

Review

Systems medicine: the future of medical genomics and healthcare

Charles Auffray*, Zhu Chen[†] and Leroy Hood[‡]

Addresses: *Functional Genomics and Systems Biology for Health, LGN-UMR 7091, CNRS and Pierre & Marie Curie University of Paris VI, 7 rue Guy Moquet, 94801 Villejuif, France. [†]Center for Systems Biomedicine, Jiao-Tong University, 200240 Shanghai, China. [‡]Institute for Systems Biology, 1441 North 34th Street, Seattle, WA 98103-8904, USA.

Correspondence: Charles Auffray. Email: charles.auffray@vjf.cnrs.fr

Published: 20 January 2009

Genome Medicine 2009, **1**:2 (doi:10.1186/gm2)

The electronic version of this article is the complete one and can be found online at <http://genomemedicine.com/content/1/1/2>

© 2009 BioMed Central Ltd

Abstract

High-throughput technologies for DNA sequencing and for analyses of transcriptomes, proteomes and metabolomes have provided the foundations for deciphering the structure, variation and function of the human genome and relating them to health and disease states. The increased efficiency of DNA sequencing opens up the possibility of analyzing a large number of individual genomes and transcriptomes, and complete reference proteomes and metabolomes are within reach using powerful analytical techniques based on chromatography, mass spectrometry and nuclear magnetic resonance. Computational and mathematical tools have enabled the development of systems approaches for deciphering the functional and regulatory networks underlying the behavior of complex biological systems. Further conceptual and methodological developments of these tools are needed for the integration of various data types across the multiple levels of organization and time frames that are characteristic of human development, physiology and disease. Medical genomics has attempted to overcome the initial limitations of genome-wide association studies and has identified a limited number of susceptibility loci for many complex and common diseases. Iterative systems approaches are starting to provide deeper insights into the mechanisms of human diseases, and to facilitate the development of better diagnostic and prognostic biomarkers for cancer and many other diseases. Systems approaches will transform the way drugs are developed through academy-industry partnerships that will target multiple components of networks and pathways perturbed in diseases. They will enable medicine to become predictive, personalized, preventive and participatory, and, in the process, concepts and methods from Western and oriental cultures can be combined. We recommend that systems medicine should be developed through an international network of systems biology and medicine centers dedicated to inter-disciplinary training and education, to help reduce the gap in healthcare between developed and developing countries.

Systems biology is developing rapidly. It is an integrative research strategy designed to tackle the complexity of biological systems and their behavior at all levels of organization (from molecules, cells and organs to organisms and ecosystems) in normal and perturbed conditions. It is based on an understanding of biological functions as system properties that are different from those of the individual interacting components (reviewed in [1-9]). It integrates the mass of data that has been collected with various global

measurement technologies (techniques that look at the complete set of genes, proteins or other features in an organism), in order to formulate predictive mathematical and computational models of functional and regulatory biological networks. Specific biological hypotheses can thus be tested by designing a series of perturbation experiments. It thus combines data-driven (bottom-up) [10] and model-driven (top-down) [11] approaches into a question-driven (middle-out) inquiry in search of basic principles [12-14]. In the end,

systems approaches must be driven by high-quality hypothesis-driven biology and not just by data-accumulating technologies or high-performance computational modeling.

Although systems biology has ancient roots in physiology, biochemistry, and molecular and cellular biology, its current development is the result of recent advances in genomics and bioinformatics, which were made possible by the continuous development of high-throughput experimental and computational platforms. The field is also revisiting previous attempts at modeling biological complexity, by taking advantage of insights from system theory [15] and engineering sciences [16,17]. It forms the basis for an extension of genetic engineering into synthetic biology: designing and building biological systems with new properties from modular components [18-21].

Evolution, development, physiology and disease are viewed in systems biology as dynamic processes that operate on widely different scales in space and time between biological states that are constrained by inter-relationships among pathway and network components. In this context, detecting, understanding and treating disease translates into identifying and manipulating global perturbed networks rather than focusing only on unique failing components.

Here we review how medical genomics [22,23], based on recent advances in high-throughput experimental and computational technologies, is evolving in the context of systems biology into a more prospective systems medicine [24-31]. This new kind of medicine will be able to overcome the current limitations of disease complexity (through stratification of patients and diseases by molecular diagnostics) and drug discovery (through the analysis and targeting of disease-perturbed networks) [32-35]. We discuss some of the technological, conceptual and organizational challenges that we will face in implementing this new vision and practice of biology and medicine, and we argue that it offers new opportunities to more efficiently tackle key medical problems in both developed and developing countries.

Technology is moving genomics from structure to function

The initial sequencing of the human genome was made possible by the automation of the DNA sequencing chemistry and by the development of data-acquisition tools and software for the reliable interpretation and assembly of the DNA sequence. It required a multi-billion-dollar investment and the participation of thousands of researchers in the public and private sectors over more than a decade. It came together with the sequencing of genomes in a variety of microorganisms, animals and plants. All these efforts combined served as test cases to trigger sustained technology developments.

With the next-generation DNA mega-sequencing technologies currently available, which enable the collection of billions of nucleotides in single instrument runs [36], it is now possible to sequence and assemble a human genome in a matter of weeks at a small fraction of the cost of the reference genome [37]. With both incremental progress and the introduction of third-generation sequencing technologies, it may soon become possible to collect large numbers of individual genomes in days for US\$1,000 or less and ascertain their unique variations. This opens up the possibility of a Personal Genome Project to find correlations between genotypes and normal or diseased phenotypes [38]. In parallel, over a period of more than 30 years, successive generations of increasingly miniaturized DNA arrays have been used for expression profiling, benefiting from the extensive sequencing of partial and complete cDNA collections. Microarray technology, because of its intrinsic complexity and that of the transcriptome, has reached an intermediate stage of maturity compared with sequencing [39]; it is possible to detect variations in expression of many but not all gene transcripts under normal and perturbed conditions.

Early on, insufficient attention was paid by users of current microarray platforms to proper design and quality assessment, which is needed to control for variation in the large number of biological and experimental parameters involved. This compromised the usefulness of these platforms, for example in the development of classification and predictive biomarkers [40-42]. The introduction of standards and guidelines for complete microarray workflows [43] is helping to rectify the problem; these need to cover all aspects, from RNA integrity assessment [44,45] to data analysis and reporting [46,47]. There has also been constant progress in the use of advanced statistical methods for multivariate classification [48] and for gene-set enrichment analysis [49] of expression profiles. At the same time, it has become clear through the combination of tiling arrays and systematic sequencing that a larger fraction of the human genome is transcribed into diverse types of RNA than was previously thought [50,51]. The increased power and reduced cost of deep sequencing thus means that it is starting to compete with high-density microarrays [52,53], to the extent that some believe this is marking the beginning of the end of microarrays [54].

However, given that each new generation of tools takes several years to mature, it is most likely that sequencing and microarrays will continue to coexist. Microarrays will probably be increasingly used for specialized applications, such as those related to transcription regulation, epigenetic modifications, and selection of subfractions of individual genomes for sequencing (for example, exons, highly conserved regions, and so on); whereas mega-sequencing will be used for deep exploration of transcriptomes. The results of transcriptome analyses will increasingly be validated by emerging technologies that

use miniaturized high-throughput reverse-transcriptase PCR [55] or multiplex direct visualization and counting of RNA molecules; the latter technology has the added advantage of avoiding biases resulting from reverse transcription [56].

From the genome and transcriptome sequences, it has been possible to derive a relatively complete parts list of genes and, by extension, of proteins, thus revolutionizing the field of proteomics. It is crucial to note that mass spectrometry is effective in the identification of peptides, and not of complete proteins. In order to identify and quantify interesting proteins by mass spectrometry, either through shotgun or directed approaches, an investigator therefore needs to know the sequence of the peptides obtained by enzymatic digestion of those proteins. The current generation of proteomic tools that are based on high-performance combinations of chromatography and mass spectrometry thus enable the identification of a growing number of proteins, and can also identify them over a wide range of abundances and when they have complex secondary modifications. The technology can achieve this using fragmentation, peptide sequencing and, as noted above, comparison with proteins that have been predicted from genome and transcriptome sequences [57-59].

Recent results indicate that the description of complete reference proteomes is now within reach in advanced centers, using multiple reaction monitoring combined with mass spectrometry; this combination is the most powerful and rapid targeted approach currently available [60-62]. These complete proteomes will probably serve as a reference for the subsequent development of simpler targeted assays [63], which will be complemented by array-based global surveys using affinity-based protein-specific reagents [64-66], and in certain cases, by single-cell proteomics using high-speed flow cytometry [67,68]. Furthermore, ongoing developments using nanomaterials are expected to provide next-generation proteomic analysis tools [69].

In addition to using chromatography and mass spectrometry, metabolomics is also taking advantage of nuclear magnetic resonance to analyze complex sets of metabolites in body fluids and tissues that reflect normal and disease states, and to study interactions with the gut microbial flora and environment factors [70-72]. Special attention is being paid increasingly to lipidomics [73,74] and glycomics [75,76] as complementary sources of biomarkers.

The development of each of these global high-throughput technologies has triggered implementation of standard operating procedures, ontologies and quality-assurance pipelines for data collection and analysis using dedicated software and databases, and this has required a change in culture in biological laboratories [77-81]. In turn, the need for independent validation of the results obtained with

these 'omics' technologies has stimulated the emergence of large-scale chemical-genetics and functional screens using cell microarrays and RNA interference [82-84].

