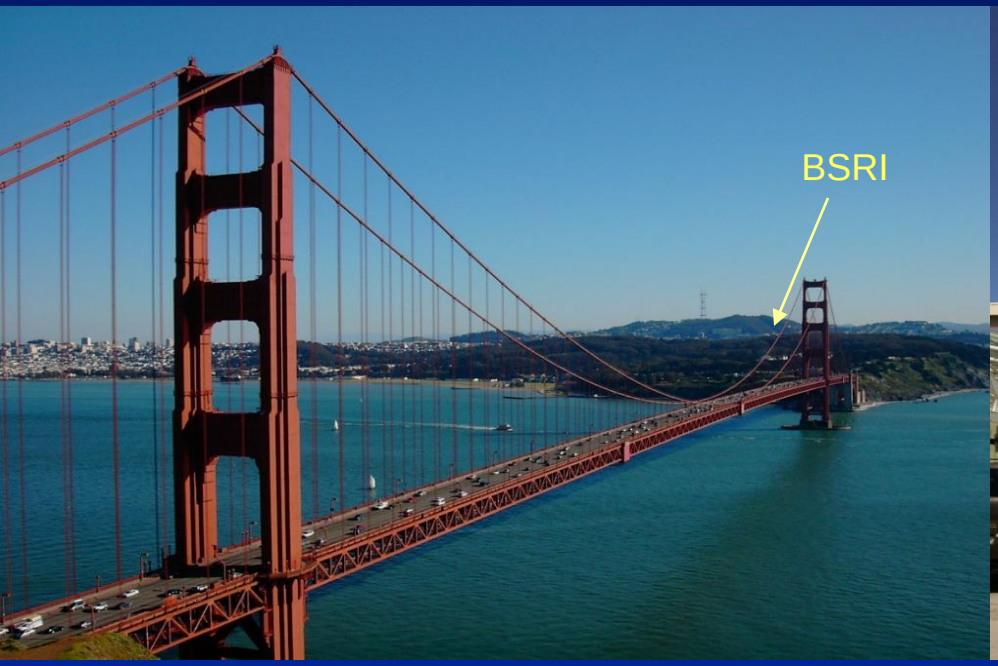
Mechanisms of antagonism of HIV-specific CD4+ T cell responses



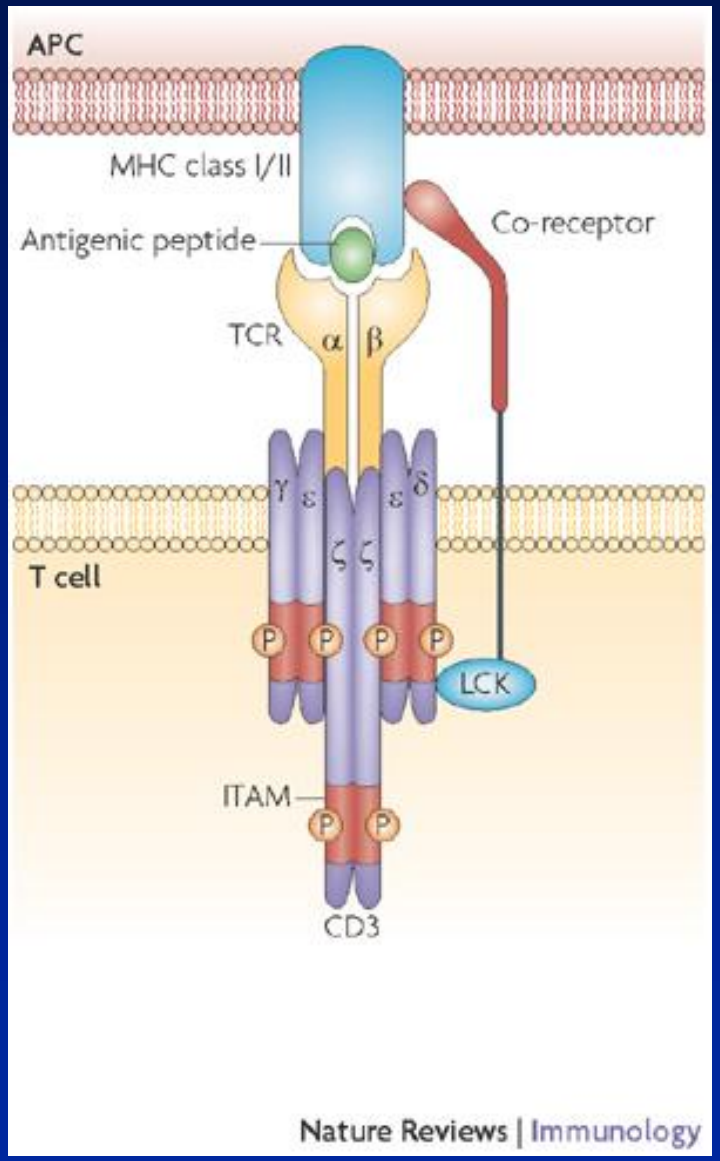
UCSF
University of California
San Francisco

Blood Systems
Research Institute

Problems

- Virus escape from immune recognition
- Antagonism of T cell responses

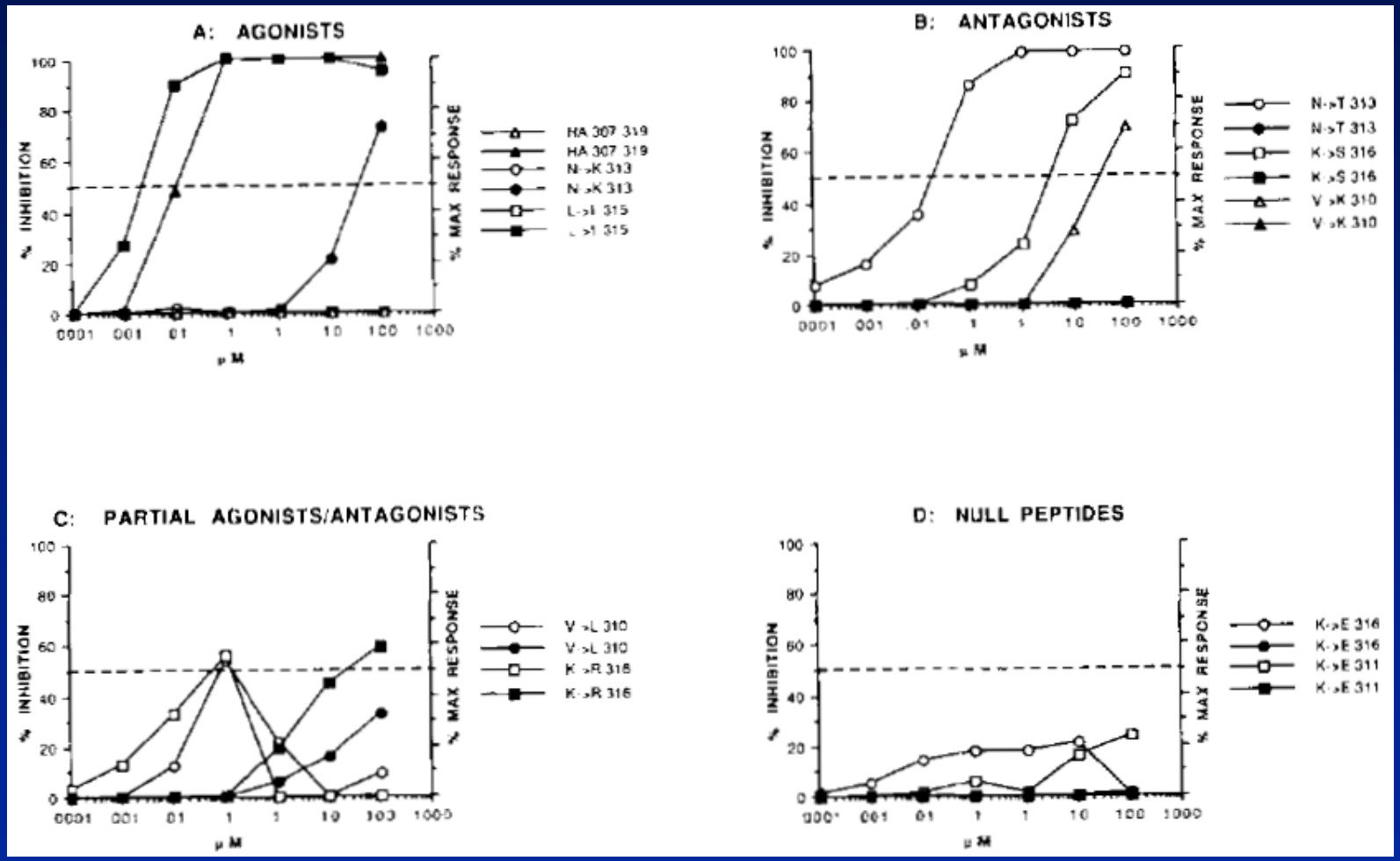
Peptide-MHC-TCR interaction



T cell antagonism

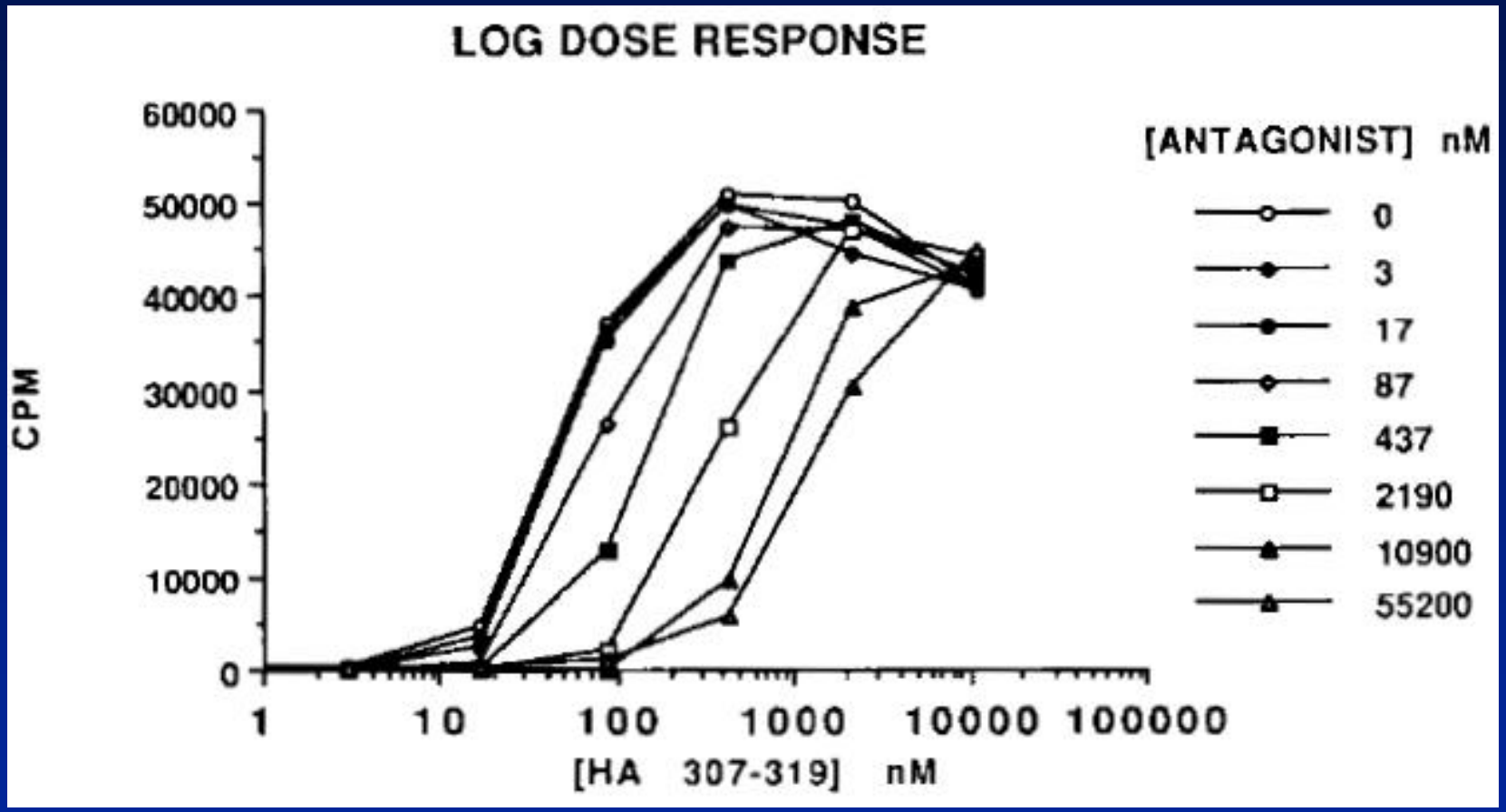
- Variants of a peptide recognized by a T cell can block recognition of the original peptide

