

Summary of Bovine Respiratory Disease Research: 1983-2009

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1983 Symposium: Perspectives into the Future of BRD Research, Dr. Robert Kahrs

- Basic experiments and field studies
 - Regardless, scholarly approach, ask *how* and *why*?
- Newer technology
- New generation of researchers, trained outside of veterinary medicine- For traditionalists in BRD research, biotechnology is horrendous
- New era of data-gathering
 - Field data, vaccine evaluation, surveillance, epidemiology

1983 Symposium: Perspectives into the Future of BRD Research, Dr. Robert Kahrs- Future Research

- Immuno- pathology, pneumonic pasteurellosis, immunomodulation
- Endemic infectious agents in cattle for BRD, investigate persistence and disease mechanisms
- Immunosuppression “alleged” by viruses and bacteria
- Pathophysiology of stress
- Environmental issues, influence of marketing of cattle
- Antiviral and antibacterial agents: prophylactic and after infections established
- New generation of vaccines
- New generation of microbiologists
- Field studies, expensive, but need to be well designed and evaluated

1983 Symposium: Perspectives into the Future of BRD Research, Dr. Robert Kahrs- Future Research

- Team approach to research
- Funding by USDA should be increased
- Producers should pioneer in an area not done before, finance research
- Biologics industry must rethink its role for research community, universities
- Establish National Institute of Veterinary Medicine: research funding
 - Due to plant research competition, increased regulations, and agriculture politics
- Another symposium in 1993 to address BRD

Research Sources and Funding

- Various types from basic, clinical, field studies
- Multistate research project supported by North Central Agricultural Experiment (AES)
- Regional, now national in scope , California to Georgia
- Outreach
 - 1983 Symposium, Amarillo, TX with the AVC
 - AVC meeting in December 2001
- Sources of funding
 - Hatch (federal AES) and ARS
 - State –AES
 - USDA competitive grants
 - Commercial companies
 - Private foundations
 - Producer groups
 - Limited funding from NIH or FDA of animal models or public health aspects of BRD therapy , and Homeland Security, DOD

Methods of Study Since 1983 Symposium

- ELISA tests for antigens and antibodies
- Monoclonal antibodies
- Recombinant DNA expressed proteins
- Deletion mutants
- Knock outs
- Pox virus and adenovirus vectored vaccines
- Restriction enzyme fragment polymorphism: DNA
- Flow cytometry
- Cell subpopulations: T-cells
- Subunit vaccines
- DNA vaccines
- Immunohistochemistry (IHC)
- Antigen capture ELISA (ACE)
- Polymerase chain reaction (PCR)
 - Real time
 - Gel-based
- Proteomics
- Metabolomics
- Sequencing of genome including segments
- Cytokines and network
- Toll- like receptors
- Vaccinology

Research Formats

- Basic studies- laboratory
 - Characterize agents, molecular, proteomics, metabolomics
 - Immune system
 - Diagnostic test, and antimicrobial development
- Experimental studies: *in vivo*
 - Pathogenesis
 - Vaccine development and evaluation
 - Antimicrobial evaluation
- Government approval and label requirements
- Surveillance
 - Evaluate and compare vaccines, antimicrobials
 - Use of diagnostic laboratory information
 - Emerging and re-emerging diseases, antimicrobial susceptibility
 - Evaluate diagnostic tests

Accountability : Outcomes for Success

- Reduction of disease incidence
- Better understanding of BRD pathogenesis
- Detection of new agents and new strains of current agents
- Understanding and application of knowledge of acquired and innate immune systems
- Development of new vaccines and therapeutic agents
- Industry and DVMs successfully applying research for BRD prevention and control
- Recognition by medical and basic science researchers of the scientific value of BRD research
- PubMed (US Library of Medicine) since 1983 through July 19,2009: 1972 papers on BRD

Are we there yet ???

Veni vidi vici
Julius Caesar 47 BC

“ I came, I saw , I conquered”

**Repeated by the late Dr. Eric Williams
to Oklahoma State University Students**

Have We Contributed to Reduced BRD and Their Economic Impact?

