新型冠状病毒信息简报

第 11 期（2020 年 3 月 29 日报）

上海科技大学免疫化学研究所生物医学大数据平台、

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1. 2020 年 3 月 28 日疫情

数据来源：WHO
发布时间：2020 年 3 月 28 日北京时间下午 5 点
链接：https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
根据 WHO 提供的数据，2020 年 3 月 28 日全球累计确诊新型冠状病毒病人 571678 例，当日新增确诊 62514 例，累计死亡 26494 例，当日新增死亡 3159。
中国累计确诊 82230 例，累计死亡 3301 例，当日新增确诊 152 例，新增死亡 3 例。

2. 雅培推出仅需 5 分钟的新冠病毒分子即时检测方法——已获美国 FDA 紧急使用授权

Abbott Launches Molecular Point-of-Care Test to Detect Novel Coronavirus in as Little as Five Minutes
来源：Abbott
发布时间：2020-03-27
来源链接： https://abbott.mediaroom.com/2020-03-27-Abbott-Launches-Molecular-Point-of-Care-Test-to-Detect-Novel-Coronavirus-in-as-Little-as-Five-Minutes#assets_2429_124393-111:19396
编译:宋张悦
内容摘要：

美国雅培公司于 2020 年 3 月 27 日发布新闻稿，宣布美国食品药品监督管理局（FDA）已授予其分子即时检测（molecular point-of-care test）紧急使用授权（EUA），它是目前应对 SARS-CoV-2 速度最快的即时检测之一，最快可在短短 5 分钟内获得阳性结果，可在 13 分钟内确认阴性结果。

雅培的最新分子即时检测将在公司的 ID NOW 平台上运行（如下图 1 所示），该系统体积小，重量轻（6.6 磅），便于携带（相当于一台小型的烤面包机），在医生办公室、紧急护理诊所和医院急诊科等广泛的医疗保健环境中提供快速的检测。作为即时诊断的全球领导者，雅培正在将其专业知识和规模用于应对 COVID-19 全球大流行。ID NOW 平台于 2014 年首次推出，是美国领先的甲型和乙型流感、链球菌 A 型和 RSV 检测的分子即时诊断平台。ID NOW 平台是一种快速、基于仪器的恒温系统，用于定性检测感染性疾病。其独有的恒温核酸扩增技术可在短短几分钟内提供分子结果（技术原理如图 3 所示），允许临床医生在患者就诊期间做出循证临床决策。关于 ID NOW 平台的其他详细介绍请参考链接：https://www.alere.com/en/home/product-details/id-now-covid-19.html。

雅培公司将在下周开始提供 ID NOW COVID-19 检测，并将增加生产，预计每天提供 5 万份检测。2020 年 3 月 18 日，雅培的另一款新冠检测产品 Abbott m2000™ RealTime SARS-CoV-2 EUA 已经获 FDA 的紧急使用授权，该试剂用于全球各大医院和实验室的 m2000 RealTime 系统上，通过 RT-PCR 技术定量检测 SARS-CoV-2 病毒（m2000 RealTime 系统和 SARS-CoV-2 检测试剂如下图 2 所示）。结合两款检测产品，雅培预计四月份的检测产能将达到 500 万人份。关于另一款新冠检测产品的详细介绍请参考链接：https://www.abbott.com/corpnewsroom/product-and-innovation/abbott-launches-novel-coronavirus-test.html。

Abbott has received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA) for the fastest available molecular point-of-care test for the detection of novel coronavirus (COVID-19), delivering positive results in as little as five minutes and negative results in 13 minutes.

- The Abbott ID NOW™ COVID-19 test brings rapid testing to the front lines
- Test to run on Abbott's point-of-care ID NOW platform - a portable instrument that can be deployed where testing is needed most (https://www.alere.com/en/home/product-details/id-now-covid-19.html)
- ID NOW has the largest molecular point-of-care installed base in the U.S. and is available in a wide range of healthcare settings
- Abbott will be making ID NOW COVID-19 tests available next week and expects to ramp up manufacturing to deliver 50,000 tests per day
- This is the company's second test to receive Emergency Use Authorization by the FDA for COVID-19 detection (https://www.abbott.com/corpnewsroom/product-and-innovation/abbott-launches-novel-coronavirus-test.html); combined, Abbott expects to produce about 5 million tests per month

