



EUROPEAN
COMMISSION

Community Research

EU-FUNDED RESEARCH PROJECT

European vigilance network for the management of drug-resistant viruses (Virgil)

Time of action: VIRGIL started in May 2004 and is scheduled to end its contract with the EC in April 2008, supposedly being autonomous afterwards.

EU budget (funding): €9 million

Abstract

Infectious diseases have an uncanny ability to fight against all our containment efforts. Many strains of pathogenic bacteria, for example, are now so resistant to a large number of antibiotics that diseases such as tuberculosis are on the rise. Viruses can likewise mutate and develop resistance to antiretroviral drugs. The phenomenon is already well documented for HIV. Will influenza do the same? Could we end up with a 'super strain' of influenza for which we have no defences?

The European Surveillance Network for Vigilance against Viral Resistance (VIRGIL) is a Network of Excellence that aims to integrate and coordinate the activities of doctors and scientists from institutions across Europe who are investigating viral resistance. Hepatitis B and C, and influenza are the three primary diseases under scrutiny.

Coordinated by the French Institute for Health and Medical Research (INSERM), the network gives structure to Europe's previously fragmented research and unites experts in the field. VIRGIL offers coherence and coordination between more than 60 organisations from 14 European countries.

VIRGIL's 7 virtual platforms for research

The network's activities started in May 2004, supported by a €9 million grants from the EC over four years. It has structured its activities into seven distinct yet cooperating platforms. VIRGIL-SURVEIL ensures the use of uniform criteria for the collection and reporting of drug resistance across Europe and will establish a central database of information on patients who have received antiviral treatments. It is also helping to implement new clinical trials for novel antiviral agents, and to disseminate best practice in the use of drugs for which resistance has already appeared. VIRGIL-CLINVIR is working in conjunction with VIRGIL-SURVEIL to implement standardised laboratory and computer tools, clinical studies, and offers a centralised facility for identifying and characterising resistance. This platform is also archiving all identified resistant viruses into a centralized European repository.

These activities are strengthened by new cell, animal and computerized 3D-models that are being developed within the VIRGIL-MODELS platform as well as by a greater understanding of the mechanisms linked to the patient (immunological, genetic), that may predispose to the development of viral resistance (VIRGIL-HOSTS). VIRGIL-INNOTECH is supporting all this activity by developing the next generation tools for viral resistance research including new, faster technologies for resistance monitoring, sequence analysis and laboratory molecular studies.

VIRGIL-DRUGPHARM, meanwhile, supports researchers in their quest for new antiviral drug candidates. It provides a core facility to the network for drug synthesis, molecular modelling, candidate drug toxicity testing and pharmacokinetics studies.

Finally, the VIRGIL-IMPACT platform is evaluating the societal impact of drug resistance in terms of morbidity, monitoring and treatment costs, and assesses the cost/benefit of different approaches to prevent or combat the problem at the European level. It is also developing the VIRGIL online consultation tool that will disseminate to the doctor community the best practices in case of treatment failure with antivirals.

As a whole, the VIRGIL network aims to act like a 'virtual institute' on all aspects of antiviral drug resistance in Europe. VIRGIL means that Europe can comprehensively address the problem of resistance at an early stage. By staying one step ahead of the virus we can hopefully always remain in control.

Status (January 2006)

The influenza sub-group of the **VIRGIL-SURVEIL** platform has designed in 2005 a standardized swab form that will be used European wide. This standardized form has been implemented in several countries, and will be of help (1) to provide information on the current use of antivirals and (2) to collect clinical signs and symptoms associated to infections with resistant viruses. This information will be collected by individual countries, centralized by VIRGIL that will ultimately provide feedback via their web-site and at the VIRGIL symposium in Lyon (23rd May 2006). During 2006, active surveillance in dedicated patients groups will be implemented in 3 pilot countries. This will provide useful information in regards to the good medical practice, to the rate of emergence of resistant viruses, and to the proper use of antivirals in case of pandemic. In 2005, the **VIRGIL-CLINVIR** platform set up several technological and common facilities (central repositories) for the study of HCV, HBV and influenza resistance, together with organizing the quality insurance within the network and started using these facilities for clinical and virological work. Most of the organizational and equipment work has been done in the expected time frame, panels for quality insurance are being built, and the facilities are now available for more specific scientific studies, as shown by preliminary scientific results already generated. For **VIRGIL-MODELS**, the specific 2006 objectives for Influenza are : 1) Implementation of standardized NA assay for screening NA1 susceptibility of influenza viruses; 2) Further improvement and implementation of a robust cell culture assay for routine evaluation of drug susceptibility of influenza viruses; 3) Usefulness of human airway cell cultures for phenotypic analyses of influenza viruses determined; 4) In vitro assays for HA-receptor binding and M2-drug binding evaluated; 5) Implementation of reverse genetics systems for phenotypic analyses of AH3N2, AH1N1 and B viruses; 6) Implementation of NA expression system for determining effects of mutations in NA; 7) Structural explanation for differences in mechanisms of resistance of different influenza NA subtypes to NAIs; 8) Evaluation of the potential clinical significance of recent oseltamivir-resistant influenza viruses. The established **VIRGIL-HOST** research scheme will be employed to gain a better understanding of the mechanism of resistance development by analysing clinical isolates or respective genetically defined recombinant viruses at the level of alterations of cellular signalling and host immune response. The newly identified candidate compounds that show a reduced tendency to induce resistant influenza virus variants will be analysed for their suitability as antivirals in animal models.

In **VIRGIL-INNOTECH**, new cell lines have been discovered or refined both for Hepatitis C and influenza whilst DNA chip design for rapid genetic analysis of drug resistant viruses has been initiated. The EU-HCV sequence database was further expanded and several additional bio-informatics based tools were implemented and integrated in the HCVdb. A study of population dynamics of influenza A virus in the horse is underway.

The **VIRGIL-IMPACT** platform will continue its main 2005 activities in three directions: 1) Development of a decision support system "VIRGIL-Doc" for the management of individual patients with antiviral resistance, taking into account efficacy, side-effects and costs / Contribution to epidemic management; 2) action on Public Health Strategies; 3) Evaluation of VIRGIL activities. The specific objectives are the following for 2006: 1) Launch viRgil IT platform after needs

assessment, marketing and training workshop; 2) Launch first version of central knowledge database and patient registry; 3) Launch pilot version of web-based case-management system for antiviral drug resistance; 4) Report on reimbursement of antiviral drugs for hepatitis B, C and influenza in each European country; 5) Implementation plan for library/reference centre on relevant publications/reports; 6) First public report of ViRgil activities with particular reference to direct societal benefits and including comments on resistant virus circulating each year.

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Website

<http://www.virgil-net.org>