新型冠状病毒信息简报

第 43 期（2020 年 4 月 30 日报）

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

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1. 2020 年 4 月 29 日疫情

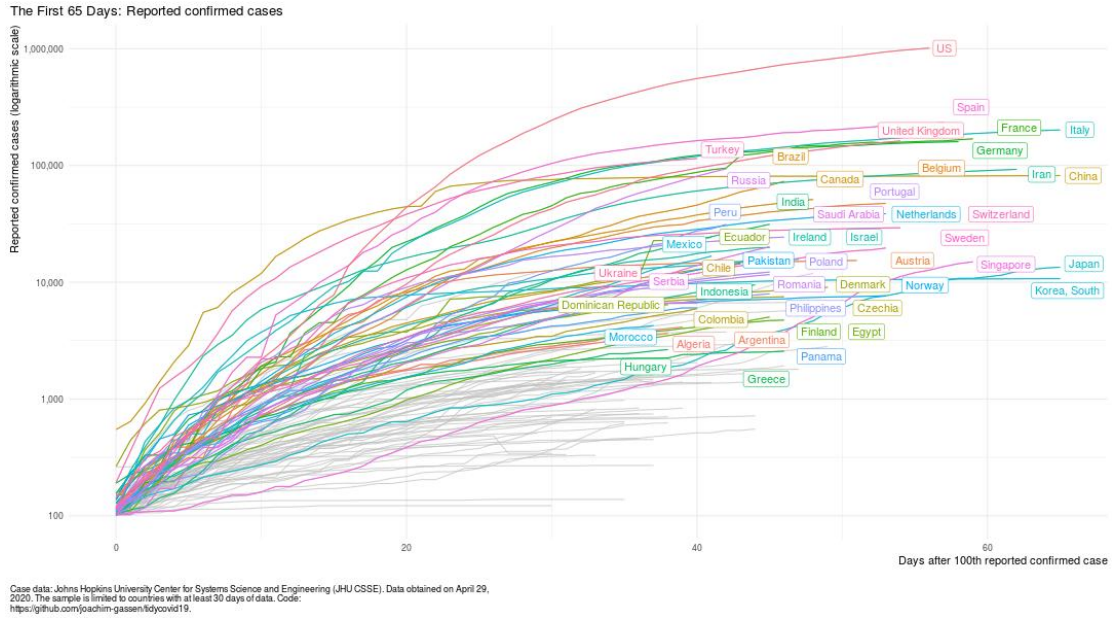
数据来源：WHO

发布时间：2020 年 4 月 29 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 4 月 29 日全球累计确诊新型冠状病毒病人 3018952 例，当日新增确诊 66276 例，累计死亡 207973 例，当日新增死亡 5376。

中国累计确诊 84369 例，累计死亡 4643 例，当日新增确诊 22 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 4 月 29 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（4 月 29 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 用 Cas13 进行大规模多重核酸检测

Massively multiplexed nucleic acid detection using Cas13

来源： nature 加速发表，文章未经编辑
发布时间： 2020-04-29
链接： https://www.nature.com/articles/s41586-020-2279-8
第一作者： Cheri M. Ackerman
通讯作者： Paul C. Blainey
通讯作者单位： Broad Institute of MIT and Harvard
DOI： https://doi.org/10.1038/s41586-020-2279-8
编译者： 蒋立春

中文摘要：

传染性疾病仍然是全球人类健康和安全的最大威胁之一。目前仍然缺乏一个光谱的监测可以对绝大部分病原微生物进行监测，成为疾病检测和监测的限制性因素。截止到2018年10月，总共有576种病原微生物已经被测序，其中169种有超过10条的公开基因组序列。对这些病原卫生物，总共只有39项被FDA批准的诊断（IVD，in vitro diagnostics，必需经过审批机构审批才能面市）。虽然一些特定机构开发了针对临床检测的实验室诊断（LDTs，laboratory developed tests。不同于IVD，LDTs可以不需要审批部门审批就可以用于临床检测），这些测试往往周转周期长，而且很少为多重检测（注：一次检测多个病原物）。

要实现常规化的疾病监测以及全面检测需要开发能够规模化、对很多样品同时进行多种病原菌进行检测的技术。

Broad 研究所的科学家们开发了一个对核酸进行多重检测的组合阵列反应（CARMEN）。这是一个可以规模化的对原微生物进行多重检测的平台(Fig.1, Fig.2)。在CARMEN平台，基于CRISPR的核酸检测试剂在微孔阵列里发生自组织，并且和包含已扩增的样品微滴形成配对，从而对每一个样品进行对应的CRISP RNA（CRISP-R）的多重复检测(编者注：基于CRISPR的检测技术中，检测信号会因为crRNA引导相关Cas酶找到目标核酸相结合而激活，所以针对性设计crRNA就可以对样品实现特定病毒微生物检测)。

将CARMEN平台和Cas13结合的检测可以在单个微阵列芯片上面检测>4500个crRNA-目标对。科学家们开发了一个同时可以检测 169 种人病毒的分析方法，并且很快加入了一个可以检测SARS-CoV-2的crRNA。作者们设计的一个检测芯片，可以同时对400个COVID-19病人的样品进行检测。在对58个真实样品进行169种病毒进行检测的测试中，该平台99.7%结果和NGS测序一致。

该平台也可以对要检测的病原微生物进行分型检测。比如文中讲到作者们实际用该平台实现了甲型流感的亚型分型，以及对HIV抗药株进行鉴定。CARMEN平台的内在多重属性以及通量能力让它可以实现规模化，和用孔板的CRSIPR的核酸检测技术SHERLOCK进行比较，CARMEN可以将试剂成本降低300倍甚至更多（单个反应体系小，故而节省试剂，）。这种易于规模化的基于CRISPR的多重核酸检测可能会改变核酸检测的方式，目前对重点样品进行特定目标检测的策略，可能会变成对大量的样品进行全面的检测，这对病人和公共卫生系统都会大有裨益。

文中的技术细节非常丰富，值得对技术感兴趣的读者仔细阅读。

比如:

1,文中提到如何针对很多种病毒基因组设计最好的crRNA（会有专门文章讲述）

2,文中讲到用4种市售的的小分子荧光开发一套1050种液相颜色代码

3,如何一步步采用合成样品、真实临床样品对检测系统进行测试和优化，确认不同病原物间的检测很少发生交叉反应

4，用高通量测序做为标准并进行比较

5，怎么用 PMDS 制作微阵列芯片，优化微阵列微孔的参数
等等

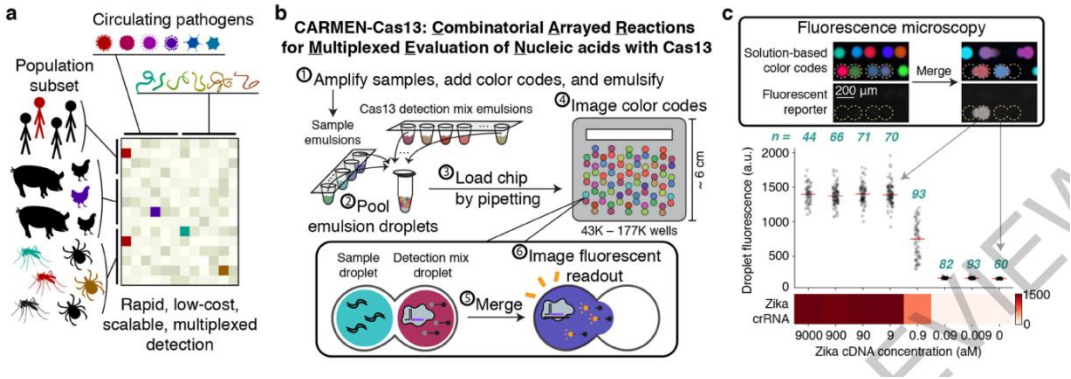


Fig.1 Combinatorial Arrayed Reactions for Multiplexed Evaluation of Nucleic acids with Cas13 (CARMEN-Cas13) achieves attomolar sensitivity. a, Identification of multiple circulating pathogens in human and animal populations represent a large-scale detection problem. b, Schematic of CARMEN-Cas13 workflow. c, Zika cDNA is detected by a single CARMEN-Cas13 assay with attomolar sensitivity and tens of replicate droplet pairs (black dots,
numbers of replicates are in blue); red lines mark medians in the graph and are used to construct the heatmap below. Representative droplet images are shown above the graph.

