新型冠状病毒信息简报

第 16 期（2020 年 4 月 3 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

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1. 2020年4月2日疫情

数据来源：WHO

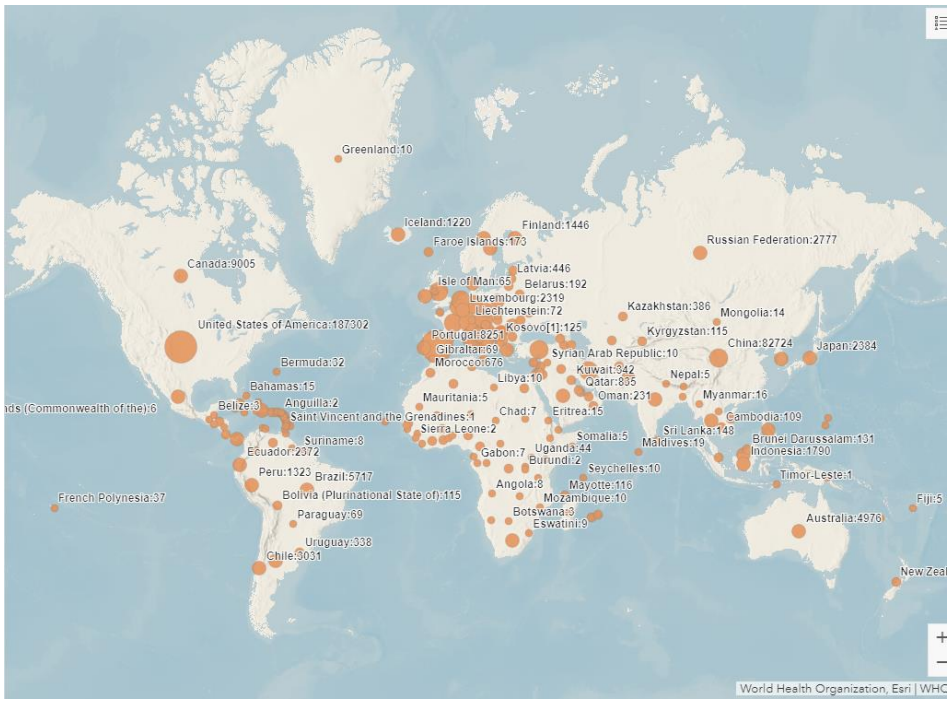
发布时间：2020年4月2日北京时间下午4点

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

编译：王玮

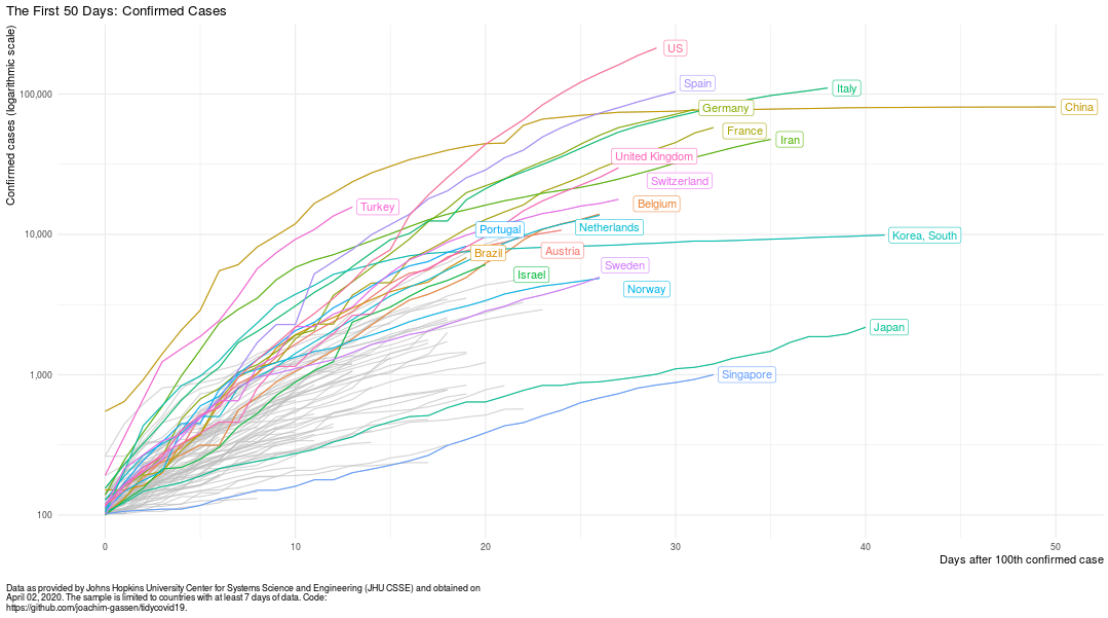
根据WHO提供的数据，2020年4月2日全球累计确诊新型冠状病毒病人896450例，当日新增确诊72839例，累计死亡45526例，当日新增死亡4924。

中国累计确诊82724例，累计死亡3327例，当日新增确诊93例，新增死亡6例。



世界各国家地区累计确诊病例总数，圆圈越大代表总病例数越多

（链接：https://experience.arcgis.com/experience/62c28590b5ae41ef920e4d5a4128504a）



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止4月2日北京时间下午4点）

2. 转载：王辰院士团队分享方舱医院经验，《柳叶刀》发表

Chen Wang etc published on lancet to share Chinese experiences on Fangcang shelter

作者：李晨阳

来源：科学网微信公众号

摘要：

截至北京时间4月3日12点30分，全球新冠肺炎累计确诊病例突破101万——在病毒肆虐的洪流中，人类需要能托举生命的“诺亚方舟”。

4月2日，中国工程院院士王辰带领的团队在《柳叶刀》发文，向全世界分享了中国方舱医院的建设和管理经验。

在国内疫情告急之时，王辰提出建立方舱医院这一关键之举。3月30日，他和美国同行分享抗“疫”经验时表示，“方舱医院是武汉抗击疫情的关键措施，我希望这种模式能为更多国家增强应对新冠肺炎的能力。”

如今，全球疫情告急，方舱医院能否同样成为扭转局势的制胜法宝？

王辰院士从以下方面阐述了方舱医院经验：

- ✧ 为何要用“方舱医院”取代“居家隔离”？
- ✧ 方舱医院3大特色、5大功能
- ✧ 方舱医院需要5大支撑
- ✧ 已协助多国构思建设方舱医院

中文评论全文请参考：

https://mp.weixin.qq.com/s?__biz=MzA5OTMxMTUzMw==&mid=2657116882&idx=1&sn=546c7ae8246db102004f9235ea6b7042&chksm=8b108810bc670106a92c79494a1487d78f962286502a5250a6872ffea4d435a7f5be85e68bae&scene=126&sessionid=1585902905&key=e6b74ea88183169c8d19336cb0b8616a7b22fc31c2a034bfa94b41c3480acceca744e9ac30e3592a3fb1e578649093fcbb2557a3e991ee0524f306715723149d42f73db2436f04e48dd33195f913cdcb&ascene=1&uin=MjgxMjY4NjgxNQ%3D%3D&devicetype=Windows+10&version=62080079&lang=zh_CN&exportkey=Ax%2Bq3iNUJth3ANNc0GcBWLk%3D&pass_ticket=ElUNyDUZRYFTaa4k0FdHlJjkmUCDqQGNLr8f1Kmqk9vnYoiWMkdcFHodONM6Nvr1

Link for English full text of the original article “Fangcang shelter hospitals: a novel concept for responding to public health emergencies”:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30744-3/fulltext

3. SARS-CoV-02样本的混合检测可以大幅度提高全世界的检测能力

Pool testing of SARS-CoV-02 samples increases worldwide test capacities many times over

来源：Goethe University Frankfurt

发布时间：2020-03-30

来源链接：https://aktuelles.uni-frankfurt.de/englisch/pool-testing-of-sars-cov-02-samples-increases-worldwide-test-capacities-many-times-over/

