新型冠状病毒信息简报

第 19 期（2020 年 4 月 6 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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免责申明：
本简报仅作为科研参考之用，不构成医疗建议，如您怀疑自己感染新型冠状病毒，请去正规医院或者咨询医生

1. 2020 年 4 月 5 日疫情

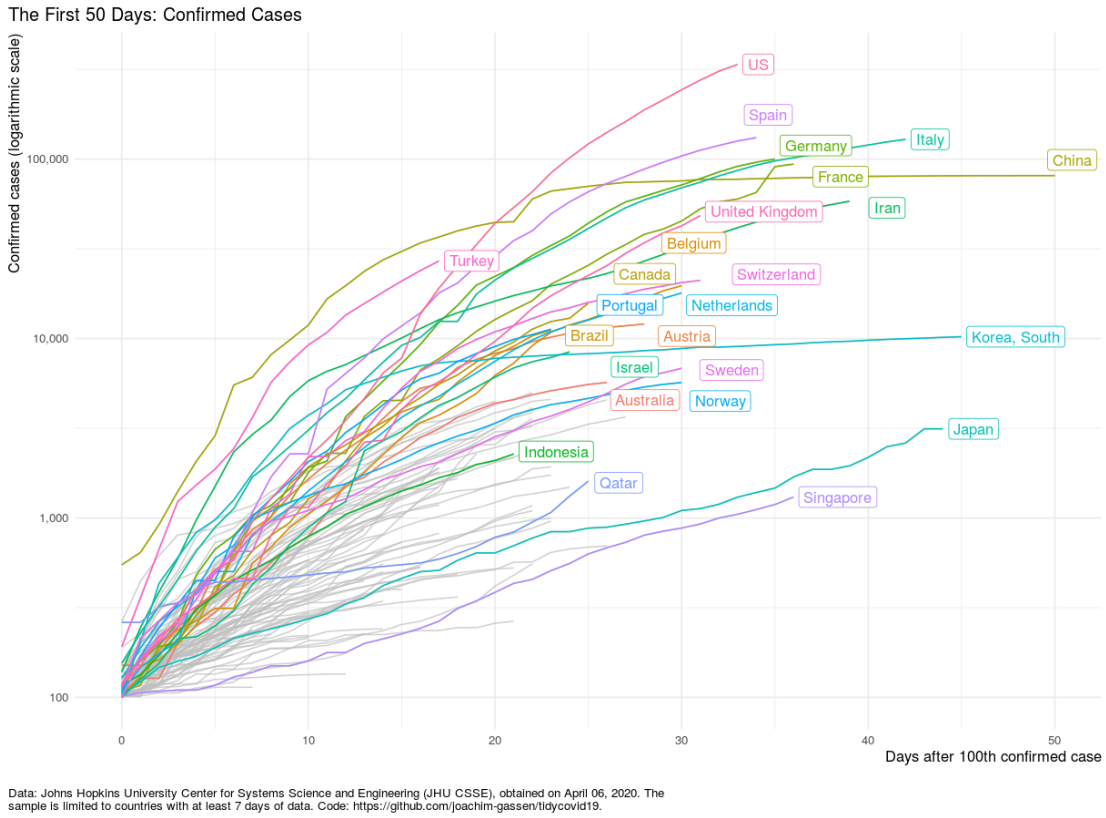
数据来源：WHO

发布时间：2020 年 4 月 5 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 5 日全球累计确诊新型冠状病毒病人 1133758 例，当日新增确诊 82061 例，累计死亡 62784 例，当日新增死亡 5798。

中国累计确诊 82930 例，累计死亡 3338 例，当日新增确诊 55 例，新增死亡 3 例。



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止 4 月 5 日北京时间下午 4 点）

2. 用混合样本贝叶斯方法可以提高 COVID-19 的检测通量和病例检出效率

Increasing testing throughput and case detection with a pooled-sample Bayesian approach in the context of COVID-19

来源：bioRxiv，预印本

发布时间：2020-04-05

来源链接：https://www.biorxiv.org/content/10.1101/2020.04.03.024216v1

作者及单位：Rodrigo Noriega1, Matthew H. Samore（美国犹他大学）

编译者：宋张悦

内容摘要：

在 COVID-19 大流行的情况下，包括美国在内的大部分国家都面临着诊断检测试剂盒短缺的问题，在对轻症患者、确诊患者的密切接触者以及无症状的疑似患者等排查中尤为重要。本文中研究人员使用贝叶斯公式，讨论了快速、利用有限资源筛查大批量样本的混合样本检测方法的可行性。混合检测的方法源自 1940s 的梅毒检测，并已应用于筛查和评估各种疾病的患病率。由 Dorfman 首次提出二步检测流程：收集病人的样本，然后随机混合成几个

样本池，如果合并检测结果为阴性，则无需进一步的检测，如果合并检测产生阳性结果，则对该池中的所有患者再分别进行检测。混合样本后检测的灵敏度可能有下降，但是预计检测通量和检出效率会大幅增加，这表明样本混合检测是规避 COVID-19 当前检测瓶颈的可行途径。

编者注：在第 16 期（2020 年 4 月 3 日）的简报中，我们已经介绍了由 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合作开发的 Mini-pool 混合检测方法，与本文有相似的结论，混合检测方法可以大幅度提高全世界的检测能力。

另：在国内进行大规模的普查也可以将上述 pool 的方法加以应用，做到经济高效。

Abstract

Rapid and widespread implementation of infectious disease surveillance is a critical component in the response to novel health threats. Molecular assays are the preferred method to detect a broad range of pathogens with high sensitivity and specificity. The implementation of molecular assay testing in a rapidly evolving public health emergency can be hindered by resource availability or technical constraints. In the context of the COVID-19 pandemic, the applicability of a pooled-sample testing protocol to screen large populations more rapidly and with limited resources is discussed. A Bayesian inference analysis in which hierarchical testing stages can have different sensitivities is implemented and benchmarked against early COVID-19 testing data. Optimal pool size and increases in throughput and case detection are calculated as a function of disease prevalence. Even for moderate losses in test sensitivity upon pooling, substantial increases in testing throughput and detection efficiency are predicted, suggesting that sample pooling is a viable avenue to circumvent current testing bottlenecks for COVID-19.

