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An automated high-throughput 384-well ADME screening workflow on the SCIEX 7600 ZenoTOF for high volume drug discovery

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Artificial Intelligence in Drug Discovery and Development

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The Future of Medicine: AI and ML Driven Drug Discovery Advancements

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R. Satheeskumar

Department of Computer Science and Engineering, Narasaraopeta Engineering College, Andhra Pradesh, 522601, India

Review | Open access | Published: 11 December 2025

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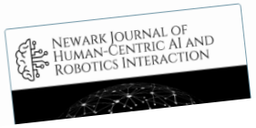


Nischay Reddy Mitta

Independent Researcher, USA

Author

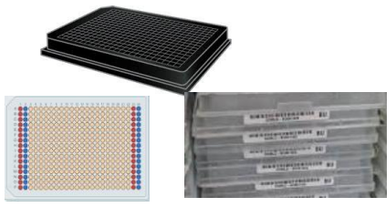
Motivation & Background

Why AI Matters To Drug Discovery and Development

- **Integrated AI Applications in Drug Discovery and Development**

Supporting Predictive Decisions

- Early prediction of ADMET
- Candidate selection
- Improved accuracy in decision-making



Early Prediction

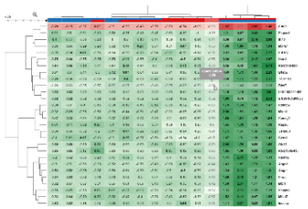
Accelerating Discovery Timelines

- Rapid virtual screening
- Faster lead optimization
- Shorten decision-making time

Time Reduction

Improving Data Analysis

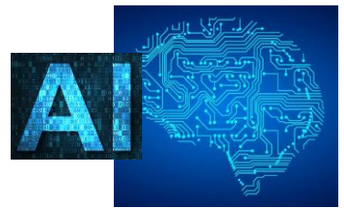
- Automated data interpretation
- Assay data harmonization
- Faster, deeper insights



Interpretations & Conclusions

Improving Human Translations

- In silico human prediction
- Translational modeling
- Cross-species extrapolation



Translational Modeling

Motivation & Background

Why High-Throughput ADME Matters for AI Drug Discovery

Current bottleneck:

- Low throughput
- Limited high-quality ADME data
- Manual processes & variability
- Integration gaps between labs & AI pipelines

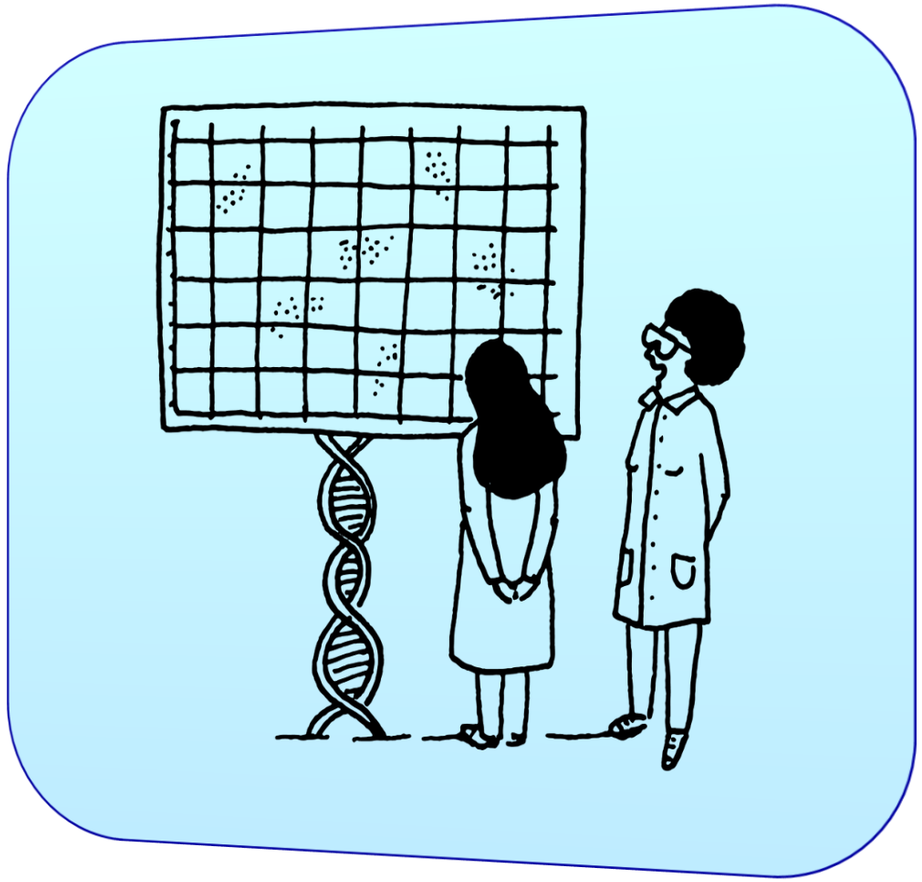
Key Issues

Path to AI Drug Discovery

Solutions

- High-Throughput ADME at scale
- Data standardization
- Automated analysis
- AI-Driven assay optimization

How We Get There



Study Objective

Automated high-throughput 384-well workflow on the SCIEX 7600 ZenoTOF

Requirements for AI models

- Increase assay throughput
- Reduce turnaround
- Minimize manual labor
- Improve consistency and reproducibility

Approaches / How

Fully Automated in 384-well format

Integrate with SCIEX 7600 ZenoTOF for rapid LC-MS analysis

Standardize data capture for AI training

Goal: Enable rapid generation of AI-ready DMPK datasets while maintaining high data quality

