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FUNCTIONAL GENOMICS AND SYSTEMS BIOLOGY FOR HEALTH

CNRS - INSTITUTE OF BIOLOGICAL SCIENCES

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EDUCATION AND PROFESSIONAL EXPERIENCE

(1968) Baccalaureate in Science with highest honors.

(1971-1976) Student-Professor at Ecole Normale Supérieure de Cachan in Physiology and Biochemistry: entered with first rank, graduated with Agrégation 1975 (qualification for professorship) and degrees in Biochemistry (University Denis Diderot of Paris VII, 1974) and Immunology (Pasteur Institute Advanced Course and CNRS Chemistry Institute of Natural Substances, Gif s/Yvette, 1976).

(1976-1981) Doctoral Student at the Pasteur Institute Genetic Engineering Unit and Pierre & Marie Curie University of Paris VI, State Doctoral Thesis in Immunology: “Contribution to the study of mouse immunoglobulin heavy chain genes”, Supervisor Dr. François Rougeon.

(1981-1983) Post-doctoral Fellow and Junior Faculty, Department of Biochemistry and Molecular Biology at Harvard University in Cambridge, MA, USA: “Molecular genetics of the human major histocompatibility complex HLA”, Supervisor Pr. Jack Strominger.

(1983-1991) Group Leader in “Molecular genetics”, CNRS and Collège de France Institute of Embryology in Nogent s/Marne, France, Director Pr. Nicole Le Douarin.

(1991-1995) Scientific Director of the Genexpress Program, Généthon Laboratory of the French Muscular Dystrophy Association in Evry, France.

(1991-2001) Director of CNRS Research Unit in Molecular Genetics and Developmental Biology in Villejuif, France.

(2002-2003) Director of CNRS Research Unit in Functional Genomics and Systems Biology for Health in Villejuif, France.

(2004-2008) Affiliated to the Pierre & Marie Curie University of Paris VI and CNRS Research Unit on Molecular Genetics of Neurotransmission, headed by Dr. Jacques Mallet.

(2004-2009) Visiting Scientist at Laboratory of Fundamental and Applied Bioenergetics, Inserm and Joseph Fourier University of Grenoble, headed by Pr. Xavier Leverve.

(2009) Affiliated to the CNRS Institute of Biological Sciences.

FELLOWSHIPS, AWARDS AND PROFESSIONAL APPOINTMENTS

(1968-1971) Fellowship from Ministry of Education.

(1971-1976) Student-Professor at *Ecole Normale Supérieure de Cachan*.

(1977-1978) Fellowship from Ministry of Research and Education (DGRST).

(1978-1979) Teaching Assistant Professor, Faculty of Medicine, University Denis Diderot of Paris VII.

(1979-1982) Research Assistant Professor (CR2 CNRS).

(1981-1982) Post-doctoral fellowship from National Institutes of Health Fogarty Center.

(1982-1983) Post-doctoral fellowship from *Ligue contre le Cancer*.

(1982-1986) Research Assistant Professor (CR1 CNRS).

(1985) Bernard Halpern Immunology Prize.

(1986-1992) Research Director (DR2 CNRS).

(1992) Alexander Bayev Memorial Lecture (Moscow, Russia).

(1992-2009) Research Director (DR1 CNRS).

Co-author of 237 original publications and books, including 175 in international journals with an editorial board, which received over 12,000 citations (h Index=47) registered in Web of Science.

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

French Immunology Society, French Neuroscience Society, HLA and Medicine (Vice-President), Human Genome Organization (Chairman of IPR Committee). Founding member, International Society of Systems Biology.

EDITOR AND REVIEWER FOR INTERNATIONAL SCIENTIFIC JOURNALS

Member of the Editorial board of *Genome Research* (1995-2003), *Transactions on Computational Systems Biology* (2004-2009), *Molecular Systems Biology* (2005-2009), Section Editor for *Systems Medicine and Informatics of Genome Medicine* (2008-2009), Guest Editor for *Journal of Biological Systems* (2002) and *Comptes Rendus Biologies* (Proceedings of the French Academy of Sciences, 2003), occasional reviewer for *Nature*, *Nature Genetics*, *PNAS*, *Gene*, *Genome Research*, *Genome Biology*, *Nucleic Acids Research*. Member of Public Library of Science Initiative (PLoS).

