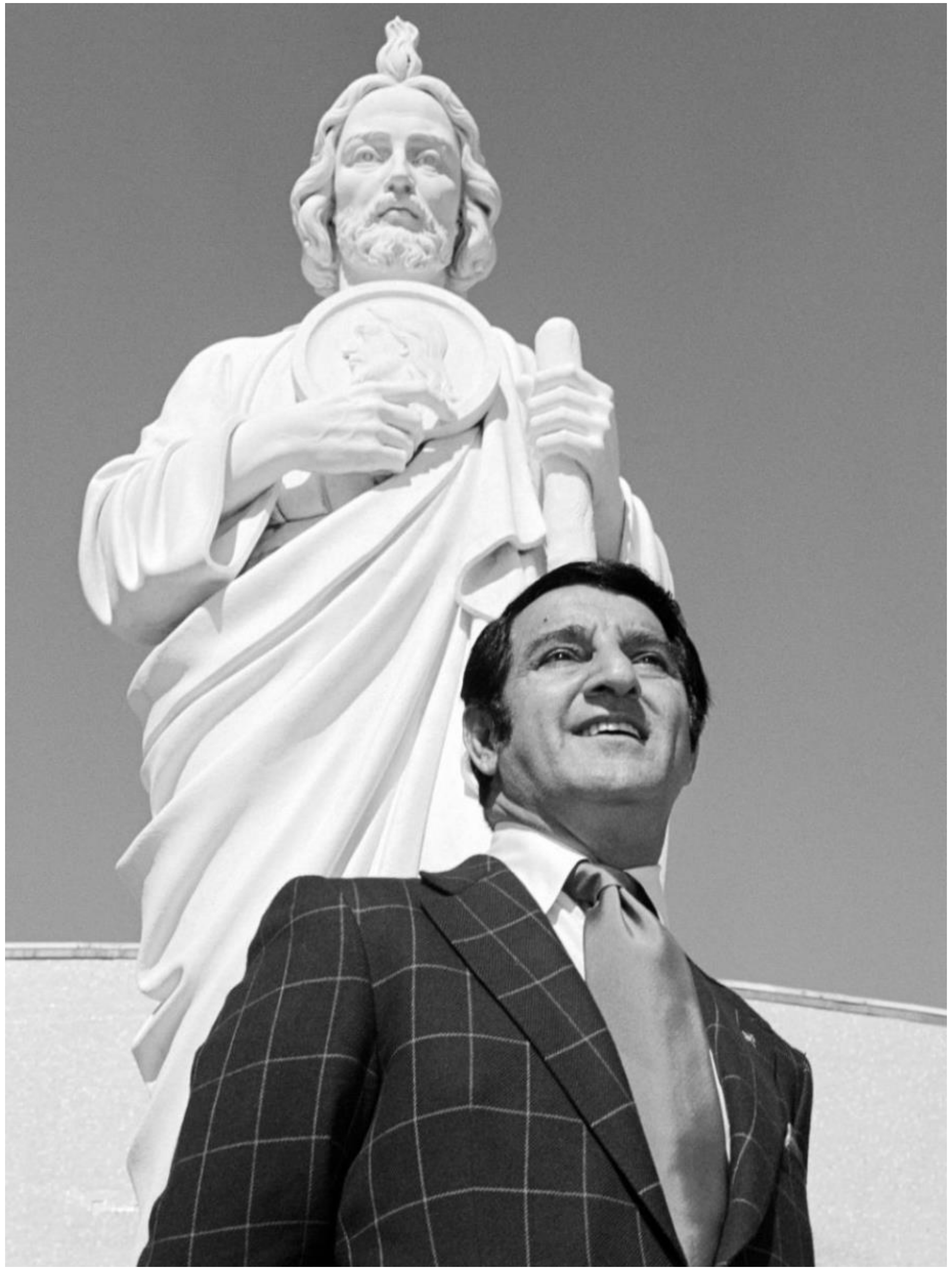
St. Jude Children's Research Hospital
Finding cures. Saving children.

Quantum Computing-Enhanced Machine Learning Algorithm Unveils Novel Inhibitors for KRAS

NASEM - Advancing Drug Discovery: A Webinar Series of the National Academies of Sciences, Engineering and Medicine

April 28th, 2025

Christoph Gorgulla, PhD
Faculty (Assistant Member)
Center of Excellent for Data-Driven Discovery
Structural Biology Department
St. Jude Children's Research Hospital

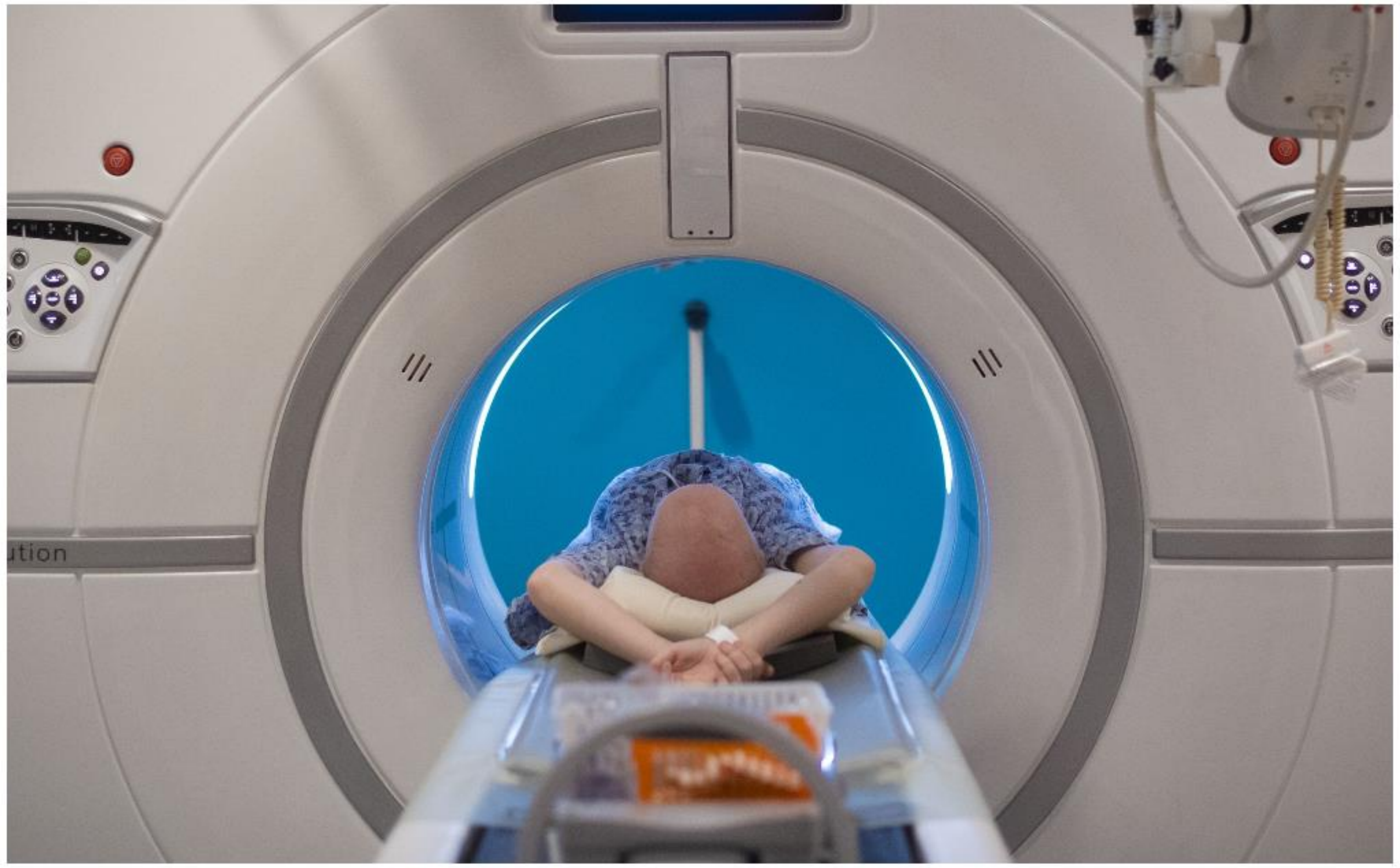



St. Jude Children's Research Hospital
Danny Thomas, Founder

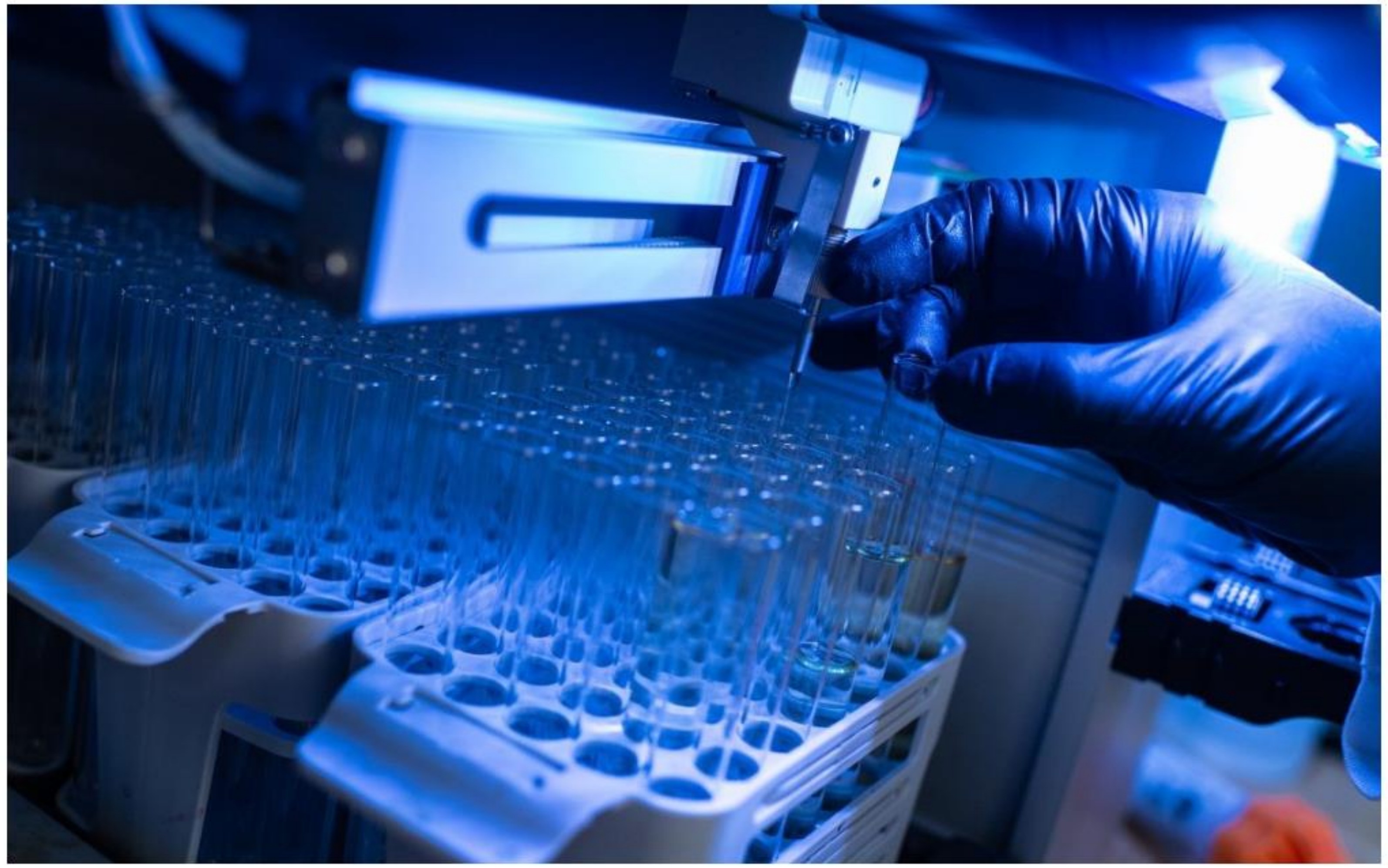
No child should die in the dawn of life...

— Danny Thomas

Mission



Treatment of Patients



Research to Cure Cancer

Families never receive a bill from St. Jude for treatment, travel, housing or food — so they can focus on helping their child live.

St. Jude has acquired the most powerful superconducting magnet in the world – it will help researchers see farther into the molecules of cells than ever before.


The First All-Civilian
Mission To Orbit
FOUR CREW MEMBERS REPRESENTED THE MISSION PILLARS OF
LEADERSHIP, HOPE, GENEROSITY, AND PROSPERITY
INSPIRATI4N
Source: https://inspiration4.com

The First All-Civilian Mission To Orbit

FOUR CREW MEMBERS REPRESENTED THE MISSION PILLARS OF
LEADERSHIP, HOPE, GENEROSITY, AND PROSPERITY

INSPIRATI4N

Hope

Hayley Arceneaux served as Medical Officer. She is a physician assistant at St. Jude Children's Research Hospital and a pediatric cancer survivor.

Meet Hayley

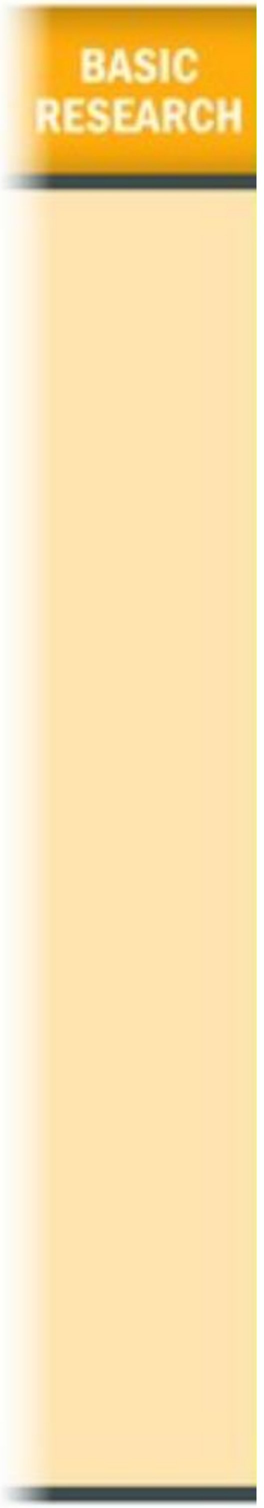
Source: https://inspiration4.com

Agenda

1. Introduction to St Jude
2. Hybrid Quantum Algorithm for Drug Discovery
3. Application to KRAS
4. Outlook

Quantum Computing for Drug Discovery

Drug Development Process



Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf (accessed Jan. 20, 2015).

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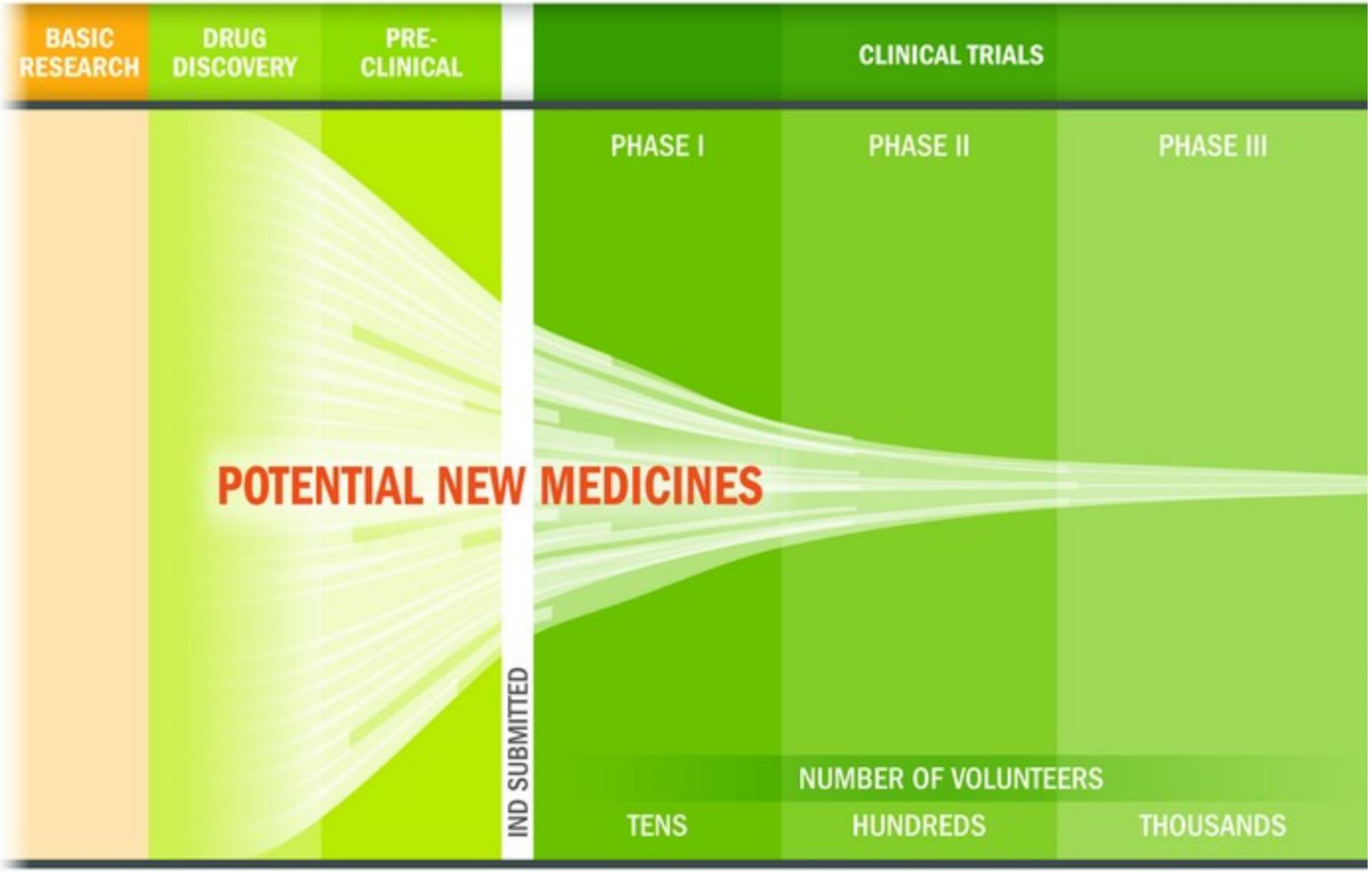

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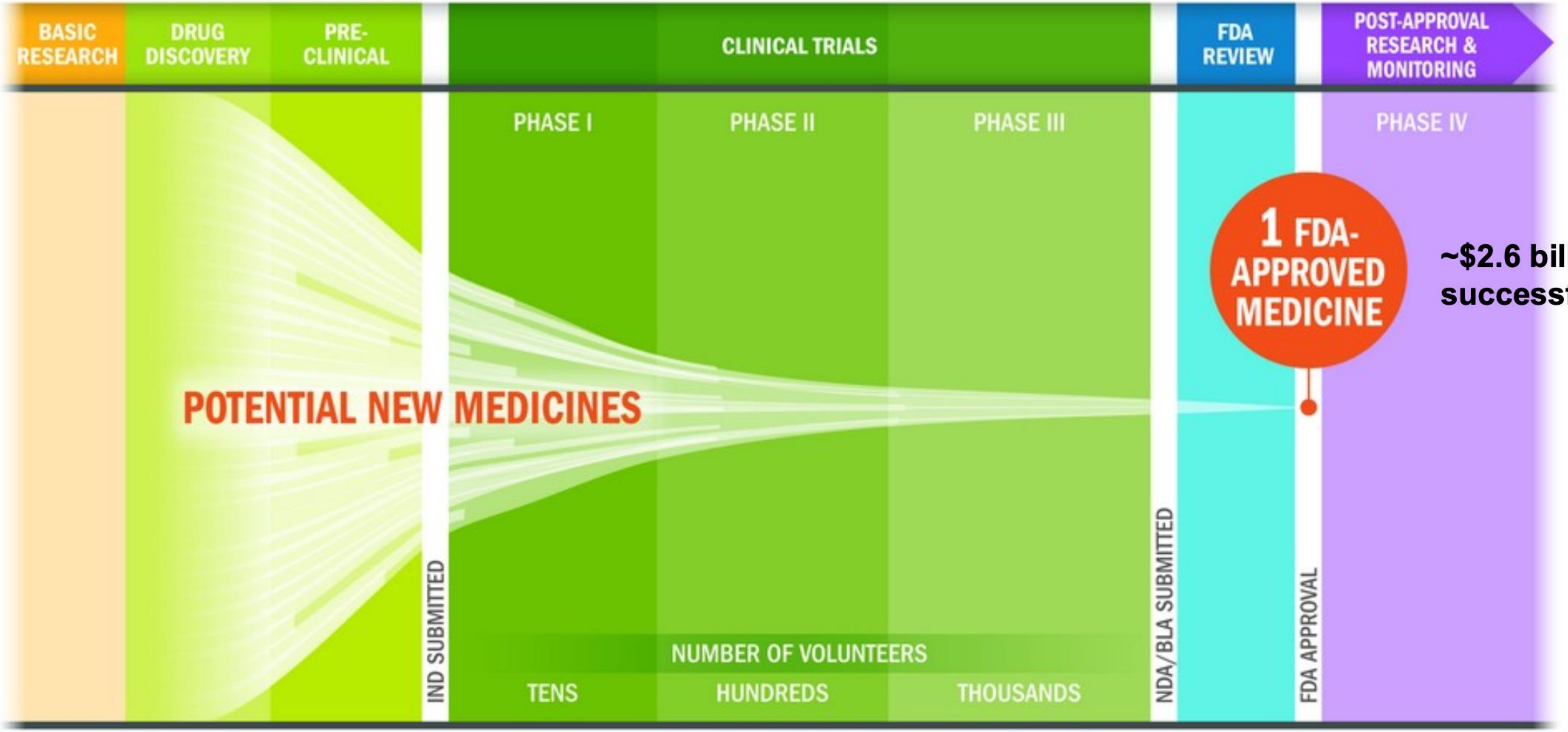

~$2.6 billion per successful drug

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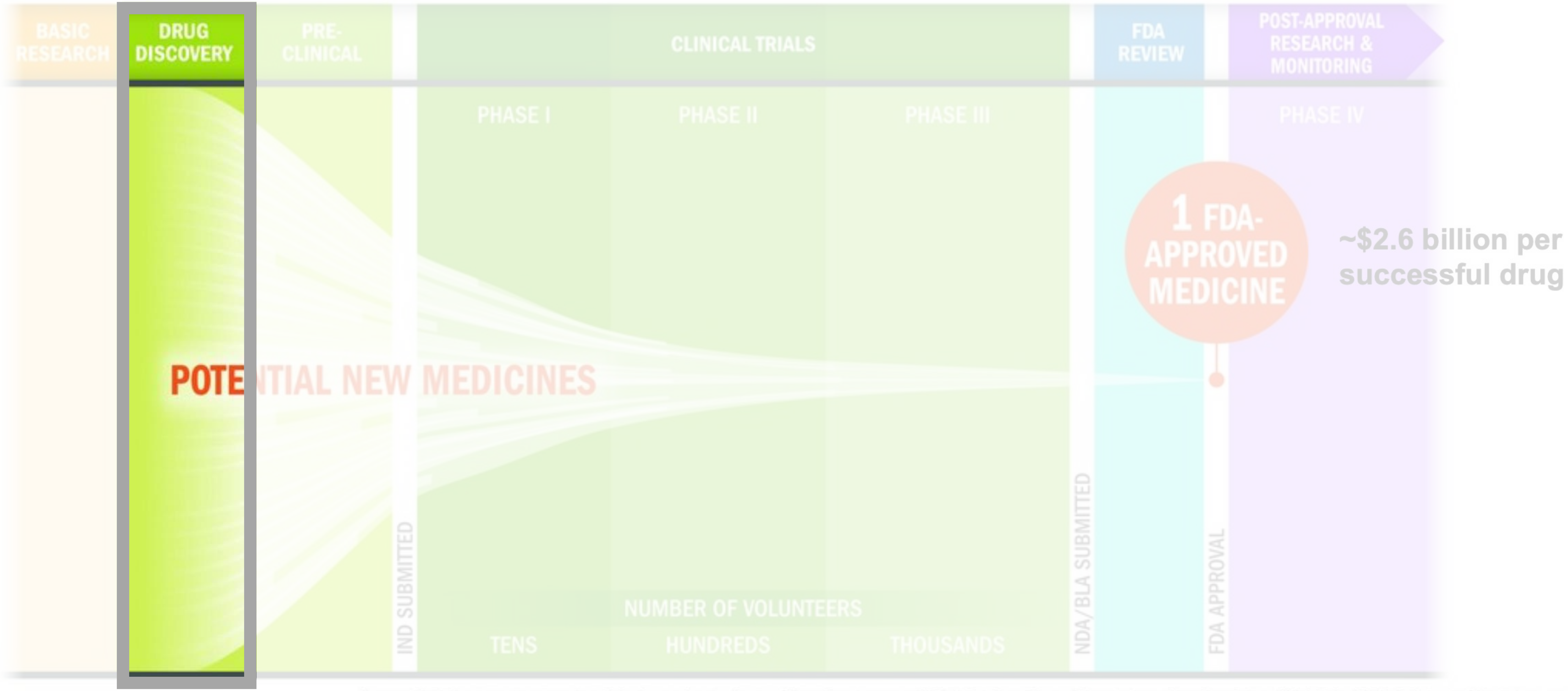

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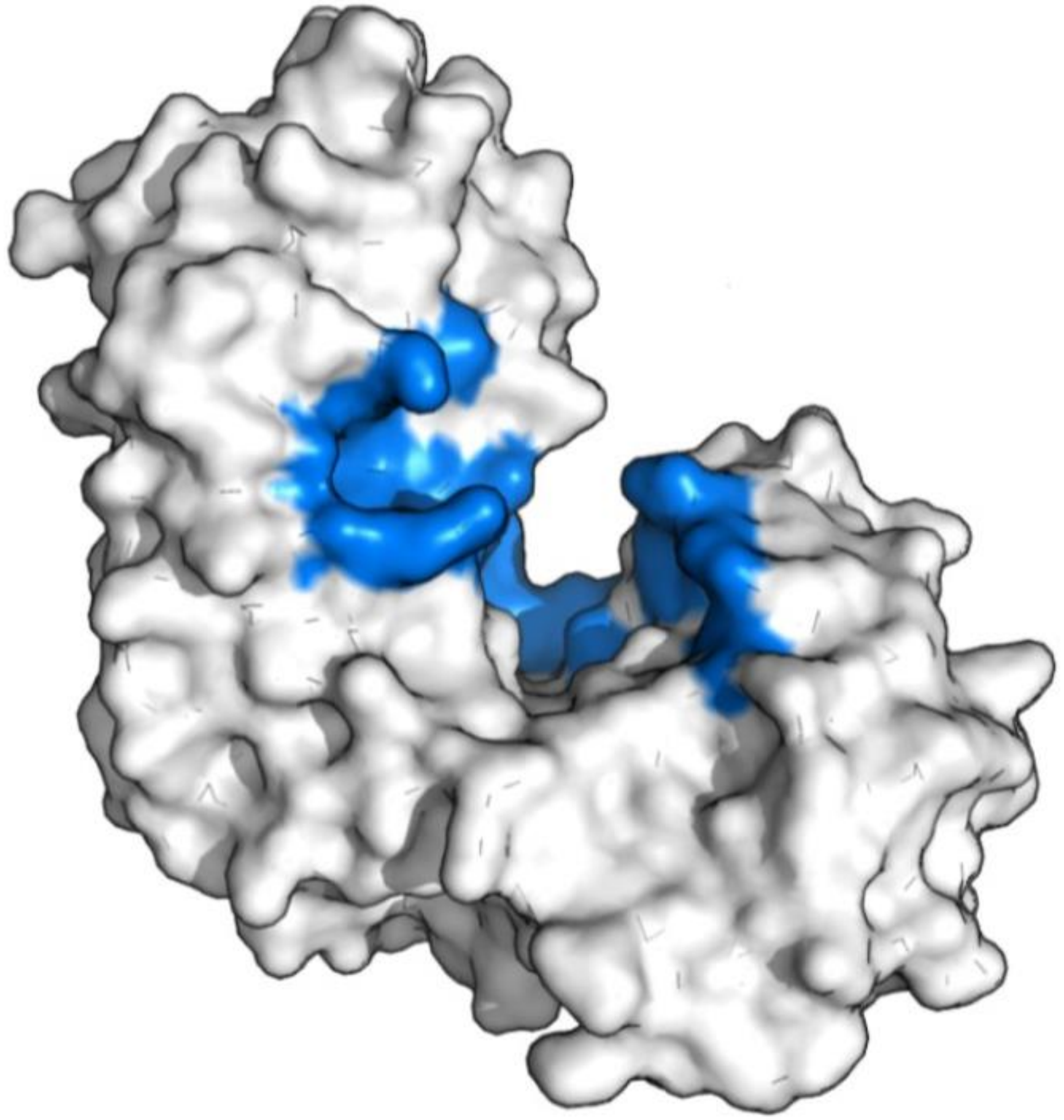
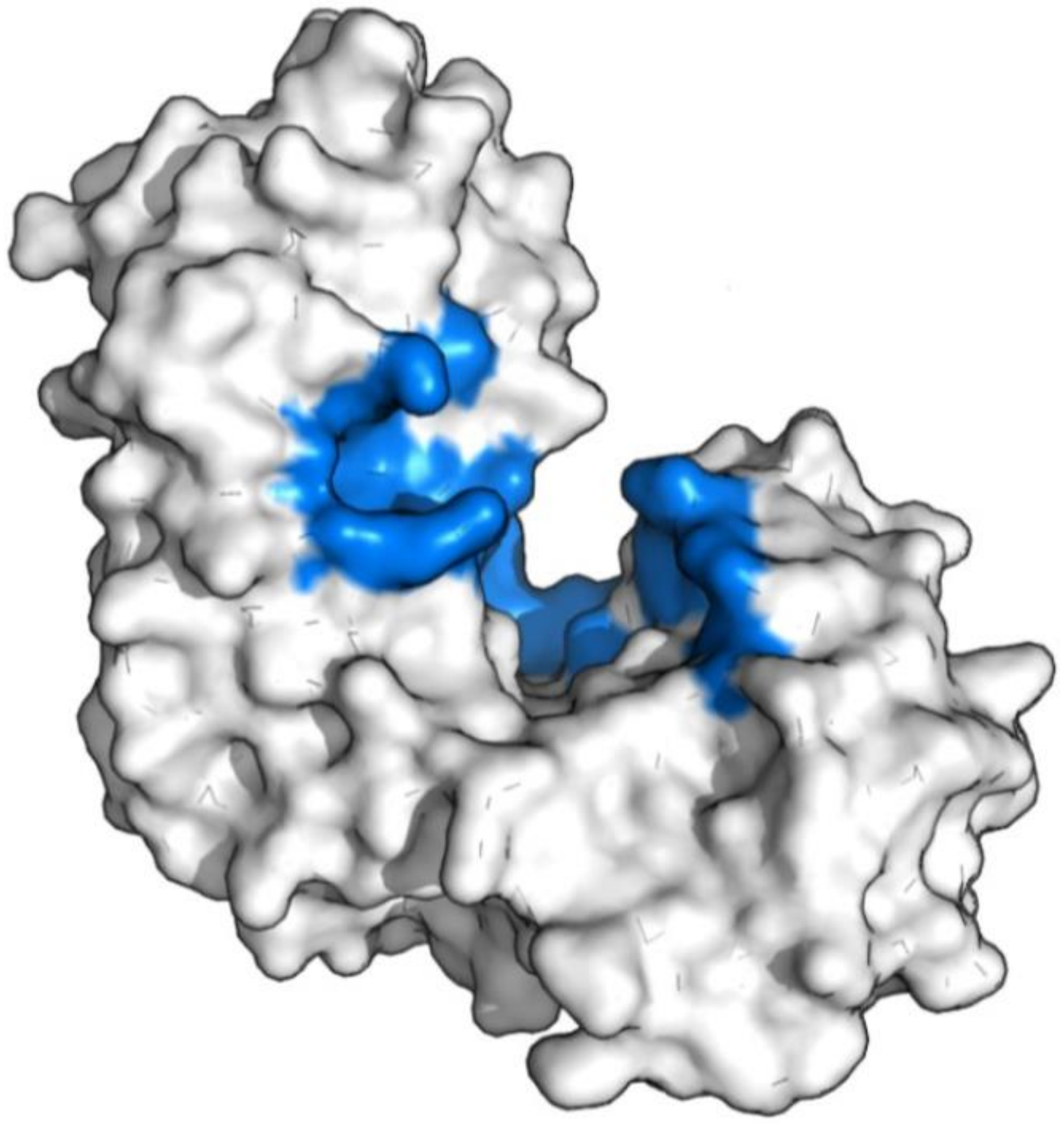
Initial Hit Discovery



