Vaccinomics:
A Tool for Personalized Vaccinology

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Disclosures

- None related to work presented

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Historical Vaccine Development
Vaccinology 1.0

Isolate → Inactivate → Inject

Smallpox
Polio
Rabies
Diphtheria
Tetanus
Anthrax
Cholera
Typhoid

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Vaccinology 2.0 1940's – 2000's

- Prophylactic only
- Childhood vaccines >>>> Adult vaccines
- Parenteral vaccines dominate (except FluMist/oral typhoid/oral shigella)
- Very few licensed adjuvants
- One "size" fits all approach
- Everybody at risk for everything so give everyone everything
- Predicated on a population-level, public health approach

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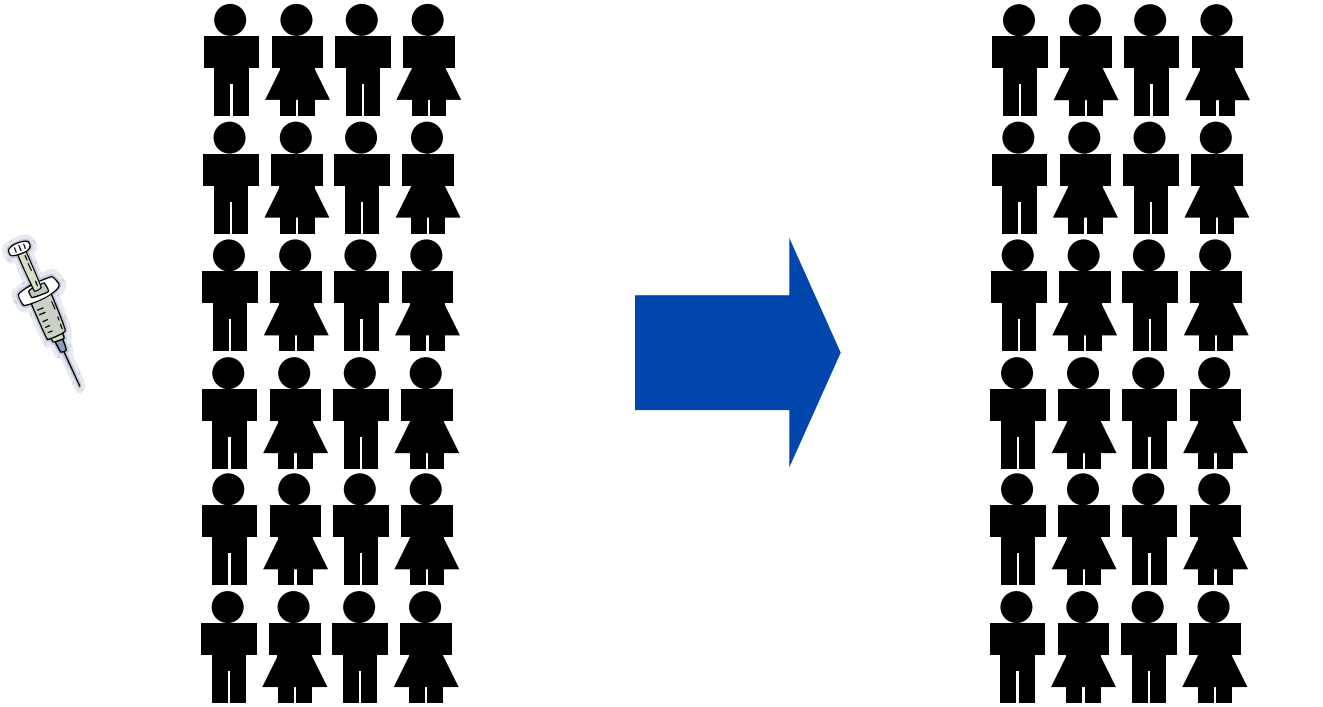
Current Vaccine Approach



Single vaccine administered to everyone

Everyone is protected

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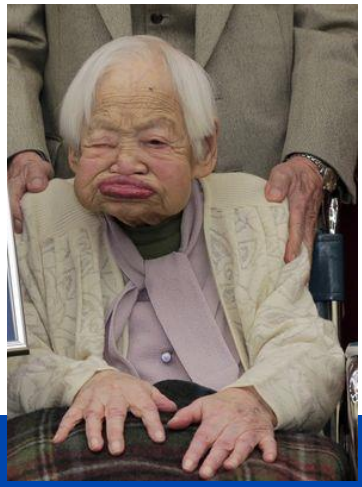
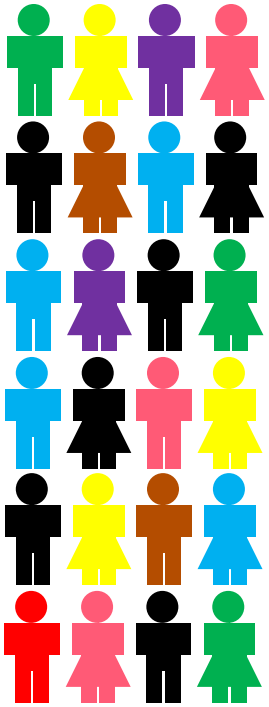
Does This Approach Make Sense?

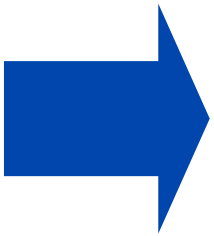


Pictures courtesy of: www.pinterest.com, www.dailymail.co.uk, www.doubletroublerunning.com, www.telegraph.co.uk, www.usatoday.com, www.lxedit.com, www.huffingtonpost.co.uk,

Vaccine Reality

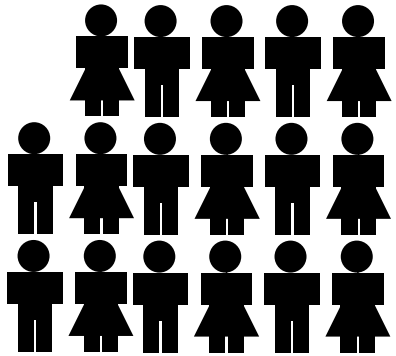


Single vaccine administered to everyone

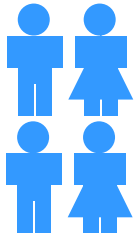


Robust, long-lived immunity

Insufficient immunity



Protective immunity



Short-lived immunity

No immune response

Adverse reaction

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Inter-individual variability in vaccine response

- 900 healthy school children from Olmsted County, MN
- All immunized with 1 dose of MMR-II
- No circulating measles in the community during their lifetimes – antibody response due to vaccine, NOT infection

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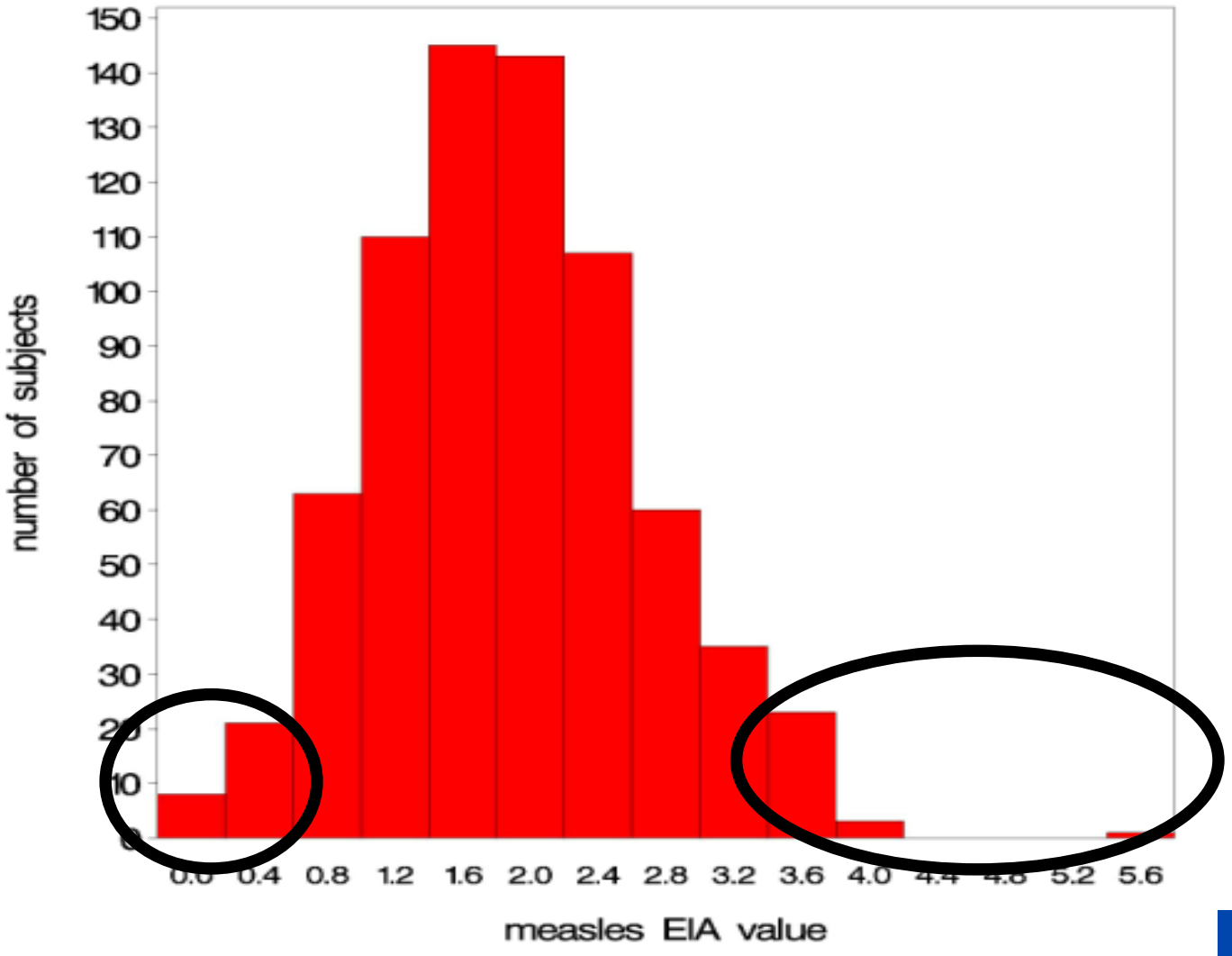
MMR Vaccine
Measles IgG Antibody Responses