图 1. 在 ID NOW™ 平台上进行分子即时检测（图片来源：雅培官网）

图 2. m2000 RealTime 系统和 SARS-CoV-2 检测试剂（图片来源：雅培官网）

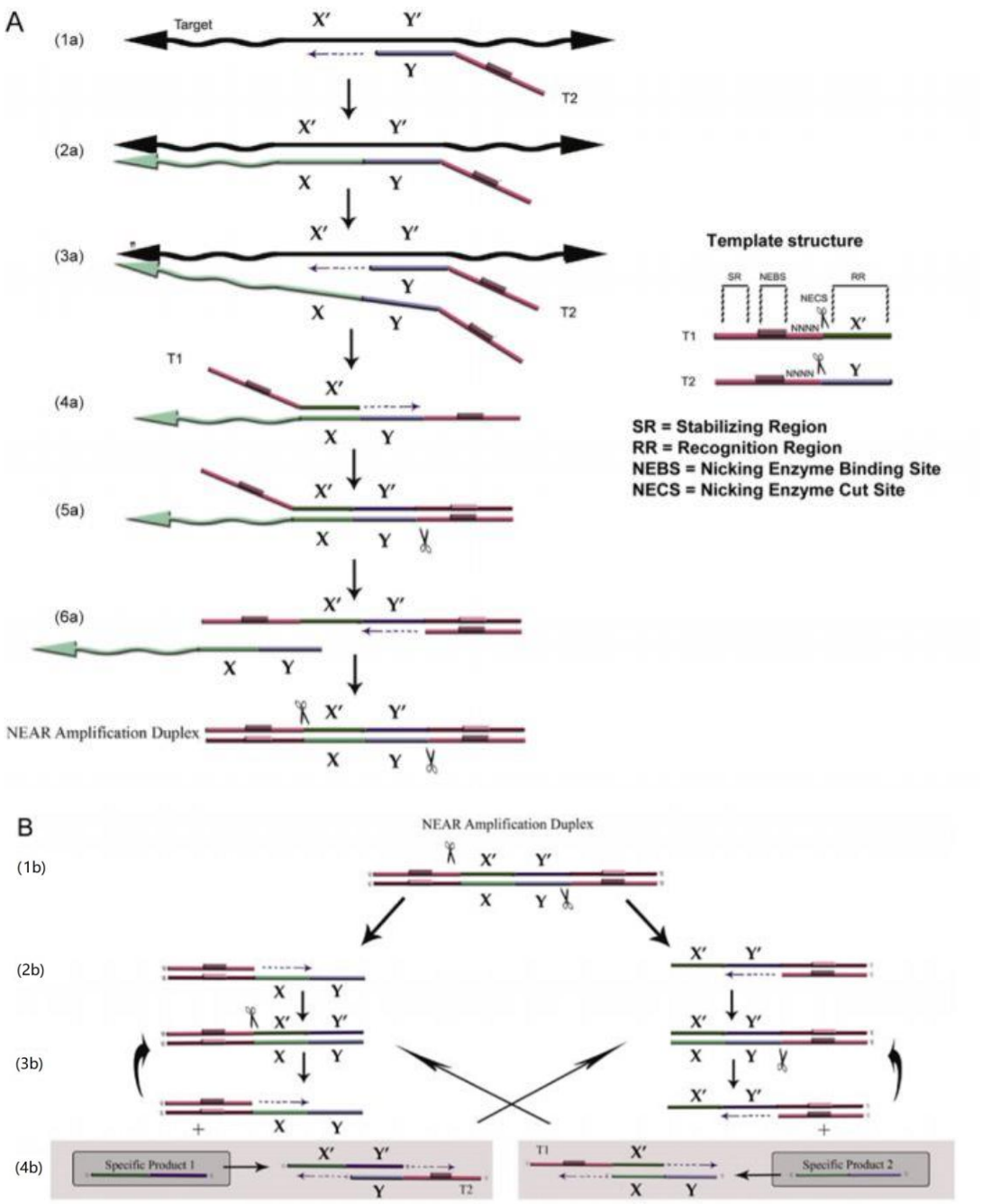

图 3. 恒温扩增技术原理。(A) Mechanism of NEAR amplification duplex formation. (1a and 2a) The recognition region of T2 binds to the complementary target region and is extended by polymerase along the target. (3a) A second T2 binds to the same target and is extended, displacing the first T2. (4a) The recognition region of T1 binds to its complement in the released strand and is extended to the 5′ end, creating a double-stranded nicking enzyme recognition site. (5a) Nicking enzyme binds and nicks (indicated by scissors). (6a) polymerase synthesizes off the cleaved 3′ OH along T1, displacing the remaining target complement, and the final extended double-stranded complex is termed the NEAR amplification duplex. (B) Mechanism of product formation. (1b and 2b) Nicking enzymes bind to both nicking enzyme recognition sites on the NEAR duplex; cleavage and strand

displacement amplification at both sites creates two complexes, each consisting of a duplex stability region, a nicking enzyme recognition region, and a single-stranded target. (3b and 4b) Repeated nicking, polymerization, and strand displacement result in the amplification of products 1 and 2. Cleaved complexes are regenerated (3b), while products 1 and 2 can anneal to T1 and T2, respectively (4b), resulting in bidirectional extension and creating duplexes that generate the opposite product upon cleavage. The products continue to recycle until the templates, deoxynucleoside triphosphates (dNTPs), or enzymes are depleted.（图片来源：https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4313160/）

3. 对浙江省杭州 70 例感染 COVID-19 出院病人临床回顾分析

Clinical retrospective analysis of 70 discharged patients with the Coronavirus disease 2019 (COVID-19) in Hangzhou, Zhejiang Province

来源：Research Square

发布时间：2020.3.28

链接：https://doi.org/10.21203/rs.3.rs-19398/v1

通讯作者：徐爱芳，杭州西溪医院检验科主任

作者单位: 杭州西溪医院

编译：张鹏伟

摘要：

自从 COVID-19 首次在中国武汉被确认，这种疾病在很多国家出现。考虑到对 COVID-19 缺乏有效的药物以及其快速的传播，作者对 70 例出院病人做了一个详细的临床回顾分析，这样可以帮助大家更好的确认这个疾病的特征。

作者从患者的住院记录中收集了人口统计学、流行病学、临床、实验室和 CT 数据，时间段是从住院第 1 天到第 7 天和最后一天。

年龄中位数为 43 岁（IQR:34-56 岁）。女性 41 例（58.6%），住院 14 天以上者 33 例（47.1%）。18 例（25.7%）为武汉市居民或近期来武汉旅游者，38 例（54.3%）与 COVID-19 密切接触。最常见的既往疾病有肝病（15.7%）、高血压（12.9%）、肾病（8.6%）、肺病（5.7%）。从发病到住院的时间为 4（IQR:2-7）天。最常见的治疗方案是洛匹那韦/利托那韦+干扰素-α 吸入+阿比妥。从第 1 天到第 7 天，接受 CT 的患者平均次数为 3 次（IQR:3-4）。

目前，还没有针对 COVID-19 的特异性抗病毒治疗方法。在此研究中，70 名 COVID-19 患者在两周内对治疗有积极反应。对于那些结果异常的出院患者，在今后的研究中需要更多的关注来控制其传播。

Abstract

Since the Coronavirus Disease 2019 (COVID-19) was first identified in Wuhan, China, the disease has been found in many countries. Considering the lack of effective drugs and rapid spread of COVID-19, we did a clinical detailed retrospective analysis of 70 discharged patients which can help us to better determine the clinical features of the disease.

We collected demographic, epidemiological, clinical, laboratory, and chest computed tomographic (CT) data from patients' hospital records, the time period were from hospitalization day1 to day7 and hospitalization last day.

The median age was 43 (IQR: 34-56) years. 41 (58.6%) patients were female, and there were 33 (47.1%) patients who were hospitalized more than 14 days. 18

(25.7%) patients were residents of Wuhan or recently travelled to Wuhan, 38 (54.3%) patients were having a close contact with the COVID-19 patients. The most common pre-existing diseases were liver disease (15.7%), hypertension (12.9%), renal disease (8.6), lung disease (5.7%).The time from illness onset to hospitalization was 4 (IQR: 2-7) days. The most common treatment regimen was Lopinavir/ritonavir (LPV) + Interferon alpha inhalation (IAI) + Arbidol. Chest computed tomography (CT) from day1 to day7 was 3 (IQR: 3-4).

Currently, there are no specific antiviral therapies for COVID-19. 70 COVID-19 patients in our study responded positively to treatment during the two-week period. For those discharged patients with abnormal results, more attention is needed in the future studies to control the transmission.

