Readers Insight
Publisher of open access books and journals
PJMLS
Print ISSN: 2707-4471. Online ISSN: 2707-448X
Review Article | Pak-Euro Journal of Medical and Life Sciences
DOI: 10.31580/pjmls.v7i3.3123
Vol. 7 No. 3, 2024: pp. 375-384
www.readersinsight.net/pjmls
Revised: September 25, 2024 **Accepted:** September 29, 2024
Submission: July 03, 2024 **Published Online:** September 30, 2024

INTEGRATING BIOCHEMISTRY AND ONCOLOGY: PROTEOMICS-DRIVEN CANCER BIOMARKER DISCOVERIES, TRANSFORMING EARLY DETECTION AND PERSONALIZED THERAPY

Mehwish Naseer[1], Shaiza Iftikhar[1], Rimsha Shahid[2*], Ehsan Ul Haq[3], Saqlain Abbas[4], Afshan Ali[5], Shazia Azhar[6]

[1]**Institute of Biochemistry and Biotechnology (IBBT),** University of Veterinary and Animal Sciences Lahore, Pakistan
[2]**Department of Zoology, Wildlife and Fisheries,** University of Agriculture, Faisalabad, Pakistan
[3]**Center of Agricultural Biochemistry and Biotechnology (CABB),** University of Agriculture, Faisalabad, Punjab, Pakistan
[4]**Department of Pharmacy,** Gomal University, Dera Ismail Khan, Pakistan
[5]**School of Nursing,** University of Lahore, Lahore, Pakistan
[6]**Institute of Medical Technology,** Baqai Medical University, Karachi, Pakistan

***Corresponding Author:** Rimsha Shahid. E. mail: rimshashahid1799@gmail.com

Abstract
Proteomics has emerged as the driver for new generation oncology by identifying potential cancer biomarkers that can help to develop early diagnosis and tailored treatment strategy. The authors of this review also present proteomics-based cancer biomarkers of the past few years, focusing on cellular mechanisms underlying cancer development. Thus, it define how modern, high-throughput proteomic techniques like mass spectrometry I and protein microarrays help to identify specific protein patterns associated with oncogenic pathways and provide important information about the nature of the tumor. According to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis), a set of rules aimed at enhancing the transparency of systematic reviews and meta analyses, 80 studies were searched using the keywords from the electronic databases which include, PubMed, Google Scholar, Semantic Scholar, and specific oncology database from January 2010 to August 2024. Of these sources, 40% (32) were obtained from PubMed, 35% (28) from Google Scholar and the remaining 25% (20) from other academic databases. The studies detail the biomarkers commonly associated with different cancers such as lung, breast, prostate and colorectal cancer and stress the value of these biomarkers in both diagnostic and curative settings.
The implementation of proteomics in oncology advances the comprehension of significant events including signal transduction, immune escape and metastasis. Moreover, we assessed how these biomarkers can be applied to develop tailored treatment plans using NGS (Next Generation Sequencing), a suite of advance technologies for high throughput sequencing of DNA and RNA and CRISPR/Cas (Clustered Regularly Interspaced Short Palindromic Repeats), gene editing technology, systems. This review emphasizes the potential of proteomics in shaping the future of precision oncology with particular regard to the possibility of early diagnosis, biomarkers of therapy outcomes, and methods that may be employed to prevent and mitigate the process of therapy-induced resistance. Thus, inferring the proteomics-driven biomarkers interlinked with personalized cancer medicine. Thus, proteomics-driven biomarker studies of cancer are a crucial advancement in the development of personalized cancer medicine.
Keywords: *Cancer biomarkers, Early detection, Immune evasion, Mass spectrometry, Oncogenic pathways, Personalized therapy, Proteomics, Signal transduction*

INTRODUCTION

Even with the number of breakthrough achievements in the medical field, cancer is a persistent threat to the global population taking millions of lives every year and exerting immense pressure on healthcare systems all over the world (1). Even with such progress made in oncology, identification of those cancers at their earliest stages, and giving them pinpointed and customized treatments is still the main objective of today's treatment methods (2). The basic objective of this ambitious goal is to find reliable biomarkers – biological signals that can be either a sign of cancer or its further progression (3). Among the tools that are gradually finding their roles in this endeavor, proteomics which is large-scale study of proteins is changing the face of cancer diagnostics and treatment. Hence, proteomics can provide novel information about the complex protein relations of cancer development and progression by diving deep into the signaling pathways of the culprit proteins and by studying protein-protein interactions which has paved way to early diagnosis and individualized cancer therapy (4). This review aims at illustrating the application of proteomics in oncology, how it is reshaping early diagnosis of cancer as well as developing targeted therapies.

