PRRSV Functional Genomics: Past Decade and Future Perspectives

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BIG KIM

Integrate EveryThing, Create Novel Thing

Integrate EveryThing, Create Novel Thing

모든 것을 조합해, 새로운 것을 창조합니다.

우리는 데이터를 통해 미래를 예측합니다.

빅데이터, 다중오믹스 분석, 인공지능 기술의 힘으로 미래를 혁신합니다.

생명체의 비밀을 해석하고 새로운 약물과 지속 가능한 식품 생산에 이르기까지
창의적인 사고와 윤리적인 실천으로 긍정적인 변화를 추구합니다.

PRRSV Functional Genomics:

Past Decade and Future Perspectives

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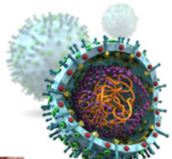
CONTENTS

1. **Introduction**
2. **Study 1** (Transcriptome in whole blood)
3. **Study 2** (Transcriptome in multiple tissues)
4. **Study 3** (Interactome between mRNAs and lncRNAs in multiple tissues)
5. **Study 4** (Single-cell transcriptome and exosomal miRNAs in BALF)
6. **Discussion**
7. **Further studies** (Epigenome and microbiome)
    - **Study 5** (Single-cell co-expression module-metabolite-microbe landscape analysis)
    - **Study 6** (PRRSV epigenomic alterations based on chromatin accessibility)

Introduction

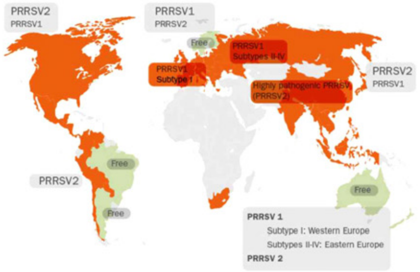
PRRSV

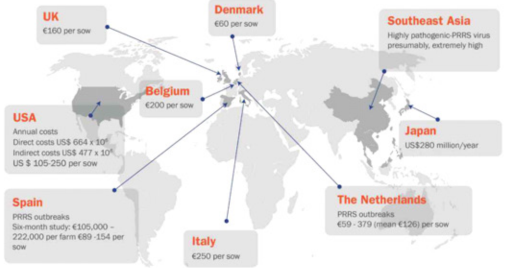
- Porcine reproductive and respiratory syndrome virus (**PRRSV**)
- Positive strand RNA virus, in the family *Arteriviridae*
- Two types – PRRSV1 (European), PRRSV2 (North American)
- Main target cells: monocyte / macrophage
  Porcine alveolar macrophage (PAM): ~5%



SYMPTOM	
Sows	Growing pigs
• Abortion • Early farrowing • Stillbirth • Mummified piglets • Weak piglets	• Respiratory problems

Economic losses by PRRSV





- PRRS is one of **the most costly disease** in pig industry
- In **Europe** and **North America**, the cost of PRRSV to the industry: $6.25-$15.25 USD per pig marketed (Holtkamp *et al.*, 2013; Nathues *et al.*, 2017)
- Economic losses in **Korea** (PRRSV1) (Kim *et al.*, 2022)
  - ① KRW 99,378 per mated female for the breeding-farrowing phage
  - ② KRW 8,968 per pig for the nursery growth phage
  - ③ KRW 245,174 per sow in the post-outbreak period

https://www.prrscontrol.com/prrs-the-disease/

PRRS host genetics consortium

Participating organizations

- Iowa State University
- Kansas State University
- Agricultural research service
- National pork board

Why was it established?

PRRSV infection shows large variation in **viral control and growth performance** among commercial pigs

PHGC was established to test whether this variation has a **genetic basis**

Consortium approach

Standardized PRRSV challenge in commercial pig populations

Core phenotypes: viral load, weight gain, immune response

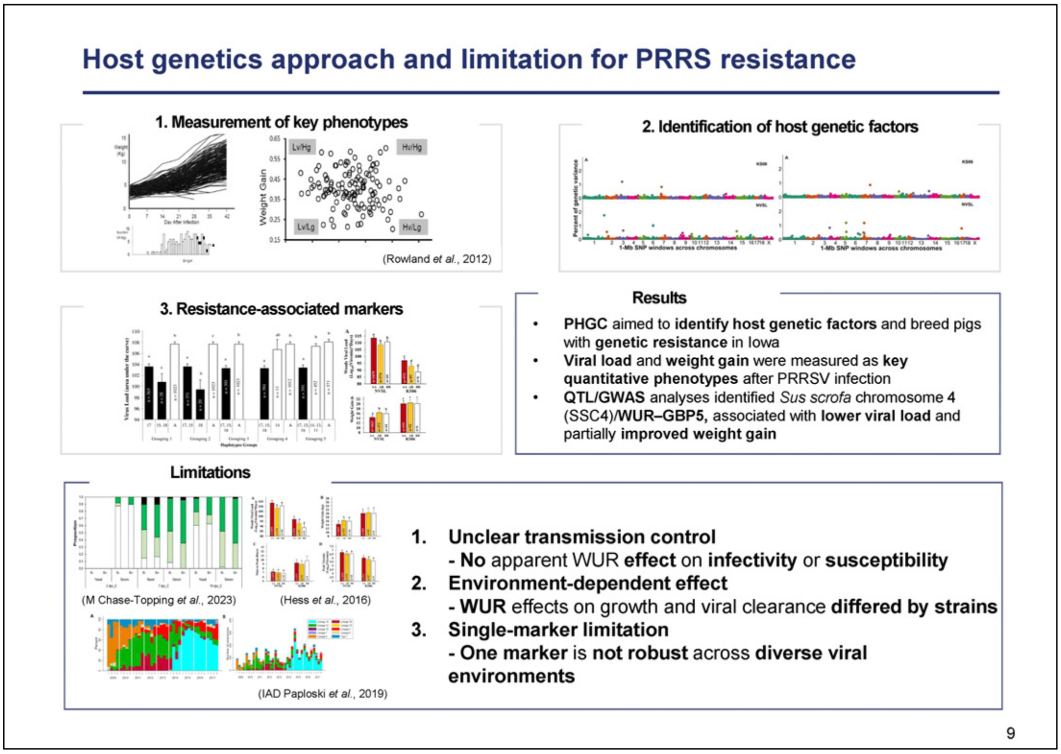
SNP genotype integration across experimental sites

Expected contribution

Identify host **genetic factors** linked to PRRS resistance and resilience

Improve understanding of host biology and **mechanisms** of protection

Provide a foundation for **mechanism-based PRRS control**



Host genetics approach and limitation for PRRS resistance

1. Measurement of key phenotypes

(Rowland *et al*., 2012)

2. Identification of host genetic factors

3. Resistance-associated markers

Results

- **PHGC** aimed to **identify host genetic factors** and breed pigs with **genetic resistance** in Iowa
- **Viral load** and **weight gain** were measured as **key quantitative phenotypes** after PRRSV infection
- **QTL/GWAS** analyses identified *Sus scrofa* chromosome 4 (SSC4)/**WUR–GBP5,** associated with **lower viral load** and partially **improved weight gain**

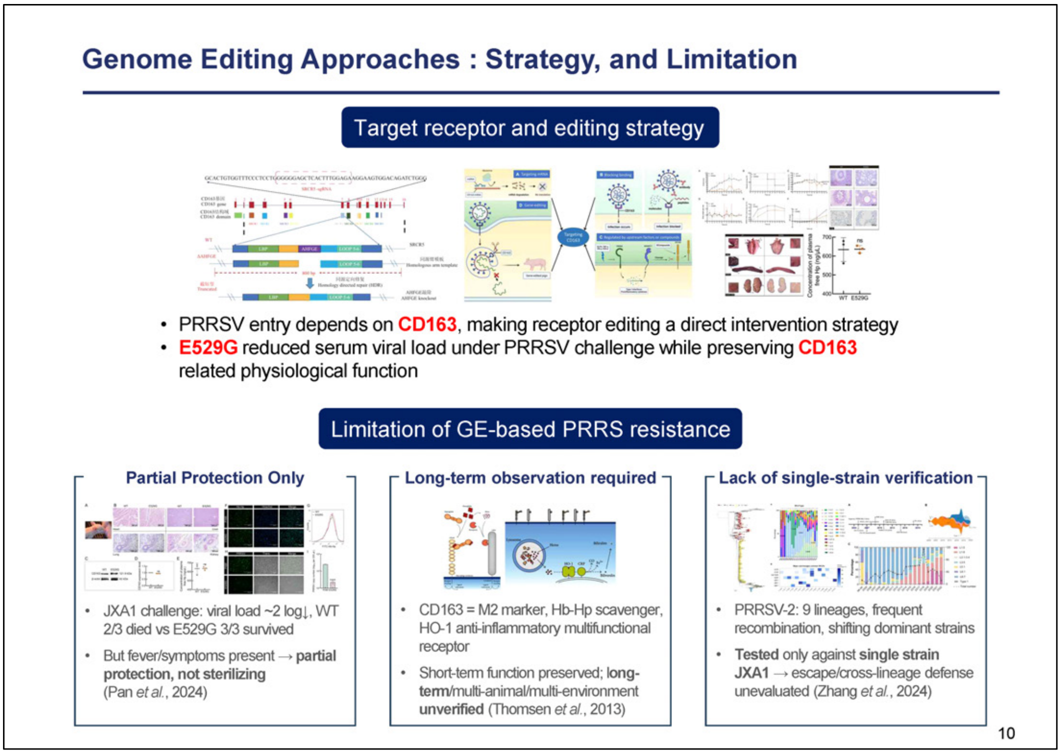
Limitations

(M Chase-Topping *et al*., 2023)

(Hess *et al*., 2016)

(IAD Paploski *et al*., 2019)

1. **Unclear transmission control**
   - **No** apparent WUR **effect** on **infectivity** or **susceptibility**
2. **Environment-dependent effect**
   - **WUR** effects on growth and viral clearance **differed by strains**
3. **Single-marker limitation**
   - **One marker** is **not robust** across **diverse viral environments**



Genome Editing Approaches : Strategy, and Limitation

Target receptor and editing strategy

- PRRSV entry depends on **CD163**, making receptor editing a direct intervention strategy
- **E529G** reduced serum viral load under PRRSV challenge while preserving **CD163** related physiological function

Limitation of GE-based PRRS resistance

Partial Protection Only

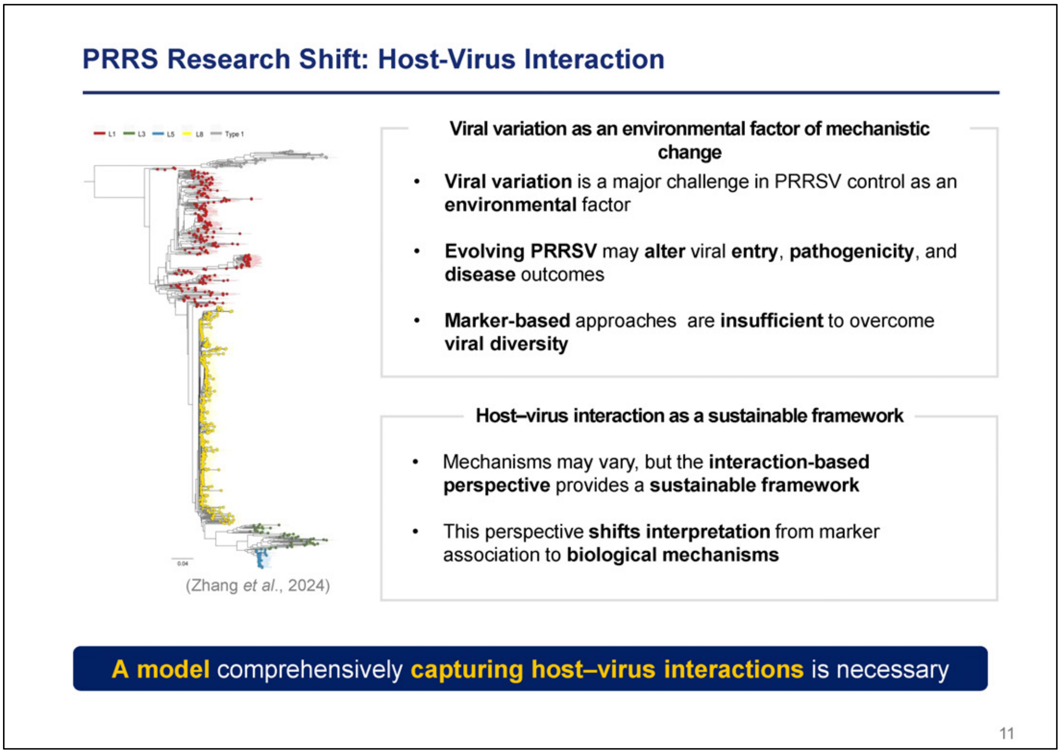
- JXA1 challenge: viral load ~2 log↓, WT 2/3 died vs E529G 3/3 survived
- But fever/symptoms present → **partial protection, not sterilizing** (Pan *et al*., 2024)

Long-term observation required

- CD163 = M2 marker, Hb-Hp scavenger, HO-1 anti-inflammatory multifunctional receptor
- Short-term function preserved; **long-term**/multi-animal/multi-environment **unverified** (Thomsen *et al*., 2013)

Lack of single-strain verification

- PRRSV-2: 9 lineages, frequent recombination, shifting dominant strains
- **Tested** only against **single strain JXA1** → escape/cross-lineage defense unevaluated (Zhang *et al*., 2024)



PRRS Research Shift: Host-Virus Interaction

(Zhang *et al*., 2024)

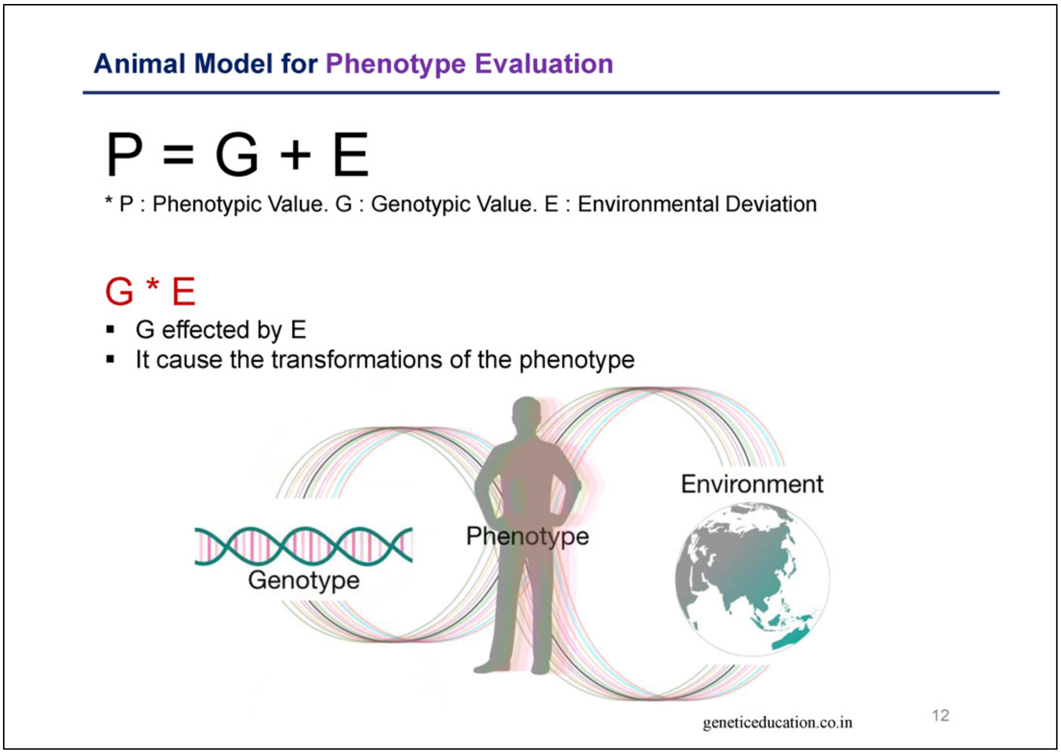
Viral variation as an environmental factor of mechanistic change

- **Viral variation** is a major challenge in PRRSV control as an **environmental** factor
- **Evolving PRRSV** may **alter** viral **entry**, **pathogenicity**, and **disease** outcomes
- **Marker-based** approaches are **insufficient** to overcome **viral diversity**

Host–virus interaction as a sustainable framework

- Mechanisms may vary, but the **interaction-based perspective** provides a **sustainable framework**
- This perspective **shifts interpretation** from marker association to **biological mechanisms**

A model comprehensively **capturing host–virus interactions** is necessary



Animal Model for Phenotype Evaluation

$$P = G + E$$

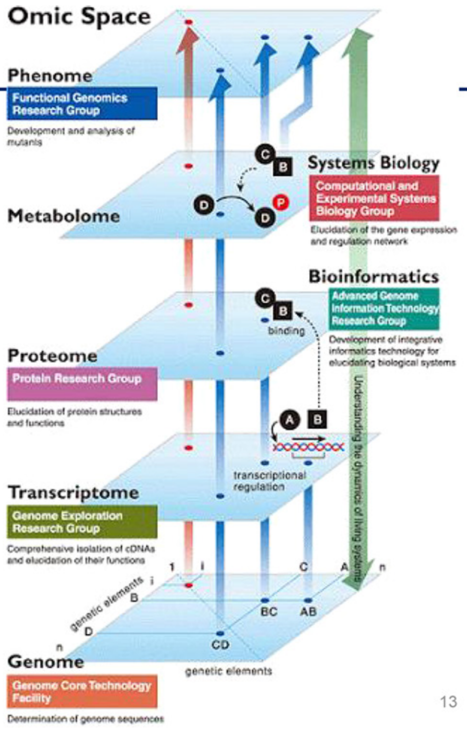
* P : Phenotypic Value. G : Genotypic Value. E : Environmental Deviation

G * E

- G effected by E
- It cause the transformations of the phenotype

geneticeducation.co.in

Functional Genomics ‘MOI’



Multi-Omics Integration ‘MOI’

Scientific Reports, 2018
Animal Genetics, 2018 & 2019
Functional Integrative & Genomics, 2019
Veterinary Research, 2020

