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Emerging Technologies and Advanced Biomarkers for Enhanced Toxicity Prediction and Safety Pharmacology

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Abstract

Background: Biomarkers are important tools in toxicology that can improve risk assessment, early detection of organ injury, and monitoring of pharmacological responses. However, rigorous validation is necessary to justify use for regulatory decision-making.

Purpose: This article reviews the current landscape surrounding established and emerging biomarkers of toxicity across multiple techniques, with a focus on assessment of merits, limitations, and validation needs.

Main Body: An overview of common clinical chemistry biomarkers used for safety monitoring of liver, kidney, heart, and inflammation is first provided, highlighting their biological relevance and applications in detecting organ dysfunction. Novel protein biomarkers emerging for enhanced sensitivity of injury detection are then discussed, such as microRNAs for liver and clusterin for kidney. Metabolomic biomarker approaches to assess biofluids and mitochondrial toxicity are outlined, along with toxicogenomic markers of susceptibility like HLA alleles. Non-invasive imaging techniques including ultrasound, MRI, and PET tracers for organ function are explored as techniques that provide additional modalities for biomarker measurement. Emerging tools like organ microphysiological systems and high-throughput omics for biomarker discovery are also described.

Conclusion: While great progress has been made, translation and qualification of novel biomarkers remains challenging. This review synthesizes key developments across biomarker categories, evaluates readiness for regulatory use, and outlines strategic considerations for fit-for-purpose biomarker validation to advance integration into drug development programs.

Keywords: Biomarkers; Toxicity; Validation; MicroRNAs; Metabolomics; Drug safety

Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; BUN: Blood Urea Nitrogen; BNP: Brain Natriuretic Peptide: CK-MB: Creatine Kinase MB; CRP-C: Reactive Protein; IL: Interleukin; TNF: Tumor Necrosis Factor; miRNA-MicroRNA; HMGB1: High Mobility Group Box1; K18: Keratin 18; NGAL:

Neutrophil Gelatinase Associated Lipocalin; HLA: Human Leukocyte Antigen; DNA: Deoxyribonucleic Acid; mtDNA - Mitochondrial DNA; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; FDG: Fluorodeoxyglucose; OCT: Optical Coherence Tomography; FDA: Food and Drug Administration; BEST: Biomarkers, Endpoints, and other Tools.

Introduction

Biomarkers are biological indicators that can be objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention [1]. Biomarkers can be classified into three main categories - exposure, effect, and susceptibility biomarkers as depicted in Figure 1 [2].

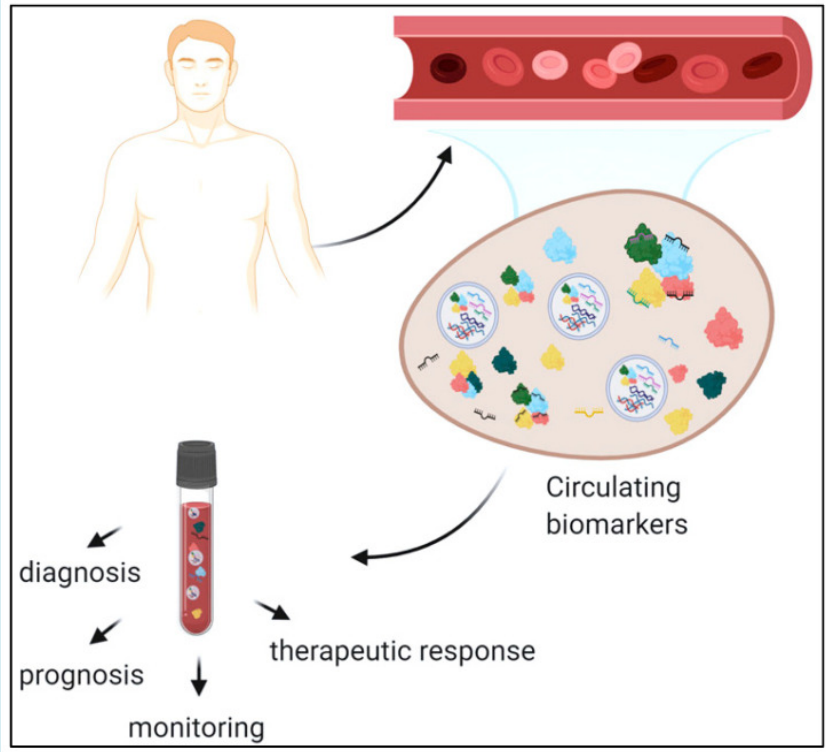

Figure 1: Biomarkers uses [2].

