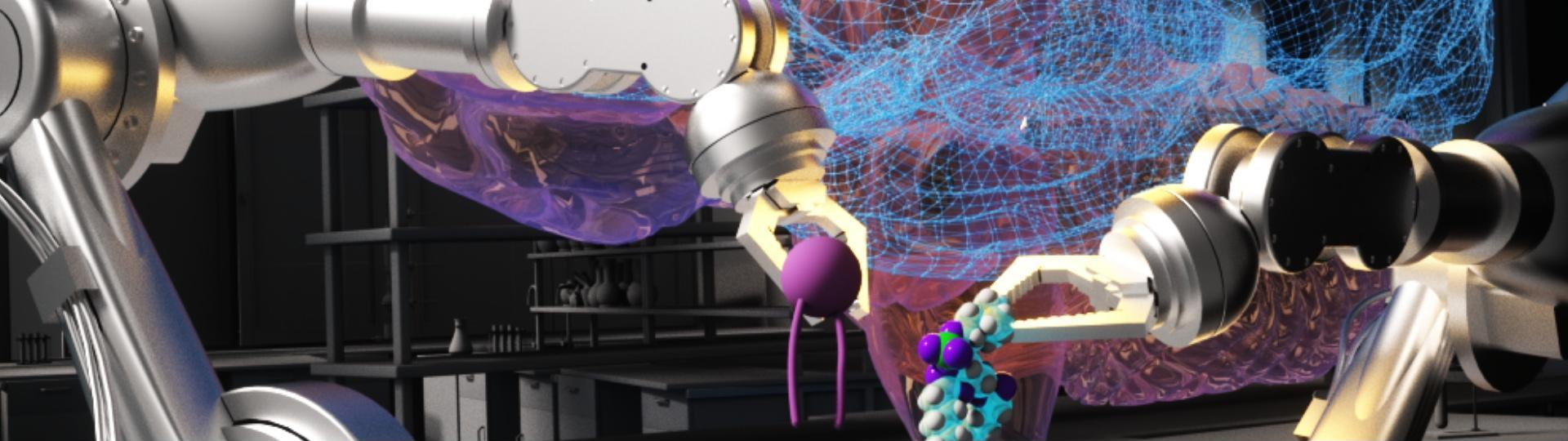




Towards the development of a self-driving laboratory for nanomedicines

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Formulations are at the heart of every pharmaceutical product.



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

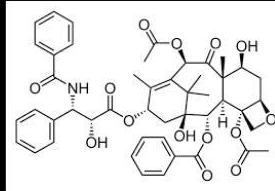
All active ingredients require formulation to ensure they are delivered in a safe and effective manner.

