Improving the effectiveness of compound design

Lessons learned from a data driven predictive platform at UCB

Marie Ledecq – UCB Biopharma

Leuven 25/10/2022

Advanced machine learning for innovative drug discovery - 3rd School

Inspired by **patients.**
Driven by **science.**

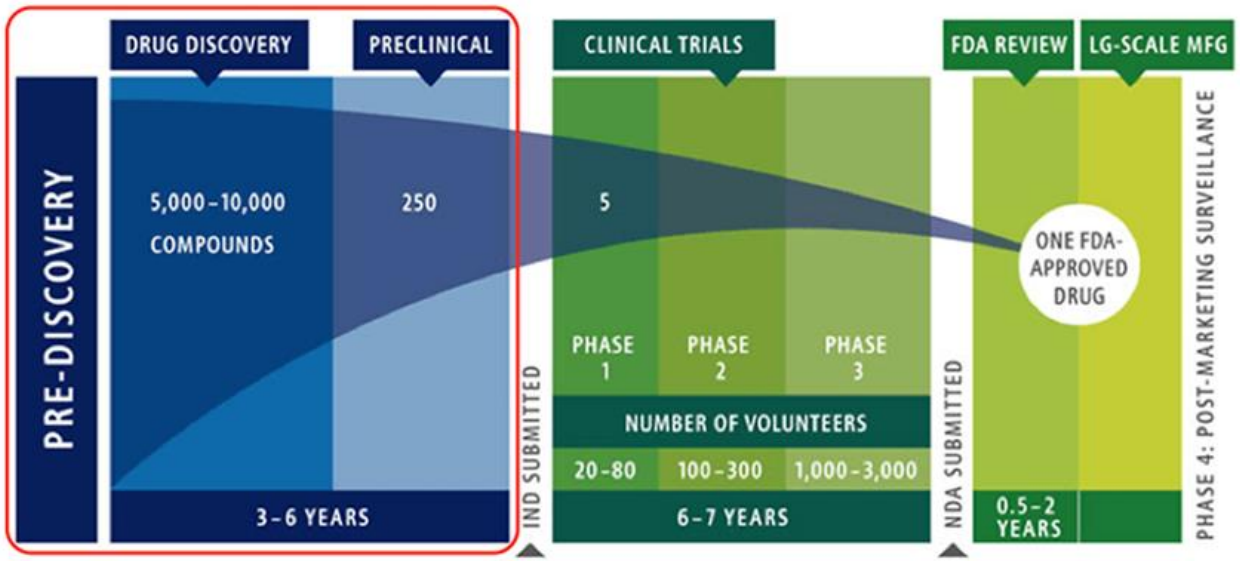
Agenda

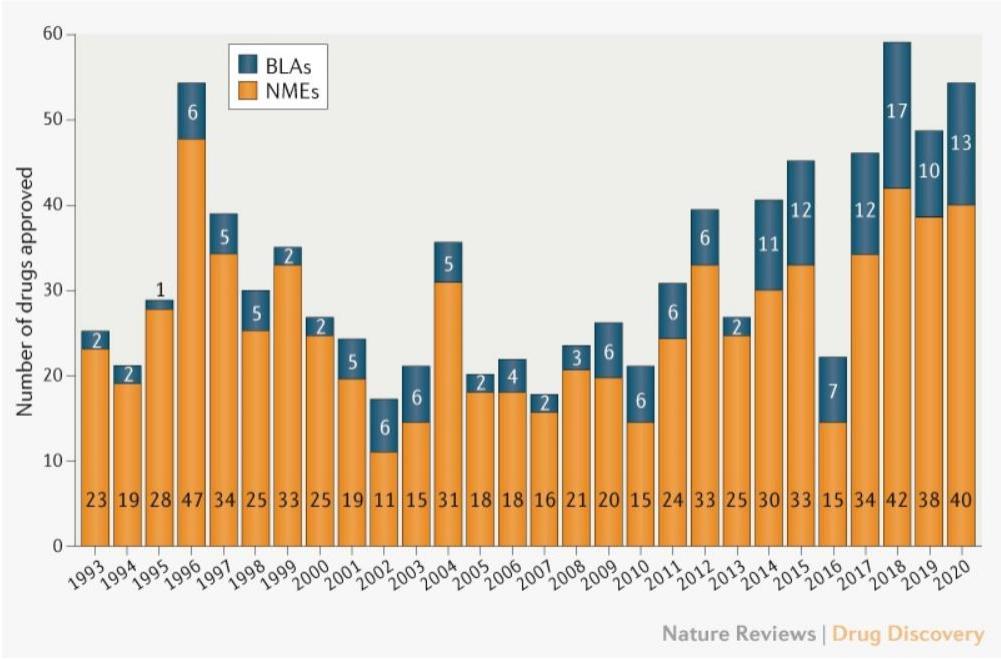
1. Building a culture of data driven design
2. Magic is not magic… key ingredients for the success

