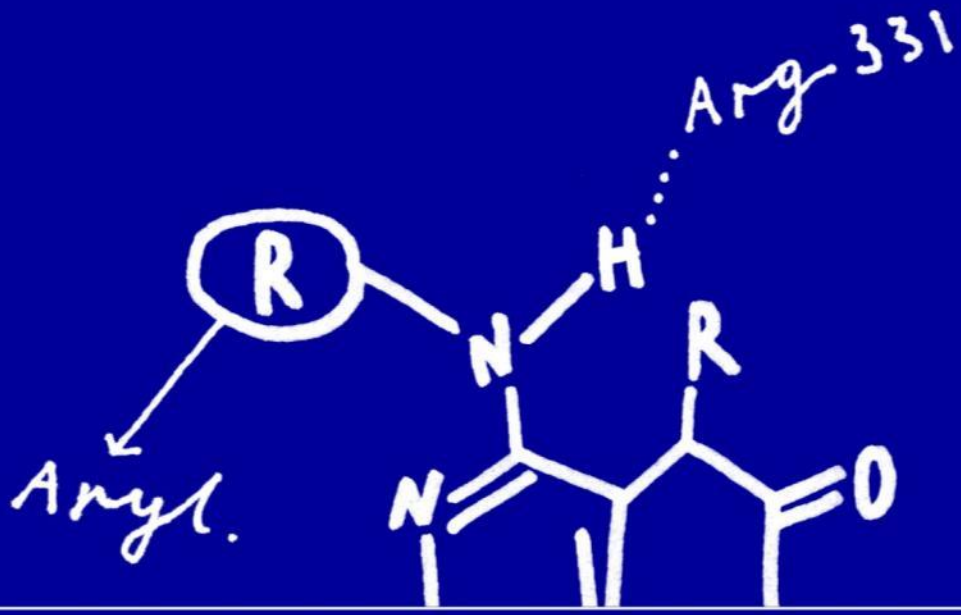
evotec

'RESEARCH NEVER STOPS'
Drug Discovery Solutions
& MORE

MX from an Industrial Perspective

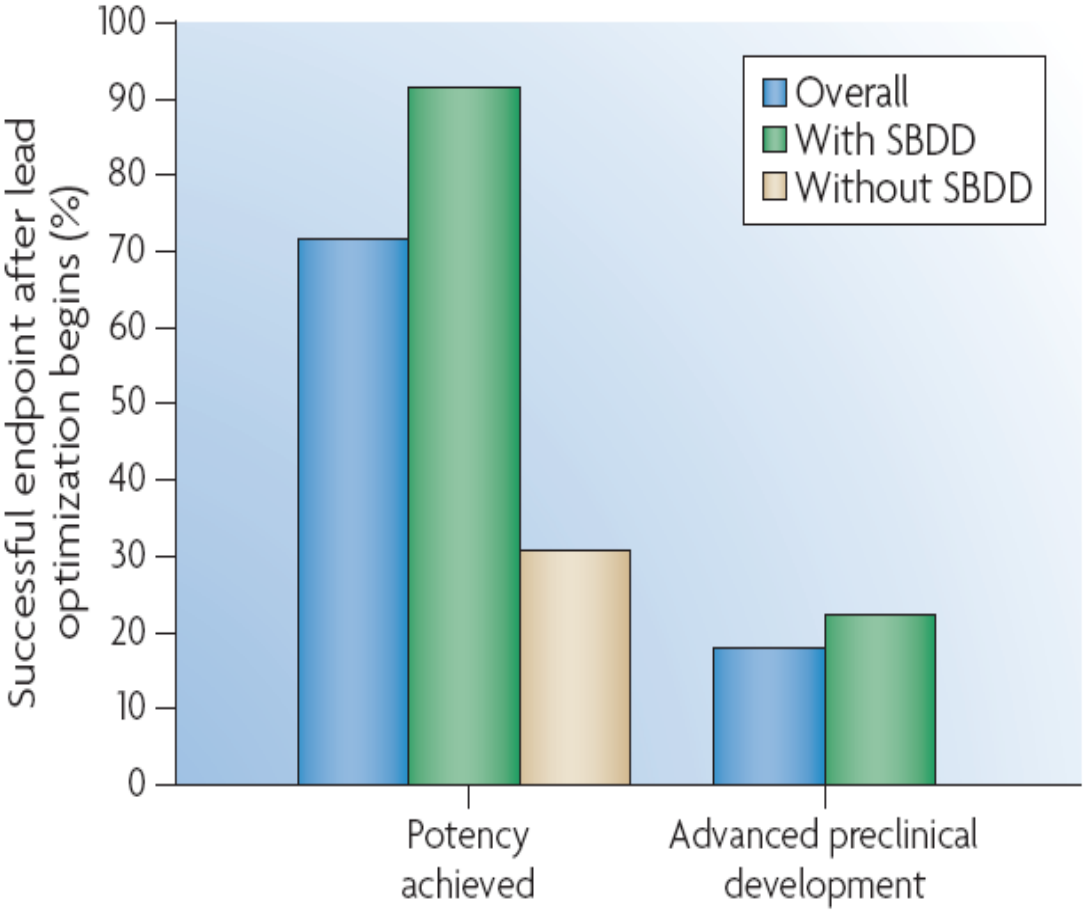
Paul McEwan Ph.D.



