

# Virtual Physiological Human

## Projects portfolio

Concertation Meeting  
Brussels, Belgium  
October, 22 2008



## Introduction

This resource book provides an overview of the set of Virtual Physiological Human (VPH) research projects managed by the ICT for Health unit of the Information Society and Media General Directorate, which are funded under the Sixth and Seventh framework Programme for Research and Development. This resource book has been produced for the ICT-BIO 2008 conference on Computer Modelling and Simulation for Improving Human Health. More information and reports about this conference can be found online at the website [http://ec.europa.eu/information\\_society/events/ict\\_bio/2008](http://ec.europa.eu/information_society/events/ict_bio/2008).

## VPH rational

At the core of the VPH lies the idea of translating all functions of the human body into a coherent set of multi-scale computer models. The scales of modelling span spatially from the whole body down to the cells and the proteins they synthesise, and temporally from years to microseconds. The VPH framework will provide ICT tools for developing patient-specific computer based models and simulations using specific patient data allowing for personalised and predictive healthcare. These multi-scale models will be used to develop an integrative approach to predicting the risk in developing a disease and to improving the diagnosis and treatments of these diseases. During drug development, such organs models could be used to assess the drug effect on a specific population.

The Virtual Physiological Human will revolutionise the way health knowledge is produced, stored and managed as well as the way in which healthcare is currently delivered. Results will include personalised disease predictions, earlier diagnoses, better surgery planning and training, and a better understanding of the links between genes, diseases and treatments. The use of predictive models will significantly improve diagnosis, treatment and monitoring of patients, and the success of the VPH challenge will have an impact on the way health knowledge is understood, formalised, represented, communicated with regards to both healthcare and economy. The area attracts not only the medical informatics, bioinformatics and biomedical engineering communities, but also capable of generating significant interest from the large pharmaceutical industries as well as the small and medium sized biotechnology companies.

A number of projects of the Sixth framework programme have been pioneering the Virtual Physiological Human, which has become one of the three objectives of Challenge 5 "Towards sustainable and personalised healthcare"<sup>1</sup> of the Seventh framework Programme.

## FP6 call 4 – 13 pioneer projects in the VPH field

Biomedical informatics (BMI) is a multidisciplinary field that arises from the synergy of medical informatics and bioinformatics. The main mission of BMI is to provide a framework for developing, integrating and sharing biomedical knowledge related to human health from very different research disciplines such as genomics, proteomics, clinical

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<sup>1</sup> [http://cordis.europa.eu/fp7/ict/programme/challenge5\\_en.html](http://cordis.europa.eu/fp7/ict/programme/challenge5_en.html)

research and epidemiology. BMI deals not only with the integration of health related data on different levels (molecular, cellular, tissue, organ, person and population), but also with computationally demanding tasks of data mining, modelling, simulation and visualisation.

BMI was addressed in the FP6 IST Call 4 "Integrated Biomedical Information for Better Health". Out of the set of projects resulting from this call, twelve research projects and one research roadmap (STEP) can be considered as the pioneers of the VPH concept as they are integrating multi-levels data in view of the modelling and simulation of human functions.

These 13 projects listed in the table below are described in this resource book.

<b>FP6 call 4 projects</b>
ACGT
ASSIST
EURESIST
Health-e-Child
I KNOW
ImmunoGrid
LHDL
Multi-Knowledge
NEURIST
Sealife
SHARE
STEP
VIROLAB

## **FP7 call 2 – First VPH call**

A total of €72 million was allocated to this field in the FP7 Call 2, which resulted in a portfolio of 15 projects that started mid-2008. Within this portfolio, 12 collaborative research projects (e.g. 3 IPs and 9 STREPs) will focus on the integration of computer based multi-scale models and/or data processing techniques on multi-level biomedical data appropriate for clinical applications in the following three areas:

- simulation for surgical training, planning and intervention;
- prediction or early diagnosis of disease by integrating patient history with biomedical imaging (from X-rays, scans and internal camera examination of the patient as well as microscopic examination of cells removed from the body);
- simulation environments for assessing the efficacy and safety of specific drugs.

One network of excellence (VPH-NoE) will integrate the European research in the field of modelling and simulation of human anatomy and physiology. The work of this NoE will strengthen the VPH community by providing services and an environment for collaboration.

The Commission also supports the use of grid capabilities (i.e. harnessing many computers across different sites in a network to increase computing power) to process the huge quantities of data involved. FP7 Call 2 included a specific call for a project to boost international co-operation with research partners in Latin America, around the

Mediterranean and in the western Balkans in order to strengthen European industry's leadership in the field of medical imaging, which led to the funding of the project ACTION-GRID.

Given that many partners in different institutions and countries may be involved in processing of patient-specific data, research work on the security and privacy aspects of such data is of particular importance. Therefore, the project RADICAL has been funded to investigate these security and privacy aspects in the context of the VPH.

The table below lists these 15 projects.

<b>FP7 call 2 projects</b>
Action-Grid
ARCH
ARTreat
CONTRA CANCRUM
euHeart
HAMAM
IMPPACT
Neo Mark
PASSPORT
PreDICT
Predict AD
RADICAL
VPH NOE
VPH2
VPHOP

The following pages list all the projects which forms part of the VPH initiative.

## FP6 Projects

- ❖ @NeurIST
- ❖ ACGT
- ❖ ASSIST
- ❖ EURESIST
- ❖ Health-e-Child
- ❖ I KNOW
- ❖ ImmunoGrid
- ❖ LHDL
- ❖ Multi-Knowledge
- ❖ Sealife
- ❖ SHARE
- ❖ STEP
- ❖ VIROLAB

# @neurIST

## Integrated Biomedical Informatics for the Management of Cerebral Aneurysms

### Towards integrative decision support systems for personalised brain aneurysm rupture risk assessment and treatment

#### Objectives of the project

When considered separately from other cardiovascular diseases, stroke ranks third among all causes of death, after heart disease and cancer. Worldwide, 3 million women and 2.5 million men die each year from stroke. Hemorrhagic stroke occurs when a blood vessel, typically an aneurysm, ruptures inside the brain. This often leads to severe disability or death. Despite considerable advances in treatment, rupture is associated with exceptionally high levels of morbidity and mortality - about 33% in each case.

Currently, invasive or minimally invasive treatment is offered to almost all patients because there is insufficient evidence to support a decision of nonintervention. It is the primary thesis of **@neurIST** that the process of cerebral aneurysm diagnosis, treatment planning and development is significantly compromised by the fragmentation of relevant data. To address this issue, **@neurIST** is developing a complete IT infrastructure for the management and processing of heterogeneous data associated with the diagnosis and treatment of cerebral aneurysms.

**@neurIST** will transform the management of cerebral aneurysms by providing new insight, personalised risk assessment and methods for the design of improved medical devices and treatment protocols.

#### Project Description

**@neurIST** is a European initiative within the Sixth Framework Programme Priority 2 of the Information Society Technologies IST. This 4 year multidisciplinary project started on January 1st 2006 and involves 28 public and private institutions from 12 European countries.

The **@neurIST** project will:

- Develop a new procedure and IT-support system for cerebral aneurysm management.
- Identify and collect all publicly-available, relevant and strategically important data from scientific studies.
- Deliver a rich, multiscale information processing chain that will provide new diagnostic indexes and insight into the process of aneurysm development and rupture.
- Develop a set of scalable and reusable integrative suites and demonstrate their value for revolutionizing the understanding and management of cerebral aneurysms.

**@neuLink** will create an IT environment for the identification of genes associated with the disease and for the integrated analysis of genetic epidemiology and clinical data.

**@neuFuse** will provide an open source environment to fuse diagnostic and modelling data (using state of

#### Scenario

As a result of a car accident, a 40 year old man is examined for possible lesions. An unrelated and asymptomatic cerebral aneurysm is discovered. Subsequent angiography provides improved image data for characterisation of aneurysm morphology. Blood samples are taken and the patient is screened **@neurIST** associated genes, by data mining. A rupture risk assessment is also carried out. The clinician verifies its presence in the patient by querying the patients' EHR and retrieving the results of her biochip analysis that discloses a positive test. The patient is informed about the risks/benefits of surgical intervention. On the basis of all available information, a personalised treatment guideline which suggests that endovascular treatment would be beneficial in this case.

the art segmentation techniques, multimodal registration and advanced visualisation techniques) into a coherent representation of the patient's condition.

**@neuRisk** will produce a personalised risk assessment and treatment guidelines by integrating all available information.

**@neuEndo** will deliver an innovative IT system for supporting the design of implantable devices (such as coils and stents) and intervention planning by simulation of the structural, haemodynamic and biological response to intervention. This will include advanced numerical-simulation tools to predict the occurrence of device-related thrombosis and drug elution.

The **@neurIST** infrastructure will not only support computationally demanding tasks such as complex modelling and simulation (@neuCompute) but also enable access to health data distributed in public and protected databases distributed all over the world (@neuInfo).

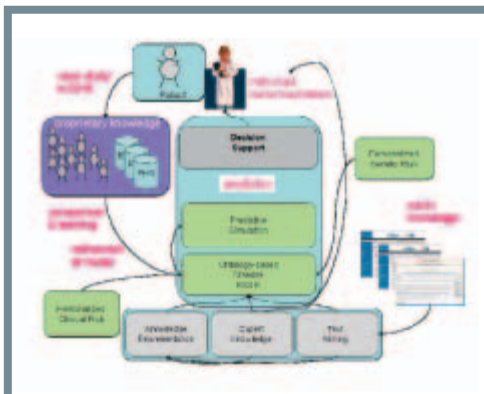
### Expected Results & Impacts

**@neurIST** will reduce health care cost by optimally targeting the relevant patient population, thus avoiding unnecessary and potentially risky interventions, and improving methods of minimally invasive treatment.

Measurable benefits of @neurIST will include the quantification of risk, including that of intervention and non-intervention, and the application of the data to improve the personalized design of endovascular devices.

By providing an objective measure of risk to the decision making project, based on all available data, @neurIST will reduce patient anxiety and unnecessary treatment by identifying aneurysms that do not have a high risk of rupture.

The potential economic benefit of this system in Europe is enormous: taking into account the prevalence of this disease [1-5%], the annual rupture rate [0.2-1%], and the average treatment and 1st-year follow-up care costs of patients [50kEuro], it is estimated that, in Europe alone, unnecessary interventional or surgical procedures costs are in the order of thousands million Euros per annum.



## @neurIST

**Integrated Biomedical Informatics for the management of Cerebral Aneurysms**

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**Timetable:** from 01/06 – to 12/09

**Total cost:** € 17.356.730,92

**EC funding:** € 12.605.239

**Instrument:** IP

**Project Identifier:**

IST-2004-027703

**Keywords:**

Decision support systems, eHealth networks and architectures, health promotion, patient safety, risk assessment

# ACGT

## Advancing Clinico-Genomic Clinical Trials on Cancer

**ACGT** aims to present the ‘next-step’ in cancer research and fill-in the technological gaps of clinical trials targeting two forms of cancer: breast cancer and *paediatric nephroblastoma*. **ACGT** will develop a Biomedical GRID infrastructure supporting seamless mediation services for sharing clinical and genomic expertise. It will help to identify quicker and more efficiently the characteristics that determine what form of treatment best suits which patient.

### Objectives of the project

**ACGT** aims to provide researchers and patients with the best means and resources to fight cancer.

**ACGT** is working towards the rapid identification of cancer profiles and best treatments.

The **ACGT** project will:

- Define common standards of data storage at each level of investigation.
- Develop new ontologies for cross-referencing terms and their biological contexts.
- Implement a bio-medical GRID infrastructure offering seamless mediation services for sharing data and data-processing.

**“ACGT hopes to trigger the emergence of latent clinico-genomic synergies to ensure faster diagnosis and more efficient therapy”**

**ACGT** will therefore deliver a unifying infrastructure allowing cancer researchers to share their data and to benefit from the innovative informatics tools that are being developed by other researchers.



### Project Description

The **ACGT** work plan relies on 3 core activities:

- **INTEGRATION.** Creation of advanced databases that combine clinical history; symptoms and signs; laboratory and histopathology; medical imaging; procedural and surgery results; and genetic data, taking into account standard clinical and genomic ontologies.
- **KNOWLEDGE GRID.** Development of Knowledge Grid infrastructures for the distributed mining and extraction of knowledge from data repositories offering information services in the domain of biomedical informatics and creating a highperforming computational environment to: (a) cope with the huge-amount of both clinical and genomic data; and (b) meet the computationally costly data processing needs.
- **CLINICAL TRIALS.** Design and implementation of specific clinico-genomic trials based on: (a) clear-cut research objectives for cancer-related clinical and genomic inquiries; (b) incorporation of the clinical-trials in an integrated GRID environment enriched with knowledge-discovery capabilities; and (c) interpretation of results into standardised clinical guidelines and protocols.

### Scenario

Imagine that for selected cancer patients, biopsies are taken before, during and after treatment, made anonymous and the analyses stored promptly in an accessible fashion. Imagine also that the patient's data can readily be compared with those from other trials. And imagine that one can search clinical and other databases in hours rather than months.



## Expected Results & Impacts

The completion of the Human Genome Project sparked the development of many new tools for current biomedical research.

The combination of clinical and genetic information to cure paediatric nephroblastoma cancer has resulted in up to 85% treatment success rate.

The **ACGT** project aims to develop a GRID platform to support and stimulate further exchanges of both clinic and genetic information, with a particular focus on breast cancer treatment. **ACGT** hopes to trigger the emergence of latent clinico-genomic synergies to ensure faster diagnosis and more efficient therapy.

In this perspective, the **ACGT** project will:

- Provide the advanced tools needed by biomedical scientific researchers in their daily lab or clinical work, so that they are properly equipped to “innovate”.
- Facilitate exchanges and interactions among clinical and genetic cancer researchers so they pool their expertise in identifying the best treatment for each and every patient.
- Allow discoveries made in laboratories to be quickly transferred to clinical management and treatment of patients. In former times, the discovery of diseases such as tuberculosis or diabetes did not immediately lead to therapies. In some cases, it took more than 60 years to improve treatment. New technologies such as insilico experimentation, Grid or data and text mining are contributing to reducing these periods of time.
- Contribute to the scientific development of new biomedical informatics approaches, where Europe is already leading the initiatives in the field, but strengthening the competitive efforts of industry to reach economic success.

### Keywords:

Rapid Identification;  
Integration Knowledge Grid;  
Clinical Trials

## A C G T

### Advancing Clinico-Genomic Clinical Trials on Cancer

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- University van Amsterdam - Philips Electronics Nederland B.V. (NL)
- Association Hospitaliere de Bruxelles – Centre Hospitalier Universitaire Bordet – Custodix - Facultes Universitaires Notre-Dame de la Paix (BE)
- Institut Suisse de Bioinformatique (CH)
- Lunds Universitet (SE)
- Universidad de Malaga - Universidad Politecnica de Madrid (ES)
- Fraunhofer-Gesellschaft zur Foerderung der angewandten Forschung - Unisersitaet Hannover - Unisersitaet des Saarland - Unisersitaet Hamburg (DE)
- Instytut Chemii Bioorganicznej pan w Poznaniu (PL)
- S.C. SIVCO ROMANIA SA (RO)
- The Chancellor, Masters and Scholars of the University of Oxford (UK)
- Hokkaido University (JP)
- Istituto Europeo di Oncologia s.r.l (IT)

**Timetable:** from 02/06 – to 01/10

**Total cost:** € 16.747.206

**EC funding:** € 11.887.000

**Instrument:** Integrated Project

**Project Identifier:**

IST-2004-026996

# ASSIST

## Association Studies Assisted by Inference and Semantic Technologies

**ASSIST aims to provide medical researchers of cervical cancer with an integrated environment that will virtually unify multiple patient record repositories, physically located at different laboratories, clinics and/or hospitals. Researchers will be able to combine phenotypic and genotypic data and perform association studies on larger sets of patient records from several clinics.**

### Objectives of the project

Cervical cancer is the second most common cancer worldwide with 60,000 new cases and 30,000 deaths each year in Europe alone, despite a significant progress in early diagnosis and treatment. Infection by the human papillomavirus (HPV) is accepted as the central risk factor for cervical cancer. However, it is unlikely to be the sole cause for developing cancer. Ongoing research investigates the role of specific genetic, environmental factors in determining HPV-persistence and subsequent progression of disease.

Association studies among genetic characteristics and environmental agents and virus characteristics can suggest pathogenetic mechanisms that will provide new markers of risk, diagnosis and prognosis, and possibly treatment.

The main objectives of **ASSIST** are to:

- Unify multiple patient records repositories
- Automate the process of evaluating medical hypotheses (association studies type)
- Allow researchers to combine phenotypic and genotypic data

- Provide an inference engine capable of statistically evaluating medical.
- Offer expressive, graphical tools for medical researchers to post their queries.

### Project Description

In order to facilitate association studies on genotypic and phenotypic factors related to cervical cancer, **ASSIST** resorts to medical inferencing applied on real patient data. Following the semantic approach, **ASSIST** will rely on available standards and recent research achievements in the area of semantics and soft computing in order to build its Medical Knowledge Base. The targeted virtual unification of the participating archives and interpretation of their content relies upon the semantic indexing of their records. Unlike the conventional way of treating stored medical information as alphanumeric data structures whose interpretation is carried out by the human user, **ASSIST**'s inference engine will:

*“ASSIST will offer virtual unification of participating medical archives and interpretation of their content”*

### Scenario

Suppose that three gynaecology clinics (A, B, C) join ASSIST mutually allowing access to their patient data. Researcher X from clinic A decides to contact a cross sectional study to test her hypothesis that “MTHFR gene polymorphism increases the risk of developing high-grade squamous intraepithelial lesions or invasive cancer”. Dr. X is able to find only 35 suitable cases in clinic A but, using ASSIST, she manages to locate a total of 240 cases that were tested against MTHFR polymorphism in all three clinics. 130 of them were positive. She feels much more confident now. Through ASSIST's graphical query language she requests a “certainty degree” regarding her hypothesis. ASSIST translates the initial hypothesis into a set of queries issued to all the participating medical repositories. Statistical analysis of the retrieved data results in the requested “certainty degree”.

- support the virtual unification of the participating archives by translating medical concepts into syntactic values that the legacy systems of the participating archives may perceive and
- undertake the whole process of statistically evaluating medical hypotheses and producing medically important associations based on the collected data.

In addition to the inference engine, **ASSIST** will incorporate two important interfacing modules:

- a) The first is the interface to its users, mainly medical researchers and geneticists. This graphical interface will be medical knowledge aware in the sense that it will allow expression of domain specific queries and particular hypotheses by referring to medical ontologies contained in the Medical Knowledge Base.
- b) The second type includes the interfaces to the participating medical archives and will support exchange of data between them and **ASSIST**'s core engine and in a way transparent to the end user.

**ASSIST** will respect and promote the ethical principles that guide current medical research activities and will be designed in full compliance to the legal and ethical national and EU requirements and code of practice. Special care will be taken so as to avoid violation of any form of patient privacy during system operation. To this end, only anonymised patient information will be handled by the **ASSIST** system, produced by state-of-the art anonymisation techniques and standards.

### Expected Results & Impacts

Upon successful completion, the **ASSIST** platform aspires to function as an important technology enabler for cervical cancer research by allowing any medical group active in this area to use its facilities and/or contribute their own results. Therefore, **ASSIST** will address the need of large sample sizes and will help to promote collaborative international biomedical research in the area of cervical cancer.

**ASSIST** will enable the cervical cancer medical researcher to use various HPV data, environmental, lifestyle and medical history items from diverse medical records, with minimal effort and cost. The investigation of associations among all these factors and genetic data will identify risk factors that can then be used at the point of care by gynecologists to identify women, who are at high risk of developing cervical cancer. Consequently, low-risk women can avoid costly and potentially morbid diagnostic and therapeutic procedures while high-risk women will receive appropriate treatment.

Through **ASSIST**, clinical researchers will be able to ask complex questions in order to extract the subset of data they need. As a result, old examination results and past findings will be easily reusable. This feature is expected to be of particular benefit for cervical cancer, whose evaluation requires long-term studies including also referral to patients' antecedents and descendants.

