



the
collaboration
for AIDS vaccine discovery

Construction and characterization of replication competent attenuated NYVAC-based vectors as potential HIV vaccines

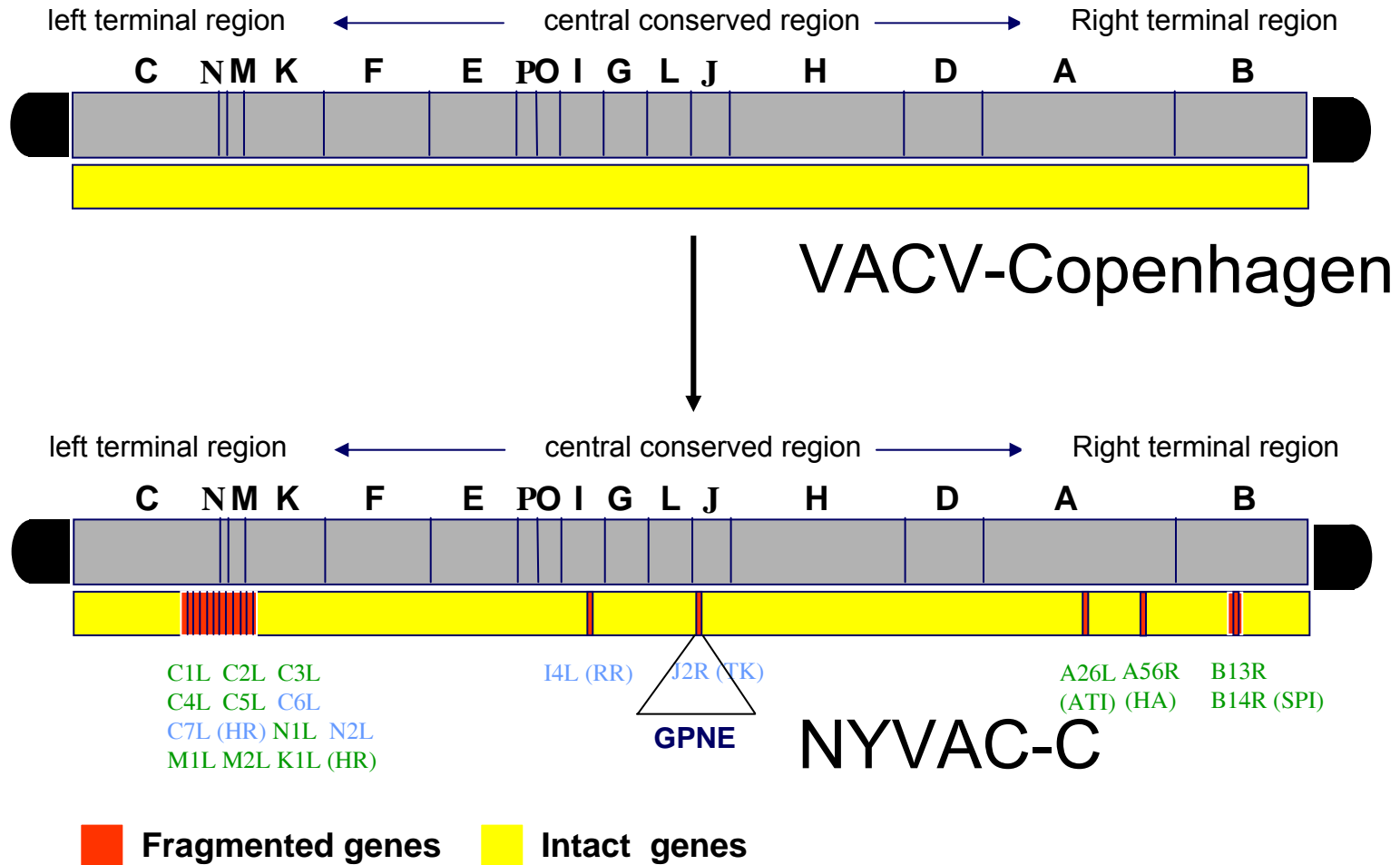
Bert Jacobs for the PTVDC
Biodesign Institute
Arizona State University

