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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1. 2020 年 6 月 4 日疫情

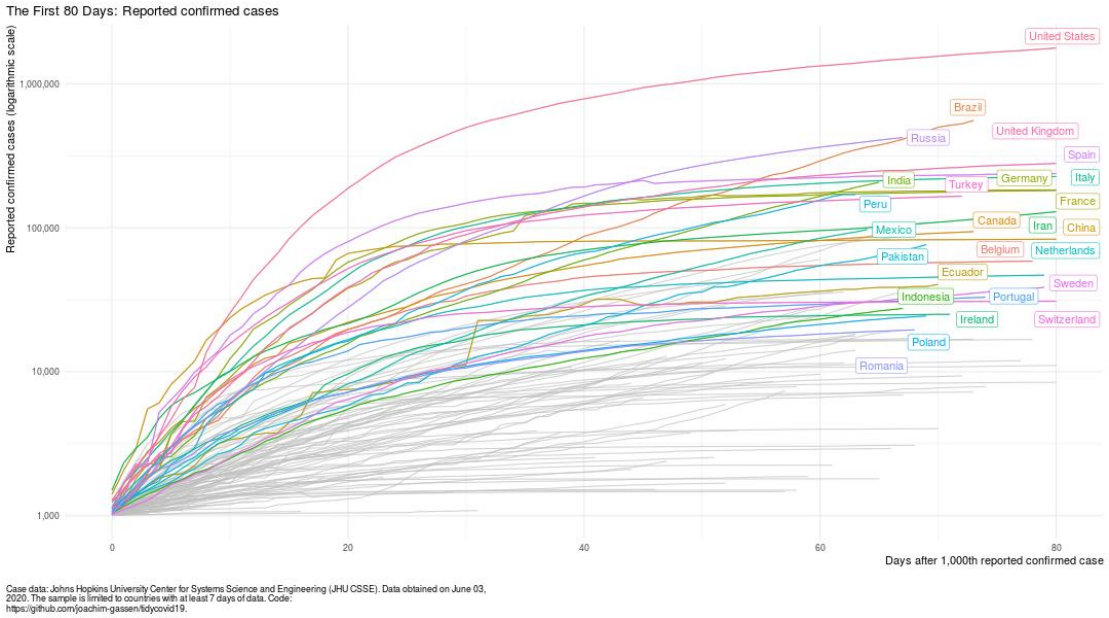
数据来源：WHO

发布时间：2020 年 6 月 4 日北京时间下午 4 点

链接：https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

根据 WHO 提供的数据，2020 年 6 月 4 日全球累计确诊新型冠状病毒病人 6416828 例，当日新增确诊 129281 例，累计死亡 382867 例，当日新增死亡 4842。

中国累计确诊 84603 例，累计死亡 4645 例，当日新增确诊 1 例，新增死亡 0 例。



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止 6 月 3 日北京时间下午 4 点）

全国新型冠状病毒肺炎新增确诊病例分布图（6月4日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 被 SARS-CoV-2 感染的母亲母乳喂养的安全性

Safety of Breastfeeding in Mothers with SARS-CoV-2 Infection

链接：https://www.medrxiv.org/content/10.1101/2020.05.30.20033407v1

中文摘要：来自华中科技大学同济医学院附属协和医院等单位的研究团队，选择了 23 例孕妇和产妇作为研究对象，评价了母乳喂养对 SARS-CoV-2 传播的影响，对母乳、母血和婴儿血中 SARS-CoV-2、IgG 和 IgM 进行了检测。未发现新生儿 SARS-CoV-2 阳性。所有母乳样本的 SARS-CoV-2 检测均为阴性。母乳中 SARS-CoV-2 的 IgM 与母亲血液相关。所有母乳样本中 SARS-CoV-2 的 IgG 检测结果均为阴性。所有婴儿均处于健康状态，其中 6 名婴儿全部或部分母乳喂养。8 名婴儿在出生后 1 个月内接受了 SARS-CoV-2 抗体检测，结果均为阴性。

3. 声称新型冠状病毒可以由无症状者传播的研究是有缺陷的

Study claiming new coronavirus can be transmitted by people without symptoms was flawed

文章链接：https://www.sciencemag.org/news/2020/02/paper-non-symptomatic-patient-transmitting-coronavirus-wrong

来源：Science Magazine

作者：Kai Kupferschmidt，德国柏林《科学》杂志的特约记者。

编译者：张怡

中文摘要：

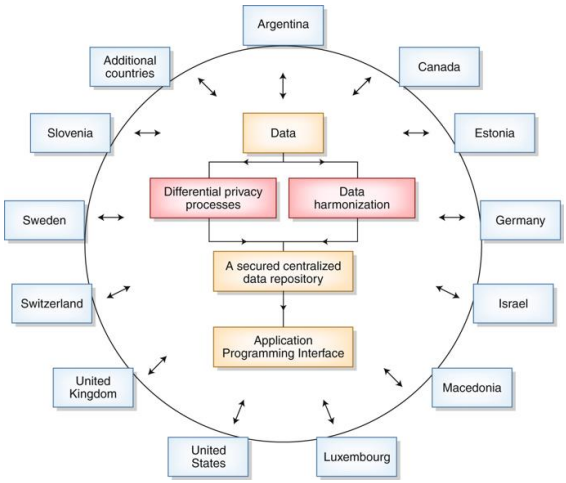
6 月 2 日下午更新，1 月 30 日发表的一篇论文在《新英格兰医学杂志》（NEJM）讲到一名无症状者将病毒传染给了四个人，因为作者们并没有直接与无症状者的中国旅客进行交谈确认。故而目前为止并没有确切证据证明无症状者会传染。但现在已经证实，症状非常轻微的人——非常轻微，以至于他们不太可能认为自己是 COVID-19——可以感染其他人，甚至引发大规模疾病暴发。

4. 构建一个跟踪新冠健康状态的国际协作

Building an international consortium for tracking coronavirus health status

文章链接：https://www.nature.com/articles/s41591-020-0929-x

Nature medicine 上于 6 月 2 日发布了多个国家科学家关于构建一个跟踪新冠健康状态的国际协作的倡议，以更准确追踪和报道新冠疫情。文章也综述了目前已经存在的疫情追踪报告系统。



5. 高度多重寡核苷酸探针连接试验可实现无提取的 SARS-CoV-2 检测和病毒基因分型

Highly multiplexed oligonucleotide probe-ligation testing enables efficient extraction-free SARS-CoV-2 detection and viral genotyping

来源：bioRxiv
发布时间：2020-06-03
链接：https://www.biorxiv.org/content/10.1101/2020.06.03.130591v1
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通讯作者单位：Johns Hopkins University, Baltimore, MD, USA
DOI 或 PUBMED ID：
编译者：张鹏伟

中文摘要：

SARS-CoV-2 的出现导致了当前的 COVID-19 大流行病，并带来了灾难性的社会影响。由于许多人在症状出现前几天就开始脱毒，许多人表现出轻微或无症状，因此迫切需要开发和部署敏感和高通量的分子诊断试验。RASL-seq 是一种用于多糖基化 mRNA 靶向分析的高度复用技术，它结合了样本条码进行大规模并行分析。文中作者提出了一种更通用的方法，捕获 RASL-seq（“cRASL-seq”），它可以分析任何靶向病原体（和/或宿主）相关的 RNA 分子。cRASL-seq 能够实现对病原体的高度敏感（低至 1-100 pfu/ml 或 cfu/ml）和高度复用（高达 10000 个目标序列）检测。重要的是，COVID-19 患者鼻咽（NP）拭子样本的 cRASL-seq 分析不涉及核酸提取或反转录，这些步骤导致了与其他分析相关的测试瓶颈。这个简化的工作流程还可以直接有效地对整个基因组中选择的、信息量大的 SARS-CoV-2 多态性进行基因分型，这可用于在种群规模上增强传播链的特征，并检测具有较高或较低毒力的病毒分支。鉴于其每个样本极低的成本、简单且自动化的流程和分析、探针面板模块化和巨大的可扩展性，作者认为 cRASL-seq 测试是一种强大的新监测技术，有可能帮助缓解当前的流行病和预防类似的公共卫生危机。

Abstract:

The emergence of SARS-CoV-2 has caused the current COVID-19 pandemic with catastrophic societal impact. Because many individuals shed virus for days before symptom onset, and many show mild or no symptoms, an emergent and unprecedented need exists for development and deployment of sensitive and high throughput molecular diagnostic tests. RNA-mediated oligonucleotide Annealing Selection and Ligation with next generation DNA sequencing (RASL-seq) is a highly multiplexed technology for targeted analysis of polyadenylated mRNA, which incorporates sample barcoding for massively parallel analyses. Here we present a more generalized method, capture RASL-seq ("cRASL-seq"), which enables analysis of any targeted pathogen- (and/or host-) associated RNA molecules. cRASL-seq enables highly sensitive (down to ~1-100 pfu/ml or cfu/ml) and highly multiplexed (up to ~10,000 target sequences) detection of pathogens. Importantly, cRASL-seq analysis of COVID-19 patient nasopharyngeal (NP) swab specimens does not involve nucleic acid extraction or reverse transcription, steps that have caused testing bottlenecks associated with other assays. Our simplified workflow additionally enables the direct and efficient genotyping of selected, informative SARS-CoV-2 polymorphisms across the entire genome, which can be used for enhanced characterization of transmission chains at population scale and detection of

viral clades with higher or lower virulence. Given its extremely low per-sample cost, simple and automatable protocol and analytics, probe panel modularity, and massive scalability, we propose that cRASL-seq testing is a powerful new surveillance technology with the potential to help mitigate the current pandemic and prevent similar public health crises.