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

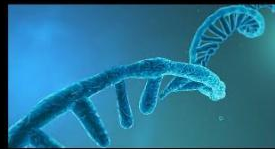
From Molecules to Medicine

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

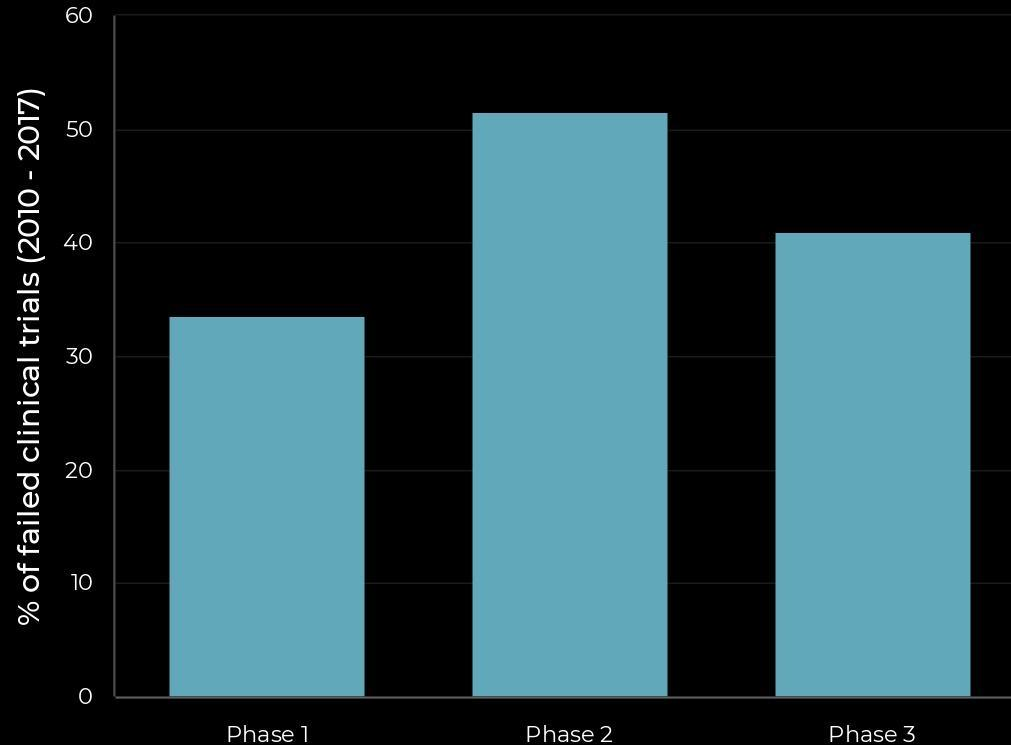


3/ Oral Tablets

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
-

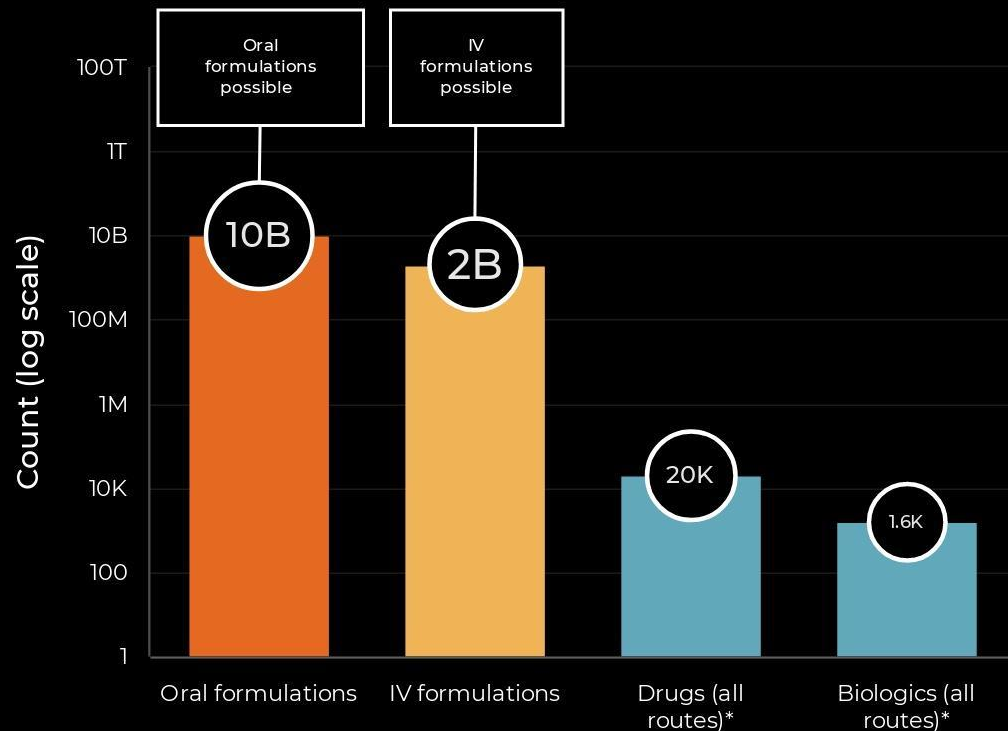
Optimized formulations address these issues



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.

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

Pauric Bannigan¹, Zeqing Bao¹, 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} ✉