LECTURES AT INTERNATIONAL MEETINGS AND CONFERENCES

In my research career, I have given over 120 invited lectures and conferences at scientific meetings and academic and industrial research centers worldwide. In the last 10 years, I gave lectures on Functional Genomics and Systems Biology at prominent international research institutions and meetings in Brazil (Rio de Janeiro, Sao Paulo), China (Shanghai, Beijing), Egypt (Alexandria), Estonia (Tartu), France (Pasteur Institute, UNESCO, etc), Germany (Heidelberg, München), Italy (Naples, Trento), Japan (Tokyo, Osaka), Switzerland (Lausanne, Zürich), Russia (Moscow), Sweden (Stockholm), Tunisia (Tunis), the United Kingdom (London), and the United States (Seattle, Washington, etc). Co-organizer of the TRANSCRIPTOME conferences « From Functional Genomics to Systems Biology » in Paris (2000), Seattle (2002), Tokyo (2003) and Shanghai (2005).

PUBLIC EDUCATION, ETHICS, BOOKS AND MASS MEDIA.

Member of the Council for the Rights of Future Generations to the French President, of the European Platform of Patient Organizations, Science and Industry (Belgium), of the UNESCO International Bioethics Committee Working Group, of the Institute for Foresight and Social Studies in Economy and Justice (Institut PRESAJE, <http://www.presaje.com>, France).

Active member of the hands-on science program *La Main à la Pâte* for science education in the French elementary and secondary school system (with physics Nobel Prize winner Georges Charpak). Conferences in elementary and secondary schools; articles in the general press, radio and TV; member of the scientific committee for the web site of the program.

Author or co-author of 11 books and chapters for public education in science, including *Le génome humain (The Human Genome)*, Flammarion, 1996, 2002; *Le Trésor, Dictionnaire des Sciences (The Treasury, Dictionary of Sciences)*, with a group of cross-disciplinary scientists in astronomy, biology, chemistry, earth science, informatics, mathematics, philosophy and history of sciences, and physics, headed by Michel Serres, Flammarion, 1997; *Qu'est-ce que la vie? (What is life?)* Le Pommier, 2001; *Graines de Sciences 1, 2, 3 (Seeds of Sciences)*, Le Pommier, 1999, 2000, 2001 ; *Paysages des Sciences (Landscapes of Sciences)*, Le Pommier, 2001.

Author or co-author (with Prs. Zhu Chen and Leroy Hood) of commentaries on international ethical, legal and social issues in genetics, stem cell research, intellectual property rights policies, and Systems Biology for *Observatoire de la Génétique* (Observatory of Genetics, University of Montréal Bioethics Center, <http://www.ircm.qc.ca/bioethique/obsgenetique>).

INSTITUTIONAL AND GRANT REVIEW COMMITTEES

Member of review committees for the European Union Framework Program and the European Research Council (Belgium), the Academy of Finland Systems Biology and Bioinformatics Program (Finland), Genome Study Section, National Committee of CNRS (France), National Cancer Institute (France), European Molecular Biology Laboratory (Germany), Advanced Industrial Science and Technology Agency (Japan), National Committee for Evaluation of Research Activities (Tunisia), DOE Genome Program (USA).

Grant reviewer for Genome Quebec (Canada), Human Science frontier Program (Strasbourg, France), the French Muscular Dystrophy Association (France), the Italian Association for Cancer Research and Italian Ministry Program for Funding of University Research (Italy), the Wellcome Trust (United Kingdom), USDA and NSF (USA).