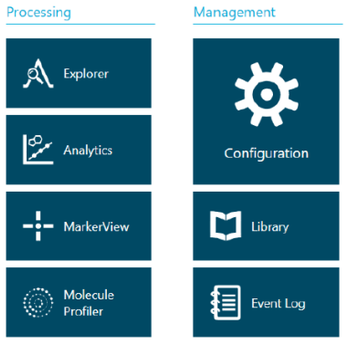
Platform Overview

Workflow for 384 format HT-Screening

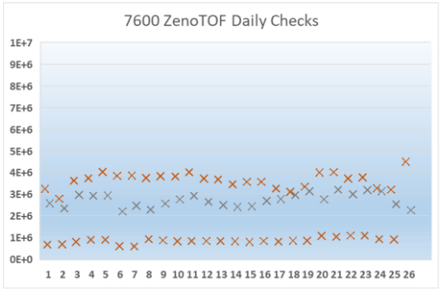
Liquid Handler

Sample Analysis

Data Processing



Data QC



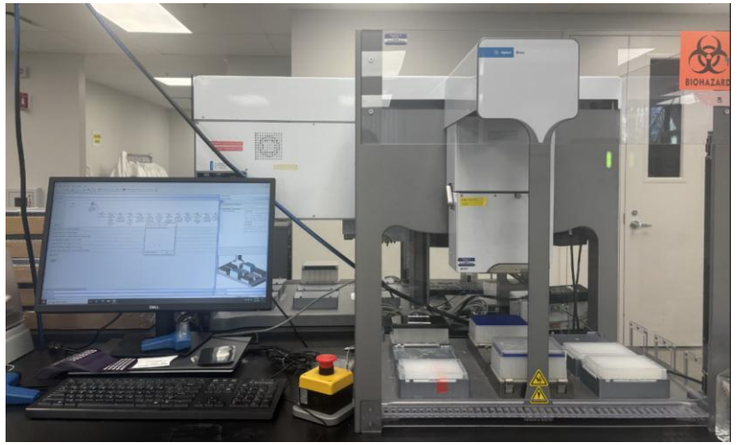
- Agilent Bravo liquid-handling system
- Fully automated reagent addition and sampling
- Reduced hands-on time and variability

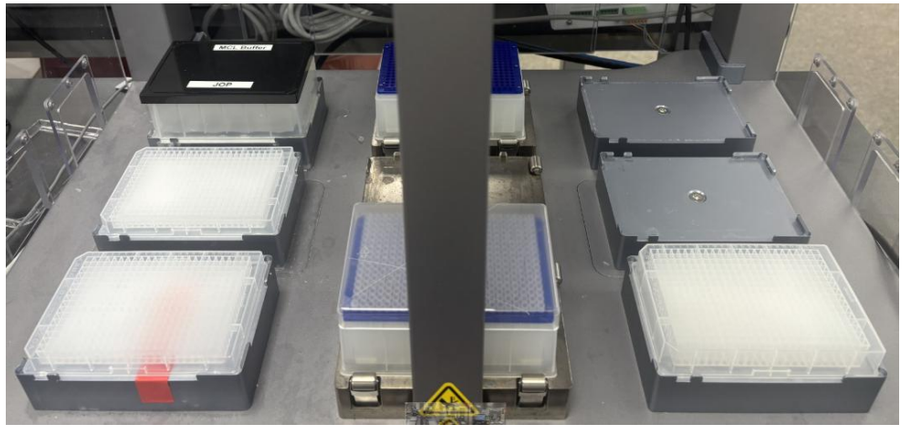
- High-resolution TOF detection
- Rapid LC-MS analysis (30s)
- Automated data processing and QC

Goal: Fully automated, high-throughput ADME screening in 384-well format

384 Examples – Hepatocytes and Microsomal Stability

Assay conditions in 384-well Format





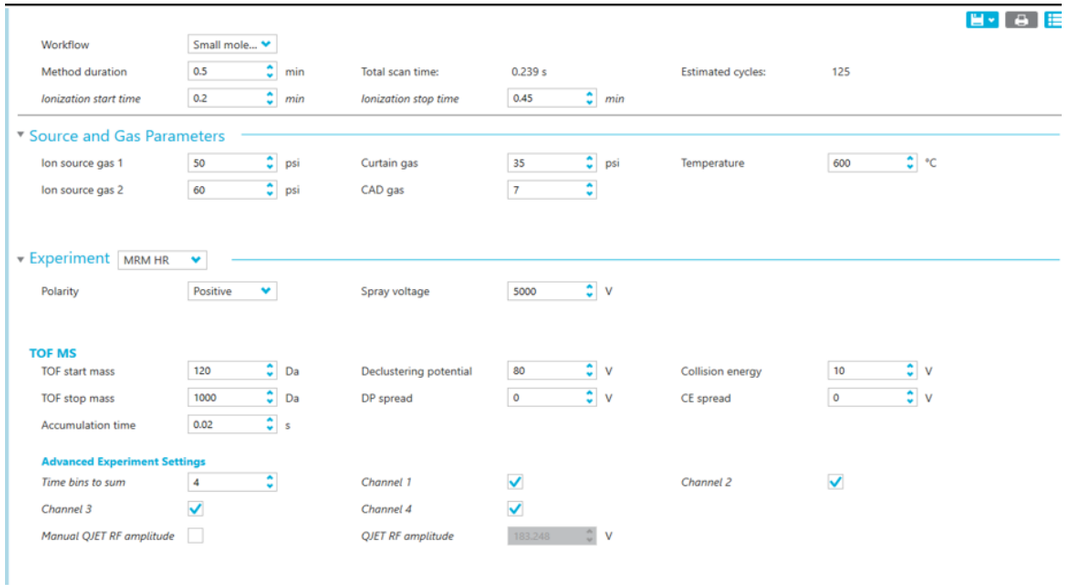
Matrix	Protein/cells Conc	Test Cmpd Conc	Time Points	Cofactor	Analysis
Microsomes	0.25 mg/mL	1 µM	0, 5, 15, 30, 45 min	1 mM NADPH	LC-MS
Hepatocytes	$0.5x10^6$ cells/mL	1 µM	0, 15, 30, 60, 120 min	---	LC-MS

