超级疫苗
Superior vaccine

-- 理论假说与研究实践
-- Theoretical hypotheses and research practice

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2024年4月26日

为什么
Why?

- 我们已经有很多疫苗，已经解决了许多问题。
  We already have a lot of vaccines that have solved a lot of problems.
- 但许多问题仍然没有得到解决。
  However, many problems remain unresolved.
- 人类流感疫苗是一个典型例子。
  The human influenza vaccine is a typical example.
- 不够高效、不够广谱、不够安全、浪费生理潜力。
  Not efficient enough, not broad-spectrum enough, not safe enough, waste physiological potential.

什么是
What?

- 我们为了解决这些现实问题提出了超级疫苗的理论概念和研究路径。

  In order to solve these practical problems, we put forward the theoretical concept and research path of Superior vaccine.

- 所谓超级就是实现更高效和更广谱保护。
  The so-called super is to achieve more efficient and broader spectrum protection.

- 超级疫苗还要更加安全并节约生理潜力。
  Super vaccines are also safer and save physiological potential.

- 显然，需要用新技术途径来解决。
  Clearly, new technological approaches are needed.

分类
Classification

- 超级高效
  Super efficient
- 超级广谱
  Super Broad Spectrum
- 满足安全与节省生理潜力的新要求
  Meets new requirements for safety and physiological sparing potential

怎么实现
How to achieve

- 精确：精确结构设计 = 精确免疫启动
  Precise: Precise structure design = precise immune priming
- 微量：纳克级免疫保护
  Trace: nanogram level of immune protection
- 纯化：减轻副作用，降低生理消耗
  Purification: Reduce side effects and physiological consumption

怎么实现
How to achieve

- 超级高效：重构主抗原
  Super Efficient: Reconstruct the main antigen
- 超级广谱：重构保守的共同抗原，多聚主抗原
  Super broad spectrum: reconstitution of conserved common antigens, multiple main antigens

研究实践
Research practice

- 技术基础
  Technical Basis
- 超级疫苗研究实践
  Superior Vaccine Research Practice
- 结论
  Conclusions

技术基础
Technical basis

- 学习、思考与感悟
  Learning, Thinking and Perception
- 寻求精确打开B细胞开关
  Seeking to turn on the B-cell switch precisely
- 结构抗原技术
  Structural Antigen Technology

学习、思考与感悟
Learning, Thinking and Perception

- 仅谈谈两点
  Only two points.
- 疫苗的里程碑
  Milestones for vaccines
- 有关疫苗的预言与实践
  Vaccine predictions and practice

疫苗的里程碑

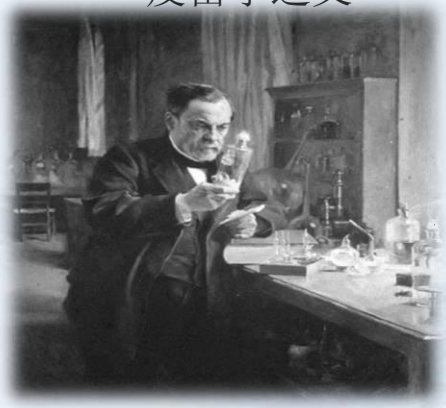
疫苗(Vaccines)

- Variolae vaccinae (smallpox of the cow)
  疫苗接种区(牛痘天花)

免疫(Vaccination)

- 天花接种(Variolation,1000)
  Smallpox vaccination (Variolation, 1000)
- 牛痘接种(Cowpox, 1798)
  Vaccination with smallpox (Cowpox, 1798)
- 减毒活菌苗(Anthrax,1881)
  Live attenuated vaccine (Anthrax, 1881)
- 活病毒疫苗(Rabies, 1885)
  Live virus vaccines (Rabies, 1885)
- 灭活菌苗(Cholera, Typhoid, 1896)
  Inactivated vaccine (Cholera, Typhoid, 1896)
- 亚单位疫苗(Toxoids, 1904)
- Subunit vaccines (Toxoids, 1904)

Edward Jenner (1749–1823)
The father of vaccinology
疫苗学之父



Louis Pasteur (1822–1895)
A 19th century pioneer of vaccinology
19世纪疫苗学的先驱

Levin. New Generation Vaccines (4th Ed.). 2010.
Levin. 新一代疫苗（第4版）， 2010.

预 言 与 实 践

70年代的预言：**2000**年完全基因工程疫苗化？
Prediction of the 1970s: Completely genetically engineered vaccines by 2000?

多肽疫苗构想：多肽是**TB**的基本识别单位：**T**细胞疫苗？多肽疫苗？
Peptide vaccine concept: Peptide is the basic recognition unit of TB: T **cell vaccine? Peptide vaccine?**

1991年的基因免疫：**Nature**和**Science**的**Gene Vaccination**令人激动。 **2020**新冠流行下的**mRNA**疫苗：仍然是进门问题！（高昂的安全代价）
Genetic immunity in 1991: Gene Vaccination **in** Nature **and** Science **is exciting.** mRNA vaccine **under the 2020 COVID-19 epidemic : It is still a matter of entry! (High safety cost)**

寻求精确打开B细胞开关
Seeking to turn on the B-cell switch precisely

- 为什么选择B细胞疫苗：现代科学技术限制。
  Why B-cell vaccines are chosen: Limitations of modern science and technology.
- B细胞疫苗免疫保护的基础：中和抗体。
  The basis of immune protection of B cell vaccine: neutralizing antibody.
- B细胞活化是前提。
  B cell activation is a prerequisite.
- B细胞活化的开关：BCR。
  Switch for B-cell activation: BCR.
- B细胞活化的条件：BCR交联。
  Conditions for B cell activation: BCR cross-linking.
- 满足精确打开B细胞开关的条件是疫苗设计的关键。
  Satisfying the conditions to precisely turn on the B cell switch is the key to vaccine design.

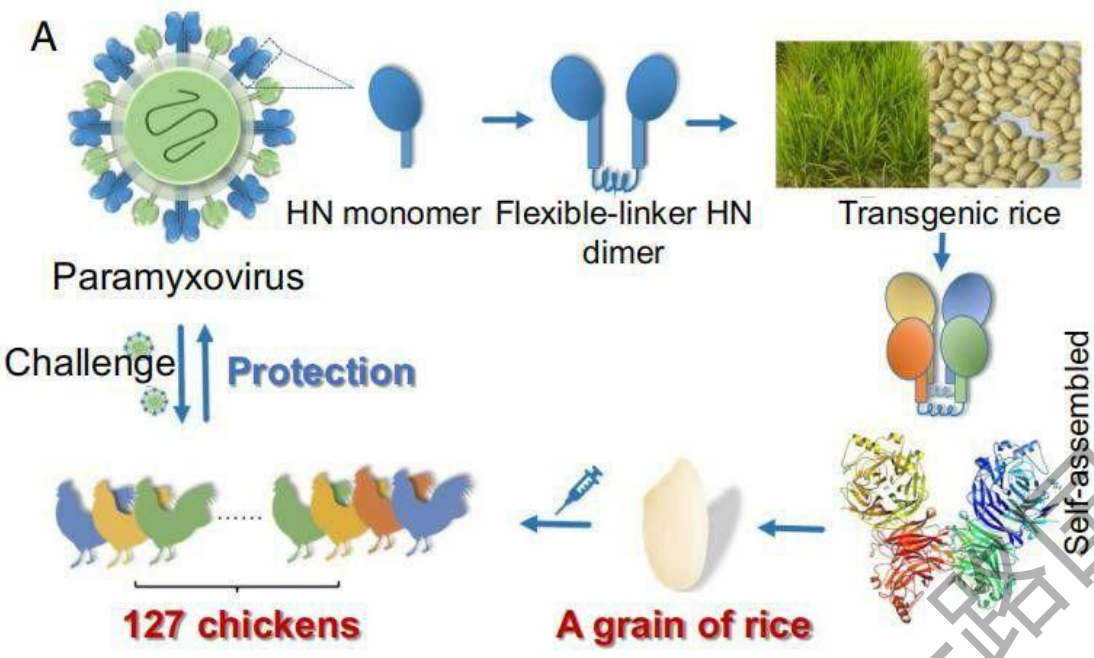
结构抗原专利技术
Structural antigen patented technology

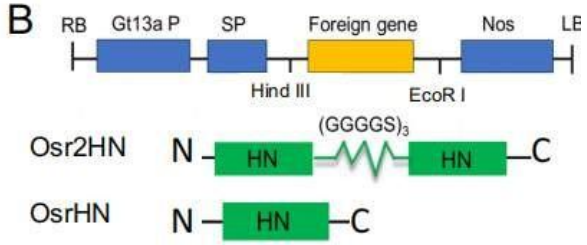
- 从无人回答我们的问题开始。
  Start with no one answering our questions.
- **7AA专利技术：交联两个抗原表位必须满足7AA。**
  7AA patented technology: Crosslinking of two antigen epitopes must meet the requirements of 7AA.
- 哑铃抗原制备专利技术。
  Dumbbell antigen preparation patent technology.
- 三叶草抗原制备专利技术。
  Clover antigen preparation patent technology.
- 俄罗斯方块抗原制备专利技术。
  Patented technology for tetris antigen preparation.
- 任意多面体抗原制备专利技术。
  Arbitrary polyhedron antigen preparation patented technology.