Initial Hit Discovery



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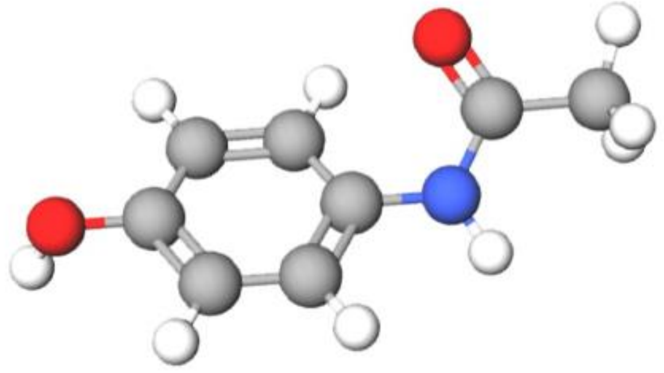
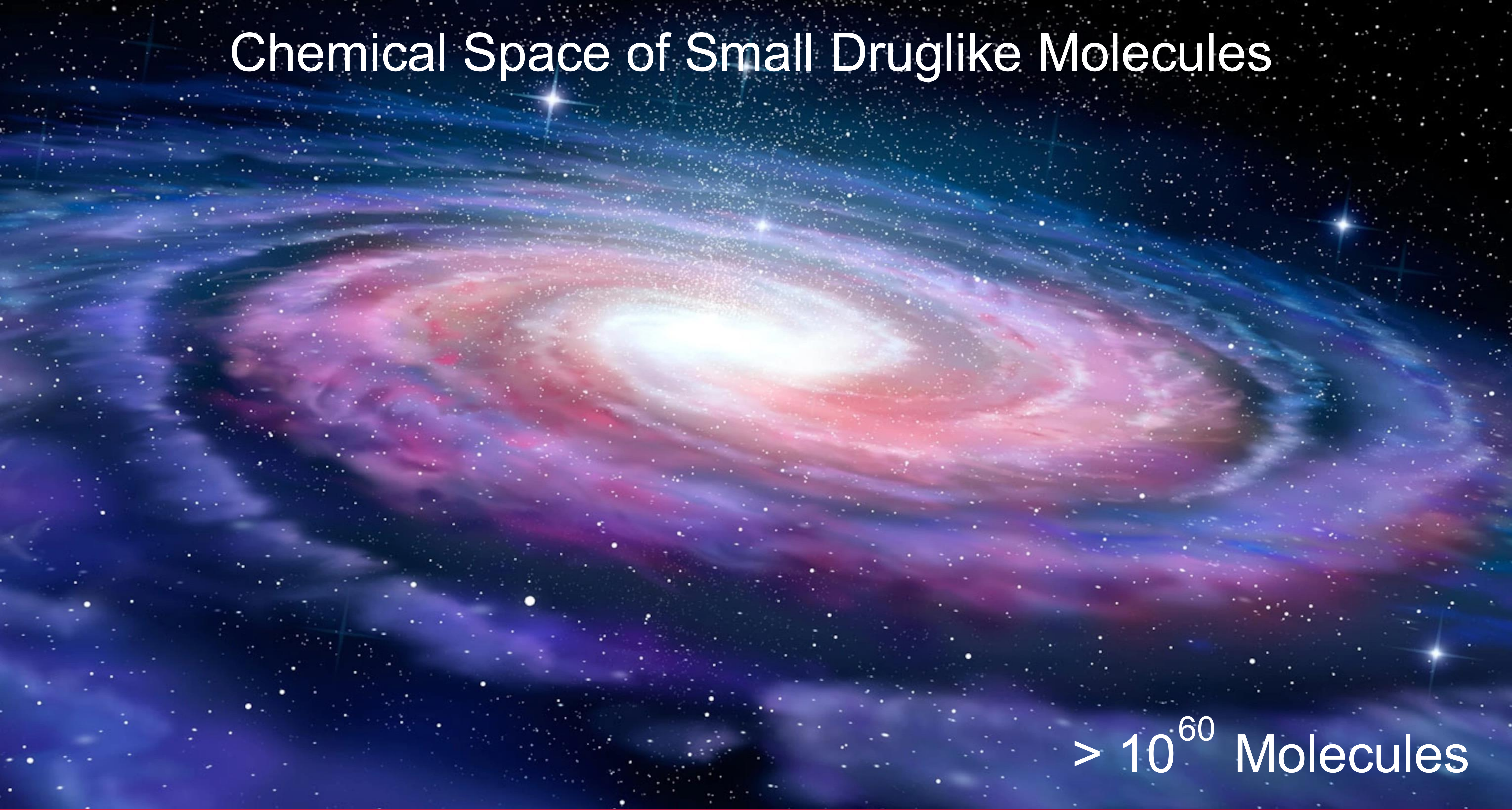


Chemical Space of Small Druglike Molecules

Chemical Space of Small Druglike Molecules



$> 10^{60}$ Molecules

Chemical Space of Small Druglike Molecules

Virtual Screening-Based Approaches

$> 10^{60}$ Molecules

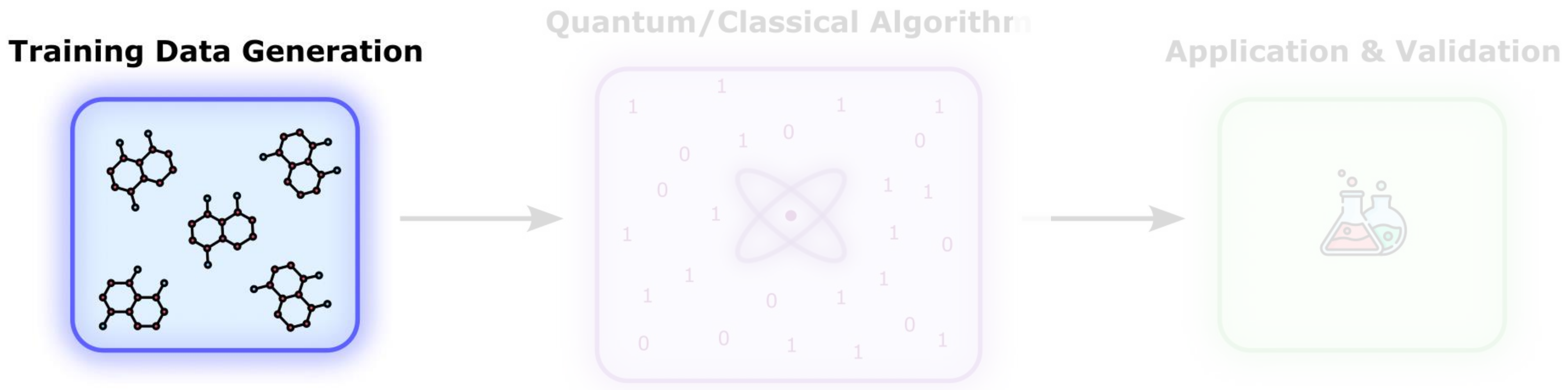
Chemical Space of Small Druglike Molecules

Virtual Screening-Based Approaches

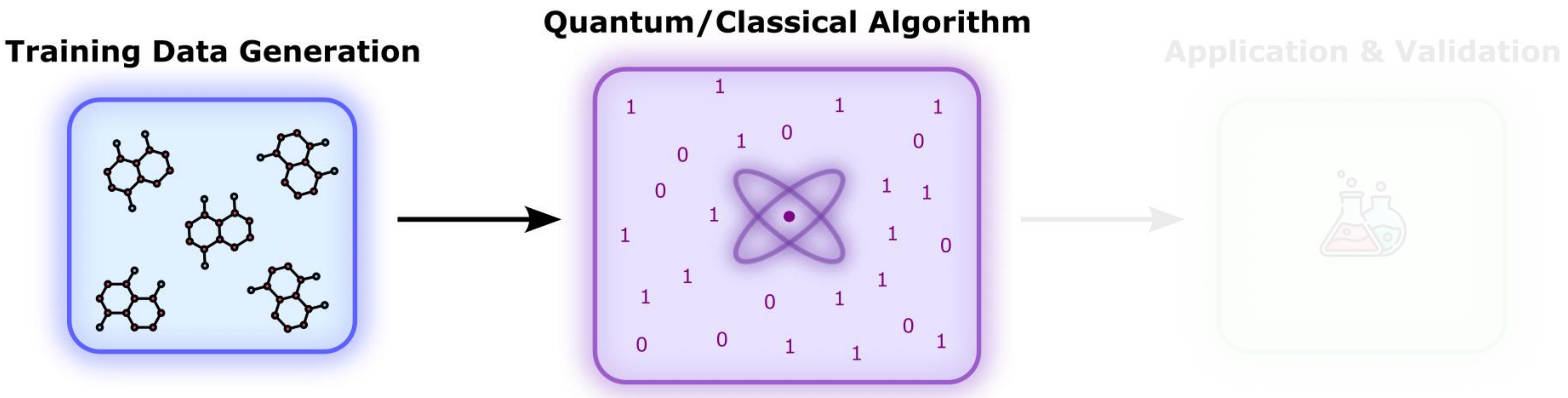
Machine Learning Approaches

$> 10^{60}$ Molecules

Hybrid Quantum-Classical Approach



Hybrid Quantum-Classical Approach



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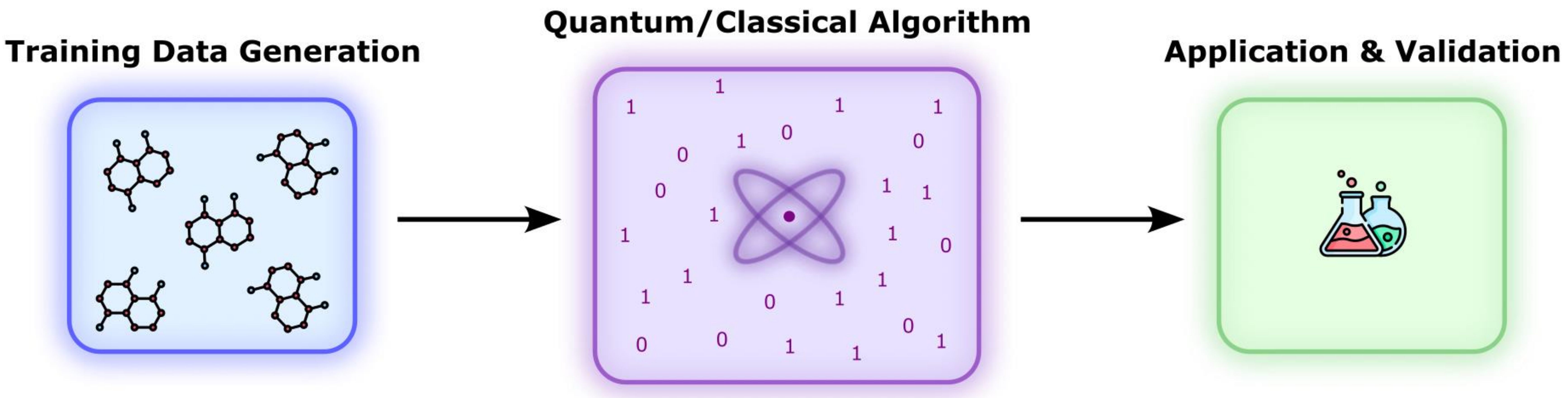

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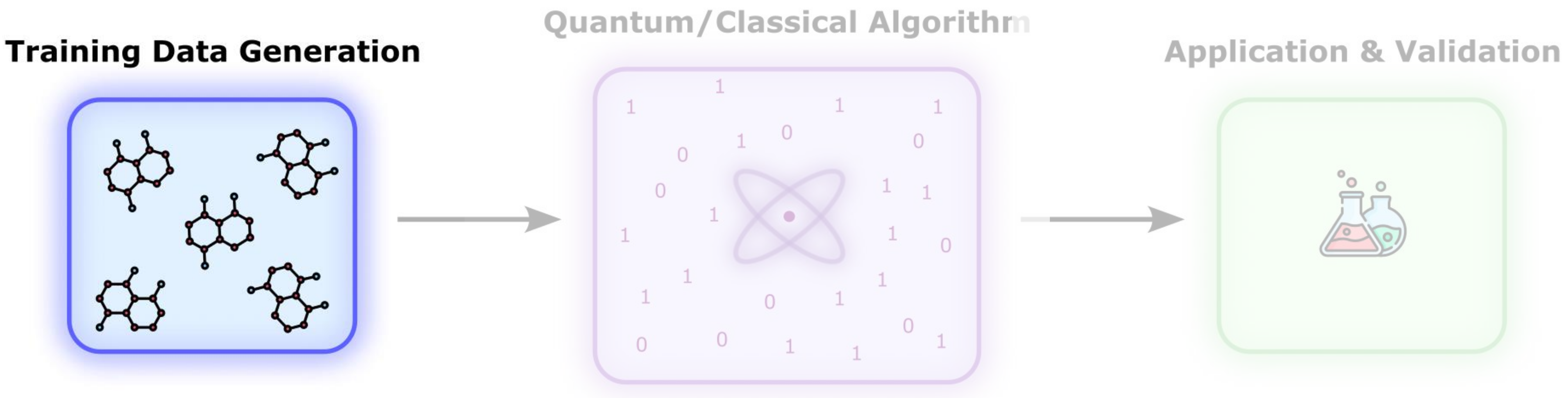
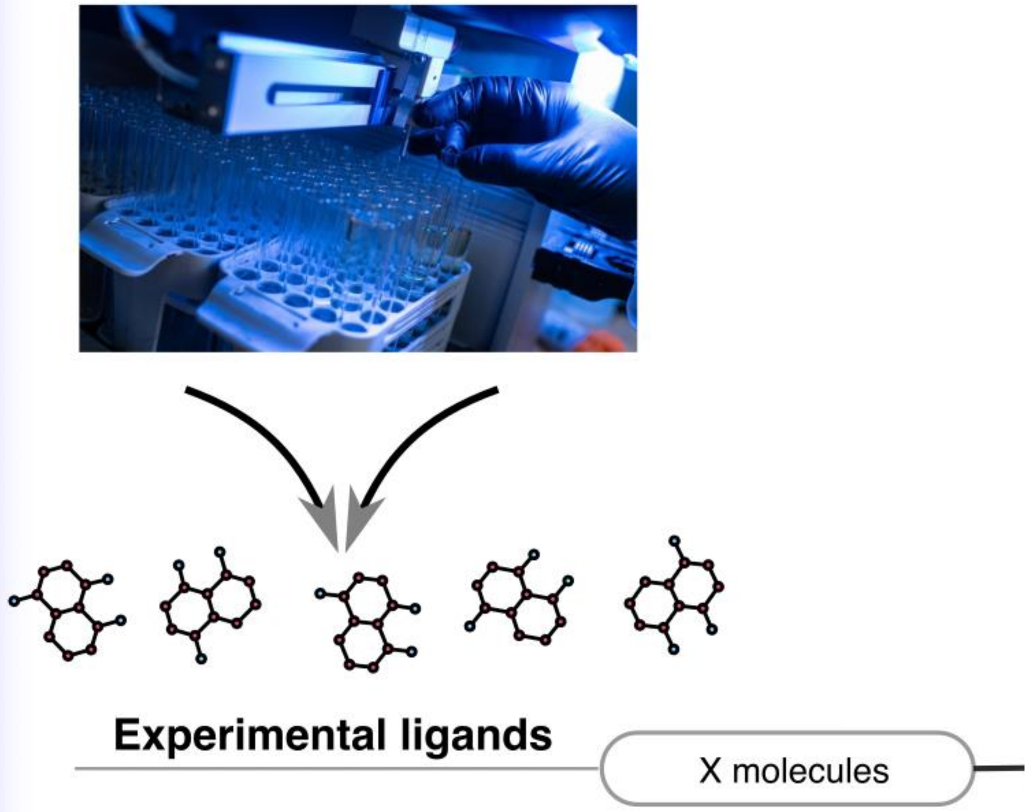


Training Data Generation



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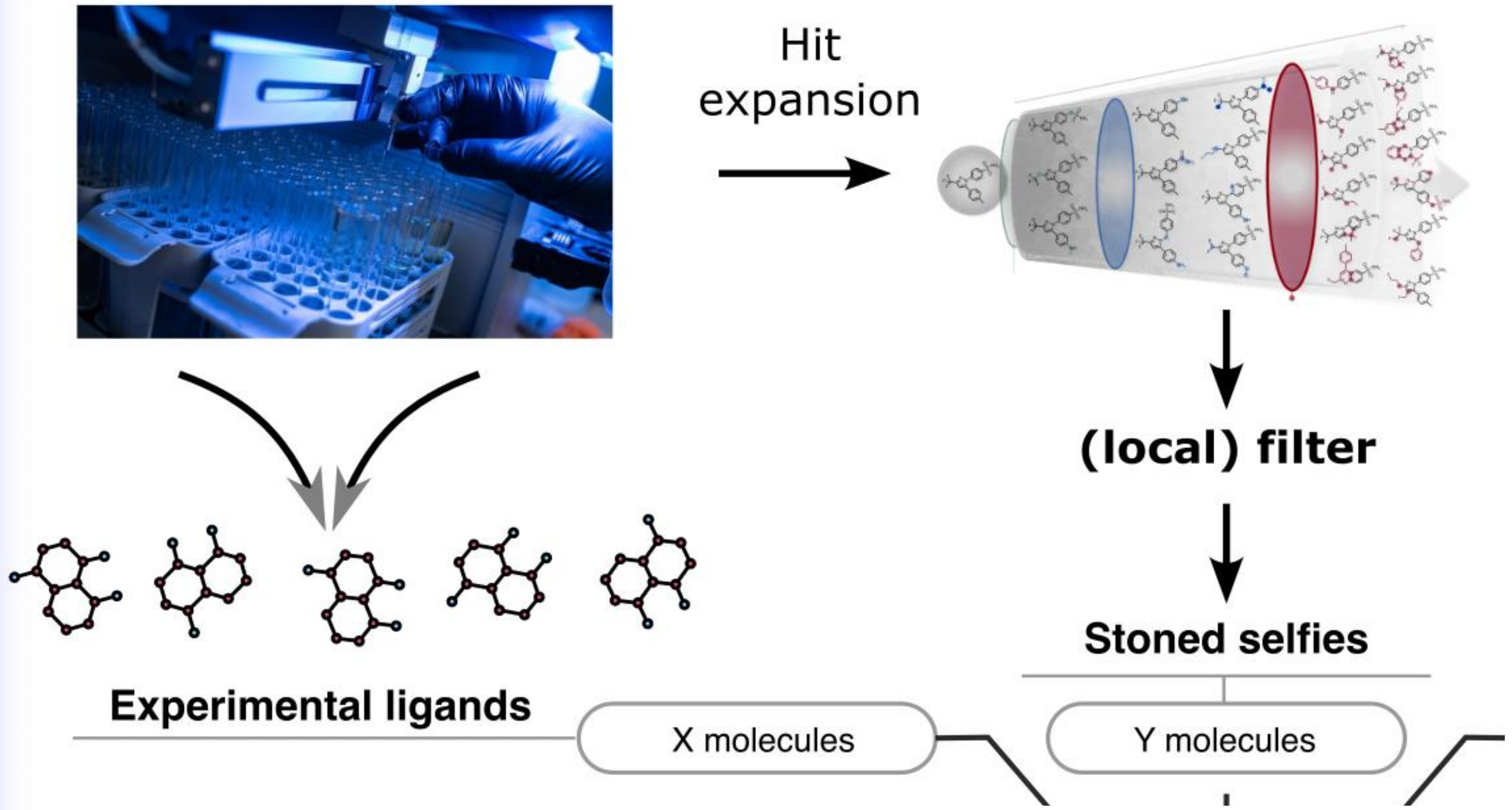
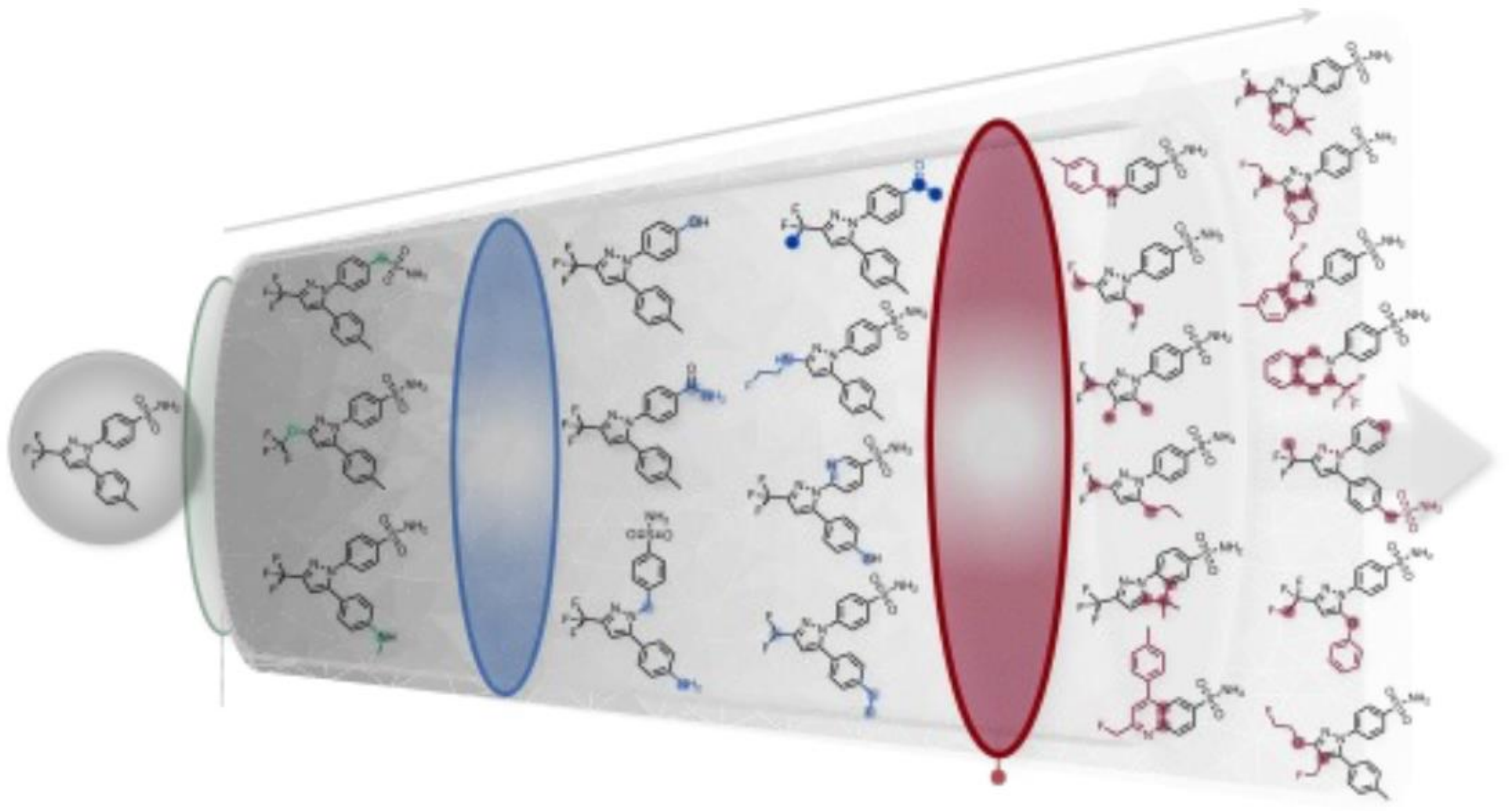


STONED Algorithm

- STONED stands for Superfast Traversal, Optimization, Novelty, Exploration and Discovery
- Alternative method to generative models for inverse molecular design
- Efficient algorithm to perform interpolation and exploration in the chemical space
- Bypasses the need for large amounts of data and training times
- Uses string modifications in the SELFIES molecular representation
- https://github.com/aspuru-guzik-group/stoned-selfies



Nigam, A. et al., 2021. Chemical science, 12(20), pp.7079-7090.

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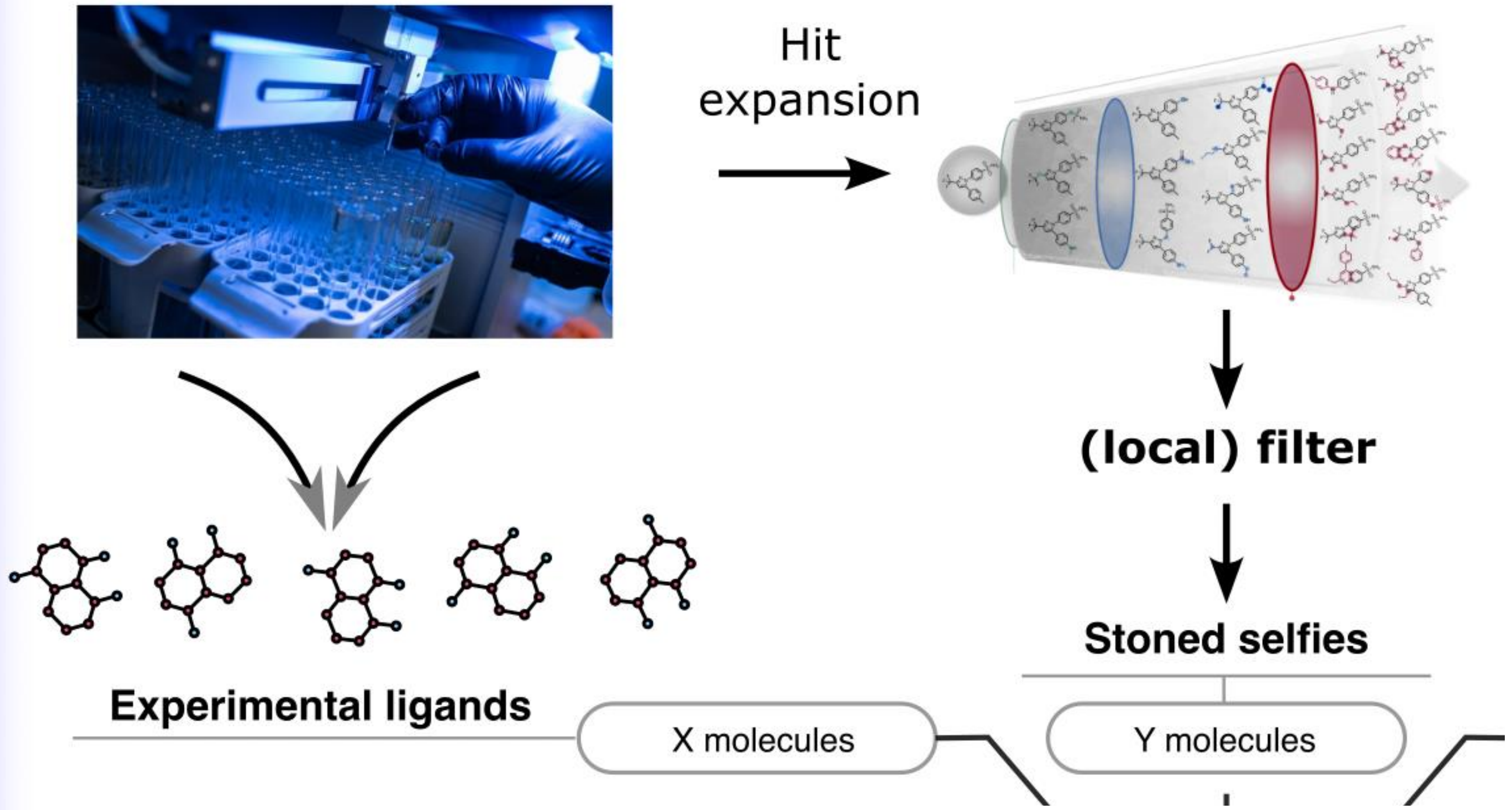

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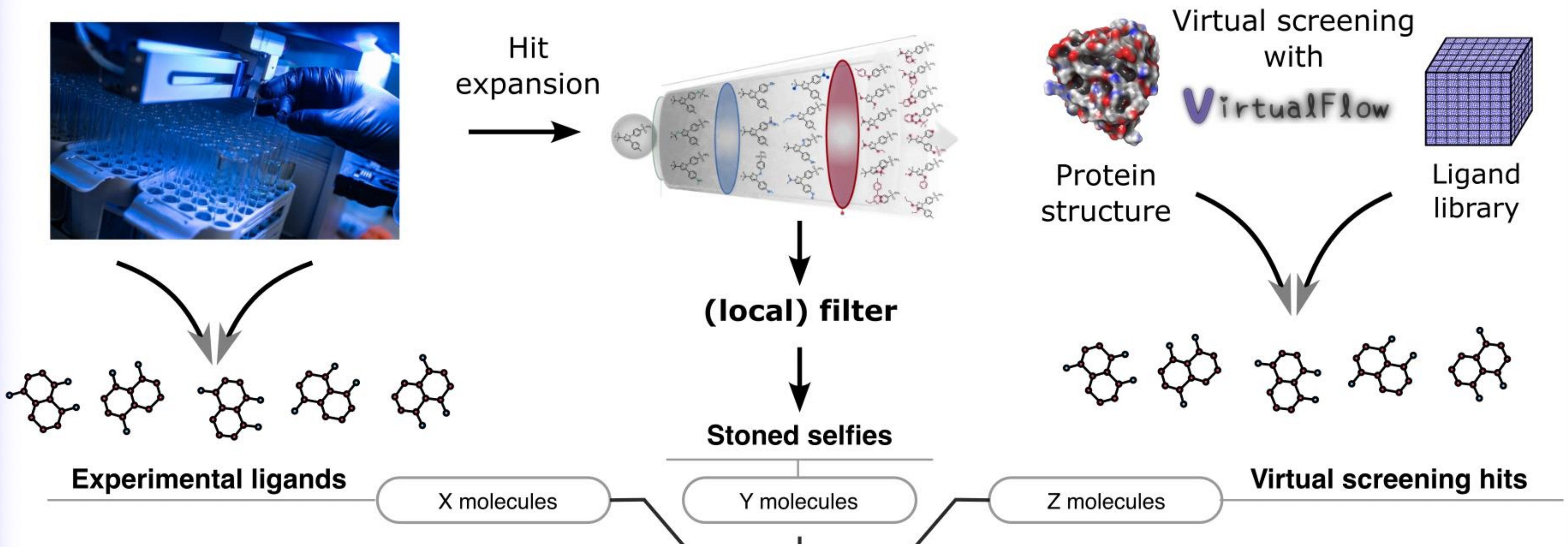

VirtualFlow

- First structure-based virtual screening platform able to screen over 1 billion molecules (Nature 2020)
- Using high-performance computer clusters and the cloud

nature

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Article | Published: 09 March 2020

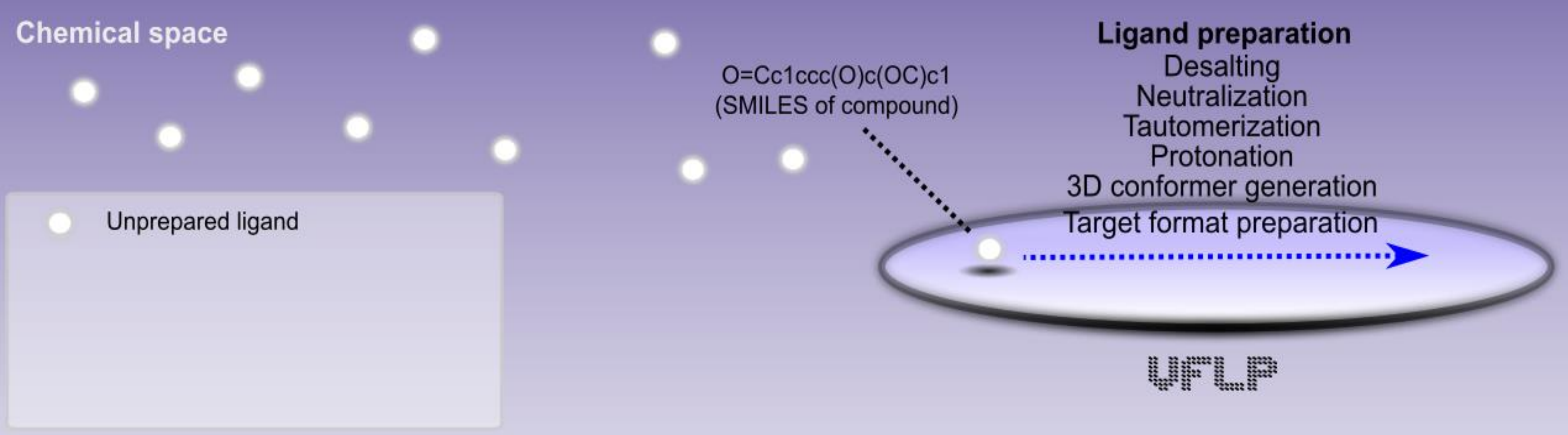
An open-source drug discovery platform enables ultra-large virtual screens

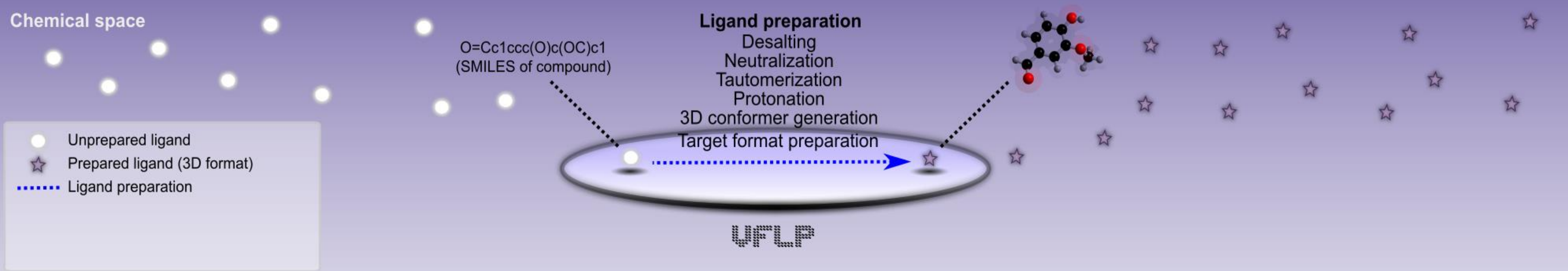
Christoph Gorgulla, Andras Boeszoermenyi, Zi-Fu Wang, Patrick D. Fischer, Paul W. Coote, Krishna M. Padmanabha Das, Yehor S. Malets, Dmytro S. Radchenko, Yurii S. Moroz, David A. Scott, Konstantin Fackeldey, Moritz Hoffmann, Iryna Iavniuk, Gerhard Wagner & Haribabu Arthanari

Nature **580**, 663–668 (2020) | Cite this article

- Freely available and open-source
- www.virtual-flow.org

Chemical space


Chemical space
Unprepared ligand
O=Cc1ccc(O)c(OC)c1
(SMILES of compound)
Ligand preparation
Desalting
Neutralization
Tautomerization
Protonation
3D conformer generation
Target format preparation
UFLP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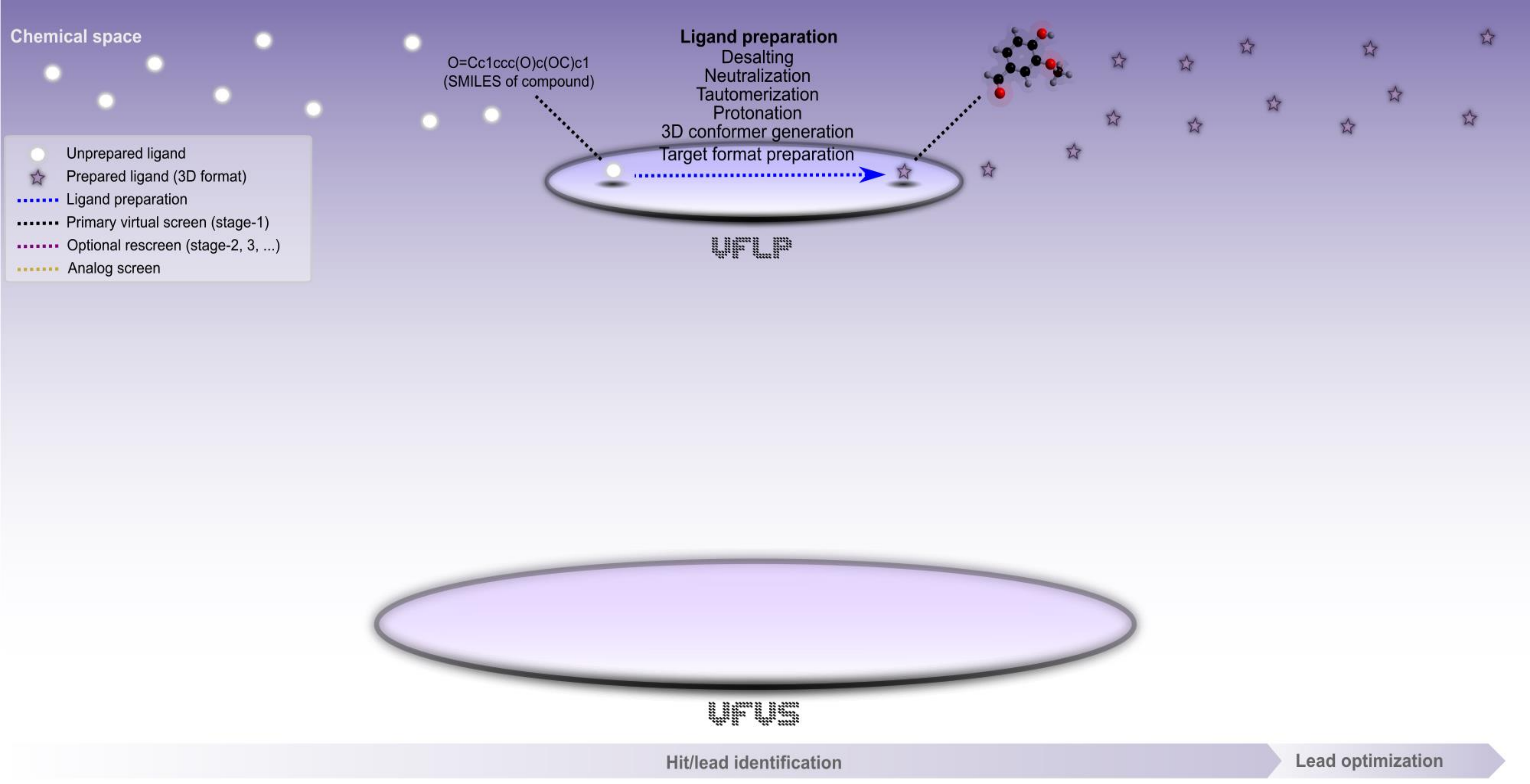

