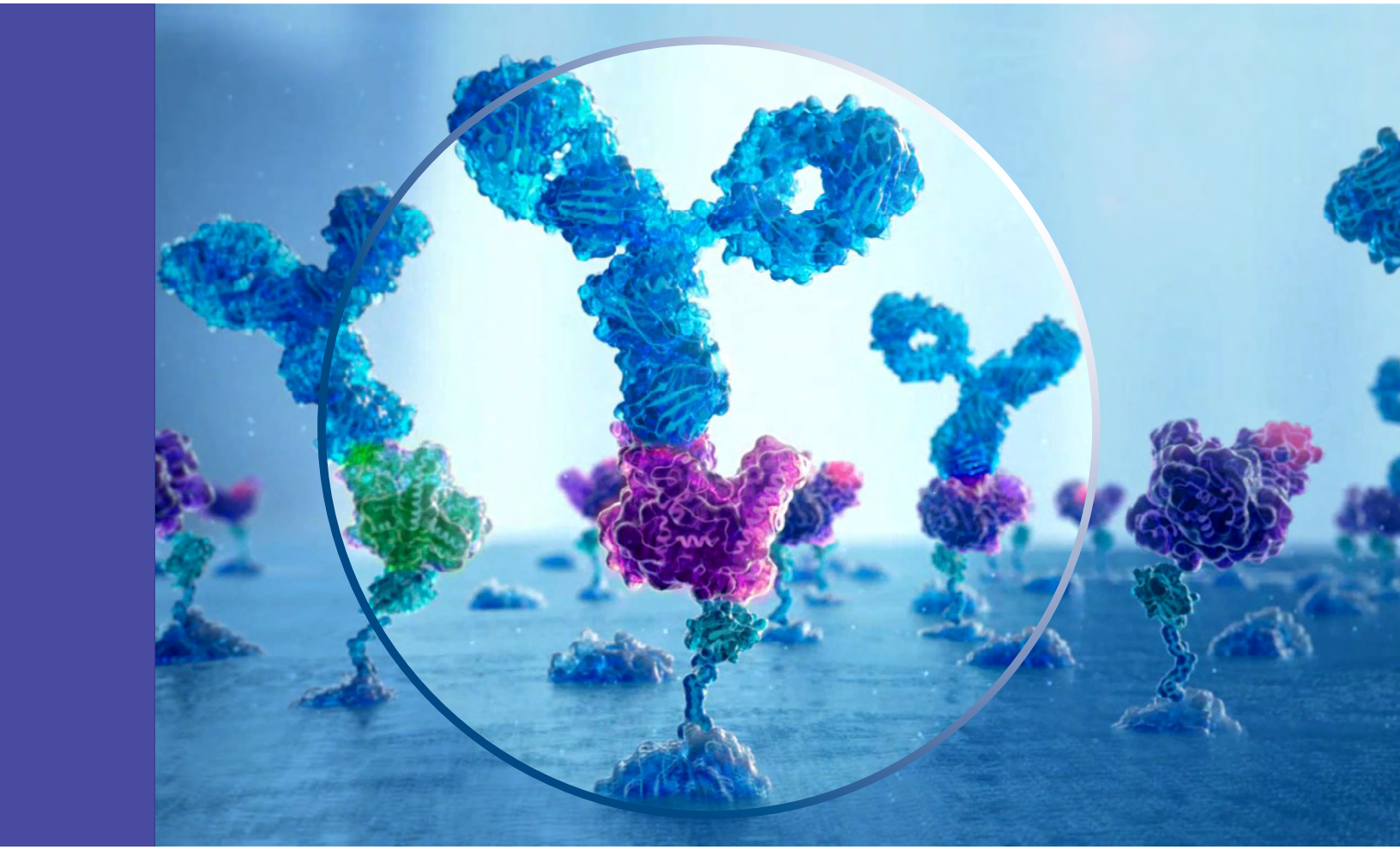
Immunoprofiling & the Humoral Immune System

A Guide to a New Era of Biomarker Discovery



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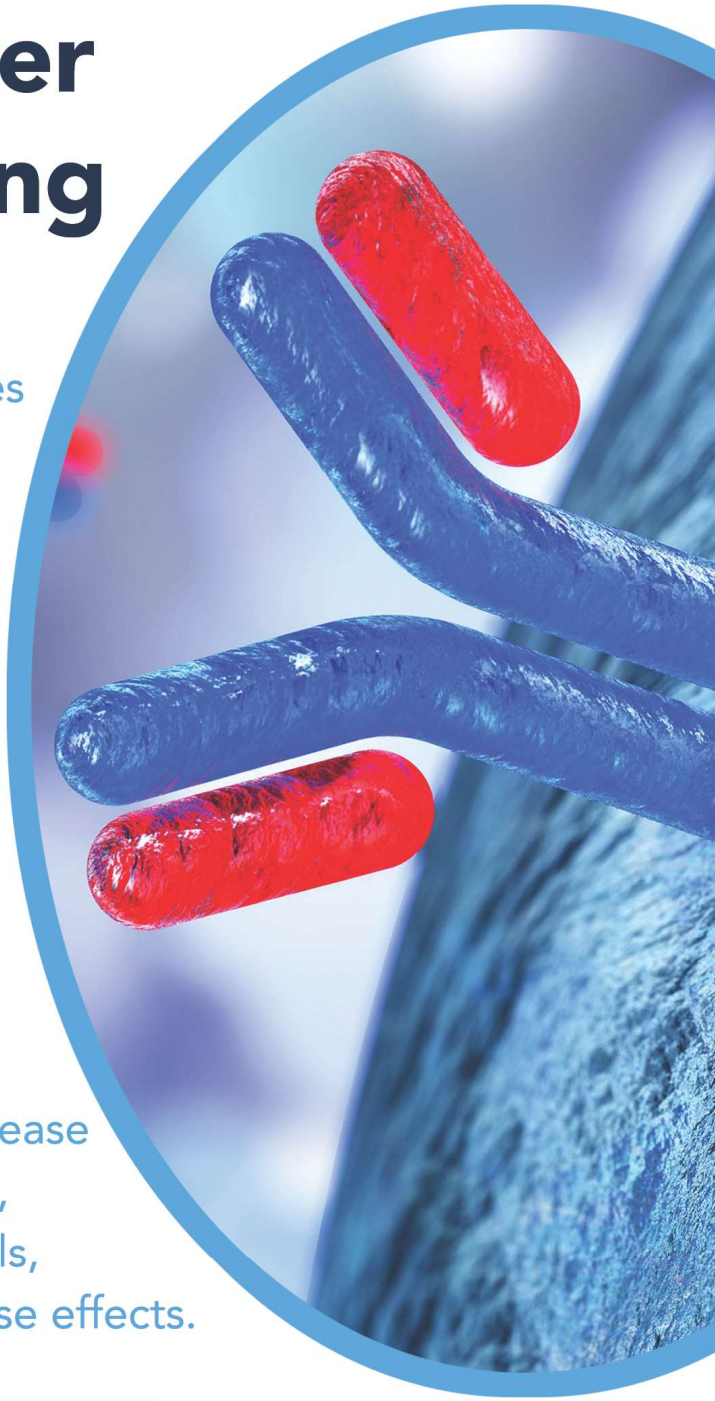

