新型冠状病毒信息简报

第 65 期（2020 年 7 月 25-7 月 31 日周报）

上海科技大学免疫化学研究所

生物医学大数据平台和高通量筛选平台领衔编译制作

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1. 2020 年 7 月 30 日疫情

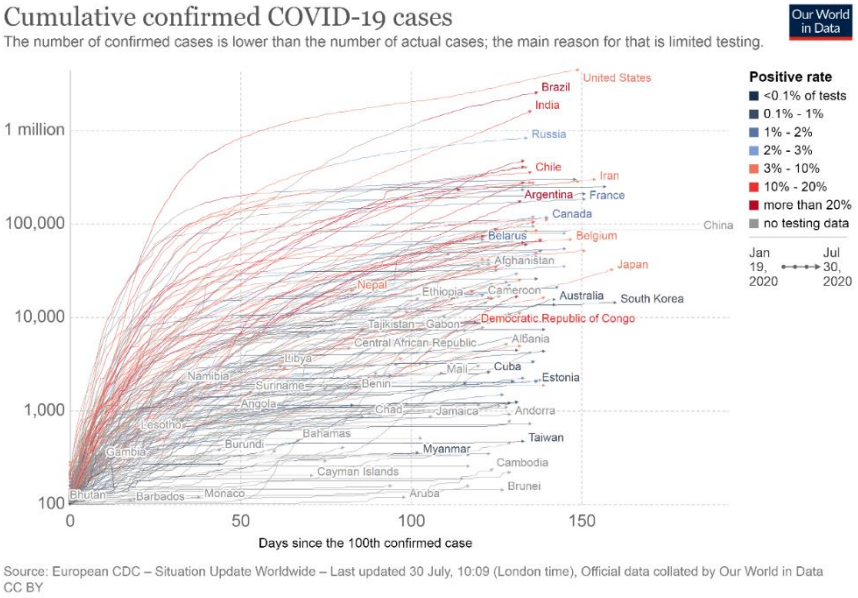
数据来源：WHO

发布时间：2020 年 7 月 30 日北京时间下午 4 点

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

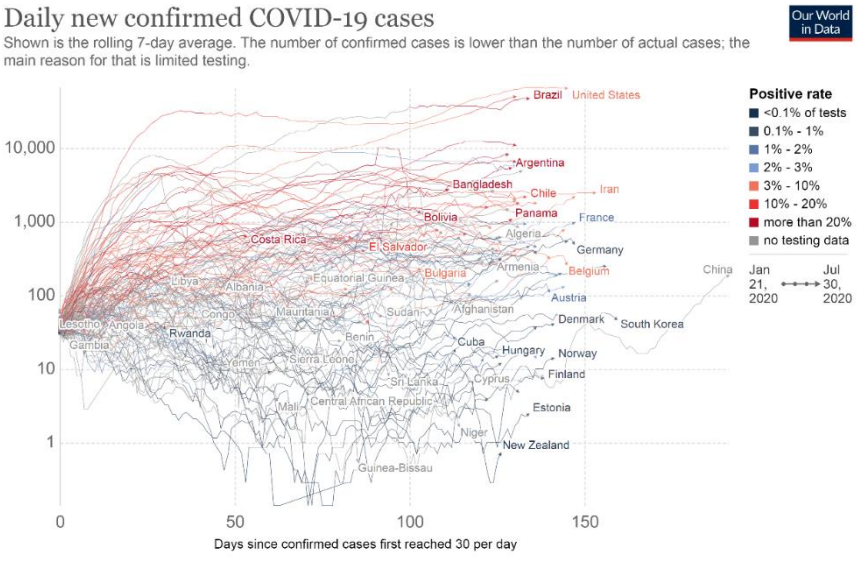
根据 WHO 提供的数据，2020 年 7 月 30 日全球累计确诊新型冠状病毒病人 **16812755** 例，当日新增确诊 **253793** 例，累计死亡 **662095** 例，当日新增死亡 **5999**。

中国累计确诊 87680 例，累计死亡 4665 例，当日新增确诊 **223** 例，新增死亡 1 例。



Source: European CDC – Situation Update Worldwide – Last updated 30 July, 10:09 (London time), Official data collated by Our World in Data
CC BY

重点国家确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）



Source: European CDC – Situation Update Worldwide – Last updated 30 July, 10:09 (London time), Official data collated by Our World in Data
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重点国家每日新增确诊数量曲线（https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases）

全国新型冠状病毒肺炎新增确诊病例分布图（7 月 30 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. 转载：五省九市出现新冠病例，新疆、大连本轮疫情扩散风险有多大

来源：知识分子 微信公众号

发布时间：2020-08-01

作者：汤佩兰

链接：https://mp.weixin.qq.com/s/I-j5HAPVTOC5sI8oy_KvHQ

3. 意大利家庭中猫和狗接触 SARS-CoV-2 的证据

Evidence of exposure to SARS-CoV-2 in cats and dogs from households in Italy

链接：https://www.biorxiv.org/content/10.1101/2020.07.21.214346v2

编译者：王玮

英国和意大利的研究者报告了一项大规模的研究，评估了 817 只生活在意大利北部的宠物的 SARS-CoV-2 感染情况，这些动物是在人类频繁感染的时候取样的。没有动物检测到 PCR 阳性。然而，3.4%的狗和 3.9%的猫具有可测量的 SARS-CoV-2 中和抗体滴度，其中来自 COVID-19 阳性家庭的狗比来自 COVID-19 阴性家庭的狗更容易检测出阳性。

4. FDA 发布关于在家里以及在其他非实验室环境比如办公室、学校等等场所进行非处方检测的指导意见

FDA Posts New Template for At-Home and Over-the-Counter Diagnostic Tests for Use in Non-Lab Settings, Such as Homes, Offices or Schools

链接：https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-posts-new-template-home-and-over-counter-diagnostic-tests-use-non

5. LabCorp 的样本池检测 COVID-19 方法获得授权

LabCorp Receives Authorization for COVID-19 Sample Pooling

来源：BioSpace
发布时间：2020-07-25
链接：https://www.biospace.com/article/releases/labcorp-receives-authorization-for-covid-19-sample-pooling/
编译者：宋张悦
中文摘要：

新方法旨在提高 COVID-19 检测效率，优化检测供应，提高整体能力。LabCorp 于 7 月 24 日收到 FDA 的紧急使用授权（EUA），用于对疑似感染 COVID-19 的患者的上呼吸道和下呼吸道样本中 SARS-CoV-2 的核酸进行定性检测。每个样本池包含 5 个独立的样本，每个矩阵包含 25 个样本。

Abstract：

New Method Aims to Improve Efficiency of COVID-19 Testing, Optimize Testing Supplies and Increase Overall Capacity.

6. 血液中的细胞游离 DNA 显示了显著的细胞、组织和器官特异性损伤，并预测了 COVID-19 的严重程度

Cell-Free DNA in Blood Reveals Significant Cell, Tissue and Organ Specific injury and Predicts COVID-19 Severity
来源：medRxiv
发布时间：2020-07-29
链接：https://www.medrxiv.org/content/10.1101/2020.07.27.20163188v1
编译者：宋张悦
中文摘要：

本文开发了一种血液测试，利用血浆中游离 DNA 的全基因组甲基化谱，来广泛量化 COVID-19 导致的细胞、组织和器官特异性损伤。对 33 名 COVID-19 患者的 104 份血浆样本进行了游离 DNA 分析，并与其他病毒感染患者和健康对照者的样本进行了比较。发现重症 COVID-19 导致肺、肝损伤和红细胞祖细胞参与的证据。这项研究指出了游离 DNA 作为监测和研究 COVID-19 的分析物的效用。

7. SARS-CoV-2 感染人淋巴细胞

Infection of human lymphomononuclear cells by SARS-CoV-2
来源：biorxiv
发布时间：2020-07-29
链接：https://www.biorxiv.org/content/10.1101/2020.07.28.225912v1
第一作者：Marjorie C Pontelli, Italo A Castro
通讯作者：Eurico Arruda
通讯作者单位：Virology Research Center, Ribeirao Preto Medical School
DOI 或 PUBMED ID：
编译者：王玮
中文摘要：

SARS-CoV-2 重症与炎症过度有关，淋巴细胞减少是一种免疫标志，与 COVID-19 预后不良有关。然而，目前尚不清楚人类循环淋巴细胞和单核细胞是否易受 SARS-CoV-2 感染。该文章对 SARS-CoV-2 感染人外周血单个核细胞(PBMCs)进行了体外和体内的实验研究。发现，健康献血者的外周血单个核细胞体外感染可产生病毒后代。结果表明，单核细胞和 B、T 淋

巴细胞对 SARS-CoV-2 的主动感染敏感，双链 RNA 检测表明病毒复制。此外，流式细胞术和免疫荧光分析显示，SARS-CoV-2 在 COVID-19 患者的单核细胞和 B 淋巴细胞中检出率较高，而在 CD4+T 淋巴细胞中检出率较低。COVID-19 患者外周血单个核细胞中 SARS-CoV-2 感染率自症状出现起随时间增加而增加。另外，用免疫组织化学方法检测到了死后肺组织中的 SARS-CoV-2 阳性单核细胞和 B、CD4+T 淋巴细胞。SARS-CoV-2 感染 COVID-19 患者的血液循环白细胞可能对疾病的发病机制、免疫功能紊乱和病毒在宿主内的传播具有重要意义。

Abstract:

Although SARS-CoV-2 severe infection is associated with a hyperinflammatory state, lymphopenia is an immunological hallmark, and correlates with poor prognosis in COVID-19. However, it remains unknown if circulating human lymphocytes and monocytes are susceptible to SARS-CoV-2 infection. In this study, SARS-CoV-2 infection of human peripheral blood mononuclear cells (PBMCs) was investigated both in vitro and in vivo. We found that in vitro infection of whole PBMCs from healthy donors was productive of virus progeny. Results revealed that monocytes, as well as B and T lymphocytes, are susceptible to SARS-CoV-2 active infection and viral replication was indicated by detection of double-stranded RNA. Moreover, flow cytometry and immunofluorescence analysis revealed that SARS-CoV-2 was frequently detected in monocytes and B lymphocytes from COVID-19 patients, and less frequently in CD4+T lymphocytes. The rates of SARS-CoV-2-infected monocytes in PBMCs from COVID-19 patients increased over time from symptom onset. Additionally, SARS-CoV-2-positive monocytes and B and CD4+T lymphocytes were detected by immunohistochemistry in post mortem lung tissue. SARS-CoV-2 infection of blood circulating leukocytes in COVID-19 patients may have important implications for disease pathogenesis, immune dysfunction, and virus spread within the host.

