CORONAVIRUS PANDEMIC: Exscalate4Cov [1] performed in Italy the most complex supercomputing experiment to identify new therapies against Sars Cov2 virus.

The goal was to test 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.

The results coming from the simulation will be shared within the scientific community on the open science portal ***mediate.exscalate4Cov.eu****. This is the* ***most comprehensive scientific wealth of knowledge on Sars Cov 2 virus*** *available globally.*

On the field project, under the coordination of ***Dompé, the molecular library Exscalate****, supercomputers* ***HPC5 of Eni and Marconi100 of Cineca*** *(81 petaflops of computing capacity) on which run the virtual screening software* ***realized and optimized by Politecnico di Milano and Cineca, and analytics from SAS****.*

The Scientific Committee of the project is chaired by the ***Nobel Prize for Computational Chemistry Prof. Arieh Warshel.***

On October 27, 2020 AIFA authorized the ***clinical study at IRCSS Lazzaro Spallanzani in Rome and IRCSS Humanitas in Milan to evaluate raloxifene (****first molecule selected by Exscalate4CoV) as a potential treatment for covid paucisymptomatic patients who are in hospital or at home.*

23 November 2020 - This weekend the public-private Consortium Exscalate4Cov, supported by the European Commission, carried out the most complex supercomputing simulation ever realized. The objective was to simulate the behavior of the Sars Cov 2 virus to identify the best therapeutic treatment.

The activity of 71.6 billion molecules on the 15 active of the virus was simulated for a total of 1074 billion interactions. The simulation performed in 60 hours - with a capacity of 5 million simulated molecules per second - produced over 65 TeraBytes of total data. This is the most complex set of information describing the interations of the Sars Cov 2 virus available today.

This has been possible thanks to the simultaneous availability of the **computing power (81 petaflops: millions of billions of operations per second)** of Eni's HPC5, the most powerful industrial supercomputer in the world, of CINECA's Marconi100, and the virtual screening software accelerated by the Politecnico di Milano and Cineca, and the Exscalate molecular library from Dompé. Using this technologies/method, it has been possible to reach the new goal of **5 million simulated molecules per second**, making the most out the Supercomputing infrastructure. As a

[1] The **Exscalate4Cov** (www.exscalate4cov.eu) consortium, supported by the the EU's Horizon 2020 programme for research and innovation, is coordinated by Dompé farmaceutici, and composed by 18 member institutions from seven European countries: **Politecnico di Milano** (Dept. of Electronics, Information and Bioengineering), Consorzio Interuniversitario **CINECA** (Supercomputing Innovation and Applications), **Università degli Studi di Milano** (Department of Pharmaceutical Sciences), **International Institute of Molecular and Cell Biology in Warsaw** (Warsaw, Poland), **KU Leuven**, **Elettra Sincrotrone Trieste**, **Fraunhofer Institute for Molecular Biology and Applied Ecology**, **BSC Barcelona Supercomputing Centre**, **Forschungszentrum Jülich**, **Università Federico II di Napoli**, **Università degli Studi di Cagliari**, **SIB Swiss Institute of Bioinformatics**, **KTH Royal Institute of Technology** (Department of Applied Physics), **Associazione Big Data**, **Istituto Nazionale di Fisica Nucleare** (INFN), **Istituto nazionale per le malattie infettive Lazzaro Spallanzani** and **Chelonia Applied Science.- https://www.exscalate4cov.eu/consortium.html League**: ENI, SAS, Alfasigma, CFEL Center for Free-Electron Laser Science, MMV Medicines for Malaria Ventures, **Esteve Pharmaceutical**, University of Basel Biozentrum, University of Basel Innovation Office, University of Basel Department of Pharmaceutical Sciences, D-wave, **Pierre fabre**, **Greenpharma**, University of Sheffield - Sheffield Institute for Translational Neuroscience – SITraN**,** Dassault Systemes- Biovia, Institute of Food Science Research, CECAM Centre Européen de Calcul Atomique et Moleculaire, Nanome, Esteco, IT4Innovation, Università degli Studi della Tuscia, Sofia University "St. Kl. Ohridski", Faculty of Physics, Institut Cochin- **https://www.exscalate4cov.eu/league.html**

comparison, the **Italian simulation is more than 300 times bigger and 500 times faster than the one realized in the USA in June this year**. RIF: (https://blogs.nvidia.com/blog/2020/05/26/covid-autodock-summit-ornl/)

The data from the simulation will be processed with SAS Viya using artificial intelligence techniques and advanced analytics. **Results will be available** on the portal **mediate.exscalate4cov.eu,** designed in collaboration with SAS to allow scientists around the world to carry out their own simulations, benefiting from "state of the art" knowledge.

Research groups around the world can use virus protein models and chemical libraries to generate new predictions using different approaches of artificial intelligence and molecular mechanics simulations.

The consortium will make available **10 million dedicated computing hours and the necessary technological infrastructure.** MEDIATE- MolEcular DockIng AT home - will give free access to the largest database available today on the Sars-CoV-2 Virus both from a structural (three-dimensional structures) and functional (proteins interacting with human cells) point of view, including all the molecular dynamics involved in cellular interaction and active sites for potential drug entry.

In this regard, the molecular bank of MEDIATE has been generated considering the main classes of molecules, which have been selected to allow an accelerated clinical development. **The library contains: 10 thousand drugs, 400 thousand natural products, 70 thousand nutraceuticals, 100 million oligopeptides, 5 million molecules already on the market for research purposes, and 72 billion de novo molecules easily synthesized.**

The MEDIATE portal will collect the predictions made by research groups around the world (crowdsourcing) combining them into a single model using the neural networks and artificial intelligence from SAS with the aim of identifying new and more effective treatments against COVID-19, in the shortest possible time.

The MEDIATE project can rely on a **scientific board** (coordinated by the project partner Chelonia Applied Science) of the highest level: **Nobel Prize for Computational Chemistry Prof. Arieh Warshel, Rossen Apostolov Executive Director of BioExcel, European Centre of Excellence for Biomolecular Computational Research, Igor Tetko of Helmholtz Zentrum München and Prof. Yang Ye of Shanghai Institute of Materia Medica.**

Phase 1 of the EXSCALATE4COV project - with a screening carried out on **400 thousand molecules** (safe-in-man drugs and natural products) and a **specific test to evaluate 9000 promising molecules** - ended with the identification of one molecule - **raloxifene – now under a phase III clinical trial project submitted and approved by AIFA**. The patent file was filed on May 6, 2020 by Dompé farmaceutici, Fraunhofer Institute at the University of Leuven in order to promote universal access to the treatments that may result, as defined by the guidelines of the consortium itself.

The data generated so far have led to the creation of **12 peer reviewed articles** and evidence from over 20 thousand in vitro experiments. The international magazine "**International Journal of Molecular Sciences**" has dedicated a special issue to the project EXSCALATE4COV (https://www.mdpi.com/journal/ijms/special_issues/Exscalate4CoV), you can find the scientific production of the consortium on the website https://www.exscalate4cov.eu/contribute.html#papers.

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