Seattle BioMed
Freedom from Infectious Disease
an Institute for Systems Biology
and Infectious Diseases






Application of Systems Biology to enable Rational Vaccine Design

Alan Aderem

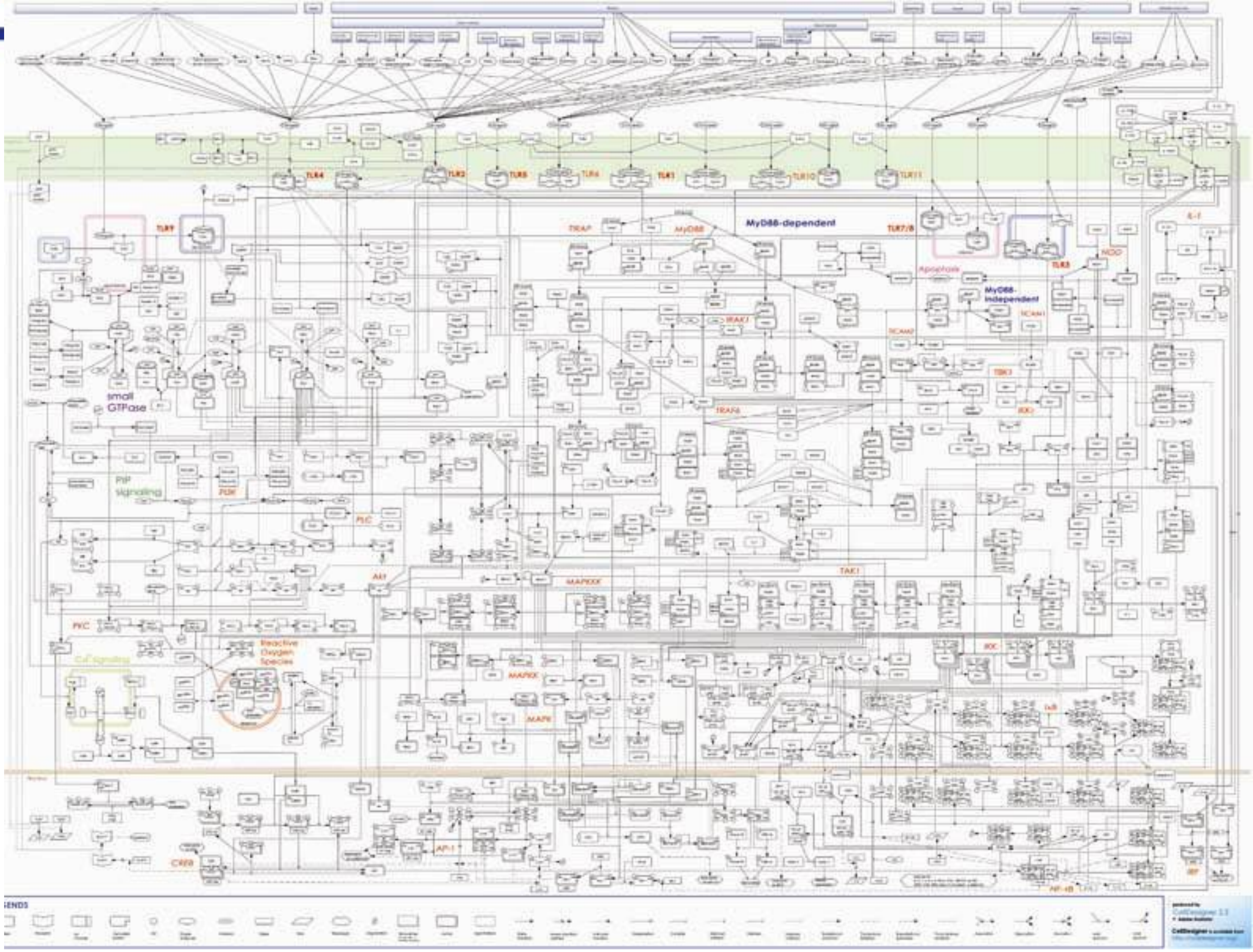
The Plotkin Lecture
ADVAC course, Annecy
May 21st , 2014

In honor of Stanley Plotkin

Simple System

Complex System

Partial Network of adjuvant signaling pathways



Lets not forget about cytokine feedback loops, NLRs, and the like!

Emergence

Complex systems display emergent properties that are not demonstrated by the individual parts, and cannot be predicted even with a full understanding of the parts alone

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Life is an emergent property; it is not inherent in DNA, RNA, proteins, carbohydrates or lipids, but is a consequence of their actions and interactions

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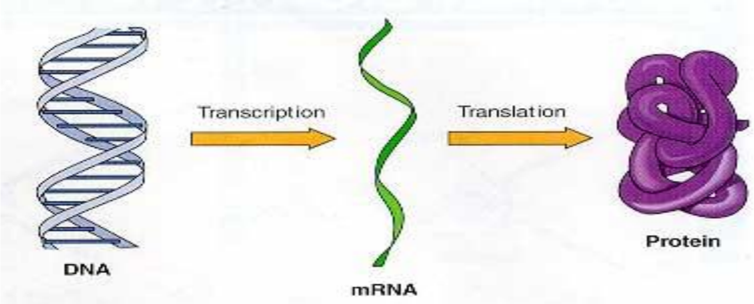
Life is an emergent property; it is not inherent in DNA, RNA, proteins, carbohydrates or lipids, but is a consequence of their actions and interactions

Systems level perspectives are necessary to understand emergence and to predict outcomes

The Practice of Systems Biology

Traditional approaches study a single gene/RNA/protein at a time

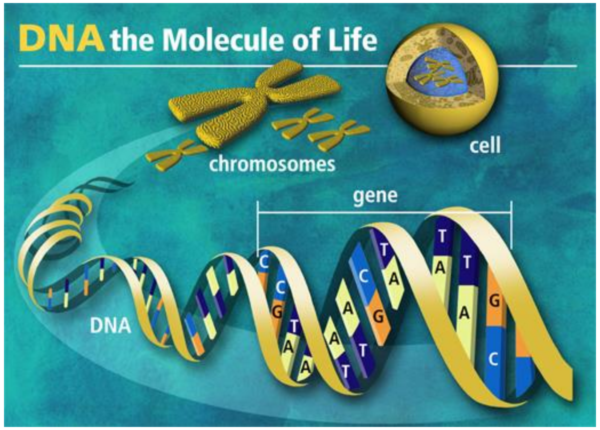
DNA → RNA → Protein

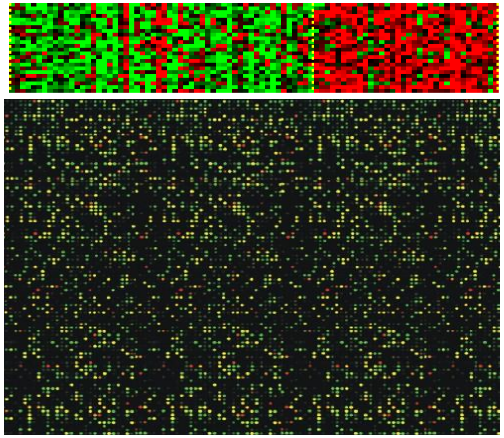


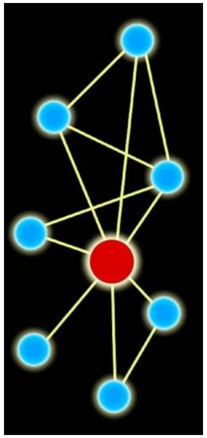
But there are tens of thousands of genes/RNA/proteins

Systems Biology

DNA → RNA → Protein



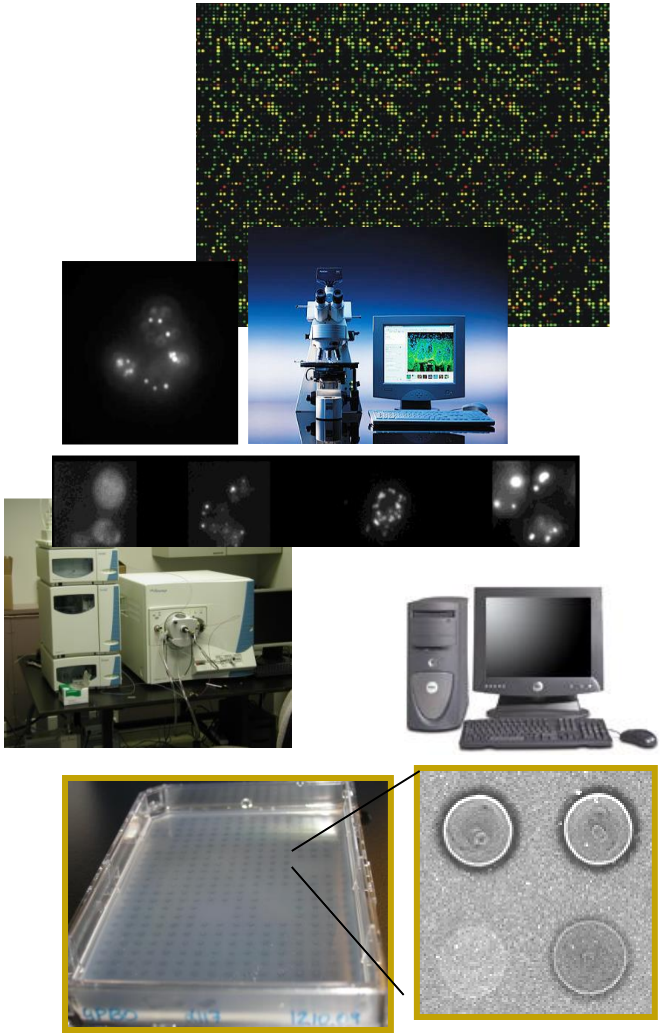




A holistic view

The Practice of Systems Biology

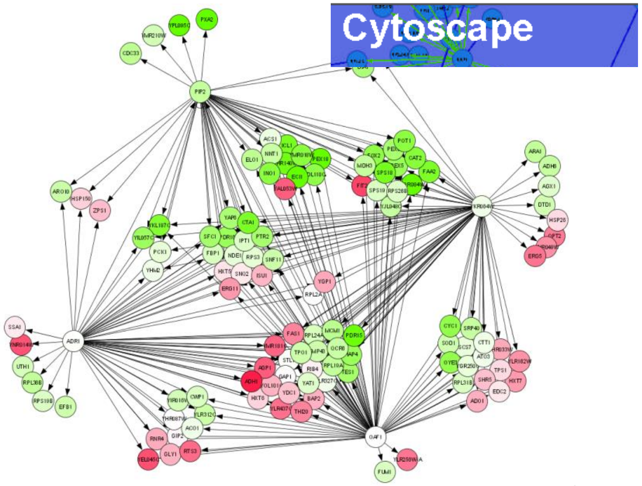
- **Enumerate parts**
  - •Quantify all molecular constituents and interactions

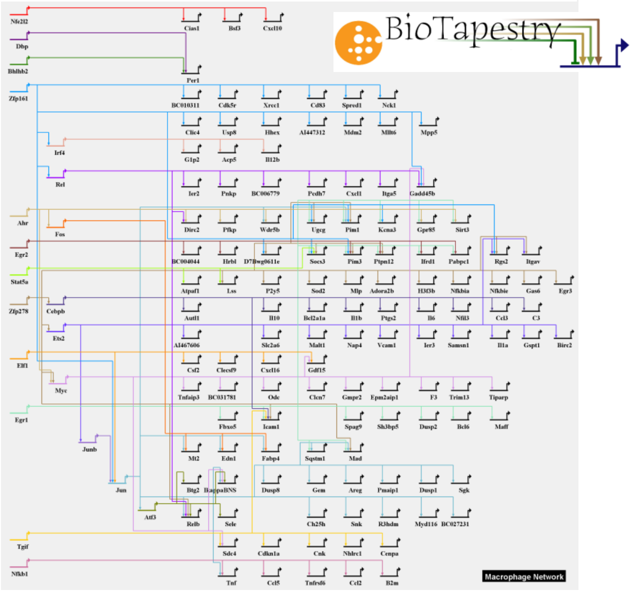


The Practice of Systems Biology

- **Enumerate parts**
  - Quantify all molecular constituents and interactions

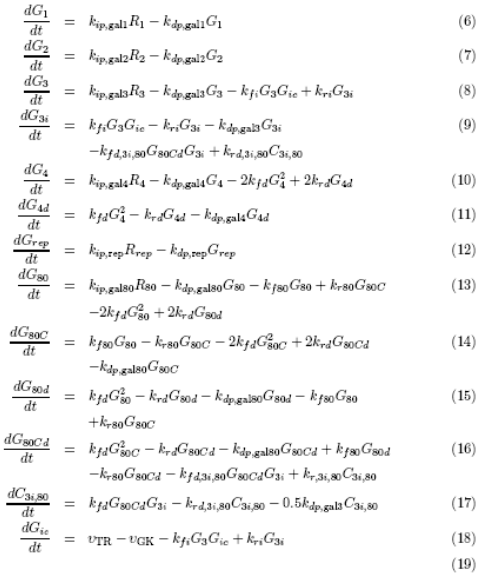
- **Extract/Define dynamic network**
  - Computationally and mathematically integrate different data types





The Practice of Systems Biology

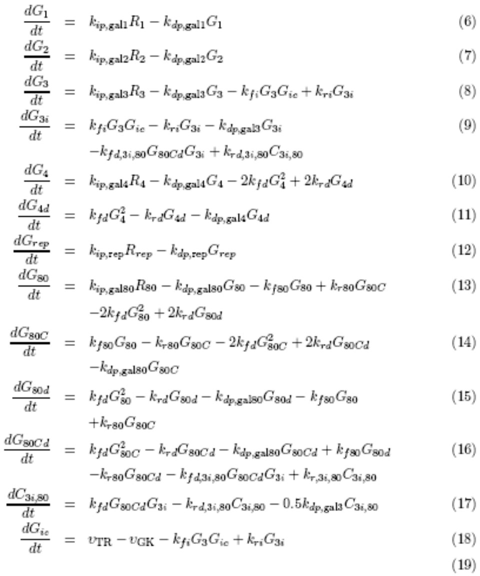
- **Enumerate parts**
  - Quantify all molecular constituents and interactions
- **Extract/Define dynamic network**
  - Computationally and mathematically integrate different data types
- **Mathematically model biological systems**
  - to predict outcomes for perturbations



$$
\begin{aligned}
\frac{dG_1}{dt} &= k_{ip,\mathrm{gal1}}R_1 - k_{dp,\mathrm{gal1}}G_1 \tag{6}\\
\frac{dG_2}{dt} &= k_{ip,\mathrm{gal2}}R_2 - k_{dp,\mathrm{gal2}}G_2 \tag{7}\\
\frac{dG_3}{dt} &= k_{ip,\mathrm{gal3}}R_3 - k_{dp,\mathrm{gal3}}G_3 - k_{fi}G_3G_{ic} + k_{ri}G_{3i} \tag{8}\\
\frac{dG_{3i}}{dt} &= k_{fi}G_3G_{ic} - k_{ri}G_{3i} - k_{dp,\mathrm{gal3}}G_{3i} \tag{9}\\
&\quad -k_{fd,3i,80}G_{80Cd}G_{3i} + k_{rd,3i,80}C_{3i,80}\\
\frac{dG_4}{dt} &= k_{ip,\mathrm{gal4}}R_4 - k_{dp,\mathrm{gal4}}G_4 - 2k_{fd}G_4^2 + 2k_{rd}G_{4d} \tag{10}\\
\frac{dG_{4d}}{dt} &= k_{fd}G_4^2 - k_{rd}G_{4d} - k_{dp,\mathrm{gal4}}G_{4d} \tag{11}\\
\frac{dG_{rep}}{dt} &= k_{ip,\mathrm{rep}}R_{rep} - k_{dp,\mathrm{rep}}G_{rep} \tag{12}\\
\frac{dG_{80}}{dt} &= k_{ip,\mathrm{gal80}}R_{80} - k_{dp,\mathrm{gal80}}G_{80} - k_{f80}G_{80} + k_{r80}G_{80C} \tag{13}\\
&\quad -2k_{fd}G_{80}^2 + 2k_{rd}G_{80d}\\
\frac{dG_{80C}}{dt} &= k_{f80}G_{80} - k_{r80}G_{80C} - 2k_{fd}G_{80C}^2 + 2k_{rd}G_{80Cd} \tag{14}\\
&\quad -k_{dp,\mathrm{gal80}}G_{80C}\\
\frac{dG_{80d}}{dt} &= k_{fd}G_{80}^2 - k_{rd}G_{80d} - k_{dp,\mathrm{gal80}}G_{80d} - k_{f80}G_{80} \tag{15}\\
&\quad +k_{r80}G_{80C}\\
\frac{dG_{80Cd}}{dt} &= k_{fd}G_{80C}^2 - k_{rd}G_{80Cd} - k_{dp,\mathrm{gal80}}G_{80Cd} + k_{f80}G_{80d} \tag{16}\\
&\quad -k_{r80}G_{80Cd} - k_{fd,3i,80}G_{80Cd}G_{3i} + k_{r,3i,80}C_{3i,80}\\
\frac{dC_{3i,80}}{dt} &= k_{fd}G_{80Cd}G_{3i} - k_{rd,3i,80}C_{3i,80} - 0.5k_{dp,\mathrm{gal3}}C_{3i,80} \tag{17}\\
\frac{dG_{ic}}{dt} &= v_{\mathrm{TR}} - v_{\mathrm{GK}} - k_{fi}G_3G_{ic} + k_{ri}G_{3i} \tag{18}\\
& \tag{19}
\end{aligned}
$$

The Practice of Systems Biology

- **Enumerate parts**
  - Quantify all molecular constituents and interactions
- **Extract/Define dynamic network**
  - Computationally and mathematically integrate different data types
- **Mathematically model biological systems**
  - to predict outcomes for perturbations
- **Test predictions**



$$
\begin{aligned}
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&\quad -k_{fd,3i,80}G_{80Cd}G_{3i} + k_{rd,3i,80}C_{3i,80} &&\\
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\frac{dG_{4d}}{dt} &= k_{fd}G_4^2 - k_{rd}G_{4d} - k_{dp,\mathrm{gal4}}G_{4d} && (11)\\
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&\quad +k_{r80}G_{80C} &&\\
\frac{dG_{80Cd}}{dt} &= k_{fd}G_{80C}^2 - k_{rd}G_{80Cd} - k_{dp,\mathrm{gal80}}G_{80Cd} + k_{f80}G_{80d} && (16)\\
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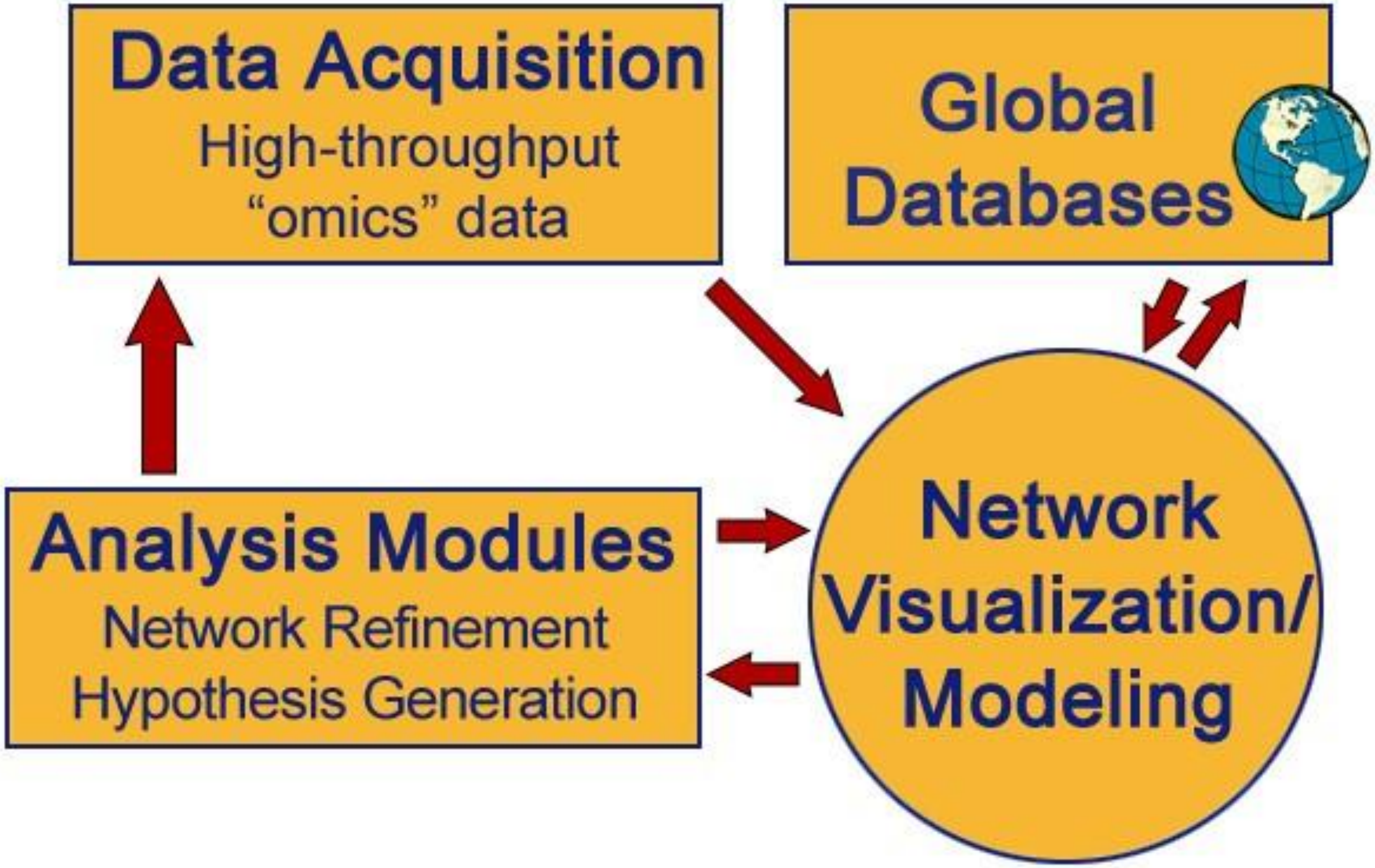
\frac{dC_{3i,80}}{dt} &= k_{fd}G_{80Cd}G_{3i} - k_{rd,3i,80}C_{3i,80} - 0.5k_{dp,\mathrm{gal3}}C_{3i,80} && (17)\\
\frac{dG_{ic}}{dt} &= v_{\mathrm{TR}} - v_{\mathrm{GK}} - k_{fi}G_3G_{ic} + k_{ri}G_{3i} && (18)\\
& && (19)
\end{aligned}
$$

