CDC Anthrax Vaccine Research Program

Non-human Primate Study Design & Application to Correlates of Protection

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Anthrax Vaccine Research Program

Three interrelated studies:

1) Human Reactogenicity and Immunogenicity Clinical Trial to Address Change in Route of Administration and Dose Reduction

2) Non-human Primate Vaccine Dose Ranging, Immunogenicity and Challenge Trial

3) Anthrax Pathogenesis, Immunology and Correlates of Protection Against Inhalational Challenge

Human Clinical Trial

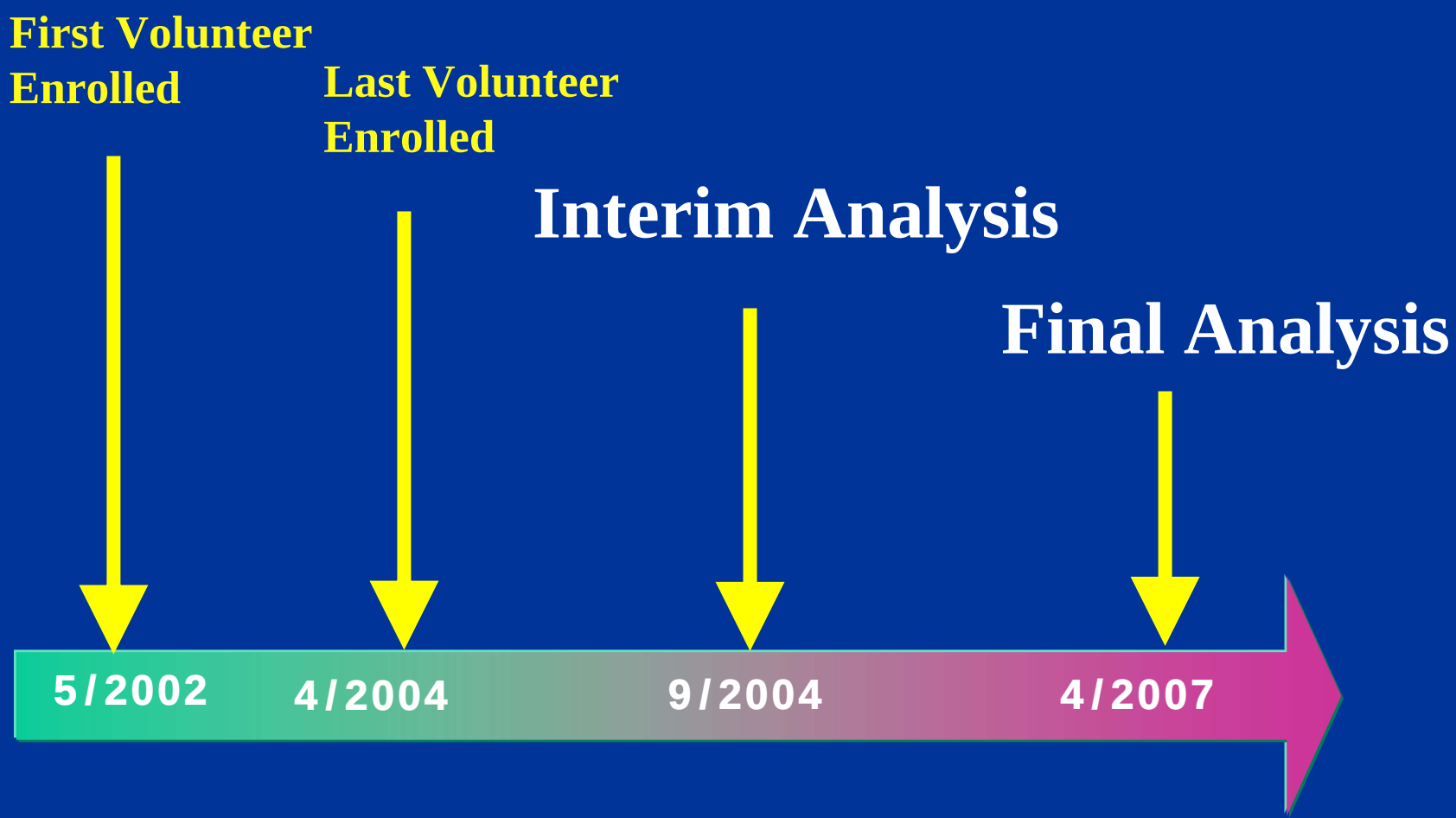
Design

- Randomized, double-blinded, placebo-controlled
- 6 study groups, N=1560 adults
- Study duration: 43 months
- Primary Endpoints
  - Immunogenicity: Four-fold rise in anti-PA IgG titer & Geometric Mean Concentration measured by ELISA
  - Reactogenicity: Local injection site reactions

