nature immunology

Systems biology of vaccination for seasonal influenza in humans

Nakaya, H., Wrammert, J., Lee, E. *et al.* (2011)

Presented by Team Sydney Brenner
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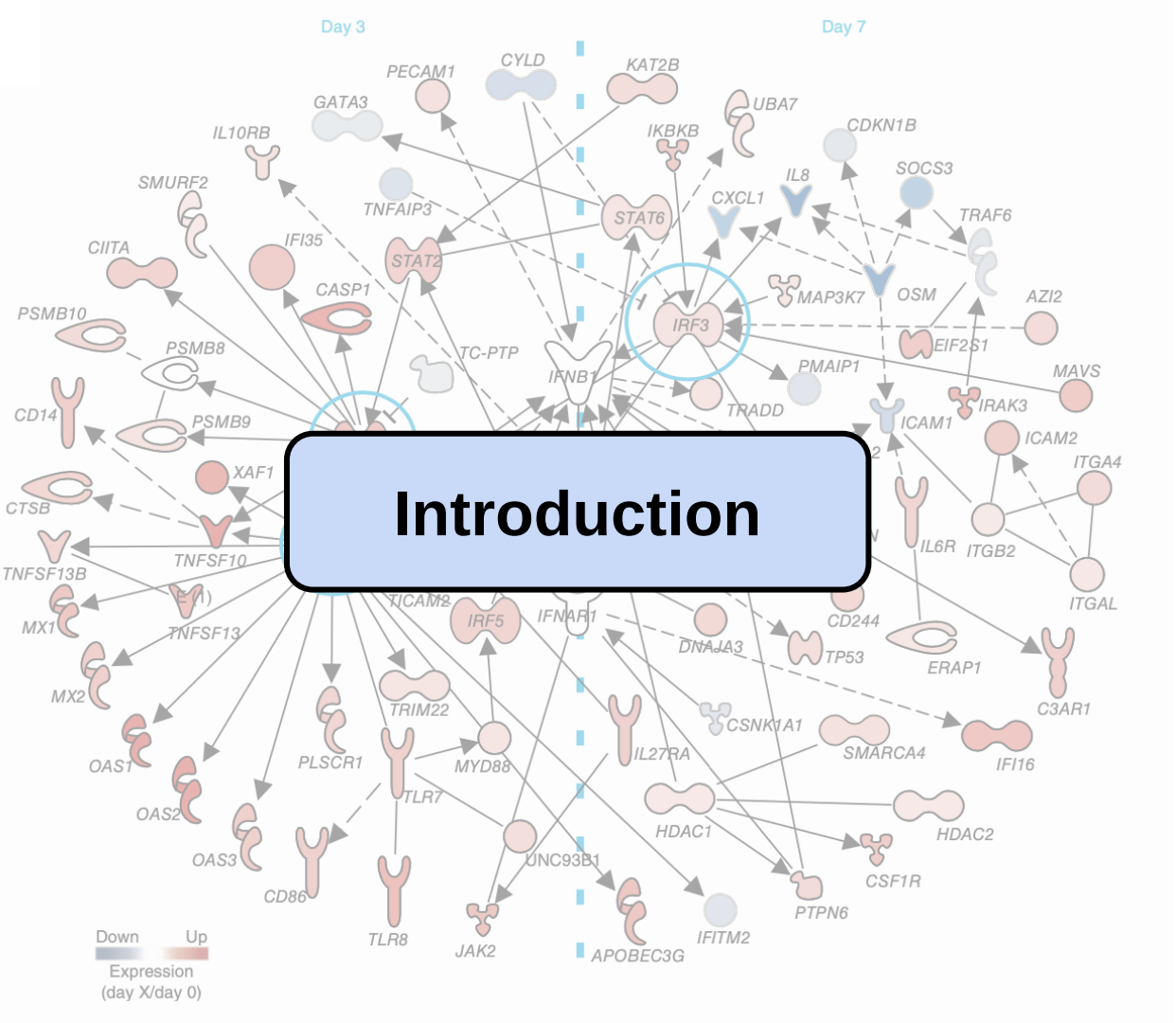
September 26, 2024



Introduction

Introduction

RESOURCE

nature immunology

Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans

Troy D Querec[1,8], Rama S Akondy[1,8], Eva K Lee[2], Weiping Cao[1], Helder I Nakaya[1], Dirk Teuwen[3], Ali Pirani[4], Kim Gernert[4], Jiusheng Deng[1], Bruz Marzolf[5], Kathleen Kennedy[5], Haiyan Wu[5], Soumaya Bennouna[1], Herold Oluoch[1], Joseph Miller[1], Ricardo Z Vencio[5], Mark Mulligan[1,6], Alan Aderem[5], Rafi Ahmed[1] & Bali Pulendran[1,7]

A major challenge in vaccinology is to prospectively determine vaccine efficacy. Here we have used a systems biology approach to identify early gene 'signatures' that predicted immune responses in humans vaccinated with yellow fever vaccine YF-17D. Vaccination induced genes that regulate virus innate sensing and type I interferon production. Computational analyses identified a gene signature, including complement protein C1qB and eukaryotic translation initiation factor 2 alpha kinase 4—an orchestrator of the integrated stress response—that correlated with and predicted YF-17D CD8⁺ T cell responses with up to 90% accuracy in an independent, blinded trial. A distinct signature, including B cell growth factor *TNFRS17*, predicted the neutralizing antibody response with up to 100% accuracy. These data highlight the utility of systems biology approaches in predicting vaccine efficacy.

