



Helping Medicinal Chemists Identify New Opportunities during Lead ID and Optimisation

Turning high quality data into actionable insights

Streamlining Drug Discovery

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The current challenges faced by the drug development industry are significant

nature
REVIEWS
DRUG
DISCOVERY

Opinion | Published: 01 March 2012

Diagnosing the decline in pharmaceutical R&D efficiency

Jack W. Scannell, Alex Blanckley, Helen Bordon &

Nature Reviews Drug Discovery **11**, 191–200 (2012)

The productivity crisis in pharmaceutical R&D

Fabio Pammolli, Laura Magazzini & Massimo Riccaboni

Nature Reviews Drug Discovery **10**, 428–438 (2011) | [Download Citation](#)

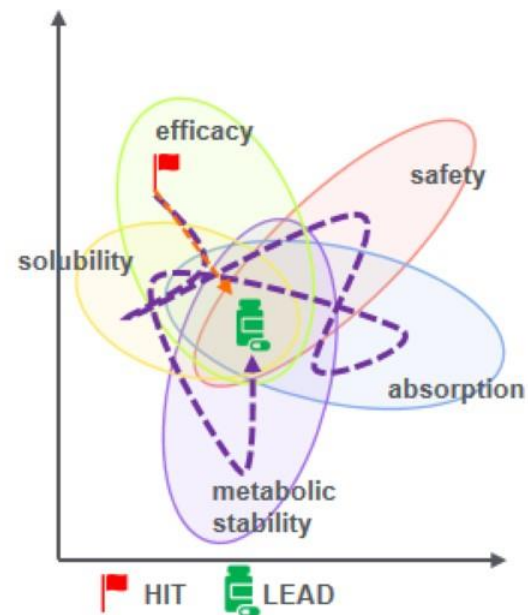
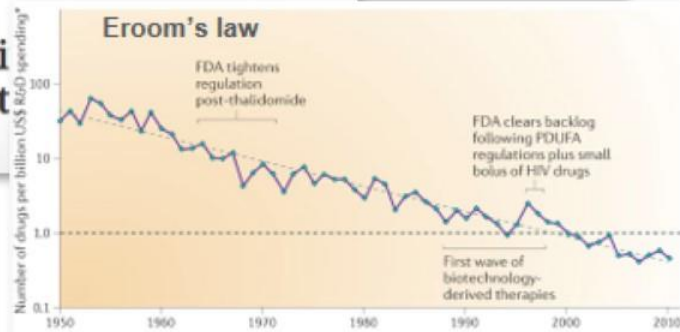
Expert Opinion on Drug Discovery >

Volume 1, 2006 - Issue 2

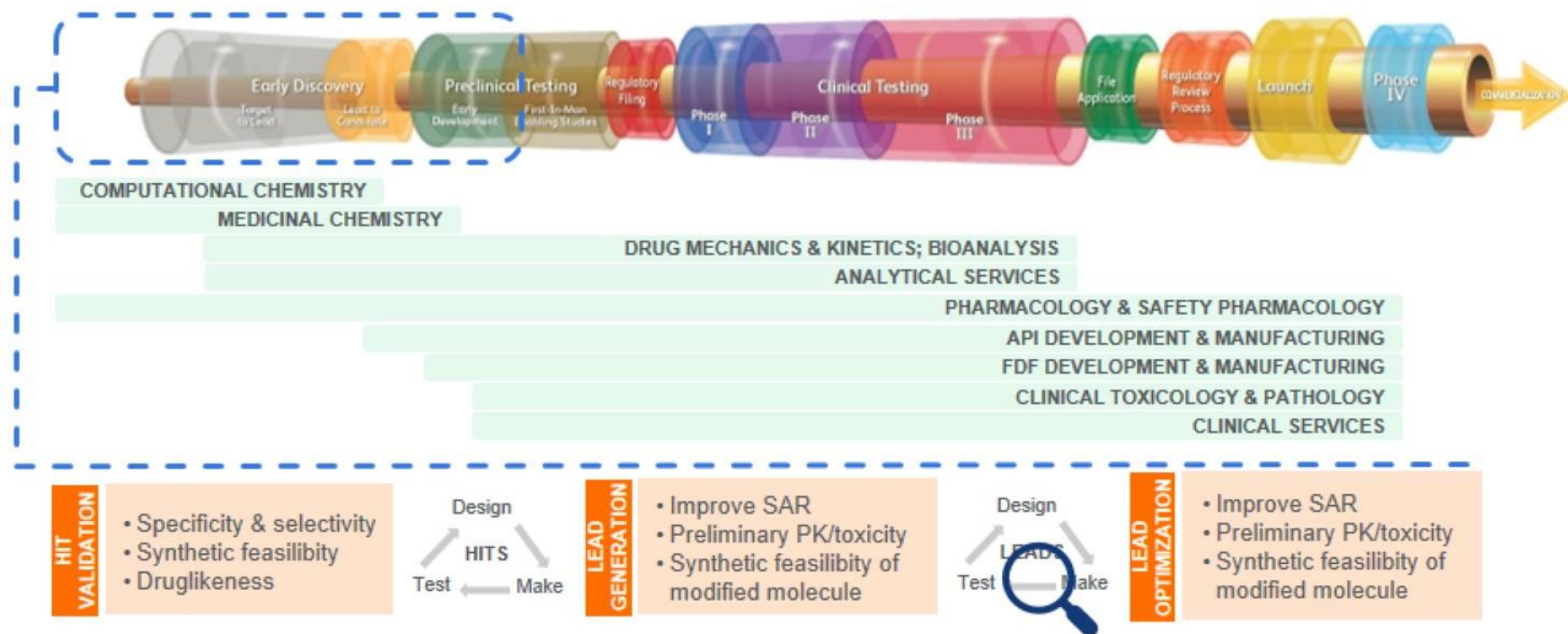
Why has R&D productivity in the pharmaceutical industry declined?

