Lecture held at the

Nobel Forum, Karolinska Institutet
Stockholm, Sweden
October 27, 2006

Conference on

HIV neutralizing antibodies: relevance to pathogenesis and vaccines

Arranged by Francesca Chiodi and Jan Albert

Understandig HIV neutralization:
What can we learn from the SIV model?

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Issues to discuss…

- Escape from autologous neutralization
- Production of neutralizing antibodies in the infected host - relationship to pathogenesis
- Broadly cross-reactive neutralization?
- The role of open or closed envelope conformation

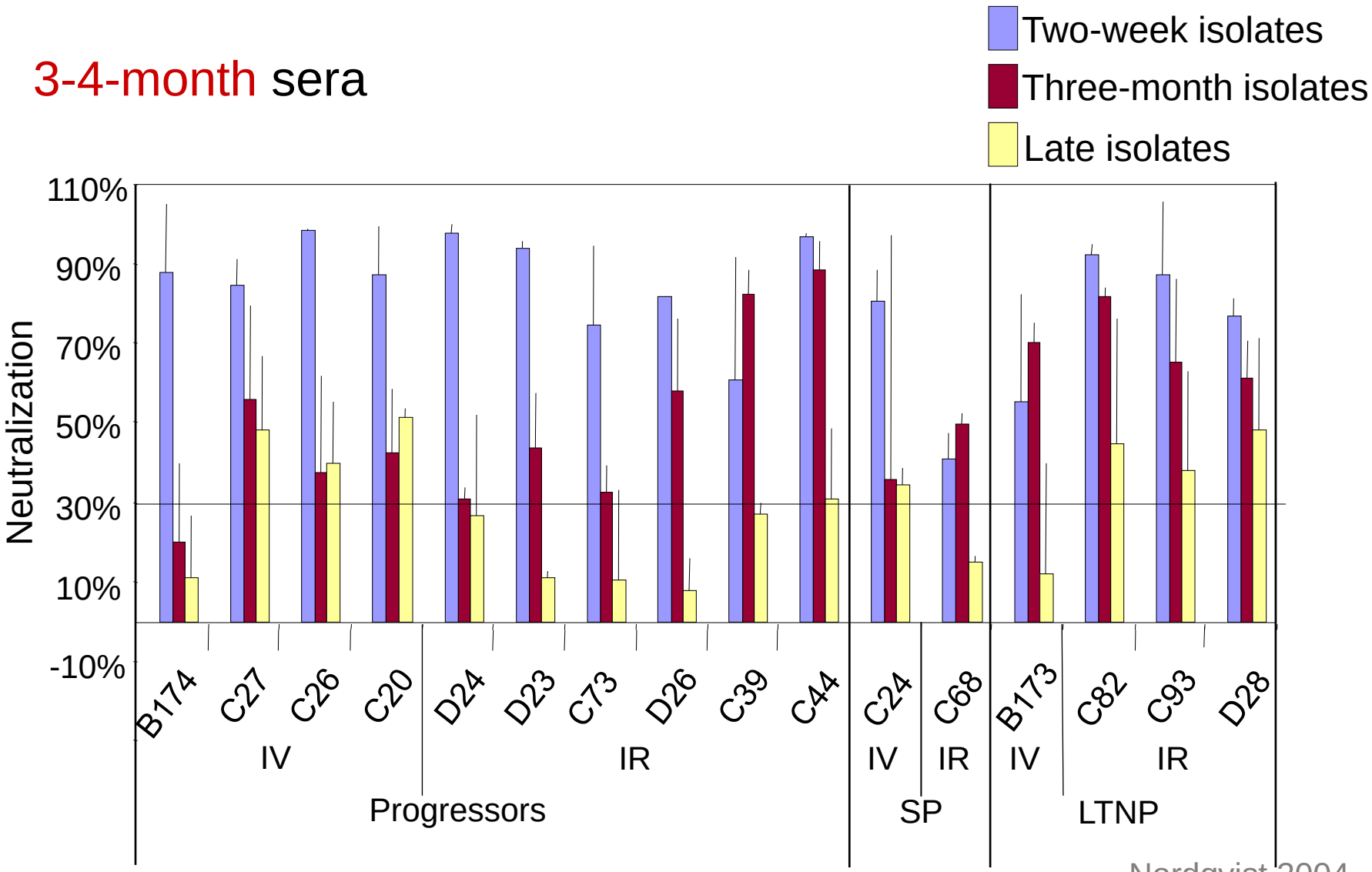
Simian immunodeficiency virus

from sooty mangabey

SIVsm

Escape from autologous neutralization

3-4-month sera



Nordqvist 2004

Emergence of neutralization escape variants is pathogenesis related

- Escape from autologous neutralisation at

  3 months:

  Six of 10 progressor monkeys

  none (or 1/6?) of slow progressor and LTNP monkeys

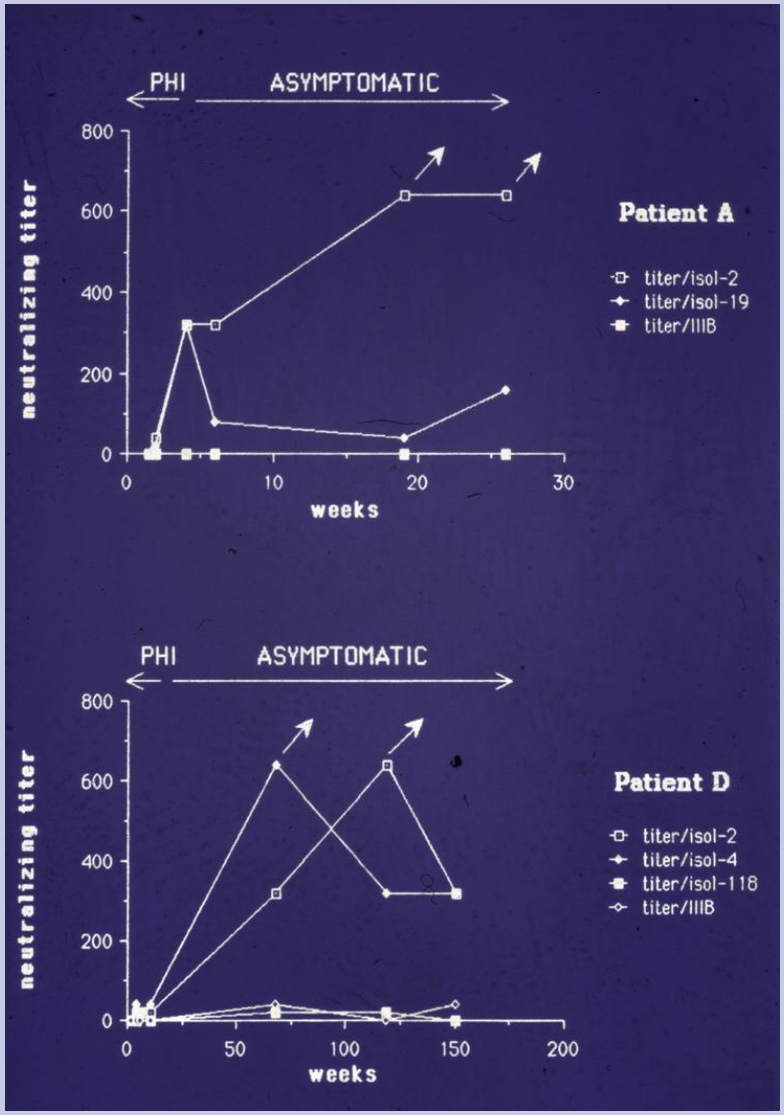
  late:

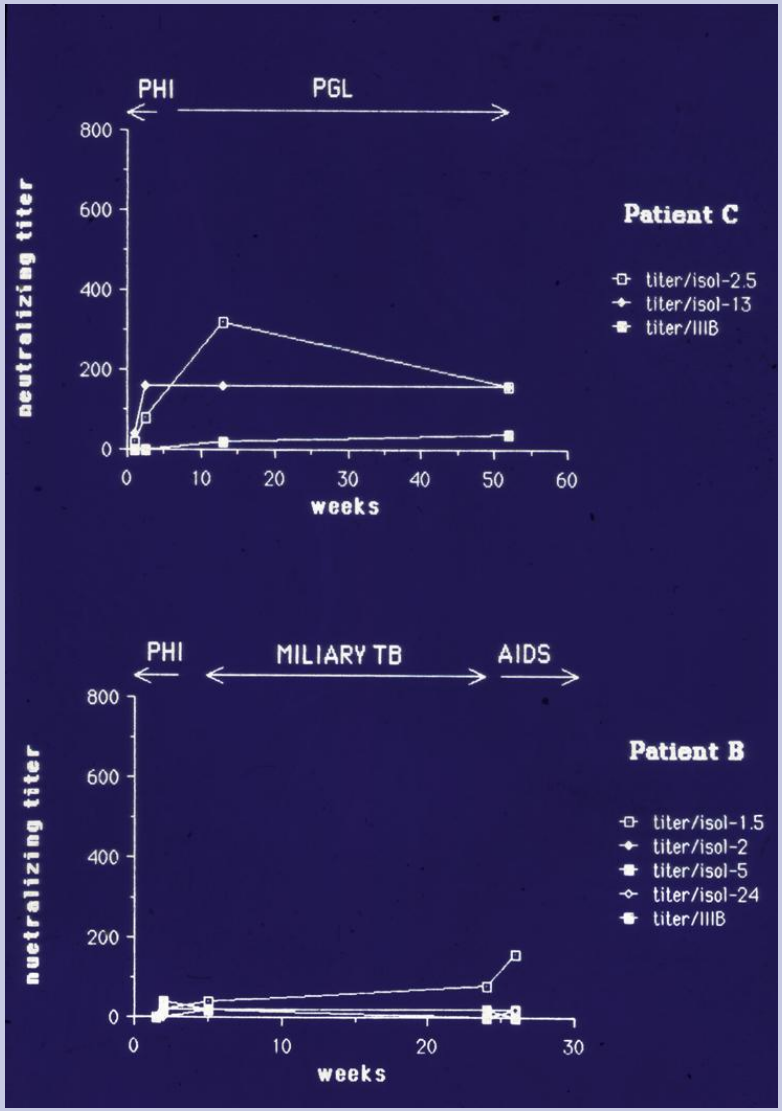
  Nine of 10 progressor monkeys

  three of six SP or LTNP monkeys

- Evolution to neutralisation resistance by heterologous sera parallels resistence to autologous neutralisation.

