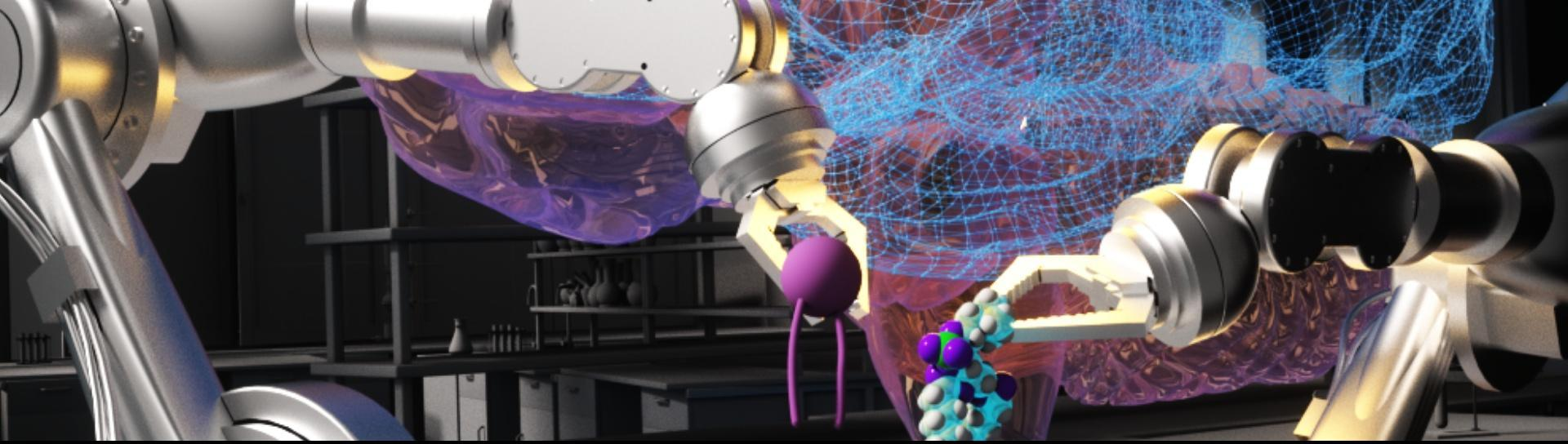

Data Driven Drug Formulation Development

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ALLEN LAB

UNIVERSITY OF TORONTO

Acceleration Consortium

the matter lab

Formulations are at the heart of every pharmaceutical product.

Pharmaceutical products are formulations of active ingredients and excipients (inactive ingredients).

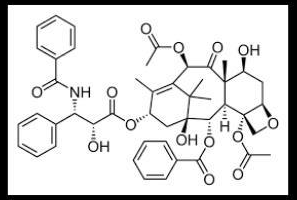
All active ingredients require formulation to ensure they are delivered in a safe and effective manner.

Some formulations are more complex (mRNA lipid nanoparticles) than others (saline solution).

From Molecules to Medicine

Formulations transform active ingredients into viable medicines:

- ensuring stability of the active ingredient
- enabling administration to patients
- increasing efficacy (by delivering therapeutic to its site of action)
- reducing or eliminating toxic side effects (by preventing distribution to non-target tissues)



Small molecule to tablet

mRNA to injectable dispersion

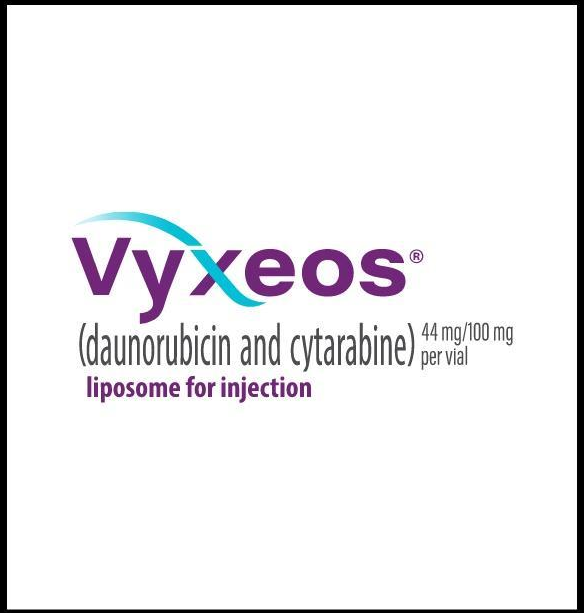
Formulation Science in Action

COVID-19 vaccine

1/ Lipid Nanoparticles

Protection of mRNA (efficacy)