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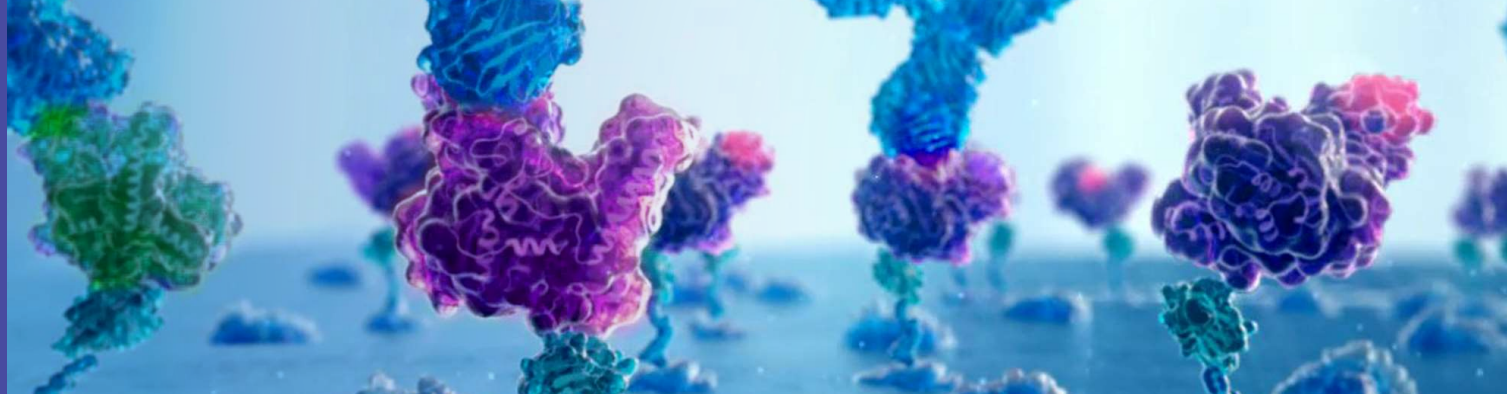

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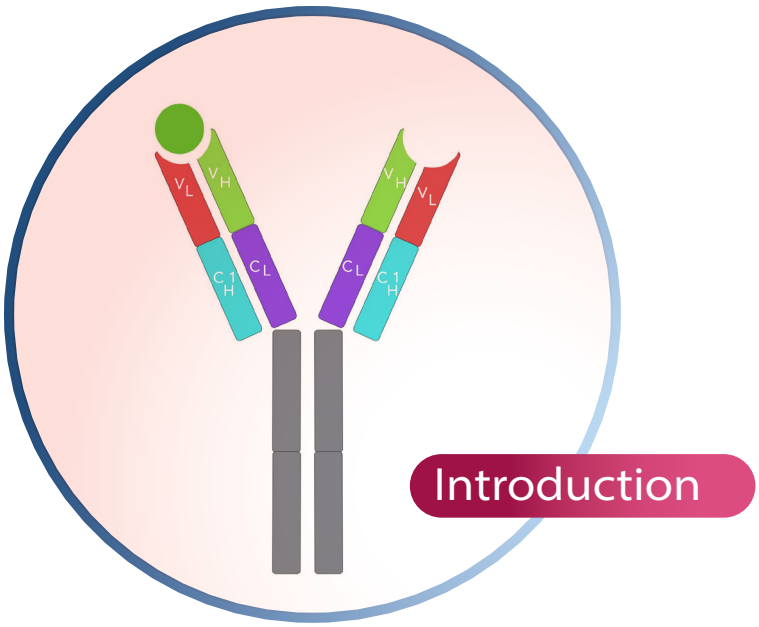

Sensitive and specific biomarkers can help accurately identify complex diseases early as well as provide clinicians with information useful for directing treatment, identifying disease endotypes, stratifying patients for clinical trials and predicting patient outcomes, including prognosis and adverse responses. An ideal biomarker is accessible, easy to measure, specific to the disease, and reproducible. Genomics and proteomics have historically produced valuable biomarkers. Genomics research has uncovered mutations with propensity for disease, such as BRCA1, while proteomics research has identified disease associated proteins, such as Tau protein and beta-amyloid (this issue chapter 4) in Alzheimer's. Both are helpful in studying disease and determining patient care, but lacking in early detection and prognostic value where the ideal biomarker may considerably improve patient outlook. Recent technological advances in microarray and machine learning technologies have made it possible for scientists to take advantage of patient antibody signatures.

Antibodies are ideal biomarkers because they are manifestations of the actual disease, occurring early, before symptoms, and persisting through the duration of the disease. Antibodies are highly specific, easy to obtain and measure and can represent different aspects of disease, enabling a mechanistic view of disease pathophysiology. New high

throughput technologies including protein arrays and machine learning have enabled researchers to identify antibody signatures, or panels of disease associated antibodies, with unprecedented insight. Signatures have much greater diagnostic and prognostic potential than single proteins or gene mutations (Bizzaro, 2007; Kathrikolly et al., 2022). In particular, an individual's immunosignature is emerging as one of the most sensitive, accurate and predictive sources of disease pathophysiology. Immunoprofiling is not new, but the ability to quantify thousands of antibodies from a small blood sample with protein microarrays provides a new unheralded level of patient detail. A new generation of biomarkers is emerging, capitalizing on the convergence of high throughput measurement techniques, advanced bioinformatics and new machine learning models. In this eBook, we review biomarker discovery, emphasizing immunoprofiling with autoantibody signatures, that once deconvoluted with machine learning, can provide insights into disease progression, potential treatment adverse effects and mechanistic information about disease physiology.

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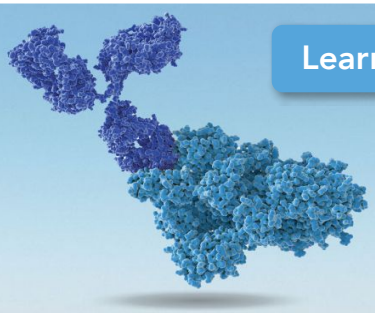
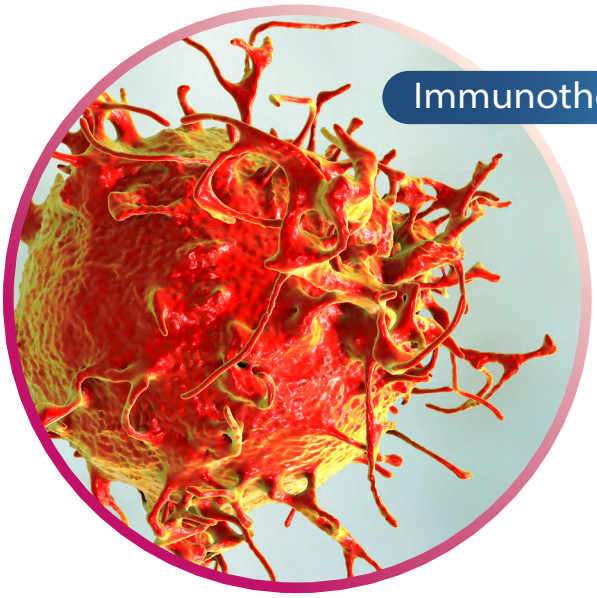




Immunotherapy News

Test May Predict Recurrence and Response to Immunotherapy in Melanoma Patients

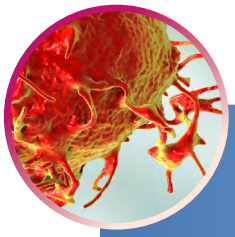
Scientists at the Perlmutter Cancer Center in the NYU Grossman School of Medicine have developed an experimental test based on a composite panel of autoantibody signatures that generates a score that can be used to predict the occurrence of severe side effects or the recurrence of cancer in melanoma patients who have received immune checkpoint blockade immunotherapies—a therapeutic modality that bolsters the patients own immune system to attack malignant cells.