8. COVID-19 的最佳预测因子是最近的嗅觉丧失：一项横断面研究

The best COVID-19 predictor is recent smell loss: a cross-sectional study

来源：medRxiv

发布时间：2020-07-28

链接：https://www.medrxiv.org/content/10.1101/2020.07.22.20157263v2

第一作者：Richard C. Gerkin, Kathrin Ohla

通讯作者：Valentina Parma

通讯作者单位：Department of Psychology, Temple University

DOI 或 PUBMED ID：

编译者：宋张悦

中文摘要：

背景：COVID-19 有异质表现，尽管最常见的症状之一是突然失去嗅觉（嗅觉丧失或减退）。我们研究了嗅觉丧失是否是 COVID-19 的可靠预测因子。

方法：这项预先注册的横断面研究使用了一份有 23 种语言的调查问卷来评估自述最近呼吸系统疾病的个体的症状。对 COVID-19 实验室检测结果报告为阳性(C19+;n=4148)或阴性(C19-;546)的参与者，使用 0-100 视觉模拟量表(VAS)量化呼吸疾病过程中化学感觉能力的变化。Logistic 回归模型确定了 COVID-19 状态和 COVID-19 后嗅觉恢复的单一和累积预测因子。

结果：C19+组和 C19-组均表现出嗅觉丧失，但 C19+组嗅觉丧失更明显(均数±SD, C19+: -82.5±27.2；C19-: -59.8±37.7)。在单一特征模型和累积特征模型(ROC AUC=0.72)中，疾病期间嗅觉丧失是 COVID-19 的最佳预测因子，其他特征对模型没有显著改善。**VAS 对嗅觉丧失的评分比二元化学感应的是/非问题或其他主要症状（如发烧或咳嗽）更具有预测性。50%的参与者在 40 天内嗅觉恢复，最好的预测是自发病以来的时间**。

结论：由于嗅觉丧失是 COVID-19 的最佳预测因子，研究人员开发了 ODoR-19 工具，用 0-10 的量表来筛查最近的嗅觉丧失。数值评分≤2 表示出现有症状的 COVID-19 的几率很高（10<OR<4），特别是当病毒实验室检测不切实际或不可用时。

Abstract：

Background: COVID-19 has heterogeneous manifestations, though one of the most common symptoms is a sudden loss of smell (anosmia or hyposmia). We investigated whether olfactory loss is a reliable predictor of COVID-19.

Methods: This preregistered, cross-sectional study used a crowdsourced questionnaire in 23 languages to assess symptoms in individuals self-reporting recent respiratory illness. We quantified changes in chemosensory abilities during the course of the respiratory illness using 0-100 visual analog scales (VAS) for participants reporting a positive (C19+; n=4148) or negative (C19-; n=546) COVID-19 laboratory test outcome. Logistic regression models identified singular and cumulative predictors of COVID-19 status and post-COVID-19 olfactory recovery.

Results: Both C19+ and C19- groups exhibited smell loss, but it was significantly larger in C19+ participants (mean±SD, C19+: -82.5±27.2 points; C19-: -59.8±37.7). Smell loss during illness was the best predictor of COVID-19 in both single and cumulative feature models (ROC AUC=0.72), with additional features providing no significant model improvement. VAS ratings of smell loss were more predictive than binary chemosensory yes/no-questions or other cardinal symptoms, such as fever or cough. Olfactory recovery within 40 days was reported for ~50% of participants and was best predicted by time since illness onset.

Conclusions: As smell loss is the best predictor of COVID-19, we developed the ODoR-19 tool, a 0-10 scale to screen for recent olfactory loss. Numeric ratings ≤2 indicate high odds of symptomatic COVID-19 (10<OR<4), especially when viral lab tests are impractical or unavailable.

9. 鼻咽部和肺部深处成对取样进行 SARS-CoV2 提示在危重病人体内存在病毒滴度梯度

Paired nasopharyngeal and deep lung testing for SARS-CoV2 reveals a viral gradient in critically ill patients: a multi-centre study

链接：https://www.medrxiv.org/content/10.1101/2020.07.19.20156869v1

中文摘要：

以往大家认为 SARS-CoV1 趋向于在下呼吸道复制，而 SARS-CoV-2 在上呼吸道复制更活跃。剑桥大学对 5 个不同的中心的 51 个危重病人的鼻咽部和肺部深处进行了成对取样，发现在鼻咽部和肺部深处存在病毒滴度梯度。这挑战了以往认识。作者们建议研究病毒怎么转移到下呼吸道以及怎样在下呼吸道复制可能是研究病人往危重发展以及发展出严重的急性呼吸窘迫的一个关键因素。

10. COVID-19 病人的多组学免疫表型分析揭示了早期的感染路径

Multiomic Immunophenotyping of COVID-19 Patients Reveals Early Infection Trajectories

来源：biorxiv

发布时间：2020-07-28

第一作者：Yapeng Yu

通讯作者： James R. Heath, the ISB-Swedish COVID19 Biobanking Unit

通讯作者单位：美国西雅图系统生物学研究所

链接：https://www.biorxiv.org/content/10.1101/2020.07.27.224063v1.full.pdf

编译：蒋立春

中文摘要:

研究者们对 50 个 COVID-19 病人的免疫表型进行了综合分析。作者们测量了血浆中 454 种蛋白以及 847 种代谢物。也对外周血单个核细胞进行了多组学分析，包括全转录组、192 个细胞表面蛋白、TCR 和 BCR 测序。最后将这些数据和临床检测数据进行了整合。该研究揭示了一些新的细胞亚群，比如增殖耗竭的 CD8+和 CD4+的 T 细胞以及细胞毒性的 CD+T 细胞可能是重症 COVID-19 的特征。将 100 万个免疫特征压缩到和很多临床数据一致的单一的免疫反应特征值，这个免疫反应特征和重症发生有关。

Abstract:

Host immune responses play central roles in controlling SARS-CoV2 infection, yet remain incompletely characterized and understood. Here, we present a comprehensive immune response map spanning 454 proteins and 847 metabolites in plasma integrated with single-cell multi-omic assays of PBMCs in which whole transcriptome, 192 surface proteins, and T and B cell receptor sequence were co-analyzed within the context of clinical measures from 50 COVID19 patient samples. Our study reveals novel cellular subpopulations, such as proliferative exhausted CD8+ and CD4+ T cells, and cytotoxic CD4+ T cells, that may be features of severe COVID-19 infection. We condensed over 1 million immune features into a single immune response axis that independently aligns with many clinical features and is also strongly associated with disease severity. Our study represents an important resource towards understanding the heterogeneous immune responses of COVID-19 patients and may provide key information for informing therapeutic development.

11. ChAdOx1 nCoV-19 疫苗可预防恒河猴的 SARS-CoV-2 肺炎

ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques

来源：Nature

发布时间：2020-07-30

链接：https://www.nature.com/articles/s41586-020-2608-y

第一作者：Neeltje van Doremalen

通讯作者：Sarah C. Gilbert & Vincent J. Munster

通讯作者单位：NIH

DOI 或 PUBMED ID：https://doi.org/10.1038/s41586-020-2608-y

编译者：张丽双

中文摘要：

研究人员发现腺病毒载体疫苗 ChAdOx1 nCoV-19，编码 SARS-CoV-2 的刺突蛋白，在小鼠中具有免疫原性，诱导产生强烈的体液和细胞介导的应答。该应答以 Th1 为主，通过 IgG 亚类和细胞因子表达谱证实。用 ChAdOx1 nCoV-19（仅限初免和初免-加强疗法）免疫可在恒河猴中诱导平衡的 Th1 / Th2 体液和细胞免疫反应。发现与对照组相比，接种 SARS-CoV-2 疫苗的恒河猴的支气管肺泡灌洗液和下呼吸道组织中的病毒载量显著降低，且未发现肺炎。但是，在疫苗组和对照组动物之间没有鼻腔病毒脱落上的差异。重要的是，未观察到在疫苗接种的动物中攻毒后有免疫增强疾病的证据。现在，将在随机对照人类临床试验中评估 ChAdOx1 nCoV-19 对有症状的 PCR 阳性 COVID-19 疾病的安全性，免疫原性和功效。

Abstract:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 and is responsible for the COVID-19 pandemic. Vaccines are an essential countermeasure urgently needed to control the pandemic. Here, we show that the adenovirus-vectored vaccine ChAdOx1 nCoV-19, encoding the spike protein of SARS-CoV-2, is immunogenic in mice, eliciting a robust humoral and cell-mediated response. This response was predominantly Th1, as demonstrated by IgG subclass and cytokine expression profling. Vaccination with ChAdOx1 nCoV-19 (prime-only and prime-boost regimen) induced a balanced Th1/Th2 humoral and cellular immune response in rhesus macaques. We observed a signifcantly reduced viral load in bronchoalveolar lavage fuid and lower respiratory tract tissue of vaccinated rhesus macaques challenged with SARS-CoV-2 compared with control animals, and no pneumonia was observed in vaccinated animals. However, there was no diference in nasal shedding between vaccinated and control animals. Importantly, no evidence of immune-enhanced disease following viral challenge in vaccinated animals was observed. Safety, immunogenicity and efcacy of ChAdOx1 nCoV-19 against symptomatic PCR-positive COVID-19 disease will now be assessed in randomized controlled human clinical trials.

