Generative AI (GenAI) for Toxicology and Drug Safety

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Disclaimer: The views expressed are of the presenter and should not be considered as the official position or policy of U.S. FDA.

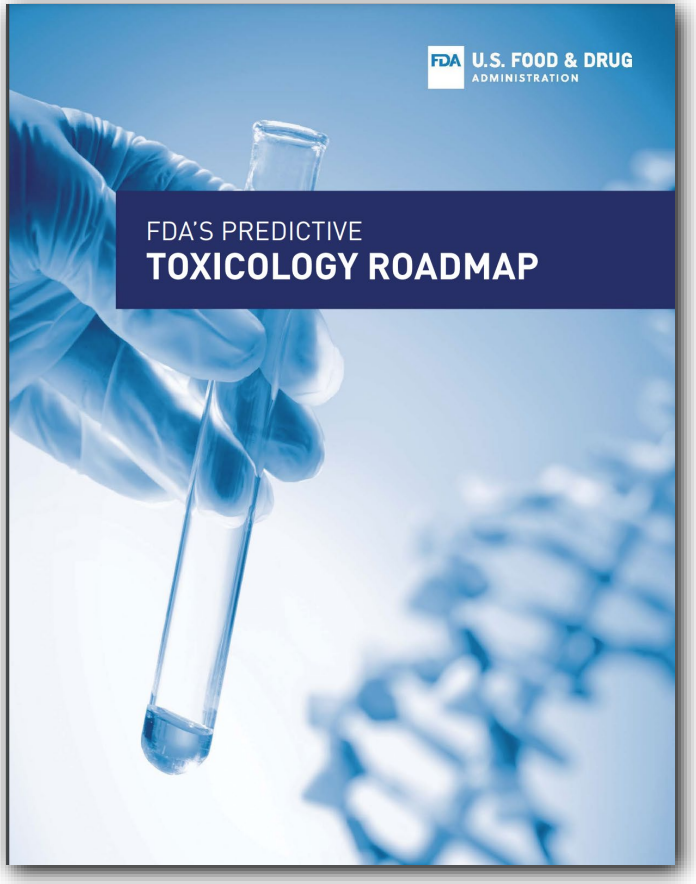
The Paradigm Shift in Toxicology

- Global community has been promoting the 3Rs principle of reducing, refining and replacing animal uses by evaluating diverse NAMs in toxicological research and even for regulatory consideration, e.g., MPS, *in vitro, in silico (*AI/ML).

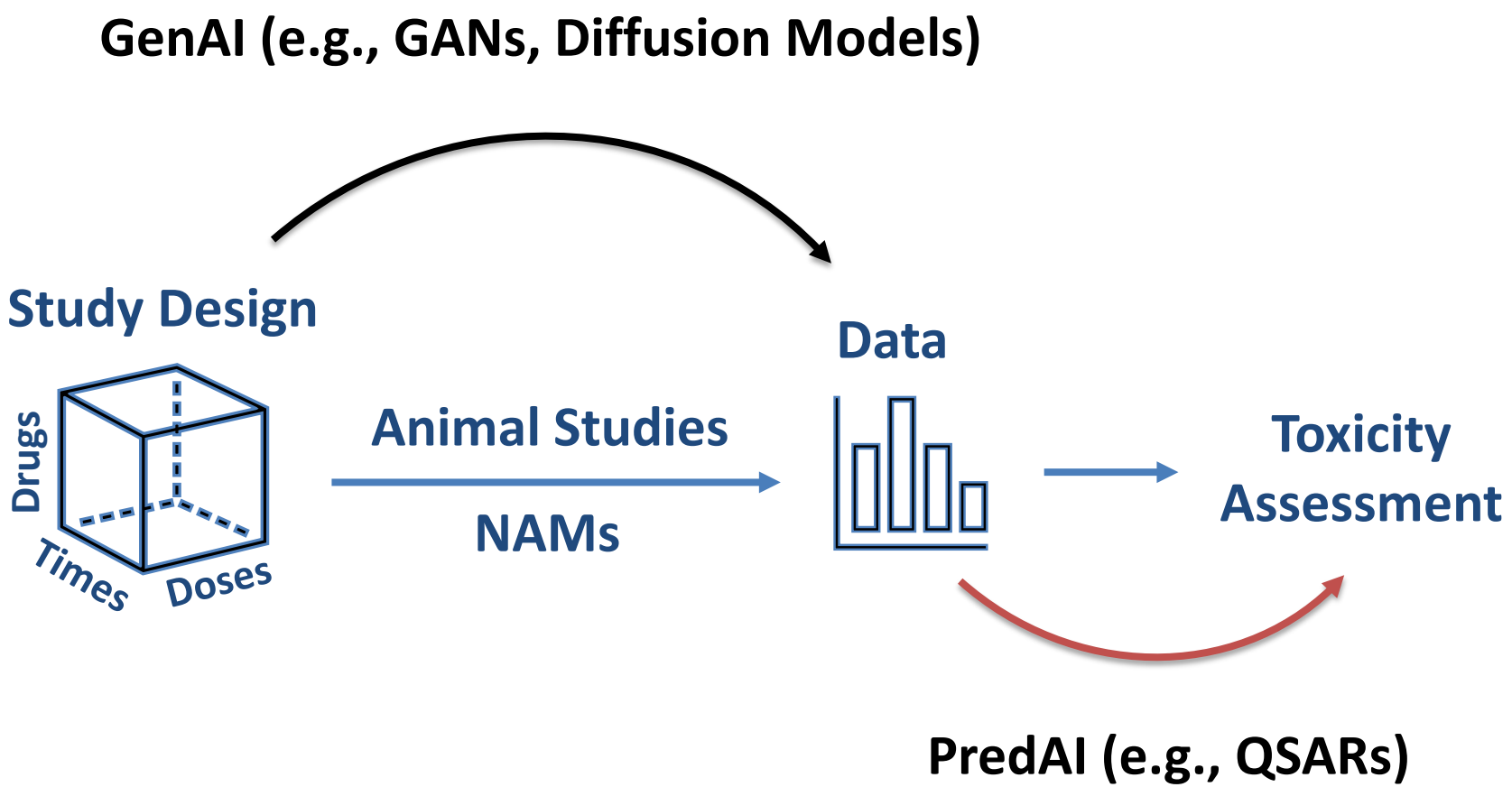
- The FDA Modernization Act 2.0 has been signed into the Law by the President; it urges the adoption of alternative methods to advance 3Rs science of animal use.

