

And finally...  
A cure for PRRS!

**Raymond (Bob) Rowland**  
**K-State Swine Day Progress Report**  
**November 17, 2016**  
**Manhattan**



# Genetic approaches for improving swine health in response to PRRSV infection

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## Collaborators

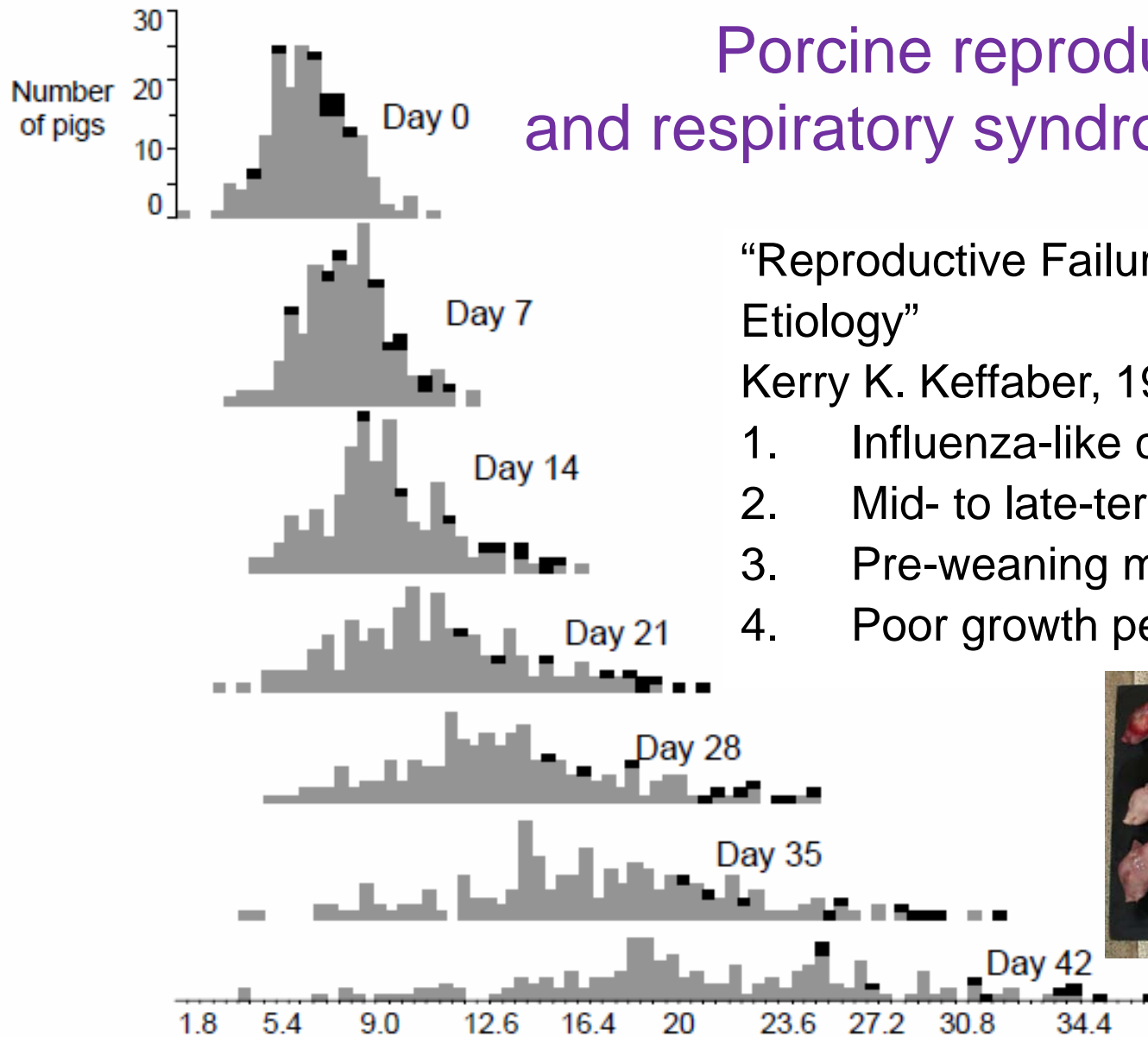
**Randy Prather**, University of Missouri- Genetically modified pigs that are disease resistant