编者：这个疫苗是牛津大学发明的。

12. 单剂 Ad26.COV2.S 疫苗让恒河猴抵抗新冠病毒

Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques

来源：nature
发布时间：2020-07-30
链接：https://www.nature.com/articles/s41586-020-2607-z_reference.pdf

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DOI 或 PUBMED ID：https://doi.org/10.1038/s41586-020-2607-z

编译者：刘焕珍

中文摘要：

作者展示了在非人灵长类动物中表达 SARS-CoV-2 刺突蛋白（S）的单剂量腺病毒血清型 26（Ad26）载体疫苗的免疫原性和保护功效。用编码 S 变异的 Ad26 载体或假对照对 52 只恒河猴进行免疫，并通过鼻内和气管内途径用 SARS-CoV-2 攻击。最佳的 Ad26 疫苗可诱导强烈的中和抗体反应，并在 SARS-CoV-2 攻击后的支气管肺泡灌洗液和鼻拭子提供完全或接近完全的保护。疫苗引起的中和抗体滴度与保护功效相关，表明保护与免疫相关。这些数据证明了

非人类灵长类动物对 SARS-CoV-2 具有强大的单次免疫保护作用。针对 SARS-CoV-2 的最佳 Ad26 载体疫苗，称为 Ad26.COV2.S，目前正在临床试验中进行评估。

Abstract:
A safe and effective vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be required to end the coronavirus disease 2019 (COVID-19) pandemic. For global deployment and pandemic control, a vaccine that requires only a single immunization would be optimal. Here we show the immunogenicity and protective efficacy of a single dose of adenovirus serotype 26 (Ad26) vector-based vaccines expressing the SARS-CoV-2 spike (S) protein in nonhuman primates. Fifty-two rhesus macaques were immunized with Ad26 vectors encoding S variants or sham control and were challenged with SARS-CoV-2 by the intranasal and intratracheal routes. The optimal Ad26 vaccine induced robust neutralizing antibody responses and provided complete or near-complete protection in bronchoalveolar lavage and nasal swabs following SARS-CoV-2 challenge. Vaccine-elicited neutralizing antibody titres correlated with protective efficacy, suggesting an immune correlate of protection. These data demonstrate robust single-shot vaccine protection against SARS-CoV-2 in nonhuman primates. The optimal Ad26 vector-based vaccine for SARS-CoV-2, termed Ad26.COV2.S, is currently being evaluated in clinical trials.

编者注：该疫苗为 J&J 公司的产品

13. 基于 Ad26 载体的编码稳定预融合的 SARS-CoV-2 刺突免疫原的 COVID-19 疫苗，可诱导有效的体液和细胞免疫反应

Ad26-vector based COVID-19 vaccine encoding a prefusion stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses

来源：biorxiv
发布时间：2020.07.30
文章链接：https://www.biorxiv.org/content/10.1101/2020.07.30.227470v1

第一作者：Rinke Bos
通讯作者：Hanneke Schuitemaker
通讯作者单位：荷兰莱顿杨森疫苗与预防公司（Janssen，J&J）

DOI：https://doi.org/10.1101/2020.07.30.227470

编译者：张怡

中文摘要：
SARS-CoV-2 的病毒表面刺突蛋白是预防措施的关键靶点，因为它对病毒的复制周期至关重要，也是中和抗体的主要靶点。体外鉴定表明，引入稳定取代物(弗林蛋白酶裂解位点突变和 S1 的铰链区两个连续的脯氨酸)增加了中和抗体和非中和抗体结合的比率，暗示了 S 蛋白的预融合构象。此外，野生型信号肽最适合进行天然折叠蛋白所需的正确切割。这些观察结果在小鼠中转化为优越的免疫原性，其中 Ad26 载体编码的膜结合稳定 S 蛋白和野生型信号肽，能有效中和向 Th1 IFN-γ小鼠极化的体液免疫和细胞免疫。这优化了针对 SARS-CoV-2 的 Ad26 载体疫苗，称为 Ad26.COV2.S。目前正在进行一期临床试验评估(ClinicalTrials.gov Identifier: NCT04436276)。

Abstract
The viral surface spike (S) protein of SARS-CoV-2 is a key target for prophylactic

measures as it is critical for the viral replication cycle and the primary target of neutralizing antibodies. In vitro characterization demonstrated that the introduction of stabilizing substitutions (i.e., furin cleavage site mutations and two consecutive prolines in the hinge region of S1) increased the ratio of neutralizing versus non-neutralizing antibody binding, suggestive for a prefusion conformation of the S protein. Furthermore, the wild type signal peptide was best suited for the correct cleavage needed for a natively-folded protein. These observations translated into superior immunogenicity in mice where the Ad26 vector encoding for a membrane-bound stabilized S protein with a wild type signal peptide elicited potent neutralizing humoral immunity and cellular immunity that was polarized towards Th1 IFN-γ. This optimized Ad26 vector-based vaccine for SARS-CoV-2, termed Ad26.COV2.S, is currently being evaluated in a phase I clinical trial (ClinicalTrials.gov Identifier: NCT04436276).
编者注：该疫苗为 J&J 公司的产品

14. 皮内注射的 DNA 疫苗可在恒河猴 SARS-CoV-2 攻毒模型中提供免疫记忆保护

Intradermal-delivered DNA vaccine provides anamnestic protection in a rhesus macaque SARS-CoV-2 challenge model
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发布时间：2020-07-29
链接：https://www.biorxiv.org/content/10.1101/2020.07.28.225649v1.full.pdf
第一作者：Ami Patel、Jewell Walters、Emma L. Reuschel、Katherine Schultheis、Elizabeth Parzych、Ebony N. Gary
通讯作者：David B. Weiner、Kate E. Broderick
通讯作者单位：美国宾夕法尼亚州费城 Wistar 研究所
DOI 或 PUBMED ID：Preprint
编译者：张丽双
中文摘要：
研究人员评估了皮内注射 SARS-CoV-2 刺突蛋白 DNA 疫苗 INO-4800 对恒河猴的免疫原性和免疫记忆保护作用。INO-4800 是目前正在临床试验中的评估疫苗。INO-4800 疫苗免疫恒河猴诱导产生对 D614 和 G614 SARS-CoV-2 刺突蛋白的 T 细胞应答和中和抗体应答。疫苗接种后数月，动物接受 SARS-CoV-2 攻毒，发现产生了快速的抗 SARS-CoV-2 刺突蛋白的 T 和 B 细胞应答。使肺中病毒载量较低和鼻腔病毒清除较快。这些研究支持了 INO-4800 可诱导获得性免疫系统中体液和细胞免疫，可能提供持久的保护。
Abstract:
Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, has had a dramatic global impact on public health, social, and economic infrastructures. Here, we assess immunogenicity and anamnestic protective efficacy in rhesus macaques of the intradermal (ID)- delivered SARS-CoV-2 spike DNA vaccine, INO-4800. INO-4800 is an ID-delivered DNA vaccine currently being evaluated in clinical trials. Vaccination with INO-4800 induced T cell responses and neutralizing antibody responses against both the D614 and G614 SARS-CoV-2 spike proteins. Several months after vaccination, animals were challenged with SARS-CoV-2 resulting in rapid recall of anti-SARS-CoV-2 spike protein T and B cell

responses. These responses were associated with lower viral loads in the lung and with faster nasal clearance of virus. These studies support the immune impact of INO-4800 for inducing both humoral and cellular arms of the adaptive immune system which are likely important for providing durable protection against COVID-19 disease.

15. 抗 COVID-19 的热稳定 mRNA 疫苗

A thermostable mRNA vaccine against COVID-19

来源：Cell

发布时间：2020-07-23

链接：https://www.sciencedirect.com/science/article/pii/S0092867420309326

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DOI 或 PUBMED ID：https://doi.org/10.1016/j.cell.2020.07.024

编译者：刘焕珍

中文摘要：

作者开发了一种脂质纳米颗粒包裹的 mRNA（mRNA LNP），它编码 SARS-CoV-2 的受体结合域（RBD）作为疫苗候选（称为 ARCoV）。在小鼠和非人类灵长类动物中，ARCoV mRNA LNP 肌肉内接种可诱导抗 SARS-CoV-2 的强大中和抗体以及 Th1 偏向的细胞反应。在小鼠中进行两次 ARCoV 免疫接种，可以完全抵御 SARS-CoV-2 小鼠适应株的挑战。此外，ARCoV 是以液体配方制造的，并且可以在室温下至少储存一周。这种新型 COVID-19 mRNA 疫苗 ARCoV 目前正在进行一期临床试验。

Abstract:

There has been an urgent need of vaccines against coronavirus disease 2019 (COVID-19) due to the ongoing SARS-CoV-2 pandemic. Among all approaches, messenger RNA (mRNA) -based vaccine has emerged as a rapid and versatile platform to quickly respond to such a challenge. Here, we developed a lipid-nanoparticle-encapsulated mRNA (mRNA-LNP) encoding the receptor binding domain (RBD) of SARS-CoV-2 as a vaccine candidate (termed ARCoV). Intramuscular immunization of ARCoV mRNA-LNPs elicited robust neutralizing antibodies against SARS-CoV-2 as well as Th1-biased cellular response in mice and non-human primates. Two doses of ARCoV immunization in mice conferred complete protection against the challenge of a SARS-CoV-2 mouse adapted strain. Additionally, ARCoV was manufactured in liquid formulation and can be stored at room temperature for at least one week. This novel COVID-19 mRNA vaccine, ARCoV, is currently being evaluated in phase 1 clinical trials.