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Primary virtual screen (stage-1)
Optional rescreen (stage-2, 3, ...)
Analog screen
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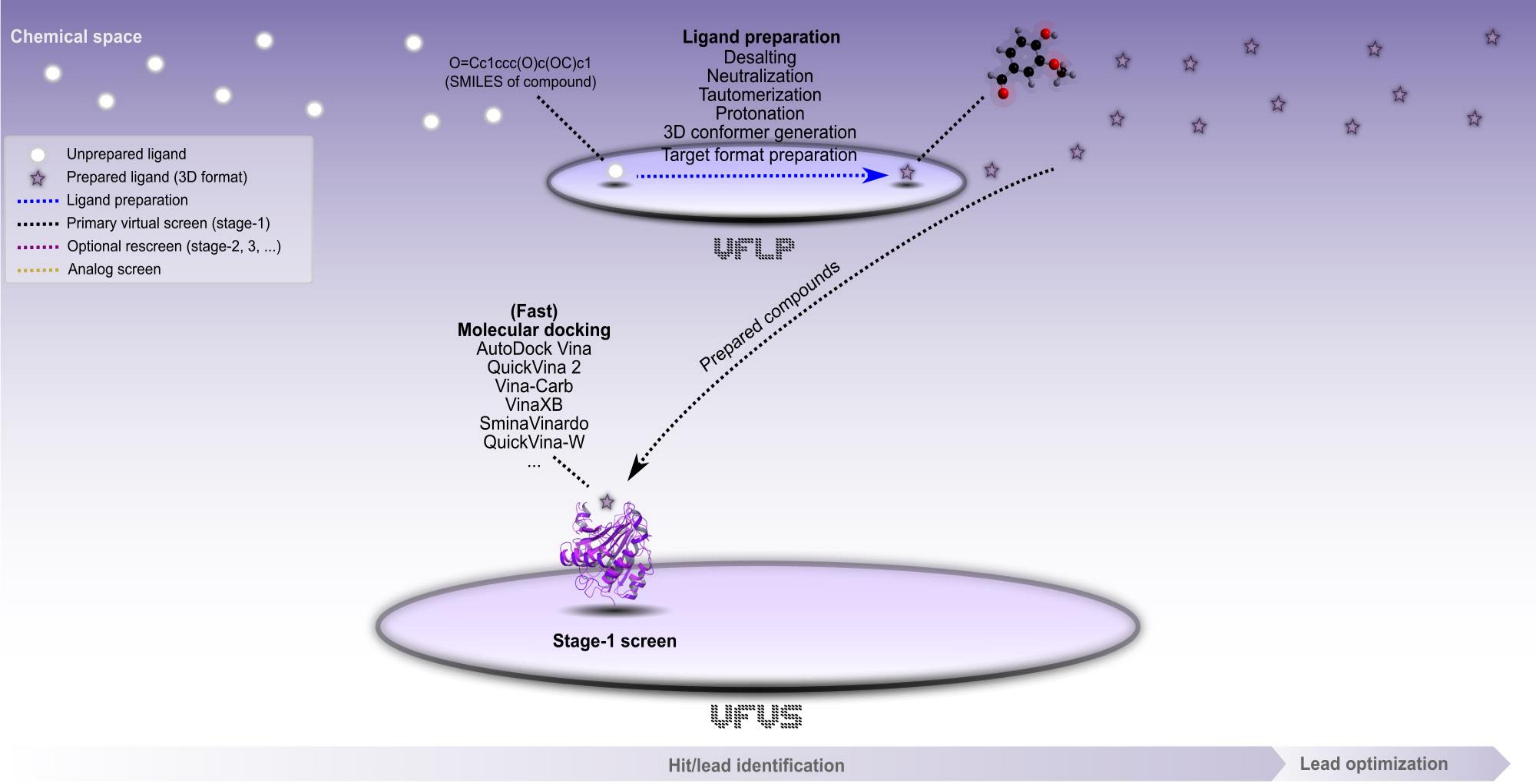
Target format preparation
VFLP
VFVS
Hit/lead identification
Lead optimization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Prepared compounds
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Molecular docking
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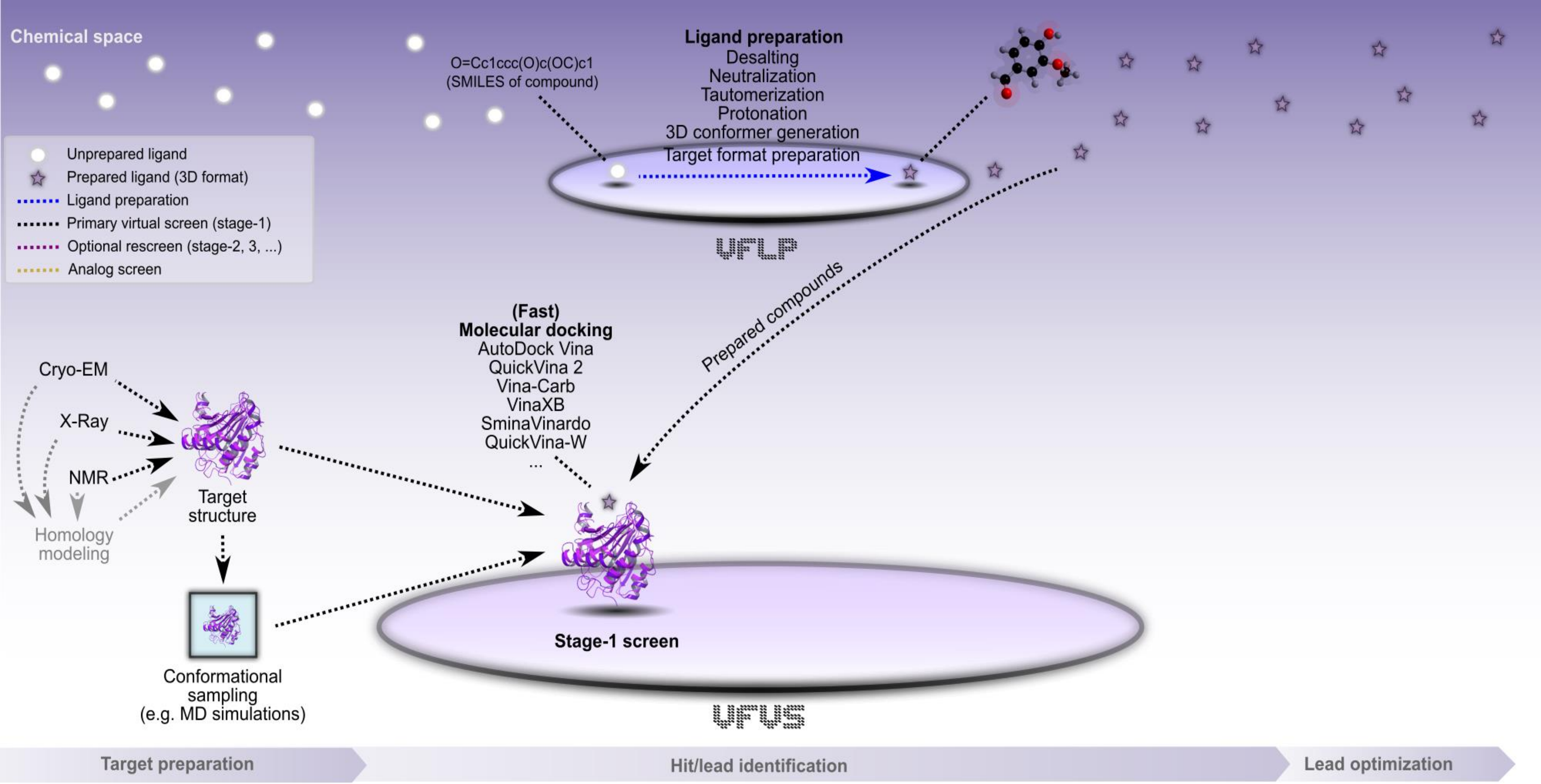
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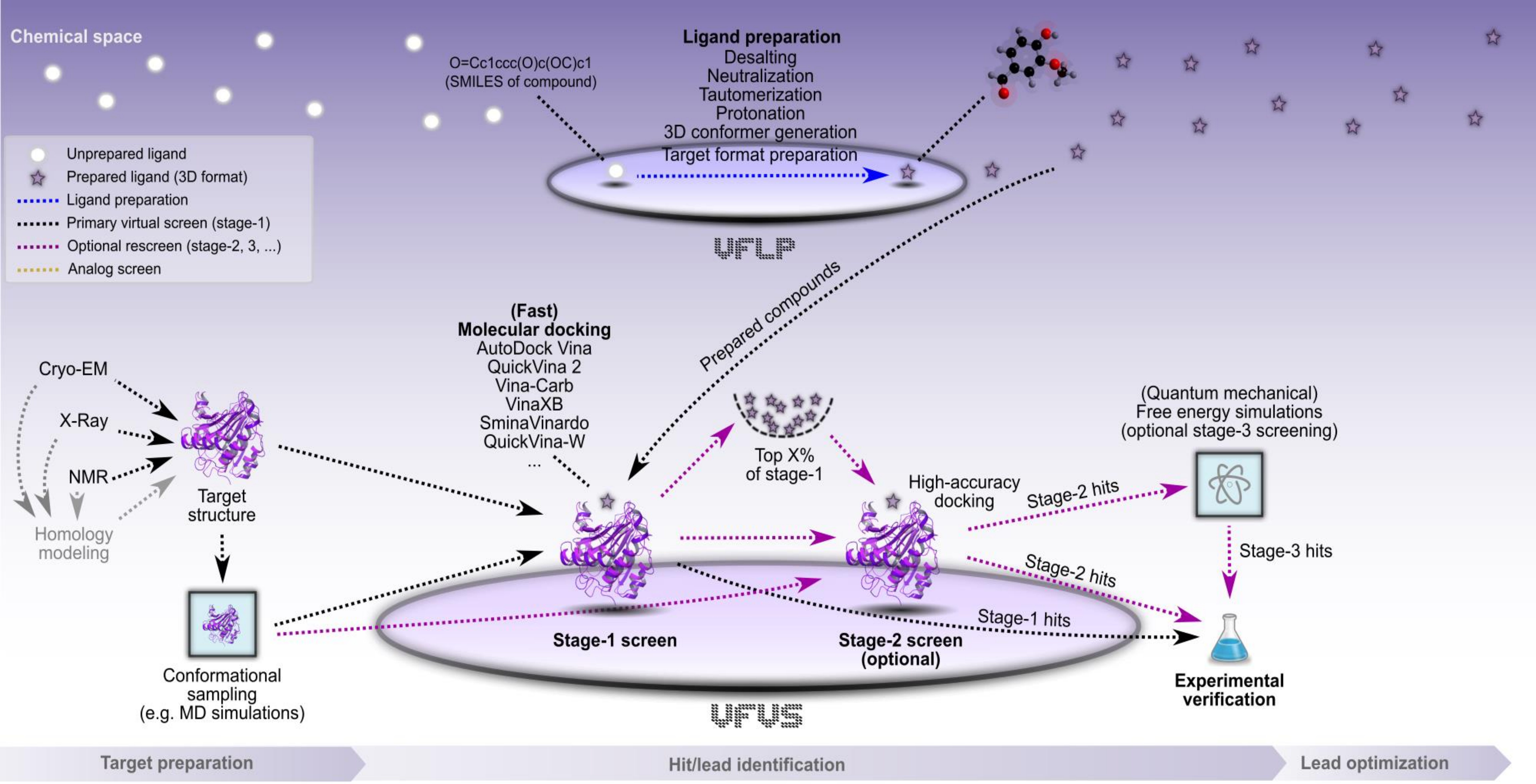
...
Cryo-EM
X-Ray
NMR
Homology modeling
Target structure
Conformational sampling
(e.g. MD simulations)
Stage-1 screen
VFVS
Target preparation
Hit/lead identification
Lead optimization



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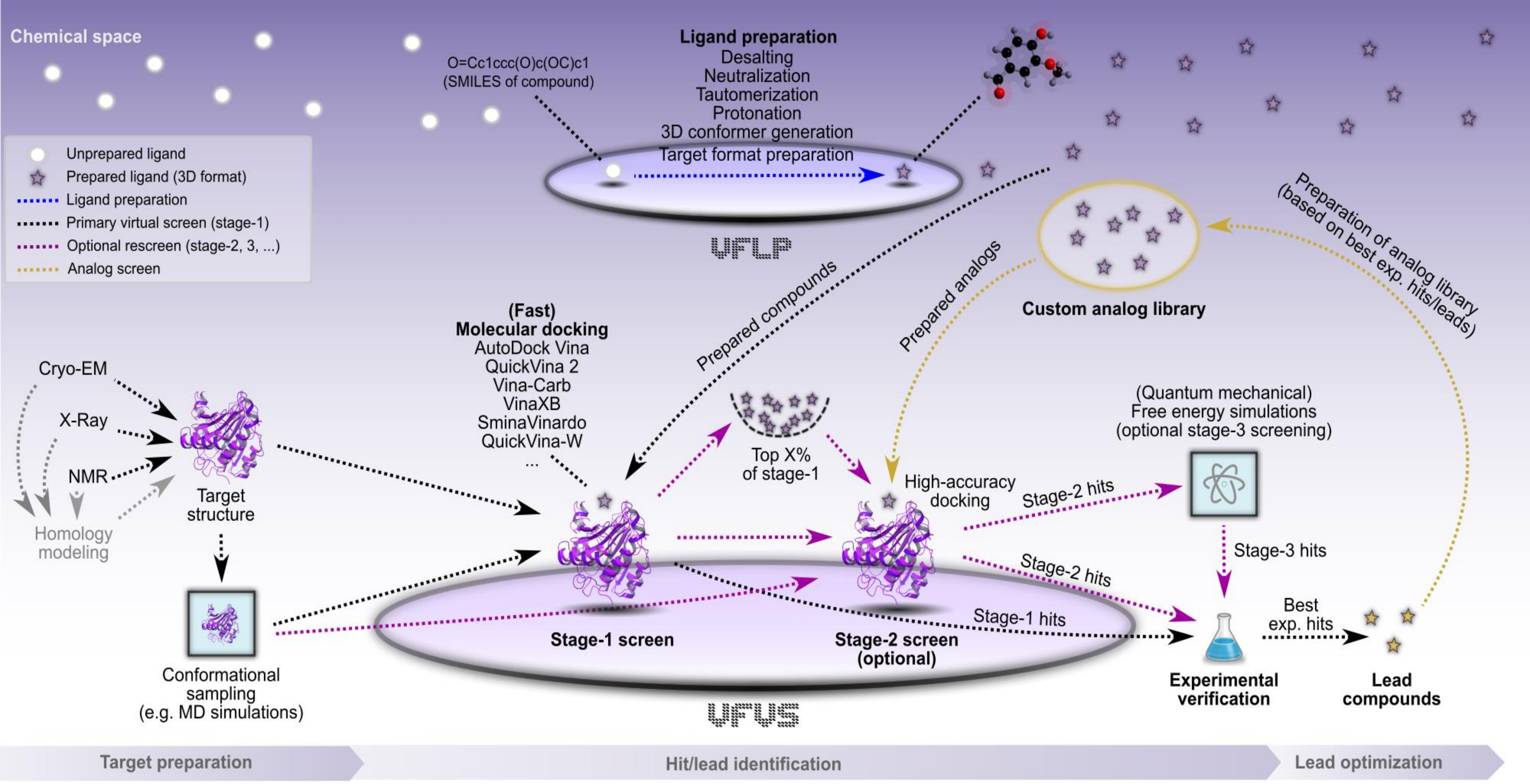
SminaVinardo
QuickVina-W
...
Cryo-EM
X-Ray
NMR
Homology modeling
Target structure
Conformational sampling
(e.g. MD simulations)
Top X%
of stage-1
High-accuracy docking
(Quantum mechanical)
Free energy simulations
(optional stage-3 screening)
Stage-2 hits
Stage-3 hits
Stage-2 hits
Stage-1 hits
Stage-1 screen
Stage-2 screen
(optional)
Experimental verification
VFVS
Target preparation
Hit/lead identification
Lead optimization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Target format preparation
UFLP
Prepared compounds
Prepared analogs
Custom analog library
Preparation of analog library
(based on best exp. hits/leads)
(Fast)
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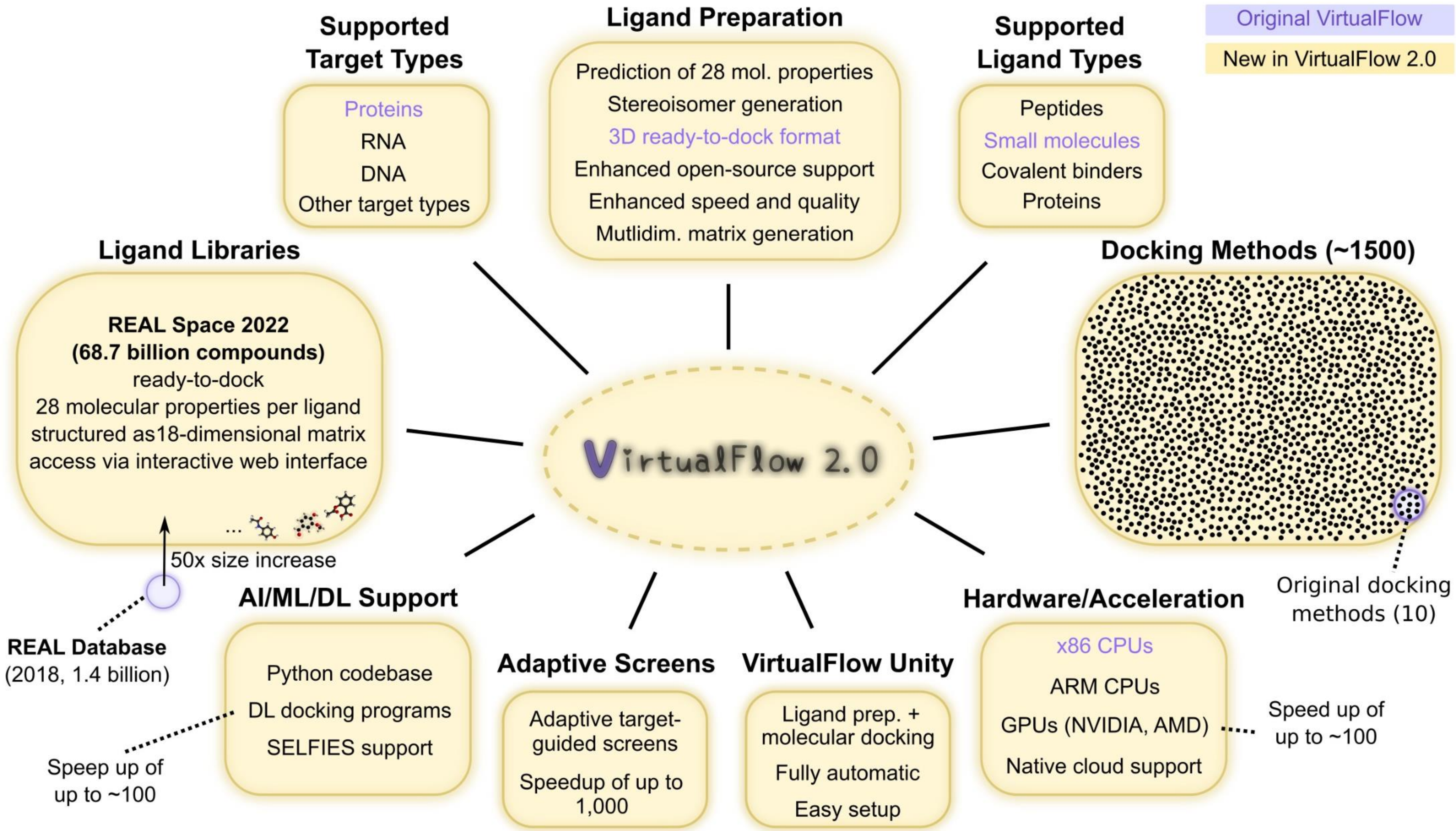
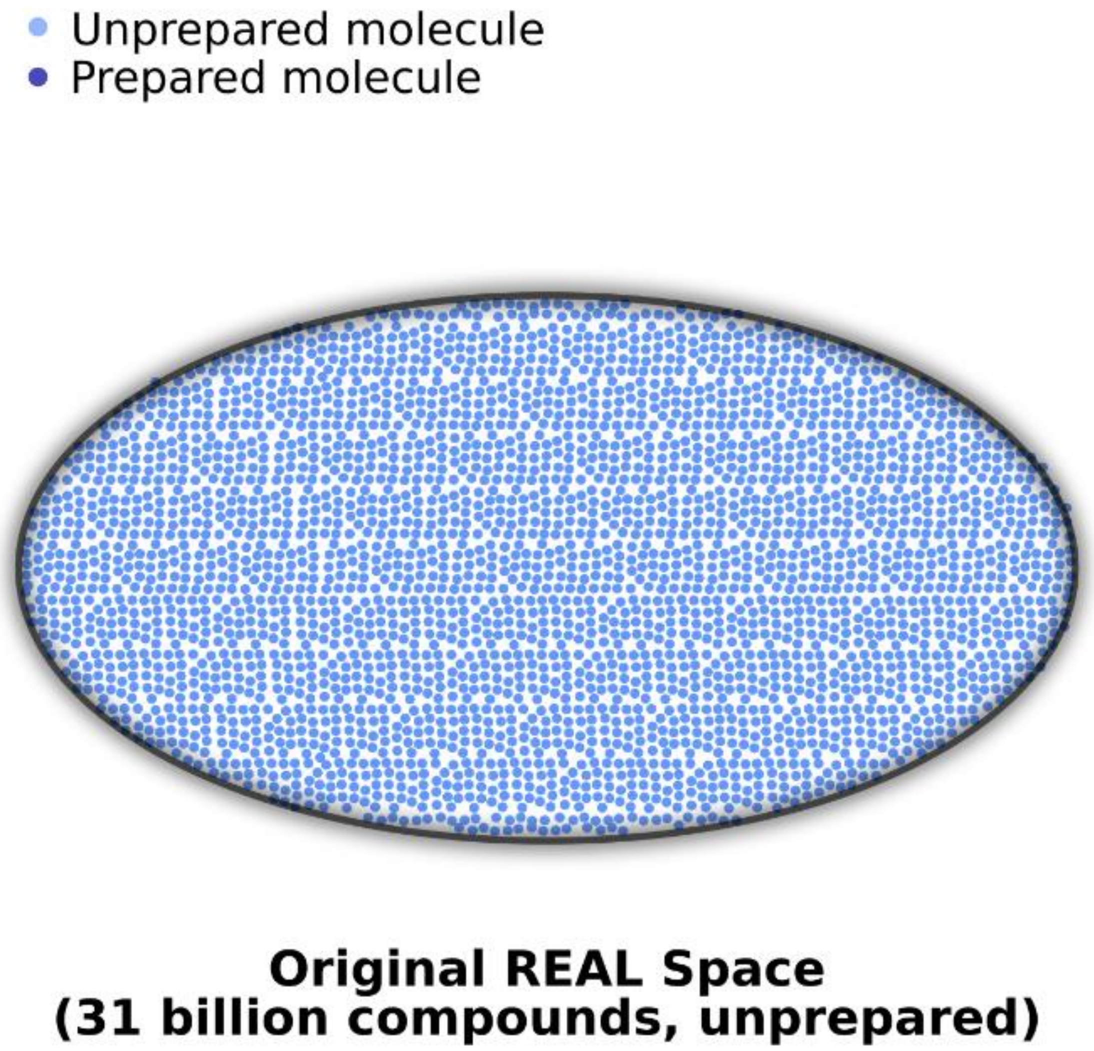
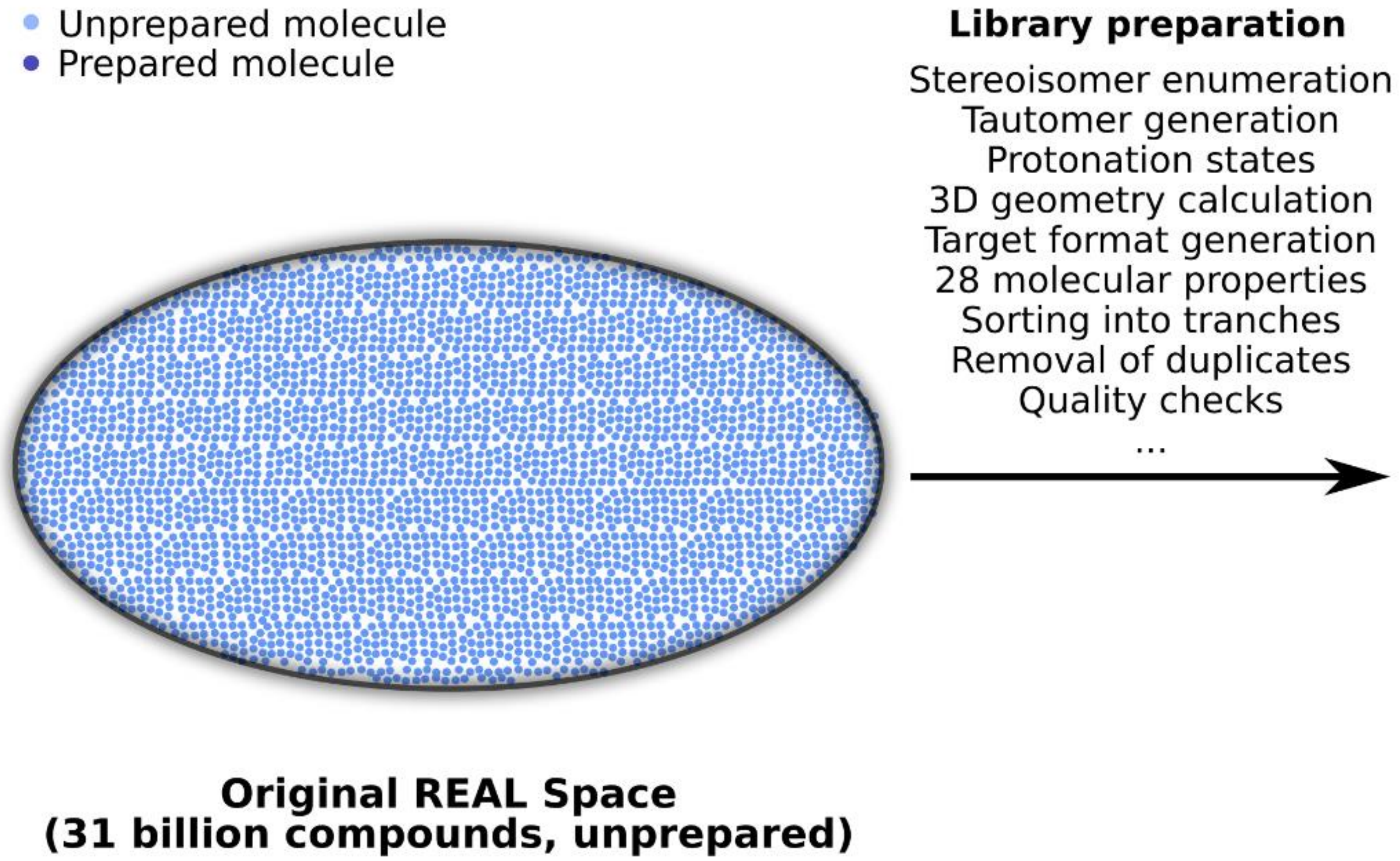


https://www.biorxiv.org/content/10.1101/2023.04.25.537981v1

Preparation of Enamine REAL Space



Preparation of Enamine REAL Space



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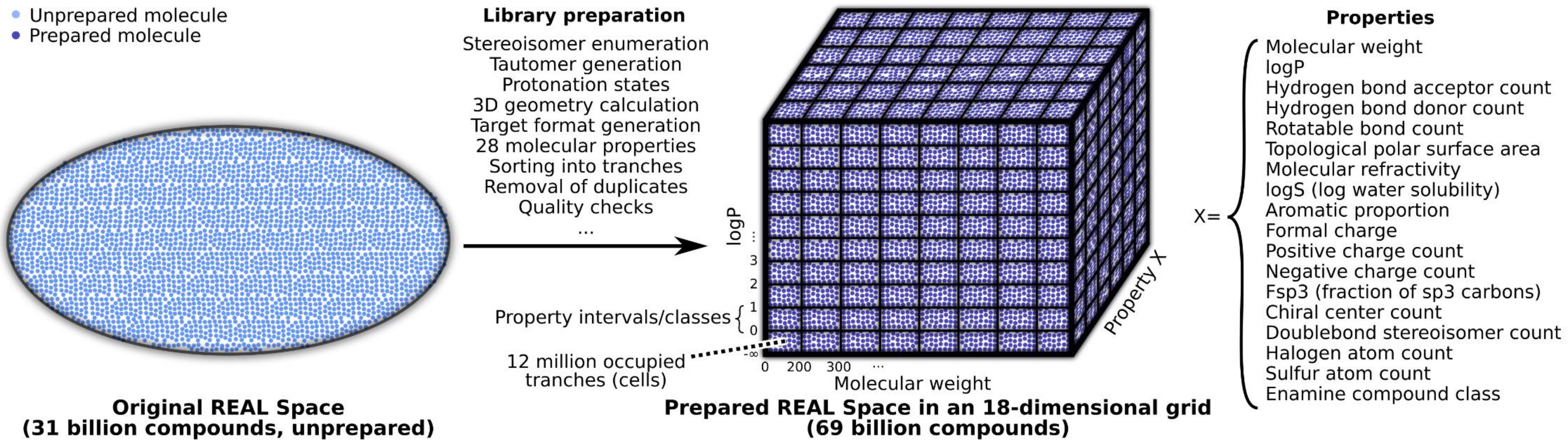
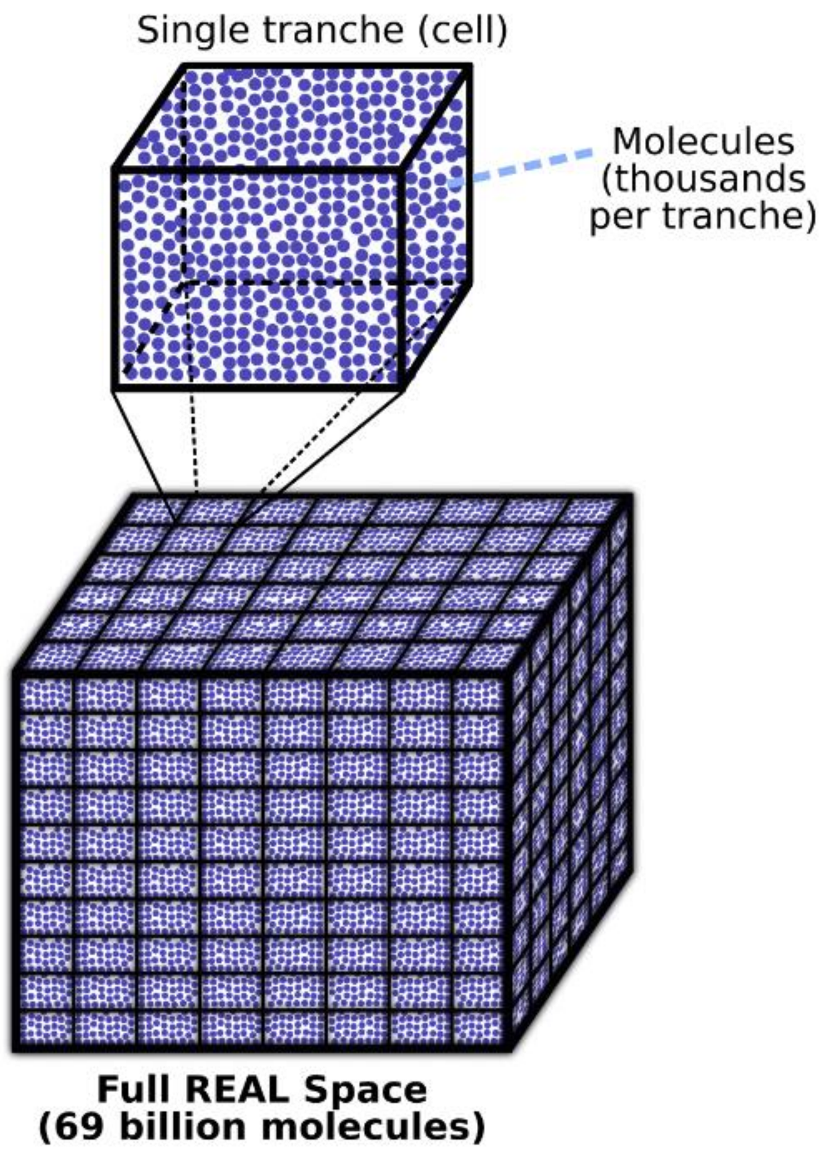


