APPLIED PHARMACEUTICAL TOXICOLOGY

May 13-15, 2025

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SOUTH SAN FRANCISCO, CA

PROGRAM GUIDE

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ABOUT OUR SPONSORS

SYSTEMIC BIO is building a next-generation platform for human-relevant therapeutic safety and efficacy assessment using bioprinted tissues. Founded in 2022 and backed by over $15M in investment, we operate from a state-of-the-art ISO 7 cleanroom facility in Houston with the capacity to produce more than 6,000 tissues per month. Our platform leverages 3D Systems' industrial-grade bioprinting technology to create vascularized models of healthy and diseased human tissue. These advanced organ-on-chip systems are being used in collaboration with leading pharmaceutical companies to develop predictive models for high-impact applications such as immune recruitment, drug-induced liver injury (DILI), and drug-induced vascular injury (DIVI).

AXOSIM is a life science company working to create a world where no one surrenders their identity, independence, and quality of life to neurological disease. In partnership with pharmaceutical companies, AxoSim builds human brains and peripheral nerves in the lab to heal memory, movement, and pain disorders. The proprietary brain-on-a-chip platform leverages tissue engineering, neural interfacing and AI to test groundbreaking interventions at scale, generating human-relevant data early in the drug development process to increase the probability of success. Visit axosim.com for more information.

CYPROTEX Founded in 1999, Cyprotex (www.cyprotex.com) has grown to become an industry leader in in vitro and in silico ADME-Tox. The company, with sites in the UK and USA, was acquired by Evotec (www.evotec.com) in 2016. The Evotec Group offer expert support from early discovery through to clinical development.

AIRA MATRIX delivers cutting-edge artificial intelligence solutions for healthcare and life sciences applications. Our innovative products and services drive efficiency, enhance diagnostic accuracy, and provide data-driven insights from digitally scanned images.

INVENTIA LIFE SCIENCE (is a pioneer in the development of phenotypically-relevant cell models through our innovative RASTRUM™ platform—including the high-throughput RASTRUM Allegro™ system—and comprehensive Discovery Services. We empower researchers to explore cell behaviors and treatments in environments that mimic the human body. Our platform integrates advanced 3D cell model architectures, matrices, and precision drop-on-demand technologies, facilitating a deeper understanding of complex biological systems. With the introduction of RASTRUM Allegro, we've expanded our capabilities to deliver fast, reproducible model generation at scale—enabling higher throughput and broader adoption. We also offer a full spectrum of custom services designed to support our partners at every step of their journey. Inventia Life Science delivers reproducible results at scale, pushing the boundaries of what's possible in our understanding of health and disease.

NEWCELLS BIOTECH is a pioneering company specializing in predictive human tissue models derived from induced pluripotent stem cells (iPSCs). Based in Newcastle upon Tyne, UK, the company develops advanced in vitro systems that replicate the structure and function of key human organs, including the retina, kidney, and liver lung. These models enable pharmaceutical and biotech companies to evaluate drug efficacy, safety, and toxicology with greater accuracy, reducing costs and accelerating development timelines.

Newcells Biotech is renowned for its kidney proximal tubule and retinal organoid models, widely used to predict nephrotoxicity and ocular toxicity in preclinical studies. Its proprietary platforms also support ADME (absorption, distribution, metabolism, and excretion) research, offering tailored solutions to enhance drug development. With a focus on innovation and collaboration, Newcells Biotech partners

with global organizations to improve translational research, reduce reliance on animal models, and deliver safer, more effective therapies for patients.

SNBL is Japan's oldest nonclinical CRO and has the largest share of the domestic nonclinical testing market. Since 1957, when SNBL was founded, we have steadily expanded our operations in Japan and globally, supporting in particular development of biologics as new therapeutic modalities. SNBL is one of the few providers in the world capable of covering all stages of nonclinical drug development, including reproductive and developmental toxicity studies in NHPs and abuse liability studies. For four decades, we have been conducting safety studies in compliance with various GLP standards, such as PMDA GLPs for medical devices and for regenerative medicine, FDA GLP, and OECD GLP and our data has been used in submissions to the US, Canada, Japan and the EMA. We are also actively involved in animal welfare and have been fully accredited by the AAALAC International.
SNBL is ready to support your drug development in our GLP facilities.

TOXPLUS MONITORING established January 2020, is a dedicated, client-focused company that provides nonclinical operations support services including study monitoring, study management, vendor audits and regulatory writing support. We serve pharmaceutical and biotech companies in early to late-stage drug development. Services include:

- Study monitoring for non-GLP and GLP nonclinical studies: Our Study Monitors are located within driving distance to most CROs. They ensure that a study is conducted in compliance with an approved protocol, protocol amendments and regulatory guidelines. They provide oversite of procedures being performed, proper data collection and documentation of study results.
- Data audit for non-GLP and GLP studies: Our Data Auditors review all study notebooks to ensure data has been collected according to protocol and any deviations resolved.
- Vendor audit/qualification: Our Auditors will ensure that a CRO has the capability to conduct a study and is qualified to do so from both a technical and quality compliance standpoint.
- Study management of nonclinical studies: Our Study Managers will ensure your nonclinical program is executed according to its planned strategy. They will interact with Study Directors to address questions and keep the client up to date on all study events and outcomes. This is ideal for start-up to mid size companies without resources to support nonclinical study oversight.
- Regulatory writing support: Our regulatory writers support the writing of INTERACT and pre-IND meeting regulatory documents, IND and NDA Module 2.0 including tabulated summaries, summaries for other regulatory agencies, IBs, and Data QCing.

ORGANIZERS' WELCOME

Welcome to the 2025 Applied Pharmaceutical Toxicology Conference.

Our organizers have gathered another excellent group of speakers for the annual APT conference. The program is arranged to incorporate extensive audience participation and discussion. We encourage attendees to take full advantage of the opportunity to engage in discussion in order to receive the maximum benefit from the APT experience. Thank you for your participation.

ORGANIZING COMMITTEES

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Chair: Jodi Goodwin, Takeda
Chair-Elect: Darcey Clark, Merck

DISCOVERY

Toxicology Workshop Organizers

Chair: Jodi Goodwin, Takeda
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Committee:
Jonathan Heyen, Treeline Bio
Prathap Kumar Mahalingaiah, AstraZeneca
Rama Pai, Merck
Yoav Timsit, Novartis
Lauren Walker, Pliant Therapeutics
Connie Wu, Genentech
Helen Yu, Vertex

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Toxicology Workshop Organizers

Chair: Betty Pettersen, Alexion
Chair-Elect: Yuan Lu, CinRx Pharma

Committee:
Surekha Akella, AbbVie
Joe Cichocki, Vertex
Ed Dere, Genentech
Birgit Fogal, Boehringer Ingelheim
Pia Kasperkovitz, Bright Peak Therapeutics
Heather Kowalski, BlueRock Therapeutics
Jon Maher, Pliant Therapeutics
Christine Mollica, Amgen
Daniella Pizzurro, Merck
Michael Santostefano, Merck
Radha Sura, Gilead
Nardos Tassew, The Janssen Pharmaceutical Companies of Johnson & Johnson

APT 2025 CONFERENCE AGENDA

TUESDAY, MAY 13
DISCOVERY TOXICOLOGY WORKSHOP

12:00 - 1:00 **Registration & Lunch**

1:00 - 1:10 **Conference Opening and Plenary Speaker Introduction**
Jodi Goodwin, Takeda

1:10 - 1:55 **PLENARY LECTURE:**
Integrating Generative AI with Active Learning to Power Next Generation Drug Discovery
Richard Bonneau, Genentech

SESSION I: Digital Pathology & Spatial Transcriptomics (Applications)
Moderators: Yoav Timsit, Novartis; Darcy Clark, Merck & Jodi Goodwin, Takeda

1:55 - 2:00 **Session Introduction**

2:00 - 2:30 **Comparison of Supervised and Unsupervised Machine Learning Scoring of Histology Images**
Tom Forest, Merck

2:30 - 3:00 **Model Detection of the Seen and Unseen:**
A Multi-paradigm Approach to Histologic Anomaly Detection
Fangyao Hu, Genentech

3:00 - 3:25 **VENDOR PRESENTATION:**
h-VIOS: A Human-relevant Drug Discovery and Development Platform Using Bioprinted Tissues
Taci Pereira, systemicBIO

3:25 - 3:50 Break

3:50 - 4:20 **Computational Pathology Applied to Toxicologic Pathology**
Byunghak (BK) Kang, Novartis

4:20 - 4:50 **Context-specific Applications Across Spatial Transcriptomic Platform**
David Gallegos, Takeda

4:50 - 5:10 **RAPID-FIRE POSTER PRESENTATIONS:**
1. Logan Porter, Lena Biosciences
2. Maria Walczak, Jagiellonian Univ. Medical College, Poland
3. Julia Co, Genentech
4. Sue Grepper, inSphero

5:10 - 5:15 **Day 1 Closing Remarks**

APPLIED PHARMACEUTICAL TOXICOLOGY

WEDNESDAY, MAY 14
DISCOVERY TOXICOLOGY WORKSHOP

7:00 - 8:00 **Registration & Breakfast**

SESSION II: Traditional & New Modalities - Case Studies
Moderators: Connie Wu, Genentech, Jonathan Heyen, Treeline Bio & Helen Yu, Vertex

8:00 - 8:05 **Session Introduction**

8:05 - 8:35 **Safety Considerations for Developing Molecular Glues and other Targeted Protein Degraders**
Jessica Sims, Genentech

8:35 - 9:05 **Global Off-Target Profiling of Targeted Protein Degraders with a Cell-Based Proteomics Platform**
Xiaoting Wang, Amgen

9:05 - 9:35 **Oligonucleotides in Discovery: A Case Study of an siRNA for the Treatment of Chronic Hepatitis B Virus Infection**
Dinah Misner, Aligos Therapeutics

9:35 - 9:50 **VENDOR PRESENTATION:**
Preclinical Neurotoxicity Prediction Using a High-Throughput Neural Spheroid Model
David A. Gallegos, Takeda

