



新型冠状病毒信息 简报

第 102 期（2021 年 4 月 24-30 日周报）

上海科技大学免疫化学研究所

生物学大数据平台和高通量筛选平台领衔编译制作

联系人：蒋立春 jianglch@shanghaitech.edu.cn

内容介绍

分类	标题名称
疫情播报	1. 2021年4月29日疫情
流行病学	2. SARS-CoV-2的再次流行：通过社区病毒监测进行检测
疾病检测	3. RCSMS的临床验证：一种快速、灵敏的CRISPR-Cas12a检测唾液中SARS-CoV-2的分子检测方法 4. 来自宿主转录的非典型crRNAs让Cas9可以同时检测多重RNA
疾病病理	5. 纵向分析显示SARS-CoV-2感染后持续的抗体反应和记忆B、T细胞的持久和广泛的免疫记忆 6. COVID-19急性后遗症的高维特征
疫苗研发	7. 公司下注可能更好抗击COVID-19的口服疫苗疗法
药物研发	8. 在叙利亚仓鼠模型中口服MK-4482抑制新型冠状病毒的复制
临床试验	9. 抗原特异性CD4+T细胞的快速诱导引导SARS-CoV-2 mRNA疫苗的体液和细胞免疫应答 10. 自然感染和mRNA疫苗接种引起的新型冠状病毒抗体应答的实质性差异
基础研究	11. 对SARS-CoV-2中和抗体及其对合胞体调节作用的结构生物学研究 12. 对SARS-CoV-2变异与SARS-CoV交叉中和的B细胞基因组学研究 13. SARS-CoV-2亚基因组RNA在时间序列临床样品中的动力学 14. miR-2392在驱动SARS-CoV-2感染中的隐藏作用
疾病模型	15. 食蟹猕猴暴露于SARS-CoV-2气溶胶中会导致比现有模型更严重的病理结果
其他	16. 4月27日快讯：Merck、Gilead采取行动扩大对COVID-19抗病毒药物的获取及其他相关；

免责声明：

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. 2021年4月29日疫情

数据来源：WHO

发布时间：2021年4月29日北京时间下午4点

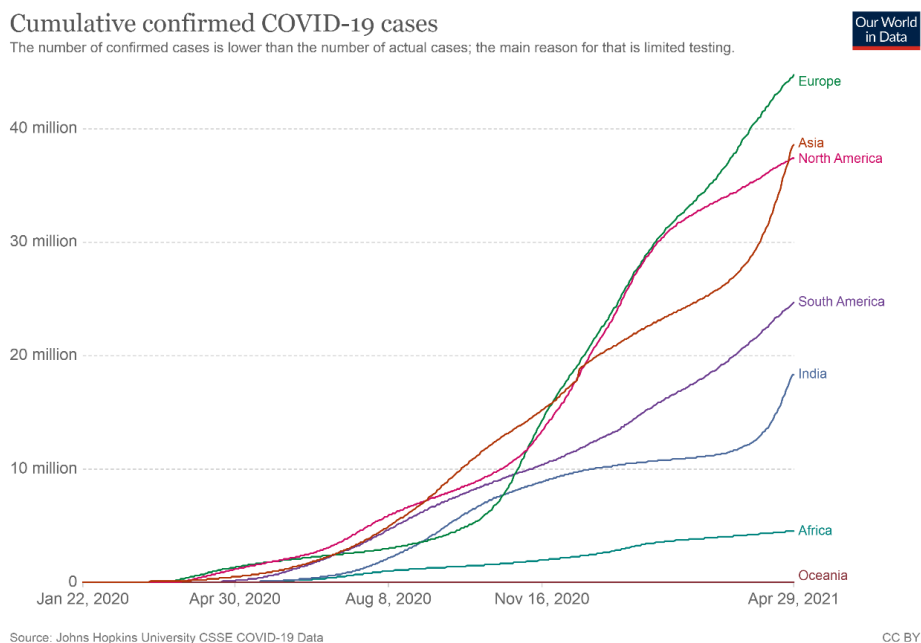
链接：<https://covid19.who.int/>

根据WHO提供的数据，2021年4月29日全球累计确诊新型冠状病毒病人**149,216,984**例，当日新增确诊**870,419**例，累计死亡**3,144,028**例，当日新增死亡**14,886**。全球至少接种一剂疫苗的人数为**514,666,913**。

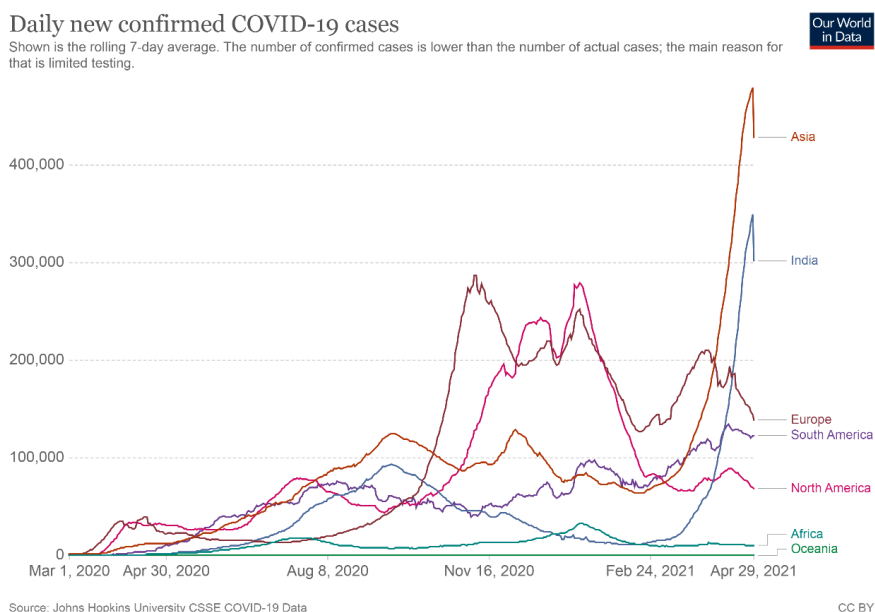
中国累计确诊103,562例，累计死亡4,857例，当日新增确诊33例，新增死亡0例。

截至2021年4月28日，31个省（自治区、直辖市）和新疆生产建设兵团累计报告接种新冠病毒疫苗24390.5万剂次

(<http://www.nhc.gov.cn/xcs/yqfkdt/202104/693f417183cb44bd8a774b2f1419c399.shtml>)



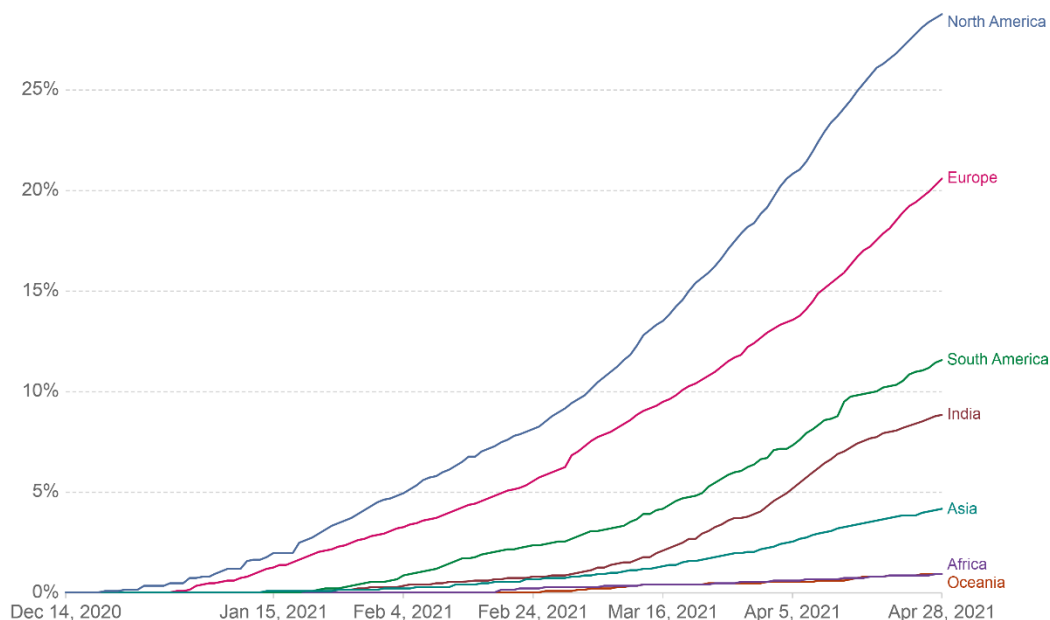
世界各洲确诊人数分布图 (https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases)



世界各洲每日新增确诊人数分布图 (https://ourworldindata.org/covid-cases?country=~OWID_WRL#what-is-the-daily-number-of-confirmed-cases)

Share of people who received at least one dose of COVID-19 vaccine

Share of the total population that received at least one vaccine dose. This may not equal the share that are fully vaccinated if the vaccine requires two doses.



