# Integrating animal genomics with animal health: Genetics of vaccine response in cattle

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## Animal health: An economically important trait

- Animal health economically important trait in beef cattle
- 37% cow-calf operations treated calves for scours (USDA, 2010)
- 54% calf loss at ≥ 3 mos. age caused by respiratory or digestive disease (USDA, 2010)
- Economic costs of BVDV $94 per animal exposed to PI cow/steer (Hessman *et al.*, 2009)



## Improving animal health

- Veterinary and management interventions
  - Vaccines
  - Preventive care
  - Treatment
  - Nutrition
  - Housing
  - Animal husbandry
- Genetic selection for improved animal health

## The limitation to this approach

"Uninfected"

"Infected"

Why are these animals "healthy"?

Animals are truly resistant to pathogen?

Animals not exposed to pathogen?

Animals have/had the disease, but you didn't know it?

"**Disease challenge**" trials often too costly and arguably unethical (given the large number of animals needed for genetic studies)



## Overcoming the exposure problem

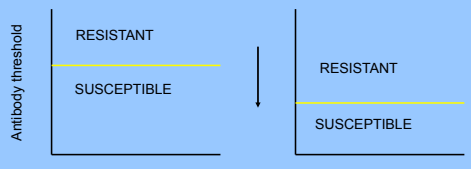
- Vaccines routinely administered in the US
- All vaccinated animals are exposed to the components of the vaccine
  - A large group of animals on-farm will be administered (and thus exposed to) the same vaccine at the same time
  - The same amount of vaccine is given to each animal, i.e., pathogen load should be similar (at least in theory)
- Can measure response of the animal to the vaccine



## Vaccine response: A primer

= increased disease protection

**However, in reality not all vaccinated individuals are protected from disease.**



## Research motivation

- Traditionally, focused on manufacturing better vaccines
- Alternative: Can we improve health by selecting for cattle that are more resistant to infection following vaccination?
- Genetic selection for stronger immune response
- Identification genes affecting vaccine response
  - Development of better vaccines



## How do we measure vaccine response?

- Humoral immune response
  - Antibodies
- Cell-mediated immune response
  - Activated immune cells
- Easier to measure humoral immune response
- Need to measure both to obtain complete picture of immune response to a vaccine

## Previous research on bovine vaccine response

- Evidence that vaccine response is heritable
  - Sire of calf associated with *B. abortus* vaccine response

    Newman *et al.* (1996) Vet Immunol Immunopathol 50: 43-54.
  - Heritability of BRSV vaccine response = 0.25 to 0.52

    O' Neill *et al.* (2006) Vaccine 24: 4007-16.
- Several genes or quantitative trait loci associated with vaccine response
  - 77 quantitative trait loci for a foot-and-mouth disease peptide vaccine

    Leach *et al.* (2010) BMC Genet 11: 107.



## Gonda Lab Research Aims

- Build a resource population to study bovine vaccine response
- Estimate heritability
- Correlation between BVDV ELISA & SN Types 1, 2
- Identify genetic loci associated with vaccine response
  - Leptin, CR-2, Other candidate genes, and WGAS
- Is vaccine response associated with morbidity/mortality and the innate immune response?



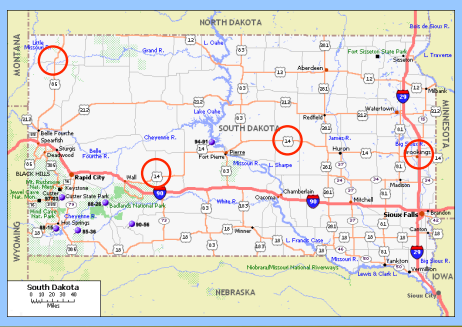
## Bovine Viral Diarrhea Virus (BVDV)

- One of several pathogens causing Bovine Respiratory Disease
  - Bovine Respiratory Syncytial Virus, Parainfluenza-3, etc.
- "Persistently-infected" animals are primary reservoir
- Can cause reproductive problems
- Suppresses immune system
- Cost to beef industry approx. $90 to $95 per animal

  Hessman et al., 2009



## Population resource



## Population resource

- SDSU Cow-calf Teaching & Research Unit, Brookings
  - Approx. 100 cow-calf pairs
  - Angus, some Simmental blood
- SDSU Cow Camp, Miller
  - Approx. 100 cow-calf pairs
  - Angus, Maine-Anjou, and Charolais crosses
  - Fall calving herd
- SDSU Antelope Research Station, Buffalo & Cottonwood Research Station, Philip
  - Approx. 330 cow-calf pairs
  - Angus and Angus crosses
  - Multi-sire pastures instead of AI for breeding



## Measuring BVDV vaccine response

Ouch! Vaccinate calves with Pyramid 5 or 10 vaccine (both include BVDV-1 & 2).