## A S S I S T

### Association Studies Assisted by Semantic and Inference Technologies

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- SWORD Technologies (LU)
- Aristotle University of Thessaloniki (GR)
- Birkbeck College, Univ. of London (UK)
- Benchmark Performance Ltd (UK)
- National Technical University of Athens (GR)
- Ebiolntel (ES)
- Pouliadis Associates Corporation (GR)
- Centre for Research and Technology Hellas-Informatics and Telematics Institute (GR)

**Timetable:** 01/06 – 12/08

**Total cost:** € 4,190,946

**EC funding:** € 2,630,000

**Instrument:** STREP

**Project Identifier:**

IST-2002-027510

**Keywords:**

biomedical informatics, electronic health records, eHealth networks and architectures, association studies, health professionals' knowledge, semantic inference

# EuResist

## Integration of viral genomics with clinical data to predict response to anti-HIV treatment

The **EuResist** project aims to develop a European integrated system for the clinical management of antiretroviral drug resistance. The system will predict patient reactions to antiretroviral treatments for HIV, thus helping clinicians to select the most appropriate drugs and drug combinations for any given HIV genetic variant. To this end a huge European integrated data set will be created, linking three of the largest existing resistance databases: ARCA, AREVIR and Karolinska.

### Objectives of the project

While combination antiretroviral treatment has made HIV a treatable condition, eradication of the infection has not yet been achieved. Treatment needs to be administered as a prolonged, possibly lifelong treatment. Long-term toxicity, difficulty in adhering to complex regimes, possible pharmacokinetics problems, and intrinsically limited potency are all factors favouring the selection of drug-resistant viral strains. The development of drug resistance is now a major cause for treatment failure.

**EuResist** aims to:

- integrate biomedical information from three large and expanding databases in different European countries collecting the required critical mass of historical and prospective data;
- develop and validate models for the effective prediction of responses to treatment based on HIV genotype and additional clinical information;
- make the prediction system available on the web for the optimisation of antiretroviral treatment.

**“The EuResist integrated data set will be the largest in the world”**

### Project Description

The **EuResist** novel approach 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 the most effective drugs and drug combinations on the basis of the available genotype data integrated with clinical data.

The **EuResist** integrated data set will be the largest in the world. It will result from the merging of three of the largest existing resistance databases: ARCA (I), AREVIR (D) and Karolinska one (S).

The **EuResist** integrated prediction system will use an array of predictors, each of them based on novel or state of the art method. The vastness of genetic and clinical data will lead to new approaches in the analysis of qualitative data:

**1.** Case Based Reasoning is a state-of-the-art method in Artificial Intelligence but has never been applied to HIV due to the lack of large data sets and difficulty to define an appropriate method.

**2.** Machine learning algorithms. The **EuResist** project will use hybrid algorithm merging the state-of-the-art generative and discriminative techniques (Bayesian networks) and support vector machine (SVM).

### Scenario

A doctor connects via Internet to **EuResist** web page. He will input the HIV genotype data and possibly CD4 and HIV RNA levels as well as information on past exposure to antiretroviral. He could indicate the treatment regime he would like to use. The web server sends this data to the Prediction System that runs some sets of equations. It returns with an ordered list of the most effective drug combinations and also of the effectiveness of treatment using a single drug. If the user did input CD4 and HIV RNA values, the system will return the trajectory and variations between these two parameters. Depending on the amount of information input, and of the available driving data, a measure of the confidence of the output data will be provided.

**3. Graph-theoretical methods.** **EuResist** adopts a statistical approach to analyse the organisation of genetic material. Graph-theoretical methods will be used to reveal the organisational and functional structures of genetic material, possibly identifying new lines in medical treatment.

**4. Evolutionary Models.** Better understanding of viral evolution under the selective pressure exerted by specific drug combinations will form an important basis for the rational design of therapies and therapy sequencing. An improved understanding of the fitness landscape of HIV under HAART will be beneficial in an evolutionary model or as features for a statistical learning method.

**5. Fuzzy Logic.** The existing fuzzy logic based predictor will be enhanced by incorporating the new standard data and training into the large database.

The predictive System will be validated through a comparative study testing the prediction tools developed, together with the reference rules-based algorithms most commonly used for HIV genotype interpretation.

### Expected Results & Impacts

The **EuResist** project, conceived to significantly improve the treatment of HIV patients in Europe will enhance the most sophisticated predictive models, by combining, in a unique and efficient way, the latest techniques or, promising techniques which have yet to be applied.

- Innovation aspects:
  - Expanded geographical representativeness of HIV variants.
  - Statistical and bioinformatics techniques used to develop the predictive engines.
- Expected advantages:

Expected advantages of the **EuResist** system include not only more effective care for patients but also decreased cost of therapy through reduced improper use of antiretroviral drugs and the resulting fall in the occurrence of infections combined with an improvement of the patient's immune status.

The project can also be considered as a pilot for HCV and HBV since a large antiviral treatment intervention have been started and the chronic nature of both of these viruses will lead to increased resistance to existing drugs. In Europe HBV and HCV are in fact more common than HIV.

## EuResist

**Integration of viral genomics with clinical data to predict response to anti-HIV treatment**

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- Karolinska Institutet (SE)
- Universitaetsklinikum Koeln (DE)
- IBM Israel - Science and technology LTD (IL)
- Max-Planck Gesellschaft zur Foerderung der Wissenschaften e.v. (DE)
- MTA KFKI Reszecske-ES Magfizikai KutatoIntezet (HU)
- Kingston University (UK)

**Timetable:** from 01/06 – to 06/08

**Total cost:** € 2.973.355

**EC funding:** € 2.143.000

**Instrument:** STREP

**Project Identifier:**  
IST-2004-027173

### Keywords:

biomedical informatics,  
decision support systems,  
HIV,  
drug resistance,  
artificial intelligence



# Health-e-Child

The Health-e-Child project aims at developing an integrated healthcare platform for European paediatrics, providing seamless integration of traditional and emerging sources of biomedical information.

## Objectives of the project

The **goal of Health-e-Child is to become the universal biomedical knowledge repository and communication conduit for the future**, a common vehicle by which all clinicians will access, analyse, evaluate, enhance and exchange biomedical data of all forms. It will be an indispensable tool in their daily clinical practice, decision making and research. It will be **accessible at any time and from anywhere**, and will offer a friendly, multi-modal, efficient and **effective interaction** and exploration environment. Pivotal to this outlook are Health-e-Child's breakthroughs in personalised medicine through integrated disease modelling, knowledge discovery and decision support.

*"The core of Health-e-Child revolves around biomedical information analysis for the advancement of personalised medicine"*

Fashioned around three paediatric diseases with at least partly unknown causes, classification and/or treatment outcomes - heart diseases (right ventricular overload [RVO], cardiomyopathies), inflammatory diseases (juvenile idiopathic arthritis [JIA]), and brain tumours (gliomas), Health-e-Child is building the **enabling tools and services** that **improve the quality of care and reduce its cost by increasing efficiency**, through:

• *Integrated disease models,*

• *Database-guided decision support systems,*

• *Cross modality information fusion and data mining for knowledge discovery.*

Key to the Health-e-Child system is the establishment of *multi-site, vertical, and longitudinal integration* of biomedical data, information and knowledge delivered via a Gridbased platform, supported by robust tools for search, optimisation and matching processes.

The core of Health-e-Child revolves around its efforts dedicated to meeting the challenges entailed in *biomedical information* analysis for the advancement of personalised medicine.

## Project Description

The following are a few examples of Health-e-Child's ongoing research activity.

### *Disease Modelling in Cardiology*

Health-e-Child's research goals are:

- identifying significant parameters for subtypes of cardiomyopathies that could lead to indications for additional genetic tests,
- adapting generic models to clinical data to extract patient-specific high level discriminative features for decision support and knowledge discovery, and
- validating new measurements for diagnosis.

### *Decision Support in Cardiology*

The project is currently developing tools for:

- monitoring RVO and decision support based on similarity search on specified features and association rules extraction.
- The prediction of whether atrial septal defect (ASD) will close by itself or will become larger, thereby precluding trans-catheterisation.

### *Knowledge Discovery in Rheumatology*

Applied to JIA, Health-e-Child focuses on:

- identifying gene variant combinations (haplotypes) correlated with particular diseases (bones/joints erosion)
- comparing the presence of different proteins in fluid at different stages of the disease to discover behaviour of cells close to fluid.

## Scenario

A child is born in a family in which there was an occurrence of idiopathic Dilated Cardiomyopathy (DCM). Her biomedical record is cohesively integrated. It is shared through a coherent view at different clinical sites. An intelligent classification algorithm combines the generative and the discriminative models in an optimal way and confirms an increased risk of DCM. Imaging data show left ventricle enlargement. An intelligent retrieval system for examining similar cases helps the doctor. A prevention/treatment plan especially fitted for her genomic or proteomic profile and existing symptoms is suggested.

- improving current classification of JIA subtypes, and identifying homogeneous groups of clinical features elaborating explicit criteria for the early prediction of disease outcome/evolution
- developing image-based methods which rapidly indicate the capacity of drugs to stop/slow down disease evolution (automatic suggestion of drug prescriptions)
- analysing correlation between genomic, proteomic, clinical and image data, establishing a candidate gene set (responsible for bone remodelling) for study.

#### Knowledge Discovery in Brain Tumours

The priority research goals of Health-e-Child in this area are:

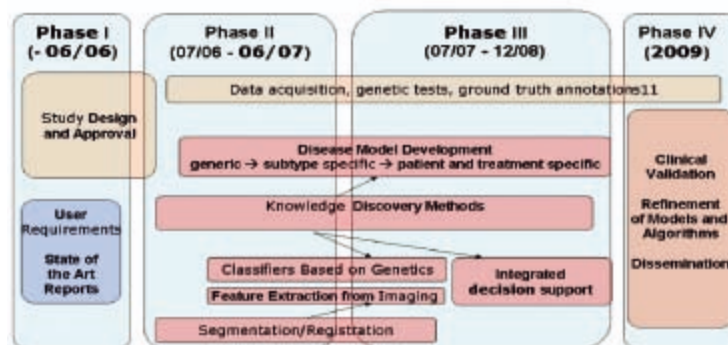
- verifying the diagnosis/categorization of low-grade gliomas
- correlating clinical, imaging, and genomic data
- correlating prognosis with tumour origin site
- defining prognosis (e.g., correlations with spectroscopy)
- suggesting treatment strategies
- predicting outcome
- providing more precise classification of diseases
- detecting correlations between age and outcome and between genetics and outcome
- elaborating meta-analyses of published findings.

### Expected Results & Impacts

**Health-e-Child** will have substantial impact on:

- **Strategy:** Enhancing level and quality of medical services offered in Europe, advancing medical research, improving competitiveness in the area of medical service provision, facilitating the adoption of new policies in member state.
- **Technology:** Bringing forward information-based medical technology and integrating mostly separate areas, i.e., vertical information integration, advanced medical querying, Grid infrastructures, disease modelling, medical imaging, knowledge discovery and data mining, and decision support.
- **Society and economy:** Improving the success rate in resolving difficult medical cases, saving children's lives. Furthermore, such improved medical decision making will often result in lowering medical cost and/or treatment duration.

### Clinical and Application Roadmap



## Health-e-Child

#### Coordinator/Executive Board Chairman:

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#### Governing Board Chairman

Alok Gupta - Siemens Medical Solutions

#### Project Management Team Leader

Edwin Morley-Fletcher - Lynkeus, S.r.l.

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- Lynkeus SRL, Rome, (IT)
- I.R.C.C.S. Giannina Gaslini, Genoa, (IT)
- University College London – Great Ormond Street Children's Hospital, London, (UK)
- Assistance Publique Hopitaux de Paris – Necker, Paris, (FR)
- European Organisation for Nuclear Research (CERN), Geneva, (CH)
- Maat G Knowledge, Toledo, (ES)
- University of the West of England, Bristol, (UK)
- University of Athens, Athens, (GR)
- DISI University of Genoa, Genoa, (IT)
- The French National Institute for research in Computer Science and Control (INRIA), Sophia Antipolis, (FR)
- European Genetics Foundation, Bologna, (IT)
- Aktsiaselts ASPER BIOTECH, Tartu, (EE)
- Gerolamo Gaslini Foundation, Genoa, (IT)

**Timetable:** from 01/06 to 12/09

**Total cost:** € 16.701.753

**EC funding:** € 12.186.270

**Instrument:** IP

**Project Identifier:**

IST-2004-027749

#### Keywords:

integrated healthcare platform;  
decision support; data mining.

## *I-Know*

# Integrating Information from Molecule to Man: Knowledge Discovery Accelerates Drug Development and Personalized Treatment in Acute Stroke.

**I-Know is a knowledge discovery IT -based tool designed to aid early stroke diagnosis, stroke treatment, drug development and identification of risk factors as targets in disease prevention for the benefit of European industry and citizens.**

### Objectives of the project

Acute stroke is a major socioeconomic burden in EU. The disabilities following the disease develop rapidly and prompt treatment of patients is imperative. Currently a drug dissolving the blood clot (rtPA – thrombolysis) is the only established treatment, but this is only implemented at highly specialised centres. There is consequently a strong geographical inequality in the availability of this treatment - nationally and internationally within EU.

At the same time there is an intense search by pharmaceutical industry and academic biomedical research to identify drugs that will stop the tissue damage progressing after acute stroke.

The knowledge discovery tool, ***I-Know*** will:

- Provide instant, user-friendly ITbased diagnosis and therapeutic guidance, reducing the infrastructural, economic and educational barriers currently hindering advanced stroke treatment at less specialised units.
- Use advanced data mining techniques to model disease progression based on large multinational databases providing state-of-the-art diagnosis of every EU citizen irrespective of knowledge barriers.
- Provide a platform for modeling beneficial or adverse effects recorded during clinical trials, allowing optimal use of preclinical data in subsequent individualized patient management.
- Be designed to integrate data across descriptive levels to devise disease models that will bring scientific progress to stroke research.

***“I-KNOW meets the challenges of an ageing population by improving care for the parallel increase in stroke victims”***

### Project Description

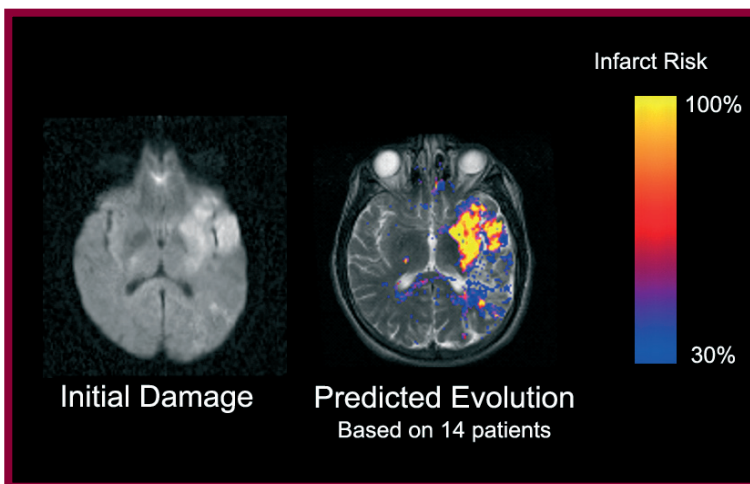
Currently, Computerized Tomography (CT) is the most widely used imaging modality in the clinical management of acute stroke. CT is very sensitive to haemorrhagic stroke and is therefore important in minimizing adverse effects in thrombolytic treatment.

Magnetic Resonance Imaging (MRI), is a growing image modality in acute stroke, and recent research has shown that MRI may delineate micro-structural damage after acute stroke by Diffusion Weighted Imaging (DWI – showing regions of cellular damage), and measure the extent of reduction of blood supply by so-called perfusion weighted imaging - PWI. More importantly MRI has high specificity in

terms of predicting final outcome in acute stroke patients, lending confidence to the development of powerful systems for the support of patient management and in the study of drug efficacy.

Currently, the logistics of performing acute MRI and the lack of access to advanced processing tools and expertise for these advanced imaging data limit health care professionals in fully exploiting the benefits of acute MRI images. Through computerized stroke disease progression models (DPMs), ***I-Know*** will provide an accurate diagnosis in individual. Interacting with the physician, ***I-Know*** will produce images, predicting the course of the disease given available therapeutic options and their specific actions recorded in other patients (DPMs from clinical trials). In a system seamlessly integrated with eHealth systems, this allows physicians to diagnose and treat the patient on the basis of a wealth of information otherwise impossible to integrate by the human mind.





## Expected Results & Impacts

The *I-Know* system is believed to result in improved diagnostic and therapeutic capability for treatment of ischemic diseases within EU.

This is anticipated to lower mortality and degree of disability of the victims, thereby improving their quality of life after an ischemic disease.

The *I-Know* system:

- Meets the challenges of an ageing population by improving care for the parallel increase in stroke victims.
- Reduces geographical inequality in access to care by facilitating advanced diagnostics and treatment locally.
- Allows full utilization of the investment placed by society in advanced diagnostic technology.
- Manages and integrates huge amounts of health information.
- Assists health professionals by providing 'best-practice' and expert advice in stroke treatment.
- Provides detailed accounts of adverse effects and outcome, providing excellent tools for bench-marking to support health managers in quality assurance in stroke care.
- Addresses the issues of interoperability and user friendliness by developing automated algorithms and separately analyze the products integration into an eHealth environment with electronic health records.

The resulting, lower socio-economic burden of cerebral ischemic diseases will allow for reallocation of resources to other measures, improving the quality of life of EU citizens as a whole.

## I - K n o w

**Integrating Information from Molecule to Man: Knowledge Discovery Accelerates Drug Development and Personalized Treatment in Acute Stroke**

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- Université Claude Bernard (FR)
- Fundació Privada Institut d'Investigació Biomèdica de Girona (SP)
- University of Cambridge (UK)
- Universitätsklinikum Hamburg-Eppendorf (DE)
- Universitätsklinikum Freiburg für die Medizinische Fakultät der Albert-Ludwigs-Universität (DE)
- Systematic Software Engineering A/S (DK)
- Dimac A/S (DK)

**Timetable:** from 05/06 – to 04/09

**Total cost:** € 3.876.347

**EC funding:** € 3.092.810

**Instrument:** STREP

### Project Identifier:

IST-2004-027294

### Keywords:

Biomedical informatics;  
Personalized health;  
Medical imaging; Early diagnosis;  
Pharmaceutical research

# ImmunoGrid

## The European Virtual Human Immune System Project

The project will focus on establishing an infrastructure for the simulation of the immune system that integrates processes at molecular, cellular, and organ levels. It will be designed for applications that support clinical outcomes such as design of vaccines and immunotherapies and optimization of immunization protocols.

### Objectives of the project

The **immune system** is a complex and adaptive learning system which has evolved to defend the individual. It has multiple levels (molecular, cellular, organ and tissue, organism, and organism-to-organism) and is also combinatorial in nature with a large number of products.

Immune intervention, such as **vaccination**, is the most effective method for the control of disease and the greatest achievements include eradication of smallpox, near-elimination of polio, and savings of some 170 million person-years. Vaccination has been used in the control of over two dozen diseases by the 50 or so successful vaccines which have been developed to date.

Large-scale studies of the immune system, also known as **immunomics**, is the key factor driving the current wave in vaccine development. The main objectives of **ImmunoGrid** are to:

- Create computational models for the real-size human immune system (the Virtual Human Immune System Simulator).
- Standardize immune system concepts, bioinformatics tools and information resources to enhance the computational models for preclinical and clinical applications.

- Validate these models with experimental data and disseminate the tools developed to users such as vaccine and immunotherapy researchers and developers.

### Project Description

Computational models are becoming increasingly important in immunomics:

- Experimental approaches are expensive and it is impossible to perform systematic experimental studies of immune processes in humans.
- Because of ethical issues, there are stringent limitations as to what experiments can be performed in humans.

**“Grid computing will allow us to approach the known complexity of the immune system”**

The main problems that prevented the use of these models in practical applications, such as design of vaccines and optimisation of immunisation regimens are:

- large combinatorial complexity of the human immune system,
- lack of understanding of specific molecular interactions that resulted in an idealisation of representation of molecular interactions as binary strings, and
- lack of experimental model data and correlation of model parameters to real-life measurements.

### Scenario

An important application of **ImmunoGrid** will be in the design of new vaccination protocols. One such protocol is the so-called “Triplex” vaccine which has been extensively studied in cancer immunoprevention. Experiments with mice will both provide input for the improved computational models and be used to validate new protocols resulting from these models, comparing with Triplex. An exciting prospect is the possibility of using **ImmunoGrid** in immunotherapy: it is found that the Triplex vaccine has minimal efficacy against established mammary carcinomas, a feature shared by most cancer vaccines, however some early studies indicate that the Triplex vaccine could be used with success in a therapeutic setup against incipient lung metastases.



Recent developments provide remedies to these problems and we are in the position to address each of these issues.

**Grid computing** has brought powerful computational infrastructure and capacity that can match the complexity of the real human immune system. Founded on experimental data **models of molecular interactions** have reached high accuracy and we are routinely using prediction methods of antigen processing and presentation to identify the best targets for vaccine constructs. Finally, **experimental models** of immune responses to tumours and infectious diseases have been successfully modelled computationally.

The specific outcome will be a tool (the Virtual Human Immune System Simulator) for use in preclinical/clinical applications, vaccine discovery and optimisation of immunisation protocols.

