Genome Medicine

MEETING REPORT

The challenges and hopes of personalized cancer medicine

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Abstract

A report on the Genome Institute of Singapore and the Fritz Bender Stiftung joint meeting on 'Personalized Cancer Medicine: Towards Individualized Cancer Treatments', Singapore, 21-23 February 2011.

The Fritz Bender Stiflung and the Genome Institute of Singapore hosted a meeting at the Biopolis to address fundamental questions of how molecular genetics could advance cancer therapies. Participating in the meeting were basic biologists and molecular geneticists who are tackling the changes accompanying cancer, as well as those immersed in new drug development, including specialists in trial design to match patients to the correct therapy. Despite the vast sums of resources devoted to cancer therapy, there remain entire classes of cancers for which present therapies offer little hope, and other classes that are chronically overtreated, with associated morbidity, because we simply cannot distinguish which patients need the treatments. Personalized medicine for cancer therapy is thus not a program of profligate drug development to counter the hundreds of changes known to occur in cancer, but rather tailoring those treatments we have to the right patients and ensuring that new therapies developed have the greatest shot at filling the major gaps in therapies that exist for nearly all cases of pancreatic cancer, gastric and esophageal adenocarcinoma, and liver cancer and glioblastoma, to name a few.

Drivers versus back-seat drivers of cancer

Edison Liu (Genome Institute of Singapore, Singapore) introduced Enrico Mihich (Dana Farber Cancer Institute, USA) as being a ray of hope because he pioneered the original chemotherapies that have brought real progress in the treatment of a host of cancers. Mihich encouraged the patience and perseverance that have led to the eradication of a number of chemotherapy-susceptible cancers in a steady process of clinical trials and histological stratifications, and suggested that the available tools and drug candidates should greatly accelerate the process he formulated so successfully. Liu discussed cancer as an evolutionary process involving point mutations, genomic rearrangements and epigenetic changes that ultimately conspired to make it less obvious as to what were 'driver' mutations versus 'passenger' mutations; he suggested that the latter might be better described as 'backseat driver' mutations influencing the drivers. He focused on the rapidly accumulating information on genomic rearrangements derived from pair-end-tag (PET) technologies, presenting evidence from MCF-7 breast cancer and breast cancer tumor genomes for fusion genes, of which nearly 50% yielded transcribed fusion proteins, and he discussed what these elements are telling us about cancers in general. Yijun Ruan (Genome Institute of Singapore, Singapore) further discussed PET technologies for rapidly assessing sequence variation in the genome and its application to gastric cancers. Early results indicate that most inversions, deletions and insertions are germline in origin, whereas cancers display tandem duplications, unpaired inversions, interchromosomal translocations and complex rearrangements. Amplifications in general are in the form of large tandem duplications by mitotic crossovers. In general, he has found that, from approximately 2,000 sequence variations introduced into the cancer genome, only 12 of these appear to be recurrent in the limited set of gastric cancers he has tested.

Stratifying drugs and patients

There were also several interesting talks discussing the challenges in oncology drug development. These were given by Richard Gaynor (Eli Lilly, USA), Eileen Dolan (University of Chicago, USA), Elizabeth Eisenhauer (Queen's University, Canada) and Sun Young Rha (Yonsei University, Korea). Gaynor highlighted that only 10% of drugs taken to clinical trial make it in the commercial market, suggesting that more information about tumor

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biology, drug action, pre-clinical models and patient selection is required. Somehow all of this information needs marshaling to stratify patients to match with drugs and drug combinations. Dolan has developed whole-genome approaches to identifying gene sets that affect sensitivity to chemotherapeutics in different ethnic populations, and has attributed these to co-regulated transcriptional blocks. Eisenhauer described the challenges of clinical trials in the face of so many new targeted therapies, such as those targeting cell surface receptors and intracellular signaling pathways, including how to define efficacy, when to identify biomarkers, and how to choose which therapeutic direction to support.

