Published in final edited form as:
Biotechnol J. 2012 August ; 7(8): 992–1001. doi:10.1002/biot.201100306.

Revolutionizing medicine in the 21st century through systems approaches

Leroy Hood[1], **Rudi Balling**[2], and **Charles Auffray**[3]

[1] Institute for Systems Biology, Seattle, WA, USA

[2] Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg

[3] European Institute for Systems Biology and Medicine, CNRS–UCBL–ENS, Université de Lyon, Lyon, France

Abstract

Personalized medicine is a term for a revolution in medicine that envisions the individual patient as the central focus of healthcare in the future. The term “personalized medicine”, however, fails to reflect the enormous dimensionality of this new medicine that will be predictive, preventive, personalized, and participatory – a vision of medicine we have termed P4 medicine. This reflects a paradigm change in how medicine will be practiced that is revolutionary rather than evolutionary. P4 medicine arises from the confluence of a systems approach to medicine and from the digitalization of medicine that creates the large data sets necessary to deal with the complexities of disease. We predict that systems approaches will empower the transition from conventional reactive medical practice to a more proactive P4 medicine focused on wellness, and will reverse the escalating costs of drug development and will have enormous social and economic benefits. Our vision for P4 medicine in 10 years is that each patient will be associated with a virtual data cloud of billions of data points and that we will have the information technology for healthcare to reduce this enormous data dimensionality to simple hypotheses about health and/or disease for each individual. These data will be multi-scale across all levels of biological organization and extremely heterogeneous in type – this enormous amount of data represents a striking signal-to-noise (S/N) challenge. The key to dealing with this S/N challenge is to take a “holistic systems approach” to disease as we will discuss in this article.

Keywords

Functional genomics; Network biology; Personalized medicine; Systems medicine

1 Why does P4 medicine require so much data?

Biology and disease are incredibly complex [1]. This is a consequence of the processes taking place during Darwinian evolution, which are not directed, but rather random and chaotic – they build changes on top of present successful, but also complex solutions, in response to adapting to the ever-changing environment. Biological complexity reminds one of the famous Rube Goldberg cartoon in which Rube had assembled 14 gadgets connected

Correspondence: Dr. Leroy Hood, Institute for Systems Biology, 401 Terry Avenue North, Seattle, WA 98109-5234, USA lhood@systemsbiology.org.

The authors declare no conflict of interest.

together to cool his soup. In order to understand how Rube's apparatus works – one would have to have a parts list of all the components, know how the parts are connected together and understand the dynamics of how the parts move with respect to one another to cool the soup (the dynamics of the soup-cooling machine). These are three of the major requirements for a systems approach to understanding biological systems – the parts list, their interconnections, and the dynamics of the parts interactions – to determine how the system functions or exhibits dysfunction.

2 Viewing biology as an information science

The informational view of biology allows data to be nicely organized around three central ideas. First, there are two types of biological information, the digital information of the genome and the environmental signals that come from outside the genome. These two types of information are integrated together to specify the central mechanisms of life – evolution, development, physiological responses, aging, and the initiation and progression of disease. Second, an interesting question is what joins the integrated information to phenotype? Two information handling structure do – biological networks that capture, transmit, integrate, and pass information on to molecular machines to execute the functions of life. Hence the dynamics of networks and molecular machines constitutes one of the central foci of systems approaches to biology and disease. Finally, biological information is hierarchical and multi-scale across all levels of biological organization – from DNA, RNA, proteins, metabolites, interactions, and cells, to organs, individuals, populations, and ecologies – all representing an intertwined ascending and descending hierarchy of information. The environment impinges upon information at each of these levels to modulate repeatedly the original digital genome signal. Hence it is essential to integrate information from the different levels to explicate the environmental contributions if one is ever to understand how the system works – for this requires understanding how the information of the genome and environment interact. These informational views of biology are also key to dealing with the S/N issues arising from the generation of large data sets with high-throughput methods. The biological information has to be integrated with clinical information and translated into efficient and reliable decision support systems for health care.

3 A systems approach to disease

Disease arises as a consequence of disease-perturbed networks in the diseased organ that propagate from one or a few disease-perturbed networks to many as the disease progresses. These initial disease perturbations may be genetic (e.g. mutations) and/or environmental (e.g. infectious organisms). These perturbations alter the information expressed in these networks dynamically – and these altered dynamics of information flow explain the pathophysiology of the disease and suggest new approaches to diagnosis and therapy [2].

