Autoantibodies: Powerful Biomarkers in Cancer Precision Medicine

Cancer is an abnormal, uncontrolled growth of cells that migrate from one tissue throughout the body, invading other distal tissues. Despite a long, thorough history of research, a cure has eluded scientists, primarily because of the heterogeneity of the disease. Cancer can begin in different places, take on different characteristics and can often be difficult to diagnose and treat. The National Cancer Institute lists over 100 different types of cancers (A to Z List of Cancer Types - NCI) each with unique screening procedures, diagnostics, and treatment protocols[3].

What are the Barriers to Curing Cancer?

The hurdles encountered by researchers and clinicians to provide effective treatments and quality care to cancer patients are overwhelming. From diagnosis, to treatment, to quality of life, the variables are innumerable. The greatest barrier to a cure is inherent heterogeneity, making diagnosis difficult, choosing treatments complicated, and prognosis uncertain[4,5]. This heterogeneity also means no single treatment is effective against all cancers. Early detection is the key. When detected early, the 5 year survival rate in the United States exceeds 90% for most cancers[6]. However, present cancer detection protocols only capture about 29% of cancers, relying heavily on patient screening methods such as imaging and symptom reporting, techniques often employed after cancer has metastasized. These techniques are costly and inconsistent[7].

Current scientific investment in understanding cancer relies heavily on genomics. Much has been learned from genetics about how various cancers develop and metastasize, but genomics data alone have not delivered on a cure, and while genomics studies continue to hold great promise, other approaches are becoming available that can have significant impact.

An unexpected observation from the very early twentieth century is now having a renaissance: Tumors stimulate production of autoantibodies[8]. While genetics may reveal potential, the autoantibody signature indicates the presence. Most importantly, autoantibodies indicate cancer presence very early in the disease, long before metastasis, and are the product of continuous immune-surveillance mechanisms that mark our disease-associated changes in the host proteome. These immunoglobulins are not only useful for early cancer detection, but can also help with patient stratification, understanding therapy resistance and uncovering potential pathways for therapeutic exploitation[9,10].

What is the Relationship between Cancer and Autoantibodies?

In early stages of tumor growth, cancer cells can elicit an immune response and initiate production of autoantibodies[11-13] (Figure 1). Cancerous cells, like any other cell, produce proteins and utilize energy to support their growth. Some expressed proteins may be novel, tumor-specific antigens (TSA), while others are existing host proteins, tumor-associated antigens (TAA). Tumor-specific antigens are produced by cancer cells as the result of mutated or variant genes or other abnormal expression or modification. Tumor-associated antigens are self-proteins that are aberrantly expressed. Often, they are produced in the wrong location or expressed at the wrong level. The immune system identifies the novel, abnormal and potentially ectopic expression and produces antibodies against these proteins, thus producing autoantibodies which flag the disease[11]. Circulating autoantibodies, therefore, mark-out these proteins long before any currently used

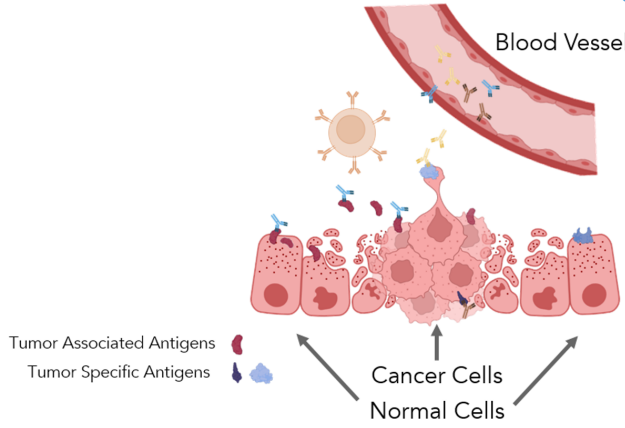

Figure 1. Tumor growth damages surrounding tissue, initiating an immune response. The antigenic proteins synthesized by cancer cells may be common to the host, tumor-associated antigens, or they may be unique, tumor-specific antigens. Autoantibodies are antibodies produced against tumor-associated and tumor -specific antigens. These are produced in detectable quantities, circulating in the blood via the Humoral Immune System.

