JUBILANT BIOSYS

Computational Chemistry

Contents

- Computational chemistry capabilities @ Jubilant
  - Software tools used in the group
  - Databases and virtual screening
- Virtual screening: How we do it
  - Virtual screening case studies
- Virtual screening workflow for protein-protein interaction inhibitors/disruptors
- Core-/Scaffold-Hopping: workflow & details
  - Scaffold-hopping case study for a kinase target
- Homology modeling: workflow & details
- QSAR modeling: workflow & details
- Virtual Lab for Computational Support (VLCS)

Computational Chemistry support for Discovery

Jubilant's proprietary in-house technologies & workflows and state-of-the-art licensed platforms (Schrodinger) enable molecular modeling tasks required for various stages of the discovery process

Hit finding	Lead finding/selection	Lead optimization
Virtual screening (LB/SB)	Core hopping (LB/SB)	Core hopping (LB/SB)
Docking	Docking	Docking
SAR analysis	SAR analysis	SAR analysis
Selectivity analysis	Selectivity analysis	Selectivity analysis
Pharmacophore modeling	Pharmacophore modeling	2D/3D-QSAR modeling
Homology modeling	Property profiling	Property profiling
Structural analysis		
Property profiling		

Computational Chemistry Technologies

Jubilant's expertise extends to various molecular modeling methodologies/technologies that are required for design assessment and prioritization

- Molecular visualization
- Docking / scoring analysis
- Structure based design
- *de novo* chemotype Design
- Ligand-based design & QSAR
- Bio- & chemo-informatics platforms
- Quantum Mechanics
- Homology Modeling
- 3D similarity assessment
- Chemical diversity analysis
- Shape/Pharmacophore database search
- Scaffold/Fragment-based Lead Gen
- Combinatorial/ Focused library design
- ADME/PK Modeling
- Core-hopping
- Compound property & lead / drug likeness analysis
- Molecular Dynamics

Software:
Schrodinger/Maestro, PyMOL, GROMACS, Cresset

Software tools used in the group

Schrodinger/Maestro

- Glide: protein-small molecule docking, virtual screening
- Phase: pharmacophore modeling, 3D-QSAR modeling, virtual screening
- Prime: homology modeling, protein refinement, loop modeling
- Canvas: collection of chemoinformatics tools for structure search, clustering, compound selection, data analysis, 2D-QSAR modeling, descriptor generation and so on
- Core-hopping: structure- and ligand-based
- Bioluminate: Homology modeling, antibody modeling, residue-scanning, protein-protein docking and so on
- Jaguar: QM calculations
- Desmond: Molecular dynamics

Cresset/Spark

- Bioisostere search
- Generation of molecular fields

- We also use a lot of open-source software tools for virtual screening, mapping of metabolic soft spots, property/descriptor calculation, binding/allosteric site detection and molecular visualization
- For virtual screening, depending on publicly-available information on the target, we may use open-source webservers for screening, collect the hits and further process them using in-house software
- **Differentiation from other groups: Though the same software tools might be available with other groups, we differ in how these are used and how the results are analyzed, interpreted and communicated. We create custom-workflows suited to the problem/aspect being addressed based on our collective experience and expertise. For example, use of data-fusion techniques for post-screening processing**

Compound databases and virtual screening

- **Databases**
  - We do not have any in-house collection of compounds/fragments
  - We do have *in silico* collection of databases and chemical catalogues of drug-like compounds, fragments and selected focused libraries from some well-known chemical vendors. These have been filtered, prepared and are ready for use in virtual high-throughput screening. The vendors from whom we have databases are: Chemdiv, Asinex, eMolecules, Enamine, Mcule, ChemBridge, UORSY, Princeton BioMolecular Research, Zelinsky Institute, Vitas-M, PBMR Labs, IBScreen, Life Chemicals, Innovapharm and Otava

