PRRS virus vaccination & control in pigs

猪蓝耳病毒免疫和控制

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History of PRRS 蓝耳病历史

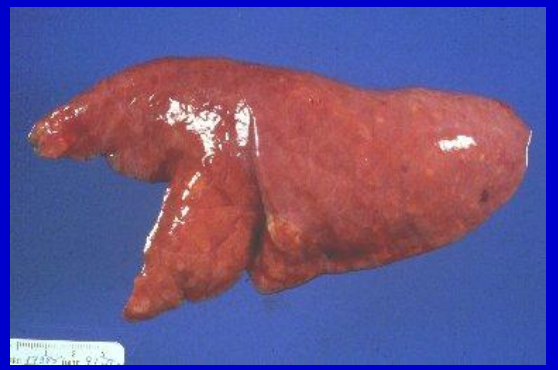
- 1987 – 1991: Mystery swine disease (unknown), SIRS, PEARS, Blue ear, PRRS 猪神秘病（未知），猪繁殖障碍综合征，猪流行性流产和呼吸综合征，蓝耳，猪繁殖与呼吸综合征
- 1991: – Etiologic agent (Lelystad virus, VR-2332) was identified using primary PAM cells 病原体（莱利斯塔德病毒，VR-2332）的鉴定使用了原代猪肺泡巨噬细胞
- 1993: MARC-145 cell was cloned from MA-104 line cells 从MA-104细胞系克隆出MARC-145细胞
- 1994: First MLV vaccine (VR-2332) 第一个弱毒疫苗（VR-2332）
- Homologous inactivated vaccine 同源性灭活疫苗
  - BEI inactivated vaccine 二乙烯亚胺灭活苗
  - MJ vaccine (Envelope proteins enriched vaccine) MJ疫苗（囊膜蛋白富集疫苗）
- Efficacy of PRRS MLV or inactivated vaccine: 蓝耳弱毒苗或灭活苗的功效：

  May be effective or ineffective 可能有效或无效

PRRSV causes two different diseases

蓝耳病毒导致两种不同疾病

Late-term abortion, Premature farrowing, stillborn & mummified fetuses
In pregnant sows 怀孕母猪妊娠晚期流产， 早产，死胎和木乃伊



Respiratory diseases with interstitial pneumonia
in growing pigs 生长猪间质性肺炎呼吸道疾病

Pathogenesis of PRRSV infection in pregnant sows 妊娠母猪感染蓝耳的病理机制

- Transplacental infection is caused by viremia and may occur in any stage of pregnancy
- 任何妊娠阶段都可能发生病毒血症导致的经胎盘感染

→ Viremia can be prevented by humoral immunity alone
单独的体液免疫就可以阻止病毒血症

- Fetal infection and tissue damage occur around 70 days of gestation when susceptible alveolar macrophages are formed in the fetus
胎儿感染和组织损失发生在妊娠期70天左右，这时胎儿体内形成易感肺泡巨噬细胞

→ Following on-farm outbreak, normal litter can be expected when mummies length show 17cm (70 days of gestation).
农场暴发后，当木乃伊胎长度17厘米时预期窝产仔正常（妊娠70天）

No mummies from sows <70 days of gestation at outbreak. 暴发时妊娠期不足70天时不会导致木乃伊胎。

- Abortion and pre-mature farrowing are caused by high fever, and no evidence was found placental lesion. 流产和早产是由发烧引起，没有证据证明胎盘损伤。

→ Anti-fever drugs may be useful for reducing abortion
退烧药可能对减少流产有用

- Stillbirth and mummification are caused by viral infection
- 死胎和木乃伊胎是由病毒感染引起

→ PRRSV can be isolated from fresh stillborn
从新鲜死胎可以分离出蓝耳病毒

PRRSV is the primary cause for PRDC in growing pigs

蓝耳病毒是生长猪呼吸道疾病综合征的首要原因

- PRRSV alone usually causes mild pneumonia but severe clinical disease in PRDC (porcine respiratory disease complex) with mixed infections.
- 单独的蓝耳病毒感染常导致慢性肺炎，但混合感染时可引起严重的临床疾病（猪呼吸道疾病综合征）
- PRDC has been observed commonly in commercial farms, and PRRSV has been most common triggering factors for PRDC.
- 猪呼吸道疾病综合征在商品猪场常见，蓝耳病毒是最常见的诱发因素。
- PRDC has been experienced in two different stages 猪呼吸道综合征经历两个不同阶段
  - Stage 1: Late nursery 阶段1：保育晚期
    - No PRRSV infection during sucking 哺乳阶段没有蓝耳病毒感染
    - PRRSV infection starts 3-6 weeks of age 蓝耳病毒感染从3-6周开始
  - Stage 2: Early to mid grower phase 阶段2：生长阶段的早期到中期
    - No PRRSV infection during suckling & nursery periods 哺乳阶段和保育阶段没有蓝耳病毒感染
    - PRRSV infection starts 10-16 weeks of age 蓝耳病毒感染从10-16周龄开始