Computational and mathematical tools empower systems biology

With the increasing availability of large amounts of data and curated information on all types of biological system components, the focus has progressively shifted to identifying the interactions they make, forming transient or permanent macromolecular structures with particular biological functions, and to looking at how the interactions can be represented computationally as metabolic, protein, microRNA and gene-regulatory networks [85,86]. This emerging 'network biology' is taking advantage of advances in functional genomics, computational methods, computing power, and network and graph theories. It is reviving the advanced biochemistry that has been published in textbooks and illustrated in static wall charts for decades [87-89]. Network biology is revealing the existence of modular structures in biological networks that may explain the robustness of biological systems when they are exposed to changing environments [90-93].

The initial attempts to identify biologically relevant protein-protein interactions using the yeast two-hybrid technology were plagued by high rates of artifactual events. Thanks to methodological improvements, the rate of false positives has been reduced. The careful curation of these interactions from targeted assays reported in the literature has led to high quality but incomplete maps of the human interactome, which are now available and which are expected to be extended to more complete coverage in the future [94-96]. Given that biological networks change their architectures dynamically during biological processes, such as development, physiological responses and disease, their complete determination will continue to be an enormous scientific and technological challenge.

Similar progress is being made in assembling human signaling, metabolic and gene regulatory networks that are based on metabolites, RNA and microRNA expression, protein-protein and protein-DNA interactions [97-100]. This has required the development of standardized languages and software tools for graphical representation of molecular interaction maps and computation of predictive and dynamic models [101-105]. Integration methodologies have also been essential to combine diverse types of data that have been collected with different platforms and in many laboratories, and thus to generate testable hypotheses [106-110]. A limitation that is often overlooked is that the quality of the annotation resources is very variable [111-114]. This has triggered sustained community efforts for integrative annotation, which combine automated computation with human-supervised curation, the use of

quality indices, text-mining tools, biological ontologies and the semantic web [115-120].

In general, the models derived from these integrated methodologies have not yet reached the level of detail and precision of those obtained through highly focused systems biology approaches, such as those that describe the transcriptional control in a free living microorganism under changing environmental conditions [121] or the early phases of development of the sea urchin [122]. It seems likely that the same operating principles of network structure and dynamics that have been revealed in these latter model systems will be relevant to human physiology and pathology [123].

In a parallel track, the Physiome Project is building on over half a century of molecular modeling of excitable cells that used ordinary and partial differential equations and is also using finite element lattices for geometric modeling of complete human organs. This project has steadily developed a computational physiology framework with its own modeling language [124,125], and initial models of the beating heart, the contracting muscle and the breathing lung are already available [126,127]. Cell and development simulation efforts use yet other types of modeling formalisms and languages, including Boolean networks, cellular automata and process algebra [128-135], and many others are being developed in computational neuroscience, which has yet to merge with systems biology [136].

This diversity of approaches for modeling biological systems highlights the renewed importance of the contributions of mathematics, informatics and physics to systems biology [137-139]. Despite the introduction of novel computational methods, given that they are often based on distinct or incompatible principles, it is difficult or impossible to integrate these methods across the multiple levels of organization and time-scales characteristic of living systems [140-142]. Thus, multi-scale integration of different types of biological information (DNA, RNA, protein, networks, organelles, cells, tissues, organs, higher level phenotypes, and so on) remains a major challenge in systems biology. The plea for more theory by some of the founders of systems biology must be tempered by the fundamental need to have theories that closely reflect biological data through hypothesis-driven model testing [143]. Recent proposals based on allometric scaling [144] and scale relativity theory [8,145] may provide the theoretical framework and mathematical tools required to overcome some of these limitations, and may reveal an important role for small fluctuations in driving the behavior of biological systems [146,147].

The transition from medical genomics to systems medicine

With the availability of increasingly powerful high-throughput technologies, computational tools and integrated

knowledge bases, it has become possible to establish new links between genes, biological functions and a wide range of human diseases [148-153]. This is providing signatures of pathological biology [154] and links to clinical research [155] and drug discovery [156,157]. These are the hallmarks of systems medicine as it is emerging from the initial, more targeted efforts of medical genomics.

Success in the identification of mutations affecting the hundreds of genes involved in inherited disorders has been a major outcome of the first generations of genetic maps of the human genome. In contrast, the reported associations between genetic polymorphisms and common complex traits have rarely been confirmed in independent studies. The situation has changed in the past two years [158], with the availability of dense maps of single nucleotide polymorphisms and the adoption by the community of medical geneticists of consensus guidelines for the optimal design of genome-wide or targeted association studies, including rules for independent replication [159,160]. Despite the very significant problems with signal-to-noise ratios that still severely limit the conclusions that can be drawn from such studies, progress has been made in identifying susceptibility loci involved in, for example, diabetes [161-163], obesity [164], and breast or lung cancer [165-167]. In the case of lung cancer, however, different scientific groups interpret the functional significance of the results differently. Further progress is expected now that the important role of other forms of genomic polymorphisms between individuals, including monozygotic twins, has been recognized; these include the effects of copy number variations and epigenetic modifications [168-170].

Taking advantage of expression-profiling surveys performed in extended human populations [171-174], systems biologists have started integrating physiopathology, network biology and DNA variations [175-177], providing novel insights into the mechanisms of various diseases, such as diabetes [178] and obesity [179]. Cancer, which can be considered as a prototypical systems disease, has benefited greatly from systems approaches and has served to a large extent as a test case to develop them [180-184]. This work has highlighted the importance of epigenetic variations in controlling transcriptional programs sustaining differentiation of normal and cancer stem cells [185,186].

Transcriptome and proteome analyses of collections of cancer samples, combined with functional annotation and modeling of modulated molecular pathways and networks, have revealed useful biomarkers for the classification and diagnosis of cancer subtypes, the prognosis of patient outcomes, the prediction of treatment responses and the identification of perturbation targets for drug development [187-196]. As an illustration of the value of systems approaches, the predictive power and robustness of biomarkers can be significantly increased by integrating transcriptome profiles with

interactome data to reveal more relevant functional subnetwork modules [197]. In a similar way, systems approaches are starting to have an impact on the study of immunological diseases [198], inflammation [199], infectious diseases such as tuberculosis [200], neurological diseases such as autism [201] and Alzheimer's [202], respiratory diseases such as asthma [203], cardiovascular and metabolic diseases [204-206] and many others. A common biological theme that emerges from many of these studies is that the control and dysfunction of energy metabolism has a central role. This is illustrated in cardiac system bioenergetics by the Frank-Starling law of cardiac muscle contraction [207,208], in cancer by the Warburg effect (the dependence of cancer cells on aerobic glycolysis) [209], and in neurodegenerative diseases and aging by increases of oxidative stress [210,211].

When East and West, North and South meet to develop systems medicine

Systems approaches are likely to help elucidate the mechanisms underlying the fundamental biological processes perturbed in human diseases and, in doing so, enable more efficient therapeutic interventions. They will change how drug targets are identified. Novel treatments will include multiple drugs interacting with key interconnected components within functional network modules, each contributing a fraction of the effects of perturbations that cause disease. It is likely that they will be effective only when combined with the multiple interactions of other drugs. This reflects the way that biological systems function and are organized to maintain themselves and constantly adapt to developmental, environmental, physiological or pathological changes. It is also reminiscent of the principles underlying traditional medicines developed empirically within Chinese or Indian cultures for the past several thousand years. Initial attempts at systems approaches, using transcriptome and proteome analyses to study the synergistic effect of combining Western drugs with Chinese medicine components in the treatment of leukemia, are starting to bear fruit [192,212,213]. Similarly, metabolome studies are being used to analyze the composition of herbal medicines and explain their properties [214], and to establish how gut microorganisms modulate human metabolic phenotypes and respond to the health or disease state of their host [215].

Systems approaches are also providing evidence on the effects of stress, relaxation, nutrition and lifestyle on the course of health and diseases [216,217]. Systems studies need to pay greater attention to gender, age and time differences in diet, disease development and treatment administration and responses [218-221]. These factors can be monitored, for example, using non-invasive metabolomics surveys of urine [222,223], and they will increasingly also be monitored using molecular fingerprints of blood

proteins that indicate relevant physiological or disease states. Other important contextual phenomena that also need to be taken into account in future studies include the effects of the mother's genetic makeup or feeding habits on the development of the fetus and the timing of its biological clock, which have been observed in animal models [224,225], and the central role of the major histocompatibility complex in the development and control of disease through immunity and inflammation [226-229].

Thus, systems biology will provide the foundation for a prospective medicine that will be predictive, personalized, preventive and participatory [230], and that takes into account the multiple components of the healthcare system, including disease outcomes as reported by the patients themselves, and public and private organizations involved in healthcare management. [231]. In addition to genomics and systems biology, the key components that will ensure the successful development of systems medicine are the modeling of physiopathology in a clinical-practice context [232], imaging [233], and bio-banking that complies with strictly enforced ethical regulations [234-236]. These intrinsically interdisciplinary endeavors will require dedicated centers and networks in which scientists of all disciplines can work together [237-239], with careful attention to clinical practice and education [240,241].