Robert R. Ruffolo

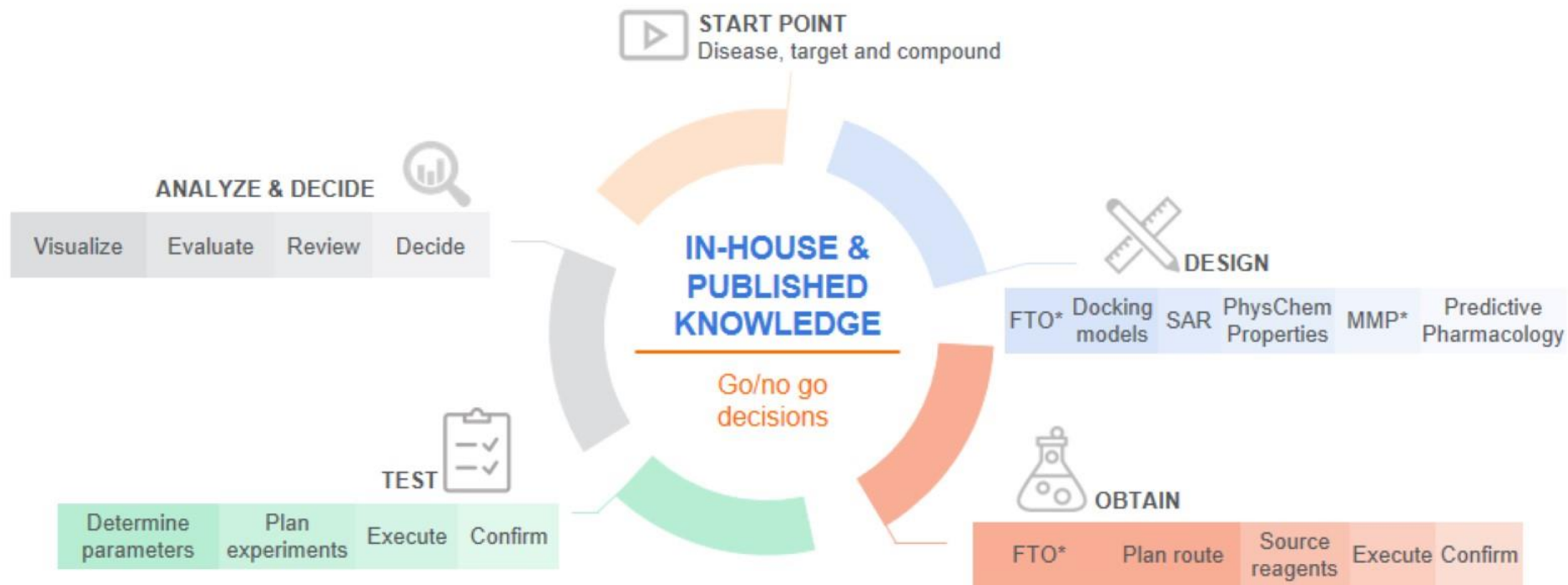
Pages 99–102 | Published online: 10 Jul 2006



The requirements for effective drug discovery are complex and command a multi-disciplinary approach



Drug design cycle leads to optimized candidates, but necessitates both in-house and published knowledge and data



The challenge in answering questions of the drug design cycle is finding, connecting and using specific knowledge



Reaxys aims to deliver actionable answers during the drug design cycle

Reaxys

- An integrated solution that augments understanding and catalyzes action in drug development
- One source of advanced approaches and best practices to reduce attrition
- Designed to help researchers identify and progress drug candidates as quickly and as safely as possible



The screenshots display the Reaxys web application. The top panel shows a search bar and navigation tabs. Below, a list of search results is shown, including 'Substances', 'Targets', and 'Reactions'. Each result includes a chemical structure and a 'View Results' button. A larger window in the foreground shows a detailed view of a reaction scheme with chemical structures and reagents.

