U.S. FOOD & DRUG ADMINISTRATION

Advancing Toxicology in Drug Discovery using Generative Adversarial Networks (GANs) – Part 1

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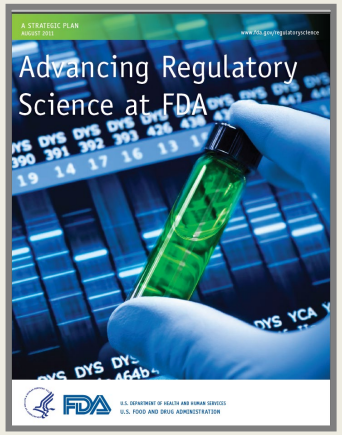
Disclaimer: The views expressed are of the presenter and should not be considered as the official position or policy of U.S. FDA.

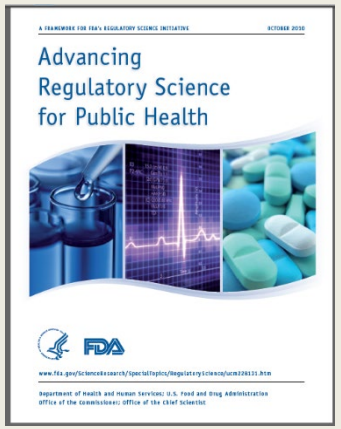
FDA's National Center for Toxicological Research

1. Center for Drug Evaluation and Research (CDER)
2. Center for Biologics Evaluation and Research (CBER)
3. Center for Food Safety and Nutrition (CFSAN)
4. Center for Device and Radiological Health (CDRH)
5. Center for Veterinary Medicine (CVM)
6. Center for Tobacco Products (CTP)
7. Office of Regulatory Affairs (ORA)
8. **National Center for Toxicological Research (NCTR)**

Regulatory Science:

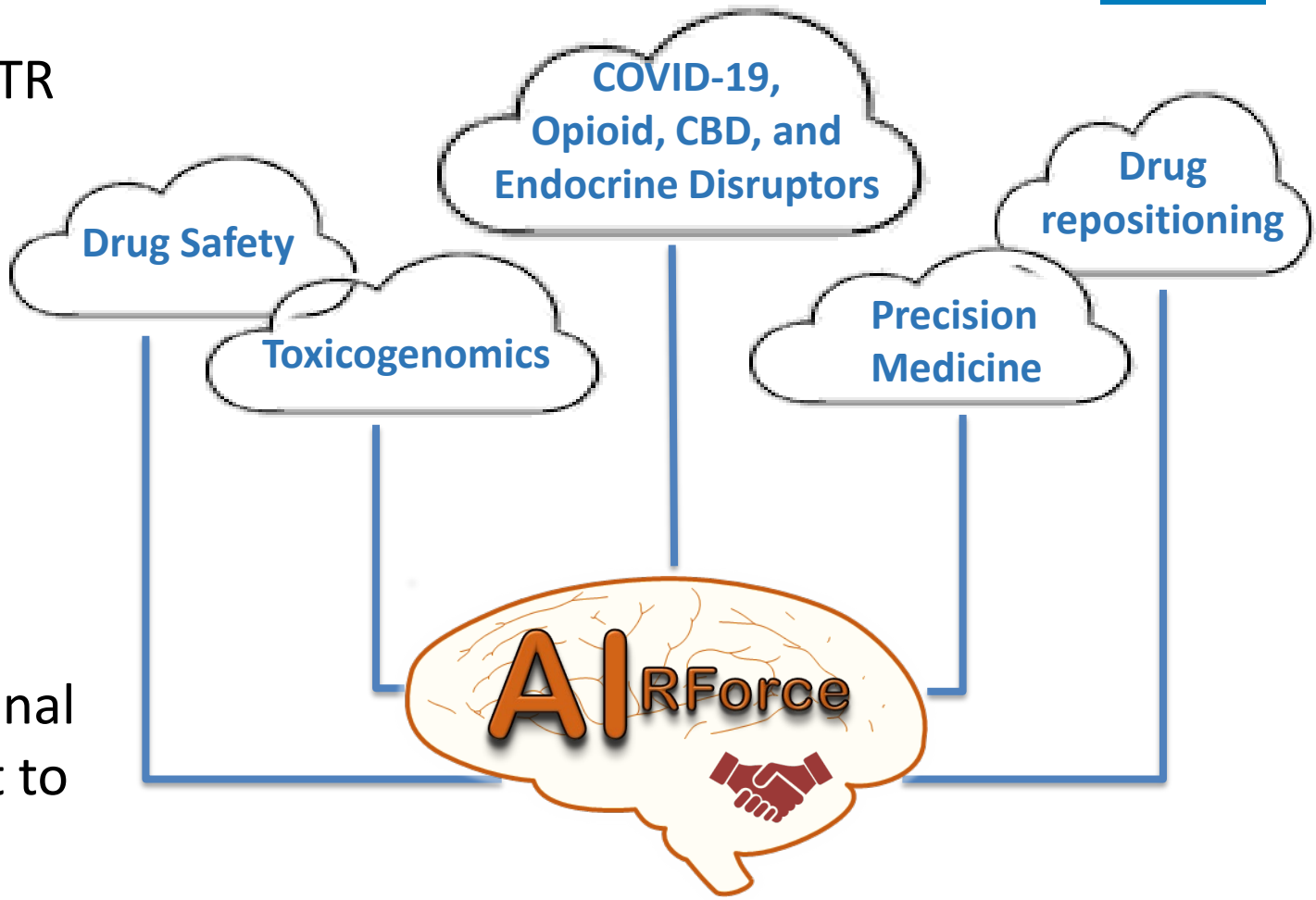
- *Regulatory science* is the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.





