The Case for Personalized Vaccinology in the 21st Century
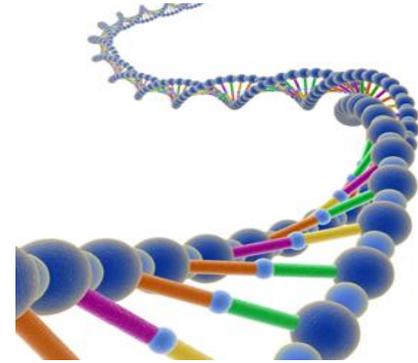
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**Editor-in-Chief, VACCINE**

Background for Change

- Risk-averse towards vaccines – extremely high levels of safety required

- The one-size-fits-all approach to vaccination ignores the complexity and diversity of the human immune system and host genome

- Increasingly large immunocompromised and elderly populations

- The promise of vaccinomics and related paradigms is to identify specific immune response profiles, immunosignatures, and biomarkers that predict vaccine safety and/or efficacy, leads to new vaccine candidates, and allows delivery of the right vaccine, to the right person, at the right dose, at the right time…*in other words personalized vaccinology*

Vaccinology 1.0

- Isolate ⟶ Inactivate/Attenuate ⟶ Inject

Smallpox
Rabies
Diphtheria
Tetanus
Anthrax
Cholera
Typhoid
Others

1940's – 2000's

- One "size" fits all approach

- Everybody at risk for everything – so give everyone everything

- Prophylactic only

- Childhood vaccines >>>> Adult vaccines

- Parenteral vaccines dominate (except FluMist and oral typhoid)

- Very few licensed adjuvants

- Predicated on a population-level, public health approach

# A Vaccine Paradox

- **The goal is to induce protective immune responses in (ideally) 100% of the population who receive a vaccine**

- **We fail at this because of:**
  - Pathogen variability
  - Host (human immune system) variability
  - Lack of variability in how we deliver vaccines to the population, i.e. a "one size fits all" population approach, and limited paradigms for vaccine discovery

Vaccine Errors In Thinking

- Smallpox vaccine – dangerous, too revolutionary, simply not possible
- Too hard/expensive to make QIV
- Not possible to make a Mening B vaccine
- One dose of measles vaccine is sufficient
- Rubella vaccine only needed for females
- HPV vaccine only needed for females
- Not possible to make 23-valent Pneum vaccines
- Not possible to give so many vaccines to infants
- Too dangerous to give vaccines to pregnant women
- Many, many others…