Classes of peptides



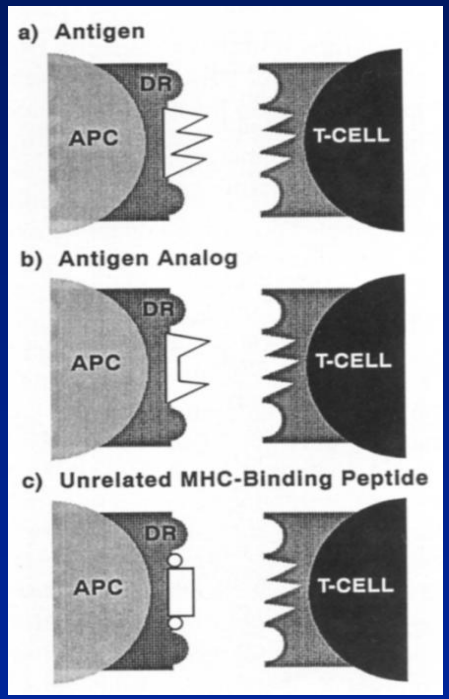
Alexander et al. J. Immunol 1993

CD4+ T cell antagonism



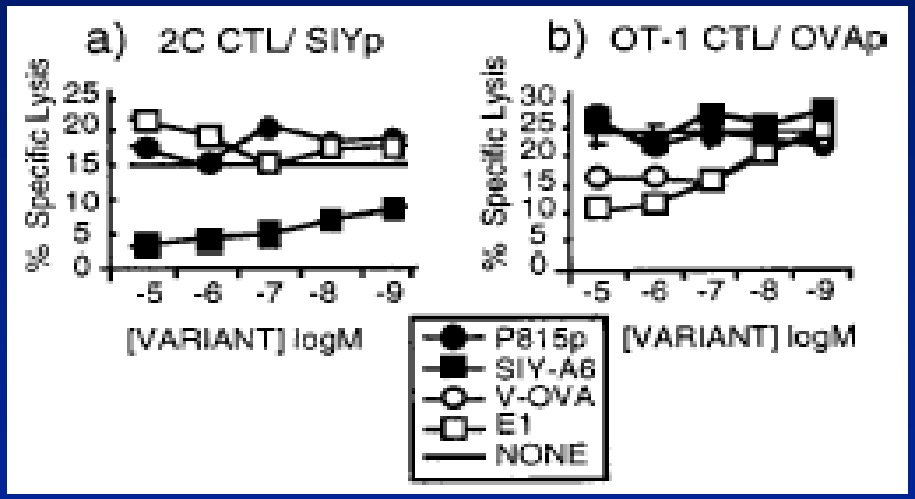
Alexander et al., J Immunol 1993
DeMagistris et al., Cell 1992
Ostrov et al., J Immunol 1993
Racciopi et al., J Exp Med 1993

Mechanism of action of TCR antagonism



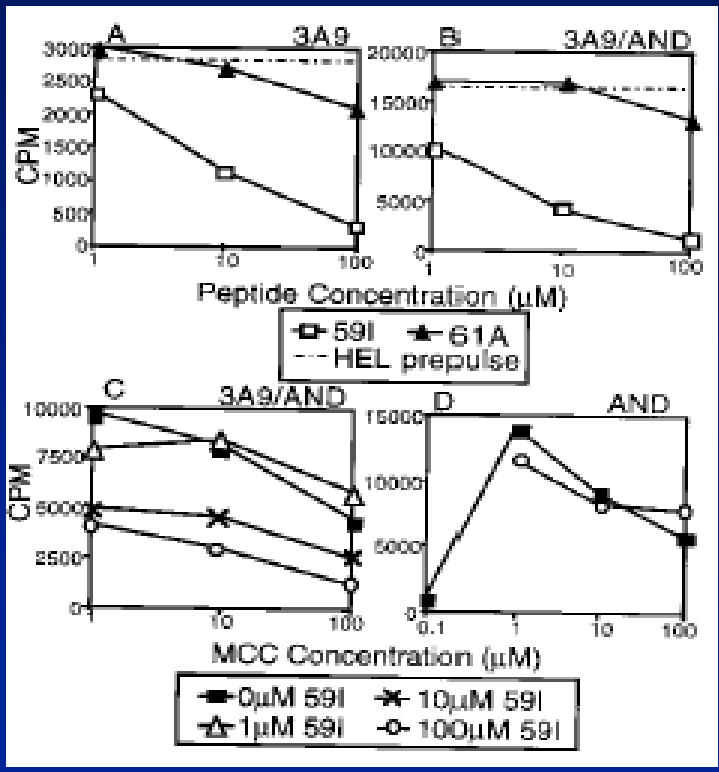
De Magistris et al., Cell 1992

No dominant negative signal in CD8+ T cells



Daniels et al., J Immunol 1999
Stotz et al., J Exp Med 1999

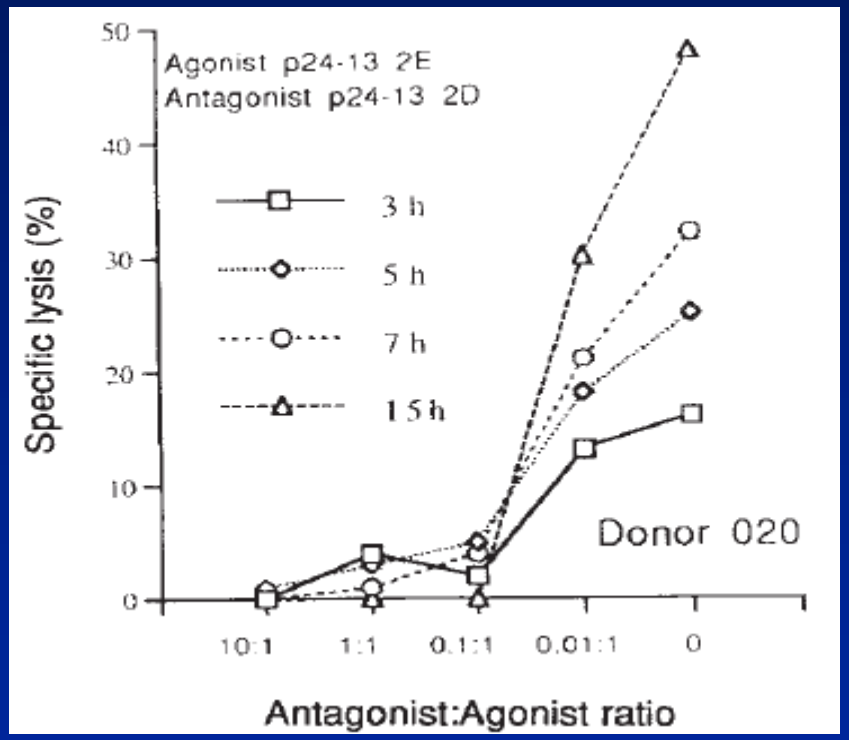
Dominant negative signal in CD4+ T cells