In order to implement this vision, academia and industry will have to work closely together in an open-access and open-source environment focusing on the initial, pre-competitive phase of the drug discovery process. This will enable the subsequent development of valuable intellectual property that will result in more effective diagnostic and therapeutic approaches. Such developments might seem very far from the priorities of the less developed countries, in which the majority of the population is excluded from basic medical care. These countries are facing major challenges to their ability to fight infectious diseases and malnutrition, a situation aggravated by the shortage of safe drinking water and economic poverty [242]. International initiatives are underway to tackle these challenges in global health, such as support for engagement of communities in research and formulation of a research and development treaty that will redefine the rules for clinical trials and management of intellectual property rights [243,244].

Strategic partnerships, such as the Systemoscope Consortium, propose guidelines and strategies for 'rethinking research, understanding life, improving health' [245]. We support the view that leaders of the developing countries should consider establishing integrative systems biology and medicine centers networked with those emerging in the developed countries. Implementing such centers at the heart of their much-needed healthcare infrastructures would ensure immediate access to the most advanced technologies, and allow developing countries to build an essential

knowledge base centered on the analyses of their populations. These centers would provide a route to the adequate healthcare that is required to reduce the ever-growing gap between the developed and underdeveloped nations.

Competing interests

CA is Research Director at CNRS, and a consultant for bioMérieux and Mérieux Alliance. ZC is the Director of the Shanghai Center for Systems Biomedicine and is supported by the National Key Program for Basic Research (973), China. LH is the President of the Institute for Systems Biology.

Acknowledgements

We thank our colleagues of the Genexpress team, the Center for Systems Biomedicine, the Institute for Systems Biology, and Haim Bendayan, Samir Brahmachari, Anthony Brookes, Dominique Charron, Eric Eveno, David Galas, Takashi Gojobori, Sandrine Imbeaud, Doron Lancet, Jacques Mallet, Xavier Lerverve, Laurent Nottale, Denis Noble, Christophe Pison, Valdur Saks, Marc Vidal, John Weinstein for insightful discussions.

References

- Ideker T, Galitski T, Hood L: **A new approach to decoding life: systems biology.** *Annu Rev Genomics Hum Genet* 2001, **2**:343-372.
- Kitano H: **Systems biology: a brief overview.** *Science* 2002, **295**:1662-1664.
- Noble D: **Modeling the heart - from genes to cells to the whole organ.** *Science* 2002, **295**:1678-1682.
- Auffray C, Imbeaud S, Roux-Rouquie M, Hood L: **From functional genomics to systems biology: concepts and practices.** *C R Biol* 2003, **326**:879-892.
- Nicholson JK, Holmes E, Lindon JC, Wilson ID: **The challenges of modeling mammalian biocomplexity.** *Nat Biotechnol* 2004, **22**:1268-1274.
- Westerhoff HV, Palsson BO: **The evolution of molecular biology into systems biology.** *Nat Biotechnol* 2004, **22**:1249-1252.
- Kirschner MW: **The meaning of systems biology.** *Cell* 2005, **121**:503-504.
- Auffray C, Nottale L: **Scale relativity theory and integrative systems biology: I. Founding principles and scale laws.** *Prog Biophys Mol Biol* 2008, **97**:79-114.
- Davidson EH, Rast JP, Oliveri P, Ransick A, Calessani C, Yuh CH, Minokawa T, Amore G, Hinman V, Arenas-Mena C, Otim O, Brown CT, Livi CB, Lee PY, Revilla R, Rust AG, Pan Z, Schilstra MJ, Clarke PJ, Arnone MI, Rowen L, Cameron RA, McClay DR, Hood L, Bolouri H: **A genomic regulatory network for development.** *Science* 2002, **295**:1669-1678.
- Guido NJ, Wang X, Adalsteinsson D, McMillen D, Hasty J, Cantor CR, Elston TC, Collins JJ: **A bottom-up approach to gene regulation.** *Nature* 2006, **439**:856-860.
- Bray D: **Molecular networks: the top-down view.** *Science* 2003, **301**:1864-1865.
- O'Malley MA, Dupre J: **Fundamental issues in systems biology.** *Bioessays* 2005, **27**:1270-1276.
- Noble D: **Claude Bernard, the first systems biologist, and the future of physiology.** *Exp Physiol* 2008, **93**:16-26.
- Wilson I: **Top-down versus bottom-up-rediscovering physiology via systems biology?** *Mol Syst Biol* 2007, **3**:113.
- Wolkenhauer O: **Systems biology: the reincarnation of systems theory applied in biology?** *Brief Bioinform* 2001, **2**:258-270.
- Ideker T, Winslow LR, Lauffenburger DA: **Bioengineering and systems biology.** *Ann Biomed Eng* 2006, **34**:1226-1233.
- Yildirim MA, Vidal M: **Systems engineering to systems biology.** *Mol Syst Biol* 2008, **4**:185.
- Brent R: **A partnership between biology and engineering.** *Nat Biotechnol* 2004, **22**:1211-1214.
- Church GM: **From systems biology to synthetic biology.** *Mol Syst Biol* 2005, **1**:2005.0032.
- Endy D: **Foundations for engineering biology.** *Nature* 2005, **438**:449-453.
- Barrett CL, Kim TY, Kim HU, Palsson BO, Lee SY: **Systems biology as a foundation for genome-scale synthetic biology.** *Curr Opin Biotechnol* 2006, **17**:488-492.
- van Ommen GJ: **Medical genomics.** *Eur J Hum Genet* 2001, **9**:729.
- Brand A, Brand H, Schulte in den Bäumen T: **The impact of genetics and genomics on public health.** *Eur J Hum Genet* 2008, **16**:5-13.
- Ahn AC, Tewari M, Poon CS, Phillips RS: **The limits of reductionism in medicine: could systems biology offer an alternative?** *PLoS Med* 2006, **3**:e208.
- Ahn AC, Tewari M, Poon CS, Phillips RS: **The clinical applications of a systems approach.** *PLoS Med* 2006, **3**:e209.
- Hood L, Heath JR, Phelps ME, Lin B: **Systems biology and new technologies enable predictive and preventative medicine.** *Science* 2004, **306**:640-643.
- Schadt EE, Lamb J, Yang X, Zhu J, Edwards S, Guhathakurta D, Sieberts SK, Monks S, Reitman M, Zhang C, Lum PY, Leonardson A, Thieringer R, Metzger JM, Yang L, Castle J, Zhu H, Kash SF, Drake TA, Sachs A, Lusis AJ: **An integrative genomics approach to infer causal associations between gene expression and disease.** *Nat Genet* 2005, **37**:710-717.
- Zerhouni EA: **Translational and clinical science - time for a new vision.** *N Engl J Med* 2005, **353**:1621-1623.
- Nicholson JK: **Global systems biology, personalized medicine and molecular epidemiology.** *Mol Syst Biol* 2006, **2**:52.
- Snyderman R, Langheier J: **Prospective health care: the second transformation of medicine.** *Genome Biol* 2006, **7**:104.
- Butte AJ: **Medicine. The ultimate model organism.** *Science* 2008, **320**:325-327.
- Butcher EC: **Can cell systems biology rescue drug discovery?** *Nat Rev Drug Discov* 2005, **4**:461-467.
- Hood L, Perlmutter RM: **The impact of systems approaches on biological problems in drug discovery.** *Nat Biotechnol* 2004, **22**:1215-1217.
- Weinstein JN, Pommier Y: **Connecting genes, drugs and diseases.** *Nat Biotechnol* 2006, **24**:1365-1366.
- Yan Q: **The integration of personalized and systems medicine: bioinformatics support for pharmacogenomics and drug discovery.** *Methods Mol Biol* 2008, **448**:1-19.
- Strausberg RL, Levy S, Rogers YH: **Emerging DNA sequencing technologies for human genomic medicine.** *Drug Discov Today* 2008, **13**:569-577.
- Wheeler DA, Srinivasan M, Egholm M, Shen Y, Chen L, McGuire A, He W, Chen YJ, Makhijani V, Roth GT, Gomes X, Tartaro K, Niazi F, Turcotte CL, Irzyk GP, Lupski JR, Chinault C, Song XZ, Liu Y, Yuan Y, Nazareth L, Qin X, Muzny DM, Margulies M, Weinstock GM, Gibbs RA, Rothberg JM: **The complete genome of an individual by massively parallel DNA sequencing.** *Nature* 2008, **452**:872-876.
- Church GM: **The personal genome project.** *Mol Syst Biol* 2005, **1**:2005.0030.
- Quackenbush J: **Weighing our measures of gene expression.** *Mol Syst Biol* 2006, **2**:63.
- Ransohoff DF: **Rules of evidence for cancer molecular-marker discovery and validation.** *Nat Rev Cancer* 2004, **4**:309-314.
- Ransohoff DF: **Bias as a threat to the validity of cancer molecular-marker research.** *Nat Rev Cancer* 2005, **5**:142-149.
- Ioannidis JP: **Why most published research findings are false.** *PLoS Med* 2005, **2**:e124.
- Imbeaud S, Auffray C: **'The 39 steps' in gene expression profiling: critical issues and proposed best practices for microarray experiments.** *Drug Discov Today* 2005, **10**:1175-1182.
- Imbeaud S, Graudens E, Boulanger V, Barlet X, Zaborski P, Eveno E, Mueller O, Schroeder A, Auffray C: **Towards standardization of RNA quality assessment using user-independent classifiers of microcapillary electrophoresis traces.** *Nucleic Acids Res* 2005, **33**:e56.
- Schroeder A, Mueller O, Stocker S, Salowsky R, Leiber M, Gassmann M, Lightfoot S, Menzel W, Granzow M, Ragg T: **The RIN: an RNA integrity number for assigning integrity values to RNA measurements.** *BMC Mol Biol* 2006, **7**:3.
- Dupuy A, Simon RM: **Critical review of published microarray studies for cancer outcome and guidelines on statistical analysis and reporting.** *J Natl Cancer Inst* 2007, **99**:147-157.

