

# e-Seminar #16

## PlayMolecule for Drug Discovery



Presenter:  
**Roberto Fino**  
(Acellera Labs SL)

**25 May 2021**

**Welcome!**



Moderator:  
**Tim Weaving**  
(University College London,  
UCL)



# e-Seminar #16

## PlayMolecule for Drug Discovery

**25 May 2021**

The e-Seminar will start  
at 1pm CEST / 12pm BST



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**Roberto Fino**  
(Acellera Labs SL)



Moderator:  
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UCL)



# PlayMolecule for Drug Discovery

Acellera, IT empowered drug discovery

**Roberto Fino**

Computational Medicinal Chemist

[r.fino@acellera.com](mailto:r.fino@acellera.com)





**FOUNDED IN 2006**

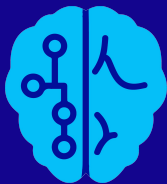
London, Barcelona



**SME**



**CUSTOMERS WORLDWIDE**



**CUTTING EDGE TECHNOLOGY**

GPU, Cloud, AI



**TOWARDS COMPUTERIZED DRUG  
DISCOVERY**

Unique innovative technology using  
ML/DL and MD



**COLLABORATIONS WITH  
PHARMACEUTICAL COMPANIES  
AND ACADEMIA**

# INNOVATION AT THE HEART OF ACELLERA'S BUSINESS



- 2021** PlayMolecule private instance
- 2020** OPENMM collaboration Chan - Zuckerberg Initiative support
- 2018** Launch of PlayMolecule - Machine Learning for Drug Design
- 2018** Cryptic pocket in aminergic GPCRs
- 2016** HTMD lowers the barrier to build, run and analyze MD
- 2015** AceCloud - MD on AWS Cloud
- 2014** Adaptive sampling reduces computational cost
- 2013** Metrocubo workstation- equipped with 4 GPUs
- 2011** Fitness of MD for drug discovery: benzamidine-trypsin
- 2009** ACEMD simulation software released - MD on GPU
- 2006** Foundation of Acellera

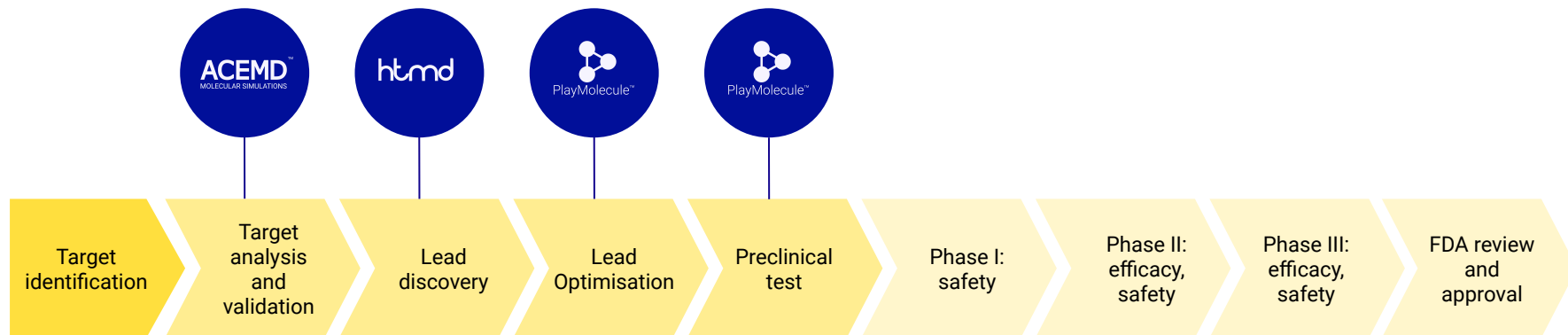
## OUR TECHNICAL EXPERTISE

Molecular dynamics simulation  
Software development  
Machine learning

## OUR SCIENTIFIC EXPERTISE

Computational chemistry  
Medicinal Chemistry  
Drug Discovery

# OUR EXPERTISE AND GOALS



ref: TUFTS/Nature review

12-15 years  
\$ 2588 million

DRUG DISCOVERY & DEVELOPMENT PIPELINE



- Lead optimization ([pub](#))



- Target deconvolution via machine learning - Repurposing ([pub](#))



- Conformation discovery ([pub](#))



- In-silico binding assay for pose prediction via simulations ([pub](#))
- Lead optimization via machine learning ([pub](#))



- Generative models ([pub](#))
- Lead optimization ([pub](#))



# PlayMolecule™

An integrated platform for drug discovery based on state-of-the-art machine learning and molecular simulations.