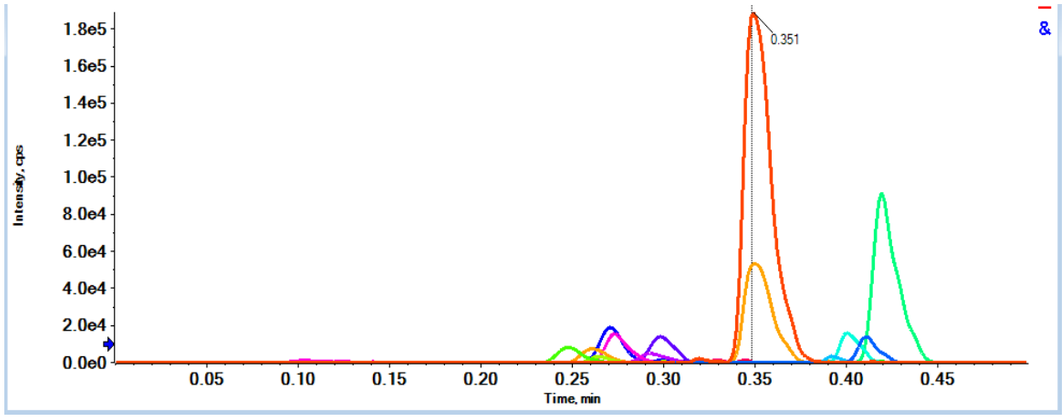
384 Examples – Hepatocytes and Microsomal Stability

LC-MS Conditions – Sciex 7600 ZenoTOF

LC Conditions:

- Column: CORTECS T3 Column, (120Å, 2.7 µm, 2.1 mm x 30 mm)
- **Total run time: 30s (51s including waiting time)**





MS Methods on 7600 ZenoTOF

- TOFMS Scan Range 120-1000
- MRM HR
- IDA

384 Examples – Hepatocytes and Microsomal Stability

LC-MS Conditions – Sciex 7600 ZenoTOF

Processing Method

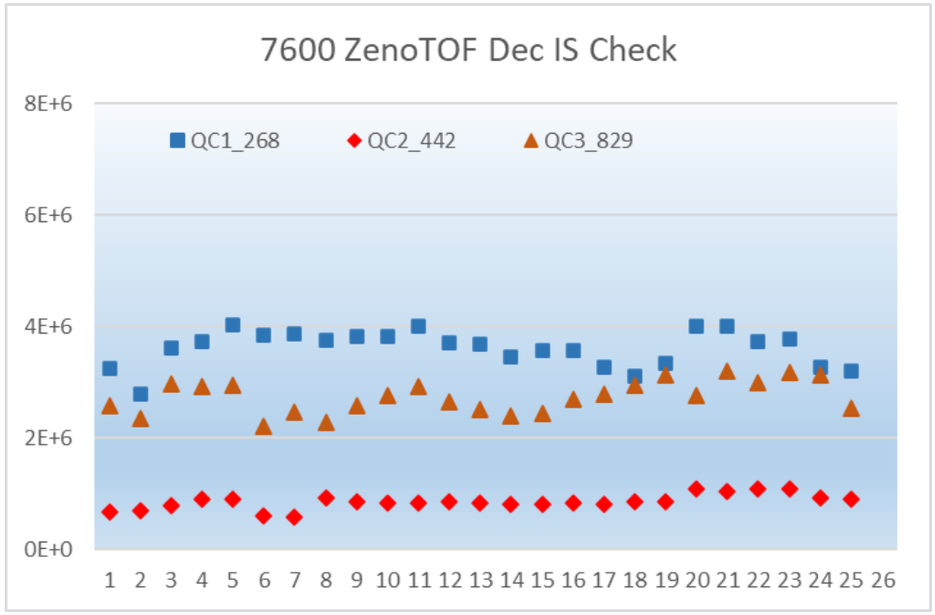
[MQ4] Untitled Method

Workflow
Components
Integration
Calculated Columns
Flagging Rules

Select or verify the analyte and internal standard names and masses.

Row	IS	Group	Name	Chemical Formula	Adduct/Ch...	Precursor (Q1) Mass (Da)	Fragment (Q3) Mass (Da)	XIC Width (Da)	Retention Time (min)
1	☐		Metoprolol	C15H25NO3	[M+H]+	268.19072		0.02	
2	☐		Sildenafil	C22H30N6O4S	[M+H]+	475.2122		0.02	
3	☐		Labetolol	C19H24N2O3	[M+H]+	329.18597		0.02	
4	☐		Imipramine	C19H24N2	[M+H]+	281.20123		0.02	
5	☐		Diclofenac	C14H11Cl2NO2	[M+H]+	296.02396		0.02	
6	☐		Verapamil	C27H38N2O4	[M+H]+	455.29043		0.02	
7	☐		Midazolam	C18H13ClFN3	[M+H]+	326.08548		0.02	
8	☐		Enalapril	C20H28N2O5	[M+H]+	377.2071		0.02	
9	☐		Propantheline	C23H30NO3	[M+H]+	369.22985		0.02	
10	☐		Warfarin	C19H16O4	[M+H]+	309.11214		0.02	
11	☐		Talinolol	C20H33N3O3	[M+H]+	364.25947		0.02	
12	☐		Ranitidine	C13H22N4O3S	[M+H]+	315.14854		0.02	
13	☐								
14	☐								