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screening method[7,10,11,13-15]. The autoantibodies remain in circulation as long as disease persists.

Early expression and persistence following tumor appearance make autoantibodies perfect liquid biopsy biomarkers for detecting and tracking cancer.

What role do autoantibodies play?

Autoantibodies in Cancer Detection & Prognosis

Cancer diagnosis is often conducted on an individual basis. Only four population screening protocols are in use including for breast, colorectal, cervical and lung cancers. Each of these tests uses some form of imaging. Consequently, the tumor must be large enough to visualize. Other forms of cancer lack reliable screening techniques and therefore rely heavily on symptom reporting and biopsy[7]. Biomarkers found in the blood hold great promise for early detection across all cancers. Blood samples contain a plethora of measurable analytes and are easy to collect. Blood tests are common practice in the medical community with the potential to provide quicker results with less discomfort to patients compared with tissue biopsies[16,17]. Numerous blood derived markers of cancer already exist[18]; however, testing for these markers is usually complimentary to tissue biopsies because in most cases only single markers are screened and these are rarely conclusive on their own. Should a blood test return a positive result, a biopsy is most often the next step. Autoantibody screening is promising for early cancer detection with the potential to improve the whole treatment decision tree.

Evaluating autoantibodies from patient sera is a less invasive, powerful approach that is well suited for early detection. Tumors induce production of several autoantibodies, not just one, thus a set, or signature, of autoantibodies across a patient population can be diagnostic, prognostic and could be used to identify potential therapeutic targets[9]. Detection of autoantibodies to p53, for example, in a lung cancer patient enabled medical practitioners to intervene before emergence of the tumor[15,19]. In a recent, comprehensive study by Patel et al. (2022), 60 different autoantibodies of interest were uncovered from a screen of more than 1600 antigens across a cohort of 157 patients with non-small cell lung cancer (NSCLC). Eighteen of the 60 autoantibodies correlated with survival rates. Evaluating various permutations of these 18 autoantibodies revealed that 13 strongly correlated with 5-year patient survival (Table 1). These 13 autoantibodies were also predictive in a validation cohort, demonstrating the strength of the approach. Interestingly, a number of these autoantibodies were cancer testis antigens[20] - fetal antigens that are silenced in all adult somatic tissues except the testes – potentially indicating that the patients with a poor prognosis had a distinct, more cancer stem cell-like sub-type of NSCLC.

Biomarker	Name
SPATA19*	Spermatogenesis-associated protein 19
TSPY3*	Cancer Testis Antigen 78/Testis Specific Protein Y-Linked 3
GLS2	Glutaminase 2
TCEA2*	Transcription Elongation Factor A2/TFIIS/Testis-Specific SII gene
TSGA10*	Testis-specific gene protein 10/Cancer Testis Antigen 79
HMGN5	High Mobility Group Nucleosome Binding Domain 5/NSBP1
LUZP4*	Leucine Zipper Protein 4/Cancer Testis Antigen 28
HDAC4	Histone Deacetylase 4
SPACA3*	Sperm Acrosome membrane-associated protein 3/Cancer Testis Antigen 54
IMPDH1	Inosine Monophosphate Dehydrogenase 1/LCA11
TXN2	Thioredoxin 2/MT-TRX/COXPD29
TFG	Trafficking from ER to Golgi Regulator/TRKT3 Oncogene/TRK-Fused Gene Protein
PPP2R1A	Protein Phosphatase 2 Scaffold Subunit alpha/Serine Threonine Protein Phosphatase 2A

Table 1. Set of autoantibodies found to strongly correlate with poor survival. *Cancer Testis Antigen.