Absolute fold change (FC) ≥ 4
Absolute correlation coefficient ≥ 0.9

630 nodes
7565 edges

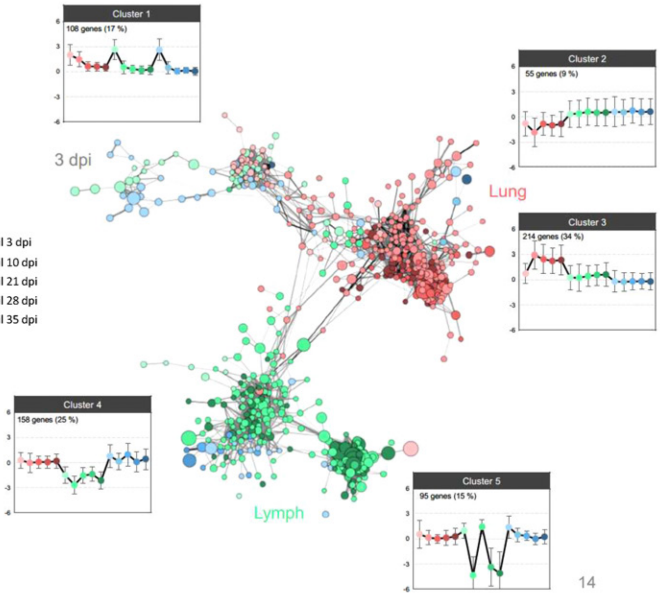
- **Node color: Tissue and day**

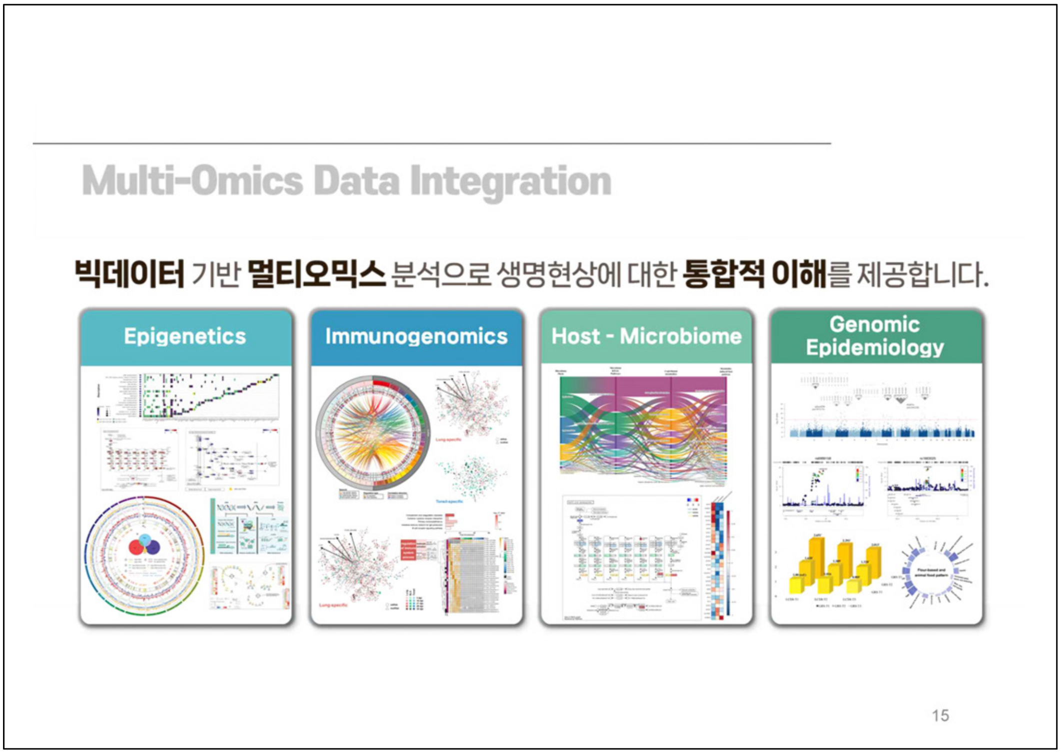
○ Lung 3 dpi	○ Lymph 3 dpi	○ Tonsil 3 dpi
○ Lung 10 dpi	○ Lymph 10 dpi	○ Tonsil 10 dpi
○ Lung 21 dpi	○ Lymph 21 dpi	○ Tonsil 21 dpi
○ Lung 28 dpi	○ Lymph 28 dpi	○ Tonsil 28 dpi
○ Lung 35 dpi	○ Lymph 35 dpi	○ Tonsil 35 dpi

- **Node size: Total max value**
- **Edge color: Up down**

▬ Up ▬ Down

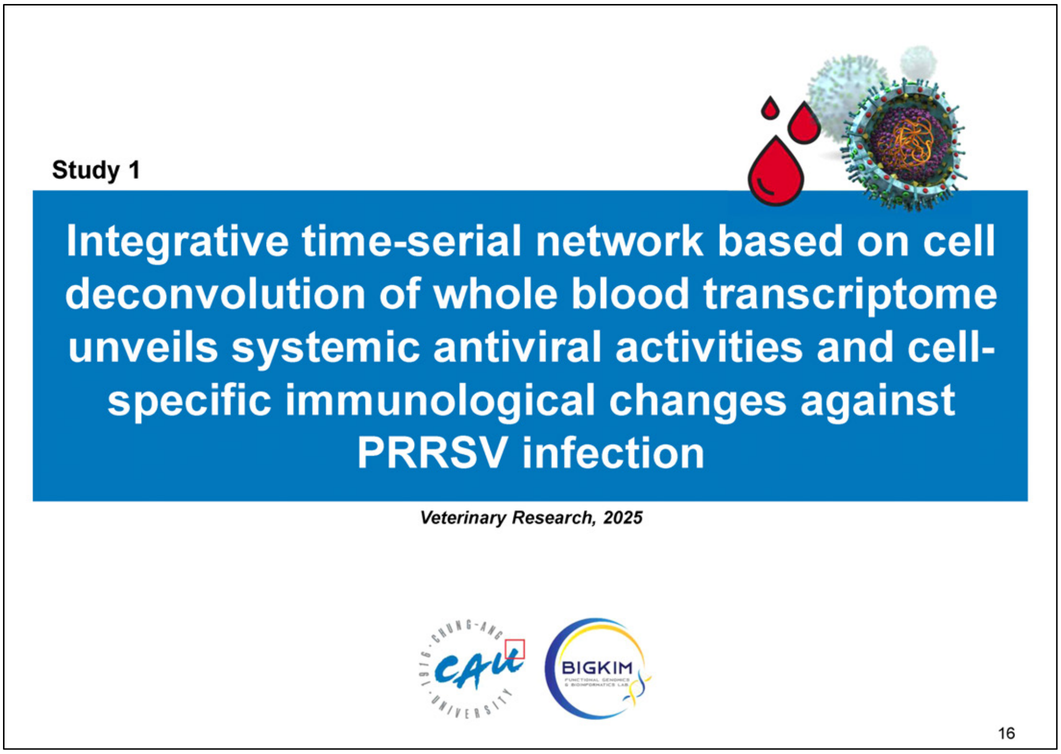
- **Edge width: Correlation coefficient value**





Multi-Omics Data Integration

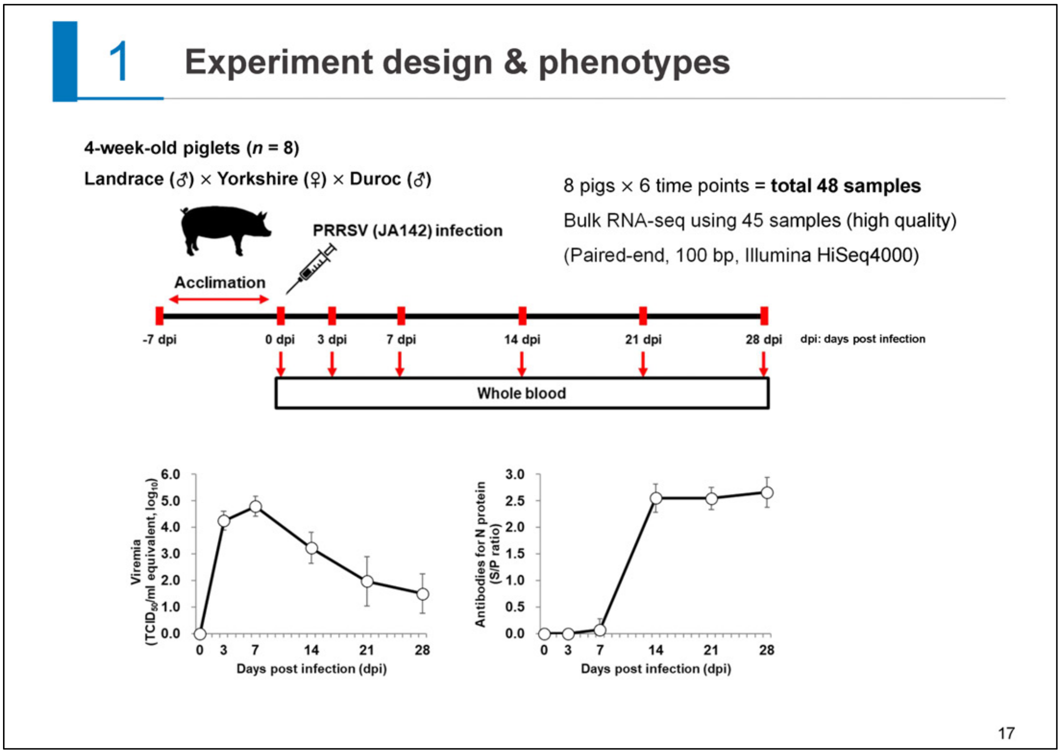
빅데이터 기반 **멀티오믹스** 분석으로 생명현상에 대한 **통합적 이해**를 제공합니다.



Study 1

Integrative time-serial network based on cell deconvolution of whole blood transcriptome unveils systemic antiviral activities and cell-specific immunological changes against PRRSV infection

Veterinary Research, 2025



1 Experiment design & phenotypes

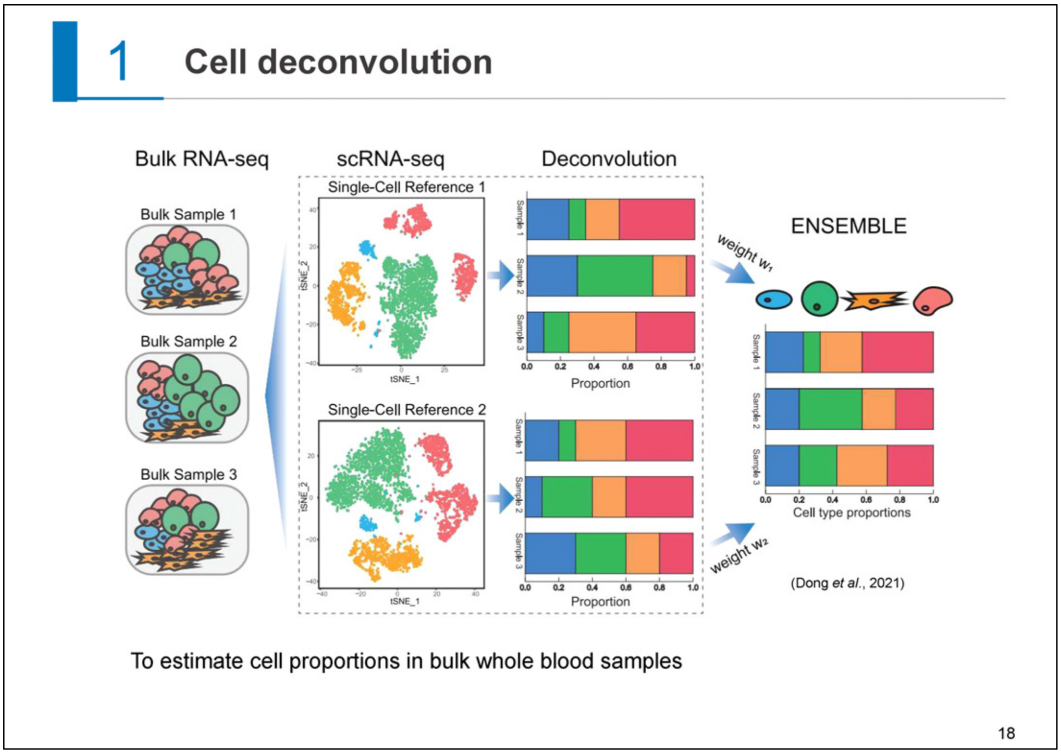
4-week-old piglets (*n* = 8)

Landrace (♂) × Yorkshire (♀) × Duroc (♂)

8 pigs × 6 time points = **total 48 samples**

Bulk RNA-seq using 45 samples (high quality)

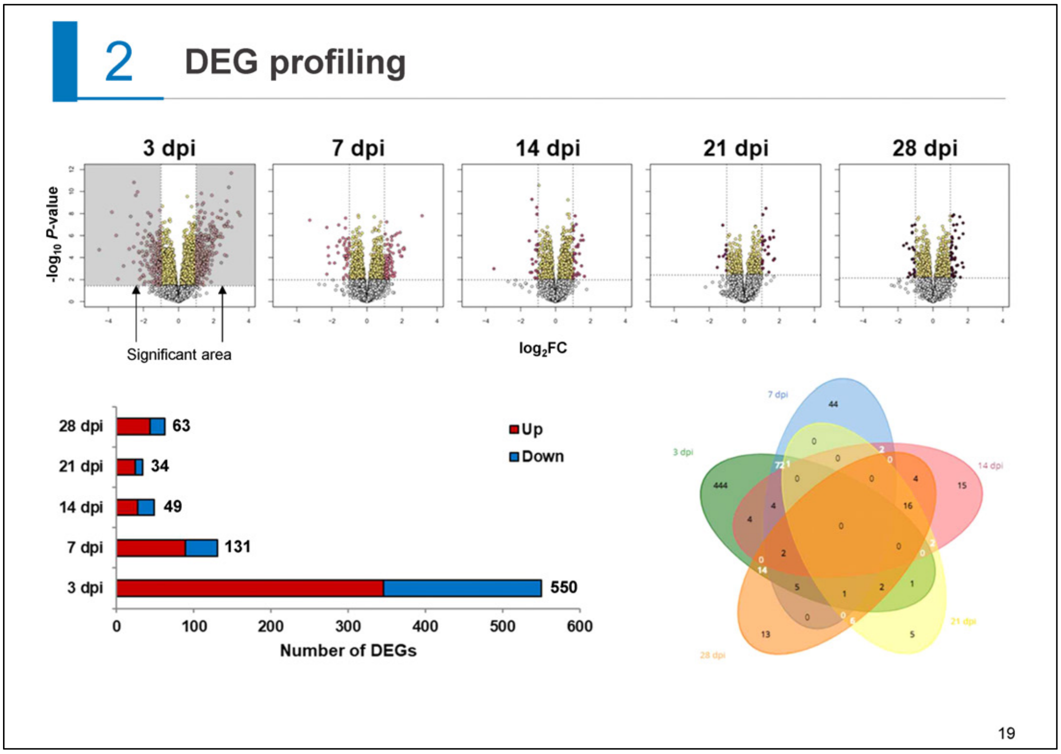
(Paired-end, 100 bp, Illumina HiSeq4000)



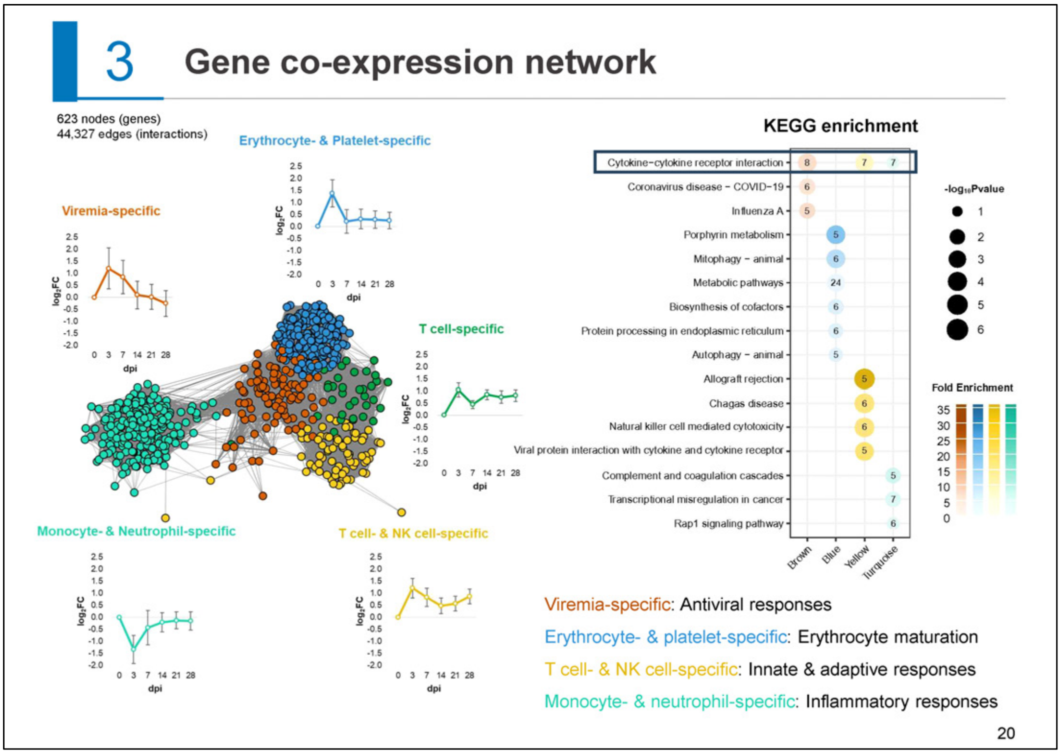
1 Cell deconvolution

(Dong *et al.*, 2021)

To estimate cell proportions in bulk whole blood samples



2 DEG profiling



3 Gene co-expression network

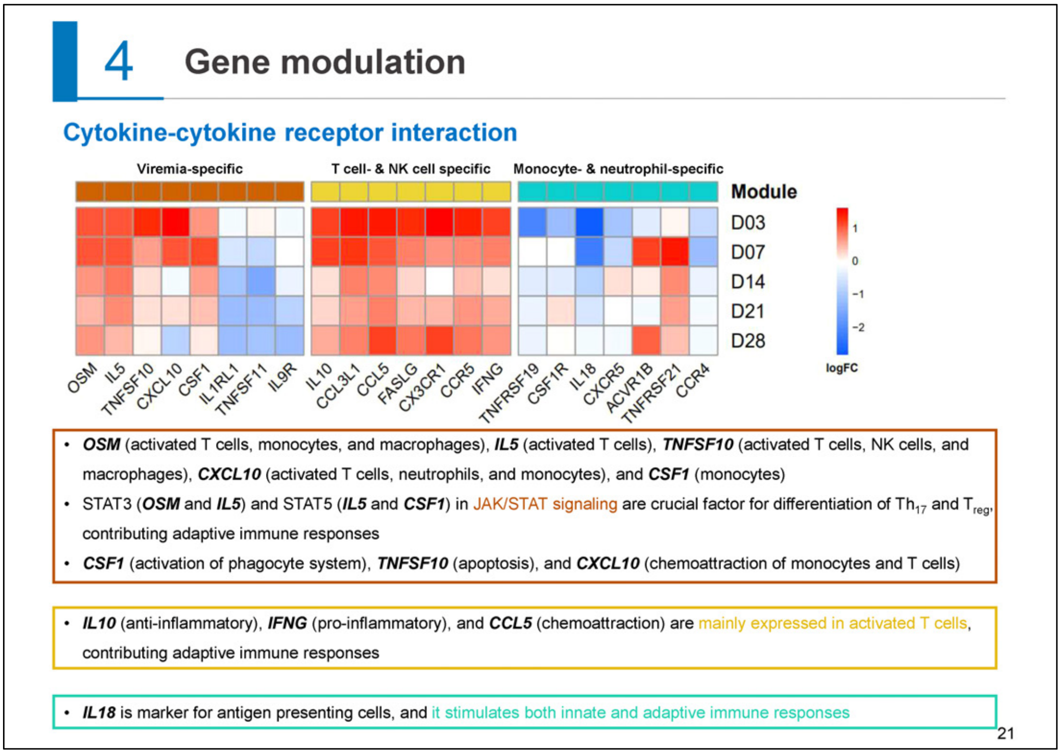
623 nodes (genes)
44,327 edges (interactions)