6. LAMP 法纳米孔 Flongle 工作流程快速检测 SARS-CoV-2 等呼吸道病毒

Rapid detection of SARS-CoV-2 and other respiratory viruses by using LAMP method with Nanopore Flongle workflow

链接：https://www.biorxiv.org/content/10.1101/2020.06.03.131474v1

湖北武汉 GrandOmics Diagnostics 提出了一种环介导的等温扩增（LAMP）反应和纳米孔 Flongle 相结合的工作流程在两小时内检测 SARS-Cov-2 感染的方法。在这种方法中，RNA 反转录和核酸扩增反应在 60-65 度恒温环境下 30 分钟内一步完成，然后纳米孔 Flongle 接合器在 10 分钟内快速连接。

7. EasyCOV：基于 LAMP 的唾液 SARS-CoV-2 快速检测

EasyCOV: LAMP based rapid detection of SARS-CoV-2 in saliva

链接：https://www.medrxiv.org/content/10.1101/2020.05.30.20117291v1

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编译者：蒋立春

中文摘要：

法国的研究人员开发了 EasyCov，一种不需要 RNA 抽提步骤直接进行基于反转录-LAMP（一种等温扩增技术）的 SARS-CoV-2 病毒检测技术。该技术可以通过检测医护人员和病人的唾液而提供稳定快速安全、简易可行的测试。研究这们对包含 93 个无症状的医护人员、10 个感染中的病人以及 20 个之前感染过的病人进行双盲测试。并将结果和传统的对鼻咽拭子进行 RT-PCR 检测的结果进行了比较。EasyCoV 的敏感度为 72.7%，医护人员中检出的特异性为 95.7%。建议该技术的无创性、简易快速，该检测有可能对于人群中大规模筛查有用处。

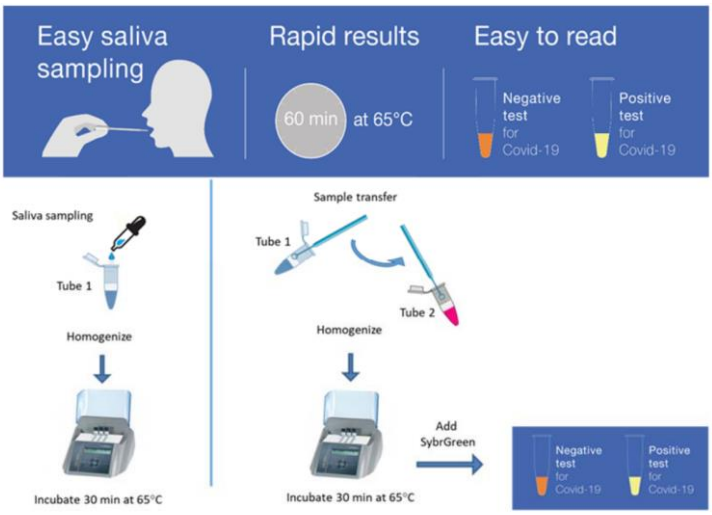

Figure 3 Schematic representation of EasyCOV steps for SARS-CoV-2 detection

Abstract
Covid-19 crisis showed us that rapid massive virus detection campaign is a key element in SARS-CoV-2 pandemic response. The classical RT-PCR laboratory platforms must be complemented with rapid and simplified technologies to enhance efficiency of large testing strategies.
To this aim, we developed EasyCoV, a direct saliva RT-LAMP based SARS-CoV-2 virus detection assay that do not requires any RNA extraction step. It allows robust and rapid response under safe and easy conditions for healthcare workers and patients. EasyCov test was assessed under double blind clinical conditions (93 asymptomatic healthcare worker volonteers, 10 actively infected patients, 20 former infected patients tested during late control visit). EasyCov results were compared with classical laboratory RT-PCR performed on nasopharyngeal samples. Our results show that compared with nasopharyngeal laboratory RT-PCR, EasyCov SARS-CoV-2 detection test has a sensitivity of 72.7%. Measured on healthcare worker population the specificity was 95.7%. LAMP technology on saliva is clearly able to identify subjects with infectivity profile. Among healthcare worker population Easycov test detected one presymptomatic subject. Because it is simple, rapid and painless for patients, EasyCov saliva SARS-Cov-2 detection test may be useful for large screening of general population.

8. 杜克-新加坡国立大学研发出快速测探中和抗体的检测试剂盒

链接：
https://mp.weixin.qq.com/s?__biz=MzA5MjA0NTA4NQ==&mid=2651048669&idx=1&sn=44f480f96ad42be8414294d50f9bc3b3&chksm=8b8440afbcf3c9b91a4e9f48cb81e0fa6efda3c8b5535d9c0d94d9e2b9ac968378505b5b5df4&mpshare=1&scene=1&srcid=&sharer_sharetime=1591098748443&sharer_shareid=80f78c62f02832698f0a70d54f98b491&key=41f971365debdfe9f4ce1553d9f5b71c663fd1c6005e0b41333d5936631a43083d09fc4b8ac709c9d1131280407fda48a1566d0eeb8299166e27005d5bc2c06d167e40a7930d0cfa4fffedb9b737eaeb&ascene=1&uin=MjgxMjY4NjgxNQ%3D%3D&devicetype=Windows+10+x64&version=62090070&lang=zh_CN&exportkey=A4txtUTHfA31EAL7yqnjmdY%3D&pass_ticket=0dq1HQ20elInpub92RrUOao8mylZjplqPOM%2BKi6hA3H1NZs9hFLuwoJzrqwDXTYo

以下为转载摘录：
根据未来论坛公众号 6 月 2 日的消息，杜克-新加坡国立大学医学院教授王林发及团队成功研发出 cPass 血清检测试剂盒，1 小时内能确定病患是否曾感染新冠肺炎。这也是全球首个能快速测探中和抗体的检测试剂盒，有助于血浆治疗法和新冠肺炎疫苗的研发。
这是全球首个中和抗体(NAbs)快速检测试剂盒，无需活性生物材料和生物防护设施，即可开展检测。中和抗体是存在于新冠病患血清中的一种特异性抗体，负责阻断病毒的入侵。
尽管市面上已有许多实验室研发的新冠病毒抗体检测试剂盒，但 cPass™是全球首个能够用于测量功能性中和抗体的试剂盒。中和抗体的传统检测需要采集活病毒和细胞，由高度熟练的工作人员通过复杂的实验室程序来操作，这些步骤既不便捷，又需要花费几天时间才能获得结果。
王林发教授表示：“我们团队开发的 cPass™可用于接触者追踪，自然宿主或中间动物宿主溯源，评估群体免疫、保护性免疫力的持久性和不同候选疫苗的有效性。无需依靠生物安全防护设施就能开展中和抗体检测，这使得包括许多发展中国家在内的所有国家都可以即时应用

这款快速检测盒。”

9. INSIGHT：一个可以扩大规模等温核酸扩增和测序结合的 COVID-19 诊断

INSIGHT: a scalable isothermal NASBA-based platform for COVID-19 diagnosis

Sanger 中心的科学家们发展了结合等温扩增快速检测和第二步进行高通量测序的 COVID-19 检测的方案。

https://www.biorxiv.org/content/10.1101/2020.06.01.127019v1

10. 在住院的 COVID-19 患者中 SARS-CoV-2 特异性抗体分泌细胞的扩增及中和抗体的产生

Expansion of SARS-CoV-2-specific Antibody-secreting Cells and Generation of Neutralizing Antibodies in Hospitalized COVID-19 Patients