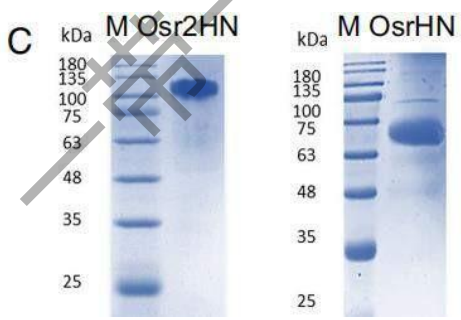
超级高效疫苗研究
Super highly effective vaccine research

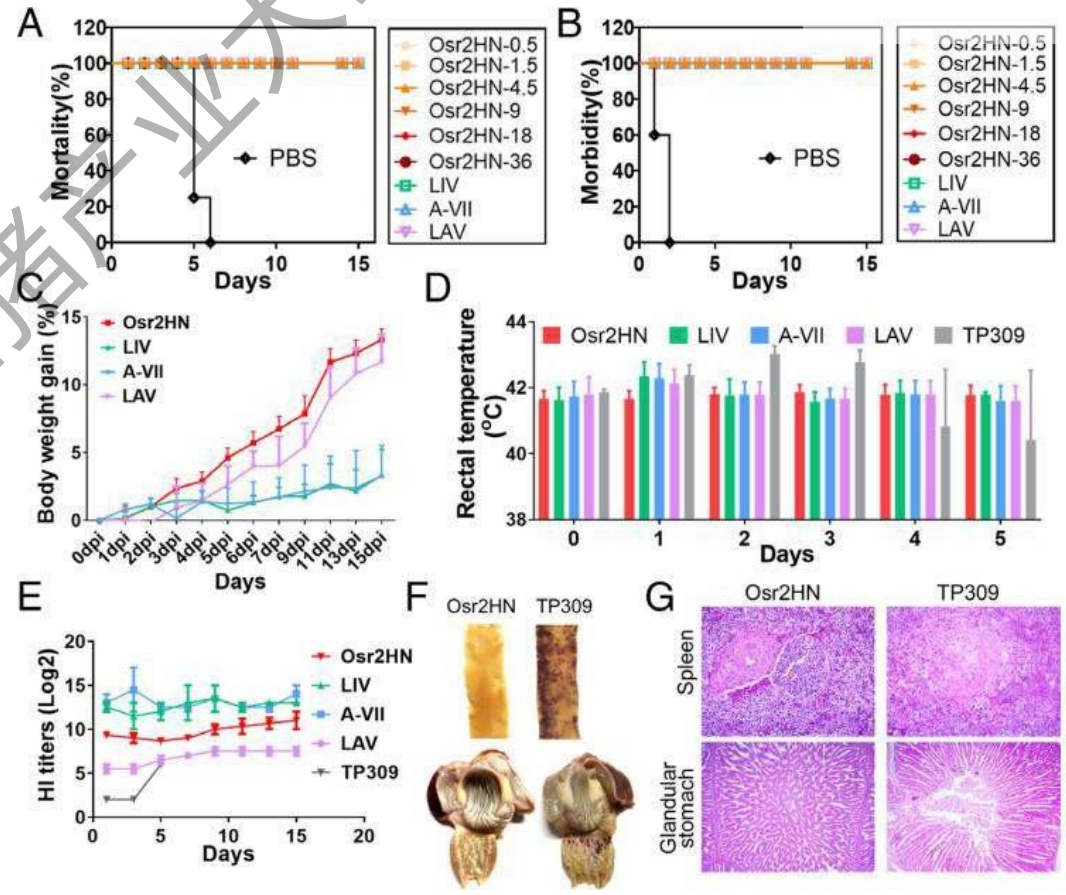
- 新城疫病毒超级疫苗
  Newcastle disease virus superior vaccine
- 猪瘟病毒超级疫苗
  Classical swine fever virus superior vaccine
- 新冠病毒疫苗
  2019-COVID vaccine
- **H5流感病毒疫苗与H9流感病毒疫苗**
  H5 and H9 influenza vaccines

ND水稻源超级疫苗
ND rice-derived superior vaccine







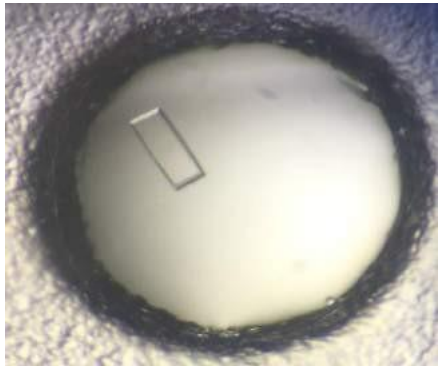


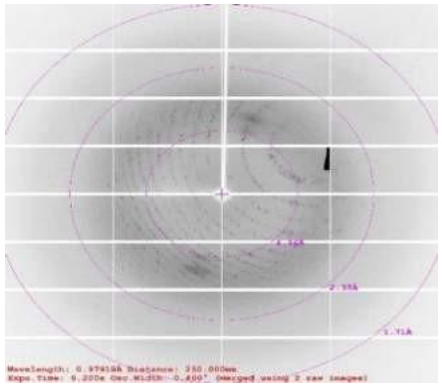
真正实现安全、微量、精准、高效的疫苗高境界

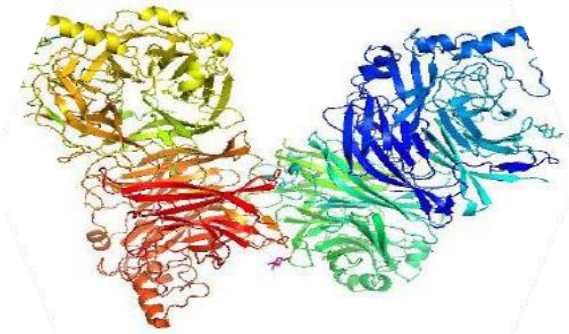
Realize the high level of safe, trace, accurate and efficient vaccines

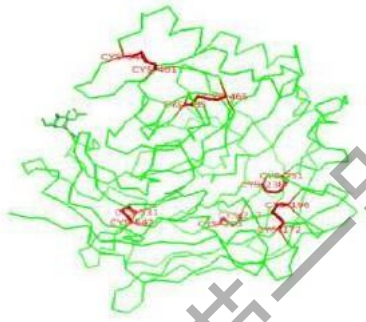
Ma *et al.* Proc Natl Acad Sci, 2024

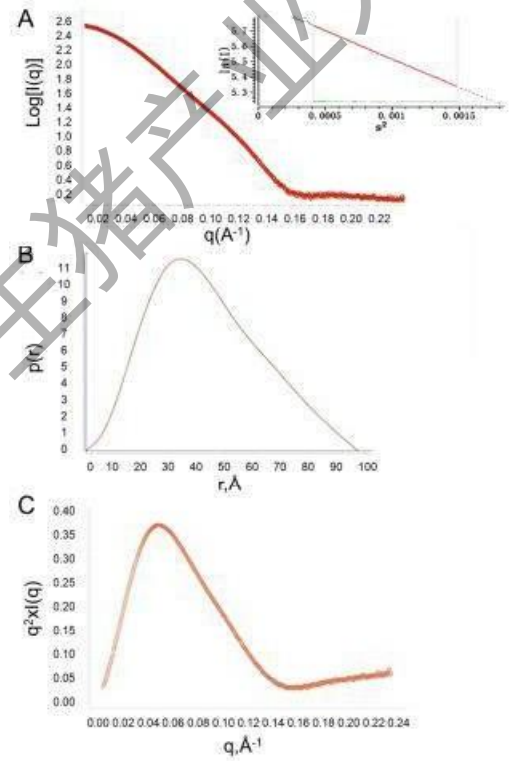
水稻源HN蛋白结构解析
Structure Elucidation of Rice-derived HN Protein

