Reaxys® Medicinal Chemistry

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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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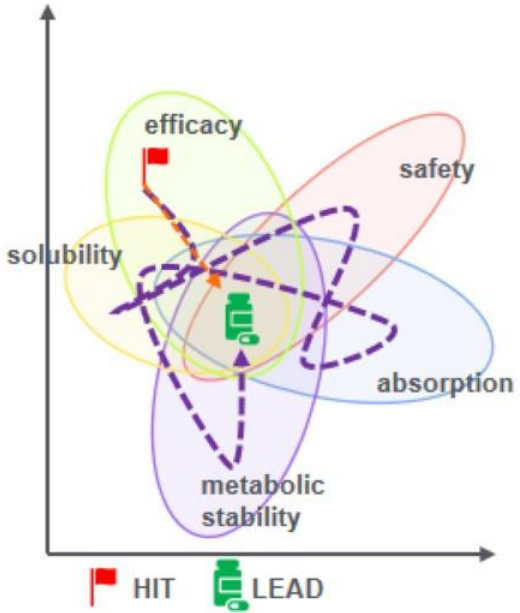
The current challenges faced by the drug development industry are significant



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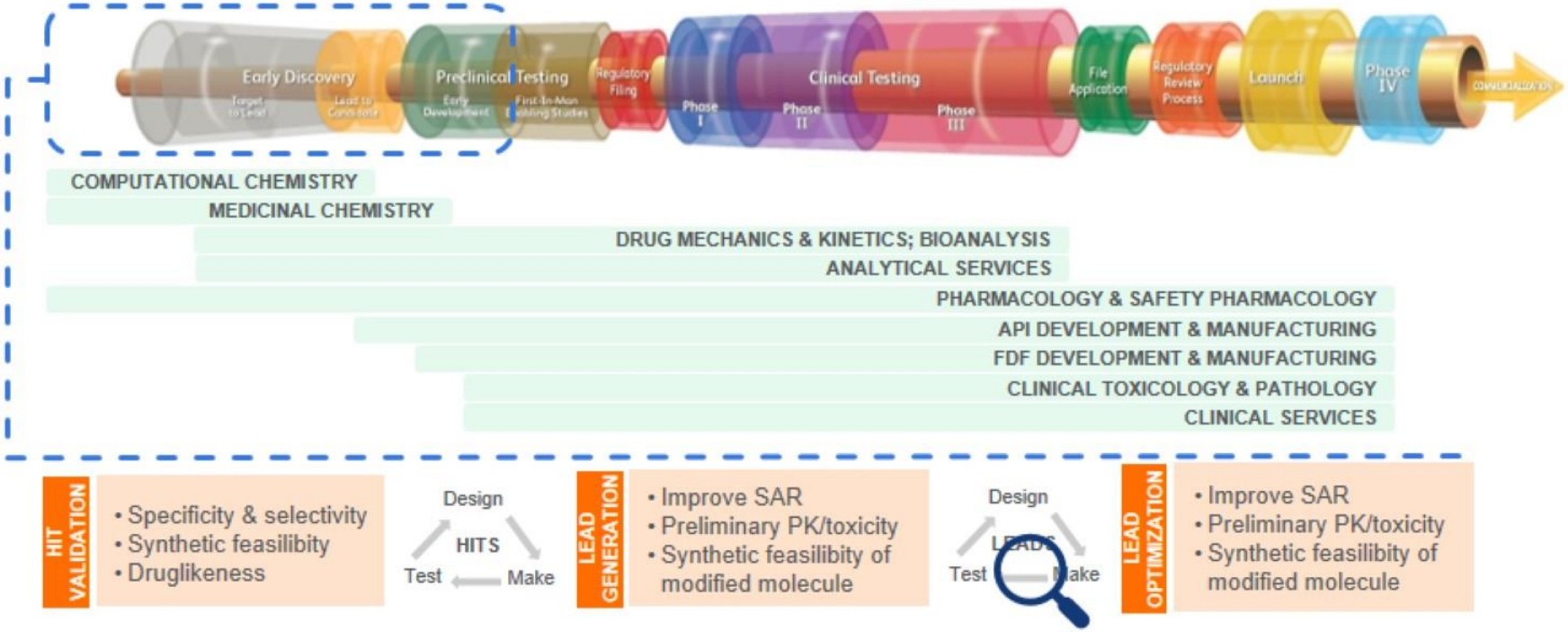
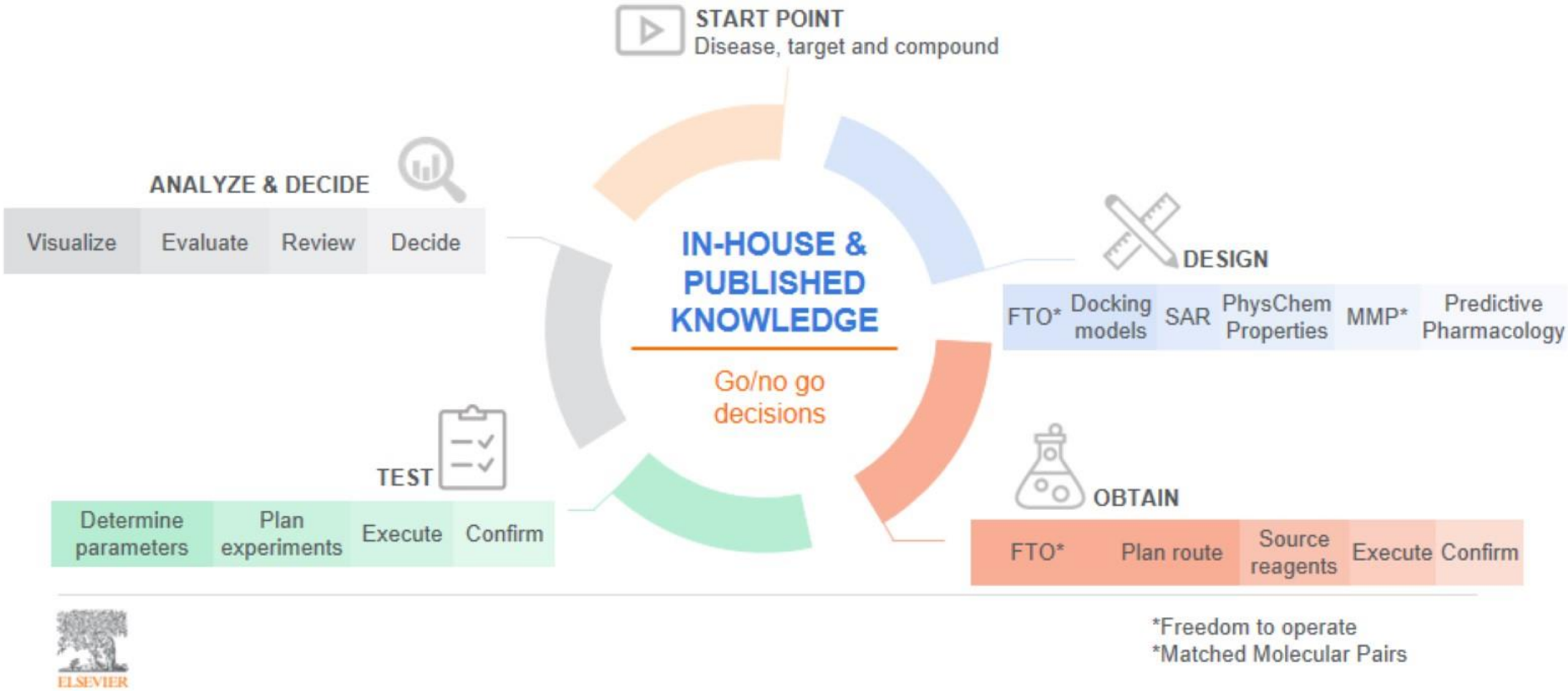
The requirements for effective drug discovery are complex and command a multi-disciplinary approach



