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News and views

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 Key-note 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). Russnes 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-

term follow-up and found 10 novel subgroups with distinct clinical outcomes (Curtis et al., 2012). These include a high-risk, estrogen-receptor-positive 11q13/14 cis-acting subgroup and a favorable prognosis subgroup devoid of copy number aberrations. Preliminary work indicates that these subgroups are stable before and after neoadjuvant therapy.

The next presentation turned from focusing on the scientific challenges to precision cancer medicine to the operational barriers, which, Barrett Rollins of Dana-Farber Cancer Institute, USA, said, are also profound. He outlined an ambitious undertaking at his institute, launched 2 years ago, to obtain genomic information on all patients who come to three hospitals in Boston for cancer-related care – that is some 16,000 new patients every year. This approach, called Profile, contrasts with the common clinical strategy of using genetic tests only in well-defined patient populations. One of the advantages of the Profile project is that it does not depend on any one technology. In fact, they have already upgraded the sequencing technology platform used at the outset to massive parallel sequencing using Illumina technology, enabling them to identify many more mutations per sample. The broad, panel-based testing for somatic alterations is performed on all specimens collected during routine clinical care and results that can be translated into clinical actions are returned to the ordering providers. Some actionable findings have already come out of the project. “In one case” related Rollins, “a patient received chemotherapy for a tumor diagnosed as atypical carcinoid on the basis of expert histopathology, but his tumor grew through his therapy. When this new growth was resected it was automatically genotyped as part of Profile. We found a distinctive genetic rearrangement that is characteristic of Ewings sarcoma, so he was switched from palliative treatment to a potentially curative treatment for that disease.”

2. Enabling more accurate tumor characterization

The increasing use of patient-derived xenograft (PDX) models, which maintain the histology, mutational profile and heterogeneity of the patient’s tumor, is facilitating more accurate characterization of tumors. Joan Seoane of the host institute, VHIO, began this session by describing ongoing work in his lab to analyze intratumoral heterogeneity using PDX mouse models of brain tumors. His lab is investigating ways to predict response to inhibitors of the transforming growth factor beta (TGF β) pathway in glioblastoma, as responses to a small molecule inhibitor of TGF β receptor, LY2157299, in the phase I setting have been varied. They found that TGF β transcription activity is regulated by a protein deubiquitinating enzyme called USP15 and that patients with USP15 amplification have poor prognosis (Eichhorn et al., 2012). In PDX models downregulation or inhibition of USP15 decreases TGF β activity, thereby decreasing the oncogenic capacity of patient-derived glioma-initiating cells. Seoane’s lab is now investigating whether heterogeneous expression of transcription factors regulated by TGF β influences the response to TGF receptor inhibitor treatment.

Another talk from a researcher at the VHIO, Yasir Ibrahim, also focused on the use of PDX models, this time to elucidate the role of the phosphoinositide 3-kinase (PI3K) pathway, which

is frequently altered in cancer. He has found that repressing this pathway in TNBC that doesn’t have BRCA1 mutations impairs DNA homologous recombination and thereby sensitizes tumors to poly ADP ribose polymerase (PARP) inhibition (Ibrahim et al., 2012). This approach is now in a phase I trial and is a promising option for these hard to treat breast cancers.

Epigenetic profiling is another aspect of tumor characterization that is starting to provide clinical value in diagnosis, prognosis, and prediction of response to therapy in cancer. Manel Esteller of the Bellvitge Biomedical Research Institute (IDIBELL), Spain, began his talk by reminding us that some DNA methylation markers are already in use in the clinic, such as the methylation of the O⁶-methylguanine DNA methyltransferase that predicts response of glioma to the drug temozolomide. Esteller explained that DNA methylation profiling could also be useful in diagnosing cancers of unknown primary, because the DNA methylation signature is like a fingerprint for each cancer type. In his lab they have found that colon cancers that are sensitive or resistant to oxaliplatin do not have differences in mutation patterns but do have a difference in DNA methylation of a BRCA1 interacting gene (Moutinho et al., 2013). This study illustrates the potential of epigenetic profiling, because, if confirmed to be associated with patient survival in other cohorts, it could be used as predictor of response.

