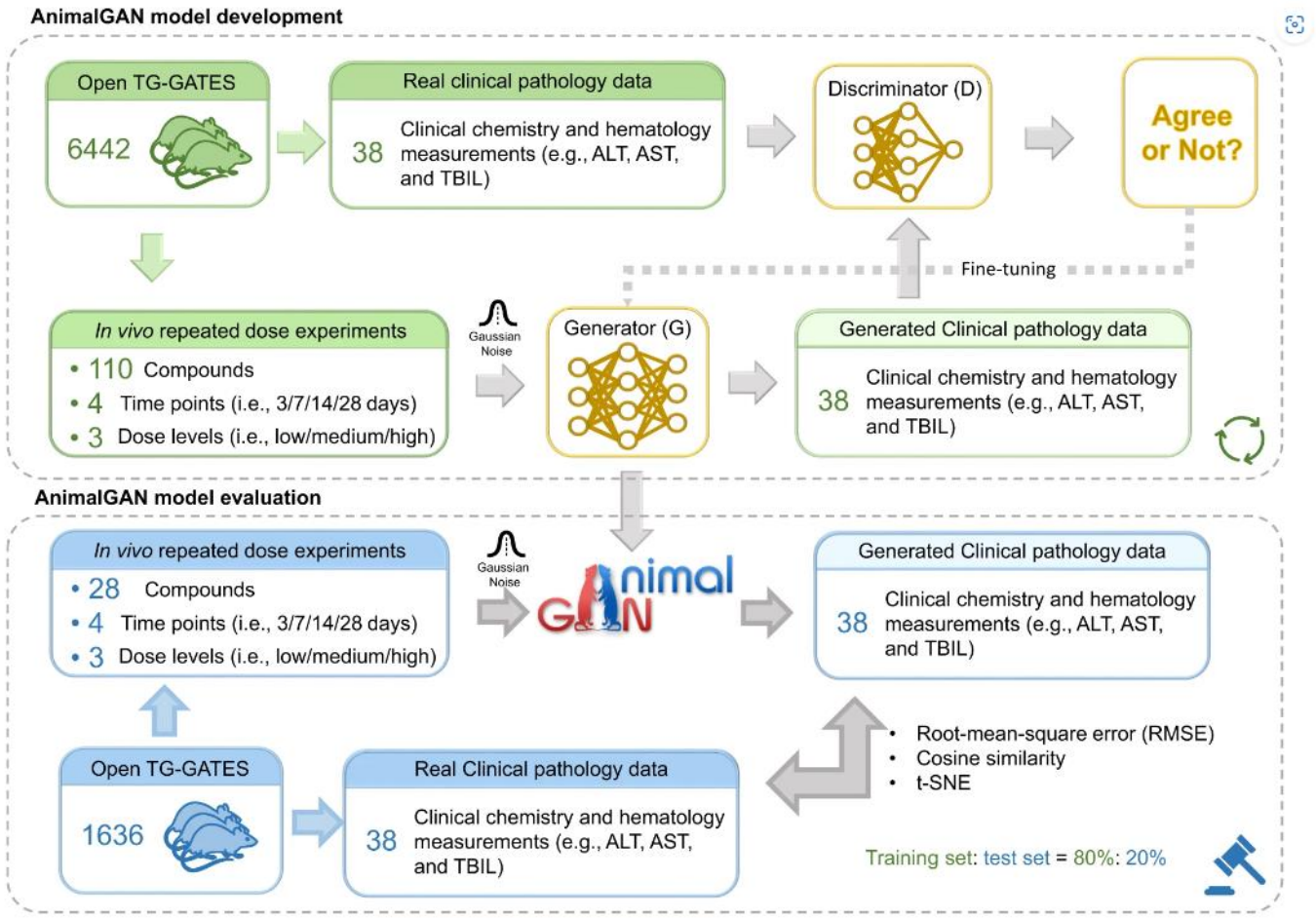
**Animal testing**

**GAN-based Virtual animal testing**

- Disparate animal species and strains
- Variability in animals for study
- Small experimental groups
- Selection of outcome measures
- Variable duration of follow up

- Learning distribution of data to generate the new data with same characteristics
- Data augmentation
- Versatility
- Improvement over time

Boehringer Ingelheim




## Input of Generator (3556-length vector)

***1828-lengthTreatment condition vector***

- Compound: Mordred descriptor (1826-length)
- Time: 3/7/14/28 days (1-length)
- Dose: low/middle/high - 1:3:10 (1-length)

***1828-length Gaussian Noise***: mimic animal variance

## Input of discriminator (1866-length vector)

- 38 real and generated clinical pathology data
- 1828-lengthTreatment condition vector

## Normalization matters

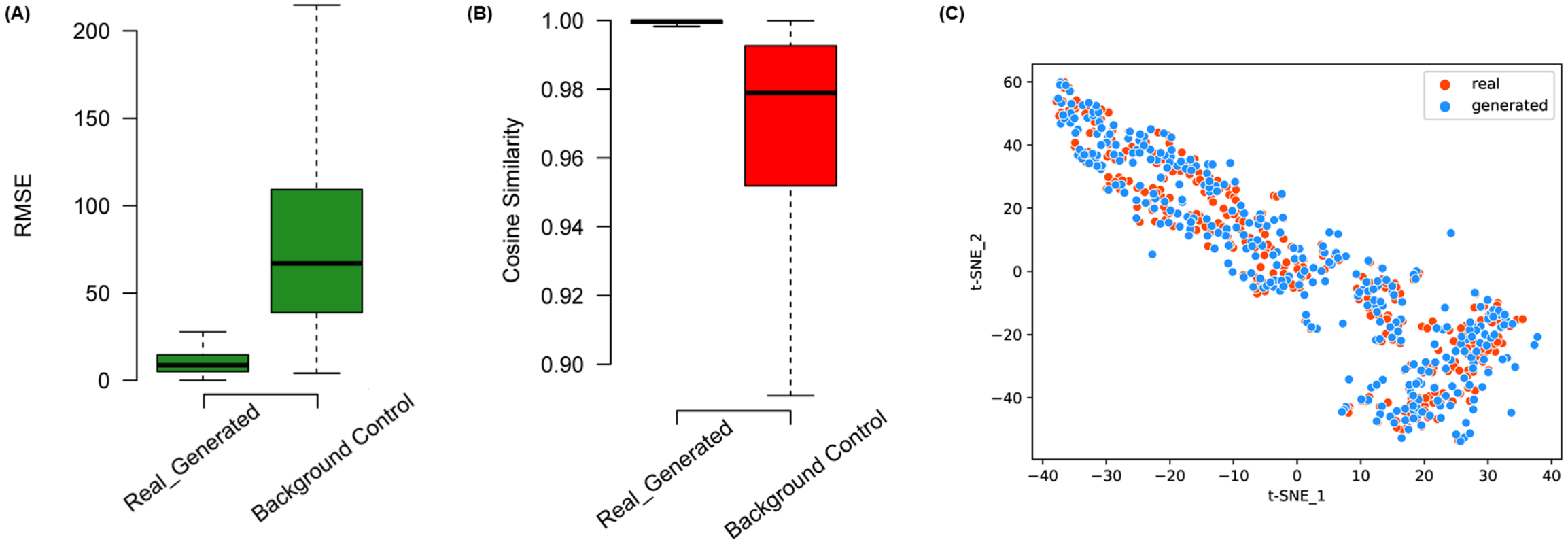
- [-1,1] for both generator and discriminator