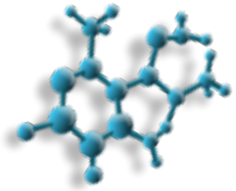
Division of Bioinformatics and Biostatistics

- One of six research divisions at NCTR
- Four Branches
  - Bioinformatics
  - Biostatistics
  - Scientific Computing
  - Research2Review (R2R)
- Current staffs: ~60 FTEs
- Objective: to conduct Regulatory Science research using computational approaches to the areas important to FDA
- AI/ML is a long-standing effort



AI Research Force (AIRForce)

AI in Predictive Toxicology



QSARs

- **Objective:** predict single outcome such as liver toxicity
- **Algorithm:** Using one neural network or ML method

GANs

- **Objective:** generate multidimensional toxicological profiles such as gene expression profiles or clinical pathology profiles
- **Algorithm:** Using 2 neural networks in a competing fashion

Poster (**P102**):	Comparing QSARs with Generative AI in predictive Toxicology
Date:	03/13 (Wednesday)
Time:	2:15-4:15PM

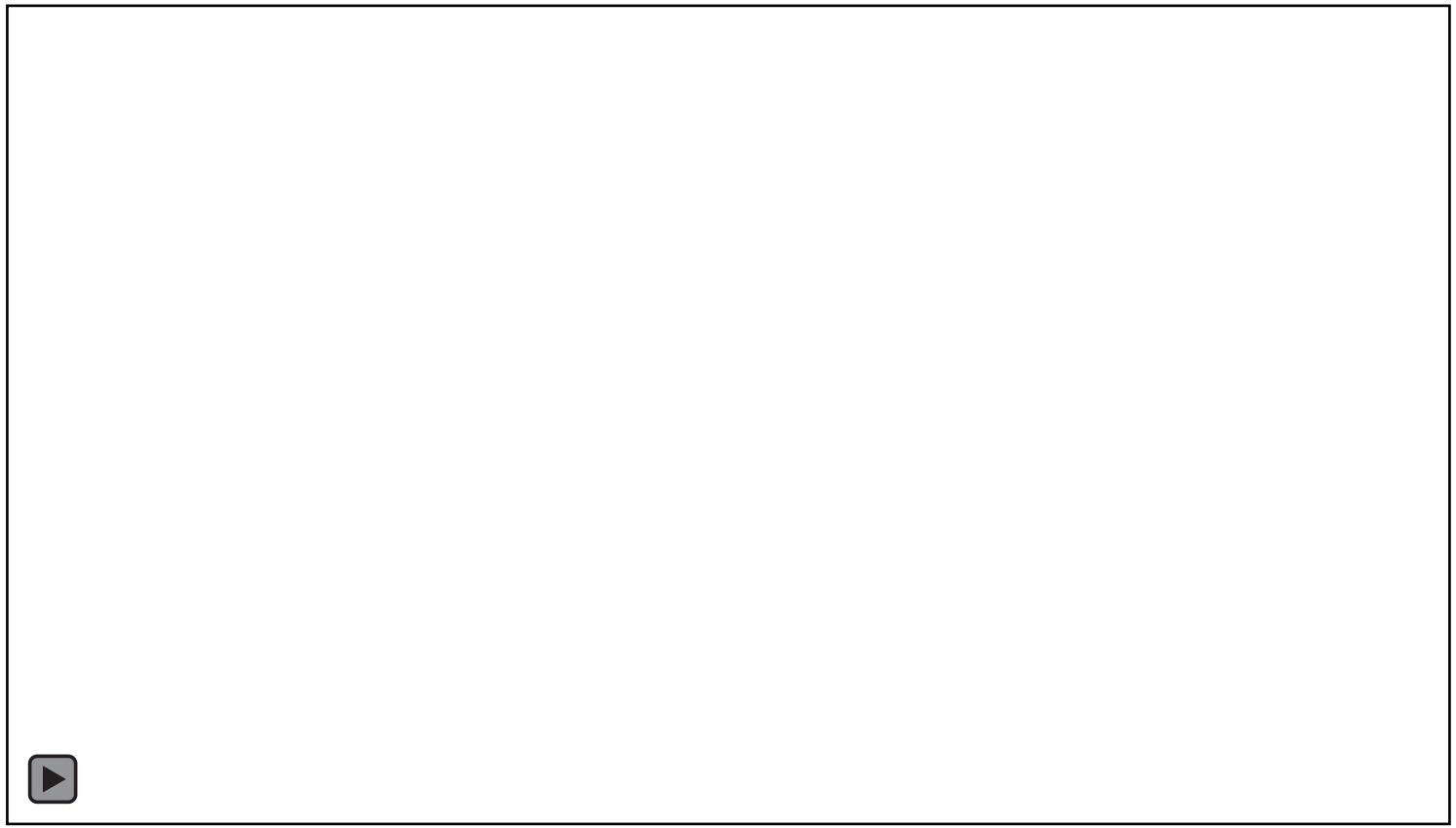
DeepFake and Generative Adversarial Networks (GANs)

- 2014: The landmark paper by Dr. Goodfellow
- 2017: Many became victims in fake adult video
- 2018: A DeepFake artwork sold for $400,000
- 2021: A DeepFake Tom Cruise Tik Tok went viral
- 2022: DeepFake performance on top 5 finalists in American Got Talent
- 2023 onward: DeepFake is everywhere
  - AI won the prestigious photography competition but the artist declined the award
  - Fake arrest of Trump
  - Scams

