MISSIONE 4
ISTRUZIONE
RICERCA

Finanziato dall'Unione europea
NextGenerationEU

Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

VITALITY

Integrated platform for hit identification and optimization: computational and biophysical assets

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1506 UNIVERSITÀ DEGLI STUDI DI URBINO CARLO BO

Ud'A

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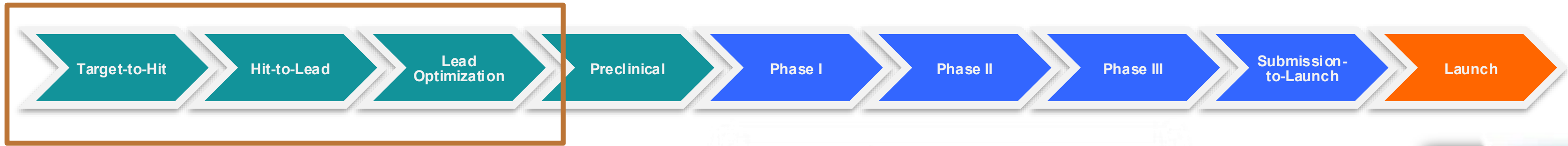
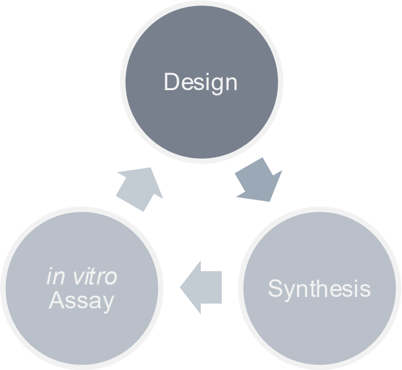
COSMOB TECHNOLOGICAL CENTER

MECCANO

WP1 - Development of a third party-accessible, enabling platform for efficient preclinical drug discovery


Target-to-Hit
Hit-to-Lead
Lead Optimization
Preclinical
Phase I
Phase II
Phase III
Submission-to-Launch
Launch


Design
Synthesis
in vitro Assay

- Ultra Large Commercial Libraries (10^9)
- DL-generated Compounds (10^7)
- Combinatorial SAR Explorations (10^4)

Compound Prioritization by Computational Means (10^2)


Biochemical or Functional Assays


Surface Plasmon Resonance (SPR)


MicroScale Thermophoresis (MST)


Circular Dichroism (CD)


Nuclear Magnetic Resonance (NMR)

Biophysical Assays

HPC platform for virtual screening campaign

TASK1.1 - Setting Up and Validating a Hit Identification Computational Facility as part of VITALITY Enabling Platform for Drug Discovery

HPC infrastructure is currently being installed @Campus Enrico Mattei (P74 01.01.01.74)

E4
COMPUTER ENGINEERING

- ☐ 2 AMD Epyc 64-Core 7713 2.00 GHz 256 MB
- ☐ 4 GPU NVIDIA RTX A6000 48 GB
- ☐ Increased storage capacity to nearly 40 TB with a shared repository:
  - ☐ Prepared libraries, including diversity sets, covalent inhibitors and biomimetics, in a readable format for docking calculations
  - ☐ Enamine REAL (2022q34) as binary 1D-fingerprints allowing for screening of commercial compounds (purchased December 2023)
  - ☐ Upcoming preparation of Python scripts allowing for:
    - ☐ batch interrogation of online databases (i.e., ChEMBL, SwissTargetPrediction, PolyPharmacologyBrowser2, etc.)
    - ☐ pipeline allowing for active learning docking to prioritize compounds for virtual screening
    - ☐ customized protocols for molecular dynamics workflows as fast virtual screening post-processing tools

HPC platform for virtual screening campaign

Software capabilities

- ☐ Virtual screening
  - ☐ Structure-based: Glide
  - ☐ Ligand-based: Shape, Phase

→ **Hit identification and validation**
Lead optimization

- ☐ Molecular dynamics/enhanced sampling simulations
  - ☐ Desmond, Amber, Gromacs
  - ☐ BiKiLifeSciences
  - ☐ Plumed