**Jack Dekkers**, Iowa State University- Genomic markers for breeding disease resistance

**Joan Lunney**, ARS-USDA- Genetics of the response of pigs to infection



# Porcine reproductive and respiratory syndrome (PRRS)



“Reproductive Failure of Unknown Etiology”

Kerry K. Keffaber, 1989, AASP

1. Influenza-like clinical signs
2. Mid- to late-term abortions
3. Pre-weaning mortality
4. Poor growth performance



Changes in Weight Distribution after Infection

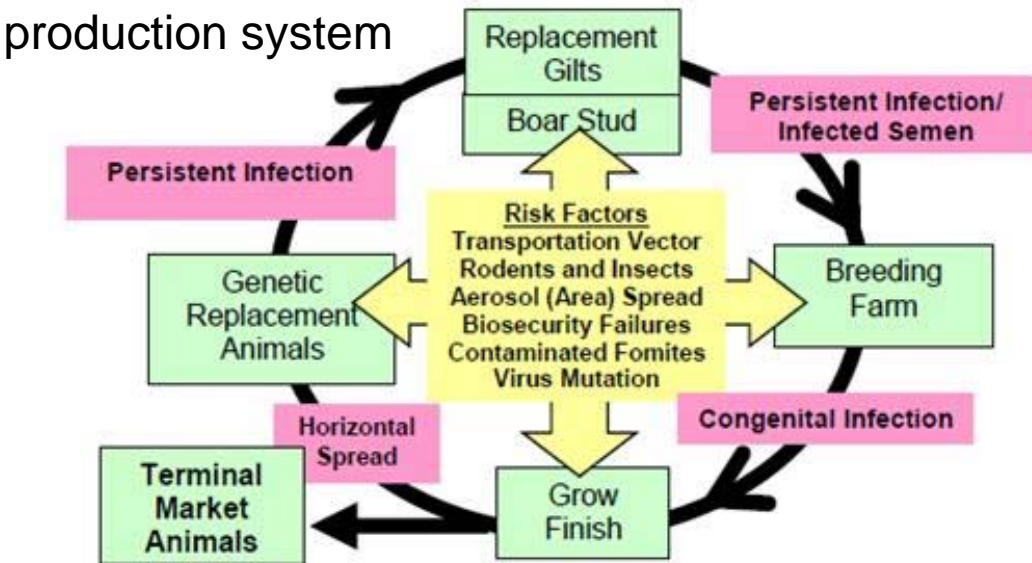
**\$14 billion in losses (\$600million/year)**



