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Molecular Medicine Tri-Conference 2010

Shaping Future Medicine

Anne Bardsley-Elliot

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Cambridge Healthtech Institute's 17th International Molecular Medicine Tri-Conference convened February 3–5, 2010, at San Francisco's Moscone North Convention Center, welcoming over 2700 attendees from 38 countries. Along with regular delegates, the 1223 participating companies, 130 exhibitors, and 44 sponsors engaged in the recurring Tri-Conference theme of 'Shaping Future Medicine.'

Medicine: Personalized

The conference again had a strong focus on personalized medicine, in all its multiple forms. Keynote speaker *John Crowley*, CEO of Amicus Therapeutics, Inc., captivated the audience with his truly personal story of social entrepreneurship in drug research, inspired by the 1998 diagnosis of glycogen storage disease type II (Pompe disease) – a rare and often fatal genetic neuromuscular disorder – in two of his infant children. Historically, drug companies have lacked the financial incentive to develop treatments for such orphan diseases. So Crowley, driven by motivation to help his own children and others affected by rare diseases, left his position at Bristol-Myers Squibb to become founding President and CEO of the startup biotech company Novazyme, and went on to raise over $US27 million in order to speed development of an enzyme replacement therapy, subsequently aided by the acquisition of Novazyme by Genzyme. Under orphan drug designation, Genzyme gained US FDA approval for alglucosidase alfa (Myozyme®) in 2006. Crowley's children participated in clinical trials of the drug, and he credits its use for their survival.

Moving from the topic of taking on childhood genetic diseases to the neurobiology of aging, Keynote speaker *Gary Small*, MD, of the David Geffen School of Medicine at UCLA, discussed brain-healthy lifestyle choices associated with lower risk for dementia. Small was author of the study 'Your Brain on Google,'[1] which featured in a PBS Frontline documentary that aired the night before the talk, and which questioned the postulated positive benefit of our digitized world on brain function, development, and aging. These are issues that all of us can personally relate to in this digital age, including the need to take on personal responsibility for one's own health and wellness.

Cancer Profiling and Pathways

Breast Cancer

Before the Keynote speakers took the stage, enlivened debate had begun in the pre-conference sessions, ahead of the official conference kickoff. *Michael Liebman*, PhD, Managing Director of Strategic Medicine, Inc., chaired one of 12 pre-conference 'short courses' on February 2, which provided three perspectives on clinical decision support in the management of patients with breast cancer. In breast cancer, tissue heterogeneity and the co-occurrence of subpathologies contribute to the complicated clinical picture. Clinical and histopathological factors, including lymph node status, tumor size, histological grade, age, and expression of known biomarkers, such as the estrogen receptor (ER) and the human epidermal growth factor receptor (HER2/neu/ERBB2), have traditionally guided treatment decisions for patients with operable breast cancer. A number of guidelines for clinical risk assessment have incorporated these factors – for example, the St Gallen guidelines,[2] the Nottingham Prognostic Index,[3] and Adjuvant! Online (www.adjuvantonline.com). Yet biomarkers such as hormone receptor status are often correlative rather than causative, and there is not a linear progression through disease. Outlining these issues, Liebman expressed the need to better utilize physician experience by collecting and evaluating critical, real-life patient response data, often gained through empirical decision-making outside the realm of clinical practice guidelines. Such information, he argued, needs to be integrated

with research and clinical trial data into treatment decision strategies.

Despite this plea for more and better data, breast cancer appears to be on the cutting edge with regard to prognostic and predictive tools, in terms of both development and implementation in clinical practice. *Laura van't Veer*, PhD, head of Diagnostic Oncology at the Netherlands Cancer Institute, and Chief Research Officer at Agendia, updated the audience on next-generation breast cancer diagnostics – in particular, those based on molecular profiling – with a focus on the Mammaprint® 70-gene signature assay. The FDA recently broadened its clearance of the Mammaprint® test for use in women of all ages for prediction of breast cancer recurrence and assessment of the need for adjuvant chemotherapy.[4] Further prospective clinical validation studies are underway, primarily the ongoing MINDACT trial (Microarray In Node-negative Disease may Avoid ChemoTherapy),[5] which is designed to assess the clinical utility of the Mammaprint® assay compared with standard clinicopathologic prognostic factors included on Adjuvant! Online for selecting patients with negative or 1–3 positive nodes for adjuvant chemotherapy.

