新型冠状病毒信息简报

第 57 期（2020 年 6 月 6-6 月 12 日周报）

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

联系人：蒋立春 jianglch@shanghaitech.edu.cn

内容介绍

分类	标题名称
疫情播报	1. 2020 年 6 月 11 日疫情
流行病学	2. 中国人群中 SARS-CoV-2 的 IgM 和 IgG 抗体的血清流行情况
疾病检测	3. 血清学证实 PCR 阴性儿童的 SARS-CoV-2 感染表现为儿科炎症多系统综合征 4. 截至 6 月 12 日国家药监局已批准 42 个新型冠状病毒检测产品 5. 日本对废水和河水中 SARS-CoV-2 RNA 的首次环境监测 6. 一种新颖的细胞内 ELISA 测定法可对 SARS-CoV-2 进行快速，自动的定量，以分析中和抗体和抗病毒化合物 7. 基于超灵敏纳米酶的化学发光试纸法快速诊断 SARS-CoV-2 型肺炎 8. 侦察狗可以通过嗅腋窝下的汗液样品识别 COVID-19 病人 9. 正在涌现的针对中和抗体检测的血清学测试 10. 一种基于 CRISPR-Cas12a 构建的更加灵敏的 SARS-CoV-2 的检测方法 11. 在诊断样品中检测到 SARS-CoV-2 的基因组和亚基因组 RNA 不是病毒活跃复制的指标 12. 鼻咽中 CXCL10 水平升高可以帮助检测没有诊断出来的 COVID-19，可以加强检测能力
疾病病理	13. SARS-CoV-2 免疫应答的性别差异 14. 重症 COVID-19 急性至恢复期的系统性免疫监测 15. IL-2/IL-2R 抑制可通过 JAK1-STAT5 导致 COVID-19 肺炎重症患者 CD8+的 T 细胞和淋巴细胞减少 16. 在 COVID-19 患者中 SARS-CoV-2 经嗅粘膜入侵作为进入中枢神经系统的通道 17. COVID-19 患者快速产生中和抗体反应 18. 抑制性髓样细胞是重症 COVID-19 的一个标志 19. COVID-19 病人中一个共同的免疫信号合并免疫保护败血症样特征和不良预后相关
疫苗研发	20. 针对 SARS-CoV-2 具有有效保护作用的灭活候选疫苗 BBIBP-CorV 的开发 21. Moderna 的 mRNA 疫苗 mRNA-1273 计划于 7 月开始和 NIAID 合作开展三期临床试验。
药物研发	22. 胆固醇-25-羟化酶　通过抑制膜融合抑制 SARS-CoV-2 的复制 23. 体外实验证明肺细胞中的 ZAP 蛋白可以抑制 SARS-CoV-2
抗体研发	24. 来自康复期患者抗体库的针对 SARS-CoV-2 和 RBD 突变的交叉中和抗体 25. 合成抗体可中和哺乳动物细胞的 SARS-CoV-2 感染

	26. 选自大流行前健康供体的 SARS-CoV-2 中和人重组抗体能在 RBD-ACE2 界面处结合
临床试验	27. 托珠单抗用于 COVID-19 肺炎患者——TOCIVID-19 的 2 期试验 28. Jak1/2 的抑制剂芦可替尼对发生严重系统性超炎反应的 COVID-19 病人的作用 29. 抑制 BTK 来治疗 COVID-19 重症病人 30. 丹麦全国性的研究表明非甾醇类抗炎药物没有影响 SARS-CoV-2 30 天主要临床情况的发生
基础研究	31. 因氢键网络和疏水相互作用增强了 SARS-CoV-2 与受体的结合能力 32. 恢复期血浆中抗 Spike 蛋白抗体滴度与 SARS-CoV-2 体外病毒中和的关系 33. SARS-CoV-2 导致急性感染而引起肺部细胞和炎症流动态变化情况，在各种非人灵长类动物中不相同 34. 猫传腹药物 GC376 抑制 SARS-CoV-2 的结构基础 35. 用假病毒以及嵌合病毒测试 SARS-COV-2 中和抗体活性 36. SARS-CoV-2 蛋白酶可以切割宿主免疫调节相关因子 37. 人诱导性多能干细胞分化的肺泡和气道上皮细胞可以在空气和液体界面进行培养，而且可以表达 SRAS-CoV-2 的宿主因子 38. neuropilin-1 (NRP1)参与了 SARS-COV-2 侵袭中枢神经系统 39. 一个最常用的用来构建针对 SARS-COV-2 的 RBD 的抗体的免疫球蛋白重链可变区 IGHV-53 的结构解析
动物模型	40. 构建一个可以广泛用于 COVID-19 疫苗和药物开发的小鼠模型
资源介绍	41. OpenData：一个实时共享有关 COVID-19 老药新用数据的门户网站

1. 2020 年 6 月 11 日疫情

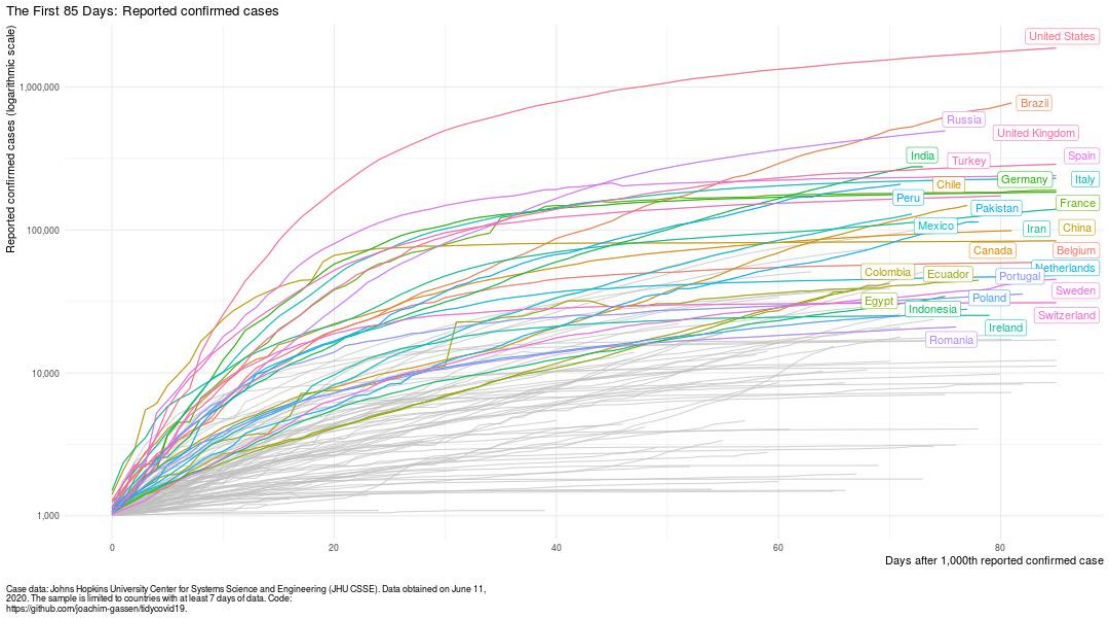
数据来源：WHO

发布时间：2020 年 6 月 11 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 11 日全球累计确诊新型冠状病毒病人 7273958 例，当日新增确诊 128419 例，累计死亡 413372 例，当日新增死亡 5347。

中国累计确诊 84652 例，累计死亡 4645 例，当日新增确诊 11 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 11 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11日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 中国人群中 SARS-CoV-2 的 IgM 和 IgG 抗体的血清流行情况

Seroprevalence of immunoglobulin M and G antibodies against SARS-CoV-2 in China

来源：Nature Medicine
发布时间：2020-06-05
链接：https://www.nature.com/articles/s41591-020-0949-6

第一作者：Xin Xu,
通讯作者：黄爱龙、杨正林、张康、侯凡凡
通讯作者单位：重庆医科大学、四川省人民医院、澳门科技大学、广州再生医学与健康广东实验室

DOI 或 PUBMED ID：https://doi.org/10.1038/s41591-020-0949-6

编译者：张丽双

中文摘要：

检测无症状或亚临床的新型人冠状病毒 SARS-CoV-2 感染对于了解 COVID-19 的总体流行率和感染潜力至关重要。为了估计 SARS-CoV-2 在中国的累积感染率，我们评估了在 2020 年 3 月 9 日至 2020 年 4 月 10 日期间,在武汉市(中国 COVID-19 大流行病的震中)和中国其他地理区域的 17368 人的 IgM 和 IgG 宿主血清学反应。武汉市不同亚群血清阳性率在 3.2%～3.8%之间。随着距震中距离的增加，其他城市的血清阳性率逐渐降低。到医院进行维持性血液透析的患者和医护人员的血清阳性率也较高，分别为 3.3%（1542 例中的 51 例，2.5-4.3%，95%可信区间）和 1.8%（4384 例中的 81 例，1.5-2.3%，95%可信区间）。需要进行更多的研究，以确定这些结果是否可推广到其他人群和地理位置,以及确定血清阳性率在多大程度上随着 COVID-19 大流行的进展而增加。血清学监测有可能为这种新型 SARS-CoV-2 的第一波感染提供更可靠的累积病毒感染率。

Abstract:

Detection of asymptomatic or subclinical novel human coronavirus SARS-CoV-2 infection is critical for understanding the overall prevalence and infection potential of COVID-19. To estimate the cumulative prevalence of SARS-CoV-2 infection in China, we evaluated the host serologic response, measured by the levels of immunoglobulins M and G in 17,368 individuals, in the city of Wuhan, the epicenter of the COVID-19 pandemic in China, and geographic regions in the country, during the period from 9 March 2020 to 10 April 2020. In our cohorts, the seropositivity in Wuhan varied between 3.2% and 3.8% in different subcohorts. Seroposivity progressively decreased in other cities as the distance to the epicenter increased. Patients who visited a hospital for maintenance hemodialysis and healthcare workers also had a higher seroprevalence of 3.3% (51 of 1,542, 2.5–4.3%, 95% confidence interval (CI)) and 1.8% (81 of 4,384, 1.5–2.3%, 95% CI), respectively. More studies are needed to determine whether these results are generalizable to other populations and geographic locations, as well as to determine at what rate seroprevalence is increasing with the progress of the COVID-19 pandemic. Serologic surveillance has the potential to provide a more faithful cumulative viral attack rate for the first season of this novel SARS-CoV-2 infection.

3. 血清学证实 PCR 阴性儿童的 SARS-CoV-2 感染表现为儿科炎症多系统综合征

Serology confirms SARS-CoV-2 infection in PCR-negative children presenting with Paediatric Inflammatory Multi-System Syndrome

来源：medRxiv
发布时间：2020-06-07
链接：https://www.medrxiv.org/content/10.1101/2020.06.05.20123117v1

第一作者：Marisol Perez-Toledo, Sian E. Faustini, Sian E. Jossi
通讯作者：Barnaby R Scholefield, Adam F. Cunningham, Alex G. Richter
通讯作者单位：伯明翰大学

DOI 或 PUBMED ID：

编译者：宋张悦

中文摘要：

背景：在 COVID-19 爆发期间，已有报告显示儿童表现出与川崎病和中毒性休克综合征重叠的多系统炎症综合征特征——儿科炎症多系统综合征——与 SARS-CoV-2 大流行暂时相关（PIMS-TS）。最初的报道发现，许多儿童的 SARS-CoV-2 呈 PCR 阴性，因此很难确定该综合征是否是病毒感染一个年龄组的晚期并发症，在很大程度上避免了这种感染的最坏后果，或者该综合征是否反映了加强的监测。

方法：在 2020 年 4 月 28 日至 5 月 8 日期间，因与 PIMS-TS 症状一致而住院的儿童，以及 SARS-CoV-2 PCR 阴性的儿童，采用 ELISA 方法检测病毒刺突糖蛋白抗体。

结果：8 名患者（年龄 7-14 岁，63%为男性）在研究期间完成了 PIMS-TS 的病例定义。8 名患者中有 6 名需要接受重症监护。所有患者对病毒刺突糖蛋白均表现出显著的 IgG 和 IgA 反应。进一步评估显示，在 PIMS-TS 患儿中检测到的 IgG 亚型属于 IgG1 和 IgG3 亚类，其分布与在 COVID-19 成年住院患者样本中观察到的分布类似。相比之下，IgG2 和 IgG4 在儿童和成人中均未检测到。在儿童中未检测到 IgM，这与成年住院 COVID-19 患者的 IgM 均为阳性形成对比。

结论：**在 PCR 阴性的 PIMS-TS 患儿中可以检测到强烈的 IgG 抗体反应。**这些患者 IgM 的低检出率与几周前发生感染相符，且在控制了 SARS-CoV-2 病毒载量后，该综合征的发病率较高，这意味着该综合病主要是免疫介导的。最后，这表明血清学在选定的患者群体中，可以作为一个适当的诊断工具。

Abstract:

Background. During the COVID-19 outbreak, reports have surfaced of children who present with features of a multisystem inflammatory syndrome with overlapping features of Kawasaki disease and toxic shock syndrome - Paediatric Inflammatory Multisystem Syndrome- temporally associated with SARS-CoV-2 pandemic (PIMS-TS). Initial reports find that many of the children are PCR-negative for SARS-CoV-2, so it is difficult to confirm whether this syndrome is a late complication of viral infection in an age group largely spared the worst consequences of this infection, or if this syndrome reflects enhanced surveillance.

