

# SIMAP

## Simulation modelling of the MAP kinase pathway

**SIMAP will develop a simulation model of the cancer related MAP-kinase pathway, integrating and analyzing data from various types of resources, which may assist in the development of better cancer treatment.**

### Objectives of the project

The completion of the human genome gave hope for a new age of medical understanding, but 4-5 years later costs of drug development are still rising and the success rate has not improved. Drugs that have already hit the market are found to have major side effects not perceived in the past and are often given to patients without discrimination on their likeliness to respond.

Large scale methodologies that thrive in recent years, allowed the industry and academia to gather more information on RNAs and proteins. However, the understanding of the molecular and cellular processes is still lacking, not to mention the connection to the clinical outcome. In order to fully use this data, a comprehensive integration and modeling effort is needed. A systematic rational hypothesis-driven research approach connecting all those levels of information

is a much needed computational tool. This is the main goal of **SIMAP** project. The ultimate goal of **SIMAP** is to develop a comprehensive simulation biochemical model of EGFR-MAP kinase pathway in connection to cancer clinical information. **SIMAP** will:

- Incorporate low-level biochemical modelling of individual molecules;
- Simulate the behaviour of the pathway;
- Add genomic and proteomic data;

- Incorporate individual patients' responses; and
- Analyze sub population of responses in the context of the biochemical behaviour and genotype data

### Project Description

The MAP-kinase pathway is a major pathway that relays signals from the plasma membrane into the nucleus. A deep understanding of this pathway is important for the development of rational anti-cancer therapies. The **SIMAP** consortium intends to develop a comprehensive and robust simulation model of the pathway, which will incorporate data from the literature, as well as experimental and clinical work. The model is expected to create qualitative predictions, followed by experimental verification. It is expected to integrate and analyze data from various types of resources ranging from single molecule information, to pathway modeling, to clinical data and patients' response.

***“The SIMAP project is tackling a key cause to many forms of cancer... it is hoped the prototype will serve as a tool to improve the bedside treatment of patients based on a multi-level genomic / proteomic profile”***

This approach is expected to enable hypothesis-driven research aimed at the establishment of systems level computational platforms available for various pharmaceutical applications.

The concepts and methods intended to be developed could help in the design of new therapeutic drugs, decrease the attrition rate of new drugs and make it possible to select patients for treatment on the basis

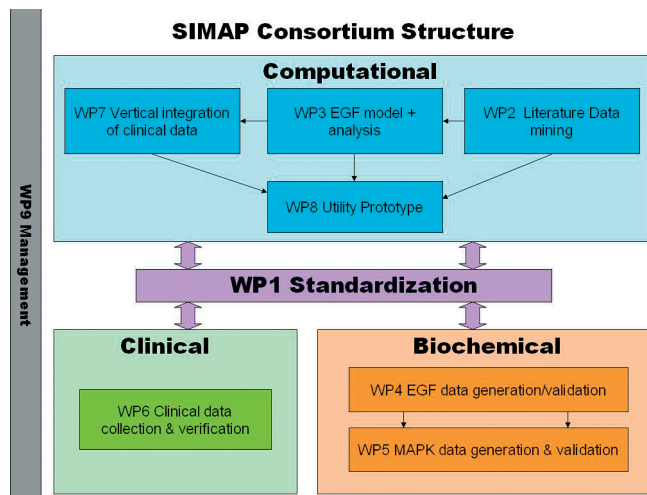
### Scenario

Mrs Cohen has been diagnosed with breast cancer. Dr. Levy would like to put her on chemotherapy and an ErbB2 inhibitor. However there are few inhibitors in the market with varied level of efficiency. Dr Levy would be very happy if she could perform some genetic tests on the biopsy taken from Mrs Cohen and predict up to a certain level which is the best inhibitor to use, what is the optimal drug administration regime that would best improve her prognosis. It is hoped that SIMAP platform will assist Dr. Levy to tailor-made a treatment to Mrs Cohen based on her individual parameters

of individual parameters. Model-driven predictions regarding the impact of drug combinations could allow dramatic improvement in the design of pre-clinical and clinical trials, enhance patient response and limit adverse effects of drugs.

**SIMAP** pioneers the integration of clinical phenotype into this improved biochemical model. Such multi-scale modelling is a step forward in the field of Systems Biology.

The project is lead by a drug and diagnostic discovery SME and interdisciplinary industrial and academic leading teams of investigators.



### Expected Results & Impacts

The **SIMAP** project offers a unique opportunity to develop a sophisticated tool to profile the population that will be treated with or without agents directed to the MAPK signalling network. **SIMAP** prototype will allow not only for better drug development but will also allow clinicians to give better treatments to patients on a case by case basis. Europe is already the leader in the development of MAP-Kinase inhibitors with many of the available molecules being patented by European Pharmaceutical companies.

The availability of a computer simulated model that will assist in better developing and trialling drugs based on these molecules will help to reduce the development costs and time to market for these companies.

**SIMAP** will contribute to the European Community's health by allowing the identification of genetic and protein markers, which will define sub-population of patients who will benefit most from targeted agents, have most toxicity (and should therefore avoid the treatment or undergo dose reduction) or who will prove resistant to these agents and should therefore be exposed to alternative therapies.

The **SIMAP** project is tackling a key cause to many forms of cancer and as such a major societal and economic challenge. In the long run it is hoped the prototype will serve as a tool to improve the bedside treatment of patients based on a multi-level genomic/proteomic profile.

## S I M A P Simulation modelling of the MAP kinase pathway

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- Compugen Ltd., (IL)
- Consejo Superior de Investigaciones Científicas, (ES)
- Halevi Dweck & Co. Arttic Israel Company Ltd., (IL)
- The Institut De Recerca Hospital Universitari Vall De Hebron, (ES)
- Istituto Nazionale Tumori, (IT)
- The Max-Planck Institute for Infection Biology, (DE)
- The University of Glasgow, (UK)
- The Weizmann Institute of Science, (IL)

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Biomedical informatics ,  
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