- Survey using feedlot monitoring by feedlot veterinary consultants. Loneragan et al, 2001
- Survey of feedlots indicated BRD was the leading cause of morbidity and mortality. Woolums et al., 2005

“I rise up reluctantly as I have not been hit by a train before!”

Spoken by a Pac-10 Athletic Director at NCAA Athletic Directors- University Presidents meeting to discuss intercollegiate athlete recruiting abuses.

We have succeeded in selected areas!!

- Viral vaccines
 - Knowledge of BVDV subtypes. Addition of BVDV2a
 - BRSV MLV and killed vaccines
- *Mannheimia haemolytica* vaccines developed
 - Bacterin, toxoid, bacterial extract
 - Live bacteria
- *Pasteurella multocida*
 - Bacterin, toxoid
 - Live bacteria
- *Mycoplasma bovis*
 - Bacterin

We have succeeded in selected areas!!

- Numerous antibiotics
- NSAID : injectable
- Diagnostic tools
 - Application of monoclonal antibodies
 - Immunohistochemistry (IHC) and antigen capture ELISA
 - Sequencing of genome of infectious agents
 - Polymerase chain reaction (PCR)
 - Sequencing of agents for confirmation and ID of new stains

Veterinary Pharmaceuticals and Biologicals 1982/1983

Antigens

- MLV (Injectable)
 - BHV-1, PI3-V, BVDV (type 1, but not designated)
 - Several companies
- Killed Viral
 - One BHV-1, PI3-V, BVDV
 - One BHV-1, PI3-V
- Intranasal (two)
 - BHV-1, PI-3V
- Often with *Lepto* bacterin
- No BRSV

Companies

- Norden
- Diamond
- Bio-Ceutic
- Wellcome Animal Health
- Dellen
- Fort Dodge
- Haver-Lockhart
- Pitman-Moore
- Beecham
- Colorado Serum

Veterinary Pharmaceuticals and Biologicals 1982/1983

Antigens

- *Pasteurella haemolytica* bacterins
- Some combined with *P. multocida*
- *Haemophilus somnus* bacterins

Companies

- Often with viral MLV vaccines (injectable)

Compendium of Veterinary Products, 11th Ed. 2008

Antigens

- MLV Injectable and nasal
 - BHV-1 (Most with same strain as 50 years ago)
 - BVDV1a and BVDV2a
 - PI-3V (SF-4)
 - BRSV (375)
- Killed
 - BHV-1, PI3-V, BVDV1a, BVDV2a, BRSV

Companies

- Pfizer
- Fort Dodge
- Intervet-Schering Plough
- Merial
- AgriLabs
- Diamond
- Novartis
- Colorado Serum
- Boehringer-Ingelheim
- Production for distributors

Compendium of Veterinary Products, 11th Ed. 2008

Antigens

- *M. haemolytica* and *P. multocida*:
- New formulations and prior vaccines
 - Bacterin-toxoids, cell extracts, bacterins
 - Live MH and PM
- *Histophilus somni* bacterins
 - Changes from 1982 ??

Companies

- Pfizer
- Fort Dodge
- Intervet-Schering Plough
- Merial
- Colorado Serum
- Boehringer-Ingelheim

Veterinary Pharmaceuticals and Biologicals 1982/1983

Antimicrobials

- **Injectable**
 - Penicillin-dihydrostreptomycin (Combiotic, Longicil)
 - Erythromycin
 - Oxytetracycline (Liquamycin)
 - Tylosin
 - Sulfas
- **Oral**
 - Tetracyclines
 - Sulfas

Companies

- Pfizer
- Upjohn
- Bio-Ceutic
- Ceva
- Squibb
- Fort Dodge
- Haver-Lockhart
- American Cyanamid
- Beecham
- Elanco
- Diamond
- Norden

Compendium of Veterinary Products, 11th Ed. 2008

Antimicrobials: NSAID

- **Injectable antimicrobials**
 - *Ceftiofur*
 - *Enrofloxacin*
 - *Florfenicol*
 - *Danofloxacin*
 - *Tilmicosin*
 - *Tulathromycin*
 - Tetracyclines
 - Penicillin, erythromycin, tylosin
 - Spectinomycin
 - Sulfas
- **Oral antimicrobials**
 - Tylosin, sulfas, and tetracyclines
- NSAID- flunixin meglumine