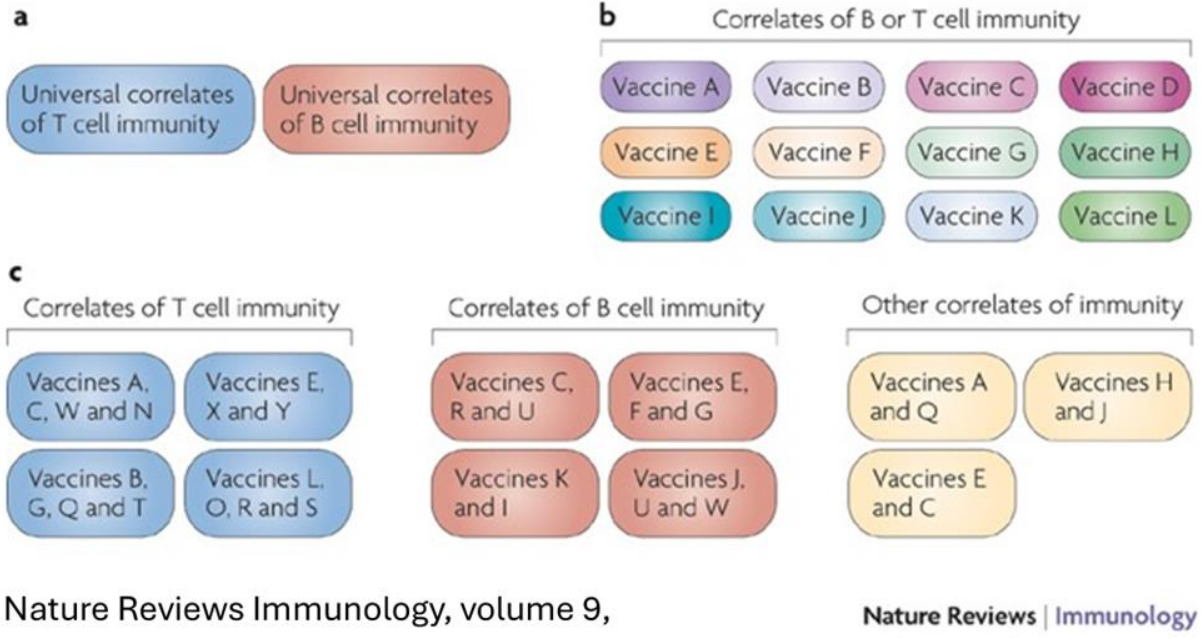
Nature Immunology volume 10, pages116–125 (2009)

Systems biology approach has been used for yellow fever vaccine YF-17D

- The **first time** they used high-throughput technologies combined with computational modeling **in vaccinology**
- Identify **early gene signatures**
- **Predicting** the subsequent adaptive immune response

Introduction

Can the signatures identified with YF-17D also be used to predict the immunogenicity of other vaccines ?



Nature Reviews Immunology, volume 9, pages741–747 (2009)

Hypothesis

a. Universal 'archetypal' signature for T and B cell immunogenicity of all vaccines
b. Each vaccine had a unique signature
c. Classes of vaccines that induce similar signatures of immunogenicity **(most likely)**

Introduction

Influenza vaccine

- trivalent inactivated influenza vaccine (**TIV**)
- live attenuated influenza vaccine (**LAIV**)

Comparison of the immune response to inactivated influenza and live attenuated influenza vaccine.

	Inactivated Influenza Vaccine	Live Attenuated Influenza Vaccine
HAI response	+++	+
Antibody secreting cells	++	+
Memory B cells	+	+
Nasal IgA	−/+	+++
NA antibody	−/+	++
CD4 T cells	++	+++
CD8 T cells	−	+?
Cross protective immunity	−/+	++

The differences from yellow fever vaccine YF-17D

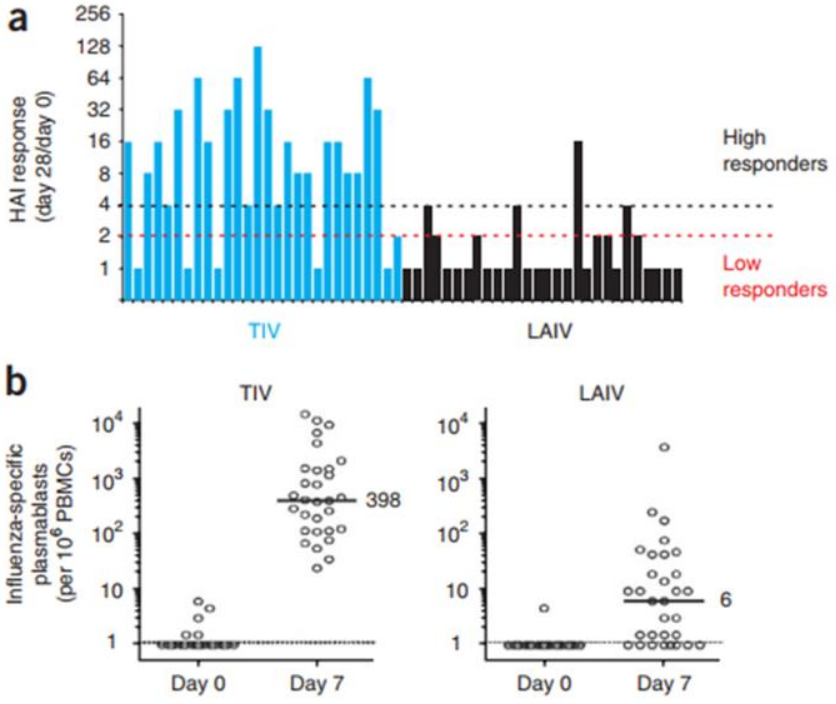
- TIV is inactivated vaccine
- Recall response from prior infections and vaccinations

The feasibility of this approach in predicting IFA vaccine's immune response

Vaccines (Basel). 2015 Jun; 3(2): 373–389.

