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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本简报仅作为科研参考之用，不构成医疗建议，如您怀疑自己感染新型冠状病毒，请去正规医院或者咨询医生。

1. 2020 年 9 月 17 日疫情

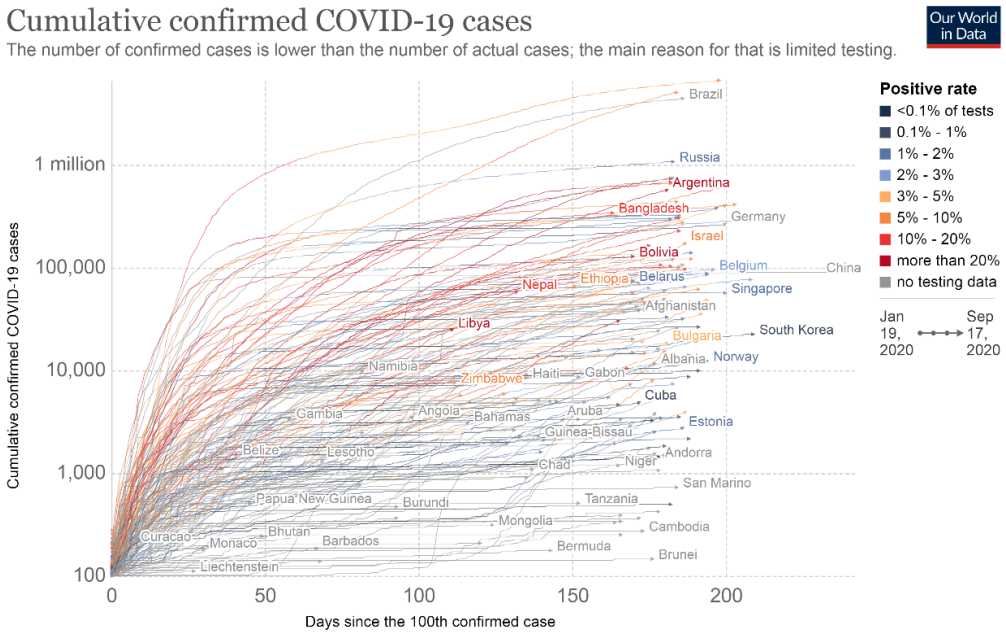
数据来源：WHO

发布时间：2020 年 9 月 17 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 9 月 17 日全球累计确诊新型冠状病毒病人 **29,737,453** 例，当日新增确诊 **292,307** 例，累计死亡 **937,391** 例，当日新增死亡 **6,057**。

中国累计确诊 90,753 例，累计死亡 4,743 例，当日新增确诊 19 例，新增死亡 0 例。



Source: European CDC – Situation Update Worldwide – Last updated 17 September, 10:35 (London time), Official data collated by Our World in Data
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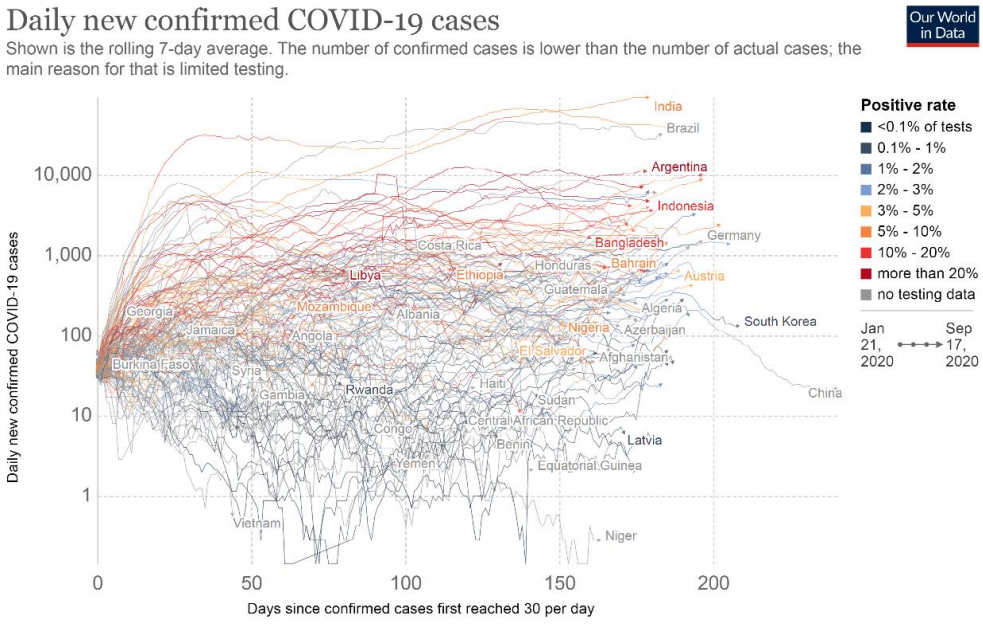
重点国家确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）



Source: European CDC – Situation Update Worldwide – Last updated 17 September, 10:35 (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（9 月 17 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 猪对实验感染 SARS-CoV-2 的易感性研究

Susceptibility of domestic swine to experimental infection with SARS-CoV-2

来源：bioRxiv

发布时间：2020-09-10

链接：https://www.biorxiv.org/content/10.1101/2020.09.10.288548v1

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DOI 或 PUBMED ID：Preprint

编译者：宋张悦

中文摘要：

本研究显示接受实验接种的猪对低水平的 SARS-CoV-2 敏感。在两组动物的口腔液和鼻腔冲洗液中检测到病毒 RNA，同时从一头猪中分离出活病毒。此外，2 只动物在感染后 11 天和 13 天可以检测到抗体，而接种后 6 天的唾液样本显示有分泌的抗体。这些数据突出表明，有必要对牲畜进行进一步评估，以更好地确定家畜可能对 SARS-CoV-2 大流行的潜在作用。

3. 大型城市下水道的污水沉淀固体中的 SARS-CoV-2 与 COVID-19 病例有关

SARS-CoV-2 in wastewater settled solids is associated with COVID-19 cases in a large urban sewershed

来源：medRxiv

发布时间：2020-09-15

链接：https://www.medrxiv.org/content/10.1101/2020.09.14.20194472v1

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DOI 或 PUBMED ID：Preprint
编译者：宋张悦
中文摘要：
基于废水的流行病学(Wastewater-based epidemiology, WBE)可能有助于为公共卫生应对由 SARS-CoV-2 引起的 COVID-19 等病毒性疾病提供信息。我们对两个污水处理厂进水和主要沉淀固体中的 SARS-CoV-2 RNA 进行了量化，以指导预分析和分析方法，并评估进水或固体中是否含有更多的病毒靶标。初始固体沉降样品比相应的进水样品产生更高的 SARS-CoV-2 检测率。同样，与两步 RT-QPCR 和两步 ddRT-PCR 相比，一步数字液滴(digital droplet, dd)RT-PCR 更容易在固体中检测出 SARS-CoV-2 RNA，这可能是因为一步 ddRT-PCR 检测的抑制作用降低了。随后，我们分析了 89 个来自单个污水处理厂的固体样品的纵向时间序列的 SARS-CoV-2 RNA，还有冠状病毒回收(牛冠状病毒)和粪便强度(辣椒轻斑驳病毒，PMMoV)对照。SARS-CoV-2 RNA 靶向的 N1 和 N2 浓度与下水道相关计数的 COVID-19 临床确诊病例数呈显著正相关。综上所述，结果表明与测量进水中的 SARS-CoV-2 相比，测定沉淀固体中 SARS-CoV-2 RNA 浓度可能是一种更为灵敏的方法。
Abstract
Wastewater-based epidemiology (WBE) may be useful for informing public health response to viral diseases like COVID-19 caused by SARS-CoV-2. We quantified SARS-CoV-2 RNA in wastewater influent and primary settled solids in two wastewater treatment plants to inform the pre-analytical and analytical approaches, and to assess whether influent or solids harbored more viral targets. The primary settled solids samples resulted in higher SARS-CoV-2 detection frequencies than the corresponding influent samples. Likewise, SARS-CoV-2 RNA was more readily detected in solids using one-step digital droplet (dd)RT-PCR than with two-step RT-QPCR and two-step ddRT-PCR, likely owing to reduced inhibition with the one-step ddRT-PCR assay. We subsequently analyzed a longitudinal time series of 89 settled solids samples from a single plant for SARS-CoV-2 RNA as well as coronavirus recovery (bovine coronavirus) and fecal strength (pepper mild mottle virus, PMMoV) controls. SARS-CoV-2 RNA targets N1 and N2 concentrations correlate positively and significantly with COVID-19 clinical confirmed case counts in the sewershed. Together, the results demonstrate that measuring SARS-CoV-2 RNA concentrations in settled solids may be a more sensitive approach than measuring SARs-CoV-2 in influent.