AxoSim

9:50 - 10:10 Break

SESSION III: 4th Generation of ADC's
Moderators: Rama Pai, Merck & Prathap Kumar Mahalingaiah, AstraZeneca

10:10 - 10:15 **Session Introduction**

10:15 - 10:40 **Nonclinical Safety Assessment of Antibody-Oligo Conjugates from IND-enabling through Late-Stage Clinical Trials**
Laura Leung, Avidity Biosciences

10:40 - 11:05 **The Use of In Vitro Assays for Novel Payload Selection in New-Generation ADCs**
Diana Lac, Genentech

11:05 - 11:30 **Opportunities and Challenges for Preclinical Assessment of Next Generation ADCs**
Haley Neff-LaFord, Pfizer

11:30 - 11:55 **Integrating PKPD Modeling and Clinical Toxicity Meta-Analysis towards Therapeutic Index prediction for Antibody-Drug Conjugate**
Mahua Roy, AstraZeneca

11:55 - 12:20 **VENDOR PRESENTATION:**
An AI Approach to Drug-Induced Liver Injury Risk: Prediction of Safe Maximum Doses from Toxicogenomic Profile
Chris Strock, Cyprotex

cyprotex AN EVOTEC COMPANY

12:20 - 1:40 **Lunch**

DEVELOPMENT TOXICOLOGY WORKSHOP

1:40 - 1:50 **Workshop Introduction and Speaker Introduction**

1:50 - 2:30 **PLENARY LECTURE:**
Harnessing Generative AI in Nonclinical Safety Evaluation
Zhichao Liu, Boehringer Ingelheim

SESSION IV: Revolutionizing Toxicology and Reducing Animal Experimentation: New Approach Methodologies (NAMs) and Virtual Controls

Moderators: Betty Pettersen, Alexion, Yuan Lu, CinRx Pharma & Surekha Akella, AbbVie

2:30 - 2:35 **Session Introduction**

2:35 - 3:05 **Opportunities and Insights From Pharma On the Use of NAMs to Replace Large Animal Studies in Nonclinical Safety Assessments for Biotherapeutics**
Kim Homan, Genentech

3:05 - 3:35 **Advancing Pre-Clinical Safety Assessment with Advanced Cell Models**
Natacha Bohin, AstraZeneca

3:35 - 3:55 Break

3:55 - 4:25 **Leveraging the Proteome: Harnessing in vitro NAMs to Understand Human and Non-Human Protein Binding Profiles for Therapeutics**
Nick Brown, Charles River Laboratories

4:25 - 4:55 **Insights into Building a Robust Virtual Control Database and Selection Methods for Use on Retrospective Analysis of Nonclinical Safety Assessment Studies**
Jillian Wendel, LabCorp

4:55 - 6:10 **Poster Viewing and Reception**

THURSDAY, MAY 15

7:00 - 8:00 **Breakfast**

DEVELOPMENT TOXICOLOGY WORKSHOP

8:00 - 8:05 **Workshop Introduction**

SESSION V: New Generations ADC's (Antibody-siRNA-Conjugates (ARC), Peptide-drug Conjugates (PDC)

Moderators: Christine Mollica, Amgen; Ed Dere, Genentech; Daniella Pizzurro, Merck & Pia Kasperkovitz, Bright Peak Therapeutics

8:05 - 8:10 **Session Introduction**

8:10 - 8:35 **Nonclinical Safety Strategies for ADC Development: Looking Back to Move Forward**
Christina de Zafra, Merck

8:35 - 9:00 **Unique Platform Toxicities of ADCs: Learnings Over the Last Decade**
Magali Guffroy, AbbVie

9:00 - 9:25 **Case Study: Regulatory Interactions and Path to IND for a Novel Antibody-Protein Conjugate**
Pia Kasperkovitz, Bright Peak Therapeutics

9:25 - 9:45 **Break**

SESSION VI: Pioneering Cell and Gene Therapies: Expanding Horizons Beyond CAR-T

Moderators: Heather Kowalski, BlueRock Therapeutics, Joe Cichocki, Vertex & Michael Santostefano, Merck

9:45 - 9:50 **Session Introduction**

9:50 - 10:15 **Protecting Allogeneic Transplants from Immune Rejection is the Key to Bringing Cell-Based Therapies to Patients**
Sonja Schrepfer, Sana Biotechnology

10:15 - 10:40 **Supporting Clinical Trials for Non-Cancer Cell Therapies: From Patient and Treatment Plans, Backwards**
Lauren Black, CRL

10:40 - 11:05 **Modeling Approaches to Support Dose Selection for Cell and Gene Therapies**
Raibatak Das, Quantilogix, LLC

11:05 - 11:10 **Conference Closing Remarks**

ABSTRACTS

DISCOVERY TOXICOLOGY WORKSHOP

PLENARY LECTURE

Integrating Generative AI with Active Learning to Power Next Generation Drug Discovery
Richard Bonneau, Genentech

We will first examine two kinds of problems, design module power and accuracy problems (tools that can be accelerated or improved with AI) and process optimization problems (connecting data and models to experimental design to speed and improve drug discovery). With this set up, we will explore how new approaches to generative AI are uniquely suited to enable faster better drug discovery; I'll illustrate this by describing the Genentech/Roche 'lab in the loop'. Powerful new design modules, like de novo hit finding will be discussed, as well as integrating multiple generative AI modules across the Genentech/Riche tech stack. With these core design modules and integrations illustrated we will proceed to describe implications for process optimization and speeding DD; with a focus on the strengths and weaknesses of both agentic and active learning frameworks. The talk will conclude with examples of how our ML-DD effort is integrated into active DD experimental teams and some of the innovations in that lab that AI and ML elicit.

SESSION I

Comparison of Supervised and Unsupervised Machine Learning Scoring of Histology Images
Tom Forest, Merck

Creating machine learning algorithms for identifying changes in histology slide images frequently involves training on prospectively identified histology findings. We previously created supervised learning models for image processing that accurately detect prospectively identified common histopathology findings in rodent nonclinical toxicology studies. While these supervised models are effective at detecting prospectively identified findings, our use-case in nonclinical toxicology study assessment requires sensitive detection of all potential histology findings. Therefore, we have studied the performance of unsupervised models capable of detecting findings not presented in training data. While these models have exhibited sensitivity comparable to experienced toxicologic pathologists, specificity has been variable and at times low. However, machine learning based annotations of the false positive results highlight genuine differences from the images patches used to train the models. Use of highly sensitive unsupervised models to score histology images from nonclinical toxicology studies will require an approach to evaluation that accommodates detection of minor deviations from training data.

Model Detection of the Seen and Unseen: A Multi-Paradigm Approach to Histologic Anomaly Detection
Fangyao Hu, Genentech

Anomaly detection presents a significant challenge in separating rare abnormalities from abundant normal data—a problem particularly relevant in toxicologic pathology where abnormal regions must be identified within slides predominantly containing normal tissue. We introduce a comprehensive framework that integrates complementary machine learning paradigms to identify and characterize tissue abnormalities across varied histological contexts. Our approach leverages advanced computational architectures to analyze whole slide images, employing both supervised and unsupervised techniques within existing pathologist workflows. Our results suggest that deep learning based anomaly detection methods are promising for real world toxicological pathology applications.

VENDOR PRESENTATION

h-VIOS: A Human-Relevant Drug Discovery and Development Platform Using Bioprinted Tissues
Taci Pereira, Systemic Bio

Over the past two decades, several innovations have significantly enhanced our ability to predict the safety and efficacy of therapeutics in humans, with the overarching goal of reducing failure rates and expediting the translation of these therapies to the clinic. These advances span a range of enabling tools, including bioprinting and tissue engineering technologies, in vitro models such as spheroids, organoids, and organ-chips, and in silico strategies that employ machine learning alongside large chemical, biological, and clinical datasets. Despite these advancements, a persistent challenge has been the generation of human-relevant, reproducible

preclinical data at scale. Traditional animal models often yield false positives and negatives due to intrinsic differences from human pathophysiology, while overly simplistic in vitro models struggle to capture the complexity of human biological processes crucial for assessing therapeutic safety and efficacy. The h-VIOS™ platform addresses this challenge by integrating bioprinted organ-chips that enable therapeutic delivery through endothelialized vasculatures into complex, three-dimensional tissues. This modular and customizable system enables the generation of multimodal data, ranging from high-content imaging to transcriptomics. In this presentation, we will explore the h-VIOS platform and discuss its applications in contexts-of-use such as drug-induced liver injury (DILI), drug-induced vascular injury (DIVI) prediction, and the evaluation of on-target, off-tumor effects of anticancer therapeutics.

Context-Specific Applications Across Spatial Transcriptomic Platform

David Gallegos, Takeda

Spatial transcriptomics platforms have revolutionized the study of gene expression by preserving the spatial context of tissue samples. This presentation will provide an overview of the various spatial transcriptomics technologies, including methods such as array-based strategies, in situ hybridization, in situ-sequencing, and microdissection methods. We will explore their unique capabilities, such as resolution, scalability, and the ability to correlate gene expression with histological features. The discussion will highlight the specific applications of these platforms across different pathology contexts, including cancer, neurodegenerative diseases, and developmental biology, demonstrating how spatial data types can enhance our understanding of tissue heterogeneity, disease progression, and microenvironmental influences.

SESSION II

Safety Considerations for Developing Molecular Glues and other Targeted Protein Degraders

Jessica Sims, Genentech

The field of targeted protein degraders is rapidly expanding and while it provides a novel and exciting way to target proteins that were previously considered to be undruggable, it presents some unique challenges in regard to developing a nonclinical safety package for regulatory filings. The different properties and characteristics of each degrader, whether it is a molecule glue, PROTAC, or other type, requires creative approaches to address potential safety liabilities. Considerations that will be discussed include proteomics and ways to assess off-target degradation, PK and protein resynthesis rates, protein and E3 ligase expression profiles, and safety species selection. As new targeted protein degraders progress through development and enter the clinic, what is required to comprehensively assess the safety of these novel modalities will continue to evolve and progress requiring toxicologists and other nonclinical safety scientists to leverage both new and old in vitro and in vivo systems and models.