Overall Project Objectives: Improve NYVAC as a Vaccine Vector

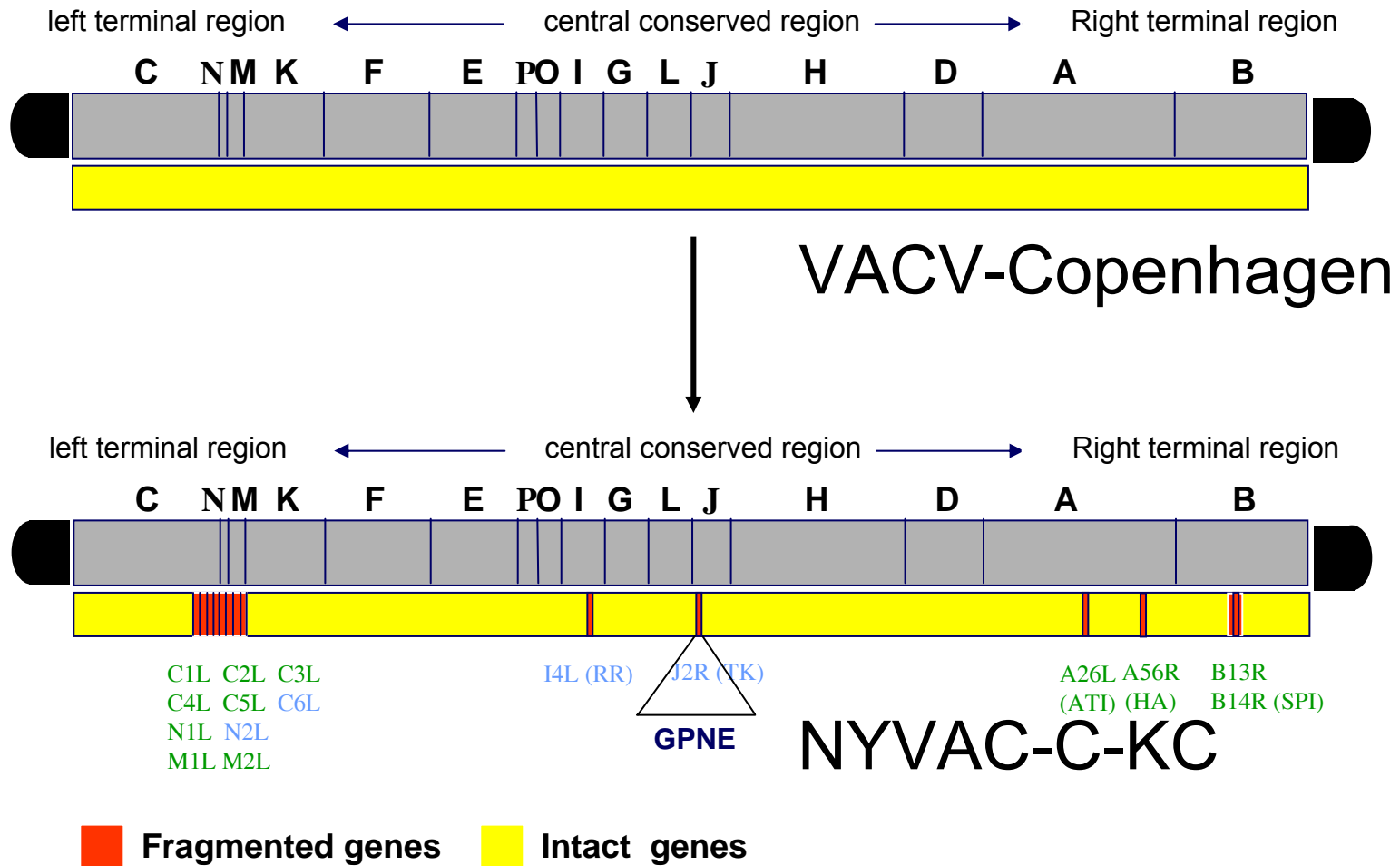
1. Develop a highly attenuated, replication competent vector.
2. Improve immunogenicity by deleting innate immune evasion genes.