来源：bioRxiv

发布时间：2020-05-29

链接：https://www.biorxiv.org/content/10.1101/2020.05.28.118729v1

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编译者：张鹏伟

中文摘要：

由 SARS-CoV-2 引起的 COVID-19 于 2019 年底出现，此后成为全球大流行。病原特异性抗体通常是保护性免疫的一个主要预测因子，然而在 COVID-19 期间 B 细胞和抗体反应尚不完全清楚。本文分析了 20 例 COVID-19 患者的抗体分泌细胞（ASC）和抗体反应。用多色荧光斑点法观察了 20 例 COVID-19 患者中 SARS-CoV-2 核衣壳蛋白特异性 ASCs 的显著扩增。在 20 名病人中，16 人在取样时已产生 SARS-CoV-2 中和抗体。此外，还发现 SARS-CoV-2 特异性 IgA、IgG 和 IgM 抗体水平与 SARS-CoV-2 中和抗体滴度呈正相关。本研究详细描述了 COVID-19 中的 B 细胞和 SARS-CoV-2 抗体反应，为研究 SARS-CoV-2 感染和疫苗免疫反应提供了工具。

Abstract:

COVID-19, caused by SARS-CoV-2, emerged in late 2019 and has since become a global pandemic. Pathogen-specific antibodies are typically a major predictor of protective immunity, yet B cell and antibody responses during COVID-19 are not fully understood. Here, we analyzed antibody-secreting cell (ASC) and antibody responses in twenty hospitalized COVID-19 patients. We observed a significant expansion of SARS-CoV-2 nucleocapsid protein-specific ASCs in all twenty COVID-19 patients using a multicolor FluoroSpot assay. Out of the 20 patients, 16 had developed SARS-CoV-2-neutralizing antibodies by the time of sampling. Additionally, we found that SARS-CoV-2-specific IgA, IgG and IgM antibody levels positively correlated with SARS-CoV-2-neutralizing antibody titers. This study constitutes a detailed description of B cell and antibody responses to SARS-CoV-2 in COVID-19, and provides tools to study immune responses to SARS-CoV-2 infection and vaccination.

11. 急性心肌损伤：COVID-19 儿童的新型临床模式

Acute myocardial injury: a novel clinical pattern in children with COVID-19

来源：The Lancet Child & Adolescent Health
发布时间：2020-06-01
链接：https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30168-1/fulltext

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DOI 或 PUBMED ID：https://doi.org/10.1016/S2352-4642(20)30168-1

编译者：张丽双

中文摘要：

越来越多的证据表明 COVID-19 在儿童中有不同的临床模式。对这家医院儿科重症监护室的 9 名儿童 COVID-19 患者中有 5 名有明显心脏损伤和轻中度心功能不全，对这 5 名儿童进行细致研究，发现没有达到所有经典或不完全川崎病的临床标准，因为他们只有五个标准中的一个或两个。这种临床表现可能是英国描述的 COVID-19 相关休克的轻度形式，现在被称为儿科多系统炎性综合征。在这两种情况下，都描述为高炎性状态，心脏受累类似非典型川崎病。COVID-19 引起细胞因子风暴；在成人中，它主要损害急性呼吸窘迫综合征患者的肺，并在较小程度上影响其他器官，如心脏，从而导致较高的死亡率，而在儿童中，它似乎有一个不同的靶点，心脏受累普遍。特别的是，这三组儿童都出现了胃肠道症状：英国 8 名儿童中的 7 名，意大利上一个病例系列中的 10 名儿童中的 4 名，我们病例系列中的所有 5 名儿童都有腹泻，伴有或不伴有呕吐和腹痛。强调 COVID-19 儿童应密切监测，以识别心脏受累，并预防严重和关键的疾病过程。

Abstract:

Reports of coronavirus disease 2019 (COVID-19) show that children usually have mild clinical signs and less severe disease than do adults,1 although the reasons for such differences are not yet completely understood.2 A previous report3 describing paediatric COVID-19 cases in China showed that 13 (0.6%) of 2135 laboratory-confirmed and suspected cases were critical, but myocardial involvement was not noted. At the time of writing, two clinical scenarios of severe paediatric COVID-19 cases have been reported from the UK and Italy: severe shock syndrome with hyperinflammation4 and Kawasaki-like-disease.5

During March 15 to April 25, 2020, nine patients were admitted to our paediatric intensive care unit (PICU) for COVID-19; PCR tests of nasopharyngeal samples for severe acute respiratory syndrome coronavirus 2 were positive for all nine patients. Five of these patients had cardiac injury and mild to moderate cardiac dysfunction; we describe these patients in this case series. All five children (mean age 84.4 months, range 2–168) were previously healthy and had fever and gastrointestinal symptoms as initial signs at home. Three patients (1, 4, and 5) had fleeting polymorphic rash; in patient 5, the rash was associated with non-exudative conjunctivitis without involvement of the oral mucosa. Only patient 2 had respiratory distress at home requiring non-invasive mechanical support during PICU stay; none developed paediatric acute respiratory distress syndrome. On PICU admission, the main clinical signs were tachycardia and hypotension. Patient

1 was oligoanuric and patients 1, 3, and 5 had mild desaturation in spontaneous breathing in room air (SpO2 94–96%). Blood examinations revealed elevated cardiac enzymes and inflammation markers. Complete demographic, clinical findings, and blood test results are shown in the appendix. All children had a mild to moderate heart dysfunction highlighted by reduced ejection fraction (mean 47.8%, SD 9.1), and all except patient 4 required a short course of intravenous epinephrine (dose range 0.05–0.1 μg/kg per min), which in patient 2 was administered with intravenous PDE3 inhibitor (milrinone 0.25 μg/kg per min).
Four children had a midbasal hypokinesis of the inferoseptal wall and inferior wall. The electrocardiogram was abnormal with non-specific changes such as sinus tachycardia, and ST and T-wave abnormalities. Patient 2 developed atrial fibrillation and had reversible acute kidney injury. Mean length of PICU stay was 3.4 days (range 1–5). All children were discharged to the ward with a normal cardiac function and good clinical conditions. Mean length of hospital stay was 7.2 days (range 5–10).
Increasing evidence shows that COVID-19 in children has different clinical patterns. Our patients did not meet all the clinical criteria for classic or incomplete Kawasaki disease because they had only one or two of the five criteria required. It is possible that this clinical picture is the mild form of the COVID-19-related shock described in the UK, which is now being labelled as paediatric multisystem inflammatory syndrome.6 In both cases, a hyperinflammatory state is described with cardiac involvement mimicking atypical Kawasaki disease. COVID-19 provokes a cytokine storm;7 in adults it mainly compromises the lung with acute respiratory distress syndrome and affects other organs such as the heart8, 9 to a lesser extent, which condition a higher mortality, whereas in children it seems to have a different target with a prevalent cardiac involvement. Interestingly, gastrointestinal symptoms occurred in all three groups: seven of eight children in the UK,4 six of ten children in the previous case series from Italy,5 and all five children in our case series had diarrhoea with or without vomiting and abdominal pain. Unexpectedly, the substantial increase in cardiac enzymes (mainly NT-proBNP, which increased to up to 30 times the normal value) was not associated with severe heart failure.
Our case series reinforces the message that children with COVID-19 should be closely monitored to recognise cardiac involvement and to prevent a severe and critical course of illness.