3. 英国政府支持牛津对 COVID-19 进行适应性临床试验

U.K. government backs Oxford’s adaptive trial for COVID-19

来源：biocentury，recoverytrial

发布时间：2020-04-04

来源链接：

https://www.biocentury.com/article/304827?editionId=ck8l0la6jjsp20998c1lwvifh&editionType=daily，https://www.recoverytrial.net/

编译: 王玮

内容摘要：

英国政府支持牛津大学的自适应临床 II 期/ III 期康复试验，评估至少三种治疗 COVID-19 的方法。卫生和社会保健部（DHSC）表示，这项研究将是世界上最大的新型冠状病毒随机临床研究。

适应性临床试验包括：

抗病毒组合洛匹那韦/利托那韦（抗 HIV）

小剂量地塞米松（一种类固醇，减轻炎症）

羟基氯喹（抗疟疾药物）

吸入式干扰素-β 1a（目前尚未开始）

在短短两周多的时间里，该试验从 132 家医院招募了近 1000 名患者；DHSC 表示，预计还会有数千名患者加入。

DHSC 在一份声明中表示，治疗的安全性和有效性的最终结果预计将在数月内得出。
英国政府承诺通过英国研究和创新（UKRI）和 DHSC 国家卫生研究所（NIHR）资助 210 万英镑（260 万美元）的研究经费。支持这项试验的还有 NIHR 牛津生物医学研究中心、Wellcome 信托基金、Bill 和 Melinda Gates 基金会、英国健康数据研究中心、医学研究委员会人口健康研究组和 NIHR 临床试验组支持基金。

Abstract
The U.K. government is backing the University of Oxford's adaptive Phase II/III RECOVERY trial evaluating at least three therapies to treat COVID-19. The Department of Health and Social Care (DHSC) said the study will be the world's largest randomized clinical study for the novel coronavirus.
The trial is testing antiviral combination lopinavir/ritonavir, which AbbVie Inc. (NYSE:ABBV) markets as Kaletra to treat HIV infection, the anti-inflammatory steroid dexamethasone and antimalarial drug hydroxychloroquine; patients will receive standard of care plus one of the study drugs, or standard of care alone.
Although the RECOVERY website lists inhaled interferon β1a as a fourth therapeutic, the site says that therapy is "not currently in use in this trial."
In just over two weeks, the trial has recruited nearly 1,000 patients from 132 hospitals; the DHSC said it expects thousands more to join.
"Definitive results on whether the treatments are safe and effective are expected within months," the DHSC said in a statement.
The U.K. government has pledged £2.1 million ($2.6 million) in funding for the study, via UK Research and Innovation (UKRI) and the DHSC's National Institute for Health Research (NIHR). Also backing the trial are NIHR Oxford Biomedical Research Centre, the Wellcome Trust, the Bill and Melinda Gates Foundation, Health Data Research UK, the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding.
The DHSC said RECOVERY is the largest of three national studies to treat COVID-19. The others are PRINCIPLE, which includes older, higher-risk patients in primary care; and REMAP-CAP, in critically ill patients with community-acquired pneumonia.
Further analysis of the coronavirus crisis can be found at https://www.biocentury.com/coronavirus.

4. Ⅰ型干扰素 对 SARS-CoV-2 的体外抗病毒活性研究
Potent Antiviral Activities of Type I Interferons to SARS-CoV-2 Infection
来源：biorxiv
发布日期：April 05, 2020
链接：https://www.biorxiv.org/content/10.1101/2020.04.02.022764v1
作者：Emily Mantlo 等
作者单位：Department of Pathology and Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, Texas, United States of America
编译：孔娟
摘要：
干扰素作为一个传统的抗病毒药物，在对抗肝炎病毒、疱疹病毒等方面有着较好的临床效果，

而在之前的 SARS、MERS 治疗中，也有一些临床研究显示其有效。本文研究者在细胞水平评估了 INF α / β 对 SARS-CoV-2 病毒复制的抑制作用。

文中分别检测了 SARS-CoV-2 在 Vero 细胞中的生长动力学及 SARS-CoV-2 对 INF α / β 的敏感性。研究中 SARS-CoV-2 以 MOI 0.01 和 1 感染 Vero 细胞，随后用 TCID50 法进行病毒滴定的测定。结果显示在这两种情况下，病毒滴度在感染后约 24 小时（hpi）达到峰值，并保持稳定直至感染后 40 小时才下降。表明病毒复制在低 MOI（MOI = 0.01）时比高 MOI（MOI = 1）更有效，此外还发现病毒感染引起了强烈的细胞毒性作用（CPE）。SARS-CoV-2 以 MOI 0.01 感染经不同浓度 INF α / β (50-1000IU) 预处理 16h 的 Vero cells，22 小时后进行病毒滴度测定。结果表明 IFN-α 在 50 IU / ml 下，使病毒滴度降低了 4 个对数级。IFN-β 在所有测试浓度（50 -1000IU / ml）下，病毒滴度均低于检测极限。 此外在较低浓度下 1-50 IU/ml INF α / β 均具有剂量依赖性的抑制病毒增殖活性。IFN-α 和 IFN-β 处理的 EC 50 分别为 1.35IU/ml 和 0.76IU/ ml，IFN-β 比 IFN-α 具有更强的抗 SARS-CoV-2 活性。此外在显微镜检查下，所有经 IFN 处理的样品均未观察到 CPE。

Abstract:

The historical outbreak of COVID-19 disease not only constitutes a global public health crisis, but also has a devastating social and economic impact. The disease is caused by a newly identified coronavirus, Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). There is an urgent need to identify antivirals to urtail the COVID-19 pandemic. Herein, we report the remarkable sensitivity of SARS-CoV-2 to recombinant human interferons α and β (IFN α / β). Treatment with IFN-α or IFN-β at a concentration of 50 international units (IU) per milliliter drastically reduce viral titers by 3.4 log or 4.5 log, respectively in Vero cells. The EC50 of IFN-α

and IFN-β treatment is 1.35 IU/ml and 0.76 IU/ml, respectively, in Vero cells. These results suggested that SARS-CoV-2 is more sensitive to many other human pathogenic viruses, including the SARS-CoV. Overall, our results demonstrate the potent efficacy of human Type I IFN in suppressing SARS-CoV-2 replication, a finding which could inform future treatment options for COVID-19.