内容推荐：聂焱

编译者：宋张悦

内容摘要：

Erhard Seifried教授领衔的德国红十字会献血部门和Sandra Ciesek教授领衔的法兰克福

大学医院医学病毒学研究所，两个研究团队成功开发了一种方法——Mini-Pool混合检测方法（如下图1所示），可以马上大幅度提高全球检测SARS-CoV-2的检测能力。通过这种方式，德国目前每天4万次检查的平均水平可以提高到每天20万到40万次，而且诊断的质量不会受到影响。该发明的专利权由法兰克福大学和德国红十字会共同持有，目前正在欧洲和美国申请专利。

将多个咽拭子或鼻拭子采样混合置入一种缓冲液，然后用聚合酶链式反应技术（PCR）检测是否感染了新冠病毒，直接扩增检测新冠病毒基因。一旦检测结果呈阴性，则其中所有的采样均无新冠病毒感染。如果检测结果呈阳性，则在以前保留的样本中进行单独检测。阳性样本可以在4小时内被识别出来。

首先将拭子放在备用试管中，然后再混合放在池容器中。由于这种合并方法不会增加合并容器中的体积，因此没有稀释，所以不会降低灵敏度。经验证新的Mini-Pool方法可以获得与单独测试相同质量的结果。新方法还在50例随机患者样本的小规模研究中进行了测试。将患者样品汇集在10个微型池中，每个池内含5个样本，然后进行平行测试。在50个患者样本中，有5个SARS CoV-2阳性的样本，这些样本分布在4个池中，所有四个Mini-Pool均产生阳性PCR结果。仅包含未感染SARS-CoV-2患者样本的微型池，始终为阴性结果。

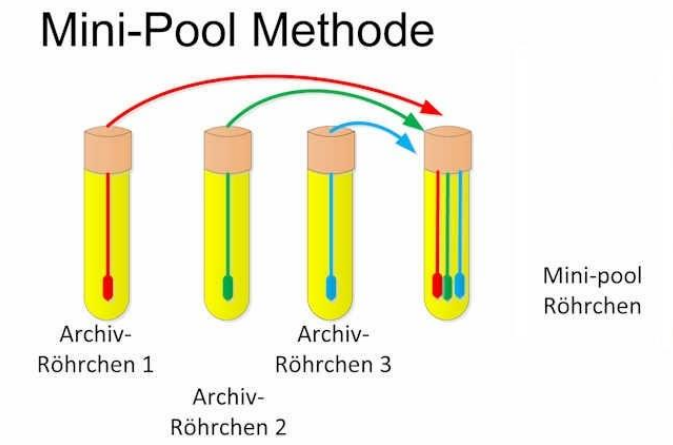


图1. Mini-Pool混合检测方法

Abstract:

Researchers at the German Red Cross Blood Donor Service in Frankfurt headed by Professor Erhard Seifried, and the Institute for Medical Virology at the University Hospital Frankfurt at Goethe University headed by Professor Sandra Ciesek succeeded in developing a procedure that makes it possible to immediately and dramatically increase worldwide testing capacities for detecting SARS-CoV-2. This allows the current number of approximately 40,000 tests per day in all of Germany to be immediately increased to 200,000 to 400,000 tests without reducing the high quality of the diagnosis. The rights to the invention, for which a patent is pending in Europe and the USA, is held jointly by Goethe University and the German Red Cross.

The background of this news are laboratory investigations in which swab samples from mucous membranes of the throat or nose are combined using specified procedures in a buffer solution, and subsequently tested using what is known as the PCR procedure (polymerase chain reaction procedure, direct genome detection

of SARS CoV-2). In the case of a negative result, all included samples have a reliable negative result. The pool testing has no influence on the detection limit. In the case of a positive mini-pool result, individual testing is carried out in previously reserved samples. The positive sample can then be identified within 4 hours.
The new method was additionally investigated in a small field study on 50 unselected patient samples. The patient samples were pooled in 10 mini-pools of 5 samples each, and also tested individually in parallel. Of the 50 patient samples, 5 samples were SARS CoV-2 positive. These samples were distributed across 4 pools. All four mini-pools resulted in a positive PCR result. Mini-pools containing only samples from patients without SARS CoV-2 always resulted in a negative result.

4. 氯喹对COVID-19患者的疗效

Treating COVID-19 with Chloroquine
来源：Journal of Molecular Cell Biology
发表时间：2020-4-1
链接：https://academic.oup.com/jmcb/advance-article/doi/10.1093/jmcb/mjaa014/5814655
作者：Hong Shan, Shanping Jiang, Jinyu Xia/ Duanqing Pei
作者单位：中山大学/广州市再生医学与健康广东省实验室
编译：刘焕珍
文摘：
从2020年1月27日到2020年2月15日，作者启动了一项临床研究，来评估氯喹在住院的COVID-19患者中的疗效和安全性。他们将洛匹那韦/利托那韦治疗作为对照组。在该研究中，通过以下方法来评估疗效：1）RT-PCR检测COVID-19病毒RNA； 2）肺部CT评估NCP的改善； 3）住院时间的长短评估患者的康复。 通过不良反应来监测评估安全性。
所有22例患者均通过RT-PCR检测为SARS-CoV-2阳性，然后将患者随机分为两组：一组10例患者（包括3例为重度和7例为中度病例），每天两次口服氯喹500mg治疗10天；另外一组12例患者（包括5例重度和7例中度病例），每天两次口服洛匹那韦/利托那韦400/100mg治疗10天。
RT-PCR检测结果显示氯喹组中的一名患者仅治疗2天后变为SARS-CoV-2阴性。 然后，转为阴性的患者数量稳步增加，直到第13天时所有氯喹组的患者均为阴性。相比之下，洛匹那韦/利托那韦组的首位患者在服药3天后变为SARS-CoV-2阴性，而12例患者中有11例患者在第14天转为阴性。这些结果表明，基于RNA检测，氯喹比洛匹那韦/利托那韦略有优势。
此外，肺部CT是临床评估NCP改善的另一有效指标。第一名通过CT成像获得肺部清除的患者是在第6天从比洛匹那韦/利托那韦组获得的，该患者在第3天变为SARS-CoV-2阴性。在氯喹组中，第一名在第8天获得肺部清除的患者是在第7天变为SARS-CoV-2阴性。到第14天，氯喹组基于CT成像的肺部改善的发生率是比洛匹那韦/利托那韦组的两倍以上。这些结果表明，用氯喹治疗的患者似乎比用洛匹那韦/利托那韦治疗的患者恢复得更好，并且更快地恢复了肺功能。
此外，与CT成像数据一致，接受氯喹治疗的患者出院的速度更快。洛匹那韦/利托那韦组第一名出院病人是在治疗的第8天出院，氯喹组第一名出院病人是在治疗的第9天出院。到第14天，来自氯喹组的所有10名患者（100％）和来自洛匹那韦/利托那韦组的6例患者（50％）出院。

在氯喹治疗期间，他们观察到5名患者共发生9种不良反应，其中3名在治疗结束后14天测量了氯喹的血清浓度。氯喹的血清浓度降至0.26 ~ 0.61μmol/ L，此浓度对患者来说是安全的。为了进一步研究该疗法对患者免疫力变化的影响，他们每两天测量一次氯喹组中10例患者的T细胞计数。 CD3 +，CD4 +，CD8 +计数的轨迹显示，在10天的治疗期间T细胞计数没有显着下降，表明短期使用氯喹对患者的免疫功能无明显影响。

初步结果表明，氯喹治疗方案可能是许多建议的治疗方法中有效且廉价的选择。作者希望这项工作可以鼓励进行更大范围的随机试验，以全面评估这种抗COVID-19的旧药。 在没有特定的治疗方法的情况下，氯喹等旧药物可能会被重新用于抵抗这种新型疾病并挽救全世界的生命。

Abstract

From 27 Jan 2020 to 15 Feb 2020, we initiated a clinical study to evaluate the efficacy and safety of Chloroquine in hospitalized patients with COVID-19. we included Lopinavir/Ritonavir treatment as a control group. In our study, efficacy was evaluated by: 1) RT-PCR for measuring COVID-19 viral RNAs, 2) lung CT for assessing the improvement of NCP, and 3) length of hospitalization for assessing patient recovery. Safety was evaluated by adverse event monitoring. All the 22 patients were tested positive for SARS-CoV-2 by RT-PCR assay. Patients were then randomized into two groups. 10 patients, including 3 severe and 7 moderate cases, were treated with Chloroquine 500mg orally twice-daily for 10 days; 12 patients, including 5 severe and 7 moderate cases, were treated with Lopinavir/Ritonavir 400/100mg orally twice-daily for 10 days.

