REPORT on

EU-USA Workshop:

How Systems Biology can Advance Cancer Research

27 October 2008

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EXECUTIVE SUMMARY

The main conclusion is that systems biology approaches can indeed advance cancer research, having already proved successful in a very wide variety of cancer-related areas, and are likely to prove superior to many current research strategies. Major points include:

- Systems biology and computational approaches can make important contributions to research and development in key clinical aspects of cancer and of cancer treatment, and should be developed for understanding and application to diagnosis, biomarkers, cancer progression, drug development and treatment strategies.

- Development of new measurement technologies is central to successful systems approaches, and should be strongly encouraged. The systems view of disease combined with these new technologies and novel computational tools will over the next 5-20 years lead to medicine that is predictive, personalized, preventive and participatory (P4 medicine).

- Major initiatives are in progress to gather extremely wide ranges of data for both somatic and germ-line genetic variations, as well as gene, transcript, protein and metabolite expression profiles that are cancer-relevant. Electronic databases and repositories play a central role to store and analyze these data. These resources need to be developed and sustained.

- Understanding cellular pathways is crucial in cancer research, and these pathways need to be considered in the context of the progression of cancer at various stages. At all stages of cancer progression, major areas require modelling via systems and developmental biology methods including immune system reactions, angiogenesis and tumour progression.

- A number of mathematical models of an analytical or computational nature have been developed that can give detailed insights into the dynamics of cancer-relevant systems. These models should be further integrated across multiple levels of biological organization in conjunction with analysis of laboratory and clinical data.

- Biomarkers represent major tools in determining the presence of cancer, its progression and the responses to treatments. There is a need for sets of high-quality annotated clinical samples, enabling comparisons across different diseases and the quantitative simulation of major pathways leading to biomarker development and analysis of drug effects.

- Education is recognized as a key component in the success of any systems biology programme, especially for applications to cancer research. It is recognized that a balance needs to be found between the need to be interdisciplinary and the necessity of having extensive specialist knowledge in particular areas.

- A proposal from this workshop is to explore one or more types of cancer over the full scale of their progression, for example glioblastoma or colon cancer. Such an exemplar project would require all the experimental and computational tools available for the generation and analysis of quantitative data over the entire hierarchy of biological information. These tools and approaches could be mobilized to understand, detect and treat cancerous processes and establish methods applicable across a wide range of cancers.

REPORT

Introduction - Cancer is a complicated, multi-stage disease. Its various stages of progression involve the biology and genetics of cells and organisms, tumour viruses, cellular oncogenes, growth factors and their receptors, cytoplasmic signalling circuitry, cell cycle, tumour suppressor genes, p53 and apoptosis, cell immortalization, tumourigenesis and senescence, multistep tumourigenesis, genomic integrity, development, angiogenesis, lymphangiogenesis, metastasis, tumour immunology and immunotherapy.

This workshop considered the state of the art in systems biology approaches to cancer and explored expected beneficial future approaches. The main conclusion is that systems biology approaches can indeed advance cancer research, having already proved successful in a very wide variety of cancer-related areas[1], such as apoptosis, and are likely to prove superior to many current research strategies. Such a conclusion is far from obvious, since there are currently huge medical and biological research programmes in course, over an extremely broad range of activities. The need for a systems biology approach that goes beyond current practice is based on the realization that many types of research data, where considered individually, are not sufficient to describe and understand the real situation in cells and in cancer progression.

Clinical background of cancer and key challenges - Key clinical aspects of cancer and of cancer treatment need to be studied in the context of where computational approaches might have an important input, specifically concerning diagnosis, biomarkers, understanding progression, and drug development. Experimentation should be close to clinical reality. We need to use well annotated and accessible samples, and to create data from clinically relevant samples. It is vital to link clinical and molecular measurements, and make best use of animal models, in order to learn how drugs act. Programmes are needed that get basic and clinical researchers together, to collect and manage clinical samples, since lack of a full analysis is currently a major limitation on diagnoses. Transparent and reproducible experimentation is required in such areas as an interactome map in the context of a proteome project, so as to understand crucial pathways. New programmes are required that enable new ways to direct experimentation towards clinical research, implying experiments that can be carried out in diverse labs and clinical centres around the world.