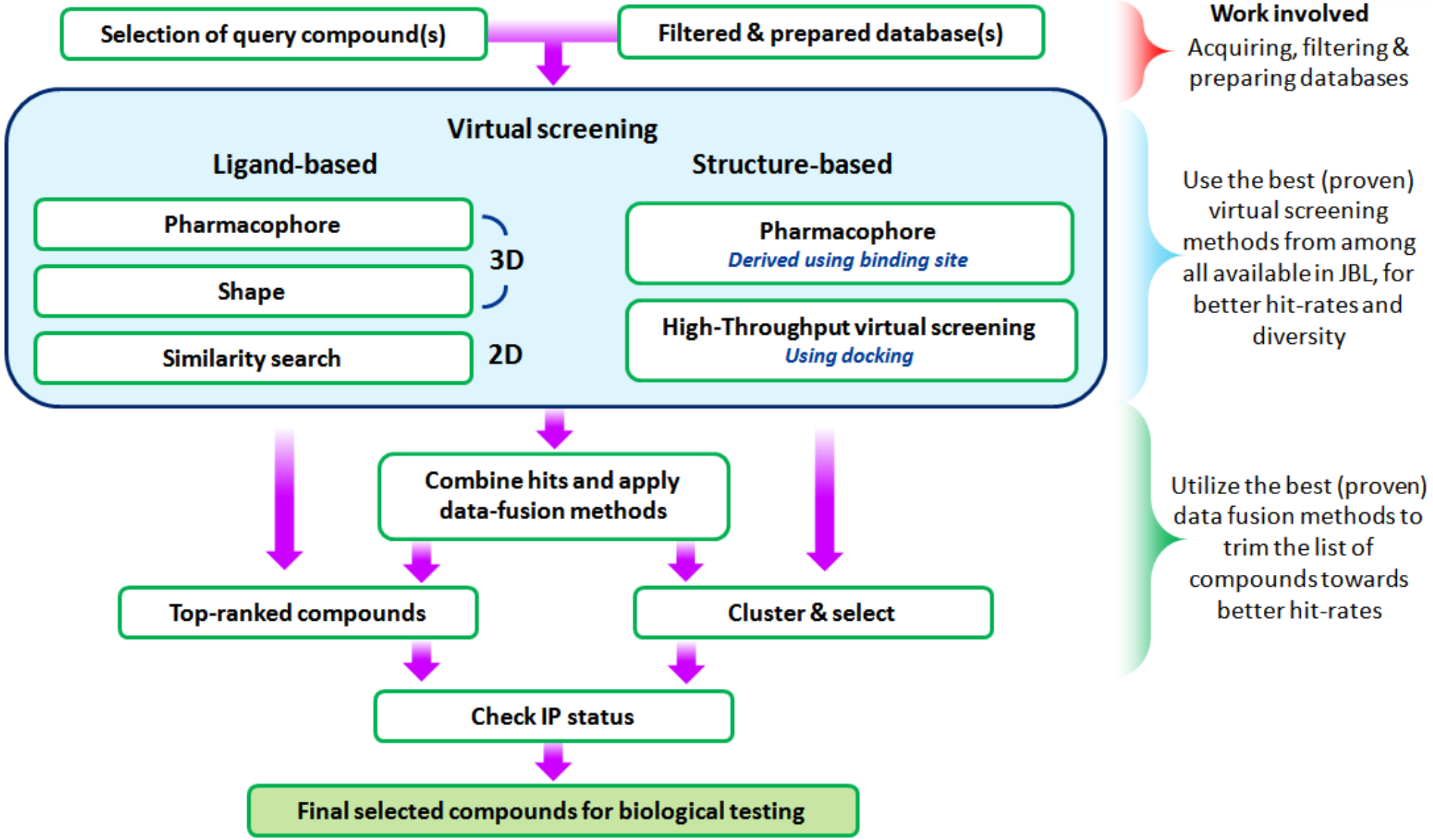
- Virtual screening @ JBL encompasses use of multiple methods – 2D, 3D, structure-based and ligand-based – for initial screening, followed by analyses of hits from each screening, consolidation, application of data-fusion techniques to ensure and enhance hit-enrichment

- In most virtual screening campaigns, succinct benchmarking studies are done to ensure selection of best methods for screening

- Much of this is based on extensive literature study to identify best methods/techniques, adopting and adapting them to the licensed tools we have, drafting workflows for each screening campaign making use of all the tools and methods available

- The experience of each campaign is made use of in tailoring and stream-lining the subsequent workflows specific for each screening need

Virtual Screening @ Jubilant



Case study 1: Virtual screening for an ion channel target

Queries: two compounds

Filtered dataset: Asinex & ChemDiv catalogue compounds

- **Shape screen – Using Phase Shape with MacroModel atomtype-based, Pharmacophore feature-based, elements-based and QSAR atom types-based scoring.**
- **Pharmacophore screen – Using Phase-generated, best pharmacophore models**
- **Molecular fields-based screening using Cresset software @ client's site**
- **Similarity search – Using fingerprints (ECFP, MOLPRINT2D, MACCS keys, Topological torsions)**
- **2D-pharmacophore based – Using CATS @ JBL**

Total 13/14 methods of screening

Hit selection: Diverse compounds that occurred in multiple screens; applied data fusion methods; used clustering methods

Visual inspection of selected hits for final list of hits >>> availability check with vendors, procurement & biological assays (297 compounds)

Total 71 hits (< 30 uM in assay) including 17 hits with < 5 uM potency

Dataset preparation: Asinex & ChemDiv catalogue compounds, totaling 1,952,672, were filtered in several ways to make a final dataset of drug-like compounds totaling 1,223,191 compounds (729,481 compounds were removed)

Query compounds: The two compounds putatively bind to 2 separate binding sites: pore and voltage sensor domain

Virtual screening results

	Total		ChemDiv		Asinex	
	Tested	Hits	Tested	Hits	Tested	Hits
Query 1	149	36	84	19	65	17
Query 2	148	35	87	23	61	12
Totals	297	71	171	42	126	29
Hit rate (%)		23.9		24.5		23.0