We initially relied on RT-PCR to measure virological outcomes and showed that one patient in the Chloroquine group became SARS-CoV-2 negative after treatment for only 2 days. There were then steady increases in the number of patients turned negative, cumulating at Day 13 when all of the Chloroquine-treated patients became negative. In comparison, the first patient in the Lopinavir/Ritonavir group became SARS-CoV-2 negative after 3 days of dosing, and 11 out of 12 turned negative at Day 14. These results suggest that Chloroquine has slight advantage over Lopinavir/Ritonavir based on RNA tests. Besides, lung CT is another effective indicator to clinically evaluate the improvement of NCP. The first patient achieved lung clearance based on CT imaging was from the Lopinavir/Ritonavir group at Day 6 and this patient became SARS-CoV-2 negative at Day 3. In the Chloroquine group, the first patient achieved lung clearance was at Day 8 who became SARS-CoV-2 negative at Day 7. By Day 14, the incidence rate of lung improvement based on CT imaging from the Chloroquine group was more than double that of the Lopinavar/Ritonavir group. These results suggest that patients treated with Chloroquine appear to recover better and regain their pulmonary function quicker than those treated with Lopinavir/Ritonavir.

In addition, consistent with the CT imaging data, patients treated with Chloroquine were discharged from hospital in a much quicker pace. The first patient to be discharged from hospital was from the Lopinavir/Ritonavir group at Day 8, and the first to be discharged from the Chloroquine group was at Day 9.By Day 14, all 10 patients (100%) from the Chloroquine group were discharged

compared to 6 patients (50%) from the Lopinavir/Ritonavir group.
During Chloroquine treatment period, we observed 5 patients who experienced a total of 9 adverse events. 3 of them had valid measurements of serum concentration of Chloroquine at 14 days after treatment completion. The serum concentration of Chloroquine decreased to the range of 0.26 ~ 0.61 μmol/L, which was safe to patients. To further investigate the change of immunity through the therapy, we measured T-cell counts of the 10 patients in the Chloroquine group every 2 days. The trajectories of CD3+, CD4+, CD8+ counts showed that there was no significant decrease of T-cell counts during the 10-day treatment period, indicating that the short-term use of Chloroquine had no significant effect on immune function of patients.
Our preliminary results suggest that Chloroquine could be an effective and inexpensive option among many proposed therapies. It is our hope that this work may encourage larger scale randomized trials to fully evaluate this old drug against COVID-19. In the absence of a specific cure, old drugs such as Chloroquine may be repurposed to fight this novel disease and save lives worldwide.

5. 利用氯喹对抗COVID-19

Combating COVID-19 with Chloroquine
来源：Journal of Molecular Cell Biology
发布时间：2020.4.1
链接：https://academic.oup.com/jmcb/advance-article/doi/10.1093/jmcb/mjaa015/5814654
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作者单位：新加坡科学技术和研究局分子与细胞生物学研究所
编译：张鹏伟
内容摘要：
自2019年12月以来，由一种名SARS-CoV-2的病毒引起的2019年冠状病毒病（COVID-19）给世界带来了前所未有的挑战。SARS-CoV-2病毒通过细胞内吞进入细胞。一旦进入细胞内，它们就会逃逸到细胞质中，释放出正链RNA基因组，从而触发病毒的复制和组装。这些病毒前颗粒在运输到高尔基体的跨高尔基网络（TGN）过程中成熟，从那里新组装的病毒颗粒从TGN转运载体出芽并与细胞表面融合被感染细胞释放，。
在本研究报告（Huang等人，2020年）中，作者通过RT-PCR跟踪病毒RNA、CT扫描肺功能和T细胞计数，测试了氯喹对患者的临床效果。在82名接受检查的患者中，有22名符合入选标准。将22例患者分为两组，一组（n=10）用氯喹（500mg，口服，每日两次）治疗，另一组（n=12）用洛匹那韦/利托那韦（400/100mg，口服，每日两次）治疗10天，共监测14天。到第13天，所有氯喹治疗的患者病毒RNA检测均为阴性。在洛匹那韦/利托那韦治疗组中，12人中有11人在第14天转为阴性。
尽管氯喹作用的分子机制尚不清楚，但可以预见，除了通过抑制内体功能直接影响内体病毒的进入和释放外，氯喹还可能间接影响病毒在ERGIC的组装和从TGN的释放。
Abstract:
Since December 2019, the world is increasingly facing an unprecedented challenge by coronavirus disease 2019 (COVID-19) caused by a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2

viruses enter the cell via endocytosis into the endosomal pathway. Once in the endosomal compartments, they escape into the cytoplasm and release the positive-stranded RNA genome to trigger viral replication and assembly. These pre-viral particles mature during the transport to the trans-Golgi network (TGN) of the Golgi apparatus, from where newly assembled viral particles are released by the infected cells via transport carriers budding from the TGN and fusing with the cell surface.

In this study report (Huang et al., 2020), the authors have tested the clinical effects of Chloroquine in patients by following viral RNA by RT-PCR, lung function by computerized tomography(CT) scanning, and T cell counts. Among 82 patients examined, 22 were identified to meet their enrolment criteria. These 22 patients were divided into two groups: one (n=10) treated with Chloroquine (500 mg, oral administration, twice daily) and another(n=12) with Lopinavir/Ritonavir (400/100mg,oral administra
-tion,twice daily) for 10 days and monitored for a total of 14days. By Day 13, all the Chloroquine-treated patients became negative for viral RNA test. In the Lopinavir/Ritonavir treated group, 11 out of 12 turned negative at Day 14.

Although the molecular mechanism underlying the action of Chloroquine remains to be defined, it is envisioned that in addition to directly affecting the endosomal viral entry and release via inhibiting endosomal function, Chloroquine may potentially affect the viral assembly at the ERGIC and/or viral release from the TGN indirectly.

References:

Huang,M.,Tang,T.,Pang,P.,et al.(2020).Treating COVID-19 with Chloroquine. J.Mol.Cell Biol.12

6. 间充质干细胞MSC治疗甲型流感（H7N9）感染所致急性呼吸窘迫综合征ARDS的临床研究——给COVID-19治疗的提示

Clinical Study of Mesenchymal Stem Cell Treatment for Acute Respiratory Distress Syndrome Induced by Epidemic Influenza A (H7N9) Infection A Hint for COVID-19 Treatment

来源：Engineering；

发表时间：2020.2.28；

链接：https://www.sciencedirect.com/science/article/pii/S2095809920300370?via%3Dihub

作者：李兰娟院士等；

编译：张丽双

摘要：

H7N9病毒在哺乳动物宿主之间迅速传播，并且在2013年爆发后具有人传人的危险。急性呼吸窘迫综合征（ARDS），肺衰竭和暴发性肺炎是H7N9患者的主要肺部疾病。间充质干细胞（MSCs）移植是治疗病毒性肺炎的理想选择，同时也是治疗H7N9诱导的ARDS的重要手段。对H7N9诱导的ARDS患者行MSCs移植，采用单中心开放式临床试验。根据自愿和知情同意的原则，将44例H7N9致ARDS患者作为对照组，而将17例H7N9致ARDS患者接受同种异体来源MSC治疗作为实验组。值得注意的是，与对照组相比，MSC移植的死亡率显著降低（MSC组死亡17.6%，对照组死亡54.5%）。此外，4例MSC移植患者在5年的随访期内未观察到对人体产