Source: Official data collated by Our World in Data

CC BY

时间各洲接受至少一剂 COVID-19 疫苗的人群比例 (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 (4月29日, 来源: <http://2019ncov.chinacdc.cn/2019-nCoV/>)

2. SARS-CoV-2 的再次流行：通过社区病毒监测进行检测

Resurgence of SARS-CoV-2: detection by community viral surveillance

来源: science

发布时间: 2021-04-23

链接: <https://science.sciencemag.org/content/early/2021/04/22/science.abf0874>

第一作者: Steven Riley

通讯作者: Steven Riley, Paul Elliott

通讯作者单位: 英国伦敦帝国理工学院, 英国帝国理工学院医疗保健, 英国国立卫生研究所帝国生物医学研究中心

DOI 或 PUBMED ID: 10.1126/science.abf0874

编译者: 刘焕珍

中文摘要:

SARS-CoV-2 疫情的监测主要依靠病例报告, 而病例报告往往受到卫生服务绩效、检测可用性和检测寻求行为的影响。我们报告了英格兰的一项全国范围的典型社区进行监视项目, 包括从 2020 年 5 月至 9 月初, 对 594000 名接受 SARS-CoV-2 检测的个人进行自我管理拭子检测, 无论其症状如何。该流行病在 2020 年 5 月至 7 月期间有所下降, 但随后从 8 月中旬开始逐渐增加, 并在 2020 年 9 月初该流行病加速增加。与通过常规监测发现的病例相比, 我们在此报告的下降期更长, 年龄分布更年轻。对 SARS-CoV-2 进行有代表性的社区抽样, 即使在流行率较低的情况下, 也能大大提高对情况的认识, 并将其纳入公共卫生对策。

Abstract:

Surveillance of the SARS-CoV-2 epidemic has mainly relied on case reporting which is biased by health service performance, test availability and test-seeking behaviors. We report a community-wide national representative surveillance program in England involving self-administered swab results from 594,000 individuals tested for SARS-CoV-2, regardless of symptoms, from May to beginning of September 2020. The epidemic declined between May and July 2020 but then increased gradually from mid-August, accelerating into early September 2020 at the start of the second wave. When compared to cases detected through routine surveillance, we report here a longer period of decline and a younger age distribution. Representative community sampling for SARS-CoV-2 can substantially improve situational awareness and feed into the public health response even at low prevalence.

3. 来自宿主转录的非典型 crRNAs 让 Cas9 可以同时检测多重 RNA

Noncanonical crRNAs derived from host transcripts enable multiplexable RNA detection by Cas9

来源: science

发布时间: 2021-04-27

文章链接:

<https://science.sciencemag.org/content/early/2021/04/26/science.abe7106>

第一作者: Chunlei Jiao

通讯作者: Chase L. Beisel

通讯作者单位: 德国亥姆霍兹感染研究中心, 德国维尔茨堡大学

DOI: 10.1126/science.abe7106

编译者：张怡

中文摘要：

CRISPR-Cas 系统利用 CRISPR RNAs (crRNAs) 识别外来遗传物质。在 II 型系统中，反式激活 crRNA (tracrRNA) 与 crRNA 杂交，驱动 Cas9 对其进行加工和利用。在分析空肠弯曲杆菌的 Cas9-RNA 复合物时，研究人员发现 tracrRNA 与细胞 RNAs 杂交，形成“非典型” crRNAs，能够引导 Cas9 靶向 DNA。研究人员的发现启发了重编程 tracrRNAs 的工程，将任何感兴趣的 RNA 与以不同 Cas9 同源物为目标的 DNA 连接起来。这种能力成为了多重诊断平台 LEOPARD(利用工程 tracrRNAs 和目标 DNAs 进行 PARALLEL RNA 检测)的基础。LEOPARD 允许在一次测试中同时检测来自不同病毒的 RNAs，并在患者样本中以单碱基分辨率区分 SARS-CoV-2 及其 D614G 变体。

Abstract

CRISPR-Cas systems recognize foreign genetic material using CRISPR RNAs (crRNAs). In Type II systems, a trans-activating crRNA (tracrRNA) hybridizes to crRNAs to drive their processing and utilization by Cas9. While analyzing Cas9-RNA complexes from *Campylobacter jejuni*, we discovered tracrRNA hybridizing to cellular RNAs, leading to formation of “noncanonical” crRNAs capable of guiding DNA targeting by Cas9. Our discovery inspired the engineering of reprogrammed tracrRNAs that link the presence of any RNA-of-interest to DNA targeting with different Cas9 orthologs. This capability became the basis for a multiplexable diagnostic platform termed LEOPARD (Leveraging Engineered tracrRNAs and On-target DNAs for PARALLEL RNA Detection). LEOPARD allowed simultaneous detection of RNAs from different viruses in one test and distinguished SARS-CoV-2 and its D614G variant with single-base resolution in patient samples.

4. RCSMS 的临床验证：一种快速、灵敏的 CRISPR-Cas12a 检测唾液中 SARS-CoV-2 的分子检测方法

Clinical validation of RCSMS: a rapid and sensitive CRISPR-Cas12a test for the molecular detection of SARS-CoV-2 from saliva

来源：medRxiv

发布时间：2021-04-27

链接：<https://www.medrxiv.org/content/10.1101/2021.04.26.21256081v1>

第一作者：Joaquín Abugattás Núñez del Prado

通讯作者：Piere Rodríguez Aliaga⁷, y Edward Málaga Trillo¹

通讯作者单位：1 Facultad de Ciencias y Filosofía, Universidad Peruana Cayetano Heredia, Lima, Perú; 7 Department of Biology, Stanford University, California, USA

DOI 或 PUBMED ID:

编译者：宋张悦

中文摘要：

利用分子技术早期检测 SARS-CoV-2 对抗 COVID-19 至关重要。由于其高灵敏度和特异性，RT-qPCR 是该方法的“金标准”。然而，其技术要求、处理时间和较高的成本阻碍了其在拉丁美洲农村和社会经济贫困地区用于 COVID-19 大规模和及时的分子检测。CRISPR-Cas 技术的出现和快速发展促进了新的病原体检测方法的发展。最近，DETECTR——一个等温 RT-LAMP 扩增和 cas12a 介导的酶检测的结合——已在荷兰和美国成功验证，作为一个快速和低成本的

替代 RT-qPCR 从鼻咽拭子中检测 SARS-CoV-2 的方法。在这里，我们评估了 RCSMS (一种当地适应型 DETECTR) 的性能，以确定在利马两家医院 (Perú) 的 276 名患者的唾液样本中存在 SARS-CoV-2 (目前共有 350 份样本)。我们表明，低成本的热化学处理与 TCEP / EDTA 足以灭活病毒颗粒和细胞核酸酶唾液，可以不再需要提取病毒 RNA 与商业试剂盒，以及繁琐的鼻咽拭子过程和生物安全二级实验室分子分析的要求。我们的临床验证表明，RCSMS 在 40 分钟内每次反应可检测到 5 个病毒拷贝，相对于 RT-qPCR，现场灵敏度和特异性分别为 93.8% 和 99.0%。由于 CRISPR-Cas 生物传感器可以通过使用不同的引导 RNA 分子轻松地重新编程，RCSMS 有潜力快速适应于新的 SARS-CoV-2 变种的检测。值得注意的是，对其阴性和阳性预测值的估计表明，RCSMS 可以自信地部署在高流行率和低流行率的环境中。此外，我们的现场研究验证了横向流动条的使用，可以方便地可视化 SARS-CoV-2 的存在，这为在使用先进诊断实验室有限的环境中部署 RCSMS 作为“即时检测”铺平了道路。总之，RCSMS 是一种快速、高效和廉价的 RT-qPCR 替代品，可用于扩大中低收入国家的 COVID-19 检测能力。

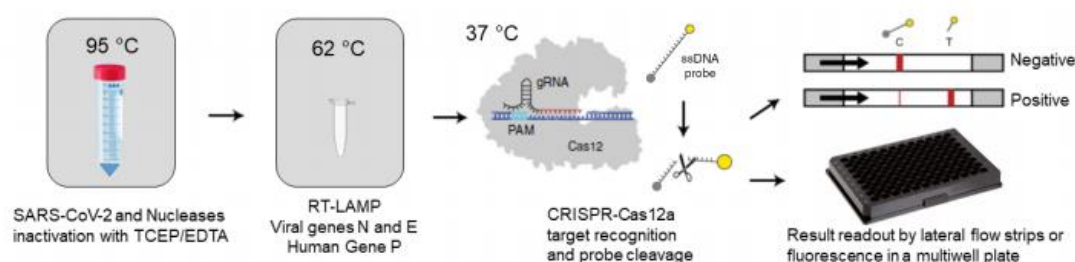


Figure 1. RCSMS detection workflow. Upon saliva treatment with TCEP/EDTA, 2 μ l of inactivated sample are added to a 10 μ l RT-LAMP reaction. A 2 μ l aliquot of the RT-LAMP product is then mixed with the RNP complex consisting of Cas12 and RNA guides. Recognition of viral target sequences by the RNP complex triggers the collateral activity of Cas12a, resulting in the cleavage of ssDNA reporter probes. For immunocromatographic (qualitative) readout, a lateral flow strip is then inserted into the CRISPR-Cas12a reaction tube or well. Within two minutes, uncleaved reporter molecules flow and accumulate into the control capture line of the strip (C band in the image), whereas cleaved reporter molecules flow towards the target capture line of the strip (T band in the image), (adapted from Broughton et al. (8) and Patchsung et al. (18)). For fluorescence (quantitative) readout, CRISPR-Cas12a reactions are recorded in real-time over 10 min using an automated plater reader; cleaved reporter molecules yield a bright fluorescent signal.