Scaling-up the model of human immune system to realistic (natural) size will provide an insight into the making of the immune system and help improve interpretations of results from mouse models. Earlier results on mouse models of cancer development indicate the utility of this approach for optimisation of immunisation protocols.

### Expected Results & Impacts



Immunology has a significant scientific and economic dimension –understanding the immune function is important for understanding the factors that maintain the organism in a healthy state, and intervention has important repercussions in improving the health of

individuals and population through improved disease prevention (diagnostics), protection (vaccines), and effective curing (therapeutics).

At the end of the project we are going to realise a common shared resource with a significant potential for strengthening European cross-disciplinary research by supporting European medical biotechnology and computer science.

The computational models and the set of tools developed will be validated with experimental data and then provided to support clinical applications for the development of immunotherapies in cancer and chronic infections and disseminated to users such as vaccine and immunotherapy researchers and developers.

## ImmunoGrid

### The European Virtual Human Immune System Project

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#### Partners:

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- National Council of Scientific Research - CNRS (FR),
- University of Queensland (AU),
- Technical University of Denmark (DK),
- Birkbeck College, Univ. of London (UK),
- University of Bologna (IT),
- University of Catania (IT)

**Timetable:** from 02/06 – to 01/09

**Total cost:** € 2.622.274

**EC funding:** € 1,951,042

**Instrument:** STREP

**Project Identifier:**

IST-2004-028069

#### Keywords:

HealthGrid,  
virtual physiological human,  
grid computing,  
immune system modelling,  
immunotherapy



## LHDL: The Living Human Digital Library

Every hospital, every research laboratory in Europe has a wealth of biomedical data locked-up somewhere that, if shared with other experts, could dramatically improve healthcare practice as well as the development of better biomedical products. LHDL finally makes it possible to share biomedical data in an easy, controlled, safe, and financially viable way. One click to upload all your data to your private space; one click to share each dataset only with those you choose; a third click to publish your data within an e-commerce service, to which access is sold at the price you set.

### Objectives of the project

**Context:** The Living Human Project (LHP) is a grass-roots initiative aimed at developing an *in silico* model of the human musculo-skeletal apparatus that can predict how mechanical forces are exchanged internally and externally, from the whole body down to the protein level, consistently with the scope of the Physiome project. To pursue this very ambitious objective, it is necessary for large research communities to share highly heterogeneous collections of data and models through a repository fully integrated, and directly accessible by any researcher in the world. Although inspired by a specific community, this problem is very general in nature, and its solution will significantly and positively affect European research, clinical and industrial practices.

**Project:** The Living Human Digital Library (LHDL) aims to develop and deploy the resource-sharing infrastructure required by the LHP community and by many other similar groups involved with biomedical research and practice. In particular, the project is developing:

- *LhpBuilder*, an application for the interactive visualisation, processing and fusion of biomedical digital data;
- *LhpRepository*, an ICT infrastructure fully integrated with *LhpBuilder* for the management and the sharing of digital resources relevant for biomedical research;
- *LhpSimul*, a service framework for the development, sharing and choreography of data processing services.

Once completed, these three elements will form the most powerful biomedical data management service in the world.

### Project Description

**Project Description:** *LhpBuilder* is a fat client software application that is being developed through the Multimod Application Framework, a European open source software framework for the creation of computer aided medicine applications. With *LhpBuilder*, every researcher can import virtually any type of biomedical data (including medical imaging, biomedical instrumentation recordings, motion analysis data, numerical modelling results, etc.) in dozens of popular formats. Once all the data are imported, they can be organised in space and time thanks to a number of powerful data fusion techniques. They can also be explored using some of the most powerful visualisation algorithms available, exposed in a fully interactive environment, within which the user can operate with extreme simplicity using a complete Graphic User Interface. 1D, 2D, 3D, and 4D data can be combined, merged, and fused in synergistic ways.

Once the data collection is ready, it can be uploaded with a single mouse click to the *LhpRepository* service. Each dataset is encrypted and uploaded through a secure channel to the remote repository, where it is stored in the user's sandbox. Through a web interface the user can see all her uploaded datasets, annotate them, curate them and decide with whom she wants to share each of them. The annotation is performed according to the LHDL Resource ontology, an advanced ontology that makes possible all most sophisticated data management services, including complex access management, traceability, data integrity assurance, semantic search services, etc. The tight integration with the *LhpBuilder* fat client makes it possible to compile automatically much of the metadata, reducing the curation work that users have to do.

### Scenario:

Part of the LHDL technology will be used by B3C, a CINECA spin-off, to deliver the first commercial biomedical data management service, fully integrated with the popular [Biomed Town](#) Internet community. The service, called *PhysiomeSpace*, is expected to enter the beta phase in the last quarter of 2008, and to start full service in the first half of 2009. Any Biomed Town user will have a free account in which up to 1 Gb of data can be stored and shared with any other user; additional space will be available for a small fee. Users will also be able to *publish* their datasets, which will then be downloadable at the cost set directly by the data owner; it will be possible to set different price tags for profit and non-profit uses.



Once the datasets are stored in the sandbox, another option is to process them with the available execution services. The LHDL Resource Ontology presents both data and service resources in the same semantic space; thus, it is possible to select some data, search for all available services that can process that data type, and choose the one we need, with only a few mouse clicks. The results of the processing are also stored in our sandbox, ready to be shared or downloaded.

The potentially complex orchestration of the services as their number increases is simplified by the use of a semantic broker that can orchestrate many services into a single goal. Goals are stored as

***LHDL is developing and deploying the resource-sharing infrastructure most VPH projects need***

services, so the user can request a goal service as a single processing action though, in reality, it is the concatenation of multiple execution services run according to a semantic rule.

Given that all these objectives have already been achieved, at least in prototypical form, we are confident that, by the time of its completion, the LHDL project will provide the biomedical research community and the European healthcare and biomedical industries with a set of highly innovative and truly enabling e-health technologies for data management.

### **Expected Results & Impacts**

- *PhysiomeSpace*, the first data management & sharing service dedicated to biomedical data;
- *LhpBuilder*, best biomedical data fusion software fully integrated with PhysiomeSpace data management services;
- *LhpSimul*, a powerful architecture of execution web services for the distributed execution of data-intensive algorithms;
- *LhpSWS*, semantic web services with full semantic brokering capable of combining storage and execution services in complex data processing flows;
- the largest collection of experimental and modelling data on the descriptive anatomy, the functional anatomy and the multiscale biomechanics of the musculoskeletal system; this collection will be deployed and shared with the worldwide research community through the PhysiomeSpace service.

### **LHDL: the Living Human Digital Library**

*Project co-ordinator:*

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The Open University (UK)

Université Libre de Bruxelles (Belgium)

Istituto Ortopedico Rizzoli (Italy)

*Timetable:* from 02/06 – to 01/09

*Total cost:* € 3,238,320

*EC funding:* € 2,250,520

*Instrument:* STREP

*Project Identifier:* FP6-IST-2004-026932

**Keywords:**

Physiome,  
Virtual Physiological Human,  
Living Human Project,  
digital libraries,  
data sharing,  
semantic web services,  
data fusion.



# MULTI-KNOWLEDGE

## Creating new knowledge in networks of medical research

The **MULTI-KNOWLEDGE Project** aims to integrate different biomedical information from heterogeneous sources (clinical, laboratory and metabolic) with data on gene and protein expression provided by new high throughput technologies in a system committed to cardiovascular risk profiling.

### Objectives of the project

The classical approach in global cardiovascular (CV) risk assessment can be faulty: classical risk factors (such as high cholesterol, high blood pressure, smoking, etc) are able to explain only 50% cases of CV events; it is furthermore not possible to assess the differential impact of risk factors in different subjects and it is still unclear whether the correction of risk factors can fetch CV risk to zero. **There arises the need to get a better prediction of the clinical events and a more efficient prevention strategy.**

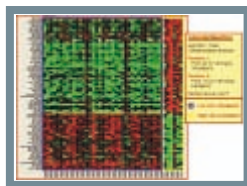
The **MULTI-KNOWLEDGE Project's** general goal is therefore the construction and implementation of a predictive algorithm combining clinical, laboratory, metabolic, gene and protein expression data to identify the presence of early signs of vessel wall atherosclerotic disease in subjects at different degree of cardiovascular disease (CVD) risk on the basis of traditional risk factors and insulin resistance level.

#### Scientific-medical objectives:

- To investigate the impact of CV risk factors on systemic inflammation using gene expression profiling
- To integrate clinical and molecular data to predict the presence of early signs of atherosclerosis

#### Technical aims:

- To implement multiuser collaborative instruments to manage and analyze data from high-throughput technologies and clinical data



### Project Description

**MULTI-KNOWLEDGE** starts from the data processing needs of a network of Medical Research Centres, in Europe and USA, Partners in the Project and co-operating in researches related to the link between metabolic diseases and cardiovascular risks. These needs are mostly related to the integration of three main sources of information: clinical data (EHR), patient-specific genomic and proteomic data (in particular data produced through Micro-arrays technology), and demographic data. The general aim of the project will be the development of a knowledge management environment to allow networks of co-operating medical research centres to create, exchange and manipulate new knowledge from heterogeneous data sources.

This will allow retrieval and analysis of millions of data through bio-informatics tools, with the intent of improving medical knowledge discovery and understanding through integration of biomedical information.

**MULTI-KNOWLEDGE** will contribute to the creation of standards to link heterogeneous data. The clusterization models produced within the project will allow discrimination between normal and pathologic and

*“MULTI-KNOWLEDGE will create an intelligent workflow environment for multi-national multi-professional research consortia aiming at cooperatively mining, modelling, visualizing biomedical data under a single common perspective.”*

### Scenario

To integrate clinical and molecular data several experts in different fields of research need to create a collaborative group supported by a single system of data entry and management accessible from different locations and suitable for direct data entry, as well as data input from clinical records and from outputs of laboratory and molecular research software. After data entry, clinical researchers, epidemiologists and biostatisticians need to access the system from several locations, operate sub-sequentially different tasks of the analysis (data cleaning, quality control, etc.), implement analysis algorithms, and make clinically/statistically oriented decisions for data analysis based on their specific competences.

produce insight for clinical research and disease management.

The MULTI-KNOWLEDGE architecture and set of tools will be tested for the development of a structured system to integrate data in a single informative system committed to cardiovascular risk assessment. Therefore this project will also contribute to establish guidelines and operating procedures to manage and combine data coming from gene expression and protein microarrays and make them easily available for the imputation of study algorithm.

### Expected Results & Impacts

The MULTI-KNOWLEDGE Project will produce

- **Strategic impacts on the health care ICT market**, contributing to the consolidation of the EU Healthcare market -which has at the moment a fragmented supply against a growing demand- and constituting a crucial intellectual asset for the involved IT professionals, thanks to the knowledge it will accumulate and the contacts among researchers it will encourage
- **Strategic impact on the EU healthcare systems**, fostering the trend towards standardization of health processes as well as helping decision makers to establish more rationalized disease management policy, satisfying the need to optimize resources because of rising costs in healthcare
- **Strategic impact on social communities**, helping improve the level of health through the implementation of evidence based disease management
- **Strategic impact on scientific research**, improving the high risk patients identification, the estimation of vascular/systemic inflammation extent and the knowledge on cellular effects of risk factors and systemic impact of specific CVD risk factors. It will represent the 1st multi-level model for the study of complex diseases and also provide novel instruments in genomic and proteomic data management and analysis

### Achievements and results

Following preliminary achievements have been gained so far:

- implementation of the **first project prototype** (Feb. 2007) including the **MK Data Entry System for data collection** (a first in the art system to support entry of diverse data types, including clinical and high throughput genomic data) and Pilot **MK Data Analysis tools** to enable preliminary interpretation of pilot data (including first in the art components)
- selection, screening and execution of full pilot activities for 50 apparently healthy subjects (including whole –genome transcriptomic analysis of circulating mononuclear cells) at low CVD risk
- identification of **first scientific results** with reference to certain data types (Gender, Smoking, LDL-cholesterol, High-Sensitivity C-reactive protein -hs-CRP-, Intima-Media Thickness)

thus enabling the following preliminary scientific conclusions:

- for the first time mild clinical and laboratory phenotypes related to CVD are correlated with high-throughput data
- Multi-Knowledge system allows to explore high-throughput differential expression profiles on continuously distributed data in a powerful and meaningful way

## MULTI-KNOWLEDGE

Creating new knowledge in networks of medical research

### Project co-ordinator:

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- KING'S COLLEGE LONDON (UK)
- PCS PROFESSIONAL CLINICAL SOFTWARE GMBH (Austria)
- S.A.T.A. - S.R.L. (Italy)
- INFORMATION MANAGEMENT GROUP LTD (UK)
- DATAMED A.E. HEALTHCARE INTEGRATOR (Greece)
- THE STANFORD LELAND JUNIOR UNIVERSITY (Usa)

**Timetable:** from 01/06 to 03/2008

**Total cost:** € 3.776.148,00

**EC funding:** € 2.440.00,00

**Instrument:** STREP

**Project Identifier:**

IST-2004-027106

### Keywords:

- Healthcare
- Genetics
- Knowledge management
- Biomedical informatics
- Electronic health records

# Sealife

## A Semantic Grid Browser for the Life Sciences applied to the study of Infectious Diseases

How can the researcher in the lab benefit from this new infra-structure to science? A technology is needed to transparently bring such services to the desks of the scientists. Sealife will develop a browser, which will link the existing Web to the currently emerging eScience infrastructure.

### Objectives of the project

Currently, much effort is spent on creating a new computational and data infrastructure to facilitate eScience, the cooperation of geographically distributed organisations, which transparently integrate their computational and data resources at a structural and semantic level. Progress has been made with standards for grid computing and semantic representations for life science data with many projects creating a host of grid-enabled services for the life sciences.

The Web started with a browser and a handful of Web pages. The vision of eScience with an underlying Grid and Semantic Web will only take off with the development of a Semantic Grid browser. The **SEALIFE** project is filling this gap by developing such a semantic grid browser. These browsers will operate on top of the existing Web, but they introduce an additional semantic level, thus implementing a Semantic Web. Using ontologies as background knowledge, the browsers can automatically identify entities such as protein and gene names, molecular processes, diseases, types of tissue, etc. and the relationships between them, in any Web document. They collect these entities and then apply further analyses to them using applicable Web and Grid services. The **SEALIFE** browser will be evaluated in three applications relating to the study of infectious diseases.

### Project Description

**SEALIFE** will solve the following problems to achieve its objectives:

- **Ontologies:** Design and integration of ontologies and associated infrastructure, which can serve as background knowledge for a Semantic Grid Browser geared towards life science applications ranging from the molecular level to the person level.
- **Concept Mapping:** Bridging the gap between the free text on the current Web and the ontologybased mark-up for the Semantic Web and Grid by developing automated mark-up modules for free text, which are based on textmining and natural language processing technologies.
- **Service Composition:** Bridging the gap between the ontologies of the Semantic Web and the services of the Grid by linking suitable ontology mark-up to applicable services and by supporting the interactive creation of such mappings for complex services.

The **SEALIFE** browser will be demonstrated within three application scenarios in evidence-based medicine, literature and patent mining, and molecular biology, all relating to the study of infectious diseases.

### Scenario

To illustrate the power of this vision consider the following applications: Evidence-based medicine: Consider a clinician, who consults the national electronic library of infections to get trusted information on infections. The user visits the site and finds an interesting page on hipatitis and its treatment: "Ribavirin with or without alpha interferon for chronic hepatitis C". Using its background knowledge, the Sealife browser identifies hipatitis as disease and interferon as an immunologic factor. With this knowledge the browser automatically offers the user the ability to query the biomedical databases Ensembl and PDB to learn more.



The three applications vertically integrate the molecule/cell, the tissue/organ and the patient/population level by covering the analysis of high-throughput screening data for endocytosis (the molecular entry pathway into the cell), the expression of proteins in the spatial context of tissue and organs, and a high-level library on infectious diseases designed for clinicians and their patients.

**“The vision of eScience with an underlying Grid and Semantic Web will only take off with the development of a Semantic Grid browser”**

### Expected Results & Impacts

These systems will be advanced through **SEALIFE** and will ensure a link to a user base. Additionally, **SEALIFE** has set up an advisory board with members from Pfizer, AstraZeneca, Unilever, and others. Dresden has spun-off Transinsight.com, which is dedicated to intelligent search for life sciences. Transinsight has secured seed funding by the German High-tech Gründerfonds and has obtained an award by the federal ministry for economic affairs.

Sealife builds on a number of relevant systems already developed by the partners:

- GoPubMed.org, an ontology-based literature search engine
- MyGrid, a Grid computing platform,
- Corese, a concept resource search engine,
- NeLL, the National electronic library of infectious diseases,
- Edinburgh Mouse Atlas.



## Sealife

**A semantic grid browser for the life sciences applied to the study of infectious diseases**

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**Partners:**

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- Harriot-Watt University, Edinburgh, (UK)
- City University, London, (UK)
- University of Manchester, (UK)
- Scionics GmbH, Dresden, (DE)
- Inria, Sophia-Antipolis, (FR)

**Timetable:** from 4/2006 to 3/2009

**Total cost:** € 2.6M

**EC funding:** € 2.2M

**Instrument:** STREP

**Project Identifier:**  
IST-2004-027269

**Keywords:**

Grid, semantic web,  
molecular biology,  
healthcare,  
bioinformatics

# Share

## Supporting and structuring HealthGrid Activities & Research in Europe: developing a roadmap

**SHARE goal is to ensure the successful take up of HealthGrids in the next 10 years by creating a roadmap for essential technology development years.**

### Objectives of the project

A major challenge for the coming years is to address the unique ICT aspects of the life sciences in an integrated way. Life science research present the need to access, analyse, protect and share massive quantities of diverse, geographically distributed information, computationally intensive analysis techniques and rapidly evolving medicine, science and technology.

The recent emergence of Grid technology opens new perspectives to enable interdisciplinary research and technology development at the cross roads of medical informatics, bioinformatics and system biology impacting healthcare.

Action on Grids for health is needed at EU level to address mobility of citizens and provide cross frontier interoperability of data, cross-frontier infrastructures, optimal exploitation of resources (both technical and medical), equitable distribution of healthcare; and definition and implementation of standards.

Such deployment requires harmonization of existing legal frameworks for storing, accessing, communicating, and processing health related data in Europe.

**SHARE** will achieve the following goals:

- To propose strategies to address some of the issues listed in the European Action Plan for e- Health.
- To define a roadmap for research and technology to allow a wide deployment and adoption of HealthGrids both in the shorter term (3-5 years) and in the longer term (up to 10 years).
- To define a complementary and integrated roadmap for e-Health RTD policy relating to Grid deployment, as a basis for improving coordination amongst funding bodies, health policy makers and leaders of Grid initiatives, avoiding legislative barriers etc.

### Project Description

The HealthGrid roadmap will cover the domain of RTD and uptake of Grid applications in healthcare comprehensively, including infrastructure, security, ethical, legal, financial, economic and other policy issues.

Each section of the roadmap will detail actions to be taken in terms of objectives and possible methods or

### Scenario

Suppose that the epidemiology department of a public health authority records primary care and drug prescription information from a regional area. A researcher from this epidemiology department has to take a decision on the preferred treatment for the disease "A" to inform medical practitioners. This information has been traditionally obtained from the drug manufacturer companies and obtained through clinical trials. However, the information registered would enable to perform more realistic cost-efficiency and safety analysis. After talking with the experts, the epidemiology researcher selects the most relevant fields and performs a correlation study of treatment length, adverse effects, treatment cost, patient physical information and medical records. This study requires consolidating the information from several databases and performing long and computationally-costly knowledge discovery processes which are executed on a grid infrastructure, taking into account the security and integrity restrictions. Final data determines that for a group of the population "X", current treatment is inadequate and costly, whereas alternative treatment "Y" seems very effective. This information is published for the medical practitioners who use this as an advisory guide for their daily work. Finally, treatment cost of disease "A" has been reduced.



*“The Share Roadmap will focus on identifying requirements for further research and technology development”*

approach as well as recommended milestones for completion, stakeholders responsible, appropriate methods of coordination etc. All sections of the roadmap will take fully into account issues related to standards and will respect the security requirements for handling medical data. Non-European issues will be factored in to our roadmap in order to ensure that European HealthGrid policy

does not inadvertently preclude international interoperability.

The conceptual work during the start-up phase of the project will also specify in detail both the general scope and specific features of the roadmap. In this sense, the roadmap will focus on identifying requirements for further research and technology development.

It will also sketch a realistic picture with respect to desirable applications/ICT implementations and indicate which technologies may have the potential to make a substantial contribution in this context. This will be supported through the presentation of good practice examples.