Companies

- Pfizer
- Fort Dodge
- ELANCO
- Intervet-Schering Plough
- Boehringer-Ingelheim
- Bayer
- Alpharma

BHV-1 Research

- BHV subtypes
 - BHV 1.1, BHV1.2a, BHV1.2b
 - BHV 1.3 (CNS)
- Sequencing of genome with specific regions
 - Essential and non-essential genes (73 ORF)
 - Unique long (UL), unique short (US), internal repeat (IR), terminal repeat (TR)
- Immunity: T-cell (CMI) and B-cell (antibodies)
- Latency- neural
 - Recrudescence
- Vaccines
 - [Cooper-Colorado](#), Baker, RLB106 (temperature –sensitive)
 - MLV injectable and intranasal
 - Killed

BHV-1 Research

- BHV-1 disease
 - Respiratory: Acute after arrival-processing
 - Respiratory: Late feeding 70-100 days after processing
 - Issues of late feeding BHV-1 disease
 - Duration of immunity from processing MLV vaccines?
 - Why do multiple MLV doses not protect?
 - New BHV-1 strains? Changes in virulence?
- BHV-1 disease in neonates- BHV-1 vaccine safety
- BHV-1 MLV vaccines in pregnant cows
 - BHV-1 MLV vaccine induced abortions- virus recovered
 - Diagnostic laboratory accessions for aborted fetuses
 - Education issues for producers
 - Problem: failure to follow label requirements
 - Move to vaccinate pregnant cows rather than pre-breeding.

BVDV Research

- Genotypes /subgenotypes- antigenic differences
 - 12 BVDV 1 subgenotypes wide and 2 BVDV2 worldwide
 - BVDV1a, BVDV1b, BVDV2a in US, limited studies for BVDV2b
 - BVDV1b is predominant PI strain in US
- Role in several disease forms in cattle: Acute, persistently infected (PI), Mucosal disease
- Interactions with several BRD pathogens
- Immunosuppression
- Diagnostic testing
 - IHC and antigen capture ELISA
 - PCR testing
- *Role of PI animal for maintenance of infection*
- Recent studies on interspecies transmission : wildlife and cattle

BVDV Research

- Subgenotypes in vaccines: BVDV1a and BVDV2a with known sequences for the strains
- Efficacy and studies for label claims for fetal protection
- Use of PI animals as challenge for vaccine efficacy
- Use of heterologous BVDV subgenotypes for challenge in vaccine efficacy
- Monitoring for world wide BVDV strains that potentially enter the US
- Educational programs and BVDV control on regional basis: potential for larger scale

BRSV Research

- Since 1983- addition of BRSV to MLV and killed viral vaccines
- Impact of host response to BRSV
- Potential of differential T-cell response (Th-1 or Th-2) on disease potential
- Animal model for human RSV- immunopathology
- Current BRSV vaccines

Bovine Coronavirus Research

- BCV associated with BRD disease and healthy animals
 - Isolated from nasal swabs, lungs, BRD cases and healthy animals
 - Seroconversions: coincided with virus reduction in nasal swabs
- BCV occurs with other viruses and pathogenic bacteria of BRD
- Specialized human cell line facilitates studies
- Challenges
 - Model for disease experimentally
- Potential candidate for vaccine for BRD

Mannheimia haemolytica Research

- Prior criticisms for *M. haemolytica* vaccines
- Current vaccines largely replaced prior vaccines
- Key advances
 - Cellular components and exotoxins
 - Immune responses to cell components and leukotoxin
 - Virulence factors
 - Experimental reproduction of disease- models for challenge studies
 - Efficacy for vaccines
 - Licensure requirements and industry use
 - Potential for novel-new vaccines

