

August 2015

A Non-Replicating Ad5 Vaccine for the Treatment of HSV-2 Infection

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VAXART

UNLOCKING THE FULL POTENTIAL OF ORAL VACCINES

VAXART

ORAL Prophylactic and Therapeutic VACCINES



PLATFORM

First-in-Class: Oral Recombinant Vaccines

- Administered by tablet
- We believe the platform is suitable for delivery of many recombinant protein antigen: Flu, HPV, Hep B, industry pipeline

STAGE

Clinical Stage Company

- H1N1 seasonal Flu tablet vaccine
- Safety/immunogenicity profile competitive with commercial vaccines after single administration

PIPELINE

Advanced Preclinical Pipeline

- Seasonal Influenza (Flu B)
- Norovirus
- RSV
- First Therapeutic Candidate—HSV2

Outline

- Background on Vaxart's oral vaccine technology
 - Non-replicating Ad5-TLR3 agonist platform
- Clinical data from phase I trials using delivery H1N1 vaccine in a tablet
- Characterization of potential T cell antigens for inclusion in our therapeutic HSV-2 vaccine

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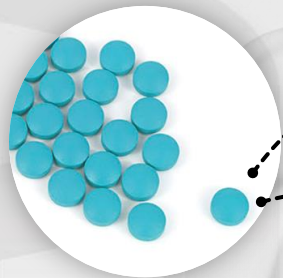
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Characterization of potential T cell antigens for inclusion in our therapeutic HSV-2 vaccine

Tablet Delivers Vectored Vaccine to Small Intestine – Antigen and Adjuvant Are Co-Expressed

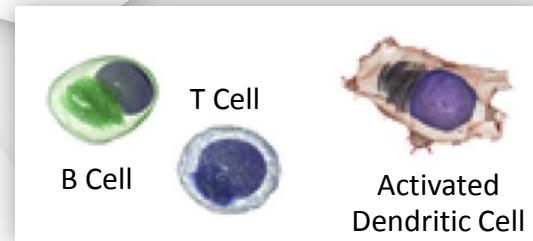
1

Enteric-coated tablet protects against stomach acid and delivers vaccine to small intestine



2

Non-replicating adenovirus 5 (Ad5) vector delivers antigen genes to mucosal epithelium for expression



3

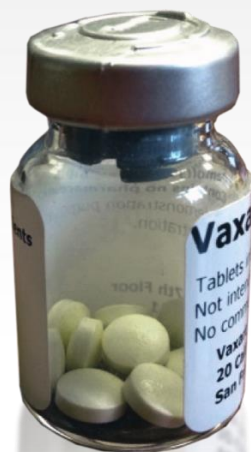
dsRNA adjuvant expressed in the same cell as the antigen activates the immune cascade

Tablet Vaccine: Easy to Distribute and Administer

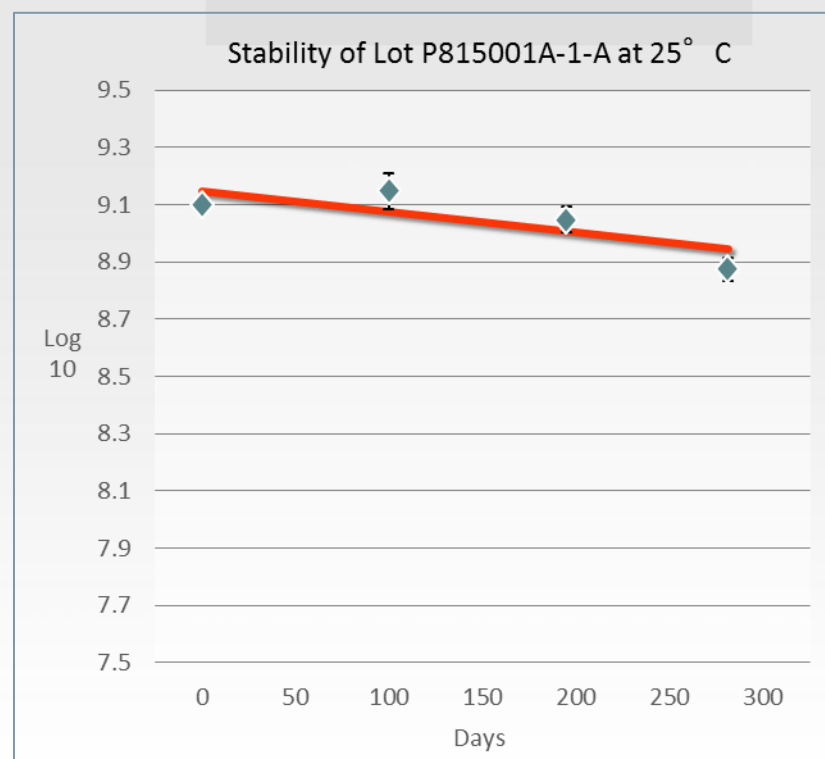
Vaxart Vaccine Advantages

- Needle Free
 - Patient acceptance
 - Ease of administration
 - No needle stick, biohazard

- No Cold Chain
 - Ease of distribution
 - Logistics are simpler
 - Costs are reduced



Stability of Vaxart's Tablet Vaccine



Stable at 25°C > 1 year
 Stable at 4°C >> 1 year

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H1N1 Influenza: Phase I Placebo-Controlled Studies

DELIVERY SYSTEM

Coated Tablets



Purpose:

- Safety and immunogenicity
- Dose ranging

STUDY DESIGN

Randomized, Double Blind, Placebo Controlled

THREE DOSE LEVELS

SUBJECTS

Placebo, 1e9, 1e10 IU

36 (3 x 12)

Placebo, 1e11 IU

24 (2 x 12)

TOTAL

60

Safety Summary: Primarily Mild Adverse Events, Evenly Distributed Between Active and Placebo

SOLICITED ADVERSE EVENTS

ADVERSE EVENT*	TOTAL AEs	1E9	1E10	1E11	PLACEBO
# Subjects		12	13	12	24
Diarrhea	3	1 ¹	1 ¹	1 ¹	0
Nausea	3	1 ¹	0	0	2 ¹
Vomiting	0	–	–	–	–
Abdominal Pain	2	1 ²	0	1 ¹	0
Hematochezia	0	–	–	–	–
Malaise	2	1 ¹	0	0	1 ¹
Anorexia	0	–	–	–	–
Headache	9	3 ¹	1 ²	1 ¹	3 ¹
Fever (Pyrexia)	1	0	0	1 ¹	0

All AEs Mild Except One Moderate Headache and Abdominal Pain

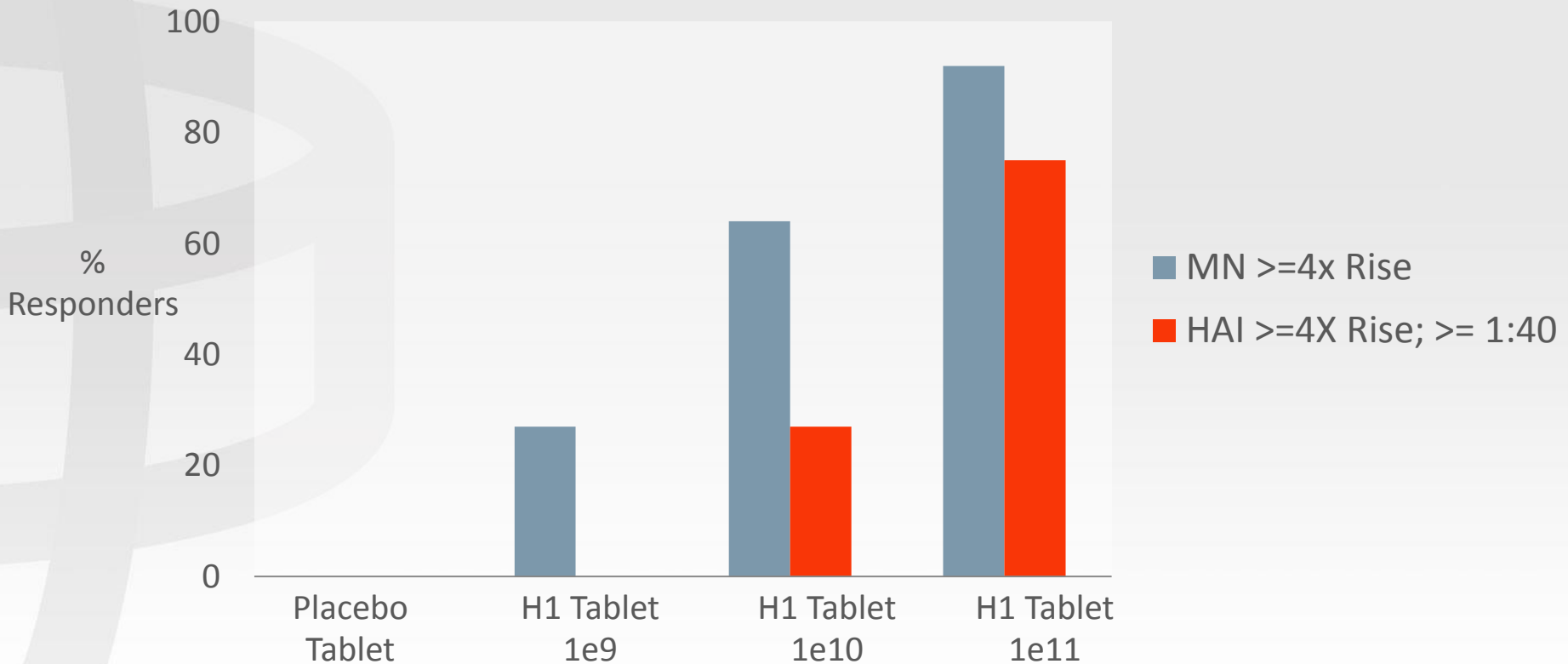
- No Notable Differences in Either Solicited and Unsolicited Adverse Events in Comparison to Placebo Recipients
- No Vaccine-Related SAEs

- Solicited local and systemic adverse events (AEs) collected for 7 days post vaccination. Unsolicited AEs and AEs of special interest (AESIs) collected for 1 year post vaccination.
- Adverse Event Severity: ¹Mild, ²Moderate, ³Severe

