AstraZeneca

Use of AI & ML in Discovery Toxicology

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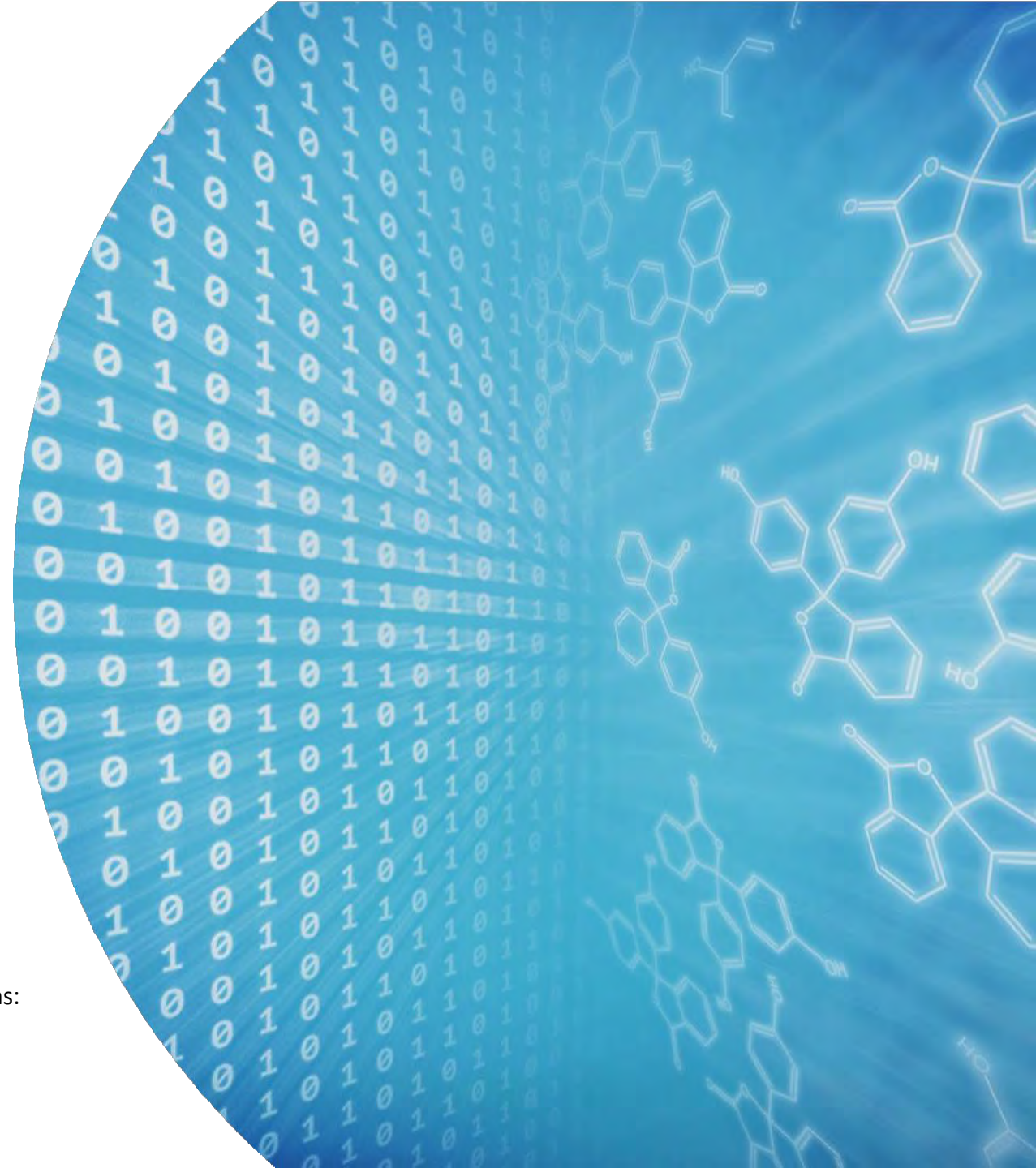
Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca Boston

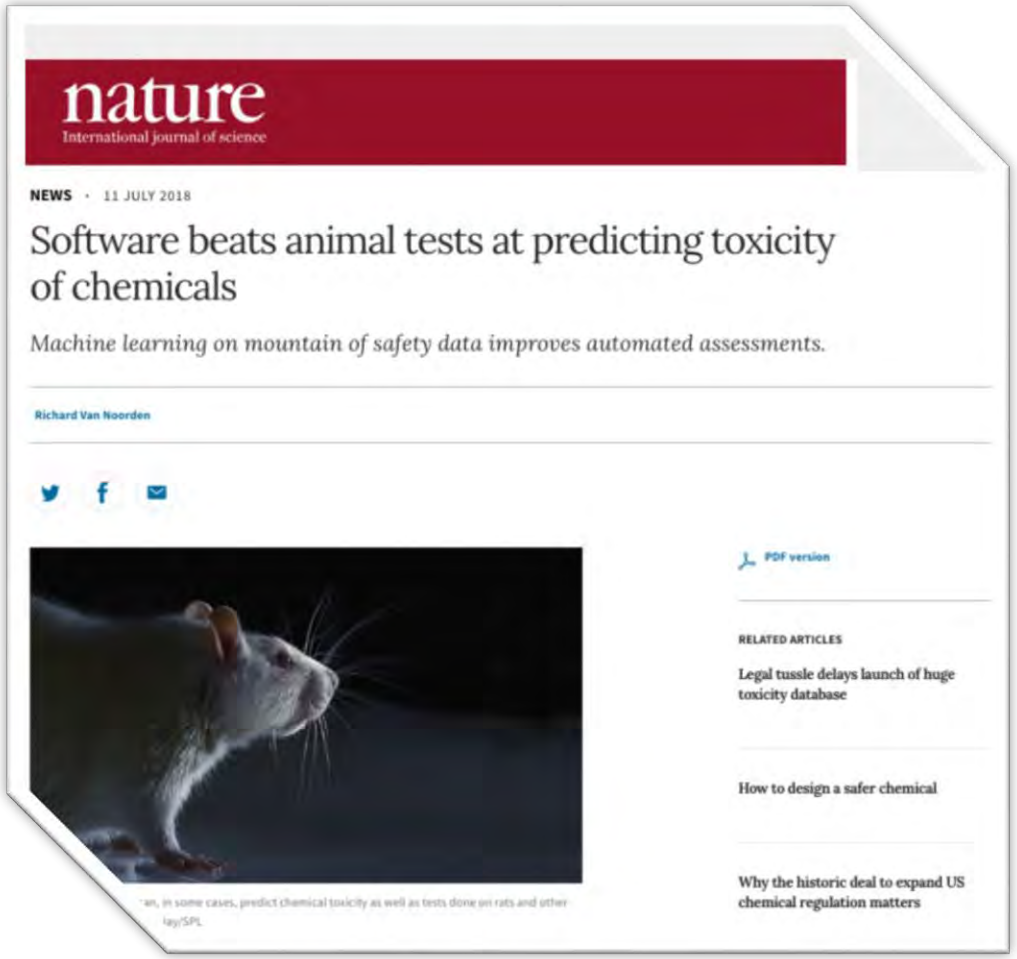


Machine Intelligence for Quantitative Modeling in Drug Discovery & Development Applications:
16 September 2022

Outline

1. What is the problem we are trying to solve?
2. Prediction of pharmacokinetics
3. The changing landscape of safety assessment
4. Applications of machine learning in early discovery toxicology
5. Imaging and toxicology & digital pathology
6. SEND and machine learning
7. Conclusions

What's the big deal about AI?



nature
International journal of science

NEWS · 11 JULY 2018

Software beats animal tests at predicting toxicity of chemicals

Machine learning on mountain of safety data improves automated assessments.

Richard Van Noorden

PDF version

RELATED ARTICLES

Legal tussle delays launch of huge toxicity database

How to design a safer chemical

Why the historic deal to expand US chemical regulation matters

Artificial Intelligence has the capability to transform drug discovery…

but…

We need to separate **reality** from the **hype**!