3.1 Systems biology of prion disease

To illustrate these principles, let us consider the studies we have carried out on neurodegeneration in mice initiated by the injection of infectious prion proteins into the brain [3]. These studies were important because we could look at the initiation and dynamics of the progression of the disease from inception (e.g. the infection) to death, focusing initially on the mRNAs expressed in the brain and how they changed across the 22-week progression of the disease. To identify the differentially expressed genes (DEGs), the diseased brain transcriptomes were subtracted from the control transcriptomes at 10 time points across the progression of the disease. These temporal dynamical studies revealed several striking points. First, 7400 RNA transcripts appeared to be changed in the course of the disease – encoded by nearly 1/3rd of the mouse genes. These data obviously represent a significant S/N problem. This noise arises from two sources: technical noise and biological

noise. Biological noise arises from measuring a particular phenotype (e.g. the brain transcriptome) that is the sum of several different aspects of biology that lie outside the phenotype of interest (in this case neurodegeneration). Approaches were developed involving eight different inbred strain/prion strain combinations for subtracting away the other types of biological variations – to focus on the biology of neurodegeneration. These subtractions suggested that about 300 DEGs are associated with neurodegeneration (these subtractions thus provided more than a 20-fold enrichment in S/N). Second, four major biological networks appeared to participate in prion disease as revealed by histopathological studies. The core 300 DEGs were mapped into the four interaction networks encoding these histopathologies at ten different time points across the 22 weeks of disease progression. Two hundred of these genes mapped into the four major networks and the remaining 100 defined six smaller networks – not previously known to be involved with prion disease. Third, the dynamics of how these transcripts changed across disease progress explained virtually every aspect of the pathophysiology of the disease – a remarkable advance in understanding disease dynamics. Fourth, the four major networks were sequentially disease-perturbed. The importance of this observation is that it provides new strategies for diagnosis and therapy that may focus on the most proximal of the disease-perturbed networks. Finally, this dynamical network analysis did suggest several new approaches to blood diagnostics using, for example, comparative organ transcriptome analyses to identify organ-specific transcripts. In this manner, more than 100 brain-specific mouse transcripts could be identified – and many of these encoded proteins that were secreted into the blood – there to constitute a brain-specific blood fingerprint that could distinguish for the brain, health from disease, and in the case of disease, the type of disease. Fifteen of these brain-specific proteins permitted early preclinical diagnosis of prion disease, the stratification of different types of neurodegenerative diseases, and the ability to follow the progression of prion disease – all from the blood. The use of such organ-specific blood fingerprints will thus be a powerful tool for diagnostics in the future [4].

3.2 Systems biology of respiratory and muscle disease

Another landmark study illustrates the power of systems biology and network modeling approaches to decipher the interplay of molecular networks in multiple organs and their perturbations in a complex chronic respiratory disease such as chronic obstructive pulmonary disease (COPD), which, in addition to progressive airway obstruction, is characterized by muscle wasting [5]. COPD is a chronic life-threatening inflammatory disease of the lungs characterized by progressive airway limitation leading to severe impairment in the quality of life of the patients. It is largely irreversible and associated with muscle wasting. It is increasing in prevalence and represents the fourth most important cause of death worldwide. Current treatments aim at reversing the disease process through a combination of exercise training, anti-inflammatory drugs and dietary supplements. In this study, transcriptomic expression profiles were collected in skeletal muscle biopsies of the COPD patients and controls at rest, before and after exercise training. Through integration of the differentially expressed genes detected with serum cytokine levels and a range of recorded physiological responses, the authors were able to identify interaction networks perturbed in the disease state. This provided supporting evidence that a distinctive feature of COPD is the uncoupling between tissue remodeling and the control of energy metabolism, and that this is the result of a perturbation of transcriptional regulation leading to the modulation of inflammatory cytokines such as interleukin (IL)-1β. Previous work had pointed to a possible role of NF-κB targets in these transcriptional regulation abnormalities [6]. In order to test the validity of this working hypothesis through a second iteration of the systems biology process, the authors designed and performed a set of validation experiments. They thus compared and combined the results obtained in human patients with those collected in animal models or previously reported in the literature, and the evidence

obtained did not support the working hypothesis. Rather, they pointed to an alternate hypothesis that specific epigenetic changes linked to histone modifiers are associated with muscle dysfunction and possibly driven by hypoxia, suggesting that they could be investigated as novel targets for therapeutic intervention to restore muscle function in COPD patients.

4 Emerging technologies

The study of leading-edge problems in biology or disease quickly pushes studies to the point that new technologies are needed to open up new dimensions of patient data space. Let us discuss six of these emerging technologies in the context of P4 medicine.