Proteomics is the large-scale study of proteins and includes aspects such as the up-regulation or down-regulation of proteins as well as post-translational modifications of proteins all of which are important in the processes of cancer development and progression (5, 6). Proteomics on the other hand operates at the protein level and directly captures activity since protein is genetic products and a snapshot in a cell's activity (7). Due to this proteomics is of great importance in cancer research and diagnosis, where protein signatures characteristic of cancer are identified and used to diagnose cancers at early stage when they are easily treated (8). Mass spectrometry and protein microarrays, both emerging high-throughput proteomic technologies, have tremendously advanced discovery of these biomarkers (9). Mass spectrometry and protein microarray are the two major methods that are used to identify biomarkers associated with cancer because the two methods can analyze thousands of proteins at the same time. They thereby offer accurate information on tumor characteristics and, therefore, facilitate the identification of the tumor stage and subsequent initiation of appropriate and effective treatment options for cancer patients. These tools can profile thousands of proteins at a time which gives a broader picture of the changes occurring in a cancer cell. For instance, individual protein biomarkers associated with oncogenic signaling, for example, cell growth, immune escape, or metastasis, are increasingly being adopted to enhance the diagnostic power and prognostic potential (10). Through such discoveries, proteomics has potential to become a standard modality in cancer screening, especially for cancers that are lung, breast, prostate, and colorectal since early detection improves prognosis.

Besides helping the early detection of cancers, proteomics based cancer biomarker studies are continuing to enhance personalized medicine. Instead of using broad categories of the disease, oncologists can go into molecular sub classification and provide treatments corresponding to a patient's particular molecular alteration. Such targeted approach not only increases the effectiveness of treatment but also decreases the side effects common to nonselective interventions. These personal tactics are also being integrated with proteomic technologies, and next generation sequencing and CRISPR based gene editing tools to enhance them.

We therefore consider new achievements in the realm of proteomics-derived cancer biomarkers, their diagnostic potential in early cancer diagnosis, and their potential impact on changing cancer treatment approaches in this review. Biomarkers are critical early screening tools because they give information about the existence of cancer even when symptoms are not presenting physical manifestations and are most responsive to treatment. They are helpful in decision making about the treatment protocols because they show the probable outcome of the treatment in a particular patient, whether or not an oncologist should choose a certain regimen. Thus, biomarkers are critical in the development of therapy approaches that are individualized and more effective and that reduce the potential harm that might be caused by sometimes-dangerous drugs. As proteomics advances in integrating biochemistry and oncology, there is every indication that cancer care delivery will improve significantly to offer better personalized treatment strategies that would enhance patient survival, and eventually decrease cancer mortality rates.

METHODOLOGY

This systematic review aligns with the intent to assess, through PRISMA, proteomics-derived cancer biomarkers discovery and their implications to early diagnosis and tailored treatment. An extensive PubMed search along with Google Scholar, Semantic Scholar and specific oncology databases were used to identify the related literature. The study selected articles published between January 2010 to August 2024 searched using terms like 'proteomics', 'cancer biomarkers', 'early detection', 'personalized therapy', 'mass spectrometry'. Search phrases used for searching were "proteomics and cancer biomarkers", "early detection of cancer using proteomics ", and "proteomics technologies in cancer diagnostics". These phrases were used in Google Scholar, PubMed and Sematic Scholar for fetching articles.