Network modeling by iterative refinement



Data Acquisition
High-throughput
"omics" data

Global Databases

Network Visualization/ Modeling

Analysis Modules
Network Refinement
Hypothesis Generation

Application of systems biology to enable rational vaccine design

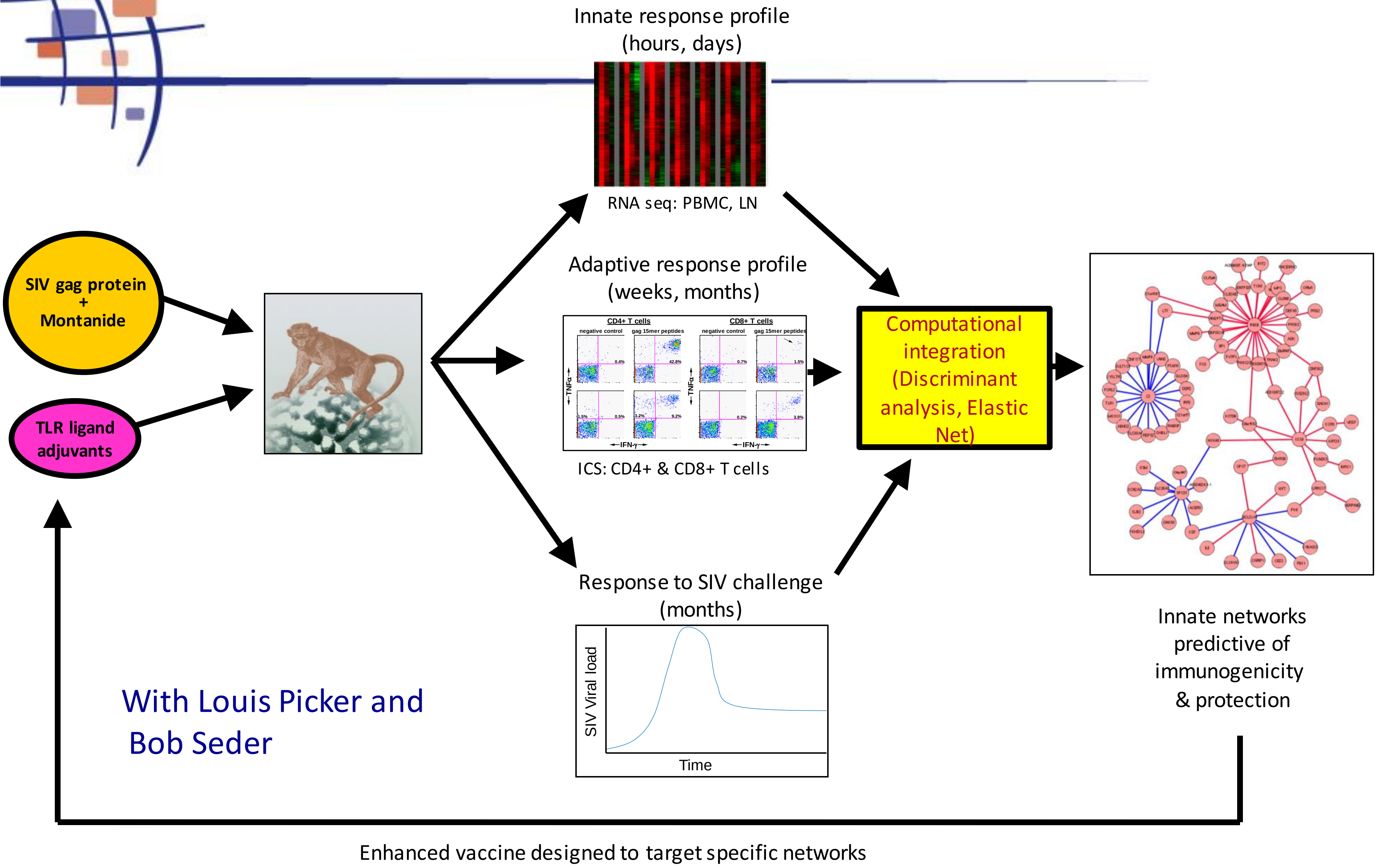
- Identify signatures of vaccine immunogenicity and protection
- To evaluate vaccine trials
- To understand the molecular networks leading to a protective response
- To reprogram the immune response to favor protection

Application of systems biology to enable rational vaccine design

- Identify signatures of vaccine immunogenicity and protection

➡ Predict SIV immunogenicity and viral load from innate immune signatures

Systems Approach to SIV immunogenicity



Innate response profile
(hours, days)

RNA seq: PBMC, LN

Adaptive response profile
(weeks, months)

ICS: CD4+ & CD8+ T cells

Response to SIV challenge
(months)

SIV gag protein
+
Montanide

TLR ligand adjuvants

Computational integration (Discriminant analysis, Elastic Net)

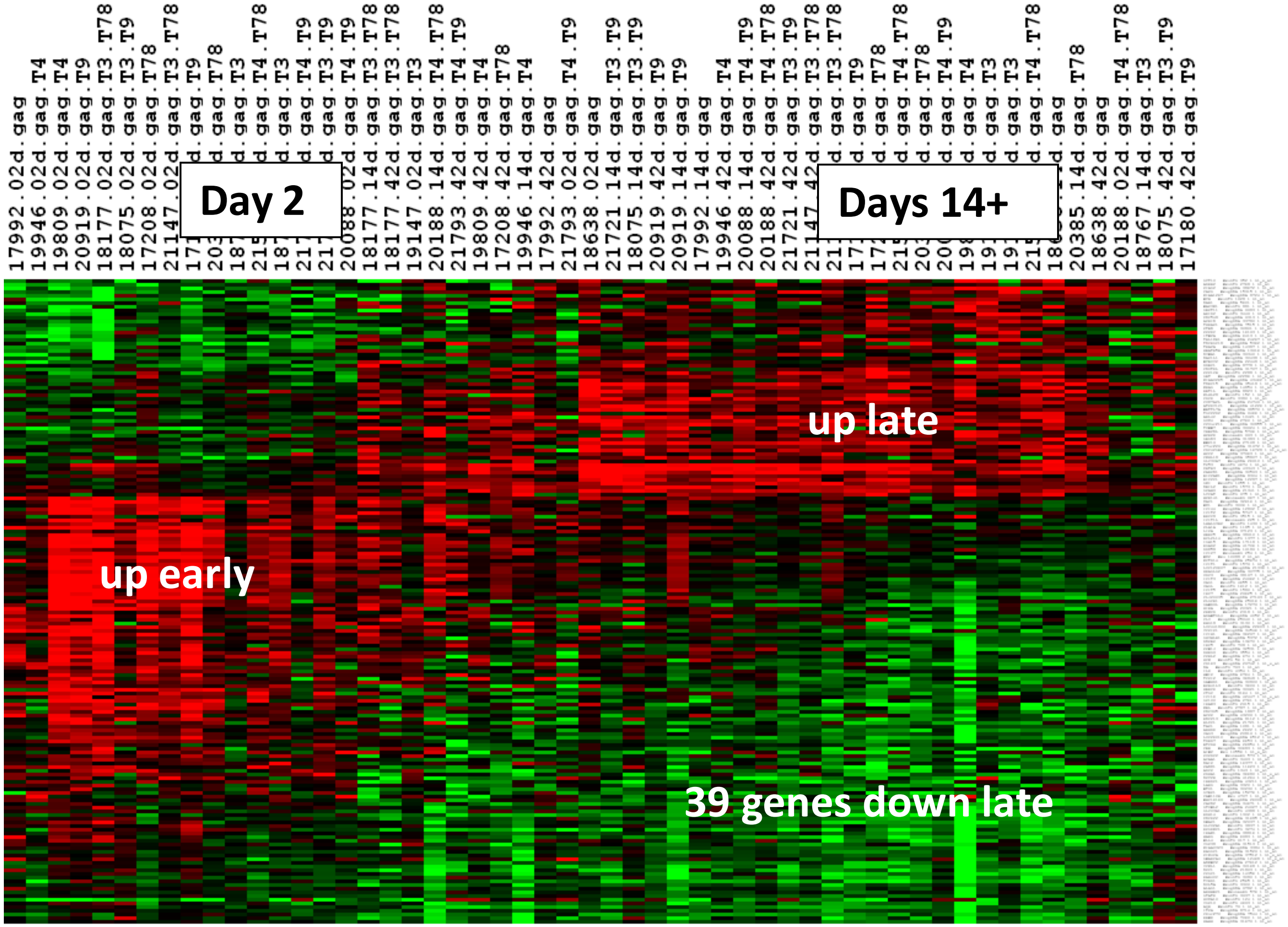
Innate networks predictive of immunogenicity & protection

Enhanced vaccine designed to target specific networks

With Louis Picker and
Bob Seder

Can innate gene expression predict the adaptive immune phenotype?

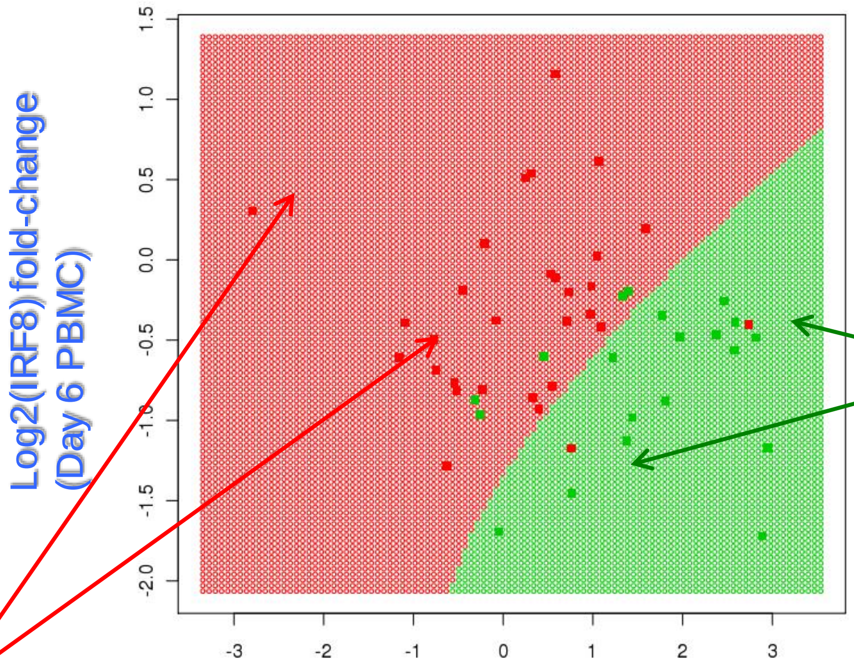
Global transcriptome response (LN)



Classify animals as “High” or “Low” $CD4^+$ responders based on pairwise comparison of gene expression in PBMCs (day 6)

Each point represents a different animal, either a “High” or “Low” responder

QDA: Fitting a model that will predict the CD4 response based on the expression of pairs of genes



Log2(C2) fold-change
(Day 6 PBMC)

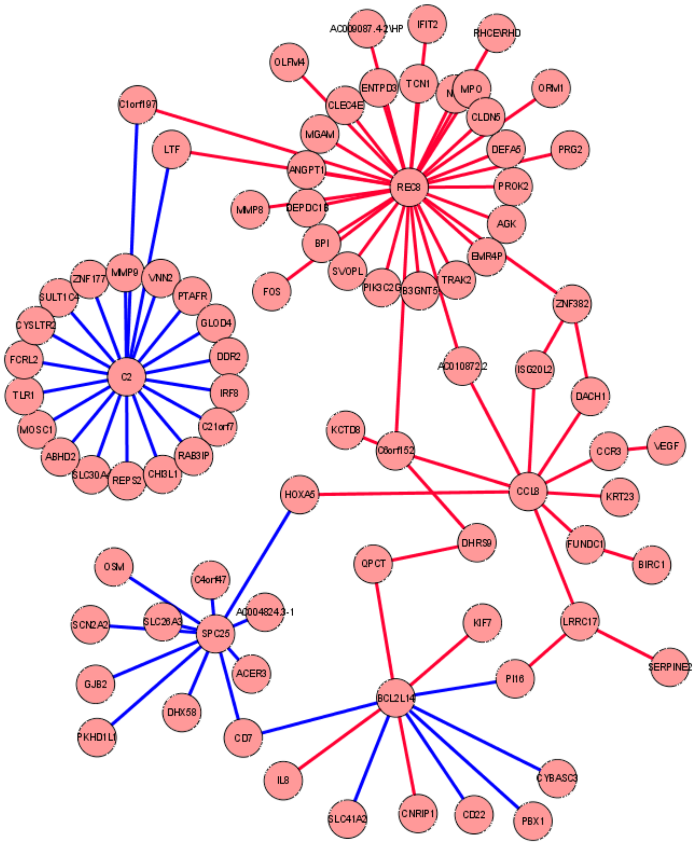
Green points:
“High $CD4^+$ responders”

Red points:
“Low $CD4^+$ responders”

56 monkeys

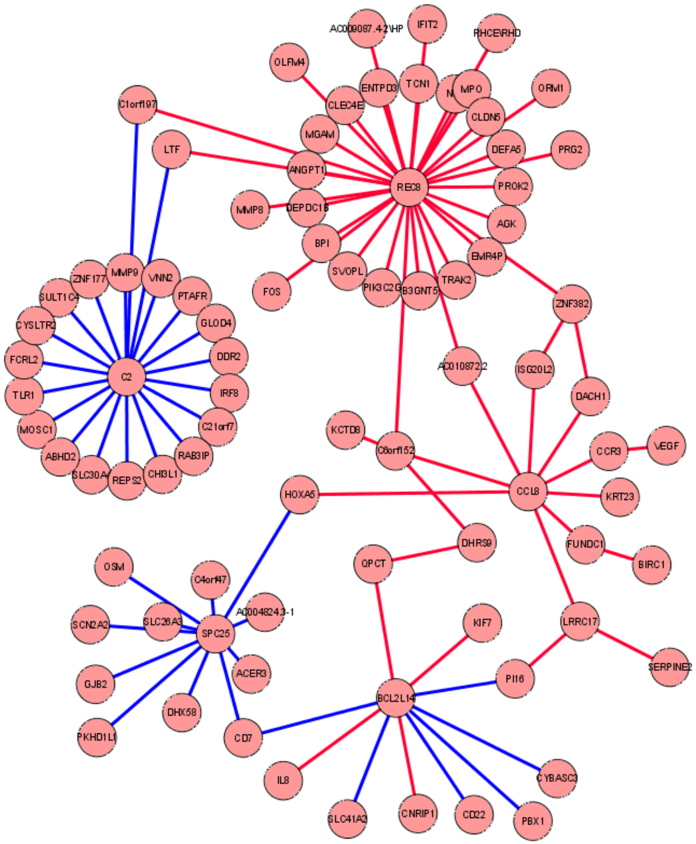
Logistical regression with the elastic net penalty is used for feature selection prio
to pair wise analysis

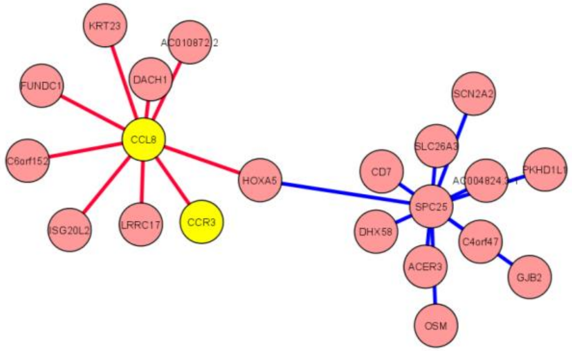
Network of gene expression signatures associated with CD4^{+} responses and SIV load



- Blue edges: gene pairs associated with enhanced CD4+ response
- Red edges: gene pairs associated with decreased viral load
- All pair-wise signatures achieved correct classification for at least 83% of animals in each individual cohort and 86% of animals overall.

Network of gene expression signatures associated with CD4$^+$ responses and SIV load

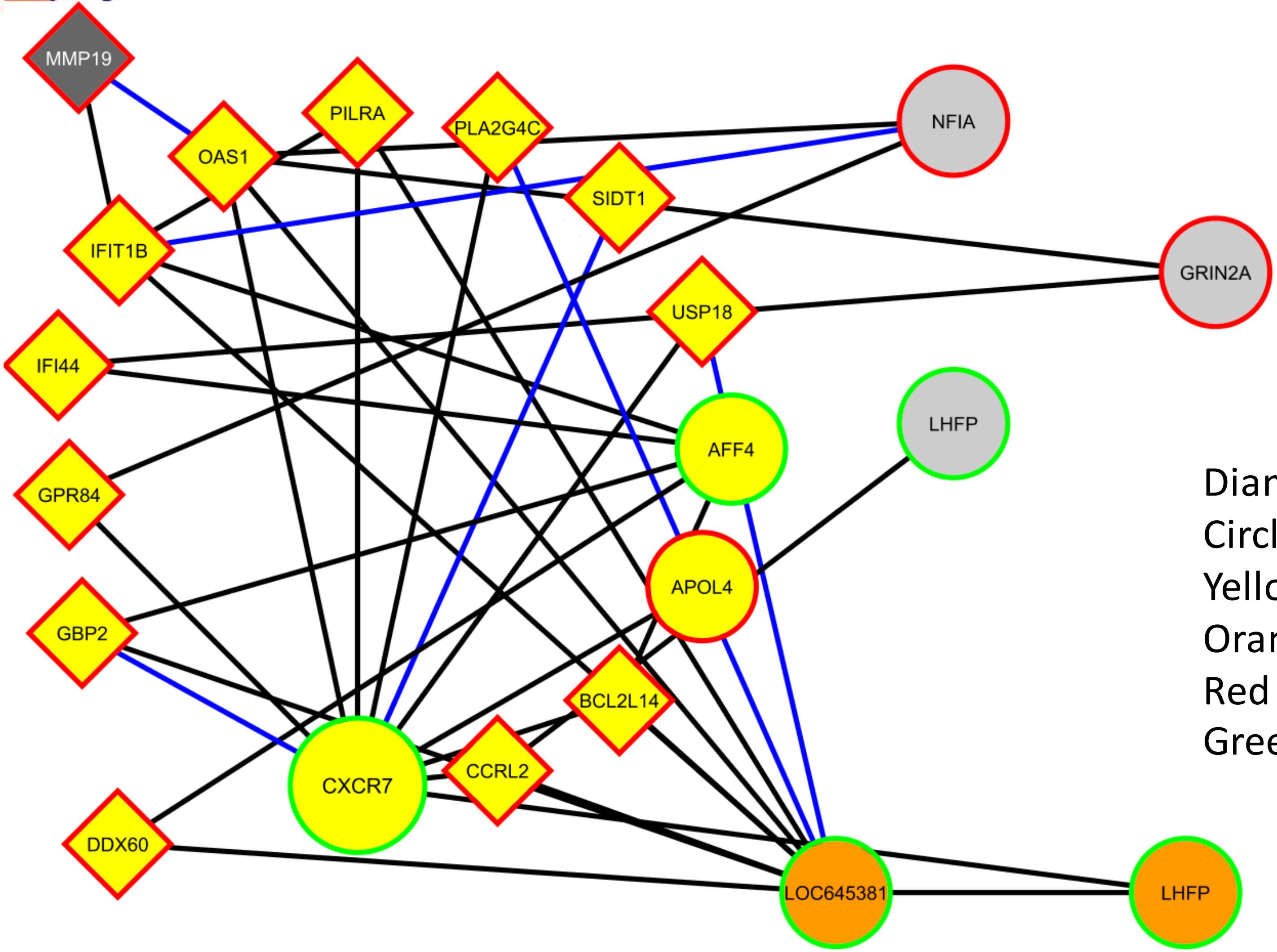




- CCL8: has anti-HIV function (competes for CCR5)
- CCR3: can function as HIV co-receptor

- Blue edges: gene pairs associated with enhanced CD4+ response
- Red edges: gene pairs associated with decreased viral load
- All pair-wise signatures achieved correct classification for at least 83% of animals in each individual cohort and 86% of animals overall.