Such trials are keenly followed by physicians treating patients with breast cancer, including *Laura Esserman*, MD, Professor of Surgery and Radiology, and Director of the Carol Franc Buck Cancer Center at UCSF, who provided a compelling argument from the clinical perspective on the challenges of personalized medicine and the implementation of genomics into clinical treatment decision strategies. She discussed using genomics to understand the impact of mammographic screening for breast cancer, noting a shift toward detection of 'good prognosis' cancers. In effect, her group and others have observed an increase in detection of localized (lymph node [LN]–) breast cancers, without a concomitant decrease in the number of detected regional (LN+) cancers. Yet the goal of screening for breast cancer is not to detect all breast abnormalities; rather, it is to prevent deaths from breast cancer. But how is this to be achieved? One major clinical issue revolves around assessing the true risk associated with screen-detected cancer and determining the value of detecting low-risk cancers. It is, of course, an emotional argument; patients and physicians are very risk averse, so often even low-risk cancers are treated, if detected. This decries the need for patient education and clearer decision tools for their treating physicians. Molecular profiles, such as the Mammaprint® 70-gene signature or the Oncotype Dx assay, can provide information on important aspects of tumor biology – for example, good versus poor prognosis, or response to chemotherapy. With Mammaprint®, an index score of >0.6 represents ultralow risk, with no distant metastases observed at 5 years. Esserman suggested that such 'indolent' tumors be referred to by a term less evocative than 'cancer' or 'tumor', calling them 'indolent lesions of epithelial origin', or 'IDLE' tumors. Based on work done in collaboration with Van't Veer, Esserman concluded that molecular profiling at the time of diagnosis would benefit women with screen-detected cancers by enabling identification of IDLE tumors and testing of less aggressive interventions. The next steps are to validate results in a prospective trial and compare molecular signatures of screen-detected versus interval cancers (those that appear between mammograms), with the goal of reducing the treatment burden for minimal risk disease and focusing on prevention for the patients at highest risk.

Furthering the topic of breast cancer decision tools from the perspective of a diagnostic/prognostic test developer, *Tracey Colpitts* of Abbott Molecular presented the example of the Pathvysion® fluorescence *in situ* hybridization (FISH) test for HER2 positivity in breast cancer patients. Colpitts reminded attendees that HER2 was initially 'on the market' as a prognostic factor to help triage patients but has since evolved into a companion diagnostic marker, though debate continues with regard to the optimal format for testing. HER2 overexpression and/or gene amplification is associated with a poor outcome in node-positive breast cancer and predicts response to trastuzumab, and HER2 testing is a prerequisite for treatment with trastuzumab. However, for HER2 assays there is an equivocal zone wherein one must retest. This zone is smaller for FISH compared with immunohistochemistry (IHC); nonetheless, the field is in need of unification to improve HER2 test interpretability regardless of methodology. From a clinical standpoint, as with any drug, the benefits of trastuzumab need to be balanced against its adverse effects.

Liver Cancer

Though breast cancer may be the poster child of genomic cancer profiling and predictive molecular testing, other cancers such as liver cancer lag somewhat behind. In the 'Cancer Profiling and Pathways' track of the conference, three talks focused on moving research closer to the bedside of patients with liver cancer. The clinical perspective was provided by *Fred Poordad*, MD, Chief of Hepatology at Cedars-Sinai Medical Center, who relayed the current clinical picture, noting surgery as still the most viable option for most patients. An alternative view was provided by *Xin Wei Wang*, PhD, of the Liver Carcinogenesis Section at the NIH National Cancer Institute, looking at systemic therapies from the lab-bench

perspective. Wang discussed development of a 'genome-coupled phenotype knowledge base' in order to define biomarkers that may be used to predict therapy response if systemic therapy is to be given. *Michael Briggs*, PhD, Senior Director of Biology at Vertex Pharmaceuticals, provided the drug development perspective on systemic therapy, with a focus on sorafenib. He described efforts to build more relevant tools, shifting from traditional cell-line testing to patient tumor-derived models, made possible through partnership between surgeons, clinicians, pathologists, and research scientists. Biomarker analysis in primary patient tumors will have value in terms of relevance and predictability, but the true proof of concept – a new drug identified by such an approach and moved into the clinic – has yet to be shown.

