Exscalate4CoV, LIGATE project and beyond

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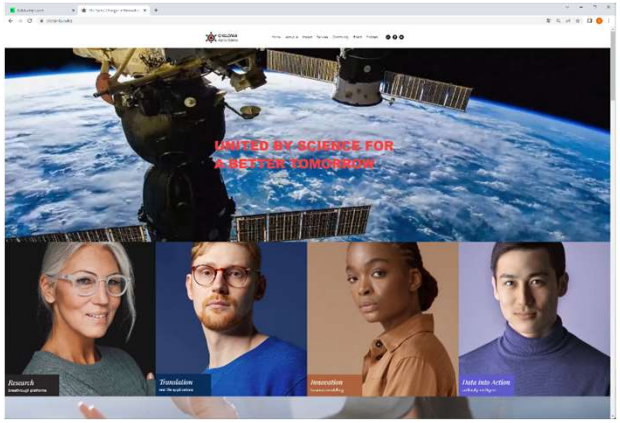
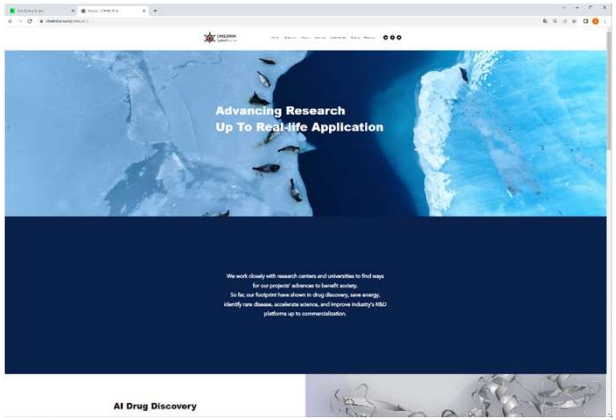
Applied Science

Silvano Coletti, Ing.
CEO Chelonia S.A.





UNLOCKING THE FULL POTENTIAL OF INNOVATION

Chelonia is a +20 years pioneering organization with a rich history supporting industry and academia. We provides the right environment to accelerate the pace of innovation. **Our vision is to channel use-inspired science in the right direction and to improve the way the world creates and advances innovation**.

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Applied Science

Dr. Arieh Warshel, Nobel Prize 2013 Chemistry
University of Southern California
Member of **Chelonia Scientific Committee**
Ambassador of Chelonia Applied Science at-Large

Dr. James Beacham, CERN physicist, ATLAS experiment
Duke University
Chelonia Staff Member
Member of **Chelonia Scientific Committee**
Ambassador of Chelonia Applied Science at-Large

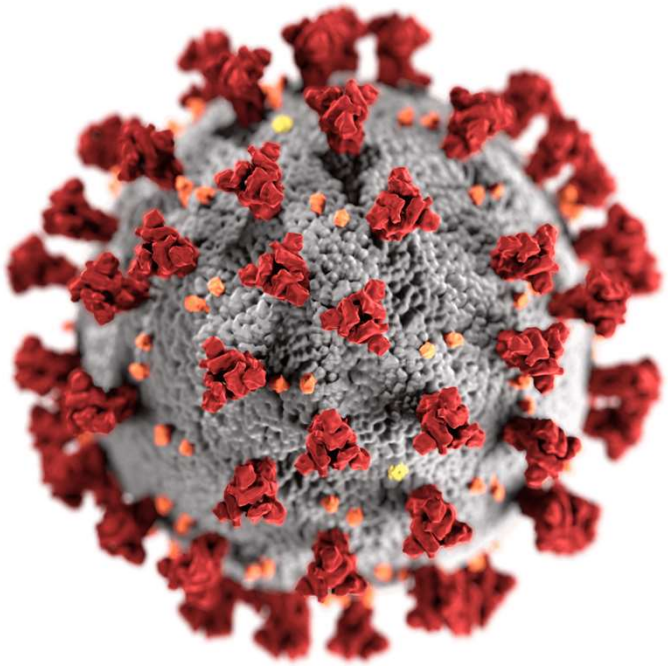
EXSCALATE4COV

Silvano Coletti, Ing.

CEO, Chelonia SA

Project Innovation Manager EXSCALATE4COV

The Begin of the Journey of SARS-CoV-2



31 Dec. 2019:

Cluster of cases of pneumonia reported

Effort to identify pathogen

12 Jan. 2020:

Virus genome sequence published

Efforts by researchers around the globe

11 Mar. 2020:

Declared pandemic by WHO

EXSCALATE 4COV

The EXSCALATE4CoV (E4C) Project

EXSCALATE4CoV = EXaSCale smart pLatform Against paThogEns for Corona Virus

Objectives:

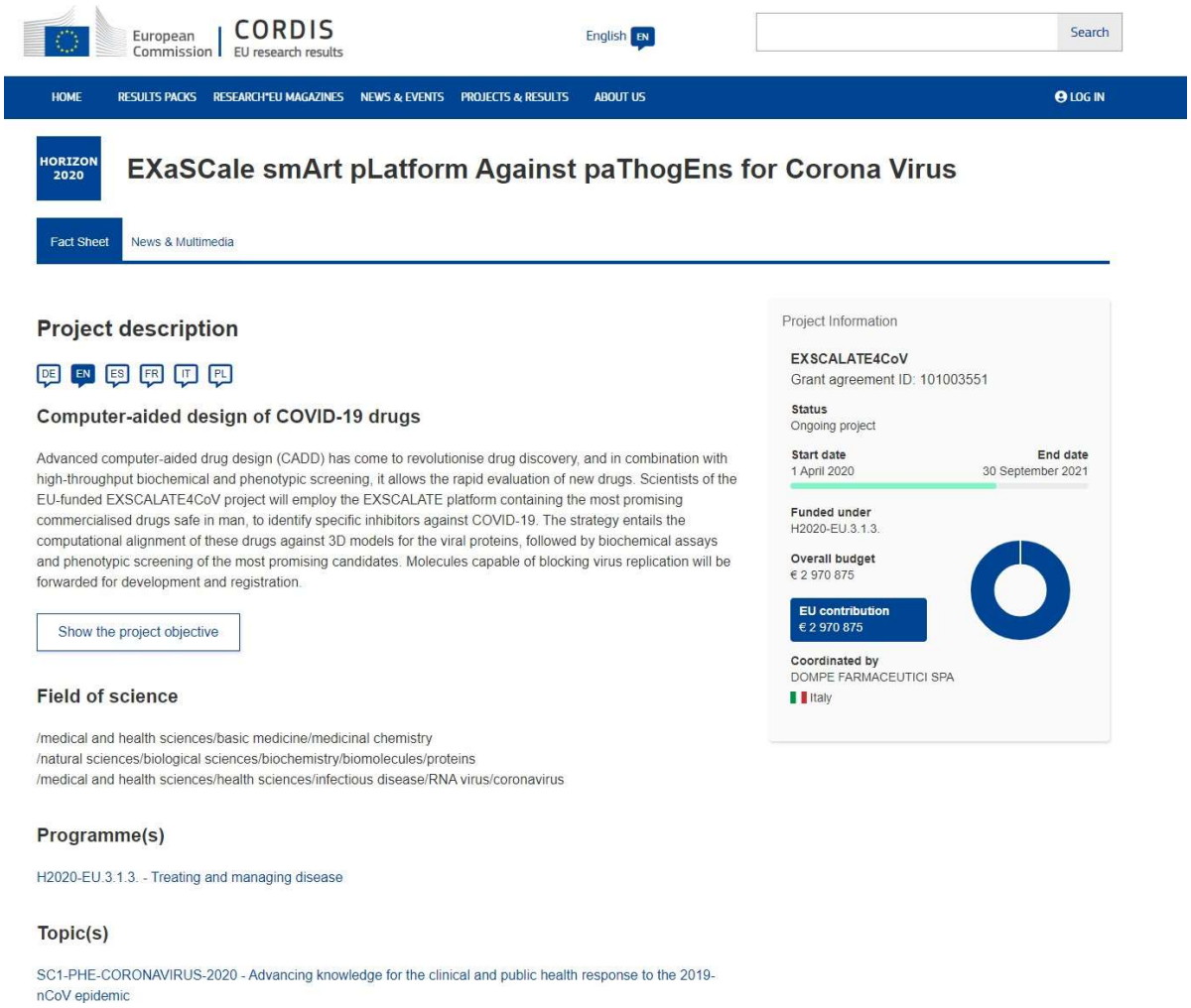
- Identify molecules capable of targeting SARS-CoV-2
- Develop effective tools to counter future pandemics
- Exploit European supercomputer capabilities

Project fact sheet:

- ~3M€ budget
- EU H2020 emergency call in response to COVID-19 in Feb 2020
- Duration: April 2020 - September 2021
- 18 partners from 7 countries

EXSCALATE 4COV

EXSCALATE4COV (2020-2021)



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HORIZON 2020

EXaSCale smArt pLatform Against paThogEns for Corona Virus

Fact Sheet | News & Multimedia

Project description

DE EN ES FR IT PL

Computer-aided design of COVID-19 drugs

Advanced computer-aided drug design (CADD) has come to revolutionise drug discovery, and in combination with high-throughput biochemical and phenotypic screening, it allows the rapid evaluation of new drugs. Scientists of the EU-funded EXSCALATE4CoV project will employ the EXSCALATE platform containing the most promising commercialised drugs safe in man, to identify specific inhibitors against COVID-19. The strategy entails the computational alignment of these drugs against 3D models for the viral proteins, followed by biochemical assays and phenotypic screening of the most promising candidates. Molecules capable of blocking virus replication will be forwarded for development and registration.

Show the project objective

Field of science

/medical and health sciences/basic medicine/medicinal chemistry
/natural sciences/biological sciences/biochemistry/biomolecules/proteins
/medical and health sciences/health sciences/infectious disease/RNA virus/coronavirus

Programme(s)

H2020-EU.3.1.3. - Treating and managing disease

Topic(s)

SC1-PHE-CORONAVIRUS-2020 - Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic

Project Information

EXSCALATE4CoV
Grant agreement ID: 101003551

Status
Ongoing project

Start date 1 April 2020
End date 30 September 2021

Funded under
H2020-EU.3.1.3.