5. Atazanavir 抑制 SARS-CoV-2 的复制和促炎细胞因子的产生

Atazanavir inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production

来源：bioRxiv

发布时间：2020.4.4

链接：https://www.biorxiv.org/content/10.1101/2020.04.04.020925v1

通讯作者：Thiago Moreno L. Souza

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编译：张鹏伟

内容简要：

SARS-CoV-2 是 2019 年 CoV 病持续流行的病原体(covid19)。与 2002 年和 2012 年两次相关致病性冠状病毒(CoVs)引发的国际关注的突发公共卫生事件相比，该病毒导致的死亡人数要多得多。任何经临床批准的药物，只要能用于治疗 COVID-19，就能在可能挽救生命的程序中迅速应用，以补充社会隔离方案。SARS-CoV-2 的主要蛋白酶(Mpro)被认为是一个有希望的药物干预靶点。然而，其他临床批准的抗逆转录病毒蛋白酶抑制剂可能更有效地与 SARS-CoV-2 的 Mpro 结合并阻止其复制的证据有限。Atazanavir (ATV)因其在呼吸道内的生物利用度而备受关注，这激发了我们对其通过一系列体外实验减少 SARS-CoV-2 复制能

力的评估。分子动力学分析表明，ATV 能够以比 LPV 更大的强度停靠在 SARS-CoV-2 Mpro 的活性位点，并在整个分子动力学分析过程中占据蛋白酶活性侧的底物间隙。在胞外蛋白酶试验中,ATV 在 10μM 浓度可以阻止 Mpro 活性。接下来,使用三种细胞，Vero 细胞、人肺上皮细胞系和原代人单核细胞进行了一系列病毒感染/复制体外模型的分析，证实 ATV 可以抑制 SARS-CoV-2 复制,单独或结合例如(RTV)。接下来，我们使用了三种细胞类型:Vero 细胞、人肺上皮细胞系和原代人单核细胞，进行了一系列体外病毒感染/复制模型的实验，证实了 ATV 可以单独或联合 ritonavir (RTV)抑制 SARS-CoV-2 的复制。此外,该病毒在这些药物的存在下诱导的 IL - 6 水平和 TNF-α减少。总之，我们的数据强烈建议，在候选的重新使用的药物中 ATV 和 ATV/RTV 应该被考虑用于对抗 COVID-19 的临床试验。

Abstract：
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent of the ongoing pandemic of 2019 CoV disease (COVID-19), which is already responsible for far more deaths than were reported during the previous public health emergencies of international concern provoked by two related pathogenic coronaviruses(CoVs) from 2002 and 2012. The identification of any clinically approved drug that could be repurposed to combat COVID-19 would allow the rapid implementation of potentially life-saving procedures to complement social distancing and isolation protocols. The major protease (Mpro) of SARS-CoV-2 is considered a promising target for drug intervenetions. However, limited evidence exists for other clinically approved anti-retroviral protease inhibitors that may bind more efficiently to Mpro from SARS-CoV-2 and block its replication. Of bioavailability within the respiratory tract,which motivated our evaluation on its ability to impair SARS-CoV-2 replication through a series of in vitro experiments. A molecular dynamic analysis showed that ATV could dock in the active site of SARS-CoV-2 Mpro with greater strength than LPV and occupied the substrate cleft on the active side of the protease throughout the entire molecular dynamic analysis. In a cell-free protease assay, ATV was determined to block Mpro activity at a concentration of 10 μ M. Next, a series of assays with in vitro models of virus infection/replications were performed using three cell types, Vero cells, a human pulmonary epithelial cell line and primary human monocytes, which confirmed that ATV could inhibit SARS-CoV-2 replication, alone or in combination with ritonavir (RTV). In addition, the virus-induced levels of IL-6 and TNF-α were reduced in the presence of these drugs. Together, our data strongly suggest that ATV and ATV/RTV should be considered among the candidate repurposed drugs undergoing clinical trials in the fight against COVID-19.

6. 利用 FDA 批准的化合物库对抗 SARS-CoV-2 小分子抑制剂的筛选

In vitro screening of a FDA approved chemical library reveals potential inhibitors 2 of SARS-CoV-2 replication

来源：biorxiv

发布日期：April 05, 2020

链接：https://www.biorxiv.org/content/10.1101/2020.04.03.023846v1

作者：Franck Touret 等

作者单位：Unité des Virus Emergents

编译：孔娟

摘要：

在这项研究中，研究者筛选了 Prestwick Chemical Library 中的 1520 种化合物。 研究者基于细胞感染后 3 天的细胞存活率（MOI 为 0.002），开发了 HTS SARS-CoV-2 筛选方法。并用广谱的抗病毒化合物——阿比朵尔对该方法的有效性进行了评估。结果显示在此实验条件下 10μM 阿比多尔可以有效抑制 SARS-CoV-2 对 VeroE6 细胞的感染，细胞活力 70-90%，EC50 为 10.7μM。 筛选中将该化合物作为计算抑制指数（Inh Index）的参考化合物。筛选结果显示在 1520 种化合物中有 90 种化合物表现出与阿比朵尔相当或更强的抑制作用(5.85%阳性率)，随后根据其化学成分和已知的治疗效果对候选化合物进行分类，然后确定其 EC50 和 CC50。阿齐霉素、奥普拉莫、奎尼丁或奥美拉唑在细胞层面较好抑制 SARS-CoV-2（2<EC50<20μM）病毒的增殖，具有潜在临床应用价值。