Inter-individual variability in vaccine response

- 1,076 military personnel (from all over the US)
- All immunized with 1 dose of Dryvax
- Smallpox eradicated since 1980, no personnel involved in any recent poxvirus outbreak – antibody response is due to vaccine, NOT infection

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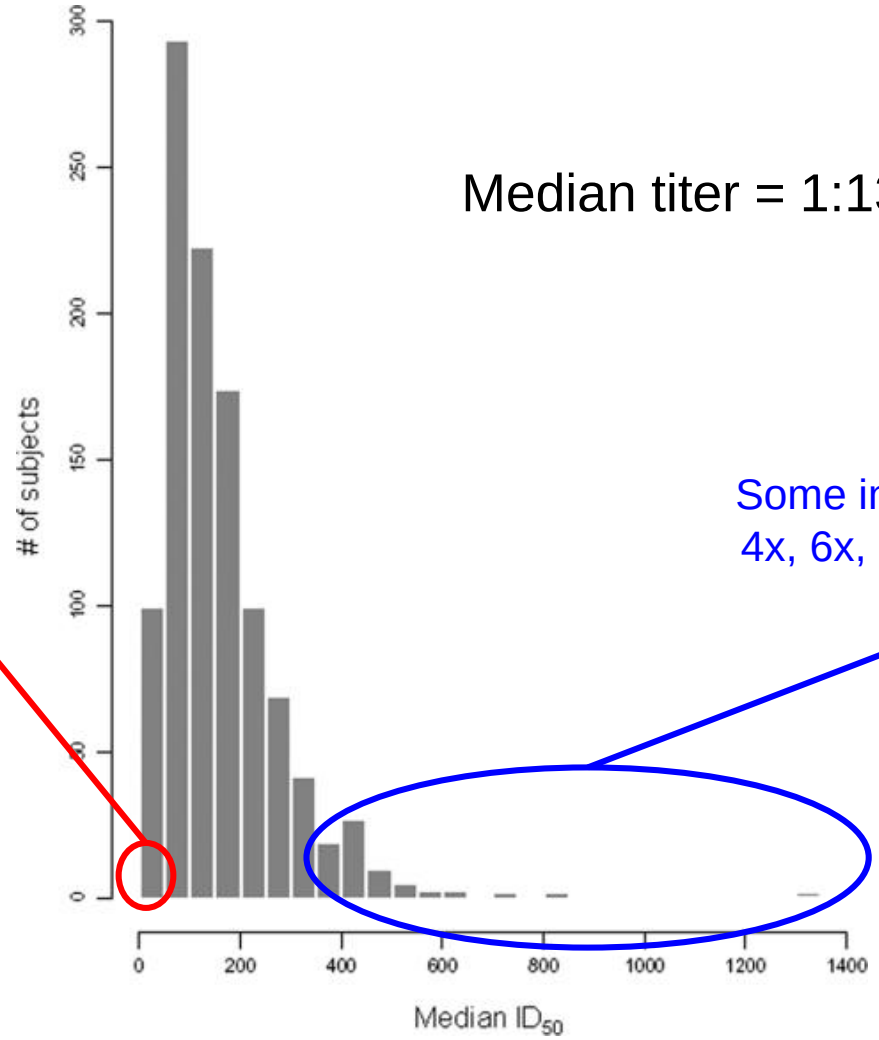
Smallpox Vaccine Neutralizing Antibody Responses

Median titer = 1:130

19/1,076 subjects with suboptimal titers

Some individuals have a titer 4x, 6x, even 10x the median titer



Kennedy et. al. Clin Vaccine Immunol 16(8):1105-1112. 2009.

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Why do people respond differently?

Vaccine Factors	Pathogen Factors	Host Factors
Lack of cold chain	Exposure level	Genetics
Past expiration date	Antigenic drift	Race/Ethnicity
Improper administration	Antigenic shift	Sex
Insufficient # of doses	Different epitopes	Age
Incorrect dose	Different serotypes	Immunosenescence
	Different organisms	Maternal Ab
		Concurrent infection
		Health
		Nutritional status
		Microbiome
		Environmental stress
		Waning immunity

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Personalized Vaccinology

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Personalized Vaccinology

- Individual (e.g. cancer vaccines)
- Sex
  - Why do females develop arthritis after rubella vaccine, but not males?
  - Why, *for all vaccines studied*, do females have better humoral immune responses than males?
- Race/Ethnic groups
- Sub-populations with specific genetic polymorphisms
- Sub-populations with specific diseases or immune states

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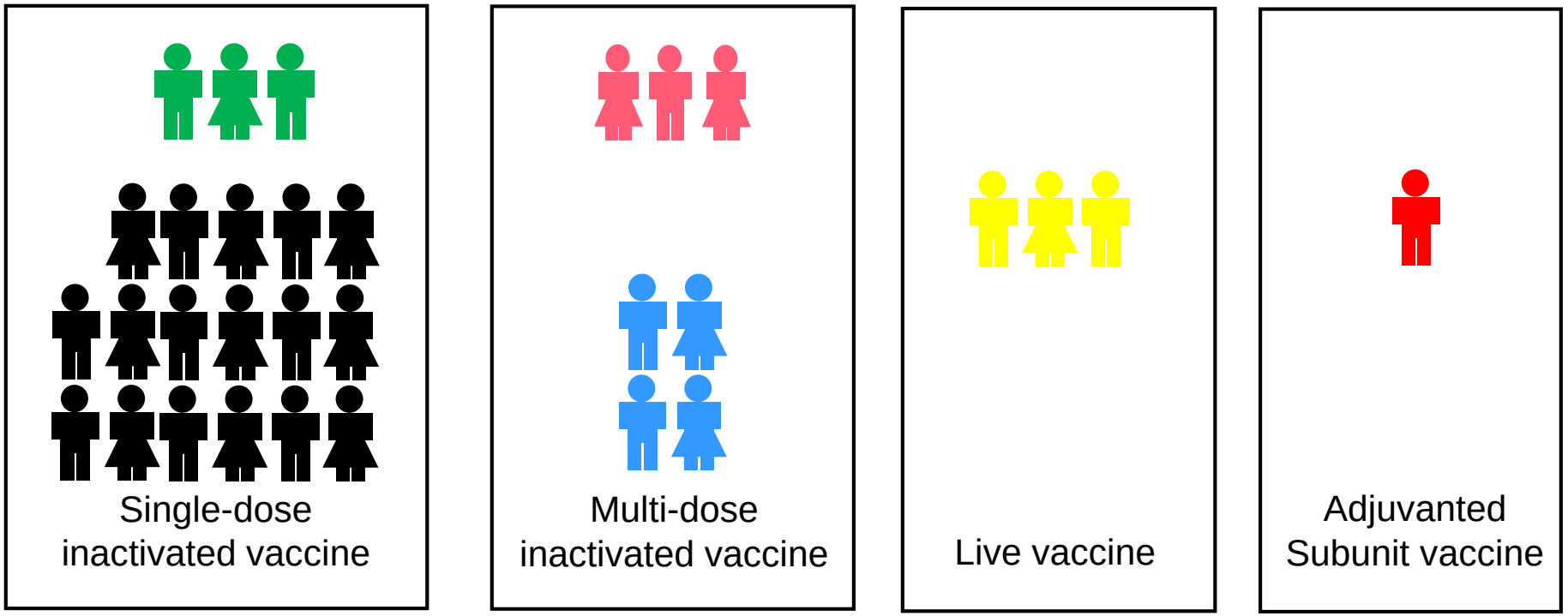
Personalized Vaccinology



Protective Immunity

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Personalized Vaccinology

Is this realistic? Is this feasible?