WE CANNOT SOLVE OUR PROBLEMS
WITH THE SAME THINKING
WE USED WHEN WE
CREATED THEM
-Albert Einstein
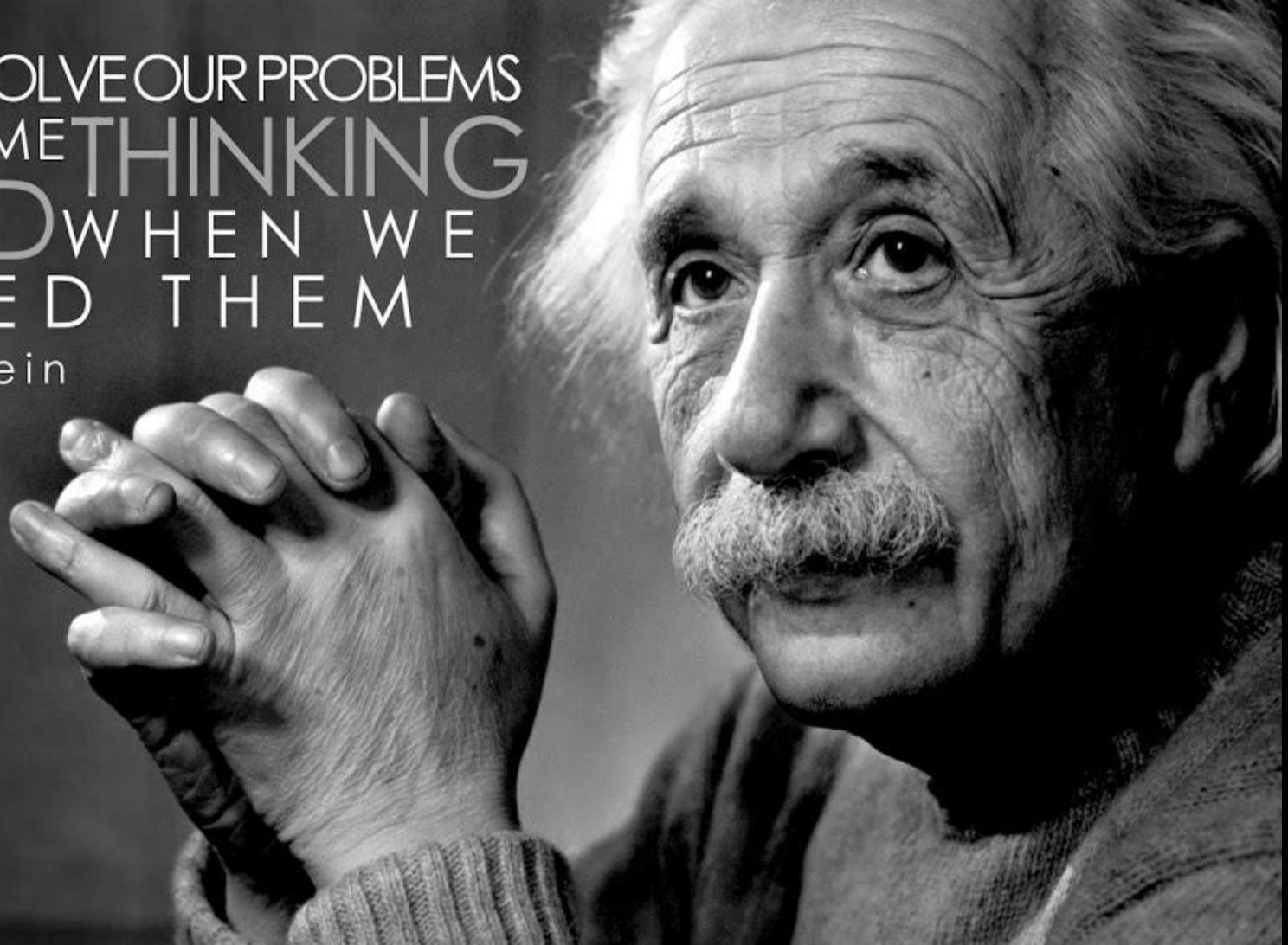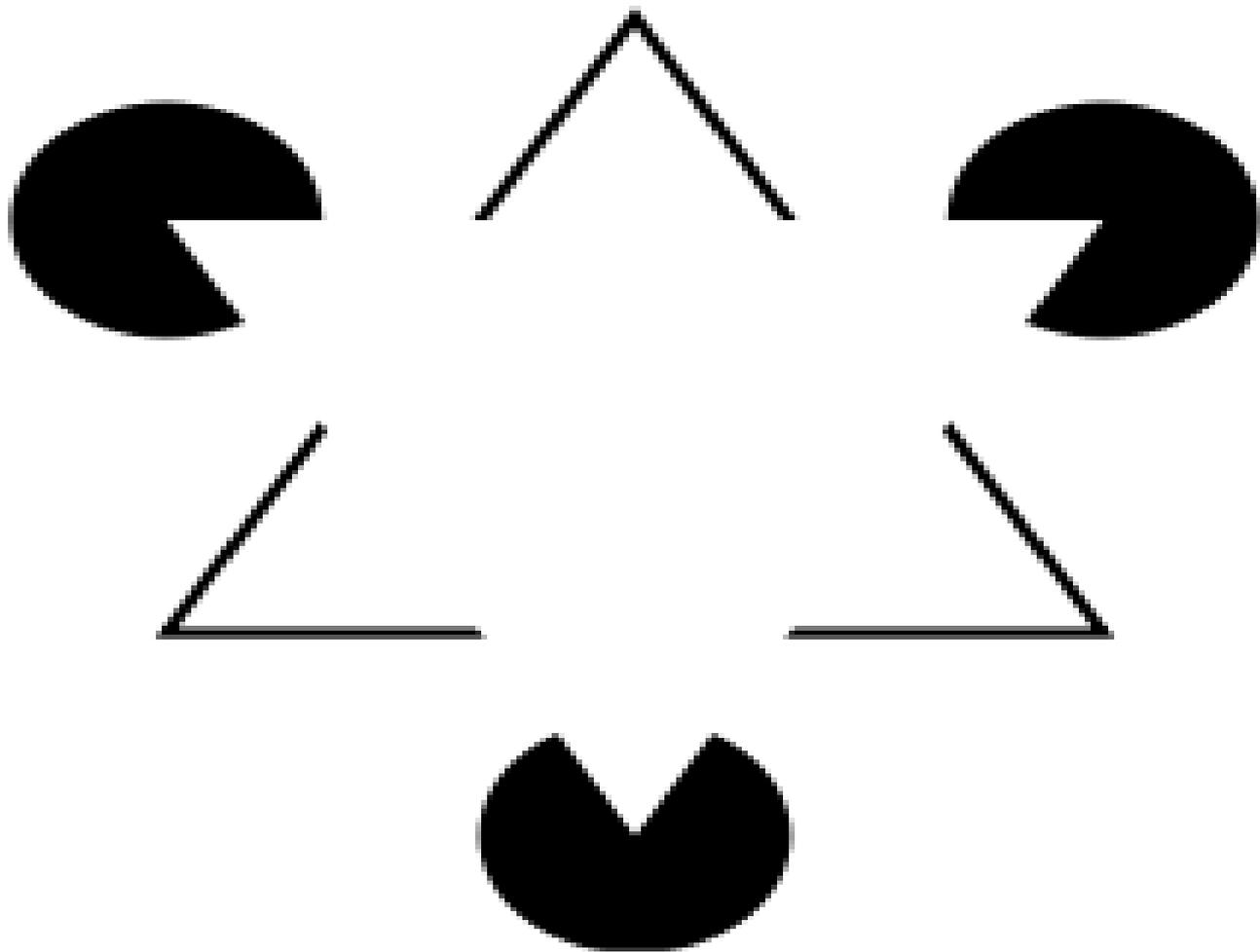
# Tomorrow – More Clever?