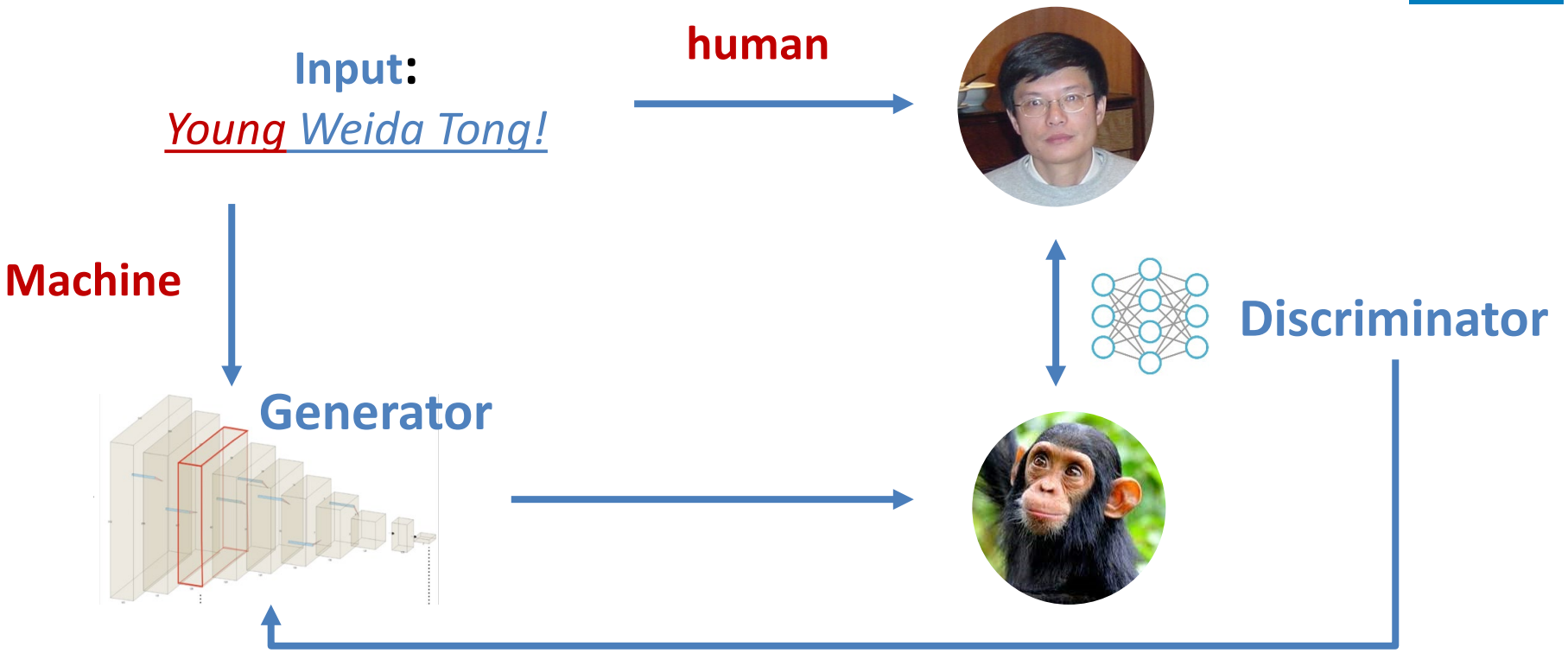
Yann LeCun, Meta's VP and Chief AI Scientist, called GANs "*the most exciting idea in machine learning in the last ten years*".

OCTOBER 30, 2023

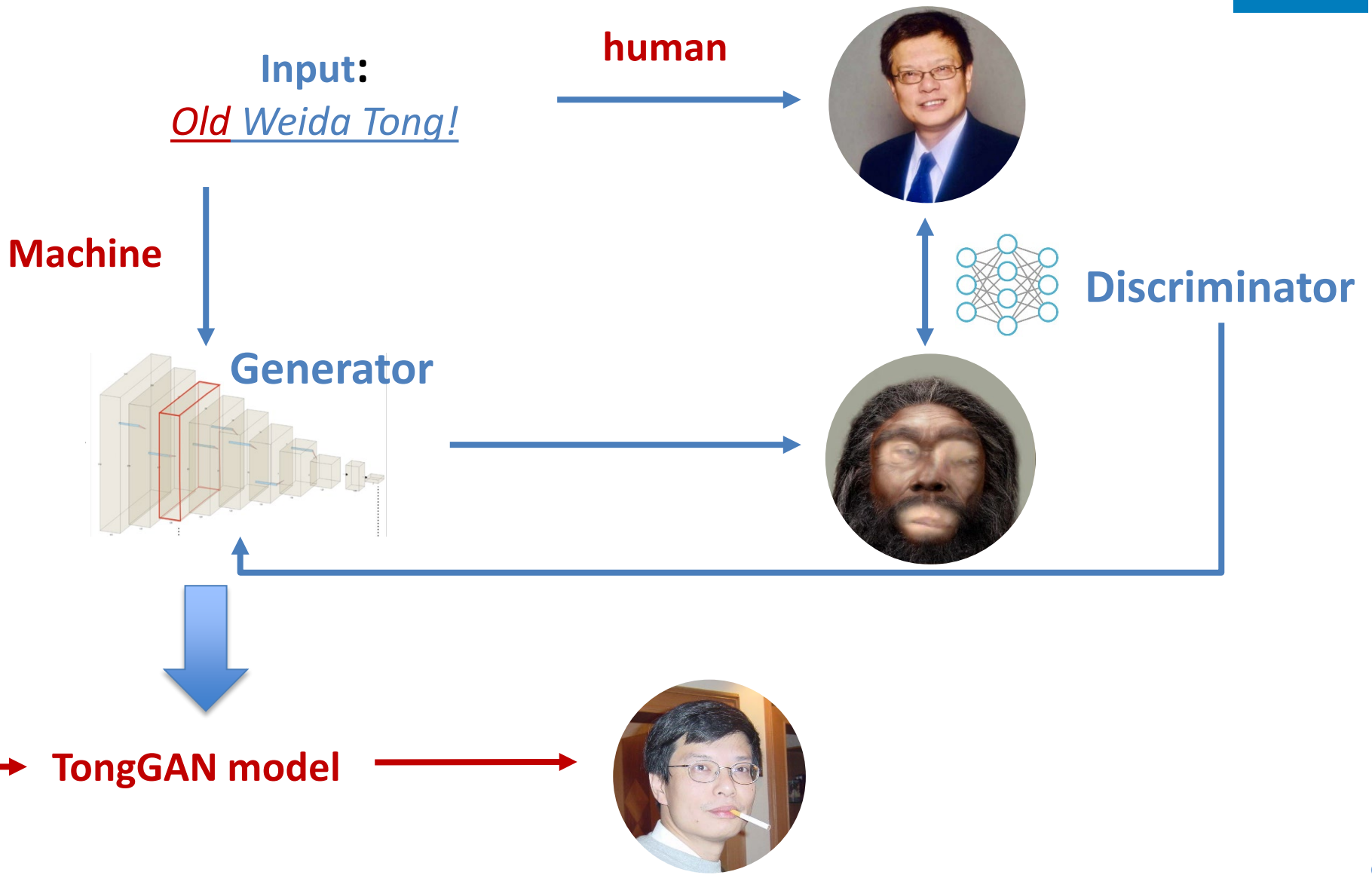
Executive Order on the Safe, Secure, and Trustworthy Development and Use of Artificial Intelligence