Methods. Children hospitalised for symptoms consistent with PIMS-TS between 28 April and 8 May 2020, and who were PCR-negative for SARS-CoV-2, were tested for antibodies to viral spike glycoprotein using an ELISA test.

Results. Eight patients (age range 7-14 years, 63% male) fulfilled case-definition for PIMS-TS during the study period. Six of the eight patients required

admission to intensive care. All patients exhibited significant IgG and IgA responses to viral spike glycoprotein. Further assessment showed that the IgG isotypes detected in children with PIMS-TS were of the IgG1 and IgG3 subclasses, a distribution similar to that observed in samples from hospitalised adult COVID-19 patients. In contrast, IgG2 and IgG4 were not detected in children or adults. IgM was not detected in children, which contrasts with adult hospitalised adult COVID-19 patients of whom all had positive IgM responses.
Conclusions. Strong IgG antibody responses can be detected in PCR-negative children with PIMS-TS. The low detection rate of IgM in these patients is consistent with infection having occurred weeks previously and that the syndrome onset occurs well after the control of SARS-CoV-2 viral load. This implies that the disease is largely immune-mediated. Lastly, this indicates that serology can be an appropriate diagnostic tool in select patient groups.

4. 截至 6 月 12 日国家药监局已批准 42 个新型冠状病毒检测产品

来源链接：http://www.nmpa.gov.cn/WS04/CL2583/
截至 2020 年 6 月 12 日，国家药监局已批准 42 个新型冠状病毒检测产品，其中新冠病毒核酸检测试剂 22 个，抗体检测试剂 20 个。详见参考文件：“国家药监局新型冠状病毒检测试剂注册信息_20200612.xlsx”。

5. 日本对废水和河水中 SARS-CoV-2 RNA 的首次环境监测

First environmental surveillance for the presence of SARS-CoV-2 RNA in wastewater and river water in Japan
链接: https://www.medrxiv.org/content/10.1101/2020.06.04.20122747v1
来自日本的研究团队的文章表明，在日本山梨县的废水中检测到 SARS-CoV-2 RNA（2.4 × 103 copies/L）。

6. 一种新颖的细胞内 ELISA 测定法可对 SARS-CoV-2 进行快速，自动的定量，以分析中和抗体和抗病毒化合物

A novel in-cell ELISA assay allows rapid and automated quantification of SARS-CoV-2 to analyse neutralizing antibodies and antiviral compounds

来源：bioRxiv
发布时间：2020-06-05
链接：https://www.biorxiv.org/content/10.1101/2020.06.05.135806v1
第一作者：Lara Schöler, Vu Thuy Khanh Le-Trilling
通讯作者：Mirko Trilling
通讯作者单位：University Hospital Essen, University of Duisburg-Essen, Essen, Germany
DOI 或 PUBMED ID：
编译者：张鹏伟
中文摘要：
由严重急性呼吸综合征冠状病毒 2（SARS-CoV-2）引起的 2019 年冠状病毒病（COVID-19）是目前最紧迫的医学和社会经济挑战。病毒中和抗体（NAbs）的测定是恢复期血浆筛选、候

选疫苗评价和免疫证明必不可少的，是保护的重要环节。与标准血清学 Elisa 相比，血小板减少中和试验（PRNTs）费时费力，费用昂贵，且仅限于专业实验室。为了用一种新的不受基因修饰病毒干扰的检测方法取代基于显微镜计数的 SARS-CoV-2 PRNTs，我们建立了一种简单、快速、自动化的 SARS-CoV-2 中和检测方法，该方法采用细胞内 ELISA（icELISA）方法。

通过对病毒特异性抗体、细胞株、病毒剂量、感染时间等参数的优化，SARS-CoV-2 感染细胞可作为定量 icELISA 的直接抗原源。利用市售的核衣壳蛋白特异性抗体，icELISA 可以很容易地在人和高度许可的 Vero E6 细胞中定量检测病毒感染。抗病毒药物，如含有 NAbs 或干扰素的人血清，剂量依赖性地降低 SARS-CoV-2 特异性信号。增加感染剂量后，icNT 对高中和能力和中等中和能力的恢复期血清的鉴别优于 PRNT。

SARS-CoV-2 icElisa 试验允许在细胞培养中使用大多数常规诊断部门提供的试剂和设备，快速（总共<48h，以秒为单位读出）和自动定量病毒感染，以评估 NAbs 和抗病毒药物的疗效。我们建议将 icELISA 和 icNT 用于 COVID-19 的研究和诊断。

Abstract:

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently the most pressing medical and socioeconomic challenge. Constituting important correlates of protection, determination of virus-neutralizing antibodies (NAbs) is indispensable for convalescent plasma selection, vaccine candidate evaluation, and immunity certificates. In contrast to standard serology ELISAs, plaque reduction neutralization tests (PRNTs) are laborious, time-consuming, expensive, and restricted to specialized laboratories. To replace microscopic counting-based SARS-CoV-2 PRNTs by a novel assay exempt from genetically modified viruses, which are inapplicable in most diagnostics departments, we established a simple, rapid, and automated SARS-CoV-2 neutralization assay employing an in-cell ELISA (icELISA) approach.

After optimization of various parameters such as virus-specific antibodies, cell lines, virus doses, and duration of infection, SARS-CoV-2-infected cells became amenable as direct antigen source for quantitative icELISA. Using commercially available nucleocapsid protein-specific antibodies, viral infection could easily be quantified in human and highly permissive Vero E6 cells by icELISA. Antiviral agents such as human sera containing NAbs or antiviral interferons dose-dependently reduced the SARS-CoV-2-specific signal. Applying increased infectious doses, the icNT was superior to PRNT in discriminating convalescent sera with high from those with intermediate neutralizing capacities.

The SARS-CoV-2 icELISA test allows rapid (<48h in total, read-out in seconds) and automated quantification of virus infection in cell culture to evaluate the efficacy of NAbs as well as antiviral drugs, using reagents and equipment present in most routine diagnostics departments. We propose the icELISA and the icNT for COVID-19 research and diagnostics.

7. 基于超灵敏纳米酶的化学发光试纸法快速诊断 SARS-CoV-2 型肺炎

Ultra-sensitive nanozyme-based chemiluminescence paper test for rapid diagnosis of SARS-CoV-2 infection

来源：bioRxiv
发布时间：2020-06-05
链接：https://www.biorxiv.org/content/10.1101/2020.06.05.131748v1
第一作者：Dan Liu, Chenhui Ju, Chao Han
通讯作者：Xiyun Yan
通讯作者单位：中国生物物理研究所纳米酶工程实验室中国北京
DOI 或 PUBMED ID：preprint
编译者：孔娟
中文摘要：
COVID-19 已经严重威胁全球公共卫生安全，早期发现对其有效控制至关重要。目前的诊断方法核酸检测复杂、设备有限且耗时，抗体检测可能导致较高的假阴性率，尤其是在病毒感染的早期阶段。因此，迫切需要对早期 COVID-19 诊断和全人群筛查进行更快速和可靠的检测。文中研究者开发了一种新型的基于纳米酶的化学发光试纸检测方法，用于快速和高灵敏度检测 SARS-CoV-2 刺突蛋白。论文中使用了一种新建立的模拟过氧化物酶的钴铁血红素纳米酶，它优于传统的试纸法和基于辣根过氧化物酶的免疫测定法。研究者利用重组表达的 SARS-CoV-2 S-RBD 抗原进行纳米酶化学发光试纸的灵敏度检测，结果显示此方法检测灵敏度低至 0.1 纳克/毫升。此外，此基于纳米酶的化学发光检测方法线性范围比 ELISA 宽 32 倍。并且与 ELISA 或核酸检测所需的 1-2 小时相比，检测在 16 分钟内完成。并能够使用智能手机摄像头进行信号检测。与传统方法相比此方法具有检测试剂成分简单易得，成本低。总之，此研究提供了一种高灵敏度的、用于检测传染性非典型肺炎-CoV-2 抗原的现场检测(POCT)方法，这将极大地提高目前对疑似感染的早期筛查能力，并大大降低对国家卫生保健资源的需求。

Abstract:
The recently emerged coronavirus disease COVID-19 has now evolved into a global pandemic. Early detection is crucial for its effective control. Nucleic acid testing for viral pathogen and serological testing for host antibodies are playing important roles in current COVID-19 diagnosis. However, while nucleic acid testing is complicated, facility-restricted and time-consuming, antibody testing may result in high rates of false-negative diagnoses, especially during the early stages of viral infection. Thus, a more rapid and reliable test for both early COVID-19 diagnosis and whole-population screening is urgently needed. Here, we developed a novel nanozyme-based chemiluminescence paper assay for rapid and high-sensitive testing of SARS-CoV-2 spike antigen. Our paper test uses a newly established peroxidase-mimic Co-Fe@hemin nanozyme instead of natural HRP that catalytically amplifies the chemiluminescent signal, allowing for target concentrations to be as low as 0.1 ng/ml. Furthermore, our nanozyme-based chemiluminescence test exhibits a linear range that is 32-fold wider compared to ELISA tests. Importantly, testing is completed in less than 16 min, compared to 1-2 h required for ELISA or nucleic acid tests. Critically, signal detection is feasible using a smartphone camera. Ingredients for our test are simple and readily available, rendering overall cost considerably lower than those used in current diagnoses. In conclusion, our novel test provides a high-sensitive, point-of-care testing (POCT) approach for SARS-CoV-2 antigen detection, which should greatly increase current early screening capacities for suspected

infections, and considerably lower demand for national healthcare resources.

8. 侦察狗可以通过嗅腋窝下的汗液样品识别 COVID-19 病人，一项验证性测试

Detection dogs as a help in the detection of COVID-19 Can the dog alert on COVID-19 positive persons by sniffing axillary sweat samples ? Proof-of-concept study

https://www.biorxiv.org/content/10.1101/2020.06.03.132134v1

9. 正在涌现的针对中和抗体检测的血清学测试

Emerging COVID-19 serology tests aim for neutralizing antibodies

根据 Biocentury 6 月 12 的报道，下一波的血清学检测将会针对性检测中和抗体。该报道讲到目前大多数的策略还是基于 S 蛋白的 RBD 的抗体，虽然这样的不一定 100%具备中和能力。报道特别提到了我们简报之前提到的新加坡-杜克大学的王林发教授发明的一个测试方法的原理—反向的看 ACE2 和 S 蛋白的结合因为被中和而照成信号消失。该方法被授权给金斯瑞。

链接：

https://www.biocentury.com/article/305429?editionId=ckbbn9y8o0ww30174kt53f84q&editionType=daily

The next wave of serology tests from big diagnostic players could get closer to telling people whether they are protected from COVID-19 by homing in on the antibodies most likely to block viral entry into cells. The new entrants highlight how far industry remains from defining ideal tests for COVID-19 exposure and immunity.