生不良影响。总之，这些结果提示MSCs可显著提高H7N9诱导的ARDS的生存率，为临床前研究和临床治疗H7N9诱导的ARDS提供了理论依据。由于H7N9和2019年冠状病毒病（COVID-19）有相似的并发症（如ARDS和肺功能衰竭）和相应的多器官功能障碍，基于MSC的治疗可能是治疗COVID-19的一种替代方法。

Abstract

H7N9 viruses quickly spread between mammalian hosts and carry the risk of human-to-human transmission, as shown by the 2013 outbreak. Acute respiratory distress syndrome (ARDS), lung failure, and fulminant pneumonia are major lung diseases in H7N9 patients. Transplantation of mesenchymal stem cells (MSCs) is a promising choice for treating virus-induced pneumonia, and was used to treat H7N9-induced ARDS in 2013. The transplant of MSCs into patients with H7N9-induced ARDS was conducted at a single center through an open-label clinical trial. Based on the principles of voluntariness and informed consent, 44 patients with H7N9-induced ARDS were included as a control group, while 17 patients with H7N9-induced ARDS acted as an experimental group with allogeneic menstrual-blood-derived MSCs. It was notable that MSC transplantation significantly lowered the mortality of the experimental group, compared with the control group (17.6% died in the experimental group while 54.5% died in the control group). Furthermore, MSC transplantation did not result in harmful effects in the bodies of four of the patients who were part of the five-year follow-up period. Collectively, these results suggest that MSCs significantly improve the survival rate of H7N9-induced ARDS and provide a theoretical basis for the treatment of H7N9-induced ARDS in both preclinical research and clinical studies. Because H7N9 and the corona virus disease 2019 (COVID-19) share similar complications (e.g., ARDS and lung failure) and corresponding multi-organ dysfunction, MSC-based therapy could be a possible alternative for treating COVID-19.

7. COVID-19临床研究核心指标集的建立（COS-COVID）

Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (COS-COVID)

来源：Engineering

发布时间：18 March 2020

链接： https://www.sciencedirect.com/science/article/pii/S2095809920300424?via%3Dihub

作者：张伯礼院士等

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编译：孔娟

摘要：

核心指标集（COS）是指同一疾病/健康领域所有临床研究应当报告的最小指标集合。建立临床研究核心指标集（COS）可使用核心指标集，可以减少同类临床研究由于不同结局指标选择导致异质性而无法纳入系统评价的情况。目前国内外临床试验平台注册的有关COVID-19的临床研究方案多达300余项，这些临床研究的干预措施多种多样，包括：抗病毒药物、中医药、免疫调节剂、康复患者的血浆等。这些治疗方法的疗效评价需要通过相应指标的测量和数据分析。所以，选择什么指标是影响临床试验结果价值的关键要素。关于COVID-19临床研究方案报告的疗效评价指标数量多达259个,基于此背景这项研究旨在开发COVID-

19临床研究核心指标集（COS），以解决COVID-19评价指标差异化、不重要等问题。
研究中COS-COVID根据国际学术组织COMET的指南进行研制。研究小组成员除医学期刊编辑外，还包括呼吸与危重医学，中医，循证医学，临床药理学和统计学方面的专家。研究通过检索临床试验注册网站（chictr.org.cn and clinicaltrials.gov）获得临床试验方案和结果库。按照COMET手册完成了条目池构建、Delphi调查和共识会议等程序，最终遴选出最重要的临床评价指标，形成了COS-COVID。来自意大利、韩国、英国和美国的代表也参与了Delphi共识过程。该研究共纳入了有关COVID-19的78个临床试验方案，收集了259个结果。标准化后，在七个不同类别中确定了132个结果，从中选择了58个制定初步结果列表并进一步达成共识。经过两轮Delphi调查和一次共识会议，确定了针对COVID-19的不同临床分类的结局指标，并完成COVID-19临床研究核心指标集（COS-COVID）。该研究对COS-COVID病情分类，从轻型、普通型、重型、危重型、康复期等5个层次分别遴选核心指标。轻型包含了1个指标：新型冠状病毒核酸转阴时间；普通型包括4个指标：住院时间、复合事件发生率、临床症状积分和新型冠状病毒核酸转阴时间；重型包括5个指标：复合事件发生率、住院时间、氧合指数(PaO2/FiO2)、机械通气时间和新型冠状病毒核酸转阴时间；危重型1个指标：全因死亡率；康复期1个指标：肺功能。
COS-COVID涵盖了新冠肺炎的整个分期，不仅可以用于评价不同干预措施（药物或非药物）疗效的临床试验，还可用于系统评价/Meta分析、临床实践指南和其他关于COVID-19证据评价和临床决策的研究。

Abstract:
Since its outbreak in December 2019, a series of clinical trials on Coronavirus Disease 2019 (COVID-19) have been registered or carried out. However, the significant heterogeneity and less critical outcomes of such trials may be leading to a waste of research resources. This study aimed to develop a core outcome set (COS) for clinical trials on COVID-19 in order to tackle the outcome issues. The study was conducted according to the Core Outcome Measures in Effectiveness Trials (COMET) handbook (version 1.0), a guideline for COS development. A research group was set up that included experts in respiratory and critical medicine, traditional Chinese medicine, evidence-based medicine, clinical pharmacology, and statistics, in addition to medical journal editors. Clinical trial registry websites (chictr.org.cn and clinicaltrials.gov) were searched to retrieve clinical trial protocols and outcomes in order to form an outcome pool. A total of 78 clinical trial protocols on COVID-19 were included and 259 outcomes were collected. After standardization, 132 outcomes were identified within seven different categories, of which 58 were selected to develop a preliminary outcome list for further consensus. After two rounds of Delphi survey and one consensus meeting, the most important outcomes for the different clinical classifications of COVID-19 were identified and determined to constitute the COS for clinical trials on COVID-19 (COS-COVID). The COS-COVID includes one outcome for the mild type (time to 2019-nCoV reverse transcription-polymerase chain reaction (RT-PCR) negativity), four outcomes for the ordinary type (length of hospital stay, composite events, score of clinical symptoms, and time to 2019-nCoV RT-PCR negativity), five outcomes for the severe type (composite events, length of hospital stay, arterial oxygen partial pressure (PaO2)/fraction of inspired oxygen (FiO2), duration of mechanical

ventilation, and time to 2019-nCoV RT-PCR negativity), one outcome for critical type (all-cause mortality), and one outcome for rehabilitation period (pulmonary function). The COS-COVID is currently the most valuable and practical clinical outcome set for the evaluation of intervention effect, and is useful for evidence assessment and decision-making. With a deepening understanding of COVID-19 and application feedback, the COS-COVID should be continuously updated.