Viremia-specific: Antiviral responses

Erythrocyte- & platelet-specific: Erythrocyte maturation

T cell- & NK cell-specific: Innate & adaptive responses

Monocyte- & neutrophil-specific: Inflammatory responses



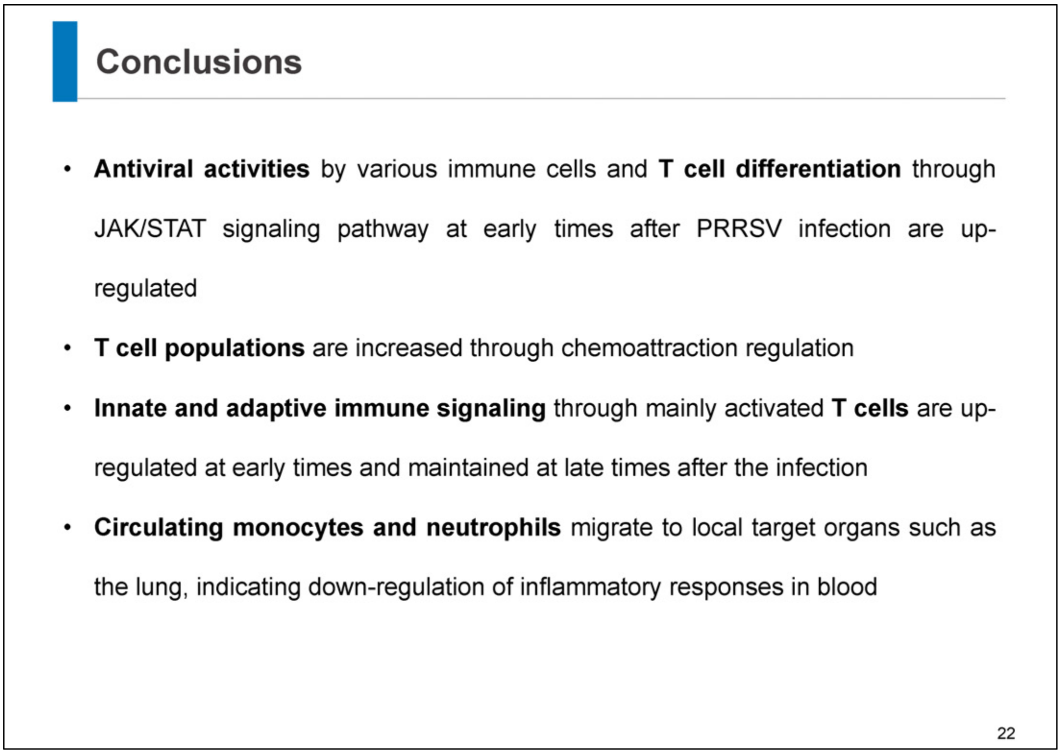
4 Gene modulation

Cytokine-cytokine receptor interaction

- ***OSM*** (activated T cells, monocytes, and macrophages), ***IL5*** (activated T cells), ***TNFSF10*** (activated T cells, NK cells, and macrophages), ***CXCL10*** (activated T cells, neutrophils, and monocytes), and ***CSF1*** (monocytes)
- STAT3 (***OSM*** and ***IL5***) and STAT5 (***IL5*** and ***CSF1***) in JAK/STAT signaling are crucial factor for differentiation of Th$_{17}$ and T$_{reg}$, contributing adaptive immune responses
- ***CSF1*** (activation of phagocyte system), ***TNFSF10*** (apoptosis), and ***CXCL10*** (chemoattraction of monocytes and T cells)

- ***IL10*** (anti-inflammatory), ***IFNG*** (pro-inflammatory), and ***CCL5*** (chemoattraction) are mainly expressed in activated T cells, contributing adaptive immune responses

- ***IL18*** is marker for antigen presenting cells, and it stimulates both innate and adaptive immune responses



Conclusions

- **Antiviral activities** by various immune cells and **T cell differentiation** through JAK/STAT signaling pathway at early times after PRRSV infection are up-regulated
- **T cell populations** are increased through chemoattraction regulation
- **Innate and adaptive immune signaling** through mainly activated **T cells** are up-regulated at early times and maintained at late times after the infection
- **Circulating monocytes and neutrophils** migrate to local target organs such as the lung, indicating down-regulation of inflammatory responses in blood

Study 2

Integrated time-serial transcriptome networks reveal common innate and tissue-specific adaptive immune responses to PRRSV infection

Veterinary Research, 2020

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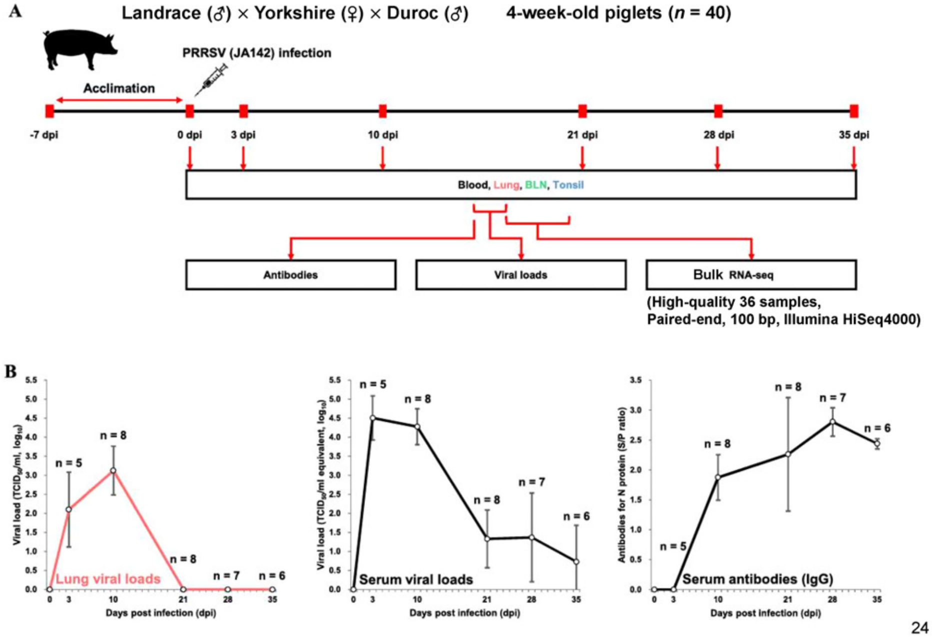
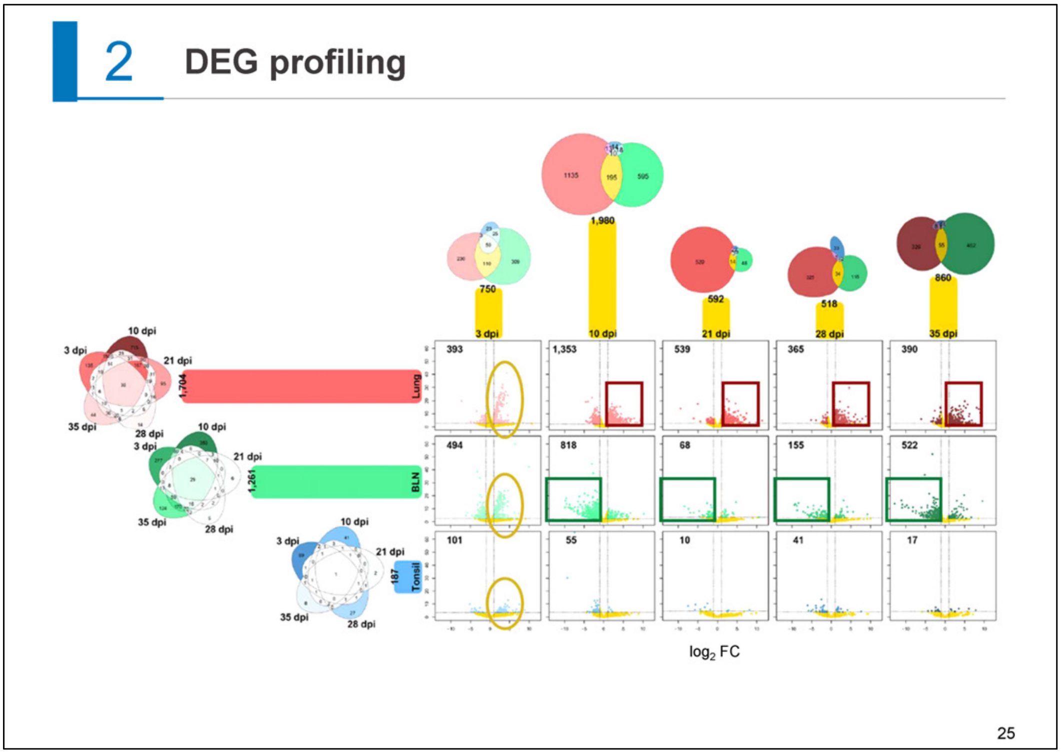
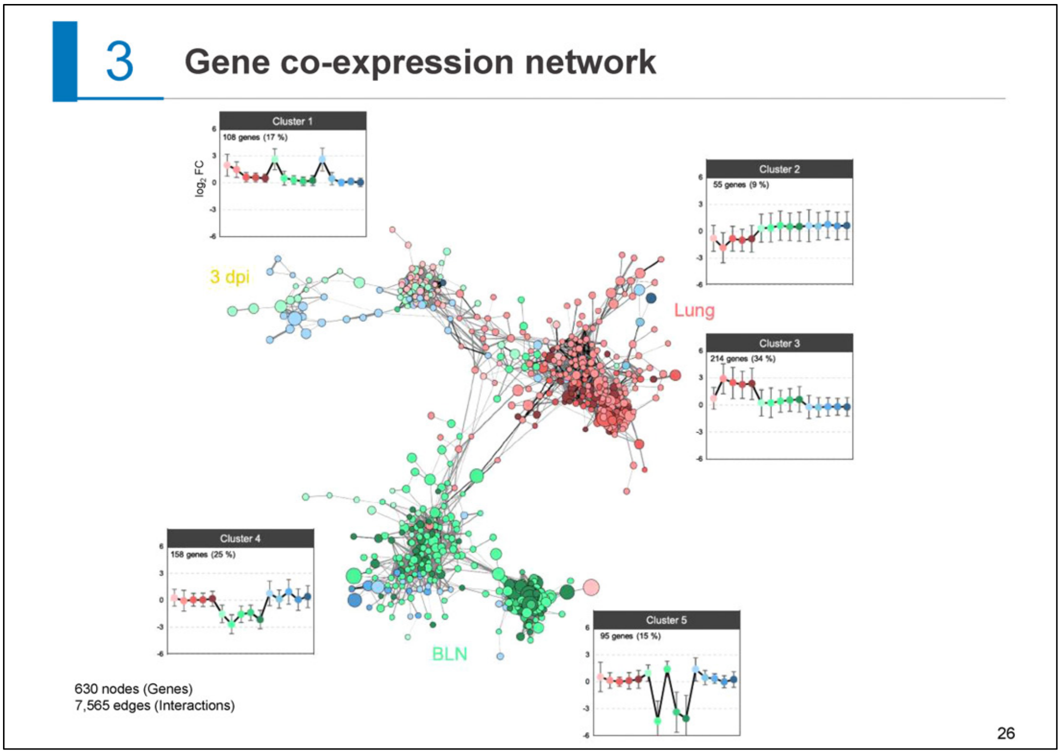
1 Experiment design & phenotypes



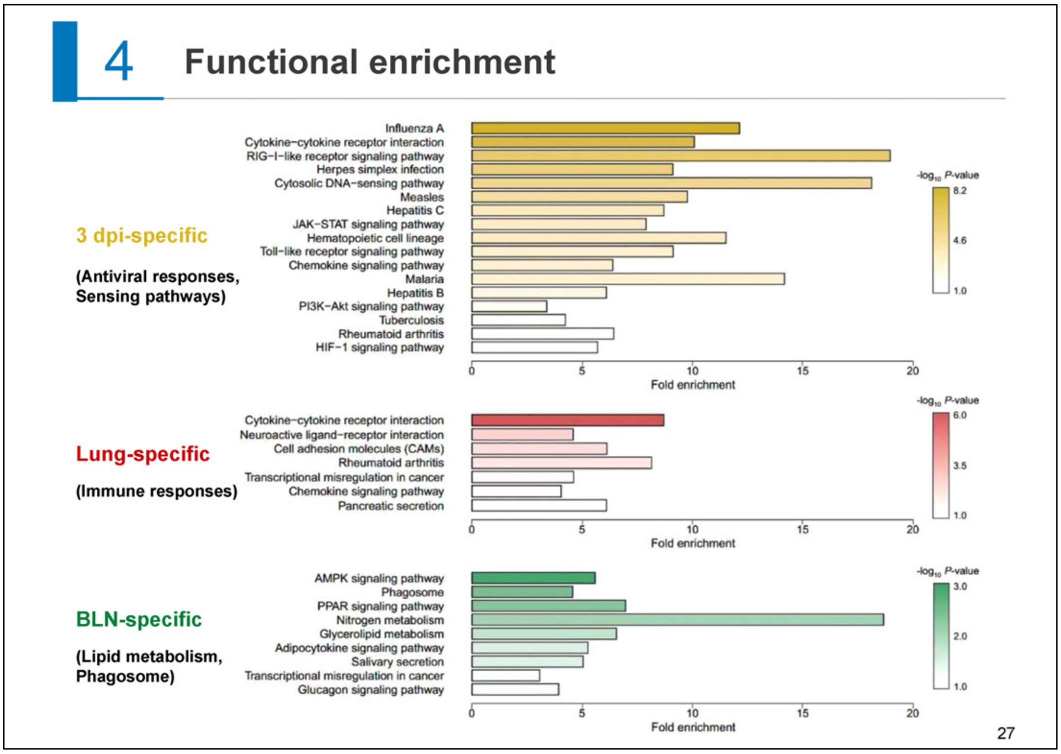


2 DEG profiling



3 Gene co-expression network

630 nodes (Genes)
7,565 edges (Interactions)



4 Functional enrichment

3 dpi-specific

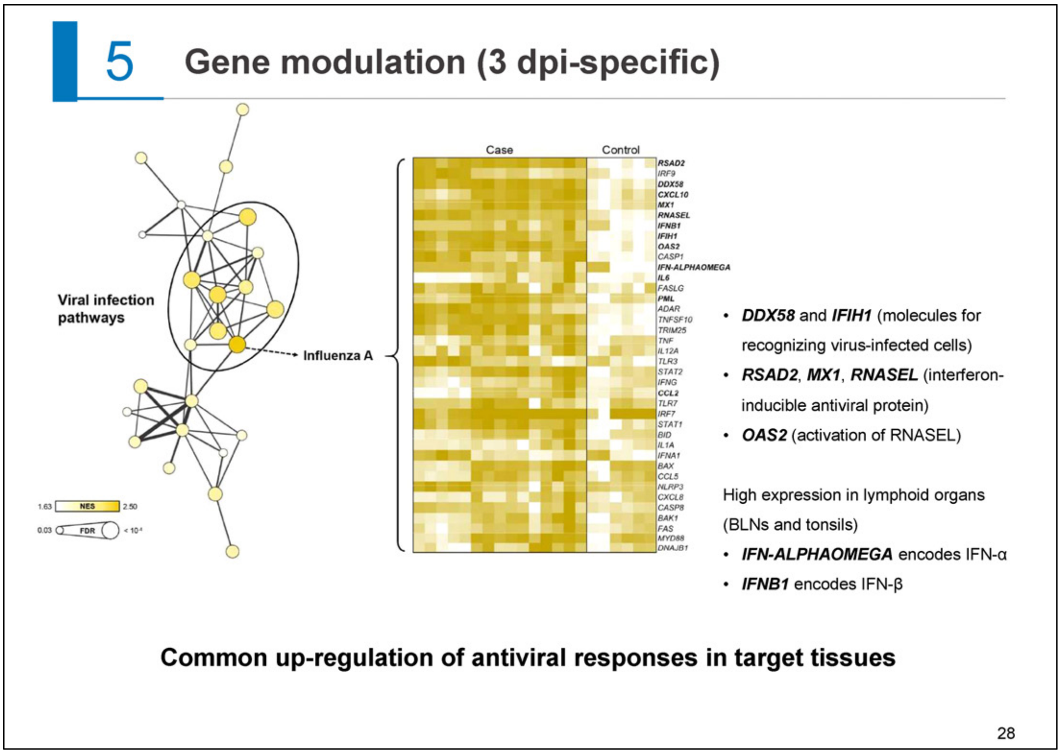
(Antiviral responses, Sensing pathways)

Lung-specific

(Immune responses)

BLN-specific

(Lipid metabolism, Phagosome)



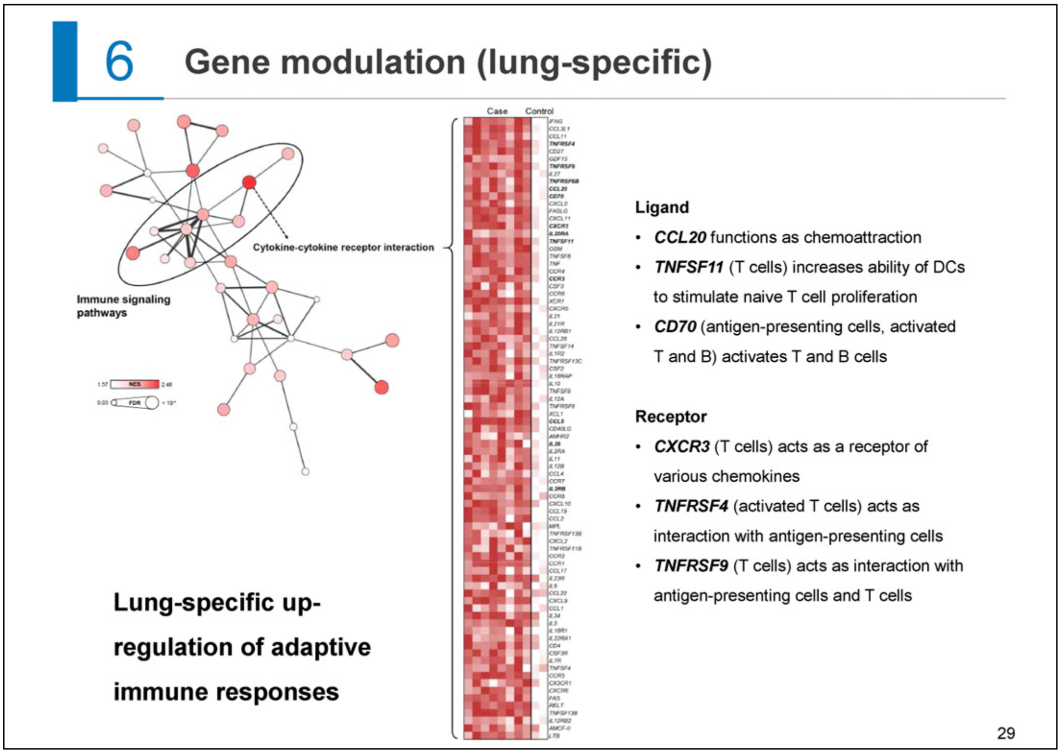
5 Gene modulation (3 dpi-specific)

- ***DDX58*** and ***IFIH1*** (molecules for recognizing virus-infected cells)
- ***RSAD2***, ***MX1***, ***RNASEL*** (interferon-inducible antiviral protein)
- ***OAS2*** (activation of RNASEL)

High expression in lymphoid organs (BLNs and tonsils)

- ***IFN-ALPHAOMEGA*** encodes IFN-α
- ***IFNB1*** encodes IFN-β

Common up-regulation of antiviral responses in target tissues



6 Gene modulation (lung-specific)

Ligand

- ***CCL20*** functions as chemoattraction
- ***TNFSF11*** (T cells) increases ability of DCs to stimulate naive T cell proliferation
- ***CD70*** (antigen-presenting cells, activated T and B) activates T and B cells