4.1 Family genome sequencing

The genome is the digital source code of life, encoding many of our most fundamental features – such as development and physiological mechanisms for responding to the environment. Both processes may be modified by epigenetic marks. With the rapid progress in sequencing technologies, family genome sequencing, that is determining the complete genome sequences of all of the members of a family, is enabling the integration of genomics and genetics with fascinating results. For example, the sequencing of the genomes of a family of four where the parents were normal and the two kids each had two genetic diseases revealed the multi-dimensional power of this approach [7]. First, about 70% of the sequencing errors could be identified by using plausibility checks on the basis of the principles of simple Mendelian genetics. Second, rare variants could be immediately identified by asking whether two or more members of the family had them (hence they could not be sequencing errors).Third, the haplotypes of the members of the family could be determined through being able to map precisely the recombination sites in the children's chromosomes and hence the linkages of their constellations of genetic variants across each of the diploid autosomes and the sex chromosomes. This is important because then one can ask for those family members with the disease – what fraction of their chromosomal haplotypes are shared, for it is in these shared chromosome regions that the disease-related genes must reside. This greatly reduces the area of chromosomal space that needs to be searched for disease-related genes. Finally, the number of disease gene candidates for the two children could be reduced to just four genes – and the proper assignments were relatively straightforward. Thus family genome sequencing, through the integration of genetics and genomics, increases enormously the S/N in most whole genome analyses while searching for disease-related genes.

We believe that in 10 years the individual complete genome sequence will be a routine part of a personal medical record – and it will provide fundamental insights into optimizing health. This is in keeping with the fact that within 5 years we predict that the cost of a complete genome sequence will be a few hundred dollars. We believe that what will be a fundamental driver of societal acceptance of complete genome sequences are "actionable gene variants." An actionable variant is one that allows a physician to specify how a patient may improve his or her health. For example, there are variants of a vitamin D transporter that lead to significant osteoporosis in the early 40's (a young age). This condition can be reversed merely by having the patient take 20 times the normal dose of vitamin D. More than 250 of these "actionable gene variants" have already been identified. It is the continually increasing number of actionable gene variants that will be the major driver in having society accept whole genome sequences as an important part of each person's medical record. Indeed, in the future our genome sequence will be checked every year to identify new actionable variants. Hence our genome sequence will be an investment in our health for the rest of our lives.

4.2 Proteomics

The proteome is the entire complement of proteins in a given biological compartment (an individual, an organ, a cell, the blood, etc). Proteins have several features that distinguish them from DNA and make their analyses more complex. First, DNA is digital in nature (e.g. the chromosomes are digital strings of Gs, Cs, As, and Ts with a diploid representation in the nucleus – only two copies of most genes), while proteins, in addition to the digital information translated from the genome sequence into strings of the 20 amino acids, are associated with analog information (e.g. they fold into complex 3D structures and they may be present in one compartment, such as the blood, as one or a few copies or 10^{10} copies – manifesting an enormous dynamic range of concentrations). While there are about 20 000 protein-coding genes in the human genome, there may be millions of proteins because proteins (translated from mRNAs) can be modified by many biological processes occurring after the genome is transcribed, including RNA editing, RNA splicing, protein processing, and chemical modification. Proteins are also dynamic – often changing their 3D structures in the context of carrying out their biological functions, thus responding to environmental changes. Proteins, together with other complex biomolecules and metabolites, execute the functions of life and hence are closer to the phenotype than DNA or RNA.

One powerful approach to the quantification and identification of proteins from complex mixtures (tissues, blood, cells, etc.) is the use of MS. Proteins are purified from other compounds, digested by an enzyme such as trypsin to create peptides and the peptides can then be analyzed (e.g. sequenced) and quantified in the mass spectrometer. Initially, MS was used in a shotgun manner to identify and quantify proteins in complex mixtures – but it was quickly determined that often most of the peptides analyzed are those from the predominant proteins in the mixture. Accordingly, a new approach termed targeted proteomics was pioneered [8] where one could identify peptides that uniquely define each protein, then determine which of these peptides behave well in the mass spectrometer – and then synthesize isotopically labeled peptides that when added to the peptide mixture would enable precise quantification. Rob Moritz at the Institute for Systems Biology, in collaboration with Ruedi Aebersold at the ETH, has recently identified 3–6 peptide assays for each of 20 000 human proteins. These assays have been placed in a database that is openly accessible to all scientists. Hence, targeted proteomics has “democratized” the human proteins in the same sense that the HGP “democratized” all human genes – namely they are now accessible to all scientists (Moritz, in preparation). These targeted proteomics assays will be powerful tools in analyzing biological and disease mechanisms and they will provide powerful approaches to the identification of disease biomarkers.