## SCIENTIFIC COMMUNITY VALIDATION

**>80.000 JOBS RUN**

Main CompChem tool for 1000s of users, 18 applications available from target validation to affinity prediction

## VALIDATED BY SEVERAL TOP PHARMA

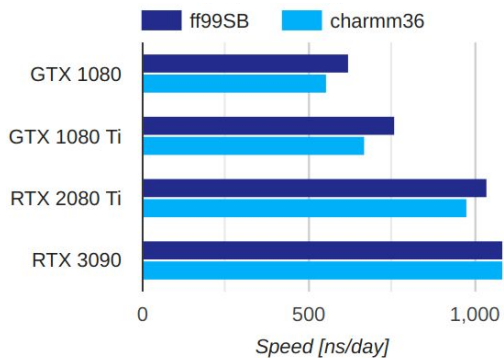
Winner at D3R, logP challenge  
Scientific articles published with  
Novartis, Pfizer, Biogen, JnJ, UCB...

## ADDED VALUE

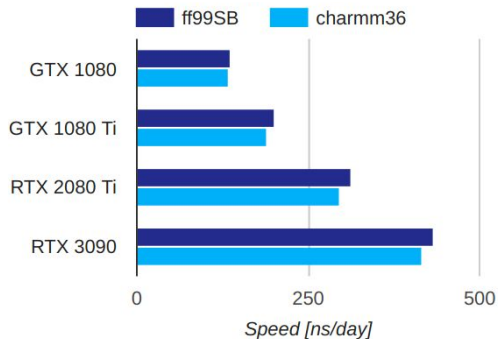
**REDUCES H2L and LO DELAY  
(BY AT LEAST FACTOR 2)**

Free energy prediction, 1.000x faster than  
FEP, robust structural analysis

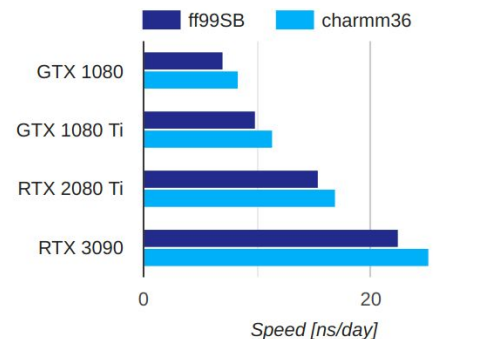
## DHFR (23,558 atoms)



## Factor IX (90,906 atoms)



## STMV (1,067.095 atoms)



# The apps

## MD simulations

- ProteinPrepare
- SystemBuilder
- MembraneBuilder
- Parameterize
- SimpleRun
- PlexView
- AdaptiveSampling