Receptor

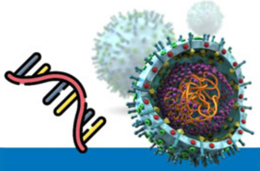
- ***CXCR3*** (T cells) acts as a receptor of various chemokines
- ***TNFRSF4*** (activated T cells) acts as interaction with antigen-presenting cells
- ***TNFRSF9*** (T cells) acts as interaction with antigen-presenting cells and T cells

Lung-specific up-regulation of adaptive immune responses

Conclusions

- **Antiviral and innate immune signaling** at early times after PRRSV infection are up-regulated
- **Adaptive immune signaling** through activated T cells at late times in **lungs** are up-regulated
- **Phagosome** is down-regulated by modulation of lipid metabolism in **BLNs** after the infection, which can affect viral persistent infection

Study 3



Integrative time-serial networks for genome-wide lncRNA-mRNA interactions reveal interferon-inducible antiviral and T-cell receptor regulations against PRRSV infection

Developmental and Comparative Immunology, 2023

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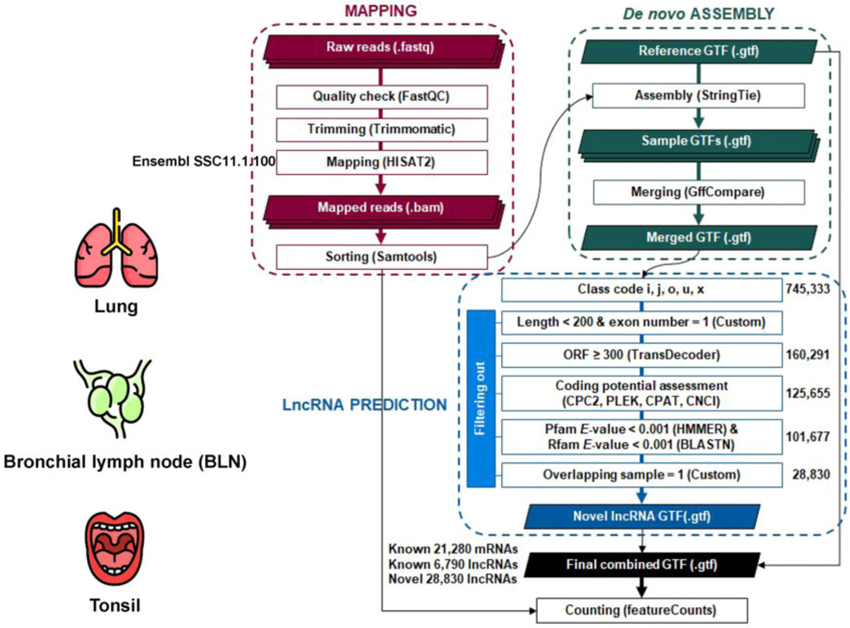
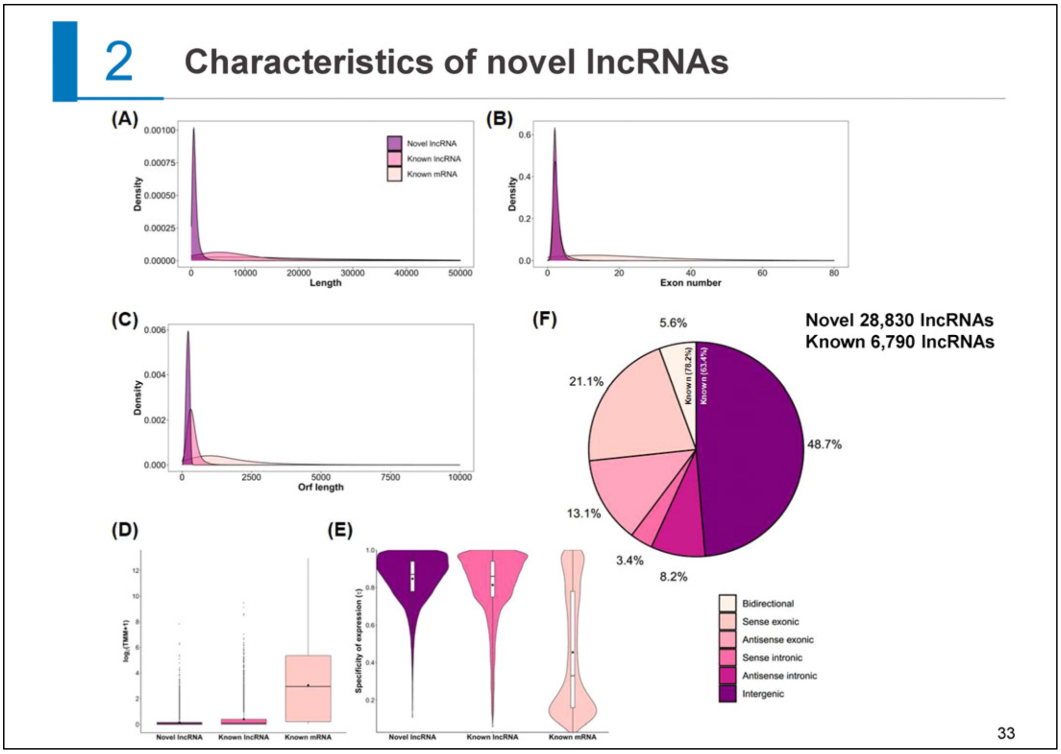
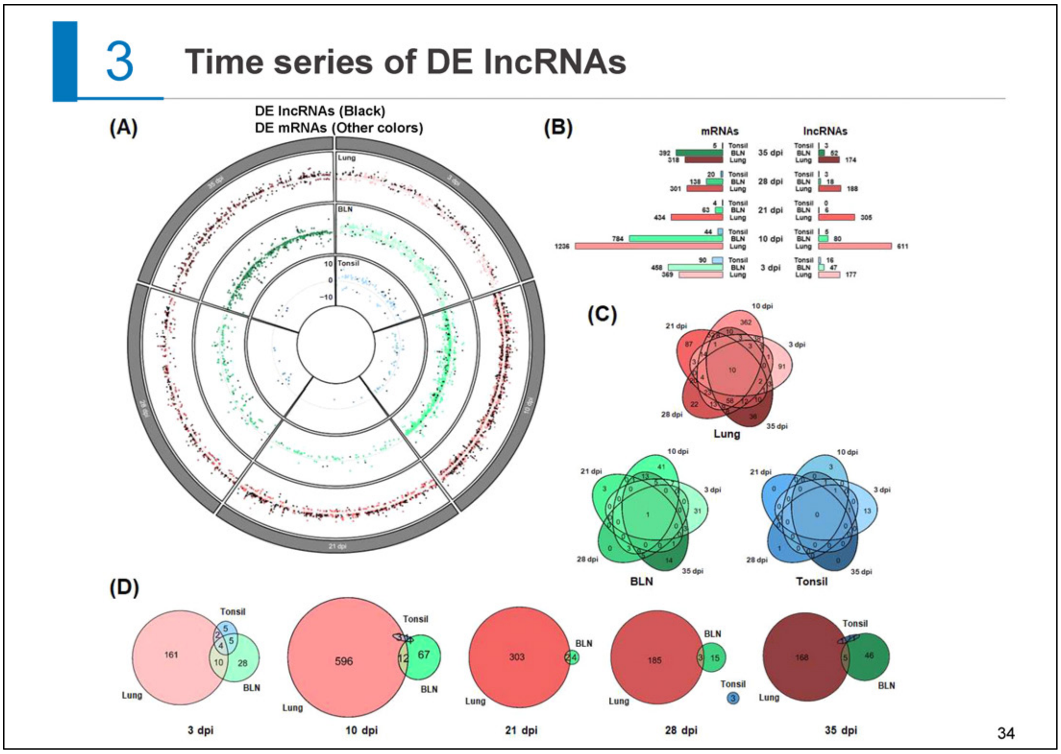
1 Data processing





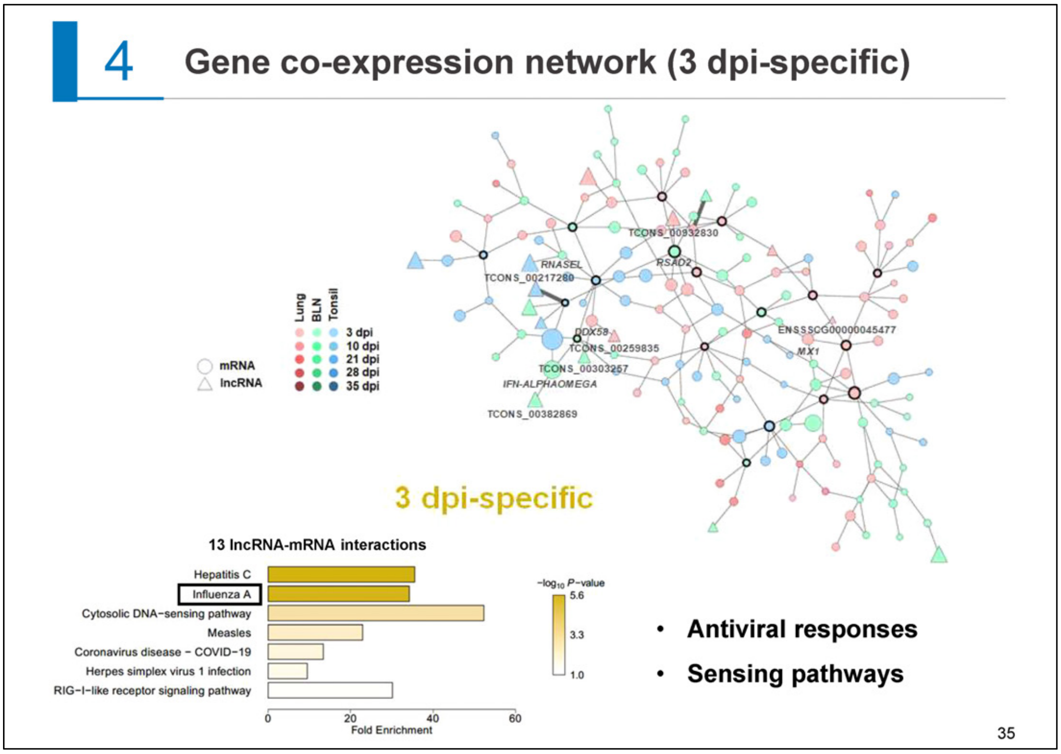
2 Characteristics of novel lncRNAs

Novel 28,830 lncRNAs
Known 6,790 lncRNAs



3 Time series of DE lncRNAs

DE lncRNAs (Black)
DE mRNAs (Other colors)

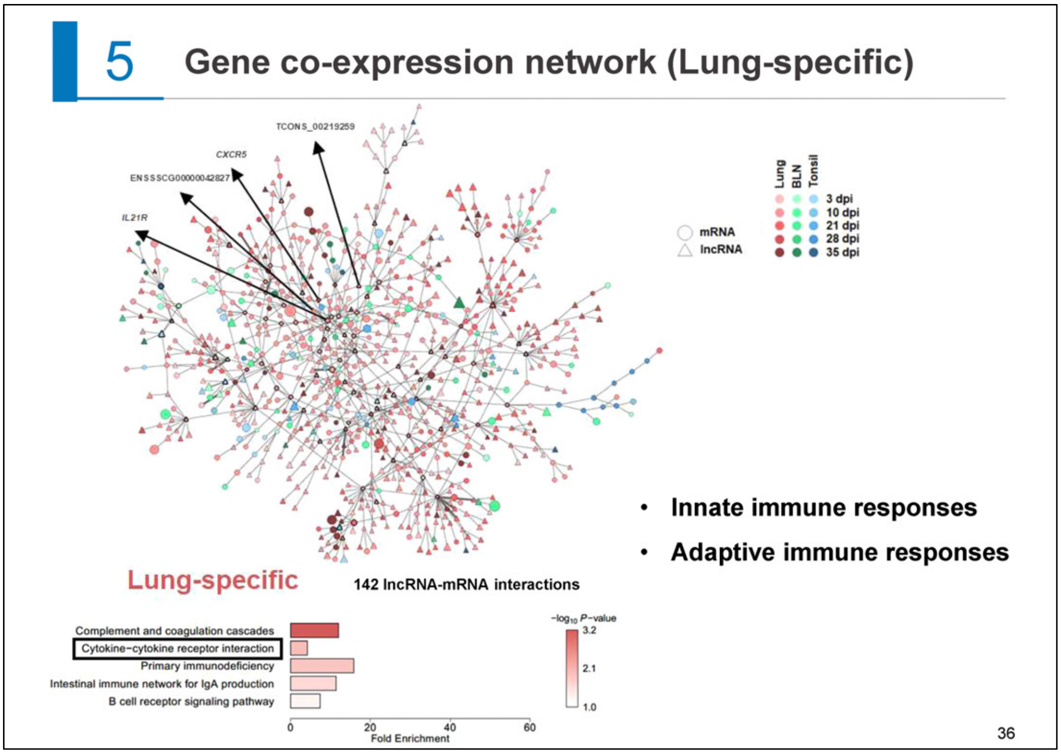


4 Gene co-expression network (3 dpi-specific)

3 dpi-specific

13 lncRNA-mRNA interactions

- **Antiviral responses**
- **Sensing pathways**

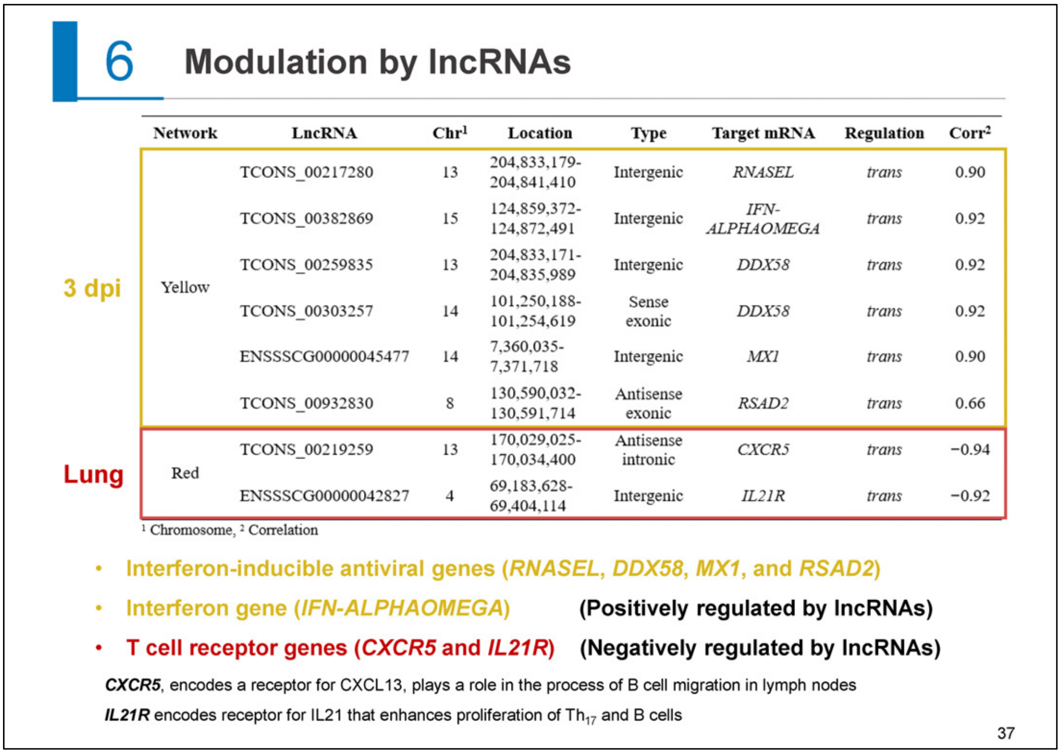


5 Gene co-expression network (Lung-specific)

- **Innate immune responses**
- **Adaptive immune responses**

Lung-specific

142 lncRNA-mRNA interactions



6 Modulation by lncRNAs

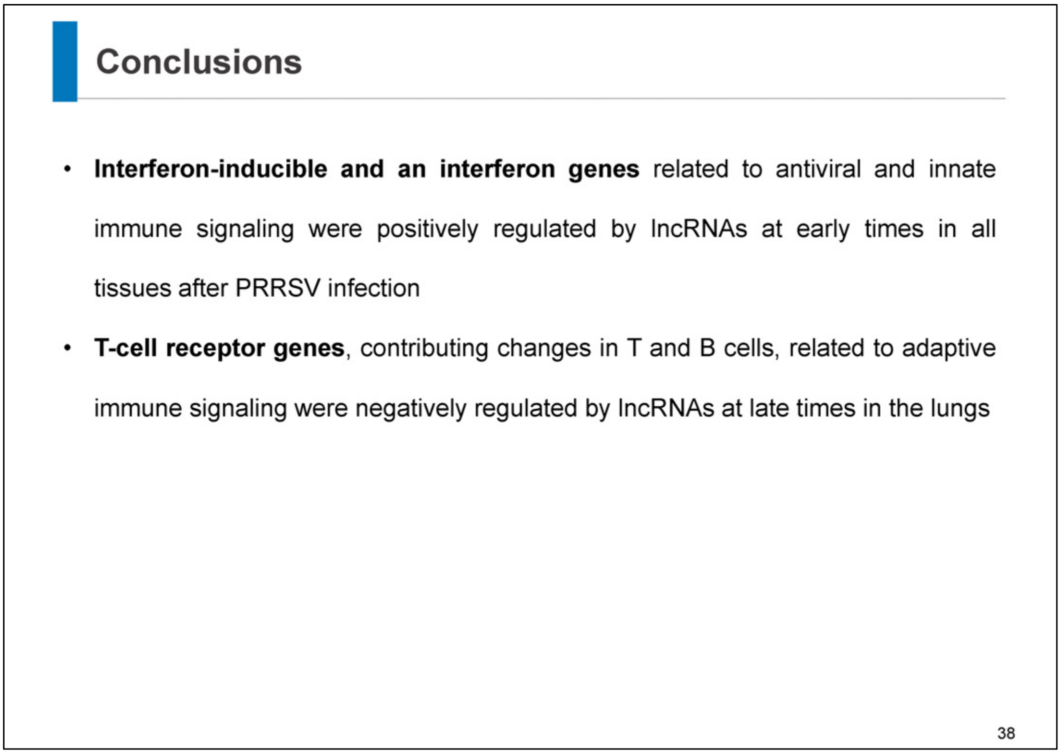
	Network	LncRNA	Chr[1]	Location	Type	Target mRNA	Regulation	Corr[2]
3 dpi	Yellow	TCONS_00217280	13	204,833,179-204,841,410	Intergenic	*RNASEL*	*trans*	0.90
		TCONS_00382869	15	124,859,372-124,872,491	Intergenic	*IFN-ALPHAOMEGA*	*trans*	0.92
		TCONS_00259835	13	204,833,171-204,835,989	Intergenic	*DDX58*	*trans*	0.92
		TCONS_00303257	14	101,250,188-101,254,619	Sense exonic	*DDX58*	*trans*	0.92
		ENSSSCG00000045477	14	7,360,035-7,371,718	Intergenic	*MX1*	*trans*	0.90
		TCONS_00932830	8	130,590,032-130,591,714	Antisense exonic	*RSAD2*	*trans*	0.66
Lung	Red	TCONS_00219259	13	170,029,025-170,034,400	Antisense intronic	*CXCR5*	*trans*	−0.94
		ENSSSCG00000042827	4	69,183,628-69,404,114	Intergenic	*IL21R*	*trans*	−0.92