Exposure biomarkers indicate exposure to exogenous substances and can detect the presence and amount of exogenous chemicals or their metabolites. Effect biomarkers measure the biochemical, physiological, behavioral, or other alterations within an organism that can be recognized as an established or potential health impairment or disease. Susceptibility biomarkers indicate an inherent or acquired ability to respond to a substance in a particular way [3-8]. The use of biomarkers has several advantages over traditional approaches for toxicity testing. Biomarkers allow for rapid and high-throughput screening, provide mechanistic insights, and enable the detection of toxicity at lower levels of biological organization. However, there are also limitations to biomarkers such as lack of specificity, high natural variability, and difficulty in establishing links between biomarkers and apical endpoints. Proper biomarker validation is therefore critical [9-12]. Validation of a biomarker requires demonstrating its link to a biological process or endpoint, determining normal baseline values, evaluating reliability, reproducibility and robustness, and assessing responses following repeated exposures. Key criteria include sensitivity, specificity, accuracy, reproducibility, and relevance of the biomarker to the biological endpoint being measured. Rigorous statistical analysis of the performance characteristics is necessary during the validation process [13-17].

While biomarkers show promise for enhancing toxicity testing and regulatory decision-making, qualification remains challenging. This review provides a comprehensive overview of state-of-the-art toxicity biomarkers across multiple techniques and biological levels. It aims to assess the current landscape of biomarker validation and application, evaluate merits and limitations of emerging technologies, highlight

key biomarkers with potential for further development, and discuss strategic considerations surrounding integration into the drug development pipeline. Critical analysis is provided to inform fit-for-purpose biomarker qualification efforts.

Clinical Biomarkers

Liver function tests are important biomarkers for detecting liver injury. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are enzymes found in hepatocytes that are released upon cell damage, resulting in elevated serum levels. Alkaline phosphatase (ALP) is also elevated with cholestasis and bile duct obstruction. Bilirubin levels reflect liver excretory capacity and increase with hepatocellular injury. These biomarkers provide insight into different types of liver toxicity [18-25]. Kidney function biomarkers include creatinine, blood urea nitrogen (BUN) and albumin. Creatinine is a byproduct of muscle metabolism filtered by the glomeruli, so elevated levels indicate impaired filtration. BUN is a nitrogenous waste product that accumulates with kidney dysfunction. Decreased albumin suggests impaired reabsorption capacity. These biomarkers help assess nephrotoxicity and are considered standard measures of renal function [26-28]. Cardiac markers are used to detect cardiac muscle injury. Cardiac troponins T and I are structural proteins specific to the heart that are released with damage. Brain natriuretic peptide (BNP) is secreted by ventricular cardiomyocytes in response to wall stress. Creatine kinase MB (CK-MB) is an enzyme present in cardiac muscle that rises acutely after myocardial infarction. These biomarkers help diagnose different forms of cardiotoxicity [29-31]. Inflammatory cytokine biomarkers and C-reactive protein (CRP) elevate in response to tissue injury, infection and inflammation. Cytokines like IL-1, IL-6, TNF-alpha and CRP are nonspecific markers of systemic inflammation that are useful for monitoring inflammatory and immunotoxic effects [32-33].