By examining autoantibodies in patient sera, Patel et al. uncovered a novel signature of 13 autoantibodies with high predictive power of poor prognosis among post-operative non-small cell lung cancer patients. At present, none of the 13 proteins identified via this autoantibody screen are listed among the Tumor Markers in Common Use by the National Cancer Institute[18]. This work illustrates the ease and power of utilizing a large autoantibody screen to reveal a set of markers highly predictive of cancer prognosis. The predictive power of using autoantibodies may exceed those of genetic approaches[20,21]. Cancer heterogeneity results in the production of numerous different tumor specific and tumor associated autoantigens across different cancers, patients, and stages. This heterogeneity can be exploited by measuring multiple autoantibodies simultaneously to identify the presence of early stage cancer as well as patient prognosis. Current genetic screens typically focus on individual genes. A signature comprised of multiple autoantibodies will have a higher predictive value than a single marker alone. Further, the autoantibody panels provide new insights and potential therapeutic targets for treating NSCLC. For example, the cancer testis antigens (CTAs) which are prominent in the signature identified by Patel et al. are typically expressed in male germ cells and during embryogenesis. Thus, their ectopic expression in NSCLC patients (male and female) may provide an excellent, well-aimed therapeutic target – indeed, certain CTAs such as NY-ESO-1 and MAGEA3 have been proposed as vaccine targets in cancers such as

melanoma. Future screens will undoubtedly unveil other prognostic panels[20].

Autoantibodies in Personalized Medicine

From the mid-1990s until around 2010, the pharmaceutical industry witnessed exponential increases in drug development costs with fewer drugs coming to market. The reasons were complex including, among other factors, increased requirements for superior efficacy, poor patient responses, and inconsistent regulations for newly developed drugs, often resulting in poor safety profiles and ineffective treatments[22-24]. Better decision making including biomarker driven targeted medicine appears to impact reversing this trend[23]. Identifying patients most likely to benefit from medication and likely to have fewer side effects can help improve safety and efficacy profiles while meeting regulatory demands[23,24]. Genetic markers have contributed to patient stratification and improved decision making regarding drug development[24]. To further this cause, autoantibodies are uniquely positioned to provide further gains in precision medicine. Autoantibody signatures are ideal for early detection, prognosis, patient stratification and treatment response prediction[9,10]. Recent research has begun to identify the predictive power of autoantibodies, most notably in immunotherapy.

Within the last 15 years, new immunotherapeutic treatments have had a positive impact on treating cancer. There are several FDA and EMA approved immunotherapy based treatment options including immune checkpoint blockade, CAR-T and anti-CTLA4 immune modulation[25,26]. Most of these treatments target non-solid tumors, such as leukemia. Despite clear successes, 40-80% of patients either fail to respond to the therapy or develop resistance over time[27]. Further, nearly all patients report adverse events at some time during the treatment, even years later[27-29]. Biomarkers are needed to identify patients most likely to respond to immunotherapy as well as predict immune-related adverse events. This will help prescribers and patients select appropriate therapies, co-therapies, and follow up options. Interestingly, autoantibody presence has been noted in patient sera following immune checkpoint inhibitor immunotherapies[29,30].

Immune checkpoint inhibition (ICI) immunotherapy is a relatively new strategy, and studies regarding immune-related adverse events are ongoing. Da Gamma Duarte et al.[31] quantified autoantibody titers against more than 1600 antigens in a Phase I dose-escalation study of 5 stage III/IV metastatic melanoma patients with the goals of identifying autoantibody signatures predictive of outcomes, including adverse events. There were several unique characteristics of this study. First, although it is known that immune checkpoint inhibitors induce classical autoimmune disease autoantibodies[32], the study by Da Gamma Duarte examined many more autoantibodies. Second, the study utilized a protein microarray composed of properly folded proteins (see x). This is an important characteristic because most protein microarrays do not employ folded proteins. Both antibodies and autoantibodies predominantly require tertiary structure for appropriate binding. Using correctly folded proteins increases specificity compared with fragmented proteins, unfolded proteins or linear peptides[1,2,33-37]. Third, the study took a novel approach to treating advanced stage melanoma. Study participants received initial treatment with Bacillus Calmette-Guerin (BCG)[38] followed 36 days later with the immune checkpoint inhibitor Ipilimumab, and then maintenance dosing with Ipilimumab every 12 weeks thereafter. Fourth, healthy donors contributed sera for comparison. This unique design enabled the researchers to examine autoantibody signatures along a timeline of therapeutic outcomes contrasted with autoantibody signatures in healthy controls. The trial terminated early due to serious adverse events, the very endpoint under investigation. With a small sample size and early termination, unique autoantibody signatures associated with adverse events require further study. However, because the researchers screened a large library of 1600+ autoantibodies, a correlation between adverse events and increased expression of autoantibodies was clearly uncovered. Other labs have yielded similar results[29,39] while still others have not reported a relationship between autoantibodies and adverse events or cancer progression[40]. However, it is important to note that these latter studies did not sample a large repertoire of autoantibodies and moreover did not use correctly folded proteins as the basis of their assays.