TRAINING AND SUPERVISION OF RESEARCHERS

Since I returned from my post-doc at Harvard University, I have trained, recruited and supervised the work of some 120 individual researchers, including 20 who obtained permanent faculty positions, 40 post-doctoral fellows and research engineers, 20 doctoral students, and 40 engineers, technicians, administrators and undergraduate trainees. In order to facilitate the promotion of the best of my co-workers and their transition to independence, I have given priority for senior authorships on joint papers and grant applications at an early stage. Many of these individuals currently hold positions in France, Europe and abroad in academic and government institutions or private companies: *James Lillie*, PhD, technician, student 1981-1983, Director at Millenium Pharmaceuticals; *François Guillemot*, PhD, student 1983-1988: Research Director CNRS, Programme Leader, National Institute for Medical Research, London, UK; *Olivier Pourquié*, PhD, student 1986-1987, Research Director CNRS, team leader, Stowers Institute, Kansas City, USA, will be the next Director of IGBMC, Strasbourg; *Guido Kroemer*, MD, PhD, post-doc 1989-1990; team leader 1993-2000, Research Director at Inserm, Director, Inserm U848, Institut Gustave Roussy, Villejuif; *Marie-Dominique Devignes*, PhD, post-doc, team leader 1990-2002, Chargée de recherches CNRS, team leader LORIA, Nancy; *Rémi Houlgatte*, PhD, post-doc, team leader 1991-1998, Research Director at Inserm, team leader and microarray platform director, Inserm U915, Nantes; *Claude Chelala*, PhD, student and post-doc 1998-2004, Lecturer, Cancer Institute, London, UK; *Sandrine Imbeaud*, PhD, post-doc, team leader 1999-2006, Research engineer CNRS, technical director, microarray platform, Gif s/Yvette.

ACADEMIC COLLABORATIONS

My research activities have been largely based on an wide array of academic collaborations with some 80 small and large research groups in France (CNRS, INRA, INSERM and INRIA) and worldwide. In 1993, I co-founded the IMAGE Consortium with Drs. Bento Soares and Mihaelis Polymeropoulos (104), and coordinated the collaboration of Genome Centers in the USA (DOE, NIH, University of Iowa), Europe (Spain, Germany, Italy, Sweden, United Kingdom), China and Japan to generate and distribute cDNA resources for Functional Genomics. In 2000, I participated to the creation of the H-INVITATIONAL Integrative Annotation Consortium coordinated by Takashi Gojobori (JBIRC/AIST, Tokyo, Japan), in which 67 teams from 40 research institutes in 12 countries collaborated to provide integrative annotation of over 21,000 human genes validated by full-length cDNA clones (151, 154, 171). In 2002, I co-founded with Prs. Zhu Chen and Leroy Hood the SYSTEMOSCOPE International Consortium to promote the development of Systems Biology and Medicine at the international level (147, 173).

INDUSTRIAL PARTNERSHIPS, INTELLECTUAL PROPERTY

My research programs have benefited from research and technology development industrial partnerships with Agilent Technologies, Amersham Biosciences (Molecular Dynamics), Genome Express, InforMax, Qiagen, and from grants in support of targeted research programs from Aventis (Rhône Poulenc Rorer, Pasteur Vaccins) and Sanofi-Synthélabo Recherche. I have been a consultant for Rhône Poulenc Santé, Pasteur Vaccins, InforMax, and I am currently a senior consultant for bioMérieux and Mérieux Alliance. As coordinator of the workpackage on bioinformatics and systems biology of the Innovative Medicines Initiative U-BIOPRED Consortium on severe asthma, I will be collaborating with the 9 major pharmaceutical companies involved (Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, Roche, UCB).

I am the co-author of international patents on immunosuppressive peptides, molecular genotyping in chickens, and an improved method for cDNA synthesis. Considering partial cDNA sequences as elements of knowledge insufficient to warrant intellectual property rights by themselves, I have advocated their release in the public domain as part of the IMAGE Consortium resources (70, 104, P4), and I have not applied for patents on the 8,000 human gene transcripts discovered by my team at Généthon (95, 99) that served for the construction of the gene map of the human genome (102, 108, 109, 117).

FINANCIAL SUPPORT, GRANTS AND SCIENCE ADMINISTRATION

After my State Doctoral Thesis at the Pasteur Institute (1976-1981) and my post-doctoral stay as Junior Faculty at Harvard University (1981-1983), I created my own group in Molecular Genetics at the Institute of Embryology in Nogent s/Marne. During the period 1983-1991, my group grew from 5 to 17 members, and I raised 6 M\$ in global support. This included 2 M\$ in salaries of permanent researchers and supporting staff, and 4 M \$ in grants for infrastructure, equipment, supplies and fellowships from national and international government agencies, charities and industrial partners.

