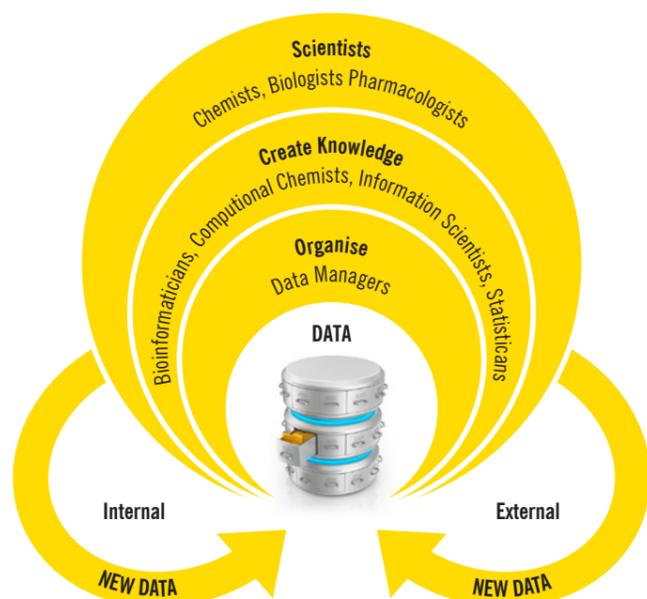


RESEARCH INFORMATICS

& *IN-SILICO* DRUG DESIGN



Mike Bodkin,
Vice President Research Informatics



OFFERING
The huge quantity of data that drug discovery generates both externally and internally requires that data informatics is at the heart of any modern research organisation. At Evotec the research informatics department smoothly integrates the disciplines of computational chemistry, bioinformatics, systems integration, data management and support informatics. The team empowers the discovery scientist to deliver data-driven design hypothesis using commercial, propri-

etary and bespoke software offerings. In short, the department delivers *in-silico* drug discovery and can be engaged in a standalone capacity or fully integrated with our discovery partners.

TARGET IDENTIFICATION
Evotec uses industry standard target interaction databases which combined with other 'omics' data can be used to construct target interaction maps. These networks can be significantly enhanced using our predictive

pharmacology tools. >200M bioassay datapoints are currently sourced for model building. Pathway analysis can be used to identify new and novel targets proposed to modulate a disease hypothesis. Such approaches are fundamental in target deconvolution and drug repurposing.

DRUGABILITY ASSESSMENT
Structure-based assessment for novel targets gives an additional read on drugability when no/few drug-like compounds are known. New

2D sequence based "switchability" calculations projected onto 3D structures have successfully been used for predicting allosteric sites for modulation, surfaces for PPIs and mAB binding.

HIT IDENTIFICATION

For virtual screening Evotec uses multiple methods using the best-of-breed commercial software. A number of compound collections are available for screening:

- ▶ EvoSource (34M)
- ▶ Evotec Diversity (400K),
- ▶ Sanofi HTS (1.4M),
- ▶ Fragments (21K),
- ▶ Diverse Phenotype Library (20K)
- ▶ Annotated Druglike Library (6K)

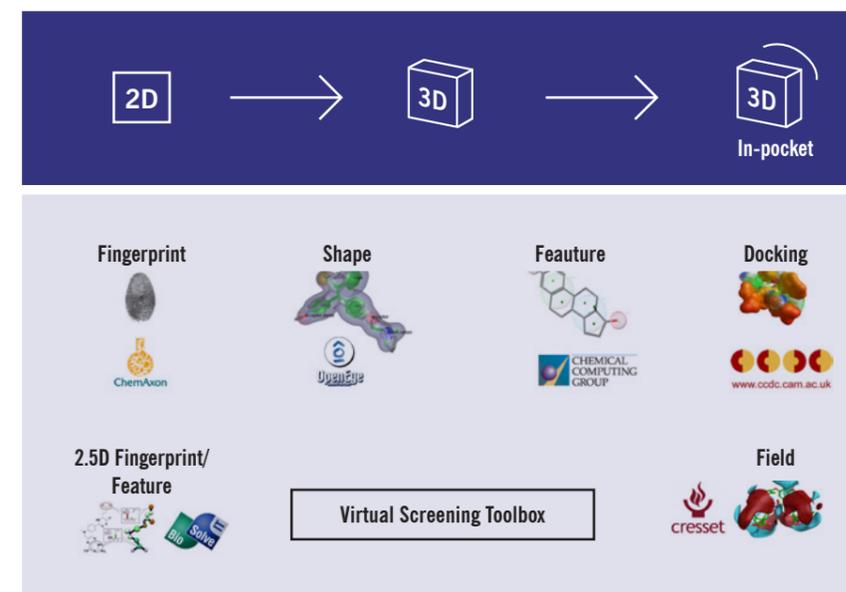
Chemgenomics and ortholog approaches also provide a good starting point for identifying novel actives. Evotec has licensed LeadIT and Spark for scaffold hopping but also has a number of in-house tools using structure merging and vector placement algorithms.

HIT EXPANSION

The hits identified from screening require expansion to provide evidence of SAR. This is traditionally based upon chemical similarity and involves searching databases for 'like' molecules. Evotec also uses predictive pharmacology so that molecules that possess a similar target pathway signature can be identified. Library design, statistical analysis and virtual chemistry tools can be used to design the most information rich set of molecules for synthesis.

MULTI-OBJECTIVE DESIGN

The Evotec ELN reaction transform library can be used to perform virtual chemistry and grow fragments within the active site of protein.



Ideas generated can be scored across a range of objectives such as an ADMET profile (Evotec has its own proprietary ADMET models), target QSARs, off-target QSARs. The method can be used for both structure-based and ligand based design.

LIGAND OPTIMISATION

Evotec possesses significant expertise in QM guided SBDD using the fragment molecular orbital (FMO) approach. FMO calculates the strength of interaction between protein residues and ligand atoms to accurately pinpoint the drivers of molecular affinity. Molecular simulation (WaterScout) and ΔG (Nautilus) approaches can be applied to identify happy and unhappy waters. Evotec's large internal HPC (high performance computing) capacity, employing multiple Intel and GPU clusters, ensures that these approaches are routinely applied.

Designing molecules for the clinic balances the multiple dimensions of medicinal chemistry and phar-

macology. Evotec has developed a number of statistical analysis tools for matched-molecular-pair analysis (MMPA) and Free-Wilson approaches. These can be used in combination with predictive modelling tools QSAR, QSPR to enable effective experimental design. PK/PD modelling is done in collaboration with the ADMET group.

THE RESEARCH INFORMATICS TEAM

The infrastructure of research informatics at Evotec is supported by a strong team of data managers who organise and securely store data from across the globe. The systems integration group maintains the computing environment and includes the software developers who build and maintain the proprietary software tools. The support informatics (training and education) and business operations teams provide the softer interface to the department and ensure the smooth operation of internal and external client relationships.