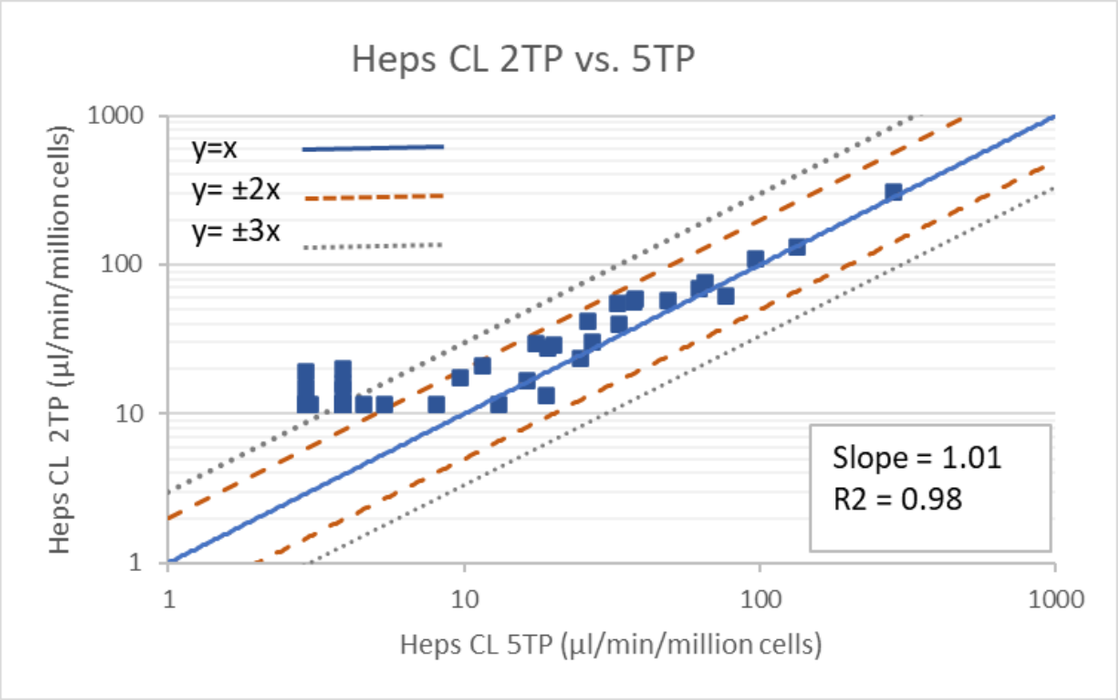
Daily IS Check



384-well vs. 96-well: Time, Cost and Efficiency

	384 - HRMS	96 - QTRAP	Improvements
Assay Time	One assay	Four assays	4x
Method Dev	Not required	~2 min per compound	100%
LC-MS Run Time	~0.5 min per sample	~2-5 min per sample	> 4x
Labor Effort	Minimal	Labor Intensive	> 4x
Efficiency & Consistency	Fully automated; high consistency	Multiple assays; higher variability	
Cost	Lower overall cost; less labware required	Higher cost due to more biological samples and consumable materials	