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

Burj Khalifa
World's tallest tower

Yearly scientific publications

SIFT THROUGH INFORMATION
Too much to read and digest
Not discoverable or actionable

- **Discover** the data you need (needle in a haystack)
- Keep **up to date** with evolving research landscape
- Find reliable and reproducible data
- Be able to **connect** the information

Only using internal knowledge or personal experience can **restrict creativity**. How do we push ourselves to "think outside of the box"?

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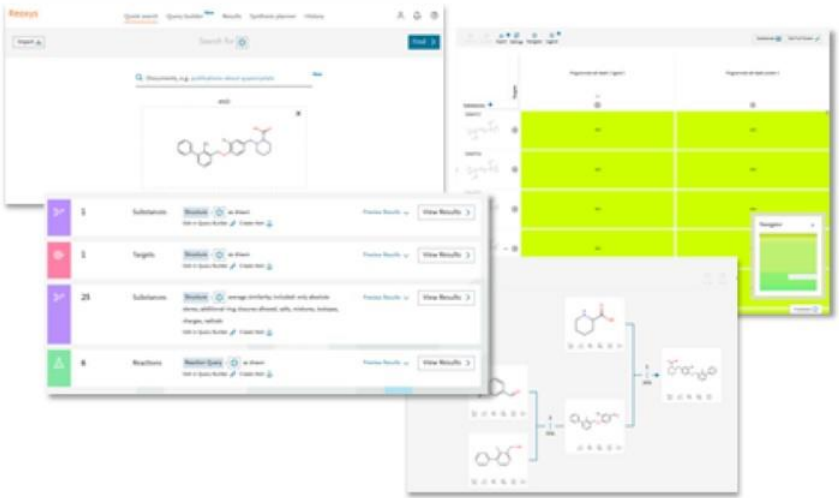
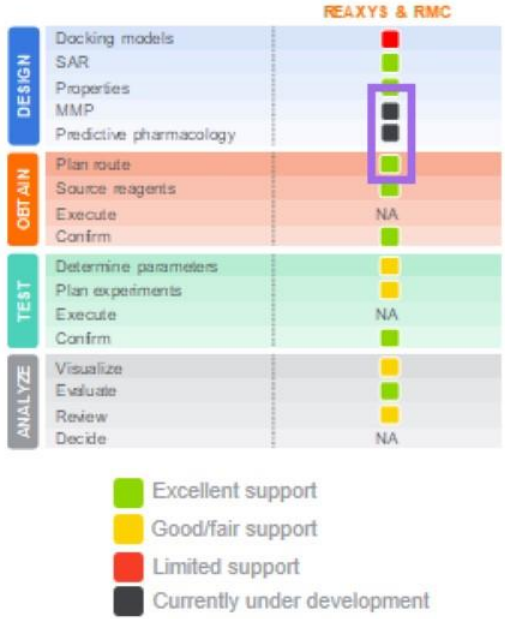
Reaxys aims to deliver actionable answers during the drug design cycle

