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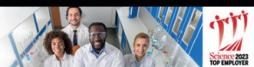
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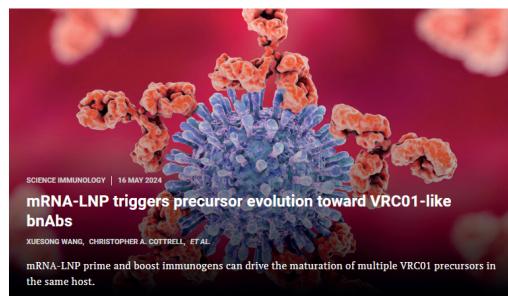


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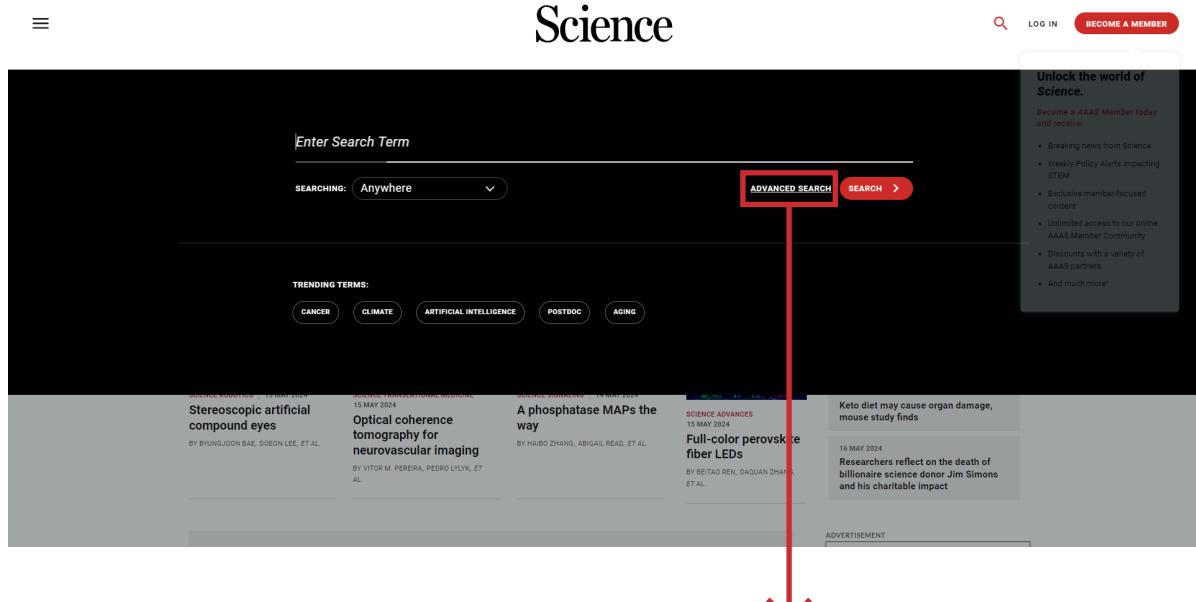
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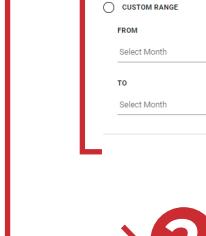
BUSCA AVANÇADA



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The screenshot shows the "ADVANCED SEARCH" page. At the top, there is a navigation bar with links for "NEWS", "CAREERS", "COMMENTARY", "JOURNALS", "LOG IN", and "BECOME A MEMBER". Below the navigation bar, the title "ADVANCED SEARCH" is displayed. The search form includes fields for "FIELD" (set to "Anywhere"), "SEARCH TERM" (with the placeholder "e.g. Neuroscience"), and "ARTICLE TYPE" (with the placeholder "e.g. Research Article"). There are also sections for "PUBLISHED IN:" (placeholder "e.g. Science Robotics") and "PUBLICATION DATE:". Under "PUBLICATION DATE:", there are three options: "ALL DATES" (selected), "LAST", and "CUSTOM RANGE". For "CUSTOM RANGE", there are dropdown menus for "FROM" and "TO" with "Select Month" and "Select Year" options. To the right of the search form, there is a "Search Tips" sidebar with sections on Boolean searches, searching for authors, searching for phrases, and DOIs. At the bottom of the search form, there are "CLEAR" and "SEARCH" buttons.