Combination therapy for cancer



2/ Liposomes

Improved efficacy

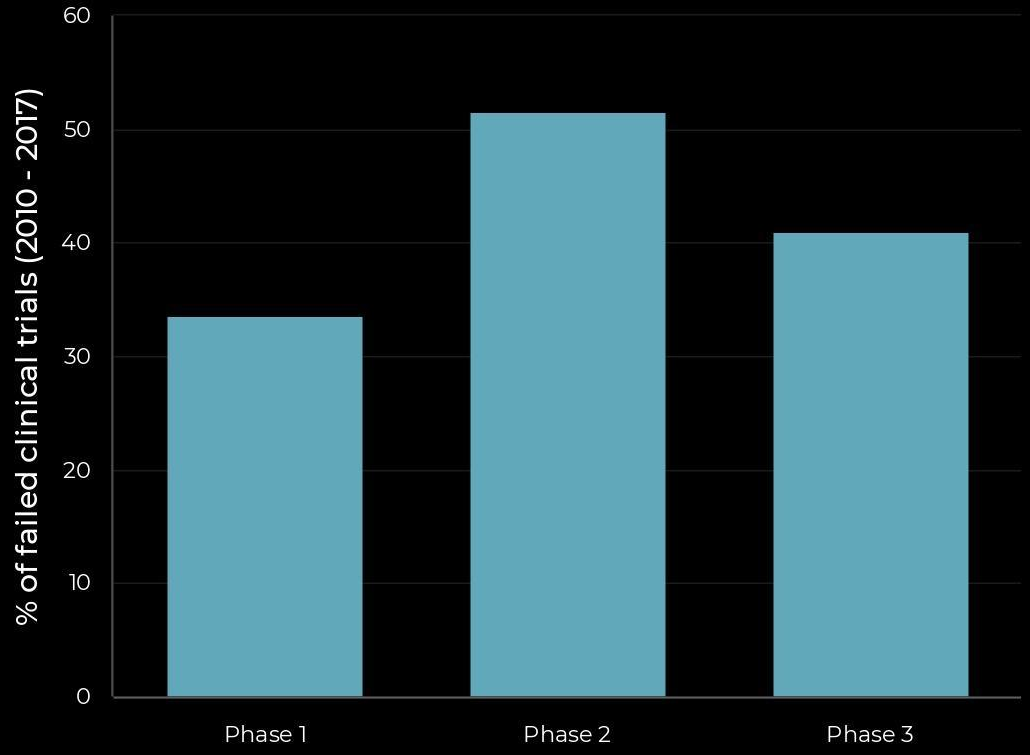
Molecular therapy for cancer

3/ Oral Tablets

Improved patient quality of life

Improved patient adherence

Why do drugs fail in the clinic?



Leading causes of clinical failures:

- lack of efficacy
- unacceptable toxicity

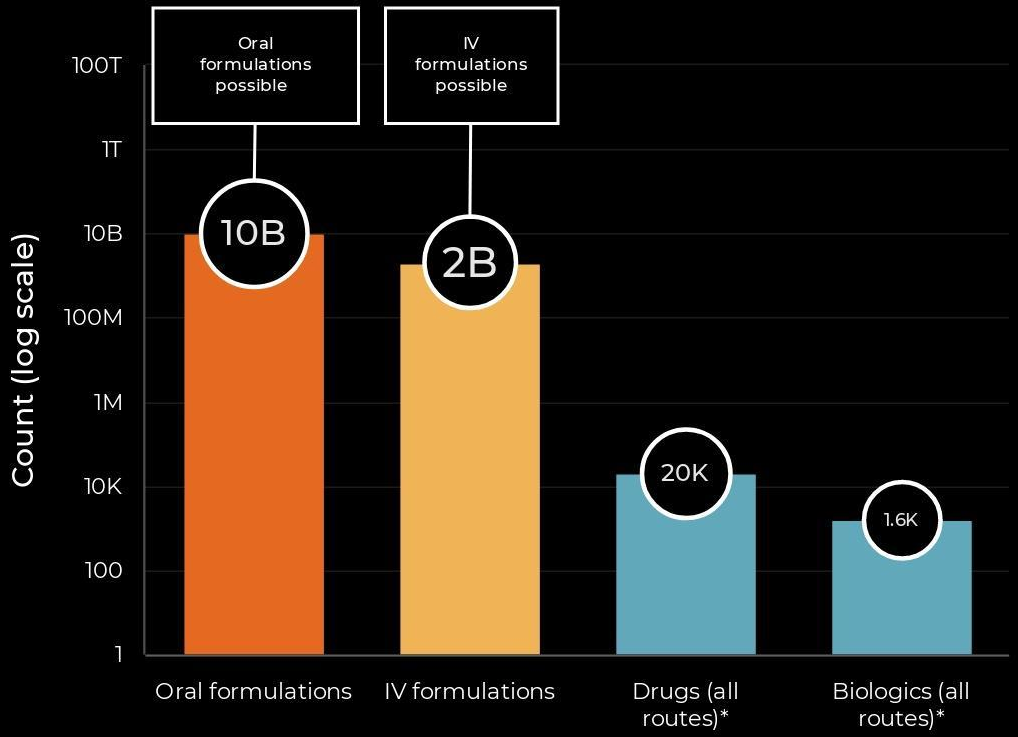
Optimized formulations address these issues

Figure adapted from Sun et al. Acta Pharma B, 12(7):3049-3062, 2022

Pharma companies are not moving the best formulations into the clinic.

Less than 0.01% of possible formulations have been explored

considering only **US FDA approved excipients**

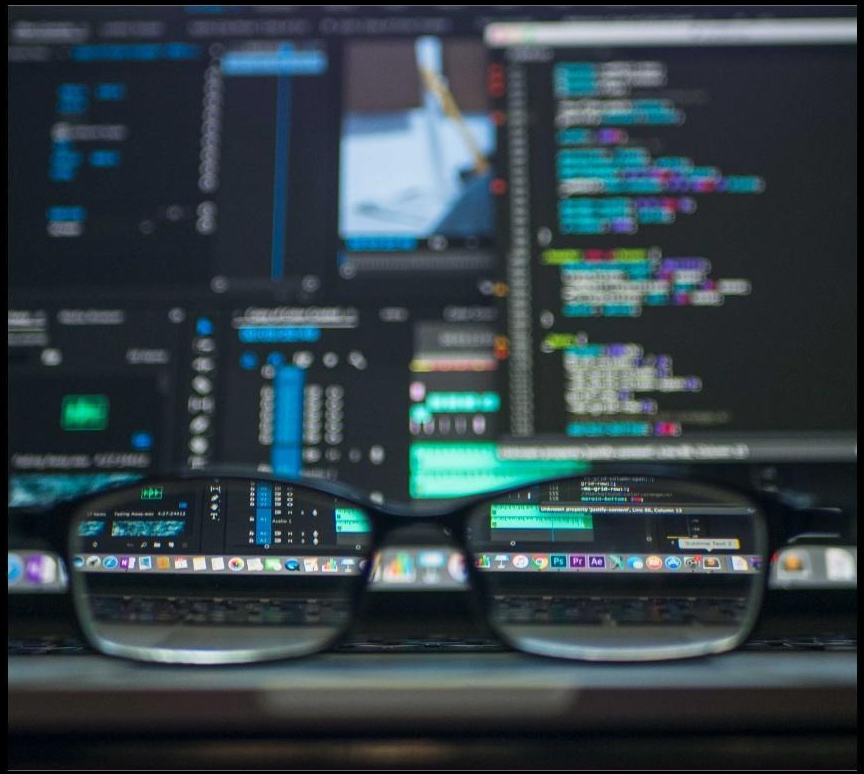


Leaving opportunity for innovation on the table

Unexplored formulations could transform the properties and performance of drugs.