## “invalid records” check:

- White blood cells (WBCs) are composed of neutrophils, eosinophils, basophils, monocytes, and lymphocytes, so the total percentages of each type of WBC should not exceed 100%.
- Cut-off: 105% by taking system errors into consideration

Boehringer Ingelheim

# High Concordance between Real Data and Generated Data

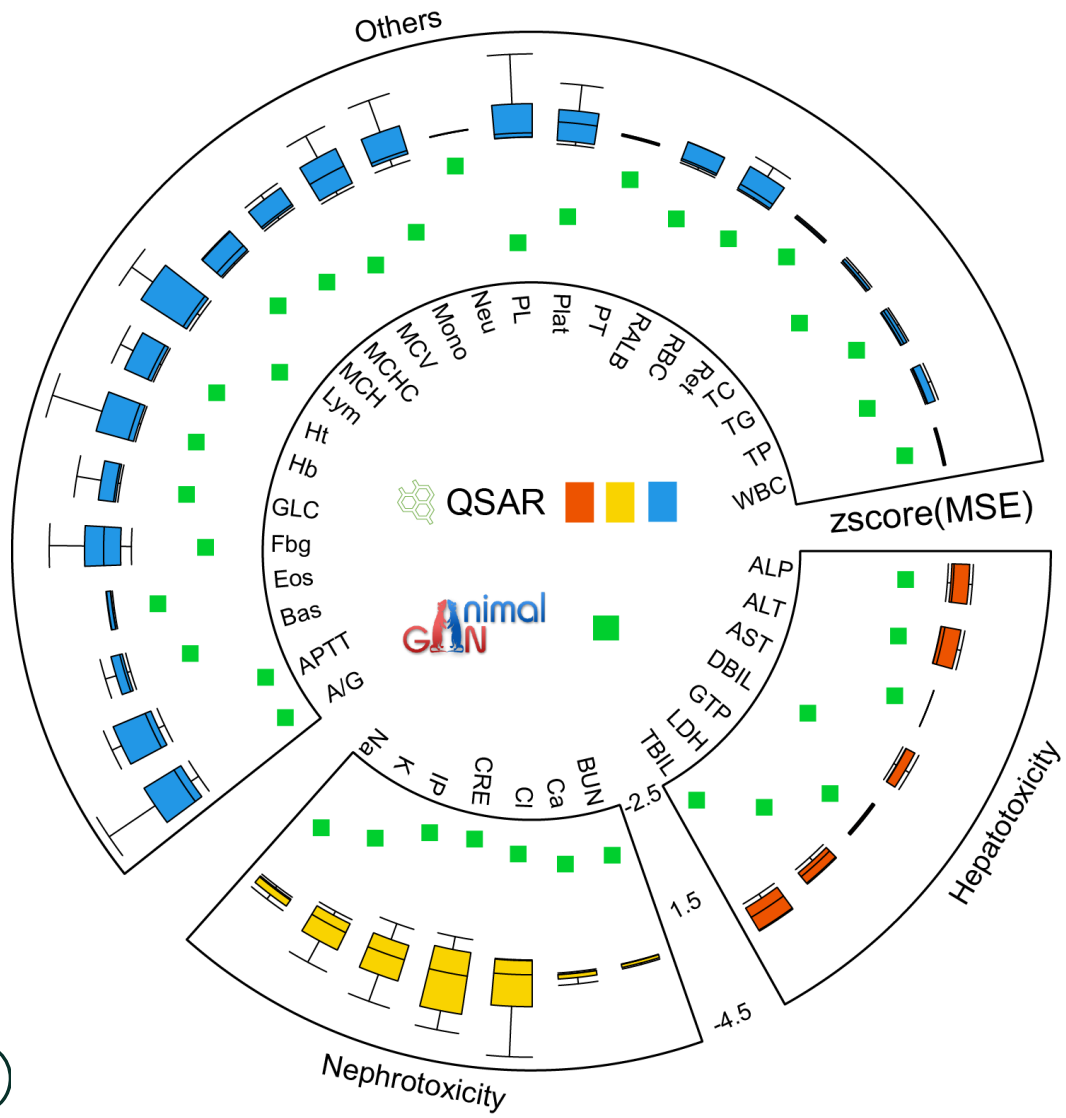



Boxplot of (A) RMSE - Root Mean Square Error, (B) Cosine Similarity between generated data and their corresponding animal testing data in the test set, and (C) t-SNE plot of test set.