- Why SDBB?
- Who/What is Evotec?
- The drug discovery pipeline- “streamlining interfaces”
- How does MX fit into the grand scheme
  - NRF2 Case study
- Summary

Structure Enabled Programmes Perform Better

Rationale design, the driver for rapid and successful progression



- The employment of SBDD demonstrated to help early and critical decisions to be made on the future of a project
- Attrition is lower with structure-based discovery to drive potency (and selectivity)
  - Efficiency of Hits carried through to Efficient Leads

‡Hajduk and Greer, *Nat Rev Drug Discov*. 2007 6, 211-219.

Adding value to our partners' research

Innovative and flexible solutions from target ID to pre-clinical candidate

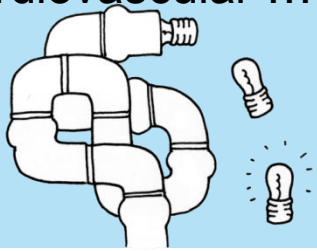
The people

Outstanding scientists (~1600)

Experienced project management

A wide therapeutic area expertise

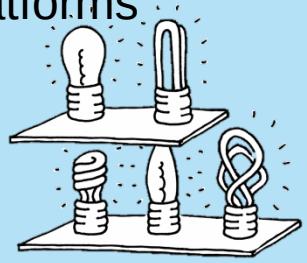
Pain, oncology, metabolics, CNS, immunology, inflammation, infection, cardiovascular …



Integrated drug discovery

State-of-the-art capabilities

Best-in-class technology platforms



Flexible deal structures

Integrated collaborations and stand-alone services

A world-class drug discovery expertise and platform to accelerate and maximise our partners' success

Global centres of excellence for external innovation

Evotec's global footprint

Hamburg (HQ), Göttingen, Munich (Germany)

~500 employees

- Hit identification
- *In vitro* & *in vivo* biology
- Chemical proteomics and Biomarker discovery and validation
- Cell & protein production
- Antibody discovery

Abingdon/ Alderley Park (UK)

~600 employees

- Medicinal chemistry
- ADME-Tox, DMPK
- **Structural biology**
- *In vitro* & *in vivo* anti-infective platform/ screening
- Process development
- CMC and Commercial manufacture
- Pre-formulation

Toulouse (France)

~330 employees

- Compound management
- Hit identification
- *In vitro* & *in vivo* oncology
- Medicinal chemistry
- ADME & PK
- Cell, protein & antibody production

Verona (Italy), Basel (CH)

~590 employees

- Hit identification
- *In vitro* & *in vivo* biology
- Medicinal Chemistry
- Biomarker discovery and validation
- INDiGO®
- CMC

Princeton, Watertown, Branford (USA)

~90 employees

- Compound ID, selection and acquisition
- Compound QC, storage and distribution
- Cell & protein production
- ADME-Tox, DMPK
- **Structural biology**

Building high-value, integrated partnerships

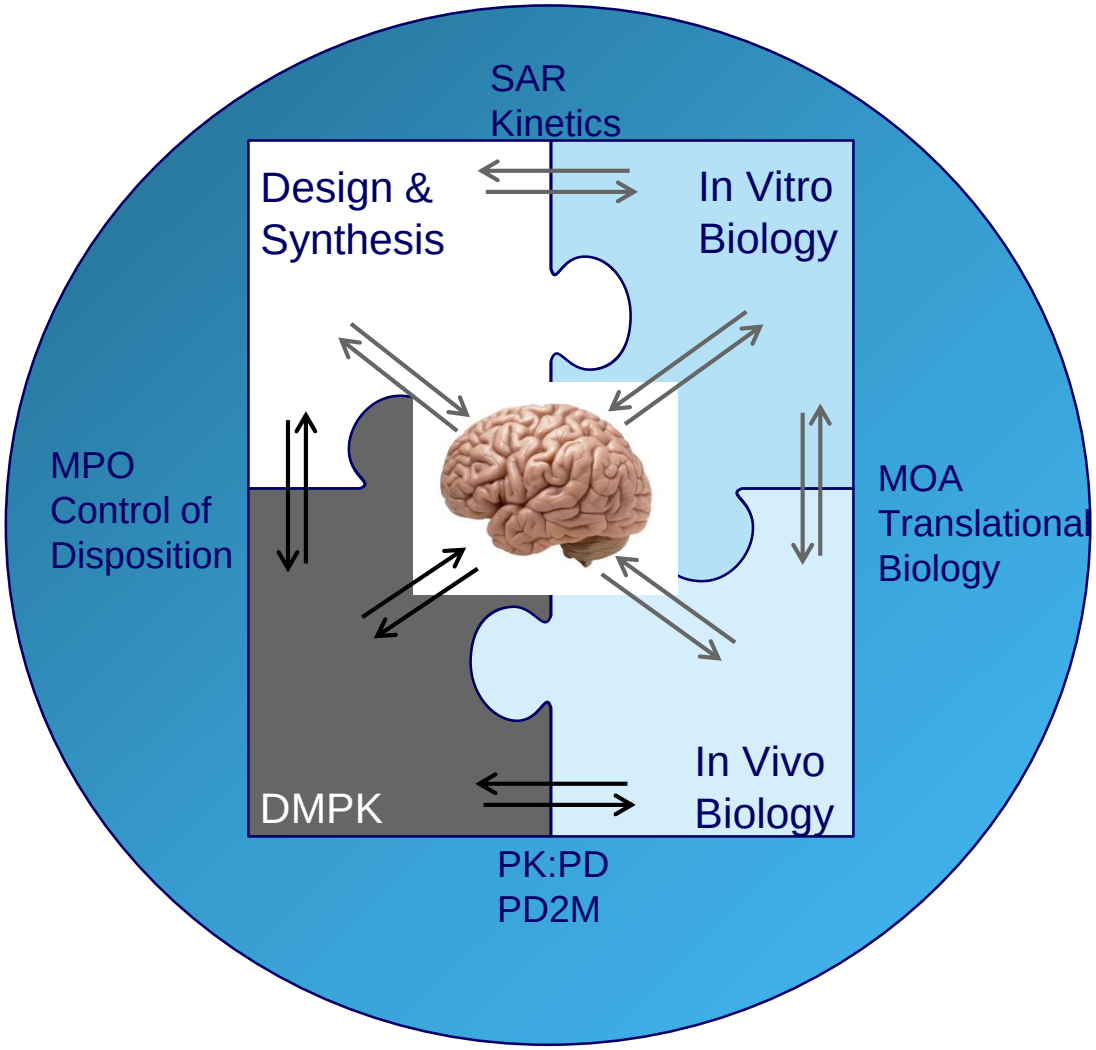
From target to pre-clinical candidate (and beyond!)