Robertson et al., J Immunol 1999

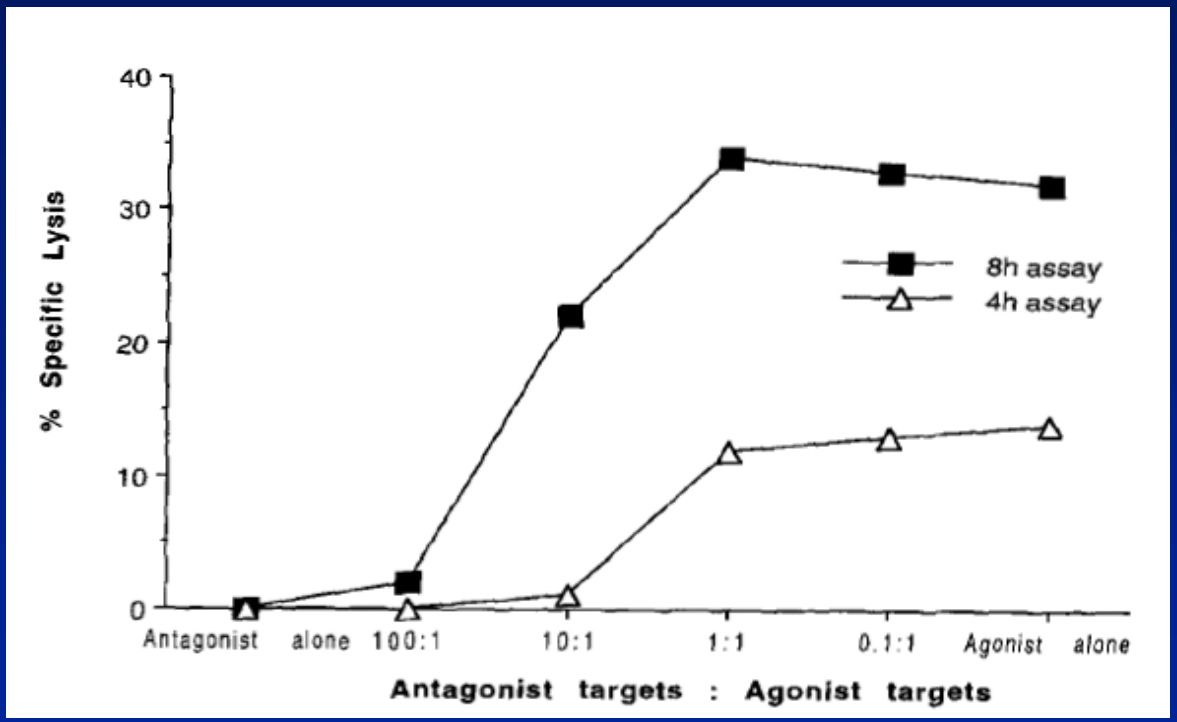
Antagonism in HIV infection

Antagonism of CTL response in HIV



Klenerman et al., Nature 1994

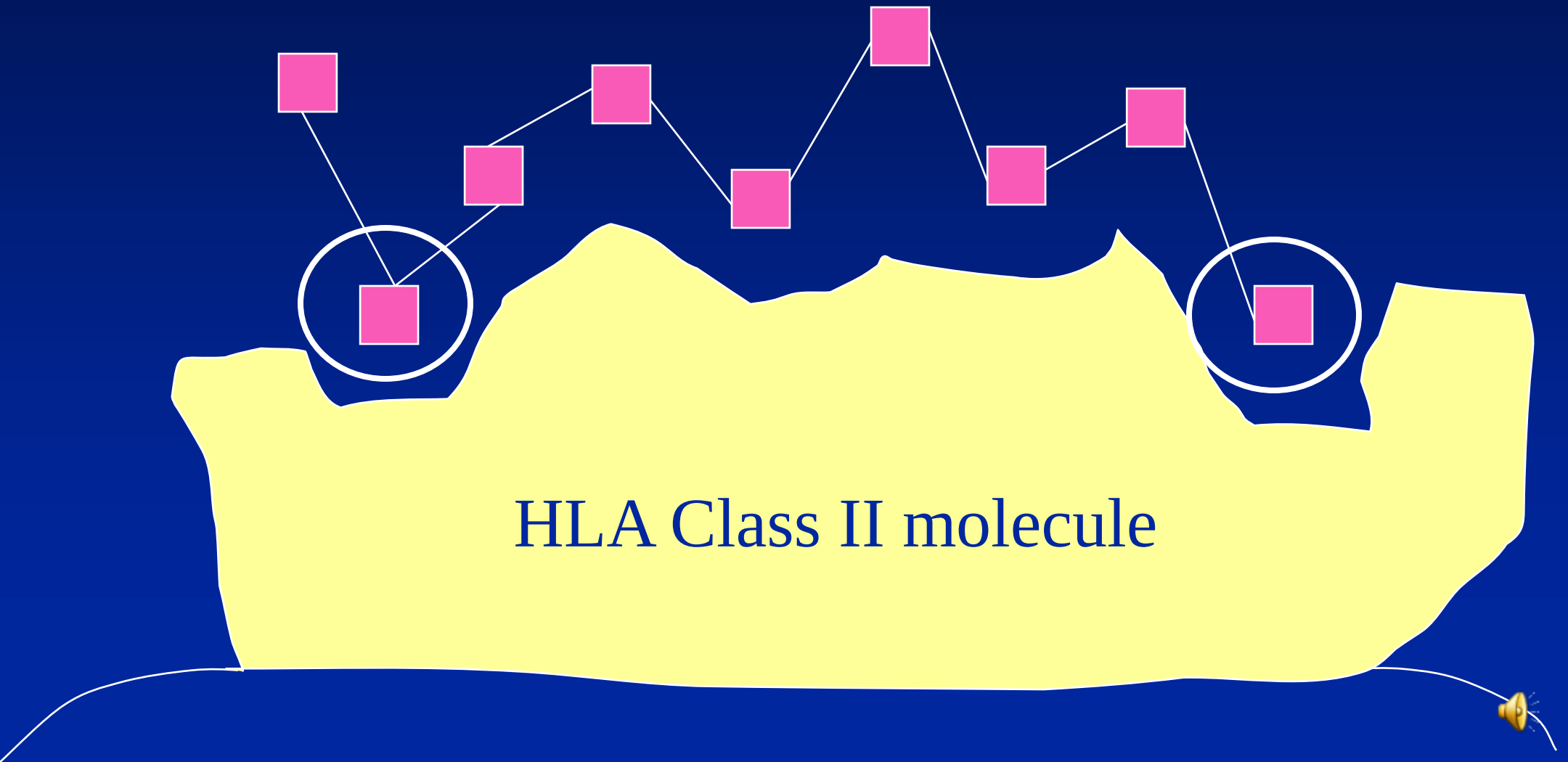
Antagonism of HIV Vaccine response



Kent et al., J Immunol 1997

T cell antagonism by a variant peptide shorter than the full length epitope

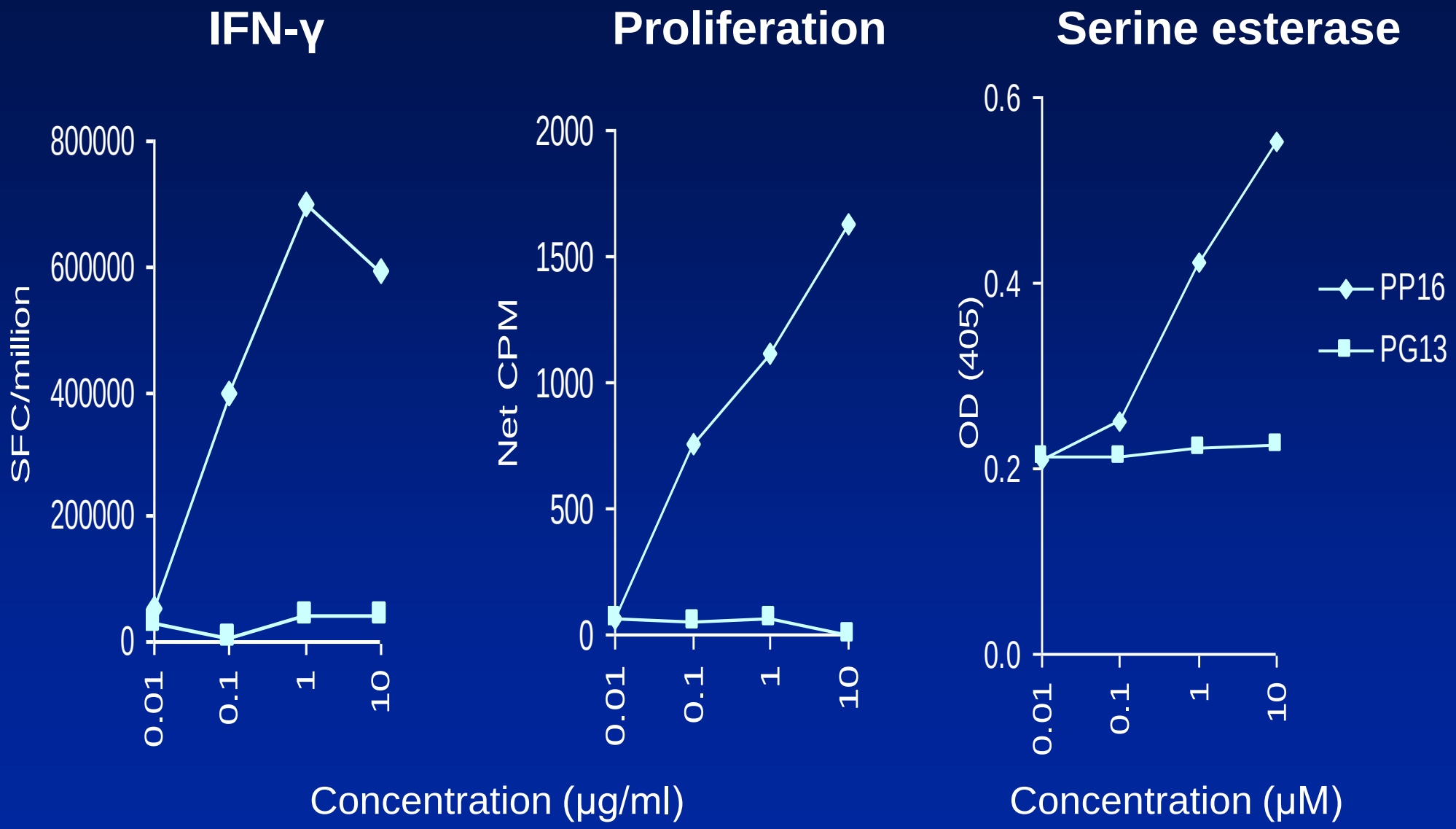
Viral peptide in HLA Binding Groove



Clone	HLA restriction	Minimum epitope
AC-01 Clone 1	**DQ5**	**EEKAFSPEVIP** (161-171)
AC-01 Clone 2	**DQ7**	**EPRGSDIAGT** (231-240)
AC-25 Clone 3	**DR1**	**PEVIPMSALSEGATP** (167-182)
161J Clone 4	**DR4**	**EVIPMFSALS** (168-177)
CTS01 Clone 5	**DQ7**	**VHAGPIAPG** (219-227)

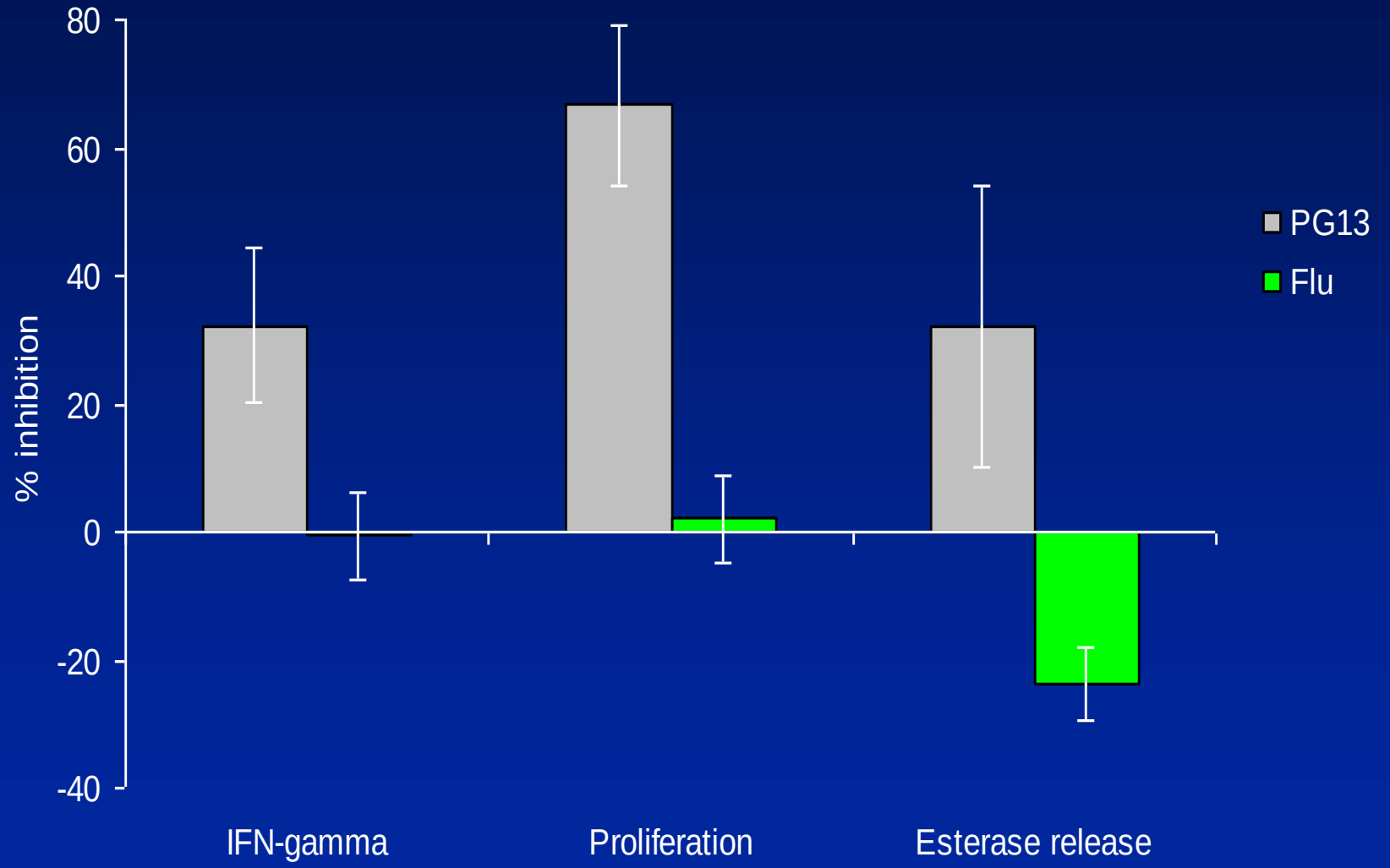
Norris et al., AIDS Res Hum Retrovirus 2004