Abstract

A novel coronavirus, named SARS-CoV-2, emerged in 2019 from Hubei region in China and rapidly spread worldwide. As no approved therapeutics exists to treat Covid-19, the disease associated to SARS-Cov-2, there is an urgent need to propose molecules that could quickly enter into clinics. Repurposing of approved drugs is a strategy that can bypass the time consuming stages of drug development. In this study, we screened the Prestwick Chemical Library composed of 1,520 approved drugs in an infected cell-based assay. 90 compounds were identified. The robustness of the screen was assessed by the identification of drugs, such as Chloroquine derivatives and protease inhibitors, already in clinical trials. The hits were sorted according to their chemical composition and their known therapeutic effect, then EC50 and CC50 were determined for a subset of compounds. Several drugs, such as Azithromycine, Opipramol, Quinidine or Omeprazol present antiviral potency with 2<EC50<20 micromolar. By providing new information on molecules inhibiting SARS-CoV-2 replication in vitro, this study could contribute to the short-term repurposing of drugs against Covid-19.

7. DESCOVY 和 TRUVADA 中两种成分的三磷酸酯是 SARS-CoV-2 聚合酶的抑制剂

Triphosphates of the Two Components in DESCOVY and TRUVADA are Inhibitors of the SARS-CoV-2 Polymerase

来源：Biorxiv

发布时间：2020.4.5

链接：https://www.biorxiv.org/content/10.1101/2020.04.03.022939v1

通讯作者：Robert N. Kirchdoerfer, Jingyue Ju

作者单位：哥伦比亚大学、威斯康星大学麦迪逊分校

编译：张丽双

摘要：DESCOVY 和 TRUVADA 是 FDA 批准的用于 HIV 感染前暴露预防的两种药。而替诺福韦和恩曲他滨作为其中的两个成分，可阻止 HIV 在体内复制和传播。本文报道了替诺福韦和恩曲他滨的三磷酸酯可充当 SARS-CoV-2 RNA 依赖性 RNA 聚合酶（RdRp）催化反应的终止剂。这些结果为评估 DESCOVY 和 TRUVADA 作为 COVID-19 的感染前预防提供了分子基础。

Abstract：SARS-CoV-2, a member of the coronavirus family, is responsible for the current COVID-19 pandemic. We previously demonstrated that four nucleotide analogues (specifically, the active triphosphate forms of Sofosbuvir, Alovudine, AZT and Tenofovir alafenamide) inhibit the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp). Tenofovir and emtricitabine are the two components in DESCOVY and TRUVADA, the two FDA-

approved medications for use as pre-exposure prophylaxis (PrEP) to prevent HIV infection. This is a preventative method in which individuals who are HIV negative (but at high-risk of contracting the virus) take the combination drug daily to reduce the chance of becoming infected with HIV. PrEP can stop HIV from replicating and spreading throughout the body. We report here that the triphosphates of tenofovir and emtricitabine, the two components in DESCOVY and TRUVADA, act as terminators for the SARS-CoV-2 RdRp catalyzed reaction. These results provide a molecular basis to evaluate the potential of DESCOVY and TRUVADA as PrEP for COVID-19.

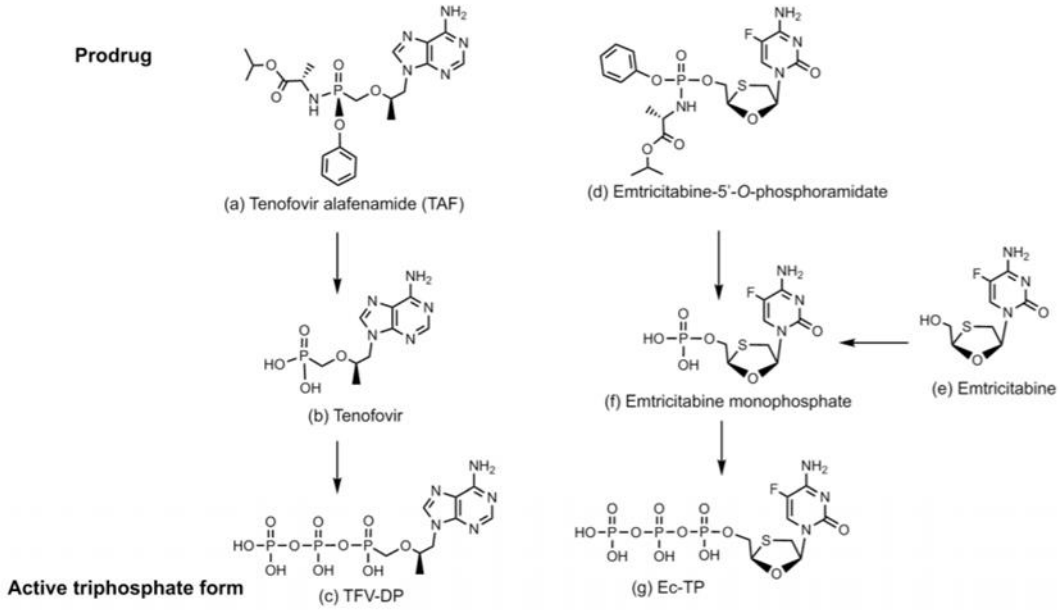

Fig. 1 Structures of prodrug viral inhibitors. Prodrugs Tenofovir alafenamide (TAF) (a), Emtricitabine-5'-O-phosphoramidate (d) and Emtricitabine (e), their monophosphate forms Tenofovir (TFV) and Emtricitabine monophosphate (b and f, respectively), and their active triphosphate forms (c and g, respectively).