Objective

- Change route of administration from SQ to IM
- Drop 3 of 6 doses from priming regimen and boost every 2-3 years

Timeline for the Human Clinical Trial



NHP Study

- Objectives -

- To identify immunological correlates of protection in macaques at 12, 30 & 42 months post vaccination
- To extrapolate for surrogate markers of protection in humans
- To support the proposed changes in AVA human route of administration and dosing schedule

NHP Study

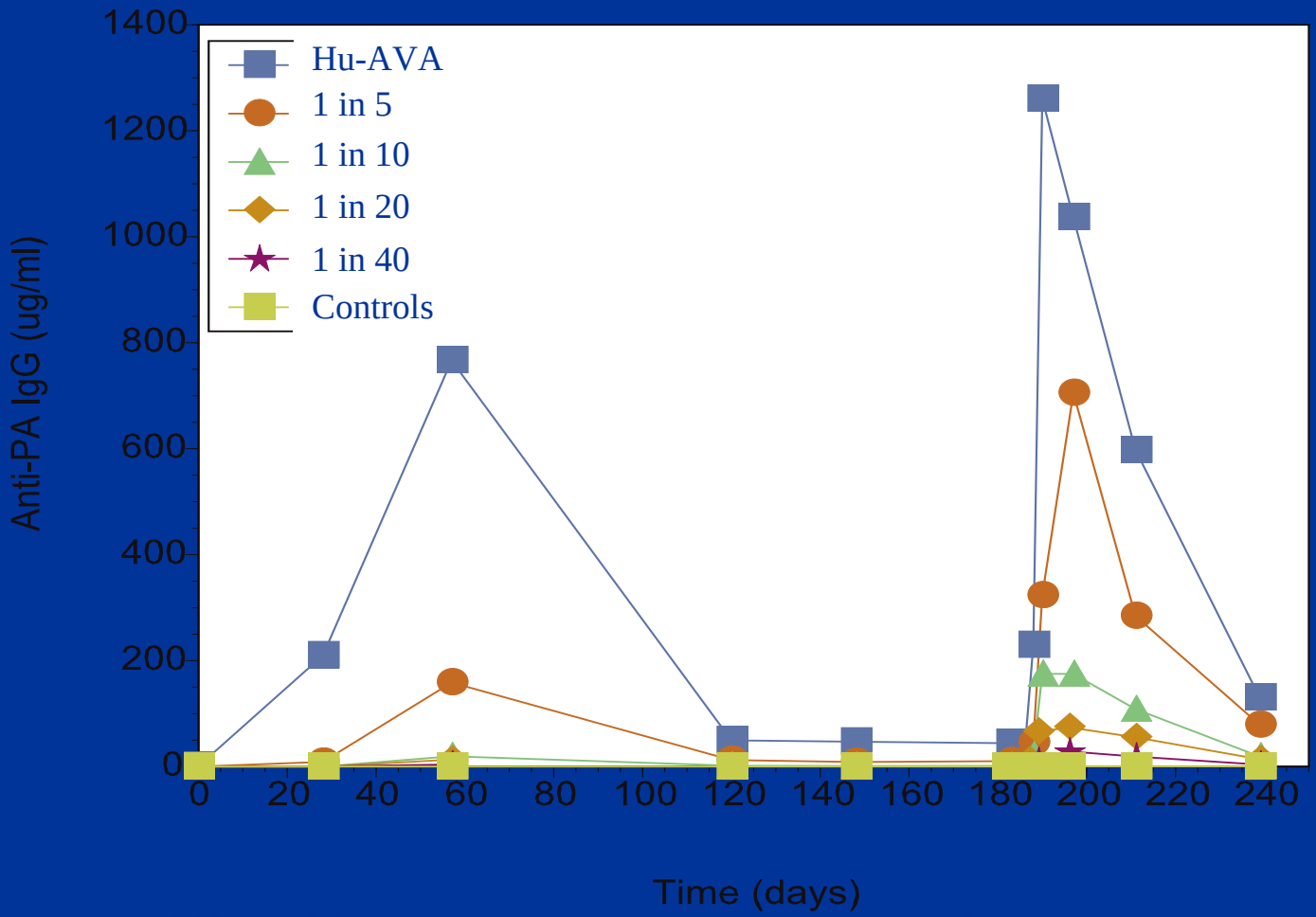
- Methods -

- Modulate NHP immune responses to AVA by dose variation
  - Human dose AVA, 1/5, 1/10, 1/20, 1/40, + controls
  - Vaccine injections at 0, 4, 26 weeks IM
- Challenge at 12, 30 & 42 months post 1st vaccination
- Immunological & protection data to build a model for predicting a defined outcome

survival

- Apply this relationship to human clinical study to predict protection of vaccinees

