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## Foreword: from the TRANSCRIPTOME conferences to the SYSTEMOSCOPE International Consortium

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### Abstract

This thematic issue of the *Comptes rendus Biologies* contains review articles, original papers and conference reports presented at the first two TRANSCRIPTOME conferences *From Functional Genomics to Systems Biology* and IMAGE Consortium Invitational workshops (Paris, November 2000 and Seattle, March 2002), and discussed during the inaugural meetings of the SYSTEMOSCOPE International Consortium (Paris, June 2003). We describe the founding principles, missions, working plan and policy for partnership and industrial development of SYSTEMOSCOPE to promote the study of the complexity of biological systems by integrating scientific, medical, ethical and economic issues in implementation of interdisciplinary projects for human health. **To cite this article:** *C. Auffray et al., C. R. Biologies 326 (2003).*

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### Résumé

**Des conférences TRANSCRIPTOME au Consortium International SYSTEMOSCOPE.** Ce numéro thématique des *Comptes rendus Biologies* contient des revues, des travaux originaux et des rapports présentés aux deux premières conférences TRANSCRIPTOME *De la génomique fonctionnelle à la biologie systémique* et ateliers du consortium IMAGE (Paris, novembre 2000 et Seattle, mars 2002), et discutés lors des réunions inaugurales du consortium international SYSTEMOSCOPE (Paris, juin 2003). Nous décrivons les principes fondateurs, les missions, le plan de travail et la politique de partenariat et de développement économique de SYSTEMOSCOPE pour promouvoir l'étude de la complexité des systèmes biologiques en intégrant les aspects scientifiques, médicaux, éthiques et économiques dans la mise en œuvre de projets interdisciplinaires pour la santé humaine.

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## 1. The TRANSCRIPTOME conferences and IMAGE Consortium Invitational workshops: from Functional Genomics to Systems Biology

### 1.1. TRANSCRIPTOME 2000

TRANSCRIPTOME 2000 was the first in a new series based on the previous conferences and coordination workshops initiated by the founders of the IMAGE Consortium (Charles Auffray, Greg Lennon, Michael Polymeropoulos, Bento Soares [1,2]) with active support from the US Department of Energy (DOE, Marvin Stodolsky) and numerous public and private organizations.

TRANSCRIPTOME 2000 followed the conference organized the previous year in Japan by Nobuo Nomura and Michio Oishi at the Kazusa DNA Research Institute. More than 80 speakers from all over the world gathered to discuss and debate with the 400 participants the most recent advances in the emerging field of functional genomics, the study of biological systems based on global knowledge of genomes, transcriptomes and proteomes as reviewed by Auffray et al. in this issue [3].

The TRANSCRIPTOME 2000 conference and IMAGE Consortium Invitational workshop were organized at the Pasteur Institute in Paris on November 6–10, 2000 by Charles Auffray (CNRS, France) (Chair), Bento Soares (University of Iowa, USA) and Sumio Sugano (University of Tokyo, Japan) under the patronage of the French Minister of Research, the French Academy of Sciences and the European Union (<http://www.vjf.cnrs.fr/transcriptome/>).

TRANSCRIPTOME 2000 was an occasion to celebrate 25 years of cDNA research, since the initial description of cDNA cloning, a milestone in the messenger saga described by François Gros [4]. Sessions on cDNA cloning and sequencing, cDNA clustering and genome annotation, transcriptome and proteome analysis and their applications in biology, biotechnology and medicine were organized to review the field in depth, and to discuss the future perspectives for further technological, scientific and medical advances in the context of emerging ethical, legal and economical issues.

TRANSCRIPTOME 2000 was followed on November 10, 2000 by IMAGE Consortium Invitational 2000, the 5th international coordination workshop on

complete cDNA sequencing and transcriptome analysis. This was a forum of academic and industrial scientists to promote sharing of resources and knowledge in functional genomics, discussing standardization and quality assurance in cDNA cloning, sequencing and expression profiling, and sharing common resources and intellectual property.

