tissue growth by day 4; 2) epithelial cell morphology similar to human colon; 3) a physiological TEER value of >300 Ω*cm^2 mimicking the colon microenvironment; and 4) expression of CK19 (epithelial cell marker), vimentin (fibroblast cell marker), and Alician blue PAS staining (mucous producing goblet cell marker) on the villi-like structure. When mixed epithelial cells and fibroblasts are seeded on tissue culture inserts, there was a self-assembly pattern of differentiation in which the fibroblasts occupy the base layer and the epithelial cells differentiate and stratify on the apical layer. This new human cell-based colon tissue model will be a useful tool for pre-clinical assessment of microbiomes, mucosal inflammation, and screening of colorectal care products for their irritation potential. Such models will also reduce the use of animals for experimentation.

3065 High-Throughput and Physiologically-Relevant Anisotropic hiPSC-Derived Cardiomyocyte Cultures Provide Better Resolution over Safety Profiles of Compounds with Known Cardiotoxic Mechanisms of Action

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Drug removal from the clinical market, as well as late-stage failures in clinical trials, are often linked to unforeseen cardiac toxicity. hiPSC-CMs are an integral component of a new paradigm, the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) Initiative, through which panels of compounds with known mechanism of cardiotoxicity are being evaluated in hiPSC-CM platforms across independent test sites and through cutting-edge technologies. Key challenges under consideration for the hiPSC-CM system are sub-ideal cardiomyocyte geometry, sub-cellular structural organization, and electro-physiological maturity. Bioengineering approaches developed to enhance hiPSC-CM maturity have shown improvements in aspects of hiPSC-CM physiology, however those approaches have limited scalability and thus are not amenable to high throughput screening. hiPSC-CMs cultures plated on a high throughput platform which passively promote cardiomyocyte alignment have been shown to display physiologically-relevant features, including more physiological cellular geometry, coherent unidirectional contraction, cardiac cell junction re-modeling, and improved calcium handling. To evaluate whether the changes induced by this platform translated into differential responses to cardio-active compounds, high throughput calcium flux assays were performed on hiPSC-CMs cultured in standard high throughput screening cell cultureware or anisotropic 384-well plates and subsequently interrogated with the 28 compounds included in the CiPA initiative. Interestingly, when combining high and intermediate risk compounds, differential responses were observed in 63% of the compounds tested. Specifically, all compounds in the high risk category showed a clearer dose-dependent progression in the severity of early afterdepolarizations (EADs). Six out of eleven compounds in the intermediate risk category, namely Pimozide, Droperidol, Cisapride, Astemizole, Domperidone and Terfanadine, showed a more sensitive response in anisotropy. No EADs were observed in either control or anisotropic conditions treated with low risk compounds. Altogether, anisotropic high throughput hiPSC-CM cultures formatted in the platform employed in this study showed better resolution over the progression and severity of pro-arrhythmic events.

3066 Whole Transcriptome Extrapolation and Mechanism of Action Analysis Using GENIE Pipeline

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The Tox21 consortium is tasked to identify patterns of chemically-induced biological responses in order to characterize toxicity and disease pathways in a high-throughput manner and prioritize compounds for more extensive toxicological evaluations. The Tox21 is pursuing alternatives to cost prohibitive gene expression assessment techniques (Microarray or RNA-seq) that enable assessment of selected transcriptomic subsets in a high-throughput manner. Subsets measured using those techniques are not readily usable with standard differential pathway detection algorithms like Gene Set Enrichment Analysis (GSEA). This can yield limited gene-level differential expression results, necessitating the extrapolation of unmeasured portions of the transcriptome using inferences from measured portions. This can be achieved by modeling gene to gene interconnectedness of the transcriptome via large curated training samples with available whole transcriptome measurements. We present results of a transcriptome extrapolation comparing two popular large data extrapolation techniques: principal component regression (PCR) and Deep Learning (DL). For PCR, an eigenvalue ratio threshold of 0.1 was applied to identify significant PCs and perform prior standardization of inputs. For DL, a multi-task multi-layer feedforward neural network consisting of one input layer, 3 hidden layers (with 3,000 hidden units each), and one output layer was customized. RMA normalized signal for all unique (N=117,559) GPL570 microarray data files from NCBI Gene Expression Omnibus (GEO) were downloaded and computed. The probe-set signal values were averaged to compute gene-level signal with NCBI's gene information database. The signal from 2,729 NCBI genes was used to extrapolate signal for 18,167 genes using each method. The extrapolation performance of each method was evaluated using 20-fold cross validation. Results indicate that PCR extrapolation outperforms DL extrapolation in terms of root mean square error (RMSE; PCR=0.39 vs. DL=0.51), median absolute error (MAE; PCR=0.20 vs. DL=0.26), and rank-biased overlap between the top 10% of true and extrapolated genes (RBO; PCR=66% vs. DL=58%). Additionally, PCR extrapolation is less computationally intensive, increasing its overall utility. These extrapolation efforts improve the scale and utility of transcriptomic data to fill in gaps between subsets of genes measured in individual studies and the ability to assess the entire transcriptome.