Hits = >50% inhibition @ 30uM

- A slightly better hit-rate (# hits against compounds tested) was observed for ChemDiv dataset

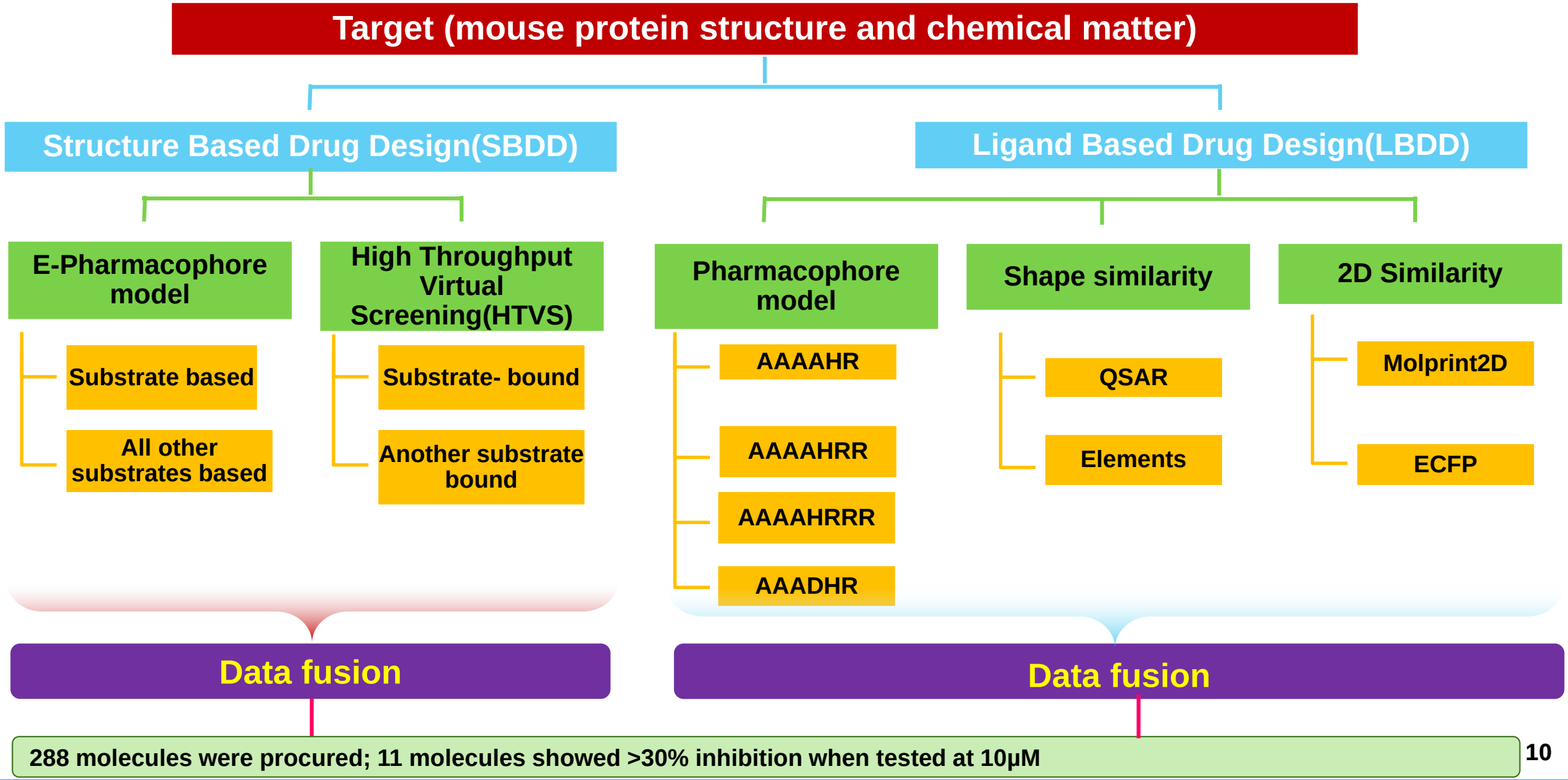
Performance evaluation of virtual screening methods

Query 2	Cresset Hits	Pharm_AA ADHR4453	Shape Elem	Shape_Mm od	Shape Pphore	Shape QSAR	FP_atmpr	FP_MACCS	FP Molprint	FP RadialDL2	FP RadialFc4	FP Topology	CAT screen
# of Cmpds	8858	8858	8858	8858	2438	8858	8858	8858	8858	8858	8858	8858	353
Hit-rate	50	47.1	41.2	30	21.1	46.4	21.1	19.6	21.3	22.2	20	23	11.1
Average Similarity	0.24	0.24	0.27	0.27	0.21	0.27	0.38	0.31	0.28	0.27	0.26	0.28	0.33