4. 国产新型“手持式 QPCR”通过验收，可 40 分钟自动化核酸检测

来源：科技日报
发布时间：2020-09-10
链接：http://news.ctocio.com.cn/yejie/2020/09/10/36517.html
编译者：宋张悦
中文摘要：
国产新型“手持全自动封闭式核酸 QPCR 分析系统”CarryOn P1000Q，日前通过海关总署科技司组织的项目验收。该设备是国内自主研发的新型现场化快速核酸检测设备，可 40 分钟

完成新冠病毒的现场自动化核酸检测。

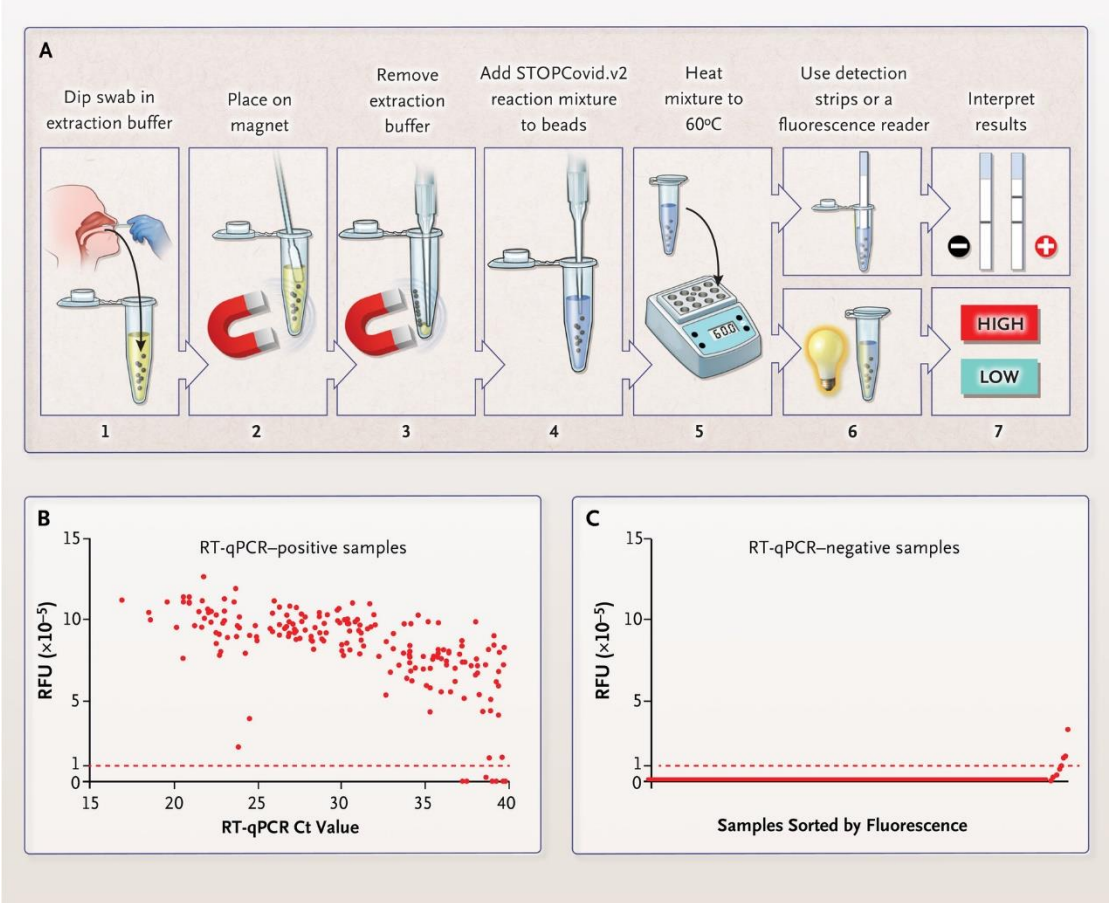
据介绍，该系统采用微流控芯片原理，整合拭子样本处理、磁珠法核酸提取纯化和实时荧光 RT-PCR 标准检测流程。实现了“样本进，结果出”的新冠病毒核酸快速检测能力，具有快速、精准、便携、全封闭体系、全自动化、结果智能判读、实时上报等功能。检测时间约 40 分钟，检测下限为拭子载量 100 个病毒颗粒，设备重量约 1kg，内置电池可续航 3.5 小时，具有无线传输数据功能，可进行远程数据收集，微流控芯片试剂盒可常温保存和运输。

5. 单管反应的 SHERLOCK 测试检测 SARS-CoV-2

Detection of SARS-CoV-2 with SHERLOCK One-Pot Testing

链接：https://www.nejm.org/doi/full/10.1056/NEJMc2026172?query=TOC

新英格兰医学杂志于 2020 年 9 月 16 日发表了张锋团队的一封通讯，讲述他们进一步优化了基于 CRISPR 的新冠核酸检测技术。在该优化的流程中，所有反应发生在一个试管里面。RNA 的抽提由原先的手动抽提改变为磁珠来抽提。在作者们的测试中，该流程检测的性能和 RT-PCR 可比。



6. UK biobank 中的数据显示循环睾酮和性激素结合球蛋白的水平和 COVID-19 致死风险无关

No association between circulating levels of testosterone and sex hormone-binding globulin and risk of COVID-19 mortality in UK biobank

链接：https://www.medrxiv.org/content/10.1101/2020.09.11.20191783v1

编译者：王玮

来自中国的研究者利用 UK biobank 中记录的 315 例 COVID-19 死亡病例（194 名男性和 121

名女性)。探讨了循环总睾酮（TT)、游离睾酮（FT）和性激素结合球蛋白（SHBG）与 COVID-19 死亡率的关系。没有发现 TT、FT 或 SHBG 与 COVID-19 死亡率之间有统计学意义的关联。该研究不支持循环睾酮或性激素结合球蛋白在 COVID-19 预后中的重要作用。

7. 透明质酸在 COVID-19 呼吸道分泌物中含量丰富

Hyaluronan is abundant in COVID-19 respiratory secretions

链接：https://www.medrxiv.org/content/10.1101/2020.09.11.20191692v1

编译者：王玮

来自美国的研究者检测了 8 例经插管治疗的 COVID-19 患者、6 例囊性纤维化（CF）对照患者的呼吸道分泌物，该疾病同样伴有厚厚的粘附性分泌物，以及 8 名健康对照。发现 CF 和 COVID-19 患者的透明质酸含量比健康对照组增加了大约 20 倍。透明质酸在 COVID-19 患者尸体肺组织的组织切片中同样丰富。

8. COVID-19 如何损伤大脑（新闻稿）

How COVID-19 can damage the brain

来源：nature

发布时间：2020-09-15

链接：https://www.nature.com/articles/d41586-020-02599-5

作者：Erik Jepsen/UC San Diego（编辑）

编译者：刘焕珍

中文摘要：

COVID-19 导致相关的神经系统并发症。最紧迫的问题是为什么大脑会受到影响。找到答案将有助于临床医生选择正确的治疗方法。Michael 说：“如果这是中枢神经系统的直接病毒感染，那么我们应该用抗病毒药物来治疗患者；如果该病毒不在中枢神经系统中，可能病毒已经离开了人体，那么我们需要使用抗炎疗法进行治疗。 Muotri 小组有明确的证据表明 SARS-CoV-2 可以感染神经元。但是，关于该病毒如何传播到人们的大脑仍存在疑问。由于嗅觉丧失是常见症状，神经科医生想知道嗅觉神经是否可能提供进入途径。Fowkes 说“我们已经在大脑中看到了病毒，电子显微镜显示出它的存在，大脑中的感染很少，并且倾向于聚集在血管周围。” 然而，这可能不是所有的病例都是这样，这意味着研究人员将需要确定能够可靠地区分病毒性脑部感染和免疫活性的生物标志物。

Abstract:

Neurological complications linked to COVID-19.The most pressing question is why the brain is affected at all. Finding an answer will help clinicians to choose the right treatments. Michael says “If this is direct viral infection of the central nervous system, these are the patients we should be targeting for remdesivir or another antiviral”, “Whereas if the virus is not in the central nervous system, maybe the virus is clear of the body, then we need to treat with anti-inflammatory therapies”. Getting it wrong would be harmful. Muotri’s team had clear evidence that SARS-CoV-2 can infect neurons. But questions remain over how the virus might reach people’s brains. Because loss of smell is a common symptom, neurologists wondered whether the olfactory nerve might provide a route of entry. Fowkes says “We have seen the virus in the brain itself, electron microscopes revealed its presence, infections in the brain are small and tend to cluster around blood vessels.” Still, this might not be true in all cases, which

means that researchers will need to identify biomarkers that can reliably distinguish between a viral brain infection and immune activity.

