e-Seminar #16
PlayMolecule for Drug Discovery

25 May 2021

Welcome!

Presenter:
Roberto Fino
(Acellera Labs SL)

Moderator:
Tim Weaving
(University College London, UCL)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 675451

The e-Seminar series is run in collaboration with:
VPH Institute
Building the Virtual Physiological Human

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PlayMolecule for Drug Discovery

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

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PlayMolecule for Drug Discovery

Acellera, IT empowered drug discovery

Roberto Fino
Computational Medicinal Chemist
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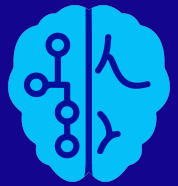
acellera®

ACELLERA

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

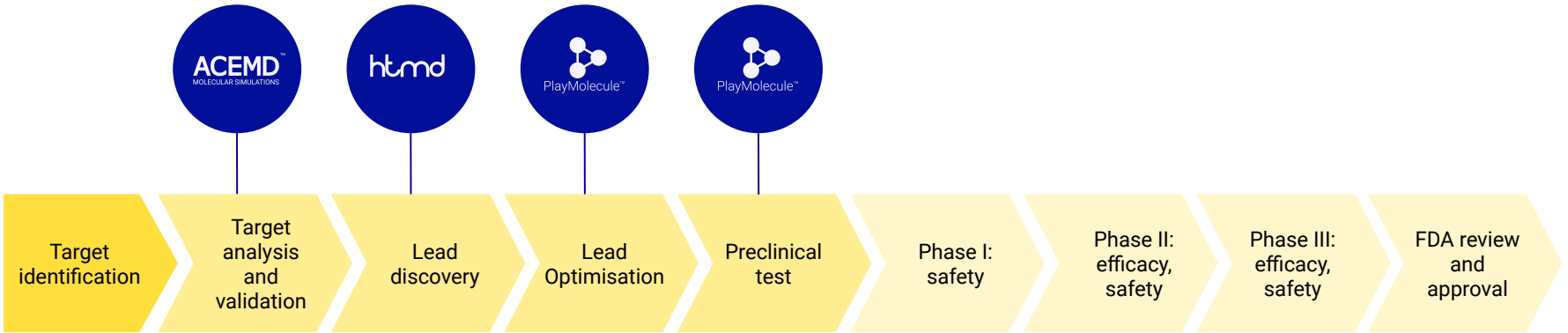
OUR TECHNICAL EXPERTISE

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

NON-CONFIDENTIAL INDUSTRIAL COLLABORATIONS

janssen

- Lead optimization (pub)

NOVARTIS

- Target deconvolution via machine learning - Repurposing (pub)

ucb

- Conformation discovery (pub)

Pfizer

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

Biogen

- Generative models (pub)
- Lead optimization (pub)

PlayMolecule™

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

PLAYMOLECULE HALLMARKS

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...

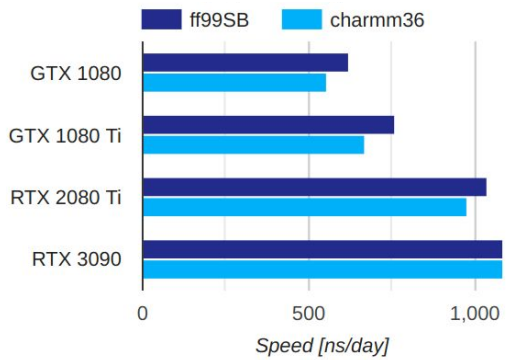
ADDED VALUE

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

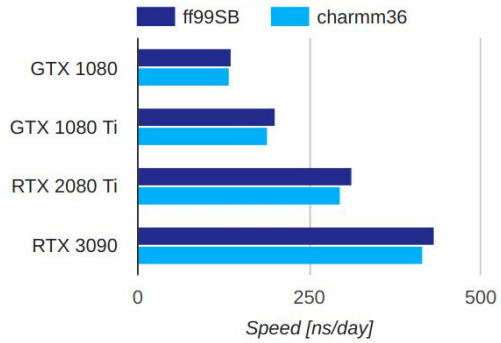
Free energy prediction, 1.000x faster than FEP, robust structural analysis