"The composite panel of autoantibody signatures can allow for the simultaneous risk stratification of patients according to their likelihood of recurring and suffering severe toxicity," the authors noted.

The development of the test was in the journal Clinical Cancer Research ("Baseline serum autoantibody signatures predict recurrence and toxicity in melanoma patients receiving adjuvant immune checkpoint blockade").

"Our results show that the new research test, by predicting whether a patient will respond to a treatment or experience side effects, has the potential to help physicians make more precise treatment recommendations," said Paul Johannet, MD, first author of the study, a postdoctoral fellow in the laboratory of Iman Osman, MD, professor of dermatology at the Perlmutter Cancer Center and a senior author of the study. "With further validation, this composite panel might help patients to better balance the chances of treatment success against severe side effects."

In contrast to antibodies that recognize foreign microorganisms such as bacteria, viruses, and fungi, autoantibodies react to proteins in the body's own cells to cause autoimmune disease.



Immune cells selectively recognize tumor cells as abnormal, but cancer cells have developed devious mechanisms to hijack checkpoints and turn off immune attacks against themselves, including the immune checkpoint protein called PD-1 (programmed death receptor 1).

The current study suggests that the presence of a newly identified panel of autoantibodies in a patient's bloodstream before immunotherapy can potentially predict the recurrence of cancer or autoimmune side effects due to the treatment.

Generally, normal cells of the body are not attacked by autoimmune antibodies since immune cells include "checkpoint" sensors. Immune cells selectively recognize tumor cells as abnormal, but cancer cells have developed devious mechanisms to hijack checkpoints and turn off immune attacks against themselves, including the immune checkpoint protein called PD-1 (programmed death receptor 1).

PD-1 inhibitor-based immunotherapies are effective against many cancers and are used as adjuvant therapy in patients with surgically removed melanomas. However, in some patients, cancer recurs following immunotherapy or they suffer severe adverse effects from the treatment regimen.

The authors of the current study hypothesized that undetected higher levels of key autoantibodies in some cancer patients before immunotherapy, trigger checkpoint inhibitors to cause greater adverse immune side effects in these patients. The researchers, therefore, identified a panel of autoantibody signatures that could predict immune-related adverse effects upon immunotherapy with two commonly used checkpoint inhibitors, nivolumab and ipilimumab, and their combination.

The study included 950 patients with advanced melanoma who received adjuvant checkpoint inhibitor immunotherapy as part of two Phase III randomized controlled trials: CheckMate 238

Iman Osman, MD, professor of dermatology at the Perlmutter Cancer Center, is a senior author of the study.

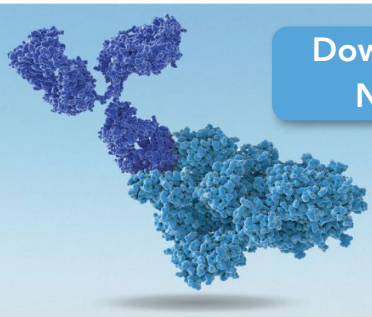
Judy Zhong, PhD, a professor of population health and environmental medicine at NYU Grossman School of Medicine, is co-senior author of the study.

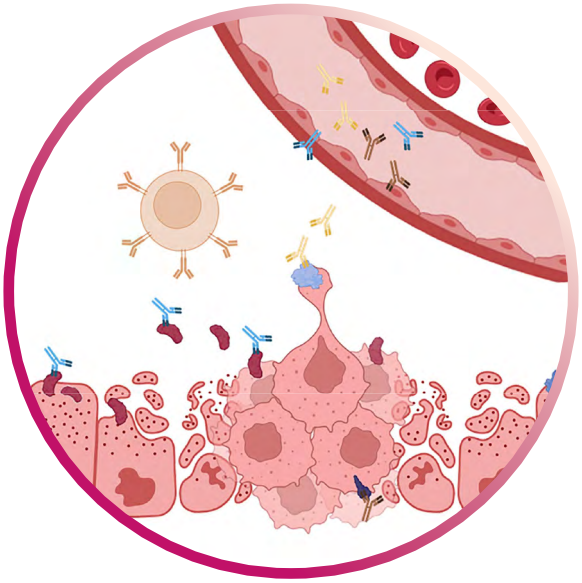
(ipilimumab vs nivolumab) and CheckMate 915 (nivolumab vs ipilimumab plus nivolumab). All patients included in the study had tumors surgically removed and blood samples collected before they received immunotherapy.

Statistical modeling based on the detection of autoantibodies, enabled co-senior author Judy Zhong, PhD, a professor of population health and environmental medicine at NYU Grossman School of Medicine, and her colleagues, to develop a score-based prediction system for each immunotherapy regimen. They found patients with a higher autoantibody score for recurrence showed recurrence of cancer after a shorter interval following immunotherapy compared to patients with a lower score. Similarly, patients with higher pre-treatment autoantibody toxicity scores were more likely to experience severe adverse effects than those with lower scores.

"That we identified 283 autoantibody signals shows that the biological phenomena underlying recurrence and toxicity are complex and cannot be driven by one or two biomarkers," said Osman. In future studies, her group will test the predictive power of the autoantibody test in patients with cancers other than melanoma, who have received immunotherapies.

This study was funded by the NYU Melanoma SPORE and NIH/NCI.





Autoantibodies as Disease Biomarkers

Chronic diseases such as autoimmune, cancer and neurological diseases are complex, difficult to diagnose, and problematic to treat due to their inherent heterogeneity. Cancer and neurodegenerative diagnostics, for example, rely heavily on symptom reporting and diagnostic imaging, procedures conducted later in the disease pathogenesis. Liquid biopsy derived markers of cancer, Alzheimer's and Parkinson's do exist (Hampel et al., 2022; Li & Le, 2020; Tumor Markers in Common Use, 2021); however, testing for these markers may be invasive (lumbar puncture), and is usually conducted following symptoms, with only one or a few markers to confirm diagnosis. Misdiagnosis can result in great patient discomfort, uncertainty, unnecessary treatments and a high cost burden (CDC, 2019; Hansson, 2021; Hunter et al., 2015). Further, current markers have not been thoroughly evaluated for long term prognosis.

Great effort is underway to discover biomarkers that are easy to obtain & detect, highly predictive and present before symptoms emerge.