Accepted: 28 November 2022

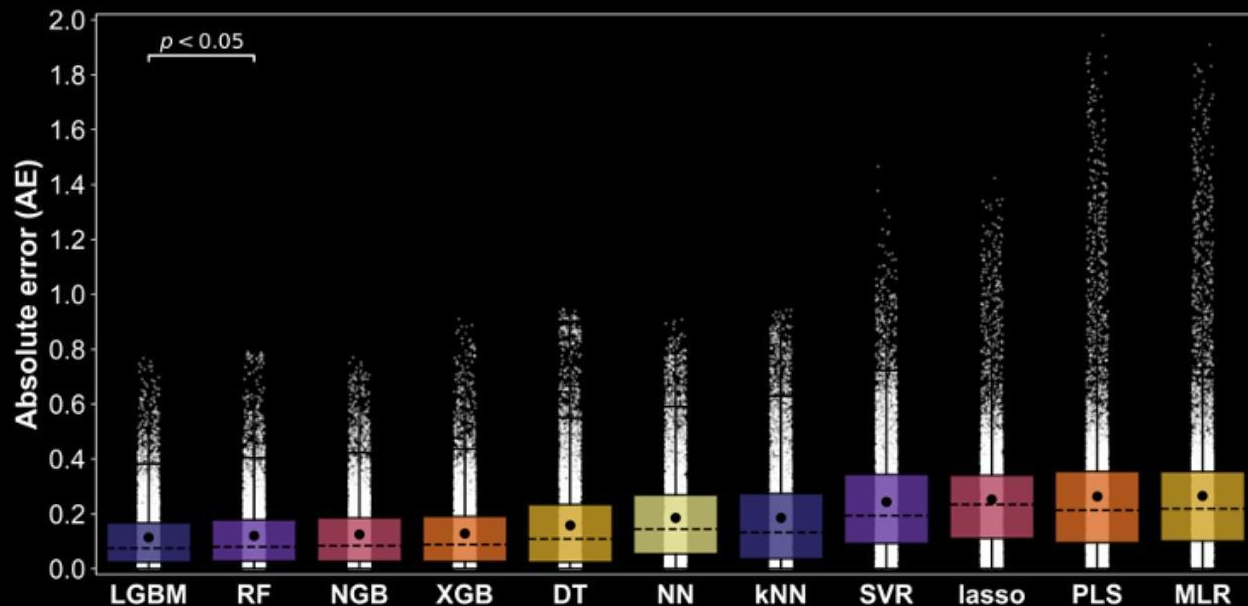


Dataset



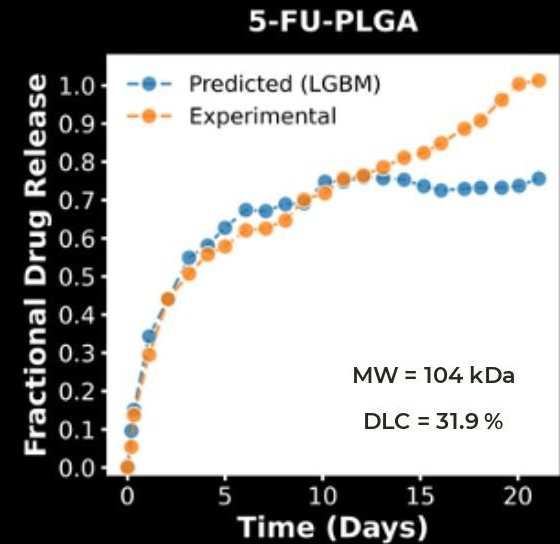
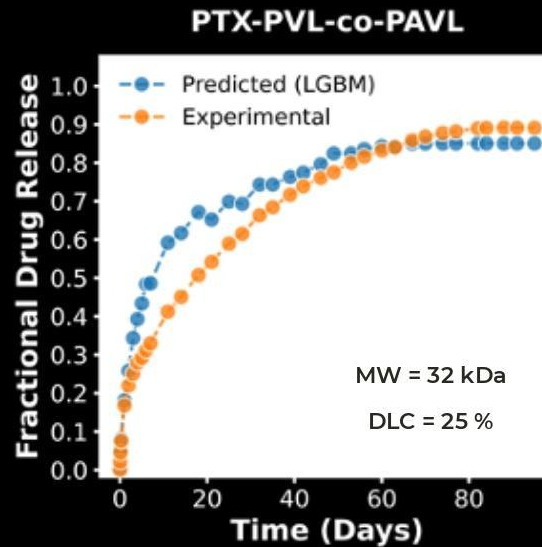
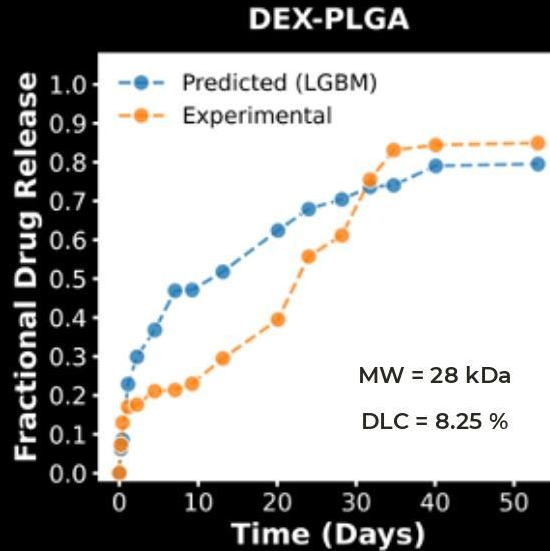
Code & Models

ML model screening and selection (few-shot)



	<u>LGBM</u>	<u>RF</u>	<u>NGB</u>	<u>XGB</u>	<u>DT</u>	<u>NN</u>	<u>kNN</u>	<u>SVR</u>	<u>lasso</u>	<u>PLS</u>	<u>MLR</u>
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)



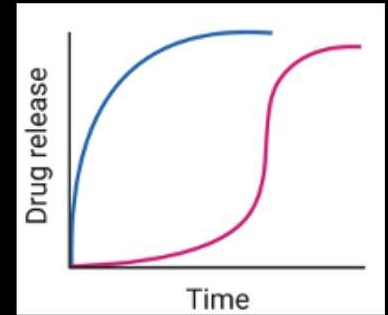
ML to accelerate the design of polymeric LAIs



LightGBM
(tree-based model)



SHAP Analysis
(powerful model
interpretation tool)