47. Simon R: **Roadmap for developing and validating therapeutically relevant genomic classifiers.** *J Clin Oncol* 2005, **23**:7332-7341.
48. Zucknick M, Richardson S, Stronach EA: **Comparing the characteristics of gene expression profiles derived by univariate and multivariate classification methods.** *Stat Appl Genet Mol Biol* 2008, **7**:Article7.
49. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, Paulovich A, Pomeroy SL, Golub TR, Lander ES, Mesirov JP: **Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles.** *Proc Natl Acad Sci USA* 2005, **102**:15545-15550.
50. Wu JQ, Du J, Rozowsky J, Zhang Z, Urban AE, Euskirchen G, Weissman S, Gerstein M, Snyder M: **Systematic analysis of transcribed loci in ENCODE regions using RACE sequencing reveals extensive transcription in the human genome.** *Genome Biol* 2008, **9**:R3.
51. Carninci P: **Hunting hidden transcripts.** *Nat Methods* 2008, **5**:587-589.
52. Mortazavi A, Williams BA, McCue K, Schaeffer L, Wold B: **Mapping and quantifying mammalian transcriptomes by RNA-Seq.** *Nat Methods* 2008, **5**:621-628.
53. Velculescu VE, Kinzler KW: **Gene expression analysis goes digital.** *Nat Biotechnol* 2007, **25**:878-880.
54. Shendure J: **The beginning of the end for microarrays?** *Nat Methods* 2008, **5**:585-587.
55. Spurgeon SL, Jones RC, Ramakrishnan R: **High throughput gene expression measurement with real time PCR in a microfluidic dynamic array.** *PLoS ONE* 2008, **3**:e1662.
56. Geiss GK, Bumgarner RE, Birditt B, Dahl T, Dowidar N, Dunaway DL, Fell HP, Ferree S, George RD, Grogan T, James JJ, Maysuria M, Mitton JD, Oliveri P, Osborn JL, Peng T, Ratcliffe AL, Webster PJ, Davidson EH, Hood L: **Direct multiplexed measurement of gene expression with color-coded probe pairs.** *Nat Biotechnol* 2008, **26**:317-325.
57. Deutsch EW, Lam H, Aebersold R: **Data analysis and bioinformatics tools for tandem mass spectrometry in proteomics.** *Physiol Genomics* 2008, **33**:18-25.
58. Gulcicek EE, Colangelo CM, McMurray W, Stone K, Williams K, Wu T, Zhao H, Spratt H, Kurosky A, Wu B: **Proteomics and the analysis of proteomic data: an overview of current protein-profiling technologies.** *Curr Protoc Bioinformatics* 2005, **Chapter 13**:Unit 13.1.
59. Hilario M, Kalousis A: **Approaches to dimensionality reduction in proteomic biomarker studies.** *Brief Bioinform* 2008, **9**:102-118.
60. Andersen JS, Mann M: **Organelle proteomics: turning inventories into insights.** *EMBO Rep* 2006, **7**:874-879.
61. Deutsch EW, Lam H, Aebersold R: **PeptideAtlas: a resource for target selection for emerging targeted proteomics workflows.** *EMBO Rep* 2008, **9**:429-434.
62. Malmstrom J, Lee H, Aebersold R: **Advances in proteomic workflows for systems biology.** *Curr Opin Biotechnol* 2007, **18**:378-384.
63. Hanash SM, Pitteri SJ, Faca VM: **Mining the plasma proteome for cancer biomarkers.** *Nature* 2008, **452**:571-579.
64. Uhlen M: **Affinity as a tool in life science.** *Biotechniques* 2008, **44**:649-654.
65. Hober S, Uhlen M: **Human protein atlas and the use of microarray technologies.** *Curr Opin Biotechnol* 2008, **19**:30-35.
66. Uhlen M, Hober S: **Generation and validation of affinity reagents on a proteome-wide level.** *J Mol Recognit* 2008. doi: 10.1002/jmr.891.
67. Irish JM, Kotecha N, Nolan GP: **Mapping normal and cancer cell signalling networks: towards single-cell proteomics.** *Nat Rev Cancer* 2006, **6**:146-155.
68. Krutzik PO, Nolan GP: **Fluorescent cell barcoding in flow cytometry allows high-throughput drug screening and signaling profiling.** *Nat Methods* 2006, **3**:361-368.
69. Johnson CJ, Zhukovsky N, Cass AE, Nagy JM: **Proteomics, nanotechnology and molecular diagnostics.** *Proteomics* 2008, **8**:715-730.
70. Fernie AR, Trethewey RN, Krotzky AJ, Willmitzer L: **Metabolite profiling: from diagnostics to systems biology.** *Nat Rev Mol Cell Biol* 2004, **5**:763-769.
71. Martin FP, Dumas ME, Wang Y, Legido-Quigley C, Yap IK, Tang H, Zirah S, Murphy GM, Cloarec O, Lindon JC, Sprenger N, Fay LB, Kochhar S, van Bladeren P, Holmes E, Nicholson JK: **A top-down systems biology view of microbiome-mammalian metabolic interactions in a mouse model.** *Mol Syst Biol* 2007, **3**:112.
72. Ellis DI, Dunn WB, Griffin JL, Allwood JW, Goodacre R: **Metabolic fingerprinting as a diagnostic tool.** *Pharmacogenomics* 2007, **8**:1243-1266.
73. Han X: **An update on lipidomics: progress and application in biomarker and drug development.** *Curr Opin Mol Ther* 2007, **9**:586-591.
74. Wiest MM, Watkins SM: **Biomarker discovery using high-dimensional lipid analysis.** *Curr Opin Lipidol* 2007, **18**:181-186.
75. Pilobello KT, Mahal LK: **Deciphering the glycode: the complexity and analytical challenge of glycomics.** *Curr Opin Chem Biol* 2007, **11**:300-305.
76. Aoki-Kinoshita KF: **An introduction to bioinformatics for glycomics research.** *PLoS Comput Biol* 2008, **4**:e1000075.
77. Brazma A, Krestyaninova M, Sarkans U: **Standards for systems biology.** *Nat Rev Genet* 2006, **7**:593-605.
78. Burgeon LD: **The need for standards, not guidelines, in biological data reporting and sharing.** *Nat Biotechnol* 2006, **24**:1369-1373.
79. Jones AR, Miller M, Aebersold R, Apweiler R, Ball CA, Brazma A, Degreef J, Hardy N, Hermjakob H, Hubbard SJ, Hussey P, Igra M, Jenkins H, Julian RK Jr, Laursen K, Oliver SG, Paton NW, Sansone SA, Sarkans U, Stoeckert CJ Jr, Taylor CF, Whetzel PL, White JA, Spellman P, Pizarro A: **The Functional Genomics Experiment model (FuGE): an extensible framework for standards in functional genomics.** *Nat Biotechnol* 2007, **25**:1127-1133.
80. Schilling M, Pfeifer AC, Bohl S, Klingmuller U: **Standardizing experimental protocols.** *Curr Opin Biotechnol* 2008, **19**:354-359.
81. Wierling C, Herwig R, Lehrach H: **Resources, standards and tools for systems biology.** *Brief Funct Genomic Proteomic* 2007, **6**:240-251.
82. Carpenter AE, Sabatini DM: **Systematic genome-wide screens of gene function.** *Nat Rev Genet* 2004, **5**:11-22.
83. Mayer TU: **Chemical genetics: tailoring tools for cell biology.** *Trends Cell Biol* 2003, **13**:270-277.
84. Wheeler DB, Carpenter AE, Sabatini DM: **Cell microarrays and RNA interference chip away at gene function.** *Nat Genet* 2005, **37** (Suppl):S25-S30.
85. Bader S, Kuhner S, Gavin AC: **Interaction networks for systems biology.** *FEBS Lett* 2008, **582**:1220-1224.
86. Vidal M: **A biological atlas of functional maps.** *Cell* 2001, **104**:333-339.
87. Barabasi AL, Oltvai ZN: **Network biology: understanding the cell's functional organization.** *Nat Rev Genet* 2004, **5**:101-113.
88. Han JD: **Understanding biological functions through molecular networks.** *Cell Res* 2008, **18**:224-237.
89. Zhu H, Huang S, Dhar P: **The next step in systems biology: simulating the temporospatial dynamics of molecular network.** *Bioessays* 2004, **26**:68-72.
90. Papin JA, Reed JL, Palsson BO: **Hierarchical thinking in network biology: the unbiased modularization of biochemical networks.** *Trends Biochem Sci* 2004, **29**:641-647.
91. Kitano H: **Towards a theory of biological robustness.** *Mol Syst Biol* 2007, **3**:137.
92. Hartwell LH, Hopfield JJ, Leibler S, Murray AW: **From molecular to modular cell biology.** *Nature* 1999, **402**:C47-C52.
93. Barkai N, Leibler S: **Robustness in simple biochemical networks.** *Nature* 1997, **387**:913-917.
94. Rachlin J, Cohen DD, Cantor C, Kasif S: **Biological context networks: a mosaic view of the interactome.** *Mol Syst Biol* 2006, **2**:66.
95. Rual JF, Venkatesan K, Hao T, Hirozane-Kishikawa T, Dricot A, Li N, Berriz GF, Gibbons FD, Dreze M, Ayivi-Guedehoussou N, Klitgord N, Simon C, Boxem M, Milstein S, Rosenberg J, Goldberg DS, Zhang LV, Wong SL, Franklin G, Li S, Albalá JS, Lim J, Fraughton C, Llamosas E, Cevik S, Bex C, Lamesch P, Sikorski RS, Vandenhaute J, Zoghbi HY, Smolyar A, Bosak S, Sequerra R, Doucette-Stamm L, Cusick ME, Hill DE, Roth FP, Vidal M: **Towards a proteome-scale map of the human protein-protein interaction network.** *Nature* 2005, **437**:1173-1178.
96. Beltrao P, Kiel C, Serrano L: **Structures in systems biology.** *Curr Opin Struct Biol* 2007, **17**:378-384.
97. Schlitt T, Brazma A: **Current approaches to gene regulatory network modelling.** *BMC Bioinformatics* 2007, **8**(Suppl 6):S9.
98. Makeyev EV, Maniatis T: **Multilevel regulation of gene expression by microRNAs.** *Science* 2008, **319**:1789-1790.
99. Min Lee J, Gianchandani EP, Eddy JA, Papin JA: **Dynamic analysis of integrated signaling, metabolic, and regulatory networks.** *PLoS Comput Biol* 2008, **4**:e1000086.
100. Coates AP, Muggleton SH, Sternberg MJ: **The identification of similarities between biological networks: application to the metabolome and interactome.** *J Mol Biol* 2007, **369**:1126-1139.
101. Kohn KW, Aladjem MI, Kim S, Weinstein JN, Pommier Y: **Depicting combinatorial complexity with the molecular interaction map notation.** *Mol Syst Biol* 2006, **2**:51.