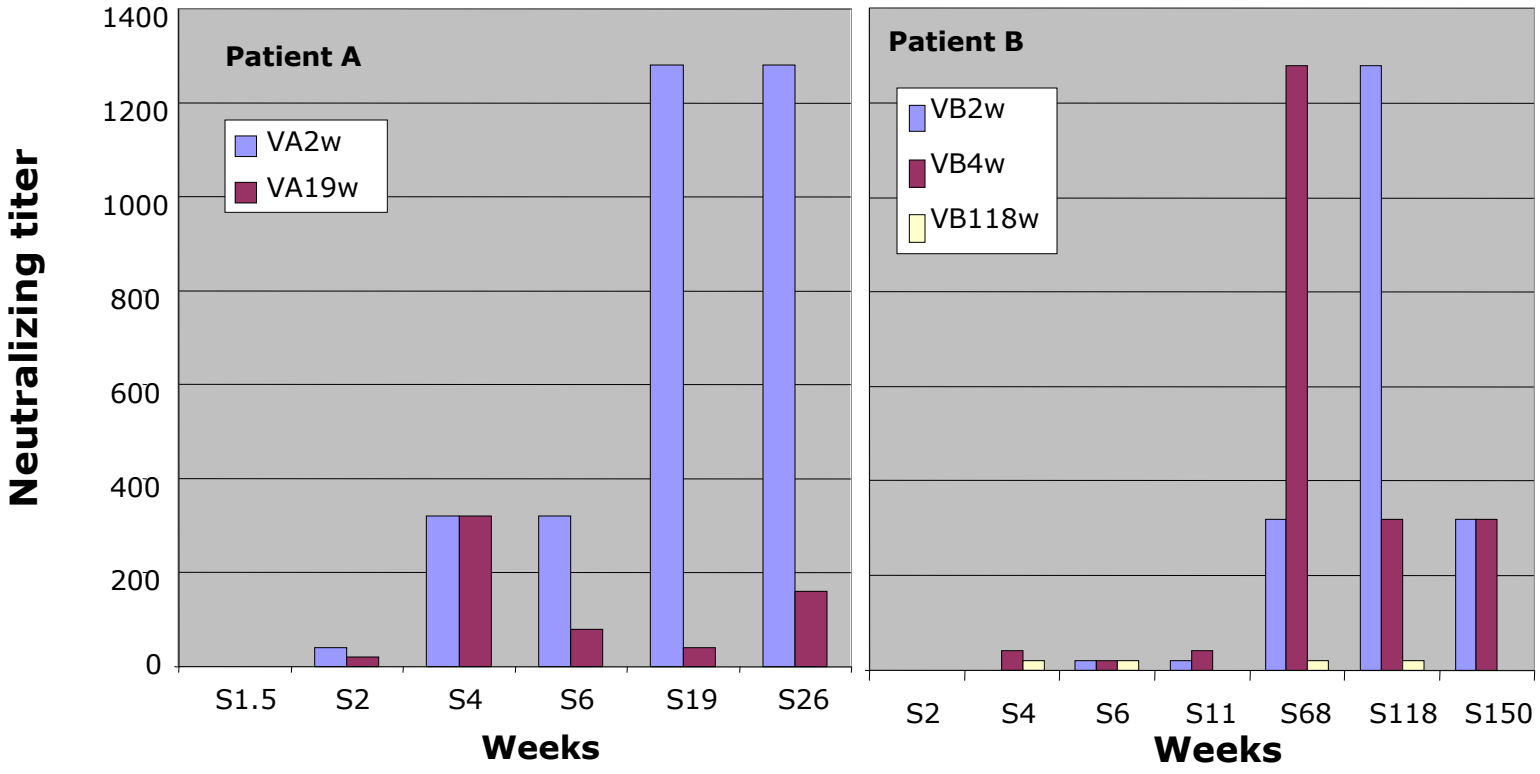
HIV-1 escape from autologous neutralization