GANs 101


Input:
Young Weida Tong!
human
Machine
Generator
Discriminator

GANs 101


Input:
Old Weida Tong!
human
Machine
Generator
Discriminator
Input:
Weida Tong is smoking!
TongGAN model

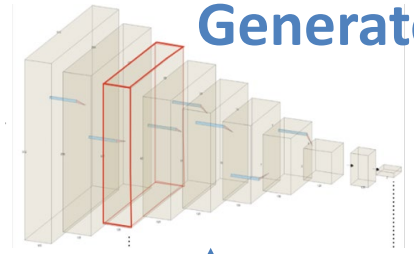
A GAN Framework to Develop AnimalGAN

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

Real Test Results

Discriminator

Generator



Synthetic Results

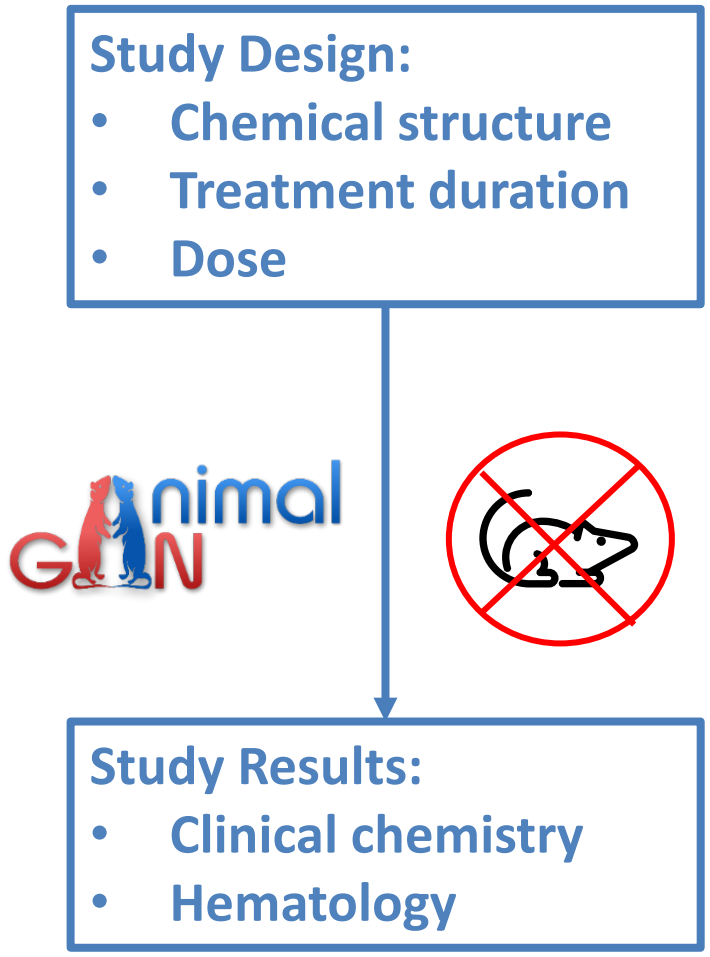
Input:
Rat was treated by a new drug at high dose and 28 days

AnimalGAN

Synthetic results for new chemicals

AnimalGAN: A Virtual Rat to Generate 38 Synthetic Clinical Pathology Measurements

- **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:** Without using animals, we could predict animal toxicity to facilitate drug development and to inform regulatory process.



AnimalGAN:A Generative Adversarial Network Model Alternative to Animal Studies for Clinical Pathology Assessment