## HTVS

- SkeleDock
- BindScope
- KDeep
- DeltaDelta
- PathwayMap

## Chemical space exploration

### Ligand-Based:

- LigaNN
- LigDream

### Structure-Based:

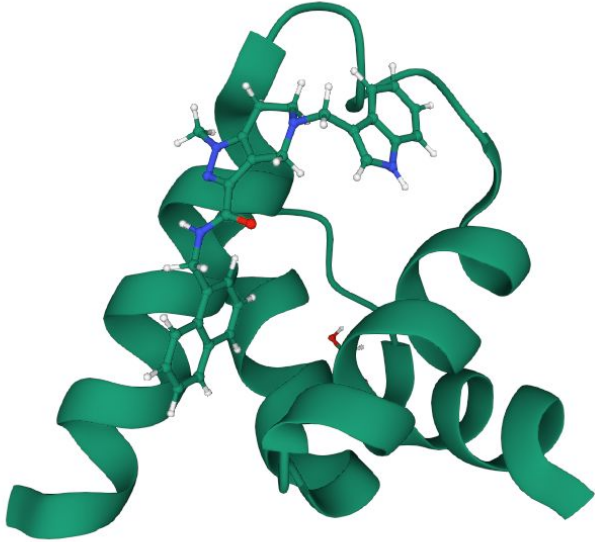
- DeepSite
- CrypticScout

# The systems

## Case studies: PEX14 and 5HT2B

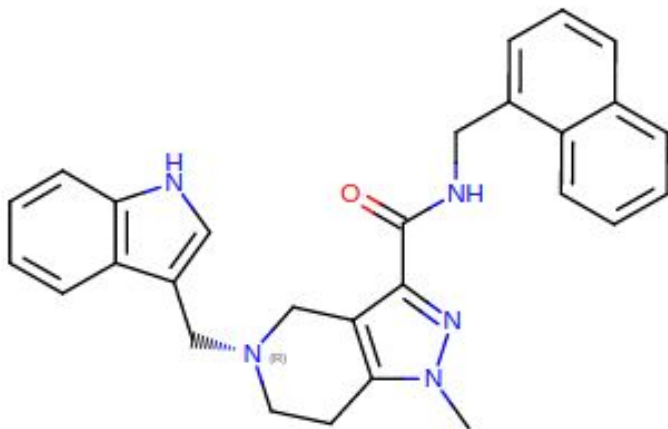
1

Globular protein: **PEX14** (PDB: 5L87)



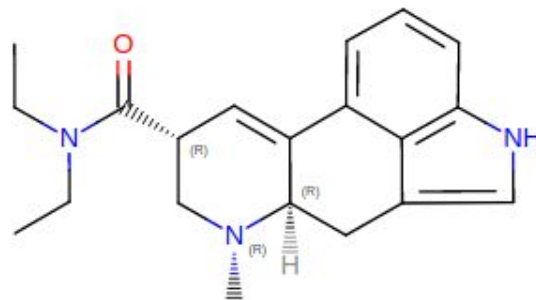
Membrane protein: **5-HT<sub>2B</sub>** (PDB: 5TVN)





## Pyrazolo[4,3-c]pyridines

*proof-of-concept of the druggability of  
PEX14 and first attempt to develop new  
Trypanocidal agents by Popowicz AG  
(HMGU/TUM)*



## LSD

*yes, THAT drug that gave us The Dark  
Side of the Moon and Sgt. Pepper's  
Lonely Hearts Club Band.  
First-ever X-ray structure of LSD bound to  
human 5HT<sub>2B</sub> serotonin receptor.*

# Ligands for training and testing



Compounds for training are taken from the SI of this article:

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## Structure–Activity Relationship in Pyrazolo[4,3-*c*]pyridines, First Inhibitors of PEX14–PEX5 Protein–Protein Interaction with Trypanocidal Activity

Maciej Dawidowski\*, Vishal C. Kalel, Valeria Napolitano, Roberto Fino, Kenji Schorpp, Leonidas Emmanouilidis, Dominik Lenhart, Michael Ostertag, Marcel Kaiser, Marta Kolonko, Bettina Tippler, Wolfgang Schliebs, Grzegorz Dubin, Pascal Mäser, Igor V. Tetko, Kamyar Hadian, Oliver Plettenburg, Ralf Erdmann, Michael Sattler\*, and Grzegorz M. Popowicz\*

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Products, Ligands, Indoles, Optimization, Aromatic compounds

Journal of Medicinal Chemistry

Testing compounds come from 2D similarity screening (Tanimoto > 0.8) against Enamine REAL database: <https://www.enaminestore.com/search>