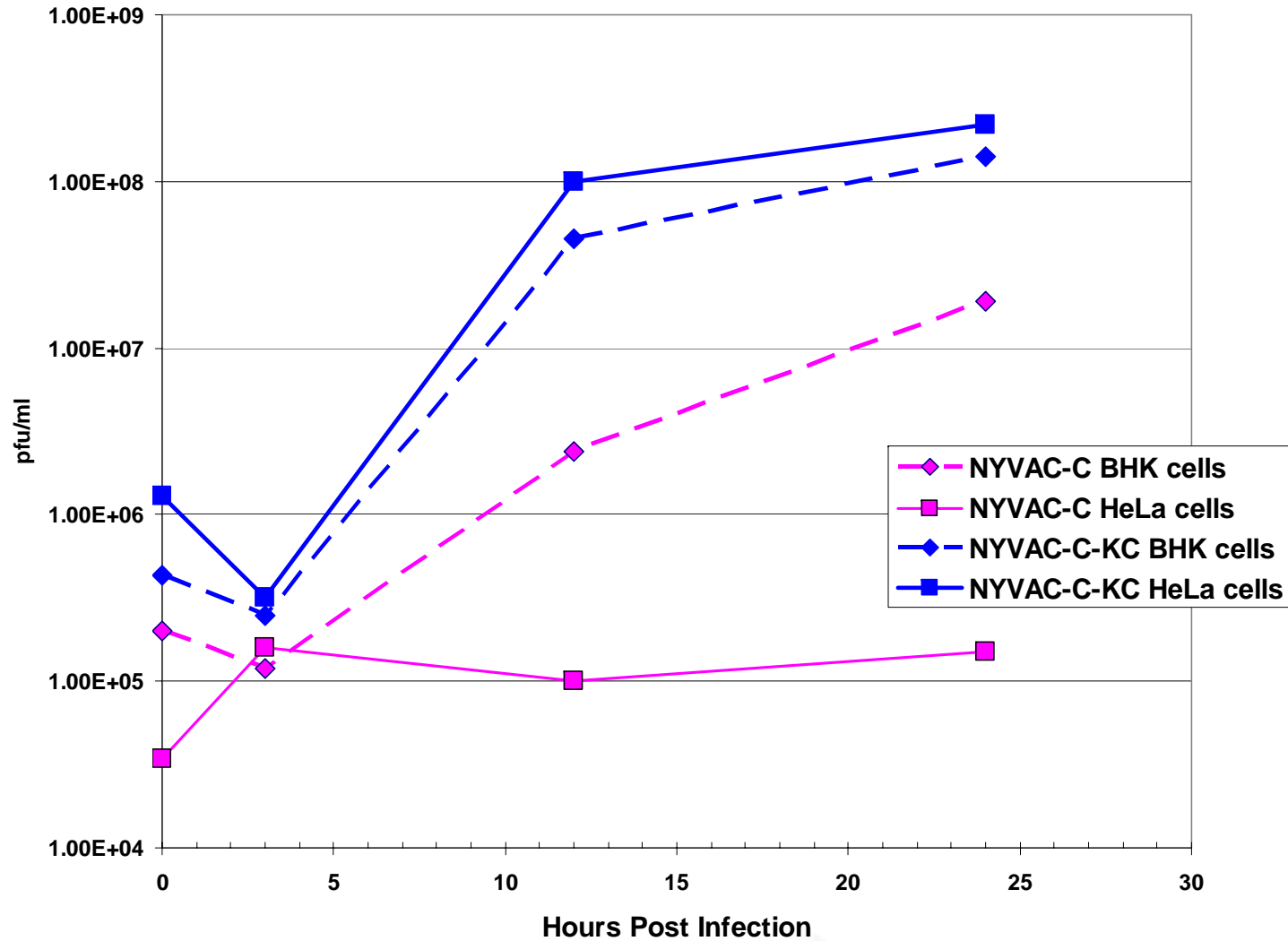
Current NYVAC Construct



Replication Competent NYVAC Construct



Replication in Human HeLa cells





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Vaccine

www.elsevier.com/locate/vaccine

Vaccine 22 (2004) 1486–1493

Mouse neurotoxicity test for vaccinia-based smallpox vaccines

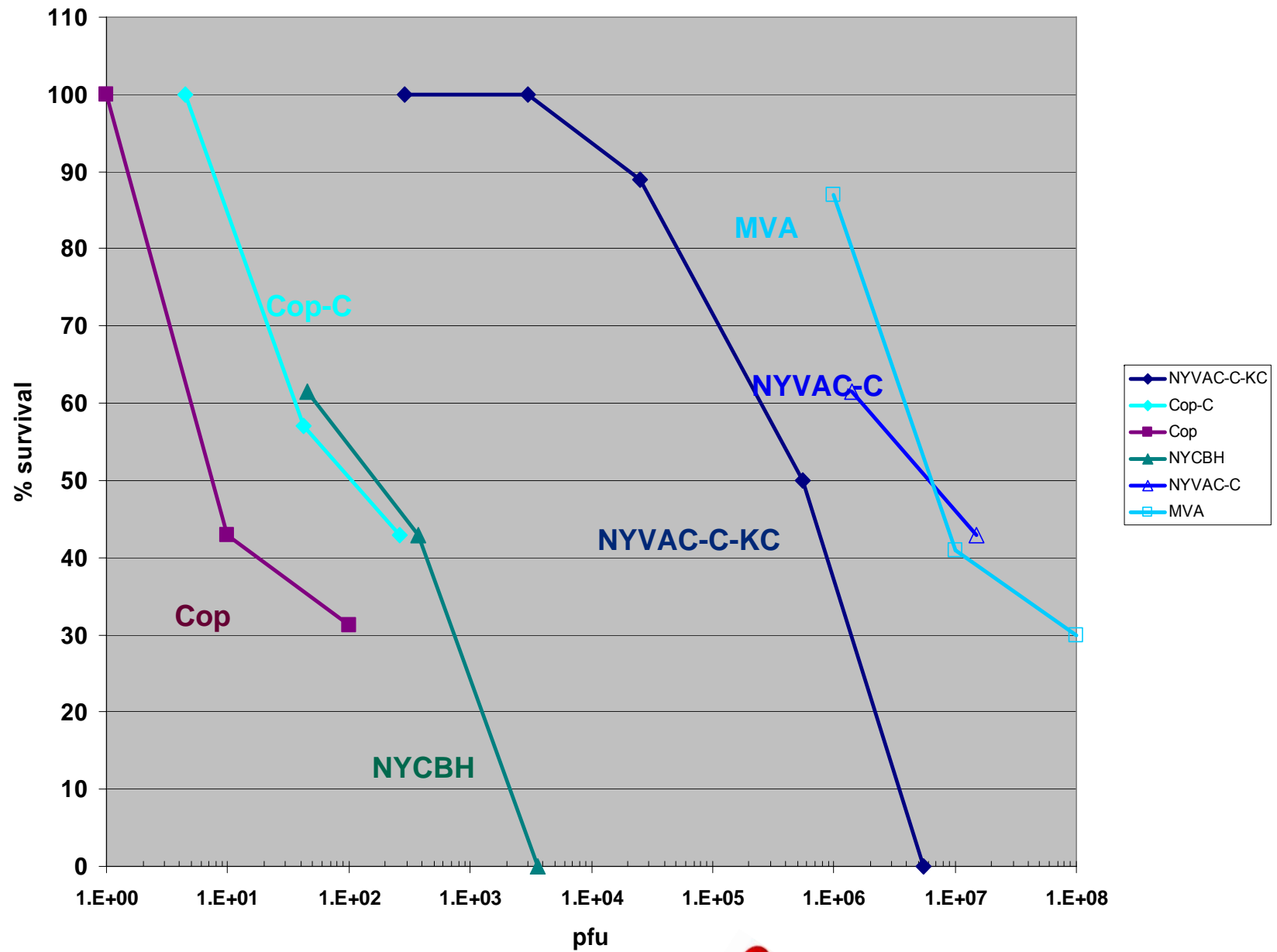
Zhongqi Li^a, Steven A. Rubin^a, Rolf E. Taffs^c, Michael Merchlinsky^b,
Zhiping Ye^a, Kathryn M. Carbone^{a,*}

^a *Laboratory of Pediatric and Respiratory Viral Diseases, OD/CBER/FDA, HFM-460, Bldg. 29B, Room 5NN22,
8800 Rockville Pike, Bethesda, MA 20892, USA*

^b *Laboratory of DNA Viruses, DVP/OVRR/CBER/FDA, HFM-460, 8800 Rockville Pike, Bethesda, MA 20892, USA*

^c *Laboratory of Bacterial, Parasitic, and Unconventional Agents, DETTD/OBRR/CBER/FDA, HFM-460, 8800 Rockville Pike,
Bethesda, MA 20892, USA*