AVA Dose Modulates the Anti-PA IgG Response



Relationship of NHP Studies to the Human Clinical Trial

- Vaccination regimen parallels target human primary series of 0-wks, 4-wks and 6 months
- Timing of challenges parallels points where dose reduction occurs for human study groups
- Timing of blood draws (+ kinetics at 6 months) in NHPs corresponds to humans

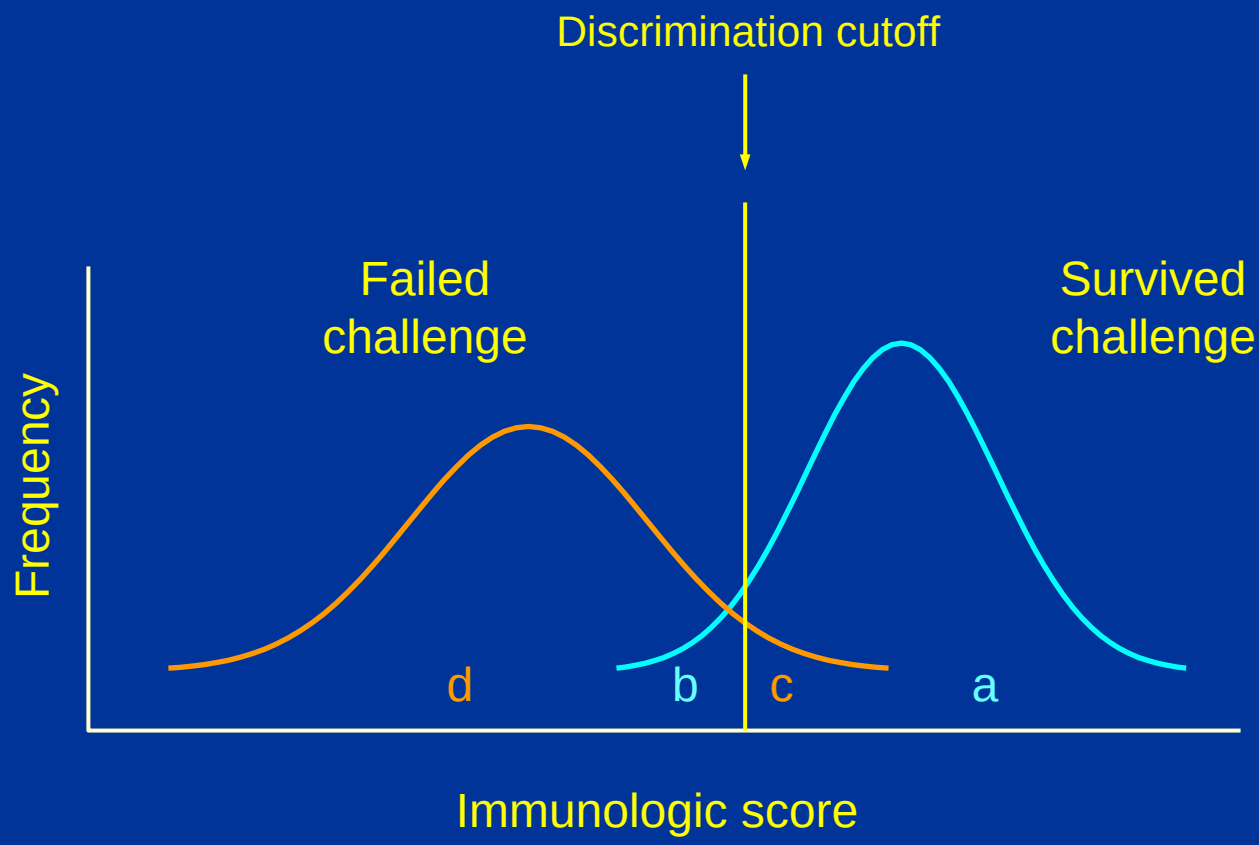
NHP Survival is Anticipated to be Dose and Time Dependent

Vaccine Dilution	Anticipated Survival		
	12 Months	30 Months	42 Months
Full Dose	100%	100%	>60%
1/5	100%	>60%	30-60%
1/10	>60%	30-60%	<30%
1/20	30-60%	<30%	0
1/40	<30%	0	0