# Landing on PlayMolecule



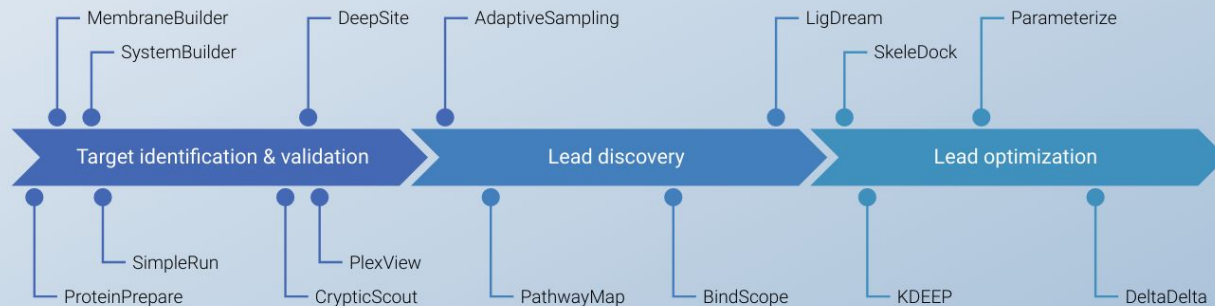
Updates: Check out the tutorials we publish on Medium <https://medium.com/playmolecule.com>

Log out | Hello [Acellera Learning](#)

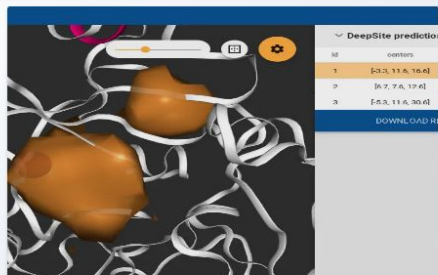
# PlayMolecule™

One-click molecular discovery

READ OUR BLOG



OPEN CHAT



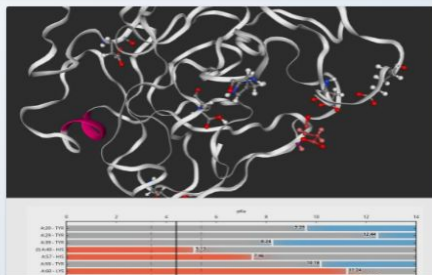
## DEEPSITE

Predict ligand binding pockets in your protein of interest by uploading a PDB file and running DeepSite, a neural network-based predictor

★★★★★ (53) 15329

[GET STARTED](#) [REQUEST COLLABORATION](#)

Tags: [neural networks](#), [binding pocket](#)



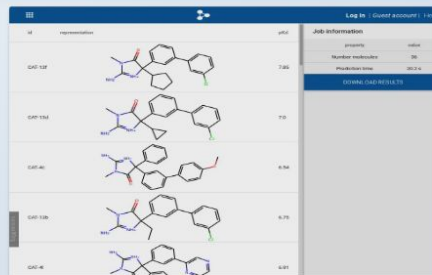
## PROTEINPREPARE

Make your protein ready for molecular dynamics simulations by titrating and protonating the protein at a desired pH and by optimizing the H-bond network

★★★★★ (88) 7101

[GET STARTED](#) [REQUEST COLLABORATION](#)

Tags: [molecular dynamics](#), [protonation](#)



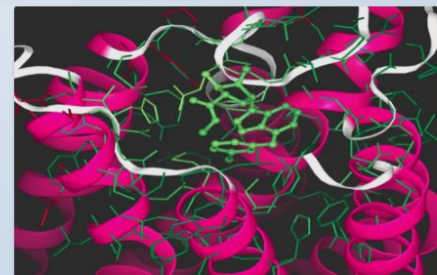
## KDEEP

Predict the binding affinity of a set of ligands docked in a protein using a state-of-the-art neural network-based predictor

★★★★★ (83) 6930

[GET STARTED](#) [REQUEST COLLABORATION](#)

Tags: [neural networks](#), [affinity](#)



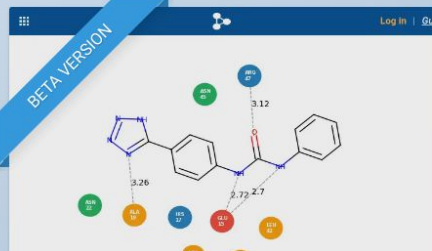
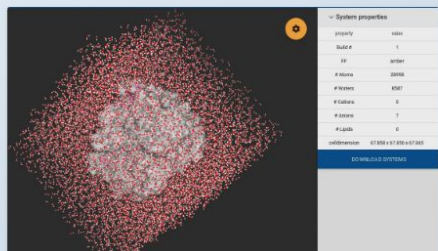
## BINDSCOPE

Perform virtual screening of a library of compounds against your protein of interest using a neural-network-based predictor of binding

★★★★★ (56) 2817

[GET STARTED](#) [REQUEST COLLABORATION](#)

Tags: [docking](#), [neural networks](#)




[OPEN CHAT](#)

# NEW: The DataCenter app



All your jobs, at a glance on the cloud.