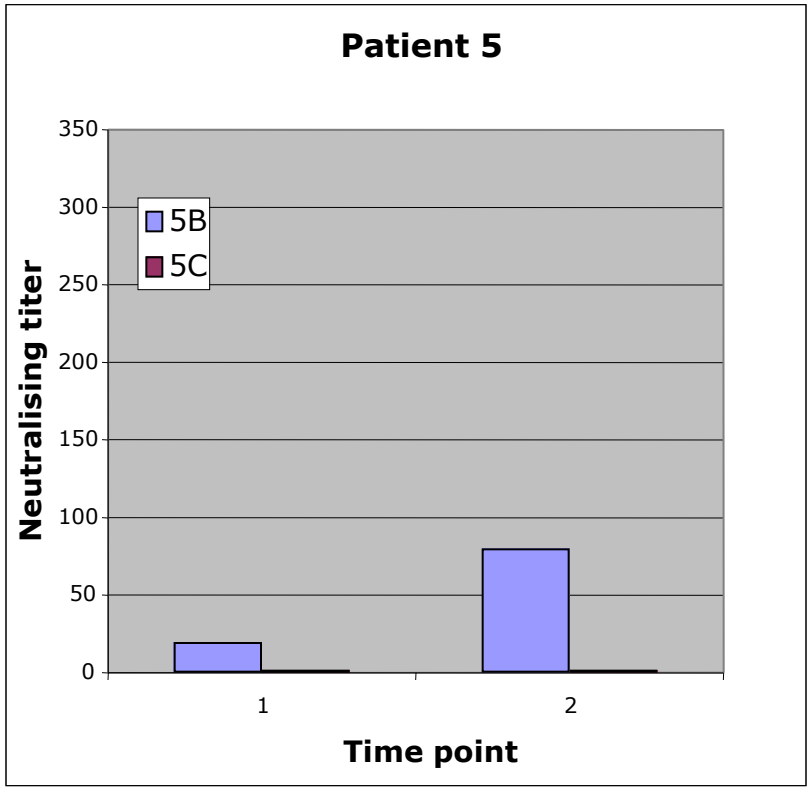
Albert 1990

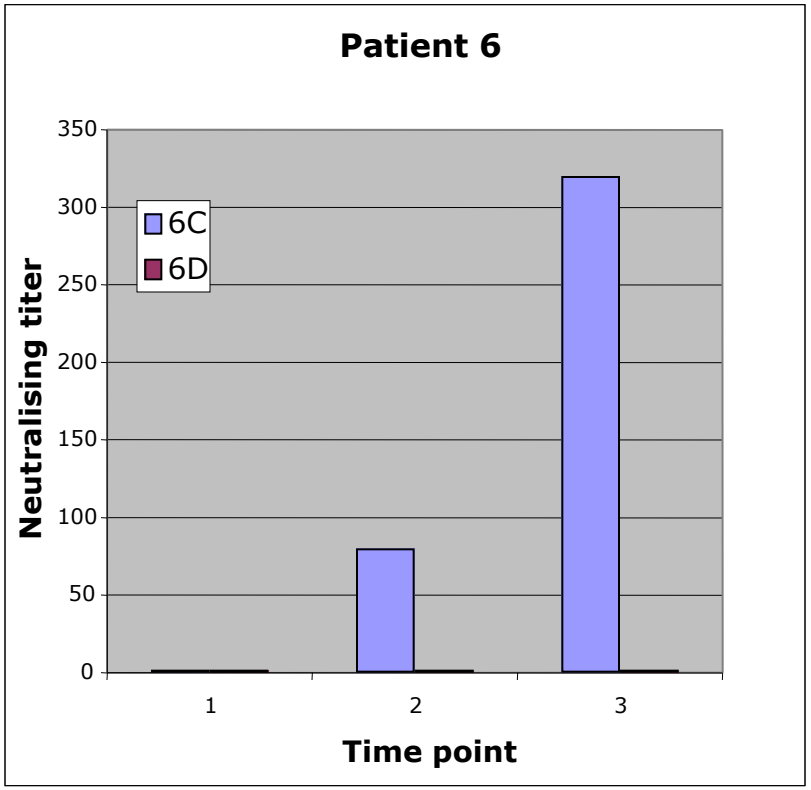
Escape from autologous neutralisation: HIV-1 in PHI



Albert 1990

Escape from autologous neutralisation:
HIV-1 in progressive disease





CD4 x10⁶/L	*226*	*100*	*470*	*450*	*197*

Von Gegerfelt 1991

HIV-2 in monkeys

non-pathogenic infection

Monkey	Virus	Neutralizing titers at months PI		
	months PI	5	9-12	21
H44	5	80	80	80
	12	20	20	20
	21	80	320	160
H45	5	40	80	>320
	9	80	20	>320
	21	320	320	320

No escape

Zhang 1994

HIV-2 in humans

Patient	Virus	% Neutralization in serum			
		1994	1996	1998	2002
2	1994	75	47	95	52
	1996	46	40	94	64
	1998	62	41	58	48
	2002	50	<	70	35
		1992	2000	2001	2002
4	1992	60	70	32	<
	2000	53	39	68	52
	2001	77	52	55	81
	2002	38	57	<	68

No escape

Shi 2005

Production of neutralizing antibodies in HIV-1 infection

LTNP

FP

	Primary HIV-1 isolates						
	A	B	C	D	E	F	G
LTNP							
Hem 1	160	40	40	640	160	20	160
2	2560	40	160	1280	320	1280	320
3	320	0	40	40	40	320	640
4	40	0	40	80	80	160	2560
5	80	40	1280	1280	40	0	320
6	40	40	320	160	160	0	320
7	160	0	80	20	0	20	1280
8	80	160	160	20	80	20	80
9	20	160	1280	20	320	40	40
10	40	320	160	40	40	0	640
IVDU11	80	1280	0	80	40	40	160
12	ND	80	5120	20	40	640	80
13	80	320	40	40	80	160	80
14	80	0	0	40	0	0	80
15	80	160	40	0	0	0	0
16	ND	160	40	40	0	1280	320
17	ND	80	40	80	20	5120	80
Progressors							
Hem 18	0	0	0	0	0	0	40
19	0	0	0	0	0	0	20
20	0	0	40	40	20	40	160
21	0	0	40	40	40	0	0
22	40	20	80	160	20	40	160
23	0	0	20	40	0	0	80
24	40	0	40	0	0	0	40
IVDU25	0	0	20	40	20	20	ND
26	0	0	0	20	0	0	ND
27	0	0	20	20	20	0	ND
28	0	0	20	20	20	80	ND
29	0	0	0	20	0	0	ND
30	0	0	0	0	0	0	ND