102. Hucka M, Finney A, Sauro HM, Bolouri H, Doyle JC, Kitano H, Arkin AP, Bornstein BJ, Bray D, Cornish-Bowden A, Cuellar AA, Dronov S, Gilles ED, Ginkel M, Gor V, Goryanin II, Hedley WJ, Hodgman TC, Hofmeyr JH, Hunter PJ, Juty NS, Kasberger JL, Kremling A, Kummer U, Le Novère N, Loew LM, Lucio D, Mendes P, Minch E, Mjolsness ED, et al.; SBML Forum: **The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models.** *Bioinformatics* 2003, **19**:524-531.
103. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T: **Cytoscape: a software environment for integrated models of biomolecular interaction networks.** *Genome Res* 2003, **13**:2498-2504.
104. Kitano H, Funahashi A, Matsuoka Y, Oda K: **Using process diagrams for the graphical representation of biological networks.** *Nat Biotechnol* 2005, **23**:961-966.
105. Jamshidi N, Palsson BO: **Formulating genome-scale kinetic models in the post-genome era.** *Mol Syst Biol* 2008, **4**:171.
106. Hwang D, Rust AG, Ramsey S, Smith JJ, Leslie DM, Weston AD, de Atauri P, Aitchison JD, Hood L, Siegel AF, Bolouri H: **A data integration methodology for systems biology.** *Proc Natl Acad Sci USA* 2005, **102**:17296-17301.
107. Hwang D, Smith JJ, Leslie DM, Weston AD, Rust AG, Ramsey S, de Atauri P, Siegel AF, Bolouri H, Aitchison JD, Hood L: **A data integration methodology for systems biology: experimental verification.** *Proc Natl Acad Sci USA* 2005, **102**:17302-17307.
108. Slater T, Bouton C, Huang ES: **Beyond data integration.** *Drug Discov Today* 2008, **13**:584-589.
109. Swedlow JR, Lewis SE, Goldberg IG: **Modelling data across labs, genomes, space and time.** *Nat Cell Biol* 2006, **8**:1190-1194.
110. Reed JL, Famili I, Thiele I, Palsson BO: **Towards multidimensional genome annotation.** *Nat Rev Genet* 2006, **7**:130-141.
111. Cannata N, Merelli E, Altman RB: **Time to organize the bioinformatics resourceome.** *PLoS Comput Biol* 2005, **1**:e76.
112. Dinov ID, Rubin D, Lorensen W, Dugan J, Ma J, Murphy S, Kirschner B, Bug W, Sherman M, Floratos A, Kennedy D, Jagadish HV, Schmidt J, Athey B, Califano A, Musen M, Altman R, Kikinis R, Kohane I, Delp S, Parker DS, Toga AW: **iTools: a framework for classification, categorization and integration of computational biology resources.** *PLoS ONE* 2008, **3**:e2265.
113. Kemmer D, Podowski RM, Yusuf D, Brumm J, Cheung W, Wahlestedt C, Lenhard B, Wasserman VVW: **Gene characterization index: assessing the depth of gene annotation.** *PLoS ONE* 2008, **3**:e1440.
114. Cohen KB, Hunter L: **Getting started in text mining.** *PLoS Comput Biol* 2008, **4**:e20.
115. Kersey P, Apweiler R: **Linking publication, gene and protein data.** *Nat Cell Biol* 2006, **8**:1183-1189.
116. Duarte NC, Becker SA, Jamshidi N, Thiele I, Mo ML, Vo TD, Srivas R, Palsson BO: **Global reconstruction of the human metabolic network based on genomic and bibliomic data.** *Proc Natl Acad Sci USA* 2007, **104**:1777-1782.
117. Jensen LJ, Saric J, Bork P: **Literature mining for the biologist: from information retrieval to biological discovery.** *Nat Rev Genet* 2006, **7**:119-129.
118. Mons B, Ashburner M, Chichester C, van Mulligen E, Weeber M, den Dunnen J, van Ommen GJ, Musen M, Cockerill M, Hermjakob H, Mons A, Packer A, Pacheco R, Lewis S, Berkeley A, Melton W, Barris N, Wales J, Meijssen G, Moeller E, Roes PJ, Borner K, Bairoch A: **Calling on a million minds for community annotation in WikiProteins.** *Genome Biol* 2008, **9**:R89.
119. Genome Information Integration Project And H-Invitational 2, Yamasaki C, Murakami K, Fujii Y, Sato Y, Harada E, Takeda J, Taniya T, Sakate R, Kikugawa S, Shimada M, Tanino M, Koyanagi KO, Barrero RA, Gough C, Chun HW, Habara T, Hanaoka H, Hayakawa Y, Hilton PB, Kaneko Y, Kanno M, Kawahara Y, Kawamura T, Matsuya A, Nagata N, Nishikata K, Noda AO, Nurimoto S, Saichi N, et al.: **The H-Invitational Database (H-InvDB), a comprehensive annotation resource for human genes and transcripts.** *Nucleic Acids Res* 2008, **36**:D793-D799.
120. Ruttenberg A, Clark T, Bug W, Samwald M, Bodenreider O, Chen H, Doherty D, Forsberg K, Gao Y, Kashyap V, Kinoshita J, Luciano J, Marshall MS, Ogbuji C, Rees J, Stephens S, Wong GT, Wu E, Zaccagnini D, Hongsermeier T, Neumann E, Herman I, Cheung KH: **Advancing translational research with the Semantic Web.** *BMC Bioinformatics* 2007, **8**(Suppl 3):S2.
121. Bonneau R, Facciotti MT, Reiss DJ, Schmid AK, Pan M, Kaur A, Thorsson V, Shannon P, Johnson MH, Bare JC, Longabaugh W, Vuthoori M, Whitehead K, Madar A, Suzuki L, Mori T, Chang DE, Diruggiero J, Johnson CH, Hood L, Baliga NS: **A predictive model for transcriptional control of physiology in a free living cell.** *Cell* 2007, **131**:1354-1365.
122. Oliveri P, Tu Q, Davidson EH: **Global regulatory logic for specification of an embryonic cell lineage.** *Proc Natl Acad Sci USA* 2008, **105**:5955-5962.
123. Hood L: **Gene regulatory networks and embryonic specification.** *Proc Natl Acad Sci USA* 2008, **105**:5951-5952.
124. Lloyd CM, Halstead MD, Nielsen PF: **CellML: its future, present and past.** *Prog Biophys Mol Biol* 2004, **85**:433-450.
125. Garry A, Nickerson DP, Cooper J, Santos RW, Miller AK, McKeever S, Nielsen PM, Hunter PJ: **CellML and associated tools and techniques.** *Philos Transact A Math Phys Eng Sci* 2008, **366**:3017-3043.
126. Hunter P, Nielsen P: **A strategy for integrative computational physiology.** *Physiology (Bethesda)* 2005, **20**:316-325.
127. Hunter PJ, Crampin EJ, Nielsen PM: **Bioinformatics, multiscale modeling and the IUPS Physiome Project.** *Brief Bioinform* 2008, **9**:333-343.
128. Takahashi K, Kaizu K, Hu B, Tomita M: **A multi-algorithm, multi-timescale method for cell simulation.** *Bioinformatics* 2004, **20**:538-546.
129. Bork P, Serrano L: **Towards cellular systems in 4D.** *Cell* 2005, **121**:507-509.
130. Johnston MD, Edwards CM, Bodmer WF, Maini PK, Chapman SJ: **Examples of mathematical modeling: tales from the crypt.** *Cell Cycle* 2007, **6**:2106-2112.
131. Smallbone K, Gatenby RA, Gillies RJ, Maini PK, Gavaghan DJ: **Metabolic changes during carcinogenesis: potential impact on invasiveness.** *J Theor Biol* 2007, **244**:703-713.
132. Schnell S, Maini PK, Newman SA, Newman TJ: **Multiscale modeling of developmental systems. Introduction.** *Curr Top Dev Biol* 2008, **81**:xvii-xxv.
133. Laforge B, Guez D, Martinez M, Kupiec JJ: **Modeling embryogenesis and cancer: an approach based on an equilibrium between the autostabilization of stochastic gene expression and the interdependence of cells for proliferation.** *Prog Biophys Mol Biol* 2005, **89**:93-120.
134. Errampalli DD, Priami C, Quaglia P: **A formal language for computational systems biology.** *OMICS* 2004, **8**:370-380.
135. Chaouiya C, de Jong H, Thieffry D: **Dynamical modeling of biological regulatory networks.** *Biosystems* 2006, **84**:77-80.
136. De Schutter E: **Why are computational neuroscience and systems biology so separate?** *PLoS Comput Biol* 2008, **4**:e1000078.
137. Cohen JE: **Mathematics is biology's next microscope, only better; biology is mathematics' next physics, only better.** *PLoS Biol* 2004, **2**:e439.
138. Coveney PV, Fowler PW: **Modelling biological complexity: a physical scientist's perspective.** *J R Soc Interface* 2005, **2**:267-280.
139. Zhuravel D, Kaern M: **Physics takes another stab at biological design principles.** *Mol Syst Biol* 2005, **1**:2005.0029.
140. Chaturvedi R, Huang C, Kazmierczak B, Schneider T, Izaguirre JA, Glimm T, Hentschel HG, Glazier JA, Newman SA, Alber MS: **On multiscale approaches to three-dimensional modelling of morphogenesis.** *J R Soc Interface* 2005, **2**:237-253.
141. Cohen IR, Harel D: **Explaining a complex living system: dynamics, multi-scaling and emergence.** *J R Soc Interface* 2007, **4**:175-182.
142. Southern J, Pitt-Francis J, Whiteley J, Stokeley D, Kobashi H, Nobes R, Kadooka Y, Gavaghan D: **Multi-scale computational modelling in biology and physiology.** *Prog Biophys Mol Biol* 2008, **96**:60-89.
143. Wolkenhauer O, Mesarovic M, Wellstead P: **A plea for more theory in molecular biology.** *Ernst Schering Res Found Workshop* 2007:117-137.
144. West GB, Brown JH: **The origin of allometric scaling laws in biology from genomes to ecosystems: towards a quantitative unifying theory of biological structure and organization.** *J Exp Biol* 2005, **208**:1575-1592.
145. Nottale L, Auffray C: **Scale relativity theory and integrative systems biology: 2. Macroscopic quantum-type mechanics.** *Prog Biophys Mol Biol* 2008, **97**:115-157.
146. Auffray C, Imbeaud S, Roux-Rouquie M, Hood L: **Self-organized living systems: conjunction of a stable organization with chaotic fluctuations in biological space-time.** *Philos Transact A Math Phys Eng Sci* 2003, **361**:1125-1139.
147. Raser JM, O'Shea EK: **Noise in gene expression: origins, consequences, and control.** *Science* 2005, **309**:2010-2013.