- **Personalized approach**
- Tiered risk and vaccination approach
- Prophylactic *and* therapeutic
- Adult vaccines >>>> Childhood vaccines
- Oral, transcutaneous, depot, and mucosal vaccine delivery
- Multiple highly specific adjuvants
- Directed vaccine development using systems biology and computational approaches
- Private, public and academic partnerships

The New Biology
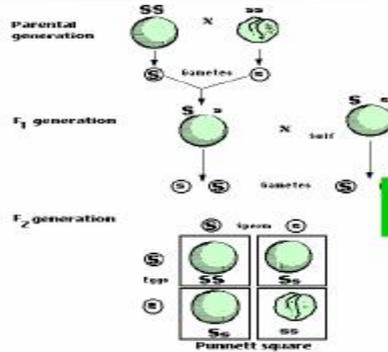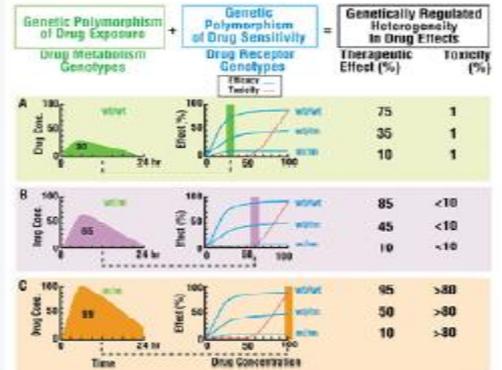
Vaccinology 3.0

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

Discover → **Validate** → **Characterize** → **Apply**

Personalized Vaccinology

- **Individual (e.g. cancer vaccines)**
- **Gender**
  - 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**

Poland, et al. Clin Pharmacol Ther. 2007 Dec;82(6):653-64

Reality

"It is not necessary to change. Survival is not mandatory."

\- Edward Deming

"The human understanding resembles not a dry light, but admits a tincture of the will and passion, which generate their own system accordingly; for *a man always believes more readily that which he prefers.* He, therefore, rejects difficulties for want of patience in investigation…; the light of experiment because of arrogance and pride….paradoxes from a fear of other men's opinions…; in short, *his feelings imbue and corrupt his understanding in innumerable and sometimes imperceptible ways*."

Francis Bacon
Aphorism XLIX
Novum Organum.

Why New Paradigms Come Slowly

- Error, myth, superstition cloud our ability to "see" the data

- We wrongly believe scientific progress is a process of *linear accretion of knowledge*

- Science is predicated on the belief that the scientific community understands what the world is like

- We suppress or resist "*fundamental novelties*" because they are seen as subversive to our firmly held beliefs of what the world is like

Thomas Kuhn. The Structure of Scientific Revolutions

Individualized Medicine

Patient group

Same diagnosis, same prescription

Drug toxic but beneficial

Drug toxic but NOT beneficial

Drug NOT toxic and NOT beneficial

Drug NOT toxic and beneficial
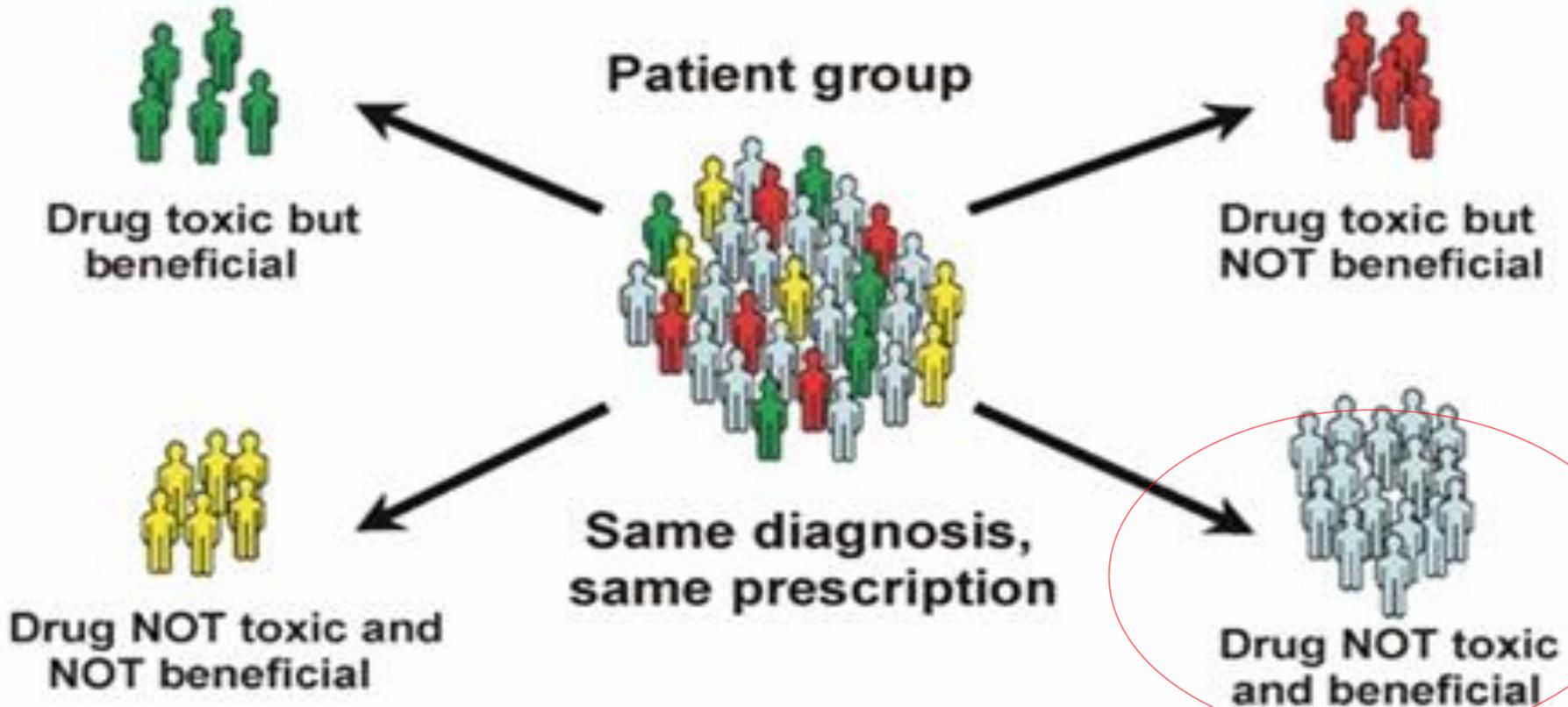
For nearly all vaccines studied, females have superior humoral immune responses compared to males – why?
They also have AE rates *significantly* higher than males – why?