9. SARS-CoV-2 对人和小鼠脑的神经侵袭作用

Neuroinvasion of SARS-CoV-2 in human and mouse brain

来源：biorxiv

发布时间：2020-09-08

链接：https://www.biorxiv.org/content/10.1101/2020.06.25.169946v2

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DOI 或 PUBMED ID：

编译者：王玮

中文摘要：

尽管 COVID-19 被认为是一种呼吸系统疾病，但 SARS-CoV-2 影响多个器官系统，包括中枢神经系统（CNS）。但是，这种病毒是否能感染大脑，或者中枢神经系统感染的后果如何，目前还没有达成共识。该研究使用三种独立的方法来检测 SARS-CoV-2 感染大脑的能力。首先，利用人脑类器官，我们观察到感染的明显证据，伴随着受感染神经元和邻近神经元的代谢变化。但是，该研究没有发现 I 型干扰素反应的证据。研究证明，神经元感染可以通过抗体阻断 ACE2 或使用 COVID-19 患者的脑脊液来预防。第二，利用过表达人 ACE2 的小鼠，该研究体内证明了 SARS-CoV-2 神经侵袭与死亡率相关，同时与呼吸道感染无关。最后，在对死于 COVID-19 的患者的脑尸检中，皮质神经元中检测到了 SARS-CoV-2，并出现与感染相关的病理特征，其中免疫细胞浸润很小。这些结果为 SARS-CoV2 的神经侵袭能力以及 SARS-CoV-2 直接感染神经元的后果提供了证据。

Abstract

Although COVID-19 is considered to be primarily a respiratory disease, SARS-CoV-2 affects multiple organ systems including the central nervous system (CNS). Yet, there is no consensus whether the virus can infect the brain, or what the consequences of CNS infection are. Here, we used three independent approaches to probe the capacity of SARS-CoV-2 to infect the brain. First, using human brain organoids, we observed clear evidence of infection with accompanying metabolic changes in the infected and neighboring neurons. However, no evidence for the type I interferon responses was detected. We demonstrate that neuronal infection can be prevented either by blocking ACE2 with antibodies or by administering cerebrospinal fluid from a COVID-19 patient. Second, using mice overexpressing human ACE2, we demonstrate in vivo that SARS-CoV-2 neuroinvasion, but not respiratory infection, is associated with mortality. Finally, in brain autopsy from patients who died of COVID-19, we detect SARS-CoV-2 in the cortical neurons,

and note pathologic features associated with infection with minimal immune cell infiltrates. These results provide evidence for the neuroinvasive capacity of SARS-CoV2, and an unexpected consequence of direct infection of neurons by SARS-CoV-2.

10. 在 COVID-19 患者的中枢神经系统中出现了不同的免疫应答

Immunologically distinct responses occur in the CNS of COVID-19 patients

来源：biorxiv

发布时间：2020-09-12

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通讯作者：Shelli F. Farhadian

通讯作者单位：Yale School of Medicine

链接：https://www.biorxiv.org/content/10.1101/2020.09.11.293464v1

编译：蒋立春

中文摘要：

一部分 COVID-19 病人展示出神经系统症状，但我们不知道 SARS-CoV-2 造成的神经系统损害是通过中枢神经系统的神经侵入感染，还是由于包括免疫反应介导的次生机制造成。作者们通过分析脑脊液来了解病人中枢神经系统免疫环境，也通过分析外周血单核细胞了解了病人在循环系统中的免疫环境。对外周血单核细胞和脑脊液进行单细胞转录组测序偶联免疫组血测序，解释 SARS-CoV-2 在中枢神经系统中存在的独特的免疫反应。抗 SARS-CoV-2 的抗体存在于该研究中所有病人（N=19）的脑脊液中,但是脑脊液中抗体表位特异性以及 B 细胞受体序列的含量和成对的血清中差异很大。用一个小鼠的病毒感染模型，作者们发现局部的中枢神经系统的免疫反应发生在病毒的神经侵入之后。这些结果表明中枢神经系统的局部免疫反应是治疗 COVID-19 神经系统症状的重要基础。

Abstract

A subset of patients with COVID-19 display neurologic symptoms but it remains unknown whether SARS-CoV-2 damages the central nervous system (CNS) directly through neuroinvasion, or if neurological symptoms are due to secondary mechanisms, including immune-mediated effects. Here, we examined the immune milieu in the CNS through the analysis of cerebrospinal fluid (CSF) and in circulation through analysis of peripheral blood mononuclear cells (PBMCs) of COVID-19 patients with neurological symptoms.

Single cell sequencing with paired repertoire sequencing of PBMCs and CSF cells show evidence for unique immune response to SARS-CoV-2 in the CNS. Strikingly, anti-SARS-CoV-2 antibodies are present in the CSF of all patients studied, but the antibody epitope specificity in the CSF and relative prevalence of B cell receptor sequences markedly differed when compared to those found in paired serum. Finally, using a mouse model of SARS-CoV-2 infection, we demonstrate that localized CNS immune responses occur following viral neuroinvasion, and that the CSF is a faithful surrogate for responses occurring uniquely in the CNS. These results illuminate CNS compartment-specific immune responses to SARS-CoV-2, forming the basis for informed treatment of neurological symptoms associated with COVID-19.

11. SARS-CoV-2 细胞进入基因和细胞死亡程序的年龄依赖性调节与 COVID-19 疾病严重程度相关

Age-dependent regulation of SARS-CoV-2 cell entry genes and cell death programs correlates with COVID-19 disease severity

来源：bioRxiv
发布时间：2020-09-13
链接：https://www.biorxiv.org/content/10.1101/2020.09.13.276923v1
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编译者：张鹏伟
中文摘要：
为了检测潜在的基于年龄的疾病严重程度相关性，我们在约 4 个月至 75 岁年龄段的 100 多个供体的人肺组织标本中，在单细胞水平上测量了 ACE2 蛋白的表达。我们发现，ACE2 在远端肺上皮细胞中的表达通常随着年龄的增长而增加，但表现出极端的个体内和个体间异质性。值得注意的是，我们还检测了新生儿气道上皮细胞和肺实质内的 ACE2 表达。在转录本水平上发现了类似的模式：ACE2 mRNA 出生后不久在肺和气管中表达，在儿童时期下调，并在成年后期在肺泡上皮细胞中再次高水平表达。此外，我们发现凋亡，这是一种针对病毒感染的天然宿主防御系统，在肺成熟过程中也受到动态调节，导致凋亡启动期增加，并依赖包括 MCL-1 在内的存活前 BCL-2 家族蛋白。SARS-CoV-2 感染人肺细胞会触发未折叠的蛋白质应激反应，并上调内源性 MCL-1 抑制剂 Noxa。在青少年中，MCL-1 抑制作用足以触发肺上皮细胞凋亡-这可能会限制病毒体的产生和炎性信号传导。总体而言，我们确定了整个生命周期中 COVID-19 疾病严重程度的强而独特的相关性，并增进了我们对 ACE2 调节和哺乳动物肺细胞死亡程序的了解。此外，我们的工作为凋亡调节药物作为 COVID-19 的新疗法提供了潜在的翻译框架。

Abstract:
Angiotensin-converting enzyme 2 (ACE2) maintains cardiovascular and renal homeostasis but also serves as the entry receptor for the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), the causal agent of novel coronavirus disease 2019 (COVID-19)1. COVID-19 disease severity, while highly variable, is typically lower in pediatric patients than adults (particularly the elderly), but increased rates of hospitalizations requiring intensive care are observed in infants than in older children. The reasons for these differences are unknown. To detect potential age-based correlates of disease severity, we measured ACE2 protein expression at the single cell level in human lung tissue specimens from over 100 donors from ~4 months to 75 years of age. We found that expression of ACE2 in distal lung epithelial cells generally increases with advancing age but exhibits extreme intra- and inter-individual heterogeneity. Notably, we also detected ACE2 expression on neonatal airway epithelial cells and within the lung parenchyma. Similar patterns were found at the transcript level: *ACE2* mRNA is expressed in the lung and trachea shortly after birth, downregulated during childhood, and again expressed at high levels in late

adulthood in alveolar epithelial cells. Furthermore, we find that apoptosis, which is a natural host defense system against viral infection, is also dynamically regulated during lung maturation, resulting in periods of heightened apoptotic priming and dependence on pro-survival BCL-2 family proteins including MCL-1. Infection of human lung cells with SARS-CoV-2 triggers an unfolded protein stress response and upregulation of the endogenous MCL-1 inhibitor Noxa; in juveniles, MCL-1 inhibition is sufficient to trigger apoptosis in lung epithelial cells – this may limit virion production and inflammatory signaling. Overall, we identify strong and distinct correlates of COVID-19 disease severity across lifespan and advance our understanding of the regulation of ACE2 and cell death programs in the mammalian lung. Furthermore, our work provides the framework for potential translation of apoptosis modulating drugs as novel treatments for COVID-19.