Xi Chen, Ruth Roberts, Zhichao Liu, Weida Tong

nature COMMUNICATIONS

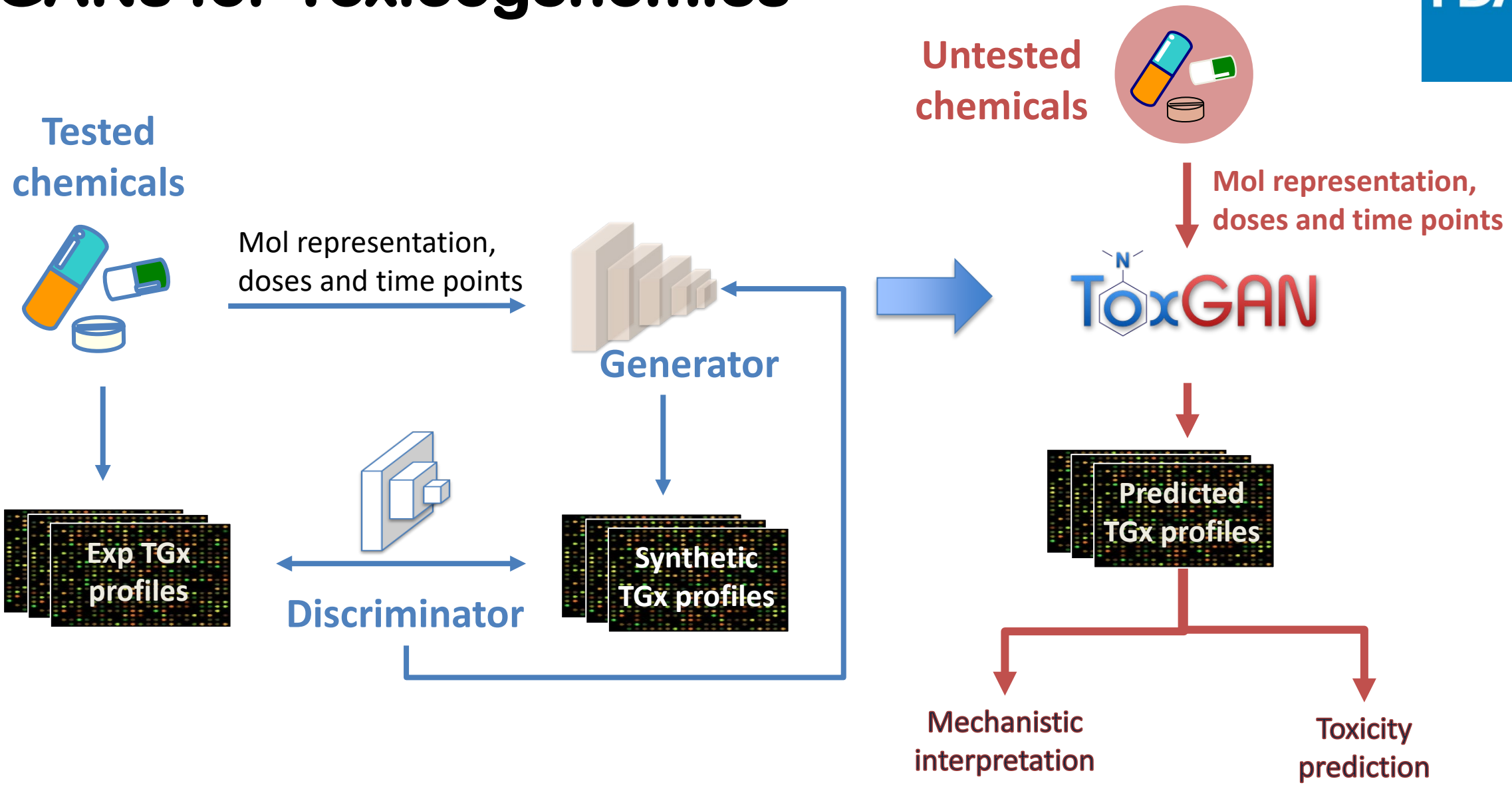
17 Hematologic measures

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

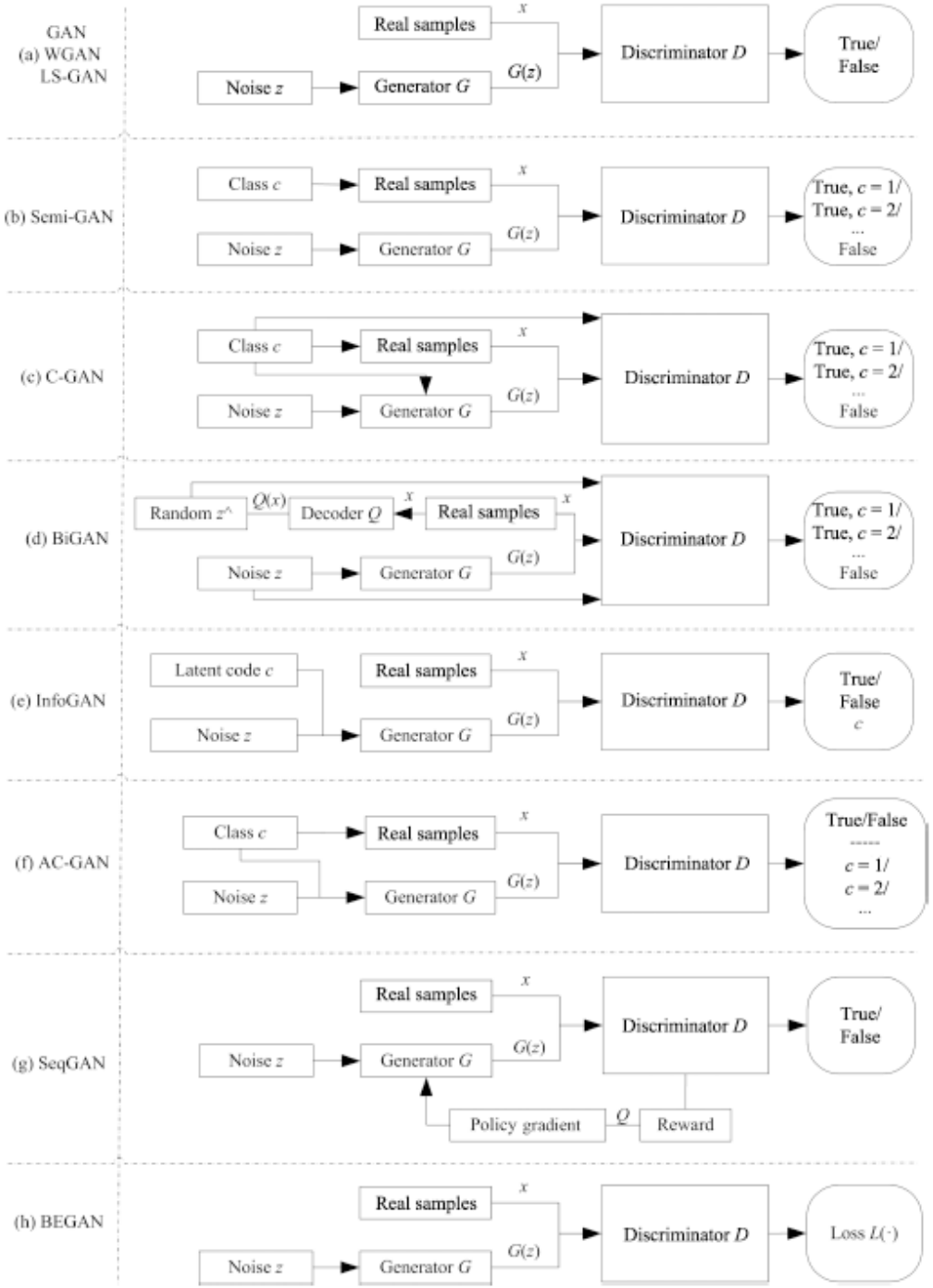
GANs for Toxicogenomics



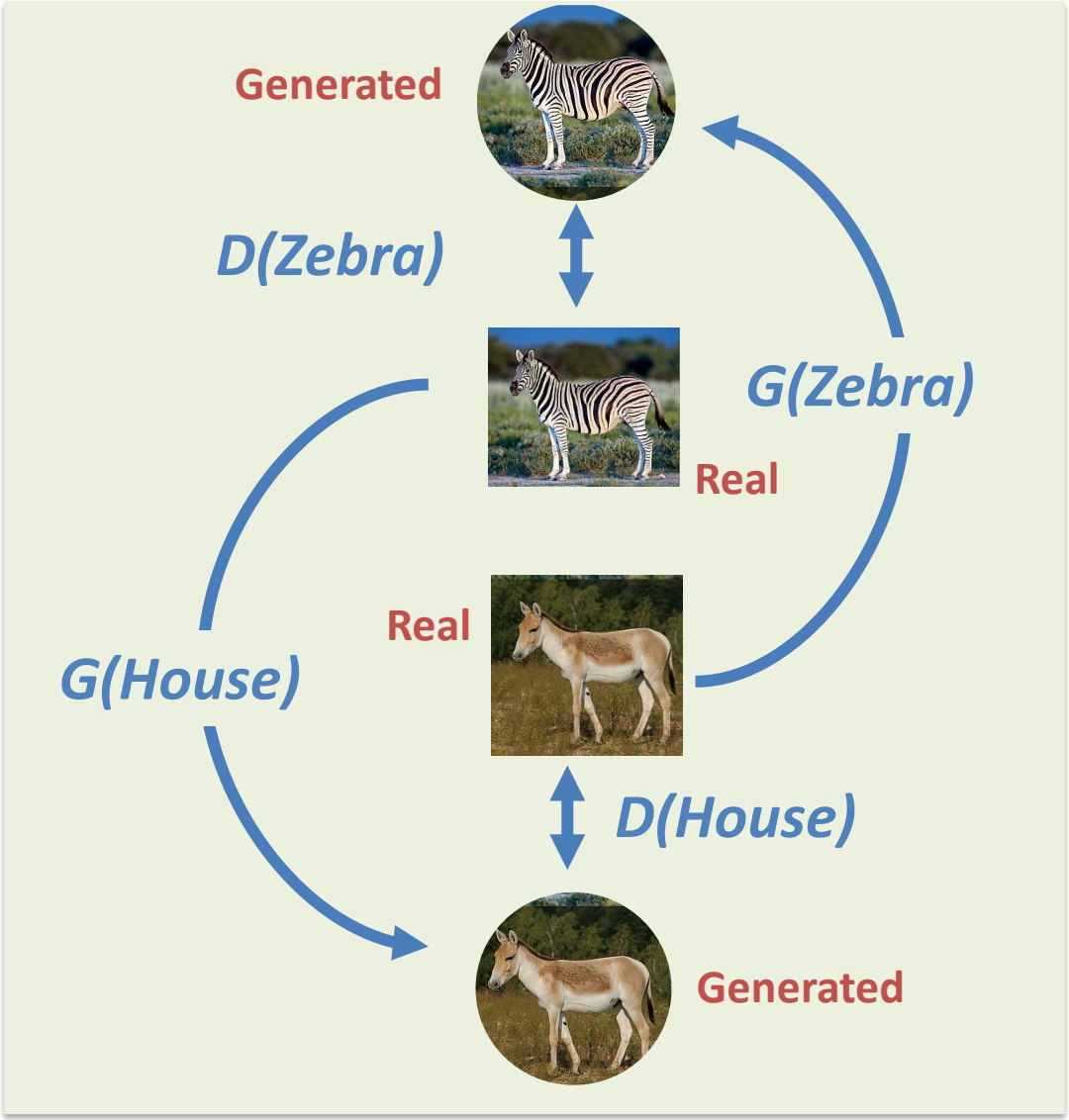
GAN Algorithms