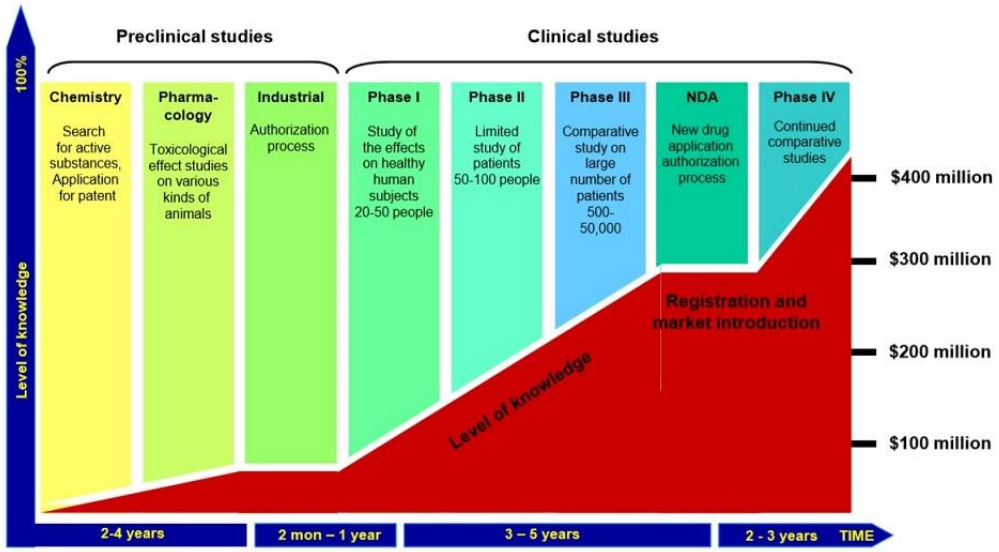
3. Impact & Learnings

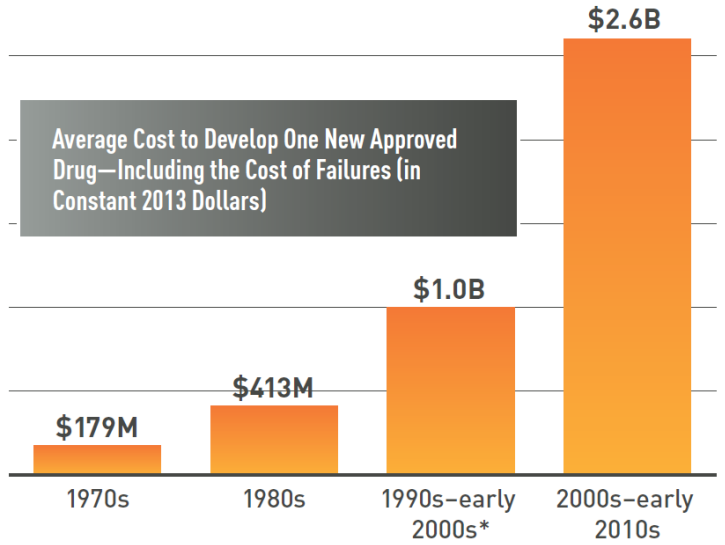
Special thanks to Dr Yogesh Sabnis, UCB

Drug Discovery – Development cycle - impacts





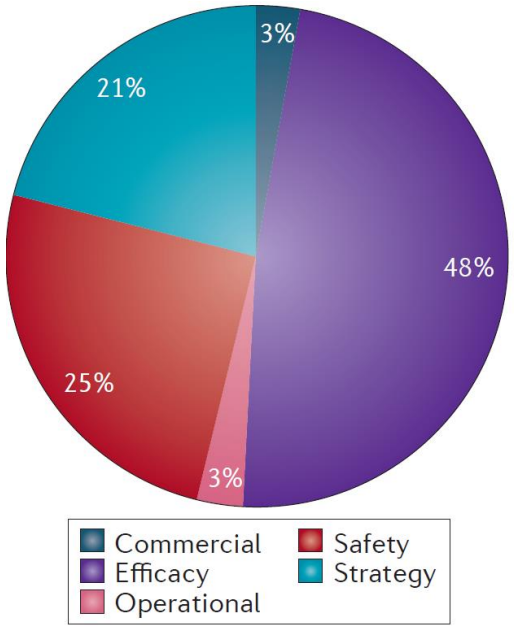




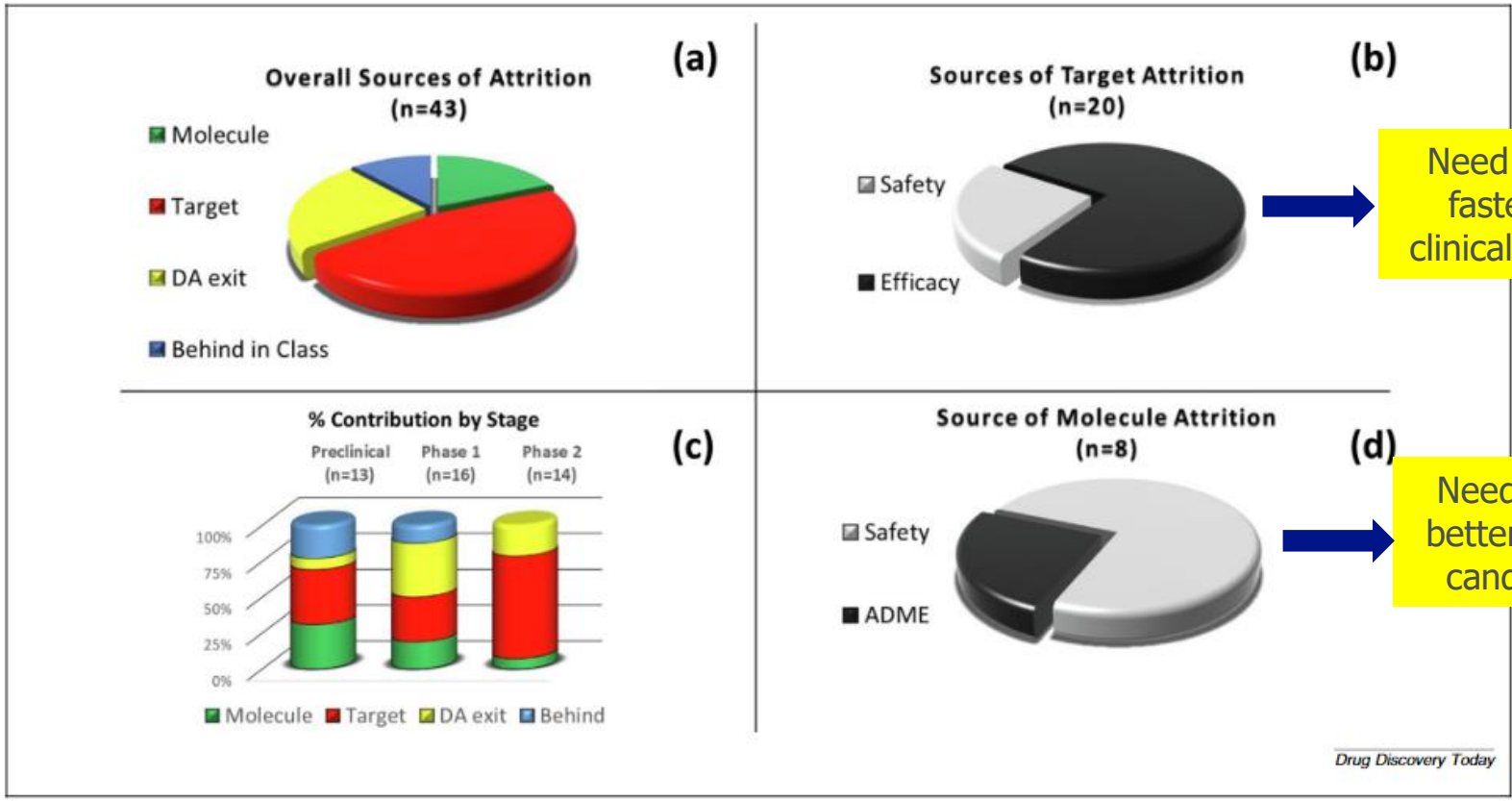
PhRMA 2016 profile, Biopharm. Res. Industry
Albericio, F, Molecules, 2019, 24, 809

Reasons for drug attrition

Phase II failures 2013 – 2015



Phase II failures at Pfizer 2015 – 2019



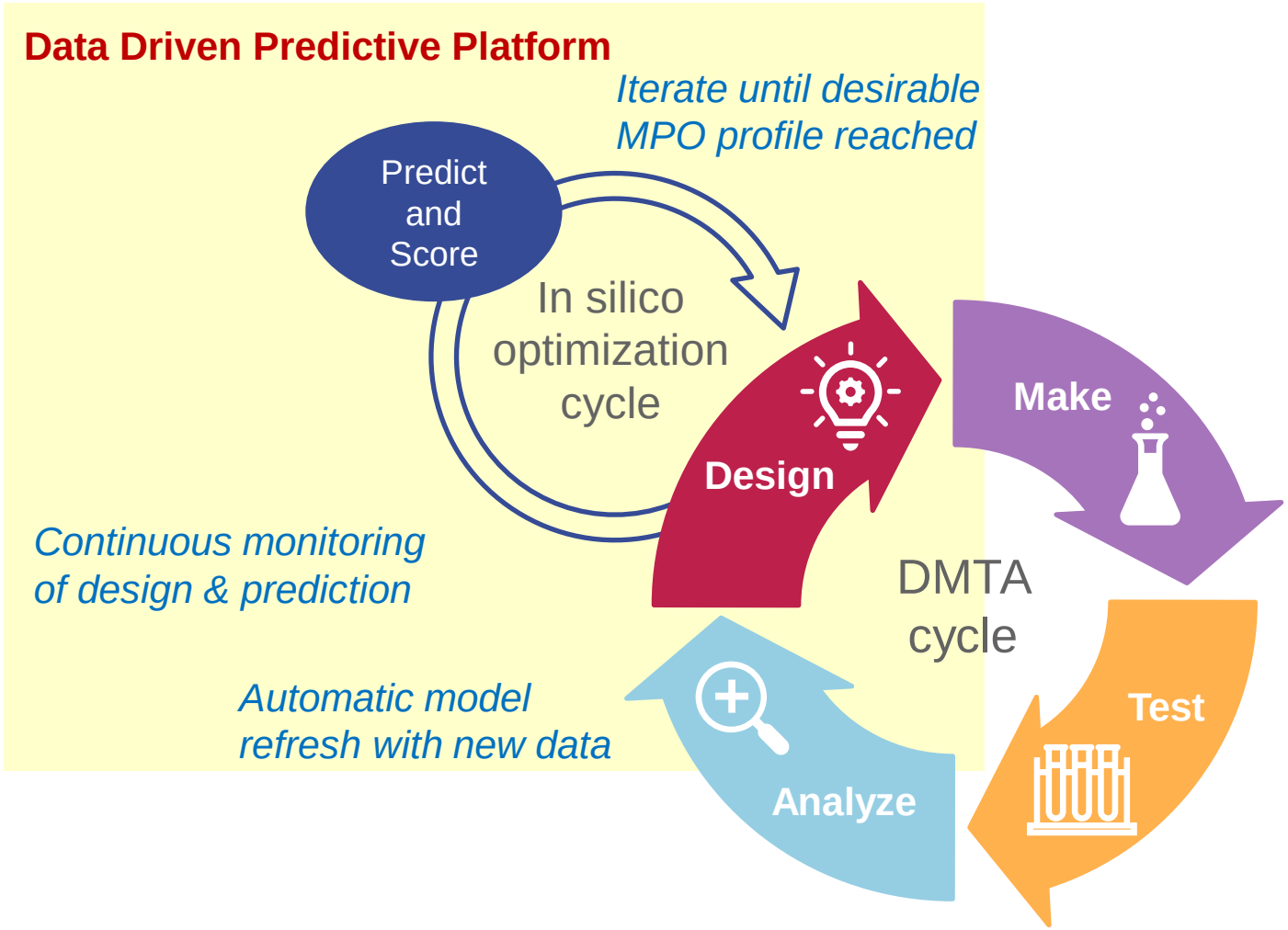
Need to go faster to clinical phase

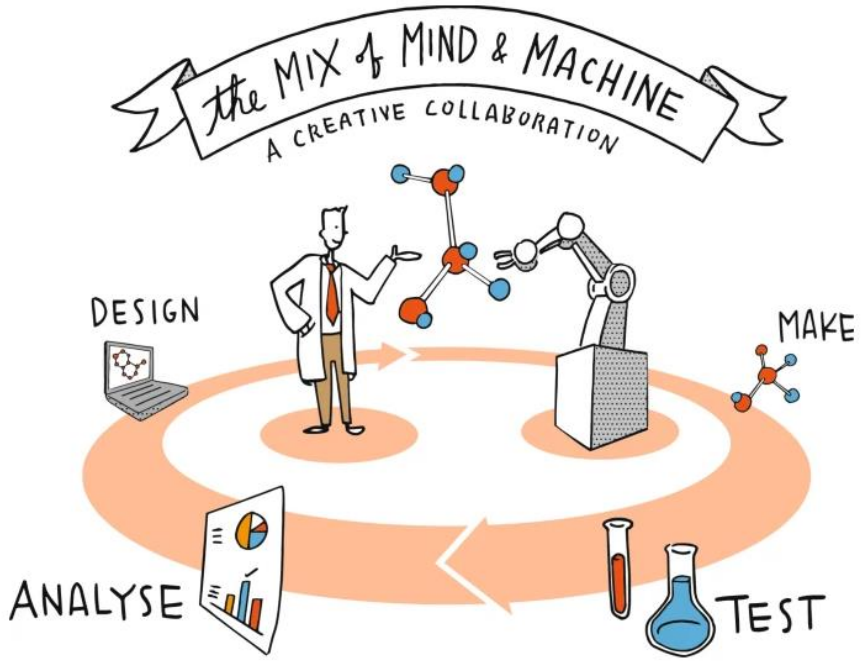
Need to get better quality candidates

TS Maurer et al, 2022, DDT, 27,2 pp 539-546

Richard K. Harrison, Nature Rev. Drug Disc. 15 (December 2016)