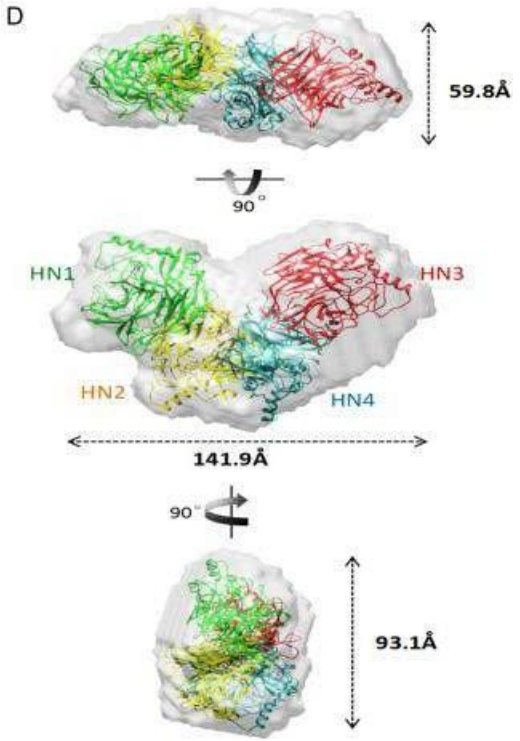










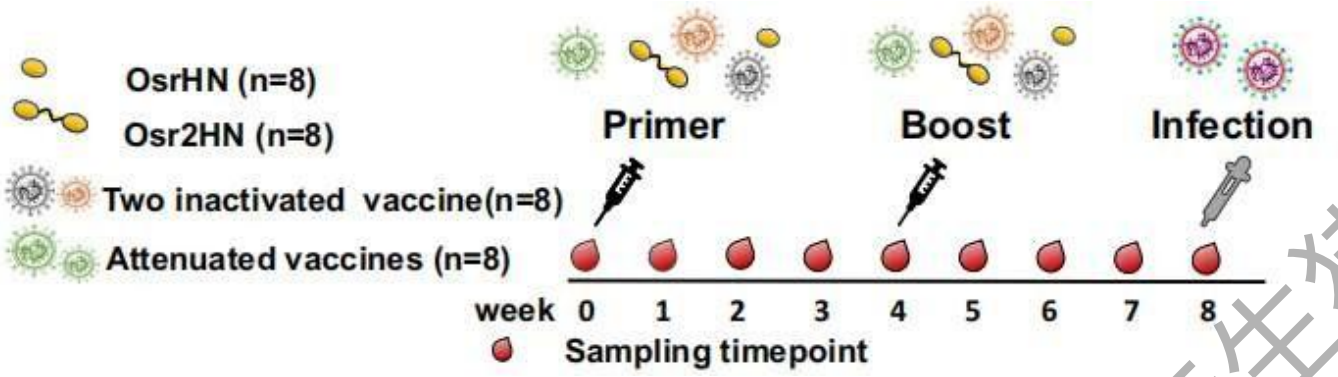


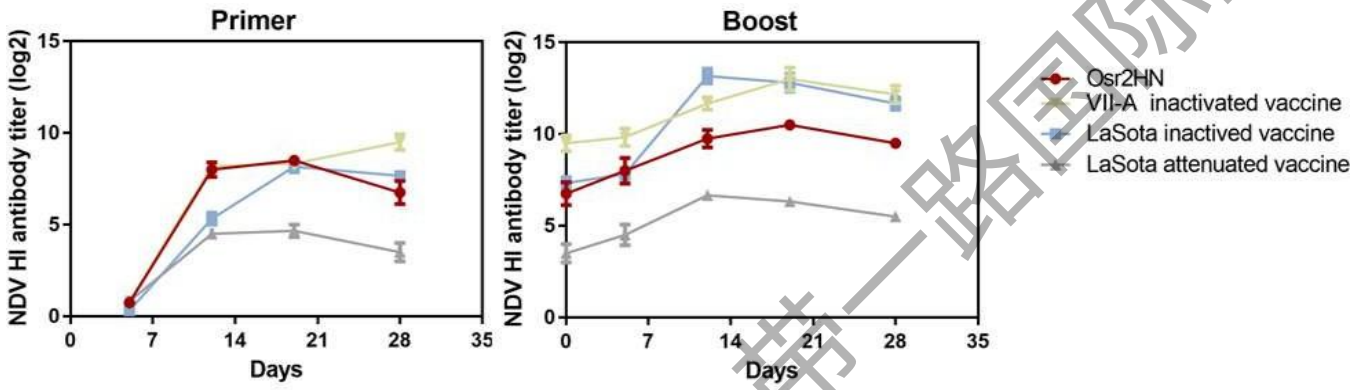
Osr2HN晶体结构，分辨率为1.9Å，SAXS结果显示，Osr2HN在可溶状态下形成HN四聚体

Osr2HN crystal structure with a resolution of 1.9Å. SAXS results show that Osr2HN forms in a soluble state. HN tetramer

Ma *et al.* Proc Natl Acad Sci, 2024

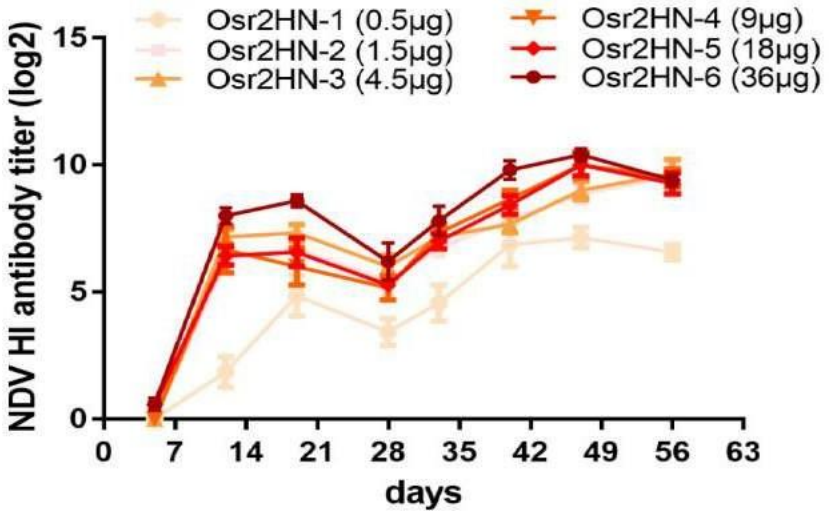
ND水稻源HN结构疫苗的免疫学评价
Immunological Evaluation of HN Structural Vaccine Derived from ND Rice





