新型冠状病毒信息简报

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上海科技大学免疫化学研究所

生物医学大数据平台和高通量筛选平台领衔编译制作

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内容介绍

分类	标题名称
疫情播报	1. 2020 年 11 月 26 日疫情
流行病学	2. 卡塔尔手工和体力劳动者中 SARS-CoV-2 感染的流行率可能高达 6 成 3. 天津最近本土病例流调初步结果 4. 上海 9 日确诊病例曾暴露于一来自北美的航空集装器 感染源为境外输入 浦东最新 2 例确诊病例行动轨迹公布 5. SARS-CoV-2 抗体与防止再感染有关
疾病病理	6. 轻微感染 COVID-19 后，功能性 SARS-CoV-2 特异性免疫记忆依然存在
疫苗研发	7. 基于 SARS-CoV-2 受体结合域（RBD）和七肽重复（HR）的纳米疫苗可引发强大的保护性免疫反应 8. SARS-CoV-2 mRNA 疫苗可促进与中和抗体产生相关的强有力的抗原特异性生发中心应答 9. 确保疫苗安全 10. 随着全球对 COVID-19 疫苗的推广，中国的目标是赢得朋友并达成协议 11. 为何牛津 COVID 疫苗的有效保护结果让科学界疑惑：初步临床数据显示低剂量疫苗免疫人群产生更有效的保护力
药物研发	12. 双重锁定的抗 SARS-CoV-2 的有效人类单克隆抗体
临床试验	13. 瑞德西韦诱导 SARS-CoV-2 感染患者病毒 RNA 和亚基因组 RNA 抑制及病毒变异的进化
基础研究	14. 靶向 SARS-CoV-2 蛋白酶作为 COVID-19 治疗策略的挑战 15. COVID-19 患者的单细胞分析：一个国际性的来自多个组织的数据来源 16. 与日本 SARS-CoV-2 系统发育相关的蝙蝠 Sarbecovirus 病毒

	的检测与特性 17. 肺部远端类器官中的前体细胞鉴定以及 SARS-CoV-2 感染研 18. 全基因组范围内对可成药的所有蛋白的孟德尔随机化分析鉴定出针对 COVID-19 的老药新用机会 19. AI 驱动的多尺度模拟揭示了 SARS-CoV-2 Spike 蛋白的动力学机理 20. 利用晶体学筛选和计算对接，发现能够与 SARS-CoV-2 Nsp3 宏结构域结合的片段

1. 2020 年 11 月 26 日疫情

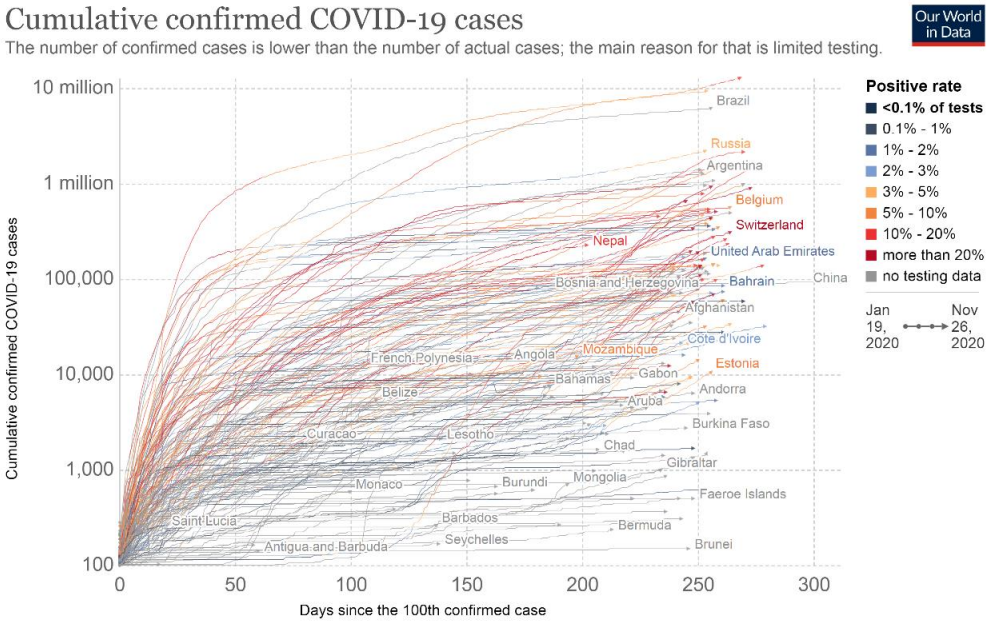
数据来源：WHO

发布时间：2020 年 11 月 26 日北京时间下午 4 点

链接：https://covid19.who.int/

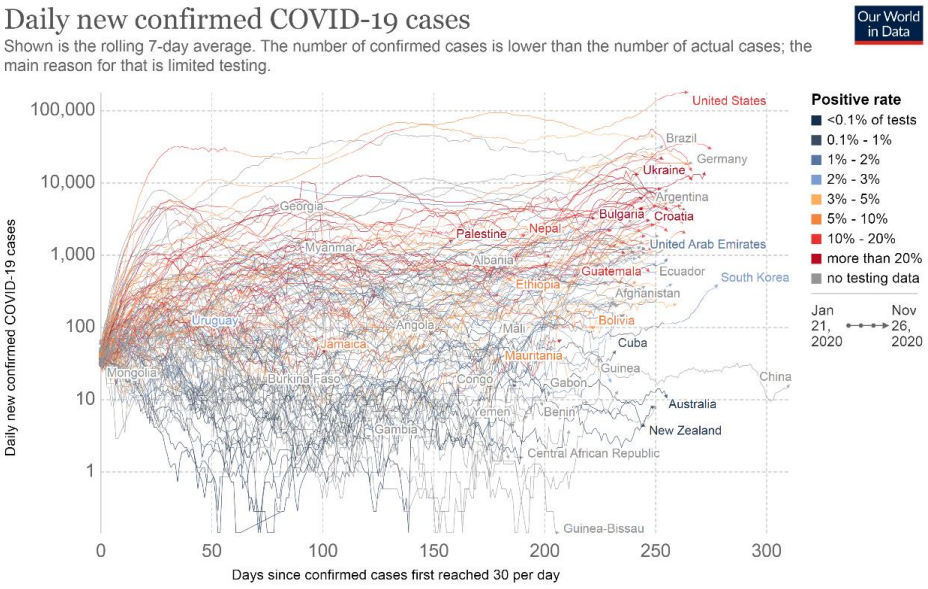
根据 WHO 提供的数据，2020 年 11 月 26 日全球累计确诊新型冠状病毒病人 **60,074,174** 例，当日新增确诊 **577,198** 例（其中美国高达 20 万例），累计死亡 **1,416,292** 例，当日新增死亡 **11,263**。

中国累计确诊 93,025 例，累计死亡 4,749 例，当日新增确诊 111 例，新增死亡 0 例。



Source: European CDC – Situation Update Worldwide – Last updated 26 November, 10:06 (London time), Official data collated by Our World in Data
CC BY

重点国家确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）



Source: European CDC – Situation Update Worldwide – Last updated 26 November, 10:06 (London time), Official data collated by Our World in Data
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重点国家每日新增确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）

全国新型冠状病毒肺炎新增确诊病例分布图（11月26日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 卡塔尔手工和体力劳动者中 SARS-CoV-2 感染的流行率可能高达 6 成

Seroprevalence of SARS-CoV-2 infection in the craft and manual worker population of Qatar

来源：medrxiv

发布时间：2020-11-24

链接：https://www.medrxiv.org/content/10.1101/2020.11.24.20237719v1

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中文摘要：

背景：卡塔尔正在经历 SARS-CoV-2 流行，对占总人口 60%的手工艺和体力劳动者（craft and manual worker, CMW）造成了不同程度的影响。本研究旨在评估该人群中曾经和/或现在感染的比例。