Autoantibody detection following immune-related adverse events has raised interest in the predictive and prognostic value of autoantibodies in immunotherapeutic treatment planning, albeit the promising early results require further validation in larger cohorts[30], and would moreover be enhanced by use of a comprehensive, high specificity technique to evaluate the large number of autoantibodies that are influenced by both the disease as well as the therapy. The work by De Gamma Duarte[31] offers a road map for thorough future investigation of autoantibody relevance in this space.

Autoantibodies in Drug Discovery

Identifying therapeutically viable targets to treat cancer is a complex process that requires pathway identification, drug modeling, safety evaluation, and potential efficacy. Patient autoantibody signatures offer a glimpse into a cancer's nature, identifying aberrant proteins that may be involved in tumor growth. Genetics approaches have been able to identify

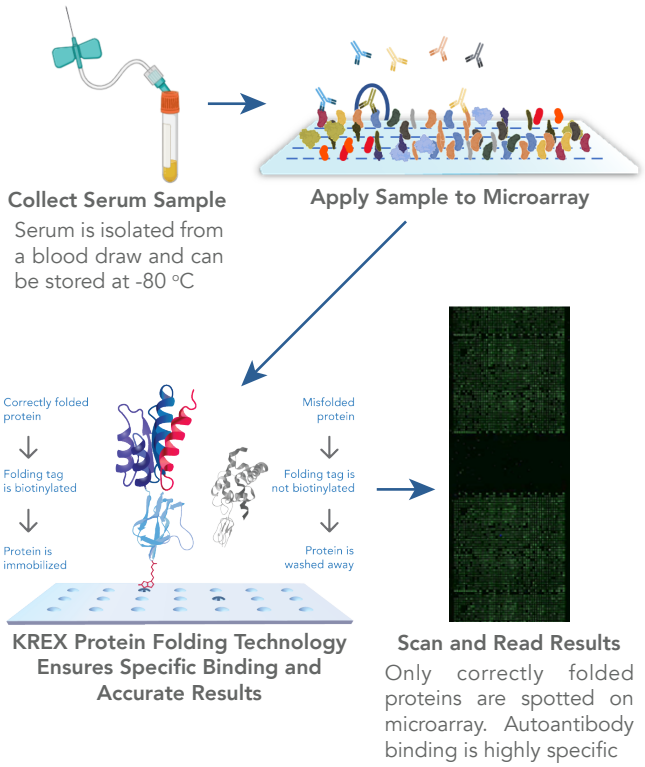
thousands of genomes for dozens of tumors, but very few therapeutic targets because the genetics do not necessary reflect the metabolism of the tumor. Aberrant protein expression, including autoantigens marked out by the presence of cognate autoantibodies, represents a functional link to tumor biology and may therefore point the way more directly to new potential therapeutic targets[41,42]. For example, the development of Caplacizumab to treat a non-cancerous disease, acquired thrombotic thrombocytopenic purpura (TTP), partly relied on the discovery of autoantibodies to help identify potential therapeutic targets, in this case the enzyme ADAMTS13[43]. Autoantibodies may also highlight pathways that can aid in the fight against cancer.