Abstract:

Early detection of SARS-CoV-2 using molecular techniques is paramount to the fight against COVID-19. Due to its high sensitivity and specificity, RT-qPCR is the “gold standard” method for this purpose. However, its technical requirements, processing time and elevated costs hamper its use towards massive and timely molecular testing for COVID-19 in rural and socioeconomically deprived areas of Latin America. The advent and rapid evolution of CRISPR-Cas technology has boosted the development of new pathogen detection methodologies. Recently, DETECTR –a combination of isothermal RT-LAMP amplification and Cas12a-mediated enzymatic detection–has been successfully validated in the Netherlands and the USA as a rapid and low-cost alternative to RT-qPCR for the detection of SARS-

CoV-2 from nasopharyngeal swabs. Here, we evaluated the performance of RCSMS, a locally adapted variant of DETECTR, to ascertain the presence of SARS-CoV-2 in saliva samples from 276 patients in two hospitals in Lima, Perú (current status over a total of 350 samples). We show that a low-cost thermochemical treatment with TCEP/EDTA is sufficient to inactivate viral particles and cellular nucleases in saliva, eliminating the need to extract viral RNA with commercial kits, as well as the cumbersome nasopharyngeal swab procedure and the requirement of biosafety level 2 laboratories for molecular analyses. Our clinical validation shows that RCSMS detects up to 5 viral copies per reaction in 40 min, with sensitivity and specificity of 93.8% and 99.0% in the field, respectively, relative to RT-qPCR. Since CRISPR-Cas biosensors can be easily reprogrammed by using different guide RNA molecules, RCSMS has the potential to be quickly adapted for the detection of new SARS-CoV-2 variants. Notably, estimation of its negative and positive predictive values suggests that RCSMS can be confidently deployed in both high and low prevalence settings. Furthermore, our field study validates the use of lateral flow strips to easily visualize the presence of SARS-CoV-2, which paves the way to deploy RCSMS as a “point of care” test in environments with limited access to state-of-the-art diagnostic laboratories. In sum, RCSMS is a fast, efficient and inexpensive alternative to RT-qPCR for expanding COVID-19 testing capacity in low- and middle-income countries.

5. 纵向分析显示 SARS-CoV-2 感染后持续的抗体反应和记忆 B、T 细胞的持久和广泛的免疫记忆

Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells

来源: medrxiv

发布时间: 2021-04-27

链接: <https://www.medrxiv.org/content/10.1101/2021.04.19.21255739v1>

第一作者: Kristen W. Cohen

通讯作者: M. Juliana McElrath

通讯作者单位: 1 Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, 98109, USA

7 Departments of Laboratory Medicine and Medicine, University of Washington, Seattle, WA 98195, USA

DOI 或 PUBMED ID:

编译者: 王玮

中文摘要:

结束 COVID-19 大流行需要对 SARS-CoV-2 的长期免疫。该研究评估了 254 名 COVID-19 患者从早期感染到 8 个月后的纵向变化, 发现主要的广泛免疫记忆反应。SARS-CoV-2 结合和中和抗体呈双相衰变, 半衰期延长 >200 天, 提示寿命更长的浆细胞的产生。此外, 还有持续的 IgG+记忆 B 细胞反应, 这预示着病毒再次暴露后抗体的迅速反应。多功能病毒特异性 CD4+ 和 CD8+T 细胞均有产生和维持, 估计半衰期为 200 天。有趣的是, CD4+T 细胞应答同样针对几种 SARS-CoV-2 蛋白, 而 CD8+T 细胞应答则优先针对核蛋白, 突出了将核蛋白作为潜在疫苗抗原的重要性。综上所述, 这些结果表明, 广泛和有效的免疫可能会长期存在于 COVID-

19 康复病人。

Abstract:

Ending the COVID-19 pandemic will require long-lived immunity to SARS-CoV-2. We evaluated 254 COVID-19 patients longitudinally from early infection and for eight months thereafter and found a predominant broad-based immune memory response. SARS-CoV-2 spike binding and neutralizing antibodies exhibited a bi-phasic decay with an extended half-life of >200 days suggesting the generation of longer-lived plasma cells. In addition, there was a sustained IgG+ memory B cell response, which bodes well for a rapid antibody response upon virus re-exposure. Polyfunctional virus-specific CD4+ and CD8+ T cells were also generated and maintained with an estimated half-life of 200 days. Interestingly, the CD4+ T cell response equally targeted several SARS-CoV-2 proteins, whereas the CD8+ T cell response preferentially targeted the nucleoprotein, highlighting the importance of including the nucleoprotein as a potential vaccine antigen. Taken together, these results suggest that broad and effective immunity may persist long-term in recovered COVID-19 patients.

6. COVID-19 急性后遗症的高维特征

High-dimensional characterization of post-acute sequelae of COVID-19

来源: Nature

发布时间: 2021-04-22

链接: <https://www.nature.com/articles/s41586-021-03553-9>

第一作者: Ziyad Al-Aly

通讯作者: Ziyad Al-Aly

通讯作者单位: Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, MO, USA

DOI 或 PUBMED ID: <https://doi.org/10.1038/s41586-021-03553-9>

编译者: 宋张悦

中文摘要:

我们对于 COVID-19 的急性临床表现特征了解甚多; 然而, 其急性后遗症尚未得到全面的阐述。在这里, 我们使用美国退伍军人事务部的国家卫生保健数据库系统全面地识别了 30 天 COVID-19 幸存者 6 个月的后遗症, 包括诊断、药物使用和实验室异常。我们的研究表明, 在患病的前 30 天, COVID-19 患者表现出更高的死亡风险和卫生资源利用。我们的高维方法确定了呼吸系统和其他一些疾病的后遗症, 包括神经系统和神经认知障碍、精神健康障碍、代谢障碍、心血管疾病、胃肠道疾病、不适、疲劳、肌肉骨骼疼痛和贫血。我们发现一些治疗药物的使用增加, 包括止痛药(阿片类药物和非阿片类药物)、抗抑郁药、抗焦虑药、抗高血压药和口服降糖药, 以及多器官系统实验室异常的证据。对一系列预先确定的结果的分析显示, 随着急性 COVID-19 感染(非住院、住院、重症监护)的严重程度, 风险梯度呈上升趋势。研究结果显示, 除了急性疾病之外, COVID-19 幸存者还会遭受严重的健康损失, 包括肺部和多个肺外器官系统。研究结果为卫生系统规划和制定多学科护理策略提供了路线图, 以减少 COVID-19 幸存者的慢性健康损失。

Abstract:

The acute clinical manifestations of COVID-19 are well characterized^{1,2}; however, its post-acute sequelae have not been comprehensively described. Here,

we use the national healthcare databases of the US Department of Veterans Affairs to systematically and comprehensively identify 6-month incident sequelae including diagnoses, medication use, and laboratory abnormalities in 30-day survivors of COVID-19. We show that beyond the first 30 days of illness, people with COVID-19 exhibit higher risk of death and health resource utilization. Our high dimensional approach identifies incident sequelae in the respiratory system and several others including nervous system and neurocognitive disorders, mental health disorders, metabolic disorders, cardiovascular disorders, gastrointestinal disorders, malaise, fatigue, musculoskeletal pain, and anemia. We show increased incident use of several therapeutics including pain medications (opioids and non-opioids), antidepressants, anxiolytics, antihypertensives, and oral hypoglycemics and evidence of laboratory abnormalities in multiple organ systems. Analysis of an array of pre-specified outcomes reveals a risk gradient that increased across severity of the acute COVID-19 infection (non-hospitalized, hospitalized, admitted to intensive care). The findings show that beyond the acute illness, substantial burden of health loss — spanning pulmonary and several extrapulmonary organ systems — is experienced by COVID-19 survivors. The results provide a roadmap to inform health system planning and development of multidisciplinary care strategies to reduce chronic health loss among COVID-19 survivors.

