Action Recommendations to CAS and MPG on Personalized Medicine

Steering Committee of the 5th Exploratory Round Table Conference

Started in 2010, the Exploratory Round Table Conferences (ERTC) is a joint project of the Max Planck Society (MPG) and the Chinese Academy of Sciences (CAS). Hosted by the Shanghai Institute for Advanced Studies under the Shanghai Institutes for Biological Science, it focuses on topics that are only just beginning to emerge in the scientific community. With this initiative MPG and CAS aim to offer a platform for a small circle of internationally leading experts and for scientists from MGP and CAS to become acquainted with new areas of research, discuss them and discover their potential. As a routine, at the end of each conference, action recommendations are given to presidents of the two organizations on which aspects of the topic should be included in their development plans, and how intensively they should be addressed. The following is the action recommendations from the 5th ERTC, which convened in Shanghai from May 14 to 17, 2014 focusing on Personalized Medicine.

The decoding of the human genome sequence and the advent of next-generation sequencing methods and other molecular techniques such as in-depth proteomics and epigenomics have dramatically changed biomedical research. New therapeutic and diagnostic approaches have become available, which however still need to demonstrate their usefulness and superiority in clinical routine. Major potential applications concern optimization of diagnosis, improved prevention and treatment. The refined diagnostic options provided by acquisition of comprehensive molecular data also greatly advance the ability to design individualized treatments for patients. In general, such approaches are termed "personalized medicine".

From the patient's perspective, personalized medicine enables customized individual healthcare raising enormous expectations and hopes. Individual data sets generated from genome, transcriptome, epigenome and metabolome can be used to develop individualized and optimized treatment regimens. Furthermore, real-time assessment of the biological status of current disease processes can be employed to adjust ongoing therapies and alter treatment strategies. So far personalized treatments have not entered the stage of broad clinical use. Present pilot projects are mainly in an early exploratory phase and dedicated personalized treatments based on comprehensive molecular profiling are restricted to a handful of patients. Major efforts seem to be required to improve acceptance and promote clinical implementation of personal medicine. Existing knowledge in the field needs to be critically evaluated, and strategies as well as respective guidelines have to be devised for the implementation of molecular personalized medicine into clinical routines.

The Exploratory Round Table Conference (ERTC) 2014 focused on questions of personalized medicine with the aim to identify key areas being of high priority. Five major themes were evaluated and discussed: 1. Reassessment of Genetic Information for Disease Prediction; 2. Stratification of Health Risk Factors; 3. Stable and Unstable Molecular Memory; 4. Erasing Acquired Health Risks: Treatment Options; and 5. Personalized Cancer Therapy.

Integrative Re-assessment of Large Data Sets

The identification of numerous mutations responsible for the development of monogenic diseases has been extremely successful in the last two decades and new data are constantly added refining the understanding of

genotype-phenotype relations and genetic variations. In contrast, the elucidation of major diseases that are affected by variants of multiple genes is markedly more challenging. Vast datasets have been acquired by the human genome project but genome-wide association studies (GWAS) yielded only limited insights in the pathogenesis of major diseases, although GWAS proved to be successful for the identification of new candidate genes involved in disease processes. The inherent complexity of major diseases, weak penetrance of individual alleles, phenotypic variability and limited understanding of the impact of environmental factors together with limitations of the applied technologies have slowed down progress in predicting, treating and curing diseases of modern societies.

In the past decade, numerous studies have been published using high-throughput sequencing technologies for transcriptome, and proteome analyses accompanied by sophisticated experiments to address regulatory mechanisms of gene expression. Although these technologies and approaches have revolutionized modern biology, several shortcomings are evident. In particular, the development and application of appropriate statistical methods did not seem to keep pace with technological improvements. In consequence, the outcome from many studies was compromised by inadequate data analysis. Several studies would benefit from a critical re-evaluation and re-assessment focusing on improved quality control. Moreover, data analysis might benefit from an integrated approach, incorporating different disciplines, e.g. cancer genomics, large cohort studies and/or GWAS as well as combination of data sets from different ethnic populations living under different environmental and social conditions. Genotypes of different populations in different living conditions need to be analyzed to identify novel pathways and therapeutic targets and evolutionary aspects of disease development need to be considered. Finally, dynamic changes within individual populations, which could be addressed by longitudinal studies, should move into focus. Currently attempts using static, single time point associations seem to have a rather limited ability to mine these data.