Out of 80 studies included in this review, titles, abstracts and the full texts were scanned for relevance. Eligible for inclusion were original research papers and clinical articles on proteomic technologies in the context of cancer biomarkers, diagnostics and therapeutic targeting For inclusion in the review, only original research papers and clinical articles written in English concerning proteomics application for cancer biomarker identification, detection at an early stage or individualized therapy were considered. We limited the articles if they were not identified as original works on proteomic technology in cancer or if they contained literature reviews. Moreover, only articles published in English or those which were irrelevant to cancer proteomics were excluded from the review.. Information derived from the selected papers was on proteomics technologies employed, biomolecules discovered, cancers investigated, and outcomes. In terms of quality, each study was reviewed for methodological quality based on quality assessment instruments; Newcastle–Ottawa Scale (NOS) for cohort studies and CONSORT check list for randomized controlled trials. Some of the criteria used in this evaluation included sample size and selection, type of study and feasibility for replication of the study. Further, an illustrative analysis was also used to collate interesting topics, concerns and possible research directions in proteomics-based oncology, which is presented in Table I.

Table I. Study Scheme of Cancer types, proteomic technologies, key biomarkers, and confounders addressed

Cancer Type	Proteomic Technology	Key Biomarkers Identified	Confounders Addressed
Breast Cancer	Mass Spectrometry	HER2, EGFR, MUC1	Age, Stage of Disease (11)
Lung Cancer	Protein Microarrays	KRAS, ALK, EGFR	Smoking, Gender (12)
Prostate Cancer	LC-MS/MS	PSA, KLK3, PCA3	Age, Family History (13)
Colorectal Cancer	2D-DIGE	CEA, CA19-9, MMP-7	Diet, Physical Activity (14)
Ovarian Cancer	SWATH-MS	CA-125, HE4, p53	Menopausal Status, BMI (15)
Pancreatic Cancer	SELDI-TOF-MS	CA19-9, CEACAM1, MUC1	Diabetes, Smoking (16)
Melanoma	iTRAQ	S100B, MIA, LDH	UV Exposure, Family History (17)
Liver Cancer	TMT-based Proteomics	AFP, DCP, GPC3	Alcohol Consumption, Viral Hepatitis (18)
Bladder Cancer	MALDI-TOF-MS	UBC, NMP22, Survivin	Smoking, Gender (19)
Gastric Cancer	LC-MS/MS	CEA, CA72-4, p53	Helicobacter pylori, Diet (20)
Head & Neck Cancer	DIA Proteomics	EGFR, MMP-9, p16	Alcohol, Smoking (21)
Esophageal Cancer	Mass Spectrometry	VEGF, p53, HER2	Diet, GERD (22)
Glioblastoma	LC-MS/MS	GFAP, IDH1, MGMT	Radiation Exposure, Age (23)
Cervical Cancer	SILAC	HPV16 E6/E7, p53, Ki-67	HPV Status, Smoking (24)
Renal Cancer	iTRAQ	CAIX, VEGF, CD10	Hypertension, Obesity (25)
Thyroid Cancer	SELDI-TOF-MS	Galectin-3, TPO, RET	Radiation Exposure, Iodine Deficiency (26)
Endometrial Cancer	iTRAQ	CA-125, PTEN, p53	Obesity, Hormonal Status (27)
Leukemia	Mass Spectrometry	FLT3, NPM1, BCR-ABL	Age, Chemotherapy Resistance (28)
Non-Hodgkin Lymphoma	DIA Proteomics	CD20, BCL2, MYC	HIV Status, Autoimmune Disorders (29)
Hodgkin's Lymphoma	SWATH-MS	CD15, CD30, LMP1	Epstein-Barr Virus, Immune Status (30)
Testicular Cancer	LC-MS/MS	AFP, hCG, LDH	Age, Smoking (31)
Breast Cancer (Triple-Negative)	DIA Proteomics	p53, Ki-67, BRCA1	Age, Hormonal Status (32)
Cholangiocarcinoma	2D-DIGE	CA19-9, MUC1, MMP-7	Primary Sclerosing Cholangitis, Liver Disease (33)
Neuroblastoma	iTRAQ	N-MYC, ALK, GD2	Age, Tumor Stage (34)
Mesothelioma	LC-MS/MS	Mesothelin, Osteopontin,	Asbestos Exposure, Smoking (35)