To ensure that the RTD roadmap ultimately to be generated will actually yield positive results and desired impacts it will be based upon and, wherever possible, justified by empirical evidence from the research domain and a bottom-up assessment involving relevant stakeholders.

In a sequential process, relevant research communities and communities of practice at EU, national and global levels will be joined up to enable an iterative refinement and extension of the initial road map.

## Achievements & Results

Health care systems in all countries are under strong pressure to reduce costs and improve (economic) efficiency. For quite some time, the European Union through the various framework programmes for RTD has strongly supported the development of ICT applications in the health sector, albeit with mixed results.

The same holds for various national activities; only recently these have gained in scope and relevance for health care professionals and citizens. The overriding societal goal of all these activities - and in line with **Share** as well - is to contribute towards better health and care across Member States, in particular through implementation and diffusion of e-health products and services on regional, national and trans-European e-healthcare infrastructures based on the Grid technology.

It is expected that this will contribute to better medical outcomes, better quality of life for citizens and patients, more efficiency and improved access - key impacts for all countries and all their citizens. As an additional result, the Share project will also offer to the whole biomedical research community a knowledge base on projects, actors and developments related to grid for health.

## S h a r e

**Supporting and structuring HealthGrid Activities & Research in Europe: developing a roadmap**

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HealthGrids Knowledge Base:

<http://kb.healthgrid.org/>

### Partners:

- CNRS (FR)
- HealthGrid (FR)
- Universidad Politecnica de Valencia (ES)
- University of the West of England, Bristol (UK)
- Facultés Universitaires Notre-Dame de la Paix (BE)
- European Health Management Association (IL)

**Timetable:** from 01/06 – to 03/08

**Total cost:** € 1.026.000

**EC funding:** € 980.000

**Instrument:** SSA

**Project Identifier:**

IST-2004-27694

### Keywords:

HealthGrid,  
eHealth networks  
and Architecture,  
Interoperability,  
Biomedical informatics,  
Electronic Health Record,  
Open Source,  
Knowledge Base

# STEP

## A Strategy for the EuroPhysiome

**STEP was a Coordination Action that sought to coordinate European activity relating to the physiome – a description of human physiology that will span multiple levels from the whole body down through the organs to the cells and beneath in an integrated manner.**

### Objectives of the project

The physiome is the integrated description of the physiology of a species. Integration has become more important because of recent results produced from the genome, molecular biology and evolutionary biology; recent advances in computer technology are now making it feasible.

European research is currently developing the concept of *Virtual Physiological Human* (VPH) to develop models that will provide an improved description of the human physiome. The VPH relates closely to the Physiome Project (more accurately described as the Physiome Initiative), which is organised under the auspices of the International Union of Physiological Sciences (IUPS).

The VPH activities will run alongside the Physiome Project but will focus on areas in which strong European work currently exists to ensure that it continues to maintain its leading position. The VPH places a heavy emphasis on research that will have a strong impact on the clinical and industrial areas.

**STEP** produced a roadmap defining the best way forward for European research in this area. To do this, it:

- engaged all interested parties in the discussion in an inclusive manner
- invited recognised experts from around the world to provide informed opinion
- organised two conferences to focus the debate.

### Project Description

**STEP** brought together all European projects that were engaged in physiome-related work at the time. **STEP** moved to a situation in which the issues were considered more holistically.

To reduce the complexity of the problem, **STEP** was organised as a two-stage process:

- initially, the overall picture was broken down into Strands related to tissue types, e.g. hard tissue, soft tissue, fluids
- once the Strands had identified how progress could best be made in their own areas, they discussed, together, how to achieve their goals in a unified and coherent manner, avoiding redundancy and overlap as much as possible.

The first conference will enabled the Strands to focus on their own specific problems and define consensual positions.

This was followed by an intense Internet-based debate in which the Strands completed their deliberations and defined positions for circulation to the other Strands.

The second conference brought these documents together and started to define the final roadmap which addressed, amongst other things, the following issues: common objectives and research challenges; the resources required; ethical, gender and legal issues; impact analysis; dissemination models; community building initiatives; exploitation models and long term sustainability.

### Scenario : Cardiome, University of Oxford

This pioneering project has grown out of work established in the 1960s and is probably the most advanced of the Physiome organ-level models. It is seeking to develop electro-mechanically representative models of cardiac structure and function of a variety of species, including human.

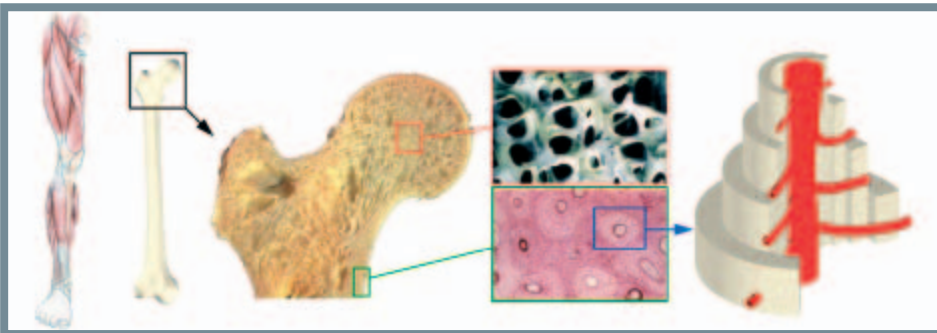
All of these studies emphasise how complex the heart is. Heart disease is influenced by many factors, not least the genes of the individual, so development of treatments must take account not only of the heart as an organ but also of factors at a subcellular level. This is why physiome-based approaches are likely to lead to many breakthroughs when the models developed reach maturity.

## Expected Results & Impacts

Given the diversity of areas on which biomechanics and biophysics impact – health, ergonomics, safety, sport – the effects on the quality of life of the individual citizen are expected to be wide ranging.

Further, given the current costs, both social and economic, of the problems that exist in these areas, the anticipated benefits in terms of personal comfort and reduction in pain, and in terms of the associated social spending are likely to be huge.

The European biomedical industry, mostly formed by SMEs, is struggling under the fierce competition of the multinational, normally US-based, companies that have gained dominance in many markets.



For application domains, the challenges include:

- enhancing our ability to study the human body, its functioning, its inter-subject variations, and to develop and validate complex models that can accurately predict a variety of physiological and pathological conditions
- allowing the European Physiome communities to create the world's largest and most sophisticated collection of information on the human body.

Physiological knowledge is so intimately linked to clinical practice that the direct impact on clinical practice will probably be substantial:

- multiscale modelling should open new scenarios in preventive medicine, or environmental medicine, in general health studies, and in the design of drugs and medical devices
- new developments in diagnosis, treatment, monitoring and rehabilitation, which may provide improved insights to assist with patient care
- support for evidence-based medicine.

For the scientific community, the roadmap addresses:

- the development of numerical simulation, interactive visualisation, and instruments for community building and collaborative working
- the evolution of core technologies to a usability level that will make them accessible by nontechnical users, such as biomedical researchers and clinical professionals
- the deployment of infrastructures that provide the necessary levels of security and trust.

## S T E P

**A Strategy for the EuroPhysiome**

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- University of Sheffield (UK)
- Aalborg Sygehus (DK)
- University of Oxford (UK)
- University of Nottingham (UK)
- CNRS-IBISC (FR)
- University College London (UK)

**Timetable:** from 01/06 – to 03/07

**Total cost:** € 1,240,770

**EC funding:** € 1,185,360

**Instrument:** CA

**Project Identifier:**

IST-2004-027642

*“The roadmap was circulated widely amongst relevant parties throughout Europe who are associated with health care and the planning of healthcare systems. It can be downloaded from <http://www.europhysiome.org>.”*

**Keywords:**

physiology, medical technology, physiome, in silico human, multiscale modelling, bioinformatics



# VIROLAB

## A Virtual Laboratory for Decision Support in Viral Disease Treatment

**ViroLab enables easy access to distributed resources as well as the sharing, processing, and analysis of virological, immunological, clinical and experimental data.**

### Objectives of the project

Genetic information is likely to become increasingly significant in many areas of medicine. This provides an unparalleled opportunity to advance the understanding of the role of genetic factors in human health and disease, to allow more precise definition of the non-genetic factors involved, and to apply this insight rapidly to the prevention, diagnosis and treatment of disease. Large numbers of complex genetic sequences are increasingly becoming available, providing a unique opportunity for studying the many diseases where genetic information will become important in future years, such as in the case of infectious diseases.

As a prototype the problem of HIV drug resistance is addressed. **ViroLab** integrates biomedical information from viruses (e.g., proteins and mutations), patients (e.g., viral load) and literature (e.g., drug resistance experiments), resulting in a rule-based distributed decision support system for drug ranking, as well as advanced tools for (bio)statistical analysis, visualization, modelling and simulation.

The **main objectives of ViroLab** are to:

- develop a virtual organisation that binds the various components of the **ViroLab**;
- develop a virtual laboratory infrastructure for transparent workflow, data access, experimental execution and collaboration support;

- virtualize and enhance the state of the art in genotypic resistance interpretation tools, integrating them into the virtual laboratory;
- establish epidemiological validation showing that **ViroLab** correctly and quantitatively predicts virological and immunological outcome, and disseminate the results to stakeholders.

### Project Description

**ViroLab** is based on Grid security infrastructure, middleware and user interfaces. The virtualization of resources such as data, compute nodes, tools, and users allows full resource transparency.

*“ViroLab will lead to new valuable clinical data and information on treatment of HIV-infected persons”*

These resources are made available by adopting Grid computing, and building on existing tools from projects such as CrossGrid, EGEE and VL-e.

The virtual organisation spans a number of geographically separated “physical” institutions across Europe, including five hospitals. **ViroLab** uses a uniform interface to available resources in the virtual laboratory, with functionality defined by well defined tasks in clinical environments. The virtual lab allows users to

### Scenario

In **ViroLab**, a specialist member of the virtual organization logs into the virtual laboratory and accesses the distributed decision support system, which interprets the genotype of a patient by using rules developed by experts in the organization on the basis of literature mining of context sensitive data. The specialist then applies a set of multi-scale methods such as molecular dynamics modelling of HIV infection, and automatically generates new rules that are checked for consistency and redundancy. The specialist then validates the new set of rules, covering this way the fast temporal and spatial scales required to infer information from a molecular (genomic) level up to patient medical data.

select either pre-defined tasks or to compose novel tasks by means of orchestration registered available resources. The virtual lab also provides a virtual whiteboard and experimental (provenance) logbook for scientists at geographically separate locations.

Since **ViroLab** offers access to many disparate kinds of data from many sources, much effort is devoted to providing a uniform interface to all of these resources by virtualizing them and coupling advanced modelling, simulation and analysis tools in a way that is highly accessible to specialists and researchers.

Since **ViroLab** offers access to many disparate kinds of data from many sources, much effort is devoted to providing a uniform interface to all of these resources by virtualizing them and coupling advanced modelling, simulation and analysis tools in a way that is highly accessible to specialists and researchers.

### Expected Results & Impacts

The collaborative research will result in a virtual laboratory for decision support in infectious diseases treatment. We focus on HIV antiviral resistance (and thereby on a specific scientific community and patient group) for the purpose of creating a prototype for the broader application for infectious diseases. It will also provide means for collaborative experimentation studies based on modelling and simulation of HIV-related processes.

The project will benefit from the development of innovative pharmaceutical research, (antiviral drug development and use of information of clinical trials). ViroLab will lead to new valuable clinical data and information on treatment of HIV-infected persons, which will provide essential insights into the prevalence of drug resistance patterns in treated individuals on a continuous basis. It is of crucial importance for future development of new drugs effective against drug resistant HIV.

ViroLab will demonstrate measurable, quantifiable benefits, respecting all aspects of confidentiality, fulfilling the urgent need for standardised rules and systems for reliable quantitative HIV-1 genotypic resistance interpretation, providing medical doctors throughout Europe with accessible and user-friendly tools for significantly improving the clinical usefulness of genotypic assay results. The virtual laboratory will function as Europe's first rule-based decision support system for drug ranking, including advanced tools for (bio)statistical analysis, modelling and simulation, enabling prediction the temporal virological and immunological response of viruses with complex mutation patterns to drug therapy, leading to better individual based treatment.

ViroLab will be validated in epidemiological studies and will include elaborate and advanced Grid security infrastructures, respecting the aspects of confidentiality, security and trust.

## VIROLAB

### A Virtual Laboratory for Decision Support in Viral Disease Treatment

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- High Performance Computing Center (DE)
- Institute of Clinical Infectious Diseases, Catholic University (IT)
- Institute de recerca de la SIDA IRSICAIXA Foundation (ES)
- Institute of Infectious and Tropical Diseases, University of Brescia (IT)
- Laboratory for Clinical and Epidemiological Virology, REGA institute, Catholic University Leuven (BE)
- Dept. of Plant Taxonomy and Ecology, Eötvös Loránd University (HU)
- GridwiseTech (PL)
- AGH University of Science and Technology (PL)
- University College London (UK)
- Virology Education B.V. (NL)

**Timetable:** from 03/06 – to 03/09

**Total cost:** € 3.499.240

**EC funding:** € 3.334.840

**Instrument:** STREP

#### Project Identifier:

IST- 2004-027446

#### Keywords:

Decision support systems, biomedical information, innovative pharmaceutical research, modelling and simulation, visualisation, virtual laboratory

## FP7 Projects

- ❖ Action-Grid
- ❖ ARCH
- ❖ ARTreat
- ❖ CONTRA CANCRUM
- ❖ euHeart
- ❖ HAMAM
- ❖ IMPPACT
- ❖ Neo Mark
- ❖ PASSPORT
- ❖ PreDICT
- ❖ Predict AD
- ❖ RADICAL
- ❖ VPH NOE
- ❖ VPH2
- ❖ VPHOP



## ACTION-Grid

### International Cooperative Action on Grid Computing and Biomedical Informatics between the European Union, Latin America, the Western Balkans and North Africa

The project aims to exchange research results and foster collaborations in nanoinformatics, Grid technologies and biomedical informatics among Latin America, the Western Balkans, North Africa and the European Union (EU). Moreover it aims to the creation of a White Paper that will provide input to the European Commission and other agencies in developing a future agenda in R&D in these areas.

#### Objectives of the project

**Context:** Over the last years, researchers in biology and medicine have produced a huge amount of new data. This exponential growth leads to the necessity of novel approaches and tools to make this data accessible. Information produced by researcher may not be familiar to the most part of clinicians. For these reasons Biomedical Informatics should develop new tools to help to extract relevant information.

Due to the increase of available data, recent methods applied by biomedicine, such as data mining, database integration and simulation, are becoming computationally demanding. The access to new approaches is needed to perform such tasks.

**Project:** ACTION-Grid will act as a multiplier of previous results in Grid and Biomedical Informatics and will disseminate these results in Latin America, the Western Balkans and North Africa.

Objectives:

- To foster training and mobility in Grid, BMI and nanoinformatics
- To develop a White Paper in collaboration with a panel of recognized experts. This document will be delivered to the EC to establish a future agenda covering the Grid/ Nano/ Bio/ Medical informatics.
- To disseminate results through divers means, e.g. conferences, articles, website, etc.



#### Project Description

**Project Description:** ACTION-Grid's main objective is to create a collaborative environment between organizations in the European Union, Latin America, the Western Balkans and North Africa in the Grid, Biomedical Informatics and Nanoinformatics areas.

The project aims to collect relevant results obtained in these fields to disseminate them among the target countries. These achievements will be reused and transferred in a wider context, having an important impact also outside the European Union.

*"ACTION-Grid is the first European initiative on Grid Computing, Biomedical Informatics and nanoinformatics"*

Other objectives of the project are:

- To promote exchanges between Grid and Biomedical Informatics professionals. These collaborations will be extended also to Nanomedicine and Nanoinformatics with the aim of creating new synergies among these areas. Previous projects inside the European Union have already worked on this kind of task: to create successful synergies between Medical Informatics and Bioinformatics leading to expanding the biomedical informatics.
- To create a White Paper in collaboration with a panel of recognized experts. Based on the idea of this document, the European Commission and other international agencies will create new projects and a future agenda in research and development in Grid, Biomedical Informatics and Nanoinformatics areas. Special attention will be given to new ideas and roadmaps that involve a strong collaboration between European Union and the other target countries.

ACTION-Grid is a Support Action. For this reason its

#### Scenario

Over the last years European Commission projects have produced interesting resources and tools that can be valuable for Biomedicine and Nanomedicine. ACTION-Grid aims to survey and disseminate Grid/ Nano/ Bio/ Medical informatics resources among countries of three continents to enhance international collaboration and help the research on these areas.

objectives are not bound with research tasks. Nevertheless, validation processes are carried out for these parts of the project that involve programmes implemented by members of the consortium, like a Resourceome of biomedical informatics and nanomedical informatics tools and a Mobility Brokerage Service. The White Paper will be created following the DELPHI methodology to ensure the quality control of the produced results.

### Expected Results & Impacts

The project will have several expected impacts:

- **To enhance synergy among Europe, Latin America, the Western Balkans and North Africa by facilitating the exchange of Grid-based methods and tools.** This implies a better interoperability of systems at specific locations and the accessibility of available results of previous research projects and experiments. ACTION-Grid will increase awareness disseminating its results using different approaches including the creation of a White Paper, a Bio-Nano-Grid-Medical Informatics resource index and a web portal.
- **To foster these synergies among all the actors in the ICT for Health area.** Institutions like hospitals, research labs or universities that work in the Health domain have similar objectives, but very different path to achieve them. ACTION-Grid encourages the cooperation of these actors in order to have a more general view of the problems they have to face. This new approach will need informatics methods in order to be as much effective as possible and to grant the access of new services to all actors.
- **To extend these synergies from Biomedical Informatics to the Nano-related areas.** Current work on Biomedical Informatics needs the integration of clinical and biological concepts. These areas have been converging, but now new fields are growing in importance and require an effort for their inclusion in this framework: Nanotechnology and Nanomedicine. ACTION-Grid looks beyond the state of art of Biomedical Informatics adding Nano-related areas.

### ACTION-Grid

#### International Cooperative Action on Grid Computing and Biomedical Informatics between the European Union, Latin America, the Western Balkans and North Africa

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 Foundation for Research and Technology (Greece);  
 Sociedad Italiana de Beneficencia en Buenos Aires (Argentina);  
 Universidad de Talca (Chile);  
 HealthGrid (France);  
 Sveuciliste u Zagrebu, Medicinski Fakultet (Croatia).

Timetable: from 06/08 – to 11/09  
 Total cost: € 1.118.402  
 EC funding: € 999.077  
 Instrument: SA  
 Project Identifier: FP7-ICT-224176

Keywords:  
 Nanoinformatics  
 Nanomedicine  
 Biomedical Informatics  
 Grid  
 Nanotechnology

## ARCH

### Patient specific image-based computational modelling for improvement of short- and long-term outcome of vascular access in patients on hemodialysis therapy

The ARCH project aims at developing image-based computational modelling tools for surgical planning and management of vascular access, the surgical arterio-venous shunt used to connect patient circulation to artificial kidney, a critical component of renal replacement therapy. The modelling tools will be validated in real-world clinical settings and provided to clinical end-users through a distributed ICT infrastructure.

#### Objectives of the project

More than 500,000 end-stage renal disease patients in Europe live on chronic intermittent haemodialysis treatment. A successful treatment critically depends on a well-functioning vascular access, a surgically created arterio-venous shunt used to connect the patient circulation to the artificial kidney.

The vascular access is subject to high rates of post-operative malfunction and is associated to long-term complications. Indeed, 15 to 20% of hospitalisations among end-stage renal disease patients are associated to vascular access-related complications, leading to extremely high healthcare and social costs.

**ARCH** has the goal of improving the outcome of vascular access creation and long-term function with an image-based patient-specific computational modelling approach.

More specifically, **ARCH** aims at:

- Developing a patient-specific computational tool for surgical planning of vascular access surgery and management of complications.
- Designing and deploying an ICT service infrastructure to make the tool available to clinical end-users.
- Validating the modelling tool experimentally and in real-world clinical settings.
- Developing non-invasive acquisition protocols for the collection of functional and imaging data for model patient-specific tailoring.
- Identifying major determinants of vascular access function and contributing to the definition of treatment strategies for prevention and management of complications.

#### Project Description

The working hypothesis for **ARCH** is that it is possible to tackle the problems concerning vascular access using a modelling approach, which accounts for anatomical, physiological and hemodynamic factors, and their complex interplay. The **ARCH** modelling strategy is made patient-specific by leveraging on non-invasive medical imaging techniques, such as magnetic resonance and ultrasound imaging, using state-of-the-art acquisition protocols and technology.