Shorter peptide PG13 not active



Norris et al., Molecular Immunol. 2006

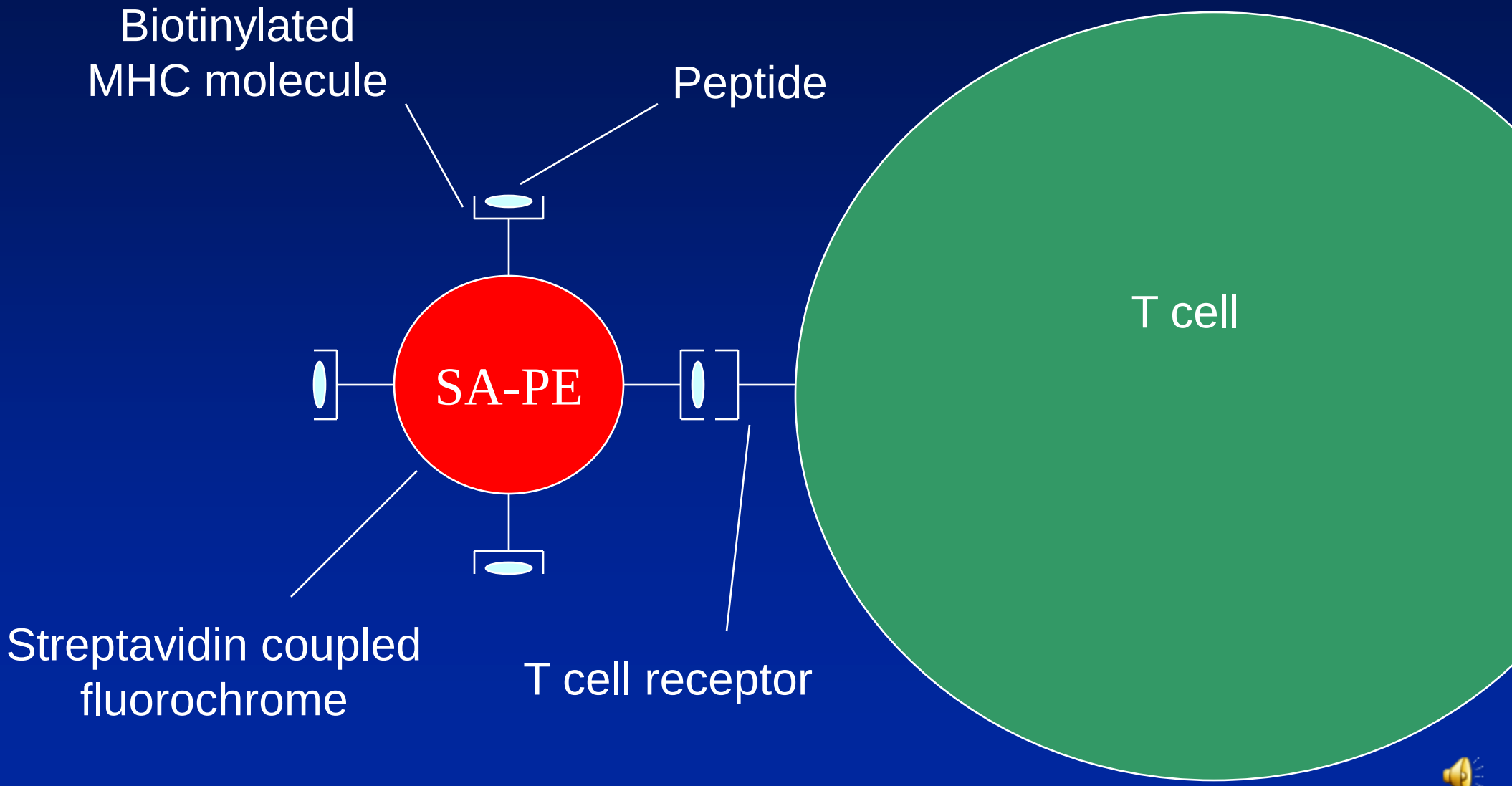
Antagonism by shorter peptide PG13



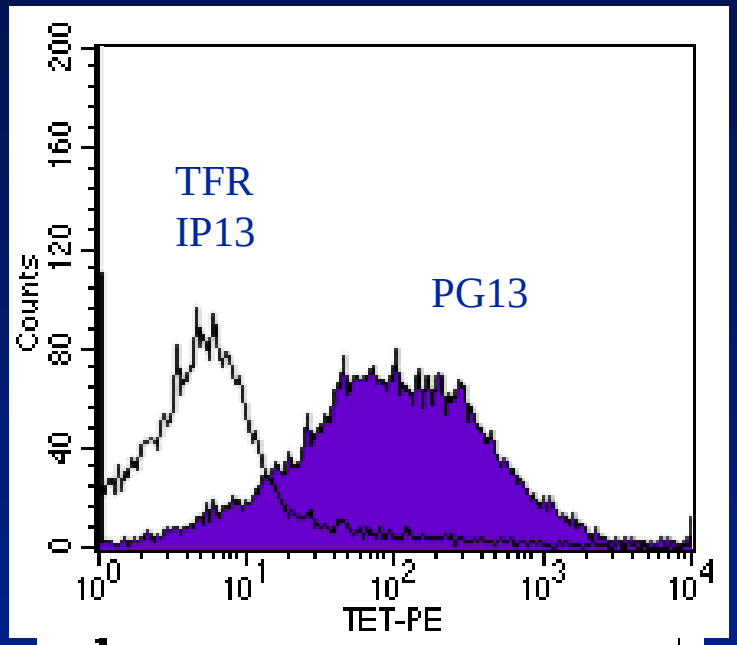
Norris et al., Molecular Immunol. 2006

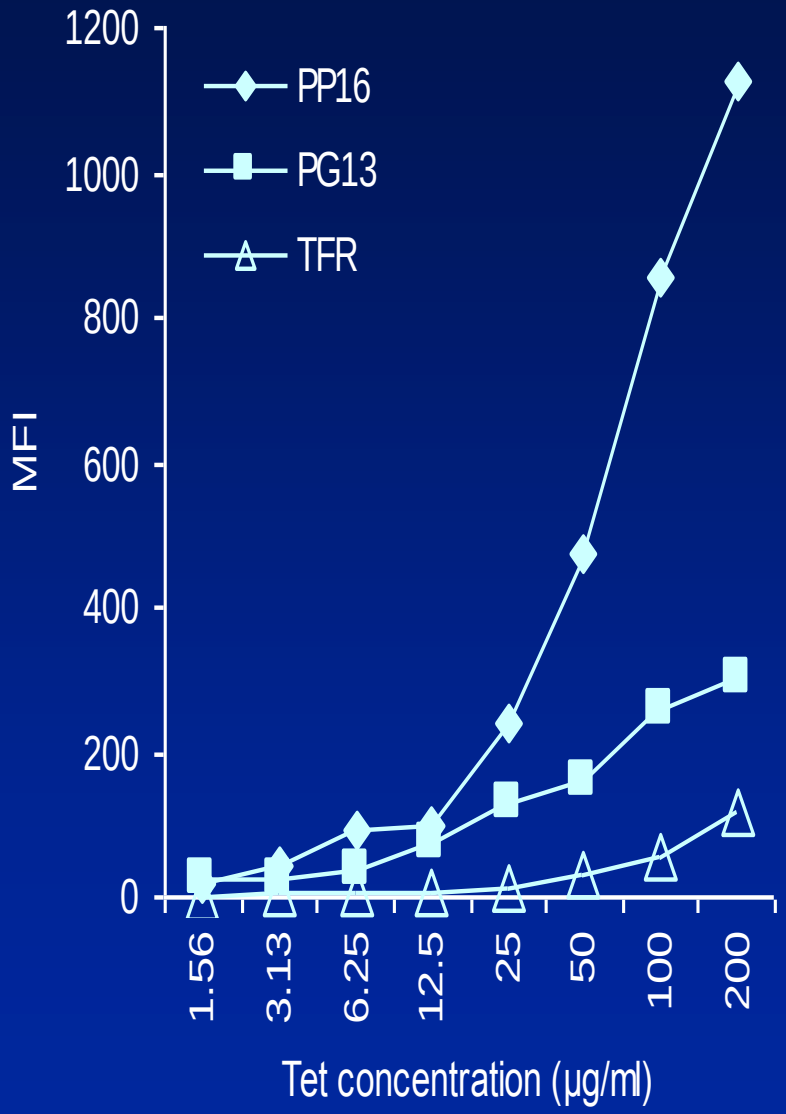
Why is the shorter peptide PG 13 an antagonist?

Tetramer staining



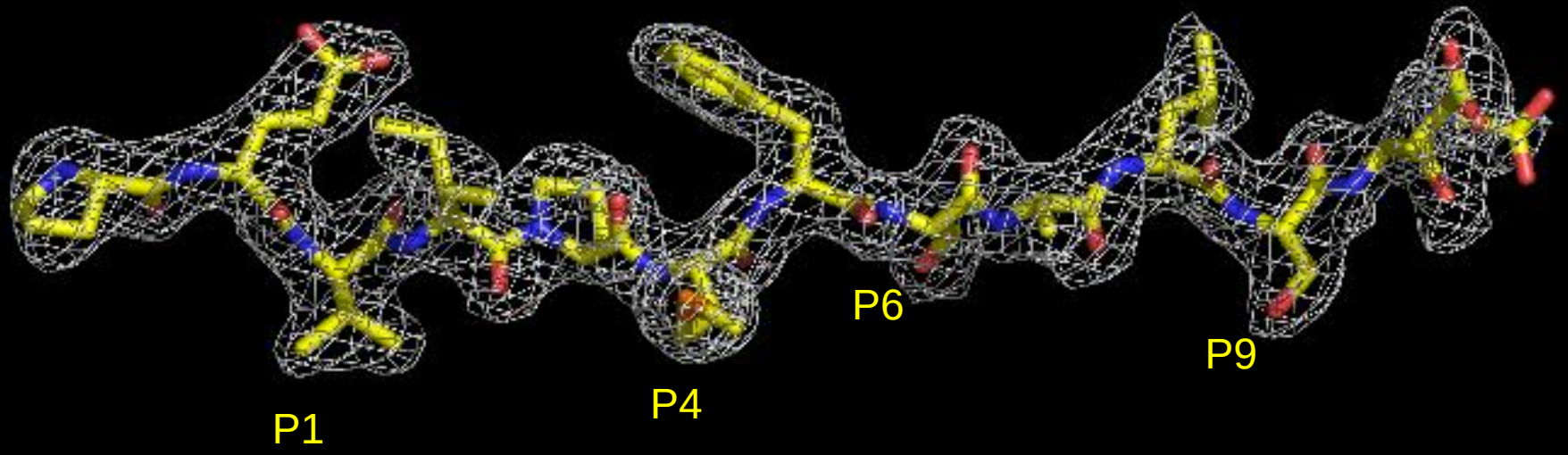
PG 13 tetramer binds with less avidity than PP16