12. SARS-CoV-2 感染的严重程度与针对刺突蛋白的过激体液免疫有关

SARS-CoV-2 infection severity is linked to superior humoral immunity against the spike

链接：https://www.biorxiv.org/content/10.1101/2020.09.12.294066v1

编译者：张丽双

芝加哥大学研究人员发现 SARS-CoV-2 感染更严重的受试者对刺突蛋白和核衣壳蛋白有更大的整体抗体反应，对刺突蛋白有更大的记忆 B 细胞反应。

13. 快讯！阿联酋批准中国新冠疫苗投入使用

链接：https://mp.weixin.qq.com/s/WYEX8rqrZPBEjNoi0ROTIg

编者：张丽双

国药集团中国生物新冠灭活疫苗不久前完成了在阿联酋临床试验（III期），研究结果表明该疫苗安全有效。当地时间 9 月 14 日，阿联酋政府已批准在一线医务人员中使用注射新冠疫苗。

14. 两种剂型中基于 rAd26 和 rAd5 载体的异源 prime boost COVID-19 疫苗的安全性和免疫原性：来自俄罗斯的两项开放的、非随机的 1/2 阶段研究

Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia

来源：thelancet

发布时间：2020-09-04

链接：https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31866-3/fulltext#supplementaryMaterial

第一作者：Denis Y Logunov

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通讯作者单位：俄国流行病学和微生物学研究中心

DOI 或 PUBMED ID：https://doi.org/10.1016/S0140-6736(20)31866-3

编译者：刘焕珍

中文摘要：

背景：我们开发了一种异源 COVID-19 疫苗，该疫苗由两个部分组成，分别是 26 型重组腺病毒（rAd26）载体和 5 型重组腺病毒（rAd5）载体，两者均携带 SARS-CoV-2 刺突糖蛋白（rAd26-S 和 rAd5-S）的基因。 我们旨在评估该疫苗的两种制剂（冷冻和冻干）的安全性和免疫原性。

方法：我们在俄罗斯的两家医院进行了两项开放的、非随机的 1/2 期研究。我们招募了 18-60 岁的健康成年志愿者（男性和女性）参与这两项研究。在每项研究的第一阶段，我们在第 0 天肌肉注射一剂 rAd26-S 或一剂 rAd5-S，并评估这两种成分 28 天的安全性。在第二阶段的研究中，我们在第一阶段疫苗接种后不早于 5 天开始，我们肌肉注射一种主要的增强型疫苗，第 0 天注射 rAd26-S，第 21 天注射 rAd5-S。主要观察指标为抗原特异性体液免疫（第 0 天、第 14 天、第 21 天、第 28 天和第 42 天通过 ELISA 测定 SARS-CoV-2 特异性抗体）和安全性（在整个研究过程中监测不良事件的参与者人数）。次要观察指标是抗原特异性细胞免疫（T 细胞反应和干扰素-γ 浓度）和中和抗体的变化（用 SARS-CoV-2 中和试验检测）。这些试验已在 ClinicalTrials.gov 上注册，NCT04436471 和 NCT04437875。

研究结果：在 2020 年 6 月 18 日至 8 月 3 日期间，我们招募了 76 名参与者参与这两项研究（每个研究 38 名）。在每项研究中，有 9 名志愿者在第 1 阶段接受 rAd26-S 的治疗，有 9 名志愿者在第 1 阶段接受 rAd5-S 的治疗，20 名志愿者在第 2 阶段接受 rAd26-S 和 rAd5-S 的治疗。两种疫苗制剂都是安全的，并且耐受性良好。最常见的不良反应是注射部位疼痛（44 例[58%]），高热（38 例[50%]），头痛（32 例[42%]），乏力（21 例[28%]），以及肌肉和关节疼痛（18 例[24%]）。大多数不良事件为轻度，未发现严重不良事件。所有参与者都产生了抗 SARS-CoV-2 糖蛋白的抗体。第 42 天，冷冻制剂和冻干制剂的受体结合域特异性 IgG 滴度分别为 14 703 和 11 143，冷冻制剂的中和抗体为 49.25，冻干制剂为 45.95，血清转化率为 100%。所有受试者在第 28 天检测到细胞介导的反应，冷冻制剂的细胞增殖中值为 2.5%CD4+和 1.3%CD8+，冻干制剂的中位数细胞增殖率为 1.3%CD4+和 1.1%CD8+。

解释：异源 rAd26 和 rAd5 载体的 COVID-19 疫苗具有良好的安全性，并在参与者中引起强烈的体液和细胞免疫反应。该疫苗预防 COVID-19 的有效性有待进一步研究。

Abstract:

Background: We developed a heterologous COVID-19 vaccine consisting of two components, a recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector, both carrying the gene for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein (rAd26-S and rAd5-S). We aimed to assess the safety and immunogenicity of two formulations (frozen and lyophilised) of this vaccine.

Methods: We did two open, non-randomised phase 1/2 studies at two hospitals in Russia. We enrolled healthy adult volunteers (men and women) aged 18–60 years to both studies. In phase 1 of each study, we administered intramuscularly on day 0 either one dose of rAd26-S or one dose of rAd5-S and assessed the safety of the two components for 28 days. In phase 2 of the study, which began no earlier than 5 days after phase 1 vaccination, we administered intramuscularly a prime-boost vaccination, with rAd26-S given on day 0 and rAd5-S on day 21. Primary outcome measures were antigen-specific humoral immunity (SARS-CoV-2-specific antibodies measured by ELISA on days 0, 14, 21, 28, and 42) and safety (number of participants with adverse events monitored throughout the study). Secondary outcome measures were antigen-specific cellular immunity (T-cell responses and interferon-γ concentration) and change in neutralising antibodies

(detected with a SARS-CoV-2 neutralisation assay). These trials are registered with ClinicalTrials.gov, NCT04436471 and NCT04437875.

Findings: Between June 18 and Aug 3, 2020, we enrolled 76 participants to the two studies (38 in each study). In each study, nine volunteers received rAd26-S in phase 1, nine received rAd5-S in phase 1, and 20 received rAd26-S and rAd5-S in phase 2. Both vaccine formulations were safe and well tolerated. The most common adverse events were pain at injection site (44 [58%]), hyperthermia (38 [50%]), headache (32 [42%]), asthenia (21 [28%]), and muscle and joint pain (18 [24%]). Most adverse events were mild and no serious adverse events were detected. All participants produced antibodies to SARS-CoV-2 glycoprotein. At day 42, receptor binding domain-specific IgG titres were 14 703 with the frozen formulation and 11 143 with the lyophilised formulation, and neutralising antibodies were 49.25 with the frozen formulation and 45.95 with the lyophilised formulation, with a seroconversion rate of 100%. Cell-mediated responses were detected in all participants at day 28, with median cell proliferation of 2.5% $CD4^+$ and 1.3% $CD8^+$ with the frozen formulation, and a median cell proliferation of 1.3% $CD4^+$ and 1.1% $CD8^+$ with the lyophilized formulation.

Interpretation: The heterologous rAd26 and rAd5 vector-based COVID-19 vaccine has a good safety profile and induced strong humoral and cellular immune responses in participants. Further investigation is needed of the effectiveness of this vaccine for prevention of COVID-19.

15. 国际科学家联合质疑俄罗斯疫苗结果

文章链接：https://cattiviscienziati.com/2020/09/07/note-of-concern/

编译者：张怡

一个由 16 名国际科学家组成的小组向《柳叶刀》杂志编辑理查德·霍顿博士以及俄罗斯 Sputnik V 疫苗试验论文的全体作者写了一封公开信，对该疫苗的试验数据的完整性提出了质疑。在论文中发表的三个图表中，几个在不同实验出现了完全相同的数据模式。例如，FIG2 在体液免疫反应图中，所有接受 Ad26-S 冷冻疫苗接种的 9 名参与者在第 21 天和第 28 天出现了相同的抗体滴度。同样，在 9 名使用冻干 rAd5-S 疫苗的志愿者中，有 7 人出现了相同的抗体滴度。一个恒定值在两个完全不相关的实验中不同，在其他两个完全不相关的志愿者群体中又相同。基于简单的概率评估，在不同的实验中观察到这么多数据点是极不可能的. 在关于细胞对不同配方反应结果的 FIG3 图中，实验点模式被认为是重复的。在这种情况下，所研究的变量(细胞增殖百分比)在本质上是连续的，使得不同实验中数据点的重合更不可能。FIG4 中显示对抗用于疫苗的腺病毒载体的中和抗体的形成，像图 2 中观察到的问题再次明显。因此，科学家们希望获得原始数据。他们称，鉴于俄罗斯疫苗试验的参与者人数很少，应该有可能迅速作出反应并分享个人水平的临床和实验室数据，以便任何有顾虑的人都可以审查数据并重新创建手稿中相当简单的数字。

16. 下一代 COVID-19 疫苗:可以呈现受体结合域和稳定 spike 的自组装纳米颗粒

Self-assembling nanoparticles presenting receptor binding domain and stabilized spike as next-generation COVID-19 vaccines