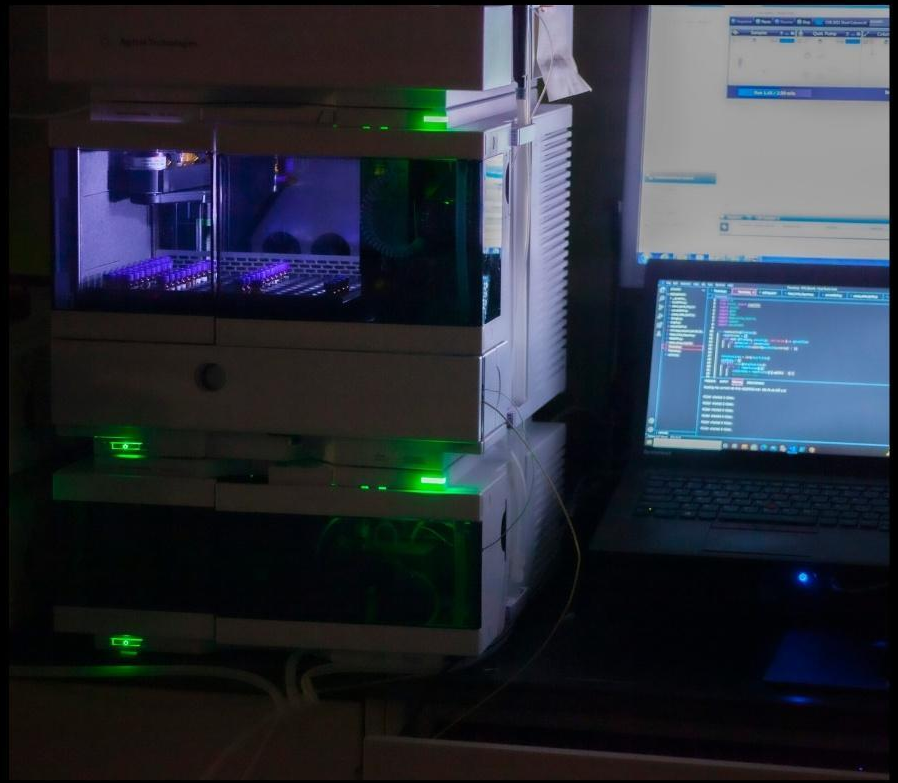
*FDA at a Glance, November 2021 (https://www.fda.gov/media/154548/download)

Re-imagining Formulation Development



- **Inverse design**
- *In silico* experimentation
- Self-driving laboratories

Inverse Design of Advanced Drug Delivery Systems (Poster 577)



nature communications

Article

https://doi.org/10.1038/s41467-022-35343-w

Machine learning models to accelerate the design of polymeric long-acting injectables

Received: 4 May 2022

Accepted: 28 November 2022

Pauric Bannigan[1], Zeqing Bao[1], Riley J. Hickman[2,3,4], Matteo Aldeghi[2,3,4], Florian Häse[2,3,4], Alán Aspuru-Guzik[2,3,4,5,6,7,8] & Christine Allen[1,8]