Novel Protein Biomarkers

MicroRNAs (miRNAs) are short non-coding RNAs that regulate gene expression at the post-transcriptional level. miR-122 and miR-192 are liver-specific miRNAs that are released into circulation upon liver injury, making them sensitive biomarkers of hepatotoxicity as depicted in Table 1. Studies have shown miR-122 can detect liver injury earlier compared to traditional enzymes like AST and ALT [34-35]. High mobility group box 1 (HMGB1) is a nuclear protein released during necrosis that promotes inflammation. Caspase-cleaved keratin 18 (K18) is a protein fragment generated during apoptosis. Both are emerging biomarkers with potential to differentiate apoptotic and necrotic cell death mechanisms in drug-induced liver injury [36]. Clusterin is a glycoprotein induced in renal tubular injury and glomerular disease. Cystatin C is a cysteine protease inhibitor that is filtered by the glomerulus and has been proposed as an alternative to creatinine. Neutrophil gelatinase-associated lipocalin (NGAL) is one of the earliest biomarkers elevated after acute kidney injury. These novel urinary proteins show promise for detecting nephrotoxicity [37].

Biomarker	Organ	Description	Advantages	Limitations
miR-122	Liver	MicroRNA released by injured hepatocytes	High sensitivity, earlier indicator than ALT/AST	Not liver specific
miR-192	Kidney	MicroRNA marker of proximal tubule injury	Sensitive marker of AKI, stable in biofluids	Expression affected by age, gender, BMI
HMGB1	Multiple	Nuclear protein released during necrosis	Indicates mechanism of cell death	Lacks organ specificity
K18	Liver	Caspase-cleaved keratin marker of apoptosis	Distinguishes apoptosis vs necrosis	Limited evidence in humans
Clusterin	Kidney	Glycoprotein induced in tubular injury	Early biomarker of renal damage	Not specific for cellular injury mechanism

Table 1: Emerging Protein Biomarkers of Organ Injury.

Metabolomics Biomarkers

Metabolomics has become a powerful approach for discovering biomarkers and evaluating toxicity over the past ten years. It involves analyzing small molecule metabolites and metabolic profiles in biological fluids and tissues. Recent advances in mass spectrometry and NMR spectroscopy enable simultaneous quantification of thousands of metabolites in biofluids and tissues, providing a comprehensive view of metabolic pathways and networks that complements other omics approaches like genomics and proteomics [38]. Ultrahigh resolution mass spectrometers can detect metabolites at very low concentrations with high reproducibility.

A key advantage of metabolomics is that metabolites give a functional readout of biochemical activity and cellular phenotype, integrating genetic and environmental influences to provide insights into mechanisms of toxicity. Metabolic profiles can be classified by pattern recognition based on global signatures, while targeted methods quantify known biomarker panels. Resources like the Human Metabolome Database allow altered metabolites to be mapped onto interconnected pathways [38]. Key applications in toxicology include detecting organ injury in liver, kidney, heart and brain using biofluids like urine, blood and cerebrospinal fluid. Mitochondrial dysfunction, oxidative stress, fatty liver disease and cholestasis can also be assessed through metabolites. Bile acids synthesized in hepatocytes rise with cholestasis, making them sensitive indicators of impaired bile flow. Specific bile acids like glycochenodeoxycholic acid show promise for diagnosing drug-induced liver injury [39]. Acylcarnitines are intermediates in mitochondrial fatty acid beta-oxidation, so elevated long-chain acylcarnitines reflect mitochondrial dysfunction and can mark toxicity from drugs like valproic acid [40,41]. Taurine-conjugated bile acids and fatty acids generated during metabolism can serve as urinary biomarkers of liver and kidney injury in animal models [42].

Genomic Biomarkers

Genomic approaches like transcriptomics, proteomics, and epigenetics are being applied to find new biomarkers. High-throughput omics profiles can screen thousands of molecular targets to identify signatures linked to toxicity pathways. Transcriptomics analyzes global mRNA expression changes. Certain human leukocyte antigen (HLA) alleles have been linked to increased risk of idiosyncratic drug-induced liver injury (DILI) with some medications, suggesting HLA genotyping could help identify susceptible individuals [43,44].