2

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RESEARCH ARTICLE Alternative epidemic indicators for COVID-19 in three settings with incomplete death registration systems BY RUTH MCCABE, CHARLES WHITTAKER, RICHARD J. SHEPPARD, NADA ABDELMAGID, ALIAJAH AHMED, ISRAA ZAIN ALABDEEN, NICHOLAS F. BRAZEAU, ABD ELHAMEED AHMED ABD ELHAMEED, ABDULLA SALEM BIN GHOUTH, ARRAN HAMLET, [...] OLIVER J. WATSON (+19 authors) • SCIENCE ADVANCES • VOL. 9, NO. 23 • 09 JUN 2023

Not all COVID-19 deaths are officially reported, and particularly in low-income and humanitarian settings, the magnitude of reporting gaps remains sparsely characterized. Alternative data sources, including burial site worker reports, satellite imagery of...

PERSPECTIVE Immune damage in Long Covid



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COVID-19 and children BY CARL A. PERCE, KEVIN C. HEROLD, BETSY C. HEROLD, JANET CHOU, ADRIENNE RANDOLPH, BINTA KANE, SAMMIE MCFARLAND, DEEPTI GURDASANI, CHRISTINA PAGEL, PETER HOTEZ, [...] SCOTT E. HENSLEY (+2 authors) Authors Info & Affiliations SCIENCE • 8 Sep 2022 • Vol. 377, Issue 6611 • pp. 1144-1149 • DOI: 10.1126/science.adk1875

Why is COVID-19 generally milder in children? Why do some children develop MIS-C? Long Covid in children and young people What is the role of children in transmission of SARS-CoV-2? The importance of vaccinating children against COVID-19 Original responses and discussions Letters against COVID-2 Acknowledgments References and Notes eLetters (0)

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Vaccine priming of rare HIV broadly neutralizing antibody precursors in nonhuman primates BY JON M. STECHEN, IVY PHONG, ET AL.

lipRNA-LNP HIV-1 trimer boosters elicit precursors to broad neutralizing antibodies BY ZHENFEI XIE, YING-QING LIN, ET AL.

Delocalized, asynchronous, closed-loop discovery of organic laser emitters BY FELIX STREITH-KALTHOFF, HAN HAO, ET AL.

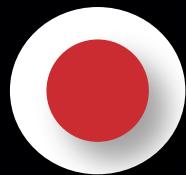
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ARTICLE TYPE

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PUBLICATION DATE

2020	2021
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SCIENCE - 18 Jan 2024 - Vol 383, Issue 6680 - pp. 292-293 - DOI: 10.1126/science.adc1077

Letters (5)

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Persistent complement dysregulation with signs of thromboinflammation in active Long Covid

BY CARLO CERVIA-HÄSLER, SARA C. BRÖNNIG, TOBIAS HÖCH ET AL. • SCIENCE - 19 JAN 2024

Acute infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cause a respiratory illness that can be associated with systemic immune cell activation and inflammation, widespread multorgan dysfunction, and thrombosis. Not everyone fully recovers from COVID-19, leading to Long Covid, the treatment of which is a major unmet clinical need (1). Long Covid can affect people of all ages, follows severe as well as mild disease, and involves multiple organs. The persistence of lingering symptoms after acute disease creates a considerable challenge for understanding the specific pathophysiology and risk factors underlying Long Covid. On page 273 of this issue, Cervia-Häslér *et al.* (2) report a multicenter, longitudinal study of 113 patients who either fully recovered from COVID-19 or developed Long Covid, identifying localized activation of the innate immune defense complement system as a likely culprit that induces thromboinflammation and prevents the restoration of fitness after acute COVID-19.