Target ID & validation	Screening	Hit-to-Lead	Lead Optimisation
• Molecular biology and cloning • Bioinformatics • *In vitro* target validation • *In vivo* target validation • Target deconvolution	• Assay development & screening • (u)HTS • High-content screening • Microbiological phenotypic screening (class 2) • Electrophysiology • *In silico* screening technologies • **Fragment-based drug discovery** • **X-ray Screening** • Compound & Sample management • proteomics	• Medicinal chemistry • Hit expansion • Library design • High-throughput chemistry • Target deconvolution • **Protein-ligand crystallography** • *In vitro* & *in vivo* biology • Early ADMET • *In vivo* proof of concept • Microbiological testing and characterization (MICs, MBCs, MoA determination)	• Medicinal chemistry • *In vitro* & *in vivo* biology Disease biology and target class expertise • Cellular selectivity analysis and MoA[1)] analysis • Translational assays • Computational chemistry and **structure-based drug design** • *In silico* & *in vitro* ADMET • Biomarker discovery • PKPD Profiling and mathematical modelling • Early drug formulation & solid form screening

[1)] Mode of action

Formation of integrated drug discovery alliances

Integrated problem-solving and drug hunting – more success



Creating success (while others fail?)

Problem-solving & Invention

Drug-hunting knowledge and experience

Slick logistics, speed

High-level intellectual engagement

Best judgment and advice

Blending human creativity, knowledge, science and process for better drug discovery

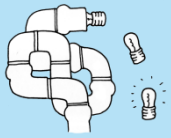
Better outcomes when five key features are successfully blended together

Human creativity, insight, intuition, inspiration

Drug discovery is still a very organic and human endeavor through true teamwork and partnership

Extensive knowledge, experience, expertise, know-how

Knowledge of analogous problems enables rapid solutions and anticipation and avoidance of problems



Multi-disciplinary awareness and close interactions

Toughest problems are at the interface between disciplines

Highest quality science – thinking and tools

Relevant, high capacity test systems, computational/predictive tools

High performance processes

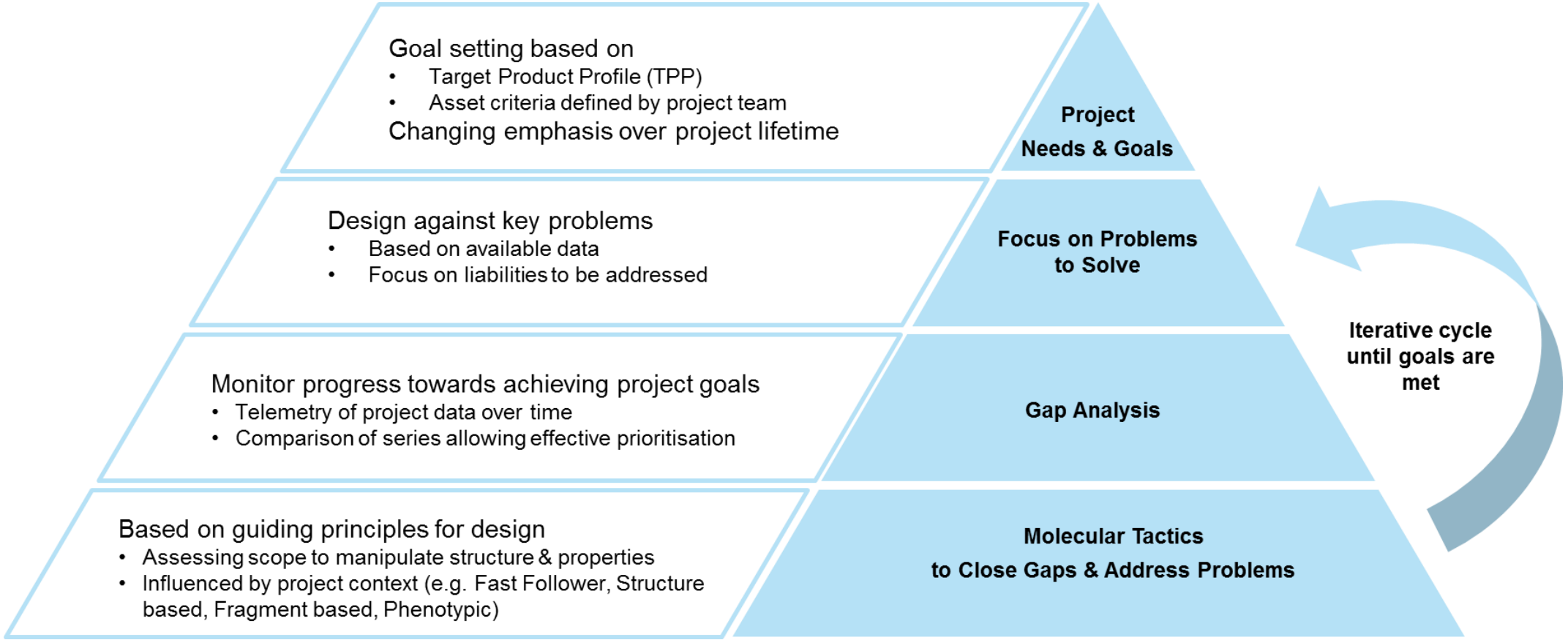
The right, well-designed experiment, the diligently designed compound, executed rapidly, “right first time”