Osr2HN VS 商业疫苗
Osr2HN VS commercial vaccine

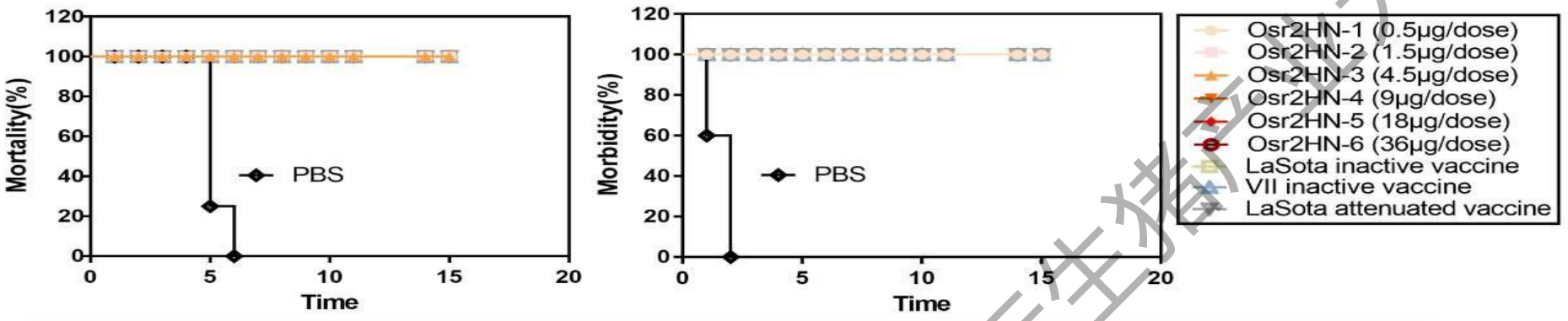
免疫应答更快
Faster immune response



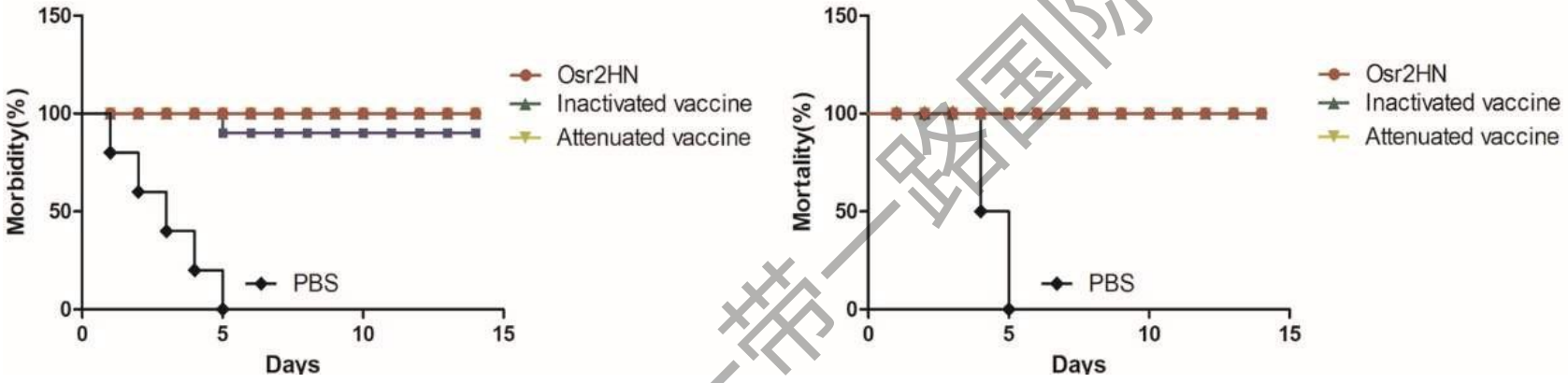
Osr2HN免疫节约免疫潜力
每克水稻可生产**6000**份疫苗
Osr2HN immunization saves immunity potential
6,000 vaccines can be produced per gram of rice

Ma *et al.* Proc Natl Acad Sci, 2024

ND水稻源HN结构疫苗的攻毒保护情况
Challenge protection of ND rice-derived HN construct vaccine



两次免疫发病率和死亡率
Double immunization morbidity and mortality

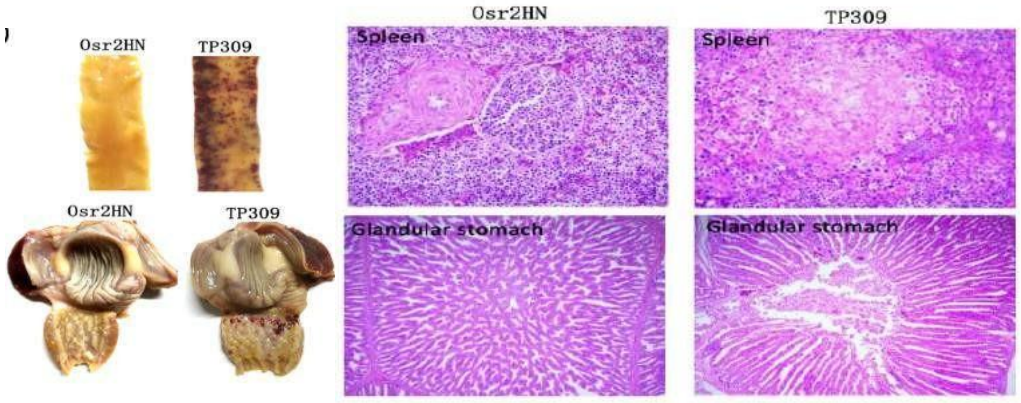


一次免疫发病率和死亡率
one time immunization morbidity and mortality

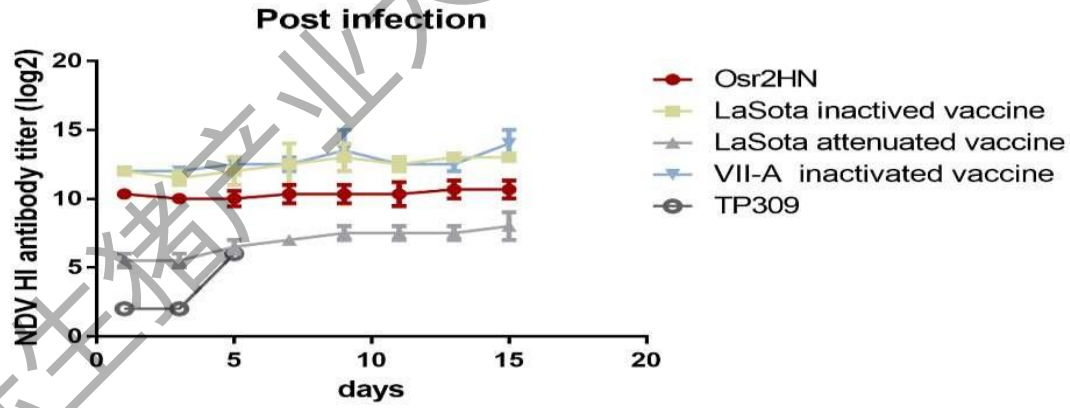
Osr2HN 0.5μg两次免疫、5 μg击一次免疫完全保护鸡免受NDV的致死性攻击
Two immunizations with 0.5 μg and one immunization with 5 μg Osr2HN completely protected chickens from lethal challenge with NDV

Ma et al. Proc Natl Acad Sci. 2024

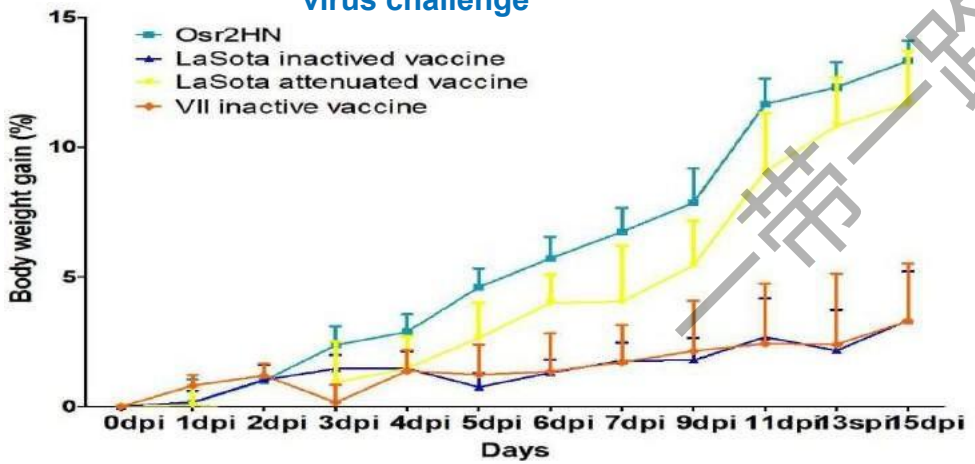
ND水稻源HN结构疫苗的攻毒保护情况
Challenge protection of ND rice-derived HN construct vaccine



