HPC in Drug Discovery

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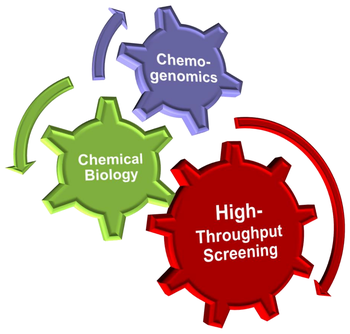
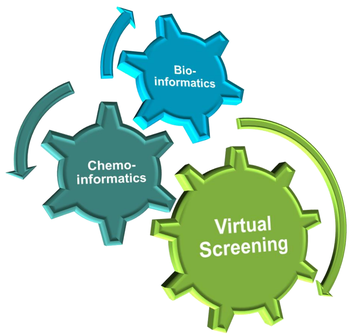
Cornerstone Technologies in Drug Discovery



Chemistry Lab based
- Expensive
- Protracted
- Difficult



HPC Simulation-based
- Inexpensive
- Very fast
- Useful for early stages

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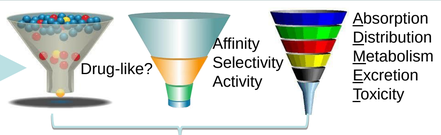
In silico Screening Complements High-throughput Screening

Chemical database
N=1,000,000

Structure-based & Ligand-based screens



Computational Tools:
- DESMOND
- GROMACS
- CHARMM
- SCHRODINGER

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Lead candidates
N=500

Inactive

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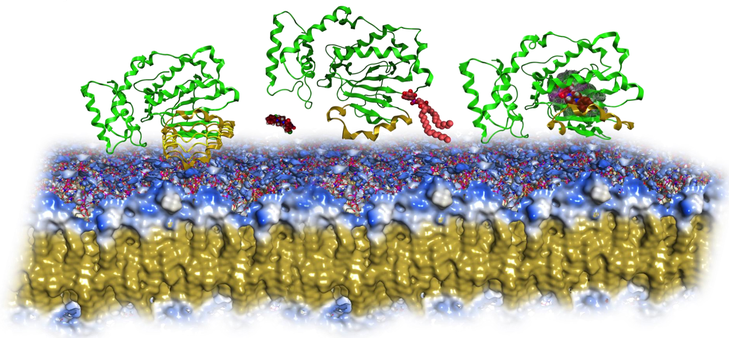
Phosphatidylinositol Transfer Proteins (PITPs) Important in Cell Function

- Important in Lipid-mediated cell signaling and metabolism.
- Derangement in Signaling: Neurodegenerative diseases and many forms of cancers.



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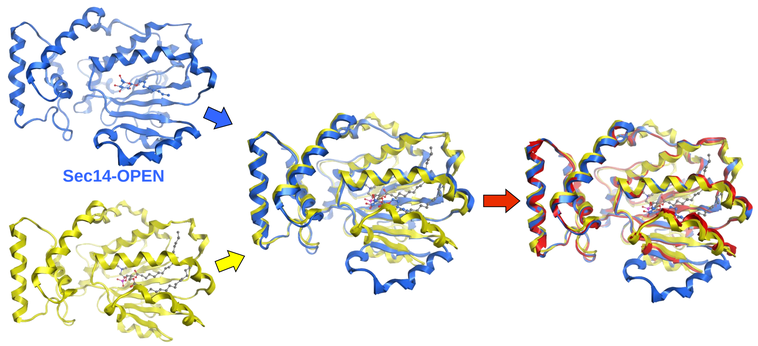
Homology Modeling of Sec14 (Closed Conformation)



Identity: 62 %
Similarity: 78 %
Homology: 77 %

Yellow: Sfh1
Blue: Sec14-OPEN
Red: Sec14 Homology Model-CLOSED

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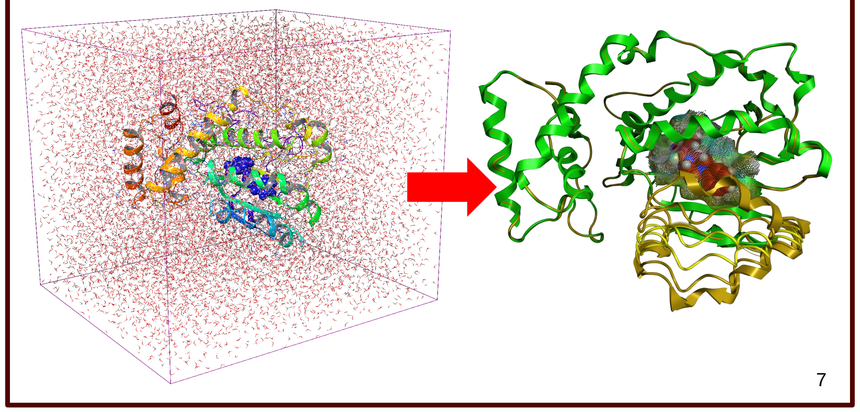
Sec14 Homology Model
All-atom MD Simulation



