The Molecules of Life: Understanding Biological Systems through Systems Biology

Matthew A. Scott, DVM, PhD
Texas A&M University
College of Veterinary Medicine and Biomedical Sciences
Veterinary Education, Research, and Outreach Program

Conflicts of Interest

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Enrique Doster

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Dana Burk

Ember Reyes

Cory Wolfe

Graduate Students

Current

Hudson McAllister

Fabiola Oyervides

Haleigh Prosser

Bradly Ramirez

Former/Graduated

Rebecca Bigelow

Mollie Greene

Colleagues and Friends

Sarah Capik

Jenna Funk

Kelsey Harvey

Brandi Karisch

Roberto Palomares

John Richeson

Kendall Samuelson

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So, so many more…

Objectives

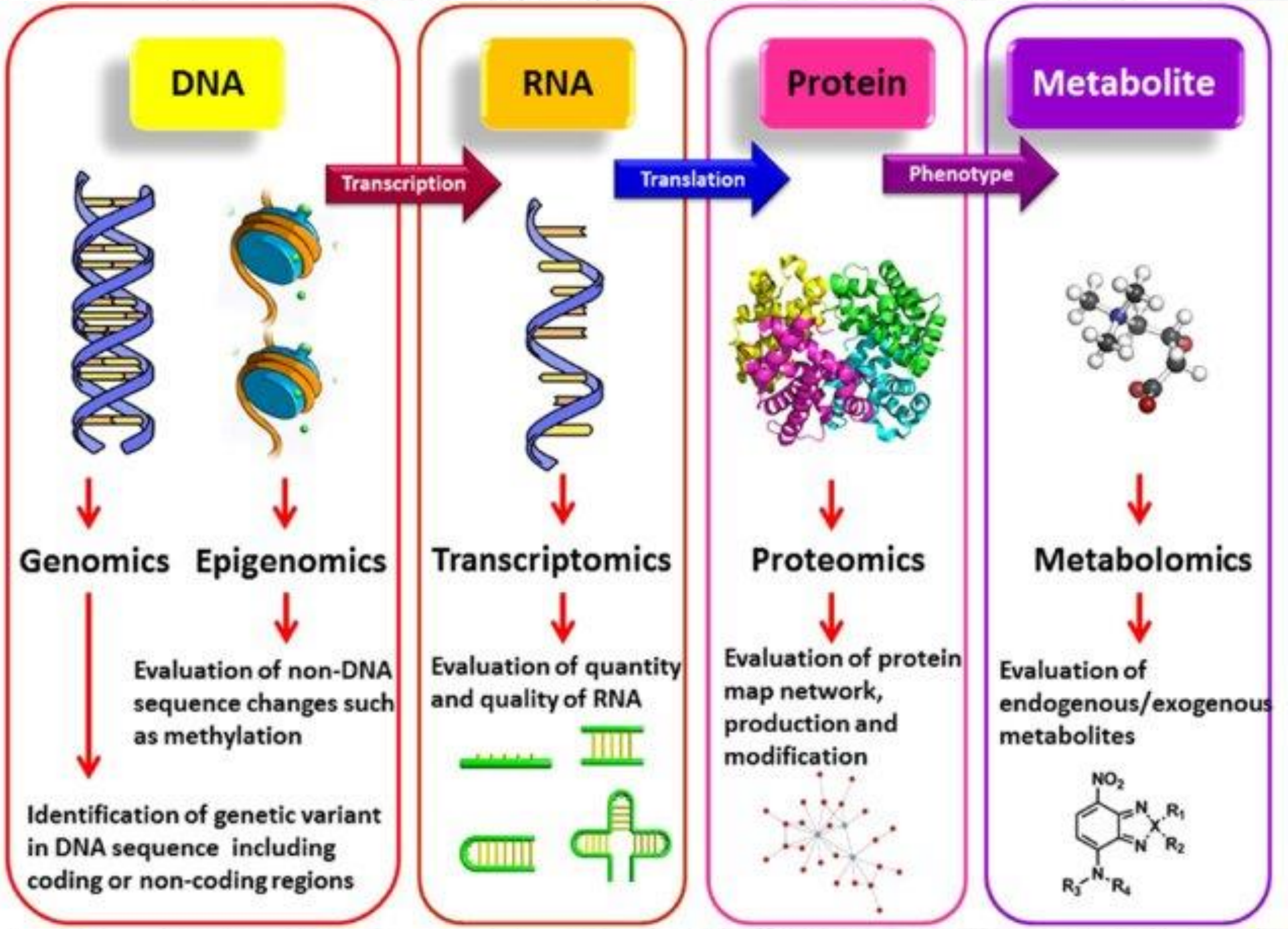
- ***What*** is being done in BRD research?
  - Defining bioinformatics, systems biology
  - Description of current “omics” pursuits
- ***How*** are we performing cutting-edge BRD research?
  - Genomics/Metagenomics
  - Proteomics/Metabolomics
  - Transcriptomics
- ***Where*** are we going?
  - Describing results of today
  - Predicting the work of tomorrow

Terminology and Philosophies

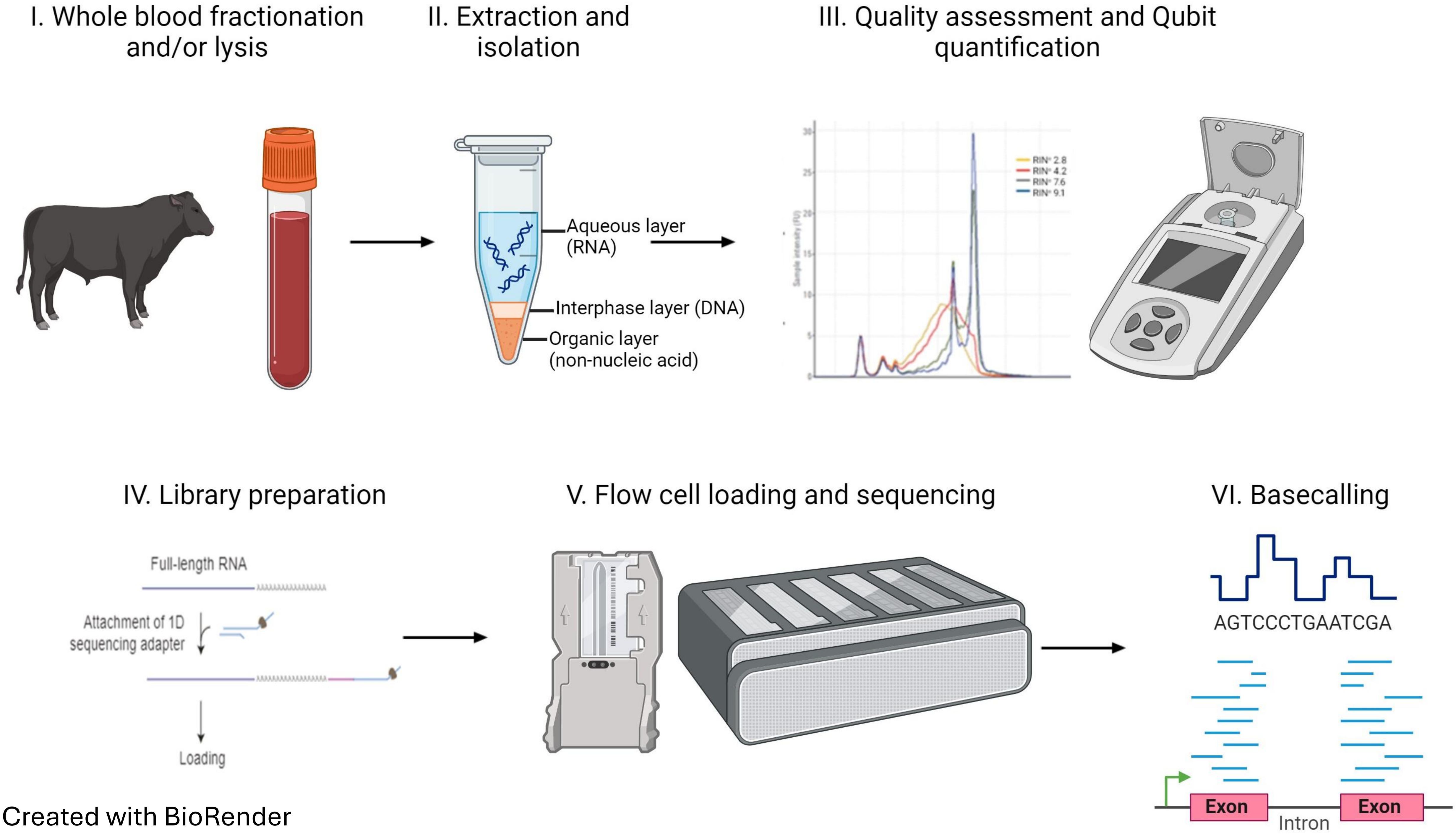
- Omics
  - Study of “–omes”
  - ***Holistically*** characterize, quantify a community/pool of biological molecules
    - Nucleic acid, peptides/proteins, metabolites/lipids
  - Goal: elucidate structures, functions, and/or interactions of these molecules from a sample in context to a given ***hypothesis***
- Bioinformatics
  - Combination of biochemistry, molecular genetics, computer science, and data analysis/statistics
    - Often described as computational biology – differences are somewhat academic
  - Can be omics application or algorithm/tool development-based
- System biology
  - Evaluation of biological systems through “big data” and/or –omics approaches
- **None of these terms are strictly/practically defined.**
  - Ask 10 researchers, get 10 opinions