Overall budget
€ 2 970 875

EU contribution
€ 2 970 875

Coordinated by
DOMPE FARMACEUTICI SPA
Italy

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E4C Consortium: 18 partners and +200 researchers

Integrated pan European drug discovery infrastructure

➞ https://www.exscalate4cov.eu/consortium.html

EXSCALATE 4COV

E4C League

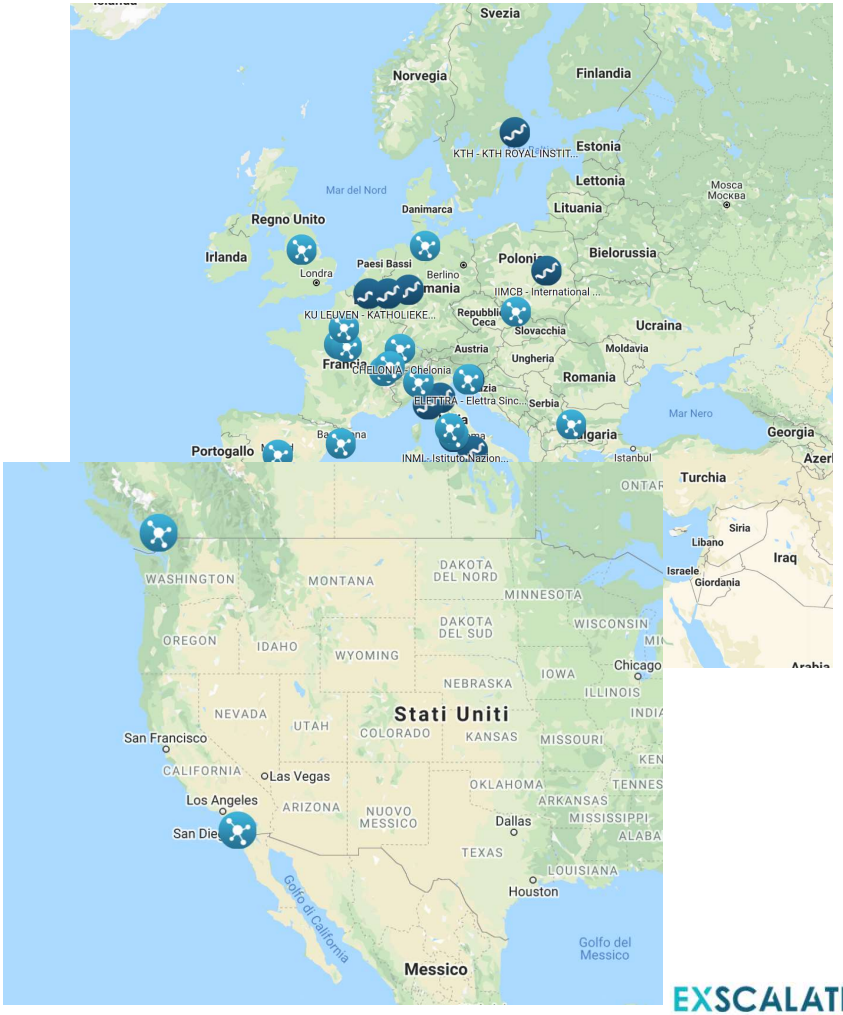
External collaborators

DrugBox

Pierre Fabre, Alfasigma, Almirall, Axxam, Esteve, Lilly, Sanofi, Greenpharma, …

Other means

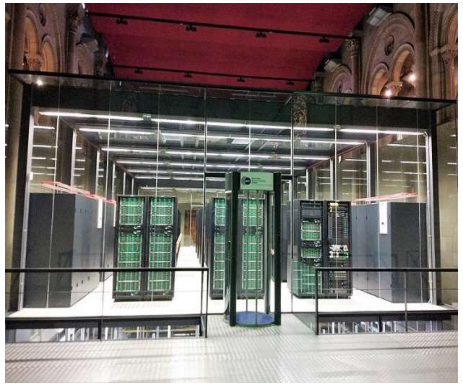
ENI, SAS, IT4Innovation, Esteco, Nanome Inc.,
https://www.exscalate4cov.eu/league.html