# PRRS is a production system disease

Endemic phase with outbreaks of severe disease

Persistence in a production system



2003-Eric Neumann

Stealthy

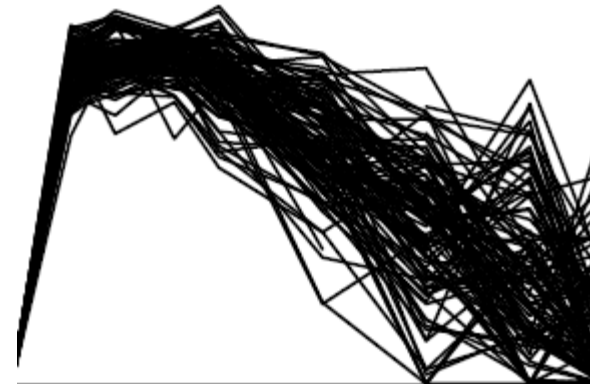
Easily transmitted

Persistent

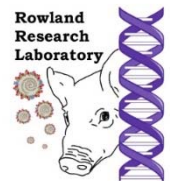
Participates in polymicrobial diseases

Viremia

Persistence in a population and within a pig



Day after infection



# The greatest cost of PRRSV is wasted feed

Sick and dead pigs  
Slow growing pigs  
Secondary infections



Corn Prices



Nutritional, Environmental and Social  
Impacts

# Integrated approach for PRRS control

## Disease Control

Vaccines  
Detection  
Ecology  
Epidemiology  
Biosecurity  
Sociology

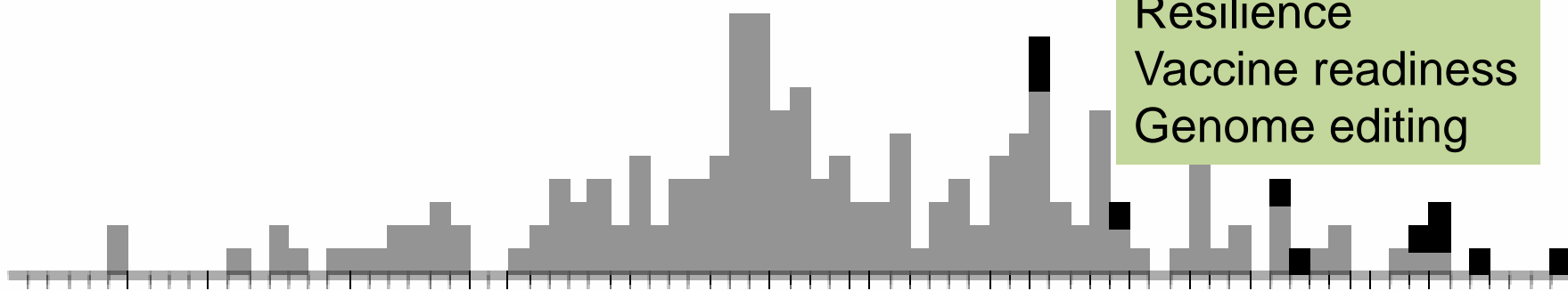
## Nutrition

Feed efficiency  
Feed formulation  
Microbiome

## Pig Genetics

Resistance  
Tolerance  
Resilience  
Vaccine readiness  
Genome editing

Getting back the 5-10% that PRRS takes



# PRRS vaccines

- Modified live virus (MLV) vaccine introduced in the U.S. 1994- approved for use in PRRSV-infected herds
- MLV limitations-virus shedding, persistent infection, incomplete immune protection, inability to differentiate infected from vaccinated animals (DIVA), potential for reversion to virulence
- Killed vaccines are not effective
- Subversion of host immunity and antigenic variation have made further advances in vaccines difficult to achieve

**Conclusions:** Vaccines are a poor option for disease control and eradication- Vaccinated animals cannot be transported to PRRSV-free regions.



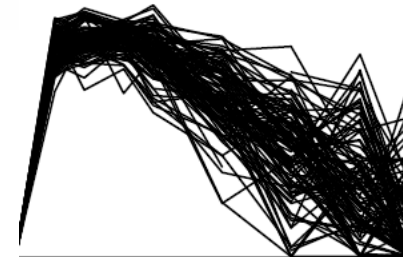
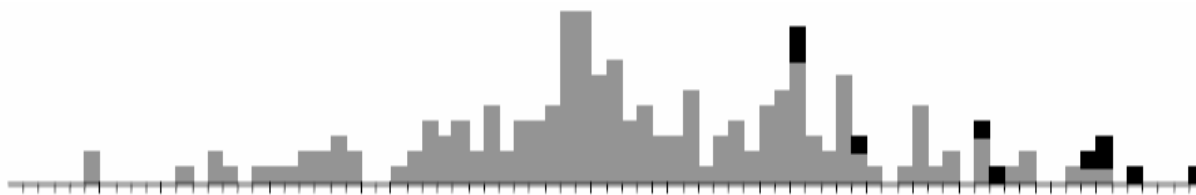
# The application of genetics for improving animal health

- Marker selected breeding to improving response
  - Genotyping
  - GWAS
- Modify genes involved in response to infection
  - Insertion of genes to promote resistance
  - Deletion of genes involved in virus susceptibility