ACEMD PERFORMANCE

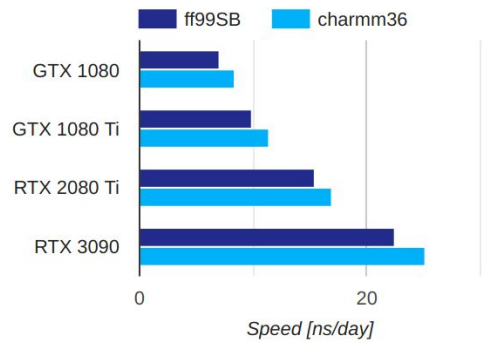
DHFR (23,558 atoms)



Factor IX (90,906 atoms)



STMV (1,067.095 atoms)



The apps

AVAILABLE 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:

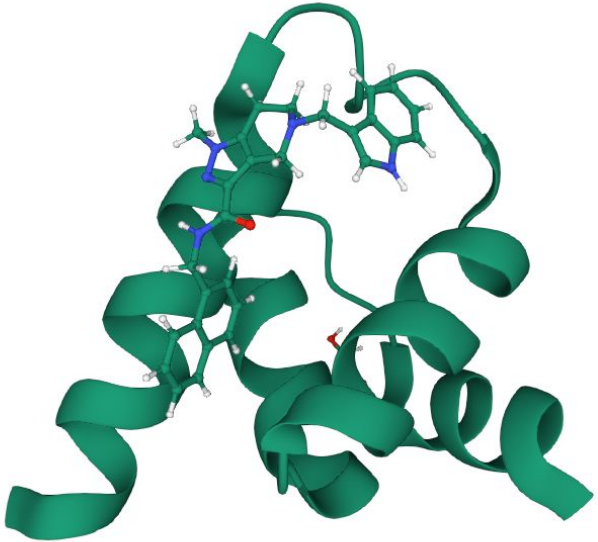
- DeepSite
- CrypticScout

ACEMD™ PLATFORM

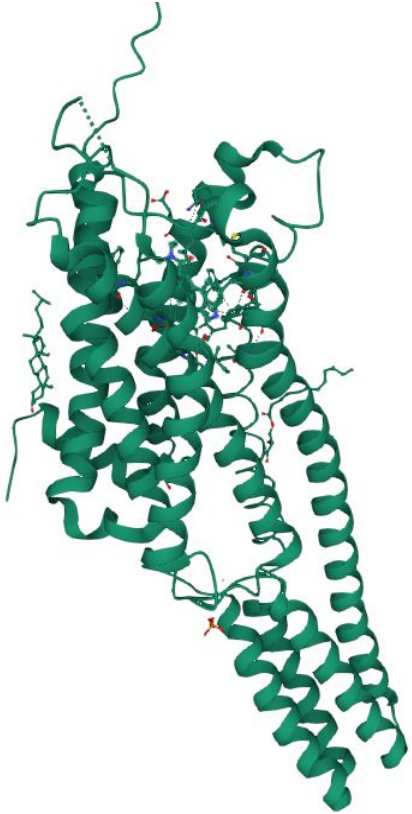
The systems

Case studies: PEX14 and 5HT2B

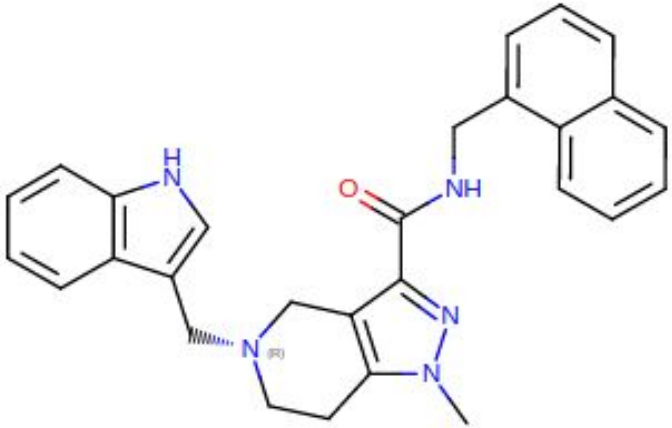
Globular protein: **PEX14** (PDB: 5L87)



Membrane protein: **5-HT$_{2B}$** (PDB: 5TVN)

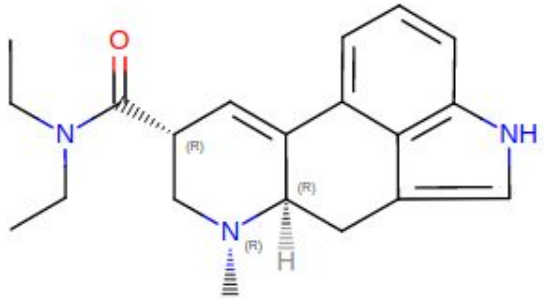


The ligands



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)