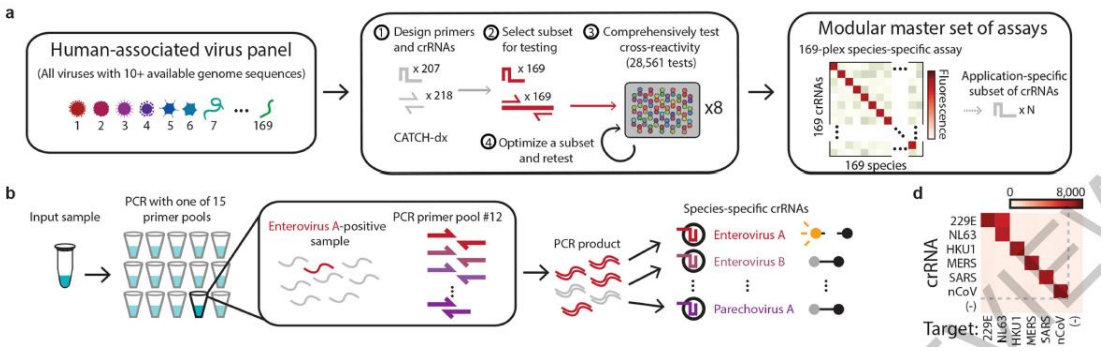


Fig.2 Comprehensive identification of human-associated viruses with CARMEN-Cas13. a, The development and testing of a panel for all 169 human-associated viruses with ⩾10 available genome sequences.
b, Experimental design using pooled PCR amplification.

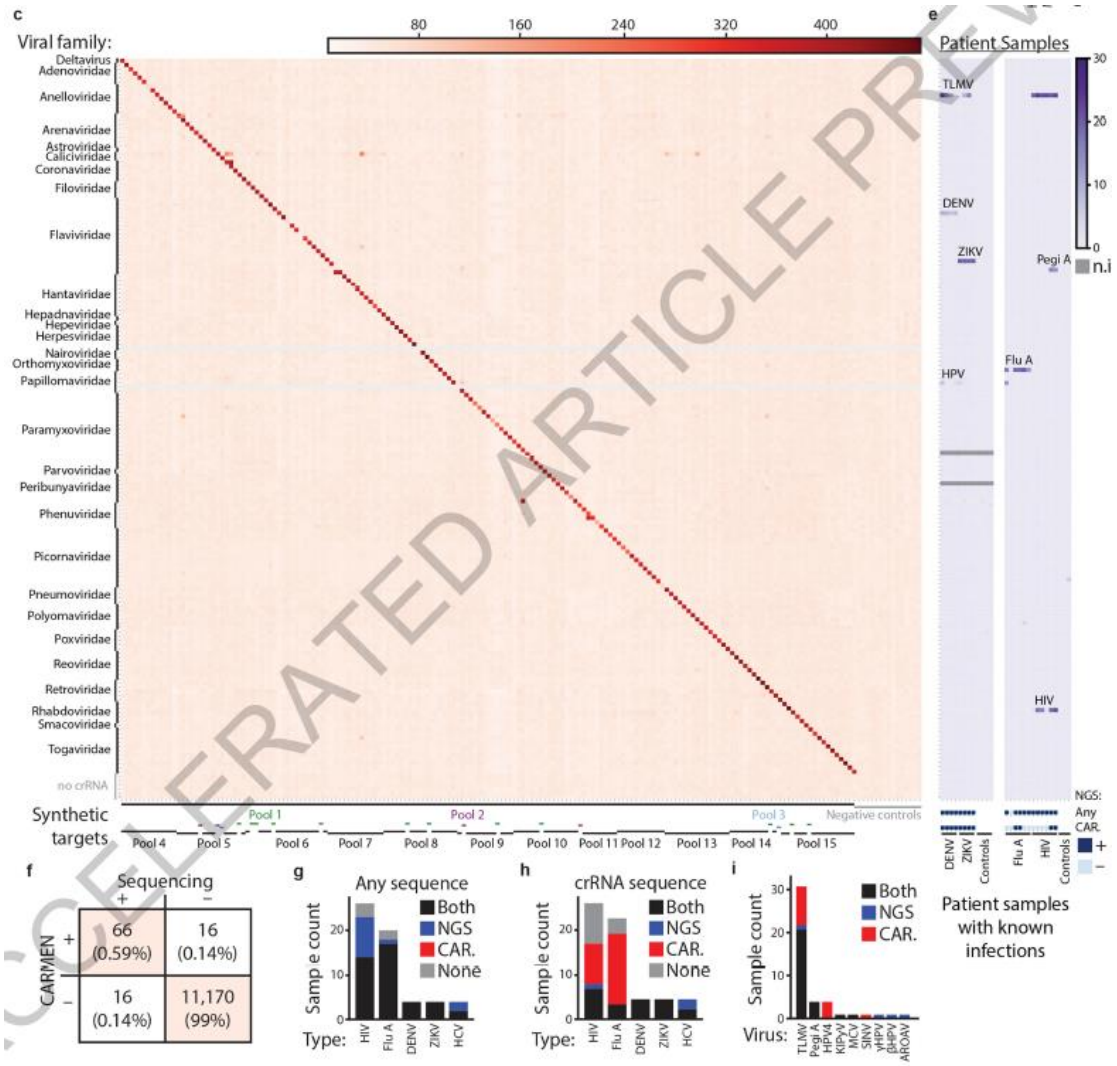


Fig.2 c, Testing a comprehensive human-associated viral (HV) panel with synthetic targets using
CARMEN-Cas13. PCR primer pools and viral families are below and to the left of the heatmap, respectively. Gray lines: crRNAs not tested. d, Multiplexed coronavirus panel. 229E, NL63, HKU1: human coronaviruses 229E, NL63, and HKU1; MERS: Middle East respiratory syndrome coronavirus; SARS: severe acute respiratory syndrome coronavirus; nCoV: novel coronavirus SARS-CoV-2. e, Testing the HV panel with patient samples (additional data: Extended Data Fig. 8a). Heatmaps indicate background-subtracted fluorescence after 1 h (c) or 30 min (d), or fold-change over background (e). f, Concordance of CARMEN and NGS for patient sample testing. Each box displays the number of tests and the percent of the total. g, Identification by NGS or CARMEN of any viral sequence from the known infections in patient samples (e.g. HIV test results for HIV samples). h, Identification by NGS or CARMEN of the crRNA target for each known infection. i, Positive test results in patient samples for viruses other than the known infections. In g-i, Black: detected by CARMEN and NGS; Blue: detected by NGS only; Red: detected by CARMEN only; Gray: not detected by CARMEN or NGS. DENV: dengue virus; ZIKV: Zika virus; HCV: hepatitis C virus;

TLMV: Torque teno-like mini virus; Pegi A: pegivirus A; HPV4: human papillomavirus 4; KIPyV: KI polyomavirus; MCV: Merkel cell polyomavirus; SINV: Sindbis virus, γHPV: gamma human papillomavirus; βHPV: beta human papillomavirus 2; AROAV: aroa virus (Note: CARMEN does not test for γHPV or AROAV because fewer than 10 γHPV or AROAV genomes had been published before Oct 24, 2018).

Abstract:
The overwhelming majority of globally circulating pathogens go undetected, undermining patient care and hindering outbreak preparedness and response. To enable routine surveillance and comprehensive diagnostic applications, there is a need for detection technologies that can scale to test many samples while simultaneously testing for many pathogens. Here, we develop Combinatorial Arrayed Reactions for Multiplexed Evaluation of Nucleic acids (CARMEN), a platform for scalable, multiplexed pathogen detection. In the CARMEN platform, nanoliter droplets containing CRISPR-based nucleic acid detection reagents self-organize in a microwell array to pair with droplets of amplified samples, testing each sample against each CRISPR RNA (crRNA) in replicate. The combination of CARMEN and Cas13 detection (CARMEN-Cas13) enables robust testing of >4,500 crRNA-target pairs on a single array. Using CARMEN-Cas13, we developed a multiplexed assay that simultaneously differentiates all 169 human-associated viruses with ≥10 published genome sequences and rapidly incorporated an additional crRNA to detect the causative agent of the 2020 COVID-19 pandemic. CARMEN-Cas13 further enables comprehensive subtyping of influenza A strains and multiplexed identification of dozens of HIV drug-resistance mutations. CARMEN's intrinsic multiplexing and throughput capabilities make it practical to scale, as miniaturization decreases reagent cost per test >300-fold. Scalable, highly-multiplexed CRISPR-based nucleic acid detection shifts diagnostic and surveillance efforts from targeted testing of high-priority samples to comprehensive testing of large sample sets, greatly benefiting patients and public health.