From cancer cell biology to the clinic

In addition, several speakers discussed their experience of translating the key findings in basic biology to clinical strategies. Carl Novina (Dana Farber Cancer Institute, USA) and Frank Slack (Yale University, USA) presented animated analyses of the role of microRNAs and their targets in cancer, including SNPs in the oncogene *KRAS* that disrupt binding sites of microRNA Let7 in patients with particular cancers. Sir David Lane (A*STAR Institute of Medical Biology, Singapore) spoke on emerging strategies focused on the common defects in the p53 pathway in cancer cells, with novel strategies to target mutant p53 but spare wild-type p53 in order to protect normal cells from therapy. Stephen Baylin (The Johns Hopkins University School of Medicine, USA) described a new understanding of how cancer cells assume epigenetic marks of stem cells, and how this knowledge is being funneled into clinical trials of drugs targeting epigenetic markers. Quang Yu (Genome Institute of Singapore, Singapore) reported that epigenetic silencing of a subunit of PP2A, common in most colorectal cancers, leads to resistance to the mammalian target of rapamycin (mTOR) inhibitor rapamycin, and that this resistance can be restored by PDK1 (pyruvate dehydrogenase kinase isozyme 1) inhibition, but not phosphatidylinositol 3-kinase pathway inhibition. Wa Xian (A*STAR Institute of Medical Biology, Singapore) and Frank McKeon (Genome Institute of Singapore, Singapore) contributed to a talk describing work to identify the origin of Barrett's esophagus using a mouse model, and how this finding can influence the diagnosis and treatment of a lethal cancer, esophageal adenocarcinoma.

Asian-specific strategies

Finally, the influence of the Asian genome in diseases was reported by Yixin Zeng (Sun Yat-Sen University Cancer Center, China) and Sin Tiong Ong (Duke-National University of Singapore Graduate Medical School, Singapore). Zeng discussed susceptibility to nasopharangeal carcinoma, which is highest in the Gaungxi province of southern China. Genome-wide association studies have clearly linked this susceptibility to HLA loci as well as additional regions on four other chromosomes, and Zeng discussed how these might interact with Epstein-Barr virus and how mechanistic studies might lead to new therapeutics to suppress these cancers. Ong presented an intriguing study of why Gleevec and related tyrosine kinase inhibitors (TKIs) are less effective in Asians with chronic myelogenous leukemia. He showed very recent data on particular structural variations in the genomes of patients from East Asia. These variations have been found to be tightly linked to resistance to TKIs and are present in 13% to 18% of the population of East Asia, and they clearly implicate defects in apoptotic mechanisms underlying resistance. Consideration of these variations is precisely the goal of personalized medicine, and Ong suggested possible therapeutic approaches to enhance TKI function in this population.

The need for better patient stratification

Kurt Zaenker summed up the meeting by reminding us of Enrico Mihich's description of the early and darker days of chemotherapy and how those drugs, as non-specific as they are, were molded over decades into highly effective therapies for a wide range of cancers. The next phase, he noted, would require a more in-depth understanding of cancers at the molecular level made possible by remarkable advances in cell and genetic technologies. This information should allow us to stratify cancers by molecular markers, assist in the identification of new drug targets, and provide the patient characteristics and biomarkers to ensure that effective new therapies achieve approval through the use of best-matched trials. So, why is there so much effort to get more new, expensive drugs into cancer treatment that might only marginally extend life (often measured in months)? Zaenker went back to Mihich's earlier experience with chemotherapeutics that showed that few cancers could be met head on with single agents. As more new drugs become approved, greater numbers of combinatorial trials and treatments will begin to address the remarkable genetic diversity apparent in the genomes of cells that comprise these cancers.

Abbreviations

HLA, human leukocyte antigen; PET, pair-end tagging; SNP, single-nucleotide polymorphism; TKI, tyrosine kinase inhibitor.

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