来源：bioRxiv

发布时间：2020-09-14

链接：https://www.biorxiv.org/content/10.1101/2020.09.14.296715v1
第一作者：Linling He
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DOI 或 PUBMED ID：
编译者：张鹏伟
中文摘要：
我们结合抗原优化和纳米颗粒展示技术，为重症急性呼吸综合征冠状病毒 2（SARS-CoV-2）提供了一种全面的疫苗策略。我们首先开发了一种用于纯化的受体结合域（RBD）特异性抗体柱，并利用 SpyTag/SpyCatcher 系统在自组装蛋白纳米粒（sapns）上显示 RBD。然后我们鉴定了七肽重复序列 2（HR2）茎段是引起 spike 亚稳定性的主要原因，设计了一个 HR2 缺失的甘氨酸帽状穗（S2GΔHR2），并在三个 SAPNs 上展示了 S2GΔHR2，具有较高的产量、纯度和抗原性。与 RBD 相比，RBD 铁蛋白 SApNP 诱导的小鼠中和抗体（NAb）反应更为强烈，与峰值相当。S2GΔHR2 诱导的 NAb 滴度比脯氨酸帽峰（S2P）高两倍，而来自多层 E2p 和 I3-01v9 60 mers 的 S2GΔHR2 sapns 诱发的 NAb 滴度高出 10 倍。呈现 I3-01v9 SApNP 的 S2GΔHR2 还诱导了急需的 T 细胞免疫，从而为对抗 COVID-19 大流行提供了下一代疫苗候选。
Abstract:
We present a comprehensive vaccine strategy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by combining antigen optimization and nanoparticle display. We first developed a receptor binding domain (RBD)-specific antibody column for purification and displayed the RBD on self-assembling protein nanoparticles (SApNPs) using the SpyTag/SpyCatcher system. We then identified the heptad repeat 2 (HR2) stalk as a major cause of spike metastability, designed an HR2-deleted glycine-capped spike (S2GΔHR2), and displayed S2GΔHR2 on three SApNPs with high yield, purity, and antigenicity. Compared to the RBD, the RBD-ferritin SApNP elicited a more potent murine neutralizing antibody (NAb) response on par with the spike. S2GΔHR2 elicited two-fold-higher NAb titers than the proline-capped spike (S2P), while S2GΔHR2 SApNPs derived from multilayered E2p and I3-01v9 60-mers elicited up to 10-fold higher NAb titers. The S2GΔHR2-presenting I3-01v9 SApNP also induced critically needed T-cell immunity, thereby providing a next-generation vaccine candidate to battle the COVID-19 pandemic.

17. 一种新的冠状病毒 3CL 蛋白酶抑制剂的发现，可作为治疗 COVID-19 的候选药物

Discovery of a Novel Inhibitor of Coronavirus 3CL Protease as a Clinical Candidate for the Potential Treatment of COVID-19
链接：https://www.biorxiv.org/content/10.1101/2020.09.12.293498v2
编译者：张丽双
美国辉瑞公司发现，磷酸盐前药 PF-07304814，可被代谢成 PF-00835321（是 3CL-pro 的一种有效的体外抑制剂），抗 SARS-CoV-2 的体外抗病毒活性很强，与伦地西韦联合使用具有加性/协同作用。

18. 瑞德西韦与标准治疗对中度 COVID-19 患者 11 天临床状态的影响

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients

With Moderate COVID-19
来源：JAMA
发布时间：2020-08-21
链接：https://jamanetwork.com/journals/jama/fullarticle/2769871
第一作者：Christoph D. Spinner, MD
通讯作者：Diana M. Brainard, MD
通讯作者单位：Gilead Sciences, Foster City, California
DOI 或 PUBMED ID：
编译者：王玮
中文摘要：

重要性 在重度 COVID-19 的安慰剂对照试验中，瑞德西韦显示出临床益处，但其在中度患者中的作用尚不清楚。

目的 比较瑞德西韦治疗 5 天或 10 天，与标准护理治疗开始后第 11 天临床状态的疗效。

设计、设置和参与者 2020 年 3 月 15 日至 4 月 18 日，在美国、欧洲和亚洲的 105 家医院，对确诊为 SARS-CoV-2 感染和中度 COVID-19 肺炎（肺部浸润和氧饱和度>94%）的住院患者进行随机、开放标签试验。最终随访日期为 2020 年 5 月 20 日。

治疗措施

患者按 1:1:1 的比例随机分组，接受 10 天疗程的瑞德西韦（n=197）、5 天疗程的瑞德西韦（n=199）或标准护理（n=200）。在第 1 天静脉注射伦地西韦 200mg，然后每天 100 mg。

主要成果和评估

主要终点是第 11 天的临床状况，从死亡（1 级）到出院（7 级）分为 7 个等级。使用比例优势模型计算瑞德西韦治疗组和标准治疗组之间的差异，并用优势比（odds ratio）表示。优势比大于 1 表明瑞德西韦组与标准治疗组在临床状态分布上有差异。

结果

在随机抽取的 596 名患者中，584 名患者接受瑞德西韦或持续标准治疗（中位年龄为 57 岁，[四分位间距，46-66]岁；227 名[39%]女性；56%患有心血管疾病，42%高血压和 40%糖尿病），533 名（91%）完成了试验。5 天组和 10 天组的平均治疗时间分别为 5 天和 6 天。在第 11 天，与接受标准治疗的患者相比，服用 5 天瑞德西韦组的患者获得更好临床状态分布，并具有统计学意义（优势比，1.65；95%CI，1.09-2.48；P=0.02）。在第 11 天，瑞德西韦组与标准治疗组之间的临床状态分布无显著差异（通过 Wilcoxon 秩和检验，P＝0.18）。到第 28 天，有 9 名患者死亡：5 天瑞德西韦组 2 例（1%），10 天瑞德西韦组 3 例（2%），标准护理组 4 例（2%）。与标准护理相比，瑞德西韦治疗的患者恶心（10%对 3%）、低钾血症（6%对 2%）和头痛（5%对 3%）更为常见。

结论和相关性

在中度 COVID-19 患者中，**那些随机接受 10 天瑞德西韦疗程的患者在开始治疗 11 天后的临床状态与标准治疗相比没有统计学上的显著差异。随机分为 5 天疗程的受试者与标准治疗组相比，临床状态有显著差异，但其临床意义尚不确定**。

试用登记

ClinicalTrials.gov Identifier: NCT04292730

Abstract

Importance Remdesivir demonstrated clinical benefit in a placebo-controlled trial in patients with severe coronavirus disease 2019 (COVID-19), but its effect in patients with moderate disease is unknown.

Objective To determine the efficacy of 5 or 10 days of remdesivir treatment compared with standard care on clinical status on day 11 after initiation of treatment.

Design, Setting, and Participants Randomized, open-label trial of hospitalized patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%) enrolled from March 15 through April 18, 2020, at 105 hospitals in the United States, Europe, and Asia. The date of final follow-up was May 20, 2020.

Interventions Patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200). Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg/d.

Main Outcomes and Measures The primary end point was clinical status on day 11 on a 7-point ordinal scale ranging from death (category 1) to discharged (category 7). Differences between remdesivir treatment groups and standard care were calculated using proportional odds models and expressed as odds ratios. An odds ratio greater than 1 indicates difference in clinical status distribution toward category 7 for the remdesivir group vs the standard care group.

Results Among 596 patients who were randomized, 584 began the study and received remdesivir or continued standard care (median age, 57 [interquartile range, 46-66] years; 227 [39%] women; 56% had cardiovascular disease, 42% hypertension, and 40% diabetes), and 533 (91%) completed the trial. Median length of treatment was 5 days for patients in the 5-day remdesivir group and 6 days for patients in the 10-day remdesivir group. On day 11, patients in the 5-day remdesivir group had statistically significantly higher odds of a better clinical status distribution than those receiving standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; P = .02). The clinical status distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different (P = .18 by Wilcoxon rank sum test). By day 28, 9 patients had died: 2 (1%) in the 5-day remdesivir group, 3 (2%) in the 10-day remdesivir group, and 4 (2%) in the standard care group. Nausea (10% vs 3%), hypokalemia (6% vs 2%), and headache (5% vs 3%) were more frequent among remdesivir-treated patients compared with standard care.

Conclusions and Relevance Among patients with moderate COVID-19, those randomized to a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, but the difference was of uncertain clinical importance.

Trial Registration ClinicalTrials.gov Identifier: NCT04292730

19. 礼来的中和抗体药物 LY-CoV555 在院外 COVID-19 病人中得到了概念验证

链接：https://investor.lilly.com/news-releases/news-release-details/lilly-announces-proof-

concept-data-neutralizing-antibody-ly
中文摘要：
根据礼来 9 月 16 日美国时间凌晨发布的消息，LY-CoV555 在院外 COVID-19 病人中得到了概念验证。
--达到临床试验的主要终点：给药的第 11 天，中剂量组可以降低病毒的载量，在 11 天之前可以看到病毒载量一致的下降
--住院率和急诊率下降：LY-CoV555 用药组为 1.7%(5/301)，安慰剂组为 6%（9/150）。
--所有测试剂量情况下，没有发生药物相关的严重副作用

礼来公司宣布了 BLAZE-1 临床试验的中期分析结果，该结果概念性验证了 LY-CoV555 的药效。这是一项随机双盲的临床二期试验，采用安慰剂做对照，用以评估 SARS-CoV-2 的中和抗体 LY-CoV555 治疗已经有症状的院外 COVID-19 病人的效果。该临床试验招募近期诊断的中轻症状 COVID-19 病人，总共分为 4 个组别（安慰剂组，700mg，2800mg 和 7000mg 组）。该临床研究还有一个臂是 LY-CoV555 和 LY-016（君实生物和礼来共同开发的针对不同抗原表位的 SARS-CoV-2 中和抗体）。该臂的研究还在继续进行中。
根据 Biocentury 的评论，礼来公司正在和 FDA 就该药能否进入紧急授权许可进行讨论。该药物低剂量和高剂量组并没有达到降低病毒载量的主要临床终点让该结果比较难于解释。另外药物高昂的价格以及礼来的公司是否能有足够的产能也存在一定的疑问。链接：https://www.biocentury.com/article/630418?editionId=ckf64htls0j9q01738ks5jtf6&editionType=daily