Personalized Diagnostics

MicroRNAs

The 'Cancer Profiling and Pathways' track aptly overlapped with the 'Personalized Diagnostics' track, with a string of talks covering the role and potential use of microRNAs in cancer. *Carlo Croce*, MD, Director of the Institute of Genetics and the Human Cancer Genetics Program at Ohio State University's Comprehensive Cancer Center, outlined the consequences of microRNA dysregulation in cancer and the development of an miRNA signature associated with prognostic factors and disease progression in chronic lymphocytic leukemia.

Jack T. Leonard, PhD, VP of Technology Commercialization at Febit Inc./Biomarker Discovery Center Heidelberg, presented the concept of specific miRNA fingerprints in patient blood samples as potential diagnostic tools. Using the example of PSA as a typical single-biomarker test, Leonard pointed out the readily apparent disadvantage, in that single markers often show low specificity and/or sensitivity. He proposed the utilization of a sophisticated yet complex set of stable biomarkers, from a pool of approximately 1000 human miRNAs, with specimens obtainable from patients' blood or urine with minimal discomfort, showing examples in lung cancer, pancreatitis, and melanoma, and suggested generation of 'disease probability plots' as a possible representation of personalized data. This would involve standardizing the sample handling and preparation, the assay technique, and the bioinformatics approach to analysis.

In her talk on microRNA binding-site polymorphisms as biomarkers, *Joanne Weidhaas*, MD, PhD, of the Department of Therapeutic Radiology at Yale University School of Medicine, noted the wide room for discovery regarding biomarkers of cancer risk. She described the discovery of a SNP in a let-7 microRNA binding site in the *KRAS* oncogene, which disrupts let-7 regulation of *KRAS*. This *KRAS* variant allele has been shown to be a potentially useful marker of cancer risk in a variety of tumor types.

Serum Biomarkers

Although the development of noninvasive diagnostic, prognostic, and predictive tests will certainly simplify some aspects of personalized medicine for patients, the technologies required may possibly be some of the most complex. A panel of sessions focusing on personalizing therapy through the identification and use of serum biomarkers was chaired by *Josip Blonder*, MD, Senior Research Scientist and Head of Quantitative Proteomics at the NIH National Cancer Institute. Blonder presented the rationale for use of clinical oncoproteomics in biomarker-based, personalized cancer care, accompanying a shift from organ-based oncology to pathway-based oncology. Following Blonder's upbeat example of the application of personalized oncoproteomics in renal cell carcinoma, *Steven A. Carr*, PhD, Director of Proteomics at the Broad Institute of MIT and Harvard, reminded the audience of the dismal failure thus far of biomarker discovery via proteomics, suggesting the potential utility of quantitative mass spectrometry as a next step.

As an alternative to proteomic analysis, *Arun Sreekumar*, PhD, of the Molecular Oncology Program at the Medical College of Georgia, spoke about his metabolomic studies in association with the Prostate Cancer SPORE (Specialized Programs of Research Excellence). Metabolomic analyses of prostate cancer progression have revealed sarcosine as a potentially important metabolic intermediary of cancer cell invasion and aggressivity, and therefore a potential marker for prognosis.

Nicholoas Dracapoli, PhD, VP of Biomarkers at Centocor R&D (Johnson & Johnson), examined the technical hurdles and successes in enumeration and characterization of circulating tumor cells as cancer biomarkers. Throwing out the question of the true clinical utility of biomarkers, he noted the fact that at present there are no complex molecular profiles approved to measure drug efficacy, and that alternative approaches must be taken. One such alternative was described by *Charles Cantor*, CSO of Sequenom, who examined the progress in noninvasive detection of nucleic acid biomarkers and the merits of nucleic acid mass spectrometry (MS)-PCR compared with real-time PCR. These include detection down

to a single molecule, the ability to detect many more loci simultaneously, and provision of long sequence information on a single platform. Combining the sensitivity of MS and the specificity of PCR, Sequenom has developed MS-PCR for quantitative, type-specific detection of HPV (AttoSense™). Other diagnostic applications in development are a noninvasive prenatal Down syndrome screening test (requiring only 4 mL of maternal blood) and oncogene mutation profiling assays – for example, for detection of *BCR-ABL* kinase domain mutations, in order to facilitate the rational deployment of targeted therapeutics.