### 1.2. TRANSCRIPTOME 2002

The TRANSCRIPTOME 2002 conference was organized in Seattle, USA on March 10–13, 2002 by Yohishide Hayashizaki (RIKEN, Japan), Winston Hide (SANBI, South Africa), John Quackenbush (TIGR, USA) (Chair), Andrew Simpson (Ludwig Institute, Brazil) and Stefan Wiemann (DKFZ, Germany), and sponsored by the Department of Energy and the National Cancer Institute (<http://www.tigr.org/conf/transcriptome/>).

At TRANSCRIPTOME 2002, more than 50 speakers attempted to highlight the fundamental mechanisms by which cells mediate their growth, function, and metabolism. They examined tools and techniques for exploring gene expression, and discussed future applications with the 300 delegates.

Technical discussions included recent advances in cDNA cloning, sequencing and analysis with a focus on genome annotation, array techniques and other approaches for assessing expression and mutation, and the development of analysis tools, techniques, and databases for managing and interpreting the large datasets we now have the pleasure and challenge of exploring.

The central focus of TRANSCRIPTOME 2002 was on using these techniques to develop a better understanding of fundamental biological processes and the detection, diagnosis, understanding, and treatment of human disease. There were sessions on the role of transcription and processing; cDNA-based gene discovery; sequence-based tools for gene discovery; gene expression, transcript abundance and disease; alternate measures of expression and the future.

IMAGE Consortium Invitational 2002, the 6th international coordination workshop on complete cDNA sequencing and transcriptome analysis, was organized by Charles Auffray, Greg Lennon, Michael Polymeropoulos and Bento Soares. It followed TRANSCRIPTOME 2002 on March 14, 2002 and was a forum

of academic scientists, industry (suppliers of technology and resources, genomics, biotechnology and pharmaceutical companies) and funding institutions (international, government, foundations and charities) to promote sharing of resources and knowledge in functional genomics and systems biology.

There were sessions on cDNA cloning, sequencing and distribution; functional use of cDNA clones and sequences; informatics and expression profiling. The last session was a roundtable discussion of the foundation of an “Expression Profile International Consortium” (EPIC), a forerunner of the SYSTEMOSCOPE International Consortium (see below).

## 2. Content of the special issue

### 2.1. *Overviews*

Transcription of DNA into RNA followed by translation of messenger RNA into proteins are the fundamental mechanisms underlying the functioning of living organisms. The discovery of reverse transcription of mRNA into DNA allowed the development of cDNA cloning, one of the fundamental techniques of genetic engineering described for the first time 25 years ago. At the conferences, some of the pioneers who contributed to the elucidation of these mechanisms presented an historic overview of this great endeavour and their vision of the future, as reported by François Gros in this special issue [4]. Jonatha Gott provides a review of how RNA editing can expand the genome capacity [5], and John Weinstein and Yves Pommier [6] review the challenges associated with transcriptome analysis with microarrays in cancer research.

### 2.2. *cDNA resources for functional genomics and proteomics*

During the last decade of the twentieth century, large-scale systematic sequencing of cDNA libraries has provided an initial description of the transcriptome, the entire set of gene transcripts of man and several animal and plant organisms. At the conferences and workshops, speakers discussed progress in full-length cDNA cloning and quality control in large-scale

sequencing programs. They also addressed the challenges of clustering the information collected to help genome annotation at the time when the complete or working drafts of genome sequences were becoming available.

This issue contains a full section on cDNA technologies and resources developed for functional genomics and proteomics in mouse, human and frog by scientists from all over the world, including Brazil, China, France, Germany, Italy, Japan, and the United States. Several reports focus on the development and use of mouse cDNA resources: Yohishide Hayashizaki [7] describes the Riken mouse genome encyclopedia; Carter et al. [8] the NIA cDNA project on mouse stem cells and embryos; and Kato [9] the use of adaptor-tagged competitive PCR to study the mammalian nervous system.