方法：于 2020 年 7 月 26 日至 9 月 9 日进行横断面人群调查，通过血清学检测和 PCR 检测对 SARS-CoV-2 的阳性率进行评估。通过回归分析确定与抗体和 PCR 阳性的相关性。
结果：本研究共纳入 2641 名受试者，其中年龄<40 岁的占 69.3%。抗 SARS-CoV-2 阳性率为 55.3%（95%CI:53.3-57.3%），并且与国籍、地理位置、受教育程度、职业、调查前两周存在的症状以及以前的感染诊断显著相关。PCR 阳性率为 11.3%（95%CI:9.9-12.8%），与地理位置、与感染者的接触以及报告两种或两种以上症状显著相关。感染阳性率（抗体和/或 PCR 阳性）为 60.6%（95%CI:9.9-12.8%）。抗体阳性的 CMWs 在先前就被诊断为 SARS-CoV-2 的比例为 9.3%（95%CI:7.9-11.0%）。只有 7 例为重症，1 例为危重症，严重感染率为 0.5%（95%可信区间：0.2-1.0%）。
结论：每 10 例 CMWs 中有 6 例感染，提示已达到群体免疫阈值。感染严重程度较低，每 200 例感染中只有一例进展为重症或危重症。每 10 例感染中只有 1 例曾被诊断为 COVID-19 提示大部分无症状或轻微感染。

Abstract

Background: Qatar experienced a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic that disproportionately affected the craft and manual worker (CMW) population who comprise 60% of the total population. This study aimed to assess the proportions of ever and/or current infection in this population.
Methods: A cross-sectional population-based survey was conducted during July 26-September 09, 2020 to assess both anti-SARS-CoV-2 positivity through serological testing and polymerase chain reaction (PCR) positivity through PCR testing. Associations with antibody and PCR positivity were identified through regression analyses.
Results: Study included 2,641 participants, 69.3% of whom were <40 years of age. Anti-SARS-CoV-2 positivity was estimated at 55.3% (95% CI: 53.3-57.3%) and was significantly associated with nationality, geographic location, educational attainment, occupation, presence of symptoms in the two weeks preceding the survey, and previous infection diagnosis. PCR positivity was assessed at 11.3% (95% CI: 9.9-12.8%) and was significantly associated with geographic location, contact with an infected person, and reporting two or more symptoms. Infection positivity (antibody and/or PCR positive) was assessed at 60.6% (95% CI: 9.9-12.8%). The proportion of antibody-positive CMWs that had a prior SARS-CoV-2 diagnosis was 9.3% (95% CI: 7.9-11.0%). Only seven infections were ever severe and one was ever critical - an infection severity rate of 0.5% (95% CI: 0.2-1.0%).
Conclusions: Six in every 10 CMWs have been infected, suggestive of reaching the herd immunity threshold. Infection severity was low with only one in every 200 infections progressing to be severe or critical. Only one in every 10 infections had been previously diagnosed suggestive of mostly asymptomatic or minimally mild infections.

3. 天津最近本土流调初步结果

来源：上观新闻
发布时间：2020-11-25

链接：https://mp.weixin.qq.com/s/5nsTeRsGx_vASwQkxjvV5A
编译者：孔娟
中文摘要：
11.25 日天津疫情防控发布会上天津市疾控中心副主任张颖女士介绍海联冷库与瞰海轩的疫情没有关联性，是两起独立的发病。判断的依据不单纯是从地理位置、人员的联系，更重要的是病毒的基因。海联冷库经过粗测序，它的病毒基因属于是 L 基因型欧洲家系 2 分支，瞰海轩属于 L 基因型欧洲家系 1 分支。还有传播模式不同，海联冷库至今没有发生进一步的人传人，只是物到人。瞰海轩从物到人后期又出现了在社区里面的其他居民感染的情况，这也是这两起疫情不同点。此外发布会表示海联冷库感染来源为北美猪头。瞰海轩小区新冠病毒感染原因为 4 号楼首例感染者曾在电梯咳嗽，跟他相隔不到两分钟的时间，未戴口罩的康某进入电梯被感染。此外，与 4 号楼该名新冠病毒感染者无关的 19 号楼内，也出现了 4 个感染者，疾控中心流调显示 19 号楼感染者可能是通过被感染者污染电梯等环境所致。

4. 上海 9 日确诊病例曾暴露于一来自北美的航空集装器 感染源为境外输入 浦东最新 2 例确诊病例行动轨迹公布

发布时间：2020.11.23
文章链接：https://mp.weixin.qq.com/s/p-gcHBNQHfTcCNo3SXdWyQ
编译者：张怡
23 日上午，上海举行疫情防控工作领导小组新闻发布会，市卫生健康委、市疾控中心、浦东新区等介绍本市疫情防控有关情况。
上海 22 日新增 2 例确诊病例详情公布 11 月 22 日，浦东新区在追踪排查确诊病例的密切接触者时，发现两例新冠肺炎可疑病例。一例为浦东机场 UPS 上海国际转运中心西区货运站确诊病例吴某某的同事，另一例为浦东机场 UPS 上海国际转运中心西区货运站确诊病例王某的妻子。
9 日确诊病例曾暴露于一航空集装器 11 月 9 日和 11 月 10 日确诊的 2 例病例曾于 10 月 30 日共同进入并清理过一个自北美地区运返回沪后的航空集装器。该集装器为密闭容器，内有大量避震用泡沫，内部环境潮湿。清理时，2 人均未佩戴口罩。同时，经基因测序，2 例病例基因高度同源，与北美流行株高度相似，这就提示感染来源为境外输入。

5. SARS-CoV-2 抗体与防止再感染有关

Antibodies to SARS-CoV-2 are associated with protection against reinfection
来源： medrxiv
发布时间：2020-11-19
链接：https://www.medrxiv.org/content/10.1101/2020.11.18.20234369v1
第一作者：Sheila F Lumley
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通讯作者单位：Microbiology Department, John Radcliffe Hospital
DOI 或 PUBMED ID：preprint
编译者：孔娟
中文摘要：
背景：了解严重急性呼吸综合征冠状病毒 2 型(SARS-CoV-2)感染是否能防止随后的再感染。
方法：文中研究者对英国牛津大学医院血清阳性和阴性 SARS-CoV-2 感染的医护人员进行了 PCR 反应阳性的发生率进行了研究。通过抗 S 蛋白/或抗核衣壳 IgG 来进行抗体水平的检测，

随访长达 30 周。使用泊松回归通过抗体状态估计 PCR 反应阳性结果和新症状感染的相对发病率，同时考虑年龄、性别和发病率随时间的变化。

结果：在参加抗体检测的 12219 名医务人员中，11052 人抗体阴性，1246 人抗体阳性，分别进行随访，79 人在随访期间血清转化。随访期间 11052 例血清阴性个体中有 89 例发生症状性感染且呈现 PCR 检测阳性 （每 0.46 例/10，000 天），而在抗 S 蛋白抗体阳性个体中没有出现症状性感染。血清阴性个体中有 76 名 PCR 检测阳性的无症状感染者(0.40 例/10，000 天)，血清阳性个体中仅有 3 名 PCR 检测阳性的无症状感染者 （0.21 例/10，000 天)。总体而言，阳性抗 S 蛋白抗体与较低的聚合酶链反应阳性率(有或无症状)相关(调整后的比率为 0.24[95%置信区间 0.08-0.76，p=0.015])。单独使用抗核衣壳抗体或与抗 S 蛋白抗体联合检测比率相似。

结论：在感染后的六个月内，既往感染 SARS-CoV-2 并产生抗体应答的患者为大多数人提供了防止再感染的保护。需要进一步的工作来确定感染后免疫的长期持续时间和相关性。

Abstract

Background It is critical to understand whether infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) protects from subsequent reinfection

Methods We investigated the incidence of SARS-CoV-2 PCR-positive results in seropositive and seronegative healthcare workers (HCWs) attending asymptomatic and symptomatic staff testing at Oxford University Hospitals, UK. Baseline antibody status was determined using anti-spike and/or anti-nucleocapsid IgG assays and staff followed for up to 30 weeks. We used Poisson regression to estimate the relative incidence of PCR-positive results and new symptomatic infection by antibody status, accounting for age, gender and changes in incidence over time.