Pasteurella multocida Research

- Increased attention
- Prior criticisms for vaccines
- Primary and Secondary Invader
- Increase in ratio of PM/ MH isolates in some diagnostic accessions
- Reproduction of disease- model for challenge studies
- Efficacy of vaccines for licensure and industry
- Cellular components
- Measurement of immunity

Histophilus somni Research

- Name change
- Remains a common isolate from BRD cases
 - Diagnostic laboratory accessions
 - More frequently associated with northern US and Canada BRD
- Research on antigens and virulence factors
- Model of synergy with BRSV
- *H. somni* bacterins available
 - Differences to prior products in 1983?
- Appears to need a better challenge method for efficacy studies
- Field evaluation of *H. somni* bacterins??
- Products recommended in some herd health vaccination programs

Mycoplasma bovis Research

- Increased reports of *M. bovis* isolates from BRD cases
- Role as primary and/or secondary invader with other bacteria
- Reports of BVDV and *M. bovis* interaction
 - Respiratory
 - Joint disease
- Characterize immune response
- Better diagnostic tools, PCR
- Vaccines available
 - Autogenous and commercial (USDA licensed)
 - Efficacy issues
- Vaccine use in standard vaccination programs?

Atypical Interstitial Pneumonia (AIP)

- Clinical description
- Pathology reports
- Clinical cases with lesions of other causes
- Mechanisms proposed/studied: not definitive
- Etiology: unclear
- Therapy: efficacy?

Immune Response and Pathogenesis

- Acquired immunity
 - Cell populations
 - T-cell- cytokines
 - CD4+ T cell
 - Th1- CMI/Pro- inflammatory
 - Th2- antibody mediated
 - CD8+ T cell- cytolytic/cytotoxic
 - T regulatory cells
 - B-cells- humoral/antibody
- Innate immunity
- Toll-like receptors
 - Proteins- receptors on cell surfaces for microbial proteins
 - Activate immune response

Pathogenesis

- Viral-bacterial synergy model- Babiuk et al.
 - BHV-1 respiratory challenge followed by aerosol challenge by *M. haemolytica*
 - Functional genomic analysis
 - Altered T-like receptor expression
 - Pro-inflammatory response
 - Use of molecular techniques : host response to viral-bacterial synergy

Prevention and Control

- What do we have ?
 - New viral vaccines: BRSV and BVDV addition to vaccines
 - Bacterial vaccines: Improved *M. haemolytica*
 - Considerable success with new antimicrobials, almost total replacement of injectable antibiotics
 - Wealth of information on basic research- agents, immune system, diagnostics, molecular aspects of infections
- Why continued presence of BRD and economic impact ?

Prevention and Control : Issues to Address

- Critical control points for vaccines and therapeutic agents
- Lessons to revisit on pathogenesis of infections
 - Vaccines-antimicrobials often too late due to prior/current infections
- Health begins in breeding herd
- Can marketing of cattle challenges be overcome?
- Issue of managing disease (high risk cattle) versus higher prices for “healthy calves”.
- New term “ metaphylaxis”
- Mixed reports on preconditioning programs- economics in 1983 symposium

Prevention and Control: Issues to Address

- Mixed results on vaccinations at entry to feedlot
- However, studies of vaccinations prior to feedlot entry reduce illness, treatment costs, and return more value
- Studies show benefit of “ preconditioned calves” – “certified health programs”
 - Return more value when sold through auctions
 - More net income under feedlot conditions

Issues for Researchers and Funding Agencies :Accountability

- Monitoring for emerging/re-emerging diseases
- Acquired immunity- T cell and antibody
- Innate immunity
- Development of innovative vaccines
- Diagnostic tests for field use
- Adjuvants for enhanced immunity and safety
- Diagnostic test differentiating vaccine induced immunity versus natural infections
- New therapeutic agents

Issues for Researchers and Funding Agencies :Accountability

- Economics of disease and control programs
- Bovine genome mapping and markers for resistance and enhanced immunity
- Application of research to current and future marketing
- Natural and organic beef and milk production
- Animal welfare issues
 - Investigator- IACUC, IBS, laboratory certification
 - Production and management
- Government regulations for use of antimicrobials
- Public views of food production
- Food safety and international marketing of food products/animals