Adding additional parameters increases the accuracy of prediction. For example: Predicting CD8+ magnitude

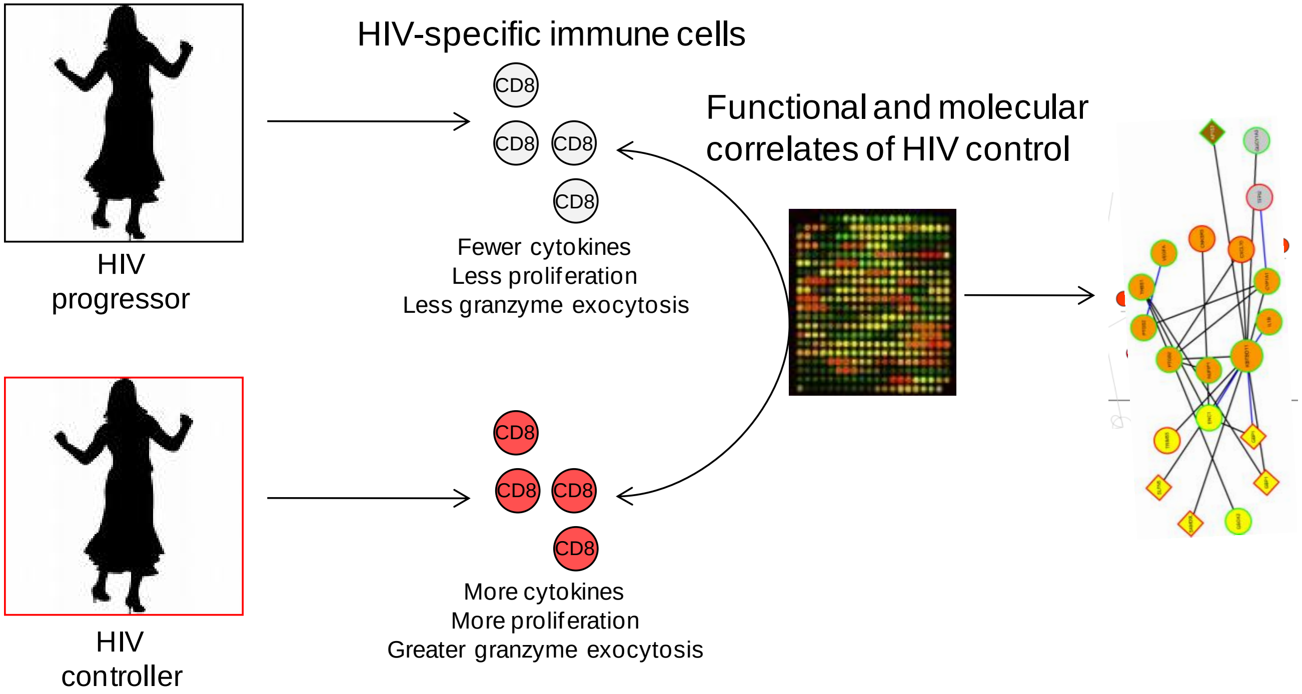


Diamonds = LN
Circles = PBMC
Yellow = Day 2
Orange = Day 6
Red = + correlation
Green = - correlation

Displayed pair-wise signatures have > 90% predictive accuracy (blue edges were most robust)

Identifying novel immune correlates from human controller/progressor populations

HIV-infected populations with differing abilities to control virus



HIV progressor

HIV-specific immune cells

Fewer cytokines
Less proliferation
Less granzyme exocytosis

Functional and molecular correlates of HIV control

Networks associated with control

HIV controller

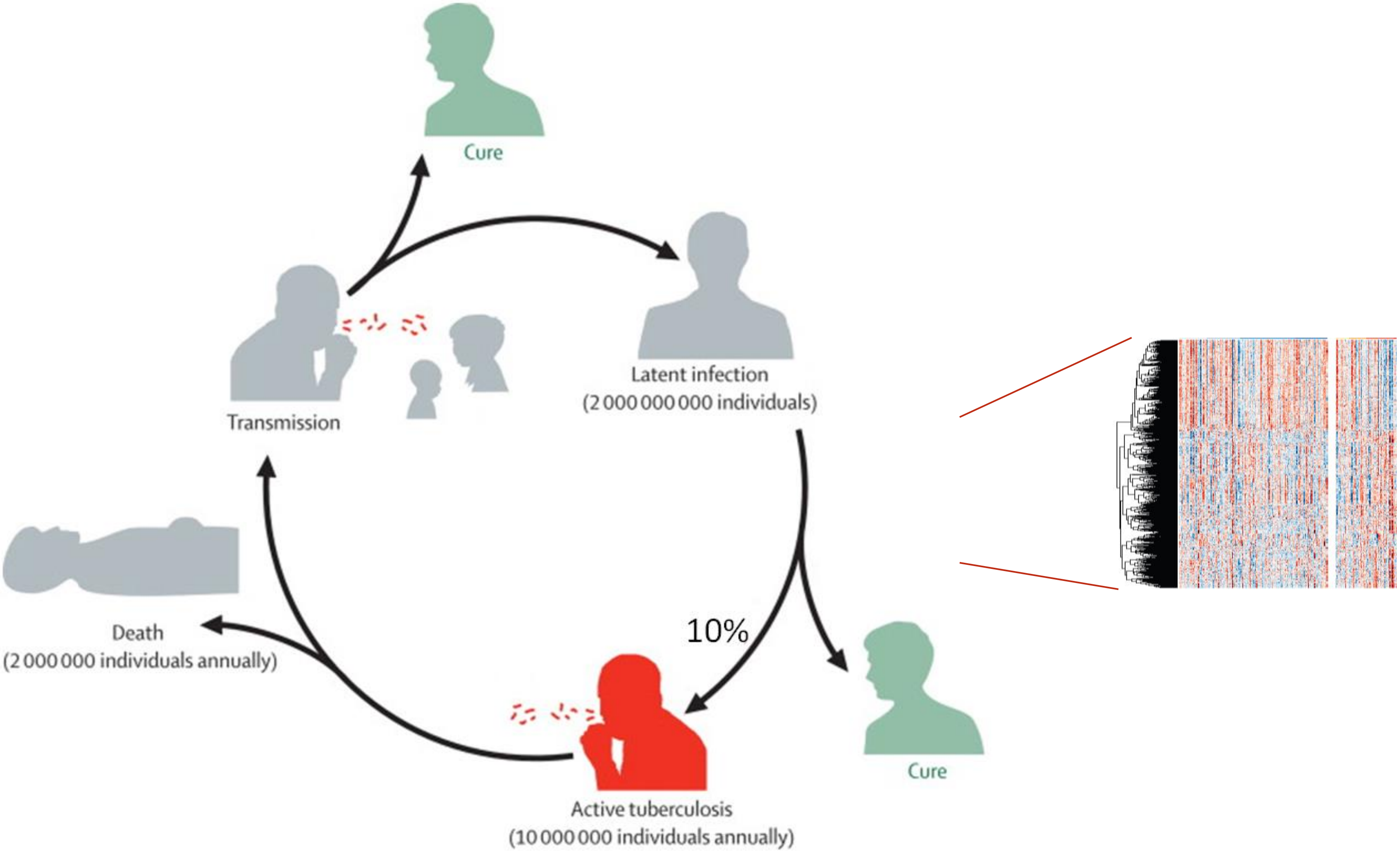
More cytokines
More proliferation
Greater granzyme exocytosis

Rappuoli and Aderem, Nature 2012

Field study

Predict and understand progression from latent to active TB

Predict and understand progression from latent to active TB



Correlates of TB disease risk in adolescents

- Collaboration with SATVI / University of Cape Town : Willem Hanekom & Tom Scriba

- **Goal**: Predict which *M.tb* infected adolescents will progress to TB disease

- **Samples**:
  - Selected from a population of 6,363 M.tb infected adolescents
  - 44 TB cases: developed TB 6 months or more after enrollment
  - 90 controls: matched to cases by age, sex, ethnicity, school
  - 1-4 time points at 6 month intervals

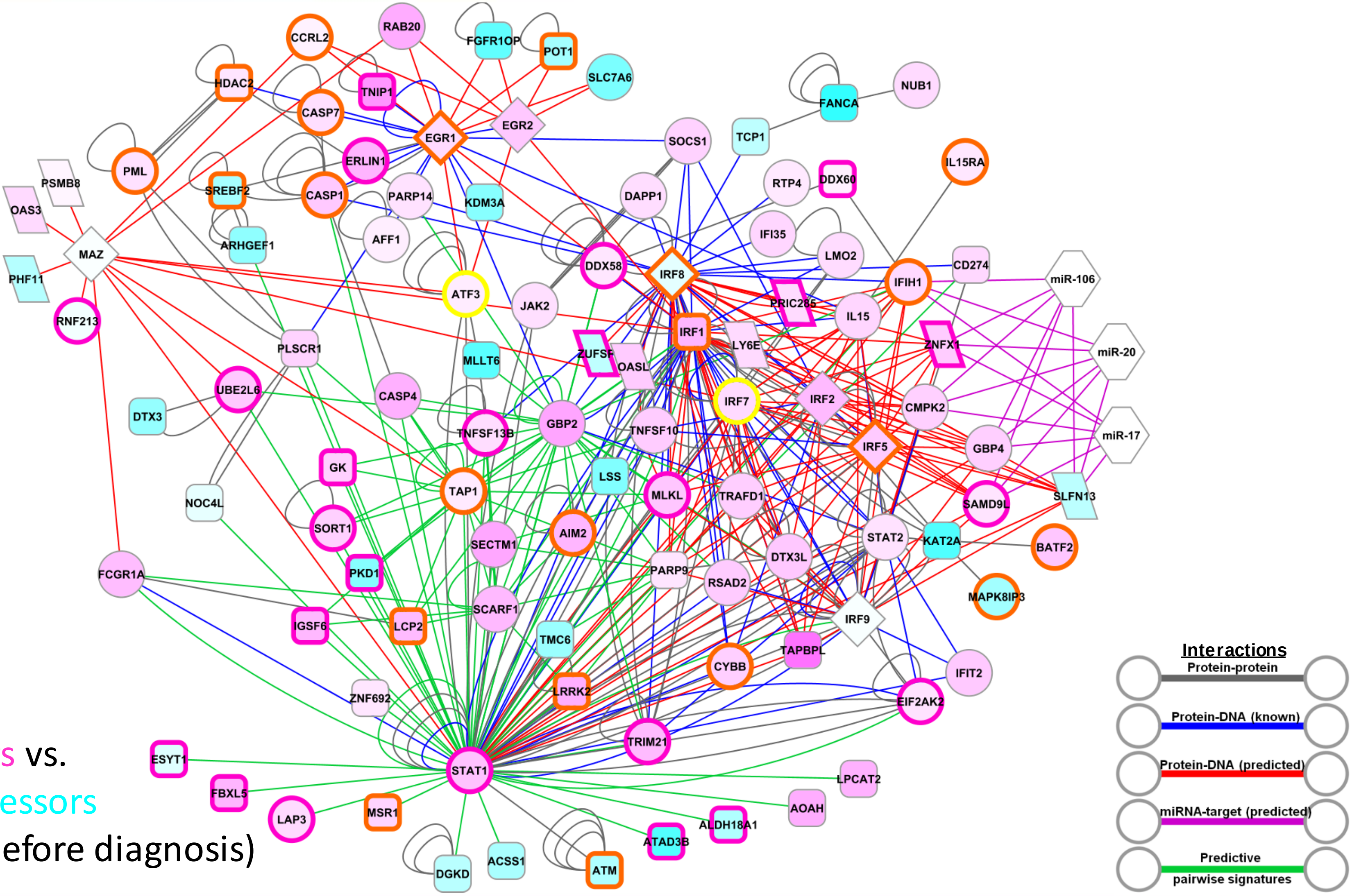
- **Analysis**: Whole blood transcriptome profiling with RNA-Seq

Training set for biomarker discovery

satvi

Seattle BioMed

Predicted innate immune response network associated with TB disease progression



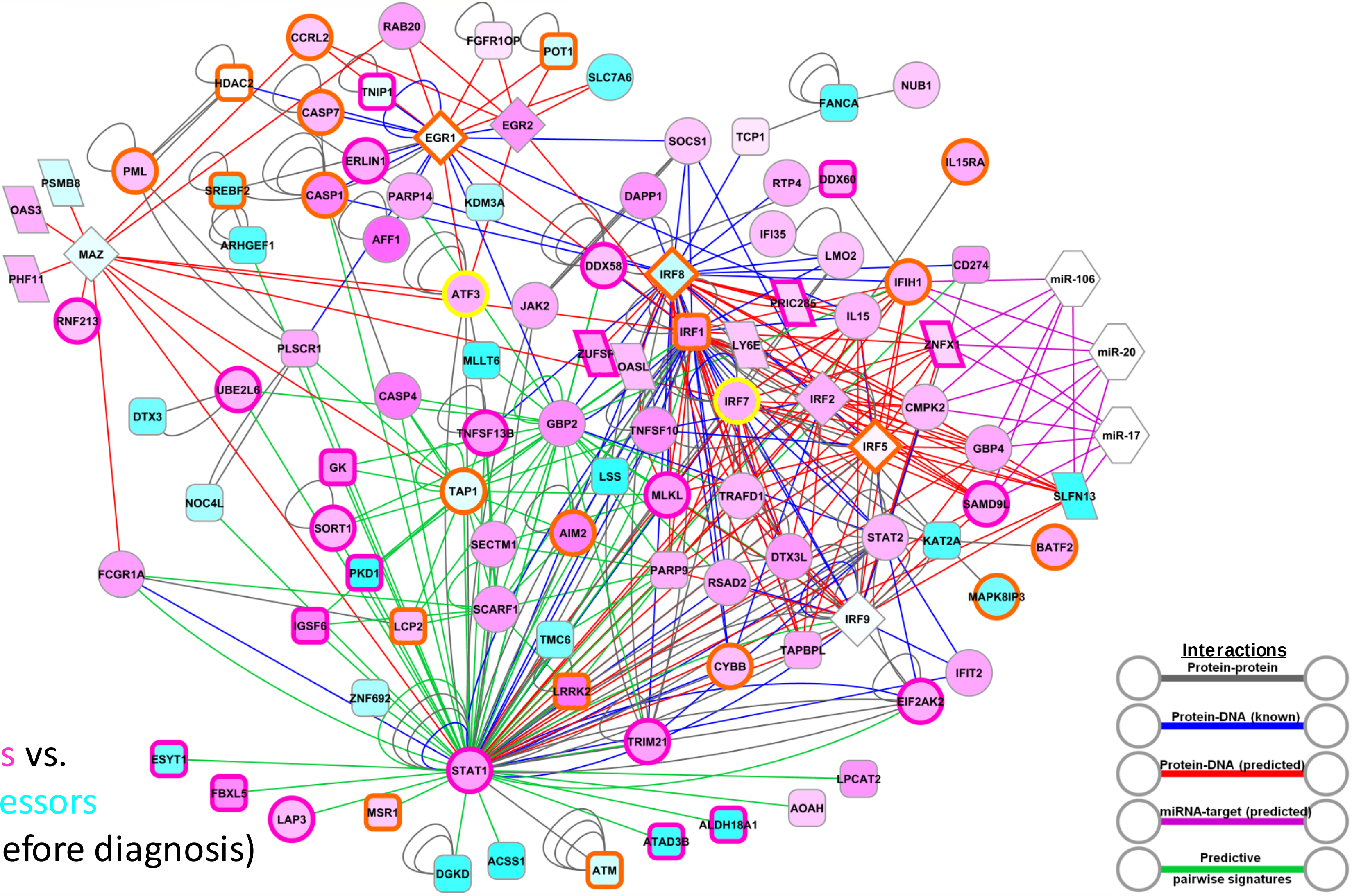
Colors:

Progressors vs.

Non-progressors

(1.5-1yrs before diagnosis)

The whole network is coordinately regulated as the adolescents progress to TB disease



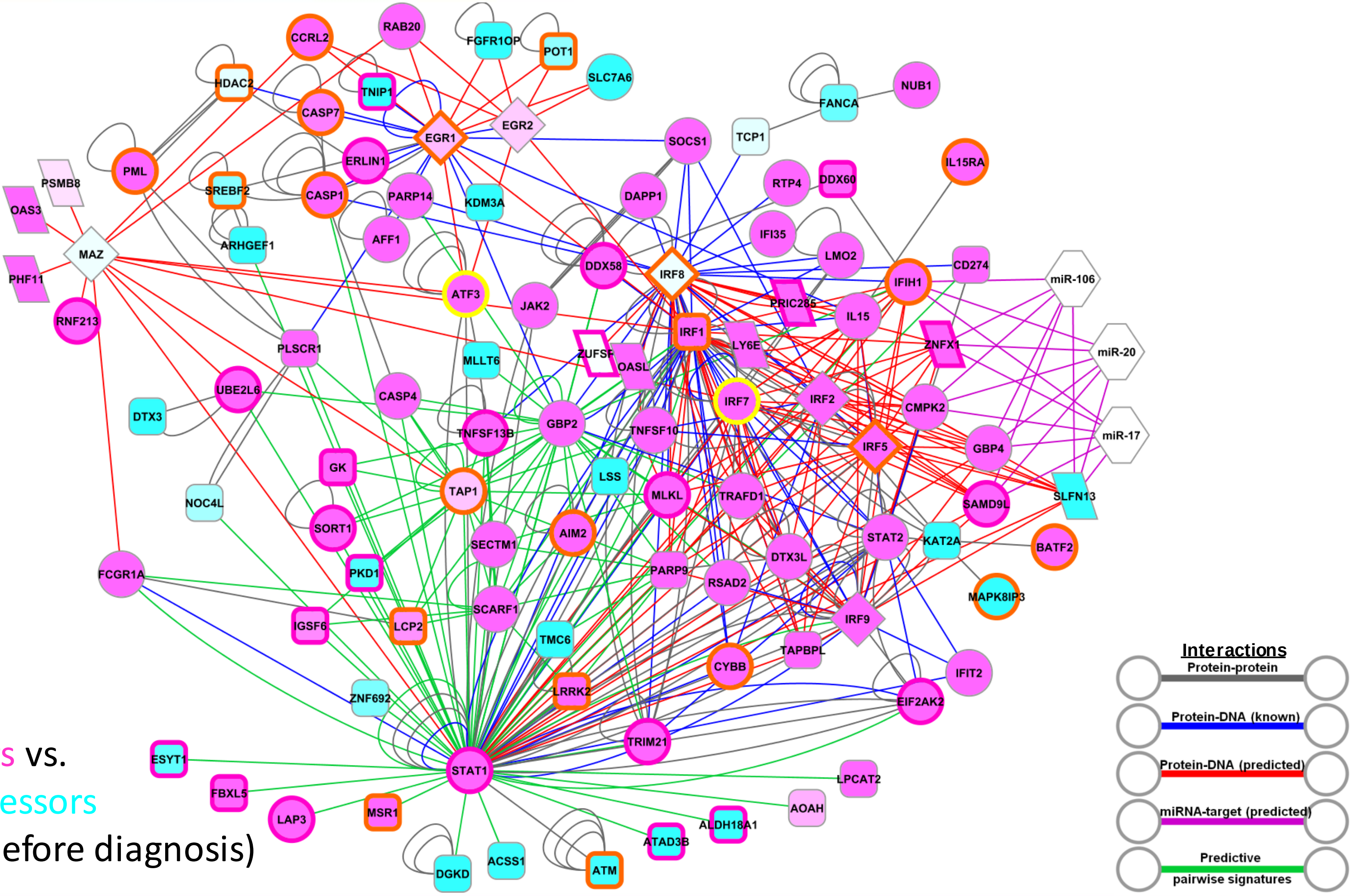
Colors:

Progressors vs.