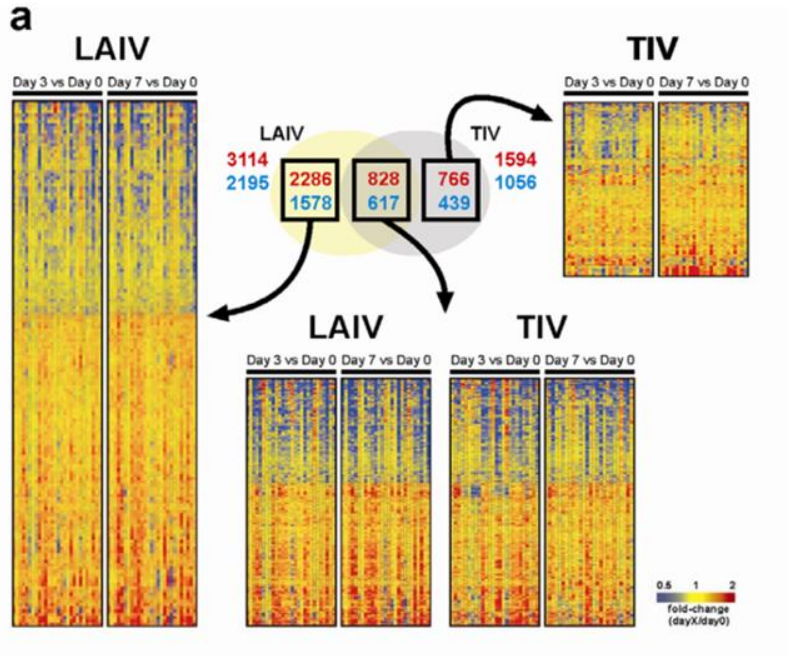
Introduction

- Antibody response after TIV and LAIV is different

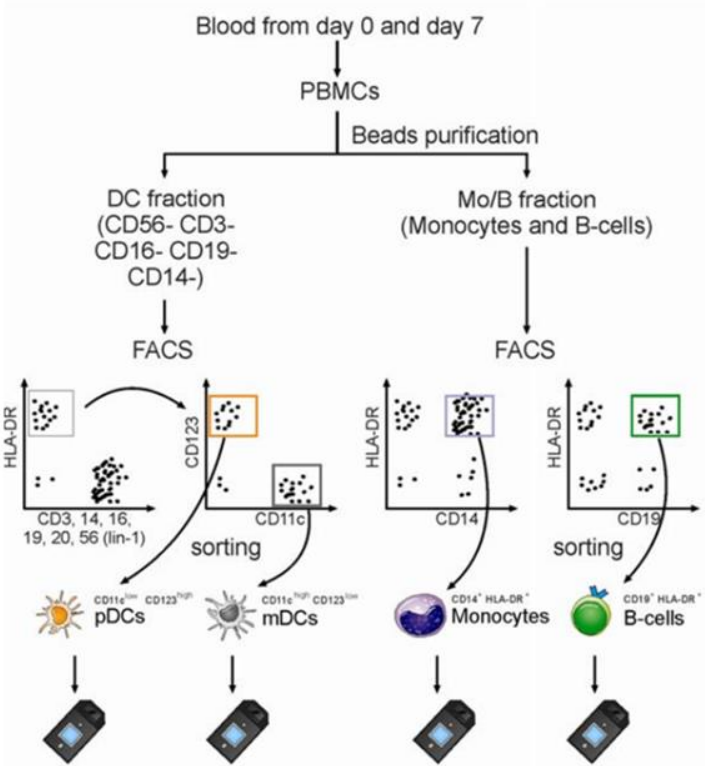


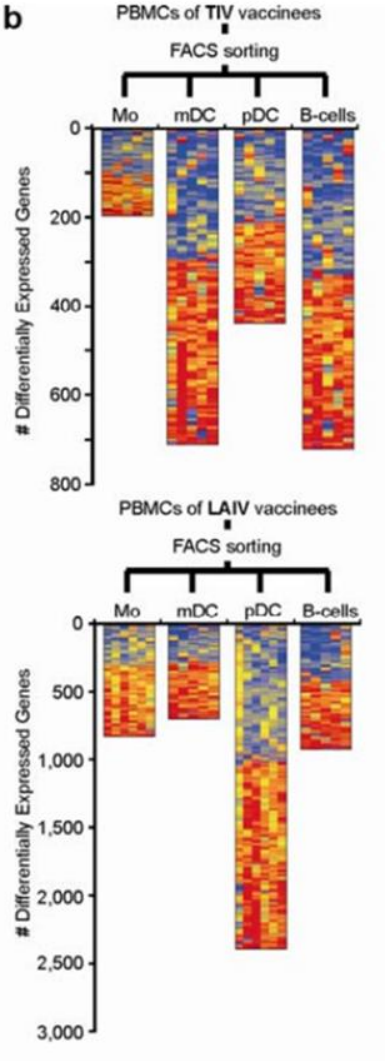
- Molecular signatures of peripheral blood mononuclear cells (PBMCs) after TIV and LAIV is different (Transcriptome analysis)