PRRSV variants 蓝耳病毒变异株

- Genetic variants 基因变异株
  - ORF5/ whole genome sequence: Epidemiologic analysis ORF5/全基因测序：流行病学分析
  - RFLP patterns: Indicate better for clinical virulence 限制性内切酶片段长度多态性分型：更好显示临床毒力
- Serologic variants 血清学变异株
  - Identical, partial or no relationship by cross serum neutralization test
  - 通过交叉血清中和试验， 可全部、部分或不能鉴别
  - Few research on serologic variants was performed 对血清学变异体的研究很少
- Immunologic variants 免疫学变异株
  - Cross protection test by challenge in host animal 通过在宿主动物体内攻毒提供交叉保护
  - No research report are available 没有研究报道

Virus sequence similarity between PRRSV at acclimation and during outbreak

在暴发和驯化期间的病毒序列相似性

PRRSV used at acclimation (A) and isolated during outbreak (O) in 4 different farms with severe reproductive clinical signs

4个暴发蓝耳均有严重繁殖临床症状的不同农场使用的驯化毒株（A）和暴发时分离到的毒株（O）

Murtaugh 2007

农场 Farm	序列对比 Sequence comparison	ORF5 ORF 5	全基因组 Whole genome
1	A:O	98.2	97.6
2	A:O	98.8	99.0
3	A:O	98.0	96.8
4	A:O	99.2	99.3

- PRRSV with high sequence similarity can cause mild or very severe clinical signs 有较高相似性的蓝耳病毒可以导致慢性或很严重的临床症状
- PRRSV sequence similarity does not predict ability of the protection
- 蓝耳病毒序列相似性不能预测保护能力

PRRSV grouping 蓝耳病毒分组

基因分组		血清或免疫学分组
Genetic group	VS	Serologic or immunologic group
序列分析		在阴性猪中进行生物测定交叉攻毒试验
- Sequence analysis		- Bioassay cross challenge test in naïve pigs
- RFLP pattern		- Potentially by cross SN test using farm specific PRRSV
限制性内切酶片段长度多态性分型		使用农场专有蓝耳病毒可潜在进行交叉血清中和试验

Identification of PRRSV serologic relationship

鉴定蓝耳病毒血清学关系

An example of serologic relationship by cross serum neutralization (SN) test 使用交叉血清中和实验鉴定血清学关系的例子

血清中和试验的蓝耳病毒　　蓝耳病毒毒株特异性高免血清

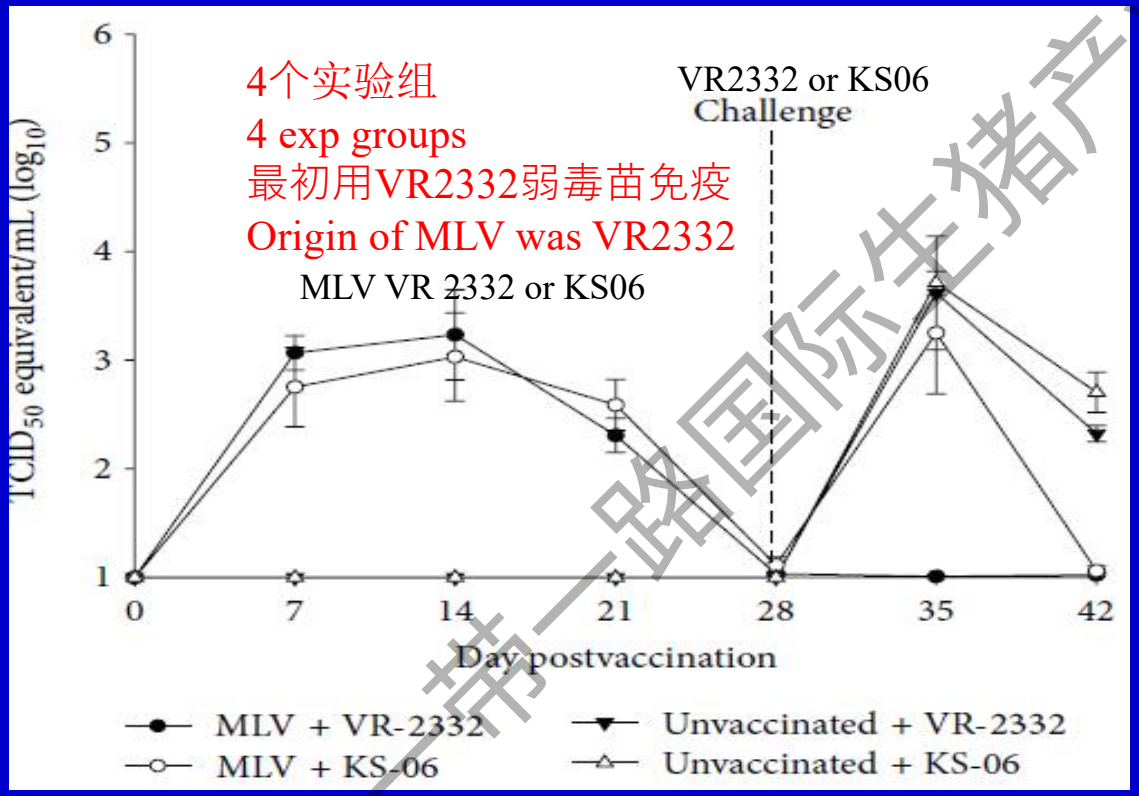
PRRSV in SN test	PRRSV strain specific hyperimmune serum to MLV1	A	B	C	MLV2
MLV1	128	64	32	16	8
A		64			
B			64		
C				64	
MLV2					64