In 1991, I created the CNRS Research Unit in Molecular Genetics and Developmental Biology of CNRS in Villejuif, with a joint appointment as one of the Scientific Directors of the Généthon Laboratory in Evry until 1995. The Research Unit grew from 17 to up to 55 members in up to 6 different teams working in Molecular and Cellular Genetics and Functional and Computational Genomics of the Immune and Neuromuscular Systems. In 2000 and 2001, several team leaders created their own research units, and we became in 2002 the CNRS Research Unit in Functional Genomics and Systems Biology for Health.

During the period of 1991-2008, we operated with a global budget of about 50 M\$, including government support for salaries of permanent scientists and supporting staff (18 M\$), and infrastructure, equipment and supplies (7 M\$). As a Principal Investigator or co-PI with associates or external collaborators, I collected 19 M\$ in grant support, fellowships and direct contributions to our research programs from charities and foundations (10 M\$), the European Union and French government agencies (6 M\$), and industrial partners (3 M\$). The remaining 6 M\$ were grants and fellowships awarded to independent investigators in the Research Unit.

RESEARCH INTERESTS AND ACHIEVEMENTS

IMMUNE SYSTEM

Immunoglobulins

I worked during the preparation of my State Doctoral Thesis (8) at the Pasteur Institute (1976-1981) under the supervision of Dr. François Rougeon on the structure and expression of immunoglobulins. We achieved the first cloning and sequencing of mouse (2-6, 10), rabbit (11) and rat (15) immunoglobulin heavy chain cDNAs and genes. In addition, I established a correlation between immunoglobulin D region structure and antigen binding specificity (7).

HLA complex

I then joined the Department of Biochemistry and Molecular Biology at Harvard University as a Post-doctoral fellow and Junior Faculty (1981-1983), working with Pr. Jack Strominger on the molecular genetics of the human major histocompatibility complex HLA. We achieved the first cloning, mapping and sequencing of HLA class II alpha and beta chain cDNAs and genes (13, 14, 16, 18, 26, 27, 29, 36), and established correlations between HLA genetic, serological and functional polymorphisms in collaboration with the group of Pr. Jean Dausset at Hôpital St Louis and CEPH in Paris (16, 19, 21, 24, 28, 35, 37, 38). As a result, the HLA complex became the first multi-megabase segment of the human genome to be extensively mapped in the mid 80s (reviewed in 22, 31, C1-C6, 64), and a prototype for the Human Genome Project.

HLA, CD4 and HIV

As an extension of this work, which was continued after I created my own group at the Institute of Embryology in Nogent s/Marne in 1983, together with my co-worker Dr. Dominique Piatier-Tonneau, we designed and tested immunosuppressive peptides derived from HLA class II antigens and CD4 in collaboration with Prs. Dominique Charron and Alain Fischer at INSERM and Luc Montagnier at the Pasteur Institute (30, 32, 46, 57, 65, 94, 103, 111). We then dissected the molecular and functional interactions between CD4, HLA class II antigens and HIV gp120 through a combination of site-directed mutagenesis, biochemical and cellular assays (60, 66, 73, 80, 85, reviewed in 63).

Chicken MHC

At the Institute of Embryology, with my co-workers Drs. François Guillemot, Guido Kroemer and Rima Zoorob, we performed the first successful cloning and molecular maps of the two chicken MHC complexes through cross-hybridization with human MHC probes (43-45, 49, 50, 53, 54, 56, 67, 74, 81, 83, 86, 88, 124, reviewed in C6, C9, 51, 52). This work was continued after we moved to Villejuif in 1991, and in collaboration with the Sanger Institute, we sequenced the B complex, which thus became the he first non-mammalian MHC complex to be described at the molecular level (126). In parallel, in collaboration with pathologists at INRA, we analyzed genetic, serological and functional polymorphisms of chicken class II antigens (34, 40, C10-C12, 47, 48, 75, 77, 101, 106, 112, 132) in relation to resistance to infectious diseases and tumor formation (C13, 59, 162), and contributed to the cytogenetic map of the chicken genome (118, 119, 134).