3. Exploiting tumor–host interactions for anticancer therapy

Olivera Finn.

More accurate classification of tumors based on genetic signatures and other characteristics is only one aspect that needs to be considered when tackling cancer in a patient. Olivera Finn of University of Pittsburgh School of Medicine, USA, began the session on tumor–host relationships by saying “there has never been a better time to be a tumor immunologist, now that the view of cancer is less tumor cell centric and the role of avoiding immune destruction is seen to be one of the main hallmarks of cancer”. Finn described her research into the abnormal self antigen, hyperglycosylated MUC1, which is found in several cancer types and stimulates cytotoxic T cells. Although a synthetic version of MUC1 entered phase I trials in 1993, immune responses have been poor. Now, she is using a push–pull approach to boost vaccine induced T-cell immunity and overcome tumor escape. This involves optimizing the immunogenicity of epitopes and improving

binding affinity to major histocompatibility complex (MHC) molecules, using cytokines and costimulatory molecules to push the response in the right direction, and blocking regulatory cells and molecules to overcome tumor immunosuppressive mechanisms and pull the response along. Another factor that can improve effectiveness of cancer vaccines is to give them at a much earlier stage of malignancy, when the highly immunosuppressive effects of both the tumor and standard therapy have not taken hold. Finn and colleagues have shown that a MUC1 vaccine was highly immunogenic in patients with advanced colonic adenomas and elicited long-term immune memory, without significant toxicity. The patients who had a poor immune response to this vaccine had high levels of circulating myeloid-derived suppressor cells pre-vaccination; these cells have an inhibitory effect on antitumor immune responses. These findings suggest that a preventive vaccine should be given at an even earlier premalignant stage (Kimura et al., 2013). A randomized phase II trial of a MUC1 prophylactic vaccine in patients with adenomas is now in progress.

Another aspect of the immune system that Paola Allavena, of the Clinical and Research Institute Humanitas, Italy is studying is tumor-associated macrophages as a therapeutic target in cancer. These macrophages are involved in cancer-promoting inflammation and suppression of T-cell anti-tumor response. Allavena has found that a key component of the antitumor activity of a recently approved antitumor DNA-binding agent called trabectedin is to selectively kill myeloid cells, particularly tumor-associated macrophages, by caspase-8-dependent apoptosis (Germano et al., 2013). It has been noted in clinical trials that while some patients have the classic tumor response to treatment with trabectedin, others have a delayed response, and Allavena thinks this is due to the impact of the drug on the tumor microenvironment and host cells. These findings provide strong proof-of-concept for targeting macrophages in patients.

The role of MHC antigens, whose job it is to present antigens to cytotoxic T cells, in tumor immune escape is another vital consideration when developing immunotherapies. Federico Garrido of Virgen de las Nieves University Hospital, Spain, explained in his presentation how tumor cells have often lost MHC class I expression, which partly accounts for the lack of success of immunotherapy. He proposed that in some tumors MHC class I alteration is reversible by cytokines (what he calls a 'soft lesion'), which means that MHC class I will be upregulated by immunotherapy, the T cell mediated response will increase and the tumor will regress. However, if the molecular defect in MHC class I is structural (a 'hard lesion'), such as loss of the MHC locus or mutation in $\beta 2$ microglobulin, MHC class I expression will remain low, tumor cells will be able to escape immune recognition and cancer immunotherapy will be ineffective. Another factor to consider is that immunotherapy can actually promote immunoselection of tumor cells with irreversible MHC class I alterations. Garrido gave an example of a patient with metastatic melanoma in whom only one lesion in six regressed with immunotherapy; they found that this lesion expressed MHC class I, while the other five did not (Carretero et al., 2012). Garrido is now working on a $\beta 2$ -microglobulin gene therapy approach to restore MHC class I expression in tumor cells.