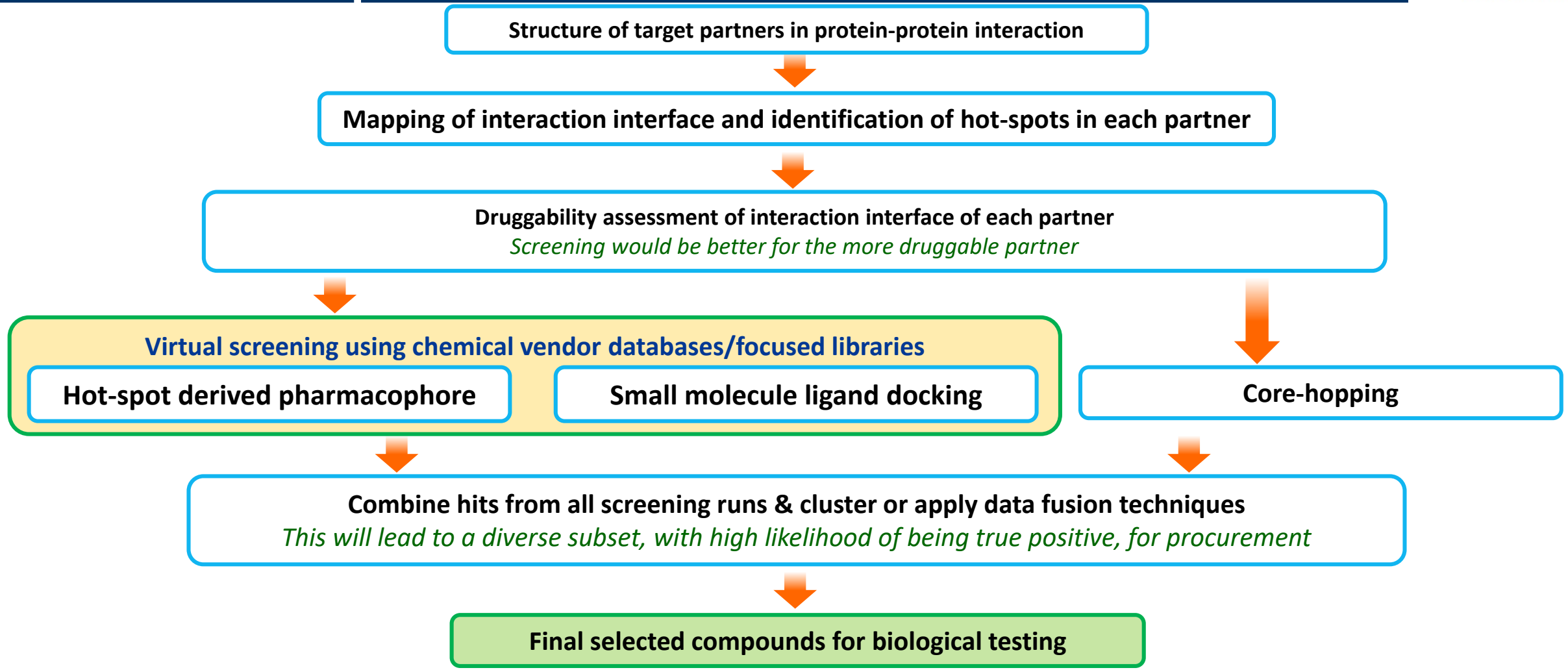
Query 1	Cresset hits	Pharm_A ARRR610 1	Pharm_ AARRR6 394	Shape elem	Shape mmod	Shape QSAR	Shape Pphore	FP AtmPr	FP MACCs	FP MolPrint	FP RadialDL2	FP RadialFC4	FP Topology	Cat search
# of Cmpds	5462	8882	8882	8882	8882	8882	2274	8882	8882	8882	8882	8882	8882	2317
Hit-rate	15.8	40.6	23.1	25	10	27.8	20	23.3	32	28.8	32.1	27.5	27.9	20
Average Similarity	0.24	0.27	0.25	0.27	0.26	0.27	0.26	0.32	0.28	0.22	0.22	0.23	0.25	0.24

- Average pair-wise similarity of hits using Tanimoto similarity based on atom-pair fingerprints
- This virtual screening campaign unearthed novel and diverse starting points. Of the novel hits found, 10 were taken up for hit-expansion
- The screening also illustrated which virtual screening methods appear effective for hit enrichment