3. 克服广泛检测的瓶颈：COVID-19 核酸检测方法的快速回顾

Overcoming the bottleneck to widespread testing: A rapid review of nucleic acid testing approaches for COVID-19 detection

来源：Twitter（聂焱老师推荐）

发布时间：2020-04-27

链接：https://gitlab.com/tjian-darzacq-lab/covid19_review

第一作者：Meagan N. Esbin

通讯作者：Robert Tjian,Tjian + Darzacq Lab

通讯作者单位：加州大学伯克利分校

DOI 或 PUBMED ID：https://doi.org/10.5281/zenodo.3776183

编译者：宋张悦

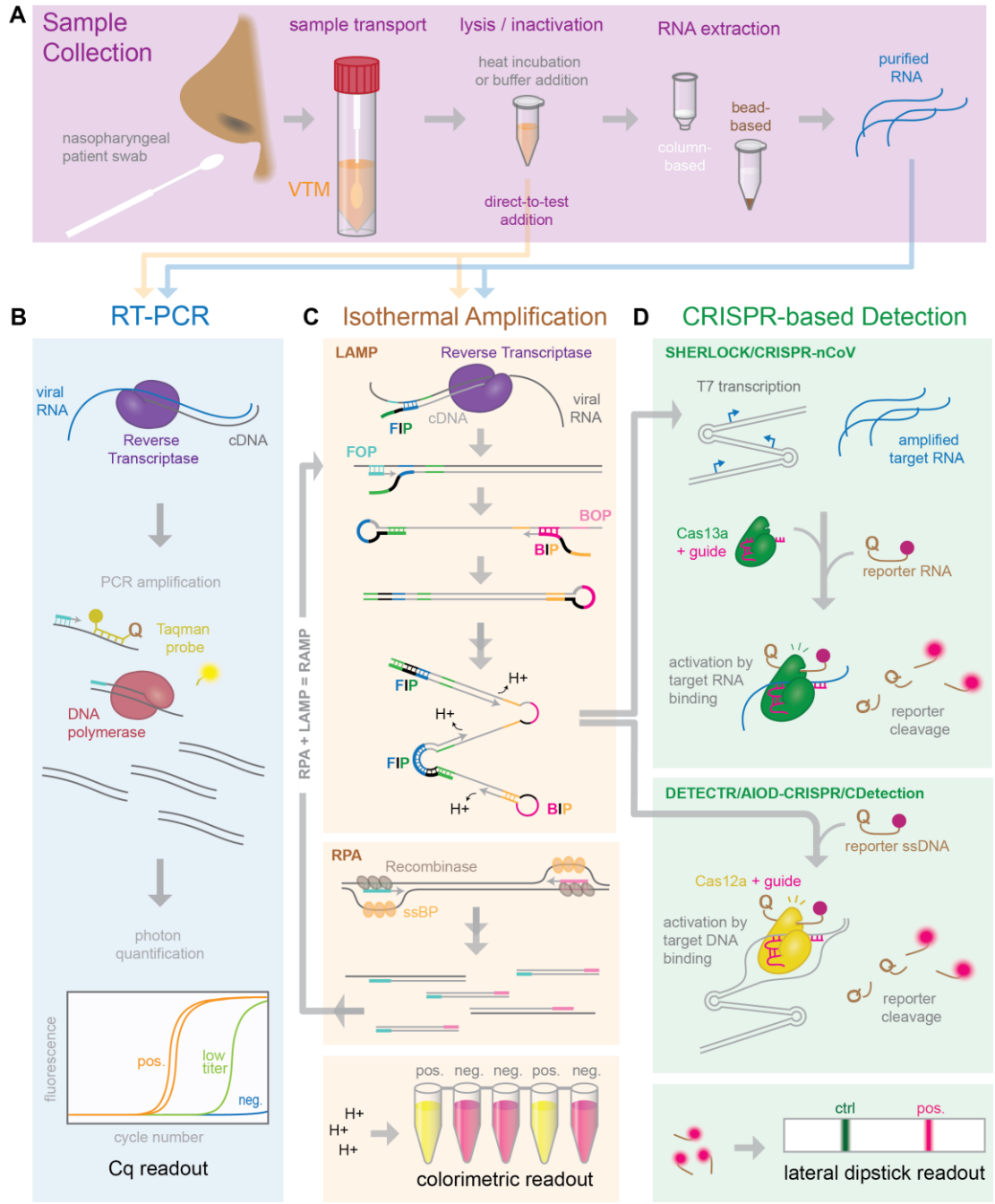
中文摘要：

目前的 COVID-19 大流行造成了严重的公共卫生危机，更广泛的检测将有助于更好地了解该

病毒的范围和传播。目前提供 COVID-19 最灵敏和早期的检测方法都是基于核酸的检测。然而，由美国疾病控制与预防中心率先提出的“金标准”检测需要几个小时才能完成，而且需要大量的人力和物力，包括可能出现供应短缺的 RNA 提取试剂盒等材料，以及相对稀缺的 qPCR 仪。很明显，需要付出巨大的努力来按数量级扩大当前的 COVID-19 检测能力。因此，迫切需要评估替代方案、试剂和方法，以便在面临这些潜在短缺的情况下继续进行核酸检测。在大流行的最初几周内，对潜在的进展、可比较的试剂和“金标准”CDC RT-PCR 检测的替代方法进行评估的论文数量出现了巨大的爆炸式增长。本文中，研究人员综述了 COVID-19 核酸检测的最新进展，包括同行评审和预印本文章。研究人员已经尽可能多地收录了出版物，但由于危机期间方法的快速方法，许多引用的来源还没有经过同行评审，因此作者敦促研究人员在他们自己的实验室进一步验证结果。作者希望这一篇综述能够紧急地整合和传播信息，可以帮助研究人员设计和实施优化的 COVID-19 检测操作流程，可以提高广泛的 COVID-19 检测的可用性、准确性和速度。

Abstract:

The current COVID-19 pandemic presents a serious public health crisis, and a better understanding of the scope and spread of the virus would be aided by more widespread testing. Nucleic acid based tests currently offer the most sensitive and early detection of COVID-19. However, the “gold standard” test pioneered by the United States Center for Disease Control & Prevention, takes several hours to complete and requires extensive human labor, materials such as RNA extraction kits that could become in short supply and relatively scarce qPCR machines. It is clear that a huge effort needs to be made to scale up current COVID-19 testing by orders of magnitude. There is thus a pressing need to evaluate alternative protocols, reagents, and approaches to allow nucleic-acid testing to continue in the face of these potential shortages. There has been a tremendous explosion in the number of papers written within the first weeks of the pandemic evaluating potential advances, comparable reagents, and alternatives to the “gold-standard” CDC RT-PCR test. Here we present a collection of these recent advances in COVID-19 nucleic acid testing, including both peer-reviewed and preprint articles. Due to the rapid developments during this crisis, we have included as many publications as possible, but many of the cited sources have not yet been peer-reviewed, so we urge researchers to further validate results in their own labs. We hope that this review can urgently consolidate and disseminate information to aid researchers in designing and implementing optimized COVID-19 testing protocols to increase the availability, accuracy, and speed of widespread COVID-19 testing.



Graphical Abstract. An overview of COVID-19 nucleic acid testing. Samples collected via nasopharyngeal swab are lysed and inactivated, and an amplification reaction is performed using either crude swab sample or purified RNA. Amplification of specific viral sequences by RT-PCR, LAMP, or RPA is detected using fluorescent or colorimetric dyes, sequence-specific CRISPR-Cas nuclease cleavage of a reporter, or separation of reaction products on a lateral flow dipstick.