[1] Chromosome, [2] Correlation

- **Interferon-inducible antiviral genes (*RNASEL*, *DDX58*, *MX1*, and *RSAD2*)**
- **Interferon gene (*IFN-ALPHAOMEGA*)** **(Positively regulated by lncRNAs)**
- **T cell receptor genes (*CXCR5* and *IL21R*)** **(Negatively regulated by lncRNAs)**

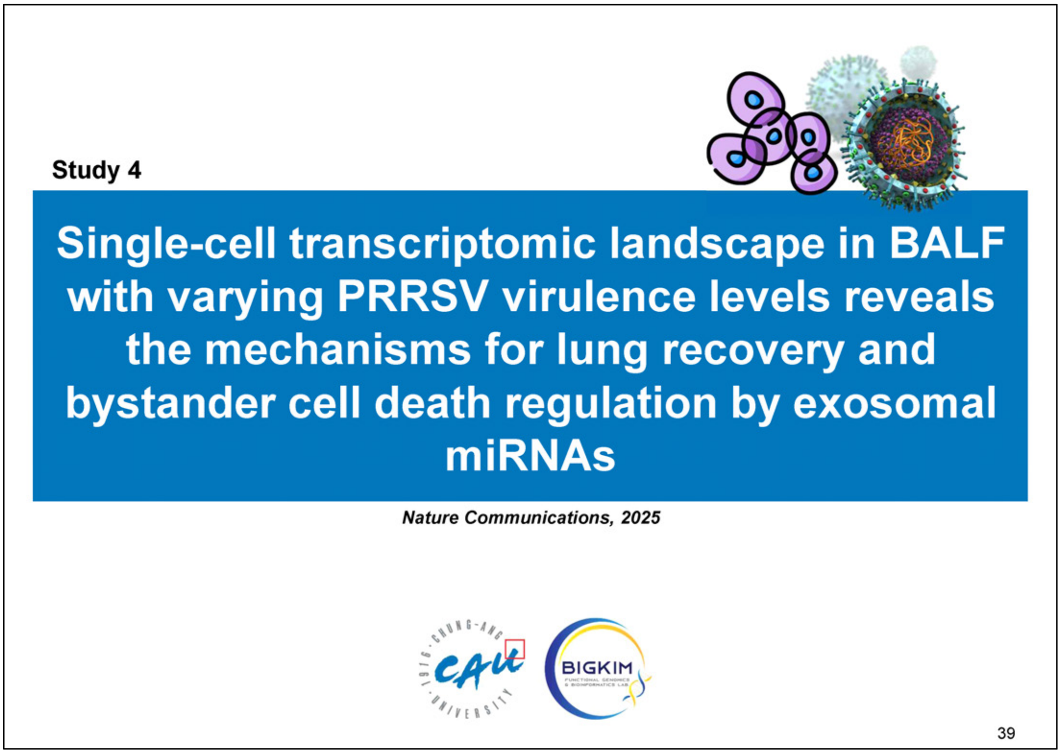
CXCR5, encodes a receptor for CXCL13, plays a role in the process of B cell migration in lymph nodes

IL21R encodes receptor for IL21 that enhances proliferation of Th_{17} and B cells



Conclusions

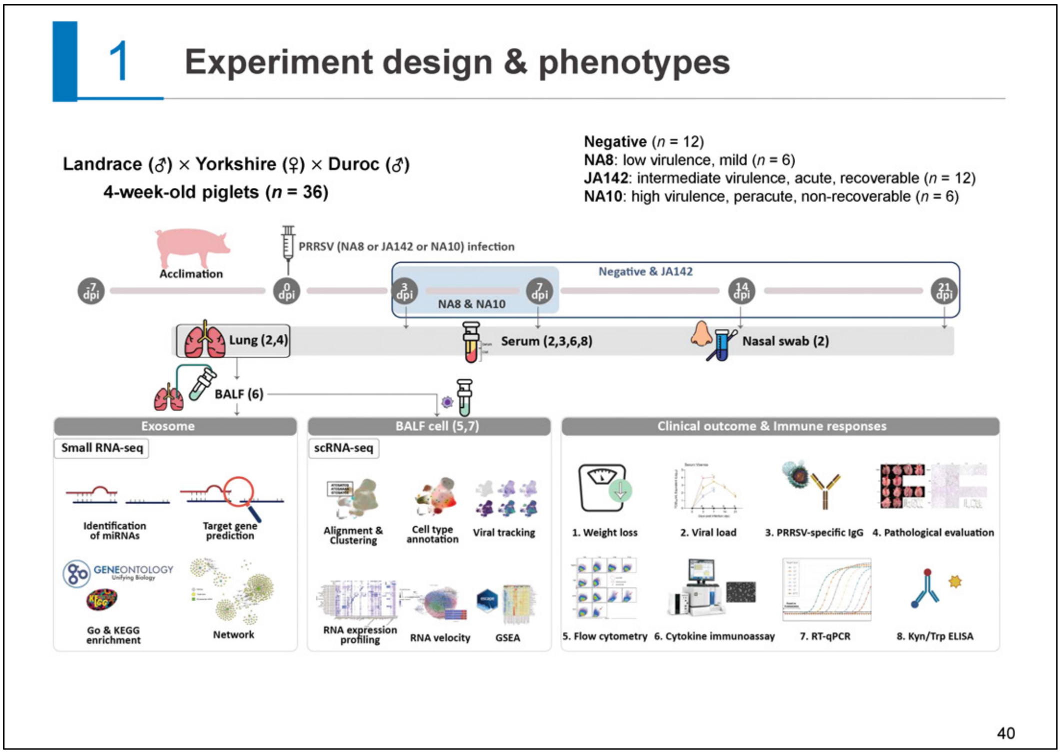
- **Interferon-inducible and an interferon genes** related to antiviral and innate immune signaling were positively regulated by lncRNAs at early times in all tissues after PRRSV infection
- **T-cell receptor genes**, contributing changes in T and B cells, related to adaptive immune signaling were negatively regulated by lncRNAs at late times in the lungs



Study 4

Single-cell transcriptomic landscape in BALF with varying PRRSV virulence levels reveals the mechanisms for lung recovery and bystander cell death regulation by exosomal miRNAs

***Nature Communications*, 2025**



1 Experiment design & phenotypes

Landrace (♂) × Yorkshire (♀) × Duroc (♂)
4-week-old piglets (*n* = 36)

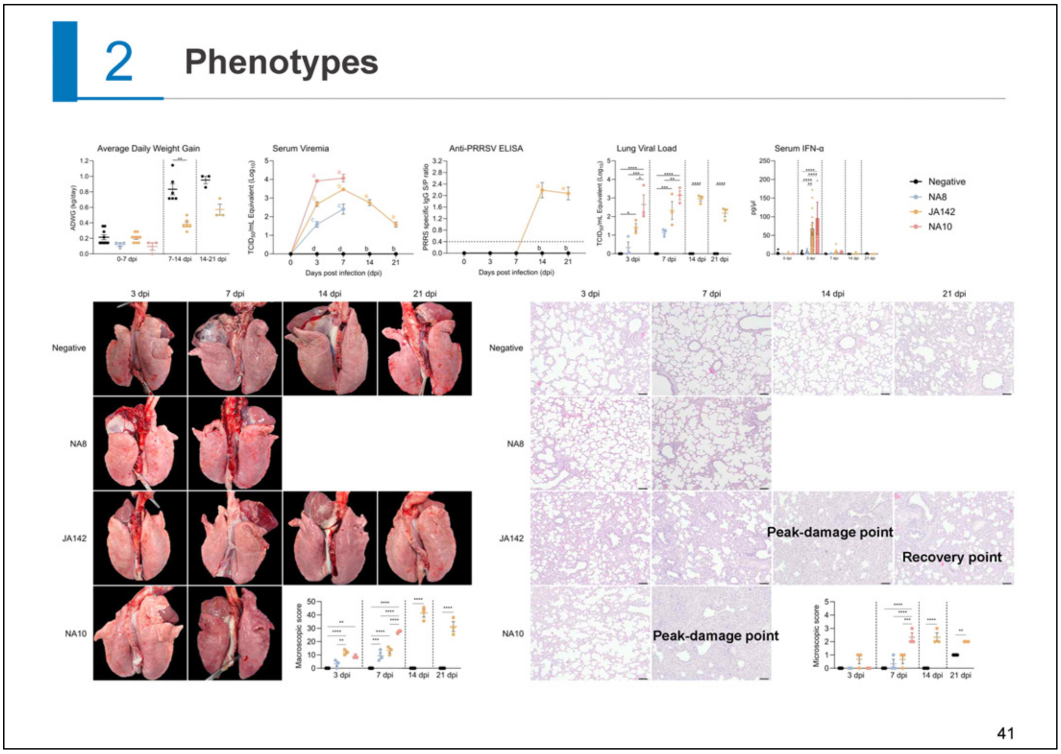
Negative (*n* = 12)
NA8: low virulence, mild (*n* = 6)
JA142: intermediate virulence, acute, recoverable (*n* = 12)
NA10: high virulence, peracute, non-recoverable (*n* = 6)

Acclimation
PRRSV (NA8 or JA142 or NA10) infection
-7 dpi
0 dpi
3 dpi
7 dpi
14 dpi
21 dpi
Negative & JA142
NA8 & NA10
Lung (2,4)
Serum (2,3,6,8)
Nasal swab (2)
BALF (6)

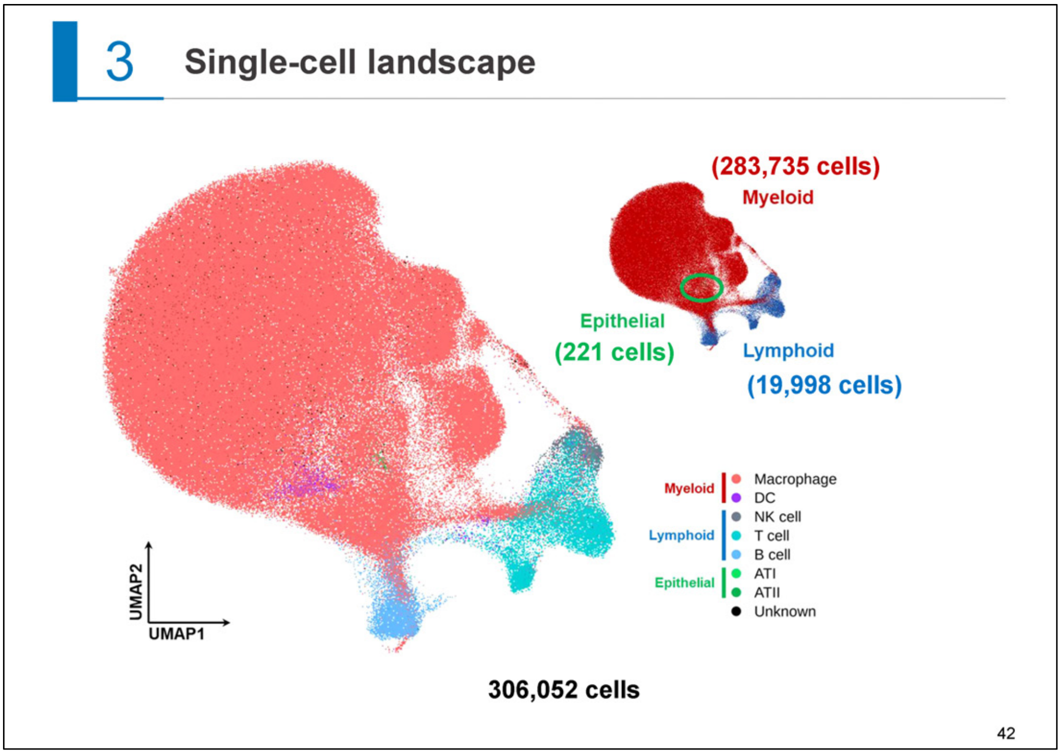
Exosome
Small RNA-seq
Identification of miRNAs
Target gene prediction
GENEONTOLOGY Unifying Biology
Go & KEGG enrichment
Network

BALF cell (5,7)
scRNA-seq
Alignment & Clustering
Cell type annotation
Viral tracking
RNA expression profiling
RNA velocity
GSEA

Clinical outcome & Immune responses
1. Weight loss
2. Viral load
3. PRRSV-specific IgG
4. Pathological evaluation
5. Flow cytometry
6. Cytokine immunoassay
7. RT-qPCR
8. Kyn/Trp ELISA