Immune Response Network Theory

- "The response to a vaccine is the cumulative result of *non-random* interactions with host genes, epigenetic phenomena, metagenomics and the microbiome, gene dominance, complementarity, epistasis, co-infections, and other factors occurring *within the system as a whole*."

- In other words, a *systems-level*, rather than reductionist, approach

*Poland et al. Clin Pharmacol Ther. 2007 Dec;82(6):653-64*

Vaccinomics

Vaccinomics is the integration of a systems biology approach with the immune response network theory, immunogenomics, *immune profiling and functional studie*s in order to understand and predict vaccine-induced immune responses; and uses this information to engineer vaccine candidates and to drive *individualized vaccinology.*

1. Poland et. al. Vaccinomics and a new paradigm for the development of preventive vaccines against viral infections. OMICS: A Journal of Integrative Biology, 2011;15(9):625-36.
2. Poland et. al. Systems biology approaches to new vaccine development. Current Opinion in Immunology 2011;23(3):436-443.
3. Poland et al. Vaccinomics and personalized vaccinology: Is science leading us toward a new path of directed vaccine development and discovery? PLoS Pathogens. 2011, 7(12):e1002344.
4. Poland GA, et al. Seminars in Immunology 2013.

Recent Theories/Approaches in Vaccinology

Theory/Model	Description	Tools used
Reverse Vaccinology	The use of genomic data and in silico analyses to rapidly identify antigens for vaccine use.	Transcriptomics, proteomics, epitope prediction algorithms, immune monitoring
Immune Response Network Theory	Describes immunity as the predictable result of sequential activation/interaction of genes and gene pathways.	Transcriptomics, proteomics, pathway analysis
Vaccinomics	A comprehensive study of immune responses to vaccination such that vaccine-induced immunity can be understood and predicted and then applied to the rationale and directed development of vaccines.	Transcriptomics, proteomics, epigenomics, Immunogenetics/immunogenomics, computational modeling, immune monitoring
Systems Vaccinology	The application of systems biology methods to understanding and predicting vaccine-induced immune responses.	Transcriptomics, proteomics, epigenomics, computational modeling
Structural Vaccinology	The use of structural biology studies to facilitate the selection of vaccine epitopes.	Proteomics, NMR, X-ray crystallography, immune monitoring
Vaccine Informatics	The use of bioinformatics approaches to facilitate vaccine development, production, testing, and licensure.	Computational modeling, epitope prediction algorithms, HLA-binding algorithms, data mining and integration, mathematical simulations of immune response

Vaccinomics and Predictive Vaccinology

High dimensional assays

Multi-parameter immune function

Immunogenetics Immunogenomics

Microbiome

Data Integration

Statistical Analyses
Data-directed, Gene, Geneset, Pathways
Networks, Immune Modules

Computational Modeling
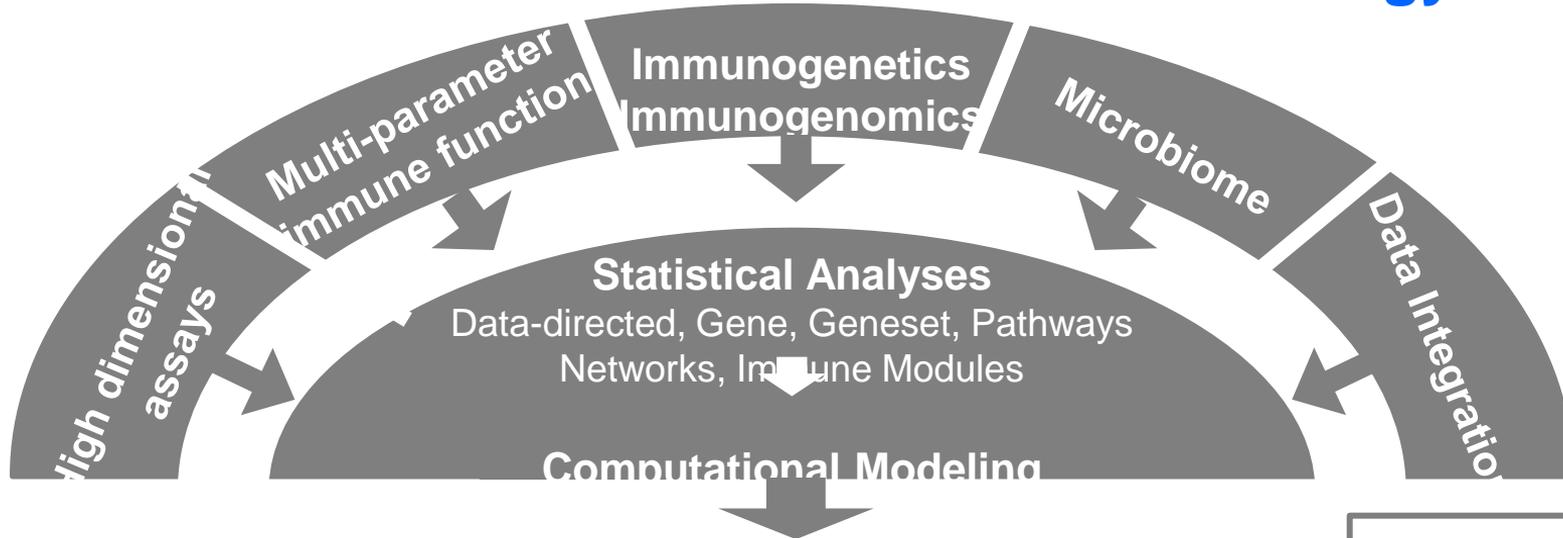
- **Novel correlates of immune protection**
- **Advanced understanding of the systems level, biological response to vaccines**
- **Predictive biomarkers of vaccine response**
- **Early immunosignatures of adverse events**
- **Directed vaccine design, development, testing, licensure**