攻毒后的组织病理变化
Histopathological changes after virus challenge



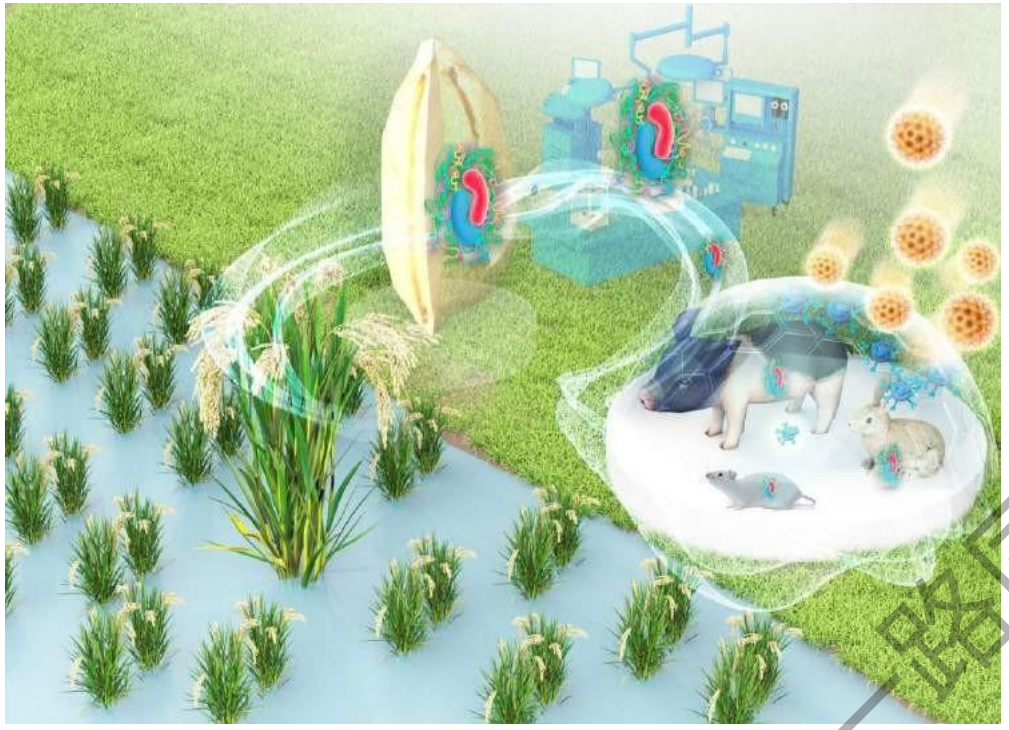
攻毒后的HI特异性抗体变化
Changes of HI specific antibody after virus challenge



Osr2HN组攻毒后体重增长最快！
The Osr2HN group had the fastest weight gain after challenge!

Ma *et al.* Proc Natl Acad Sci, 2024

水稻源猪瘟超级疫苗
Superior Vaccine of Classic Swine Fever from Rice



Plant Biotechnology Journal
Open Access

Research Article | Open Access

Rice-produced classical swine fever virus glycoprotein E2 with herringbone-dimer design to enhance immune responses

Qianru Xu, Fanshu Ma, Daichang Yang, Qingmei Li, Liming Yan, Jiquan Ou, Longxian Zhang, Yunchao Liu, Quan Zhan, Rui Li, Qiang Wei, Hui Hu, Yanan Wang, Xueyang Li, Shenli Zhang, Jifei Yang, Shujun Chai, Yongkun Du, Li Wang, Erqin Zhang ✉, Gaiping Zhang ✉

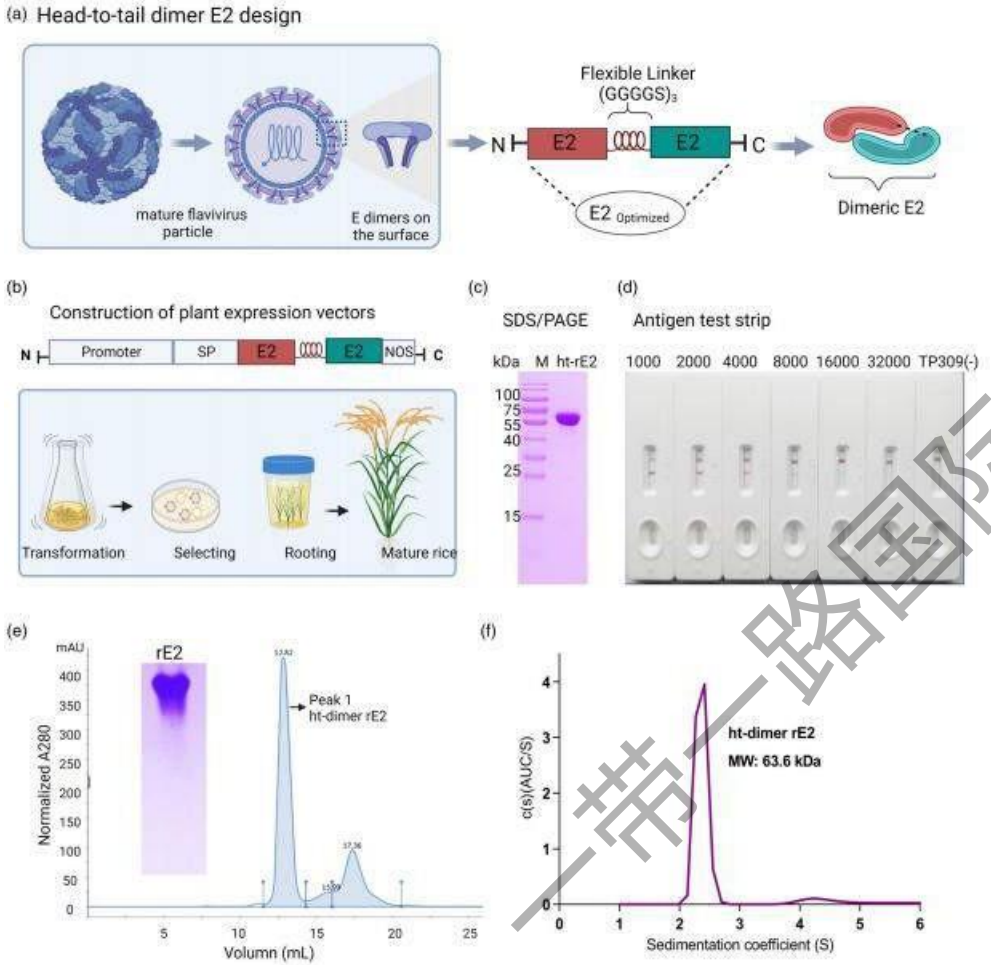
First published: 12 August 2023 | **https://doi.org/10.1111/pbi.14152**

通过水稻表达所设计的超级结构，阐明水稻表达系统具备精准表达体外设计蛋白的潜力。
Through the super structure designed by rice expression, it was demonstrated that the rice expression system has the potential to accurately express proteins designed in vitro.

该疫苗同时具备安全、易于大规模生产和低成本的特点。
The vaccine has the characteristics of safety, easy large-scale production and low cost.