7. 公司下注可能更好抗击 COVID-19 的口服疫苗疗法

Companies Betting Oral Vaccines, Therapies Will Boost Fight Against COVID-19

来源: BioSpace

发布时间: 2020-04-28

链接: <https://www.biospace.com/article/companies-betting-oral-vaccines-therapies-will-boost-fight-against-covid-19/>

第一作者: Alex Keown

通讯作者: Alex Keown

通讯作者单位:

DOI 或 PUBMED ID:

编译者: 张鹏伟

中文摘要:

随着 COVID-19 疫苗继续在全球范围内推广, 不仅可以对抗病毒的初始毒株, 还可以对抗出现的众多变种, 研究人员正在继续开发下一代疗法和口服疫苗, 以克服某些疫苗效果缓慢的缺点。

本月早些时候, 位于海湾地区的瓦克斯进行了一项民意调查, 发现如果有口服方案, 大量不打算接种注射疫苗的美国人会改变主意。根据民意调查, 近 1900 万不想接种注射疫苗的美国人将服用口服剂量。

根据 Vaxart 的说法, 民意调查结果表明, 其他接种疫苗的人群中, 大约有一半来自少数民族, 而这些少数民族群体中没有接种疫苗的比例过高。此外, 70%的受访者说他们更喜欢吃药而不是打针。

Vaxart 是众多开发多种病毒口服疫苗的公司之一, 包括 COVID-19。今年 2 月, 该公司公布

的第一阶段初步数据显示,其口服疫苗候选 VXA-CoV2-1 耐受性良好,并产生免疫原性反应。虽然在第一阶段的临时信息中没有发现中和抗体,但该公司表示,其候选疫苗 VXA-CoV2-1 引发了针对 SARS-CoV2 抗原的多种免疫反应,包括对病毒刺蛋白的 CD8+细胞毒性 T 细胞反应。

Vaxart 并不是唯一一家致力于口服疫苗的公司。上个月,Oravax 医疗公司由 Oramed 和 Premas 生物技术公司合资成立,旨在开发针对 COVID-19 的口服疫苗。该公司的疫苗口服候选疫苗是一种病毒样颗粒(VLP)三抗原疫苗,针对病毒上的三种结构蛋白,这可能有利于对抗变异形式的新型冠状病毒。

Oramed 在 Oravax 的发布会上说,一项试验性动物研究显示,口服疫苗通过免疫球蛋白 G (IgG)和免疫球蛋白 A(IgA)促进全身免疫,免疫球蛋白 G 是血液和体液中最常见的抗体,可防止病毒感染。该公司预计在 2021 年第二季度启动一项临床研究。

ImmunityBio, Inc., 最近与南科威斯特合并,也在开发口服疫苗-片剂和舌下制剂。今年 3 月,该公司公布了第一阶段研究的中期安全数据。这些试验预计将在今年第二季度全部登记。两个阶段的 Ib 试验研究了皮下/舌下和口服 ImmunityBio 的 hAd5 T 细胞 COVID-19 候选疫苗制剂的组合。该公司表示,根据这些试验的结果,将确定给药途径和剂量的最佳组合,并进入第二/三阶段设计。

除了口服疫苗,公司也在开发口服疗法。默克公司和 Ridgeback 生物疗法公司正在开发莫努比拉韦,一种口服抗病毒药物,用于治疗 COVID-19。

本月早些时候,默克公司宣布,根据研究第二阶段的中期分析计划,将进入第二/三阶段 COVID-19 门诊患者迁出研究的第三阶段。然而,在住院患者中进行的 II/III 期入住研究的 III 期部分将不会继续进行,因为数据表明莫那比拉韦不太可能在该患者群体中显示出临床益处。

辉瑞公司在美国拥有三种已获授权的 COVID-19 疫苗之一,该公司也正在开发一种口服抗病毒药物。上个月,该公司启动了一项第一阶段的研究,对健康成人进行了评估,评估了一种 SARS-CoV2-3CL 蛋白酶抑制剂 PF-07321332。BioSpace 先前报道,这种药物在实验室对 SARS-CoV-2 以及其他冠状病毒的检测中显示出了强大的抗病毒活性。

该公司还正在调查静脉注射蛋白酶抑制剂 PF-07304814,目前正在对住院的 COVID-19 患者进行 Ib 期试验。

辉瑞首席执行官博拉(albertbourla)今早在接受 CNBC 采访时表示,这种口服制剂具有明显的优势,因为它不需要到医院就诊。

“这可能会改变游戏规则。这种化合物...是一种蛋白酶抑制剂。好的是,这也是第一个来自这类的分子,这是好的,因为你可以把它和其他类结合起来。另外,作用机制,是这样的,它不会受到突变的影响,特别是因为它不作用于尖峰,我们都知道,我们现在听到的所有突变都是在尖峰的蛋白质中看到的。这一个在那里不起作用,所以这让我们相信,这将是更有效地对付多种变种。所以,都是好消息。我们现在正在进行研究,夏天前后会有更多的消息,”布尔说,根据一份记录。

红山生物制药公司也在推进其口服治疗。本月早些时候,该公司表示,在第四次独立数据安全监测委员会(DSMB)安全审查之后,其口服奥帕加尼的 II/III 期研究收到了一致建议,建议继续进行。目前正在对需要住院治疗和补充氧气治疗的严重 COVID-19 肺炎患者进行 Opaganib 评估。第二阶段的数据显示,在 14 天后治疗结束时,opaganib 在降低需氧量方面表现出更为显著的改善。

除了口服疫苗和疗法外,一些公司还专注于鼻内治疗。BioSpace 在二月份对这些项目进行了一次综述。

Abstract:

As COVID-19 vaccines continue to roll out across the globe to combat not only the initial strain of the virus but the numerous variants that have popped up, researchers are continuing to develop next-generation therapeutics and oral vaccines that could overcome some vaccine hesitancy.

Earlier this month, Bay Area-based Vaxart conducted a poll that found a significant number of Americans who did not intend to receive an injectable vaccine would change their mind if an oral option were available. According to the poll, nearly 19 million Americans who did not want to receive an injectable vaccine would take an oral dose.

Poll results suggest that about half of the other vaccinated groups would be drawn from minority populations, communities that have disproportionately not been vaccinated, according to Vaxart. Additionally, 70% of those polled said they prefer a pill over an injection.

Vaxart is one of the numerous companies developing an oral vaccine for multiple viruses, including COVID-19. In February, the company released preliminary Phase I data that showed its oral vaccine candidate VXA-CoV2-1 was well-tolerated and generated an immunogenic response. While neutralizing antibodies were not seen in the interim Phase I information, the company said its vaccine candidate VXA-CoV2-1 triggered multiple immune responses against SARS-CoV-2 antigens, including CD8+ cytotoxic T-cell response to the viral Spike (S) protein.

Vaxart isn't the only company aiming for an oral vaccine. Oravax Medical was formed in a joint venture by Oramed and Premas Biotech last month to develop oral vaccines against COVID-19. The company's vaccine oral candidate is a virus-like particle (VLP) triple antigen vaccine that targets three structural proteins on the virus, which could be beneficial against mutated forms of the novel coronavirus.

A pilot animal study showed the oral vaccine promoted systemic immunity through Immunoglobulin G (IgG), the most common antibody in blood and bodily fluids that protects against viral infections, and Immunoglobulin A (IgA), Oramed said at the launch of Oravax. The company anticipates initiating a clinical study during the second quarter of 2021.

ImmunityBio, Inc., which recently merged with NantKwest, is also developing oral vaccines - a tablet and a sublingual formulation. In March, the company announced positive interim safety data for its Phase I study. The trials are expected to be fully enrolled in the second quarter of this year.

The two Phase Ib trials study a combination of subcutaneous/ sublingual and oral formulations of ImmunityBio's hAd5 T-cell COVID-19 vaccine candidate. Based on the findings of these trials, the optimal combination of administration route and dose will be determined and entered into the Phase II/III design, the company said.

In addition to oral vaccines, companies are developing oral therapeutics as well. Merck and Ridgeback Biotherapeutics are developing molnupiravir, an orally available antiviral candidate for the treatment of COVID-19.

Earlier this month, Merck announced it was moving into the Phase III portion of

the Phase II/III MOVE-OUT study in outpatient COVID-19 patients based on a planned interim analysis from the Phase II part of the study. However, the Phase III portion of the Phase II/III MOVE-IN study in hospitalized patients will not proceed based on data that suggests molnupiravir is unlikely to demonstrate a clinical benefit in that patient population.

Pfizer, which has one of three authorized COVID-19 vaccines in the United States, is also developing an oral therapeutic against the virus. Last month, the company launched a Phase I study assessing PF-07321332, a SARS-CoV2-3CL protease inhibitor, in healthy adults. The drug has shown potent antiviral activity in laboratory assays against SARS-CoV-2, as well as against other coronaviruses, BioSpace previously reported.