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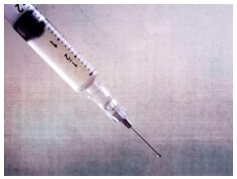
Influenza Vaccines

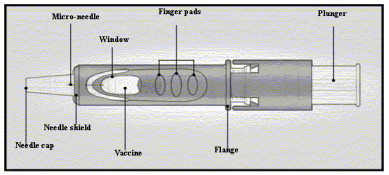


IIV
Quadrivalent inactivated

> 6 months

HD-IIV
High dose TIV for the elderly

>65 yrs



ID-IIV
Intradermal TIV

18 – 64 yrs

LAIV
Cold-adapted live attenuated intranasal spray

2-49 yrs

Non-egg based flu vaccines

RIV
Recombinant subunit

18-49 yrs

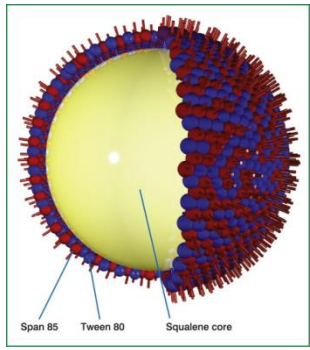
ccIIV
Cell culture

≥18 yrs

Adjuvanted vaccine

Fluad®
MF59 adjuvant

≥65 yrs



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Perspectives in Vaccinology 1(1):89-113. 2011

SARS-CoV-2 Vaccines

COVID19 VACCINE TRACKER

Vaccine platforms designed to train our immune system

TYPES OF COMPONENT VIRAL VACCINES

Protein Subunit
Contains isolated and purified viral proteins

Virus-like particles (VLP)
Contains viral proteins that mimic the structure of the virus, but no genetic material

DNA-based
Contains viral genetic material (such as mRNA) which provides the instructions for making viral proteins

RNA-based

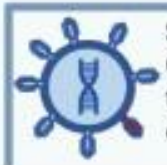
Non-Replicating Viral Vector
Contains viral genetic material packaged inside another harmless virus that **cannot** copy itself

Replicating Viral Vector
Contains viral genetic material packaged inside another harmless virus that **can** copy itself

TYPES OF WHOLE VIRUS VACCINES

Inactivated
Contains copies of the virus that have been killed (inactivated)

Live-Attenuated
Contains copies of the virus that have been weakened (attenuated)



SARS-CoV-2 is the virus that causes COVID-19. The **spike protein** on the surface of SARS-CoV-2 is an example of an antigen.

Vaccines are the best way to train our immune system to recognize viruses, or pieces of viruses, called **antigens.** Our immune system creates **antibodies** and other defenses to protect us.

When a vaccinated person is exposed to **SARS-CoV-2**, their immune system will recognize the viral antigens and spring into action to keep them healthy. There are many different types of vaccines, as shown above.

https://covid19.trackvaccines.org/types-of-vaccines/

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Vaccinomics / Systems Vaccinology

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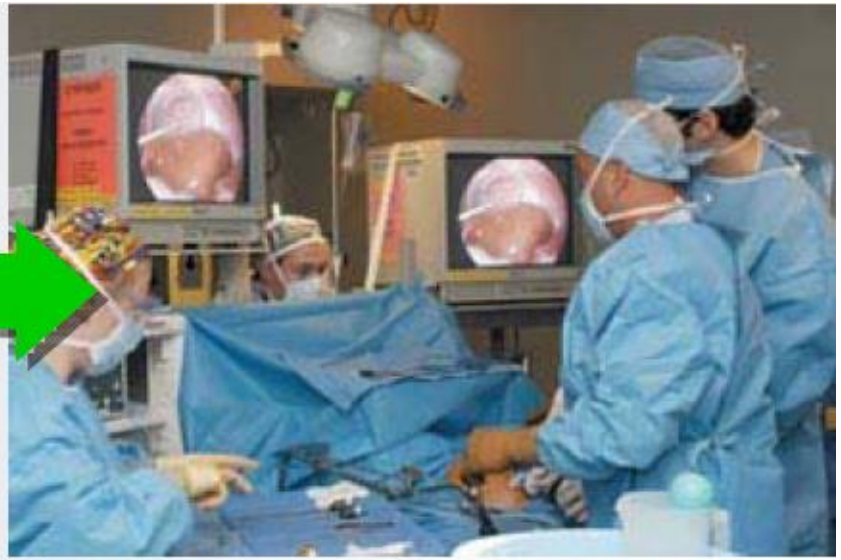
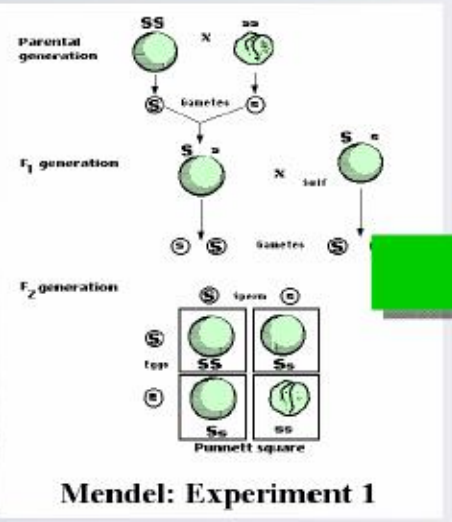
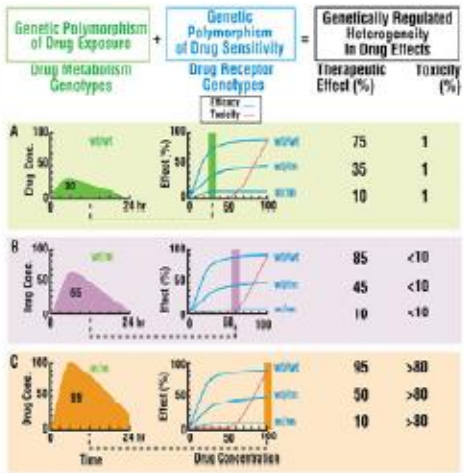
Scientific Advancements







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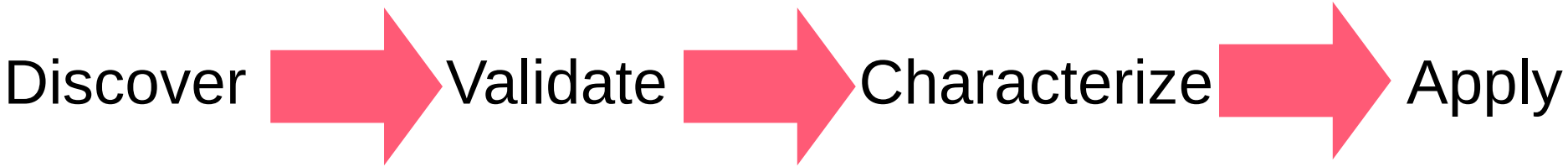
Vaccinology 3.0

- Vaccinology 3.0
  - Vaccinomics/system biology approaches
  - Advanced adjuvants/antigen packaging (nanoparticles)
  - New vaccines for specific subgroups (genetic, other)
  - **Personalized vaccinology – Precision vaccinology**



