Innovative Medicines Initiative

Immunity ≠ Immunological Memory

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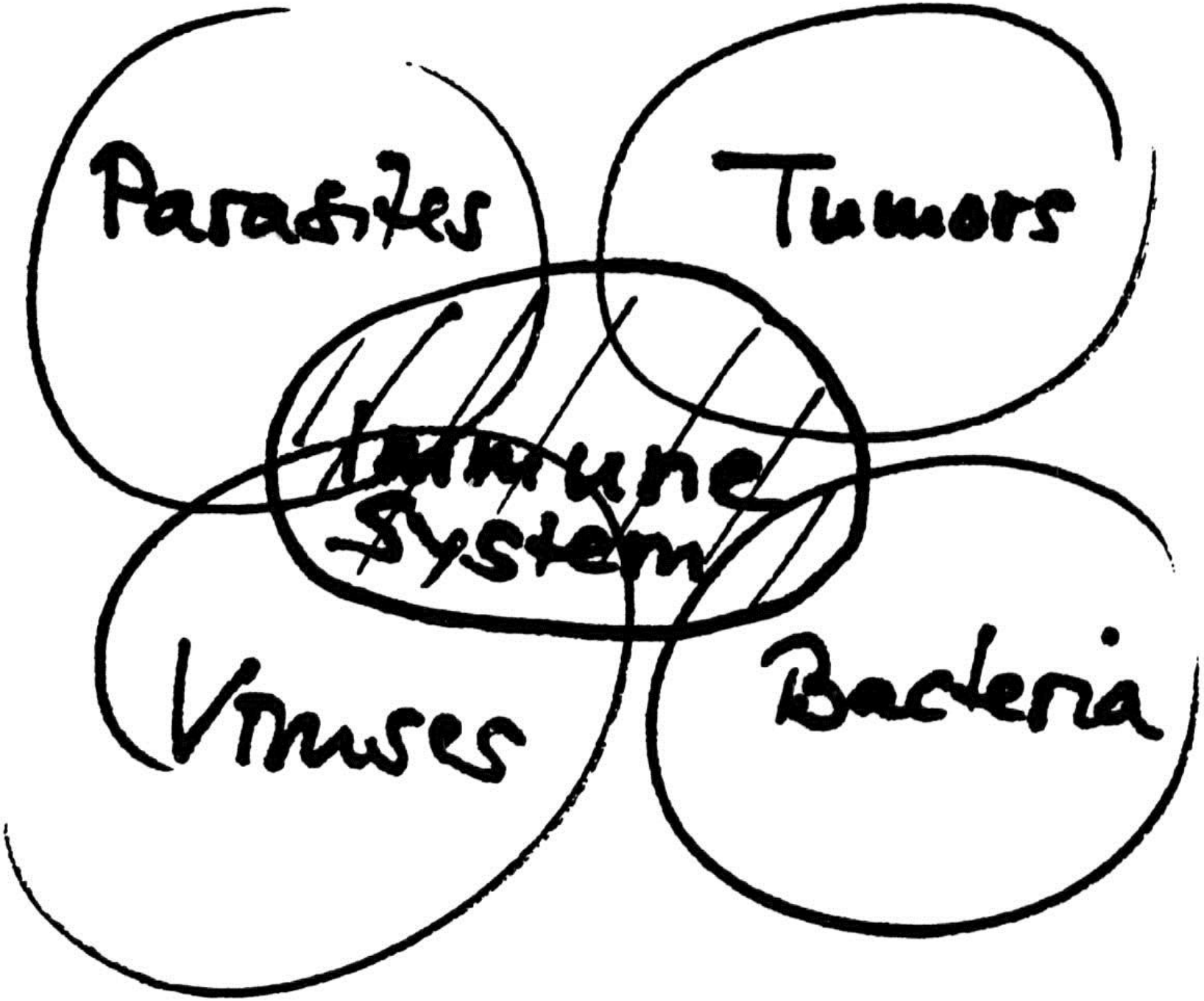
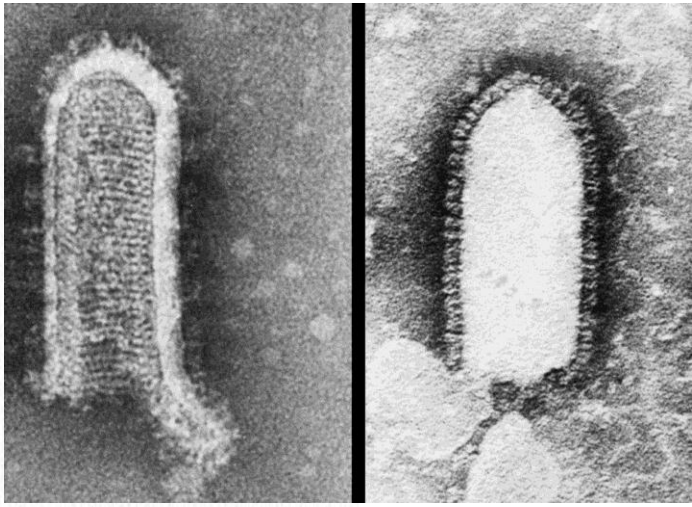

Parasites
Tumors
Immune System
Viruses
Bacteria

- Protective vaccines imitate co-evolution of infectious agents and hosts.
- We cannot do better than evolution by using the same tools, only when introducing ‘new’ tools (antibiotics, antivirals, autoantibodies, behavioural changes)
- Vaccines against solid tumours (carcinomas, sarcomas) and chronic persistent infections are theoretically not impossible but practically highly unlikely!