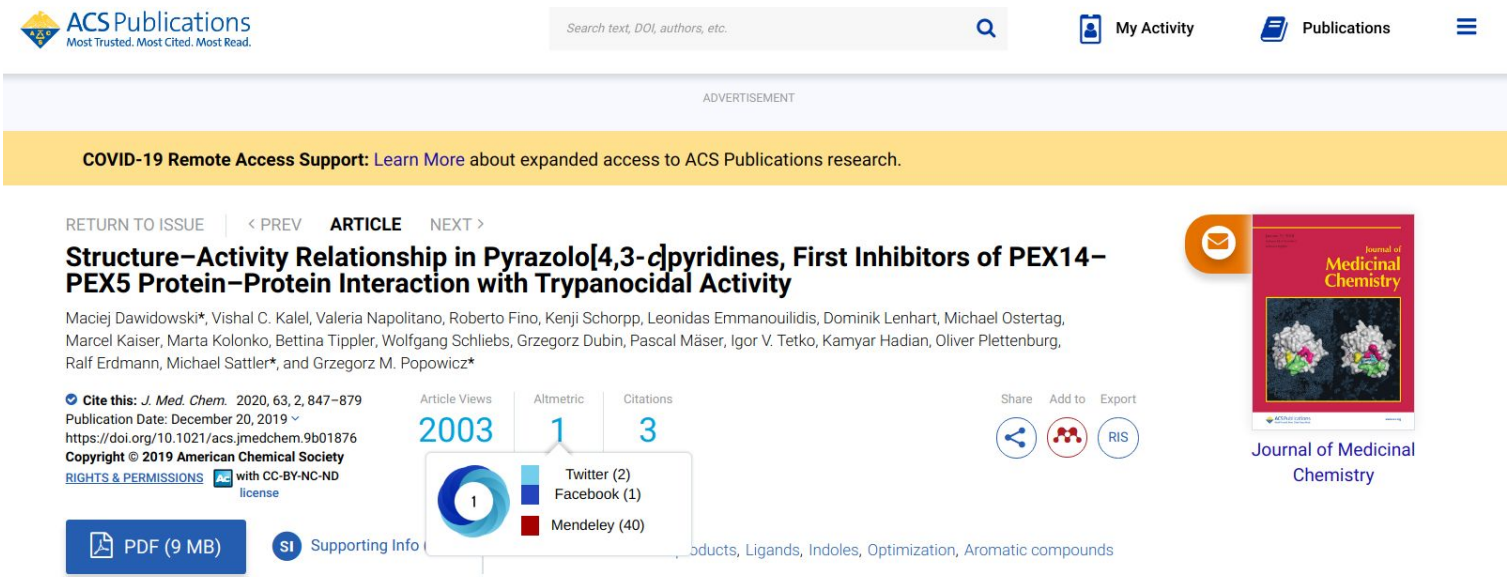


LSD

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 $5HT_{2B}$ serotonin receptor.

