Personalized Medicine in Cancer

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Introduction
Cancer is caused by genomic alterations including mutations in oncogenes and tumor suppressor genes. Such genetic alterations have been shown to play critical roles in the formation, progression and metastasis of cancer. Profiling and identifying the complete landscape of genomic changes in individual cancers would be invaluable not only for understanding the basic mechanisms of cancer development and progression, but also in developing personalized cancer treatments.

Technologies
Genomics technologies such as microarray platforms and the latest so-called next-generation sequencing (NGS)¹ are advancing at breakneck speed and the cost is dropping so fast that in the foreseeable future, it will become a routine for every cancer case to be extensively profiled at the genomic level just like radiological or pathological investigations being performed on each case today. Not only will the cancer tissues be profiled but the hosts’ (patients) constitutional genetic blueprints will also be studied². The former will allow us to understand the inherent properties of cancer tissues and how they behave and their response to drugs while the latter will give us an insight into how the patients’ bodies may react to cancer tissues and if they can tolerate cancer drugs, among other things³. Already, we are witnessing the nascent application of these technologies and a deluge of genomic information. Massive data sets of human cancers deeply characterized at multiple-omic platforms (genomic or exome sequences, copy number and single nucleotide polymorphisms, transcriptome) are regularly being published in high profile journals and/or deposited into public domain databases⁴. It has to be emphasized that in order to handle, analyse and interpret such a gargantuan amount of data, one would need a team bio-informatics experts to carry out these tasks which involves the highly specialized use of newly developed analytical tools⁵.

Diagnostics
Deeper characterization and cataloguing of the genomic abnormalities in cancer also provides diagnostic opportunities for cancer detection. Distinct genomic profiles, whether gene expression pattern or mutation
spectrum, have been correlated with distinct histological subtypes or clinical behaviour including its predilection for metastasis and response to treatment. For example, in kidney cancer, more than a dozen subtypes have been described which are characterized by distinct gene expression signatures and mutation spectrum. Molecular diagnosis and sub-classification will therefore more likely contribute to accurate clinical diagnosis and impact subsequent disease management. Furthermore, some of the detected novel genes have also been associated with survival outcomes. Today the challenge in getting genomic profiling done lies in mainly the cost of the studies and logistics or convenience in getting the cancer tissues in the appropriate condition from the operating theatre to the laboratory. However, with continuing improvement in technology, and biospecimen science (knowledge in handling and processing tissues), the latter will become less of a challenge.

**Therapeutics**

Studies of genetic variations in cancer have impacted cancer management. At the somatic level, cancers exhibit substantial molecular heterogeneity leading to diverse clinical outcomes using ‘one-size fits all’ treatment approaches. A paradigm shift has transformed oncology drug development with a new focus on rationally designed targeted therapies deployed in specific molecular subgroups of cancers identified by robust biomarkers. Compelling developments in rational drug development in cancer include Trastuzumab in HER2 amplified breast cancer, Imatinib in c-kit mutated gastrointestinal stromal tumors, Gefitinib in EGFR mutated lung cancers, PARP inhibitors in BRCA mutants, BRAF inhibitors in V600E Melanoma and ALK inhibitors in tumors with ALK fusion genes. This behoves us to identify and characterize other subgroups of cancer with a focus on specific therapeutic opportunities coupled with biomarker assay development for patient enrichment. In addition, studies on genetic polymorphisms in the patients may also provide insights into drug toxicities, response and outcomes with current treatment regimens. Information about germline genotype in relation to drug exposure and/or toxicity are already being used to guide physicians in individualising drug treatments for cancer patients. No doubt harvesting the enormous potential of genomic tools to accomplish tangible clinical benefit requires an appreciation of the natural history of cancer in relation to the opportunities for intervention in the prevention, detection and treatment of cancer.

**Prevention**

Finally, as our understanding of the complexity of oncogenesis improves, knowledge of putative risk loci and novel cancer genes opens new horizons and raises provocative prospects. Candidate polymorphisms of genes involved in carcinogen metabolism, cell cycle control, DNA regulation and repair have been shown to be related to elevated risk in developing particular cancers. Whilst true genetic syndromes are rare, personal genomics may allow individualized assessment of risk of developing specific cancers. Chemoprevention trials in the general population have largely been futile. Understanding individualized susceptibility may allow trials evaluating customised chemoprevention or lifestyle intervention strategies or targeted screening strategies.