Case study 2: Virtual Screening metal-containing enzyme



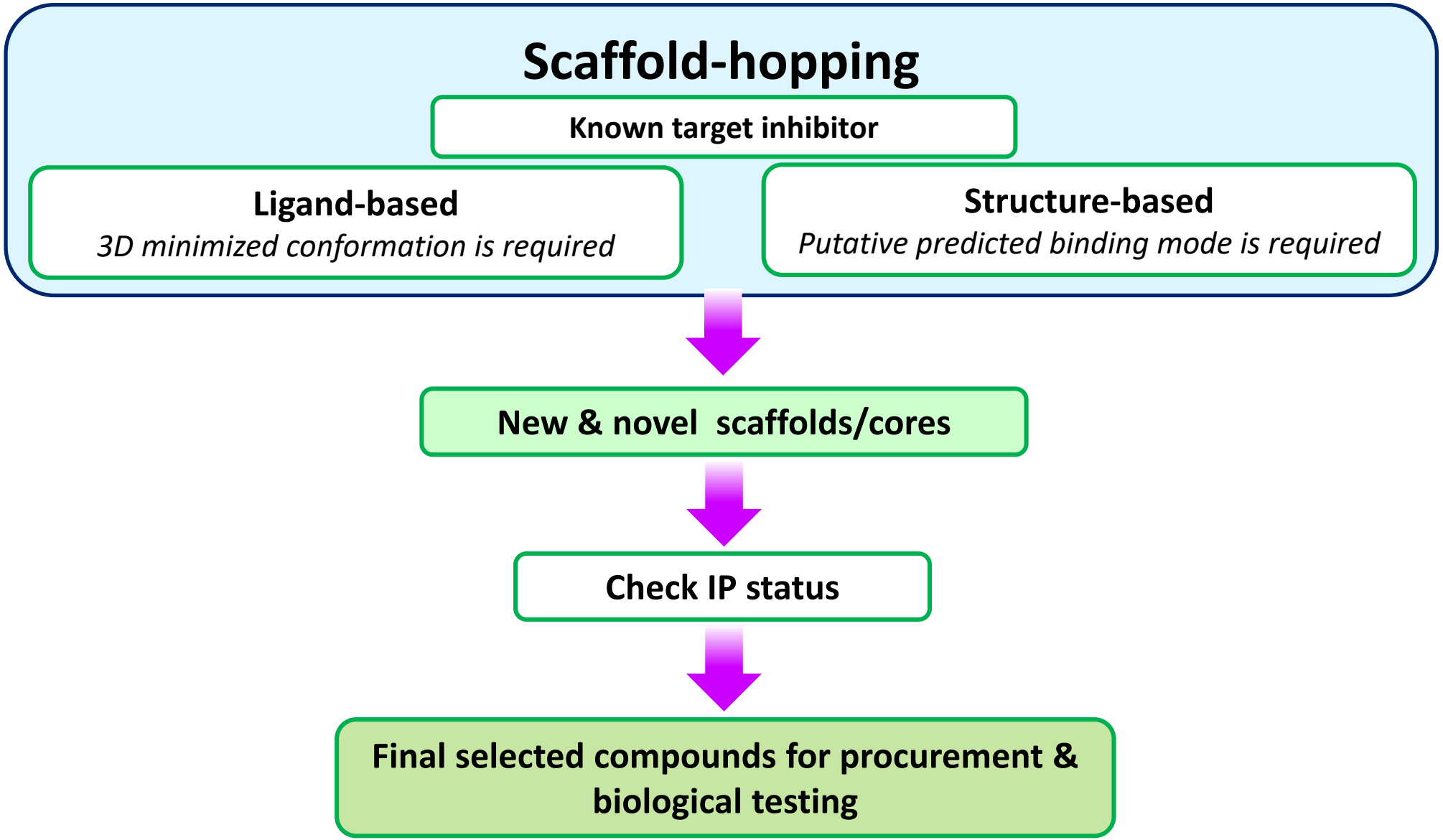
Virtual screening workflow for protein-protein interaction inhibitors/disruptors