Blended together, leads to:

- Faster progress towards…
- Better quality drug candidates with higher probability of success through development…
- At lower costs for partners

Hit evolution to candidate is a continuum

Directed and focused chemistry on problem-solving



Excellence in molecular evolution

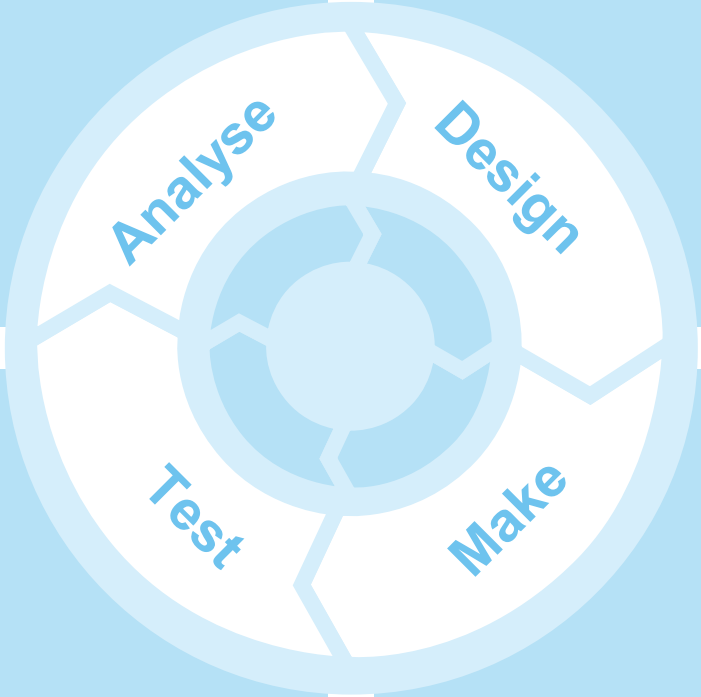
Integrating data workflows throughout the DMTA cycle

Analyse

Powerful combination of analysis tools to identify best compounds and track progress against optimisation goals

Design

Efficient collaborative design of high quality compounds enabled by ideas repository linked to visualisation tools



Test

Rapid, relevant, high-capacity efficacy and non-efficacy testing

Make

Rapid and efficient synthetic execution enabled by real time monitoring of key metrics (cycle time, work in progress etc.)

Structural Biology

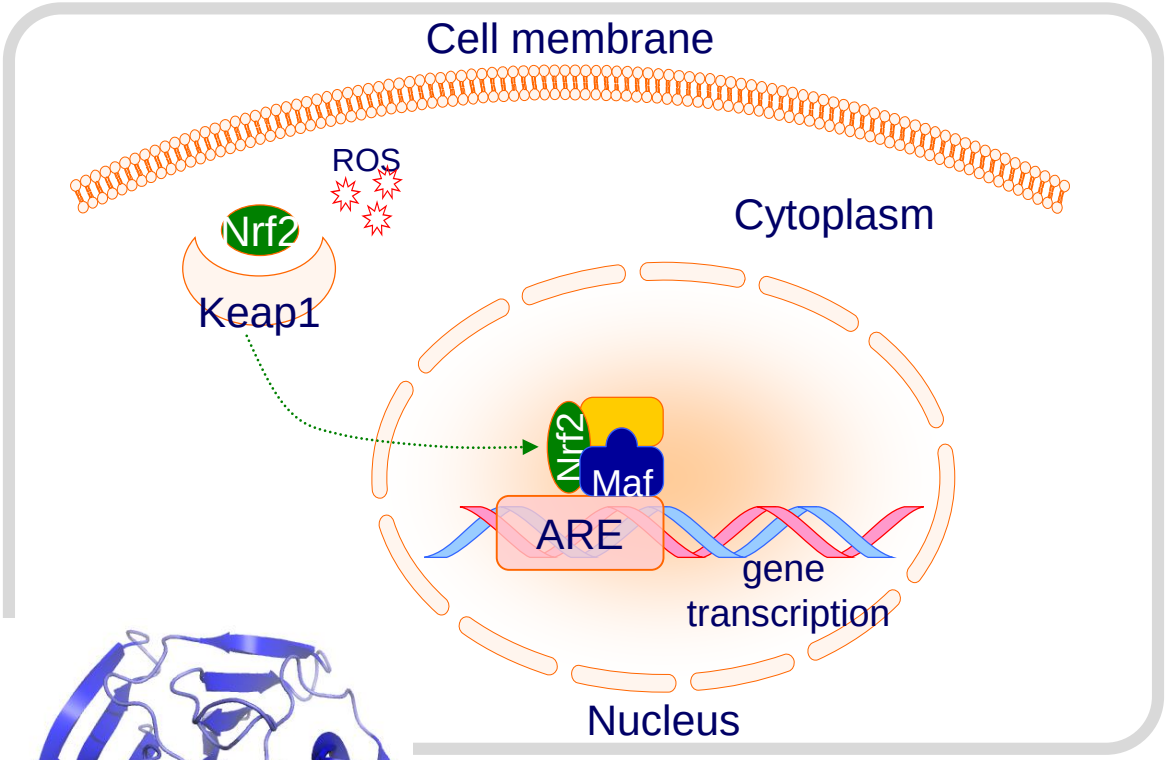
Integrated and stand-alone drug-discovery programs