Types of Omics in BRD Research

- Genomics
- Metagenomics
- Epigenomics
- Transcriptomics
- Proteomics
- Metabolomics



Farshbaf et al., 2021; DOI: 10.1007/s11033-021-06286-0



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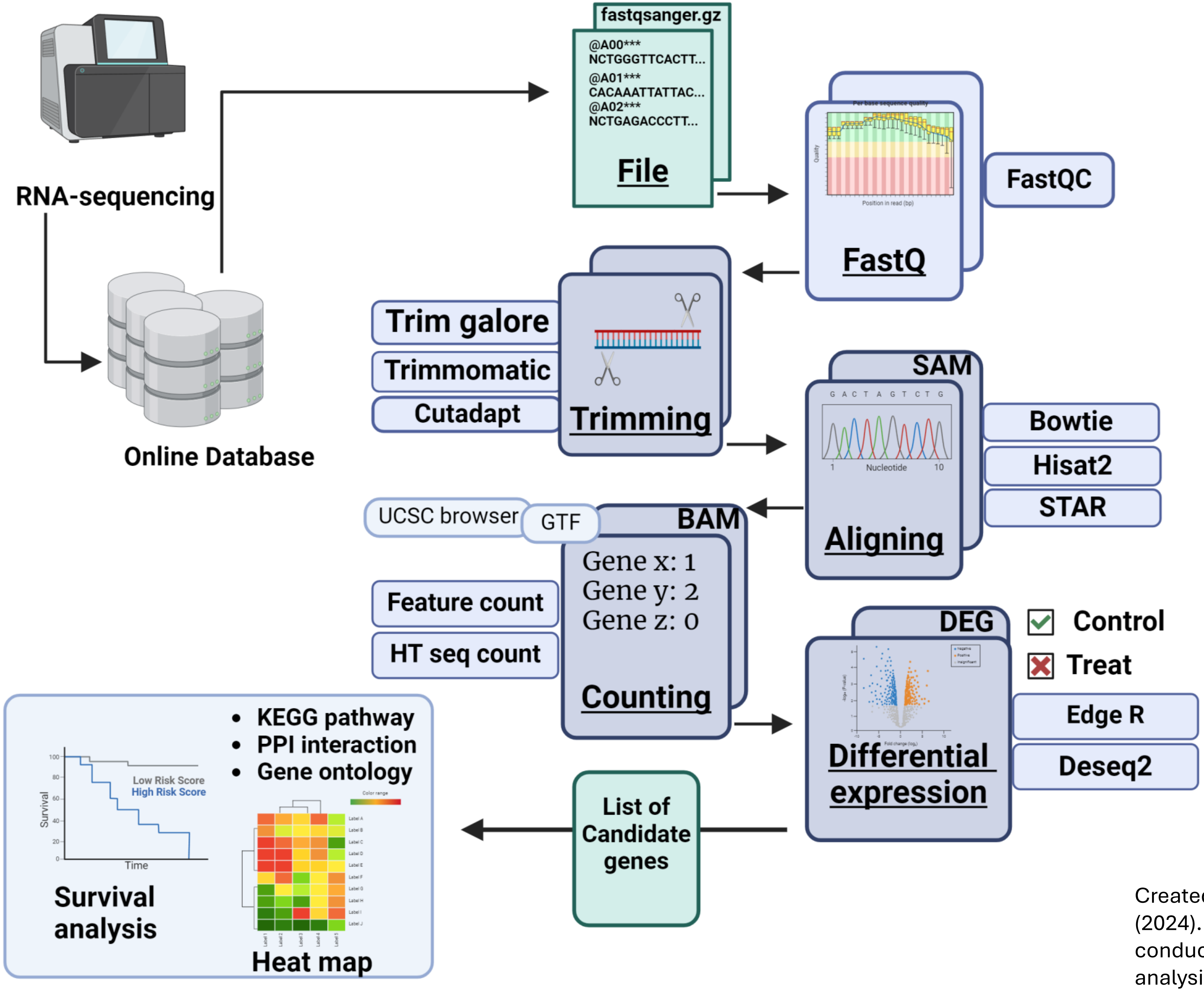


RNA-sequencing

Online Database

fastqsanger.gz

@A00***
NCTGGGTTCACTT...
@A01***
CACAAATTATTAC...
@A02***
NCTGAGACCCTT...

File

FastQ

FastQC

Trim galore

Trimmommatic

Cutadapt

Trimming

SAM

Aligning

Bowtie

Hisat2

STAR

UCSC browser

GTF

BAM

Gene x: 1
Gene y: 2
Gene z: 0

Counting

Feature count

HT seq count

DEG

Differential expression

☑ **Control**

☒ **Treat**

Edge R

Deseq2

List of Candidate genes

- **KEGG pathway**
- **PPI interaction**
- **Gene ontology**

Survival analysis

Heat map

Created with BioRender. Sabbaghian A. (2024). User friendly procedure for conducting bulk RNA sequencing analysis using the GALAXY.eu platform.