Zhang, Fracasso 1997

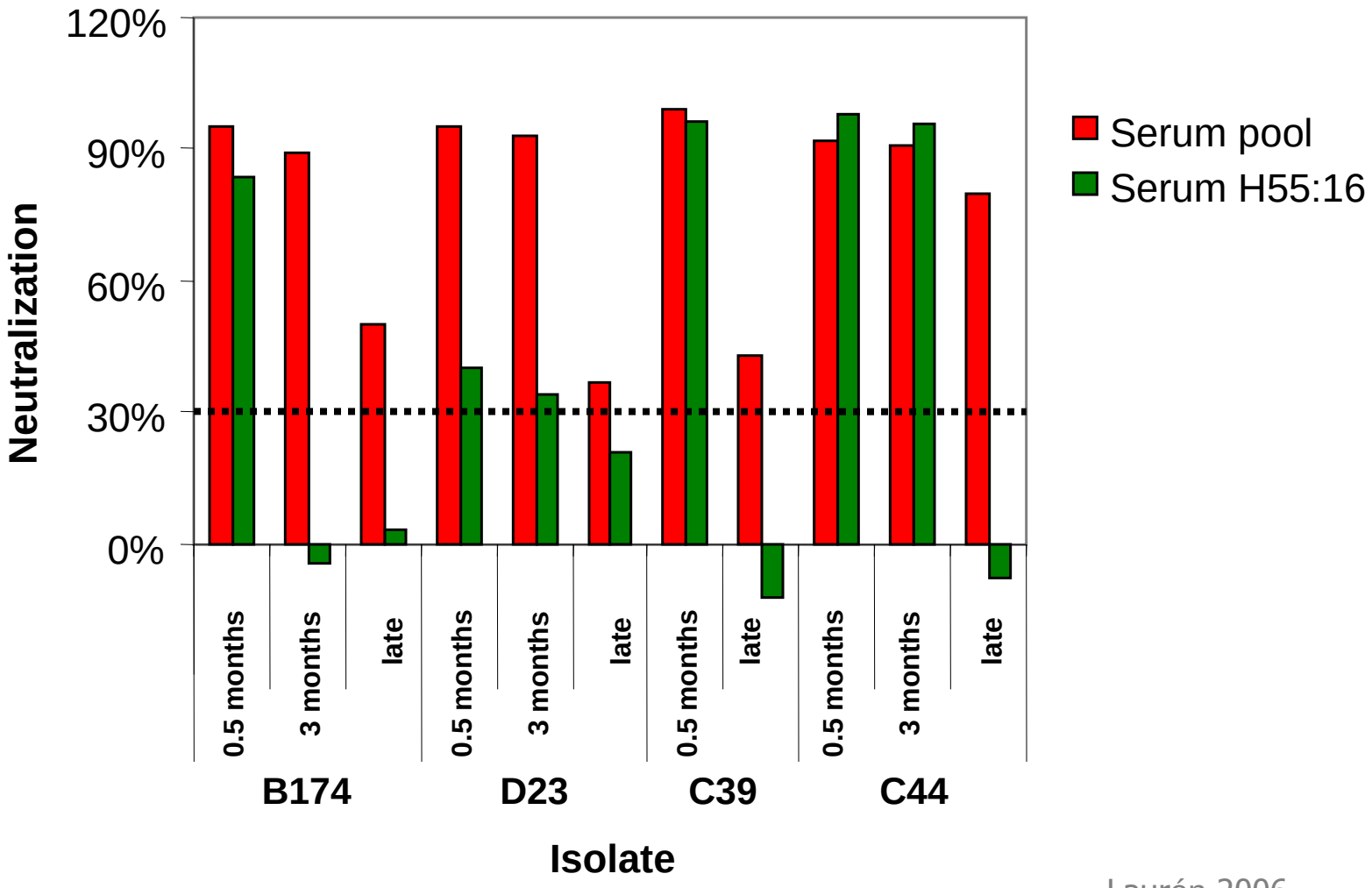
Frequent high-titer HIV-1 neutralising activity in LTNP sera

No. of patients	Neutralising titer (range and median) against virus					
	1	2	3	4	5	6
LTNP 17	**20-2560** 80	**0-1280** 80	**0-5120** 80	**0-1280** 40	**0-5120** 60	**0-320** 60
FP 13	**0-40** 0	**0-20** 0	**0-80** 25	**0-160** 10	**0-80** 0	**0-40** 20
P=	**<.001**	**<.001**	.1	.09	**.03**	.09

Zhang, Fracasso 1997

How broadly cross-reactive is the neutralizing response?