8. 新闻特辑：在追寻COVID-19疫苗时应避免遇到陷阱

News Feature: Avoiding pitfalls in the pursuit of a COVID-19 vaccine

来源：PNAS

发表时间：2020-3-30

链接：https://www.pnas.org/content/early/2020/03/27/2005456117

作者：Lynne Peeples

编译：雷颖

摘要：

争相开发针对新型冠状病毒疾病（COVID-19）疫苗的研究人员团队显然正面临着科学和后勤方面的一些重大挑战。最紧迫的问题之一：了解免疫系统如何不仅与病原体相互作用，而且还与疫苗本身相互作用，这在尝试开发安全有效的疫苗时至关重要。当他们竞相设计疫苗时，研究人员正在努力确保他们的候选疫苗不会刺激产生一种适得其反的，甚至是危险的，被称为免疫增强的免疫系统反应。

专家们普遍认为，在向公众发放疫苗之前，这种针对新型严重急性呼吸综合征冠状病毒2（SARS-CoV-2）引起的COVID-19候选疫苗的动物实验和人类临床试验，应要仔细评估可能的免疫并发症。他们说，如果确实涉及任何正在研究的免疫增强机制，那么由此带来的风险是真实的。马萨诸塞州波士顿市哈佛大学公共卫生学院的流行病学家马克·利普西奇（Marc Lipsitch）说：“你真的必须仔细地测试一种疫苗，而不是仅仅因为迫于流行性疾病情况下人们大声疾呼，就把它推广出来。”

Abstract

The teams of researchers scrambling to develop a coronavirus disease 2019 (COVID-19) vaccine clearly face some big challenges, both scientific and logistical. One of the most pressing: understanding how the immune system interacts not only with the pathogen but with the vaccine itself—crucial insights when attempting to develop a safe and effective vaccine. As they race to devise a vaccine, researchers are trying to ensure that their candidates don't spur a counterproductive, even dangerous, immune system reaction known as immune enhancement.

Experts generally agree that animal experiments and human clinical trials of candidate vaccines for COVID-19, which is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), should include a careful assessment of possible immune complications before releasing the vaccine to the public. If any of the mechanisms under investigation are indeed involved, they say, the resulting risks are real. “You really have to test a vaccine carefully,” says Marc Lipsitch, an epidemiologist at the Harvard Chan School of Public Health in Boston, MA, “and not just roll it out because people are

clamoring for it with an epidemic underway."

9. 针对人口规模免疫的SARS-CoV-2疫苗接种策略

A SARS-CoV-2 Vaccination Strategy Focused on Population-Scale Immunity

来源：biorxiv

发表时间：2020-4-2

链接：https://www.biorxiv.org/content/10.1101/2020.03.31.018978v1

通讯作者：John M. Maris, MD

作者单位：美国费城儿童医院

编译：雷颖

摘要：

本文作者提出了一种SARS-CoV-2的疫苗接种策略，该策略基于对病毒高度保守区域的识别和MHC I类和II类在绝大多数人群中呈现的新获得的适应性，与人类蛋白质组高度不同，并预测了B细胞表位。作者提出了65种肽序列，这些序列有望产生一种安全有效的疫苗，可以在DNA，mRNA或合成的肽构建物中对其进行快速测试。这些肽序列包含很多表位，其中有据报道通过增加与ACE2受体的结合而增加感染性的刺突蛋白的进化趋异区域内的表位，以及被认为会增加膜融合作用的新的弗林蛋白酶切位点内的表位。这种疫苗接种策略特别针对SARS-CoV-2的独特弱点，并应会在绝大多数人群中引发强有力的适应性免疫反应。

Abstract

Here we propose a vaccination strategy for SARS-CoV-2 based on identification of both highly conserved regions of the virus and newly acquired adaptations that are presented by MHC class I and II across the vast majority of the population, are highly dissimilar from the human proteome, and are predicted B cell epitopes. We present 65 peptide sequences that we expect to result in a safe and effective vaccine which can be rapidly tested in DNA, mRNA, or synthetic peptide constructs. These include epitopes that are contained within evolutionarily divergent regions of the spike protein reported to increase infectivity through increased binding to the ACE2 receptor, and within a novel furin cleavage site thought to increase membrane fusion. This vaccination strategy specifically targets unique vulnerabilities of SARS-CoV-2 and should engage a robust adaptive immune response in the vast majority of the human population.

3月30日我们简报第7条综述了目前在研疫苗的情况。今天匹兹堡大学发表了第一篇关于疫苗的同行评议文章，根据Biocentry.com的报道，该疫苗正在计划申请新药物一期临床。

10. 微针阵列给药的重组冠状病毒疫苗：免疫原性和快速临床研发

Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development

来源：EBioMedicine

发布日期：2020.4.1

链接：https://www.thelancet.com/pdfs/journals/ebiom/PIIS2352-3964(20)30118-3.pdf

作者：匹兹堡大学 Louis D. Falo 和Andrea Gambotto

这篇文章里作者将研发MERS疫苗的系统用于SARS-CoV-2疫苗的快速研发，在病毒基因组发布4周内就完成了疫苗的临床前开发。作者应用的技术路线主要包括：

将S蛋白的S1亚基进行密码子优化后，表达形成三聚体；辅以免疫佐剂；微针阵列皮内吸收的方法接种疫苗。研究者们基于这个技术路线开发的MERS-S1 亚基疫苗在小鼠里持续产生强的抗原特异性的抗体反应。COVID-19疫情出现后，研究者们用该技术系统开发了SARS-CoV-2的微针阵列接种的SARS-CoV-2的S1亚基疫苗。小鼠被接种后两周后就激起了强劲的抗原特异性的抗体反应。作者总结说临床前数据支持该疫苗转向临床开发。
作者文中提到，微阵列的疫苗给药方式有以下优点：
是非侵入性的，减少接种痛苦，降低接种难度
在皮肤局部产生高浓度，刺激免疫反应发生，减少毒性和成本
可能可以不依赖冷链运输和存储抗体(有文献报道，微针阵列疫苗可以在室温下存储一个月仍然保持抗原性)

Background: Coronaviruses pose a serious threat to global health as evidenced by Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and COVID-19. SARS Coronavirus (SARS-CoV), MERS Coronavirus (MERS-CoV), and the novel coronavirus, previously dubbed 2019-nCoV, and now officially named SARS-CoV-2, are the causative agents of the SARS, MERS, and COVID-19 disease outbreaks, respectively. Safe vaccines that rapidly induce potent and long-lasting virus-specific immune responses against these infectious agents are urgently needed. The coronavirus spike (S) protein, a characteristic structural component of the viral envelope, is considered a key target for vaccines for the prevention of coronavirus infection. Methods: We first generated codon optimized MERS-S1 subunit vaccines fused with a foldon trimerization domain to mimic the native viral structure. In variant constructs, we engineered immune stimulants (RS09 or flagellin, as TLR4 or TLR5 agonists, respectively) into this trimeric design. We comprehensively tested the pre-clinical immunogenicity of MERS-CoV vaccines in mice when delivered subcutaneously by traditional needle injection, or intracutaneously by dissolving microneedle arrays (MNAs) by evaluating virus specific IgG antibodies in the serum of vaccinated mice by ELISA and using virus neutralization assays. Driven by the urgent need for COVID-19 vaccines, we utilized this strategy to rapidly develop MNA SARS-CoV-2 subunit vaccines and tested their pre-clinical immunogenicity in vivo by exploiting our substantial experience with MNA MERS-CoV vaccines. Findings: Here we describe the development of MNA delivered MERS-CoV vaccines and their pre-clinical immunogenicity. Specifically, MNA delivered MERS-S1 subunit vaccines elicited strong and long-lasting antigen-specific antibody responses. Building on our ongoing efforts to develop MERS-CoV vaccines, promising immunogenicity of MNA-delivered MERS-CoV vaccines, and our experience with MNA fabrication and delivery, including clinical trials, we rapidly designed and produced clinically-translatable MNA SARS-CoV-2 subunit vaccines within 4 weeks of the identification of the SARS-CoV-2 S1 sequence. Most importantly, these MNA delivered SARS-CoV-2 S1 subunit vaccines elicited potent antigen-specific antibody responses that were evident beginning 2 weeks after immunization. Interpretation: MNA delivery of coronaviruses-S1 subunit vaccines is a

promising immunization strategy against coronavirus infection. Progressive scientific and technological efforts enable quicker responses to emerging pandemics. Our ongoing efforts to develop MNA-MERS-S1 subunit vaccines enabled us to rapidly design and produce MNA SARS-CoV-2 subunit vaccines capable of inducing potent virus-specific antibody responses. Collectively, our results support the clinical development of MNA delivered recombinant protein subunit vaccines against SARS, MERS, COVID-19, and other emerging infectious diseases.