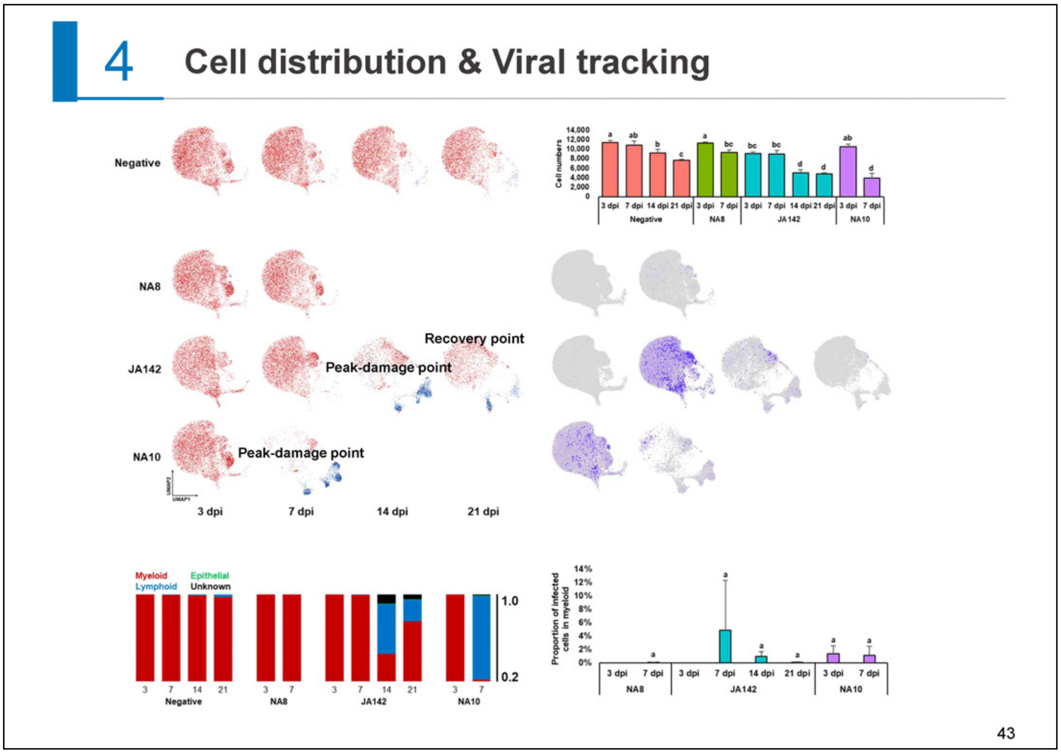


2 Phenotypes

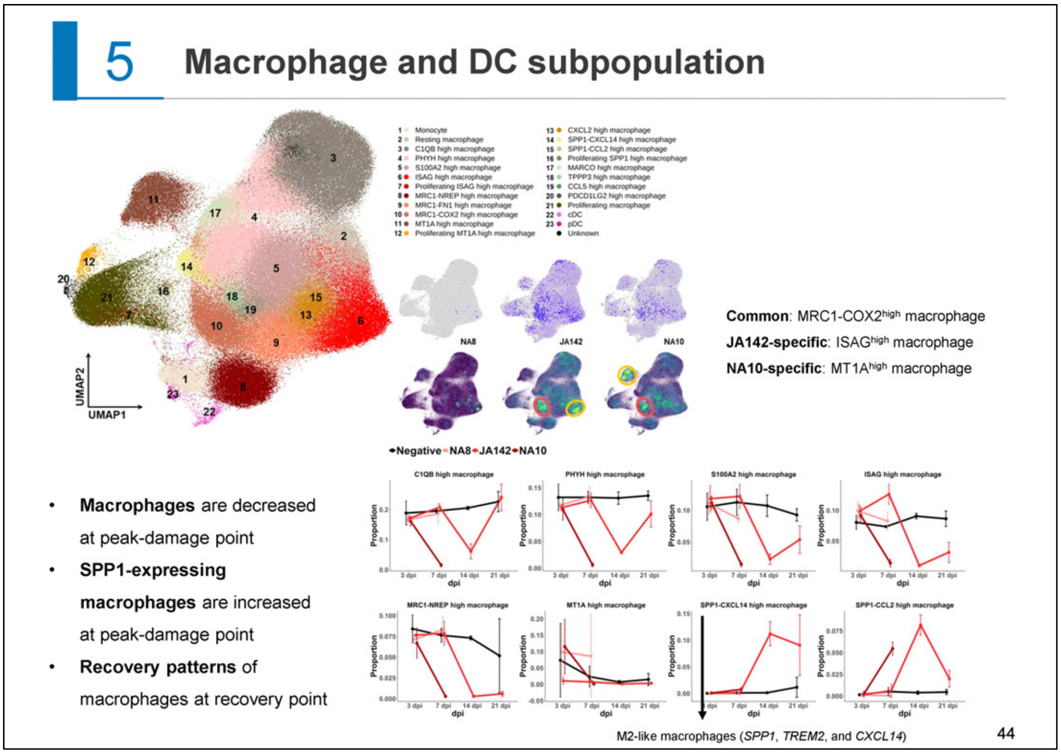


3 Single-cell landscape

306,052 cells



4 Cell distribution & Viral tracking



5 Macrophage and DC subpopulation

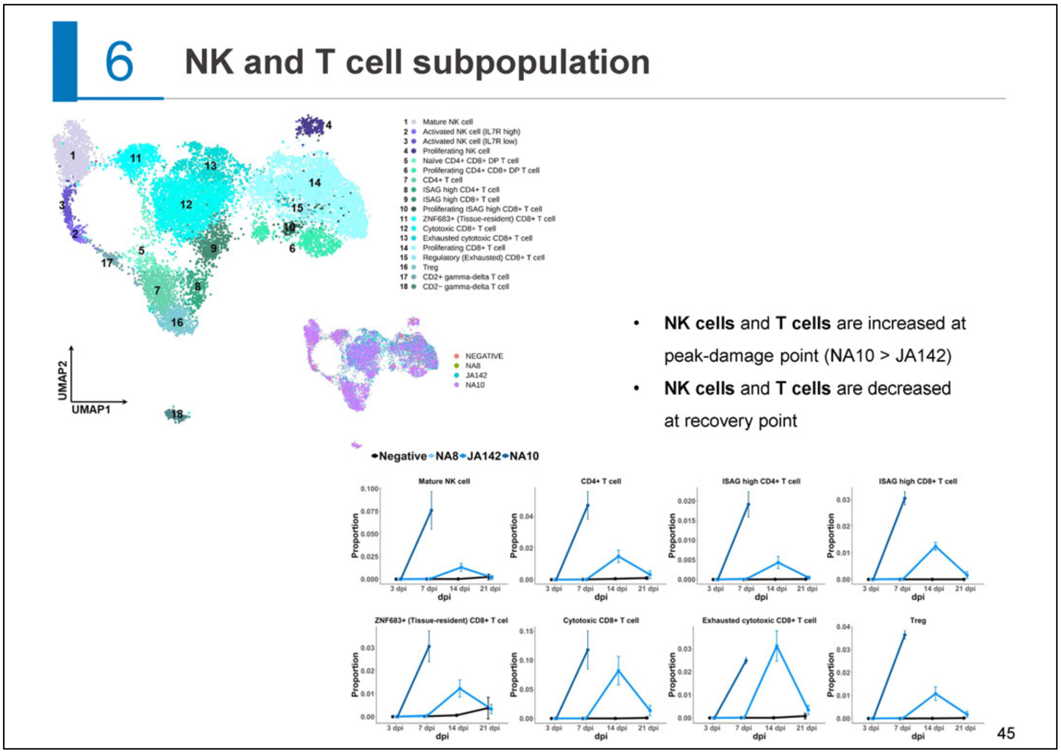
Common: MRC1-COX2^{high} macrophage

JA142-specific: ISAG^{high} macrophage

NA10-specific: MT1A^{high} macrophage

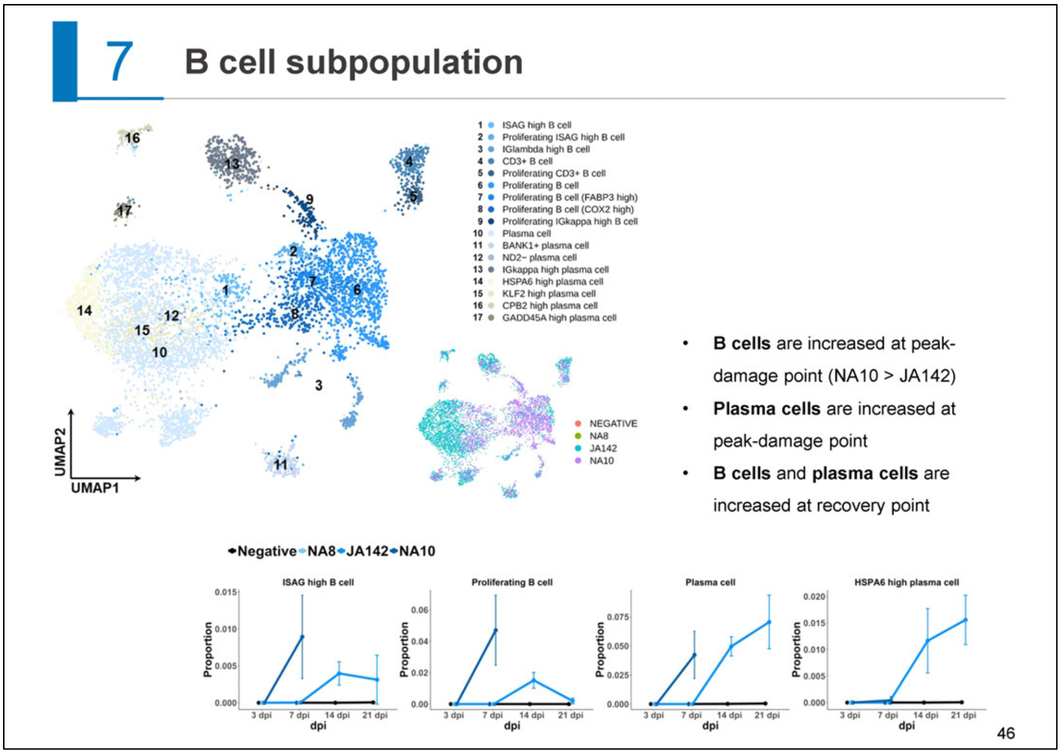
- **Macrophages** are decreased at peak-damage point
- **SPP1-expressing macrophages** are increased at peak-damage point
- **Recovery patterns** of macrophages at recovery point

M2-like macrophages (*SPP1*, *TREM2*, and *CXCL14*)



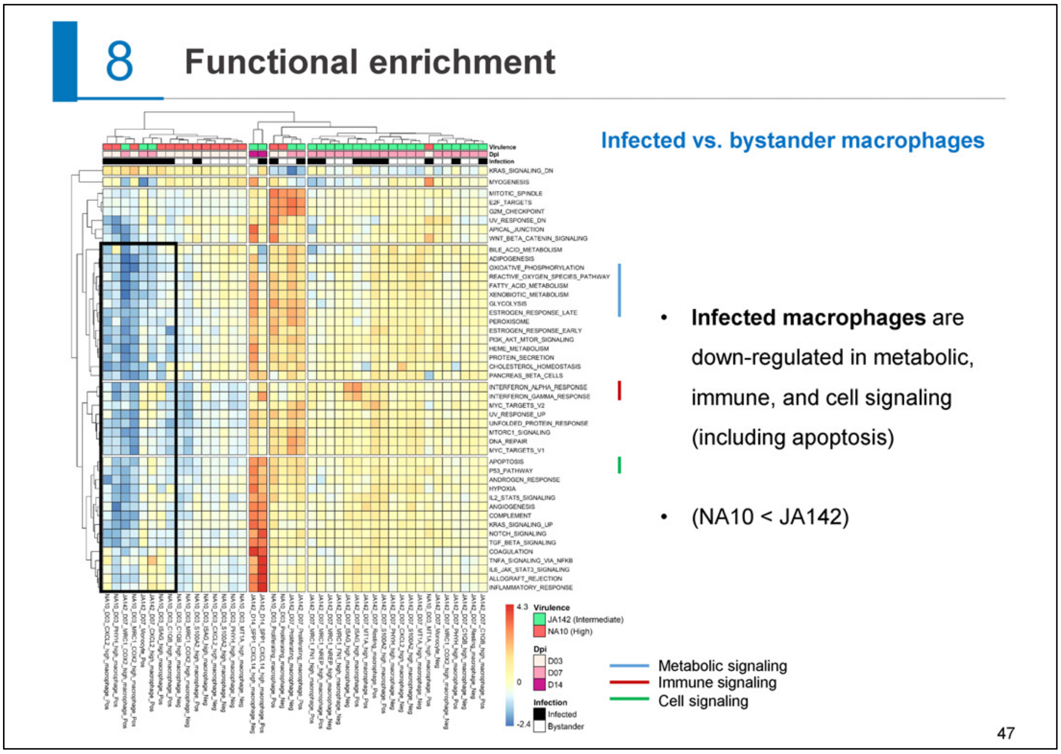
6 NK and T cell subpopulation

- **NK cells** and **T cells** are increased at peak-damage point (NA10 > JA142)
- **NK cells** and **T cells** are decreased at recovery point



7 B cell subpopulation

- **B cells** are increased at peak-damage point (NA10 > JA142)
- **Plasma cells** are increased at peak-damage point
- **B cells** and **plasma cells** are increased at recovery point

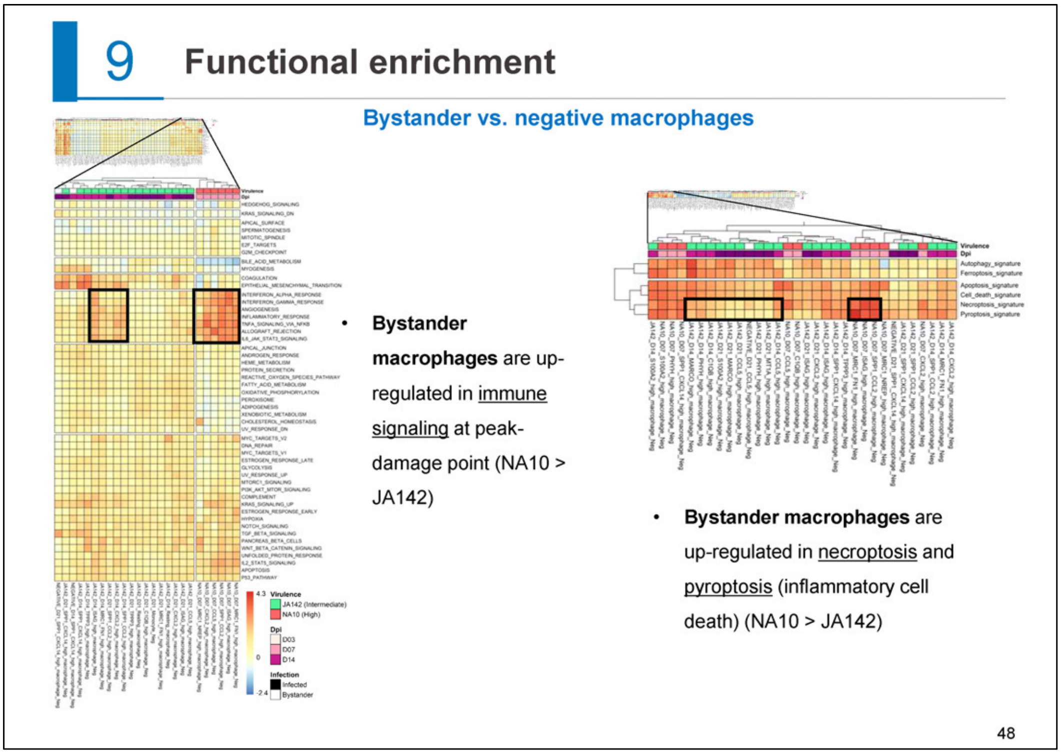


8 Functional enrichment

Infected vs. bystander macrophages

- **Infected macrophages** are down-regulated in metabolic, immune, and cell signaling (including apoptosis)
- (NA10 < JA142)

Metabolic signaling
Immune signaling
Cell signaling

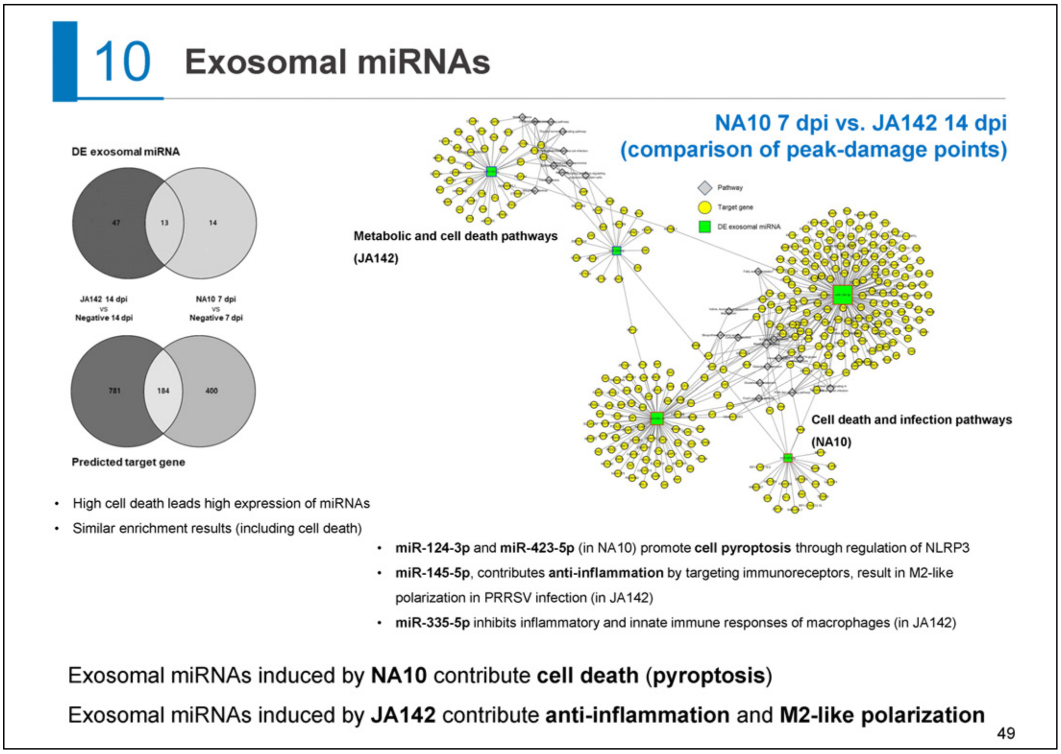


9 Functional enrichment

Bystander vs. negative macrophages

- **Bystander macrophages** are up-regulated in <u>immune signaling</u> at peak-damage point (NA10 > JA142)

- **Bystander macrophages** are up-regulated in <u>necroptosis</u> and <u>pyroptosis</u> (inflammatory cell death) (NA10 > JA142)



10 Exosomal miRNAs

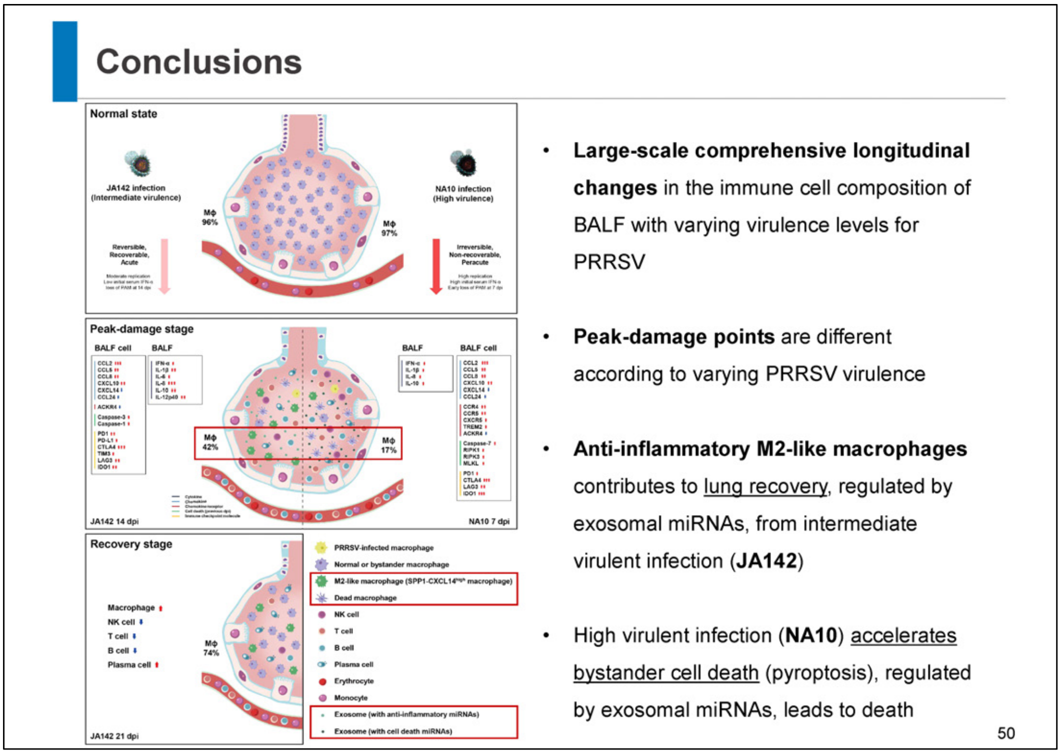
NA10 7 dpi vs. JA142 14 dpi (comparison of peak-damage points)

- High cell death leads high expression of miRNAs
- Similar enrichment results (including cell death)

- **miR-124-3p** and **miR-423-5p** (in NA10) promote **cell pyroptosis** through regulation of NLRP3
- **miR-145-5p**, contributes **anti-inflammation** by targeting immunoreceptors, result in M2-like polarization in PRRSV infection (in JA142)
- **miR-335-5p** inhibits inflammatory and innate immune responses of macrophages (in JA142)

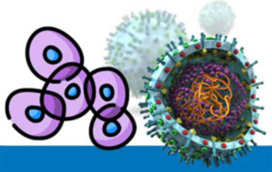
Exosomal miRNAs induced by **NA10** contribute **cell death** (**pyroptosis**)

Exosomal miRNAs induced by **JA142** contribute **anti-inflammation** and **M2-like polarization**



Conclusions

- **Large-scale comprehensive longitudinal changes** in the immune cell composition of BALF with varying virulence levels for PRRSV
- **Peak-damage points** are different according to varying PRRSV virulence
- **Anti-inflammatory M2-like macrophages** contributes to lung recovery, regulated by exosomal miRNAs, from intermediate virulent infection (**JA142**)
- High virulent infection (**NA10**) accelerates bystander cell death (pyroptosis), regulated by exosomal miRNAs, leads to death



Study 5

Single-cell co-expression module-metabolite-microbe landscape in BALF with varying PRRSV virulence reveals tempo-graded macrophage immune collapse

Lim et al., 2026, *In progress*

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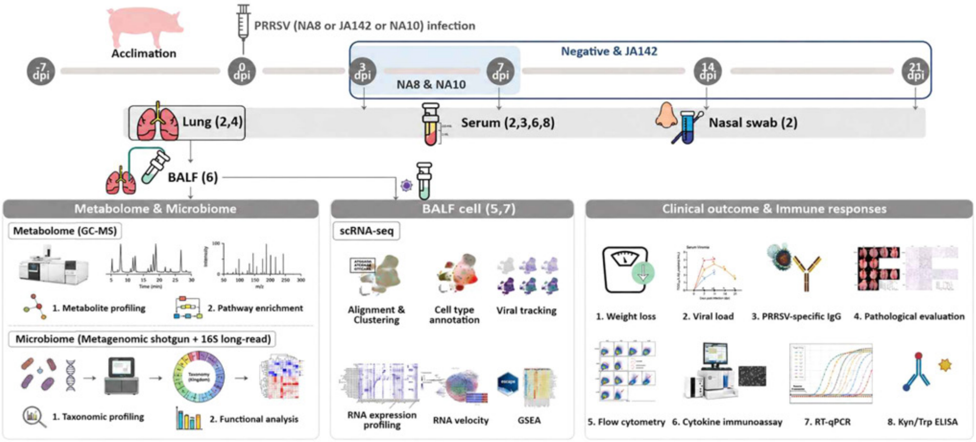
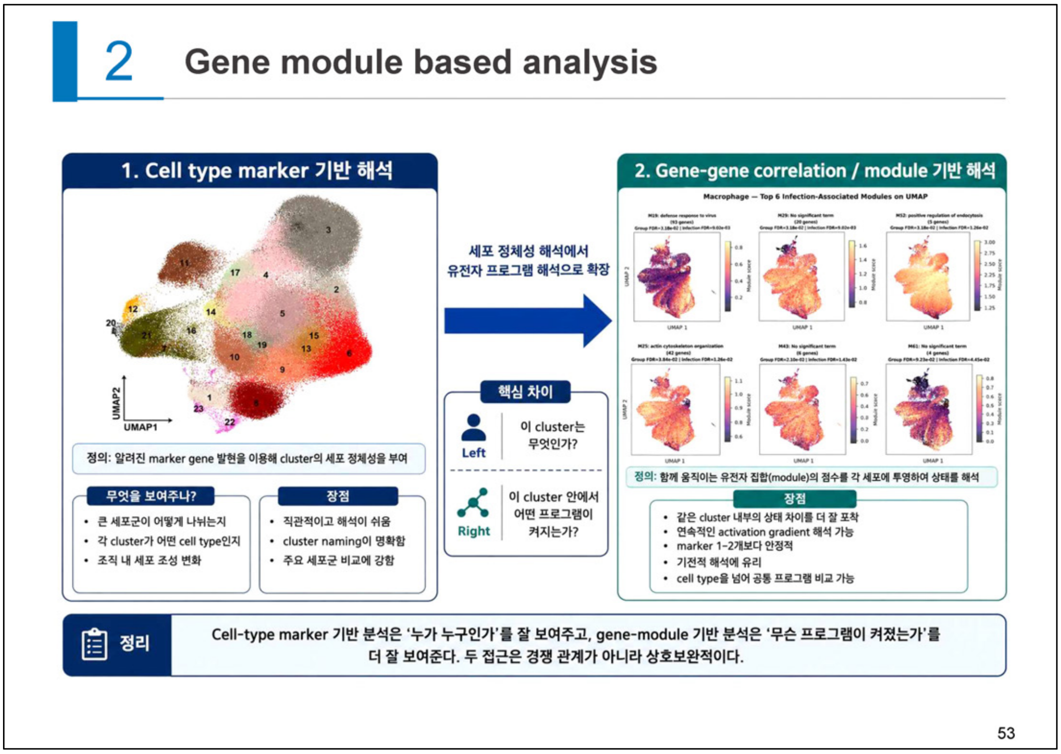
1 Experiment design & phenotypes

Landrace (♂) × Yorkshire (♀) × Duroc (♂)
4-week-old piglets (*n* = 36)

Negative (*n* = 12)
NA8: low virulence, mild (*n* = 6)
JA142: intermediate virulence, acute, recoverable (*n* = 12)
NA10: high virulence, peracute, non-recoverable (*n* = 6)





2 Gene module based analysis

1. Cell type marker 기반 해석

정의: 알려진 marker gene 발현을 이용해 cluster의 세포 정체성을 부여

무엇을 보여주나?