The Challenges of Drug Discovery

Complex Disease Targets

Too Long in Body

Adverse Reactions

Poor Absorption

Low Levels in Body

Not Effective Enough

Not Sufficiently Selective

Side Effects

Unsafe

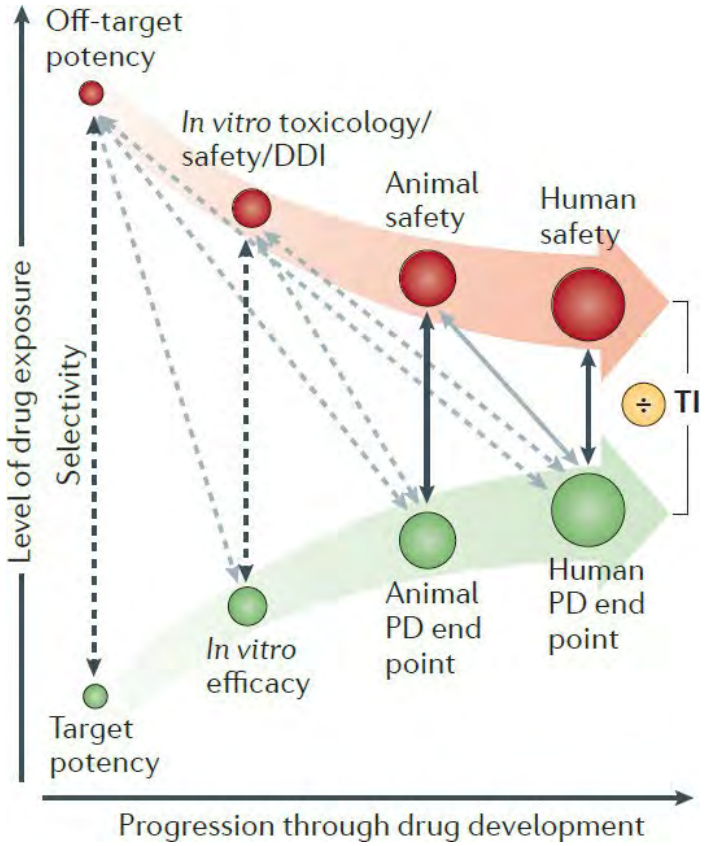
Unstable

Competition

Impractical To Make

Most Molecules Do Not Become Medicines

Therapeutic index is often uncertain at candidate nomination



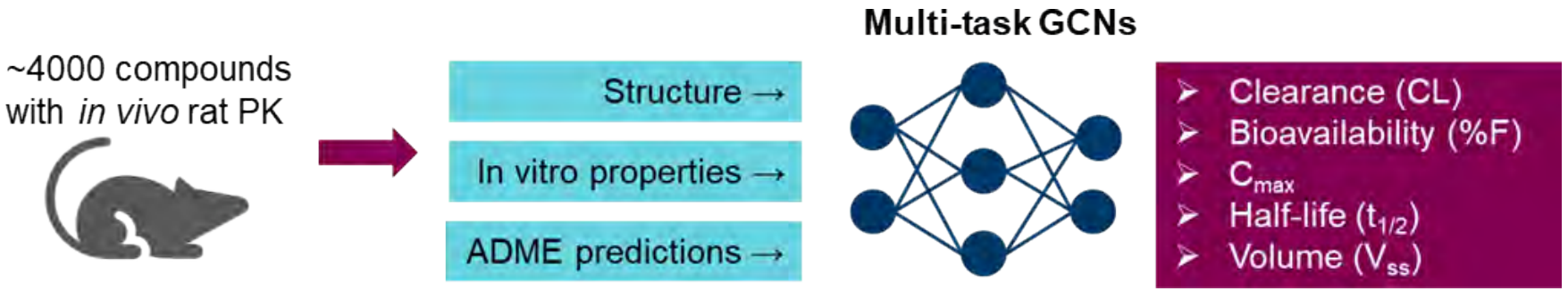
Muller & Milton (2012). Nat Rev Drug Discovery

Decreasing a safe dose is easier than increasing it

Dose makes the poison

- Efficacy = f(potency, exposure)
- Safety = f(hazard, exposure)
- Safety and efficacy of a drug is fixed by its dose
- The dose gives a specific time vs concentration curve
- This is solely a property of the molecule selected

An AI model to predict rat PK



AI model predicts from chemical structure and measured *in vitro* ADME properties

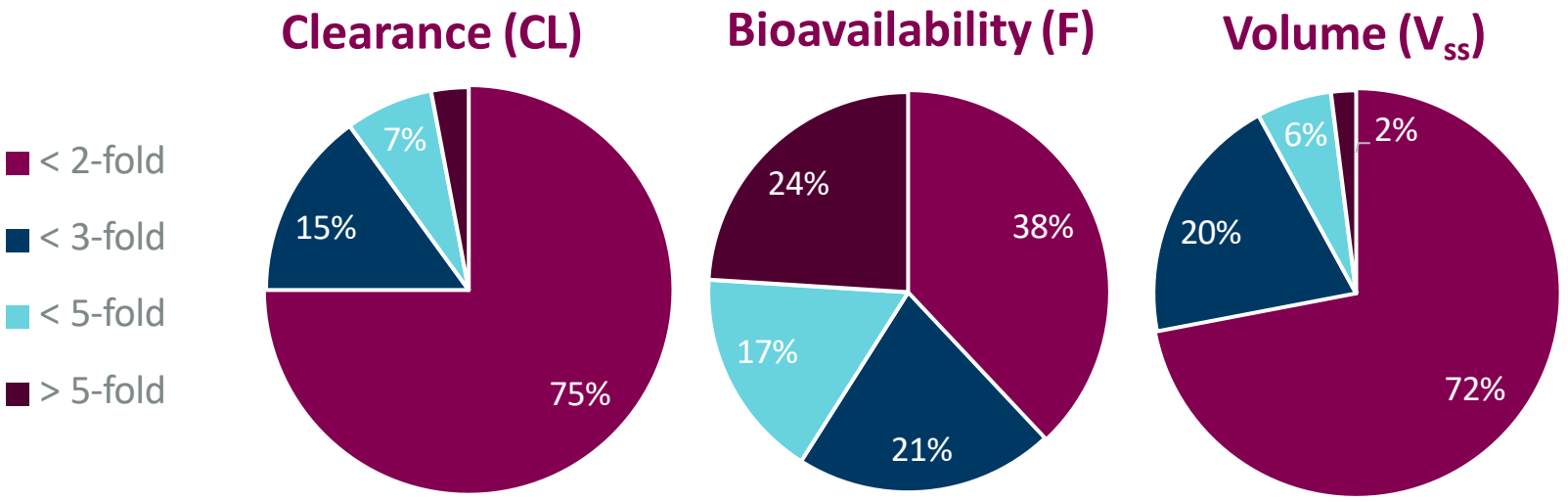
- Chemical structure is encoded by graph convolutional neural network (GCN)
- *In vitro* ADME and physicochemical properties are used as input features
- *In silico* predictions are used in case of missing *in vitro* data

Yang *et al*. JCIM 2019

MIT MLPDS
Machine Learning for Pharmaceutical Discovery and Synthesis Consortium

Rat PK model accuracy

Percentage of compounds with 2-3-5-fold error



Good accuracy achieved on key PK parameters CL, F, Vss

Accuracy is evaluated on the test set

Metrics are in log-transformed space for CL, Vss and logit-transformed for F

R^2 – coefficient of determination

RMSE – root mean square error

	R^2	RMSE	Experimental variability
CL	0.57	0.28	0.18
F	0.48	0.72	0.55
Vss	0.50	0.28	0.21

RMSE is close to experimental variability in the data

Human Clinical data from FDA & EMA

1001
unique molecules

12
parameters

PharmaPendium. Amsterdam, Netherlands. Elsevier. http://www.pharmapendium.com. (accessed Aug 26, 2020).

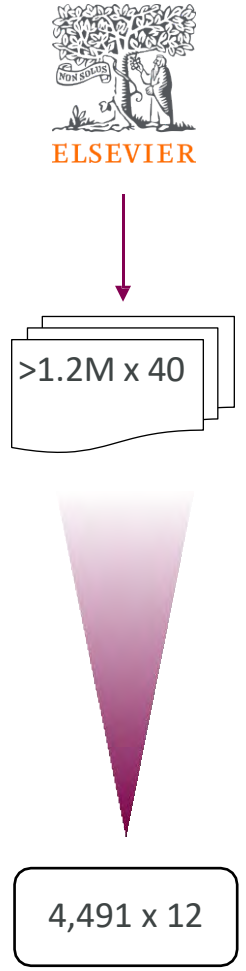
Human clinical data curated according to expert opinions from across the organization

Included:

- Adult healthy volunteers and oncology patients
- Single dose PK for compounds with MW ≤750 Da
- Non-tissue specific measurements

Excluded:

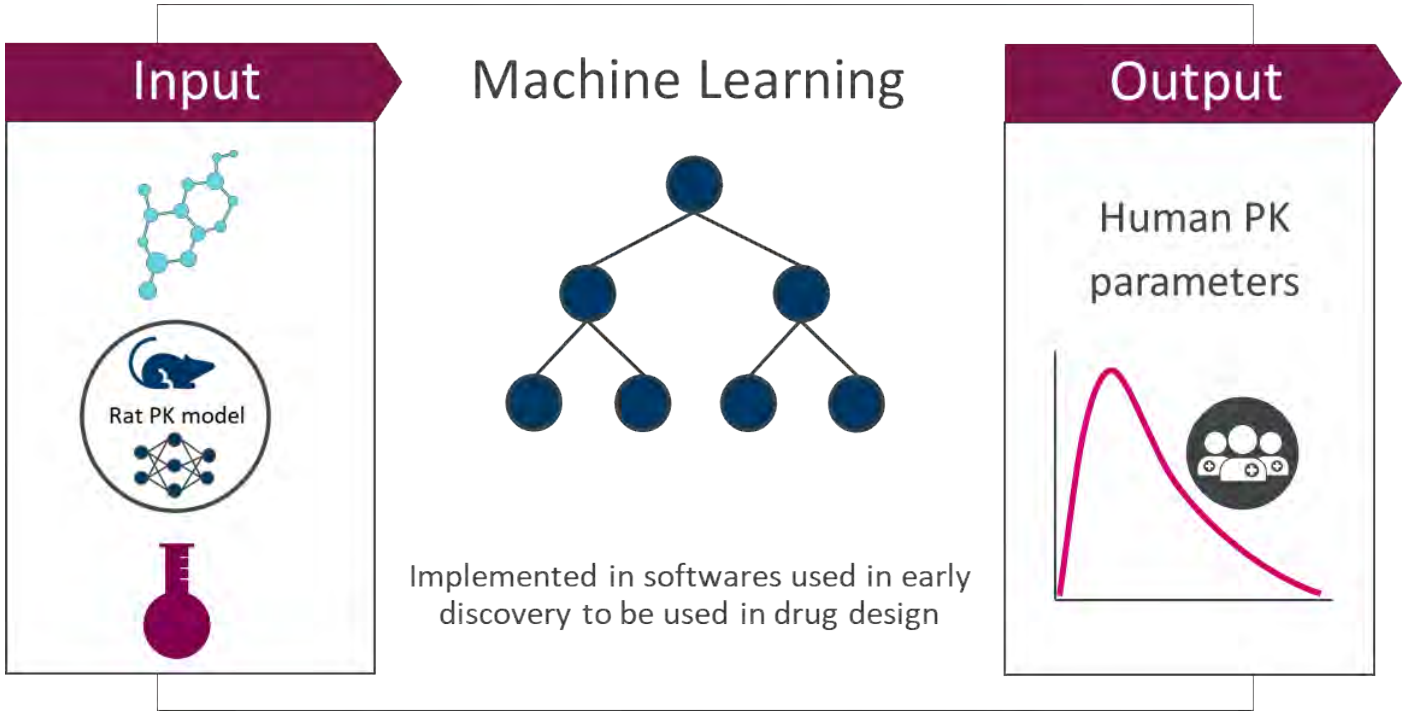
- Patient groups with signs of decreased PK functionality
- Incompatible assay technologies
- Concomitants with potential impact on PK
- *Plus others…*



Building a human PK model

Rat PK & *in vitro* predictions used as features in the model

- Random forest chosen as method after benchmarking
- Validated on both external and internal clinical data

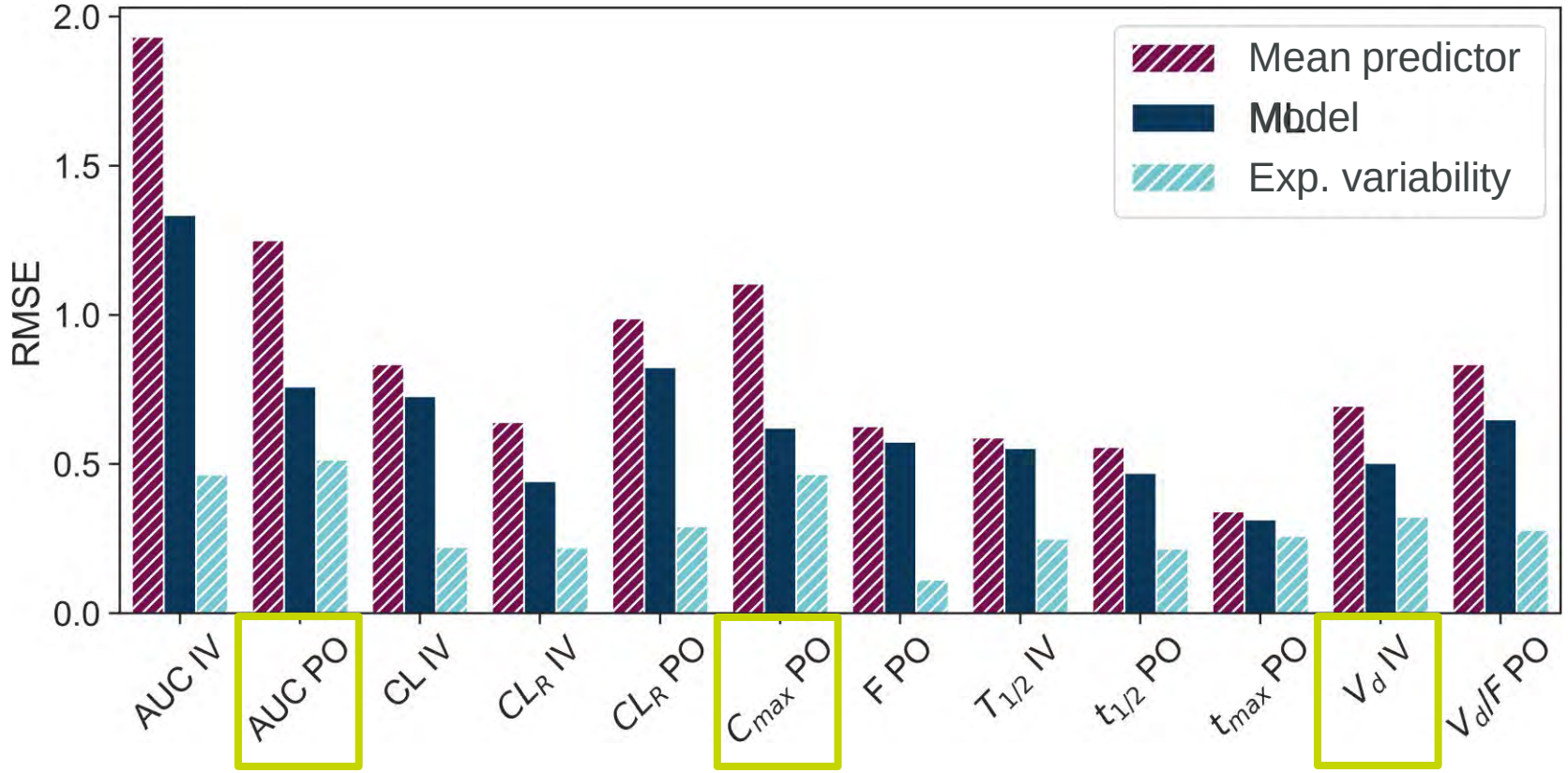


Miljković, Filip, *et al.* "Machine learning models for human in vivo pharmacokinetic parameters with in-house validation." *Molecular pharmaceutics* 18.12 (2021): 4520-4530.

Three models, AUC, Cmax & Vd are fit for purpose

- Putting performance in context with experimental variability
- Data distributions and availability impact model performance