12. COVID-19 中 T 细胞表型变化的开放资源，产生 IL-10 的调节性 T 细胞为重症患者的特征

An open resource for T cell phenotype changes in COVID-19 identifies IL-10-producing regulatory T cells as characteristic of severe cases
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发布时间：2020-06-02
链接：https://www.medrxiv.org/content/10.1101/2020.05.31.20112979v1
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DOI 或 PUBMED ID：
编译者：王玮
中文摘要：
COVID-19 的临床表现因人而异。SARS-CoV-2 免疫应答的变化可能是这种临床变化的基础。利用高维度的免疫学平台，对 6 例健康人、23 例轻中度 COVID-19 患者和 20 例重度 COVID-19 患者的外周血细胞进行了分析。在轻中度和重度 COVID-19 患者的外周血中发现明显的免疫特征，包括 T 细胞淋巴细胞减少，因此该研究认为外周低免疫比高免疫激活可能性更高。严重 COVID-19 病例中，分泌 IL-10 调节性 T 细胞的比例显著增加，这是一种已知的在肺部具有抗炎特性的细胞。相关数据公开可用：https://flowrepository.org/experiments/2713。
Abstract:
The pandemic spread of the novel coronavirus SARS-CoV-2 is due, in part, to the immunological properties of the host-viral interaction. The clinical presentation varies greatly from individual to individual, with asymptomatic carriers, mild to moderate-presenting patients and severely affected patients. Variation in immune response to SARS-CoV-2 may underlie this clinical variation. Using a high dimensional systems immunology platform we have analysed the peripheral blood compartment of 6 healthy individuals, 23 mild-to-moderate COVID-19 patients and 20 severe COVID-19 patients. We identify distinct immunological signatures in the peripheral blood of the mild-to-moderate and severe COVID-19 patients, including T cell lymphopenia, more consistent with peripheral hypo- than hyper-immune activation. Unique to the severe COVID-19 cases was a large increase in the proportion of IL-10-secreting regulatory T cells, a lineage known to possess anti-inflammatory properties in the lung. Annotated data is openly available (https://flowrepository.org/experiments/2713) with clinical correlates, as a systems immunology resource for the COVID-19 research community.

13. 靶向免疫抑制区分 COVID-19 与中、重度流感

Targeted Immunosuppression Distinguishes COVID-19 from Influenza in Moderate and Severe Disease
链接：https://www.medrxiv.org/content/10.1101/2020.05.28.20115667v1
中文摘要：来自美国华盛顿大学等单位的研究团队，在细胞和蛋白质水平上评估了 COVID-19 和流感患者的免疫应答情况。对部分受试者外周血单个核细胞进行了单细胞 RNA 转录组分析。他们发现 COVID-19 患者中的 I 型和 II 型干扰素信号受到严重抑制。

14. 炎症细胞因子信号有助于预测 COVID-19 的严重程度和死亡

An inflammatory cytokine signature helps predict COVID-19 severity and death
链接：https://www.medrxiv.org/content/10.1101/2020.05.28.20115758v1
中文摘要：西奈山伊坎医学院和牛津大学的研究者们通过对 1484 名病人的数据分析发现，

血清中 IL-6 和 TNF-α 的水平独立于其他因素，是 COVID-19 症状严重程度以及死亡的重要预测因子。

15. 在成年 COVID-19 病人中发现肺泡可以重新生长

Pulmonary alveolar regrowth in an adult COVID-19 patient

链接：https://www.medrxiv.org/content/10.1101/2020.05.10.20097634v1

16. 一种可推广的针对 SARS-CoV-2 的外用载体疫苗候选

A Scalable Topical Vectored Vaccine Candidate Against SARS-CoV-2

来源：biorxiv

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文章链接：https://www.biorxiv.org/content/10.1101/2020.05.31.126524v1

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中文摘要：

2019 年，严重急性呼吸道综合征-冠状病毒 2 型(SARS-CoV-2)在全球引发了前所未有的冠状病毒病公共卫生危机。死亡率的急剧上升，病毒对生活的影响以及经济的动荡都迫切需要开发安全、有效和可推广的 SARS-CoV-2 疫苗。作者提出了一种全新的基于禽类 orthoavulavirus 1(AOaV-1)的合成的外用呼吸道候选疫苗，以对抗 COVID-19。新城疫病毒和 AOaV-1 原型病毒无毒毒株被设计表达全长刺突（S）糖蛋白，该蛋白是 SARS-CoV-2 的高度中和性和主要保护性抗原。大规模体外鉴定重组候选疫苗显示 AOaV-1 的血细胞凝集素-神经氨酸苷酶(HN)和 SARS-CoV-2 的 S 蛋白高效共表达，并在细胞培养模型中观察到相似的复制动力学。该重组疫苗候选株病毒不依赖外源性胰蛋白酶在细胞内活跃复制和传播。有趣的是，将 SARS-CoV-2 的 S 蛋白重组到重组的 AOaV-1 颗粒中，发现其对 anti-SARS-CoV-2 抗血清具有敏感性，而对 anti-AOaV-1 抗血清的敏感性更为显著。最后，作者的结果表明，重组疫苗载体在鸡胚培养多次繁殖后稳定表达 S 蛋白，且该表达对重组疫苗的体外增殖特性没有显著影响。综上所述，目前提出的候选呼吸道疫苗在灵长类动物中本身高度减毒，在人类中既安全又没有先前就免疫的问题，并具有加速开发用于临床研究的 COVID-19 疫苗的潜力。

Abstract

The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) caused an ongoing unprecedented global public health crises of coronavirus disease in 2019 (CoVID-19). The precipitously increased death rates, its impact on livelihood and trembling economies warrant the urgent development of SARS-CoV-2 vaccine which would be safe, efficacious and scalable. Owing to unavailability of the vaccine, we propose a de novo synthesised avian orthoavulavirus 1 (AOaV-1)-based topical respiratory vaccine candidate against CoVID-19. Avirulent strain of Newcastle disease virus, proto-type virus of AOaV-1, was engineered to express full length spike (S) glycoprotein which is highly neutralizing and major protective antigen of the SARS-CoV-2. Broad-scale in vitro characterization of recombinant vaccine candidate demonstrated efficient co-expression of the

hemagglutinin-neuraminidase (HN) of AOaV-1 and S protein of SARS-CoV-2, and comparable replication kinetics were observed in cell culture model. The recombinant vaccine candidate virus actively replicated and spread within cells independently of exogenous trypsin. Interestingly, incorporation of S protein of SARS-CoV-2 into the recombinant AOaV-1 particles attributed the sensitivity to anti-SARS-CoV-2 antiserum and more prominently to anti-AOaV-1 antiserum. Finally, our results demonstrated that the recombinant vaccine vector stably expressed S protein after multiple propagation in chicken embryonated eggs, and this expression did not significantly impact the in vitro growth characteristics of the recombinant. Taken together, the presented respiratory vaccine candidate is highly attenuated in primates per se, safe and lacking pre-existing immunity in human, and carries the potential for accelerated vaccine development against CoVID-19 for clinical studies.

17. 羊驼纳米抗体通过阻断受体相互作用来中和 SARS-CoV-2

An alpaca nanobody neutralizes SARS-CoV-2 by blocking receptor interaction
链接：biorxiv.org/content/10.1101/2020.06.02.130161v1
编译者：张丽双
瑞典研究人员发现羊驼来源的纳米抗体以高特异性高亲和力结合 SARS-CoV-2 刺突蛋白，阻断受体相互作用来中和病毒，具备作为有效且可广泛使用的 SARS-CoV-2 抗病毒药的潜力。
文章分类：药物研发

18. AbCellera 公司与礼来公司合作开发的全球首个抗 SARS-CoV-2 治疗性抗体进入临床 I 期

Phase I start marks first for anti-SARS-CoV-2 mAbs, first for AbCellera
来源：Biocentury
发布时间：2020-06-02
链接：https://www.biocentury.com/article/305346
作者：SANDI WONG（编辑）
编译者：孔娟
中文摘要：
礼来和 AbCellera 公司合作开发的 COVID-19 单克隆抗体成为**全球首个进入临床 I 期的的抗体类抗 SARS-CoV-2 病毒药物**。Ly-CoV555 的第一阶段研究正在进行安全性评估。
礼来公司宣布，已对第一期 J2W-MC-PYAA 研究的首批患者进行了给药，正在进行的一项随机、安慰剂对照试验以评估 Ly-CoV555 的安全性和药代动力学/药代动力学，数据将于本月底公布。礼来方面还表示，如果一期的的结果表明此抗体的安全性，计划在未住院的新冠患者中进行针对 LY-CoV555 二期的试验。制药公司还将在易受感染人群的预防性环境中测试该单克隆抗体，重点关注不是疫苗最佳候选人的易受感染人群，例如老年人和免疫功能低下的个体。
AbCellera 与礼来公司从三月初开始合作抗 SARS-CoV-2 抗体药物的研发，AbCellera 公司从康复患者血液样本中鉴定出数百种其他潜在的病毒中和性单克隆抗体，Ly-CoV555 是其中之一。该公司表示，**从抗体发现到临床研究用了不到三个月的时间**，自 2018 年与美国国防高级研究项目署签署协议以来，该公司一直注重发展其应对大流行病的能力。AbCellera 公司的联合创始人卡尔·汉森曾表示，公司的目标是让合作伙伴在一年内从构思、发现、优化

和发展到临床，而这个过程通常至少需要三年时间。

上周，在礼来的参与下，该公司在一系列的 B 轮融资中筹集了 1.05 亿美元，以通过扩大其 R&D 的业务来加快到临床的进程。另外，Celltrion 公司(KSE:068270)周一宣布，计划在 7 月份开始对其 COVID-19 抗病毒抗体 CT-P59 进行人体测试。至少还有三家公司计划在今年夏天将中和病毒的单克隆抗体引入临床，其中包括礼来公司，该公司正与上海君实生物科技有限公司(HKEX:1877)合作开发 JS016。

Abstract

A COVID-19 mAb from Eli Lilly and AbCellera has become the first against the virus to start human trials and is also the Vancouver-based company's first product to enter the clinic. While the Phase I study of Ly-CoV555 is assessing safety, its evaluation in hospitalized COVID-19 patients leaves room for exploratory observations that may hint at efficacy.