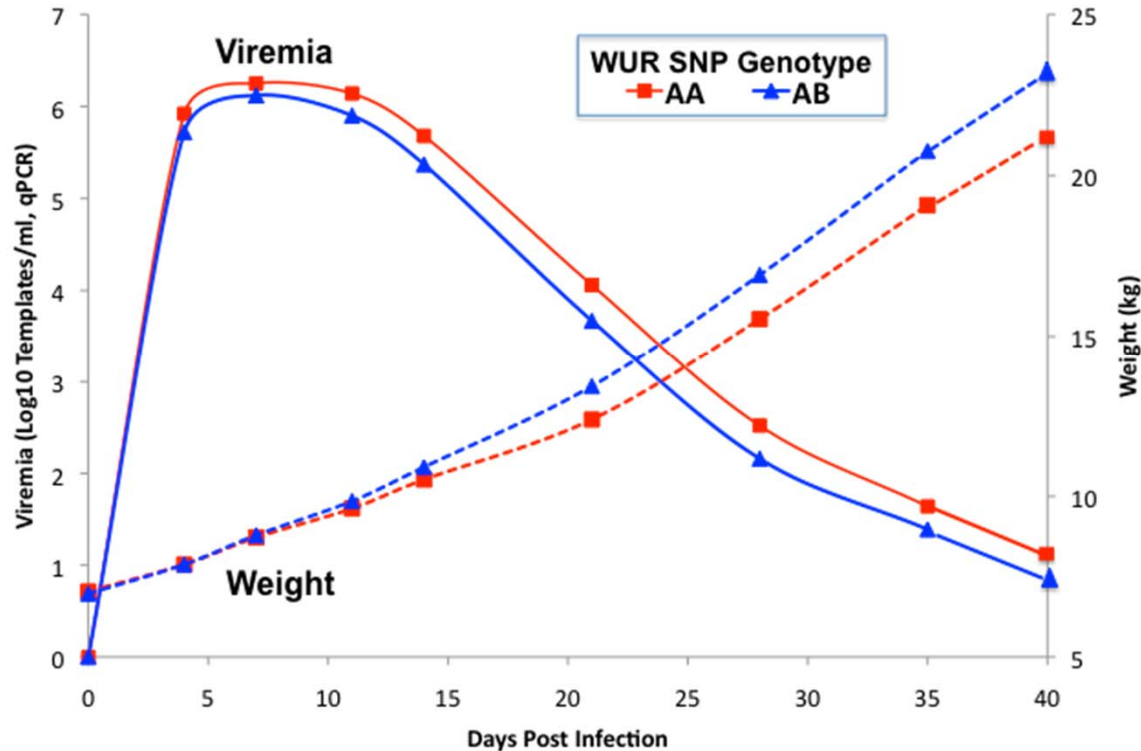


# Important findings

- Approximately 40% of how a pig responds to PRRSV infection is inherited
- The remaining 60% is dependent on
  - Maternal effects
  - Environment
  - Virus
- Impact- breed pigs for improved disease resistance



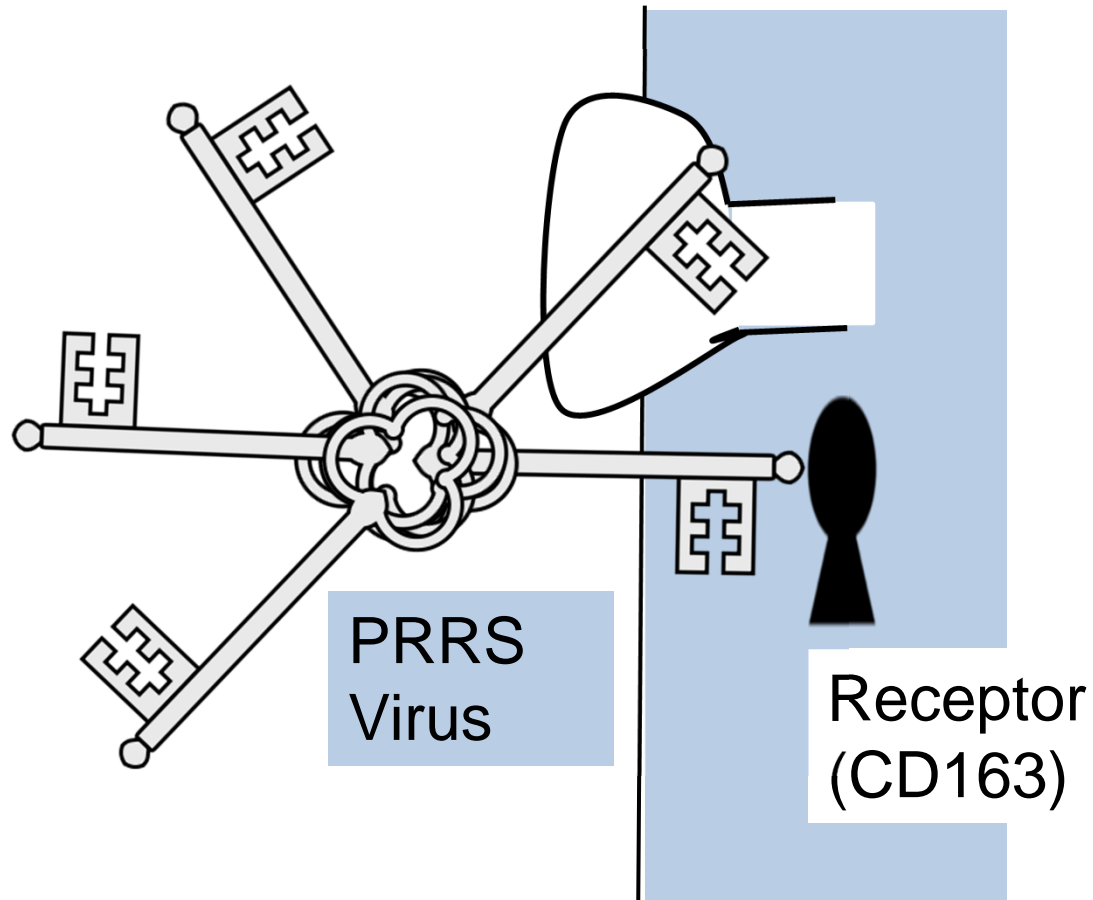
The favorable SSC4 marker, WUR, results in a 10% increase in weight and a decrease in viremia