Cellular and clinical database resources for cancer research - Databases play a central role in cancer research at the cellular level, with a central role currently played by expression array data

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[1] - Integrative Cancer Biology Program of the USA National Cancer Institute, http://icbp.nci.nih.gov ;
 - Manoussaki, E. (editor) (2006) Cancer Research – Projects funded under FP6, European Commission EUR 22051;
 - Marcus, F (2008) Bioinformatics and Systems Biology: Collaborative Research and Resources, Chapter 8 Cancer, Springer-Verlag Heidelberg http://www.springer.com/life+sci/bioinformatics/book/978-3-540-78352-7

and its analysis. Data resources need to be developed in a sustainable manner, and continued infrastructure funding of databases established in a research environment is a major problem. Analysing them requires quantitative models, for which the data must be organised to aid in determining causal relationships.

Modellers have the choice between going through lots of papers published over past several decades on individual experiments, or using high throughput datasets. Datasets mostly have static rather than time-dependent data, but do reflect what can happen and they are important as a kind of scaffold information. Data and infrastructure requirements include:

- Biochemical definitions of chromatin composition
- Factors that read, write and erase.
- Analysis of Post Translational Modifications: histone (>80) and non-histone proteins
- Characterization of proteins (complexes) involved in transcription and chromatin organization
- Identification of (epi)enzymes that can be drug targets
- Deciphering the epigenome of a cell i.e. to determine where in the genome and when in normal or cancer cells/tissue a given factor binds or epigenetic mark is present
- Global chromatin interaction networks (ChiA-PET)
- DNA methylation patterns, Loss of heterozygosity
- Reactivated genes using epidrugs
- Detailed knowledge of oncoproteins, tumour suppressor proteins
- Growth-associated miRNAs
- Networks that are reasonably well mapped out

Methods and resources for generating this data include:

- Comprehensive and quantitative omics-level experimental approaches
- Sequencing, epigenomics, microarrays/deep transcript sequencing, polysome profiling, proteomics, RNAi screens etc.
- Progress in quantitative and real-time single cell approaches
- Microscopy and image analysis, flow/FACS…
- Agreed and implemented standards for sample and data collection and representation
- Clinical proteomics for diagnosis and pronostics
- A repository of high-quality and well-annotated clinical sample collections
- Improved high-precision omics and imaging measurements from molecules to cells
- Mouse models: For studying systems biology of cancer it would be good to have mouse models that show specific human cancers and where we can study specific tissues.

Necessary aids to analysis include:

- Web-service technology linking molecular level databases, registries and biobank data
- Enabling experimental data compatibility by coordinating assay and cell type aspects
- Software platforms for data and document management, facilitating remote communication
- Systems biology approaches that include a changing chemical environment
- Linking medical informatics and molecular systems biology
- Correlation analysis between different diseases
- Insisting on data availability
- New web-service based bioinformatics infrastructure in Europe
- A common information infrastructure for data exchange, analysis and modelling
- Standardized data integration and meta-analysis methodologies
- Formal concepts that support an optimal design of experiments

Genetic variation databases and computational analysis resources for cancer research - Major initiatives are in progress to gather extremely wide ranges of genetic variation data for both somatic and germ-line variations that are cancer relevant, especially the International Cancer Genome Consortium and the Cancer Genome Atlas (TCGA). The data from these initiatives should be used to provide scientific input to bioinformatics and systems biology analyses to understand the biology of cancer or its response to drugs. Relevant systems biology modelling requires the development of new technologies and computational/mathematical tools driven by the biology requirements, leading to a transformational approach in cancer biology, diagnosis, treatment and ultimately prevention. A number of important systems biology bioinformatics analysis tools have already been developed and are being applied to improve our understanding of various key processes in cancer. The growing number of technologies able to generate high throughput data of very complex nature makes data integration the first obvious problem.