Increasing the odds to identify candidate molecule faster





- **Reduce attrition** of the compound design by augmenting human decision making through prediction
- **Increased effectiveness** in the design of molecules leading to identifying high-quality candidate molecules **faster**

P. Schneider et al, 2020, Nat Rev Drug Disc, 19 pp 353-364

The vision

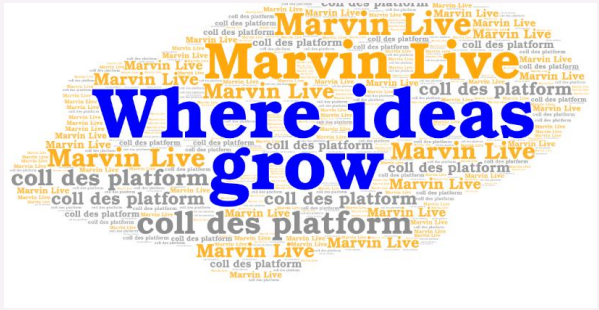
- *Centralized*
- *Modular*
- *Sustainable*
- *Facile*
- *State-of-the-art*

D2P2

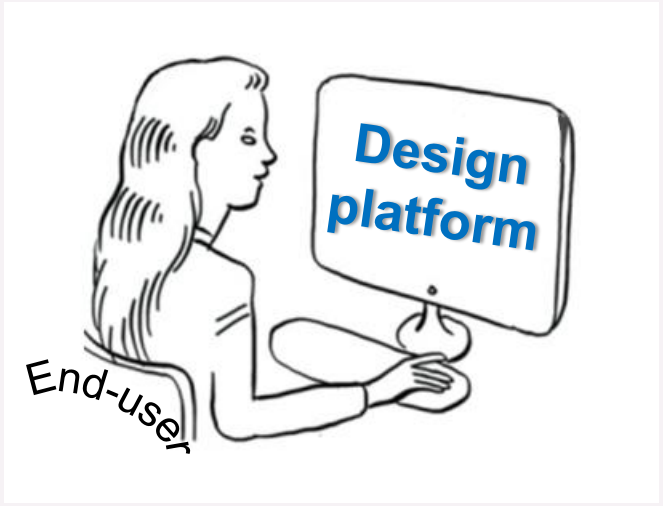
data driven

Predictive platform

Back-end
prediction crunching



- *Real time predictions*
- *Informed prioritization*



Front-end
accessing predictions

Keys to success

Collaborative workflow

- Multidisciplinary cross functional team
- Journey involving project teams at each step

→ Define the scope of the model

→ Understand the data & define the datasets

→ Identify the project specificities, needs, challenges

Autonomous automation

- Where possible minimize the human intervention

→ In continuous, for the model building, update & monitoring

→ Optimize the predictive performance & domain of applicability

→ Highlight areas requiring further attention

Autonomous KPI

- Continuously seek for measure of succes

→ Monitor the model performances over the time

→ Provide an estimation of the accuracy of 'real world' predictions

→ Provide guidelines on how to use the models

The recipe for building a predictive platform

- What potion do you want to cook?
- Ingredients
- Receipe

Goller et al, 2022, Meth. Mol. Biol, 2390, pp 61-96

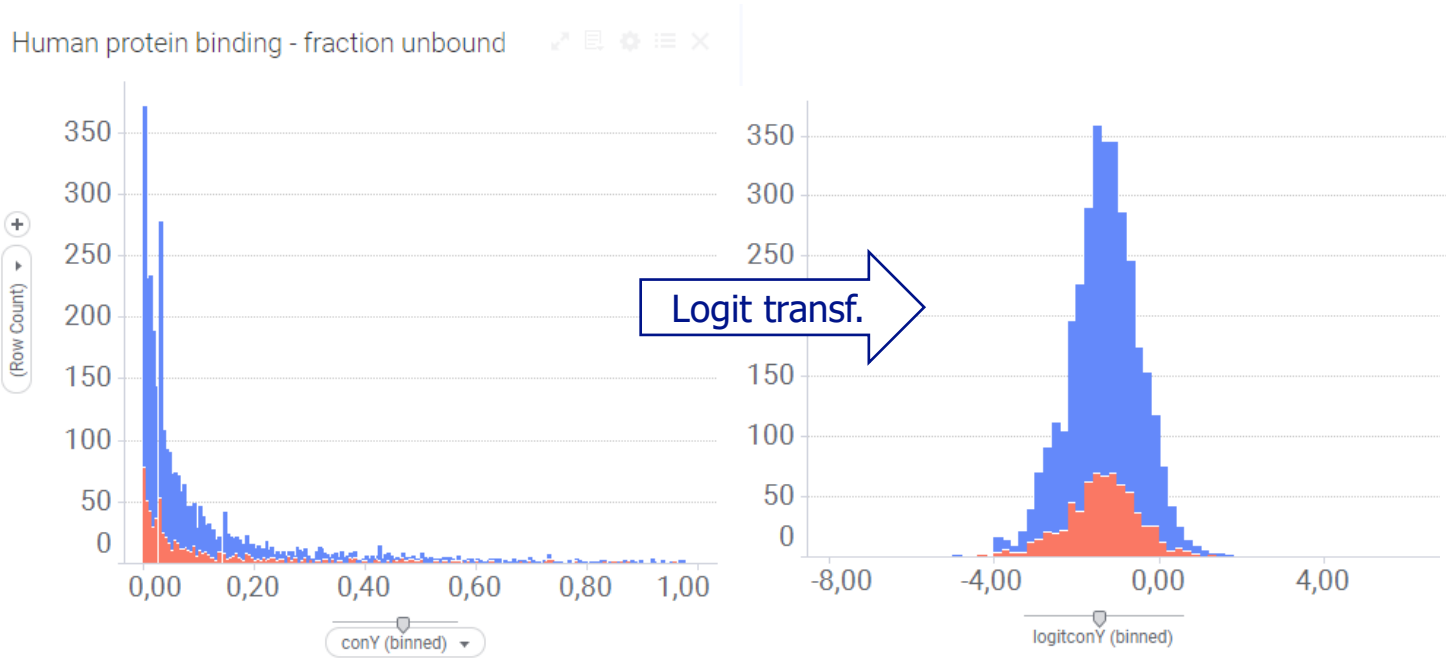
Data

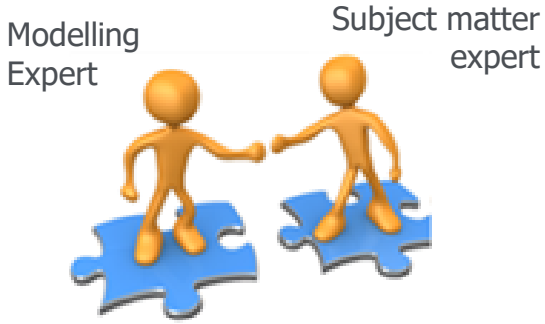
Without appropriate dataset even the most sophisticated model is useless

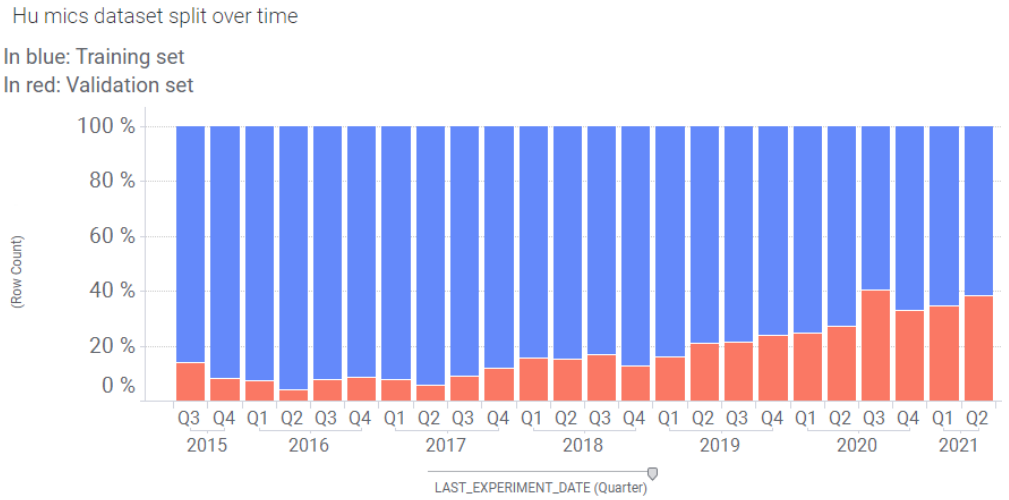
Collaborative workflow

Data must be

- FAIR: Findable Accessible (internally – externally) Interoperable Reusable
- Analyzed and understood (scope, limitations, outliers, chemical space coverage, experimental error, etc)
- Curated (curation rules to be defined: non alphanumerical data, unusual chemistries, stereochemistry, etc)
- In the right shape (data distribution, data balance, data range, possibility to apply log and logit transformations, etc)
- Split into training set/validation set/external set (random split, time split, etc)







Inspired by patients. Driven by science.