4. COVID-19 流行与嗅觉功能障碍爆发的巧合

Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak

来源：medrxiv

发表时间：2020-3-27

链接：https://www.medrxiv.org/content/10.1101/2020.03.23.20041889v1

通讯作者：Babak Ghalehbaghi，医学博士，过敏症和临床免疫学家

作者单位：伊朗德黑兰伊朗医学大学五感研究所耳鼻喉科和头颈部研究中心。

编译：雷颖

摘要：

近来在伊朗耳鼻喉专科诊所就诊的患者中嗅觉功能障碍的人数激增，与此同时伊朗正在爆发 COVID-19 流行病，这促使作者评估嗅觉缺失/减退患者以发现这两个事件之间的关联。作者对一份线上检查表进行了横向研究，该表列出了 2020 年 3 月 12 日至 17 日在伊朗所有省份的自愿病例。病例主要为 4 周内（从伊朗 COVID-19 流行病爆发开始）自主报告嗅觉缺失/减退的患者。变量包括临床表现，相关的既往病史，近期呼吸道感染的家族史和住院情况。结果表明，在本研究中，10069 名年龄在 32.5 +/- 8.6（7-78）岁的参与者完成了在线检查表，其中女性为 71.13%，非吸烟者为 81.68%。10.55%报告有外出旅行经历，并且有 1.1%最近因呼吸系统疾病住院了。在家庭成员中，最近几天有严重呼吸系统疾病史的比例为 12.17%，而患有嗅觉缺失/减退的比例为 48.23%。到 2020 年 3 月 16 日为止，在所有 31 个省份中，嗅觉障碍数量与报告的 COVID-19 患者之间的相关性非常显着（Spearman 相关系数= 0.87，p 值<0.001）。填写问卷时嗅觉缺失的发生率突增为 76.24%，而在此之前嗅觉减退的患者一直稳定保持在 60.90%。这些患者中还有 83.38%存在与嗅觉障碍相关的味觉下降。结论是伊朗在 COVID-19 流行期间，似乎同时爆发了嗅觉功能障碍。COVID-19 病人嗅觉缺失/减退的机理还需要进一步的调查。

Background

Recent surge of olfactory dysfunction in patients who were referred to ENT clinics and concurrent COVID-19epidemic in Iran motivated us to evaluate anosmic/hyposmic patients to find any relation between these two events.

Methods

This is a cross-sectional study with an online checklist on voluntary cases in all provinces of Iran between the 12th and 17th March, 2020. Cases was defined as self-reported anosmia/hyposmia in responders fewer than 4 weeks later (from start the of COVID-19 epidemic in Iran). Variables consist of clinical

presentations, related past medical history, family history of recent respiratory tract infection and hospitalization. Results In this study 10069 participants aged 32.5 +/- 8.6 (7-78) years, 71.13% female and 81.68% non-smoker completed online checklist. They reported 10.55% a history of a trip out of home town and 1.1% hospitalization due to respiratory problems recently. From family members 12.17% had a history of severe respiratory disease in recent days and 48.23% had anosmia/hyposmia. Correlation between the number of olfactory disorder and reported COVID-19 patients in all 31 provinces till 16th March 2020 was highly significant (Spearman correlation coefficient=0.87, p-Value<0.001). The onset of anosmia was sudden in 76.24% and till the time of filling the questionnaire in 60.90% of patients decreased sense of smell was constant. Also 83.38 of this patients had decreased taste sensation in association with anosmia.

Conclusions

It seems that we have a surge in outbreak of olfactory dysfunction happened in Iran during the COVID-19 epidemic. The exact mechanism of anosmia/hyposmia in COVID-19 patients needs further investigations.

5. SARS-CoV-2 进入基因在嗅觉上皮细胞中的非神经表达表明 COVID-19 患者发生嗅觉异常的机制

Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients

来源：biorxiv

发表时间：2020-3-28

链接：https://www.biorxiv.org/content/10.1101/2020.03.25.009084v2

通讯作者：Sandeep Robert Datta，MD，PhD，神经生物学副教授

作者单位：哈佛医学院神经生物学系

编译：雷颖

摘要：

最近的报道表明，COVID-19 与嗅觉功能改变之间存在关联。本文作者分析了大量细胞和单细胞 RNA-Seq 的数据集，以鉴定表达介导 SARS-CoV-2（CoV-2）（COVID-19 中的致病因子）感染分子的嗅觉上皮细胞类型。我们在小鼠和人类数据集中都发现，嗅觉感觉神经元不表达参与 CoV-2 进入的两个关键基因 ACE2 和 TMPRSS2。相反，嗅觉上皮支持细胞和干细胞都表达这两个基因，鼻呼吸道上皮细胞也是如此。综上所述，这些发现提示了 CoV-2 感染会导致嗅觉缺失或其他形式的嗅觉功能障碍的可能机制。

Abstract

Recent reports suggest an association between COVID-19 and altered olfactory function. Here we analyze bulk and single cell RNA-Seq datasets to identify cell types in the olfactory epithelium that express molecules that mediate infection by SARS-CoV-2 (CoV-2), the causal agent in COVID-19. We find in both mouse and human datasets that olfactory sensory neurons do not express two key genes involved in CoV-2 entry, ACE2 and TMPRSS2. In contrast, olfactory epithelial support cells and stem cells express both of these genes, as do cells in the nasal respiratory epithelium. Taken together, these findings suggest possible

mechanisms through which CoV-2 infection could lead to anosmia or other forms of olfactory dysfunction.

6. SARS-CoV-2 的核衣壳蛋白干扰人多能诱导干细胞的多能性

The Nucleocapsid Protein of SARS-CoV-2 Abolished Pluripotency in Human Induced Pluripotent Stem Cells

第一作者及通讯作者：

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来源：bioRxiv

发布时间：2020-03-26

来源链接：https://www.biorxiv.org/content/10.1101/2020.03.26.010694v1

编译：刘焕珍

摘要：

作为潜在的疫苗和治疗靶点的核衣壳蛋白 SARS-CoV-2（nCoVN），其功能室包装病毒基因组和病毒自组装。在这项研究中，我们首先提出 nCovN 干扰了 iPSC 的多能性，降低了细胞的增殖速率，但并未引起 iPSC 的凋亡。我们通过慢病毒表达系统产生了过表达 nCoVN 的 iPSC（iPSC-nCoVN），来研究 nCoVN 对人诱导多能干细胞（iPSC）的影响。出乎意料的是：nCoVN 表达两周后，iPSC 的形态和增殖率发生了改变。在 iPSC-nCoVN 中检测不到多能性标记 SSEA4 和 TRA-1-81。同时，采用常规的分化方案时，iPSC-nCoVN 不能分化成为心肌细胞。我们的数据表明，nCoVN 干扰了 iPSC 的多能性，并将其转变为成纤维细胞，这为 SARS-CoV-2 的致病机理提供了新的认识。另外，nCovN 如何破坏 iPSC 的多能性维持仍然是一个谜。尽管机理尚不清楚，但 nCovN 的毒性作用很明显，这提醒我们 SARS-CoV-2 可能损害生殖系统和造血系统。