Linking cancer research with human diversity studies is one of the most obvious needs (including the ongoing 1000 human genome project and the ENCODE scale-up project). At another level, the integration of clinical and medical resources (clinical records), epidemiological information with molecular information (genomics) is a very obvious need. The GEN2PHEN project has already made a beginning in linking this wide variety of data, but this effort needs to be extended. Logistic, technical and legal problems are inherent to the strategic area. In a parallel development the public availability of chemical libraries and the corresponding databases and their integration in molecular biology research are also an essential strategic area.

Supporting laboratory and clinical technologies - Development of new measurement technologies is central to successful research, and should be strongly encouraged. The systems

view of disease combined with these new technologies and novel computational tools will over the next 5-20 years lead to medicine that is predictive, personalized, preventive and participatory (P4 medicine).

Emerging technologies for medical research are key, including: the next generation DNA sequencing, microfluidic/nanotechnology approaches to measuring proteins in complex mixtures; the creation of new chemistries for generating new protein-capture agents, single-cell analyses and new in vivo and in vitro imaging technologies. Technology development is critical. Most data is in the genomic area right now, and we need more information in other areas! There exist large volumes of data but which are not necessarily useful for systems biology. Many important types of measurements cannot be collected now, in particular spatial and time resolved quantitative measurements. We need to find ways to use genomic data to guide and organize other areas, e.g. protein measurements, and to support technology development programmes focussed on the specific needs of systems biology research.

Systems biology analysis of cellular pathways in cancer - Understanding cellular pathways is crucial in cancer research, and these pathways need to be considered in the context of the progression of cancer at various stages. Mathematical modelling and computer simulation involve a variety of methods. Some models give less predictability but more coverage. The methods chosen need to be adapted to the questions posed and the answers required.

Since cancer involves many molecular processes, interaction of these processes lead to new mechanisms. For example the formation of a life-threatening group of breast carcinoma cells leads to the formation of new blood vessels, which requires the cells to become insensitive to growth inhibition and the endothelial cells to become activated for new blood vessel formation. As illustrated by these processes, cancer is a disease based on dangerous correlations between systems properties of the organism. -That's why systems biology approaches may be of decisive importance in our efforts to combat cancer. In this sense, it seems necessary to focus our attention on the identification of molecular differences between healthy and carcinoma cells. -The problem is complex in view of the fact that molecules from many parallel signal transduction pathways are involved. Their functions seem to be controlled by multiple factors. Numerous nonlinear effects of regulatory feedbacks, pathway cross-talk and non-stationary biochemical processes complicate the understanding and prediction of these intracellular dynamics. Formal methods need to be developed that help identify subsystems (networks/pathways) which can be studied in focussed experimental studies. Mathematical methods should support the design of experiments that allow the distinction of alternative hypothesized network structures on the basis of experimental data.

Related to these complications is the question whether so-called inhibiting deregulated pathways affect the carcinoma cells so that the disease will go into remission. To answer such questions, we need to determine how important different enzymes are for signalling in a pathway, and for cell survival and growth. By comparing similar determinations for normal cells and cancer ones, we would be able to reveal which enzymes or pathways make the most effective targets for carcinoma treatment. For these analyses, we especially need:

- cell-context specific molecular interaction maps in Cancer (Cancer Interactomes)
- widely available experimental platforms for rapid biochemical validation
- a detailed ORFeome (Protein and tagger protein expression)
- siRNA screening assays
- Instrumented cells (reporter genes for all genes in a cancer cell model)
- unbiased hypotheses about oncogenic lesions and processes
- cellular network based contexts for the integration of orthogonal data modalities, including gene expression, SNPs, gene copy number, epigenetic data, etc.
- information on pathway synergy for therapeutic intervention

- Assembly and Validation of Cell-Context Specific Molecular Interaction Maps for Cancer Cells (Genes, Proteins, miRNA, Lipids, metabolites, etc.)