384 Examples – Hepatocytes 2TP vs. 5TP

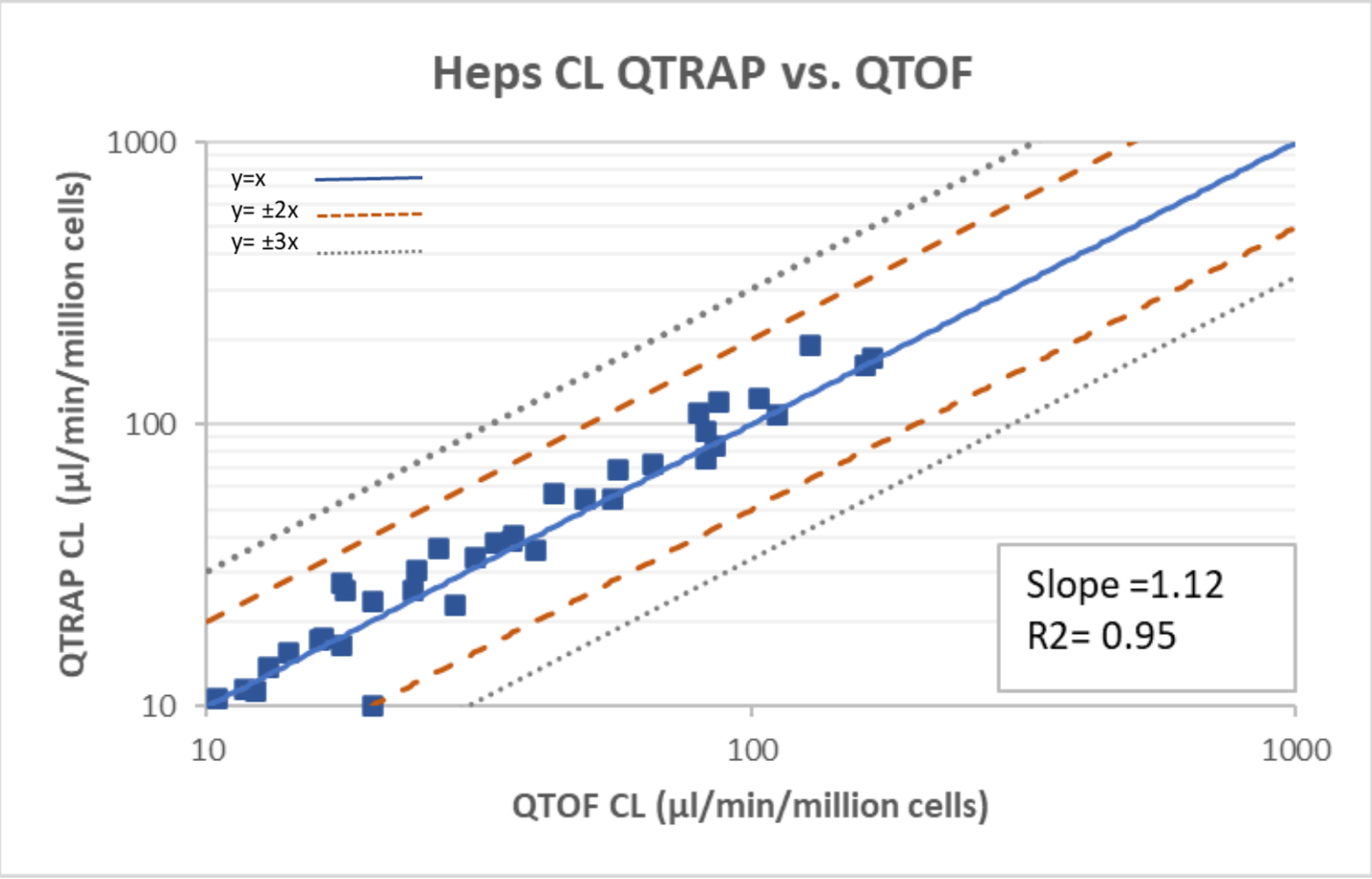


	2TP Heps	5TP Heps
Bravo Tips	T70 tips	T70 tips
Time Points	0, 30 min	0, 15, 30, 60, 120 min
Incubation Vol	75 µL	120 µL
Cell Conc	0.5 million cells /mL	0.5 million cells /mL

		Clearance (µl/min/10^6cells)	Half Life (min)
Min CL	2TP	<11.6	>120
	5TP	<2.9	>480
Max CL	2TP	>184.8	<7.5
	5TP	>369.7	<3.75