Three serologic groups 3个血清学分组

1. Identical or related: Same titer or 2 fold different e.g. MLV1 and A or A and B
   可鉴定或相关：同等滴度或2倍差异，如MLV1和A或者A和B
2. Partially related: 4 or 8 fold different e.g. MLV1 & B or A & B
   部分相关：4或8倍差异，如MLV1&B或者A&B
3. Unrelated: 16 or more fold different e.g. MLV1 & MLV2 or A MLV2
   不相关：16倍或更多倍差异，如MLV1&MLV2或A MLV2

Viremia in PRRS MLV vaccinated pigs following a homologous or heterologous challenge

免疫蓝耳弱毒苗的猪在同源或疫苗毒株攻毒后的病毒血症



Two groups of pigs vaccinated with VR2332, and another 2 groups without vaccination.
2组猪免疫了VR2332，另外2组没有免疫。

Challenge with VR2332 or heterologous PRRSV of KS-06 使用VR2332或者异源的KS-06的PRRSV毒株攻毒

Li et al 2014

Homologous vs heterologous PRRSV challenge 同源VS异源蓝耳病毒攻毒

	病毒血症 Viremia			攻毒 Challenge	病毒血症 Viremia		
Group 分组	7	14	21	28	28	35 (13)	42
1. VR 2332	++	+++	+	VR2332	-	-	-
2. VR 2332	++	+++	+	KS-06	-	+++	-
3. None 无	-	-	-	VR2332	-	+++	++
4. None 无	-	-	-	KS06	-	+++	++

* Complete protection against homologous strain but no protection against heterologous virus KS-06 对同源毒株有完全保护但是对异源病毒KS-06无保护

* VR2332 and KS-06 are immunologically unrelated VR2332和KS-06无免疫学相关性

How long protective immunity last against homologous PRRSV strain?

对同源蓝耳毒株的保护性免疫能持续多久？

Lager & Mengeling 1997 Vet Microbiol 58:127

Group A A组

1. 11 gilts were infected with a field virus via oral at the same time and bred each gilts between 143 – 514 days after infection.

同时对11头后备母猪经口感染野毒，并在感染后143-514天进行配种。

2. Homologous challenge to all gilts was made in 90-days of pregnancy

对所有后备母猪在妊娠90天时进行同源病毒攻毒

562 and 604 days post-exposure 暴露后的562天和604天

*All gilts were housed in strictly isolated rooms before challenge

所有后备母猪在攻毒前饲养在严格分离的房间

Group B B组

At the time of challenge, 10 age matched PRRS free pregnant sows were purchased and challenged as control without previous infection history

攻毒时，购买10头日龄相当的无感染病史的蓝耳阴性怀孕母猪进行攻毒作为对照。

Duration of PRRS virus protective immunity in pregnant sows: Experimental results 怀孕母猪的蓝耳病毒保护性免疫力的持续时间：试验结果

Demonstration of transplacental infection 胎盘感染的展示

0/9 (11) previously infected sows; 0% infection

0/9 （11）之前感染的母猪；0%感染

8/10 PRRS free sows; 80% infection

8/10 蓝耳阴性母猪；80%感染

Conclusion 结论

1.Homologous protection persist for 604 days post infection

同源保护力能在感染后持续604天

(may persist for life-time 也可能持续终生）

2. No need to vaccinate repeatedly with same vaccine for up to 604 days

在长达604天的时间里没有必要重复免疫相同疫苗

3. Instead of using same vaccine repeatedly, vaccinate different vaccine

使用不同疫苗免疫来取代重复用相同疫苗免疫

to get **broader protection** 来获得保护的范围更广

Lager & Mengeling 1997 Vet Microbiol 58:127

How to choose a commercial MLV for your farm
如何给你的农场选择一个商品化弱毒苗

Cross-sectional SN titer distribution in a sow farm
一个母猪场的血清中和抗体滴度的队列分布

	母猪血清 Sow Serum	血清编号 No. of serum	对蓝耳弱毒苗A,B,C的平均血清中和抗体滴度 Mean SN titers to PRRS MLV A, B or C		
			A	B	C
1胎	Parity 1	5			
3胎	Parity 3	5			
5胎	Parity 5	5			
7胎	Parity 7	5			
总计	Total	20	8	32	64