A detailed model of the patient's circulation, accounting for arterial and venous characteristics, vascular geometry and adaptation to changes in the haemodynamic environment, will be generated on the basis of the available information. In a pre-operative setting, the model will allow the prediction of post-operative flow distribution and short-term function for different types of vascular access, allowing the surgeon to plan the optimal access for the patient. During vascular access management, the model will allow prediction or early detection of complications, such as steal syndrome, intimal hyperplasia and cardiac overload, and will provide the surgeon with a guide for planning vascular access salvage.

The **ARCH** modelling framework will be consolidated in a computational tool provided to end-users

***ARCH is expected to advance the state-of-the-art in vascular access creation and management through the integration of clinical and imaging data, and patient-specific mathematical models***

#### Scenario

Because of end-stage renal disease, a 50 years old human is enrolled in a chronic haemodialysis treatment program. One month before starting the treatment, MRI and ultrasound investigations of the upper extremity circulation and cardiac function are performed. From images and clinical data, the vascular surgeons use a computer based modelling tool, developed within the ARCH project, to examine vessel morphology and blood flow distribution. The system simulates the effect of surgical creation of an arteriovenous shunt that will be used to connect the patient to the artificial kidney machine, and allows to indicate the best surgical plan to optimise chances for vascular access maturation, long term function and to minimize changes in cardiac function.

(applied researchers and clinicians) through an ICT-based service infrastructure. Besides enabling remote access to the modelling tool, the infrastructure will provide advanced computational power and data storage and retrieval capabilities, allowing the implementation of surgical-planning strategies and the generation of outcome predictions in the clinical setting.

Within **ARCH**, strong emphasis is placed upon validation, which will be carried out at multiple levels. Computational models will be first validated experimentally using state-of-the-art *in vitro* set-ups. The modelling framework will then be thoroughly verified in-vivo on extensive datasets acquired from healthy volunteers and from patients.

Finally, the **ARCH** modelling framework will be applied in the context of clinical follow-up studies focused on four major clinical challenges regarding vascular access creation and management, namely short-term maturation, long-term patency, steal syndrome and cardiac failure.

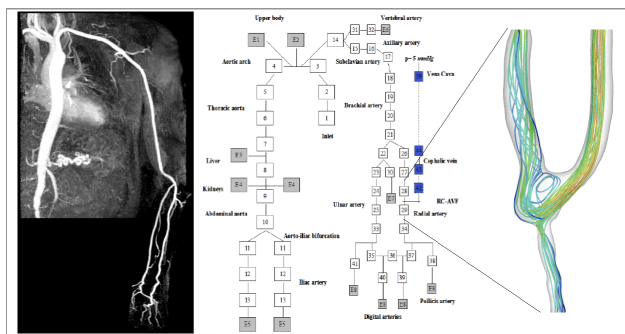
The studies will be designed to allow both calibration and validation of the modelling tool, and to lead to the identification of major determinants of vascular access-related complications.

### Expected Results & Impacts

**ARCH** is ultimately expected to advance the state-of-the-art in vascular access creation and management through the integration of clinical and imaging data and patient-specific mathematical models.

Improvement in vascular access maturation rates, longer vascular access patency, reduced incidence of steal syndrome and heart failure in end-stage renal disease patients undergoing haemodialysis treatment will have a large potential impact on society and healthcare.

Improving vascular access outcome directly translates in better quality of life for the patient and decreased costs for healthcare deriving from reduced hospitalizations and more effective haemodialysis treatment.



## ARCH

**Patient specific image-based computational modelling for improvement of short- and long-term outcome of vascular access in patients on hemodialysis therapy**

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Univerzitetni Klinikni Center Ljubljana (SL)

The University of Sheffield (UK)

Academisch Ziekenhuis Maastricht (NL)

Philips Medical Systems Nederland B.V. (NL)

Philips Electronics Nederland B.V. (NL)

Esote Europe B.V. (NL)

**Timetable:** from 06/2008 – to 05/2011

**Total cost:** 5.683.805 €

**EC funding:** 3.759.499 €

**Instrument:** STREP

**Project Identifier:** FP7-2008-IST-224390

### Keywords:

Clinical decision support systems,  
Surgical planning,  
Hemodynamic simulation,  
Improvement of hemodiaysis therapy,  
Clinical results,  
Clinical image-base IT infrastructure



## Multi-level patient-specific artery and atherogenesis model for outcome prediction, decision support treatment and virtual hand-on training

ARTreat aims at developing a patient-specific computational model of the cardiovascular system, which will be used to improve the quality of prediction for the atherosclerosis progression and propagation into life-threatening events that need to be treated accordingly.

### Objectives of the project

Obstructive lesions (atherosclerotic plaques) become clinically relevant when causing significant local changes that obstruct blood flow. In such cases, they are treated as anatomic problems, focusing only at restoring the specific lesion anatomy and allowing normal flow. However, every time a vasoactive drug is administered, or a lesion is inflated, or a stent is implanted, flow changes occur both locally and globally within the arterial tree, distally or proximally to an intervened lesion or in parallel vessels. Consequently, any intervention changes the local anatomy and blood flow dynamics, thus biologically triggering new sites of plaque formation and/or other mal-conditions on site.

**ARTreat** aims at modelling the mechanical and biological development mechanisms, leading to a better understanding of the process, its treatment, and the individualized prediction of plaque rupture and prognosis of stent re-stenosis.

ARTreat targets the following objectives:

- The development and validation of patient-specific three-level model of the vasculature, integrating artery anatomy, blood flow and particle dynamics that describe the formation and growth of atherosclerotic plaque.
- The development and testing of Treatment Decision Support Tools for assisting cardiologists in (a) selecting appropriate patient treatment and (b) stent positioning during clinical interventions.
- The development and testing of a virtual-training environment for stent-positioning for interventional cardiologists.

### Project Description

The ultimate goal of ARTreat is to develop a patient-specific computational model of the cardiovascular system, which will be used to improve the quality of prediction for the atherosclerosis progression and propagation into life-threatening events that need to be treated accordingly.

It will provide a three-level patient model describing the 3D arterial tree anatomy, the patient-specific blood flow and blood particle dynamics and the biological processes that lead to the creation and progression of atherosclerotic plaques.

ARTreat will apply the developed patient-specific model on two main applications: clinical decision support and training. ARTreat will produce two decision support tools to assist clinical cardiologists into providing personalized treatment selection and real-time, on-the-fly advice during invasive interventions, such as stent positioning. The aim is to minimize future therapy costs, by providing higher than ever personalised treatment support. The same patient-specific model will also be used to develop a real-case training simulator, which will support realistic hands-on training for skill development of clinical cardiologists.

Finally, ARTreat is coupled with advanced clinical support tools for plaque characterization, and the discovery of new knowledge; associations among heterogeneous data, that can improve the predictive power of the patient-model. It thus supports the medical expert into programming the accumulated knowledge into the existing model and generating an adaptive patient-specific computational tool.

### Case studies

ARTreat will focus on the study of two cases, the treatment of carotid stenosis, and the treatment of coronary stenosis with stent positioning. In the first case, the aim is to provide individualized guidance for the selection of the most appropriate treatment regime, either pharmaceutical or invasive intervention. In the second case, the aim is to provide suitable guidance as to the positioning, size and characteristics of the stent used for stenosis treatment, in order to avoid the development of future lesions due to structural changes caused by the invasive intervention and materials used. Coupled with simulation capabilities, ARTreat will also provide a virtual training environment for interventional cardiologists.

## Expected Results & Impacts

ARTreat will contribute to the creation of the future healthcare services, which combine knowledge from the molecule/gene to the cell and the organ/system level. Its results are expected to impact on:

### ● Healthcare productivity by:

- Enhancing the skills and ability of cardiologists to take more informed decisions for the provision of more personalised and adequate treatments
- Enabling the easy accumulation of new knowledge and its quick introduction to the improved prediction capability system

### ● Healthcare quality of service by:

- Assisting in the provision of personalised treatments and elevating healthcare services
- Assisting the patient to better understand the effects of his/her actions to his/her health

### ● Lives and Resource savings by:

- Minimising future invasive interventions through the provision of greater predictive and assistive value services, and therefore minimising the total cost of therapy
- Providing appropriate medical assistance to individualised problems and cases

### ● Patient Safety by:

- Optimising the medical intervention and preventing possible interventional errors

### ● Healthcare Market by:

- Providing a new healthcare product-solution enhanced with more predictive power based on molecule-cell-organ level interaction knowledge
- Enhancing the introduction of new evidenced-based healthcare strategies
- Providing an environment for the testing of new interventional techniques and therapies
- Enabling integration of various resources and interoperability with other systems
- Contributing into the building of the next generation applications that allow the semantic interoperability of different systems to explain biological procedures

### ● EU leadership on medical imaging industry by:

- Strengthening its ability to produce the next generation healthcare systems, enhanced with more predictive power coming from the combination of the available knowledge and science advances at all levels.
- Supporting and enabling the collaboration among specialists from different disciplines, an area of crucial importance to the production of the next generation healthcare services.



## ARTreat

Multi-level patient-specific artery and atherogenesis model for outcome prediction, decision support treatment and virtual hand-on training

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- Intercon, PL
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- Università degli Studi di Parma, IT
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- Consiglio Nazionale delle Ricerche, IT
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- Université de Paris 5 Rene Descartes, FR
- Tecnic, PT
- ASD Advanced Simulation and Design, DE
- EURO (PMS), UK
- Lanza & Thompson, IT
- Computer Sharing Bucuresti, RO

**Timetable:** 09/2008 – 08/2011

**Total cost:** € 10,515,715

**EC funding:** € 7,647,290

**Instrument:** IP

**Project Identifier:** FP7-224297

### Keywords:

Atherogenesis,  
Patient-specific modeling,  
Decision support treatment,  
Virtual training

# ContraCancrum

## Clinically Oriented Translational Cancer Multilevel Modelling

The ContraCancrum project aims at developing a composite multilevel platform for simulating malignant tumour development and tumour and normal tissue response to therapeutic modalities and treatment schedules in order to optimise the disease treatment procedure in the patient's individualized context.

### Objectives of the project

ContraCancrum aims at significantly contributing to the understanding of hypercomplex biological phenomena through the multilevel modelling of cancer in the clinical setting. This will take cancer modelling research a step further by integrating molecular, cellular, tissue and higher level modelling concepts into a single technological entity that will simulate therapy outcome based on the individual patient information. This could serve as a powerful weapon to better understand and fight cancer.

The main objectives of the ContraCancrum project are:

- Develop a composite multilevel simulation model of malignant tumour growth and tumour and normal tissue response to therapeutic modalities and treatment schedules.
- Validate the models, by exploiting the outcome of pertinent clinical trials and designing and carrying out new dedicated clinicogenomic studies in (a) gliomas (b) lung cancer.
- Promote the development of individualised therapies and in silico therapy optimisation.
- Translate, in the mid and long term validated multilevel cancer models into clinical practice.

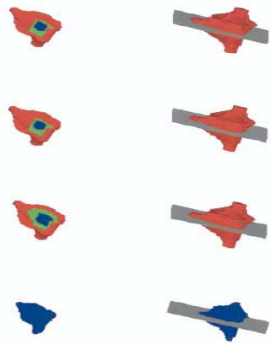
*By utilizing a simulator, the clinician will be able to perform in silico (on the computer) experiments corresponding to different candidate therapeutic scenarios for any cancer patient in order to facilitate and better substantiate his or her treatment decisions.*

### Project Description

**ContraCancrum** aims to enhance the existing tumour simulators well beyond the state-of-the-art, especially on the biochemical level (molecular dynamics), on the molecular level (detailed molecular networks) and on the cellular and upper biocomplexity levels (angiogenesis, embryology considerations, biomechanics, medical image analysis etc.). More significantly, it will bring together different levels of biocomplexity producing an integrated oncosimulator and validating it on two dedicated clinical studies concerning gliomas and lung cancer. The project will model and simulate cancer/normal tissue behaviour at different levels of biocomplexity, and also model a facet of the systemic circulation via pharmacokinetics and synthesize models of hematological reactions to chemotherapy. The models will be positioned markedly beyond the state of the art of the available models and will be clearly multilevel.

In order to construct multi-level simulation models of tumour growth and tumour and normal tissue response to treatment schemes and schedules Contra Cancrum will:

- Develop medical image analysis algorithms and software for extracting pathophysiological information from different levels of diagnostic information (e.g. MRI, CT, PET, and ultrasound). Several bio-medical parameters/markers will be tested in order to optimize information extraction from treatment monitoring medical images.
- Develop macroscopic biomechanical finite element models of the brain and lung to calculate the



### Scenario

It has been established that gliomas are the most common primary central nervous system neoplasms, while Lung cancer is the leading category of cancer death in men, and—since the late 1980s—it has surpassed breast cancer as the leading category of cancer death in women. ContraCancrum will integrate and optimise the simulator for implementing two clinical studies-scenarios corresponding to the two tumour types to be considered. Six University Hospital Departments possessing world acclaimed expertise in running clinical trials will provide multilevel and multimodality sets of data for about 200 patients per year (including both glioma and lung cancer cases).

stress/strain in these tissues. Deformations of both tumour and neighbouring normal tissues will be simulated based on tissue biomechanical properties and detailed anatomic atlases.

- Deploy two important clinical studies for validating the models, one on lung cancer and one on gliomas. The crucial validation work will be based on comparing the multi-level therapy simulation predictions with the actual medical data (including medical images), acquired before and after therapy. ContraCancrum aims to pave the way for translating clinically validated multilevel cancer models into clinical practice.

- Create a workflow environment that will allow remote access to clinical data and will assist the end clinical user to validate the cancer models by using its web services. The project will use open-source software that will allow for future extensions of models as well as the extension to large scale clinical trials.

Data pseudonymization will ensure adoption of the European legal and ethical data handling guidelines.

*ContraCancrum is expected to contribute to the achievement of higher cancer cure rates for the potentially curable patients whereas for the non curable patients it is expected to contribute to the achievement of increased life expectancy and better quality of life.*

### Expected Results & Impacts

ContraCancrum will lead to a 'modelling aided' optimal treatment design for cancer patients that will positively influence the treatment outcome. The project will:

- Achieve more effective healthcare by selecting the optimal therapy for an individual patient.
- Contribute to the development of safer drugs and medical devices [e.g. radiotherapy treatment systems] by providing estimates of the adverse effects of chemotherapy and radiotherapy in parallel with the predictions of tumour response.
- Attract the pharmaceutical industry back to Europe, since its methods will allow the implementation of clinical trials in a more cost effective way.
- Contribute to the understanding of mechanisms of carcinogenesis and tumour growth at several biocomplexity levels.
- Optimise of the design and efficiency of new clinical trials aiming at improving cancer treatment in groups of patients sharing some common pathological characteristics.
- Educate both medical students and interested patients or patients' parents via simulation experiments and visualization of the model's predictions.

## ContraCancrum

### Oriented Translational Cancer Multilevel Modelling

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University College London, UCL UK

Universität Bern UBERN Switzerland

University of Bedfordshire, BED, UK

Univerzita Karlova V Praze, CUNI, Czech Republic

Philips Technologie GmbH, PFL-H, Germany

Timetable: from 01 August 2008 – 30 July 2011

Total cost: €5,167,660

EC funding: €3,786,557

Instrument: STREP

Project Identifier: FP7-2008-IST-223979

#### Keywords:

Cancer multilevel modelling, therapy simulation, molecular modelling, biochemical modelling, cancer imaging, cancer biomechanics.





## euHeart

### Personalised & Integrated Cardiac Care: Patient-specific Cardiovascular Modelling and Simulation for In Silico Disease Understanding & Management and for Medical Device Evaluation & Optimization

The euHeart project aims to use patient-specific cardiovascular modeling as biophysically-based integration framework to improve the diagnosis, planning, and treatment of cardiovascular disease and to reduce the allied healthcare costs.

#### Objectives of the project

Cardiovascular disease (CVD) is a highly relevant and epidemiologically significant contributor to loss of quality and quantity of life within Europe with considerable impact on the European economy.

Numerous diagnostic techniques are available to assess the presence and severity of CVD, ranging from electrocardiography (ECG) through imaging techniques (e.g. magnetic resonance imaging) to invasive tests. These techniques have been continuously refined, and can now derive exact and quantitative data. However, in current clinical practice data from different modalities are not optimally combined. Results from different tests may

*"euHeart will allow to select the best therapy and to optimize treatment outcome for individual patients affected by cardiovascular disease"*

even be contradictory, as they measure different aspects of disease, which vary considerable even in healthy people.

**euHeart** aims to improve diagnosis, planning and treatment of CVD by using new computing tools and modelling approaches to generate patient-specific models of the heart and

the aorta in clinical environments.

**euHeart** will use multi-scale models linking molecular, sub-cellular and cellular functions to whole organ performance, via physiological function. This will improve CVD outcomes by providing a consistent, biophysically-based framework for the integration of the fragmented and inhomogeneous data currently available. In addition, these models help to understand the complex and multi-factorial disease mechanisms which play a key role in the pathology of disease.

#### Project Description

**Clinical focus – euHeart** will collect evidence of clinical benefit to quantify the potential impact of multi-scale modelling for a number of CVD and associated therapies which are significant in terms of both healthcare spent and quality of life in Europe: namely:

- heart failure through cardiac resynchronization therapy (CRT)
- heart failure through congenital cardiac surgery and left ventricular assist devices
- cardiac rhythm disorder through radiofrequency ablation
- coronary artery disease through revascularization using coronary stents
- diagnosis and treatment of valvular and aortic diseases.

Each of the selected clinical applications provides a complementary focus for the resulting integrated models of cardiac fluid-electro-mechanical function.

**Validation** – The validation of the models will be carried out in clinical environments on cohorts of patients using dedicated prototypes. In addition, one small-scale multicenter pilot trial, including approximately 120 patients, will be performed to demonstrate the clinical benefit in determining the optimal lead placement and pacing sequence in CRT, a treatment that improves the coordination of the heart's contraction.

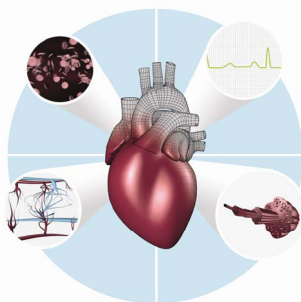
**Multi-disciplinary project** – The development of clinical prototypes requires the integration of numerous multi-disciplinary tools which will be developed leveraging the complementary expertise available within the **euHeart** consortium. More specifically, we will focus on the following activities:

#### Scenario

Jim M., 70 years old, survived a severe heart attack which affected part of his heart muscle irrecoverably, leading to congestive heart failure. As the symptoms worsen despite optimal drug therapy, Jim's cardiologist thinks about implanting a pacemaker system (CRT) to optimize his heart function. The wide range of anatomical and functional data collected during the examinations is then provided to the **euHeart** system which personalises a virtual heart model to reflect Jim's conditions. This personalised computer model predicts that Jim will respond well to the implantation. It also proposes an optimal treatment plan indicating where to position the pacemaker leads in the heart and how to operate them. This plan is finally combined with interventional data to guide the cardiologist during his manipulations.



- To develop, exchange and integrate multi-physics and multi-scale models of the heart and aorta in normal and pathological conditions using the international encoding standards CellML and FieldML.
- To develop and apply specific and general strategies for model personalisation, i.e. to adapt the model parameters to reflect the condition of a specific patient using anatomical and functional information. Effective personalisation is a crucial component to enable personalisation of care.
- To develop and validate automated methods for the consistent interpretation of multi-modal clinical images, a prerequisite to enable translation into clinical environments.
- To develop tools for the fusion and visualization of the clinical data and physiological information into the same spatial and temporal domains.
- To develop environments for the optimization of surgical interventions and tuning of devices for better treatment delivery and clinical outcome.