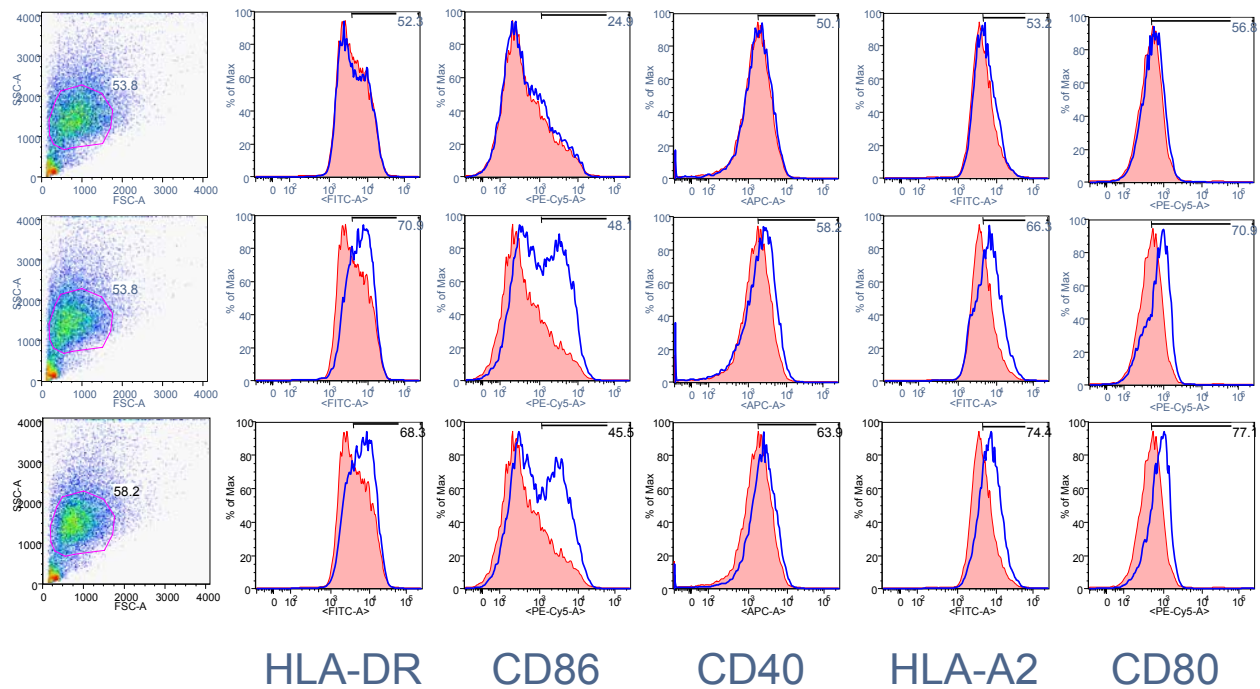
Improve Immunogenicity by Deleting Viral Innate Immune Evasion Genes

B8R/B19R-Soluble interferon- γ and - α/β binding proteins
 Δ B19R
 Δ B8R/ Δ B19R



Induction of Co-Stimulatory Molecules on DC

Human moDC



NYVAC-C

ΔB19R

ΔB8R/ΔB19R

HLA-DR

CD86

CD40

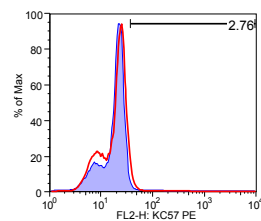
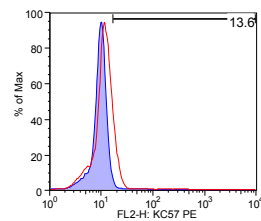
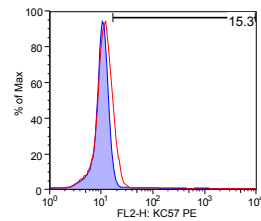
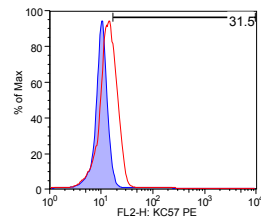
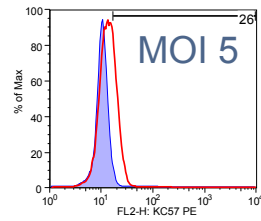
HLA-A2

CD80

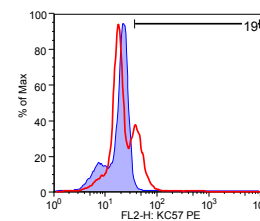
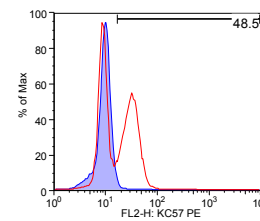
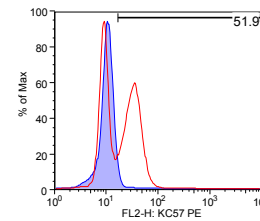
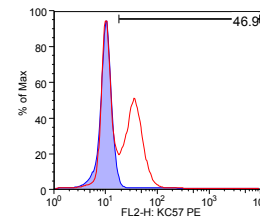
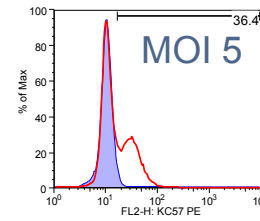
Improved NYVAC Vectors: NYVAC-C-KC NYVAC-C-KC- Δ B8R/ Δ B19R