How to GO FAIR - GO FAIR (go-fair.org)

P. Schneider et al, 2020, Nat Rev Drug Disc, 19 pp 353-364

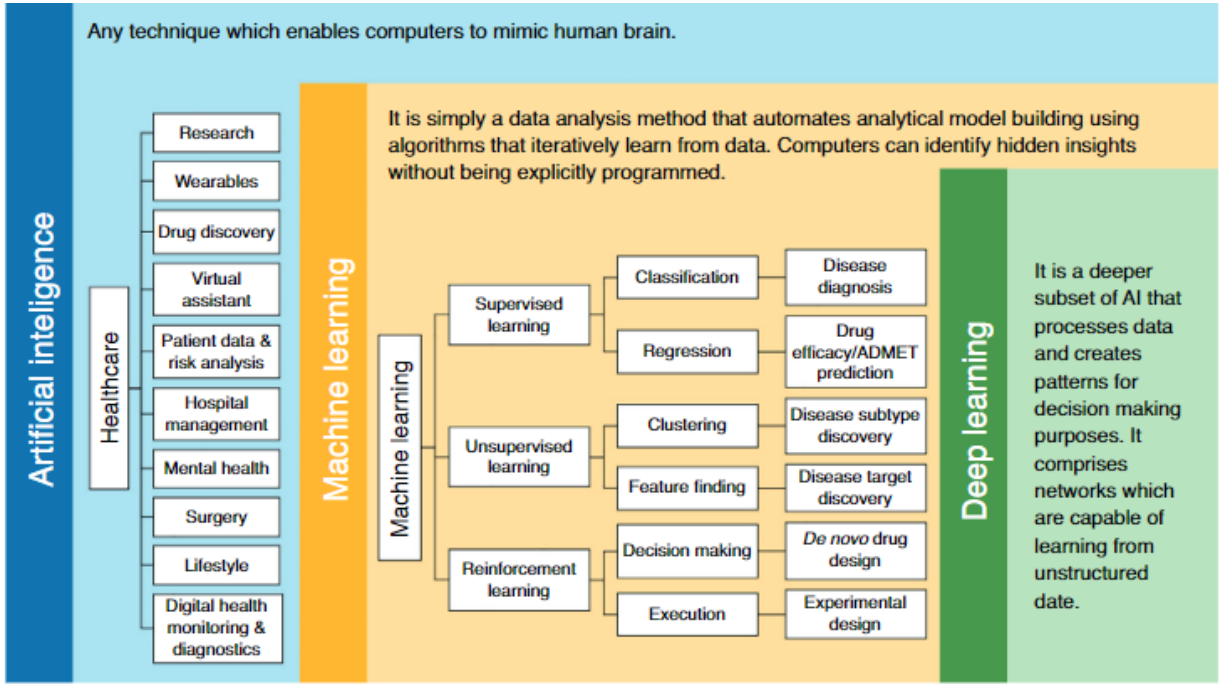
This is not a molecule!

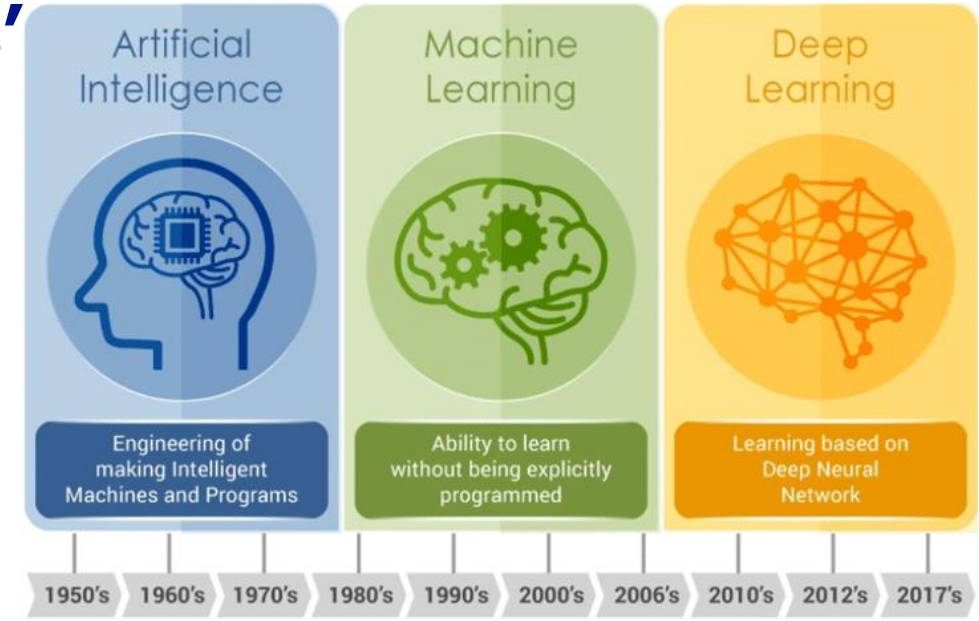
« La trahison des images –
The treachery of images »
Magritte 1929

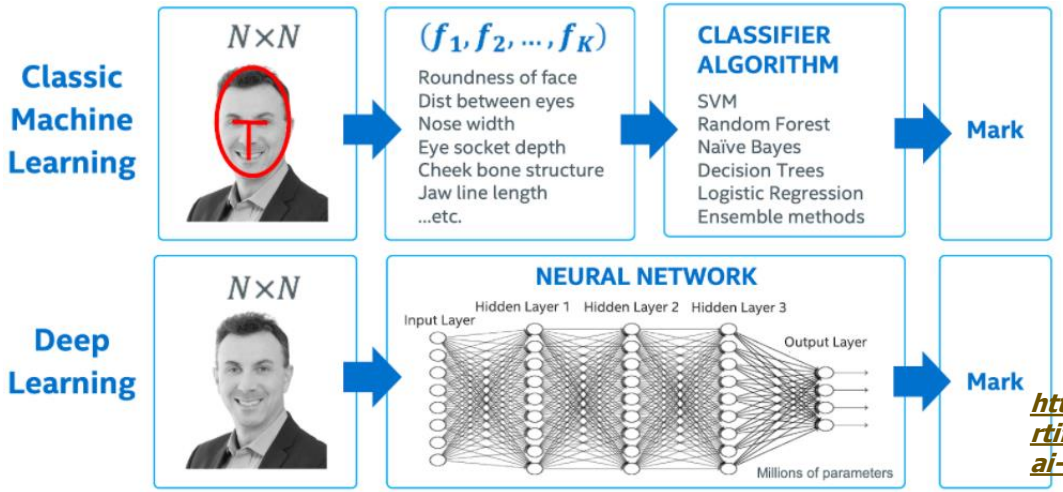
- By definition a representation induces a loss of information
- Huge variety of molecular representations & descriptors (0D to 4D including fingerprints, graphs, etc)
- Combinations are possible → what is the best set that will explain the max % of variance of the dataset?
- Feature selection & data reduction are needed to avoid overfitting
- Interpretabilitiy vs predictability

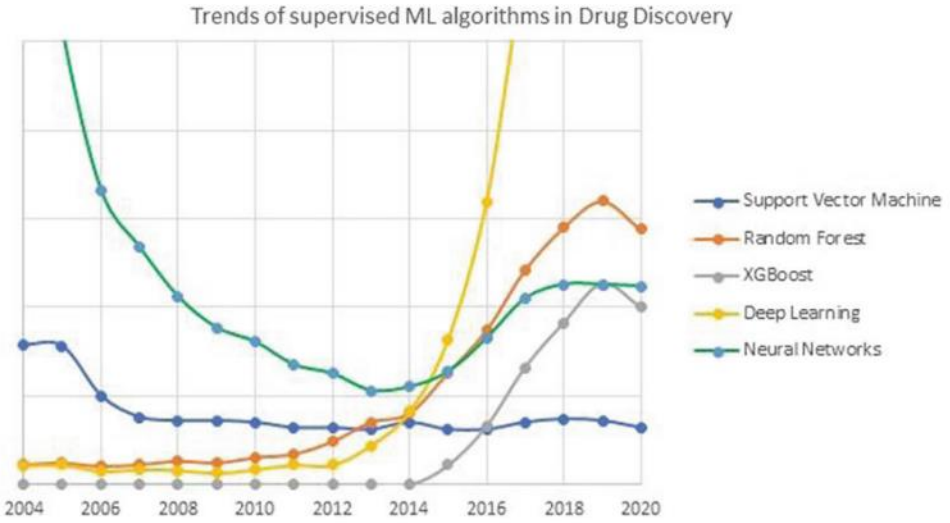
Danishuddin & A.U. Kahn, 2016, DTT, 21,8, pp 1291-1302
Goller et al, 2022, Meth. Mol. Biol, 2390, pp 61-96

The confusion over 'learnings'