Ligands for training and testing

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

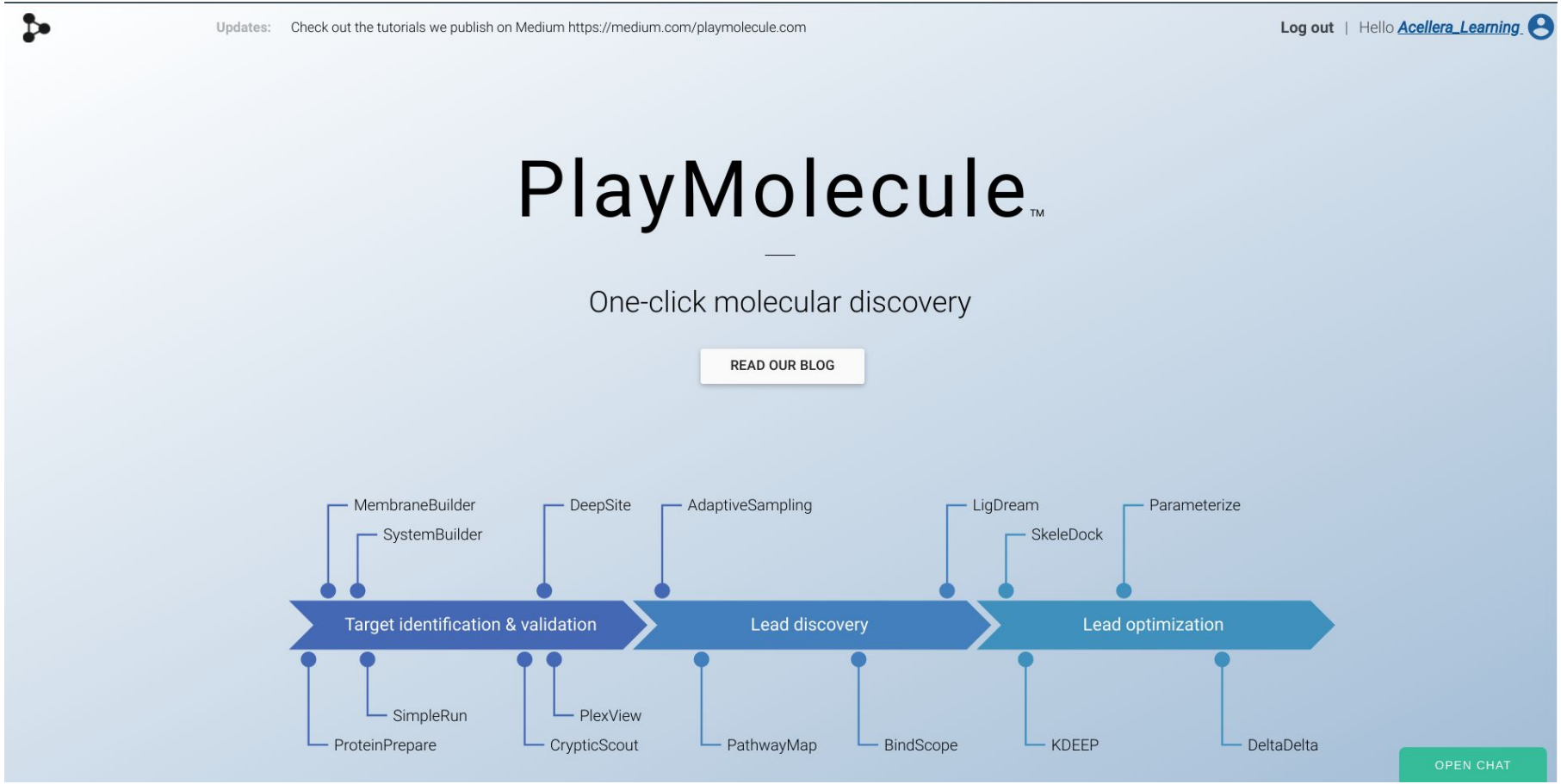


Testing compounds come from 2D similarity screening (Tanimoto > 0.8) against Enamine REAL database: https://www.enaminestore.com/search