Generative Adversarial Networks: Introduction and Outlook

Kunfeng Wang, Chao Gou, Yanjie Duan, Yilun Lin, Xinhu Zheng, and Fei-Yue Wang



CycleGAN



Potential Applications:

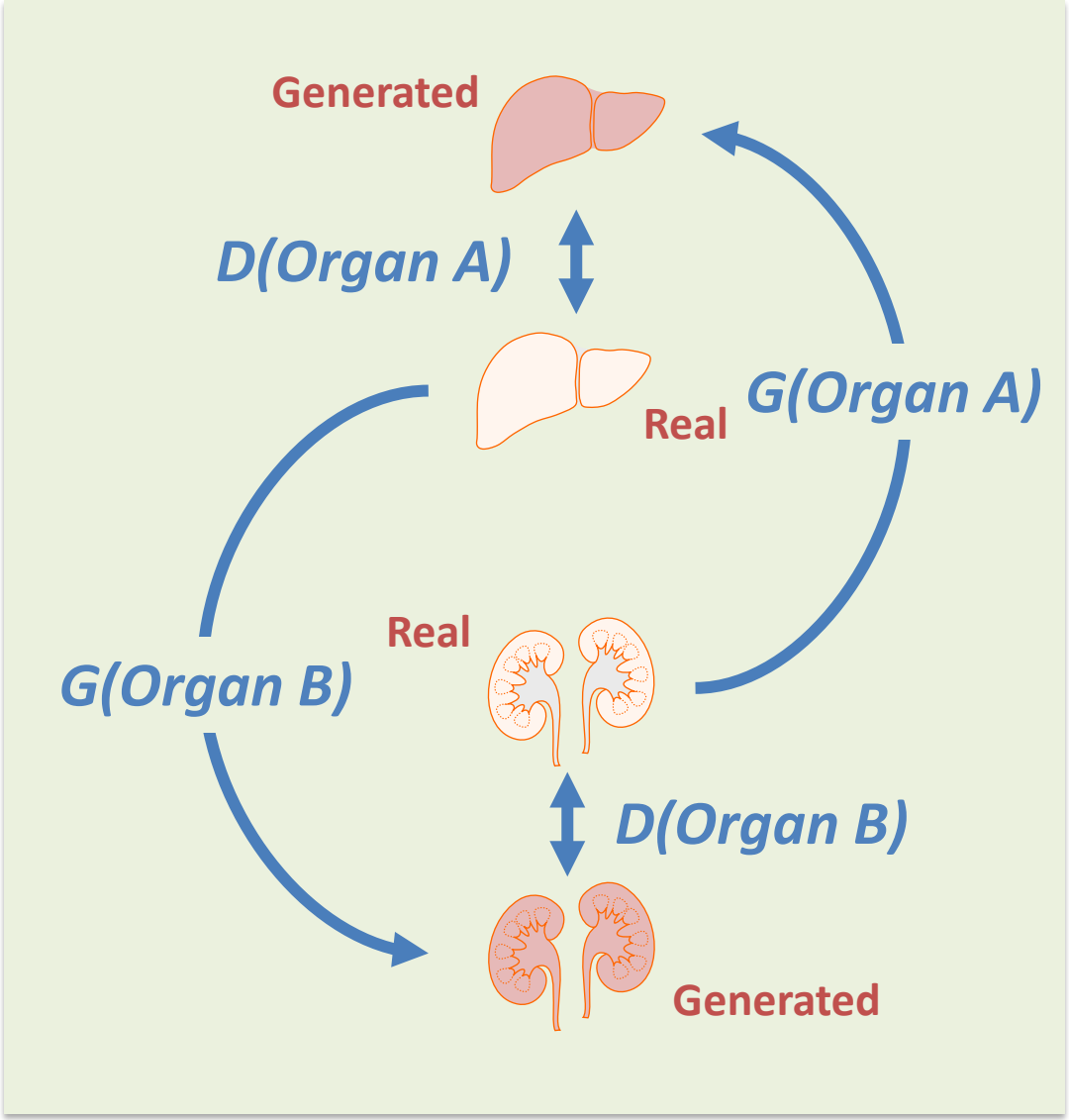
- *In vitro* to *in vivo* extrapolation (IVIVE)
- Microarrays to RNASeq
- One organ to the others
- …