8. LY6E 限制人类冠状病毒的侵入（包括目前大流行的 SARS-CoV-2）

LY6E Restricts the Entry of Human Coronaviruses, including the currently pandemic SARS-CoV-2

来源：bioRxiv

发布时间：2020-04-02

链接：https://www.biorxiv.org/content/10.1101/2020.04.02.021469v1

通讯作者：

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编译：刘焕珍

文摘：

本文的工作证明 LY6E 是一种关键的抗病毒免疫效应物，可通过独特的机制控制冠状病毒的感染和发病机理。C3A 是 HepG2 细胞系的一个亚克隆，具有很强的生长接触抑制作用。作者发现 C3A 比 HepG2 更易感染人冠状病毒 HCoV-OC43，主要是因为病毒高效率的侵入 C3A 细胞。他们发现 ADAP2，GILT 和 LY6E 这三种细胞蛋白在 HepG2 中的表达水平明显更高。功能分析表明，HEK 293 中 LY6E 的异位表达抑制了 HCoV-OC43 的侵入。LY6E 在 C3A 和 A549 中的过表达有效地抑制了 HCoV-OC43 的感染，敲除 HepG2 中的 LY6E 则增

加了 HepG2 对 HCoV-OC43 感染的敏感性。此外，LY6E 还有效地限制了由其他人类冠状病毒的包膜刺突蛋白介导的侵入，包括当前流行的 SARS-CoV-2。丝氨酸蛋白酶 TMPRSS2 的过表达或两性霉素的处理显着中和了 IFITM3 对人冠状病毒侵入细胞的限制，但并未损害 LY6E 对人冠状病毒进入的影响。

Abstract：

The work reported herein thus demonstrates that LY6E is a critical antiviral immune effector that controls CoV infection and pathogenesis via a distinct mechanism.C3A is a sub-clone of human hepatoblastoma HepG2 cell line with the strong contact inhibition of growth. We fortuitously found that C3A was more susceptible to human coronavirus HCoV-OC43 infection than HepG2, which was attributed to the increased efficiency of virus entry into C3A cells. In an effort to search for the host cellular protein(s) mediating the differential susceptibility of the two cell lines to HCoV-OC43 infection, we found that ADAP2, GILT and LY6E, three cellular proteins with known activity of interfering virus entry, expressed at significantly higher levels in HepG2 cells. Functional analyses revealed that ectopic expression of LY6E, but not GILT or ADAP2, in HEK 293 cells inhibited the entry of HCoV-OC43. While overexpression of LY6E in C3A and A549 cells efficiently inhibited the infection of HCoV-OC43, knockdown of LY6E expression in HepG2 significantly increased its susceptibility to HCoV-OC43 infection. Moreover, we found that LY6E also efficiently restricted the entry mediated by the envelope spike proteins of other human coronaviruses, including the currently pandemic SARS-CoV-2. Interestingly, overexpression of serine protease TMPRSS2 or amphotericin treatment significantly neutralized the IFITM3 restriction of human coronavirus entry, but did not compromise the effect of LY6E on the entry of human coronaviruses.

9. 藉由社区力量快速开发一个对 SARS-CoV-2 从组织水平进行模拟的系统

Rapid community-driven development of a SARS-CoV-2 tissue simulator

来源：biorxiv

发布时间：2020.4.5

通讯作者: Paul Macklin

通讯作者单位：Department of Intelligent Systems Engineering, Indiana University. Bloomington, IN USA

链接：https://www.biorxiv.org/content/10.1101/2020.04.02.019075v1

编译：蒋立春

由美国印第安纳大学智能系统工程系（Department of Intelligent Systems Engineering）以及多家北美研究机构共同报道了一个由社区驱动快速开发的 SARS-CoV-2 的组织水平的模拟

系统。

SARS-CoV-2 如何致病，有哪些因素会导致病人发生严重的症状，以及人体免疫和病毒的交互作用机制，药物如何起作用等等都涉及到复杂的非线性过程。该研究中集结了不同领域的科学家，在今年 3 月对 SARS-CoV-2 建立了一个多尺度的模拟模型的原型。这个模型涉及的数据、代码以及交互式网页版全部都第一时间向全球公开。这个模型希望借助于全球在病毒学、免疫学、数学生物学、定量系统生理学、云计算和高性能计算以及其他领域的专长来加快我们对应对这场全球健康威胁。

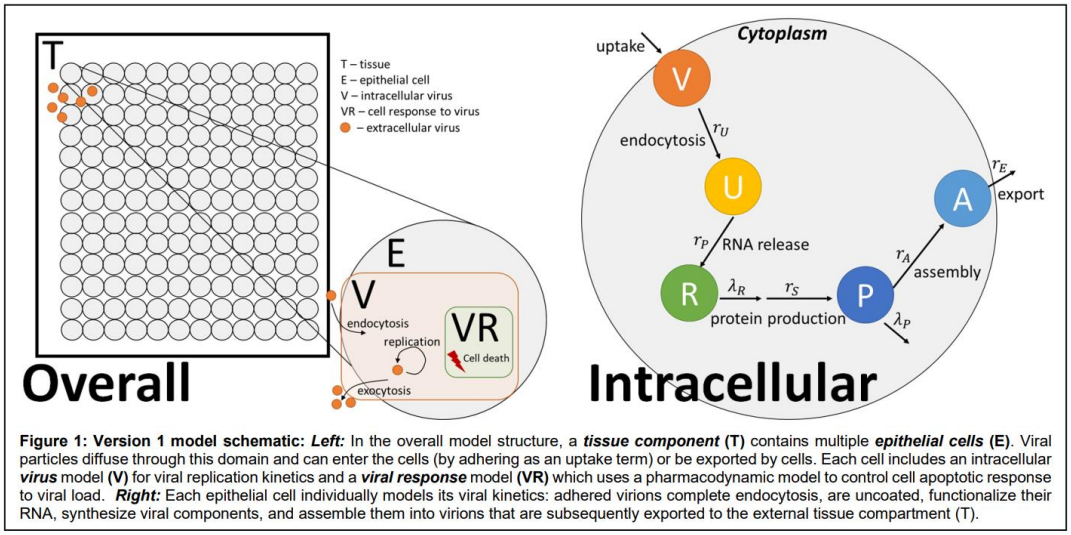

Figure 1: Version 1 model schematic: ***Left:*** In the overall model structure, a ***tissue component*** **(T)** contains multiple ***epithelial cells*** **(E)**. Viral particles diffuse through this domain and can enter the cells (by adhering as an uptake term) or be exported by cells. Each cell includes an intracellular ***virus*** model **(V)** for viral replication kinetics and a ***viral response*** model **(VR)** which uses a pharmacodynamic model to control cell apoptotic response to viral load. ***Right:*** Each epithelial cell individually models its viral kinetics: adhered virions complete endocytosis, are uncoated, functionalize their RNA, synthesize viral components, and assemble them into virions that are subsequently exported to the external tissue compartment (T).