…

But two other diagnostic giants, Siemens Healthineers AG (Xetra:SHL) and the Beckman Coulter unit of Danaher Corp. (NYSE:DHR), think their new tests will be more predictive of protective immunity because they detect antibodies against the receptor binding domain (RBD) of the virus' spike protein, which is thought to be key to viral entry into cells (see "Insights from Spike Protein Structure").

…

While most serology tests detect antibodies by looking for the presence of a color or fluorescent signal, GenScript's test looks for its absence.

The lab-based immunoassay involves coating the bottom of a plate with ACE2 protein, flowing through patient sera, and then exposing the plate to a labeled version of the spike protein RBD. If a patient's antibodies blocked the interaction between ACE2 and the RBD, the label will not be detected.

10. 一种基于 CRISPR-Cas12a 构建的更加灵敏的 SARS-CoV-2 的检测方法

A CRISPR-Cas12a-based specific enhancer for more sensitive detection of SARS-CoV-2 infection

https://www.medrxiv.org/content/10.1101/2020.06.02.20119735v1

11. 在诊断样品中检测到 SARS-CoV-2 的基因组和亚基因组 RNA 不是病毒活跃复制的指标

SARS-CoV-2 genomic and subgenomic RNAs in diagnostic samples are not an indicator of active replication
https://www.medrxiv.org/content/10.1101/2020.06.01.20119750v1

12. 鼻咽中 CXCL10 水平升高可以帮助检测没有诊断出来的 COVID-19，可以扩大检测能力

Host response-based screening to identify undiagnosed cases of COVID-19 and expand testing capacity
https://www.medrxiv.org/content/10.1101/2020.06.04.20109306v1

13. SARS-CoV-2 免疫应答的性别差异

Sex differences in immune responses to SARS-CoV-2 that underlie disease outcomes
来源：medrxiv
发布时间：2020-06-09
链接：https://www.medrxiv.org/content/10.1101/2020.06.06.20123414v1
第一作者：Takehiro Takahashi, Patrick Wong
通讯作者：Akiko Iwasaki
通讯作者单位：Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520
Howard Hughes Medical Institute, Chevy Chase, MD 20815
DOI 或 PUBMED ID：
编译者：王玮
中文摘要：
越来越多的证据表明 COVID-19 临床结果存在性别差异。 然而，对 SARS-CoV-2 的免疫反应是否有性别差异，以及这种差异能否解释男性对 COVID-19 的易感性，目前依然未知。该研究检测和比较了不同性别的患者的病毒载量，SARS-CoV-2 特异性抗体滴度、血浆细胞因子和血细胞表型。该研究将分析重点放在那些没有接受免疫调节药物治疗的中轻度患者，结果显示男性患者具有更高的血浆天然免疫细胞因子和趋化因子水平，包括 IL-8、IL-18 和 CCL5，会伴随着非经典单核细胞的更强大的激活。相反，女性患者 SARS-CoV-2 感染期间，T 细胞活性显著高于男性患者感染，老年患者亦然。该研究发现一个不良的 T 细胞反应与患者年龄呈负相关，可预测男性患者病情恶化，但女性患者没有。相反，女性患者体内天然免疫细胞因子水平较高与病情恶化相关，但男性患者没有。这些发现揭示 COVID-19 中观察到的性别差异的可能解释，并为发展以性别为基础的 COVID-19 治疗和护理方法提供了重要基础。

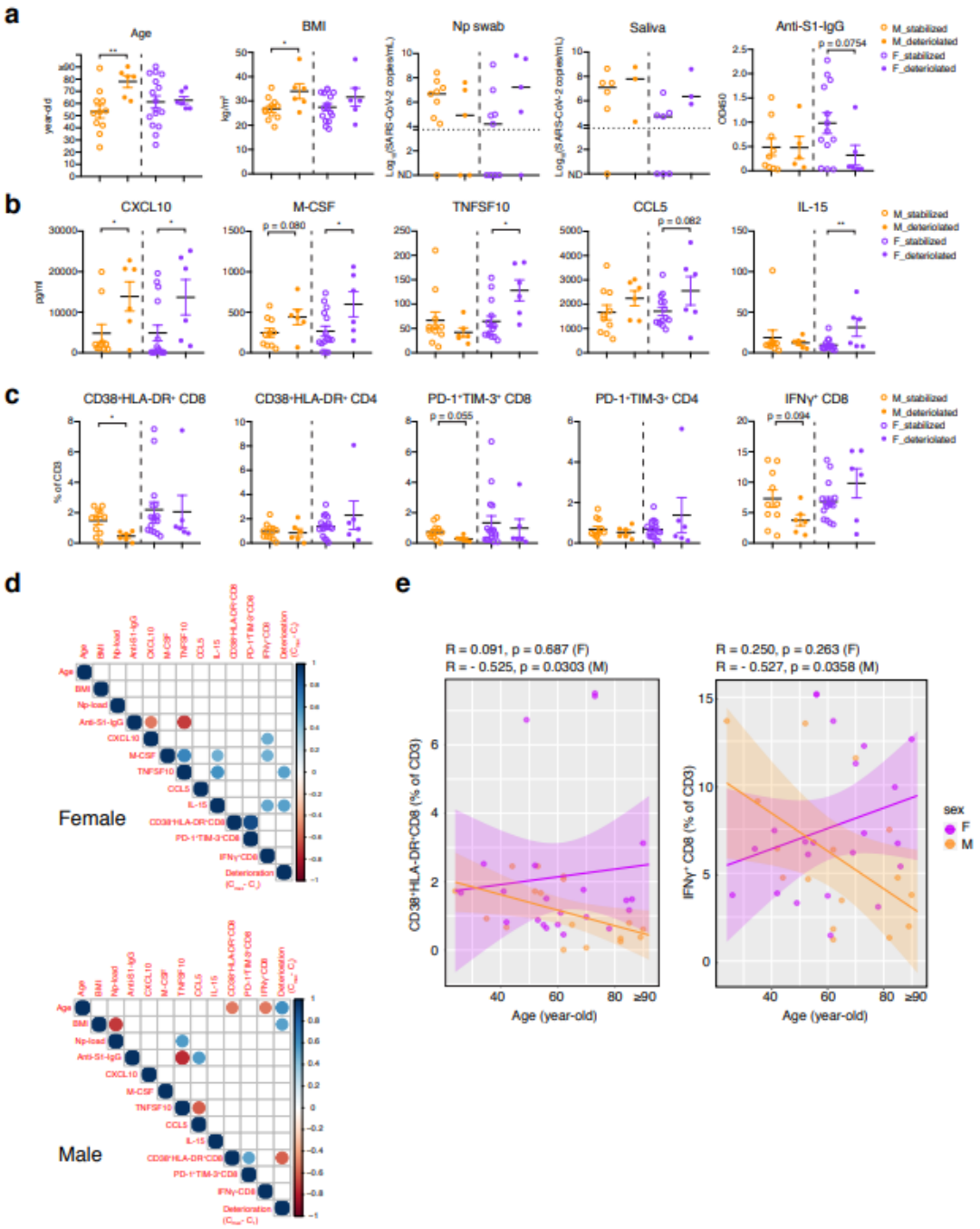


Fig. 4 Differential immune phenotypes related to COVID-19 disease progression between sexes. Patients in Cohort A are divided into stabilized group and deteriorated group, depending on the comparison between maximum clinical score after sampling and the score at the sampling (M_stablized ; M_deteriorated : F_stablized : F_aggravated= 11:6:16:6). **a,** The differences in the patients' age, BMI, nasopharyngeal/saliva virus RNA copies, and anti-S1-IgG antibody are compared. For virus concentration panels, dotted lines indicate the detection limit, and median values are indicated for each group. **b,** Cytokine/chemokine comparison between stabilized and deteriorated group. **c,** Proportions of activated (CD38+HLA-DR+) and terminally differentiated (PD-1+TIM-3+) CD4/CD8 T cells, and IFNγ+CD8 T cells in CD3-positive T cells are shown. **d,** Pearson correlation heatmaps of the indicated parameters are shown for each sex. For viral load levels and cytokine/chemokine levels, log-transformed values were used for the calculation of the correlations. The size and color of the circles indicate the correlation coefficient (R), and only statistically significant correlations ($p < 0.05$) are shown. Clinical deterioration from the first time point is scored by C_{max}- C_1. **e,** Correlation between age and CD38+HLA-DR+ CD8 T cells (left) and IFNγ+CD8 T cells (right, both in % of CD3 T cells). Linear regression lines and 95% confidence intervals are shown. Pearson correlation coefficient (R) and p-values for each correlation and for each sex are shown on top of each plot. Data are mean ± SEM and unpaired t-test was used to compare the differences between stabilized group and deteriorated group about each sex in **a, b, c**. For the age panel in **a** and correlation plots for age and T cells (**e**), data points for individuals ≥ 90-year-old are plotted as 90-year-old. *P < 0.05, **P < 0.01. All p-values < 0.10 are shown in the panels.

Abstract:
A growing body of evidence indicates sex differences in the clinical outcomes of coronavirus disease 2019 (COVID-19). However, whether immune responses against SARS-CoV-2 differ between sexes, and whether such differences explain male susceptibility to COVID-19, is currently unknown. In this study, we examined sex differences in viral loads, SARS-CoV-2-specific antibody titers, plasma cytokines, as well as blood cell phenotyping in COVID-19 patients. By focusing our analysis on patients with mild to moderate disease who had not received immunomodulatory medications, our results revealed that male patients had higher plasma levels of innate immune cytokines and chemokines including IL-8, IL-18, and CCL5, along with more robust induction of non-classical monocytes. In contrast, female patients mounted significantly more robust T cell activation than male patients during SARS-CoV-2 infection, which was sustained in old age. Importantly, we found that a poor T cell response negatively correlated with patients' age and was predictive of worse disease outcome in male patients, but not in female patients. Conversely, higher innate immune cytokines in female patients associated with worse disease progression, but not in male patients. These findings reveal a possible explanation underlying observed sex biases in COVID-19, and provide important basis for the development of sex-based approach to the treatment and care of men and women with COVID-19.

14. 重症 COVID-19 急性至恢复期的系统性免疫监测

Systems-level immunomonitoring from acute to recovery phase of severe COVID-19

来源：medrxiv
发布时间：2020.06.07
文章链接：https://www.medrxiv.org/content/10.1101/2020.06.03.20121582v2
第一作者：Lucie Rodriguez, Pirkka Pekkarinen, Lakshmi Kanth Tadepally, Ziyang Tan, Camila Rosat Consiglio, Petter Brodin
通讯作者：Petter Brodin
通讯作者单位：瑞典卡罗林斯卡医学院妇女和儿童健康生命科学实验室，瑞典卡罗林斯卡大学医院儿科风湿病科
DOI： https://doi.org/10.1101/2020.06.03.20121582
编译者：张怡
中文摘要：
对 SARS-CoV2 的免疫反应正在深入研究中，但目前还没有完全了解。严重疾病的特征是肺内强烈的炎症反应，常在病情稳定 5-7 天后突然发作。调节这种过度炎症和相关的急性呼吸窘迫综合征的努力，依赖于阐明免疫细胞的相互作用和细胞因子驱动这样的反应。系统层面的分析需要同时捕获所有免疫细胞群和细胞间通讯的蛋白介质。由于每个被分析的病人都将在其感染的不同阶段，因此对免疫反应的纵向监测至关重要。在此，报告了 39 名住院的成年 COVID-19 重症患者的系统水平血液免疫监测研究，并随访了从急性期到恢复期的 14 份血液样本。作者描述了一个 IFNγ-的嗜酸性粒细胞在肺过度炎症之前被激活，以及在疾病的不同阶段中细胞和细胞协同调节的变化。作者还绘制了重症 COVID-19 患者康复期间的免疫轨迹。
Abstract

The immune response to SARS-CoV2 is under intense investigation, but not fully understood at this moment. Severe disease is characterized by vigorous inflammatory responses in the lung, often with a sudden onset after 5-7 days of stable disease. Efforts to modulate this hyperinflammation and the associated acute respiratory distress syndrome, rely on the unraveling of the immune cell interactions and cytokines that drive such responses. Systems-level analyses are required to simultaneously capture all immune cell populations and the many protein mediators by which cells communicate. Since every patient analyzed will be captured at different stages of his or her infection, longitudinal monitoring of the immune response is critical. Here we report on a systems-level blood immunomonitoring study of 39 adult patients, hospitalized with severe COVID-19 and followed with up to 14 blood samples from acute to recovery phases of the disease. We describe an IFNγ - Eosinophil axis activated prior to lung hyperinflammation and changes in cell-cell coregulation during different stages of the disease. We also map an immune trajectory during recovery that is shared among patients with severe COVID-19.