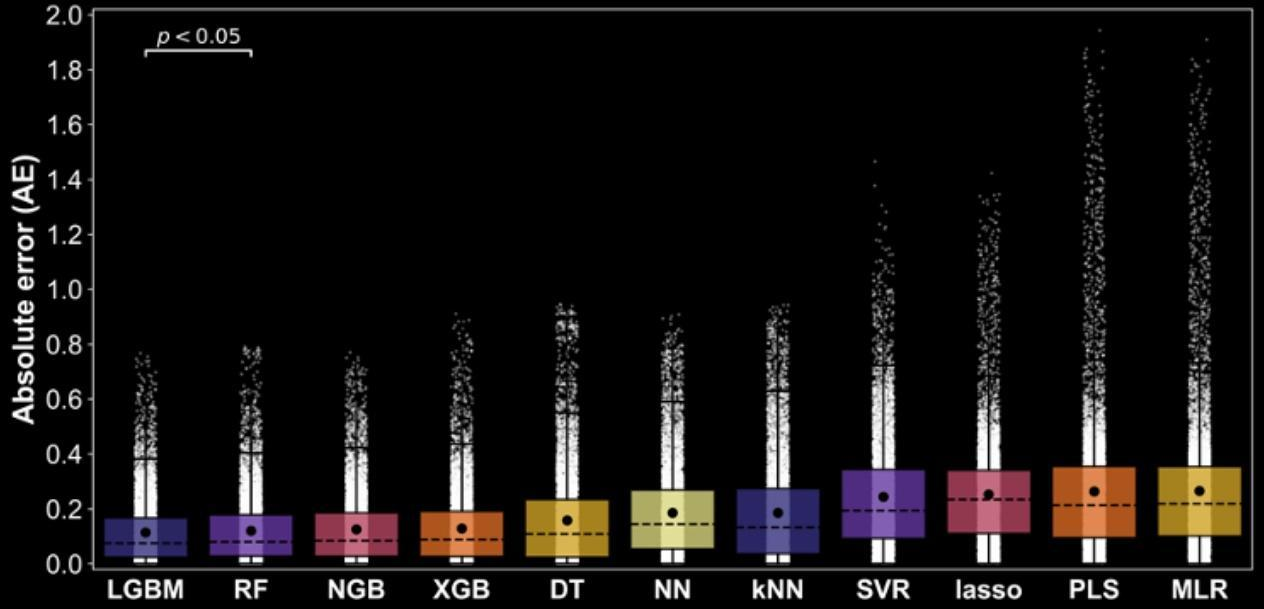
ALLEN LAB

Dataset

ALLEN LAB

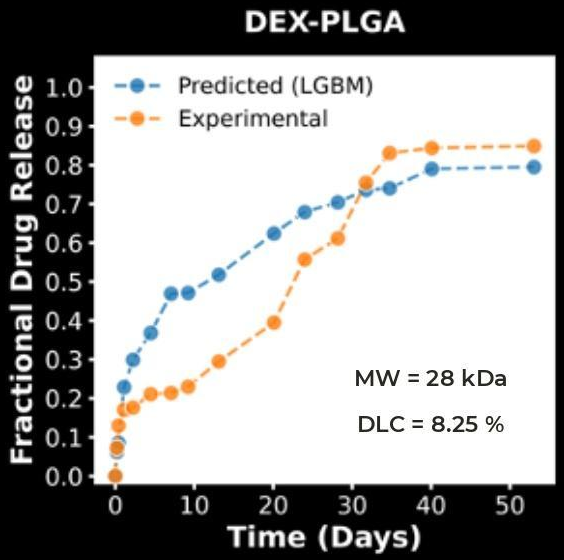
Code & Models

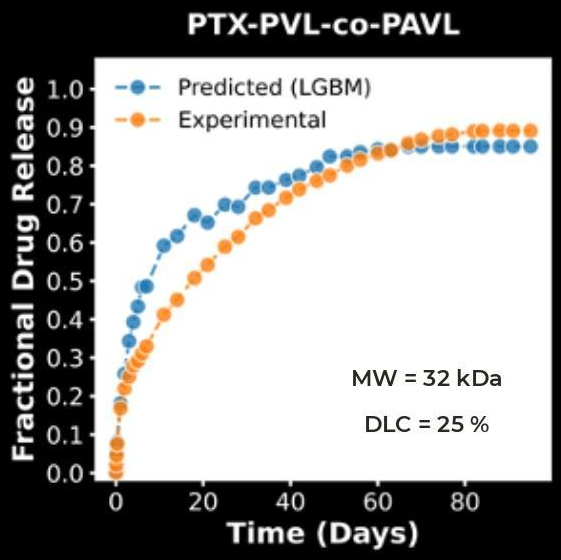
ML model screening and selection (few-shot)

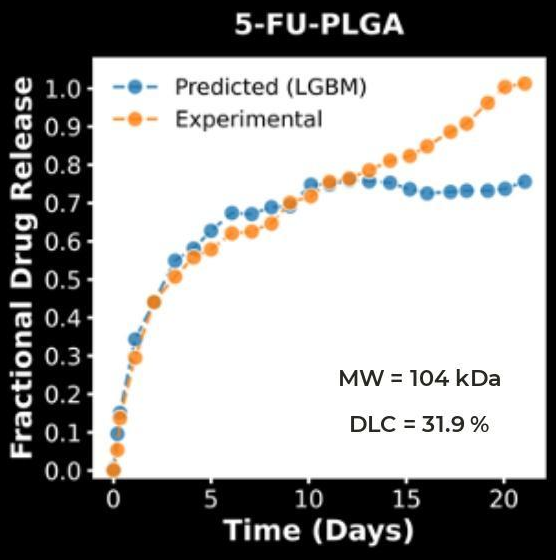


	LGBM	RF	NGB	XGB	DT	NN	kNN	SVR	lasso	PLS	MLR
Mean	0.114	0.120	0.125	0.129	0.158	0.185	0.186	0.244	0.252	0.263	0.265
Stdev	0.117	0.123	0.127	0.133	0.170	0.165	0.184	0.200	0.188	0.247	0.244
Median	0.075	0.080	0.084	0.088	0.109	0.145	0.133	0.194	0.234	0.213	0.218

Selected Model Predictions (LightGBM)







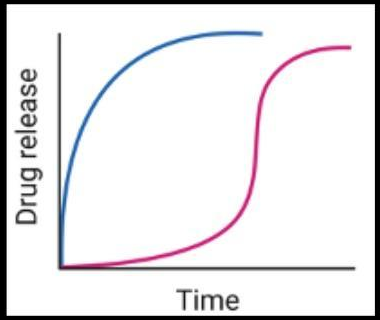
ML to accelerate the design of polymeric LAIs

LightGBM

(tree-based model)

SHAP Analysis

(powerful model interpretation tool)



"fast" release

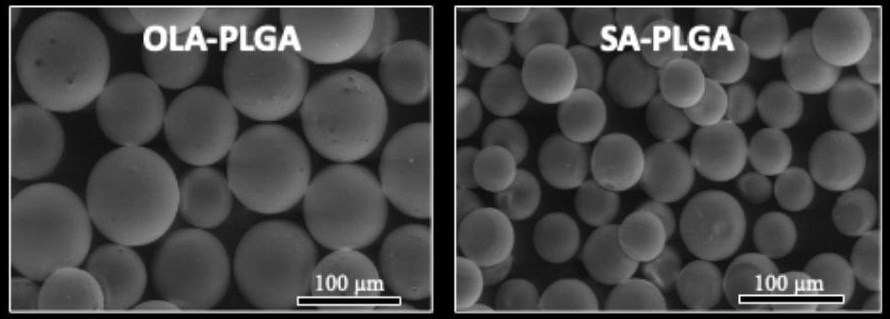
"slow" release

SHAP values are a measure of how each input feature contributes to the final prediction