Global Off-Target Profiling of Targeted Protein Degraders with a Cell-Based Proteomics Platform

Xiaoting Wang, Amgen

Targeted protein degraders (TPDs), a novel class of small molecule therapeutics, can significantly reduce the levels of target proteins. However, current in vitro secondary pharmacology assays that assess off-target binding or activity of small molecules may not adequately predict off-target protein degradation by TPDs. To address this limitation, we developed a proteomics-based platform using a manageable number of human cell lines to comprehensively evaluate off-target proteins critical to the central nervous, cardiovascular, and respiratory systems. This platform was validated with the well-studied molecular glue pomalidomide and a heterobifunctional degrader, MZ-1. Beyond profiling off-target activity, this platform may have potential to inform species selection for nonclinical safety assessments. Overall, global proteomic profiling represents a powerful new approach methodology (NAM) for aiding TPD candidate selection by detecting off-target protein degradation early in the drug development process.

Oligonucleotides in Discovery: A Case Study of an siRNA for the Treatment of Chronic Hepatitis B Virus Infection

Dinah Misner, Aligos Therapeutics

A case study for the discovery of a small interfering RNA (siRNA) for the treatment of chronic hepatitis B patients will be presented. The basic discovery paradigm, including in silico, in vitro, and in vivo assessment, will be presented along with non-traditional models utilized to evaluate safety. In silico approaches to identify potential adverse effects caused by hybridization of oligonucleotides to non-targeted genes and human micro-RNA by complementary base pairing will be discussed. Follow-up in vitro studies to assess potential hybridization-dependent off-target hits, along with additional studies utilizing RNAseq methods to examine unwanted gene knockdown more globally, will be outlined. The road to the selection of the final candidate and the ultimate outcome of

this novel siRNA will be presented.

VENDOR PRESENTATION

Preclinical Neurotoxicity Predictions using a High-Throughput Neural Spheroid Model

David A. Gallegos, Takeda

The drug development process is fraught with failure due to either safety issues or poor efficacy. When considering safety profile, neurotoxicity is the leading cause of clinical failure [1]. Furthermore, 12% of drugs withdrawn between 1960-1999 were caused by CNS-related adverse events [2]. The use of advanced in vitro models (AIVM) derived from human tissue has dramatically expanded in recent years, promising to provide the necessary biological complexity to improve clinical translation and scale to enable adoption early in drug development pipelines. We have worked with AxoSim on the development of and modeling around a cortical brain organoid model that exhibits robust spontaneous calcium waveform activity that is compatible with HTS methodology and provides a clinically relevant endpoint for phenotypic profiling. In 2022, this organoid platform was used to develop a predictive clinical neurotoxicity model that showed remarkable specificity (>90%) and good sensitivity (>50%), making it an ideal pre-screening method prior to standard 2-species animal testing [3]. Here, we tested the stability and reproducibility of these predictions over time and used these replicate experiments to refine and automate neurotoxicity score predictions

SESSION III

Nonclinical Safety Assessment of Antibody-Oligo Conjugates from IND-enabling through Late-Stage Clinical Trials

Laura Leung, Avidity Biosciences

Antibody oligonucleotide conjugates (AOCs) combine the tissue specificity of monoclonal antibodies with the precision and potency of oligonucleotides to enable the targeted delivery of oligonucleotides to previously untreatable tissues and cell types. AOC 1001 is comprised of a siRNA conjugated to an antibody targeting human transferrin receptor 1 (TfR1), designed for functional delivery to muscle cells, where it can reduce the levels of myotonic dystrophy protein kinase (DMPK) mRNA implicated in myotonic dystrophy type 1 (DM1) pathogenesis. DM1 is a rare dominantly inherited progressive neuromuscular disease caused by toxic gain-of-function mutation in the DMPK gene. The nonclinical safety strategy and regulatory feedback of AOC 1001 supporting IND through late-stage clinical trials will be discussed.

The Use of In Vitro Assays for Novel Payload Selection in New-Generation ADCs

Diana Lac, Genentech

Antibody-drug conjugates (ADCs) have made remarkable progress in recent years. Traditionally, ADCs utilized cytotoxic agents as their payloads. However, the latest generation of ADCs features innovative payloads, including new small molecules, antibiotics, immune-modulating agents, and oligonucleotides, offering a broader spectrum of biological activity. Historically, the efficacy and safety of cytotoxic payloads were assessed using a robust set of well-established in vitro assays. The emergence of new generation ADCs with unique mechanistic actions and diverse toxicity profiles necessitates a different strategic approach. There is a need for continuous innovation in assay development to address the complexities introduced by these payloads. We present payloads that pose distinct toxicity challenges, which require the development of tailored in vitro assays capable of predicting in vivo outcomes. This discussion will focus on the importance of adapting in vitro methodologies to meet the demands of cutting-edge ADC payloads.

Opportunities and Challenges for Preclinical Assessment of Next Generation ADCs

Haley Neff-LaFord, Pfizer

Despite the clinical success of ADCs in the last decade, several challenges persist in their widespread approval and use as anticancer therapeutics. These include undesired adverse events, insufficient tumor penetration or lack of activity, complex pharmacokinetics (PK), and drug resistance. However, many opportunities exist that may allow for “drugging the undruggable” with next generation ADCs. These new ADCs employ novel cytotoxic payloads or payloads with different mechanisms of action, new linkers, dual payloads or targets, and peptide or other small format backbones. Each of these approaches individually or in combination presents its own nonclinical challenges – from pharmacologic and PK assessments to unexpected species differences. This presentation will provide case studies with examples of some of these new formats and the nonclinical strategies employed to assess their activity and toxicity.

Integrating PKPD Modeling and Clinical Toxicity Meta-Analysis towards Therapeutic Index prediction for Antibody-Drug Conjugate

Mahua Roy, AstraZeneca

Antibody-drug conjugates (ADCs) are rapidly evolving class of targeted therapeutics that deliver a potent cytotoxic payload (and disease specific novel non cytotoxic payload) with an enhanced tumor specificity, minimizing systemic toxicity. However, predicting their therapeutic index (TI) remains challenging due to complex multi-component pharmacokinetics (PK) and pharmacodynamics (PD). PKPD and quantitative systems pharmacology (QSP) modeling offer a robust quantitative framework that integrates species scaling of drug disposition, target engagement, and payload release kinetics to support preclinical-to-clinical efficacy translation and early toxicity assessment.

Herein, we present a few approaches that showcase the use of semi-mechanistic and regression-based models to bridge preclinical efficacy and clinical toxicity towards prediction of therapeutic index for ADCs. Hematotoxicity (characterized by neutropenia, thrombocytopenia and anemia) is a major dose limiting toxicity of ADC's, primarily driven by systemic payload exposure inducing toxicity to hematopoietic progenitors in bone marrow. Model-based simulations help establish the exposure-response relationship for hematologic adverse effects, capturing neutrophil suppression and recovery dynamics. Additionally, meta-analysis of dose-response data in clinical toxicity evaluations identifies off-target toxicities linked to specific payload classes and aids in predicting exposure-response relationships. Overall, by integrating experimental and clinical data, PKPD modeling serves as a critical tool to optimize dosing regimens based on patient specific factors (e.g. antigen expression) to balance efficacy and toxicity, enabling safer dose selection to enhance clinical success.

DEVELOPMENT TOXICOLOGY WORKSHOP

PLENARY LECTURE

Harnessing Generative AI in Nonclinical Safety Evaluation

Zhichao Liu, Boehringer Ingelheim

Generative AI (GenAI) has revolutionized nonclinical drug safety evaluations, offering innovative solutions and unprecedented insights into the safety of drug candidates before they reach clinical trials. In this presentation, I will delve into the transformative applications of GenAI in various aspects of nonclinical safety assessment: (1) Potential Target Liability Assessment: Leveraging GenAI to harvest target liabilities for identifying and mitigating risks early, we can enhance the safety profile of drug candidates. (2) Tox-Specific AI Assistants: Introducing AI assistants designed specifically for toxicology, which can automate and streamline the generation of tox reports, accelerate data analysis, and provide real-time insights into safety evaluations. (3) Virtual Animal Models for Toxicity Prediction: Utilizing GenAI to create sophisticated virtual animal models that can simulate biological responses to drug candidates, reducing the need for extensive live animal testing and providing accurate toxicity prediction. (4) AI-Powered Translational Safety: Employing GenAI to bridge the gap between preclinical findings and clinical outcomes, ensuring that nonclinical safety assessments translate effectively to human trials and therapeutic use. Throughout the presentation, I will also highlight the challenges and lessons learned in integrating GenAI into nonclinical drug safety practices. Understanding how to harness GenAI effectively can lead to more reliable safety evaluations, streamlined processes, and ultimately, safer drugs for patients.

SESSION IV

Opportunities and Insights From Pharma On the Use of NAMs to Replace Large Animal Studies in Nonclinical Safety Assessments for Biotherapeutics

Kim Homan, Genentech

Sharing New Approach Methodology (NAM)-based regulatory experiences is crucial for improving human risk assessment and reducing animal use in drug safety testing. To foster broader adoption, the Biotechnology Innovation Organization surveyed companies about NAM usage and collected case studies showcasing NAM-based regulatory filings for biotherapeutics, where NAMs replaced large animal studies for safety assessment. This talk will cover the survey results and describe cases where these scientifically justified approaches were generally accepted by global health authorities, particularly in the context of species relevance limitations, prior target modulation experience, and/or when addressing severe disease. Despite successes with NAM-based global regulatory filings, there are concerns from companies about global regulatory harmonization and clinical translatability. NAMs have the potential for greater uptake with enhanced guidance and industry–regulatory agency collaboration being key to their adoption.

