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Lipophilicity – A Tale of 3 pHs

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Agenda

1

Introduction

Drug Discovery Process
ADME
Physchem Props
Lipophilicity – Then & Now

2

ChromlogD @ 3 pHs

Why?
How?
PFI
Acid/Base classification
Comparison with pKa

3

in silico ChromlogD models

How are they generated?
How are they utilised?

4

Impact of ChromlogD

LLE
Optimizing PROTACs

5

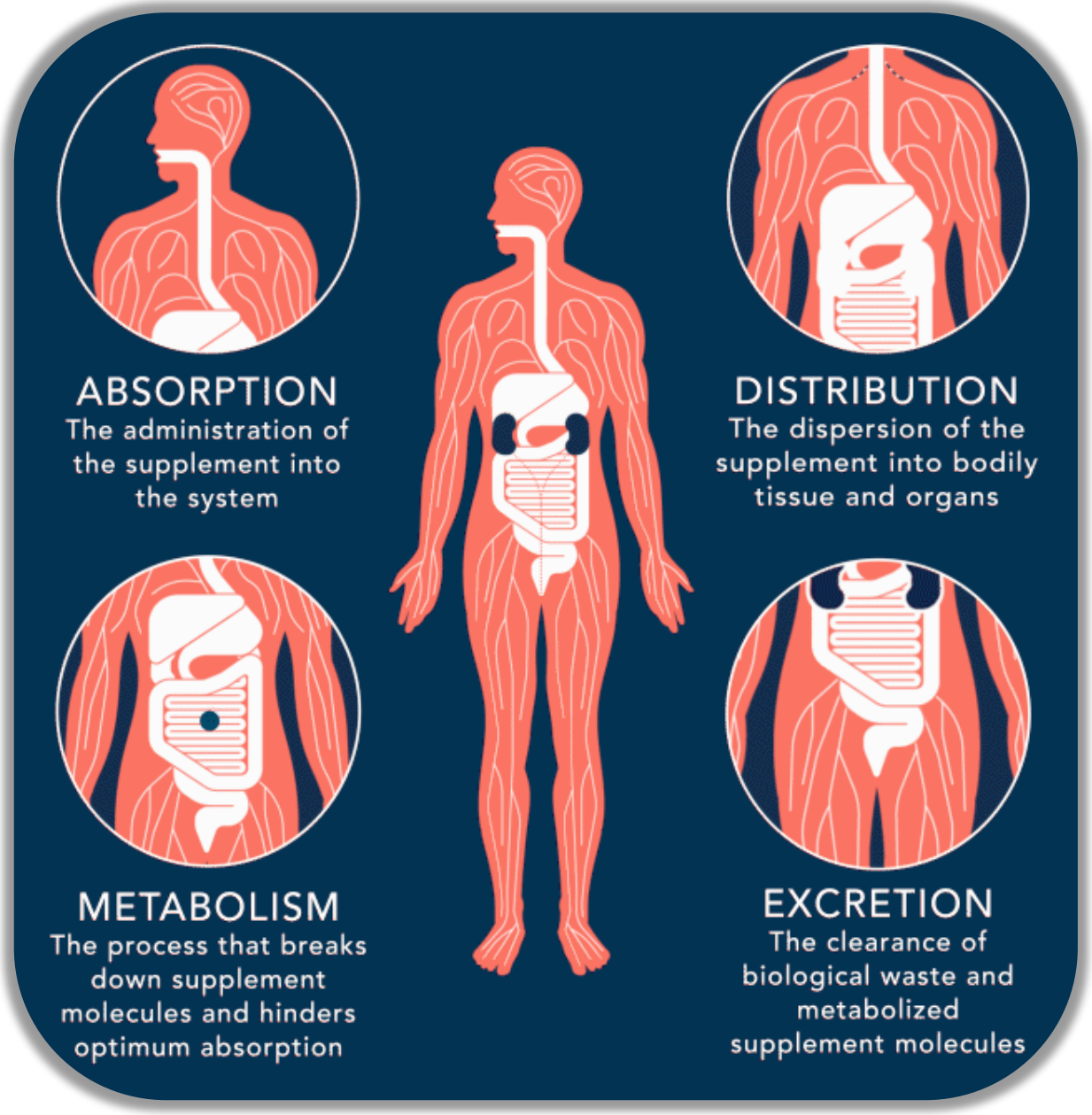
Conclusion

Key Messages

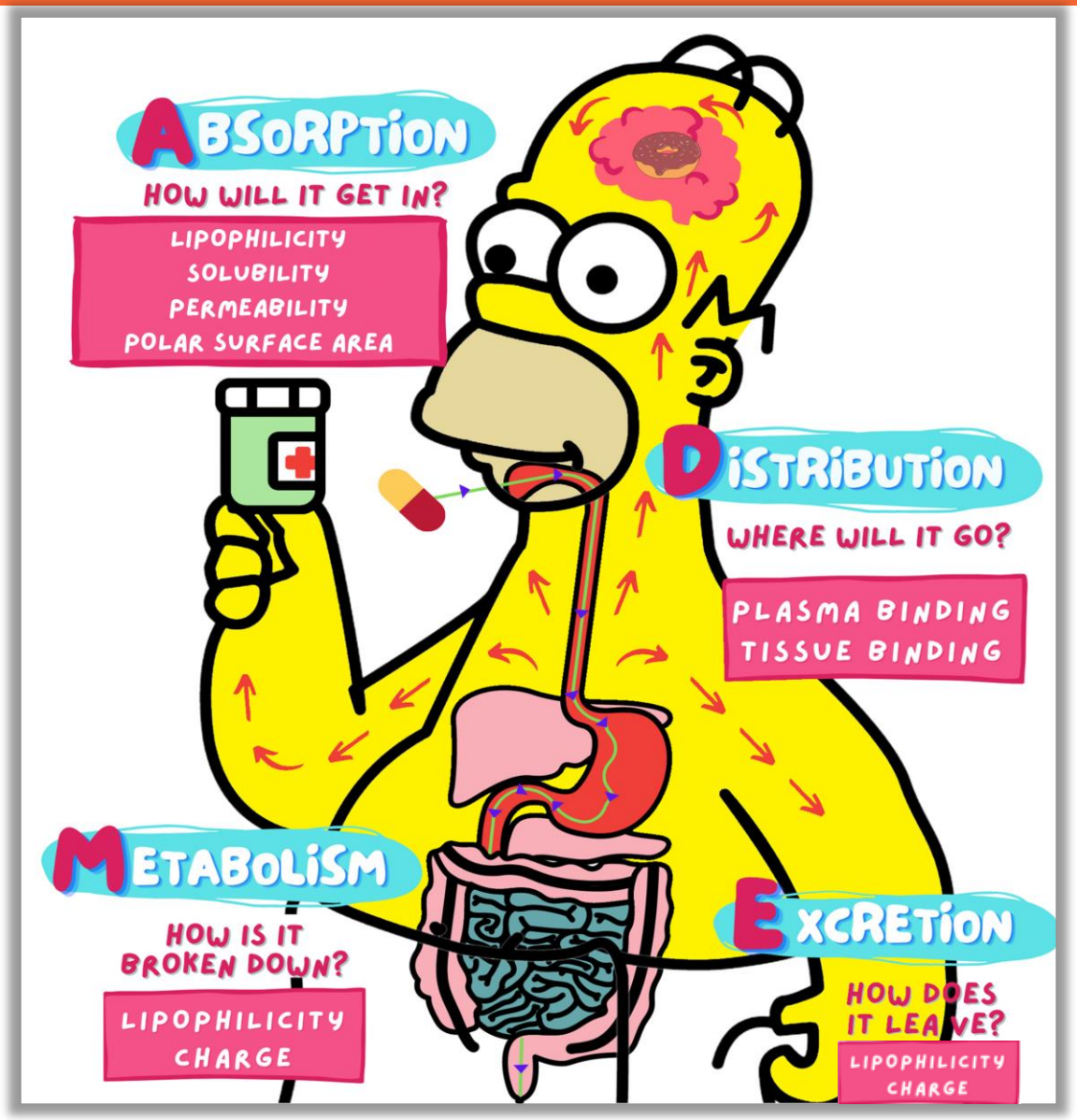
1 – Introduction

ADME

One of the major causes of the high attrition rate in the drug industry is **poor ADME properties** which are influenced by Physchem properties.