3067 Improving Efficiency in Systematic Reviews by Automated Data Extraction: A Case Study Using NTP's SRIE Challenge Dataset

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Systematic reviews are labor-intensive exercises, especially the data extraction step in which subject matter experts must review full-text documents to extract specific data elements. While natural language processing-based information retrieval technologies are now widely used to increase the efficiency of the upstream literature screening and prioritization steps in systematic reviews, the use of information extraction algorithms in data extraction is still nascent, potentially owing to the lack of publicly available annotated datasets. In July 2018, the National Toxicology Program (NTP) conducted a public challenge, in which our group participated, to develop and apply information extraction algorithms to an annotated test dataset of 100 articles related to toxicology. The articles were annotated with respect to commonly extracted data elements such as species, strain, dose, dose units, dose duration, endpoints, sample size, test article, and vehicle. In this research, we leverage NTP's publicly accessible training dataset to test the accuracy and performance of various cutting edge information extraction algorithms. (The NTP's test datasets were not publicly available at the time of performing this research, nor were the results of the challenge). Specifically, we split the NTP's publicly available training dataset of 100 annotated articles randomly into a set of 80 articles used for model building (our training dataset) and a set of 20 articles used for validating results (our validation dataset). We fit a pipeline of information extraction algorithms including conditional random fields (CRF) models, long short-term model (LSTM) networks, and dictionary-based approaches to annotate the text in the validation dataset. We compared our predicted annotations with NTP's gold standard annotations using NTP's publicly available evaluation software that was custom developed for this challenge. For the various data elements predicted, we found extraction recall (sensitivity) rates ranging from 23% to 87%, with F1-scores ranging from 16% to 63%. We assess reasons for the differing levels of performance across various data elements, including challenges with the annotation framework and issues with the detection of phrases. We also compare the performance of the individual algorithms and their performance in sequence to assess their relative strengths. We estimate potential time savings from the use of this technology and, based on our empirical findings, propose a framework to minimize relevant data losses and maximize efficiency.

3068 Using Liquid Chromatography Mass Spectrometry (LC-MS) to Assess the Effect of Age, Diet, and Rat Strain on the Global Metabolome

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The exposome encompasses the entire environmental exposures of an individual during a lifetime. These exposures include diet, lifestyle, environmental toxins, and workplace exposures. The interactions of combined exposures can lead to exacerbation of disease. The goal of this study was to use liquid chromatography mass spectrometry (LC-MS) to assess metabolic changes in three distinct animal strains based on two different diets. Sprague-Dawley (SD), Fischer 344 (F344), and Brown-Norway (BN) male rats were maintained on a high fat, Western (HF), or regular diet for 24 weeks. Serum was collected at 4, 12, and 24 weeks to assess metabolite changes. A cold methanol buffer was used to extract metabolites. Metabolite extracts were analyzed