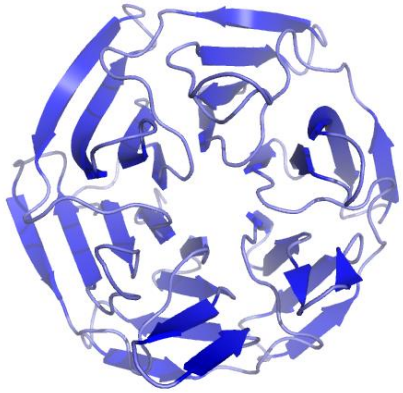
- Team of 26 scientists (18 PhDs) in UK (additional 2 PhDs USA)
  - 12 are dedicated PhD level crystallographers
  - 14 in protein production (7 PhD)
- Protein production group supports both internal assay, biophysics and crystallography teams but also supplies services directly to other organisations
- Comprehensive platforms to handle the most challenging protein supply and crystallography targets
- Minimum biweekly visits, in-situ and microfocus beam time available for crystallography and SAXS data collection
- Access to specialised facilities at Diamond Light Source and the national Membrane Protein Laboratory
- Access to eBIC nation electron microscopy facility

NRF2:Keap1

Background

- Neuroprotective effects observed with increased expression of the antioxidant and anti-inflammatory transcription factor Nrf2
  - Potential role in several diseases including Parkinson's and Alzheimer's disease, Epilepsy
- HTS hits observed but SAR not matching the predicted model
- Structurally enabled with high resolution *apo* crystal system and bound peptide complex
- Challenge to deliver a small molecule complex structure to assist modelling and chemistry

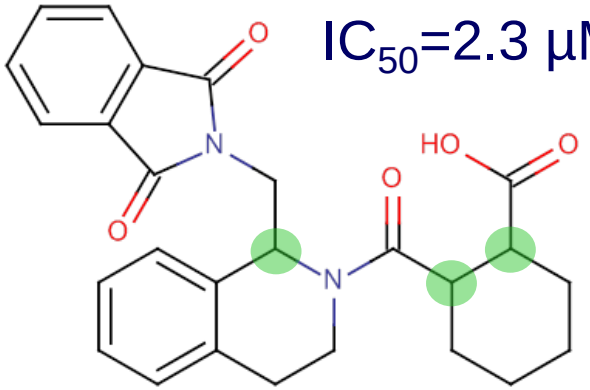




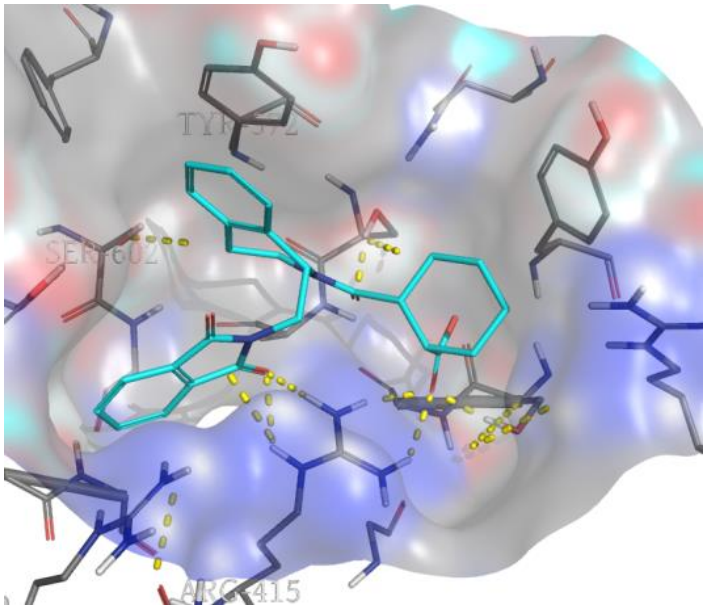
Kelch domain of Keap 1

Starting point

- One start point identified via mining of public NIH screening data
- Multiple crystal structures of the Keap1 binding domain present in the literature
- The starting compound was complex
  - 3 unknown chiral centres
  - S,R,S stereoisomer identified as most active by chiral separation of synthesised species and small molecule X-ray structure.
- Co-complex crystallography and chemistry initiated
- Docking was utilised to build a basis for rational compound development
- However, the selected computational model did not track with anticipated activity