### Expected Results & Impacts

**euHeart** is expected to have substantial impact for:

#### The patients / society:

- improvement of treatment through personalisation of care (vs. population-based metrics)
- increased safety of care through integration into image guided interventional systems
- reduction of medical costs and treatment duration

#### The clinicians:

- higher confidence in decisions through better quantification of CVD
- improved therapy outcome through *in silico*-based optimised planning
- better understanding of the underlying pathology
- consistent biophysically-based platform for the integration of the fragmented and inhomogeneous data acquired throughout the cardiac care cycle

#### The industry:

- improved analysis software moving from purely descriptive data interpretation towards biophysically-based disease quantification and prediction of disease progression
- personalisation of implantable devices through patient-specific simulations optimizing treatment outcome
- enhancement of interventional devices

### euHeart

Personalised & Integrated Cardiac Care: Patient-specific Cardiovascular Modelling and Simulation for In Silico Disease Understanding & Management and for Medical Device Evaluation & Optimization

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- Universitat Pompeu Fabra (SP)
- The University of Sheffield (UK)
- Institut National de Recherche en Informatique et Automatique, INRIA (FR)
- King's College London (UK)
- Academisch Medisch Centrum bij de Universiteit van Amsterdam (NL)
- Universitaet Karlsruhe (TH) (DE)
- Institut National de la Santé et de la Recherche Médicale, INSERM (FR)
- Deutsches Krebsforschungszentrum Heidelberg (DE)
- Hospital Clínico San Carlos de Madrid (SP)
- Philips Medical Systems Nederland BV (NL)
- Berlin Heart GmbH (DE)
- HemoLab BV (NL)
- Volcano Europe SA / NV (BE)
- PolyDimensions GmbH (DE)
- Philips Ibérica S.A. (SP)

**Timetable:** from 06/08 – to 05/12

**Total cost:** € 19.053.465

**EC funding:** € 13.900.000

**Instrument:** IP

**Project Identifier:** FP7-2008-IST-224495

#### Keywords:

Cardiac disease and diagnosis, personalised and integrated treatment, virtual physiological heart, biophysical simulations, clinical validations



# HAMAM

## Highly Accurate Breast Cancer Diagnosis through Integration of Biological Knowledge, Novel Imaging Modalities, and Modelling

Improving breast cancer diagnosis

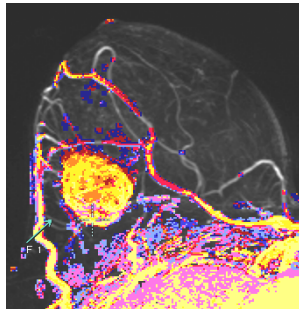
HAMAM will tackle the challenge of early detection and accurate diagnosis of breast cancer by integrating available multi-modal images and patient information on a single clinical workstation. Based on knowledge gained from a large multi-disciplinary database, populated within the scope of this project, suspicious breast tissue will be characterised and classified.

### Objectives of the project

Despite tremendous advances in modern imaging technology, both early detection and accurate diagnosis of breast cancer are still unresolved challenges. Unnecessary biopsies are taken and tumours frequently go undetected until a stage where therapy is costly or unsuccessful.

**HAMAM** will tackle this challenge by providing a means to seamlessly integrate the available multi-modal images and the patient information on a single clinical workstation. Based on knowledge gained from a large multi-disciplinary database, populated within the scope of this project, suspicious breast tissue will be characterised and classified.

The exact diagnosis of suspicious breast tissue is ambiguous in many cases. **HAMAM** will resolve this using statistical knowledge extracted from the large case database. The clinical workstation will suggest additional image modalities that may be captured to optimally resolve these uncertainties. The workstation thus guides the clinician in establishing a patient-specific optimal diagnosis. This ultimately leads to a more specific and sensitive individual diagnosis.



**HAMAM** advances the state-of-the-art as it proposes a sound statistical and mathematical framework to integrate and combine the whole spectrum of patient information. **HAMAM** also goes beyond currently available technology by developing a prototypical solution that will be able to efficiently integrate all relevant clinical and imaging information within a single platform.

The overall strategy of the project is to foster the exchange and collaboration between basic scientists, clinicians, and IT experts, and to condense all information and knowledge in a common database and prototypical platform for multi-modal breast diagnosis.

### Project Description

Breast cancer diagnostics is in a phase of transition. This is characterised by the fact that new imaging technologies specially designed for breast imaging, such as 3D ultrasound or tomosynthesis, complement the conventional imaging technologies like mammography and 2D ultrasound. A rational use of these new modalities is currently the major challenge of breast cancer diagnosis. To meet this challenge, **HAMAM** integrates excellent European centres for imaging science with strong skills on breast imaging. To ensure the clinical impact, leading European clinicians in the area of breast cancer diagnosis are contributing as members of the clinical advisory board. The translation of the final results into medical products and patient benefit is guaranteed through the industrial partner MeVis Medical Solutions AG (MMS) with outstanding experience and performance in translating research projects into successful products in the field of breast cancer diagnosis.

**HAMAM** is a successor of the very successful EU-projects SCREEN and SCREEN-TRIAL. These projects brought major advances in European breast cancer diagnosis, meaning that today Europe is the world leader in diagnostic systems for digital mammography. With **HAMAM**, Europe has the potential to strengthen its leadership in the whole area of image-based breast cancer diagnoses.

**HAMAM** will:

1 – Build the tools needed to integrate datasets from multiple modalities into a single interface. This will

Include patient clinical history, family history, pathology and clinical outcomes,

Provide comparison and analysis of modalities and

Include adaption of individual patients and local clinical practices.

2 – Provide pre-processing / standardisation tools that will allow for optimal comparison of disparate data

### Scenario

Fighting cancer would ideally be accomplished by preventing the onset of the disease. For breast cancer, the most widespread cancer among women, prevention in its proper sense is not foreseen as its causes remain undiscovered. Around 350,000 new breast cancer cases are found and 130,000 women die of breast cancer in Europe every year. This amounts to 26% of all new cancer cases among women and over 17% of cancer deaths. Currently, the primary goal of fighting breast cancer is its early detection in order to prevent a fully developed stage of the disease.

3 – Build spatial correlation information datasets to allow for new similarity and multi-modal tissue models. These will be key in the detection and diagnosis of breast cancer.

4 – Build in adaptability that allows for the integration of other sources of knowledge such as

Tumour models,

Known risk factors including family history of cancer, hormonal and environmental factors,

Genetic data including mutation status at high risk loci,

Tumour pathology, prognostic factors such as tumour size, nodal status, distant metastasis and receptor, treatment and outcome and

Standardised imaging.

5 – Build a teaching file that will be used to train clinicians in actually using the technologies and knowledge acquired in this project.

### Expected Results & Impacts

The final results of **HAMAM** will provide the tools for the improvement of both the sensitivity and specificity of breast cancer detection and diagnosis. **HAMAM** is not driven by the extensive utilisation of technological achievements or by fostering a high-tech medicine that applies virtually every available diagnostic option to all patients in question.

Instead, the goal is to deliver objective information that is fundamental for assessing the value of various new modalities for breast cancer diagnosis. This represents a major challenge, to provide the necessary tools to efficiently use the set of multi-modal imaging techniques towards an optimised and individualised patient care.

Before any of the new technologies can replace existing modalities for breast cancer screening, knowledge must be gathered to objectively compare their potentials for specific clinical questions.

To this end, a dedicated knowledge base that comprises a unique set of multi-modal breast imaging and histological data will be assembled during the project.

From a technological perspective, the project will develop clinical software tools that integrate imaging and quantitative data from all relevant modalities and combine it with knowledge extracted from a large sample case database. Physiological and biophysical modelling will also serve as a basis for a standardised analysis of functional and morphological data.

### HAMAM

Highly Accurate Breast Cancer Diagnosis through Integration of Biological Knowledge, Novel Imaging Modalities, and Modelling

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MeVis Research gGmbH (DE),  
MeVis Medical Solutions AG (DE),  
Eidgenoessische Technische Hochschule Zuerich (CH),  
Radboud Universiteit Nijmegen - Stichting Katholieke Universiteit (NL),  
The University of Dundee (IE),  
Charite-Universitätsmedizin Berlin (DE),  
Boca Raton Community Hospital, Inc (US)

Timetable: from 09/08 – to 08/11

Total cost: € 4,245,012

EC funding: € 3,099,723

Instrument: STREP

Project Identifier: IST-2007-224538

Keywords:

breast cancer,  
diagnosis, imaging,  
early detection,  
modelling





## Image-based Multi-scale Physiological Planning for Ablation Cancer Treatment

IMPACT develops an intervention planning system for Radiofrequency Ablation of malignant liver tumours accounting for patient specific physiological factors. Validation is performed at multiple levels through comparison of simulation and treatment results gathered in animal studies and during patient treatment.

### Objectives of the project

Radiofrequency Ablation (RFA) is a minimally invasive form to treat cancer without open surgery, by placing a needle inside the malignancy and destroying it through intensive heating. Though the advantages of this approach are obvious, the intervention is currently hard to plan, almost impossible to monitor or assess, and therefore is not the first choice for treatment.

IMPACT will develop a physiological model of the liver and simulate the RFA intervention's result, accounting for patient specific physiological factors.

- Closing gaps in the understanding of particular aspects of the RFA treatment by multi-scale studies on cells and animals;
- Embedding microscopic findings into a macroscopic model for heat conductivity by liver tissues;
- Extending the long-established bio-heat equation to incorporate multiple scales;
- Cross checking validity for human physiology by comparison against images from ongoing patient treatments;
- Visual comparison of simulation and treatment results gathered in animal studies and during patient treatment;
- Validating results at multiple levels and with a user-centred software to guarantee best suitability of the model for clinical practice;

### Project Description

Predicting the intervention result physiologically correct demands an accurate and verified patient specific mathematical model. A bottleneck on the way towards the patient specific planning tool is our

so far limited understanding of processes during tissue heating and, ultimately, tissue death as the result of that heating. IMPACT aims at opening this bottleneck by generating new insight into **physiological processes and biochemical reactions in the context of tissue heating.**

Heating has a strong influence on perfusion of tissue, reaction rates in chemical processes, as well as the organ's and overall system's health condition. Local hyperthermia can be used to kill a limited volume of cells while keeping surrounding parts vital and healthy. Many different treatment strategies rely on this approach.

IMPACT attacks the challenge of predicting the RFA process by **computational modelling and simulation.**

The long existing bio-heat equation needs to be revised. Cellular behaviour during heating and cell death (microscopic level) determine the final (macroscopic) shape of the necrosis zone significantly, but these processes have not yet been adequately modelled. Furthermore, constants in the presently used equation are in fact not universal but **patient specific parameters.**

The necessary **multi-scale simulation** approach leads to numerically solving partial differential equations in 3D using the finite element method. Results and variations will be handled in a flexible solution space to allow

*IMPACT will create the Intervention Planning System (IPS) as a clinically relevant application.*

*To model the RFA process properly and in a verified manner, its mathematical description has to be validated against experimental results.*

### Scenario

A patient diagnosed with tumours in the liver enters the hospital to be treated by RFA. Several radiological images are taken from him as preparation for the intervention. A patient specific model is created and prepared for interactive simulation of results. Now the radiologist in charge uses the model simulations to predict the intervention results. Based on personal assessment of the situation the radiologist selects a good needle position and ablation protocol. The model allows watching the intervention result prior to the treatment while testing a variety of alternative approaches before taking final decision on the best intervention plan. The patient receives the best possible treatment for his specific case and leaves the hospital two days later with minimal side effects on his life.



**interactive planning and visualization** of treatment results. All modifications as well as simulation results will be **validated in phantom and animal experiments and cross compared to ongoing clinical patient treatment.** Accurate reconstruction of identifiable and physiologically meaningful 3D anatomical structures from images demands new image processing tools. A workflow oriented approach guarantees its suitability to clinical practice.

Furthermore, an **augmented reality training simulator** will teach surgeons optimal RFA application, before they start using this treatment. ***Augmented reality training simulator raises acceptance for the Intervention Planning System*** IMPPACT will bring RFA from its last resort status up to the treatment of choice for hepatic cellular carcinomas and liver metastases. In creating the training simulator a methodology for identifying the key features in every simulation step and aspect will be developed and thereby push research on medical augmented reality training simulators far forwards.

### Expected Results & Impacts

IMPPACT will be modelling a physiological organ including the metabolism and patient specific tissue properties. This alone is a huge step forward as compared to the state-of-the-art intervention planning systems that do not address this issue.

The IPS will allow prediction of treatment results on a patient specific base. It will therefore bring down the risk of local recurrences and eliminate the nowadays so common repeated treatments of the same tumour, making RFA an as effective treatment as resection.

At the same time the IPS will make RFA treatment much safer. By reliably predicting tissue heating it will warn of possible damage to surrounding organs in advance and allows choosing a safe needle position and path.

The greatest impact will be achieved by installing the created application in many hospitals in Europe. To be able to directly use the IPS in clinical practice medical personnel in those hospitals needs to be trained in using it. The augmented reality training simulator provides an excellent opportunity as it trains surgeons directly with the IPS.

All developed software will be open source and run with common hospital equipment. Its deployment to virtually every hospital in Europe is solely a question of using a deployment infrastructure.

## IMPPACT

### Image-based Multi-scale Physiologically Planning of Ablation Cancer Treatment

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Teknillinen korkeakoulu (Finland)

The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom)

NUMA Engineering Services Ltd (Ireland)

Timetable: from 01/09/2008-to 31/08/2011

Total cost: € 4,351,275

EC funding: € 3,463,367

Instrument: STREP

Project Identifier: FP7-2008-IST-223877

#### Keywords:

Medical visual computing

Patient-specific modelling

Multi-scale validation

Interactive simulation

Augmented-reality simulator

# NeoMark

## ICT Enabled Prediction of Cancer Recurrence

**NeoMark** will record and combine heterogeneous clinical, laboratory, molecular and imaging data to develop a data integration environment facilitating **multiscale and multilevel modelling**, aimed at advancing models and methods currently in use to **predict neoplastic recurrences**, and to apply it to the study of **oral cancer**.

### Objectives of the project

#### The clinical problem

The continuous improvement in treatment protocols for neoplastic diseases has substantially increased the number of patients who achieve a complete disappearance of the disease after treatment. At this stage there are no clinical, laboratory or imaging evidences of the neoplastic mass, but there can still be invisible residual disease that can evolve overtime and metastasize. A strict follow-up is usually undertaken and adjuvant treatments are planned to reduce the risk of disease recurrence, however they have important side-effects that may harm also patients who are already completely recovered. **Knowing in advance which patients have the higher risk of disease recurrence** would be important to focus resources and initiate adjuvant treatments only in a limited, high-risk subgroup of patients and would allow **starting an appropriate treatment in time with the potential to improve patient survival and quality of life**.

#### NeoMark Project

**NeoMark** will pursue the identification of imaging

and genomic/ proteomic markers aimed at modelling recurrence of neoplastic disease with two major **clinical/scientific purposes**:

1. identify subjects at higher risk of recurrence after reaching remission;
2. early diagnose the presence of a recurrence.

The **technical target** of NeoMark will be the development of two functional environments: one for the definition of biomarker profiles and one for the follow-up of the evolution of the disease.

### Project Description

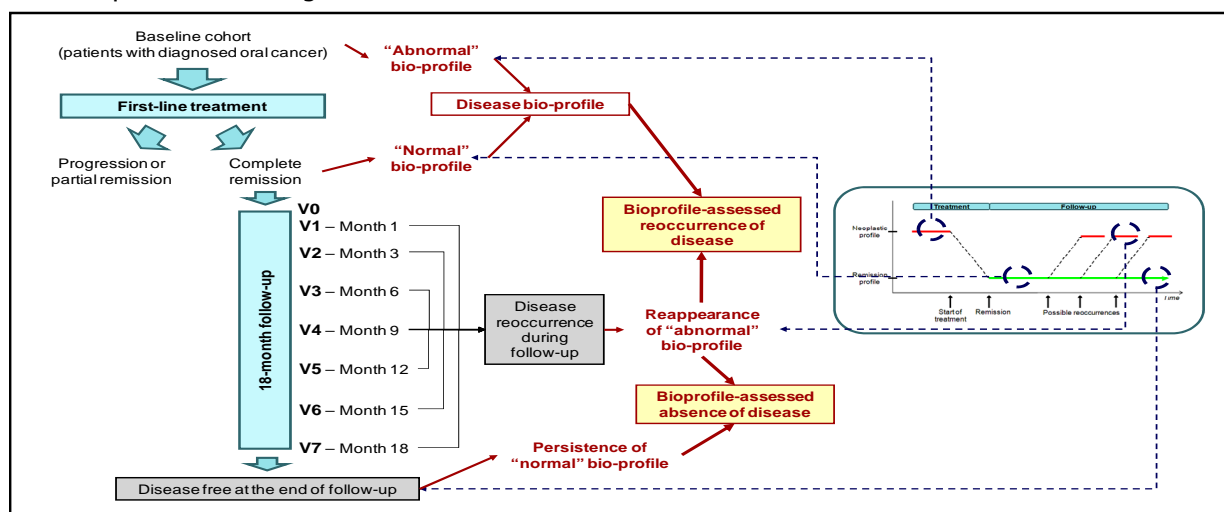
The **NeoMark** project starts from the need of researchers and clinicians in the field of oncology to improve the representation of biological processes related to onset, growth and dissemination of human cancer. The approach chosen by **NeoMark** is to address this need through in-silico representation, modelling and prediction of biological phenomena linked to the disease evolution (so-called Virtual Physiological Human approach, or VPH in short).

The **NeoMark** scientific approach envisions the

### Scenario of future clinical applications

**NeoMark** identifies the patient-specific markers (fingerprint) for oral cancer so detecting low-risk and high-risk for recurrence patients so enabling the most adequate, more targeted and less invasive treatments, optimising medical end financial resources and improving patients' quality of life.

For patients with high risk of recurrence NeoMark will prepare a patient-specific biological signature for recurrence and will elaborate a personalized model of disease evolution. The patient is strictly followed-up and whenever the signature reappears, the patient is considered as probably having a recurrence and adequate further diagnostic and treatment measures are undertaken.



**integration of heterogeneous clinical, laboratory, molecular and imaging data** – each of which belongs to a different level of biological complexity, and therefore provides a different level of representation of the disease – to **produce a synergic effect on tumour biology representation**. The aim is to provide researchers and clinicians with a higher-level of complexity in disease information and to apply this view to clinical oncology, especially in the complex field of the early identification of disease reoccurrence after complete remission. This includes the **"individualization of the disease"**, which means the identification of sets of markers that are specific for the disease in a specific patient (patient's "fingerprint" of the disease). Therefore NeoMark will tackle the challenge of identifying both a **"disease-specific"** and a **"patient-specific"** profile of oral cancer.

The outcomes of the project will be validated in two primary Clinical Centres in Spain and in Italy. The early exploitation of NeoMark will also be assessed through the use of a **new technical device** (RT-PCR platform) to develop highly individual diagnostic tests to be used both at the time of first diagnosis, as well as for reoccurrence identification.

### Expected Results & Impacts

Oral cancer holds the eight position in the cancer incidence ranking worldwide, squamous cell carcinoma representing 5% of all cancers for men and 2% for women (WHO). Patients with oral cancer have to deal with the **impact of the disease and its treatment on physical appearance and on the ability to eat and to speak**, with a significant decrease of the quality of life. Despite advances in salvage treatment of patients with recurrent cancer, outcomes for re-treatment are generally poor. Hence the importance of the identification of specific "markers" for oral cancer whose appearance during follow-ups will enable early and softer interventions and decrease the risks of death.

**NeoMark** expects to develop a system able to early detect the "markers" specific for oral cancer and so enable:

- early and more specific diagnosis of cancer reoccurrences;
- more targeted and effective interventions based on the patient-specific disease profile;
- avoiding unnecessary treatments for patients at very low risk of reoccurrence;
- optimising the work of physicians and the usage of resources;
- improving the scientific and medical knowledge on oral cancer processes;
- improve patients' quality of life;
- increase the life duration for patients with cancer reoccurrence.

## NeoMark

### ICT Enabled Prediction of Cancer Reoccurrence

#### Project co-ordinator:

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- STMicroelectronics S.R.L. (Italy)
- Fundacion MD Anderson International España (Spain)
- Link Consulting – Tecnologias de Informaçao S.A. (Portugal)
- Universidad Politécnic de Madrid (Spain)
- MultiMed S.R.L. (Italy)
- Panepistimio Ioanninon (Greece)
- PLANET AE (Greece)

**Timetable:** from June 2008– to August 2010

**Total cost:** € 4,205,555.47

**EC funding:** € 2,896,600.00

**Instrument:** STREP

**Project Identifier:** FP7-2007-ICT-224483

#### Keywords:

eHealth,  
Virtual Physiological Human,  
Integromics, IT,  
Monitoring,  
Predictive Modelling

# PASSPORT

## Patient Specific Simulation and PreOperative Realistic Training for liver surgery

PASSPORT aims at developing a dynamic liver modelling, which thanks to a preoperative surgical planning simulator, will allow to predict a surgery's feasibility and thus increase the rate of surgical treatment so as to save patients suffering from liver pathologies.

### Objectives of the project

The liver is one of the major organs in the human body and is in charge of more than 100 vital functions. Because of its many functions, its pathologies are also varied, numerous and unfortunately often lethal. In 2006, over 45.000 European citizens died of liver cirrhosis and 44.000 additional citizens of liver cancer, knowing that the same year 48.700 new liver cancer cases were declared and that the 5-year survival rate of liver cancer is 10%. The eligibility of a patient for a tumour resection is linked to a large set of parameters provided by clinical examination, medical imaging and biological analysis.