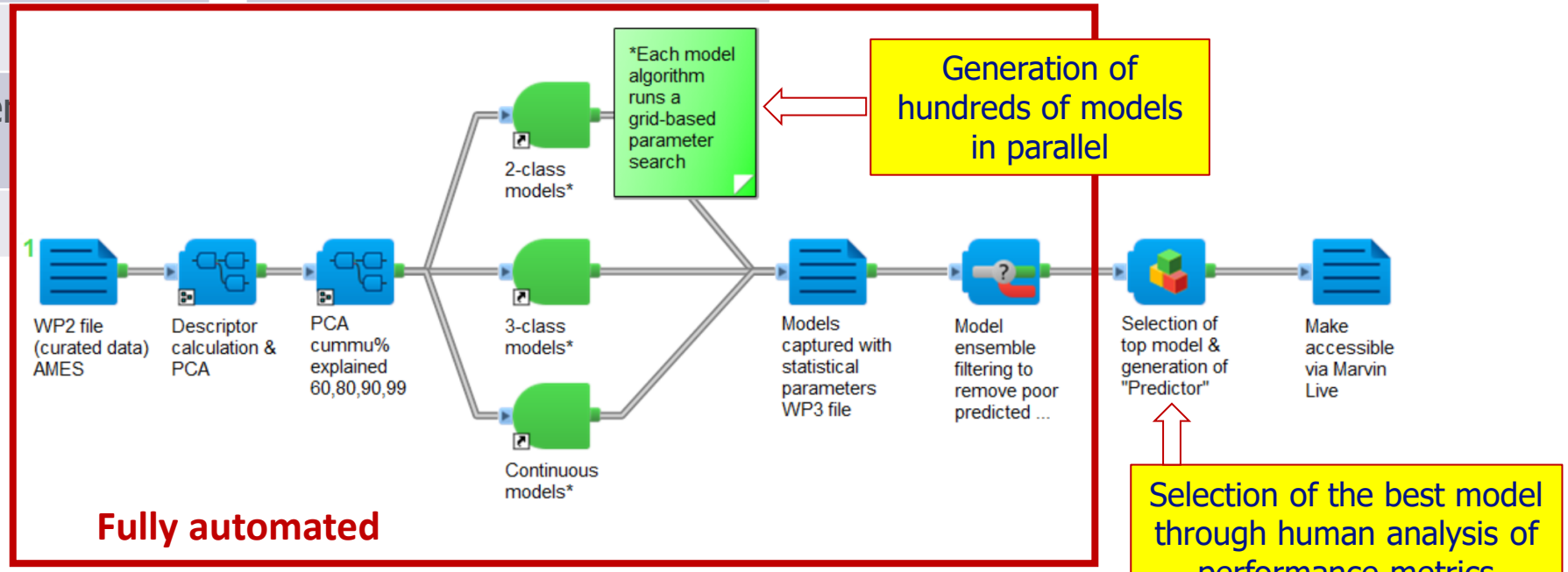
https://www.intel.com/content/www/us/en/artificial-intelligence/posts/difference-between-ai-machine-learning-deep-learning.html

K.-K. Mak et al, 2019, DDT, 24, 3, pp 773-780
A. Goller et al, 2022, Meth. Mol. Biol., 2390, pp 61-96
Z. Jiao et al, 2020, ACS Chem. Health Saf., 27, 316-334

Navigating through algorithms & parameters

Autonomous automation

Classification	Regression
Logistic regression	Linear regression
Gaussian Naive Bayes	PLS
Support Vector classifiers	Support Vector Regressors
K-NN	Decision Tree
Decision Tree	Random Forest
Random Forest	
Stochastic Gradien Descent	
Extra-Trees	

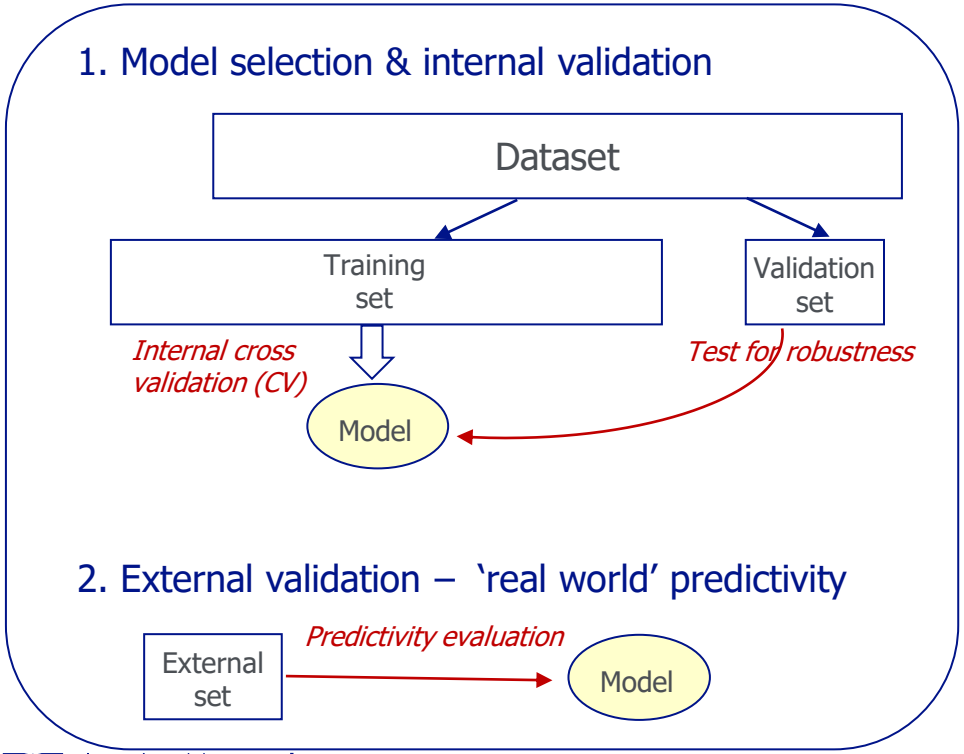


Scheme for illustration purpose

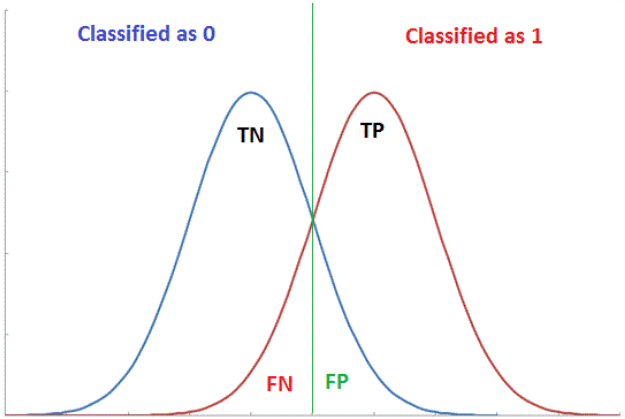
Assessing model quality through performance metrics

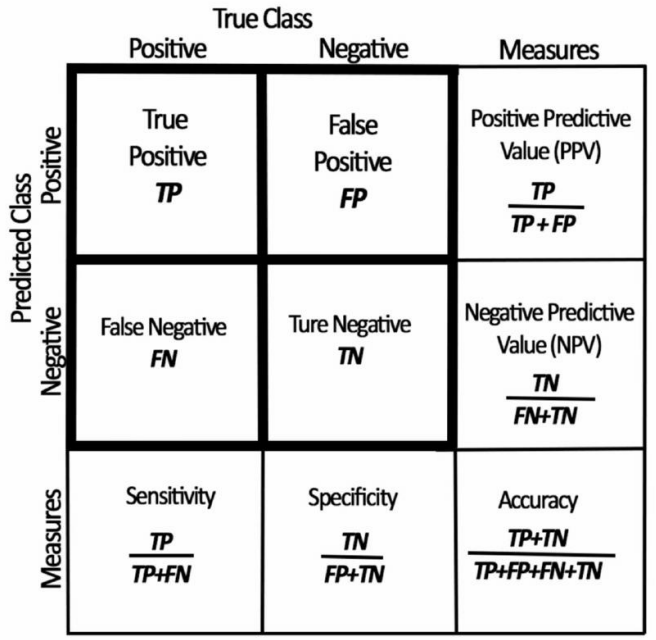
Statistical parameters obtained from

- Validation set
- Training set
- Cross Validation
- External set



Classification (Confusion matrix)	Regression
Accuracy	R^2 - coefficient of determination
Balanced accuracy	RMSE - standard deviation of residuals
Specificity – true negative rate	MAE - mean absolute error
Sensitivity – true positive rate/recall	Spearman's rho – rank correlation coefficient
Positive predictive value/precision	
Negative predictive values	
MCC	
Kappa	
F-Score	
ROC_AUC	





Putting all the pieces together: a recipe in 5 steps

Collaborative workflow | Autonomous automation | Autonomous KPI

DATA EXTRACTION
Live lookup
UCB+ext

DATA CURATION
Rules definitions
Recommendations

MODEL BUILDING & SELECTION
10 sets of descriptors (mol. prop. & FP)
20 ML algorithms & related parameters (class. & reg.)
Statistical performance matrix

SME ME

Deliverable
Raw data file

Deliverable
Curated data file

Deliverable
Final model

- ✓ *Fully automated*
- ✓ *Independant updates* *biweekly*
- ✓ *Performance monitoring*

- ✓ *Centralized*
- ✓ *Modular*
- ✓ *Sustainable*
- ✓ *Continuous*

MODEL PRODUCTIONIZATION
Central access point

MODEL CONTAINERIZATION
Exposed as rest API

- ✓ *Portable*
- ✓ *Robust*
- ✓ *Stable*
- ✓ *Reproducible*
- ✓ *Scalable*

Deliverable
Packaged model

CLIENT APPS
Web applications
Design platforms
Excel/Spotfire
Generative design
CADD WF