- FDA Predictive Toxicology Roadmap promotes the role of NAMs and alternative methods to support regulatory science and application.

- FDA ISTAND program (Innovative Science and Technology Approaches for New Drugs) qualifies the new tools to support drug discovery and development.

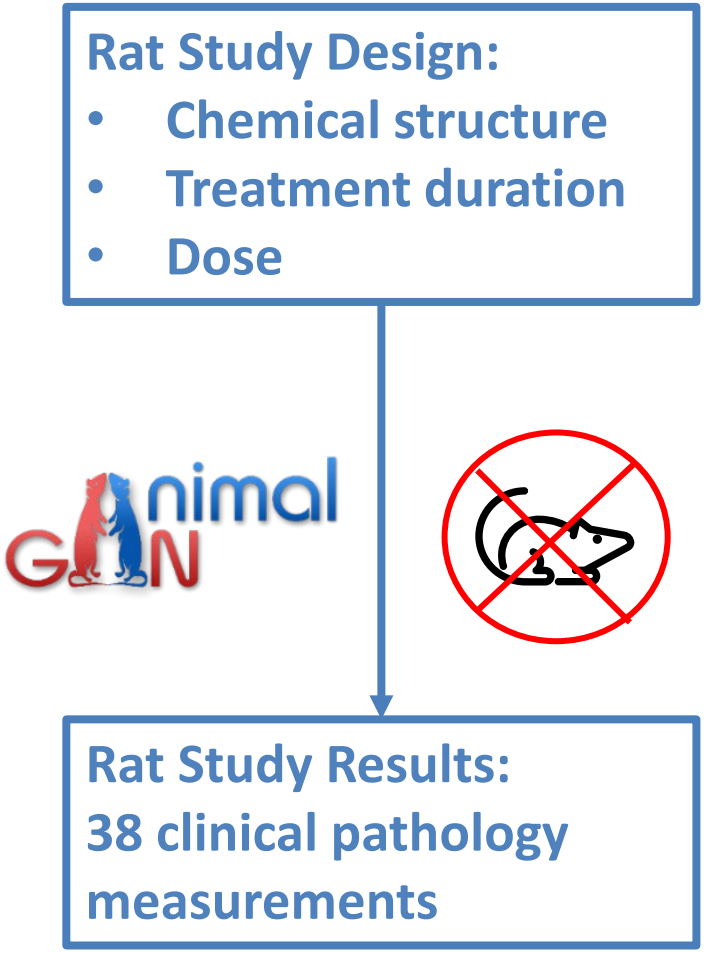


Generative AI vs Predictive AI



Virtual Animal models to Generate Animal Study Results with Generative AI

- **Why?** Animal studies assess safety of consumer products, but they are expensive and can pose ethical concerns. Can AI learn from past animal study data to generate animal study results of new untested compounds without using animals?
- **How? AnimalGAN** was developed using a Generative Adversarial Networks (GANs) framework (a DeepFake algorithm) to learn from the legacy animal data to produce new animal data *without using animals*.
- **Impact:** AnimalGAN can aid in assessing animal toxicity, potentially reducing or replacing animal testing in specific contexts.



Chen X., Liu Z., and Tong W. **A Generative Adversarial Network Model Alternative to Animal Studies for Clinical Pathology Assessment**. *Nature Communications*. 2023, 14, 7141.

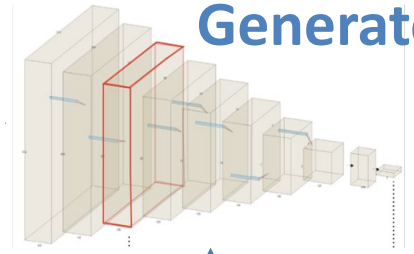
A GAN Framework for Animal Study

Input:
Rat was treated by APAP at high dose in 28 days

Real Test Results

Discriminator

Generator



Synthetic Results

Input:
Rat was treated by xxx drug at xxx dose and xxx days

Animal GAN

Synthetic results for new chemicals

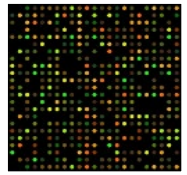
Proof-Of-Concept Studies with TG-GATEs Data

Study Design
- 138 compounds
- 3 doses (L/M/H)
- 5 rats per group

Repeated dose studies in SD rats

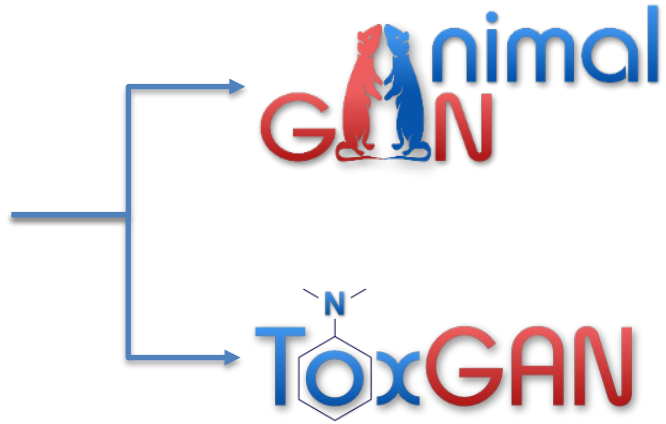
0 3d 7d 14d 28d

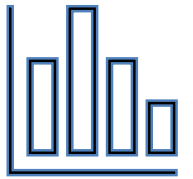
38 clinical pathology measures



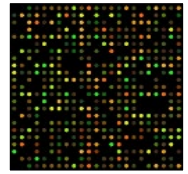
Gene expression profiles

A new compound
- Chemical descriptors
- Dose (L, M, or H)
- Time (3d, 7d, 14d, or 28d)