How do Physchem Properties influence ADME/Pharmacokinetics?



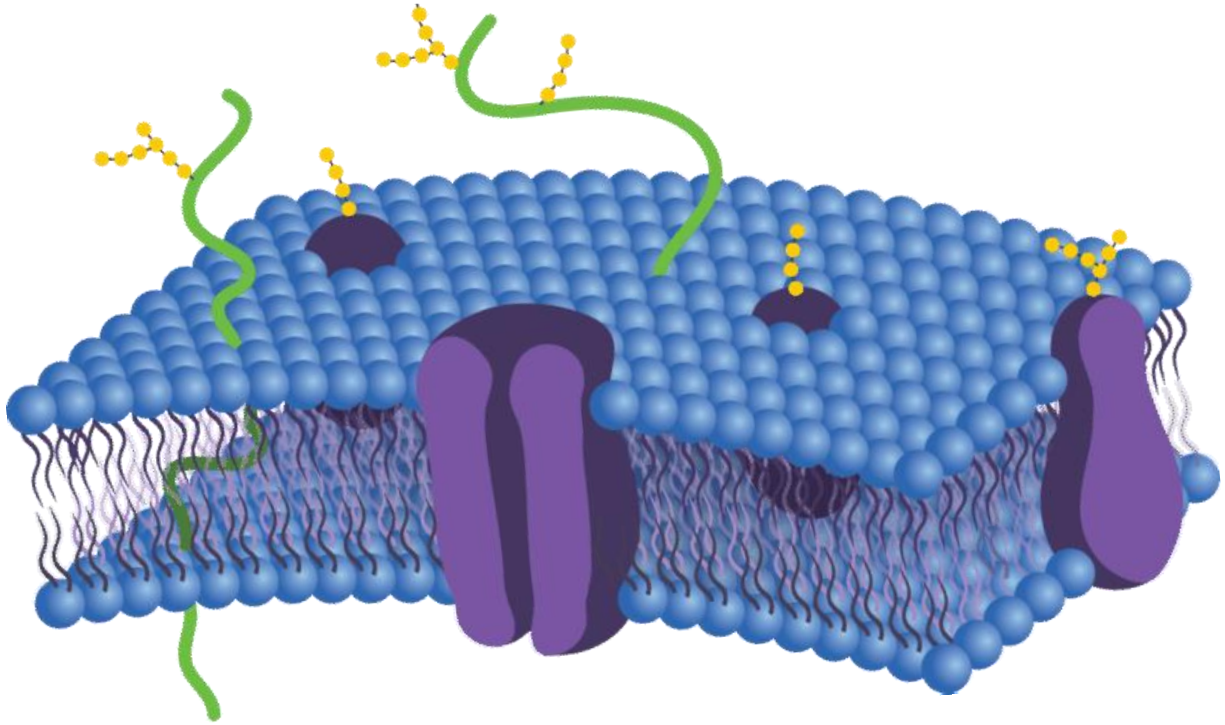
Lipophilicity – The Key Drug-Like Property

Ability of a compound to dissolve in fats and non-polar solvents *"Fat-liking"*

Affects pharmacokinetic and pharmacodynamic behaviour.

Assessed by Octanol-Water Log P

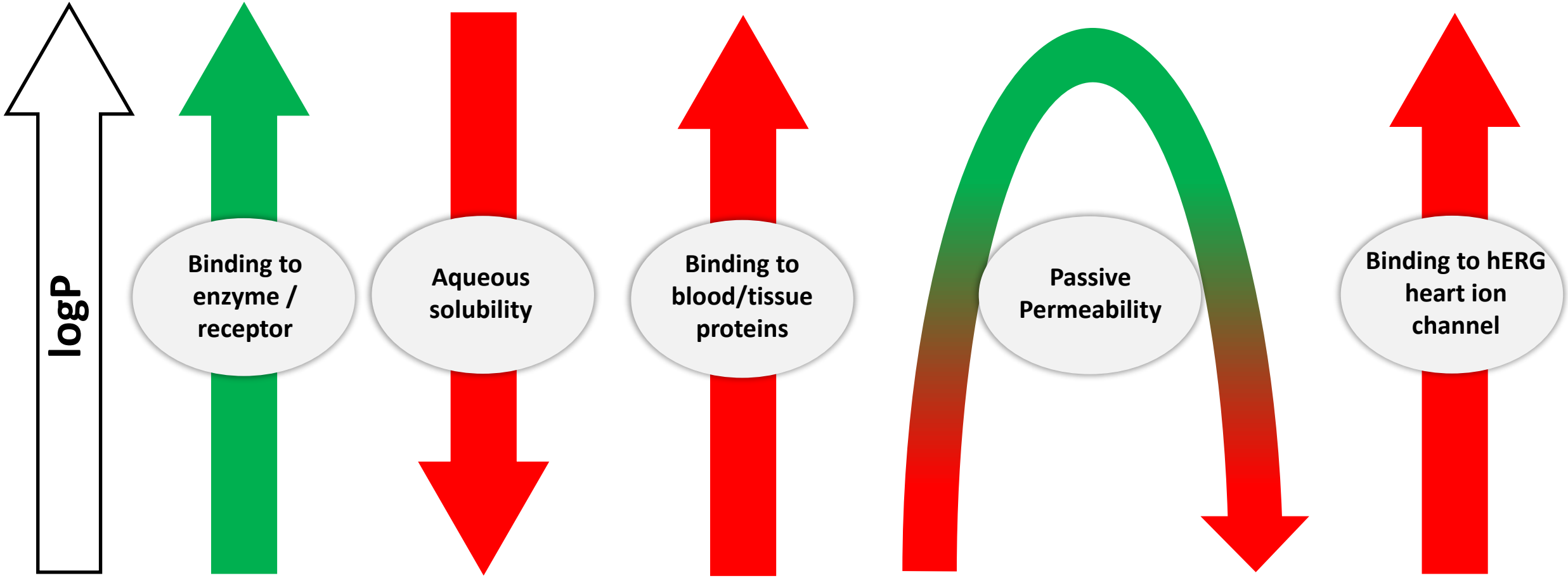
Lipophilic molecules prefer lipid environments. Hydrophilic molecules prefer aqueous environments.



LogP: partition coefficient of the **neutral** form of the compound.

LogD: distribution coefficient of the **ionised** form of the compound, hence **pH dependent**

What does lipophilicity (log P) affect?