Adaptive Target-Guided Virtual Screening



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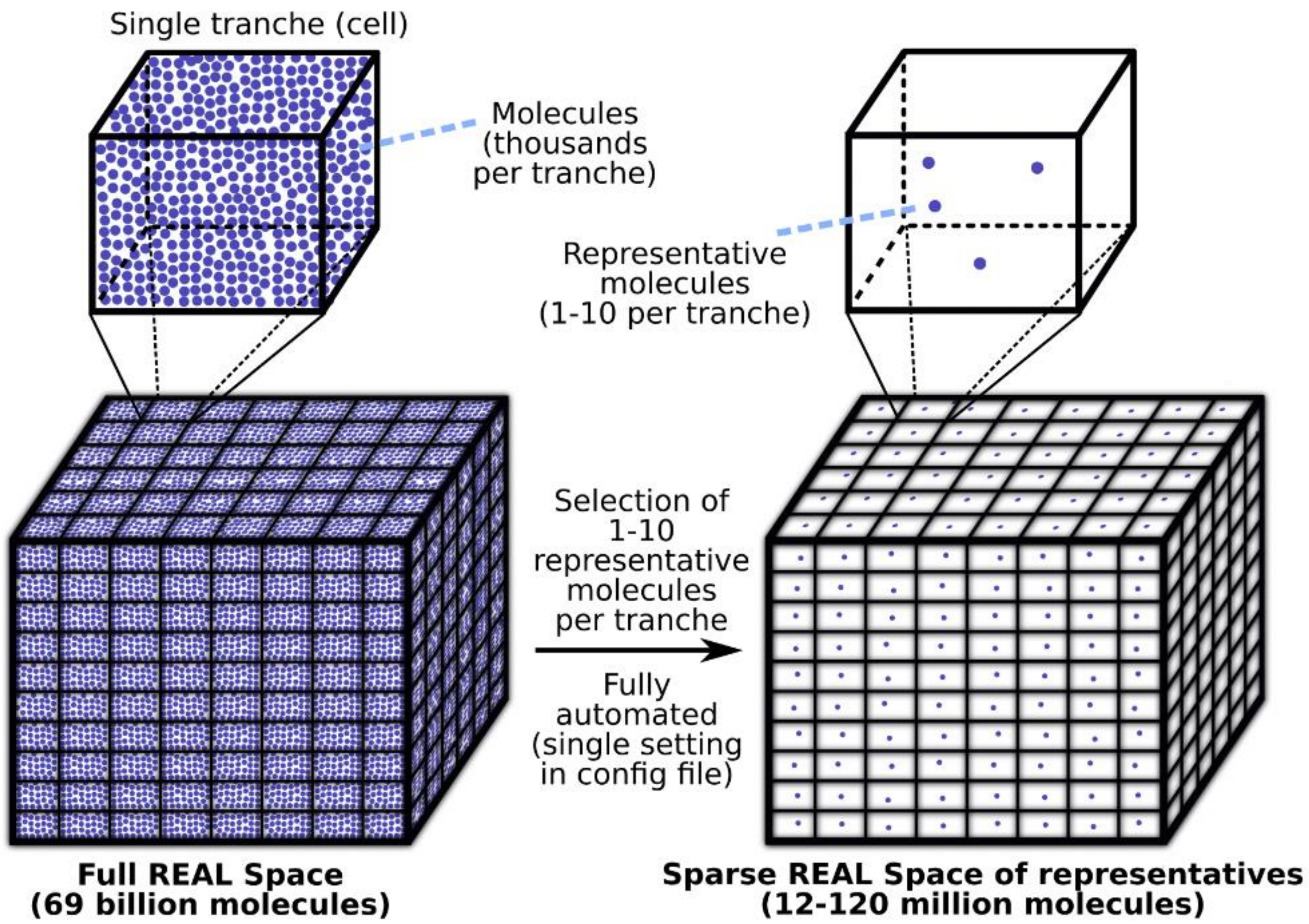

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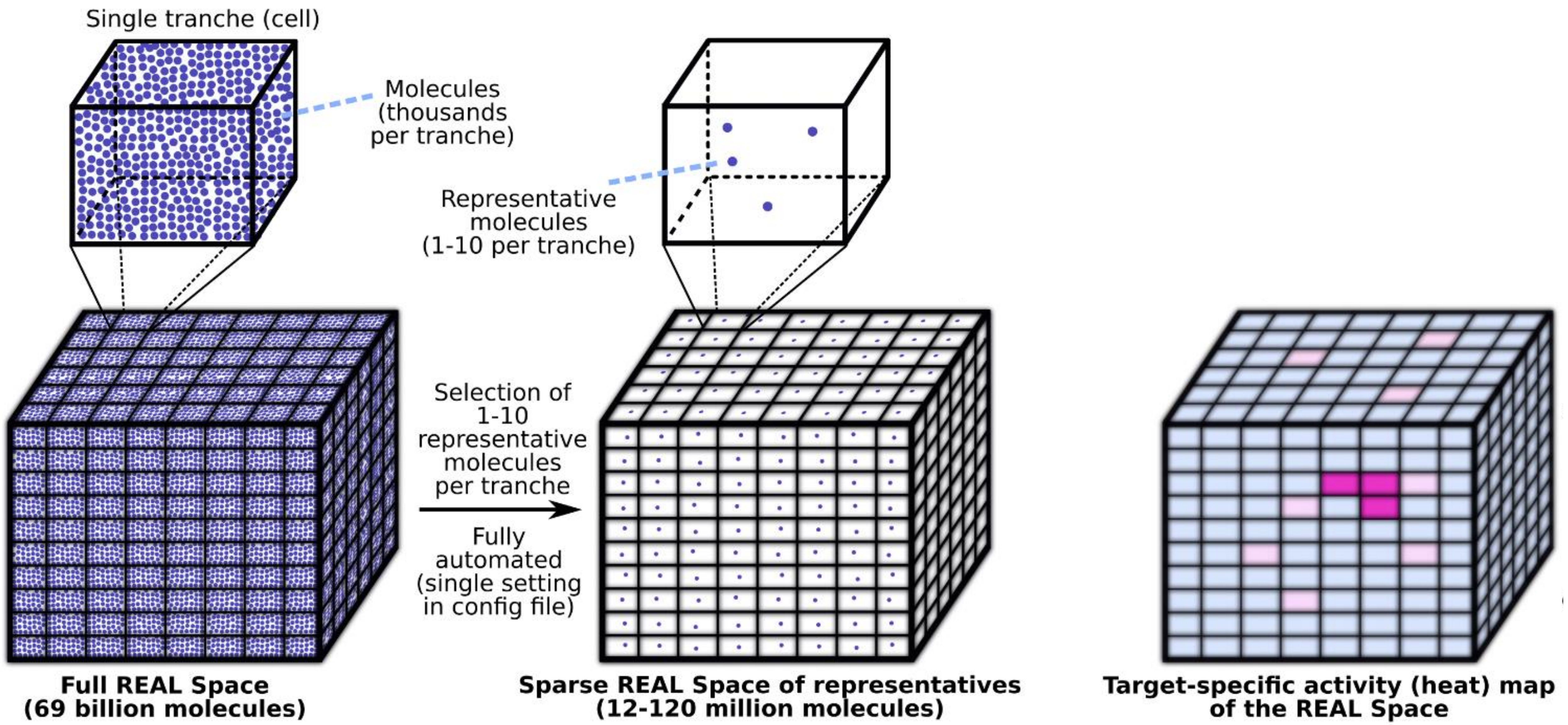

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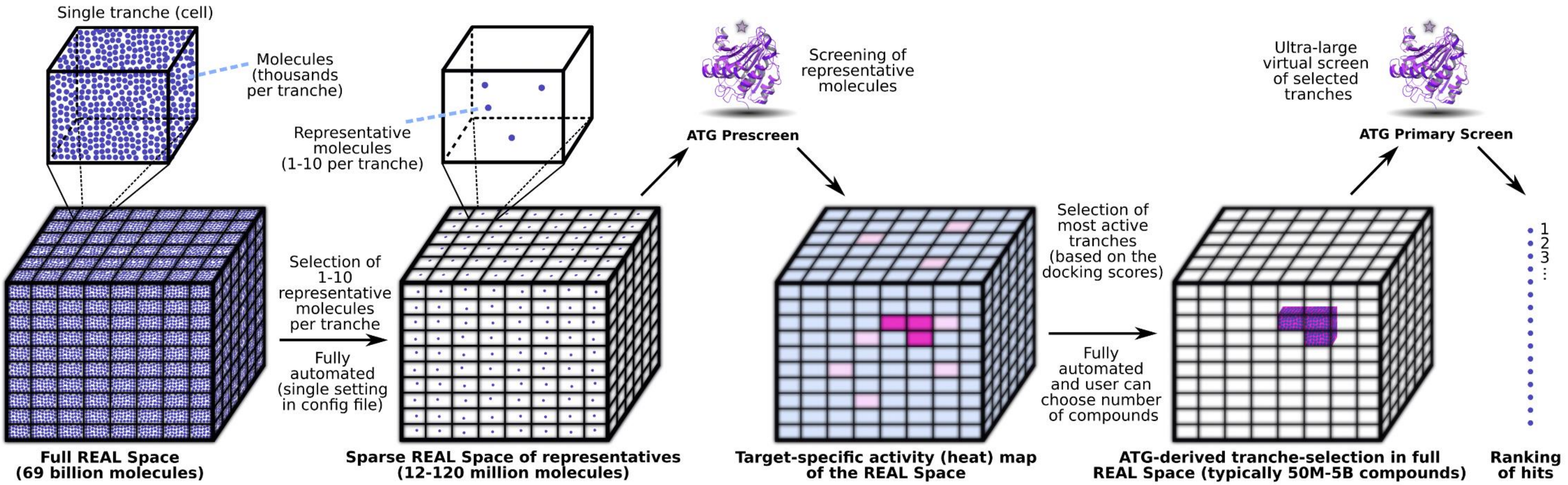
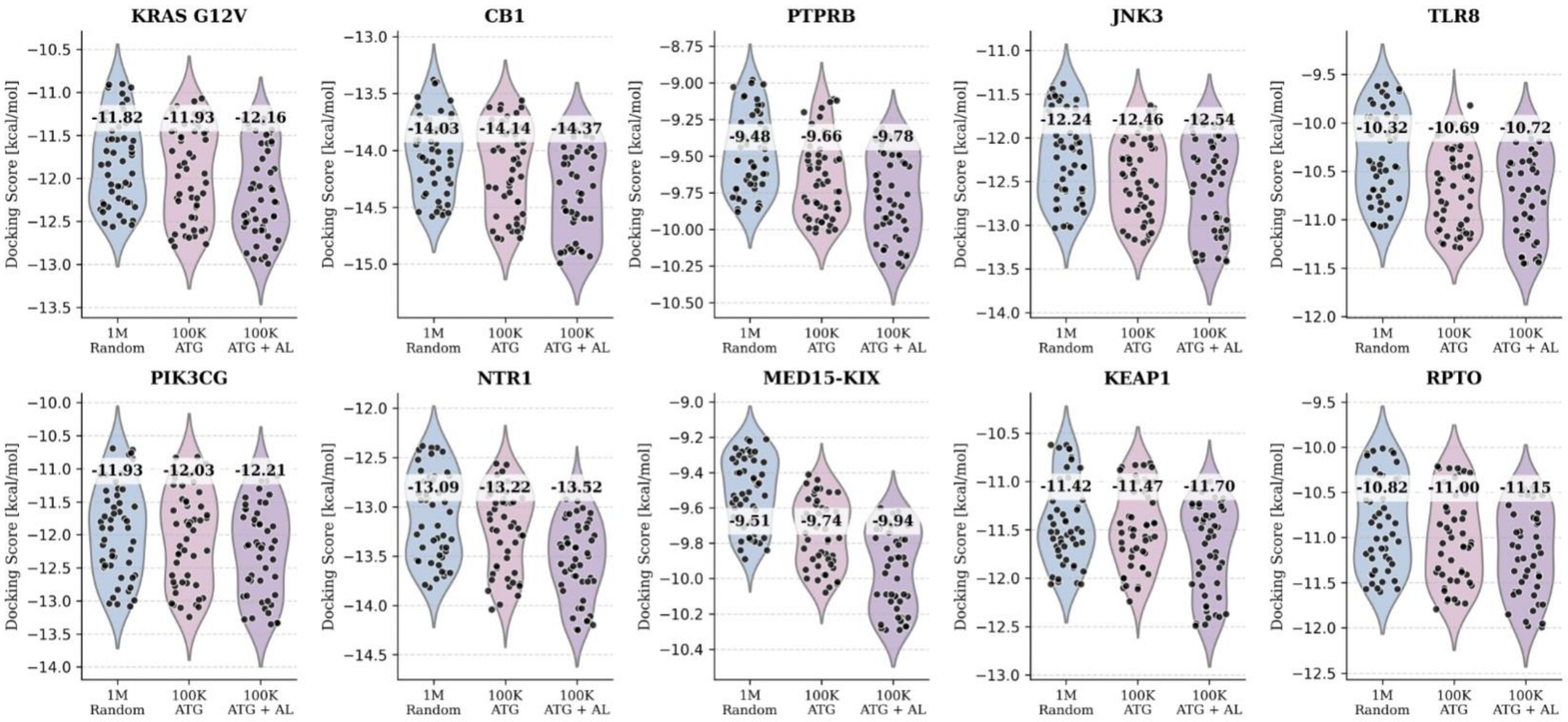
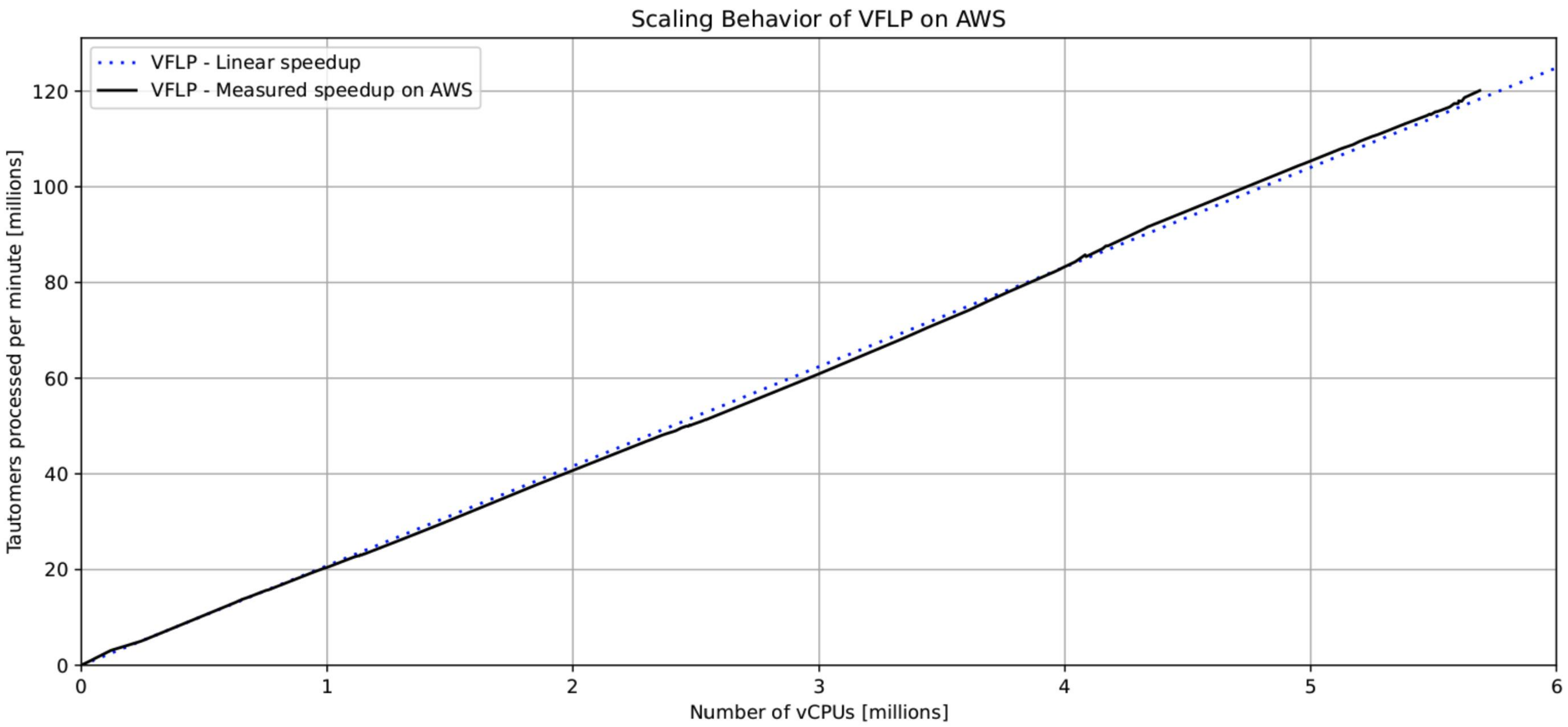


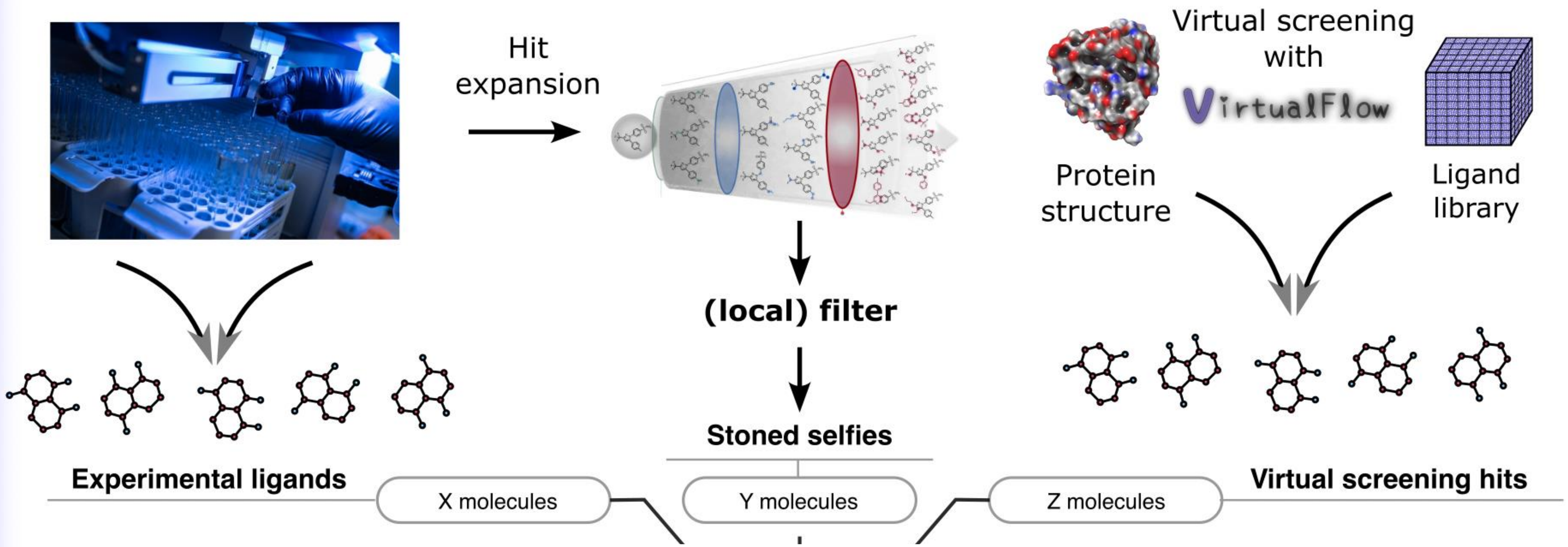
Benchmarks - Docking Scores



Benchmarks – Scaling Behavior



Training Data Generation



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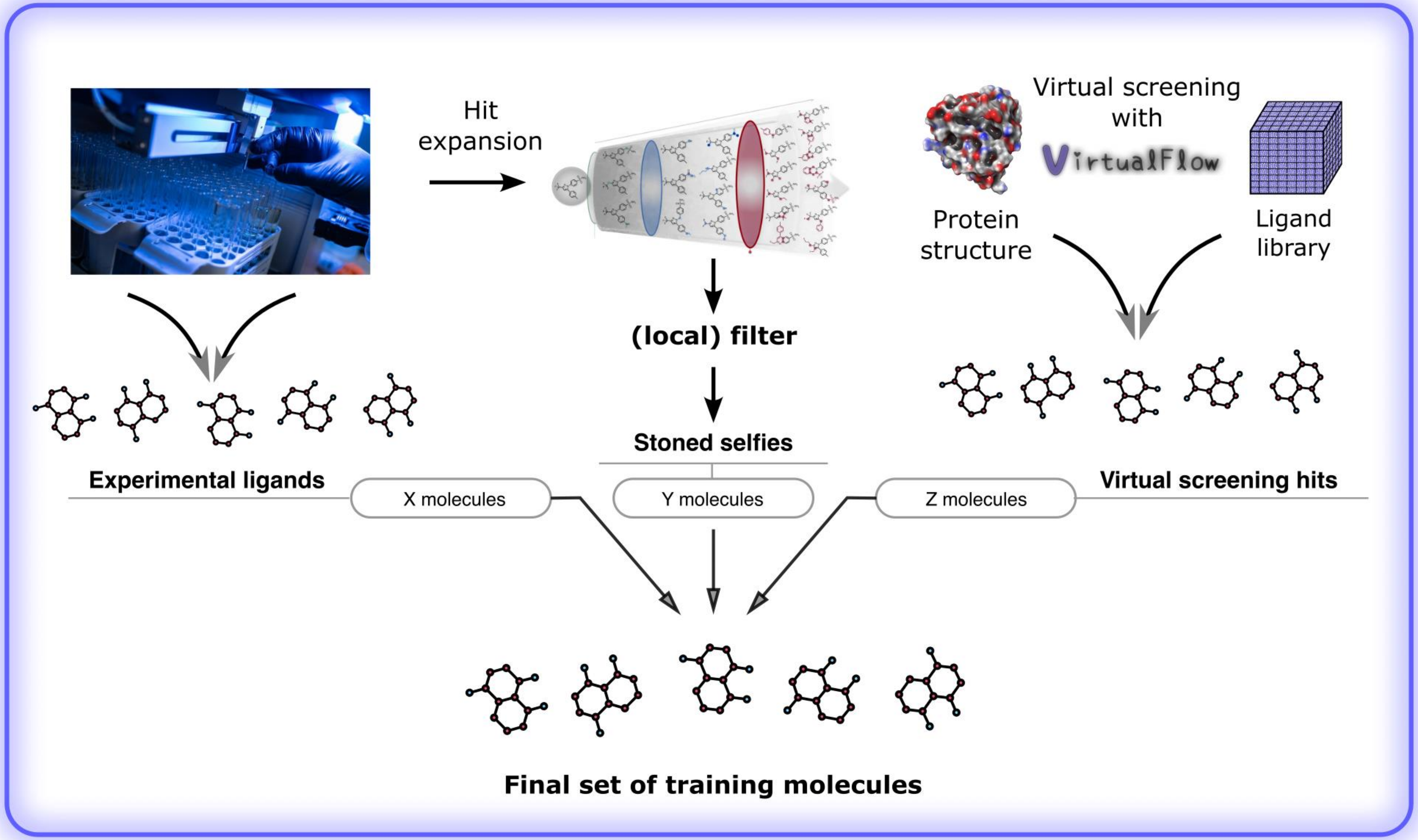
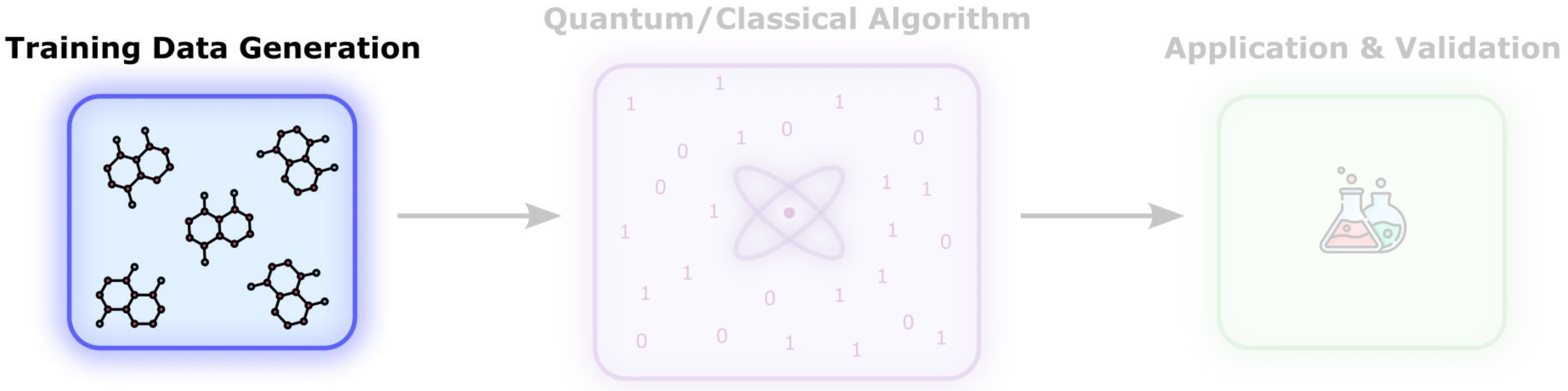


Hybrid Quantum-Classical Approach



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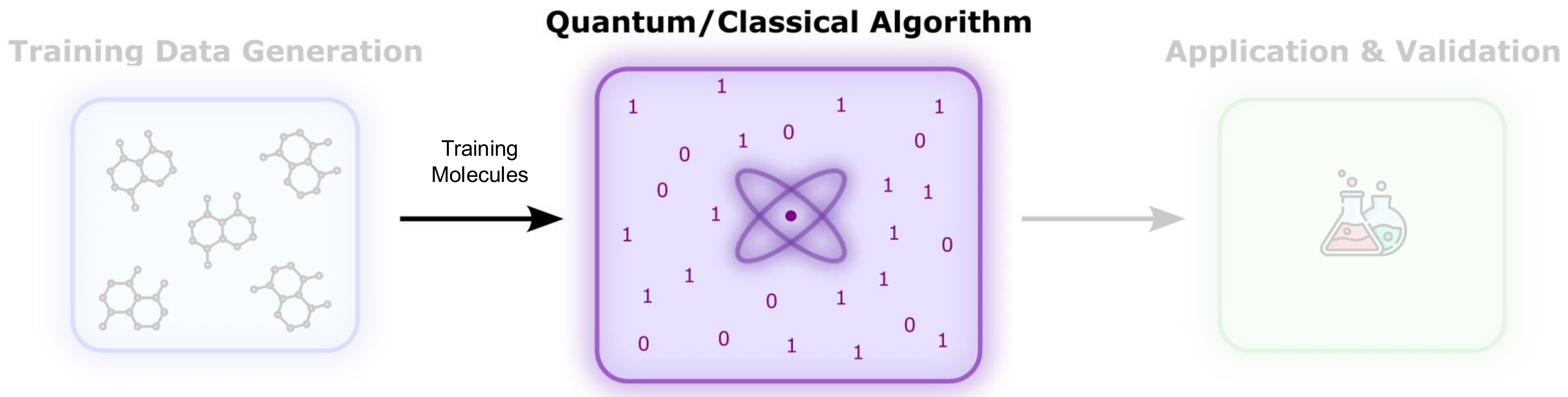
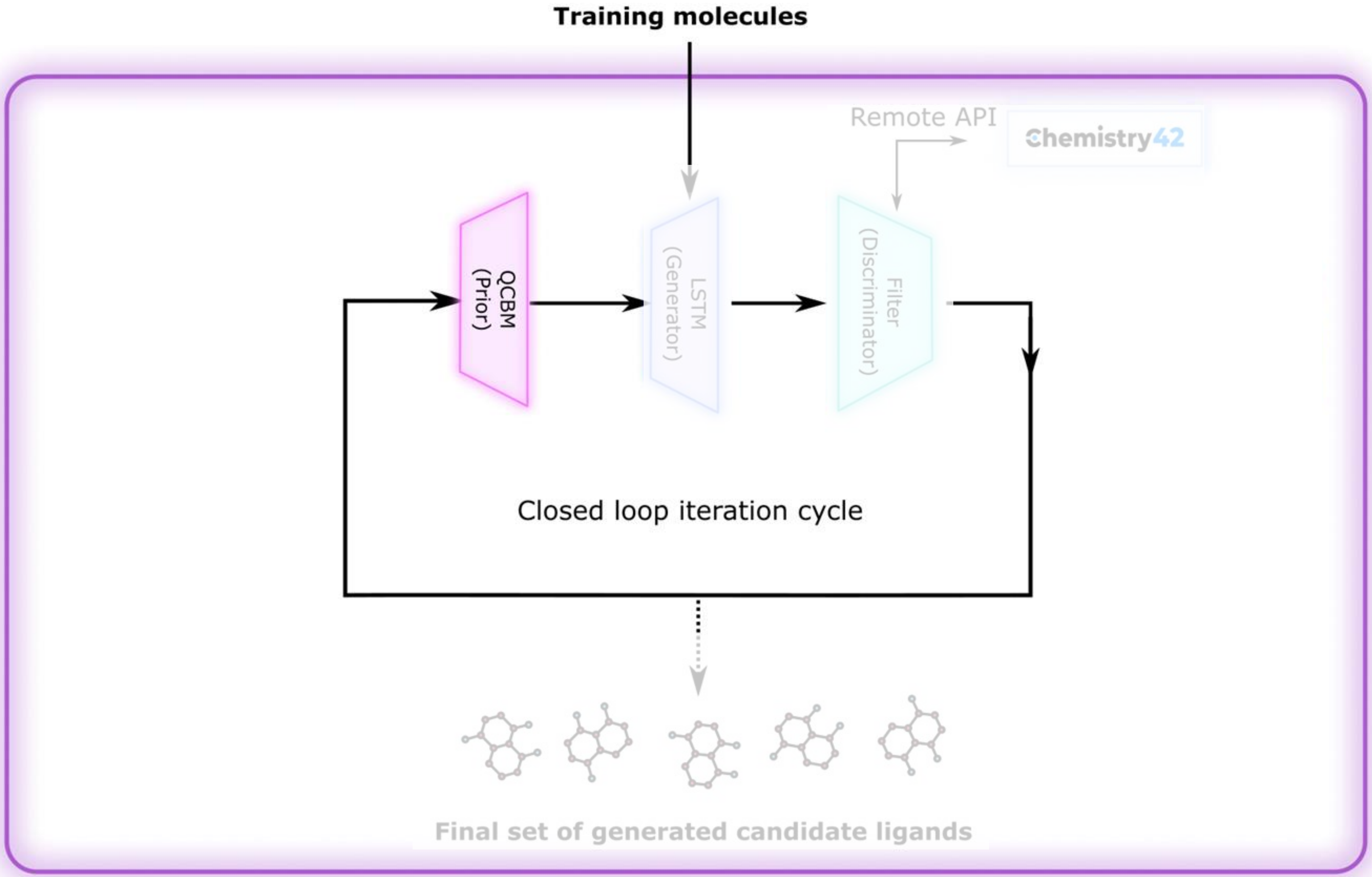


Hybrid Quantum-Classical Algorithm



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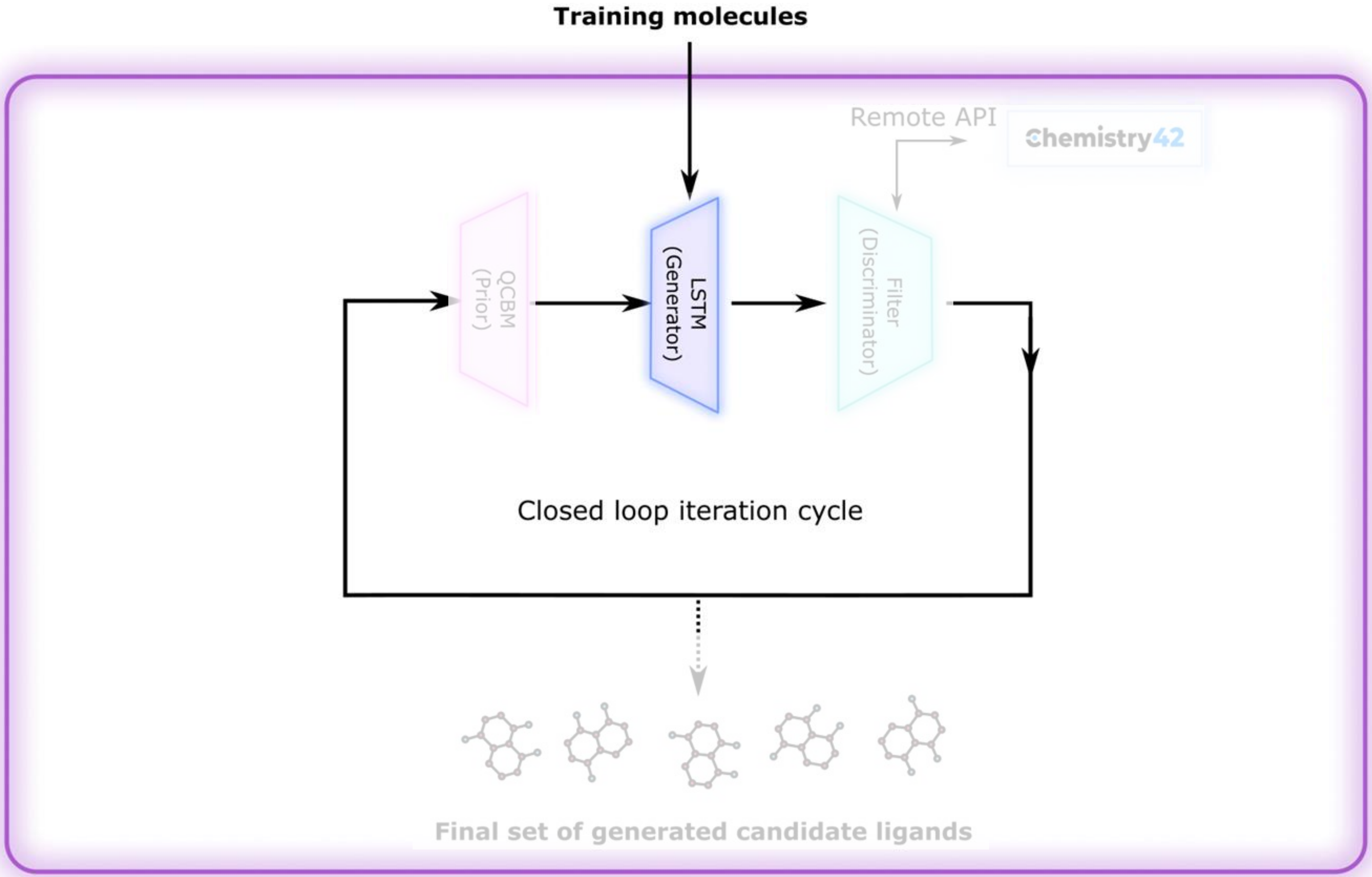