External validation on FDA and EMA data

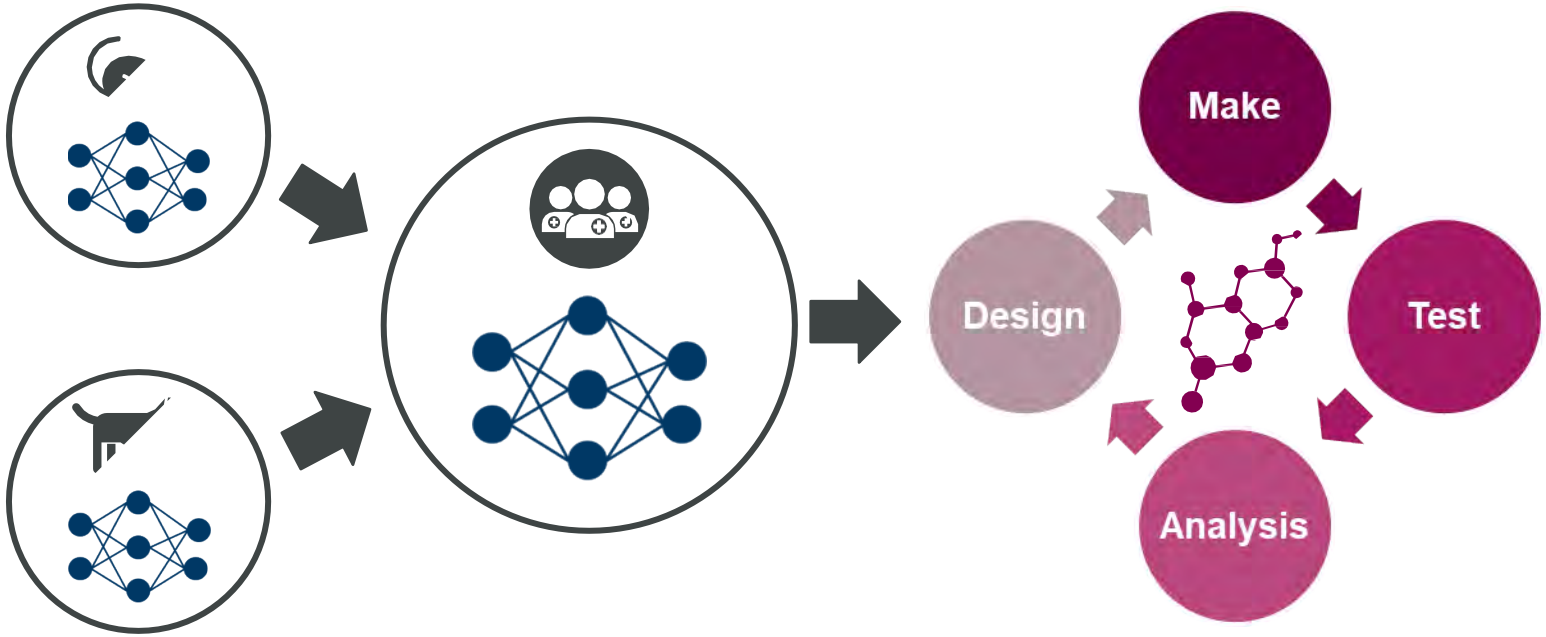


Values are log10 transformed
RMSE – root mean square error

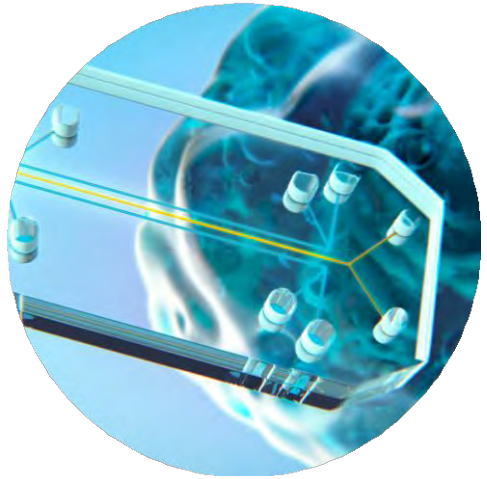
Improving human PK predictions

- Use rat and dog PK as part of a *feature set* for modelling human PK
- Utilize power of ***transfer learning*** to learn from one similar task to another

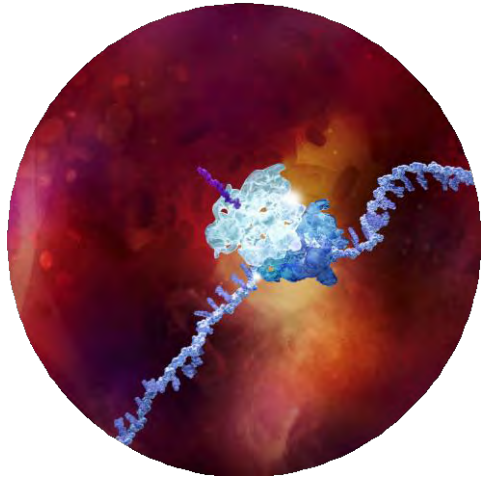
Enable human PK prediction at the point of design using chemical structure and dose



The changing face of toxicology



New HT multiplexed approaches for studying the effects of molecules on a biological system



Multi-omics technologies becoming mainstream generating 100k+ data points

Data science, machine learning and AI are improving the way we analyze and use data

Common approaches to early safety assessment

- Compounds of interest are tested against a wide range of assays
- Emphasis on **Cardiovascular**, **Hepatic** & CNS (**Secondary Pharmacology**)
- High quality compounds will be inactive, or have good selectivity in the *in vitro* safety assays
- Compounds with good selectivity have an increased chance of having large safety margins (Therapeutic Index) in vivo, or in the clinic.

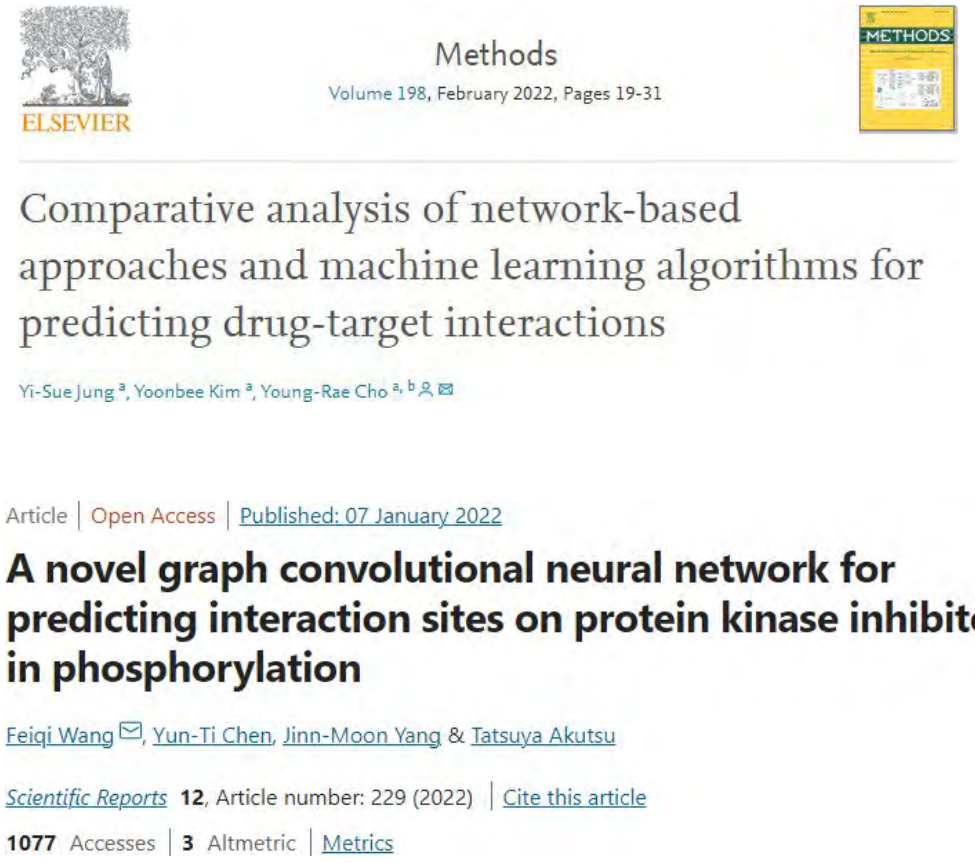
Target Organ	Assay
Cardiovascular	hERG
	NaV1.5
	Iks
	Kv4.3
	L-type calcium channel
	Cardiomyocyte
	Structural Cardiovascular Tox
Hepatic	Glu/Gal Mitochondrial Assay
	High Content Mitotox assay
	Cytotoxicity
	Hepatic Spheroid
	Liver Transporters (BSEP & MRP2)
Genetic Toxicity	AMES Mutagenicity Test
	In vitro Micronucleus
Various	**Secondary Pharmacology** Panels
	Phospholipidosis
	AhR (CYP1a1)

Broad Panel Pharmacological Profiling

"Every drug has two actions – the one you know about, and the one you don't"

Sir John Gaddum 1900-1965

- The off target profile cannot be predicted by the primary therapeutic target
- 75% of adverse drug reactions (ADR) are dose-dependent and predictable from pharmacology (Type AADRs)
- All large pharma adopt broad *in vitro* profiling strategies



ELSEVIER

Methods

Volume 198, February 2022, Pages 19-31

Comparative analysis of network-based approaches and machine learning algorithms for predicting drug-target interactions

Yi-Sue Jung [a], Yoonbee Kim [a], Young-Rae Cho [a, b]

Article | Open Access | Published: 07 January 2022

A novel graph convolutional neural network for predicting interaction sites on protein kinase inhibitors in phosphorylation

Feiqi Wang, Yun-Ti Chen, Jinn-Moon Yang & Tatsuya Akutsu

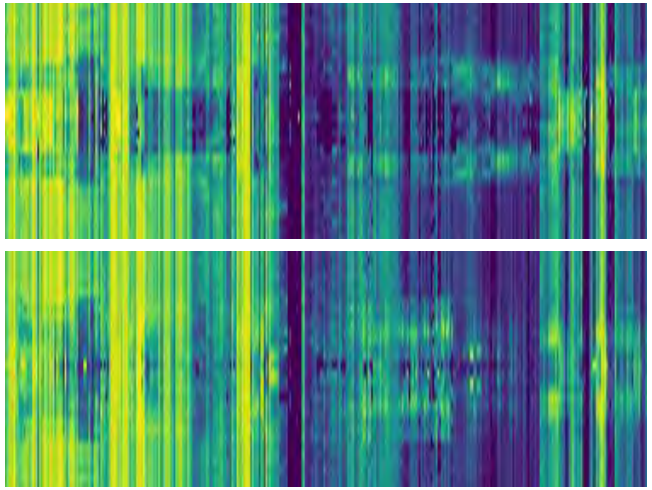
Scientific Reports **12**, Article number: 229 (2022) | Cite this article