16. 一种新一代双价人 Ad5-COVID-19 疫苗同时携带刺突蛋白抗原和核衣壳抗原，可诱导 Th1 显性 CD4+、CD8+T 细胞和中和抗体反应

A Next Generation Bivalent Human Ad5 COVID-19 Vaccine Delivering Both Spike and Nucleocapsid Antigens Elicits Th1 Dominant CD4+, CD8+ T-cell and Neutralizing Antibody Responses

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DOI 或 PUBMED ID：
编译者：张鹏伟
中文摘要：
我们在这里报告了一种新一代双价人腺病毒血清型 5（hAd5）疫苗，它能够在已有腺病毒免疫的患者中诱导免疫，包括一个为细胞表面表达而优化的 S 序列（S-融合）和一个保守的核衣壳（N）抗原，设计用于运输到内质亚细胞室，具有产生持久免疫保护的潜力。我们的研究表明，这种新一代双价疫苗的免疫原性得到了优化，如下结果所证明：（i）优化的 S 融合显示 S 受体结合域（RBD）细胞表面表达较 S-WT 有所改善，而 S-WT 几乎没有表面表达；（ii）S 融合表达的 RBD 保留了构象完整性和 ACE2 Fc 的识别能力；（iii）经增强 T 细胞刺激域（ETSD）修饰的病毒 N 蛋白，定位于内质/溶酶体亚细胞室，用于 MHC I/II 呈现；以及（iv）对 S 和 N 的优化（S 融合和 N-ETSD）产生增强抗原初始临床前模型中的新生抗原特异性 B 细胞和 CD4+和 CD8+T 细胞反应。T 细胞和抗体对 S 和 N 的免疫反应均表现为 T 辅助因子 1（Th1）偏向。两个独立的 SARS-CoV-2 中和试验证明抗体反应是中和的。基于这些发现，我们正在推进下一代双价 hAd5s 融合+N-ETSD 疫苗作为我们的主要临床候选疫苗，以测试其对 SARS-CoV-2 感染提供强大、持久的细胞介导和体液免疫的能力。进一步的研究正在进行中，以探索在口服、鼻内和舌下制剂中使用这种疫苗结构，除了细胞介导和体液免疫外，还可以诱导黏膜免疫。理想的 COVID-19 疫苗的最终目标是产生长期的 T 和 B 细胞记忆。

Abstract:
In response to the health crisis presented by the COVID-19 pandemic, rapid development of safe and effective vaccines that elicit durable immune responses is imperative. Recent reports have raised the concern that antibodies in COVID-19 convalescent patients may not be long lasting and thus even these individuals may require vaccination. Vaccine candidates currently in clinical testing have focused on the SARS-CoV-2 wildtype spike (S) protein (S-WT) as the major antigen of choice and while pre-clinical and early clinical testing have shown that S elicits an antibody response, we believe the optimal vaccine candidate should be capable of inducing robust, durable T-cell responses as well as humoral responses. We report here on a next generation bivalent human adenovirus serotype 5 (hAd5) vaccine capable of inducing immunity in patients with pre-existing adenovirus immunity, comprising both an S sequence optimized for cell surface expression (S-Fusion) and a conserved nucleocapsid (N) antigen designed to be transported to the endosomal subcellular compartment, with the potential to generate durable immune protection. Our studies suggest that this next generation bivalent vaccine is optimized for immunogenicity as evidenced by the following findings: (i) The optimized S-Fusion displayed improved S receptor binding domain (RBD) cell surface expression compared to S-WT where little surface expression was detected; (ii) the expressed RBD from S-Fusion retained conformational integrity and recognition by ACE2-Fc; (iii) the viral N protein modified with an enhanced T-

cell stimulation domain (ETSD) localized to endosomal/lysosomal subcellular compartments for MHC I/II presentation; and (iv) these optimizations to S and N (S-Fusion and N-ETSD) generated enhanced de novo antigen-specific B cell and CD4+ and CD8+ T-cell responses in antigen-naive pre-clinical models. Both the T-cell and antibody immune responses to S and N demonstrated a T-helper 1 (Th1) bias. The antibody responses were neutralizing as demonstrated by two independent SARS-CoV-2 neutralization assays. Based on these findings, we are advancing this next generation bivalent hAd5 S-Fusion + N-ETSD vaccine as our lead clinical candidate to test for its ability to provide robust, durable cell-mediated and humoral immunity against SARS-CoV-2 infection. Further studies are ongoing to explore utilizing this vaccine construct in oral, intranasal, and sublingual formulations to induce mucosal immunity in addition to cell-mediated and humoral immunity. The ultimate goal of an ideal COVID-19 vaccine is to generate long-term T and B cell memory.

17. 中国的疫苗开发包括复星的 IND 获批，重庆智飞启动临床二期试验

Vaccine developments in China include IND acceptance for Fosun, Phase II start for Chongqing Zhifei

来源：BIOCENTURY

发布时间：2020-07-17

链接：https://www.biocentury.com/article/305727/vaccine-developments-in-china-include-ind-acceptance-for-fosun-phase-ii-start-for-chongqing-zhifei?tag=cov19count&return_feed=%2Fcoronavirus

作者：Danielle Golovin And Hongjiang Li

作者单位：BIOCENTURY

DOI 或 PUBMED ID：

编译者：刘焕珍

中文摘要：

上海复星医药集团有限公司（上海：600196；香港证券交易所：2196）周二宣布，中国国家药品监督管理局(NMPA)接受了 BNT162b1 的 IND,BNT162b1 是 BNT162 计划中四种候选 COVID-19 疫苗之一。上海复星是 BioNTech SE（NASDAQ：BNTX）在中国的 BNT162 开发合作伙伴，德国公司的合作伙伴是辉瑞公司（NYSE：PFE）。BNT162b1 和 BNT162b2 是目前正在开发的最先进的 COVID-19 疫苗之一；BNT162b1 在人类试验中诱导了一些最高的中和抗体效价。辉瑞和 BioNTech 计划在本月将其四个候选药物中的一个纳入 30000 人参与的 IIb/III 阶段试验（见“BioNTech,辉瑞疫苗产生高滴度”)。另外,重庆智飞生物制品有限公司(SZSE:300122）开展了其 COVID-19 疫苗的中国 II 期试验，该疫苗是一种重组刺突蛋白受体结合域（RBD）二聚体。

Abstract:

Shanghai Fosun Pharmaceutical Group Co. Ltd. (Shanghai:600196; HKSE:2196) announced Tuesday that China’s National Medical Products Administration (NMPA) accepted an IND for BNT162b1, one of four COVID-19 vaccine candidates in the BNT162 program. Shanghai Fosun is the BNT162 development partner for BioNTech SE (NASDAQ:BNTX) in China, outside of which the German company’s partner is Pfizer Inc. (NYSE:PFE). BNT162b1 and BNT162b2, which have Fast Track designation, are

among the most advanced COVID-19 vaccines in development; and BNT162b1 has induced some of the highest neutralizing antibody titers in a human trial to date. Pfizer and BioNTech plan to move one of its four candidates into a 30,000-participant Phase IIb/III trial this month (see “BioNTech, Pfizer Vaccine Yields High Titers”). Separately, Chongqing Zhifei Biological Products Co. Ltd. (SZSE:300122) launched a Chinese Phase II trial of its COVID-19 vaccine, a recombinant spike protein receptor binding domain (RBD) dimer.