Abstract

As a potential vaccine and therapeutic target, the nucleocapsid protein of SARS-CoV-2 (nCoVN) functions in packaging the viral genome and viral self-assembly. In this study, we first presented that nCovN abolished pluripotency, reduced the proliferation rate, but did not cause apoptosis in human induced pluripotent stem cells.To investigate the biological effect of nCoVN to human induced pluripotent stem cells (iPSC), genetically engineered iPSC overexpressing nCoVN (iPSC-nCoVN) were generated by lentiviral expression systems. Unexpectedly, the morphology and proliferation rate of iPSC were changed after nCoVN expressing for two weeks. The pluripotency markers SSEA4 and TRA-1-81 were not detectable in iPSC-nCoVN. Meanwhile, iPSC-nCoVN lost the ability for differentiation into cardiomyocytes when using a routine differentiation protocol. Our data suggested that nCoVN disrupted the pluripotent properties of iPSC and turned them into fibroblasts, which provided a new insight to the pathogenic mechanism of SARS-CoV-2. In addition, how nCovN breaks the pluripotency maintenance of iPSC is

still a riddle. Although the mechanism is unknown, the toxic effects of nCovN are clear, which reminds us that SARS-CoV-2 could impair the reproductive system and hematopoietic system.

7. 新冠病毒刺突蛋白表面覆盖大量的糖基化修饰，可能会造成免疫逃避并加大疫苗开发的难度

来源：Emerging Microbes & Infections
发布时间：2020.3.17
来源链接：https://doi.org/10.1080/22221751.2020.1739565
编译：赵素文

摘要：澳大利亚莫纳什大学的 NaVeen Vankadari 和 Jackie Wilce 使用生物信息学的方法分析了新冠病毒的刺突糖蛋白（简称 S 蛋白）。S 蛋白以同源三聚体的形式分布在病毒包膜上，构成了冠状病毒的“皇冠”状刺突。作者发现，每个 S 蛋白的同源三聚体含有 66 个 N-连接糖基化位点和 12 个 O-连接糖基化位点，比 SARS 冠状病毒的 S 蛋白多出十多个糖基化位点。预测的 60 多个 N-链接糖基化位点，被最近发表在 bioRxiv 上的 Site-specific analysis of the SARS-CoV-2 glycan shield 一文用质谱实验证证实。

新冠病毒 S 蛋白表面覆盖的大量糖基化修饰，可能会造成免疫逃避（immune evasion）和遮蔽抗原表位，这可能会增大以 S 蛋白（或 S 蛋白的一部分）为抗原的疫苗开发的难度。

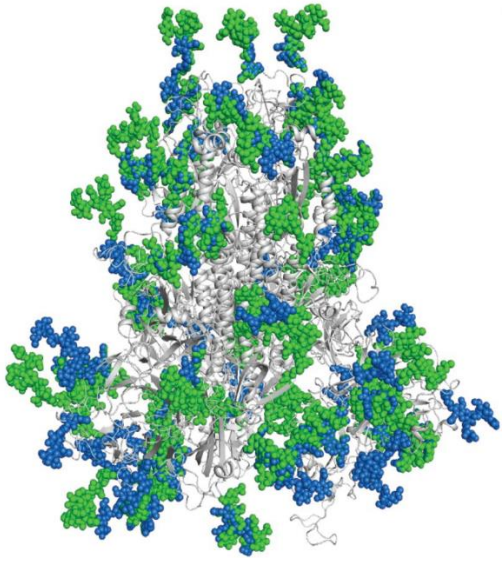

图 1：新冠病毒 S 蛋白上预测的糖基化位点（绿色），和 SARS 病毒 S 蛋白上预测的糖基化位点（蓝色）。

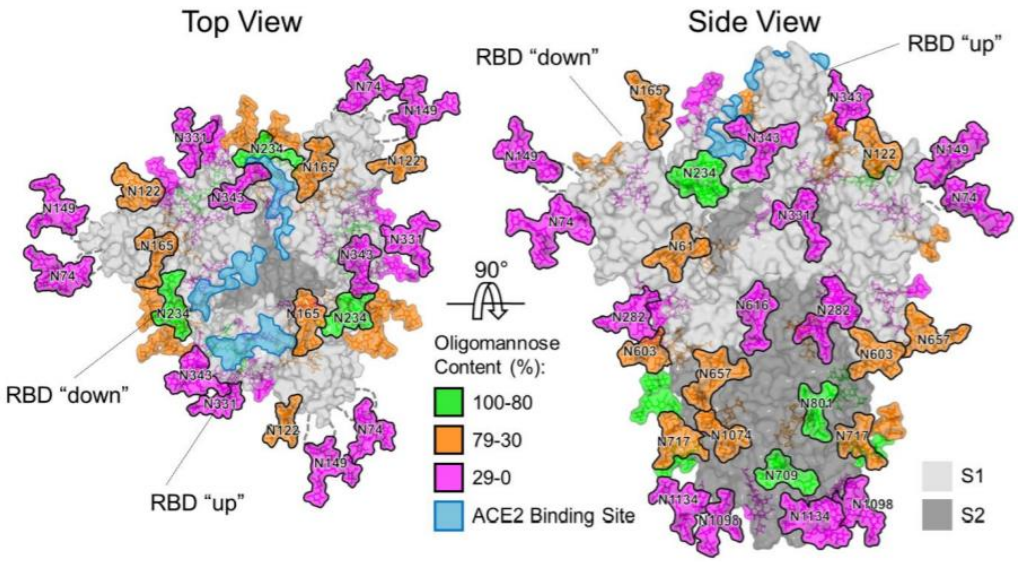

图 2：新冠病毒 S 蛋白上通过实验观察到的糖基化位点。

8. 在叙利亚金色仓鼠模型中重塑 COVID-19 的发病机制以及传染性等等临床和病理特征

Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility

来源：Clin Infect Dis

发布日期：2020-03-26

链接:https://doi.org/10.1093/cid/ciaa325

编译：蒋立春

编者注：

我们前面介绍过 hACE2 的转基因小鼠以及猕猴的 COVID-19 模型。香港大学袁国勇教授团队发现叙利亚金色仓鼠可能是一种好的小动物模型。

关于对常见的实验动物的 ACE2 和 SARS-CoV-2 的刺突蛋白的受体结合区域的分子进行分子对接实验，发现叙利亚金色仓鼠可能是一个选择。研究团队对叙利亚金色仓鼠中进行了病毒接种、接触传播、被动免疫等等实验。并且对各种组织器官和血液进行了病毒载量、细胞因子、趋化因子、中和抗体滴度等等进行了一系列分析。