→ **Hit prioritization**
Lead optimization
Mechanistic studies

- ☐ QM / QM-MM calculations
  - ☐ Amber, Jaguar

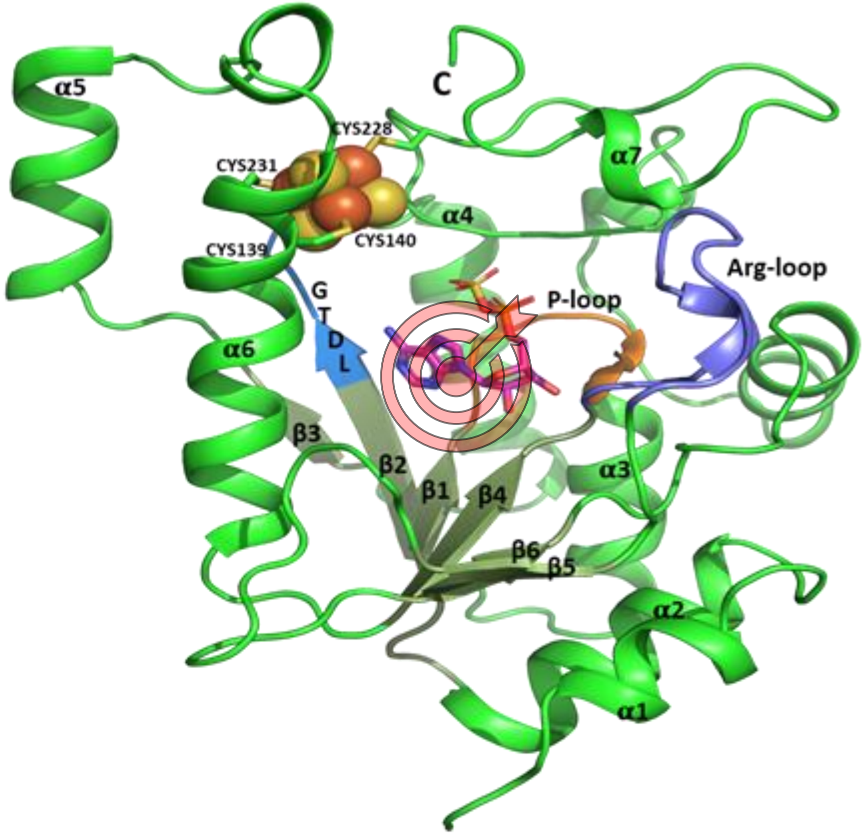
→ **Lead optimization**
Mechanistic studies
Support to synthetic organic chemistry

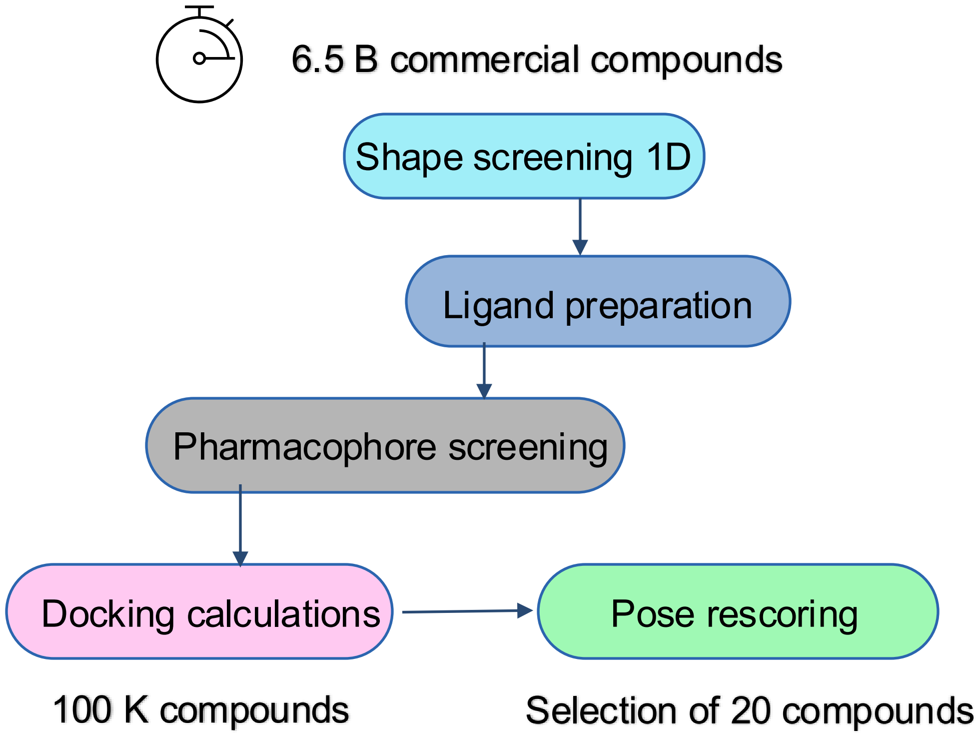
- ☐ Data processing
  - ☐ DataWarrior, Knime
  - ☐ RDKit, Python libraries