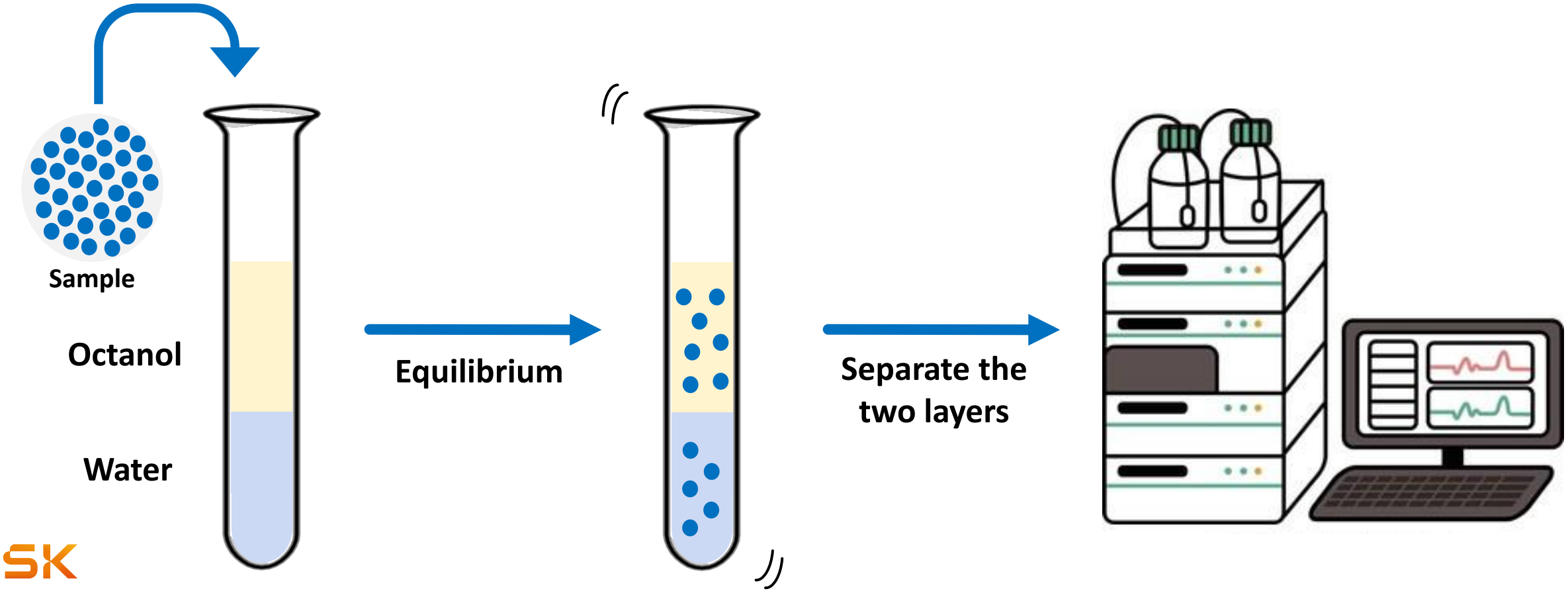


So log P needs to be *optimised*

Lipophilicity Measurements – Then and Now

Octanol-Water LogP

The "gold standard" measurement of lipophilicity



Lipophilicity Measurements – Then and Now

Octanol-Water LogP

The “gold standard” measurement of lipophilicity

Doesn’t cater for new chemical spaces

Requires more resources.

Issues with insoluble or highly lipophilic compounds.

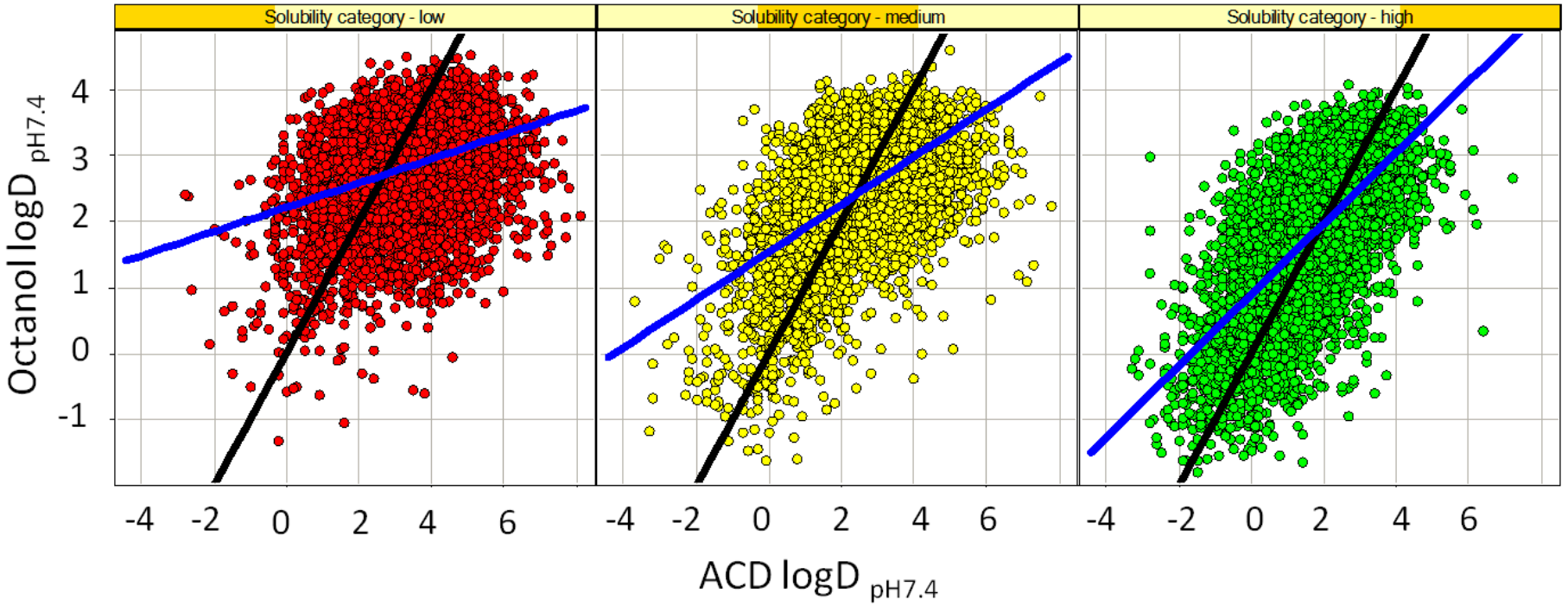
Insufficient dynamic range.

Lipophilicity Measurements – Then and Now

Octanol-Water LogP

The "gold standard" measurement of lipophilicity

Measured vs Calculated OctanolLogD$_{pH7.4}$



Data colour coded by measured kinetic aqueous solubility at pH7.4
Red < 30uM
Yellow 30-200uM
Green >200uM

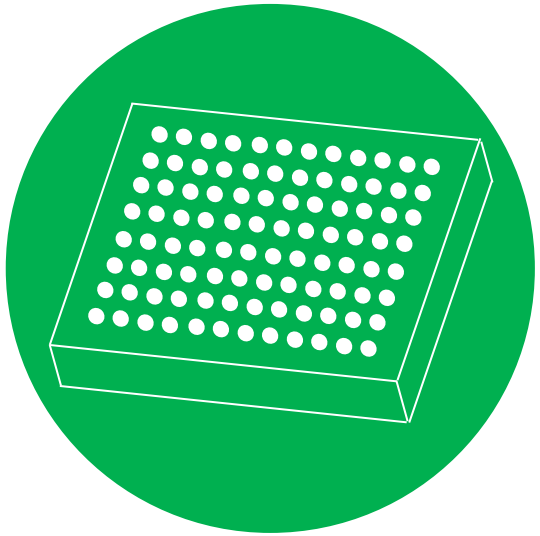
Black line: y=x
Blue line: regression line

Robert J. Young: Physical Properties in Drug Design, Book Chapter in Tactics in Contemporary Drug Design, Volume 9 of the series Topics in Medicinal Chemistry, 2015 pp 1-68

Lipophilicity Measurements – Then and Now

Chromatographic LogD

Chromatographic-based measurement of lipophilicity



Easily automated and high-throughput method

Robust and reliable

Covers a dynamic range (Chromlog$D_{7.4}$ -1 – 9)

Measured at various pHs

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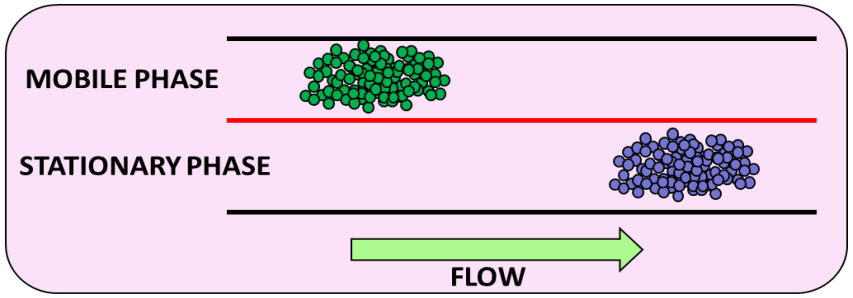
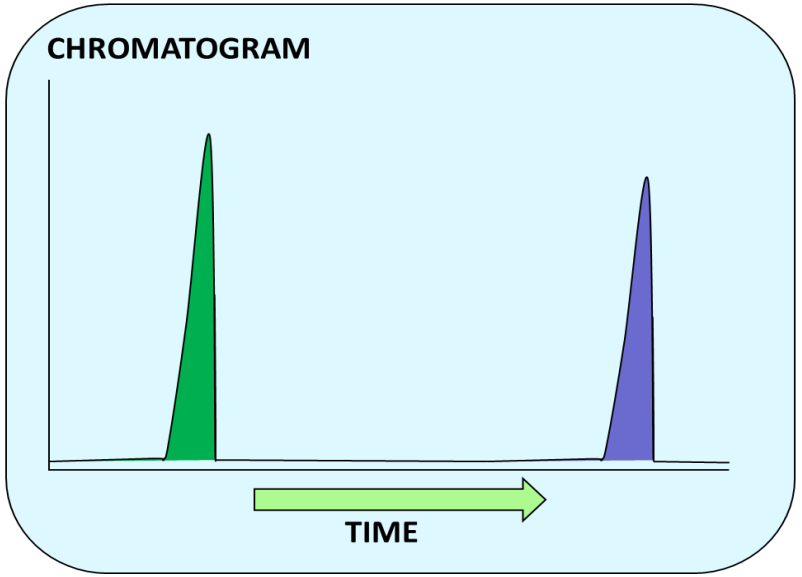
2 – Chromatographic LogD @ 3 pHs