Robust and Dose-Dependent Neutralizing Antibody Responses in 92% of Subjects



75% of Subjects Seroconverted by HAI after Single Dosing

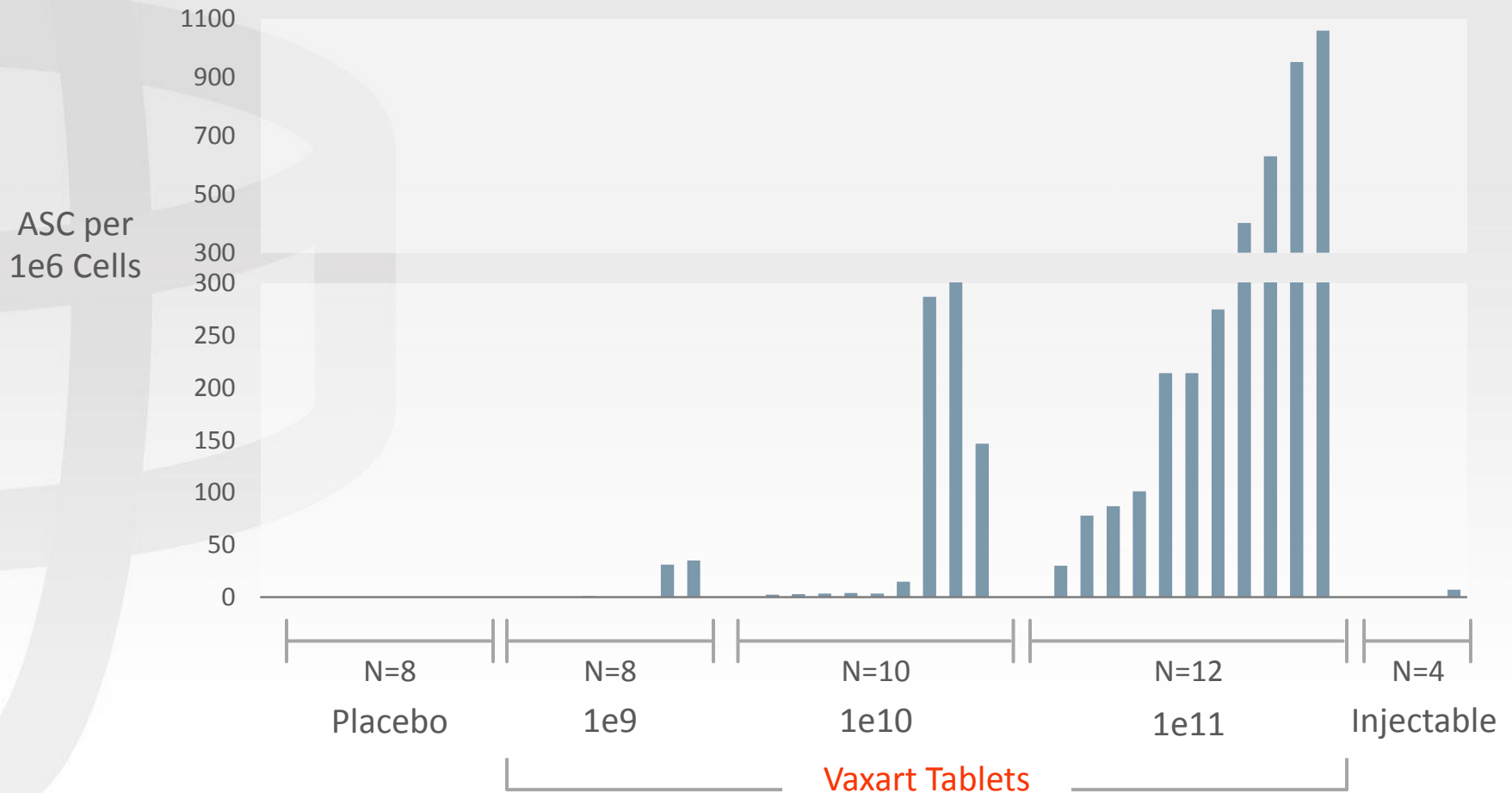


- Hemagglutinin Inhibition (HAI) and Microneutralization (MN) assays conducted by Focus Diagnostics

Advantage-Strong and Dose Dependent Mucosal IgA Immune Response

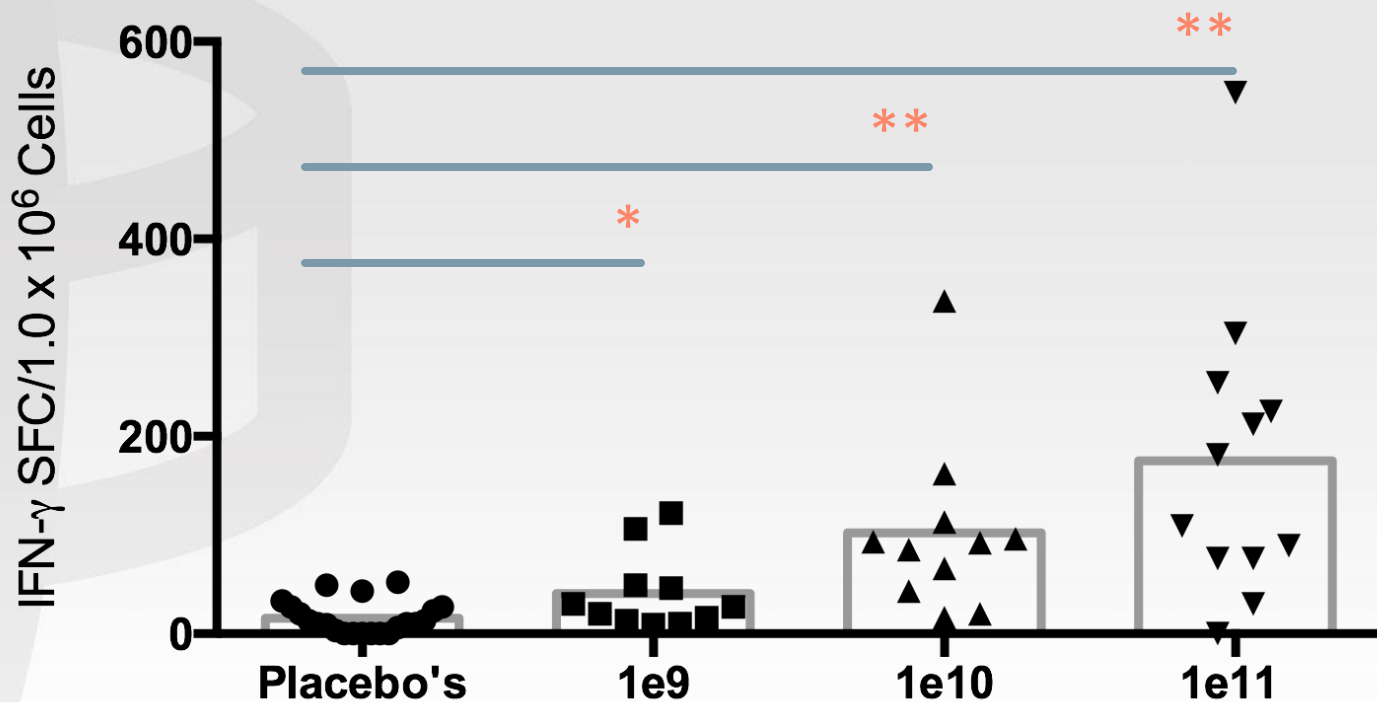


No Mucosal Response when Vaccinated with Commercial Vaccine



IgA Antibody Secreting Cells (ASC) present in peripheral blood at Day 7

Dose Dependent Cell Mediated T Cell Responses



* P \leq 0.05

**P \leq 0.01

Mean

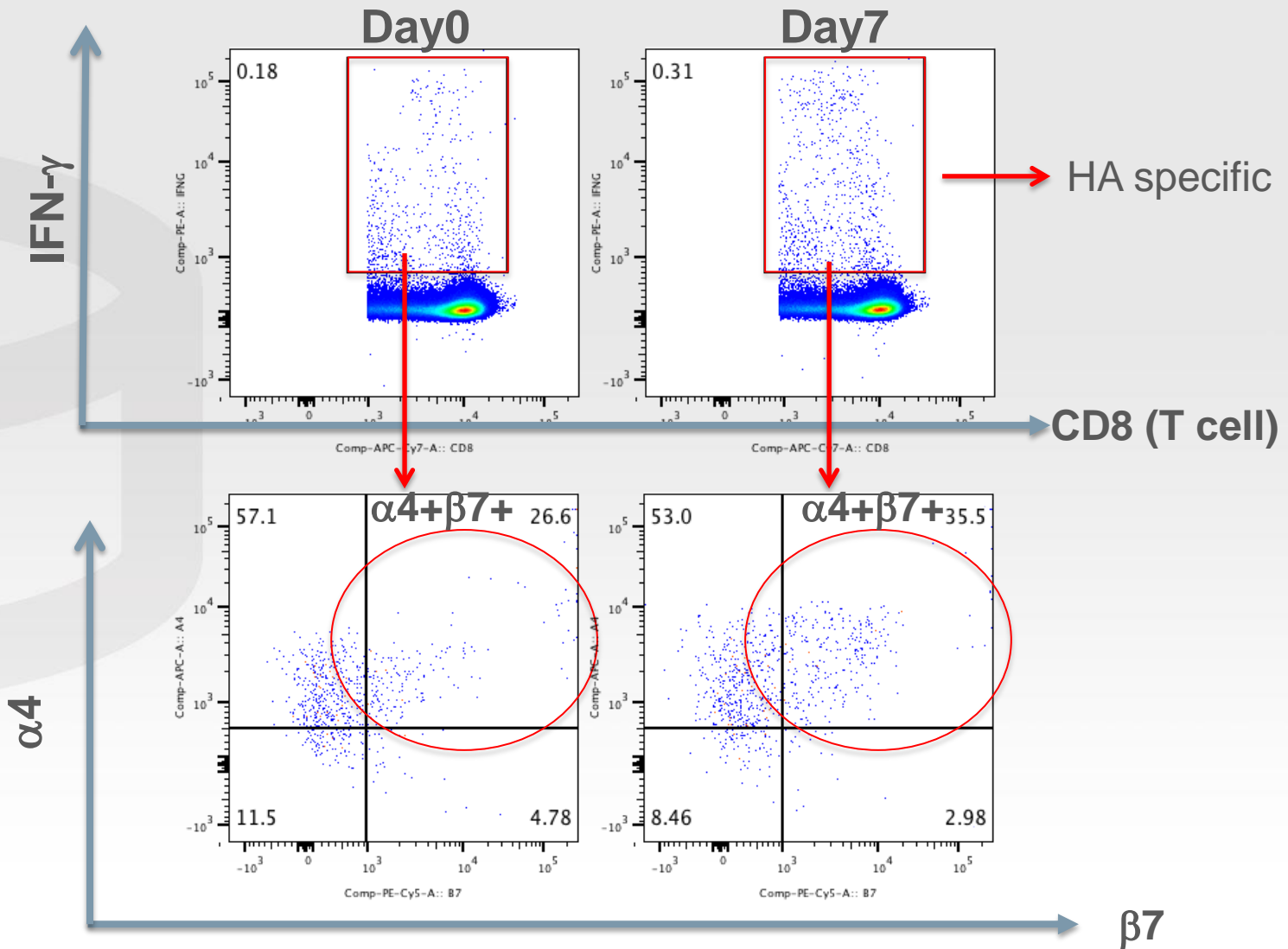
9

41

102

175

Mucosal Homing T Cells Expressing $\alpha 4\beta 7$



$\alpha 4\beta 7$ Directs Genital Tract T Cell Homing

- Trimble et al 2010. Human Papillomavirus 16-Associated Cervical Intraepithelial Neoplasia in Humans Excludes CD8 T Cells from Dysplastic Epithelium. *Journal of Immunology*
- Shannon B et al 2014. Impact of Asymptomatic Herpes Simplex Virus Type 2 Infection on Mucosal Homing and Immune Cell Subsets in the Blood and Female Genital Tract. *Journal of Immunology*

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Vaxart's Therapeutic HSV-2 Vaccine Program