**Average 100 generated clinical pathology measures that passed "invalid records" check were used!!!**

Boehringer Ingelheim

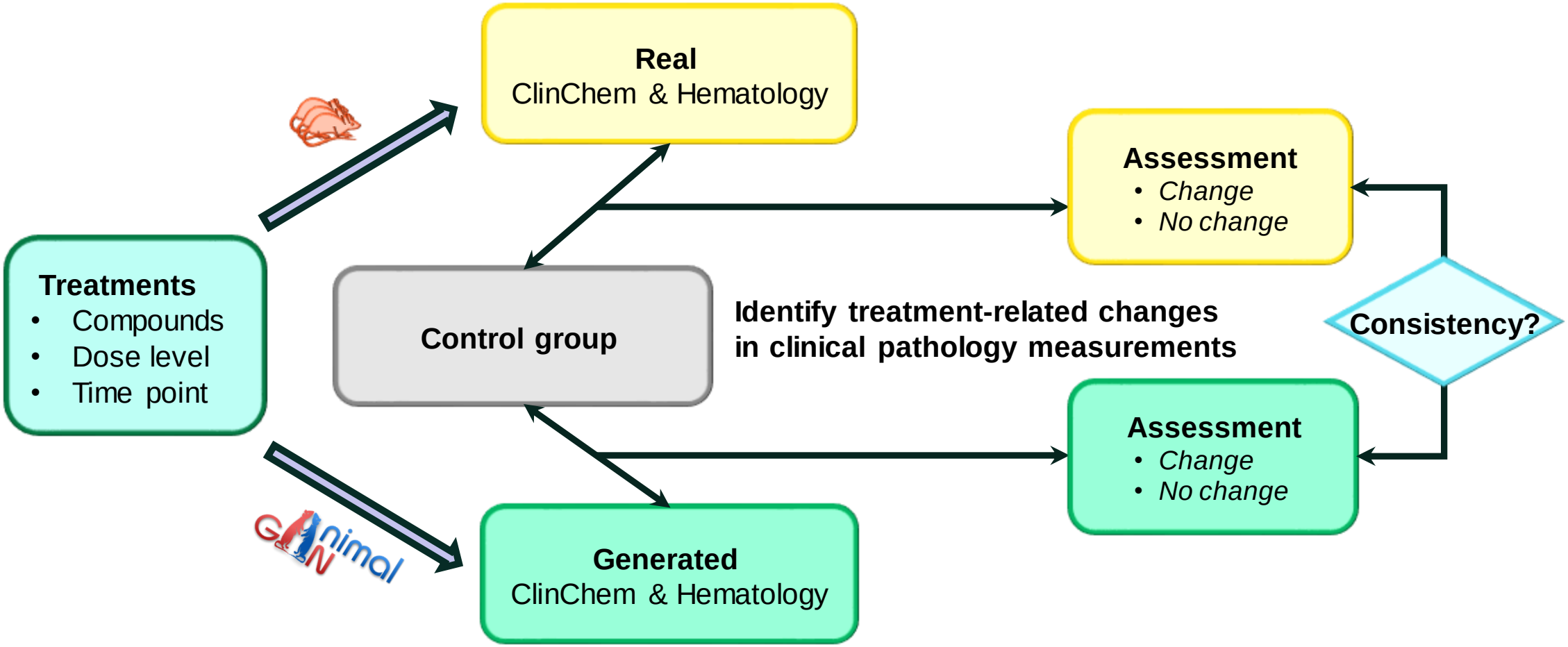
# AnimalGAN vs. QSAR model




**QSARs**

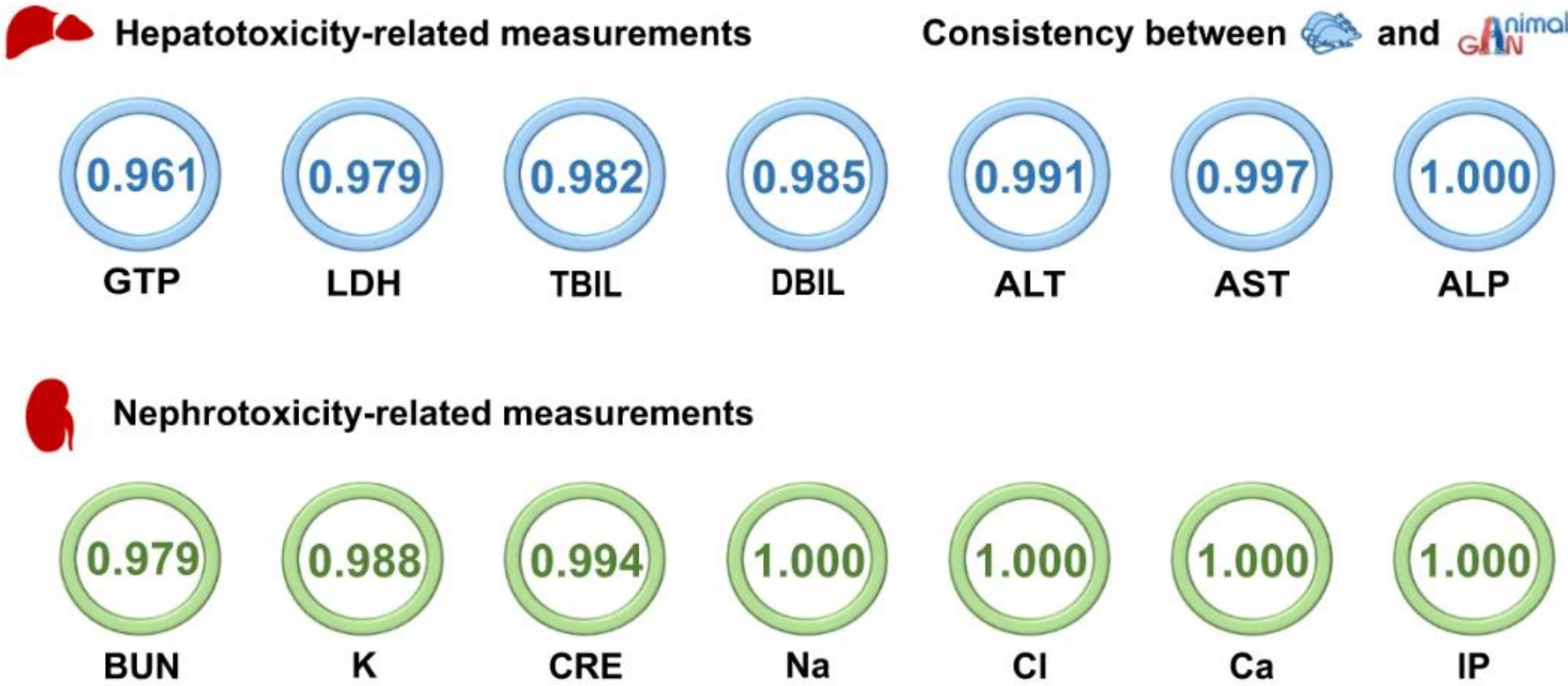
- 12 regressors (i.e., k-nearest neighbors, decision tree, extremely randomized tree, random forest, epsilon support vector regression, linear support vector regression, stochastic gradient descent, AdaBoost, gradient boosting, Bayesian ARD regression, Gaussian process regression and multi-layer perceptron)
- 5-fold cross validation for hyperparameter optimization – same training set