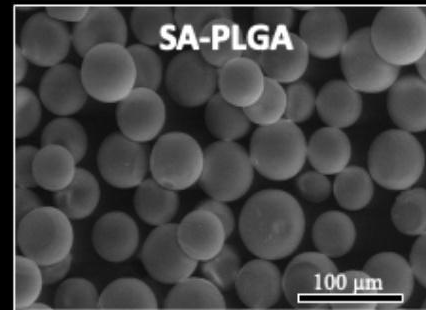
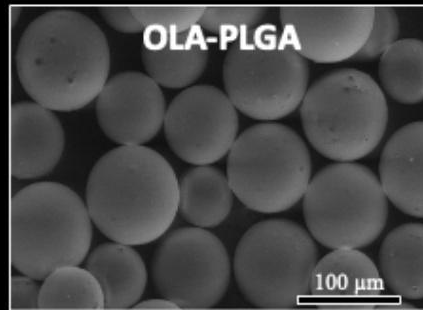
"fast" release
"slow" release

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

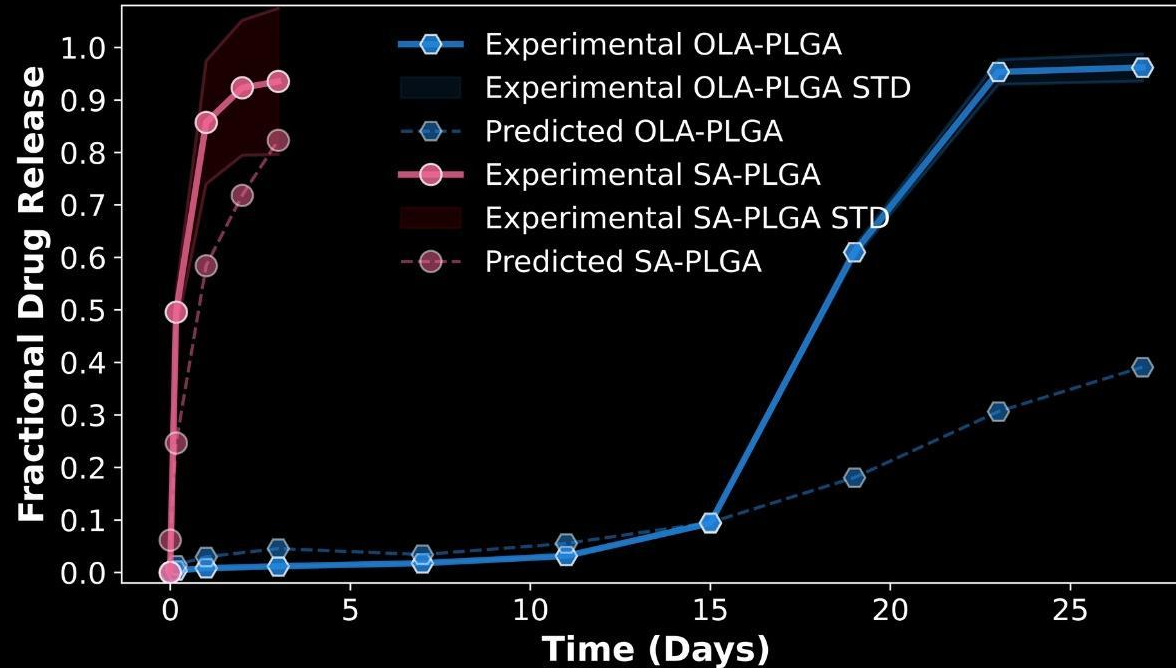
Design Criteria for PLGA systems

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.