20. 用于治疗新冠肺炎患者血凝块的最佳药物和疾病阶段的 ACTIV-4 临床试验相关报道

ACTIV-4 trials to zero in on best agents and disease stages for addressing blood clots in COVID-19
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发布时间：2020-09-11
链接：https://www.biocentury.com/article/630242/activ-4-trials-to-zero-in-on-best-agents-and-disease-stages-for-addressing-blood-clots-in-covid-19?tag=cov19count&return_feed=%2Fcoronavirus
作者： Sandi Wong, Assistant Editor
编译者：孔娟
中文摘要：
美国国家心脏、肺和血液研究所(NHLBI)周四宣布启动首批两项预防新冠肺炎患者血栓形成的三期研究:开放标签 ACTIVI-4-抗血栓药物住院试验和双盲 ACTIVI-4-抗血栓药物门诊试验。以评估不同类型的血液稀释剂用于治疗被诊断为 COVID-19 的成年人的安全性和有效性。尽管血凝块在大流行早期被确定为新冠肺炎的一种并发症，但最佳药物及其剂量仍有待确定。这些试验将在全球 100 多个地点进行，将涉及各种临床情况的患者，尚未住院的患者、目前住院的患者和因中重度疾病住院后出院的患者。许多新冠肺炎患者的 D-二聚体蛋白水平升高，D-二聚体蛋白是凝血的生物标志物，通过 ACTIVI-4，将能够在研究中更系统地表征这一点；以及更好的指导对哪些患者进行最集中的治疗以预防血栓。在门诊研究中从受试者身上收集的血液样本也可能使研究人员能够识别新药靶点和其他并发症的生物标志物。ACTIVI-4 抗血栓门诊将招募约 7000 名新诊断的新冠肺炎患者，他们将接受低剂量或高剂量阿哌沙班、阿司匹林或安慰剂。主要终点是因心血管或肺部事件、症状性深静脉血栓形成、肺栓塞、动脉血栓栓塞、心肌梗死、缺血性中风和 45 天以上全因死亡率而需

要住院治疗的综合结果。根据注册表，门诊和住院研究的预计主要完成日期分别为2021年1月和2021年3月。

Abstract:

The National Heart, Lung and Blood Institute (NHLBI) announced Thursday the launch of the first two Phase III studies to prevent blood clots in COVID-19 patients: the open-label ACTIV-4-Antithrombotics Inpatient trial and the double-blind ACTIV-4-Antithrombotics Outpatient trial. On the call, although blood clots were identified early in the pandemic as a complication of COVID-19, optimal medications and their dosages remain to be defined. The third study will enroll patients discharged from the hospital after moderate to severe disease,these patients have residual risk of developing blood clots. Many COVID-19 patients have elevated levels of D-dimer proteins, a biomarker of coagulation, and that through ACTIV-4 We'll be able to characterize that more systematically in the study; and indeed that may be used to derive who's at greatest risk for a clot, and who should we treat most intensively to prevent the clot." Blood samples collected from subjects in the outpatient study may also enable researchers to identify new drug targets and biomarkers of other complications.

ACTIV-4-Antithrombotics Outpatient will enroll about 7,000 newly diagnosed COVID-19 patients who will receive low or high dose Eliquis apixaban from Bristol Myers Squibb Co. (NYSE:BMY), aspirin or placebo. The primary endpoint is a composite of need for hospitalization due to cardiovascular or pulmonary events, symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, ischemic stroke and all-cause mortality over 45 days. ACTIV-4-Antithrombotics Inpatient is comparing a low, prophylactic dose of heparin with a high dose in about 7,000 patients. Gibbons said that it's fairly standard in the inpatient setting for COVID-19 patients to receive low doses of anticoagulants, and that in the ACTIV-4 inpatient study the prophylactic heparin dose will be the comparator for the high, therapeutic dose. The primary endpoint is the number of days free of supplemental oxygen, invasive or non-invasive ventilation, or vasopressor therapy over the first 21 days, according to ClinicalTrials.gov. The key secondary endpoint is a composite of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction or ischemic stroke at hospital discharge or 28 days. According to the registry, the estimated primary completion dates for the outpatient and inpatient studies are January 2021 and March 2021, respectively.

21. 免疫治疗COVID-19的B细胞激活抗CD73抗体的鉴定和一期试验

Characterization and Phase 1 Trial of a B Cell Activating Anti-CD73 Antibody for the Immunotherapy of COVID-19

来源：medrxiv

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doi: https://doi.org/10.1101/2020.09.10.20191486
编译者：张怡
中文摘要：
CD73 存在于大多数人类 B 细胞和 T 细胞亚群中，它在淋巴细胞的激活和迁移中发挥作用。CD73 也是一种将 AMP 转化为腺苷的胞外酶，具有免疫抑制作用。作者报道了 CPI-006，一种人源化的 FcgR 结合缺陷 IgG1 antiCD73 抗体，它可以阻断 CD73 酶活性，直接激活 CD73POS B 细胞，诱导分化为造浆细胞、免疫球蛋白类转换和不依赖腺苷的抗体分泌。对接受 CPI-006 的晚期癌症患者外周血的免疫表型分析显示 B 细胞激活、克隆扩增和记忆性 B 细胞的发育。这些免疫效应表明，CPI-006 可能有效地增强体液和细胞反应对 SARS-CoV-2 等病毒的反应的规模、多样性和持续时间。
因此，在住院的轻至中度 COVID-19 患者中启动了一期单剂量、剂量递增试验。本试验的目的是评估 CPI-006 在 COVID-19 患者中的安全性，并确定 CPI-006 对抗 SARS-CoV-2 抗体应答和记忆 B 细胞和 T 细胞发育的影响。10 名患者被纳入试验，接受 0.3 mg/kg 或 1.0 mg/kg 的剂量。所有可评估的患者治疗前血清对 SARS CoV-2 三聚体刺突蛋白及其受体结合结构域的抗病毒抗体水平均较低，与入组前 COVID-19 相关症状持续时间无关。CPI-006 治疗后第 7 天出现抗病毒抗体应答，滴度在第 56 天后继续升高。治疗 28 天后观察到记忆 B 细胞和效应/记忆 T 细胞的频率增加。这些初步结果表明，在 COVID-19 患者中，CPI-006 激活 B 细胞，并可能增强和延长抗 SARS-CoV-2 抗体反应。这种方法可用于 COVID-19 的治疗，或作为提高疫苗疗效的佐剂。

Abstract
CD73 is present on the majority of human B cells and a subset of T cells where it plays a role in lymphocyte activation and migration. CD73 also functions as an ectoenzyme that converts AMP into adenosine, which can be immunosuppressive. Here we report on CPI-006, a humanized FcgR binding-deficient IgG1 antiCD73 antibody that blocks CD73 enzymatic activity and directly activates CD73POS B cells, inducing differentiation into plasmablasts, immunoglobulin class switching, and antibody secretion independent of adenosine. Immunophenotypic analysis of peripheral blood from advanced cancer patients receiving CPI-006 revealed evidence of B cell activation, clonal expansion, and development of memory B cells. These immune effects suggested that CPI-006 may be effective at enhancing the magnitude, diversity, and duration of humoral and cellular responses to viruses such as SARS-CoV-2.
We have therefore initiated a Phase 1, single-dose, dose-escalation trial in hospitalized patients with mild to moderate COVID-19. The objectives of this trial are to evaluate the safety of CPI-006 in COVID-19 patients and to determine effects of CPI-006 on anti-SARS-CoV-2 antibody responses and the development of memory B cell and T cells. Ten patients have been enrolled in the trial receiving doses of 0.3 mg/kg or 1.0 mg/kg. All evaluable patients had low pre-treatment serum levels of anti-viral antibodies to the SARSCoV-2 trimeric spike protein and its receptor binding domain, independent of the duration of their COVID-19 related symptoms prior to enrollment. Anti-viral antibody responses were induced 7 days after CPI-006 treatment and titers continued to rise past Day 56. Increases in the frequency of memory B cells and effector/memory T cells were observed 28

days after treatment. These preliminary results suggest that CPI-006 activates B cells and may enhance and prolong anti-SARS-CoV-2 antibody responses in patients with COVID-19. This approach may be useful for treating COVID-19 or as an adjuvant to enhance the efficacy of vaccines.