11. 在SARS-CoV-2基因组中鉴定到一个常见的刺突蛋白片段缺失

Identification of a common deletion in the spike protein of SARS-CoV-2

来源：biorxiv

发布时间：2020-04-02

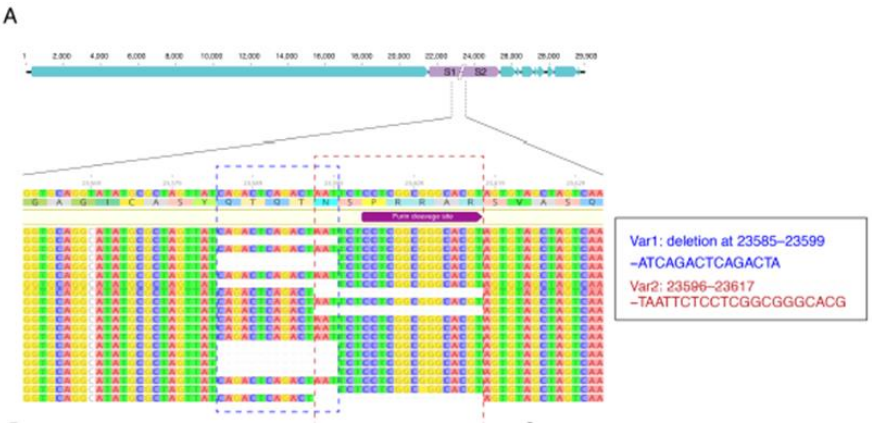
来源链接：https://www.biorxiv.org/content/10.1101/2020.03.31.015941v1

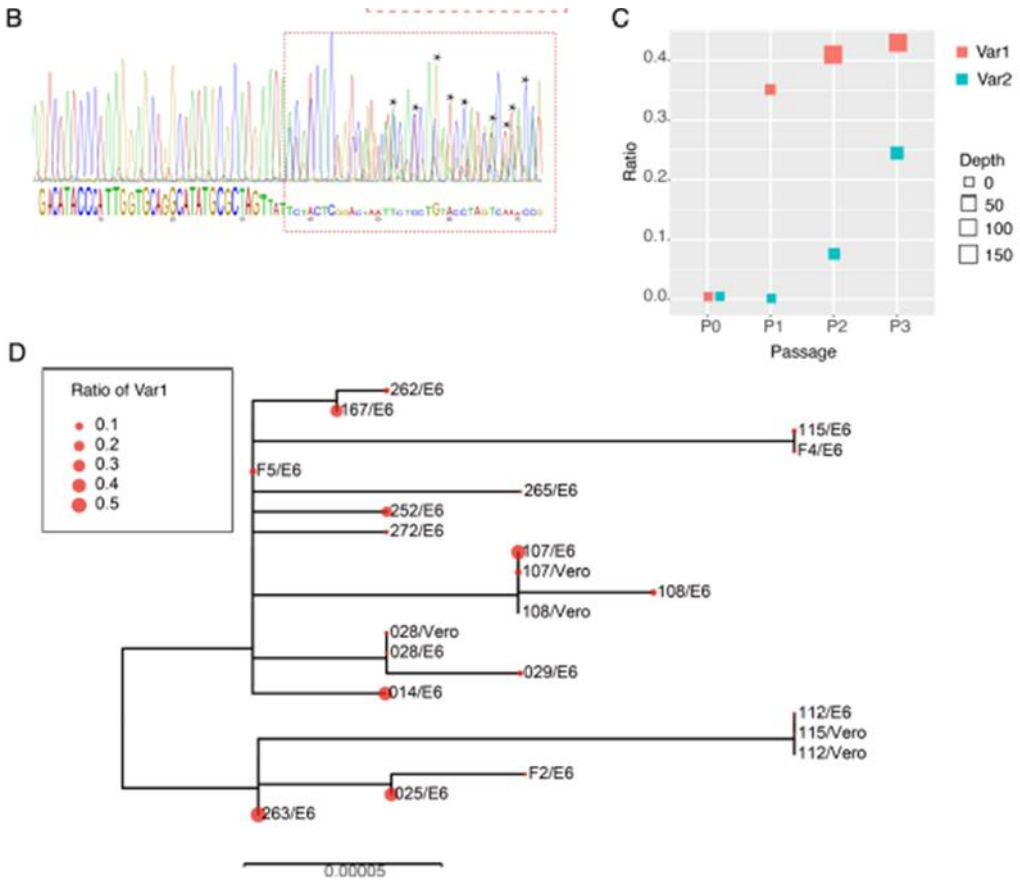
作者单位：广东省卫生厅，广东省疾病预防控制中心等单位

通讯作者：Jing Lu

内容摘要：

SARS-CoV-2基因组具有两个显著的特征：（1）SARS-CoV-2的受体结合域（RBD）不同于蝙蝠起源SARs相关病毒（RaTG13），SARS-CoV-2的RBD与人受体ACE2具有高度亲和力；（2）在S1和S2交界处有12个核苷酸或4个氨基酸（PRRA）的独特插入。对于第一个特征，在穿山甲SARs样病毒中发现的相似RBD表明，SARS-CoV-2中的RBD在传播到人类之前可能已经存在于动物宿主中。剩下的谜团是SARS-CoV-2刺突蛋白中S1/S2边界的标志性插入片段的起源和功能。该研究从第一株广东省SARS-CoV-2细胞株中，用不同测序手段鉴定出两种变异，在多碱基裂解位点（PRRAR）及其侧翼位点上存在缺失突变（图一）。更广泛的筛选表明，在68个临床样本中的3个和22个体外分离的病毒株中的一半可以检测到PRRAR侧翼位点的缺失。这些数据表明：（1）多碱基裂解位点侧翼QTQTN的缺失可能有利于SARS-CoV-2的体外复制或感染，但在体内的强纯化选择下，很少在临床标本中发现这种类型的缺失；（2）可能有一个有效的从病毒基因组中删除23585-23599区域的机制，因为该区域的丢失变异通常在两轮细胞传代后检测到。导致SARS-CoV-2基因改变的体外适应和体内纯化过程（或逆转）的机制需要进一步研究。该研究为进一步研究刺突蛋白功能和病毒进化提供了有价值的线索。在疫苗研发过程中应注意在体外分离中发现的这些缺失突变。





图一 Deletion variants identified in SARS-CoV-2 cell strains.
(A) High-throughput sequencing of the cell isolated strain (014) from the first SARS-CoV-2 patient (EPI 403934) in Guangdong, China. Representative reads mapping to the SARS-CoV-2 genome (MN908947.3 used as reference genome) showed two deletion variants. (B) Sanger sequencing of the 014 cell strains. The heterozygous peaks highlighted with a red box and the sites with distinct three peaks were marked with * (C) High-throughput sequencing showed the ratio of deletion variants in original clinical sample SF014 (P0) and cell strainsafter 3 rounds of cell passage (P1-3). (D) Phylogenetic tree of genome sequences of all 22 SARS-CoV-2 cell strains. The size of red dots is proportional to the ratio of Var1 (deletion at 23585–23599).

Abstract
Two notable features have been identified in the SARS-CoV-2 genome: (1) the receptor binding domain of SARS-CoV-2; (2) a unique insertion of twelve nucleotide or four amino acids (PRRA) at the S1 and S2 boundary. For the first feature, the similar RBD identified in SARs-like virus from pangolin suggests the RBD in SARS-CoV-2 may already exist in animal host(s) before it transmitted into human. The left puzzle is the history and function of the insertion at S1/S2 boundary, which is uniquely identified in SARS-CoV-2. In this study, we identified two variants from the first Guangdong SARS-CoV-2 cell strain, with deletion mutations on polybasic cleavage site (PRRAR) and its flank sites. More

extensive screening indicates the deletion at the flank sites of PRRAR could be detected in 3 of 68 clinical samples and half of 22 in vitro isolated viral strains. These data indicate (1) the deletion of QTQTN, at the flank of polybasic cleavage site, is likely benefit the SARS-CoV-2 replication or infection in vitro but under strong purification selection in vivo since it is rarely identified in clinical samples; (2) there could be a very efficient mechanism for deleting this region from viral genome as the variants losing 23585-23599 is commonly detected after two rounds of cell passage. The mechanistic explanation for this in vitro adaptation and in vivo purification processes (or reverse) that led to such genomic changes in SARS-CoV-2 requires further work. Nonetheless, this study has provided valuable clues to aid further investigation of spike protein function and virus evolution. The deletion mutation identified in vitro isolation should be also noted for current vaccine development.