REAXYS & RMC

DESIGN	Docking models	Excellent support
	SAR	Good/fair support
	Properties	Limited support
	MMP	Currently under development
OBTAIN	Predictive pharmacology	Good/fair support
	Plan route	Excellent support
	Source reagents	Good/fair support
	Execute	NA
TEST	Confirm	Excellent support
	Determine parameters	Good/fair support
	Plan experiments	Good/fair support
	Execute	NA
ANALYZE	Confirm	Excellent support
	Visualize	Good/fair support
	Evaluate	Excellent support
	Review	Good/fair support
	Decide	NA

- Excellent support
- Good/fair support
- Limited support
- Currently under development

Building next generation predictive capabilities using clean and linked data from Reaxys

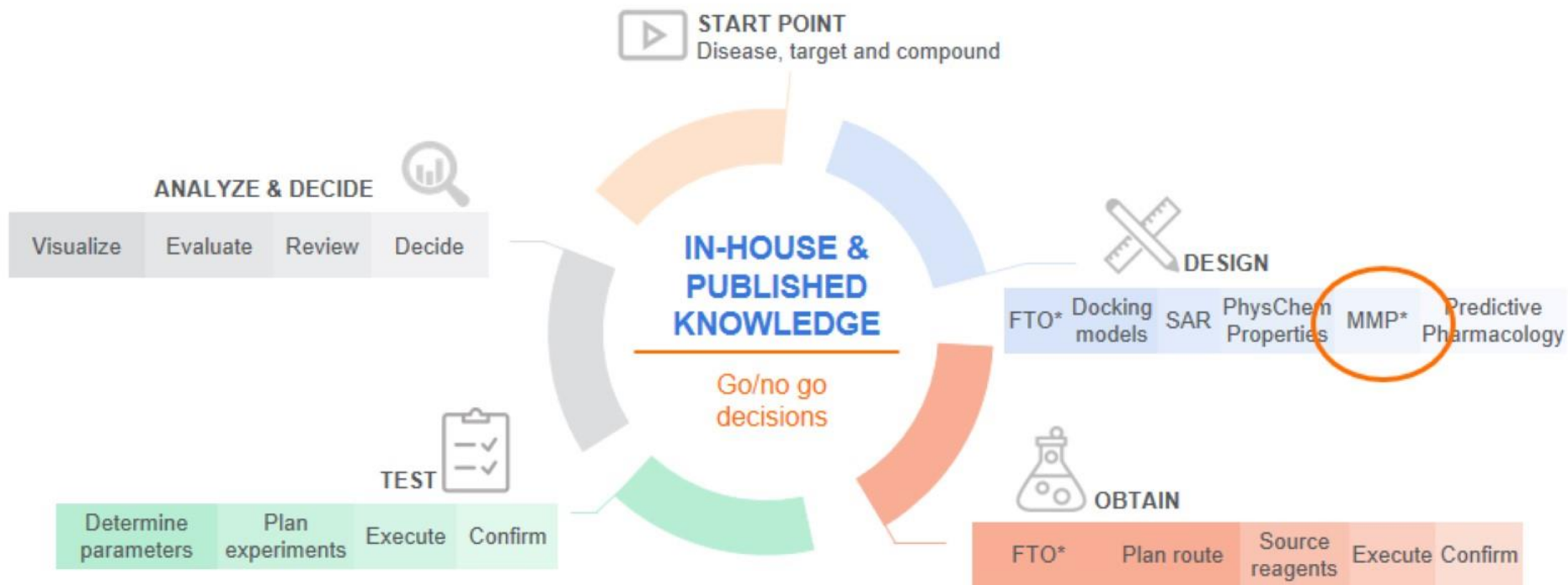
Vas Narasimhan, CEO of Novartis AG

"The first thing we've learned is the importance of having outstanding data to actually base your ML on. In our own shop, we've been working on a few big projects, and we've had to spend most of the time just cleaning the data sets before you can even run the algorithm. That's taken us years just to clean the datasets. I think people underestimate how little clean data there is out there, and how hard it is to clean and link the data."

Forbes, Jan 2019



Using data from Reaxys we want to strengthening our support for the drug design cycle



Typical problems in lead optimization

Optimizing PK and ADME properties



“A part of my current lead structure is thought to be responsible for poor cell permeability. My plan is to **replace this substructure** with something that is:

- a) chemically feasible and
- b) likely keeping the activity against the primary target.”