叙利亚仓鼠可以持续被 SARS-CoV-2 感染。被感染仓鼠临床上出现呼吸加速、体重减轻、以及一系列病理变化。在病毒感染的第一周内研究者们观察到很多的临床病理表现。最初期是伴随广泛的细胞凋亡的弥散性肺泡损失的渗出阶段。后面是和细胞因子激活相关的组织修复增殖，病毒核衣壳蛋白在气道和肠道的表达，肺部出现高的病毒滴度，脾脏和淋巴萎缩等等症状。肺部的病毒滴度在 10 万到 1000 万 TCID50/g 之间。和被接种过的仓鼠养在一个笼子里的仓鼠都可以被感染，这些仓鼠除了体重没有减轻，其他症状和接种感染的仓鼠症状相似。感染 14 天后所有仓鼠都自己恢复并且产生了滴度高于 1:427 的中和抗体。用恢复早期的血浆被动免疫过的仓鼠肺部的病毒载量会明显更低，但是肺部病变并没有较少。从感染的仓鼠中分离出的病毒里没有出现病毒刺突蛋白发生一致的适应性非同义氨基酸突变（编著注:病毒在适应不同的宿主时，可能会通过刺突蛋白发生突变而加强对新宿主的适应性。这篇文章全文网络原因没有下载到，不知道作者用了多少只仓鼠。）

除了满足科赫法则，仓鼠模型是一个很好的研究 SARS-CoV-2 病毒传播、发病机制、治

疗以及疫苗开发的重要工具。

BACKGROUND:

A physiological small animal model that resembles COVID-19 with low mortality is lacking.

METHODS:

Molecular docking on the binding between angiotensin-converting enzyme 2 (ACE2) of common laboratory mammals and the receptor-binding domain of the surface spike protein of SARS-CoV-2 suggested that the golden Syrian hamster is an option. Virus challenge, contact transmission, and passive immunoprophylaxis were performed. Serial organ tissues and blood were harvested for histopathology, viral load and titre, chemokine/cytokine assay, and neutralising antibody titre.

RESULTS:

The Syrian hamster could be consistently infected by SARS-CoV-2. Maximal clinical signs of rapid breathing, weight loss, histopathological changes from the initial exudative phase of diffuse alveolar damage with extensive apoptosis to the later proliferative phase of tissue repair, airway and intestinal involvement with virus nucleocapsid protein expression, high lung viral load, and spleen and lymphoid atrophy associated with marked cytokine activation were observed within the first week of virus challenge. The lung virus titre was between 105-107 TCID50/g. Challenged index hamsters consistently infected naïve contact hamsters housed within the same cage, resulting in similar pathology but not weight loss. All infected hamsters recovered and developed mean serum neutralising antibody titre ≥1:427 fourteen days post-challenge. Immunoprophylaxis with early convalescent serum achieved significant decrease in lung viral load but not in lung pathology. No consistent non-synonymous adaptive mutation of the spike was found in viruses isolated from infected hamsters.

CONCLUSIONS:

Besides satisfying the Koch's postulates, this readily available hamster model is an important tool for studying transmission, pathogenesis, treatment, and vaccination against SARS-CoV-2.

9. COVID-19 恢复期血浆治疗 5 例危重症患者

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

来源：JAMA.

发布时间：2020.3.27

链接：https://jamanetwork.com/journals/jama/fullarticle/2763983

通讯作者：刘颖霞，医学博士；张郑，医学博士；刘磊，医学博士。

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编译：张丽双

摘要：

本文目的是对恢复期血浆输注治疗 SARS-CoV-2 感染重症的初步临床经验进行描述。本研究于 2020 年 1 月 20 日至 2020 年 3 月 25 日在中国深圳市第三人民医院传染病科进行，最终随访日期为 2020 年 3 月 25 日。

入组条件：实验室确诊的 COVID-19 危重症患者，尽管进行了抗病毒治疗，但进展迅速且病毒载量持续高的重症肺炎； Pao2/Fio2<300；并使用了机械通气。

满足受供者 ABO 相容性。于供者供血当天连续输注 200-250mL。所有供者均为实验室确诊 SARS-CoV-2 感染治愈患者，检测 SARS-CoV-2 和其他呼吸道病毒，以及乙型肝炎病毒、丙型肝炎病毒、艾滋病病毒和梅毒均为阴性。献血者至少 10 天都没有症状，血清 SARS-CoV-2 特异性 ELISA 抗体滴度大于 1:1000，中和抗体滴度大于 40。受供双方均有书面知情同意。

结果:血浆输注后，病毒载量降低明显（见下表）。5 例患者中有 4 例在 3d 内体温恢复正常，12 天内 SOFA 评分下降，PAO2/FIO2 升高（范围：输注前 172～276，输注后 284～366）。病毒载量在输血后 12 天内下降并呈阴性，输血后 SARS-CoV-2 特异性 ELISA 和中和抗体滴度增加（范围：输血前 40-60 和输血后第 7 天 80-320）。4 例 ARDS 在输血后 12 天得到缓解，3 例在治疗后 2 周内脱离机械通气。5 例患者中，3 例出院（住院时间：53、51、55 天），2 例输血后 37 天病情稳定。

结论:在 5 例 COVID-19 和 ARDS 危重患者病例中，应用含中和抗体的恢复期血浆可改善其临床状况，但这种方法需要在随机临床试验中进行评估。

Abstract

Importance Coronavirus disease 2019 (COVID-19) is a pandemic with no specific therapeutic agents and substantial mortality. It is critical to find new treatments.

Objective To determine whether convalescent plasma transfusion may be beneficial in the treatment of critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Design, Setting, and Participants Case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who met the following criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; PAO2/FIO2 <300; and mechanical ventilation. All 5 were treated with convalescent plasma transfusion. The study was conducted at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020, to March 25, 2020; final date of follow-up was March 25, 2020. Clinical outcomes were compared before and after convalescent plasma transfusion.

Exposures Patients received transfusion with convalescent plasma with a SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immunosorbent assay [ELISA]) and a neutralization titer greater than 40 (end point dilution titer) that had been obtained from 5 patients who recovered from COVID-19. Convalescent plasma was administered between 10 and 22 days after admission.

Main Outcomes and Measures Changes of body temperature, Sequential Organ Failure Assessment (SOFA) score (range 0-24, with higher scores indicating more severe illness), PAO2/FIO2, viral load, serum antibody titer, routine blood biochemical index, ARDS, and ventilatory and extracorporeal membrane oxygenation (ECMO) supports before and after convalescent plasma transfusion.