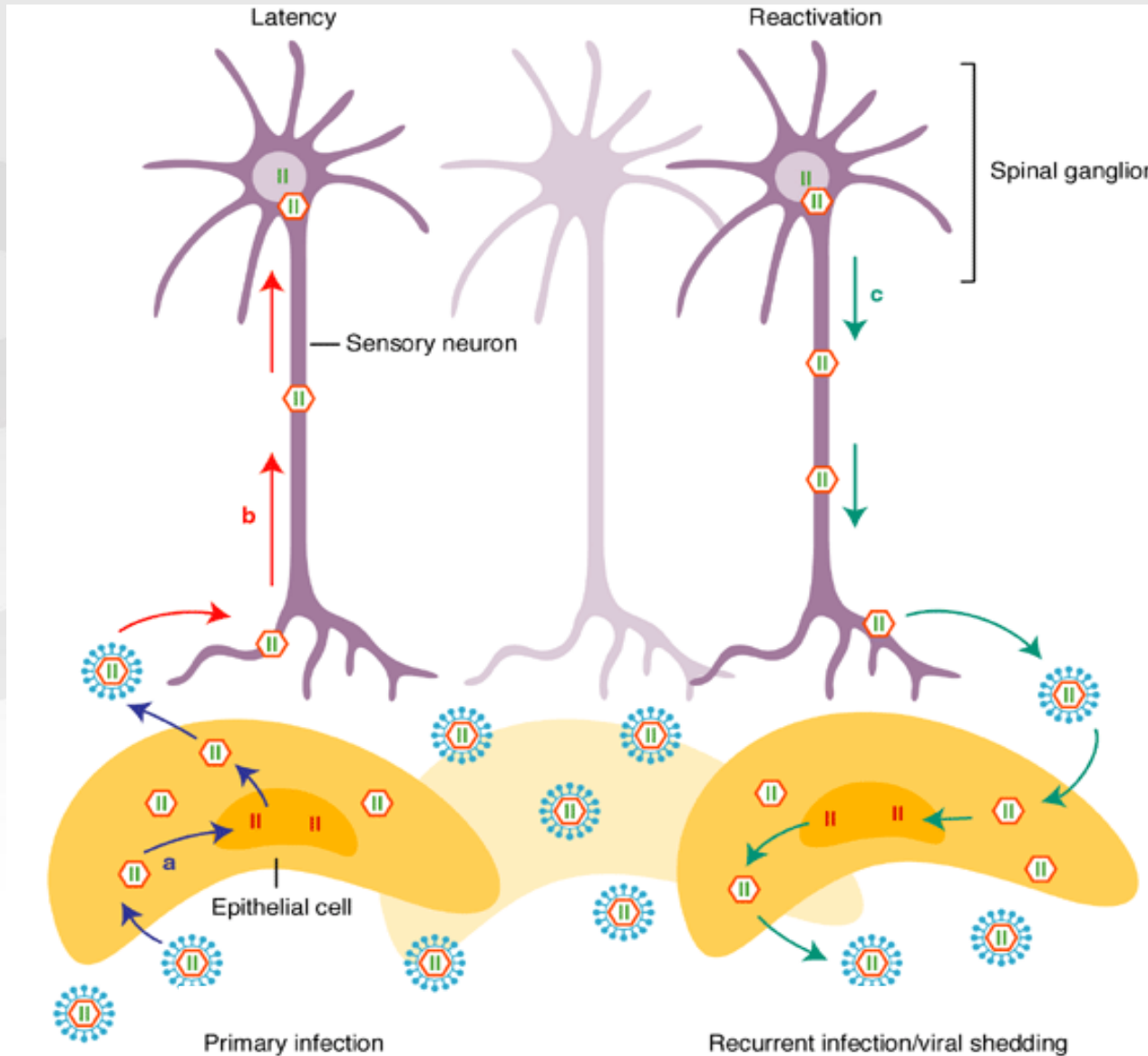
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HSV-2 Life Cycle



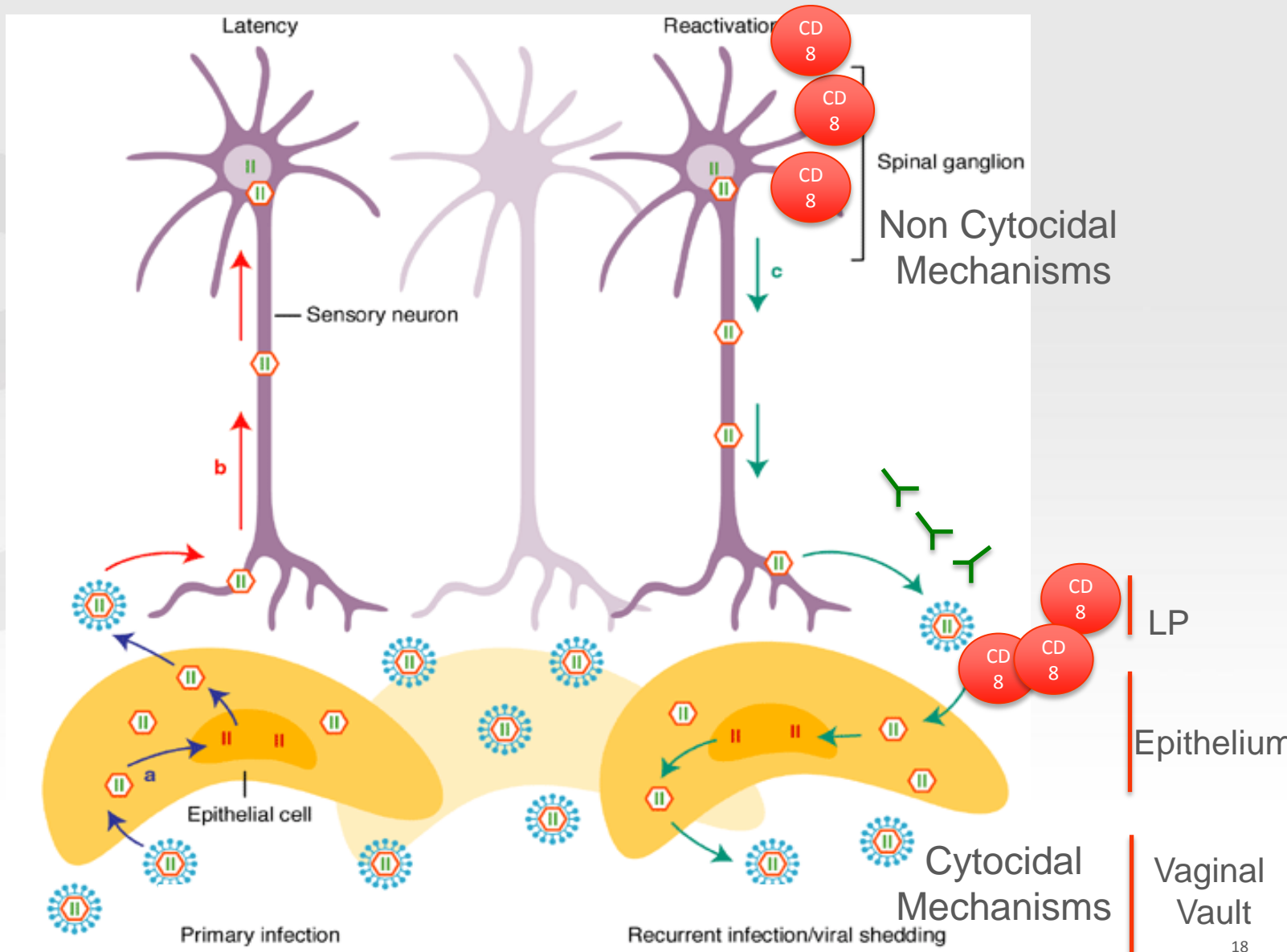
LP

Epithelium

Vaginal Vault

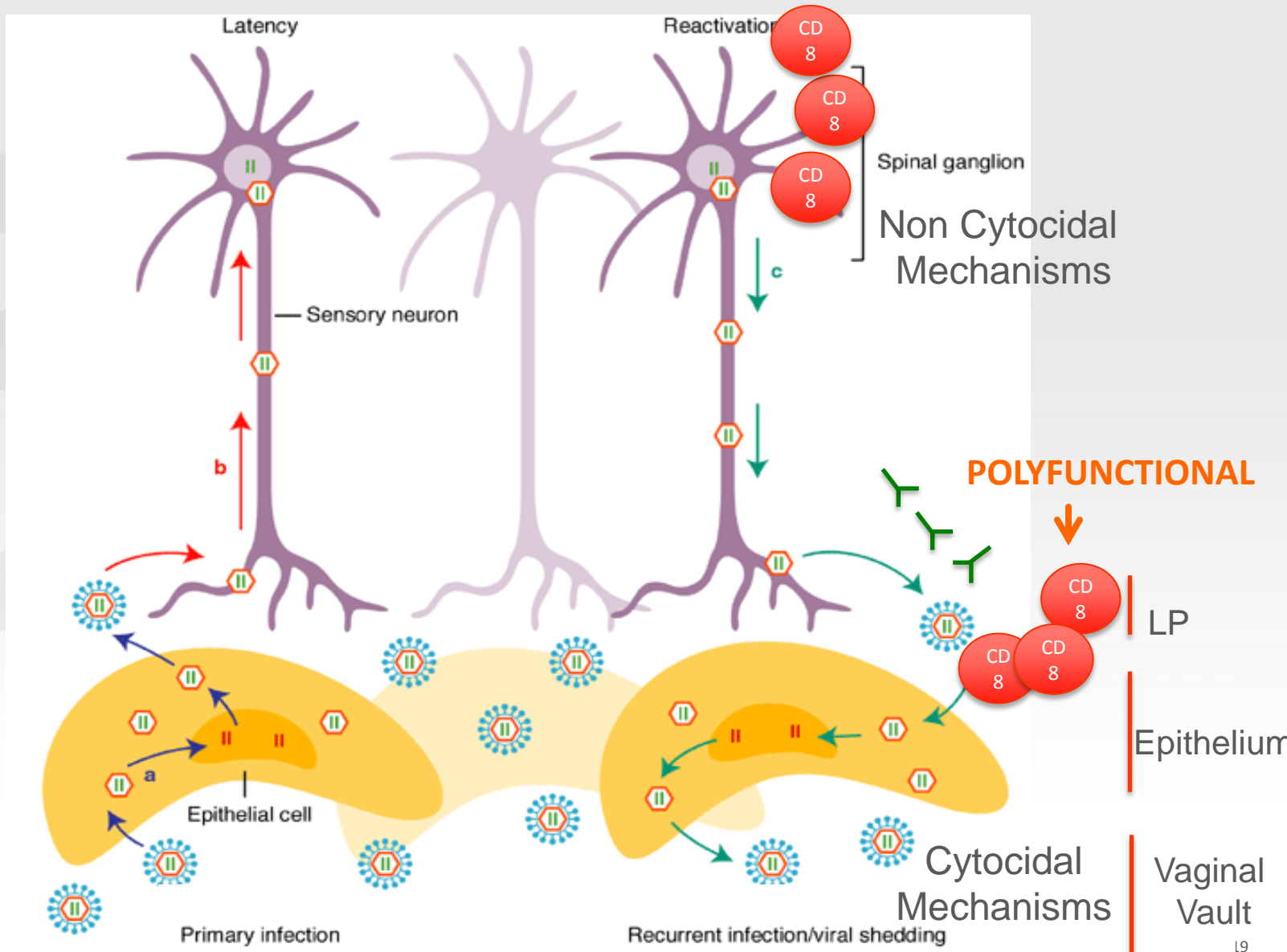
Adapted from Expert Reviews in Molecular Medicine 2003

HSV-2 Life Cycle-Therapeutic Vaccination



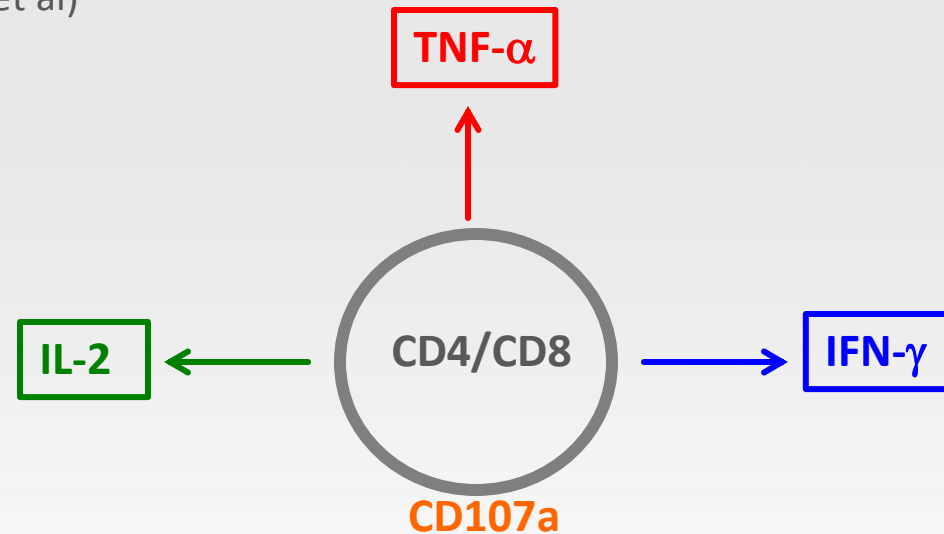
Adapted from Expert Reviews in Molecular Medicine 2003

HSV-2 Life Cycle-Therapeutic Vaccination



Why Polyfunctional CD8 T Cells?