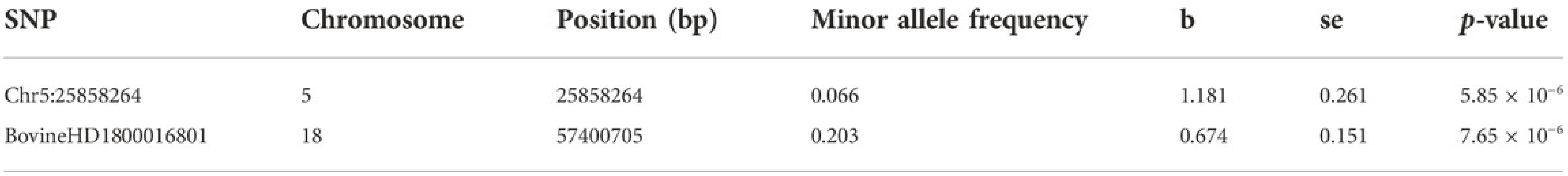
Genomics

- Complete set of DNA from an organism (microbial or cattle)
  - Structure
  - Predicted function
  - Evolution/phylogenetics
  - Exon mapping/annotation
  - Genome-wide associations

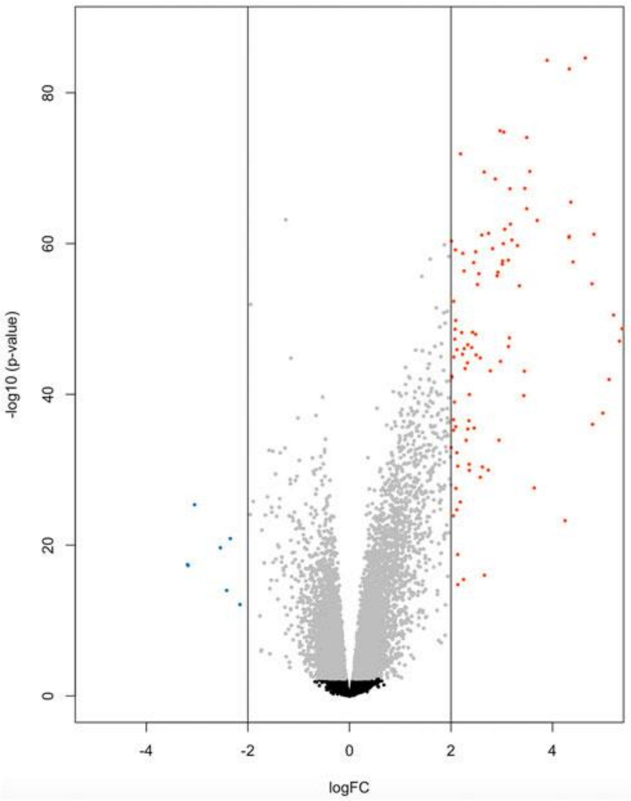
Applying multi-omics data to study the genetic background of bovine respiratory disease infection in feedlot crossbred cattle

Jiyuan Li, Robert Mukiibi, Janelle Jiminez, Zhiquan Wang, Everestus C. Akanno, Edouard Timsit, Graham S. Plastow

DOI: 10.3389/fgene.2022.1046192

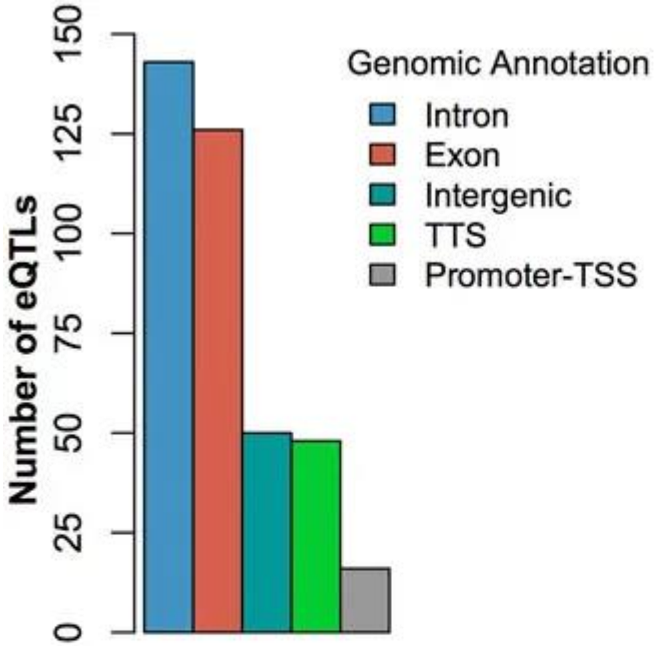


SNP	Chromosome	Position (bp)	Minor allele frequency	b	se	*p*-value
Chr5:25858264	5	25858264	0.066	1.181	0.261	5.85×10^{-6}
BovineHD1800016801	18	57400705	0.203	0.674	0.151	7.65×10^{-6}



↑ *IL1RAP, IL3RA, IL12B, LRG1, S100A9/12, CFB, CATHL3*

↓ *HBB, HBA1, ALOX15, ARG1*



"Furthermore, within the inflammatory response function, enriched innate immune response related processes such as leukocyte immune response, activation and migration of macrophages and neutrophils, and antimicrobial response were predicted to be activated or upregulated in the BRD animals."