Results A total of 12219 HCWs participated and had anti-spike IgG measured, 11052 were followed up after negative and 1246 after positive antibody results including 79 who seroconverted during follow up. 89 PCR-confirmed symptomatic infections occurred in seronegative individuals (0.46 cases per 10,000 days at risk) and no symptomatic infections in those with anti-spike antibodies. Additionally, 76 (0.40/10,000 days at risk) anti-spike IgG seronegative individuals had PCR-positive tests in asymptomatic screening, compared to 3 (0.21/10,000 days at risk) seropositive individuals. Overall, positive baseline anti-spike antibodies were associated with lower rates of PCR-positivity (with or without symptoms) (adjusted rate ratio 0.24 [95%CI 0.08-0.76, p=0.015]). Rate ratios were similar using anti-nucleocapsid IgG alone or combined with anti-spike IgG to determine baseline status.

Conclusions Prior SARS-CoV-2 infection that generated antibody responses offered protection from reinfection for most people in the six months following infection. Further work is required to determine the long-term duration and correlates of post-infection immunity.

编者注：另有一篇 Garmian 大学的研究人员进行了有关新冠肺炎恢复后血清抗体阴性患者的 SARS-CoV-2 再感染的研究。文章对 829 例康复后患者 SARS-CoV-2 再感染情况进行了研究，829 例中 87 例抗 SARS-CoV-2 IgG 阴性，IgG 阴性的 87 名患者中，有 25 名在首次感染后 1 至 3 个月内再次感染。而在 IgG 水平可检测的患者中，仅有一例在初步康复后 4.5 个

月出现无症状再感染。在抗 SARS-CoV-2 IgG 阴性的新冠肺炎康复的患者似乎仍然更容易受到 SARS-CoV-2 的再感染，且没有明显的免疫力。
文章链接：https://www.medrxiv.org/content/10.1101/2020.11.20.20234385v1

6. 轻微感染 COVID-19 后，功能性 SARS-CoV-2 特异性免疫记忆依然存在

Functional SARS-CoV-2-specific immune memory persists after mild COVID-19
来源：Cell
发布时间：2020.11.17
文章链接：https://www.cell.com/cell/fulltext/S0092-8674(20)31565-8
第一作者：Lauren B. Rodda
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DOI: https://doi.org/10.1016/j.cell.2020.11.029
编译者：张怡
中文摘要：

SARS-CoV-2 病毒造成了全球疾病蔓延并且病例仍在继续上升。大多数感染的人经历了轻微的 COVID-19 症状，但是仍然不清楚这是否能够诱导持久的免疫记忆，从而促进免疫。研究者们对已从轻微 COVID-19 感染康复的人群开展了一项纵向评价，以确定他们是否发展并维持着 SARS-CoV-2 特异性免疫记忆。康复人群产生了 SARS-CoV-2 特异性 IgG 抗体，中和抗体，记忆 B 细胞和记忆 T 细胞，这些可以维持至少 3 个月。研究数据进一步显示 SARS-CoV-2 特异性 IgG 抗体记忆 B 细胞随着时间增加。SARS-CoV-2 特异性记忆淋巴细胞表现出与强效抗病毒的功能相关的特征，记忆 T 细胞分泌细胞因子，并在抗原再次出现时扩张，而记忆 B 细胞在表达单克隆抗体时，表达可以中和病毒的受体。然而轻度 COVID-19 诱导记忆淋巴细胞可以持续存在，并表现出抗病毒免疫作用的功能特征。

Abstract

The SARS-CoV-2 virus is causing a global pandemic and cases continue to rise. Most infected individuals experience mildly symptomatic coronavirus disease 2019 (COVID-19), but it is unknown whether this can induce persistent immune memory that could contribute to immunity. We performed a longitudinal assessment of individuals recovered from mild COVID-19 to determine if they develop and sustain multifaceted SARS-CoV-2- specific immunological memory. Recovered individuals developed SARS-CoV-2-specific IgG antibodies, neutralizing plasma, memory B and memory T cells that persisted for at least three months. Our data further reveal that SARS-CoV-2-specific IgG memory B cells increased over time. Additionally, SARS-CoV-2-specific memory lymphocytes exhibited characteristics associated with potent antiviral function: memory T cells secreted cytokines and expanded upon antigen re-encounter, while memory B cells expressed receptors capable of neutralizing virus when expressed as monoclonal antibodies. Therefore, mild COVID-19 elicits memory lymphocytes that persist and display functional hallmarks of antiviral immunity.

7. 确保疫苗安全

Ensuring vaccine safety

来源：Science
发布时间：2020-11-17
链接：https://science.sciencemag.org/content/early/2020/11/16/science.abf0357

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DOI 或 PUBMED ID：10.1126/science.abf0357

编译者：刘焕珍

中文摘要：

如果监管机构维持其有据可查的安全测试协议，则 COVID-19 疫苗将是安全的。在疫苗发现、开发和测试的每个阶段都应考虑安全性。疫苗开发的历史经验为疫苗的临床前和临床测试铺平了道路，以确保其安全性和有效性，从而研制出安全的疫苗，挽救了数百万人的生命。经验表明，在发放许可证和广泛使用疫苗前，必须彻底评估疫苗制剂的安全性。必须对所有批次的疫苗进行安全性测试。通过了解疫苗的作用机理和免疫保护的相关性，可以提高疫苗安全性。如果在临床试验中发现严重不良事件，则需要进行额外的临床试验。目前正在并行进行多项 COVID-19 疫苗试验，并在临床前开发中增加了许多候选药物。为了通过提高透明度来增强公众对疫苗的信心，FDA 生物学评估和研究中心（CBER）发布了 SARS-CoV-2 疫苗安全性和有效性评估的主要方案。总体而言，疫苗接种者、疫苗开发商、制药公司和监管机构的利益在确保疫苗安全性的重要性上是一致的。必须在整个 COVID-19 疫苗开发过程中遵循既定的临床安全性测试规程，包括部署前和部署后。

Abstract:

COVID-19 vaccines will be safe if regulatory agencies maintain their well-documented safety testing protocols. Safety should be considered at every phase of vaccine discovery, development, and testing. The historical experience with vaccine development has paved the way for a well-developed path for preclinical and clinical testing of vaccines to ensure their safety and efficacy, leading to safe vaccines that have saved millions of lives. Empirical experience indicates the importance of thoroughly assessing safety of vaccine preparations before licensing and widespread use. All batches of vaccines must be tested for safety. An additional level of vaccine safety is provided by understanding the mechanism of action and immune correlates of protection. If serious adverse events are detected in a clinical trial, then additional clinical testing is indicated. Multiple COVID-19 vaccine trials are currently being conducted in parallel, with many additional candidates in preclinical development.To enhance public confidence in vaccines by providing transparency, the FDA Center for Biologics Evaluation and Research (CBER) has published master protocols for SARS-CoV-2 vaccine safety and effectiveness evaluation. Overall, the interests of vaccinees, vaccine developers, pharmaceutical companies, and regulatory agencies are aligned on the importance of ensuring vaccine safety. The COVID-19 vaccines must follow the established clinical safety testing protocols throughout vaccine development, including both preand postdeployment.