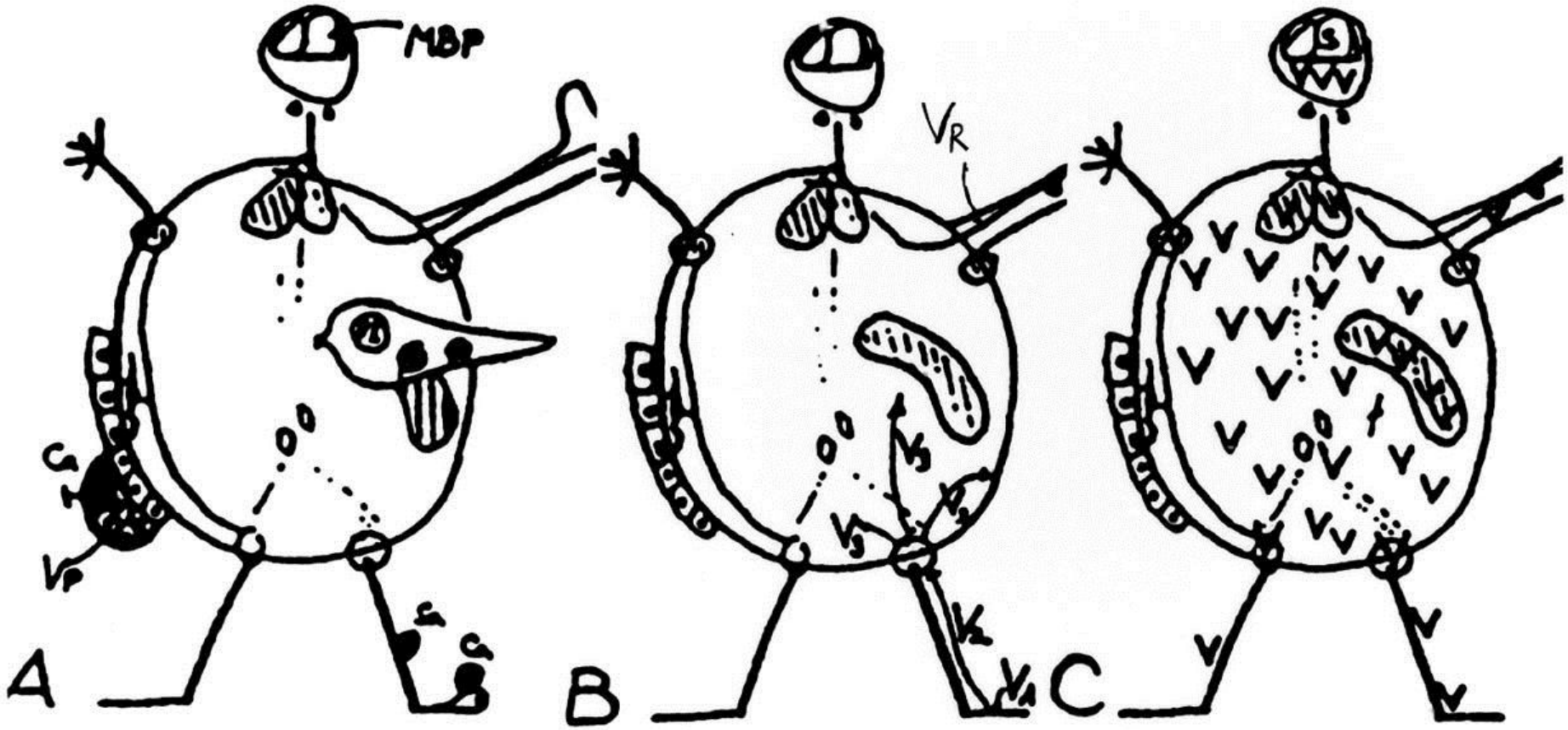
Vaccines successful	**Not available**
Polio 1, 2, 3	TB
bact. toxins	Leprosy
measles	HIV
Haem. infl.	malaria
	(cholera)
Neutr. / opsonising antibodies igG	effector T cells antibodies
	(IgA)