IE

COMMUNICATION
Education
Feedback
Advocate

Deliverable
Communication sessions

SME ME

SME: subject matter expert
ME: modeling expert
IE: IT expert

Global and local models at UCB

Collaborative workflow | Autonomous automation

A collaborative workflow built upon the existing global models creates a 'predictive dashboard' across all projects & available endpoints

Endpoints
Adsorption
Distribution
Metabolism
Toxicity
PhysChem

Global models

Endpoints	Project1 –series1	Project1 –series2	Project2 –series1
Adsorption	**Local Model dashboard** Project/series specific		
Distribution			
Metabolism			
Toxicity			
PhysChem			
Potency			

- ✓ Automatically built and refresh every 2 weeks
- ✓ Showing the statistical parameters of the top model & the number of avalaible datapoints
- ✓ Covering the NCE projects portfolio

⇒ **Allow a quick identification of potential deployment of new models**

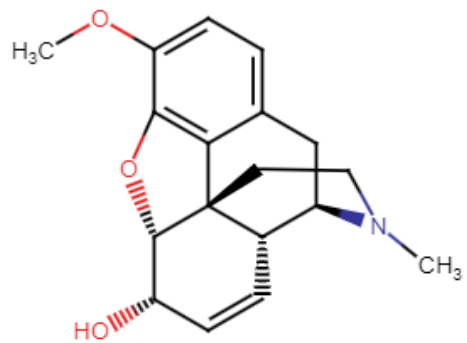
Real-time predictions at the inception of design

Collaborative workflow

Exposing the predictions to maximize their use in the decision making process and improve the effectiveness of compound design

SAVE

ADD PROPERTY



Ex: Codeine

Safety Predictive Models

	Prediction	Confidence
ames	negative	high
Cell health	low risk	high
hERG channel inhibition	negative	low

Physchem Predictive Models

	Prediction	Confidence
kinetic solubility threshold at 90 uM	high	high

DMPK Predictive Models

	Prediction	Confidence
Plasma protein binding (Mouse) ()	0.92	high
Papp (Caco2) (nm/sec)	165.80	high
Efflux Ratio(Caco2) ()	2.04	low
Plasma protein binding (Human) ()	0.11	low
Plasma protein binding (Rat) ()	0.28	high
Mouse Microsomal Clint Continuous (µL/min/mg prot)	59.30	low
Human Microsomal Clint Continuous (µL/min/mg prot)	17.38	low

Calculated Properties

	Current	Pinned
▼ Mass	299.36	494.58
▼ cLogP	1.3	2.7
▼ cLogD	0.26	2.4
▼ TPSA (Å²)	41.93	108.05
▲ pKa (str. acidic)	14.17	7.64
▲ pKa (str. basic)	8.4	7.01
▼ FSP3	0.56	0.63

Last edited by Marie Ledecq 1m

Design Hub

Next phase: Extending the outreach

CADD workflows

Library
- BRiCS prioritised scaffolds
- Drugs/clinical trials/future clinical trials
- available reagents

Generation
- Choice of scaffold to grow from
- Combinatorial growth vectors
- Enumeration with stability / tractability filters
- Multi-million sets

ULVS – Cloud based Dynamic Structural Scoring
- Multiple Protein conformations
- ULVS Cloud Platform
- 1million molecules per hour

D2P2 Property Prediction
- Local Model Ranking
- Clearance, Heps, solubility

Design/Analysis Platforms

TIBCO Spotfire

StarDrop™

Generative design

Chemistry42

inspyra

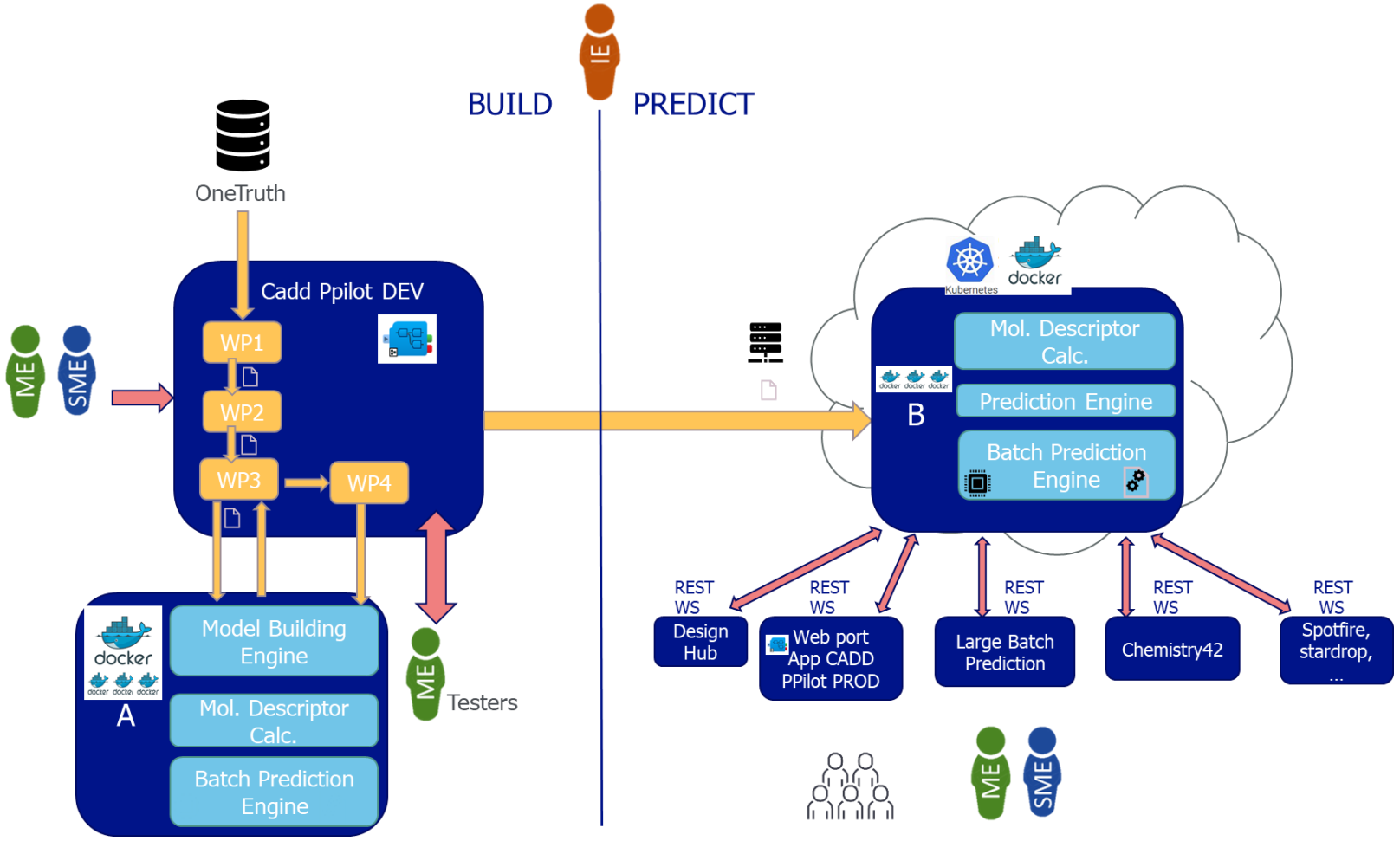
Adapted infrastructure

Collaborative workflow

Autonomous automation

When you embark on building a platform you need to ensure that you have the right infrastructure