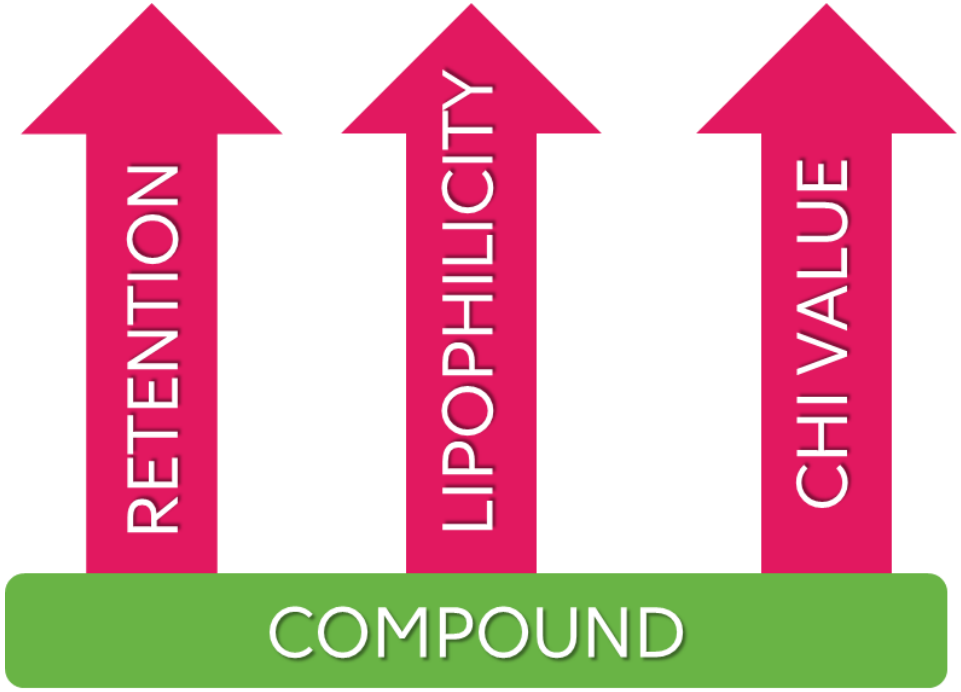
How is it measured?

Chromatographic retention (Rt) on a non-polar stationary phase using aqueous mobile phase shows good correlation with compound's lipophilicity.





Retention time is converted to **Chromatographic Hydrophobicity Index (CHI)**



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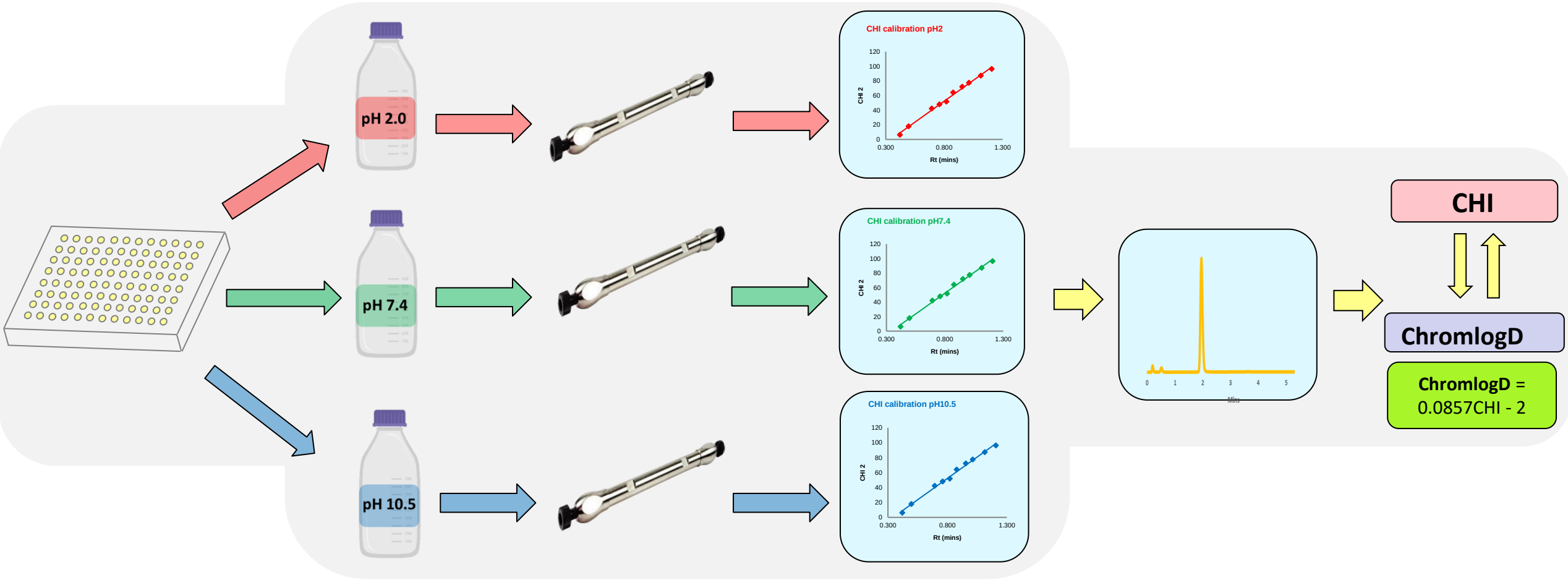
How is it measured?



Compounds injected into HPLC alongside a **calibration test mix**

A calibration graph is produced at each pH.

Retention time is converted into a CHI value using calibration parameters.

CHI is converted to a log scale, **ChromlogD**

Producing High-Quality Data: **System Suitability Checks**

	CHI PH2 Original	CHI PH2 this run	CHI PH7.4 Original	CHI PH7.4 this run	CHI PH10.5 Original	CHI PH10.5 this run	Acid/Base Character	Difference		
Carbamazepine	59.60	61.35	60.20	61.02	60.15	58.76	**Neutral**	1.75	0.82	-1.39
Budenoside	80.00	82.64	77.79	79.23	79.45	79.24	**Neutral**	2.64	1.44	-0.21
Warfarin	82.94	83.98	43.94	43.68	31.17	31.95	**Acidic**	1.04	-0.25	0.77
Ketoprofen	75.14	76.28	41.49	41.60	34.82	34.75	**Acidic**	1.13	0.11	-0.07
Indomethacin	90.47	91.82	55.30	56.08	48.12	47.06	**Acidic**	1.35	0.78	-1.06
Haloperidol	38.25	39.68	69.61	70.46	94.45	94.47	**Basic**	1.44	0.85	0.02
Chlorpromazine	43.52	46.54	85.48	87.24	127.64	128.11	**Basic**	3.02	1.76	0.47
Nicardipine	40.88	43.60	104.58	105.02	109.33	109.58	**Basic (weak)**	2.72	0.44	0.25

CHI data should be within +/- 5 of the original data

Calibration curve	CHI PH2 before	CHI PH2 after	CHI PH7.4 before	CHI PH7.4 after	CHI PH10.5 before	CHI PH10.5 after
Slope	122.38	121.90	**109.72**	109.79	121.88	122.21
Intercept	-44.27	-43.74	**-34.22**	-34.09	-43.50	-43.69
R2	0.9942	0.9943	0.9948	0.9949	0.9933	0.9933

R^2 should be greater than 0.985

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Why is it measured?