These analyses should:
- Provide a deeper understanding of causal relationships in cancer initiation, progression and treatment (data-driven functional and regulatory networks; cancer stem cells)
- Allow accurate prediction of disease and treatment outcomes (diagnosis and prognosis)
- Enable engineering of novel therapeutic interventions (molecular, cellular, physical)

Enabling this analysis requires:
- More systems biology research grants for data-driven modelling and the development of novel mathematical analytical tools.
- Centres of Excellence (e.g. ICBP/NCBC) for bootstraping infrastructure and science.
- Increasing focus on cross-disciplinary education and funding

Systems biology modelling at the physiological and tumour level - At all stages of cancer progression, major areas requiring modelling via systems and developmental biology methods include immune system reactions, angiogenesis and tumour progression. Key research areas include:

- Biomarkers: The use of organ-specific blood protein fingerprints for diagnosis.

- Genomic data: Genomic data is central to making disease predictions (when integrated with environmental information).

- Emerging technologies for medicine: next generation DNA sequencing, microfluidic/ nanotechnology approaches to measuring proteins in complex mixtures; the creation of new chemistries for generating new protein-capture agents, single-cell analyses and new in vivo and in vitro imaging technologies.

- The cancer aging link

- A focus on one particular system, e.g. colon cancer or gliobastoma

- Comparisons of mouse models, cell lines and human samples.

Modelling across scales is a major challenge. There are dynamic models needing a lot of data and higher order models which need different types of information. Experimentalists and modellers need to mutually discuss how to produce the right data and the right models and provide the right way to store the data. When people think of multiscale modelling, the focus is on cells and organs.

Important hypotheses for developing relevant models include:

- The lesions that cause cancer perturb molecular networks.

- Different types of cancer may be caused by perturbations of the same, overlapping or different networks.

- Perturbed molecular networks can be detected using advanced analytical technologies.

- Types and states of cancer can be classified based on perturbed molecular networks and their response to stress.

- Perturbed molecular networks in tissue/cells leave footprints in serum/plasma.

These hypotheses could lead to specific research programmes:

- Determine and measure networks in healthy and diseased cells and tissues, which needs high throughput, quantitative, complete and sensitive measurements of networks.

- Integrate data to generate models of perturbed networks that predict behaviour of cell and tissue. Lot of work is going on, which needs an intense computational, modelling and data mining effort.

- Infer from perturbed networks the critical nodes for pharmacological interference (drug targets), which requires high throughput quantitative technologies.

- From perturbed networks, infer and measure proteins most likely to be detectable in serum or plasma (biomarkers). There is a need high throughput and highly selective measurements in complex matrices.

Types of biological networks with relevance for cancer include:

- protein-protein interaction networks

- networks of kinases and their substrates

- gene regulatory networks

- metabolic networks.

Mathematical systems biology approaches - A number of mathematical models of an analytical or computational nature have been developed that can give detailed insights into the dynamics of cancer relevant systems. These models should be further developed in conjunction with analysis of laboratory and clinical data. In breast cancer modelling, mathematical models can be used to look at development. We can do a lot: type the tumour and the mutations in it and observe the effects of the interactions. Most cancer drugs don't work very well with most patients, and more could be done to develop individualised medicine. We can do more than look at early diagnosis. We can speed up the development of drugs and target the available drugs much better than is done now.

Cancer biology and oncology generate vast data sets but reductionist approaches inhibit synthesis. We need theoretical models to form conceptual frameworks to organize extant data and integrate new material. Cancer treatment is increasingly multimodal, and the degrees of freedom are virtually infinite. Therefore, there is a critical need for models to reduce parameter space and understand tumour adaptive strategies. New directions to be encouraged include:

- Integration of mathematicians with experimentalists and clinicians is essential. There is no way forward without this.

- Cancer therapy modelling in partnership with oncologists, surgeons, radiation therapists.

- Personalized medicine.