The benefits of understanding autoantibody physiology have yet to be fully realized. Found not only in autoimmune diseases and cancer, autoantibodies in healthy humans were noted some time ago[44,45], and as a result, they have been considered in disease protection. Studies in the 80's indicated that autoantibodies may have beneficial functions including antibacterial, housekeeping and immunoregulation[44,46] . More recently, Klunk et al (2022) discovered a unique level of genetic selection involving autoantibodies in a study that examined samples dating back to 14th century Europe. Possessing two copies of a variant form of ERAP2, an antigen-presenting aminopeptidase, imparted some level of protection against bubonic plague. Interestingly, the variant ERAP2 has been associated with Crohn's Disease[47]. The ramifications of this finding for cancer and other infectious disease research involve a role for autoantibodies in evolutionarily induced protection against disease. They may also highlight exploitable pathways involved in cancer progression. For example, Shah et al (2019) found lower incidence of cancer in scleroderma patients whose sera contained autoantibodies against RNA polymerase I (anti-RPA194)[48], thus indicating that this polymerase might be a good drug target. By contrast, certain autoimmune diseases are now recognized as risk factors for specific cancers (e.g., SLE and multiple myeloma; Crohn's disease and colorectal cancer), whilst immune-related adverse events following cancer therapies can resemble classic autoimmune diseases (e.g., autoimmune hepatitis; inflammatory arthritis; cutaneous disorders). The causal associations between autoimmune diseases, cancers and immune-related adverse events is thus an emerging area that requires further investigation.

Conclusions

When discovered, autoantibodies were initially dismissed as representative of disease or tissue damage and not the normal work of the immune system[8]. Even from these early days, though, it was evident that autoantibodies held great diagnostic potential. The unique patterns of autoantibody production mirror the highly heterogeneous nature of cancer. Cancer heterogeneity means a similar tumor in different patients may grow at different rates, metastasize differently, result in different symptoms, respond differently to non-invasive therapies and so forth. To accomplish these activities, cancerous cells utilize numerous biochemical pathways and as a result churn out ectopically expressed and aberrant proteins compared to healthy tissue, giving themselves away early to an immune system surveying the landscape for anything out of place. Historically, scientists and clinicians have looked for single, yet powerful, targets among these pathways to limit or destroy the cancer. For example, targets that may regulate proliferation (paclitaxel and trabectedin), or transcription (doxorubicin). These drugs are used selectively and are prescribed for specific types of cancer. Hence, while cancer is heterogeneous, the approach to treat cancer has been less so. Autoantibody signatures represent a set of proteins unique to the cancer. Keys to successfully identifying predictive autoantibodies include using a

SIDEBAR 1: How KREX Protein Folding Technology Works



SIDEBAR 1: A major breakthrough in autoantibody screening methods is the production of correctly folded proteins[1,2]. Using full-length, properly folded proteins help ensure appropriate antibody/antigen binding and high specificity. Sengenics microarrays use KREX technology to ensure that array proteins are full-length, properly folded and functional. KREX stands for correctly folded recombinantly expressed protein and refers to Sengenics patented technology for expressing and immobilizing correctly folded, fully functional proteins on a streptavidin-coated surface using biotin carboxyl carrier protein (BCCP) as a folding marker. A misfolded or fragmented protein results in BCCP misfolding, making its biotinylation site unavailable and preventing it from binding to the streptavidin coated surface. Incorrectly folded proteins are simply washed away. This technology maintains conformational epitopes and ensures optimal antibody-epitope binding and was designed to produce exemplary signal-to-noise for fine detection of autoantibody signatures.

high-fidelity expression system, high throughput processing, powerful machine-learning-based bioinformatics methods and correctly folded proteins. High density microarrays allow researchers to examine hundreds or thousands of proteins. Machine learning simplifies the task of studying various autoantibody permutations while taking into account specific patient variables, ultimately providing highly specific, predictive biomarkers.

SIDEBAR 2: How are Autoantibodies Measured?