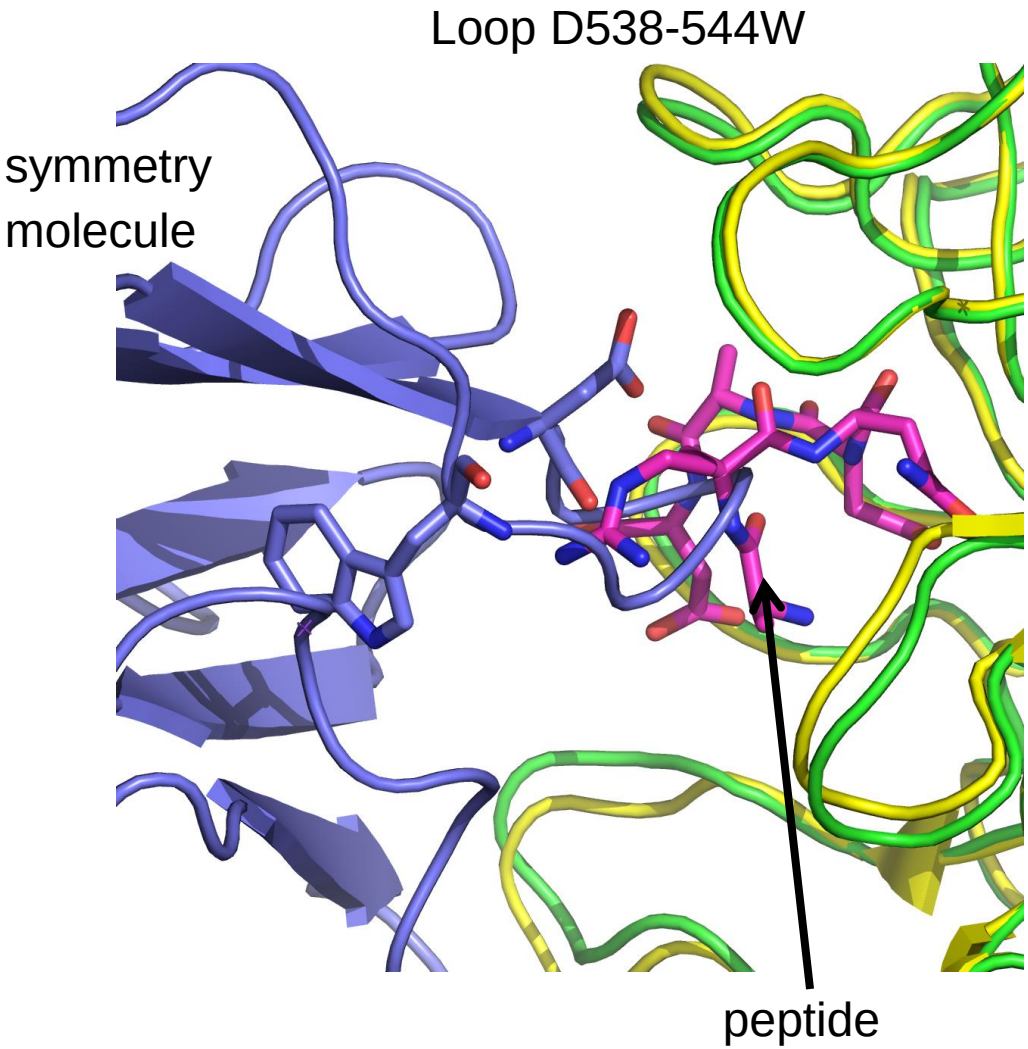


IC_{50}=2.3 µM



NRF2

A classic issue in protein:protein targets



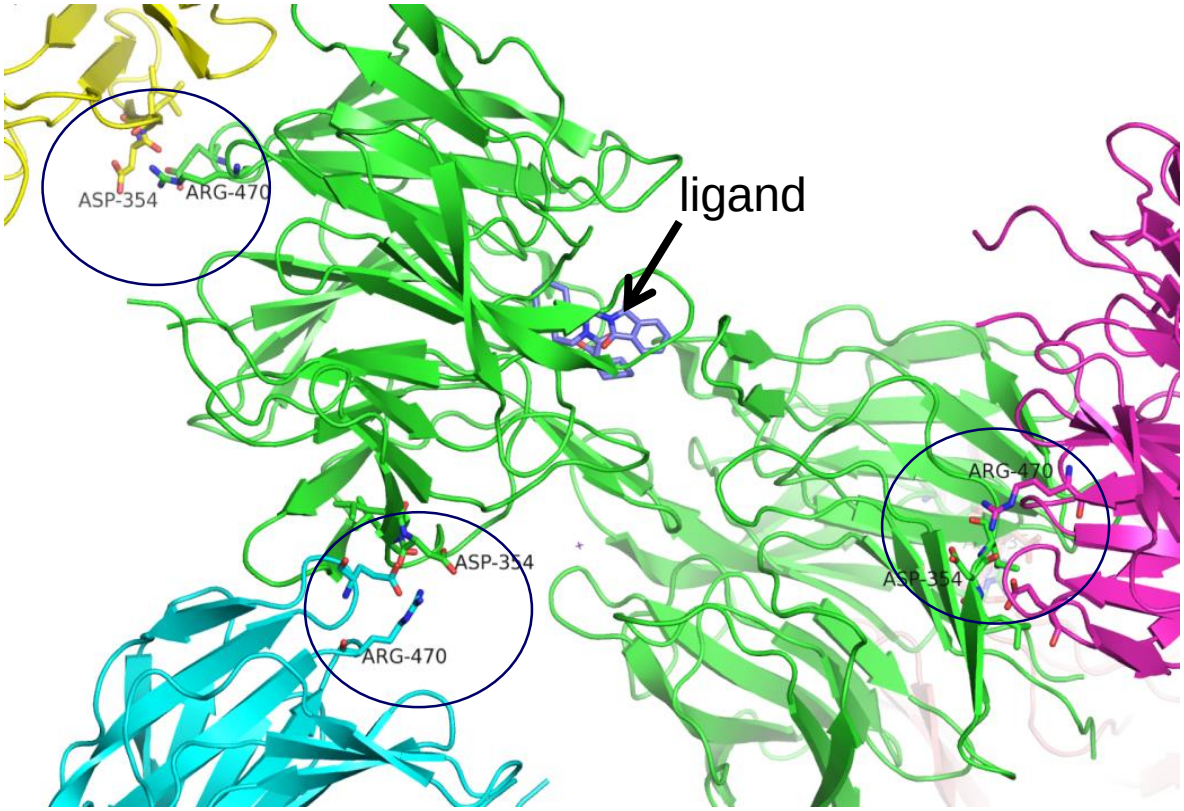
- Crystal packing of the *apo* KEAP1 results in a loop region of the neighbouring molecule occluding the binding site
- Multiple approaches taken to address the issue
  - Focussed point mutations to destabilise the crystal contacts in the region of the binding site
  - Surface entropy changes to induce novel crystallisation
  - Fusion partners to engineer new crystal forms
- Rapid construct triage via parallel expression studies to identify candidates for large scale production and crystallisation

Solved keap1 (in-house)	Yellow/Purple
1ZGK	Green
NRF2 Peptide	Pink

NRF2

What worked and why?

Crystal packing of R354D Keap1



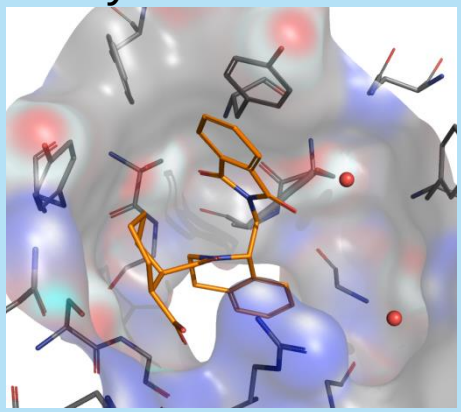
- 16 Keap1 single point mutants (*human* & *mouse*) designed
  - Small scale testing and large scale purification of soluble mutants completed
  - Purified mutant proteins assayed to verify activity