1077 Accesses | **3** Altmetric | Metrics

Machine learning approaches are improving safety read outs

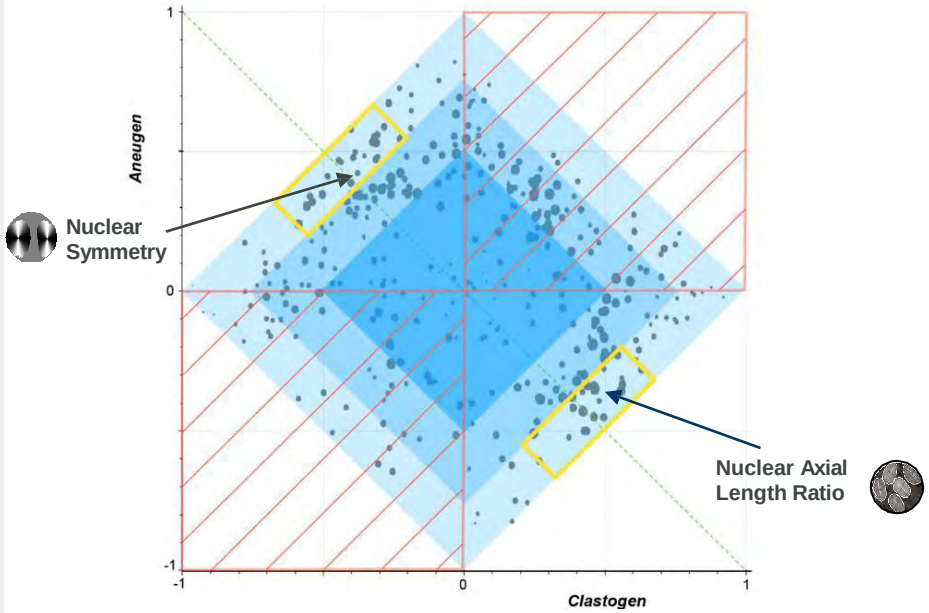
Applying machine learning to high content imaging data reveals new insights

Interpretation and visualisation of results



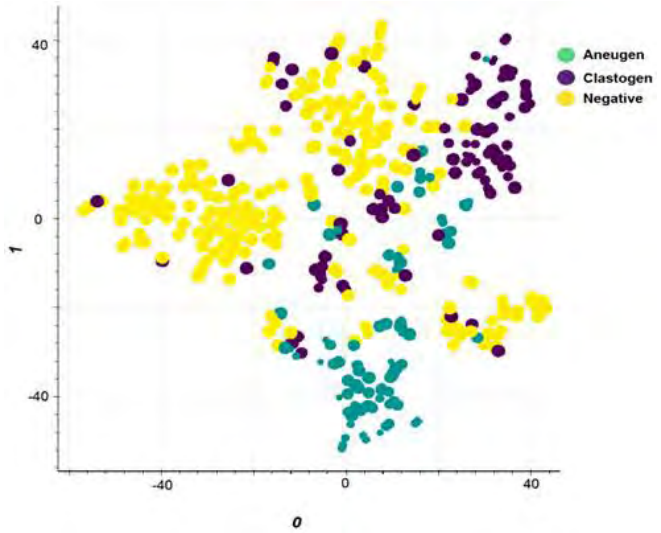
Suitable for deep learning techniques

Gain insights into data that were not previously available



Nuclear morphology alone can predict compound MOA

Generate accurate, unbiased predictions



98% compounds correctly classified (Confidence >80%)

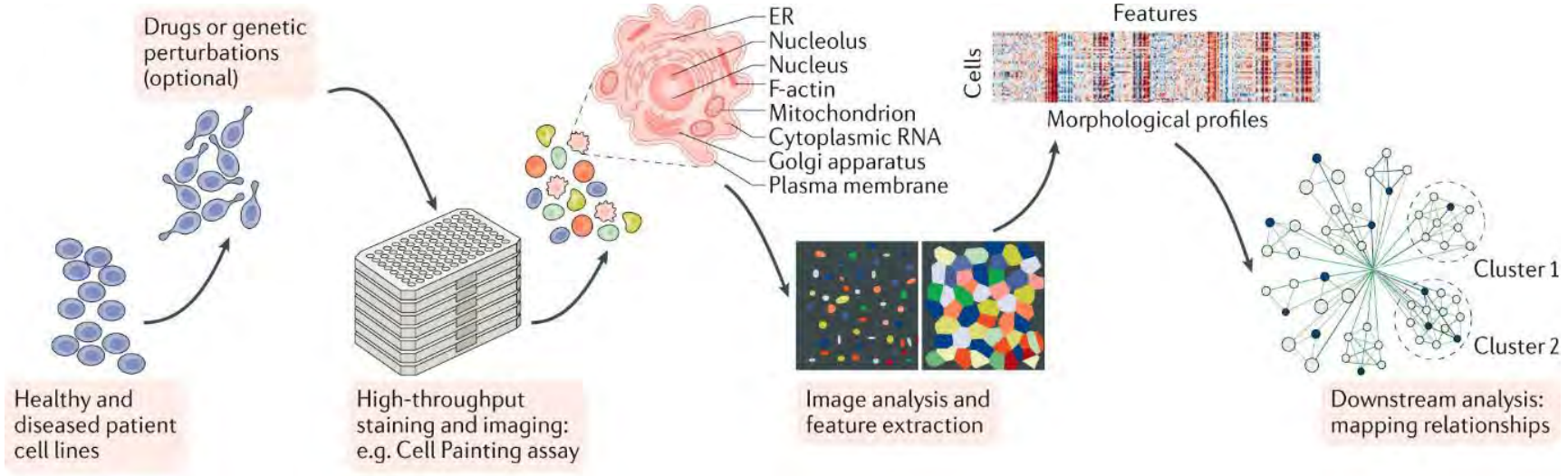
Significantly reduce time required for data analysis and increase throughput of the assay

In collaboration with Imperial College London, Tim Ebbles and Xiaokai Cui

New technologies for assessing hazards e.g. cell painting

Cell Painting, a high-content image-based assay for morphological profiling using multiplexed fluorescent dyes

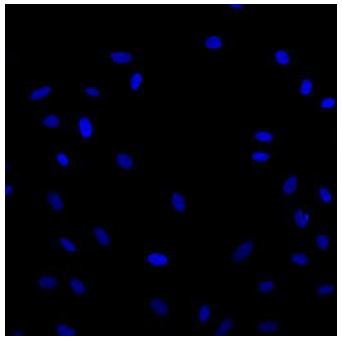
Mark-Anthony Bray[1], Shantanu Singh[1], Han Han[2], Chadwick T Davis[2], Blake Borgeson[2], Cathy Hartland[3], Maria Kost-Alimova[3], Sigrun M Gustafsdottir[3], Christopher C Gibson[2] & Anne E Carpenter[1]



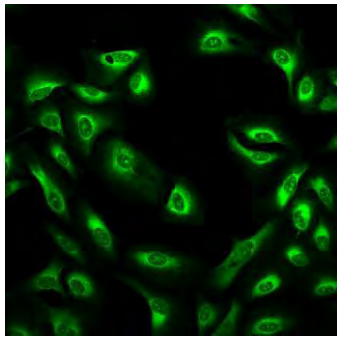
- Cell Painting captures 5 images per cell, 100s of cells per well
- Rich morphological description of cellular states

Chandrasekaran et al. (2020)

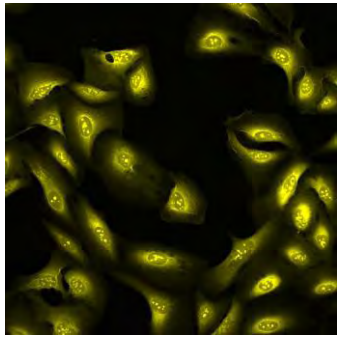
6 fluorescent dyes label 8 cellular compartments:



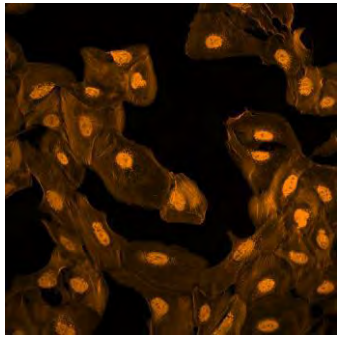
Nuclei
Hoechst



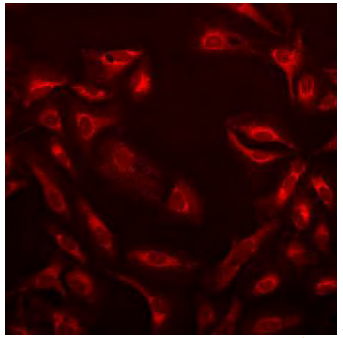
ER
Concanavalin A



RNA
SYTO 14



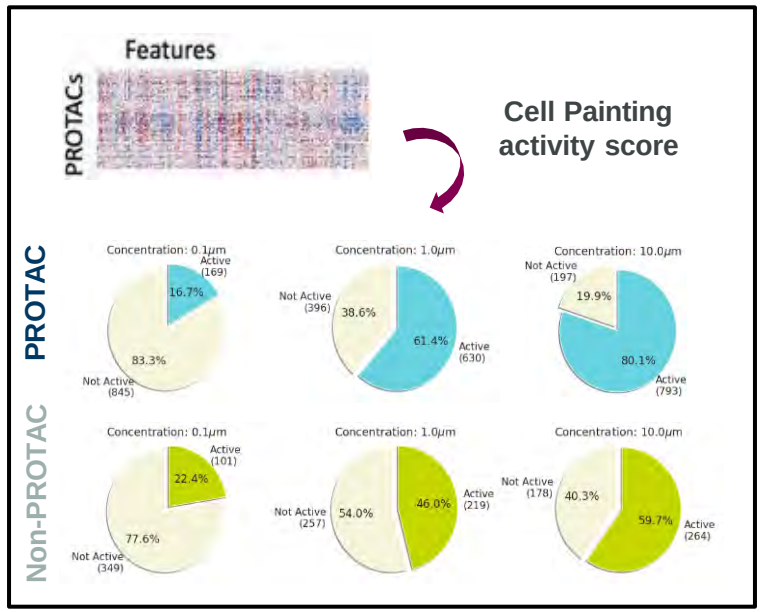
Actin, Golgi & Plasma membrane
Phalloidin & WGA



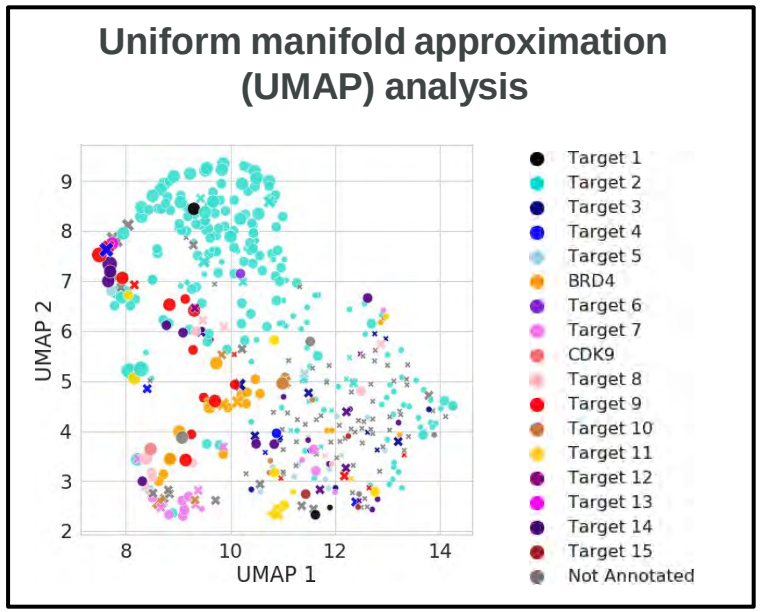
Mitochondria
Mitotracker

High throughput imaging for safety profiling

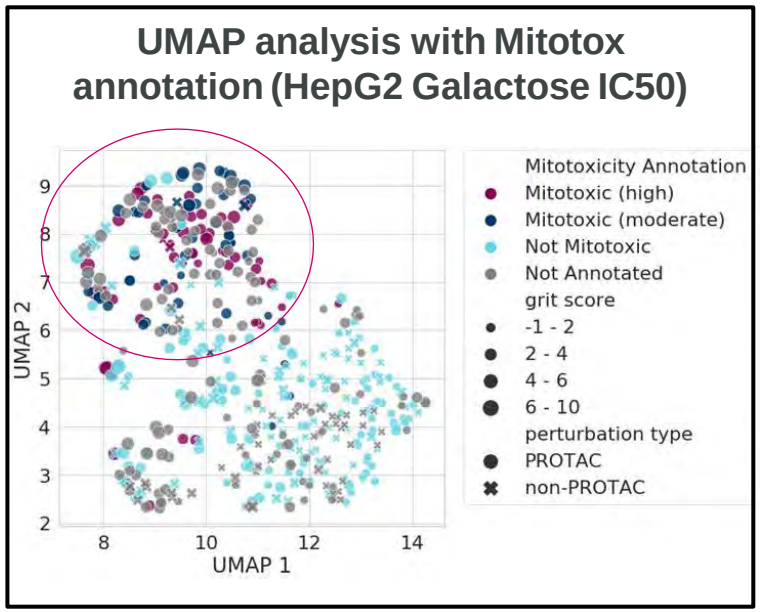
Cell Painting enables compound scoring



…enables chemical clustering



…enables safety prediction



Multi-omics technologies create a “data avalanche”

- Multi-omics allow for the generation of tens of thousands of data points per sample
- Machine learning approaches enable the digestion and use of high dimensional data sets
- Predictions of liver injury across a range of exposures enables the determination of a “safe” dose

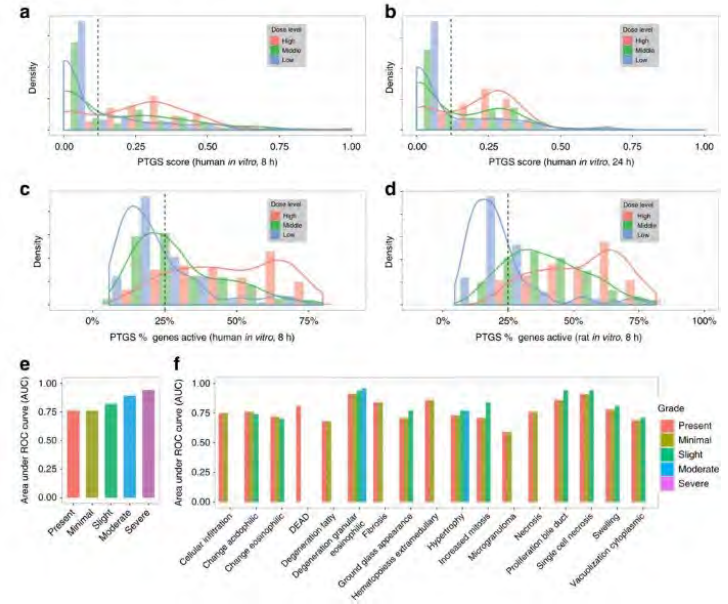
Open Access | Published: 03 July 2017

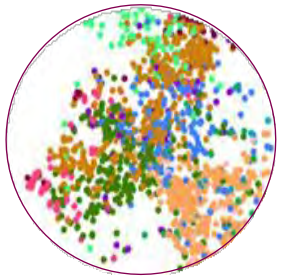
A transcriptomics data-driven gene space accurately predicts liver cytopathology and drug-induced liver injury

Pekka Kohonen, Juuso A. Parkkinen, Egon L. Willighagen, Rebecca Ceder, Krister Wennerberg, Samuel Kaski & Roland C. Grafström

Nature Communications **8**, Article number: 15932 (2017) | Cite this article

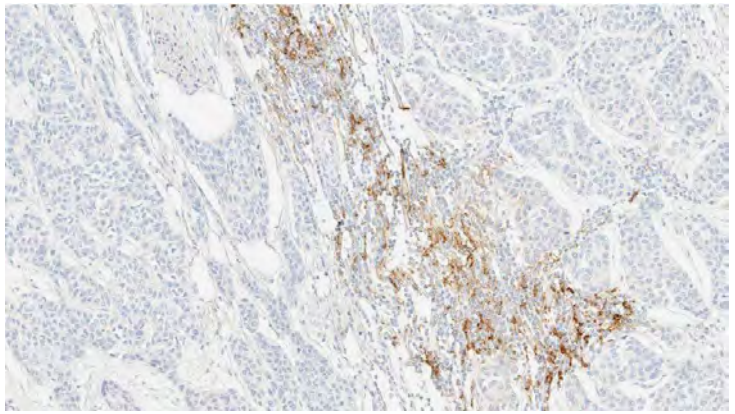
Figure 5: Validation of the PTGS using *in vitro* and *in vivo* profiles from the TG-GATEs toxicogenomics database.