- 큰 세포군이 어떻게 나뉘는지
- 각 cluster가 어떤 cell type인지
- 조직 내 세포 조성 변화

장점

- 직관적이고 해석이 쉬움
- cluster naming이 명확함
- 주요 세포군 비교에 강함

세포 정체성 해석에서
유전자 프로그램 해석으로 확장

핵심 차이

Left	이 cluster는 무엇인가?
Right	이 cluster 안에서 어떤 프로그램이 켜지는가?

2. Gene-gene correlation / module 기반 해석

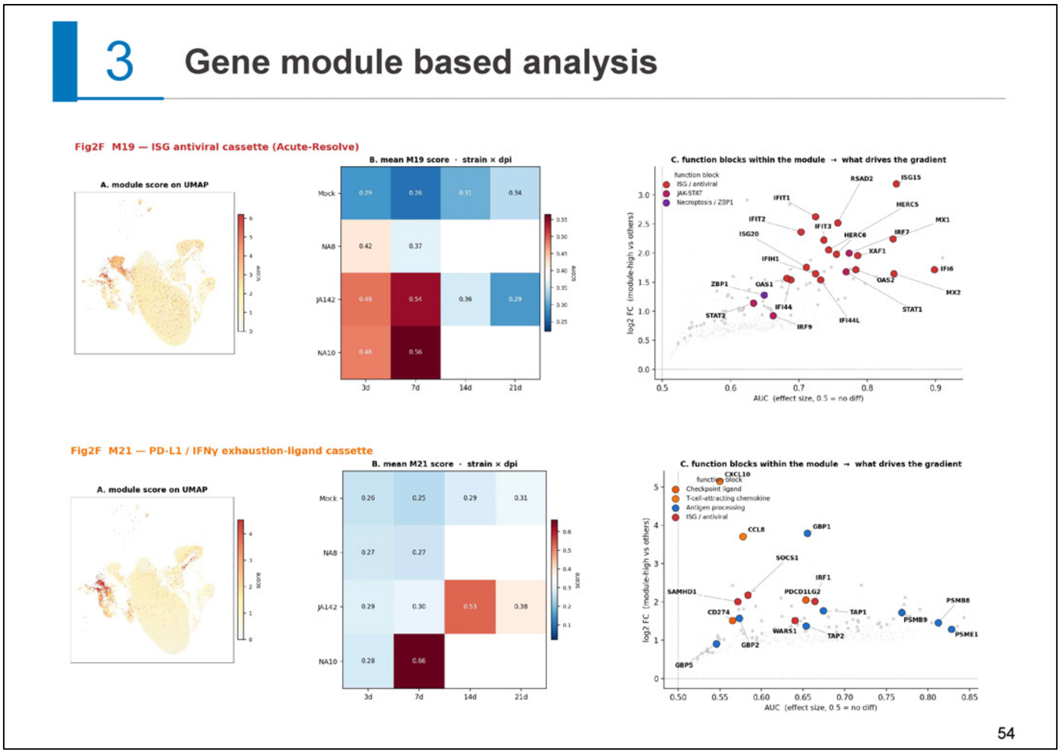
Macrophage — Top 6 Infection-Associated Modules on UMAP

정의: 함께 움직이는 유전자 집합(module)의 점수를 각 세포에 투영하여 상태를 해석

장점

- 같은 cluster 내부의 상태 차이를 더 잘 포착
- 연속적인 activation gradient 해석 가능
- marker 1–2개보다 안정적
- 기전적 해석에 유리
- cell type을 넘어 공통 프로그램 비교 가능

정리 Cell-type marker 기반 분석은 '누가 누구인가'를 잘 보여주고, gene-module 기반 분석은 '무슨 프로그램이 켜졌는가'를 더 잘 보여준다. 두 접근은 경쟁 관계가 아니라 상호보완적이다.



3 Gene module based analysis

Fig2F M19 — ISG antiviral cassette (Acute-Resolve)

A. module score on UMAP

B. mean M19 score · strain × dpi

	3d	7d	14d	21d
Mock	0.29	0.26	0.31	0.34
NA8	0.42	0.37		
JA142	0.49	0.54	0.36	0.29
NA10	0.48	0.56		

C. function blocks within the module → what drives the gradient

Fig2F M21 — PD-L1 / IFNγ exhaustion-ligand cassette

A. module score on UMAP

B. mean M21 score · strain × dpi

	3d	7d	14d	21d
Mock	0.26	0.25	0.29	0.31
NA8	0.27	0.27		
JA142	0.29	0.30	0.53	0.38
NA10	0.28	0.66		

C. function blocks within the module → what drives the gradient

4 Gene module based analysis

Fig3F T_M11 — ISG antiviral cassette (mirrors Mac_M19)

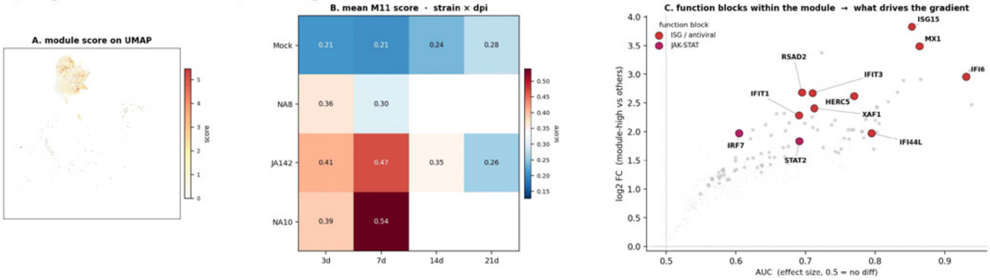
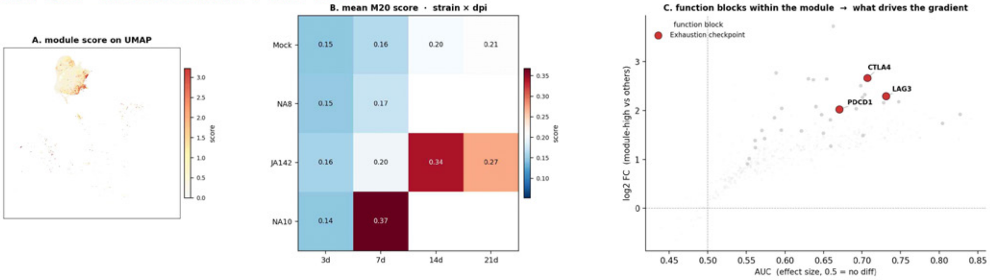


Fig3F T_M20 — Exhaustion receiver (PD-1 · LAG3 · CTLA4)



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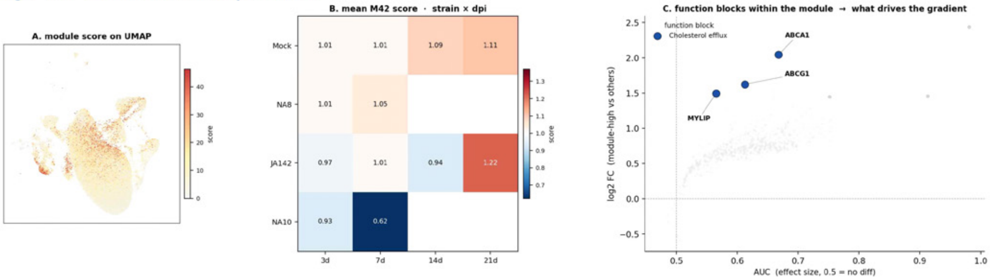
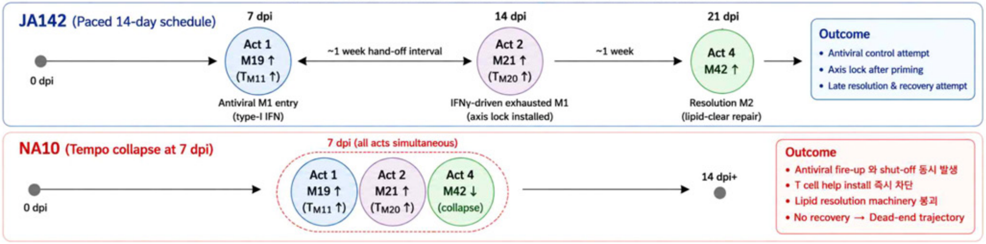
5 Gene module based analysis

Fig2F M42 — Cholesterol efflux / M2 lipid resolution



Tempo Compression in NA10: Three Acts Collapsed into 7 dpi



JA142 (Paced 14-day schedule)

0 dpi → 7 dpi: Act 1 M19 ↑ (T_{M11} ↑) — Antiviral M1 entry (type-I IFN)

↔ ~1 week hand-off interval → 14 dpi: Act 2 M21 ↑ (T_{M20} ↑) — IFNγ-driven exhausted M1 (axis lock installed)

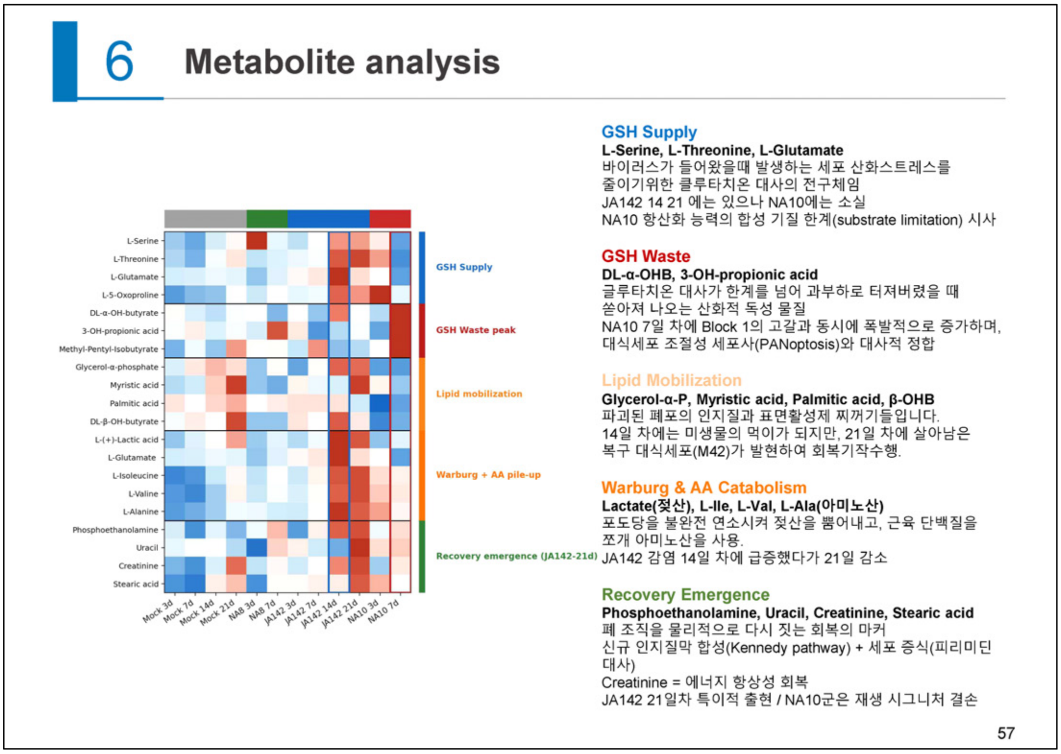
→ ~1 week → 21 dpi: Act 4 M42 ↑ — Resolution M2 (lipid-clear repair) →

Outcome
- Antiviral control attempt
- Axis lock after priming
- Late resolution & recovery attempt

NA10 (Tempo collapse at 7 dpi)

0 dpi → 7 dpi (all acts simultaneous): Act 1 M19 ↑ (T_{M11} ↑) · Act 2 M21 ↑ (T_{M20} ↑) · Act 4 M42 ↓ (collapse) → 14 dpi+

Outcome
- Antiviral fire-up 와 shut-off 동시 발생
- T cell help install 즉시 차단
- Lipid resolution machinery 붕괴
- No recovery → Dead-end trajectory



6 Metabolite analysis

GSH Supply

L-Serine, L-Threonine, L-Glutamate

바이러스가 들어왔을때 발생하는 세포 산화스트레스를
줄이기위한 글루타치온 대사의 전구체임
JA142 14 21 에는 있으나 NA10에는 소실
NA10 항산화 능력의 합성 기질 한계(substrate limitation) 시사

GSH Waste

DL-α-OHB, 3-OH-propionic acid

글루타치온 대사가 한계를 넘어 과부하로 터져버렸을 때
쏟아져 나오는 산화적 독성 물질
NA10 7일 차에 Block 1의 고갈과 동시에 폭발적으로 증가하며,
대식세포 조절성 세포사(PANoptosis)와 대사적 정합

Lipid Mobilization

Glycerol-α-P, Myristic acid, Palmitic acid, β-OHB

파괴된 폐포의 인지질과 표면활성제 찌꺼기들입니다.
14일 차에는 미생물의 먹이가 되지만, 21일 차에 살아남은
복구 대식세포(M42)가 발현하여 회복기작수행.

Warburg & AA Catabolism

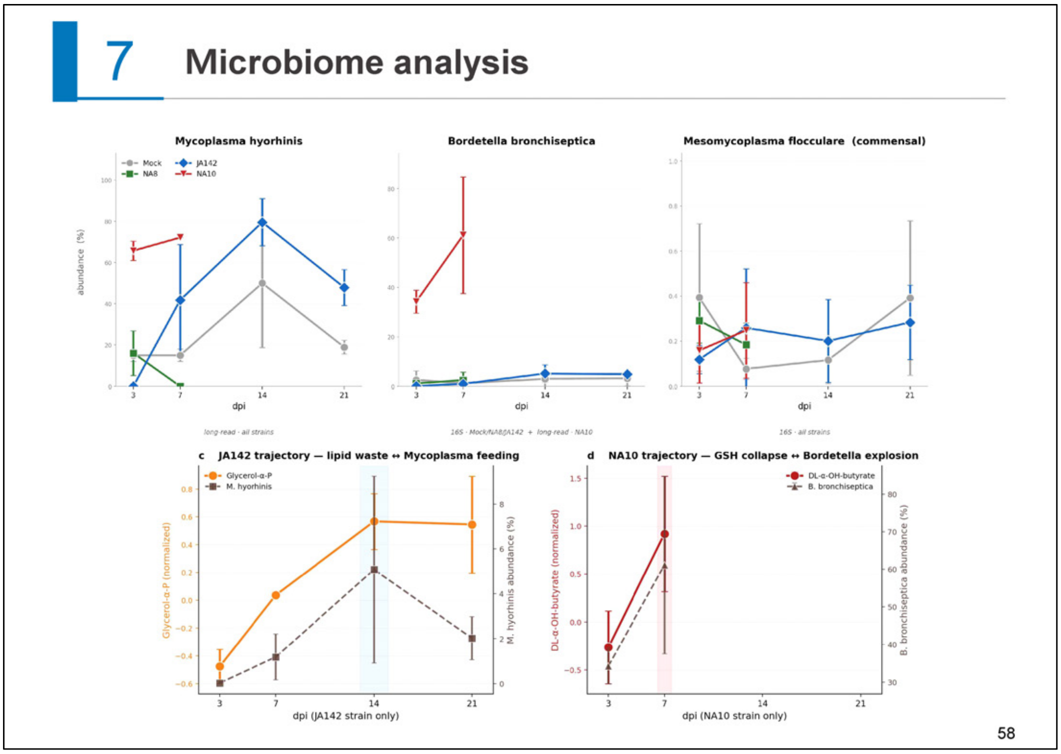
Lactate(젖산), L-Ile, L-Val, L-Ala(아미노산)

포도당을 불완전 연소시켜 젖산을 뿜어내고, 근육 단백질을
쪼개 아미노산을 사용.
JA142 감염 14일 차에 급증했다가 21일 감소

Recovery Emergence

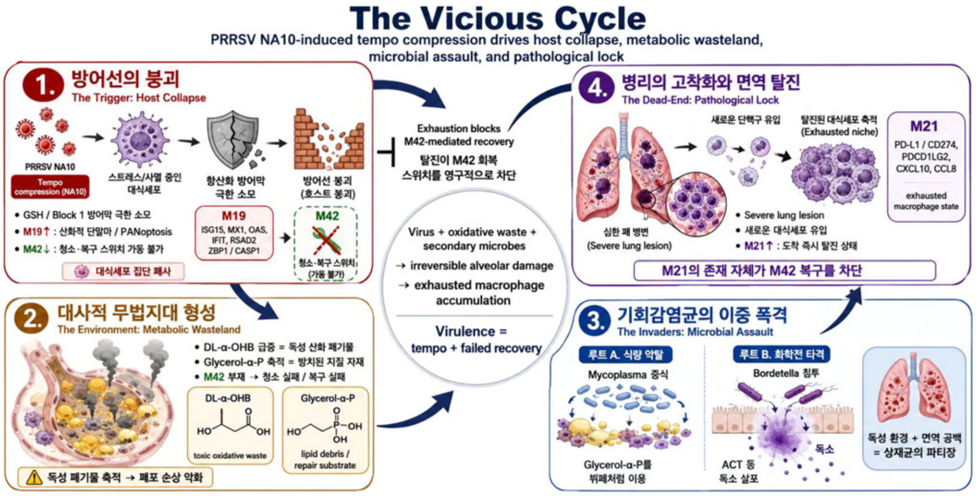
Phosphoethanolamine, Uracil, Creatinine, Stearic acid

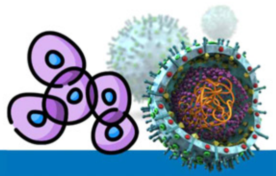
폐 조직을 물리적으로 다시 짓는 회복의 마커
신규 인지질막 합성(Kennedy pathway) + 세포 증식(피리미딘
대사)
Creatinine = 에너지 항상성 회복
JA142 21일차 특이적 출현 / NA10군은 재생 시그니처 결손



7 Microbiome analysis

Suggestive mechanism



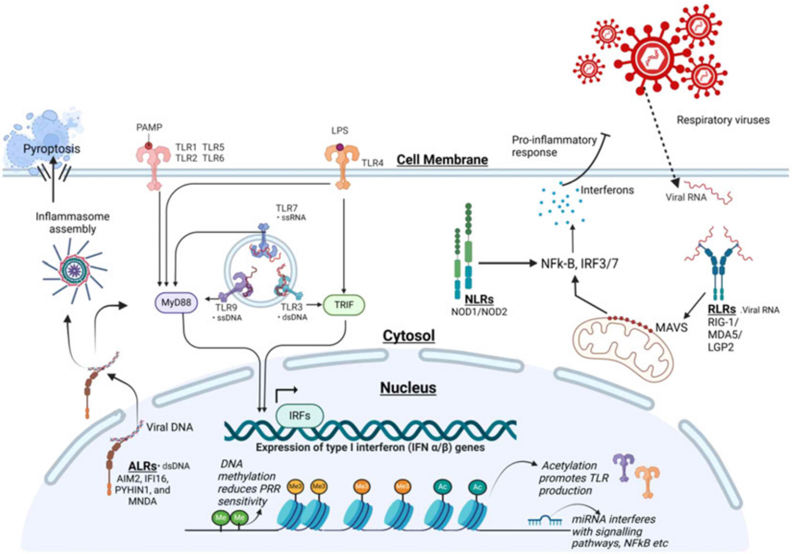


Study 6

Identification of epigenomic alterations based on chromatin accessibility and histone modification against varying PRRSV virulence