Poland GA, et al. Seminars in Immunology 2013

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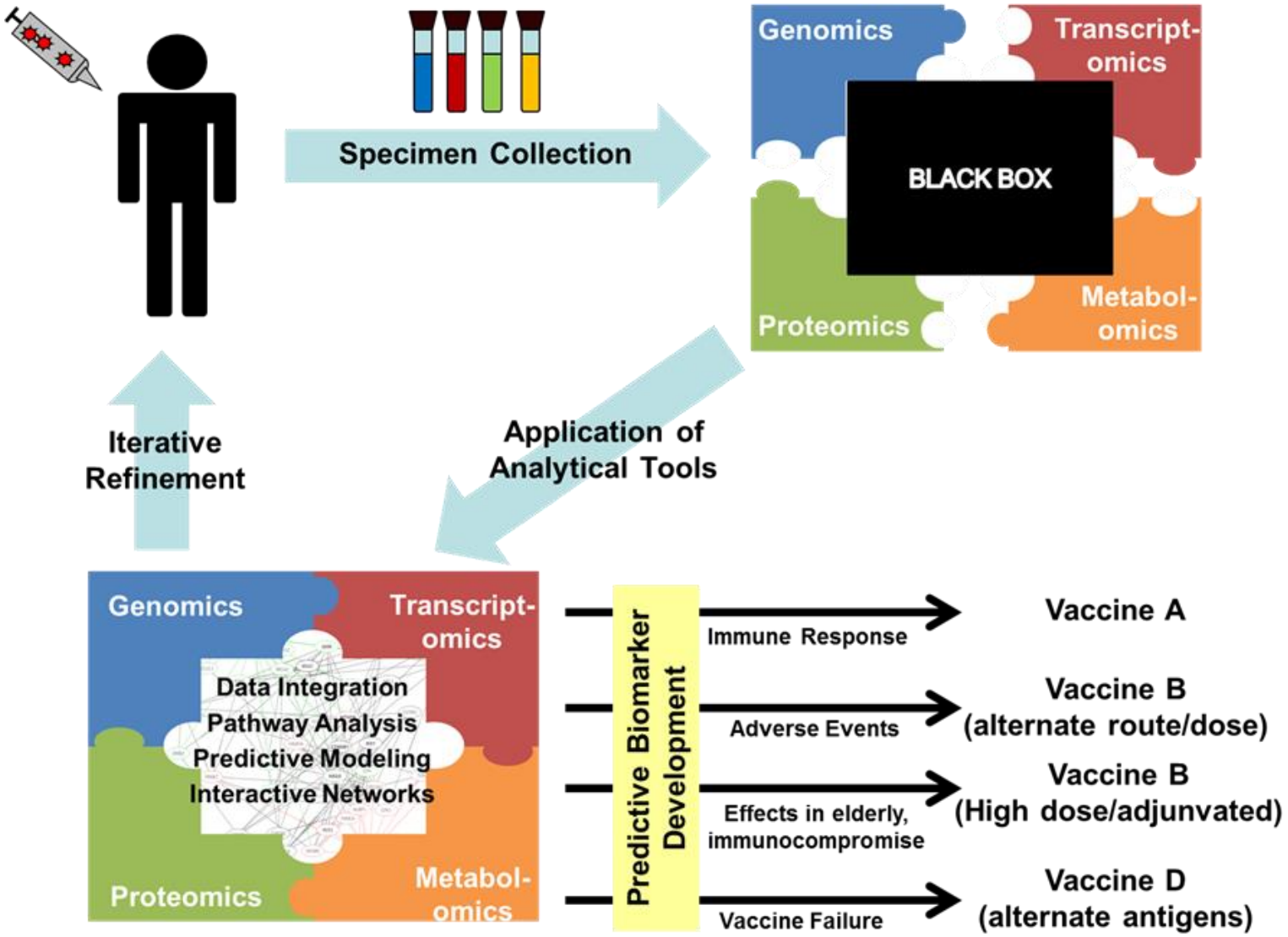
Vaccinomics



Poland GA, et al. Seminars in Immunology 2013.

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Vaccine Research Group – Current Projects

- **Immunogenetics studies**
  - Measles, Mumps, Rubella, Smallpox
- **Immunosenescence studies**
  - Influenza, Herpes Zoster
- **Systems biology studies**
  - Measles, Mumps, Rubella, Influenza
- **Mechanisms of vaccine failure**
  - Measles, Mumps
- **Immune epitope identification**
  - Zika, Smallpox, Influenza, Measles, Rubella, SARS-CoV-2
- **Vaccine Immunogenicity in Vulnerable Populations**
  - Influenza, Zoster, SARS-CoV-2

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Immunogenetics

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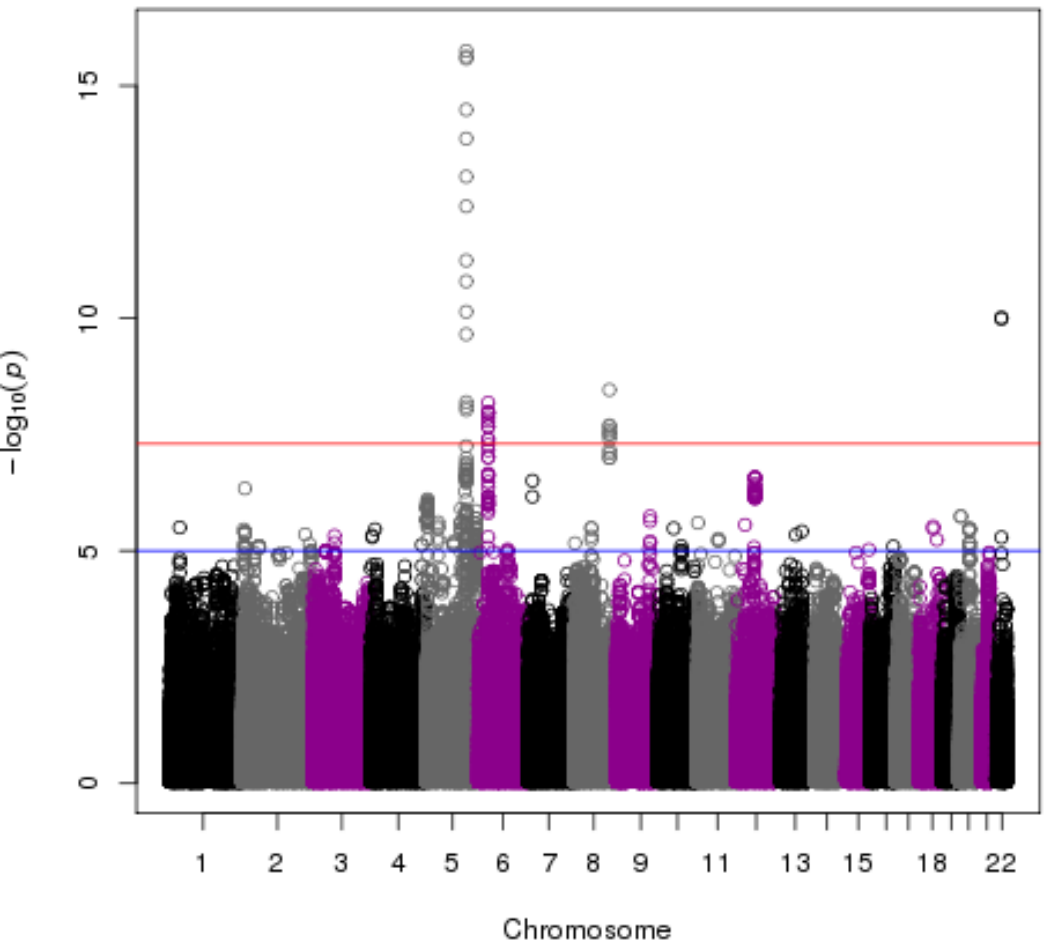
Smallpox Vaccine
Genome-Wide SNP Associations – IFNα



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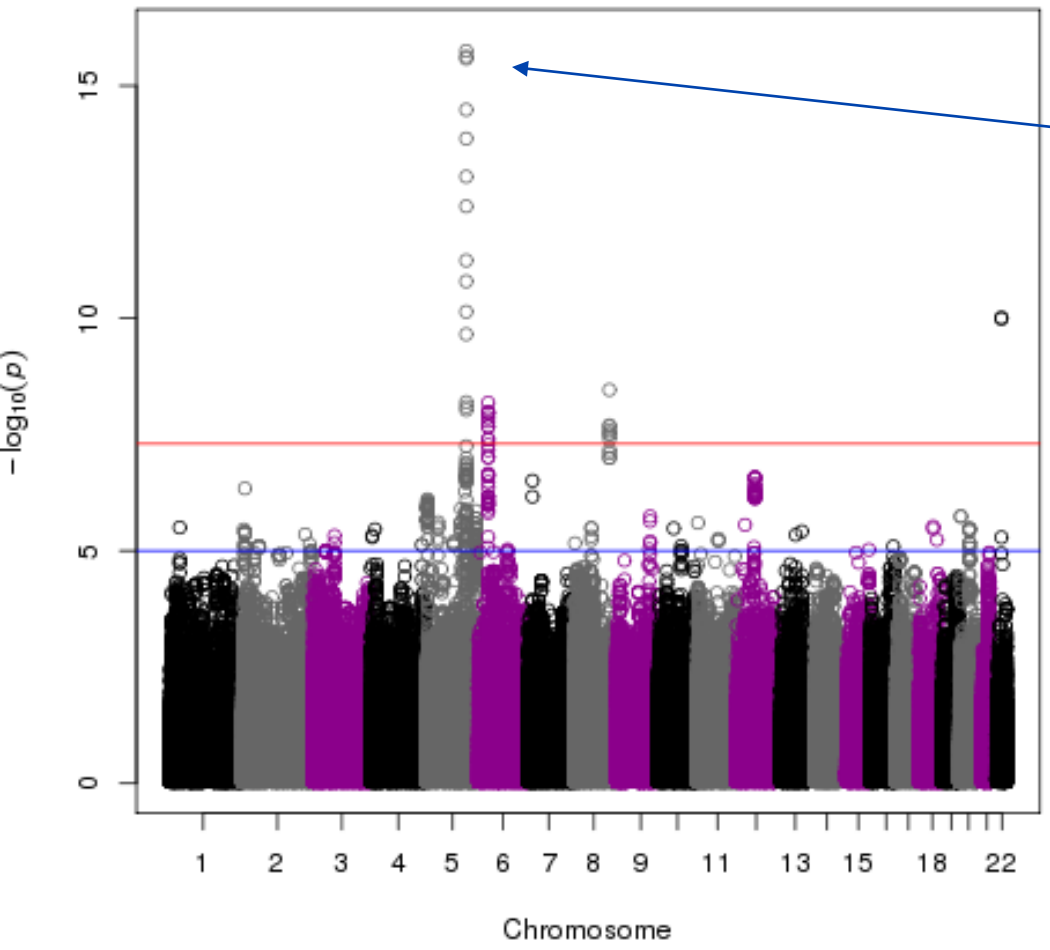
Smallpox Vaccine
Genome-Wide SNP Associations – IFNα



