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Editorial

Lung cancer biomarkers: Raising the clinical value of the classical and the new ones

Stefan Holdenrieder[a,*], Huub H. van Rossum[b] and Michel van den Heuvel[c]
[a]*Institute for Laboratory Medicine, German Heart Centre, Technical University of Munich, Munich, Germany*
[b]*Department of Laboratory Medicine, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[c]*Department of Pulmonology, Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands*

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Abstract. Blood-based diagnostics for lung cancer support the diagnosis, estimation of prognosis, prediction, and monitoring of therapy response in lung cancer patients. The clinical utility of serum tumor markers has considerably increased due to developments in serum protein tumor markers analytics and clinical biomarker studies, the exploration of preanalytical and influencing conditions, the interpretation of biomarker combinations and individual biomarker kinetics, as well as the implementation of biostatistical models. In addition, circulating tumor DNA (ctDNA) and other liquid biopsy markers are playing an increasingly prominent role in the molecular tumor characterization and the monitoring of tumor evolution over time. Thus, modern lung cancer biomarkers may considerably contribute to an individualized companion diagnostics and provide a sensitive guidance for patients throughout the course of their disease. In this special edition on Tumor Markers in Lung Cancer, experts summarize recent developments in clinical laboratory diagnostics of lung cancer and give an outlook on future challenges and opportunities.

Keywords: Lung cancer, tumor markers, liquid biopsy, diagnosis, prognosis

1. Introduction

Blood carries a vast amount of information on the health status of the body. Various analytes can be distinguished that are relevant within the realm of oncology. While the current focus lies mainly on the detection of deoxyribonucleic acid (DNA) in the blood, past techniques primarily concentrated on the detection of proteins. Embracing new technologies will be a major step forward, yet the available protein detection technologies have much to offer for both current and future clinical practice.

2. A brief history of blood biomarkers

One of the first biomarkers used as indicators of a malignant disease were serum tumor markers. These are proteins that that can be assessed in the blood or other bodily fluids of individuals who

*Corresponding author: Prof. Stefan Holdenrieder, Munich Biomarker Research Center, Institute of Laboratory Medicine, German Heart Centre, Technical University of Munich, Munich, Germany. Tel.: +49 89 1218 1011; E-mail: s.holdenrieder@tum.de.

suffer from a neoplastic disease. The identification and extraction of two tumor-associated molecules, alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA), paved the way for the development of the first tumor marker immunoassays over 50 years ago [1–4]. Since that time, plenty new cancer-related surface, cytoskeletal or intracellular proteins or peptides have been characterized and used as the basis for diagnostic immunoassays in various cancers. Since the early 1970ies, the International Society for Oncology and Biomarkers (ISOBM) has been a forum of basic cancer research, laboratory and clinical oncology experts from the USA, Russia, Japan, Israel and Europe who regularly meet at annual conferences and discuss the current developments and improvements [1]. Among the founders of ISOBM were pioneers like Phil Gold (CEA), Hidematsu Hirai (AFP) and Garri Abelev (AFP) who initiated the scientific exchange despite the geopolitical tensions at the time of the "Cold War". Soon after, experts from Europe and other countries joined the ISOBM marking a pivotal moment for oncological research and the development and evaluation of high-quality immunoassays for the hybridoma markers CA 19-9, CA 125, CA 15-3 and CA 72-4, the prostate-specific antigen (PSA), cytokeratin markers like CYFRA 21-1, TPA, and TPS and endocrine markers, such as NSE, in the 1980ies and 1990ies. They were followed by some more recent markers like progastrin-releasing peptide (ProGRP) and human epidymidis protein 4 (HE4) which resulted from proteomic research in the early 2000 years [1].

During this time, multiple tissue differentiation (TD)-workshops have been established within the ISOBM to characterize the antigen binding sites and identify the best sets of antibodies for the most sensitive and accurate detection of the cancer antigens [5–8]. These workshops also aimed to promote harmonization and standardization of the assays. Several oncological laboratories around the globe simultaneously performed comprehensive clinical studies to evaluate the clinical utility of the tumor marker immunoassays. This clinical approach has particularly been driven by the centers at Barcelona led by Rafael Molina, and Munich led by Petra Stieber. They have contributed an extensive repository of data encompassing the release of all relevant tumor markers in malignant and non-malignant diseases along with the description of physiologically influencing factors [9–14]. Additionally, they have introduced algorithms for interpretating multiple markers and marker kinetics, to improve diagnostic results in cancer detection, monitoring and prognosis [14–16]. Notably, many discussions and findings from ISOBM groups have also influenced other societies and resulted in numerous guidelines for the use of tumor markers, such as from the National Academy of Clinical Biochemistry [NACB; 17, 18] or the European Group on Tumor Markers [EGTM; 19–21].