Autoantibodies were first associated with disease and cancer over 100 years ago[8,49-52]. Originally, identification of autoantibodies was determined via complement fixation, a method in which erythrocyte cell lysis occurred when bathed in patient sera containing autoantibodies. Although the concept of immunodiagnosis was born through these research endeavors[14], complement fixation was not an amenable technique for biomarker discovery. Technology capable of delivering high throughput, high specificity results with autoantibodies was not available until the mid-2000's[1,2,36,37,53]. By the late 1990's microarrays offered the most comprehensive elucidation of expressed genes but translating this technology to proteins lagged mainly because the human genome contains ~20K genes while the proteome is thought to contain >1m proteoforms[33]. Labeling, capturing, and analyzing this large a library takes time, effort, and significant computing power.

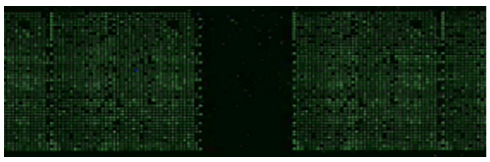


Figure 2. A sample-labeled Sengenics i-Ome Microarray Chip

For antibody detection, proteins or peptides are typically adhered to a solid surface (e.g. glass slide) in a known arrangement. Thousands of proteins or peptides can be attached on a single slide and are therefore capable of identifying thousands of different antibodies from a small sample of patient sera. In most cases, sample labeling and identification occur via indirect immunofluorescence[33,36,54]. For autoantibody detection, the array is incubated with patient sera containing autoantibodies that bind their respective epitopes. Labeling is completed by adding a fluorescently labeled secondary antibody (Figure 2). It is important that the autoantigen is accurately encoded and retains its shape otherwise specific binding is lost[33-35]. Commercial protein microarrays usually produce the proteins and peptides recombinantly through expression vectors. The design, expression system, vector, protein adhesion process, surface chemistry and tertiary structure of the protein all influence the quality of antibody detection results[36]. The KREX technology used with the i-Ome protein microarray is a good example of managing all these variables (see Sidebar 1).