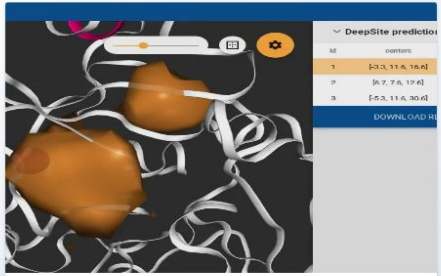
Enamine

Landing on PlayMolecule

The welcome screen



App menu



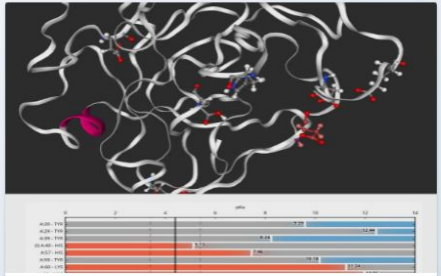
DEEPSITE

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

★★★★½ (53) 15329

GET STARTED REQUEST COLLABORATION

Tags: *neural networks* , *binding pocket*



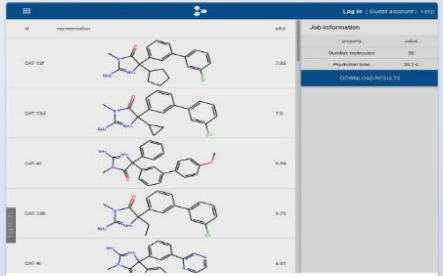
PROTEINPREPARE

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

★★★★½ (88) 7101

GET STARTED REQUEST COLLABORATION

Tags: *molecular dynamics* , *protonation*



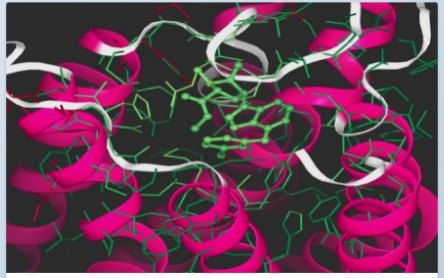
KDEEP

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*



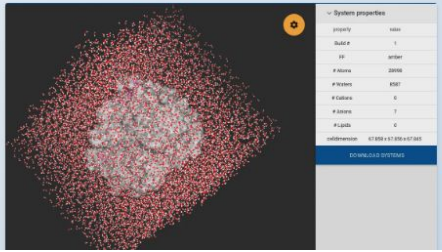
BINDSCOPE

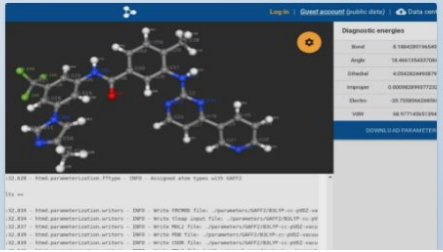
Perform virtual screening of a library of compounds against your protein of interest using a neural-network-based predictor of binding