In the future we will want to create protein assays that can analyze thousands of proteins from a fraction of a droplet of blood on hundreds of millions of patients each year. MS will not be extendable to analyses of this dimension. For example, we envision being able to analyze perhaps 50 organ-specific blood proteins from each of 50 human organs on a biannual basis. Jim Heath at Caltech has pioneered a microfluidic protein ELIZA chip that can make 50 measurements in 5 min from 300 nL of blood [9]. To be able to expand 50 measurements to 2500 measurements (50 times 50) will require developing new types of protein-capture agents for the ELIZA assays – both peptide capture agents [10] and aptamer capture agents [11] appear promising.

4.3 Metabolomics

MS is the method of choice to determine the metabolome of individual patients. Currently MS or LC coupled to GC are able to resolve 300–500 metabolites, such as amino acids, fatty acids, nucleotides, and many other small molecules [12]. Whereas the targeted or untargeted quantification of metabolites provides the most “proximal” phenotype, this information is

still static in nature. Currently in vivo, whole organism methods are under development using stable isotopes that allow to follow the fate and rate of individual metabolites, the measurement of metabolite fluxes and enzyme rates, thereby tremendously increasing the information about disease progression and potential adaptive, compensatory physiological and patho-physiological mechanisms. The MS-based methods are now being complemented by pattern-recognition array-sensors that capture volatile organic compounds in exhaled breath, providing disease-specific molecular signatures. These so-called “electronic noses” are non-invasive diagnostic devices, which have shown promising results, e.g. in the early detection of diseases such as lung cancer [13], and the distinction between asthma and COPD [14].

4.4 Single-cell analyses

Virtually all studies until very recently have been carried out on complex mixtures of cells (either from tissues or from the blood). It is clear that much biology is executed by virtue of cells of different types interacting with one another – or by interactions with environmental signals from tissue scaffolds or other cells. Hence in order to understand fundamental biological or disease mechanisms – single cell analyses will be critical. Microfluidic techniques have been developed that allow single cells to be analyzed at the genomics and proteomics levels. One of the fundamental questions that can be answered with single-cell analyses is the number of discrete (quantized) populations of cells that exist within a tissue or organ. Once the single-cell analyses have been carried out, the uniquely defining cell-surface molecules can be identified that will permit the separation of the quantized populations by cell sorting. Then the cells of these quantized populations can be investigated to see how they respond to environmental signals or the interaction with cells from other quantized populations. One can also use single-cell analyses to characterize disease states (e.g. how many quantized populations are there in tumors), or to separate the 10 or so classes of white blood cells to determine whether and how they can be useful in the diagnosis of disease. Our prediction is that single-cell analyses will transform profoundly our understanding of health and disease.

4.5 Imaging

Spatial and temporal information will be key for the development of reliable disease models that allow the identification of actionable network components. For this reason advanced high-resolution and high-content imaging technology is being developed [15, 16], to enable the reliable interpretation of molecular and cellular disease processes and eventually the integration into molecular diagnostics and medical decision support systems.

4.6 Induced pluripotent stem cells

Induced pluripotent stem (iPS) cells from individual patients will be useful in exploring mechanisms of disease initiation and progression, in revealing fundamental aspects of development and in creating the differentiated cell types of patients in a test tube which can be analyzed with environmental probes (ligands, drugs, etc.) eventually to stratify disease by virtual of different responses for each subtype of a disease that has its own unique combination of disease-perturbed networks [17, 18]. iPS cells derived from blood white cells and skin or cheek fibroblasts will be complemented by iPS cells derived from cells of the immune system that have undergone Tcr or Bcr recombination, opening the possibility for treating antigen-specific autoimmunity and allergies.

The combination of an informational view of medicine, the systems approaches to disease, the emergence of new technologies and strategies that open up new dimensions of patient data space and pioneering analytical tools (mathematical and computational) enable the development and implementation of P4 medicine in healthcare and society.

5 P4 medicine

Systems medicine provides the strategies, tools, and computational and analytical abilities to analyze enormous amounts of information [19]. P4 medicine uses these strategies and tools to attack disease (and wellness) for the benefit of the individual [20]. P4 medicine also must deal with the societal challenges of systems medicine. Let us consider at a high level where we will be with the 4Ps in 10 or so years.

5.1 Predictive

We suggest in 10 years that genomes will be a routine part of each patient's medical record. From the actionable gene variants we will be able to provide each patient with critical information for optimizing his or her wellness as well as dealing with the future potential for disease development. We predict the availability of a small handheld device that can prick your thumb, measure 2500 organ-specific proteins, send this information to a server for analysis and feedback the information on the state of your 50 organ systems. These measurements will be longitudinal in nature throughout our lives, immediately identifying any transitions from health to disease, sending alerts early on and suggesting preventive measures such as changes in dietary or exercising habits. These measurements will thus also be used to optimize wellness.