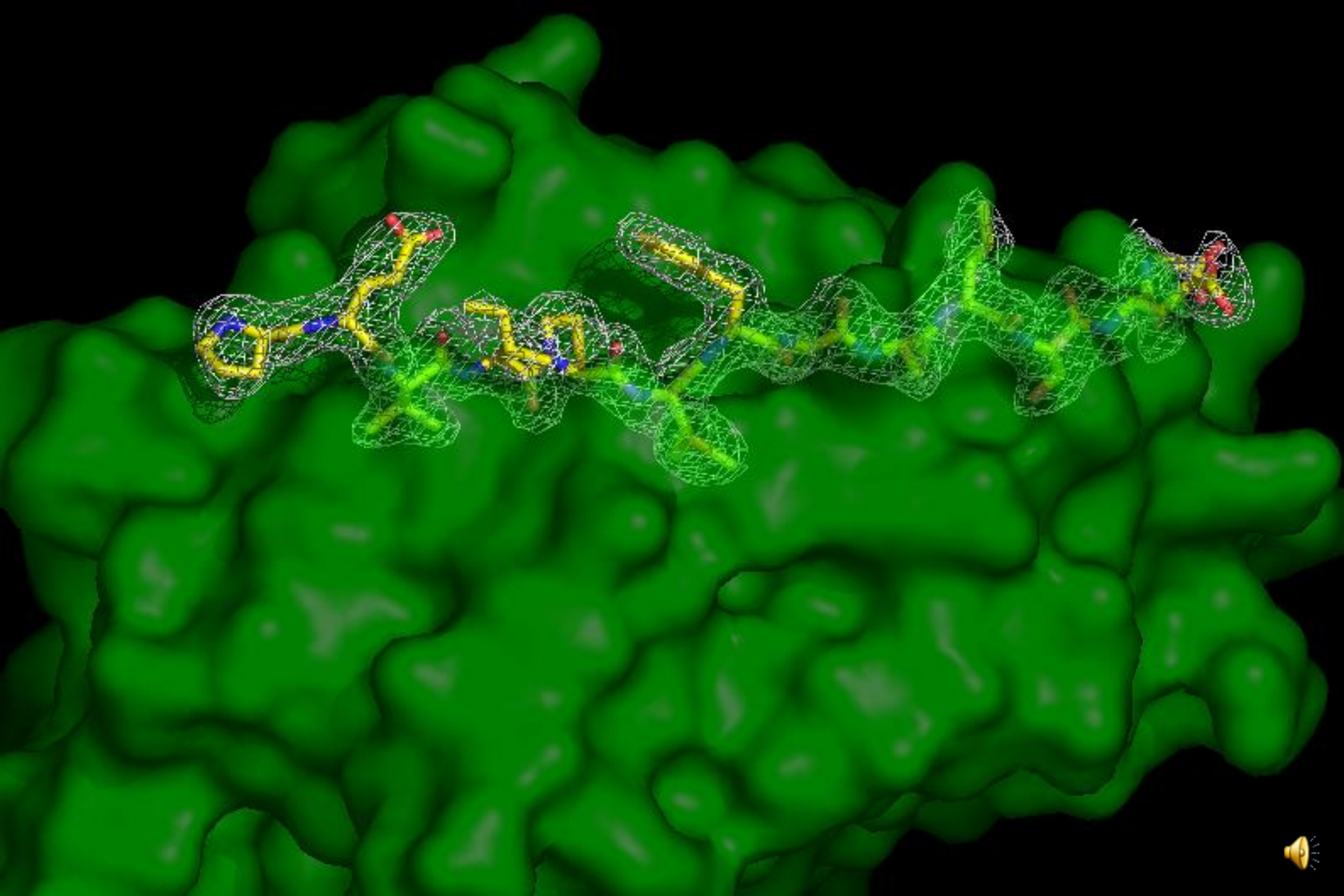


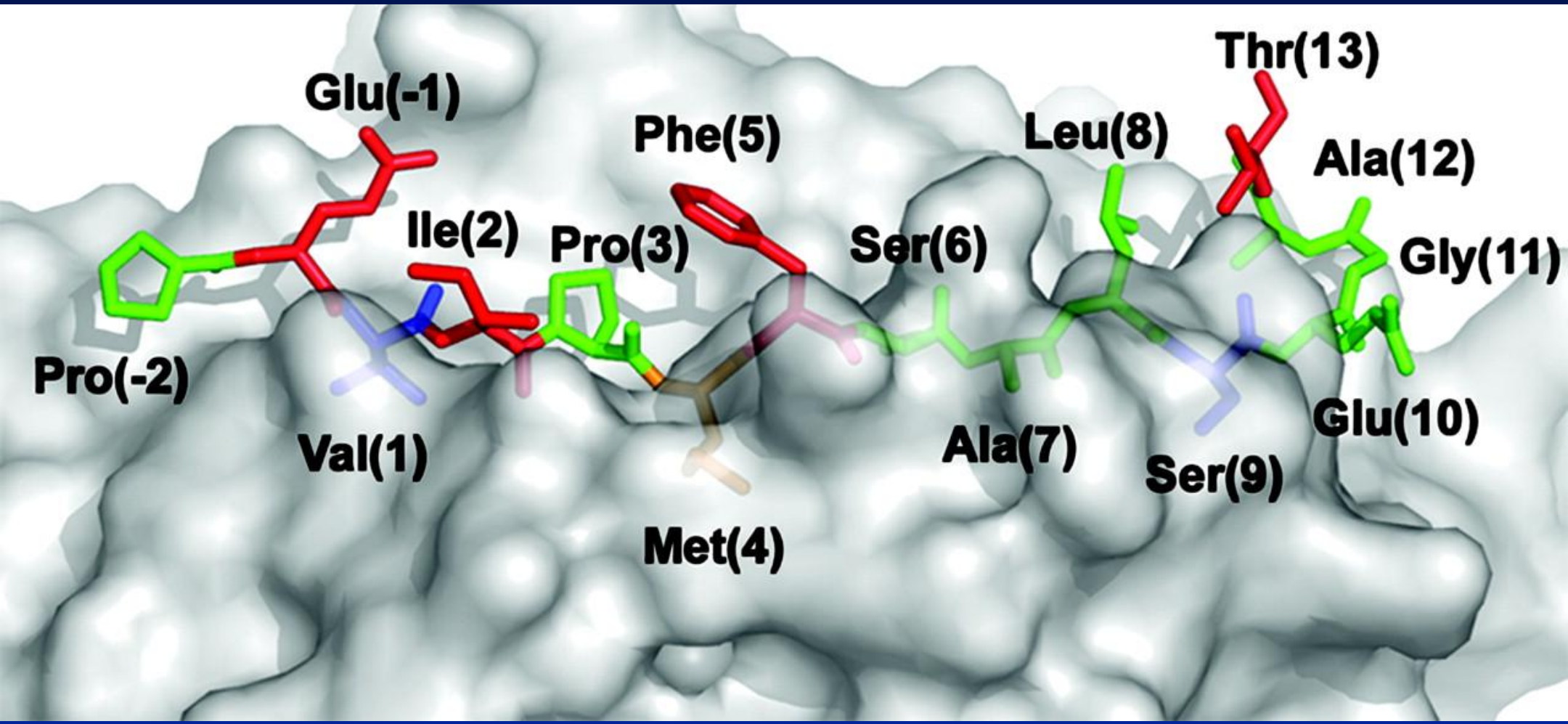


Norris et al., Molecular Immunol. 2006

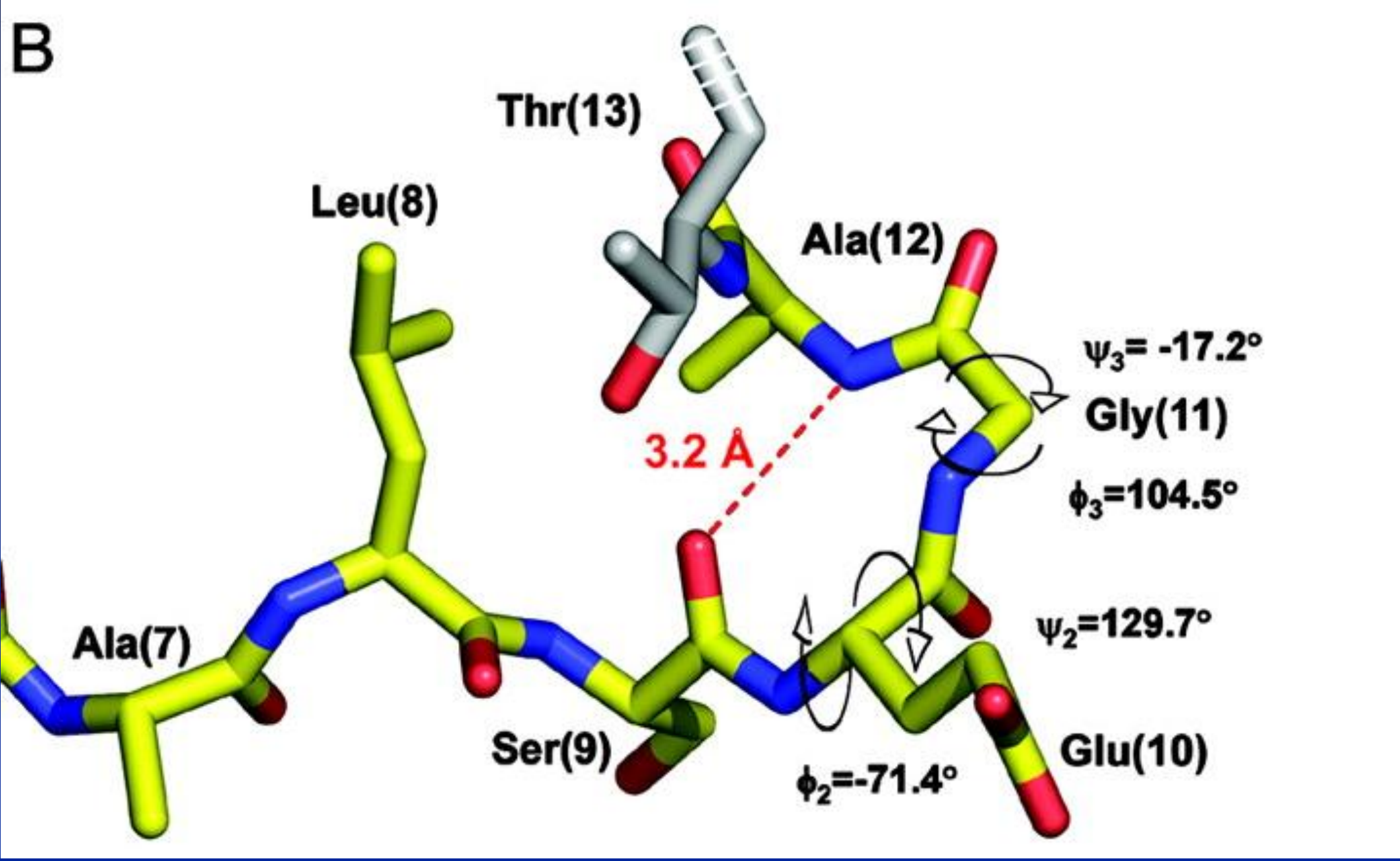
Does binding of shorter vs. longer peptide reveal function?