# A Framework to Evaluate Consistency on Toxicity Assessment



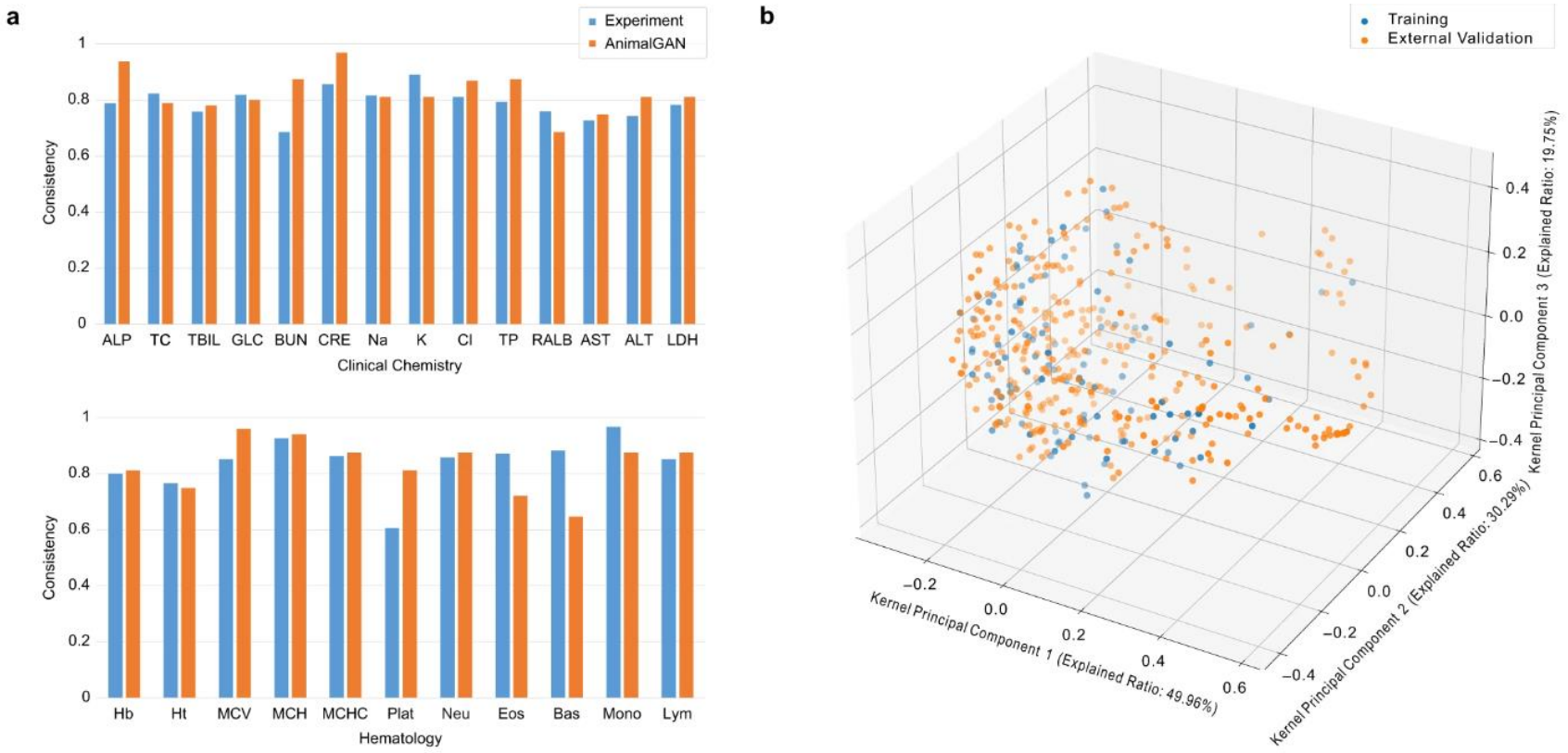

Boehringer Ingelheim

# High Consistency Between Real and Generated Results for Hepatotoxicity and Nephrotoxicity-related Clinical Pathology Measurements




Boehringer Ingelheim

# External validation with DrugMatrix




- 70 common compound (175 treatment) for baseline: 81.20%
- 355 external validation (717 treatment condition): 82.85%

**Criteria for validation set**

- Same rat strain and sex
- A similar repeated dose study design as TG-GATEs
- Common compounds tested by TG-GATEs to establish a baseline in comparison
- Contained clinical pathology measurements that significantly overlapped with those tested by TG-GATEs.

Boehringer Ingelheim

# AnimalGAN for iDILI Detection – Enhancing the Statistical Power of Small Experimental Groups through Data Augmentation with AnimalGAN

| Criteria | Troglitazone | Pioglitazone | Rosiglitazone |
|---|---|---|---|
| **ALT>ULN** | 1230 | 1820 | 1467 |
| **AST>ULN** | 7413 | 4315 | 4591 |
| **TBIL>ULN** | 3421 | 2083 | 2215 |
| **ALT>ULN or AST>ULN, and TBIL>ULN** | **375** | **161** | **158** |

The number of rats exhibiting drug-induced liver injury estimated by AnimalGAN for the three thiazolidinediones under the 28-day study with high dose in 100,000 rats

Boehringer Ingelheim

# Potential Improvement and Context of Use

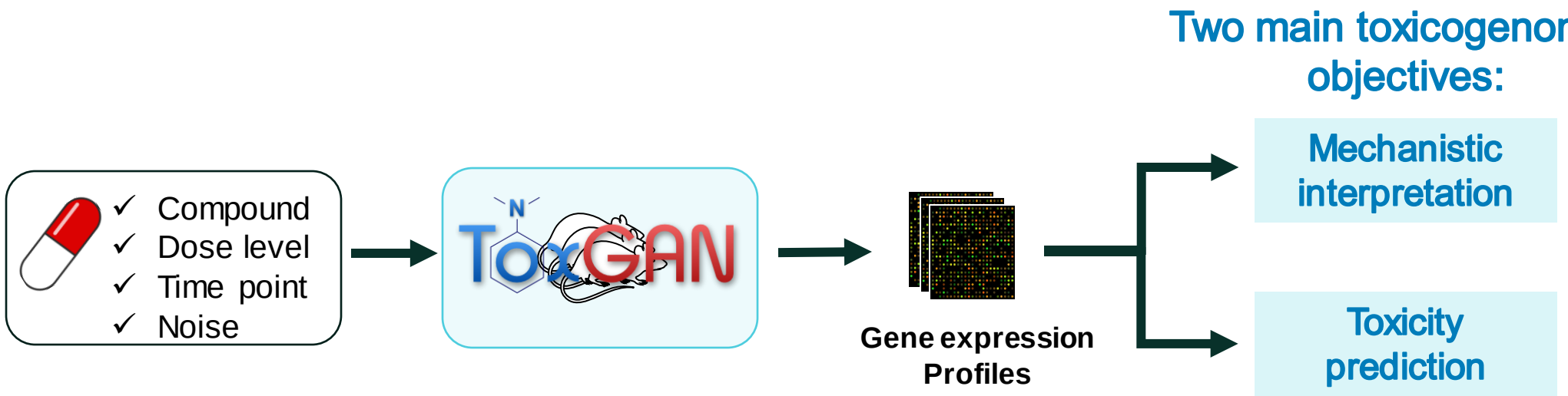
| Problems | Potential improvement |
|---|---|
| Input (compounds descriptor 1826 + dose 1 + time + 1) | Strategies to emphasize the wight of dosage<br>• Embedding-based representation<br>• Attention is all you need<br><br>Chemical descriptors matter?<br>• Chemical embedding from large chemical-based language models |
| Controls (matched control in TG-GATEs) | How to deal with new compound without matched control?<br>• Toward implementing virtual control groups in nonclinical safety studies (PMID: 38043132) |
| Model architecture | How to adjust loss functions are more for toxicology applications?<br>• Adjust Loss function + biological-based criteria |
| Data sets | How to develop more robust AnimalGAN model?<br>• SEND data |

**Context of Use**

- Experiment design specific model – repeated dose experiment design of Open TG-GATEs
- AnimalGAN is particularly suitable for screening purposes, excelling in the detection of toxicology signals and iDILI

