

Fighting coronavirus: European supercomputers join pharmaceutical companies in hunt for new drugs

Behind the Exscalate4CoV project stands an unprecedented consortium of the best scientific minds in the technological and bio-medical fields. Supported by €3 million of emergency EU funding, an increasing number of pharmaceutical companies and research institutes have recently joined the quest to find a drug to treat the coronavirus.



Exscalate4CoV (E4C) consists of a coalition between public and private partners located across seven European countries (Belgium, Germany, Italy, Poland, Spain, Sweden and Switzerland), working together to combat the spread of the novel coronavirus. Coordinated by the Italian pharmaceutical company Dompé and disposing of the best researchers in their respective fields, along with three powerful high-performance computing (HPC) centres in Bologna, Barcelona and Jülich, E4C is searching for potential drugs to fight the COVID-19 disease.

With new contributors from the pharmaceutical industry, research institutions, and biological laboratories signing non-disclosure agreements with E4C on an almost daily basis, the chances of finding molecules to create an antiviral medication continue to grow. Eight European companies – Pierre Fabre, Alfasigma, Almirall, Axxam, Esteve, Lilly, Sanofi and Greenpharma – have already joined the scheme since 10 April 2020, and discussions with other companies are now in the works, such as Merck, Takeda, Abbott and many more.

Pharma companies are opening their medical libraries to testing and donating molecules via the online DrugBox data platform to provide E4C access to new and existing drugs, enlarging its database

and increasing the probability of identifying and producing a fully repurposed treatment.

United against the coronavirus

The strengths of Exscalate4CoV emerge from synergies between the partners' different scientific backgrounds. The project will build on two distinct but interconnected streams of activities, both converging to the biological screening. One mostly relies on supercomputer capacities, in combination with artificial intelligence (AI), bioinformatic and chemoinformatic technologies. The other combines the available project knowledge with a genomic, biochemical and biological approach so as to identify interesting molecules that could be used for a potential drug.

The first step is to obtain the structure of the virus. Three partners – the International Institute of Molecular and Cell Biology (IIMCB), Elettra Sincrotrone Trieste and the Swiss Institute of Bioinformatics (SIB) – use their technologies to crystallise the virus' protein and provide its 3D structure. E4C has identified 25 different protein models that are constantly evolving, with various mutations received weekly, which are translated into a digital form for further testing.

The next step is the docking operations. E4C has a database of over 10,000 drugs and 500 billion molecules; with a computing capacity of 50 million billion operations per second, the three European supercomputers are able to match the digital signature of coronavirus proteins against molecules from the chemical library, in the aim of identifying a drug and ultimately saving thousands of lives. The pharma companies joining the project will provide new molecules under the DrugBox initiative, boosting the potential to find possible COVID-19 treatments.

From the initial implementation of its two working streams of activities, the project has already identified a set of 93 antiviral molecules, now under biological screening at KU Leuven, Fraunhofer IME and the University of Cagliari. These screenings determine the potency of each compound; 10 compounds have already been identified as promising candidates and are still under successive screening, with the hope that some could finally undergo clinical trials, in the hope for a possible cure to be used on patients in the upcoming months.

The virus multiplies by attaching itself to cells via its internal spiral structure, so the goal is to find a substance that could damage the spiral or inhibit its protein from sticking to other cells. As confirmed by Nobel Prize winner Dr. Robert Gallo, the coronavirus has a complex nature, and therapy will likely involve a cluster of different molecules rather than a single one. Based on the molecules selected after the biological screening, E4C partners will test the candidate compounds for safety, after which it may be possible to proceed to a first dosage in humans, with the aim to identify a possible treatment for COVID-19 patients. The project will follow EU regulations on clinical trials, working with the European Medicines Agency (EMA), and will be managed by partner Lazzaro Spallanzani INMI. These tests are expected to be completed within the next few weeks, and the consortium is therefore discussing with the EMA the future regulatory process and how to receive their support when moving from the clinical testing period to the approval stage.