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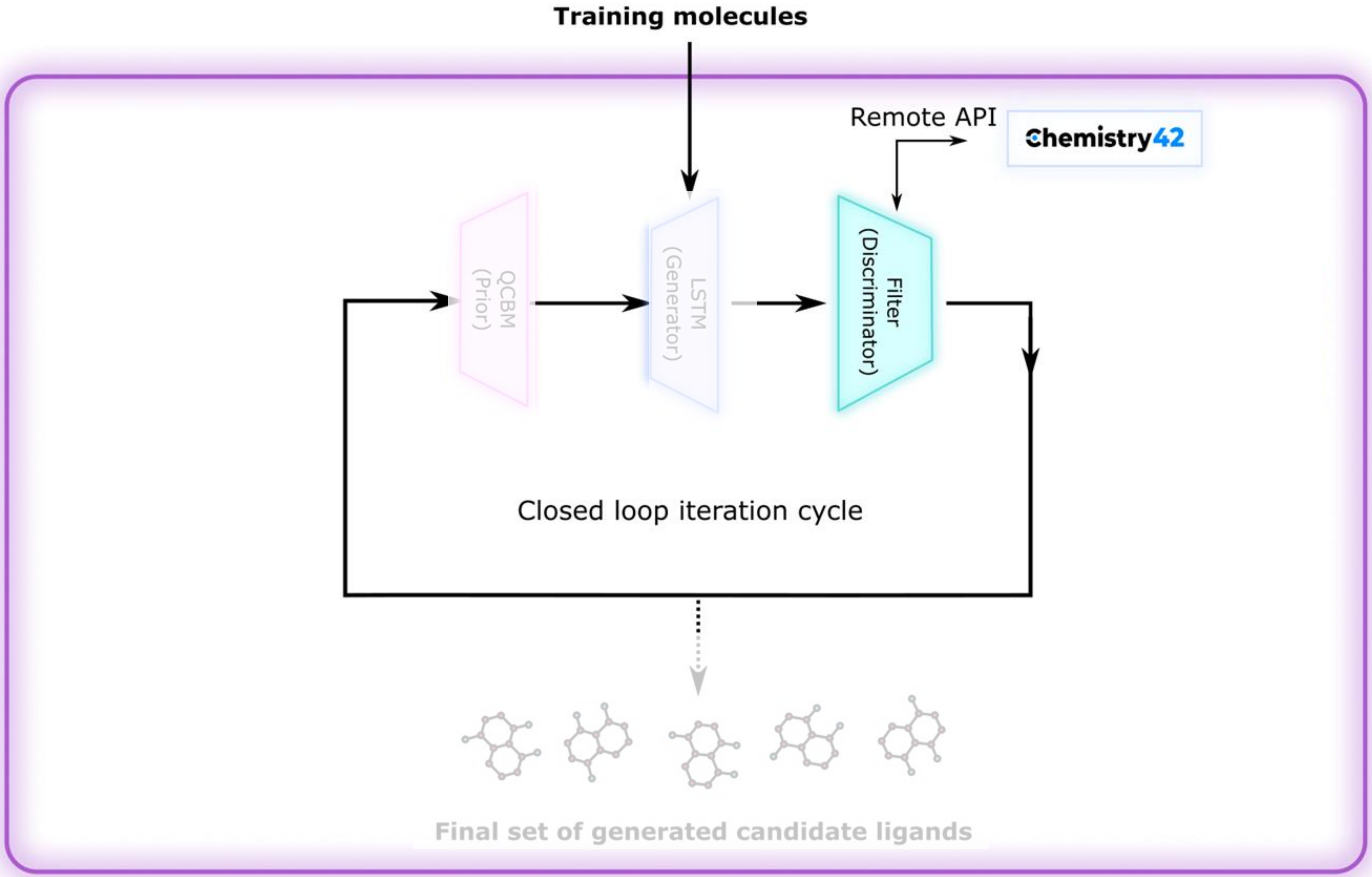

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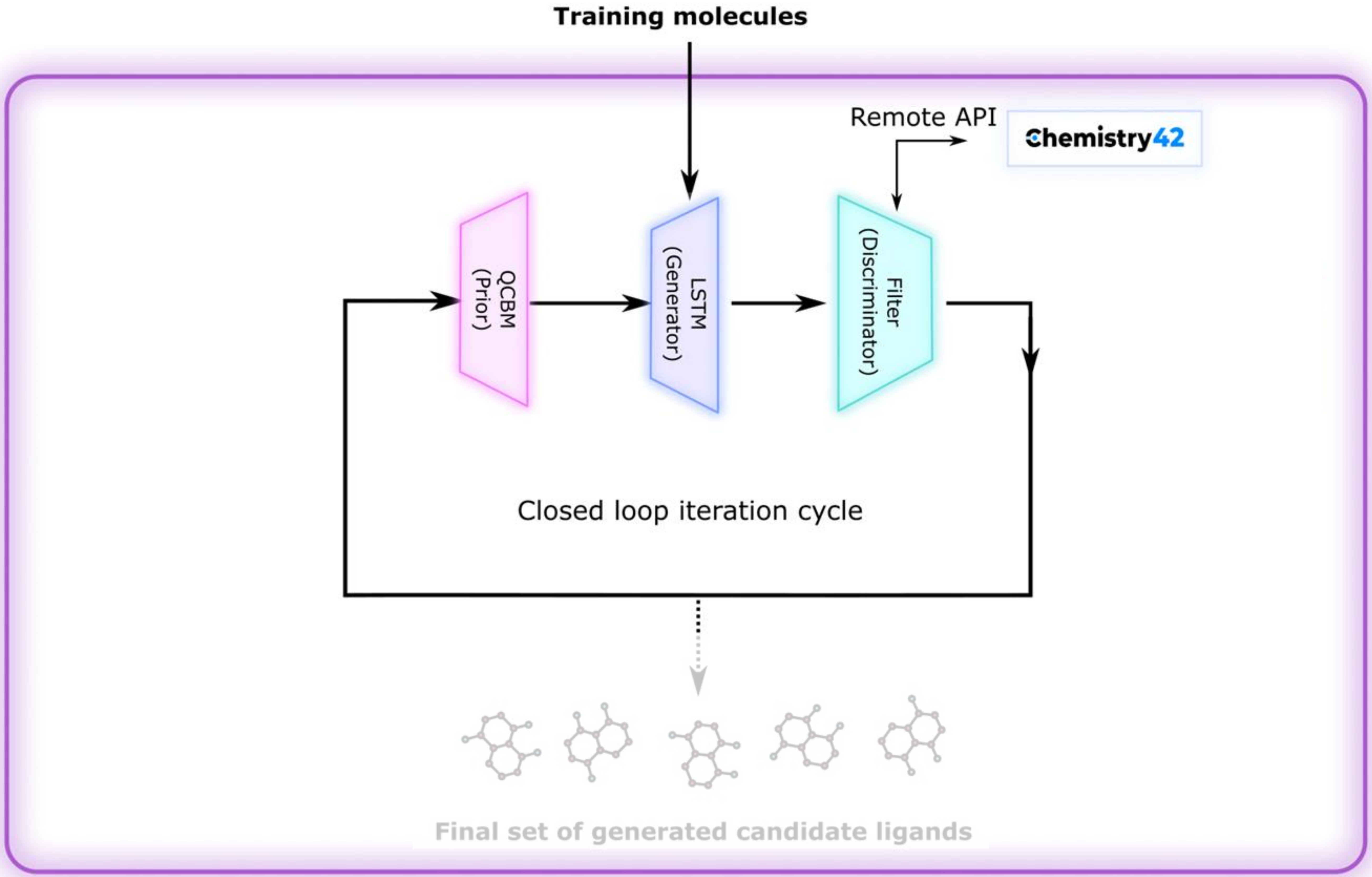

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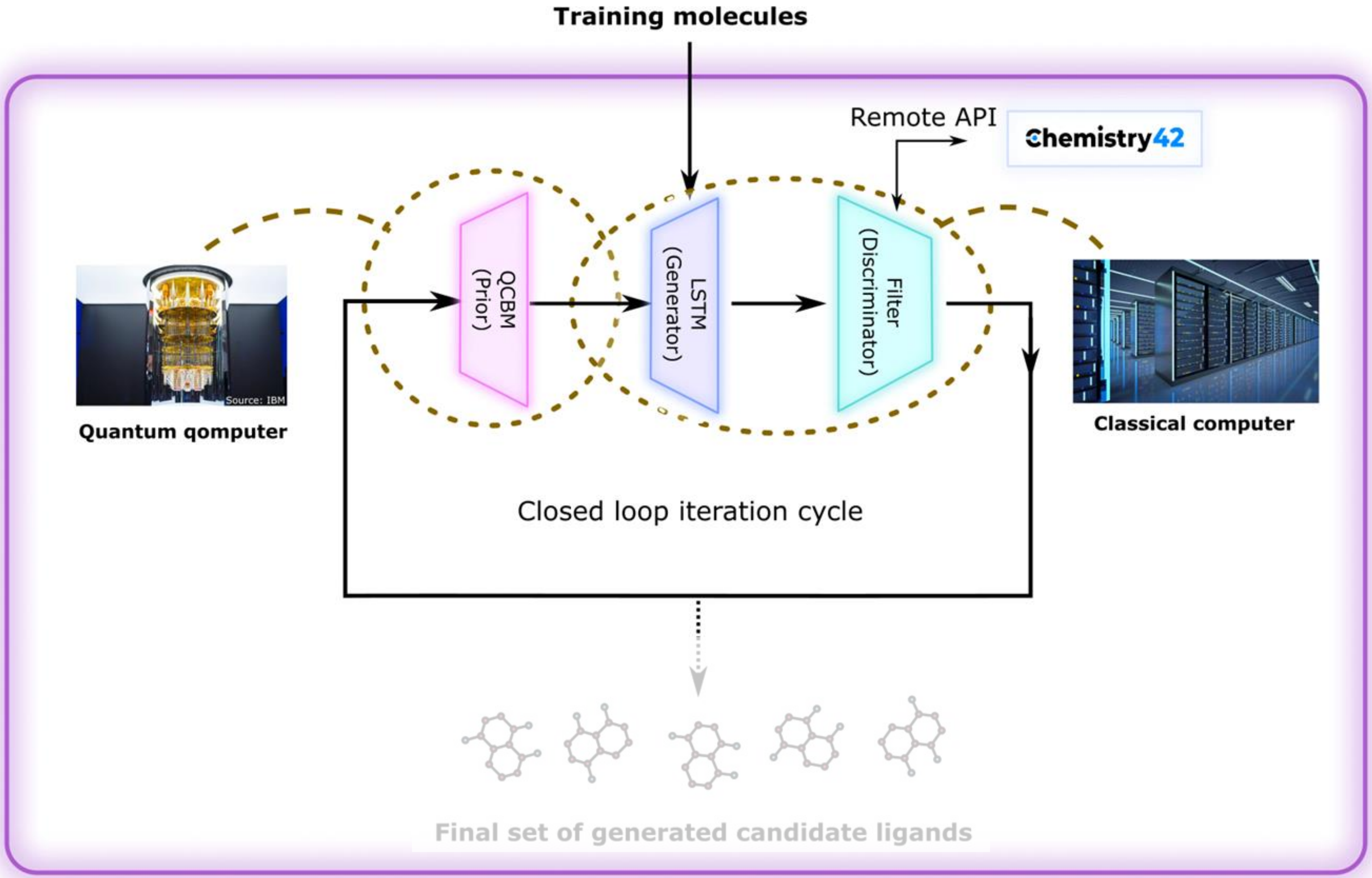
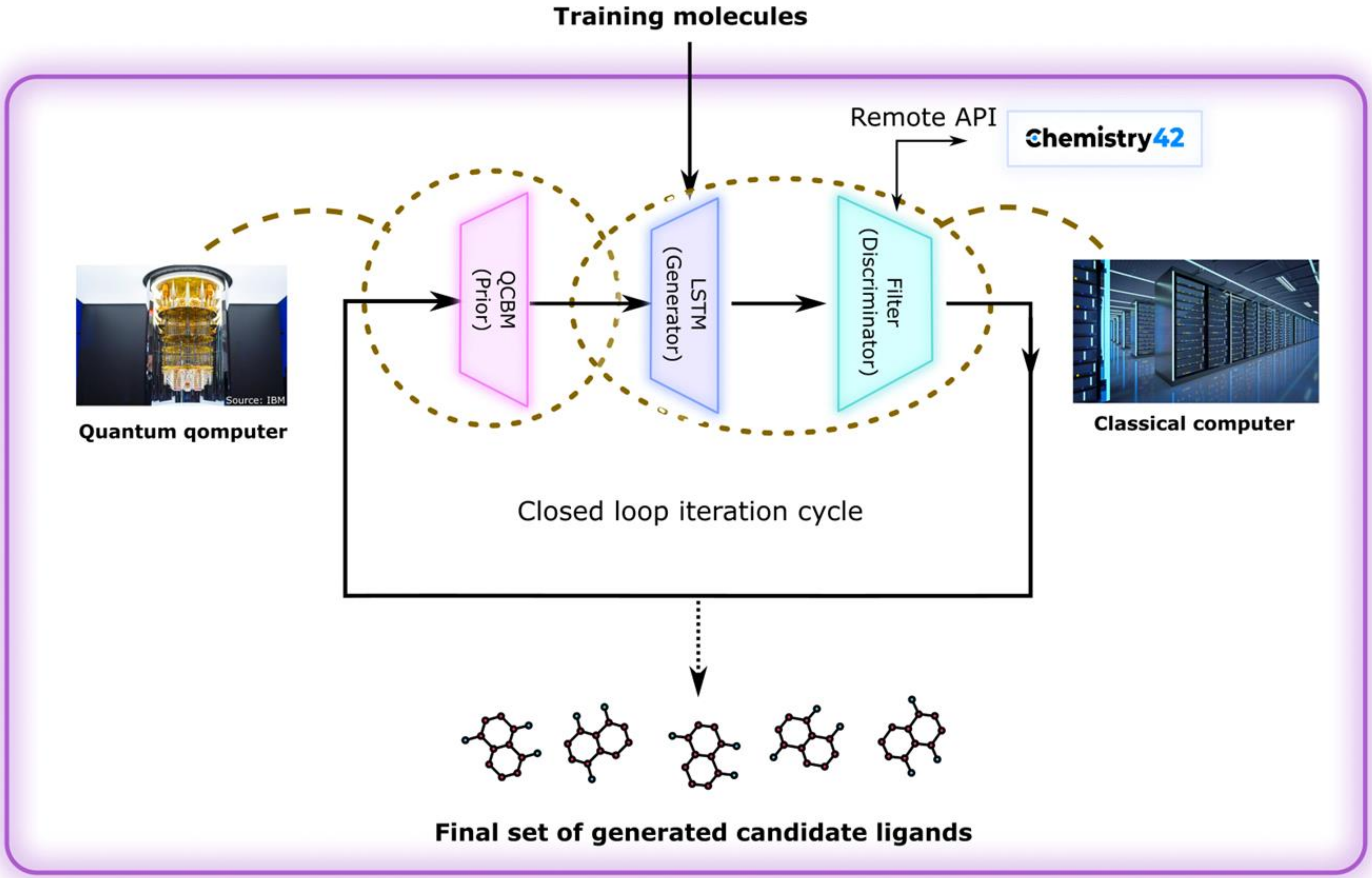
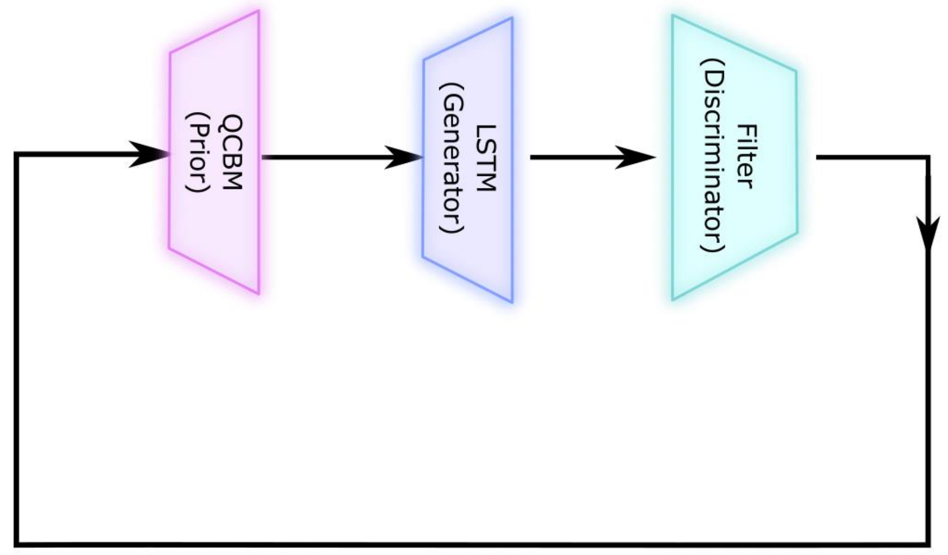


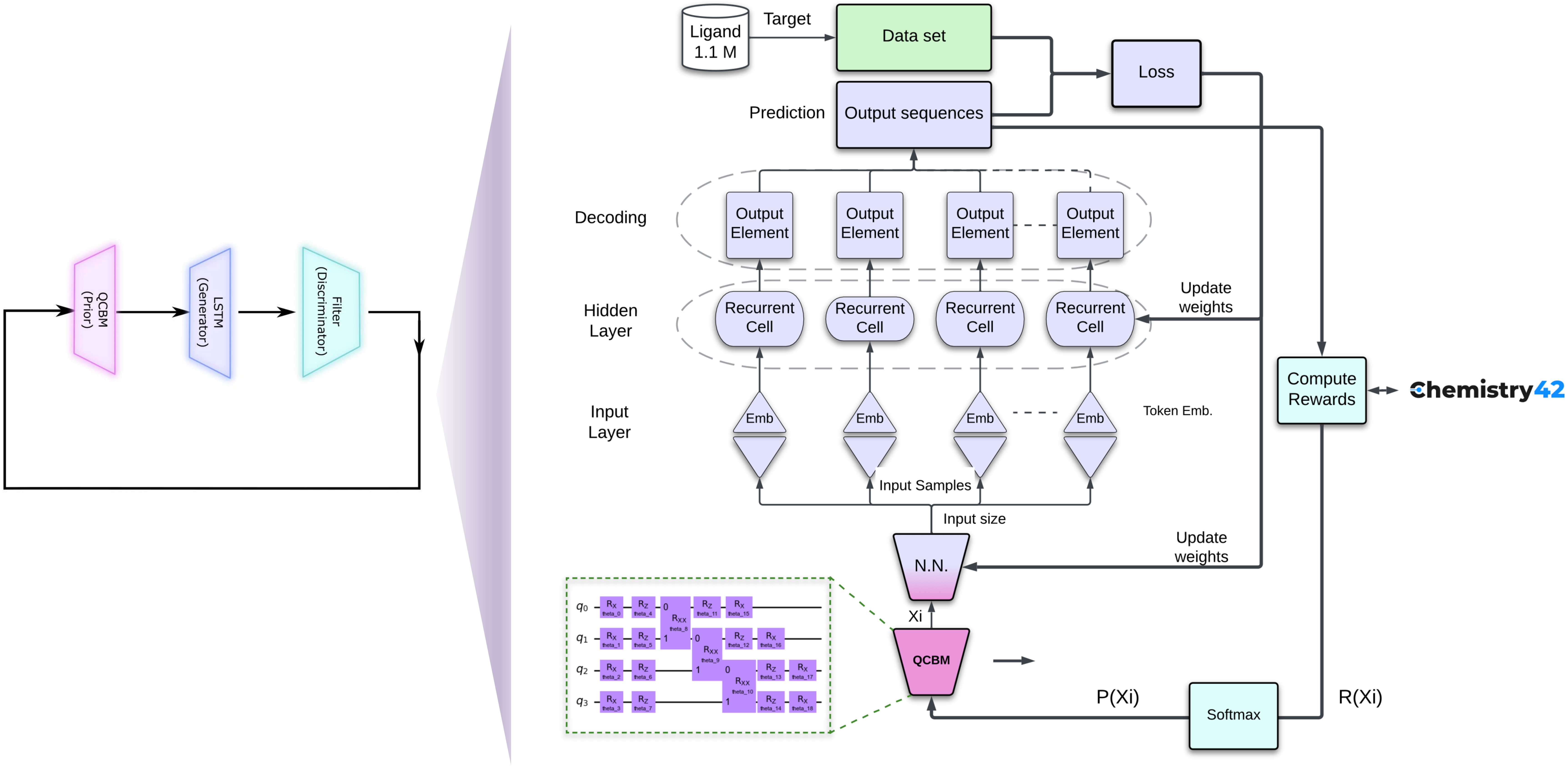
Hybrid Quantum-Classical Algorithm



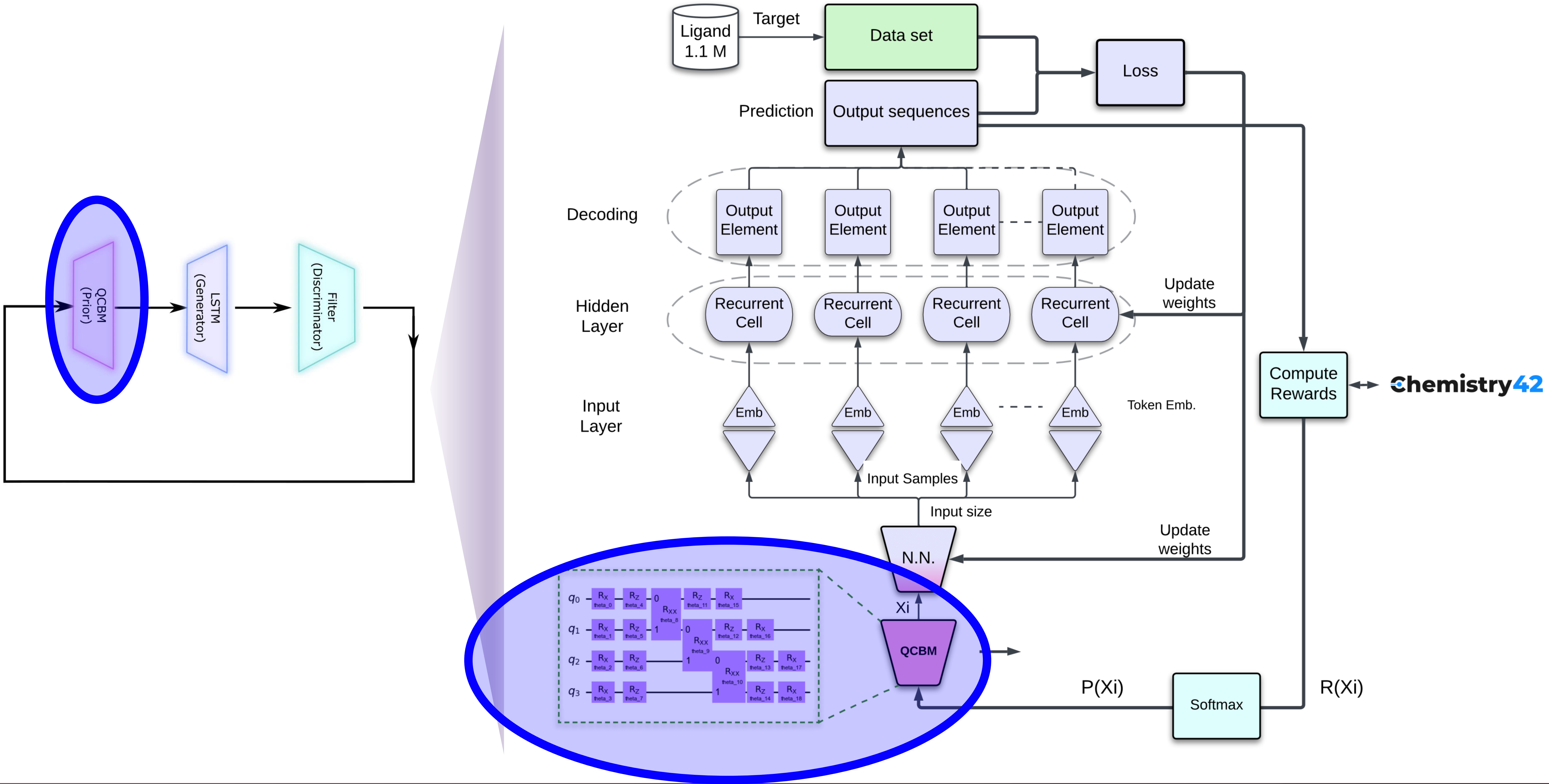
Hybrid Quantum-Classical Algorithm



Hybrid Quantum-Classical Algorithm



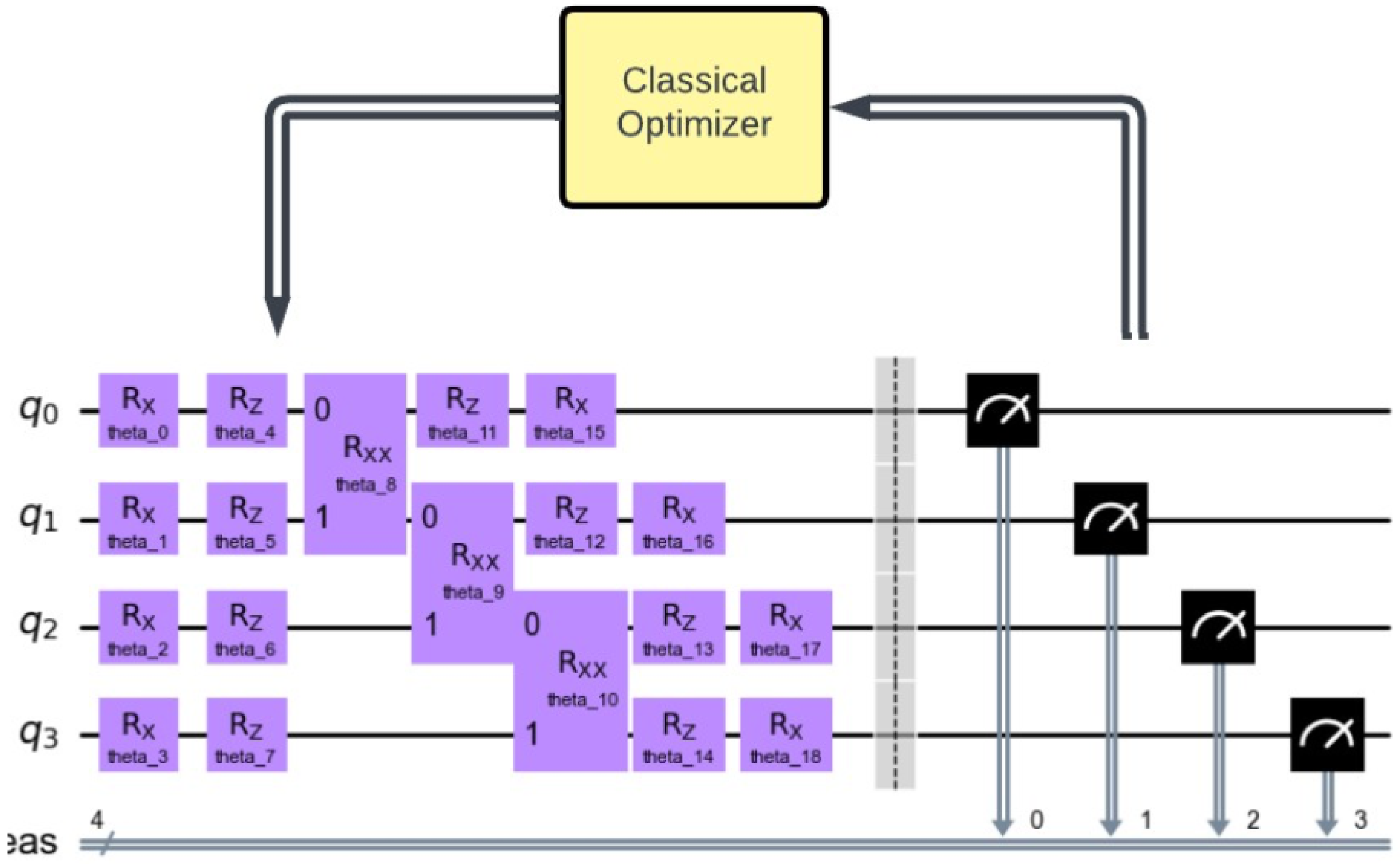
Hybrid Quantum-Classical Algorithm



Quantum Circuit Born Machine (QCBM)

- Generative quantum machine learning algorithm
- Uses a parametrized quantum circuit (PQC) in combination with gradient-based optimization
- Leverages the Born rule to generate complex probability distributions

$$\mathrm{NLL}(\theta) = -\sum_x P_{target}(x)\log(P(x))$$



$$|0\rangle \xrightarrow{U(\theta)} |\psi(\theta)\rangle \xrightarrow{\text{measure}} \text{outcome}$$

$$P(x) = |\langle x|\psi(\theta)\rangle|^2$$

Liu, J.G. and Wang, L., 2018. Physical Review A,Â 98(6), p.062324.

Maintain Industrial-Grade Security

Avoid data leaks by training generative models in your own environment, on your own secure data.

Leverage the Best Hardware Available

Optimize for cost, speed, or model performance by running applications on the best hardware available.

Use the Best Software Tools for the Job

Build complete solutions using best-in-class software services, libraries and the latest algorithmic techniques. Use existing integrations or integrate your own favorite tools.

Avoid Vendor Lock-in

Stay flexible with modular, fluid, and forward-compatible solutions. Orchestrate compute across on-premises, hybrid or multi-cloud environments.

Accelerate Collaboration

Enable cross-team collaboration between scientists, developers, IT and domain experts. Control user access and easily share private data, benchmarks and prototypes.

Manage the Entire Application Lifecycle in One Place

Orquestra supports the entire application lifecycle – from research to development to deployment and long-term maintenance needs.

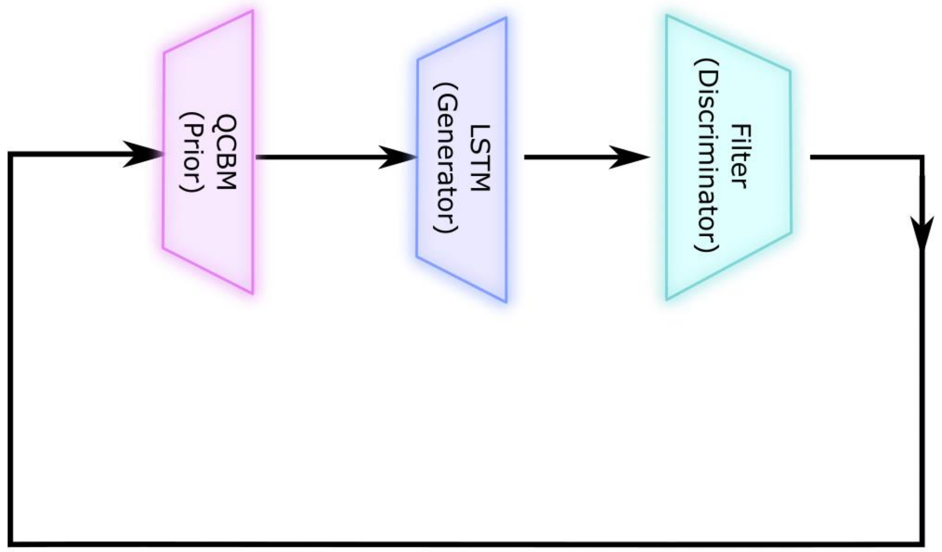
Optimize for Data Velocity

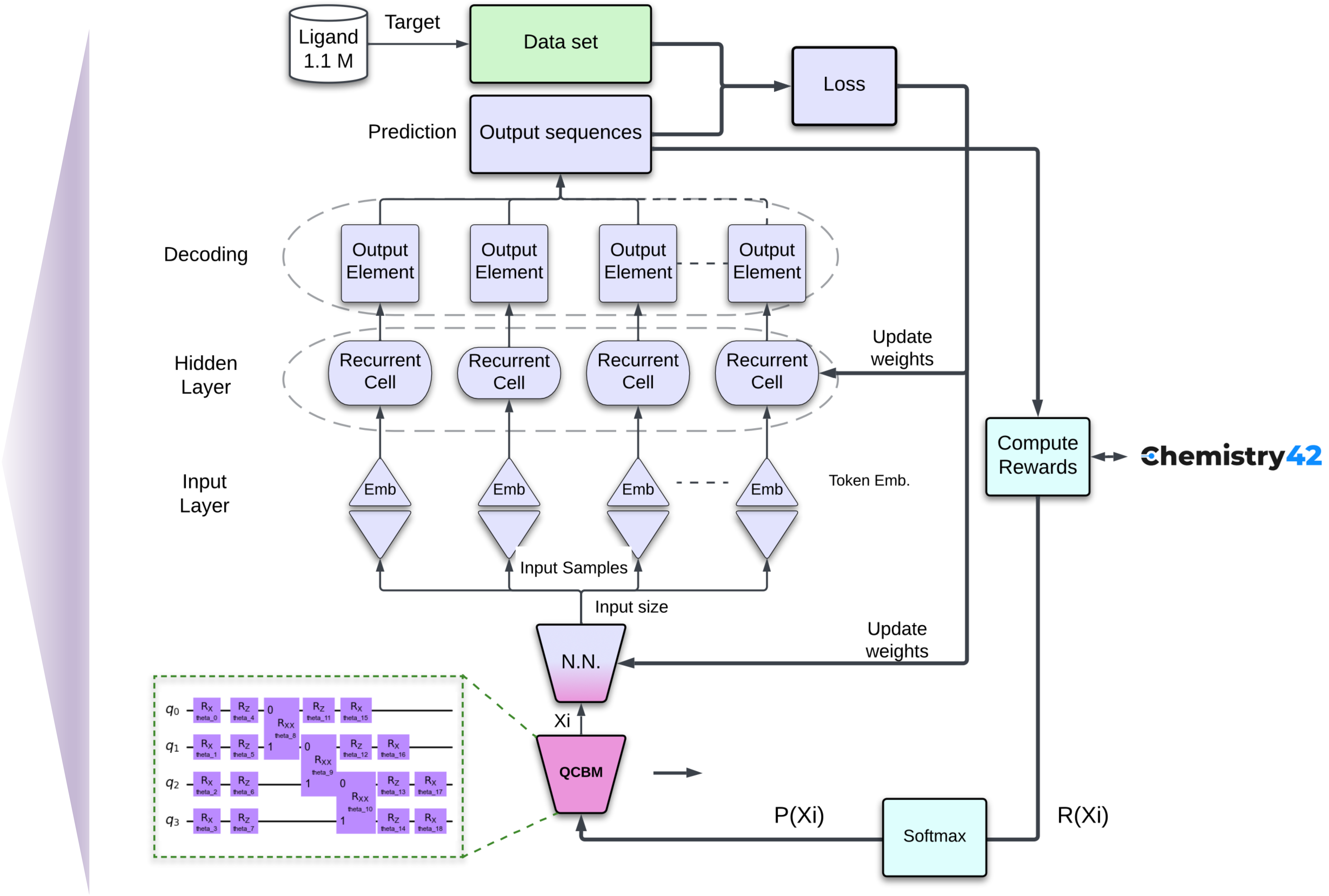
Build workflows to automate data cleaning and processing in parallel. Reduce latency by colocating compute and data in the same environment.