Eli Lilly and Co. (NYSE:LLY) announced Monday it had dosed the first patients in the Phase I J2W-MC-PYAA study, a randomized, placebo-controlled trial evaluating safety and PK/PD of Ly-CoV555. Data are due by the end of this month.

If the mAb against the SARS-CoV-2 spike is safe, Lilly plans to proceed to Phase II testing in non-hospitalized COVID-19 patients. The pharma will also test the mAb in a preventative setting in vulnerable populations that historically have not been optimal candidates for receiving vaccines, such as the elderly and immunocompromised individuals.

Ly-CoV555 is the first candidate out of AbCellera Biologics Inc.'s partnership with Lilly, which began in March. The two had already been in discussions regarding a collaboration on multiple targets when SARS-CoV-2 emerged, at which point they focused the deal's initial scope on the emerging pandemic. The pair expanded the deal two weeks ago to discover antibodies for up to eight additional targets selected by the pharma.

AbCellera discovered Ly-CoV555, along with hundreds of other potentially virus-neutralizing mAbs, using blood from an individual who recovered from COVID-19.

The company, which said it took less then three months to go from screening to human studies, has been developing its pandemic response capabilities since 2018, when it signed a deal with the U.S. Defense Advanced Research Projects Agency (see "AbCellera, Vir Find Partners").

AbCellera co-founder and CEO Carl Hansen previously told BioCentury the company's goal is to enable its partners to go from ideation through discovery, optimization and development to the clinic within a year, and that the process typically takes at least three years. The company raised $105 million last week in a series B round, with participation from Lilly, to speed the path to the clinic by expanding its R&D capabilities (see "Fresh of Lilly Deal, AbCellera Readies to Deploy $105M").

Separately, Celltrion Inc. (KSE:068270) announced Monday plans to begin human testing in July of its COVID-19 antiviral antibody CT-P59. At least three more companies plan to bring virus-neutralizing mAbs into the clinic this summer, including Lilly, which is developing JS016 with Shanghai Junshi Biosciences Co. Ltd. (HKEX:1877).

The other two are Vir Biotechnology Inc. (NASDAQ:VIR), which is partnered with GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), and Regeneron Pharmaceuticals Inc. (NASDAQ:REGN).

19. 羟氯喹作为 Covid-19 暴露后预防的随机试验，羟基氯喹没有预防作用

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

链接：https://www.nejm.org/doi/full/10.1056/NEJMoa2016638

编译者：孔娟

6 月 3 日，国际顶级医学期刊之一的《新英格兰医学杂志》发表的研究结果再次显示，羟氯喹在预防新冠病毒疾病方面并不比安慰剂药片更好。Boulware 带领的研究团队在美国和加拿大部分地区进行了一项随机、双盲、安慰剂对照试验，测试羟氯喹作为暴露后预防手段。在高风险或中等风险暴露于 Covid-19 后，羟基氯喹不能预防与 Covid-19 相关的疾病，羟氯喹预防新冠效果无异于安慰剂副作用轻微。

20. 托珠单抗治疗机械通气 COVID-19 患者

Tocilizumab for treatment of mechanically ventilated patients with COVID-19

链接：https://www.medrxiv.org/content/10.1101/2020.05.29.20117358v1

编译者：张丽双

密歇根大学的研究人员发现在机械通气的 COVID-19 患者中，尽管重复感染发生率较高，IL-6 抗体托珠单抗的使用与死亡风险降低 45%相关。

21. 意大利-西班牙全基因组关联分析中 ABO 血型位点和 3 号染色体基因簇与 SARS-CoV-2 呼吸衰竭相关

The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis

来源：medRxiv

发布时间：2020-06-02

链接：https://www.medrxiv.org/content/10.1101/2020.05.31.20114991v1

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DOI 或 PUBMED ID：

编译者：宋张悦

中文摘要：

背景：呼吸衰竭是重症 Covid-19 的一个关键特征，也是导致死亡的关键因素，但由于定义不清的原因，感染 SARS-CoV-2 的患者中只有不到 10%受到影响。

方法：本研究在意大利和西班牙的 7 个中心（米兰、蒙扎、马德里、圣塞巴斯蒂安和巴塞罗那）收集了 1980 例 Covid-19 呼吸衰竭患者，进行全基因组关联分析。在质量控制和排除人群异常值后，来自意大利的 835 名患者和 1255 名人群衍生对照，以及来自西班牙的 775 名患者和 950 名对照被纳入最终的分析。研究人员总共分析了 8,582,968 个单核苷酸多态性

（SNPs），并对两个病例-对照组进行了 meta 分析。

结果：本研究检测到在 3p21.31 号染色体上的 rs11385942 和 9q34 号染色体上的 rs657152 的交叉复制关联（cross-replicating associations），在两个研究组的 meta-分析中都是全基因组范围的显著性（$P<5x10^{-8}$），两组分别是 odds ratio[OR]=1.77；95%置信区间[CI]:1.48-2.11；$P=1.14x10^{-10}$和 OR=1.32；95% CI：1.20-1.47；$P=4.95x10^{-8}$。在 3p21.31 的 6 个基因中，SLC6A20 编码一个已知的与血管紧张素转换酶 2（ACE2）有互作的蛋白。9q34 的关联信号位于 ABO 血型位点，血型特异性分析显示 A-阳性个体的风险较高（OR=1.45，95% CI：1.20~1.75，$P=1.48x10^{-4}$），对 O 血型组有保护作用（OR=0.65，95% CI：0.53~0.79，$P=1.06x10^{-5}$）。

结论：本文报道了 Covid-19 呼吸衰竭发生的第一个稳定遗传易感位点。已识别的变异可能有助于指导重症 Covid-19 病理生理学的靶向探索。

Abstract:

Background. Respiratory failure is a key feature of severe Covid-19 and a critical driver of mortality, but for reasons poorly defined affects less than 10% of SARS-CoV-2 infected patients.

Methods. We included 1,980 patients with Covid-19 respiratory failure at seven centers in the Italian and Spanish epicenters of the SARS-CoV-2 pandemic in Europe (Milan, Monza, Madrid, San Sebastian and Barcelona) for a genome-wide association analysis. After quality control and exclusion of population outliers, 835 patients and 1,255 population-derived controls from Italy, and 775 patients and 950 controls from Spain were included in the final analysis. In total we analyzed 8,582,968 single-nucleotide polymorphisms (SNPs) and conducted a meta-analysis of both case-control panels.

Results. We detected cross-replicating associations with rs11385942 at chromosome 3p21.31 and rs657152 at 9q34, which were genome-wide significant ($P<5x10^{-8}$) in the meta-analysis of both study panels, odds ratio [OR], 1.77; 95% confidence interval [CI], 1.48 to 2.11; $P=1.14x10^{-10}$ and OR 1.32 (95% CI, 1.20 to 1.47; $P=4.95x10^{-8}$), respectively. Among six genes at 3p21.31, SLC6A20 encodes a known interaction partner with angiotensin converting enzyme 2 (ACE2). The association signal at 9q34 was located at the ABO blood group locus and a blood-group-specific analysis showed higher risk for A-positive individuals (OR=1.45, 95% CI, 1.20 to 1.75, $P=1.48x10^{-4}$) and a protective effect for blood group O (OR=0.65, 95% CI, 0.53 to 0.79, $P=1.06x10^{-5}$).