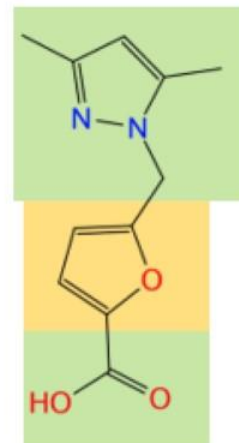
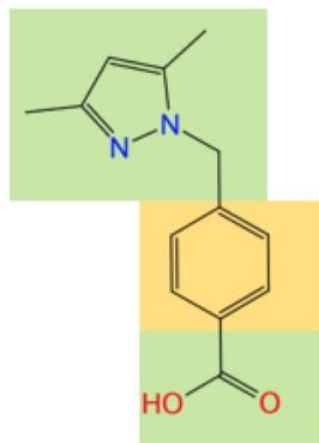
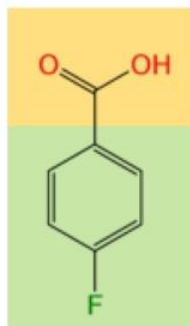
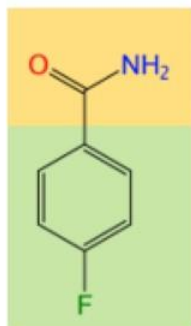
Researchers must identify, optimize and make lead compounds with **less PK and ADME issues** whilst **maintaining high affinity** for the identified target.

Critical to understand is **how to best modify a compound to achieve desired activity, PK or PD properties**

“What should we make next?”

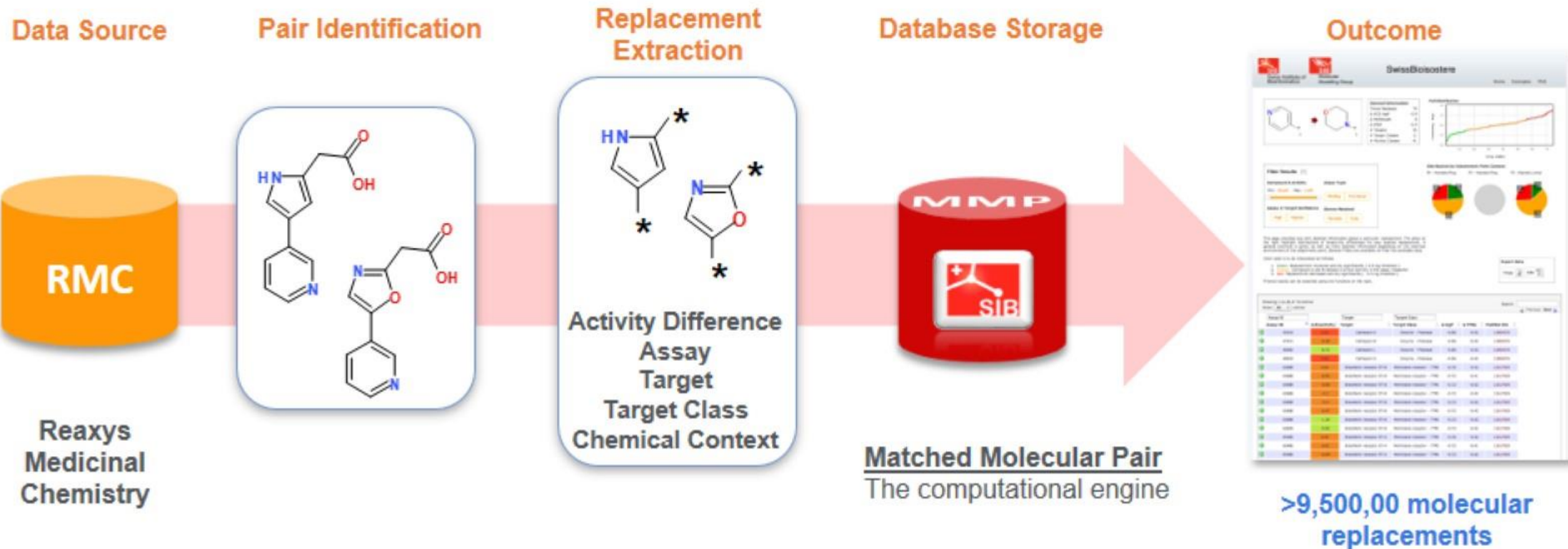
Matched Molecular Pair (MMP) analysis

Pairs of compounds with a small sub-structural exchange

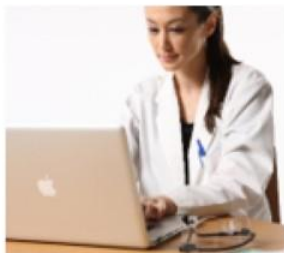


Used to understand the impact of sub-structural replacements on a given parameter of interest – particularly popular with bioactivity data

Matched Molecular Pair (MMP) analysis – a collaboration with the Swiss Institute of Bioinformatics using RMC data



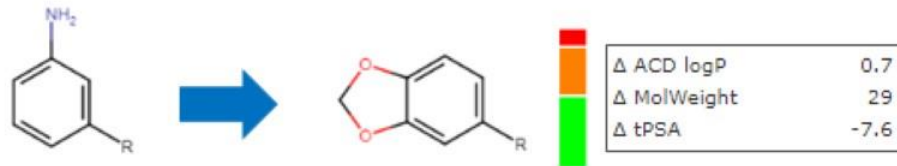
RMC data derived Matched Molecular Pair web application – user feedback