Iterative cycle of discovery, replication, validation, and application
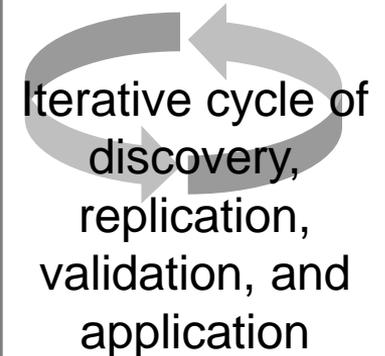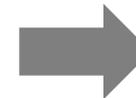
Vaccinomics: The Future

- We predict a new era of personalized "*Predictive Vaccinology*" whereby we:
  - Abandon a "one size and dose fits all vaccine approach"
  - Predict whether to give a vaccine based on likelihood of response (and perhaps need)
  - Predict the likelihood of a significant adverse event to a vaccine
  - Predict the number of doses likely to be needed to induce a protective response to a vaccine (HBV , HPV, measles examples)
  - Design/develop new vaccines

Blaise Pascal

"The majority opinion is the best way because it can be seen and is strong enough to command obedience; <u>but it is the opinion of the least clever.</u>"

What Would Kuhn Say?

- We make the mistake of requiring new theories to explain *all* the facts with which it can be confronted – and reject those that don't

- New advances require attracting adherents away from current dogma and other competing theories

Thomas Kuhn, The Structure of Scientific Revolutions, 1962

Personalized Vaccinology

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Vaccinomics: Scientists Are Devising Your Personal Vaccine

A new breed of vaccine is being developed that will make possible immunizations tailored to your genetic profile. But how long will it be until your personalized booster shots are ready?

ONE-OFF SHOT: Although truly personalized vaccine regimes might seem a far-off dream, some researchers are looking to genomics to usher in an era of vaccinomics.

Gregory Poland, the head of the Mayo Clinic's Vaccine Research Group, has been working to unite the fields of genomics and vaccinology—what he calls "vaccinomics"—

Acceptance of Vaccinomics

- "…one of the most innovative scientific concepts of the decade" (*Vaccinomics: Scientists are Devising Your Personal Vaccine.* Scientific American)

- "…one of the hottest "omics" fields" (*Thinking Outside the Genome.* The Scientist)

Vaccinology 3.0

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

Discover → Validate → Characterize → Apply

Poland GA, et al. Seminars in Immunology 2013

Discover: Keys to the Black Box

A.

Genetics/Genomics	Transcriptomics
SNP typing	mRNA-Seq
Copy Number Variation	SAGE
Gene sequence data	Microarray
miRNA/siRNA profiles	

Proteomics	Metabolomics
Quantitative MS	Quantitative MS
2D gel electrophoresis	X-ray crystallography
Yeast-2 hybrids	Mag. Res. Spectroscopy
NMR	Pos. Emission Tomography

Epigenomics	Immune Profiles
ChIP-Seq	Epitope prediction algorithms
MDIP-Seq	Multi-color flow cytometry
MRE-Seq	CyTOF
MethylC-Seq	Pathogen protein array

Metagenomics/Microbiome
Targeted rRNA amplicons
Shotgun metagenomics
T-RFLP

B.

Stochastic models	Network Models
Mechanistic models	Pathways
Predictive models	Genesets
Predictive algorithms	Interactions
Neural networks	Data integration

Bioinformatics tools	Databases
Support vector machines	Machine learning algorithms
Replication and validation	Data reduction

False discovery rate	Linear discriminant analysis
Level of significance	Support vector machines
Principal components	Random forests
Clustering	