SCIEX QTRAP vs 7600 ZenoTOF - Heps

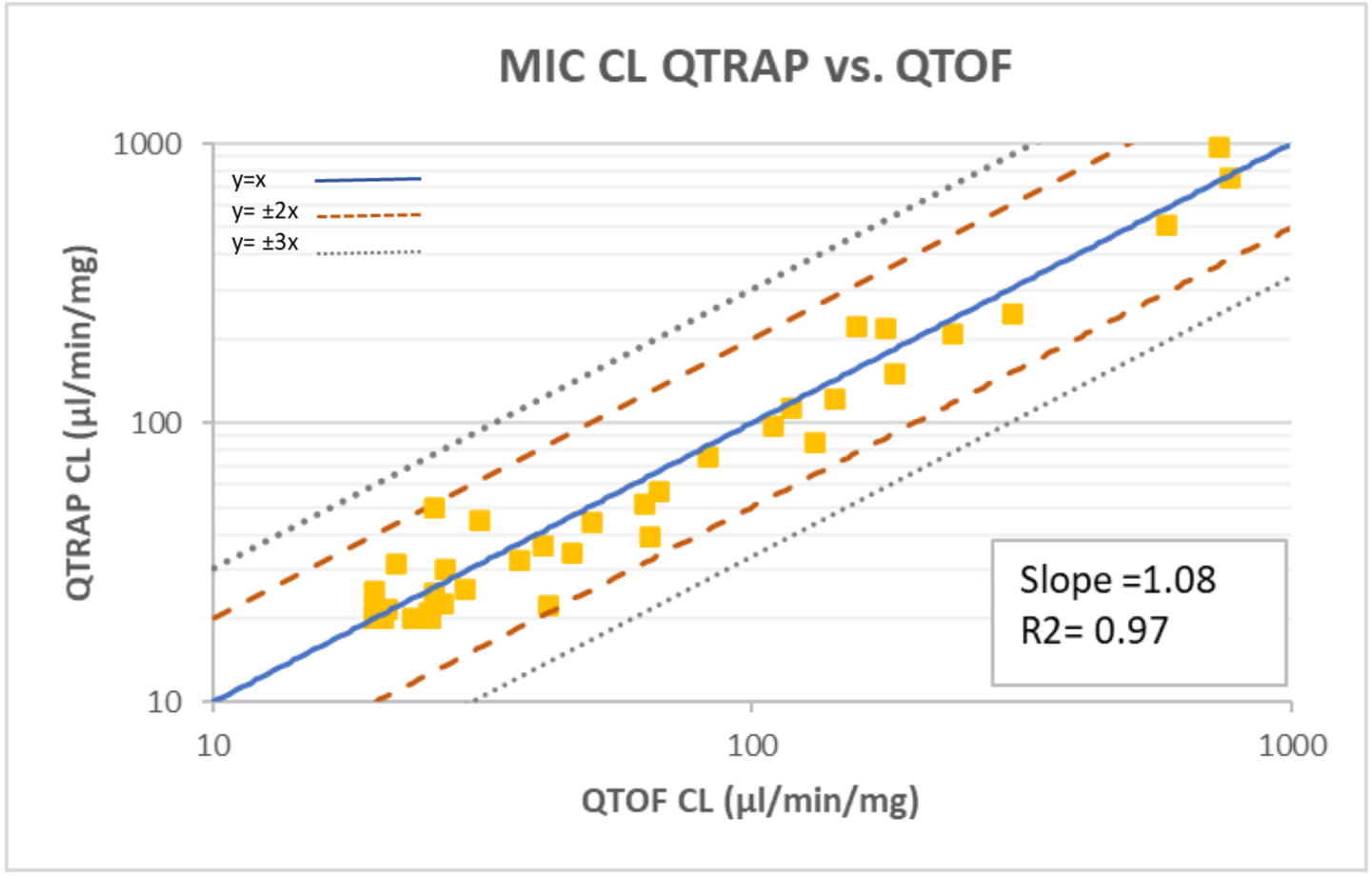
Cross-Platform Comparison



High correlation observed between QTRAP and QTOF results

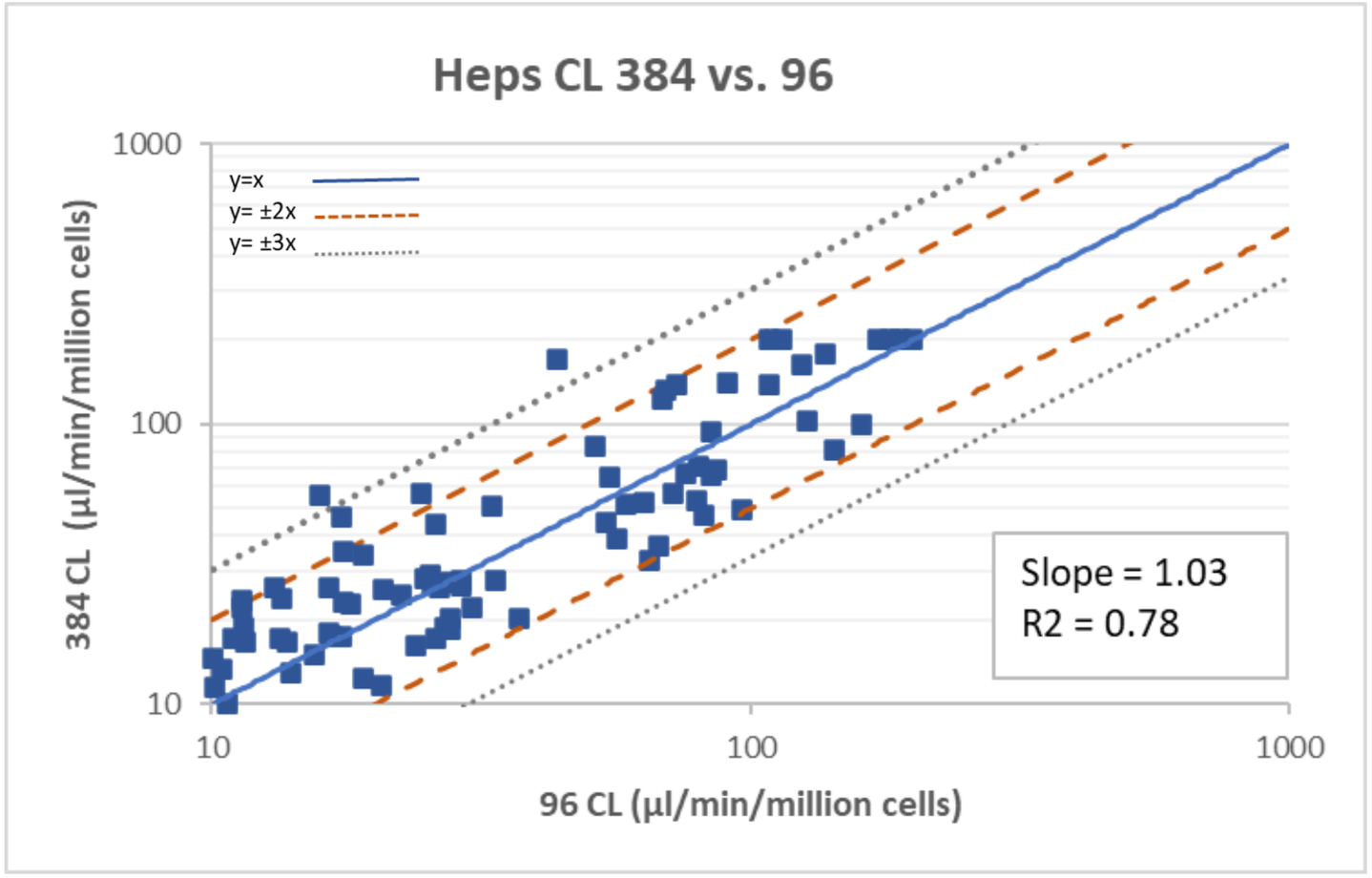
SCIEX QTRAP vs 7600 ZenoTOF - MCL

Cross-Platform Comparison



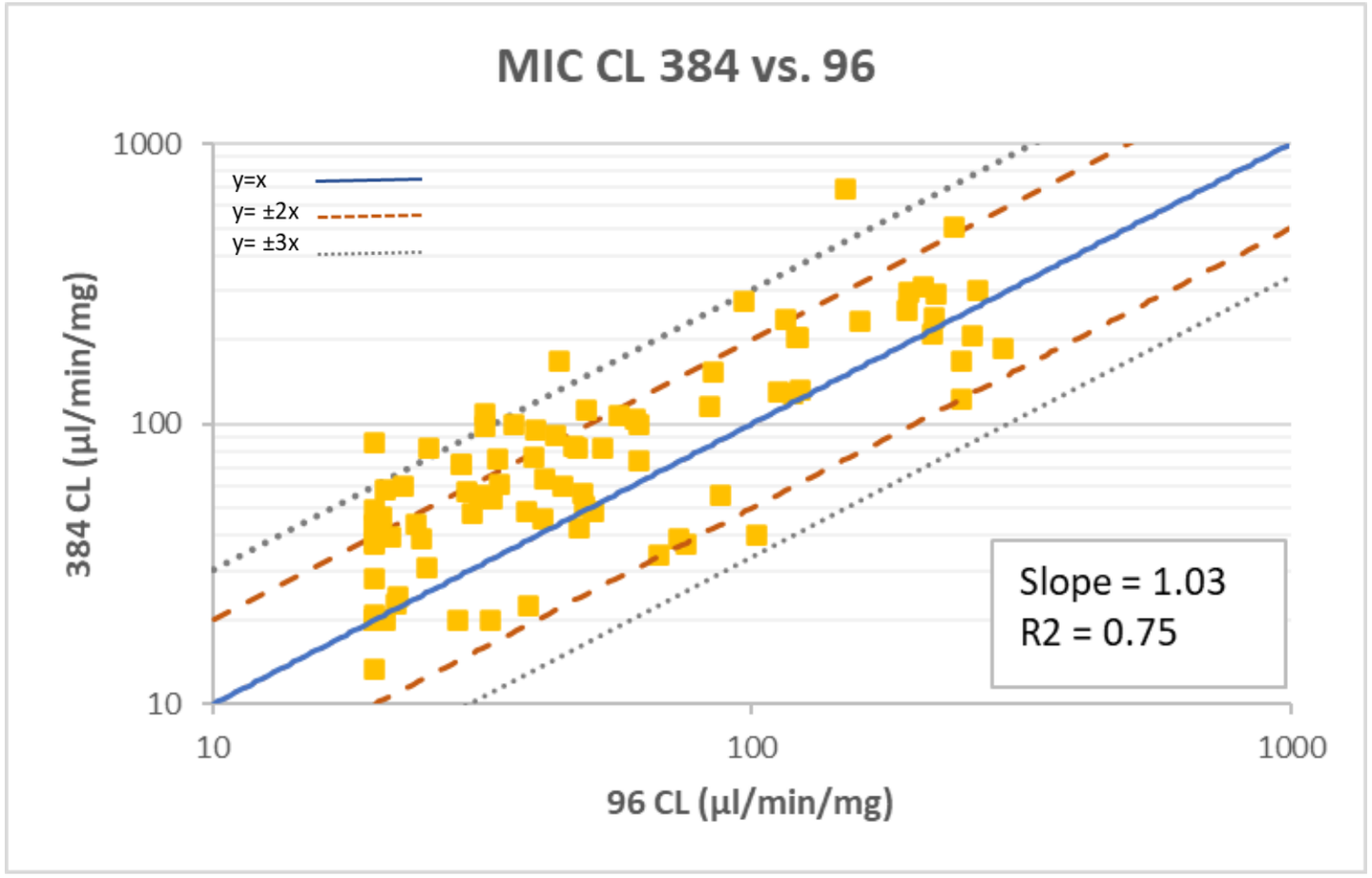
High correlation observed between QTRAP and QTOF results