A key focus for modelling is the tumour microenvironment, and in particular exploring how the phenotype affects the environment. Tumours make an environment which is good for them but bad for their competitors. Important areas for mathematical modelling include:

- Carcinogenesis

- Tumour microenvironment and its role in malignant growth and invasion

- Therapy

Biomarkers - Biomarkers represent major diagnostic tools in determining the presence of cancer, its progression and the responses to treatment. There is a need for sets of annotated, high quality clinical samples, and comparisons across different diseases. Quantitative simulations of major pathways leading to biomarker development should be encouraged. The identification, standardisation and validation of effective biomarkers would dramatically impact the quality of decision making in cancer drug development. An integrated research programme should use systems biological platforms to assist in the identification and prioritisation of potential biomarkers. This would include the use of modelling and the simulation of cellular and extra-cellular pathways/networks to select from, amongst a variety of options through sensitivity analysis and similar approaches.

Other approaches would include analysis of tissues and body fluids to assemble a profile of gene expression, protein and metabolite distribution. Such triomic signatures would be associated with specific biological processes, such as metastasis and invasion, supported and validated by appropriate multivariate statistical analysis. An integrated, well planned biomarker programme should be established across diseases, including sample collection availability, and define the relevant marker questions.

The focus of cancer biomarker research in the past has been on 'simple' or mechanistic biomarkers using standard biochemical and pathological techniques. Increasingly, biomarkers are being developed that use a variety of evolving platform technologies, including genetics, omics, molecular pathology and imaging. This raises many interesting challenges. The identification, standardisation and validation of these biomarkers is fundamental if they are to be effective in drug development and the regulatory process. These biomarkers can be used at various stages during drug development, including:

- Diagnostic and prognostic markers (cancer specific);
- Patient stratification by genotyping;
- Predictive markers for efficacy;
- Surrogate 'markers' (end-points) for long-term drug efficacy;
- Predictive tumour genotyping for efficacy (responders/non-responders and safety).

Systems biology and bioinformatics approaches to drug development - Pathway simulation of drug effects is key to drug development. Quantitative simulations of major pathways leading to biomarker development and analysis of drug effects should be encouraged. Models are described where the effects of drugs are simulated, and biomarkers are quantified. Several bioinformatics tools have been enlisted in the drug development process, including structural biology approaches to determining binding characteristics of small molecules.

Development of vertically integrated multi-scale (VIMS) models is required to understand why some molecular components and interactions affect higher-level physiological (and pathophysiological) processes and others do not. The major barrier is an experimental lack of systematic quantitative information, such as concentrations of components at specific locations within the cell and kinetic constants, including interaction & enzymatic rates; diffusion and movement rates. Major programmes are needed for systematic measurement of concentrations of cellular components and rate constants for 3-5 types of human cells, e.g. hepatocyte, myocytes, hippocampal neurons, T cells, mast cells. To focus on cancer, major kinases/phosphatases should be measured which are related to cancer and their substrates, or cells that are responsible for major types of cancer world wide.

The field of systems pharmacology involves network analyses to define relationships between cancer drugs and disease genes (mutations & polymorphisms) within the context of cellular/tissue networks. For example, it is possible to understand by means of computational models intermediate complexity the dynamics of the cyclin-cdk network controlling cell cycle progression This approach can be used to clarify differences in dynamical behaviour between normal and tumour cells. A model for the dynamics of the cell cycle may contribute to pinpoint targets for controlling cell proliferation. Computational models and simulations can also help to predict optimal patterns for cancer chronotherapy, which takes into account the effect of circadian rhythms on the effect of anticancer drugs.

There is a need to provide robust and credible data in areas of pharmacological/ medical significance. Improved understanding of the dynamics of underlying networks and how they respond to perturbation is essential. Models should be developed to investigate the effect of combination therapies as opposed to "magic bullet" approaches, by using modelling to refine, focus and "pre-test" experimental work, both in vivo & in vitro.

Large scale collaborative research projects in cancer systems biology and bioinformatics - Systems biology approaches and technologies are sufficiently advanced to create cancer projects that could vertically integrate virtually all of the skills and technologies of systems biology on one or more of the more tractable cancer systems. The project APO-SYS already provides an example of how computational, laboratory and clinical resources can be united to study several aspects of cancer.

A proposal from this workshop is to establish frameworks and funding to explore one or more types of cancer over the full scale of their progression, for example human glioblastoma, liver or colon cancer. Large strategic partnerships and collaborations are developing to attack the problems of

understanding the combined effects of genetic and environmental information using individual genome sequencing and biomarkers.