The company is also investigating an intravenously administered protease inhibitor, PF-07304814, currently in a Phase Ib trial in hospitalized COVID-19 patients.

In an interview with CNBC this morning, Pfizer Chief Executive Officer Albert Bourla said the oral formulation has distinct advantages because it doesn't require a hospital visit to be administered.

“That could be a game changer. The compound... is a protease inhibitor. The good thing is that this is also the first molecule that is coming from this type of class, this is good thing because you can combine it with other classes. Also, the mechanism of action, it is such that it's not expected to be subject to mutations, particularly because it's not acting on the spike, as we all know, all the mutations that we are hearing right now are seeing this in the proteins of the spike. This one doesn't work there so that allows us to believe that will be way more effective against the multiple variants. So, all good news. We are now progressing the studies and we will have more news around summer,” Bourla said, according to a transcript.

RedHill Biopharma is also moving forward with its oral therapeutic. Earlier this month, the company said its Phase II/III study of orally-administered opaganib received a unanimous recommendation to continue, following a fourth independent Data Safety Monitoring Board (DSMB) safety review. Opaganib is being assessed in patients with severe COVID-19 pneumonia requiring hospitalization and treatment with supplemental oxygen. Phase II data showed opaganib demonstrated more significant improvement in reducing oxygen requirement by the end of treatment after 14 days.

In addition to oral vaccines and therapeutics, some companies are focused on an intranasal treatment. BioSpace examined a roundup of those programs in February.

8. 在叙利亚仓鼠模型中口服 MK-4482 抑制新型冠状病毒的复制

Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model

来源: Nature communications

发布时间: 2021-04-16

链接: <https://pubmed.ncbi.nlm.nih.gov/33863887/>

第一作者: Kyle Rosenke

通讯作者: Heinz Feldmann

通讯作者单位: Laboratory of Virology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT, USA

DOI 或 PUBMED ID: 10.1038/s41467-021-22580-8.

编译者: 孔娟

中文摘要:

在世界许多地区, COVID-19 大流行病的进展有增无减。在高风险暴露后口服使用的有效抗 SARS-CoV-2 抗病毒药, 对控制 COVID-19 大流行具有实质性的益处。在这里, 我们表明, 口服给药的核苷类似物 MK-4482 在叙利亚仓鼠模型中抑制 SARS-CoV-2 的复制。在高风险暴露模型中, 在感染前 12 h 或感染后 12 h 给药时, 在动物中观察到 MK-4482 对 SARS-CoV-2 复制的抑制作用。这些数据支持 MK-4482 在控制高风险暴露后的人群中控制 SARS-CoV-2 感染以及治疗 COVID-19 患者的潜在效用。

Abstract:

The COVID-19 pandemic progresses unabated in many regions of the world. An effective antiviral against SARS-CoV-2 that could be administered orally for use following high-risk exposure would be of substantial benefit in controlling the COVID-19 pandemic. Herein, we show that MK-4482, an orally administered nucleoside analog, inhibits SARS-CoV-2 replication in the Syrian hamster model. The inhibitory effect of MK-4482 on SARS-CoV-2 replication is observed in animals when the drug is administered either beginning 12 h before or 12 h following infection in a high-risk exposure model. These data support the potential utility of MK-4482 to control SARS-CoV-2 infection in humans following high-risk exposure as well as for treatment of COVID-19 patients.

9. 抗原特异性 CD4+T 细胞的快速诱导引导 SARS-CoV-2 mRNA 疫苗的体液和细胞免疫应答

Rapid induction of antigen-specific CD4+ T cells guides coordinated humoral and cellular immune responses to SARS-CoV-2 mRNA vaccination

来源: BioRxiv

发布时间: 2020-04-21

链接: <https://www.biorxiv.org/content/10.1101/2021.04.21.440862v1.full.pdf>

第一作者: Mark M. Painter

通讯作者: E. John Wherry

通讯作者单位: Institute for Immunology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

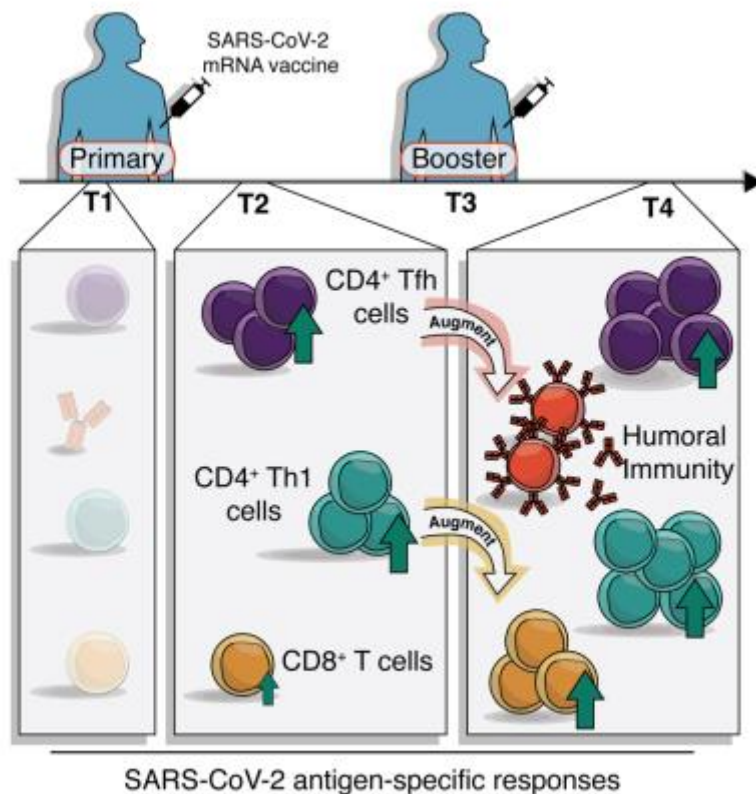
DOI 或 PUBMED ID: <https://doi.org/10.1101/2021.04.21.440862> doi:

编译者: 张鹏伟

中文摘要:

SARS-CoV-2 mRNA 疫苗已显示出显著的临床疗效, 但 T 细胞启动的性质和动力学仍存在疑问。我们在 mRNA 疫苗接种后对健康个体进行纵向抗原特异性 T 细胞分析。在第一次接种疫苗后, 所有受试者的疫苗都能诱导快速接近最大的抗原特异性 CD4+T 细胞反应。CD8+T 细胞反应在第一次和第二次给药后逐渐发展, 并且是可变的。疫苗诱导的 T 细胞具有中枢记忆特征, 包括 Tfh 和 Th1 亚群, 与自然感染相似。第一次给药后的 Th1 和 Tfh 反应分别预测增强后 CD8+T 细胞和中和抗体水平。对 26 个抗原特异性 T 细胞和体液反应的综合分析揭示了疫

苗免疫应答的协同特征。最后，加强免疫提高了 SARS-CoV-2na 中 CD4+和 CD8+T 细胞的应答 i 在受试者中，第二剂量疫苗对 SARS-CoV-2 恢复个体的 T 细胞反应几乎没有影响。因此，纵向分析显示，T 细胞对 mRNA 疫苗接种反应强烈，并强调了抗原特异性 CD4+T 细胞的早期诱导。



Abstract:

The SARS-CoV-2 mRNA vaccines have shown remarkable clinical efficacy, but questions remain about the nature and kinetics of T cell priming. We performed longitudinal antigen-specific T cell analyses in healthy individuals following mRNA vaccination. Vaccination induced rapid nearmaximal antigen-specific CD4⁺ T cell responses in all subjects after the first vaccine dose. CD8⁺ T cell responses developed gradually after the first and second dose and were variable. Vaccine-induced T cells had central memory characteristics and included both Tfh and Th1 subsets, similar to natural infection. Th1 and Tfh responses following the first dose predicted post-boost CD8⁺ T cell and neutralizing antibody levels, respectively. Integrated analysis of 26 antigen-specific T cell and humoral responses revealed coordinated features of the immune response to vaccination. Lastly, whereas booster vaccination improved CD4⁺ and CD8⁺ T cell responses in SARS-CoV-2 naïve subjects, the second vaccine dose had little effect on T cell responses in SARS-CoV-2 recovered individuals. Thus, longitudinal analysis revealed robust T cell responses to mRNA vaccination and highlighted early induction of antigen-specific CD4⁺ T cells.