Effects on:

- Gag expression
- Cross-presentation
- Re-call of memory HIV-1-specific CD8 T-cell responses *in vitro*



NYVAC-C



NYVAC-C-KC

DC

2 h

4 h

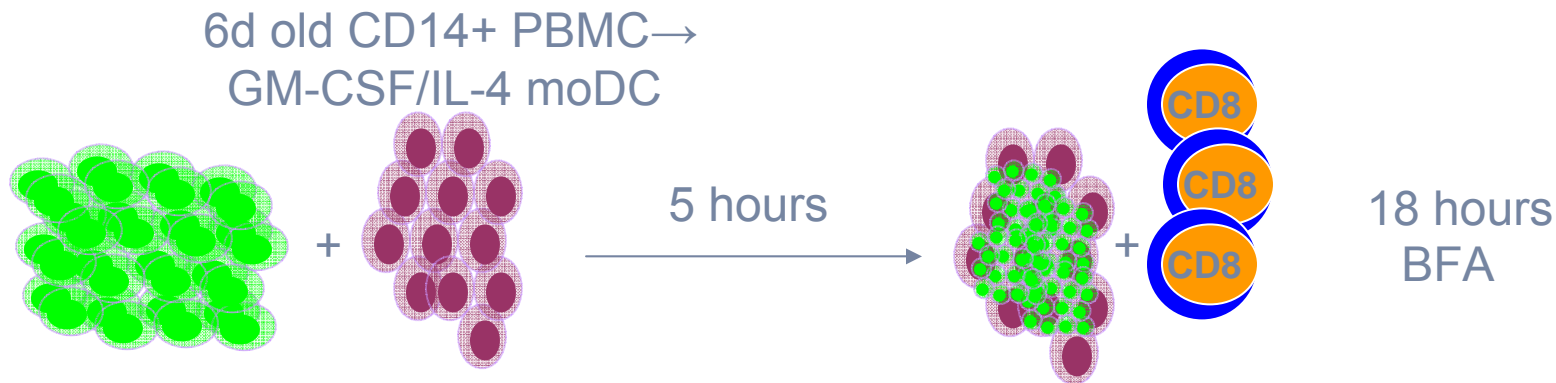
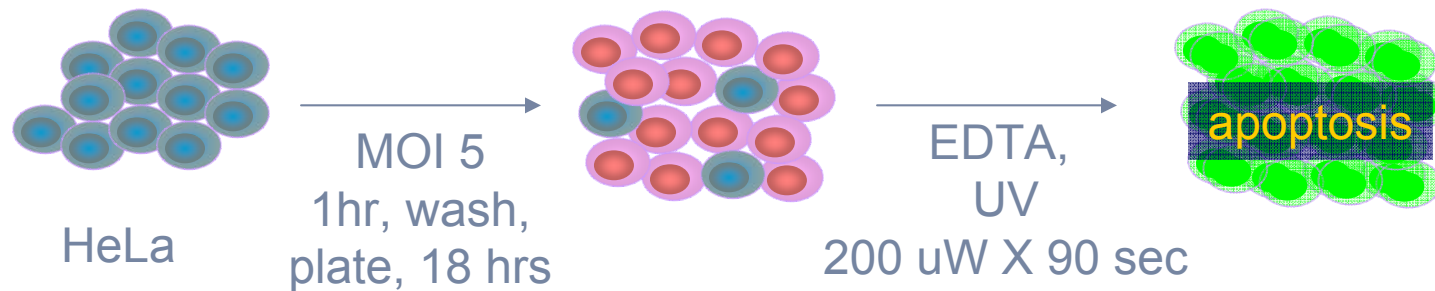
6 h