- ✓ Quick assessment of the **acid/base character** of a compound
- ✓ LogP of the unionised form
- ✓ **Lipophilic Ligand Efficiency (LLE)**
- ✓ Property Forecast Index (PFI)

LE = (1.37 x pIC_{50})/HA
LLE = pIC_{50} - LogP or LogD
where HA is the number of heavy (nonhydrogen) atoms
pIC_{50} is the activity/potency

2 – ChromlogD @ 3 pHs

Property Forecast Index (PFI) parameter forecasts potential developability issues

PFI = $ChromlogD_{7.4}$ + Number of Aromatic Rings

TABLE 2

Percentages of compounds achieving defined target values in the various developability assays categorised by PFI or iPFI bins[a]

	PFI = mChrom log $D_{pH7.4}$ + #Ar								
Assay / target value	<3	3-4	4-5	5-6	6-7	7- 8	8-9	9-10	>10
Solubility >200 μM	89	83	72	58	33	13	5	3	2
%HSA <95%	88	80	74	64	50	30	17	8	4
2C9 pIC_{50} <5	97	90	83	68	48	32	23	22	38
2C19 pIC_{50} <5	97	95	91	82	67	52	42	42	56
3A4 pIC_{50} <5	92	83	80	75	67	60	58	61	66
Cl_{int} <3 ml/min/kg	79	76	68	61	54	42	41	39	52
Papp >200 nm/s	20	30	46	65	74	77	65	50	33
	iPFI = mChrom log P + #Ar								
hERG pIC_{50} <5 (+1 charge)	86	93	88	70	54	36	29	21	11
Promiscuity <5 hits with pIC_{50} >5	85	78	74	65	49	30	20	13	7

[a] Colouring refers to the % chance of achieving benchmark value in that PFI bin: green, ≥67%; yellow, 34–67%; and red, <33%.

PFI <7 = less developability issues

Optimise ChromLogD7.4

↓

Better PFI

↓

Less Developability issues

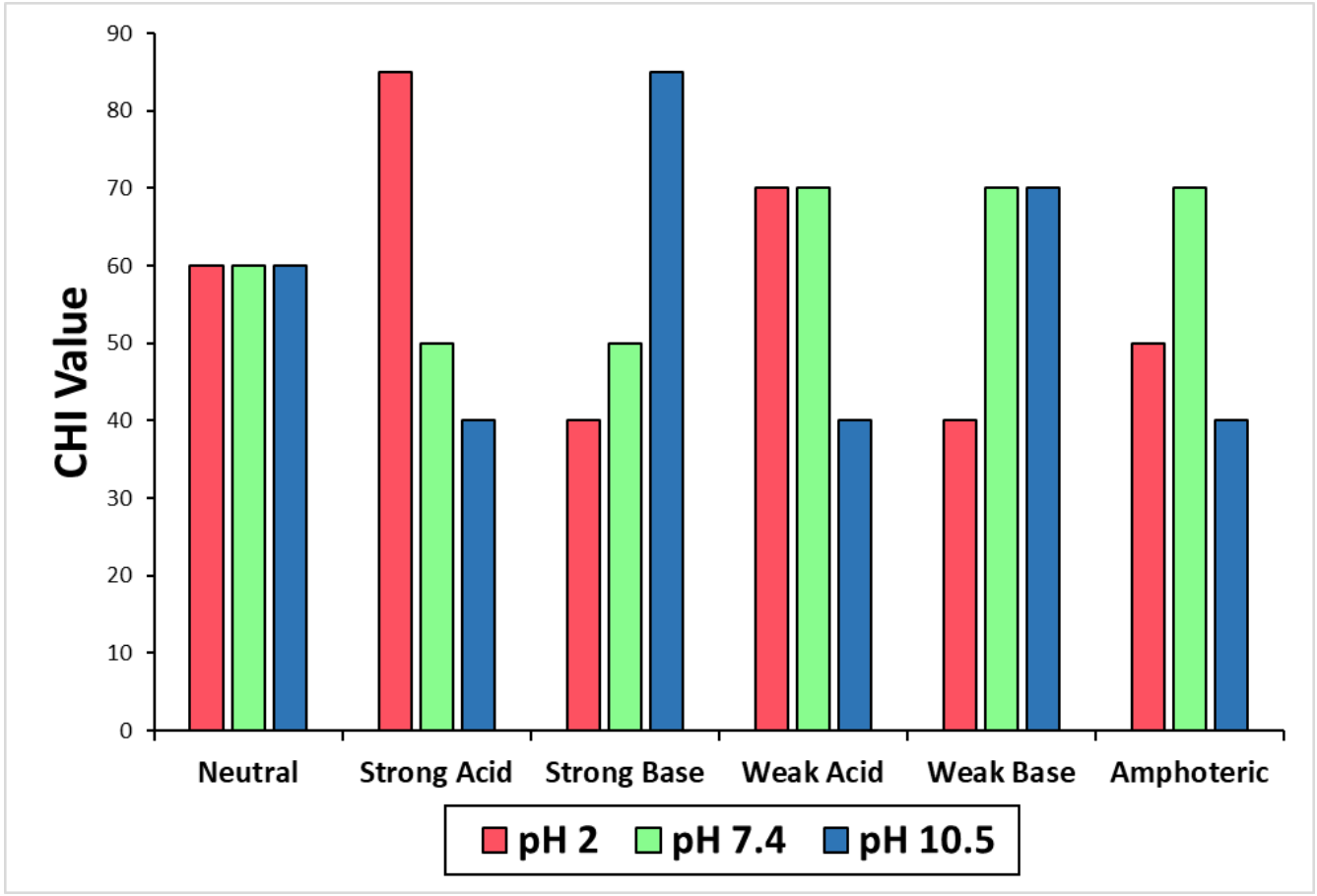
Robert J. Young, Darren V.S. Green, Christopher N. Luscombe, Alan P. Hill; Getting physical in drug discovery II: the impact of chromatographic hydrophobicity measurements and aromaticity Drug Discovery Today, Volume 16, Issues 17–18, September 2011, Pages 822–830

Acid/Base Classification

Compounds can be categorised using CHI values

- **Acid**
- **Base**
- **Weak Acid**
- **Weak Base**
- **Neutral**
- **Amphoteric**

- **Prediction of Acid/Base character without the need of a structure**



Comparison of Measured pKa with CHI Acid/Base Classification

Compound ref	Measured CHI			CHI Acid/Base Classification	Measured pKa*	
	pH 2.0	pH 7.4	pH 10.5		pKa (most acidic)	pKa (most basic)
1	9	49	47	Weak Base		7.0
2	28	51	51	Weak Base		4.0
3	16	36	67	Basic		10.0
4	17	39	83	Basic		9.9
5	94	91	73	Weak Acid	8.4	
6	66	63	44	Weak Acid	8.1	
7	100	58	52	Acidic	3.7	
8	81	54	47	Acidic	3.7	
9	46	63	53	Amphoteric	4.7	8.8
10	46	60	49	Amphoteric	4.6	9.2

*pKa data measured using the Sirius T3 Titrator (manufactured by Pion)

Comparison of Measured pKa with CHI Acid/Base Classification

Compound ref	CHI Acid/Base Classification	Measured pKa		Predicted pKa*	
		pKa (most acidic)	pKa (most basic)	pKa (most acidic)	pKa (most basic)
1	Weak Base		7.0		9
2	Weak Base		4.0		2.9
3	Basic		10.0		9.7
4	Basic		9.9		10.1
5	Weak Acid	8.4		9.6	
6	Weak Acid	8.1		9.9	
7	Acidic	3.7		2.9	
8	Acidic	3.7		3.1	
9	Amphoteric	4.7	8.8	3.6	8.8
10	Amphoteric	4.6	9.2	3.6	8.6