10. 自然感染和 mRNA 疫苗接种引起的新型冠状病毒抗体应答的实质性差异

Substantial Differences in SARS-CoV-2 Antibody Responses Elicited by Natural Infection and mRNA Vaccination

来源: biorxiv

发布时间: 2021-04-19

链接: <https://www.biorxiv.org/content/10.1101/2021.04.15.440089v2>

第一作者: Rafael Assis

通讯作者: Rafael Assis

通讯作者单位: University of California Irvine, School of Medicine and the Vaccine R&D Center

DOI 或 PUBMED ID: preprint

编译者: 孔娟

中文摘要:

研究者分析了两项正在进行的血清学调查数据,用于比较对新型冠状病毒自然感染和疫苗接种的抗体应答。一项来自加利福尼亚大学欧文医学中心对卫生保健工作者的队列研究,另一项开展于圣安娜市的社区研究。此外,研究者在多个时间点连续检测了 9 名志愿者,以更详细地分析疫苗诱导抗体应答的时间过程。分别对 1060 名卫生保健工作者(HCW)在疫苗接种前 2020 年 5 月和 12 月,采集了手指血样本。随后采集了 2021 年 1 月、2 月和 3 月接种疫苗期间的手指血样本。使用冠状病毒抗原微阵列(COVAM)探测并分析了总计 8,729 份手指血样本中的 IgG 和 IgM 抗体。微阵列包含 10 种新型冠状病毒抗原(包括核蛋白(NP)和尖峰蛋白的几个不同片段),以及 4 种 SARS、3 种 MERS、12 种常见 CoV 和 8 种流感抗原。根据基于随机森林的预测算法,在 5 月至 12 月疫苗推广前,我们观察到 HCW 队列中的血清阳性率从 4.5% 上升至 13%。2020 年 12 月 16 日,启动了 mRNA 疫苗强化接种运动,在 3 周内为 6,724 名医务人员接种了疫苗。2021 年 1 月最后一周采集的 HCW 标本观察到的血清阳性率升至 78%,到 2 月最后一周达到 93%,并在 3 月达到 98% 血清阳性的峰值。自然暴露诱导的抗体特征与 mRNA 疫苗接种后诱导的特征不同。mRNA 疫苗诱导了针对新型冠状病毒 S 蛋白的受体结合结构域(RBD)的抗体(Ab)反应性水平升高,以及针对 SARS 和 MERS RBD 结构域的交叉反应性应答。核衣壳蛋白(NP)是自然暴露诱导的免疫显性抗原,对疫苗接种样本无反应,可用作过去暴露的生物标志物。结果表明,自然暴露的个体接种疫苗后对 S 蛋白的反应比以前没有暴露的个体具有更高的水平。以大约每周一次的间隔从 9 只个体中采集的纵向标本显示出对 mRNA 疫苗的应答发生了变化,其中一些标本显示出对第一剂(主要剂量)的强烈应答,而其他标本则需要随后的一剂(加强剂量)才能达到较高的抗 SARS-CoV-2 水平。通过连续稀释样本测定的抗体滴度用于准确比较这些样本中的抗体水平。增强后的 mRNA 疫苗比从自然暴露中恢复的供体恢复期血浆具有更高的 Ab 滴度(高达 10 倍)。本研究的结果例证了在其他机构中进行的类似 mRNA 大规模疫苗接种活动的时间过程和预期结果。

Abstract:

We analyzed data from two ongoing serologic surveys, a longitudinal cohort of health care workers (HCW) from the University of California Irvine Medical Center (Orange County, CA, USA), collected from May and December 2020 through March 2021, and a cross sectional county-wide study in July 2020 (act0C; Orange County, CA) and a more focused community study in the city of Santa Ana (Santa Ana Cares; Orange County, CA, USA), collected in December 2020 - in order to compare the antibody responses to SARS-CoV-2 natural infection and vaccination. In addition, we serially tested 9 volunteers at multiple time points to analyze the time

course of vaccine-induced antibody response in more detail. In May 2020, 1060 HCW were enrolled and had finger stick samples collected. Finger stick samples were again collected in December 2020, before vaccination, as well as January, February and March 2021 during vaccination campaign. A total of 8,729 finger stick blood specimens were probed and analyzed for IgG and IgM antibodies using a coronavirus antigen microarray (COVAM). The microarray contained 10 SARS-CoV-2 antigens including nucleocapsid protein (NP) and several varying fragments of the spike protein, as well as 4 SARS, 3 MERS, 12 Common CoV, and 8 Influenza antigens. Based on a random forest based prediction algorithm, between May and December, prior to vaccine rollout, we observed that seropositivity in the HCW cohort increased from 4.5% to 13%. An intensive vaccination campaign with mRNA vaccines was initiated on December 16, 2020 and 6,724 healthcare workers were vaccinated within 3 weeks. The observed seropositivity of the HCW specimens taken in the last week of January 2021 jumped to 78%, and by the last week in February it reached 93%, and peaked at 98% seropositive in March. The antibody profile induced by natural exposure differed from the profile induced after mRNA vaccination. Messenger RNA vaccines induced elevated antibody (Ab) reactivity levels against the Receptor Binding Domain (RBD) domain of SARS-CoV-2 spike, and cross-reactive responses against SARS and MERS RBD domains. Nucleocapsid protein (NP), which is an immunodominant antigen induced after natural exposure, is not present in the vaccine and can be used as a biomarker of past exposure. The results show that naturally-exposed individuals mount a stronger anti-spike response. upon vaccination than individuals that were not previously exposed. Longitudinal specimens taken at approximately weekly intervals from 9 individuals show variation in the response to the mRNA vaccine, with some showing a vigorous response to the first dose (prime) and others requiring a subsequent dose (boost) to reach high anti-SARSCoV-2 levels. Antibody titers determined by serial dilution of the specimens were used to accurately compare antibody levels in these samples. mRNA vaccinees after the boost have higher Ab titers (up to 10 times higher) than convalescent plasmas from donors who recovered from natural infection. The results of this study exemplify the time course and outcomes expected from similar mRNA mass vaccination campaigns conducted in other institutions.

11. 对 SARS-CoV-2 中和抗体及其对合胞体调节作用的结构生物学研究

Structural insight into SARS-CoV-2 neutralizing antibodies and modulation of syncytia

来源: Cell

发布时间: 2021-04-23

链接: [https://www.cell.com/cell/fulltext/S0092-8674\(21\)00536-5#%20](https://www.cell.com/cell/fulltext/S0092-8674(21)00536-5#%20)

第一作者: Daniel Asarnow, Bei Wang

通讯作者: Aashish Manglik³, Yifan Cheng³, Charles S. Craik³, Cheng-I Wang²

通讯作者单位:

² Singapore Immunology Network, Agency for Science, Technology and Research

(A*STAR), 8A Biomedical Grove, Immunos, Singapore 138648, Singapore.

3 QBI COVID-19 Research Group (QCRG), San Francisco, CA, USA

DOI 或 PUBMED ID: 10.1016/j.cell.2021.04.033

编译者: 宋珂

亮点:

- 中和抗体的亲和力并不总与其抗病毒能力正相关
- 受体阻断抗体即可以抑制、也能够促进合胞体的形成
- 利用 Cryo-EM 技术, 发现了一种通过限制融合前的 Spike 蛋白来抑制合胞体形成的抗体
- 另一种能够充当变构因子的抗体可以促进合胞体的形成

中文摘要:

SARS-CoV-2 病毒的 Spike 蛋白与宿主受体血管紧张素转化酶 2 (ACE2) 的结合引发了病毒的感染过程, 随后病毒与宿主的膜发生融合。尽管阻断这种相互作用的抗体已被紧急用作早期 COVID-19 的治疗药物, 但抗体中和能力的确切决定因素仍不明确。本文中, 作者发现了一系列能有效阻断 ACE2 与病毒结合的抗体, 但这些抗体对活病毒的中和功效差异明显。更令人惊讶的是, 这些中和抗体表现出即可以抑制、也能够促进 Spike 蛋白介导的膜融合, 并形成和合胞体的作用。形成合胞体的过程与 COVID-19 患者的慢性组织损伤有关。利用 Cryo-EM 技术, 作者解析出了多个 Spike 蛋白-抗体复合物的结构, 揭示出多个独特的结合模式。这些结合模式中, 有些能够阻断 ACE2 与病毒的结合, 有些可以改变由 ACE2 结合触发的 Spike 蛋白的构象循环。作者的结果表明, 不同的 Spike 蛋白构象稳定性的差异, 起到了调节 Spike 蛋白介导的膜融合过程的作用, 对 COVID-19 的病理学和免疫学认识具有深远的影响。

结构数据:

- Spike:5A6 complex I has accession codes PDB: **7KQB** and **EMD-22993**.
- The focused refinement of Spike:5A6 using a mask including 5A6 and two RBDs has accession codes PDB: **7M71** and **EMD-23707**. Maps for Spike:5A6 complex II and III are provided as additional maps in the same entry.
- Spike:3D11 has accession codes PDB: **7KQE** and **EMD-22997**.
- The focused refinement of Spike:3D11 using a mask 20 including 3D11 and one RBD has accession codes PDB: **7M7B** and **EMD-23709**.
- Cryo-EM maps only were deposited for Spike protein alone, with accession **EMD-22995**, as well as for Spike:2H4 complexes I-III, accession cod **EMD-22994**.