5.2 Preventive

Systems approaches to studying disease-perturbed networks will provide a completely new approach to the identification of drug targets, through reengineering of disease-perturbed networks to make them behave in a more normal or manageable fashion through the use of multiple drugs to perturb the networks. We will have to learn how to analyze and interpret reconstructed disease networks from individual patients and identify optimal interference strategies. In a first phase we will need to re-engineer networks with drugs in microorganisms in order to elucidate the general engineering principles that will then be applied to humans. From a disease prevention point of view the most proximal disease-perturbed networks will be the most promising ones to address first with this strategy.

Systems approaches will enable us to understand, for the first time, how to effectively induce cellular immunity. Hence we will be able to generate vaccines that can deal with infectious challenges such as AIDS, malaria, and tuberculosis. But most important for prevention, we will increasingly focus on optimizing wellness for the individual. This will be done through identification of metrics that will let us assess wellness and its dynamics for each individual. The digital revolution of medicine that will make enormous amounts of the individual's data available to him or her will play a critical role in optimizing wellness. Already now 60 or more digital parameters can be measured for each patient – providing unique opportunities for driving the optimization of individual wellness [21].

5.3 Personalized

On average, humans differ from one another by 6 million nucleotides in their genome sequence, and an uncharacterized number of subsequent changes in other biomolecules. Hence each of us is unique – and will have to serve as our own control for following transitions from health to disease or vice versa. This is the essence of personalized medicine – medicine must focus on each individual uniquely.

In 10- or 15-years, with the fast decline in the cost of next-generation sequencing, we will potentially have access to the complete genomes and attendant medical, molecular, cellular, and environmental data for a growing fraction of the human population in both developed and developing countries. This will afford us an unparalleled opportunity to mine these data

for the predictive medicine of the future – but only if these data are made readily available for qualified researchers and health practitioners. Our view is that it is critical that society should have access to the data of each person and patient and that these data, after anonymization, should be available to qualified investigators to mine for the predictive medicine of the future that will transform healthcare for our children and grandchildren (as well as us). After all, society has created the resources that led to the emergence of P4 medicine – and these resources should be leveraged through extensive data mining to pioneer the development of the future of medicine. It will be important to provide legal safe-guards against discriminatory use of these data – e.g. by employers and insurance companies.

5.4 Participatory

The patient will participate in many of the different dimensions of P4 medicine. First, patients or healthcare customers will increasing participate in patient-driven social networks that will sustain the process of the acceptance of P4 medicine by demanding better healthcare for each person individually. Second, patients will need to be informed and educated as to the opportunities and challenges of P4 medicine. This holds true for physicians and indeed the entire healthcare community, which will have to be educated as to the revolution that P4 medicine is bringing through a profound revision of the medical training curriculum. We believe there will be a critical role for information technology in this education process. Third, patients will have to actively participate in the process of making available their billions of bytes of digitized data for the healthcare database of the future. The challenges involved in IT for healthcare in acquiring, validating, storing, mining, integrating, and finally modeling these highly heterogeneous data are daunting – and not being effectively approached yet by any of the current players in the information technology for healthcare landscape. We need to develop user-friendly software solutions for crowd-sourcing enabling an efficient highly interactive patient–healthcare interface. Finally, it will be important to create a “gold standard” for healthcare information on the internet – so that patients (and physicians) can obtain reliable healthcare information.

6 General features of P4 medicine

P4 medicine is concerned with understanding for the individual patient of his or her “network of networks” – a hierarchy of networks operating across multiple, complex, dynamic, and intertwined levels of biological organization encompassing both the individual and his or her environment. A genetic network can be defined by analyzing how defects in pairs of genes affect the phenotype of the organism. Gene regulatory networks result from the interaction of transcription factors with their cognate *cis*-regulatory elements on chromosomes. The proteins produced through transcription and translation in turn interact with one another and with other small molecules within functional protein interaction networks: e.g. metabolites and enzymes interact in metabolic networks. These diverse biochemical activities are integrated at the level of cells interacting with one another within cellular, tissular, and organ networks, all of which are assembled together within an individual organism in the context of its extended environment (e.g. humans interacting in social networks). Each of these networks is interfacing with the other types of networks to form the “network of networks.” Obviously disease-perturbations in one network will reflect throughout the other networks as a consequence of their integrated interfaces. Thus one challenge of disease is to ultimately understand how to construct these individual networks from individual patient data, to determine how these networks are integrated and finally to ascertain how disease-perturbations reflect throughout the “network of networks” to modify its information content. Hence P4 medicine is about integrating the information from each of these networks so as to be able to understand how the digital genome information and

environmental information combine to generate the normal and disease phenotypes. The assessment of each of these networks is fundamental to capturing the environmental signals that impinge at each of these levels upon the core digital signal. Hence a true understanding of biology and disease mechanisms requires capturing the information of each of these networks and a better understanding of the systems properties that emerge from their combinations.