8. 随着全球对 COVID-19 疫苗的推广，中国的目标是赢得朋友并达成协议

With global push for COVID-19 vaccines, China aims to win friends and cut deals

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中文摘要：

由于中国事实上已经基本扑灭新冠病毒，所以作者认为中国在新冠疫苗上的巨大投入不仅仅是在寻找有前途的临床试验场所，而是在玩一场全球性的游戏，承诺向正在为其候选国进行试验的国家提供任何经证实的疫苗，或分享其背后的技术。尽管美国和欧洲部分国家并不信任中国疫苗，但他们已经在五大洲的其他 15 个国家进行临床试验的有效性测试。随着过去一个月里辉瑞公司、摩登纳公司、阿斯利康公司、牛津大学以及俄罗斯公布的令人鼓舞的 COVID-19 疫苗临床三期中期结果，人们开始关注中国在研疫苗的临床结果，预计近期将有一个或多个海外临床机构公布中国疫苗的三期结果。今年 10 月中国宣布加入 COVAX，莫里森说，这是一次外交行动，同时如果疫苗成功的话，将使中国国内的疫苗产业得到长足发展。

Abstract:

China isn’t just seeking promising venues for clinical trials. Not urgently needing the vaccines at home to fight a virus it has largely quashed, it is playing a global game by pledging to send any proven vaccine to countries that are conducting trials for its candidates, or to share the technologies behind them. “They know they don’t need a vaccine to contain the epidemic in China,” Yip says. “They can take their sweet time.”

China chose to navigate Brazil’s daunting politics because with an out-of-control pandemic—it is third in the world in total infections, with more than 100,000 new cases every week—the country is a magnet for vaccine testing and is desperate for vaccines. São Paulo state in September committed $90 million to Sinovac for 46 million doses. (This, notably, is 10 times cheaper than what the U.S. government is paying for the Pfizer/BioNTech and Moderna mRNA vaccines.) And Brazil could augment the supply by making vaccine itself. Sinovac says it may transfer its technology to the Butantan Institute, a major vaccine manufacturer in São Paulo, a collaboration Meng describes as a “win-win.”

China has had warmer receptions in other countries. Turkey in September launched a 13,000-person efficacy trial of Sinovac’s vaccine. Serhat Ünal, who heads the Hacettepe University Vaccine Institute—which is similar to Butantan in Brazil—and is on the scientific board of the Ministry of Health, says Turkey has “a good infrastructure for the phase III studies” and, unlike the United States and much of Europe, welcomed a Chinese vaccinemaker.

The three Chinese manufacturers also have large efficacy trials planned or underway in Indonesia, Pakistan, Saudi Arabia, Mexico, and Chile (see map, above).

It’s a good strategy, Ünal says. “When you do the phase III in different countries, it’s more transparent, it’s more trustworthy,” he says.

9. 为何牛津 COVID 疫苗的有效保护结果让科学界疑惑：初步临床数据显示低剂量疫苗免疫人群产生更有效的保护力

Why Oxford’s positive COVID vaccine results are puzzling scientists: Preliminary data suggest that the immunization was more effective in trial participants who received a lower dose.

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中文摘要：

11 月 23 日，赋予厚望的阿斯利康公司与牛津大学共同研发新冠腺病毒载体疫苗的III期临床试验初步分析结果公布：平均有效保护率为 70%。这一临床结果公布令人鼓舞同时也令人挠头。因为数据结果显示：与安慰剂组相比，牛津-阿斯利康疫苗两次全剂量免疫组的有效保护率为 62%，而第一针半剂量，第二针全剂量给药组显示出 90%的有效保护率。这一数据结果带给科学家一个疑问：为何第一针半剂量免疫效果更好呢？一种解释是：试验群体规模不足以衡量两种免疫剂量组之间的差异，因为更有效的“半剂量、全剂量”免疫组数据结果是基于 2741 名受试者，而效果较差的全剂量组数据却有源于 8895 名受试者，若折算后，“半剂量，半剂量”组仅有 66%的有效保护率。另一种解释是低剂量的疫苗可更有效地刺激辅助产生抗体的 T 细胞。牛津-阿斯利康疫苗载体是猩猩体内分离的腺病毒经改造使病毒载体在细胞中无法复制。疫苗免疫后，仅在细胞内合成新冠病毒的 spike 蛋白从而激发机体产生特异性抗体。但不排除疫苗载体可能也会激发机体产生相应的免疫反应可能，且第一次免疫使用全剂量可能会弱化这种疫苗载体的免疫源性。尽管临床结果存在不对等性，表明牛津疫苗有效性还存在着不确定性。亦有科学家称：当前人们急于比较不同疫苗间免疫效果好坏的危险境地，其实疫苗临床数据全面公布之前还有很长的路要走。但与 mRNA 疫苗相比，牛津-阿斯利康疫苗具备产能和运输优势，其可在 2-8℃的正常冷藏温度下稳定保存六个月。

Abstract:

A highly anticipated COVID-19 vaccine has delivered some encouraging — but head-scratching — results. The vaccine was found to be, on average, 70% effective in a preliminary analysis of phase III trial data. A regimen consisting of two full doses given a month apart looked to be just 62% effective. But, surprisingly, participants who received a lower amount of the vaccine in a first dose and then the full amount in the second dose were 90% less likely to develop COVID, compared with participants in the placebo arm. A top priority for researchers is understanding why the vaccine seems to have performed so much better with a lower first dose. One explanation could lie in the data: the trial might not have been big enough to gauge the difference between the two regimens. The more effective ‘half-dose, full dose’ results were based on 2,741 trial participants, whereas the less efficacious arm included 8,895 volunteers. Another explanation based on lower doses of vaccine

doing a better job at stimulating T cells that support the production of antibodies. The immune system's response against the chimpanzee virus. The vaccine triggers an immune response not only to the SARS-CoV-2 spike protein, but also to components of the viral vector. It's possible that the full first dose blunted this reaction. The Oxford–AstraZeneca vaccine is made from a cold-causing 'adenovirus' that modified so that it no longer replicates in cells. Even with a question mark hanging over its efficacy, the Oxford–AstraZeneca vaccine is stable at refrigerator temperatures.

10. 基于 SARS-CoV-2 受体结合域（RBD）和七肽重复（HR）的纳米疫苗可引发强大的保护性免疫反应

Nanoparticle Vaccines Based on the Receptor Binding Domain (RBD) and Heptad Repeat (HR) of SARS-CoV-2 Elicit Robust Protective Immune Responses

来源：Immunity

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中文摘要：

针对全球 COVID-19 大流行，人们提出了各种疫苗策略，每种策略都有独特的诱导免疫反应的策略。在这里，我们通过将自组装的 24-mer 铁蛋白共价结合到严重急性呼吸综合征冠状病毒 2（SARS-CoV-2）棘突蛋白的受体结合域（RBD）和/或七肽重复序列（HR）亚单位来开发纳米疫苗。与单体疫苗相比，纳米颗粒疫苗可诱导更为强健的中和抗体和细胞免疫应答。用 RBD 和/或 RBD-HR 纳米粒接种 hACE2 转基因小鼠后，SARS-CoV-2 攻击后肺部病毒载量降低。RBD-HR 纳米颗粒疫苗也能促进中和抗体和对其他冠状病毒的细胞免疫反应。恒河猴的纳米颗粒疫苗在增强免疫前诱导了中和抗体和 T 细胞和 B 细胞反应；这些反应持续了 3 个月以上。因此，基于 RBD 和 HR 的纳米颗粒为 SARS-CoV-2 和其他冠状病毒提供了一种很有前途的疫苗接种方法。

Abstract:

Various vaccine strategies have been proposed in response to the global COVID-19 pandemic, each with unique strategies for eliciting immune responses. Here, we developed nanoparticle vaccines by covalently conjugating the self-assembled 24-mer ferritin to the receptor binding domain (RBD) and/or heptad repeat (HR) subunits of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) spike (S) protein. Compared to monomer vaccines, nanoparticle vaccines elicited more robust neutralizing antibodies and cellular immune responses. RBD and RBD-HR nanoparticle vaccinated hACE2 transgenic mice vaccinated with RBD and/or RBD-HR nanoparticles exhibited reduced viral load in the lungs after SARS-CoV-2 challenge. RBD-HR nanoparticle vaccines also promoted neutralizing antibodies and cellular immune responses against other coronaviruses. The nanoparticle vaccination of rhesus macaques induced neutralizing antibodies, and T and B

cell responses prior to boost immunization; these responses persisted for more than three months. RBD- and HR-based nanoparticles thus present a promising vaccination approach against SARS-CoV-2 and other coronaviruses.