- More than 50,000 conditions screened
  - Attempt to obtain alternate crystal forms to the 1ZGK occluded system
  - Thermofluor experiments used on available compounds to assess likelihood of success in co-crystallisation
- R354D point mutant produced co-crystals with confirmed hit compound
  - 6 X His tag relocated to the c-terminus (compared to 1ZGK)
  - D354 involved in major crystal lattice contact between dimers
  - Reorientation of the dimer interface compared to 1ZGK
  - One polypeptide chain in the dimer contained ligand

Complex crystallography confirmed

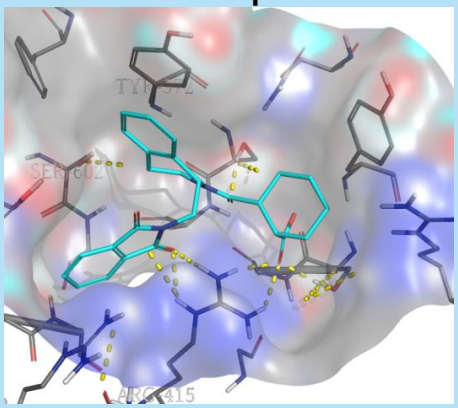
Ligand conformation different from computational model

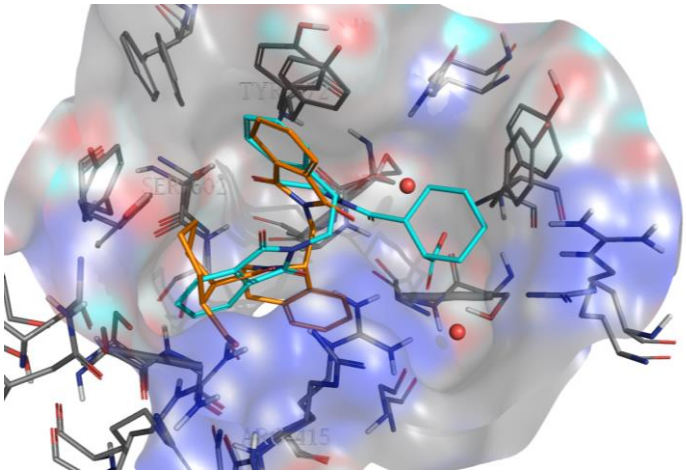
- Structure of bound inhibitor shows an unexpected axial conformation not predicted by modelling
- Small molecule complexes delivered both in human and rodent
- Structure of bound inhibitor shows an unexpected axial conformation not predicted by modelling
- Firm foundation for future design cycles
- Several other small molecule complexes delivered