- ✓ Robust
- ✓ Stable
- ✓ Modular
- ✓ Scalable

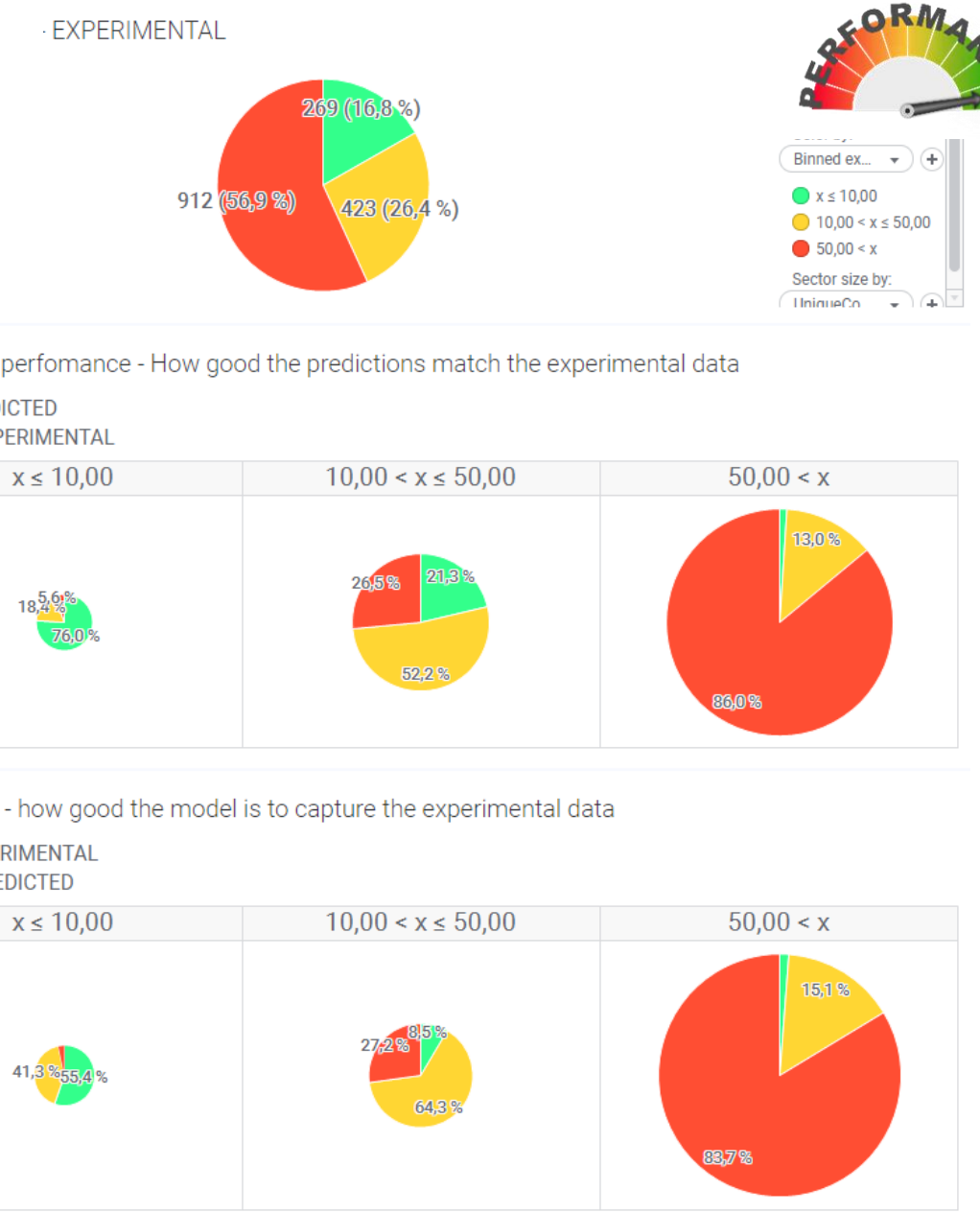


The power of data to change mindset

Autonomous KPI

Increasing the confidence in the model

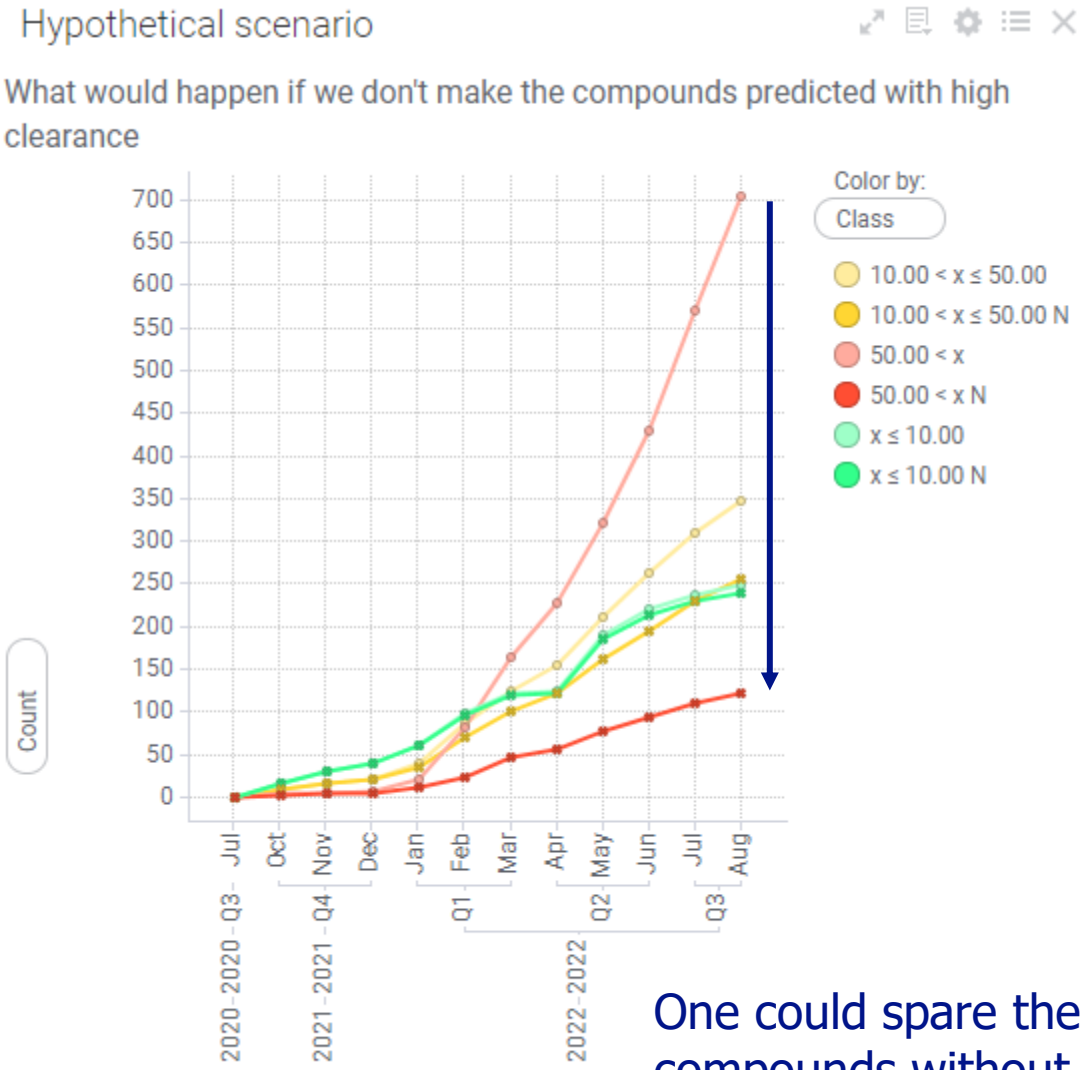
- Model performance monitoring on prospective predictions
  - Automatic prediction of new data before the retrain of the model.
  - Accumulation of prospective predictions (= 'external' dataset) over the time (biweekly)
  - Annotated: assay name, project name, date of prediction, model version, etc
- Mock up illustration – global model
  - What is the current performance of the design teams – the prevalence?
  - How good is the model to predict good or bad stabilities?
  - If a model is predicted as bad, what is the probability to be bad – or good? What are the consequences if I decide not making compounds predicted as bad?
  - What are the trends among projects? Over the time?

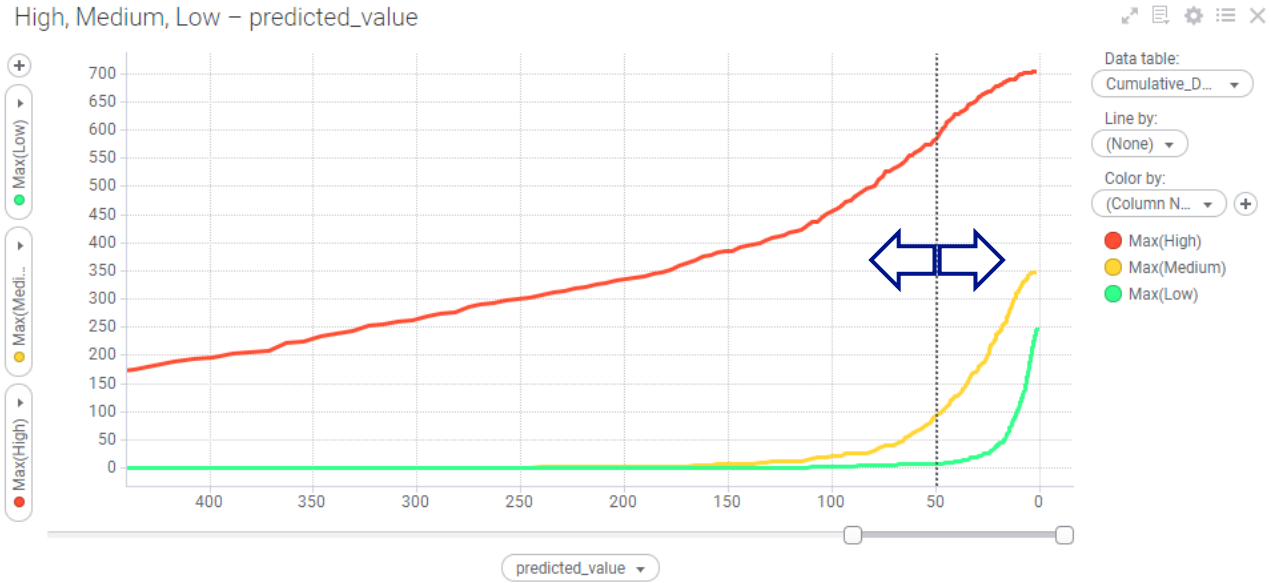


The power of data to change mindset

Autonomous KPI

Guiding the decision making process

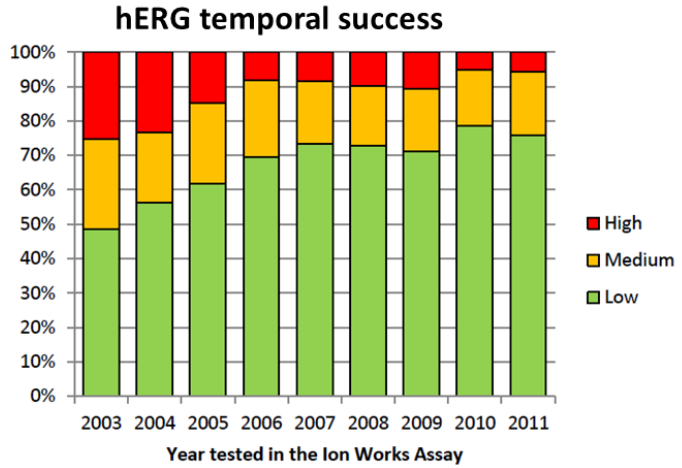




Depending on the project needs, one can decide from which predicted value synthetizing the compound ideas

One could spare the synthesis of ~600 'bad property' compounds without loosing any good ones

Patient value – demonstrated impact in the pharma industry



AstraZeneca's global HERG QSAR model70 has contributed to the reduction in the synthesis of 'red flag' compounds (compounds that are measured to have an HERG potency of <1μM)

from 25.8% of all compounds tested in 2003 to only 6% in 2010.