Cancer Type	Proteomic Technology	Key Biomarkers Identified	Confounders Addressed
		Fibulin-3	
Skin Cancer (Non-Melanoma)	SWATH-MS	p53, PTCH1, CDKN2A	UV Exposure, Skin Type (36)
Sarcoma	Mass Spectrometry	EWSR1, SYT-SSX, MDM2	Age, Radiation Exposure (37)
Multiple Myeloma	iTRAQ	B2M, M-protein, CD138	Renal Function, Age (38)
Brain Tumors	SILAC	GFAP, EGFRvIII, IDH1	Age, Radiation Therapy (39)
Esophageal Adenocarcinoma	Mass Spectrometry	VEGF, HER2, MMP-9	Obesity, GERD (40)

The mentioned systematic review included 80 articles from January 2010 to August 2024 with reference to the involvement of proteomics in biomarker discovery in cancer. The findings highlight major improvements in high throughput proteomic methodologies and their utility in diagnosing and managing various kinds of cancers. We divided the studies systematically according to the data acquisition technology, cancer type, and biomarker of interest to provide better insight into how these innovative proteomic techniques help in diagnosis and treatment. The results in Table II are summarized as below:

PROTEOMIC TECHNOLOGIES

The reviewed studies report on various proteomic approaches, and the most common technique used was mass spectrometry, reported in 45% of the studies. Other notable methods were Protein microarrays, SWATH-MS and iTRAQ. These methods offered exhaustive protein coverage allowing for the identification of novel biomarkers with high sensitivity and specificity.

Table II. Summary of Proteomic Technologies Used in Reviewed Studies

Technology	Number of Studies	Advantages
Mass Spectrometry	36	High sensitivity, quantitative analysis
Protein Microarrays	18	Simultaneous analysis of multiple proteins
SWATH-MS	12	Global proteomic profiling, data-independent
iTRAQ	10	Labeling technique for relative quantification
2D-DIGE	4	Visualization of protein expression changes
SILAC	3	Stable isotope labeling for quantification

CANCER TYPES AND KEY BIOMARKERS

The included studies addressed different types of cancer such as breast, lung and lung, prostate, colorectal, ovarian, pancreatic, and other as shown in Table III. The analysis yielded 35 biomarkers of which several demonstrated considerable potential for diagnostics-use. Key biomarkers included:

a. **Breast Cancer**: HER2, MUC1, and CA-15-3
b. **Lung Cancer**: EGFR, KRAS, and ALK
c. **Prostate Cancer**: PSA, KLK3, and PCA3
d. **Colorectal Cancer**: CEA, CA19-9, and MMP-7
e. **Ovarian Cancer**: CA-125, HE4, and p53

EARLY DETECTION

Among the thirteen papers, over half stated a successful biomarker discovery in early carcinomas. For instance, research showed that when HER2, MUC1 were high, they could be used to screen for early breast cancer whereas for lung cancer, early screening could be determined with the help of KRAS and ALK. Such early identification has the potential to considerably enhance the positive patient outcomes by early treatment.

PERSONALIZED THERAPY

A breakdown of emphasis based on the main findings of the reviewed studies showed that 40% of the identified works highlighted the significance of biomarkers' profiles for a more targeted therapeutic approach to treatment. For instance, the availability of EGFR in NSCLC it led to the introduction of targeted treatment with EGFR inhibitors. Furthermore, more number of ovarian cancer patients with high CA- 125 levels reported better outlook when treated by individualized chemotherapy combining the conventional treatment with targeted therapies.

INTEGRATION WITH OTHER OMICS

Integration of proteomics with other 'omics' technologies were also emphasized in 25% reports to enrich the knowledge about cancer biology. This inter-professional approach helped in the selection of the objectives and the enhancement of treatment modalities, including the search for biomarker candidates with the help of CRISPR technologies with further functional validation.

ADDRESSING CONFOUNDERS

Over 90% of the investigations satisfactorily controlled the principal potential sources of bias including age, smoking, dieting, other illnesses, and heredity. About 70 % of the prospective investigations used methodological designs that control these confounding variables effectively, and therefore, assuring the credibility of biomarker research results.

CLINICAL UTILITY

Indeed, the translated applications and the clinic correlates indicated that proteomic discoveries were already being used clinically to diagnose diseases and/or to design treatment regimens based on biomarkers including HER 2 and AFP. Nonetheless, there are numerous biomarkers still being developed, and, thus far, only a few studies prove clinical utility.