- Efficacious vaccines
 - Yellow Fever (Akondy et al, Miller et al)
 - Small Pox (Miller et. al)
- HIV Non-progressors (Betts et. Al)
- “Asymptomatic” HSV seropositive (Srivastava R et. al)



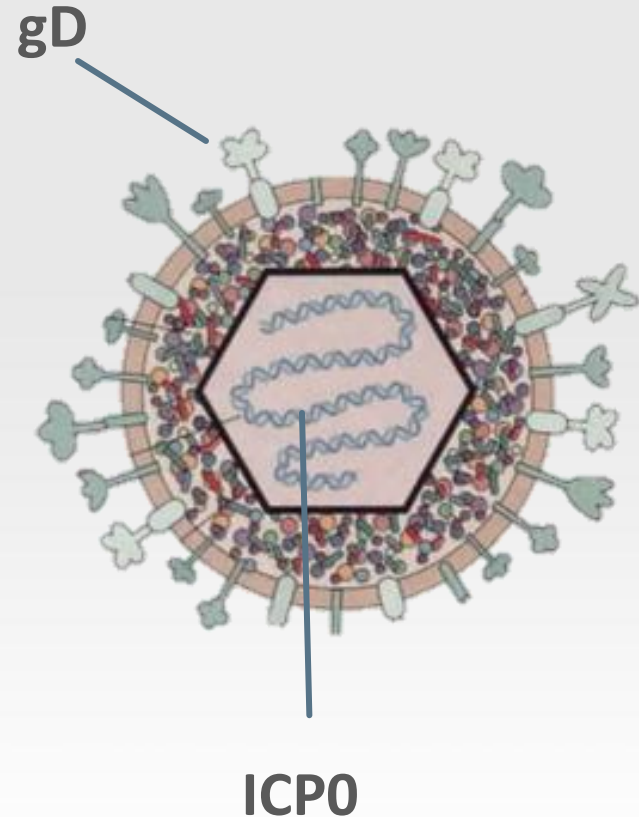
Vaxarts HSV Vaccine-gD Plus T Cell Antigen ICP0^{mut}

gD-Late Gene

- Envelope glycoprotein
- Good neutralizing Ab target
- Used to enter host cell
- Documented T cell epitopes

ICP0-Immediate Early Gene

- First gene expressed as HSV reactivates
- Rapid Immune response -Ag is presented early after infection
- Documented CD8 T cell epitopes