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





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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

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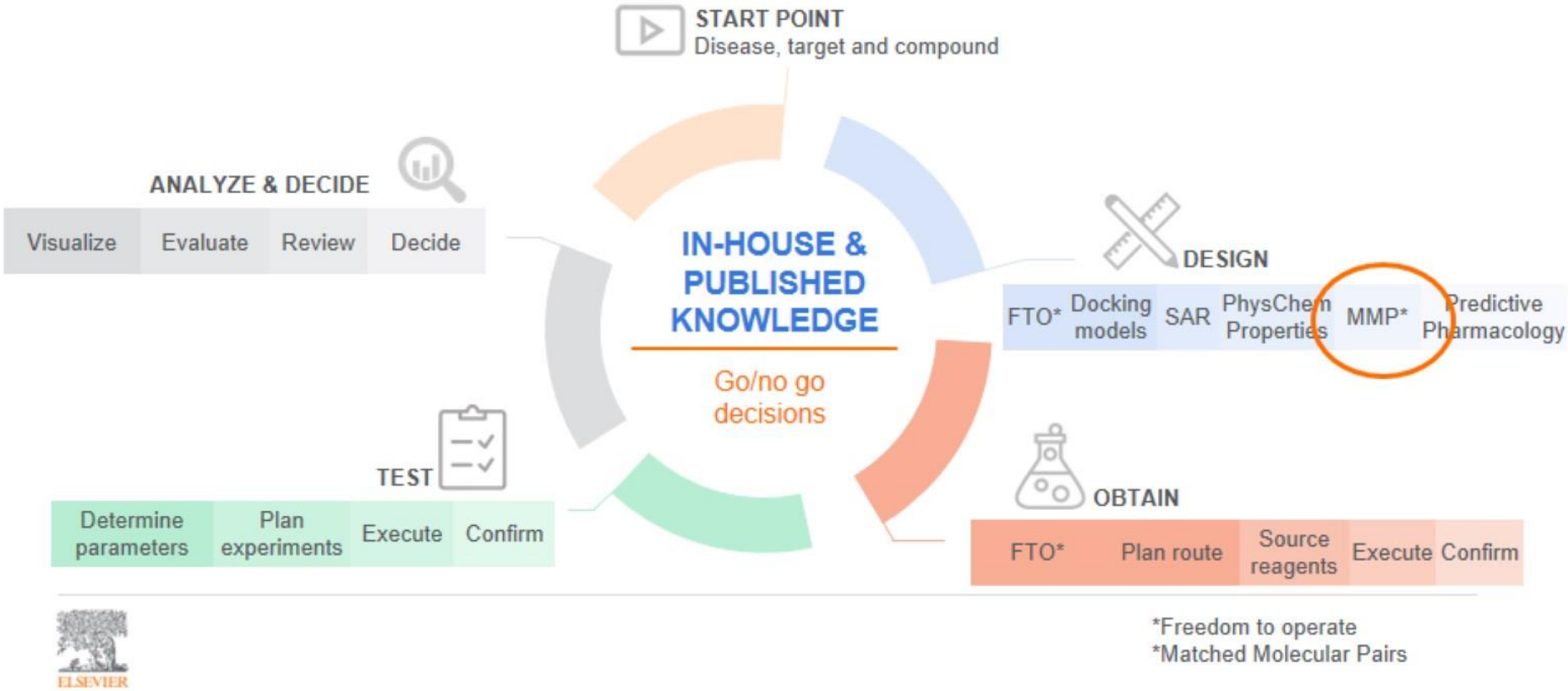
Using data from Reaxys we want to strengthening our support for the drug design cycle



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."