The 2019 novel coronavirus, SARS-CoV-2, is an emerging pathogen of critical significance to international public health. Knowledge of the interplay between molecular-scale virus-receptor interactions, single-cell viral replication, intracellular-scale viral transport, and emergent tissue-scale viral propagation is limited. Moreover, little is known about immune system-virus-tissue interactions and how these can result in low-level (asymptomatic) infections in some cases and acute respiratory distress syndrome (ARDS) in others, particularly with respect to presentation in different age groups or pre-existing inflammatory risk factors like diabetes. A critical question for treatment and protection is why it appears that the severity of infection may correlate with the initial level of virus exposure. Given the nonlinear interactions within and among each of these processes, multiscale simulation models can shed light on the emergent dynamics that lead to divergent outcomes, identify actionable “choke points” for pharmacologic interactions, screen potential therapies, and identify potential biomarkers that differentiate response dynamics. Given the complexity of the problem and the acute need for an actionable model to guide therapy discovery and optimization, we introduce a prototype of a multiscale model of SARS-CoV-2 dynamics in lung and intestinal tissue that will be iteratively refined. The first prototype model was built and shared internationally as open source code and interactive, cloud-hosted executables in under 12 hours. In a sustained community effort, this model will integrate data and expertise across virology, immunology, mathematical biology, quantitative systems physiology, cloud and high performance computing, and other domains to accelerate our response to this critical threat to international health.

由于网站 http://physicell.org/covid19/提供了更简洁的信息，我编译如下
Introduction

在 2020 年 3 月，我们集结了一个国际联盟开发一个全面的对 SARS-CoV-2 进行多尺度模拟的工作框架。我们的目标是理解以及测试不同干预情况下 COVID-19 的动力学。包括：

- 病毒在组织里的扩散
- 病毒颗粒怎么和细胞上的 ACE2 受体结合

- 病毒怎么内吞进细胞
- 病毒怎么去包裹、复制、组装成新的病毒
- 病毒怎么分泌到细胞之外
- 单个细胞对感染的反应、包括代谢怎么受到扰动、干扰素的分泌以及细胞死亡

免疫反应

- 免疫激活以及淋巴结的扩增
- 免疫细胞怎么浸润进被感染组织以及怎么对抗病毒
- 组织损坏，包括引起急性呼吸窘迫综合症的肺水肿

生成了一个多尺度的模拟工作框架后，我们就可以通过问如果怎样就会发生什么来鉴定病毒复制、感染过程中对什么因素敏感，以及找到控制免疫反应从而避免副作用发生的办法。
为了做成这件事情，我们形成了一个多学科的、包括病毒学家、数学生物学家、计算科学家、以及来自工业界的药理学家。这个团队都承诺分享数据以及各自专长，这样我们可以推进得比单个团队行动快得多。
我们将分享整个模拟模型、科学资料以及开源我们的代码。这样整个研究社区都会得益于这个多学科领域的专家的合作，集中精力校准和验证这个模型，而不是去构建和加速模型。我们将以开放科学的原则分享我们的进展，包括通过交互式网站的模型来频繁地进行科学推广，公开征求社区的反馈，以及不断发布以及跟新预印本科学研究结果。
我们正在使用快速构建原型的办法：我们会以 7-10 天为周期更新模型。每一次更新都会发布包括充分测试过注释好的开源代码，以及对应的交互式网站版。
目前的原型：
请尝试 https://nanohub.org/tools/pc4covid19.
您可以怎么帮忙：
尝试这个模型 https://nanohub.org/tools/pc4covid19
给我们反馈
如果您可以提供数据或者专长请联系我们
读对应的预印本文章
帮我们宣传，让大家知道我们的工作
关注我们的更新

In March 2020, we assembled an international coalition to develop a comprehensive multiscale simulation framework for SARS-CoV-2 (coronavirus) infections in lung and gut tissues. We aim to understand and test interventions in the coupled dynamics of COVID-19, including:
Virus spread in tissue
Virion adhesion to ACE2 receptors on cells
Endocytosis (active transport into the cell)
Viral uncoating, replication, and assembly into new virions
Viral exocytosis (release of completed virions)
Single-cell responses to infection, including disrupted metabolism, secretion of interferons, and cell death
Inflammatory responses
Immune activation and expansion in lymph nodes
Immune cell infiltration and predation in infected tissue
Tissue damage, including edema that can lead to acute respiratory distress syndrome

(ARDS)

By rapidly creating a multiscale framework, we can ask what if questions that identify vulnerabilities in viral replication and the spread of the infection, and seek approaches to control the immune response to avoid adverse reactions.

To drive this, we have assembled a multidisciplinary team of virologists, mathematical biologists, computer scientists, and industrial pharmacologists, who have all pledged to share data and expertise to proceed much faster as a group than we could alone.
We will share the entire model, scientific documentation, and code as open source, so that the entire community can benefit from this diverse domain expertise and focus on calibrating and validating the model, rather than building and accelerating it. We are sharing our progress with open science principles, including frequent scientific dissemination through interactive web models, open calls for community feedback, and frequent release and update of scientific preprints.

And we are using rapid prototyping: we aim for a 7-10 day release cycle, where each release improved upon the last. Each release includes a well-tested and documented open source code release, an interactive web-hosted version for accelerated scientific communication, public feedback, and an updated preprint.
Current interactive prototype
Try the model at https://nanohub.org/tools/pc4covid19.
How can you help?
Try the model: https://nanohub.org/tools/pc4covid19
Give feedback:
Google Form: https://forms.gle/SVUMYWhipSHfX8nS8
pc4covid19 slack workspace: [invite link]
Let us know if you can offer data or expertise.
Read the preprint: [link]
Spread the word: share this page on twitter
Keep an eye on this page for improvements!