Blood derived biomarkers are advantageous because sera contains a plethora of accessible, easy to measure analytes. Because blood tests are common practice in the medical community, they offer the potential to provide quicker results with less discomfort to patients compared with tissue biopsies or lumbar puncture (Hampel et al., 2022; Hayes Balmadrid et al., 2017; Laranja et al., 2019). Evaluating antibodies from patient sera is a minimally invasive, powerful approach. Antibodies are manifestations of disease, direct consequences of illness that appear early and persist in blood circulation throughout the disease. In fact, antibodies have been shown to predate cancer and autoimmune disease diagnosis by years (Anderson & Labaer, 2005;

Arbuckle et al., 2003; Trivers et al., 1996). In addition to the antibody production stimulated by infectious organisms, chronic diseases result in autoantibody production. Aberrantly expressed proteins that result from the disease process induce production of autoantibodies. Tumors, for example, can produce unique tumor specific proteins as well as ectopically express host proteins. In ALS, the transactivating enzyme TDP-43 becomes overexpressed, inducing anti-TDP43 autoantibody production (Conti et al., 2021). The humoral immune system recognizes these inconsistencies and produces autoantibodies as a result, sensing disease often before symptoms appear. This is why antibody screening and immunodiagnostics have existed for over a century. Antibodies offer the promise of more robust biomarkers for early disease detection with greater prognostic value compared with many current biomarkers in clinical use (Bizzaro, 2007; Damoiseaux et al., 2015; Wang et al., 2020; Zaenker & Ziman, 2013).

Until recently, it was difficult to capture all the information held by antibodies. Protein microarrays provide an excellent mix of throughput, sensitivity and cost. Thousands of antibodies from a single sample can be quickly evaluated for disease association on a single slide. However, antibodies recognize small discontinuous antigen epitopes (Barlow et al., 1986; Muro et al., 1994). Antibody-antigen binding is highly sensitive to antigen shape and not sequence. Protein microarray data benefits from the use of properly folded proteins on the microarray, for example the i-Ome array from Sengenics. This technology maintains conformational epitopes and ensures optimal antibody-epitope binding for the rigors of antibody screening. Coupled with modern machine learning, protein microarrays have advanced biomarker discovery by uncovering antibody signatures, panels of antibodies related to health and disease. Multiple markers are more likely to be indicative and prognostic of disease pathophysiology than single makers. Further, antibody signatures can help identify endotypes that can stratify patients into therapeutically efficacious categories while also enriching clinical trials.

In a recent, comprehensive study by Patel et al. (Patel et al., 2022), 60 different autoantibodies of interest were uncovered from a screen with the Sengenics i-Ome microarray 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 with machine learning revealed that 13 strongly correlated with poor 5-year patient survival. These 13 autoantibodies were also predictive in an independent validation cohort, demonstrating the reproducibility of the approach. Interestingly, a number of these autoantibodies were cancer testis antigens (CTA) (Patel et al., 2022) - fetal antigens that are silenced in all adult somatic tissues except the testes – potentially indicating that the patients with a poor prognosis (male and female) had a

Because blood tests are common practice in the medical community, they offer the potential to provide quicker results with less discomfort to patients compared with tissue biopsies or lumbar puncture.

distinct, more cancer stem cell-like sub-type of NSCLC. These findings provide new insights and potential therapeutic targets for treating NSCLC. For example, the ectopic expression of CTAs 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 (Patel et al., 2022).

Antibodies have been used to detect disease for over a century. With high specificity for disease related antigens, antibodies are ideal biomarkers. Modern technologies like the Sengenics KREX technology and new machine learning algorithms provide comprehensive immunoprofiles with antibodies that can advance patient care by detecting complex diseases and predicting patient outcomes including survival, adverse events, and therapeutic response.

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Translational Medicine

Comorbidities Impact Biomarker Levels to Hinder Alzheimer's Blood Test Development

New research shows that much more work needs to be done before a simple blood test to diagnose Alzheimer's disease, perhaps even years before symptoms appear, will be available. The study "Performance of plasma phosphorylated tau 181 and 217 in the community" appears in Nature Medicine.

Two hallmarks of Alzheimer's disease are tau tangles and beta-amyloid plaques. Tau is a protein found in neurons in the brain. In a healthy brain, tau helps transport nutrients in nerve cells. When an abnormal form of tau builds up, tau tangles are formed. Beta-amyloid plaques are accumulations of brain protein fragments, which can impact cognition.

The interaction of these proteins may speed up brain changes that can lead to Alzheimer's disease. Tau and beta-amyloid levels can be tested in cerebrospinal fluid, which is retrieved through a lumbar puncture, or through PET imaging of the brain.

"Blood-based biomarkers are the goal in screening for and diagnosing Alzheimer's disease because they are less costly and invasive, but we need to understand these biomarkers in community-based populations before we use them clinically," said Michelle Mielke, PhD, professor and chair of epidemiology and prevention at the Wake Forest University School of Medicine and the study's principal investigator.

Promising new biomarkers

Two blood markers, phosphorylated tau 181 and 217 (p-tau181 and p-tau217), are promising new biomarkers specific to Alzheimer's disease and may provide a new avenue for screening or detecting Alzheimer's disease in the general population. However, comorbidities such as

"Plasma phosphorylated tau 181 (P-tau181) and 217 (P-tau217) are indicators of both amyloid and tau pathology in clinical settings, but their performance in heterogeneous community-based populations is unclear."

chronic kidney disease or history of stroke can also increase these levels and potentially give false positive results, according to Mielke, who added that "Before these blood-based biomarkers enter clinical use, it's critical that we establish reference ranges and understand the differences age, sex and any underlying health conditions might play."

"Plasma phosphorylated tau 181 (P-tau181) and 217 (P-tau217) are indicators of both amyloid and tau pathology in clinical settings, but their performance in heterogeneous community-based populations is unclear. We examined P-tau181 and P-tau217 (n = 1,329, aged 30–98 years), in the population-based Mayo Clinic Study of Aging," write the investigators.

"Continuous, unadjusted plasma P-tau181 and P-tau217 predicted abnormal amyloid positron-emission tomography (PET) (area under the receiver operating characteristic curve (AUROC) = 0.81–0.86) and tau PET entorhinal cortex (AUROC > 0.80), but was less predictive of a tau PET temporal region of interest (AUROC < 0.70). Multiple comorbidities were associated with higher plasma P-tau181 and P-tau217 levels; the difference between participants with and without chronic kidney disease (CKD) was similar to the difference between participants with and without elevated brain amyloid.

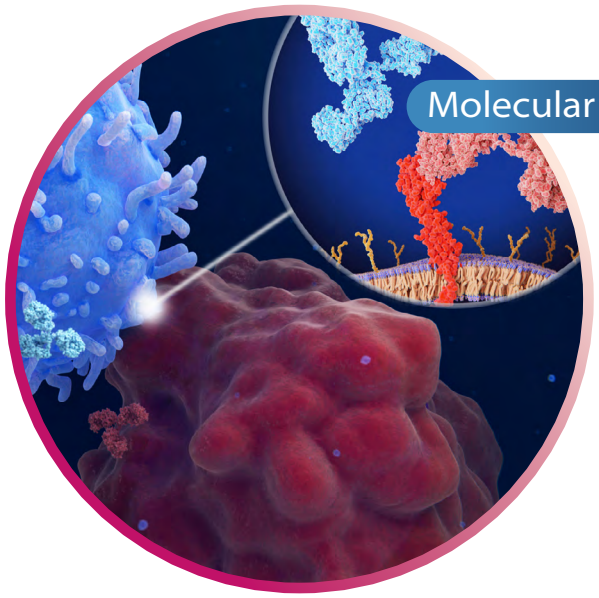
"The exclusion of participants with CKD and other comorbidities affected the establishment of a normal reference range and cutpoints. Understanding the effect of comorbidities on P-tau181 and P-tau217 levels is important for their future interpretation in the context of clinical screening, diagnosis, or prognosis at the population level."

