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Focus on: Precision Antibodies

Article from the journal *Science Translational Medicine*:

The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in nonhuman primates

Abstract: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) poses a public health threat for which preventive and therapeutic agents are urgently needed. Neutralizing antibodies are a key class of therapeutics that may bridge widespread vaccination campaigns and offer a treatment solution in populations less responsive to vaccination. Here, we report that high-throughput microfluidic screening of antigen-specific B cells led to the identification of LY-CoV555 (also known as bamlanivimab), a potent anti-spike neutralizing antibody from a hospitalized, convalescent patient with coronavirus disease 2019 (COVID-19). Biochemical, structural, and functional characterization of LY-CoV555 revealed high-affinity binding to the receptor-binding domain, angiotensin-converting enzyme 2 binding inhibition, and potent neutralizing activity. A pharmacokinetic study of LY-CoV555 conducted in cynomolgus monkeys demonstrated a mean half-life of 13 days and a clearance of 0.22 ml hour^{-1} kg^{-1}, consistent with a typical human therapeutic antibody. In a rhesus macaque challenge model, prophylactic doses as low as 2.5 mg/kg reduced viral replication in the upper and lower respiratory tract in samples collected through study day 6 after viral inoculation. This antibody has entered clinical testing and is being evaluated across a spectrum of COVID-19 indications, including prevention and treatment.

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Articles from the journal *Science Advances*:

BRD4 methylation by the methyltransferase SETD6 regulates selective transcription to control mRNA translation

Abstract: The transcriptional coactivator BRD4 has a fundamental role in transcription regulation and thus became a promising epigenetic therapeutic candidate to target diverse pathologies. However, the regulation of BRD4 by posttranslational modifications has been largely unexplored. Here, we show that BRD4 is methylated on chromatin at lysine-99 by the protein lysine methyltransferase SETD6. BRD4 methylation negatively regulates the expression of genes that are involved in translation and inhibits total mRNA translation in cells. Mechanistically, we provide evidence that supports a model where BRD4 methylation by SETD6 does not have a direct role in the association with acetylated histone H4 at chromatin. However, this methylation specifically determines the recruitment of the transcription factor E2F1 to selected target genes that are involved in mRNA translation. Together, our findings reveal a previously unknown molecular mechanism for BRD4 methylation–dependent gene-specific targeting, which may serve as a new direction for the development of therapeutic applications.

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MYO10 drives genomic instability and inflammation in cancer

Abstract: Genomic instability is a hallmark of human cancer; yet the underlying mechanisms remain poorly understood. Here, we report that the cytoplasmic unconventional Myosin X (MYO10) regulates genome stability, through which it mediates inflammation in cancer. MYO10 is an unstable protein that undergoes ubiquitin-conjugating enzyme H7 (UbcH7)/β-transducin repeat containing protein 1 (β-TrCP1)–dependent degradation. MYO10 is upregulated in both human and mouse tumors and its expression level predisposes tumor progression and response to immune therapy. Overexpressing MYO10 increased genomic instability, elevated the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING)–dependent

inflammatory response, and accelerated tumor growth in mice. Conversely, depletion of MYO10 ameliorated genomic instability and reduced the inflammation signaling. Further, inhibiting inflammation or disruptin *Myo10* significantly suppressed the growth of both human and mouse breast tumors in mice. Our data suggest that MYO10 promotes tumor progression through inducing genomic instability, which, in turn, creates an immunogenic environment for immune checkpoint blockades.

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Emerging SARS-CoV-2 variants of concern evade humoral immune responses from infection and vaccination

Abstract: Emerging SARS-CoV-2 variants of concern (VOCs) pose a threat to human immunity induced by natural infection and vaccination. We assessed the recognition of three VOCs (B.1.1.7, B.1.351, and P.1) in cohorts of COVID-19 convalescent patients (n = 69) and Pfizer-BioNTech vaccine recipients (n = 50). Spike binding and neutralization against all three VOCs were substantially reduced in most individuals, with the largest four- to sevenfold reduction in neutralization being observed against B.1.351. While hospitalized patients with COVID-19 and vaccinees maintained sufficient neutralizing titers against all three VOCs, 39% of nonhospitalized patients exhibited no detectable neutralization against B.1.351. Moreover, monoclonal neutralizing antibodies show sharp reductions in their binding kinetics and neutralizing potential to B.1.351 and P.1 but not to B.1.1.7. These data have implications for the degree to which pre-existing immunity can protect against subsequent infection with VOCs and informs policy makers of susceptibility to globally circulating SARS-CoV-2 VOCs.

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An array of 60,000 antibodies for proteome-scale antibody generation and target discovery

Abstract: Antibodies are essential for elucidating gene function. However, affordable technology for proteome-scale antibody generation does not exist. To address this, we developed Proteome Epitope Tag Antibody Library (PETAL) and its array. PETAL consists of 62,208 monoclonal antibodies (mAbs) against 15,199 peptides from diverse proteomes. PETAL harbors binders for a great multitude of proteins in nature due to antibody multispecificity, an intrinsic antibody feature. Distinctive combinations of 10,000 to 20,000 mAbs were found to target specific proteomes by array screening. Phenotype-specific mAb-protein pairs were found for maize and zebrafish samples. Immunofluorescence and flow cytometry mAbs for membrane proteins and chromatin immunoprecipitation–sequencing mAbs for transcription factors were identified from respective proteome-binding PETAL mAbs. Differential screening of cell surface proteomes of tumor and normal tissues identified internalizing tumor antigens

for antibody-drug conjugates. By finding high-affinity mAbs at a fraction of current time and cost, PETAL enables proteome-scale antibody generation and target discovery.

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Technology Feature:

Pandemic pivot: How scientists answered the call for diagnostic tests

In medicine as well as in sports, the best defense is a good offense. When it comes to the current COVID-19 pandemic, the offense entails large-scale diagnostic testing that can rapidly, accurately, and reliably detect SARS-CoV-2. Although vaccines are currently being distributed, diagnostic tests—many of which are produced by companies that have already used similar technology to combat other diseases—remain key to containing the pandemic and preventing more deaths.

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AAAS Highlights

New Statistical Tools Can Make Sense of Biased Policing Data

Dean Knox, recipient of the inaugural 2021 NOMIS & Science Young Explorer Award, applies new statistical techniques to imperfect data to reveal the extent and severity of racial bias in policing.

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AAAS Fellow Paul Anastas Wins 2021 Volvo Environment Prize

Paul Anastas—a scientist, entrepreneur, and elected Fellow of the American Association for the Advancement of Science -- was awarded the 2021 Volvo Environment Prize this week.

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