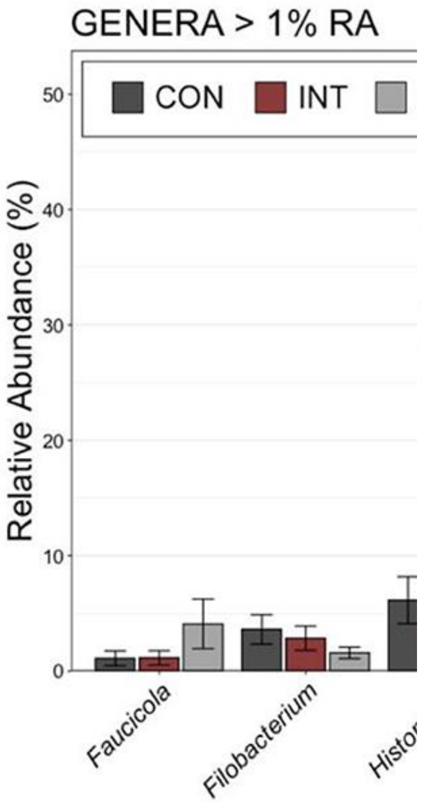
Metagenomics

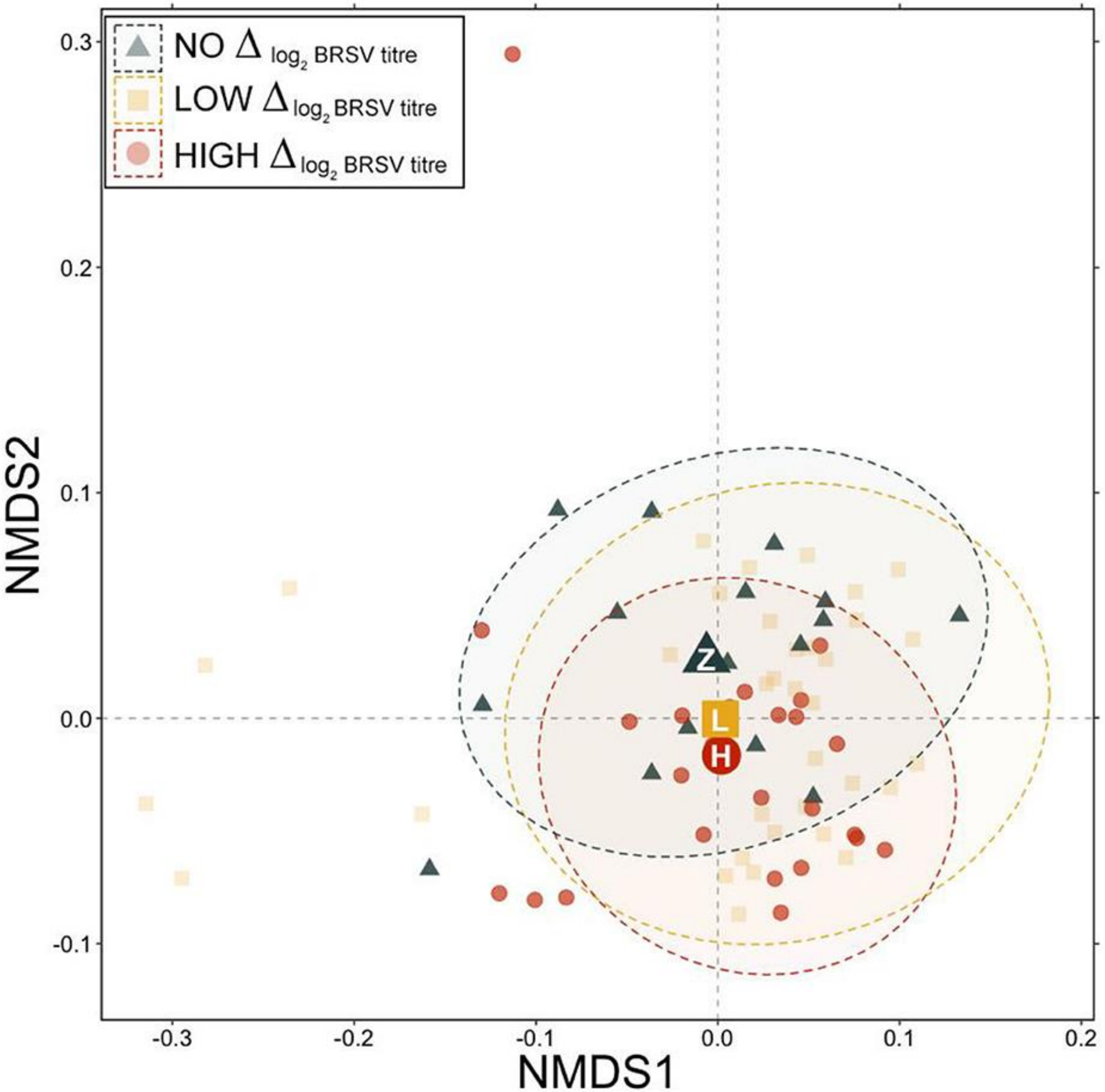
- Mixed genetic material recovered from an “environmental” sample
  - Virome/mycobiome/bacteriome/resistome – think of the microbiome as a living, dynamic organ
    - “Our second genome” – Grice and Segre, 2012 (10.1146/annurev-genom-090711-163814)
    - Organ system: “…collection of tissues…in a structural unit to serve a common function…” – Widmaier, Raff, and Strang, 2008 (ISBN: 9780071283663)
  - Richness and diversity of microbial community
  - Differential abundance; dominating taxa
  - Assessment of rare and/or fastidious organisms

Effects of respiratory virus vaccination and bovine respiratory disease on the respiratory microbiome of feedlot cattle

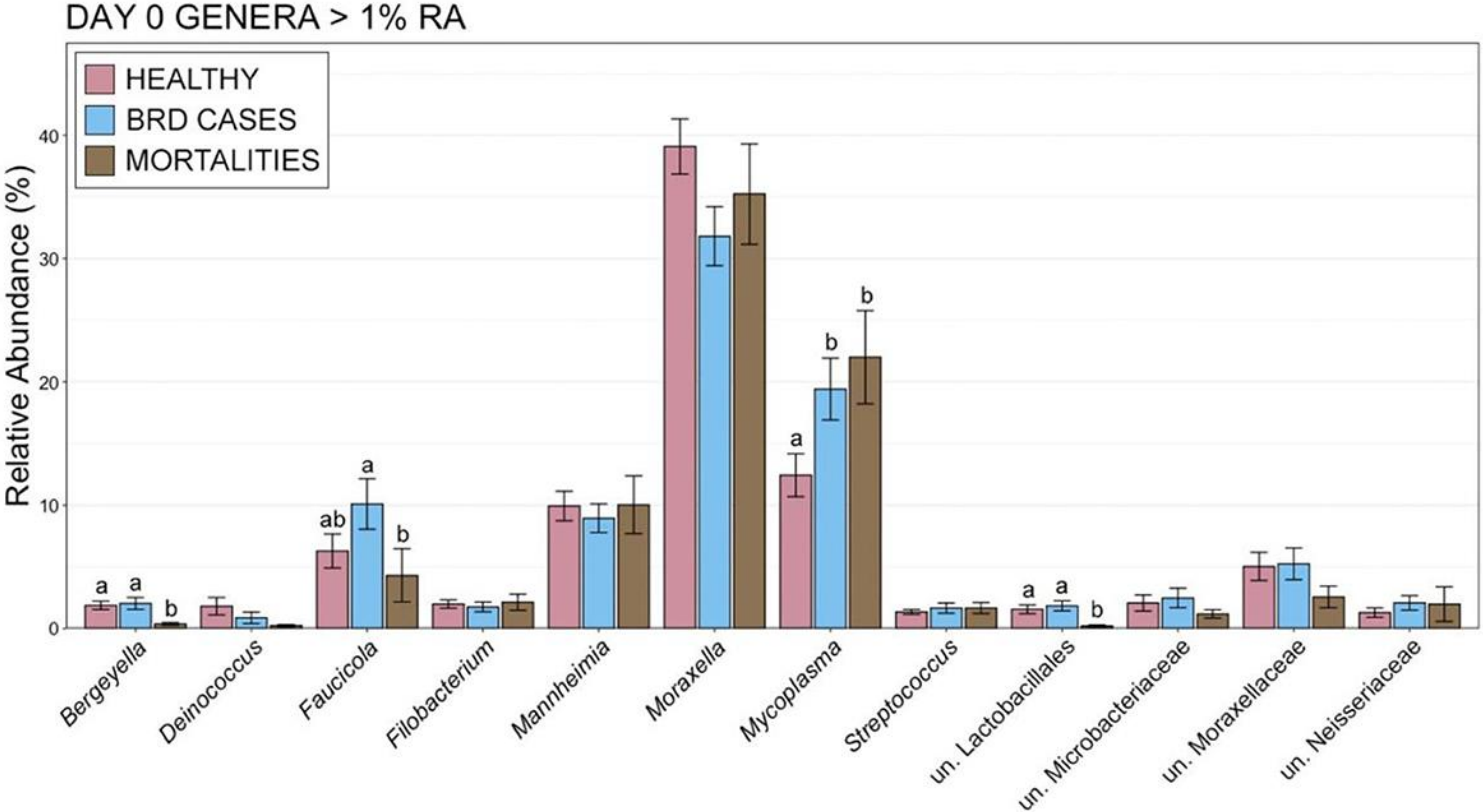
Taylor B. McAtee, Lee J. Pinnell, Sherri A. Powledge, Cory A. Wolfe, Paul S. Morley, John T. Richeson