NEURONAL AND MUSCULAR SYSTEMS

Nervous system

During my State Doctoral Thesis, I contributed to the first cloning of an acetylcholine receptor alpha subunit cDNA in *Torpedo marmorata* in collaboration with Pr. Jean-Pierre Changeux (12). At the Institute of Embryology, with my co-workers Drs. Angelica Keller and Marie-Dominique Devignes we performed the first cloning, mapping and immunochemistry of chicken beta NGF (33, 58, 71, 72, 152) and tyrosine hydroxylase (69, 79) genes.

This work was extended in Villejuif to build integrated physical, genetic and genomic maps around the human neurotrophin genes *BDNF* at 11p13 in relation to WAGR syndrome (89, 125), *NGF* at 1p13 (100), and at 20 p12 in relation to Alagille syndrome (115). We also performed expression profiling studies of cerebral-dependent neuronal apoptosis (139), of cerebral gene expression induced by TGF beta 1 (140), and cerebral ischemia in baboon in collaboration with Dr. Denis Vivien with support from Synthelabo Recherche (141).

Muscular system

Through my joint appointment at Généthon, we initiated with my co-workers Drs. Geneviève Piétu and Pascal Pomiès expression profiling and functional studies of muscle-specific proteins (107, 120, 128) in relation to human diseases LGMD (87, 96), FSHD (121, 144), DMD (133), during differentiation and aging of satellite muscle cells (149, 156), in collaboration with CNRS and INSERM teams, and in bovine muscle development in collaboration with INRA scientists (145).

CANCER

During the past years, together with my co-workers Drs. Sandrine Imbeaud, Geneviève Piétu and Dominique Piatier-Tonneau, we have initiated several large-scale expression profiling studies of drug resistance and metastasis formation in colorectal cancer in partnership with Dr. Bernard Sordat at ISREC in Lausanne (143), and Pr. Marc Ychou and Pr. Bernard Pau at CRLC and CNRS in Montpellier with support from Aventis (142, 164).

My recent work has focused on the study breast carcinomas (174), hepatocellular carcinomas in collaboration with Dr. Jessica Zucman-Rossi at INSERM and CEPH (167, 172), and leukaemia in collaboration with Pr. Zhu Chen at the Institute of Haematology in Shanghai, China (158, 162).

FUNCTIONAL GENOMICS AND THE HUMAN GENOME PROJECT

Since 1990, I conceived, organized and coordinated large-scale human cDNA cloning and sequencing programmes at Généthon, CNRS and through the IMAGE Consortium which I co-founded with Drs. Greg Lennon (DOE), Mihaelis Polymeropoulos (NIH) and Bento Soares (Columbia) in 1993 (95, 104, reviewed in 76, 78), promoting the free dissemination of DNA sequences and cDNA resources through a Declaration to UNESCO in 1992 (70, 175, P4).

With my co-workers of the Genexpress team at Généthon, we discovered through systematic cDNA sequencing of muscle and brain cDNAs some 8,000 human genes (95) which were extensively analyzed and registered in the Genexpress Index (99) and IMAGE Knowledge Base of the Human Genome and Brain and Muscle Transcriptomes (122, 128, B17).

We also actively collaborated with a large number of research teams and genome centers all over the world, to establish a radiation hybrid map of the human genome (102) and maps of 30,000 genes (108, (109, 117). We also established detailed maps of chromosome 1 (110, 131), 3 (135), 5 (116), 8 (113), 11 (98, 125), 13 (105), 16 (90), 21 (155), 22 (137) and X (114).

Since 2000, I have been involved in the organization of the H-INVITATIONAL Consortium coordinated by Pr. Takashi Gojobori (JBIRC/AIST, Tokyo and DDBJ/NIG, Mishima). With 10 members of my team, in collaboration with 67 research teams from 40 institutes in 12 countries, we actively participated in the integrative annotation of 21,037 human genes validated by full-length cDNA clones (151, 171), with emphasis on linking DNA polymorphism and disease, identifying non-coding regulatory RNAs, and providing cross-platform comparison of expression profiling data (154).

