Biomarkers, Early Prediction of Vaccine Efficacy and Safety

Giuseppe Pantaleo, M.D.
Professor of Medicine
Head, Division of Immunology and Allergy
Executive Director, Swiss Vaccine Research Institute
Lausanne University Hospital, Lausanne, Switzerland
General Considerations I

- Existing vaccines have been mostly developed empirically.
- Vaccine targets such as TB, malaria, HIV, CMV and many others are more challenging and require the development of a more rationale approach.
- Clinical development costs have exploded and the cost of failures at a late clinical stage is not any more sustainable.
General Considerations II

- New tools are needed to predict the safety and efficacy of vaccine candidates at an earlier stage of development.

- New algorithms to guide the decision-making process of vaccine development from pre-clinical/early clinical into advanced clinical development need to be developed through the identification of robust biomarkers of safety and of efficacy.
General Considerations III

The empirical approach has been based on

- **CLINICAL ENDPOINTS**
- **BIOMARKERS**
- **BIOLOGICAL MECHANISMS**

The rationale approach has to be based on

- Prediction of Safety and Efficacy
- Identification of Effector Mechanisms
Definition of Biomarkers I

- “A biochemical feature or facet that can be used to measure the progress of disease or the effects of treatment” (MedicineNet dictionary)
- Biomarkers indicate
  - A current biological state (diagnostic), or
  - The likelihood of a future biological state (predictive)
- Can replace clinical endpoints that would be measurable only later (plasma HIV RNA)
Biomarkers of Safety I

- **Safety of vaccine is related to immunotoxicity**
  - **Inflammation**
    - Reactogenicity is mainly due to the stimulation of innate immunity
    - Local and systemic reactogenicity can be assessed in the:
      - preclinical setting
      - clinical setting
    - Current *in vivo* assessment methods of inflammation are not adapted to fast screening
Biomarkers of Safety II

- **Autoimmunity**
  - Difficult to characterize autoimmune humoral and cellular responses
  - Autoimmune responses can be transient
  - No straightforward causal relationship between autoimmunity and clinical disease
  - How to define a threshold?
  - Also potential bystander activation of pre-existing autoimmune response
  - Analysis of antigen sequence for homology with host proteins
  - Which response to look for?
Biomarkers of Safety III

- **Very common and common adverse events**
  - Early assessment can be made pre-clinically and in Phase I trials
  - Attempts are made to develop biomarkers using partially *in vitro* reconstituted immune systems

- **Rare and very rare adverse events**
  - Low frequency is a major issue, they cannot be addressed pro-actively
  - Cases are very valuable and should be extensively studied using all available technologies
    - Example of Pandemrix and narcolepsy
Innovation in Biomarkers of Safety: The BioVacSafe EU Project

- The EU is investing in the enhancement of vaccine safety through BioVacSafe (http://www.biovacsafe.eu/), an Innovative Medicine Initiative (IMI)
  - The overall objective of the project is the development of cutting edge tools to speed up testing of vaccine safety, both before and after launch
  - Two of the three specific objectives focus on biomarkers
    - The characterization of early inflammation and the identification and validation of biomarkers of early inflammation and allergic responses
    - The identification and validation of early biomarkers of autoimmunity and their use to help identifying population at risk of developing autoimmunity
Innovation in Biomarkers of Safety: The BioVacSafe EU Project

- Baselines will be defined using existing vaccines considered to be safe

- Responses in animal models will be compared with those obtained in humans
Innovation in Biomarkers of Safety: The BioVacSafe EU Project
Biomarkers Also Known as Immune Correlates of Protection: Definition By Stanley A. Plotkin

- **Immune Correlate:**
  - An immune response that is responsible for and statistically interrelated with protection

- **Surrogate:**
  - An immune response that substitutes for the true immunologic correlate of protection, which may be unknown or not easily measurable
Biomarkers of Efficacy: Antibodies

- Why antibodies are the primary immune correlate of efficacy?
  - Pathogens may reach the target organ(s) through the bloodstream
  - Pathogens may be pathogenic through the secretion of toxins
  - Pathogens may replicate at the port of entry, i.e. at mucosal level

- Antibodies may efficiently intercept and neutralize the pathogens when present in an extracellular state and/or toxins
  - Circulating antibodies
  - Mucosal antibodies
Antibodies: Effector Mechanisms

- Neutralization
- Bactericidal
- Opsonophagocytosis
- Neutralization of toxins
Biomarkers of Efficacy: T-cells

- T-cells (CD4 T-cells) have been proposed as immune correlates of protection from infection with/or without antibodies in:
  - BCG
  - VSV
  - Smallpox
  - Influenza (?)

- T-cells are however critical for providing B-cell help and generation of:
  - Plasmablasts
  - Memory B-cells
  - High affinity antibodies
Innovation in Biomarkers of Protection

- **Systems Biology and Vaccine Development**
  - Instrumental in the identification of unique gene expression signatures between different vaccines and primary viral infections at cell population level
  - **Limitations of Systems Biology**
    - Data are generated at cell population level without any information about the diversity at single cell level
    - It does not provide information about the function(s) of the cells responding to vaccination
    - It does not provide information about the biological mechanism of efficacy
Polysaccharide response

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Novel Powerful Technological Developments
Gene expression profile in lymph node (LN) memory CD4 T-cell populations from healthy individuals

Differential gene expression between the CD4 T-cell populations fdr <0.05
Memory CD4+ T-cell populations from LN of healthy subjects

Gene expression profile at single cell level by Fluidigm

Cumulative data of 8 LNs
Multiparameter Mass Cytometry

- Cells stained with antibodies labeled with elemental isotopes
- Single cell droplets introduced into mass cytometer
- Argon plasma at >7000 ºC vaporizes cells leaving elements
- Data for each cell is integrated into an FCS file

**Modular design of panels**

- **Core panel** to differentiate immune cell populations
  - 10 labeled antibodies
- **Refined selection of individual cell populations**
  - 5-10 antibody channels
- **Cytokine, transcription factor and cell signaling panels**
  - 15-20 antibody channels

**Cell populations and phenotype**

- B-cells
- DC
- NK
- Co-inhibitors

**Functional characterization**

- Cytokines
- Transcription factors
- Phospho signaling
Analysis of Multiparametric Mass Cytometry Data

SPADE software analyses cellular hierarchies and maps immune cell lineages based on surface expression markers.
Conclusions

- Identification of early biomarkers of vaccine safety and efficacy remains challenging and innovative approaches are needed.

- Innovative and comprehensive approaches such as the BioVacSafe EU initiative have the possibility to advance substantially the field.

- The BioVacSafe Initiative should be used as a model for the development of similar comprehensive programs for the identification of early biomarkers of efficacy.

- The development of a Biomarker Vaccine Efficacy initiative which brings together the polyvalent technological expertise necessary to link systems biology to function(s) and biological mechanism(s) may represent a powerful strategy for the identification of early biomarkers/immune correlates of efficacy.