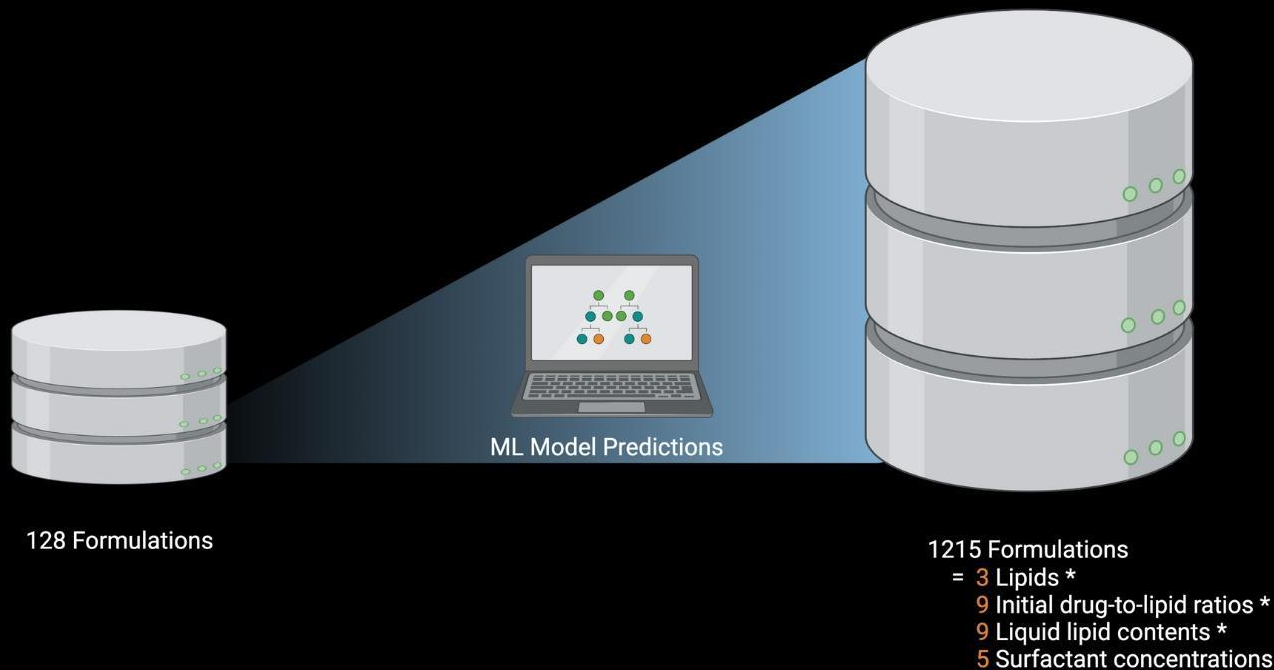
Re-imagining Formulation Development



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

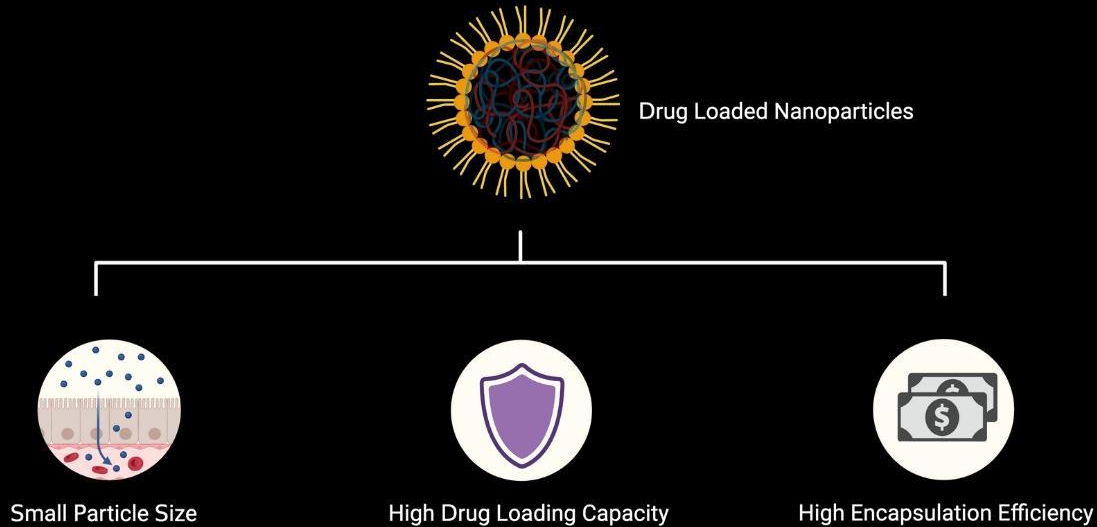
Machine learning to extrapolate (Poster 604)

In silico experimentation

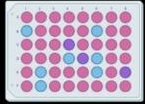


Proof of Concept Study:

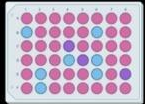
Design NPs to improve the apparent aqueous solubility of a hydrophobic drug



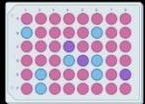
Expedited Data Generation (1 week)



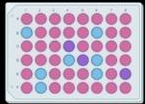
Experiments 1 - 32 (n=3)



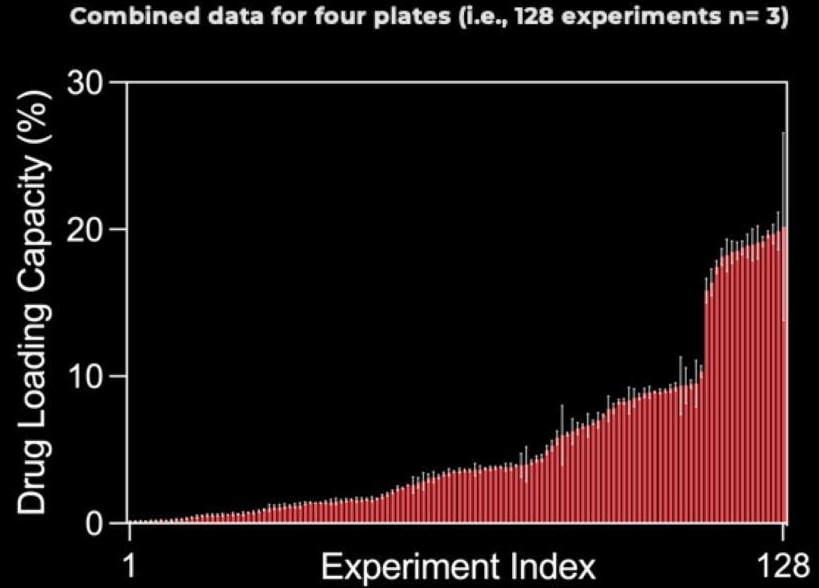
Experiments 33 - 64 (n=3)