38 clinical pathology measures



Gene expression profiles

17 Hematologic measures

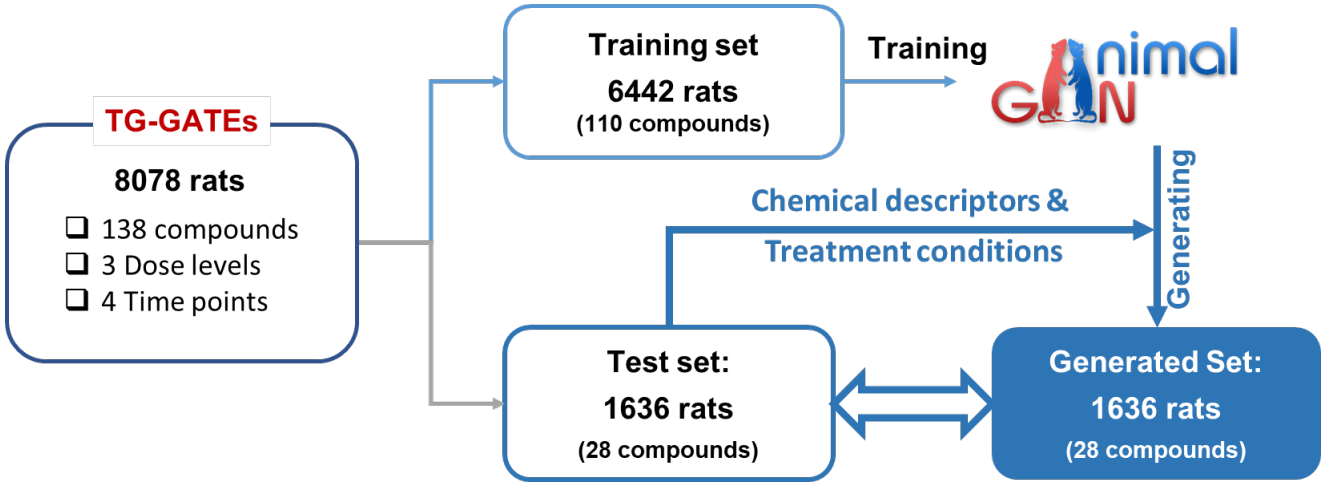
Short Name	Full name
RBC(x10_4/ul)	Erythrocytes
Hb(g/dL)	Hemaglobin
Ht(%)	Hematocrit (%)
MCV(fL)	Mean corpuscular volume
MCH(pg)	Mean corpuscular hemaglobin
MCHC(%)	Mean corpuscular hemaglobin concentration
Ret(%)	Reticulotcytes
Plat(x10_4/uL)	Platlets
WBC(x10_2/uL)	Leukocytes
Neu(%)	Neutrophils
Eos(%)	Eosinophils
Bas(%)	Basophils
Mono(%)	Monocytes
Lym(%)	Lymphocytes
PT(s)	Prothrombin Time
APTT(s)	Activated Partial Thromboplastin Time
Fbg(mg/dL)	Fibrinogen

21 Clinical Chemistry

	Short Name	Full name
Hepatotoxicity	ALP(IU/L)	Alkaline phosphatase
	TBIL(mg/dL)	total bilirubin
	DBIL(mg/dL)	direct bilirubin
	AST(IU/L)	aspartate aminotransferase
	ALT(IU/L)	Alanine aminotransferase
	LDH(IU/L)	Lactate Dehydrogenase
	GTP(IU/L)	Gamma-glutamyltranspeptidase
Nephrotoxicity	BUN(mg/dL)	Blood Urea Nitrogen
	CRE(mg/dL)	Creatinine (mg/dL)
	Na(meq/L)	sodium
	K(meq/L)	potassium
	Cl(meq/L)	chlorine
	Ca(mg/dL)	calcium
	IP(mg/dL)	inorganic phosphorus
	TC(mg/dL)	Cholesterol
	TG(mg/dL)	Triglycerides
	PL(mg/dL)	Phospholipid
	GLC(mg/dL)	glucose
	TP(g/dL)	Total protein
	RALB(g/dL)	Albumin
	A/G	Albumin/globulin ratio

AnimalGAN Study Design and Performance

Predict 38 measurements of clinical pathology (e.g., ALT, ALP)



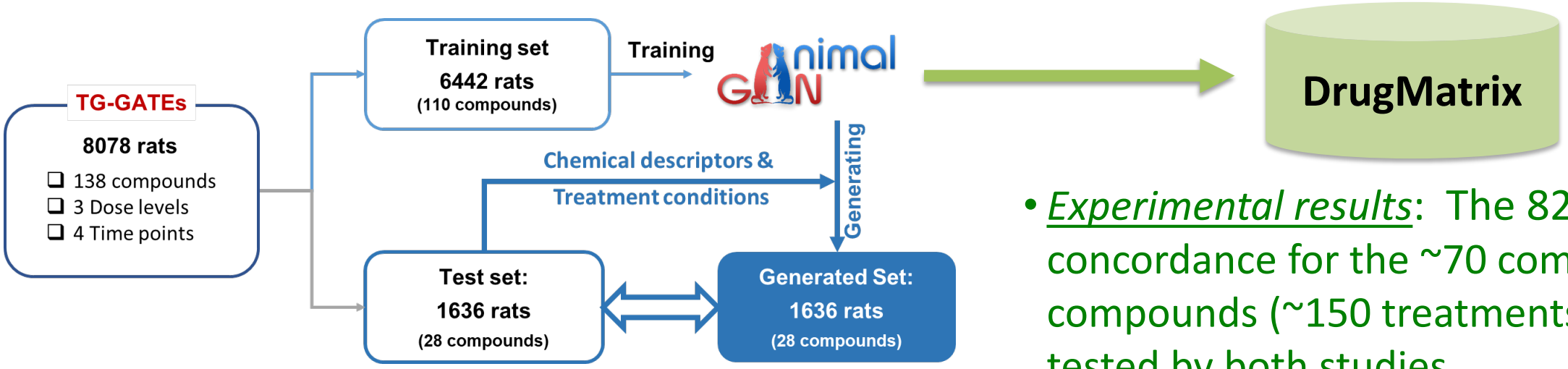
98% concordance in absolute value by comparing to the experimental results for 28 different compounds