**Future is Now**

Very few people would doubt the power of the technologies and their clinical implications. The key question is cost, i.e., if the patients...
can afford it, or if the cost will be covered by medical insurance or healthcare providers. However, we have witnessed the sharp drop in the cost of performing these studies and it is only a matter of time when they will be adopted as part of the routine clinical investigations. To date, Next-Generation Sequencing (NGS), which allows characterizing the whole genomic landscape of every cancer tissue, is already being adopted by some of the world-leading cancer centres to study their cancer patients, albeit on a trial basis. The data and its interpretation has to be shared and discussed with a multi-disciplinary team, including translational scientists, oncologists, and pathologists, to design an action plan that will translate into selecting the most suitable treatment for the patients. No doubt, it is timely for Singapore and other Asian countries to consider starting such programs because it is well-known that Asian cancers exhibit their distinct genetic profiles, compared with those of Caucasian origin – it is only logical to study Asian cancer in Asia. As a pilot feasibility study, for example we can sequence advanced cancer patients for whom conventional treatment has been exhausted and for whom tumor tissues are available for analysis. The aim of the pilot study is the feasibility of employing next generation techniques to identify actionable genetic aberrations leading to rationale enrolment in appropriate clinical trials.

References
About the Authors

Professor Bin Tean Teh obtained his medical degree (1992) from the University of Queensland, Australia and his Ph.D. (1997) from the Karolinska Institute, Sweden. Following postdoctoral work in multiple endocrine neoplasia 1 at Karolinska Institute, Dr Teh joined the Van Andel Research Institute (VARI, USA) as a Senior Scientific Investigator in the Laboratory of Cancer Genetics since January 2000. He is currently a Professor at the Duke-NUS Graduate Medical School, Singapore and serves as the Group Director for Translational Research at SingHealth. He also holds Adjunct Professorships Universities/Institutes in Sweden, USA, and China. He also co-directs the Kidney Cancer Research Program at the Van Andel Research Institute in the USA. Additionally, Dr. Teh has published extensively over 270 publications in high impact scientific journals and also sits on various Editorial Boards such as Lancet Oncology, Cancer Research, International Journal of Oncology, the Journal of Endocrine Genetics, the Journal of Clinical Endocrinology and Metabolism, Clinical Genitourinary Cancer, and the American Journal of Translational Research.

Dr. Patrick Tan holds a joint appointment as an Associate Professor at the Duke-NUS Graduate Medical School and a Group Leader at the Genome Institute of Singapore. He is a Program Leader in Genomic Oncology at the Cancer Science Institute of Singapore, National University of Singapore and a Research Associate Professor in the Institute of Genome Sciences and Policy at Duke University, USA. His research focuses on the application of genomics to cancer and infectious disease. He received his B.A. (summa cum laude) from Harvard University and MD PhD degree from Stanford University, where he received the Charles Yanofsky prize for Most Outstanding Graduate Thesis in Physics, Biology or Chemistry. Locally, he has received the President’s Scholarship, Loke Cheng Kim foundation scholarship, Young Scientist Award (A-STAR), Singapore Youth Award (twice), and the Singhealth Investigator Excellence Award.

He is an editorial board member of the journals BMC Medical Genomics, PLOS One, and SGH Proceedings. He is a member of the Local Review Panel (LRP) to the National Medical Research Council and Biomedical Research Council, a member of Specialists Accreditation Board, Translational Medicine, and Bioethics Advisory Committee (BAC), a national body that provides advice to the Singapore government on ethical issues related to biomedical research.

Dr. Iain Tan is an Associate Consultant Medical Oncologist at National Cancer Centre Singapore, specializing in Gastrointestinal and Hepatobiliary cancers. His interests are focused on luminal gastrointestinal cancers and how next generation genomics can be integrated into patient care. He is concurrently pursuing a PhD in cancer genomics in Dr. Patrick Tan’s laboratory at Duke-NUS under a National Research Foundation Scholarship.