ADAPTIVESAMPLING

BINDSCOPE

CRYPTICSOUT









**DATACENTER**

DEEPSITE

DELTADELTA

KDEEP

KDEEPTRAINER

|                                     |   |          |                        |
|-------------------------------------|---|----------|------------------------|
| DeltaDelta/models/158F8356          |   | 235.8KiB | 5/7/2021, 3:18:48 PM   |
| ProteinPrepare/output/9914B73D      |   | 115.9KiB | 5/7/2021, 12:57:16 PM  |
| PDB: 5TVN Chain: A pH: 7.4          |   |          |                        |
| ProteinPrepare/output/0627A43B      |   | 20.8KiB  | 5/7/2021, 12:56:14 PM  |
| PDB: 5L87 Chain: A pH: 7.4          |   |          |                        |
| /webinar/MD_apps                    |   |          |                        |
| 5L87_ligand_parameterize            |   | 1.8KiB   | 5/7/2021, 9:56:05 AM   |
| systembuilder/examples              |   |          |                        |
| Example files for systembuilder app |   | 215.8KiB | 3/29/2021, 11:32:32 AM |
| parameterize/examples               |   |          |                        |
| Example files for parameterize app  |   | 965.0B   | 3/29/2021, 11:32:31 AM |
| pathwaymap/examples                 |   |          |                        |
| Example files for pathwaymap app    |   | 701.0B   | 3/29/2021, 11:32:31 AM |
| plexview/examples                   |   |          |                        |
| Example files for plexview app      |   | 20.0KiB  | 3/29/2021, 11:32:31 AM |

Input

File to upload \*

Choose File

Remote Path

Comments

Tags (separated by ,)