TransOrGAN v1 Model Development

Organ translation between:

- 9 organs (liver, kidney, heart, lung, adrenal gland, brain, muscle, spleen, and thymus)
- 4 developmental stages (i.e., Juvenile, adolescence, adult and old)
- Both sexes (male and female)

SOT Poster **P228**
03/13 (Wednesday)
2:15-4:15PM

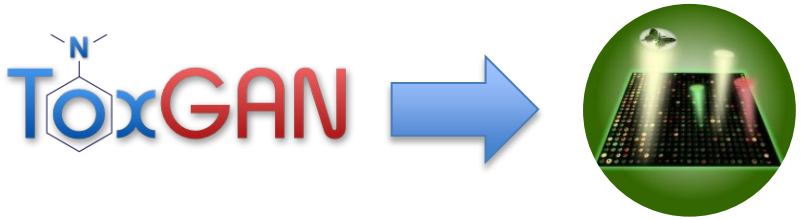


Abbreviations:

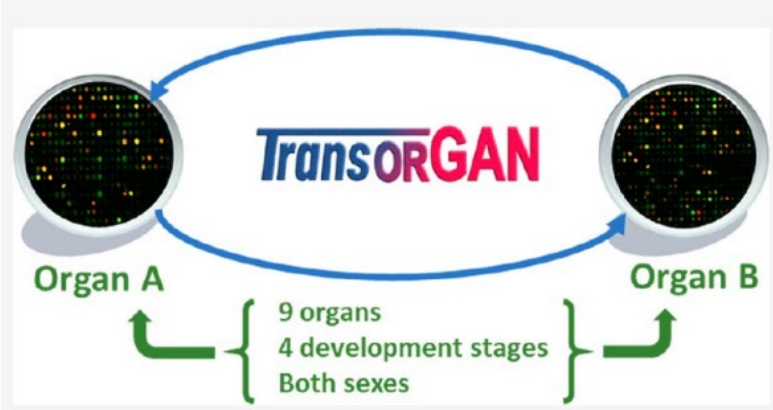
- ***G(Organ A):*** Organ A Generator to generate A gene expression profiles based on input of organ B profiles
- ***D(Organ A):*** Organ A Discriminator to distinguish fake and real profiles of A
- ***G(Organ B)*** and ***D(Organ B)*** are the same as ***G(Organ A)*** and ***D(Organ A)*** but for organ B
- **A** and **B** can be any one of the 9 organs, e.g., A: liver; B: kidney