文章分类：疾病病理

15. IL-2/IL-2R 抑制可通过 JAK1-STAT5 导致 COVID-19 肺炎重症患者 CD8+的 T 细胞和淋巴细胞减少

The inhibition of IL-2/IL-2R gives rise to CD8+ T cell and lymphocyte decrease through JAK1-STAT5 in critical patients with COVID-19 pneumoniaa

来源：nature

发布时间：2020.06.08

文章链接：https://www.nature.com/articles/s41419-020-2636-4

第一作者：Hongbo Shi, Wenjing Wang

通讯作者：金荣华，陈德喜

通讯作者单位：首都医科大学附属北京佑安医院肝病研究所，北京精密医学工程研究中心肝炎和肝癌的转化

DOI： https://doi.org/10.1038/s41419-020-2636-4

编译者：张怡

中文摘要：

COVID-19 肺炎患者多数预后良好，但部分患者发展为重症或危重症，危重病例死亡率高达 61.5%。然而，关于 COVID-19 重症患者免疫反应的具体分子信息尚不清楚。共纳入 54 例患者，分为三组，常见组 34 例，重症组 14 例，危重组 6 例。用 CyTOF 分析患者外周血单核细胞(PBMC)的组成。使用 luminex 检测患者血浆中的细胞因子。采用 qRT-PCR 方法研究患者 PBMC 中 IL-2 信号通路。与普通和重症患者相比，重症患者淋巴细胞计数和百分率明显下降。与正常对照组相比，危重患者的 T 细胞、B 细胞和 NK 细胞明显减少。危重患者 CD8+ T 细胞百分率明显低于 COVID-19 肺炎的普通和重症患者。PBMC 中 IL-2R、JAK1、STAT5 表达降低，但 IL-2 在重症患者中升高，在 COVID-19 肺炎危重症患者中降低。COVID-19 肺炎重症患者 CD8+ T 细胞减少可能与 IL-2 信号通路有关。IL-2/IL-2R 抑制可通过 JAK1-STAT5 导致 COVID-19 肺炎重症患者 CD8+ T 细胞和淋巴细胞减少。

Abstract

Although most patients with COVID-19 pneumonia have a good prognosis, some patients develop to severe or critical illness, and the mortality of critical cases is up to 61.5%. However, specific molecular information about immune response in critical patients with COVID-19 is poorly understood. A total of 54 patients were enrolled and divided into three groups, among which 34 were common, 14 were severe, and 6 were critical. The constitution of peripheral blood mononuclear cells (PBMC) in patients was analyzed by CyTOF. The profile of cytokines was examined in plasma of patients using luminex. The IL-2 signaling pathway was investigated in the PBMC of patients by qRT-PCR. The count and percentage of lymphocytes were significantly decreased in critical patients compared to common and severe patients with COVID-19 pneumonia. The count of T cells, B cells, and NK cells was remarkably decreased in critical patients compared to normal controls. The percentage of CD8+ T cells was significantly lower in critical patients than that in common and severe patients with COVID-19 pneumonia. The expression of IL-2R, JAK1, and STAT5 decreased in PBMC of common, severe, and critical patients, but IL-2 level was elevated in severe patients and decreased in critical patients with COVID-19 pneumonia. The decrease of CD8+ T cells in critical patients with COVID-19 pneumonia may be related to the IL-2 signaling pathway. The inhibition of IL-2/IL-2R gives rise to CD8+ T cell and lymphocyte decrease through JAK1-STAT5 in critical patients with COVID-19 pneumonia.

16. 在 COVID-19 患者中 SARS-CoV-2 经嗅粘膜入侵作为进入中枢神经系统的通道

Olfactory transmucosal SARS-CoV-2 invasion as port of Central Nervous System entry in COVID-19 patients

来源：bioRxiv

发布时间：2020-06-04

链接：https://www.biorxiv.org/content/10.1101/2020.06.04.135012v1

第一作者：Jenny Meinhardt, Josefine Radke, Carsten Dittmayer

通讯作者：Frank L. Heppner

通讯作者单位：corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Germany

DOI 或 PUBMED ID：

编译者：张鹏伟

中文摘要：

新发现的严重急性呼吸综合征冠状病毒 2（SARS-CoV-2）引起 COVID-19，一种以发热、咳嗽和肺炎为主要症状的流行性呼吸道疾病。此外，已经描述了包括中枢神经系统（CNS）在内的整个体内的血栓栓塞事件。考虑到在大多数 COVID-19 患者中大脑和脑脊液中存在病毒 RNA 的第一个迹象，并且鉴于神经系统症状，中枢神经系统可能会出现 SARS-CoV-2-渗透。通过对 32 例死于 COVID-19 的患者的口咽部和大脑进行精确的研究和解剖定位，我们不仅描述了脑血栓栓塞导致的中枢神经系统梗死，而且还证明了 SARS-CoV-2 神经嗜性。SARS-CoV-2 利用嗅粘膜和神经组织（包括敏感的嗅觉和神经末梢）之间的紧密联系通过侵入嗅粘膜的神经-粘膜界面进入神经系统。随后，SARS-CoV-2 遵循明确的神经解剖结构，穿透明确的神经解剖区域，包括延髓的主要呼吸和心血管控制中心。

Abstract:
The newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19, a pandemic respiratory disease presenting with fever, cough, and often pneumonia. Moreover, thromboembolic events throughout the body including the central nervous system (CNS) have been described. Given first indication for viral RNA presence in the brain and cerebrospinal fluid and in light of neurological symptoms in a large majority of COVID-19 patients, SARS-CoV-2-penetrance of the CNS is likely. By precisely investigating and anatomically mapping oro- and pharyngeal regions and brains of 32 patients dying from COVID-19, we not only describe CNS infarction due to cerebral thromboembolism, but also demonstrate SARS-CoV-2 neurotropism. SARS-CoV-2 enters the nervous system via trespassing the neuro-mucosal interface in the olfactory mucosa by exploiting the close vicinity of olfactory mucosal and nervous tissue including delicate olfactory and sensitive nerve endings. Subsequently, SARS-CoV-2 follows defined neuroanatomical structures, penetrating defined neuroanatomical areas, including the primary respiratory and cardiovascular control center in the medulla oblongata.

17. COVID-19 患者快速产生中和抗体反应

Rapid generation of neutralizing antibody responses in COVID-19 patients

来源：Cell Reports Medicine
发布时间：2020-05-29
链接：https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30052-5
第一作者：Mehul S. Suthar
通讯作者：Mehul S. Suthar, Jens Wrammert
通讯作者单位：美国埃默里大学，美国耶克斯国家灵长类动物研究中心
DOI 或 PUBMED ID：https://doi.org/10.1016/j.xcrm.2020.100040
编译者：刘焕珍
中文摘要：
SARS-CoV-2 是导致 COVID-19 的病毒，它引起了可怕的全球流行病，我们迫切需要了解 SARS-CoV-2 急性感染期间体液免疫反应的发展、特异性和中和能力。我们对 44 例住院 COVID-19 患者的刺突蛋白受体结合区（RBD）的抗体反应和病毒中和活性的横断面进行研究。PCR 确诊后的 6 天里，所有患者均可检测到 RBD 特异性 IgG 反应。同型转变为 IgG 发生得很快，主要是 IgG1 和 IgG3。PCR 确诊后的 6 天里，使用临床分离的 SARS-CoV-2，所有患者均可检测到中和抗体滴度，并与 RBD 特异性结合 IgG 滴度相关。在 231 份 PCR 确诊的 COVID-19 患者样本中，RBD 特异性结合数据得到进一步验证。这些发现对了解 SARS-CoV-2 的保护性免疫、免疫血浆的治疗应用和疫苗的研发具有一定的意义。
Abstract:
SARS-CoV-2, the virus responsible for COVID-19, is causing a devastating global pandemic and there is a pressing need to understand the development, specificity, and neutralizing potency of humoral immune responses during acute infection. We report a cross-sectional study of antibody responses to the receptor-binding domain (RBD) of the spike protein and virus neutralization activity in a cohort

of 44 hospitalized COVID-19 patients. RBD-specific IgG responses are detectable in all patients 6 days after PCR confirmation. Isotype switching to IgG occurs rapidly, primarily to IgG1 and IgG3. Using a clinical SARS-CoV-2 isolate, neutralizing antibody titers are detectable in all patients by 6 days after PCR confirmation and correlate with RBD-specific binding IgG titers. The RBD-specific binding data were further validated in a clinical setting with 231 PCR-confirmed COVID-19 patient samples. These findings have implications for understanding protective immunity against SARS-CoV-2, therapeutic use of immune plasma, and development of much-needed vaccines.

18. 抑制性髓样细胞是重症 COVID-19 的一个标志

Suppressive myeloid cells are a hallmark of severe COVID-19

来源：medrxiv

发布日期：2020-06-05

链接： https://www.medrxiv.org/content/10.1101/2020.06.03.20119818v1

第一作者：Jonas Schulte-Schrepping

通讯作者：Leif Erik Sander

通讯作者单位：German Center for Lung Research

编译者：蒋立春

德国 Deutsche COVID-19 OMICS Initiative 团队用单细胞 RNA 测序以及单细胞蛋白组学技术分析了两个中心（46+54）100 个 COVID-19 病人的全血和 PBMC。两个中心都包含了轻中度症状病人以及重症病人。作者们在轻中度症状病人中观察到了高 HLA-DR 高 CD11c 的炎性单核细胞特异性的升高。这些炎性单核细胞表现初很强的干扰素刺激的基因信号。相反在重症 COVID-19 病人中，研究者们发现有紧急骨髓生成的迹象，以免疫抑制性的中心粒细胞前体、不成熟的中性粒细胞以及没有功能和抑制性的成熟中性粒细胞，以及低 HLA-DR 的抑制性单核细胞为特征。

Abstract

'Severe Acute Respiratory Syndrome - Coronavirus-2' (SARS-CoV-2) infection causes Coronavirus Disease 2019 (COVID-19), a mild to moderate respiratory tract infection in the majority of patients. A subset of patients, however, progresses to severe disease and respiratory failure with acute respiratory distress syndrome (ARDS). Severe COVID-19 has been associated with increased neutrophil counts and dysregulated immune responses. The mechanisms of protective immunity in mild forms and the pathogenesis of dysregulated inflammation in severe courses of COVID-19 remain largely unclear. Here, we combined two single-cell RNA-sequencing technologies and single-cell proteomics in whole blood and peripheral blood mononuclear cells (PBMC) to determine changes in immune cell composition and activation in two independent dual-center patient cohorts (n=46 + n=54 COVID-19 samples), each with mild and severe cases of COVID-19. We observed a specific increase of HLA-DR high CD11c high inflammatory monocytes that displayed a strong interferon (IFN)-stimulated gene signature in patients with mild COVID-19, which was absent in severe disease. Instead, we found evidence of emergency myelopoiesis, marked by the occurrence of immunosuppressive pre-neutrophils and immature neutrophils and

populations of dysfunctional and suppressive mature neutrophils, as well as suppressive HLA-DR low monocytes in severe COVID-19. Our study provides detailed insights into systemic immune response to SARS-CoV-2 infection and it reveals profound alterations in the peripheral myeloid cell compartment associated with severe courses of COVID-19.