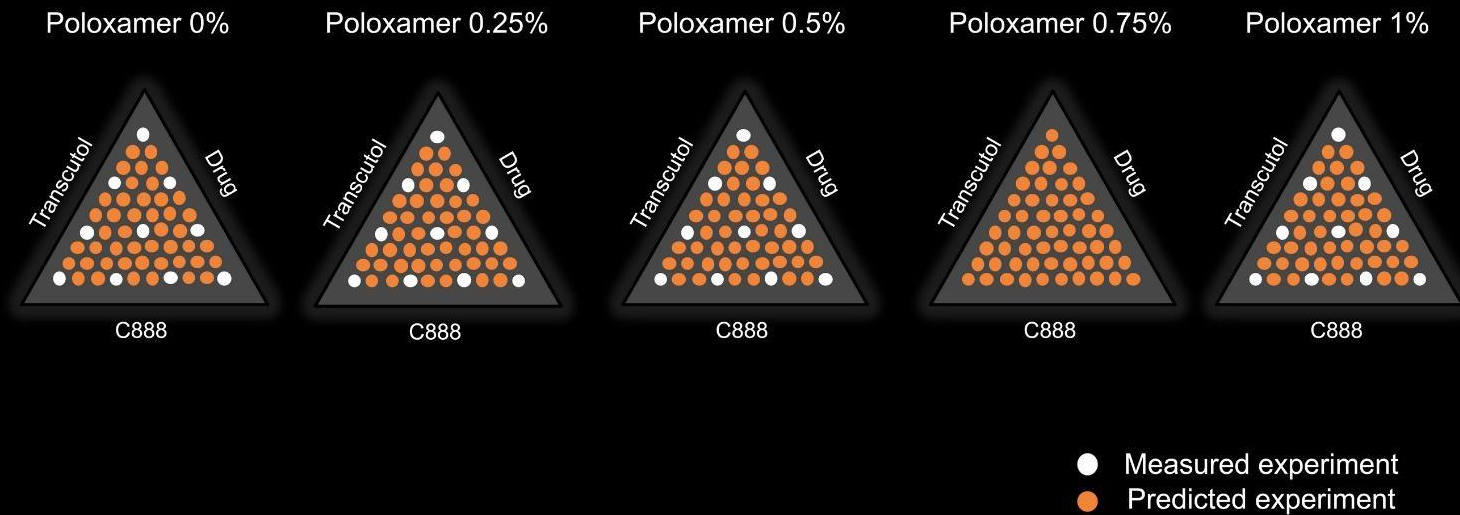
Experiments 65 - 96 (n=3)



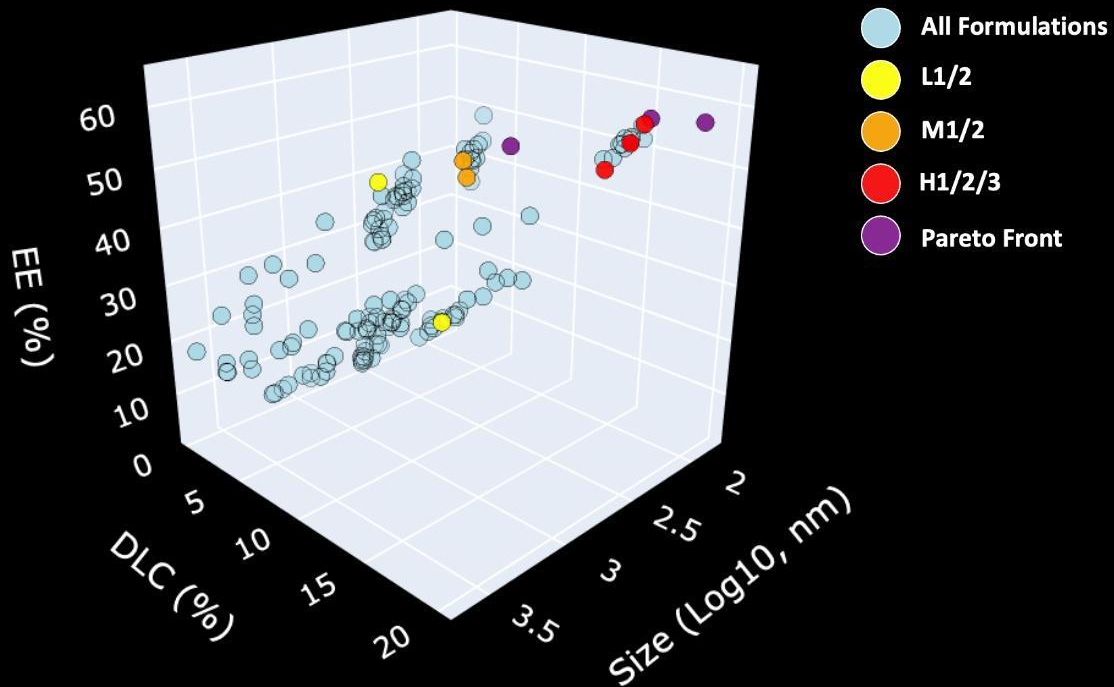
Experiments 97 - 128 (n=3)