using high resolution accurate mass (HRAM) mass spectrometry coupled to ultra-high performance liquid chromatography. The results of the global metabolomics revealed significant changes based on both age and diet within all three strains. Principal component analysis revealed that the influence of diet caused a greater variation in the significantly changing metabolites ($p < 0.05$) than that of age for the BN and F344 strains, while the SD strain showed a large influence from diet at the 4 week time point. As expected, metabolites involved in lipid metabolism and bile acid formation were upregulated in the animals maintained on a HF diet compared to the regular diet. There were also significant changes observed in acetyl-coA concentrations between the two diets at all of the time points for all strains. A targeted LC-MS/MS quantification of TCA cycle intermediates was performed on liver metabolite extracts. The results of this targeted analysis revealed significant increases in α-ketoglutarate, succinyl-coA, and fumarate for the HF diet across all three strains. The BN strain showed a significant increase in malate in the HF diet compared to the regular diet, whereas the SD strain had a significantly higher concentration of citrate in the liver of the HF diet than the other two strains. The results of this study show that Sprague-Dawley showed greater metabolic variability to diet changes than Fisher 344 or Brown Norway strains. It also shows that age is an important experimental variable to consider when performing metabolic studies.

3069 Physicochemical Characterization and *In Vitro* Toxicity of Emissions from a 3D Printer

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Three dimensional (3D) printers are widely used for prototyping and building small physical objects in schools, home and businesses. Feedstock material used in 3D printing is polymer thermoplastic filament that may contain additives such as metals, ceramics, wood fiber, carbon fiber, graphene, or silica to impart aesthetic or functional properties. The use of 3D printers with polymer thermoplastics is of concern for workers and consumers because they emit a mixture of ultrafine particles and volatile organic compounds (VOCs) that are associated with respiratory and cardiovascular diseases. The scope of this study was to characterize aerosolized emissions from 3D printers and evaluate their toxic effects in human small airway epithelial cells (SAEC). Emissions were generated from a commercially available 3D printer while operating for 1.5 h with acrylonitrile butadiene styrene (ABS) or polycarbonate (PC) filaments. Both particles and VOCs were collected using an impinger sampler. Samples were characterized for their physicochemical properties, cellular cytotoxicity, oxidative stress response, apoptotic effects, and cytokine production. Results showed that printers with PC filaments generated two-fold more particles/ml than ABS. Mean sizes of PC and ABS-emitted particles in cell culture media were 201 ± 8 nm and 198 ± 10 nm, respectively. Bisphenol A and styrene were the predominant VOCs collected in the media for the PC and ABS emissions, respectively. At 24 h post exposure, both PC and ABS emissions elicited significantly increased cytotoxicity, with PC being more toxic than ABS. Moreover, PC induced higher production of reactive oxygen species, and decreased in total antioxidant capacity and glutathione peroxidase activity than ABS. Furthermore, both PC and ABS emissions induced apoptosis in SAEC with the PC emissions induced four-fold more apoptotic cells than the ABS emission. Cytokine and chemokine profiling showed that PC emissions induced higher production of seven proinflammatory cytokines and chemokines than ABS. Taken together, the results indicate that the emissions generated by PC and ABS filaments induce toxicity in SAEC, and the exposure to the PC emission induces more toxicity than that of the ABS emission.

3070 Capture Compound Mass Spectrometry: Elucidating Off-Target Binding to Deconvolute Drug Toxicity

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Understanding both the on- and off-target protein binding interactions of small molecules is an essential part of the drug discovery process. A large proportion of toxicity findings in non-clinical or clinical studies are precipitated by the parent drug or a metabolite binding an off-target protein target, such as an enzyme or receptor, modifying its function resulting in cellular dysfunction and toxicity. Capture Compound® Mass Spectrometry (CCMS) is an unbiased, proteome-wide approach for the identification of specific-binding protein targets for small molecules and peptides. The technology combines medicinal chemistry and *in vitro* pharmacology, coupled to high resolution proteomics mass spectrometry to isolate and identify target proteins that are responsible for an observed biological response. Thus, through *in vitro* investigation in target tissues of interest, the candidate proteins and pathways causing *in vivo* toxicity can be elucidated. An overview of CCMS technology and its application in identification of off-target compound activity is presented. The CCMS technology has been used to determine on- and off-target interactions of the catechol-O-methyl transferase (COMT) inhibitor tolcapone in a human liver cancer cell line (HepG2). A comprehensive interaction profile was generated, revealing both on- and off-target binding proteins. Differential profiles of tolcapone which causes liver toxicity and entacapone that does not were elucidated and highlighted 3-hydroxyisobutyrly-CoA hydrolase (HIBCH) as a candidate target mediating toxicity. Medicinal chemistry was then initiated focusing on molecules without HIBCH activity resulting in 'tolcapone-like' molecules with reduced toxicity profiles that could lead the way to the development of improved COMT inhibitors.