Non-progressors

(1-0.5yrs before diagnosis)

The whole network is coordinately regulated as the adolescents progress to TB disease



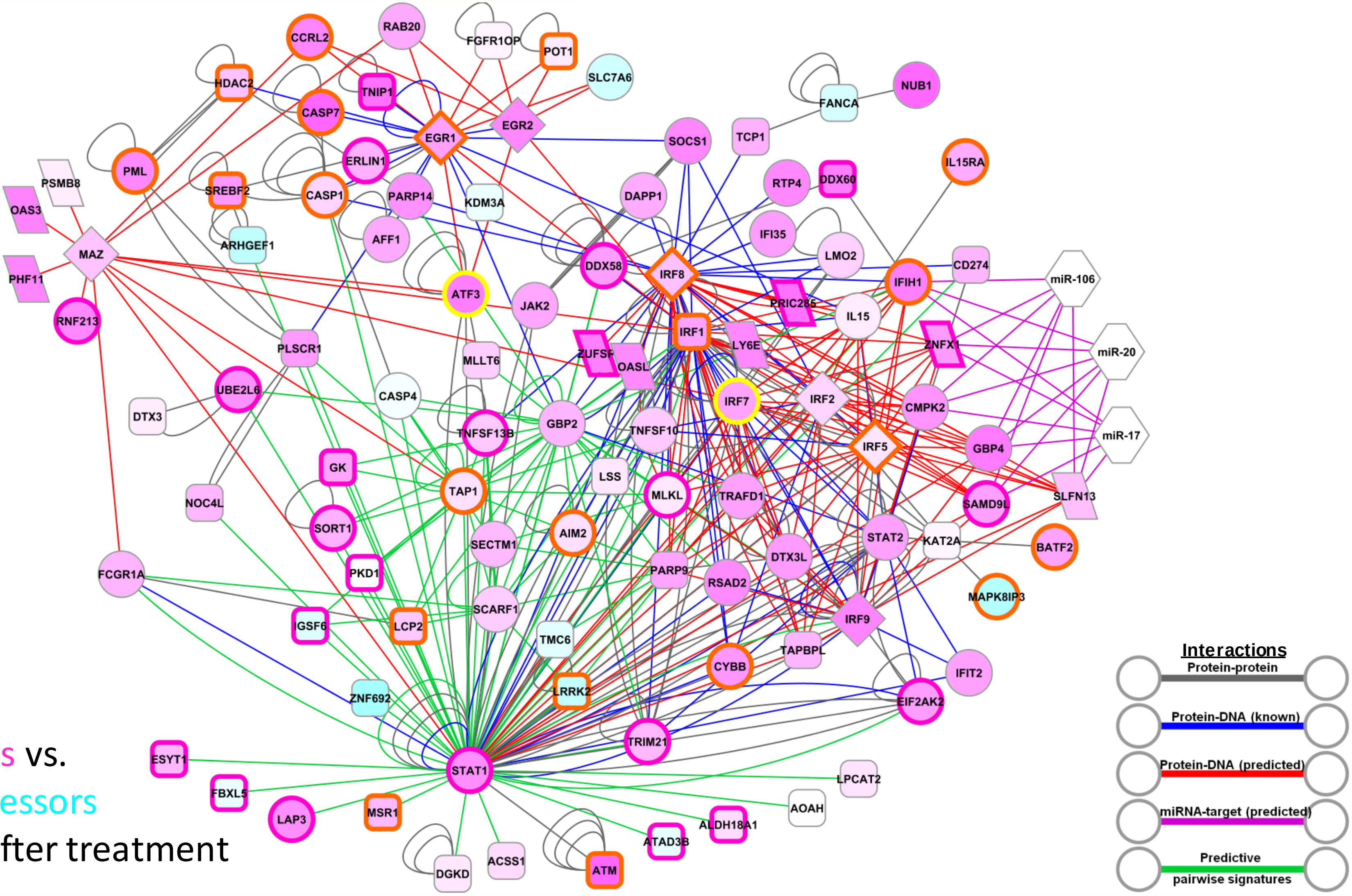
Colors:

Progressors vs.

Non-progressors

(0.5-0yrs before diagnosis)

The whole network is coordinately relaxed after treatment



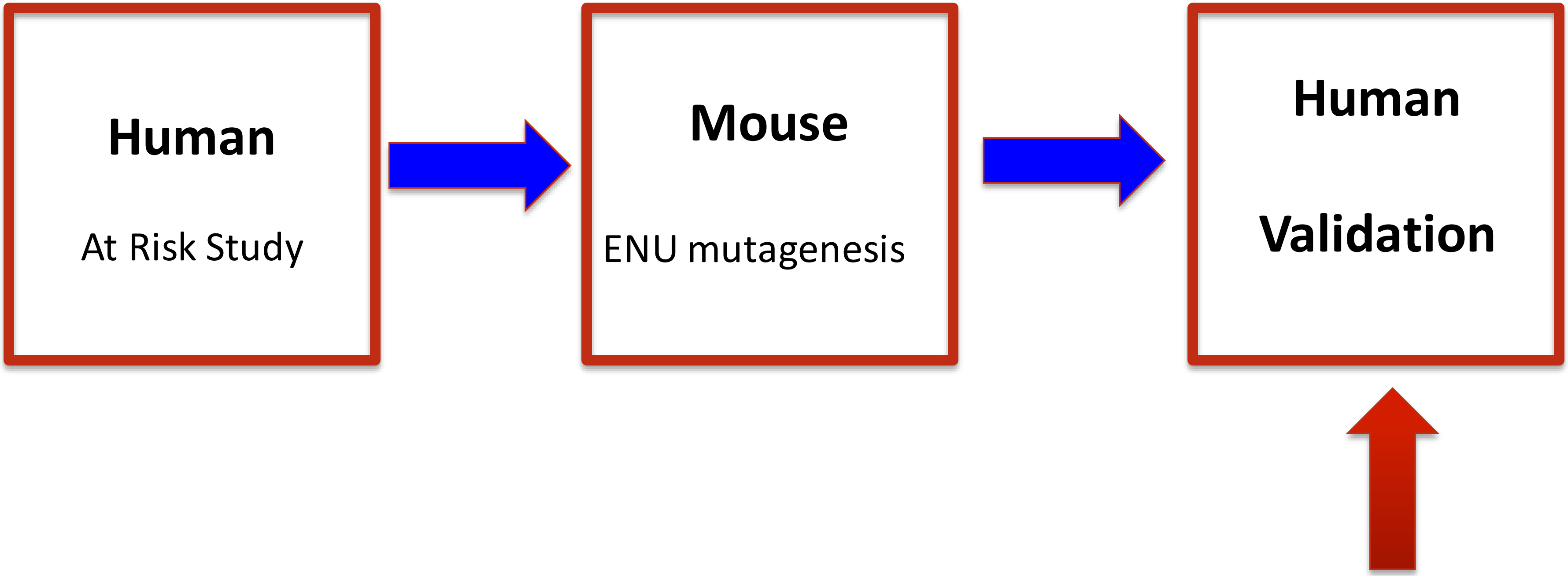
Colors:

Progressors vs.

Non-progressors

(0-0.5yrs after treatment

Identification of networks underlying the latent to active switch



Human

At Risk Study

Mouse

ENU mutagenesis

Human

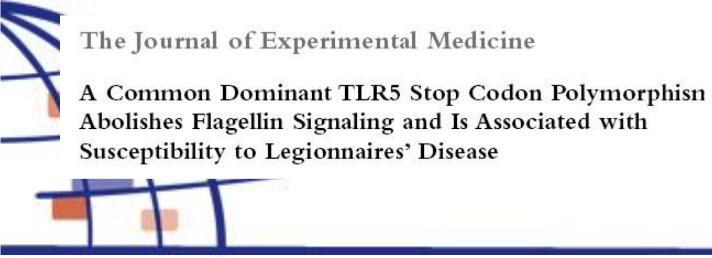
Validation

RNA knockdowns

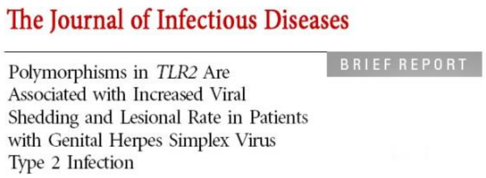
CRISPR genome-editing

Human Genetics

Hawn, Bochud, Aderem


The Journal of Experimental Medicine

A Common Dominant TLR5 Stop Codon Polymorphism Abolishes Flagellin Signaling and Is Associated with Susceptibility to Legionnaires' Disease


The Journal of Infectious Diseases

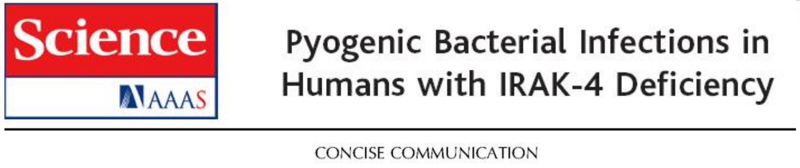
BRIEF REPORT

Polymorphisms in *TLR2* Are Associated with Increased Viral Shedding and Lesional Rate in Patients with Genital Herpes Simplex Virus Type 2 Infection


Review

THE LANCET Infectious Diseases

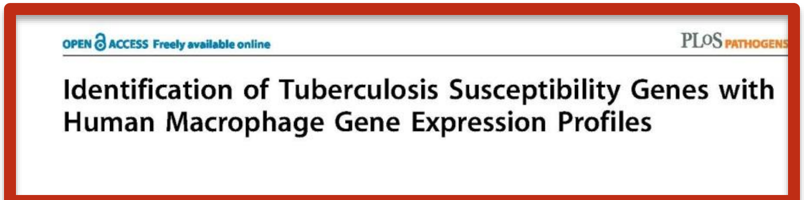
Innate immunogenetics: a tool for exploring new frontiers of host defence


Science AAAS

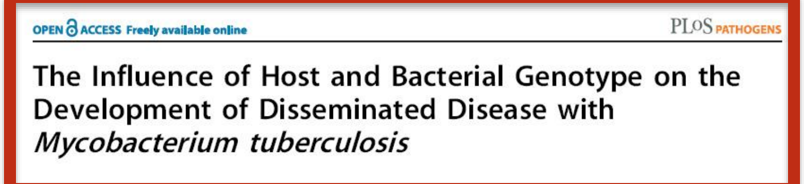
Pyogenic Bacterial Infections in Humans with IRAK-4 Deficiency

CONCISE COMMUNICATION

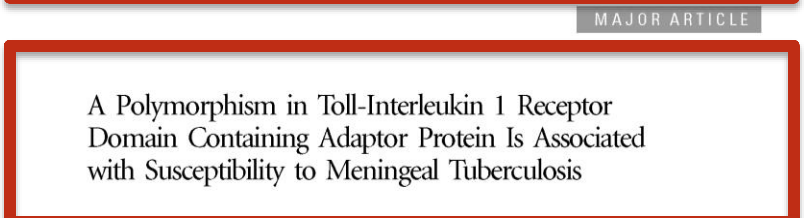

Polymorphisms in Toll-like receptor 9 influence the clinical course of HIV-1 infection


OPEN ACCESS Freely available online PLoS PATHOGENS

Identification of Tuberculosis Susceptibility Genes with Human Macrophage Gene Expression Profiles


OPEN ACCESS Freely available online PLoS PATHOGENS

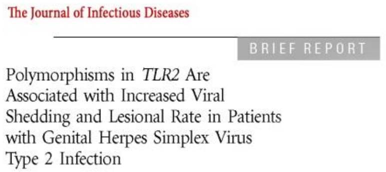
The Influence of Host and Bacterial Genotype on the Development of Disseminated Disease with *Mycobacterium tuberculosis*


MAJOR ARTICLE

A Polymorphism in Toll-Interleukin 1 Receptor Domain Containing Adaptor Protein Is Associated with Susceptibility to Meningeal Tuberculosis


OPEN ACCESS Freely available online PLoS NEGLECTED TROPICAL DISEASES

Human TLR1 Deficiency Is Associated with Impaired Mycobacterial Signaling and Protection from Leprosy Reversal Reaction


The Journal of Infectious Diseases

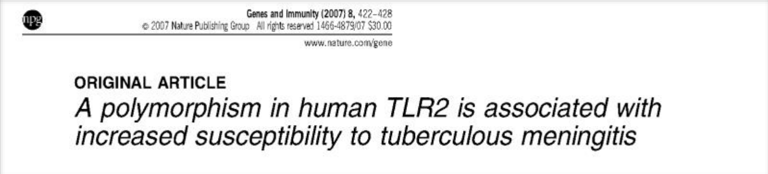
BRIEF REPORT

Polymorphisms in *TLR2* Are Associated with Increased Viral Shedding and Lesional Rate in Patients with Genital Herpes Simplex Virus Type 2 Infection


The NEW ENGLAND JOURNAL of MEDICINE

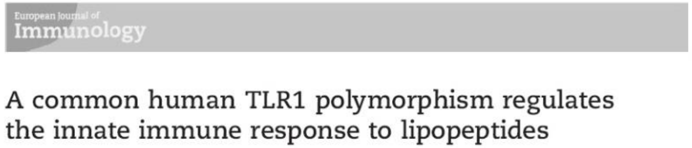
ORIGINAL ARTICLE

Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation

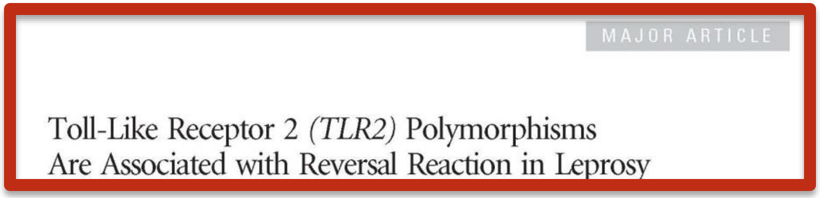

Genes and Immunity (2007) 8, 422–428
© 2007 Nature Publishing Group All rights reserved 1466-4879/07 $30.00
www.nature.com/gene

ORIGINAL ARTICLE

A polymorphism in human TLR2 is associated with increased susceptibility to tuberculous meningitis


European Journal of Immunology

A common human TLR1 polymorphism regulates the innate immune response to lipopeptides


MAJOR ARTICLE

Toll-Like Receptor 2 (*TLR2*) Polymorphisms Are Associated with Reversal Reaction in Leprosy


PNAS

Toll-like receptor 4 polymorphisms are associated with resistance to Legionnaires' disease

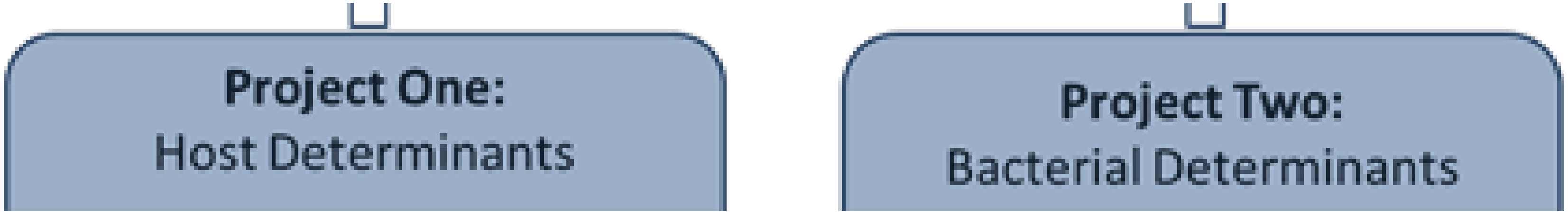

THE JOURNAL OF IMMUNOLOGY

CUTTING EDGE

Cutting Edge: A Toll-Like Receptor 2 Polymorphism That Is Associated with Lepromatous Leprosy Is Unable to Mediate Mycobacterial Signaling[1]

Omics of TB Disease Progression

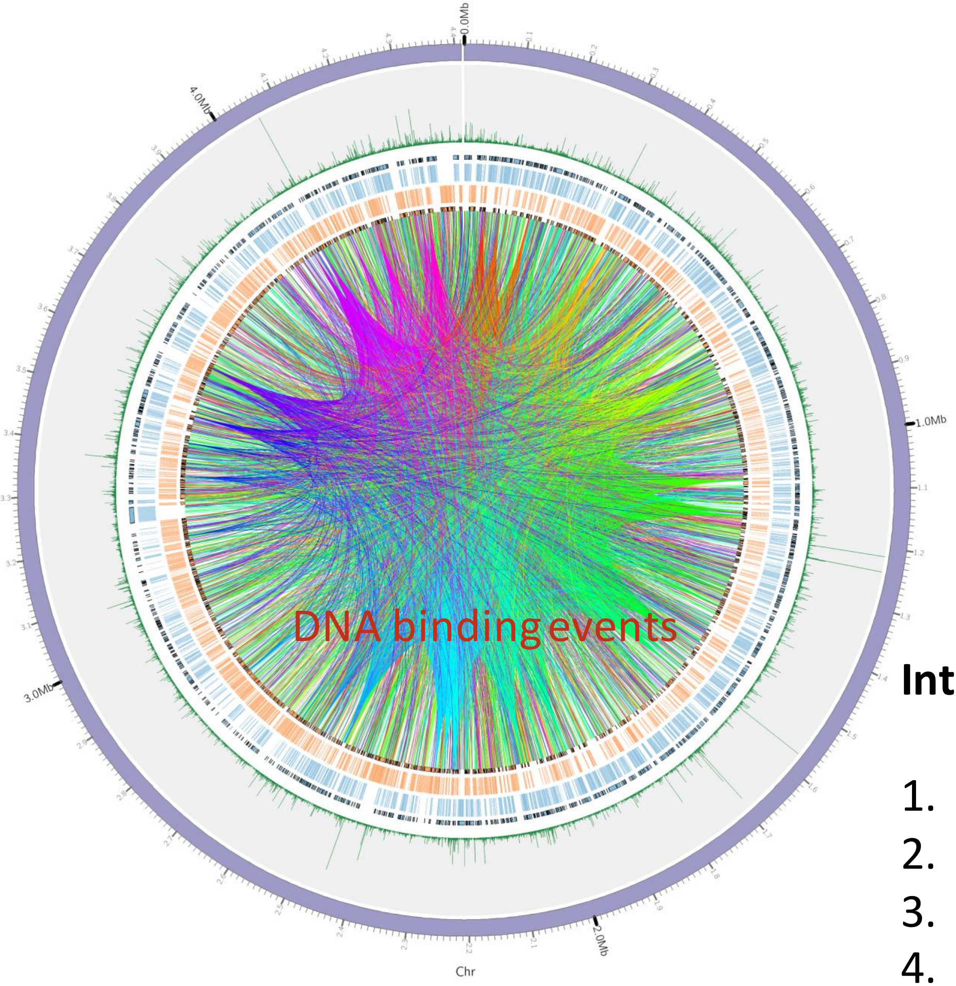
Map the regulatory networks within the host and
the mycobacterium during TB disease containment or progression



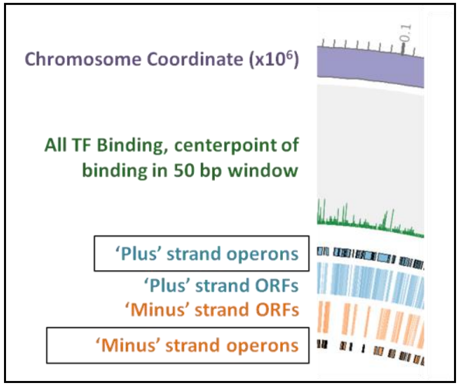
Project One:
Host Determinants

Project Two:
Bacterial Determinants

Mapping transcriptional and signaling networks within MTB that undermine host responses



With David Sherman



~7100 sites

207 TFs

$P<0.001$

Integrate Host and Bacterial Networks to Identify:

1. which networks regulate latency,
2. which render MTB most susceptible to the host
3. which host networks lead to protection
4. can we reprogram the host response to elicit protection

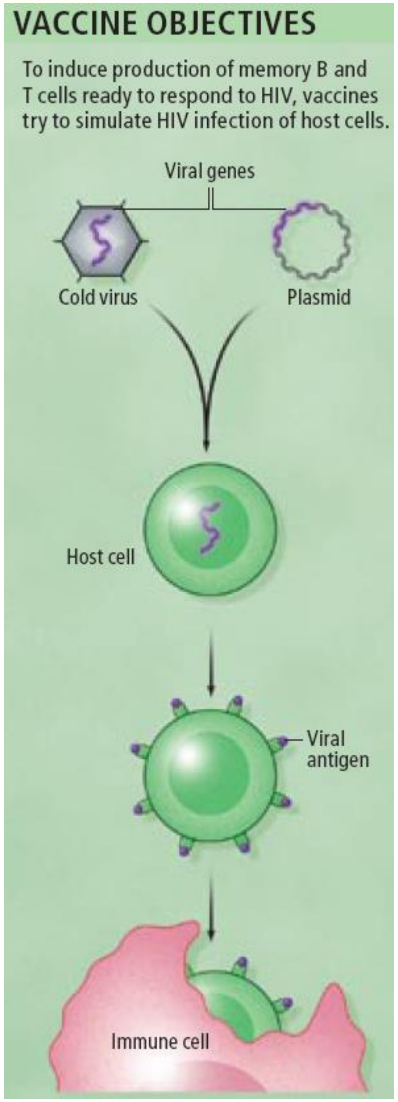
Application of systems biology to rational vaccine design

- Identify signatures of vaccine immunogenicity and protection

- To evaluate vaccine trials

→ Evaluation of the Merck STEP trial

Analyzing the Step Trial



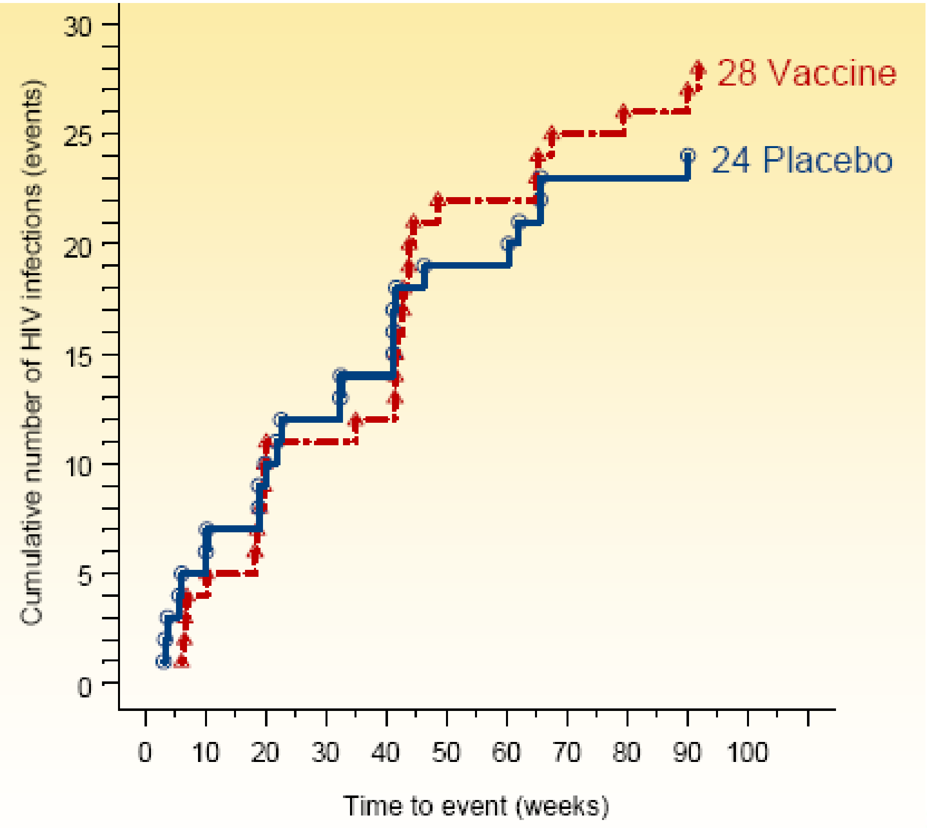
VACCINE OBJECTIVES

To induce production of memory B and T cells ready to respond to HIV, vaccines try to simulate HIV infection of host cells.