EXSCALATE 4COV

European High Performance Computing

#6
HPC5
Eni S.p.A.
Italy



#37
MareNostrum
Barcelona (BSC)
Spain

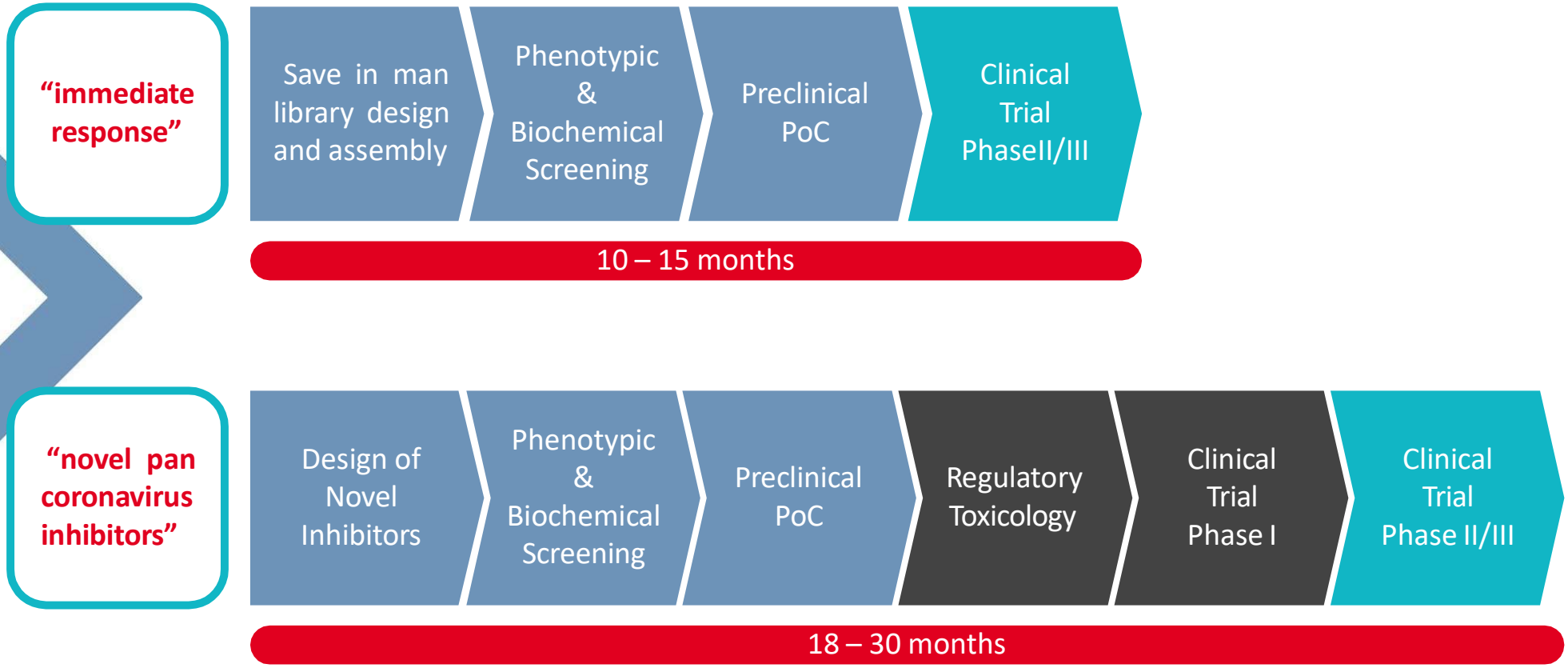
#9
Marconi-100
CINECA
Italy

#65
JURECA
Juelich (FZJ)
Germany

EXSCALATE 4COV

E4C Main Goals

EXSCALATE 4COV

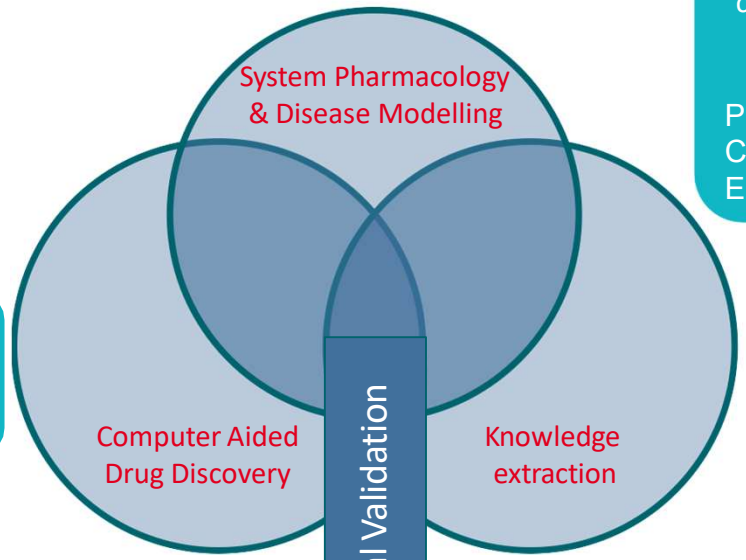



EXSCALATE
4COV
European
Commission

First Outcome of the E4C Project: Raloxifene

Evident protective role of estrogens in coronavirus infection and a protective action of SERM in a relevant *in vivo* model:

Phospholipidosis
Cholesterol lowering effect
Elevation of nitric oxide level



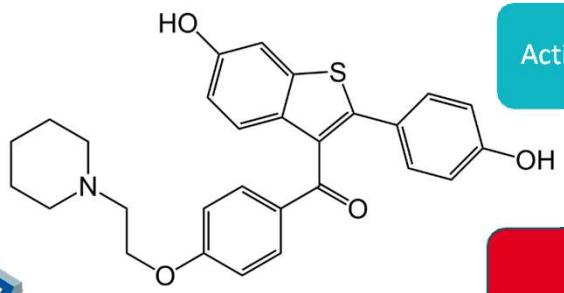
Suitable in Silico Poly-pharmacolgy

Drug Bio-distribution in Lungs

Experimental Validation

Active in the Phenotypic Assay

Inhibitor of the ACE2-Spike protein-protein interaction

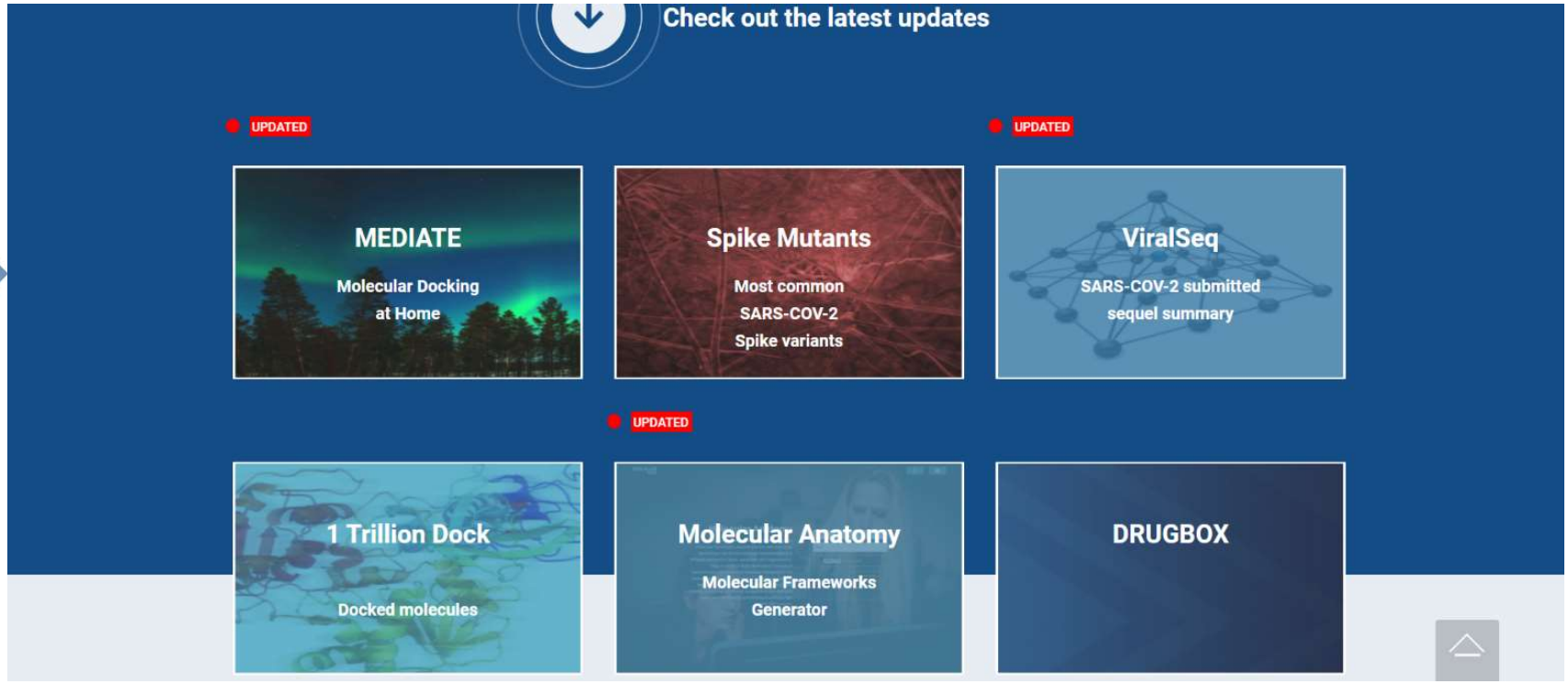


Clinical Trial Ongoing

EXSCALATE 4COV

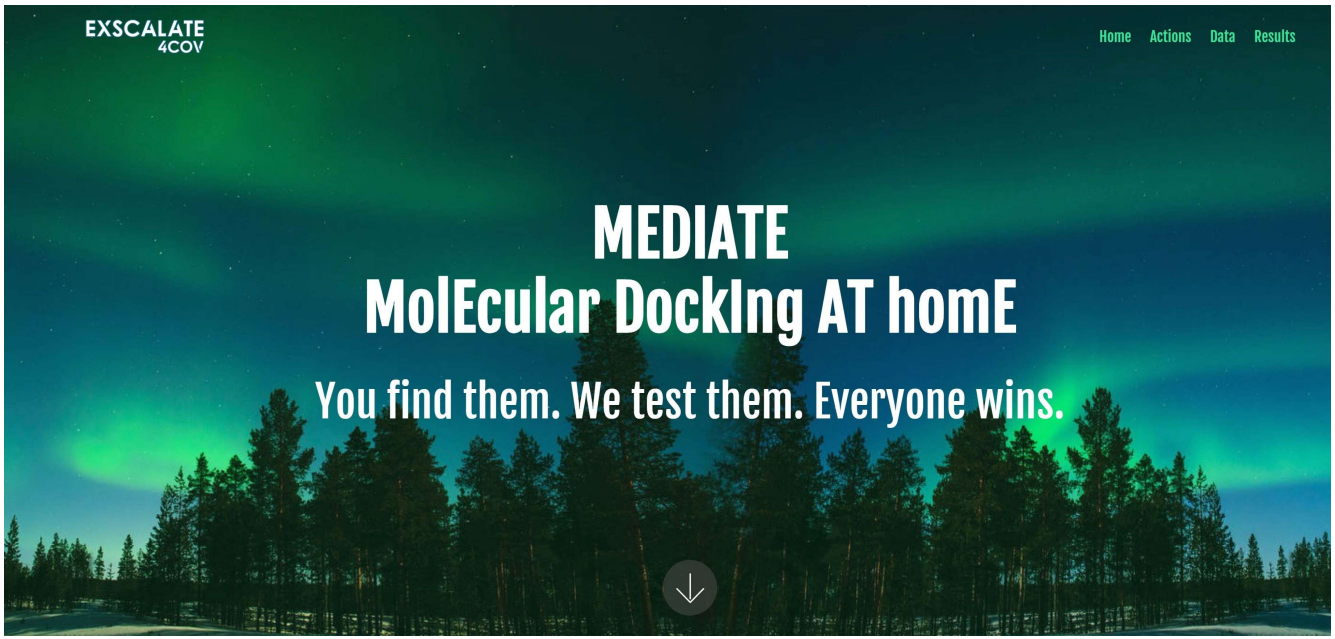
Open Science at E4C

We opened at least 6 “windows” on data produced and still now updated from the consortium. Visit www.exscalate4cov.eu to know more and access data



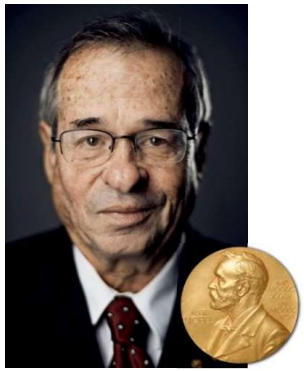
MEDIATE initiative: Crowdsource virtual screening collection from the pharma computational chemistry & AI/ML communities

Requested by the EU commission to support the EU research of the research groups not already involved in H2020 projects



https://mediate.exscalate4cov.eu/

Scientific Advisory Board



Arieh Warshel
Nobel Prize in Computational Chemistry

Rossen Apostolov
Executive Director at BioExcel CoE

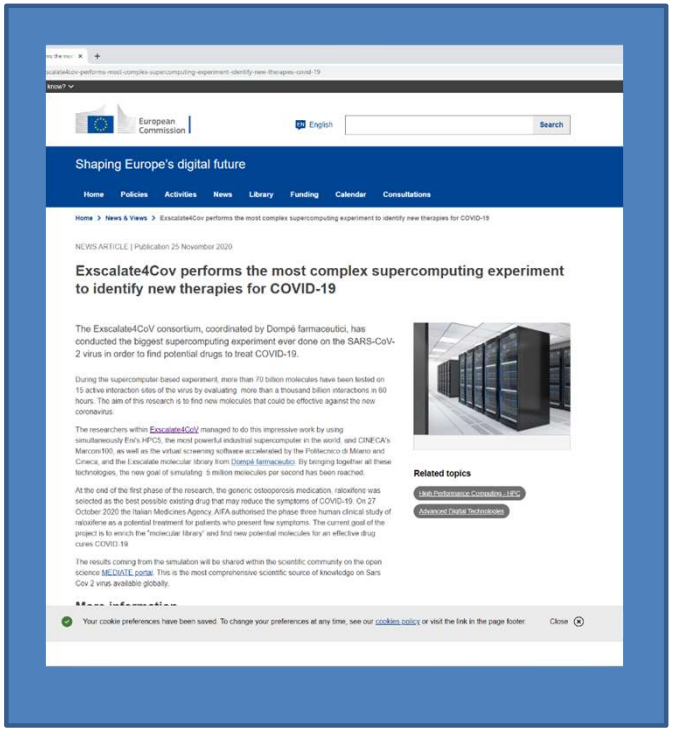
Igor V. Tetko
Executive Committee member at European Neural Network Society

Ye Yang
Deputy director of
Shanghai Institute of Materia Medica

23 Nov 2020 - Exscalate4Cov performed in Italy the most complex supercomputing experiment to identify new therapies against Sars Cov2 virus.

1 Trillion Docking (https://1trilliondock.exscalate4cov.eu/)

We tested 70 billion molecules on 15 "active sites" of the virus by evaluating one trillion interactions. The simulation lasted 60 hours (5 million simulated molecular interactions per second), with the generation of 65 TeraBytes of results that represent the most in-depth knowledge of the interaction of the virus with possible drugs.



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EXSCALATE 4COV

LiGen™ 3.0 : 1 Trillion Docking Experiment

	KPI	EXSCALATE	Scripps Research	EXSCALATE FoI
Simulation	Number of Molecules	71600000000	1400000000	51.1
	Number of proteins	12	1	12
	Number of Binding Sites	15	2	7.5
	Number of Docked Molecules	1.05E+12	2800000000	**375**
Performance	Docking Speed per GPU / sec	500	1.03	**485.4**
	Number of Docked Molecules / Node	2000	6.18	323.6
	Throughput Docking /sec	4600000	28477.44	161.5
	Throughput Docking per day	3.9744E+11	2460450816	161.5