8 h

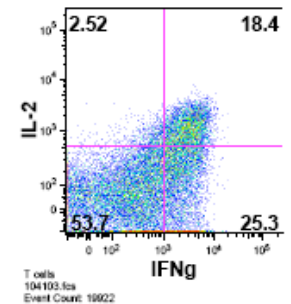
24 h



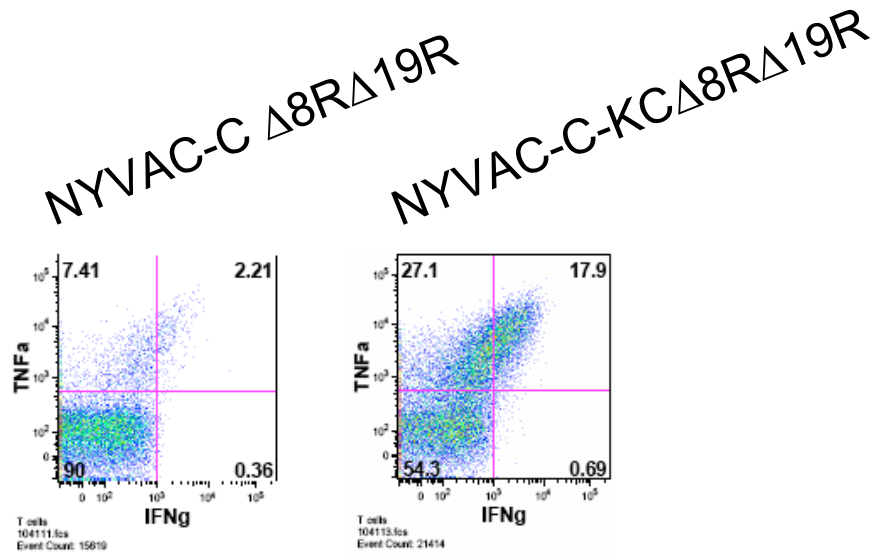
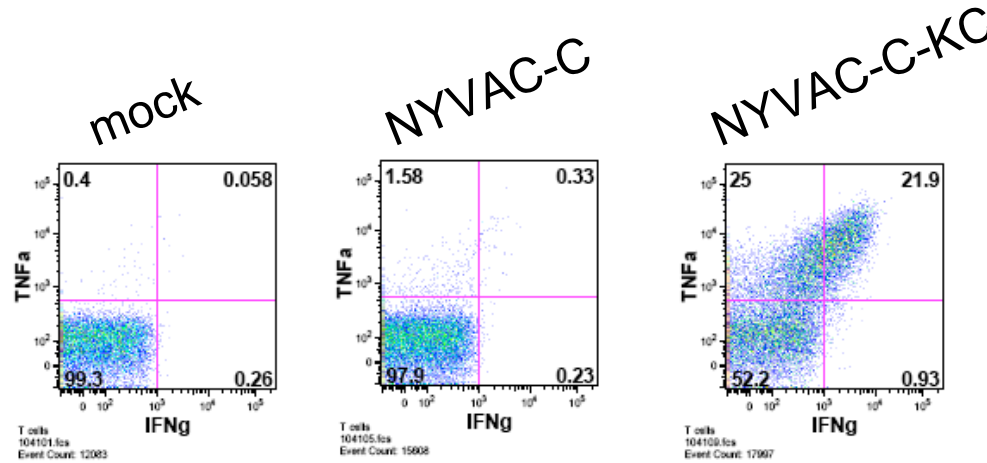
Cross-Presentation of Vaccinia Epitopes to Human Vaccinia-Specific CD8 T-Cell Clones