A. High dimensional approaches to assess response to vaccination

B. Bioinformatics approaches to interpreting the data from "A"

IMMUNE PROFILES

OMICS DATA

CLINICAL PHENOTYPE

Computational Modeling

Molecular Signatures
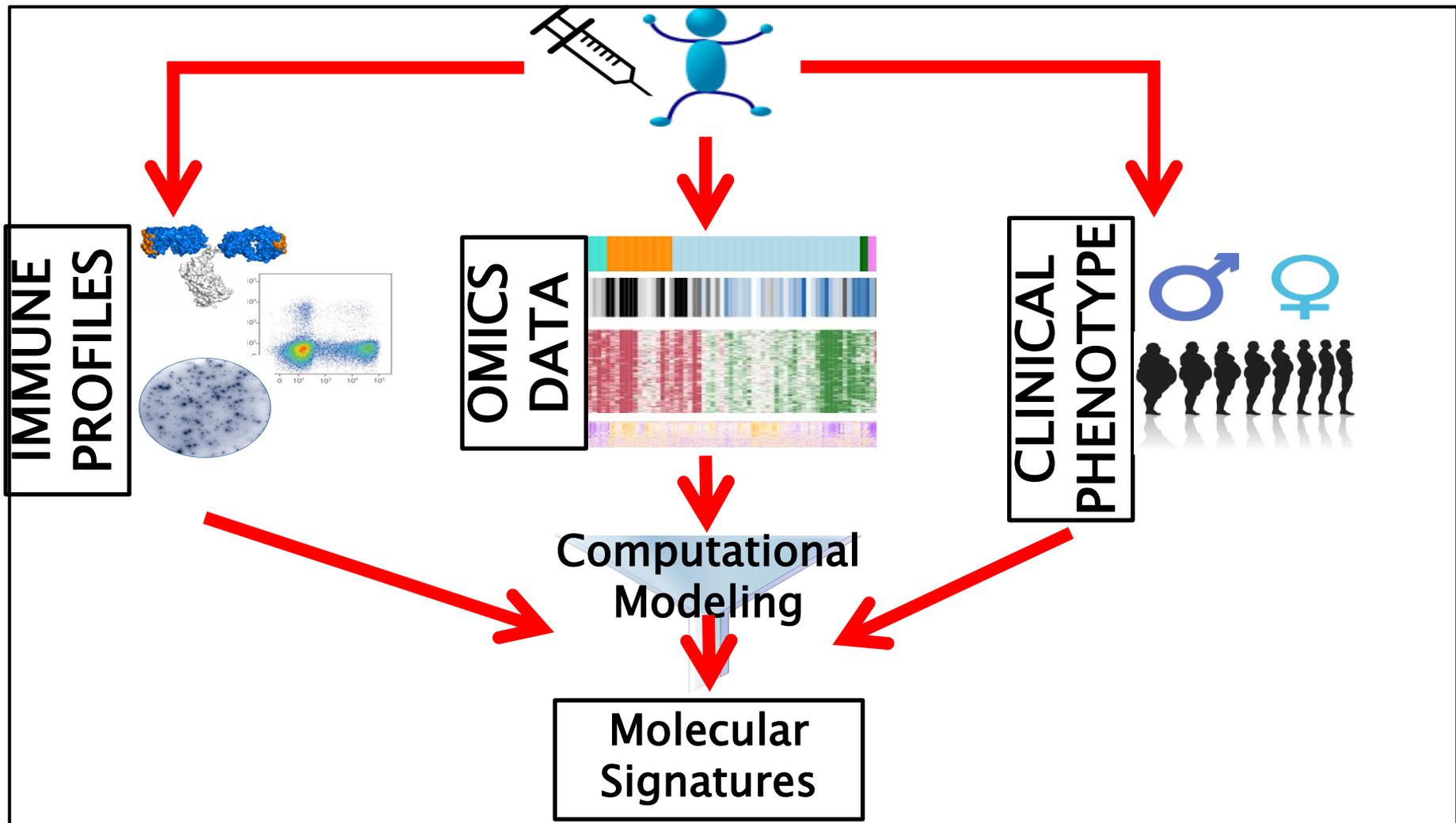
Vaccinomics and the New Vaccinology

Poland GA, et al. Seminars in Immunology 2013.
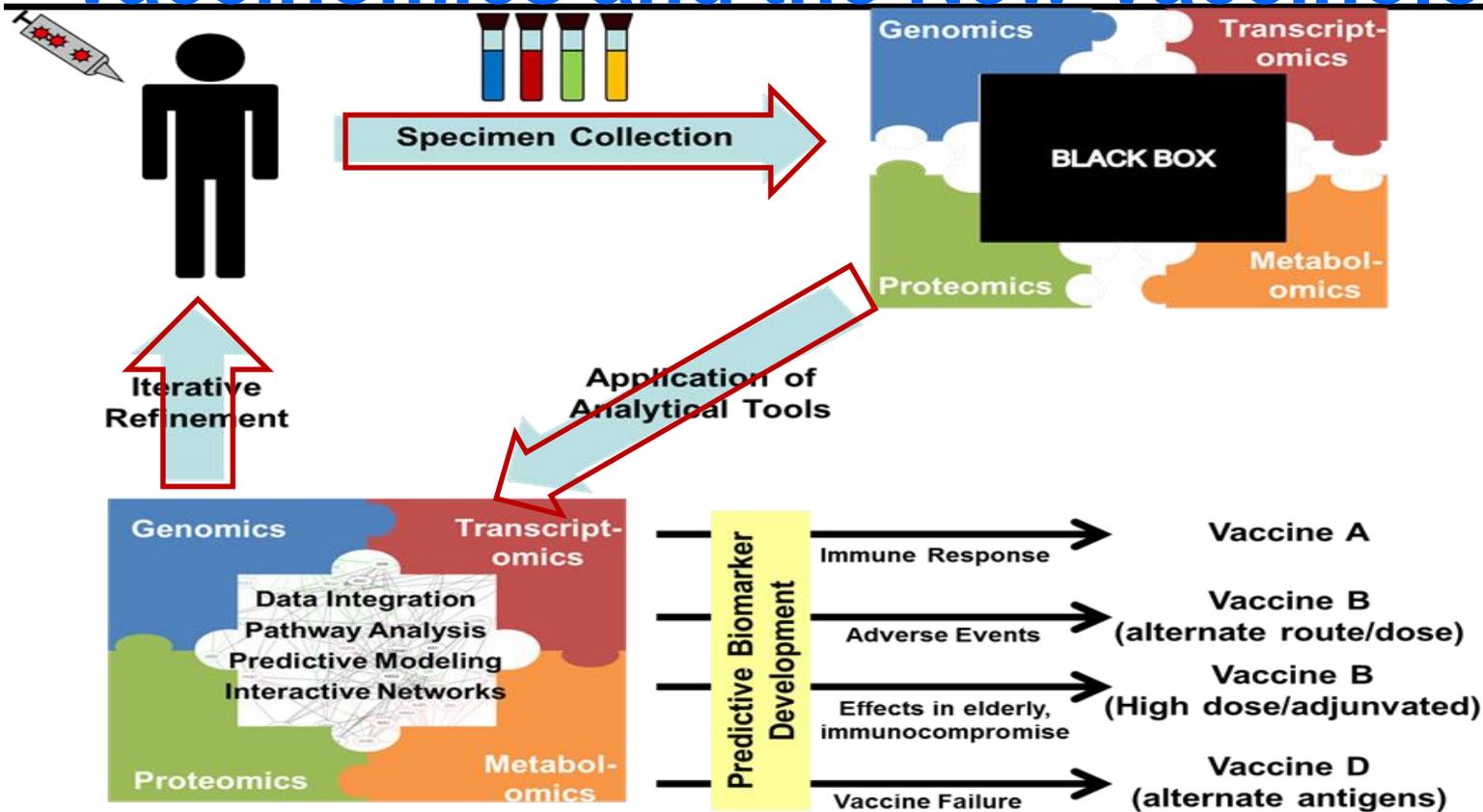
Validate