Medicinal Chemist in Pharma

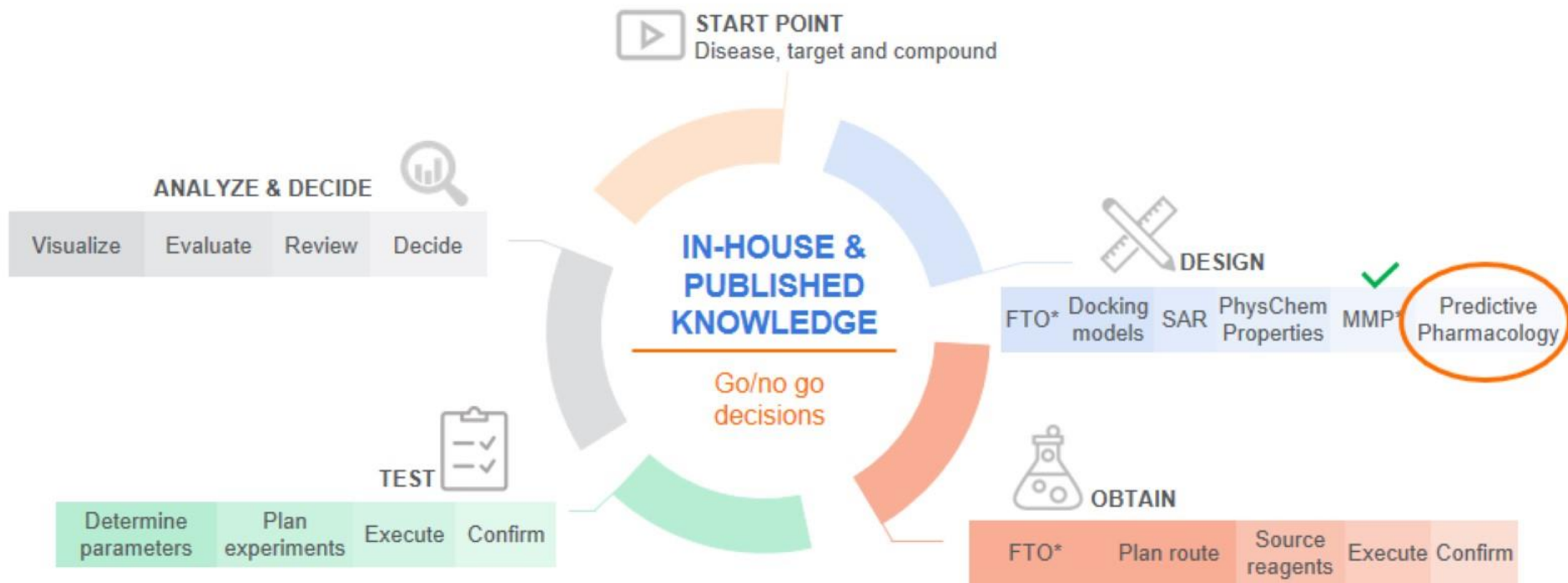
- Used on a current drug design project
 - “Gave me new ideas and helped creativity”
 - New ideas were handed to my computational chemistry colleagues for docking and initiated further discussion
- Expected impact on research decisions:
 - Extend chemical space due to larger knowledge base
 - Trigger decisions more quickly when identifying and evaluating good/bad replacements

Illustrative example:



1197662	-1.54	Cyclooxygenase-2	Enzyme	0.47	-7.36
Reaxys Compound_ID:	7725904	Reaxys Compound_ID:	7729355		
Activity [pIC50]:	5.23		6.77		
Structure:		→			

Using data from Reaxys we want to strengthening our support for the drug design cycle



Typical problems in lead optimization

Safety pharmacology issues



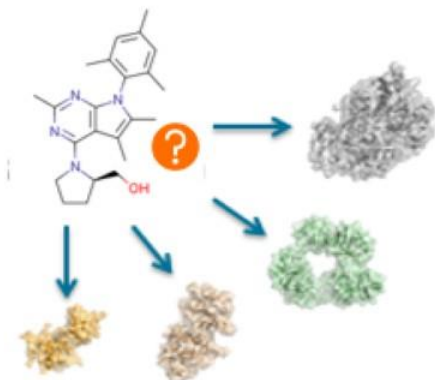
“I know my lead compound has good activity on my primary target but what other targets could it be active on? I need to understand if my compound could be responsible for any **unwanted effects** in a **safety assay**.”

Researchers must identify, optimize and make lead compounds with **less toxicity or safety pharmacology issues** whilst **maintaining high affinity** for the identified target.