Advancing Pre-Clinical Safety Assessment with Advanced Cell Models

Natacha Bohin, AstraZeneca

Early detection of safety liabilities of new therapies is a critical biopharmaceutical challenge. Addressing this challenge could significantly advance drug discovery. Advanced human cell models, including microphysiological systems (MPS), aim to recapitulate the architecture, cell-to-cell interactions, and microenvironment of a given tissue, making them more representative of complex in vivo biology than standard two-dimensional culture. Hence, human MPS are particularly well-suited suited to enhancing translation of pre-clinical model outcomes to clinical settings.

In Clinical Pharmacology and Safety Sciences at AstraZeneca, we are developing advanced human cell models tailored to various organs and safety applications, depending on the context of use. This presentation will showcase one example of successful adoption of MPS for pre-clinical safety assessment: our human 3D static and fluidic (MPS) bone marrow (BM) models. Our models recapitulate key aspects of living BM, maintaining stem/progenitor cells and supporting differentiation into erythroid, myeloid and megakaryocyte lineages. This allows capture of lineage-specific haematotoxicity associated with monotherapy and combination therapies, informing candidate drug selection, and guiding oncology drug combination dosing and scheduling. Integrating data from these models with Quantitative Systems Toxicology modeling approaches is crucial for accurate safety assessments and clinical translation. Despite the potential of advanced cell models to enhance the human relevance of pre-clinical safety assessments, challenges to their widespread adoption and development in the pharmaceutical industry remain. These challenges include a lack of standardization, high costs and time requirements, and low sample quantities for downstream analyses. This presentation will also address these challenges and present opportunities to further improve advanced cell models and thereby drive their adoption in the industry.

Leveraging the Proteome: Harnessing in vitro NAMs to Understand Human and Non-Human Protein Binding Profiles for Therapeutics

Nick Brown, Charles River Laboratories

New Approach Methods (NAMs) are critical tools to facilitate the continuous refinement, reduction, and replacement of animal usage in therapeutic development. In this presentation, I will highlight a particular NAM, the innovative Retrogenix® Platform, which is able to accurately identify on/off-target protein binding interactions for a wide variety of therapeutic modalities, and de-risk drugs against the world's highest-quality in vitro human proteome. Furthermore, I will describe a new workflow to triage and confirm binding against non-human protein orthologues of key toxicology species, providing practical data to support informed species selection prior to in vivo studies.

Insights into Building a Robust Virtual Control Database and Selection Methods for Use on Retrospective Analysis of Nonclinical Safety Assessment Studies

Jillian Wendel, LabCorp

A key and required step in pharmaceutical development is in vivo nonclinical safety assessment. Efforts towards new approach methodologies (NAMs) and minimization of animal usage wherever feasible continue to be embraced by the pharmaceutical industry and encouraged by regulatory bodies, although animal studies remain the standard at this time. One emerging strategy supporting the 3Rs principles of replacement, reduction, and refinement is the usage of virtual control groups. The virtual control group strategy utilizes the collective historical control data available to generate representative datasets to reduce or replace concurrent control animals. As virtual control groups are not currently widely used, there is limited regulatory framework or descriptive guidance on selection criteria or usage of virtual control groups. However, many efforts towards the usage of virtual controls on nonclinical safety assessment studies have concluded that the virtual controls should be chosen in a way that mimic the conditions and study design for the intended study.

The purpose of this work was to determine the selection criteria required to generate a robust, consistent, and representative virtual control dataset. Additionally, the purpose of this work was to challenge the usage of virtual controls through a toxicological review using selected virtual control groups in a retrospective analysis of a nonclinical safety assessment study. Historical control data from 26 4-week repeat dose oral gavage rat studies run between 2019 and 2024 at Labcorp Madison were collated and used to evaluate the criteria necessary to build a robust virtual control database. One study was selected as the test study with data from the remaining 25 studies acting as the virtual control pool. Quantitative endpoints of body weight, clinical pathology, and organ weight data were collated for evaluation of key criteria for virtual control group selection. In total, 10,000 iterations of virtual control groups of equal size (n=10) to the test study were generated via random sampling without replacement. Virtual control groups were

then assessed against the test study concurrent control group to detect differences between groups. Several virtual control groups were selected and compared to the test article-treated groups in the test study. These virtual control groups were selected from the 10,000 iterations to cover a wide range of characteristics of the Day 1 body weights (for example, virtual control groups from the tails of the full distribution of 10,000 generated).

The data from the virtual control groups and test article treated groups were presented to representative scientists for review and the interpretations based on the virtual control group dataset were compared.

This body of work has affirmed the necessity of a well curated historical control database, clear selection criteria ensuring comparability with the test study animals, and the statistical methodology necessary to support study variability. Continued efforts towards the generation and support of virtual control groups are poised to reduce the animal usage on nonclinical safety assessment studies in the years to come.

SESSION V

Nonclinical Safety Strategies for ADC Development: Looking Back to Move Forward

Christina de Zafra, Merck

Antibody-drug conjugates (ADCs) have been studied as treatments for cancer for nearly 3 decades. Since the first FDA approval of an ADC in 2000, an additional 12 molecules have been marketed and hundreds are in various stages of development in oncology as well as non-oncology indications. Numerous vedotin ADCs have been developed by the legacy-Seagen (now Pfizer) organization. A comprehensive review of nonclinical toxicology and pharmacokinetic data for vedotin ADCs in clinical development through marketing highlights similarities between molecules that can serve as a springboard for the recommendation of best practices to streamline nonclinical toxicology evaluation of ADCs. Key principles from the ADC molecule class may be applied to other biologic platforms, such as CD3 bispecific antibodies and possibly cell and gene therapy. Widespread adoption of these approaches should lead to a reduction in the use of animals in nonclinical toxicology evaluation and more rapid delivery of new medicines to patients with unmet medical needs.

Unique Platform Toxicities of ADCs: Learnings Over the Last Decade

Magali Guffroy, AbbVie

Antibody-drug conjugates (ADCs) leverage the targeting specificity of monoclonal antibodies and enhance the delivery of pharmacological agents to target-expressing cells while limiting systemic toxicities. However, despite the original promise, non-target-mediated toxicities have often been development limiting, with contribution of both free payload in systemic circulation and non-specific ADC uptake into normal cells. In addition to effects on tissues with rapidly dividing cells (eg. bone marrow, GI tract, reproductive organs), oncology ADCs with cytotoxic agents have been associated with unique non-target-mediated toxicities that may reflect novel payload distribution pathways and toxicity mechanisms. These unique toxicities of ADCs include liver sinusoidal injury with the potential to progress to sinusoidal obstruction syndrome, kidney medullary injury and associated fluid retention, ocular corneal epitheliopathy, and interstitial lung disease. The presentation will cover some of these unique toxicities with description of nonclinical findings, discussion of potential toxicity mechanism, and indication of clinical translation. The presentation will also stress how understanding of these toxicities might further inform ADC discovery strategy and improve clinical monitoring of patients.

Case Study: Regulatory Interactions and Path to IND for a Novel Antibody-Protein Conjugate

Pia Kasperkovitz, Bright Peak Therapeutics

This talk describes a case study for a first-in-class antibody-cytokine conjugate using a novel, chemical linkage platform enabling site-specific conjugation of the Ab and the payload (cytokine). The development path for this compound from first in vivo demonstration of efficacy until IND approval took two years. Due to the novelty of the compound, Bright Peak Tx had both an INTERACT and a pIND meeting with FDA, for which questions and responses will be discussed. The talk will describe the nonclinical rationale and the IND package and how these were informed by FDA input. The final response from the nonclinical FDA reviewer to the IND will also be shared.

SESSION VI

Protecting Allogeneic Transplants from Immune Rejection is the Key to Bringing Cell-Based Therapies to Patients

Sonja Schrepfer, Sana Biotechnology

In order to make allogeneic "off-the-shelf" cell therapies clinically useful and avoid rejection absent immunosuppression (IS), they need to evade host immune responses, a property we refer to as being "hypoimmune". To overcome the allogeneic immune response, engineered cells must overcome both, adaptive and innate immunity. We demonstrated in various pre-clinical models using different cell types that protecting allogeneic transplants from rejection is feasible using genetic engineering to create hypoimmune cells.

In an IST the first patient with type-1 diabetes (T1D) was now treated with hypoimmune islet cells from an allogeneic donor; the study met all of its initial goals. The patient is doing well and is now making his own insulin for the first time in decades without immunosuppression.

The data from this first-in-human study are an important first step towards the ultimate goal of a potentially curative islet cell therapy for the broad T1D population and establish proof of concept of the hypoimmune technology.

Modeling Approaches to Support Dose Selection for Cell and Gene Therapies

Raibatak Das, Quantilogix, LLC

A variety of pharmacokinetics and pharmacodynamics models, such as compartmental PK models, and exposure-response models are used to relate dose to efficacy and toxicity for small molecules and bioconjugates. But cell and gene therapies present unique challenges in their mechanism of action and the dynamics of the target response that require more sophisticated models. This presentation will outline these challenges, survey the current state modeling in this area, and propose approaches to inform clinical dose selection for non CAR-T cell and gene therapies.

APPLIED PHARMACEUTICAL TOXICOLOGY

SPEAKER BIOGRAPHIES

Natacha Bohin, PhD, AstraZeneca Dr. Bohin is an Associate Director in Oncology Targeted Discovery Safety Combinations within Safety Sciences at AstraZeneca, and a lead scientist for bone marrow microphysiological systems (MPS). With an academic foundation in stem cell and cancer biology and a decade of experience leveraging advanced cell models for biological insights, Natacha joined AstraZeneca in 2021 and has been critical in establishing its bone marrow MPS model. Integration of pre-clinical bone marrow MPS data with Quantitative Systems Toxicology modelling to predict clinical haematotoxicity is a novel, industry-first approach directly supporting the development of safer and more effective targeted treatments and combinations across therapy areas. Central to AstraZeneca's Bone Marrow Target Organ Strategy, Natacha's work focuses on investigating drug-induced bone marrow toxicity for various therapeutic combinations to advance drug development and inform successful clinical implementation. Further, as an IQ MPS Affiliate contributor, Natacha actively supports innovation, implementation, and qualification of MPS approaches across the industry to improve clinical translation and delivery of safer next-generation therapeutics.