Signature for immunogenicity of different vaccines could be different



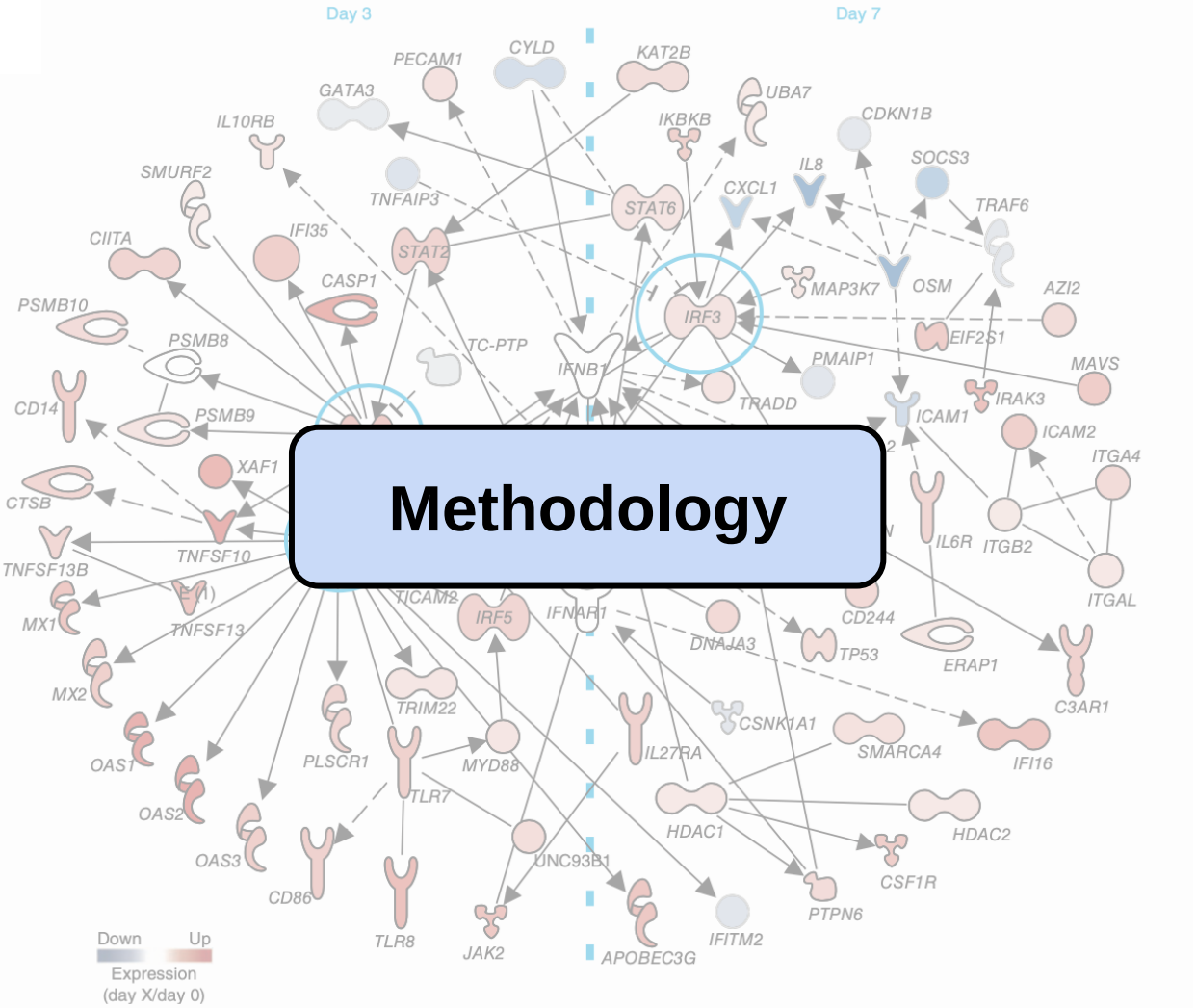
Introduction





- Logistically: need to use freshly isolated samples to prevent the 'preferential' loss of certain cell types
- Financially: the need for large numbers of gene chips

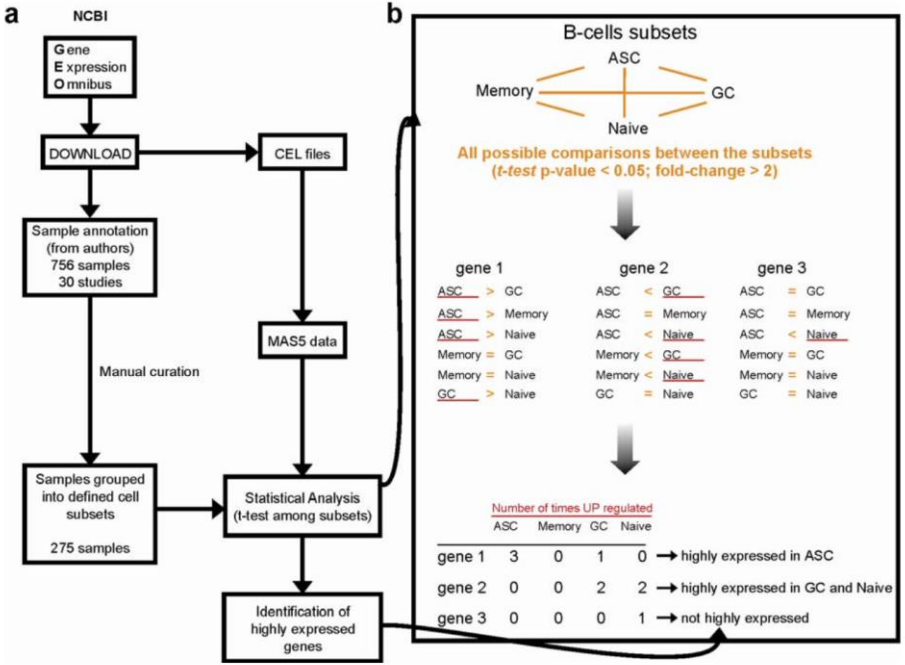
DAMIP(a very powerful supervised-learning classification method for predicting various biomedical and 'biobehavioral' phenomena) + RT-PCR



Methodology

Why meta-analysis?