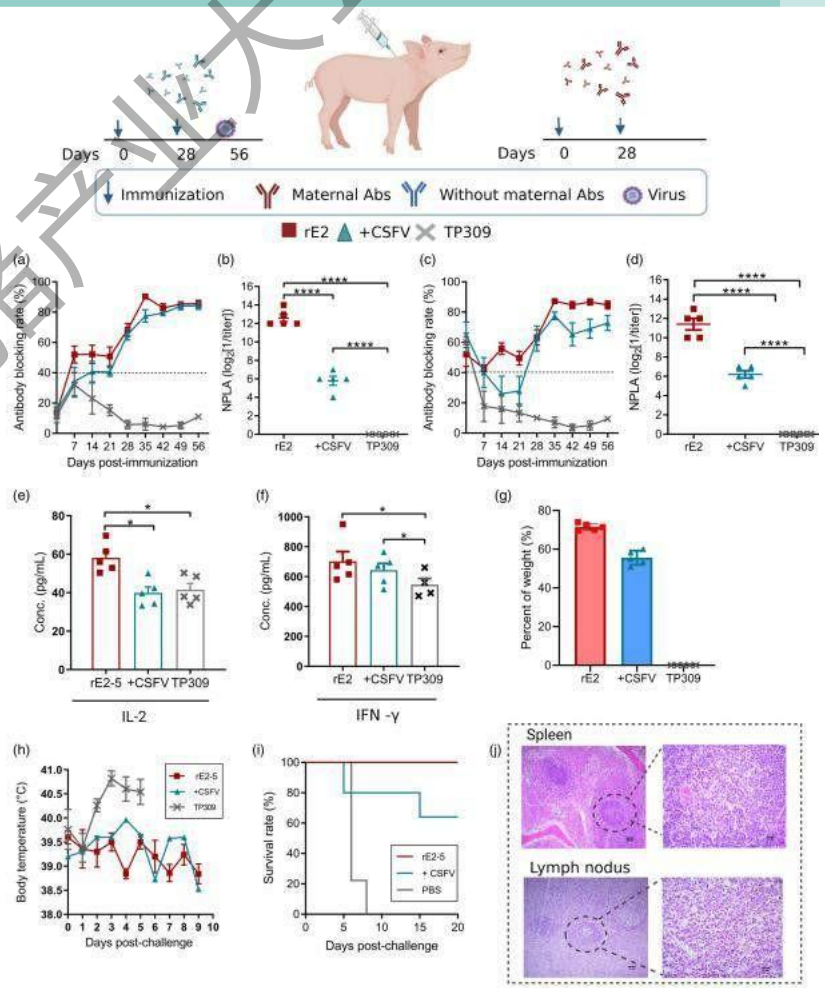
水稻源猪瘟超级疫苗免疫评价

Immune Evaluation of Superior Vaccine of Classical Swine Fever from Rice



水稻源超级猪瘟疫苗的表达

Expression of Super Vaccine of Classical Swine Fever from Rice

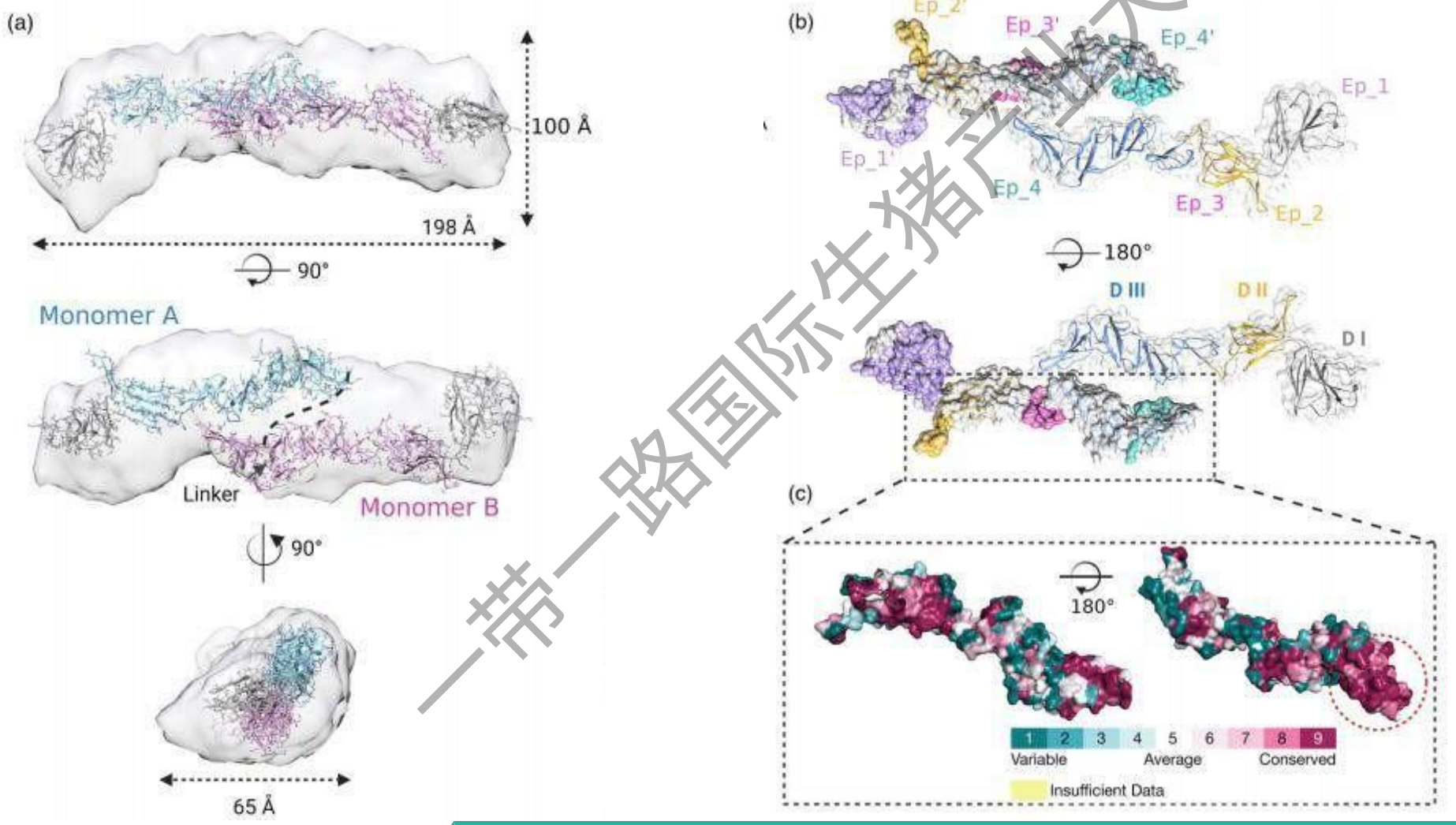


疫苗诱导猪产生体液免疫应答

Humoral Immune Response Induced by Vaccine in Pigs

Xu *et al*. Plant Biotechnol J. 2023

疫苗抗原晶体结构
Crystal structure of vaccine antigen



Xu *et al*. Plant Biotechnol J. 2023

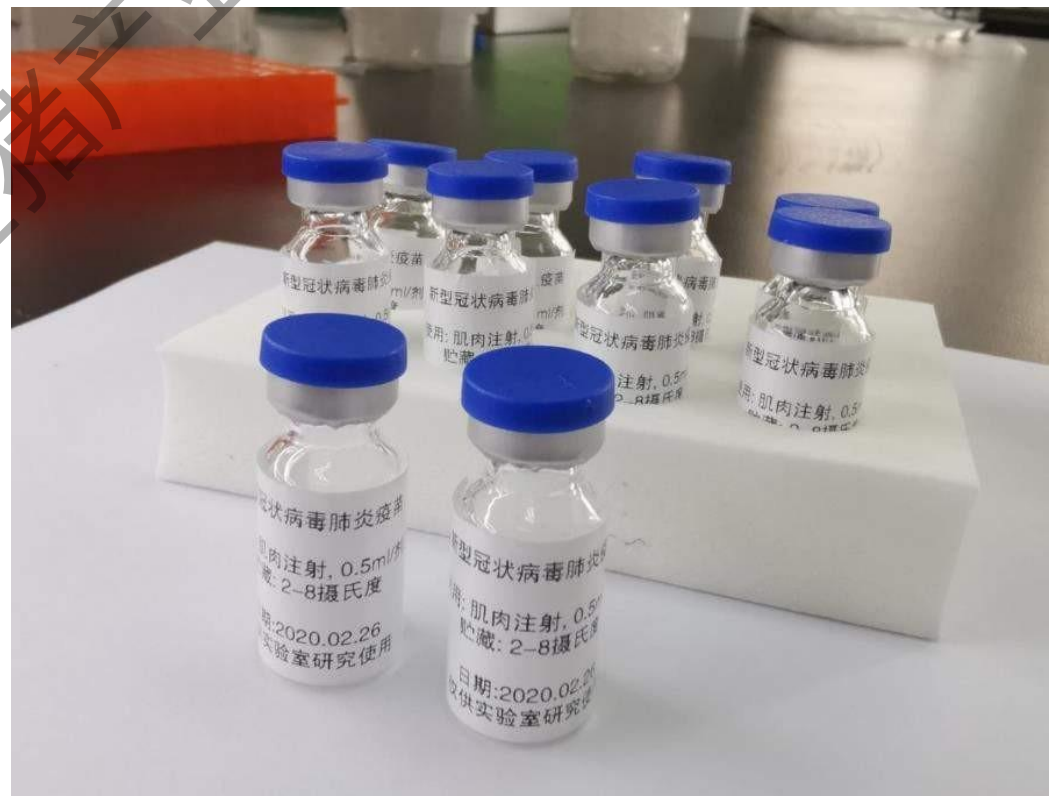
水稻源猪瘟超级疫苗
Superior Vaccine of Swine Fever from Rice

- 与正常的转基因E2相比，效率为10 x。
  10 x efficiency compared to normal transgene E2.
- 每粒种子16剂疫苗。
  16 doses of vaccine per seed.
- 最小保护剂量：280 ng。
  Minimum protective dose: 280 ng.
- 攻毒后唯一一组体重增加。
  The only group gained weight after challenge.