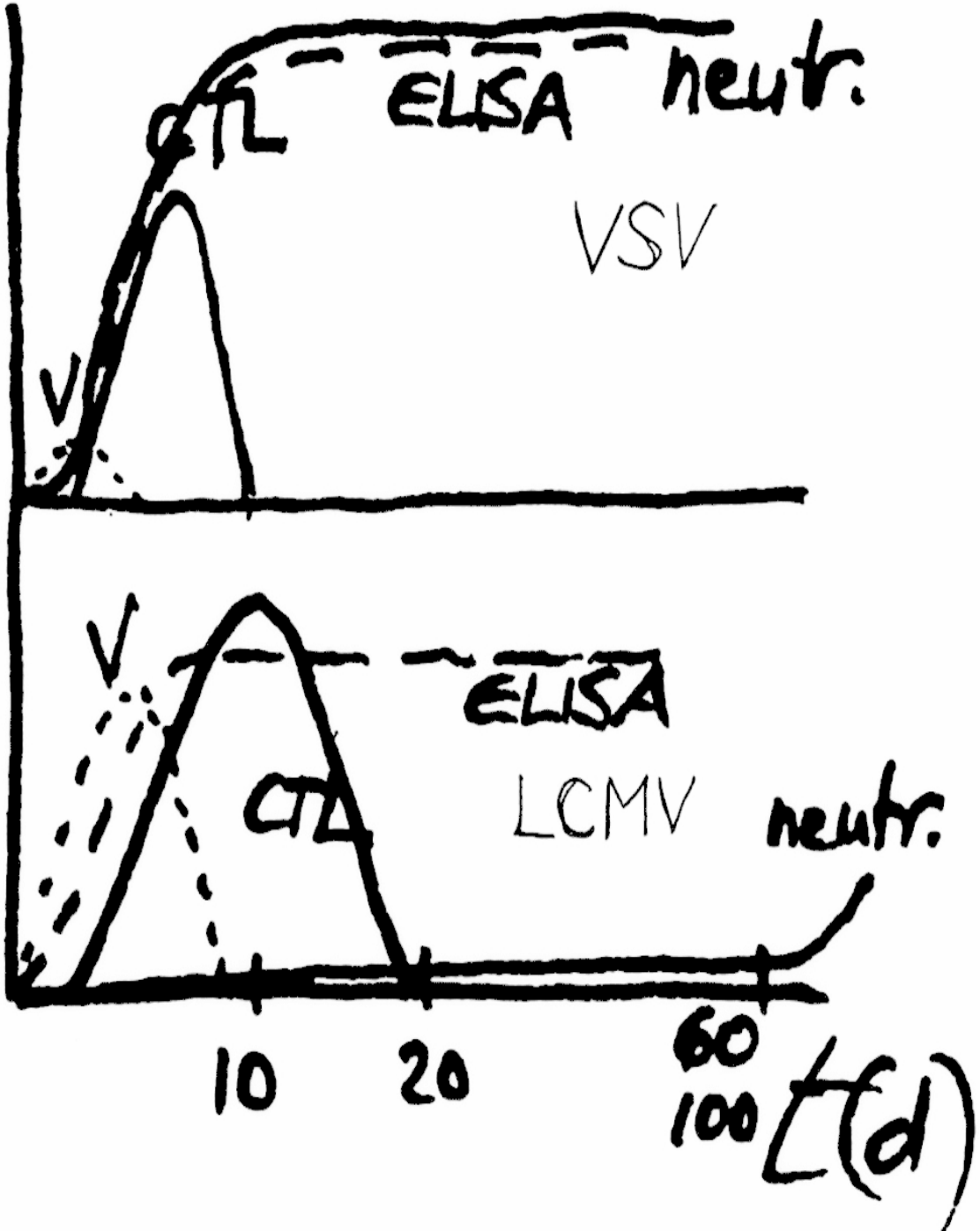
IMMUNITY

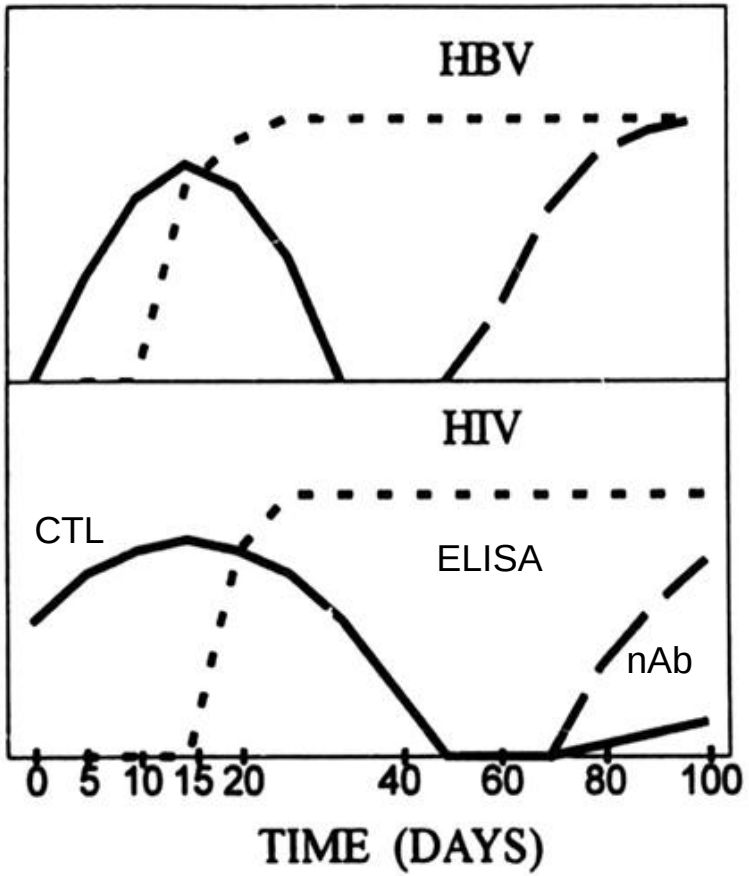
- "innate resistance" > 95 %
- Ab in eggs
- protective memory via Ab (vaccines)
- TB: no vaccine
- autoimmunity > 30 y, female > male
  5 : 1
- tumors > 30 years
- Is what we measure biologically important ?
  (e.g. acad. memory: earlier + greater)



V
noncytopathic
cytopathic
T
T


MBP
VR
A
B
C

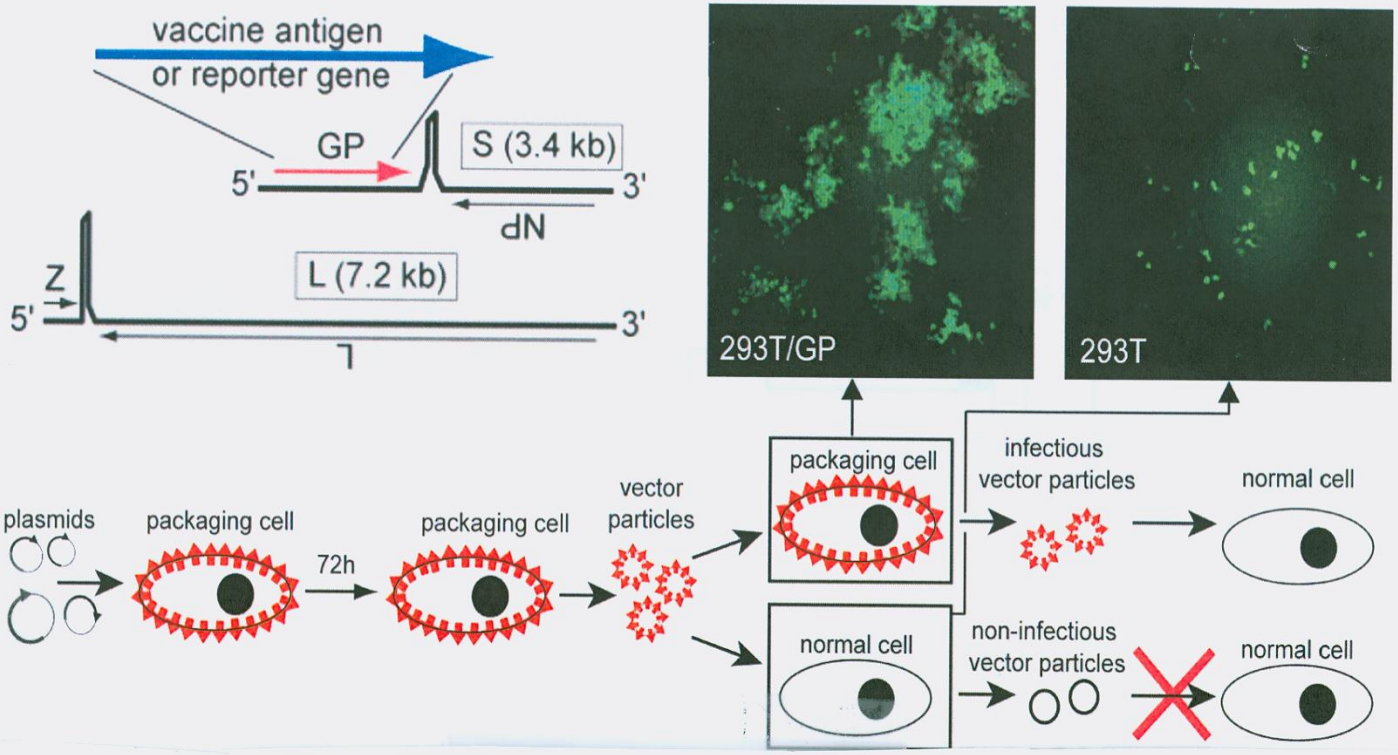

CTL
ELISA
neutr.
VSV
V
V
ELISA
CTL
LCMV
neutr.
10
20
60
100
t (d)