Advantages of glioblastoma include the facts that:

- tumours that are relatively homogeneous in tumour cells and are adequate in size for all of the potential analyses;

- these tumours are easily converted into cell lines with virtual 100% success;

- it is possible to isolate tumour stem cells;

- we can attempt to clone stoma cells to look at cellular interactions;

- we can study tumour cells and cell lines with single cell analyses;

- we can follow patients longitudinally—onset-treatment-reoccurrence-treatment-etc;

- there are interesting epigenetics;

- reasonable mouse model systems exist;

- there is some understanding of disease-perturbed pathways (networks);

- we can use cell lines to test and phenotype drugs; and

- we can use to drive the development of critical genomic, proteomic and single-cell technologies.

Accordingly, glioblastoma is an ideal tumour systems for studying across all of the informational, multistage dimensions—DNA, RNA, proteins, metabolites, interactions, networks, organs and tissues, etc. Mechanisms and organisation of research need to be developed, involving interdisciplinary research networks and large scale but focused projects, often with industry involvement.

Colorectal cancer also represents a prototypic solid tumour disease to be studied by systems biology. It displays

- well understood morphological and molecular pathogenesis (e.g. adenoma-carcinoma sequence; role of genetic and epigenetic alterations)
- availability of established experimental models (cell culture and animals)
- availability of screening methods for early diagnosis in humans (e.g., colonoscopy);
- access to tissue samples of various stages of the disease (benign and malign tumours)
- novel molecular therapies have recently been introduced into clinical practice and shown to be efficient

- Genetic mutations associated to high risk of colon cancer have been reported and prevalent mutations as in codon 12 and codon 13 of K-Ras ontogeny have been reported.
- Nutritional interventions with antioxidants for instance can be tested in cell culture as several of this natural compounds (i.e. polyphones as EGG the major component of green tea) have been reported to attaint the colon.

These two examples show some of the key considerations for choosing model systems.

Education

Education is recognized as a key component in the success of any successful systems biology programme, especially for applications to cancer research. It is recognized that a balance needs to be found between the need to be interdisciplinary and the necessity of having extensive specialist knowledge in particular areas. Collaborative research is a key method of uniting the skills necessary for large projects, while ensuring that there is proper communication and understanding among all participants concerned.

In developing training for systems biology, we should adapt the education of undergraduates and graduate students so as to integrate big, cross-disciplinary science and small science.

Role of funding agencies

There are already major funding initiatives in place, both at the national (e.g. USA, UK, Germany, Switzerland), European (European Commission) and international levels (bilateral national and EC-USA agreements). This cooperation could and should be extended to encourage more extensive research in applying systems biology methods to cancer research. Funding agencies could support programmes of bilateral collaborations with focused collaborations and criteria linked to downstream goals and being interdisciplinary.

Projects – A proposal from this workshop is to explore one or more types of cancer over the full scale of its progression, for example glioblastoma or colon cancer. Such a project draws together almost he entire hierarchy of information, and would require all the computational tools and generation of quantitative data, which could be mobilized to understand, detect and treat cancerous processes and establish methods applicable across a wide range of cancers.

APPENDIX I: MEETING AGENDA

<u>**Monday, 19 May 2008 (8:30 - 17:00)**</u>

9:00 Welcome and Introduction
Official Host Welcome
Marija Seljak, Director General Public Health
Health Ministry, Republic of Slovenia (EU Council Presidency)

9:15 Introductions from European Commission and NCI organisers
Manuel Hallen, Acting Director of Health Research
Research Directorate General, European Commission

Dan Gallahan, Deputy Director
National Cancer Institute, National Institutes of Health

9:30 Introduction
Lee Hood
Institute for Systems Biology

10:00 Session 1 - State-of-the-Art in Cancer Systems Biology:
Summarize the State-of-the-Art in Cancer Systems Biology and identify Collaborative
Research projects with characteristics that have made this research successful and relevant.
Chair Introduction
Chair – Marc Vidal
Dana-Farber Cancer Institute