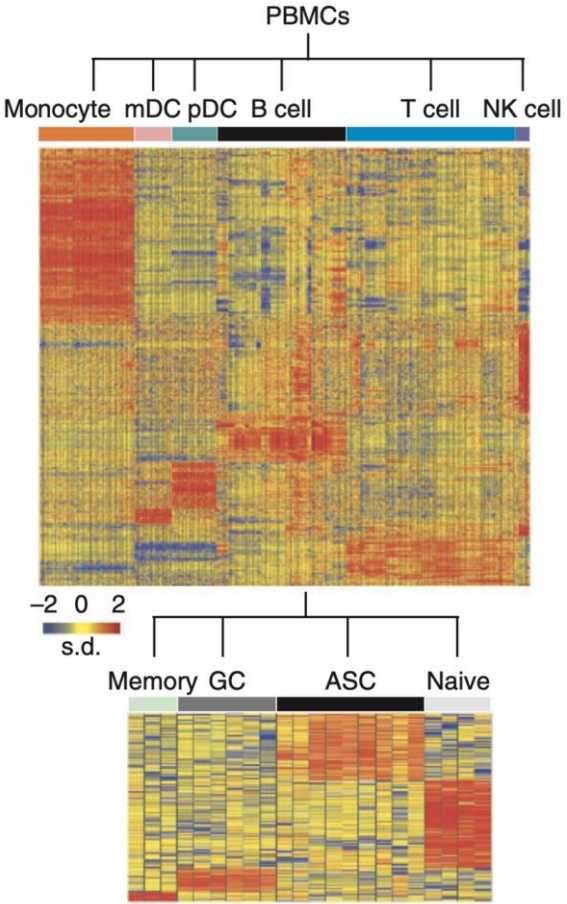
- Self-conducted microarray analysis via flow cytometry = **time and resource consuming**
- **Meta-analysis:** combining and analysing data from several studies to identify gene-expression patterns
    - **Larger sample** set
    - **More efficient** analysis
    - **Cell-specific** results



Meta-analysis of microarray data

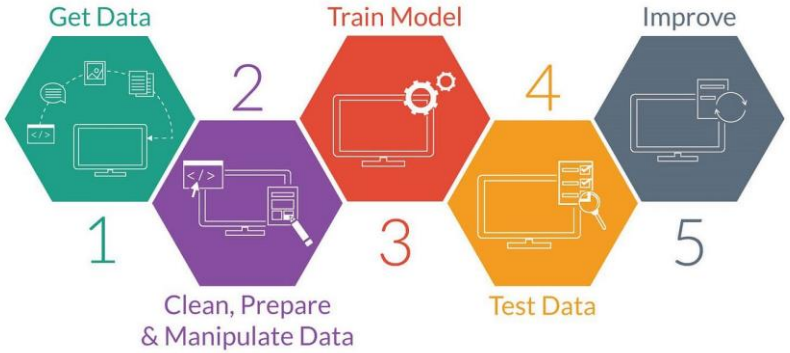
- Publicly available **PBMC microarrays** divided into:
  - T cells, B cells, monocytes, natural killer cells
  - B cell subsets: naive, memory, germinal center, ASCs
- Identified **highly expressed genes** in each subset
- Compared to **microarray data of plasmacytoid and myeloid dendritic cells** post-TIV and LAIV vaccination

Output: early gene signatures from vaccine response



Machine Learning: Background

- Machine Learning (ML) allows systems to learn and improve from data
- ML relies on algorithms to complete a task using data patterns
- Supervised Learning
  - often used for classification algorithms
  - model is trained with a known, labeled dataset
  - using results data from one dataset to classify results of another dataset

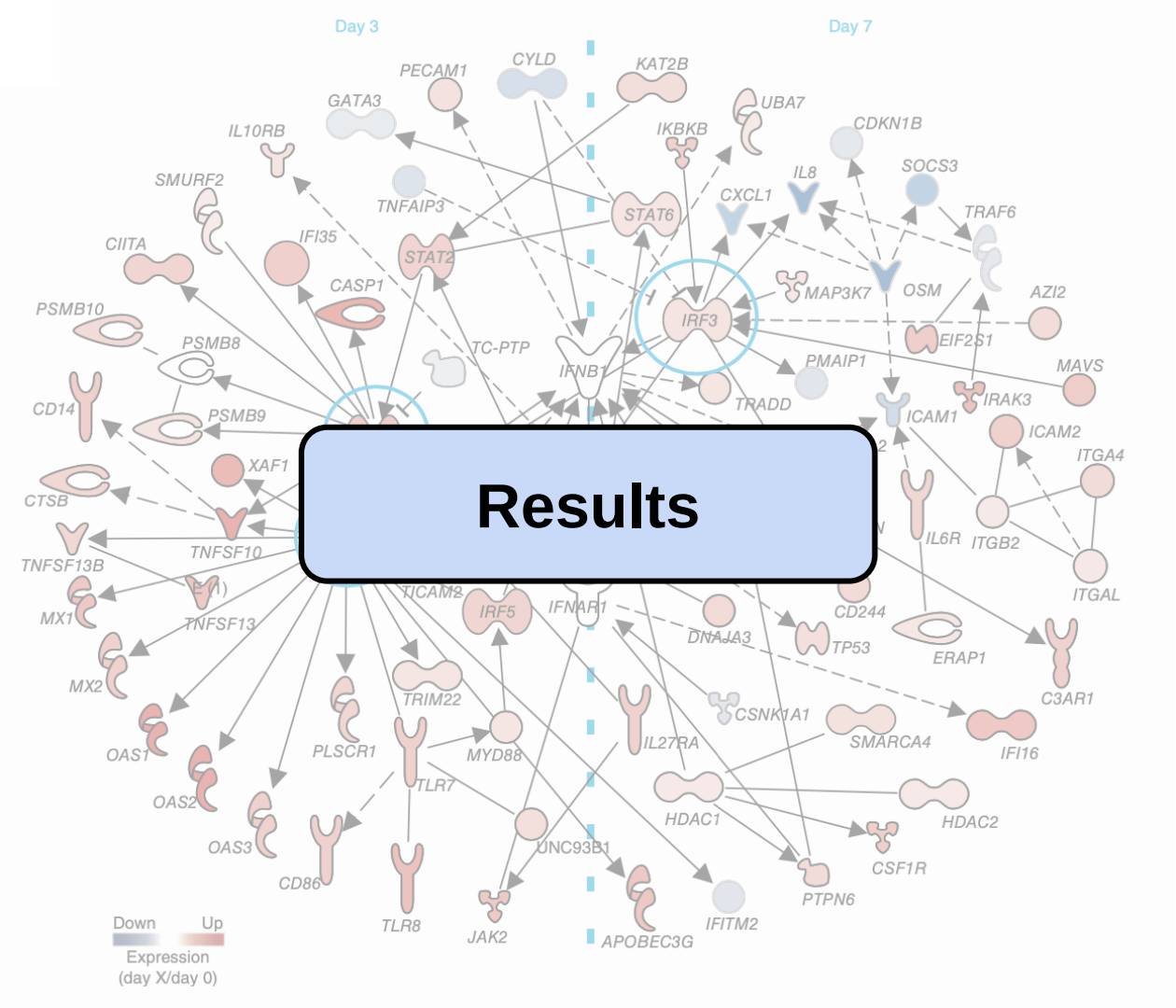


DAMIP Machine Learning

- Discriminant Analysis via Mixed Integer Programming
- Supervised ML → the training and testing datasets have known results
- Frequently used for predicting and classifying biological processes