Richard Bonneau, PhD, Genentech Dr. Bonneau leads Prescient Design, a molecular design accelerator at Genentech, a member of the Roche Group, that pioneers new methods for combining machine learning and molecular modeling. Dr. Bonneau's research spans multiple levels of biological structure learning and modeling biological networks to predicting and designing macromolecular and biomimetic structure. Rich received his Ph.D. at the University of Washington, Seattle, where he pioneered new methods to predict biomolecular structure (Rosetta). At Genentech Research and Early Development (gRED), Bonneau and his team build new methods for applying machine learning to the design molecular composition, function and interfaces and in ways that span all drug modalities.

Nick Brown, Charles River Laboratories Nick leads Charles River's Client Services team covering the Retrogenix® Platform, and has been responsible for the technology's growth, study design, project set-up, and client communications for >5 years. Prior to this, Nick worked in the Centre for Stem Cell Biology at the University of Sheffield, culturing and genetically characterising iPSCs for differentiation into human cardiomyocytes. Nick has a Master of Science degree in Stem Cell and Regenerative Medicine from the University of Sheffield, UK.

Raibatak Das, PhD, Quantilogix LLC Dr. Das is the founder of Quantilogix LLC - a modeling and simulation company supporting R&D groups in pharma and biotech. Previously he was part of Applied BioMath where he was involved in a number of industry-funded research projects in diverse therapeutic areas, including, cell and gene therapies, bioconjugates, neuroscience, and immuno-oncology. He has over 20 peer-reviewed publications, and was the recipient of an NIH small business innovation research (SBIR) grant to model targeted cytokine therapies. Raibatak received his Ph.D in Chemistry & Chemical Biology from Cornell University, followed by postdoctoral research in Mathematical Biology at the University of British Columbia.

Christina de Zafra, PhD, Pfizer Dr. de Zafra received her PhD in Toxicology from the University of Rochester and conducted postdoctoral research at the University of Colorado. Christina has been a part of the nonclinical toxicology departments at Genentech, Amgen, and Seagen, supporting development of multi-modality biotherapeutics (including mAbs, fusion proteins, ADCs, and oncolytic viruses) across a range of therapeutic areas, and is currently an Associate Research Fellow in Drug Safety R&D at Pfizer. Christina's interests include product quality risk assessments and the 3Rs of ethical animal use, and she is a member of the Society of Toxicology and a Diplomate of the American Board of Toxicology.

Thomas Forest, DVM, PhD, DACVP, Merck Dr. Forest graduated from the University of California, Davis, School of Veterinary Medicine, and completed a residency program in veterinary anatomic pathology followed by a PhD in virology at Cornell University. He is a Diplomate of the American College of Veterinary Pathologists and a member of the Society of Toxicologic Pathologists currently employed as a Distinguished Scientist by Merck Research Laboratories in the Department of Nonclinical Drug Safety.

He conducts primary evaluations of GLP nonclinical toxicology studies, represents nonclinical safety on drug development teams, and has a longstanding interest in investigative pathology with focus on image analysis, quantitative assessments, and digital pathology. He is currently leading a project to digitize and incorporate machine learning-based automation into the nonclinical GLP histology workflow in Merck Research Laboratories.

David Gallegos, PhD, Takeda Dr. Gallegos received his PhD in Neurobiology in the lab of Anne West at Duke University, where most of his work existed at the crossroads of neuronal activity-regulated transcription, epigenomic modification, and mechanisms of neuronal plasticity. He subsequently pursued an R-Authority postdoctoral position at the U.S. Environmental Protection Agency, where he applied multiple single-cell genomic and transcriptional profiling methods into more diverse organ systems and advanced in vitro organ/developmental models. Currently, David is a Senior Scientist at Takeda Pharmaceuticals on their Investigative Toxicology Team within the department of Drug Safety Research and Evaluation. In his role at Takeda, he supports all manner of cross-project single-cell/spatial Omics analysis, Advanced in vitro Neuronal models, cross-platform Neurotoxicity assessments, and Bioinformatics.

Magali Guffroy, DVM, AbbVie Dr. Guffroy currently leads the Global Pathology department in Preclinical Safety at AbbVie and also spearheads the Emerging Therapeutic Platforms that include antibody-drug conjugates and targeted protein degraders. Before joining AbbVie in 2018, Magali was employed with Sanofi and legacy companies in France until 2010 and with Pfizer in the UK and the US from 2010 to 2018. Magali is a board-certified veterinary pathologist with over 25 years of comprehensive experience in most aspects of nonclinical drug safety assessment, including general and reproductive toxicity, clinical and anatomic pathology, computational pathology, and portfolio management. She has a high interest in investigative activities to further understand mechanism and mitigation of toxicities. Magali obtained her DVM degree from Toulouse Veterinary School in France and completed her anatomic pathology residency at Cornell University Veterinary College.

Kim Homan, PhD, Genentech Dr. Homan is a Sr. Director and Distinguished Scientist at Genentech and she runs the Complex in vitro Systems lab, a core group focused on employing new predictive tools to enhance clinical translational outcomes. She has prior experience holding key leadership positions in two biotech startups, one of which she co-founded while in graduate school at UT Austin. Prior to that, as a co-appointed postdoc at Roche and at the Wyss Institute in Harvard, Kim invented methods to bioprint human tissues and use them to model drug disposition, mode of action, and safety. Kim holds a B.S. degree in chemical engineering and Ph.D. in biomedical engineering; she is also a former United States Marine Corps officer and veteran.

Fangyao Hu, PhD, Genentech Dr. Hu is the leading computational scientist in the Genentech Safety Assessment digital pathology group. He received his Ph.D. in Biomedical Engineering from Duke University. His work at Genentech focuses on developing machine learning and deep learning approaches to enhance digital pathology workflow in toxicologic pathology. He has pushed the boundaries of AI in toxicologic pathology, and has been instrumental in positioning pathologists to do digital pathology. He has driven and led the development of computational approaches that transform our ability to routinely extract reproducible quantitative data from images, and gain both increased insights, and more opportunities for cross-study comparisons and predictive safety approaches.

Byunghak Kang (BK), PhD, Novartis Dr. Kang is an ACVP board-certified pathologist. He earned his Master's degree in Applied Data Science from the University of Michigan and his PhD in Pathobiology and Cancer Biology from Johns Hopkins University, where he also completed his pathology residency training. Currently serving as an Associate Director at Novartis, BK specializes in preclinical efficacy and safety assessment. He leverages AI-driven computational pathology and advanced molecular pathology technologies, such as spatial omics, to drive innovations in drug development.

Pia Kasperkovitz, PhD, Bright Peak Therapeutics Dr. Kasperkovitz is the Senior Director of Toxicology at Bright Peak Therapeutics, based in the Basel area of Switzerland. She oversees nonclinical safety activities supporting the development of novel antibody-protein/peptide conjugates. Her career spans leadership roles in both biotech and large pharmaceutical companies, including Roche (Switzerland) and Takeda, Bluebird Bio, and Alnylam (United States).

Pia's diverse professional experience as a toxicologist includes immuno-oncological therapies (CAR T cells, T cell engagers, agonists, and checkpoint modulators), as well as gene therapies, RNA therapies, and vaccines, and comprises various modalities and therapeutic areas.

Prior to her industry career, Pia was a Research Fellow at Harvard Medical School and Massachusetts General Hospital in Boston. She earned her PhD in Immunology from VU University in Amsterdam, the Netherlands.

Laura Leung, PhD, Avidity Biosciences Dr. Leung is a Principal Scientist in the Toxicology team at Avidity Biosciences, where she leads the nonclinical development of several antibody oligonucleotide conjugate (AOC) programs for neuromuscular and cardiovascular therapeutic applications. Her expertise lies in advancing the safety and therapeutic profiles of innovative platform-based molecules and contributions to early discovery programs.

Before joining Avidity, Laura worked at NGMBio specializing in the safety assessment of biologics for ocular and immuno-oncology indications. She also contributed to groundbreaking research at Circuit Therapeutics, where she explored the use of optogenetics as a therapeutic strategy for neurodegenerative diseases. These roles helped her develop a strong foundation in both preclinical assessments and cutting-edge biomedical technologies.

Laura holds a PhD in environmental toxicology from UC Irvine and completed postdoctoral research at UCSF Gladstone Institute of Neurological Disease, focusing on advancing novel therapeutic approaches for neurological diseases.

Zhichao Liu, PhD, Boehringer Ingelheim Pharmaceuticals Dr. Zhichao Liu is the Director of AI and Digital Innovation at Global NCS&DMPK of Boehringer Ingelheim Pharmaceuticals. At Boehringer, Dr. Liu spearheads efforts to develop AI-based solutions for next-generation drug safety evaluation and risk assessment, including AI-powered target liability assessment, predictive toxicology, ToxGPT, tox report automation, translational safety, and digital pathology. Prior to joining Boehringer, Dr. Liu led the Artificial Intelligence Research Force (AIRForce) at the US FDA/NCTR. Dr. Liu's expertise spans chemistry, biology, and computer science, and he has led numerous cutting-edge projects over the past decade, designing, implementing, and deploying AI/ML solutions for advanced drug development and regulatory science. His accomplishments are reflected in over 100 peer-reviewed publications and numerous scientific awards.

Dinah Misner, PhD, DABT, DSP, Aligos Therapeutics Dr. Misner received her PhD in Biomedical Sciences and was originally trained as an electrophysiologist in neuroscience at UCSD and was a post-doc at the Salk Institute. She has now been in the pharmaceutical industry for ~25 years. She has both conducted and led groups running safety pharmacology and toxicology studies internally, and outsourced safety pharmacology and toxicology studies externally. She has been an author on numerous posters and publications related to safety pharmacology and toxicology. Dr. Misner is currently a Vice President at Aligos Therapeutics, where she serves as a toxicology project team representative on both discovery and development teams and is responsible for the design and conduct of in vitro and in vivo toxicology and safety pharmacology studies for treatment of liver diseases, encompassing small molecules as well as oligonucleotides. Lastly, she is a board-certified toxicologist and safety pharmacologist.