148. Giallourakis C, Henson C, Reich M, Xie X, Mootha VK: **Disease gene discovery through integrative genomics.** *Annu Rev Genomics Hum Genet* 2005, **6**:381-406.
149. Goh KI, Cusick ME, Valle D, Childs B, Vidal M, Barabasi AL: **The human disease network.** *Proc Natl Acad Sci USA* 2007, **104**:8685-8690.
150. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC, Wrobel MJ, Lerner J, Brunet JP, Subramanian A, Ross KN, Reich M, Hieronymus H, Wei G, Armstrong SA, Haggarty SJ, Clemons PA, Wei R, Carr SA, Lander ES, Golub TR: **The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease.** *Science* 2006, **313**:1929-1935.
151. Liang M: **Integrative pathway knowledge bases as a tool for systems molecular medicine.** *Physiol Genomics* 2007, **30**:209-212.
152. Schuster-Bockler B, Bateman A: **Protein interactions in human genetic diseases.** *Genome Biol* 2008, **9**:R9.
153. Wu X, Jiang R, Zhang R, Li S: **Network-based global inference of human disease genes.** *Mol Syst Biol* 2008, **4**:189.
154. Nicolau M, Tibshirani R, Borresen-Dale AL, Jeffrey SS: **Disease-specific genomic analysis: identifying the signature of pathologic biology.** *Bioinformatics* 2007, **23**:957-965.
155. Pepperkok R, Wiemann S: **Integrating systems biology with clinical research.** *Genome Biol* 2008, **9**:314.
156. Searls DB: **Data integration: challenges for drug discovery.** *Nat Rev Drug Discov* 2005, **4**:45-58.
157. Yildirim MA, Goh KI, Cusick ME, Barabasi AL, Vidal M: **Drug-target network.** *Nat Biotechnol* 2007, **25**:1119-1126.
158. van Ommen GJ: **Popper revisited: GWAS here, last year.** *Eur J Hum Genet* 2008, **16**:1-2.
159. NCI-NHGRI Working Group on Replication in Association Studies, Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, Thomas G, Hirschhorn JN, Abecasis G, Altshuler D, Bailey-Wilson JE, Brooks LD, Cardon LR, Daly M, Donnelly P, Fraumeni JF Jr, Freimer NB, Gerhard DS, Gunter C, Guttmacher AE, Guyer MS, Harris EL, Hoh J, Hoover R, Kong CA, Merikangas KR, Morton CC, Palmer LJ, Phimister EG, Rice JP, et al.: **Replicating genotype-phenotype associations.** *Nature* 2007, **447**:655-660.
160. Skol AD, Scott LJ, Abecasis GR, Boehnke M: **Optimal designs for two-stage genome-wide association studies.** *Genet Epidemiol* 2007, **31**:776-788.
161. Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V, Bailey R, Nejentsev S, Field SF, Payne F, Lowe CE, Szeszeko JS, Hafler JP, Zeitels L, Yang JH, Vella A, Nutland S, Stevens HE, Schuilenburg H, Coleman G, Maisuria M, Meadows W, Smink LJ, Healy B, Burren OS, Lam AA, Ovington NR, Allen J, Adlem E, Leung HT, et al.: **Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes.** *Nat Genet* 2007, **39**:857-864.
162. Nejentsev S, Howson JM, Walker NM, Szeszeko J, Field SF, Stevens HE, Reynolds P, Hardy M, King E, Masters J, Hulme J, Maier LM, Smyth D, Bailey R, Cooper JD, Ribas G, Campbell RD, Clayton DG, Todd JA; Wellcome Trust Case Control Consortium: **Localization of type 1 diabetes susceptibility to the MHC class I genes HLA-B and HLA-A.** *Nature* 2007, **450**:887-892.
163. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshzhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C, Froguel P: **A genome-wide association study identifies novel risk loci for type 2 diabetes.** *Nature* 2007, **445**:881-885.
164. Benzinou M, Creemers JW, Choquet H, Lobben S, Dina C, Durand E, Guerardel A, Boutin P, Jouret B, Heude B, Balkau B, Tichet J, Marre M, Potoczna N, Horber F, Le Stunff C, Czernichow S, Sandbaek A, Lauritzen T, Borch-Johnsen K, Andersen G, Kiess W, Körner A, Kovacs P, Jacobson P, Carlsson LM, Walley AJ, Jørgensen T, Hansen T, Pedersen O, et al.: **Common nonsynonymous variants in PCSK1 confer risk of obesity.** *Nat Genet* 2008, **40**:943-945.
165. Thorgerisson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, Manolescu A, Thorleifsson G, Stefansson H, Ingason A, Stacey SN, Bergthorsson JT, Thorlacius S, Gudmundsson J, Jonsson T, Jakobsdottir M, Saemundsdottir J, Olafsdottir O, Gudmundsson LJ, Bjornsdottir G, Kristjansson K, Skuladottir H, Isaksson HJ, Gudbjartsson T, Jones GT, Mueller T, Gottsäter A, Flex A, Aben KK, de Vegt F, et al.: **A variant associated with nicotine dependence, lung cancer and peripheral arterial disease.** *Nature* 2008, **452**:638-642.
166. Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, Lissowska J, Rudnai P, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, Chen C, Goodman G, Field JK, Liloglou T, Xinarianos G, Cassidy A, McLaughlin J, Liu G, Narod S, Krokkan HE, Skorpen F, Elvestad MB, Hveem K, Vatten L, Linseisen J, et al.: **A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25.** *Nature* 2008, **452**:633-637.
167. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, Struwing JP, Morrison J, Field H, Luben R, Wareham N, Ahmed S, Healey CS, Bowman R; SEARCH collaborators, Meyer KB, Haiman CA, Kolonel LK, Henderson BE, Le Marchand L, Brennan P, Sangrajrang S, Gaborieau V, Odeyrey F, Shen CY, Wu PE, Wang HC, Eccles D, Evans DG, Peto J, et al.: **Genome-wide association study identifies novel breast cancer susceptibility loci.** *Nature* 2007, **447**:1087-1093.
168. Human Genome Structural Variation Working Group, Eichler EE, Nickerson DA, Altshuler D, Bowcock AM, Brooks LD, Carter NP, Church DM, Felsenfeld A, Guyer M, Lee C, Lupski JR, Mullikin JC, Pritchard JK, Sebat J, Sherry ST, Smith D, Valle D, Waterston RH: **Completing the map of human genetic variation.** *Nature* 2007, **447**:161-165.
169. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suñer D, Cigudosa J, Urioste M, Benitez J, Boix-Chornet M, Sanchez-Aguilera A, Ling C, Carlsson E, Poulsen P, Vaag A, Stephan Z, Spector TD, Wu YZ, Plass C, Esteller M: **Epigenetic differences arise during the lifetime of monozygotic twins.** *Proc Natl Acad Sci USA* 2005, **102**:10604-10609.
170. Feuk L, Carson AR, Scherer SW: **Structural variation in the human genome.** *Nat Rev Genet* 2006, **7**:85-97.
171. Cobb JP, Mindrinos MN, Miller-Graziano C, Calvano SE, Baker HV, Xiao W, Laudanski K, Brownstein BH, Elson CM, Hayden DL, Herndon DN, Lowry SF, Maier RV, Schoenfeld DA, Moldawer LL, Davis RW, Tompkins RG, Baker HV, Bankey P, Billiar T, Brownstein BH, Calvano SE, Camp D, Chaudry I, Cobb JP, Davis RW, Elson CM, Freeman B, Gamelli R, Gibran N, et al.: **Inflammation and Host Response to Injury Large-Scale Collaborative Research Program: Application of genome-wide expression analysis to human health and disease.** *Proc Natl Acad Sci USA* 2005, **102**:4801-4806.
172. Dixon AL, Liang L, Moffatt MF, Chen W, Heath S, Wong KC, Taylor J, Burnett E, Gut I, Farrall M, Lathrop GM, Abecasis GR, Cookson WO: **A genome-wide association study of global gene expression.** *Nat Genet* 2007, **39**:1202-1207.
173. Elemento O: **Developing a systems-level understanding of gene expression.** *Genome Biol* 2007, **8**:304.
174. Wolfe CJ, Kohane IS, Butte AJ: **Systematic survey reveals general applicability of "guilt-by-association" within gene coexpression networks.** *BMC Bioinformatics* 2005, **6**:227.
175. Degnan JH, Lasky-Su J, Raby BA, Xu M, Molony C, Schadt EE, Lange C: **Genomics and genome-wide association studies: An integrative approach to expression QTL mapping.** *Genomics* 2008, **92**:129-133.
176. Göring HH, Curran JE, Johnson MP, Dyer TD, Charlesworth J, Cole SA, Jowett JB, Abraham LJ, Rainwater DL, Comuzzie AG, Mahaney MC, Almsy L, MacCluer JW, Kissebah AH, Collier GR, Moses EK, Blangero J: **Discovery of expression QTLs using large-scale transcriptional profiling in human lymphocytes.** *Nat Genet* 2007, **39**:1208-1216.
177. Stranger BE, Forrest MS, Dunning M, Ingle CE, Beazley C, Thorne N, Redon R, Bird CP, de Grassi A, Lee C, Tyler-Smith C, Carter N, Scherer SW, Tavaré S, Deloukas P, Hurles ME, Dermitzakis ET: **Relative impact of nucleotide and copy number variation on gene expression phenotypes.** *Science* 2007, **315**:848-853.
178. Chen Y, Zhu J, Lum PY, Yang X, Pinto S, MacNeil DJ, Zhang C, Lamb J, Edwards S, Sieberts SK, Leonardson A, Castellini LW, Wang S, Champy MF, Zhang B, Emilsson V, Doss S, Ghazalpour A, Horvath S, Drake TA, Lusk AJ, Schadt EE: **Variations in DNA elucidate molecular networks that cause disease.** *Nature* 2008, **452**:429-435.
179. Emilsson V, Thorleifsson G, Zhang B, Leonardson AS, Zink F, Zhu J, Carlson S, Helgason A, Walters GB, Gunnarsdottir S, Mouy M, Steinthorsdottir V, Eiriksdottir GH, Bjornsdottir G, Reynisdottir I, Gudbjartsson D, Helgadóttir A, Jonasdottir A, Jonasdottir A, Styrkarsdottir U, Gretarsdottir S, Magnusson KP, Stefansson H, Fossdal R, Kristjansson K, Gislason HG, Stefansson T, Leifsson BG, Thorsteinsdottir U, Lamb JR, et al.: **Genetics of gene expression and its effect on disease.** *Nature* 2008, **452**:423-428.
180. Kitano H: **Cancer as a robust system: implications for anticancer therapy.** *Nat Rev Cancer* 2004, **4**:227-235.
181. Liu ET, Kuznetsov VA, Miller LD: **In the pursuit of complexity: systems medicine in cancer biology.** *Cancer Cell* 2006, **9**:245-247.

