Centre for BioSystems & Genomic Network Medicine
CBS.GenNetMed University of Ioannina

Introduction

The innovative research "Centre for BioSystems and Genomic Network Medicine" (CBS.GenNetMed) joined recently (5/2012) the Network of Research Laboratories at the University of Ioannina. The CBS.GenNetMed aims in innovative biomedical research with integrated genomic analysis of biological samples from patients with cancer and other complex disorders. To assess a genotype-phenotype map, genomic discoveries and clinical data will be analyzed with innovative computational biological approaches and mathematical predictive models. The Centre has a strong patient-oriented strategy to reach personalized medicine through systems science. The future of medicine, i.e.'Clinical Innovation', is now being shaped by research in how to correlate clinical data with genome architecture-based information applying recent network biology and bioinformatics advances aiming in developing innovative therapeutic targets and biomarkers.

«Clinical Innovation»

The term "clinical innovation" [1] was introduced to emphasize the need to choose the most rational research field, from a plethora of available ones, to reach the earliest possible clinical practice.

Revolutionary genome-wide mapping technologies

Innovation is needed to radically improve health care. The innovative high-throughput technologies (HT) and in particular the next generation sequencing (NGS) technologies, in conjunction to microarrays techniques, have revolutionized biomedical research. These modern technologies provide a comprehensive analysis of human genome. The technological advancement and the development of new scientific fields, such as systems computational biology and predictive mathematical models of molecular interactions networks, are dramatically changing biomedical science. In 2012, research efforts have been shifted into how to bring innovative genomic discoveries into clinical practice. These advances in clinical genome and dynamic network biology pave now the way of future network medicine [1-10].

Despite multiple challenges, application of HT-NGS in clinical samples has started [11], aiming to translate genomic data into clinical practice in order to improve the treatment in a variety of diseases including cancer [11-20], diabetes mellitus [21], neurodegenerative diseases such as schizophrenia and autism [22,23] and other complex diseases.

First results - challenges

The first published results of clinical genomics analysis of biological samples [14-16] illustrate that the translation of discoveries from the microscopic fundamental unit of genome (base pair) by using NGS to the patient is much more complicated and difficult than it was initially appreciated [2,3,11].

Clinical genome necessity

As it is known, cancer is a major health problem worldwide. The official statistics of the U.S. (SEER) for 2012 confirm that cancer is the most common cause of death, while World Health Organization (WHO) estimates that by the years the number of people afflicted by cancer and deaths caused by it, will be dramatically increased. Furthermore, an increase will appear in the years to come for diabetes mellitus, Alzheimer's disease and other chronic diseases. These data indicate the slow improvement of traditional biology and clinical medicine.

Without innovative research in human genome structure and function, there will be no impressive improvement of health care [2,3]. Therefore it is necessary to record the enormous number of mutations involved in each disease and each patient, aiming to understand the function of all genes (~21,000 genes/exome), non-coding DNA and the whole genome, in order to conceive cellular behavior and homeostasis in tissues and organs through dynamic signaling pathways and interaction network [1-3,24-27].

Fundamental of Genomic Network Medicine

Changes in the structure and function of the human genome lead to cancer or other complex diseases. The revolutionary technologies (HT-NGS, arrays) provide a unique opportunity to identify all types of mutations. Therefore, the HT-NGS-based explosion in countries (Norway) and universities in USA that target to clinical applications of personalized medicine is justified, despite increased cost [11].

Complex biological systems and dynamic networks

Although the capacity of HT sequencing and arrays-based technologies to detect all classes of mutations (SNPs, indel, CNVs/CNAs, translocations) fast, cheap and reliably, there is still a number of challenges. Current research is expected to overcome most of these problems in order to achieve clinical applications. These problems are related to the extreme heterogeneity of mutations from patient to patient with the same disease and the standard clinico-pathological characteristics [14-16]. On the other hand, the biggest challenge for the 21st century is to understand how these mutations deregulate gene expression and signaling transduction pathways, and in general to acquire deeper insights into changes in the structural and functional architecture of the genome responsible for disease development [1,8]. Understanding the function of biological systems (transcriptome, non-coding RNA including microRNAs,

epigenome) and their elements' interaction networks (transcription factors, histones, DNA-binding proteins) in regulating gene expression, it is extremely difficult and still at an early phase. However, this research is important and necessary in order to raise clinical applications since the deregulation of expression of interacting genes leading to disease has a major impact in pharmaceutical industry for the discovery of network-based next-generation drugs [1-3, 24-27].

Aim of the Centre

The aim of the Centre is to set the fundamentals to obtain cutting edge technology (HT-NGS/arrays) and to develop and translate genomic discoveries and dynamic network biology advances into clinical applications. Thus, CBS.GenNetMed is shaping the background for the future to approach the Genomic Network Medicine at the University of Ioannina. Our highest goal, in collaboration with research centers in leading academic institutions abroad and the private sector (pharmaceutical, biotechnology), is to participate in the development of novel biomarkers and therapeutic targets. This goal will be based on the correlation of genomics and molecular networks data with clinical data, so that using computational and algorithmic models to predict phenotypic outcomes (prediction of disease outcome, and therapeutic response before initiating therapy).

The methodology to achieve the objectives of the Centre is shown in figure 1 [11]. In brief, it involves three main phases: a) collection of biological samples (fresh frozen and FFPE tissue, blood) and clinical data of patients b) application of HT-NGS in these samples, and c) systems biology approaches and predictive network models to correlate genomics with clinical data.