18. 疫苗之前，COVID-19 抗体治疗可能在 9 月份上市

COVID-19 antibody treatments could be available in September, ahead of vaccines
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发布时间：2020-07-31
链接：
https://www.biocentury.com/article/305826?editionId=ckd9lu50w15wc0174zzcp4eh9&editionType=daily
作者：ELIZABETH S. EATON
作者单位：biocentury
DOI 或 PUBMED ID：
编译者：雷颖
中文摘要：
一位政府高级官员周四表示，COVID-19 抗体疗法有望最早在 9 月份获得批准，疫苗有望在秋季晚些时候上市。这位官员还与辉瑞和 BioNTech 讨论了美国政府的采购疫苗交易，称每剂量 19.50 美元的价格“非常有竞争力”。这位不愿透露姓名的官员说，抗体开发商，例如再生元制药公司（NASDAQ：REGN），礼来公司（NYSE：LLY）和阿斯利康公司（LSE：AZN; NYSE：AZN），将开始一系列研究在接下来的几周内将进行一系列的临床试验，这些试验将遵循 NIH 监督的通用协议。Regeneron 的 REGN-COV2 是由两种针对 SARS-CoV-2 刺突蛋白的单克隆抗体组成的混合物，于 6 月中旬开始进行 I/II/III 期临床试验，现已进入 II/III 期临床试验。礼来与 AbCellera Biologics Inc.合作开发的 mAb Ly-CoV555 于 6 月 1 日开始进行 I 期测试，数周后进行单独的 II 期试验。阿斯利康（AstraZeneca）已从范德比尔特大学（Vanderbilt University）获得了六种单抗的许可，并计划在八月份将两种单抗作为联合疗法引入临床。如果抗体在临床上获得成功，该官员预计“今年秋天，在 9 月中旬至 11 月 1 日之间，将会有大量的产品上市。” 这些可能会在疫苗问世之前出现，而这种疫苗将在秋天晚些时候问世。”
Abstract
COVID-19 antibody therapeutics could be authorized as early as September, with vaccines expected to be available later in the fall, a senior government official said Thursday. In addition to updating the countermeasure timeline, the official discussed the U.S. government’s procurement vaccine deal with Pfizer and BioNTech, calling the $19.50 per dose price “very competitive.”
The official, who declined to be identified, said antibody developers such as Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Eli Lilly and Co. (NYSE:LLY) and AstraZeneca plc (LSE:AZN; NYSE:AZN) will start a series of clinical trials in the next couple of weeks that will follow a common protocol overseen by NIH.
Regeneron’s REGN-COV2, a cocktail of two mAbs targeting the SARS-CoV-2 spike

protein, started a pair of Phase I/II/III trials in mid-June and has progressed into the Phase II/III stage in both trials.
Ly-CoV555, the mAb that Lilly is developing with AbCellera Biologics Inc., began Phase I testing on June 1 and a separate Phase II trial weeks later.
AstraZeneca has licensed six mAbs from Vanderbilt University and plans to bring two into the clinic as a combination therapy in August.
If the antibodies are successful in the clinic, the official anticipates "significant volumes hitting the market this fall, between the middle of September and the first of November. These will likely precede the availability of vaccines, which will come a little bit later in the fall."
文章分类：疫苗研发

19. 应用 mRNA 纳米技术快速生成循环和黏膜 ACE2 诱饵用于 SARS-CoV-2 的潜在治疗

Rapid generation of circulating and mucosal decoy ACE2 using mRNA nanotherapeutics for the potential treatment of SARS-CoV-2
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第一作者：Jeonghwan Kim
通讯作者：Gaurav Sahay
通讯作者单位：College of Pharmacy, Robertson Life Sciences Building, Oregon State University, Portland, OR, USA
DOI 或 PUBMED ID：
编译者：张鹏伟
中文摘要：
严重急性呼吸综合征冠状病毒 2（SARS-CoV-2）通过呼吸道进入肺部感染，对易受感染的患者造成致命的肺损伤。这种病毒在其包膜上含有与气道细胞表面表达的人血管紧张素转换酶 2（hACE2）结合的 spike 蛋白，使病毒能够进入引起感染。在严重的情况下，病毒进入循环系统，导致多器官衰竭。可溶性形式的 hACE2 与 SARS-CoV-2 蛋白结合，阻止病毒进入靶细胞。此外，可溶性重组 ACE2 可改善肺损伤，但其半衰期短，限制了其治疗作用。在这里，我们设计合成的 mRNA 来编码一种可溶性形式的 hACE2（hsACE2），以防止病毒感染。新型脂质纳米粒（LNPs）被用于包装 mRNA 和转染哺乳动物细胞以提高分泌蛋白的产生。静脉注射 LNP 导致了 mRNA 的肝脏传递。这导致 hsACE2 在 2h 内分泌到血液循环中，循环 hsACE2 的水平在 6h 达到高峰，并在数天内逐渐降低。由于 SARS-CoV-2 的主要进入和发病部位是肺部，我们将 LNPs 注入肺部，并在 24 小时内检测到支气管肺泡灌洗液中的 hsACE2，持续 48 小时。通过免疫共沉淀，我们发现 hsACE2 的 mRNA 能够与 SARS-CoV-2 spike 蛋白的受体结合域结合。此外，hsACE2 对 SARS-CoV-2 假病毒感染有较强的抑制作用（90%以上）。我们的原则证明研究表明，基于 mRNA 的纳米治疗技术可以用于 SARS-CoV-2 的肺中和和肺外中和，为 COVID-19 开辟新的治疗机会。
Abstract:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters through the airways and infects the lungs, causing lethal pulmonary damage in vulnerable patients. This virus contains spike proteins on its envelope that binds to human angiotensin-converting enzyme 2 (hACE2) expressed on the surface of airway cells,

enabling entry of the virus for causing infection. In severe cases, the virus enters the circulatory system, contributing to multiorgan failure. Soluble form of hACE2 binds to SARS-CoV-2 spike protein and prevents viral entry into target cells. Moreover, soluble recombinant ACE2 ameliorates lung injury but its short half-life limits its therapeutic utility. Here, we engineered synthetic mRNA to encode a soluble form of hACE2 (hsACE2) to prevent viral infection. Novel lipid nanoparticles (LNPs) were used to package mRNA and transfect mammalian cells for enhanced production of secreted proteins. Intravenously administered LNP led to hepatic delivery of the mRNA. This elicited secretion of hsACE2 into the blood circulation within 2 h, and levels of circulating hsACE2 peaked at 6 h and gradually decreased over several days. Since the primary site of entry and pathogenesis for SARS-CoV-2 is the lungs, we instilled LNPs into the lungs and were able to detect hsACE2 in the bronchoalveolar lavage fluid within 24 h and lasted for 48 h. Through co-immunoprecipitation, we found that mRNA-generated hsACE2 was able to bind with the receptor binding domain of the SARS-CoV-2 spike protein. Furthermore, hsACE2 was able to strongly inhibit (over 90%) SARS-CoV-2 pseudovirus infection. Our proof of principle study shows that mRNA-based nanotherapeutics can be potentially deployed for pulmonary and extrapulmonary neutralization of SARS-CoV-2 and open new treatment opportunities for COVID-19.

20. 人源化糖基化抗 SARS-CoV-2 多克隆猪抗体的高中和效果

High neutralizing potency of swine glyco-humanized polyclonal antibodies against SARS-CoV-2

来源：biorxiv

发布时间：2020.07.25

文章链接：https://www.biorxiv.org/content/10.1101/2020.07.25.217158v1

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DOI：https://doi.org/10.1101/2020.07.25.217158

编译者：张怡

中文摘要：

异源多克隆抗体引发人的异种抗体反应，特别是针对动物型碳水化合物表位，主要是 N-glycolyl 形式的神经氨酸(Neu5Gc)和 Gal alpha1,3-galactose （α-Gal），最终形成免疫复合物，并可能导致血清疾病或过敏。为了克服这些缺陷，我们设计了缺乏胞苷单磷酸-N-乙酰神经氨酸羟化酶(CMAH)和α1,3-半乳糖转移酶(GGTA1)的动物，以生产缺乏 Neu5Gc 和α-Gal 表位的糖化人源化多克隆抗体(GH-pAb)。作者还发现，这些 IgG Fc 结构域不能与人的 Fc 受体相互作用，因此在避免巨噬细胞依赖加重炎症反应或引发抗体依赖增强(ADE)方面具有安全优势，这两个缺陷可能与抗体对 SARS-CoV-2 的反应有关。因此，作者用 SARS-CoV-2 刺突受体结合区域(RBD)区域免疫 CMAH/GGTA1 双敲除(DKO)猪以获得中和抗体。动物快速产生高免疫血清，其终效价结合稀释倍数超过 1-100 万，终效价中和稀释倍数为 1:10,000。按照临床良好生产规范纯化和制定的 IgG 片段，命名为 XAV-19，中和了浓度< 1 微克/mL 的 Spike/ACE-2 相互作用，并在细胞病理检测中抑制了 SARS-CoV-2 对人体细胞的感染。这些数据以及在人体内使用糖人源化猪抗体积累的安全优势，值得对 XAV-19 对抗 COVID-

19 进行临床评估。

Abstract

Heterologous polyclonal antibodies trigger human natural xenogeneic antibody responses particularly directed against animal-type carbohydrate epitopes, mainly the N-glycolyl form of the neuraminic acid (Neu5Gc) and the Gal alpha1,3-galactose (α-Gal), ultimately forming immune complexes and potentially leading to serum sickness or allergy. To circumvent these drawbacks, we engineered animals lacking the cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMAH) and alpha1,3-galactosyltransferase (GGTA1) enzymes to produce glyco-humanized polyclonal antibodies (GH-pAb) lacking Neu5Gc and α-Gal epitopes. We also found that these IgG Fc domains fail to interact with human Fc receptors and thereby should confer the safety advantage to avoiding macrophage dependent exacerbated inflammatory responses or elicit antibody-dependent enhancement (ADE), two drawbacks possibly associated with antibody responses against SARS-CoV-2. Therefore, we immunized CMAH/GGTA1 double knockout (DKO) pigs with the SARS-CoV-2 spike receptor binding domain (RBD) domain to elicit neutralizing antibodies. Animals rapidly developed hyperimmune sera with end-titers binding dilutions over one to a million and end-titers neutralizing dilutions of 1:10,000. The IgG fraction purified and formulated following clinical Good Manufacturing Practices, named XAV-19, neutralized Spike/ACE-2 interaction at a concentration < 1microgram/mL and inhibited infection of human cells by SARS-CoV-2 in cytopathic assays. These data and the accumulating safety advantages of using glyco-humanized swine antibodies in humans warrant clinical assessment of XAV-19 to fight against COVID-19.

