21 November 2020

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

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 will 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.***

Objective: to test 70 billion molecules on 15 "active sites" of the virus processing ***a thousand billion interactions in just 60 hours (5 million molecules simulated per second).***

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 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.*

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

More than **70 billion molecules will be simulated on the 15 active interaction sites** of the virus for a total of **more than a thousand billion interactions evaluated in just 60 hours**. This will be 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 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 in real time on the portal 1trilliondock.exscalate4cov.eu** and then on the portal

[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**

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.

Exscalate4CoV (E4C) - funded with 3 million euros by the European Commission through the European call for proposals within the Horizon 2020 project dedicated to the coronavirus emergency - is structured as follows:

- Establish a sustainable scientific standard to provide rapid responses to any pandemic scenario. The model is based on the use of a supercomputing platform integrated with artificial intelligence systems, 3D modeling supported by X-ray diffractometry for the identification of the best candidates for the clinic and subsequent validation laboratory testing on predictive cellular models (virus, bacterium, etc.);
- Identify virtually and rapidly available drugs, or drugs in advanced development, potentially effective;
- Define a screening model to validate potentially effective molecules and possible mechanisms of action and mutation of the pathogen;
- Structure together with EMA - European Medicine Agency - a model of effective experimentation on the molecule identified to speed up its therapeutic use;
- Identify the genes involved in the development of the pathology.

The supercomputing centers Eni, CINECA (Italy), BSC (Spain) and Jülich (Germany) are performing the molecular dynamics simulations of viral proteins and the ultra-fast virtual screening of the E4C library. The University of Milan and the Politecnico di Milano are engaged respectively in supporting the virtual screening activity and in accelerating the computational process.

Results from the virtual screening will drive to the selection of active compounds to be tested in phenotypic screening phase at the KU Leuven research infrastructure through a multiparameter high throughput screening platform on live pathogens at high (level 3) or unknown biosafety risk.

The Fraunhofer Institute for Molecular Biology and Applied Ecology (IME) will integrate phenotypic screening with the biochemical assay on targets of different putative viruses through access to the Fraunhofer BROAD Repurposing Library.

The University of Cagliari will complete the biological evaluation by defining the mechanism of action of inhibitors and the selection of mutants in systems. This information will be crucial to define the genetic barriers of potential drugs and to select more promising molecules to develop.

The Elettra Synchrotron Trieste and the International Institute of Molecular and Cellular Biology will produce the X-ray structures for the most interesting viral enzymes and related inhibitors in order to support the rational design of new chemical structures able to inhibit Corona viruses.

The Medical Chemistry team of the University of Naples Federico II will support the EXSCALATE team in the selection of the best compounds, as well as dealing with the chemical synthesis of the best candidates.

The National Institute for Infectious Diseases Lazzaro Spallanzani is the reference center for ongoing clinical trials that will be activated by the consortium.

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