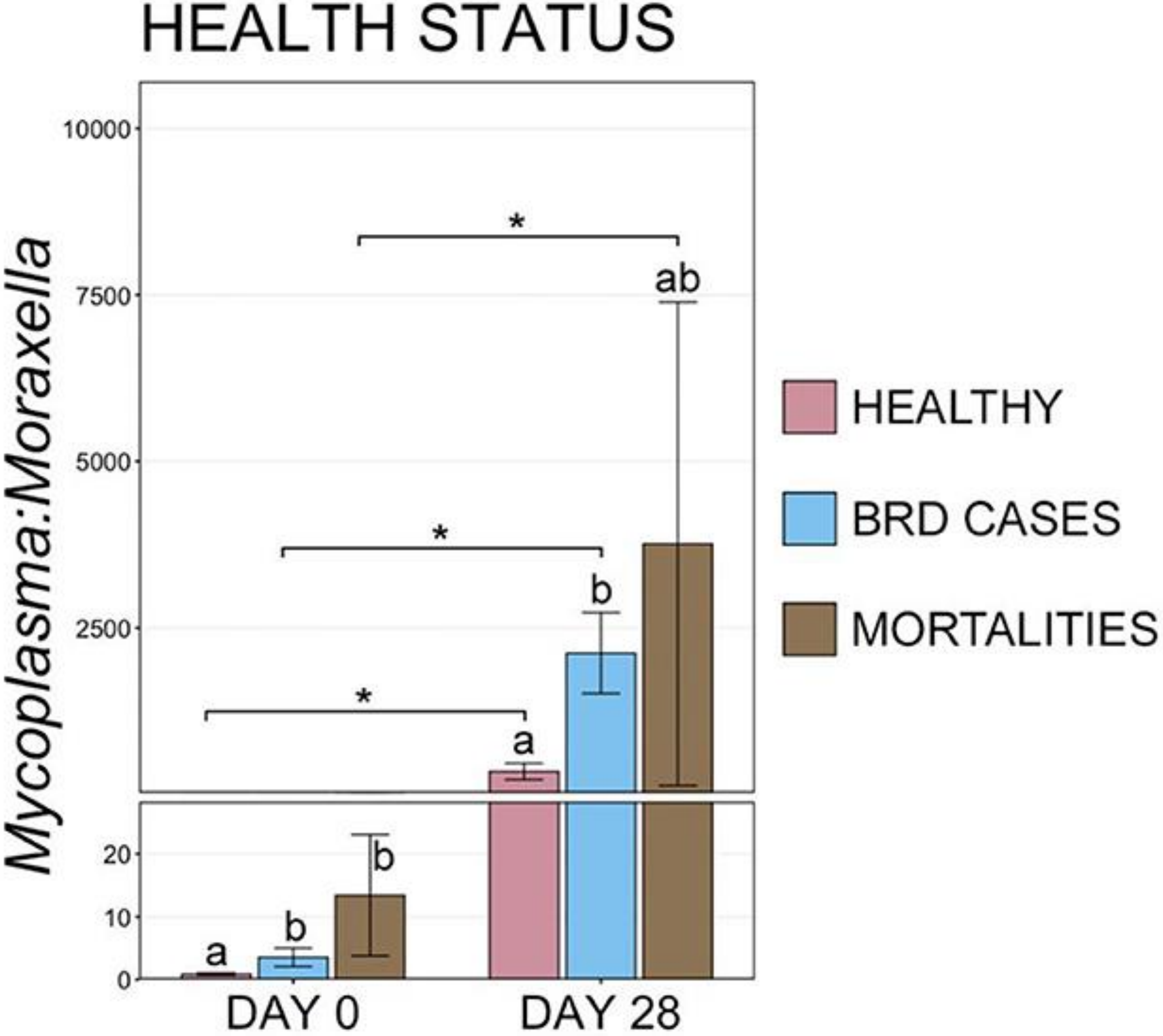
DOI: 10.3389/fmicb.2023.1203498





"…[upper respiratory tract] URT microbiome differed in cattle that were vaccinated intra-nasally with MLV targeting respiratory viruses compared with cattle that were vaccinated parenterally against the same viruses or unvaccinated CON cattle. However, changes in serum antibody titers to BRSV were not associated with differences in URT microbiome composition. Together, these findings suggest that changes in URT microbial communities were mediated by local immunity or interactions among microbial features within the respiratory tract as opposed to being mediated by systemic immune responses."


DAY 0 GENERA > 1% RA
HEALTHY
BRD CASES
MORTALITIES
Relative Abundance (%)
0
10
20
30
40
a
a
b
ab
a
b
a
b
b
a
a
b
Bergeyella
Deinococcus
Faucicola
Filobacterium
Mannheimia
Moraxella
Mycoplasma
Streptococcus
un. Lactobacillales
un. Microbacteriaceae
un. Moraxellaceae
un. Neisseriaceae


HEALTH STATUS
Mycoplasma:Moraxella
10000
7500
5000
2500
20
10
0
*
ab
*
b
*
a
b
b
a
DAY 0
DAY 28
HEALTHY
BRD CASES
MORTALITIES

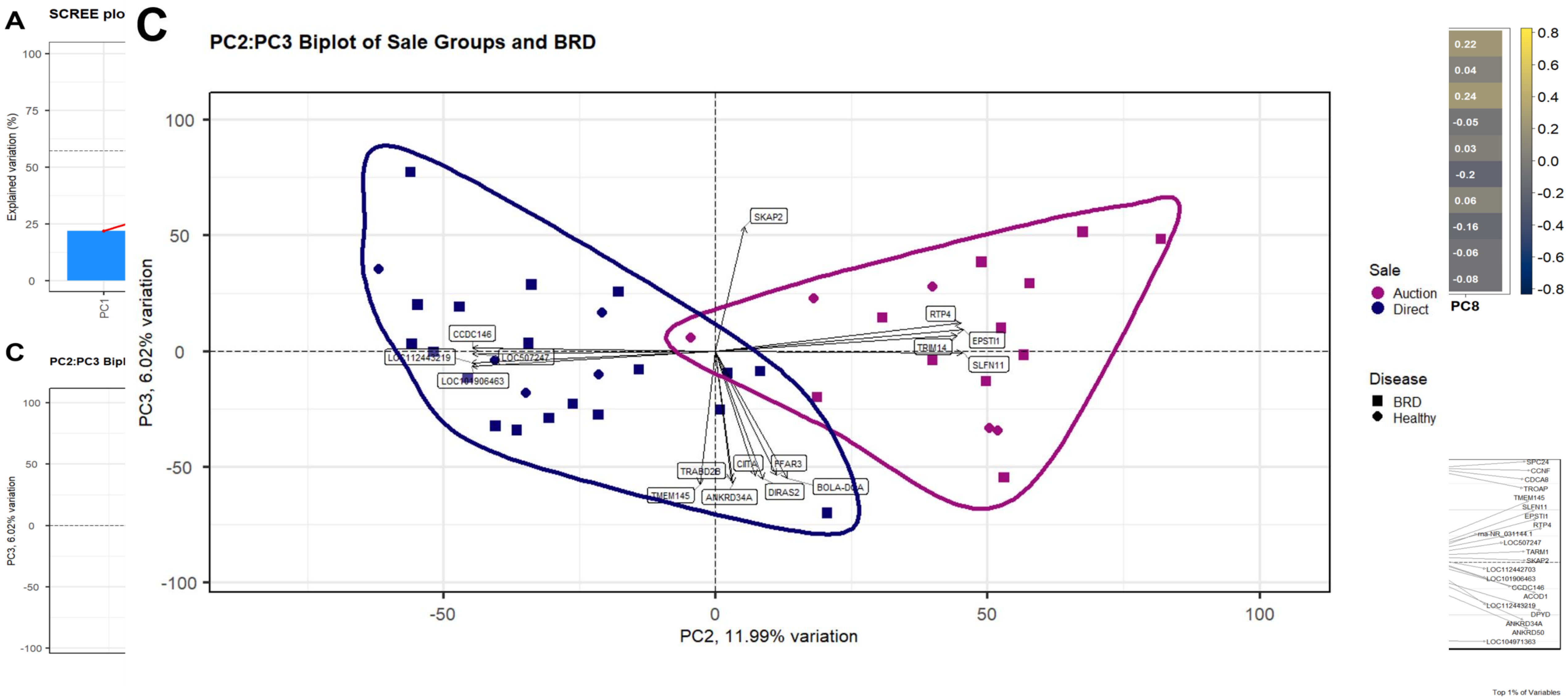
Transcriptomics

- Comprehensive evaluation of coding and/or non-coding RNA transcripts produced by transcription
  - Differential gene expression
  - Co-expression pattern association
  - Dynamic/trend-wise changes
  - Isoform exploration
  - Spatial/single cell analysis