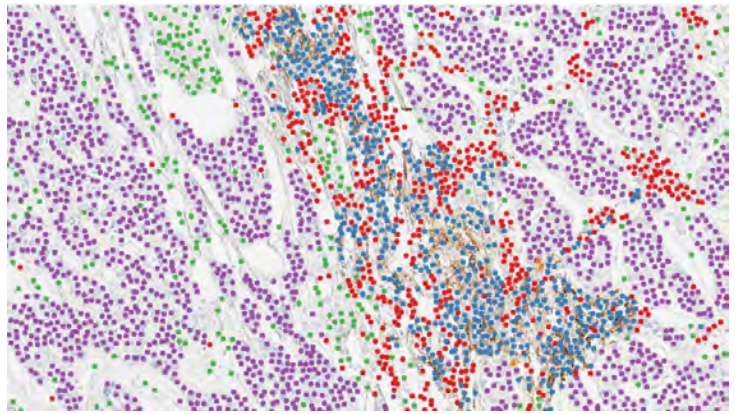
Digital pathology and beyond

Human assessment



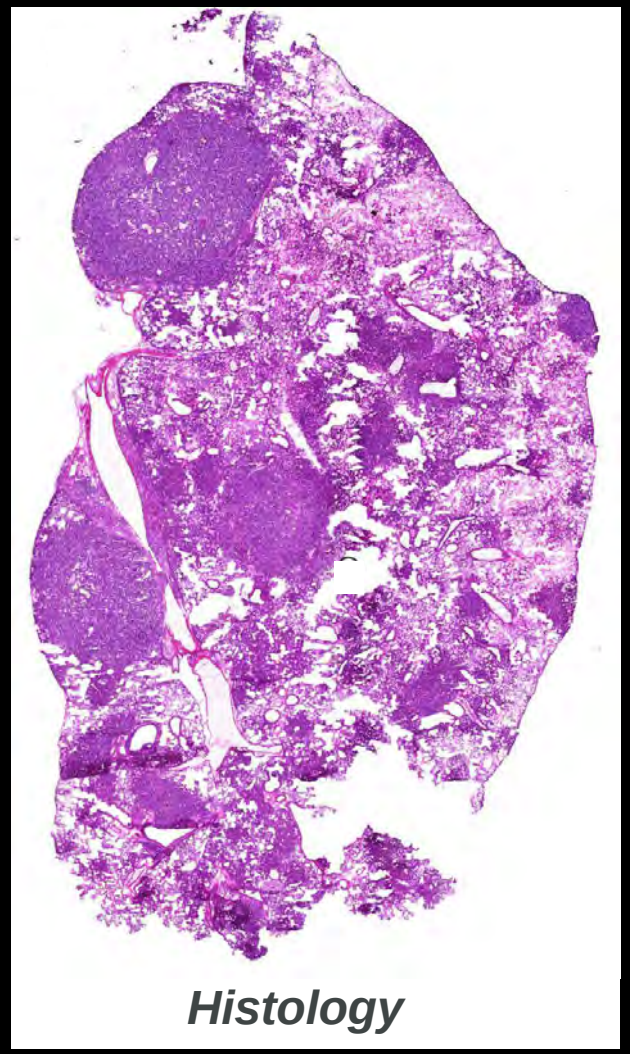
Complexity : **+++**
Training : **years**
Time : **20min**
Error rate : **10-20%**

AI-based assessment

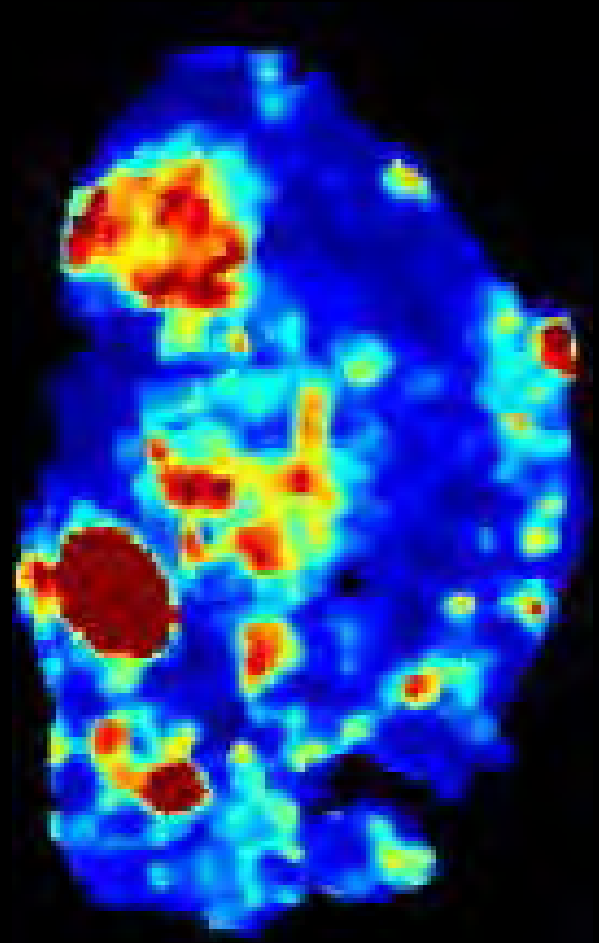


Complexity : **+++**
Training : **days**
Time : **seconds**
Error rate : **0.65%**

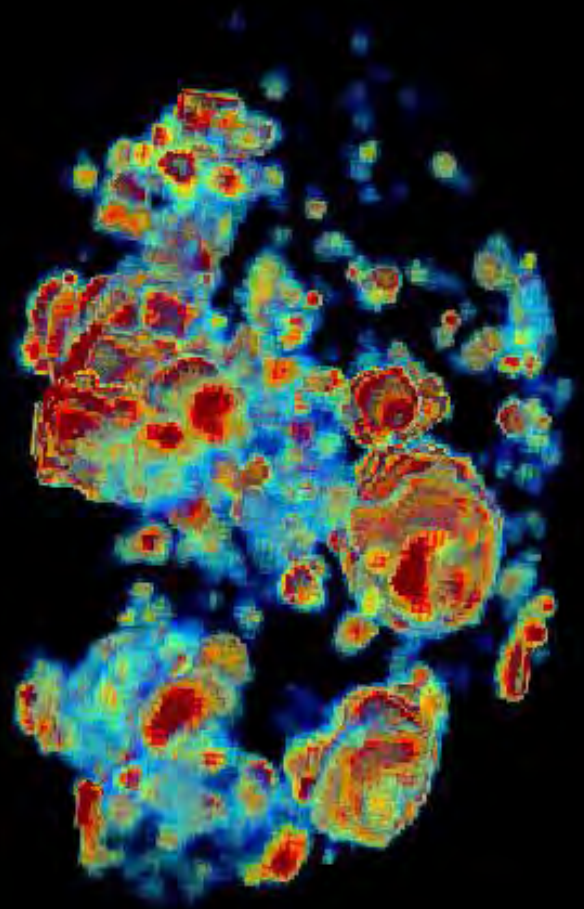
Advanced imaging is changing the way we can understand disease and evaluate drug safety



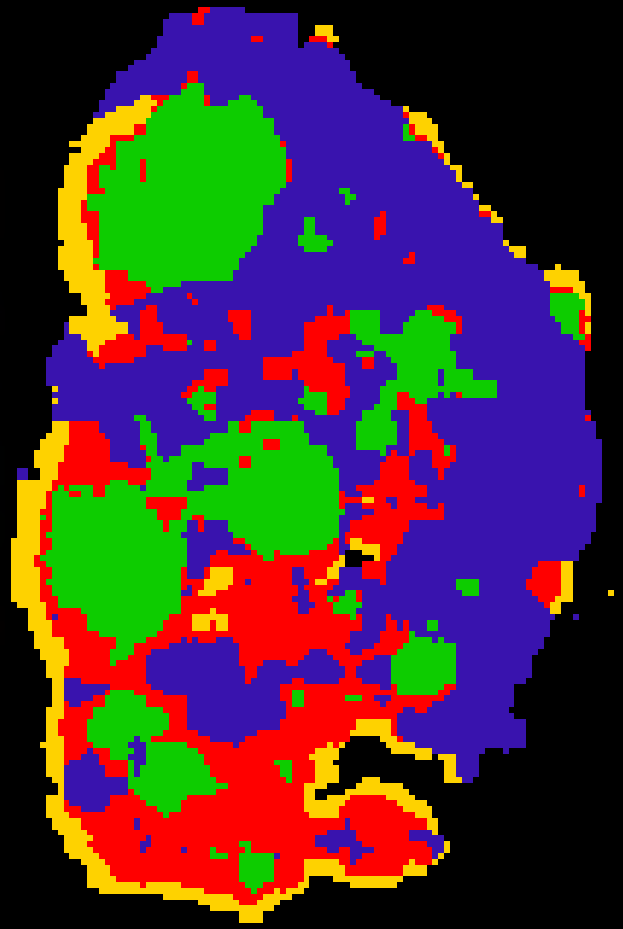
Histology



MSI



3D-MSI



Spatial Clustering

Standard for Exchange of Nonclinical Data (SEND)

- Nonclinical data standard developed by Clinical Data Interchange Standards Consortium (CDISC)
- Guide for organization, structure and format of electronic data files
- Data for individual/pooled animals
- SEND became a requirement for submissions to the FDA for studies started on or after:
  - **18th December 2016** for NDA, and
  - **18th December 2017** for IND

2.3 THE SENDIG STANDARD DOMAIN MODELS

The following standard domains with their respective domain codes have been defined or referenced by the CDISC SEND Team in this document.