19. COVID-19 病人中一个共同的免疫信号合并免疫保护败血症样特征和不良预后相关

A consensus Covid-19 immune signature combines immuno-protection with discrete sepsis-like traits associated with poor prognosis

链接:https://www.medrxiv.org/content/10.1101/2020.06.08.20125112v1

20. 针对 SARS-CoV-2 具有有效保护作用的灭活候选疫苗 BBIBP-CorV 的开发

Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2

来源：cell

发布时间：2020-06-08

链接：https://www.cell.com/cell/fulltext/S0092-8674(20)30695-4

第一作者：Hui Wang, Yuntao Zhang, Baoying Huang, Wei Deng, Yaru Quan, Wenling Wang,Wenbo Xu

通讯作者：高福、秦川、谭文杰、娄智勇、李长贵、武桂珍、徐苗、杨晓明

通讯作者单位：北京生物制品研究所有限责任公司、中国疾病预防控制中心、中国医学科学院、北京协和医学院、清华大学等

DOI 或 PUBMED ID：https://doi.org/10.1016/j.cell.2020.06.008

编译者：孔娟

中文摘要：

2019 年冠状病毒病(COVID-19)大流行已经严重威胁全球公共健康，迫切需要开发一种疫苗来预防和控制 COVID-19。文中研究者报道了一种灭活的候选疫苗(BBIBP-CorV)的中试生产，该疫苗在小鼠、大鼠、豚鼠、兔和非人灵长类动物(食蟹猴和恒河猴)中能迅速诱导高滴度的中和抗体，从而提供对新冠病毒的保护。研究团队以非人灵长类动物（恒河猴）为模型开展了进一步实验。研究发现所有接受疫苗的猴子，肺叶中均没有检测到病毒，肺部保持正常，仅少数肺叶有局部轻度组织病理学改变。在恒河猴中，使用 2 微克/剂量的 BBIBP-CorV 双剂免疫接种便足以产生高效的保护作用并且实验中也没有发现抗体依赖性增强（ADE）感染。此外，BBIBP-CorV 在疫苗生产中表现出高效的生产率和良好的遗传稳定性。这些结果支持在临床试验中进一步评估 BBIBP-CorV。

Abstract:

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) threatens global public health. The development of a vaccine is urgently needed for the prevention and control of COVID-19. Here, we report the pilot-scale production of an inactivated SARS-CoV-2 vaccine candidate (BBIBP-CorV) that induces high levels of neutralizing antibodies titers in mice, rats, guinea pigs, rabbits and nonhuman primates (cynomolgus monkeys and rhesus macaques) to provide protection against SARS-CoV-2. Two dose immunizations using 2 μg/dose of BBIBP-CorV provided highly efficient protection against SARS-CoV-2 intratracheal challenge in rhesus

macaques, without detectable antibody-dependent enhancement of infection. In addition, BBIBP-CorV exhibits efficient productivity and good genetic stability for vaccine manufacture. These results support the further evaluation of BBIBP-CorV in a clinical trial.

21. Moderna 的 mRNA 疫苗 mRNA-1273 计划于 7 月开始和 NIAID 合作开展三期临床试验。

链接：

https://www.biocentury.com/article/305427?editionId=ckbbn9y8o0ww30174kt53f84q&editionType=daily

摘要：

根据 biocentury 6 月 12 日的报道，Moderna 宣布于 7 月开始和 NIAID 合作开展 mRNA-1273 疫苗的三期临床试验。这个研究计划招募 3 万个志愿者，按照 1:1 随机分布到疫苗组和安慰剂组。有专家说在一个疾病发生率为 3%的地区，按照招募 3 万到到 10 万个志愿者计算，最终能确定疫苗的效果可能需要 3 到 4 个月。

Strategies for late-stage clinical testing of COVID-19 vaccine candidates are coming into focus with the announcement of a July start for a Phase III trial of Moderna’s mRNA-1273.

…

Moderna and NIAID plan to enroll 30,000 people in the Phase III trial, randomized 1:1 between the vaccine candidate and placebo.

…

If a Phase III trial of a COVID-19 vaccine candidate enrolled 30,000 to 100,000 individuals and was conducted in a location with a 3% incidence of the disease, it would take three or four months to demonstrate efficacy, Stoffels said.

22. 胆固醇-25-羟化酶　通过抑制膜融合抑制 SARS-CoV-2 的复制

Cholesterol 25-hydroxylase suppresses SARS-CoV-2 replication by blocking membrane fusion

https://www.biorxiv.org/content/10.1101/2020.06.08.141077v1

23. 体外实验证明肺细胞中的 ZAP 蛋白可以抑制 SARS-CoV-2

The Zinc Finger Antiviral Protein restricts SARS-CoV-2

https://www.biorxiv.org/content/10.1101/2020.06.04.134379v2

24. 来自康复期患者抗体库的针对 SARS-CoV-2 和 RBD 突变的交叉中和抗体

Cross-neutralization antibodies against SARS-CoV-2 and RBD mutations from convalescent patient antibody libraries

链接：https://www.biorxiv.org/content/10.1101/2020.06.06.137513v1

编译者：雷颖

华东师范大学的刘明耀团队用噬菌体展示的方法从 17 名不同的 COVID-19 康复患者的抗体库中筛选针对 SARS-CoV-2 的中和抗体，获得了具有结合 RBD 的能力且能更好地抑制 S 蛋白与 ACE2 之间的相互作用的抗体，并在真假病毒体系中均证实其抗病毒感染能力。

25. 合成抗体可中和哺乳动物细胞的 SARS-CoV-2 感染

Synthetic antibodies neutralize SARS-CoV-2 infection of mammalian cells

链接：https://www.biorxiv.org/content/10.1101/2020.06.05.137349v2

编译者：雷颖

加拿大多伦多大学的 Sidhu 团队找到一组基于人 IgG 框架的合成单克隆抗体，这些抗体能与 SARS-CoV-2 的 S 蛋白结合，竞争 ACE2 结合，从而有效地抑制 SARS-CoV-2，其抗病毒感染能力在细胞水平上得到了验证。

26. 选自大流行前健康供体的 SARS-CoV-2 中和人重组抗体能在 RBD-ACE2 界面处结合

SARS-CoV-2 neutralizing human recombinant antibodies selected from pre-pandemic healthy donors binding at RBD-ACE2 interface

链接：https://www.biorxiv.org/content/10.1101/2020.06.05.135921v1

编译者：雷颖

德国不伦瑞克技术大学的 Hust 团队使用噬菌体展示技术从人类通用初始抗体基因库中选择能够抑制与 ACE2 相互作用的 HAL9/10 抗 SARS2 刺突蛋白的抗体，并将其在细胞水平上验证。

27. 托珠单抗用于 COVID-19 肺炎患者——TOCIVID-19 的 2 期试验

Tocilizumab for patients with COVID-19 pneumonia. The TOCIVID-19 phase 2 trial

来源：medRxiv

发布时间：2020-06-05

链接：https://www.medrxiv.org/content/10.1101/2020.06.01.20119149v1

第一作者：Francesco Perrone, Maria Carmela Piccirillo

通讯作者：Francesco Perrone

通讯作者单位：Clinical Trial Unit, Istituto Nazionale Tumori di Napoli

DOI 或 PUBMED ID：

编译者：宋张悦

中文摘要：

背景：托珠单抗阻断了可能在间质性肺炎发病机制中起重要作用的 IL-6 的促炎活性。

目的：评价托珠单抗治疗 COVID-19 肺炎的疗效。

设计：多中心单臂 2 期试验，在 14 天和 30 天内检测到绝对致死率降低 10%，预期致死率降低 20%和 35%。还对一个连续的前瞻性验证队列进行了评估。

地点：在冠状病毒爆发期间，意大利 185 家公立医院。

患者：2020 年 3 月 19 日- 24 日肺炎住院患者 1221 例。

干预：托珠单抗 8 mg/kg，静脉注射，每隔 12 小时 1-2 次。

测量：14 天和 30 天的致死率：根据 CTCAE 安全。

结果：在 2 期和验证组中有 301 例和 920 例可以进行意向治疗(intention-to-treat, ITT)分析。由于药物供应延迟，60%的患者接受了托珠单抗，而且有些延迟。在第二阶段，67 名患者死亡；14 天和 30 天的致死率分别为 18.4% (97.5%CI: 13.6-24.0, P=0.52)和 22.4% (97.5%CI: 17.2-28.3, P<0.001)。在仅包括接受治疗的患者的改良的 ITT (modified ITT , mITT)中报告了较低的发生率(15.6%和 20.0%)。在 14 天和 30 天期间，在 ITT 和 mITT 人群中，验证队列中的致死率低于二期。多变量 logistic 回归模型表明，托珠单抗对于基线时不需要机械呼吸支持的患者更有效。未见特异性药物毒性相关信号报告，许多严重不良事件与疾病相关。

限制：单臂设计。此外，由于药物的延迟诱发了指征偏差和不朽时间偏差。

结论：**与预期相比，托珠单抗在 30 天而不是 14 天时降低了致死率，没有显著毒性。在不需要机械呼吸支持的患者中，疗效更明显。**

Abstract:

Background: Tocilizumab blocks pro-inflammatory activity of interleukin-6 (IL-6) which might be important in the pathogenesis of interstitial pneumonia.

Objective: to evaluate efficacy of tocilizumab in COVID-19 pneumonia patients.

Design: multicenter single-arm phase 2 trial, powered to detect 10% absolute lethality rate reduction at 14 and 30-days, with 20% and 35% expected rates. A consecutive prospective validation cohort was also evaluated.

Setting: 185 Italian public hospitals, during coronavirus breakout.

Patients: 1221 patients hospitalized with pneumonia, from March 19th to 24th, 2020.

Intervention: tocilizumab 8 mg/kg, intravenously, one or two administrations with 12 hours interval.

Measurements: lethality rates at 14 and 30-days; safety according to CTCAE.

Results: 301 and 920 cases were available for intention-to-treat (ITT) analysis in phase 2 and validation cohorts. Due to delayed drug availability, 60% of patients received tocilizumab, and with some delays. In phase 2, 67 patients died; lethality rates were 18.4% (97.5%CI: 13.6-24.0, P=0.52) and 22.4% (97.5%CI: 17.2-28.3, P<0.001) at 14 and 30-days. Lower rates (15.6% and 20.0%) were reported in the modified ITT including only treated patients (mITT). Lethality rates in the validation cohort were smaller than in phase 2, at 14 and 30 days and in ITT and mITT populations. Multivariable logistic regression model suggests tocilizumab be more effective in patients not requiring mechanical respiratory support at baseline. No relevant signal of specific drug toxicity was reported, many severe adverse events being disease-related.

Limitations: single-arm design. In addition, delayed availability of the drug induced indication bias and immortal time bias.

Conclusion: Tocilizumab reduced lethality rate at 30 but not at 14-days, compared with the expectations, without significant toxicity. Efficacy was more evident among patients not requiring mechanical respiratory support.