Highlights:

- The affinity of neutralizing antibodies does not always predict antiviral potency
- Receptor blocking antibodies can either inhibit or enhance syncytia formation
- Cryo-EM reveals one antibody inhibits syncytia by trapping the pre-fusion Spike
- Another antibody acts as an allosteric effector that promotes syncytia formation

Summary:

Infection by SARS-CoV-2 is initiated by binding of viral Spike protein to host receptor angiotensin-converting enzyme 2 (ACE2), followed by fusion of viral and host membranes. While antibodies that block this interaction are in emergency use as early COVID-19 therapies, precise determinants of neutralization potency remain unknown. We discovered a series of antibodies that all potently block

ACE2 binding, yet exhibit divergent neutralization efficacy against live virus. Strikingly, these neutralizing antibodies can either inhibit or enhance Spike-mediated membrane fusion and formation of syncytia, which are associated with chronic tissue damage in COVID-19 patients. Multiple cryogenic electron microscopy structures of Spike-antibody complexes reveal distinct binding modes that not only block ACE2 binding, but also alter the Spike protein conformational cycle triggered by ACE2 binding. We show that stabilization of different Spike conformations leads to modulation of Spike-mediated membrane fusion, with profound implications in COVID-19 pathology and immunity.

12. 对 SARS-CoV-2 变异与 SARS-CoV 交叉中和的 B 细胞基因组学研究

B cell genomics behind cross-neutralization of SARS-CoV-2 variants and SARS-CoV
来源: cell

发布时间: 2021-04-23

链接: [https://www.cell.com/cell/fulltext/S0092-8674\(21\)00535-3](https://www.cell.com/cell/fulltext/S0092-8674(21)00535-3)

第一作者: Johannes F. Scheid

通讯作者: Ramnik J. Xavier

通讯作者单位: 1 Broad Institute of the Massachusetts Institute of Technology and Harvard University, Cambridge, MA 02142.

2 Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114.

3 Center for Computational and Integrative Biology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114.

7 Klarman Cell Observatory, Broad Institute of MIT and Harvard, Cambridge, MA 02142.

12 Department of Molecular Biology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114

DOI 或 PUBMED ID:

编译者: 王玮

中文摘要:

单克隆抗体 (mAbs) 是对抗 SARS-CoV-2 及其变种的疫苗和治疗设计中的一个热点。该研究将 B 细胞分类与单细胞 VDJ、RNA-seq 和 mAb 结构相结合来表征 B 细胞对 SARS-CoV-2 的应答。发现 SARS-CoV-2 特异性 BCR 由转录上不同的 B 细胞群组成, 其中产生潜在中和抗体 (nAbs) 的细胞分布在两个类似记忆和活化 B 细胞的簇中。从这两个簇中选择的与 SARS-CoV-2 刺突蛋白三聚体复合的 nAbs 的冷冻电子显微镜结构显示对各种受体结合域 (RBD) 表位的识别。其中一种单克隆抗体 BG10-19 将尖峰三聚体锁定在一个封闭的构象中, 从而有效地中和 SARS-CoV-2、最近出现的突变体 B. 1. 1. 7 和 B. 1. 351 以及 SARS-CoV, 并与异源 RBDs 交叉反应。总之, 该研究的结果描述了 SARS-CoV-2 特异性 B 细胞之间的转录差异, 并揭示了交叉中和 Ab 靶点, 这将为免疫原和抗冠状病毒的治疗设计提供信息。

Abstract:

Monoclonal antibodies (mAbs) are a focus in vaccine and therapeutic design to counteract SARS-CoV-2 and its variants. Here, we combined B cell sorting with single-cell VDJ and RNA-seq and mAb structures to characterize B cell responses against SARS-CoV-2. We show that the SARS-CoV-2-specific B cell repertoire

consists of transcriptionally distinct B cell populations with cells producing potently neutralizing antibodies (nAbs) localized in two clusters that resemble memory and activated B cells. Cryo-electron microscopy structures of selected nAbs from these two clusters complexed with SARS-CoV-2 spike trimers show recognition of various receptor-binding domain (RBD) epitopes. One of these mAbs, BG10-19, locks the spike trimer in a closed conformation to potently neutralize SARS-CoV-2, the recently arising mutants B.1.1.7 and B.1.351, and SARS-CoV and cross-reacts with heterologous RBDs. Together, our results characterize transcriptional differences among SARS-CoV-2-specific B cells and uncover cross-neutralizing Ab targets that will inform immunogen and therapeutic design against coronaviruses.

13. SARS-CoV-2 亚基因组 RNA 在时间序列临床样品中的动力学

SARS-CoV-2 subgenomic RNA kinetics in longitudinal clinical samples

来源: medrxiv

发布时间: 2021-04-27

链接: <https://www.medrxiv.org/content/10.1101/2021.04.26.21256131v1>

第一作者: Renu Verma

通讯作者: Jason R. Andrews

通讯作者单位: Stanford University School of Medicine, Stanford, CA, USA

DOI 或 PUBMED ID: preprint

编译者: 蒋立春

中文摘要:

背景 基于 COVID-19 的病人临床恢复后仍然可以检测到病毒 RNA。病毒 RNA 亚基因组被报道可能是能表征 SARS-CoV-2 活性的分子标记 (这样, 不需要高安全级别的实验室进行分离培养, 并且减少假阴性)。但是和基因组 RNA 比起来, 关于 RNA 亚基因组在临床样品中的时序动力学数据很少。

方法 我们对来自于 205 个 COVID-19 病人的 536 个样品进行了分析, 包括 Peginterferon Lambda-1a 治疗的门诊病人 (Lamba; n=177) 以及 favipiravir (n=359)。Lamba 组在 3 个时间点进行了采样 (第 1, 4, 6 天) 进行鼻拭子采集, favipiravir 组在 (第 1, 5, 10 天) 进行鼻拭子采样。并进行 N 基因的基因组 RNA 和亚基因组 RNA 进行 RT-qPCR 检测。为了研究其在体外的衰减动力学, 我们测定了感染 SARS-CoV-2 的 A549ACE2+ 细胞在进行瑞德西韦或者 DMSO 对照处理后的基因组 RNA 和亚基因组 RNA 水平。

结果 在 Lambda 试验组的第 6 天, 以及 favipiravir 试验的第 10 天, 亚基因组 RNA 分别在 51.6% (32/62) 的 Lambda 组样品 and 49.5% (51/106) 的 favipiravir 组样品中可以检测到。

基因组 RNA 和亚基因组 RNA 的 Ct 值高度线性相关 (Pearson's r 为 0.87), 在 Lambda 的变化速率也差不多 (均为 1.36 cycle/天对 1.36 cycle/天, p 值为 0.97) 或者 favipiravir (1.03 cycle/天对 0.94 cycles/天; p=0.26)。对于症状出现 15-21 天之后采集的样品, 48.1% (40/83) 的受试者中可以检测到亚基因组 RNA。在感染 SARS-CoV-2 并采用瑞德西韦处理过的 A549ACE2+ 细胞, 基因组 RNA 和亚基因组 RNA 的 Ct 增加速率没有差异。

结论 在临床样品以及体外系统中, 亚基因组 RNA 和基因组 RNA 高度相关, 没有不同的衰减模式, 不能支持它作为表征一个病毒活性的分子标志物。

总结 我们在鼻拭子中比较长时间可以检测到亚基因组 RNA; 在时序追踪的鼻拭子以及瑞德

西韦处理过的感染 SARS-CoV-2 的 A549ACE2+ 细胞中，亚基因组 RNA 和基因组 RNA 表现中相同的衰减速率。这些数据一起说明 SARS-CoV-2 的亚基因组稳定性和基因组 RNA 稳定性可比，所以对亚基因组的检测并不是检测到活跃复制病毒更准确的指标。

Abstract:

Background Given the persistence of viral RNA in clinically recovered COVID-19 patients, subgenomic RNAs (sgRNA) have been reported as potential molecular viability markers for SARS-CoV-2. However, few data are available on their longitudinal kinetics, compared with genomic RNA (gRNA), in clinical samples.

Methods We analyzed 536 samples from 205 patients with COVID-19 from placebo-controlled, outpatient trials of Peginterferon Lambda-1a (Lambda; n=177) and favipiravir (n=359). Nasal swabs were collected at three time points in the Lambda (Day 1, 4 and 6) and favipiravir (Day 1, 5, and 10) trials. N-gene gRNA and sgRNA were quantified by RT-qPCR. To investigate the decay kinetics *in vitro*, we measured gRNA and sgRNA in A549ACE2+ cells infected with SARS-CoV-2, following treatment with remdesivir or DMSO control.

Results At six days in the Lambda trial and ten days in the favipiravir trial, sgRNA remained detectable in 51.6% (32/62) and 49.5% (51/106) of the samples, respectively.