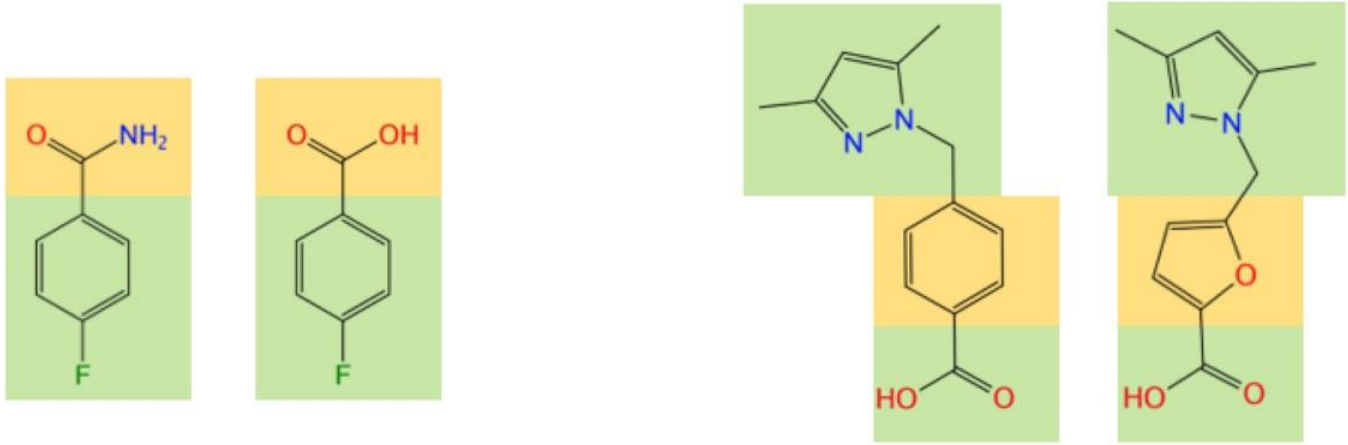
Researchers must identify, optimize and make lead compounds with **less PK and ADME issues** whilst **maintaining high affinity** for the identified target.

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

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Hussain et al., *JCIM*, **2010**, 50, 339-348

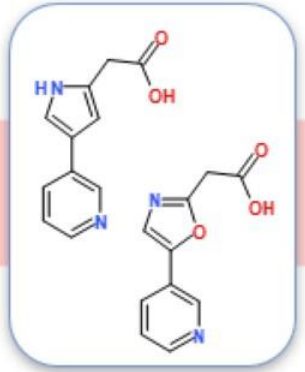
Matched Molecular Pair (MMP) analysis – a collaboration with the Swiss Institute of Bioinformatics using RMC data

Data Source

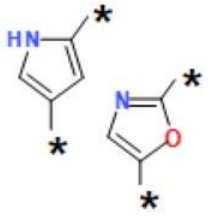
RMC

Reaxys Medicinal Chemistry

Pair Identification



Replacement Extraction



Activity Difference
Assay
Target
Target Class
Chemical Context

Database Storage

MMP

SIB

Matched Molecular Pair
The computational engine

Outcome

>9,500,00 molecular replacements

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SIB Swiss Institute of Bioinformatics

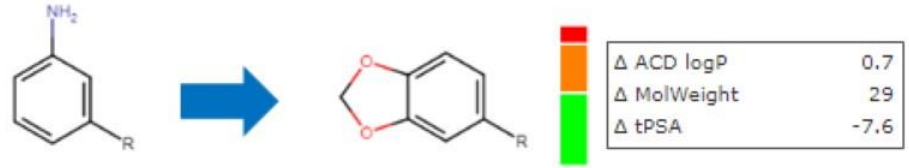
With, M.; Zoete, V.*; Michielin, O.*; Sauer, W. H. B*. SwissBioisostere: a database of molecular replacements for ligand design. *Nucleic Acids Res.* **2013**, *41*, D1137–43.

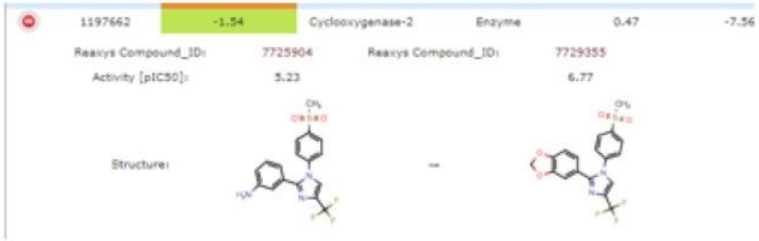
RMC data derived Matched Molecular Pair web application – user feedback