11. SARS-CoV-2 mRNA 疫苗可促进与中和抗体产生相关的强有力的抗原特异性生发中心应答

SARS-CoV-2 mRNA vaccines foster potent antigen-specific germinal center responses associated with neutralizing antibody generation

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中文摘要：

亮点：

SARS-CoV-2 mRNA 疫苗诱导生发中心（GC）B 细胞应答

GC 应答与产生强力中和抗体有关

SARS-CoV-2 mRNA 疫苗促进抗原特异性 T 滤泡辅助细胞（Tfh）

SARS-CoV-2 mRNA 疫苗调节 Tfh 细胞程序的关键因素

部署有效的 SARS-CoV-2 疫苗是根除 COVID-19 大流行的关键。许多获得许可的疫苗通过诱导长寿命浆细胞（LLPC）和记忆 B 细胞（MBC）来提供保护，这些细胞类型通常在生发中心（GC）反应中产生。研究人员直接比较了两种疫苗平台——mRNA 疫苗和用 MF59 样佐剂配制的重组蛋白——随时间的推移，其定量和定性影响 SARS-CoV-2 特异性初级 GC 反应的能力。结果证明，单一免疫 SARS-CoV-2 mRNA，而不是重组蛋白疫苗，可以诱导有效的 SARS-CoV-2 特异性 GC B 和 T 滤泡辅助（Tfh）细胞反应以及 LLPC 和 MCB。重要的是，GC 反应与中和抗体的产生密切相关。mRNA 疫苗更有效地诱导 Tfh 细胞程序的关键调节因子，并影响 Tfh 细胞的功能特性。总的来说，这项研究确定 SARS-CoV-2 mRNA 疫苗是促进强有力的 GC 源性免疫反应的有力候选。

Abstract:

Highlights

•SARS-CoV-2 mRNA vaccines elicit potent germinal center (GC) B cell responses

•GC responses are associated with a robust development of neutralizing antibodies

•SARS-CoV-2 mRNA vaccines promote antigen-specific T follicular helper (Tfh) cells

•Key elements of the Tfh cell program are modulated by SARS-CoV-2 mRNA vaccines

Summary

The deployment of effective vaccines against SARS-CoV-2 is critical to eradicate the COVID-19 pandemic. Many licensed vaccines confer protection by inducing long-lived plasma cells (LLPC) and memory B cells (MBC), cell types canonically generated during germinal center (GC) reactions. Here, we directly

compared two vaccine platforms -mRNA vaccines and a recombinant protein formulated with an MF59-like adjuvant- for their ability to quantitatively and qualitatively shape SARS-CoV-2-specific primary GC responses over time. We demonstrated that a single immunization with SARS-CoV-2 mRNA, but not with the recombinant protein vaccine, elicited potent SARS-CoV-2-specific GC B and T follicular helper (Tfh) cell responses as well as LLPC and MCB. Importantly, GC responses strongly correlated with neutralizing antibody production. mRNA vaccines more efficiently induced key regulators of the Tfh cell program and influenced the functional properties of Tfh cells. Overall, this study identifies SARS-CoV-2 mRNA vaccines as strong candidates for promoting robust GC-derived immune responses.

12. 双重锁定的抗 SARS-CoV-2 的有效人类单克隆抗体

Double Lock of a Potent Human Monoclonal Antibody against SARS-CoV-2

来源：bioRxiv

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编译者：张鹏伟

中文摘要：

受体识别和随后的膜融合对于成功感染 SARS-CoV-2 至关重要。停止这些步骤可以治愈 COVID-19。在这里，我们已经鉴定并鉴定了一种有效的人单克隆抗体 HB27，它可以在 nM 以下的浓度下阻断 SARS-CoV-2 与其细胞受体的结合。值得注意的是，HB27 还可以防止 SARS-CoV-2 膜融合。因此，在两个已建立的小鼠模型中，单剂量的 HB27 赋予了针对 SARS-CoV-2 的有效保护。当给予 10 倍有效剂量的 HB27 恒河猴时，没有显示出明显的不良事件。对 SARS-CoV-2 三聚体 S 与 HB27 Fab 的复合物的冷冻 EM 研究表明，三个 Fab 片段协同作用以阻止 SARS-CoV-2 与 ACE2 受体结合。抗体的结合还抑制了 RBD 的任何进一步构象变化，可能会干扰从融合前到融合后的进程。这些结果表明 HB27 是针对 COVID-19 的免疫疗法的有希望的候选者。

Abstract:

Receptor recognition and subsequent membrane fusion are essential for the establishment of successful infection by SARS-CoV-2. Halting these steps can cure COVID-19. Here we have identified and characterized a potent human monoclonal antibody, HB27, that blocks SARS-CoV-2 attachment to its cellular receptor at sub-nM concentrations. Remarkably, HB27 can also prevent SARS-CoV-2 membrane fusion. Consequently, a single dose of HB27 conferred effective protection against SARS-CoV-2 in two established mouse models. Rhesus macaques showed no obvious adverse events when administrated with 10-fold of effective dose of HB27. Cryo-EM studies on complex of SARS-CoV-2 trimeric S with HB27 Fab reveal that three Fab fragments work synergistically to occlude SARS-CoV-2 from binding to ACE2 receptor. Binding of the antibody also restrains any further

conformational changes of the RBD, possibly interfering with progression from the prefusion to the postfusion stage. These results suggest that HB27 is a promising candidate for immuno-therapies against COVID-19.

13. 瑞德西韦诱导 SARS-CoV-2 感染患者病毒 RNA 和亚基因组 RNA 抑制及病毒变异的进化

Remdesivir induced viral RNA and subgenomic RNA suppression, and evolution of viral variants in SARS-CoV-2 infected patients

来源：medRxiv

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中文摘要：

虽然 SARS-CoV-2 病毒载量随时间的变化已被记录在案，但关于 remdesivir 的影响以及它如何改变宿主内病毒进化的详细信息是有限的。从住院儿童的上呼吸道回收的 SARS-CoV-2 的连续病毒载量和深度测序结果显示，remdesivir 治疗抑制了一名患者的病毒 RNA 水平，但在另一名感染了同一菌株的患者中没有。找不到解释这种差异的耐药性证据。 在第二位患者治疗期间，亚基因组（sg）RNA 水平降低，表明 remdesivir 对病毒复制的额外作用与病毒 RNA 水平无关。单体型重建在四名患者中发现了持久性 SARS-CoV-2 变异基因型。我们的结论是，这些很可能是由宿主内部进化而来，而不是共同传播，尽管在一种情况下不能排除重叠感染。变异基因型丰富的样本之间的异质性可以通过诊断性拭子中不完整的种群采样在肺中存在离散的病毒种群来最好地解释。这种分隔在由流感和结核分枝杆菌引起的严重肺部感染中被很好地描述，并且与不良的药物渗透，欠佳的治疗和耐药性有关。我们的数据提供了证据，证明瑞德昔韦能够在体内抑制 SARS-CoV-2 复制，但其功效可能会因降低渗透到肺部的因素而受损。根据流感和结核分枝杆菌肺部感染的数据，我们得出结论，现在应该评估瑞姆昔韦与其他药物联合使用的早期使用情况。

Abstract:

While changes in SARS-CoV-2 viral load over time have been documented, detailed information on the impact of remdesivir and how it might alter intra-host viral evolution is limited. Sequential viral loads and deep sequencing of SARS-CoV-2 recovered from the upper respiratory tract of hospitalised children revealed that remdesivir treatment suppressed viral RNA levels in one patient but not in a second infected with an identical strain. Evidence of drug resistance to explain this difference was not found. Reduced levels of subgenomic (sg) RNA during treatment of the second patient, suggest an additional effect of remdesivir on viral replication that is independent of viral RNA levels. Haplotype reconstruction uncovered persistent SARS-CoV-2 variant genotypes in four patients. We conclude that these are likely to have arisen from within-host evolution, and not co-transmission, although superinfection cannot be excluded in one case. Sample-to-sample heterogeneity in the abundances of variant

genotypes is best explained by the presence of discrete viral populations in the lung with incomplete population sampling in diagnostic swabs. Such compartmentalisation is well described in serious lung infections caused by influenza and *Mycobacterium tuberculosis* and has been associated with poor drug penetration, suboptimal treatment and drug resistance. Our data provide evidence that remdesivir is able to suppress SARS-CoV-2 replication *in vivo* but that its efficacy may be compromised by factors reducing penetration into the lung. Based on data from influenza and *Mycobacterium tuberculosis* lung infections we conclude that early use of remdesivir combined with other agents should now be evaluated..