EXPERIMENTAL AND BIOINFORMATICS METHODS

Molecular and cellular biology

During my State Doctoral Thesis, I developed a simple and efficient method for RNA extraction with LiCl and urea (1) which is widely used and has received over 2,800 citations in the scientific literature.

With my co-worker Dr. François Amblard, in collaboration with Pr. Alain Fisher, we developed a flow chamber for flow cytometry analysis over an extended range of velocities enabling measurement of inter-lymphocyte cellular adhesion forces (68, 84).

With my co-worker Dr. Marie-Dominique Devignes, we developed a method for efficient site-directed by homologous recombination (97).

Transcriptome and proteome analysis

During my State Doctoral Thesis, since 1977, I have been using arrays of cDNA clones ordered by hand on Nylon membranes, and hybridized differentially with ³²P-labeled cDNA probes analyzed by autoradiography, to clone cDNAs for mouse immunoglobulin chains (2, 4, 6, 8), the *Torpedo marmorata* acetylcholine receptor alpha subunit (12). I also used this first generation semi-quantitative differential hybridization manual method at Harvard University to clone cDNAs for the HLA class II alpha chains (13, 14).

At Généthon, with my co-workers, we established in 1992 the first fully integrated line of modules for automated colony picking, PCR amplification, spotting on Nylon membranes, quantitative hybridization with ³³P-labelled cDNAs prepared by reverse transcription in the presence of dideoxynucleotides to increase sensitivity of cDNA array hybridization (127), analysis on phosphor screens, and statistical analysis in support of large-scale expression profiling studies in the muscular and nervous systems, and in cancer (95, 107, 128, 133, 139-143, 145, 149, 156, 158, reviewed in 129, 159, 160).

In Villejuif, since 1998, with my co-worker Dr. Sandrine Imbeaud, in partnership with Agilent Technologies, Amersham Biosciences, and Iobion, Interscan, Qbiogene and Qiagen, we established an instrument and bioinformatics pipeline for RNA extraction and quality assessment using user-independent classifiers (157), aRNA amplification of mRNA-poor samples, automated hybridization to arrays of PCR-amplified IMAGE cDNA clones spotted on glass arrays with two-color fluorescence-labelled cDNAs, fluorescence scanning, normalization and extensive statistical analyses and modelling. This third generation platform has been used in a variety of research programs on cancer and the muscle system (149, 156, 158, 161, 162, 164, 167, 172, 74, reviewed in 159, 160).

In collaboration with Dr. Ivan Lefkovits in Basel and Chris Coleclough in Memphis, we developed a method enabling correlation between transcriptome and proteome using pooled cDNAs, coupled *in vitro* transcription and translation, and 2D gel electrophoresis (92, 93,130).

Bioinformatics

At Harvard University, in collaboration with Dr. Jiri Novotny, I developed a software program for protein secondary structure prediction and application to HLA (23) which was included by Dr. Amos Bairoch in his first bioinformatics COMPSEQ package.

At Généthon, with my co-worker Dr. Geneviève Piétu, we performed the first statistical analysis of microarray data which made the cover page of Genome Research (107), and developed X-Dots Reader, a program for automatic quantitation of hybridization signals on cDNA arrays in partnership with the software company COSE (138).

SYSTEMS BIOLOGY

Since 1996, through my personal interaction with Pr. Leroy Hood and frequent visits in Seattle, and through my own work in Villejuif, I have been involved in building the conceptual and experimental framework to establish Systems Biology on the foundations of Molecular Genetics and Functional and Computational Genomics. Our shared vision was presented at the Nobel Foundation Symposium on self-organization in the Summer of 2002. A fundamental working hypothesis and conjectures for Systems Biology were published in a paper co-authored with Pr. Leroy Hood in a special issue of the Philosophical Transactions in Physics, Mathematics and Engineering of the Royal Society (146).