Researchers found that while p-tau181 and p-tau217 increase with age, the increase is mainly among people who are amyloid positive, which provides additional evidence that these biomarkers are specific to Alzheimer's disease and not other neurodegenerative diseases.

The study's findings also confirmed that plasma p-tau181 and p-tau217 are predictors of elevated brain amyloid and tau, as measured by PET imaging, but the results were not as good as those previously reported in patients seen in specialized memory clinics. A reason for this is that the study showed that multiple comorbidities such as chronic kidney disease, history of myocardial infarction or clinical stroke were also associated with higher plasma p-tau levels.

According to Mielke, this elevation is likely attributed to the underlying conditions and not Alzheimer's disease and should be considered in the development of cut points for clinical use.

"More research is needed in larger studies, especially in more diverse populations," Mielke continued. "It's important for patients and providers to understand that, although these blood markers are very promising, it will take time to implement in the clinic. We need more data first."



Molecular Diagnostics

Strata Oncology Validates Clinical Utility of Solid Tumor Predictive Biomarker

A new study published in the Nature Press publication Communications Medicine validates the clinical utility of a pan-solid tumor biomarker, IRS (Immunotherapy Response Score), that predicts the benefit of anti-PD-1/PD-L1 checkpoint inhibitor monotherapy ("Development and validation of an integrative pan-solid tumor predictor of PD-1/PD-L1 blockade benefit").

IRS was developed and validated by Strata Oncology, a next-generation precision oncology company, using treatment data and comprehensive, clinically validated genomic and transcriptomic profiling of tumor tissue from the observational Strata Trial (NCT03061305), an ongoing clinical trial evaluating the impact of molecular profiling for patients with advanced solid tumors.

The IRS algorithm, developed using Cox modeling and validated in an independent cohort of trial patients, captures the biology of the tumor and its microenvironment by combining TMB (tumor mutation burden) analysis with the quantitative expression of CD274, PDCD1, ADAM12, and TOP2A to predict pembrolizumab rwPFS (real-world progression-free survival).

"Our Immunotherapy Response Score [IRS] meets a significant unmet medical need for an integrative diagnostic test that better predicts likelihood of benefit from anti-PD-1/PD-L1 checkpoint inhibitor monotherapy, across solid tumor types," said Scott Tomlins, MD, PhD, Strata Oncology co-founder and chief medical officer. "Current pan-tumor biomarkers for these treatments identify only a fraction of responsive patients, meaning far too many people who could benefit from these therapies are not being identified."

Tomlins added, "Additionally, immunotherapy is now often combined with chemotherapy. Our exploratory data in non-small cell lung cancer indicate that IRS may be a useful tool to help determine which patients can achieve similar benefits without the toxic effects of chemotherapy."

Checkpoint inhibitors such as anti-PD-1/PD-L1 checkpoint inhibitors, activate the immune system and have been successfully used to treat patients with advanced cancers. However, not all cancer patients benefit from these wonder drugs and many patients rapidly develop resistance to them. Therefore, the development of biomarkers and molecular tests that identify patients who would benefit from checkpoint inhibitors is important.

Based on data collected from over 20,000 patients with more than 20 types of advanced cancers, the investigators demonstrated that IRS can better predict the benefit of anti-PD-1/PD-L1 checkpoint inhibitor therapy than tests that are in current use. IRS identified nearly 8% of patients with advanced cancer who may benefit from checkpoint inhibitors but would not receive them at present based on current molecular tests, thereby offering clinicians a better decision-making tool to stratify patients who should receive checkpoint inhibitor therapy.

IRS predicted rwPFS and overall survival (OS) in anti-PD-1/PD-L1 monotherapy-treated patients across tumor types. A high IRS predicted a similar duration of benefit as high TMB across tumor types, but IRS identified twice as many patients who may benefit from checkpoint inhibitor treatment as TMB. Moreover, patients with non-small cell lung cancer (NSCLC) patients and a high IRS status showed no significant benefit of combination therapy (pembrolizumab + chemotherapy) compared to monotherapy (pembrolizumab).

"Immunotherapy has transformed cancer care and now with IRS we have the ability to predict benefit across tumor types," said Dan Rhodes, PhD, Strata Oncology co-founder and CEO. "We are excited to put this novel biomarker into the hands of physicians to help them ensure every patient gets their best possible therapy."

Liquid Biopsy: Autoantibodies in Neurodegenerative Diseases

Neurodegenerative diseases are complex, chronic debilitating diseases often with no known cause and uncertain pathology. Diagnosis is difficult, relying on a combination of behavioral symptoms, cognitive testing, functional imaging, and biomarker screening, most often collecting samples via lumbar puncture. Consequently, most diagnoses happen after symptoms occur. Detecting disease before symptoms can have a profound scientific impact by enabling early intervention, providing greater detail on disease pathophysiology, and contributing to the development of new treatment strategies to abrogate disease progression. A great deal of research is underway to identify new, reliable, blood-based biomarkers for neurodegenerative diseases. This has been challenging because of the blood-brain barrier and privileged nature of the central nervous system. Until recently, scientists believed the best source of fluid biomarkers was cerebrospinal fluid (CSF), the fluid surrounding the brain and spine, that contains measurable levels of the protein aggregates identified in many neurological diseases. However, the concentration and number of markers in CSF is limited and access requires lumbar puncture, a delicate, uncomfortable procedure.

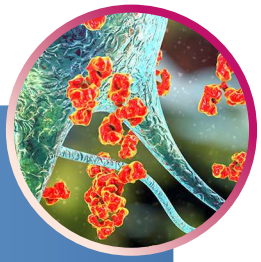
Serum antibodies are ideal biomarkers because they are linked directly to disease, have been shown in cancer and autoimmune diseases to predate symptoms by years, are easily accessible and highly reliable. In neurodegenerative diseases, antibodies have been underexplored, partly because antibodies are too large to cross the blood brain barrier and the lack of clarity regarding B cell access to intracellular proteins known to contribute to neurodegenerative diseases. Evidence is accumulating, though, that antibodies and autoantibodies are prominent in many neurodegenerative diseases.

Over the last 15 years, scientists have discovered numerous cases of overlap between the humoral immune system and neurological disease, most notably with the discovery of an anti-NMDAR autoantibody in autoimmune encephalitis (Pruss, 2021). This has prompted many neuroscientists to examine the diagnostic, prognostic, and therapeutic potential of sera antibodies in neurodegenerative diseases. In Alzheimer's, for example, anti-nuclear autoantibodies are found in Alzheimer's patients with cognitive impairment, suggesting that blood circulating antibodies could be useful in detecting Alzheimer's (Lopez et al., 1992). In amyotrophic lateral sclerosis (ALS), the human endogenous retrovirus HML-2, a normally silent component of the human genome, activates near the onset of symptoms, and once activated, initiates production of antiviral autoantibodies. The autoantibody titers diminish as the disease progresses, implying a protective role for the anit-HML2 antibody (Garcia-Montojo et al., 2022). In this case, the HML-2 antibody has potential to both predict and provide guidance for the treatment of ALS.