rs1131769
non-synonymous SNP in
TMEM173

Arg-His change at position 232

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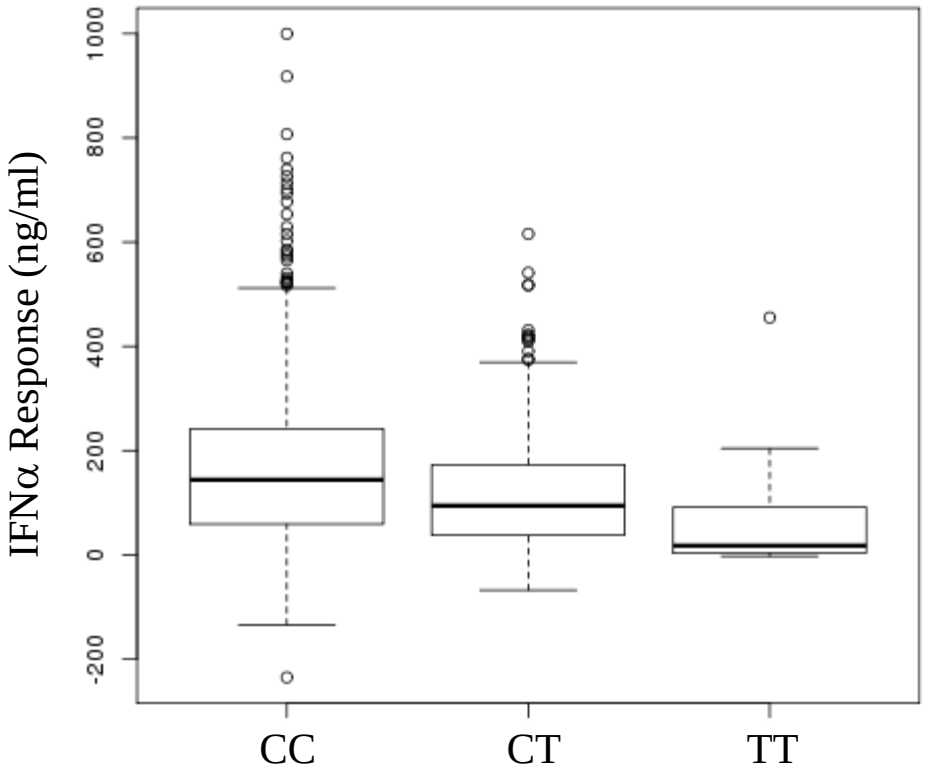
Effect of rs1131769 variants on IFNα

	rs1131769 genotype		
	CC	CT	TT
Median IFNα (pg/mL)	**143.6**	93.6	**17.7**



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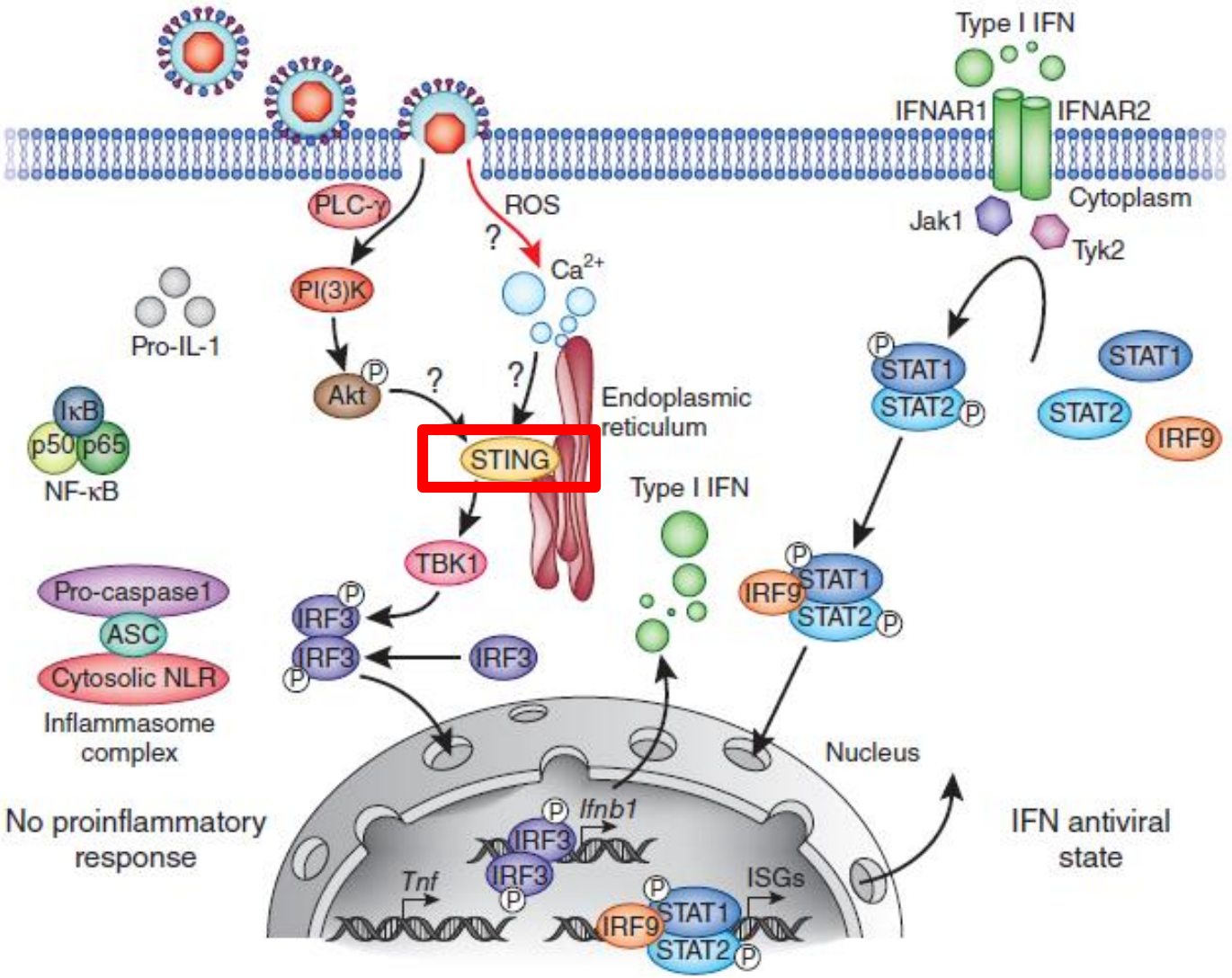
STING Pathway



Why is this important?

- Reduced innate immunity → reduced adaptive immunity
- STING controls IFN responses to DNA viruses and bacteria
- STING polymorphisms may alter susceptibility to multiple pathogens

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How can we use this information?

- Genetic biomarkers of vaccine response
- Genetic biomarkers of disease susceptibility
- Adjuvant selection for vaccines with enhanced immunogenicity

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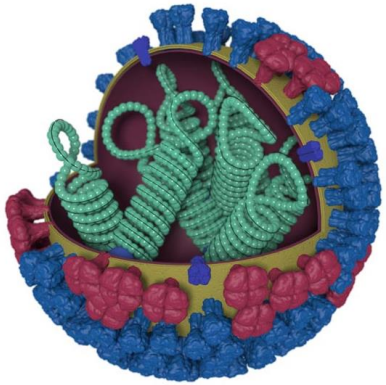
Vaccinology 3.0 Applied to Influenza

- Orthomyxoviridae: segmented, negative ssRNA viruses. Three major strains: A, B, C. Subtypes labeled by H (18 types) and N (11 types) proteins
- Seasonal outbreaks
- Periodic pandemics
  - 1918 “Spanish flu” (H1N1) - tens of millions of deaths
  - 1950s “Asian flu” (H2N2)
  - 1960s “Hong Kong flu” (H3N2)
  - 2000s “bird flu” (H5N1) - high pathogenicity
  - 2009 “swine flu” (H1N1)



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Influenza

	2017-2018	2021-2022*
Infections	41 million	9 million
Medical visits	21 million	4 million
Hospitalizations	710,000	100,000
Deaths	52,400	5,000

The vast majority occur in adults >65 years of age.