Haley Neff-LaFord, PhD, DABT, Pfizer Haley is an Executive Director and the Oncology ADC Therapeutic Area Lead for Pfizer Drug Safety R&D. Her team characterizes the safety of novel anti-cancer therapies with a focus on the development strategy for ADCs. Prior to her time at Pfizer, Haley was at Seagen for 16 years where she contributed to the development of multiple ADCs and targeted therapies from research through global registration. She is active in consortia and outreach including the IQ DruSafe Leadership Team, the HESI ADC Safety Committee, and the PNW chapter of SOT. Haley received her PhD in Pharmacology/Toxicology from Washington State University and her postdoctoral training at the University of Washington. She is certified by the American Board of Toxicology.

Taci Pereira, PhD, Systemic Bio Dr. Pereira is the Chief Executive Officer of Systemic Bio, a 3D systems company developing a platform for drug discovery and development using human-relevant data from bioprinted tissues. She previously served as the Vice President and General Manager of Bioprinting at 3D Systems and the Chief Scientific Officer at Allevi, acquired by 3D Systems in 2021. Taci holds a Bachelor of Science in Bioengineering from Harvard University and has conducted research on biomaterials for cancer immunotherapy at the Wyss Institute for Biologically Inspired Engineering under the advisory of David Mooney, Ph.D. Taci was recognized as a Forbes Brazil Under 30 honoree in 2022, a Houston Business Journal 40 under 40 in 2023, an MIT Innovator Under 35 (Brazil) in 2024, and won the SLAS Innovation Award (2025).

Mahua Roy, PhD, AstraZeneca Dr. Roy is an Associate Director within the ADC Clinical Pharmacology group at AstraZeneca, with over 10 years of expertise in systems pharmacology modeling. Prior to this role, she was part of the Biomedicine Design group at Pfizer, where she led model-informed preclinical-to-clinical translation of large molecule therapeutics. Mahua earned her PhD

in Computational Biophysics from the University of California, Irvine, and completed postdoctoral research at the University of Southern California, focusing on Quantitative Systems Pharmacology models for cancer metabolism.

Sonja Schrepfer, PhD, Sana Biotechnology Work by Dr. Sonja Schrepfer is at the forefront of stem immunobiology and paves the way for treatment of a wide range of diseases – from supporting functional recovery of failing myocardium to the derivation of other cell types to treat diabetes, blindness, cancer, lung, neurodegenerative, and related diseases. Her work demonstrates that protecting transplanted cells from immune rejection is the key to unlocking the potential of regenerative medicine.

Dr. Schrepfer is Professor at the Cedars Sinai Medical Center (in the Departments of Surgery and Regenerative Medicine) and a Scientific Founder and SVP (Head of the Hypoimmune Platform) of Sana Biotechnology, Inc.

Jessica Sims, PhD, Genentech Dr. Sims is a board-certified toxicologist and a Senior Principal Scientist in the Translational Safety Department at Genentech. As a project toxicologist, she is part of both small and large molecule project teams where she provides non-clinical safety support for programs from discovery through late-stage development and IND filing. She is a SME for molecular glues/targeted protein degraders and has expertise in small molecule discovery and oncology programs. Jessica received her doctorate in Cellular and Molecular Physiology from Tufts University-School of Biomedical Sciences and went on to do a Postdoctoral Fellowship in the Department of Biomedical Sciences at Cedars-Sinai Medical Center. Jessica has over 15 years of combined academic and industry experience in target identification, drug screening and drug development. She has served on the executive board for the SOT Biotechnology Specialty Section and currently represents Genentech on the Degrader IQ Consortium Working Group.

Chris Strock, Cyprotex Chris Strock has been at Cyprotex for 14 years and is currently the Site Head and head of Scientific Operations. Before taking on that role, he was the Head of in vitro Tox group in the US and developed models for predicting organ toxicity in liver, neuro, and cardiac. He is responsible for developing the industry accepted MEA assays for Neuro and cardiac toxicity and has been involved in the development of Machine Learning models of liver toxicity.

Xiaoting Wang, PhD, LabCorp Dr. Wang is the director of the Translational Safety and Bioanalytical Sciences group at Amgen located in South San Francisco. Her expertise lies in immunology, immunotoxicology and in vitro NAMs. She serves as the project lead toxicologist for inflammation and oncology projects and supervises a team of scientists developing in vitro systems to predict and evaluate potential clinical toxicity such as immunotox, off-target effects, and organ toxicity.

Xiaoting earned her PhD in Viral Immunology and Pathology from UMass Chan Medical School in Massachusetts and completed her postdoctoral training in tumor immunology at the La Jolla Institute of Immunology in California.

Jillian Wendel, PhD, LabCorp Dr. Wendel has had a varied scientific career from cell regeneration in horseshoe crabs, neurobehavior and teratology in rodent models, generation of mouse models recapitulating gynecological disorders, to in vitro scaffold-free three-dimensional modeling of ovarian tissue. In her current role as a Study Director at Labcorp in Greenfield Indiana, Jillian is responsible for in vivo studies assessing the safety of chemicals and novel therapeutics under compliance of various regulatory agencies. Dr. Wendel uses her training in neuroscience and neurobehavior, her early passions as the subject matter expert for her team. At the 2023 Society of Toxicology annual meeting, she learned about and was enamored by the concept of virtual control groups on non-clinical toxicology studies. Upon her return, she shared her excitement with management. Serendipitously, Labcorp shared this interest and efforts were starting to get underway, Jillian enthusiastically joined the global team on this effort. Appropriate and interpretable usage of virtual controls will be a long and steady road to fruition but there is significant joy in the journey. Jillian has particularly appreciated the opportunities to work cross-functionally and continuously learn from her colleagues.

POSTER ABSTRACTS

Detecting the toxicity trigger for drug-induced liver injury in one dose

James T. Shoemaker, Logan N. Porter, Michael Gray and J. Vukasinovic.
Lena Biosciences, Atlanta, GA.

Purpose

Drug-induced liver injury (DILI) is a significant problem for drug developers and regulators because it is detected late. Idiosyncratic DILI is patient-specific. It is usually detected in post-marketing, after the drug was approved and used in a wider population. Liver function tests and biopsies help with detection and diagnosis, but do not shed much light on the origin of toxicity because the same drug such as carbamazepine can cause different types of liver injury. What can be concluded? The offending drug caused liver injury, but the outcomes were different in patients. To solve the DILI problem, we need to find and understand the DILI trigger. Lena Biosciences find-the-trigger approach was validated with over 20 drugs which were difficult to de-risk for DILI. What is the trigger? The trigger is the first function that fails and does not recover. Because the trigger is the first function that fails, a drug metabolism-competent model and very sensitive assays were deployed. Using this approach, the trigger was isolated in a single drug treatment at IC50/Cmax < 5 for withdrawn drugs (e.g., Troglitazone IC50/Cmax = 0.09 and Trovafloxacin IC50/Cmax = 1.48), and drugs with DILI warnings such as Sorafenib IC50/Cmax = 0.19 which benefits outweigh the risks.

Methods

A panel of over 40 drugs, including DILI-positive and structurally similar, less toxic drugs (e.g., Troglitazone/Pioglitazone, Tolcapone/Entacapone, Sitaxentan/Ambrisentan etc.), and drugs with the same mechanism of action such as protein kinase inhibitors were tested using proprietary assays which scanned through cellular vulnerabilities to find the trigger. Perfused Organ Panel microphysiological system (MPS) with 3D cell cultures perfused by synthetic hemoglobin was used to develop the model. The MPS brings cellular oxidative metabolism, drug metabolism, and mitochondrial utilization closer to physiological levels required for drug activity and reactions to the drug. Proprietary assays were then used in a two-tiered screening approach. The purpose of the primary screen (at least 8 assays) was to identify in which cellular compartment the trigger was located. The function with the lowest IC50 identified the trigger compartment. The purpose of the secondary screen was to answer what the trigger was, i.e., the battery of assays probed the functions in the trigger compartment to find the function with the lowest IC50. An empirical IC50/Cmax < 25 was used as a criterion to classify DILI-positive drugs using a single drug treatment and the 24-hour readout.

Results

With sensitive assays and drug metabolism-competent model, the trigger was isolated for drugs withdrawn from the market close to their therapeutic Cmax. Boxed warnings vs. post-marketing reports were predicted based on IC50/Cmax (e.g., Tolcapone IC50/Cmax = 0.06 vs. Entacapone IC50/Cmax = 9.47). Structurally similar drugs were rank-ordered correctly based on their known DILI potentials such as Nefazodone IC50/Cmax = 1.84 vs. Trazodone IC50/Cmax = 33 vs. Buspirone IC50/Cmax = 26,010. The same was true for protein kinase inhibitors (Sorafenib IC50/Cmax =0.19, Ceritinib IC50/Cmax = 1.34, Crizotinib IC50/Cmax = 8.02, and Ruxolitinib IC50/Cmax = 19.3). For drugs with certain types of reactive metabolites, the primary screen identified the mitochondrial compartment as the trigger. For idiosyncratic DILI drugs such as Isoniazid, the DILI trigger was an overlooked function. The domain of validity of 1x drug treatment and 24-hour readout was established and reserved for the drugs which do not take a long time to reach steady state, dramatically change protein expression over time, or slowly interfere with nuclear or mitochondrial DNA replication such as Fialuridine. Although an extensive primary screen was run for a smaller number of drugs such as Phenformin, Metformin, Diclofenac, Troglitazone, Isoniazid, and Tolcapone, it was found that the pattern recognition could be applied for the drugs in the same class, e.g., biguanides, in order to establish a decision-making tree for future DILI predictions. The most important result was that the toxicity trigger could be identified at a very low dose for both intrinsic and idiosyncratic DILI drugs using a random 10-donor pool of primary human hepatocytes, and even a single donor. Because the function that fails,

fails at a very low dose in donors with no known genetic risk factors for that function, the patients with risk factors for that function could be identified early. How can this be deduced? First, the odds of having a person with a genetic risk for the trigger function in a random 10-donor pool is low. Second, if the function fails in an “average” donor, it will most likely fail in patients with risk factors for that function.