Similar findings have been noted with the 43 kd transactive response DNA binding protein, TDP-43, known to form aggregates throughout the ALS brain. TDP-43 overexpression and protein assemblies result in antibody production found in Alzheimer's and ALS patient sera, encouraging researchers to study this protein as a biomarker for these and other neurodegenerative diseases. In sera from ALS patients, TDP-43 antibodies have been observed that may not only indicate the disease but may also be prognostic and protective. The research indicates that TDP-43 antibodies may hold greater diagnostic value than the TDP-43 protein levels. Antibodies were easier to collect, not requiring a spinal tap, and more consistently linked to diagnosis across patients (Conti et al., 2021).

In Parkinson's, diagnosis still relies heavily on motor symptoms, primarily bradykinesia, resting tremor and rigidity (Li & Le, 2020), however, research is ongoing to find fluid-based biomarkers that appear early and are clearly associated with Parkinson's. In fact, high-affinity anti-α-synuclein natural autoantibodies have been identified, and disappear as Parkinson's worsens (Brudek et al., 2017). Altogether, the common neurodegenerative disease associated protein aggregates stimulate antibody production.

Until recently, most examination of sera autoantibodies in neurodegenerative diseases focused on targeting autoimmune disease related autoantibodies or natural autoantibodies such as anti-TDP-43 antibodies. Knowledge that these proteins stimulate antibody titers measurable in sera samples has motivated researchers to engage high throughput technologies to search for additional novel markers. Protein microarray technology with machine learning is now being applied to find antibodies and antibody panels associated with disease for early detection and diagnosis. Antibody panels are more likely to detect disease and predict prognosis than single markers while also uncovering potential disease



A major advantage of detection of serum autoantibodies over those found in CSF is the greater number and concentration of markers available in the specimen.

related biochemical pathways. In one small pilot study of mild dementia, using the Sengenics i-Ome protein microarray composed of 1600+ antigens, six autoantibodies were identified in clinically diagnosed Alzheimer's patients compared with non-Alzheimer's dementia patients. The panel distinguished between the patient groups, and provided new pathways to investigate with potential to illuminate new facets of pathology and new therapeutic targets. For example, pantothenic acid kinase 3 (PANK3) antibodies in Alzheimer's patients. PANK3 is an enzyme involved in the production of Coenzyme A utilizing vitamin B5 as a precursor. This finding supports previous research connecting metabolic dysfunction to Alzheimer's and suggests diet could play a role in the disease pathology (Wang et al., 2020).

A major advantage of detection of serum autoantibodies over those found in CSF is the greater number and concentration of markers available in the specimen. In a larger screen of early stage Alzheimer's patients with mild cognitive impairment and low Aβ42 levels, 193 autoantibodies were found unique to the patients compared with healthy control subjects, the top 50 correlating with Alzheimer's disease at 99.6% accuracy. The panel discriminated among disease severities as well (Demarshall et al., 2016). Autoantibody profiling may also be more powerful for identifying and predicting disease than current markers. In a recent longitudinal study of Parkinson's patients, researchers followed the progress of at-risk patients with hyposmia with and without dopamine transporter deficit (DAT) who showed no other symptoms of Parkinson's. Overall, 116 autoantibodies were unique to hyposmia subjects. A subpanel of 22 autoantibodies in the hyposmia with DAT group correlated significantly with phenotype conversion (pheno-conversion) to Parkinson's

over the 4-year observation period. The panel performed with 90.5% sensitivity and 70.6% specificity. This meant autoantibodies were able to discriminate among at risk patients and predict prognosis. In addition, pathway analysis revealed 56 new biomarkers not previously associated with Parkinson's related genes (Anuar et al., 2022).

The humoral immune system is an accessible component of human physiology that can be exploited for early detection of disease. Immunoprofiling with antibodies can offer the benefit of early disease detection, stratification of patients by disease subtypes and new biochemical pathways to explore.

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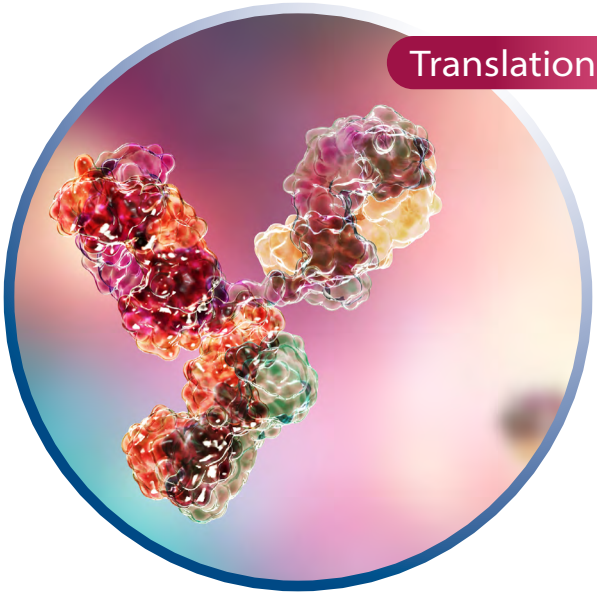


Translational Medicine

Common Autoantibodies Shared by Healthy Individuals

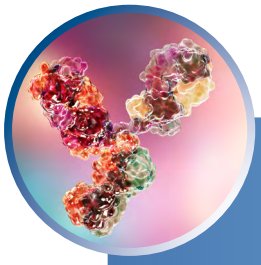
While autoantibodies have been implicated as central players in a range of serious autoimmune diseases, researchers from Arizona State University published a study "Serum autoantibodyome reveals that healthy individuals share common autoantibodies" in Cell Reports that showed that autoantibodies are also found in healthy individuals. This fact may make the diagnostic use of autoantibodies as sentinels of autoimmune disease more challenging, according to the scientists.

"Autoantibodies are a hallmark of both autoimmune disease and cancer, but they also occur in healthy individuals. Here, we perform a meta-analysis of nine datasets and focus on the common autoantibodies shared by healthy individuals. We report 77 common autoantibodies based on the protein microarray data obtained from probing 182 healthy individual sera on 7,653 human proteins and an additional 90 healthy individual sera on 1,666 human proteins. There is no gender bias; however, the number of autoantibodies increase with age, plateauing around adolescence," write the investigators.

"We use a bioinformatics pipeline to determine possible molecular-mimicry peptides that can contribute to the elicitation of these common autoantibodies. There is enrichment of intrinsic properties of proteins like hydrophilicity, basicity, aromaticity, and flexibility for common autoantigens. Subcellular localization and tissue-expression analysis reveal that several common autoantigens are sequestered from the circulating autoantibodies."