Design Space Exploration



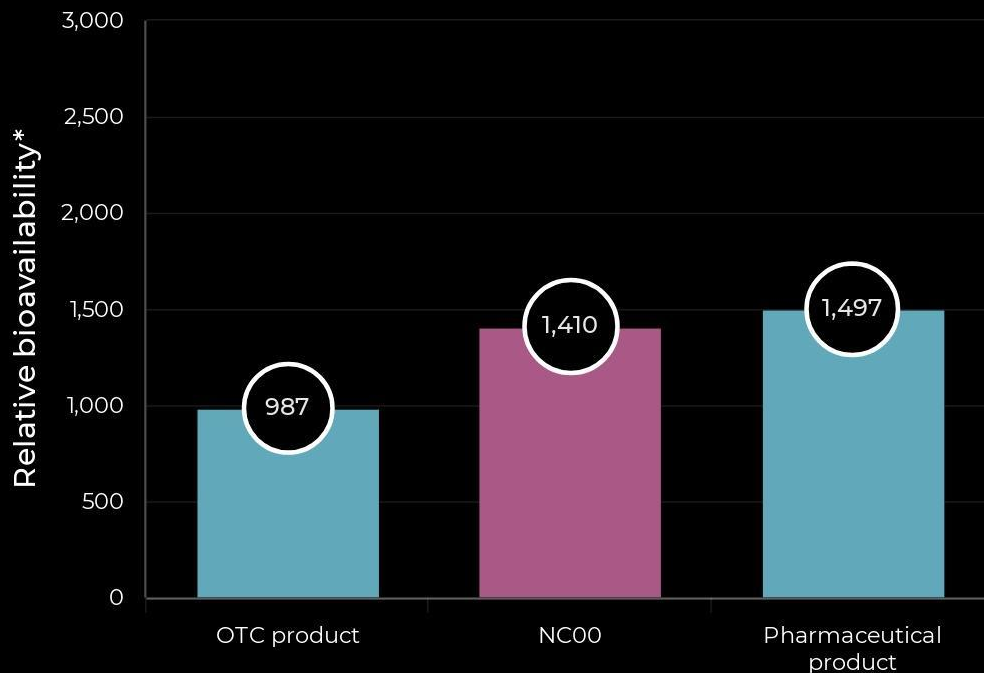
Pareto Front



Evaluation of Pharmacokinetics

Lead candidate 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)

Re-imagining Formulation Development



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

Next Steps - closing the loop

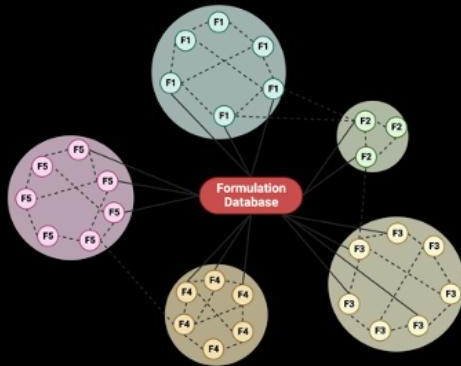
Matter

CellPress

Perspective

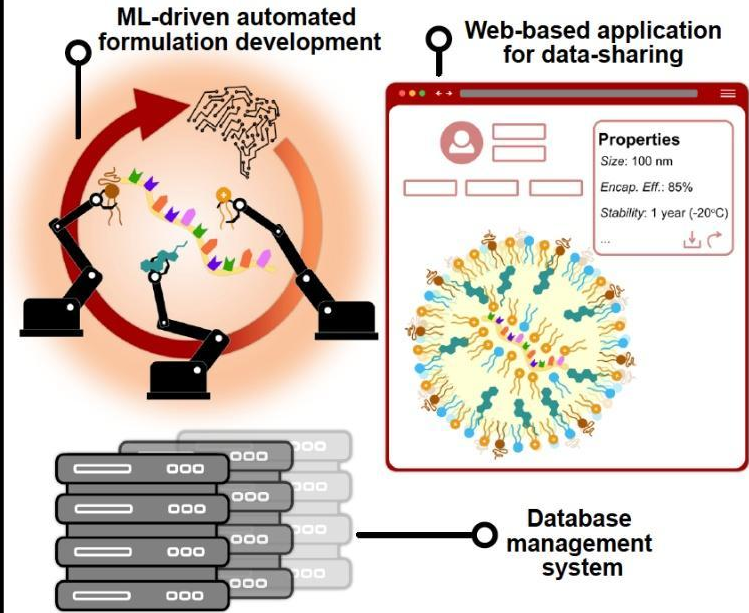
Self-driving laboratories: A paradigm shift in nanomedicine development