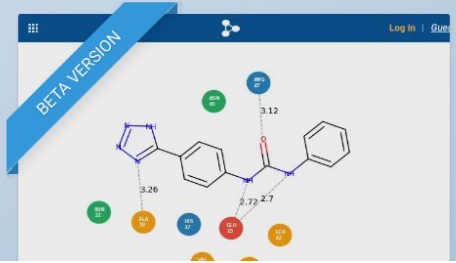
★★★★½ (56) 2817

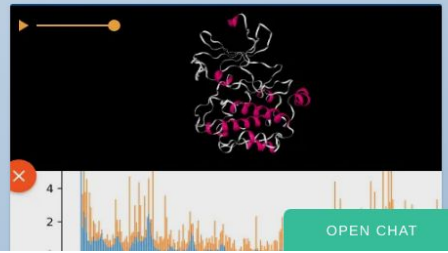
GET STARTED REQUEST COLLABORATION

Tags: *docking* , *neural networks*



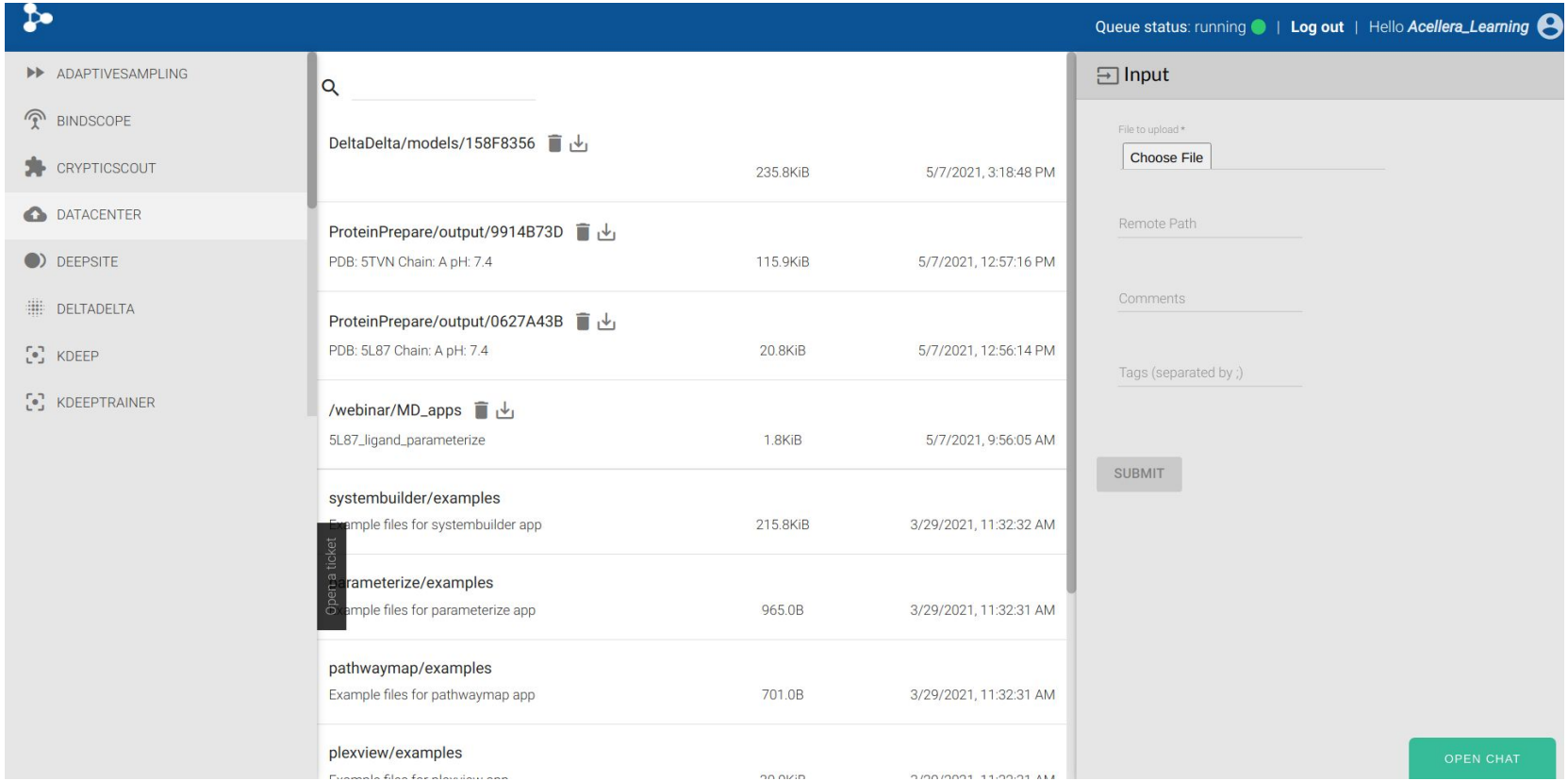






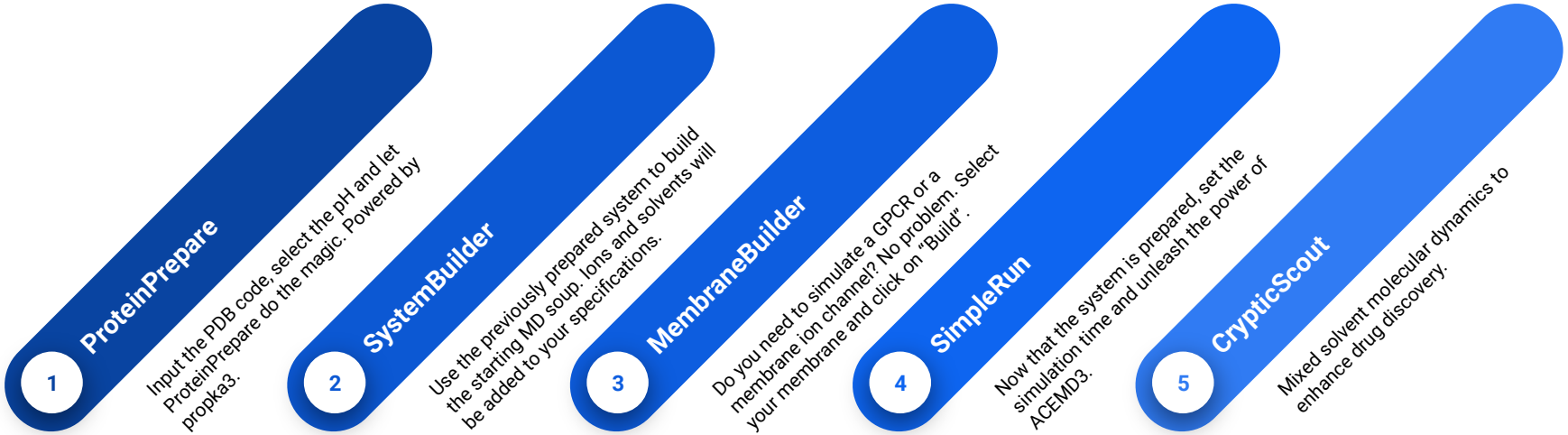
NEW: The DataCenter app

All your jobs, at a glance on the cloud.