选择使用疫苗A（最低的平均血清中和抗体滴度）

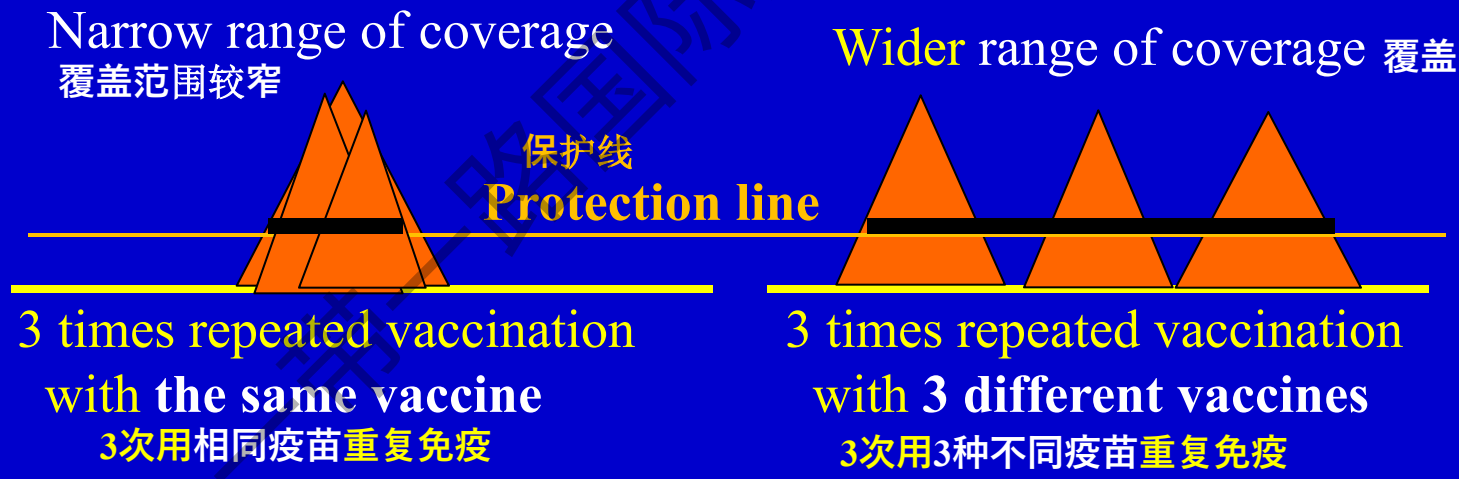
**Use of vaccine A the choice (Lowest mean SN titers)

Vaccination strategy: MLV
免疫策略：弱毒苗

Genetic/Antigenic variation range up to 25%
基因/抗原变异高达25%

使用1个疫苗免疫3次好，还是3次免疫使用3种不同疫苗更好？

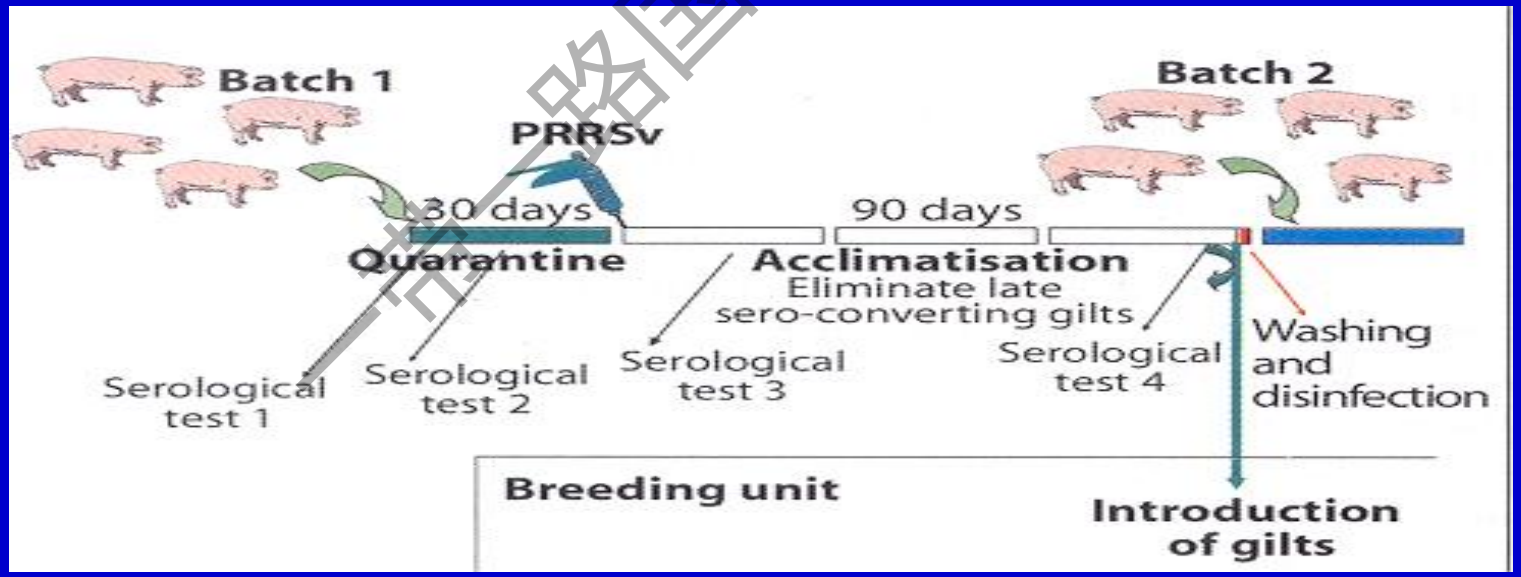
Which one is better to vaccinate between one vaccine 3 times ad 3 different vaccines 3 times??