Despite all of these efforts, in the event that no promising results are found, the project will begin phase two: a wider search for a completely new drug, which would include several months of clinical testing. Nevertheless, with all of the pharmaceutical data received, the process endured and the experience gained, the platform may hold the answer for dealing with future outbreaks.

More data, better the chances

The project has been expanding since it began. Over just a few weeks, Exscalate4CoV has evolved

from a small supercomputing experiment to a pan-European network. It grew from its 18 original members to a group of over 33, thanks to two open calls for new participants: one targeting pharma companies, currently in the process of joining, and the other asking research institutions to donate new molecules for the database. Since 27 March, about 20 institutions have already submitted samples for evaluation, increasing the likelihood of discovering an effective antiviral drug.

All partners contribute to the work of the three supercomputing centres, sharing and processing molecules and data using AI and cloud technologies, as well as expertise in molecular and cell biology, applied physics and biochemistry. Italian oil and gas company Eni has been an asset to E4C, since the company agreed to freely make available its supercomputing infrastructure and its molecular modelling skills in an action against COVID-19, thus substantially increasing the project's supercomputing power.

E4C is also setting up a project called MEDiate (MolEcular DockIng AT home), which will make protein models and drug libraries available to the computational community. These elements will be mediated, and the proposed compounds will be acquired and tested during E4C's second phase.

The E4C consortium

Developed by ANTAREX project between 2015-2018, EXSCALATE (EXaSCale smArt pLatform Against paThogEns) is one of the world's most powerful supercomputing platforms, created to identify active molecules during the Zika virus crisis. The platform has vastly improved advanced computer-aided drug design in Europe, with its use of both AI and HPC technologies to compliment the traditional "trial and error" clinical approach.

Led by Dompé, the consortium includes three powerful supercomputing centres – CINECA in Italy, BSC in Spain, and FZJ in Germany – and several large institutions and research centres situated across Europe: the Polytechnic University of Milan (POLIMI), the University of Milan (UNIMI), KU Leuven, the International Institute of Molecular and Cell Biology (IIMCB), Elettra Sincrotrone Trieste, Fraunhofer IME, Lazzaro Spallanzani National Institute for Infectious Diseases (INMI), the University of Naples (UNINA), the University of Cagliari (UNICA), the Swiss Institute of Bioinformatics (SIB), KTH Royal Institute of Technology, Associazione BigData, the National Institute for Nuclear Physics (INFN), and Chelonia Applied Science.

The members boost one another's efforts in various ways. Dompé developed the platform together with CINECA and POLIMI, providing the project's original drug library. To understand the virus' 3D structure, crystallisation of its protein and X-ray diffraction of the crystals is operated at Elettra and IIMCB radiation facilities, to digitise the structures for the docking operations. SIB then provides the homology models for the viral proteins to be virtually screened. Based on these activities, the supercomputing facilities at CINECA, BSC and FZJ perform simulations and an ultrafast virtual screening of the E4C database, further supported by KTH. The project used INFN's data-sharing infrastructure to complement its molecular simulations, and received support from UNIMI and POLIMI during virtual screening experiments.

From the virtual screenings, newly identified compounds are sent for phenotypic screening at KU Leuven, with biochemical screening taking place at Fraunhofer IME in order to find molecules that are capable of blocking virus replications. Other than Dompé, KU also receives molecules from IME, the second library available to E4C. UNICA will complete the biological assessment and UNINA will synthesise the identified compounds for experimental testing, supporting E4C during the data analysis phase. After retrieving positive results from the virtual screening, Lazzaro Spallanzani INMI will be the eligible centre for tests to be carried out in patients.

Some very promising outcomes are emerging, and E4C is getting closer to discovering a possible treatment for COVID-19. But as the project's success largely depends on the data at its disposal, the project remains open for further potential collaboration.

More information

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COVID-19: Could AI and supercomputers unlock the pathogen puzzle?

Video | 10 June 2020

How and to what extent can Artificial Intelligence and High Performance Computing help in the fight against Covid-19? In the hunt for answers, European scientists are combining algorithms, biochemistry and molecular screenings as part of a research project that's seeking to identify potentially new molecules that could be used for drugs against the coronavirus.

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