SIV *serum pool from 4 LTNP monkeys is broadly neutralizing*



Laurén 2006

Neutralisation of other than B clade HIV-1 by LTNP sera

	Genetic subtype of isolates				
Sera Subtype B	**A1**	**A2**	**B (7 isolates)**	**D**	**E**
1	320	160	20-160	-	-
2	640	160	40-2560	160	-
8	320	40	20-160	-	-
10	80	20	0-640	-	-
11	320	160	0-1280	80	-
12	320	160	20-5120	-	-
17	80	80	20-5120	-	80
Total no. of positive reactions	7/7	7/7	45/47	2/7	1/7
Control1	160	160	160	-	320

Zhang, Fracasso 1997

Distribution of neutralising activities

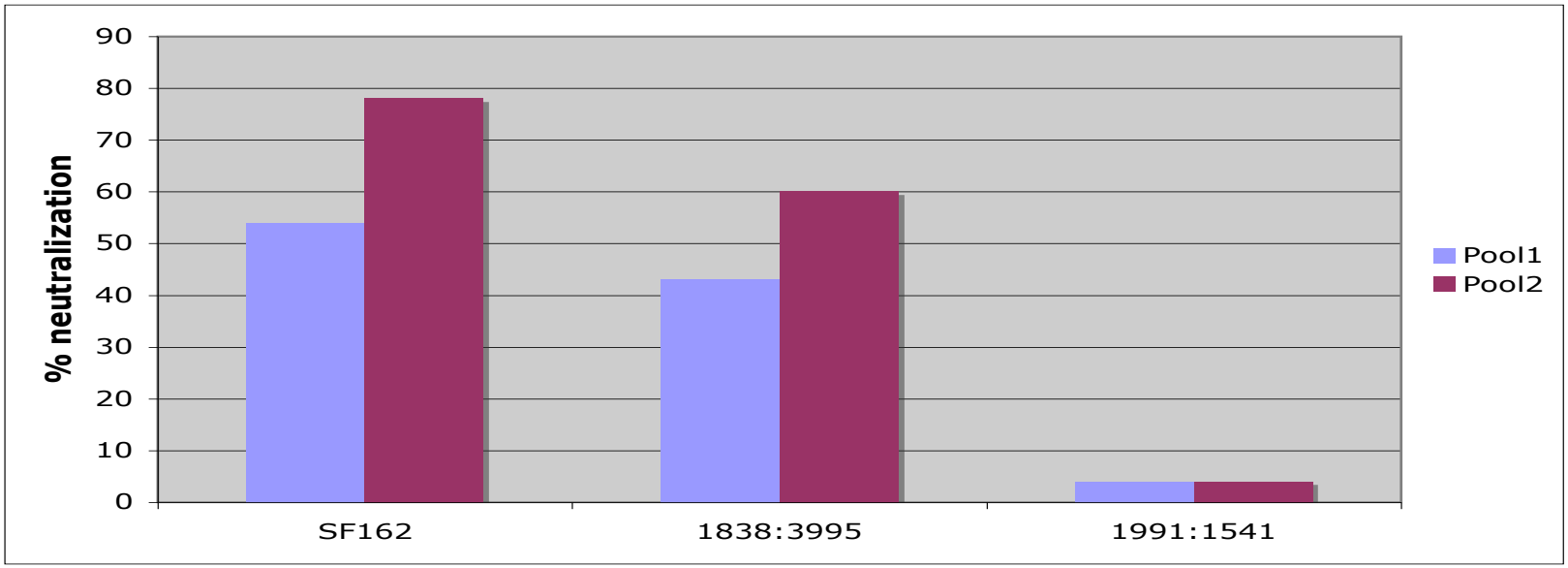
of plasma with ≥1:80 neutralising antibody titer against at least one isolate.

Plasma	A1	A2	B1	B2	C	D1	D2	E1
A1	80	80	20	20	40	-	-	-
A2	-	80	-	-	-	-	-	-
A3	40	80	80	-	40	20	160	40
B1	80	20	-	-	-	-	-	-
B3	-	40	20	80	-	-	20	320
B4	40	40	20	20	-	20	-	320
C	20	80	-	-	-	-	20	-
D2	20	40	-	80	-	80	80	-
E2	40	40	20	20	20	20	20	20
Control1	160	160	160	80	>320	80	-	320

HIV-1 isolates of genetic subtypes A, B, C, D and E from the WHO Network for HIV Isolation and Characterisation