Next-Generation Sequencing

Chairing a series of talks on next-generation sequencing as a clinical tool, *German Pihan*, MD, of the Department of Pathology at Beth Israel Deaconess Medical Center, Harvard Medical School, described the growing role of novel sequencing technologies in enabling personalized medicine. He shared his belief that when the cost of whole-genome sequencing drops to the long-anticipated $US1000 per genome mark, it will become cost effective to offer this to patients for purposes of personalized disease diagnosis, risk assessment, and therapy, and for pharmacogenomic assessment of the risk/benefit ratio of various therapeutic options.

Molecular Detection of Pathogens: Meeting the Needs of the Community

Improved diagnostics for infectious diseases will be in high demand for the foreseeable future. *Karen Kaul*, MD, PhD, Director of the Molecular Diagnostics Division, NorthShore University Health System, and Clinical Professor of Pathology, University of Chicago Pritzker School of Medicine, discussed tests for real-time detection and characterization of influenza, outlining trends from the influenza season of 2004–2005, when use of culture systems and enzyme immunoassay (EIA) techniques was prevalent, through to the situation today, when PCR assays are standard protocol. Kaul noted that EIA had a false-negative rate in adults for influenza A of approximately ~50%, and ~75% for influenza B. There is clearly a need for automation, platforms that function in a variety of settings, and the ability to handle annual sequence variations and emergence of new strains. With influenza, it is necessary to revalidate tests every year and during flu season to ensure delivery of adequate and clinically relevant results. Unfortunately, rapid tests are falling short on sensitivity. Kaul contended that there remains a place for laboratory-derived tests, particularly considering the nimbleness of labs in their ability to validate tests against emerging new strains.

Kaul's colleague *Lance Peterson*, MD, also of the University of Chicago, discussed MRSA surveillance programs and the role of test choice. According to CDC data, in 1974, MRSA represented only 2% of staphylococcal infections in US ICUs. By 1995 this had increased to 22%, and to 63% in 2004. It has now reached pandemic levels. MRSA biology suggests that an effective strategy for management and control – including surveillance, isolation, and decolonization – is possible, but success will depend on who is tested, the sensitivity of test(s), and the time required to report the results. Looking at specific tests, Peterson compared the BD GeneOhm® MRSA Assay with the Cepheid Xpert™ MRSA Assay and the Roche LightCycler® MRSA Advanced Test, and determined these tests to be roughly equivalent for surveillance purposes. The Roche test is not yet available in the US.

Trends in Translational Medicine

In the 'Translational Medicine' track, Merck Research Labs' *Douglas Bergstrom*, MD, PhD, provided a framework for working backwards from clinical data, using drug-induced feedback loops to identify indications and combination partners. Utilizing this approach in a hair follicle study in healthy volunteers, his group has identified Notch pathway inhibition in response to γ-secretase inhibitors in tumors, and generated data supporting the combination of γ-secretase inhibitors with phosphoinositide-3-kinase (PI3K) inhibitors in cancer therapy. Such studies provide target information data for development of both new drugs and novel treatment strategies using existing agents.

The urgent need for translational approaches to studying stroke was discussed by *Giora Feuerstein*, MD, Assistant Vice President and Head of Discovery Translational Medicine at Pfizer Global Research & Development. It was somewhat startling to realize that despite five centuries understanding the clinical problem, and technical advances in the last 20 years, we are still struggling to manage the clinical situation in stroke. The only FDA-approved treatment for stroke is tissue plasminogen activator (tPA), which has had limited clinical impact as it must be used within 3 hours of the stroke, so it is not available as a therapeutic option for most patients. There are currently no phase III trials with a new medical entity for treating or preventing stroke. Trials of agents for neuroprotection have been disappointing. Reiterating the principles of

personalized medicine, Feuerstein stated the need to identify the right target, with the right compound, in the right patient, at the right time. In this regard, drug development needs to be looked at from a translational medicine perspective using biomarkers, stressing congruency between preclinical data and clinical integration. The issue with stroke is that the targets are transient, coming into play preceding the event and disappearing afterward. There are hundreds of changes happening during a stroke, making it difficult to identify a suitable target. Markers can be pleiotrophic, redundant, or of unknown function, and both pro- and anti-'stroke' markers show up. It appears that chasing a dynamic target will continue to be a challenge for translational and personalized medicine well into the future.