P4 medicine stands in striking comparison to more conventional evidence-based medicine. In contrast to evidence-based medicine, P4 medicine is proactive rather than reactive; is focused on wellness-maintenance rather than disease; employs many measurements on the individual patient rather than few; is individual-centric rather than population based; integrates and mines large aggregated patient data sets to pioneer the P4 medicine of the future; employs patient-driven societal networks as a catalyst for change; and stratifies diseases into their distinct subtypes for impedance matches against proper drugs. The quantized self – that is, the collection of many digital measurements on each individual will give us real time and readily digestible insights into optimizing our wellness – and minimizing our disease. The article by Larry Smarr [21] in this issue illustrates beautifully this principle.

P4 medicine has two central goals – the quantification of wellness and the demystification of disease – and the two become intimately related for each individual.

7 Impact of P4 medicine on society

P4 medicine will mandate that every sector of the public and private healthcare systems rewrite their business plans over the next 10 years in accordance with the imperatives of each of the 4Ps. In our experience, the bureaucracies and conservative leaderships of healthcare providers will constitute major barriers to adapting to P4 medicine. The interesting point is that many new companies will emerge during the next 10 years that will be focused on the needs of P4 medicine. Hence there are enormous economic opportunities ahead of us.

P4 medicine will in time turn around the ever escalating costs of healthcare – and indeed bring them down to the point that P4 medicine will be exportable to the developing world (just as the digitization of communications made the cell phone available and affordable both to individuals in the developed nations as well as the developing nations). Hence we can contemplate the previously unthinkable – the possibility of a worldwide “democratization” of healthcare. The cost reductions will come from the revolutions that are being initiated by systems medicine (making blood a window for health and disease; the stratification of disease, therapy by reengineering disease-perturbed networks with drugs, and the metrics for wellness, etc.), the digitization of medicine (hence making data incredibly cheap – and thus bringing costs down) and the advance of exciting areas in contemporary medicine (cancer, stem cells, aging, neurodegeneration, etc.).

As noted above, P4 medicine will lead to a digitalization of medicine – with very broad implications (the creation of patient/consumer-driven social networks, the quantification of self, the information technology for healthcare which will capture the digitalized data of individuals to create a database for the predictive medicine of the future). The quantification of wellness and the demystification of disease will create wealth for the institutions and organizations that are at the leading edge of this paradigm change. For example, we predict that a wellness industry will emerge over the next 10–15 years that will far exceed the healthcare industry – leading to a unique series of potential economic oportunities.

8 How do we bring P4 medicine to patients?

There are general challenges to bringing P4 medicine to patients. First, we must invent the systems strategies, technologies, and analytical tools necessary to implement the P4 medicine vision in practice. Second, P4 medicine poses a host of challenges to society – ethics, privacy, confidentiality, legal, economic, regulatory, national policy, etc. These social challenges represent the greatest barrier to implementation of P4 medicine. Hence there must be integrated efforts for bringing P4 medicine to patients – for each is essential to the vision of P4 medicine.

P4 medicine represents a fundamental paradigm change in healthcare. Paradigm changes are always met with enormous skepticism [22]. We believe the key to convincing skeptical physicians, payers, providers, and indeed the many players in the healthcare systems is the successful completion of pilot projects that demonstrate the revolutionary power of P4 medicine.

P4 medicine is a comprehensive and challenging problem for medicine, the healthcare system and society. It requires a systems-driven, cross-disciplinary, large data-generating and data-analysis, integrative, and milestone-driven effort with visionary leadership. At our institutions we became convinced of the power of national and international strategic partnerships some years ago. These partnerships allow one to select the best scientists and engineers to help solve discrete sub-problems within the P4 context; to choose partners with complementary skills and technologies; to enable completely new approaches to fundraising that is essential for attacking big scientific and medical problems; and to bring together complementary resources (hospital infrastructure), materials (patient samples), and data (patient records).

ISB has fashioned key strategic partnerships for P4 medicine. We have developed a strategic partnership with the Grand Duchy of Luxembourg that fostered the creation of the LCSB at the University of Luxembourg, a partnership focusing on neurodegenerative diseases and Parkinson disease initially, that is being expanded to sustain the development of the EISBM in Lyon in relation with the local hospitals and authorities, academic and industrial partners of the Lyonbiopole competitive cluster.