Weber, Fenyö 1996

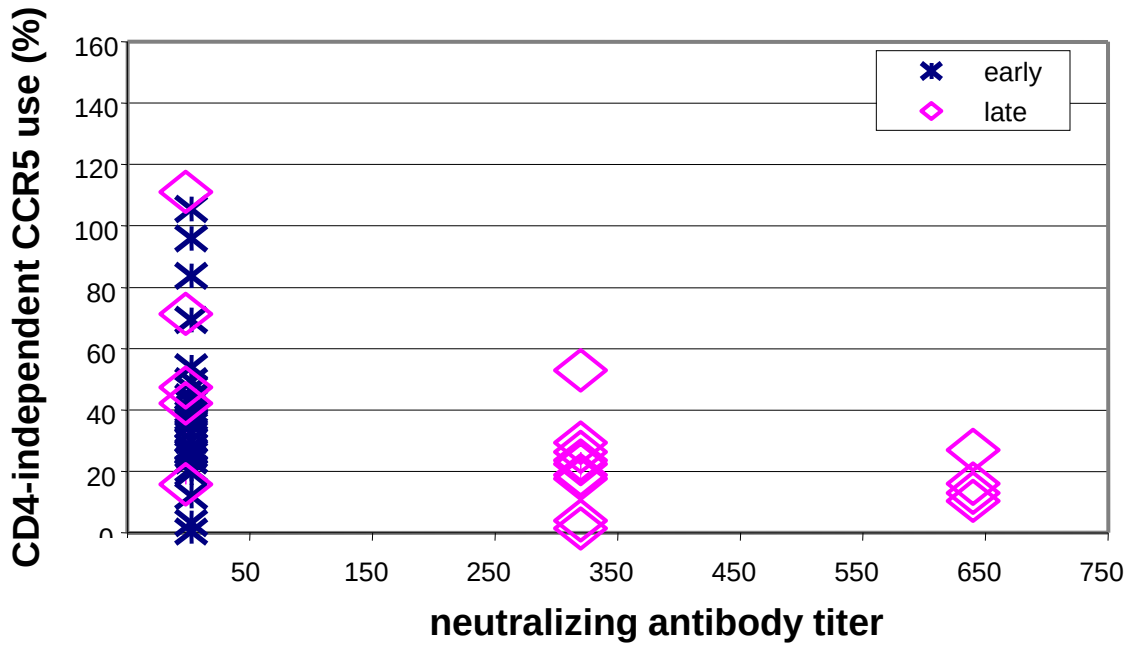
HIV-1 envelope immunized mice



- Highest neutralizing activity against the virus used as immunogen (SF162).
- Neutralization of one of the other 2 isolates tested.

Open or closed envelope conformation?

- Cloned SIV envelopes tested for CD4-independent use of CCR5 in a fusion assay.
- Relationship to neutralizing antibody production by the original monkey?



Vödrös 2003

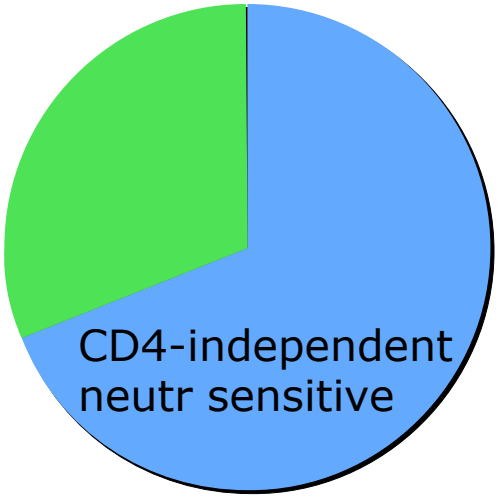
Open or closed envelope conformation?

- CD4-independent use of CCR5 taken as the measure of open envelope conformation - signals neutralization sensitive virus?
- Phenotypes accordingly:
  - CD4-independent/neutralization sensitive: CD4-/neutr+
  - CD4-dependent/neutralization resistent: CD4+/neutr-
- CD4-independence measured in NP-2/CCR5 cells as syncytia induction and RT production

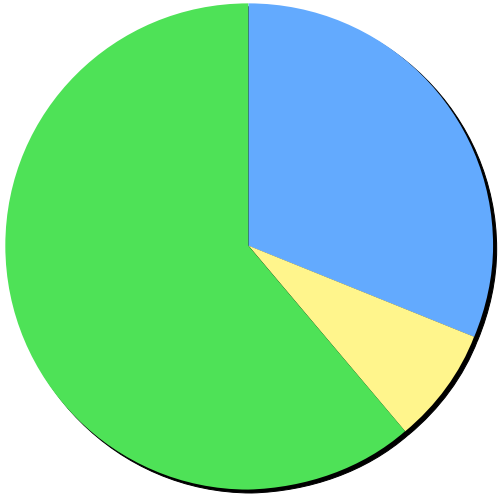
SIV evolution over time

13 monkeys

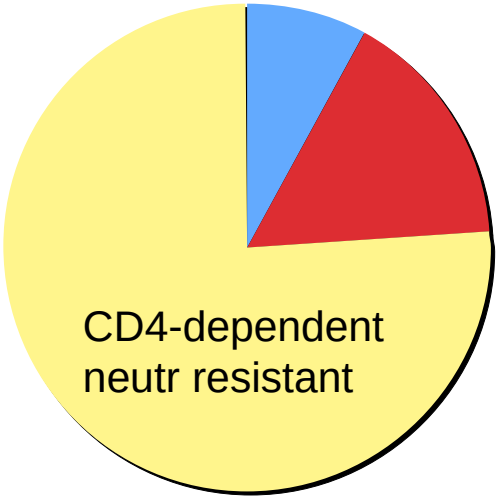
2-week isolates



3-4-month isolates



Late isolates



- CD4-independent/neutr sensitive
- CD4-independent/neutr resistant
- CD4-dependent/neutr resistant
- CD4-dependent/neutr sensitive