Therapeutic Guinea Pig Model of HSV-2

HSV-2

Primary Disease

Monitor Lesion Scores/Shedding

D0

D14

D21

D28

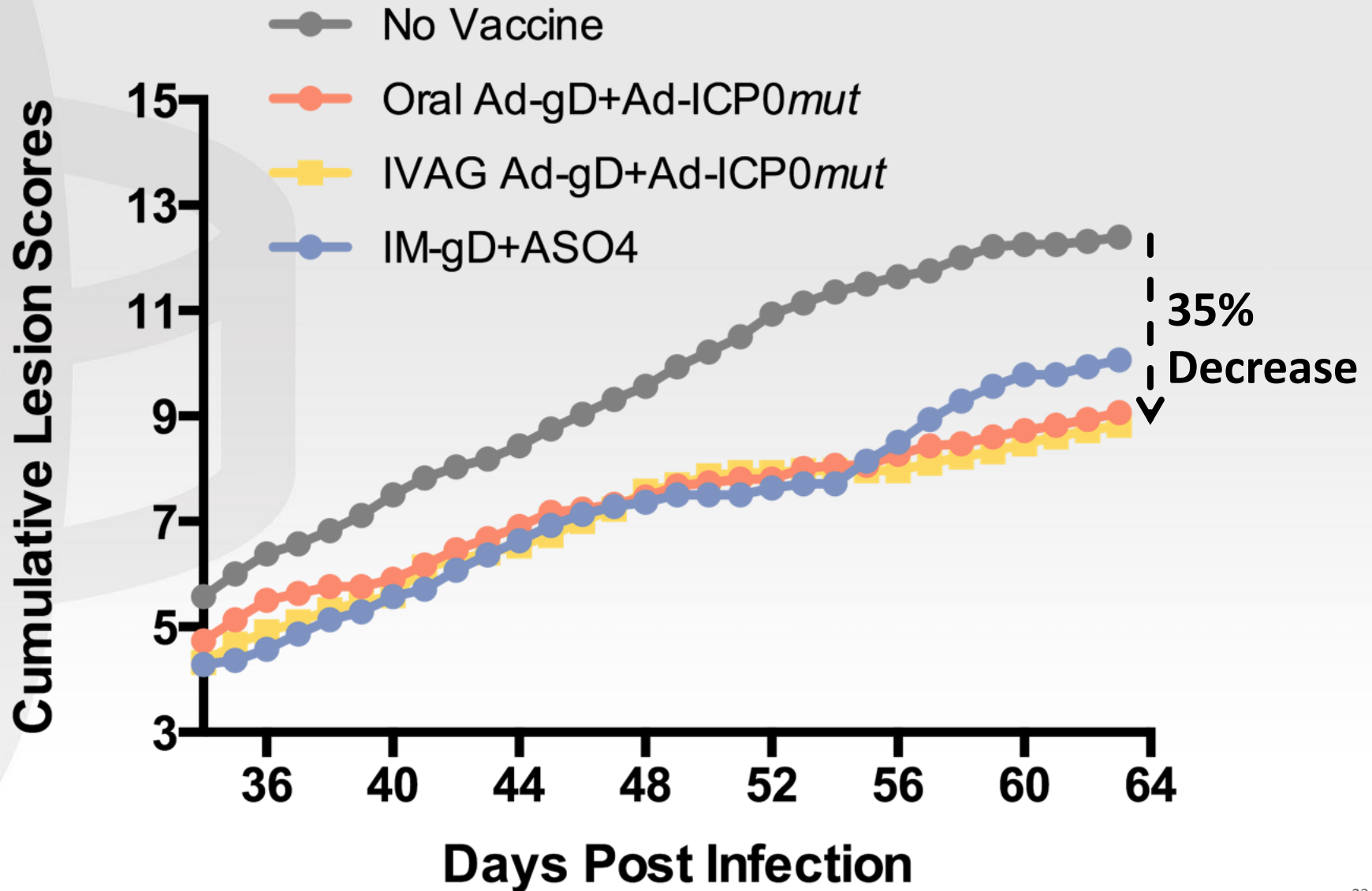
D63

Ad5-gD-ICP0-dsRNA

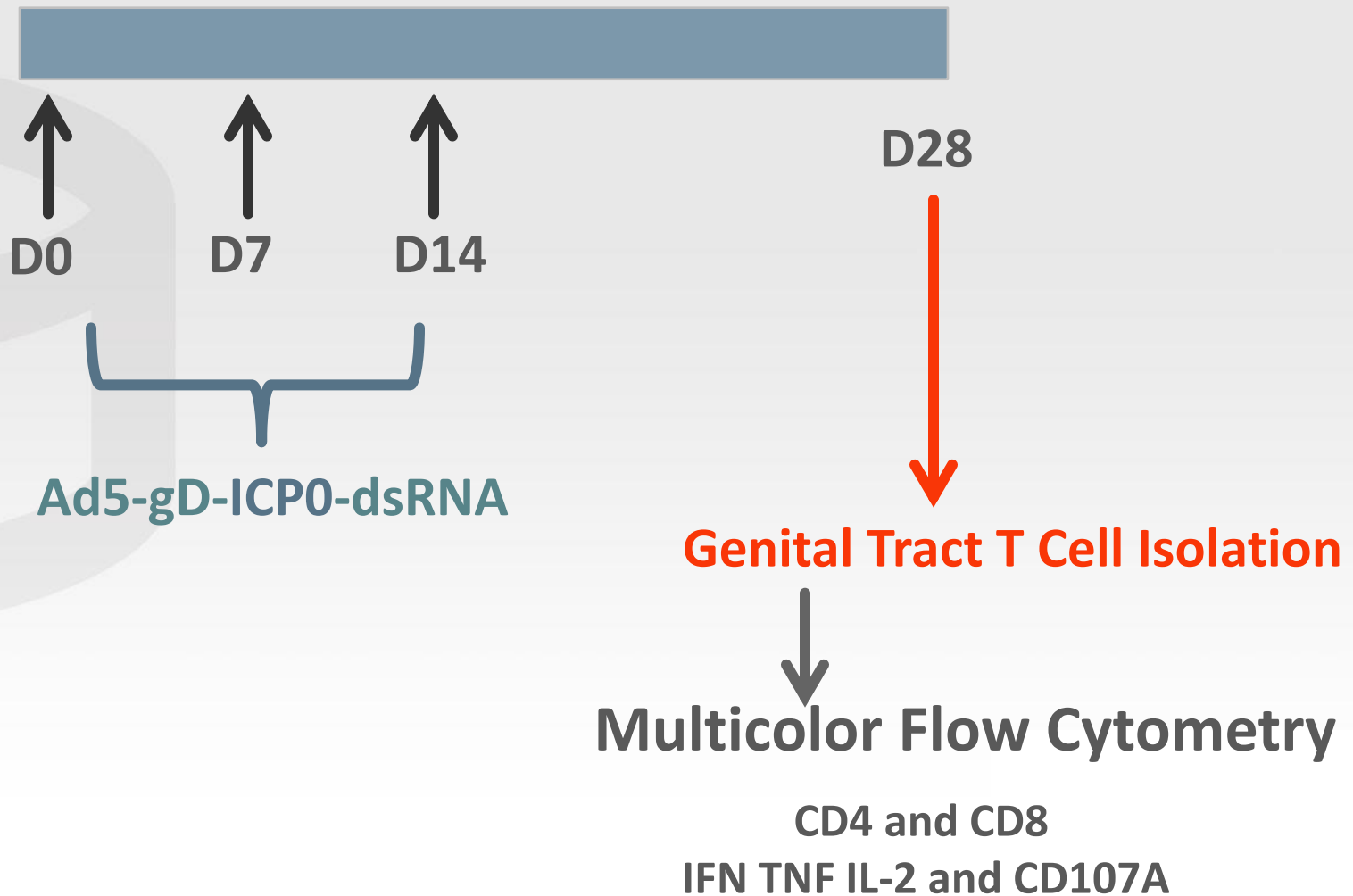
R. Cardin,
D. Bernstein



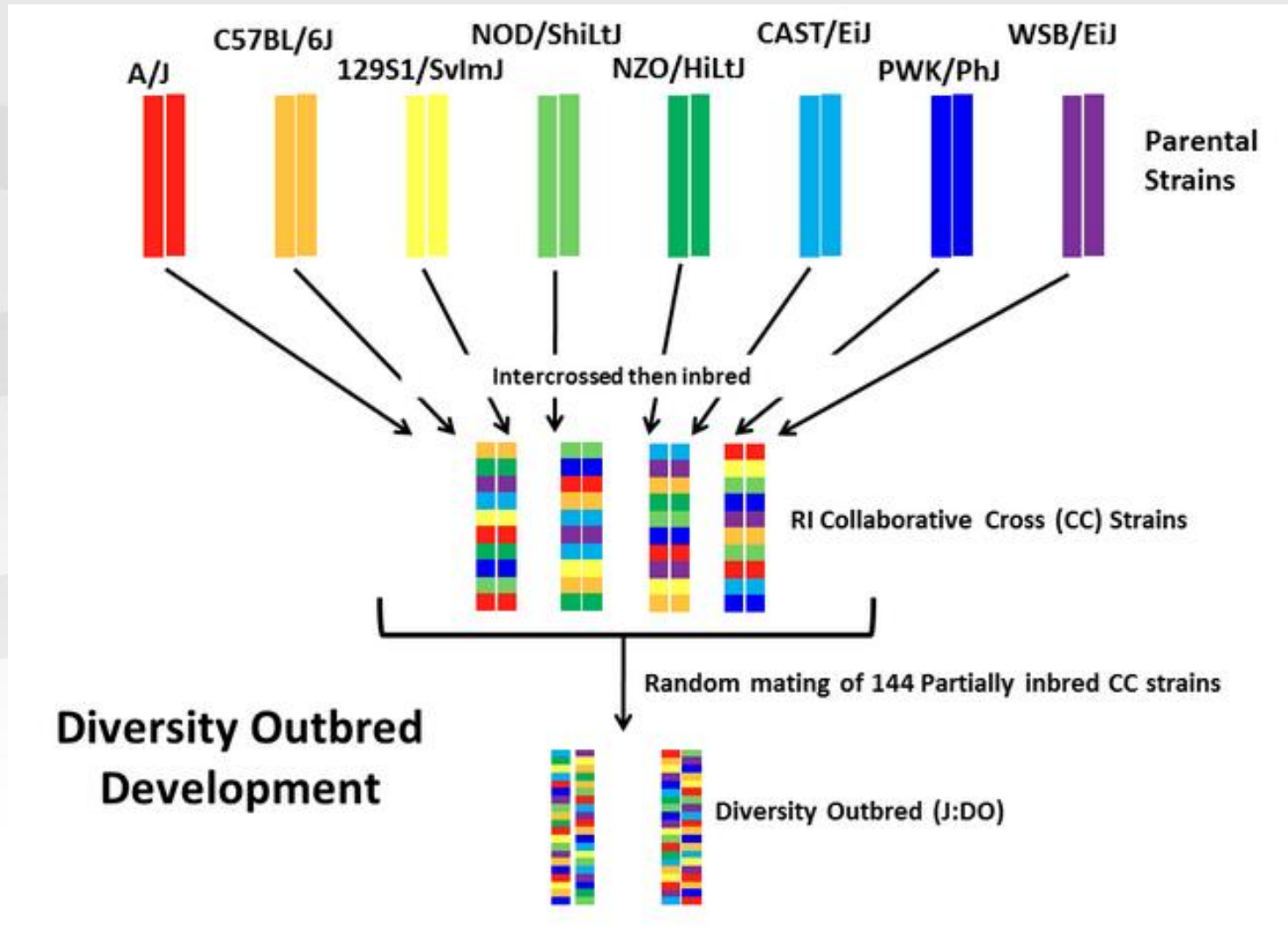
Cummulative Lesion Scores Reduced After gD+ICP0^{mut} Vaccination



Mouse Genital Tract T Cell Characterization

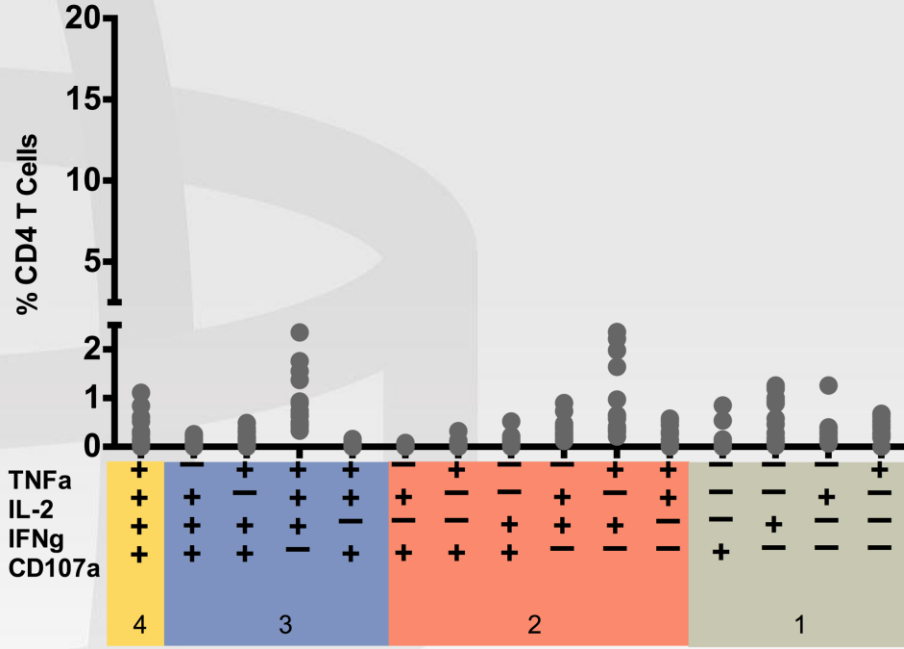


Jax Diversity Outbred Mice J:DO-To Mimic Outbred Human Population Immune Response

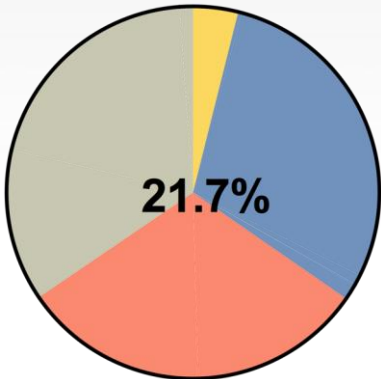
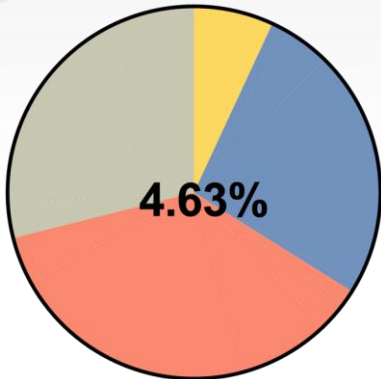
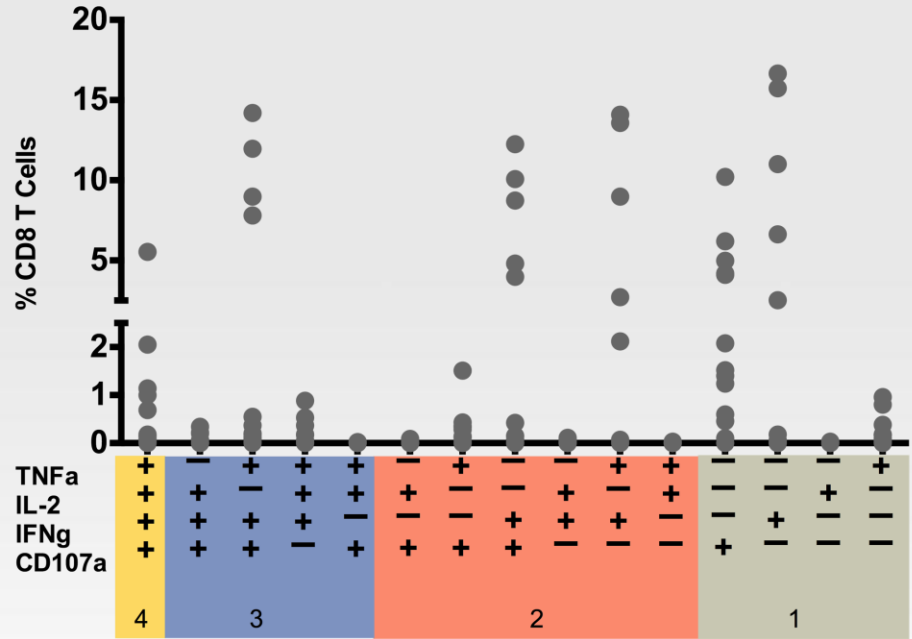


Analysis of T cell Subsets in the Genital Tract Induced After Vaccination with Ad-gD-dsRNA