Crystal structure

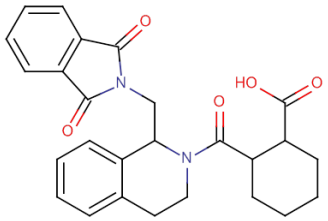


Docked pose



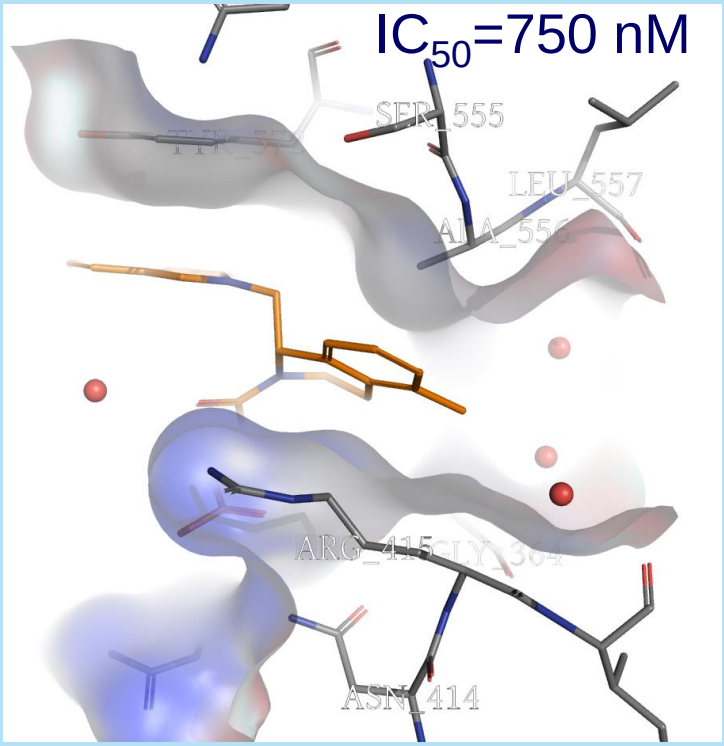


Overlay



Understanding the small molecule conformation

- Delivery of ligand complexes critical for driving the drug design process
- Based on x-ray crystal structure focussed optimisation of the hit compound became possible
- Structure Activity Relationships (SAR) were elucidated
  - Compounds with increased potency could be synthesised
  - Exploration of further interactions possible
  - Other biological experiments (e.g. *in vivo* brain exposures) could be initiated
- Optimised compound designed
  - Exploring central channel
  - Potency improvement realised over initial hit



- Effective communication across the team critical to the adding value beyond a simple structure

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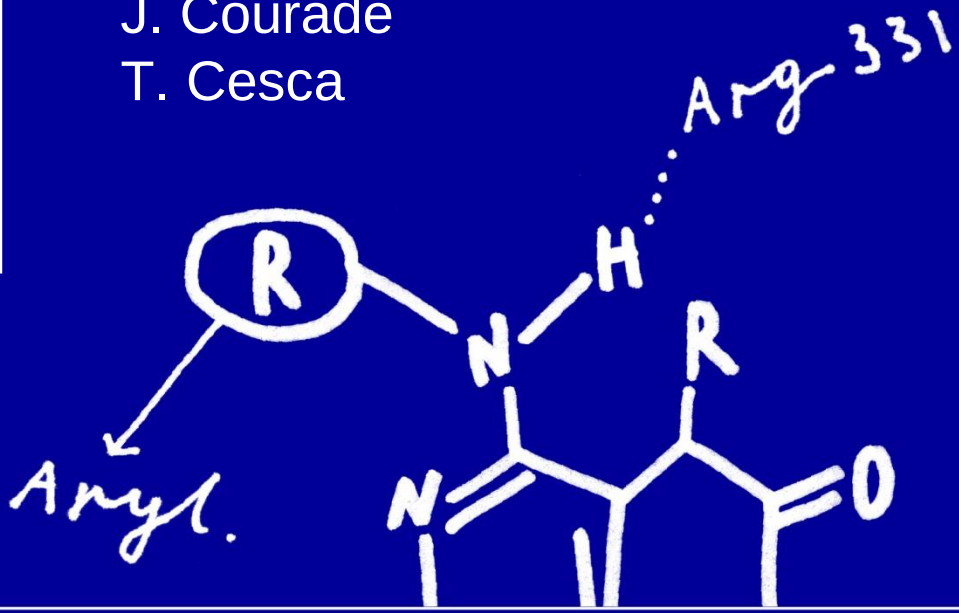
‘RESEARCH NEVER STOPS’

Building innovative drug discovery alliances

C. Albrecht
J. Barker
O. Barker
E. Beaumont
S. Bromidge
F. Brookfield
M. Brooks
C. Bubert
G. Dawson
S. Duclos
T. Fryatt J Kwong
R. Maghames
I. Mushi
R. Pike
M. Smith
C. Stimson

UCB Inspired by patients. Driven by science.

E. Jnoff
C. Genicot
E. Jigorel
Z. Sands
J. Courade
T. Cesca



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