* Preliminary estimates

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Aging and Immunosenescence

“Age-related immune dysfunction”

- Features
  - Low grade inflammation
  - Increased susceptibility to infectious diseases
  - Increased autoimmune responses
  - Compromised immune memory
  - Reduced effectiveness of vaccines

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Aging and Immunosenescence

Macrophage changes
- Phenotype shift to CD14dim/CD16bright
- Reduced production of IFNg
- Diminished nitric oxide/H2O2 production
- Inhibited response to growth factors

Overall changes
- Decreased telomerase activity
- Replicative senescence
- Rise in pro-inflammatory cytokine levels
- Increased tumor incidence
- Increased susceptibility to infection
- Increased autoimmune/inflammatory reactions

NK cell changes
- Decline in NK cell function
- Increased numbers of NK cells
- Impaired cytotoxic capacity

B cell changes
- Decreased number
- Reduced BCR repertoire
- Decreased generation of new B cells
- Reduced proliferative capacity
- Increases in autoantibody titers
- Increased levels of IgG and IgA

T cell changes
- Reduced TCR diversity
- Diminished functional capacity of naïve T cells
- Decline in naïve T cell production
- Accumulation of non-functional memory T cells
- Shift in surface expression to NK cell phenotype

Immun Ageing. 2019 Sep 13;16:25.
Exp Gerontol. 2019 Sep;124:110632.
Curr Opin Immunol. 2014 Aug;29:62-8.

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Immunosenescence

- We do not yet see the whole picture
- We do not know the root causes

- This limits our ability to circumvent or overcome these limitations

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Study Design

Study Cohort

- 159 subjects (ages 50 – 74)
- All subjects received seasonal influenza vaccine
- Blood draws before (Day 0) and after (Days 3, 28, and 75) vaccination

Immunologic Parameters Measured

- HAI, VNA, Memory B cell ELISPOT – all H1N1-specific
- Cytokine production
- Immunophenotyping by flow cytometry

High Dimensional Data

- mRNA-Seq (Illumina Hi-Seq 2000)
- miRNA-Seq (Illumina Hi-Seq 2000)
- Illumina 450K DNA Methylation array
- Quantitative proteomics (iTRAC)

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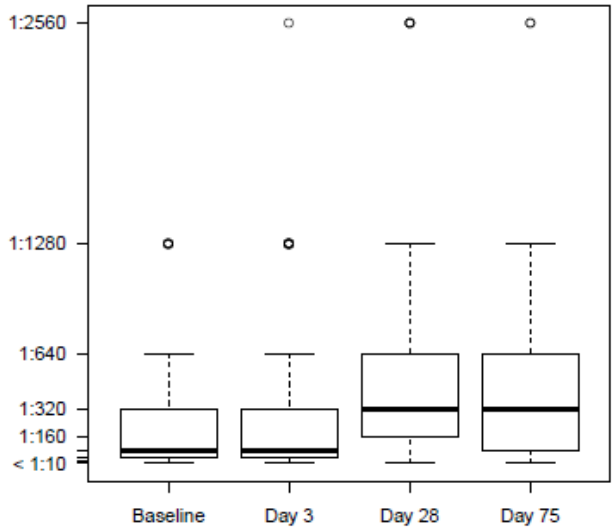
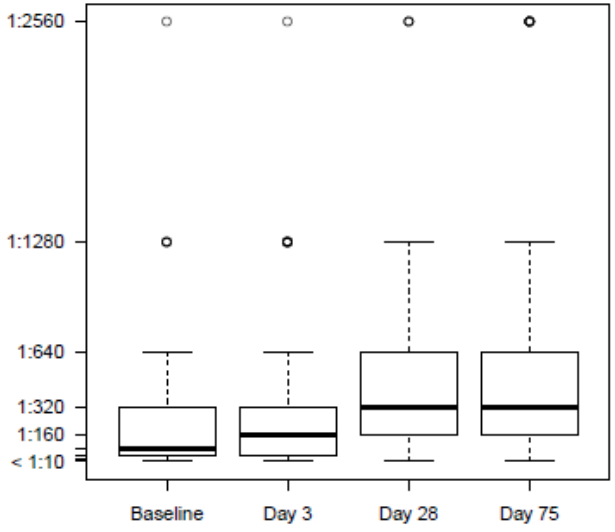
Cohort Immune Responses

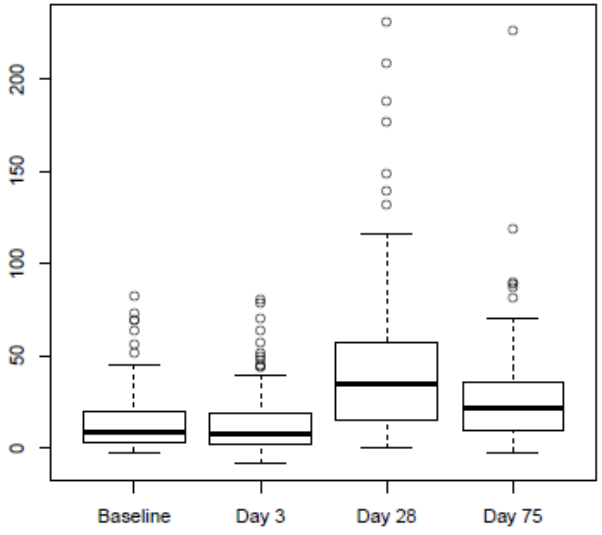
HAI Titer (H1N1)



VNA Titer (H1N1)



B Cell ELISPOT (H1N1)



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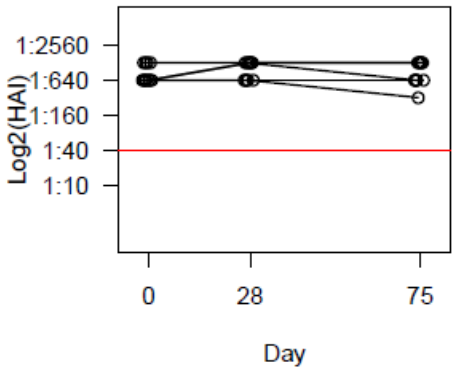
Individual Immune Responses

Glass Ceiling



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Individual Immune Responses

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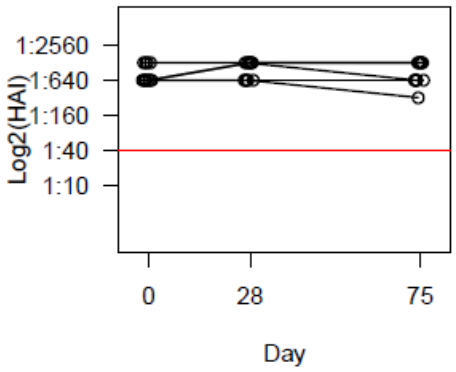
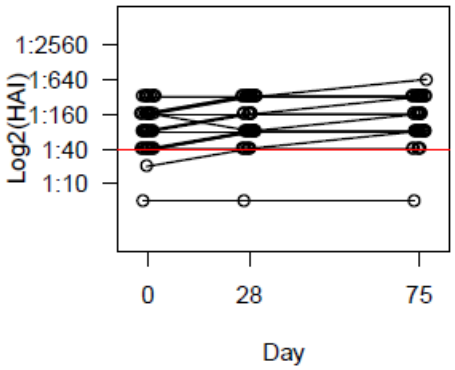
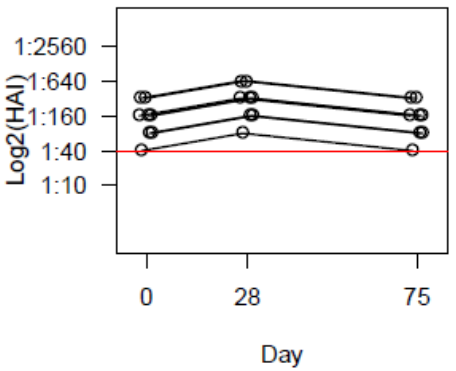


Vaccine Non-Responsive

No response



Marginal response



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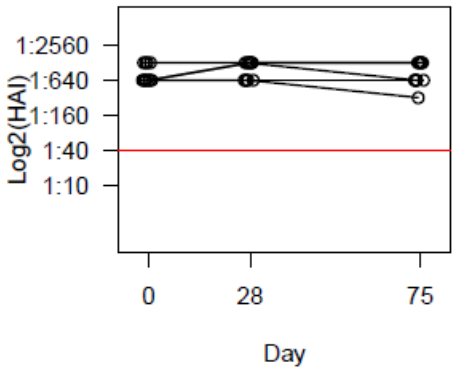
Individual Immune Responses