Boehringer Ingelheim

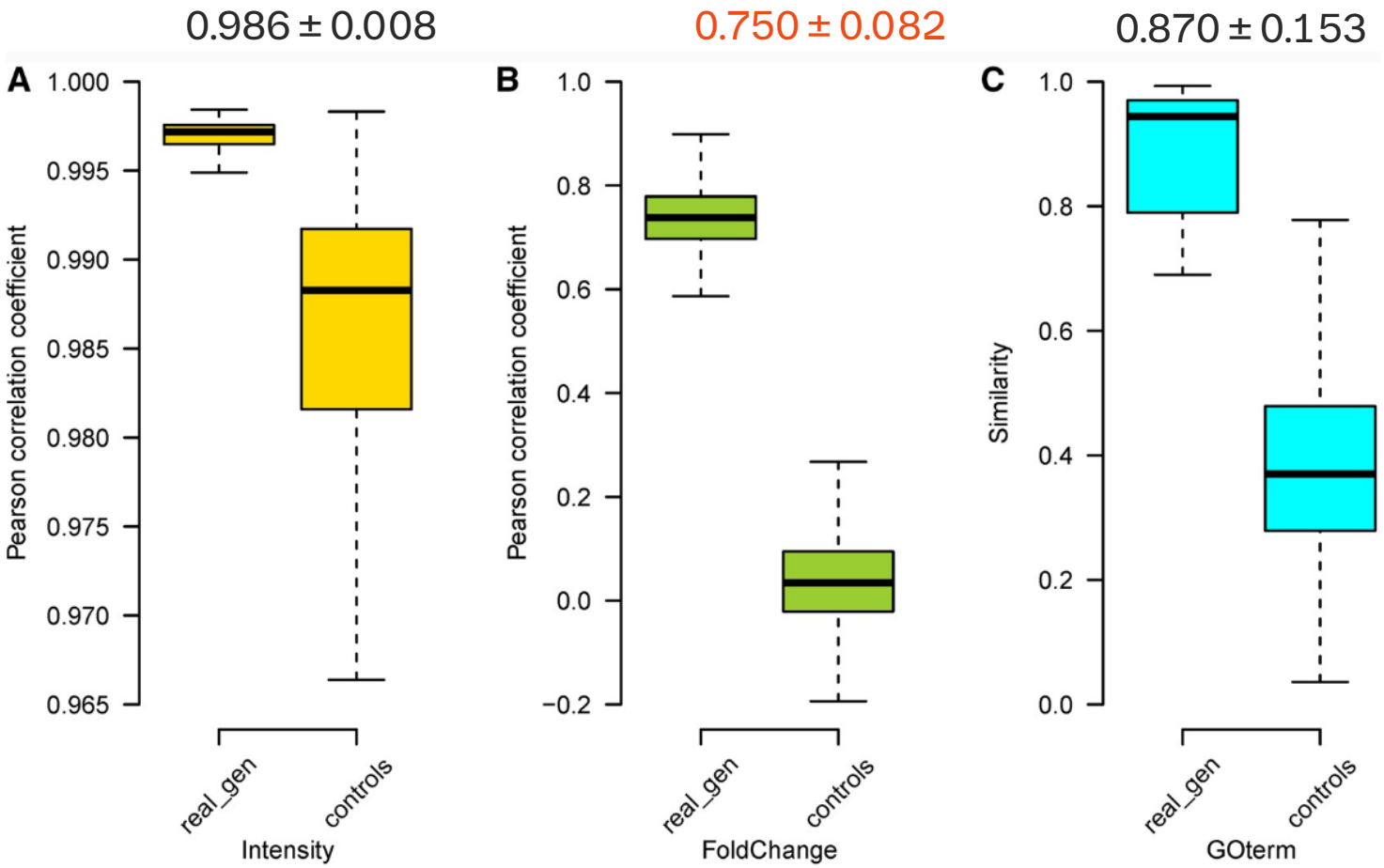
# ToxGAN for Toxicogenomics




Boehringer Ingelheim

Toxicological Sciences 186 (2), 242-25, 2022

# Concordance between Real Data and Generated Data

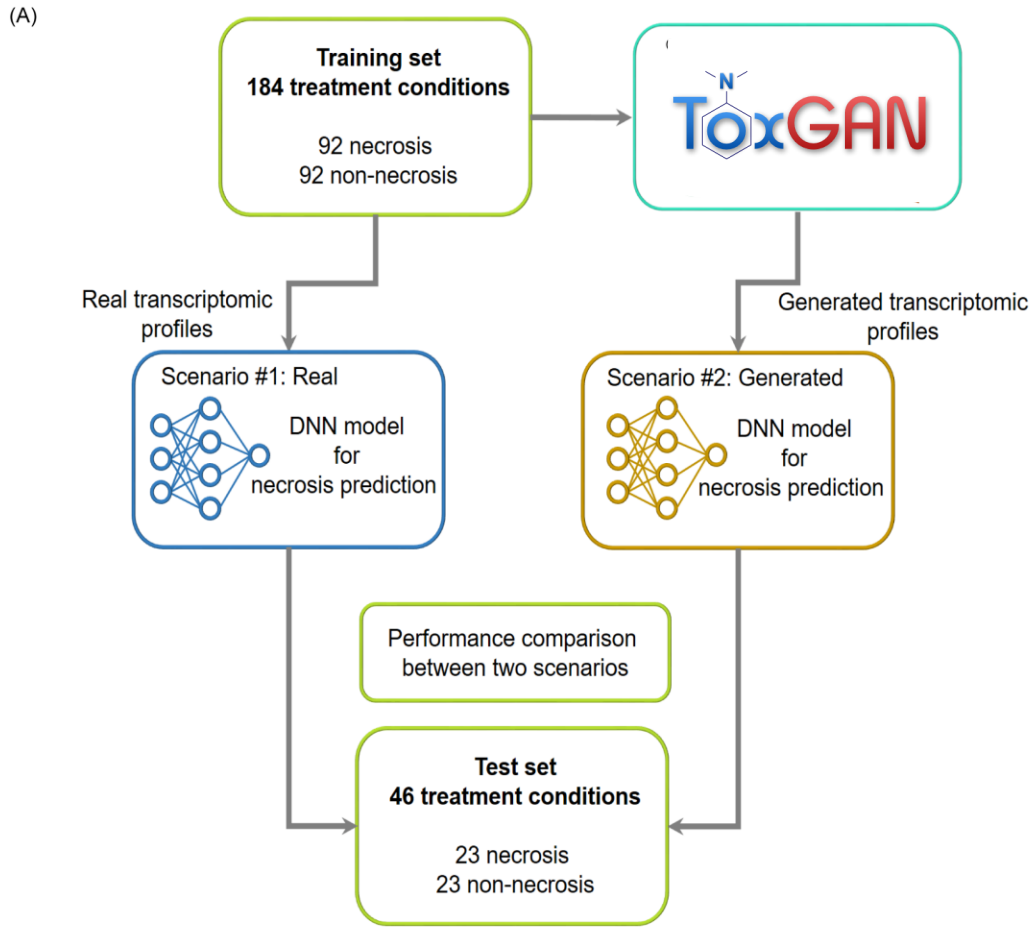


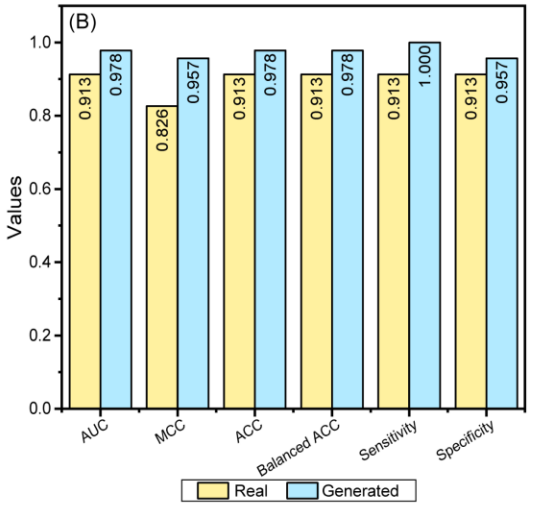

- High concordance in the intensity level
- Suboptimal concordance in fold change level
- Acceptable concordance in the functional level