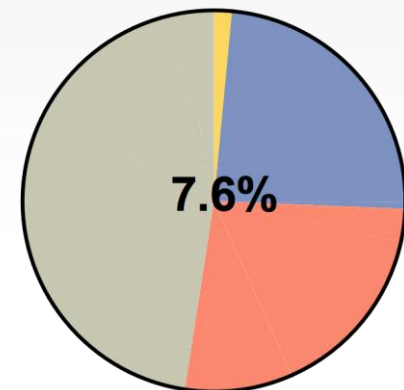
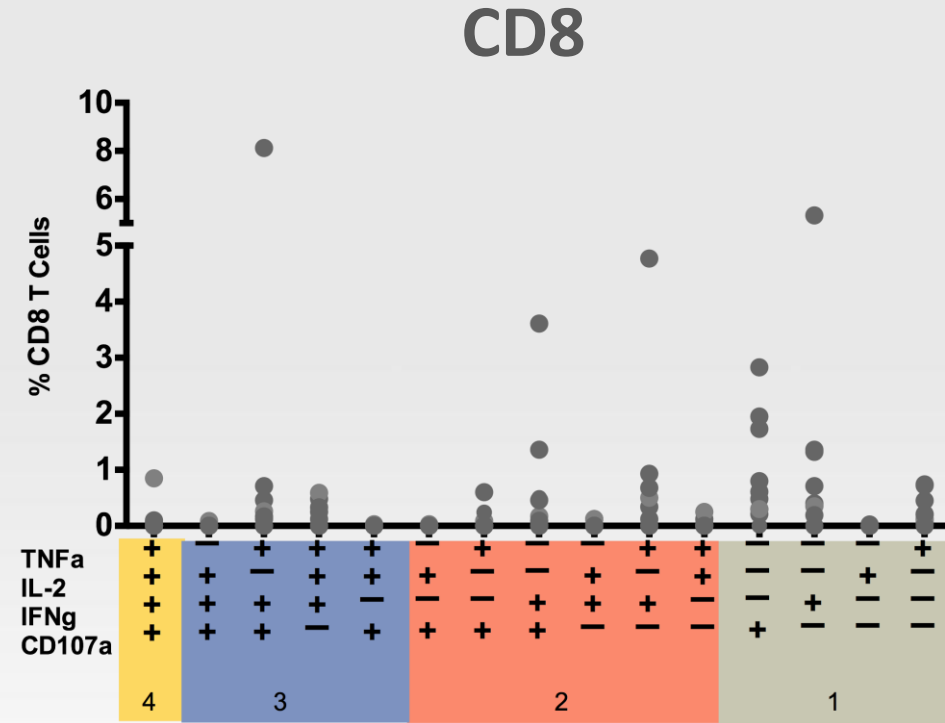
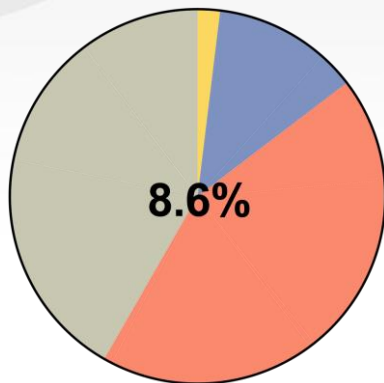
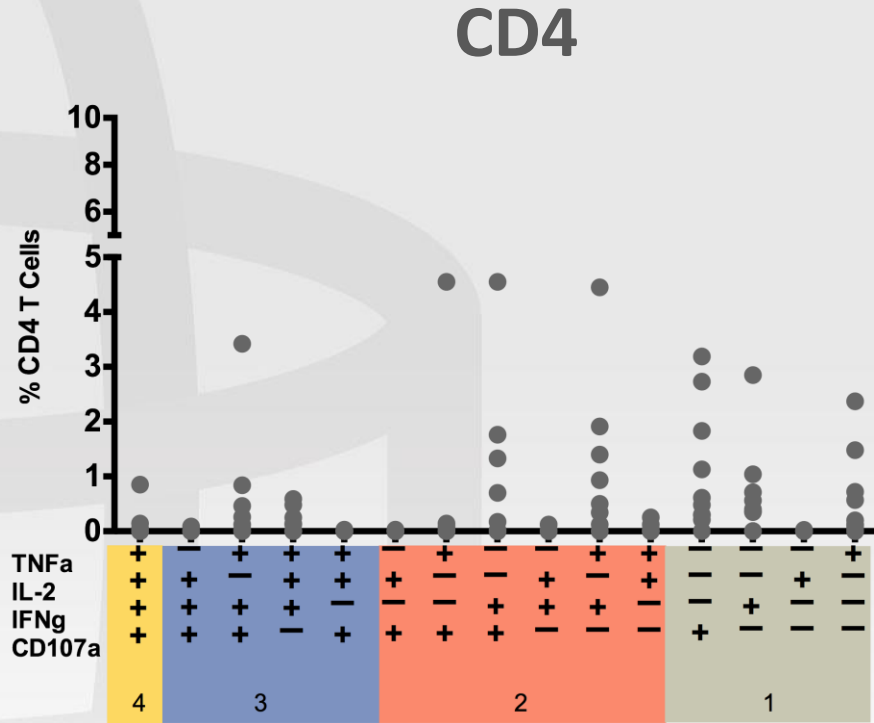
CD4



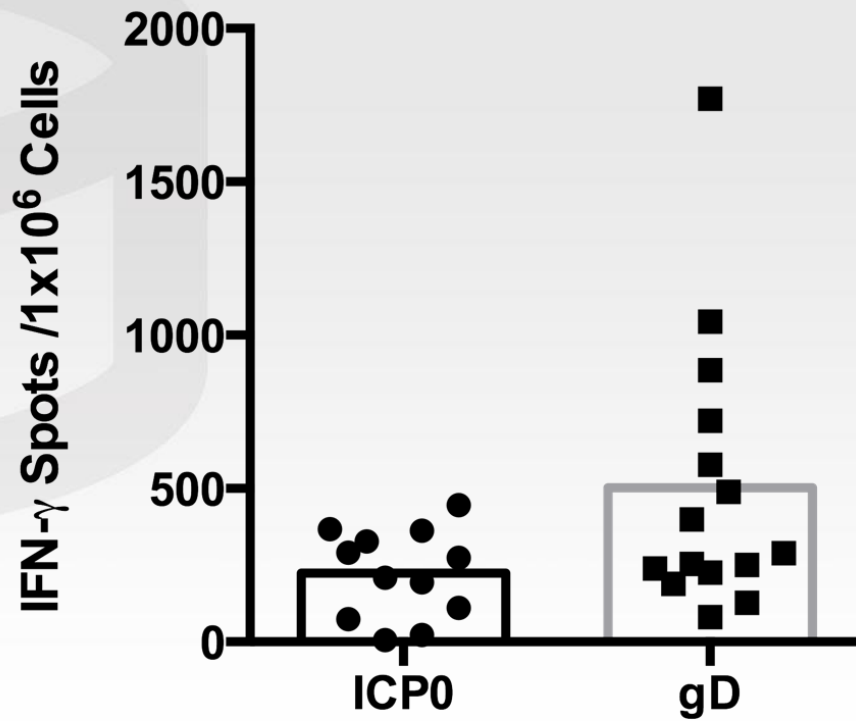
CD8



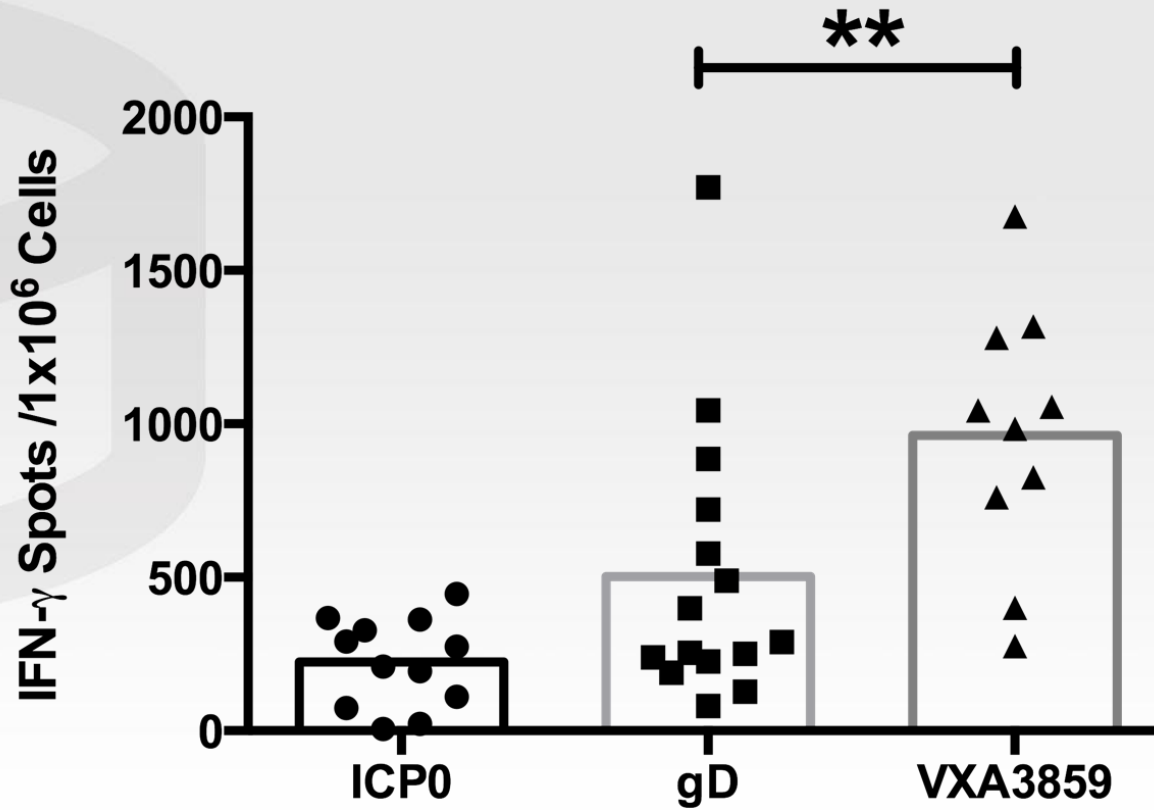
Analysis of T cell Subsets in the Genital Tract Induced After Vaccination with Ad-ICP0^{mut}-dsRNA