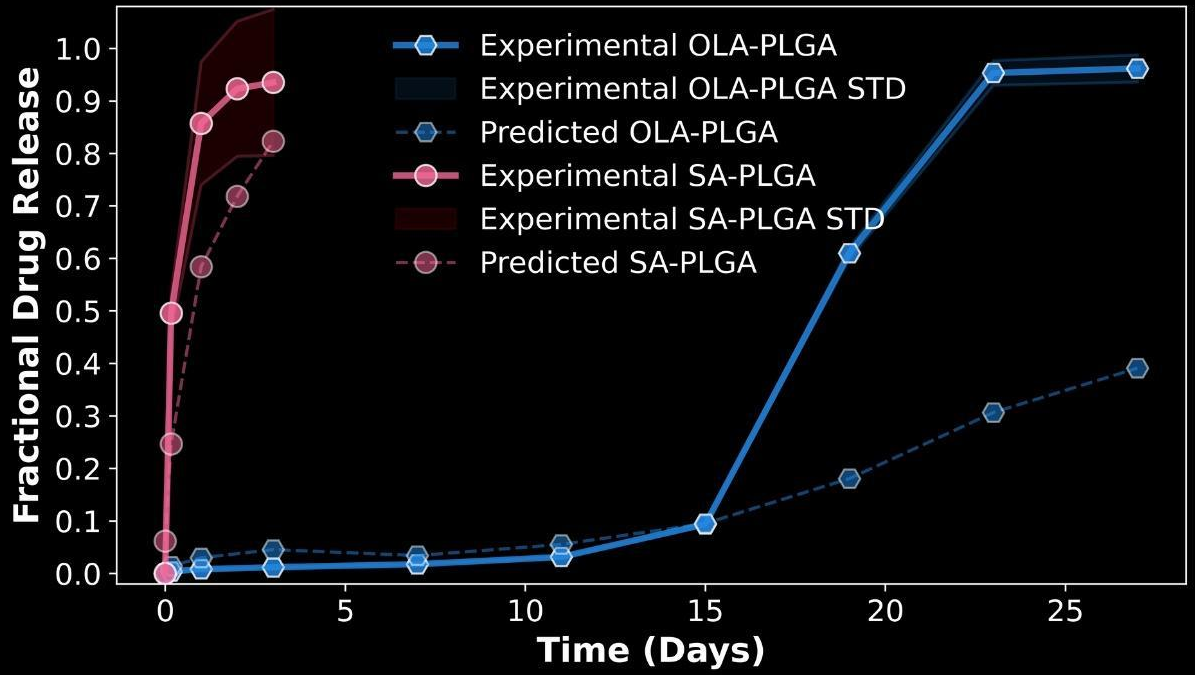
Design Criteria for PLGA systems

Likely outcome (SHAP analysis)	Drug_Mw	Polymer_MW	Drug_TPSA	SA-V (Size)	DLC	EE
Slow release	**Olaparib** (MW: 434 g/mol)	PLGA 50K Da (L/G: 50:50)	86 Å^2	*~ 75 (~ 80 µm)*	28.9%	72.2%
Fast release	**Salicylic acid** (MW: 138 g/mol)	PLGA 10K Da (L/G: 50:50)	58 Å^2	*~ 140 (~ 40 µm)*	1.6%	4.8%

SEM IMAGES

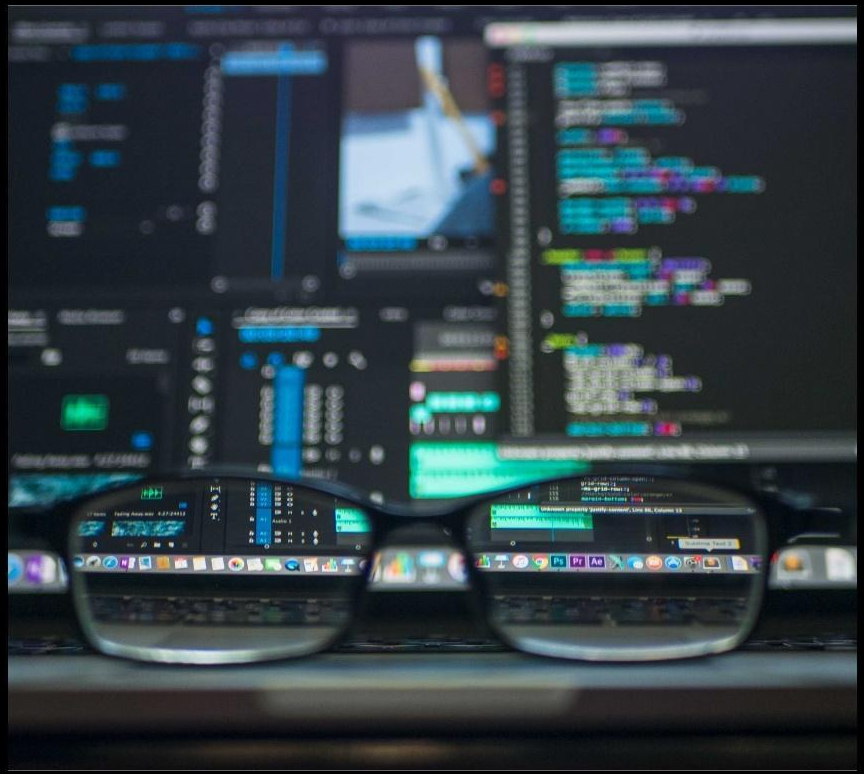


In vitro release (validation)



Highlights need for: more data on slow release PLGA-based formulations and/or integration of information on time dependent hydrolysis of PLGA into model.

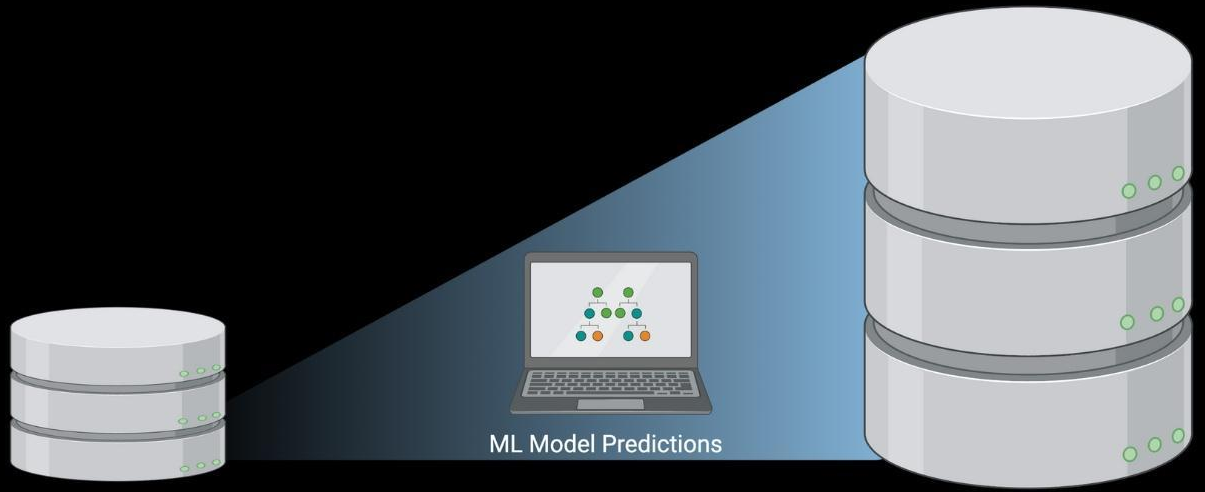
Re-imagining Formulation Development



- Inverse design
- ***In silico* experimentation**
- Self-driving laboratories

Machine learning to extrapolate (Poster 604)