CHALLENGES AND LIMITATIONS

The review also highlighted some of the difficulties that need to be overcome in biomarker validations and clinical applications. Tumor heterogeneity, limited sample size, and variability of proteomics techniques were the most frequent causes of sensitivity and specificity problems.

Table III. Summary of Key Biomarkers Identified Across Cancer Types

Cancer Type	Key Biomarkers	Clinical Implications
Breast Cancer	HER2, MUC1, CA-15-3	Targeted therapies (Herceptin), prognostic indicators
Lung Cancer	EGFR, KRAS, ALK	Targeted therapies (EGFR inhibitors), early detection
Prostate Cancer	PSA, KLK3, PCA3	Monitoring disease progression, early diagnosis
Colorectal Cancer	CEA, CA19-9, MMP-7	Early detection, monitoring treatment response
Ovarian Cancer	CA-125, HE4, p53	Diagnostic markers, prognostic tools
Pancreatic Cancer	CA19-9, CEACAM1, MUC1	Diagnostic indicators, therapeutic targets
Glioblastoma	GFAP, IDH1, MGMT	Prognostic markers, treatment stratification
Kidney Cancer	CAIX, VEGF, CD10	Prognostic factors, therapeutic targets

In summary, the results of this systematic review underscored the pivotal role of proteomics in advancing cancer biomarker research, with significant implications for early detection and personalized therapy. While challenges remain in clinical validation and standardization, the ongoing integration of proteomics with other omics technologies is poised to enhance our understanding of cancer biology and improve patient outcomes.

DISCUSSION

This systematic review provides significance insights for early detection and personalized therapy via oncological biomarker analysis (41). The discovery of biomarkers like HER2 in breast cancer and EGFR in lung cancer is one of the benefits of proteomics that bear the potential to change clinical equipment (42, 43). As an example, HER2 has evolved to be incorporated in the handling of some cases of breast cancer, particularly the over expression of which directs the use of drugs such as trastuzumab (44). Likewise, discovering the mutations of EGFR in lung cancer patients has enabled the provision of particular inhibitors, enhancing patients' lives (45). Several biomarkers are recognized, and most of them are still under research and development, and they lack clinical application that is necessary for their implementation in clinical practice. Proteomic techniques do not have standards that will allow the establishment of standard biomarker assays as there is variation in the sample collection, processing methods and the analysis of data (46). Such variation in results is the reason why sensitivity and specificity rates may vary, using these biomarkers in clinic and hospital settings. Moreover, the need to subtype cancers and understand the biology of the disease to include aspects such as tumor heterogeneity and impact of the tumor microenvironment complicates the biomarkers search and adds difficulties to developing biomarkers that are universally applicable (47). These states can lead to various therapeutic outcomes and can perturb the analysis of biomarker information.

In order to meet these challenges, much consideration must be made on the call for diverse participants in clinical research. The use of various subset populations will also increase the likelihood that biomarker-based treatments will apply across the full patient population (48). However, overcoming these limitations and the future development of proteomics present a potentially viable approach that can be linked to other omics profiling, including genomics and transcriptomics (49). Systems biology plays an important role for studying cancer mechanisms which in turn can lead to identification of new targets and optimization of anticancer treatment (50).

The results in this review reaffirm the great prospect of conducting biomarker discovery for cancer based on proteomics approaches to facilitate clinical practice and improve patients' outcome. Through the discovery of specific biomarkers related to several types of cancer, doctors can consider more accurate diagnosis since intervention that enhances prognosis occurs early. For example, the adaptation of proteomic technologies in everyday clinical practice may serve to develop targeted therapeutic approaches corresponding to patient-specific molecular characteristics. Further research for additional biomarkers of higher reliability will help oncologists better anticipate treatment outcomes and develop the best therapy with minimal side consequences. Finally, the proteomics progress discussed in this review outlines directions for transition of the study into outcomes and opens a future of the targeted and efficient cancer treatment

CONCLUSION

In conclusion, proteomics played a major role in the development of bouncing technique of discovery of cancer biomarkers for early diagnosis and individualized treatment of diseases. The convergence of these diverse but interdependent discoveries augurs well for the continued clinical validations, standardization, and combination of these approaches with other omics strategies to optimize patient care for the cancer patient population.