Riley J. Hickman,^{1,2,3,9} Pauric Bannigan,^{4,9} Zeqing Bao,⁴ Alán Aspuru-Guzik,^{1,2,3,5,6,7,8} and Christine Allen^{4,*}



Database construction

NanoMAP



AUTONOMOUS LAB WILL IMPROVE DRUG FORMULATION DEVELOPMENT

By: Eileen Hoftzyer

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



Allen Lab



Pauric



Leila



Delaram



Lucy



Max



Zeqing



Jack



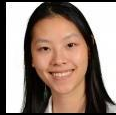
Xuehan



Jonathan



Linyu



Fion



UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY



Matter Lab

Our Collaborators



Alán



Matteo



Riley

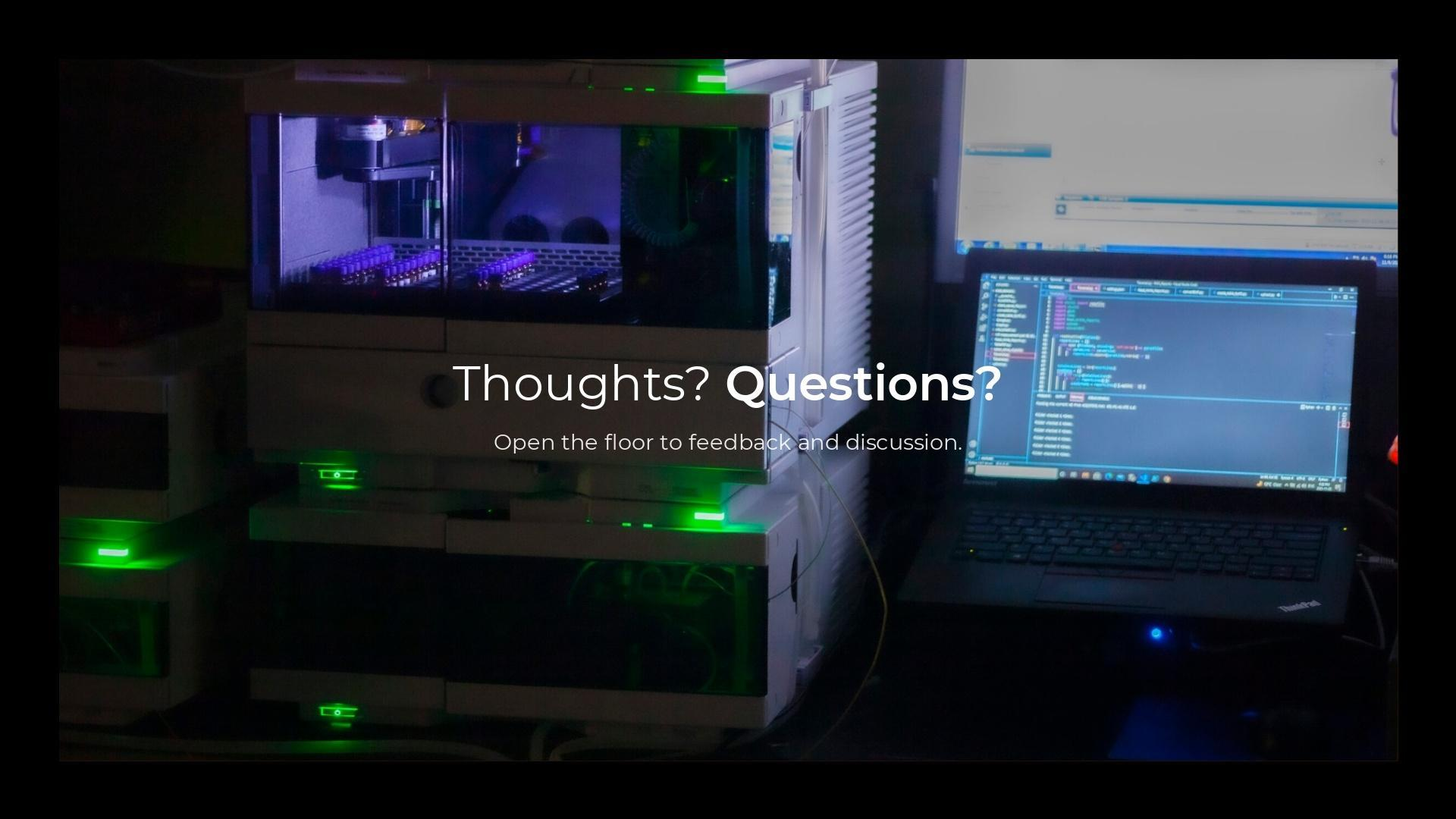


Florian



Ella





Thoughts? Questions?

Open the floor to feedback and discussion.