Addendum #3: Experimental Endpoints for Small Molecule Models

The following experimental endpoints were used to generate TuneLab™ models and represent the types of data that participating organizations contribute to the federated learning program.

Absorption	Endpoint	Data Format
Core	HTSA pH2 Classifier (0.01 mg/mL)	Binary classification
Core	HTSA pH2 Classifier (0.1mg/mL)	Binary classification
Core	HTSA pH6 Classifier (0.01 mg/mL)	Binary classification
Core	HTSA pH6 Classifier (0.1 mg/mL)	Binary classification
Core	HTSA pH7.4 Classifier (0.01 mg/mL)	Binary classification
Core	HTSA pH7.4 Classifier (0.1 mg/mL)	Binary classification
Core	MDCK Permeability Predictor	Continuous (Papp values)
Core	MDCK Permeability 2C Classifier	Binary classification
Core	Thermodynamic Aqueous Solubility	Continuous (mg/mL)
Core	Human Passive Intestinal Permeability	Continuous (Papp)
Core	Pgp Substrate Recognition	Binary classification
Additional	Caco-2 Permeability	Papp (10^{-6} cm/s)
Additional	PAMPA Permeability	Pe (10^{-6} cm/s)
Additional	Oral Bioavailability	%F (in vivo or predicted)
Additional	BCRP Substrate/Inhibitor	Binary or IC50
Additional	OATPIB1/1B3 Substrate	Binary or uptake rate
Additional	OCT2 Substrate/Inhibitor	Binary or IC50

Distribution	Endpoint	Data Format
Core	Fraction Unbound Microsome	Continuous (fu)
Core	Fraction Unbound Plasma	Continuous (fu)
Core	Fraction Unbound Brain	Continuous (fu,brain)
Core	Total Brain Concentration	Continuous (brain/plasma)
Core	Kp Brain	Continuous ratio
Additional	Volume of Distribution (Vdss)	L/kg (in vivo or predicted)
Additional	Blood-to-Plasma Ratio	Ratio

Additional	HSA Binding	%bound or Kd
Additional	AGP Binding	%bound or Kd
Additional	Tissue Distribution (Kp values)	Tissue/plasma ratios

Metabolism	Endpoint	Data Format
Core	Mouse Microsomal Clearance	Continuous (µL/min/mg)
Core	Rat Microsomal Clearance	Continuous (µL/min/mg)
Core	Human Microsomal Clearance	Continuous (µL/min/mg)
Core	Mouse Metabolic Stability	Continuous (t1/2)
Core	Rat Metabolic Stability	Continuous (t1/2)
Core	Human Metabolic Stability	Continuous (t1/2)
Core	Dog Metabolic Stability 2C	Binary classification
Core	Mouse Metabolic Stability 2C	Binary classification
Core	Human Metabolic Stability 2C	Binary classification
Core	Rat Metabolic Stability 2C	Binary classification
Core	Monkey Metabolic Stability 2C	Binary classification
Core	Mouse Hepatocyte Clearance	Continuous (µL/min/10^6 cells)
Core	Rat Hepatocyte Clearance	Continuous (µL/min/10^6 cells)
Core	Human Hepatocyte Clearance	Continuous (µL/min/10^6 cells)
Core	Dog Hepatocyte Clearance	Continuous (µL/min/10^6 cells)
Core	Rat IV Clearance	Continuous (mL/min/kg)
Core	Rat IV Vd Area Classifier	Binary classification
Core	Rat IV CL Class (50 mL/min/kg)	Binary classification
Additional	UGT Inhibition Panel	IC50 values
Additional	Metabolite Identification	Major metabolites list
Additional	Species Comparison (Met ID) Cross-species metabolites	Cross-species metabolites
Additional	Aldehyde Oxidase Substrate	Binary or % metabolism
Additional	FMO Substrate	Binary or % metabolism

Distribution	Endpoint	Data Format
Additional	Renal Clearance	mL/min/kg
Additional	Biliary Excretion	% dose in bile

Additional	Total Body Clearance mL/min/kg	mL/min/kg
Additional	Terminal Half-life	hours
Additional	Mean Residence Time	hours