European Union 2020 - Innovation

To overcome these challenges, EU finances new research approaches. On the 2020 Innovation Horizon for Life Science, EU gives emphasis and priority in clinical Personalized Medicine. To achieve this goal, major funding by EU in the next years will be directed into Genomics Medicine and Systems Medicine referred also as Network Medicine. The experience gained by the scientific director of "CBS.GenNetMed" participating as an evaluator of such research programs for 2011 and 2012 in weekly meetings in Brussels (License) and the decision of the University of Ioannina to propose him for the position of EU "Innovation Board Member" for the period 2014-2020, is valuable for the aim of the Centre.

International Partnerships

The complexity and innovative subject of the Centre require cooperation with scientists from different scientific areas embracing apart of traditional Medicine, Biology, Physics, Engineering, Mathematics, the new scientific fields of genomics technology and analysis, systems computational biology, bioinformatics and predictive models.

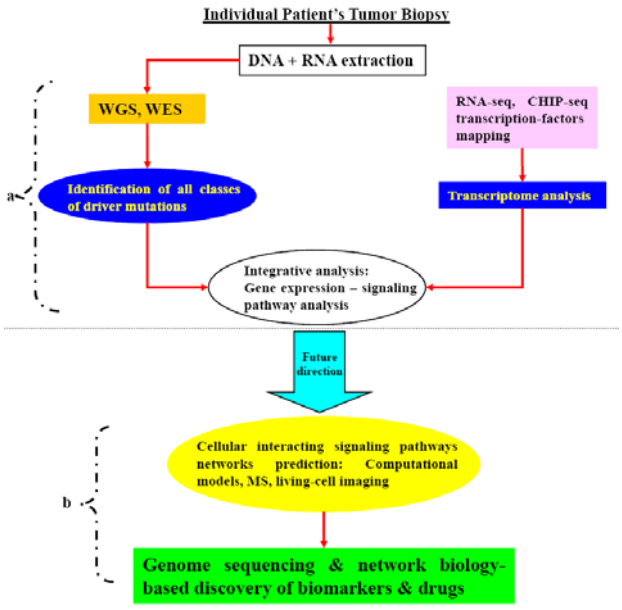

FIG. 1 Current and emerging clinical cancer genome for personalized treatment.
a. Current approach. Sequencing DNA alone or plus RNA or transcriptome mapping by ChIP-seq can identify either causal mutations or differential DNA-binding proteins regions that potentially can be used as predictive biomarkers for selecting efficient drug(s).
b. Future perspective. Mapping of intracellular physical protein connections and DNA-binding proteins and functional (gene) interactions provides a comprehensive picture of signaling transduction interactions networks. This can be a platform for discovering next-generation network-based drugs and biomarkers.
WGS: whole genome sequencing, WES: whole-exome sequencing, RNA-seq: RNA sequencing, ChIP-seq: chromatin immunoprecipitation followed by high-throughput sequencing, MS: mass spectrometry

Modified from Roukos & Ku, Ann Surg Oncol 2012 [11].

Cooperation has already been established with experts in genome-wide mapping technologies and systems biology and Centres:

1. Dr. Chee Seng Ku, Department of Medical Epidemiology and Biostatistics, **Karolinska Institutet, Stockholm, Sweden**. His expertise is in HT-NGS and Genomic Medicine. This close cooperation is represented by a number of distinguished publications in this field in top peer-reviewed journals such as Molecular Psychiatry [11,12,20-23,28] and a relevant book [29].
2. Dr Evangelos Simeonidis, **Luxembourg Centre for Systems Biomedicine - LCSB University of** Luxembourg **and Institute for Systems Biology, Seattle WA, 98109, USA**.
3. Dr. Philippos C. Patsalis, Chief Executive Medical Director, Professor of Molecular Medicine, **Institute of Neurology and Genetics Cyprus** (http://www.cing.ac.cy).
4. Dr. William Cho, Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, China. Expertise in molecular individualized oncology [18].

Management, Strategic Planning and Personnel of Center

The Scientific Committee of the Centre shapes the strategic goals of innovative research direction of the Centre. It creates partnerships with specialized Research Centers, Universities and private sector of innovative biotech companies towards Genomic Network Medicine. In addition, it arranges to find financial resources from participation in EU funded programs and other international partnerships, donations and sponsorships, as well as promotes and directs doctoral thesis. The Scientific Committee cares for the efficient production

of research work. Also it is responsible for the assessment of the Centre based on multiple criteria with emphasis on participation in international research projects and consortiums, influential publications, citations and invited lectures in international meetings.

The Scientific Committee

The CBS.GenNetMed is supervised by a Scientific Committee composed of the Chairman and the members as follows:

1. Dimitrios Roukos, Assoc. Professor of Medicine, Chairman of the Committee and Scientific Director of the Centre.
2. Margaret Tzaphlidou, Professor of Medical Physics, University of Ioannina.
3. Dr. Chee Seng Ku, Karolinska Institutet, Stockholm (HT-NGS).
4. Ioannis Georgiou, Professor of Medical Genetics, Medical School, University of Ioannina.
5. Christos Katsios, Professor of Surgery, University of Ioannina.
6. Dr Evangelos Simeonidis, Luxembourg Centre for Systems Biomedicine and Institute for Systems Biology, Seattle WA, USA
7. Costas Papaloukas, Asst. Professor Department of Biological Applications and Technology, University of Ioannina.

Responsible for the competent operation of the Center's infrastructure is Demosthenes Ziogas, PhD, Medical School, University of Ioannina.

Scientific Advisor and Honorary Member of the Committee

Panagiotis Soukakos, Honorary Professor, University of Ioannina.

Publications on genomic network medicine

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