



<b>Project number</b>	IST-2004-027173	<b>Tot Funding</b>	2.143.000 €
<b>Starting date</b>	01/01/2006	<b>Duration</b>	30 months
<b>Project partners:</b>			
Informa S.r.l. (coordinator) - ITALY			
Università degli Studi di Siena - ITALY			
Karolinska Institutet Karolinska - SWEDEN			
Universitaetsklinikum Koeln - GERMANY			
IBM Israel – Science and technology LTD - ISRAEL			
Max-Planck Gesellschaft zur Foerderung der Wissenschaften e.v. – GERMANY			
MTA KFKI Reszecske-ES Magfizikai Kutatolntezet - HUNGARY			
Kingston University – UK			

### ***Project objective(s)***

The *EuResist* project aims at developing a European integrated system for clinical management of antiretroviral drug resistance. The system will provide the clinicians with a prediction of response to antiretroviral treatment in HIV patients, thus helping the clinicians to choose the best drugs and drug combinations for any given HIV genetic variant. To this end a huge European integrated data set will be created, linking some of the largest existing resistance databases.

### ***The problem***

While combination antiretroviral therapy has made HIV infection a treatable condition, eradication of infection is not yet achievable and antiretroviral therapy needs to be administered as a prolonged, possibly lifelong treatment. Long-term toxicity, difficulty in adhering to complex regimens, possible pharmacokinetics problems, and intrinsically limited potency are all factors favoring the selection of drug-resistant viral strains. Development of drug resistance is nowadays a major cause for treatment failure.

### ***The “old” solution***

The basic method for defining the drug resistance profile of a given virus population implies culturing the virus in the presence of each single drug and measuring the extent of virus replication in a well controlled virus-cell system. Unfortunately, considerable efforts are required to develop and standardize a test of this kind (‘phenotypic’ assay). Moreover, inferring clinical resistance from in vitro data is not straightforward, particularly for some drugs.

Recent advances in molecular diagnostics have made available a more practical and cost-effective approach to drug resistance testing, based on direct sequencing of the relevant regions of the virus genome (genotype). Mutations detected in the virus genotype are then used to infer the drug susceptibility profile based on known correlations between genotype and phenotype.

These methods, still immersed in a phenotype-based theoretical framework, provide predictions which can be inaccurate for clinical purposes, particularly considering that both phenotypic and genotypic assays provide an estimate of susceptibility to single drugs while three- or four-drugs combinations are commonly used in vivo.

### ***The EuResist proposed solution***

A novel approach is proposed which is based on using **viral genotype data integrated with treatment response data from clinical practice** to predict the resistances of a given HIV genotype.

This strategy bypasses the genotype-phenotype correlation step and points directly to indicate the most effective drugs and drug combinations on the basis of the available genotype data integrated with clinical data.

In line with this approach, EuResist aims at

- (i) integrating biomedical information from three large and expanding databases in different European countries collecting the required critical mass of historical and prospective data
- (ii) developing and validating models for effective prediction of the response to treatment based on HIV genotype and additional clinical information,
- (iii) making the predictive system publicly available on the web for optimization of antiretroviral treatment.

More specifically the project has the following scientific and technological objectives:

**Integration of genotype-response data from several national initiatives.** The already existing ARCA database (one of the biggest in the world – Italy), AREVIR database (Germany) and data coming from Karolinska Infectious Diseases and Clinical Virology dep. will be joined in a comprehensive new database. It will include treatment histories, the standard surrogate markers of treatment response and the sequence of the relevant part of the HIV genome (genotype). (M1 – month 12)

**The noise and the entropy of the DB** will be studied in order to cope with the problem of data information rate and correspondence to reality (errors, noise...). **The possibility to cluster the viral genotypes** and to define evolution trees of genotypes will be studied. (month 12)

Intensive work will be carried out on **the definition of ‘standard datum’**, an essential task aimed at determining the minimum number of variables that maximise the information. (month 6). Key factors include the content of the DB, medical considerations and updated knowledge on viral dynamics.

**A system will be developed made of models for prediction** using information derived from the large resulting resistance database.

Different methods will be studied to realise the predictive engine (M2 - month 18):

- a. Case-Based Reasoning
- b. Bayesian Networks and Support Vector Machines
- c. mutual-information based data-mining
- d. graph-theoretical methods
- e. evolutionary models.

The different methods will be compared and **combinations of these methods** will be studied to realise the final **EuResist Predictive System**. (M3 - month 24)

The System will be evaluated against the existing methods on the base of prediction correlation and standard error. (month 30)

**Networking activity** is foreseen and already started with Virolab project and with other projects in the same area.