21. AI 治疗公司宣布启动治疗 COVID-19 患者的 LAM-002A（阿匹莫特二甲磺酸盐）临床 II 期试验

AI Therapeutics Announces Start of Phase II Trial of LAM-002A (apilimod dimesylate) for Treatment of COVID-19 Patients

来源：biospace

发布时间：2020-07-27

链接：https://www.biospace.com/article/releases/ai-therapeutics-announces-start-of-phase-ii-trial-of-lam-002a-apilimod-dimesylate-for-treatment-of-covid-19-patients/

作者：Averill Meadow

作者单位：AI Therapeutics

DOI 或 PUBMED ID：N/A

编译者：雷颖

中文摘要：

AI 治疗公司是一家生物制药公司，致力于开发通过专有的人工智能算法识别出的新颖疗法，以将药物与新适应症相匹配。最近 AI 治疗公司宣布启动与耶鲁大学合作的治疗新诊断的 COVID-19 患者的临床 II 期试验。这项随机，双盲，安慰剂对照研究（NCT04446377）最多将招募 142 位门诊患者，以评估 LAM-002A 在确诊 COVID-19 的受试者中降低病毒载量的安全性、耐受性和疗效。还将评估其他临床疗效指标，包括死亡，住院和氧饱和度。LAM-002A 是

一流的、高度选择性的 PIKfyve 激酶抑制剂，已证明对几种 SARS-CoV-2 分离株具有有效的体外抗病毒活性。现在有几项研究表明，LAM-002A 会干扰 SARS-CoV-2 病毒在细胞中的进入和运输。鉴于其作用机理，LAM-002 也有可能成为联合疗法的一部分，尤其是与靶向病毒蛋白或功能（例如病毒复制）的其他药物一起使用。

Abstract

AI Therapeutics announced the start of Phase II clinical trial for the treatment of newly diagnosed COVID-19 patients in collaboration with Yale University. AI Therapeutics is a biopharmaceutical company that develops novel therapies identified through a proprietary artificial intelligence algorithm for matching drugs to new indications (Guardian Angel™). The randomized, double-blind, placebo-controlled study (NCT04446377) will enroll up to 142 outpatients to evaluate the safety, tolerability, and efficacy of LAM-002A in reducing viral load in subjects with a confirmed COVID-19. Additional measures of clinical efficacy will be evaluated, including death, hospitalization, and oxygen saturation. LAM-002A is a first in class, highly selective PIKfyve kinase inhibitor that has demonstrated potent in vitro antiviral activity against several isolates of SARS-CoV-2, the virus responsible for COVID-19. Indeed, several studies now have shown that LAM-002A interferes with the entry and trafficking of the SARS-CoV-2 virus in cells. Given its mechanism of action, LAM-002 also has the potential to become part of combination therapies, especially with other drugs that target viral proteins or functions, such as viral replication.

22. COVID-19 患者形成记忆 CD8+ T 细胞，可识别 SARS-CoV-2 中的一小部分共享免疫抗原表位

COVID-19 Patients Form Memory CD8+ T Cells that Recognize a Small Set of Shared Immunodominant Epitopes in SARS-CoV-2

来源：medRxiv

发布时间：2020-07-27

链接：https://www.medrxiv.org/content/10.1101/2020.07.24.20161653v1

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通讯作者：Gavin MacBeath

通讯作者单位：TScan Therapeutics, Waltham, MA 02451, USA

DOI 或 PUBMED ID：Preprint

编译者：张丽双

中文摘要：

开发检测，治疗或预防 COVID-19 的有效策略需要对 SARS-CoV-2 的天然免疫应答（包括 T 细胞介导的细胞应答）有深刻的了解。我们使用了一种无偏见的全基因组筛选技术（称为 T-Scan）来识别 SARS-CoV-2 中的特定表位，这些表位可被 25 名 COVID-19 康复期患者的记忆 CD8+ T 细胞识别，针对六种最普遍的 HLA 类型递呈的表位，对于每种 HLA 类型，患者的 T 细胞识别 3-8 个免疫优势表位，这些抗原表位在患者之间广泛共享。总共，我们在所研究的六种 HLA 类型中确定了 29 个共享表位。靶向大多数这些免疫优势表位的 T 细胞（29 个中的 27 个）不会与引起普通感冒的地方性冠状病毒发生交叉反应，并且这些表位不会出现在具有高突变变异性的区域。值得注意的是，我们鉴定出的 29 个表位中只有 3 个存在于刺突蛋

白中，这突显了对新型疫苗的需求，这些新型疫苗旨在引发更广泛的 CD8+ T 细胞反应。

Abstract:
Development of effective strategies to detect, treat, or prevent COVID-19 requires a robust understanding of the natural immune response to SARS-CoV-2, including the cellular response mediated by T cells. We used an unbiased, genome-wide screening technology, termed T-Scan, to identify specific epitopes in SARS-CoV-2 that are recognized by the memory CD8+ T cells of 25 COVID-19 convalescent patients, focusing on epitopes presented by the six most prevalent Human Leukocyte Antigen (HLA) types: A*02:01, A*01:01, A*03:01, A*11:01, A*24:02, and B*07:02. For each HLA type, the patients' T cells recognized 3-8 immunodominant epitopes that are broadly shared among patients. Remarkably, 94% of screened patients had T cells that recognized at least one of the three most dominant epitopes for a given HLA, and 53% of patients had T cells that recognized all three. Subsequent validation studies in 18 additional A*02:01 patients confirmed the presence of memory CD8+ T cells specific for the top six identified A*02:01 epitopes, and single-cell sequencing revealed that patients often have >5 different T cell clones targeting each epitope, but that the same T cell receptor Valpha and Vbeta regions are predominantly used to recognize these epitopes, even across patients. In total, we identified 29 shared epitopes across the six HLA types studied. T cells that target most of these immunodominant epitopes (27 of 29) do not cross-react with the endemic coronaviruses that cause the common cold, and the epitopes do not occur in regions with high mutational variation. Notably, only 3 of the 29 epitopes we identified reside in the spike protein, highlighting the need for new classes of vaccines that are designed to elicit a broader CD8+ T cell response.

23. SARS-CoV-2 病毒 RNA 加帽修饰的结构基础

Structural basis of RNA cap modification by SARS-CoV-2

来源：Nature Communications
发布时间：2020-07-24
链接：https://www.nature.com/articles/s41467-020-17496-8

第一作者：Thiruselvam Viswanathan, Shailee Arya
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DOI 或 PUBMED ID：10.1038/s41467-020-17496-8

编译者：宋珂

中文摘要：

SARS-CoV-2 病毒是导致 COVID-19 疾病的病原体，在全球范围内已造成了数百万人感染。在 SARS 冠状病毒中，非结构蛋白 16（nsp16）与非结构蛋白 10（nsp10）协同，在病毒编码的 mRNA 的 5'端引入甲基化修饰，以此来模拟细胞 mRNA，从而保护病毒免受宿主的先天免疫抵抗。本文中，作者报道了其解析的包含同源 RNA 底物类似物的 SARS-CoV-2 nsp16 和 nsp10，以及甲基供体 S-腺苷甲硫氨酸（SAM）的三元复合物的高分辨率结构。其中，nsp16/nsp10 异质二聚体的构象是 SARS-CoV-2 mRNA 的第一个核苷酸的核糖上的 2'-O 正在被甲基化时的

构象。作者发现，随着底物的结合，酶从二元复合物转变为三元复合物的状态，其相应的构象也发生了很大的变化。该诱导匹配模型为病毒 mRNA 加帽过程中的 2'-O 甲基化修饰提供了机理解释。作者还发现了一个 SARS-CoV-2 特有的较远的（25 Å）配体结合位点，这是除了 RNA 帽和 SAM 口袋外，一个新的可用作抗病毒药物研发的靶点。