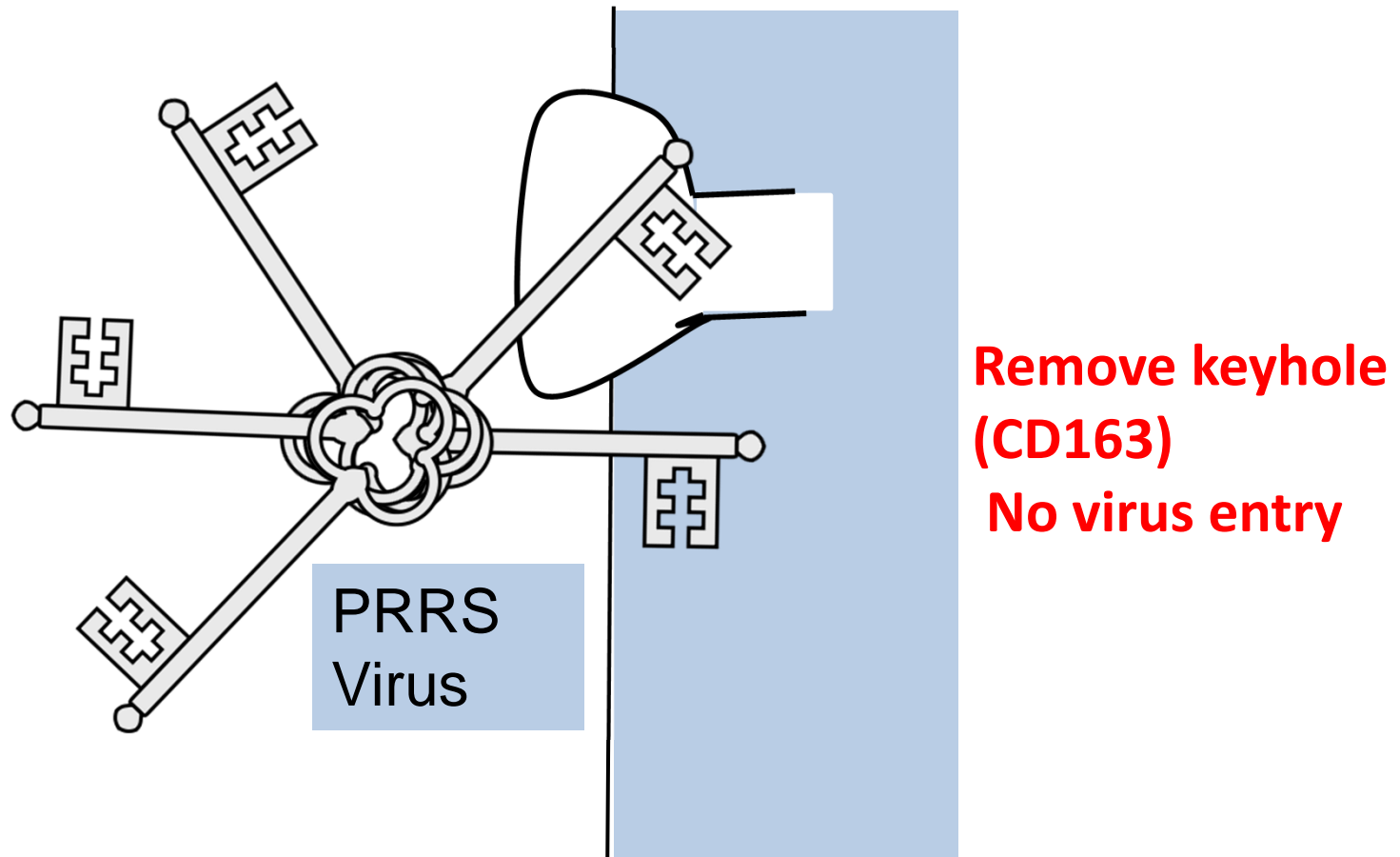
Boddicker, et al. 2012. Evidence for a major QTL associated with host response to porcine reproductive and respiratory syndrome virus challenge. J Anim Sci. 90:1733-1746