Splenocyte IFN- γ Response to HSV-2 Antigens

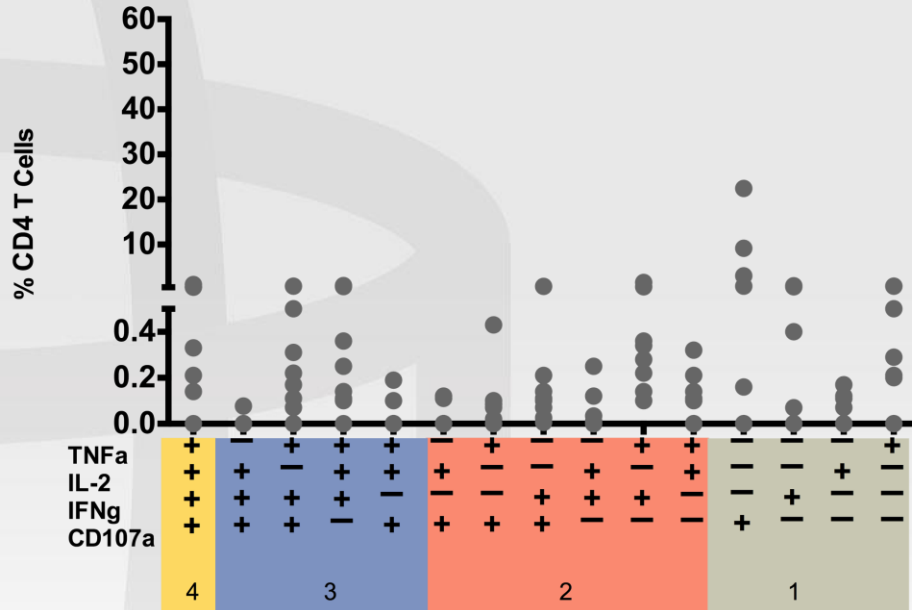


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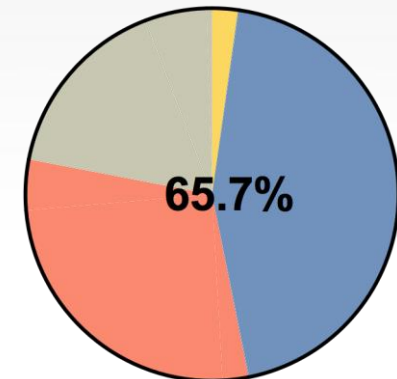
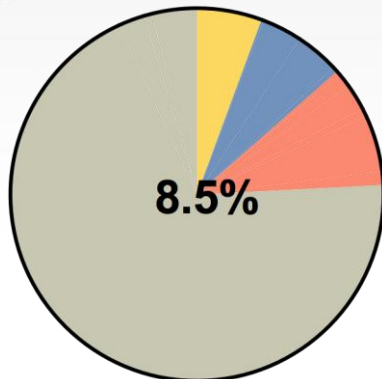
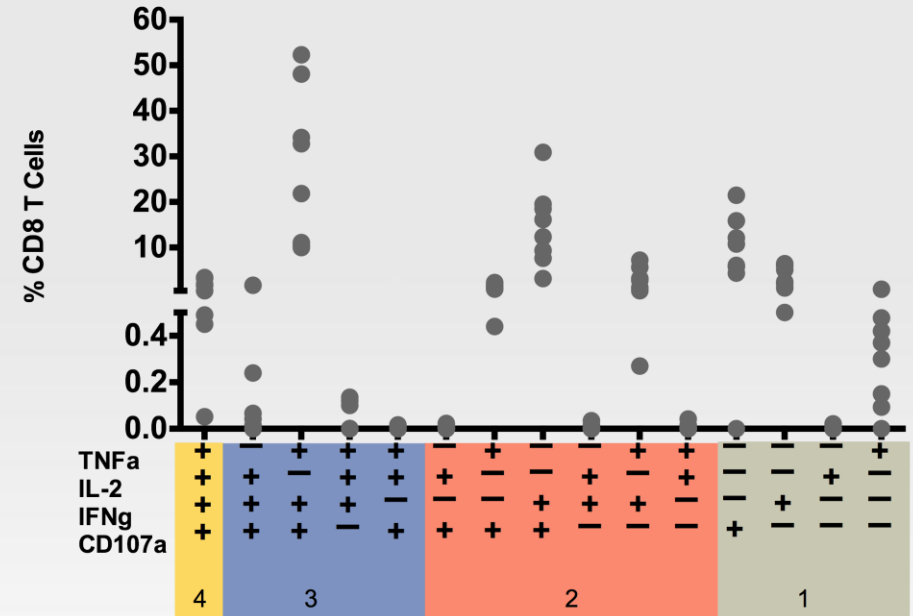


Analysis of T cell Subsets in the Genital Tract Induced After Vaccination with Ad-VXA3859-dsRNA

CD4



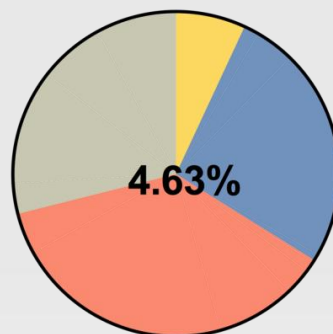
CD8



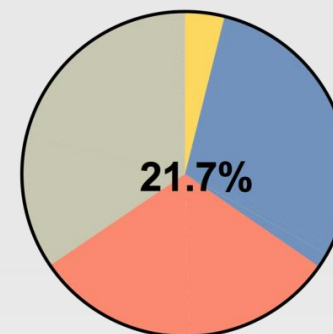
Proportions of T cell Subsets Induced by HSV-2 Antigens

gD

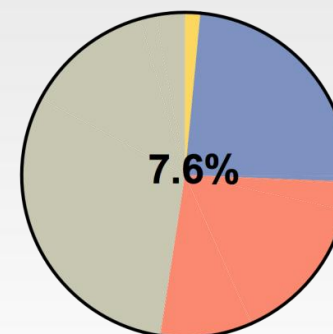
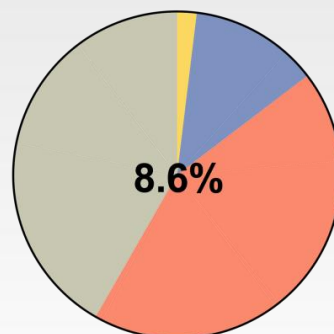
CD4



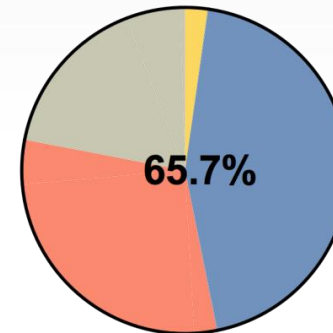
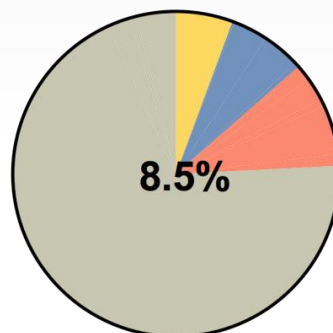
CD8



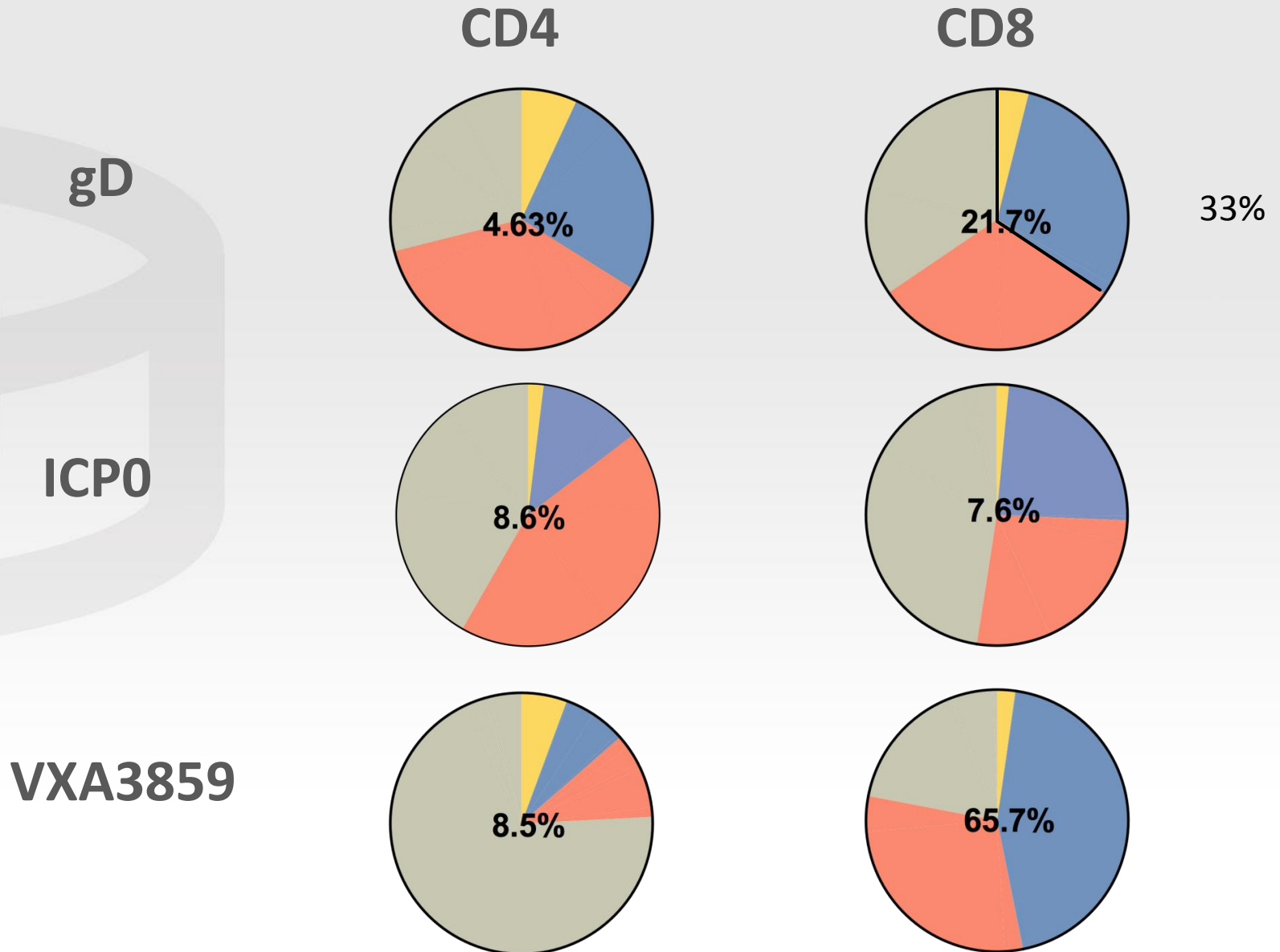
ICP0



VXA3859



Proportions of T cell Subsets Induced by HSV-2 Antigenes After Vaccination



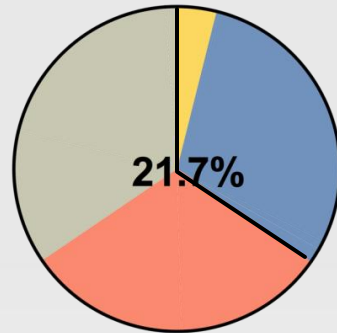
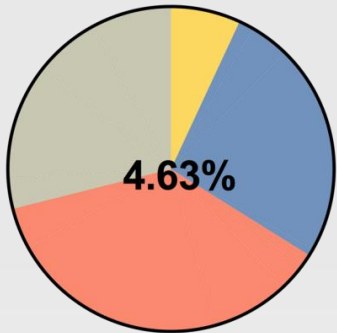
Proportions of T cell Subsets Induced by HSV-2 Antigenes After Vaccination



gD

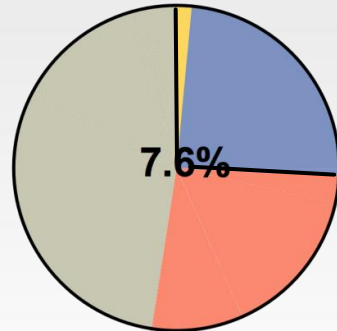
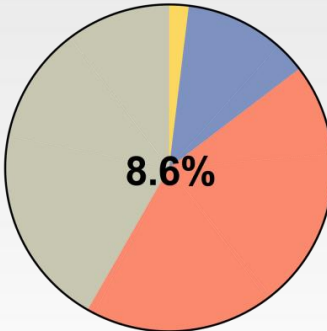
CD4

CD8



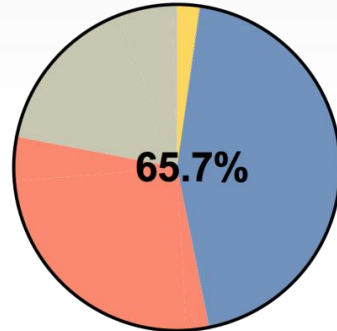
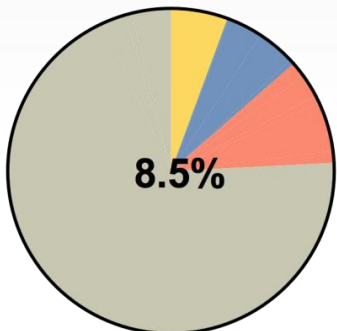
33%