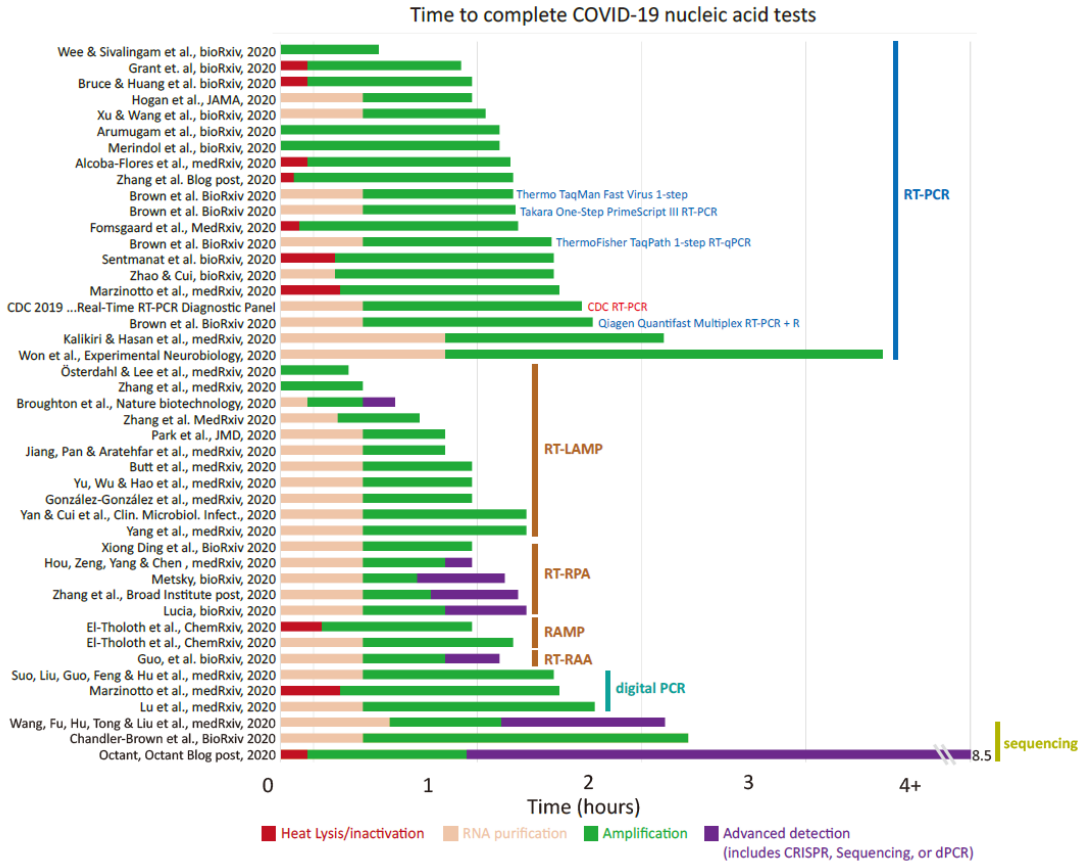


Figure 3. Examination of the total workflow for published COVID-19 testing methods. Each step of the workflow is shown with colored bars. Four example commercial RT-PCR kits are included for reference (blue)and were directly compared within a single publication. The CDC RT-PCR test is shown in red. Raw data available in Table S1.

编者注：之前有简要报道（文献 1）讲到 COVID-19 病亡病人有 71%在住院期间发生了血管内凝固，故而凝血管理在 COVID-19 中有重要意义。

文献 1： Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

https://onlinelibrary.wiley.com/doi/full/10.1111/jth.14768

4. 肝素诱导的血小板减少症与接受肝素相关治疗的 COVID-19 危重症患者的高死亡率相关

Heparin-induced thrombocytopenia is associated with a high risk of mortality in critical COVID-19 patients receiving heparin-involved treatment

来源：medRxiv

发布时间：2020-04-28

链接：https://www.medrxiv.org/content/10.1101/2020.04.23.20076851v1

第一作者：Xuan Liu, Xiaopeng Zhang, Yongjiu Xiao, Ting Gao, Guangfei Wang

通讯作者：卞修武[3,6]，毛青[3,6]，曹诚[1]

通讯作者单位：1 北京生物技术研究所，3 陆军军医大学第一附属医院（西南医院），6 武汉火神山医院

DOI 或 PUBMED ID：

编译者：宋张悦

中文摘要：

背景：2019 年冠状病毒传染病(COVID-19)已发展为全球大流行。为了降低 COVID-19 的总死亡率，有必要研究其临床特点，发现可能导致严重疾病的潜在危险因素。

方法：本研究纳入 61 例重症监护室(ICU)的 COVID-19 患者和 93 例重症非 ICU 患者(武汉，中国)。分析和比较了 COVID-19 患者的医疗记录，包括人口统计学、血小板计数、肝素相关治疗、肝素诱导的血小板减少症(HIT)相关实验室检测和死亡结局。

结果：61 例在 ICU 接受治疗的危重 COVID-19 患者包括 15 名幸存者和 46 名病亡者。其中 41%(25/61)患有严重的血小板减少症，血小板计数(PLT)低于 $50x10^9$/L，其中 76%(19/25)的患者血小板水平较基线下降 50%；96%的患者(24/25)有致命的结局。在 46 名病亡者中，52.2%(24/46)患有严重的血小板减少症，而在幸存者中这一比例为 6.7%(1/15)。此外，持续肾脏替代治疗(CRRT)可导致 81.3%的重症 CRRT 患者 PLT 显著降低(13/16)，从而导致死亡。此外，在大多数 ICU 患者中发现了高水平的 HIT 标志物——抗肝素-PF4 抗体。令人惊讶的是，**HIT 不仅发生在有肝素暴露的患者(如 CRRT)中，也发生在无肝素暴露的患者中，提示 COVID-19 可能发生自发性 HIT**。

解释：在危重症的 COVID-19 患者中诱导抗肝素-PF4 抗体，会导致血小板进行性下降。暴露于高剂量的肝素可能引发进一步的严重血小板减少症，并有致命的后果。除了肝素外，还应使用其他抗凝药物治疗 COVID-19 危重症患者。

Abstract:

Background Coronavirus infectious disease 2019 (COVID-19) has developed into a global pandemic. It is essential to investigate the clinical characteristics of COVID-19 and uncover potential risk factors for severe disease to reduce the overall mortality rate of COVID-19.

Methods Sixty-one critical COVID-19 patients admitted to the intensive care unit (ICU) and 93 severe non-ICU patients at Huoshenshan Hospital (Wuhan, China) were included in this study. Medical records, including demographic, platelet counts, heparin-involved treatments, heparin-induced thrombocytopenia-(HIT) related laboratory tests, and fatal outcomes of COVID-19 patients were analyzed and compared between survivors and nonsurvivors.

Findings Sixty-one critical COVID-19 patients treated in ICU included 15 survivors and 46 nonsurvivors. Forty-one percent of them (25/61) had severe thrombocytopenia, with a platelet count (PLT) less than 50x109/L, of whom 76% (19/25) had a platelet decrease of >50% compared to baseline; 96% of these patients (24/25) had a fatal outcome. Among the 46 nonsurvivors, 52.2% (24/46) had severe thrombocytopenia, compared to 6.7% (1/15) among survivors. Moreover, continuous renal replacement therapy (CRRT) could induce a significant decrease in PLT in 81.3% of critical CRRT patients (13/16), resulting in a fatal outcome. In addition, a high level of anti-heparin-PF4 antibodies, a marker of HIT, was observed in most ICU patients. Surprisingly, HIT occurred not only in patients with heparin exposure, such as CRRT, but also in heparin-naive patients, suggesting that spontaneous HIT may occur in COVID-19.

Interpretation Anti-heparin-PF4 antibodies are induced in critical COVID-19

patients, resulting in a progressive platelet decrease. Exposure to a high dose of heparin may trigger further severe thrombocytopenia with a fatal outcome. An alternative anticoagulant other than heparin should be used to treat COVID-19 patients in critical condition.