14. 靶向 SARS-CoV-2 蛋白酶作为 COVID-19 治疗策略的挑战

Challenges for targeting SARS-CoV-2 proteases as a therapeutic strategy for COVID-19

来源：bioRxiv

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中文摘要：

由 SARS-CoV-2 病毒产生的两种蛋白酶 M^{pro} 和 PL^{pro} 对病毒复制至关重要，已成为 COVID-19 治疗药物开发项目的焦点。我们筛选了一个高度聚焦的含有共价弹头的化合物库，用以靶向半胱氨酸蛋白酶，以鉴定 M^{pro} 和 PL^{pro} 蛋白酶的新的先导分子骨架。这些努力为 M^{pro} 蛋白酶找到了少量的活性化合物，而对 PL^{pro} 蛋白酶没有找到可行的活性化合物。在被鉴定为纯化重组蛋白酶抑制剂的 M^{pro} 活性化合物中，只有两种化合物在细胞感染检测中抑制了病毒的感染性。然而，我们观察到 TMPRSS2 的表达显著降低了抗病毒效力，TMPRSS2 是一种跨膜丝氨酸蛋白酶，是除了溶酶体组织蛋白酶之外的另外一种病毒进入途径。这种效力的丧失是由于我们的主要 M^{pro} 抑制剂也是宿主细胞半胱氨酸组织蛋白酶的有效抑制剂。为了确定这是否是 M^{pro} 抑制剂的一般特性，我们评估了最近报道的几种化合物，发现它们也是纯化的人组织蛋白酶 L 和 B 的有效抑制剂，并在表达 TMPRSS2 的细胞中表现出类似的抗病毒效力损失。我们的结果强调了靶向 M^{pro} 和 PL^{pro} 蛋白酶的挑战，并证明需要仔细评估 SARS-CoV-2 蛋白酶抑制剂的选择性，以防止通过抑制冗余病毒进入途径发挥作用的化合物进入临床开发。

Abstract

Two proteases produced by the SARS-CoV-2 virus, M^{pro} and PL^{pro}, are essential for viral replication and have become the focus of drug development programs for treatment of COVID-19. We screened a highly focused library of compounds containing covalent warheads designed to target cysteine proteases to identify new lead scaffolds for both M^{pro} and PL^{pro} proteases. These efforts identified a

small number of hits for the M^{pro} protease and no viable hits for the PL^{pro} protease. Of the M^{pro} hits identified as inhibitors of the purified recombinant protease, only two compounds inhibited viral infectivity in cellular infection assays. However, we observed a substantial drop in antiviral potency upon expression of TMPRSS2, a transmembrane serine protease that acts in an alternative viral entry pathway to the lysosomal cathepsins. This loss of potency is explained by the fact that our lead M^{pro} inhibitors are also potent inhibitors of host cell cysteine cathepsins. To determine if this is a general property of M^{pro} inhibitors, we evaluated several recently reported compounds and found that they are also effective inhibitors of purified human cathepsin L and B and showed similar loss in activity in cells expressing TMPRSS2. Our results highlight the challenges of targeting M^{pro} and PL^{pro} proteases and demonstrate the need to carefully assess selectivity of SARS-CoV-2 protease inhibitors to prevent clinical advancement of compounds that function through inhibition of a redundant viral entry pathway.

15. COVID-19 患者的单细胞分析：一个国际性的来自多个组织的数据来源

Single cell profiling of COVID-19 patients: an international data resource from multiple tissues

来源：medrxiv

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中文摘要：

在 2019 年末到 2020 年，COVID-19 大流行席卷全球，对理解和治疗一种以前未知的疾病提出了科学和医学挑战。为了帮助人们更好地理解 COVID-19，科学界迅速动员起来，联合起来研究 SARS-CoV-2 的感染、发病机制及其独特的疾病轨迹。COVID-19 的紧迫性为利用相对新的工具、技术和新生的协作网络提供了一个紧迫的用例。单细胞生物学就是这样一个例子，它在过去的十年里作为一种强有力的方法出现了，它为生物过程的细胞和分子基础提供了前所未有的解决办法。应用单细胞技术的早期基础工作，包括人类细胞图谱，利用已发表和未发表的数据，根据病毒受体 ACE2 和相关进入因子 TMPRSS2 和 CTSL 的表达，对从不同器官的 SARS-CoV-2 的可能的靶细胞的特征进行了研究（Muus 等人，2020 年；Sunnaka 等人，2020 年；Ziegler 等人，2020 年）。该参考数据的初步表征为气道和其他器官中的感染和病理的形成提供了重要的基础。然而，最初的分析仅限于来自未感染捐赠者和其他先前抽样的疾病适应症的样本。本报告概述了从 COVID-19 患者的样本中提取的单细胞数据源，以及对数据重用和探索的初步观察和指导。

编者注：

此前我们介绍过该研究的数据共享平台：https://www.covid19cellatlas.org/

Abstract

In late 2019 and through 2020, the COVID-19 pandemic swept the world, presenting

both scientific and medical challenges associated with understanding and treating a previously unknown disease. To help address the need for great understanding of COVID-19, the scientific community mobilized and banded together rapidly to characterize SARS-CoV-2 infection, pathogenesis and its distinct disease trajectories. The urgency of COVID-19 provided a pressing use-case for leveraging relatively new tools, technologies, and nascent collaborative networks. Single-cell biology is one such example that has emerged over the last decade as a powerful approach that provides unprecedented resolution to the cellular and molecular underpinnings of biological processes. Early foundational work within the single-cell community, including the Human Cell Atlas, utilized published and unpublished data to characterize the putative target cells of SARS-CoV-2 sampled from diverse organs based on expression of the viral receptor ACE2 and associated entry factors TMPRSS2 and CTSL (Muus et al., 2020; Sungnak et al., 2020; Ziegler et al., 2020). This initial characterization of reference data provided an important foundation for framing infection and pathology in the airway as well as other organs. However, initial community analysis was limited to samples derived from uninfected donors and other previously-sampled disease indications. This report provides an overview of a single-cell data resource derived from samples from COVID-19 patients along with initial observations and guidance on data reuse and exploration.

16. 与日本 SARS-CoV-2 系统发育相关的蝙蝠 Sarbecovirus 病毒的检测与特性

Detection and Characterization of Bat Sarbecovirus Phylogenetically Related to SARS-CoV-2, Japan

来源：CDC

发布时间：2020-11-02

链接：https://wwwnc.cdc.gov/eid/article/26/12/20-3386_article

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DOI 或 PUBMED ID：10.3201/eid2612.203386

编译者：宋张悦

中文摘要：

蝙蝠 β-冠状病毒，Sarbecovirus 病毒亚属的流行病学研究在很大程度上还是未知的，尤其是在中国以外。我们在一只保存于冰箱中的于 2013 采集的日本的角菊头蝠中发现了一种与严重急性呼吸综合征冠状病毒 2 型相关的 sarbecovirus 病毒 Rc-o319。sarbecovirus 病毒的刺突蛋白特异性识别角菊头蝠的血管紧张素转换酶 2，而不是人类作为进入受体。该病毒序列和 SARS-CoV-2 存在 81%的相似性。

编者注：根据 NATURE 2020 年 11 月 23 日一则通讯，除了日本在蝙蝠中发现类似 SARS-CoV-2 病毒，柬埔寨研究人员在一个 2010 年在柬埔寨捕获的 Shamel 的马蹄蝠中也发现了与 SARS-CoV-2 相关的冠状病毒。

Coronaviruses closely related to the pandemic virus discovered in Japan and Cambodia

链接：https://www.nature.com/articles/d41586-020-03217-0

Abstract
Epidemiology of bat Betacoronavirus, subgenus Sarbecovirus is largely unknown, especially outside China. We detected a sarbecovirus phylogenetically related to severe acute respiratory syndrome coronavirus 2 from Rhinolophus cornutus bats in Japan. The sarbecovirus' spike protein specifically recognizes angiotensin-converting enzyme 2 of R. cornutus, but not humans, as an entry receptor.