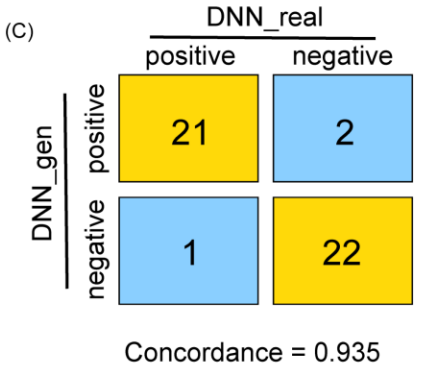
Boehringer Ingelheim

# #1: ToxGAN for Biomarker Development

**Q1: Can ToxGAN generate a reliable biomarker?**



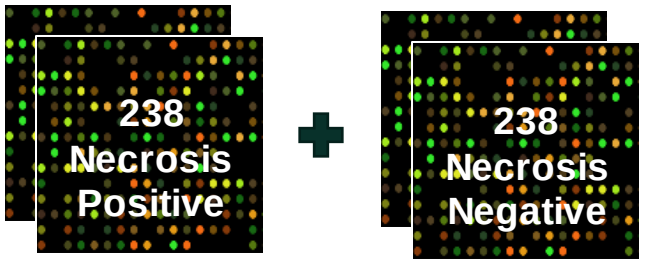




Concordance = 0.935

Boehringer Ingelheim

# #2: ToxGAN for Biomarker Application




Develop a model (biomarker) for necrosis with real gene expression data

Deep Neural Networks

**Necrosis biomarkers**

**Q2: How well an existing biomarker perform on ToxGAN data for screening purpose?**

**Test set:** 336 Treatments (Cmpd, dose, time)

***Microarray "real" data***

***generated data***

| Data | Real | Generated |
|---|---|---|
| Accuracy | 0.73 | 0.79 |
| MCC | 0.43 | 0.60 |

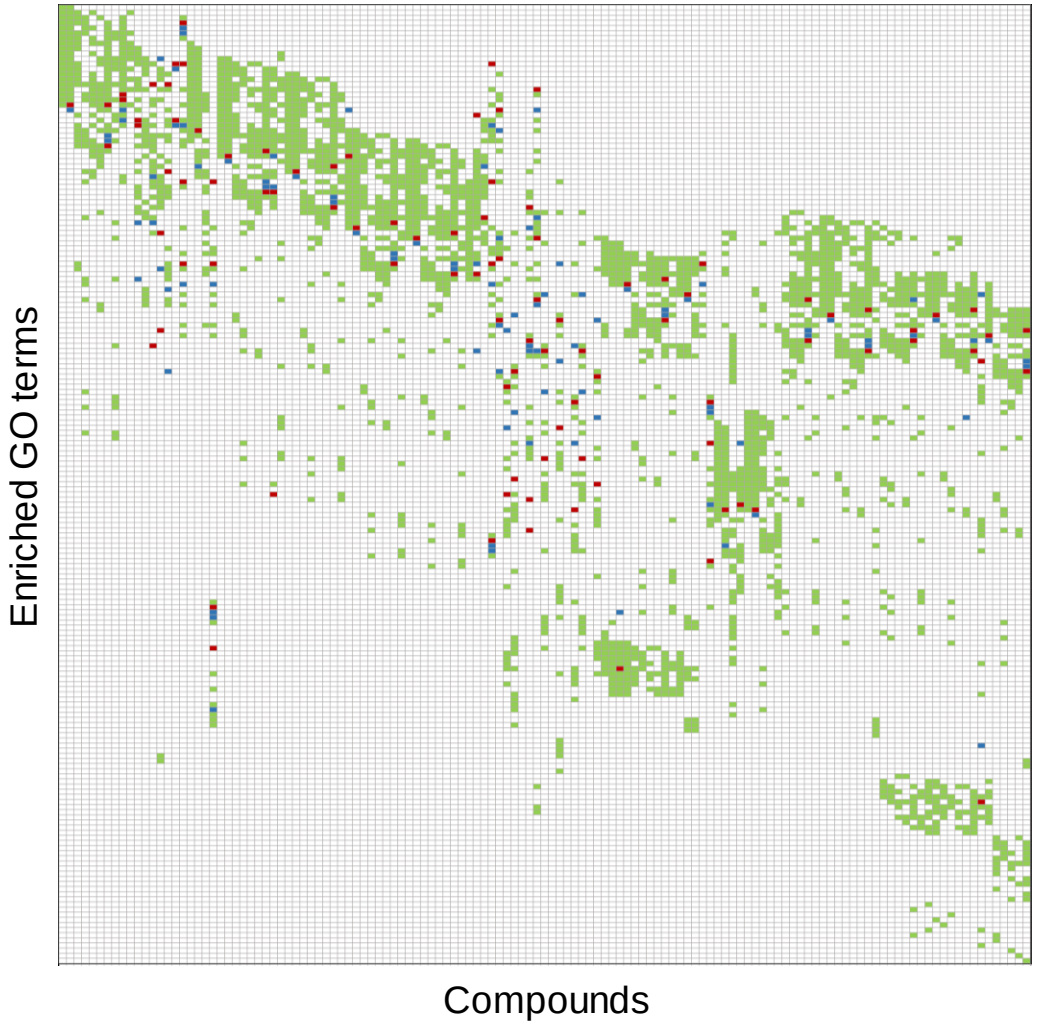
Boehringer Ingelheim

# ToxGAN Recapitulated Significant GO Terms

**Study Design:** to compare significant GO terms from gene expression data in 28-day repeated dose studies:

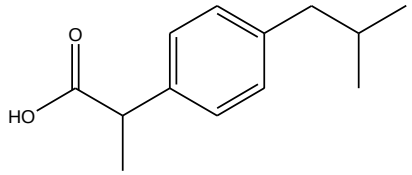
- Real data from microarray exp
- ToxGAN generated data