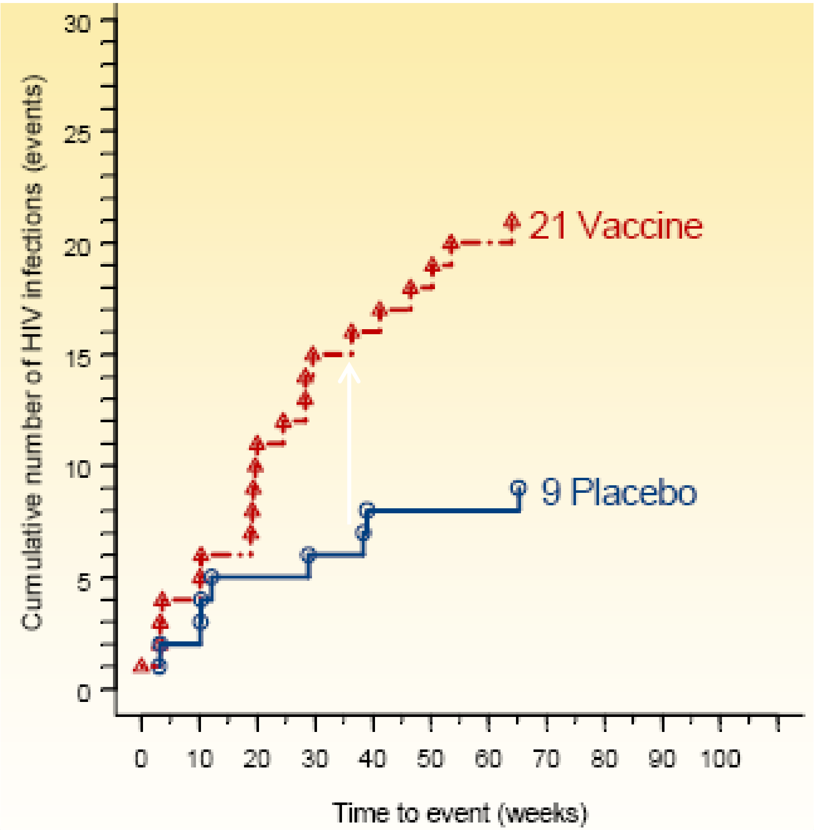
Trivalent MRKAd5 HIV-1 gag/pol/nef from the Step Trial

Analyzing the Step Trial

People *without* pre-existing antibodies to the viral vector (“Seronegative”)



People *with* pre-existing antibodies to the viral vector (“Seropositive”)



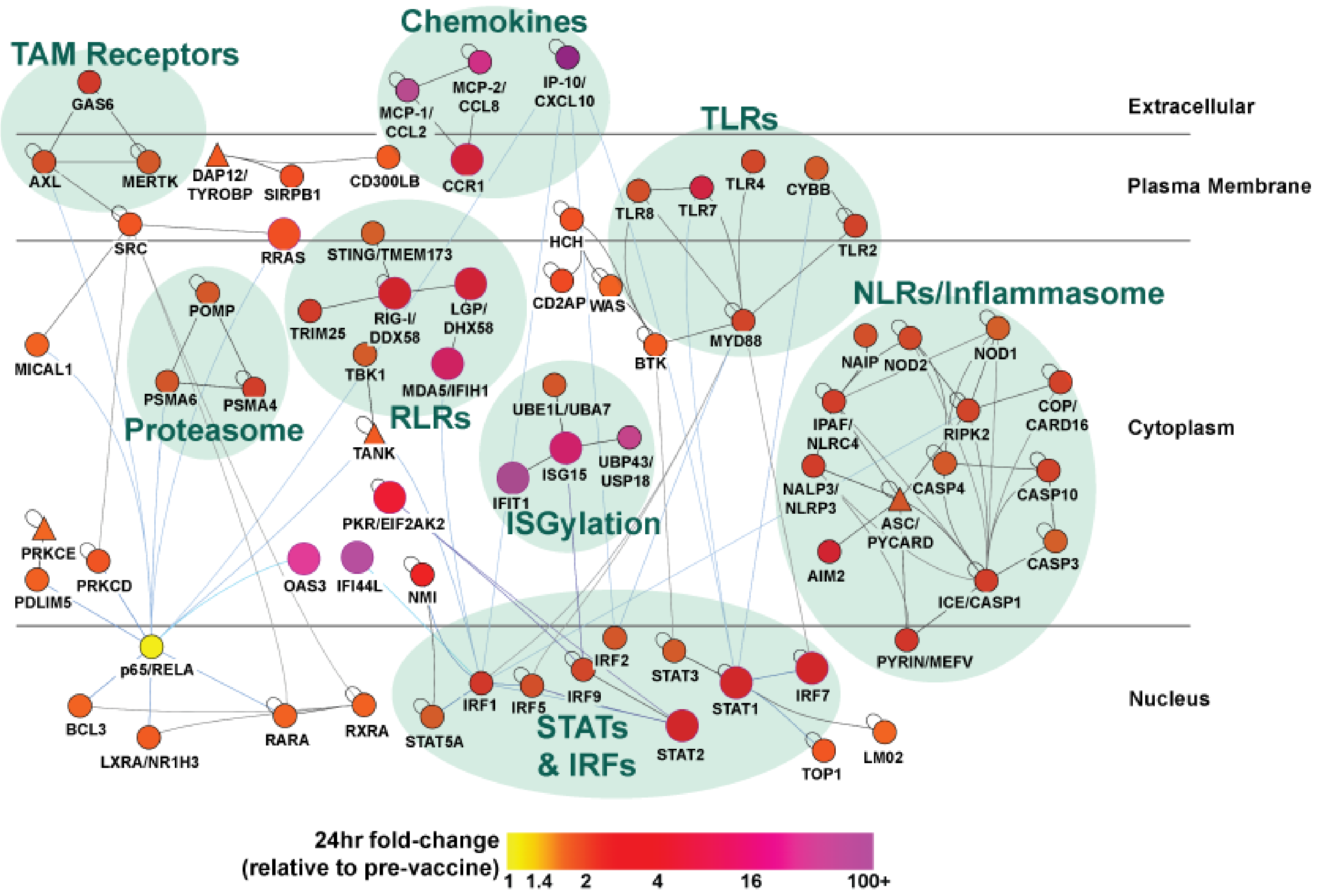
Analyzing the Step Trial

- Seattle subjects vaccinated with trivalent MRKAd5 HIV-1 gag/pol/nef from the Step trial
- Subjects had varying pre-vaccination immunity to vaccine vector (Ad5+)
- Microarray profiling of PBMC innate immune responses 6, 24, 72, and 168hr after primary vaccination
- Intracellular Cytokine Staining (ICS) used to profile HIV-specific T cell responses

With Julie McElrath

FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

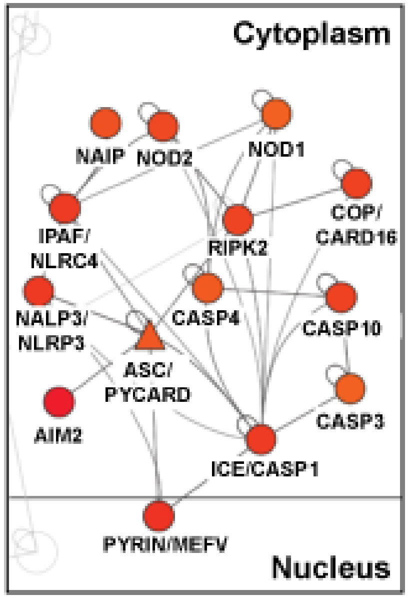
Functional networks regulated by MRKAd5 vaccination



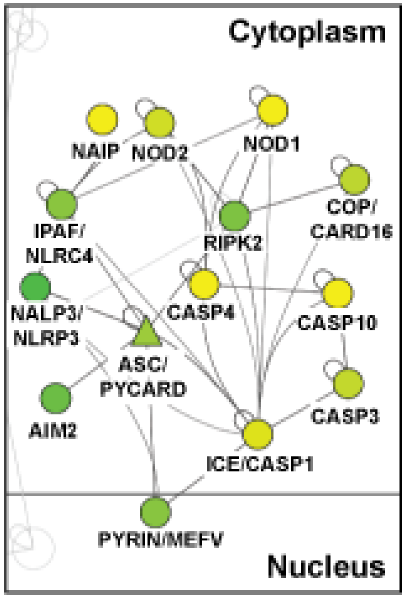
Induction of innate antiviral networks are attenuated in Ad5 seropositive subjects

Pre-existing vector immunity dramatically alters the innate response to vaccination

Inflammasome Network



Ad5 Negative

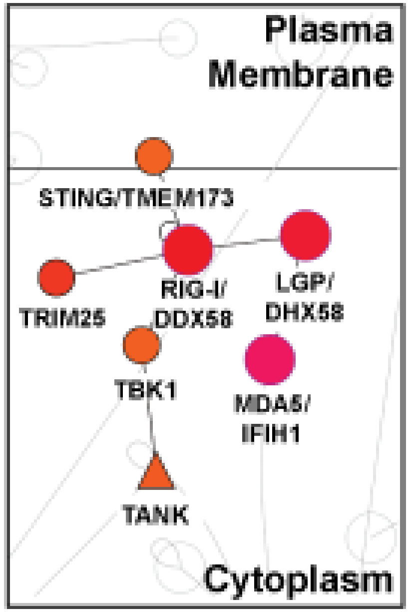


Ad5 Positive

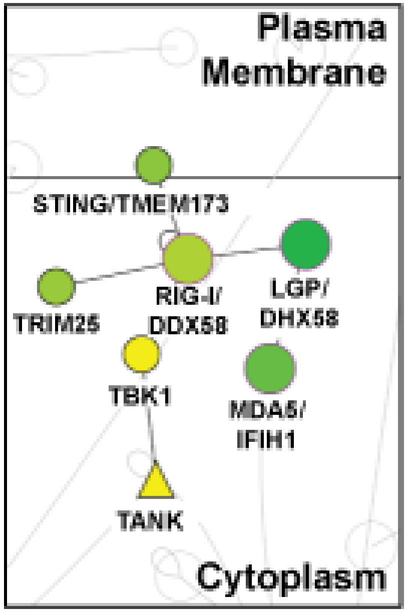
Induction of innate antiviral networks are attenuated in Ad5 seropositive subjects

Pre-existing vector immunity dramatically alters the innate response to vaccination

RIG-I Network



Ad5 Negative



Ad5 Positive

Zak et al, Proc. Natl. Acad. Sci., 2012

Virus responsive innate immune networks appear to be attenuated in Ad5 positive vaccinees

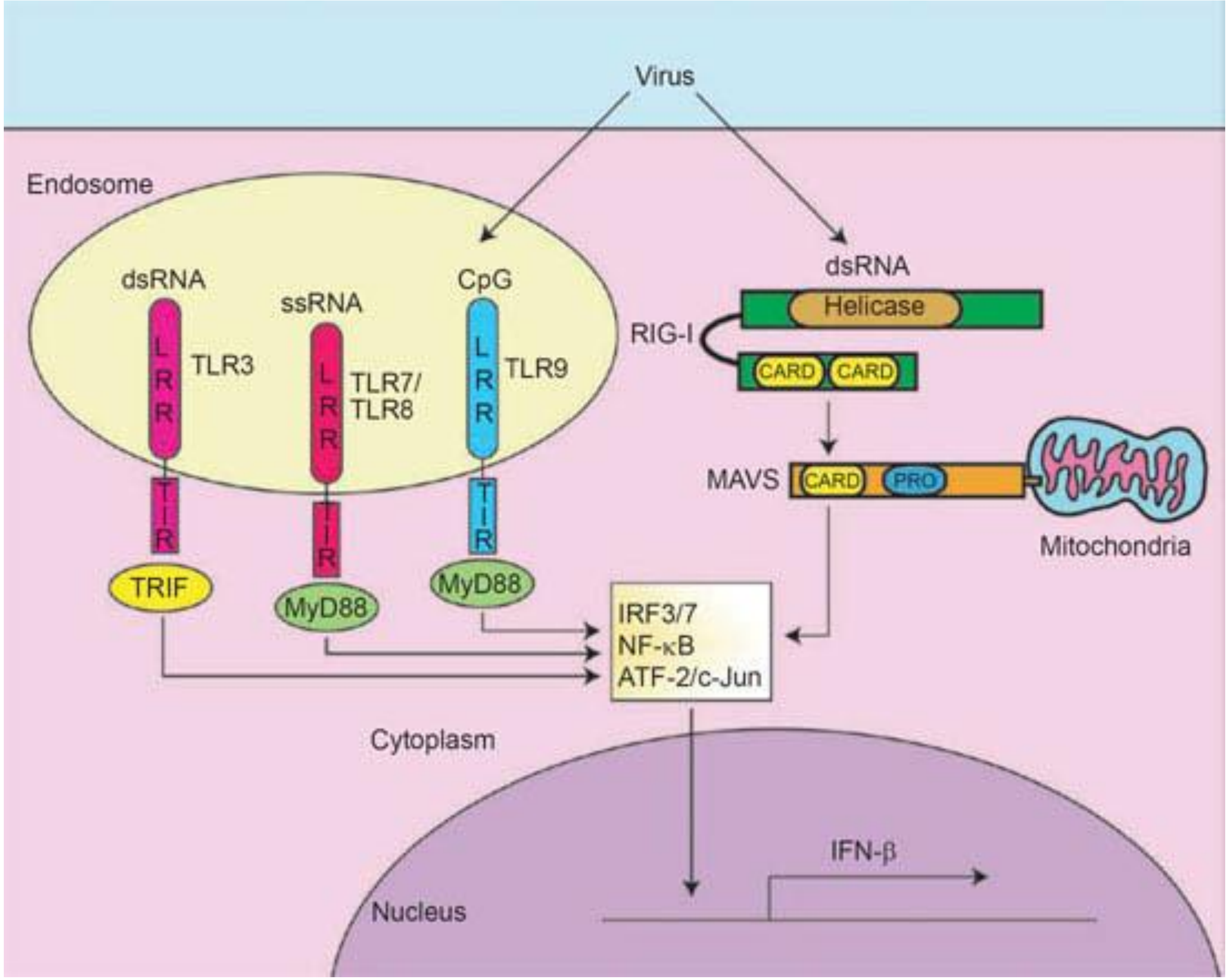
Application of systems biology to enable rational vaccine design

- Identify signatures of vaccine immunogenicity and protection
- To evaluate vaccine trials
- To understand the molecular networks leading to a protective response
  - 5 examples

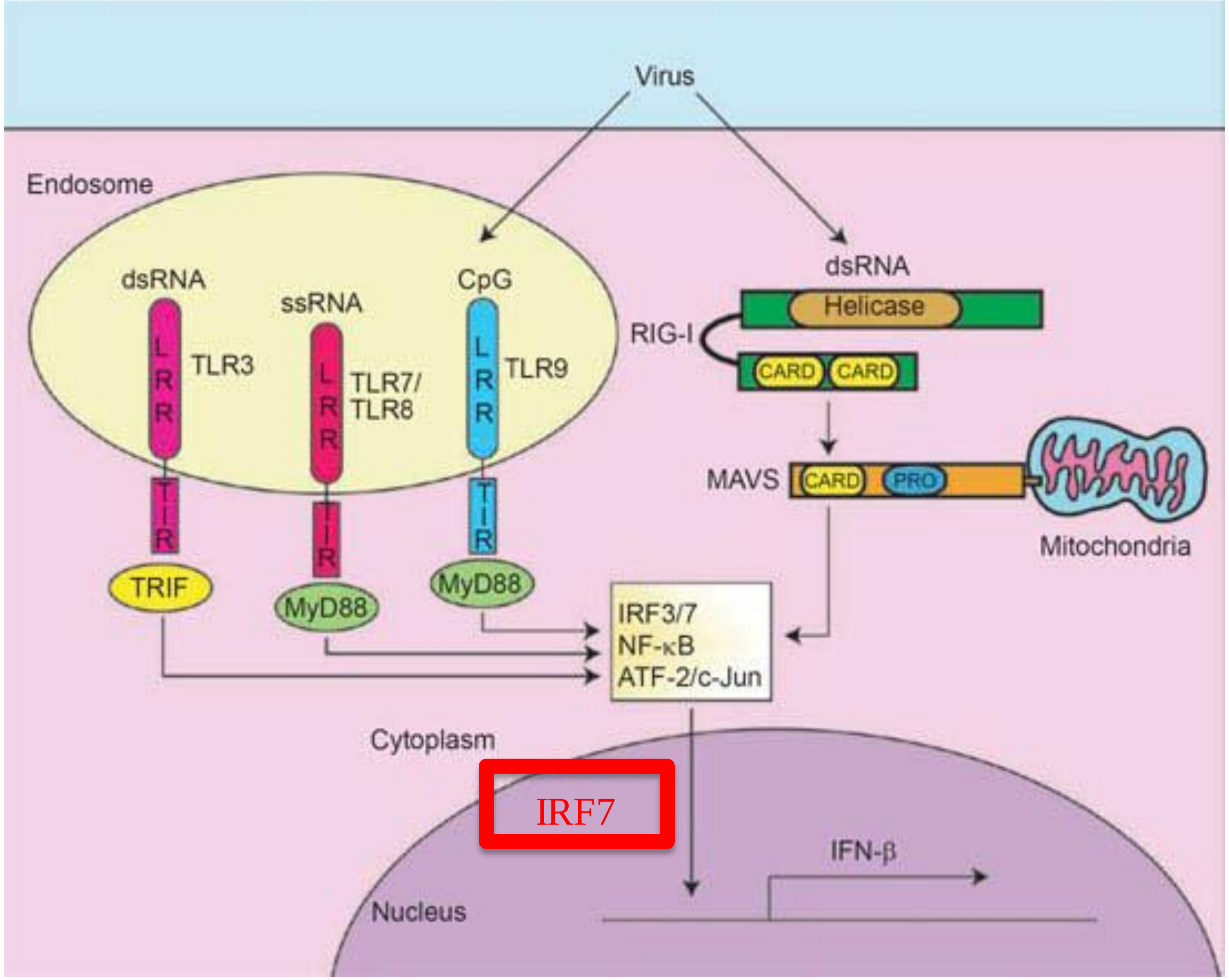
Regulation of the IRF7 pathway

- A Foxo3 - IRF7 anti-viral regulatory circuit
- An IRF7 - microRNA-144 anti-viral regulatory circuit