Collect blood sample
1. Test for persistently infected animal
2. Maternal antibody concentration in blood
3. DNA isolation

20-30 days post-vaccination

"Hey, what are you doing back with that needle??"

Collect blood sample
1. Measure BVDV-specifc Abs



## Measuring vaccine response

- Need to account for maternal antibodies at time of vaccination.
- (Day 20-30 Abs) – (Day 0 Abs) = Vaccine response
- Total BVDV-specific antibodies (ELISA)
- Include age, herd, gender, breed composition, and vaccine lot number in model



## Measuring BVDV-specific antibodies

- Enzyme-linked immunosorbent assay (ELISA) may be used as a surrogate for SN titers.
- Cheaper, faster, and subject to less inter-laboratory variation.
- Measures total BVDV-specific antibodies, regardless of whether antibodies can protect an animal from infection.
- BVDV-specific Antibody ELISA (IDEXX)

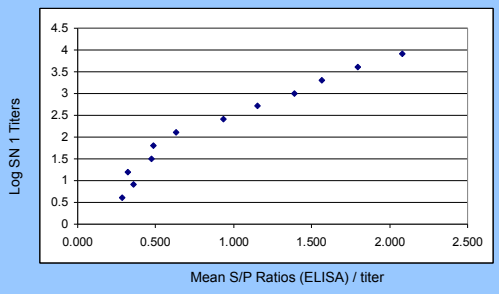


## Comparison of SN and ELISA

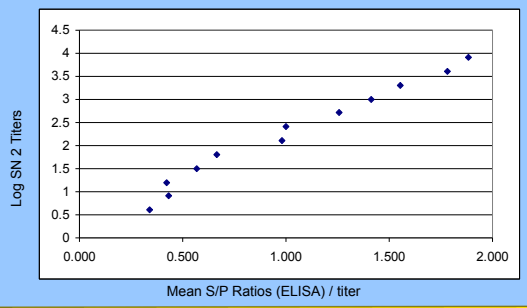
- Collected 406 sera or plasma samples from 193 Angus or Angus-cross calves
- ELISA
  - BVDV-1 and BVDV-2 antibodies
- Serum neutralization type 1
  - BVDV-1 protective antibodies
- Serum neutralization type 2
  - BVDV-2 protective antibodies



## Relationship between ELISA & SN 1



## Relationship between ELISA & SN 2






## Correlations between ELISA, SN 1, and SN 2

- ELISA, SN 1 ρ = 0.809
- ELISA, SN 2 ρ = 0.638
- SN 1, SN 2 ρ = 0.708
- *Conclusions*
  - The BVDV ELISA can be used as an indicator trait (or "surrogate") for SN 1 & SN 2
  - The correlation is strongest between the ELISA and SN 1
  - Weaker relationship between the ELISA and SN at low titers



## Molecular genetic studies on vaccine response

- Leptin
- CR-2 (or CD-21)
- Future candidate gene loci
- Whole-genome association?



## Candidate gene approach

- Leptin (*Lep*)
  - Associated with backfat, marbling, and average daily gain
  - Also involved in pathways affecting immune response; associated with humoral rabies vaccine response in cattle (Asiamah et al., 2009)
  - No evidence for association with BVDV humoral vaccine response (n = 267; *P* = 0.26)
  - **Sire of calf was associated with BVDV vaccine response (*P* < 0.05)**

## Candidate gene approach

- Complement Receptor-2 (*Cr-2*)
  - Co-receptor that binds with antibody complexes on surface of B-cells
  - Synonymous polymorphism in *Cr-2* not associated with BVDV vaccine response (*P* > 0.05)
- Candidate gene approach = "shot in the dark"

## Whole-genome association

- Genotype animals with 3K or 50K SNP panel
- Measure more immune response parameters
  - Humoral immune response to other components of the vaccine (i.e., BRSV, $PI_3$, etc.)
  - Cell-mediated immune response to vaccine
- Less biased than candidate gene approach

## Unanswered questions

- Is measurement of antibodies in response to vaccination sufficient for characterizing immune response?
- How heritable is vaccine response in U.S. beef animals?
- Relationship between immune response and clinical protection?
- Can we develop a DNA test for vaccine response/ animal health?



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