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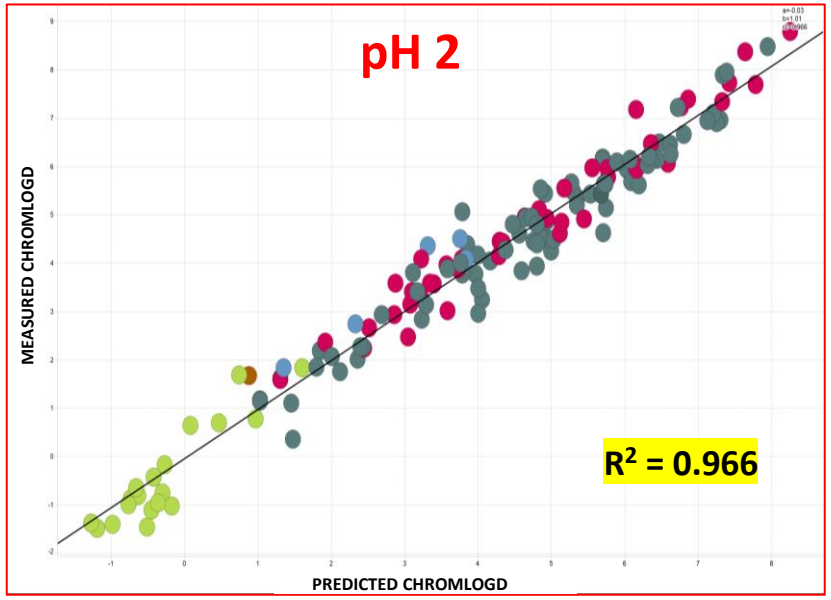
*Predicted using ChemAxon v.18.4.11

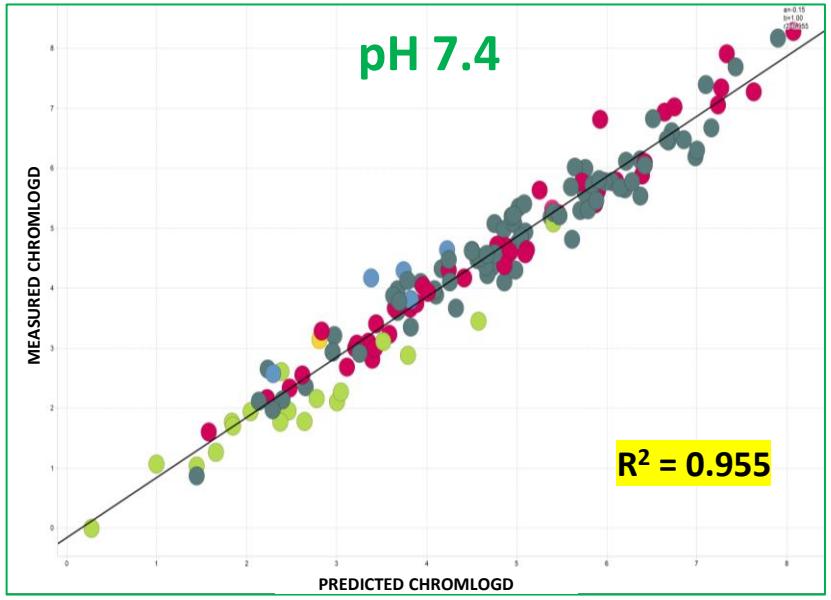
3 – *in silico* ChromlogD models

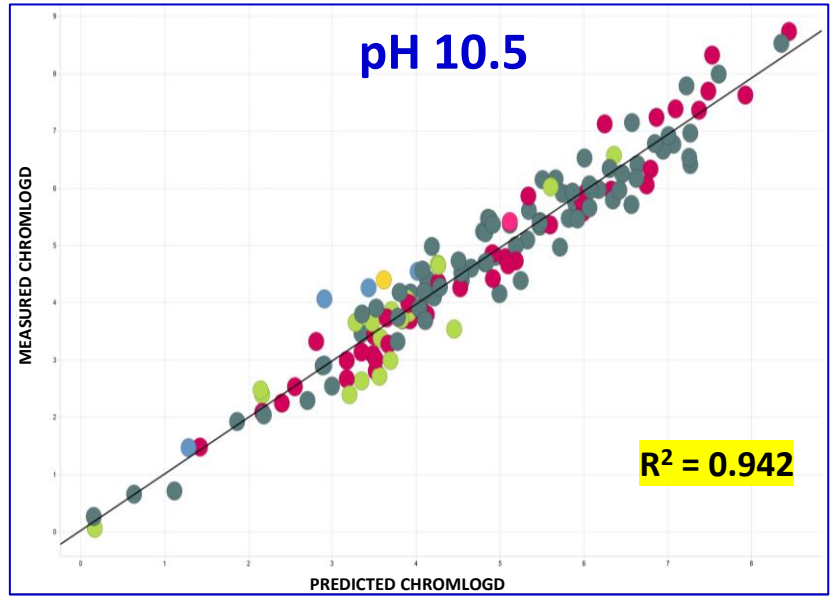
How are they generated?

GSK's "Predict First" Aspiration

- Predictive tools of the physchem properties using AI/ML
- *In-silico* models of ChromlogD at 3 pHs (2.0, 7.4, 10.5)
- Built in collaboration with our Computational Chemists using in house measured ChromlogD data







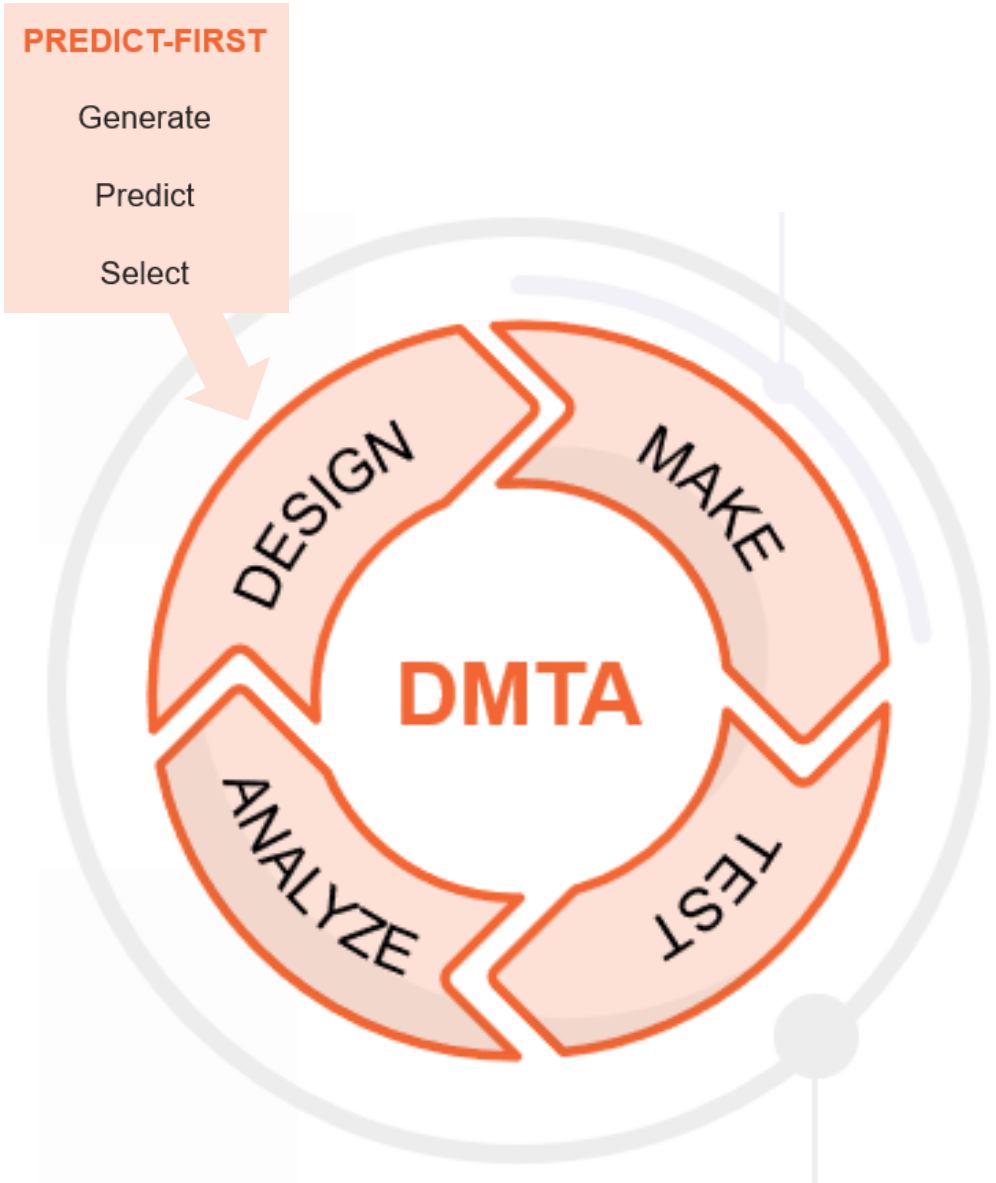
How are they utilised?