**PASSPORT** aims at offering the first patient-specific modelling that combines anatomical, mechanical, appearance and biological preoperative modelled information in a unified model of the patient so as to propose the first complete "Virtual Liver". To reach this objective, **PASSPORT** will:

- develop an innovative open-source and multi-level patient-specific model combining anatomical, mechanical, functional and biological liver properties,
- develop novel dynamic modelling, integrating predictive liver regeneration, organ motion and deformation and providing the patient-specific minimal safety standardized FLR,
- generate a highly realistic simulation environment for liver surgery planning and training,
- validate all simulation models with internationally renowned medical experts.

### Project Description

A 3-year work schedule will help to reach the scientific and technological objectives of **PASSPORT**.

The first step will consist in defining the 4 anatomical, mechanical, appearance and biological models on all information available on liver pre-operative images and surrounding anatomical and pathological structures. It includes anatomical information extracted from CT-scan, MRI or US, mechanical properties extracted from elastographic imaging, functional and biological information extracted from biopsy and blood analysis. These first 4 research orientations will each be dedicated to the development of one specific model.

Then, dynamics will have to be added to this static modelling through the development of organ motion and deformation modelling. All these 5 models will then be integrated in an open-source framework allowing to exploit them in a unified patient-specific modelling, which is the "heart" of the **PASSPORT** project.

As a result of all this data, the next step will consist in developing patient-specific pre-operative liver surgery planning, not only limited to liver volume and geometry, but also integrating the previous unified modelling by providing the minimal safety standardized Future Liver Remain (FLR). In parallel to this development, the project will develop patient-specific simulators for liver surgery allowing:

- the education of such procedures
- pre-operative simulation.

The described models will be integrated for simulation on an international open-source platform allowing both a better dissemination of results and a possible extension of results in other areas of the

### Scenario

A patient undergoes a CT-scan and an elastography depicting 2 tumours and a hepatic fibrosis. From these images the PASSPORT software provides a geometrical, topological, mechanical, anatomical and appearance model of the liver and neighbouring organs. From a microscopic biopsy image combined with a diffusion image of the liver another PASSPORT software provides a biological modelling of the liver defining thus the minimal safety standardized FLR of the patient. All these models are then used in a preoperative surgical simulator allowing to plan the surgical intervention and train surgeons demonstrating the feasibility of the gesture that initially seemed impossible.

human body as well as other types of pathologies.

All these research developments will lead to a demonstration software which will be evaluated and tested by medical experts in liver surgery.

Due to the large number of static or dynamic models, **PASSPORT** is based on a large number of renowned partners or associated partners; each specialized in one or two modelling techniques or providing a clinical validation of the result. Each hospital and surgical team will be directly involved, as associated partner, in the validation of project outcomes which is vital for the development and success of that kind of technology.

**Expected Results & Impacts**

Eligibility for surgical resection is not only based on geometrical information (total liver volume) or topological information (vascular networks), but also on the physiological and biological state of patients (due to chemotherapy or pathology such as fibrosis). The resulting minimal safety standardized FLR is therefore a dynamic patient-specific value. The current evaluation of this value remains approximate and is very generic, reducing surgical eligibility. **PASSPORT** proposes to solve this complex limitation by developing the first patient-specific virtual liver, which will be composed of several integrated models providing all required information: anatomy, mechanics, appearance, and microbiology. By integrating these models in a unified virtual liver, **PASSPORT** allows the development of regeneration simulation and patient-specific preoperative surgical planning and simulation. This contributes to realize safe, controlled and predictable liver surgeries and thus, potentially increases the rate of operative solutions which will heal and save patients with serious liver diseases.

**PASSPORT** also helps reinforcing the European competitiveness and market perspectives. Indeed, the international market in surgical simulation is currently changing due to the involvement of the surgical industry. **PASSPORT** will offer Europe's leading company in surgical instrumentation a real and efficient competitive tool on the surgical market against its international competitors.

**PASSPORT**

**PATient Specific Simulation and PreOperative Realistic Training for liver surgery**

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*Realizing safe, controlled and predictable liver interventions.*

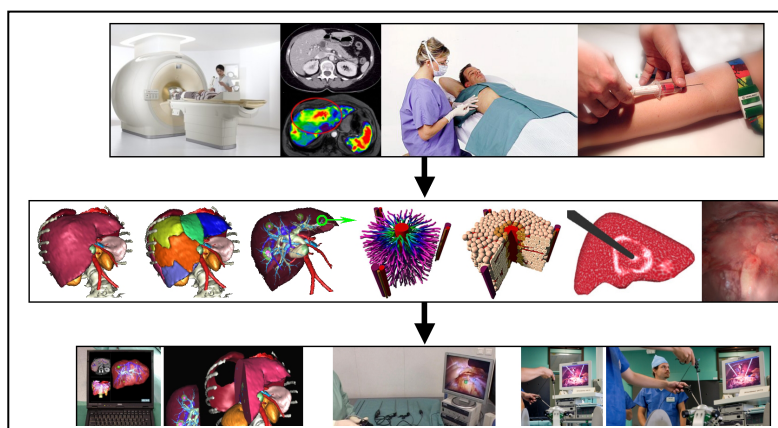
Partners:

- Eidgenoessische Technische Hochschule Zuerich, Switzerland
- Technische Universitaet Muenchen, Germany
- Imperial College of Science, technology and Medicine, UK
- Institut National de Recherche en Informatique et en Automatique, France
- Universitaet Leipzig, Germany
- University College London, UK
- Université Louis Pasteur, France
- KARL STORZ GmbH & CO. KG, Germany
- Institut National de la Santé et de la Recherche Médicale, France

Timetable: from 1<sup>st</sup> June 2008 to 31<sup>st</sup> March 2011  
 Total cost: 5.46 million €  
 EC funding: 3.64 million €  
 Instrument: STREP  
 Project Identifier: FP7 ICT-2007-223894

**Keywords:**

Liver, 3D Mesher, Segmentation, Anatomical modelling, Elastography, Texture, Biological, Dynamic, Vertical integration.





# preDiCT

(Computational Prediction of Drug Cardiac Toxicity)  
Predicting Drug Interactions



The preDiCT project will model and ultimately predict the impact of pharmaceutical compounds on the heart's rhythm using computer simulation. Using this information, the project hopes to identify new biomarkers which will provide more reliable indication of harmful drug side effects.

## Objectives of the project

### Problem or Context:

Current best practice in pharmaceutical development relies on the Q-T interval (the spacing of two points on an electrocardiogram) as a proxy for potentially dangerous side effects. However, it is known that some drugs which fail this test do not lead to arrhythmia (e.g. Ranolazine, whose safety was demonstrated by researchers at the University of Oxford). We hope to be able to develop more accurate gauges of potential cardiotoxicity.

A significant and growing number of drug candidates fail to reach market due to adverse effects on heart rhythm which only show up during clinical trials. We hope to achieve a better understanding of the underlying mechanisms, which may lead to refinement of the drug development process to avoid these side effects.

### Project:

The preDiCT project will model and ultimately predict the impact of pharmaceutical compounds on the heart's rhythm using computer simulation.

This will require advances beyond the current state-of-the-art in:

- Mathematical models of individual ion channels, which control the electrical activation of each heart cell;
- Tissue models, which encapsulate chemical processes and physical relationships between millions of individual muscle cells in

the heart; and

- The computer code, which must compute these relationships as a series of complex equations, to enable faster-than-real-time simulation of a beating heart.

## Project Description

The preDiCT project aims to create an advanced ICT environment for investigating the efficacy and safety of specific drugs, using computer models to simulate drug interactions faster than real-time.

To do this, currently available mathematical models of cardiac cells will be checked, refined and extended to include drug interactions. The models will take into account known genetic mutations of important ion channels, to enable population-specific risk assessment for a given drug, and some types of patient-specific risk-assessment will also be possible.

These models will be built from, and validated against, experimental data from the scientific literature and provided by preDiCT's pharmaceutical industry partners. Significant work will be required to 'normalise' these data with respect to the experimental protocols used to acquire them, in order to make them directly comparable.

The project will investigate new algorithms for comparing animal species and human data at the level of cells, which is the largest source of experimental data. These results will then be incorporated into tissue models, to include the effects of interaction between cells.

In order to compute drug effects on human ventricles faster than real-time, the project will need to research and develop highly efficient numerical

## Scenario

Given that most of the costs of bringing a new drug to market are incurred during the clinical trials phases, there would be a huge economic and clinical impact for being able more accurately to predict which drugs are likely to cause arrhythmias. Even when drugs do make it through to clinical trials, the statistical power of those trials is often insufficient to predict adverse effects which may (As recently in the cases of Vioxx and Celebrex) appear only when the drug is given to large numbers of patients over long periods of time. A more predictive approach holds out hope of being able to spot and preempt these very-low-probability effects.

algorithms and their implementation on massively parallel computers. The consortium will make use of extensive high-performance computing facilities in the UK, Italy and Japan.

A better understanding of the factors determining species-dependent drug interactions, combined with analysis of ECG signals and the assessment of arrhythmogenic factors, will enable the investigation of new and better biomarkers to complement current drug-safety metrics.

All the tools will be integrated into a Virtual Research Environment: an integrative portal to the complex set of tools and information needed to conduct *in silico* experiments. The VRE will be designed for everyday use by academic researchers and pharmaceutical industry scientists, to facilitate more extensive use of *in silico* methods in the drug discovery and development process.

The traceability of the complete project will be ensured by storing all the results and simulations, including the metadata describing the *in silico* experiments, and the models developed will be provided to the wider community via the CellML 1.1 repository.

### Expected Results & Impacts

The preDiCT project aims to improve our understanding of the mechanisms of negative drug actions on the heart, which will:

- Improve safety testing for new drugs;
- Help speed up and streamline the drug discovery process by identifying likely profiles of 'good' and 'risky' compounds (the pharmaceutical industry currently spends nearly €3bn per new approved drug);
- Help pave the way to patient-specific healthcare through simulation;
- Push the boundaries of simulation and high-performance computing, enabling progress in scientific research in many areas.

Furthermore, by extending the frontiers of *in silico* experimentation, our project will enable future researchers to refine, replace and ultimately reduce the use of animals in pharmaceutical and other cardiac research.

### preDiCT

#### Computational Prediction of Drug Cardiac Toxicity

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- Centro di Ricerca, Sviluppo e Studi Superiori in Sardegna (CRS4, Italy)
- Fujitsu Laboratories of Europe (UK)
- GlaxoSmithKline Research and Development (UK)
- Novartis Pharma (Switzerland)
- F Hoffmann-LaRoche (Switzerland)
- Szegedi Tudományegyetem (University of Szeged, Hungary)
- Universidad Politécnica de Valencia (Spain)
- University of Oxford (UK)

Timetable: 06/08 – 05/11

Total cost: €5.5M

EC funding: €4.1M

Instrument: STREP

Project Identifier: FP7-2008-IST-224381

#### Keywords:

Cardiac, heart, drug, toxicity, arrhythmia, simulation

## PredictAD

### From Patient Data to Personalised Healthcare in Alzheimer's Disease

PREDICTAD aims to develop an objective tool for enabling earlier diagnosis of Alzheimer's disease. Biomarkers derived from various data sources of patient monitoring, such as neuropsychological tests, medical imaging, electrical brain activity measurements and blood samples will be studied and combined.

#### Objectives of the project

**Context:** Alzheimer's disease (AD) causes long and oppressive suffering and imposes enormous costs on society. Because Alzheimer's disease is expected to quadruple its global prevalence to 106 million by 2050, dementia will be one of the main health issues of the next decades. Currently, there is no curative treatment for AD. When new drugs or prevention strategies become available, early detection, even pre-symptomatic, of the disease will become essential in selecting patients for treatment. Today there is no single test or biomarker that can predict whether a particular person will develop the disease.

**Project:** PredictAD's goal is to provide a standardised and objective tool for enabling earlier diagnoses of AD, improved monitoring of treatment efficacy, and improved cost-effectiveness of diagnostic protocols. The main objectives are to

- define efficient biomarkers from heterogeneous patient data and integrate them for making early diagnosis and progress monitoring of AD more efficient, reliable and objective,
- improve the cost-effectiveness of AD diagnostics by optimizing diagnostic protocols, and
- develop and validate an efficient software tool that physicians can use to diagnose and to monitor the progress of AD in real clinical conditions using heterogeneous patient data.

#### Project Description

Heterogeneous data including clinical data such as neuropsychological test scores, MRI imaging, PET (FDG/PIB) imaging, TMS/EEG and biomarkers detected from blood (metabolomic, proteomic) will be integrated to identify an efficient combination of markers for early diagnosis of AD and longitudinal follow up.

The project can be divided into three main parts: data quantification, biomarker discovery and visualisation, and validation (Fig. 1).

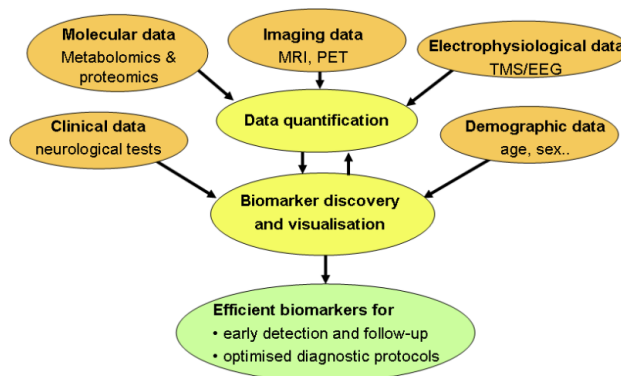


Fig. 1. PredictAD approach.

**Data quantification.** Methods are developed and applied for extracting various biomarkers from data. For example with imaging data, this includes the development of image segmentation methods for quantifying MRI images.

**Biomarker discovery and visualisation.** Hundreds of biomarkers, also completely new biomarkers, are defined from the clinical, genetic, imaging, electrophysiological, metabolomic and proteomic data. Thorough statistical analysis will be applied to these biomarkers to define the relevance and the efficient set of biomarkers, and the optimal way to combine them. The statistical model developed will be strictly evidence-based allowing personalised healthcare, e.g., taking into account the age and gender of the patient during the analysis. In addition, a software tool will be developed visualising data and analysis results for a clinician. The emphasis is in the accuracy and the usability.

**Validation.** Data from several cohorts will be used to build the statistical model and validate the performance of the developed methods. The main

*Heterogeneous data will be integrated to identify an efficient combination of markers for early diagnosis of AD.*

#### Scenario

New disease modifying drugs for Alzheimer's disease are being developed and are currently in clinical trials. Therefore, efficient therapies for Alzheimer's disease may become available in the near future. The selection of patients, at the earliest possible phase, will be essential for successful treatment. The backbone of the selection is early diagnosis based on sensitive biomarkers for Alzheimer's disease. These markers must be able to detect the disease already from weak symptoms. Our scenario is that the PredictAD tool will provide a systematic, objective and reliable way for choosing patients for treatment, and for monitoring the efficacy of the treatment.

criterion for the evaluation is the diagnostic accuracy. In addition, the cost-effectiveness of various combinations of biomarkers in AD diagnostics will be studied. This information is used to optimise diagnostic protocols.

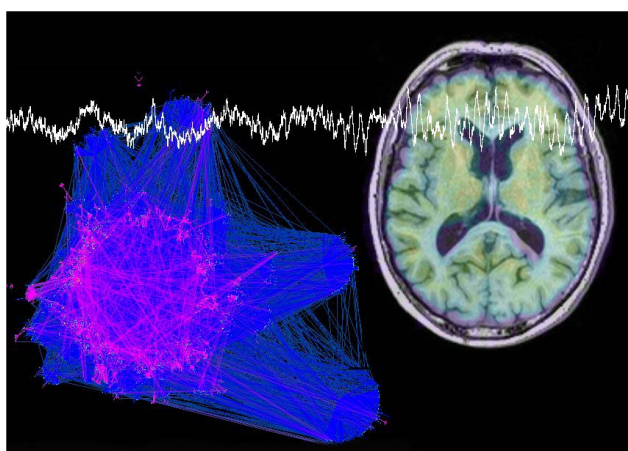
### Expected Results & Impacts

PredictAD will produce a software tool for early diagnosis of Alzheimer's disease and for progress monitoring. The backbone of the tool is the statistical model including information about numerous biomarkers measured from a high number of subjects. PredictAD will also generate information about the cost-effectiveness of various patient measurement procedures and new knowledge of biomarkers characteristic to Alzheimer's disease.

Clinicians are currently facing an enormous challenge in AD diagnostics. An early diagnosis may enable doctors to provide medical care at an earlier stage, at a time when clinical diagnosis using only signs and symptoms of disease is challenging.

A major breakthrough in AD prevention and treatment is vital also in the economical sense: the costs of AD to European society are more than 55 billion € per annum and dramatic increase in the number of AD patients is expected in the near future. Early diagnosis combined with future drugs and prevention strategies will delay or stop the onset or the progress of AD. This can be shifted directly to reduced costs.

Finally, PredictAD will affect a single citizen in two aspects. First, having diagnosis earlier and hence also treatment earlier during the disease process will mean reduced suffering for the individual. Second, it reduces the burden of citizen as a taxpayer.



### PredictAD

#### From Patient Data to Personalised Healthcare in Alzheimer's Disease

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GE Healthcare Ltd (UK)

Nexstim Oy (Finland)

University of Kuopio (Finland)

Imperial College London (UK)

University of Uppsala (Sweden)

University of Milan (Italy)

Rigshospitalet (Denmark)

Timetable: from 06/08 – to 05/11

Total cost: 3,981,565 €

EC funding: 2,891,526 €

Instrument: STREP

Project Identifier: FP7-2008-IST-224328

#### Keywords:

Alzheimer's disease, early diagnosis, personalised healthcare, statistical modelling, multimodal data

## **RADICAL**

### **Road mapping technology for enhancing security to protect medical & genetic data**

*RADICAL* coordination action aims at approaching coherently, studying in depth and revealing scientifically, the beyond the state-of-the-art research and policy roadmap for security and privacy enhancement in Virtual Physiological Human, taking into consideration technology advancements, business and societal needs, ethics and challenges that should be addressed and answered.

#### **Objectives of the project**

1. Identifying and launching a framework of Security and Privacy minimal requirements in VPH research projects.
2. Identify the societal needs and challenges that should be addressed in order to protect health patient records and their usage.
3. Bring in the stakeholders' thinking the implications of the use of genetic & medical data.
4. Creating a forum where policy makers, IT and technology providers, academia, NGOs, and citizens interact as to create a critical mass of identifying risks in health data usage and measures that should be adopted to comply with the relevant Legislation.
5. Capitalize on existing knowledge by creating a vast pool of R&D approaches in the issue.
6. Develop a Good Practice Guide, presenting the best practices that should be adopted, in order for security and privacy to be enhanced in Medical and Genetic data dispersed over different networks.
7. Develop a Policy Paper Roadmap for the Future Agenda with recommendations for promoting privacy and security enhancement in health related data processed over distributed networks.
8. Creating a network of stakeholders in the area, for raising awareness and strengthening the European Research area in security and privacy technologies.

#### **Project Description**

The **RADICAL** Project constitutes a crucial complement to the Virtual Physiological Human framework. The aim is to study and reveal the requirements for enhancing security and privacy in the management of medical and genetic data, as well as to articulate the strategy for achieving this goal.

In order to fulfil its role successfully and comprehensively, the **RADICAL** policy should take into account technological advances and trends, business needs, as well as legal, financial, social, technological, and other significant issues with respect to the personal and sensitive nature of medical and genetic data communicated during the process of realisation of the VPH concept.

The **RADICAL** vision is based on four different interconnected/interrelated postulates:

- a) the need for increased security in handling and communicating confidential medical and genetic data,
- b) the ethical requirements for improved public understanding and consensus regarding the ongoing research in relevant fields in conjunction with the significance of obtaining and processing such data,
- c) the establishment of a legal framework at a supranational and, if possible, at an international level, capable of regulating efficiently the proper use of sensitive data handling and ensure respect of the fundamental rights and freedoms,
- d) the creation and support of the technological capabilities to build secure networks of different types and databases for digital data as a means of communication between a great number of institutions and individuals

Looking at the horizon of the project's completion, the goals and vision will be served and fulfilled through the identification of technological requirements for security and privacy, the identification of societal needs regarding fair and lawful use of medical and genetic information, the demonstration of legal, institutional and social implications of using medical and genetic data to stakeholders, the creation of a Forum where policy makers, technology providers, academics, organisations and citizens can interact in



order to express their concerns and ideas, identify risks and discuss/propose the measures necessary to eliminate such risks.

Thus, through the capitalisation on existing knowledge, the European Research Area will have been strengthened in privacy and security technologies. ***Overall, improvement of people's lives through safe and improved information services in VPH is the ultimate element of the RADICAL vision.*** A state-of-the-art framework with a potentially accurate and precise diagnostic ability like VPH, which aims to offer a simulation of the human system from the anatomical to the molecular level, is the field of such a service.

