



EUROPEAN
COMMISSION

Community Research

EU-FUNDED RESEARCH PROJECT

Comparative structural genomics on viral enzymes involved in replication (VIZIER)

Time of action: VIZIER started in November 2004 and is scheduled to end in October 2009

EU budget (funding): €13 million

Abstract

This project aims to have a ground-breaking impact on the identification of potential new drug targets against RNA viruses by characterising the replicative machinery of a diverse set of viruses.

RNA viruses can cause gastroenteritis (responsible for more than 1 million deaths annually), measles (45 million cases and about 1 million deaths annually), influenza (100 million cases annually), dengue fever (300 million cases annually), enteroviruses and encephalitis (several million cases of meningitis annually), and hepatitis C (more than 180 million infected persons in the world). The SARS outbreak has dramatically demonstrated the extent of the economic cost of an epidemic caused by an emerging virus. And costs are rising every day, as many governments are forced to make costly arrangements to cope with the threat of bio-terrorism, which lists some deadly RNA viruses in its arsenal.

The VIZIER project team brings together leading authorities on RNA viruses in the EU and elsewhere, and many leading European structural biologists. It includes three partners with P4 facilities (an uncommon type of facility with a high-level of bio-security) as well as leaders in the field of structural genomics. The development of protocols for high-throughput (HTP) protein production, facilitated by national and European projects such as the pilot Integrated Project SPINE, means that a concerted programme of structure determination is now feasible.

In the framework of this project, the core enzymes/proteins of the replication machinery of 300 different RNA viruses, including strains of medical interest, will be characterised. Understanding the sequence, structure and function of these enzymes is expected to greatly advance our understanding of how RNA viruses replicate.

Regarding influenza, four drugs are currently available for the treatment of infections with influenza viruses. These are the first-generation anti-influenza drugs Amantadine and Rimantadine, and the second-generation anti-influenza drugs Oseltamivir (Tamiflu) and Zanamivir (Relenza).

However, influenza viruses become readily resistant to Amantadine and Rimantadine; H5N1 strains resistant to these drugs are already circulating in Asia. Oseltamivir and Zanamivir are more potent and resistance does not appear so readily. However, recently oseltamivir-resistant H5N1 strains have been identified in infected patients in Asia.

Since the resistance profiles of Oseltamivir and Zanamivir overlap to some extent, it is of utmost importance to have other drugs at hand that have a different mode of action (and thus

a different resistance profile). Scientists in VIZIER are studying various targets of the influenza replication cycle, including the non-structural proteins. Understanding the precise function and unravelling the structure of these proteins will be key to identifying compounds that inhibit their function and thus the replication of influenza viruses.

A unique feature of VIZIER when compared to other structural genomics projects, is the integration of a major structural effort within a broad multidisciplinary study, having virology upstream and target validation (lead design) downstream.

As a result, the implementation plan of the VIZIER project is structured into 6 interacting sections:

- (1) Bioinformatics, for genome annotation, target selection and data integration
- (2) Virus production and genome sequencing
- (3) HTP protein production
- (4) HTP crystallisation and structural determination
- (5) Target validation, to assess the function of enzymes and design strategies for virus inhibition
- (6) Training, implementation and dissemination.

Status (January 2006)

The status of each of the above mentioned sections is:

- (1) Bio-informatic tools have been established to annotate, predict and manage viral genomes and domains, and feed other sections.
- (2) Virologists have reached a fair throughput of target cDNAs and viral sequences.
- (3) Platforms are running quite smoothly and have proposed tractable proteins.
- (4) Crystallographers are studying the proteins obtained from their section 3 colleagues.
- (5) The first all-VIZIER successes have been recorded, with several crystal structures of druggable enzymes (polymerases and protease). Although not crystallised yet, several enzymes are now HTS-ready. A number of molecules have been identified that inhibit the replication of a variety of RNA viruses.
- (6) VIZIER is gaining in visibility worldwide. A workshop entitled "Discovery of Antiviral Compounds" is planned for April 2006 to disseminate results, better integrate the sections, establish contacts with chemists and the pharmaceutical industry, and demonstrate the VIZIER approach.

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FR – AFMB Architecture et Fonction des Macromolécules Biologiques, Marseille

FR – Alma Consulting Group SA, Lyon

NL – LUMC Leiden University Medical Center, Leiden

FR – UVE, Marseille

UK – NERC Natural Environment Research Council, Oxford

SE – SMI Swedish Institute for Infectious Disease Control, Solna

SK – SAS Institute of Zoology, Slovak Academy of Sciences, Bratislava

FR – Institute Pasteur, Paris

DE – IVTUD Institut für Virologie, Technische Universität, Dresden

FR – Bioxtal SA, Gif-sur-Yvette

UK – UOXF Chancellor, Masters and Scholars of the University of Oxford

DE – EMBL European Molecular Biology Laboratory Hamburg Outstation, Hamburg

IT – INFM National Institute for the Physics of Matter, Genova
IT – UNIPV University of Pavia
ES – IBMB Departamento de Biología Estructural / Instituto de Biología Molecular de Barcelona
UK – GPhL Global Phasing Limited, Cambridge
SE – ICMB Institute of Cell & Molecular Biology, Uppsala Universitet
DE – IFBL Institut für Biochemie, Universität Luebeck
BE – REGA Rega Institute for Medical Research, Katholieke Unversiteit Leuven
IT – UNICA Università degli Studi di Cagliari, Cagliari
DE – BNI Bernard Nocht Institute, Hamburg
GABON – Institut de Recerche pour le Developpement, Gabon
RU – IPCB-MSU Moscow State University, A.N. Belozersky Institute of Physico-Chemical Biology
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External collaborators/contacts:

CA – SPP Special Pathogens Program, National Microbiology Laboratory, Canadian Science Centre for Human and Animal Health, Winnipeg
US – CDC Centers for Disease Control and Prevention, Atlanta

Website

<http://www.vizier-europe.org/>