P1
P4
P6
P9



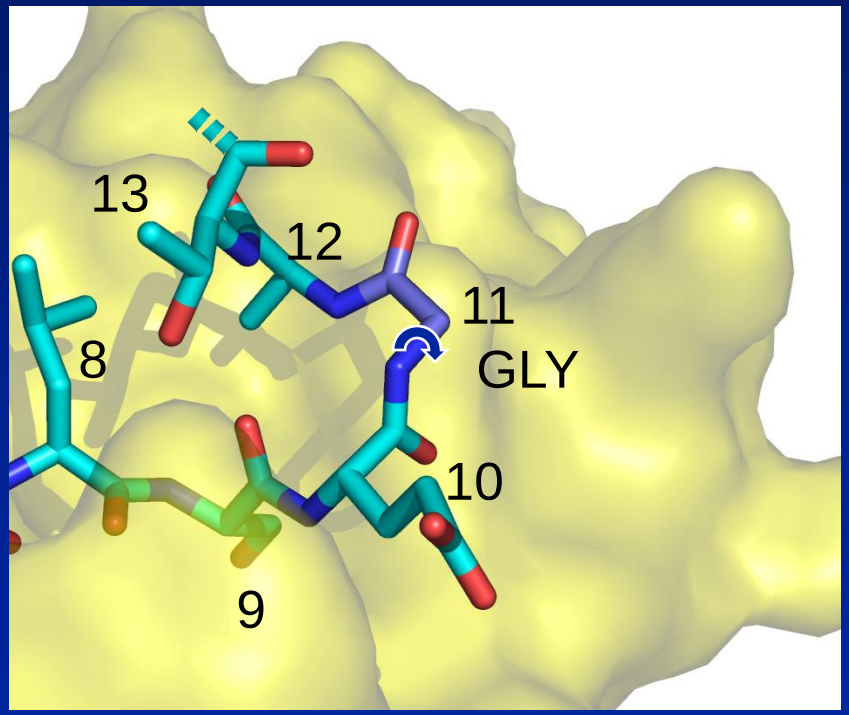


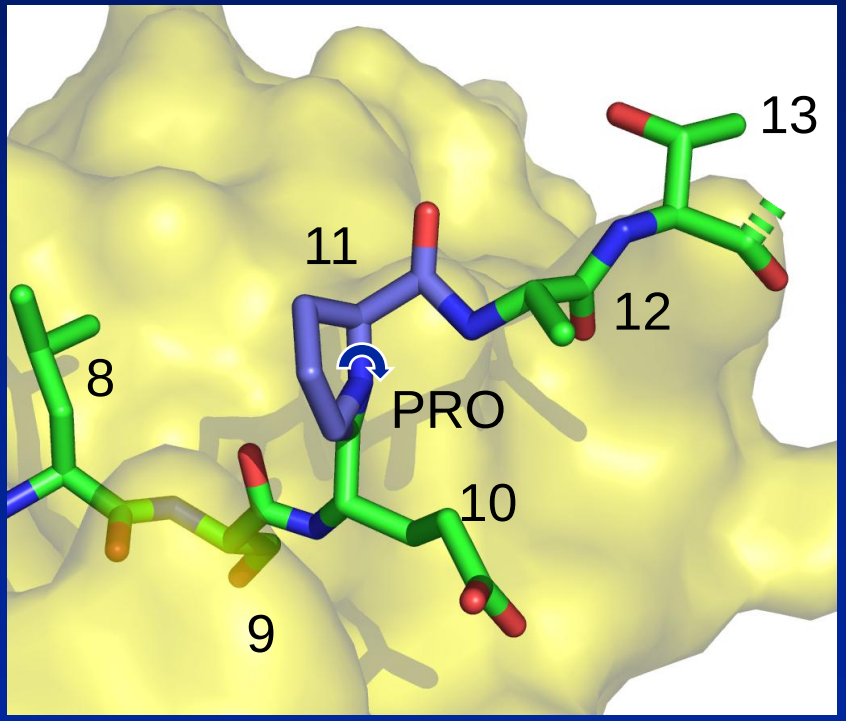
Zavala-Ruiz et al., PNAS 2004



Zavala-Ruiz et al., PNAS 2004

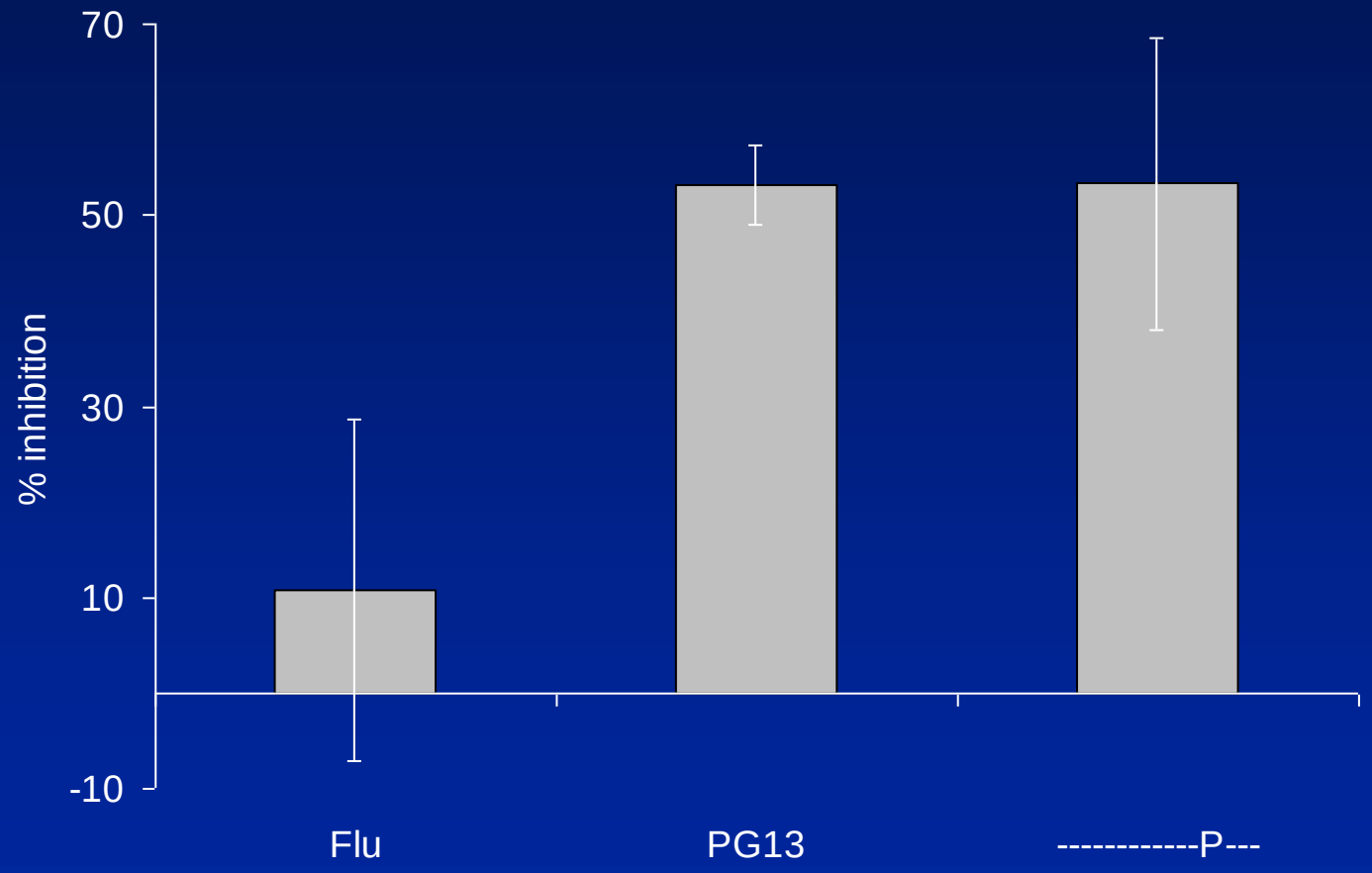
Glycine turn abolished





Norris et al., Molecular Immunol. 2005

Engineered antagonist peptide



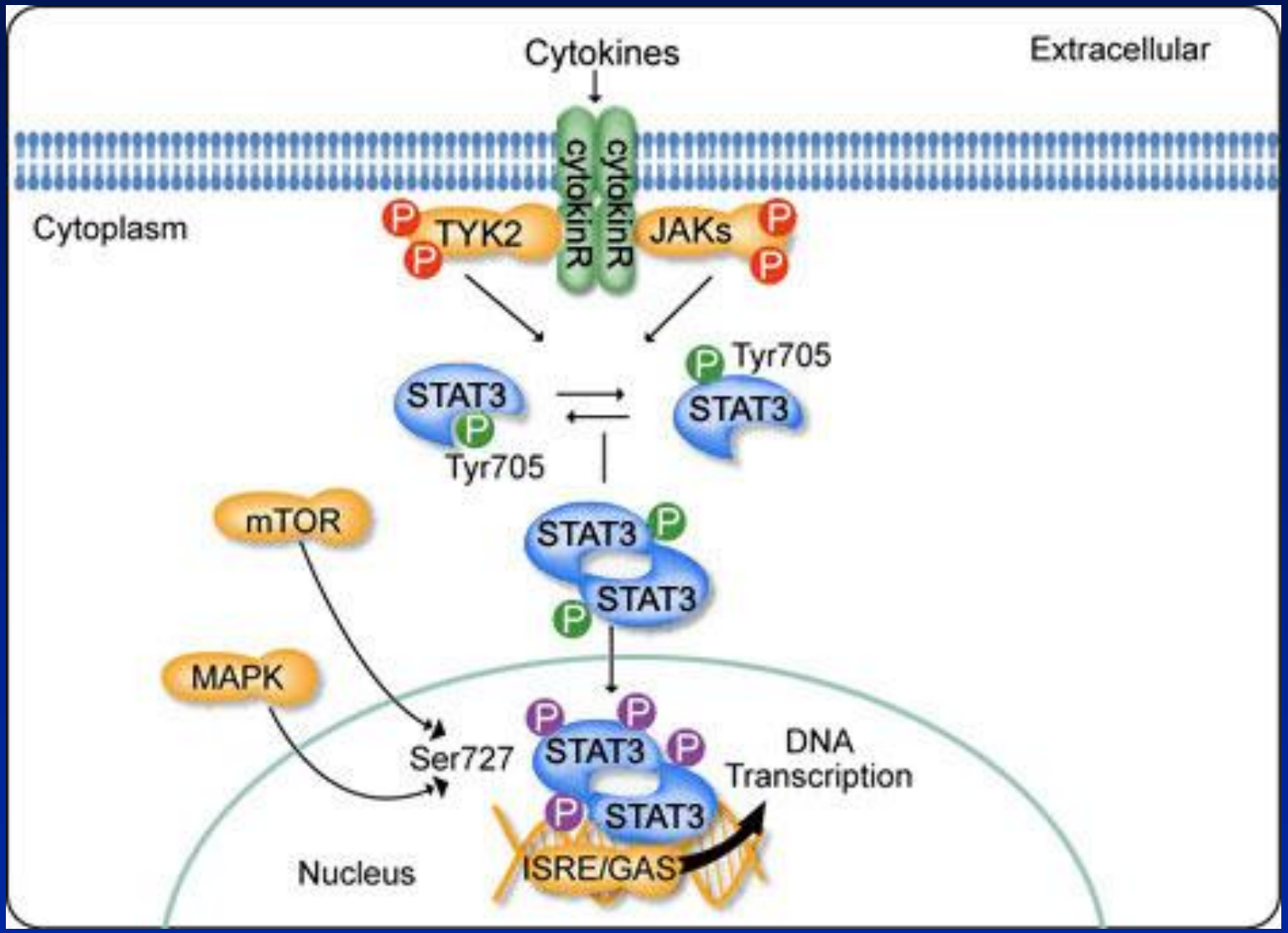
Norris et al., Molecular Immunol. 2005

Conclusions I

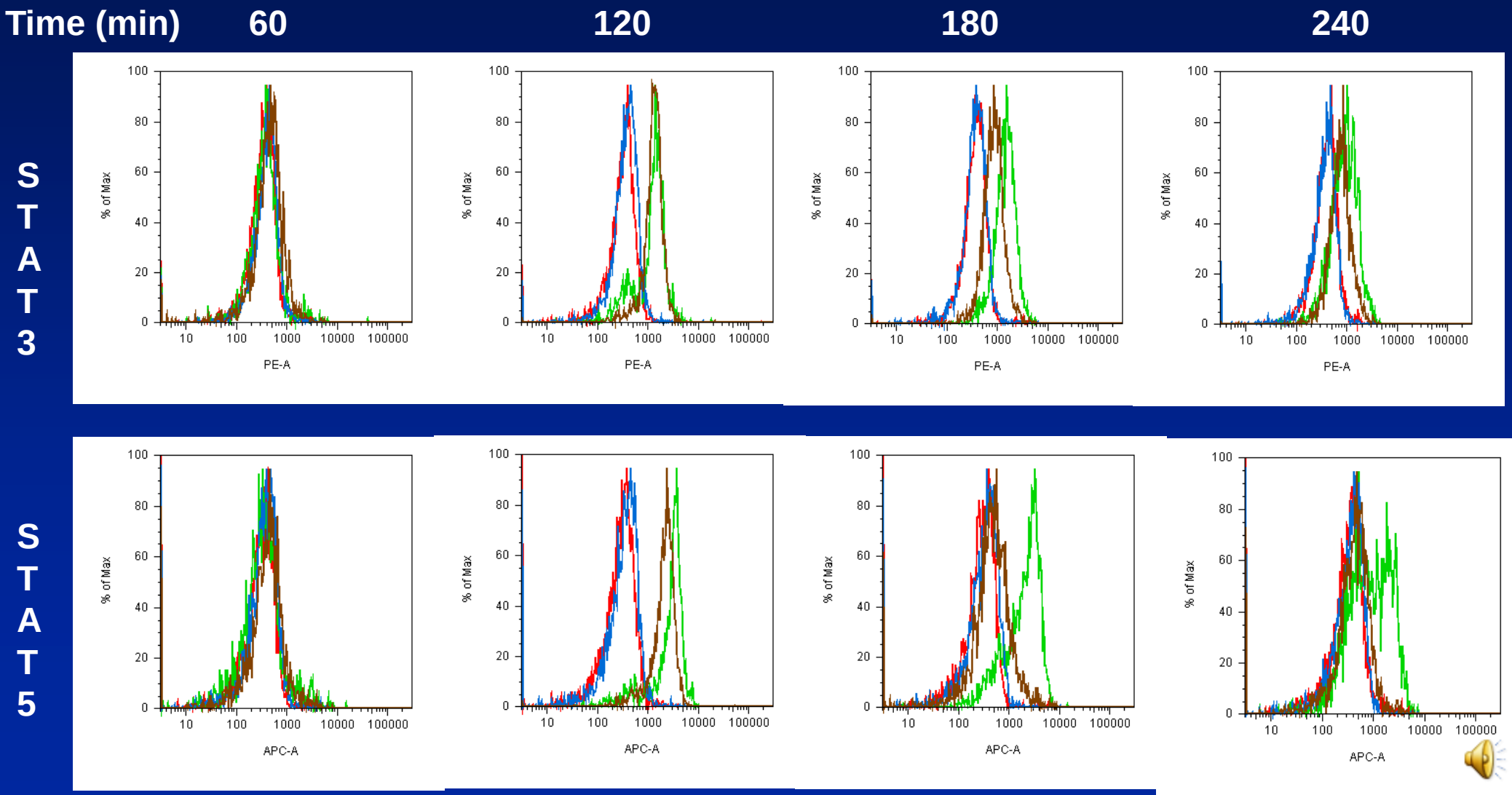
- Residues outside the MHC binding core can interact with and activate the T cell
- Partial T cell receptor engagement results in antagonism
- Antagonist peptide-MHC maintains ability to bind TCR with lower affinity than agonist

What gene pathways are disrupted after antagonist peptide exposure?