Glass Ceiling



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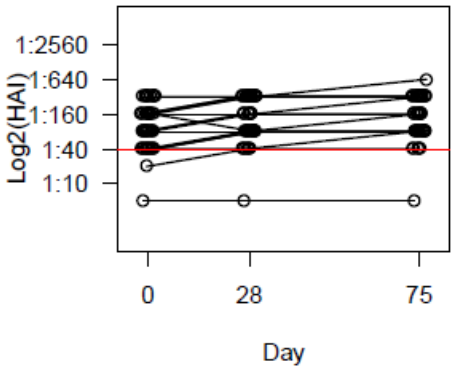
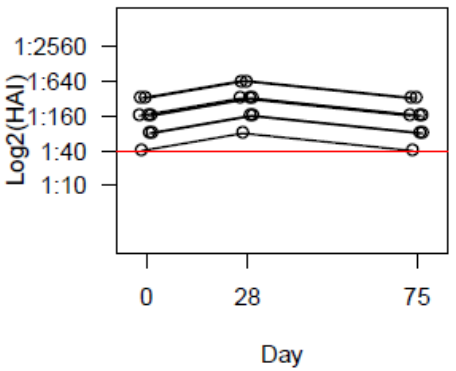
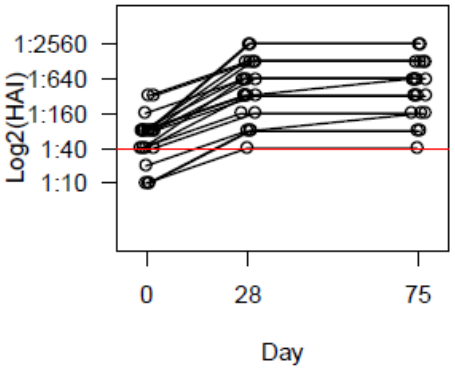


Marginal response

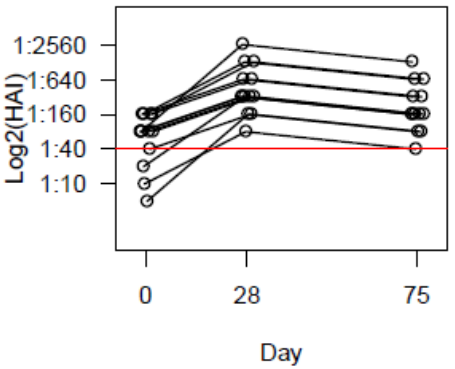


Vaccine Responsive

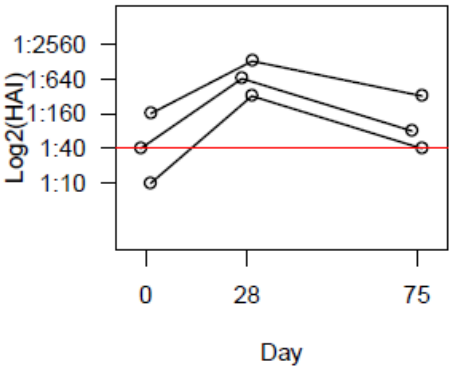
No waning



Some evidence of waning



Clear evidence of waning



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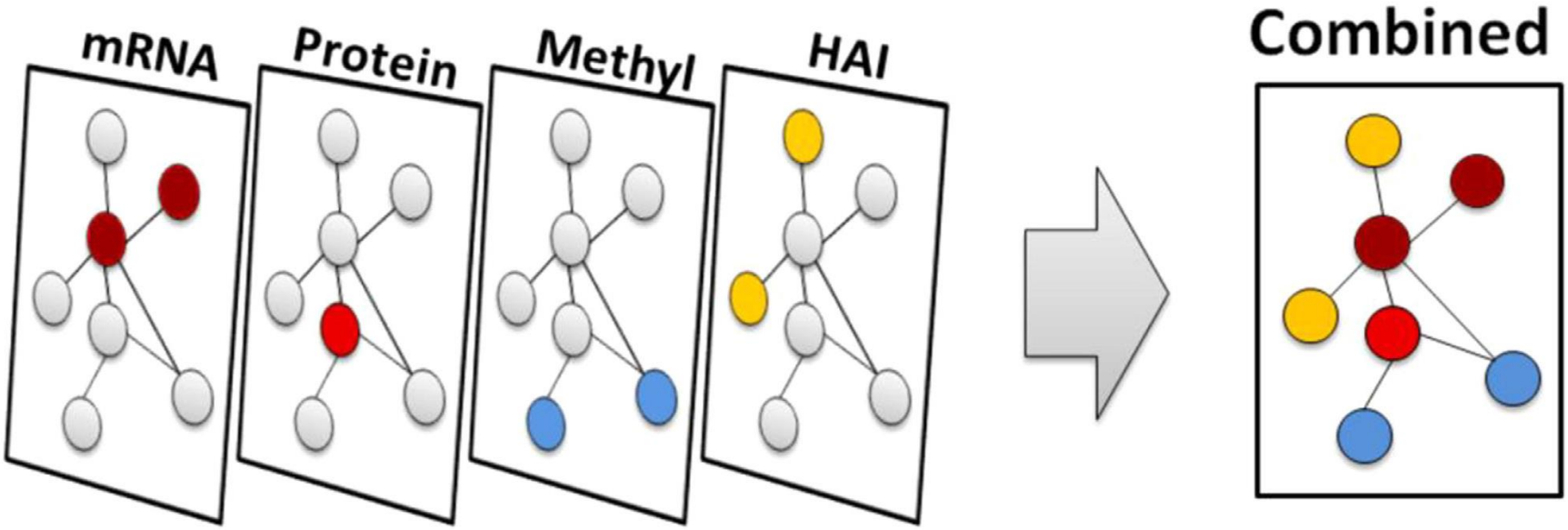
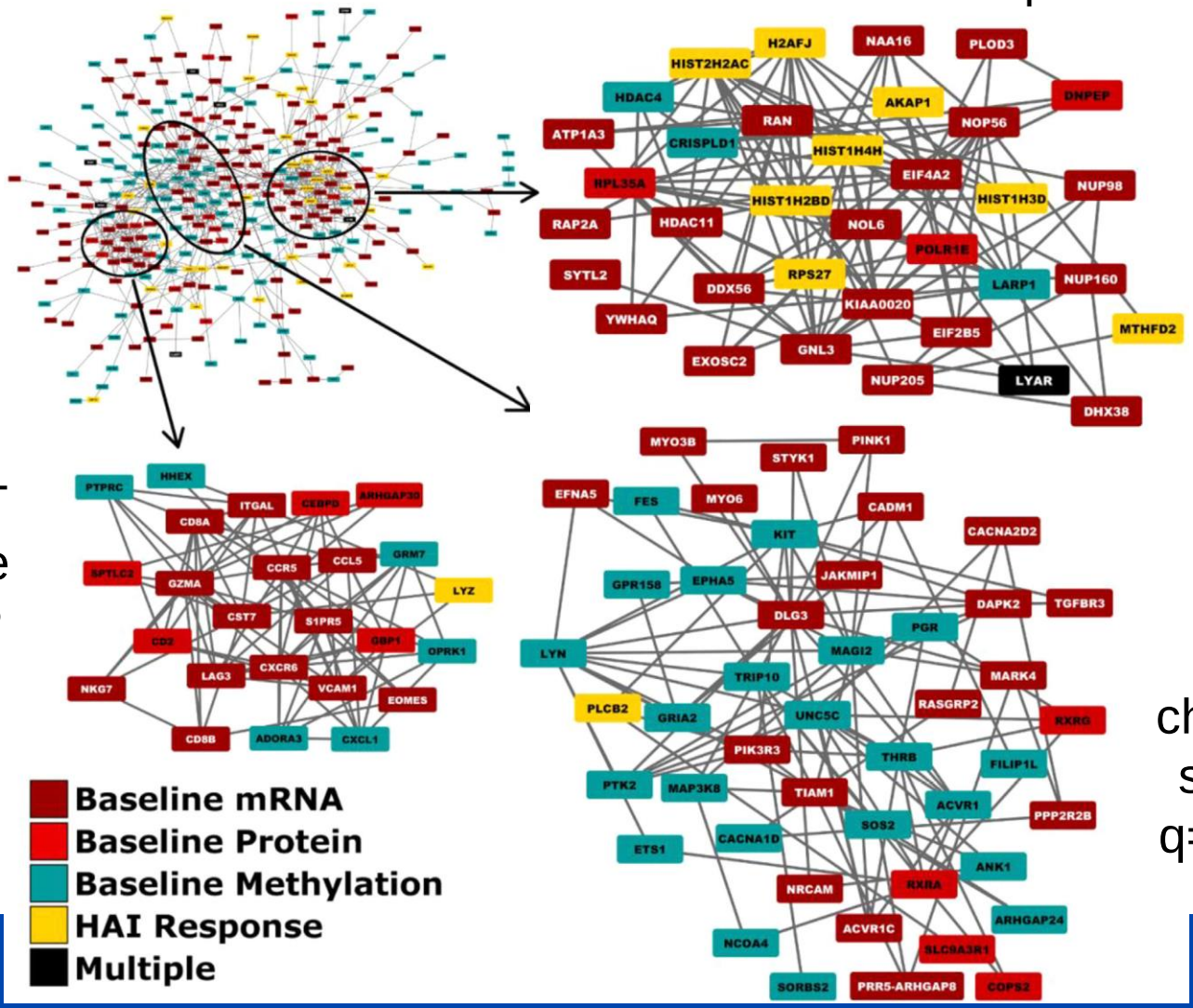
Network Biology



Network Biology Analysis

M7.16
Unknown function
$q=1.3x10^{-7}$



M3.6
Cytotoxic T cell module
$q=6.3x10^{-5}$

KEGG chemokine signaling
$q=4.0x10^{-5}$

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Why is this important?