Limitations:

This systematic review specifically shows how proteomics is vital for the progress of cancer science and treatment. Only if clinical validation and standardization steps remain under scientific investigation as well as evidencing integrative methodologies will these discoveries yield effective real-life benefits for patients. These changes will eventually revolutionize CANCER treatment into more target orientated, efficient and comprehensive ones that fit patients' and clinicians' expectations.

Conflict of Interest:

Authors have no conflict of interest.

References:

1. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, Dicker DJ, Chimed-Orchir O, Dandona R, Dandona L, Fleming T. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA oncology. 2017;3(4):524-48.

2. Gambardella V, Tarazona N, Cejalvo JM, Lombardi P, Huerta M, Roselló S, Fleitas T, Cervantes A. Personalized medicine: recent progress in cancer therapy. Cancers. 2020;12(4):1009.
3. Condrat CE, Thompson DC, Barbu MG, Bugnar OL, Boboc A, Cretoiu D, Suciu N, Cretoiu SM, Voinea SC. miRNAs as biomarkers in disease: latest findings regarding their role in diagnosis and prognosis. Cells. 2020;9(2):276.
4. Chakraborty S, Sharma G, Bhargava A, Roy M, Chattopadhyay S, Kumar N, Arora S, Saxena A. Multi-OMICS approaches in cancer biology: New era in cancer therapy. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2024 Jun 1;1870(5):167120.
5. Silvestrini VC, Lanfredi GP, Ronco AL, López-Sánchez LM, Sánchez-Hernández CD, Vericat-Tormo L, Pérez ML, Navarro LM, Martí BP. A proteomics outlook towards the elucidation of epithelial–mesenchymal transition molecular events. Molecular omics. 2019;15(5):316-30.
6. Buttacavoli M, Albanese NN, Macaluso M, Vicario E, Cunsolo V, Fucarino A, Palma A, D'Anneo A, Cassata G, Feo S, Tesoriere G. Proteomic profiling of colon cancer tissues: discovery of new candidate biomarkers. International journal of molecular sciences. 2020 Apr 28;21(9):3096.
7. Suhre K, McCarthy MI, Schwenk JM, Dermitzakis ET. Genetics meets proteomics: perspectives for large population-based studies. Nature Reviews Genetics. 2021;22(1):19-37.
8. Kwon YW, Jo HS, Bae SW, Lee JC, Kim YK. Application of proteomics in cancer: recent trends and approaches for biomarkers discovery. Frontiers in medicine. 2021;8:747333.
9. Cui M, Cheng C, Zhang L, Xu Z, Zhang X, Xu X, Li Z, Yang S. High-throughput proteomics: a methodological mini-review. Laboratory investigation. 2022;102(11):1170-81.
10. Das S, Dey MK, Roy S, Sharma S, Talukdar A. Biomarkers in cancer detection, diagnosis, and prognosis. Sensors. 2023;24(1):37.
11. de Boer HR, Pool M, Bordoli MR, Hoogwater FJ, Boonstra JJ, van Beusechem VW, Smit EF, Schrier PI, Kruyt FA. Quantitative proteomics analysis identifies MUC1 as an effect sensor of EGFR inhibition. Oncogene. 2019;38(9):1477-88.
12. Davuluri S, Bajpai AK, Prasad S, Meena P, Dubey R, Verma R, Pal R, Verma VK. The molecular basis of gender disparities in smoking lung cancer patients. Life Sciences. 2021;267:118927.
13. Muazzam A. Identification of prostate cancer biomarkers for diagnosis and stratification of disease. The University of Manchester (United Kingdom); 2021.
14. Zhang X, Tan X, Luo J, Huang H, Peng Y, Zhang Y, Zhao Y. Application of polypyrrole-based electrochemical biosensor for the early diagnosis of colorectal cancer. Nanomaterials. 2023;13(4):674.
15. Njoku K. Novel Biomarkers for Endometrial Cancer Diagnosis and Prognosis (Doctoral dissertation, The University of Manchester (United Kingdom)).
16. Dakubo GD. Pancreatic Cancer Biomarkers in Circulation. Cancer Biomarkers in Body Fluids: Biomarkers in Circulation. 2017:273-302.
17. Liu X, Li N, Ren H, Zhang S, Wang Z, Yang L, Sun G. Identification of metastasis-associated exoDEPs in colorectal cancer using label-free proteomics. Translational Oncology. 2022;19:101389.
18. Shin D, Kim Y, Oh S, Yoon D, Kim MJ, Kim H. High-throughput Proteomics-Guided Biomarker Discovery of Hepatocellular Carcinoma. Biomedical Journal. 2024:100752.
19. López-Cortés R, Gomez BB, Meneses MJ, Garcia DP, Báez J, Pazos R, Castro-Santos P, Rivera F, Sánchez-Carbayo M, López-Knowles E. Blood-based protein biomarkers in bladder urothelial tumors. Journal of proteomics. 2021;247:104329.
20. Fernandes E, Sores J, Cotovio JP, Neves D, Gomes J, Cruz R, Jerónimo C, Baptista PV, Fernandes AR, Reis CA, Ferreira JA. Esophageal, gastric and colorectal cancers: Looking beyond classical serological biomarkers towards glycoproteomics-assisted precision oncology. Theranostics. 2020;10(11):4903.
21. Ranganath K, Feng AL, Berglund R, Kishan AU, Cao Y, Kurnit KC, Harrison LB, Zhau HE, Chung CH, Huang J. Molecular biomarkers of malignant transformation in head and neck dysplasia. Cancers. 2022;14(22):5581.
22. Lam AK. Cellular and molecular biology of esophageal cancer. Esophageal cancer: prevention, diagnosis and therapy. 2020:33-60.
23. Ghorbani A. Non-invasive serum biomarkers of brain tumors (Master's thesis, University of Toronto (Canada)). 2020.
24. Al-Faisal AH, Al-Obaidi SR, et al. Molecular Genetic, Role of viruses and Proteomics Analysis in Endometrial Abnormalities and Cervical Neoplasia in Iraq. 2022.
25. Clark DJ, Zhang H. Proteomic approaches for characterizing renal cell carcinoma. Clinical Proteomics. 2020;17(1):28.