Another series describe ongoing efforts dealing with human cDNAs and transcriptomes: Han et al. [10] provide an overview of various transcriptome studies across China; Nagase et al. [11] report on the Kazusa project for identification of unknown human transcripts; Dalla et al. [12] describe the LNCIB full-length cDNA collection, and Gutaratne et al. [13] improvements in the concatenation cDNA sequencing process for transcriptome analysis. Sakabe et al. [14] report that Open Reading Frame ESTs (ORESTES) are enriched in rare exon variants affecting the encoded proteins, while Yamashita et al. [15] highlight the presence of small open reading frames in 5′ untranslated regions of mRNAs.

This section ends with three reports describing the use of cDNA resources for localization of expression in organs and cells. Minamikawa-Tachino et al. [16] describe the development of high-throughput imaging of cells transfected with human cDNA clones; Wiemann et al. [17] report on the efforts of the German Consortium to use cDNAs for functional genomics and proteomics; and Pollet et al. [18] provide access to their database of *in situ* analysis of gene expression in *Xenopus* embryos.

### 2.3. *Expression profiling with microarrays*

Differential hybridization using arrays of cDNA clones is as old as cDNA cloning. Recent advances in materials, optics, electronics, robotics, chemistry, genetic engineering and informatics have permitted

the development of integrated platforms allowing the parallel study of tens of thousands of transcripts in a variety of normal and pathological conditions.

This issue contains reports on technological advances in expression profiling with microarrays, including issues related to the RNA amplification, fidelity and reproducibility addressed by Li et al. [19], and their applications in the study of breast carcinomas with Nylon microarrays described by Bertucci et al. [20]. Agrawal et al. [21] used microarrays to identify osteopontin as a colon cancer tumor marker, and Strominger et al. [22] to investigate the regulation of dendritic cells and their role in autoimmune disease. Zhao et al. [23] describe the largest expression profiling time series reported thus far, with 27 time points in muscle regeneration, while Shmueli et al. [24] provide extensive whole genome expression profiles in normal human tissues.

#### 2.4. *Expression databases and computational genomics*

Speakers at the conferences and workshops discussed the challenges in quality assessment, formatting, comparing and validating the large amount of data collected using various platforms, the need for a public repository of cDNA array and *in situ* hybridization data, and similar problems which are arising in the study of proteomes, the entire sets of proteins which are governing the functioning of cells, organs and organisms.

Illustrating these challenges and the current trends, this issue contains reports on two of the emerging expression profiling databases: Rocca-Serra et al. [25] describe ArrayExpress at EBI and Ikeo et al. [26] CIBEX at DDBJ. Bellgard et al. [27] address the challenge of microarray analysis using bioinformatics audit trails, Hide et al. [28] report controlled vocabularies for unifying gene expression data, and Ogasawara et al. [29] an explanation of the application of Zipf's law to human transcriptome using an evolutionary model.

#### 2.5. *Ethical, legal and social issues in genomics*

Advances in genome research provide everyday a deeper insight into the mechanisms of life, thereby promising to change our vision of the world and of

ourselves, and to speed the understanding and treatment of diseases. Public outreach programs and intense media coverage are triggering both growing public awareness and concern. There is a need for both open, universal dissemination of genomics knowledge and promotion of innovation through mechanisms ensuring the sustainable development of new diagnostics, drugs and treatments.

At the conferences, legal and political international experts discussed on the ethical, legal, economic and social issues related to genome research and its applications in society. Thus this issue contains reports by James Basingthwaite [30] on the macro-ethics of genomics to health, by Joseph Straus [31] on product patents on human DNA sequences, by Rebecca Eisenberg [32] on patenting genome research tools and the law, by Federico Mayor [33] on the universal Declaration on the human genome and Human Rights, and by Noëlle Lenoir [34] on patentability of life and ethics, issues which are still actively debated worldwide.