5. 新冠肺炎患者呼吸道的先天免疫反应增强

Heightened innate immune responses in the respiratory tract of COVID-19patients

来源：Cell Host and Microbe
发布时间：2020-04-28
链接：https://www.cell.com/pb-assets/products/coronavirus/chom2304.pdf
第一作者：Zhuo Zhou
通讯作者：李明锟，王健伟
通讯作者单位：中国科学院北京基因组研究所，中国医学科学院/北京协和医学院
DOI 或 PUBMED ID：10.1016/j.chom.2020.04.017
编译者：刘焕珍

中文摘要：

由 SARS-CoV-2 感染引起的新冠肺炎爆发对全球公共卫生构成了严重威胁。目前尚不清楚人类的免疫系统如何应对这种感染。文中作者使用了转录组测序技术，对 8 例新冠肺炎病例的支气管肺泡灌洗液中的免疫特征进行了分析。与社区获得性肺炎患者和健康对照相比，COVID-19 病例中促炎基因（尤其是趋化因子）的表达明显升高，表明 SARS-CoV-2 感染会引起高细胞血症。与被认为诱导干扰素（IFN）反应不足的 SARS-CoV 相比，SARS-CoV-2 强烈触发了许多 IFN 诱导型基因（ISG）的表达。这些 ISG 显示出免疫致病性潜力，与炎症相关基因的过量表达。转录组数据还用于估计免疫细胞群，揭示了活化的树突状细胞和中性粒细胞的增加。总的来说，这些宿主对 SARS-CoV-2 感染的反应可以进一步加深人们对疾病发病机制的了解并指出抗病毒策略。

Abstract:

The outbreaks of 2019 novel coronavirus disease (COVID-19) caused by SARS-CoV-2 infection has posed a severe threat to global public health. It is unclear how the human immune system responds to this infection. Here, we used meta transcriptomic sequencing to profile immune signatures in the broncho alveolar lavage fluid of eight COVID-19 cases. The expression of proinflammatory genes, especially chemokines, was markedly elevated in COVID-19 cases compared to community-acquired pneumonia patients and healthy controls, suggesting that SARS-CoV-2 infection causes hypercytokinemia. Compared to SARS-CoV, which is thought to induce inadequate interferon (IFN) responses, SARS-CoV-2 robustly triggered expression of numerous IFN-inducible genes (ISGs). These ISGs exhibit immunopathogenic potential, with overrepresentation of genes involved in inflammation. The transcriptome data was also used to estimate immune cell populations, revealing increases in activated dendritic cells and neutrophils. Collectively, these host responses to SARS-CoV-2 infection could further our understanding of disease pathogenesis and point towards antiviral strategies.

6. 影响肾素-血管紧张素-醛固酮系统的药物对 COVID-19 易感性和严重性的作用：来自中国浙江省的一项大型病例对照研究

Role of Drugs Affecting the Renin-Angiotensin-Aldosterone System on Susceptibility and Severity of COVID-19: A Large Case-Control Study from Zhejiang Province, China.

来源： medRxiv
发布时间： 2020-04-24
链接： https://www.medrxiv.org/content/10.1101/2020.04.24.20077875v1
第一作者： Hua dong Yan
通讯作者： Ting Cai
通讯作者单位： 宁波市第二医院华美医院
DOI 或 PUBMED ID： Preprint
编译者： 孔娟

中文摘要：

背景：相关医学社论建议，在 2019 年冠状病毒病(COVID-19)大流行期间，血管紧张素转换酶抑制剂(ACEIs)和血管紧张素受体阻滞剂(ARBs)不应用于动脉高血压患者，因为其潜在的临床预后不良风险增加，钙通道阻滞剂(CCBs)应作为替代药物使用。

方法：文中研究者纳入了浙江省的 610 例 COVID-19 病例和 48，667 例对照，测试了 ACEIs、ARBs、CCBs 和其他药物的使用对 COVID-19 风险和严重程度的作用。研究者根据年龄、性别和体重指数以及相关并发基础病的存在对分析进行了调整。

结果:高体重指数、糖尿病和心脑血管疾病是 COVID-19 发展的独立危险因素。**服用 CCBs 的高血压患者出现 COVID-19 症状的风险显著增加[OR=1.67 (95%置信区间 1.2-2.9)]，而服用 ARBs 和利尿剂的患者疾病风险显著降低(OR=0.24 95%置信区间 0.17-0.34，或 OR=0.32；95%置信区间 0.19-0.57)。**其他抗高血压药物与严重或严重感染风险的增加无关。糖皮质激素的使用与 COVID-19 的严重/临界形式显著相关(OR=7.56 95% 置信区间 1.17-48.93)。

解释:作者没有发现在大流行背景下改变 ARBs 或 ACEIs 治疗的证据。服用皮质类固醇的 COVID-19 患者发生严重 COVID-19 的风险更高，因此应密切监测。

Abstract

Background. Medical editorials have suggested that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) should not be given to people with arterial hypertension during the coronavirus disease 2019 (COVID-19) pandemic because of a potential increased risk of worse clinical outcomes and that calcium channel blockers (CCBs) should be used as an alternative.

Methods Using a cohort of 610 COVID-19 cases and 48,667 population-based controls from Zhejiang, China we have tested the role of usage of ACEIs, ARBs, CCBs and other medications on risk and severity of COVID 19. Analyses were adjusted for age, sex and BMI and for presence of relevant comorbidities.

Findings: Higher BMI, diabetes and cardio/ cerebrovascular disease are independent risk factors for the development of COVID-19. Individuals with hypertension taking CCBs had significantly increased risk [odds ratio (OR)= 1.67 (95% CI 1.2-2.9)) of manifesting symptoms of COVID-19 whereas those taking ARBs and diuretics had significantly lower disease risk (OR=0.24; 95% CI 0.17-0.34 and OR=0.32; 95%CI 0.19-0.57 respectively). Other antihypertensive drugs were

not associated with increased risk of severe or critical form of the infection. Use of glucocorticoids was significantly associated with a severe/critical form of COVID-19 (OR=7.56; 95% CI 1.17-48.93).
Interpretation: We found no evidence to alter ARBs or ACEIs therapy in the context of the pandemic. Patients on corticosteroids with COVID-19 are at higher risk of developing a severe form of COVID-19and therefore should be monitored closely.

7. 冠状病毒疫苗竞赛：图解指南

The race for coronavirus vaccines: a graphical guide

来源：Nature

发布时间：2020-04-28

链接：https://www.nature.com/articles/d41586-020-01221-y

第一作者：Ewen Callaway

通讯作者：Ewen Callaway

通讯作者单位：记者

DOI 或 PUBMED ID：新闻

编译者：雷颖

中文摘要：

世界各地的公司和大学的研究小组正在研制 90 多种针对 SARS-CoV-2 的疫苗。研究人员正在试验不同的技术，其中一些以前还没有被用于许可的疫苗。至少有 6 个小组已经开始在安全试验中向志愿者注射制剂；其他小组则开始在动物中进行试验。至少有八种类型的基于不同的病毒或病毒部位的疫苗被尝试用来对抗冠状病毒。

病毒疫苗：至少有 7 个团队正在开发使用病毒本身的疫苗，以减弱或灭活的形式。许多现有的疫苗都是以这种方式生产的，如麻疹和脊髓灰质炎疫苗，但它们需要广泛的安全测试。北京的 Sinovac 生物技术公司已经开始测试人类 SARS-CoV-2 的灭活版本。

病毒载体疫苗：大约 25 个团队声称他们正在研究病毒载体疫苗。这种疫苗是通过基因改造某种病毒，例如麻疹或腺病毒，以便它能在人体内产生冠状病毒蛋白。这些病毒被削弱了，所以它们不能引起疾病。这些病毒有两种类型：一种是仍可以在细胞内复制的，一种是因关键基因缺失而不能复制的。

核酸疫苗：至少有 20 个团队的目标是使用遗传指令（以 DNA 或 RNA 的形式）来获得冠状病毒蛋白，从而引发免疫反应。核酸被插入到人类细胞中，然后产生病毒蛋白的拷贝；这些疫苗大多编码病毒的刺突蛋白。

蛋白疫苗：许多研究人员希望将冠状病毒蛋白直接注射到体内。类似冠状病毒外壳的蛋白质或蛋白质外壳碎片也可以使用。

编者注：该文为每一种疫苗技术配了图解，限于篇幅不在此展示，有兴趣读者可以自行查看原文。

Abstract

More than 90 vaccines are being developed against SARS-CoV-2 by research teams in companies and universities across the world. Researchers are trialing different technologies, some of which haven’t been used in a licensed vaccine before. At least six groups have already begun injecting formulations into volunteers in safety trials; others have started testing in animals. There are