Conclusions

The combination of an oxidative- and drug metabolism-competent liver model with sensitive assays provides the first evidence that DILI trigger is the same for everyone, because the same function fails. However, individual patient outcomes can vary based on the cascade of events following the trigger and the ability to adapt. The trigger function can thus be used to exclude toxic candidates early in drug discovery, or to identify the patients who may be at risk in clinical trials and in post-marketing.

Acute toxicity and toxicokinetics of a new compound with antiepileptic activity

Maria Walczak*
*Chair and Department of Toxicology, Faculty of Pharmacy
Jagiellonian University Collegium Medicum, Medyczna 9, str. 30-688 Krakow, Poland

Purpose
To investigate the acute toxicity and toxicokinetics of a new compound with proven antiepileptic activity in rats.

Methods
In silico and in vivo studies in Wistar rats has been applied. An acute toxicity study in line with the OECD 420 procedure has been carried out. The linearity of kinetic processes after compound intragastric administration to rats in increasing doses was assessed. The effect of the compound on the liver was examined by assessing biochemical parameters and histopathological examinations. The degree of renal elimination was examined and the identification of metabolites was performed.

Results
A novel compound is characterized by a non-linear kinetics, and the ADME processes become saturated between the dose of 250 mg/kg and 500 mg/kg. The percentage of the fraction of the eliminated dose after intravenous administration, not exceeding 5%, indicate a small participation of the kidneys in removing compound from the organism. The results of biochemical determinations of plasma samples show increased levels of markers of liver damage, e.g. alanine aminotransferase, sorbitol dehydrogenase, hepatic arginase or aspartate aminotransferase, indicating a likely hepatotoxic effect of the compound administered at high doses. An acute toxicity study in line with the OECD 420 procedure, showed that the compound belongs to class 4 according to the GHS.

Conclusions
The results obtained indicate that compound is safe when administered intragastrically at a dose lower than 2000 mg/kg and may be investigated in further stages of safety assessment.

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Keywords: OECD 420, toxicokinetics, antiepileptic compound, rats, GHS

The differentiation state of small intestinal organoid models influences prediction of drug-induced toxicity

Jessica Klein, Julia Heidmann, Tomomi Kiyota, Aaron Fullerton, Kimberly Homan, Julia Co

Drug-induced intestinal toxicity (GIT) is a frequent dose-limiting adverse event that can impact patient compliance and treatment outcomes. In vivo, there are proliferative and differentiated cell types critical to maintaining intestinal homeostasis. Traditional in vitro models using transformed cell lines do not capture this cellular complexity, and often fail to predict intestinal toxicity. Primary tissue-derived intestinal organoids, on the other hand, are a scalable Complex in vitro Model (CIVM) that recapitulates major intestinal cell lineages and function. Intestinal organoid toxicity assays have been shown to correlate with clinical incidence of drug-induced diarrhea, however existing studies do not consider how differentiation state of the organoids impacts assay readouts and predictivity. We employed distinct proliferative and differentiated organoid models of the small intestine to assess whether differentiation state alone can alter toxicity responses to small molecule compounds in cell viability assays. In doing so, we identified several examples of small molecules which elicit differential toxicity in proliferative and differentiated organoid models. This proof of concept highlights the need to consider which cell types are present in CIVMs, their differentiation state, and how this alters interpretation of toxicity assays

Mitigation of liver toxicity effects of bispecific T-cell engagers in immune-competent liver-tumor co-culturing high-throughput platform

Sue Grepper[1], Michal Rudnik[1], Lisa Hölting[1], Tamara Häfeli[1], Ozlem Yavaş Grining[1], Frauke Greve[1], Daniela Ortiz Franyuti[2], Ramona Matheis[2], Laure-Anne Ligeon[1], Ekaterina Breous-Nystrom[2], Olivier Frey[1]

[1] InSphero AG, Schlieren, Switzerland
[2] Roche Pharma Research & Early Development, Roche Innovation Center Basel, Switzerland

Purpose
There is a need for complex human-based models to simultaneously measure efficacy and potential toxicity of ADC therapeutics. InSphero and Roche have partnered to develop such a model, which is able to recapitulate in vivo findings through multiple readouts.

Methods
The Akura™ Twin microfluidic platform was utilized, which allows for two types of spheroids (in this case, tumor spheroids and primary liver spheroids) to interact via a common media. The spheroids were treated with HER2xCD3, EpCAMxCD3, GD2xCD3, ControlxCD3 bispecific antibodies (1 µg/ml) in the presence of PBMCs (5k cells, E:T ratio 1:5). Secretion of cytotoxic T-cell cytokines were measured by CBA at 24h. Liver-specific viability was measured by secreted ALT measurements.

Results
Treatment with HER2xCD3, EpCAMxCD3, GD2xCD3, ControlxCD3 bispecific antibodies (1 µg/ml) in the presence of PBMCs (5k cells, E:T ratio 1:5) resulted in secretion of cytotoxic T-cell cytokines at 24h time point (measured by CBA). Administration of bispecific antibodies (1 µg/ml) in the presence of 5k PBMCs resulted in liver damage measured as ALT release at day 3 timepoint. The addition of mitigation compounds resulted in decreased release of ALT.

Conclusions
We have developed a high-throughput human platform for the evaluation of novel immunotherapies, which closely reflects clinical scenarios. The high throughput capabilities of the assay represent a powerful screening tool for clinical candidate development.

APPLIED PHARMACEUTICAL TOXICOLOGY

Improving the stability and reproducibility of clinical neurotoxicity predictions from a high-throughput compatible neural organoid platform

Andrew S. LaCroix[1], Victoria K. Alstat[1], Nicholas S. Coungeris[1], David Gallegos[3], J. Lowry Curley[2]

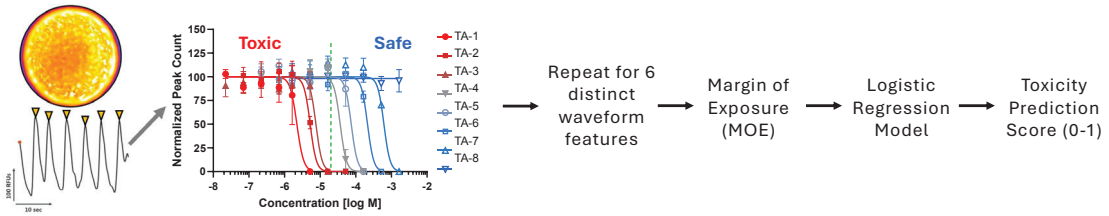
[1] AxoSim Inc., Maple Grove, MN, USA.
[2] AxoSim Inc., New Orleans, LA, USA.
[3] Takeda Pharmaceuticals, Cambridge, MA, USA

Background and Purpose

The drug development process is fraught with failure due to either safety issues or poor efficacy. When considering safety profile, neurotoxicity is the leading cause of clinical failure [1]. Furthermore, 12% of drugs withdrawn between 1960-1999 were caused by neuro-related adverse events [2]. The use of complex in vitro models (CIVM) derived from human tissue has dramatically expanded in recent years, promising to provide the necessary biological complexity to improve clinical translation and scale to enable adoption early in drug development pipelines. We have developed a cortical brain organoid model that exhibits robust spontaneous "waveform" activity that is compatible with HTS methodology and provides a clinically-relevant endpoint for phenotypic profiling. In 2022, this organoid platform was used to develop a predictive clinical neurotoxicity model that showed remarkable specificity (>90%) and good sensitivity (>50%), making it an ideal pre-screening method prior to standard 2-species animal testing [3]. Here, we tested the stability and reproducibility of these predictions over time and used these replicate experiments to refine and automate neurotoxicity score predictions.

Methods

3D cortical organoids were derived from healthy donor iPSCs, which were differentiated into NPCs, then seeded seeded into ultra-low attachment 384-well plates, wherein they self-organize and co-differentiate into cortical neurons and astrocytes. After 10 weeks of differentiation, once cultures exhibited strong coordinated network activity, acute (0 - 4 hours) neuromodulation screening of 84 known neurotoxic and safe compounds was performed using a calcium flux assay and high-throughput kinetic plate reader (FLIPR).

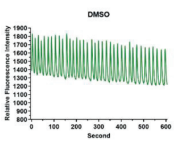


Changes in the number, size, shape, and variability of the spontaneous activity waveforms were quantified using custom written code in Python. A margin of exposure (MOE) value was calculated for each waveform feature as the ratio of total plasma C_{max} (tpC_{max}) to the EC/IC_{50}. MOE values were used to train and test a logistic regression model to predict safe (category 1) or neurotoxic (category 2, 3, 4) compounds.