Cycle threshold (Ct) values for gRNA and sgRNA were highly linearly correlated (Pearson's $r=0.87$) and the rate of increase did not differ significantly in Lambda (1.36 cycles/day vs 1.36 cycles/day; $p = 0.97$) or favipiravir (1.03 cycles/day vs 0.94 cycles/day; $p=0.26$) trials.

From samples collected 15–21 days after symptom onset, sgRNA was detectable in 48.1% (40/83) of participants. In SARS-CoV-2 infected A549ACE2+ cells treated with remdesivir, the rate of Ct increase did not differ between gRNA and sgRNA.

Conclusions In clinical samples and *in vitro*, sgRNA was highly correlated with gRNA and did not demonstrate different decay patterns to support its application as a viability marker.

Summary We observed prolonged detection of subgenomic RNA in nasal swabs and equivalent decay rates to genomic RNA in both longitudinal nasal swabs and in remdesivir-treated A549ACE2+ cells infected with SARS-CoV-2. Taken together, these findings suggest that subgenomic RNA from SARS-CoV-2 is comparably stable to genomic RNA and that its detection is therefore not a more reliable indicator of replicating virus.

14. miR-2392 在驱动 SARS-CoV-2 感染中的隐藏作用

The Great Deceiver miR-2392's Hidden Role in Driving SARS-CoV-2 Infection

来源: biorxiv

发布时间: 2021.04.26

文章链接: <https://www.biorxiv.org/content/10.1101/2021.04.23.441024v3>

第一作者: J. Tyson McDonald

通讯作者: Afshin Beheshti

通讯作者单位: COVID-19 国际研究团队, 美国哥伦比亚大学放射研究中心, 美国亚特兰大莫尔豪斯医学院

doi: <https://doi.org/10.1101/2021.04.23.441024>

编译者: 张怡

中文摘要:

MicroRNAs (miRNAs) 是参与转录后基因调控的小的非编码 RNAs, 对许多疾病有重大影响, 并为抗病毒治疗提供了途径。根据患者转录组学数据, 研究人员们发现了一个循环 miRNA, miR-2392, 在宿主感染期间直接参与 SARS-CoV-2 机制。具体而言, 研究人员们发现 miR-2392 在推动下游线粒体基因表达抑制、增加炎症、糖酵解和缺氧以及促进与 COVID-19 感染相关的许多症状方面发挥了关键作用。研究人员证实, miR-2392 存在于 COVID-19 患者的血液和尿液中, 但在 COVID-19 阴性患者中未检测到。这些发现为开发一种新型、微创的 COVID-19 检测方法提供了可能。最后, 利用体外人和体内仓鼠模型, 研究人员开发了一种基于 miRNA 的靶向 miR-2392 的新型抗病毒治疗方法, 可显著降低 SARS-CoV-2 的活性, 并可能抑制宿主中的 COVID-19 疾病状态。

Abstract

MicroRNAs (miRNAs) are small non-coding RNAs involved in post-transcriptional gene regulation that have a major impact on many diseases and provides an exciting avenue towards antiviral therapeutics. From patient transcriptomic data, we have discovered a circulating miRNA, miR-2392, that is directly involved with SARS-CoV-2 machinery during host infection. Specifically, we found that miR-2392 was key in driving downstream suppression of mitochondrial gene expression, increasing inflammation, glycolysis, and hypoxia as well as promoting many symptoms associated with COVID-19 infection. We demonstrate miR-2392 is present in the blood and urine of COVID-19 patients tested, but not detected in COVID-19 negative patients. These findings indicate the potential for developing a novel, minimally invasive, COVID-19 detection method. Lastly, using both in vitro human and in vivo hamster models, we have developed a novel miRNA-based antiviral therapeutic targeting miR-2392 that significantly reduces SARS-CoV-2 viability and may potentially inhibit a COVID-19 disease state in the host.

15. 食蟹猕猴暴露于 SARS-CoV-2 气溶胶中会导致比现有模型更严重的病理结果

Aerosol Exposure of Cynomolgus Macaques to SARS-CoV-2 Results in More Severe Pathology than Existing Models

来源: bioRxiv

发布时间: 2021-04-27

链接: <https://www.biorxiv.org/content/10.1101/2021.04.27.441510v1>

第一作者: Sandra L. Bixler

通讯作者: Sandra L. Bixler

通讯作者单位: United States Army Medical Research Institute of Infectious Diseases, 1301 Ditto Avenue

DOI 或 PUBMED ID:

编译者: 宋珂

中文摘要:

SARS-CoV-2 导致的疫情出现以来, 人们对建立能够真实再现人类 COVID-19 疾病显著特征动物模型的需求十分迫切。这些动物模型对于医疗对策的快速筛选、测试和评估是十分必要的。本文中, 作者对两种非人灵长类动物: 恒河猴和食蟹猕猴在两种不同的 SARS-CoV-

2 暴露途径(气管内/鼻内结合暴露和小颗粒气溶胶暴露)下的特征进行了直接比较。虽然所有四个实验组都显示出较少的临床症状,但在放射影像和尸检时都发现了轻中度呼吸系统疾病的证据。通过气溶胶途径暴露的食蟹猕猴产生了最一致的发热反应,并有最严重的呼吸道疾病和病理。这项研究表明,虽然所有四种模型都适合描述冠状病毒引起的轻度疾病症状,但暴露于 SARS-CoV-2 气溶胶的食蟹猕猴产生了最严重的疾病症状,这可能为评估治疗方法和疫苗的效果提供了额外的临床终点。

Abstract:

The emergence of SARS-CoV-2 pandemic has highlighted the need for animal models that faithfully recapitulate the salient features of COVID-19 disease in humans; these models are necessary for the rapid down-selection, testing, and evaluation of medical countermeasures. Here we performed a direct comparison of two distinct routes of SARS-CoV-2 exposure, combined intratracheal/intranasal and small particle aerosol, in two nonhuman primate species: rhesus and cynomolgus macaques. While all four experimental groups displayed very few outward clinical signs, evidence of mild to moderate respiratory disease was present on radiographs and at the time of necropsy. Cynomolgus macaques exposed via the aerosol route also developed the most consistent fever responses and had the most severe respiratory disease and pathology. This study demonstrates that while all four models were suitable representations of mild COVID-like illness, aerosol exposure of cynomolgus macaques to SARS-CoV-2 produced the most severe disease, which may provide additional clinical endpoints for evaluating therapeutics and vaccines.

16. 4月27日快讯: Merck、Gilead 采取行动扩大对 COVID-19 抗病毒药物的获取及其他相关消息;

April 27 Quick Takes: Merck, Gilead move to expand access to COVID-19 antivirals; plus Exscientia-Softbank, Lilly, Aldeyra, LogicBio, Canbridge, Daiichi, Ultivue, Provention

来源: biocentury

发布时间: 2021-04-28

链接: <https://www.biocentury.com/article/635990/april-27-quick-takes-merck-gilead-move-to-expand-access-to-covid-19-antivirals-plus-exscientia-softbank-lilly-aldeyra-logicbio-canbridge-daiichi-ultivue-provention>

编辑: BIOCENTURY STAFF

编译者: 刘焕珍

中文摘要:

Gilead 将为其七个印度许可合作伙伴提供技术援助,对他们的新制造设施给予支持并且捐赠原料药 API,以扩大瑞德西韦的生产。该公司还向印度捐赠了至少 45 万瓶瑞德西韦。Gilead 的全球治疗许可计划向 9 家公司提供免专利税许可证,以支持 127 个国家的使用。默克公司已经与五家知名的印度仿制药公司签订了 molnupiravir 的非排他性许可协议,以加快印度和 100 多个低收入和中等收入国家对口服抗病毒药物的获取。

COVID-19 抗体的销售弱于预期,导致 Eli-Lilly and Co. 未能达到第一季度的预期,但财报也显示出 Lilly 更广泛产品线变化。该公司将 2021 年每股收益下调至 7.80-8 美元,以反映 COVID-19 抗体销售的变化。

Abstract:

Gilead is providing its seven Indian licensing partners with technical assistance, support for new manufacturing facilities and donated API to scale up production of Veklury remdesivir. The company is also donating at least 450,000 vials of Veklury to India. Gilead's global licensing program for the therapy provides royalty-free licenses to nine companies to support access in 127 countries. Merck has entered into non-exclusive licensing agreements for molnupiravir with five established Indian generics companies to accelerate access to the oral antiviral in India and more than 100 low- and middle-income countries. It was weaker-than-expected COVID-19 antibody sales that led Eli Lilly and Co. (NYSE:LLY) to miss its first quarter estimates, but the earnings report also revealed shifts in Lilly's broader pipeline. The company lowered 2021 earnings per share guidance to \$7.80-\$8 to reflect the shift in COVID-19 antibody sales.