Results All 5 patients (age range, 36-65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature

normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PAO2/FIO2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion.

Conclusions and Relevance In this preliminary uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials.

10. 骆驼科动物单域抗体有效中和β-冠状病毒的结构基础

Structural Basis for Potent Neutralization of Betacoronaviruses by Single-domain Camelid Antibodies

来源：biorxiv

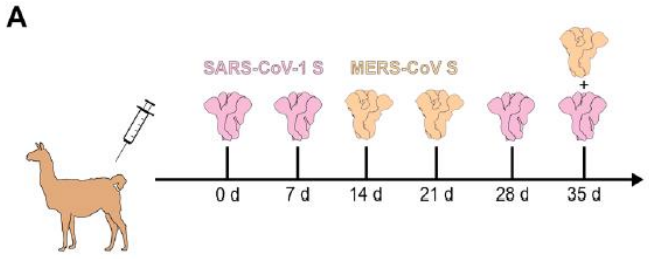
发布时间：2020-03-28

来源链接：https://www.biorxiv.org/content/10.1101/2020.03.26.010165v1

编译:王玮

内容摘要：

三类冠状病毒 MERS-CoV，SARS-CoV-1 和 SARS-CoV-2 均曾或者正在人群中传播，并造成了严重后果。这类病毒利用一种名为刺突蛋白的大型包膜蛋白与宿主细胞受体结合并催化膜融合。由于这些刺突蛋白起着至关重要的作用，刺突蛋白可成为开发治疗这些高致病性冠状病毒的有效靶标。来自得克萨斯大学奥斯汀分校，VIB Center for Medical Biotechnology，根特大学和 NIH 等单位的研究人员从对预融合稳定的冠状病毒刺突蛋白（MERS-CoV 和 SARS-CoV-1 的刺突蛋白，图一）免疫的美洲驼中分离和鉴定出单域抗体（VHHs，图二）。这些 VHHs 能够有效中和 MERS-CoV 或 SARS-CoV-1s 假病毒颗粒。这些 VHHs 与各自的病毒靶点结合的晶体结构显示出两种不同的表位，但它们都能够阻断冠状病毒与宿主受体的结合。该研究还发现针对 SARS-CoV-1s 的 VHH 和 SARS-CoV-2s 之间的交叉反应，具有这种交叉反应的 SARS VHH-72，改造成二价 VHH-72-Fc 能够中和 SARS-CoV-2s 假病毒颗粒。这些数据为 VHHs 中和致病性β-冠状病毒提供了分子基础，并提示这些 单域抗体可能在冠状病毒爆发期间能够成为有效的治疗手段。



图一 从美洲驼中分离出针对 SARS-CoV-1 刺突蛋白和 MERS-CoV 刺突蛋白的 VHHs 的免疫策略示意图

图二 针对 MERS-CoV 和 SARS-CoV-1 的 VHHs 的序列比对

Abstract

The pathogenic Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV-1) and COVID-19 coronavirus (SARS-CoV-2) have all emerged into the human population with devastating consequences. These viruses make use of a large envelope protein called spike (S) to engage host cell receptors and catalyze membrane fusion. Because of the vital role that these S proteins play, they represent a vulnerable target for the development of therapeutics to combat these highly pathogenic coronaviruses. Here, we describe the isolation and characterization of single-domain antibodies (VHHs) from a llama immunized with prefusion-stabilized coronavirus spikes. These VHHs are capable of potently neutralizing MERS-CoV or SARS-CoV-1 S pseudotyped viruses. The crystal structures of these VHHs bound to their respective viral targets reveal two distinct epitopes, but both VHHs block receptor binding. We also show cross-reactivity between the SARS-CoV-1 S-directed VHH and SARS-CoV-2 S, and demonstrate that this cross-reactive VHH is capable of neutralizing SARS-CoV-2 S pseudotyped viruses as a bivalent human IgG Fc-fusion. These data provide a molecular basis for the neutralization of pathogenic betacoronaviruses by VHHs and suggest that these molecules may serve as useful therapeutics during coronavirus outbreaks.

11. 17 种 FDA 批准的广谱抗病毒药物可以抑制 SARS-CoV-2FDA

FDA approved drugs with broad anti-coronaviral activity inhibit SARS-CoV-2 in vitro

来源：biorxiv

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链接:https://www.biorxiv.org/content/10.1101/2020.03.25.008482v1

编译：蒋立春

马里兰大学医学院 Matthew Frieman 教授团队从 FDA 批准的药物中筛选到 17 种在体

外细胞实验中可以抑制 SARS-CoV-2 的药物。团队之前采用高通量筛选的方法对 290 个 FDA 批准的药物中筛选既能抑制 SARS-CoV 也能抑制 MERS-CoV 的药物。他们从这个筛选里找到的 27 个药物分子优先选择了 20 个进行对 SARS-CoV-2 抑制性的研究。在绿猴肾细胞的感染实验体系中，总共筛选出 17 个药物在无细胞毒的浓度范围内对 SARS-CoV-2 有好的抑制性。作者特意重复了氯喹和羟氯喹的体外实验，发现羟氯喹比氯喹的抑制活性更高。

SARS-CoV-2 emerged in China at the end of 2019 and has rapidly become a pandemic with over 400,000 recorded COVID-19 cases and greater than 19,000 recorded deaths by March 24th, 2020 (www.WHO.org). There are no FDA approved antivirals or vaccines for any coronavirus, including SARS-CoV-2. Current treatments for COVID-19 are limited to supportive therapies and off-label use of FDA approved drugs. Rapid development and human testing of potential antivirals is greatly needed. A potentially quicker way to test compounds with antiviral activity is through drug re-purposing. Numerous drugs are already approved for use in humans and subsequently there is a good understanding of their safety profiles and potential side effects, making them easier to test in COVID-19 patients. Here, we present data on 20 FDA approved drugs tested for antiviral activity against SARS-CoV-2 that we have previously found to inhibit SARS-CoV and MERS-CoV. We find that 17 of these also inhibit SARS-CoV-2 at a range of IC50 values at non-cytotoxic concentrations. From these we specifically followed up with hydroxychloroquine sulfate and chloroquine phosphate.

IC50 and CC50 values for 20 FDA approved drugs against SARS-CoV2.