Joaquin Arribas of the VHIO wrapped up this session with a talk on the heterogeneity of HER2 receptor overexpression that occurs in about 20% of breast cancers and an associated secretory phenotype that creates a microenvironment that might favor tumor progression. Arribas and his team have found that patients with constitutively active truncated HER2 fragments, collectively known as p95HER2, have a worse outcome on the HER2 inhibitor trastuzumab than those without this form of HER2 (Morancho et al., 2013). p95HER2 induces premature senescence with an associated secretory phenotype composed of several growth factors, cytokines and proteases (Angelini et al., 2013). They are now investigating the role of this senescent phenotype in tumor progression in PDX models and are also looking for combinations of inhibitors that will be effective in tumors expressing p95HER2.

4. Identifying therapeutic targets, developing effective drugs and overcoming resistance

For the last session of the symposium, the presentations focused in on the huge task of not only finding therapeutic targets, but also developing effective drugs to those targets and tackling drug resistance.

Joe Gray and Antoni Ribas.

Developing strategies to identify therapeutically targetable molecular features of tumors is the goal of Joe W. Gray, of Oregon Health and Science University, USA, who is using state-of-the-art measurement technologies to facilitate this. His lab uses high throughput omic analysis of cancer cell lines to identify targetable regulatory networks and then employs multiscale imaging to elucidate the 3D architecture of tissues, cells and proteins as well as the functions of the networks in tumorigenesis and progression. Gray's team also uses image analysis to assess the responses of cancer cell lines to over 100 different therapies by looking at the effect on 40+ molecular markers of the tumor and microenvironment. As different drug combinations are applied, Gray has seen evidence of steering between subpopulations of cells in various differentiation states, which should be borne in mind when treating heterogeneous tumors with multiple therapies.

The complex process of cancer small molecule drug discovery, from identifying and validating a potential therapeutic target that has a biomarker of activity, through target

validation, small molecule fragment generation and chemical optimization, to the clinic, is the focus of Michelle Garrett's team at the Institute of Cancer Research, UK. The example Garrett gave of this process was starting with AKT as a drug target, as deregulated PI3K pathway signaling through kinases such as AKT is a key driver of multiple cancers. They tested about 200 small molecule fragments and obtained two orally bioactive AKT competitive inhibitor lead candidates, one of which is in phase I/II trials for solid tumors. PIK3CA and AKT mutations are hypothesized to be predictive of response, and three patients with mutations in these molecules have had tumor responses so far. In addition, the pharmacokinetic and pharmacodynamic profile of the drug in patients is consistent with its profile in preclinical models (Yap et al., 2012). Garrett's team are also already thinking about potential drug resistance mechanisms and have observed that cancer cell lines resistant to AKT inhibitors are sensitive to inhibitors of the insulin-like growth factor-1 receptor.

Finding better ways to treat cancer is not always about developing new drugs, it can be about applying old agents in different ways. Peter A. Jones of the University of Southern California Norris Cancer Center, USA discovered more than 25 years ago that 5-aza-cytidine acts as a powerful DNA methylation inhibitor, and it is now the standard treatment for myelodysplastic syndromes. Demethylation of DNA by these drugs results in altered gene expression, leading to decreased tumor growth, as well as increased chemosensitivity and immunogenicity. Jones hopes that low doses of these drugs can soon be used to treat solid tumors, perhaps in combination with chemotherapy. There is concern that tumor promoting genes will be reactivated following inhibition of DNA methylation, but Jones has found that the specificity of the drugs lies not in the genes that become demethylated but in the kinetics of remethylation after drug treatment. Methylation of gene bodies – a largely ignored phenomenon that causes the gene to be expressed – occurs more rapidly than remethylation of promoters, and Jones and his team is working to further understand this process.

Although the RAF inhibitors, vemurafenib and dabrafenib, have transformed responses in BRAF-driven melanoma, resistance often develops quickly. Levi Garraway, of Dana-Farber Cancer Institute, Boston, USA, talked about how his work on genome sequencing has provided insights into this drug resistance and of the hope of overcoming it.

Levi Garraway.