In silico experimentation

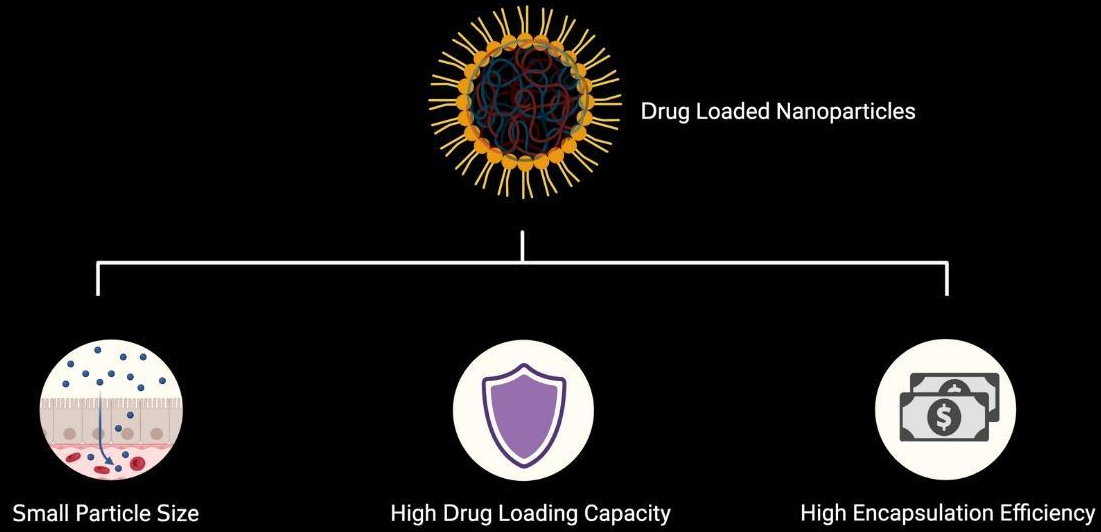


128 Formulations

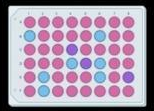
1215 Formulations
= 3 Lipids *
9 Initial drug-to-lipid ratios *
9 Liquid lipid contents *
5 Surfactant concentrations

Proof of Concept Study:

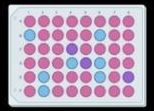
Design NPs to improve the apparent aqueous solubility of a hydrophobic drug



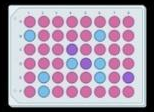
Expedited Data Generation (1 week)



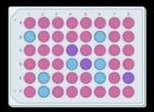
Experiments 1 - 32 (n=3)



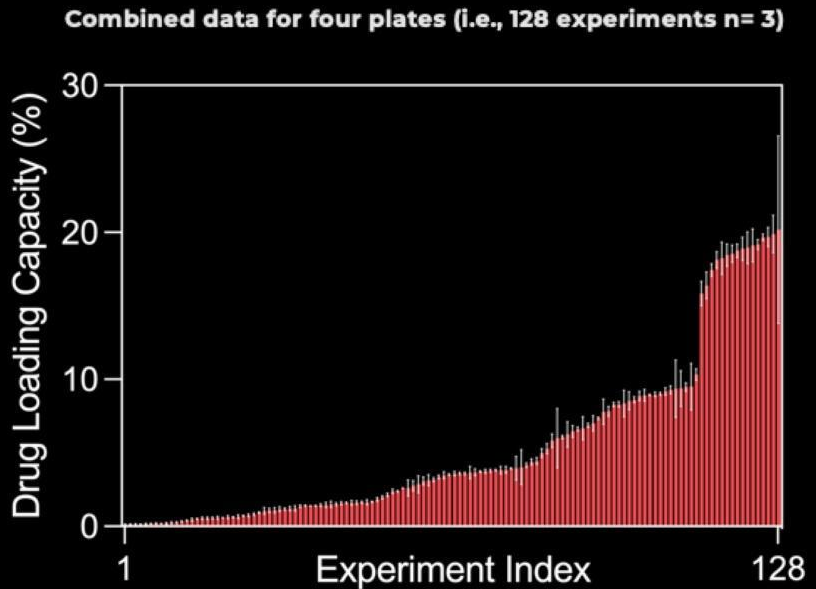
Experiments 33 - 64 (n=3)



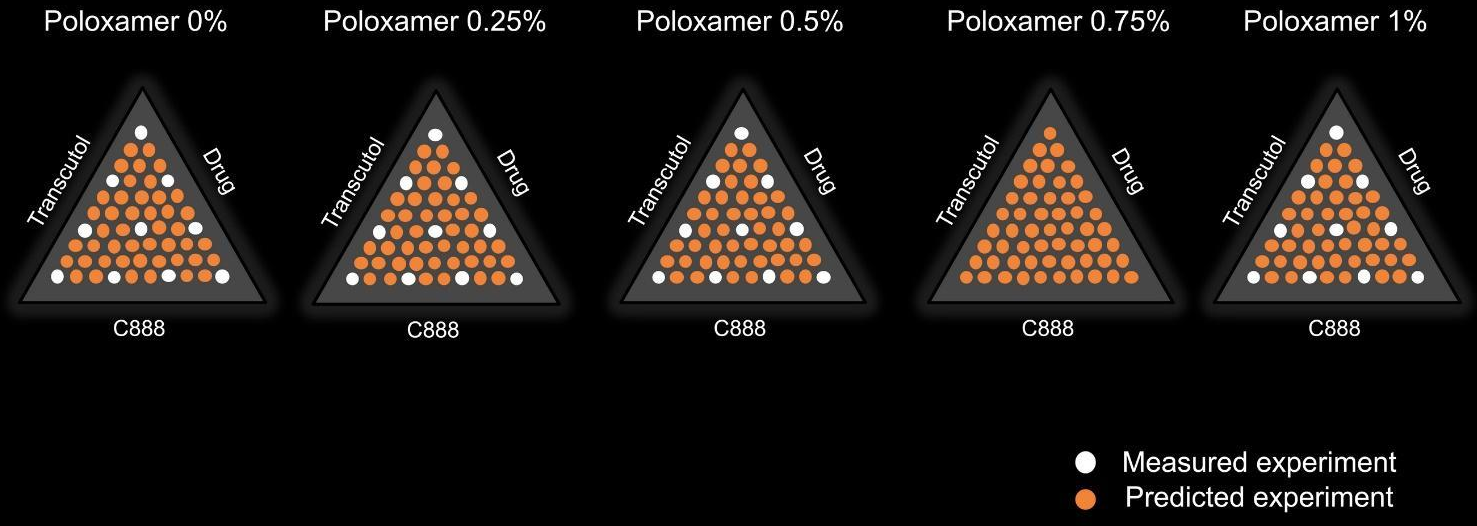
Experiments 65 - 96 (n=3)