Toxicity	Endpoint	Data Format
Core	Rat Primary Hepatocyte Cytolethality	Continuous (IC50)
Core	hERG Binding Classifier	Binary classification
Core	HepG2 Phospholipidosis	Binary classification
Core	HepG2 Lysotracker	Continuous or binary
Core	Mutagenicity (Mini Ames) Class	Binary classification
Core	Rat Primary Hepatocyte Phospholipidosis	Binary classification
Additional	Mitochondrial Toxicity	Glu/Gal IC50 ratio
Additional	Bile Salt Export Pump (BSEP)	IC50 or % inhibition
Additional	Reactive Metabolite Formation	GSH adduct levels
Additional	Genotoxicity (Micronucleus)	Binary or fold increase
Additional	Chromosome Aberration	Binary classification
Additional	Carcinogenicity Alerts	Structural alerts count
Additional	Skin Sensitization	LLNA EC3 or in vitro
Additional	Phototoxicity	PIF or MPE values
Additional	Eye Irritation	Score or classification
Additional	Developmental Toxicity	Binary or severity score
Additional	Cardiotoxicity (beyond hERG) Multi-ion channel panel	Multi-ion channel panel
Additional	Neurotoxicity Panel	Multiple endpoints
Additional	Immunotoxicity Markers	Cytokine levels or ratios
Additional	Nephrotoxicity Biomarkers	KIM-1, NGAL levels
Additional	Endocrine Disruption Panel	Nuclear receptor activation

Pharmacology	Endpoint	Data Format
Core	5HT2B Agonist (Ca Mobilization)	IC50/EC50 or % inhibition
Core	5HT2B Antagonist (Ca Mobilization)	IC50 or % inhibition
Core	ADORA2A Agonist/Antagonist	IC50/EC50 or % inhibition
Core	ADRalA Agonist/Antagonist	IC50/EC50 or % inhibition

Core	ADRb2 Agonist (cAMP)	EC50 or % activation
Core	ADRb2 Antagonist (Arrestin)	IC50 or % inhibition
Core	Cav1.2 (Ca Channel)	IC50 or % inhibition
Core	D2L Agonist/Antagonist	IC50/EC50 or % modulation
Core	hERG Channel Binding	IC50 or Ki
Core	GABAA Ion Channel	IC50 or % modulation
Core	Glucocorticoid Receptor Binding	IC50 or Ki
Core	HIR/HRH1 Agonist/Antagonist	IC50/EC50 or % modulation
Core	Kainate Receptor	IC50 or % modulation
Core	LXRα Binding	IC50 or Ki
Core	M2 Muscarinic Agonist/Antagonist	IC50/EC50 or % modulation
Core	Nav1.5 Sodium Channel	IC50 or % inhibition
Core	PDE10A Binding	IC50 or Ki
Core	PDE3A Binding	IC50 or Ki
Core	PDE4D Binding	IC50 or Ki
Core	PPARγ Binding	IC50 or Ki
Core	RARα Binding	IC50 or Ki
Core	RXRα Binding	IC50 or Ki
Core	rAMPA Receptor	IC50 or % modulation

Drug-Drug Interaction	Endpoint	Data Format
Core	CYP2C9 SP 2 Class	Binary classification
Core	CYP2D6 SP 2 Class	Binary classification
Core	CYP3A4 SP 2 Class	Binary classification
Core	CYP3A4 Time Dependent Inh.	Binary classification
Additional	CYP1A2 Inhibition	Binary classification
Additional	CYP2C19 Inhibition	Binary classification
Additional	CYP2C8 Inhibition	Binary classification
Additional	CYP2B6 Inhibition	Binary classification
Additional	CYP Induction (PXR activation)	Fold induction or EC50
Additional	CYP Induction (CAR activation)	Fold induction or EC50
Additional	CYP Induction (AhR activation)	Fold induction or EC50

Addendum #3 : Experimental Endpoints – Small Molecules

Emerging/Specialized	Endpoint	Data Format
Additional	PROTAC Ternary Complex Formation	Binary or Kd
Additional	PROTAC Hook Effect	Dose-response profile
Additional	PROTAC Degradation Kinetics	t1/2 degradation
Additional	Molecular Glue Activity	Binary or EC50
Additional	Targeted Covalent Inhibitor Kinetics	kinact/Ki
Additional	Lysosomal Accumulation	Fold accumulation
Additional	Autophagy Modulation	LC3B ratio or flux
Additional	Ferroptosis Induction	Lipid ROS levels
Additional	Environmental Toxicity	EC50 aquatic species
Additional	Bioaccumulation Factor	BCF or LogP-based
Additional	Gut Microbiome Impact	Growth inhibition panel