Maximize Model Performance

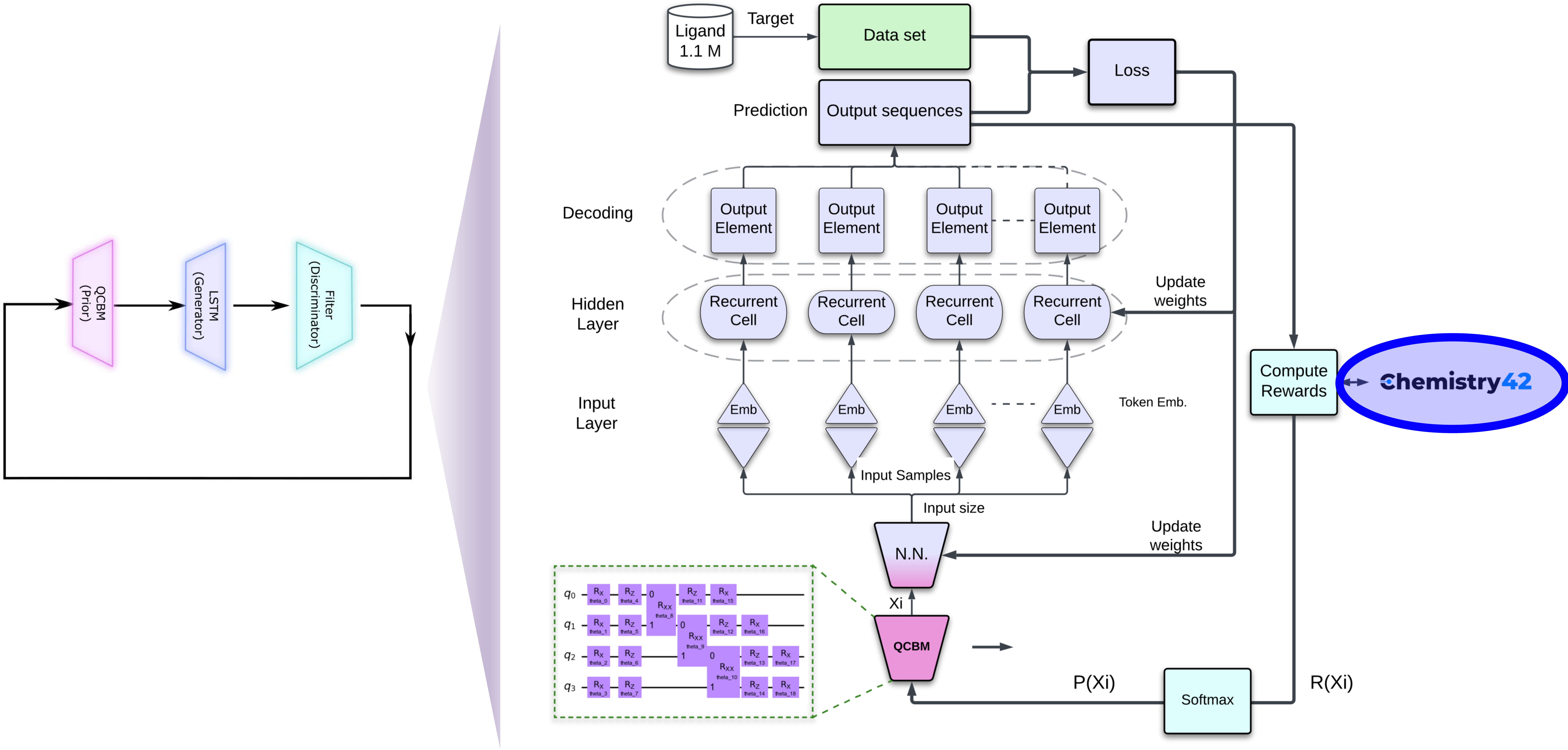
Benchmark your models to get the best performance possible. Build workflows to drive model selection and tune hyperparameters.

Hybrid Quantum-Classical Algorithm





Hybrid Quantum-Classical Algorithm



Chemistry42 – AI Platform for Generative Drug Design

Chemistry42

Insilico Medicine

Medicinal & **Computational** Chemists

1. SET YOUR OBJECTIVE

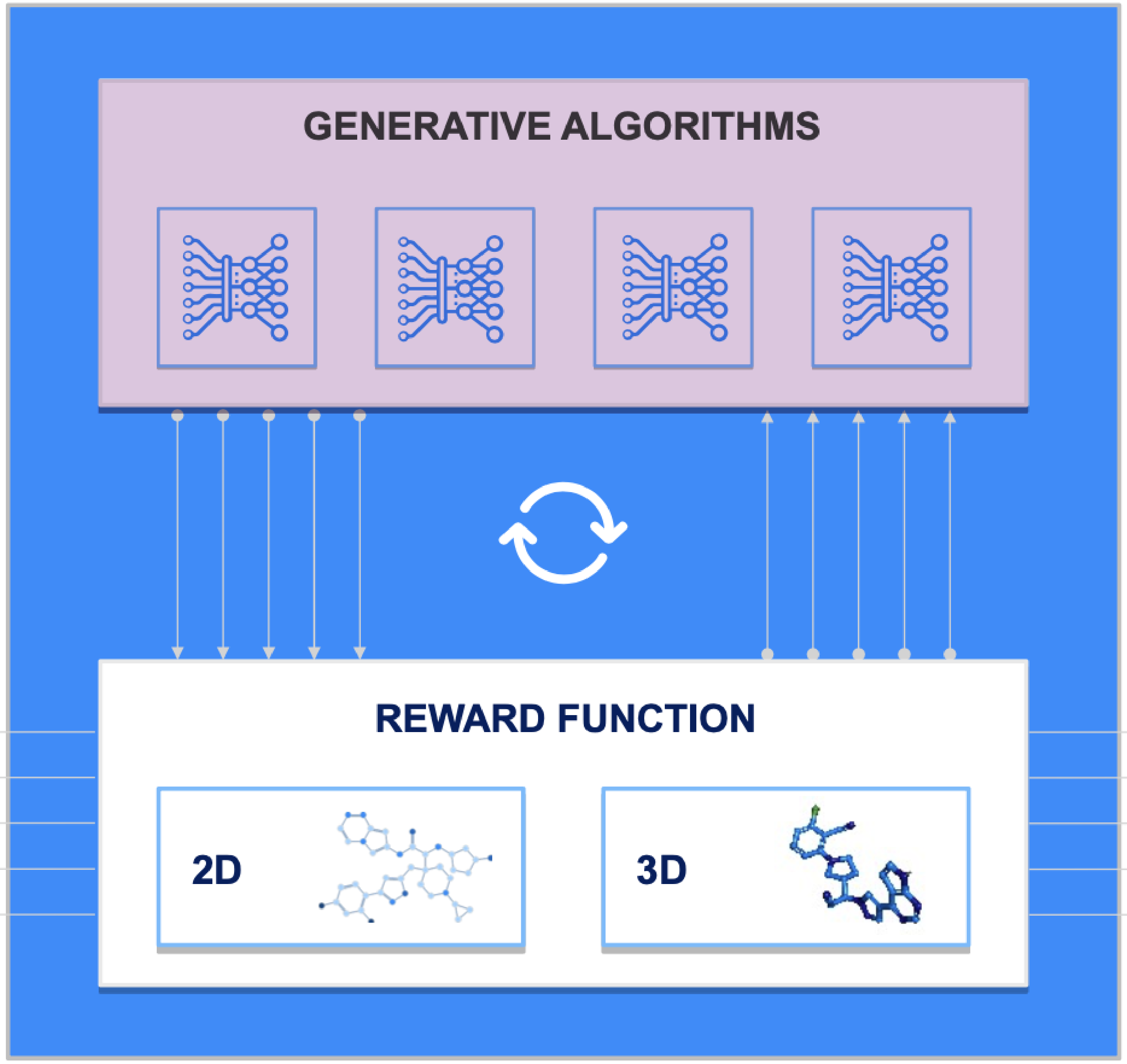
Define your target product profile

2. CONFIGURE THE PLATFORM

LBDD: 2D or 3D ligand structure (.sdf or .mol2)

SBDD: Co-crystal structure

Virtual screening: Compound Library



Data-driven Decision Making, Empowered by AI

Medicinal & **Computational** Chemists

3. OUTPUT

Visualize the generated molecules in **3D**

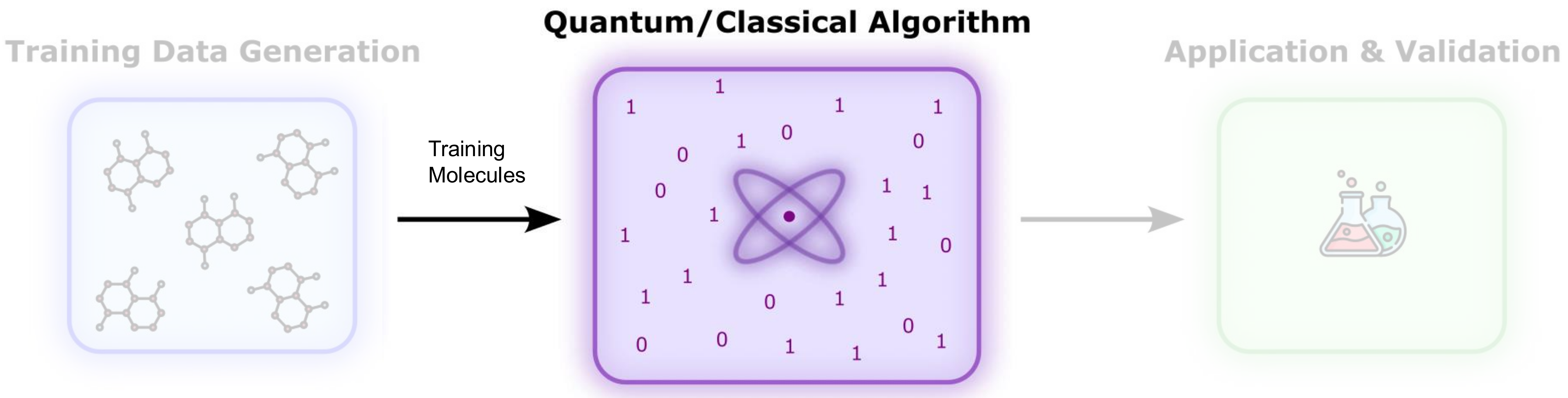
Rank and **filter** the molecules by **MPO score**

Statistically analyze generative model performance

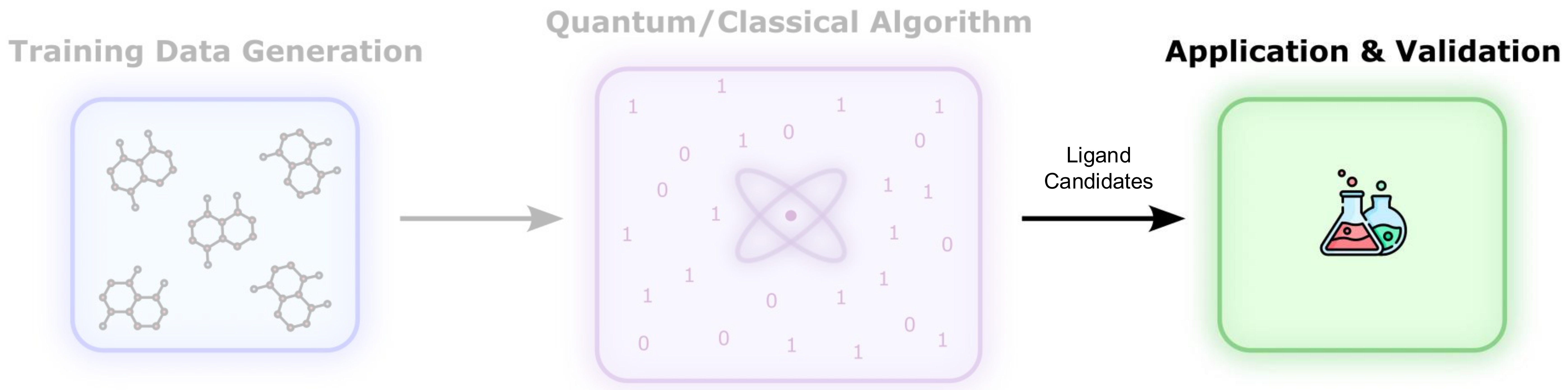
Download your favourites molecules as .sdf files

J. Chem. Inf. Model.Â 2023, 63, 3, 695-701

Hybrid Quantum-Classical Approach



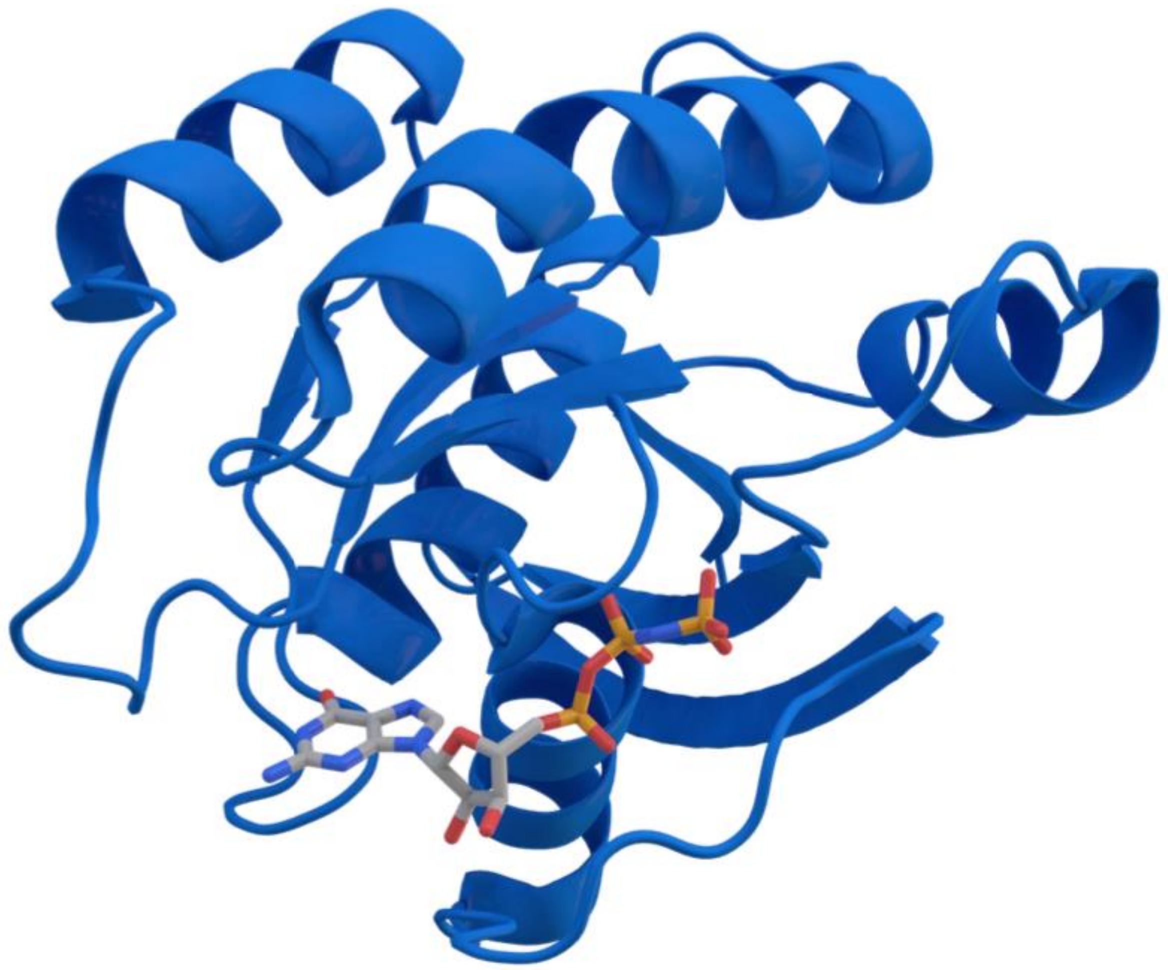
Hybrid Quantum-Classical Approach



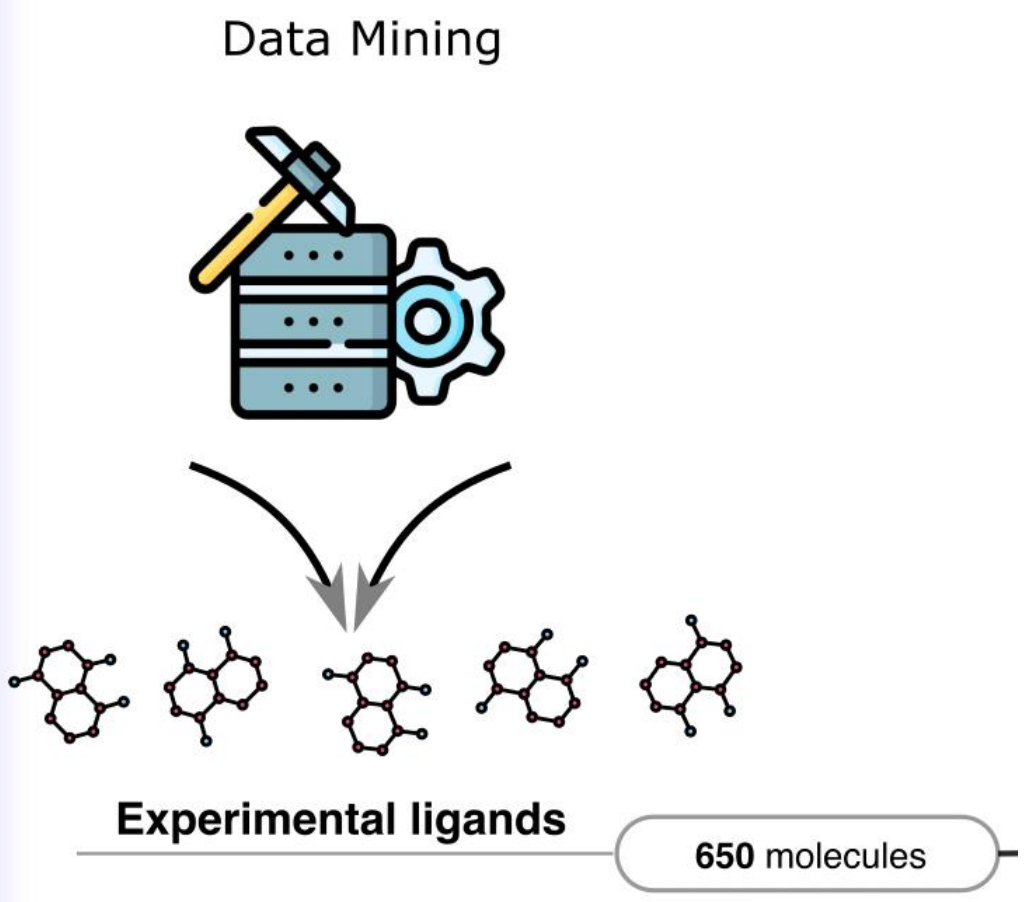
Application to KRAS

KRAS – Introduction

- Cancer is one of the leading causes of death
- KRAS is one of the most mutated oncogene in cancer
- KRAS was historically considered to be “undruggable”
- First success for KRAS G12C mutant was reported in the last few years
- Many other mutants, e.g. G12D, do not have approved drugs yet



KRAS G12D – Training Data Generation



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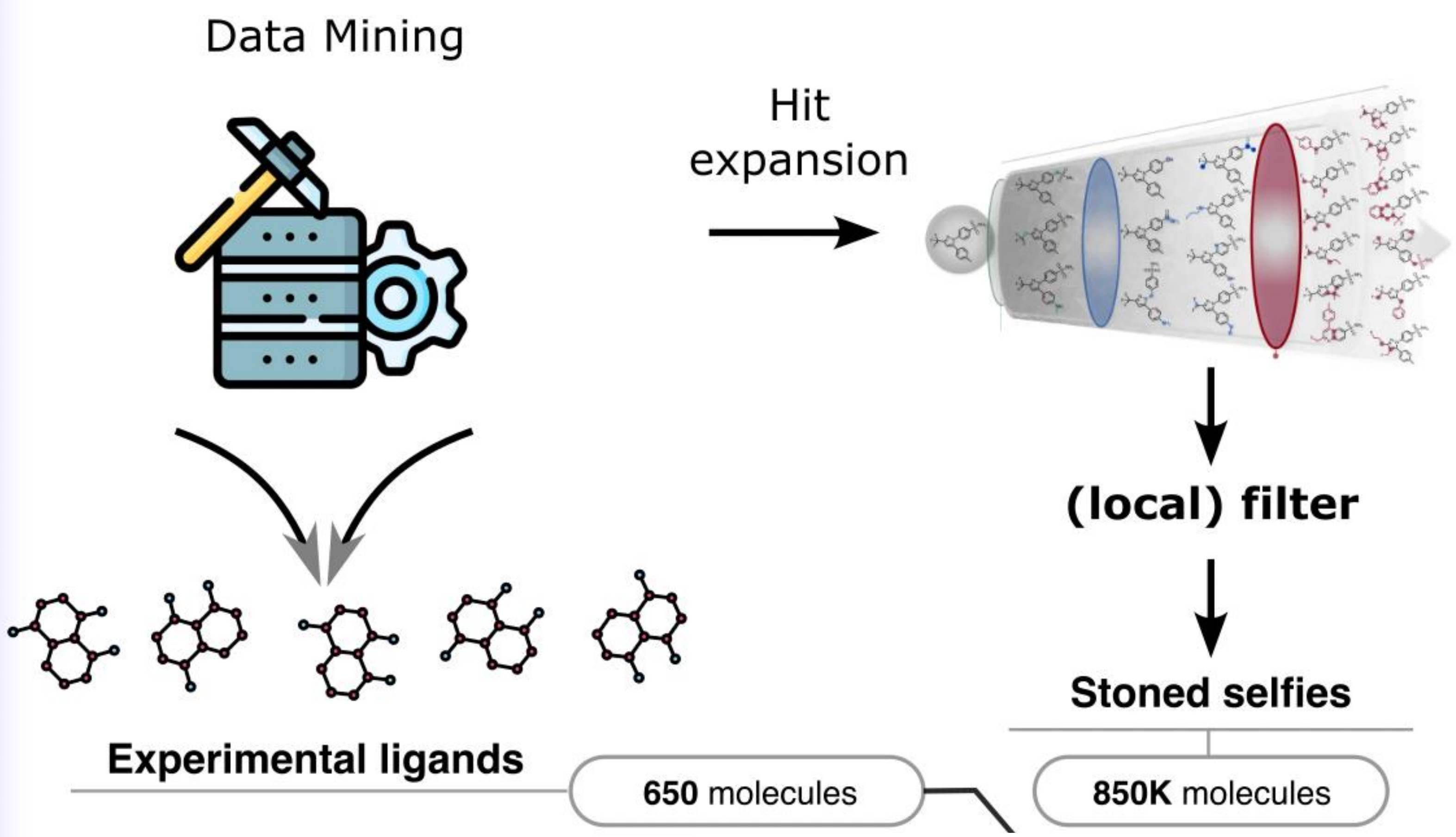

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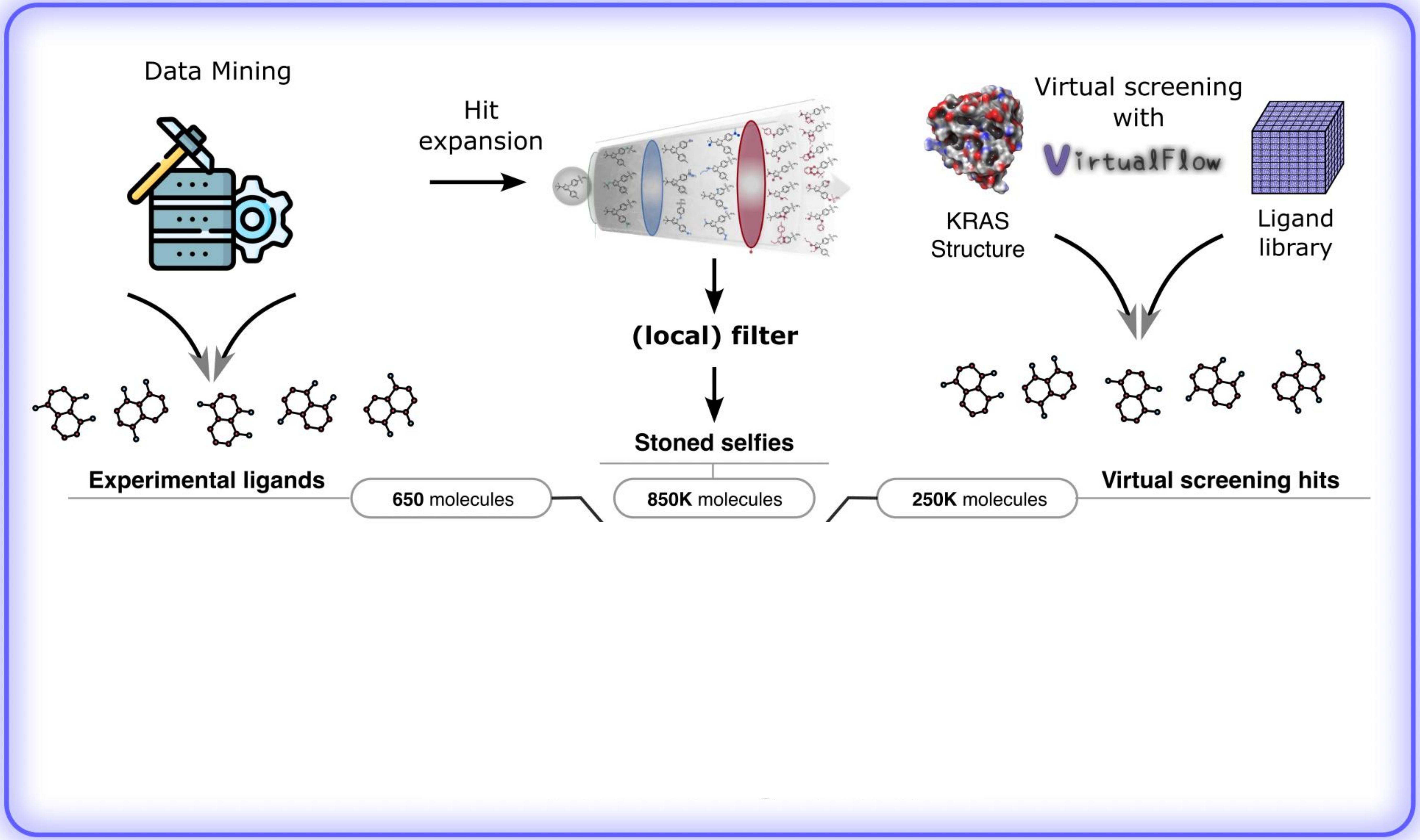

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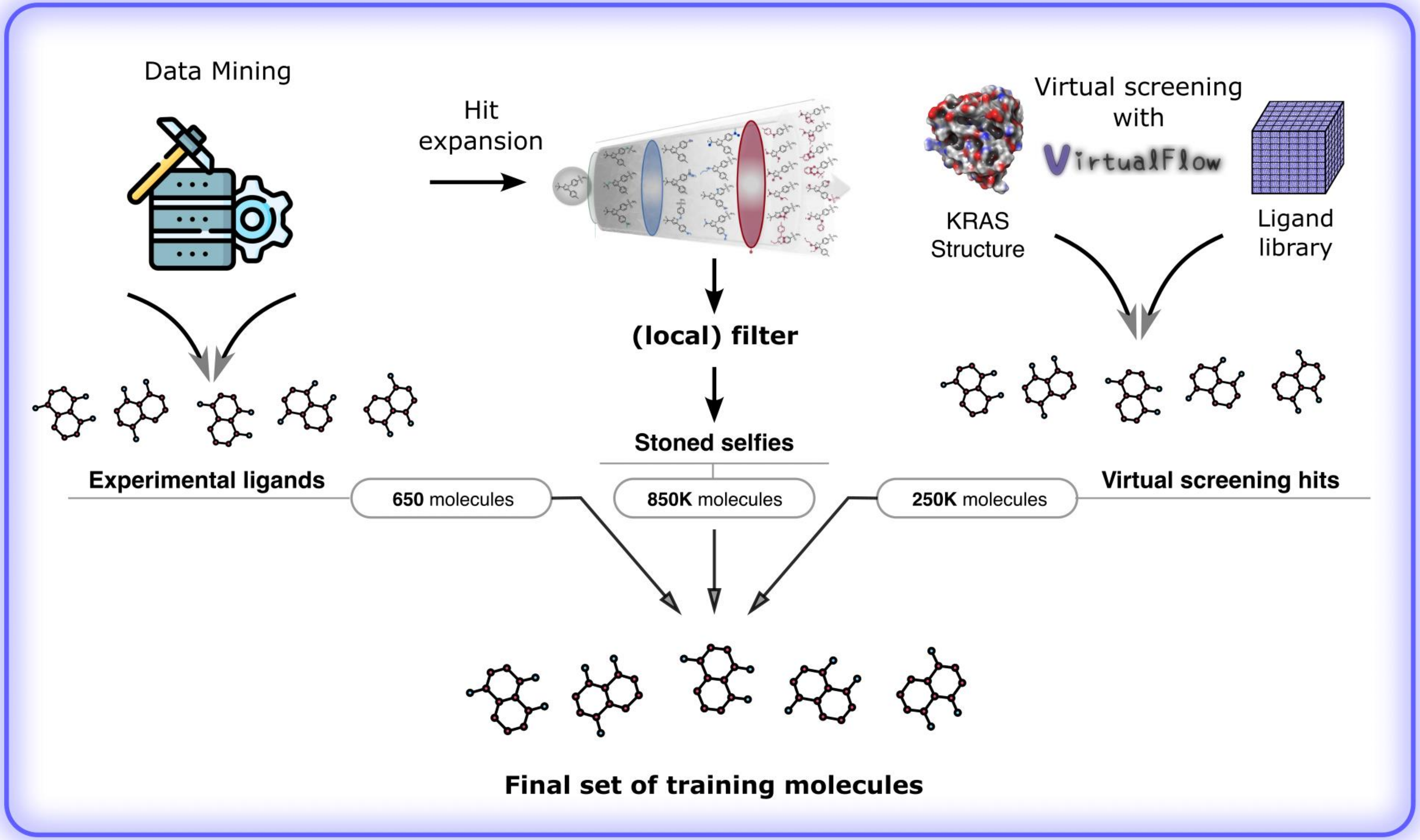
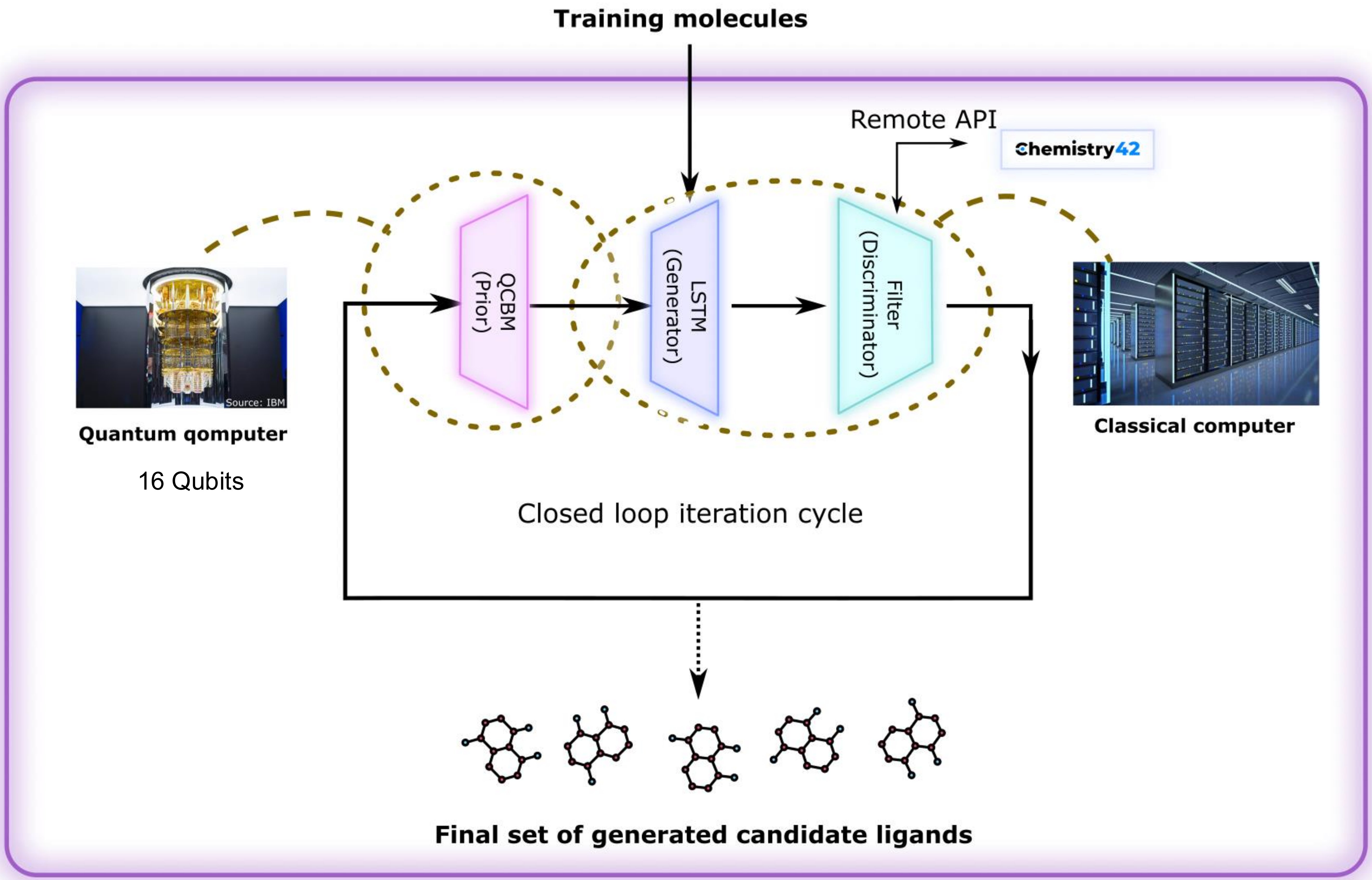