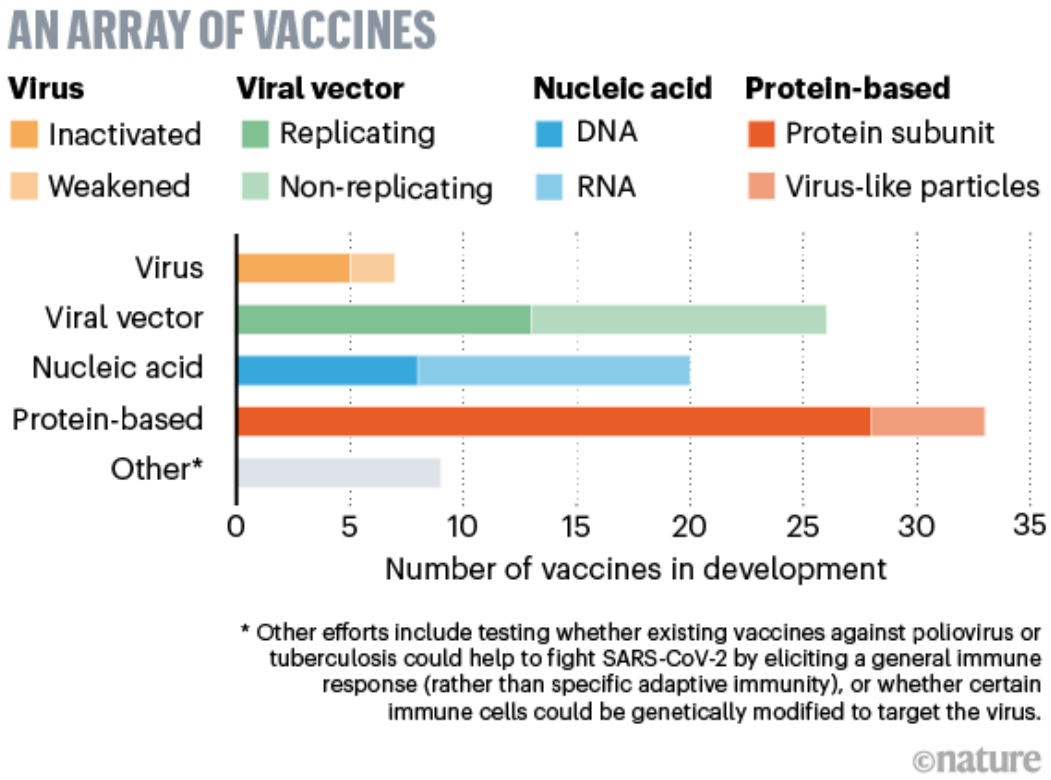
at least eight types being tried against the coronavirus, and they rely on different viruses or viral parts.

Virus vaccines: At least seven teams are developing vaccines using the virus itself, in a weakened or inactivated form. Many existing vaccines are made in this way, such as those against measles and polio, but they require extensive safety testing. Sinovac Biotech in Beijing has started to test an inactivated version of SARS-CoV-2 in humans.

Viral-vector vaccines: Around 25 groups say they are working on viral-vector vaccines. A virus such as measles or adenovirus is genetically engineered so that it can produce coronavirus proteins in the body. These viruses are weakened so they cannot cause disease. There are two types: those that can still replicate within cells and those that cannot because key genes have been disabled.

Nucleic-acid vaccines: At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein; most of these vaccines encode the virus's spike protein.

Protein-based vaccines: Many researchers want to inject coronavirus proteins directly into the body. Fragments of proteins or protein shells that mimic the coronavirus's outer coat can also be used.



8. 瑞德西韦治疗成人重症 COVID-19：随机、双盲、安慰剂对照、多中心试验

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

来源：The Lancet
发布时间：2020-04-29
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第一作者：Yeming Wang, Dingyu Zhang, Guanhua Du, Ronghui Du, Jianping Zhao, Yang Jin, Shouzhi Fu, Ling Gao, Zhenshun Cheng, QiaofaLu,Yi Hu, Guangwei Luo
通讯作者：曹彬，王辰
通讯作者单位：中日友好医院呼吸与危重症医学科，北京协和医学院
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编译者：雷颖

中文摘要：

背景：没有一种特异性抗病毒药物被证明能有效地治疗 COVID-19。瑞德西韦（GS-5734）是一种核苷类似物前体药物，对致病性动物和人类冠状病毒，包括 SARS-CoV-2 具有体外抑制作用，并抑制中东呼吸综合征冠状病毒、SARS-CoV-1 和 SARS-CoV-2 在动物模型中的复制。

方法：在湖北 10 家医院进行随机、双盲、安慰剂对照、多中心试验。符合条件的患者是成人（≥18 岁），经实验室证实患有 SARS-CoV-2 感染，从症状开始到入院的间隔为 12 天或以下，血氧饱和度为 94%或以下，动脉血氧分压与部分激发氧的比值为 300 毫米汞柱或以下，以及胸片证实的肺炎。患者以 2：1 的比例被随机分配在静脉注射瑞德西韦（200 毫克在第 1 天，然后 100 毫克在第 2-10 天在单日输注）或相同体积的安慰剂输注 10 天。患者被允许同时使用洛皮那韦-利托那韦，干扰素和皮质类固醇。主要终点是临床改善的时间，直到第 28 天，定义为从随机化到临床状态的六点顺序量表（从 1=出院到 6=死亡）或活着出院的时间（以天为单位），以先到者为准。在治疗意向(ITT)人群中进行了初步分析，并对所有开始指定治疗的患者进行了安全性分析。本试验注册于 ClinicalTrials.gov，NCT04257656。

结果：在 2020 年 2 月 6 日至 2020 年 3 月 12 日期间，237 名患者被登记并随机分配到一个治疗组（158 名为瑞德西韦，79 名为安慰剂）；安慰剂组中的一名患者在随机化后退出，不包括在 ITT 人群中。瑞德西韦的使用与临床改善的时间差异无关(风险比为 1.23[95%CI 为 0.87-1.75])。**虽然没有统计学意义，但在症状持续时间为 10 天或更短的患者中，接受瑞德西韦的患者比接受安慰剂的患者有更快的临床改善时间（风险比为 1.52[0.95-2.43]）**。不良事件报告中，155 名瑞德西韦接受者有 102（66%）例，78 名安慰剂接受者有 50（64%）例。在 18 例（12%）患者中，瑞德西韦由于不良事件而早期停止，而 4 例（5%）患者早期停止安慰剂。

解释：在本研究中，对于因重症 COVID-19 入院的成人患者，瑞德西韦未表现出统计学意义上的临床益处。然而，那些早期治疗可获得更快临床改善的发现需要在更大的研究中确认。

Abstract

Background: No specific antiviral drug has been proven effective for treatment of patients with severe coronavirus disease 2019 (COVID-19). Remdesivir (GS-5734), a nucleoside analogue prodrug, has inhibitory effects on pathogenic animal and human coronaviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro, and inhibits Middle East respiratory syndrome coronavirus, SARS-CoV-1, and SARS-CoV-2 replication in animal models.

Methods: We did a randomised, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China. Eligible patients were adults (aged ≥18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, oxygen saturation

of 94% or less on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia. Patients were randomly assigned in a 2:1 ratio to intravenous remdesivir (200 mg on day 1followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. Primary analysis was done in the intention-to-treat (ITT)population and safety analysis was done in all patients who started their assigned treatment. This trial is registered with ClinicalTrials.gov, NCT04257656.

Findings: Between Feb 6, 2020, and March 12, 2020, 237 patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo); one patient in the placebo group who withdrew after randomisation was not included in the ITT population. Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0.87–1.75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1.52 [0.95–2.43]). Adverse events were reported in 102 (66%) of155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early.

Interpretation: In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement inthose treated earlier requires confirmation in larger studies.