ICP0

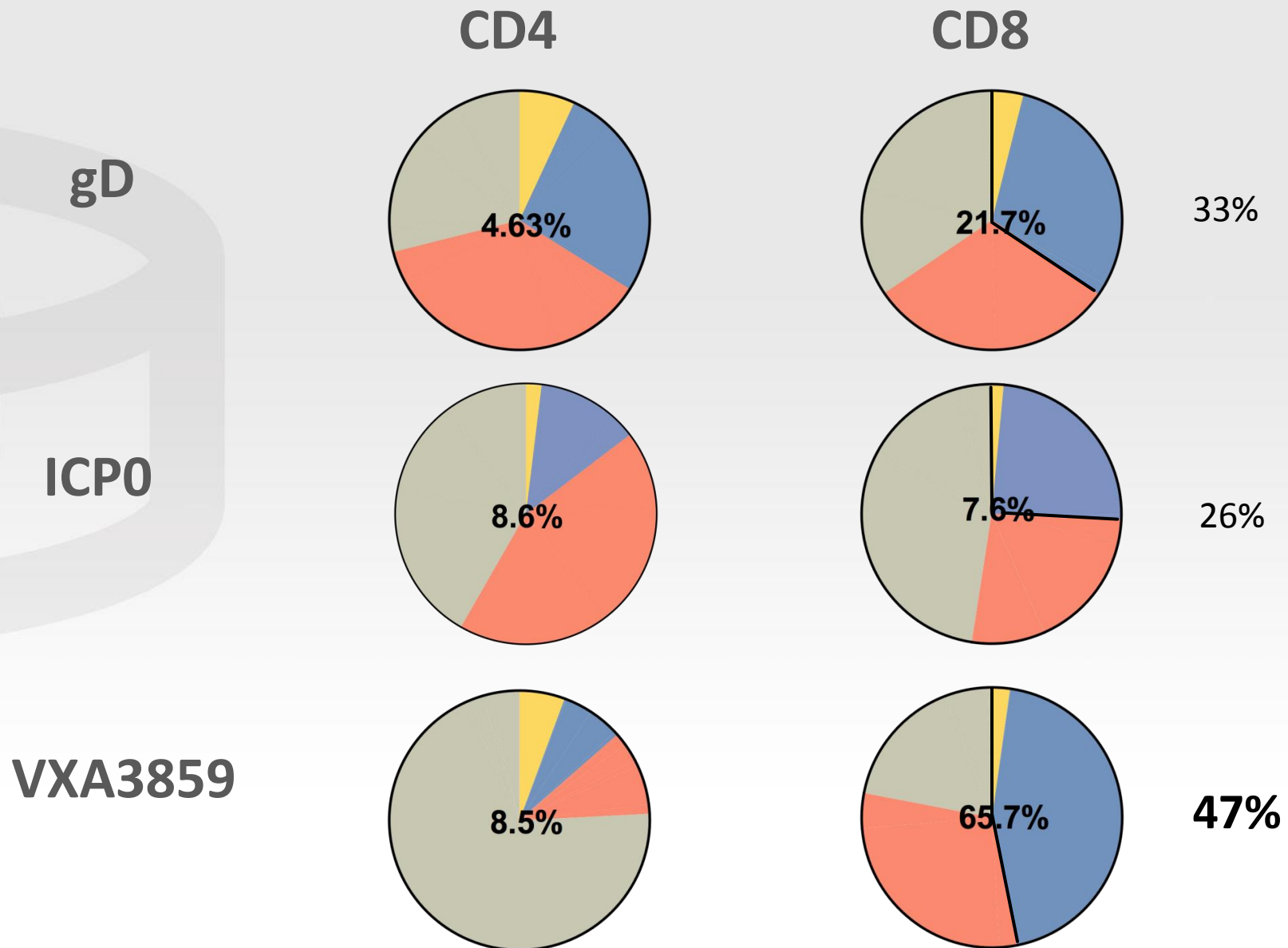


26%

VXA3859



Proportions of T cell Subsets Induced by HSV-2 Antigens After Vaccination



Summary

Clinical Trials-Tablet Influenza Vaccine

- Neutralizing antibody responses induced comparable to seasonal IM vaccines
- Mucosal IgA responses elicited
- Mucosal homing, IFN- γ producing, CD8 T cells induced

Preclinical HSV-2 Therapeutic Vaccine

- Identified a potential T cell antigen with immunodominant epitope/s
- Elicits a high % of polyfunctional CD8 cytotoxic T cells
- Efficacy study vaccinating with gD plus VXA3859 is on going

Acknowledgements



- Sean Tucker
- Katie Hodgson
- Josefina Martinez

- Leesun Kim
- Jennifer Brandl

- Ciaran Scallan
- Jon Lindbloom
- Emery Dora



- David Bernstein
- Rhonda Cardin

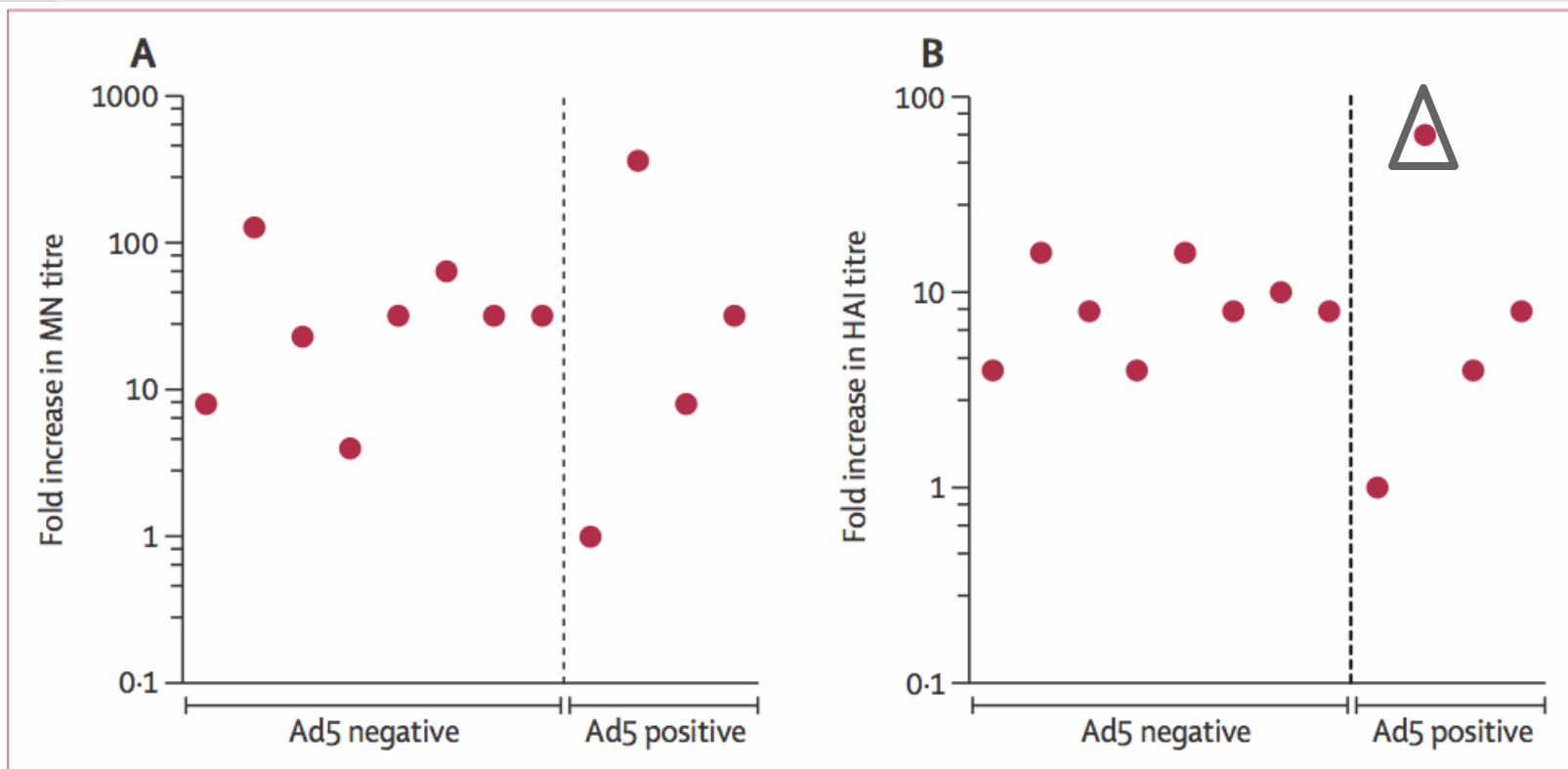
Appendix



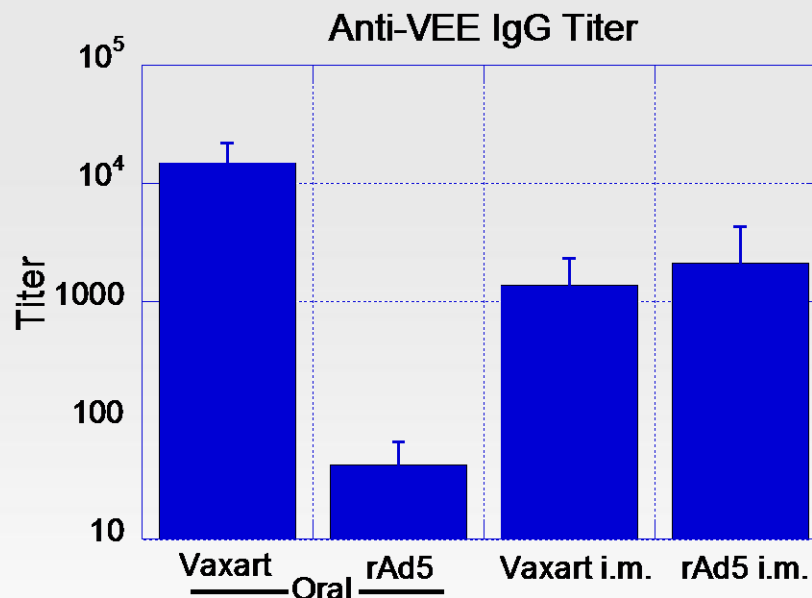
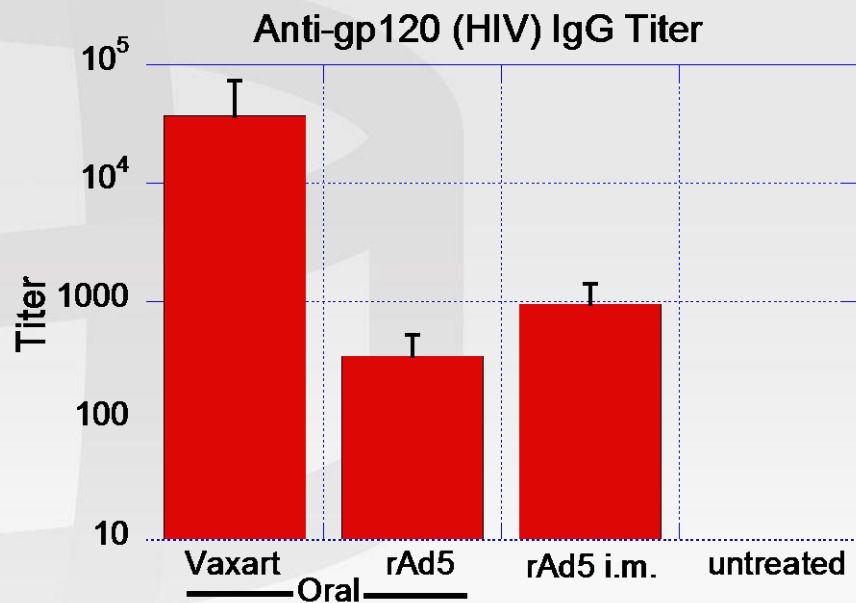
Neutralizing Titers to Transgene Not Affected by Pre-Existing Immunity to Ad5

Microneutralization Titer

HAI Titer



TLR3 Adjuvant Improves Immune Response with Oral Delivery



“Vaxart” = recombinant Ad5 with dsRNA

“rAd5” = recombinant Ad5, no adjuvant

Balb/c mice, 6 animals per group