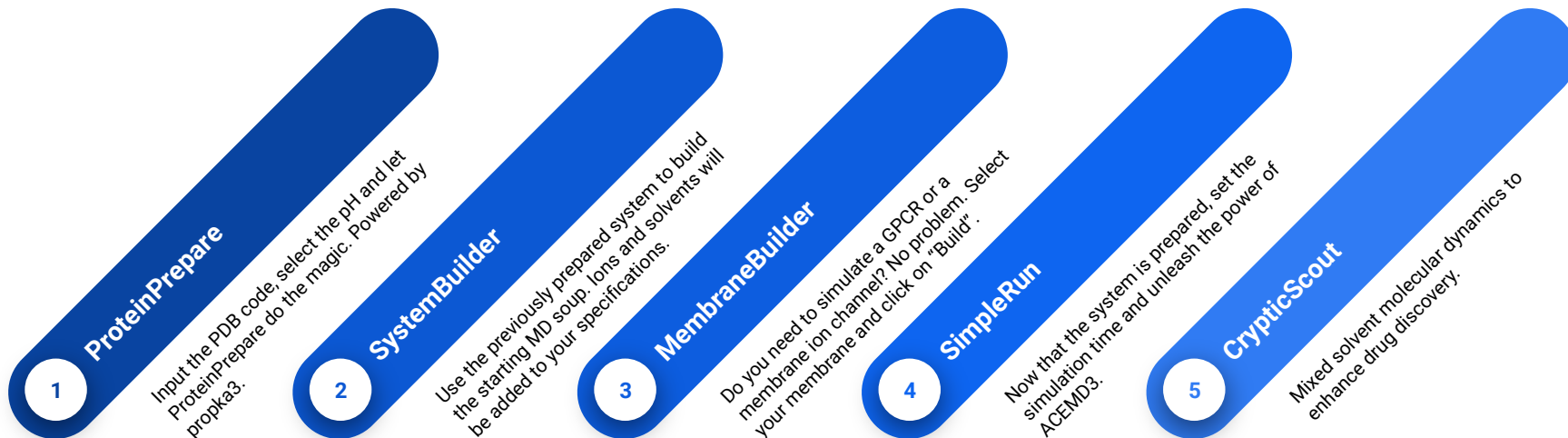
SUBMIT

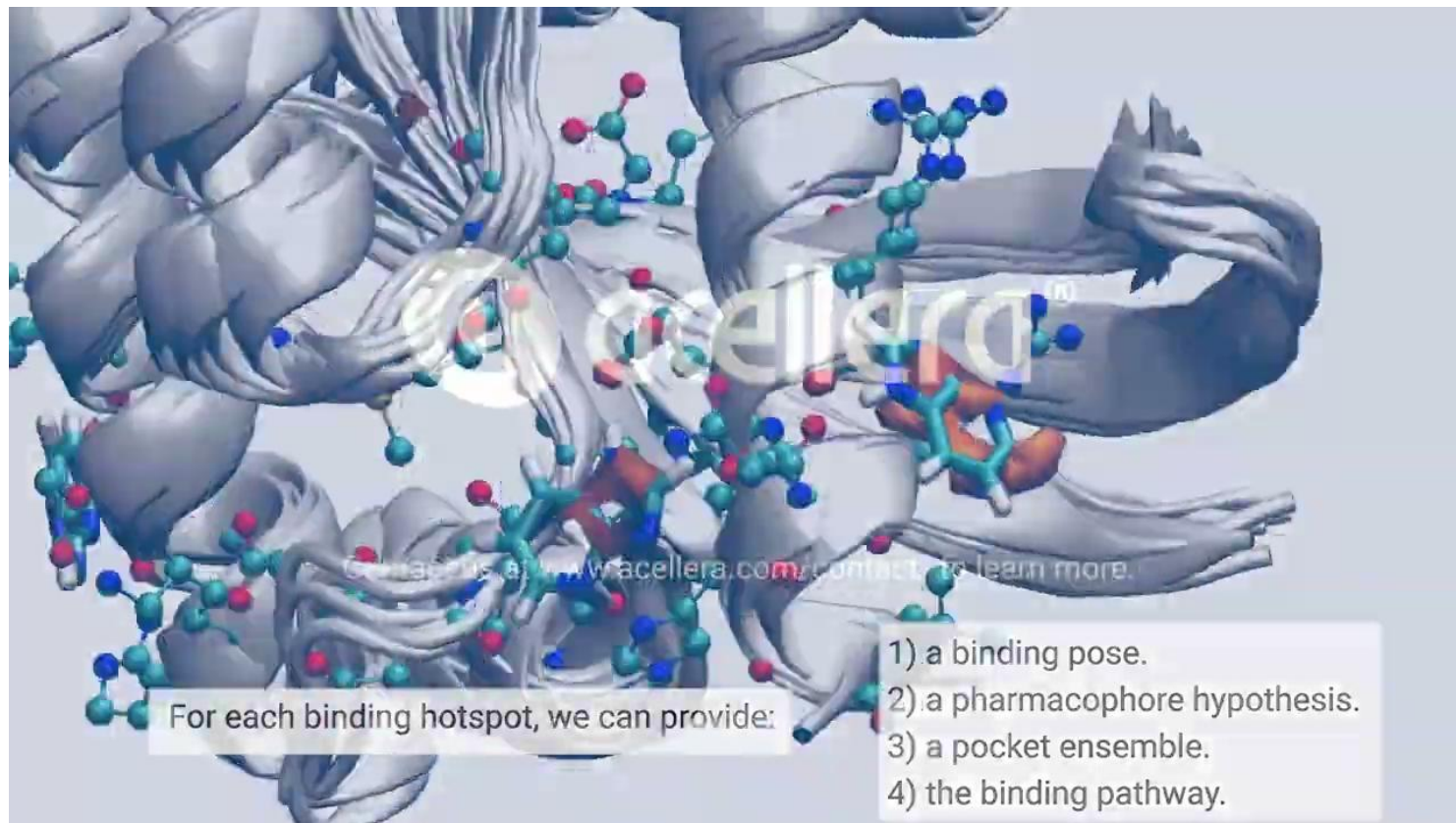
OPEN CHAT

Queue status: running  | Log out | Hello *Acellera\_Learning* 

Open a ticket

## 1. From PDB to fully-simulated systems





## 2. Screen a target against a library of selected molecules

1

### SkeleDock

A congeneric MCS scaffold alignment-based docking. Very useful when it comes to analyze the binding modes of congeneric compounds.