12. COVID-19病人的外周血单核细胞里的病毒-宿主蛋白相互作用网络和蛋白质组学研究揭示可能影响SARS-CoV-2发病机制的病毒因子

Virus-host interactome and proteomic survey of PBMCs from COVID-19 patients reveal potential virulence factors influencing SARS-CoV-2 pathogenesis

来源：biorxiv

发布时间：2020-04-02

链接：https://www.biorxiv.org/content/10.1101/2020.03.31.019216v1

通讯作者：复旦大学Qiming Liang, 张江实验室国家蛋白质中心（上海） 彭超, 复旦大学Tongyu Zhu 和同济大学Zhenshan Liu

编译：蒋立春

为了研究SARS-CoV-2的致病机制，来自复旦大学、张江实验室蛋白质中心和同济大学的研究者们系统地研究了病毒里面以及病毒和宿主之间的蛋白蛋白相互作用。

首先研究者们对病毒的蛋白组通过酵母双杂交和共免疫沉淀的办法对SARS-CoV-2编码的所有蛋白质进行了研究，以揭示病毒里蛋白蛋白相互作用。

进一步更好了解病毒蛋白在病毒生命周期里的功能，研究者们在人HEK293细胞中过表达了N端带 3个Flag的 SARS-CoV-2的蛋白。然后通过亲和纯化的办法考察病毒蛋白和哪些HEK293细胞相结合。

为了阐述SARS-CoV-2的感染在病人里的致病机制，研究者们比较了病人和健康人外周血单核细胞中的蛋白质谱差异。研究者们一共收集了6个健康人，22个轻症COVID-19病人，13个的重症病人（所有人甲流检测呈阴性）。从人外周单核细胞里，该研究鉴定出了251个和SARS-CoV-2结合的人体宿主蛋白，另外有200多个宿主蛋白的表达量在病人中发生了改变。该研究鉴定出病毒的非结构蛋白nsp9和nsp10和宿主蛋白NKRF—一个NF-kB的抑制因子结合。可能参与到由IL-8/IL-6介导的中性粒细胞的趋化反应以及病人里观察到的免疫过激反应。

Figure 1. SARS-CoV-2 病毒内部蛋白蛋白相互作用网络---酵母双杂交和免疫共成沉淀结果

Figure 1. SARS-CoV-2 intra-viral protein-protein interaction network

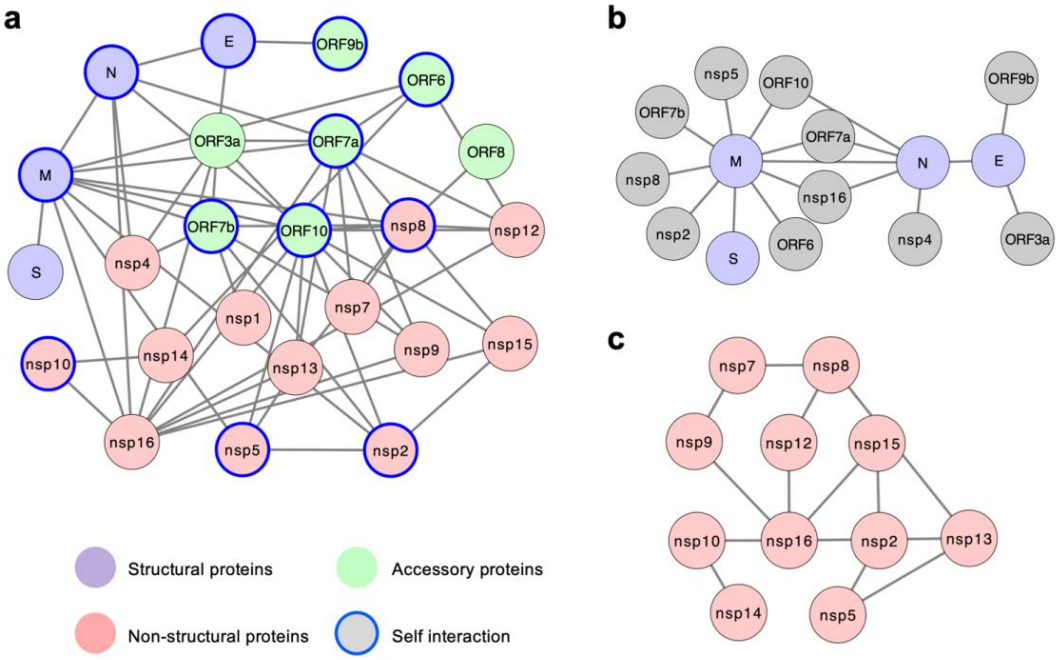
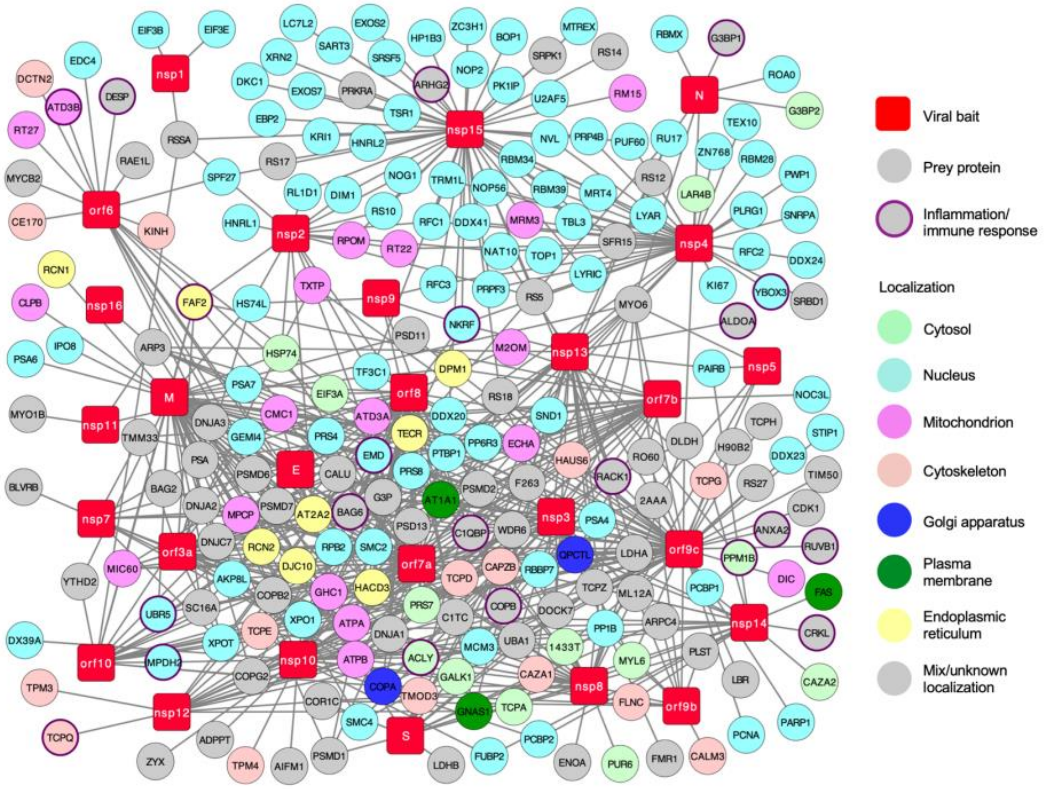