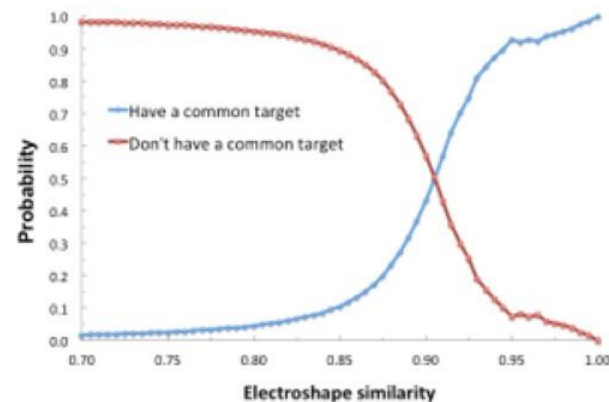
Critical to understand if a compound has potential to be active on **secondary targets** so that any **unwanted interactions/effects can be assessed and addressed**

“What can we expect from our compound?”

Target Prediction by molecular similarity



Assumption: if two molecules are very similar, they are more likely to be active on the same target



Target prediction (reverse screening):

Molecule with unknown target

Similarity

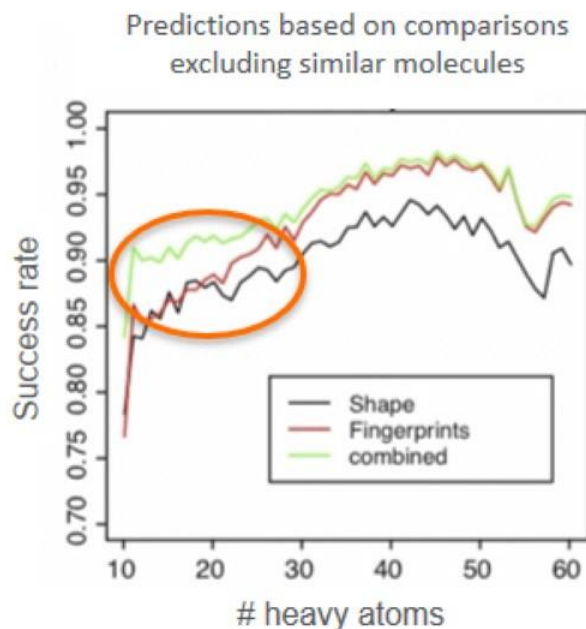
RMC

Library of molecules with known targets

List of possible targets

Target Prediction by molecular similarity

The dual scoring function, based on both 2D and 3D molecular similarity, gives high performing predictions



RMC data*

Unique small molecules	521,445
Datapoints	745,106
Total protein targets included (human, rat & mouse)	2,590

* Only compounds having activity < 10 nM

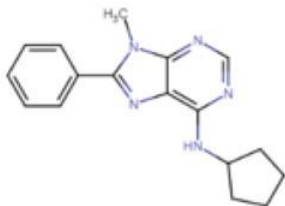
RMC data derived Target Prediction web application – user feedback



Medicinal Chemist in Pharma

- Used on a current drug design project
 - Looked for potential **off-target** pharmacology and assess safety
 - Used to **prioritise** targets to be included in kinase panel for screening
 - "I took the predictions into lab tests and I was very pleased with the results!"
- Expected impact on research decisions:
 - Would be used by research teams in idea and project **prioritisation**
 - Doing **drug safety tests much earlier** in the research process would help reduce surprises later on
 - Doing the tests on focused panels **saves costs**

Illustrative example:



Taken from Lambertucci *et al.*, *Eur. J. Med. Chem.* 151 (2018), 199-213 as an A1 adenosine receptor antagonist (K_i 2.8 nM)