Correlation to NHP Survival

- Select variables (assay combinations) with greatest discriminating power
- Calculate immunologic ‘score’ for all subjects
- Discriminant cutoff may be placed to maximize sensitivity or specificity
- In this study, cutoff will be placed to optimize sensitivity (set to 95%)

Logistic Discriminant Analysis



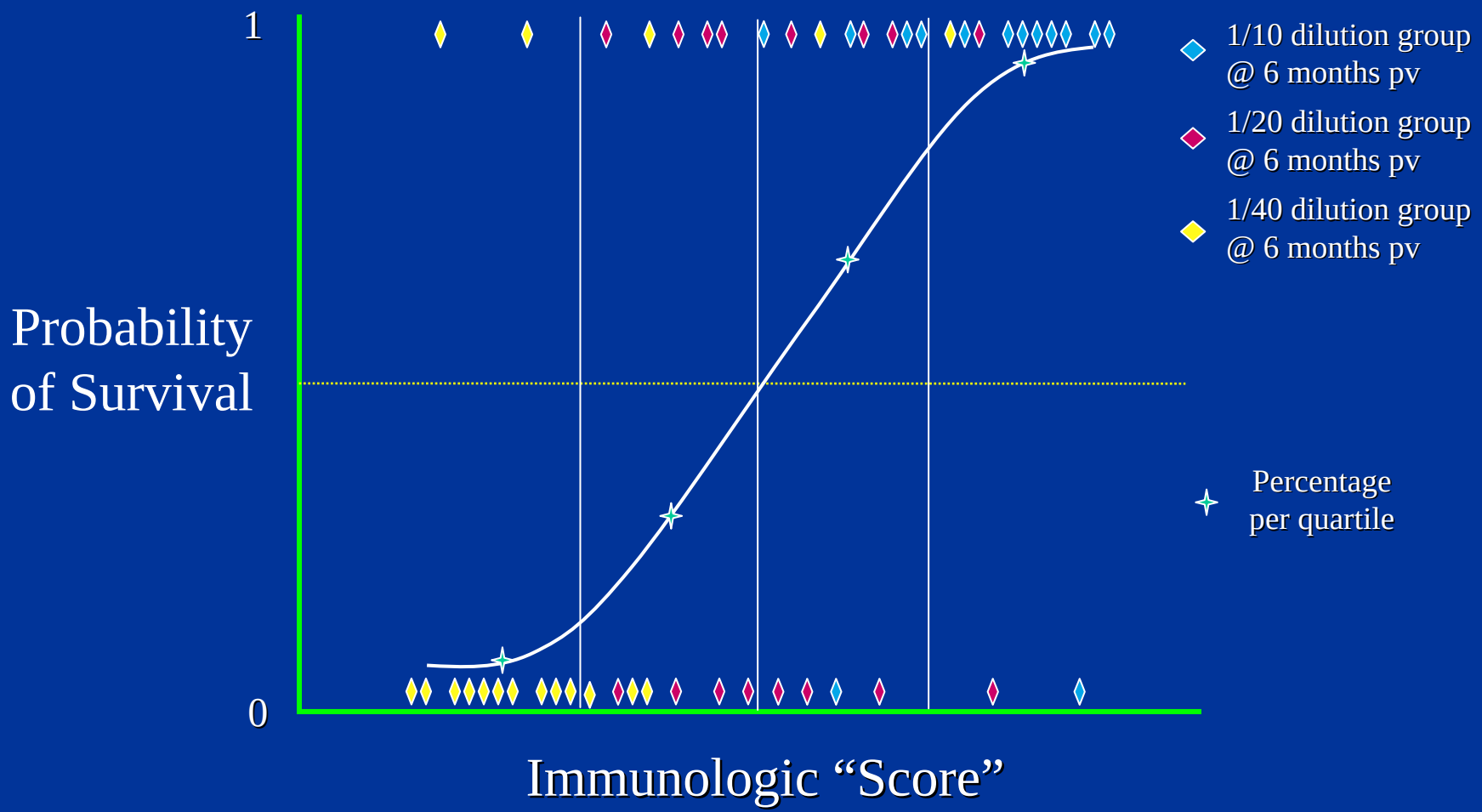
a = survivors correctly classified as survivors

