Omicron variant of SARS-CoV-2 imposes a new challenge for the global public health

George F. Gao

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Receptor binding and structural bases of Omicron
Variant of concerns

- **Prototype**: SP NTD RBD S2 TM CT
- **B.1.1.7 (Alpha)**: SP NTD RBD S2 TM CT
- **B.1.351 (Beta)**: SP NTD RBD S2 TM CT
- **B.1.617.2 (Delta)**: SP NTD RBD S2 TM CT

**Variant of concern**

- **BA.1 (Omicron)**: SP NTD RBD S2 TM CT
- **BA.2 (Omicron)**: SP NTD RBD S2 TM CT
- **BA.3 (Omicron)**: SP NTD RBD S2 TM CT
Omicron, delta, and prototype SARS-CoV-2 RBDs show similar binding strength to hACE2.

The complexes of SARS-CoV-2-RBD with hACE2 for omicron and delta variants were resolved.

The roles of key residues in the omicron RBD for receptor recognition were identified.

P. Han, et al. Cell. 2022
The currently known host range of SARS-CoV-2.

- (A) Species that have been reported to be infected by SARS-CoV-2 in nature.

- (B) Species that have reportedly been infected by SARS-CoV-2 via infection experiments.

Note: A solid arrow indicates that there is clear evidence showing the cross-species transmission direction of SARS-CoV-2, while a dashed arrow indicates a possible cross-species transmission direction of SARS-CoV-2.
Cross-species recognition of CoVs to different ACE2 orthologs

- SARS-CoV, SARS-CoV-2, RaTG13, GX/P2V/2017 and GD/1/2019 have a wide range of host receptor binding.
Omicron variant of SARS-CoV-2 expand its host range

- Host-adapting mutations, such as residues 493, 498 and 501, are observed in the Omicron RBD.
- Omicron efficantly infects wildtype mice.
- Omicron replicated efficiently and induced significant pathological changes in lungs and tracheas, accompanied by elevated proinflammatory cytokines in the lungs and sera.
- It is necessary to evaluate the interspecies transmission risk of Omicron.
First line of the vaccine development in China
Virus Variants and Human Immune System

永恒的猫鼠游戏
(Tom and Jerry)

中国古语:
魔高一尺, 道高一丈
Global 7 major platforms of COVID-19 vaccines

Dai and Gao, Nat Rev Immunol. 2021

BBIBP-CorV (Sinopharm 中国国药)
CoronaVac (Sinovac 中国科兴)
KCONVAC (Minhai Biotechnology 中国康泰生物)
Covaxin (Bharat Biotech 印度巴拉特生物)
KoviVac (Chumakov Center 俄罗斯丘马科夫中心)
COViran Barekat (Shifa Pharmed Industrial Co 伊朗)

ZF2001 (Zhifei 中国智飞龙科马)
COOVAX (Novavax 美国诺瓦瓦克斯)
CIGB-66 (CIGB 古巴)
EpiVacCorona (FBRI 俄罗斯)
MVC-COV1901 (Medigen 中国台湾高端疫苗)
COVAX-19 (Vaxine 澳大利亚/CinnaGen Co 伊朗)

mRNA-1273 (Moderna 美国莫德纳)
BNT162b2 (Pfizer 美国辉瑞/BioNTech 德国拜恩泰科)
TAK-919 (Takeda 日本武田制药) - Moderna配方

Ad5-nCoV (CanSino 中国康希诺)
Ad26.COV2-S (Janssen 美国强生)
ADZ1222 (AstraZeneca 英国阿斯利康/Oxford 牛津)
Sputnik V (Gamaleya 俄罗斯加马利亚研究所)
Sputnik Light (Gamaleya 俄罗斯加马利亚研究所)
Covishield (Serum Institute of India 印度血清研究所) - Oxford/AstraZeneca 配方
RBD-dimer-based COVID-19 vaccine development

- A universal design of betacoronavirus vaccines

  *Dai et al, 2020, Cell*

- The first approved protein subunit COVID-19 vaccine in the world

  *ZF2001*
Phase 3 clinical trial of ZF2001

- Randomized, placebo-controlled, multinational phase 3 clinical trial from 5 countries, including China, Uzbekistan, Indonesia, Ecuador, and Pakistan from 2020, December
- Three doses of ZF2001 or placebo were vaccinated, 30 days apart
- 224 endpoint cases were noted after 7 days after full vaccination

<table>
<thead>
<tr>
<th>Analysis group</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td>Symptomatic Covid-19</td>
<td>81.4 %</td>
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<tr>
<td>Severe or critical Covid-19</td>
<td>92.9 %</td>
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<tr>
<td>Death by Covid-19</td>
<td>100 %</td>
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<table>
<thead>
<tr>
<th>Variant</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td>Alpha variant</td>
<td>92.7 %</td>
</tr>
<tr>
<td>Delta variant</td>
<td>81.4 %</td>
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</tbody>
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Unpublished
Prolonged booster interval largely enhanced neutralization of Omicron

Zhao et al, NEJM, 2022
Prolonged interval vaccination is beneficial for neutralization of Omicron

Multiple vaccine boosts and prolonged intervals of ZF2001 provide high neutralization antibody titer against variants including omicron.

Zhao et al, NEJM, 2022
Current challenges
• Waning immunity
• Breakthrough infections by omicron variant

Countermeasures
• Booster vaccination
• Mix and Match vaccination
Inactivated vaccine boosted with protein subunit vaccine (2)

- ZF2001 vaccine as the booster for CoronaVac largely enhanced the sera neutralization of Prototype SARS-CoV-2 and its variants
- Good safety profile

<table>
<thead>
<tr>
<th></th>
<th>3xCoronaVac</th>
<th>2xCoronaVac+1xZF2001</th>
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<tbody>
<tr>
<td>Prototype</td>
<td>793.5</td>
<td>1305.7</td>
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<tr>
<td>Beta</td>
<td>122.6</td>
<td>301.2</td>
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<tr>
<td>Gamma</td>
<td>162.3</td>
<td>274.3</td>
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<tr>
<td>Delta</td>
<td>85.8</td>
<td>205.2</td>
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If the world does not share the vaccine, viruses will take on the world.
谢谢！

George F. Gao