9. 吉利德公布了在重症 COVID-19 患者中使用抗病毒药物瑞德西韦的三期试验结果

Gilead Announces Results From Phase 3 Trial of Investigational Antiviral Remdesivir in Patients With Severe COVID-19

来源：加利福尼亚州福斯特市（商业通讯社）

发布时间：2020-04-29

链接：http://investors.gilead.com/news-releases/news-release-details/gilead-announces-results-phase-3-trial-investigational-antiviral?from=singlemessage

第一作者：吉利德

通讯作者：吉利德

通讯作者单位：吉利德科学

DOI 或 PUBMED ID：新闻

编译者：张丽双

中文摘要：

2020 年 4 月 29 日——吉利德科学今天公布了开放标签 SIMPLE 三期试验结果，该试验评估了新型冠状病毒肺炎的重症住院患者中，一个较短的 5 天疗程的瑞德西韦是否能达到与多

个正在进行的瑞德西韦研究中使用的 10 天治疗方案相似的疗效。评价指标：患者需要有肺炎和氧气水平降低的证据，在研究开始时不需要机械通气。临床改善：是在预先确定的七点量表上，从基线到两个或多个点的改善。临床康复：如果患者不再需要氧气支持和医疗护理，或者出院。

在这个研究中，50%的患者在 5 天治疗组和 10 天治疗组中的临床改善时间分别为 10 天和 11 天。在第 14 天，5 天治疗组 64.5%（n=129/200）的患者和 10 天治疗组 53.8%（n=106/197）的患者实现了临床康复。结果表明，**接受瑞德西韦 5 天疗程的患者与接受 10 天瑞德西韦疗程的患者的临床改善相似**（在第 14 天优势比：0.75[95%CI 0.51 - 1.12]）。在这两个治疗组中都没有发现新的瑞德西韦的安全信号。部分患者有可能可以接受 5 天的治疗方案，这将显著扩大在瑞德西韦目前的可供应量内接受治疗的患者数量。

另外在一项探索性分析中，研究中在症状出现后 10 天内接受瑞德西韦治疗的患者与在症状出现后 10 天以上接受瑞德西韦治疗的患者相比，其治疗效果有所改善。到第 14 天，62%的早期治疗患者能够出院，相比之下，49%的晚期治疗患者能够出院。

Abstract:

Apr. 29, 2020-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced topline results from the open-label, Phase 3 SIMPLE trial evaluating 5-day and 10-day dosing durations of the investigational antiviral remdesivir in hospitalized patients with severe manifestations of COVID-19 disease. The study demonstrated that patients receiving a 10-day treatment course of remdesivir achieved similar improvement in clinical status compared with those taking a 5-day treatment course (Odds Ratio: 0.75 [95% CI 0.51 - 1.12] on Day 14). No new safety signals were identified with remdesivir across either treatment group. Gilead plans to submit the full data for publication in a peer-reviewed journal in the coming weeks.

	5-Day RDV n=200	10-Day RDV n=197	Baseline adjusted p-value[1]
Clinical Efficacy Outcomes at Day 14			
≥ 2-point improvement in ordinal scale	129 (65)	107 (54)	0.16
Clinical recovery	129 (65)	106 (54)	0.17
Discharge	120 (60)	103 (52)	0.44
Death	16 (8)	21 (11)	0.70
Safety			
Any adverse event (AE)	141 (71)	145 (74)	0.86
Grade ≥3 study drug-related AE	8 (4)	10 (5)	0.65
Study drug-related serious adverse event (SAE)	3 (2)	4 (2)	0.73
AE leading to discontinuation	9 (5)	20 (10)	0.07

[1]Adjusted for baseline clinical status

10. NIH 临床试验显示瑞德西韦加速晚期 COVID-19 恢复

NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19

来源：NIAID（美国国家过敏和传染病研究所）

发布时间：2020-04-29

链接：https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

DOI 或 PUBMED ID：新闻
编译者：雷颖
中文摘要：
根据从 2 月 21 日开始的一项随机对照试验中得到的初步数据分析，接受瑞德西韦治疗的患有晚期 COVID-19 和肺部受累的患者比接受安慰剂的类似患者恢复得更快。该试验(称为适应性 COVID-19 治疗试验，或 ACTT)，由国家过敏和传染病研究所(NIAID，美国国立卫生研究院的一部分)赞助，是第一个在美国启动的评估 COVID-19 实验治疗的临床试验。
监督试验进展的 DSMB（一个独立的数据和安全监测委员会）于 4 月 27 日举行会议，审查数据，并与研究小组分享其初步分析。根据他们对数据的回顾，他们指出，从主要终点恢复时间(这是流感试验中经常使用的指标)的角度来看，瑞德西韦比安慰剂更好。在这项研究中，恢复被定义为足够出院或恢复到正常的活动水平。
初步结果表明，**接受瑞德西韦的患者比接受安慰剂的患者恢复时间快 31%（p<0.001）。具体来说，瑞德西韦治疗的患者恢复时间中位数为 11 天，而接受安慰剂的患者则为 15 天**。结果还表明，接受瑞德西韦组的死亡率为 8.0%，安慰剂组为 11.6%（p=0.059）。
该试验已于 4 月 19 日停止接受新注册。NIAID 还将提供 ACTT 试验进展计划的最新情况。这项试验是一项适应性试验，旨在纳入额外的调查治疗。

Abstract
Hospitalized patients with advanced COVID-19 and lung involvement who received remdesivir recovered faster than similar patients who received placebo, according to a preliminary data analysis from a randomized, controlled trial involving 1063 patients, which began on February 21. The trial (known as the Adaptive COVID-19 Treatment Trial, or ACTT), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, is the first clinical trial launched in the United States to evaluate an experimental treatment for COVID-19.
An independent data and safety monitoring board (DSMB) overseeing the trial met on April 27 to review data and shared their interim analysis with the study team. Based upon their review of the data, they noted that remdesivir was better than placebo from the perspective of the primary endpoint, time to recovery, a metric often used in influenza trials. Recovery in this study was defined as being well enough for hospital discharge or returning to normal activity level.
Preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo (p<0.001). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group (p=0.059).
The trial closed to new enrollments on April 19. NIAID will also provide an update on the plans for the ACTT trial moving forward. This trial was an adaptive trial designed to incorporate additional investigative treatments.

11. 一种新的蛋白质药物，Novaferon，作为 COVID-19 的潜在抗病毒药物

A Novel Protein Drug, Novaferon, as the Potential Antiviral Drug for COVID-19

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第一作者： Fang Zheng, Yanwen Zhou, Zhiguo Zhou, Fei Ye
通讯作者： Yongfang Jiang, YuanlinXie, Wenjie Tan, Guozhong Gong
通讯作者单位： 中南大学湘雅二医院传染病科
长沙市第一医院传染病科
中国疾病预防控制中心国家病毒性疾病预防控制研究所
中南大学湘雅二医院传染病科
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编译者： 张鹏伟
中文摘要：
背景：Novaferon,一种新的蛋白质药物在中国被批准用于治疗慢性乙型肝炎，显示出强大的抗病毒活性。本研究目的是在体外测定 Novaferon 的抗 SARS-CoV-2 作用，并进行随机、开放、平行分组研究，探讨 Novaferon 对 COVID-19 的抗病毒作用。
方法：在实验室条件下，研究了 Novaferon 对 SARS-CoV-2 感染细胞病毒复制和 SARS-CoV-2 进入健康细胞的抑制作用。在使用 Novaferon、Novaferon 加 Lopinavir/Ritonavir 或 Lopinavir/Ritonavir 的 COVID-19 患者中评估了 Novaferon 的抗病毒作用。主要终点为治疗第 6 天的 SARS-CoV-2 清除率，次要终点为 COVID-19 患者达到 SARS-CoV-2 清除的时间。
结果：Novaferon 抑制病毒在感染细胞中的复制（EC_{50}=1.02ng/ml），保护健康细胞免受 SARS-CoV-2 感染（EC_{50}=0.1ng/ml）。来自 89 名入组的 COVID-19 患者的结果表明，Novaferon 和 Novaferon 加 Lopinavir/Ritonavir 在第 6 天的 SARS-CoV-2 清除率均明显高于 Lopinavir/Ritonavir 组（分别为 50.0%对 24.1%，p=0.0400；60.0%对 24.1%，p=0.0053）。三组 SARS-CoV-2 清除的中位时间分别为 6 天、6 天和 9 天，表明 Novaferon 和 Novaferon 加 Lopinavir/Ritonavir 组的 SARS-CoV-2 清除时间均比 Lopinavir/Ritonavir 组缩短 3 天。
结论：Novaferon 在体外和 COVID-19 患者中均表现出抗 SARS-CoV-2 的作用。这些数据证明了对 Novaferon 的进一步评估是正确的。