"Stress" Test of AnimalGAN:

1. **Applicability Domain** – The 28 drugs were structurally unsimilar to the 110 drugs used for training.
2. **Cross-Drug Classes Application** – The 28 drugs belong to the therapeutic classes that were not represented in the training set.
3. **Cross-Year Application –** The 28 drugs were approved in the late years compared to the training set drugs.

AnimalGAN: Validation on DrugMatrix

Predict 25 clinical pathology measures



	TG-GATEs	DrugMatrix
Rat strain, sex and age	SD, male, and 6 weeks	SD, male, and 6-8 weeks
Treatment duration	**3**/7/14/28 days	0.25/1/**3**/4/5/7/14 days
Dose	• MTD is based on 7 days • 3 treatment doses	• MTD is based on 5 days • Most are 2 doses

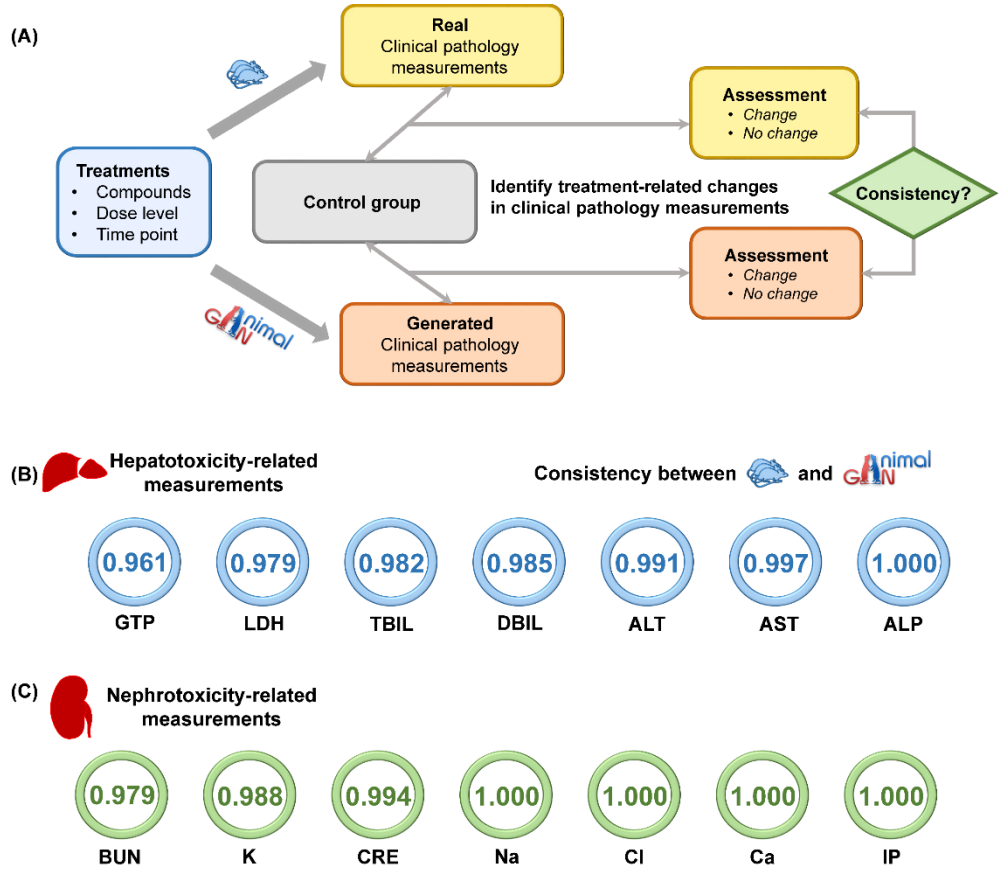
- *Experimental results*: The 82% concordance for the ~70 common compounds (~150 treatments) tested by both studies.

- *AnimalGAN predicted results:* the 83% concordance for 355 compounds (>700 treatments) that were tested in DrugMatrix but not by TG-GATEs.