Francesco Marincola, MD, Chief of the Infectious Disease and Immunogenetics Section at NIH, described a paradigm shift in the approach to studying immune-mediated tissue-specific destruction. Such destruction follows a common pathway independent of the originating cause and disease context. In cases of delayed allergic reactions, it also presents an immunologic paradox, with cytotoxic T cells coexisting with their targets and resulting in no obvious clinical effect. Marincola proposed strategies to measure the dynamics of immune response during clinical trials, analyzing signatures associated with tumor response to treatment with vaccine/high-dose interleukin-2 and developing an immune algorithm governing tumor growth during immunotherapy. This work is contributing to a unified theory about the converging mechanisms leading to immune-mediated tissue-specific rejection.

New Cancer Biologics

Hans Peter Gerber, Senior Director of Biotherapeutics at Pfizer, chaired the 'Biologics' track's session on the closing day of the conference. Gerber, whose group is currently focusing on antibody-drug conjugates (ADCs), described his recent transition from Wyeth to Pfizer as "like being in a candy store" with regard to the wide variety of available tools for developing antibody-targeted chemotherapy. Gerber presented the rationale for developing ADCs, based on the limited efficacy of naked antibodies in carcinomas, which represent 70% of new cancers in the US. Naked monoclonal antibodies that interface with cell signaling (e.g. cetuximab, trastuzumab, and bevacizumab) are the most effective, but they have limited complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) activities. These antibodies work well in liquid tumors but not in solid tumors. Coupling tumor-targeting antibodies to cytotoxic drugs is an alternative approach, and although the theory is promising, it is interesting to note that only one such agent has been approved in the last 20 years. This slow progress in bringing ADCs to the clinic reflects the more complex development compared with naked antibodies, mainly relating to the persistent problem of immunogenicity, and limitations with linker stability and subsequent induction of systemic toxicity. Nevertheless, ADCs have been pursued successfully by Wyeth/Pfizer in their unique platform of antibody-calicheamicin conjugates. Calicheamicin is a DNA-binding agent like the duocarmycins. It is released from the ADC following targeting to the tumor and is triggered to cause DNA strand breaks. The only ADC approved thus far is Pfizer's antibody-calicheamicin conjugate gemtuzumab ozogamacin (anti-CD33; Mylotarg®), which is indicated for patients with CD33+ acute myeloid leukemia who are over 60 years of age and who are not candidates for traditional cytotoxic chemotherapy.

Pfizer is now working on an anti-CD22 directed ADC, inotuzumab ozogamacin (CMC-544), which is internalized readily and is therefore ideal for targeted drug delivery. The prelinical safety profile of inotuzumab ozogamacin is consistent with the toxicities of calichaemicin, with target organs (bone marrow, liver) being independent of the targeted antigen. The toxicities were manageable and reversible, with no impact on the cardiovascular system or the CNS, and efficacy has been demonstrated against follicular and diffuse B-cell lymphoma. Inotuzumab ozogamacin is currently in phase II/III development.

Elsewhere in ADC development, traditional agents such as doxorubicin, taxol, and etoposide are still being explored. Duocarmycins/CC-1065 are being pursued by Medarex and others, maytansines by ImmunoGen (as presented at another session by *John Lambert*, CSO), and auristatins by Gerber's former employer, Seattle Genetics.

Conclusions – the Outlook

Overall, the pace of progress in 'shaping future medicine' continues to be encouraging, though a myriad of challenges are still looming, many of which involve financial constraints and the ever-increasing pressure on all parties – drug developers, diagnostics developers, physicians, and even patients – to make the right decisions among a vast and increasing array of potential approaches to managing health and disease. A fitting summary was presented by *Wayne Rosencrans*, PhD, Chairman

and President of the Personalized Medicine Coalition and Distinguished Fellow at the MIT Center for Biomedical Innovation, challenging the sustainability of the current healthcare situation. Rosencrans expressed the new refrain for healthcare as being to 'pay for what works,' a proposition eliciting a new series of questions surrounding what actually works best, for whom, and under what circumstances. These questions are increasingly being addressed via new avenues, including comparative clinical effectiveness, personalized healthcare, and real-world effectiveness research, looking beyond market approval to 'clinical embedment'. He added to the theme of personalized medicine, in that it needs to deliver the right care to the right person, at the right time and, not least of all, for the right price.

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