- Are findings from a discovery cohort able to be replicated in a validation cohort?
  - Test replication and validation in subgroups of interest

Characterize: Determine Polymorphism Effects

- Functional studies of well-characterized genetic variants

- Altered secretion patterns of cytokines

- Altered transcription of important genes (signaling molecules) and gene products

- Differential binding, processing, and expression/presentation of antigenic peptides

- Differential range of presented peptides (genetic restriction)

- *Altered binding of virus/antigens by membrane-based receptors (TLR, other)*

- *Differential receptor function, expression, affinities*

Measles Virus Receptors SLAM and CD46 and Measles Virus Epithelial Cell Receptor Nectin–4

SLAM

CD46

MV binding domains

Variable ← V

Constant ← C

1
2 → Short consensus repeats (SCR)

3
4 → Serine-threonine-proline (STP) domain

Membrane

Cytoplasm
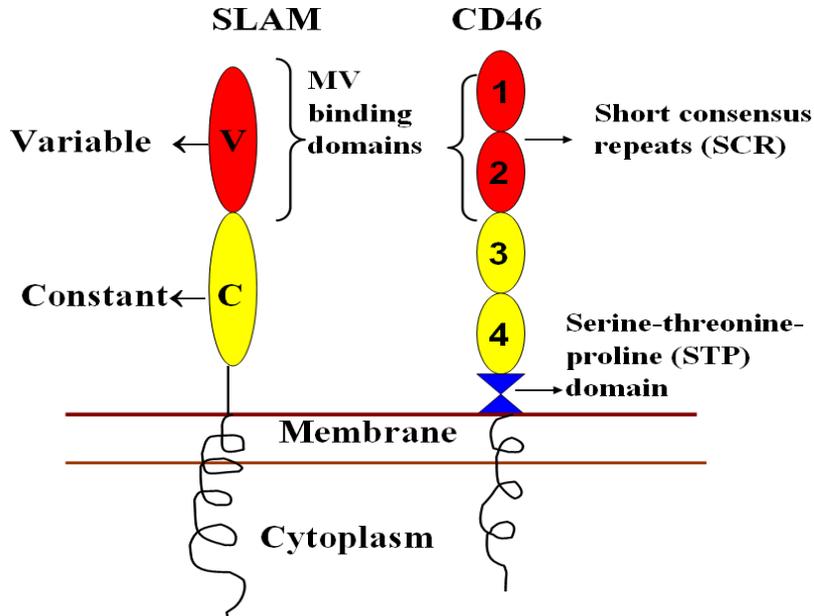
Adhesion Molecule Nectin-4
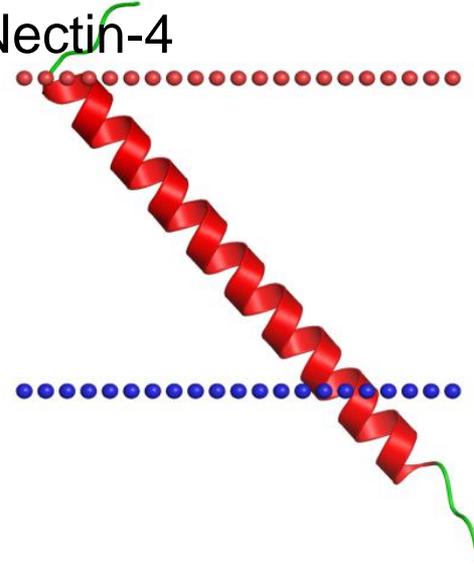
Viral usage: SLAM (measles vaccine type strains, some wild type strains)
CD46 (wild type measles virus strains, vaccine (Edmonston) strains)

SLAM SNP Associations

SNP ID	Location	Genotype	Median Ab (IU/mL)	P-value
rs3796504	**Thr-Pro (Ex-7)**	**GG/GT/TT**	**1589/1066/497**	**0.01**
rs164288	**Thr-Thr (Ex-3)**	**GG/GA/AA**	**1602/1102/497**	**0.03**
rs164283	Intronic	TT/TC/CC	1670/1265/1848	<0.01
rs1503854	Intronic	AA/AG/GG	1619/1348/1863	0.01
rs12076998	5' UTR	TT/TC/CC	1467/1991/*	0.01
rs2025515	Intronic	GG/GT/TT	1477/1796/*	0.02
rs11265452	Intronic	AA/AG/GG	1553/1453/1924	0.04
rs11265449	Intronic	CC/CG/GG	1559/1445/1796	0.05
rs16832283	Intronic	TT/TC/CC	1553/1476/1924	0.05