4 月 2 日 science 杂志发表了我们之前 3 月 19 日编译过的一个预印本文章。

10. 一个在 SARS-COV-2 和 SARS-COV 受体结合域（RBD）中高度保守的隐性抗原表位

A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV
Meng Yuan, Nicholas C. Wu, Xueyong Zhu, Chang-Chun D. Lee, Ray T. Y. So, Huibin Lv, Chris K. P. Mok, Ian A. Wilson
来源：science
发布时间：2020.4.3
链接:https://science.sciencemag.org/content/early/2020/04/02/science.abb7269.full
原编译：宋珂
由 SARS-CoV-2 病毒引起的 COVID-19 肺炎爆发后，在全球范围内持续传播。但是至今对病毒的表位仍知之甚少。在本文中，作者解析了 SARS-CoV-2 spike(S) 蛋白的受体结合区

域(RDB)和 CR3022 抗体的复合物结构。作为一种从康复的 SARS 病人体内分离出来的中和抗体，CR3022 的靶点位置具有高度的保守性，能够在 SARS-CoV 和 SARS-CoV-2 间发生结合交叉反应。 复合物的结构模型进一步展示出，在 S 蛋白的三聚体中，当至少有 2 个 RDB 处于“up”构象时，才能暴露出结合位点。简言之，本研究从结构和分子视角揭示了 SARS-CoV-2 的免疫原性。

复合物晶体结构已上传至 RCSB PDB， PDB ID：6W41 (Unreleased)

Table 1. Binding affinity of CR3022 to recombinant RBD and S protein

Affinity (Kd in nM)	CR3022 IgG	CR3022 Fab
SARS-CoV-2 RBD	< 0.1	115±3
SARS-CoV RBD	< 0.1	1.0±0.1

Abstract of the final science paper:

The outbreak of COVID-19 caused by SARS-CoV-2 virus has now become a pandemic, but there is currently very little understanding of the antigenicity of the virus. We therefore determined the crystal structure of CR3022, a neutralizing antibody previously isolated from a convalescent SARS patient, in complex with the receptor-binding domain (RBD) of the SARS-CoV-2 spike (S) protein to 3.1 Å. CR3022 targets a highly conserved epitope, distal from the receptor-binding site, that enables cross-reactive binding between SARS-CoV-2 and SARS-CoV. Structural modeling further demonstrates that the binding epitope can only be accessed by CR3022 when at least two RBD on the trimeric S protein are in the “up” conformation and slightly rotated. Overall, this study provides molecular insights into antibody recognition of SARS-CoV-2.

11. SARS-CoV-2 的核衣壳蛋白识别 RNA 的结构基础

Structural basis of RNA recognition by the SARS-CoV-2 nucleocapsid phosphoprotein

来源：bioRxiv

发布时间：2020.4.5

通讯作者：Vaclav Veverka，Evzen Boura

通讯作者单位：Charles University, Vinicna 7, 128 10 Prague 2, Czech Republic

链接：https://www.biorxiv.org/content/10.1101/2020.04.02.022194v1

编译：宋珂

由 SARS-CoV-2 病毒引起的 COVID-19 已经对世界人口的健康造成了严重影响，扰乱了全球的经济。SARS-CoV-2 属于+RNA 病毒家族，以单链正向 RNA 分子为遗传基因。与其他冠状病毒类似，SARS-CoV-2 拥有相较于+RNA 病毒来说异常大的基因组，负责编码结构蛋白，如：matrix（M），small envelope（E），spike（S）和 nucleocapsid phosphoprotein（N），以及其他 16 个非结构蛋白（nsp1-16），这些蛋白一起协同工作，确保病毒在宿主细胞中的复制。Nucleocapsid phosphoprotein N 蛋白是病毒基因与病毒膜连接的重要结构。其 N 端 RNA 结合结构域（N-NTD）捕获 RNA 基因，同时 C 端结构域通过与 M 蛋白相互作用，将核糖核蛋白复合物锚定在病毒膜上。本文中，作者使用 NMR 技术，测定了 N-NTD 的结构，以及其与 RNA 的相互作用。作者发现，在 N-NTD 表面存在一个由精氨酸（Arg）组成的带正电荷的凹面，推测此为 N-NTD 与 RNA 的结合位点。作者进一步使用 RNA 双链进行了 NMR 滴定实验。通过观察 N-NTD 的 NMR 谱上信号位置的变化，作者进一步构建了 N-NTD 和 RNA 的复合物结构。

注：

1，N-NTD 结构已上传至 PBD (PDB ID: 6YI3，unreleased)和 BMRB(code:34511)