Hepatoxicity Assessment

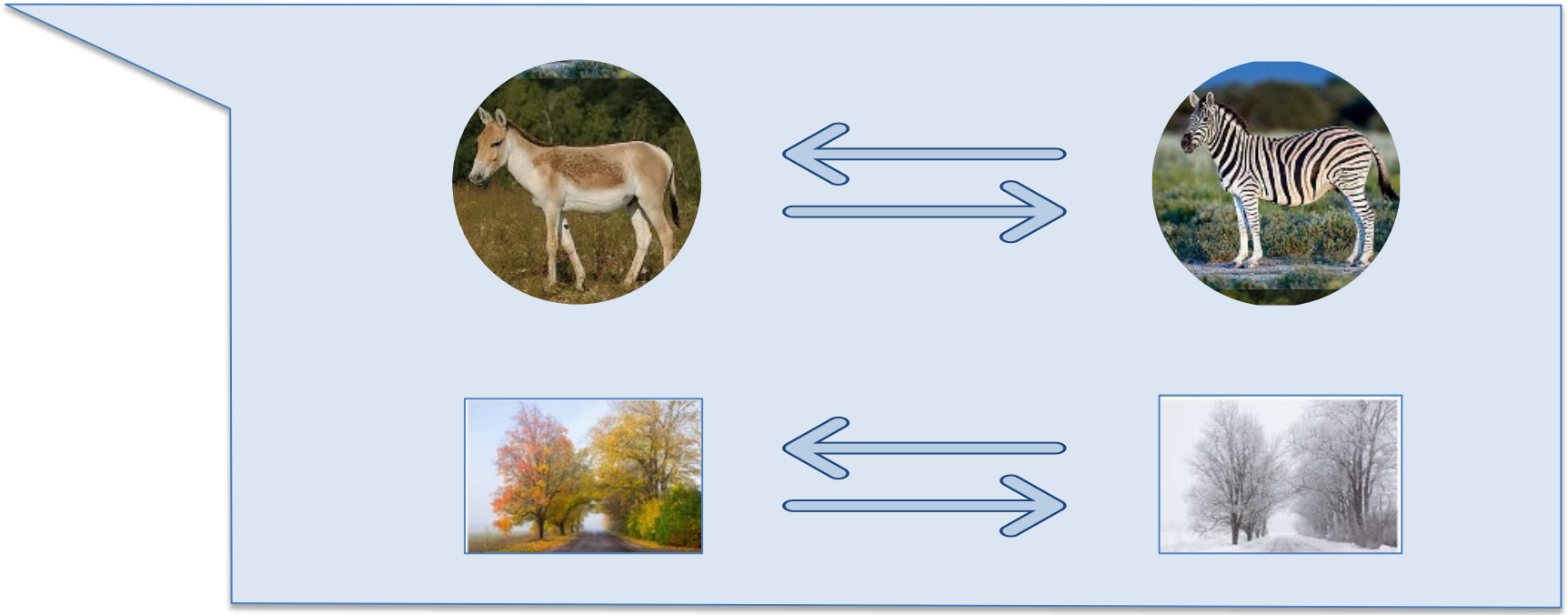
Consistency between real and synthetic results for hepatotoxicity assessment:

- Assessed hepatotoxicity based on FDA Guidance
  - ALT > 3 of normal condition indicates **intermediate hepatotoxicity**: **100%** in agreement
  - ALT = 1-2 of normal condition indicates **minor hepatotoxicity**: **83%** in agreement
- Assessed hepatotoxicity patterns
  - ALT/ALP > 5 indicates **hepatocellular** injury: **100%** in agreement
  - ALT/ALP < 2 indicates **cholestatic** injury: **99%** in agreement
  - ALT/ALP = 2-5 indicates **mixed** Injury: **81%** in agreement



GAN Variations

- C-GAN
- CycleGAN
- BiGAN
- SemiGAN
- DC-GAN
- StackGAN
- StyleGAN
- DualGAN
- …

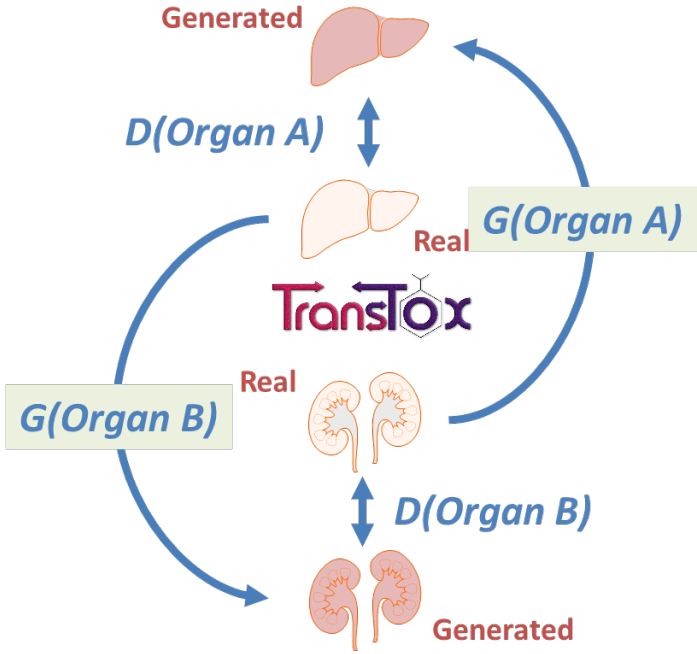


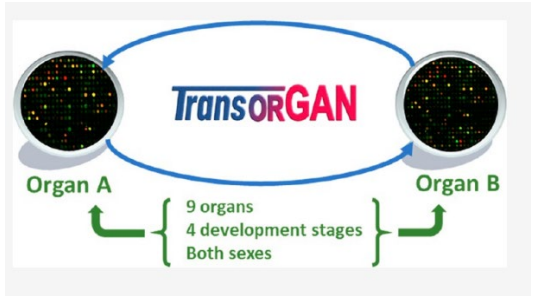
Translational Research with Generative AI

Objective: To translate experimental findings across domains where the data are scarce or difficult to obtain with generative AI.