Special-Purpose Domains (Section 5)

- Demographics – DM
- Subject Elements – SE
- Comments – CO

Interventions General Observation Class (Section 6.1)

- Exposure – EX

Events General Observation Class (Section 6.2)

- Disposition – DS

Findings General Observation Class (Section 6.3)

- Body Weights – BW
- Body Weight Gains – BG
- Clinical Observations – CL
- Death Diagnosis – DD
- Food and Water Consumption – FW
- Laboratory Test Results – LB
- Macroscopic Findings – MA
- Microscopic Findings – MI
- Organ Measurements – OM
- Palpable Masses – PM
- Pharmacokinetics Concentrations – PC
- Pharmacokinetics Parameters – PP
- Subject Characteristics – SC
- Tumor Findings – TF
- Vital Signs – VS
- ECG Test Results – EG

Trial Design Domains (Section 7)

- Trial Elements – TE
- Trial Arms – TA
- Trial Sets – TX
- Trial Summary – TS

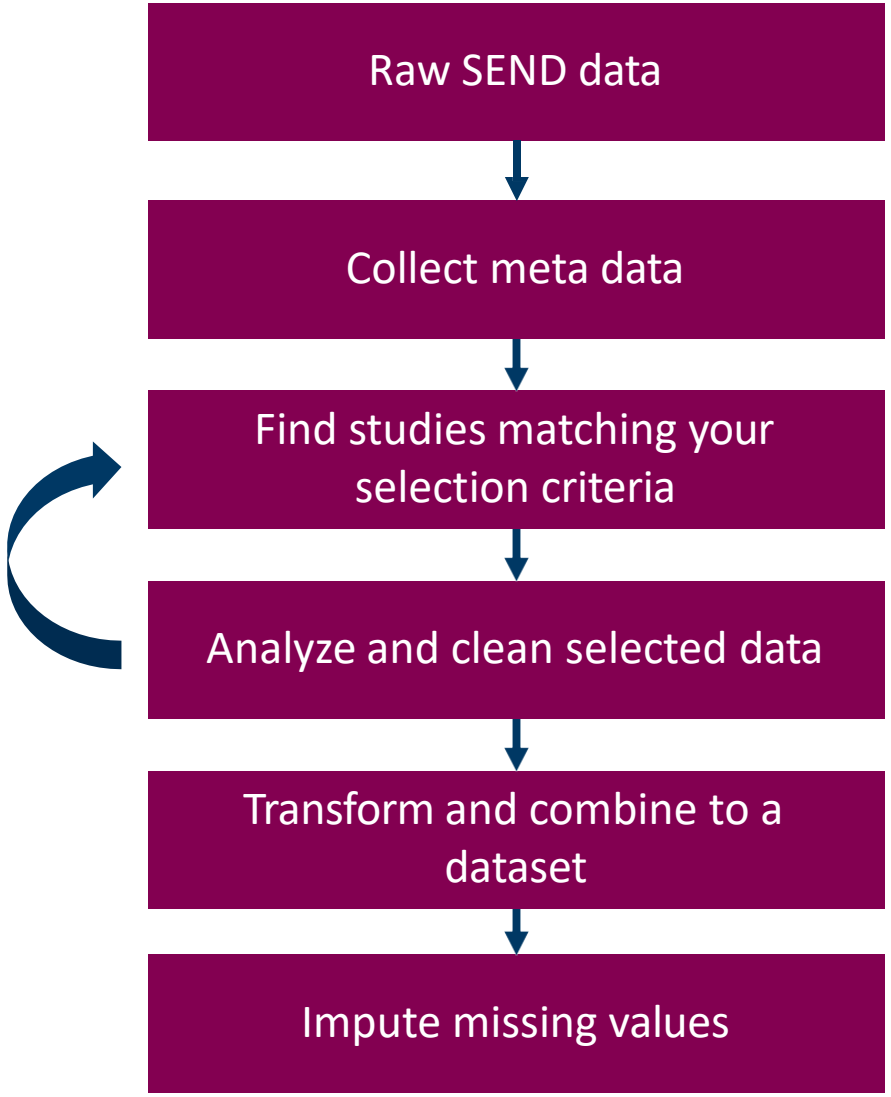
Relationship Datasets (Section 8)

- Supplemental Qualifiers – SUPP--datasets
- Related Records – RELREC
- Pooling – POOLDEF

SEND data harmonization is challenging

Before using SEND formatted data, it requires extensive harmonization:

- Unit standardization
- Correcting misspellings
- Grouping of similar terms
- Removing low frequency terms
- Removing rows with missing data in important columns



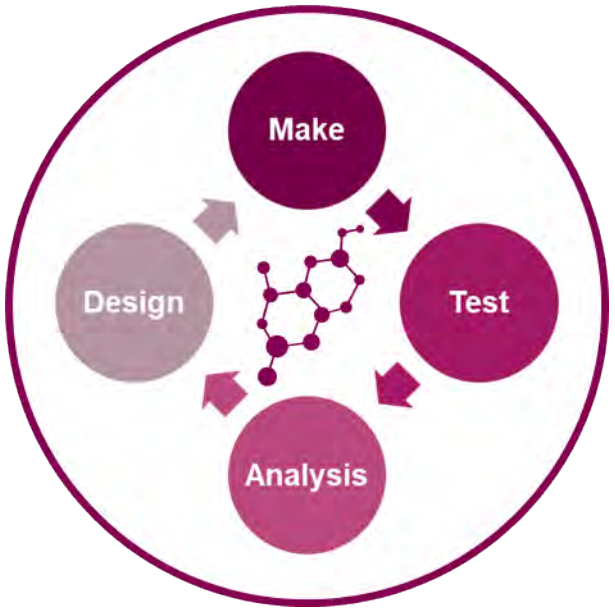
Example: Histopathology (MI domain) data challenges

- It is hard for non-experts to know which of these terms have the same meaning
- Are any terms meaningless in toxicity context?
  - E.g., PIGMENTED MACROPHAGE
- Other organs have similar situation

Example: male rat heart findings

NORMAL	612
UNREMARKABLE	257
INFILTRATION, MONONUCLEAR CELL	30
DEGENERATION/NECROSIS	18
INFILTRATE	7
CARDIOMYOPATHY	4
NECROSIS/INFLAMMATORY CELL INFILTRATE, CARDIOMYOCYTE	4
DEGENERATION	3
MINERALIZATION	3
INFILTRATE, INFLAMMATORY CELL	2
NECROSIS	2
INFILTRATE, INFLAMMATORY CELL, MYOCARDIUM	1
MONONUCLEAR CELL INFILTRATE/FIBROSIS	1
FIBROSIS	1
INFLAMMATION, EPICARDIUM	1
PIGMENTED MACROPHAGE	1
INFLAMMATION, MONONUCLEAR CELL	1

ML models enable efficient compound design



Integrated into Augmented Drug Design tools to improve speed and efficiency in DMTA cycle

Help design compounds with better safety and PK properties early in drug discovery

Modelling human PK gives confidence in preclinical translation to the patient

Why is now the time for change?

"Artificial intelligence will not replace scientists, but those who don't use AI will be replaced by those who do."

Acknowledgements

- Richard Goodwin
- Mishal Patel
- Andreas Bender
- Graham Smith
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- Filip Miljković
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- Piotr Grabowski
- Werngard Czechtizky
- Samantha Hughes
- Anders Hogner
- Paulius Mikulskis
- Martin Johnson
- Andy Sykes
- Kevin Moreau
- Beth Williamson
- Susanne Winiwarter
- Emma Evertsson
- Prakash Rathi
- Gianmarco Ghiandoni
- Vignesh AJ

And many, many others….

Session 4 Panelists

Panelist

Dr. Fabio Broccatelli
Associate Director, DMPK
Group Leader
Bristol Myers Squibb

Panelist

Dr. Beth Joshi
Executive Director, Discovery
Metabolism and Pharmacokinetics

Bristol Myers Squibb

Panelist

Dr. Prashant Desai
Senior Principal Scientist

Genentech

Moderator

Dr. Cornelis "Marcel" Hop
Vice-President

Genentech

Speaker

Dr. Richard Bonneau
Co-founder & Executive Director
Prescient Design
Genentech

Speaker

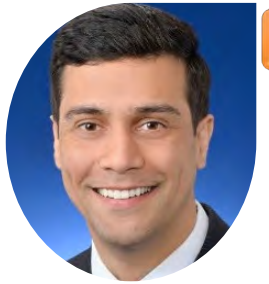
Dr. John Sanders
Senior Director

Merck & Co., Inc.

Speaker

Dr. Nigel Greene
Senior Director, Imaging &
Data Analytics

AstraZeneca



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