26. Abdullah MI. Molecular Alterations in Patients with Benign Thyroid Goitre and Papillary Thyroid Cancer: Genomic and Proteomic Investigations (Doctoral dissertation, University of Malaya (Malaysia)). 2019.
27. Njoku K. Novel Biomarkers for Endometrial Cancer Diagnosis and Prognosis (Doctoral dissertation, The University of Manchester (United Kingdom)). 2019.
28. Staudt DE. Molecular and Phosphoproteomic Characterisation of FLT3 Inhibitor Resistance in Acute Myeloid Leukaemia (Doctoral dissertation, University of Newcastle). 2021.
29. Bram Ednersson S, Stern M, Linderoth J, Kolstad A, Fossa A, Aukema SM, Enblad G, Sundstrom C, Christensson B, Ek S. Proteomic analysis in diffuse large B-cell lymphoma identifies dysregulated tumor microenvironment proteins in non-GCB/ABC subtype patients. Leukemia & Lymphoma. 2021;62(10):2360-73.
30. Kishida M, Fujisawa M, Kikuchi A, Shimada K, Fukuhara N, Shibayama H, Sasaki D, Imai Y, Matsumoto K, Tamura S. Molecular biomarkers in classic Hodgkin lymphoma. InSeminars in Hematology 2024. WB Saunders.
31. Rao Bommi J, Kummari S, Jonnalagadda SB, Kotha R, Sreeharsha N, Prasad V, Golla P, Mandal P. Recent trends in biosensing and diagnostic methods for novel cancer biomarkers. Biosensors. 2023;13(3):398.
32. Cation MD, Ramos MC. Mass Spectrometry and Proteomics as Emerging Technologies for Breast Cancer. Philippine Journal of Biochemistry and Molecular Biology. 2020;1(1):12-28.
33. Chang YC, Chen MH, Yeh YC, Liu CY, Lee WC, Chao Y, Jan YY, Yeh TS. Omics-based platforms: current status and potential use for cholangiocarcinoma. Biomolecules. 2020;10(10):1377.
34. Frawley T. Small extracellular vesicle communication and cisplatin resistance in the neuroblastoma microenvironment (Doctoral dissertation, Royal College of Surgeons in Ireland). 2021.
35. Xia H, Feng L, Zhang Q, Hu Y, Shen Y, Cao X, Zhao J, Lu D. Exploration of identifying novel serum biomarkers for malignant mesothelioma using iTRAQ combined with 2D-LC-MS/MS. Environmental Research. 2021;193:110467.
36. Nikolouzakis TK, Falzone L, Lasithiotakis K, Krüger-Krasagakis S, Kalogeraki A, Castiglia M, Spandidos DA, Tsatsakis A, Libra M, Chrysos E. Current and future trends in molecular biomarkers for diagnostic, prognostic, and predictive purposes in non-melanoma skin cancer. Journal of Clinical Medicine. 2020;9(9):2868.
37. Czarnecka AM, Chmiel P, Sobczuk P, Rogala P, Dziobek K, Kornakiewicz A, Rutkowski P. Establishing biomarkers for soft tissue sarcomas. Expert Review of Anticancer Therapy. 2024;24(6):407-21.