**At least 2 months interval in case of using different MLV vaccines
若使用不同弱毒疫苗，至少要有2个月时间间隔

On-farm PRRSV control program
农场上的蓝耳控制

- Following an acute outbreak in a naïve farm, no additional vaccination may be necessary except for naïve incoming gilts with home farm virus (serum)
  先天阴性场急性暴发蓝耳后，可能不需要额外的免疫，除非是入群的阴性后备母猪可以用农场毒株（血清）免疫
- Inoculation with serum containing farm specific PRRSV will be helpful for all incoming gilts in most commercial farms
- 在大部分商品场对入群的后备母猪使用农场专有蓝耳病毒血清接种是有帮助的。



Serum inoculation接种血清

Artificial infection/immunization of PRRS virus PRRS 病毒的人工感染/免疫

- Goal – ELISA positive in 100% of the naïve pigs after 2 weeks of the serum inoculation
- 目标-血清接种2周后100%阴性猪ELISA阳性。

- Preparation of PRRSV inoculum 制备蓝耳病毒接种液

1. Pool of serum from PRRS suspected pigs 对蓝耳可疑猪的血清进行合样
   PRRSV from stillborn or weak-born vs nursery pigs
   从死胎或弱仔VS保育猪中准备蓝耳病毒
   PRRSV from nursery pigs may not be effective for reproductive form
   保育猪中的蓝耳病毒可能对繁殖问题无效
2. Pool of serum from PRRSV infected pigs 用蓝耳感染猪的血清进行合样
   On-farm virus culture using PRRS naïve pigs
   使用蓝耳先天阴性猪培养农场自身病毒
3. In-clinic virus culture using PAM cells in large companies 大型公司可用猪肺泡巨噬细胞进行临床病毒培养

- Problems: 问题
  - Insufficient amount of virus 病毒量不足
  - Contamination of unwanted pathogen 污染了其他病原
  - Incorrect immunotype of PRRSV in the serum 血清中蓝耳病毒的免疫型不对
  - Incorrect measurement of virus 病毒测量不对

No PRRSV infection in gene edited pigs with lack of CD163 receptor

缺乏CD163受体的基因编辑猪不感染蓝耳病毒

PRRSV infection to alveolar macrophages require CD 163 receptor

蓝耳病毒感染巨噬细胞需要CD163受体

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Genetically modified pigs lacking CD163 PSTII-domain-coding exon 13 are completely resistant to PRRSV infection

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ABSTRACT

CD163 expressed on cell surface of porcine alveolar macrophages (PAMs) serves as a cellular entry receptor for porcine reproductive and respiratory syndrome virus (PRRSV). The extracellular portion of CD163 contains nine scavenger receptor cysteine-rich (SRCR) and two proline-serine-threonine (PST) domains. Genomic editing of pigs to remove the entire CD163 or just the SRCR5 domain confers resistance to infection with both PRRSV-1 and PRRSV-2 viruses. By performing a mutational analysis of CD163, previous *in vitro* infection experiments showed resistance to PRRSV infection following deletion of exon 13 which encodes the first 12 amino acids of the 16 amino acid PSTII domain. These findings predicted that removal of exon 13 can be used as a strategy to produce gene-edited pigs fully resistant to PRRSV infection. In this study, to determine whether the deletion of exon 13 is sufficient to confer resistance of pigs to PRRSV infection, we produced pigs possessing a defined *CD163* exon 13 deletion (ΔExon13 pigs) and evaluated their susceptibility to viral infection. Wild type (WT) and CD163 modified pigs, placed in the same room, were infected with PRRSV-2. The modified pigs remained PCR and serologically negative for PRRSV throughout the study; whereas the WT pigs supported PRRSV infection and showed PRRSV related pathology. Importantly, our data also suggested that removal of exon 13 did not affect the main physiological function associated with CD163 *in vivo*. These results demonstrate that a modification of CD163 through a precise deletion of exon 13 provides a strategy for protection against PRRSV infection.