The steering committee suggests the following measures for the integrative analysis of large data sets:

1. Integration of data sets from Europe and China: The collaboration between the MPG and CAS should feature the integration of large data sets from Europe and China. Exchange and integration of data will allow the respective groups to verify their own studies and provide opportunities to design future bilateral studies. Different disease entities, e.g. cancer types, show different prevalence in European and Chinese populations. Therefore, combined analysis of data sets derived from Europe and China may potentially help to identify novel loci associated with diseases. Mutual access to data sets should lead to joint projects and collaborative publications.

2. Establishment of a network for data sharing and identification of collaborators/common interests: To foster collaborations, a formal joint network needs to be established enabling sharing of data and expertise. Support should be given to organizers of such a network in order to identify groups with common research interests/goals. A database or website with restricted access should be set up to catalogue ongoing projects, current data collections and groups working in these areas.

3. Promote links to large data collection consortia: Efforts of MPG and CAS should be linked to other consortia acquiring and maintaining large data collections. To increase efficiency and reduce costs bilateral efforts should be strategically complemented using the input from the existing networks/resources. Implementation and integration of quality-controlled large data sets from various institutions with a clear emphasis on MPG-CAS promoted projects should be given high priority.

Assessment of Added Value of Epigenetic Information for Personalized Medicine

GWAS are assumed to provide important information about individual disease risks. The complexity of GWAS, low statistical correlations, input of unknown genetic modifiers, lack of mechanistic interpretation for the majority of genetic variations and variable genotype-phenotype associations call for a paradigm shift and argue for the integration of epigenetic information. The definition of the "epigenome" normally includes the combination of all genome-wide chromatin modifications, direct chemical modification of nucleotides and effects of small non-coding RNAs in a cell type affecting gene expression patterns. Epigenomes are subjected to dynamic changes during development, respond to extrinsic factors and are altered during the progress of diseases. Thus, inclusion of epigenomic information will be of great value for the understanding of major common diseases.

It seems self-evident that epigenetic factors significantly impact disease development. However, the potential of epigenomic analysis for personalized medicine in terms of disease stratification and prediction has not been fully explored yet. In particular, aspects such as the predictive value of epigenetics, disease stratification on the basis of epigenetic changes, specific impact on disease onset and progression as well as the general impact of

epigenetic changes on diseases have not been demonstrated conclusively. Importantly, the role of the epigenome for obtaining mechanistic insights in understanding the disease pathogenesis still remains elusive.

We suggest the following actions to address the above-mentioned issues and to improve the added value of epigenetics in personalized medicine.

1.Establishment of a resource network between CAS and MPG: A resource network should be established by identifying groups working on different aspects of epigenetics and by initiating a joint action program. The network should tackle key questions in epigenetic research, and intensify efforts for understanding the mechanistic role of epigenetic regulations underlying disease pathogenesis, for developing cutting-edge technologies that allow efficient and sensitive detection of epigenetic changes, for assessing the value of epigenetic drugs, for applying the epigenome as a tool for biomarker research in specific disease areas, and for exploring its potency to measure drug-targeting efficacy. This network should meet on a regularly basis, should integrate with national and international consortia and should partner with other European initiatives, focusing on the strategic goal to harness results from epigenetic research to combat major health threats in Europe and Asia.

2. Analysis of tissue-specific epigenomes in longitudinal studies: The contribution of epigenetic variability to disease susceptibility in humans has not been explored fully. Since epigenomes also vary in time and are cell type-specific, different strategies need to be established for the characterization of the epigenome in longitudinal studies using tissues relevant to specific diseases. Groups at MPG and CAS cover a wide-spectrum of diseases (e.g. neuronal, liver, cardiovascular and lung), have extensive understanding of the pathobiology and access to human samples, although it will be difficult to obtain tissue-specific human specimens for longitudinal studies. Networking and sharing of expertise, resources and methodologies would allow for epigenome mapping in normal and disease states and would provide key mechanistic insights into perturbed regulatory pathways. A comprehensive catalogue of epigenetic changes in different cell types at different stages of disease will greatly enhance our understanding of the contributions of epigenetics to disease predisposition and prognosis, and might enable the discovery of novel preventive and treatment strategies. Another important focus could be to investigate cross tissue epigenetic changes and their correlation in health and disease. Such markers may serve as peripheral biomarkers for disease risk and progression.