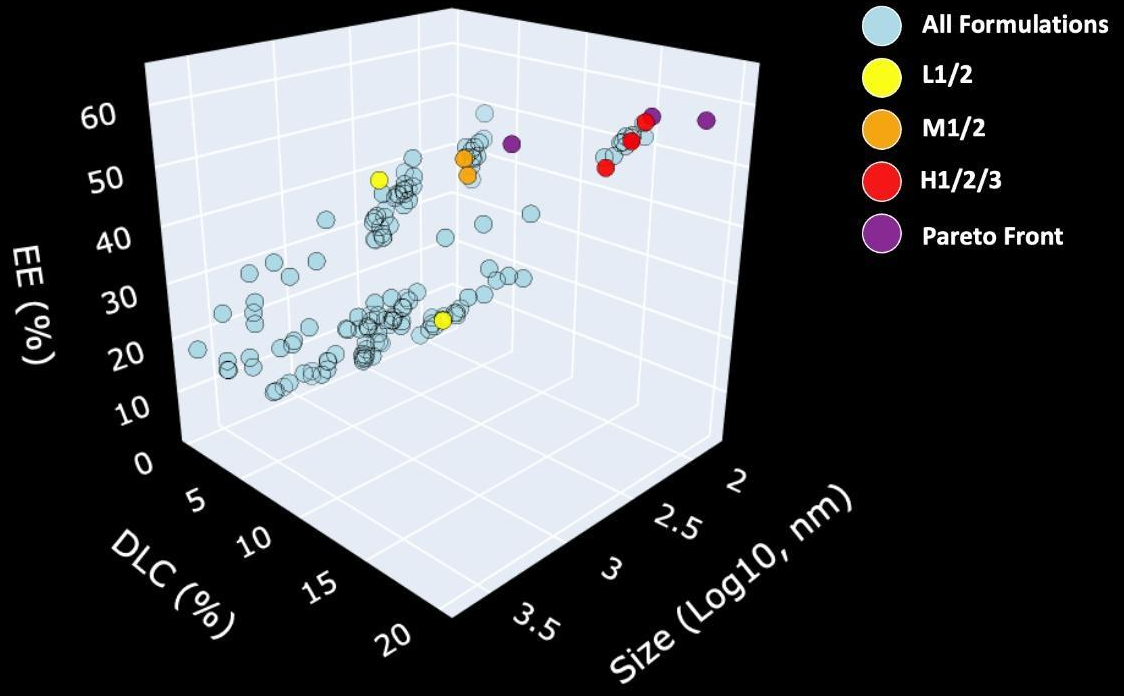
Experiments 97 - 128 (n=3)



Design Space Exploration



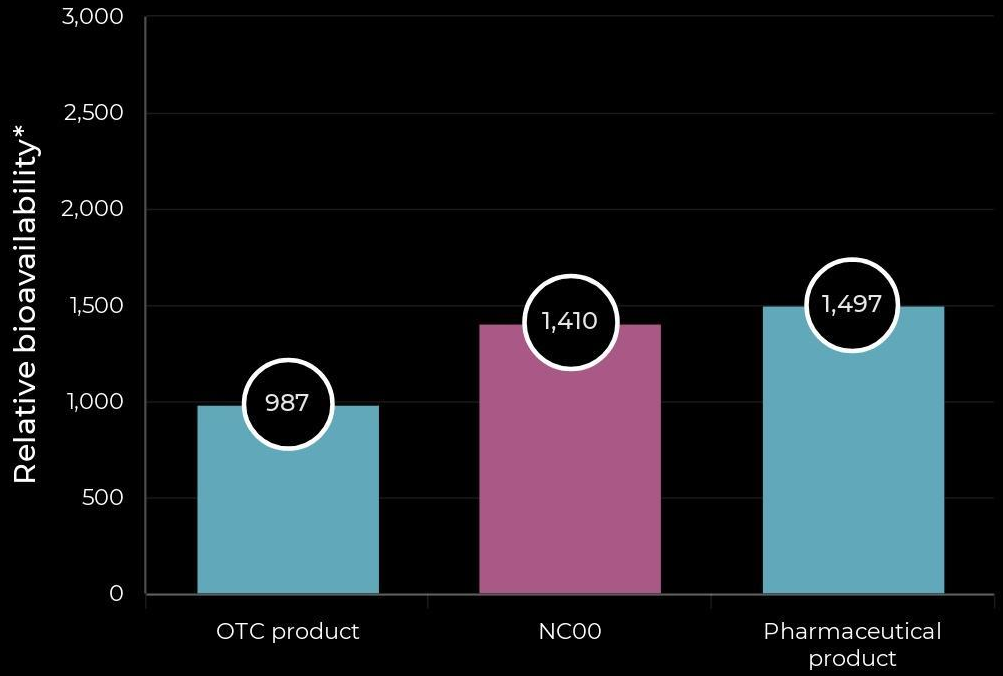
Pareto Front



Evaluation of Pharmacokinetics

Lead canidate formulation(s)