Medicinal Chemist in Pharma

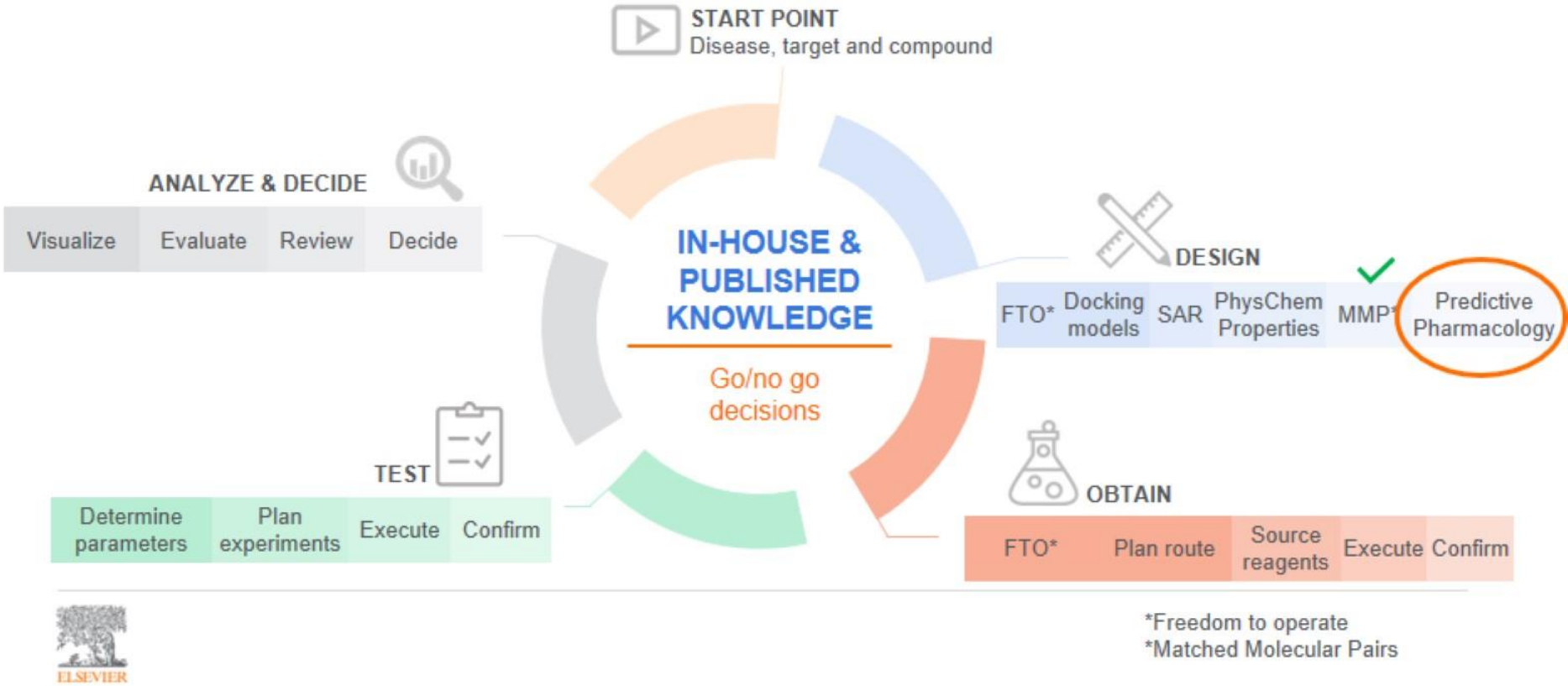
- Used on a current drug design project
  - "Gave me new ideas and helped creativity"
  - New ideas were handed to my computational chemistry colleagues for docking and initiated further discussion
- Expected impact on research decisions:
  - Extend chemical space due to larger knowledge base
  - Trigger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

Illustrative example:





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



*Freedom to operate
*Matched Molecular Pairs

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?"

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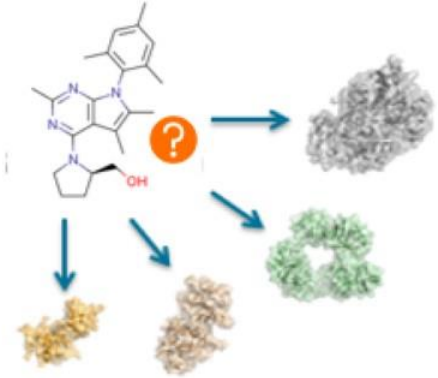
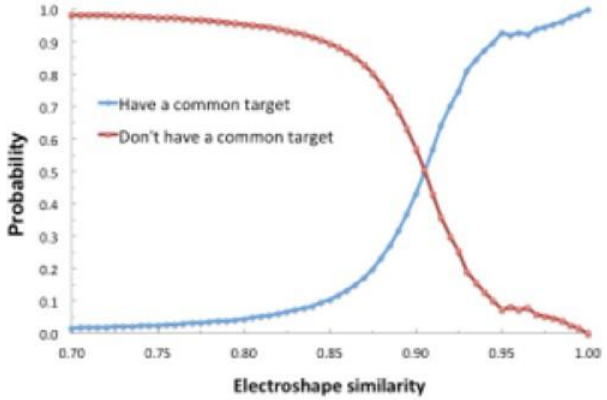
Target Prediction by molecular similarity