### Expected Results & Impacts

Societal impact: Security and Protection of medical and Genetic Data represent a topic of strategic importance in health with major impact in health systems and health care service. As Security and Privacy is in the core of ICT technology advancements, by altering the landscape of health services, change the everyday life of European citizen affecting his/her life and its quality. **RADICAL** project with its focus in defining the Policy roadmap in Security and Privacy in Medical and Genetic Data use, taking into consideration the experts' and the industry's scientific views and fore-thinking, affects in a mature and careful way the societal challenges in health. **RADICAL** project will capitalize on international scientific networks in delivering policy guidelines to be adopted by public stakeholders, in order to diffuse the innovation approaches into the society.

Economic impact: Networked companies and stakeholders create a critical mass in security and privacy of medical and genetic data use, boosting competitiveness and effective usage of research resources in medical informatics' and ICT in general industry. In this way, the market could exploit the full potential of available funds in national and international level, returning to society in kind, the public funds invested.

### RADICAL

#### Road mapping technology for enhancing security to protect medical & genetic data

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PLIROFORKIS KAI ROMPOTIKIS EPE, Greece

EUROPEAN HEALTH TELEMATICS ASSOCIATION,  
Belgium

IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY AND  
MEDICINE, UK

FRAUNHOFER GESELLSCHAFT ZUR FOERDERUNG  
DER ANGEWANDTEN FORSCHUNG E.V., Germany

MITROU EVANGELIA, Greece

Timetable: from 07/08 – to 07/10

Total cost: € 1.248.495

EC funding: € 842.038

Instrument: Coordination action (CA)

Project Identifier: FP7-2008-ICT-223965

#### Keywords:

Security, Privacy, Medical & Genetic  
Data, Databases, Communication.

## VPH2

### Virtual Pathological Heart of the Virtual Physiological Human

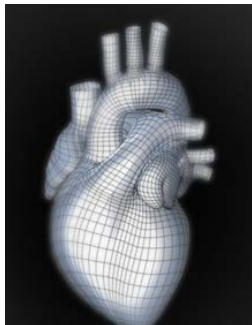
VPH2 (Virtual Pathological Heart of the Virtual Physiological Human) aims to develop a patient-specific computational modelling of the heart to assist cardiologists/cardiac surgeons in defining the severity and extent of disease in patients with post-ischemic Left Ventricular Dysfunction (LVD), with or without ischemic mitral regurgitation (IMR).

#### Objectives of the project

**Problem or Context:** Heart failure accounts for almost a quarter of all hospital admissions due to cardiovascular events, has a high mortality (median survival around 18 months), and places a great burden on all healthcare systems, with estimated direct costs of £905m (€1350m) in the United Kingdom in 2000, 2% of total NHS expenditure.

**Project:** The task of the "Virtual Pathological Heart of the Virtual Physiological Human" is the development of a high power framework platform aiming at improving the management processes of heart diseases in defining the severity and extent of disease in patients with post-ischemic LVD, and in particular at:

- Integrating clinical, biological and genetic data retrieved from medical records and laboratories research results in order to offer an innovative therapeutic tool for the surgical and medical decision making;
- Supporting cardiac surgeons with advanced simulation and modelling tools to be applied for obtaining better selection and simulation of specific surgical procedures;
- Providing a new framework and multimodal approach that will be then useful in other clinical scenarios of cardiology and cardiac-surgery involving for example hybrid imaging PET-CT, molecular and functional imaging, etc.



#### Project Description

VPH2 will provide a fundamental framework clearly beyond the current state of the art which will allow to build *subject-specific multiscale model of the heart (from tissue to genes) and the valves* targeting a specific clinical application area. Research and Technology Development results will be:

- Cross-correlation methods and computational models for *representing and interpreting heterogeneous data sets* (such as clinical data, genomics, environmental and biological ones).
- Creation of a *computational model to simulate pathology and disease progression* in order to assist clinical decision making and new technology development.
- Advanced imaging and visualisation techniques with particular emphasis on *advanced multimodal visualisation and modelling algorithms*, 4-D representation.

The final VPH2 system will be installed in test-beds and its services will be exercised. The objective of this task is to make the VPH2 system available to non-IT partners or other end users to assess it from an operational point of view. In order to accomplish this objective, a series of scenarios on the use of the system will be realised by the respective partners. The scenarios will be described for each validation site and measurable indicators will be identified. During this task, a questionnaire will be prepared and distributed to the users of the system in order to provide clear results on the ease of use, efficacy and validity of services.

#### Scenario

Mr Miller has been admitted to the hospital for dyspnoea six months after myocardial infarction. High blood levels of BNP and PCR are measured. Genetic variant for MMP-9 has been identified. MRI depicts ventricular remodelling, moderate mitral incompetence and areas of scar by gadolinium. Despite optimal pharmacologic therapy, the VPH2 model predicts unfavourable evolution of the disease, unless this is prevented by surgical myocardial restoration. Simulation of the intervention displays the virtual cut of fibrosis and patch size to be applied, with no need for mitral repair. Surgery is successfully attained; the two surgeons compare live the operation in the operating room with the virtual VPH2 restoration.

## Expected Results & Impacts

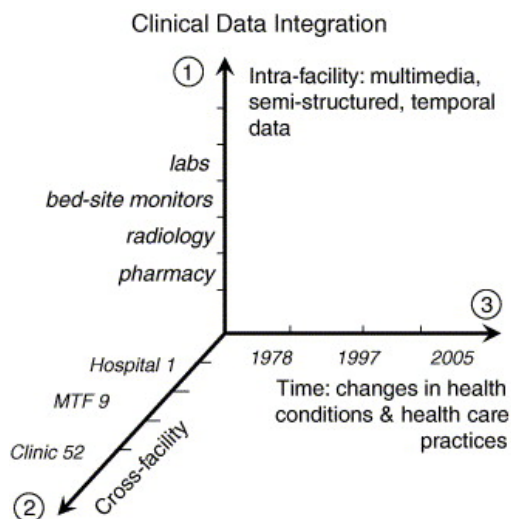
VPH2 is a simulation-based medical planning system for cardiovascular diseases to evaluate other options than surgical treatment.

One important factor is *the availability of tools for collecting, storing, analysing and linking different types of data*: this will help clinicians in their daily activity and allow researchers to look at all data originated by scientific instrumentation or available in databanks.

VPH2 will affect the costs of managing chronic diseases. The direct medical costs of CVD treatment range from 1% to 2% of the total health expenditures in several countries, and two thirds of CVD costs derive from hospitalization. Readmission rates at six months range from 15% to 50% in different studies.

The simulation of the heart function offers *a tool to better understand the pathogenesis of heart failure* (HF) and to develop proper treatment strategies to reduce readmissions.

The Healthcare system will finally benefit from a reduction in surgical operations numbers. A tailored patient-specific pharmacological treatment will help doctors to simulate alternative drug treatments and to decide for the surgical intervention only as a last option. On the other hand, in case it appears unavoidable, cardiac-surgeons will have the possibility to simulate and predict the final result.



## VPH2

### Virtual Pathological Heart of the Virtual Physiological Human

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REGIONE LOMBARDIA (IT)

SCS SRL (IT)

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE (CH)

UNIVERSITY OF BEDFORDSHIRE (UK)

SORIN BIOMEDICA CARDIO S.R.L. (IT)

EURO (PMS) LIMITED (UK)

AMINIO AB (SE)

QUALITY & RELIABILITY A.E. (EL)

ΕΡΕΥΝΗΤΙΚΟ ΑΚΑΔΗΜΑΪΚΟ ΙΝΣΤΙΤΟΥΤΟ ΤΕΧΝΟΛΟΓΙΑΣ ΥΠΟΛΟΓΙΣΤΩΝ (EL)

INTERCON SP. Z O.O. (PL)

PATMOS S.R.L. (IT)

Timetable: from 07/2008 to 06/2011

Total cost: € 5,179,049.89

EC funding: € 3,778,500.00

Instrument: STREP

Project Identifier: FP7-2008-ICT-224635

#### Keywords:

Human Heart Modelling, Knowledge Extraction, Genomics, Post-ischemic Dysfunction, Drug Treatment

# VPH NoE

## Virtual Physiological Human Network of Excellence

The Virtual Physiological Human Network of Excellence (VPH NoE) has been designed with 'service to the community' of VPH researchers as its primary purpose. The aims of the network range from the development of a VPH ToolKit and associated infrastructural resources, integration of models and data across the various relevant levels of physiological structure and functional organisation, through to VPH community building, training activities and support.



### PROJECT OBJECTIVES

- Inter-institution and interdisciplinary research projects;
- Development of the VPH ToolKit: shared and mutually accessible resource of data;
- Facilitation of development of horizontal and vertical model/data integration;
- Development of interdisciplinary training activities and VPH careers;
- Establishing a core set of VPH-related dissemination and networking activities;
- Implementation of key working groups to pursue integration of VPH research worldwide
- Creation of Industrial, Clinical and Scientific Advisory Boards for consultation

By involving clinical and industrial stakeholders, the VPH network of Excellence also plans to create a reliable foundation to support sustainable interactions and collaboration between research and healthcare communities.

### *The Challenge:*

One of the key challenges in the development of quantitative, integrative and predictive models that describe human physiology is the provision of the necessary research infrastructure. This includes methodologies, databases and computational tools, that will allow scientists working in different scientific fields (at various physiological levels and scales) to communicate, exchanging data and technologies in a standardised manner. The scale of data to be generated, processed, and exchanged requires software tools and massive computer storage and that are currently not widely available. Dissemination is another key challenge as the VPH NoE scope is by definition multidisciplinary and only a very limited number of journals currently accept physiome - related papers.

Scientists able to deal with multidisciplinary topics are required, necessitating a need for training of multidisciplinary individuals and VPH specialists.

***The VPH NoE will perform as an inwardly integrated and progressive networking action, at the centre of a wider network of VPH researchers throughout Europe***

### *The Way Forward:*

The VPH NoE objectives outlined reflect the above challenges, and will be addressed by a core group of project members - 13 institutions who are fully committed at the highest institutional level to the concept of the VPH NoE. They represent centres of excellence in physiological modelling; data processing and analysis; high performance computing; genomics; bioinformatics and medical informatics. Many Partners have shown prior commitment to integration within the European Research Area through leadership of, or involvement in, European Commission Sixth Framework Networks of Excellence and Collaborative Projects. The 13 organisations have clinical and industrial associations crucial for the creation of a VPH research environment with active end-user involvement. The core membership is augmented by a large and growing general/associate membership, comprised of institutions, organisation and commercial enterprise interested in VPH activities.

### PROJECT DESCRIPTION

This leading group of universities, institutes and organisations aim to promote the creation of a virtual environment that actively supports and nurtures interdisciplinary research, education, training and strategic development. In keeping with the general ethos of the VPH NoE, Exemplar Projects (EPs) will be developed (see box on page 1). EPs work towards integration amongst VPH researchers, in order to address specific research problems or

### **VPH NoE Exemplar Project: Supporting integrative, interdisciplinary research**

VPH NoE Exemplar project (EP) support will be awarded through an annual competitive grant mechanism open to all VPH NoE member organisations. Individual EP support will be manifest as a grant of 6-12 months duration, to fund personnel strictly focussed on integration of VPH-related research already underway and which addresses an area of need. The EPs will foster new collaborative links, benefiting from transfer of skills from related VPH activities, with the mandate to make output (models, data repositories etc.) available to the VPH community via the VPH ToolKit, and with the expectation that such support will contribute to the ability of the recipients to obtain follow-on funding.

challenges. The aim is to provide solid examples of horizontal and vertical model/data integration, which may only be achieved through the integration of disparate knowledge and research infrastructure.

The VPH ToolKit aims to provide the technical and methodological framework to support and enable VPH research. The Toolkit will be a shared and mutually accessible source of research equipment, managerial and research infrastructures, facilities and services. Other VPH projects, including the Exemplar Projects (EPs) will both be able to add and draw capacity from it. In pooling these activities within the VPH research area, issues of interoperability, standards and – more broadly - integrative VPH research, will be addressed.

The VPH NoE recognises a necessity for scientists able to deal with multidisciplinary topics. The VPH NoE will create a framework to support and facilitate this training. We will address training and career development for both early and in-career VPH researchers and training activities will pay special attention to the outcomes generated from other VPH-related projects and existing European Commission initiatives (e.g. Marie Curie).

Through dissemination, the "impact" of VPH NoE initiatives relating to VPH EPs, the VPH ToolKit, and interdisciplinary training will be maximised. In addition, an emphasis will be placed on the development of clear and consistent lines of communication and information dissemination within and beyond the VPH NoE itself – crucial to the ongoing success of the VPH initiative as a whole.

### EXPECTED RESULTS & IMPACTS

The VPH NoE, within the broader VPH Initiative, should be responsible for:

- Strengthening the leadership role and increased interdisciplinarity of European research in biomedical research by fostering cooperation between disciplines and institutions
- Creating a more cohesive VPH research community, both within and beyond the EU.
- Improving semantic interoperability of biomedical information and contribution to a common EU health information infrastructure.
- Creation of new environments for predictive, individualised, evidence-based healthcare - to improve efficacy and safety.
- Acceleration of device and drug intervention development through predictive in silico modelling.
- Enhancing recognition on a national level of the importance of modelling and simulation in biomedicine.
- Increasing emphasis on interdisciplinary training in both biological and biomedical-engineering/physics curricula

## VPH NoE Virtual Physiological Human Network of Excellence



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2. The Chancellor, Masters and Scholars of the University of Oxford, UK
3. Centre National de la Recherche Scientifique, France
4. Universite Libre de Bruxelles, Belgium
5. Institut National de Recherche en Informatique et en Automatique, France
6. The University of Nottingham, UK
7. University Pompeu Fabra, Spain
8. University of Auckland, New Zealand
9. European Molecular Biology Laboratory, Germany
10. The University of Sheffield, UK
11. Karolinska Institutet, Sweden
12. Institut Municipal d'Assistencia Sanitaria, Spain
13. GEIE ERCIM, France

**Timetable:** June 2008 to November 2012

**Total cost:** €9,649,516.60

**EC funding:** €7,999,366.20

**Instrument:** NoE

**Project Identifier:** FP7-2007-IST-223920

### Keywords:

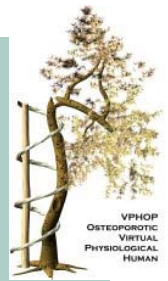
Interdisciplinary, Multilevel,  
Integration, Physiome, Modelling,  
Simulation.





# VPHOP: the Osteoporotic Virtual Physiological Human

The fight with Osteoporosis now has a new ally. The VPHOP research project will develop, validate and deploy to pilot clinical studies the next generation of technology for predicting the risk of fracture in patients with low bone mass and assisting clinicians in prognosis and treatment planning (both pharmacological and interventional). The most advanced multiscale modelling technologies will be used to predict the patient-specific risk of fracture, and how it would change as a result of the various potential treatment options.



## Objectives of the project

**Context:** Nearly four million osteoporotic bone fractures cost the European health system more than € 30 billion per year. This figure could double by 2050. After the first fracture, the chances of having another one increase by 86%. We need to prevent osteoporotic fractures.

**Osteoporotic fractures cost the European health system is more than €30 billion per year**

The first step is an accurate assessment of the patient-specific risk of fracture that considers not only the skeletal determinants but also the neuromuscular condition.

**Project:** The aim of VPHOP is to develop multiscale modelling technology based on conventional diagnostic imaging methods that makes it possible, in a clinical setting, to assess *for each patient individually*, the strength of his/her bones, how this strength is likely to change over time, and the probability that the he/she will overload his/her bones during daily life. With these three assessments, the evaluation of the risk of bone fracture will be much more accurate than any estimation based on external and indirect determinants, as happens in current clinical practice. These assessments will be used to improve the diagnostic accuracy of current clinical standards, and to provide the foundation for an evidence-based prognosis with respect to the natural evolution of the disease, to pharmacological treatments, and/or to preventive interventional treatments aimed at selective skeletal strengthening. The various modelling technologies developed during the project will be validated not only *in vitro*, on animal models, or against retrospective clinical outcomes, but will also be assessed in term of clinical impact and safety on small cohorts of patients enrolled at four different clinical sites, providing the factual basis for effective clinical and industrial exploitation.

## Project Description

**Project Description:** Currently, the risk of fracture is estimated empirically, i.e. based on observations of past cases. However, in theory we could imagine developing a patient-specific computer model that is capable of assessing the risk of fracture in a deterministic way, with much higher accuracy. The problem is that the occurrence of an osteoporotic fracture is a multiscale event:

- the daily loading spectrum, which includes para-physiological overloading events is defined at the Body level;
- the fracture event occurs at Organ level;
- the bone elasticity is due to the tissue, which is defined at the Tissue level;
- the composition and the morphology of the bone tissue changes over time due to the metabolic activity, which is defined at the Cell activity level;
- the strength of the tissue is due to the molecular composition of the bone matrix, which is defined at the Constituents level.

By creating a patient-specific hypermodel – a model composed by many sub-models, each describing the relevant phenomena taking place at one of the many dimensional scales involved – we will be able to solve this incredibly complex problem.

This modelling technology will be specialised to solve four clinically relevant problems:

- a. Screening (level 1): to supplement the conventional Dual X-ray Absorptiometry (DXA) screening of subjects at risk, in order to include in the diagnosis also the propensity to fall, and possibly 3D densitometric information.
- b. Diagnosis (level 2): In osteoporotic subjects, use 3D densitometry information to develop a personalised assessment of the risk of fracture

### Scenario:

The best-case scenario is a complete multiscale model parameterised on all clinically available information on the patient, but also on a full population-based probabilistic representation of such inputs. Independently from the level of specificity of the input parameters, the model will always predict the risk of fracture of all critical bones, with an associated confidence interval, large or smaller depending on how detailed are the available information on the patient. The practical effect of this would be possibility to design clinical protocols progressively demanding in terms of costs, time, and invasiveness. The VPHOP technology would not only drastically improve the clinical practice, but also help in modulating the level of detail of the clinical assessment to the severity of the disease.



- at the hip and the lower spine that clinicians can use to better modulate the life-style recommendations and the treatment options.
- c. Prognosis (level 3): for patients at high risk of fracture, develop a predictive model based on tissue-level imaging that estimates the variation of such risk over time due to bone remodelling with and without pharmacological treatment.
  - d. Interventional treatment planning: simulation-based pre-operative planning to decide which vertebral body is at higher risk, and in which region of that vertebrae the augmentation would be more effective.

## Expected Results & Impact

### *Clinical innovations:*

- prognosis
  - o predicting the risk of femoral or vertebral fracture under low energy loading
  - o predicting, at the tissue level, the probability of developing micro-fractures
- pharmacological treatment planning
  - o predicting changes over time due to the evolution of the disease and to the pharmacological treatment
- interventional treatment planning
  - o Predicting the location within each bone that is most susceptible to fracture
  - o Predicting the changes in risk due to interventional augmentation

### *Industrial innovations:*

- Imaging technology to generate whole bone patient-specific models with very low radiation dose
- Wearable activity monitor capable of capturing the patient's life style for one week including para-physiological events
- Hypermodelling technology for the creation of massive multiscale models using heterogeneous codes
- Tissue level imaging in vivo at the spine and hip with clinically acceptable radiation doses
- Cellular activity models, capable of predicting the functional outcome of different pharmacological modulations of bone metabolism
- Software technology for patient-specific deterministic prediction of fracture risk

## VPHOP the Osteoporotic Virtual Physiological Human

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ANSYS France SAS (FR)

Katholieke Universiteit Leuven (BE)

University of Bedfordshire (UK)

Haskoli Islands (IS)

Uppsala Universitet (SE)

Institut National de la Santé et de la Recherche Médicale (FR)

Biospace med SA (FR)

Societe d'Etudes et de Recherch. de l'Ecole Nat. Sup. d'Arts et Metiers (FR)

BrainLAB AG (DE)

Philips Medical Systems Nederland BV (NL)

Timetable: from 09/2008 – to 08/2012

Total cost: € 12,073,349

EC funding: € 8,989,363

Instrument: Integrated Project

Project Identifier: FP7-ICT-2008-223865

### **Keywords:**

Virtual Physiological Human,  
Physiome, Multiscale Modelling,  
Osteoporosis, Bone Fracture



**"Virtual Physiological Human" Projects portfolio  
prepared for the Project Concertation Meeting**

**<http://www.vph-noe.eu/vph-initiative-forum>**

**Brussels, Belgium  
October, 22 2008**

**Taking place before the ICT-BIO2008 Conference  
[http://ec.europa.eu/information\\_society/events/ict\\_bio/2008](http://ec.europa.eu/information_society/events/ict_bio/2008)**

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**Better Healthcare for Europe**

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