Garraway's lab has also unexpectedly found that highly recurrent somatic mutations occur in regulatory regions of the genome of melanoma cells, and, specifically, that 70% of melanomas have mutations in the promoter of the telomerase reverse transcriptase (TERT) gene (Huang et al., 2013). These mutations increase the transcriptional activity of TERT, leading to prevention of telomere shortening, which is advantageous for tumor cells. In another study from Garraway's lab, analysis of paired pre- and post-treatment samples from patients revealed that mutations in MEK1/2 led to drug resistance (Van Allen et al., 2013) and that there is heterogeneity of resistance within a single tumor site. Finally, Garraway described a large-scale gain-of-function screen that delineated a novel resistance pathway to RAF–MEK–ERK inhibition, involving a cyclic-AMP-dependent melanocytic signaling network in melanoma (Johannessen et al., 2013). Although there is still much to learn about signaling networks that mediate individual resistance mechanisms, targeting common downstream effectors of such pathways might help overcome resistance.

Antoni Ribas of the University of California Los Angeles, USA also talked about ways of overcoming resistance to vemurafenib and dabrafenib. It is thought there are two main phases of resistance to RAF inhibitors – an early adaptive rebound survival signaling resistance phase, due to network crosstalk, and a later acquired expansion of tumor subclones with increased fitness, due to selective mutations in, for example, N-RAS or K-RAS, reactivation of the MAPK pathway or amplification of BRAF. Combination with immunotherapy, such as the anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody ipilimumab, which is also approved for first-line use in metastatic melanoma, may improve the durability of responses. A phase I trial of ipilimumab with vemurafenib conducted by Ribas and colleagues showed promising efficacy in patients with BRAF-driven metastatic melanoma but had to be stopped due to hepatotoxicity (Ribas et al., 2013). This experience highlights the need for carefully conducted trials of new combination therapies, even when both agents have regulatory approval and have distinct mechanisms of action.

Finding suitable therapeutic targets and developing targeted inhibitors is not a linear but a cyclical process, as observations in the clinic can feed back into research. For instance, clinical experience increasingly suggests that molecular prescreening and biomarker enrichment strategies in phase I trials with targeted therapies will improve the outcomes of patients with cancer. Josep Tabernero of the VHIO explained that as part of the VHIO personalized oncology program, tumors from patients with advanced chemorefractory colorectal cancer were analyzed for specific aberrations (for instance, mutations in KRAS, BRAF and PIK3CA, as well as expression levels of PTEN and pMET) (Dienstmann et al., 2012). Patients were then offered phase I trials with matched targeted agents directed at the identified anomalies. However, disappointingly, they found that matching chemorefractory patients with colorectal cancer with targeted agents in the phase I setting using the currently available molecular profiles did not confer a significant clinical benefit. Tabernero explained that despite

The auditorium at the VHIO.

significant progress in elucidating genomic signatures of colorectal cancer (such as Roepman et al., 2013) there is no clear picture of molecular subtypes of colorectal cancer. Tabernero's group is part of an ongoing collaborative project of unsupervised analysis of all the published signatures to derive a molecular classification of colorectal cancer that can be utilized in the clinical arena.

5. Conclusions

Overall, the topics discussed and debated during this symposium show that this is a time of great promise and expectation for the application of knowledge about mechanisms underlying cancer towards more effective management of individual patients with any tumor type. As Julio Celis of the Danish Cancer Society Research Center, Denmark and Chair of the European Cancer Organisation Policy Committee made clear in his presentation, having a unified vision and clear strategy for how to translate research discoveries into concrete benefit for patients would be of enormous benefit. Celis described that recently a political agreement has been reached in Europe on the need for a comprehensive and long-term scientific strategy to accelerate research and facilitate innovations, with the establishment of a Scientific Panel for Health for the next European Union framework program for research funding, Horizon 2020. "A global focus on cancer policy and collaboration across basic, translational and clinical research, involving all the relevant stakeholders, will be needed to make a major impact on this devastating disease", suggested Celis.

Big themes ran through this meeting, including understanding and tackling intratumoral heterogeneity, dealing with huge datasets and utilizing emerging powerful technologies, integrating immunotherapy and targeted therapy to hit both the microenvironment and epithelial cancer cells, and honing the drug development process with integration of biomarkers and ways to overcome resistance. If the enthusiastic response to the talk on choosing a career in cancer research by Gerard Evan of the University of Cambridge, UK, is anything to go by, we have a very keen and intellectually stimulated generation of young researchers gearing up to take on all these challenges.

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