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Towards individualized cancer therapy: Challenges and prospects

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ABSTRACT

At the 17th International Symposium in the annual series of prestigious meetings organized by the Fritz Bender Foundation, 07–09 November 2013, researchers, clinicians and students gathered to discuss and exchange knowledge on individualized cancer therapies. Co-organized and hosted by the Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, the sessions covered genetic profiling of patients, tumor characterization, tumor–host relationships and therapeutic targets, with talks from many international experts in the field. The presentations summarized in this report illustrate the current status of our knowledge and the future directions for cancer research in these broad topic areas.

The 17th Fritz-Bender-Foundation International Symposium was held at the Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain in November 2013 and was chaired by Josep Tabernero of the VHIO, Enrico Mihich of Dana-Farber Cancer Institute, USA and Kurt S. Zaenker of the University of Witten/Herdecke, Germany. The theme this year was Progress towards individualized cancer treatments, the ultimate goal of which is to be able to analyze a patient's tumor for genetic abnormalities, prescribe a drug (or combination of drugs) targeted to those abnormalities and track the response of the tumor using molecular markers. At the moment this paradigm only applies to small numbers of patients – such as patients with chronic myeloid leukemia that expresses the *BCR-ABL* fusion gene, who can be selected for treatment with imatinib and then their *BCR-ABL* status analyzed to

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monitor disease status. Despite huge progress in genomic profiling of cancers in recent years and the development of ever more powerful data-mining techniques, there are considerable challenges faced by researchers striving to realize the goal of individualized cancer treatment for more cancer types. "In an age in which we are deluged with data, the steps needed to convert data to knowledge take considerable time, money and resources; but what we need to individualize cancer therapies is wisdom, and this will be the longest and deepest step", said Geoff Wahl of the Salk Institute, USA, who gave the Keynote Address on the first day of the symposium.

Geoff Wahl.

Wahl expanded on the challenges involved, emphasizing that identifying the mutations that drive a specific tumor type at each stage of its progression will be essential to picking the right targets against which to develop new drugs. While interpatient heterogeneity is a big challenge, intratumoral heterogeneity may be the most daunting, as this can foster tumor evolution and adaptation, and hinder individualized medicine strategies that depend on results from single tumor-biopsy samples. This not only applies to the tumor at diagnosis but during its progression and its response to drugs, with acquired, adaptive and architectural resistance all making tumors a moving target. The remarkable heterogeneity and variability embedded in cancer cells is further complicated by the cell types that make up the supportive and interactive stroma of the tumor microenvironment, whose diversity in form, regulation, function, and abundance may prove to rival that of the cancer cells themselves.

There were too many excellent presentations at this symposium to cover in this report, but those summarized here illustrate the current status of our knowledge and the future directions for cancer research in the broad topic areas of genetic profiling, tumor characterization, tumor–host relationships and therapeutic targets.

1. Improving clinical management using genetic profiling

Breast cancer is a good example of how classification by gene expression, in addition to classical histological subtyping, family history and age, can make a difference to patients. Gene signatures can be used on single patient samples to categorize breast cancers as luminal A, luminal B, HER2 enriched, claudin-low or basal-like, to inform treatment choice and predict risk of recurrence. Several talks in this first session focused on further understanding and improving classification of breast cancers.

Recently, the Wahl lab has found that the gene signature of mouse fetal mammary stem cells is significantly enriched for genes characteristic of basal-like triple-negative breast cancer (TNBC), a tumor type that lacks estrogen receptors and progesterone receptors and does not have amplification of the *HER2* gene. This breast cancer type is particularly hard to treat as the targets of currently available drugs are missing. By investigating the mouse fetal mammary stem cells at the single cell level, Wahl and colleagues have found that only basal cytokeratin positive cells that express the transcription factor SOX10 can form mammary outgrowths when injected into fat pads of mice, and that these cells have bilineage potential (Spike et al., 2012). Significantly, they also found that many of the fetal mammary stem cell growth regulatory pathways seem to be enriched in patients with aggressive and chemoresistant basal-like breast cancer and TNBC. These findings might open up novel avenues for targeting strategies.

Looking for better ways to classify single patient samples at the genomic level, particularly in breast cancer is the goal of Hege Russnes of Oslo University Hospital, Norway. Russnes and colleagues have generated new platform-independent algorithms to analyze patient samples for patterns of genomic architecture distortions – complex chromosomal events that are associated with worse prognosis (Russnes et al., 2010). Rusness explained that these data augment the prognostic information of different subtypes of breast cancer and added that including other levels of analysis, such as copy number alterations and pathway activity in cancer cells and the surrounding stroma, will also be necessary.

Marco Pierotti of Istituto Nazionale Tumori, Italy continued the focus on breast cancer to talk about women with an inherited susceptibility for the disease. Many genetic loci are known to contribute to familial risk, including high-risk genes, such as *BRCA1* and *BRCA2* that are responsible for about 20% of familial breast cancer, moderate-risk genes, such as *ATM* and *CHEK2*, and lower risk alleles that are common in the general population. At the moment these low-penetrance alleles are seen as having no clinical relevance, but as only about 30–40% of familial breast cancer can be attributed to the impact of known genetic factors, the remaining cases must be due to variants of unknown significance or low/moderate risk genes yet to be identified. Pierotti's lab is currently searching for modifiers of BRCA1/2 in a genome-wide association study. The goal is to provide more accurate predicted risks for carriers of mutations that have been associated with increased breast cancer risk (Couch et al., 2013; Michailidou et al., 2013), which would be an important step forward in the clinical management of BRCA1 carriers.

Carlos Caldas of the Cancer Research UK Cambridge Institute, UK, began his presentation by saying "it is time to move from the expression-based intrinsic subtypes of breast cancer, to a reclassification of breast cancer into ten different diseases with distinct genomic drivers". He related how his group conducted an integrated analysis of copy number aberrations and gene expression in 2000 primary breast tumors with long-