Abstract:
Background:
Novaferon, a novel protein drug approved for the treatment of chronic hepatitis B in China, exhibits potent antiviral activities. We aimed to determine the anti-SARS-CoV-2 effects of Novaferon in vitro, and conducted a randomized, open-label, parallel group study to explore the antiviral effects of Novaferon for COVID-19.
Methods:
In laboratory, the inhibition of Novaferon on viral replication in cells infected with SARS-CoV-2, and on SARS-CoV-2 entry into healthy cells was determined. Antiviral effects of Novaferon were evaluated in COVID-19 patients with treatment of Novaferon, Novaferon plus Lopinavir/Ritonavir, or Lopinavir/Ritonavir. The primary endpoint was the SARS-CoV-2 clearance rates on day 6 of treatment, and the secondary endpoint was the time to the SARS-CoV-2 clearance in COVID-19 patients.
Results:
Novaferon inhibited the viral replication in infected cells (EC_{50}=1.02 ng/ml),

and protected healthy cells from SARS-CoV-2 infection (EC_{50}=0.1 ng/ml). Results from the 89 enrolled COVID-19 patients showed that both Novaferon and Novaferon plus Lopinavir/Ritonavir groups had significantly higher SARS-CoV-2 clearance rates on day 6 than the Lopinavir/Ritonavir group (50.0% vs.24.1%, p = 0.0400, and 60.0% vs.24.1%, p = 0.0053). Median time to SARS-CoV-2 clearance were 6 days, 6 days, and 9 days for three groups respectively, suggesting a 3-dayreduction of time to SARS-CoV-2 clearance in both Novaferon and Novaferon plus Lopinavir/Ritonavir groups compared with Lopinavir/Ritonavir group.
Conclusions:
Novaferon exhibited anti-SARS-CoV-2 effects in vitro and in COVID-19 patients. These data justified the further evaluation of Novaferon.

12. 肝素抑制 SARS-CoV-2 侵入细胞：Spike 蛋白 S1 受体结构域与肝素相互作用的结构基础

Heparin inhibits cellular invasion by SARS-CoV-2: structural dependence of the interaction of the surface protein (spike) S1 receptor binding domain with heparin.

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第一作者：Courtney J. Mycroft-West, Dunhao Su, Isabel Pagani, Timothy R. Rudd, Stefano Elli

通讯作者：Mark A. Skidmore[1, 2]

通讯作者单位：

1. Molecular & Structural Biosciences, School of Life Sciences, Keele University, Newcastle-Under-Lyme, Staffordshire, ST5 5BG, UK.
2. Department of Biochemistry and Systems Biology, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, L69 7ZB, UK.

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编译者：宋珂

中文摘要：

宿主细胞会通过数百种胞外蛋白与细胞表面的氨基聚糖（GAG）硫酸乙酰肝素（HS）间的相互作用来调节内部稳态。许多病原微生物就利用了这一点，作为粘附和入侵宿主细胞的途径。多糖肝素作为一种广泛使用的抗凝药物，其结构与 HS 相似。被认为能够模仿 HS 的特性，是常见的实验替代物。外源增加肝素含量可以防止多种病毒的感染，例如 HSR1 冠状病毒株。本文中作者发现，向 Vero 细胞添加肝素（100 μg.ml-1）后，抑制 SARS-CoV-2 侵入细胞的比例达 70%。作者还通过表面等离振子共振和圆二色光谱实验证实，肝素的结合位点在 Spike 蛋白 S1 的受体结构域（RBD）上，并通过结合诱导了受体结构域发生构象变化。作者还使用肝素衍生物和片段大小一定的分子库研究了肝素的结构特征，正是这些结构特征决定了肝素和 Spike 蛋白的相互作用。相对于 N-硫酸化，2-O 或 6-O 位置上的硫酸化对肝素的结合能力，以及后续的构象变化的影响更强。与在肝素结合过程中发生的构象变化相比，在二级结构中诱导构象变化需要聚己糖结构。Enoxapari，一种临床使用的低分子量抗凝剂，也可以和 S1RBD 结合，并诱导构象变化。已有结果表明，重新利用肝素，或定制基于 GAG 的新一代

针对 SARS-CoV-2 或其他冠状病毒的抗病毒药物，对于快速开发一线的治疗药物具有重要价值。

译者注：4 月 17 日的简报中，也报道过肝素相关的研究工作《Glycosaminoglycan binding motif at S1/S2 proteolytic cleavage site on spike glycoprotein may facilitate novel coronavirus (SARS-CoV-2) host cell entry》

本文通过细胞实验，证实了外源增加肝素可以抑制 SARS-CoV-2 感染 Vero 细胞。但文章的大部分内容是通过实验手段确定肝素的结构相关的特性。如：与 SpikeS1RDB 的结合位点，结构对结合能力和构象变化的影响等。

17 日的文章主要通过动力学实验测定了肝素和 Spike 蛋白的 KD 值和 IC50 值。结合位点的预测则是通过 Modeling 和 Docking 模拟得到的。也预测出在 Spike 的 RDB 存在结合位点，但和今日文章中的位点稍有差异。

两篇文章都提出，肝素可以作为潜在的抑制 SARS-CoV-2 感染细胞的药物。但人体内细胞膜表面的 heparan sulfate proteoglycan (HSPG)蛋白，可能作为受体，介导了 SARS-CoV-2 病毒的侵入。

Abstract:

The dependence of the host on the interaction of hundreds of extracellular proteins with the cell surface glycosaminoglycan heparan sulphate (HS) for the regulation of homeostasis is exploited by many microbial pathogens as a means of adherence and invasion. The closely related polysaccharide heparin, the widely used anticoagulant drug, which is structurally similar to HS and is a common experimental proxy, can be expected to mimic the properties of HS. Heparin prevents infection by a range of viruses if added exogenously, including S-associated coronavirus strain HSR1 and here, we show that the addition of heparin (100 μg.ml-1) to Vero cells inhibits invasion by SARS-CoV-2 by 70%. We also demonstrate that heparin binds to the Spike (S1) protein receptor binding domain and induces a conformational change, illustrated by surface plasmon resonance and circular dichroism spectroscopy studies. The structural features of heparin on which this interaction depends were investigated using a library of heparin derivatives and size-defined fragments. Binding is more strongly dependent on the presence of 2-O or 6-O sulphation, and the consequent conformational consequences in the heparin structure, than on N-sulphation. A hexasaccharide is required for conformational changes to be induced in the secondary structure that are comparable to those that arise from heparin binding. Enoxaparin, a low molecular weight clinical anticoagulant, also binds the S1 RBD protein and induces conformational change. These findings have implications for the rapid development of a first-line therapeutic by repurposing heparin as well as for next-generation, tailor-made, GAG-based antiviral agents against SARS-CoV-2 and other members of the Coronaviridae.

Figure 1.

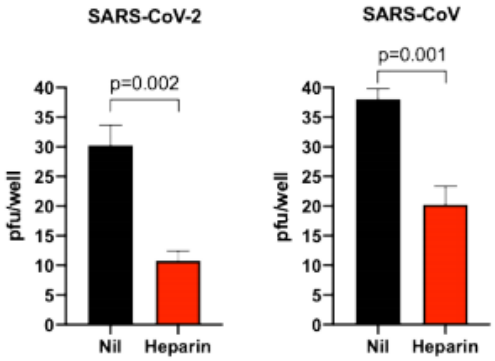

Figure 1. The heparin-mediated inhibition of SARS-CoV-2 viral invasion of Vero cells. The effect of unfractionated porcine mucosal heparin (100 μg.ml^{-1}) added one hour before the infection of Vero cells with 50 PFU of SARS-CoV-2 or SARS-CoV. Nil represents no treatment. The results are expressed as number of PFU per well and represent the mean ± SD of quadruplicate cultures. The *p* value was calculated using the Mann-Whitney U test.