Toxicogenomics examines global gene expression changes. Toxicogenomics can differentiate compounds causing liver, kidney, heart, or nervous system toxicity in preclinical models. Machine learning methods have defined genomic biomarker signatures that can distinguish DILI compounds from non-hepatotoxicants in preclinical models. These signatures could aid toxicity screening if sufficiently validated [45,46].

Proteomics assesses protein expression and post-translational modifications using techniques like mass spectrometry. Multiplex protein assays can measure panels of biomarkers, improving predictive capacity over individual proteins. Proteomic analysis of biofluids or tissues can provide mechanistic insights. Epigenetic DNA modifications like methylation and histone alterations mediate environmental influences on gene expression. Epigenetic biomarkers are still at early stages, but DNA methylation changes have been associated with exposures like metals, enabling detection of prior insults. Mitochondrial DNA (mtDNA) is more vulnerable to damage from reactive metabolites versus nuclear DNA. mtDNA damage and mutations have been proposed to underlie mitochondrial toxicity. Assays detecting decreased mtDNA content or increased deletions show promise for monitoring mitochondrial genotoxicity [47].

Imaging Biomarkers

Imaging technologies are being explored as non-invasive methods to assess organ toxicity. Quantitative ultrasound can measure liver fat content by analyzing tissue echogenicity, attenuation, and backscatter properties. Ultrasound elasticity imaging is also being developed to stage liver fibrosis. MRI can quantify liver and kidney fibrosis through techniques like elastography which visualize tissue stiffness. Advanced imaging techniques like ultrasound, MRI, CT, and nuclear imaging are being explored as noninvasive methods to assess organ function and toxicity. These modalities provide spatial information and enable repeated measures over time [48]. Positron emission tomography (PET) involves injecting targeted radiotracers to quantitatively image tissue receptors, transporters, and enzymes in vivo. Nuclear imaging with PET and SPECT tracers allows visualization of organ metabolism, blood flow, receptors, and transporters. PET tracers for mitochondria function, neuroinflammation, and drug transporters are in development to detect early functional changes that may precede gross organ damage. Radioisotope clearance studies can also assess kidney and liver function. PET tracers for things like mitochondrial function, dopamine receptors, and drug transporters are being developed to detect organ-specific functional changes that may precede gross toxicity [49,50].

Emerging Technologies

Microphysiological systems incorporate human cells into engineered microenvironments mimicking tissues and organs on a small scale. These “organs-on-chips” allow high-throughput toxicity screening and measurement of functional biomarkers in a human-relevant context. Systems have been developed for liver, kidney, lung, heart, intestine, brain and other organs. Organ-on-a-chip microfluidic devices contain human cells in an engineered microenvironment mimicking physiological tissue and organ functions as depicted in Table 2. Organs-on-chips overcome limitations of conventional cell cultures by modeling key factors like tissue-tissue interfaces, spatiochemical gradients, mechanical forces and immune components. This provides more predictive toxicity assessment and mechanistic insights compared to standard in vitro assays. These systems allow high-throughput toxicity screening and measurement of mechanistic biomarkers in a

human-relevant context [51,52]. Stem cell derived organoids are self-organized 3D tissue cultures that recapitulate aspects of the developmental program and architecture of organs. Organoids can be used to model diseases, screen drugs, and test toxicities in a human-specific manner. Biomarkers related to things like liver enzymes, fibrosis, and lipid accumulation have been evaluated. Multiplexed protein assays using techniques like mass spectrometry allow simultaneous quantification of hundreds of proteins in a small volume. This facilitates screening of large compound libraries and derivation of multigene toxicity signatures. However, signatures developed on animal models require validation in human trials [53]. Multiplex cytokine panels are being applied to assess panels of cytokine biomarkers. Multiplex assays enhance throughput but can suffer from technical issues like cross-reactivity [54,55]. These emerging technologies provide new capabilities for toxicity assessment and biomarker discovery. However, integration into drug development requires extensive validation of clinical utility and correlation with apical measures of organ injury or function.