17. 肺部远端类器官中的前体细胞鉴定以及 SARS-CoV-2 感染研究

Progenitor identification and SARS-CoV-2 infection in human distal lung organoids
来源：nature
发布时间：2020-11-25
链接：https://www.nature.com/articles/s41586-020-3014-1
第一作者：Ameen A. Salahudeen,
通讯作者：Calvin J. Kuo
通讯作者单位：Stanford University School of Medicine
DOI 或 PUBMED ID：
编译者：蒋立春
中文摘要：
自然科研公众号文章：https://mp.weixin.qq.com/s/AjgLCr_rd7MJ_eWgjG6IFw
利用培养系统模拟新冠病毒肺部感染 |《自然》论文

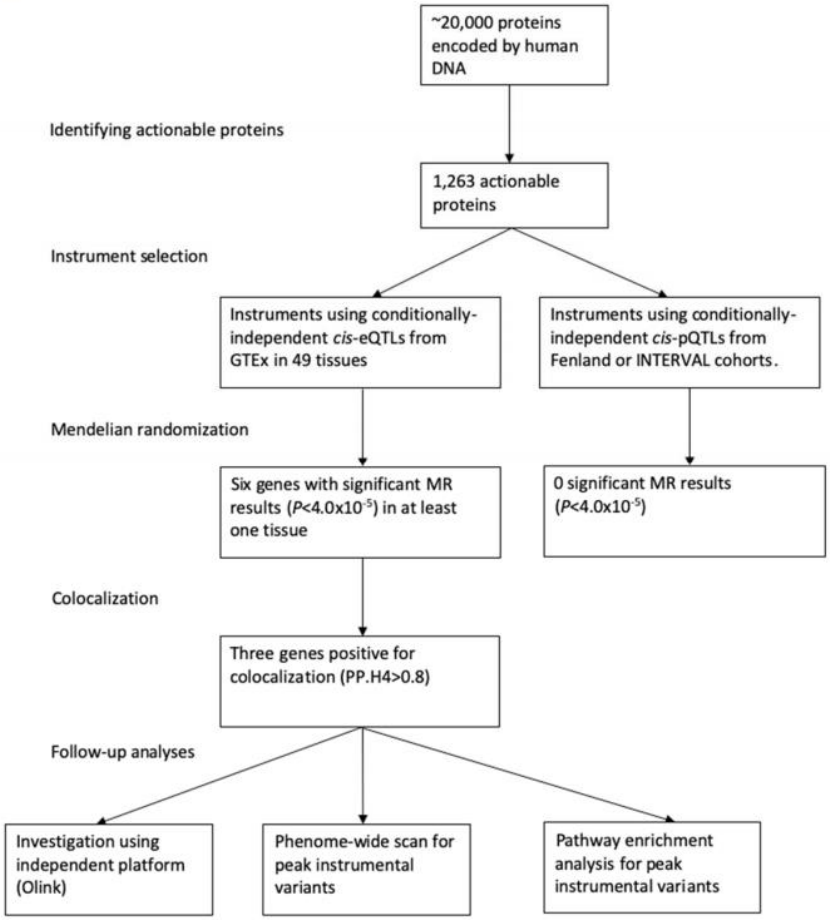
18. 全基因组范围内对可成药的所有蛋白的孟德尔随机化分析鉴定出针对 COVID-19 的老药新用机会

Actionable druggable genome-wide Mendelian randomization identifies repurposing opportunities for COVID-19
来源：medrxiv
发布时间：2020-11-23
链接：https://www.medrxiv.org/content/10.1101/2020.11.19.20234120v1
第一作者：Liam Gaziano
通讯作者：Juan P Casas
通讯作者单位：Harvard Medical School
DOI 或 PUBMED ID：
编译者：蒋立春
中文摘要：
老药新用是面对紧急的 COVID-19 快速找到治疗的方法之一。为了找到 COVID-19 相关的治疗靶点，作者们基于转录组和蛋白组数据对 1263 个可以作为药靶的蛋白进行了孟德尔随机试验。用宿主遗传学项目和百万退伍军人项目中的总结性的统计数据，作者们对 7554 个住院的 COVID-19 病人以及一百万对照人群进行了研究。作者们发现 3 个蛋白在孟德尔随机化分析中显示出显著结果（ACE2: P=1.6×10－6, IFNAR2: P=9.8×10－11, and IL-10RB: P=1.9×10-14），这三个基因在通过 cis-eQTL 遗传分析中也和 COVID-19 住院有强相关。为了理清 IL10RB 和 IFNAR2 的重叠的 eQTL 信号，作者们开展了表型组相关性扫描以

及通路富集分析。这些分析提示 IFNAR2 更可能在 COVID-19 住院中起到作用。作者们的发现建议应该有限考虑靶向 IFNAR2 和 ACE2 来对 COVID-19 病人进行早期治疗。

图 1：研究方案

Figure 1.



Abstract:

Drug repurposing provides a rapid approach to meet the urgent need for therapeutics to address COVID-19.To identify therapeutic targets relevant to COVID-19, we conducted Mendelian randomization (MR) analyses, deriving genetic instruments based on transcriptomic and proteomic data for 1,263 actionable proteins that are targeted by approved drugs or in clinical phase of drug development.

Using summary statistics from the Host Genetics Initiative and the Million Veteran Program, we studied 7,554 patients hospitalized with COVID-19 and >1 million controls.

We found significant Mendelian randomization results for three proteins （ACE2: P=1.6×10－6, IFNAR2: P=9.8×10－11, and IL-10RB: P=1.9×10－14 ） using cis-eQTL genetic instruments that also had strong evidence for colocalization with COVID-19 hospitalization. To disentangle the shared eQTL signal for *IL10RB* and *IFNAR2*, we conducted phenome-wide association scans

and pathway enrichment analysis, which suggested that *IFNAR2* is more likely to play a role in COVID-19 hospitalization. Our findings prioritize trials of drugs targeting IFNAR2 and ACE2 for early management of COVID-19.