Application:

- Influenza vaccine → determine minimum number of genes required to get an accurate classification of response type
- DAMIP used to be able to predict HAI response to TIV vaccine
- Trained with existing datasets to predict response in other influenza seasons
- Make connections between identified genes and other vaccine responses


Day 3
Day 7
PECAM1
CYLD
KAT2B
GATA3
UBA7
IL10RB
IKBKB
CDKN1B
SMURF2
TNFAIP3
STAT6
IL8
SOCS3
CXCL1
TRAF6
CIITA
IFI35
STAT2
CASP1
MAP3K7
OSM
AZI2
PSMB10
IRF3
PSMB8
TC-PTP
IFNB1
EIF2S1
PMAIP1
MAVS
CD14
PSMB9
TRADD
IRAK3
ICAM1
ICAM2
XAF1
ITGA4
CTSB
IL6R
ITGB2
TNFSF10
TNFSF13B
ITGAL
MX1
TNFSF13
IRF5
IFNAR1
CD244
DNAJA3
TP53
ERAP1
C3AR1
MX2
TRIM22
CSNK1A1
SMARCA4
IFI16
OAS1
PLSCR1
MYD88
IL27RA
TLR7
HDAC1
HDAC2
OAS2
OAS3
UNC93B1
CSF1R
CD86
PTPN6
TLR8
JAK2
IFITM2
APOBEC3G
Down
Up
Expression
(day X/day 0)

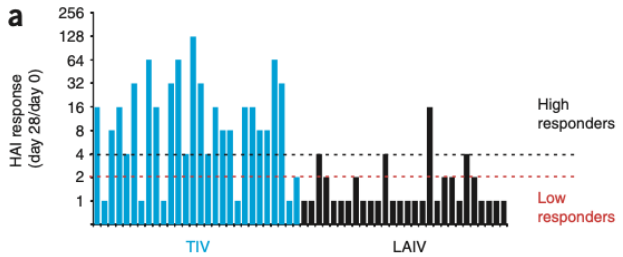
Results

Meta-Analysis Results

- TIV
  - genes upregulated are associated with high **B cell expression**
  - genes encode for antibody parts and immunoglobulins
  - results align with flow cytometry results
  - indicate high antibody response in mechanism of action in TIV
- LAIV
  - gene upregulated are associated with high **T cell and monocyte expression**
  - genes encode for natural killer cells
  - results align with flow cytometry results
  - indicate innate response important in mechanism of action in LAIV

DAMIP: Background + Initial Testing

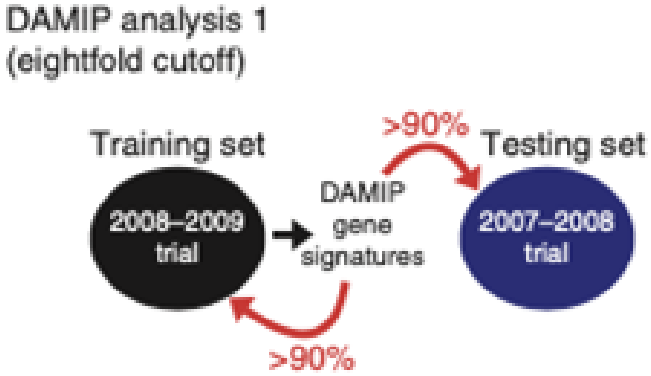
- **Goal: ID minimum number of genes needed to predict HAI response**
- DAMIP
  - supervised learning method for prediction biological phenomena
  - using TIV vaccine responses only



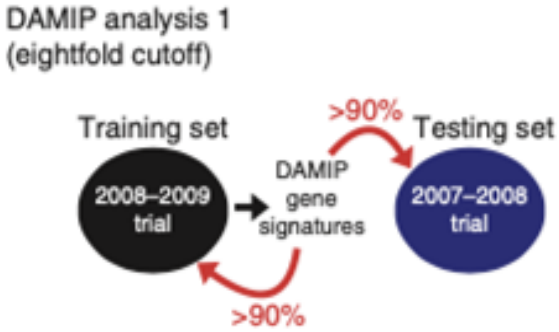
- HAI titers response: measures level of antibodies in serum used to inhibit influenza
  - higher HAI → higher protection from influenza

DAMIP: Initial Testing

- Initial Testing:
  - extreme HAI classification groups
    - very high HAI responders ≥ 8x HAI response
    - very low HAI responders ≤ 2x HAI response
  - training establishes unbiased estimate of correct classification
  - 2008-2009 influenza season data used for training



DAMIP: Initial Test Results

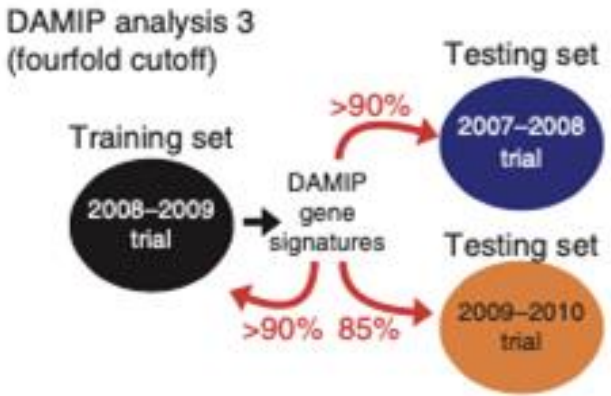


- Training Data: 2008-2009 influenza season
- Testing Data: 2007-2008 influenza season
- Results:
  - DAMIP identified **12 gene sets** (each with 2-4 individual genes)