HBV
HIV
CTL
ELISA
nAb
0 5 10 15 20 40 60 80 100
TIME (DAYS)

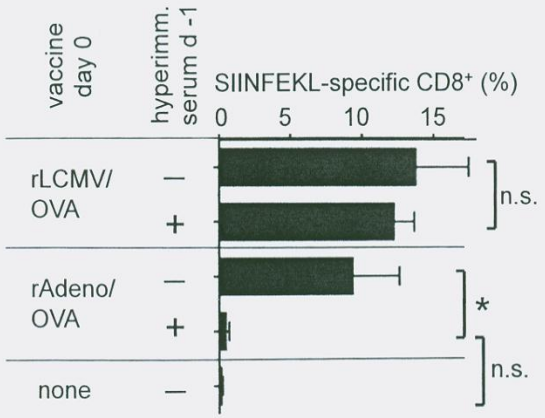
Development of replication-defective lymphocytic choriomeningitis virus vectors for the induction of potent CD8+ T cell immunity

nature medicine

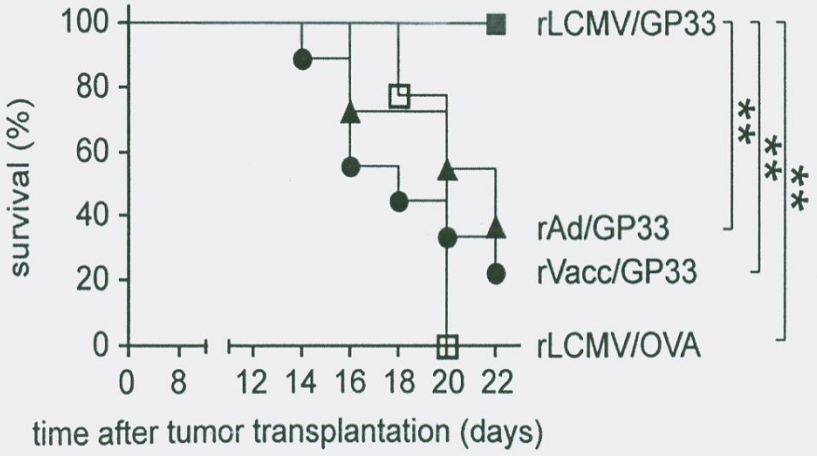
Lukas Flatz[1–3], Ahmed N Hegazy[2,4,5,16], Andreas Bergthaler[1,2,6,16], Admar Verschoor[2,7,16], Christina Claus[8], Marylise Fernandez[1,9], Luca Gattinoni[10], Susan Johnson[1,9], Florian Kreppel[11], Stefan Kochanek[11], Maries van den Broek[2,12], Andreas Radbruch[4,5], Frédéric Lévy[13,15], Paul-Henri Lambert[9], Claire-Anne Siegrist[1,9,14], Nicholas P Restifo[10], Max Löhning[2,4,5], Adrian F Ochsenbein[8], Gary J Nabel[3] & Daniel D Pinschewer[1,2,9]



Lack of antibody inhibition: efficient homologous prime-boost using arenavirus vector