19. AI 驱动的多尺度模拟揭示了 SARS-CoV-2 Spike 蛋白的动力学机理

AI-Driven Multiscale Simulations Illuminate Mechanisms of SARS-CoV-2 Spike Dynamics

来源：bioRxiv

发布时间：2020-11-20

链接：https://www.biorxiv.org/content/10.1101/2020.11.19.390187v1

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DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

作者开发了一套通用型的 AI 驱动的工作流程，该流程可以利用异构的 HPC 资源来探索分子系统随时间演化的动力学性质。作者利用此工作流程研究了 SARS-CoV-2 spike 蛋白的感染机制。这种工作流程能够在各种复杂的环境中更加高效地研究 spike 蛋白的动力学性质，包括对含有完整 SARS-CoV-2 病毒包膜的 spike 蛋白体系进行模拟计算。该模拟体系包含 3.05 亿个原子，使用 NAMD 在 ORNL Summit 上运行时表现出强大的加速性能。文中介绍了一些新颖的科学发现，包括阐明了 spike 蛋白的完整聚糖壳层，spike 蛋白中的聚糖在调节病毒感染能力中的作用，并表征了 spike 蛋白与人 ACE2 受体之间灵活的相互作用。作者还演示了 AI 如何在不同的系统中加速构象采样，并为将来使用此类方法研究 SARS-CoV-2 或其他分子系统铺平了道路。

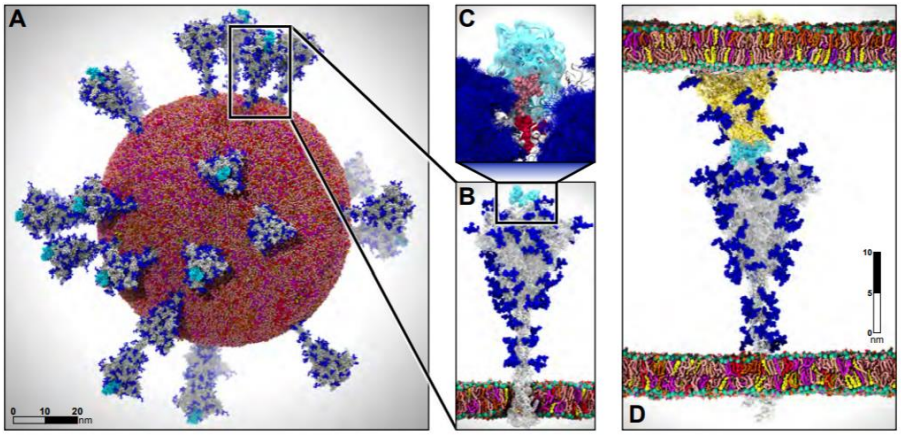

Figure 1: Multiscale modeling of SARS-CoV-2. **A)** All-atom model of the SARS-CoV-2 viral envelope (305 M atoms), including 24 spike proteins (colored in gray) in both the open (16) and closed states (8). The RBDs in the "up" state are highlighted in cyan) N-/O-Glycans are shown in blue. Water molecules and ions have been omitted for clarity. **B)** Full-length model of the glycosylated SARS-CoV-2 spike protein (gray surface) embedded into an ERGIC-like lipid bilayer (1.7 M atoms). RBD in the "up" state is highlighted in cyan. **C)** The glycan shield is shown by overlaying multiple conformations for each

glycan collected at subsequent timesteps along the dynamics (blue bushlike representation). Highlighted in pink and red are two N-glycans (linked to N165 and N234, respectively) responsible for the modulation of the RBD dynamics, thus priming the virus for infection. The RBD “up” is depicted with a cyan surface. **D)** Two-parallel-membrane system of the spike-ACE2 complex (8.5 M atoms). The spike protein, embedded into an ERGIC-like membrane, is depicted with a gray transparent surface, whereas ACE2 is shown with a yellow transparent surface and it is embedded into a lipid bilayer mimicking the composition of mammalian cell membranes. Glycans are shown in blue, whereas water has been omitted for clarity. Visualizations were created in VMD using its custom GPU-accelerated ray tracing engine.

Abstract
We develop a generalizable AI-driven workflow that leverages heterogeneous HPC resources to explore the time-dependent dynamics of molecular systems. We use this workflow to investigate the mechanisms of infectivity of the SARS-CoV-2 spike protein, the main viral infection machinery. Our workflow enables more efficient investigation of spike dynamics in a variety of complex environments, including within a complete SARS-CoV-2 viral envelope simulation, which contains 305 million atoms and shows strong scaling on ORNL Summit using NAMD. We present several novel scientific discoveries, including the elucidation of the spike’s full glycan shield, the role of spike glycans in modulating the infectivity of the virus, and the characterization of the flexible interactions between the spike and the human ACE2 receptor. We also demonstrate how AI can accelerate conformational sampling across different systems and pave the way for the future application of such methods to additional studies in SARS-CoV-2 and other molecular systems.

20. 利用晶体学筛选和计算对接，发现能够与 SARS-CoV-2 Nsp3 宏结构域结合的片段

Fragment binding to the Nsp3 macrodomain of SARS-CoV-2 identified through crystallographic screening and computational docking

来源：bioRxiv
发布时间：2020-11-24
链接：https://www.biorxiv.org/content/10.1101/2020.11.24.393405v1

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DOI 或 PUBMED ID：
编译者：宋珂

中文摘要：

SARS-CoV-2 病毒的非结构蛋白 3（Nsp3）中的宏结构域（Mac1）能够阻碍宿主介导的抗病毒 ADP-核糖基化信号传导。由于催化突变可以使病毒失去致病性，因此该酶是一种潜在的抗病毒靶点。本文中，作者介绍了其大规模的晶体学筛选和计算对接工作，并发现了主要针对宏结构域中活性位点的新化合物。从包含 2683 个各种片段的库中，利用晶体学筛选，发现了 214 个独特的能够与宏结构域结合的片段。从包含 2000 万个片段的虚拟库中，利用对接筛选出另外 60 个活性分子，其中 20 个分子在晶体学上得到了确认。在生理温度下收集到的超高分辨率 X-ray 数据，可以用来评估活性位点周围的构象异质性。作者进一步利用其他三种生物物理技术（DSF，HTRF，ITC）对几个使用晶体学和对接方法发现的命中片段在溶液中的结合情况进行了验证。总体而言，作者通过对广泛的化学型进行搜索，发现了 234 个片段结构，为开发有效的 SARS-CoV-2 宏结构域抑制剂进行了先期探索。

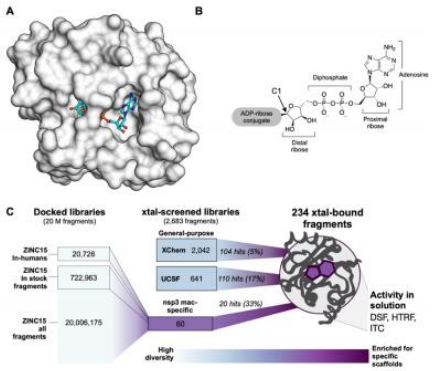

Figure 1. Overview of the fragment discovery approach for SARS-CoV-2 Nsp3 Mac1 presented in this study. A) Surface representation of Nsp3 Mac1 with ADP-ribose bound (cyan) in a deep and open binding cleft. **B)** Nsp3 Mac1 possesses ADP-ribosylhydrolase activity which removes ADP-ribosylation modifications attached to host and pathogen targets. ADP-ribose is conjugated through C1 of the distal ribose. **C)** Summary of the fragment discovery campaign presented in this work. Three fragment libraries were screened by crystallography: two general-purpose (XChem and UCSF), and a third bespoke library of 60 compounds, curated for Mac1 by molecular docking of over 20M fragments. Crystallographic studies identified 214 unique fragments binding to Mac1, while the molecular docking effort yielded in 20 crystallographically confirmed hits. Several crystallographic and docking fragments were validated by ITC, DSF, and an HTRF-based ADPrpeptide displacement assay.

Abstract

The SARS-CoV-2 macrodomain (Mac1) within the non-structural protein 3 (Nsp3) counteracts host-mediated antiviral ADP-ribosylation signalling. This enzyme is a promising antiviral target because catalytic mutations render viruses non-pathogenic. Here, we report a massive crystallographic screening and computational docking effort, identifying new chemical matter primarily targeting the active site of the macrodomain. Crystallographic screening of diverse fragment libraries resulted in 214 unique macrodomain-binding fragments, out of 2,683 screened. An additional 60 molecules were selected from docking over 20 million fragments, of which 20 were crystallographically confirmed. X-ray data collection to ultra-high resolution and at physiological temperature enabled assessment of the conformational heterogeneity around the active site. Several

crystallographic and docking fragment hits were validated for solution binding using three biophysical techniques (DSF, HTRF, ITC). Overall, the 234 fragment structures presented explore a wide range of chemotypes and provide starting points for development of potent SARS-CoV-2 macrodomain inhibitors.