An EU-funded project’s state-of-the-art approach could accelerate the discovery of new antiviral drugs for some of the world’s deadliest diseases. The project has identified 20 potential antiviral drugs for further development to treat infections such as dengue fever, West Nile encephalitis and hand, foot, and mouth disease.

**Ebola virus**

**Latest on Silver (September, 2015)**

Harmful viruses that contain ribonucleic acid (RNA) rather than DNA include those responsible for diseases such as poliomyelitis, influenza hepatitis, and more recently, epidemic Ebola haemorrhagic fever and Middle East Respiratory Syndrome (MERS).

For many years, RNA viruses have puzzled scientists hunting effective treatments for the diseases they cause. In some cases, research has been neglected due to lack of funding, or has not advanced because the emerging viruses are so novel that there has been insufficient time to develop effective drugs.

The EU-funded project SILVER confronted these issues using a streamlined approach to quickly identify potential treatments for disease outbreaks caused by newly emerging RNA viruses. By the time the project ended in March 2015, its researchers had discovered 20 promising leads for new drugs, with 8 patents filed so far.

One potential drug against enteroviruses – a wide variety of RNA viruses that can cause diseases such as polio and meningitis – has been licensed for further development by a leading pharmaceutical company. This could lead to preclinical and clinical trials.
Three other potential drugs are in the process of being patented for use against chikungunya and flaviviruses – a class of RNA viruses that causes diseases such as encephalitis, haemorrhagic fever, and polyarthritis.

One patent was filed for a novel synthetic process to boost drug development and another is pending whilst the results are processed for the refinement of a potential treatment for rabies.

“Suffice it to say, the SILVER project has far exceeded its expectations,” says project coordinator Ernest Gould of Aix-Marseille University in France. “Our aim was to identify potential inhibitor leads and to demonstrate proof of concept, which we did. At this stage, the work is transferred to pharmaceutical companies through licences.”

**Ongoing research**

Research using SILVER’s methodologies will continue with the goal of uncovering other potential viral inhibitors, he added.

“Whilst discovering several potential antiviral inhibitors, many assays were developed which are now available for further research,” says Gould. “In addition, studies on Ebola, MERS and chikungunya virus are continuing since these all emerged towards the end of the SILVER project.”

**The hunt for a solution**

SILVER’s researchers began work by screening nearly one million molecules, compounds and approved drugs, looking for any properties that could inhibit the reproduction of a wide variety of pathogenic RNA viruses.

As the project developed, the researchers improved the antiviral discovery process through advanced genomic and data analysis techniques. They narrowed the search to about 600 promising leads. Additional testing identified 20 that warranted further study as they seemed to inhibit a range of viruses.

“When you find antivirals that appear to work against a broad spectrum of viruses, you feel you’ve really hit the jackpot,” Gould explains.

The project also developed a toolbox of assays – test methods for analysis – to accelerate the process of identifying novel inhibitors.

“The outcomes will help the pharmaceutical industry, biotechnology companies and European laboratories to develop antivirals more rapidly,” says Gould.

He adds: “Silver’s partners have a long history of working together on discovering antivirals. Antiviral discovery is an ongoing process and we continue to collaborate. It is great to be working with the best people in the field. It is work that can take a long time but is very exciting. When you get a good lead, your hair stands on end!”

**Leading the fight against neglected and emerging viruses (January 2015)**

EU-funded researchers have developed a streamlined approach for identifying and testing antiviral compounds that promises to accelerate the search for treatments for a range of deadly diseases including Ebola, SARS and dengue fever. Negotiations are underway for a class of compounds which are nearly ready for the pharmaceutical industry to pursue.
In the battle against viral epidemics, such as the recent Ebola outbreak in West Africa or the emergence of Middle East Respiratory Syndrome (MERS) in Saudi Arabia in 2012, time is always of the essence. But until recently a number of diseases caused by viruses – including Ebola – have not been considered suitable targets for drug discovery by the global pharmaceutical industry because it was not deemed commercially viable.

EU funding is helping to fill this void through the SILVER project, which brings together some of Europe and Asia’s leading virologists, molecular biologists, crystallographers, biochemists, medicinal chemists and bioinformaticists.

Over four years, they have screened thousands of molecules, compounds and proprietary drugs for their inhibitory activity against a range of RNA viruses that have either been largely neglected by the pharmaceutical industry, such as human enteroviruses, respiratory viruses, rabies, West Nile encephalitis and dengue haemorrhagic fever, or viruses that are emerging as epidemic threats, such as the SARS and MERS coronaviruses.

SILVER partners have identified a large number of compounds that selectively inhibit the replication of one or more viruses. The activity of the most promising inhibitors was optimised by chemical modification, and proof of concept studies were performed using in vivo model systems.

Additionally, a toolbox of assays (test substances for analysis) was developed to facilitate identification of novel inhibitors of viral replication at low bio-containment levels, thereby reducing costs and improving safety for operators.

The project is negotiating with pharmaceutical companies to test a class of compounds and data packages that includes at least three inhibitors.

“Even if only one finally shows good efficacy in humans, this would be a major achievement,” explains project coordinator Ernest Gould of Aix-Marseille Université in France.

**Finding effective antiviral compounds faster**

In the case of emerging viruses and epidemic threats, the streamlined, multidisciplinary pipeline approach adopted by the SILVER consortium – from initial screening of inhibitors to proof of concept – significantly accelerates the process of identifying potentially effective antiviral compounds.

Gould notes that the MERS outbreak in the Middle East occurred two years after the SILVER project was launched. By dedicating some of the project’s funds to screening for inhibitors against the emerging respiratory disease, the team was able to identify potential candidates within a matter of weeks.

“Our pipeline strategy was conceived to ensure total integration and automatic progression of all the necessary stages, from compound discovery to proof of concept studies of inhibitors that are ready to be presented to the pharmaceutical industry,” Gould explains. “However, developing drugs from these inhibitors will still require preclinical and clinical studies. This stage of drug development falls outside the scope and mission of the consortium.”

The SILVER team are hopeful that their work will spur the development of new treatments for neglected and emerging viruses – a process that may nonetheless take several years due to the cost and complexity of conducting clinical trials. Nonetheless, the high quality data packages generated by the project provide the pharmaceutical industry with an excellent starting point for further optimisation, preclinical and clinical development and assessment of antiviral compounds.
According to Gould, “The Ebola outbreak has certainly raised global awareness of the problem of emerging diseases that face mankind, but there are many other neglected viruses that cause billions of infections and kill millions of people annually.”

Several of the SILVER project partners are hoping to continue their work in follow-up projects, and may seek funding under the EU's Horizon 2020 programme.

A view of the broad-spectrum antiviral compound SG85 in the binding site of the main protease of MERS coronavirus. The structure of this complex has been modelled on the basis of the crystal structure of the bat coronavirus HKU4, determined by Yibei Xiao, Qingjun Ma, and Rolf Hilgenfeld, University of Lübeck, Germany. The compound SG85 was synthesized by Shyla George and Rolf Hilgenfeld, University of Lübeck.

See also:
CORDIS [3]

Project:
Small-molecule Inhibitor Leads Versus emerging and neglected RNA viruses
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SILVER
Project website:
Contact:
Contact [4]

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Links