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**

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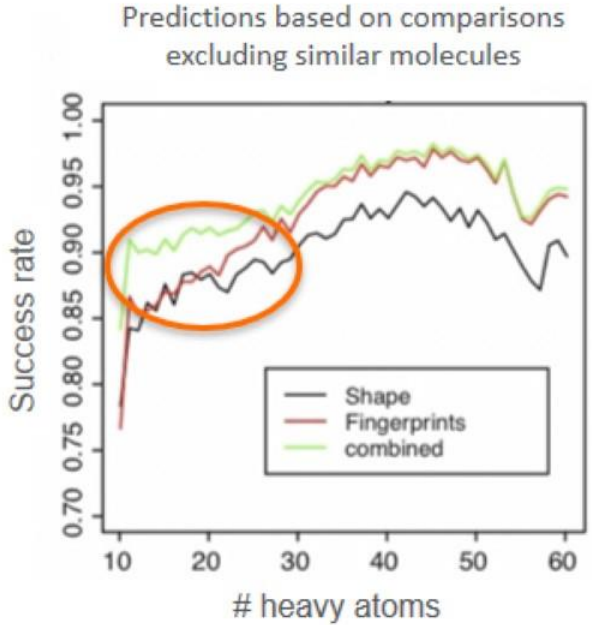
SIB Swiss Institute of Bioinformatics

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

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SIB Swiss Institute of Bioinformatics

Gfeller, D.; Michielin, O.; Zoete, V. Shaping the Interaction Landscape of Bioactive Molecules. *Bioinformatics*. **2013**, *29*, 3073–3079.

Gfeller, D.; Grosdidier, A.; Wirth, M.; Daina, A.; Michielin, O.; Zoete, V. SwissTargetPrediction: a Web Server for Target Prediction of Bioactive Small Molecules. *Nucleic Acids Res.* **2014**, *42(Web Server issue)*, W32-8.

Gfeller D., Zoete V. Protein homology reveals new targets for bioactive small molecules. *Bioinformatics*. **2015**, *31*, 2721-7.

RMC data derived Target Prediction web application – user feedback

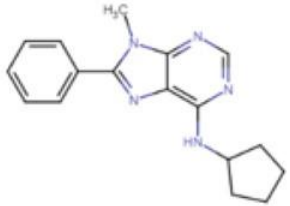
Medicinal Chemist in Pharma

- 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 (Ki 2.8 nM)