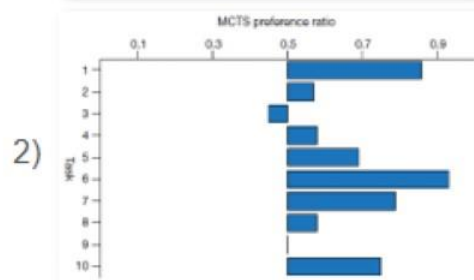
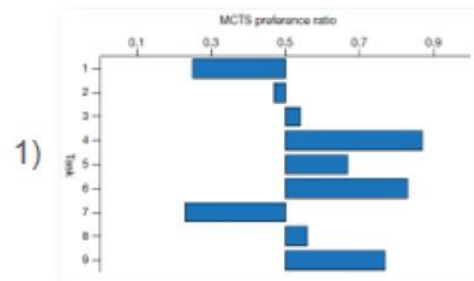
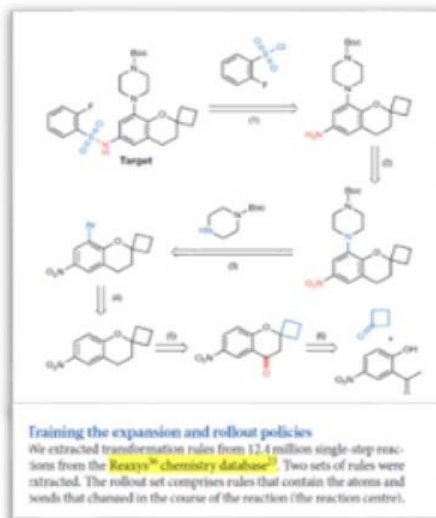
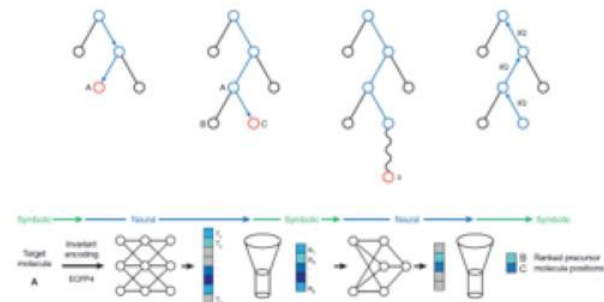
Target prediction					
Target	Compound name	Target ID	Target Class	Predictability	Report action (00/100)
Adenosine receptor A1	AC11000	P00074	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A2	AC11000	P00075	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A3	AC11000	P00076	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A4	AC11000	P00077	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A5	AC11000	P00078	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A6	AC11000	P00079	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A7	AC11000	P00080	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A8	AC11000	P00081	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A9	AC11000	P00082	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A10	AC11000	P00083	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A11	AC11000	P00084	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A12	AC11000	P00085	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A13	AC11000	P00086	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A14	AC11000	P00087	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A15	AC11000	P00088	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A16	AC11000	P00089	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A17	AC11000	P00090	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A18	AC11000	P00091	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A19	AC11000	P00092	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A20	AC11000	P00093	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A21	AC11000	P00094	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A22	AC11000	P00095	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A23	AC11000	P00096	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A24	AC11000	P00097	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A25	AC11000	P00098	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A26	AC11000	P00099	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A27	AC11000	P00100	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A28	AC11000	P00101	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A29	AC11000	P00102	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A30	AC11000	P00103	Adenosine receptor	<div><div></div></div>	100/100
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Adenosine receptor A32	AC11000	P00105	Adenosine receptor	<div><div></div></div>	100/100
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Adenosine receptor A34	AC11000	P00107	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A35	AC11000	P00108	Adenosine receptor	<div><div></div></div>	100/100
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Adenosine receptor A44	AC11000	P00117	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A45	AC11000	P00118	Adenosine receptor	<div><div></div></div>	100/100
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Adenosine receptor A49	AC11000	P00122	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A50	AC11000	P00123	Adenosine receptor	<div><div></div></div>	100/100
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Adenosine receptor A60	AC11000	P00133	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A61	AC11000	P00134	Adenosine receptor	<div><div></div></div>	100/100
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Adenosine receptor A97	AC11000	P00170	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A98	AC11000	P00171	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A99	AC11000	P00172	Adenosine receptor	<div><div></div></div>	100/100
Adenosine receptor A100	AC11000	P00173	Adenosine receptor	<div><div></div></div>	100/100

Using data from Reaxys we want to strengthening our support for the drug design cycle



Predictive Retrosynthesis: rewiring chemistry and redesigning synthetic routes

The challenge: Merck quotes that 55% of the time, a benchmarked catalytic reaction fails to deliver the desired product*. Therefore a radical and innovative step change in synthesis is needed.



*Science 02, Jan 2015

- 1) Performance vs literature routes
- 2) Performance vs other predictive models

Predictive Retrosynthesis: rewiring chemistry and redesigning synthetic routes

The solution: Reaxys will offer a new approach to retrosynthesis in 2019 using deep neural networks and symbolic AI in collaboration with Prof. Mark Waller. The new approach will extend syntheses of small organic molecules into predictive modeling of previously unpublished synthetic pathways

Retrosynthesis benefits...



Augment chemist knowledge

- Via scrutinization of millions of synthetic pathways and presenting a highly customized route to the researcher



Reduce time to discovery / development / synthesis

- Design successful synthesis pathway for novel molecules where previous attempts may have failed



Reduce cost

- Design improved lead series, reduce risk of late stage failure
- Design more efficient synthesis routes (improved yield, reduced production costs)



Support IP strategy

- Identify alternative synthesis routes to a patented route for a commercial product
- Identify novel synthesis routes for a new molecule

..leading to improved business outcomes



Improve speed to market

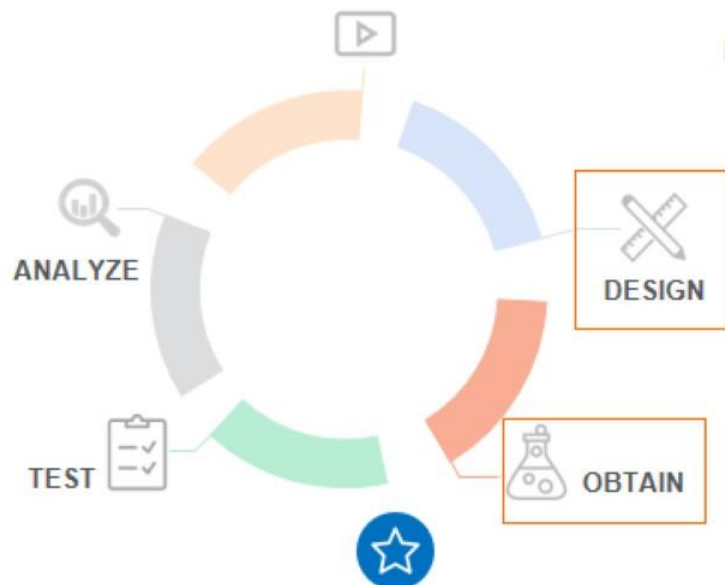


Embed / Leverage next-gen technology to out-compete



Increase productivity

Summary and outlook



Curated, clean, linked and normalized Reaxys/RMC data underpins all three applications