Drug	MOI	Plate Replicates	IC50 (avg.)	CC50 (avg.)	SI (avg.)
Fluphenazine Dihydrochloride	0.004	3,2[a]	6.36	20.02	3.15
	0.01	2	8.98	20.02	2.23
Benztropine Mesylate	0.004	3	13.8	>>50[c]	>>3.62[c]
	0.01	2,3[a]	17.79	>>50[c]	>>2.81[c]
Amodiaquin Hydrochloride	0.004	3	2.36	>38.63[b]	>16.37[b]
	0.01	3	5.64	>38.63[b]	>6.84[b]
Chlorpromazine Hydrochloride	0.004	2,3[a]	3.14	11.88	3.78
	0.01	2,3[a]	4.03	11.88	2.94
Toremifene Citrate	0.004	2,3[a]	4.77	20.51	4.30
	0.01	3	11.30	20.51	1.81
Amodiaquin Dihydrochloride Dihydrate	0.004	2,3[a]	2.59	34.42	13.31
	0.01	3	4.94	34.42	6.97
Thiethylperazine Maleate	0.004	3	7.09	18.37	2.59
	0.01	3	8.02	18.37	2.29
Mefloquine Hydrochloride	0.004	3	7.11	18.53	2.61
	0.01	3	8.06	18.53	2.30
Triparanol	0.004	2,3[a]	4.68	21.21	4.53
	0.01	2,3[a]	6.41	21.21	3.31
Terconazole Vetranal	0.004	3	11.92	41.46	3.48
	0.01	2,3[a]	16.14	41.46	2.57
Anisomycin	0.004	3	ND	<0.39	ND
	0.01	3	ND	<0.39	ND
Gemcitabine Hydrochloride	0.004	3	ND	23.22	ND
	0.01	3	ND	23.22	ND
Imatinib Mesylate	0.004	3	3.24	>30.86[b]	>9.52[b]
	0.01	3	5.32	>30.86[b]	>5.80[b]
Fluspirilene	0.004	3	3.16	30.33	9.61
	0.01	3	5.32	30.33	5.71
Clomipramine Hydrochloride	0.004	2,3[a]	5.63	>29.68[b]	>5.27[b]
	0.01	3	7.59	>29.68[b]	>3.91[b]
Hydroxychloroquine Sulfate	0.004	3	9.21	>>50[c]	>>5.43[c]
	0.01	3	11.17	>>50[c]	>>4.48[c]
Promethazine Hydrochloride	0.004	3	9.21	>42.59[b]	>4.62[b]
	0.01	3	10.44	>42.59[b]	>4.08[b]
Emetine Dihydrochloride Hydrate	0.01	2,3[a]	ND	<0.39	ND
Chloroquine Phosphate	0.004	3	42.03	>50[b]	>1.19[b]
	0.01	3	46.80	>50[b]	>1.07[b]
Tamoxifen Citrate	0.004	2	34.12	37.96	1.11
	0.01	1,2[a]	8.98	37.96	4.23

Abbreviations: "MOI", multiplicity of infection; "IC50", half maximal inhibitory concentration; "CC50", half maximal cytotoxic concentration; "avg.", average; "ND", not determined;
[a]Run totals listed as "IC50,CC50"
[b]at least one CC50 could be extrapolated from the curve fit, suggesting toxicity and SI are slightly higher than listed
[c]no CC50 could not be extrapolated from the curve fit, suggesting toxicity and SI are much higher than listed

编者注：其中 Anisomycin,Gemicitabine Hydrochloride,Emetine Dihydrocholride Hydrate 细胞毒性过高被排除掉。

12. 加速寻找 COVID-19 治疗方案

Race to find COVID-19 treatments accelerates
来源：Science
发布时间：2020-03-27
链接：https://science.sciencemag.org/content/367/6485/1412

Kai Kupferschmid 和 Joh Cohen 日前在 Science 杂志上发表了一篇深度评论（in depth）讲到怎么加速 COVID-19 治疗方案的研发。到目前为止，已经至少有 12 种可能有潜力的药物被测试，包括治疗 HIV 和疟疾的药物，还有一些在动物实验中有效果的实验药物，以及恢复期血浆。不同的治疗方案可能会适用于感染的不同阶段，但是科学家认为，最大的挑战是临床上很难决定到底什么时候该用哪个药。

研究者们呼吁要及时开展临床试验，保证临床试验能招募到足够多的病人。

WHO 在 3 月 20 日宣布了一个叫做 SOLIDARITY 的项目,这是一个前所未有的项目，希望能在大流行期间推动大家整合力量积累可靠的科学数据。该项目强调简单可操作性即使医院在忙于应对 COVID-19 的病人的情况下也能参与到研究里面来。WHO 的网站将依据当地标准治疗的方案或者 4 个药物中的方案进行病人随机化分配，用当地可以提供的医疗方案来进行治疗。医生们只需要填病人出院或者去世的时间，总住院的时间以及是否需要吸氧和插管。

虽然不可避免会出现安慰剂效应，为了试验的进度，这些临床试验不设盲，

与其花多年去从头测试新药，WHO 以及其他方面都希能从已经获批的药物里面找到安全性可以接受又有效果的药物。另外，也会考察在动物实验里证明对 SARS 和 MERS 有效果的药物。最后，会集中考虑那些现存足够治疗相当多病人的药物。

WHO 选取了实验药物瑞德西韦（remdesivir）;治疗疟疾的氯喹(或者它的化学衍生物羟氯喹)； 一个治疗 HIV 的物洛匹拉韦（lopinavir）和利托那韦（ritonavir）复方制剂; 以及洛匹拉韦（lopinavir）和利托那韦（ritonavir）复方制剂加上 beta-干扰素——一个可以给人体免疫系统来抑制病毒的信号. The treatments would stop the virus by different mechanisms, but each has drawbacks.这些药物用不同的作用机制抑制病毒，每个药物有自己的缺点。

瑞德西韦 Remdesivir, 是由于 Gilead 公司开发的用来治疗 Ebola 和相关病毒感染的实验药物。它的作用机理是通过抑制病毒的 RNA 多聚酶而抗病毒。这个药物在 2019 年在刚果开展的一个治疗 Ebola 的临床试验没有疗效。在 2017,在体外试验以及动物实验中，该药显示了抗 SARS and MERS 病毒的活性。

这个药物目前在美国和欧洲有开始临床试验。在中国进行的临床试验预期于 4 月 17 日揭晓试验结果。

和其他抗急性感染的药物一样，瑞德西韦在早期使用会更有效果。专家表示这可能会有一个问题：因为这个药物需要静脉注射，而且很贵，而我们知道 85%的病人可能不会发展成重症，所以很难给每个有轻微症状的病人来一针。

氯喹（Chloroquine）和羟氯喹（hydroxychloroquine）可以降低细胞胞内体的 PH 值，胞内体是细胞用来摄取外来物质或者一些病毒感染时候内吞病毒的细胞器. SARS-CoV- 2 的主要侵入途径不一样，用刺突蛋白结合人细胞表面的受体进去细胞。体外实验证明氯喹可以抑制 SARS-CoV-2，但是往往需要比较高的剂量，这个剂量可能会导致严重的毒性。 专家说科学家们以往将这个药物在一个又一个病毒上进行测试，在人体试验中都没有成功。