Innate anti-Viral detectors and pathways



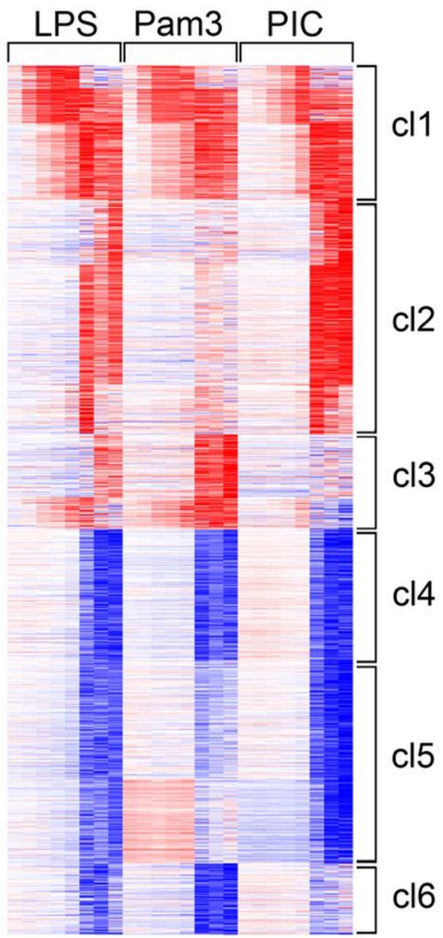
Innate anti-Viral detectors and pathways

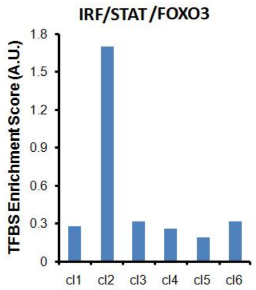


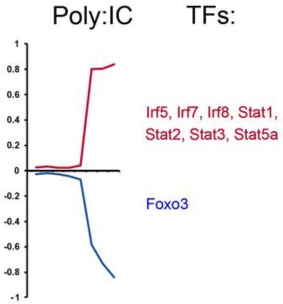
Regulation of the IRF7 pathway

- A Foxo3 - IRF7 anti-viral regulatory circuit
- An IRF7 - microRNA-144 anti-viral regulatory circuit

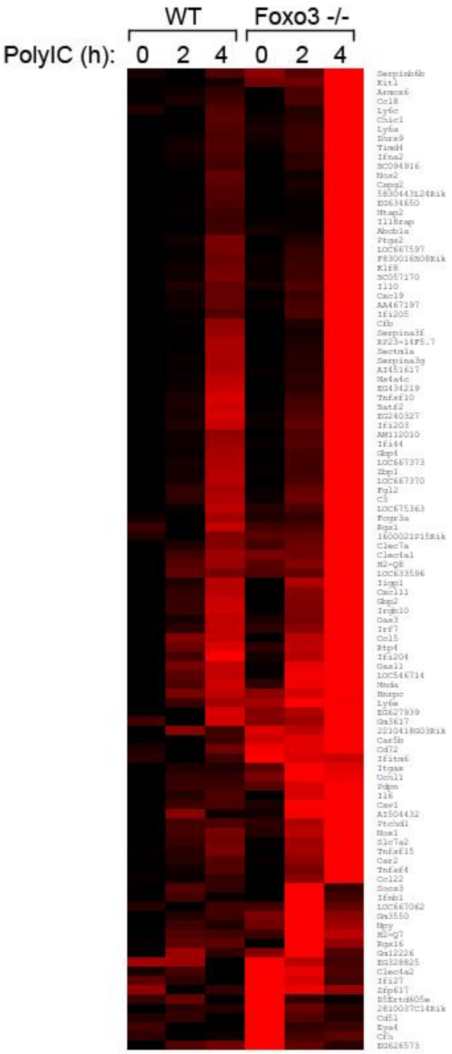
Predicting regulatory circuits controlling TLR-induced responses



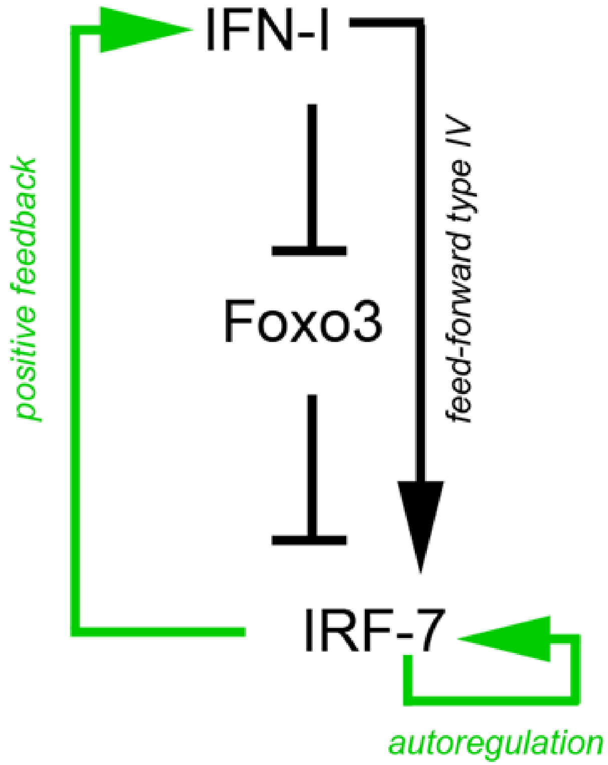




Further computational analysis suggested that Foxo3 is a negative regulator of a subset of PIC-induced genes



Foxo3 restrains the IFN-I/IRF7 positive feedback circuit



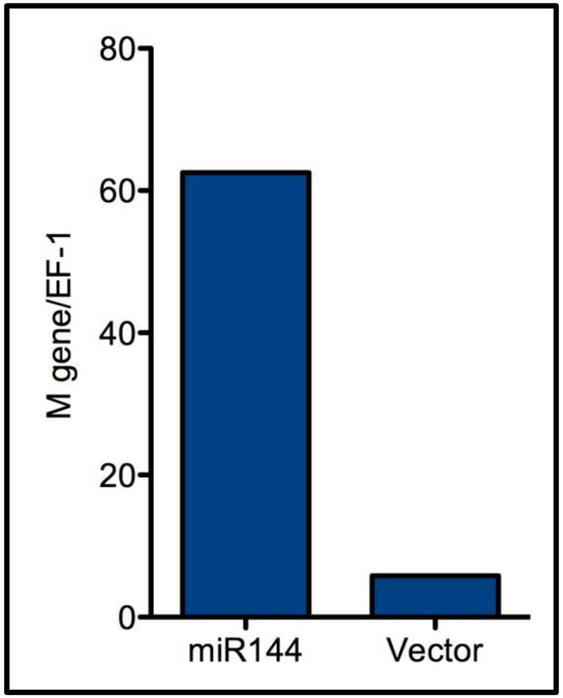
Litvak et al, Nature 2012

- Foxo3 keeps basal levels of IRF7 in check (prevents leakage and IRF7 auto-amplification)
- IFN-I represses Foxo3 thereby relieving restraint
- Dynamic interplay between IFN-I/Foxo3/IRF7 constrain rampant IFN-I production

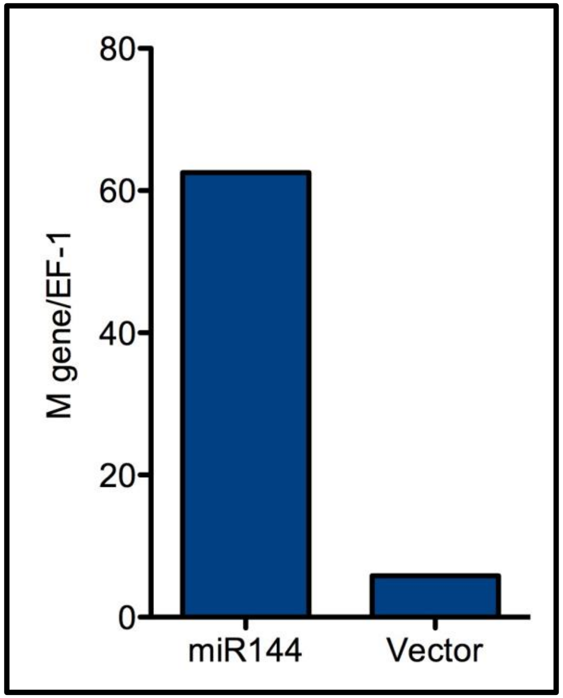
Regulation of the IRF7 pathway

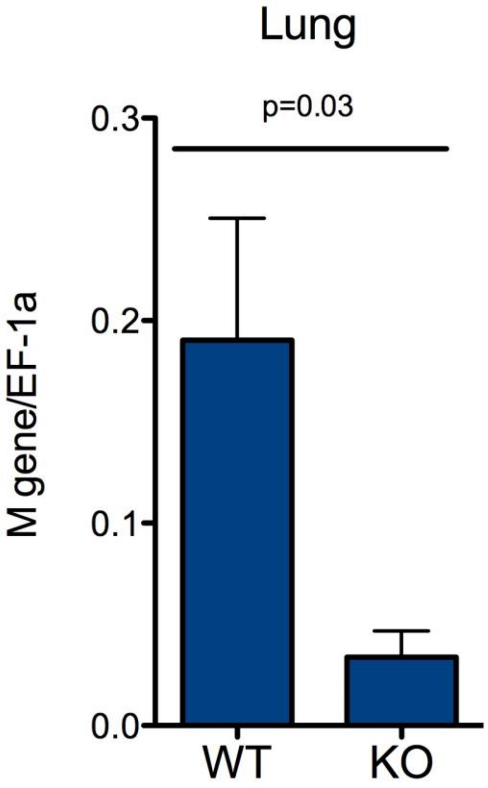
- A Foxo3 - IRF7 anti-viral regulatory circuit
- An IRF7 - microRNA-144 anti-viral regulatory circuit

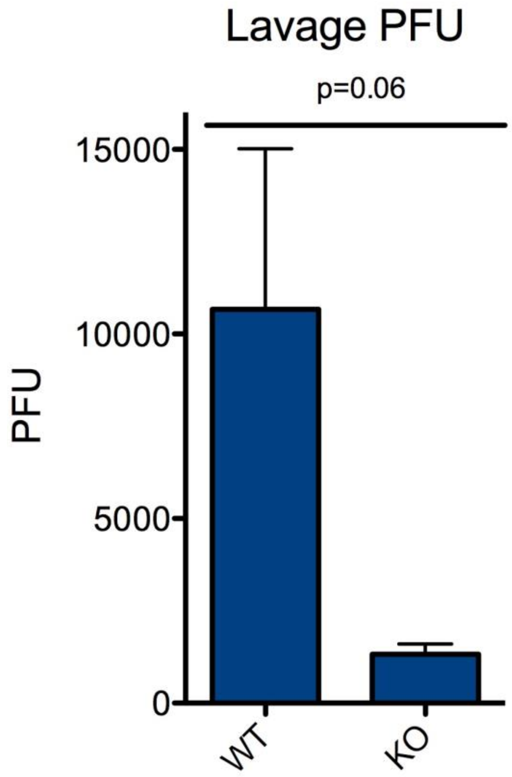
miR-144 Regulates Influenza Replication *in vivo*



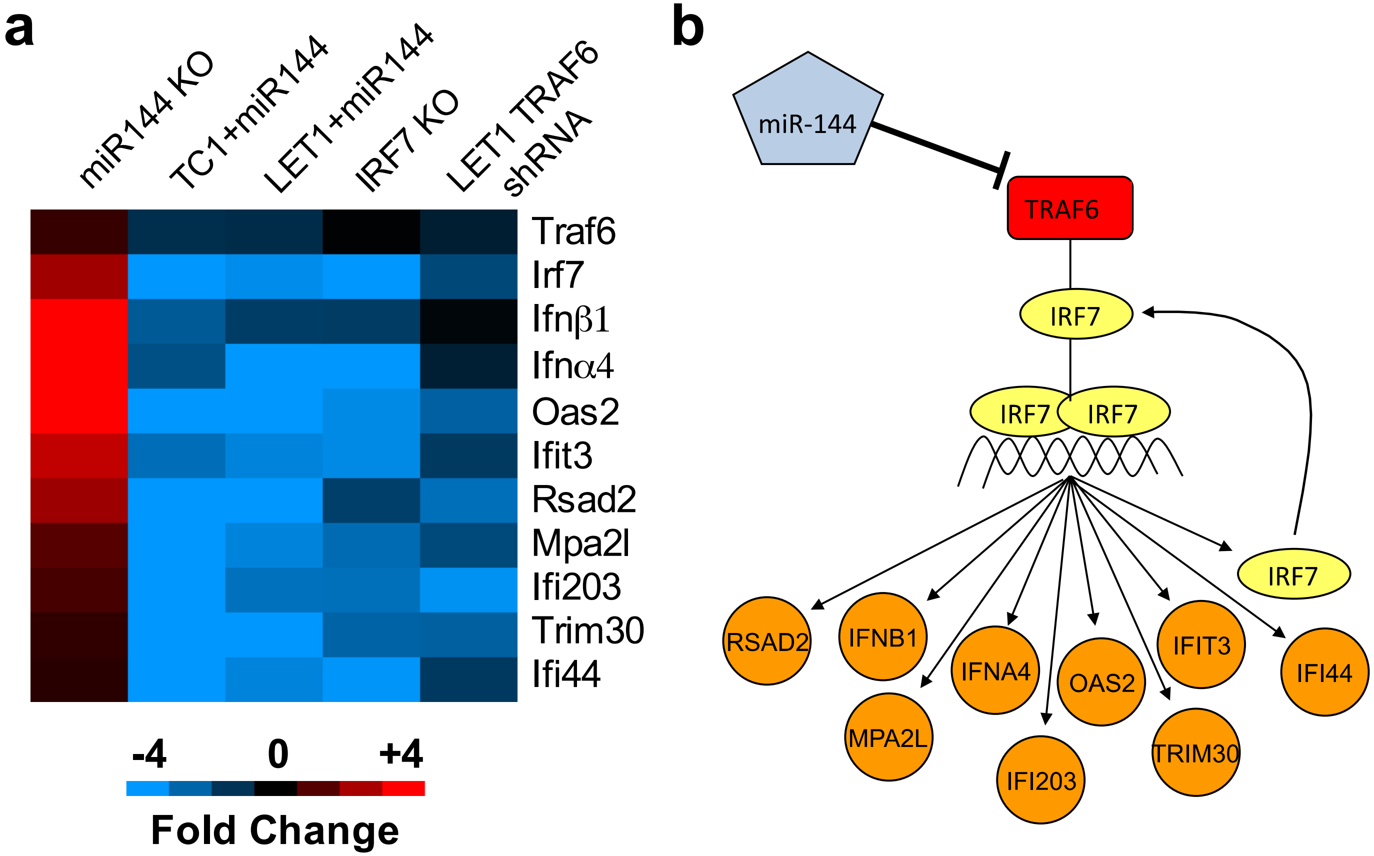
miR-144 Regulates Influenza Replication *in vivo*







Model for Regulation of a TRAF6-IRF7-Antiviral Gene Expression Network by miR-144

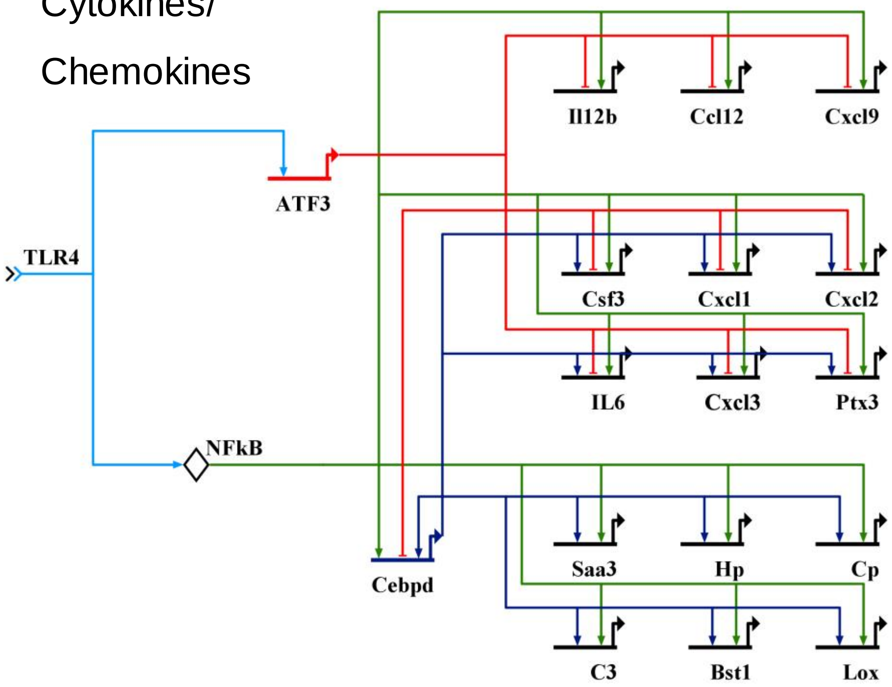


Reciprocal phenotypes in knockout and gain-of-function studies.

Characterization of an NFκB, CEBPδ, and ATF3 transcriptional sub-network that regulates cytokine production

Cytokines/

Chemokines



NFκB initiated/

ATF3 attenuated

NFκB initiated/

CEBPδ amplified/

ATF3 attenuated

NFκB initiated/

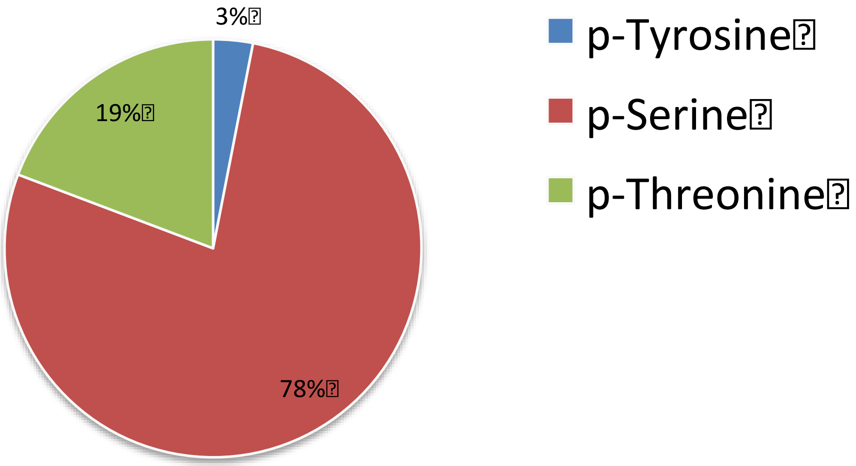
CEBPδ amplified

Gilchrist et al., Nature 2006
Litvak et al, Nature Immunology 2009

Cellular Signaling Networks

Benchmarking phospho-peptide identification

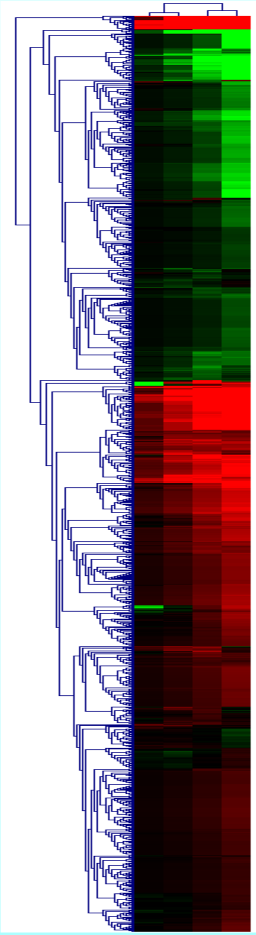
BMDM stimulated for 15 min with LPS
14,499 p-Sites in 4250 proteins