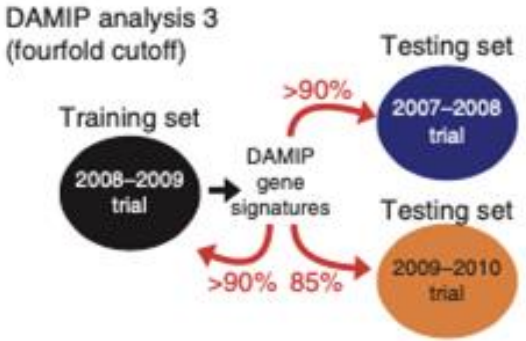
90+% of the low/high HAI response guesses for test data were correct based on learning from training data

DAMIP: Repeat Testing

- Repeat Testing:
  - less extreme HAI classification groups
    - high HAI responders ≥ 4x HAI response
      - 4x HAI response is the widely defined seroconversion after vaccination
    - very low HAI responders ≤ 2x HAI response
  - 2008-2009 influenza season data used for training



DAMIP: Repeat Test Results



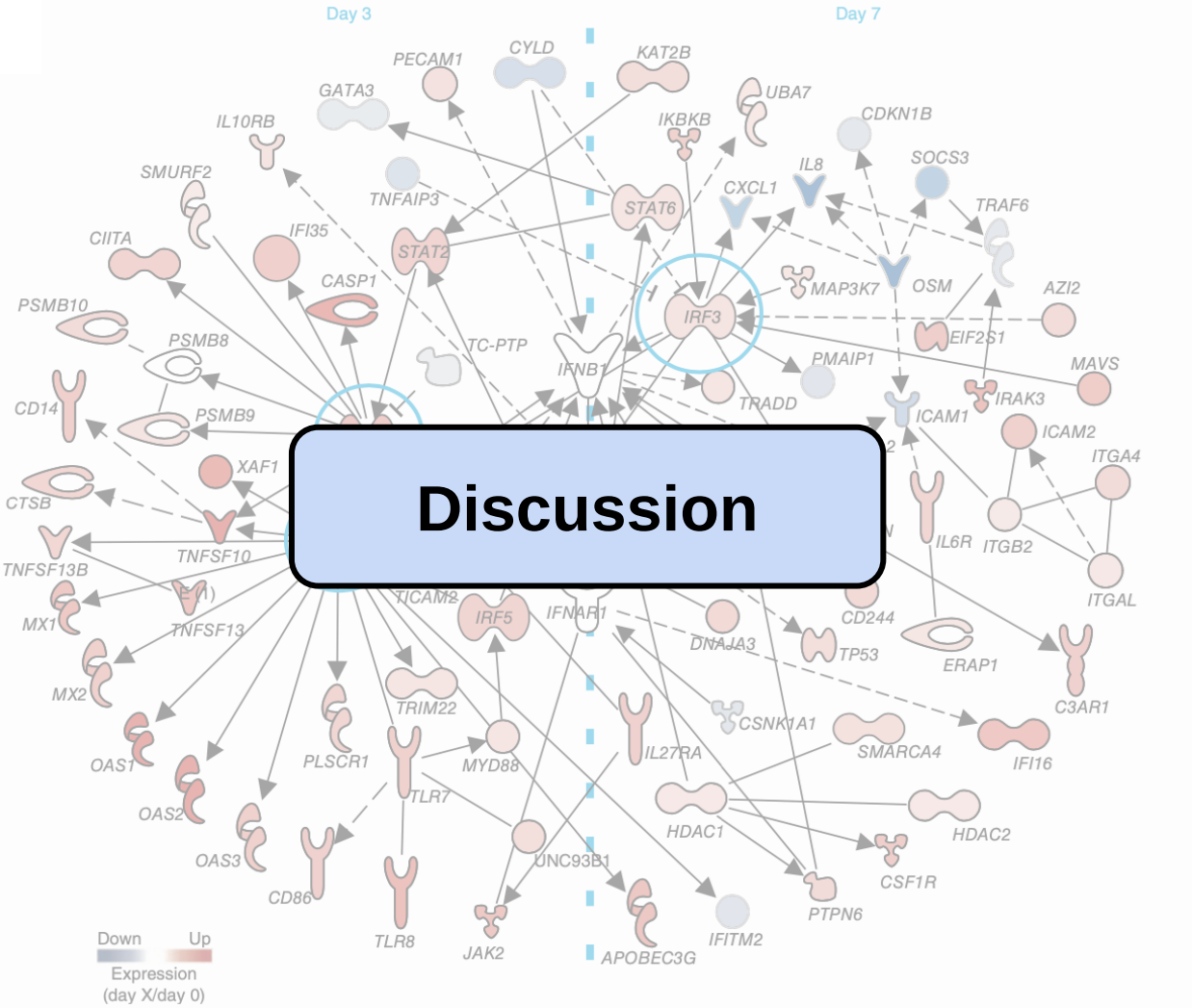
- Training Data: 2008-2009 influenza season
- Testing Data 1: 2007-2008 influenza season
- Testing Data 2: 2009-2010 influenza season
- Results
    - DAMIP identified **42 gene sets** (each with 3-4 individual genes)

85% of the low/high HAI response guesses for test data were correct based on learning from training data

Interesting Finds!