Conclusions. We herein report the first robust genetic susceptibility loci for the development of respiratory failure in Covid-19. Identified variants may help guide targeted exploration of severe Covid-19 pathophysiology.

22. SARS-CoV-2 在蝙蝠而非人类进化中的重要自然选择证据

Evidence of significant natural selection in the evolution of SARS-CoV-2 in bats, not humans

来源：bioRxiv

发布时间：2020-05-29

链接：https://www.biorxiv.org/content/10.1101/2020.05.28.122366v1

第一作者：Oscar A. MacLean, Spyros Lytras
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DOI 或 PUBMED ID：
编译者：宋张悦
中文摘要：
RNA 病毒由于其快速的突变率而擅长于转换到新的宿主物种。在这个假设中隐含的是，需要在新的宿主物种中进化适应，以有效地利用它们的细胞。然而，自大流行开始以来，SARS-CoV-2 不需要对人类进行重大的适应，迄今为止没有观察到有选择性的大清除。本研究中，将菊头蝠中的 *Sarbecoviruses* 病毒的正向选择和重组作用与人类中 SARS-CoV-2 的进化进行了对比。尽管方法可以检测到 SARS-CoV-2 正向选择的一些证据，但研究人员证明这些主要是由于重组和测序背景噪音引起的。纯化选择（负选择）在 SARS-CoV-2 中也比在相关的蝙蝠 *Sarbecoviruses* 病毒中要弱得多。相比之下，本研究的结果证明，针对蝙蝠病毒谱系 SARS-CoV-2 有正向的、明确的情景性选择（episodic selection）。这种选择的特征也可以在同义替换中观察到，例如，与祖先的 CpG 缺失有关。研究人员证明了蝙蝠病毒 RmYN02 在 Spike 上有重组 CpG 含量（recombinant CpG content），表明蝙蝠在没有其他物种参与的情况下发生了共感染和进化。**本研究结果表明，SARS-CoV-2 能够在人类之间传播，这是其在蝙蝠中自然进化的结果。**

Abstract:
RNA viruses are proficient at switching to novel host species due to their fast mutation rates. Implicit in this assumption is the need to evolve adaptations in the new host species to exploit their cells efficiently. However, SARS-CoV-2 has required no significant adaptation to humans since the pandemic began, with no observed selective sweeps to date. Here we contrast the role of positive selection and recombination in the *Sarbecoviruses* in horseshoe bats to SARS-CoV-2 evolution in humans. While methods can detect some evidence for positive selection in SARS-CoV-2, we demonstrate these are mostly due to recombination and sequencing artefacts. Purifying selection is also substantially weaker in SARS-CoV-2 than in the related bat *Sarbecoviruses*. In comparison, our results show evidence for positive, specifically episodic selection, acting on the bat virus lineage SARS-CoV-2 emerged from. This signature of selection can also be observed among synonymous substitutions, for example, linked to ancestral CpG depletion on this bat lineage. We show the bat virus RmYN02 has recombinant CpG content in Spike pointing to coinfection and evolution in bats without involvement of other species. Our results suggest the non-human progenitor of SARS-CoV-2 was capable of human-human transmission as a consequence of its natural evolution in bats.

23. 基于结构设计稳定的预融合状态 SARS-CoV-2 Spike 蛋白

Structure-based Design of Prefusion-stabilized SARS-CoV-2 Spikes
来源：bioRxiv
发布时间：2020-05-30

链接：https://www.biorxiv.org/content/10.1101/2020.05.30.125484v1

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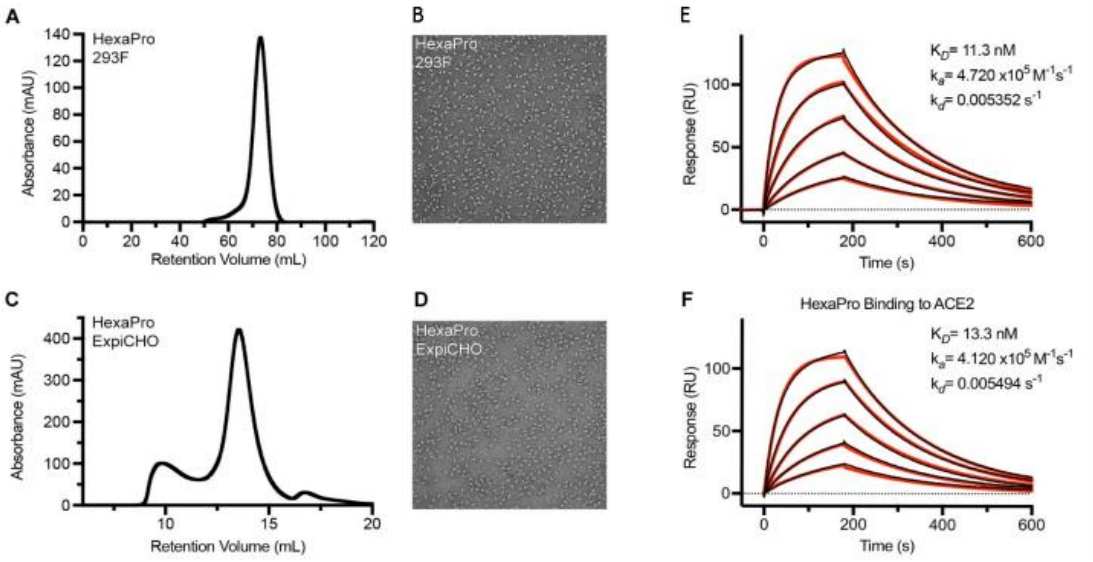
DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

由 SARS-CoV-2 病毒引起的 COVID-19 疫情，急需人们加快对其诊断和治疗方法，以及疫苗的开发进度，进而缓解此次公共卫生紧急事件的影响。Spike (S) 蛋白是上述目标的关键靶点。作为一种 I 类融合蛋白的大型三聚体，S 蛋白的结构稳定性不是非常高，因此难以大量重组生成。本文中，作者基于此前利用 cryo-EM 解析的 SARS-CoV-2 预融合状态的 Spike 蛋白结构，以结构为导向，设计并表达了 100 多种 Spike 蛋白的突变体。对这些突变体进行生化，生物物理和结构表征后，确定了多个独特的氨基酸替换位点，这些替换可以提高蛋白的产量和稳定性。最好的突变体，HexaPro，存在 6 个有益的脯氨酸取代，从而使表达量比其亲本构建物提高了约 10 倍，并且能够承受热应激，能在室温下储存和多次冻融。作者同时利用 cryo-EM 解析了 HexaPro 的结构，分辨率为 3.2Å。通过对结构的分析，证实其保留了融合前的构象。大量地生产稳定的预融合状态 S 蛋白，可以加速针对 SARS-CoV-2 疫苗的开发和血清学诊断方法。