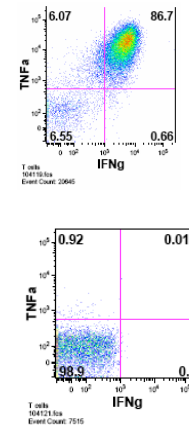
ICS assay



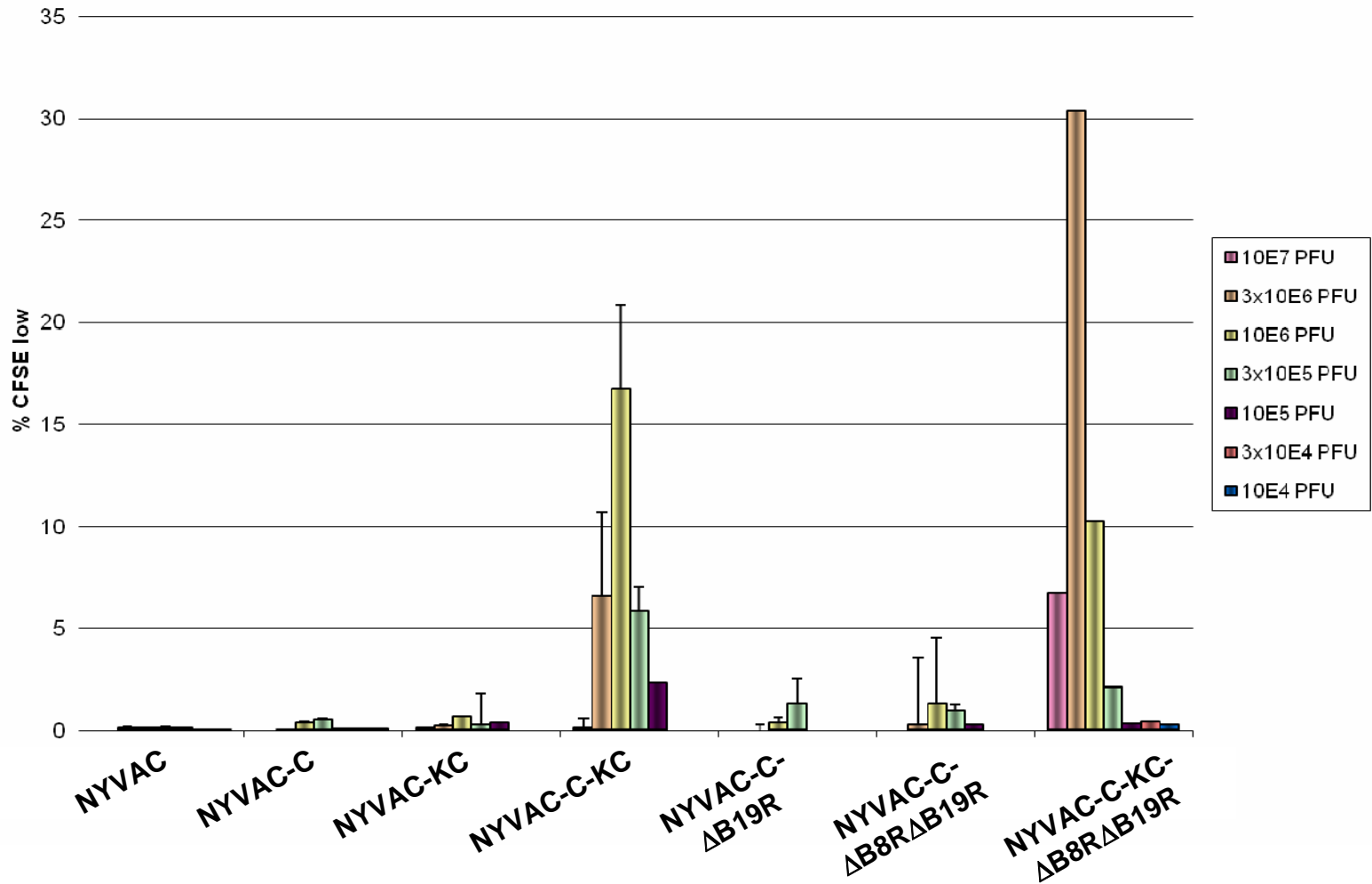
Results IFN γ /TNF α



direct presentation controls
LCL+peptide



Induction of Re-Call HIV-1-Specific CD8 T-Cell Responses by Modified NYVAC Vectors



Conclusions

- Restoration of replication competence increases gag expression and cross-presentation of antigen in moDCs.
- Deletion of B19R leads to increased immunogenicity as measured by increased co-stimulatory molecule expression on DCs.
- Replication competent variants, and our combined platform lead to induction of HIV-specific CD8 recall responses.
- These highly attenuated, replication competent NYVAC vectors have the attributes of an improved poxvirus vector.



Collaborations

Primary Grantee
CHUV (PI: Giuseppe Pantaleo) 

Discovery Core

Core Leader:
Jim Tartaglia 

Mariano Esteban 

Geoffrey Smith 

Bertram Jacobs 

Ralf Wagner 

David Koelle 

Immunology Core

Core Leader:
Cornelis Melief 

A. Lanzavecchia 

Giuseppe Pantaleo 

Thierry Calandra 

Rafick Sekaly 

Simon Mallal 

Jon Heeney 

Clinical Core

Core Leader:
Larry Corey 

Giuseppe Pantaleo 

Jonathan Weber 

Yves Levy 

P17-23

Enhanced expression of HIV antigens and improved antigen presentation after infection with replication competent attenuated vaccinia virus in vitro

E.D. Quakkelaar¹, A. Redeker¹, N.M. Loof¹, S. van Duikeren¹, B. Perdiguero², P. Heinen², J. Nieto², M. Esteban², K. Kibler³, B. Jacobs³, G. Pantaleo⁴ and C.J.M. Melief¹

P19-32

HIV-1 Vaccine Design based on Human Vaccine Trials to Improve Gag, Pol, Nef and Env Specific Immune Responses

Josef Köstler, Jens Wild, Simon Bredl, Katharina Böckl, Kathrin Kindsmüller and Ralf Wagner