Improved Awareness of the Role of Autoantibodies

An improved awareness of the pervasiveness and role of autoantibodies in human health



The researchers performed a meta-analysis of nine datasets. The tool of choice for exploring the common autoantibodies is a protein microarray.

and disease may ultimately help in the design of better diagnostics and therapeutics against a range of illnesses, notes Joshua LaBaer, MD, PhD, executive director of ASU's Biodesign Institute as well as the director of the Biodesign Virginia G. Piper Center for Personalized Diagnostics.

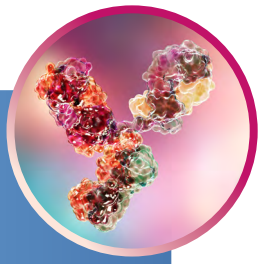
"Historically, we looked for autoantibodies present only in disease, but we've always been intrigued because our healthy controls always had autoantibodies too," he says. "So, we decided to see if any of these 'healthy autoantibodies' were common in healthy people and sure enough many of them were. Knowing about these will help us avoid confusion in future studies."

Though these common autoantibodies do not appear to cause disease, they nevertheless appear in as many as 40% of the people tested. It is likely that at least some of these common autoantibodies have been mistakenly identified as disease antibodies.

The researchers performed a meta-analysis of nine datasets. The tool of choice for exploring the common autoantibodies is a protein microarray. Here, thousands of individual proteins are affixed to a glass slide. When a sample of blood is spread over the microarray, antibodies, (in this case, autoantibodies) bind with specific protein antigens.

The microarrays were subjected to two rounds of screening. In the first round, 182 blood samples from healthy individuals were screened against 7,653 human proteins. In the second round, 90 blood samples were screened against 1,666 human proteins. The experiments identified a total of 77 common autoantibodies.

The blood samples came from healthy individuals of both sexes, ranging in age from

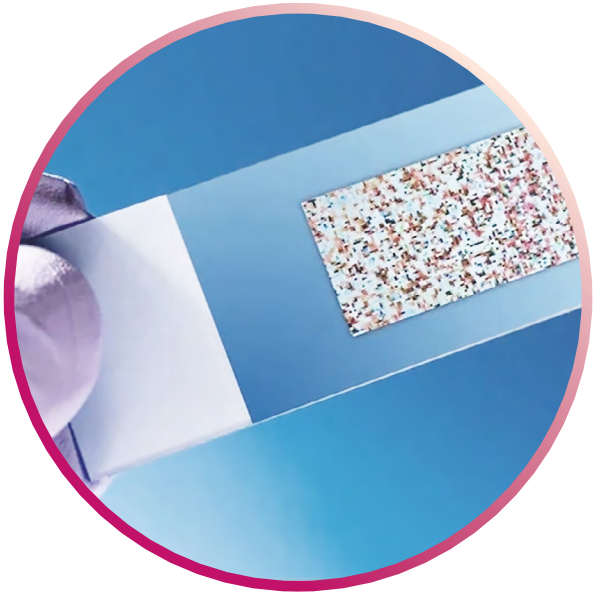


It is believed that autoimmune pathology requires autoantibodies to bind and form complexes with autoantigens, and this may be blocked in the case of common autoantibodies.

infancy to 84 years old. The results showed that the number of autoantibodies increased from birth up to the age of adolescence and then plateaued. Further, the number of autoantibodies detected was the same regardless of sex, a surprising outcome given the large disparity between men and women in the prevalence of autoimmune disease.

Another underlying enigma is why common autoantibodies fail to produce autoimmune disease. Although such antibodies appear to have evaded the screening process leading to immune tolerance, their occurrence in the body remains benign. It is believed that autoimmune pathology requires autoantibodies to bind and form complexes with autoantigens, and this may be blocked in the case of common autoantibodies.

Future research promises to unlock many more secrets concerning the nature of autoantibodies, says LaBaer, adding that the current study examined less than half of all human proteins. Most likely, additional common autoantibodies remain to be uncovered.



The Evolution of Protein Microarrays

In the late 1970's, using antibody fragments (Fc region), lymphoma cells were immobilized onto a slide so researchers could film the lysing activity of cytotoxic T-cells. This study became the forerunner to modern protein microarray technology (Rothstein et al., 1978). Later, in 1983, Tse Wen Chang applied a series of different antibody spots across a slide in order to capture cells bearing different antigens (Chang, 1983), producing the first analytical protein microarray, in this case an antigen capture microarray. The technique was tedious, required manual spotting, and was limited by available antibodies. Further, imaging instrumentation in 1983 lacked the sensitivity and automation to measure numerous tiny samples on a small slide. Genetics capitalized on array technology because of the interest in understanding the genome and relative ease of working with DNA compared with proteins. DNA microarrays developed ahead of protein microarrays which drove the development of the necessary printing and imaging equipment (Lausted et al., 2004; Ramdas & Zhang, 2006; Schena et al., 1995).

Protein arrays lagged behind DNA arrays due to numerous obstacles. In situ hybridization is a direct measure of cDNA which is easily illuminated and quantified with fluorescence. cDNA is stable and easy to construct from RNA. Nucleic acids can be amplified with PCR. Proteins, on the other hand, are difficult to isolate from tissue, with a tertiary structure easily lost during isolation. Protein labeling often utilizes indirect immunofluorescence, a technique requiring specific primary antibodies (Duarte & Blackburn, 2017; Hu et al., 2011). There are far more proteins than genes, and proteins are more complex than nucleic acids. Proteins can assume different isoforms and acquire post translational

modifications, resulting in greater interpretive complexity than genes. However, this is also an advantage of proteins, they provide richer information than DNA or mRNA. Isoforms and modifications reflect specific cellular processes, not detected by genetic mutations. Another hurdle for protein microarrays is the manufacture and amplification of the proteins, which require a cDNA library. The most common method of producing the proteins is through a living expression system, such as a cell line, yeast, or bacteria. The expression system can introduce errors, and for some systems, certain proteins may be difficult to express. For protein microarrays to be useful, these issues needed to be addressed. DNA microarray data does not always correlate with protein expression, identify post translational modifications or address cellular function. And although DNA microarrays helped identify drug targets, most targets were proteins, especially kinases (Petricoin, 2013). The need grew for protein screening to validate and complement the genetic data.