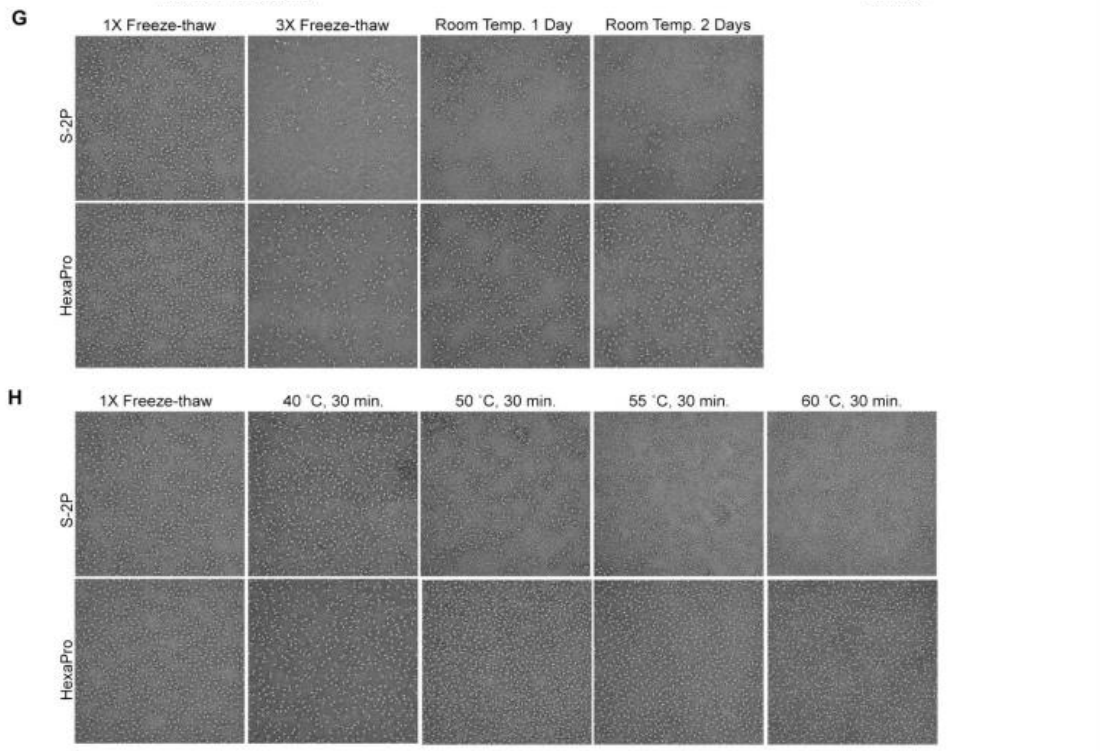


Figure 4. HexaPro exhibits enhanced expression and stability compared to S-2P. (A) SEC trace of a portion of the HexaPro purified from a 2L culture of FreeStyle 293-F cells. (B) Negative stain electron micrograph of HexaPro purified from FreeStyle 293-F cells. (C) SEC trace of HexaPro after purification from a 40 ml culture of ExpiCHO cells. (D) Negative stain electron micrograph of HexaPro purified from ExpiCHO cells. (E-F) Binding of S-2P (E) and HexaPro (F) to human ACE2 assessed by surface plasmon resonance. Binding data are shown as black lines and the best fit to a 1:1 binding model is shown as red lines. (G-H) Assessment of protein stability by negative stain electron microscopy. The top row of micrographs in (G) and (H) corresponds to S-2P, the bottom row corresponds to HexaPro.

Abstract:

The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has led to accelerated efforts to develop therapeutics, diagnostics, and vaccines to mitigate this public health emergency. A key target of these efforts is the spike (S) protein, a large trimeric class I fusion protein that is metastable and difficult to produce recombinantly in large quantities. Here, we designed and expressed over 100 structure-guided spike variants based upon a previously determined cryo-EM structure of the prefusion SARS-CoV-2 spike. Biochemical, biophysical and structural characterization of these variants identified numerous individual substitutions that increased protein yields and stability. The best variant, HexaPro, has six beneficial proline substitutions leading to ~10-fold higher expression than its parental construct and is able to withstand heat stress, storage at room temperature, and multiple freeze-thaws. A 3.2 Å-resolution cryo-EM structure of HexaPro confirmed that it retains the prefusion spike conformation. High-yield production of a stabilized prefusion spike protein will accelerate the development of vaccines and serological diagnostics for SARS-CoV-2.

24. 与 SARS-CoV-2 刺突蛋白结合的人类抗体的结构揭示了抗体的共同表位和复发特征

Structures of human antibodies bound to SARS-CoV-2 spike reveal common epitopes and recurrent features of antibodies

来源：bioRxiv

发布时间：2020-05-29

链接：https://www.biorxiv.org/content/10.1101/2020.05.28.121533v1

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DOI 或 PUBMED ID：Preprint

编译者：刘焕珍

中文摘要：

中和抗体对冠状病毒的反应主要集中在刺突蛋白三聚体上，大部分是针对受体结合域(RBD)。文中作者表征了来自 COVID-19 恢复期个体的多克隆 IgG 和 Fab，用于识别冠状病毒刺突蛋白。血浆 IgG 对 RBD 表位的关注程度，对 SARS-CoV、MERS-CoV 和轻度冠状病毒的识别程度，以及亲和力效应如何促进 IgG 在 Fab 上的结合/中和作用均有所不同。电子显微镜对多克隆血浆 Fab-spike 复合物的重建显示了对 $S1^A$ 和 RBD 表位的识别。一个中和性单克隆 Fab-S 复合物的 3.4Å 冷冻电镜结构揭示了一个表位，该表位阻碍 ACE2 受体与“向上”构象 RBD 的结合。建模表明，靶向这些位点的 IgG 在病毒上具有不同的链间交联潜能，并且不会受到已确定的 SARS-CoV-2 刺突蛋白突变的影响。这些研究从结构上定义了衍生自 *VH3-53/VH3-66* 的复发性抗 SARS-CoV-2 抗体类别，并与 SARS-CoV *VH3-30* 抗体相似，为评估疫苗诱导的抗体提供了标准。

Abstract:

Neutralizing antibody responses to coronaviruses focus on the trimeric spike, with most against the receptor-binding domain (RBD). Here we characterized polyclonal IgGs and Fabs from COVID-19 convalescent individuals for recognition of coronavirus spikes. Plasma IgGs differed in their degree of focus on RBD epitopes, recognition of SARS-CoV, MERS-CoV, and mild coronaviruses, and how avidity effects contributed to increased binding/neutralization of IgGs over Fabs. Electron microscopy reconstructions of polyclonal plasma Fab-spike complexes showed recognition of both $S1^A$ and RBD epitopes. A 3.4Å cryo-EM structure of a neutralizing monoclonal Fab-S complex revealed an epitope that blocks ACE2 receptor-binding on ”up” RBDs. Modeling suggested that IgGs targeting these sites have different potentials for interspike crosslinking on viruses and would not be greatly affected by identified SARS-CoV-2 spike mutations. These studies structurally define a recurrent anti-SARS-CoV-2 antibody class derived from *VH3-53/VH3-66* and similarity to a SARS-CoV *VH3-30* antibody, providing criteria for evaluating vaccine-elicited antibodies.

25. SARS-CoV-2 刺突蛋白的两个线性表位诱导 COVID-19 患者产生中和抗体

Two linear epitopes on the SARS-CoV-2 spike protein that elicit neutralising antibodies in COVID-19 patients

来源：nature communications

发布时间：2020-06-01

链接：https://www.nature.com/articles/s41467-020-16638-2
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通讯作者：Lisa F. P. Ng
通讯作者单位：新加坡国立大学，利物浦大学
DOI 或 PUBMED ID：https://doi.org/10.1038/s41467-020-16638-2
编译者：刘焕珍
中文摘要：
鉴于 SARS-CoV-2 流行病的持续存在，针对冠状病毒刺突糖蛋白的免疫原性靶标的鉴定将为开发敏感的诊断工具和潜在的候选疫苗靶标提供重要的依据。在这项研究中，使用重叠的线性 B 细胞肽库，作者发现了 SARS-CoV-2 刺突糖蛋白上的两个 IgG 免疫优势区域，COVID-19 康复患者的血清可以识别这些区域。值得注意的是，位于受体结合域附近的一个优势区域，对 SARS-CoV-2 具有特异性。位于融合肽处的另一个优势区域，可能作为泛 SARS 靶点发挥作用。从功能上讲，抗体耗竭分析表明，靶向这些免疫优势区域的抗体会显著改变病毒的中和能力。综上所述，这些中和的 B 细胞表位的鉴定和确认将为针对这种高优先级冠状病毒的诊断和疫苗候选的设计提供见解。
Abstract:
Given the ongoing SARS-CoV-2 pandemic, identification of immunogenic targets against the coronavirus spike glycoprotein will provide crucial advances towards the development of sensitive diagnostic tools and potential vaccine candidate targets. In this study, using pools of overlapping linear B-cell peptides, we report two IgG immunodominant regions on SARS-CoV- 2 spike glycoprotein that are recognised by sera from COVID-19 convalescent patients. Notably, one is specific to SARS-CoV-2, which is located in close proximity to the receptor binding domain. The other region, which is localised at the fusion peptide, could potentially function as a pan-SARS target. Functionally, antibody depletion assays demonstrate that antibodies targeting these immunodominant regions significantly alter virus neutralization capacities. Taken together, identification and validation of these neutralising B-cell epitopes will provide insights towards the design of diagnostics and vaccine candidates against this high priority coronavirus.