Registration. EudraCT (2020-001110-38); clinicaltrials.gov (NCT04317092)

编者注：

除上述来自意大利的托珠单抗治疗研究外，近期在 medRxiv 还发表了两篇来自西班牙的托珠单抗治疗的相关临床试验结果的文章。

参考文献 1：Tocilizumab is associated with reduction of the risk of ICU admission and mortality in patients with SARS-CoV-2 infection

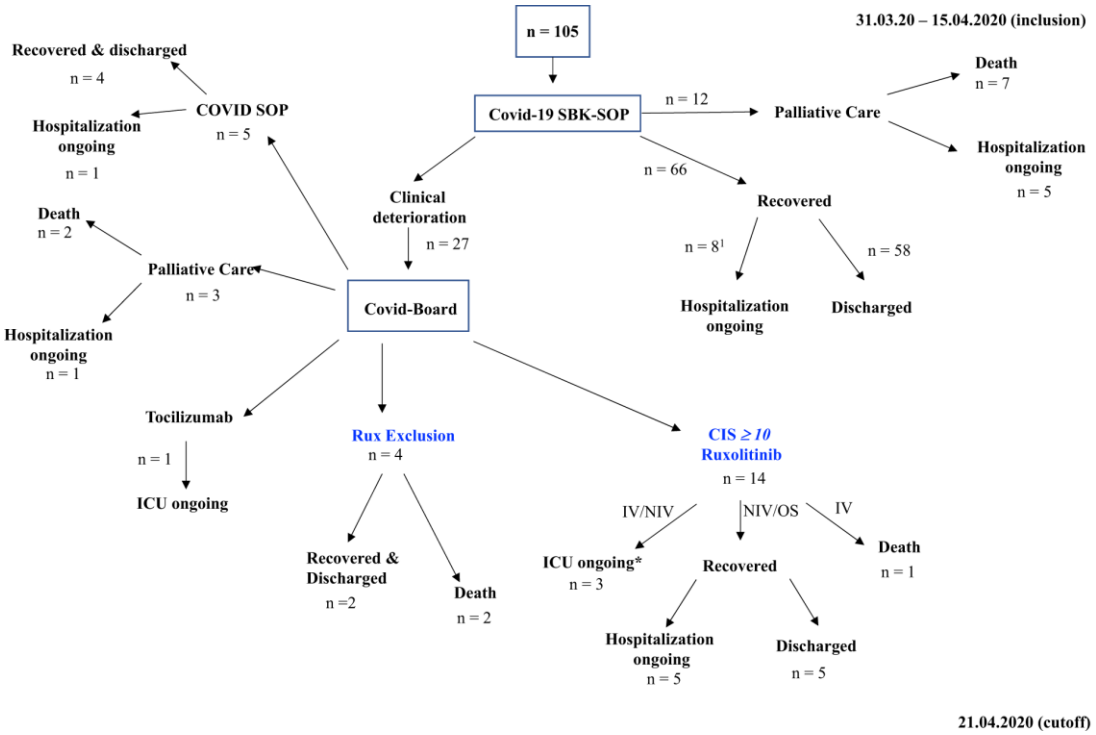
链接：https://www.medrxiv.org/content/10.1101/2020.06.05.20113738v1）

中文摘要:来自西班牙巴塞罗那 Hospital Clínic-Universitat de Barcelona 的研究人员，回顾性研究了 171 例 SARS-CoV-2 感染患者，其中，77 例患者接受托珠单抗治疗，94 例未接受。研究发现**托珠单抗在炎症发作早期，可减少 ICU 住院和机械通气的使用。接受托珠单抗治疗的患者的死亡率为 10.3%，似乎低于其他报告。**

参考文献 2：Effects of Tocilizumab on Mortality in Hospitalized Patients with COVID-19: A Multicenter Cohort Study
链接：https://www.medrxiv.org/content/10.1101/2020.06.08.20125245v1
中文摘要：来自西班牙马德里 Hospital Universitario Ramón y Cajal, Facultad de Medicina, Universidad de Alcalá (IRYCIS)的研究人员，对 2020 年 1 月 31 日至 4 月 23 日来自西班牙马德里 17 家医院的 1229 例住院的 COVID-19 患者进行了队列研究。使用逆概率加权来拟合随时间变化的协变量调整的边际结构模型，来确定托珠单抗的使用和结局之间的因果关系。发现托珠单抗的使用和高 C 反应蛋白(CRP)水平之间的显著相互作用，**本研究更支持在 C 反应蛋白（CRP）水平较高的受试者中使用托珠单抗**。

28. Jak1/2 的抑制剂芦可替尼对发生严重系统性超炎反应的 COVID-19 病人的作用

The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation
来源：Leukemia
发布时间：2020-06-09
链接：https://www.nature.com/articles/s41375-020-0891-0
第一作者：F.La Rosee
通讯作者：P.La Rosee
通讯作者单位： 德国弗里德里希·席勒大学耶拿大学医学院
DOI 或 PUBMED ID：https://doi.org/10.1038/s41375-020-0891-0
编译者：蒋立春
中文摘要：
德国的研究者们从对 105 个病人根据炎症打分选出了 14 个 COVID-19 炎症分数（CIS）大于 10（总分为 16 分）的病人接受 Jak1/2 的抑制剂芦可替尼治疗。治疗的时长中位数为 9 天，累积剂量的中位数为 135mg.一共有 12 个病人在第 7 天的时候 COVID-19 炎症分数降低了至少 25%，其中 11 个病人取得了稳定的临床改善，并且没有发生芦可替尼诱导的急性毒性的红色警戒。这个试验性案例系列显示，芦可替尼用于治疗超炎性 COVID-19 的病人，是一种有效干扰细胞因子释放综合征防止多器官衰竭的安全有效的方案。
编者注：
5 月 29 日的第 56 期简报我们报道过中国的一项多中心、单盲、随机对照试验的使用芦可替尼治疗 COVID-19 病人的报告。该研究（n=21）显示了卢可替尼的有效性。



Abstract:

A subgroup of patients with severe COVID-19 suffers from progression to acute respiratory distress syndrome and multiorgan failure. These patients present with progressive hyperinflammation governed by proinflammatory cytokines. An interdisciplinary COVID-19 work flow was established to detect patients with imminent or full blown hyperinflammation. Using a newly developed COVID-19 Inflammation Score (CIS), patients were prospectively stratified for targeted inhibition of cytokine signalling by the Janus Kinase 1/2 inhibitor ruxolitinib (Rux). Patients were treated with efficacy/toxicity guided step up dosing up to 14 days. Retrospective analysis of CIS reduction and clinical outcome was performed. Out of 105 patients treated between March 30th and April 15th, 2020, 14 patients with a CIS ≥ 10 out of 16 points received Rux over a median of 9 days with a median cumulative dose of 135 mg. A total of 12/14 patients achieved significant reduction of CIS by ≥25% on day 7 with sustained clinical improvement in 11/14 patients without short term red flag warnings of Rux-induced toxicity. Rux treatment for COVID-19 in patients with hyperinflammation is shown to be safe with signals of efficacy in this pilot case series for CRS-intervention to prevent or overcome multiorgan failure. A multicenter phase-II clinical trial has been initiated (NCT04338958).

29. 抑制 BTK 来治疗 COVID-19 重症病人

Inhibition of Bruton tyrosine kinase in patients with severe COVID-19

美国国立卫生研究院的团队报道了用 BTK 抑制剂治疗 COVID-19 重症病人的一项临床研究。在 10 到 14 天的治疗过程中， BTK 的抑制剂 acalabrutinib 提到了大部分病人的氧供应。病人以及离体试验都证明 BTK 抑制剂改善了免疫反应。

4 月 19 第 6 篇也报道了 BTK 抑制剂治疗 COVID-19 的临床效果

链接：https://immunology.sciencemag.org/content/5/48/eabd0110

30. 丹麦全国性的研究表明非甾醇类抗炎药物没有影响 SARS-CoV-2 30 天主要临床情况的发生

Adverse Outcomes and Mortality in Users of Non-Steroidal Anti-Inflammatory Drugs tested positive for SARS-CoV-2: A Danish Nationwide Cohort Study
https://www.medrxiv.org/content/10.1101/2020.06.08.20115683v1

31. 因氢键网络和疏水相互作用增强了 SARS-CoV-2 与受体的结合能力

Enhanced receptor binding of SARS-CoV-2 through networks of hydrogen-bonding and hydrophobic interactions
来源：PNAS
发布时间：2020-06-05
链接：https://www.pnas.org/content/early/2020/06/04/2008209117
第一作者：Yingjie Wang
通讯作者：Jiali Gao
通讯作者单位：Institute of Systems and Physical Biology, Shenzhen Bay Laboratory, Shenzhen 518055, China
DOI 或 PUBMED ID：10.1073/pnas.2008209117
编译者：宋珂
中文摘要：

通过分子动力学模拟和自由能计算，阐明了常见受体蛋白 ACE2 和导致 COVID-19 疫情的 SARS-CoV-2 病毒的受体结合结构域之间，以及 ACE2 和造成 2002-2003 年间 SARS 的 SARS-CoV 病毒的受体结合结构域之间，蛋白-蛋白相互作用存在差异的结构原因。通过对动力学模拟轨迹的分析作者发现，疏水相互作用是 SARS-CoV-2 病毒与 ACE2 相互作用的主要成分，同时还存在精巧的氢键网络。相比于 SARS-CoV 病毒，SARS-CoV-2 中一个关键的突变是 SARS-CoV 中一个疏水性的残基突变为 SARS-CoV-2 中的 Lys417，并在疏水接触区域的中心形成了一个盐桥。在和其他极性残基突变的共同作用下，形成了比 SARS-CoV 复合物更大的静电互补效应。此外，在一段包含 12 个残基的短 loop 区域中，SARS-CoV 包含五个脯氨酸，而 SARS-CoV-2 则只保留了一个，从而增强了其疏水堆积效应。同 SARS-CoV 复合物相比，在静电作用和增强的疏水堆积效应共同作用下，SARS-CoV-2 复合物的构象发生了轻微改变，形成了更倾斜的凹型结合。另一方面，SARS-CoV 病毒与中和抗体 80R 的复合物中的疏水相互作用，由于 SARS-CoV-2 中的突变，在利用同源建模方法得到的 SARS-CoV-2/80R 复合物模型中也被破坏，这可以解释 80R 识别 SARS-CoV-2 失败的原因。

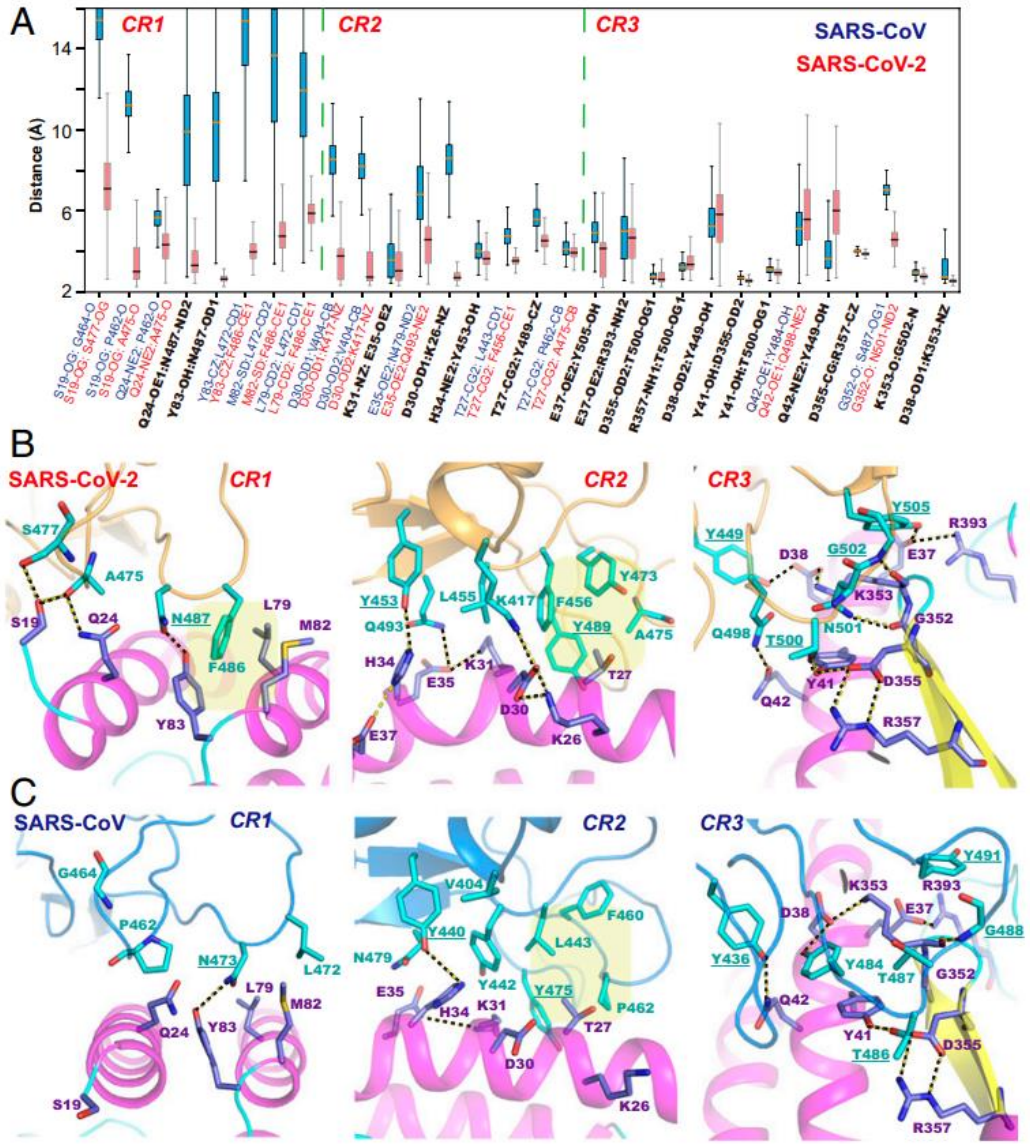


Fig. 3. Computed averages and fluctuations of interaction distances of selected residues (A) and structural depiction of key interfacial interactions between ACE2 and the RBM of SARS-CoV-2 (B) and SARS-CoV (C) in the three contact regions at the N-terminal end of ACE2 (CR1), the central region (CR2) of the RBM, and the β-turn contact region of ACE2 (CR3). Key hydrogen bonds and salt bridges are highlighted with dashed lines, and hydrophobic contacts are shaded in yellow background. Legends for A are colored light blue for residues in the ACE2–SARS-CoV complex, light maroon for residues in ACE2–SARS-CoV-2, and black for conserved residues found in both sequences at the corresponding sites.

