North American PRRS Symposium on PRRS, Emerging and Foreign Animal Diseases and National Swine Improvement Federation NAPRRS-NSIF Joint Conference

December 1-3, 2017
Intercontinental Chicago Magnificent Mile

November 24, 2017- Conference registration deadline
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

Persistence in a population and within a pig

Viremia

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

• Modify genes involved in response to infection
  Insertion of genes to promote resistance
  Deletion of genes involved in virus susceptibility

“Genome Editing”
The favorable SSC4 marker, WUR, results in a 10% increase in weight and a decrease in viremia.


Resistance
Tolerance
Resilience
Genetic modification
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  ..........
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
Gene-edited pigs are protected from porcine reproductive and respiratory syndrome virus.

CD163-Positive

No CD163

Virus

Antibody

No CD163

No key-lock

No PRRSV
Reproductive PRRS
Infection of pregnant gilt/sow at 90 days of gestation
Prevention of reproductive PRRS
The end of a disease

Table 1. CD163 parental and fetal genotypes used in this study

<table>
<thead>
<tr>
<th>Gilt No.</th>
<th>CD163 Genotype</th>
<th>Day of Infection*¹</th>
<th>Day of Gestation*²</th>
<th>No. of Fetuses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Dam</td>
<td>Fetus</td>
<td></td>
</tr>
<tr>
<td>138</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>91</td>
</tr>
<tr>
<td>139*³</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>91</td>
</tr>
<tr>
<td>140</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
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<tr>
<td>84</td>
<td>+/+</td>
<td>-/-</td>
<td>+/-</td>
<td>89</td>
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<td>87</td>
<td>+/+</td>
<td>-/-</td>
<td>+/-</td>
<td>89</td>
</tr>
<tr>
<td>122</td>
<td>+/+</td>
<td>-/-</td>
<td>+/-</td>
<td>89</td>
</tr>
<tr>
<td>86</td>
<td>-/-</td>
<td>-/-</td>
<td>-/-</td>
<td>90</td>
</tr>
<tr>
<td>121</td>
<td>-/-</td>
<td>-/-</td>
<td>-/-</td>
<td>90</td>
</tr>
</tbody>
</table>

*¹ Gestation day when dams were infected
*² Gestation day when fetuses were removed
*³ PRRSV-infected dam aborted at 106 days of gestation
Prevention of reproductive PRRS
The end of a disease

<table>
<thead>
<tr>
<th>Dam No.</th>
<th>Genotype Dam</th>
<th>Genotype Fetus</th>
<th>Right Uterine Horn</th>
<th>Left Uterine Horn</th>
</tr>
</thead>
<tbody>
<tr>
<td>138 (3.6)</td>
<td>+/+</td>
<td>+/+</td>
<td>6.9</td>
<td>5.3</td>
</tr>
<tr>
<td>140 (4.1)</td>
<td>+/+</td>
<td>+/+</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>84 (N)</td>
<td>-/-</td>
<td>+/-</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>87 (N)</td>
<td>-/-</td>
<td>+/-</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>122 (N)</td>
<td>-/-</td>
<td>+/-</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>86 (N)</td>
<td>-/-</td>
<td>-/-</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>121 (N)</td>
<td>-/-</td>
<td>-/-</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
The end of a disease

- The absence of CD163 in the dam surrounds the developing fetus with a protective barrier, preventing infection with PRRSV
- The piglets are born with normal CD163 levels and are susceptible to PRRSV
- Still need that miracle vaccine
Mapping the regions where PRRSV interacts with CD163
The NBAF, a new, state-of-the-art biosafety level (BSL) 3 & 4 facility located in Manhattan, KS, will enable the U.S. to conduct comprehensive research, develop vaccines and anti-virals, and provide enhanced diagnostic capabilities to protect our country from numerous foreign animal, emerging and zoonotic diseases to assist in protecting our food supply and the nation’s agriculture economy and public health.
NBAF-associated projects in the Rowland lab (Biosecurity Research Institute)

African swine fever virus (ASFV) and classical swine fever virus (CSFV)

Vaccines
Diagnostics
Genetics of disease resistance
Risks for introduction
Co-Directors
USDA ARS BARC
Joan Lunney
Kansas State University
RRR (Bob) Rowland
Iowa State University
Jack Dekkers

PHGC

Kansas NBAF Transition Fund

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