We have also created the non-profit P4 Medicine Institute (P4MI) with Ohio State Medical School. The objective of P4MI is to help create a network of 5–6 clinical centers and ISB to employ conventional and ISB clinical assays in pilot projects to demonstrate the power of P4 medicine. We are now embarking on pilot projects that include wellness and premature pre-term births. P4MI will also help recruit selected industrial partners to this network. P4MI has a fellows program that will begin writing white papers on some of the key societal challenges to P4 medicine. Similarly, plans are materializing for the formation of a School of Medicine at the University of Luxembourg that will implement systems principles in the training curriculum, and is forming a Personalized Medicine Consortium with regional and international clinical partners.

Ultimately, after successful pilot projects performed by ISB and its partners in a growing worldwide network of systems P4 medicine centers and institutes, we would like to persuade a small nation, state or region to consider adopting a global P4 healthcare system. It would be a unique opportunity to pioneer medicine of the future and play a leadership role in transforming medicine from its current reactive mode to the proactive P4 mode. It goes without saying that any nation that is a leader in the P4 revolution will potentially encounter striking economic opportunities.

Acknowledgments

We would like to acknowledge the support of the Luxembourg Centre for Systems Biomedicine and the University of Luxembourg (LH and RB), the NIH General Medical Sciences Center for Systems Biology GM076547 (LH) and a Department of Defense contract on Liver Toxicity W911SR-09-C-0062 (LH). The formation of the European Institute for Systems Biology & Medicine hosted at Claude Bernard University is supported by the Lyonbiopole competitive cluster and its academic, industrial, and local authority partners, including Grand Lyon, Région Rhône-Alpes, Direction de la Recherche et de la Technologie, and the Finovi Foundation (CA).

Biographies

Dr. Leroy Hood received an MD from John Hopkins and a PhD from Caltech where he was a faculty member for 22 years. In 1992 he founded the cross-disciplinary University of Washington Department of Molecular Biotechnology in Seattle where in 2000 he co-founded the Institute for Systems Biology. Dr. Hood is pioneering the transition from current reactive medicine to a proactive (P4) medicine. He has published >700 peer-reviewed papers and textbooks, holds 32 patents and founded 13 biotechnology companies, including Amgen, Applied Biosystems, Systemix, Darwin, Rosetta, Integrated Diagnostics and the Accelerator. Dr. Hood is a member of the National Academy of Sciences, the American Philosophical Society, the American Association of Arts and Sciences, the Institute of Medicine and the National Academy of Engineering. He has received the 1987 Lasker Award, the 2002 Kyoto Prize and the 2011 Russ Prize and was awarded 17 honorary degrees from various academic institutions worldwide.

Dr. Rudi Balling studied nutrition at the Universities of Bonn, Germany, and Washington State University, USA. After receiving his PhD in Human Nutrition from the University of Bonn in 1985 he held research positions at the Mount Sinai Research Institute in Toronto, Canada and the Max Planck Institutes of Biophysical Chemistry and Immunobiology in Göttingen and Freiburg. In 1993 he became Director of the Institute of Mammalian Genetics at the Helmholtz Centre for Environment and Health in Munich. From 2001 to 2009 he was Scientific Director of the Helmholtz Centre for Infection Research in Braunschweig. He has published >150 papers in leading international journals. In September 2009 he became the founding director of the Luxembourg Centre for Systems Biomedicine (LCSB) at the University of Luxembourg in partnership with Leroy Hood and the ISB in Seattle, dedicated to the development of P4 medicine with an initial focus on Parkinson's disease.

Dr. Charles Auffray graduated in Physiology and Biochemistry (Ecole Normale Supérieure), obtained a PhD in Molecular Immunology (Pierre & Marie Curie Paris University and Pasteur Institute). He was Post-doctoral Fellow and Junior Faculty (Harvard University); Group Leader (Institute of Embryology, Nogent s/Marne); Scientific Director (Généthon, Evry); Head of CNRS Research Unit (Functional Genomics and Systems Biology for Health, Villejuif). In 2010, he founded the European Institute for Systems Biology & Medicine in Lyon. Dr. Charles Auffray develops a systems approach to cancer and the physio-pathology of the immune, neuro-muscular and respiratory systems by integrating functional genomics, mathematical, physical and computational approaches through public-private partnerships and EU-funded projects. He has published >250 original papers and 11 books. He cofounded the Systemoscope International Consortium with Profs Leroy Hood (Seattle Institute for Systems Biology) and Zhu Chen (Shanghai Center for Systems Biomedicine) to support the development of systems (P4) medicine.