2，N-NTD 与 RNA 的复合物结构是通过 Docking 建模得到的。其中 RNA 分子以 PDB:4U37 为模板，同源建模构建。

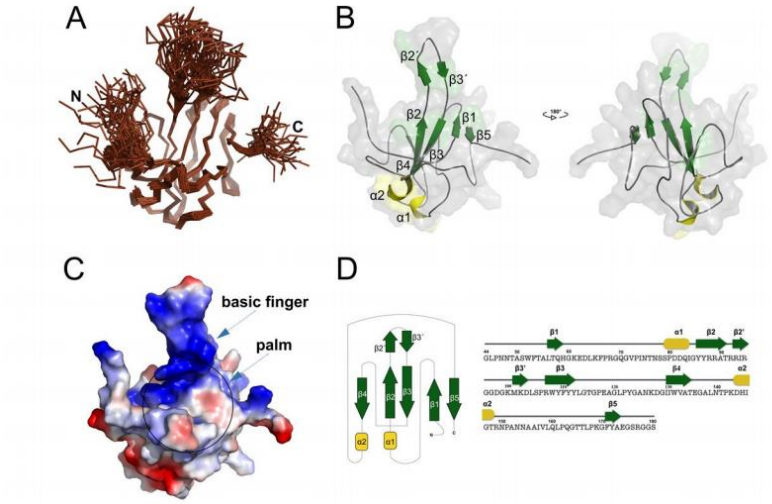

Figure 2 – Solution structure of the SARS-CoV-2 N-NTD RNA binding domain (A) Backbone representation of the 40 converged structures of N-NTD obtained by NMR spectroscopy. (B) Cartoon representation of the lowest energy structure (structural elements are highlighted in color: α1-α2 helices (yellow), β1-(β2'-β3')-β5 (green), and loops (gray))show the overall U-shaped antiparallel β-sheet platform (the palm) and a protruding β-hairpin (the basic finger). (C) The N-NTD molecular surface electrostatic potentials revealed a basic patch extended between the finger and the palm, with positively charged surface shown in blue and negatively charged surface in red. (D) Topology diagram of the N-NTD.

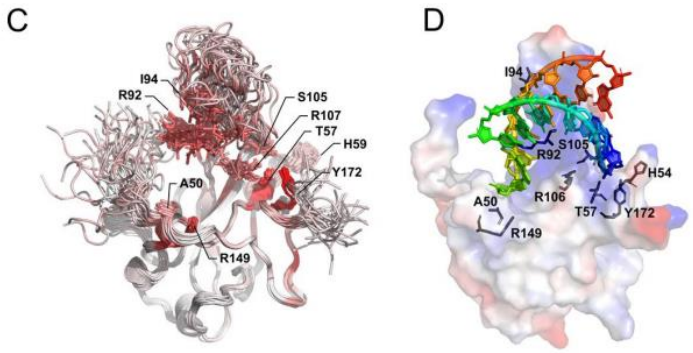

Figure 3 – NMR-based mapping and a model of the N-NTD:RNA complex. (C) The CSPs highlighted on as a red-color gradient on the ribbon representation of 40 converged structures of N-NTD. The majority of the perturbed residues form a large continuous patch from R92 to Y172 on one side of the positively charged cleft and a smaller patch formed by A50 and R149 on the opposite side of the cleft. The solvent exposed sidechains of the most perturbed residues are shown as sticks. (D) N-NTD:RNA complex. The RNA duplex

is shown as a cartoon structure over the electrostatic surface of SARS-CoV-2 N-NTD and the interacting residues are highlighted as sticks.

Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the Coronavirus disease 2019 (COVID-19) which is currently negatively affecting the population and disrupting the global economy. SARS-CoV-2 belongs to the +RNA virus family that utilize single-stranded positive-sense RNA molecules as genomes. SARS-CoV-2, like other coronaviruses, has an unusually large genome for a +RNA virus that encodes four structural proteins - the matrix (M), small envelope (E), spike (S) and nucleocapsid phosphoprotein (N) - and sixteen nonstructural proteins (nsp1-16) that together ensure replication of the virus in the host cell. The nucleocapsid phosphoprotein N is essential for linking the viral genome to the viral membrane. Its N-terminal RNA binding domain (N-NTD) captures the RNA genome while the C-terminal domain anchors the ribonucleoprotein complex to the viral membrane via its interaction with the M protein. Here, we characterized the structure of the N-NTD and its interaction with RNA using NMR spectroscopy. We observed a positively charged canyon on the surface of the N-NTD lined with arginine residues suggesting a putative RNA binding site. Next, we performed an NMR titration experiment using an RNA duplex. The observed changes in positions of signals in the N-NTD NMR spectra allowed us to construct a model of the N-NTD in complex with RNA.

12. 新型冠状病毒肺炎防治专家意见

来源：中华结核和呼吸杂志

发布时间：2020.4.5 网络预发表

作者：中华医学会呼吸病学分会，中国医师协会呼吸医师分会

链接：http://rs.yiigle.com/yufabiao/1187175.htm

摘要重点内容摘抄：

随着对疾病防控及诊疗经验的不断积累和全面认识，有必要汇总这些研究的成果和经验，指导防控和临床诊治工作。本文总结了目前 COVID-19 病原学、发病机制、流行病学、临床特点、治疗原则、康复与预防以及防控措施等方面的进展和专家意见。

仅摘出文章最后一部分“未来研究重点”以飨读者

1．进一步开展病毒的追踪溯源、变异演化、生物学特性、感染途径等研究，为传染病防控、疫苗及药物研发提供理论依据。

2．SARS-CoV-2 损害靶器官的机制：包括对免疫细胞的攻击、淋巴细胞降低的机制。肺脏作为新冠病毒首先和主要的靶器官，病理及病理生理发生了哪些变化。除了肺脏，对其他重要脏器包括心肌损害、肝肾损害、凝血细胞、病毒性脑炎等的发生机制研究。

3．疾病演化的规律：包括患者从轻症到重症、危重症的危险因素，患者死亡的危险因素及相关预警模型的研究。

4．干预措施和实施的时机：包括抗病毒药物的疗效、不良反应、疗程及适用人群，糖皮质激素的使用时机、剂量疗程及不良反应，有创机械通气及 ECMO 的给予时机和指征及其获益等。

5．抗病毒药物的研发及如何在紧急状况下开展规范有序的临床试验：在了解病毒生物特性的基础上开发新型抗冠状病毒的药物，现有药物包括洛匹那韦/利托那韦、瑞德西韦、阿比多尔、氯喹和羟氯喹以及中药药物的疗效和机制。制定合理的规则指导临床规范有序，层次分明，步调一致的开展各项临床药物试验。

6．梳理现有制度短板和风险点：包括如何改进现有传染病报告制度，使之更加灵敏高效；如何提高应对重大紧急突发公共事件的能力，疫情防控不只是医药卫生问题，而是全方位的工作。方舱医院在本次抗疫中发挥了重要的作用，我们需要未雨绸缪，在城市设计和建设中就应该融入灾难意识，大型场馆建造时考虑到改造为临时医院的需求