References

1. Matsuoka, K., et al., Simple screening method for autoantigen proteins using the N-terminal biotinylated protein library produced by wheat cell-free synthesis. J Proteome Res, 2010. 9(8): p. 4264-73.
2. Beeton-Kempen, N., et al., Development of a novel, quantitative protein microarray platform for the multiplexed serological analysis of autoantibodies to cancer-testis antigens. Int J Cancer, 2014. 135(8): p. 1842-51.
3. Cancer Types. 2019 [cited 2022 10/31/2022]; Available from: https://www.cancer.gov/types.
4. Hinohara, K. and K. Polyak, Intratumoral Heterogeneity: More Than Just Mutations. Trends Cell Biol, 2019. 29(7): p. 569-579.
5. Robertson-Tessi, M. and A.R. Anderson, Big Bang and context-driven collapse. Nat Genet, 2015. 47(3): p. 196-7.
6. UnitedStatesCancerStatistics. Cancer. 2020 [cited 2020; Available from: Www.cdc.gov. https://www.cdc.gov/cancer/uscs/.
7. Hackshaw, A., et al., Estimating the population health impact of a multi-cancer early detection genomic blood test to complement existing screening in the US and UK. Br J Cancer, 2021. 125(10): p. 1432-1442.
8. Simon, C.E., M. Assisted by Drs. Elizabeth, and R. Mary, On Auto-Antibody Formation and Antihemolysis. J Exp Med, 1909. 11(5): p. 695-717.
9. Duarte, J.S., J; Mulder, N; Blackburn, J., Protein Functional Microarrays: Design, Use and Bioinformatic Analysis in Cancer Biomarker Discovery and Quantitation, in Bioinformatics of Human Proteomics, X. Wang, Editor. 2013, Springer Science+Business Media Dordrecht. p. 39-74.
10. Aziz, F. and J. Blackburn, Autoantibody-Based Diagnostic Biomarkers:Technological Approaches to Discovery and Validation, in Autoantibodies and Cytokines, W.A. Khan, Editor. 2018, IntechOpen. p. 159-188.
11. de Jonge, H., et al., Anti-Cancer Auto-Antibodies: Roles, Applications and Open Issues. Cancers (Basel), 2021. 13(4).
12. Da Gama Duarte, J., J.M. Peyper, and J.M. Blackburn, B cells and antibody production in melanoma. Mamm Genome, 2018. 29(11-12): p. 790-805.
13. Zaenker, P. and M.R. Ziman, Serologic autoantibodies as diagnostic cancer biomarkers--a review. Cancer Epidemiol Biomarkers Prev, 2013. 22(12): p. 2161-81.
14. Rose, N.R., The Concept of Immunodiagnosis, in Autoantibodies (Third Edition), Y. Shoenfeld, P.L. Meroni, and M.E. Gershwin, Editors. 2014, Elsevier. p. 3-10.
15. Tan, E.M. and J. Zhang, Autoantibodies to tumor-associated antigens: reporters from the immune system. Immunol Rev, 2008. 222: p. 328-40.
16. Laranja, W.W., et al., The Biopsychosocial Burden of Prostate Biopsy at the Time of Its Indication, Procedure, and Pathological Report. Prostate Cancer, 2019. 2019: p. 2653708.
17. Hayes Balmadrid, M.A., et al., Anxiety prior to breast biopsy: Relationships with length of time from breast biopsy recommendation to biopsy procedure and psychosocial factors. J Health Psychol, 2017. 22(5): p. 561-571.
18. Tumor Markers in Common Use. 2021 [cited 2022 10/31/2022]; Available from: https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-list.
19. Lubin, R., et al., Serum p53 antibodies as early markers of lung cancer. Nat Med, 1995. 1(7): p. 701-2.
20. Patel, A.J., et al., A highly predictive autoantibody-based biomarker panel for prognosis in early-stage NSCLC with potential therapeutic implications. Br J Cancer, 2022. 126(2): p. 238-246.
21. Kratz, J.R., et al., A prognostic assay to identify patients at high risk of mortality despite small, node-negative lung tumors. JAMA, 2012. 308(16): p. 1629-31.
22. Van Norman, G.A., Overcoming the Declining Trends in Innovation and Investment in Cardiovascular Therapeutics: Beyond EROOM's Law. JACC Basic Transl Sci, 2017. 2(5): p. 613-625.
23. Schulthess, D., et al., Medicine adaptive pathways to patients (MAPPs): using regulatory innovation to defeat Eroom's law. Chin Clin Oncol, 2014. 3(2): p. 21.
24. Ringel, M.S., et al., Breaking Eroom's Law. Nat Rev Drug Discov, 2020. 19(12): p. 833-834.
25. FDA Approval Timeline of Active Immunotherapies. 2021 9/7/2022 [cited 2022 10/31/2022]; Available from: https://www.cancerresearch.org/fda-approval-timeline-of-active-immunotherapies.
26. Medicines. 2020 [cited 2022 10/31/2022]; Available from: https://www.ema.europa.eu/en/medicines.
27. Jenkins, R.W., D.A. Barbie, and K.T. Flaherty, Mechanisms of resistance to immune checkpoint inhibitors. Br J Cancer, 2018. 118(1): p. 9-16.
28. Zhang, Y., et al., Biomarkers and risk factors for the early prediction of immune-related adverse events: a review. Hum Vaccin Immunother, 2022. 18(1): p. 2018894.
29. Iwama, S., T. Kobayashi, and H. Arima, Clinical Characteristics, Management, and Potential Biomarkers of Endocrine Dysfunction Induced by Immune Checkpoint Inhibitors. Endocrinol Metab (Seoul), 2021. 36(2): p. 312-321.
30. Ghosh, N., et al., Autoantibodies in Patients With Immune-Related Adverse Events From Checkpoint Inhibitors: A Systematic Literature Review. J Clin Rheumatol, 2022. 28(2): p. e498-e505.