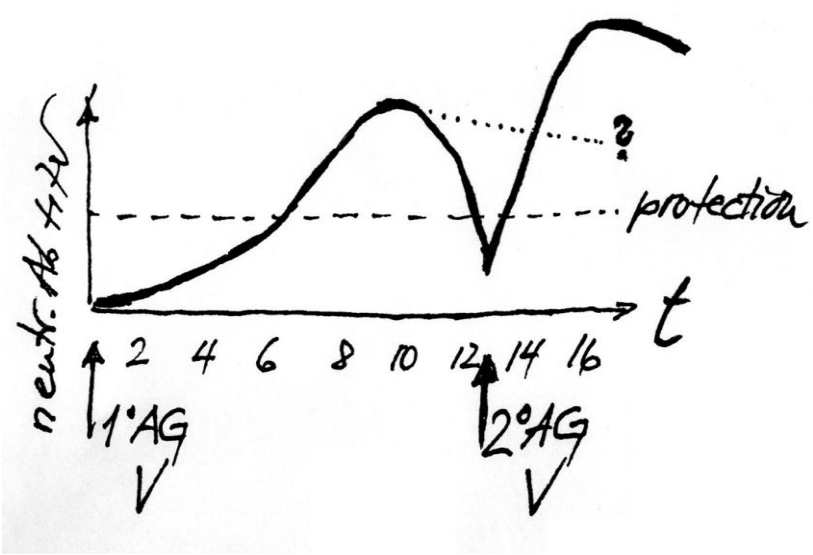


Superior CD8+ T cell-based immunotherapy of established solid tumor



Immunology

- ‚Memory‘
- quicker - higher

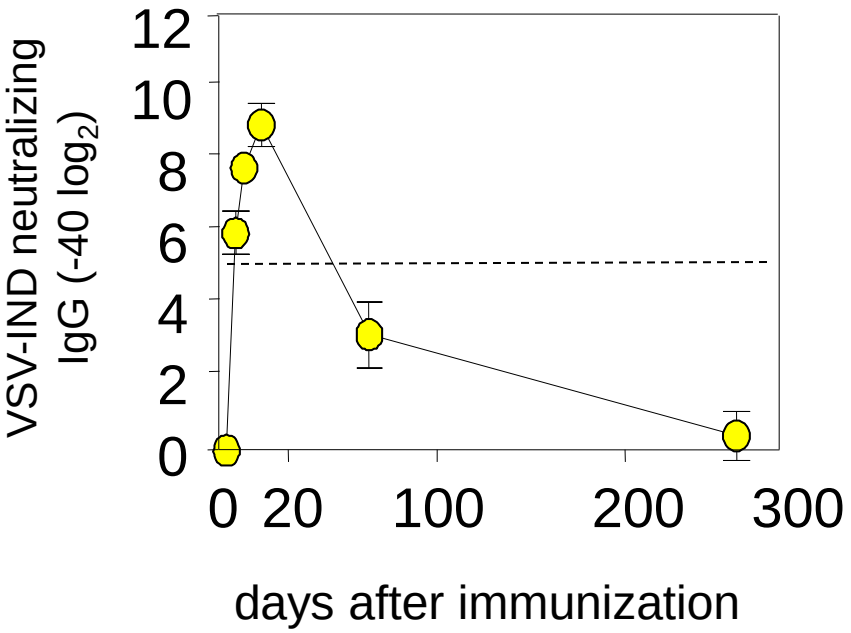


Immunity Protection

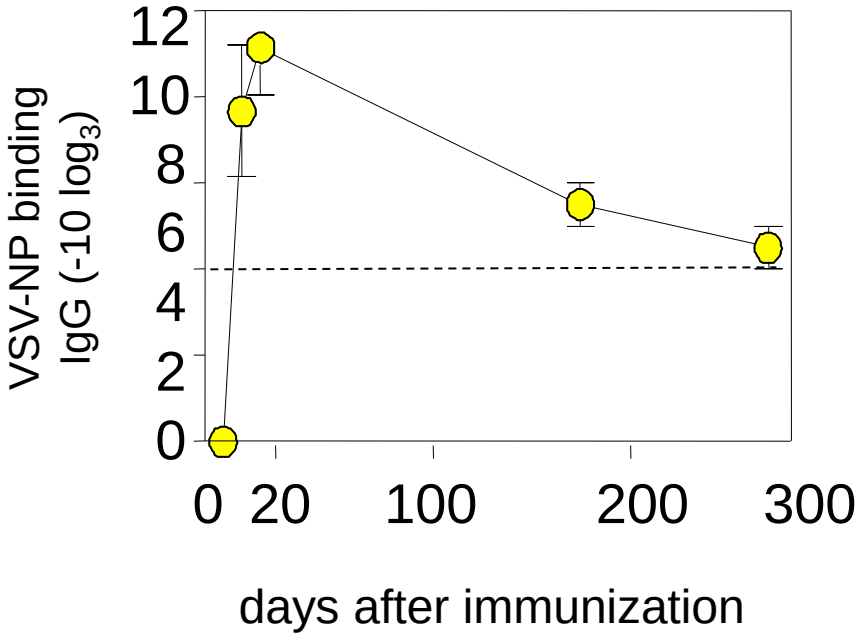
- Small pox ✓
- Poliomeningitis ✓
- Measles ✓
- HIV, malaria -
- Tuberculosis ±

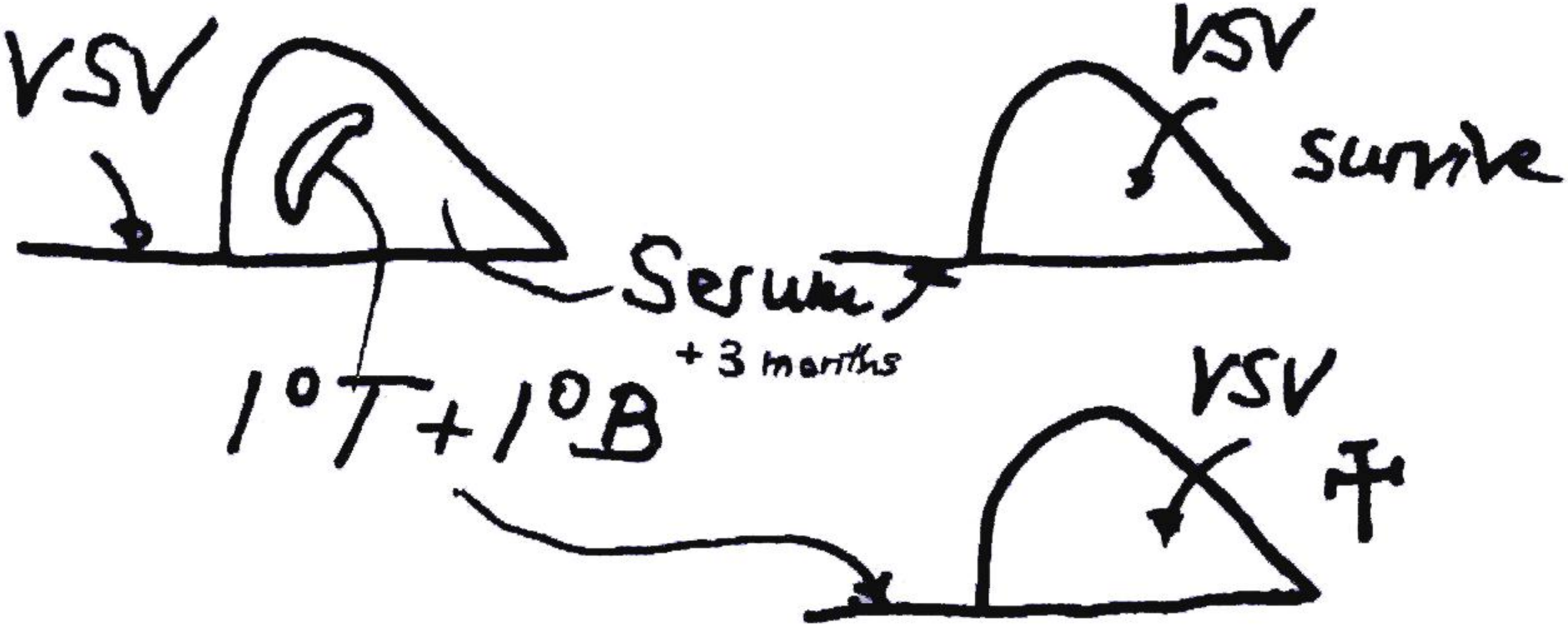
Antibody Memory after immunization with VSV