3. The presence and the future

While new OMICS technologies like proteomics, metabolomics, genomics and epigenomics came up with highly promising results at a first glance, they always had to show their clinical utility and reliability against the backdrop of established marker sets to prove their superiority or additive value. In this process, many hurdles became evident that novel quantitative assays have to overcome before reaching clinical applicability. These experiences and challenges now serve as touchstones for the emerging genetic and epigenetic markers identified on cell-free tumor DNA (ctDNA) in blood plasma that are crucial for stratifying patients for targeted and immune therapies and for the characterization of tumor evolution over time. While the detection of the presence of a specific mutation primarily relies on the sensitivity of the technology, quantitatively tracking mutational load over time will encounter all challenges seen in earlier times with the quantitative assessments of proteins.

Currently, circulating tumor cells, extracellular vesicles, ctDNA and epigenetic marker patterns are about to considerably enrich and expand the diagnostic portfolio [22–25]. It is expected that these non-invasive liquid biopsies will change the way we diagnose, treat and monitor cancer disease. As

they are closely linked to therapy, they are much more appealing than the traditional tumor markers. Nevertheless, protein-based diagnostics still have many important advantages, as they are sensitive, quantitative, robust, automatable, cost-effective, and, particularly, closely aligned with cellular function. Therefore, they also have a place in estimating prognosis, response prediction and monitoring of targeted and immune therapies – especially when not employed in an old-fashioned manner with fixed single marker cutoffs, but as part of multiparametric algorithms for improved decision-making.

4. Special issue on "Lung Cancer Tumor Markers"

The current special issue on "Lung Cancer Tumor Markers" that we are providing to you focuses on both sides, the protein and the other molecular markers. As both types of diagnostics have their strengths, they may be used in combination for optimized and individualized precision medicine in the future – depending on the cancer type and the clinical question.

The first contribution of this issue highlights the laboratory perspective of lung cancer tumor marker analysis [26]. This gives the framework of the needs and challenges for a high-quality diagnostic tool encompassing the development and clinical application of appropriate assays; the harmonization and standardization requirements, the quality control aspect, and the interpretation of the results on the background of the clinical questions and other diagnostics information. In particular, it addresses the preanalytical, analytical and postanalytical contexts and the application of tumor markers in screening, differential diagnosis, prognosis and monitoring of cancer disease.

Canki et al. [27] provide insights in the preanalytical stability of several tumor markers used for lung cancer diagnostics, namely CEA, CYFRA 21-1, NSE, CA125 and HE4. The influencing role of the processes occurring between blood drawing and laboratory analysis is often invisible and therefore neglected by oncologists and attending physicians, but understanding such possibly interfering factors is crucial for lab doctors in order to make an accurate and informative interpretation of the results.

Qian and Meng [28] establish a bridge for circulating lung cancer biomarkers, connecting translational research with clinical practice. Thereby, currently used as well as newly emerging lung cancer biomarkers are discussed in terms of their clinical potential to detect, predict, or monitor subtypes of lung cancer.

Similar to preanalytics, it is crucial to know whether non-malignant clinical or physiological conditions may influence the release, metabolization, or elimination of tumor markers. Trape et al. [29] provide a valuable and comprehensive overview of those possibly interfering non-malignant conditions that have to be considered when interpreting tumor marker concentrations in the blood. This is a must have reference for each specialist in laboratory medicine supervising tumor marker measurements, particularly to support clinical validation procedures and in case of clinically doubtful test results.

Tumor markers can be applied for detecting cancer disease in various scenarios. The most challenging application is the "cancer screening" setting, where the testing is performed in the overall population or in a subgroup of individuals without any specific symptoms, because the prevalence of the lung cancer is typically low in such cases. Van den Broek and Groen [30] address the challenges and opportunities of blood-based biomarkers for screening approaches in lung cancer.

In the daily hospital routine setting, patients mostly present with specific symptoms or suspicious findings, and a differential diagnosis has to be done to determine whether the underlying cause is cancer or another benign disease. As there are several markers available for lung cancer diagnosis, Trulson et al. [31] investigated whether the combination of multiple protein tumor markers improves the differential diagnosis of lung cancer and its histological subtypes.

However, tumor marker may not only be measured in blood serum or plasma. Trapé et al. [32] show how lung cancer tumor markers can guide diagnosis when assessed in serous effusions and other body fluids.