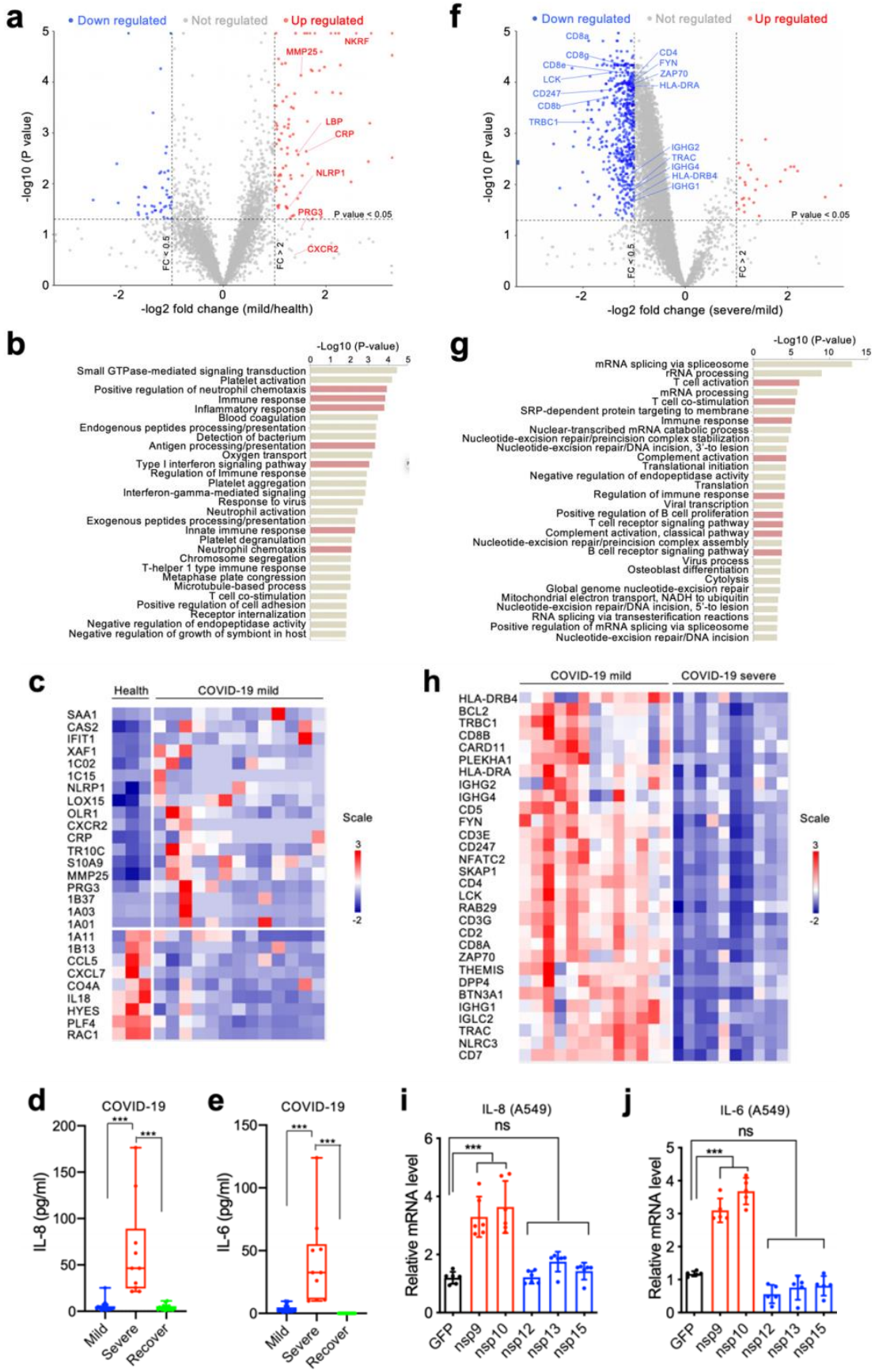
Figure 2. SARS-CoV-2-human protein-protein interaction network



Network representation of the high-confidence SARS-CoV-2-host interactome in HEK293 cells. There are 27 SARS-CoV-2 bait proteins (red squares) and 251 interacting host protein (circles). Subcellular localizations of host proteins are labelled with indicated colors. Proteins with known functions in inflammation or immune responses are circled in purple.

Figure 3. COVID-19病人相比健康人外周血单核细胞里蛋白组学变化提示SARS-CoV-2的的nsp9/nsp10可能通过作用于NKRF激活IL-6/8的表达激活中性粒细胞

Proteome profile change in PBMCs of COVID-19 patients suggests a potential role of the nsp9/nsp10-NKRF-IL-6/8 axis in neutrophil activation



The ongoing coronavirus disease (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a global public health concern due to relatively easy person-to-person transmission and the current lack of effective antiviral therapy. However, the exact molecular mechanisms of SARS-CoV-2 pathogenesis remain largely unknown. We exploited an integrated proteomics approach to systematically investigate intra-viral and virus-host interactomes for the identification of unrealized SARS-CoV-2 host targets and participation of cellular proteins in the response to viral infection using peripheral blood mononuclear cells (PBMCs) isolated from COVID-19 patients. Using this approach, we elucidated 251 host proteins targeted by SARS-CoV-2 and more than 200 host proteins that are significantly perturbed in COVID-19 derived PBMCs. From the interactome, we further identified that non-structural protein nsp9 and nsp10 interact with NKRF, a NF-kB repressor, and may precipitate the strong IL-8/IL-6 mediated chemotaxis of neutrophils and overexuberant host inflammatory response observed in COVID-19 patients. Our integrative study not only presents a systematic examination of SARS-CoV-2-induced perturbation of host targets and cellular networks to reflect disease etiology, but also reveals insights into the mechanisms by which SARS-CoV-2 triggers cytokine storms and represents a powerful resource in the quest for therapeutic intervention.

13. 在体外重建的鼻和支气管人气道上皮系统中研究SARS-CoV-2的特征和治疗方法

Characterization and treatment of SARS-CoV-2 in nasal and bronchial human airway epithelia

来源：biorxiv

发布时间：2020.4.2

通讯作者：法国里昂大学的Olivier Terrier和 Manuel RosaCalatrava

链接：https://www.biorxiv.org/content/10.1101/2020.03.31.017889v1

编译:蒋立春

该研究用体外重建的鼻/支气管气道上皮组织的模型对SARS-CoV-2的病毒感染动力学、对组织水平的细胞结构的改变以及被感染组织的转录水平的免疫特征进行了研究。该研究表明这个模型可以用来作为临床前评估抗病毒药物的效果。研究者们证明了瑞德西韦（remdesivir）的抗病毒活性，也进一步证明瑞德西韦（remdesivir）-地尔硫卓（diltiazem）的联用会产生更好的抗病毒效果，因此可能是COVID-19治疗的一个可选方案。

注：地尔硫卓（diltiazem）本身是一个心血管药物，作者们之前的研究表明这个药物可以诱导宿主产生干扰素，可以老药新用作为一个有效的流感药物。

Abstract: In the current COVID-19 pandemic context, proposing and validating effective treatments represents a major challenge. However, the lack of biologically relevant pre-clinical experimental models of SARS-CoV-2 infection as a complement of classic cell lines represents a major barrier for scientific and medical progress. Here, we advantageously used human reconstituted airway epithelial models of nasal or bronchial origin to characterize viral infection

kinetics, tissue-level remodeling of the cellular ultrastructure and transcriptional immune signatures induced by SARS-CoV-2. Our results underline the relevance of this model for the preclinical evaluation of antiviral candidates. Foremost, we provide evidence on the antiviral efficacy of remdesivir and the therapeutic potential of the remdesivir-diltiazem combination as a rapidly available option to respond to the current unmet medical need imposed by COVID-19.