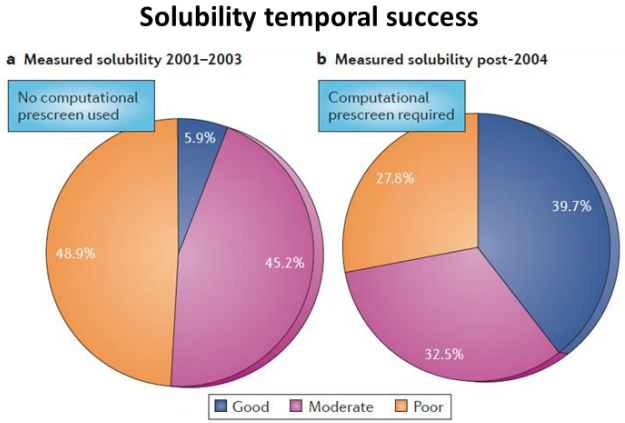
Cumming, J.G., Davis, A.M. et al. Nat. Rev. Drug Disc. (2013) 12, 948–962

Journal of Medicinal Chemistry

Cite This: J. Med. Chem. 2017, 60, 9097-9113

In Silico Absorption, Distribution, Metabolism, Excretion, and Pharmacokinetics (ADME-PK): Utility and Best Practices. An Industry Perspective from the International Consortium for Innovation through Quality in Pharmaceutical Development

Alkermes Inc.
Computational ADME, Drug Disposition, Eli Lilly and Company
Vertex Pharmaceuticals Inc.
AbbVie, Inc.
Roche Pharmaceutical Research and Early Development
Pfizer Inc.
Discovery Drug Disposition, R&D Global Early Development, EMD Serono
Drug Safety and Metabolism, AstraZeneca R&D Gothenburg
Genentech Inc.



synthesized compounds over time. Even though good computational models of aqueous solubility had been available from before 2001 (REF. 101), this did not result in an improvement in the solubility of the compounds synthesized. **b** | A marked improvement in the properties of compounds only occurred when management expectations on quality at the design stage were enforced in 2004; the chart shows the distributions for ~14,000 compounds synthesized between 2004 and 2012.

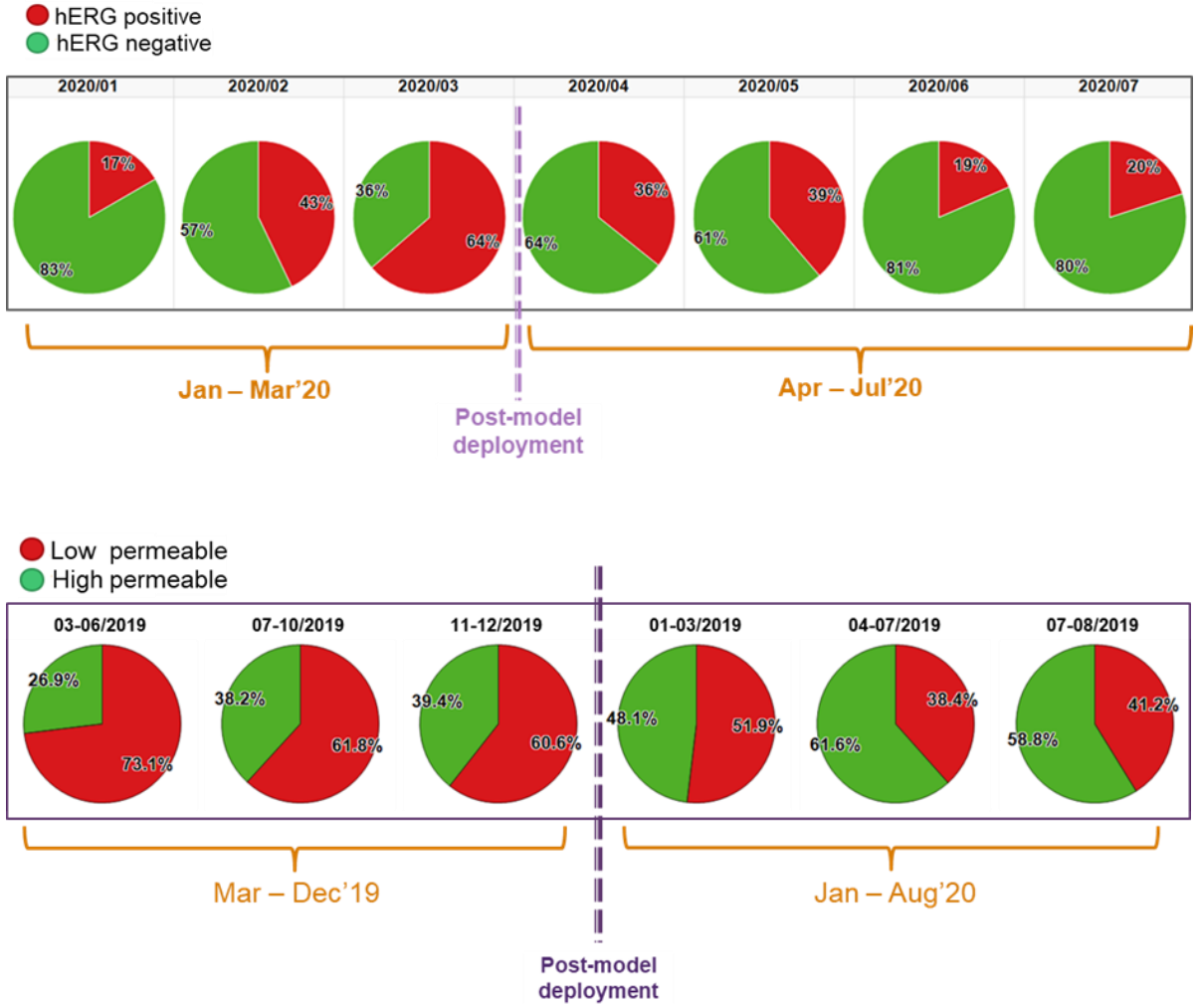
Patient value – Early impacts at UCB

Faster to candidate value creation

- Accelarate ML model building: **from weeks to hours**
- Expanded NCE portfolio support coverage: **from 33% to 100%**
- Informing drug design with latest experimental data thanks to **continuous** instead of episodic model building
- Example of succes in project:

  Augmenting project team to dial-out hERG liability and dial-in permeability

  - Urgent need to address **hERG** liability in March 2020; highly predictive model built & deployed **within 1 day**
  - **Passive permeability** model deployed in Dec 2019. Project team delivered **63%** of compounds with desirable high passive permeability post model deployement **versus 37%** before deployment



Lessons learned & further thoughts

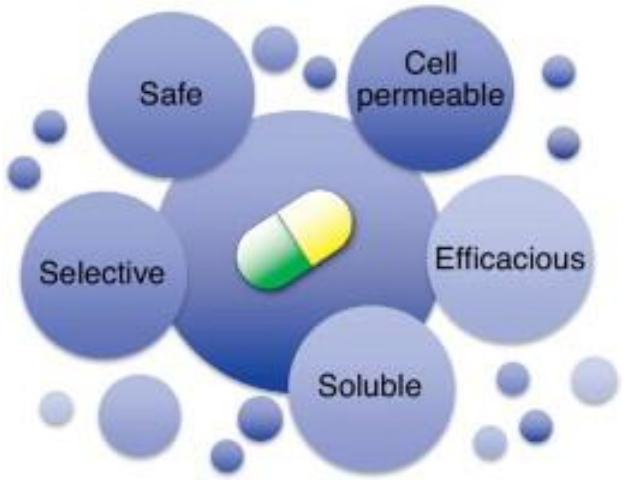
Seeking for accuracy – how to improve the model quality

- Better datasets – Active learning
- Better methodologies/algorithms

Drug design is a MPO problem

- How to deal with trade-offs – predicting composite score
- Error in the prediction and decision making
- Is generative design the solution

Beyond classical NCE - Exploring other modalities



C. Nicolaou et al, 2013, DDT, 10, 3, pp e427-e435
G. Lambrinidis et al, 2021, Exp Op Drug Discov, 16, 6 pp 647-658

In summary…

Collaboration, communication, education

- Maximizing the adoption
- Demystifying AI

Vision

- Flexibility & adaptability

Measuring the succes - how good are we?

- Model performance
- Impact on project: improving the effectiveness of the DMTA cycle

AI will never replace human experience & expertise – however, it will help to accelerate the ability to process & analyze data.

Acknowledgements

D2P2 team & UCB management