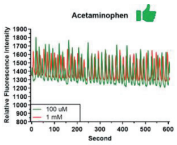
	Sets	Neurotoxicity severity category[a]		Drugs
Model Training	CNS-targeting set (N = 58)	1. Negative (N = 17)		Tolcapone, pimavanserin, L-DOPS (droxidopa), sertindole, duloxetine HCl, galantamine, zotepine, talipexole, raffinamide, MK-8931 (verubecestat), levodopa, benzatropine mesylate, bicifadine, tasimelteon, reserpine, lazabemide, moclobemide
		2. Rare (N = 9)		Varenicline tartrate, mifepristone, maprotiline, rotigotine, ketorolac, pramipexole, chlorprothixene, almotriptan malate, lidocaine
		3. Infrequent (N = 13)		Enoxacin, pergolide, cefazolin, sertraline, safinamide, propranolol HCl, cyclobenzaprine, ropinirole, memantine HCl, riluzole, ropivacaine, atomoxetine HCl, aripiprazole
		4. Frequent (N = 8)		Rivastigmine, chlorpromazine, theophylline, aminophylline, bupropion, donepezil HCl, BIA 10-2474, indomethacin
		5. Anticonvulsant (N = 11)		Topiramate, lamotrigine, divalproex Na, levetiracetam, oxcarbazepine, ziconotide, carbamazepine, valproic acid, zonisamide, vigabatrin, tetrabenazine
Model Testing	Test set (N = 26)	1. Negative (N = 13)		Pilocarpine HCl, atropine, flupirtine, ambroxol, nifedipine, ibuprofen, acetaminophen, aspirin, naproxen, diclofenac, bupirone HCl, fluoxetine HCl, paroxetine
		2. Rare (N = 2)		Simvastatin, pravastatin
		3. Infrequent (N = 1)		Gabapentin
		4. Frequent (N = 10)		Doxorubicin, cisplatin, paclitaxel, vincristine, carboplatin, ixabepilone, isoniazid, colchicine, aminopyridine (dalfampridine), phenytoin

Modified from Wang et al., ALTEX 2022 (Takeda)

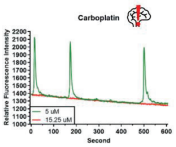
Compounds were classified into 1 of 4 categories based on its clinical adverse event rate: 1: negative (<0.01%), 2: rare (0.01-0.1%), 3: infrequent (0.1%-1%), 4: frequent (>1%). Dosing concentrations were selected to span 0.1x – 100x the in vivo Cmax in 7-point dose response.



Normalize activity data to vehicle control wells



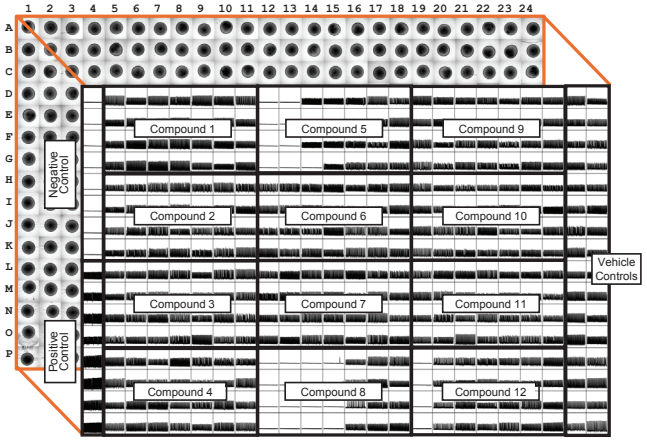
Safe compounds show little-to-no functional changes



Toxic compounds show strong modulation and functional deterioration

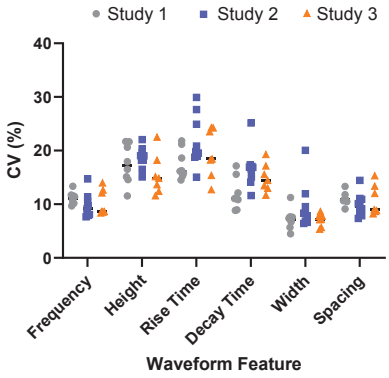
APPLIED PHARMACEUTICAL TOXICOLOGY

Consistency of Cortical Organoid Function



1 Study = 7 plates = 84 compounds

Representative plate-view of waveform traces shows consistency between replicate organoids.



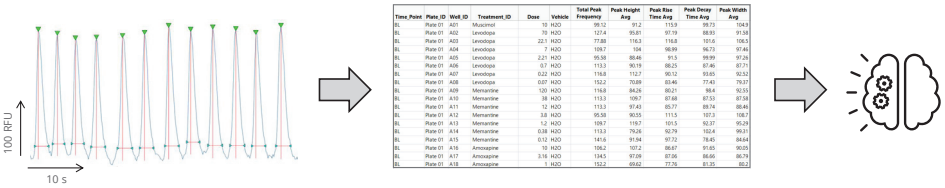
Cortical organoids exhibited consistent spontaneous functional activity at 10 weeks of differentiation across multiple studies.

Building an Automated Analysis Pipeline

Three automations were used to stabilize predictions and remove user-bias from waveform analysis.

1 Remove user-bias from peak detection

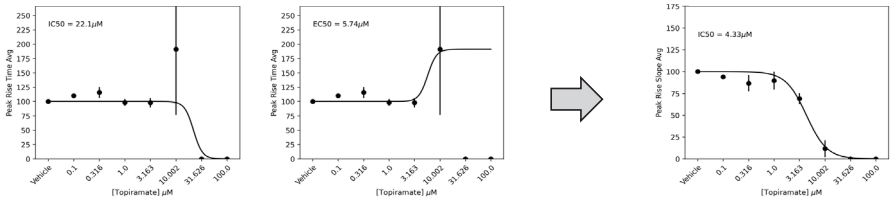
AnalytiX™ software detects and quantifies six robust features describing the number, size, and shape of organoid spontaneous activity bursts, which are then utilized in the clinical neurotoxicity prediction model.



2 Adjust features describing peak shape

TIME features - Difficult to assess potency in rise and decay time features that often display biphasic responses.

SLOPE features - Monotonic responses are amenable to standard IC_{50} curve fitting.



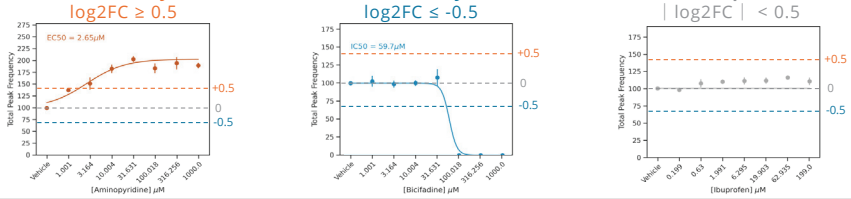
3 Automate detection of excitatory vs inhibitory compound responses

Quantitative criteria were selected to automate response-type assignments to each waveform feature.

Excitatory log2FC ≥ 0.5

Inhibitory log2FC ≤ -0.5

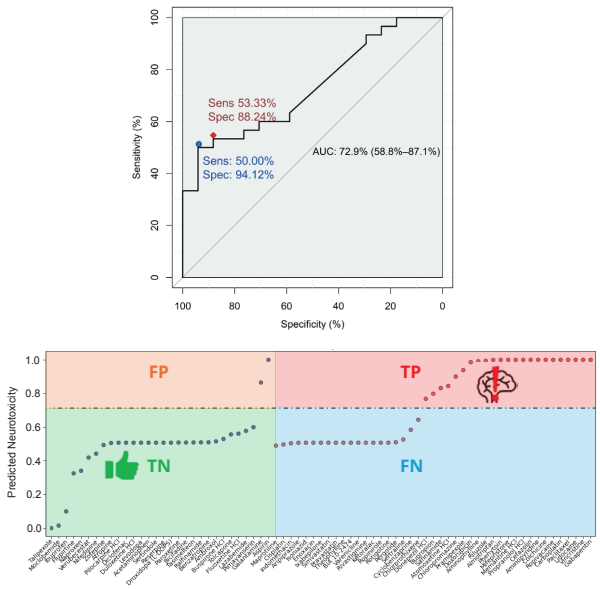
No Response | log2FC | < 0.5



Reproducible Clinical Neurotoxicity Predictions

Clinical neurotoxicity predictions, originally published by Takeda [3] were replicated years later in a different lab using a new cell bank. The automated analysis pipeline did not alter model performance on the original dataset (left) and revealed highly-reproducible model performance when trained on the 2024 dataset (right)

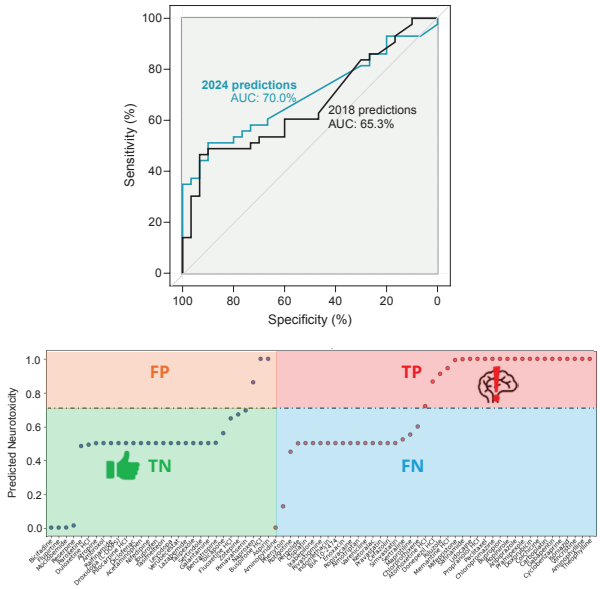
Wang *et al.*, ALTEX 2022



Sensitivity = 23/43 (**53.5%**)
...of toxic drugs were identified as toxic

Specificity = 28/30 (**93.3%**)
...of safe drugs were identified as safe

Current work



Sensitivity = 23/43 (**53.5%**)
...of toxic drugs were identified as toxic

Specificity = 27/30 (**90.0%**)
...of safe drugs were identified as safe

Conclusions & Future Directions

- Functional measurements from human iPSC-derived cortical brain organoids predict clinical neurotoxicity with high specificity (≥90%) and good sensitivity (>50%).
- The stability of neurotoxicity predictions is driven by the reproducibility of the organoid model and was further enhanced through improved peak detection, waveform feature engineering, and automated potency calculations.
- High specificity was maintained across independent experiments conducted at different sites over multiple years with various cell banks, demonstrating model robustness.
- This CIVM approach can enhance preclinical drug screening by identifying neurotoxicity risks without prematurely eliminating viable drug candidates.
- Implementation in drug development pipelines may reduce costly clinical failures by improving the quality of drug candidates before human trials.

References

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[3] Wang Q, Cohen JD, Yukawa T, Estrella H, Leonard C, Nunes J, Choi C, Mishra N, Lewis L, Baker KS, Kuga K. Assessment of a 3D neural spheroid model to detect pharmaceutical-induced neurotoxicity. ALTEX. 2022 Oct 18;39(4):560-82.

APPLIED PHARMACEUTICAL TOXICOLOGY

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