WITHIN THE WIDER ORGANISATION

- Used to estimate properties of novel molecules
- Predict behaviour of compounds allowing potential liabilities to be addressed
- Ranking compounds

WITHIN THE PHYSCHEM TEAM

- Comparison of measured and predicted ChromlogD data
- Used for data validation by detecting anomalous data



How are they utilised?

Input SMILES into models

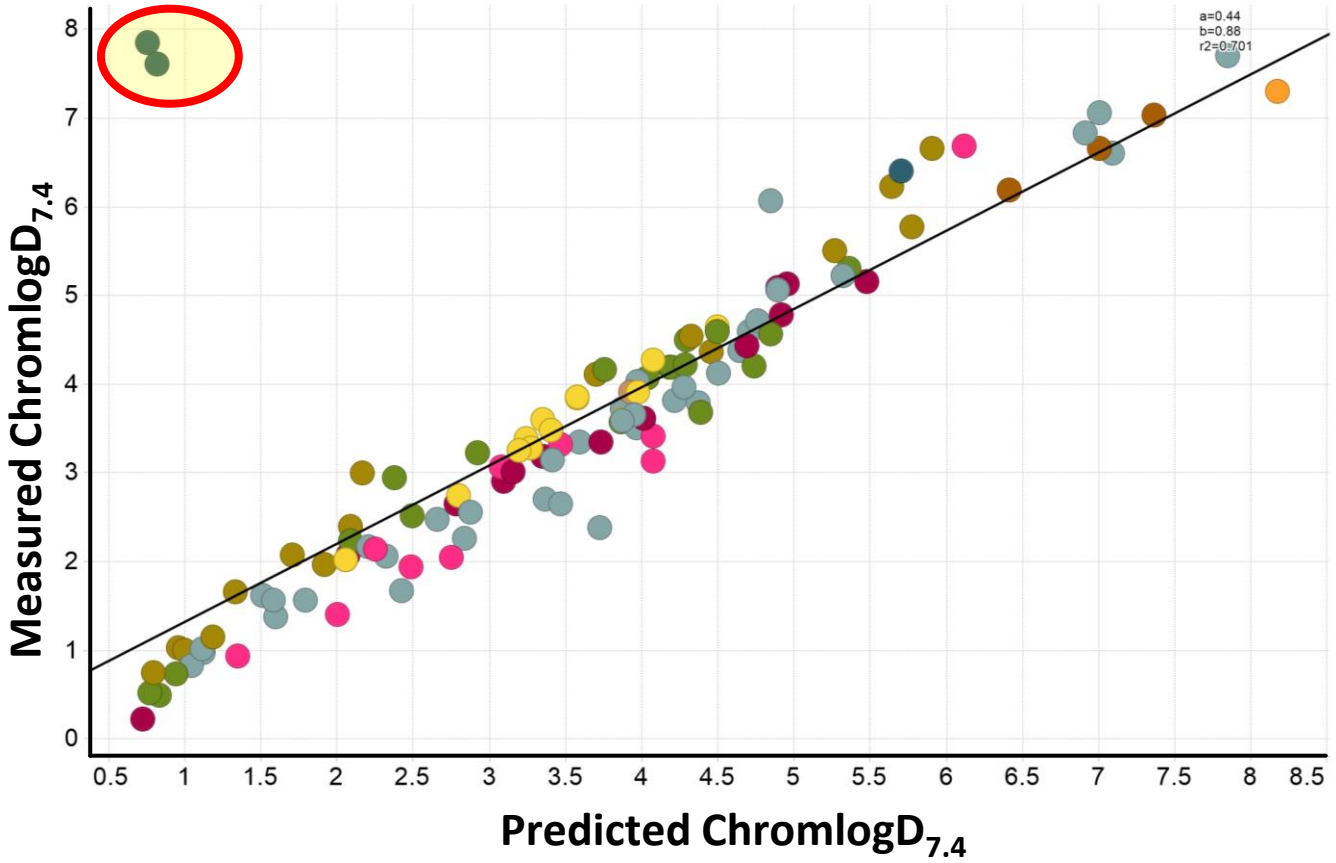
Generate predicted data

Compare measured & predicted data

Spot anomalous data

Check raw data & correct errors

Generate SMILES or Structure



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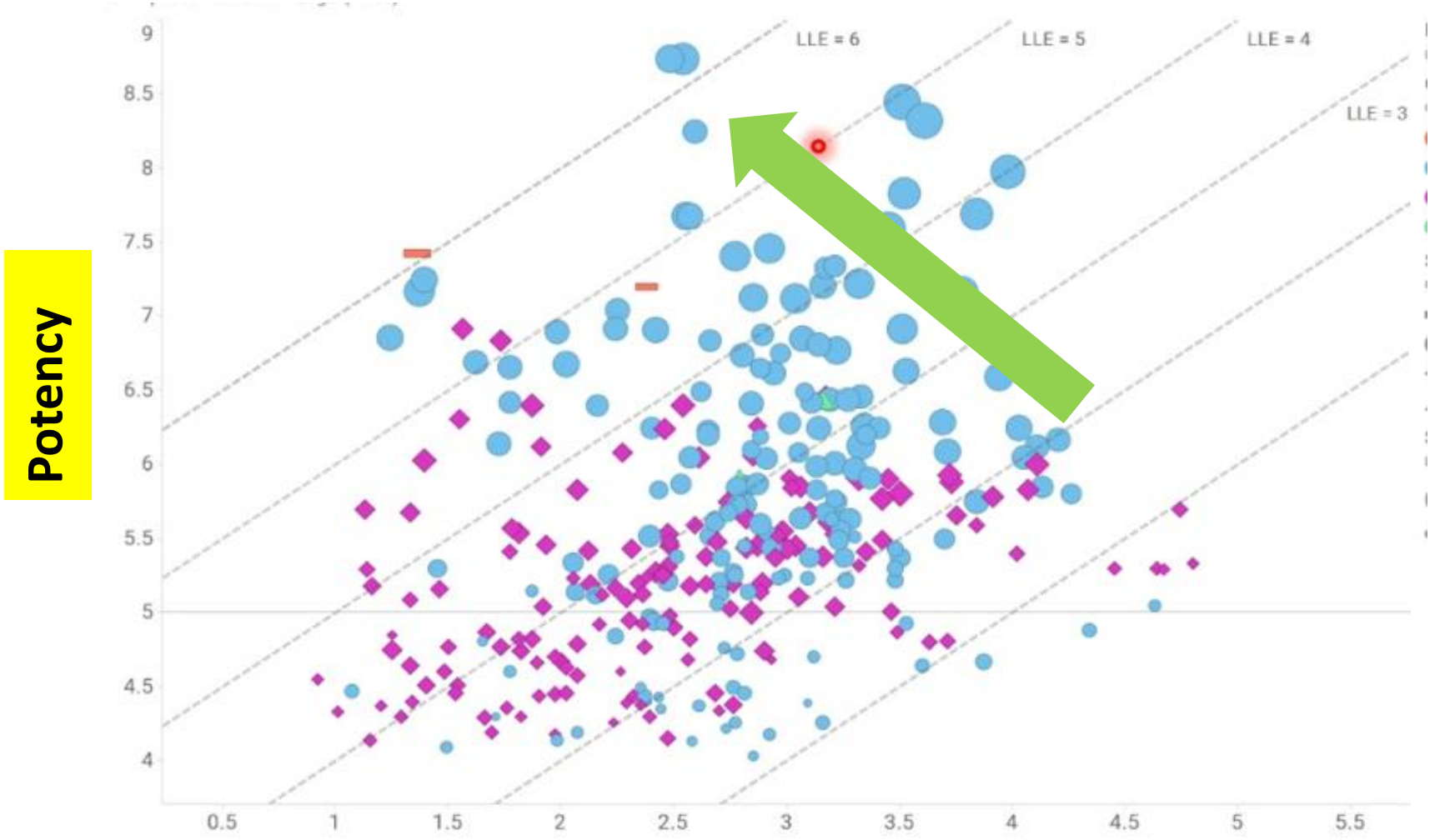
4 – Impact of ChromlogD measurements