Abstract:
Molecular dynamics and free energy simulations have been carried out to elucidate the structural origin of differential protein-protein interactions between the common receptor protein angiotensin converting enzyme 2 (ACE2) and the receptor binding domains of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) and the SARS coronavirus

in the 2002–2003 (SARS-CoV) outbreak. Analysis of the dynamic trajectories reveals that the binding interface consists of a primarily hydrophobic region and a delicate hydrogen-bonding network in the 2019 novel coronavirus. A key mutation from a hydrophobic residue in the SARS-CoV sequence to Lys417 in SARS-CoV-2 creates a salt bridge across the central hydrophobic contact region, which along with polar residue mutations results in greater electrostatic complementarity than that of the SARS-CoV complex. Furthermore, both electrostatic effects and enhanced hydrophobic packing due to removal of four out of five proline residues in a short 12-residue loop lead to conformation shift toward a more tilted binding groove in the complex in comparison with the SARS-CoV complex. On the other hand, hydrophobic contacts in the complex of the SARS-CoV–neutralizing antibody 80R are disrupted in the SARS-CoV-2 homology complex model, which is attributed to failure of recognition of SARS-CoV-2 by 80R.

32. 恢复期血浆中抗 Spike 蛋白抗体滴度与 SARS-CoV-2 体外病毒中和的关系

Relationship between Anti-Spike Protein Antibody Titers and SARS-CoV-2 In Vitro Virus Neutralization in Convalescent Plasma

来源：bioRxiv

发布时间：2020-06-09

链接：https://www.biorxiv.org/content/10.1101/2020.06.08.138990v1

第一作者：Eric Salazar

通讯作者：James M. Musser

通讯作者单位：德克萨斯州休斯顿休斯敦卫理公会医院

DOI 或 PUBMED ID：Preprint

编译者：张丽双

中文摘要：

新出现的病原体 SARS-CoV-2 突显了对体外检测可能具有保护性的中和抗体的迫切需求。研究人员评估了抗 spike 胞外域（ECD）和抗受体结合域（RBD）IgG 滴度与 SARS-CoV-2 病毒中和（VN）滴度之间的关系，是通过两次不同的体外检测方法（使用从 68 位 COVID-19 患者获得的恢复血浆样品，包括 13 名多次捐献血浆的患者）得到的。只有 23%（16/68）的捐献者住过院。还对无症状个体进行监测筛查时发现的具有抗 spike 蛋白 IgG 的受试者的 16 个样品进行了研究。研究人员发现血浆抗 RBD 和抗 ECD 的 IgG 滴度与体外 VN 滴度之间有很强的正相关性。抗 RBD 的 IgG 滴度比抗 ECD 的 IgG 滴度与 VN 滴度之间的相关性稍好。当抗 RBD 或抗 ECD 滴度≥1:1350 时，VN 滴度≥160 的可能性为 80%或更高。37%（25/68）的恢复期血浆供体不具备 VN 滴度≥160，而这是 FDA 推荐的用于 COVID-19 治疗的恢复期血浆中的 VN 滴度。呼吸困难、住院和疾病严重程度与更高的 VN 滴度显著相关。频繁捐赠恢复性血浆并不能显著降低 VN 或 IgG 滴度。对 2,814 名无症状成人进行的分析发现，有 27 个人的抗 RBD 或抗 ECD 的 IgG 滴度≥1:1350，且 VN≥1:160。综上，研究人员得出结论，抗 RBD 或抗 ECD 的 IgG 滴度可以作为 VN 滴度的替代物，以鉴定合适的血浆供体。血浆抗 RBD 或抗 ECD 滴度≥1:1350 可能提供有关预防 COVID-19 疾病的重要信息。

Abstract:

Newly emerged pathogens such as SARS-CoV-2 highlight the urgent need for assays that detect levels of neutralizing antibodies that may be protective. We studied

the relationship between anti-spike ectodomain (ECD) and anti-receptor binding domain (RBD) IgG titers, and SARS-CoV-2 virus neutralization (VN) titers generated by two different in vitro assays using convalescent plasma samples obtained from 68 COVID-19 patients, including 13 who donated plasma multiple times. Only 23% (16/68) of donors had been hospitalized. We also studied 16 samples from subjects found to have anti-spike protein IgG during surveillance screening of asymptomatic individuals. We report a strong positive correlation between both plasma anti-RBD and anti-ECD IgG titers, and in vitro VN titer. Anti-RBD plasma IgG correlated slightly better than anti-ECD IgG titer with VN titer. The probability of a VN titer ≥160 was 80% or greater with anti-RBD or anti-ECD titers of ≥1:1350. Thirty-seven percent (25/68) of convalescent plasma donors lacked VN titers ≥160, the FDA-recommended level for convalescent plasma used for COVID-19 treatment. Dyspnea, hospitalization, and disease severity were significantly associated with higher VN titer. Frequent donation of convalescent plasma did not significantly decrease either VN or IgG titers. Analysis of 2,814 asymptomatic adults found 27 individuals with anti-RBD or anti-ECD IgG titers of ≥1:1350, and evidence of VN ≥1:160. Taken together, we conclude that anti-RBD or anti-ECD IgG titers can serve as a surrogate for VN titers to identify suitable plasma donors. Plasma anti-RBD or anti-ECD titer of ≥1:1350 may provide critical information about protection against COVID-19 disease.

33. SARS-CoV-2 导致急性感染而引起肺部细胞和炎症流动态变化情况，在各种非人灵长类动物中不相同

SARS-CoV-2 infection leads to acute infection with dynamic cellular and inflammatory flux in the lung that varies across nonhuman primate species

来源：bioRxiv
发布时间：2020-06-05
链接：https://www.biorxiv.org/content/10.1101/2020.06.05.136481v1
第一作者：Dhiraj Kumar Singh
通讯作者：Luis D.Giavedoni, Ricardo Carrion, Jr., Deepak Kaushal
通讯作者单位：美国西南国家灵长类动物研究中心，美国德州生物医学研究所
DOI 或 PUBMED ID：https://doi.org/10.1101/2020.06.05.136481
编译者：刘焕珍
中文摘要：
对于 COVID-19 流行病，目前尚无治疗方法或疫苗。动物模型对于快速跟踪新干预措施必不可少，其他传染病的非人灵长类动物（NHP）模型已被证明非常有价值。在这里，我们比较了三种实验上感染 SARS-CoV-2 的 NHP（恒河猴、狒狒和狨猴）。在头 3 天中，猕猴出现了病毒感染和全身性炎症的临床特征，并伴随着病毒复制、轻度至中度间质性和肺泡性肺炎以及肺外病理的早期证据。锥束 CT 扫描显示中度肺炎的病程超过 3 天。纵向研究表明，尽管年轻和年老的猕猴都出现了 COVID-19 的早期症状，但两组猕猴都在两周内恢复了。恢复的特点是肺部病毒持续性低，这表明免疫系统受损的个体可能对延长和进行性 COVID-19 敏感。肺室包含一个复杂的早期炎症环境，内有先天性和适应性免疫细胞（特别是间质巨噬细胞、中性粒细胞和浆细胞样树突状细胞）大量涌入，以及显著的 I 型干扰素反应。当猕猴发展成

中度疾病时，狒狒在感染后表现出长时间的病毒脱落和广泛的病理变化，而绒猴则表现出较温和的感染形式。各种 NHP 属概括了 COVID-19 的异质性进展。恒河猴和狒狒发展出不同的，可量化的疾病特征，使其立即可用于测试新疫苗和疗法的基本模型。

Abstract:

There are no known cures or vaccines for COVID-19, the defining pandemic of this era. Animal models are essential to fast track new interventions and nonhuman primate (NHP) models of other infectious diseases have proven extremely valuable. Here we compare SARS-CoV-2 infection in three species of experimentally infected NHPs (rhesus macaques, baboons, and marmosets). During the first 3 days, macaques developed clinical signatures of viral infection and systemic inflammation, coupled with early evidence of viral replication and mild-to-moderate interstitial and alveolar pneumonitis, as well as extra-pulmonary pathologies. Cone-beam CT scans showed evidence of moderate pneumonia, which progressed over 3 days. Longitudinal studies showed that while both young and old macaques developed early signs of COVID-19, both groups recovered within a two-week period. Recovery was characterized by low-levels of viral persistence in the lung, suggesting mechanisms by which individuals with compromised immune systems may be susceptible to prolonged and progressive COVID-19. The lung compartment contained a complex early inflammatory milieu with an influx of innate and adaptive immune cells, particularly interstitial macrophages, neutrophils and plasmacytoid dendritic cells, and a prominent Type I-interferon response. While macaques developed moderate disease, baboons exhibited prolonged shedding of virus and extensive pathology following infection; and marmosets demonstrated a milder form of infection. Various NHP genera recapitulate heterogeneous progression of COVID-19. Rhesus macaques and baboons develop different, quantifiable disease attributes making them immediately available essential models to test new vaccines and therapies.

34. 猫传腹药物 GC376 抑制 SARS-CoV-2 的结构基础

Structure Basis for Inhibition of SARS-CoV-2 by the Feline Drug GC376

https://www.biorxiv.org/content/10.1101/2020.06.07.138677v1

35. 用假病毒以及嵌合病毒测试 SARS-COV-2 中和抗体活性

Measuring SARS-CoV-2 neutralizing antibody activity using pseudotyped and chimeric viruses

https://www.biorxiv.org/content/10.1101/2020.06.08.140871v1

36. SARS-CoV-2 蛋白酶可以切割宿主免疫调节相关因子

SARS-CoV-2 proteases cleave IRF3 and critical modulators of inflammatory pathways (NLRP12 and TAB1): implications for disease presentation across species and the search for reservoir hosts

研究者们通过筛选实验，发现 SARS-CoV-2 的蛋白酶 NSP3 and NSP5 可以切割宿主的 IRF3 以及免疫通路的调节因子 NLRP12 和 TAB1。该发现可能可以解释 COVID-19 疾病在不同物种间的差异性表现，可能帮助搜索中间宿主有帮助。

https://www.biorxiv.org/content/10.1101/2020.06.05.135699v1

37. 人诱导性多能干细胞分化的肺泡和气道上皮细胞可以在空气和液体界面进行培养，而且可以表达 SRAS-CoV-2 的宿主因子

Human iPSC-derived alveolar and airway epithelial cells can be cultured at air-liquid interface and express SARS-CoV-2 host factors

https://www.biorxiv.org/content/10.1101/2020.06.03.132639v1

38. neuropilin-1 (NRP1)参与了 SARS-COV-2 侵袭中枢神经系统

本周两篇分别来自德国和英国团队的预印本报道细胞受体 neuropilin-1 (NRP1)参与了 SARS-COV-2 侵袭中枢神经系统

Neuropilin-1 facilitates SARS-CoV-2 cell entry and provides a possible pathway into the central nervous system

链接：https://www.biorxiv.org/content/10.1101/2020.06.07.137802v2

Neuropilin-1 is a host factor for SARS-CoV-2 infection

链接：https://www.biorxiv.org/content/10.1101/2020.06.05.134114v1

39. 一个最常用的用来构建针对 SARS-COV-2 的 RBD 的抗体的免疫球蛋白重链可变区 IGHV-53 的结构解析

Structural basis of a public antibody response to SARS-CoV-2

https://www.biorxiv.org/content/10.1101/2020.06.08.141267v1

40. 构建一个可以广泛用于 COVID-19 疫苗和药物开发的小鼠模型

Generation of a Broadly Useful Model for COVID-19 Pathogenesis Vaccination, and

来源：Cell

发布时间：2020-06-09

链接：https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2930741-8

第一作者：Jing Sun

通讯作者：

Paul B. McCray, Stanley Perlman, Jincun Zhao(赵金存)