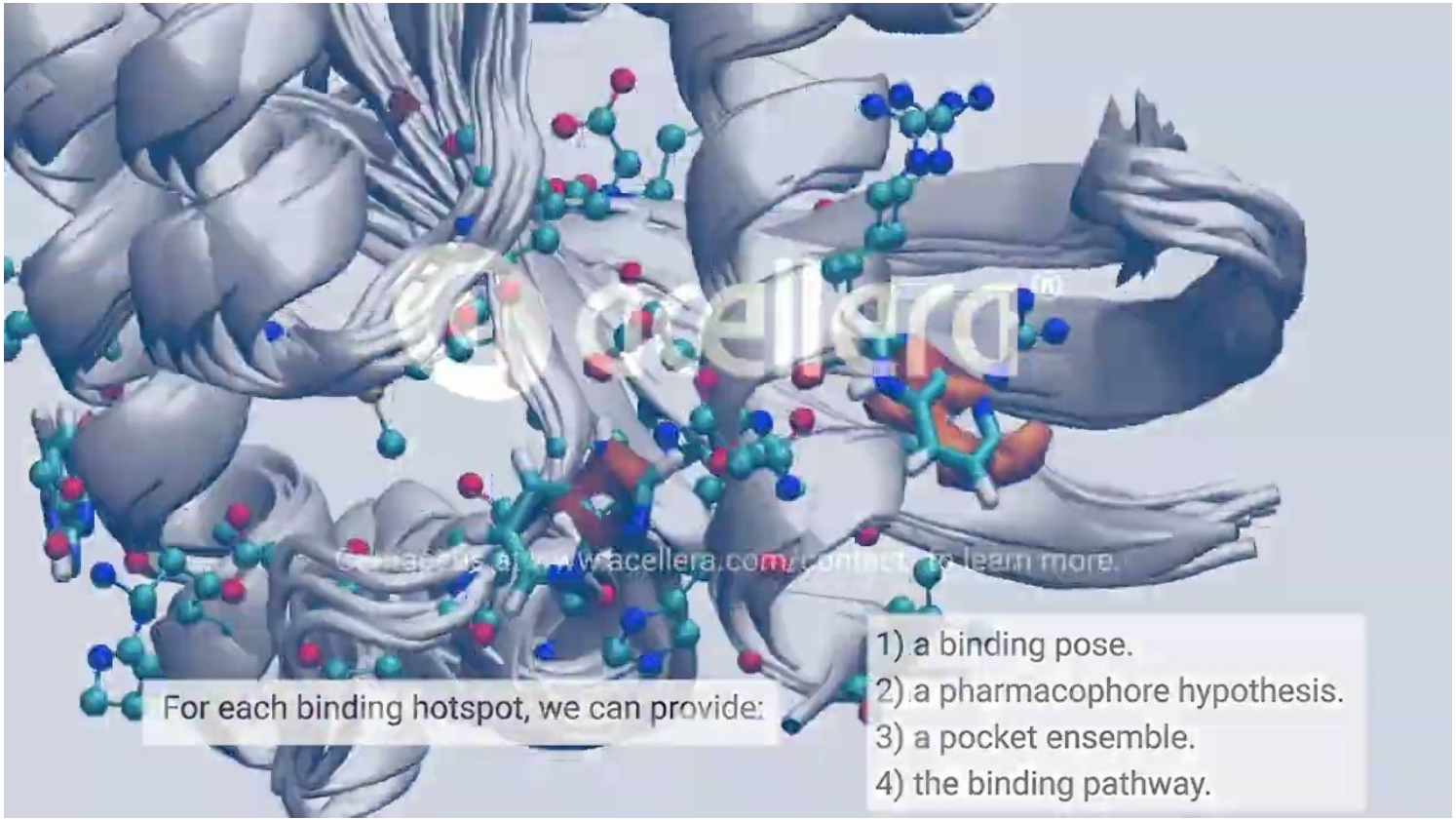


The workflows

1. From PDB to fully-simulated systems

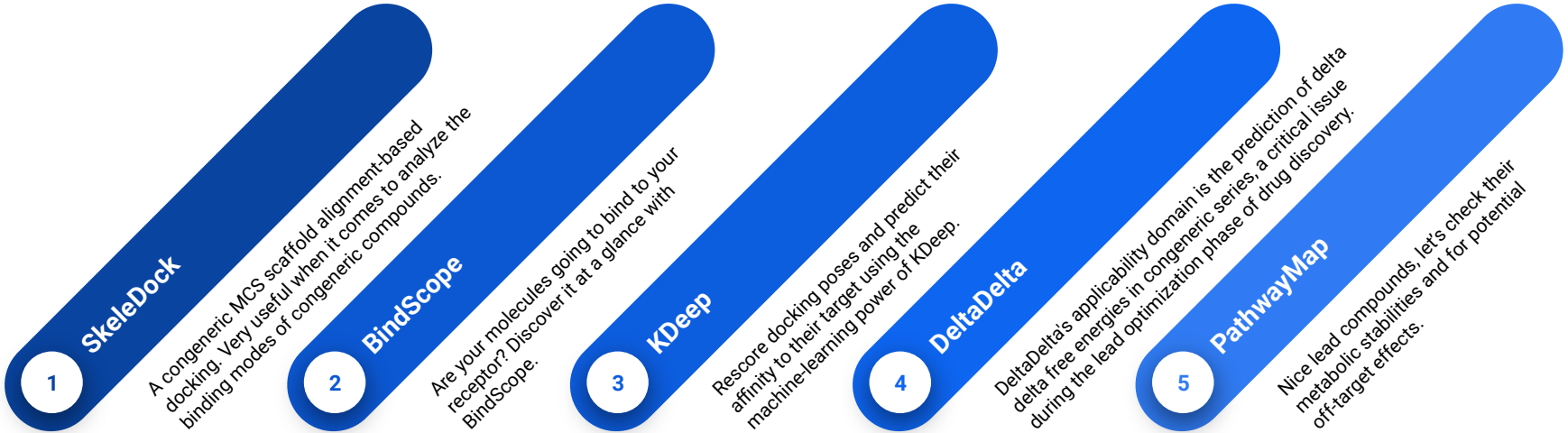


CRYPTICSCOUT - Mixed solvent MD



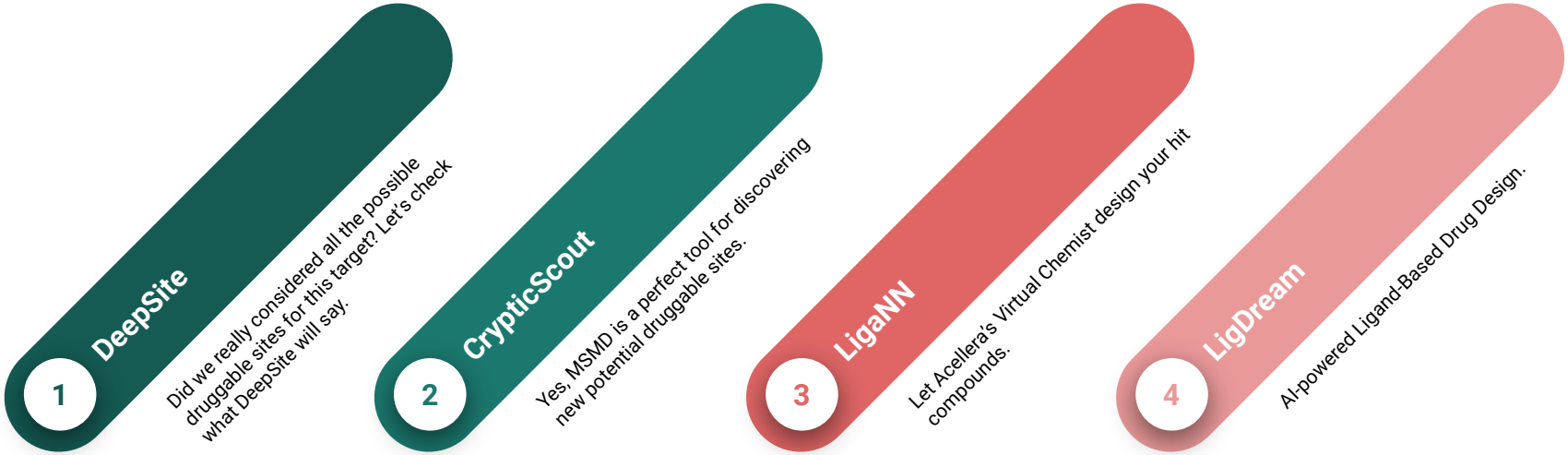
Docking and HTVS

2. Screen a target against a library of selected molecules



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

3. Explore new possibilities using AI-based methods



Structure-Based

Ligand-Based

Ok, now let’s see how it works...

Q&A

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

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 675451

Thank you for participating!

…don't forget to fill in our feedback questionnaire…

Visit the CompBioMed website (www.compbiomed.eu/training)
for a full recording of this and other e-Seminars,
to download the slides
and to keep updated on our upcoming trainings

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