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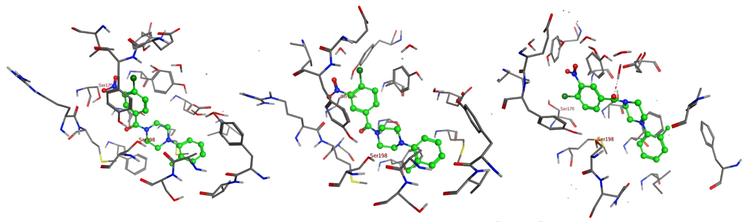
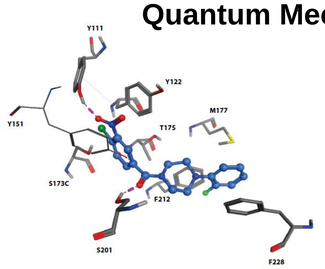
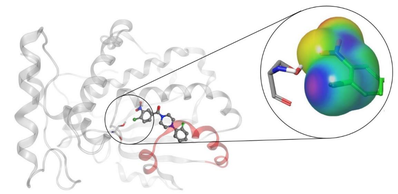
Drug Binding Analysis and Mechanism of Action



Quantum Mechanics Calculations





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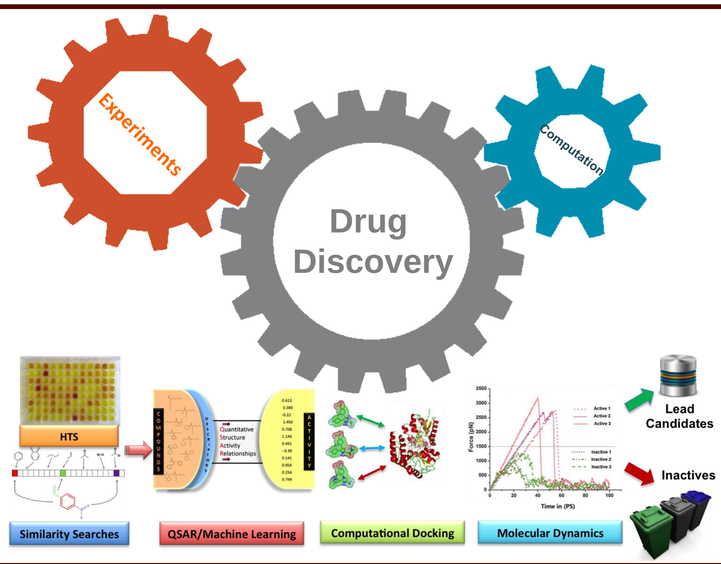

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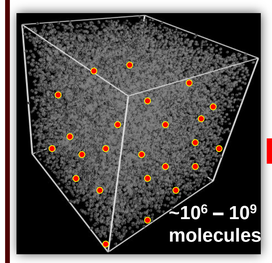
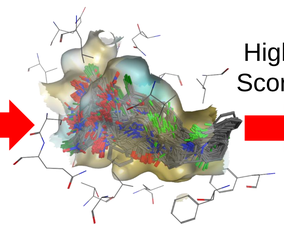
Computational Docking based Screening

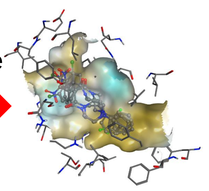


Chemical Database



Target Protein

High Score



Top Ranking Hits

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Summary

- Identified first ever small molecule inhibitor against Sec14-like PITP.
- Validated PITPs as ‘druggable’ target protein.
- Computational Docking provided insights into drug binding to PITP.
- Large scale all atom MD simulations explored drug binding modes and conformational dynamics of PITP.
- Predictive computational modeling guided experimental studies to validate mechanism of action.
- We have established a High-throughput Screening (HTS) and HPC based Cheminformatics platform for Drug Screening and Discovery.

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