PLENARY SESSION 6: Using new knowledge in clinical trials

O6.1

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Molecular medicine in lung cancer - Insights in molecular pathogenesis driving better therapies

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Traditionally, tumors are classified by histopathological criteria, i.e., based on their specific morphological appearances. Consequently, current therapeutic decisions in oncology are strongly influenced by histology rather than underlying molecular or genomic aberrations. The increase of information on molecular changes however, enabled by the Human Genome Project and the International Cancer Genome Consortium as well as the manifold advances in molecular biology and high-throughput sequencing techniques, inaugurated the integration of genomic information into disease classification. We have therefore introduced multiplex deep sequencing of informative gene sets into routine histopathological diagnostics and molecular pathology. This comprehensive approach integrating morphological and molecular information is currently changing cancer diagnostics in five categories: (1) Somatic genomic or epigenomic alterations acquired during cancerogenesis may be used for disease classification as we show this approach adding important information to conventional morphological classifications. (2) A significant portion of solid tumors depend on oncogenic driver lesions, which provide molecular targets for prediction of effective and selective therapies. (3) Genomic alterations in signal transduction cascades and gene expression pattern may be used as prognostic parameters predicting the need and extent of adjuvant therapy. (4) In the case of multiple syn- or metachronous tumors, genomic profiling assists allocation of metastases from tumors with unknown primary (CUP) and correct staging as multiple small primary tumors and systemic metastases are reliable being discriminated. (5) Finally, mutational profiling of tumor circulating tumor DNA may facilitate monitoring the response of tumors to therapy and development of secondary resistance. In addition, immune checkpoint inhibitor therapies have been implemented and proved to provide significant benefit for tumors lacking drugable oncogeneic driver lesion. We therefore have implemented hybrid capture-based NGS and expression profiles of PD-L1 to select specifically patients for immune checkpoint inhibitor therapies.Taken together, comprehensive molecular tumor pathology and oncology paves the way for a new rational and.

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Genomic Predictors of Treatment Response in Prostate Cancer: A New Era

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Prostate cancer (CaP) remains the most common male malignancy worldwide. Although some localized cancers can be indolent, others can manifest aggressive biology with abnormal cancer metabolism and genetic instability. These men need intensified treatment to prevent metastatic castrate-resistant disease (mCRPC). However, the genomic landscape of prostatic cancer heterogeneity relative to outcome is not known. We analyzed the whole-genomes and methylomes of close to 500 men with sporadic prostate cancers treated by surgery or radiotherapy. Unlike mCRPC. these tumours have few clinically-actionable mutations despite a high level of important genomic rearrangements associated with chromothripsis and kataegis. Even pathologically similar cancers have great heterogeneity in clinical outcome and this associated with a unique 5-feature signature consisting of mutations, copy-number alterations and altered methylation. We have broadened our genomics approach to two other aggressive features of prostate cancer: (1) aggressive sub-pathologies such as intracductal carcinoma with cribiform architecture (IDC-CA), and (2), BRCA2-associated prostate cancers. The poor outcome associated with IDC and CA sub-pathologies was found to be associated with a constellation of genomic instability, SChLAP1 expression, and hypoxia. We posit a novel concept in IDC/CA+ prostate cancer, "nimbosus" (gathering of stormy clouds, Latin), which manifests as increased metastatic capacity and lethality. Prostate cancers that develop in mtBRCA2-carriers are associated with an aggressive course with 50% mortality at 5 years. We observed increased genomic instability and a mutational profile that more closely resembles metastastic, rather than localized sporadic disease, in mtBRCA2 PCa. These tumours also show genomic and epigenomic dysregulation of the MED12L/MED12 axis, which is involved in beta-catenin-WNT signaling-usually only dysregulated in mCRPC. Our data strongly suggests that novel therapeutic approaches should also focus on recurrent non-mutation targets in sporadic, localized prostate cancer in order to improve cures a priori. IDC-CA and BRCA2 prostate cancer variants should be further treated with intensification.

O6.6 Concluding Remarks

Systems Medicine, Big Data and Scientific Wellness are transforming Healthcare

Leroy Hood

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Systems medicine, the application of systems approaches to disease, places medicine at a fascinating tipping point—promising a revolution in the practice of medicine. I will discuss how systems biology approaches have framed systems medicine and I will discuss some of the new systems-driven technologies and strategies that have catalyzed this tipping point. Moreover, four converging thrusts—systems medicine, big data (and its analytics), the digitalization of personal measurements and patient-activated social networks—are leading to a proactive medicine that is predictive, personalized, preventive and participatory (P4). I will contrast P4 medicine with contemporary medicine and discuss its societal implications for healthcare. P4 medicine has two central thrusts—wellness and disease.

I will discuss our successful effort to introduce P4 medicine into the current healthcare system with a P4 pilot program on scientific wellness—a longitudinal, high-dimensional data cloud study on each of 108 well patients over 2014. The preliminary results both with regard to data analyses and patient responses from these studies are striking. They point to the emerging discipline of scientific wellness—and the fact that it will catalyze several new thrusts in healthcare: 1) optimizing wellness, 2) identifying the earliest disease transitions for all common diseases and learning how to reverse them and 3) employing the dense, dynamic, personal data cloud approach to study diseases (e.g. cancer, Alzheimer's, diabetes) and their responses to therapy. Scientific wellness will also pioneer N=1 experiments to deconvolute the staggering complexity of human biology and

disease. We started Arivale, a company focused on scientific wellness for the consumer, in 2015 and already have 1500 individuals enrolled. I will also discuss some preliminary results from the Arivale studies.

My institute, the Institute for Systems Biology (ISB), in 2016 affiliated with Providence St. Joseph Health to become its research arm and LH its Chief Science Officer. Providence is one of the largest non-profit healthcare systems in the US—and ISB/Providence will be initiating a series of "translational pillars" moving applications of systems (P4) medicine from the bench to the bedside. These pillars include scientific wellness, bringing scientific wellness to cancer survivors, making Alzheimer's a reversible and preventive disease, rather than a relentlessly progressive disease, taking a systems approach to type 2 diabetes and exploring how the deep, dynamic, personal data clouds can be used to gain a deep understanding of glioblastoma and provide new diagnostic and therapeutic approaches to this inevitably fatal tumor. It is fair to say that dense, dynamic, personal data clouds followed longitudinally on hundreds of thousands of patients will allow us to see the earliest wellness to disease transitions for all of the common cancers—and generate biomarkers for early detection and identify the drug targets or strategies (e.g., immunotherapy) that will allow us to reverse the disease before it ever manifests itself as a disease phenotype.

Thus scientific wellness will catalyze a transformation in contemporary healthcare and it will provide eventually millions of dense, dynamic, personal data clouds that will present striking new opportunities for pharma, biotech, nutrition and diagnostic companies to identify biomarkers and drug target candidates. As the cost of the assays for the dense, dynamic, personal data clouds decline; scientific wellness can be brought to the developing world leading to a democratization of healthcare unimaginable even a few years ago.