a) neutralizing antibodies



b) ELISA

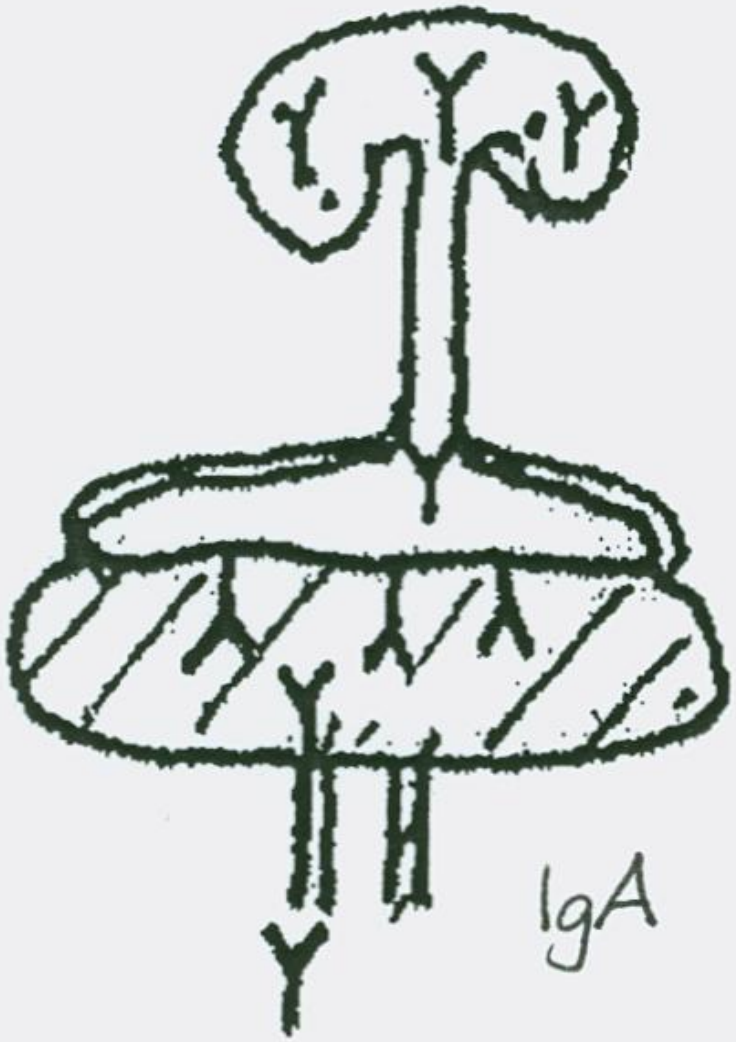



VSV
VSV
survive
Serum
+ 3 months
$1^0T + 1^0B$
VSV
T

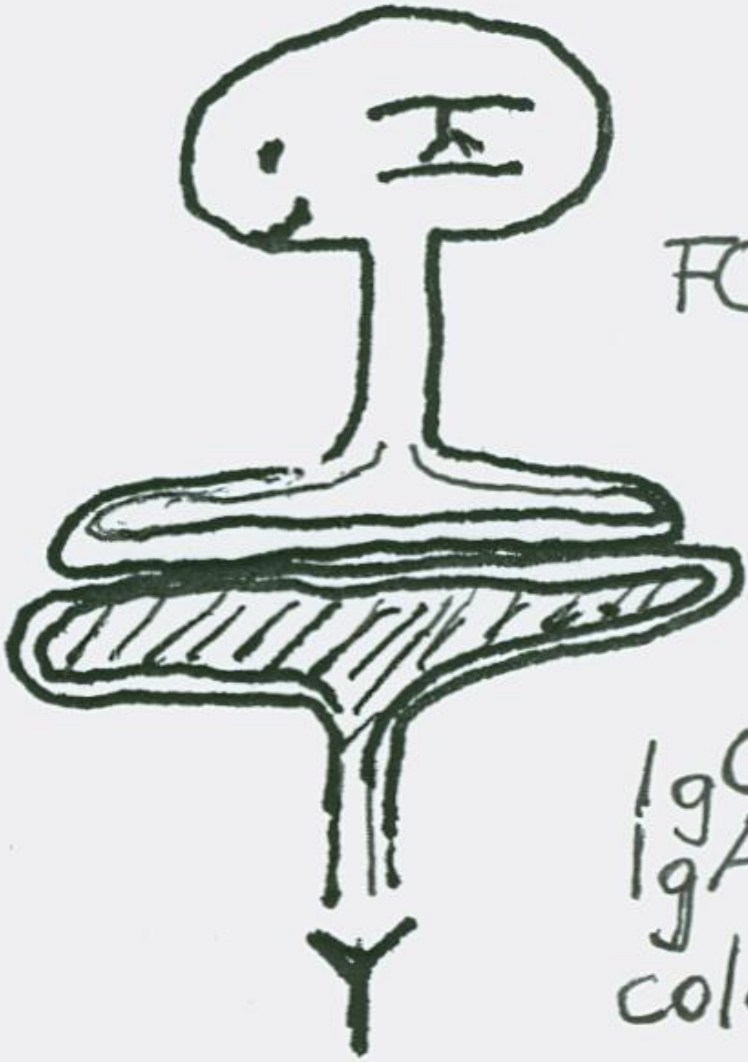
Why immunological Memory ?
Protection (immunity) counts !