KRAS G12D – Computational Benchmarks



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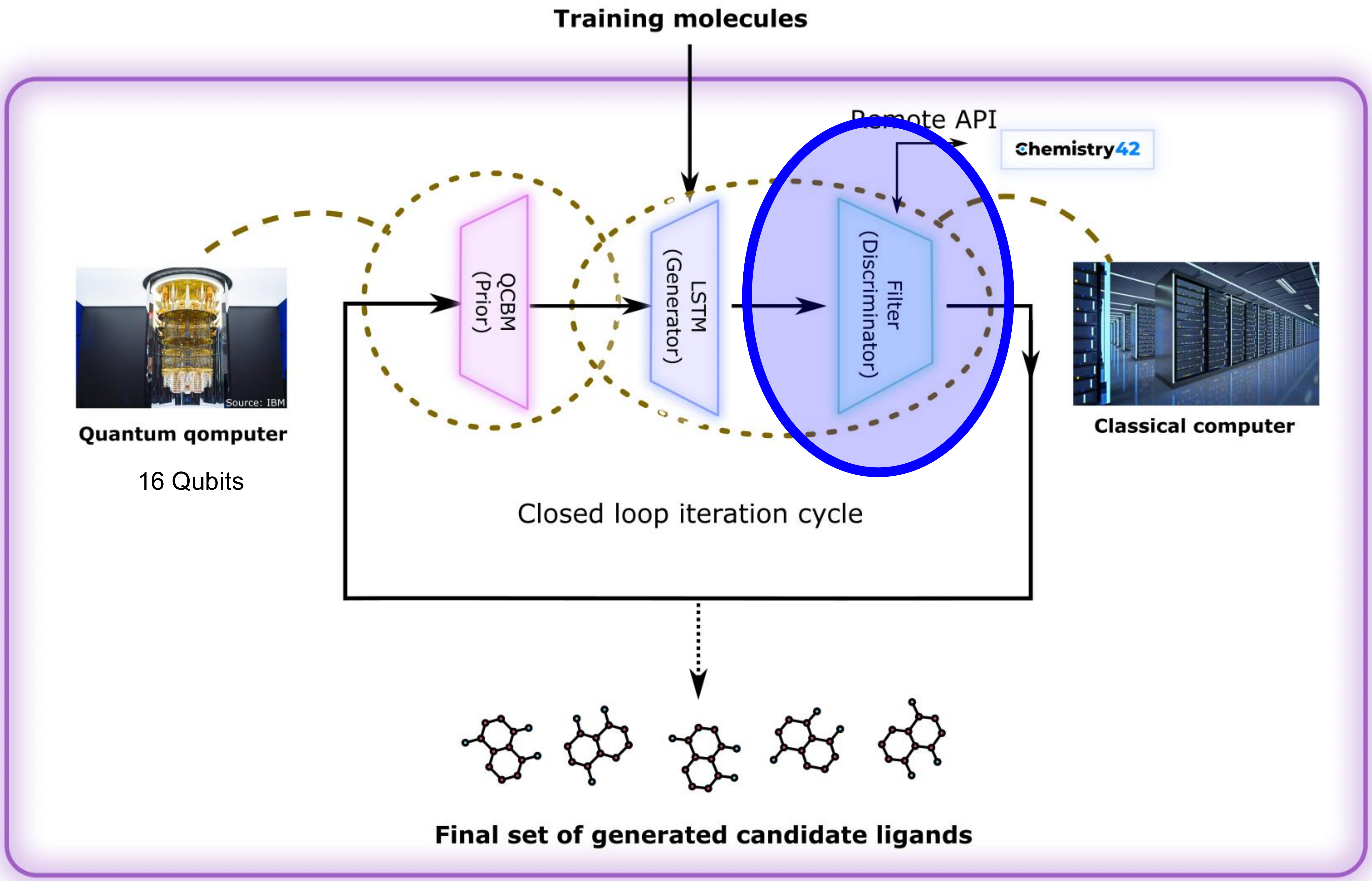

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Success Rate (SR) = (passed compounds) / (total compounds generated)

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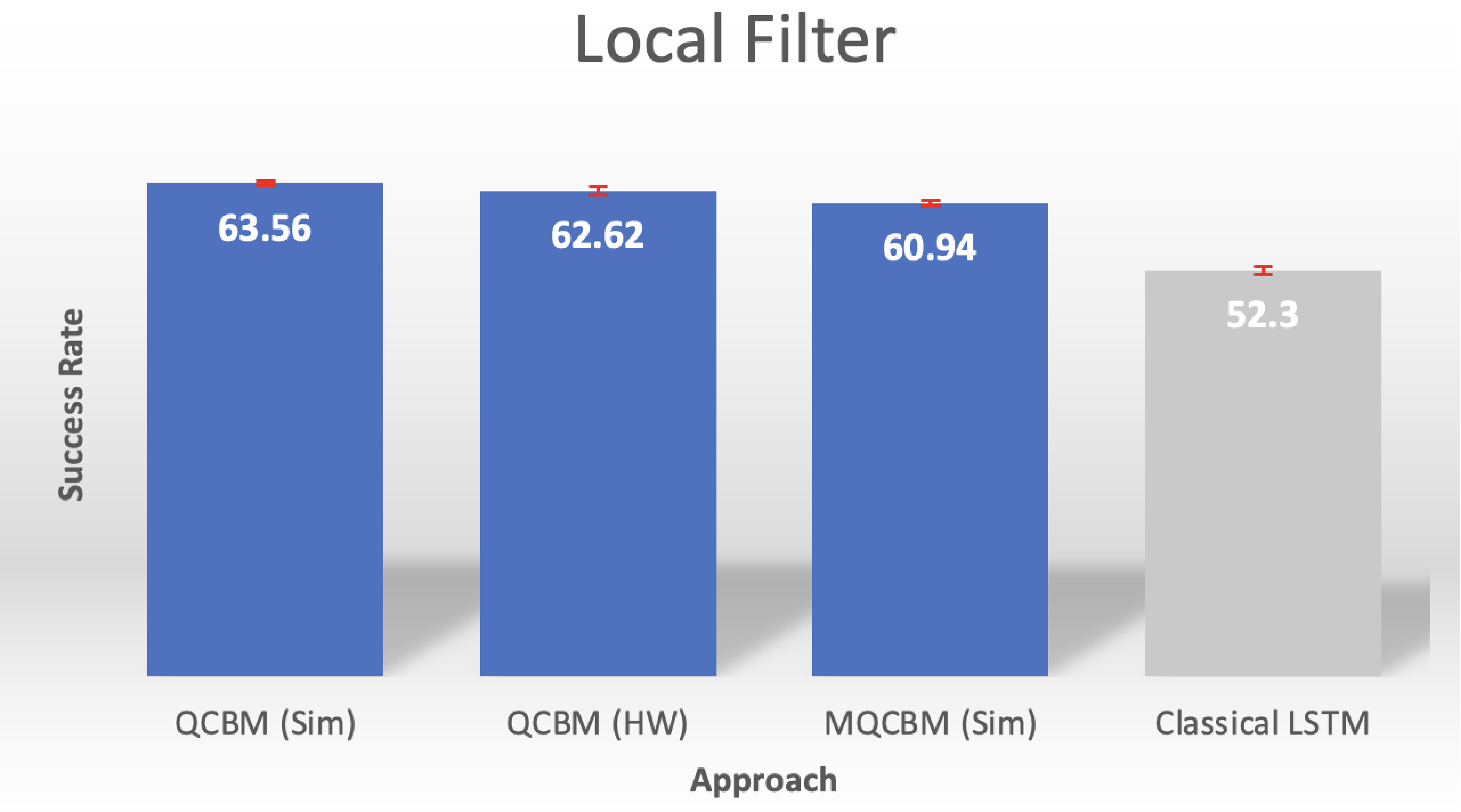

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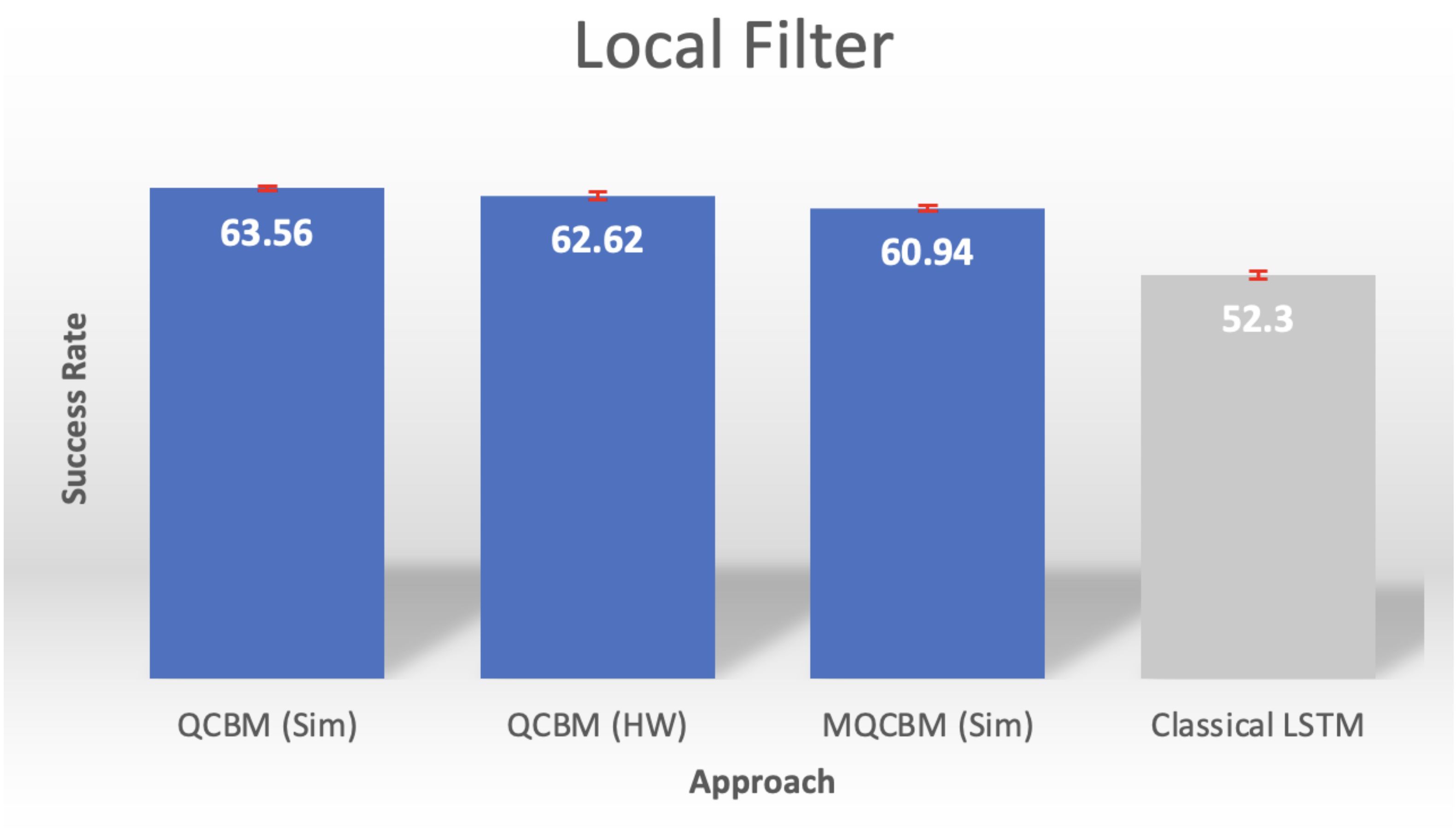
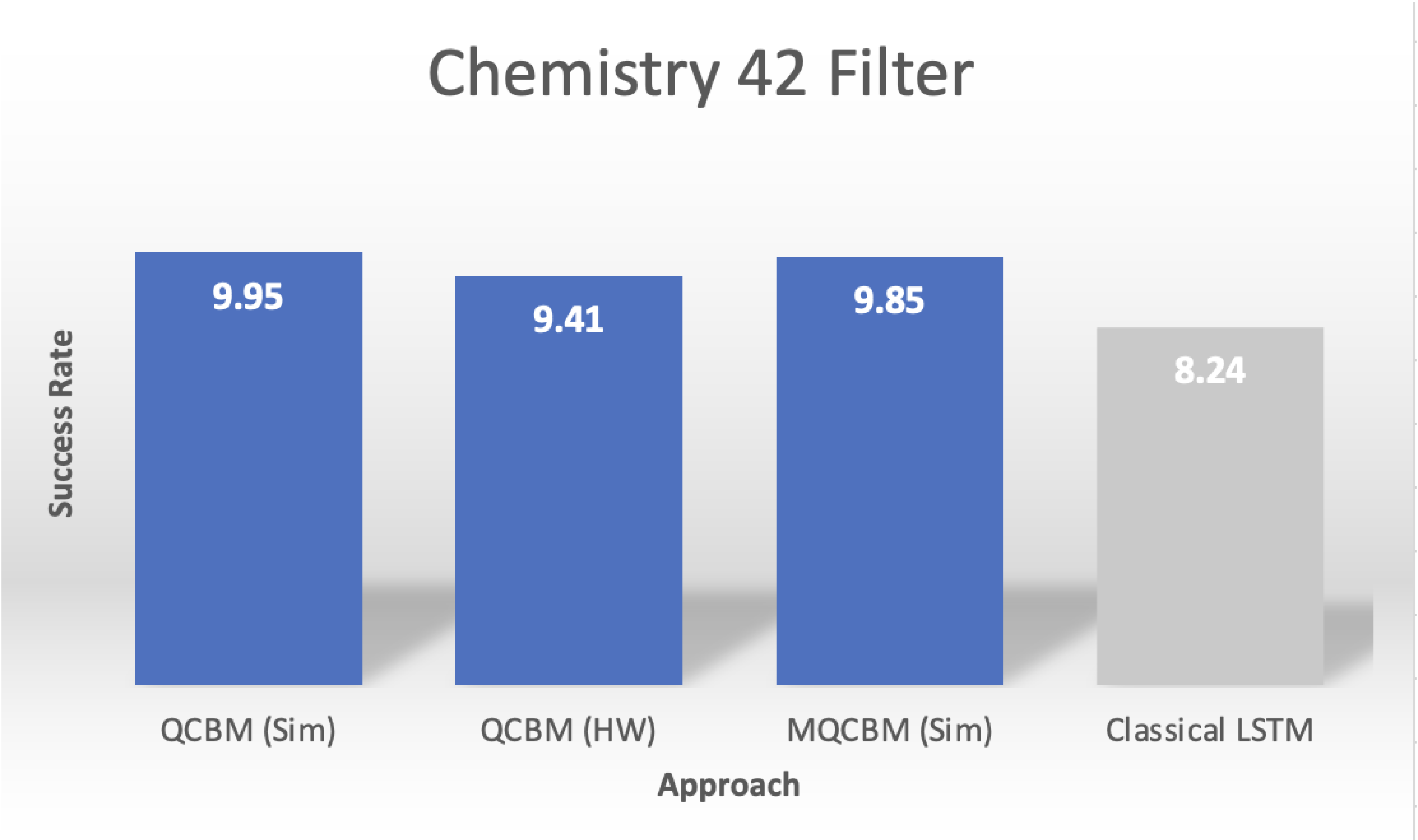
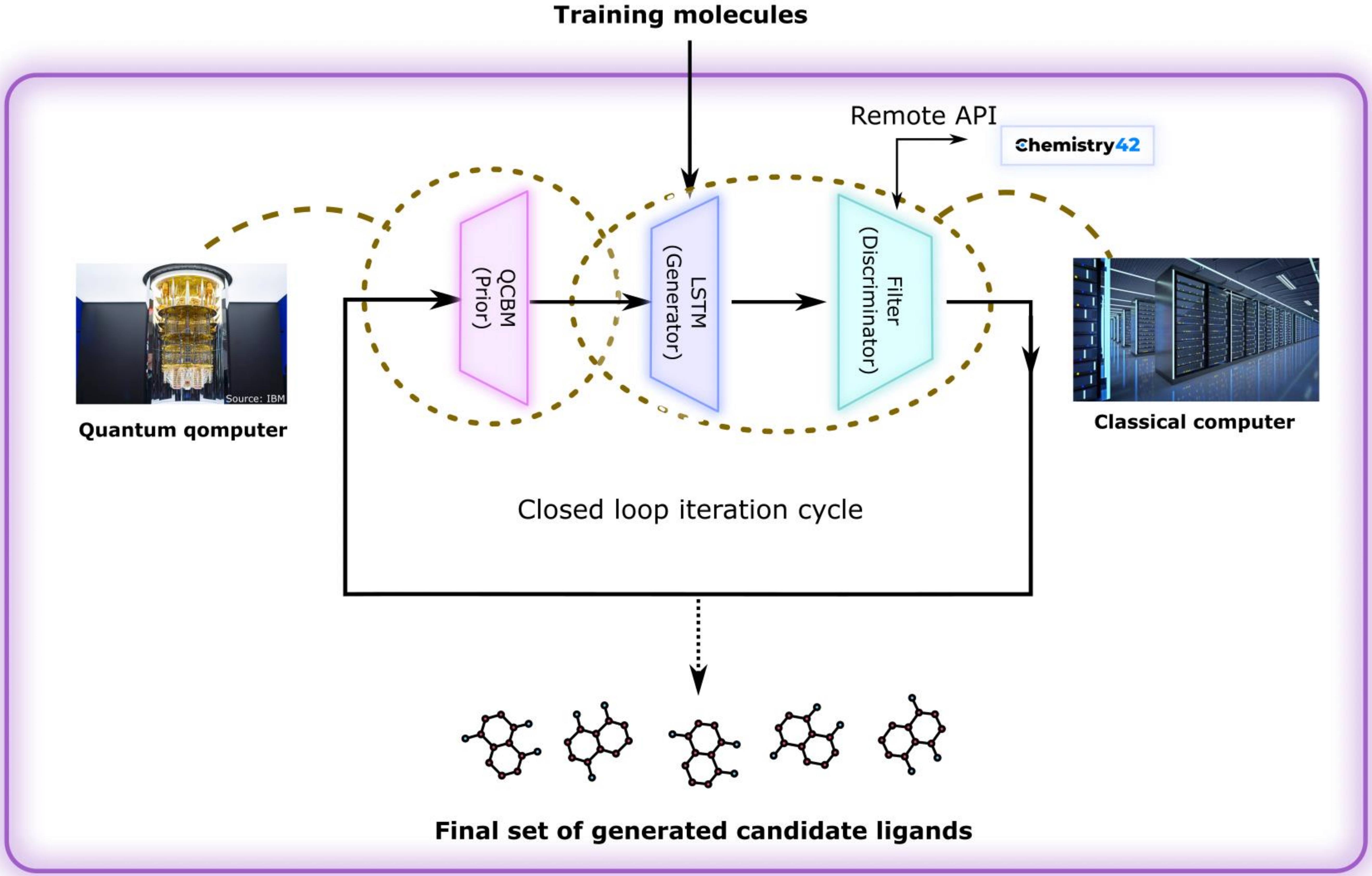




KRAS G12D – Experimental Validation



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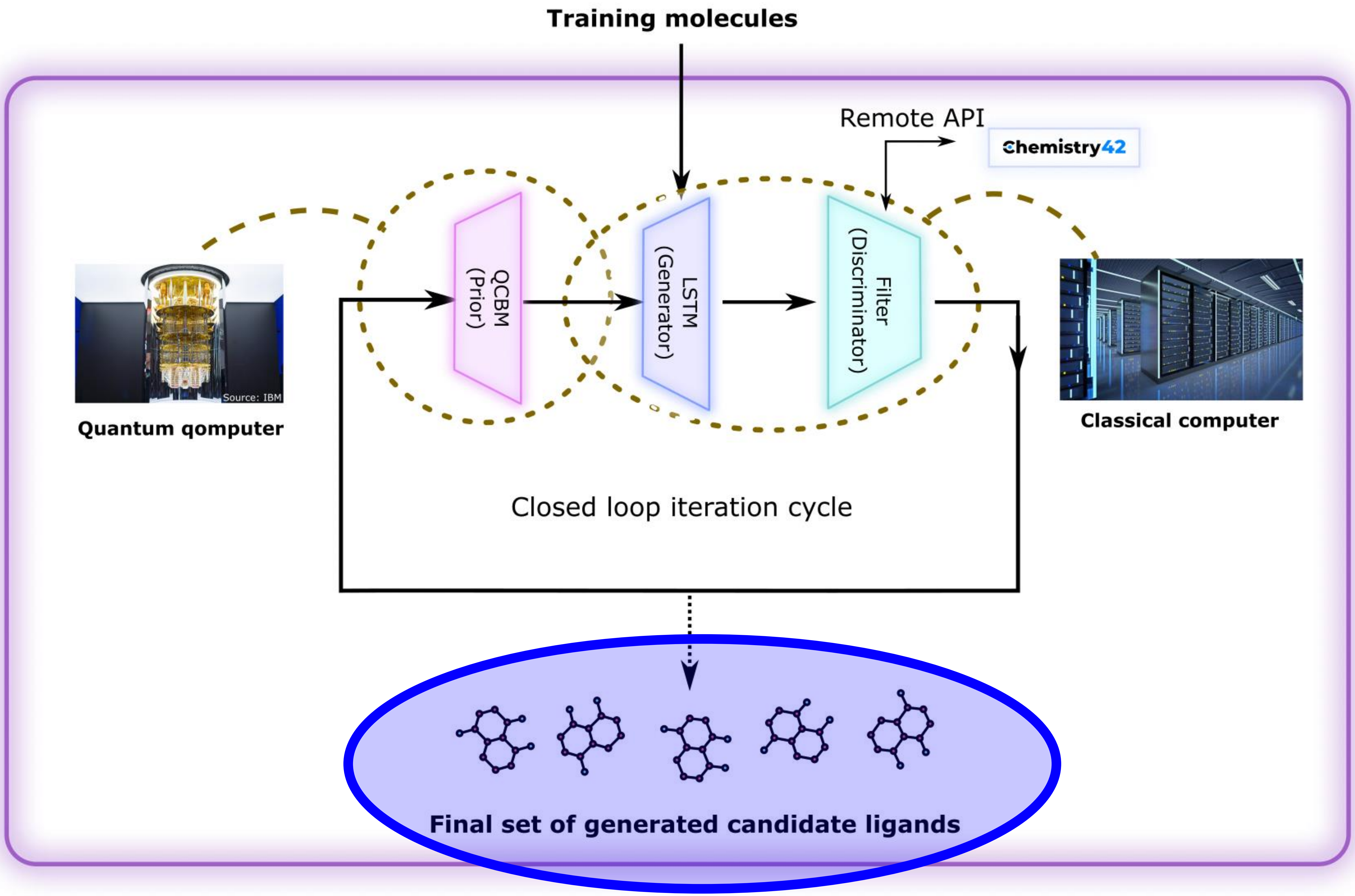
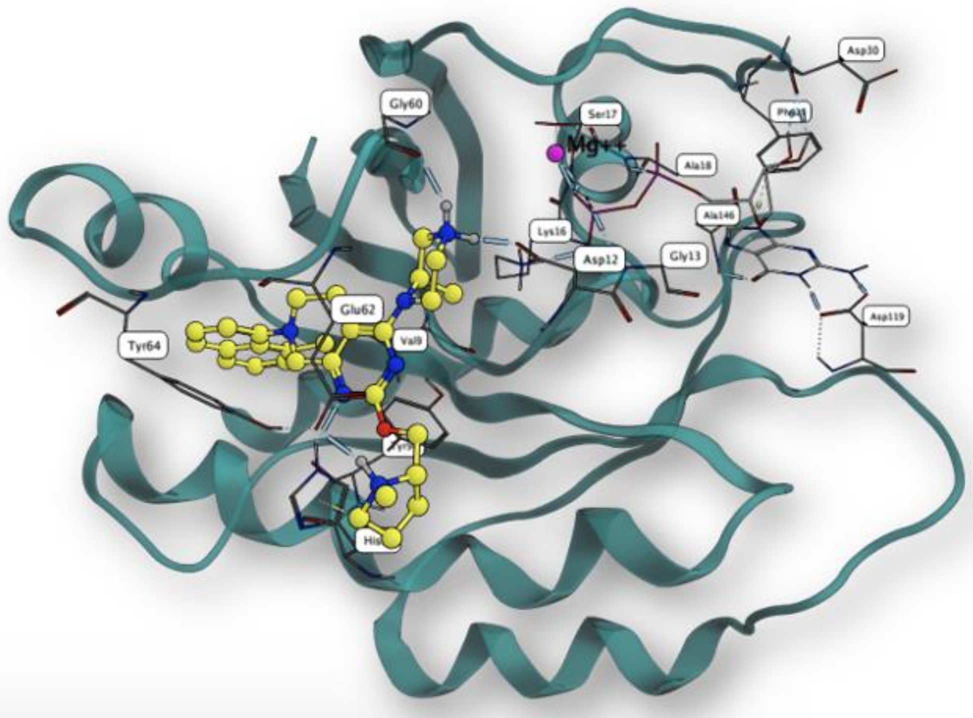


KRAS G12D – Experimental Compound Selection



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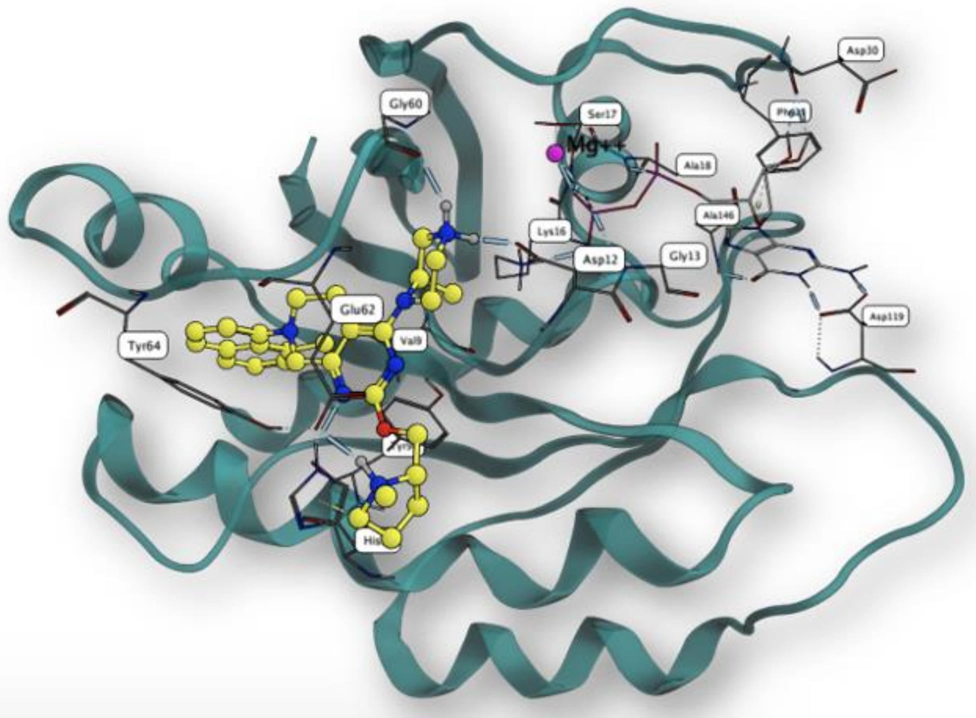

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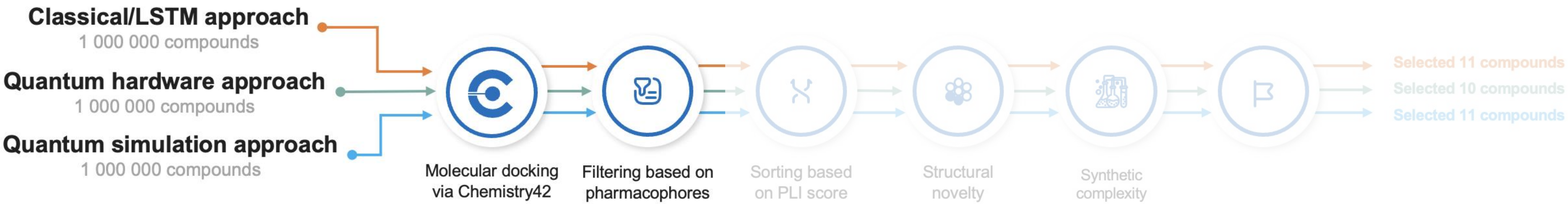

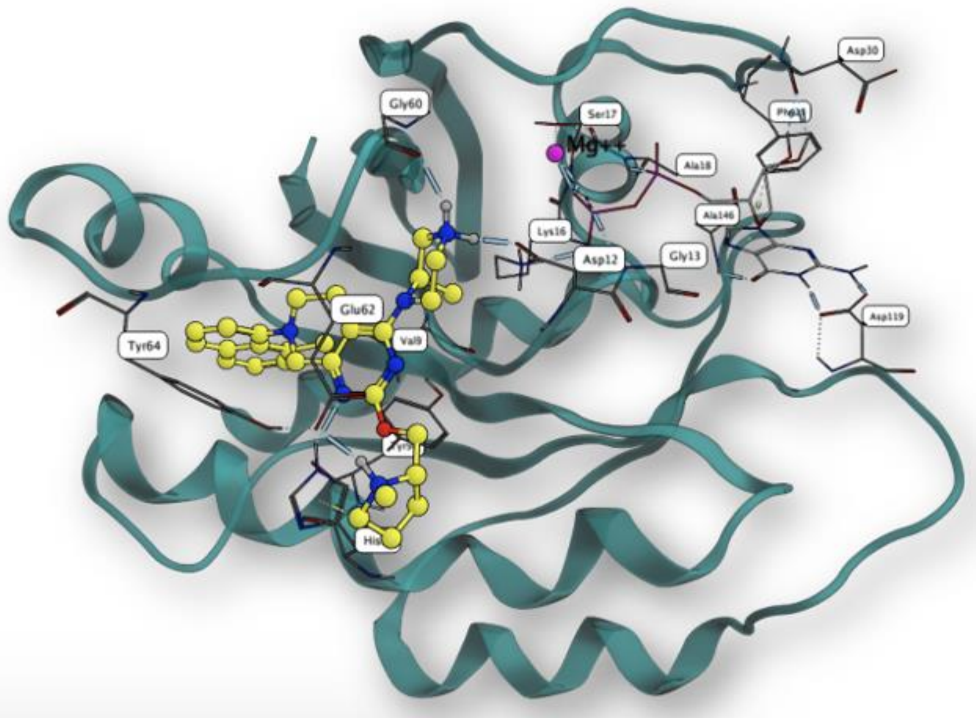

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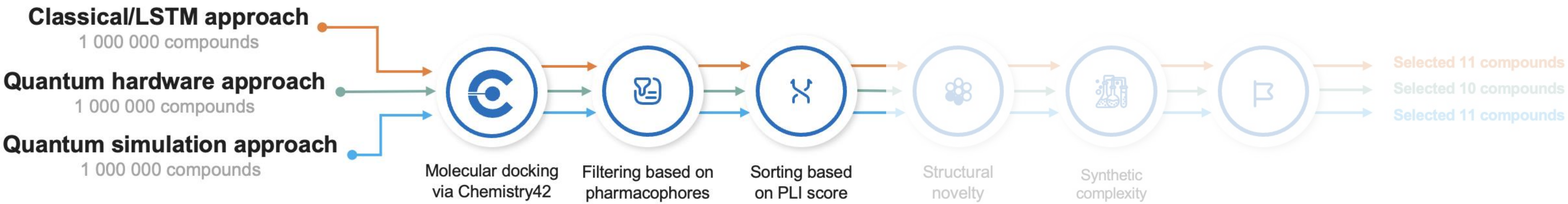

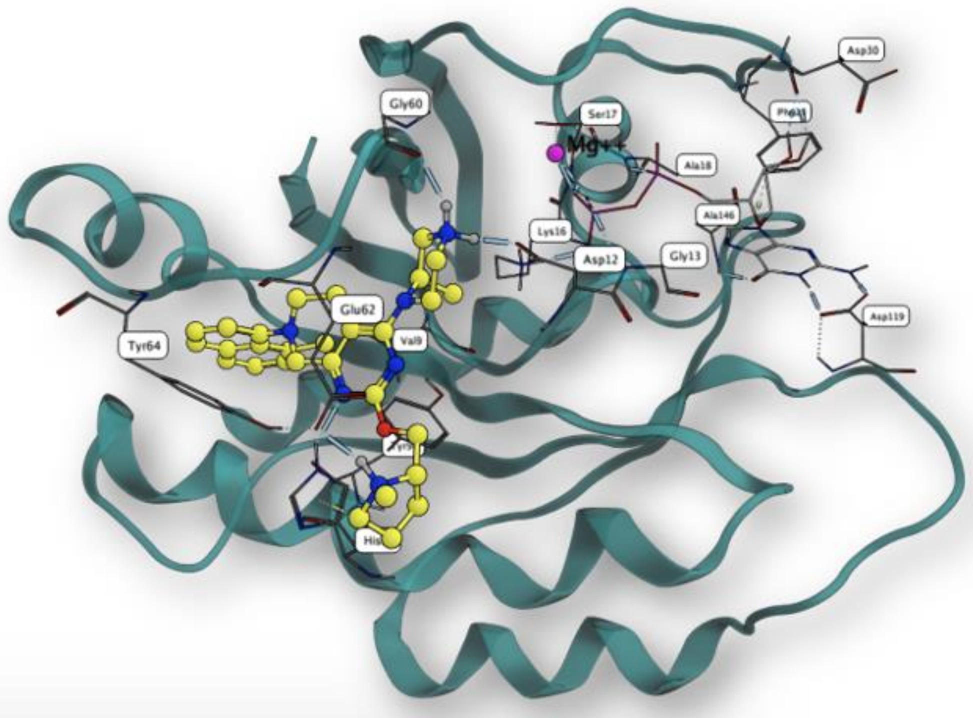

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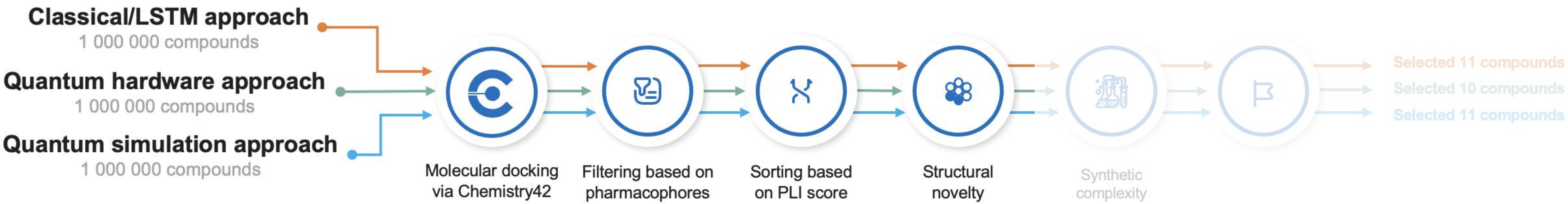