22. 用于过继细胞治疗的抗糖皮质激素 SARS-CoV-2 T 细胞的开发

Generation of glucocorticoid resistant SARS-CoV-2 T-cells for adoptive cell therapy

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DOI 或 PUBMED ID：preprint

编译者：孔娟

中文摘要：

具有病毒特异性 T 细胞的过继细胞疗法已成功用于治疗严重的病毒感染，从而支持了该方法针对 COVID-19 的应用。研究者使用不同的培养条件对 COVID-19 供体和对照的外周血中的 SARS-CoV-2 T 细胞进行了扩增。结果发现细胞因子的选择对 SARS-CoV-2 T 细胞的扩增、表型及对抗原识别的强度具有不同的调节作用。相比其它细胞因子，IL-2/4/7 培养条件下的 SARS-CoV-2 T 细胞是扩增前样品的 1000 倍，同时稳定的维持了其表型、功能和抗原识别能力。扩增的 CTL 能够识别 SARS-CoV-2 蛋白，包括 S 蛋白的受体结合结构域。然而非暴露对照组外周血中 SARS-CoV-2 T 细胞并不能够在体外有效扩增。另外针对皮质类固醇用于严重新冠肺炎病的治疗这一方案，研究者开发了一种有效的策略，可以使用 CRISPR-Cas9 基因编辑来灭活 SARS-CoV-2 CTL 中的糖皮质激素受体基因（NR3C1）。

Abstract：

Adoptive cell therapy with viral-specific T cells has been successfully used to treat life-threatening viral infections, supporting the application of this approach against COVID-19. We expanded SARS-CoV-2 T-cells from the peripheral blood of COVID-19-recovered donors and non-exposed controls using different culture conditions. We observed that the choice of cytokines modulates the expansion, phenotype and hierarchy of antigenic recognition by SARS-CoV-2 T-cells. Culture with IL-2/4/7 but not other cytokine-driven conditions resulted in >1000 fold expansion in SARS-CoV-2 T-cells with a retained phenotype, function and hierarchy of antigenic recognition when compared to baseline (pre-expansion) samples. Expanded CTLs were directed against structural SARS-CoV-2 proteins, including the receptor-binding domain of Spike. SARS-CoV-2 T-cells could not be efficiently expanded from the peripheral blood of non-exposed controls. Since corticosteroids are used for the management of severe COVID-19, we developed an efficient strategy to inactivate the glucocorticoid receptor gene (NR3C1) in SARS-CoV-2 CTLs using CRISPR-Cas9 gene editing.

23. SARS-CoV-2 Spike 受体结合结构域中导致抗体识别逃逸的突变完整图谱

Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition

来源：bioRxiv

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DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

作为一种有希望的治疗手段，人们正在大力开发靶向 SARS-CoV-2 Spike 蛋白受体结合结构域（RBD）的抗体，同时也为研究由病毒感染引发的中和抗体响应做出了重要贡献。本文中，作者介绍了其利用深度突变扫描方法考察了 RBD 中所有氨基酸的突变对抗体结合能力的影响，并将该方法应用于研究 10 种人源单克隆抗体中。作者发现，免疫逃逸突变聚集在 RBD 的几个表面上，而这些表面的分布与结构定义的抗体表位明显一致。然而，即使靶向同一个 RBD 表面的不同抗体，也常常对应独特的逃避突变。完整的逃逸图谱可以预测在单一抗体存在的情况下，病毒发生哪些突变后可以维持其生长，并能够帮助我们设计出抵抗逃逸的抗体混合物。其中包括与 RBD 相同表面竞争结合，却具有不同逃逸突变的抗体混合物。总之，完整的逃逸突变图谱可用来理性设计抗体药物，并评估病毒进化的抗原影响。

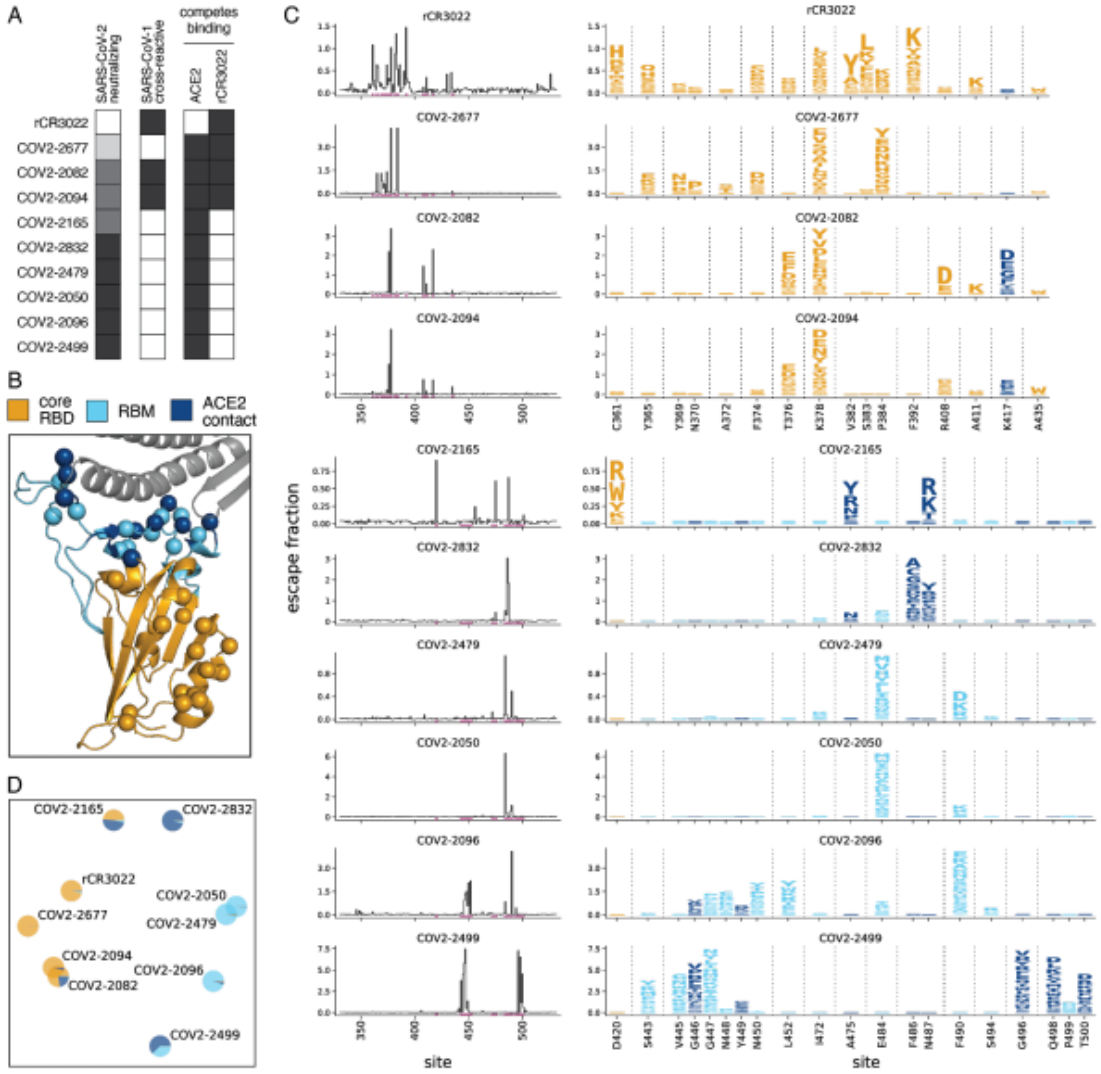

Figure 2. Complete maps of escape mutations from 10 human monoclonal antibodies. (A) Properties of the antibodies as reported by Zost et al. (2020a). SARS-CoV-2 neutralization potency is represented as a gradient from black (most potent) to white (non-neutralizing). Antibodies that bind SARS-CoV-1 spike or compete with RBD binding to ACE2 or rCR3022 are indicated in black. **(B)** Structure of the SARS-CoV-2 RBD (PDB: 6M0J, (Lan et al., 2020)) with residues colored by whether they are in the core RBD distal from ACE2 (orange), in the receptor-binding motif (RBM, light blue), or directly contact ACE2 (dark blue). ACE2 is in gray. RBD sites where any antibody in the panel selects escape mutations are indicated with spheres at their alpha carbons. **(C)** Maps of escape mutations from each antibody. The line plots show the total escape at each RBD site (sum of escape fractions of all mutations at that site). Sites with strong escape mutations (indicated by purple at bottom of the line plots) are shown in the logo plots. Sites in the logo plots are colored by RBD region as in (B), with the height of each letter representing the escape fraction for that mutation. Note that different sites are shown for the rCR3022-competing antibodies (top four) and all other antibodies (bottom six). **(D)** Multidimensional scaling projection of the escape-mutant maps, with antibodies having similar escape mutations drawn close together. Each antibody is shown with a pie chart that uses the color scale in (B) to indicate the RBD regions where it selects escape mutations.

Abstract
Antibodies targeting the SARS-CoV-2 spike receptor-binding domain (RBD) are being developed as therapeutics and make a major contribution to the neutralizing antibody response elicited by infection. Here, we describe a deep mutational scanning method to map how all amino-acid mutations in the RBD affect antibody binding, and apply this method to 10 human monoclonal antibodies. The escape mutations cluster on several surfaces of the RBD that broadly correspond to structurally defined antibody epitopes. However, even antibodies targeting the same RBD surface often have distinct escape mutations. The complete escape maps predict which mutations are selected during viral growth in the presence of single antibodies, and enable us to design escape-resistant antibody cocktails - including cocktails of antibodies that compete for binding to the same surface of the RBD but have different escape mutations. Therefore, complete escape-mutation maps enable rational design of antibody therapeutics and assessment of the antigenic consequences of viral evolution.