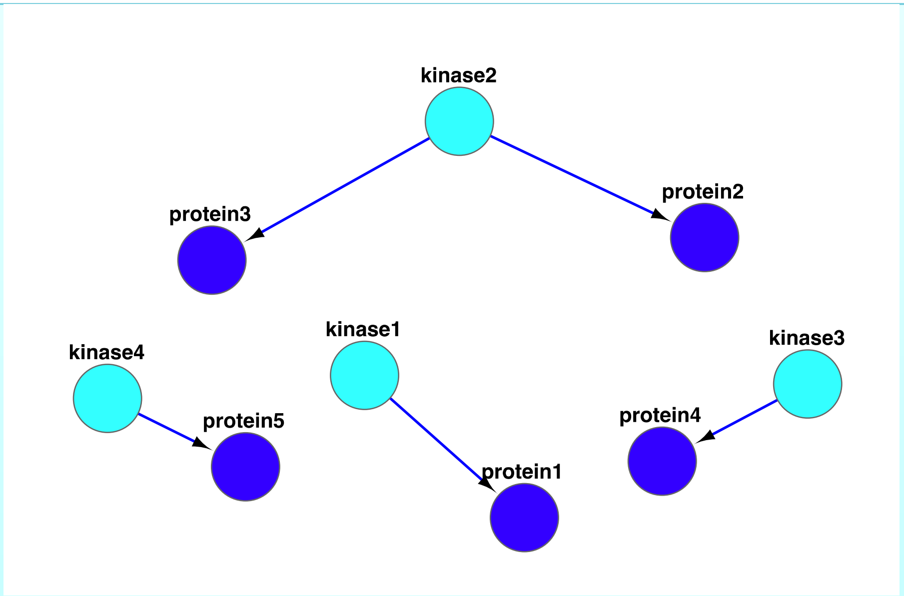


7,000 of the phospho-sites have
not been reported before

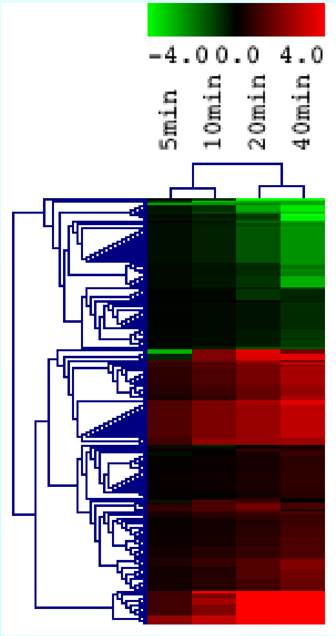
Inferring kinase networks

phosphorylation



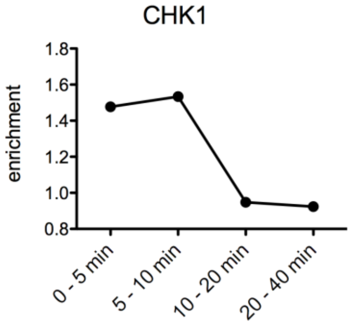


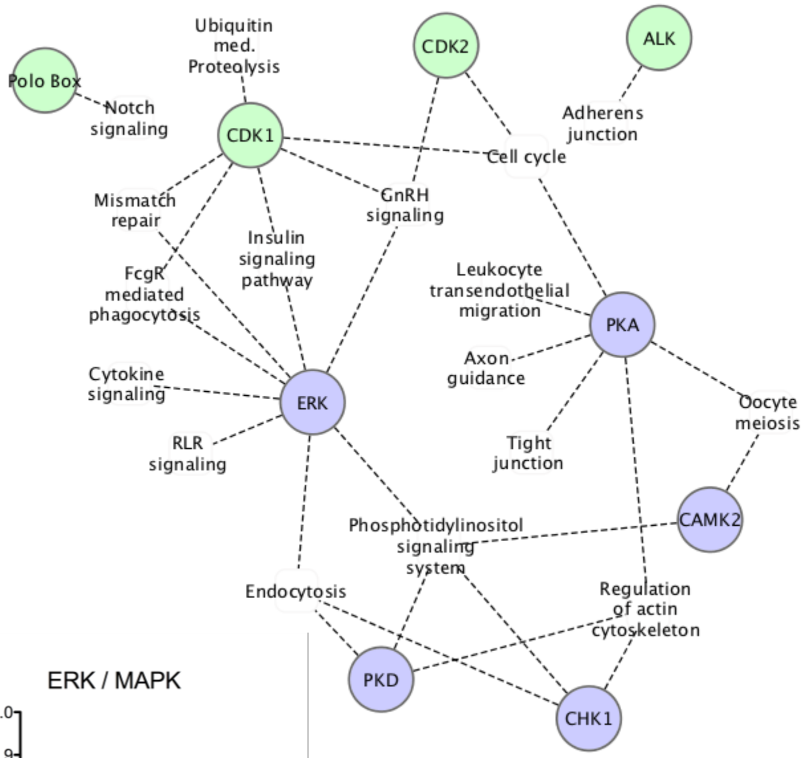
kinase activity

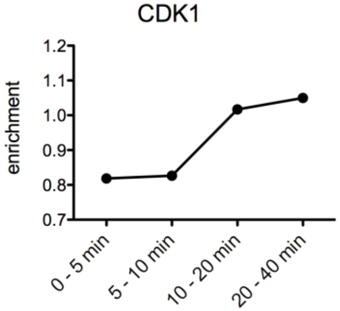


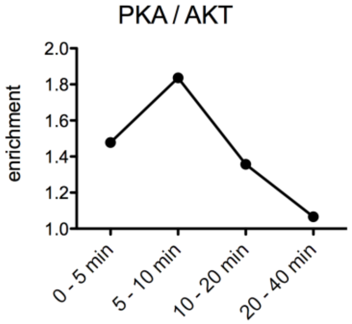
Infer kinase activity using protein-protein interaction data, phosphorylation motifs, and phosphorylation data

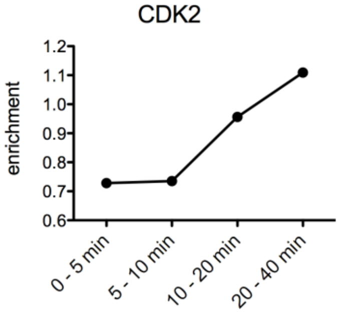
Unbiased prediction of kinase-regulated cellular functions from global phosphorylation measurements

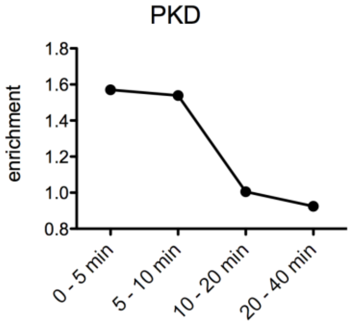

CHK1

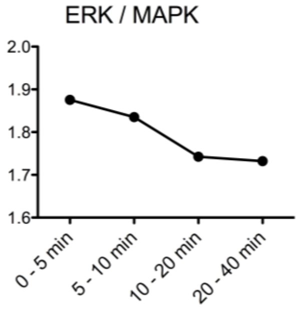


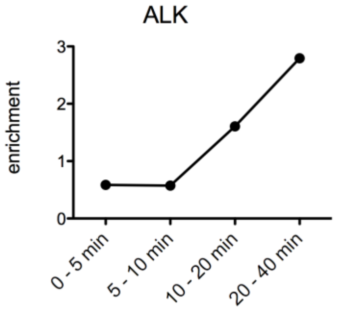

CDK1


PKA / AKT


CDK2


PKD

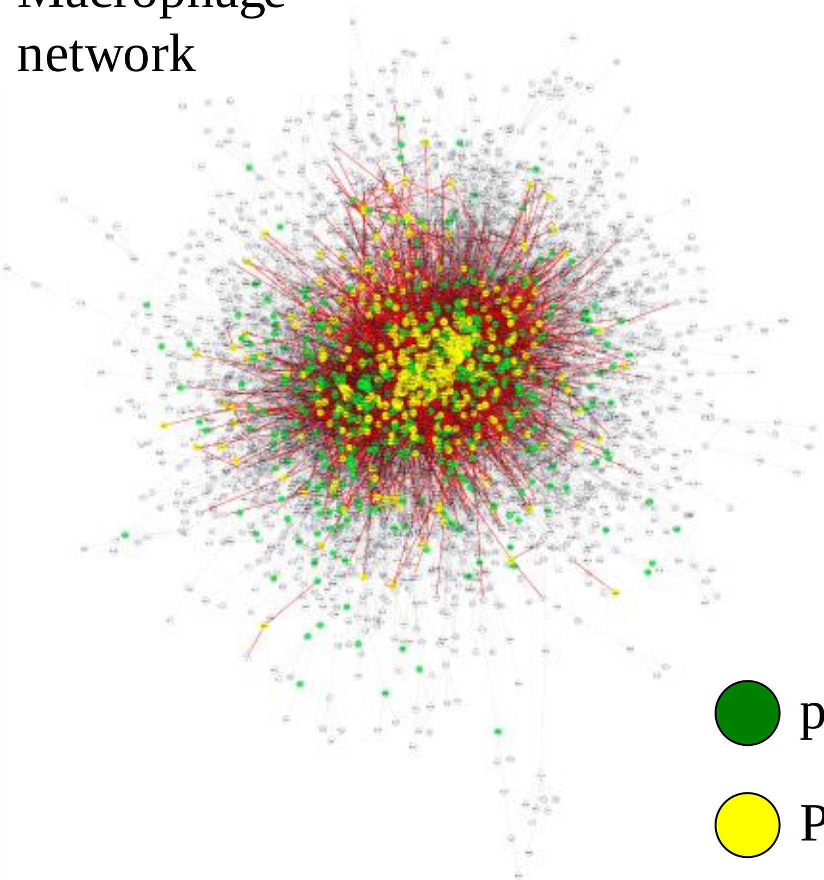

ERK / MAPK

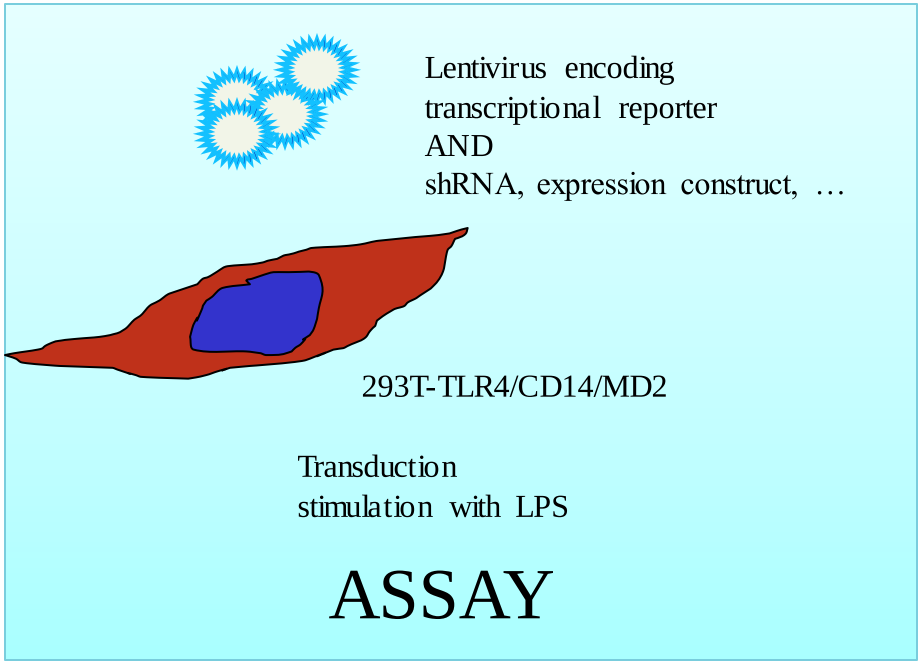

ALK

● motifs enriched early
● motifs enriched late

High throughput analysis of phosphorylation events in TLR mediated transcription

Macrophage network





Lentivirus encoding transcriptional reporter
AND
shRNA, expression construct, …

293T-TLR4/CD14/MD2

Transduction
stimulation with LPS

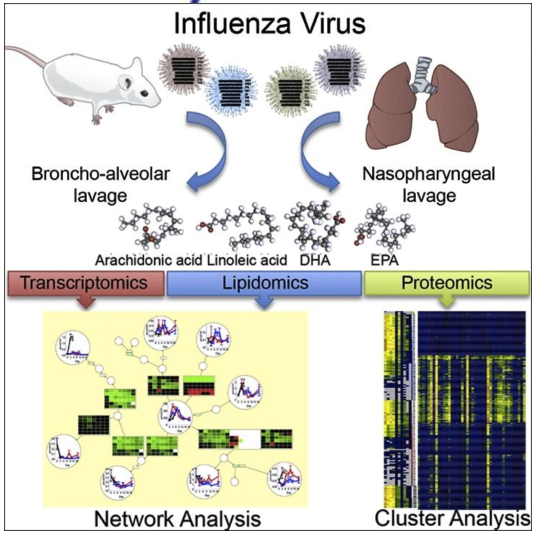
ASSAY

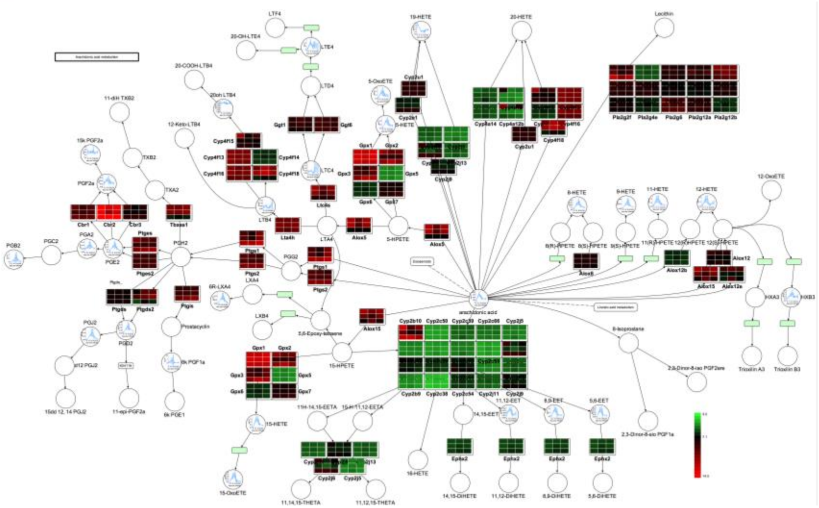
🟢 phosphorylation detected by MS

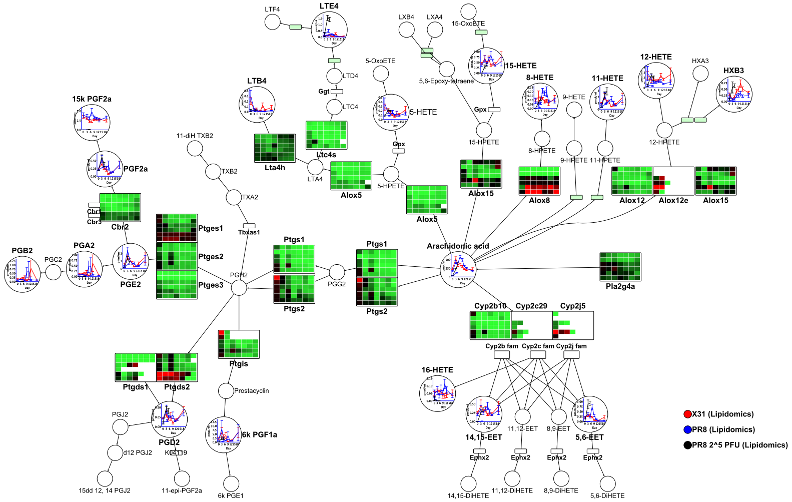
🟡 Proteins with kinase activity

Zak and Aderem, Nat. Biotech., 2009

Lipidomic profiling of Influenza Infected lungs Identifies a network of lipid mediators that induce/resolve Inflammation

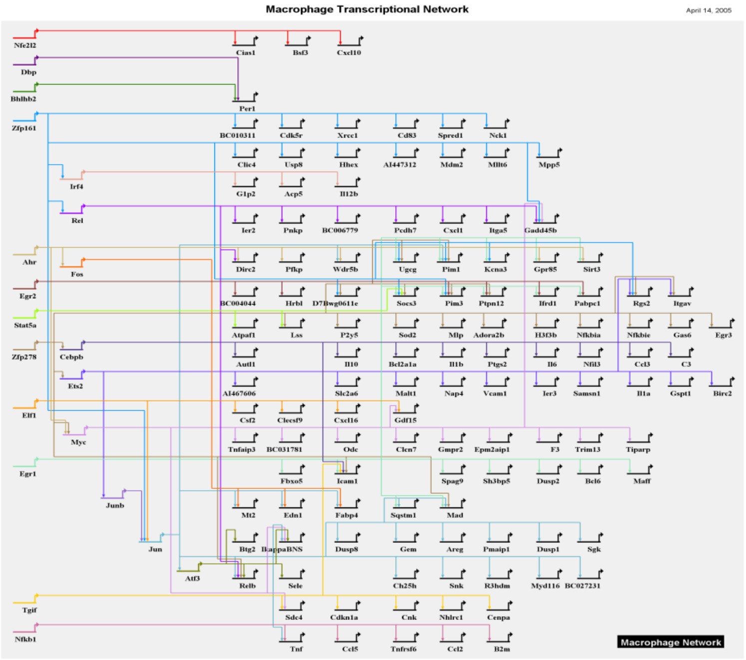


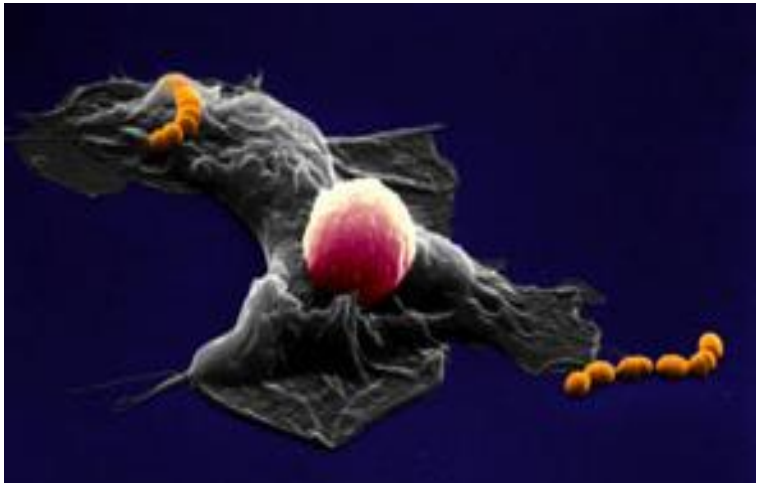


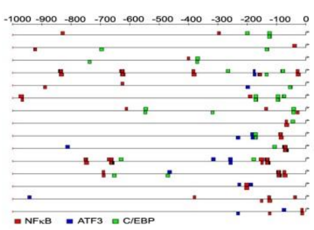


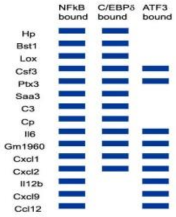
Tam et al, Cell, 2013

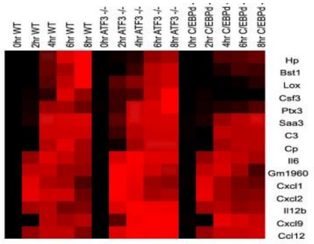
Transcriptional networks leading to dendritic cell activation



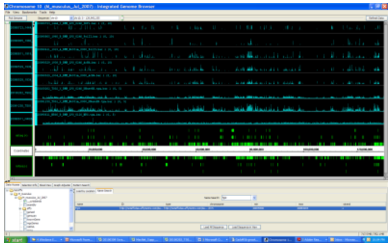




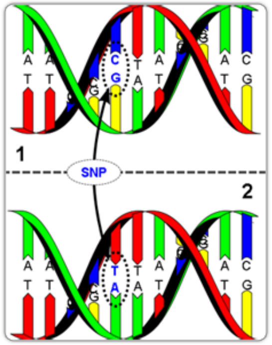




Motif scanning ChIP Transcripomics

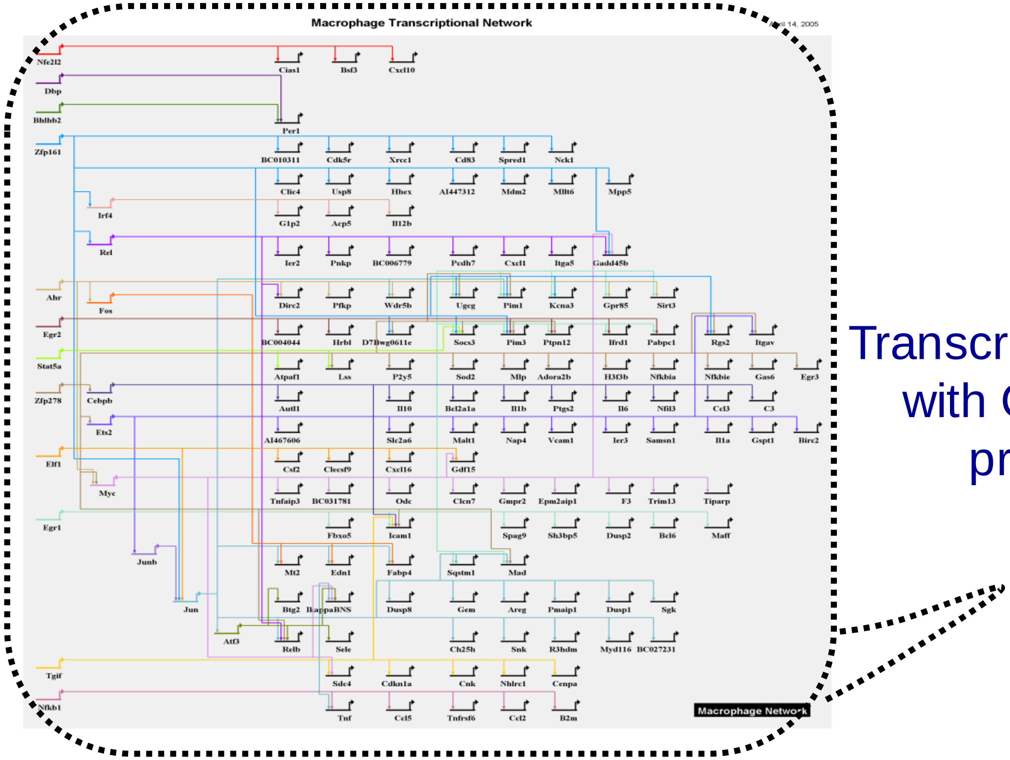


epigenetic profiling



genotyping

Signaling and regulatory networks within Dendritic cells that instruct Th1 responses