**Findings: GO concordance between real and generated gene expression profile were high**

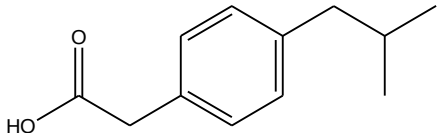



Boehringer Ingelheim

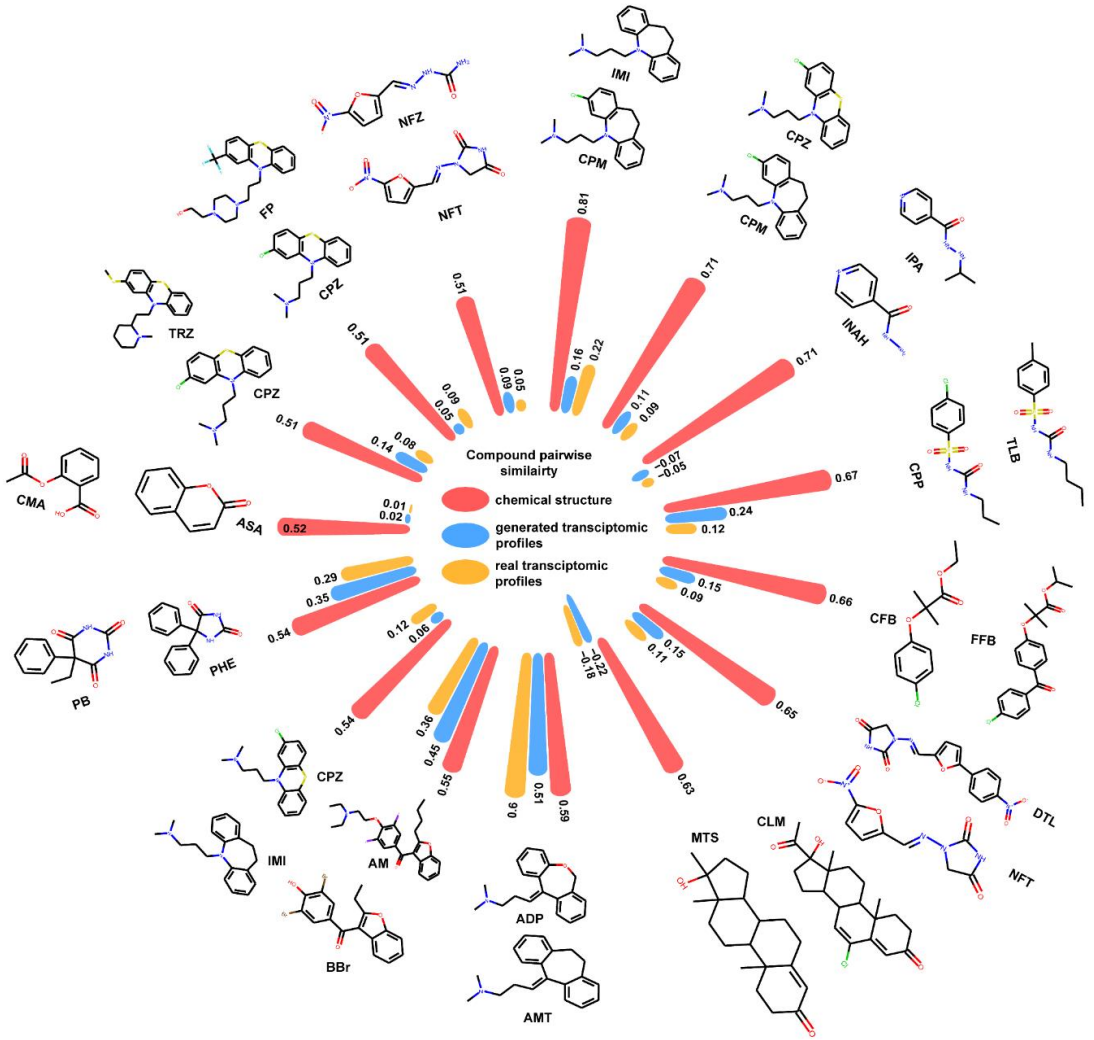
# ToxGAN for Improved Read Across




**Ibuprofen** – OTC drug
On the market >30 yrs with not much hepatotoxicity




**Ibufenac** – withdrawal
Marketed in 1966 and withdrawn in 1968 due to hepatotoxicity (no facts given). Late study demonstrated elevated ALT in 12/36 patients and jaundice in 5/400 cases




Boehringer Ingelheim

# Potential Improvement and Context of Use

| Problems | Potential improvement |
|---|---|
| Input (compounds descriptor 1826 + dose 1 + time + 1) | Strategies to emphasize the wight of dosage<br>• Embedding-based representation<br>• Attention is all you need<br><br>Chemical descriptors matter?<br>• Chemical embedding from large chemical-based language models |
| Suboptimal performance of TG-GAN$_{fold_change}$ | • Extra bias taken from autoencoder<br>• Biological variance is enlarged in fold change level |
| Model architecture | How to adjust loss functions are more for toxicology applications?<br>• Adjust Loss function + biological-based criteria |
| Data sets | How to develop more robust ToxGAN model?<br>• LINCS data |

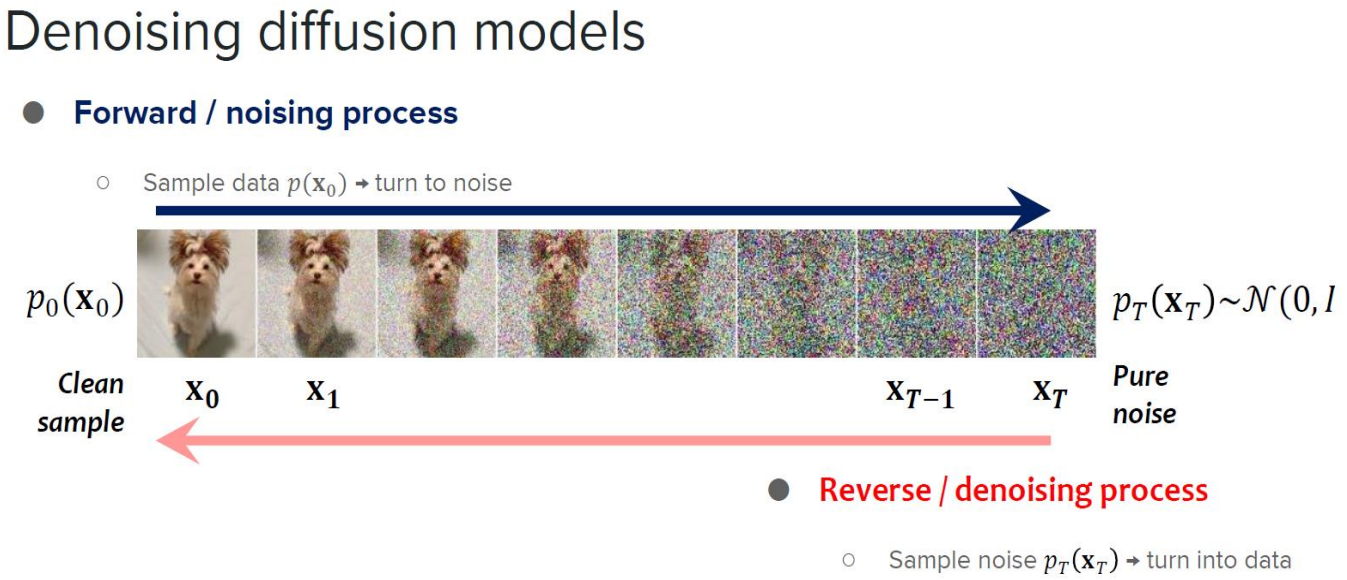
**Context of Use**

- Experiment design specific model – repeated dose experiment design of Open TG-GATEs
- ToxGAN is particularly suitable for (1) genomics-based prediction model; (2) biological data-based ReadAcross; and (3) Initial prioritization of key functions or AOPs

Boehringer Ingelheim

# Take-home Messages

- No one-fit-all AI solution – context of use
- Position different GAN models into specific toxicological questions
- Beyond GANs – Diffusion models??