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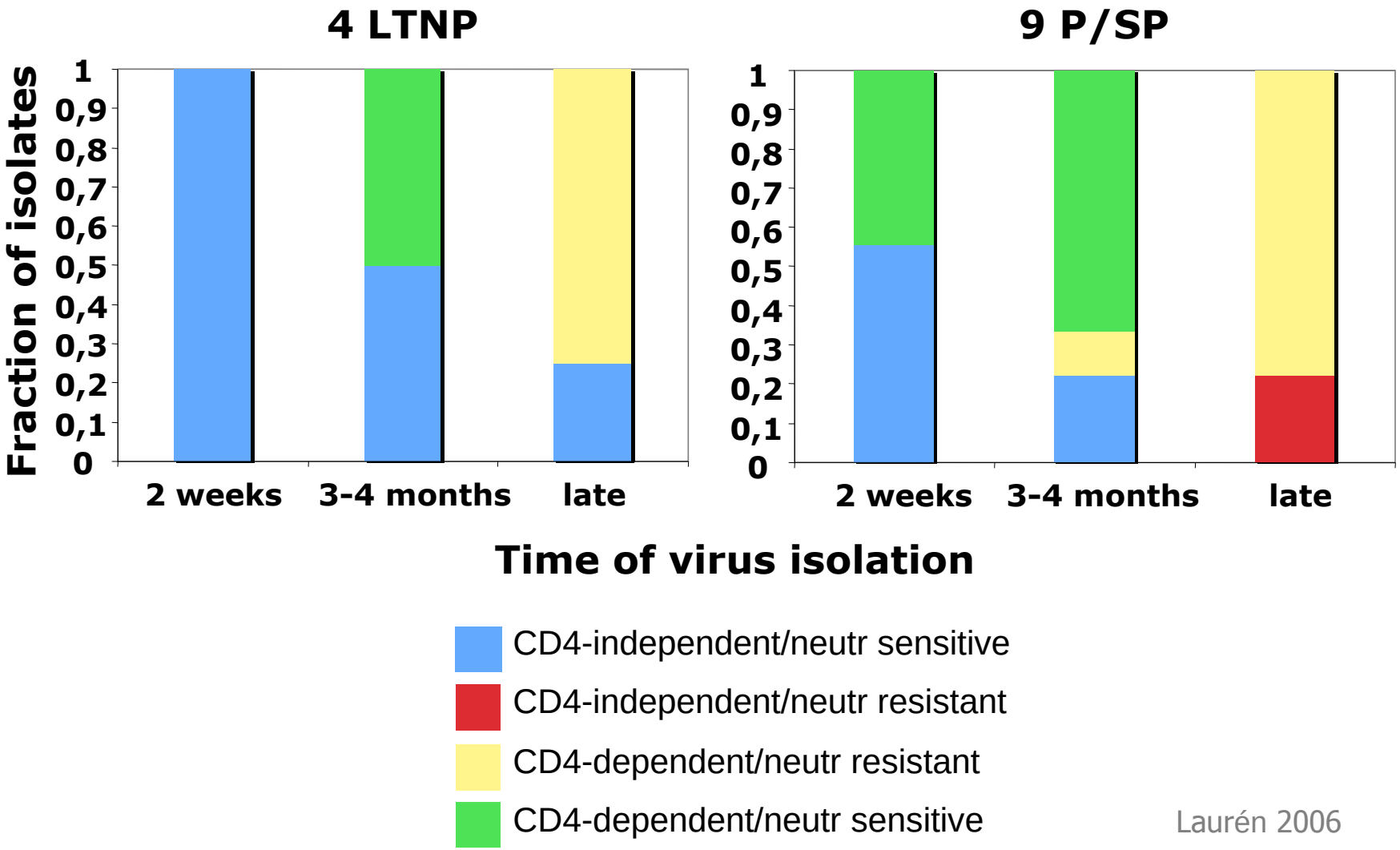
SIV evolution over time



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SIV

1. Phenotypic shift of virus populations over time:
   CD4-/neutr+ → CD4+/neutr-
2. Faster evolution to CD4 dependence than to neutralization resistence,

   intermediate phenotype: CD4+/neutr+
3. Difference between P/SP and LTNP,

   the rate of evolution is slower in LTNP.
4. CD4-independent use of CCR5 and neutralisation resistence only in P/SP (late in infection).

Comparison of HIV-1, HIV-2 and SIV

1. CD4-independent use of CCR5

   NP-2/CCR5 cells cocultivated w PBMC

2. Mode of CCR5 use

   CCR5/CXCR4 chimeric receptors expressed in U87.CD4 cells

CD4-independent
use of CCR5

Isolate		Chimeric coreceptors						
								
		CCR5	CXCR4	FC-1	FC-2	FC-4b	Prod. Inf.	Cocult. PBMC
HIV-1	1023:6761	+++	++	++	++	++	-	+++
	1276:962	+++	-	-	-	-	-	-
	1276:3514	+++	-	-	++	-	-	-
	2242:1886	++++	-	+	++	-	-	-
	2242:4874	++++	++++	+	+	++++	-	-
HIV-2	1010	+	+++	+	++	++++	-	-
	1808	+++	-	++	+	+/-	-	+
	1812	+++	-	++	+++	+	-	+
	1654	+++	-	-	+	-	-	+
	1682	+++	+/-	++	+	+/-	+/-	+++
SIVsm	C73:14	++	+	+	+/-	+/-	-	++
	C73:540	++++	+	++	+	-	+	+++
	C39:14	+++	-	++	+	+	++	+++
	C39:540	+++	-	+++	++	+	+	+++
	C44:14	++	++	+	+	+/-	-	+++
	C44:810	++++	-	++	++	+	-	+++

Comparison of HIV-1, HIV-2 and SIV

1. The order of CD4-independent CCR5 use is: SIV > HIV-2 > HIV-1
    - The HIV-1 envelope has the most closed conformation
2. CCR5 is used in a different mode by HIV-1 than by HIV-2 or SIV
    - HIV-1 envelope less flexible than SIV?

Main participants

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