→ **Data analysis**
Machine learning applications
Lead optimization

HPC platform for virtual screening campaign

Case study: Selection of potential adenosine 5′-phosphosulfate reductase potential inhibitors





6.5 B commercial compounds

Shape screening 1D

Ligand preparation

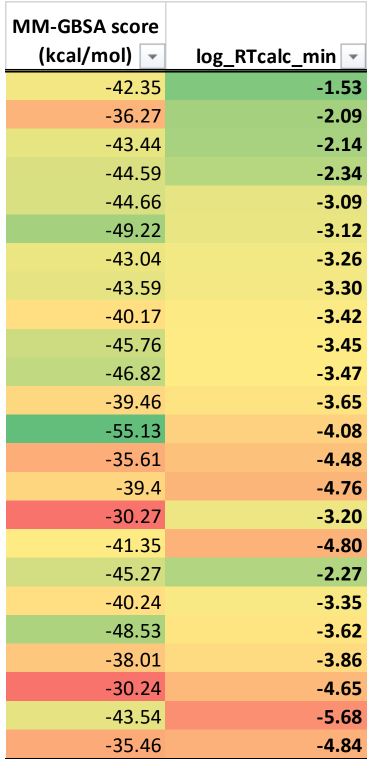
Pharmacophore screening

Docking calculations

Pose rescoring

100 K compounds

Selection of 20 compounds



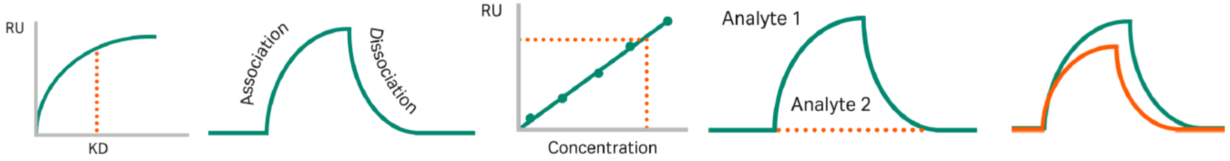
MM-GBSA score (kcal/mol)	log_RTcalc_min
-42.35	**-1.53**
-36.27	**-2.09**
-43.44	**-2.14**
-44.59	**-2.34**
-44.66	**-3.09**
-49.22	**-3.12**
-43.04	**-3.26**
-43.59	**-3.30**
-40.17	**-3.42**
-45.76	**-3.45**
-46.82	**-3.47**
-39.46	**-3.65**
-55.13	**-4.08**
-35.61	**-4.48**
-39.4	**-4.76**
-30.27	**-3.20**
-41.35	**-4.80**
-45.27	**-2.27**
-40.24	**-3.35**
-48.53	**-3.62**
-38.01	**-3.86**
-30.24	**-4.65**
-43.54	**-5.68**
-35.46	**-4.84**