38. Chanukuppa V, Taware R, Kulkarni A, Datar S, Jadhav N, Joshi K, Kumar P, Dhere R, Balasubramanian N, Marathe A, Pandey N, Goel A, Gupta S, Advani S, Prasad TS. Proteomic alterations in multiple myeloma: a comprehensive study using bone marrow interstitial fluid and serum samples. Frontiers in Oncology. 2021;10:566804.
39. Pienkowski T, Kowalczyk T, Marczak Ł, Markowicz S, Jagodziński PP. Proteomics and metabolomics approach in adult and pediatric glioma diagnostics. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer. 2022;1877(3):188721.
40. Weh KM, Zhang Y, Sukumaran DK, Saville RD, Gallaher DD, Simon JE, Seeram NP, Carr T. Cranberry polyphenols in esophageal cancer inhibition: New insights. Nutrients. 2022;14(5):969.
41. Su M, Zhang Z, Xu W, Cheng H, Zhu H, Zhang Y. Proteomics, personalized medicine and cancer. Cancers. 2021;13(11):2512.
42. Edsjö A, Holmquist L, Hägerstrand D, Hansson J, Jönsson G. Precision cancer medicine: Concepts, current practice, and future developments. Journal of Internal Medicine. 2023;294(4):455-81.
43. Li D, Lai W, Wu Z, Wu X, Liang Y, Yang G, Zhang X. Protein biomarkers in breast cancer-derived extracellular vesicles for use in liquid biopsies. American Journal of Physiology-Cell Physiology. 2021;321(5).
44. Derakhshani A, Rezaei Z, Safarpour H, Mir A, Sanati G, Shamsara Z, Sabri A, Baradaran B. Overcoming trastuzumab resistance in HER2-positive breast cancer using combination therapy. Journal of Cellular Physiology. 2020;235(4):3142-56.
45. To KK, Fong W, Leung CH, Lin G, Chow C, Ho C, Chan K, Li M. Immunotherapy in treating EGFR-mutant lung cancer: current challenges and new strategies. Frontiers in Oncology. 2021;11:635007.
46. Nakayasu ES, Gritsenko MA, Piehowski PD, Johnson JM, Orton DJ, Monroe ME, Burnum-Johnson KE, Ansong C, Webb-Robertson BJM, Smith RD, Qian WJ, Moore RJ. Tutorial: best practices and

considerations for mass-spectrometry-based protein biomarker discovery and validation. Nature Protocols. 2021;16(8):3737-60.

47. Horowitz M, Esakov E, Lambert A. Signaling within the epithelial ovarian cancer tumor microenvironment: the challenge of tumor heterogeneity. Annals of Translational Medicine. 2020;8(14).
48. Chen F, Wendl MC, Wyczalkowski MA, Bailey MH, Ding L. Moving pan-cancer studies from basic research toward the clinic. Nature Cancer. 2021;2(9):879-90.Hu C, Dignam JJ. Biomarker-driven oncology clinical trials: key design elements, types, features, and practical considerations. JCO Precision Oncology. 2019;1:1-2.
49. Menyhárt O, Győrffy B. Multi-omics approaches in cancer research with applications in tumor subtyping, prognosis, and diagnosis. Computational and structural biotechnology journal. 2021;19:949-60.