3071 A Practical High-Throughput Co-Culture Plate to Screen Paracrine and Endocrine Interactions

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Traditional HTS in microtiter plates is limited to one cell type, excluding important paracrine and endocrine cell:cell interactions, while Transwell® inserts are not compatible with 384 and 1536 well robotic HTS. We have developed a microtiter plate based co-culture system dubbed MICRO-MT as a solution to fulfill the HTS co-culture and multi-culture needs of the drug discovery and toxicity testing market. In the MICRO-MT, cells are monocultured in individual wells of a microtiter plate with standardized dimensions as usual, but by simply increasing fluid volume, the media from monocultures in adjacent wells are bridged through the integrated microchannels allowing co-culture through diffusion of metabolites between wells. Because the MICRO-MT operates by simple diffusion and in a traditional microtiter plate footprint, it doesn't require additional equipment beyond that already in use and is compatible with existing infrastructure. To illustrate the utility of this approach we developed a conferred steroid metabolism assay using an estrogen receptor driven luminescent reporter cell line, MVLNs alone or in co-culture with HepG2 cells. HepG2 cells contain high levels of aromatase activity which converts testosterone to estrogen, while MVLN cells do not express aromatase. MVLN cells in monoculture treated with 17B-estradiol ranging 100pM to 10nM showed high luminescent activity, whereas testosterone treatment showed no luminescent activity as predicted. In contrast, co-culture of MVLN and HepG2 cells in the MICRO-MT showed dose-responsive increases in MVLN luminescent activity in response to testosterone treatment ($EC50 = 4.1nM$) indicating HepG2 cells converted testosterone to estrogen which then diffused in the reporter well containing MVLN cells activating the luminescent reporter. We have also found that this platform recapitulates a paracrine Sonic Hedgehog (SHH) signaling response, whereby SHH ligand produced from GMSM-K SHH transfected epithelium generates robust SHH pathway activation in co-cultured Shh Light II cells that is antagonized receptor antagonists vismodegib and cyclopamine, but also secretory antagonists Ruski-43 and U18666A. These studies show that the MICRO-MT plate is a viable solution to support paracrine and endocrine interactions in a technically simple format that is amenable to HTS.

3072 Evaluation of Transdermal Drug Delivery and Toxicity in a Microphysiological Body-on-a-Chip System

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Body-on-a-chip (BoaC) *in vitro* systems are a promising technology for increasing the predictive power of drug efficacy and toxicity in humans compared to traditional animal models. These interconnected multi-organ systems can be improved by expanding drug delivery methodologies to include oral and transdermal applications. Towards that goal, we have developed a heart-liver-"skin" BoaC system to assess the toxicity of topically administered drugs dosed acutely and chronically. To validate the topical delivery system, the moderate permeation drug diclofenac (1.5 and 3% solutions), and the low permeation compounds ketoconazole (0.11%), hydrocortisone (1%), and acetaminophen (1.5%) were applied to a synthetic skin surrogate (Strat-M membrane) and toxic effects on liver and cardiac physiology were compared to data generated from an acute drug exposure applied systemically. Medium concentration of each drug after topical application was monitored over time

58TH ANNUAL MEETING & ToxExpo · MARCH 10–14, 2019

The Toxicologist

Supplement to *Toxicological Sciences*

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 168, Issue 1
March 2019

www.academic.oup.com/toxsci

The Official Journal of the Society of Toxicology

SOT | Society of Toxicology

Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

www.toxicology.org

Publication Date: February 18, 2019