Modality	Biomarker Potential	Examples	Limitations	Regulatory Status
Ultrasound	Liver steatosis/fibrosis	Controlled attenuation parameter, acoustic structure quantification	User/technique dependent	Not qualified
MRI Elastography	Liver/kidney fibrosis	Shear stiffness measurement	Limited standardization	FDA qualified for liver
PET Imaging	Organ function, transporters/ receptors	FDG, 11C-metformin	Radiation exposure, high cost	Exploratory stage
OCT Imaging	Cell/tissue morphology	High-resolution microscopy	Limited depth, lack of quantification	Preclinical utility

Table 2: Imaging Modalities as Emerging Toxicity Biomarkers.

Future Directions

One major future direction should be advancing qualification of emerging biomarker modalities like metabolomics, proteomics, transcriptomics and imaging. This requires studies directly correlating findings from these technologies with organ histopathology and injury in human clinical trials. Multiplexed platforms that integrate complementary biomarker modalities like proteins, metabolites, and gene expression signatures to enhance predictive capacity beyond individual biomarkers also need further development and qualification [56]. Additional future directions include leveraging high-throughput omics and bioinformatics to efficiently screen large patient cohorts for discovery and validation of biomarker signatures, while remaining vigilant of overfitting. Expanding open-access data repositories and biobanks to share biomarker data across translational phases will facilitate collective progress [57]. Providing regulatory guidance on appropriate study designs and evidentiary requirements for biomarker qualification is also important to advance translation [58]. Finally, further developing microphysiological systems and organs-on-chips to provide advanced human models for biomarker discovery prior to clinical validation remains an area for future investment [59]. Exploring emerging technologies like circulating miRNAs, photoacoustics, radiomics, and targeted imaging probes for non-invasive assessment of organ function and injury also holds great promise for the future [60].

Conclusion

This review demonstrates that while traditional biomarkers of organ toxicity like liver enzymes and serum creatinine remain clinically useful, an expanding array of novel biomarkers show promise for improving sensitivity, specificity, and prediction of tissue injury in drug development. Notably, newer techniques like metabolomics profiling, genomic signatures, and molecular imaging provide complementary modalities to assess discrete aspects of toxicity pathways from exposure to functional impairment. Though still early in qualification, microRNA panels, bile acid metabolites, elastography, and multiplex protein assays exemplify approaches with translational potential if rigorous fit-for-purpose validation is conducted.

Recommendations

To advance regulatory qualification and clinical integration of promising toxicity biomarkers, several strategic recommendations can be made:

- Prioritize biomarker development efforts around gaps in sensitivity of current gold standards, focusing on clinical relevance.

- Employ fit-for-purpose validation encompassing analytical validity, clinical association with histopathology, kinetics in reversible vs irreversible injury, and testing across diverse patient populations.
- Develop biomarkers with multiple applications across drug development, such as utility for both preclinical screening and clinical diagnostics.
- Collect preliminary biomarker data in early clinical trials to guide integration into subsequent efficacy studies and risk management programs.
- Utilize public-private partnerships and regulatory feedback to align with evidentiary requirements for biomarker qualification.
- Establish biobanks and open-access data repositories to support biomarker research from discovery through validation stages.
- Employ fit-for-purpose multivariate signatures and assess utility of emerging biomarkers over traditional methods in combined models.
- Explore clinically relevant multiplexed platforms that enable evaluation of biomarker panels for enhanced predictive capacity.

Ethics Approval and Consent to Participate

Not Applicable

Consent for Publication

Not Applicable

Availability of Data and Materials

All data are available and sharing is available as well as publication.

Competing Interests

The authors hereby that they have no competing interests.

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Authors Contributions

The authors completed the study protocol and were the primary organizers of data collection and the manuscript's draft and revision process. Tamer A. Addissouky wrote the article and ensured its accuracy. All authors contributed to the discussion, assisted in designing the study and protocol and engaged in critical discussions of the draft manuscript. Lastly, the authors reviewed and confirmed the final version of the manuscript.

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