Our ideas were also extensively discussed during with the scientific community at the International TRANSCRIPTOME conferences 'From Functional Genomics to Systems Biology' I co-organized in Paris (2000), Seattle (2002), Tokyo (2003) and Shanghai (2005) with the help and participation of Pr. Leroy Hood, and in a position paper presented at the Conference on Computational Methods for Systems Biology organized by Pr. Corrado Priami in 2003 (C16).

In 2002, with Pr. Zhu Chen from the Chinese Academy of Sciences and Pr. Leroy Hood, we co-founded the SYSTEMOSCOPE International Consortium to promote the study of the complexity of living systems at the international level, particularly in scientifically and medically emerging countries of the South, by integrating scientific, ethical, legal and social issues in partnership with academic, government, charities, and industrial organizations. The charter of the SYSTEMOSCOPE International Consortium, and our current vision of concepts and practice in Systems Biology published in a special issue of *Comptes Rendus Biologies* I co-edited (147, 148), and more recently in a review in the inaugural issue of *Genome Medicine* (173). It is currently extended in collaboration with Pr. Denis Noble (176).

ONGOING RESEARCH PROGRAMS AND FUTURE PLANS

RESEARCH PROGRAMS IN FUNCTIONAL GENOMICS

During the past years, with my co-workers Drs. Sandrine Imbeaud, Eric Eveno, Dominique Piatier-Tonneau and Patrick Zaborski, we have initiated several large-scale expression profiling studies of drug resistance and metastasis formation in colorectal cancer in partnership with Dr. Bernard Sordat at ISREC in Lausanne, and Pr. Marc Ychou and Pr. Bernard Pau at CRLC and CNRS in Montpellier with support from Aventis. My recent work has focused on the study breast carcinomas (174); on hepatocarcinomas in collaboration with Dr. Jessica Zucman-Rossi at Inserm and St Louis Hospital in Paris, (167, 172), and in collaboration with Pr. Zhu Chen at the Institute of Haematology in Shanghai, China to study combined chemotherapy of leukemia (158, 162). In addition, in collaboration with Pr. Christophe Pison and Dr. Valdur Saks at Albert Michallon Hospital and Inserm in Grenoble, we are further investigating muscle function and dysfunction through an integrated study of systemic myopathy associated with chronic obstructive pulmonary diseases. This led us to participate in the UBIO-PRED Consortium (Unbiased Biomarkers for Pulmonary and Respiratory Diseases) composed of 31 academic and SME partners collaborating with 9 major pharmaceutical companies, which will be supported by the EU Innovative Medicines Initiatives for 2009-2014. I am the co-leader of the workpackage on bioinformatics and systems biology.

TECHNOLOGY RESEARCH AND DEVELOPMENT

The ongoing programs were all designed, under the supervision of Dr. Sandrine Imbeaud, through a common advanced project engineering scheme allowing *a priori* modelling of experimental power, and prediction of anticipated false positive and false negative differential hybridizations. It takes into account sample collection features such as the total number of samples and the size of the groups with similar biological features. We take great care to minimize experimental variance through performance of quadruplicate comparative hybridizations of each sample with a common Universal Reference, and inclusion of inversed color (flip-flop) labelling of the probes.

The expression profiling experiments are performed using the third generation microarray platform that we have established in Villejuif since 1998, in partnership with Agilent Technologies (Bioanalyzer), Amersham Biosciences (Lucidea spotter and scanner), Interscan (bar code tracking database), Iobion (GeneTraffic microarray database and analysis), Qbiogene (PCR amplification) and Qiagen (laboratory automation). It consists in an instrument and bioinformatics pipeline for RNA extraction and integrity assessment using user-independent classifiers, aRNA amplification of mRNA-poor samples, automated hybridization to arrays of PCR-amplified IMAGE cDNA clones spotted on glass arrays with two-color fluorescence-labelled cDNAs, fluorescence scanning, normalization and extensive statistical analyses and modelling.

A detailed description of the instruments, experimental procedures, and an extensive suite of bioinformatics tools and software for image analysis, data preprocessing, data mining, network and pathway reconstruction and analysis, text and literature mining, data annotation, and a variety of freely available software and web-based tools are available on the Array s/IMAGE web site (http://arraysimage.free.fr/array_sIMAGE.htm).