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INSIGHTS | PERSPECTIVES

MEDICINE

Immune damage in Long Covid

Links between the complement and coagulation systems could lead to Long Covid therapies

By Wolfram Ruf^{1,2}

Acute infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause a respiratory illness that can be associated with systemic immune cell activation and inflammation, widespread multorgan dysfunction, and thrombosis. Not everyone fully recovers from COVID-19, leading to Long Covid, the treatment of which is a major unmet clinical need (1). Long Covid can affect people of all ages, follows severe as well as mild disease, and involves multiple organs. The persistence of lingering symptoms after acute disease creates a considerable challenge for understanding the specific pathophysiology and risk factors underlying Long Covid. On page 273 of this issue, Cervia-Häslér *et al.* (2) report a multicenter, longitudinal study of 113 patients who either fully recovered from COVID-19 or developed Long Covid. Identifying localized activation of the innate immune defense complement system as a likely culprit that induces thromboinflammation and prevents the restoration of fitness after acute COVID-19.

Patients with Long Covid display signs of complement activation and endothelial damage (2), persistent immune cell activation (3), and autoimmune antibody production (4). These are also observed in patients with COVID-19. Cervia-Häslér *et al.* undertook a proteomic screen measuring serum levels of proteins that were increased by at least 2289 epoxide-specific DNA oligonucleotide aptamer probes. The patients with severe acute COVID-19 had a higher incidence of the acute infection and 6 months later, comparison of the 40 Long Covid patients, 73 recovered patients, and 90 healthy controls

several alternative pathways, in which C3b recruits complement factor B, leading to its proteolysis, can amplify complement activation on cell surfaces. The consecutive proteolytic cleavage of C3b and Bb results ultimately generate C3s that binds IgG and C3bBb serves as the cell membrane anchor for the formation of the C5 convertase, which recruits C5 and C9 in the terminal complement complex (TCC), which mediates complement-dependent cytotoxicity (CDC).

Focusing on Long Covid-specific proteome changes and taking into consideration age, sex, and ethnicity of the patients, the authors detected increased C3bBb levels, supporting excessive complement activation. However, complement activation in Long Covid showed surprisingly decreased levels. Careful validation of the upturn target specificity revealed that the C3bBb increase was due to TCC components, but not of free C3. The reduced levels of circulating C7-containing complexes

Complement-coagulation cross-talk at the endothelial interface

Complement C3b and C5a are activated in various tissues in Long Covid patients. Endothelial damage by membrane attack of the complement C5bC9 complex results in VWF and tPA release. This is highly problematic because the released tPA activates the coagulation cascade, which can lead to thrombosis and fibrin deposition. Interactions with platelets. Additionally, ADAMTS13 in Long Covid patients promotes the accumulation of ultrahuge VWF multimers, which induces C3b binding and stimulates the alternative pathway of complement activation. This leads to increased complement-dependent cytotoxicity and inflammation, as well as generating microclots that could underlie some of the features of Long Covid.

Local complement activation
Endothelial cell damage
Persistent complement activation

The complement system is crucial for life. It is indicated that ensemble of C9 with C3bBb

2

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7



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The screenshot shows the Science magazine website. At the top, there is an advertisement for the "SLAS 50TH EUROPEAN CONFERENCE" with the text "REGISTER TODAY". Below the ad, the Science logo is visible. The main content area features an article titled "Immune damage in Long Covid" by Wolfram Rie. A red box highlights the article's title and a small bell icon in the top right corner of the article's preview. To the right, the "CURRENT ISSUE" section is shown, featuring a seal on the cover of the journal. The "PDF" button is located in the bottom right corner of this section.

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Immune damage in Long Covid

Links between the complement and coagulation systems could lead to Long Covid therapies

WOLFRAM RUF Authors Info & Affiliations

SCIENCE • 19 Jan 2024 • Vol 383, issue 6680 • pp. 202-203 • DOI:10.1126/science.ad1077

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