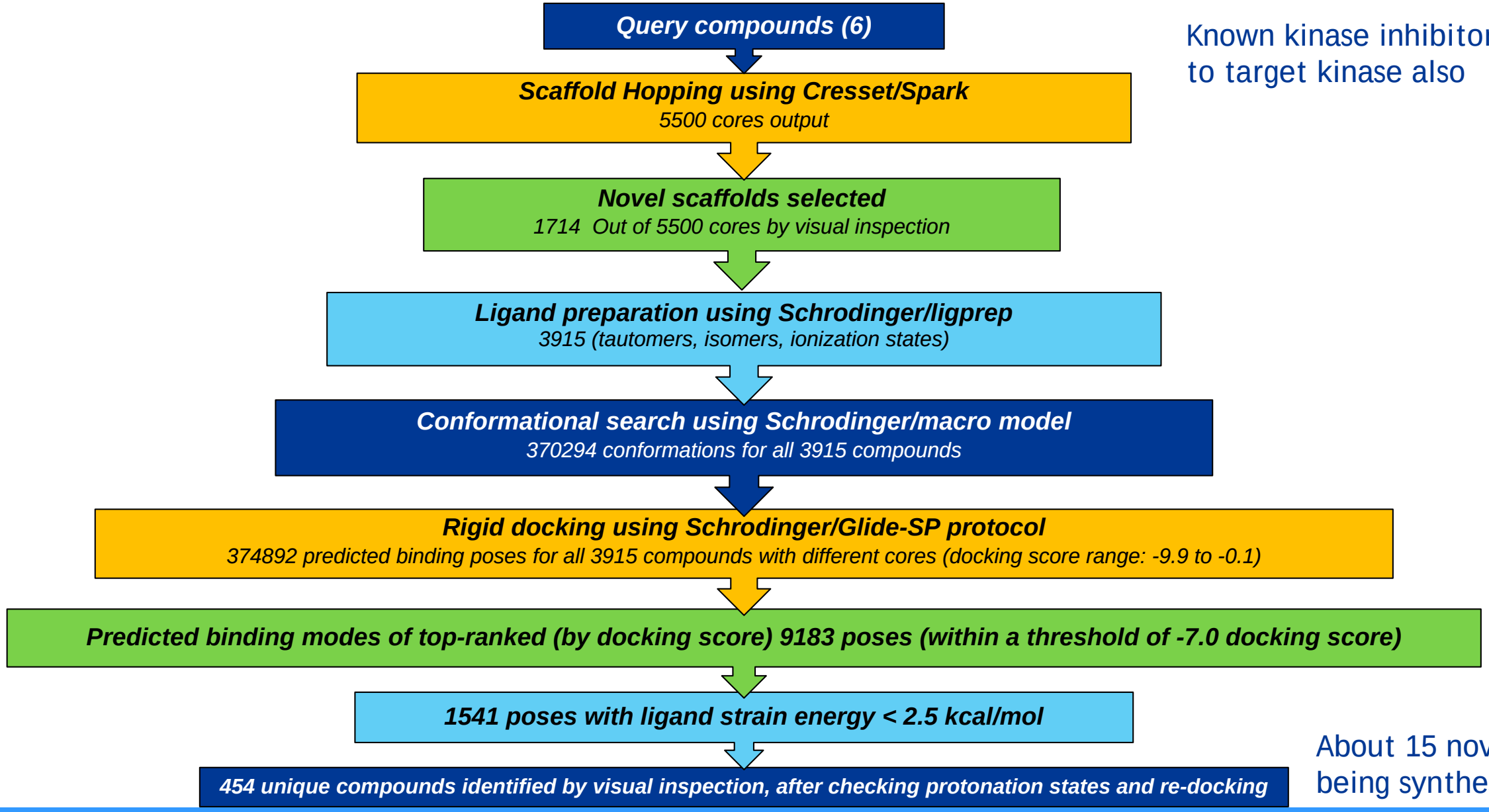
Notes

- If experimental target structures are not available, homology models can be helpful though less reliable
- Druggability as assessed using Schrodinger/SiteMap would help in determining which of the partner proteins has a more druggable interface
- Focused libraries of protein-protein interaction inhibitors are available from a few vendors like Asinex, Otava and so on
- Core-hopping can be used if a target-small molecule structure is available or from interacting peptide

Scaffold-hopping workflow



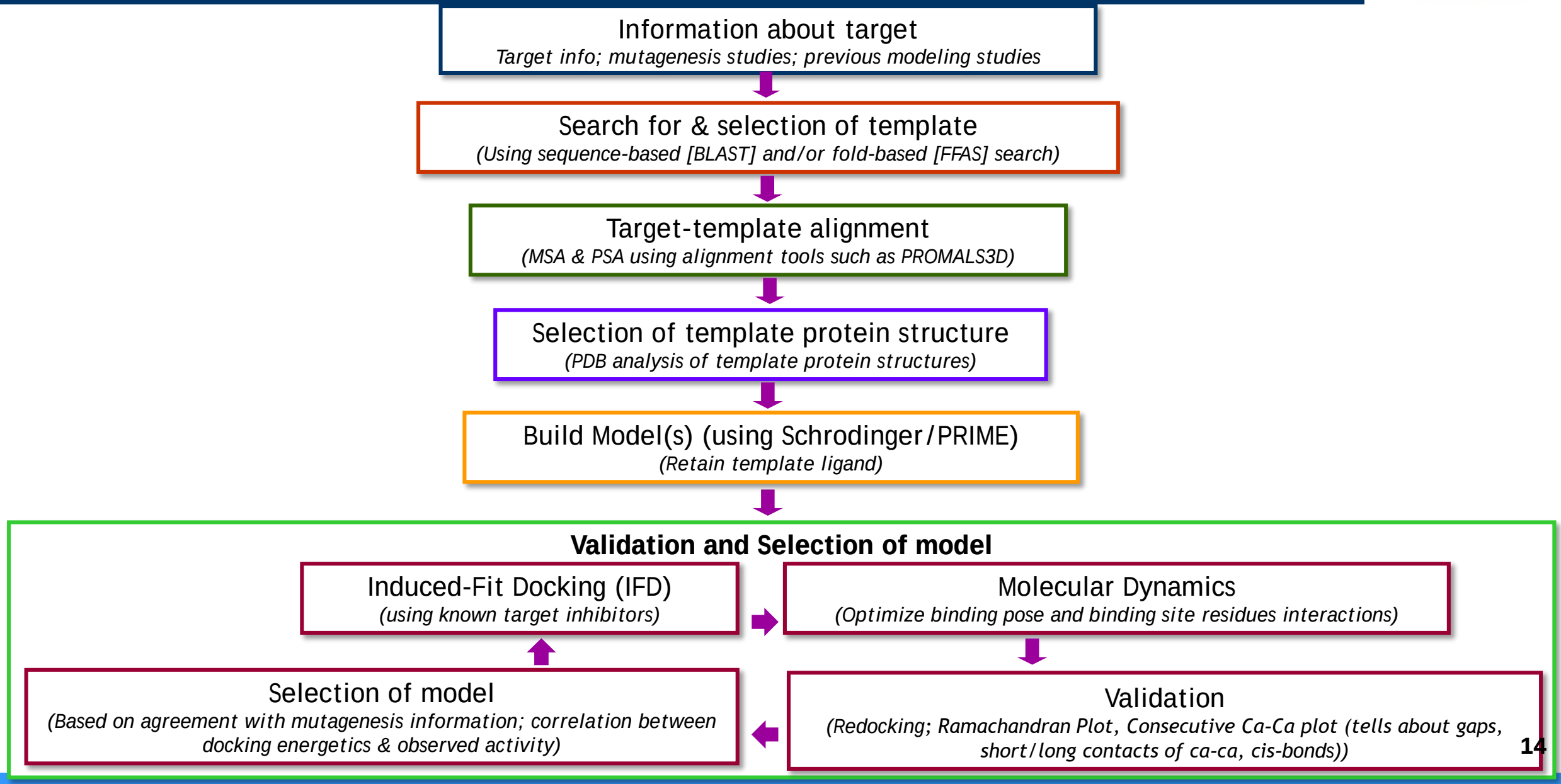
Scaffold Hopping case study: A kinase target