### 3. The emergence of Systems Biology

#### 3.1. *Scientific context*

As discussed extensively during the TRANSCRIPTOME conferences and IMAGE Consortium workshops, the emergence of systems biology represents a transition from mostly analytical, hypothesis-driven research to a complementary global, exploratory mode based on the tools of functional genomics that will ultimately bridge understanding of chemistry and physiology by integrating knowledge of the fine details of all molecular structures and mechanisms together with their natural or pathological variations (reviewed by Auffray et al. [3] in this issue and discussed below).

#### 3.2. *Biology is in a transition phase*

Contemporary biological sciences are in a transition phase in the process of collecting data and transforming it into information and knowledge similar to that experienced previously in physics and chemistry. From an emphasis on strictly hypothesis-driven, analytical, reductionist approaches of discovery, based on identification and classification of individual elements and mechanisms, which has been the hallmark of the

very successful era of molecular biology, with the Human Genome Project, the balance has been shifting over the past decade towards exploratory, global, systematic approaches of biological systems. These have been largely technology-driven, as illustrated by the development of so-called omics sciences (genomics, transcriptomics, proteomics, metabolomics, physiomics), and discussed in this issue by John Weinstein and Yves Pommier [6].

### 3.3. *The need of a new paradigm*

From the cumulative work of the past decades in molecular and cellular biology, biochemistry and genetics, however, it has become apparent that exhaustive knowledge of the structure, function and relation of the components of biological systems, characteristic of the analytical paradigm, is necessary but insufficient to understand phenotypes, and therefore to develop proper applications for the treatment of human diseases. As a consequence, although the ongoing completion of the sequence of the genomes of human and other animal, plant and microbial genomes has been widely advertised as a landmark of biology, it falls short of providing the capacity to develop the expected improvements in public health.

### 3.4. *Integration for a new conceptual framework*

Understanding biological systems require apprehending them not merely as collections of interacting parts, but as complex systems in which such properties as feedback, redundancy and modularity ensure their optimal stability and robustness. In other words, it has become indispensable to complement the analytical reductionist approach to living systems with other approaches based on other theoretical frameworks taking into account progress made in other areas of science. The challenge is to integrate the theories of system and control, information, non-linear dynamics, chaos and complexity, and to revisit the cybernetics and systemic paradigms.

### 3.5. *Interdisciplinarity and networking*

The successful development of the study of complex systems through the means of functional genomics and systems biology require the implementa-

tion of integrated and standardized experimental and software platforms for data collection and analysis, visualization and simulation, hypothesis generation and testing in an iterative mode. Because of the magnitude and scope of the effort required, such an endeavour requires integration of a wide range of expertises from various disciplines (physics, chemistry, mathematics, informatics, engineering, epistemology, history of sciences, law and ethics). Essential to its success are new modes of training, exchange, and program development. This will be best achieved by the creation of a network of laboratories with an open architecture, where scientists from different disciplines will work together on joint projects in close collaboration with patient organizations and with industry.

## 4. **The SYSTEMOSCOPE International Consortium**

In order to implement this vision, we propose to establish an International Consortium, SYSTEMOSCOPE, based on the following principles, missions, pilot projects, working plan and policy for partnership and industrial development.

### 4.1. *Founding principles*

The SYSTEMOSCOPE International Consortium will aim at developing fundamental research on the complexity of biological systems and its biomedical applications, with a long term commitment of its partners to bring the tools of functional genomics and the results of systems biology from the laboratory to the patient.

The SYSTEMOSCOPE International Consortium will develop as a not-for-profit organization federating world leading biomedical research organizations in partnership with patient organizations and charities, instrumentation, reagent, informatics companies, government agencies and pharmaceutical and biotechnology companies.