# Key-Lock mechanism for virus entry into cells



# Key-Lock mechanism for virus entry



Gene modification to remove the keyhole mechanism  
(CD163 receptor protein) and block infection

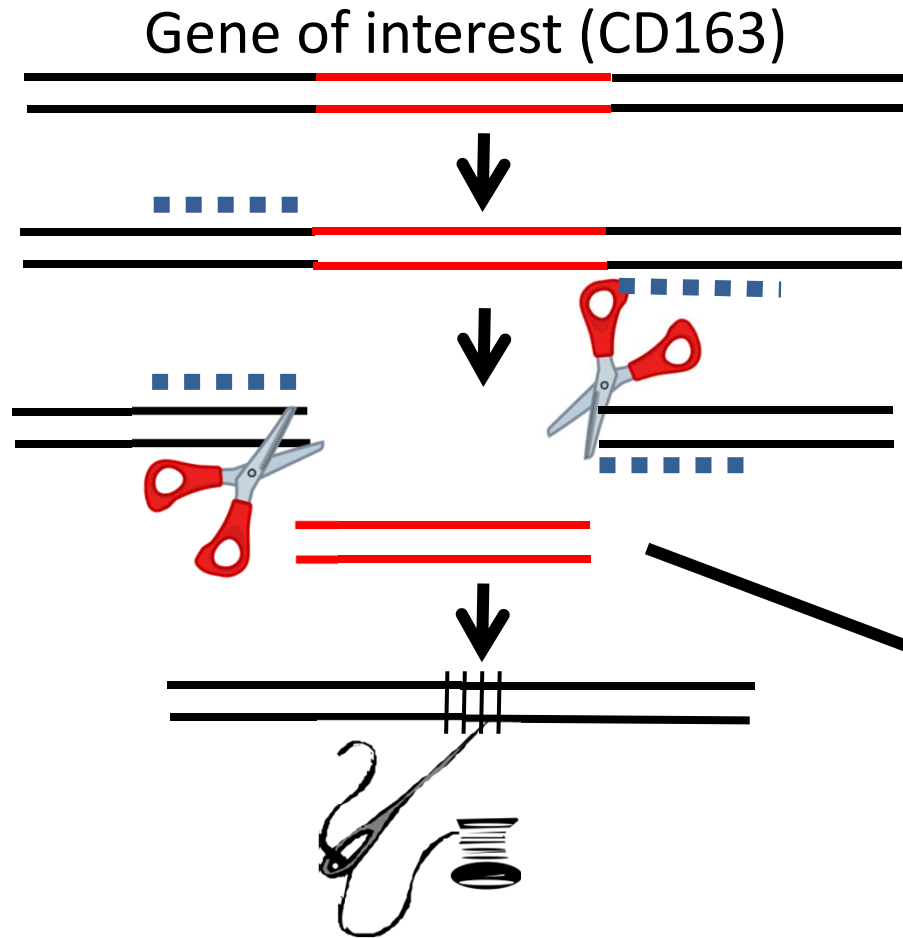


# CRISPR/Cas 9 system: a revolution in genetic modification

- Traditional transgenic techniques
  - Difficult and cumbersome
  - Insertion of foreign DNA into the genome
