And finally…
A cure for PRRS!

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K-State Swine Day Progress Report
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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

$14 billion in losses ($600 million/year)
PRRS is a production system disease
Endemic phase with outbreaks of severe disease

Persistence in a production system
Stealthy
Easily transmitted
Persistent
Participates in polymicrobial diseases

2003-Eric Neumann

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

Nutritional, Environmental and Social Impacts

Corn Prices
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.

Key-Lock mechanism for virus entry into cells

PRRS Virus

Receptor (CD163)
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

Gene of interest (CD163)

Guide sequences direct were the genome is cut

Molecular scissors cut out DNA segment

Segment is removed and the DNA ends rejoined

Guide sequence

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

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a) CD163-Positive

b) No CD163

No CD163
No key-lock
No PRRSV

Virus

Antibody
Future directions

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