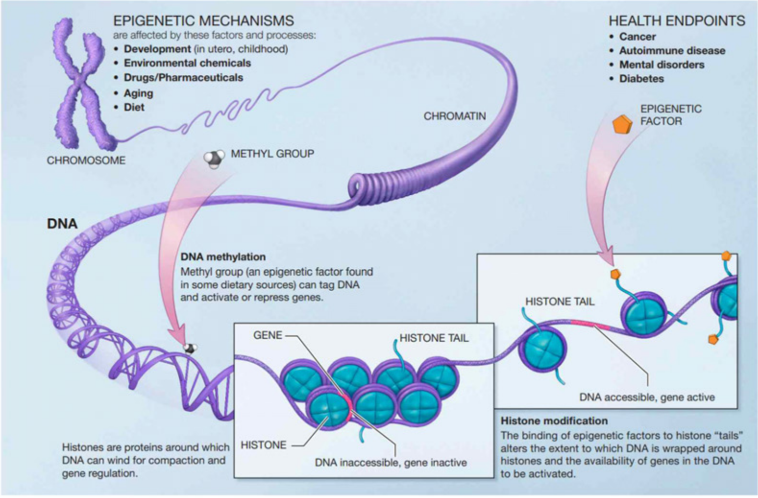
Lim et al., 2026, *In progress*

Epigenetic alteration by viral infection



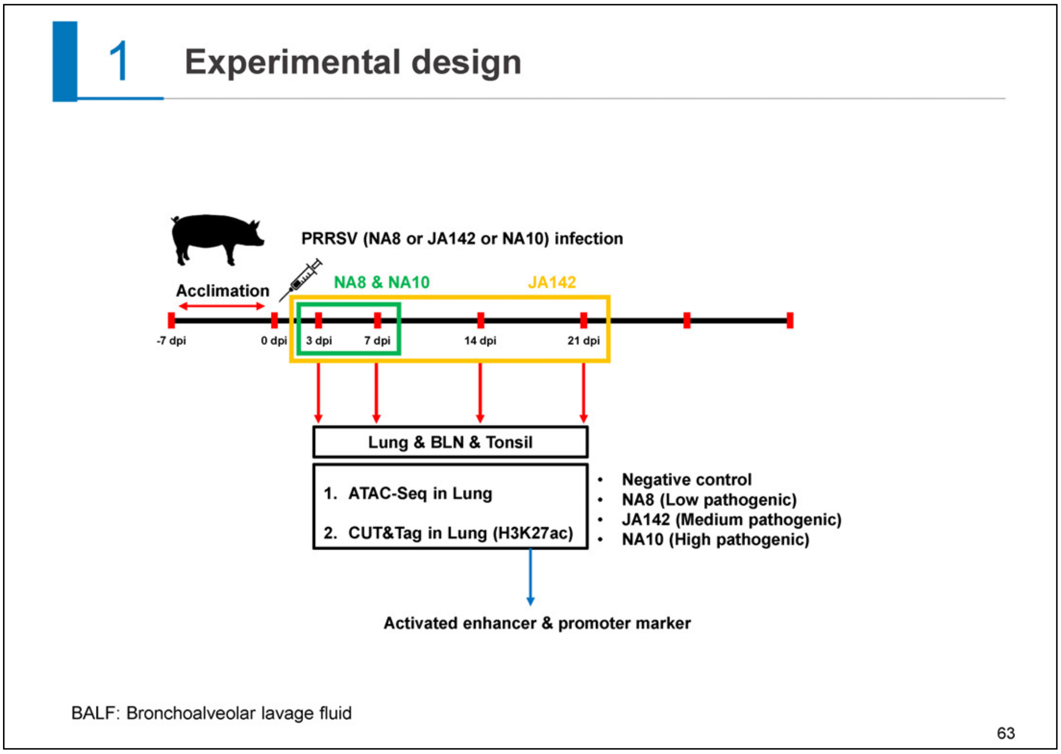
(Saha et al., 2025)

Epigenomics



- ATAC-seq (**A**ssay for **T**ransposase-**A**ccessible **C**hromatin using sequencing)
- ChIP-seq (**Ch**romatin **I**mmuno**p**recipitation **S**equencing)

NIH



1 Experimental design

Lung & BLN & Tonsil

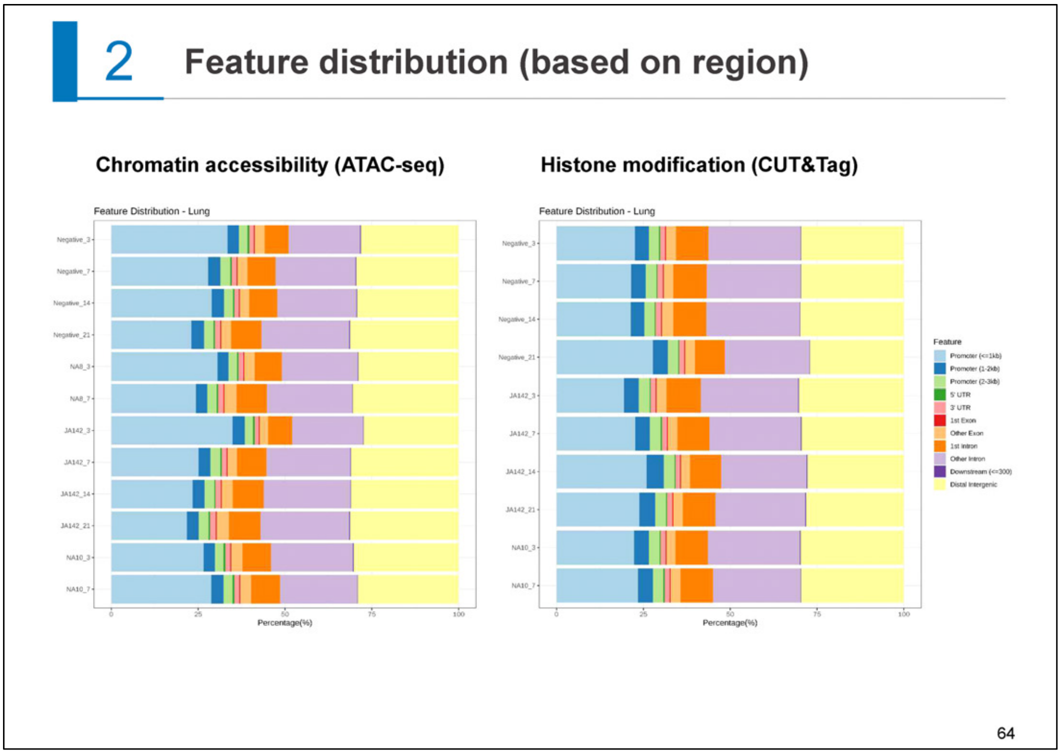
1. ATAC-Seq in Lung
2. CUT&Tag in Lung (H3K27ac)

- Negative control
- NA8 (Low pathogenic)
- JA142 (Medium pathogenic)
- NA10 (High pathogenic)

Activated enhancer & promoter marker

BALF: Bronchoalveolar lavage fluid

63

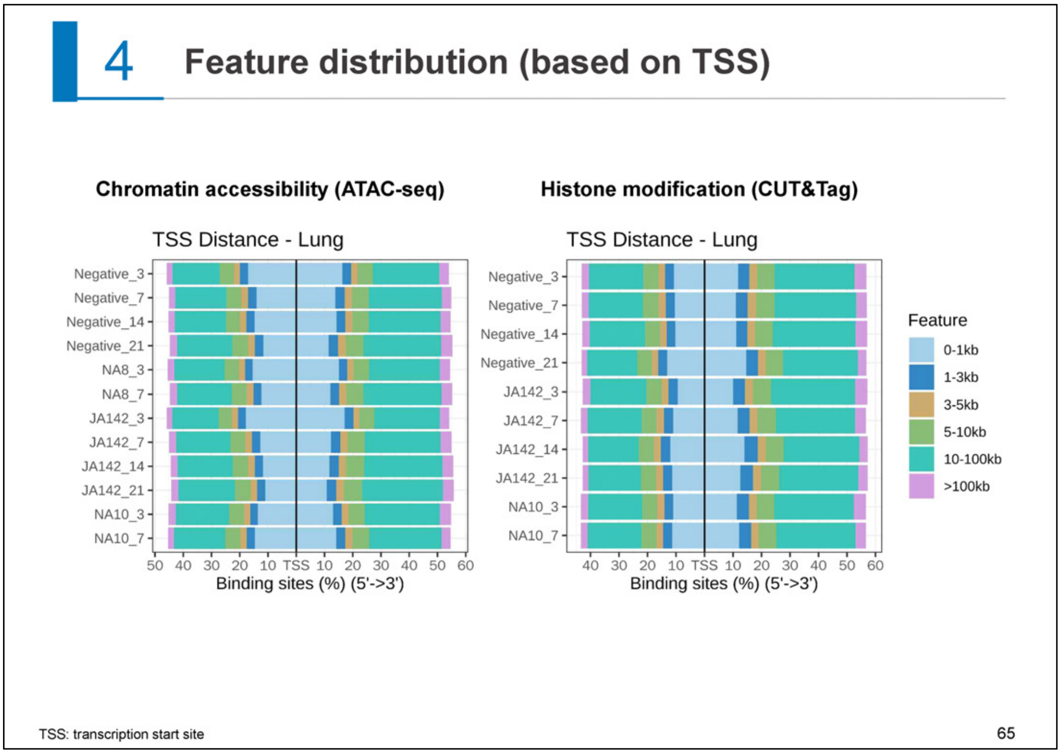


2 Feature distribution (based on region)

Chromatin accessibility (ATAC-seq)

Histone modification (CUT&Tag)

64

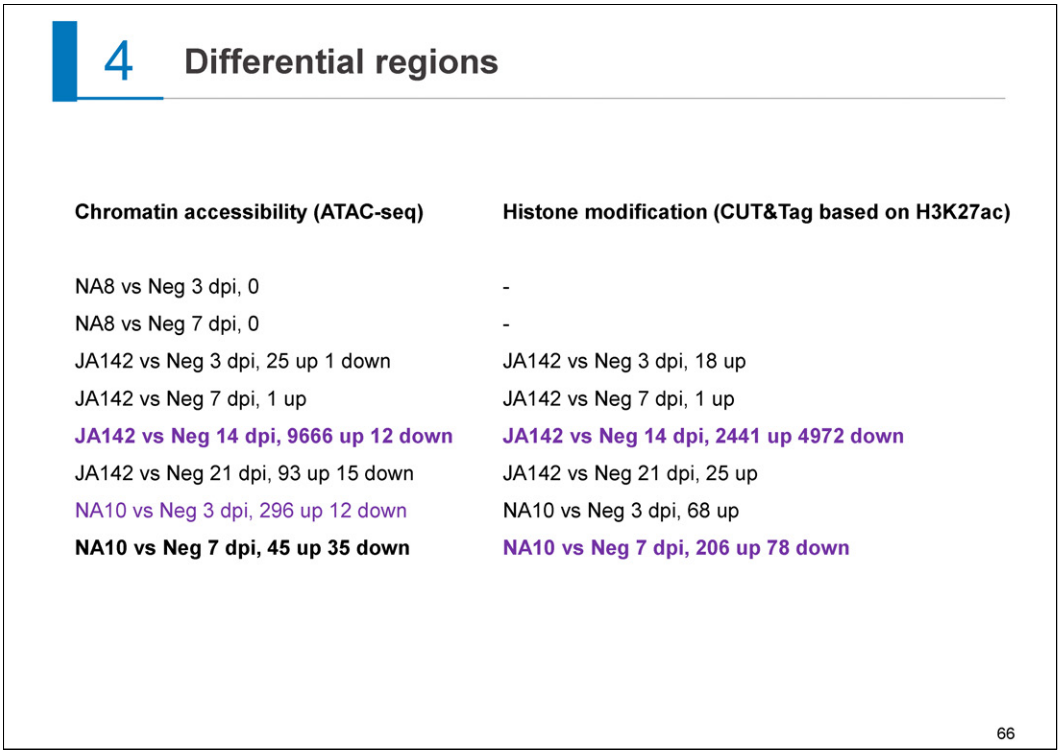


4 Feature distribution (based on TSS)

Chromatin accessibility (ATAC-seq)

Histone modification (CUT&Tag)

TSS: transcription start site



4 Differential regions

Chromatin accessibility (ATAC-seq)	**Histone modification (CUT&Tag based on H3K27ac)**
NA8 vs Neg 3 dpi, 0	-
NA8 vs Neg 7 dpi, 0	-
JA142 vs Neg 3 dpi, 25 up 1 down	JA142 vs Neg 3 dpi, 18 up
JA142 vs Neg 7 dpi, 1 up	JA142 vs Neg 7 dpi, 1 up
JA142 vs Neg 14 dpi, 9666 up 12 down	**JA142 vs Neg 14 dpi, 2441 up 4972 down**
JA142 vs Neg 21 dpi, 93 up 15 down	JA142 vs Neg 21 dpi, 25 up
NA10 vs Neg 3 dpi, 296 up 12 down	NA10 vs Neg 3 dpi, 68 up
NA10 vs Neg 7 dpi, 45 up 35 down	**NA10 vs Neg 7 dpi, 206 up 78 down**

5 Functional enrichment

Chromatin accessibility (ATAC-seq)

JA142 vs Neg 14 dpi, promoter, up (top 10)
- Chemokine signaling pathway
- Osteoclast differentiation
- Natural killer cell mediated cytotoxicity
- T cell receptor signaling pathway
- Human cytomegalovirus infection
- B cell receptor signaling pathway
- Th17 cell differentiation
- Th1 and Th2 cell differentiation
- Human immunodeficiency virus 1 infection
- Apoptosis

NA10 vs Neg 3 dpi, promoter, up
- RIG-I-like receptor signaling pathway
- Hepatitis C
- Influenza A
- Coronavirus disease - COVID-19
- Measles
- Epstein-Barr virus infection
- Human papillomavirus infection

Peracute

Histone modification (CUT&Tag based on H3K27ac)

JA142 vs Neg 14 dpi, promoter, up (top 10)
- Viral protein interaction with cytokine and cytokine receptor
- Th1 and Th2 cell differentiation
- T cell receptor signaling pathway
- Cytokine-cytokine receptor interaction
- Cell adhesion molecules
- Chemokine signaling pathway
- Natural killer cell mediated cytotoxicity
- Autoimmune thyroid disease
- PD-L1 expression and PD-1 checkpoint pathway in cancer
- Graft-versus-host disease

Acute

JA142 vs Neg 14 dpi, promoter, down (top 10)
- Cytoskeleton in muscle cells
- Focal adhesion
- ECM-receptor interaction
- PI3K-Akt signaling pathway
- Human papillomavirus infection
- Protein digestion and absorption
- Choline metabolism in cancer
- AGE-RAGE signaling pathway in diabetic complications
- Signaling pathways regulating pluripotency of stem cells
- Axon guidance

In peracute high-virulence PRRSV infection, there is insufficient time for epigenetic remodeling, whereas in acute intermediate-virulence infection, such remodeling is activated

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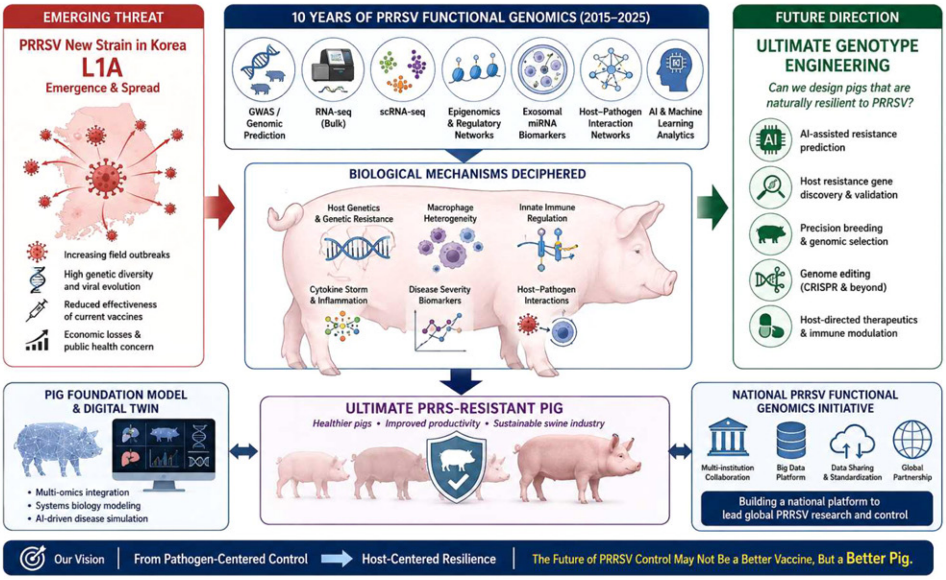
Further Perspectives

From PRRSV Functional Genomics to Ultimate Genotype Engineering

Engineering the Next Generation of Disease-Resilient Pigs Beyond Vaccination



EMERGING THREAT

PRRSV New Strain in Korea

L1A

Emergence & Spread

- Increasing field outbreaks
- High genetic diversity and viral evolution
- Reduced effectiveness of current vaccines
- Economic losses & public health concern

10 YEARS OF PRRSV FUNCTIONAL GENOMICS (2015–2025)

- GWAS / Genomic Prediction
- RNA-seq (Bulk)
- scRNA-seq
- Epigenomics & Regulatory Networks
- Exosomal miRNA Biomarkers
- Host–Pathogen Interaction Networks
- AI & Machine Learning Analytics

BIOLOGICAL MECHANISMS DECIPHERED

- Host Genetics & Genetic Resistance
- Macrophage Heterogeneity
- Innate Immune Regulation
- Cytokine Storm & Inflammation
- Disease Severity Biomarkers
- Host–Pathogen Interactions

FUTURE DIRECTION

ULTIMATE GENOTYPE ENGINEERING

Can we design pigs that are naturally resilient to PRRSV?

- AI-assisted resistance prediction
- Host resistance gene discovery & validation
- Precision breeding & genomic selection
- Genome editing (CRISPR & beyond)
- Host-directed therapeutics & immune modulation

PIG FOUNDATION MODEL & DIGITAL TWIN

- Multi-omics integration
- Systems biology modeling
- AI-driven disease simulation

ULTIMATE PRRS-RESISTANT PIG

Healthier pigs • Improved productivity • Sustainable swine industry

NATIONAL PRRSV FUNCTIONAL GENOMICS INITIATIVE

- Multi-institution Collaboration
- Big Data Platform
- Data Sharing & Standardization
- Global Partnership

Building a national platform to lead global PRRSV research and control

Our Vision | From Pathogen-Centered Control → Host-Centered Resilience | The Future of PRRSV Control May Not Be a Better Vaccine, But a **Better Pig.**

BIGKIM

FUNCTIONAL GENOMICS & BIOINFORMATICS LAB.

Thank you!