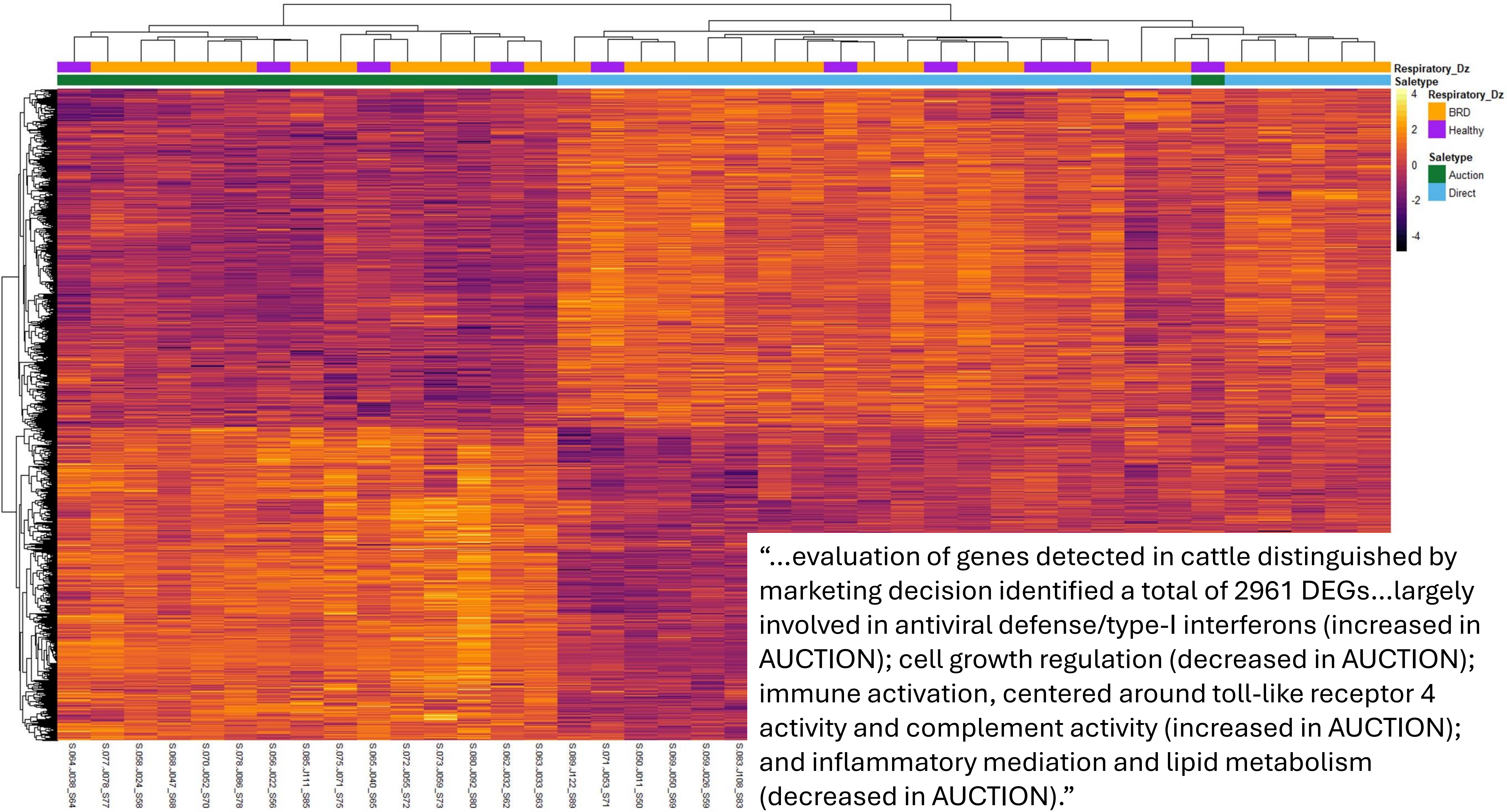
Influence of the at-arrival host transcriptome on bovine respiratory disease incidence during backgrounding

Mollie M. Green, Amelia R. Woolums, Brandi B. Karisch, Kelsey M. Harvey, Sarah F. Capik, Matthew A. Scott