31. Da Gama Duarte, J., et al., Autoantibodies May Predict Immune-Related Toxicity: Results from a Phase I Study of Intralesional Bacillus Calmette-Guerin followed by Ipilimumab in Patients with Advanced Metastatic Melanoma. Front Immunol, 2018. 9: p. 411.
32. Giannicola, R., et al., Early blood rise in auto-antibodies to nuclear and smooth muscle antigens is predictive of prolonged survival and autoimmunity in metastatic-non-small cell lung cancer patients treated with PD-1 immune-check point blockade by nivolumab. Mol Clin Oncol, 2019. 11(1): p. 81-90.
33. Yu, X., B. Petritis, and J. LaBaer, Advancing translational research with next-generation protein microarrays. Proteomics, 2016. 16(8): p. 1238-50.
34. Van Regenmortel, M.H., Immunoinformatics may lead to a reappraisal of the nature of B cell epitopes and of the feasibility of synthetic peptide vaccines. J Mol Recognit, 2006. 19(3): p. 183-7.
35. Barlow, D.J., M.S. Edwards, and J.M. Thornton, Continuous and discontinuous protein antigenic determinants. Nature, 1986. 322(6081): p. 747-8.
36. Duarte, J.G. and J.M. Blackburn, Advances in the development of human protein microarrays. Expert Rev Proteomics, 2017. 14(7): p. 627-641.
37. Robinson, W.H., et al., Autoantigen microarrays for multiplex characterization of autoantibody responses. Nat Med, 2002. 8(3): p. 295-301.
38. Morton, D.L., et al., BCG immunotherapy of malignant melanoma: summary of a seven-year experience. Ann Surg, 1974. 180(4): p. 635-43.
39. Les, I., et al., Association of immune-related adverse events induced by nivolumab with a battery of autoantibodies. Ann Med, 2021. 53(1): p. 762-769.
40. Barth, D.A., et al., Evaluation of autoantibodies as predictors of treatment response and immune-related adverse events during the treatment with immune checkpoint inhibitors: A prospective longitudinal pan-cancer study. Cancer Med, 2022. 11(16): p. 3074-3083.
41. Adhikari, S., et al., A high-stringency blueprint of the human proteome. Nat Commun, 2020. 11(1): p. 5301.
42. Yang, J., et al., Early screening and diagnosis strategies of pancreatic cancer: a comprehensive review. Cancer Commun (Lond), 2021. 41(12): p. 1257-1274.
43. Peyvandi, F., et al., Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med, 2016. 374(6): p. 511-22.
44. Schattner, A., The origin of autoantibodies. Immunol Lett, 1987. 14(2): p. 143-53.
45. Guilbert, B., G. Dighiero, and S. Avrameas, Naturally occurring antibodies against nine common antigens in human sera. I. Detection, isolation and characterization. J Immunol, 1982. 128(6): p. 2779-87.
46. Schwartz, R.S. and B.D. Stollar, Origins of anti-DNA autoantibodies. J Clin Invest, 1985. 75(2): p. 321-7.
47. Klunk, J., et al., Evolution of immune genes is associated with the Black Death. Nature, 2022.
48. Shah, A.A., et al., Protective Effect Against Cancer of Antibodies to the Large Subunits of Both RNA Polymerases I and III in Scleroderma. Arthritis Rheumatol, 2019. 71(9): p. 1571-1579.
49. Korngold, L. and D. Pressman, The localization of antilymphosarcoma antibodies in the Murphy lymphosarcoma of the rat. Cancer Res, 1954. 14(2): p. 96-9.
50. Graham, J.B. and R.M. Graham, Antibodies elicited by cancer in patients. Cancer, 1955. 8(2): p. 409-16.
51. Makari, J.G., Recent studies in the immunology of cancer. III. Detection of cancer antibodies and auto-antibodies by an intradermal reaction, with a review of the detection in human serum of cancer antigens by the Schulz-Dale method. J Am Geriatr Soc, 1960. 8: p. 16-29.
52. Rose, N.R., S. Shulman, and E. Witebsky, Studies of normal and malignant tissue antigens. Cancer Res, 1956. 16(9): p. 831-41.
53. Ganesan, V., D.P. Ascherman, and J.S. Minden, Immunoproteomics technologies in the discovery of autoantigens in autoimmune diseases. Biomol Concepts, 2016. 7(2): p. 133-43.
54. Irure-Ventura, J. and M. Lopez-Hoyos, The Past, Present, and Future in Antinuclear Antibodies (ANA). Diagnostics (Basel), 2022. 12(3).