384-Well vs. 96-Well Comparison - Heps



Good correlation observed between 384-well and 96-well format results.

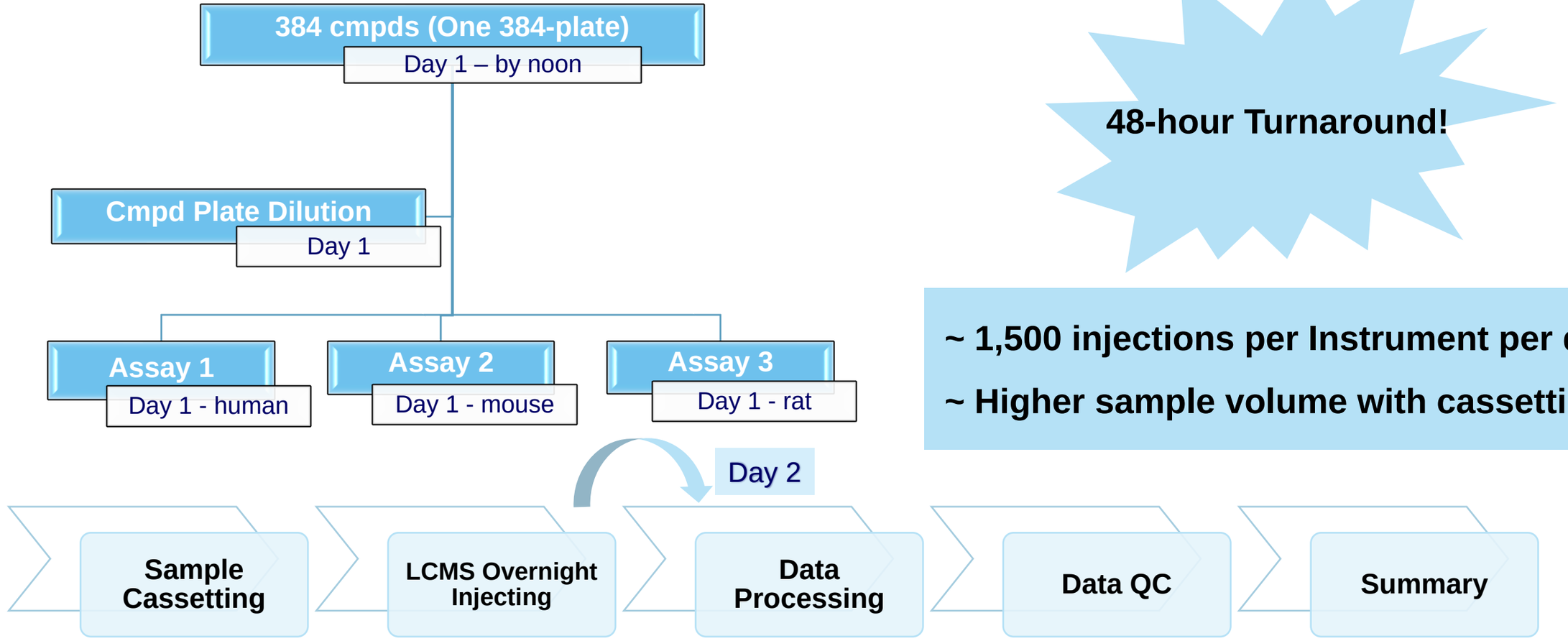
384-Well vs. 96-Well Comparison - MCL



Good correlation observed between 384-well and 96-well format results.

An example of typical workflow

One plate of 384 compounds



48-hour Turnaround!

~ 1,500 injections per Instrument per day!

~ Higher sample volume with cassetting!