2

### BindScope

Are your molecules going to bind to your receptor? Discover it at a glance with BindScope.

3

### KDeep

Rescore docking poses and predict their affinity to their target using the machine-learning power of KDeep.

4

### DeltaDelta

DeltaDelta's applicability domain is the prediction of delta delta free energies in congeneric series, a critical issue during the lead optimization phase of drug discovery.

5

### PathwayMap

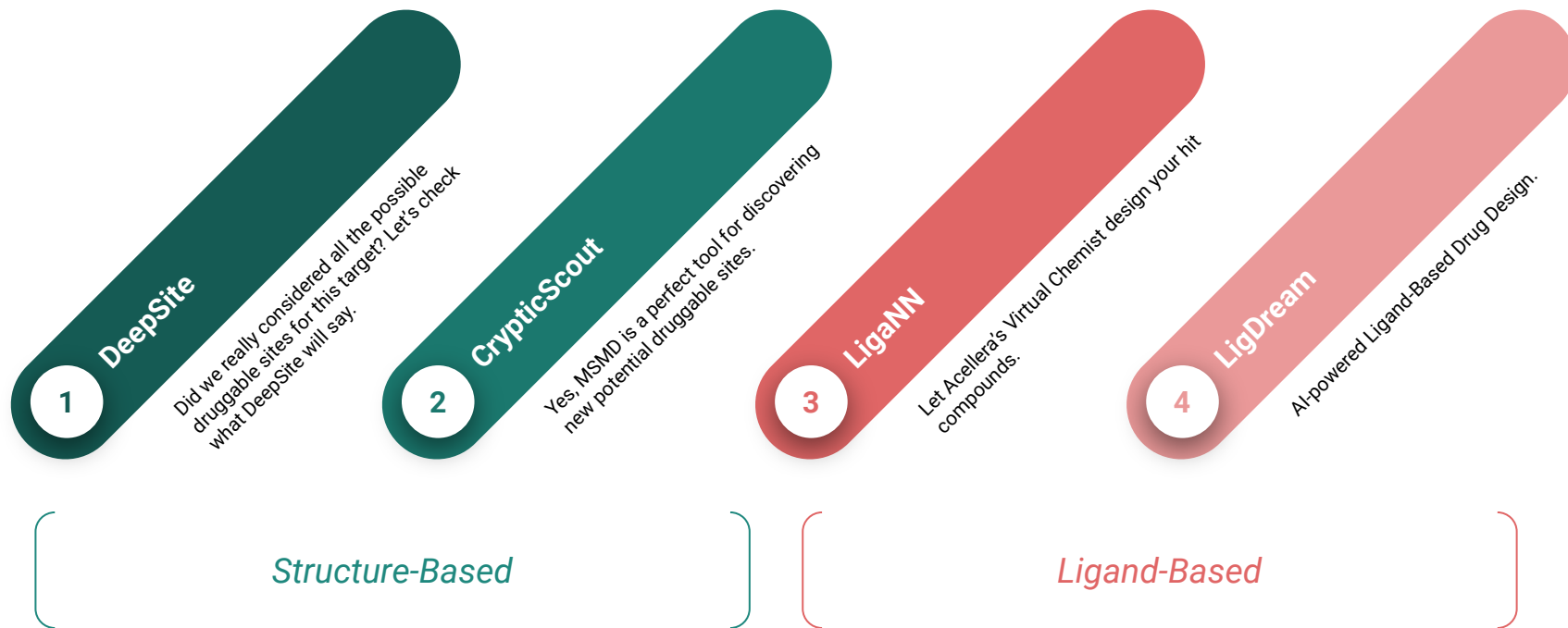
Nice lead compounds, let's check their metabolic stabilities and for potential off-target effects.



# This is Major Tom to Ground Control: exploring the chemical space



## 3. Explore new possibilities using AI-based methods





Ok, now let's see how it works...

# Q&A

To pose a question, you can write your question  
in the “Questions” tab



**Thank you for participating!**

**...don't forget to fill in our feedback questionnaire...**

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