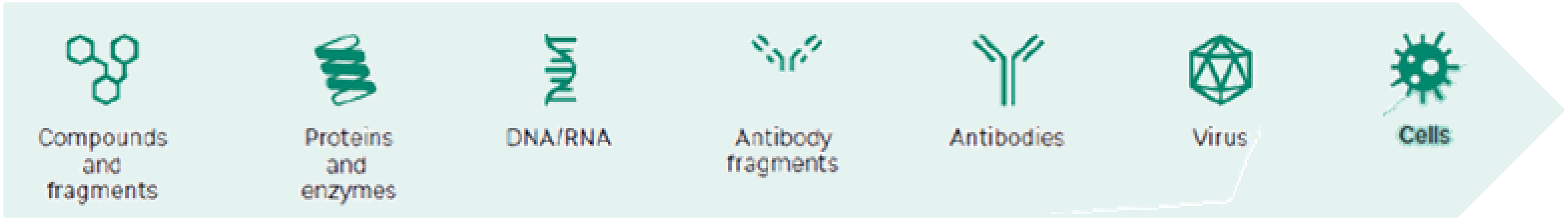
in collaboration with Michele Mari and Emanuela Frangipani

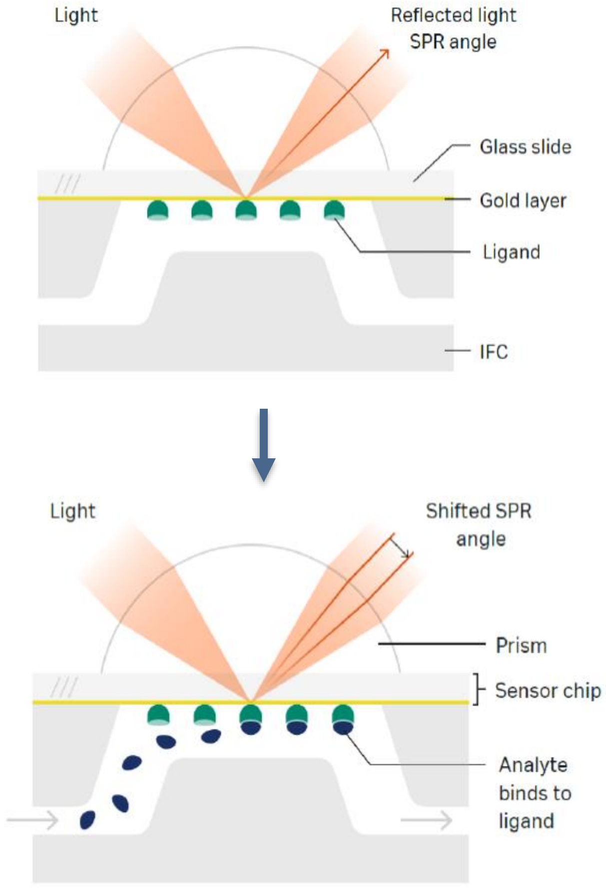
Surface Plasmon Resonance

Cytiva Biacore™ 1K

How strong?	How fast?	How much?	How specific?	How similar?
Affinity reflects the binding strength	**Kinetics** determine how fast/slow a complex forms or dissociates	Qualitative and quantitative determination of active analyte **concentration**	Is the molecule **specific** for its target?	**Comparable** to reference product or not?