- CRISPR- Genome editing
  - Fast (3 months)
  - No foreign DNA
  - Imitates processes that normally occur during evolution or breeding



# CRISPR/Cas 9 system



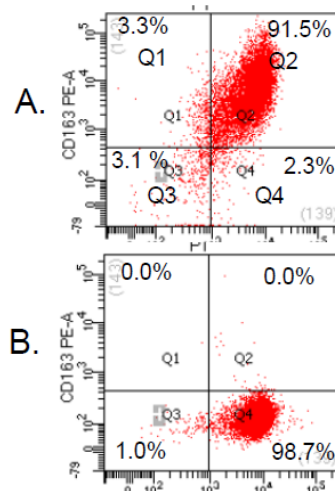
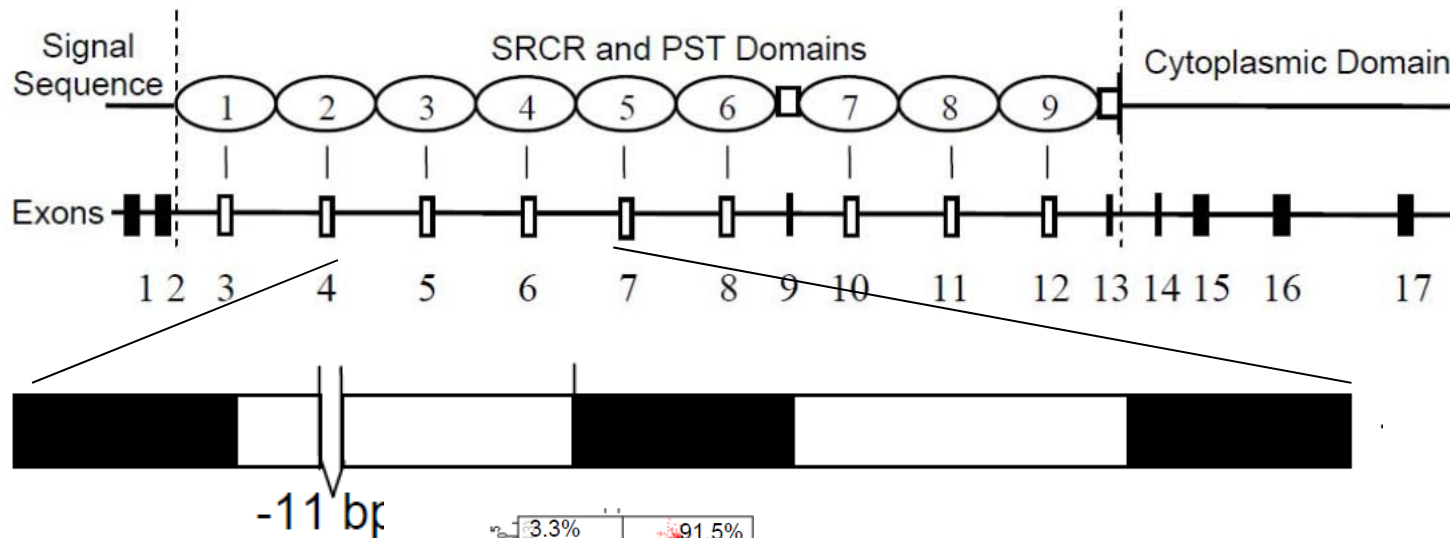
Guide sequences direct where the genome is cut

Molecular scissors cut out DNA segment

Segment is removed and the DNA ends rejoined

Guide sequence .....