Beyond cancer detection, tumor markers provide important information on tumor characteristics and prognosis in patients with early and late-stage cancer. Based on an earlier work, Trulson and Holdenrieder [33] give an updated critical review of publications between 2008 and 2022 on the prognostic value of blood-based protein biomarkers in non-small cell lung cancer (NSCLC) and provide a checklist for prognostic and predictive serum tumor marker studies.

The prognostic value of tumor markers can be assessed both before and at defined time points during the course of disease. Thereby, they are particularly valuable if they provide additional prognostic information to clinical or imaging findings. Muley et al. [34] impressively show that CYFRA 21-1, CA 125, and CEA have such additional prognostic value in NSCLC patients with stable disease at the first CT scan. Thus, they can help to guide clinical decision-making in an otherwise unclear therapy response situation. A very similar original study is presented by Mang et al. [35] who found the combined use of CYFRA 21-1 and CA 125 to be highly predictive for the survival of patients with metastatic NSCLC and stable disease in the Impower150 trial. Geiger et al. [36] have conducted a biomarker substudy of the CEPAC-TDM trial, testing eight tumor markers before and during chemotherapy for their relevance in prognosis and predicting therapy response in advanced NSCLC patients. Finally, Buma et al. [37] review the utility of serum tumor markers in predicting prognosis and treatment response in advanced NSCLC.

Tumor markers are also meaningful for estimating prognosis in patients with small cell lung cancer (SCLC) prior and during therapy. Muley et al. [38] show the prognostic value of ProGRP, NSE and CYFRA 21-1 in SCLC patients who present with chemotherapy-induced remission in radiological staging. Thus, they may support guidance for further therapy application or intensified monitoring.

As tumor markers are measured in minimal-invasively accessible blood samples, their levels can easily be monitored over time during anticancer therapy. Beyond classical chemotherapies they could become important diagnostic tools for modern therapies. This is shown in a review of van den Heuvel et al. [39] on the role of serum tumor markers for response prediction and monitoring the response to immunotherapy and targeted therapies.

In order to facilitate the interpretation of multiple tumor marker kinetics in individual patients, algorithms have been developed that integrate absolute concentrations and changes in serum tumor markers for a better estimation of response to anticancer therapies. Van Delft et al. [40] compare such modeling strategies combining changes in multiple serum tumor biomarkers for the early prediction of immunotherapy non-response in NSCLC patients. Beyond pure analytics, the bioinformatic interpretation could cause a significant leap forward for the use of tumor markers – especially if they give timely information on the efficacy of the immune therapeutic strategy.

As mentioned above, molecular markers on ctNDA may be a "game changer" for the characterization of lung cancer subtypes, stratification for specific therapies and monitoring minimal residual disease. Michael J. Duffy [41] comprehensively reviews the potential of ctDNA as a biomarker for lung cancer and its applications for early detection, monitoring and therapy prediction. As accurate ctDNA diagnostics depends strongly on standardized preanalytical sample handling, Bronkhorst et al. [42] provide a useful pocket companion to cell-free DNA (cfDNA) preanalytics. Finally, Moes-Sosnowska et al. [43] give an update on the clinical significance of TP53 alterations in advanced NSCLC patients treated with EGFR, ALK and ROS1 tyrosine kinase inhibitors.

While many markers are already in clinical application, research on new markers for lung cancer diagnostics is ongoing. Although results in some studies may not be as promising as expected beforehand, they deserve to be mentioned if the studies were performed and evaluated in well-designed biomarker trials. Muller et al. [44] show that blood platelet RNA profiles do not enable nivolumab response prediction in NSCLC patients. Rupp et al. [45] find a lack of clinical utility of serum macrophage migration inhibitory factor (MIF) for monitoring therapy response and estimating prognosis in advanced lung

cancer. And Geiger et al. [46] report on missing prognostic value of soluble PD-1, PD-L1 and PD-L2 in lung cancer patients undergoing chemotherapy.

Altogether, this special issue provides a colourful bouquet of many biomarkers and their diagnostic applications in lung cancer. It reveals the achievements of the past, stimulates future intensified research, and illustrates that we are continuing "on the shoulders of giants" of tumor marker research. We would like to thank all authors and wish you a lot of pleasure when "raising the treasure of the old and young biomarkers" in this special issue.

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Author contributions

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PREPARATION OF THE MANUSCRIPT: SH.
REVISION FOR IMPORTANT INTELLECTUAL CONTENT: SH, HvR, MvH.
SUPERVISION: SH.

Conflict of interest

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