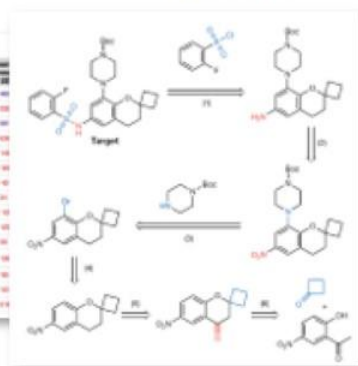
Matched Molecular Pair analysis



Target Prediction

Target	Compound name	Original ID	Target Class	Probability	Reaxys article ID
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%
Metastable receptor 10	4034349	4034349	Metastable receptor	100%	100%

Predictive Retrosynthesis

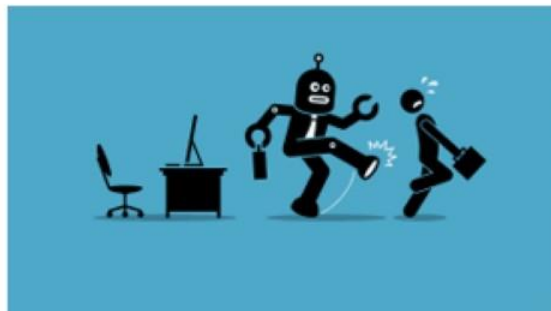


AI in pharma – high quality data will make a difference

Many emerging technologies so no “one size fits all”

Summary and Outlook

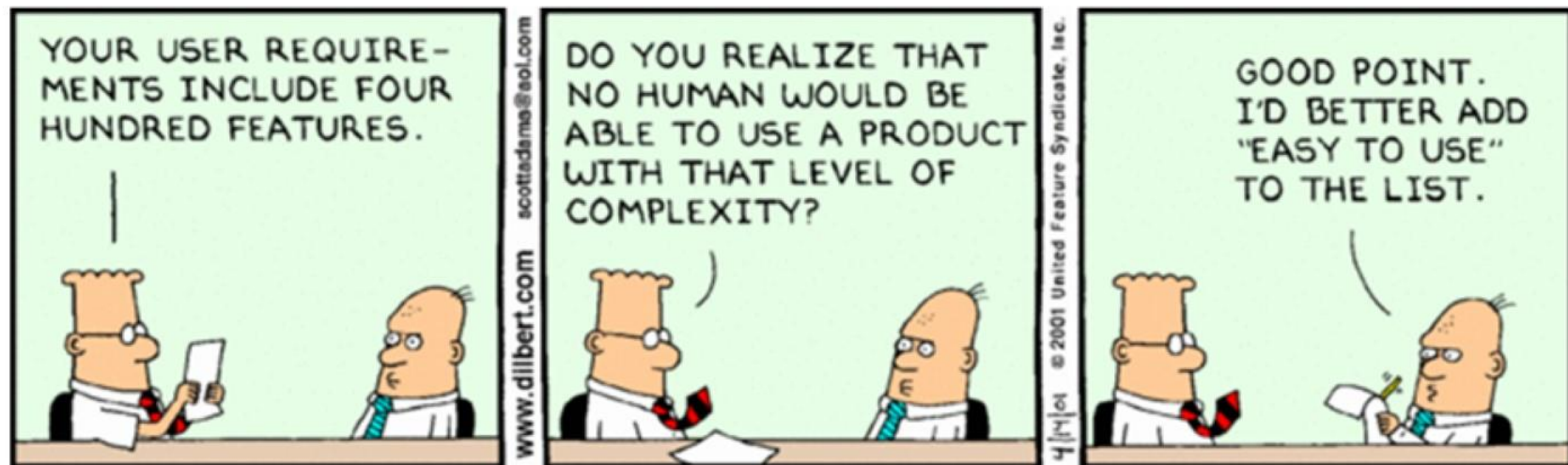
- Huge cultural challenge and change
 - Many chemists fear that AI/ML technologies will replace them



Our approach: AI/ML technology will assist chemists, not replace them!

Summary and Outlook

- Our challenge



Acknowledgments

Antoine Daina

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Bioinformatics



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Olivier Barberan

Ivan Kristic

Jürgen Swienty-Busch

Elena Herzog

Abhinav Kumar

Mark Waller

Marwin Segler



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r.sankey@elsevier.com