Platform Overview – Assays in 384 Format

Liquid Handler

- **384-head Bravo x 4**
- **96-head Bravo x 4**
- 96-head Mini-Integra x3
- Others – Hamilton

MS Spec

- **Sciex ZenoTOF 7600 x 6**
- Others – Sciex Qtrap 5500, 6500, Waters TQ-XS, TQ Absolute XR

- Log D
- PPB *
- Blood to plasma ratio
- Microsomal Clearance
- Hepatocytes Clearance
- Permeability *
- CYP inhibition (HLM, IC50, IC50 Shift)
- CYP inhibition in Heps
- BSEP
- PXR
- AhR

Conclusions & Future Perspectives

- A **robust, automated high-throughput** ADME screening workflow using **384-well** plates on the **SCIEX 7600 ZenoTOF** was developed and designed to accelerate AI-driven drug discovery.
- This workflow enables **faster, smarter drug discovery**, bridging **high-throughput experimental ADME data** with **AI-driven predictive modeling** to improve more **cost-efficient** decision-making while maintaining the same **high data quality**.

- Cyprotex is committed to providing high quality and fast turn around time HT ADME assays:
  - We offer 48 hour turn around times so that decisions can continue quickly
  - Most other assays are available with 1 week turn around time
- Cyprotex is always working to develop novel assays and technologies to support drug development moving forward
- Cyprotex can work with you to establish assays according to your requirements

AI-Driven Drug Discovery with Cyprotex

Physicochemical Profiling
- Lipophilicity (CHI, log D shake flask)
- Solubility & chemical stability
- Plasma, blood, microsomal & tissue binding

Drug Metabolism
- CYP & non-CYP
- UGT
- Microsomal, hepatocyte, S9, plasma, blood and recombinant enzyme stability
- Reversible & time-dependent inhibition
- CYP induction
- Nuclear receptor activation
- Metabolite identification & profiling

Drug Permeability & Transporters
- PAMPA
- Caco-2 & MDCK-MDR1 permeability
- ABC & SLC transporter evaluation

Bioanalysis
- Small molecules and diverse modalities

Various *in vitro* toxicity assays

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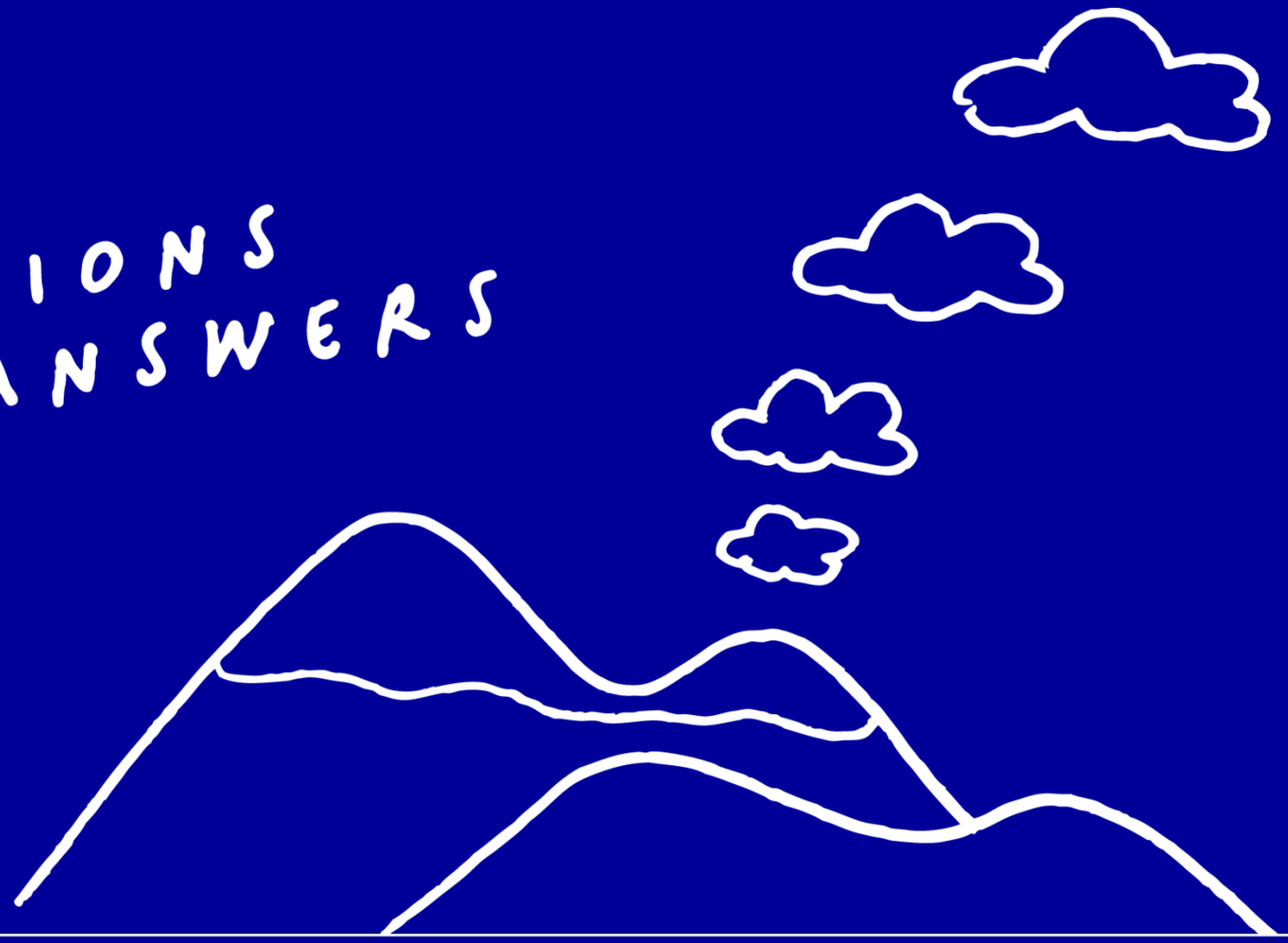
QUESTIONS AND ANSWERS