3.Assessment of the value of epigenetic drugs and the potential of epigenetic marks as predictive pre-disease biomarkers: The knowledge gained from the measures mentioned above will not only help to uncover important disease-associated epigenetic mechanisms, but might also spur the development of novel therapeutics. The therapeutic efficacy of drugs modulating the epigenetic landscape needs to be explored in pre-clinical and clinical studies. In addition, drug-targeting efficacy needs to be evaluated in order to optimize therapeutic success and reduce adverse outcomes. Since certain epigenetic alterations precede disease pathology, the potential of epigenetic changes as predictive biomarkers for pre-disease diagnosis, prognosis and monitoring should be evaluated.

Strengthening Translational Medicine in MPG and CAS

New cutting-edge techniques provide unprecedented insights into disease-relevant biological process but only few molecular findings have been successfully translated into novel therapeutic interventions. This translational gap was extensively discussed throughout the 5th ERTC on Personalized Medicine and identified as a crucial target for further actions. In particular, the proceedings of the conference emphasized the limited integration and interaction between clinicians and clinical as well as basic researchers. Such interactions were assumed to be essential for further progress in the field and were found mandatory for continuous adaptation of research problems to the most pressing clinical needs. It seems unlikely that without integrated collaborative efforts new research findings can be effectively channeled to clinical research and use. The current lack of a conceptual consensus upon translational practices was also highlighted as an impediment for the development of effective translational programs. Current limitations of translational approaches create an enormous challenge, but it was felt that this translational gap could be bridged by taking certain measures in both MPG and CAS.

Specific measures to strengthen translational medicine in MPG and CAS were identified during the conference as follows:

1.Establishments of dedicated translational research groups: Dedicated translational research groups should be identified and recruited both by MPG and CAS concentrating on groups that have a proven track record at the interface of basic and clinical research and share similar research interests. Matching research groups should meet on a regular basis, provide updates and feedback on recent findings, and decide on future research directions. Establishment of these groups would greatly enhance

interactions among scientists from different disciplines and promote the orchestrated research efforts within specific fields. The steering committee of ERTC 2014 was convinced that the establishment of such groups will have a wider impact on the perception of translational medicine in both institutions and will serve as a paradigmatic example of a discipline that has gained widespread public attention.

2. Matching efforts between CAS and MPG: While translational efforts within each institution are essential, coordinated efforts across both institutions will offer additional drive and accelerate translation. The two institutions have partly complementary expertise, resources, and access to different model animals and clinical samples that could be combined to answer a number of specific research problems. The ERTC provided a fertile stage for initial networking, but continuous efforts are required from both institutions to maintain the momentum. The establishment of trans-institutional translational research groups or alternative specific funding for translational research groups will contribute to such an aim.

3. Reach out to medical community: Interactions with the medical community are fundamental for promoting any translational approach since after all, clinicians have to apply translational findings and find practical means to treat patients with innovative therapies. In view of ERTC 2014 interactions between clinicians and basic researchers need to be institutionalized and formalized to guarantee mutual flow of information ensuring that some future research endeavors are tailored to the most pressing clinical needs of a changing society. Spreading novel translational findings beyond the boundaries of the two institutions to the broader medical community could also offer improved options to test novel findings.

In conclusion, closing the translational gap in medical research offers tremendous opportunities to facilitate development of novel therapeutic interventions. The measures described above would strengthen translational medicine in both MPG and CAS, orchestrate efforts across the two institutions, and facilitate the timely translation of research findings into personalized treatments.

● **About the Steering Committee of the 5th ERTC**

On MPG side

　　Chair: Thomas Braun (Max Planck Institute for Heart and Lung Research)

　　Elisabeth Binder, Max Planck Institute of Psychiatry

　　Werner Seeger, Max Planck Institute for Heart and Lung Research

　　Martin Vingron, Max Planck Institute for Molecular Genetics and CAS-MPG Partner Institute for Computational Biology

On CAS side

　　Chair: ZHANG Xu, Vice President of Shanghai Branch, CAS; Institute of Neuroscience, SIBS, CAS

　　DING Jian, Shanghai Institute of Materia Media, CAS

　　JIN Li, School of Life Sciences, Fudan University

　　HE Lin, Bio-X Institutes, Shanghai Jiao Tong University

● **About Previous Sessions of ERTC:**

The first ERTC was launched from 19 to 21 October 2010 focusing on Synthetic Biology. The second took place from 2 to 4 November 2011 on "Quantum Information Science". The third, occurring from 1 to 3 November 2012, covered the topic "Space-Based Research". The fourth conference from 18 to 20 November 2013 dealt with "Electrochemistry – revisited".