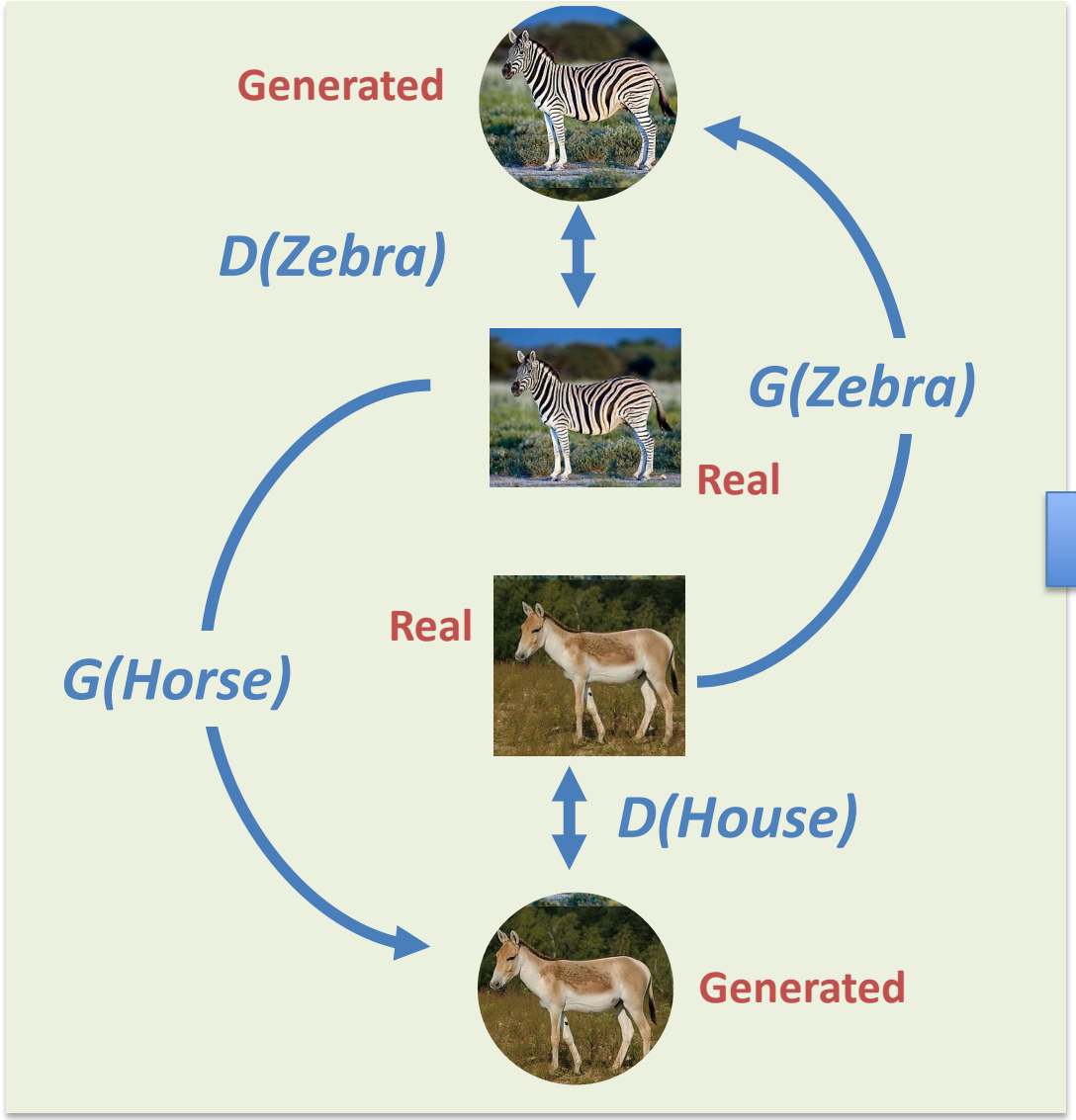
Projects:

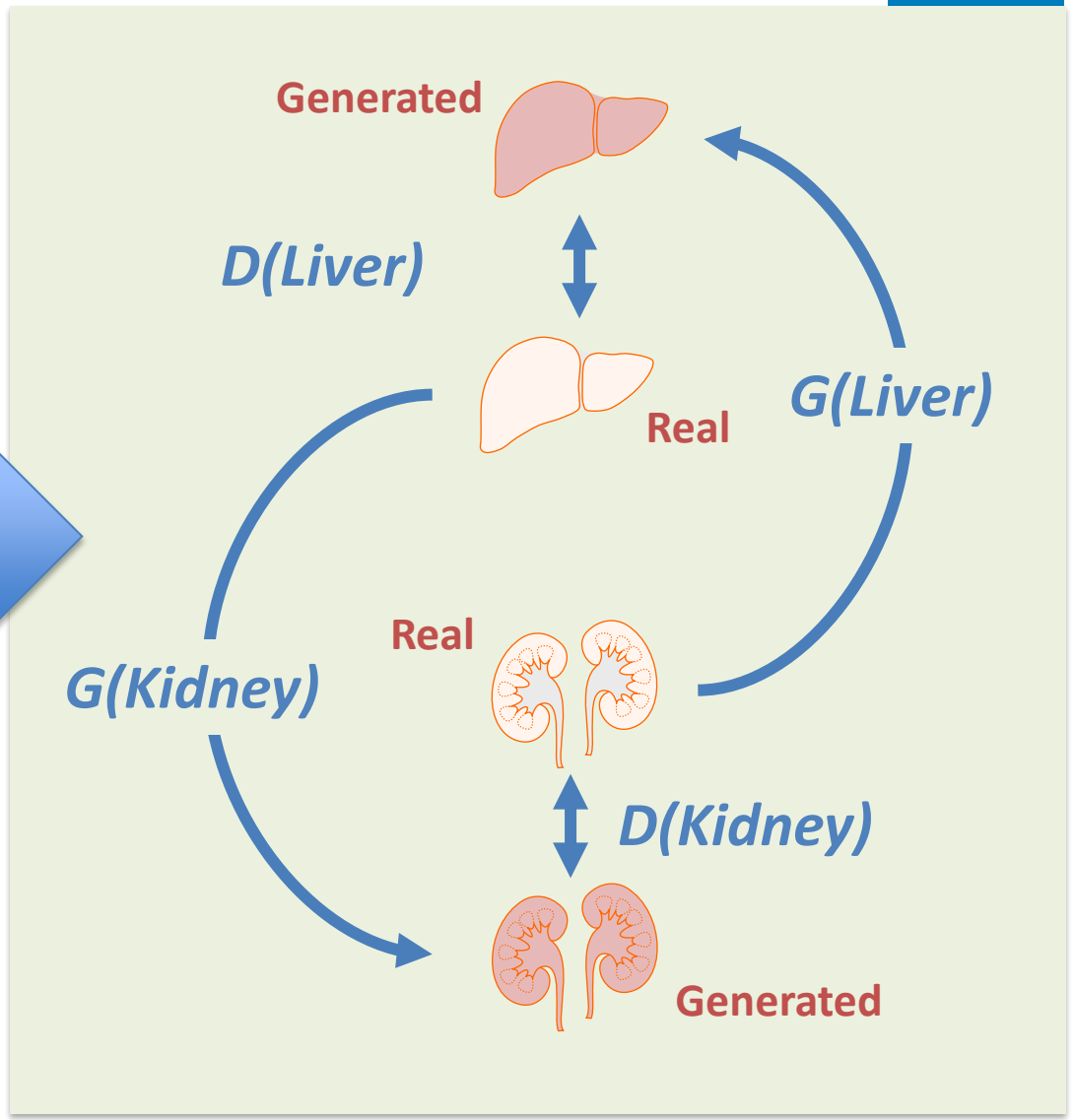
1. Translating rat genomic profiles across 10 organs at 4 development stages and with both sexes (published)
2. Bridging transcriptomics data between liver and kidney under the drug treatment (submitted)
3. Converting microarray data to RNA-seq to leverage the past investment (in preparation)
4. In vitro to in vivo extrapolation (IVIVE) to advance 3Rs (on-going)