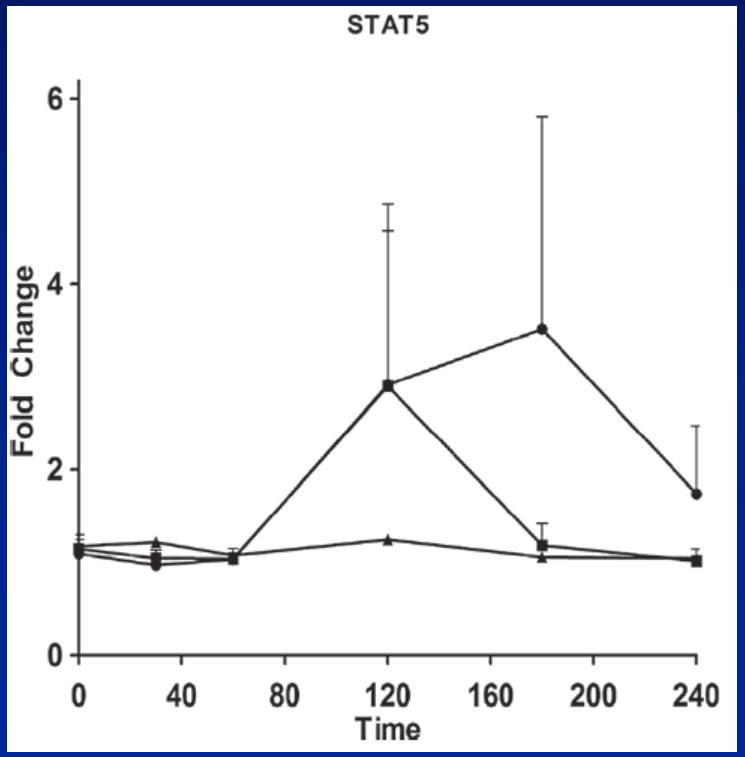
STAT signaling pathway

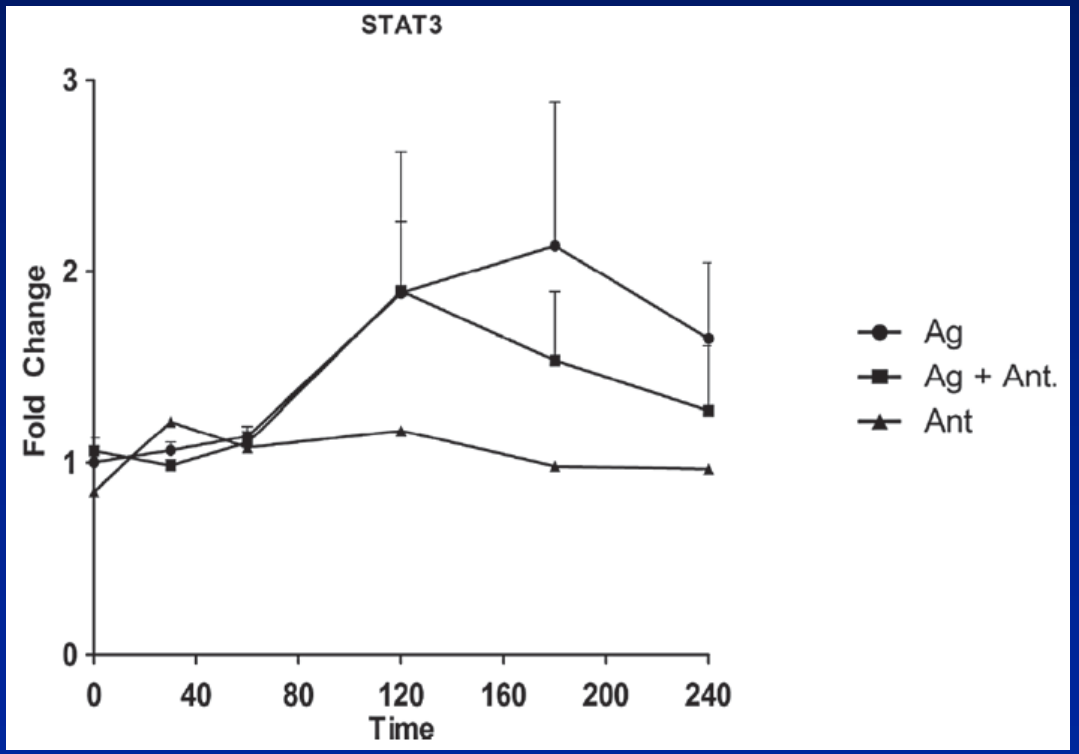


Activation truncated by antagonist

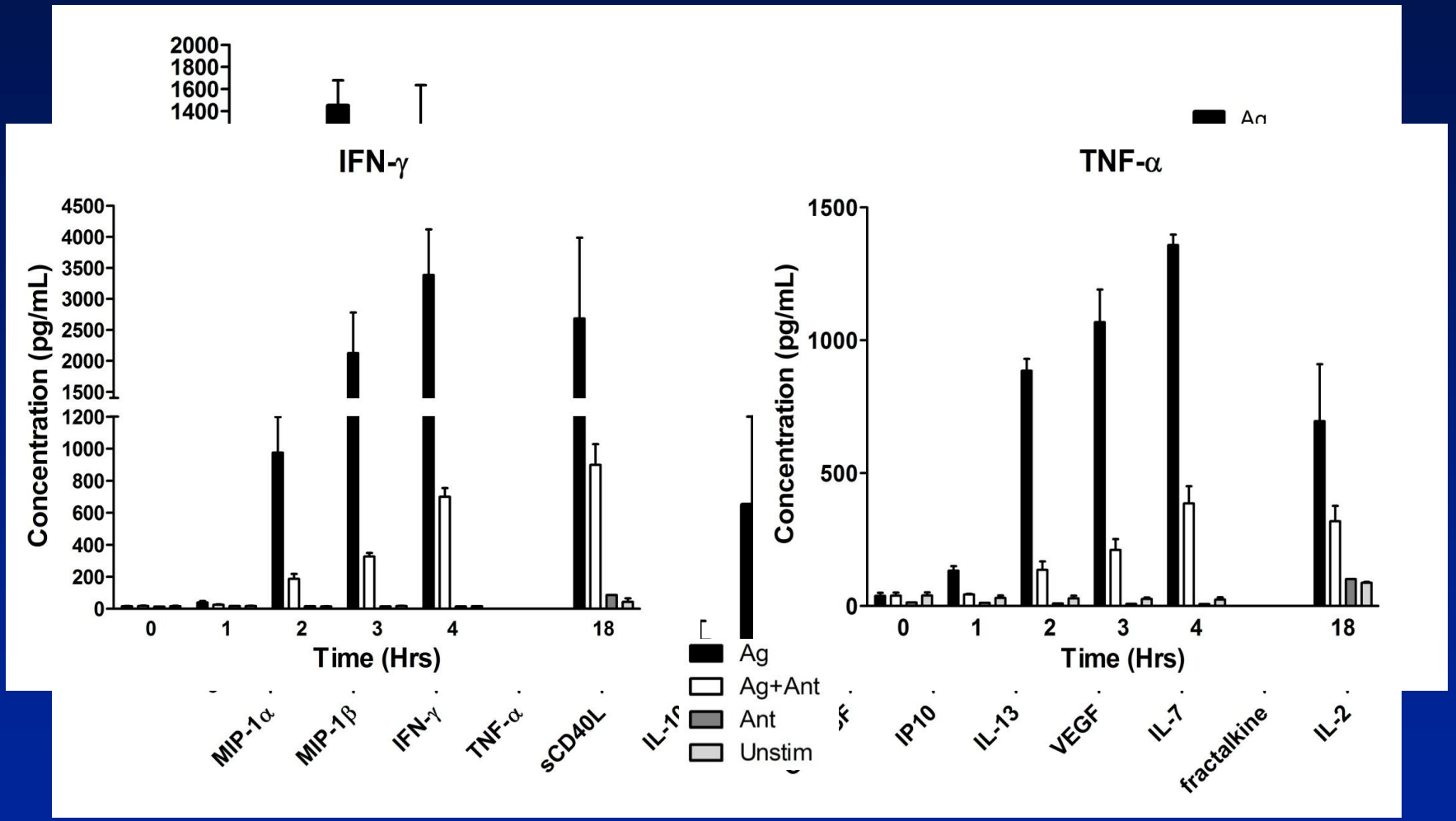


Activation truncated by antagonist



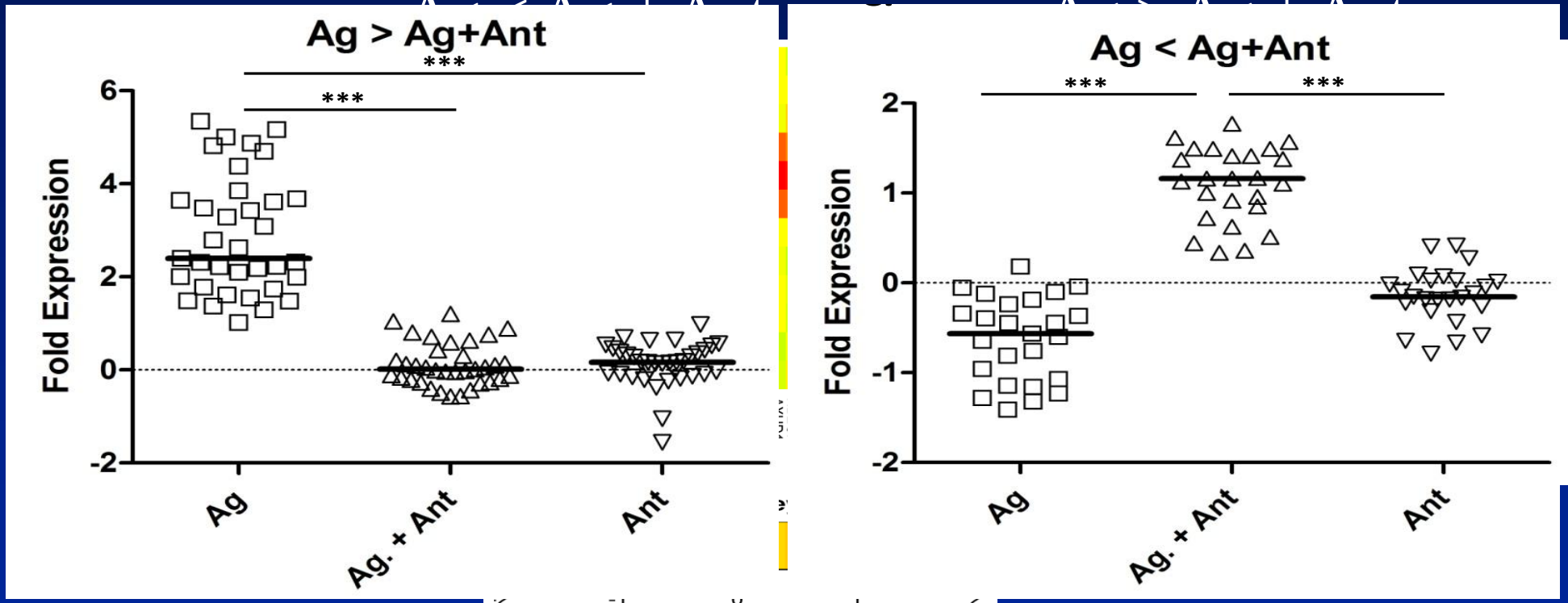


Multiplex detection of secreted cytokines



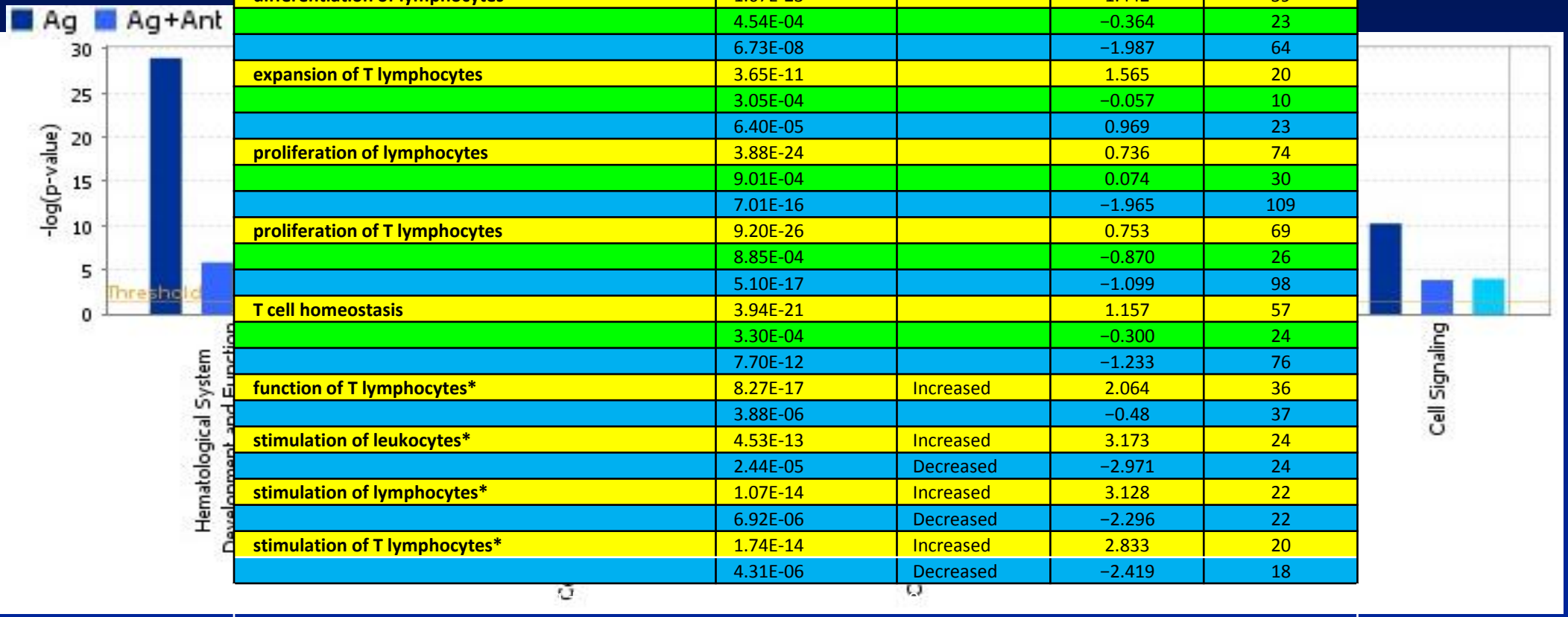
Jacobs et al., Retrovirology 2014

Genes with 1.5 fold greater difference in expression between Ag and Ag+Ant



Jacobs et al., Retrovirology 2014

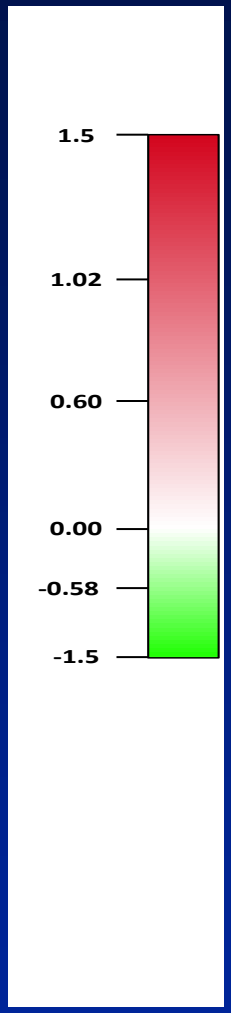
IPA Comparison of gene array data

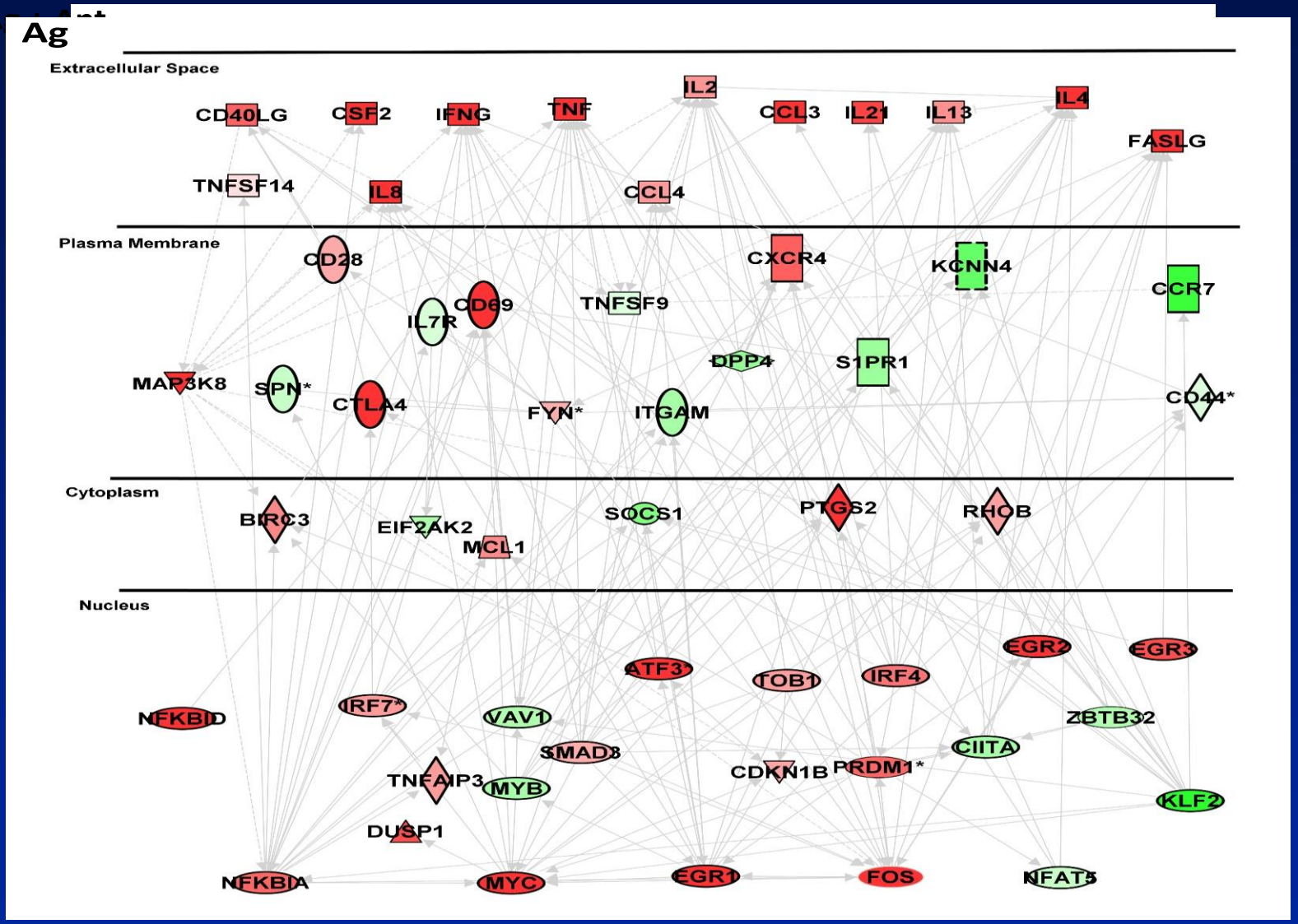


Yellow = Ag, Green = Ag + Ant, Blue = Ant Annotated Function	p-Value	Predicted Activation State	Activation z-score	# Molecules
activation of T lymphocytes	2.93E-19		1.541	45
	6.31E-04		0.179	18
	6.09E-09	Decreased	−3.854	53
differentiation of lymphocytes	1.67E-23		1.442	59
	4.54E-04		−0.364	23
	6.73E-08		−1.987	64
expansion of T lymphocytes	3.65E-11		1.565	20
	3.05E-04		−0.057	10
	6.40E-05		0.969	23
proliferation of lymphocytes	3.88E-24		0.736	74
	9.01E-04		0.074	30
	7.01E-16		−1.965	109
proliferation of T lymphocytes	9.20E-26		0.753	69
	8.85E-04		−0.870	26
	5.10E-17		−1.099	98
T cell homeostasis	3.94E-21		1.157	57