### 4.2. *Missions*

The missions of the SYSTEMOSCOPE International Consortium will be:

- to promote an ethics of responsibility and sharing between academy and industry, and the North and

South, through the establishment of an openly shared common pool of tools, reagents, data and intellectual property rights;

- to conceive and implement integrated interdisciplinary approaches standardized under quality assurance to study the complexity of biological systems and human diseases, with the goal to develop reagents and methods for diagnostic, prevention and therapy, for the benefit of the patient;
- to use advanced information and communication technologies, such as emerging computer grids, in order to facilitate cooperation through networks, and disseminate quickly the tools of functional genomics and systems biology;
- to collaborate in very large scale projects integrating the unique tools and resources of the academic partners in close collaboration with the patient organizations, the technology providers and the pharmaceutical and biotechnology companies.

#### 4.3. Pilot projects

The SYSTEMOSCOPE International Consortium will initially develop pilot projects in the areas of activation of the immune system and infectious diseases, cancer and regeneration, and development and pathology of the neuromuscular system.

The pilot projects will aim at demonstrating the value of integration of the results of genome, transcriptome, proteome and metabolome studies, creating a leverage effect from the contribution of small and large teams, as shown through the example of the ongoing work undertaken by the H-Invitational international consortium for integrative annotation of the human transcriptome.

The pilot projects will be organized following the characteristic process of emerging systems biology, combining in an iterative manner exploration of the complexity of biological systems on a global scale, generation of hypotheses, modelling and simulation, and experimental testing of the hypotheses.

#### 4.4. A working plan for the SYSTEMOSCOPE International Consortium

The goal of the Consortium will be to study the behaviour and relations of all the components of a biological system while it is functioning, with a shift

of emphasis from the component to the system. This will require integration of data obtained at each level of analysis with systematic exploratory methods to build predictive models and formulate hypotheses that can be tested experimentally in order to move from description to prediction, and identify key mechanisms or objects for the understanding or manipulation of the system studied. The use of informatics tools and methods for graphic visualization, modelling and engineering will be an indispensable step to shift from interpretation to intervention.

The SYSTEMOSCOPE International Consortium projects to study the complexity of biological systems will therefore proceed in iterations of three basic steps: (1) define the components of a biological system, collect the available biochemical and genetic data, and use them to formulate an initial model of the system; (2) systematically perturb the components of the system, study the result on a global scale, and compare the observed responses to those predicted by the initial model; (3) refine the model so that its prediction fit best to the experimental observations, then conceive and test new experimental perturbations to distinguish between the multiple competing hypotheses.

Diverse types of data will be collected and integrated on specific biological systems under study, including the identification and characterization of genes, transcripts and proteins, coding regions, functional domains, regulatory sequences, polymorphisms, structure/function relationships, organization and regulation of metabolic pathways and networks, the role of other molecules and of the environment in relation with physiology and pathologies. Advantage will be taken of the similarities and differences between organisms and developmental stages through the comparison of model organisms which have evolved separately during long periods.

High-capacity experimental and informatics platforms will be used for: (1) quantitative data collection of sequences, expression profiles (transcripts with cDNA and oligonucleotide microarrays; proteins and interaction maps with mass spectrometry, chromatography, electrophoresis and protein and antibody arrays), regulatory networks, cell structure and function (imaging, cell sorting); (2) systematic perturbation of biological systems by targeted inactivation, replacement, modification with RNAi and antisense technologies, and the use of shuttle expression vec-

tors using integration/excision and homologous recombination; (3) storage and distribution of diverse types of data, followed by their analysis, annotation and integration to produce information and knowledge through simple, complex and global queries, based on distributed annotation and textual analysis, and to tackle the challenges of completeness, exactness, and updating; (4) computer-assisted conception, model inference, prediction, engineering of biological systems to detect emerging properties using kinetic and stochastic models, and formulate hypotheses.