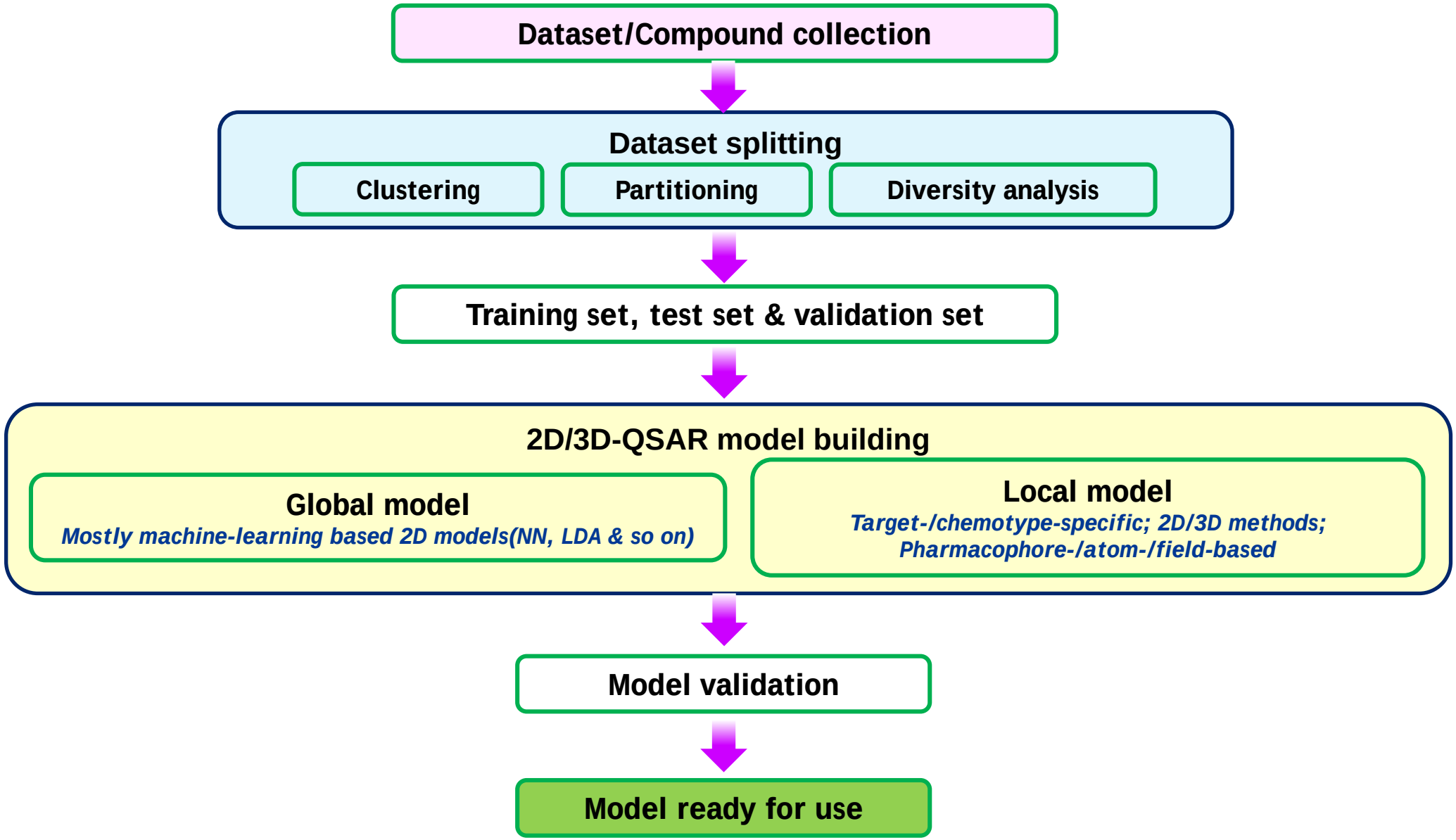
Known kinase inhibitors that bind to target kinase also