10:15 Short individual presentations (5 min) of session participants and general discussion
        Charles Auffray, CNRS
        Soren Brunak, Danish Technical University
        Andrea Califano, Columbia University
        Albert Goldbeter, ULB
        Jim Ferrell, Stanford University
        Ursula Klingmueller, DKFZ
        Henk Stunnenberg, University Nijmegen
        Olaf Wolkenhauer, Rostock University
        Blaž Zupan, University of Ljubljana

11:30 General Discussion on session 1

14:00 Session 2 – Supporting Research and Infrastructures:
Identify the technological and resource needs required to enable global systems biology
approaches to cancer understanding and cures. What is available now, what will be required in the
future, and what we can do to make it happen? Identify how we can generate and integrate large
amounts of relevant and appropriate data generated for systems approaches and what resource
(samples, reagents, computer tools, data resources) are required to make systems approaches to
cancer broadly applicable.

Chair Introduction
Chair – Ruedi Aebersold
Institute of Molecular Systems Biology, ETH Zurich

14:15 **Short individual presentations (5 min) of session participants and general discussion**

> **Amos Bairoch**, Swiss Institute for Bioinformatics
> **Alvis Brazma**, European Bioinformatics Institute
> **Atul Butte**, Stanford University
> **Julio Celis,** Danish Institute for Cancer Biology
> **David Galas**, Institute for Systems Biology
> **Ravi Iyengar,** Mount Sinai School of Medicine
> **Ollie Kallioniemi**, VTT Technical Research Centre of Finland
> **Garry Nolan,** Stanford University
> **Lukas Pelkmans**, Swiss Federal Institute of Technology
> **Chris Sander**, Memorial Sloan-Kettering
> **Giulio Superti-Furga** Center of Molecular Medicine-CeMM, Vienna
> **Mathias Uhlen**, Sweden Royal Institute of Technology

15:40 **General Discussion on session 2**

Tuesday, 20 May 2008 (9:00 - 16:30)

9:30 **Session 3: Targeted Research Approaches:**

Discuss the ways to facilitate the transition and incorporation of research from a single researcher (one gene – one cancer paradigm) to a more collaborative and systems approach to mobilize the resources appropriate to the complexity of the problem. Identify the key areas of interest from basic to translational research leading to treatments from academic and industrial perspectives.

> **Chair Introduction**
> **Chair - Boris Zhivotovsky**
> Institute for Environmental Medicine, Karolinska Institutet

09:45 **Short individual presentations (5 min) of session participants and general discussion**

> **Tanja Čufer**, Institute of Oncology Ljubljana
> **Robert Gatenby**, University of Arizona
> **Adriano Henney,** AstraZeneca
> **Walter Kolch**, Beatson Institute Cancer research
> **Hans Lehrach**, MaxPlanckInstituteMolecularGenetics
> **Anil Potti,** Duke University
> **John Weinstein**, MD Anderson
> **Dennis Wigle**, Mayo Clinic
> **Michael Williams,** University of Virginia
> **Andrei Zinovyev,** Institute Curie

11:05 **General Discussion on session 3**

13:30 **Session 4 - The Way Forward:**

Identify strategic areas for applying systems biology to cancer research and the level and complexity of modelling needed. Identify infrastructures and research support required; discuss how to unify standards, protocols, and data quality. Develop specific suggestions for research areas and international collaboration.

Introduction and sessions 1,2,3 summary by chair, followed by discussion on state of the art
and   *recommendations for the future, ending with overall conclusions by session chair*
Chair – Lee Hood

15:45 Funder's discussion
Chair Patrik Kolar
A representative from each of the 5 "funding centres" represented, e.g. NCI, BBSRC, BMBF, European Commission, Slovenian Presidency, gives a 5 minute discussion/ presentation, about (i) their relevant programmes; (ii) their current funding plans; and (iii) some first impressions from the workshop

16:15 Closing Remarks by European Commission and NCI

APPENDIX II - Terms of Reference

The goals of this workshop are to:

- Summarize the State-of-the-Art in Cancer Systems Biology, and to identify Collaborative Research projects, along with the characteristics that have made this research successful and relevant.
- Identify the required supporting Research and Infrastructures. Identify the technological and resource needs required to enable global systems biology approaches to cancer understanding and cures. What is available now, what will be required in the future, and what we can do to make it happen? Identify how we can generate and integrate large amounts of relevant and appropriate data generated for systems approaches and what resources (samples, reagents, computer tools, data resources) are required to make systems approaches to cancer broadly applicable.
- Identify Targeted Research Approaches. Discuss the ways to facilitate the transition and incorporation of research from a single researcher (one gene − one cancer paradigm) to a more collaborative and systems approach to mobilize the resources appropriate to the complexity of the problem. Identify the key areas of interest from basic to translational research leading to treatments from academic and industrial perspectives.
- Produce a report of the state of the field and synthesize The Way Forward:
    - Identify strategic areas
    - Identify the level and complexity of modelling needed
    - Identify infrastructures and research support required
    - Discuss how to unify standards, protocols, data quality
    - Develop specific suggestions for International collaboration

Motivation of the Organizers for preparing this workshop

Cancer is, after decades of research, still a devastating disease, responsible for roughly one quarter of deaths. Cancer is clearly one of the most urgent problems we are facing, and will therefore have to have a very high priority due to the large number of deaths it is responsible for, the enormous human suffering caused by this disease, but also by the enormous health care and other costs associated with it. While progress has been made in the treatment of rare childhood cancers, little progress has been made in the treatment of the common forms of cancer, responsible for most of the death toll. Even highly successful new anticancer drugs like Herceptin or Glivec are successfully used for only a fraction of patients with individual characteristics.

Essentially, the two main causes for cancer are genetic predisposition and environmental influence, including infection and inflammation. However, on a more analytical and molecular level the ontogeny of cancer is less evident, and both clinical as well as basic research suggests that cancer is the result of the accumulation and interaction of many factors that promote tumour growth and metastasis. It is clear that because of this complexity of cancer, a more systematic approach is needed for understanding and improving further cancer treatment.

It is the goal of this workshop to establish a framework for identifying how a systems biology approach can help to combat cancer. The starting point of this workshop is based on existing resources of leading research groups in Europe and the USA. It unites participants with a strong clinical focus, with experience in high throughput functional genomics as well as with those involved in computational and systems biology projects and approaches. Moreover, it brings together groups from some of the largest European and American cancer research organisations and centres. While limited in scope, the workshop will attempt to represent the vast range of cancer biology and researchers.

A critical factor in any systems biology approach involves discrepancies and coherencies in the various data sources. Standardization is needed to lead to new insights and give a comprehensive

overview for the relevant biological objects. Furthermore, a cancer-relevant model repository is needed consisting of known pathways and gene regulatory networks associated with cancer, the role of specific mutations or other changes in key genes/gene products in these pathways, and, as far as available, detailed clinical data with special emphasis on the influence of different anti-cancer drugs on these pathways.

We need to identify important research areas that combine experimental and clinical data with theoretical models. This will guide further analyses and approaches of the participating groups, including, for example, in silico models of cancer-related (e.g. signalling) pathways analysing particularly the feedback of theoretical models and experimental data and the construction of a complete human metabolic network in order to test responses to drugs and chemical treatments. These models and approaches will also have to address the multi-scale nature of a biological disease system dealing with both the molecular and cellular pathways and mechanisms.

This workshop aims to stimulate the development of networks of leading groups in the field of cancer research, genomics, proteomics and computational biology and to strengthen the expertise and research infrastructure in Europe and the USA. Moreover, it will provide the basis to develop and coordinate activities that will provide opportunities for improving health and training, developing public-private partnerships, and fostering new technologies. Finally, this workshop will underscore the importance of a systems biology approach to cancer research and establish productive collaborations between the United States and Europe and on the international level in general. To further this goal, the workshop will be concluded with a "Funders' Forum," where means of implementing the workshop goals and conclusions may be explored.