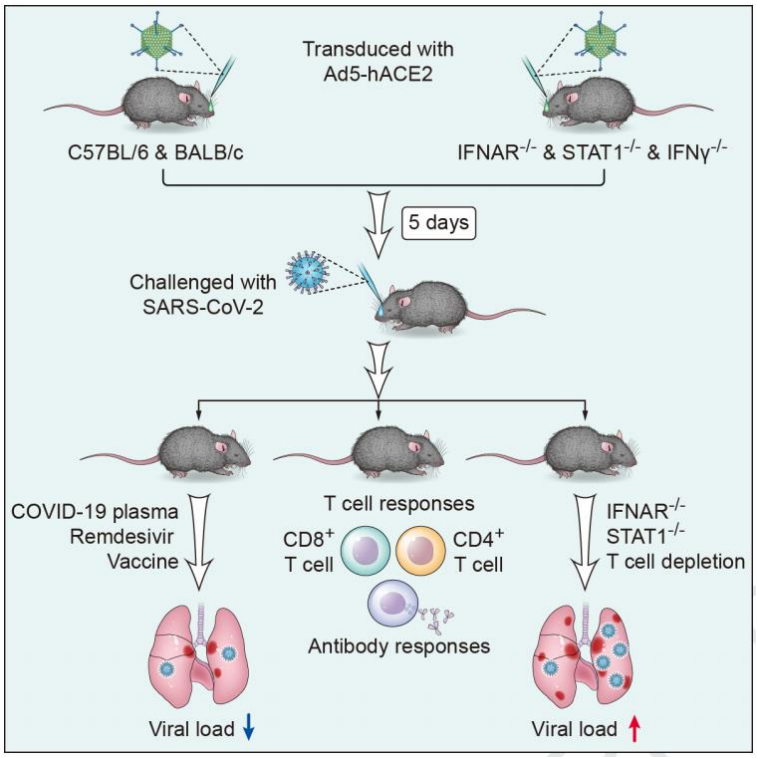
通讯作者单位：美国爱荷华大学，广州医科大学第一附属医院，

DOI 或 PUBMED ID：https://doi.org/10.1016/j.cell.2020.06.010

编译者：蒋立春

中文摘要：

小鼠是一个用于测试疫苗和治疗方案的优秀的动物模型。但是小鼠对 SARS-CoV-2 抵抗，不容易感染。作者们通过鼻饲将表达人 ACE2 的复制缺陷腺病毒（Ad5-hACE2）喂给小鼠将小鼠变成对 SARS-CoV-2 敏感。这些敏感的小鼠在接种病毒后发生了肺炎的症状，包括体重减轻，严重的肺部病变，以及在肺部发现高滴度的病毒复制。I 型干扰素，T 细胞以及最重要的，STAT1 对这些小鼠中的病毒清除和症状解除起到关键作用。Ad5-hACE2 小鼠使得研究者们可以快速的对康复者血浆来源的疫苗以及两个抗病毒分子进行测试（poly I:C 和瑞德西韦）。



Summary

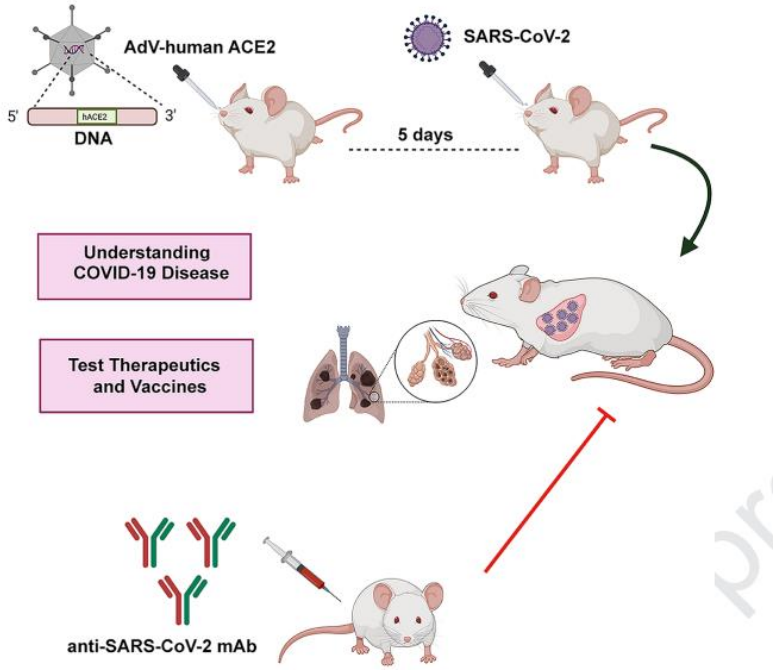
COVID-19, caused by SARS-CoV-2, is a virulent pneumonia, with >4,000,000 confirmed cases worldwide and >290,000 deaths as of May 15, 2020. It is critical that vaccines and therapeutics be developed very rapidly. Mice, the ideal animal for assessing such interventions, are resistant to SARS-CoV-2. Here, we overcome this difficulty by exogenous delivery of human ACE2 with a replication-deficient adenovirus (Ad5-hACE2). Ad5-hACE2-sensitized mice developed pneumonia characterized by weight loss, severe pulmonary pathology, and high-titer virus replication in lungs. Type I interferon, T cells and, most importantly, signal transducer and activator of transcription 1 (STAT1) are critical for virus clearance and disease resolution in these mice. Ad5-hACE2-transduced mice enabled rapid assessments of a vaccine candidate, of human convalescent plasma, and of two antiviral therapies (poly I:C and remdesivir). In summary, we describe a murine model of broad and immediate utility to investigate COVID-19 pathogenesis, and to evaluate new therapies and vaccines.

编者注：另一篇圣路易斯华盛顿大学研究团队采用相同的策略将小鼠变成 COVID-19 的动物模型，并测试了中和抗体的疗效。

一个 SARS-CoV-2 感染的小鼠模型揭示中和性抗体的保护作用

A SARS-CoV-2 infection model in mice demonstrates protection by neutralizing antibodies

链接：https://www.cell.com/action/showPdf?pii=S0092-8674%2820%2930742-X



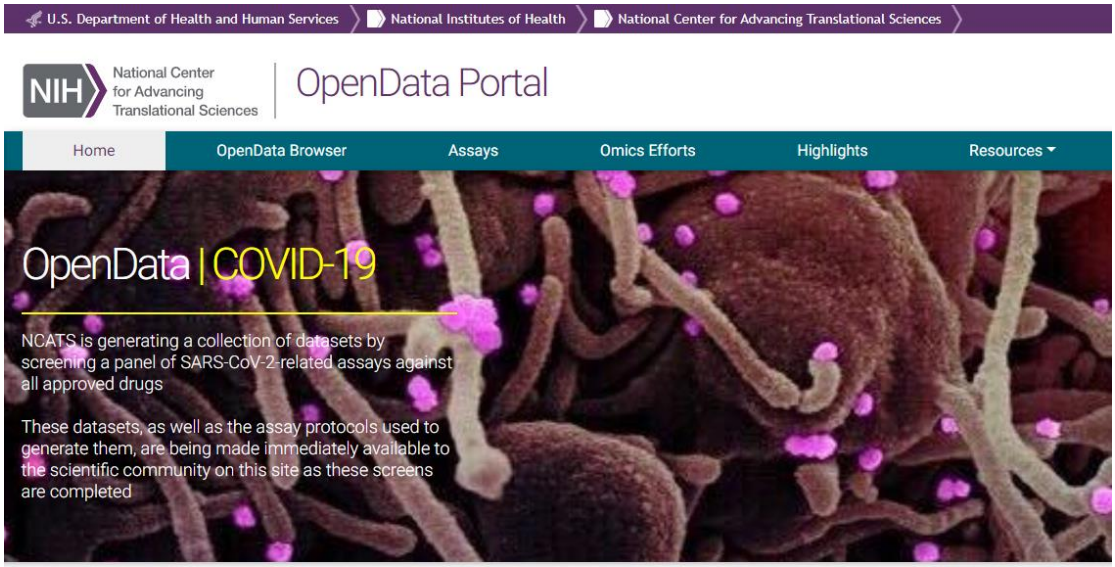
41. OpenData：一个实时共享有关 COVID-19 老药新用数据的门户网站

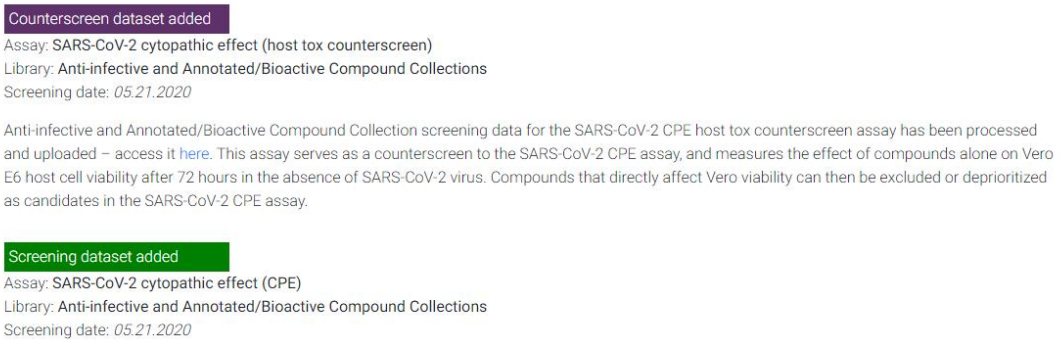
An OpenData portal to share COVID-19 drug repurposing data in real time

来源：bioRxiv
发布时间：2020-06-05
链接：https://www.biorxiv.org/content/10.1101/2020.06.04.135046v1
第一作者：Kyle R. Brimacombe, Tongan Zhao, Richard T. Eastman
通讯作者：Matthew D. Hall, Min Shen
通讯作者单位：National Center for Advancing Translational Sciences, National Institutes of Health
DOI 或 PUBMED ID：
编译者：宋珂
中文摘要：

美国国家转化科学促进中心（NCATS）为其关于 COVID-19 老药新用的项目开发了一个开放的科学数据门户网站，名为 OpenData。主要目的是实时共享各种与 SARS-CoV-2 相关的实验的数据。涉及的实验涵盖了广泛的 SARS-CoV-2 病毒生命周期，包括病毒和人类（宿主）靶点。在多个注释过的小分子化合物库中，总计有超过 10000 种化合物，在完整浓度响应范围内进行了测试。包括已获批的药物，老药新用的候选药物，以及为调节其他多种细胞靶点而设计的实验性治疗化合物。以期通过开放的数据共享和分析工具，来支持研究科学家，临床研究人员和公共卫生官员，促进针对 SARS-CoV-2 的干预措施的开发，并从未来 COVID-19 治疗方法发展的角度，对有潜力的化合物或老药新用的药物进行排序。

Figure 2. NCATS SARS-CoV-2 assays currently employed to address a range of both viral and host targets. Overview of established assays and those in development. These include assays for specific viral targets, viral-host interaction assays, viral detection assays and viral cytopathic effect and replication assays, among others.





网站地址：https://opendata.ncats.nih.gov/covid19/

Abstract:

The National Center for Advancing Translational Sciences (NCATS) has developed an online open science data portal for its COVID-19 drug repurposing campaign – named OpenData – with the goal of making data across a range of SARS-CoV-2 related assays available in real-time. The assays developed cover a wide spectrum of the SARS-CoV-2 life cycle, including both viral and human (host) targets. In total, over 10,000 compounds are being tested in full concentration-response ranges from across multiple annotated small molecule libraries, including approved drug, repurposing candidates and experimental therapeutics designed to modulate a wide range of cellular targets. The goal is to support research scientists, clinical investigators and public health officials through open data sharing and analysis tools to expedite the development of SARS-CoV-2 interventions, and to prioritize promising compounds and repurposed drugs for further development in treating COVID-19.