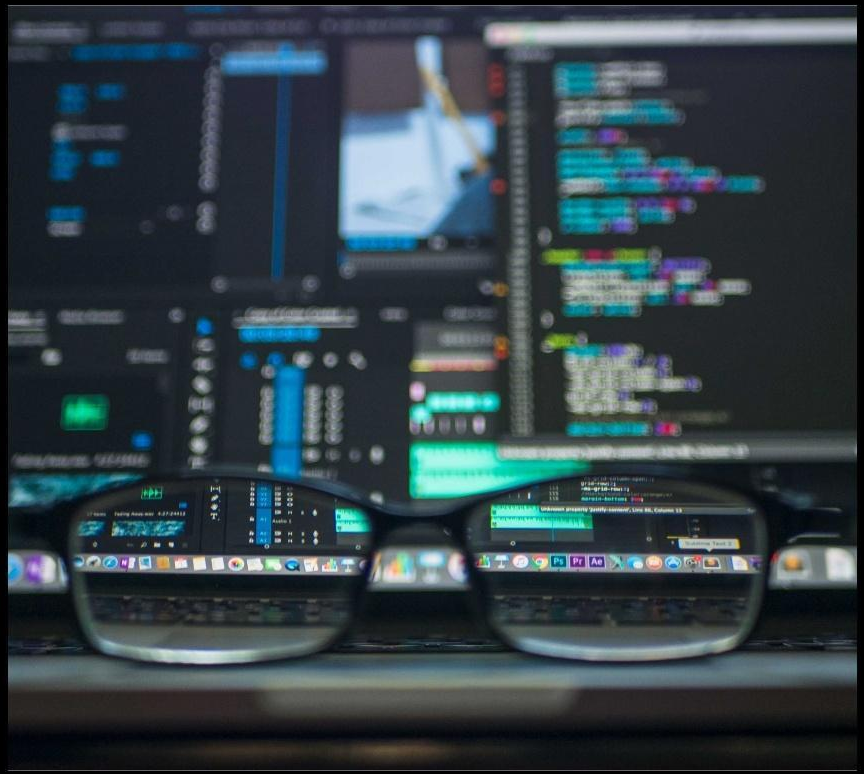
- Nanosuspensions (SLN or NLC) were administered via oral gavage to Sprague Dawley rats (20 mg/kg).
- Pharmaceutical product is equivalent in composition to Epidiolex.
- OTC product is equivalent to the majority of over-the-counter CBD products.
- PK profiles of these commercial formulations were previously published by our group.[1]



AUC (0-4 h) (ng.h/mL)

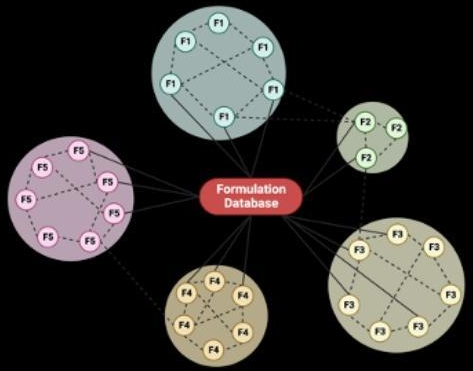
1. Kok et al.,European Journal of Pharmaceutical Sciences, 2022 (168).

Re-imagining Formulation Development

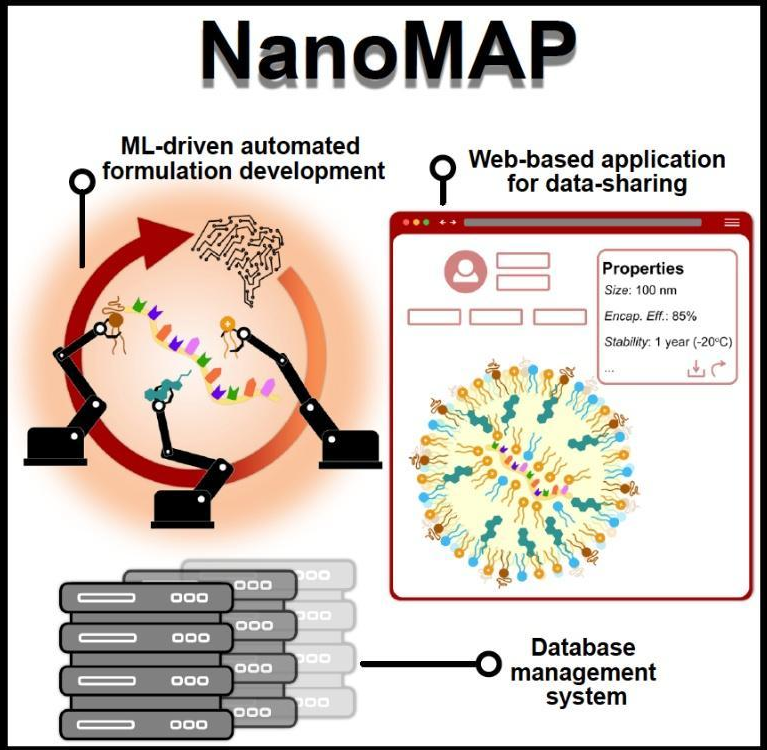


- Inverse design
- *In silico* experimentation
- **Self-driving laboratories**

Next Steps - closing the loop



Database construction



AUTONOMOUS LAB WILL IMPROVE DRUG FORMULATION DEVELOPMENT

By: Eileen Hoftyzer

Home – News – Autonomous lab will improve drug formulation development

JULY 12, 2023

From left: Phd trainee Zeqing Bao, Allen Lab Director of Research and Partnerships Pauric Bannigan, and Professor Christine Allen

Self-driving lab at Leslie Dan Faculty of Pharmacy is one of six at U of T being funded through $200-million grant to Acceleration Consortium

A new autonomous lab that uses machine learning is being built in the Leslie Dan Faculty of Pharmacy and will help to design and optimize formulations that will improve bioavailability, stability and efficacy of a variety of drugs. Christine Allen, professor at the Leslie Dan Faculty of Pharmacy, is co-leading the lab with engineering professor **Frank Gu**.

> "The world is finally understanding the impact of formulation technology and how powerful it is. Now we can marry that technology with AI and machine learning, so we're kind of unstoppable."

"U of T's Acceleration Consortium receives $200-million grant to support 'self-driving labs' research"

https://acceleration.utoronto.ca

acceleration@utoronto.ca

Prof. Alan Aspuru-Guzik, Thursday @ 9 am

UNIVERSITY OF TORONTO | Acceleration Consortium

Allen Lab


Pauric


Leila


Delaram


Lucy


Max

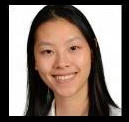

Zeqing


Jack


Xuehan


Jonathan


Linyu


Fion

UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY

ALLEN LAB

Our Collaborators

the matter lab

Alán

Matteo

Riley

Florian

Ella


Thoughts? **Questions?**
Open the floor to feedback and discussion.