A Family of GANs

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

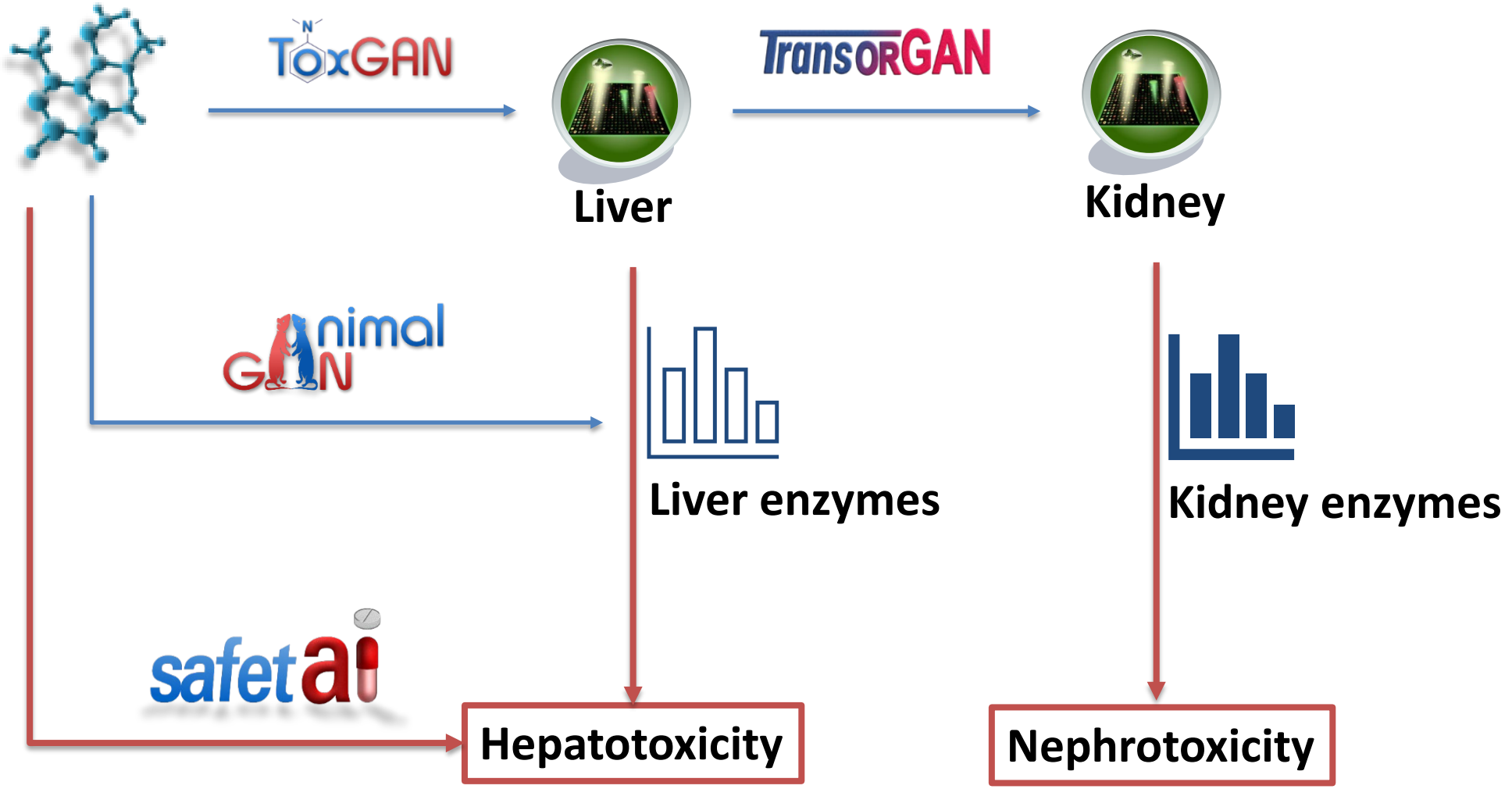


[Tox-GAN: An Artificial Intelligence Approach Alternative to Animal Studies—A Case Study With Toxicogenomics].
Chen X., Roberts R., Tong W. et al.
Toxicological Sciences. 2022,186:242-259



[TransOrGAN: An Artificial Intelligence Mapping of Rat Transcriptomic Profiles between Organs, Ages, and Sexes.]
Li T, Roberts R, Liu Z, Tong W.
Chem Res Toxicol. 2023

A Family of GANs for Drug Safety



Summary

- 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

- AI can be used as an alternative way to animal studies in two ways: generative and discriminatory
  - AnimalGAN is a generative AI like ChatGPT; it generates clinical pathology data
  - SafetAI is QSAR-like approach to predict organ toxicities with a novel DL framework

- A family of AI methods (including both GANs and QSARs) have been developed to address drug safety

Acknowledgment

AIRForce Team at NCTR

- Xi Chen and Dan Li (ToxGAN and AnimalGAN)
- Ting Li (SafetAI and TransOrGAN)
- Skylar Connor (Adaptive AI)
- Leihong Wu (BERTox and AI Bias)
- Joshua Xu (Branch Chief, PathologAI)

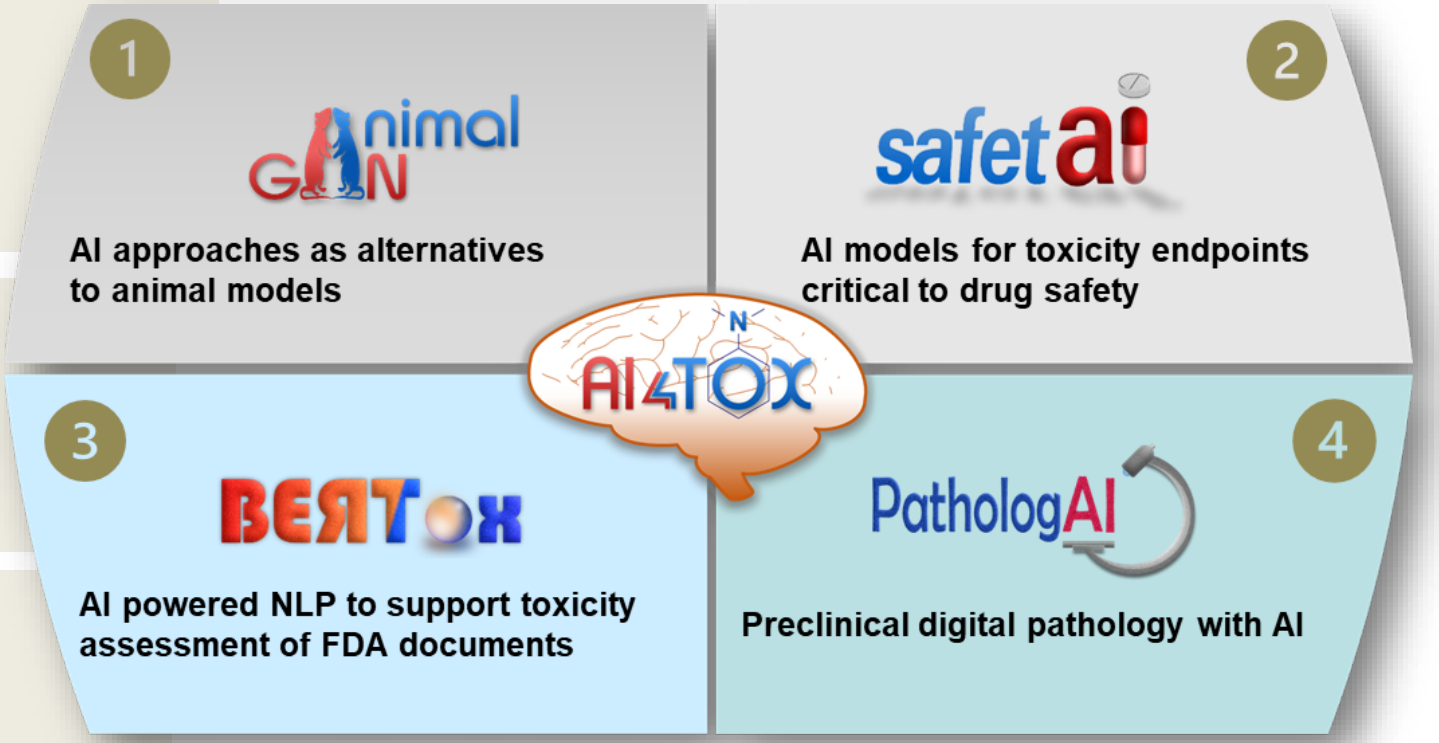
CDER Collaborators

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

External Collaborators:

- Ruth Roberts (ApconiX and U of Birmingham at UK)
- Scott Auerbach (NIEHS)
- Zhichao Liu (BI)

AI4Tox consists of 4 initiatives



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