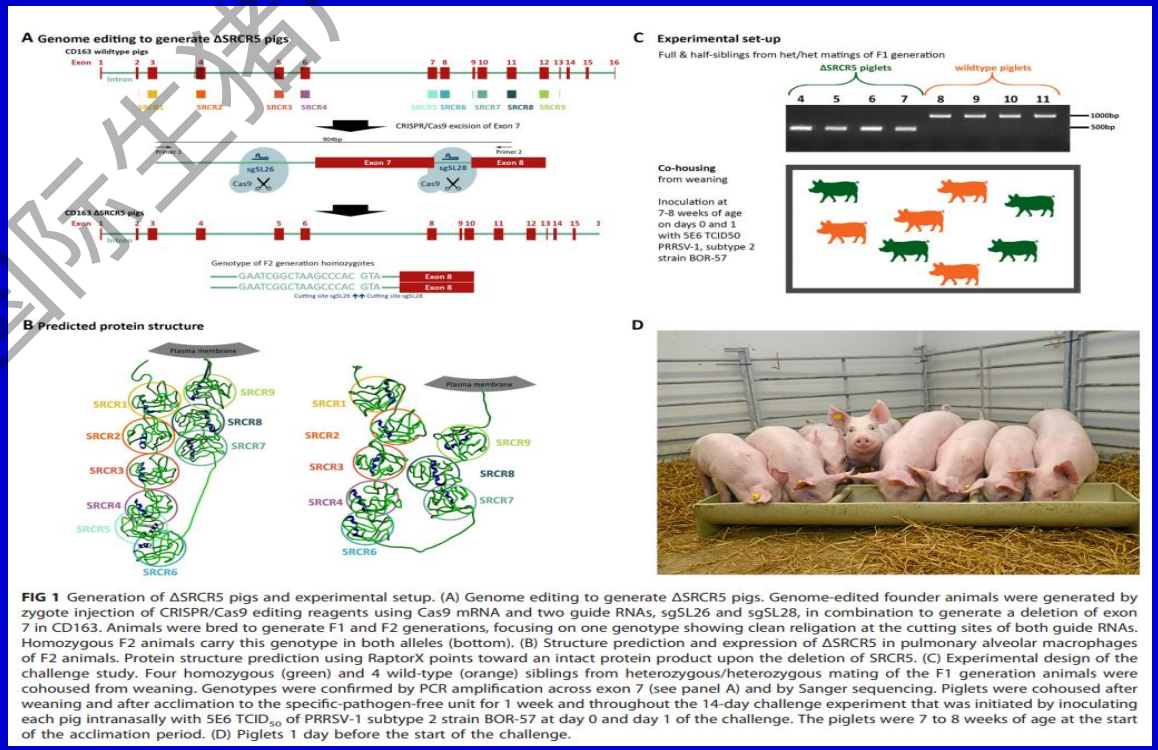


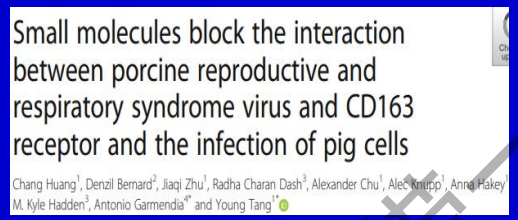
FIG 1 Generation of ΔSRCR5 pigs and experimental setup. (A) Genome editing to generate ΔSRCR5 pigs. Genome-edited founder animals were generated by zygote injection of CRISPR/Cas9 editing reagents using Cas9 mRNA and two guide RNAs, sgSL26 and sgSL28, in combination to generate a deletion of exon 7 in CD163. Animals were bred to generate F1 and F2 generations, focusing on one genotype showing clean religation at the cutting sites of both guide RNAs. Homozygous F2 animals carry this genotype in both alleles (bottom). (B) Structure prediction and expression of ΔSRCR5 in pulmonary alveolar macrophages of F2 animals. Protein structure prediction using RaptorX points toward an intact protein product upon the deletion of SRCR5. (C) Experimental design of the challenge study. Four homozygous (green) and 4 wild-type (orange) siblings from heterozygous/heterozygous mating of the F1 generation animals were cohoused from weaning. Genotypes were confirmed by PCR amplification across exon 7 (see panel A) and by Sanger sequencing. Piglets were cohoused after weaning and after acclimation to the specific-pathogen-free unit for 1 week and throughout the 14-day challenge experiment that was initiated by inoculating each pig intranasally with 5E6 $TCID_{50}$ of PRRSV-1 subtype 2 strain BOR-57 at day 0 and day 1 of the challenge. The piglets were 7 to 8 weeks of age at the start of the acclimation period. (D) Piglets 1 day before the start of the challenge.

Future research on PRRS control
蓝耳控制的未来研究

- Development of PRRSV vaccines to have broaden cross-protective efficacy - Universal vaccine

  开发有广谱交叉保护力的蓝耳疫苗-通用疫苗

- Development of antiviral substance for PRRSV replication
- 开发对蓝耳病毒复制有抗病毒作用的物质
  - Compounds targeting CD163 靶向CD163的复合物


Small molecules block the interaction between porcine reproductive and respiratory syndrome virus and CD163 receptor and the infection of pig cells

Chang Huang[1], Denzil Bernard[2], Jiaqi Zhu[1], Radha Charan Dash[3], Alexander Chu[1], Alec Kruppo[1], Anna Hakey[1], M. Kyle Hadden[3], Antonio Garmendia[4*] and Young Tang[1*]


Recent advances in inhibition of porcine reproductive and respiratory syndrome virus through targeting CD163

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Journal of Virology

VACCINES AND ANTIVIRAL AGENTS

Identification of New Compounds against PRRSV Infection by Directly Targeting CD163

Jiaqi Zhu,[a] Xin He,[b] Denzil Bernard,[c] Jianing Shen,[a] Yue Su,[a] Andrew Wolek,[a] Brianna Issacs,[a] Neha Mishra,[d] Xiuchun Tian,[a] Antonio Garmendia,[d] Young Tang[a,b]

