Clinical Chemistry

October 2014 Audio Summary

This is the October 2014 issue of *Clinical Chemistry*, Volume 60, Issue 10.

On the cover this month: Steven Soldin. An accomplished violinist. A world traveler. A collector of fine art. A lover of literature, ballet, and music. And yes, a renowned clinical chemist in 3 areas — therapeutic drug monitoring, pediatrics, and endocrinology. Born in Johannesburg, his career has spanned from teaching poor South Africans towards a high school diploma to his current post as a senior scientist in the department of laboratory medicine at the National Institutes of Health. In this month's Inspiring Minds feature, readers have the opportunity to learn about this special person for whom "the arts and sciences dance together."

ERCC1-Positive Circulating Tumor Cells in the Blood of Ovarian Cancer Patients as a Predictive Biomarker for Platinum Resistance

By Jan Dominik Kuhlmann, et al.

Primary tumor-based detection of DNA excision repair protein *ERCC1*-nuclease has been controversial and finally shown to be inaccurate for predicting platinum-resistance. To investigate whether *ERCC1*-expression in circulating tumor cells may be superior in predicting platinum-resistance, the authors of this study immunomagnetically enriched circulating tumor cells from the blood of ovarian cancer patients and analyzed circulating tumor cells-based *ERCC1*-expression by RT-PCR. They found the presence of *ERCC1*-positive circulating tumor cells at primary diagnosis to be an independent predictor for recurrence, survival and platinum-resistance, whereas *ERCC1*-expression in corresponding primary tumors was noninformative. Therefore, this report proposes a blood-based biomarker for platinum-resistance at primary diagnosis of ovarian cancer.

Genomic High-Resolution Profiling of Single CKpos/CD45neg Flow-Sorting Purified Circulating Tumor Cells from Patients with Metastatic Breast Cancer

By Rui P. L. Neves, et al.

Circulating tumor cells detected by the CellSearch system have clinical prognostic value and represent a very promising source of biological and clinically relevant information. Evidence has shown that circulating tumor cells within a patient are heterogeneous and therefore the isolation of single cells and their molecular characterization at a single-cell level are needed to better assess the real potential of this population of rare cells. In this article the authors describe a protocol for the systematic isolation of CellSearch circulating tumor cells by flow cytometry and their subsequent molecular characterization. This approach might serve as a basis for the molecular screening of circulating tumor cells in the clinical setting.

Noninvasive Detection of a Balanced Fetal Translocation from Maternal Plasma

By Taylor J. Jensen, et al.

The noninvasive detection of fetal aneuploidies and other copy number variations by sequencing circulating cell-free DNA from maternal plasma has proven to be technically and clinically feasible; however, challenges have remained in detecting

copy-number-neutral rearrangements. In this article the authors demonstrate the feasibility of identifying the precise breakpoint of a balanced fetal translocation at single base resolution, highlighting the first proof of concept that extends noninvasive prenatal detection methods beyond copy number variations.

Microfluidic Genotyping by Rapid Serial PCR and High-Speed Melting Analysis
By Scott Sundberg, et al.

In this article the authors introduce a new instrument that performs genetic typing by combining rapid cycle PCR and high-speed melting. Four single nucleotide variants in 100 patients were typed after blinding to demonstrate 100% instrument accuracy. This method provides rapid serial analysis as a new protocol for genetic testing.

Integrative Bioinformatics Analysis Reveals New Prognostic Biomarkers of Clear Cell Renal Cell Carcinoma
By Henriett Butz, et al.

The authors of this study integrated mRNA, protein, and miRNA data from 593 clear-cell renal cell carcinoma and 389 normal kidney specimens by use of pathway and network analysis and employed 882 clear-cell renal cell carcinoma and 152 normal samples as a validation set. The authors identified 3 novel molecules: Aryl-hydrocarbon-receptor, Grainyhead-like-2, and KIAA0101 as novel factors in the disease pathogenesis and as biomarkers. Unique aspects of this study are that it attempts to overcome the problem of tumor and patient heterogeneity using an integrated analysis of a high number of samples, multilevel data, and the unbiased network approach. The translational outcome of this bioinformatics/network analysis is presented by linking it to clinical data and functional biology.

Cardiac Troponin I Associated with the Development of Unrecognized Myocardial Infarctions Detected with MRI
By Charlotte Ebeling Barbier, et al.

176 community-living women and men without known myocardial infarction underwent magnetic resonance imaging at a baseline age of 70 with follow-up at 75 years of age, and cardiac troponin I was measured with a high-sensitivity assay. New or larger previously unrecognized myocardial infarctions were detected in 37 individuals at follow-up. Plasma concentrations of cardiac troponin I at baseline, which were largely within the reference interval, were found to be related to new or larger unrecognized myocardial infarctions at follow-up with an Odds Ratio of 1.98. Thus, cardiac troponin I as measured with a high-sensitivity assay in 70-year-old community-living women and men was associated with the development of unrecognized myocardial infarctions within 5 years that were detected using magnetic resonance imaging.

Tacrolimus Pharmacodynamics and Pharmacogenetics along the Calcineurin Pathway in Human Lymphocytes
By Ofelia Noceti, et al.

The immunosuppressive effects of calcineurin inhibitors are extremely variable. Pharmacokinetic variability only represents a portion of this variability, and pharmacodynamic variability needs to be further investigated. In this study the authors investigated the inhibitory effect of tacrolimus along the calcineurin pathway, the interindividual variability at each stage and the potential contribution of genetic polymorphisms to such variability. The tacrolimus effects on isoform 1 of the nuclear factor of activated T-cells (abbreviated NFAT1) in peripheral blood mononuclear cell nuclei, IL-2 positivity in CD4/CD8 positive cells, and CD25 positivity in CD3 positive cells nicely fit I/Imax models. Tacrolimus IC50 increased along the calcineurin cascade. Allosteric sigmoidal models adequately described tacrolimus signal transduction from NFAT1 to IL-2 and CD25. Polymorphisms in genes for Cyclophilin A, calcineurin A catalytic subunit alpha, or CD25 were strongly associated with tacrolimus pharmacodynamic variability. The authors conclude that pharmacodynamic monitoring based on appropriate targets may improve calcineurin inhibitor dose adjustment, while pharmacogenetics may help choose the starting dose.