182. Hornberg JJ, Bruggeman FJ, Westerhoff HV, Lankelma J: **Cancer: a Systems Biology disease.** *Biosystems* 2006, **83**:81-90.
183. Liu ET, Lemberger T: **Higher order structure in the cancer transcriptome and systems medicine.** *Mol Syst Biol* 2007, **3**:94.
184. Ao P, Galas D, Hood L, Zhu X: **Cancer as robust intrinsic state of endogenous molecular-cellular network shaped by evolution.** *Med Hypotheses* 2008, **70**:678-684.
185. Lotem J, Sachs L: **Epigenetics and the plasticity of differentiation in normal and cancer stem cells.** *Oncogene* 2006, **25**:7663-7672.
186. Price ND, Foltz G, Madan A, Hood L, Tian Q: **Systems biology and cancer stem cells.** *J Cell Mol Med* 2008, **12**:97-110.
187. Reymond MA, Schlegel W: **Proteomics in cancer.** *Adv Clin Chem* 2007, **44**:103-142.
188. Bild AH, Yao G, Chang JT, Wang Q, Potti A, Chasse D, Joshi MB, Harpole D, Lancaster JM, Berchuck A, Olson JA Jr, Marks JR, Dressman HK, West M, Nevins JR: **Oncogenic pathway signatures in human cancers as a guide to targeted therapies.** *Nature* 2006, **439**:353-357.
189. Chin L, Gray JW: **Translating insights from the cancer genome into clinical practice.** *Nature* 2008, **452**:553-563.
190. Graudens E, Boulanger V, Mollard C, Mariage-Samson R, Barlet X, Grémy G, Couillault C, Lajémi M, Piatier-Tonneau D, Zaborski P, Eveno E, Auffray C, Imbeaud S: **Deciphering cellular states of innate tumor drug responses.** *Genome Biol* 2006, **7**:R19.
191. van't Veer LJ, Bernards R: **Enabling personalized cancer medicine through analysis of gene-expression patterns.** *Nature* 2008, **452**:564-570.
192. Zheng PZ, Wang KK, Zhang QY, Huang QH, Du YZ, Zhang QH, Xiao DK, Shen SH, Imbeaud S, Eveno E, Zhao CJ, Chen YL, Fan HY, Waxman S, Auffray C, Jin G, Chen SJ, Chen Z, Zhang J: **Systems analysis of transcriptome and proteome in retinoic acid/arsenic trioxide-induced cell differentiation/apoptosis of promyelocytic leukemia.** *Proc Natl Acad Sci USA* 2005, **102**:7653-7658.
193. Ludwig JA, Weinstein JN: **Biomarkers in cancer staging, prognosis and treatment selection.** *Nat Rev Cancer* 2005, **5**:845-856.
194. Sawyers CL: **The cancer biomarker problem.** *Nature* 2008, **452**:548-552.
195. Mani KM, Lefebvre C, Wang K, Lim WK, Basso K, Dalla-Favera R, Califano A: **A systems biology approach to prediction of oncogenes and molecular perturbation targets in B-cell lymphomas.** *Mol Syst Biol* 2008, **4**:169.
196. Lin B, White JT, Lu W, Xie T, Uteleg AG, Yan X, Yi EC, Shannon P, Khrebtkova I, Lange PH, et al.: **Evidence for the presence of disease-perturbed networks in prostate cancer cells by genomic and proteomic analyses: a systems approach to disease.** *Cancer Res* 2005, **65**:3081-3091.
197. Chuang HY, Lee E, Liu YT, Lee D, Ideker T: **Network-based classification of breast cancer metastasis.** *Mol Syst Biol* 2007, **3**:140.
198. Braga-Neto UM, Marques ET Jr: **From functional genomics to functional immunomics: new challenges, old problems, big rewards.** *PLoS Comput Biol* 2006, **2**:e81.
199. Vodovotz Y, Csete M, Bartels J, Chang S, An G: **Translational systems biology of inflammation.** *PLoS Comput Biol* 2008, **4**:e1000014.
200. Young D, Stark J, Kirschner D: **Systems biology of persistent infection: tuberculosis as a case study.** *Nat Rev Microbiol* 2008, **6**:520-528.
201. Abrahams BS, Geschwind DH: **Advances in autism genetics: on the threshold of a new neurobiology.** *Nat Rev Genet* 2008, **9**:341-355.
202. Miller JA, Oldham MC, Geschwind DH: **A systems level analysis of transcriptional changes in Alzheimer's disease and normal aging.** *J Neurosci* 2008, **28**:1410-1420.
203. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, Depner M, von Berg A, Bufe A, Rietschel E, Heinzmann A, Simma B, Frischer T, Willis-Owen SA, Wong KC, Illig T, Vogelberg C, Weiland SK, von Mutius E, Abecasis GR, Farrall M, Gut IG, Lathrop GM, Cookson WO: **Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma.** *Nature* 2007, **448**:470-473.
204. Lusis AJ: **A thematic review series: systems biology approaches to metabolic and cardiovascular disorders.** *J Lipid Res* 2006, **47**:1887-1890.
205. Zethelius B, Berglund L, Sundstrom J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlöv J: **Use of multiple biomarkers to improve the prediction of death from cardiovascular causes.** *N Engl J Med* 2008, **358**:2107-2116.
206. Shreenivasaiah PK, Rho SH, Kim T, Kim do H: **An overview of cardiac systems biology.** *J Mol Cell Cardiol* 2008, **44**:460-469.
207. Saks V, Dzeja P, Schlattner U, Vendelin M, Terzic A, Wallimann T: **Cardiac system bioenergetics: metabolic basis of the Frank-Starling law.** *J Physiol* 2006, **571**:253-273.
208. Saks V, Favier R, Guzun R, Schlattner U, Wallimann T: **Molecular system bioenergetics: regulation of substrate supply in response to heart energy demands.** *J Physiol* 2006, **577**:769-777.
209. Ferguson EC, Rathmell JC: **New roles for pyruvate kinase M2: working out the Warburg effect.** *Trends Biochem Sci* 2008, **33**:359-362.
210. Lin MT, Beal MF: **Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases.** *Nature* 2006, **443**:787-795.
211. Kriete A, Sokhansanj BA, Coppock DL, West GB: **Systems approaches to the networks of aging.** *Ageing Res Rev* 2006, **5**:434-448.
212. Bradbury J: **From Chinese medicine to anticancer drugs.** *Drug Discov Today* 2005, **10**:1131-1132.
213. Wang L, Zhou GB, Liu P, Song JH, Liang Y, Yan XJ, Xu F, Wang BS, Mao JH, Shen ZX, Chen SJ, Chen Z: **Dissection of mechanisms of Chinese medicinal formula Realgar-Indigo naturalis as an effective treatment for promyelocytic leukemia.** *Proc Natl Acad Sci USA* 2008, **105**:4826-4831.
214. Qiu J: **'Back to the future' for Chinese herbal medicines.** *Nat Rev Drug Discov* 2007, **6**:506-507.
215. Li M, Wang B, Zhang M, Rantalainen M, Wang S, Zhou H, Zhang Y, Shen J, Pang X, Zhang M, Wei H, Chen Y, Lu H, Zuo J, Su M, Qiu Y, Jia W, Xiao C, Smith LM, Yang S, Holmes E, Tang H, Zhao G, Nicholson JK, Li L, Zhao L: **Symbiotic gut microbes modulate human metabolic phenotypes.** *Proc Natl Acad Sci USA* 2008, **105**:2117-2122.
216. Dusek JA, Otu HH, Wohlhueter AL, Bhasin M, Zerbini LF, Joseph MG, Benson H, Libermann TA: **Genomic counter-stress changes induced by the relaxation response.** *PLoS ONE* 2008, **3**:e2576.
217. Ornish D, Magbanua MJ, Weidner G, Weinberg V, Kemp C, Green C, Mattie MD, Marlin R, Simko J, Shinohara K, Haqq CM, Carroll PR: **Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention.** *Proc Natl Acad Sci USA* 2008, **105**:8369-8374.
218. Vassalle C, Maffei S, Boni C, Zucchelli GC: **Gender-related differences in oxidative stress levels among elderly patients with coronary artery disease.** *Fertil Steril* 2008, **89**:608-613.
219. DeMeo DL: **The Yin and Yang of COPD: sex/gender differences in the National Emphysema Treatment Trial.** *Am J Respir Crit Care Med* 2007, **176**:222-223.
220. Federman DD: **The biology of human sex differences.** *N Engl J Med* 2006, **354**:1507-1514.
221. Franconi F, Brunelleschi S, Steardo L, Cuomo V: **Gender differences in drug responses.** *Pharmacol Res* 2007, **55**:81-95.
222. Psihogios NG, Gazi IF, Elisaf MS, Seferiadis KI, Bairaktari ET: **Gender-related and age-related urinalysis of healthy subjects by NMR-based metabonomics.** *NMR Biomed* 2008, **21**:195-207.
223. Holmes E, Loo RL, Stamlor J, Bictash M, Yap IK, Chan Q, Ebbels T, De Iorio M, Brown IJ, Veselkov KA, Daviglus ML, Kesteloot H, Ueshima H, Zhao L, Nicholson JK, Elliott P: **Human metabolic phenotype diversity and its association with diet and blood pressure.** *Nature* 2008, **453**:396-400.
224. Cote F, Fligny C, Bayard E, Launay JM, Gershon MD, Mallet J, Vodjani G: **Maternal serotonin is crucial for murine embryonic development.** *Proc Natl Acad Sci USA* 2007, **104**:329-334.
225. Ohta H, Xu S, Moriya T, Iigo M, Watanabe T, Nakahata N, Chisaka H, Hanita T, Matsuda T, Ohura T, Kimura Y, Yaegashi N, Tsuchiya S, Tei H, Okamura K: **Maternal feeding controls fetal biological clock.** *PLoS ONE* 2008, **3**:e2601.
226. Charron D: **Immunogenetics today: HLA, MHC and much more.** *Curr Opin Immunol* 2005, **17**:493-497.
227. Macdonald TT, Monteleone G: **Immunity, inflammation, and allergy in the gut.** *Science* 2005, **307**:1920-1925.
228. Orr CF, Rowe DB, Mizuno Y, Mori H, Halliday GM: **A possible role for humoral immunity in the pathogenesis of Parkinson's disease.** *Brain* 2005, **128**:2665-2674.
229. Licastro F, Candore G, Lio D, Porcellini E, Colonna-Romano G, Franceschi C, Caruso C: **Innate immunity and inflammation in ageing: a key for understanding age-related diseases.** *Immun Ageing* 2005, **2**:8.
230. Weston AD, Hood L: **Systems biology, proteomics, and the future of health care: toward predictive, preventative, and personalized medicine.** *J Proteome Res* 2004, **3**:179-196.