From CycleGAN to TransTox



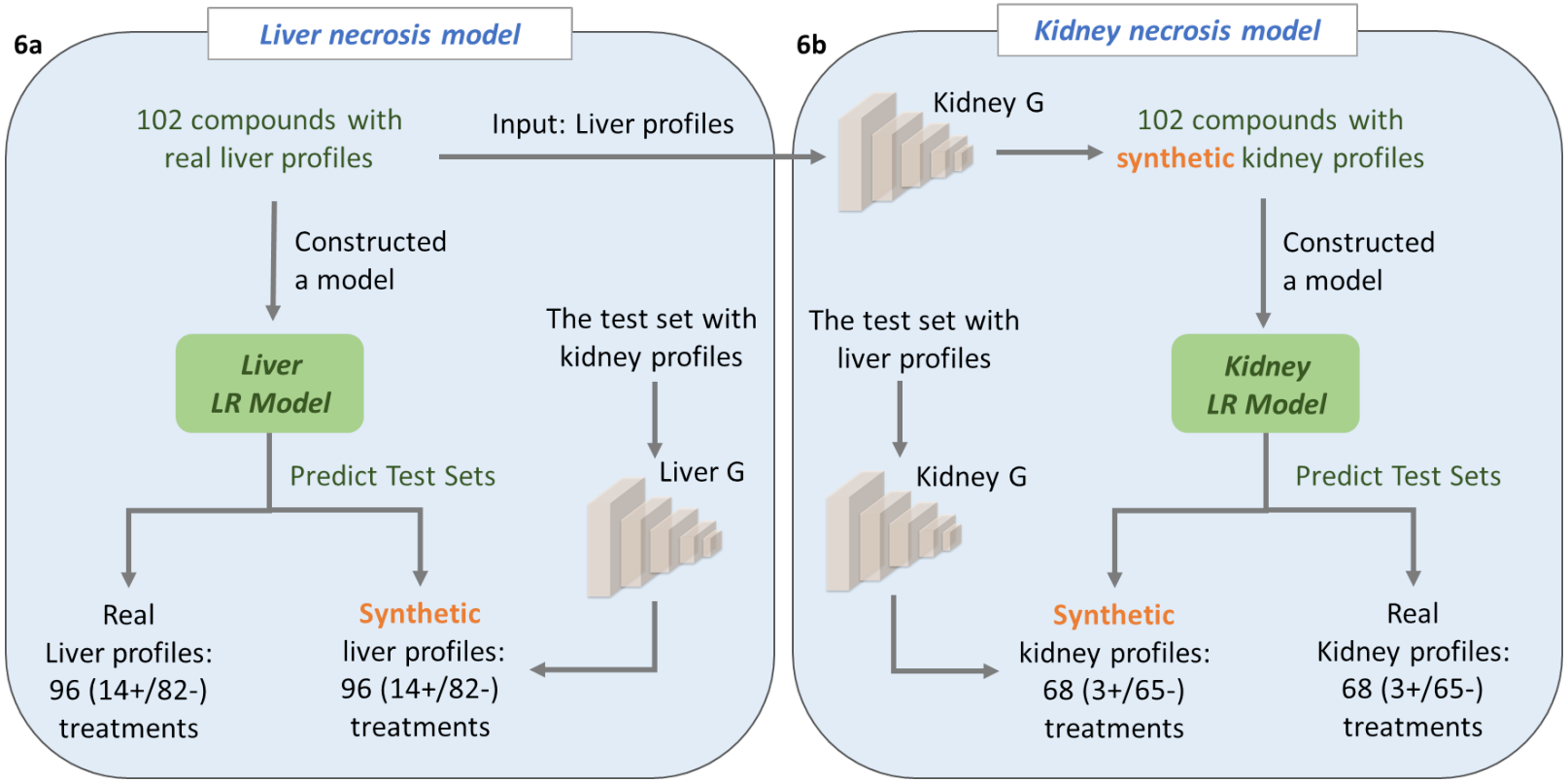


TransTox Results

- Validated with data from the same lab as well as from a different lab
- Compared the synthetic profiles against data from a real experimental setting in elucidating toxicity mechanisms
- Predictive model necrosis prediction