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  - Feed additive to inhibit viral replication - Medium chain fatty acids
  - 抑制病毒复制的饲料添加剂-中链脂肪酸

Li L, Wang H, Dong S, Ma Y. Supplementation with alpha-glycerol monolaurate during late gestation and lactation enhances sow performance, ameliorates milk composition, and improves growth of suckling piglets. Journal of Animal Science and Biotechnology. 2023; 14(1): 1-12. https://doi.org/10.1186/s40104-023-00848-x

Antiviral effect of MCFA to PEDV
中链脂肪酸对流行性腹泻病毒的抗病毒作用

Medium chain fatty acids 中链脂肪酸

- Feed additive fatty acids with 6, 8, 10 or 12 carbon atoms
饲料添加剂脂肪酸含有6、8、10、12个碳原子
- Ability to make weak certain types of bacteria or viruses
对某些细菌或病毒有致弱能力

Table 1: Effects of medium chain fatty acids, Sal CURB, and fat source on porcine epidemic diarrhea virus infectivity measured by pig fecal swabs and cecum content by qRT-PCR analysis[1]

	PEDV N-gene Real Time-PCR, cycle threshold						
		Fecal swabs					*Cecum contents*[5]
Item	Feed CT[3]	0 dpi[2]	2 dpi	4 dpi	6 dpi	7 dpi	7 dpi
Day 0							
PEDV negative	> 40.0	---[4]	---	---	---	---	> 45.0
PEDV positive	28.3	---	-- +	+++	+++	+++	22.2
Day 1							
PEDV positive	29.7	---	- ++	+++	+++	+++	20.9
Sal CURB[6]	33.0	---	---	---	---	---	> 45.0
1% MCFA (non-aero)	38.3	---	---	---	---	---	> 45.0
0.66 % Caproic	35.0	---	---	---	---	---	> 45.0
0.66% Caprylic	35.7	---	---	---	---	---	> 45.0
0.66% Capric	30.7	---	---	---	---	---	> 45.0
0.66 % Lauric	30.7	---	---	+++	+++	+-+	28.4
0.3% FRA C12[7]	30.7	---	---	+++	+++	+++	30.2
1% Choice white grease	30.0	---	---	+++	+++	+++	15.3
1% Soybean oil	30.0	---	---	+++	+++	+++	24.0
1% Canola oil	30.7	---	---	+++	+++	+++	20.3
1% Palm kernel oil	30.0	---	---	+++	+++	+++	22.1
1% Coconut oil	30.3	---	---	---	---	+-+	42.1

[1]An initial tissue culture containing 10^6 $TCID_{50}$/mL PEDV was diluted to 10^5 $TCID_{50}$/mL PEDV. Each treatment was inoculated with the 10^5 $TCID_{50}$/mL PEDV resulting in 10^4 $TCID_{50}$/g PEDV inoculated feed matrix. Three feed samples per day and treatment were collected and diluted in PBS. The supernatant from each sample was then collected for pig bioassay. The supernatant was administered one time via oral gavage on d 0 to each of three pigs per treatment (10 mL per pig). Thus, the cecum contents are represented by a mean of 3 pigs per treatment. Pigs were inoculated at d 12 age.

Day post inoculation.

A cycle threshold (CT of > 40 was considered negative for presence of PEDV RNA. Feed CT analysis was carried out at Kansas State University.

[4]In each instance a (–) signals a negative pig in the bioassay and a (+) represents a positive fecal swab in the bioassay. Each day post inoculation within each treatment has three symbols within each row and column which represents one of the three pigs in each treatment.

[5] A cycle threshold (CT of > 45 was considered negative for presence of PEDV RNA. Cecum content analysis was carried out at Iowa State University.

[6] Formaldehyde, Kemin Industries, Des Moines, IA.

[7] Framelco, Raamsdonksveer, Netherlands.

Sal CURB, 1% MCFA, 0.66% caproic, 0.66% caprylic and 0.66% capric acids enhance the RNA degradation of PEDV in swine feed.