Xu *et al*. Plant Biotechnol J. 2023

新型冠状病毒肺炎疫苗
Coronavirus Disease Vaccine

- 中和抗体效价高（高于1万）；
  High neutralizing antibody potency (higher than 10,000);
- 抗体持续期长；
  Long duration of antibody;
- 免疫保护完全；
  Complete immune protection;
- 无ADE效应；
  No ADE effect;
- 抗原产量高；
  High antigen yield;
- 生产成本低。
  Low production cost.



新型冠状病毒肺炎疫苗
Coronavirus Disease Vaccine

- **2020-02-08 首免猪和小鼠**
  2020-02-08 First immunization of pigs and mice
- **用自己研制的抗体试纸检测**
  Test with self-developed antibody test paper

首免
First immunization

二免
Second immunization

三免
Third immunization

0	12	27	40
猪抗体效价 Porcine antibody titer	1：3000	1：10万	1：100万 1: 1 million

哈兽研P3实验室结果 Results of HVRI P3 Laboratory

HNSP-重组新型冠状病毒疫苗免疫小鼠攻毒试验

Challenge of mice immunized with HNSP-recombinant novel coronavirus vaccine

接种疫苗& vaccination&	小鼠编号 Mice No.	攻毒后不同时间（天）组织病毒核酸检测及感染病毒滴定# Virus nucleic acid detection and infectious virus titration in tissues at different times (days) after challenge#							
		鼻甲 Nasal turbinate				肺 Lung			
		核酸拷贝 Nucleic acid copy （lg copies/g）		噬斑形成单位 Plaque-forming unit （lg PFU/g）		核酸拷 Nucleic acid copy （lg copies/g）		噬斑形成单位 Plaque-forming unit （lg PFU/g）	
		3	5	3	5	3	5	3	5
HNSP	S1	7.0	/	≤	/	≤	/	≤	/
	S2	≤	/	≤	/	≤	/	≤	/
	S3	≤	/	≤	/	≤	/	≤	/
	S4	/	≤	/	≤	/	≤	/	≤
	S5	/	≤	/	≤	/	≤	/	≤
	S6	/	≤	/	≤	/	≤	/	≤
安慰剂 Placebo	C1	9.36	/	5.18	/	8.83	/	5.08	/
	C2	8.15	/	5.15	/	9.17	/	6.23	/
	C3	8.93	/	5.56	/	9.60	/	6.73	/
	C4	/	8.51	/	3.28	/	7.07	/	3.61
	C5	/	8.36	/	3.50	/	7.0	/	3.36
	C6	/	8.56	/	3.30	/	7.0	/	3.20

Balb/c小鼠4-6周龄，间隔3周皮下接种二次；#，接种后第10天，采用 3.6 lg PFU剂量（~1000MID_{50}）小鼠适应SARC-CoV-2（HRB26M株）滴鼻攻击。 “≤”，低于核酸拷贝检测下限3.0 lg copies/g 或感染病毒滴定检测下限2.0 lg PFU/g； “/”,未检测。

Balb/c mice were 4-6 weeks old and vaccinated subcutaneously twice at an interval of 3 weeks; #, 10 days after vaccination, challenged with 3.6 lg PFU (~1000 MID_{50}) of mouse-adapted SARC-CoV-2 (HRB26M strain) by intranasal drops. “≤”, below the detection limit of nucleic acid copies of 3.0 lg copies/g or the detection limit of infectious virus titration of 2.0 lg PFU/g; “/”, not detected.

新冠疫苗研究教训
Lessons from 2019-COVID vaccine research

- 没有走到应用
  Did not go to the application
- 没有申请国家专项
  Did not apply for national special plan
- 缺乏信任
  Lack of confidence
- 认知有误，没能与大型企业紧密结合
  Misunderstanding and failure to closely integrate with large enterprises

H5与H9流感病毒疫苗
H5 and H9 influenza virus vaccines

- 水稻表达
  Expression in rice
- 保护剂量：1微克
  Protective dose: 1 μg
- 已转让
  Transferred

超级疫苗转化
Superior Vaccine Transformation

成果转化： 流感-鸡新城疫二联蛋白质疫苗
Achievement transformation: influenza-Newcastle disease bivalent protein vaccine

- 水稻胚乳生物反应器
  Rice endosperm bioreactor
- 转让金额:3000万元
  Transfer amount: RMB 30 million

龙湖现代免疫实验室-河南牧翔集团新型疫苗合作转让签约

时间：2023-08-29 编辑：管理员 来源：龙湖现代免疫实验室 点击：545

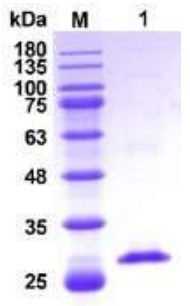
2023年8月28日上午，龙湖现代免疫室与河南牧翔集团疫苗合作转让签约仪式在河南郑州举行。董事长申贵章先生、总裁郑宝振先生及团队代表、股东代表，龙湖现代免疫实验室主任张改平教授、部门负责人和团队主要研究成员代表出席签约仪式，签约仪式由王选年教授主持。

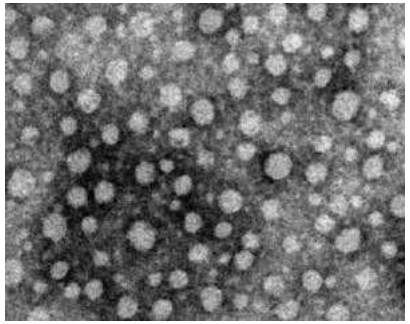

龙湖现代免疫实验室
河南祺祥生物科技有限公司
鸡新城疫、H9N2 亚型禽流感新型二联疫苗合作转让协议

超级广谱疫苗研究
Super broad-spectrum vaccine research

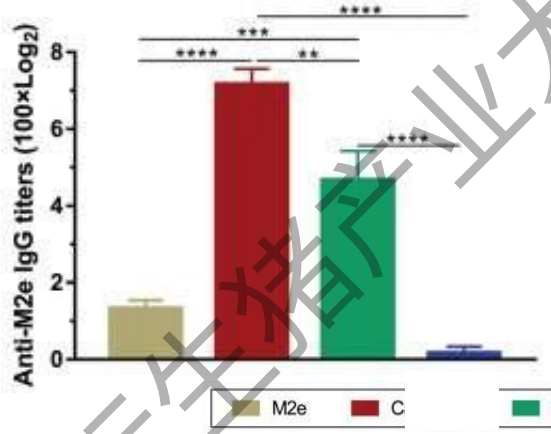
- 重构保守的共同抗原策略（流感病毒M2e）
  Reconstructing a Conserved Common Antigen Strategy (Influenza M2e)
- 多聚主抗原策略（四价流感病毒疫苗）
  Multiple Main Antigen Strategy (Quadrivalent Influenza Vaccine)

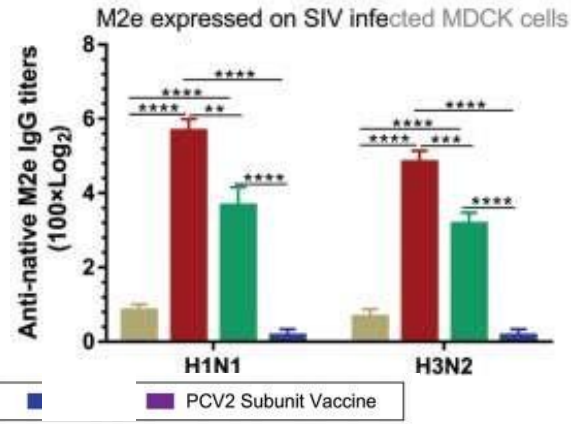
基于M2e的通用型流感纳米疫苗
Universal influenza nanovaccine based on M2e