Boehringer Ingelheim

# Acknowledgement


**NDS US**
- Charles Wood
- Matthew Bogdanffy

**FDA/NCTR**
- Weida Tong
- Xi Chen
- Ting Li

**External Collaborators**
- Ruth Roberts (ApconiX and U of Birmingham at UK)
- Scott Auerbach (NIEHS)

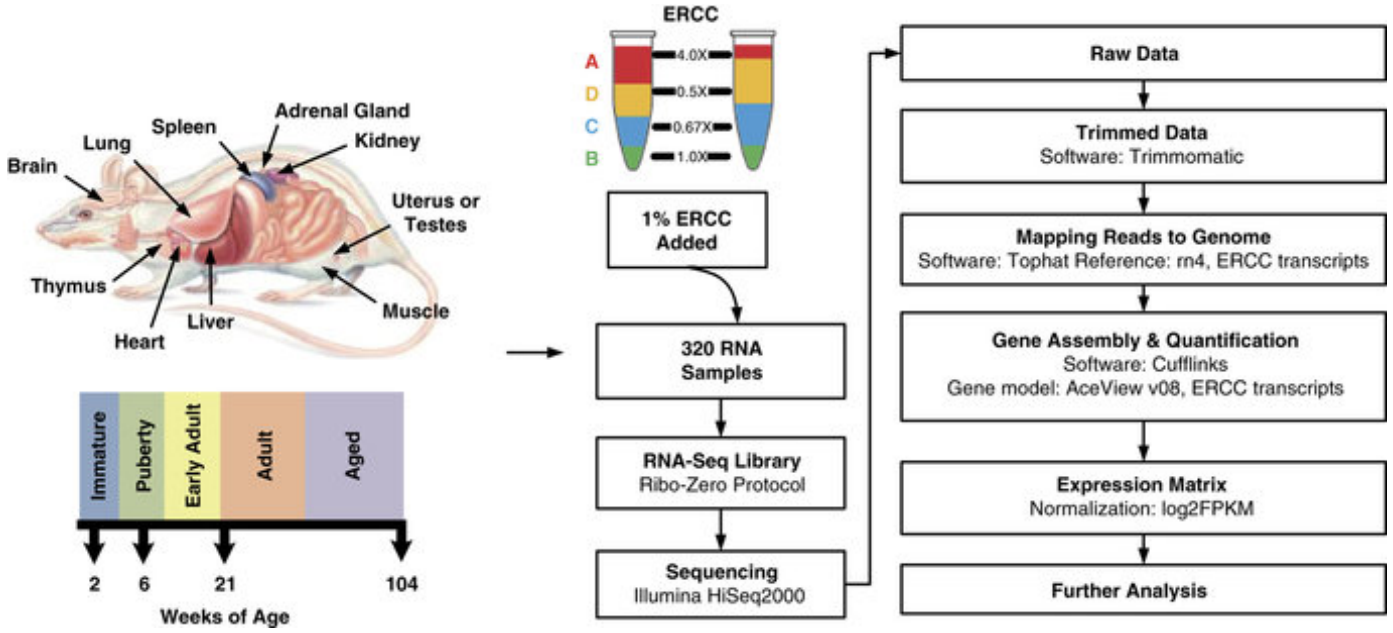


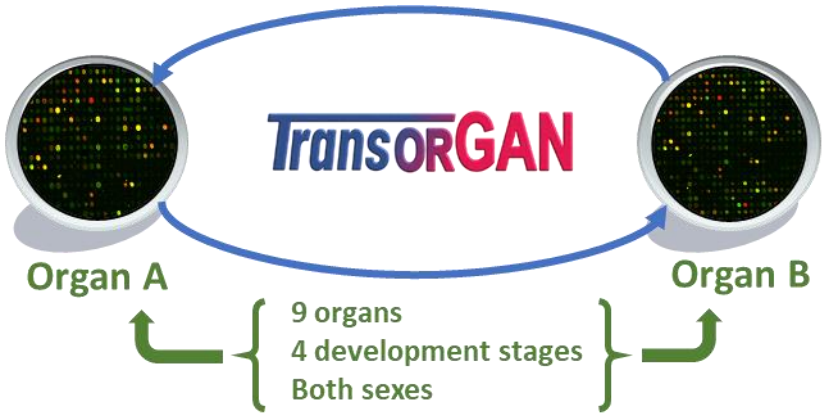
Boehringer Ingelheim


Boehringer Ingelheim

# Backups

# TransORGAN Mapping of Rat Transcriptomic Profiles Between Organs, Ages, and Sexes

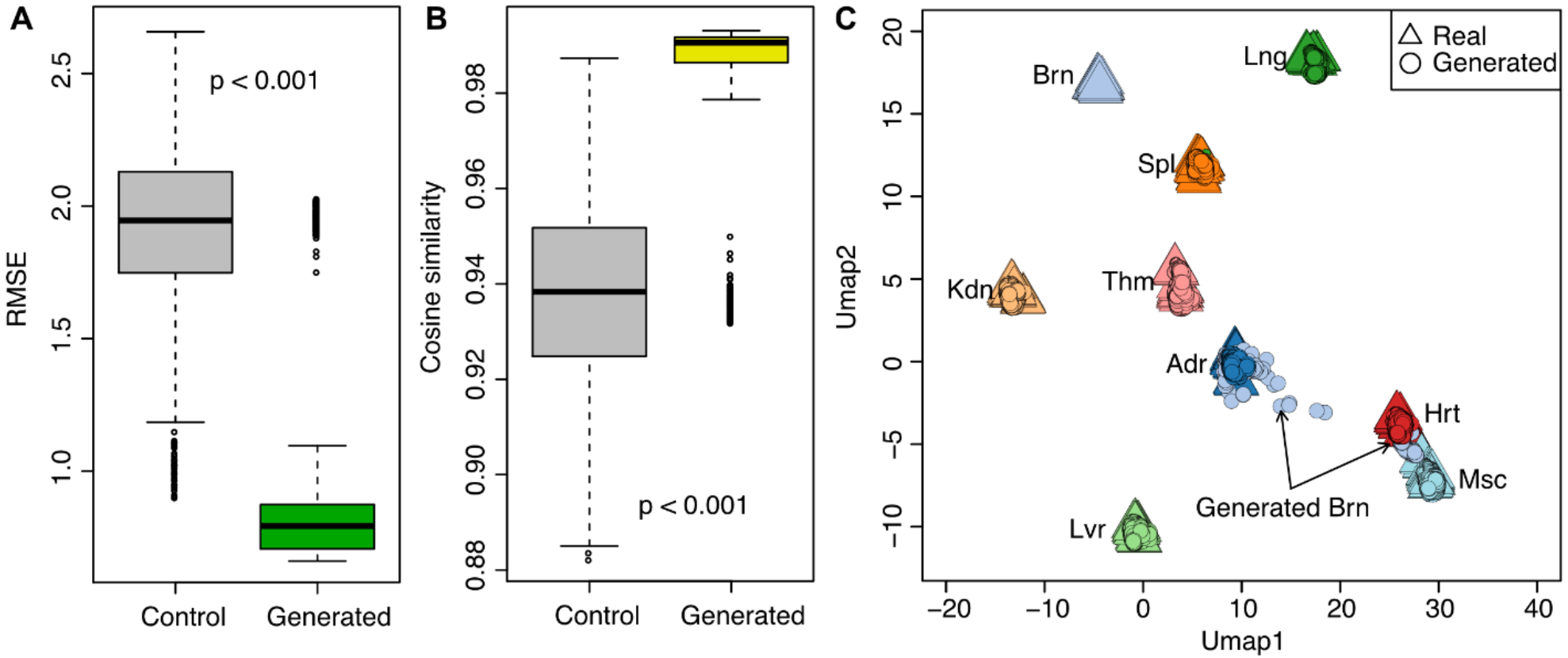



Rat BodyMap: Nature Communications volume 5, 3230 (2014)

Boehringer Ingelheim

# TransOrGAN could Translate Transcriptomic Profiles from One Organ to Another




Boehringer Ingelheim