#### 4.5. *Conferences and inaugural meetings of the SYSTEMOSCOPE International Consortium*

This initiative was discussed in the context of the TRANSCRIPTOME series of conferences “From Functional Genomics to Systems Biology” started in Paris (November 2000) and Seattle (March 2002), which will continue in Tokyo (November 2003), Naples (March 2005), Washington (November 2006) and Shanghai (March 2008). The TRANSCRIPTOME 2003 conference and IMAGE Consortium Invitational workshop are organized in Tokyo, Japan on November 9–15, 2003 by Charles Auffray (CNRS, France), Zhu Chen (Academy of Sciences, China) (co-Chair), Sumio Sugano (University of Tokyo, AIST, Japan) (Chair), Winston Hide (SANBI, South Africa) and Leroy Hood (ISB, USA) in conjunction with the second edition of the H-Invitational International workshop for integrative annotation of the human transcriptome organized by Takashi Gojobori, Nobuo Nomura and Sumio Sugano (JBIRC, AIST, Japan).

The scientific inaugural meetings of the SYSTEMOSCOPE International Consortium were organized in Paris by Charles Auffray (CNRS), Dominique Charon (Inserm, Institut Biomédical des Cordeliers) and Magali Roux-Rouquié (CNRS, Institut Pasteur) from June 18 to 21, 2003 under the high patronage of Mr Jacques Chirac, President of the French Republic, with the sponsorship of Mrs Claudie Haigneré, Minister in charge of Research and New Technologies, under the Honorary Presidency of Edgar Morin (<http://www.systemoscope.net>).

They consisted in (1) a symposium on “Complexity of biological systems” at Institut Pasteur, followed by a roundtable “Complexity and interdisciplinarity”

at the Faculty of Medicine of the Necker Hospital; (2) a roundtable “Annotation and modeling of biological information” at the House of Research of the Medical Research Foundation, and (3) of sessions of the working groups of the H-Invitational workshop for annotation of the human transcriptome at Institut Pasteur, Forum des Halles, CNRS, and Institut Biomédical des Cordeliers.

#### 4.6. *Consortium policy for partnership and industrial development*

The academic and industrial partners of the Consortium recognize that, in order to achieve their goals of rendering the tools of functional genomics and systems biology useful for human health, it will be absolutely essential to develop a common language and a shared set of data and tools. They consider that there is no hope of developing advanced in depth knowledge of biological systems based on sophisticated informatics tools if the experimental data is not of the highest possible quality. This is particularly important because the challenge we face is to develop the ability to measure accurately large numbers of small variations of weak signals which underlie the functioning of living systems [35]. Therefore the common language should be that of quality assurance in research and technology development, including project design and engineering, standardized operating procedures and quality control, electronic notebooks, and knowledge management of shared information systems operating through emerging computer grids.

This will ensure that all sets of data of a given type, when produced under commonly agreed rules, will be comparable, irrespective of its size or of that of the group generating it. This will produce an immediate leveraging effect for individual projects of all sizes, which will be able to analyze their data in the context of extremely large and growing data sets. The Consortium partners will also develop a common policy to ensure that a pre-competitive set of data and tools are shared openly in public access, starting with reference expression profile data sets, enabling to focus the development of intellectual property rights, including patents, through regular collaboration, material transfer agreements and contracts for competitive applications.

## 5. Sponsors and partners

The TRANSCRIPTOME 2000 conference and IMAGE Consortium Invitational workshop were sponsored by Amersham Pharmacia Biotech, Department of Energy (DOE), the ‘Ligue nationale contre le cancer (CIT Program)’, the French ‘Ministère de la Recherche’ and the National Cancer Institute (NCI), with additional support from the ‘Association française contre les myopathies’ (AFM), Biospace Instruments et Mesures, the ‘Centre national de la recherche scientifique’ (CNRS), Compaq, InforMax, the ‘Institut national de la santé et de la recherche médicale’ (INSERM), the Institut Pasteur, the French ‘Ministère de l’Économie, des Finances et de l’Industrie’.

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