Progression of a Program Series using LLE



Colour by:

Purple: C2MC

Blue: H2L

Size by LE Target:

LE>0.3

LLE>3

Objective: Higher potency, lower lipophilicity

LLE = pIC $_{50}$ - LogP or LogD

pIC $_{50}$ is the activity/potency

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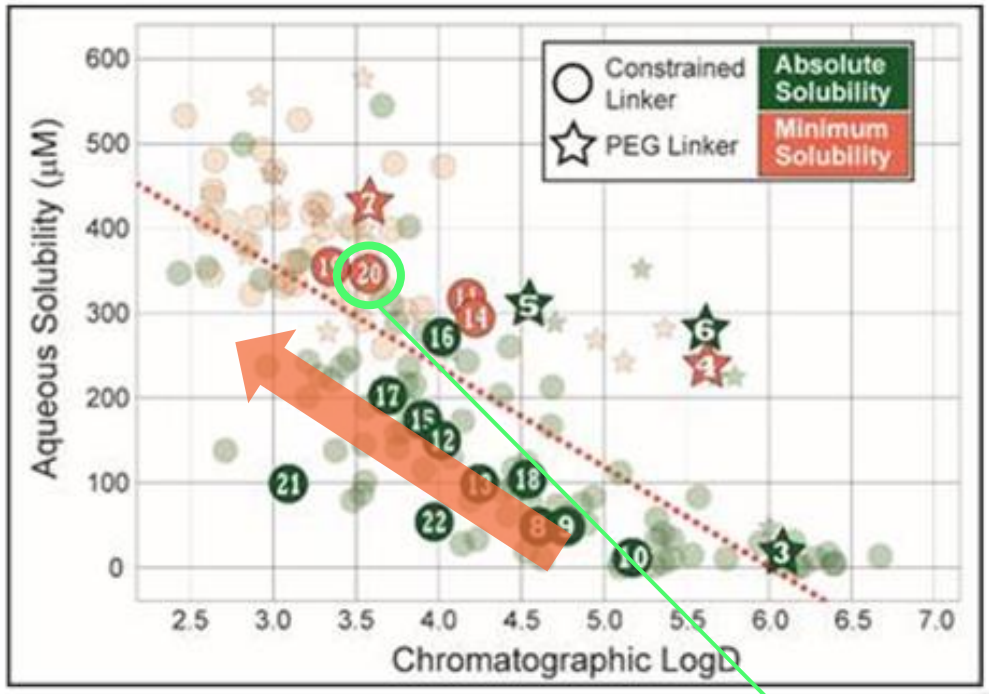
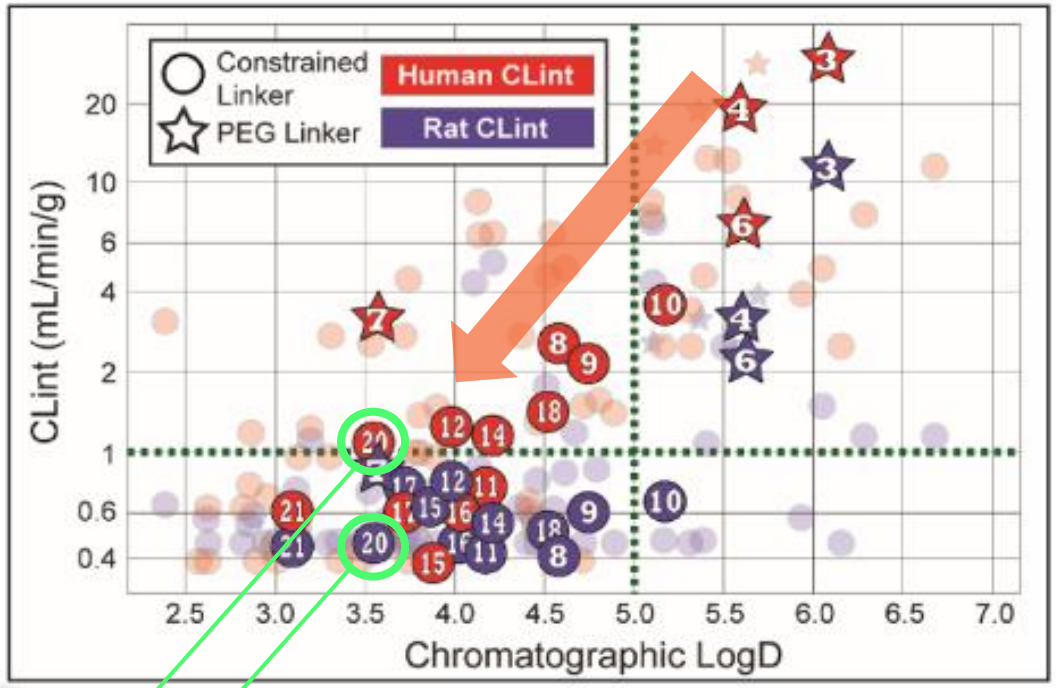
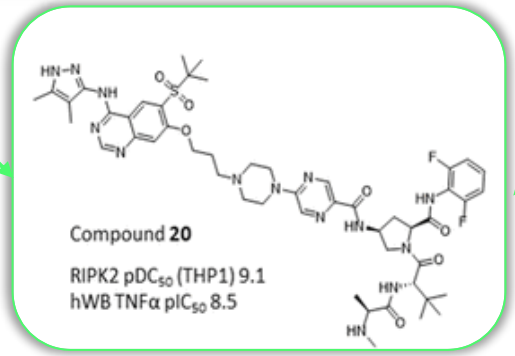
PROTAC Optimisation Strategy







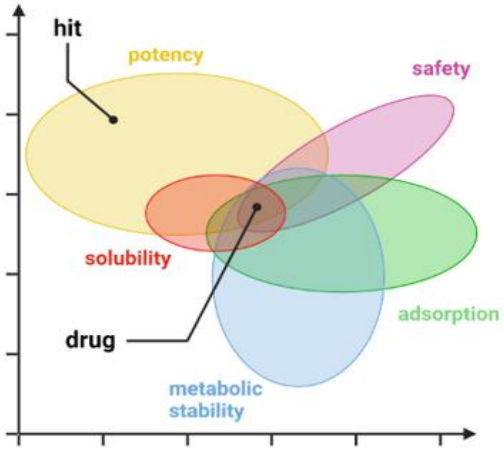
Compound with the desired profile of good solubility and both low rat and human clearance

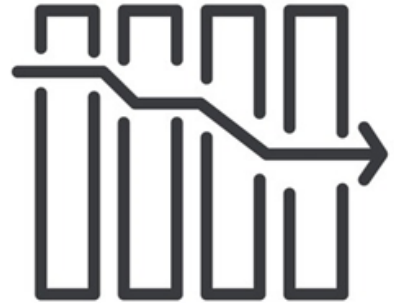
PROTAC (Proteolysis Targeting Chimera)

Optimization of a Series of RIPK2 PROTACs, A. H. Miah *et al, J. Med. Chem. 2021, 64, 17, 12978–13003*

5 – Conclusions

Key Messages





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PHYSCHEM
GSK

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Klis Ramdeen-Lessey

Paul Gurton

Rob Armstrong

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Thank you for listening!

Any questions?

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Further Reading

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