231. Bar-Yam Y: **Improving the effectiveness of health care and public health: a multiscale complex systems analysis.** *Am J Public Health* 2006, **96**:459-466.
232. Boissel JP, Ribba B, Grenier E, Chapuisat G, Dronne MA: **Modelling methodology in physiopathology.** *Prog Biophys Mol Biol* 2008, **97**:28-39.
233. Weissleder R, Pittet MJ: **Imaging in the era of molecular oncology.** *Nature* 2008, **452**:580-589.
234. Cambon-Thomsen A, Rial-Sebbag E, Knoppers BM: **Trends in ethical and legal frameworks for the use of human biobanks.** *Eur Respir J* 2007, **30**:373-382.
235. Kauffmann F, Cambon-Thomsen A: **Tracing biological collections: between books and clinical trials.** *JAMA* 2008, **299**:2316-2318.
236. Yuille M, van Ommen GJ, Brechot C, Cambon-Thomsen A, Dagher G, Landegren U, Litton JE, Pasterk M, Peltonen L, Taussig M, Wichmann HE, Zatloukal K: **Biobanking for Europe.** *Brief Bioinform* 2008, **9**:14-24.
237. Aderem A: **Systems biology: its practice and challenges.** *Cell* 2005, **121**:511-513.
238. Ideker T, Bafna V, Lemberger T: **Integrating scientific cultures.** *Mol Syst Biol* 2007, **3**:105.
239. Hood L, Rowen L, Galas DJ, Aitchison JD: **Systems biology at the Institute for Systems Biology.** *Brief Funct Genomic Proteomic* 2008, **7**:239-248.
240. Boulos MN, Maramba I, Wheeler S: **Wikis, blogs and podcasts: a new generation of Web-based tools for virtual collaborative clinical practice and education.** *BMC Med Educ* 2006, **6**:41.
241. Eddy SR: **"Antedisciplinary" science.** *PLoS Comput Biol* 2005, **1**:e6.
242. Gandy M: **Deadly alliances: death, disease, and the global politics of public health.** *PLoS Med* 2005, **2**:e4.
243. Dentico N, Ford N: **The courage to change the rules: a proposal for an essential health R&D treaty.** *PLoS Med* 2005, **2**:e14.
244. Tindana PO, Singh JA, Tracy CS, Upshur RE, Daar AS, Singer PA, Frohlich J, Lavery JV: **Grand challenges in global health: community engagement in research in developing countries.** *PLoS Med* 2007, **4**:e273.
245. Auffray C, Chen Z, Hood L, Soares B, Sugano S: **Foreword: from the TRANSCRIPTOME conferences to the SYSTEMSCOPE international consortium.** *C R Biol* 2003, **326**:867-875.