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DEVELOPMENT OF SYSTEMS BIOLOGY AND THE SYSTEMOSCOPE INTERNATIONAL CONSORTIUM

During the past years, I have developed in collaboration with Pr. Leroy Hood, the founder of the Institute for Systems Biology a shared vision of Systems Biology as a hypothesis-driven, integrative and iterative process based on interdisciplinarity and networking. In particular, I proposed as a working hypothesis that living systems self-organize as the result of a conjunction of a stable organization with chaotic fluctuations in biological space-time. I have also emphasized that the importance of the need to measure small changes of a large number of weak signals makes it essential to develop quality assurance in Functional Genomics and Systems Biology, taking our experience of transcriptome analysis with microarrays as an example.

Based on the lessons taken from experimental approaches to Systems Biology conducted at the Institute for Systems Biology, such as galactose utilization in yeast, and endomesodermal development in sea urchin, we have identified future directions and challenges to address in Systems Biology in order to explore the vast space of biological data using nanotechnology for single cell and molecule analysis, and computational and mathematical methods for data integration and modelling.

This analysis led us, together with Pr. Leroy Hood and Pr. Zhu Chen of the Institute of Hematology in Shanghai to propose the establishment of an International Consortium, 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.

This initiative was discussed in the context of the series of TRANSCRITOME conferences « From Functional Genomics to Systems Biology » which I co-organized in Paris (2000), Seattle (2002), Tokyo (2003) and Shanghai (2005). I have organized the inaugural scientific conferences of the SYSTEMOSCOPE International Consortium in Paris in June 2003. Further conferences are scheduled in Paris and Seattle.

The first SYSTEMOSCOPE pilot projects in which we are involved deal with systems biology of combined drug treatment of leukaemia, systems biology of muscle diseases associated with pulmonary diseases, and will greatly benefit from the integrative annotation of the human genome, transcriptome and proteome performed by the worldwide H-INVITATIONAL workshop coordinated by Pr. Takashi Gojobori. These pilot projects form the basis from which I intend to develop a trans-disciplinary systems biology programme in collaboration with biologists, clinicians, engineers, mathematicians and physicists.

The objectives will be to measure dysfunctions of energy metabolism and modulations of gene expression profiles in skeletal muscles of patients with pulmonary diseases or cardiac failure, and in some cases after lung or cardiac transplantation, before and during rehabilitation of systemic myopathy; to identify underlying functional and regulatory networks using tools developed for systems biology; to measure influence of the immune and nervous systems through genetic polymorphism studies; to formulate working hypothesis and test them; to iterate the process and assess improvement of models and methods.

This will require the use of standardized measurement, annotation and biovalidation technologies for experiment description and data integrity assessment, in order to enable functional genomics technologies to provide the accurate and consistent data required to capture the multiple moderate but biologically important fluctuations which escape meta-analyses.

In order to contribute to the mathematical and conceptual framework for systems biology, mathematical and computational tools will be used to infer, model and simulate functional networks from large-scale expression datasets combined with genetic and phenotypic data; to develop robust measures for biological functions and complexity; to simulate cellular differentiation with the selective model of stochastic gene expression regulated by dynamic constraints and epigenetic modifications; to construct a theoretical framework to model attractors with variable numbers of dimensions in biological systems; to combine the elements of modeling of scale relativity developed by Dr. Laurent Nottale to describe the effects induced by non-linear scale laws, in order to relate properties of complex biological systems to underlying physical first principles.

This programme will favour cross-disciplinary training of young and experienced scientists, dissemination of the results through open-access publications and protection of inventions, and emergence of novel research programmes in systems biology at the interface between the relevant disciplines. It is currently being developed in collaboration with Dr. Laurent Nottale, a theoretical astrophysicist at the Paris Observatory in Meudon and Pr. Denis Noble, a renowned cardiac physiologist, systems biologist and modeller at Oxford University.

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DR. CHARLES AUFFRAY - PUBLICATION LIST – APRIL 2009

RECEIVED OVER 12,000 CITATIONS (WEB OF SCIENCE)

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