- One of the 42 identified genes (TNFRSF17) in the repeat test also identified with predicting antibody response in YF-17D (Yellow Fever) vaccine

- Five of the 42 identified genes in the repeat test are members of leukocyte immunoglobulin receptor family
  - Expressed by immune cells in myeloid and lymphoid lineages
  - Immunomodulatory roles in innate and adaptive immune system
  - Regulate T cells and autoimmunity
  - **Indicates possibility of innate immune receptors in regulating antibody response**


Day 3
Day 7
PECAM1
CYLD
KAT2B
GATA3
UBA7
IL10RB
IKBKB
CDKN1B
SMURF2
TNFAIP3
STAT6
IL8
SOCS3
CXCL1
TRAF6
CIITA
IFI35
STAT2
CASP1
MAP3K7
OSM
AZI2
PSMB10
IRF3
PSMB8
TC-PTP
IFNB1
EIF2S1
PMAIP1
MAVS
CD14
PSMB9
TRADD
IRAK3
ICAM1
ICAM2
XAF1
ITGA4
CTSB
IL6R
ITGB2
TNFSF10
TNFSF13B
ITGAL
MX1
TNFSF13
IRF5
IFNAR1
CD244
DNAJA3
TP53
ERAP1
C3AR1
MX2
TRIM22
CSNK1A1
SMARCA4
IFI16
OAS1
PLSCR1
MYD88
IL27RA
TLR7
HDAC1
HDAC2
OAS2
OAS3
UNC93B1
CSF1R
CD86
PTPN6
TLR8
JAK2
IFITM2
APOBEC3G
Down
Up
Expression
(day X/day 0)

Discussion

Discussion: Strengths

- **Meta-analysis** of microarray studies >>> traditional flow cytometry
- New **insight to molecular mechanism** of vaccine response
  - Immunity with **LAIV vs. TIV**
  - Identified **CaMKIV** & **LILRs**
- **Machine learning as prediction tool** for immunogenicity of vaccine
  - Predicted TIV with **accuracy >90%**
  - **Predicts seroconversion** weeks before it occurs

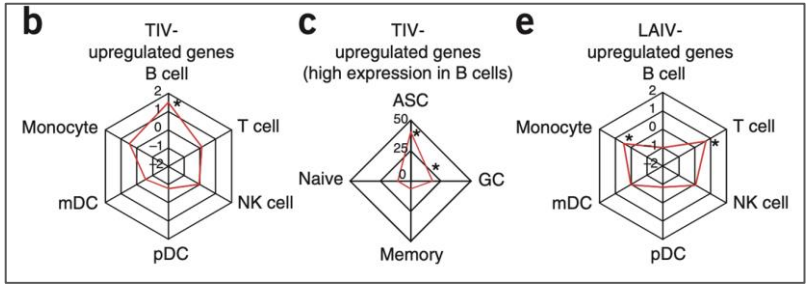


Figure 3. Genes upregulated by TIV and LAIV

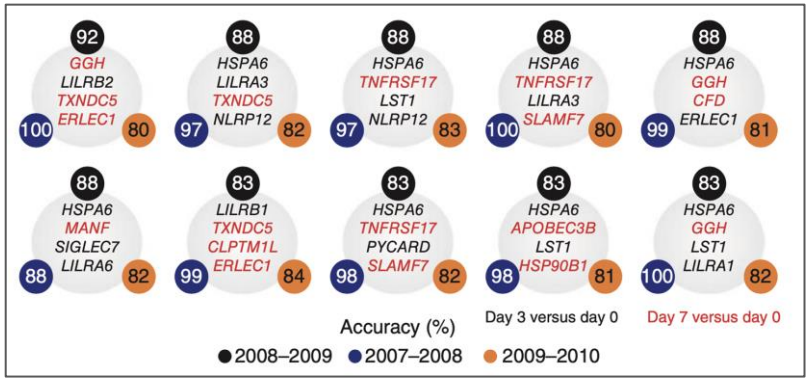


Figure 5c. Accuracies of machine learning technique

Discussion: Limitations

- **Broad utility** still uncertain – gene signatures will vary for different vaccines
  - Overlapping genes with previous YF-17D study suggest some commonality across vaccines
- Predicting vaccine efficacy is not 100% accurate
  - **Immunogenicity ≠ Efficacy**
  - HAI response is not the only factor influencing vaccine protection
  - **Protective antibody concentrations vary** by individual, viral strain, etc.
  - Only workaround = increasing HAI parameter → excludes protected vaccinees with lower HAI responses

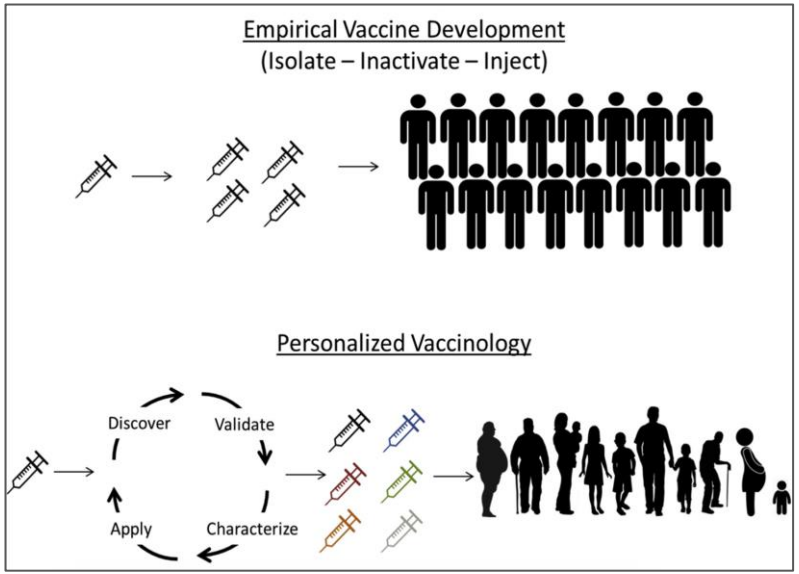
Discussion: Future steps

Improvements:

- Identify **other markers** for vaccine protection in conjunction with HAI response
- **Adapt the system** to other vaccines

Other applications:

- Monitoring **suboptimal immune responses** in weaker individuals
- **Personalized vaccinations** based on predictive modeling of individuals' immune systems



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