b = survivors incorrectly classified as failures

d = failures correctly classified as failures

c = failures incorrectly classified as survivors

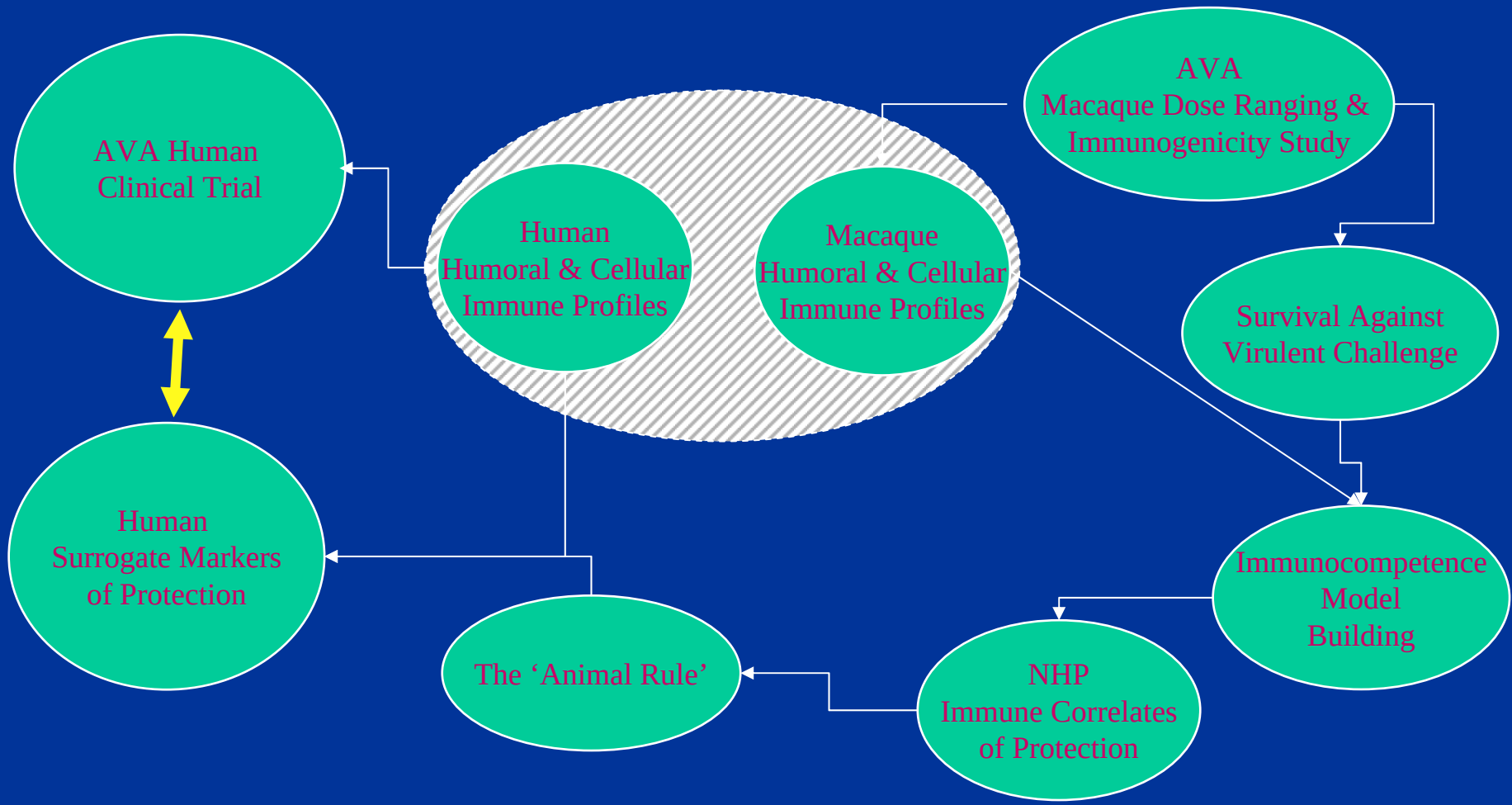
Immune Response vs. Survival
~ Model Building ~



Correlation to Human Study

- Assumes NHP immunogenicity-survival curve can be used to predict protection in humans
- Application of the ‘Animal Rule’
- Apply discriminant function to Immune Correlates Study clinical trial subset data
- Examine how vaccinated and unvaccinated individuals are ‘scored’
- Determine if these variables convey information about onset of protection & potential for survival

An Integrated Study in Humans & Non-Human Primates



Acknowledgements

- Microbial Pathogenesis and Immune Response Laboratory, CDC
- Biostatistics and Information Management Branch, CDC
- National Immunization Program, CDC
- Anthrax Vaccine Immunization Program, DoD
- US Army Medical Research Institute for Infectious Diseases, DoD
- Mayo Clinic and Foundation
- University of Alabama at Birmingham
- Battelle Memorial Institute
- Baylor College of Medicine
- Walter Reed Army Institute for Research
- Emory University School of Medicine
- Emory University Vaccine Center
- Ohio State University
- BioPort Corporation
- Technical Resources International
- Datametrics Incorporated