	3.30E-04		−0.300	24
	7.70E-12		−1.233	76
function of T lymphocytes*	8.27E-17	Increased	2.064	36
	3.88E-06		−0.48	37
stimulation of leukocytes*	4.53E-13	Increased	3.173	24
	2.44E-05	Decreased	−2.971	24
stimulation of lymphocytes*	1.07E-14	Increased	3.128	22
	6.92E-06	Decreased	−2.296	22
stimulation of T lymphocytes*	1.74E-14	Increased	2.833	20
	4.31E-06	Decreased	−2.419	18

Jacobs et al., Retrovirology 2014

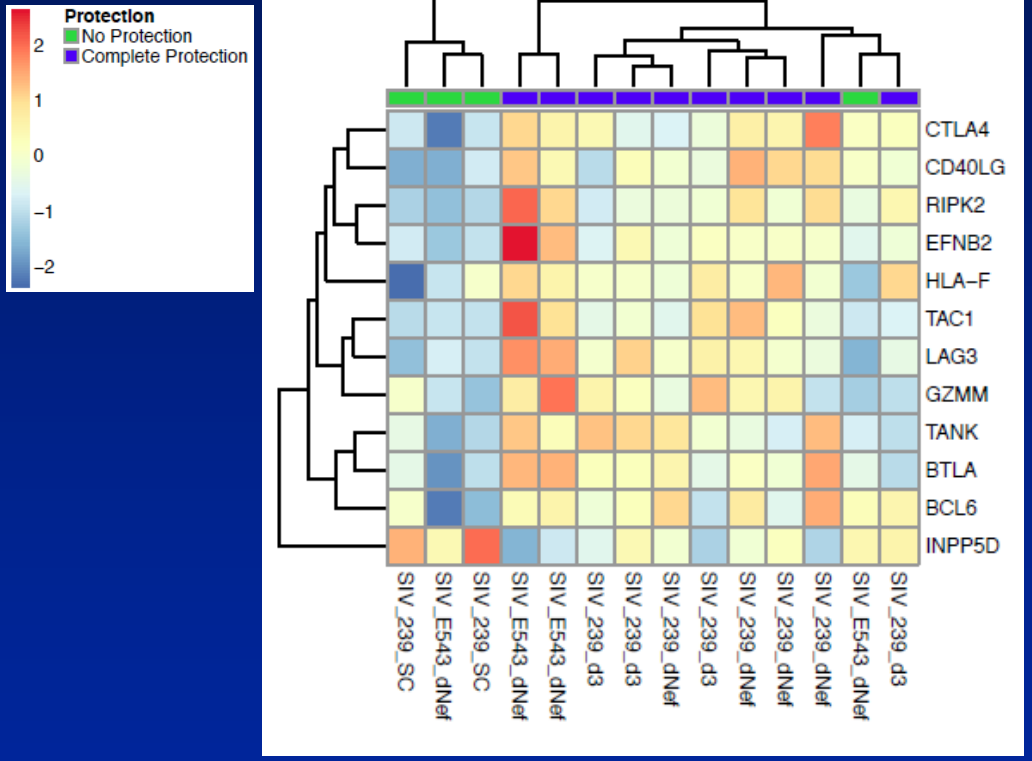
IPA Comparison of gene array data



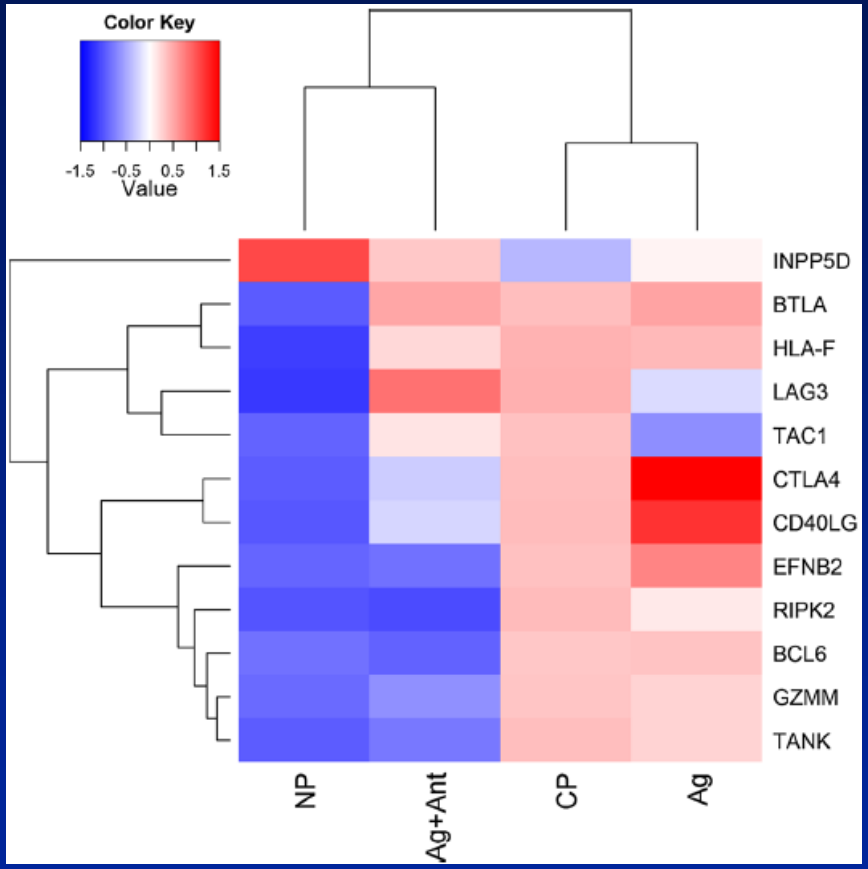


Jacobs et al., Retrovirology 2014

Gene expression profile of T cell stimulation matches that of SIV vaccine trial



Fukazawa et al., Nat Med 2012



Jacobs et al., Retrovirology 2014

Conclusions II

- Antagonism results in aborted activation due to a dominant negative signal
- Link to existing vaccine study where Ag + Ant treatment showed similar profile to vaccine failure

Acknowledgments

BSRI

- John Heitman
- Dale Hirschkorn
- Evan Jacobs

Harvard

- Howell Moffett
- Margaret Clark
- Eric Rosenberg
- Bruce Walker

University of Massachusetts

- Thomas Cameron
- Zarixia Zavala-Ruiz
- Jennifer Stone
- Larry Stern

University of Toronto

- Des Persad
- Luoling Xu
- Longsi Ran
- David Kelvin