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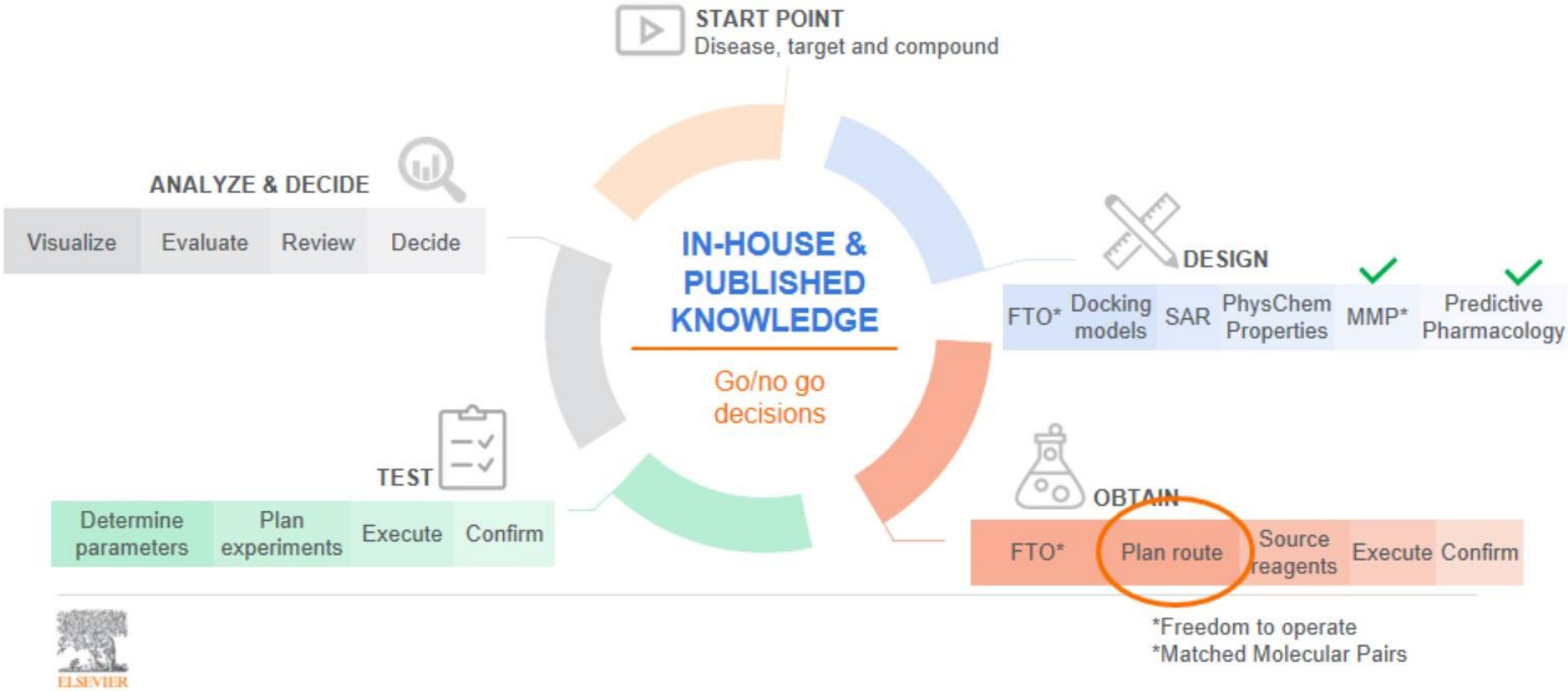
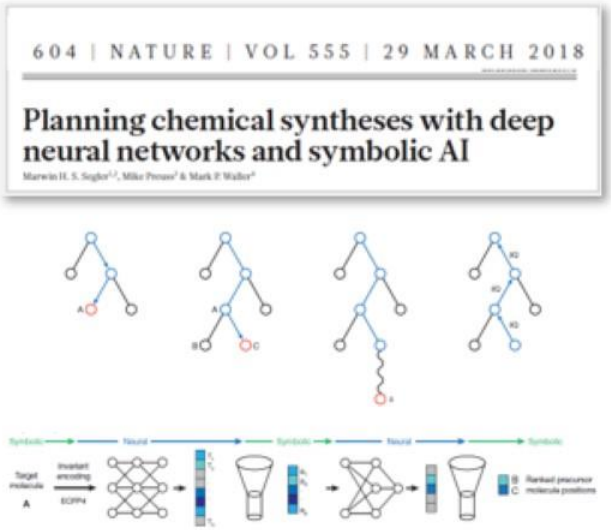
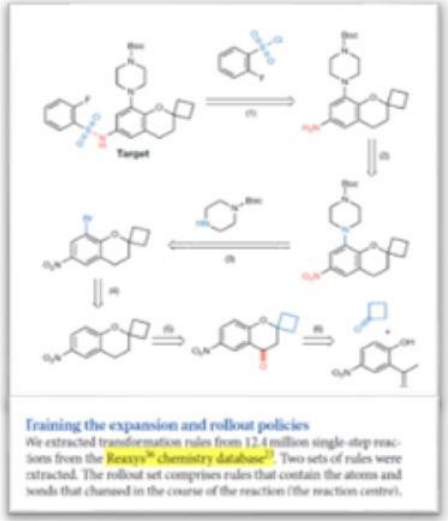


Predictive Retrosynthesis: rewiring chemistry and redesigning synthetic routes

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.





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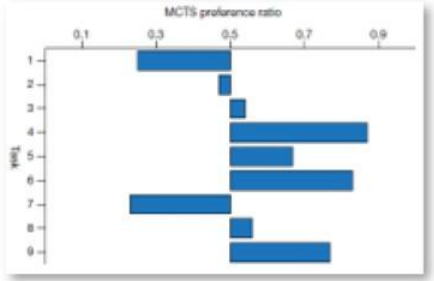

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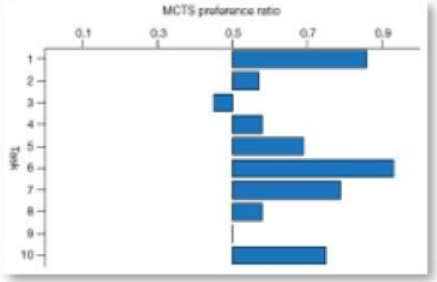