24. SARS-CoV-2 Nsp1 蛋白改变肌动球蛋白的细胞骨架，复制了 PKP2 突变导致的心律失常性心肌病的表型

SARS-CoV-2 protein Nsp1 alters actomyosin cytoskeleton and phenocopies arrhythmogenic cardiomyopathy-related PKP2 mutant

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中文摘要：

Desmosomal Plakophilin-2（PKP2）基因中的突变是造成心律失常性心肌病（ACM）的最普遍原因，也是年轻运动员猝死的常见原因。然而，阐明 ACM 中心脏功能紊乱背后的 PKP2 细胞机制的伴侣蛋白大多尚不明确。本文中，作者鉴定出基于肌动蛋白的马达蛋白 Myh9 和 Myh10 是关键的 PKP2 相互作用蛋白，并证明与 ACM 相关的 PKP2 R735X 突变体的表达能够改变肌动蛋白纤维的组织和细胞力学刚度。作者还发现，SARS-CoV-2 Nsp1 蛋白的作用与这种已知的致病性 R735X 突变非常类似，能够改变肌动球蛋白组分在心肌细胞中的分布。结果显示，Nsp1 将 PKP2 劫持到细胞质中，并模仿出非局部的 R735X 突变的效果。现有结果表明，细胞质中的 PKP2 造成了肌动球蛋白的失调和结构崩溃，同时有验证了 PKP2 的分布位置对肌动球蛋白结构调控的关键作用。Nsp1 和 R735X 具有相似的表型这一事实也证明，被 SARS-CoV-2 直接感染心脏后，可在 COVID-19 患者中诱发短暂性类似 ACM 的疾病，可能在预后较差的患者中引起右心室功能紊乱。

Abstract
Mutations in desmosomal Plakophilin-2 (PKP2) are the most prevalent drivers of

arrhythmogenic-cardiomyopathy (ACM) and a common cause of sudden death in young athletes. However, partner proteins that elucidate PKP2 cellular mechanism behind cardiac dysfunction in ACM are mostly unknown. Here we identify the actin-based motor proteins Myh9 and Myh10 as key PKP2 interactors and demonstrate that expression of the ACM-related PKP2 mutant R735X alters actin fiber organization and cell mechanical stiffness. We also show that SARS-CoV-2 Nsp1 protein acts similarly to this known pathogenic R735X mutant, altering the actomyosin component distribution on cardiac cells. Our data reveal that Nsp1 hijacks PKP2 into the cytoplasm and mimics the effect of delocalized R735X mutant. These results demonstrate that cytoplasmic PKP2 drives actomyosin deregulation and structural collapse, validating a critical role of PKP2 localization in the regulation of actomyosin architecture. The fact that Nsp1 and R735X share similar phenotypes also suggests that direct SARS-CoV-2 heart infection could induce a transient ACM-like disease in COVID-19 patients, which may contribute to right ventricle dysfunction, observed in patients with poor prognosis.

25. pH 值对 SARS-CoV-2 感染和 COVID-19 严重程度的影响

The influence of pH on SARS-CoV-2 infection and COVID-19 severity

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中文摘要：

SARS-CoV-2 可以通过宿主受体血管紧张素转换酶 2 (ACE2)感染广泛的人体组织。与无合并症的患者相比，伴有严重 COVID-19 的合并症患者肺部 ACE2 水平更高，细胞应激、葡萄糖水平升高和缺氧等情况也可能增加 ACE2 的表达。我们发现，与正常鳞状食管相比，Barrett 食管(BE)患者在 BE 组织中 ACE2 的表达较高，而与 BE 相关的较低 pH 值可能促使其表达增加。在降低 pH 条件下培养的人原代单核细胞在 SARS-CoV-2 感染后显示 ACE2 表达和病毒载量增加。我们还**在两个独立的 COVID-19 患者组中发现，与未使用药物的患者相比，先前使用质子泵抑制剂的患者的死亡风险高出 2-3 倍。**我们的研究表明，pH 值对 SARS-CoV-2 感染和 COVID-19 严重程度有很大影响。

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can infect a broad range of human tissues by using the host receptor angiotensin-converting enzyme 2 (ACE2). Individuals with comorbidities associated with severe COVID-19 display higher levels of ACE2 in the lungs compared to those without comorbidities, and conditions such as cell stress, elevated glucose levels and hypoxia may also increase the expression of ACE2. Here we showed that patients with Barrett's esophagus (BE) have a higher expression of ACE2 in BE tissues compared to normal

squamous esophagus, and that the lower pH associated with BE may drive this increase in expression. Human primary monocytes cultured in reduced pH displayed increased ACE2 expression and viral load upon SARS-CoV-2 infection. We also showed in two independent cohorts of COVID-19 patients that previous use of proton pump inhibitors is associated with 2- to 3-fold higher risk of death compared to those not using the drugs. Our work suggests that pH has a great influence on SARS-CoV-2 Infection and COVID-19 severity.

26. SARS-CoV-2 的核衣壳蛋白和病毒基因组 RNA 形成凝聚物

SARS CoV-2 nucleocapsid protein forms condensates with viral genomic RNA

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链接：https://www.biorxiv.org/content/10.1101/2020.09.14.295824v2

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中文摘要：

将病毒基因组包装进新生病毒颗粒是由核衣壳 N 蛋白介导的，但是其具体作用机制目前不清楚。该研究表明核衣壳 N 蛋白在体外和哺乳动物中都可以和病毒 RNA 凝聚在一起形成生物大分子。核衣壳 N 蛋白和没有结构的 RNA 形成圆形的组合，它们和含有二级结构的 RNA 链形成网格样结构。交联质谱分析鉴定出 N 蛋白一个内部无序的区域在凝聚物中相互间存在结合作用，将这一段截断会破坏相分离。体外对 1200 个 FDA 批准的药物分子进行筛选，作者们鉴定中一个激酶抑制剂 nilotinib(尼洛替尼)在体外可以影响 N 蛋白体外的凝聚，干扰体内的 N 蛋白的相分离。这些结果提示 N 蛋白在被感染的细胞可以通过液相-液相相分离来划分病毒 RNA，这个过程可以被一个可能的候选药物干扰。

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes COVID-19, a pandemic that seriously threatens global health. SARS CoV-2 propagates by packaging its RNA genome into membrane enclosures in host cells. The packaging of the viral genome into the nascent virion is mediated by the nucleocapsid (N) protein, but the underlying mechanism remains unclear. Here, we show that the N protein forms biomolecular condensates with viral RNA both in vitro and in mammalian cells. While the N protein forms spherical assemblies with unstructured RNA, it forms mesh like-structures with viral RNA strands that contain secondary structure elements. Cross-linking mass spectrometry identified an intrinsically-disordered region that forms interactions between N proteins in condensates, and truncation of this region disrupts phase separation. By screening 1,200 FDA approved drugs in vitro, we identified a kinase inhibitor nilotinib, which affects the morphology of N condensates in vitro and disrupts phase separation of the N protein in vivo. These results indicate that the N protein compartmentalizes viral RNA in infected cells through liquid-liquid phase separation, and this process can be disrupted by a possible drug candidate.

27. 对 SARS-CoV-2 刺突蛋白 D614G 变异的结果和功能分析

Structural and Functional Analysis of the D614G SARS-CoV-2 Spike Protein Variant

链接：https://www.cell.com/cell/fulltext/S0092-8674(20)31229-0#%20

7 月 10 日简报第 27 条报告了该研究的预印本文章，文章指出 SARS-CoV-2 刺突蛋白的 D614G 变异增加了病毒的感染力，不改变对靶向受体结合域的敏感度。

D614G 变异在人群中的概率一直在稳步增加；D614G 使得病毒对人肺细胞系、表达 ACE2 的蝙蝠和穿山甲细胞感染力增强；靶向刺突蛋白的受体结合域的抗体仍然对包含该变异的病毒具备完全的中和效应；D614G 变异使得 S 蛋白的构象朝着构象向 ACE2 结合状态迁移。

Highlights:

The SARS-CoV-2 D614G S protein variant supplanted the ancestral virus in people

D614G increases infectivity on human lung cells or cells with bat or pangolin ACE2

D614G is potently neutralized by antibodies targeting the receptor binding domain

D614G shifts S protein conformation towards an ACE2-binding fusion-competent state

28. 一个装载在细菌人工染色体载体上的非感染性 SARS-CoV-2 复制子

A bacterial artificial chromosome (BAC)-vectored noninfectious replicon of SARS-CoV-2

链接：https://www.biorxiv.org/content/10.1101/2020.09.11.294330v1

复旦大学 Zhigang yi 团队构建了一个非感染性的 SARS-CoV-2 的细菌人工染色体。