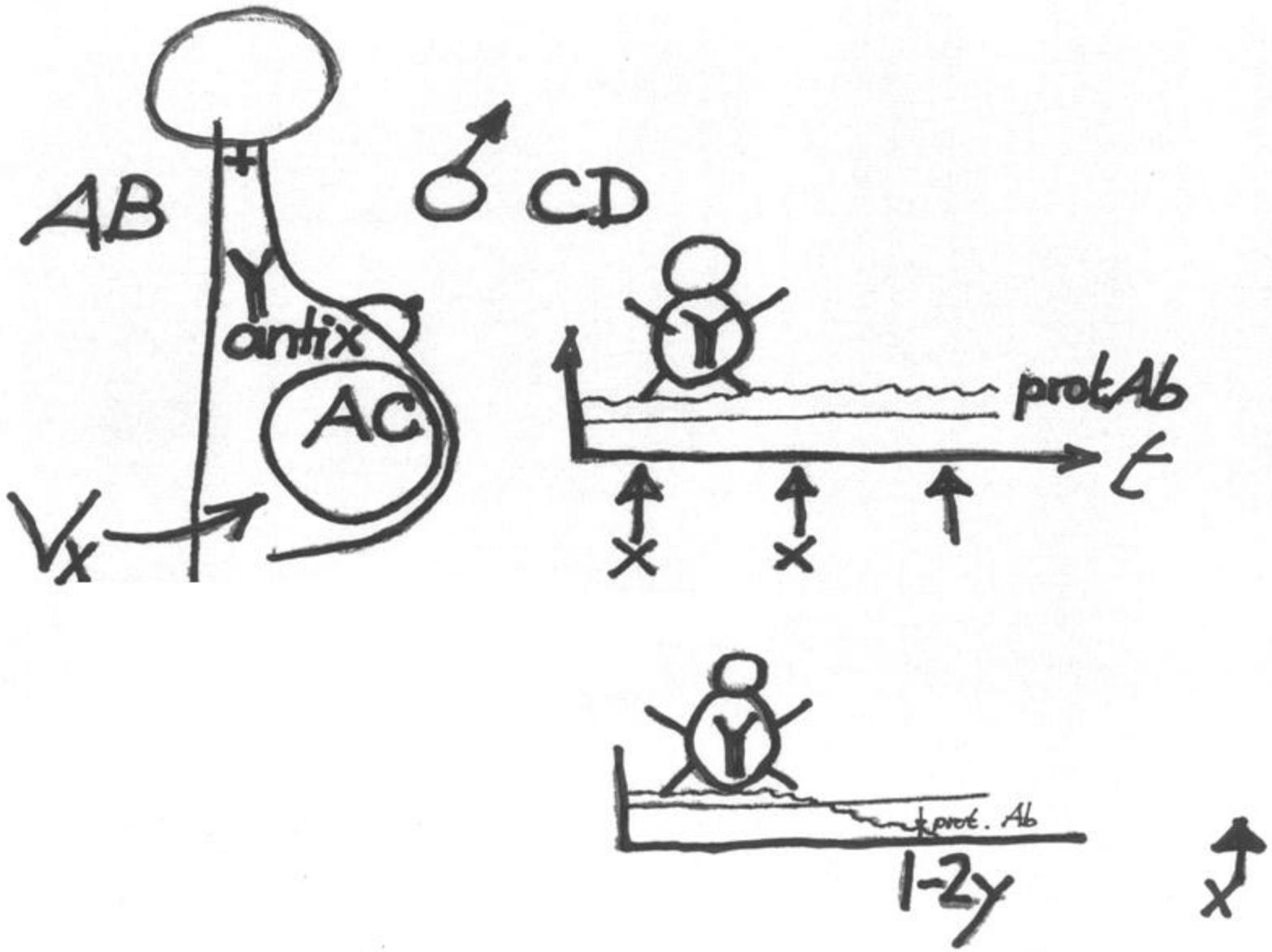
- Earlier + better
- If first infection survived
  ⟶ no need for memory
- If first infection kills
  ⟶ no need for memory
- All vaccines that function protect via preex. neutr. antibodies? (autoantibodies ♀?)
- Protection is antigen dependent

Humans



calves




AB
CD
antix
AC
V_x
prot.Ab
t
prot. Ab
1-2y
x

Structural Basis for Broad and Potent Neutralization of HIV-1 by Antibody VRC01

Tongqing Zhou,[1] Ivelin Georgiev,[1*] Xueling Wu,[1*] Zhi-Yong Yang,[1*] Kaifan Dai,[1] Andrés Finzi,[2] Young Do Kwon,[1] Johannes F. Scheid,[3] Wei Shi,[1] Ling Xu,[1] Yongping Yang,[1] Jiang Zhu,[1] Michel C. Nussenzweig,[3] Joseph Sodroski,[2,4] Lawrence Shapiro,[1,5] Gary J. Nabel,[1] John R. Mascola,[1] Peter D. Kwong[1†] 2010 Science 329. 811

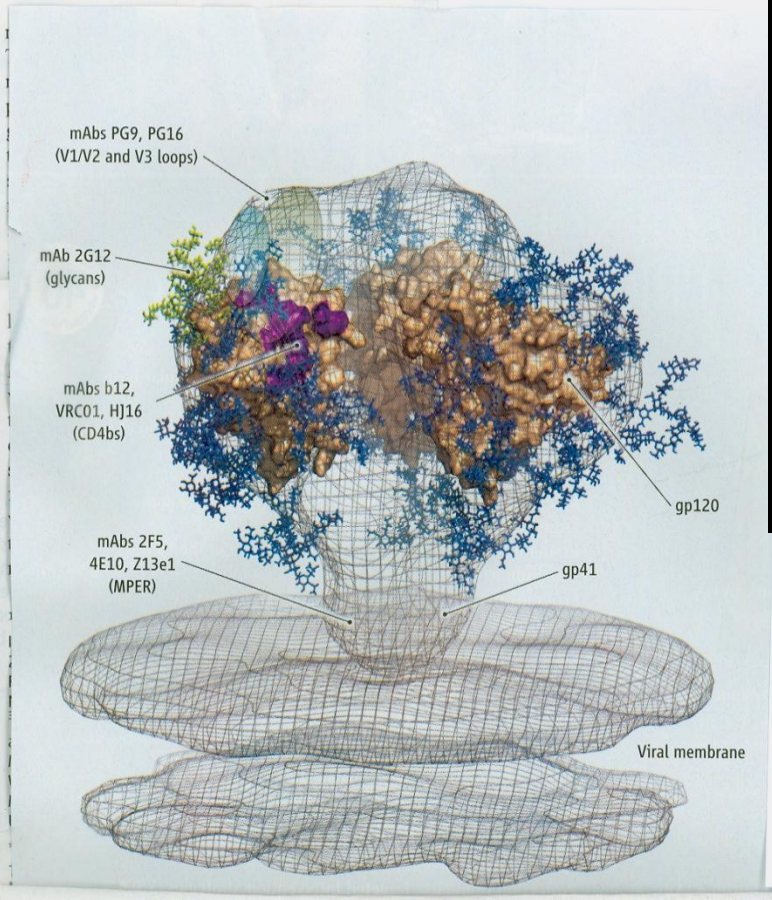
During HIV-1 infection, antibodies are generated against the region of the viral gp120 envelope

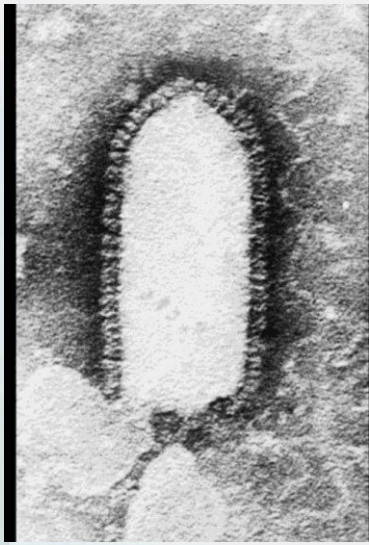
Rational Design of Envelope Identifies Broadly Neutralizing Human Monoclonal Antibodies to HIV-1

Science 329, 856 (2010)