Abbreviations

COPD	chronic obstructive pulmonary disease
DEG	differentially expressed genes
iPS	induced pluripotent stem cell

9 References

1. Hood L. Deciphering complexity: A personal view of systems biology and the coming of “Big” science. Genet. Eng. Biotechnol. News. 2011; 31:131.
2. Del Sol A, Balling R, Hood L, Galas D. Diseases as network perturbations. Curr. Opin. Biotechnol. 2010; 21:566–571. [PubMed: 20709523]

3. Hwang D, Lee IY, Yoo H, Gehlenborg N, et al. A systems approach to prion disease. Mol. Syst. Biol. 2009; 5:252. [PubMed: 19308092]
4. Shizhen Q, Zhou Y, Lok A, Tsodikov A, et al. SRM targeted proteomics in search for biomarkers of HCV-induced progression of fibrosis to cirrhosis in HALT-C patients. Proteomics. 2012; 12:1244–1252. [PubMed: 22577025]
5. Turan N, Kalko S, Stincone A, Clarke K, et al. A systems approach identifies molecular networks defining skeletal muscle abnormalities in chronic obstructive pulmonary disease. PLoS Comput. Biol. 2011; 7:e1002129. [PubMed: 21909251]
6. Langen RC, Schols AM, Kelders MC, Wouters EF, Janssen-Heininger YM. Inflammatory cytokines inhibit myogenic differentiation through activation of nuclear factor-kappab. FASEB J. 2001; 15:1169–1180. [PubMed: 11344085]
7. Roach JC, Glusman G, Smit AR, Huff CD, et al. Analysis of genetic inheritance in a family quartet by whole genome sequencing. Science. 2010; 328:636–639. [PubMed: 20220176]
8. Picotti P, Bodenmiller B, Mueller N, Domon B, Aebersold R. Full dynamic range proteome analysis of S. cerevisiae by targeted proteomics. Cell. 2009; 138:795–806. [PubMed: 19664813]
9. Wang J, Ahmad H, Ma C, Shi Q, et al. A self-powered, one-step chip for quantitative and multiplexed detection of proteins from pin-pricks of whole blood. Lab Chip. 2010; 10:3157–3162. [PubMed: 20924527]
10. Millward SW, Henning RK, Kwong GA, Pitram S, et al. Iterative in situ click chemistry assembles a branched capture agent and allosteric inhibitor for Akt1. J. Am. Chem. Soc. 2011; 133:1820–1828.
11. Ostroff RM, Bigbee WL, Franklin W, Gold L, et al. Unlocking biomarker discovery: Large-scale application of aptamer proteomic technology for early detection of lung cancer. PLoS ONE. 2010; 7:e15003. [PubMed: 21170350]
12. Hiller K, Metallo CM, Kelleher JK, Stephanopoulos G. Nontargeted elucidation of metabolic pathways using stable-isotope tracers and mass spectrometry. Anal. Chem. 2010; 82:6621–6628. [PubMed: 20608743]
13. Peng G, Tisch U, Adams O, Hakim M, et al. Diagnosing lung cancer in exhaled breath using gold nanoparticles. Nat. Nanotechnol. 2009; 4:669–673. [PubMed: 19809459]
14. Fens N, Roldaan AC, van der Schee MP, Boksem RJ, et al. External validation of exhaled breath profiling using an electronic nose in the discrimination of asthma with fixed airways obstruction and chronic obstructive pulmonary disease. Clin. Exp. Allergy. 2011; 41:1371–1378. [PubMed: 21732998]
15. Supatto W, Truong TV, Débarre D, Beaurepaire E. Curr. Opin. Genet. Dev. 2011; 21:538–548.
16. Sigrist SJ, Sabatini BL. Optical super-resolution microscopy in neurobiology. Curr. Opin. Neurobiol. 2012; 22:86–93. [PubMed: 22051692]
17. Park IH, Arora N, Huo H, Maherali N, et al. Disease-specific induced pluripotent stem cells. Cell. 2008; 134:877–886. [PubMed: 18691744]
18. Zhu H, Lensch MW, Cahan P, Daley GQ. Investigating monogenic and complex diseases with pluripotent stem cells. Nat. Rev. Genet. 2011; 12:266–275. [PubMed: 21386866]
19. Auffray C, Chen Z, Hood L. Systems medicine: The future of medical genomics and healthcare. Genome Med. 2009; 1:2. [PubMed: 19348689]
20. Hood L, Friend SH. Predictive, personalized, preventive, participatory (P4) cancer medicine. Nat. Rev. Clin. Oncol. 2011; 8:184–187. [PubMed: 21364692]
21. Smarr L. Quantifying your body: A how-to guide from a systems biology perspective. Biotechnol. J. 2012 7. DOI: 10.1002/biot.201100495.
22. Kuhn, T. The Structure of Scientific Revolutions. University of Chicago Press; USA: 1962.