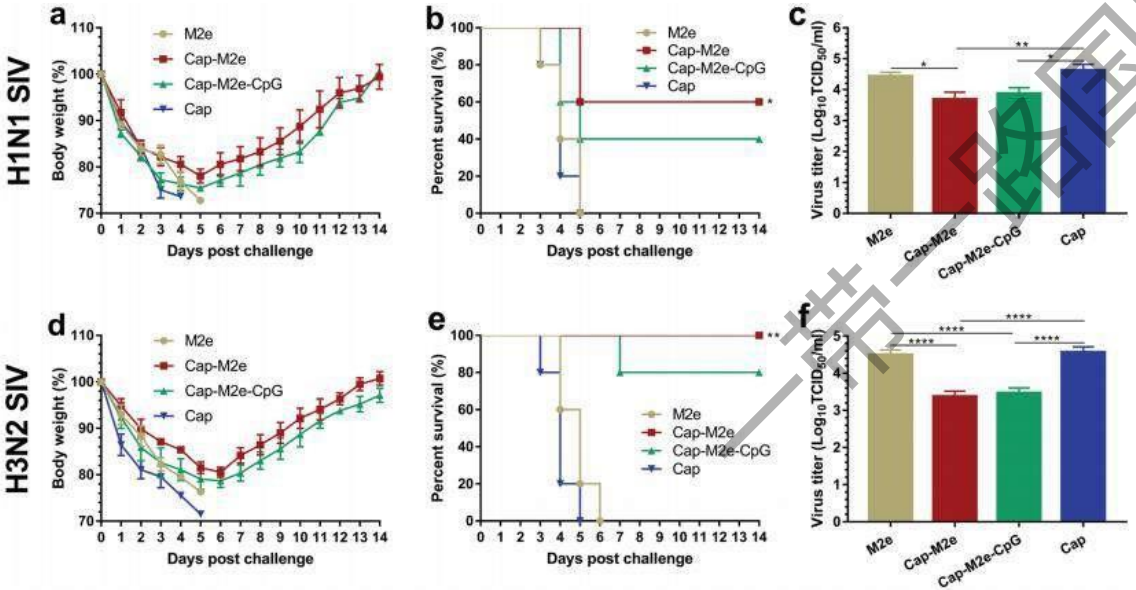


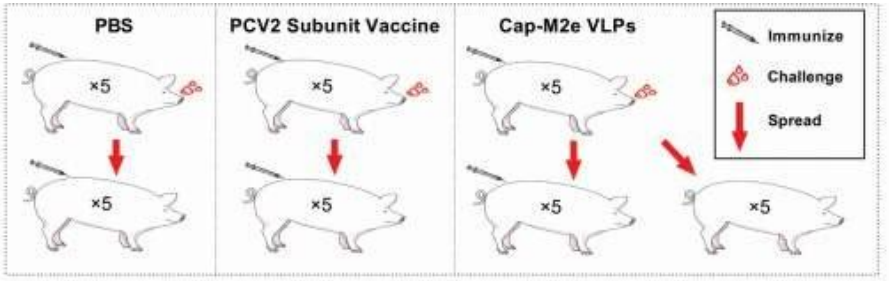


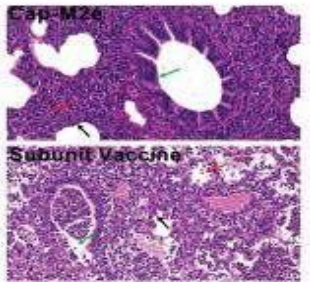
Cap-M2e

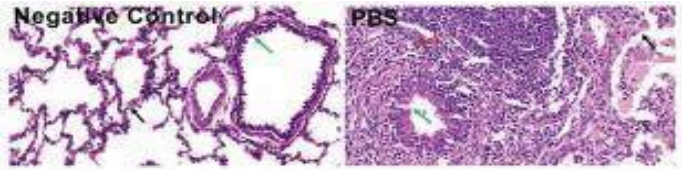






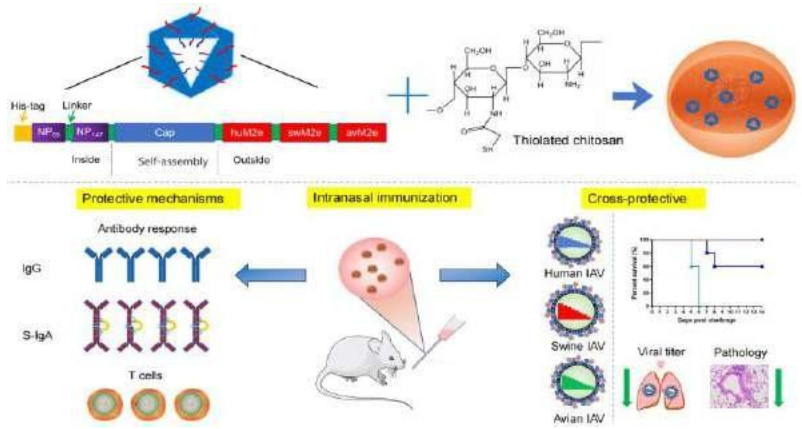


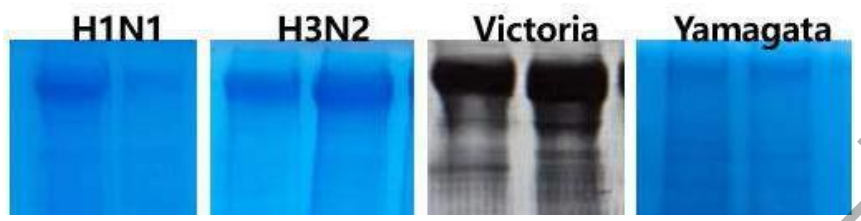




Ding *et al*. Adv. Healthcare Mater. 2019

四价流感超级疫苗
Quadrivalent influenza superior vaccine



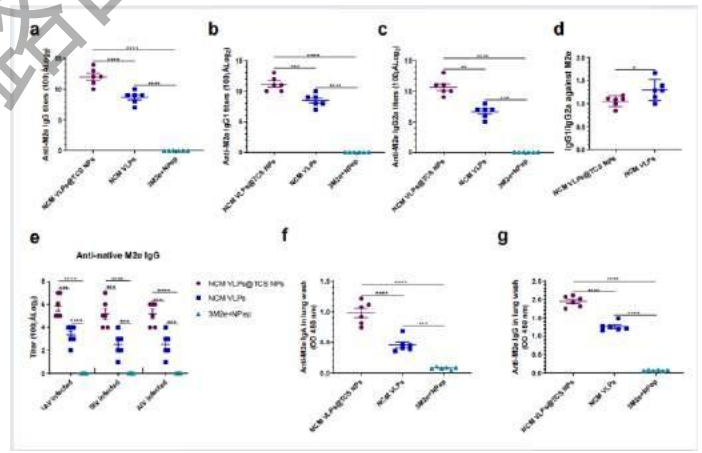


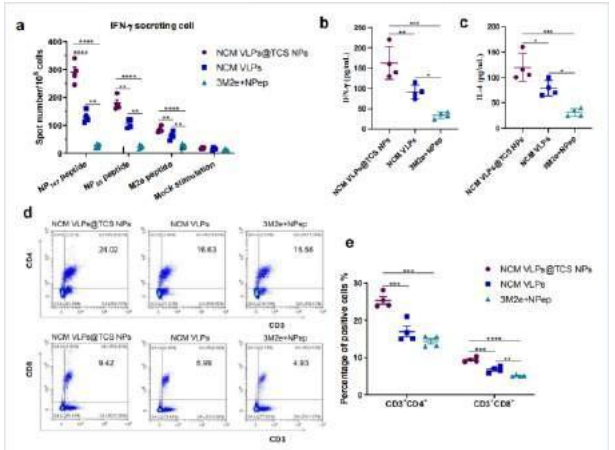
四价流感疫苗滴鼻免疫的小鼠血清血凝抑制效
Serum hemagglutination inhibition effect of intranasal immunization with quadrivalent influenza vaccine in mice

价高于NIBSC提供的标准阳性血清
Higher valent than the standard positive serum provided by NIBSC

论文
Papers

发明专利
Patent for invention





Ding *et al*. Carbohydrate Polymers. 2024

结论
Conclusions

- 超级高效疫苗可以通过重构主抗原实现。
  Super-efficient vaccines can be achieved by reconstituting the main antigen.
- 超级广谱疫苗不能通过重构所谓的“共同抗原”实现。
  Super broad-spectrum vaccines cannot be achieved by reconstituting so-called "common antigens."
- 超级广谱疫苗可以通过多聚主抗原实现。
  Super broad-spectrum vaccines can be achieved with multiple major antigens.
- 超级疫苗真正实现了“高效、广谱、安全”。
  The superior vaccine has truly achieved "high efficiency, broad spectrum and safety."
- 不浪费生理潜力是健康，是更多高质量肉、蛋、奶。
  Not wasting physiological potential is health, more high-quality meat, eggs and milk.

敬请批评指正！谢谢！

Thank you!