https://blogs.nvidia.com/blog/2020/05/26/covid-autodock-summit-ornl/

Project Results in Numbers

1
Approved clinical trials: RALOXIFENE

3
Clinical Candidates

348
Molecules found to be active in experimental assays

20.000
Biological experiments performed

4
Biological assays developed

>1 Trillion
Molecules simulated

45
Proteins simulated in molecular dynamics experiments

>60 million
calculation hours
Used for molecular dynamics simulations

35
Crystallographic structures generated

15
Number of publications

3
Number of patents

18
Number of partners

30
League members

€ 3+1* milioni
Project budget

>23.000
Results for "exscalate4cov" in Google Search

(*) EXSCALATE4COV + COVIRAL grants

EXSCALATE 4COV

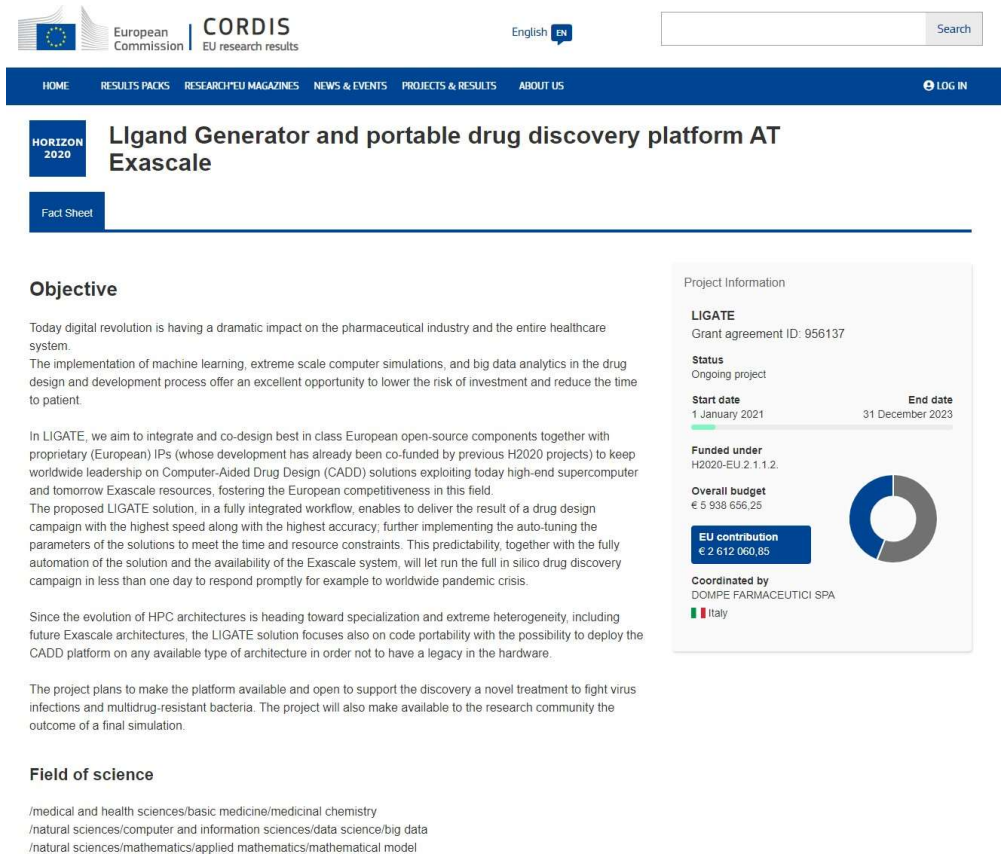
LIGATE

EuroHPC Joint Undertaking

European Commission

This project has received funding from the European High-Performance Computing Joint Undertaking Joint Undertaking (JU) under grant agreement No 956137. The JU receives support from the European Union's Horizon 2020 research and innovation programme and Italy, Sweden, Austria, Czech Republic, Switzerland.

LIGATE (2021-2023)



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HORIZON 2020

LIgand Generator and portable drug discovery platform AT Exascale

Fact Sheet

Objective

Today digital revolution is having a dramatic impact on the pharmaceutical industry and the entire healthcare system.
The implementation of machine learning, extreme scale computer simulations, and big data analytics in the drug design and development process offer an excellent opportunity to lower the risk of investment and reduce the time to patient.

In LIGATE, we aim to integrate and co-design best in class European open-source components together with proprietary (European) IPs (whose development has already been co-funded by previous H2020 projects) to keep worldwide leadership on Computer-Aided Drug Design (CADD) solutions exploiting today high-end supercomputer and tomorrow Exascale resources, fostering the European competitiveness in this field.
The proposed LIGATE solution, in a fully integrated workflow, enables to deliver the result of a drug design campaign with the highest speed along with the highest accuracy; further implementing the auto-tuning the parameters of the solutions to meet the time and resource constraints. This predictability, together with the fully automation of the solution and the availability of the Exascale system, will let run the full in silico drug discovery campaign in less than one day to respond promptly for example to worldwide pandemic crisis.

Since the evolution of HPC architectures is heading toward specialization and extreme heterogeneity, including future Exascale architectures, the LIGATE solution focuses also on code portability with the possibility to deploy the CADD platform on any available type of architecture in order not to have a legacy in the hardware.

The project plans to make the platform available and open to support the discovery a novel treatment to fight virus infections and multidrug-resistant bacteria. The project will also make available to the research community the outcome of a final simulation.

Field of science

/medical and health sciences/basic medicine/medicinal chemistry
/natural sciences/computer and information sciences/data science/big data
/natural sciences/mathematics/applied mathematics/mathematical model

Project Information

LIGATE
Grant agreement ID: 956137

Status
Ongoing project

Start date 1 January 2021
End date 31 December 2023

Funded under
H2020-EU.2.1.1.2.