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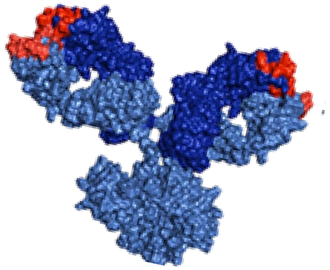
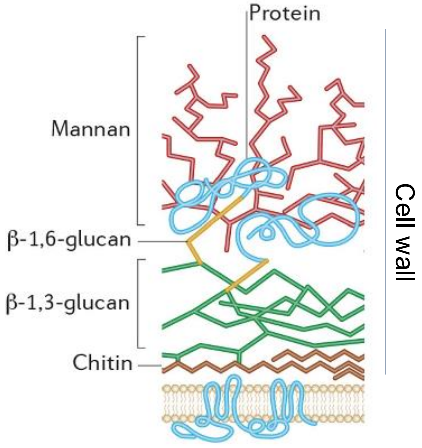
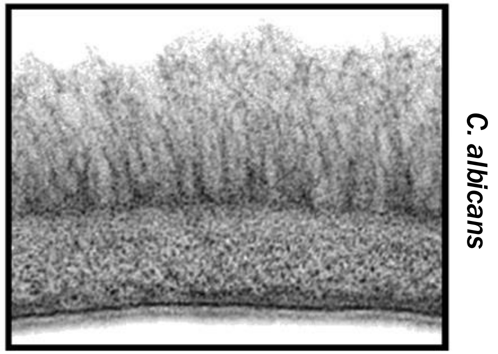
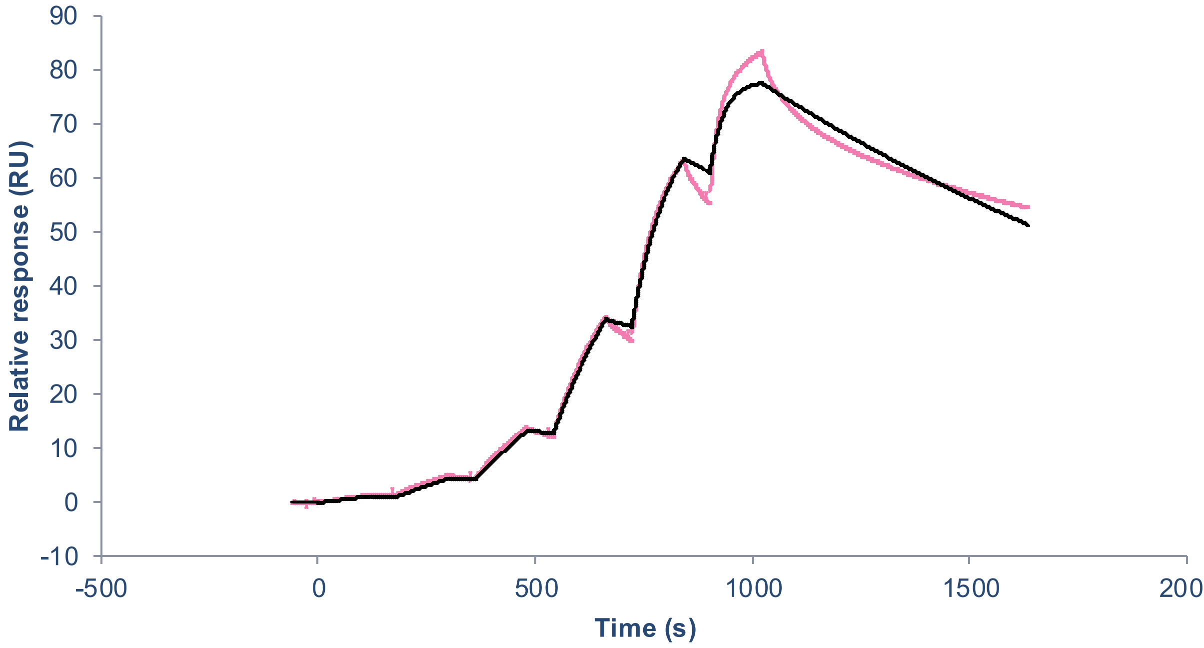




N. Gow et al. 2017





Cycle	Flow cell	Sensorgram type	Analysis step purpose	Single cycle kinetics 1 Solution	Single cycle kinetics 1 Concentrations (nM)	SCK binding late_1_6 Relative (RU)	Capture level_2 Relative (RU)
7	2-1	Reference subtracted	Analysis	Laminarin	0.69 2.06 6.17 18.52 55.57 166 [nM]	112.9	2592.0

Group	General Kinetics model	Curve markers	Flow cell	Injection variables Capture 1 Solution	Single cycle kinetics 1 Solution	Quality Kinetics Chi² (RU²)	1:1 binding ka (1/Ms)	kd (1/s)	KD (M)	Rmax (RU)	tc
1	1:1 binding		2-1	Irrilevant mAb	Laminarin	3.29e+00	1.87e+05	6.71e-04	3.59e-09	79.7	1.02e+12