氯喹在人体试验中是否有效现在还未知。中国科学家讲用这个药治疗了 100 多个病人有效果，但是目前还没有公开任何数据。WHO 也宣传，在中国开展的其他 20 多个氯喹相关的临床试验也没有任何公开的数据。法国的微生物学家报道了一个包含少数病人的临床试验，但是这个试验并没有随机化设计，另外也没有报道病人的临床结局。

羟氯喹的副作用很可能比作用大，有非常多的副作用，在很少的一些情况下，甚至危及心脏。目前已经有病人自己用药发生中毒事件。

很多冠状病毒的研究者们同样也质疑洛匹拉韦（lopinavir）和利托那韦复合制剂.这个药是 HIV 的药物，通过抑制蛋白酶从而阻断病毒蛋白组装形成病毒颗粒。该药在 SARS 和

MERS 中的疗效不是很明确. 在武汉开展的一个 199 危重病人的对照试验中，这个药物组并没有取得比标准疗法更好的效果。

SOLIDARITY 试验的第四个臂是洛匹拉韦（lopinavir）和利托那韦复合制剂加上干扰素-beta。这个药物可以减轻 MERS 感染的绒猴的症状。不过也有专家指出，对于 COVID-19 重症患者，这个药可能很危险，因为它可能加剧组织损伤。

SOLIDARITY 项目希望项目的结果能给公共健康提供一个提供一个快捷、有用的判断。在此基础上，欧洲会用同样的药物做一个包含（包括羟氯喹而没有氯喹）的 3200 个病人的临床试验，会收集更多的临床数据比如血氧浓度、肺部的影像学资料等等。

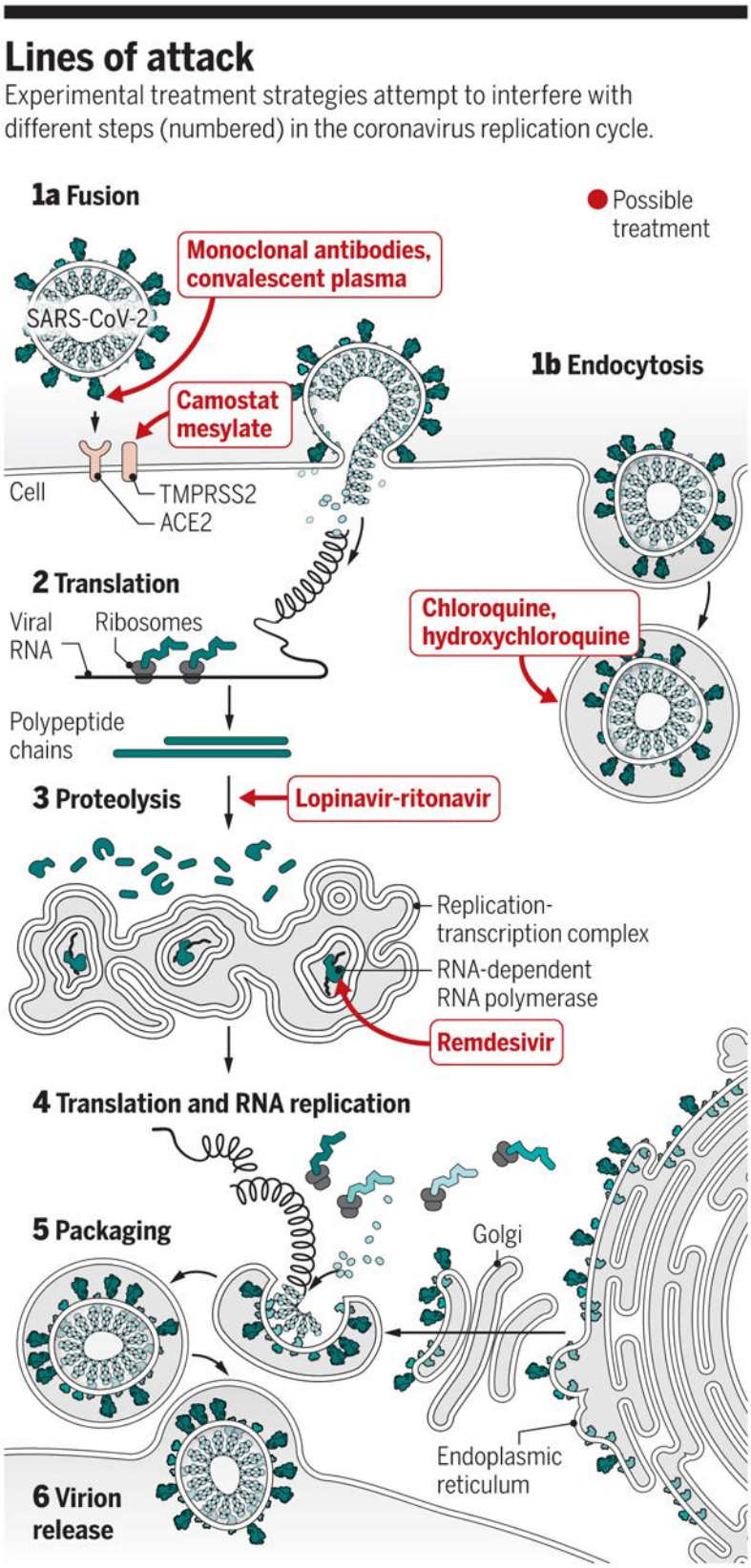
其他临床试验也已经或者尽快开展。包括降低炎症反应的皮质内固醇和治疗关节炎的 baricitinib (JAK 抑制剂)

一些研究者对一个在日本获批的治疗急性胰腺炎的药物卡莫司他（camostat mesylate）抱有很大期望. 其他抗病毒的药物比如治疗流感的法匹拉韦以及另一个 HIV 药物 antiretrovirals 也有机会得到测试. 研究人员也计划采用恢复期血浆或者 SARS-CoV-2 的单抗来提高人们对该病毒的免疫力。

最聪明有效的办法是在那些据预测可能会变严重的病人中发病早期就进行试验。现在需要找到能预测疾病进程的血液生物标志物。

科学家们强调面对这个前所未有的挑战，大家必须团结一致找到解决方案。

--转下页：几种潜在药物的作用机制



几种潜在抗 SARS-CoV-2 药物作用机理示意图

GRAPHIC: V. ALTOUNIAN/*SCIENCE*