Overall budget
€ 5 938 656,25

EU contribution
€ 2 612 060,85

Coordinated by
DOMPE FARMACEUTICI SPA
Italy

https://cordis.europa.eu/project/id/956137

LIGATE is the public-private consortium composed of 11 Partners from 5 EU Countries

Dompé

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KTH VETENSKAP OCH KONST

UNIVERSITÀ DEGLI STUDI DI SALERNO

University of Basel

VSB TECHNICAL UNIVERSITY OF OSTRAVA | IT4INNOVATIONS NATIONAL SUPERCOMPUTING CENTER

E4 COMPUTER ENGINEERING

tofmotion depth sensing and imaging

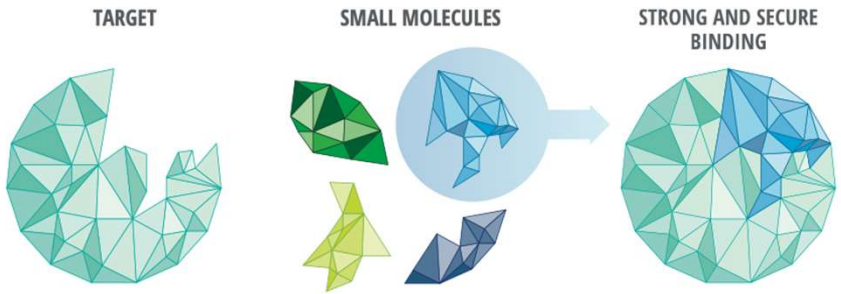
universität innsbruck

LIGATE: PROJECT AMBITION

No automated industrial software solutions are available for drug discovery, integrating:

- Geometrical scoring,
- Pharmacophoric scoring function,
- Molecular dynamic free energy estimation

The main goal of the LIGATE project is to develop such a portable and tunable drug discovery platform ready for Exascale HPC systems to respond promptly to worldwide pandemic crises but also to propose to the market a platform “game-changer” in the drug discovery and development industrial processes.



Source: Deloitte analysis.

OBJECTIVES

GROUND-BREAKING OBJECTIVES OF THE PROJECT

- **Provide the platform in the form of a highly scalable workflow**
- **Code and Performance Portability on Heterogeneous Accelerators**
- **Integrated automatic setup and execution of free energy calculations**
- **Exploit state-of-the-art AI techniques to further speedup the virtual screening phase**
- **Exploit state-of-the-art Big Data technologies for HPC to manage huge databases and I/O**
- **The platform to be a full integrated industrial solution**

Technology behind Exscalate4COV

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EXSCALATE

Exscalate mission

EXSCALATE

“ improve clinical success rate
through drugs’ poly-pharmacology profile
enabled with the highest quality chemical probes
exploited by exascale AI Driven Medicine Design ”

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Exscalate key unique elements vs other entities cover all the value chain from chemistry to biology and AI & Molecular simulations

	EXSCALATE	Pharma & Startup
CHEMISTRY (entry point)	• Highest **quality** de **novo molecules designed** and **synthetized** to **address the peculiarity** of the **targets & disease**	• **Pre assembled Libraries** mols or frags • **Drug repurposing** • **Analogues based** drug discovery
BIOLOGY (Translational Pharmacology)	• **Tailored disease & safety (Poly)Pharmacology** profiling (in silico & experimental)	• **1 drug > 1(2) target > 1 disease** • **standard selectivity profiling**
Artificial Intelligence & Molecular Simulations	• Fully **integrated exa-scale A.I.M.S. platform**	• **Collection of vertical solutions**

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A quick and “helicopter view” of how the Exscalate platform works

Exscalate aims to **master state of art in-silico technologies / features** to support the **Drug Discovery process**, from **hit-to-candidate**, reducing costs, accelerating time and increasing probability of success

Hit	Lead	Candidate
• Disease dependent drug product profile (DPP) • Design of the DPP chemical space • Training and Validation of the Virtual Screening protocols and of the in silico hit profiling cascade • Experimental Validation in translational in vitro models (phenotypic, functional, SPR)	• Re-training of the Virtual Screening protocols • Project specific AI/ML to optimize in silico the key features of the leads • Experimental extended evaluation of early ADMET of the lead series • X-ray/Cryo-EM • Validation of translational in vivo models	• **Tox** • **ADME** • **All additional IND-enabling activities**
Deliverables		
High Quality Lead-like Hits	**Preclinical Candidate identified in 2-3 rounds of optimization**	**IND ready molecule**

Timing strictly dependent on project characteristics – e.g. 1,5 years for IL-17 for IND-enabling phase

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Exscalate platform is composed by three main in-silico components, structurally interlinked, with state of art technologies / breadth of content

Tangible Chemical Space

- Comprehensive **Tangible Chemical Space** (“TCS”) with **2 trillion of molecules**
- TCS built to be flexible to filter **molecules** to **match project specific constraints** & **requirements.**

Comprehensive Therapeutic Target Database

- **Comprehensive Therapeutic Target Database** (“CTTD”) that **combines all** known **annotate druggable targets** with decades of studies on **protein-ligand interactions models**
- **CTTD is ready to be virtual screened**

Exascale Structure Based Virtual Screening

- Among (if not the most) powerful **Structure Based Virtual Screen Tool**
- **Developed** to deliver **extremely high performance simulations** to increase the quality of **chemical probes**

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