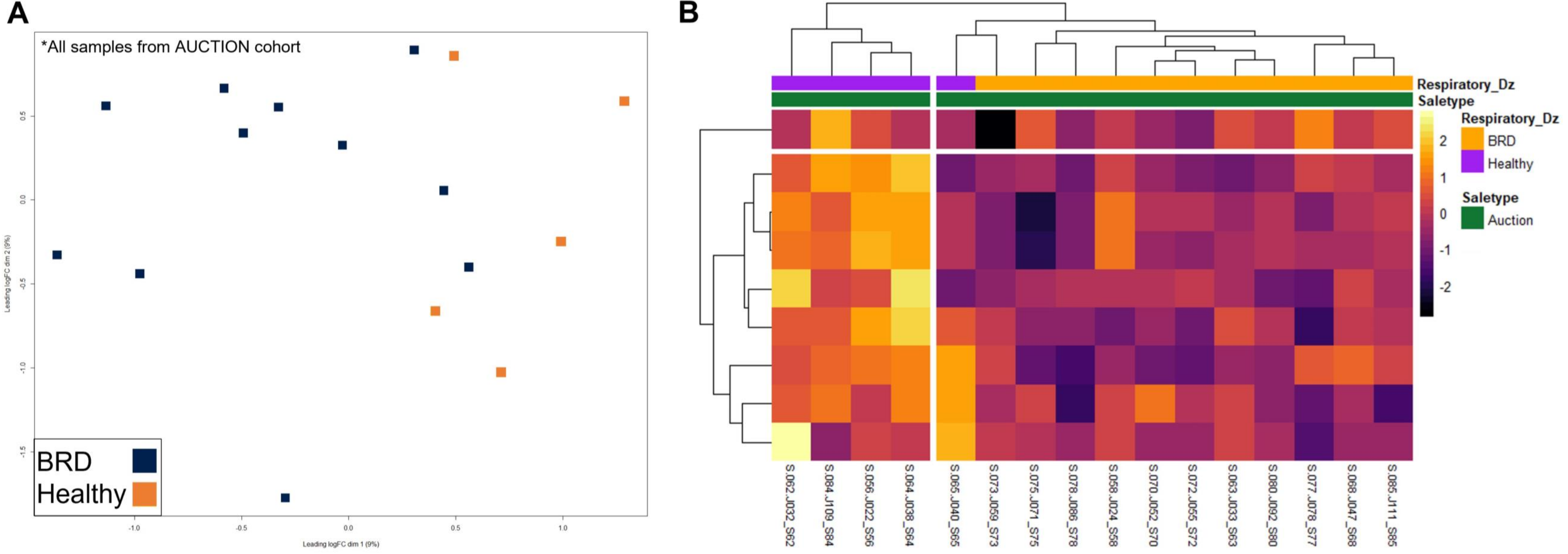
DOI: 10.3390/vetsci10030211



B



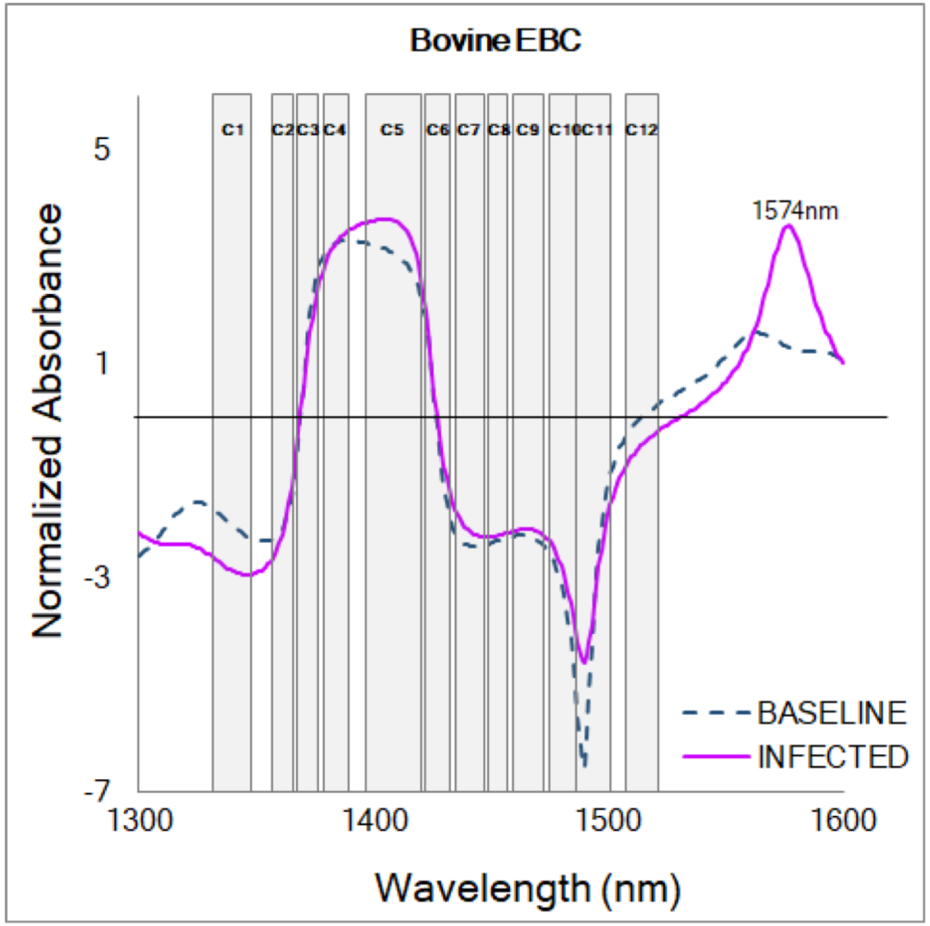
“...evaluation of genes detected in cattle distinguished by marketing decision identified a total of 2961 DEGs...largely involved in antiviral defense/type-I interferons (increased in AUCTION); cell growth regulation (decreased in AUCTION); immune activation, centered around toll-like receptor 4 activity and complement activity (increased in AUCTION); and inflammatory mediation and lipid metabolism (decreased in AUCTION).”



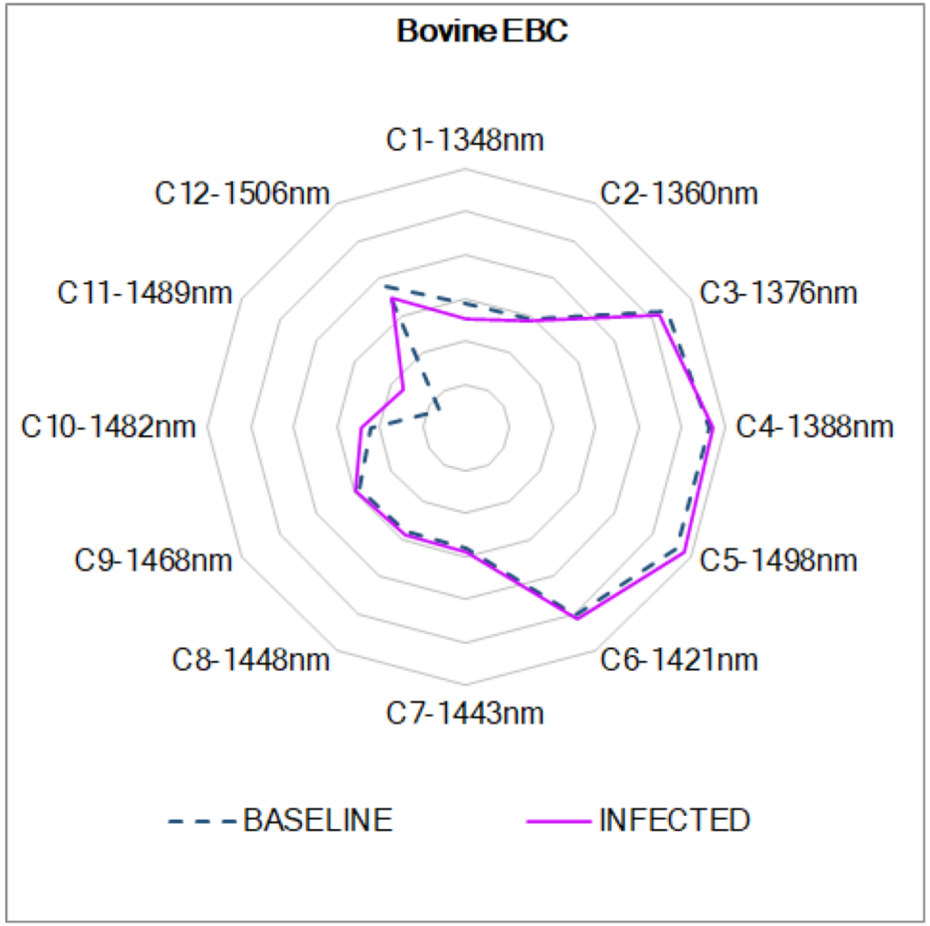
"...with[in] the AUCTION group, we identified...nine DEGs between HEALTHY and BRD. These DEGs primarily are involved in collagen biosynthesis and modification and platelet adhesion and aggregation...increased in HEALTHY calves...COL1A1 and COL1A2, the genes driving the aforementioned mechanisms, [are] down-regulated genes in whole blood collected from BRSV-challenged calves compared to sham-control calves...involved in airway macrophage-driven cell clearance, metalloproteinase regulation, and fibrogenesis."