Transcriptome and miRNA profiling combined with ChIP-seq, phospho-proteomics and protein-protein interaction network

Task: Reengineer the innate immune networks within dendritic cells so that they shape an appropriate adaptive immune response

Application of systems biology to rational vaccine design

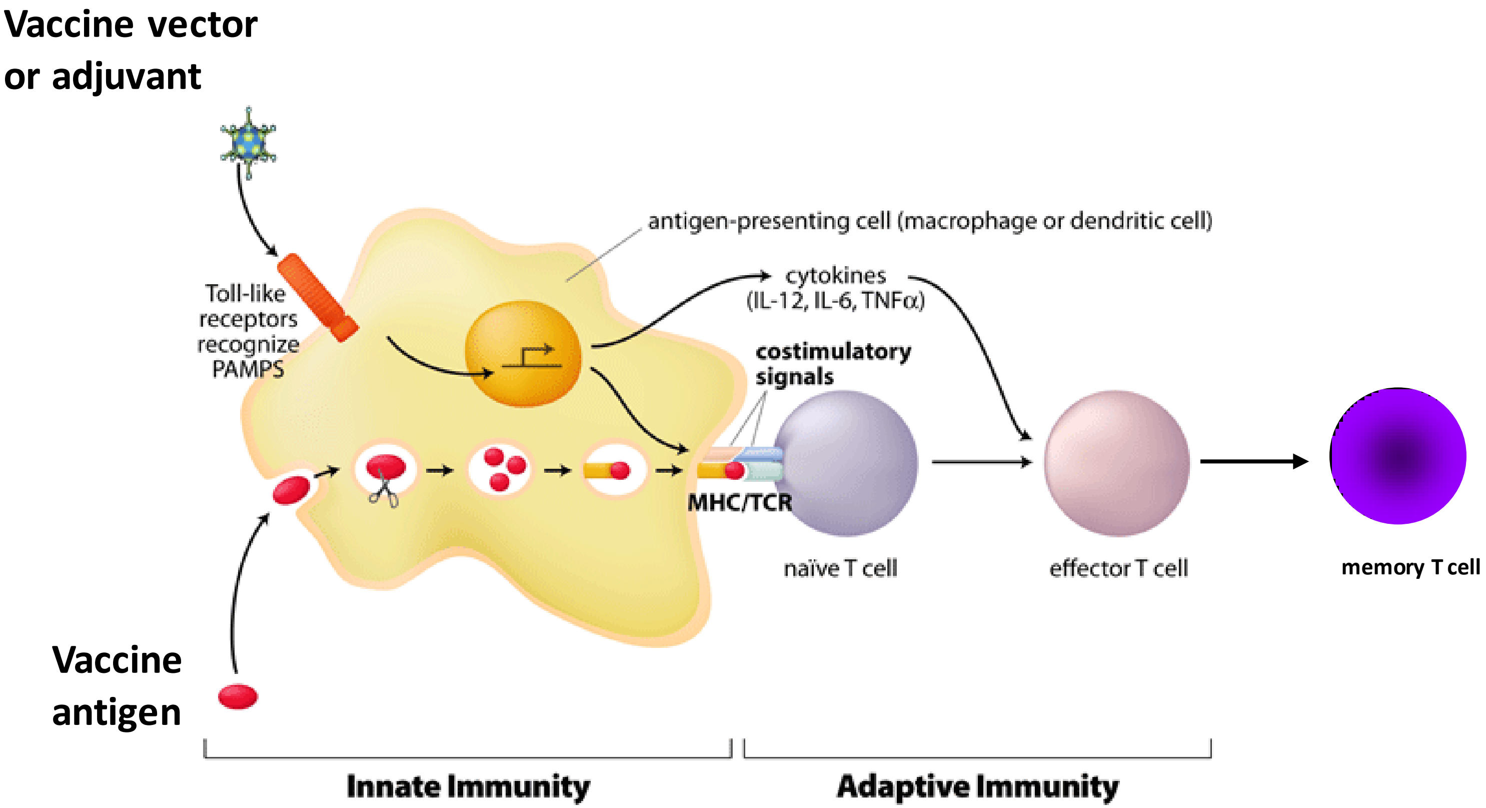
- Identify signatures of vaccine immunogenicity and protection

- To evaluate vaccine trials

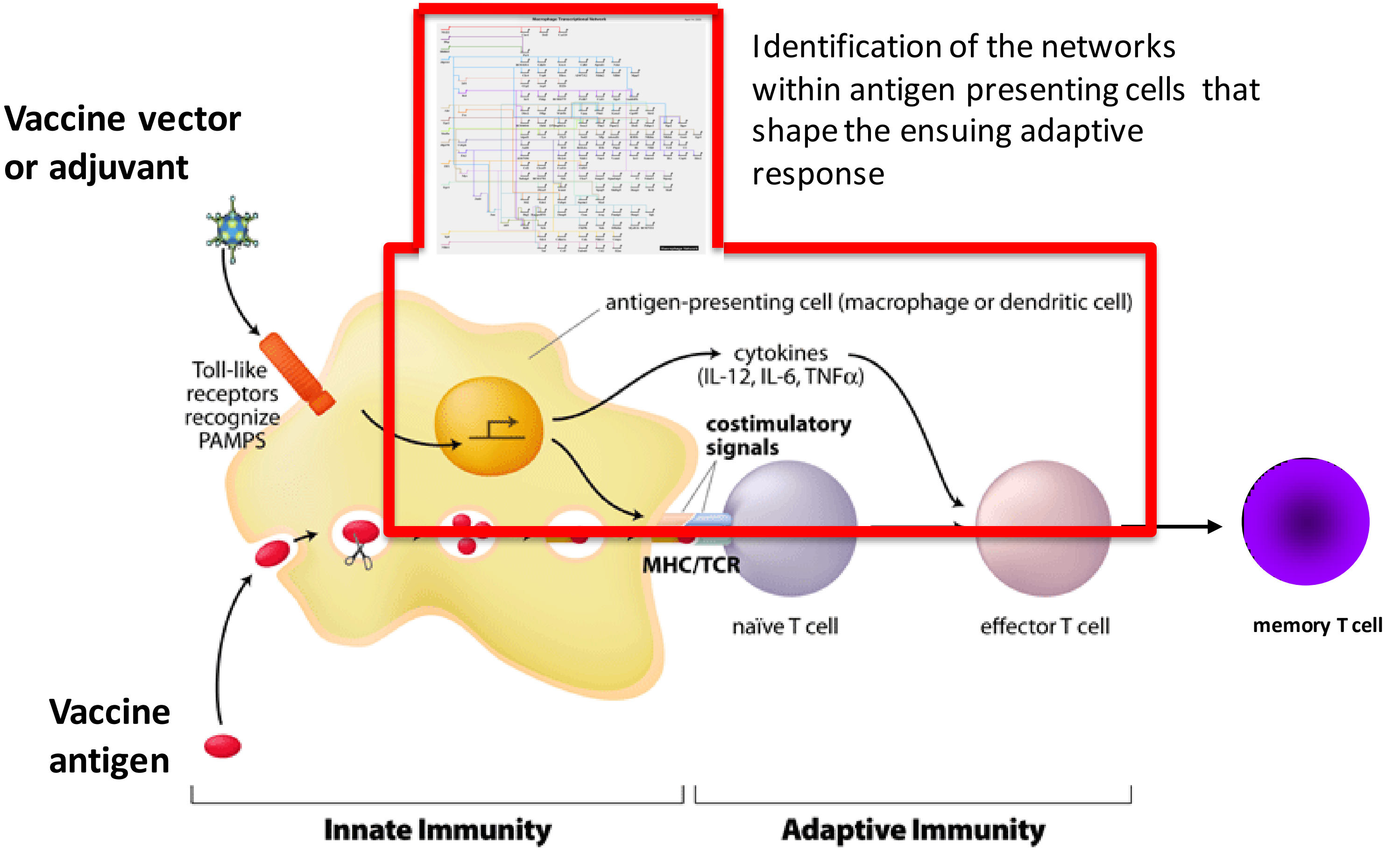
- To understand the molecular networks leading to a protective response

→ To reprogram the immune response to favor protection

Innate immune responses shape the quantity, quality and longevity of the adaptive response

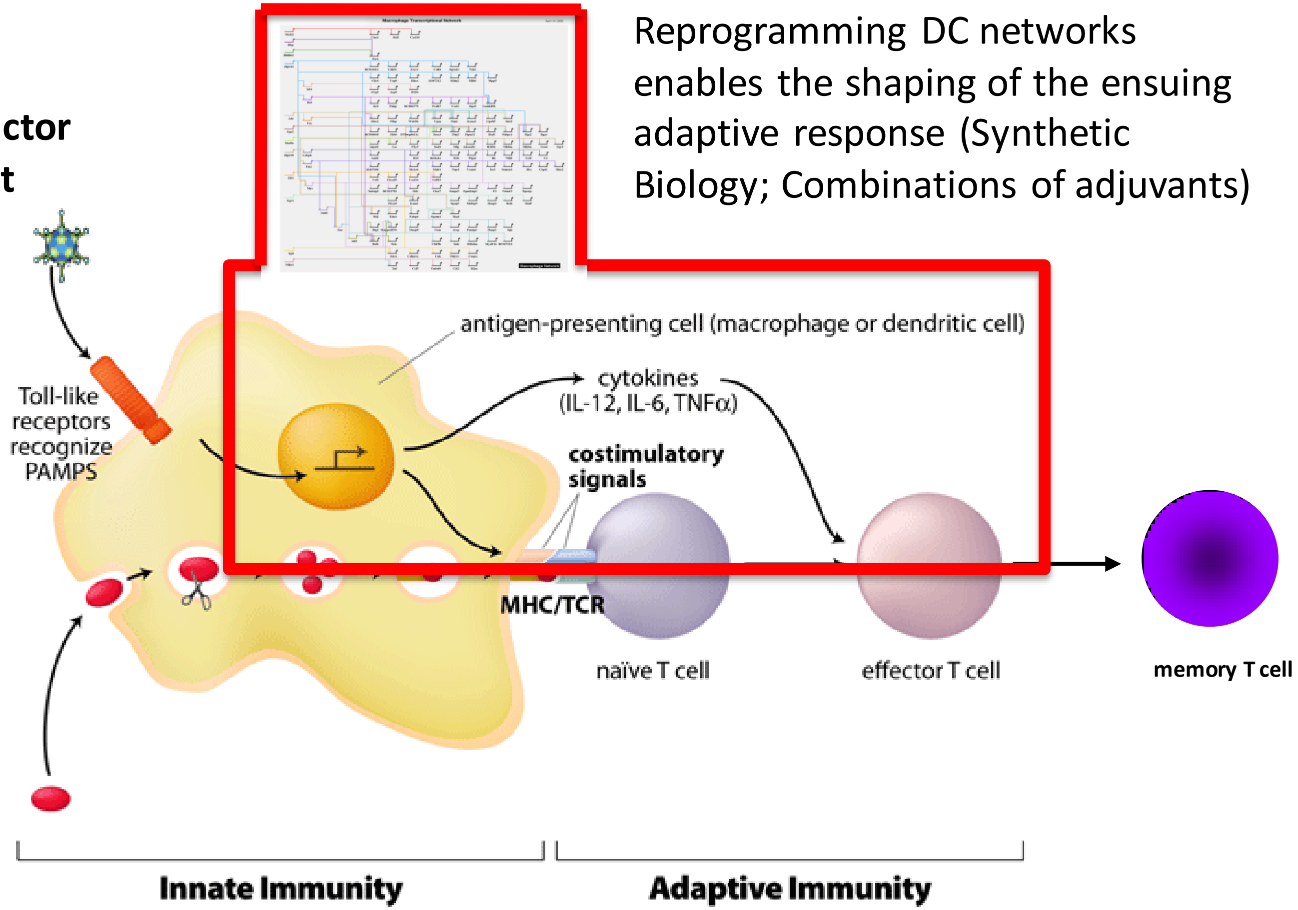


Innate immune responses shape the quantity, quality and longevity of the adaptive response



Identification of the networks within antigen presenting cells that shape the ensuing adaptive response

Innate immune responses shape the quantity, quality and longevity of the adaptive response



Reprogramming DC networks enables the shaping of the ensuing adaptive response (Synthetic Biology; Combinations of adjuvants)

Vaccine vector or adjuvant

Toll-like receptors recognize PAMPS

antigen-presenting cell (macrophage or dendritic cell)

cytokines (IL-12, IL-6, TNFα)

costimulatory signals

MHC/TCR

naïve T cell

effector T cell

memory T cell

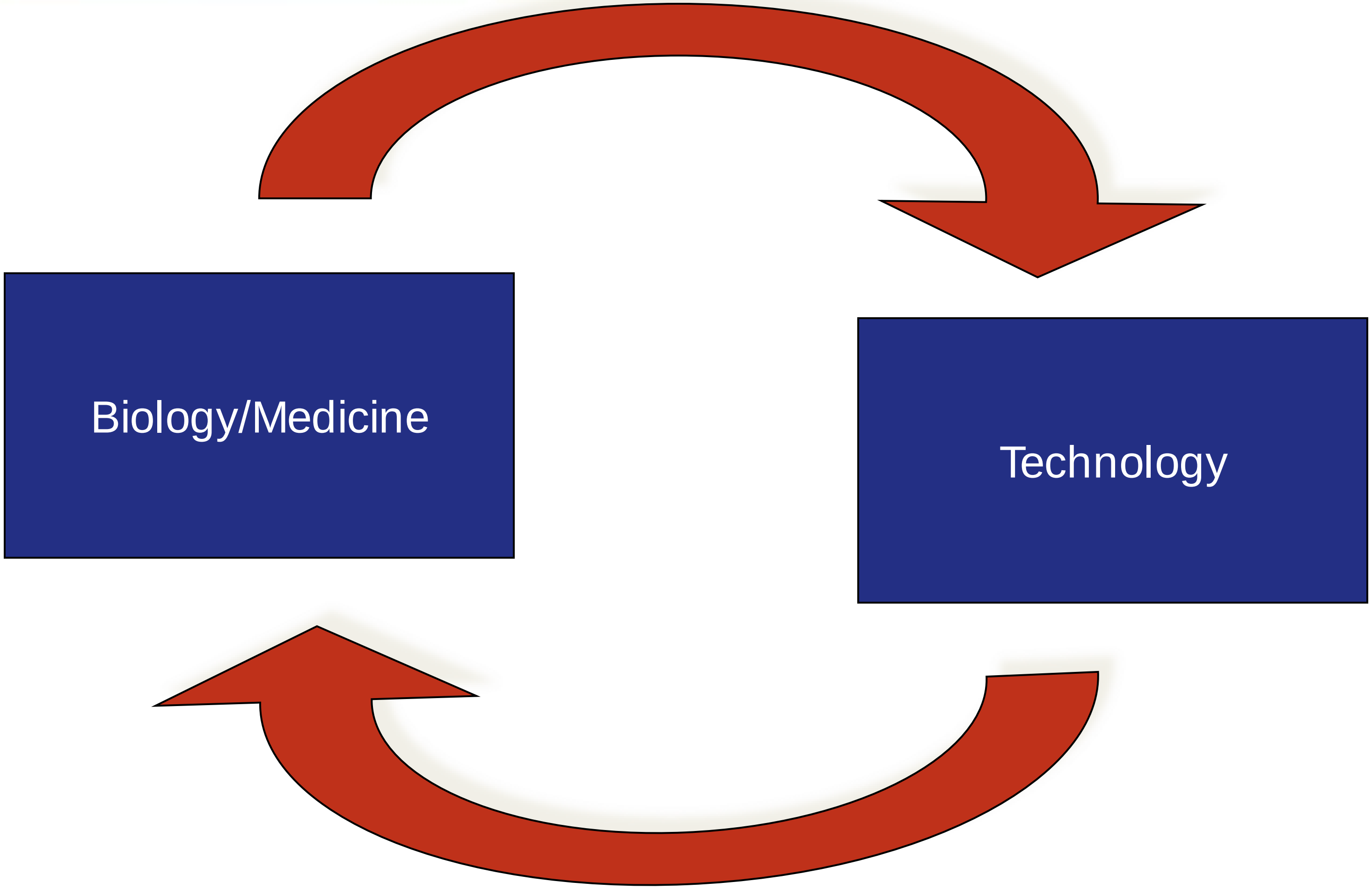
Vaccine antigen

Innate Immunity

Adaptive Immunity

Rappuoli and Aderem, Nature 2012

The Systems Biology Paradigm

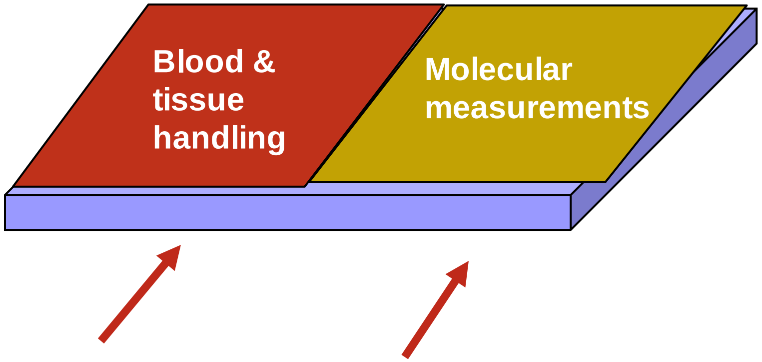


Biology/Medicine

Technology

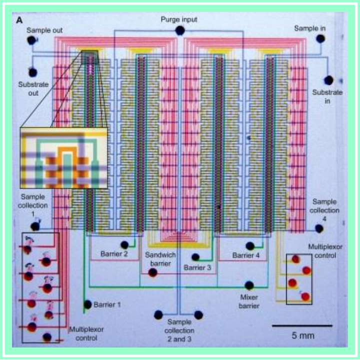
Biology dictates what new technology should be developed; technology opens new frontiers in biology for exploration.

Measurement of molecular pathways and signatures in rare cells

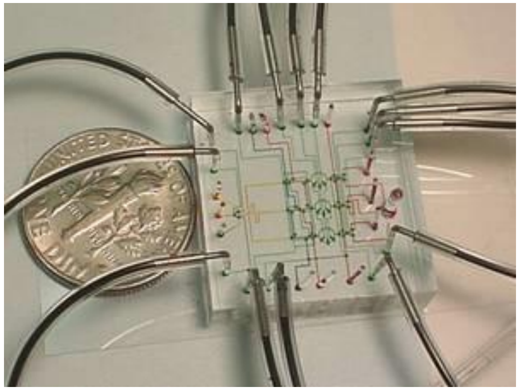


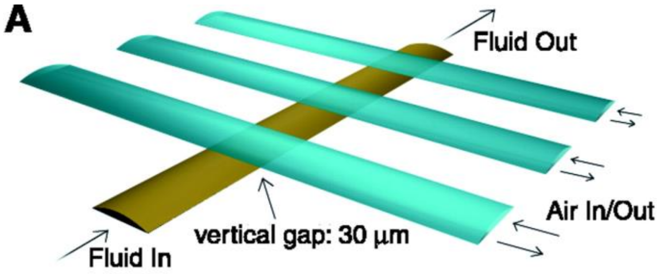
Blood & tissue handling

Molecular measurements



With Steve Quake





- Molecular signatures will define:
- The nature of the pathogen
- The nature of the host response
- Correlates of Immunity

The diagnostic device will be:

- Portable
- Inexpensive
- Data obtained in real time
- Use cell phones to communicate with central computers

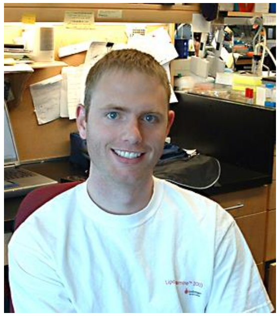
Dan Zak

Mark Gilchrist

Steve Ramsey

Katy Kennedy

Carrie Rosenberger



Rich Rogers

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Lynn Amon
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Xuguang Hu
Carrie Johnson
Rebecca Podyminogin
Garnet Navarro

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

Willem Hanekom
Thomas Scriba
Adam Penn-Nicholson

OREGON HEALTH & SCIENCE UNIVERSITY

Louis Picker
Haesun Park
Scott Hansen

FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

Julie McElrath

Erica AndersenNissen
Mingchao Shen
Greg Spies

NATIONAL INSTITUTES OF HEALTH

Bob Seder

BILL & MELINDA GATES foundation

CAVD the collaboration for AIDS vaccine discovery

NATIONAL INSTITUTES OF HEALTH