

PLENARY SESSION 4: Next great steps in cancer therapy

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Proteogenomics: New Opportunities in Cancer Biology and Precision Medicine

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Despite significant progress in understanding cancer through massively parallel sequencing genome programs, the complexity that comprises its diseases remains a daunting barrier. Today we know that molecular drivers of cancer are derived not just from DNA alterations alone, but from protein expression and activity at the cellular pathway level - proteomics. To predict the downstream effects of gene alterations, orthogonal technologies such as next-generation proteomics are needed. This proteogenomics approach (interplay between proteome and genome) is anticipated to transform oncology care from one that relies mainly on trial-and-error treatment strategies based on the anatomy of the tumor, to one that is more precisely based on the tumor's molecular profile. This seminar will discuss how genomics, transcriptomics, and proteomics must all be brought together in the quest to understand the etiology of cancer, in addition to highlighting efforts by the U.S. National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC) program in this area of biomedical research. CPTAC began with the purpose of developing standardized (rigor & reproducibility) proteomic assays and workflows, in order to complement genomic and transcriptomic analyses. CPTAC's proteogenomics approach was recently successful in demonstrating the scientific benefits of integrating proteomics with genomics to produce a more unified understanding of cancer biology and possibly therapeutic interventions for patients, while creating open community resources that are widely used by the global cancer community. This seminar will also highlight the recently announced APOLLO (Applied Proteogenomics Organizational Learning and Outcomes) program and the efforts of the International Proteogenomic Consortium. APOLLO brings together the U.S. National Cancer Institute, U.S. Department of Defense, and the U.S. Department of Veterans Affairs to create the nation's first healthcare system in which cancer patients will be routinely screened for genomic abnormalities and proteomic information with the goal of matching their tumor type to a specific targeted therapy.

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Cancer Genome Sequencing in a Multi-Institutional Clinical Setting: The MASTER Study of the German Cancer Consortium

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Precision oncology implies the ability to predict which patients will likely respond to specific cancer therapies based on increasingly accurate, high-resolution molecular diagnostics as well as the functional and mechanistic understanding of individual tumors. While molecular stratification of patients can be achieved through different means, a promising approach is next-generation sequencing of tumor DNA and RNA, which can reveal genomic alterations that have immediate clinical implications. Furthermore, certain genetic alterations are shared across multiple histologic entities, raising the fundamental question of whether tumors should be treated by molecular profile and not tissue of origin. We here describe MASTER (Molecularly Aided Stratification for Tumor Eradication Research), a clinically applicable platform for prospective, biology-driven stratification of younger adults with advanced-stage cancer across all histologies and patients with rare tumors. We illustrate how a standardized workflow for selection and consenting of patients, sample processing, whole-exome/genome and RNA sequencing, bioinformatic analysis, rigorous validation of potentially actionable findings, and data evaluation by a dedicated molecular tumor board enables categorization of patients into different intervention baskets and formulation of evidence-based recommendations for clinical management in a multi-institutional clinical setting. Critical next steps will be to increase the number of patients that can be offered comprehensive molecular analysis through collaborations and partnering, to explore ways in which additional technologies can aid in patient stratification and individualization of treatment, to stimulate clinically guided exploratory research projects, and to gradually move away from assessing the therapeutic activity of targeted interventions on a case-by-case basis towards controlled clinical trials of genomics-guided treatments.