Proteomics/Metabolomics

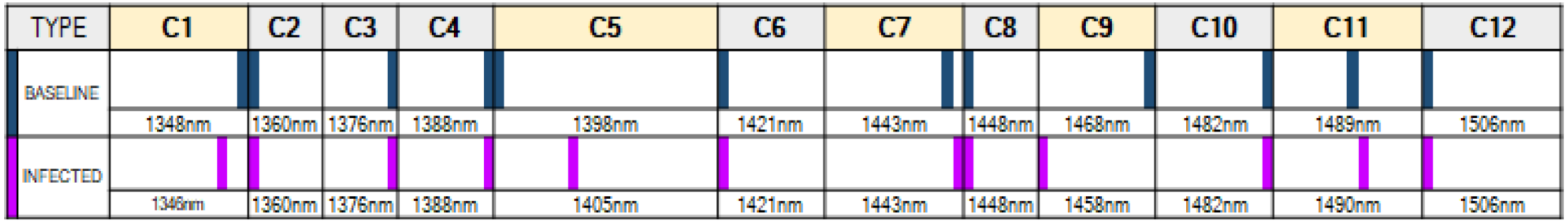
- Study of the entire set of proteins or small-molecule chemicals found within a biological sample produced or modified by an organism
  - Cellular/metabolic processes
  - “End-stage” genomic regulation
  - Cell-cell interactions/signaling events
  - Molecule discovery (therapeutics, prediction/prognosis assay development)



(a)



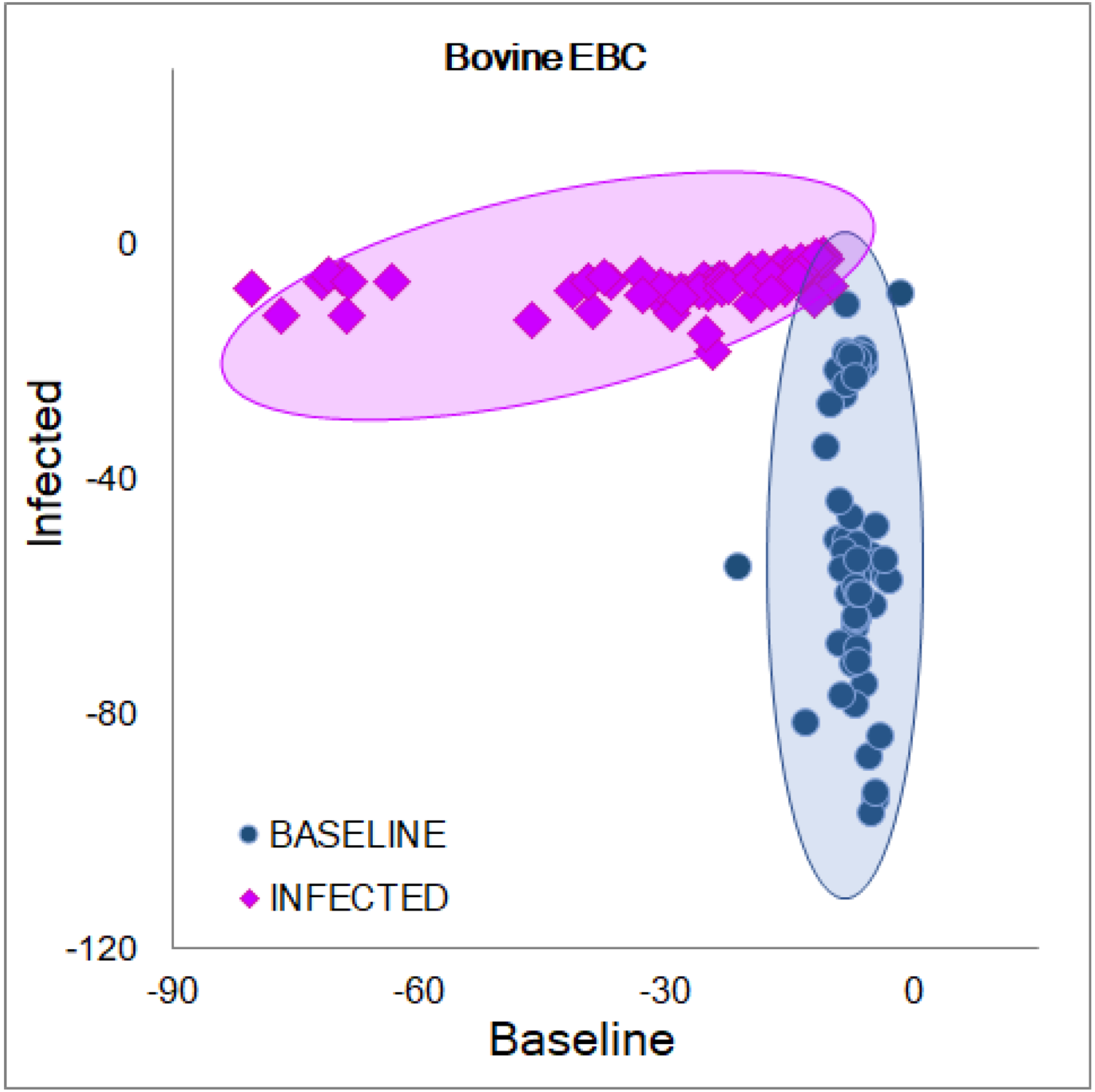
(b)



TYPE	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
BASELINE												
	1348nm	1360nm	1376nm	1388nm	1398nm	1421nm	1443nm	1448nm	1468nm	1482nm	1489nm	1506nm
INFECTED												
	1346nm	1360nm	1376nm	1388nm	1405nm	1421nm	1443nm	1448nm	1458nm	1482nm	1490nm	1506nm

(c)

“The aquaphotomic analysis for NIR [near-infrared] spectral signatures collected for breath condensate from dairy calves infected with BRSV revealed a consistent and expected spectral water pattern in the wavelength range between 1300 and 1600 nm. This region corresponds to the first overtone of the functional groups O-H, C-H, and N-H forming molecules containing water (H2O), alcohols (ROH), phenols (ArOH), simple amides (CONH2), amides (CONHR), monoamides (RNH2), methylene (CH2), and methyl radicals (CH3).”



"The exhaled breath condensate (EBC) comprises >99.9% condensed water vapor and <0.1% aerosols…In healthy animals, hydrogen peroxide (H_2O_2), which is a volatile molecule in EBC, is well-known for its involvement in airway homeostasis. During respiratory disease, H_2O_2 in EBC is considered a biomarker of inflammation and oxidative stress caused by the release of reactive oxygen species (ROS) and nitrogen species (RNS) from inflammatory leukocytes…"

"Increased levels of LTB_4 in EBC were detected in two out of four calves infected with BRSV in comparison with baseline values…The observed changes in the aquaphotomics parameters, a left shift of C1 and C9, for inducing localized water structure would be consistent with increases in LTB_4, and other lipid-based compounds known to increase in response to infection."

What's the point? Where are we going?

- Research ***today*** associated with BRD is involved in:
  - Describing mutagenic regions and genetic variants
  - Exploring microbial community structures within and around the host
  - Defining host gene expression patterns and features
  - Identifying proteins and molecular components at clinical presentation
- Leading us to management tools and paradigm shifts of ***tomorrow***
  - Breeding or genetic knockout programs; development of targeted therapy
  - Predictive indicators or risk association modeling around microbial communities
  - Synthetic mRNA construction and/or improved understanding of current tools
  - Rapid chute-side assay development for sub-clinical disease detection

Thank you for your time!

https://www.veroresearch.org/

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VERO – VETERINARY EDUCATION, RESEARCH, AND OUTREACH CENTER
Texas A&M University – West Texas A&M University

Matthew A. Scott, DVM, PhD
Assistant Professor

3201 Russell Long Blvd.
Canyon, Texas, 79015

mascott@cvm.tamu.edu