About 15 novel cores are being synthesized

Homology Modeling Workflow



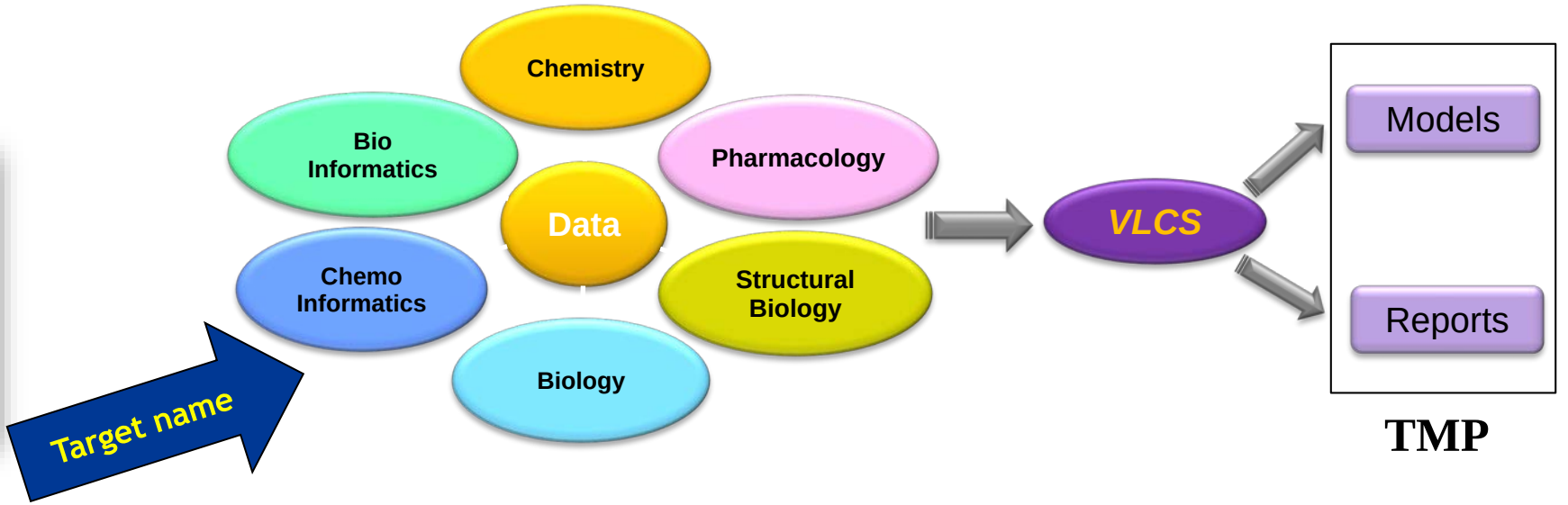
QSAR modeling workflow



Virtual Lab for Computational Support: TMP

Jubilant's VLCS empowers NCE discovery scientists to deploy ready-to-use models and make faster and wiser decisions: Given a target name, right information from varied sources is digested into knowledge by creating,

Target Modeling Package (TMP)



Docking	Pharmacophore	QSAR	Homology modeling	Miscellaneous
◈ Validated docking models ◈ Protein-ligand interactions ◈ Docking analysis of literature compounds and client compounds ◈ SAR analysis ◈ Selectivity analysis	⊙ Validated pharmacophore models ⊙ Database search ⊙ Activity prediction ⊙ SAR analysis ⊙ Selectivity analysis	◈ Validated 3D-/2D-QSAR models ◈ Activity predictions ◈ SAR analysis ◈ Selectivity analysis	⊙ Template search ⊙ Validated homology models ⊙ Sequence analysis ⊙ Structural analysis	◈ Analysis of PDBs ◈ Compare & characterize binding sites ◈ PDB water analysis ◈ Calculate ligand properties ◈ Correlate activity & properties

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Thank You for your Time

OUR PROMISE
Caring, Sharing, Growing

We will, with utmost care for the environment and society, continue to enhance value for our customers by providing innovative products and economically efficient solutions; and for our stakeholders through growth, cost effectiveness and wise investment of resources

Our Values

INSPIRE CONFIDENCE

ALWAYS STRETCH

NURTURE INNOVATION

EXCELLENT QUALITY