结构数据：RCSB PDB ID：6WKS

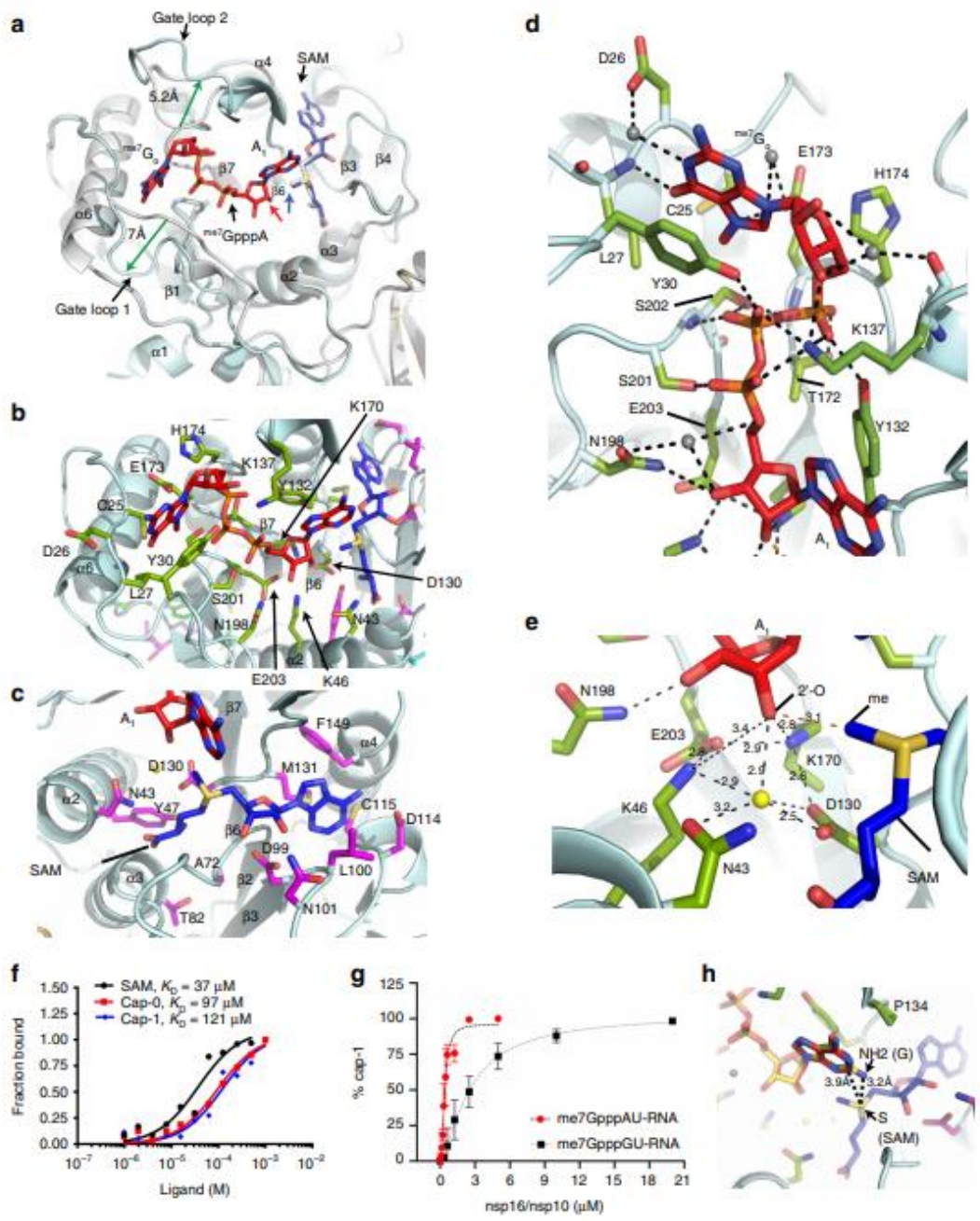

Fig. 2 Binding modes of RNA cap analogues and SAM and mechanism of methyl transfer. a Overlay of a binary (S-adenosyl methionine or SAM-bound; gray cartoons) and ternary (SAM, RNA cap-bound; light cyan cartoons) complexes shows outward motions (green arrows: 7 Å in gate loop 1, and 5.2 Å in gate loop 2) after RNA cap binding to nsp16. RNA cap, red stick; SAM in ternary complex, blue stick; SAM in binary complex, gray stick. **b** green sticks; nsp16 residues that interact with RNA cap. **c** magenta sticks; nsp16 residues that contact with SAM. **d** A close-up view of Cap-nsp16 interactions reveals a network of hydrogen bonding with successive phosphates, me7GO and A1 nucleotides of cap. Water,

gray spheres, h-bonds, black dashed lines. **e** A water (yellow sphere) coordinates with the target 2′-O atom of A1, and catalytic tetrad residues and N43. The methyl group of SAM is positioned for direct in-line attack from the 2′-O. **f** Binding isotherms and fitting of data for nsp16 binding to RNA cap-0 (me7GpppA), cap-1 (me7GpppAm) analogues, and SAM. Each data point represents average of two independent experiments (n = 2). **g** The 2′-O methyltransferase activity measured as percentage of Cap-0 to Cap-1 conversion is plotted against nsp16/nsp10 protein concentration. Higher enzymatic activity is observed on an RNA substrate with A (red circles) as the target base for 2′-O methylation (N1), compared to an identical RNA but with G (black square) as N1 or initiating nucleotide. Results are average of three independent experiments (n = 3) with one standard deviation (s.d.) for each RNA shown as error bars. Source data are provided as a Source Data file. **h** Guanine base (yellow stick) is modeled at N1 position of cognate adenine (red stick). The N2 amine of guanine intrudes into the SAM pocket and may be repelled by positively charged sulfur of SAM (blue stick).

Abstract:
The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19 illness, has caused millions of infections worldwide. In SARS coronaviruses, the non-structural protein 16 (nsp16), in conjunction with nsp10, methylates the 5′ -end of virally encoded mRNAs to mimic cellular mRNAs, thus protecting the virus from host innate immune restriction. We report here the high-resolution structure of a ternary complex of SARS-CoV-2 nsp16 and nsp10 in the presence of cognate RNA substrate analogue and methyl donor, S-adenosyl methionine (SAM). The nsp16/nsp10 heterodimer is captured in the act of 2′ -O methylation of the ribose sugar of the first nucleotide of SARS-CoV-2 mRNA. We observe large conformational changes associated with substrate binding as the enzyme transitions from a binary to a ternary state. This induced fit model provides mechanistic insights into the 2′ -O methylation of the viral mRNA cap. We also discover a distant (25 Å) ligand-binding site unique to SARS-CoV-2, which can alternatively be targeted, in addition to RNA cap and SAM pockets, for antiviral development.

24. SARS-CoV-2 病毒复制-转录复合物中解旋酶-聚合酶协同的结构基础

Structural basis for helicase-polymerase coupling in the SARS-CoV-2 replication-transcription complex

来源：Cell
发布时间：2020-07-22 (Accepted)
链接：https://www.cell.com/cell/fulltext/S0092-8674(20)30941-7#%20
第一作者：James Chen, Brandon Malone
通讯作者：Seth A. Darst, Elizabeth A. Campbell
通讯作者单位：Laboratory of Molecular Biophysics, the Rockefeller University, New York, NY, 10065 USA.
DOI 或 PUBMED ID：10.1016/j.cell.2020.07.033
编译者：宋珂
中文摘要：

SARS-CoV-2 病毒是导致 2019-2020 年疫情的病原体。SARS-CoV-2 通过 RNA 依赖的 RNA

聚合酶全酶（包含亚结构 nsp7/nsp8$_2$/nsp12）以及一系列其他辅助因素，完成自身基因组的复制和转录。nsp13 解旋酶就是诸多辅助因素之一。holo-RdRp 和 nsp13 都是病毒复制时必需的酶，同时也是治疗 COVID-19 的重要靶标。本文中，作者介绍了其利用 cryo-EM 技术解析的包含一个 RNA 模板-产物的 SARS-CoV-2 holo-RdRp，以及两个 nsp13 解旋酶分子的复合物结构。其中，每个 nsp13 解旋酶分子中具有特定巢状病毒顺序的 N 端结构域都与 nsp8 的一个副本的 N 端延伸区域存在相互作用。同时一个 nsp13 还与 nsp12-thumb 区域接触。该结构里，解旋酶中核酸结合 ATPase 的区域被直接置于复制转录的 holo-RdRp 之前，从而限制了 nsp13 功能的模式。作者还观察到 ADP-Mg2+结合在 nsp12 N 端区域中与巢状病毒 RdRp 核苷酸转移酶相关的结构域，为开发抗病毒治疗药物发现了新的结合口袋。