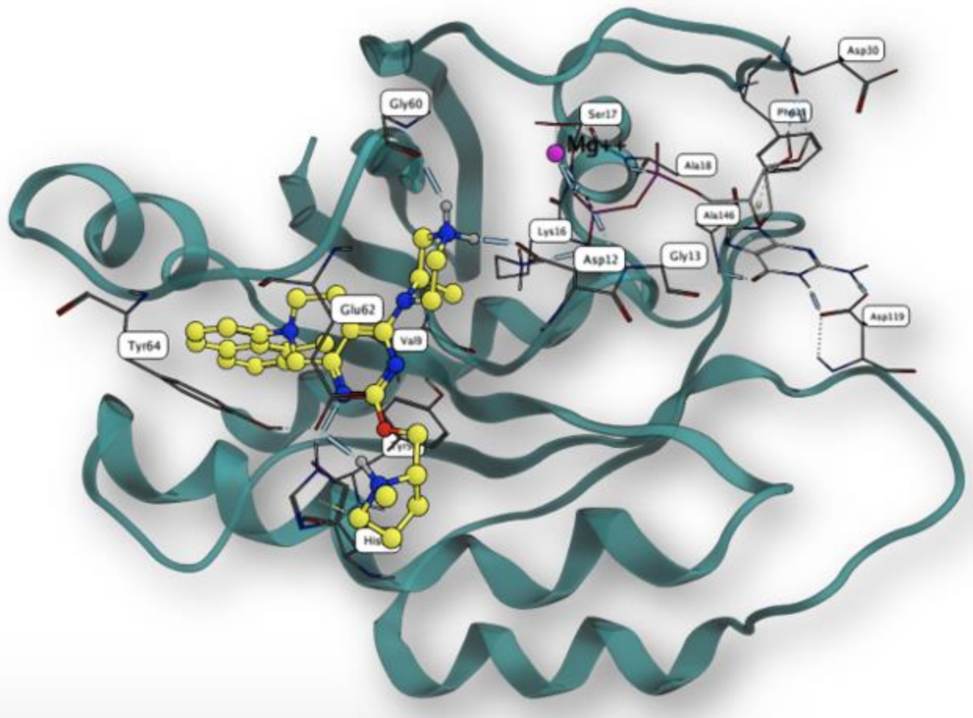

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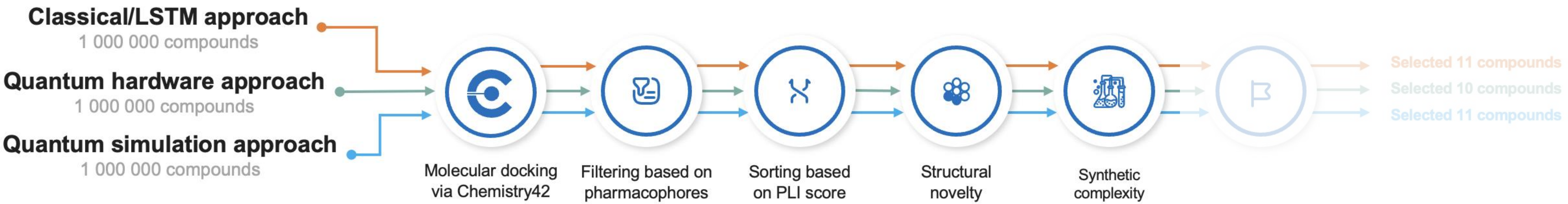

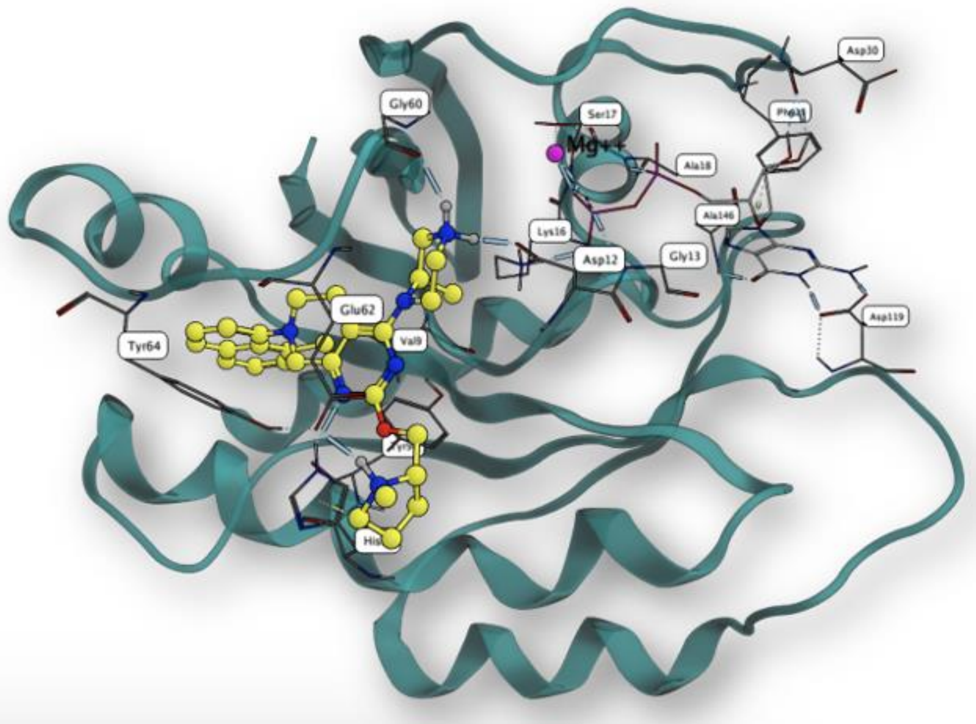

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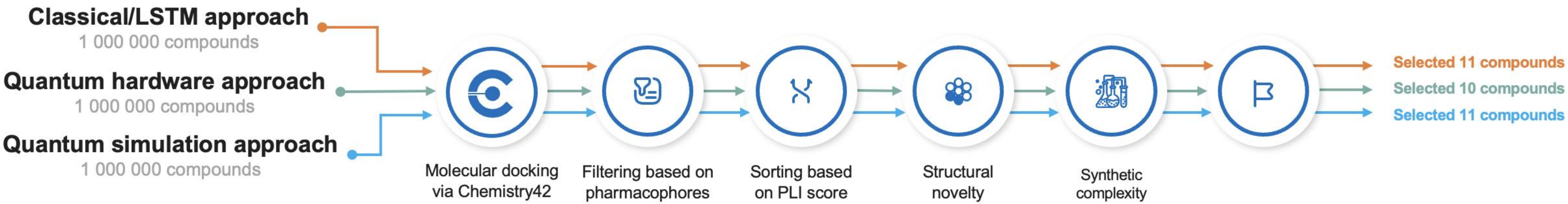

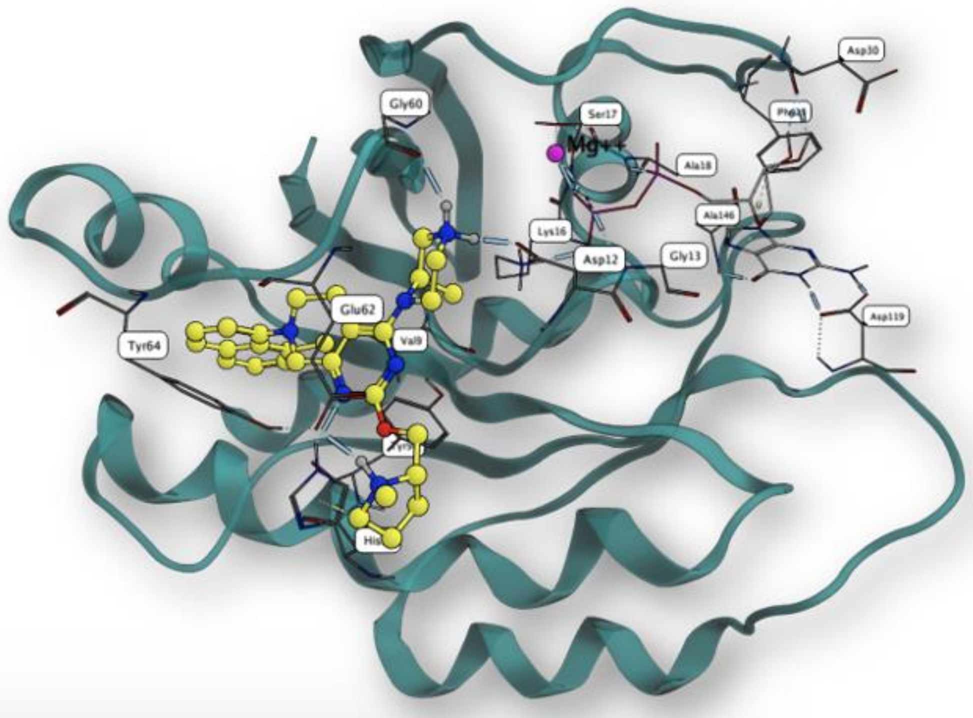

KRAS G12D – Experimental Validation (SPR)

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Approach

- Selected compounds are synthesized via CROs.
- Synthesized compounds are tested for binding to KRAS G12D via SPR (Surface Plasmon Resonance).
- Compounds that are active in the first test were retested a second time to ensure confidence in the results.

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Experimental Setup

- Biacore 8K system, Sensor Chip SA.
- 1x HBS-EP+, 2mM TCEP, 2% DMSO as running buffer, protein concentration was 5µg/mL, injected for 60s at a flow rate of 30µL/min and dissociation time was 180s.
- The stability of the experimental system was tested using BI-2852 and MRTX-1133.
- Calculation of K_d values.

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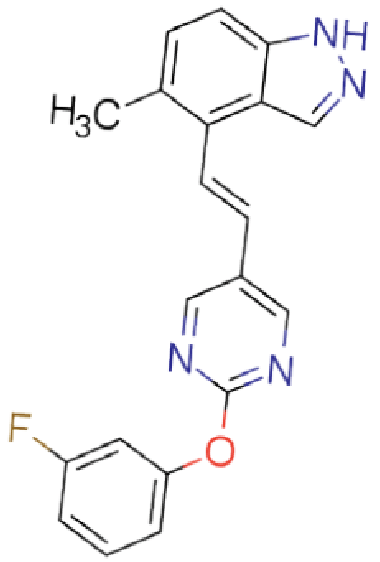
Results

- We have synthesized/tested 15 compounds with SPR: 8 from the quantum hardware batch, 4 from the quantum simulation batch, and 3 from the LSTM (classical) batch.
- 3 compounds from the quantum hardware batch are binding, 2 compounds from the quantum simulation batch, and 1 compound from the LSTM (classical) batch.
- The strongest compounds are from the quantum batches: Best K_d value is 1.4 µM for the quantum hardware batch, and 39 µM from the classical LSTM batch.
- The compounds are diverse between the classical and quantum batches.
- The initial binders can serve as starting compounds for further optimization

a



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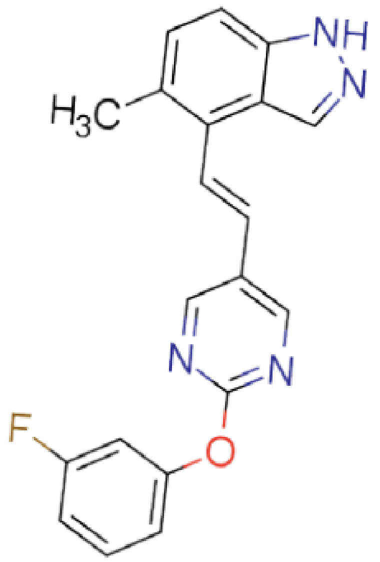
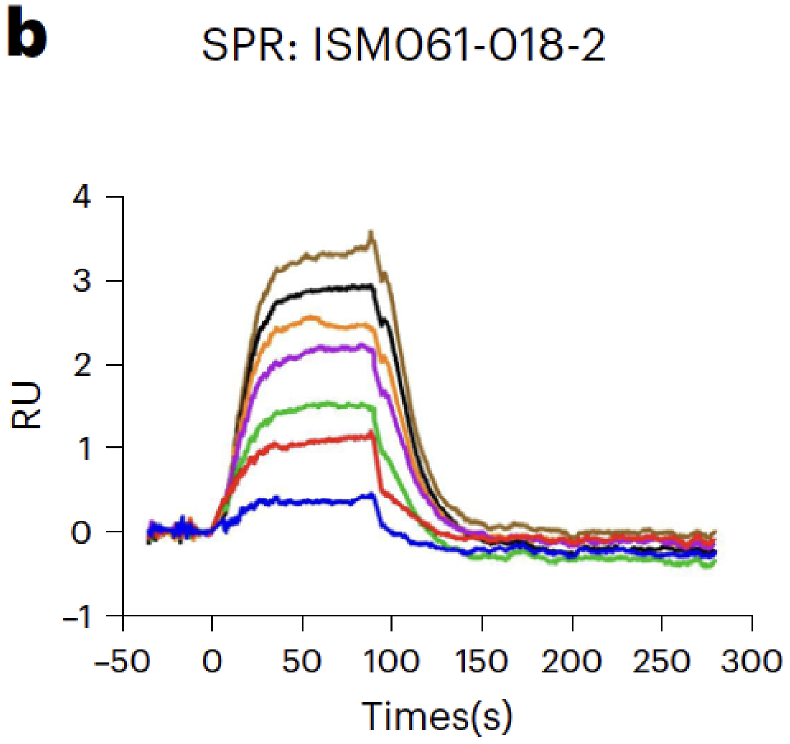
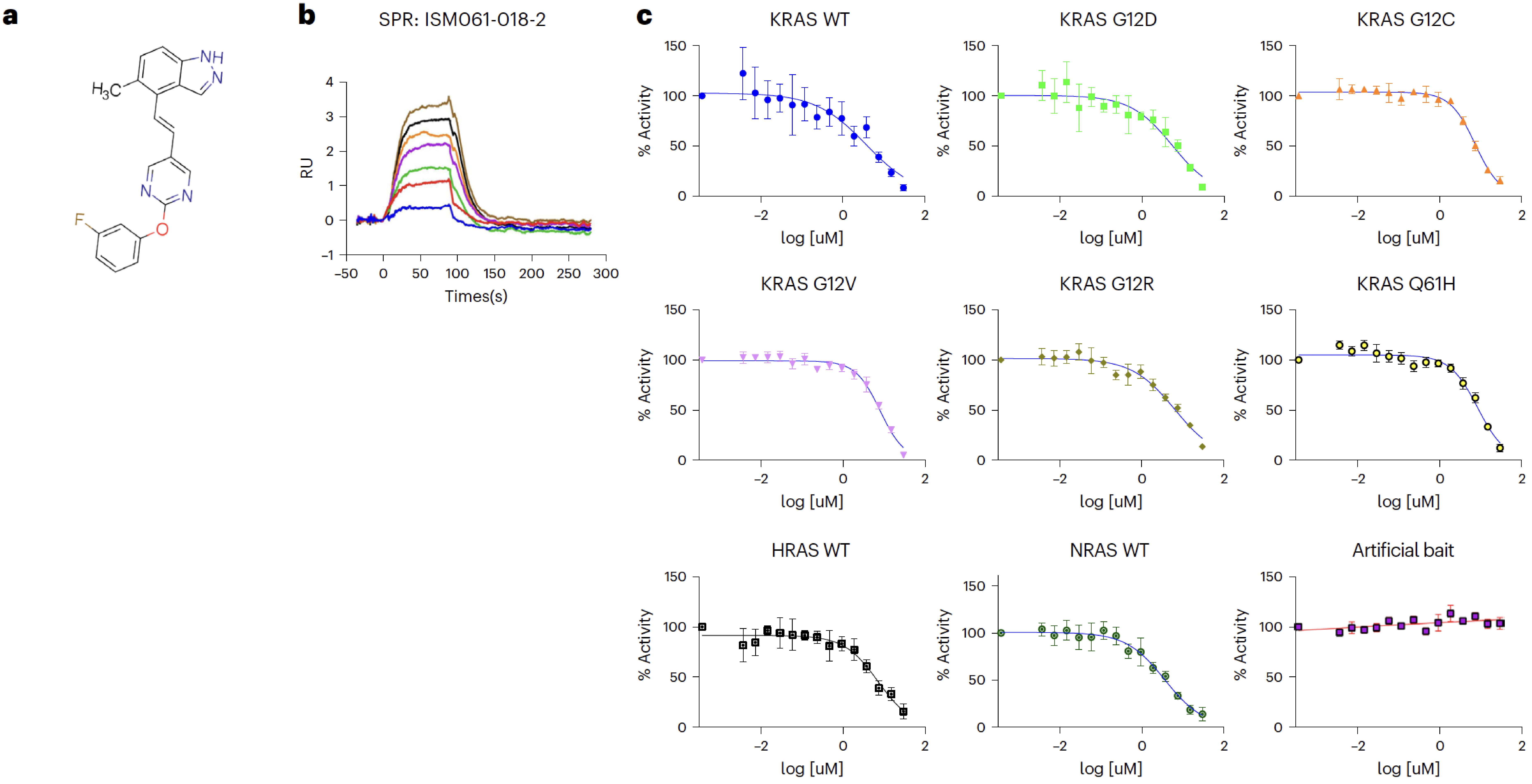
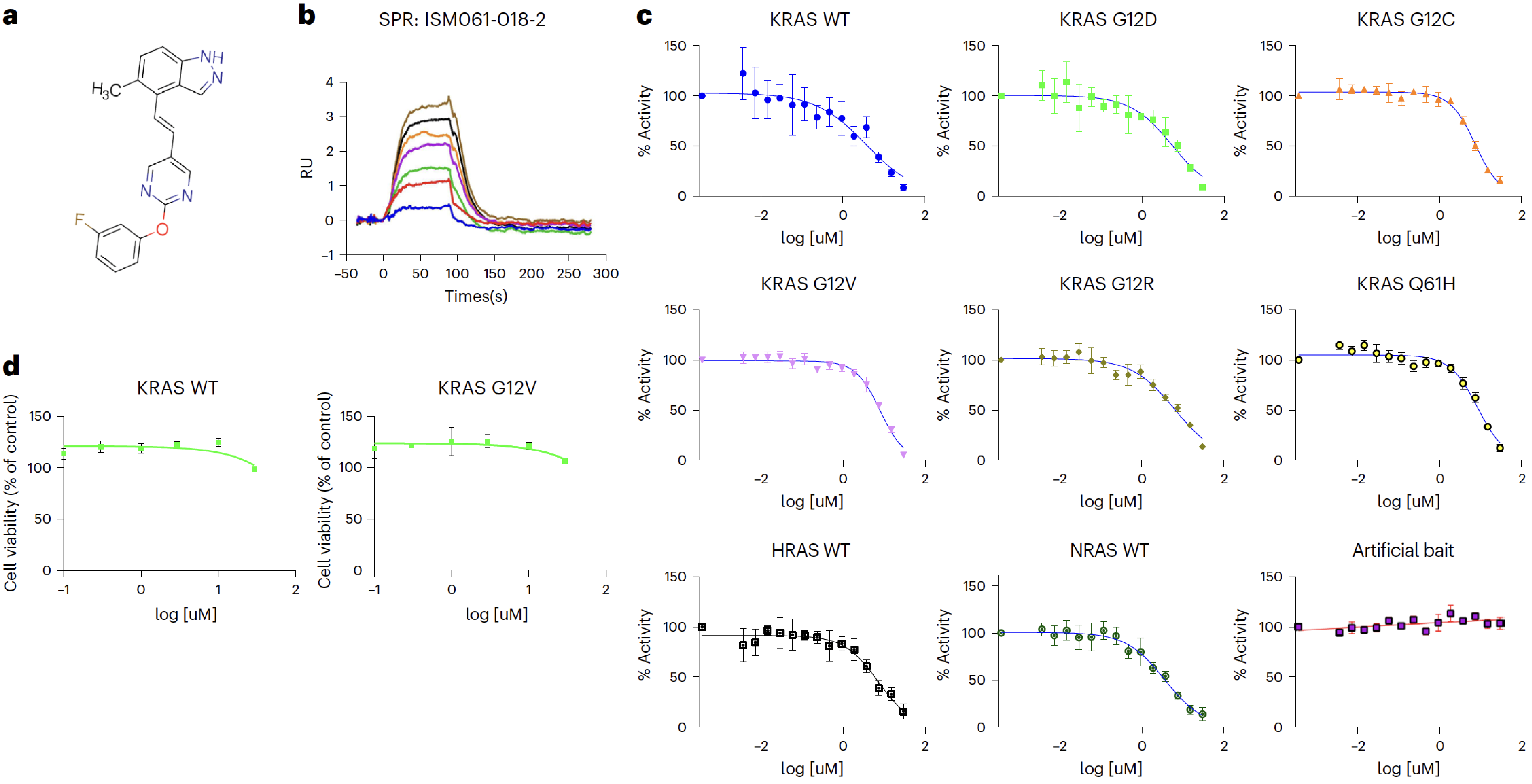

NH
N
H3C
N
N
F
O

b


SPR: ISM061-018-2
RU
4
3
2
1
0
-1
-50
0
50
100
150
200
250
300
Times(s)

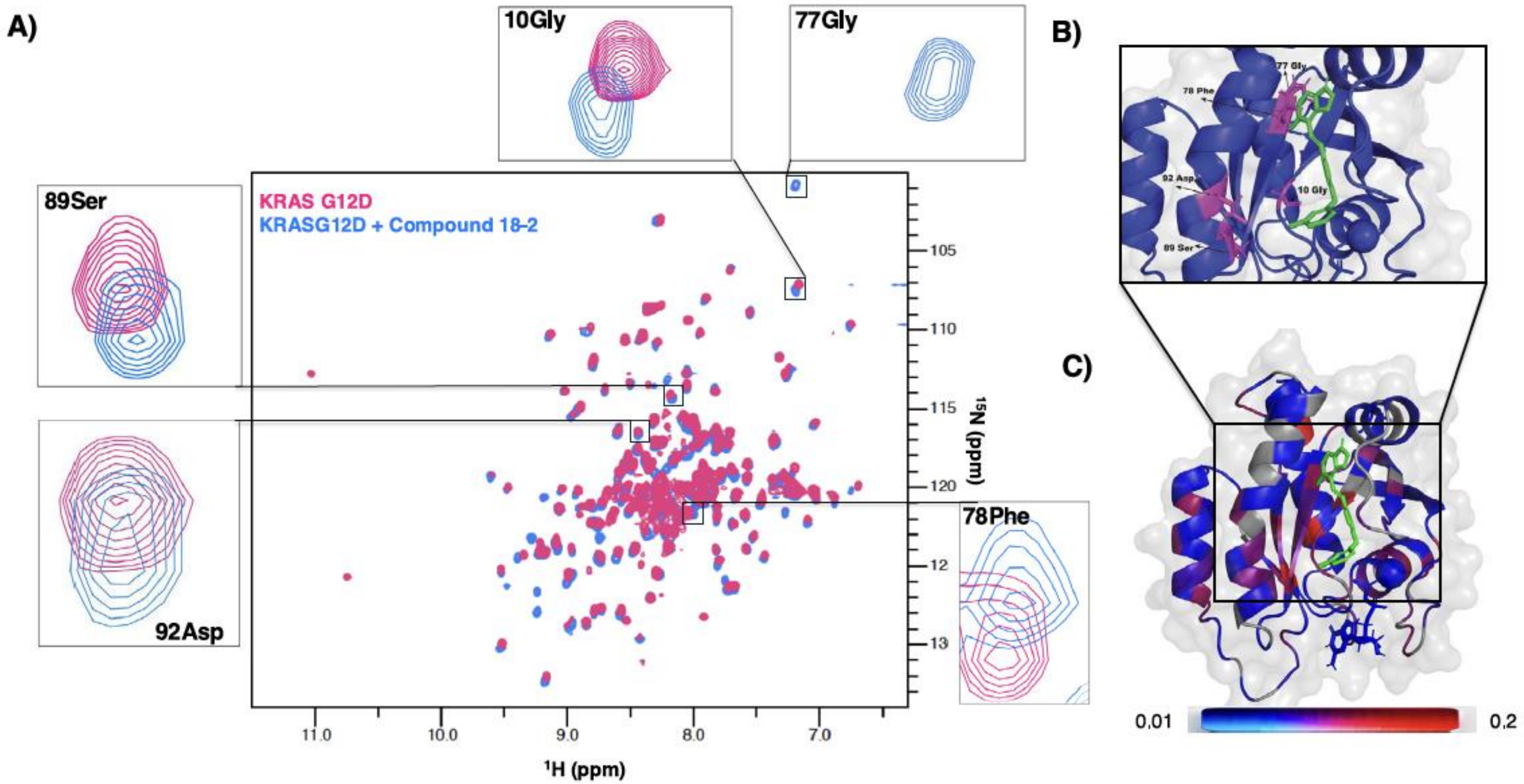


a
H3C
NH
N
N
N
O
F
b
SPR: ISM061-018-2
RU
4
3
2
1
0
−1
−50
0
50
100
150
200
250
300
Times(s)
c
KRAS WT
KRAS G12D
KRAS G12C
KRAS G12V
KRAS G12R
KRAS Q61H
HRAS WT
NRAS WT
Artificial bait
% Activity
150
100
50
0
−2
0
2
log [uM]

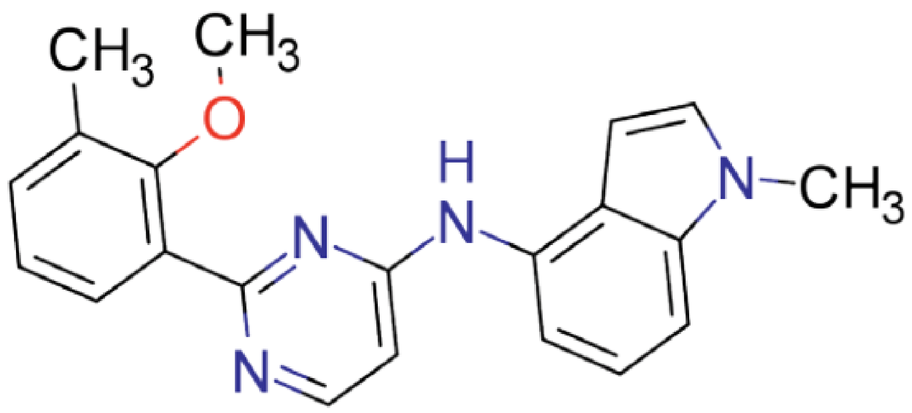


a
H_3C
NH
N
N
N
O
F
b
SPR: ISM061-018-2
RU
Times(s)
c
KRAS WT
KRAS G12D
KRAS G12C
KRAS G12V
KRAS G12R
KRAS Q61H
HRAS WT
NRAS WT
Artificial bait
% Activity
log [uM]
d
KRAS WT
KRAS G12V
Cell viability (% of control)
log [uM]

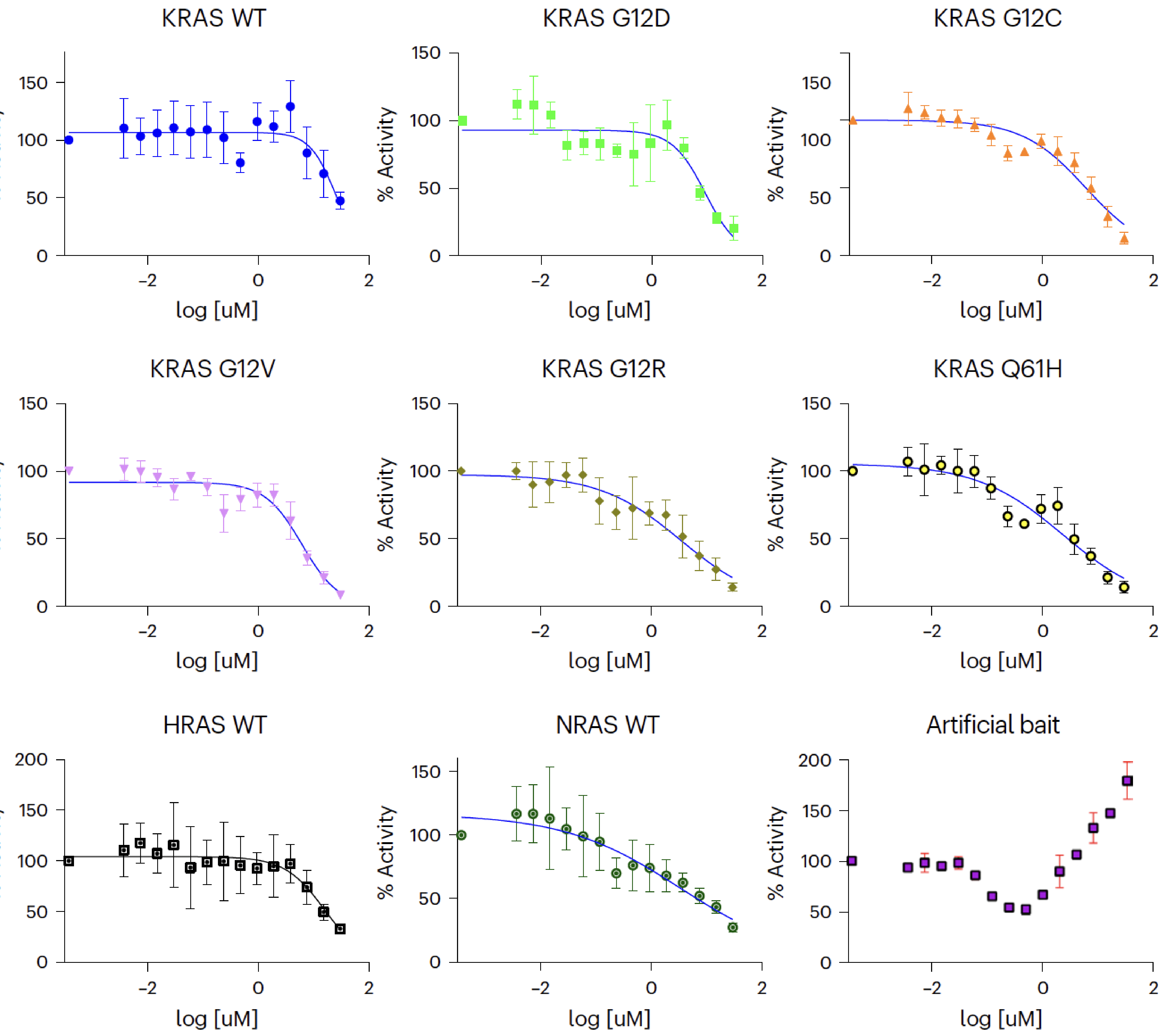
Protein-Detected NMR Experiments (TROSY-HSQC)



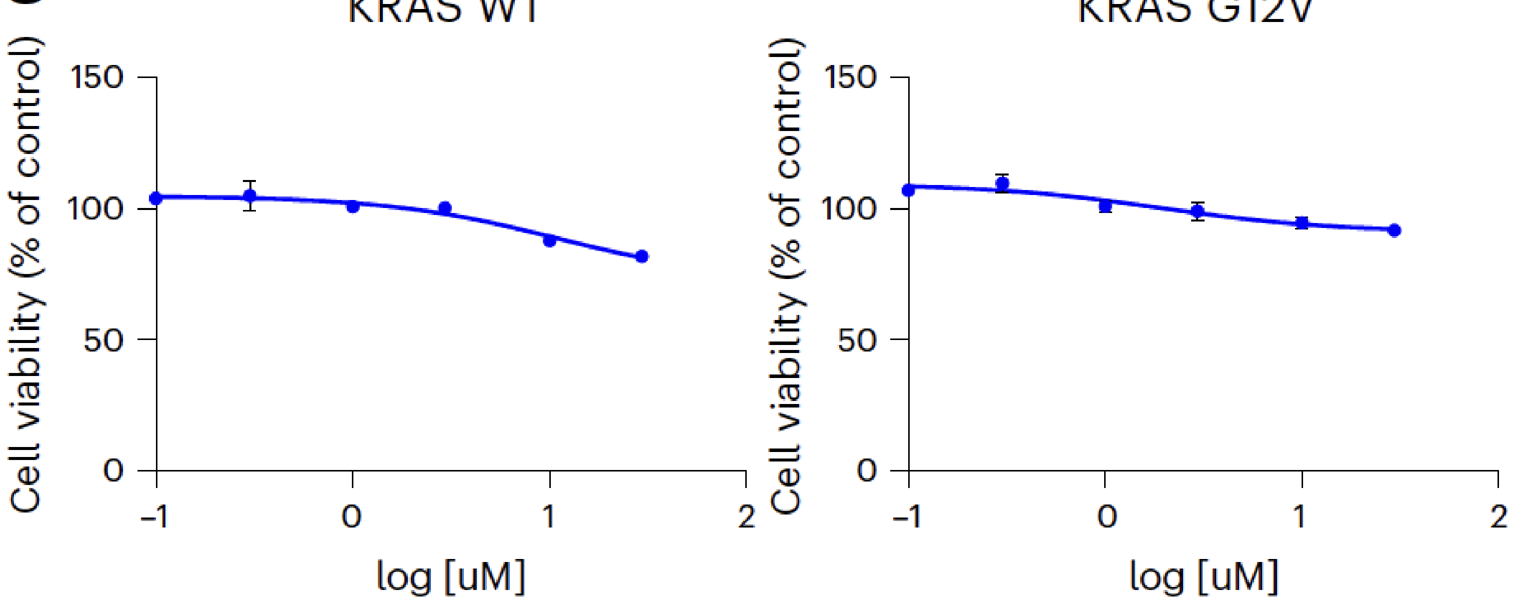
e


CH3
CH3
O
H
N
N
N
N
N
CH3

f


KRAS WT
KRAS G12D
KRAS G12C
KRAS G12V
KRAS G12R
KRAS Q61H
HRAS WT
NRAS WT
Artificial bait
% Activity
log [uM]

g


KRAS WT
KRAS G12V
Cell viability (% of control)
log [uM]

nature biotechnology

Brief Communication

https://doi.org/10.1038/s41587-024-02526-3

Quantum-computing-enhanced algorithm unveils potential KRAS inhibitors

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Check for updates

Mohammad Ghazi Vakili[1,2], Christoph Gorgulla[3,4], Jamie Snider[5], AkshatKumar Nigam[6], Dmitry Bezrukov[7], Daniel Varoli[8], Alex Aliper[7], Daniil Polykovsky[9], Krishna M. Padmanabha Das[10,11], Huel Cox III[11], Anna Lyakisheva[5], Ardalan Hosseini Mansob[5,12], Zhong Yao[5], Lela Bitar[5,13], Danielle Tahoulas[5,14], Dora Čerina[14,15], Eugene Radchenko[7], Xiao Ding[7], Jinxin Liu[7], Fanye Meng[7], Feng Ren[7], Yudong Cao[16], Igor Stagljar[5,12,14,17], Alán Aspuru-Guzik[1,2,18,19,20,21] & Alex Zhavoronkov[7]

We introduce a quantum–classical generative model for small-molecule design, specifically targeting KRAS inhibitors for cancer therapy. We apply the method to design, select and synthesize 15 proposed molecules that could notably engage with KRAS for cancer therapy, with two holding promise for future development as inhibitors. This work showcases the potential of quantum computing to generate experimentally validated hits that compare favorably against classical models.

Summary

- We used a hybrid quantum/classical algorithm deploying a QCBM to generate new ligands for KRAS
- The benchmarks indicated that the quantum algorithm outperformed a similar classical model
- Quantum algorithms and computers can already be deployed in a useful way in real world drug discovery applications

Acknowledgments

- **Mohammad Ghazi Vakili**
- Jamie Snider
- **AkshatKumar Nigam**
- **Dmitry Bezrukov**
- Daniel Varoli
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Thank You!

Questions?