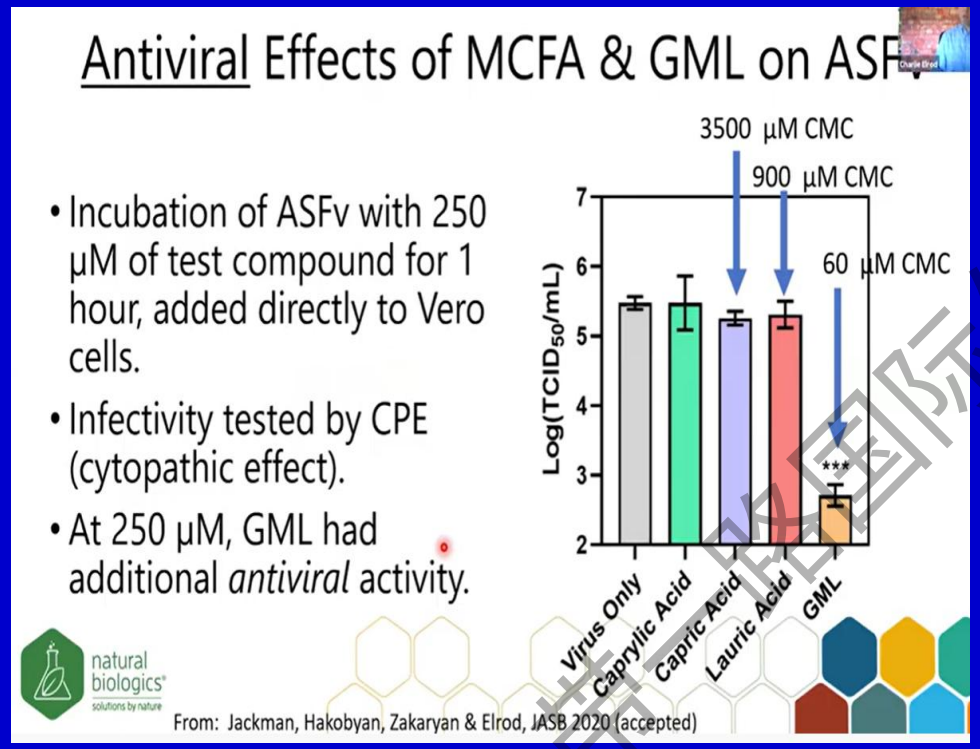
Sal-CURB、1%中链脂肪酸、0.66%己酸、0.66%辛酸和0.66%癸酸促进猪饲料中PEDV的RNA降解。

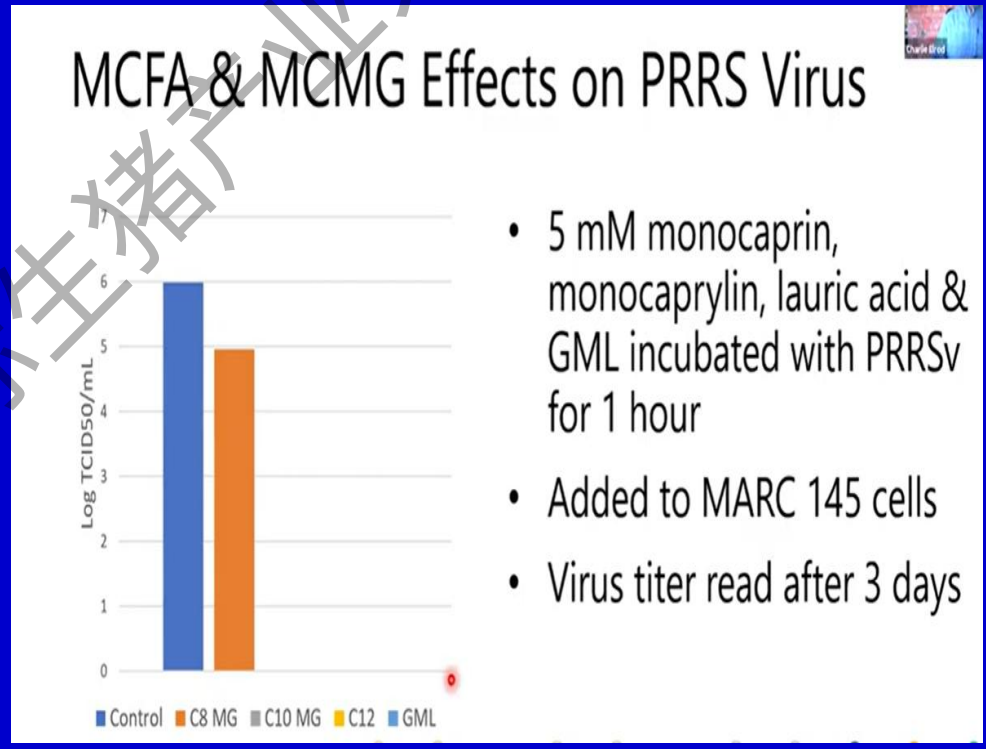
Negative bioassay in the pigs showing that the treatments prevented infection

在猪上进行的阴性生物测定表明，这些处理可以预防感染。

Inhibition of viral growth *in vitro* following treatment with MCFA

使用中链脂肪酸处理在体外抑制了病毒生长





Significant reduction of ASFV with GML
月桂酸甘油酯能显著减少非瘟病毒

No PRRSV was detected with C10MG, C12 or GML
使用C0MG,C12或月桂酸甘油酯处理检测不到蓝耳病毒

Summary
总结

- History, clinical signs, pathogenesis 历史，临床症状，发病机制
  - Reproductive vs respiratory forms 繁殖型VS呼吸型
- PRRSV variants & grouping 蓝耳病毒变异体&分组
  - Genetic vs serologic groups 基因分类VS血清分类
- Homologous vs heterologous challenge 同源性攻毒VS异源性攻毒
  - Protection up to 604 days for reproductive form against homologous challenge
  - 繁殖型的病毒保护力对抗同源攻毒的时间长达604天
- Vaccination strategy 免疫策略
  - MLV: Repeated vaccination with different MLV
  - 弱毒苗：使用不同弱毒苗重复免疫
  - Inactivated vaccine: Repeated vaccination with farm-specific virus
  - 灭活疫苗：使用农场专有病毒重复免疫