*Science 02, Jan 2015

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**

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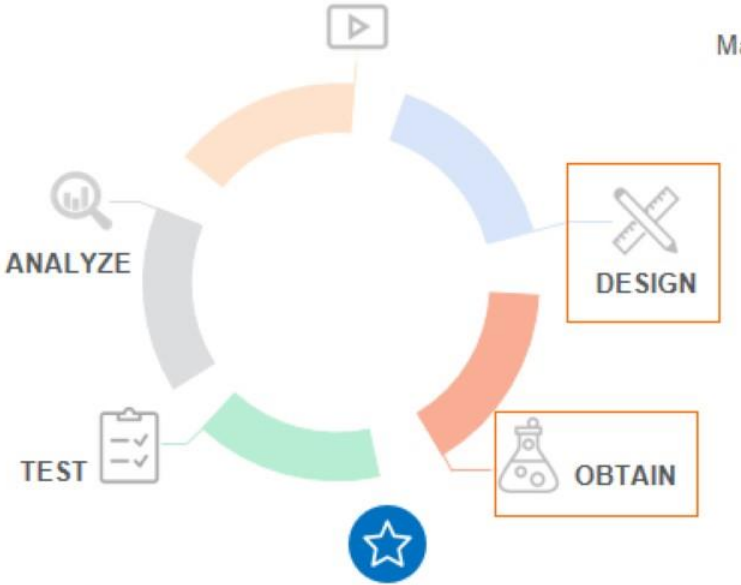
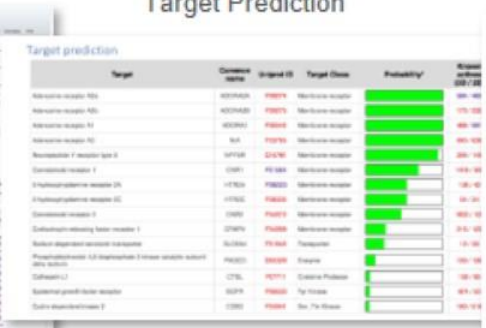
Summary and outlook

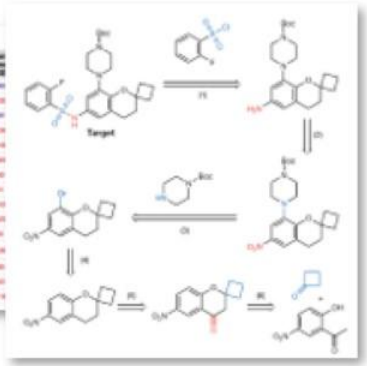


Matched Molecular Pair analysis

Target Prediction



Predictive Retrosynthesis



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

AI in pharma – high quality data will make a difference

Many emerging technologies so no “one size fits all”

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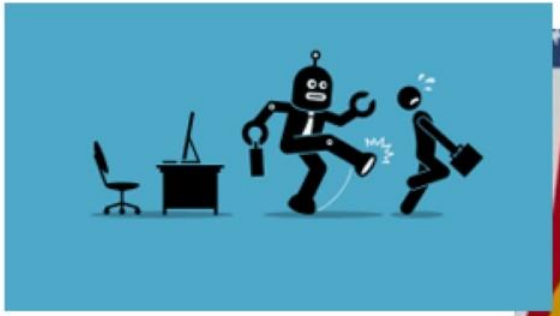
Summary and Outlook

- **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!

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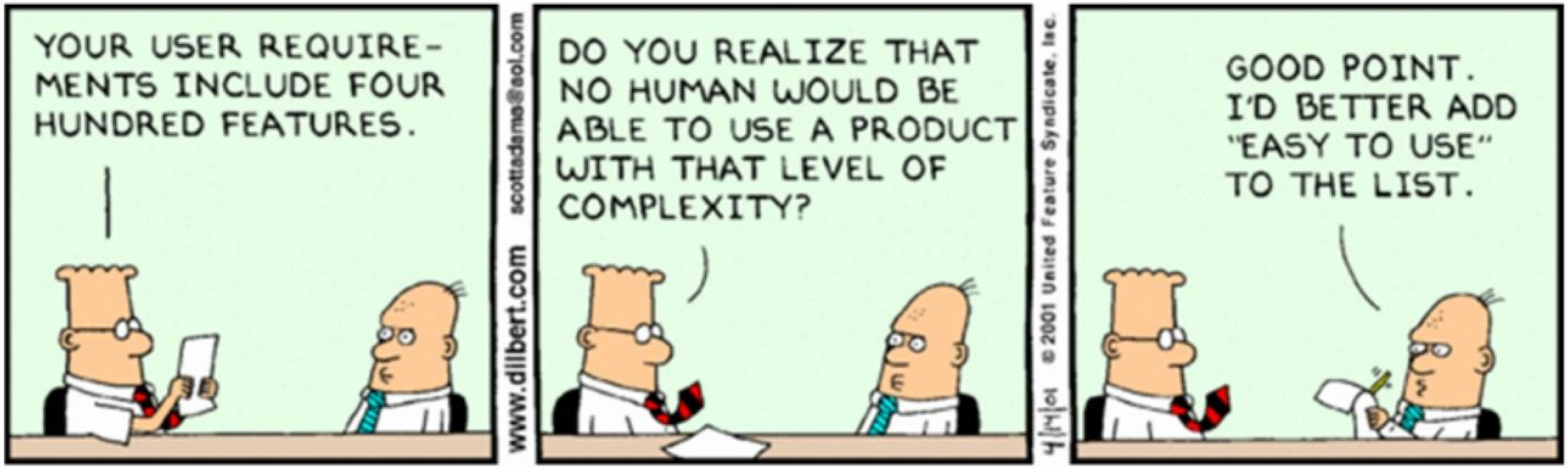
Summary and Outlook

- **Our challenge**



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