26. 深入研究 SARS-Cov-2 聚合酶复合物：识别新的变构位点并对氢键网络和相关动力学性质进行分析

A Deep Dive into the SARS-Cov-2 Polymerase Assembly: Identifying Novel Allosteric Sites and Analyzing the Hydrogen Bond Networks and Correlated Dynamics
来源：bioRxiv
发布时间：2020-06-03
链接：https://www.biorxiv.org/content/10.1101/2020.06.02.130849v1
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通讯作者单位：Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada.
DOI 或 PUBMED ID：

编译者：宋珂

中文摘要：

基因复制是 SARS-CoV-2 病毒生命周期中的重要环节。近期的研究已证明，抑制 SARS-CoV-2 复制酶功能是对抗病毒的一种有希望的手段。然而，还有与 SARS-CoV-2 聚合酶的结构、功能和动力学性质相关的一些问题仍需要解决。其中包括：了解聚合酶各亚结构域的动态特性；在水环境中分析活性位点和 RNA 模板入口处的氢键网络；研究核苷酸在活性位点上的结合方式；在新生成的 RNA 链的不同核苷酸上标注出核苷酸可能发生取代的位置；发现聚合酶结构内可能的变构位点，并研究它们与催化位点相关的动力学性质。本文中，通过将各种先进的模拟工具与近期解析的 SARS-CoV-2 聚合酶 cryo-EM 结构相结合，填补了相关知识的空白。作者详细分析了聚合酶各部分的氢键网络，并提出了可能被聚合酶复合物接受的核苷酸上的取代位置。作者还在 nsp12 RdRp 中发现了 3 个可以被小分子抑制剂靶向的变构位点。进一步的相关运动分析表明，其中 1 个新识别的变构位点的动态性质与活性位点相关，说明靶向该位点可显著影响 SARS-CoV-2 聚合酶的催化活性。

Abstract:

Replication of the SARS-CoV-2 genome is a fundamental step in the virus life cycle and inhibiting the SARS-CoV2 replicase machinery has been proven recently as a promising approach in combating the virus. Despite this recent success, there are still several aspects related to the structure, function and dynamics of the CoV-2 polymerase that still need to be addressed. This includes understanding the dynamicity of the various polymerase subdomains, analyzing the hydrogen bond networks at the active site and at the template entry in the presence of water, studying the binding modes of the nucleotides at the active site, highlighting positions for acceptable nucleotides substitutions that can be tolerated at different positions within the nascent RNA strand, identifying possible allosteric sites within the polymerase structure and studying their correlated dynamics relative to the catalytic site. Here, we combined various cutting-edge modelling tools with the recently resolved SARS-CoV-2 cryo-EM polymerase structures to fill this gap in knowledge. Our findings provide a detailed analysis of the hydrogen bond networks at various parts of the polymerase structure and suggest possible nucleotides substitutions that can be tolerated by the polymerase complex. We also report here three druggable allosteric sites within the nsp12 RdRp that can be targeted by small molecule inhibitors. Our correlated motion analysis shows that the dynamics within one of the newly identified sites are linked to the active site, indicating that targeting this site can significantly impact the catalytic activity of the SARS-CoV-2 polymerase.

27. 一个具有潜在治疗能力的 SARS-CoV-2 和 SARS-CoV 抗体的中和能力的结构基础

Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody

中国医学科学院和生物物理所等单位的研究人员用 cryo-EM 解析了一个人源化单克隆的 SARS-COV-2 和 SARS-COV 的中和性抗体 H014 的 Fab 片段和 SARS-CoV-2 S 蛋白三聚体的结构。该结构分析揭示了一个只有当 RBD 处于开放状态时的构象表位。

链接：https://www.biorxiv.org/content/10.1101/2020.06.02.129098v1

28. 一个在 COVID-19 病人中天然发生的在 S 蛋白 S1/S2 切割位点附近发生缺失突变的 SARS-CoV-2 病毒准种

Naturally occurring SARS-CoV-2 gene deletions close to the spike S1/S2 cleavage site in the viral quasispecies of COVID19 patients

西班牙 VHIR 研究所的研究者们对他们急症室来就诊的 10 个轻中度症状以及 8 个重症 COVID-19 病人来源的 SARS-CoV-2 病毒进行测序，发现了一个在 S 蛋白的 S1/S2 切割位点附近出现了一个中止密码子突变。带有这个突变以较少的比例（2.2%）存在于病人中，其中轻中度症状病人都有这个突变，而只有一半重症病人体内有这个突变病毒。作者们猜想这个突变可能让病人体内有一定的游离 S1 可以对病毒的结合起到竞争 ACE2 的作用，这也许是病毒的一种减轻病症严重程度同时保存传染性的策略（不要烧掉房子的生存策略）。

文章链接：https://www.biorxiv.org/content/10.1101/2020.06.03.129585v1

29. 欧洲生物信息研究所的 COVID-19 数据门户

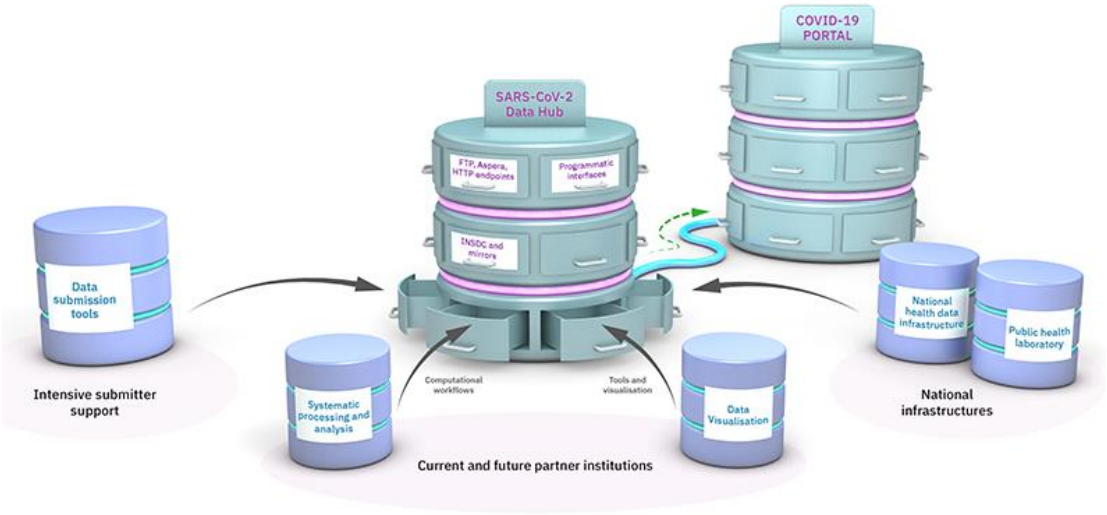
EBI COVID-19 portal

链接：https://www.covid19dataportal.org/expression?db=atlas-sc#search-content

中文摘要：从 2020 年 4 月开始，EBI 欧洲生物信息研究所上线了 COVID-19 portal，一个包括了 COVID-19 相关的病毒序列，基因表达数据，蛋白质和结构、药物分子以及文献的可视化平台。

下图展示了该可视化平台和背后的数据库以及其他数据工具之间的关系。

其中基因表达调控数据对 COVID-19 相关 RNA-SEQ 数据以及单细胞测序数据做了分析结果的图形化展示。



30. NIH 需要努力应付仓促从美国国会获得的 36 亿美元计的 COVID-19 疫情相关研究经费

NIH grapples with rush to claim billions in pandemic research funds

6 月 3 日的 Science 期刊报告了美国 NIH 从国会获得了 36 亿美元 COVID-19 研究经费。该文讨论了 NIH 面临该怎么在短期内把这巨量的科研经费投放给研究组，以及面临如何把关申请研究项目的质量等困难。

A flood of pandemic funding

Congress has provided $3.6 billion to the National Institutes of Health for a variety of pandemic-related programs.

	Amount	Purpose
National Institute of Allergy and Infectious Diseases	$1.53 billion	Basic research, drugs and vaccines
Office of Director	1.03 billion	Rapid testing
National Institute of Biomedical Imaging and Bioengineering	560 million	Rapid testing
National Cancer Institute	306 million	Serological testing
National Heart, Lung, and Blood Institute	103 million	Therapeutics and longitudinal studies
National Center for Advancing Translational Sciences	36 million	Drug screening
National Institute of Environmental Health Sciences	10 million	Worker safety
National Library of Medicine	10 million	Research resources

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

31. **根据 science 的报告，以一家数据公司提供的 COVID-19 数据为基础发表在柳叶刀和新英格兰医学杂志上的研究数据不可靠**

https://www.sciencemag.org/news/2020/06/mysterious-company-s-coronavirus-papers-top-medical-journals-may-be-unraveling

具体解读可以参考赛先生的公众号文章：学界丑闻，神秘公司如何炮制氯喹试验结果戏耍顶级机构

https://mp.weixin.qq.com/s/R7LVanQ-yx01KYJVITiGeQ