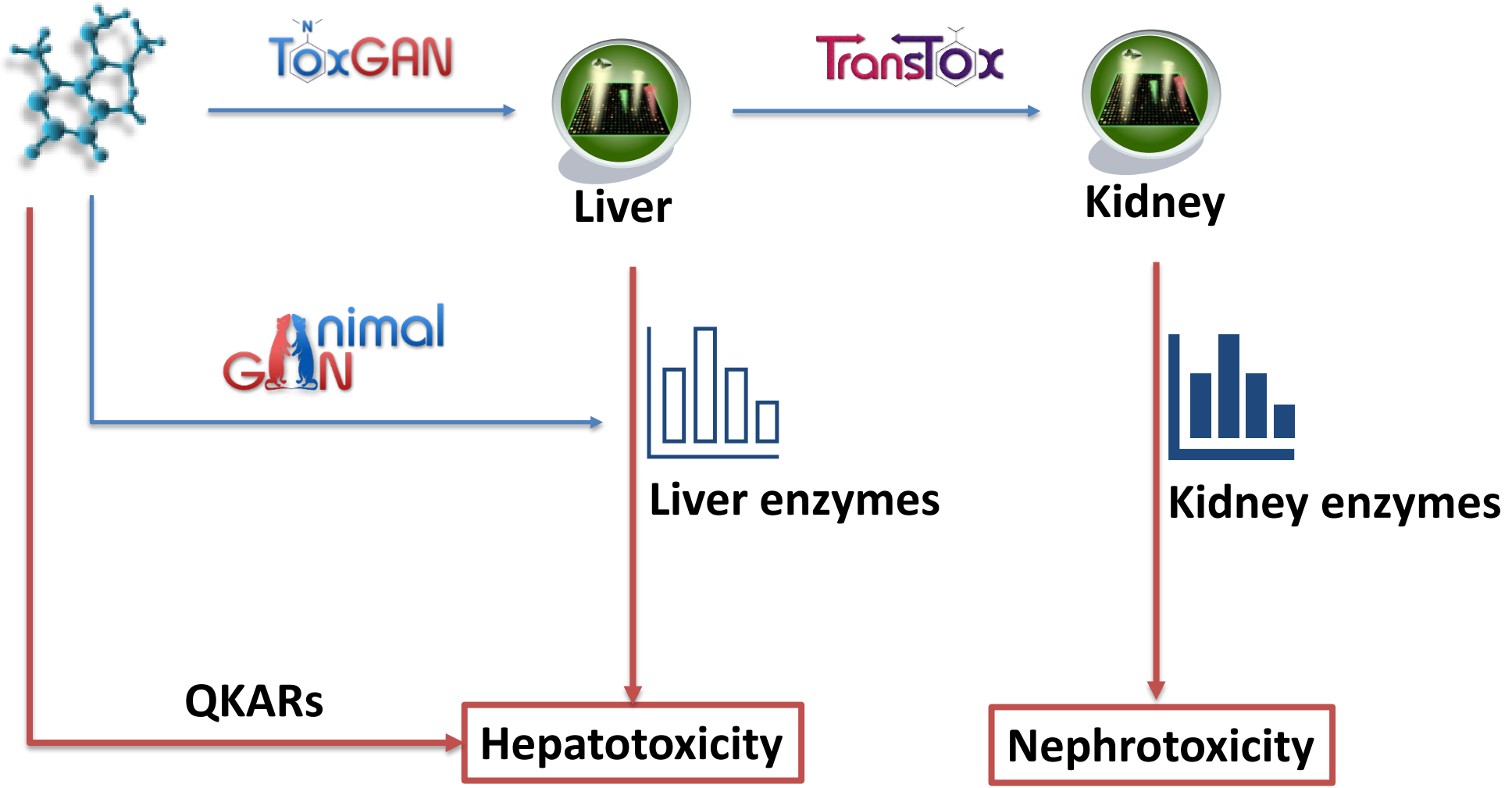
Can the synthetic data serve as "digital twin" for diagnosis

Can the synthetic data be used to develop a reliable predictive model



Ting Li, Xi Chen, Weida Tong, **Bridging Organ Transcriptomics for Advancing Multiple Organ Toxicity Assessment with a Generative AI Approach,** NPJ Digital Medicine (in revision)

GenAI Application in Drug Safety Assessment: A Scenario



FDA/NCTR AI Program for Toxicology (AI4TOX)

LLMs for FDA documents to improve regulatory efficiency, enhance information retrieval, and maintain institutional memory at FDA

Predictive models for safety endpoints critical to drug safety review, particularly in IND Application review at CDER

Virtual animals to generate animal study results with generative AI to advance 3Rs for animal use and digital twin

Generative AI models to translate experiment findings across different domains such as across organs, in vitro-to-in vivo (IVIVE), and between genomic technologies

AI-driven digital pathology for preclinical histopathology images

https://www.fda.gov/about-fda/nctr-research-focus-areas/artificial-intelligence


YOUR ONLY
LIMITATION IS YOUR
IMAGINATION !
AI

Acknowledgment

AIRForce Team at NCTR

- Xi Chen (ToxGAN and AnimalGAN)
- Ting Li (DeepDILI, TransOrgan, and TransTox)
- Leihong Wu (BERTox and eXplainable AI)
- Joshua Xu (PathologAI and R2R Branch Chief)
- Hadi Salman (TransOmics)
- Skylar Connor (Adaptive AI)
- Yanyan Qu (CardioTox and QSARs)
- Shivangi Shrimali (MPS and women's health)
- Alex Chen (AnimalGAN)

CDER Collaborators on AnimalGAN

- Shraddha Thakkar (OCS and SafetAI)
- Kevin Snyder (OND)
- Paul Brown (OND)

FDA Leadership

- Principle Deputy Commissioner and Chief Scientist
- CDER Leadership: Lilliam Rosario (OCS), ShaAvhree Buckman Garner (OTS), and Bob Ball (OSE)

External Collaborators:

- Zhichao Liu (the former technical lead of AIRForce and now at BI)
- Ruth Roberts (ApconiX and U of Birmingham at UK)
- Cesare Furlanello (HK3Lab, Italy)
- AbbVie, BI, and GSK