Xueling Wu,[1*] Zhi-Yong Yang,[1*] Yuxing Li,[1*] Carl-Magnus Hogerkorp,[1†] William R. Schief,[4] Michael S. Seaman,[5] Tongqing Zhou,[1] Stephen D. Schmidt,[1] Lan Wu,[1] Ling Xu,[1] Nancy S. Longo,[1] Krisha McKee,[1] Sijy O'Dell,[1] Mark K. Louder,[1] Diane L. Wycuff,[1] Yu Feng,[1‡] Martha Nason,[2] Nicole Doria-Rose,[3] Mark Connors,[3] Peter D. Kwong,[1] Mario Roederer,[1] Richard T. Wyatt,[1‡] Gary J. Nabel,[1§] John R. Mascola[1§]

Cross-reactive neutralizing antibodies (NAbs) are found in the sera of many HIV-1–infected individuals, but the virologic basis of their neutralization remains poorly understood. We used knowledge of HIV-1 envelope structure to develop antigenically resurfaced glycoproteins specific for the structurally conserved site of initial CD4 receptor binding. These probes were used to identify sera with NAbs to the CD4-binding site (CD4bs) and to isolate individual B cells from such an HIV-1–infected donor. By expressing immunoglobulin genes from individual cells, we identified three monoclonal antibodies, including a pair of somatic variants that neutralized over 90% of circulating HIV-1 isolates. Exceptionally broad HIV-1 neutralization can be achieved with individual antibodies targeted to the functionally conserved CD4bs of glycoprotein 120, an important insight for future HIV-1 vaccine design.





A Boost for HIV Vaccine Design

Dennis R. Burton[1,2] and Robin A. Weiss[3] 2010 Science 329. 770

Antibodies that potently neutralize almost all HIV isolates could aid the rational design of a vaccine.

A major roadblock to the development of an effective vaccine against the human immunodeficiency virus (HIV-1) is the lack of an immunogen that elicits broadly protective antibodies (*1*). Passive transfer studies in animal models have associated protection with neutralizing antibodies and, encouragingly, serum studies show that a subset of HIV-infected individu-

856 of this issue, Wu *et al.* (*3*) describe the isolation of particularly potent monoclonal broadly neutralizing antibodies using a novel selection strategy, and on page 811, Zhou *et al.* (*4*) solve the crystal structure of the most effective of these antibodies in complex with its target gp120, a viral envelope glycoprotein. These studies further invigorate the currently active field of discovering broadly

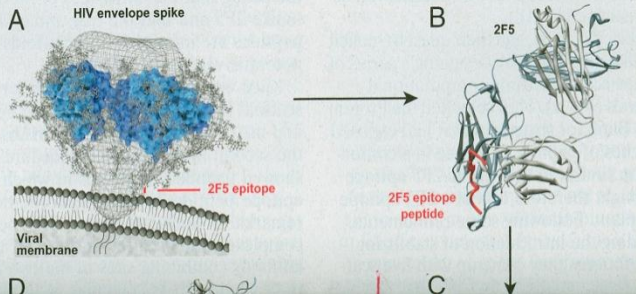
Scaffolding to build a rational vaccine design strategy

Dennis R. Burton[a,b,1]

[a]*Department of Immunology and Microbial Science and International AIDS Vaccine Initiative Neutralizing Antibody Center, The Scripps Research Institute, La Jolla, CA 92037; and* [b]*The Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University, Boston, MA 02114*

2010 PNAS 107. 17859

Conventional vaccines, going back to the work of Jenner and Pasteur, are based on a rather direct mimicry of the offending pathogen using an attenuated or killed version of the microbe or purified or recombinant proteins from the microbe surface. These vaccines have been enormously successful against a range of pathogens. However, the conventional approaches have faltered for other pathogens, such as HIV, that have evolved an

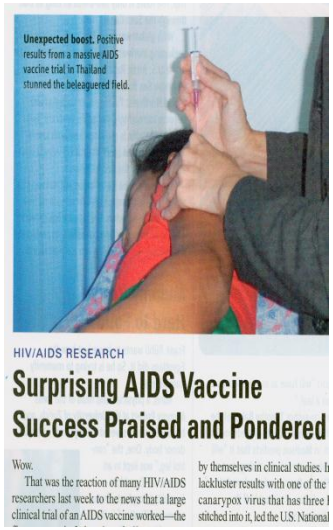


Theoretical vaccines

Theoretical HIV (or TB) vaccine

- persistence at low levels for T cell activation (TB)
- combination of 10^4 – 10^7 GP variants, or mutating vaccine
- low-no immunopatholgy (TB)

- anti-virals, antibiotics, wait until HIV-1 ~ HIV-2?


Unexpected boost. Positive results from a massive AIDS vaccine trial in Thailand stunned the beleaguered field.

HIV/AIDS RESEARCH

Surprising AIDS Vaccine Success Praised and Pondered

Wow.

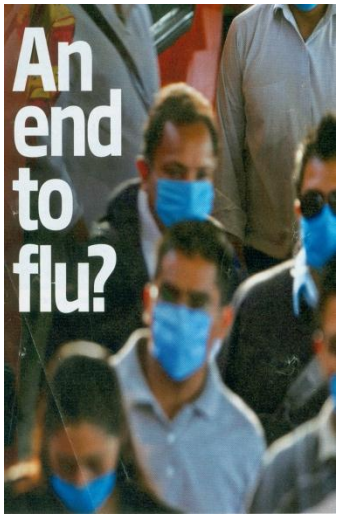
That was the reaction of many HIV/AIDS researchers last week to the news that a large clinical trial of an AIDS vaccine worked—the

by themselves in clinical studies. h lackluster results with one of the canarypox virus that has three l stitched into it, led the U.S. National

Theoretical Influenza vaccine

- combination of all possible hemagglutinins ~ 10^3 variants?
- repeat vaccinations

- crossprotective vaccine not possible



Conclusions

- „Memory“, a nice idea,
  but is a laboratory artefact
- Protection depends on preinfect.
  nAb titers and / or activated T cells
  (variability: HIV, malaria)
- Both are antigen-driven
  (reencounter, persistence in host,
  antigen-antibody complexes on FDC)

H. Hengartner

A. Althage
M. Bachmann
A. Ciurea
St. Freigang
L. Hunziker
U. Karrer
Th. Kündig
B. Ludewig
M. Martinic
A. Ochsenbein
B. Odermatt
M. Pericin
D. Pinschewer
M. Recher
HP. Roost
Th. Rülicke
C. de la Torre
M. Whitt


順路
THIS WAY

Thank you!