- mRNA, miRNA, CpG, protein data all capture a different piece of the puzzle
- Therefore, these data provide unique insights into the biological functions associated with immunosenescence markers
- Studies combining data types is often useful in developing the ‘complete picture’.

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The Future of Vaccinology

- Better tools
  - Will provide deeper insights into immune function
- Personalized vaccines
  - Different dose, vaccines for different population groups
  - Predictive biomarkers
- New adjuvants
- Novel types of vaccines
    - DNA/RNA vaccines
    - Vector-based vaccines
    - Peptide-based vaccines

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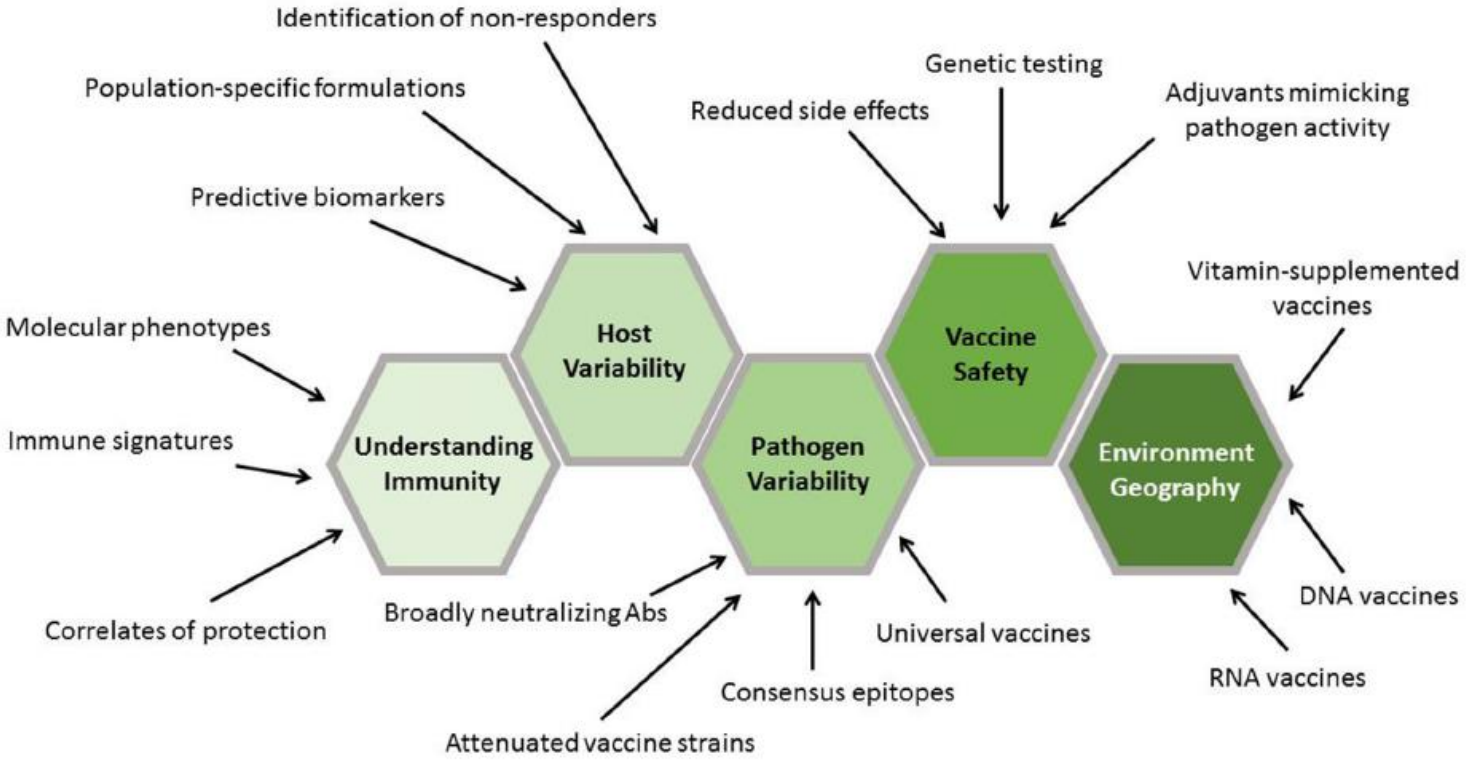
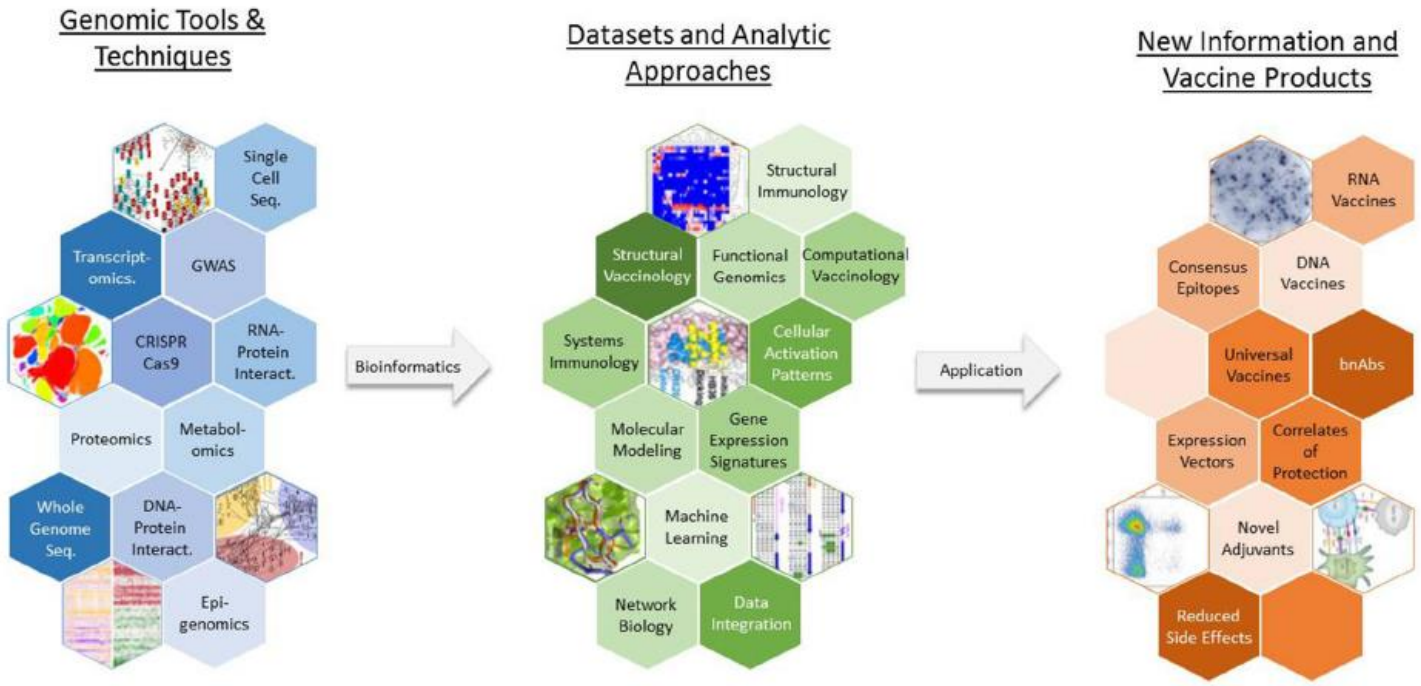
How to apply this work?

- Understand immune “signature profiles” from a vaccinomics perspective
- Development of a vaccine response “marker”
  - Personalized vaccinology
  - Go – no go candidate vaccine studies
  - Inform new vaccine development
- Reinvigorate vaccine development




Genomic Tools & Techniques
Single Cell Seq.
Transcript-omics.
GWAS
CRISPR Cas9
RNA-Protein Interact.
Proteomics
Metabol-omics
Whole Genome Seq.
DNA-Protein Interact.
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DNA Vaccines
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Expression Vectors
Correlates of Protection
Novel Adjuvants
Reduced Side Effects

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Next Gen Sequencing
Flow Cytometry

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