结构数据：RCSB PDB ID：6XEZ

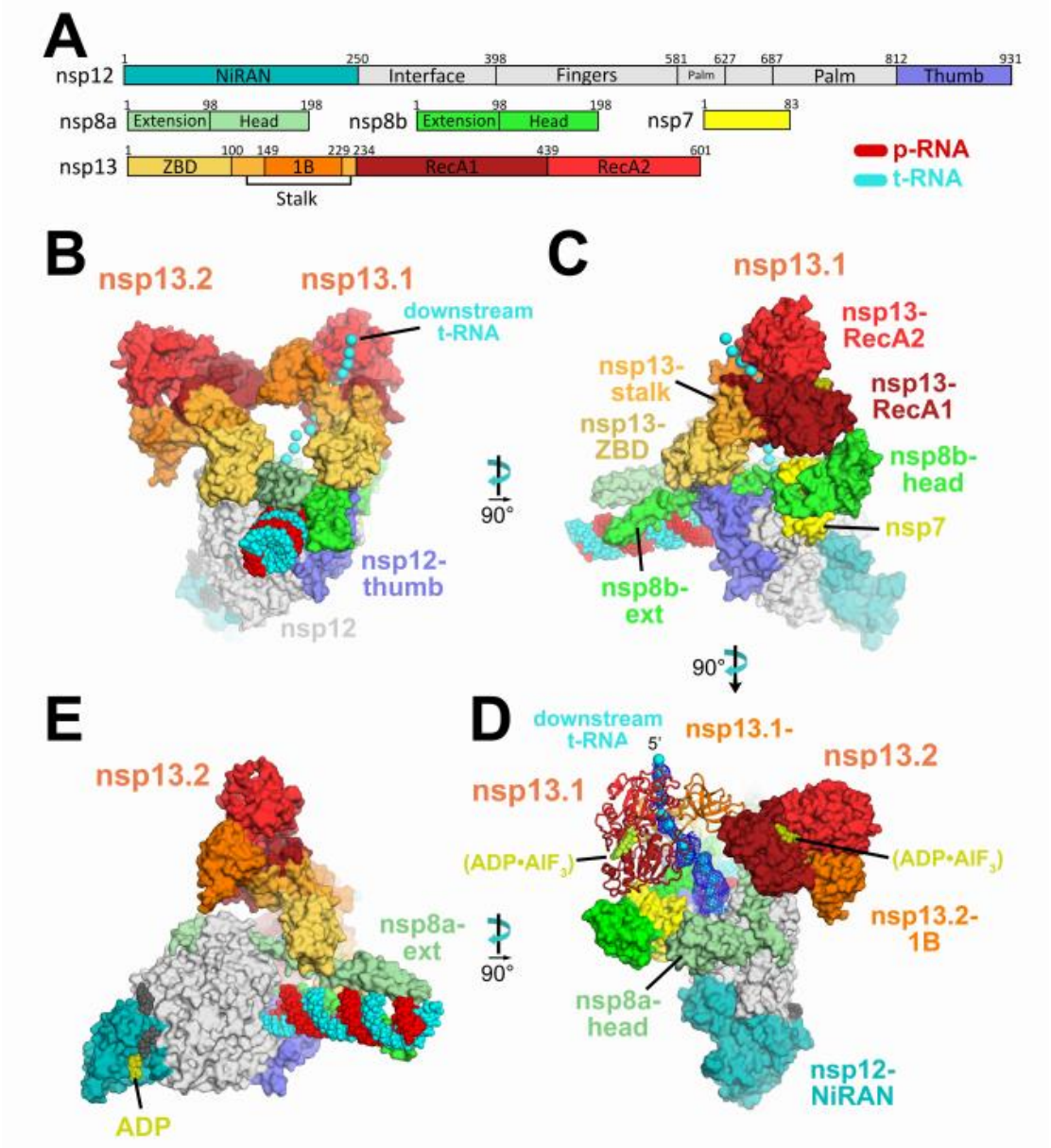

Figure 2. Overall structure of the SARS-CoV2 nsp13 helicase with the holo-RdRp:RNA replication/transcription complex (RTC). A. Schematic illustrating domain structure of SARS-CoV-2 holo-RdRp (nsp7, nsp8, nsp12) and nsp13. Structural domains discussed in the text are labeled. The color-coding corresponds to the figures throughout this manuscript unless otherwise specified. **B-E.**

Orthogonal views showing the overall architecture of the nsp132-RTC. Proteins are shown as molecular surfaces (except nsp13.1 in panel d), RNA as atomic spheres. Adventitious CHAPSO detergent molecules are shown as atomic spheres and colored dark grey. The path of downstream t-RNA through the nsp13.1 helicase, shown as cyan spheres, is revealed with low460 pass filtered (6 Å) difference density (shown in panel d). **B.** Two copies of the nsp13 helicase bind to the RTC. Nsp13.1 forms a tripartite interaction with the nsp8b-extension and the nsp12-thumb via the nsp13.1-ZBD. The 5'-end of the tRNA extrudes through the nucleic acid binding channel of nsp13.1. The two helicases interact via the nsp13.1-1B domain and the nsp13.2-RecA1 domain. **C.** In addition to the nsp13.1-ZBD:nsp8b-extension:nsp12-thumb tripartite interaction, nsp13.1-RecA1 interacts with nsp7 and the nsp8b-head. **D.** ADP-AlF3 is modeled in the NTP binding site of each helicase. The low-pass filtered (6 Å) cryo-EM difference density revealing the path of the downstream t-RNA is shown (dark blue mesh). **E.** The nsp13.2-ZBD interacts with the nsp8a-extension. ADP-Mg2+ 469 is bound to the NiRAN domain.

Abstract:
SARS-CoV-2 is the causative agent of the 2019-2020 pandemic. The SARS-CoV-2 genome is replicated and transcribed by the RNA-dependent RNA polymerase holoenzyme (subunits nsp7/nsp8$_2$/nsp12) along with a cast of accessory factors. One of these factors is the nsp13 helicase. Both the holo-RdRp and nsp13 are essential for viral replication and are targets for treating the disease COVID-19. Here we present cryo-electron microscopic structures of the SARS-CoV-2 holo-RdRp with an RNA template-product in complex with two molecules of the nsp13 helicase. The Nidovirus-order-specific N-terminal domains of each nsp13 interact with the N-terminal extension of each copy of nsp8. One nsp13 also contacts the nsp12-thumb. The structure places the nucleic acid-binding ATPase domains of the helicase directly in front of the replicating-transcribing holo-RdRp, constraining models for nsp13 function. We also observe ADP-Mg2+ bound in the nsp12 N-terminal nidovirus RdRp-associated nucleotidyltransferase domain, detailing a new pocket for anti-viral therapeutic development.

25. 包含 IGHV3-53 基因的抗体和 SARS-CoV-2 的受体结合域的具有不同的结合模式

An alternative binding mode of IGHV3-53 antibodies to the SARS-CoV-2 receptor binding domain IAN WILSON 的工作

来源：biorxiv

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链接：https://www.biorxiv.org/content/10.1101/2020.07.26.222232v1

第一作者：Nicholas C. Wu

通讯作者：Ian A. Wilson

通讯作者单位：Scripps Institute

编译：蒋立春

中文摘要：

编者注 7 月 17 日的简报第 20 条报告过该团队发表在 SCIENCE 上，关于 SARS-CoV-2 的中和抗体中一个共同的 V 基因 IGHV3-53 的报道。由于和 SARS-CoV-2 的刺突蛋白受体结合限制，这些抗体的 CDR H3 一般都很短。这篇新的研究表明也有一部分 IGHV3-53 抗体包含更长的 CDR H3.通过晶体结构分析，作者们发现包含更长 CDR H3 的 IGHV3-53 中和抗体可以以不同

的结合模式来结合 SARS-CoV-2 的刺突蛋白受体结合域。

Abstract:
IGHV3-53-encoded neutralizing antibodies are commonly elicited during SARS-CoV-2 infection and target the receptor-binding domain (RBD) of the spike (S) protein. Such IGHV3-53 antibodies generally have a short CDR H3 due to structural constraints in binding the RBD (mode A). However, a small subset of IGHV3-53 antibodies to the RBD contain a longer CDR H3. Crystal structures of two IGHV3-53 neutralizing antibodies here demonstrate that a longer CDR H3 can be accommodated in a different binding mode (mode B). These two classes of IGHV3-53 antibodies both target the ACE2 receptor binding site, but with very different angles of approach and molecular interactions. Overall, these findings emphasize the versatility of IGHV3-53 in this common antibody response to SARS-CoV-2, where conserved IGHV3-53 germline-encoded features can be combined with very different CDR H3 lengths and light chains for SARS-CoV-2 RBD recognition and virus neutralization.

26. 北美鹿鼠易感染 SARS-CoV-2

North American deer mice are susceptible to SARS-CoV-2

链接：https://www.medrxiv.org/content/10.1101/2020.07.11.20149344v1

编译者：王玮

加拿大的研究者发现成年鹿鼠在鼻腔接触人类分离物后易感染 SARS-CoV-2，导致病毒在上呼吸道和下呼吸道复制，几乎没有疾病症状。此外，在鼻腔冲洗液、口咽拭子和直肠拭子中可检测到病毒，粪便和尿液中偶尔也可检测到病毒 RNA。鹿鼠能够通过直接接触将 SARS-CoV-2 传播给初生的鹿鼠。

27. β-冠状病毒利用溶酶体细胞器进行释放

β-Coronaviruses use lysosomal organelles for cellular egress

链接：https://www.biorxiv.org/content/10.1101/2020.07.25.192310v1

编译者：王玮

美国的研究者利用影像学方法结合病毒特异性报告元件证明 β-冠状病毒利用溶酶体运输实现释放。该途径由 Arf-like small GTPase Arl8b 调节；病毒释放对生物合成分泌途径的抑制剂不敏感。冠状病毒感染导致溶酶体脱酸，溶酶体降解失活，抗原递呈途径中断。

28. SARS-CoV-2 刺突变异 D614G 更趋向于开放的构象状态

The SARS-CoV-2 Spike Variant D614G Favors an Open Conformational State

链接：https://www.biorxiv.org/content/10.1101/2020.07.26.219741v1

洛斯阿拉莫斯国家实验室的研究者们采用微秒级全原子模拟方法研究了 D614G 变异对 SARS-CoV-2 的刺突蛋白结构状态。作者们的研究表明 D614G 更趋向于开放的构象状态。

29. SARS-CoV-2 刺突变异 D614G 让 SARS-CoV-2 对抗体的中和性更敏感

D614G Spike Mutation Increases SARS CoV-2 Susceptibility to Neutralization

链接：https://www.medrxiv.org/content/10.1101/2020.07.22.20159905v1

美国杜克大学和滨州大学的研究者们发现刺突蛋白 D614G 的假病毒粒子对抗体的中和作用更为敏感。

30. COVID-19 和类风湿关节炎有共同的髓系病理和免疫消除通路

COVID-19 and Rheumatoid Arthritis share myeloid pathogenic and resolving pathways

链接：https://www.biorxiv.org/content/10.1101/2020.07.26.221572v1

作者们通过对肺部灌洗液里和类风湿关节炎滑液关节的巨噬细胞进行了单细胞转录组测序。单细胞转录组测序分析表明重症 COVID-19 和类风湿关节炎有共同的髓系病理通路。其中在体外实验中，地塞米松可以通过其中巨噬细胞 MerTK 通路来抑制组织里的炎症反应。

31. SARS-CoV-2 适应 BALB/c 小鼠，为测试疫苗的有效性提供动物模型

Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy

链接：science.sciencemag.org/content/early/2020/07/29/science.abc4730

复旦大学和北京微生物与流行病学研究所通过将病毒接种到 BALB/c 小鼠，继续接种到小鼠，再分离再接种，第六代病毒 MACSp6 既可以有效感染年老的 BALB/c 小鼠，也可以有效感染年轻小鼠，并且导致中度的肺炎以及炎症反应。

5 月 6 日的简报第 12 条报道过该工作的预印版。