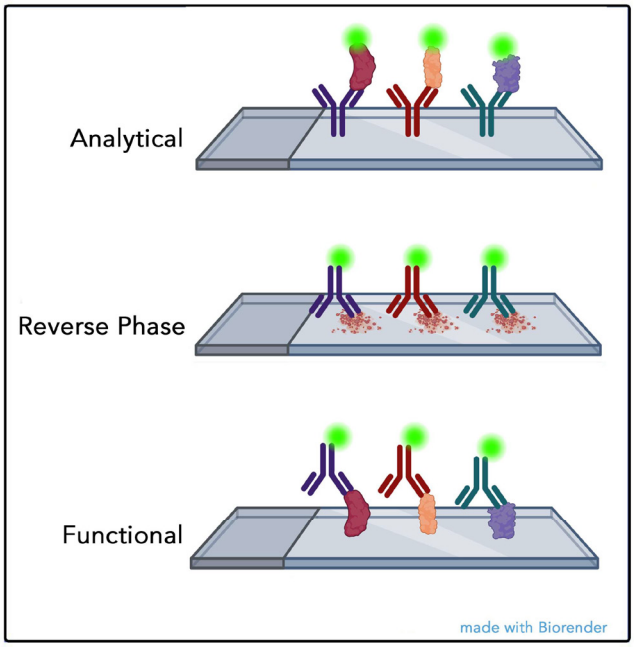


Figure 1. Three main types of protein microarrays

There are three basic types of protein microarrays, analytical, reverse phase and functional, distinguished by the material printed on the slide (Figure 1). Analytical arrays use antibodies, reverse phase arrays use cells or lysates, and functional arrays use protein. An analytical protein microarray uses antibodies coated onto a slide surface to capture other molecules or cells. Advantages of this technique include cell separation, comparison of different cell and tissue types (disease versus normal), cell or tissue classification, protein profiling, protein quantification and binding affinity. As with most protein arrays, the quality of the antibodies is critical to success. Reverse phase protein microarrays (RPMA) appeared in 2001 (Paweletz et al., 2001). Reverse phase protein microarrays spot-print cell or tissue lysates, instead of antibodies, onto nitrocellulose coated slides. Using target specific antibodies, protein detection and quantification are measured via immunofluorescence or chemiluminescence. RPMA is often used to identify specific disease related proteins or posttranslational modifications in patient lysates. Some advantages of RPMA assays include ability to detect proteins from patient samples, small sample requirement (picograms per spot), thousands of proteins can be screened simultaneously, and protein levels are quantifiable. Disadvantages include sample quality, sample processing that can damage

As precision medicine and biomarker discovery grow, protein microarrays will play a critical role in generating data to usher in the next generation of diagnostics, therapeutics, and overall patient care.

epitopes, quality of the primary antibody, and each experiment requiring printing for the desired lysate.

Functional protein microarrays, that also appeared in 2001,(Sutandy et al., 2013),utilize full length proteins or functional domains printed onto a coated slide surface (Hall et al., 2007; Sauer, 2017). As in analytical and reverse phase microarrays, proteins are visualized using a primary antibody and immunofluorescence. Functional arrays excel at immunoprofiling whereby the primary antibodies for the assay are present in the subject's serum. Thousands of antibodies can be identified and classified according to patient status, providing a means to identify biomarkers to detect disease, predict patient outcomes, endotype patients into disease subsets and stratify patients to enrich clinical trials. Functional protein microarrays have recently been used to predict patient prognosis up to five years in Parkinson's and non-small cell lung cancer (Anuar et al., 2022; Patel et al., 2022). Functional arrays also provide rich information on enzyme activity, and protein interactions with other biological molecules. They are the most common protein microarray currently in use. Functional protein microarrays do have some disadvantages including noisy data due to nonspecific antibody-antigen binding, reproducibility, and interpretation. However, foresight in the construction of these arrays and modern advances in artificial intelligence have helped address the disadvantages.

For these assays to be effective, the quality and adherence of the protein or peptide is critical. Most often, proteins are expressed in live material, such as transfected yeast, bacteria, insect or human cell lines. Insect cell lines offer a good compromise of accuracy, maintenance of post translational sites and titer. While yeast and bacteria have higher yields, they do not always maintain post translational modification

machinery. Human cell lines are ideal, but difficult to culture, transfect and maintain. Manufacturers may employ different cells or cell lines depending on titer required and the expression accuracies of the biological host to produce desired proteins. Once produced, proteins are isolated and printed onto a coated slide to create the array. Coatings include hydrogel, nitrocellulose, poly-L-Lysine, aldehydes or in some cases proprietary coatings. Hydrogel provides an aqueous environment preventing protein and peptide flattening and possible misfolding. Affinity tags or streptavidin are sometimes used to ensure uniform orientation across the slide. Lastly, because antibodies bind to discontinuous conformational epitopes formed during proper protein folding, it is important to preserve tertiary structure. This can be tested using denaturing agents on the array to disrupt protein folding, resulting in no labeling compared to an untreated control (Venkataraman et al., 2018), or protein folding can be insured using technologies such as KREX from Sengenics, Inc., in which only properly folded proteins bind to the surface of the slide (Blackburn et al., 2012).

Data interpretation has been made easier with machine learning (Toh et al., 2019), using computer algorithms such as Random Decision Forests, to detect panels of serum antibodies, from among thousands of antibodies, that correlate with disease. These panels are useful not only for detecting disease, but also predicting patient outcomes and stratifying disease subtypes. Because the antibody repertoire is heterogeneous across individuals, antibody panels – combinations of predictive antibodies - yield higher diagnostic and prognostic value compared with single antibodies, DNA or RNA (Damoiseaux et al., 2015; Kathrikolly et al., 2022). As a result of these breakthroughs, functional protein microarrays have become powerful research tools.

Protein microarrays continue to contribute valuable data for health and biology. As precision medicine and biomarker discovery grow, protein microarrays will play a critical role in generating data to usher in the next generation of diagnostics, therapeutics, and overall patient care.

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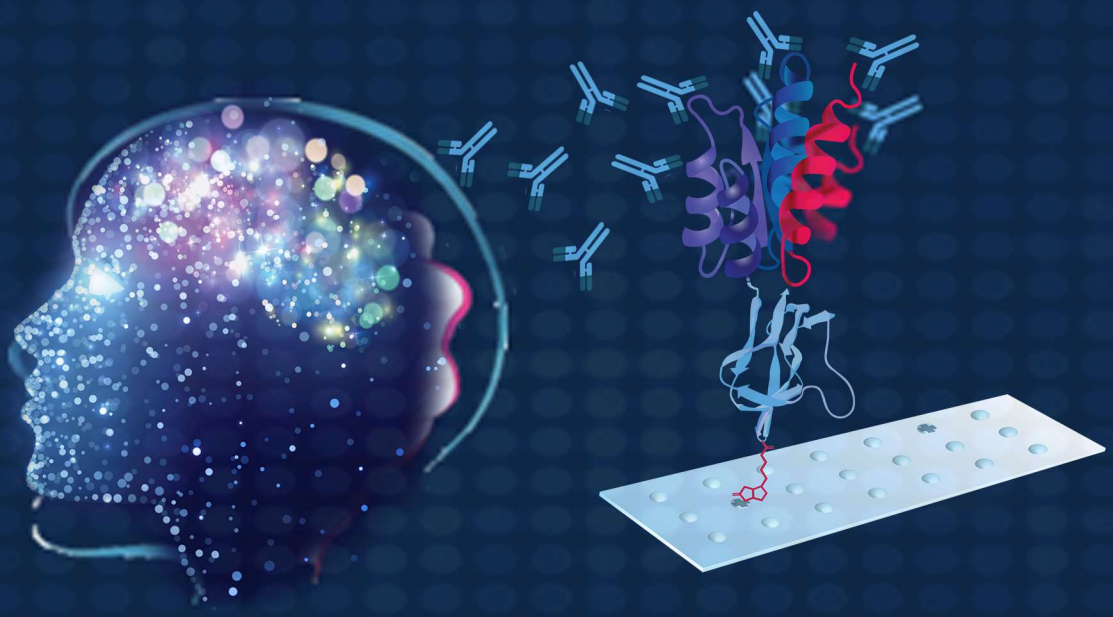
The Immune System is Trying to Tell You Something

Do you have the tools to listen?



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