A total of 21 SNPs were tested; only those found to be statistically significant (p≤0.05) shown

*No subject in that genotype

N=339

Associations between SNPs in the SLAM Gene and Measles Immune Responses

Immune measure	SNP (Location)	Genotype	Median IgG antibody level (IU/ml)	P–value
Antibody	rs164288 (coding)	GG/GA/AA	1602/1102/497	0.03

Discovery study: Dhiman et al, J Allergy Clin Immunol 120:666-672, 2007
A total of 21 SNPs were examined in 339 subjects

Immune measure	SNP	Genotype	Median (SFC per 2 x 10^5 PBMCs	P–value
IFNγ Elispot	rs164288 (coding)	GG/GA/AA	29/10/––	0.04

Replication study: *Ovsyannikova et al, Human Heredity, 2011;72(3):206-223.*
A total of 55 SNPs were examined in 745 subjects; SFC – spot-forming cell
-- No subject in that genotype

The result of our work to date is that we can explain and predict about 30% of the inter-individual variation in measles vaccine response

Apply: "*Predictive Vaccinology*"

- Predict whether to give a vaccine based on likelihood of response
  - HBV extended haplotype
  - HPV vaccine biomarker

- *Design/develop new vaccines*
  - Peptide vaccines (measles, smallpox, CHIK, ZIKA)
  - Measles vaccine based on genotype (SLAM, CD46)

Benefits of Vaccinomics – Personalized Vaccinology

- ## Design of new vaccine candidates by:
  - Understanding how immune responses are generated across age, gender, race, medical condition using a *systems-level* approach
  - A **directed, rather than empiric**, approach
  - Vaccine monitoring in clinical trials (gene signatures)

- ## Adversomics
  - Understanding genetic drivers of aberrant immune, auto-immune, or non-immune responses (vaccine failure) to a vaccine

- ## Clinical practice – Individualized Vaccinology
  - What vaccines, what doses, what type of vaccine, in what individual/group

Adversomics Studies

- **JID 2006;194:444**
  - Cytokine gene expression and fever after smallpox vaccine

- **JID 2007;196:212**
  - Smallpox vaccine and fever
    - IL-1A, IL-18 SNPs

- **JID 2008;198:16**
  - Smallpox vaccine and AE (fever, rash, enlarged LN)
    - MTHFR, IRF1, IL-4 SNPs and haplotypes

- **J Biomed Sem 2012;20:18**
  - Generic fever gene networks (TNFa)

- **Nature Genetics 2014;46:1274**
  - MMR and febrile seizure
    - IFI44L, CD46, SCN1A, 2A, TMEM16 (ANO3) SNPs

How Will We Get To Personalized Vaccinology?

- Demand by public and HCP's for safety and better value proposition

- $100 genome

- Large genotype–phenotype databases

- Funding for vaccinomics/system biology vaccine studies (NIH–HIPC, others)

- Education of providers

- Different public health paradigm
  - Away from "one dose fits all" and "every vaccine for everyone" to "best vaccine for this individual if they are at risk for this disease"

The Usual Objections

- **Are you really going to develop a unique vaccine for everyone?**
  - No! (although that is one pathway cancer vaccines are pursuing)
  - Subgroups
    - Age
    - Gender
    - Genetic profile
    - Immune status/Disease

- **Too expensive!**
  - Not when HPV vaccine costs $175 a dose – many respond after 1-2 doses, some have no response after 3 doses!

The Usual Objections

- **Isn't it far away?**
  - Already doing it with flu vaccine
  - Already understanding adversomics – public perceptions of safety may drive further use
  - $100 genome coming…soon!

- **Just too difficult!**
  - A different paradigm of medical practice
  - Already being done for certain chemotherapy drugs, resistant depression and hypertension, other drugs and disease states

MAYO CLINIC

Personalized Influenza Vaccines

- IIV3 and IIV4

- LAIV4 (2–49 yrs)

- HD–IIV3 [> 65 yrs]

- ID–IIV4) [18–64 yrs]

- MF59–adjuvanted IIV3

- RIV4 (> 18 yrs)

- IIV3 by jet injector (18–64 y/o)

- ccIIV3 (> 18y/o)

- More coming…

The Future Has Already Started!

- **Personalized Vaccinology**
  - Disease Model
    - Different HBV doses for CRF
  - Age Model (infant, child, adolescent, immunosenescent adults)
    - Smaller doses, 2 doses for infants
    - HDFlu or MF59Flu for elderly
  - Vaccine Model
    - Influenza vaccines (9 different types!)
  - Next up…Genetic Model
    - HLA types (SLAM, CD46, others)

"**Knowing is not enough; we must apply,**

Willing is not enough; _we must do_"

- Goethe

The Future

- **Vaccinomics and Predictive Vaccinology**
  - Abandon a "one size and dose fits all vaccine approach"
  - Predict whether to give a vaccine based on likelihood of response
  - Predict the likelihood of a significant adverse event to a vaccine
  - Predict the number of doses likely to be needed to induce a response to a vaccine (HBV and measles examples)
  - Design/develop new vaccines
  - Next – apply vaccinology 3.0 to a new paradigm of personalized vaccinology…

Acknowledgments

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