# Knocking out CD163 by deleting 11 of 2.7 billion bases of the pig genome (Randy Prather)



Normal pig  
CD163 is present

CD163 knockout pig  
CD163 is absent

December 7, 2015

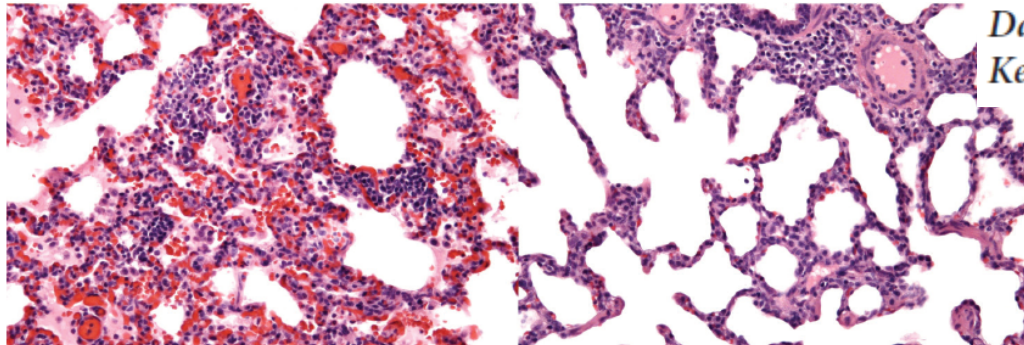
# Gene-edited pigs are protected from porcine reproductive and respiratory syndrome virus

NATURE BIOTECHNOLOGY

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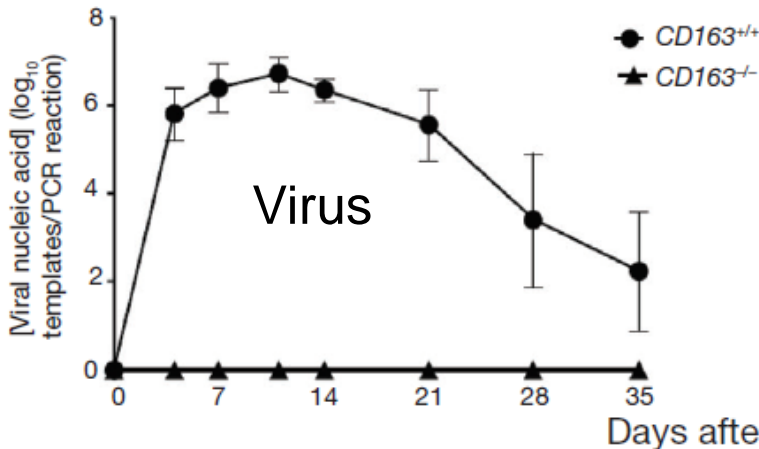
a CD163-Positive

b No CD163

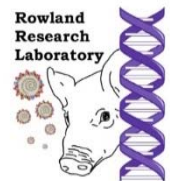
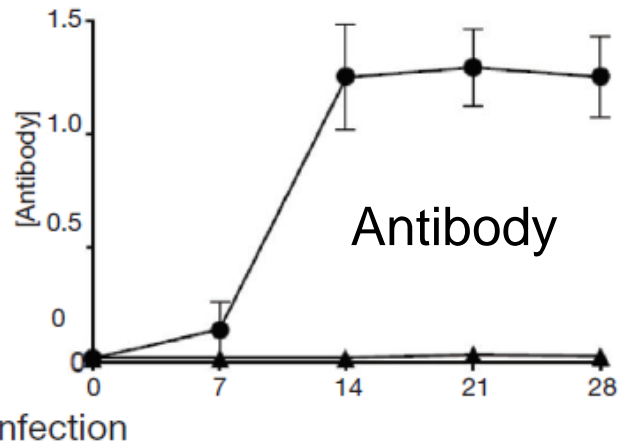


No CD163  
No key-lock  
No PRRSV

a



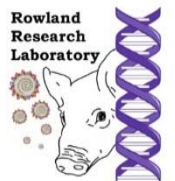
b





# Future directions

- National Bio and Agro-Defense Facility (NBAF)
- Refining the CD163 knockout
- Extending the technology to other pig viruses



**PHGC**

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**Iowa State University**  
Jack Dekkers



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- Genus PIC

