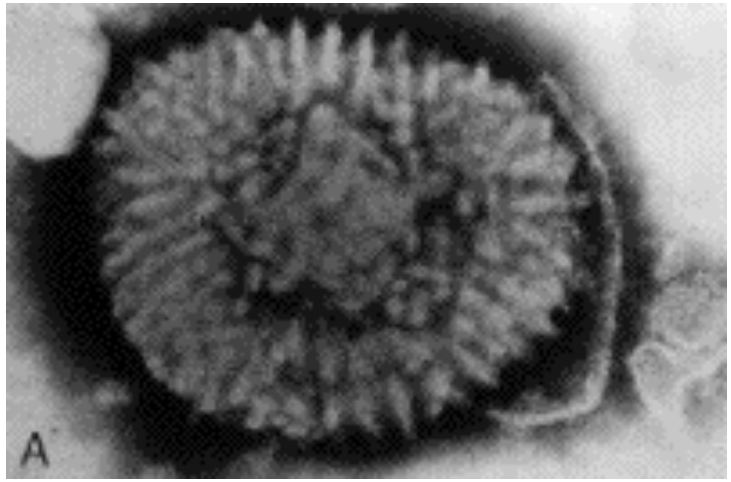
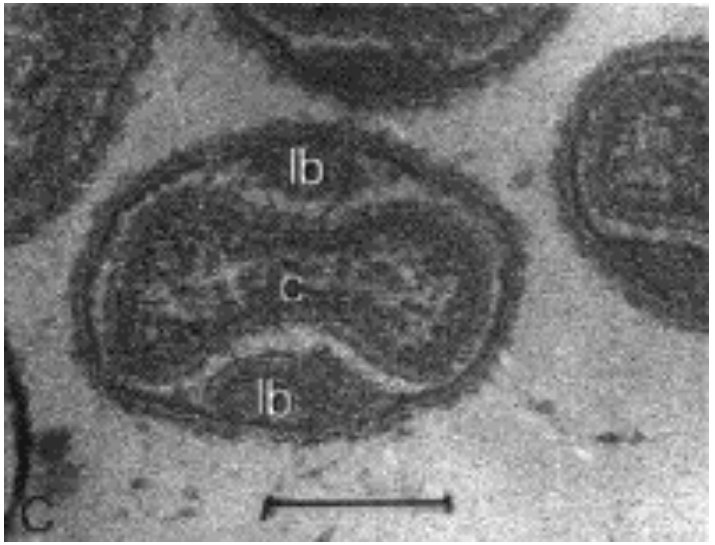
Engineering Viral Genomes:
Vaccinia Virus Vectors

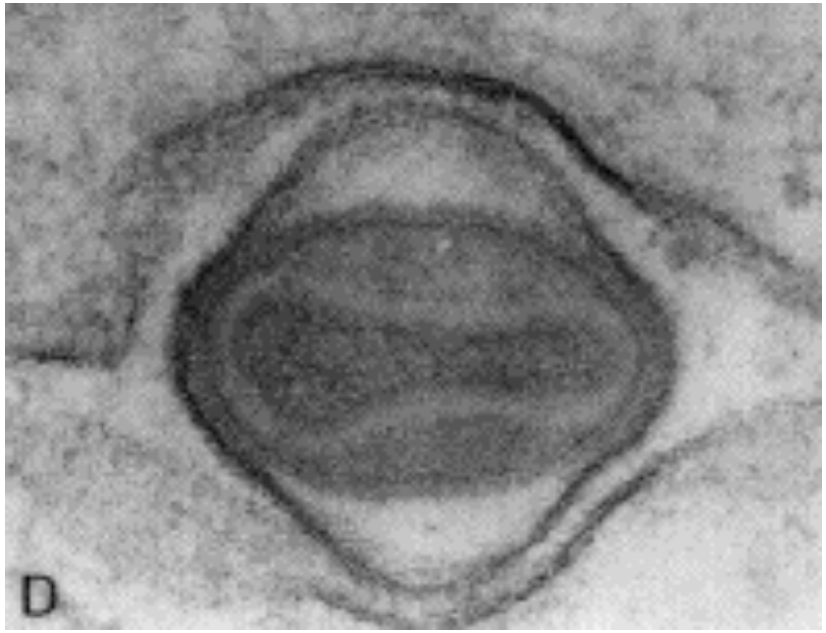
Viral vectors

Virus	Insert size	Integration	Duration of expression	Advantages	Potential disadvantages
Adeno-associated virus	~4.5–9 (?) kb	Low efficiency	Long	Nonpathogenic, episomal, infects nondividing cells	Immunogenic, toxicity, small packaging limit
Adenovirus	2–38 kb	No	Short	Efficient gene delivery, infects nondividing cells	Transient, immunogenic
Alphavirus	~5 kb	No	Short	Broad host range, high level expression	Virulence
Epstein-Barr virus	~120 kb	No; episomal	Long	High capacity, episomal, long-term expression	
Gammaretrovirus	1–7.5 kb	Yes	Shorter than formerly	Stable integration	May rearrange genome, insertional mutagenesis require cell division
Herpes simplex virus	~30 kb	No	Long in central nervous system, short elsewhere	Infects nondividing cells; neurotropic, large capacity	Virulence, persistence in neurons, immunogenic
Lentivirus	7–18 kb	Yes	Long	Stable integration; infects nondividing and terminally differentiated mammalian cells	Insertional mutagenesis
Poliovirus	~300 bp for helper-free virus; ~3 kb for defective virus	No	Short	Excellent mucosal immunity	Limited capacity; reversio to neurovirulence
Rhabdovirus	Unknown	No	Short	High-level expression, rapid cell killing	Virulence, highly cytopathic
Vaccinia virus	At least ~25 kb, probably ~75–100 kb	No	Short	Wide host range, ease of isolation, large capacity, high-level expression	Transient, immunogenic

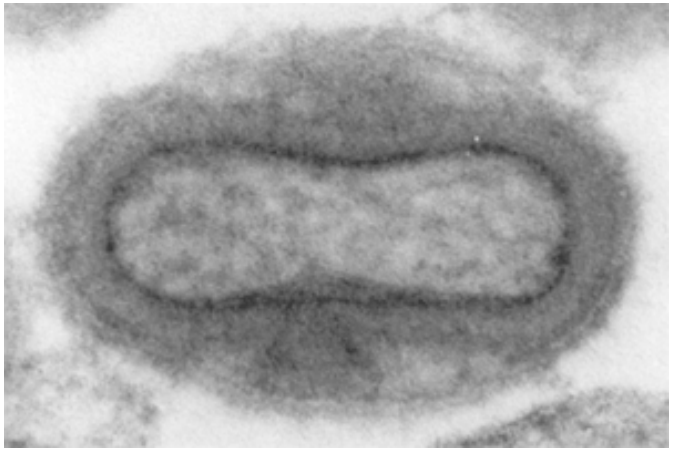


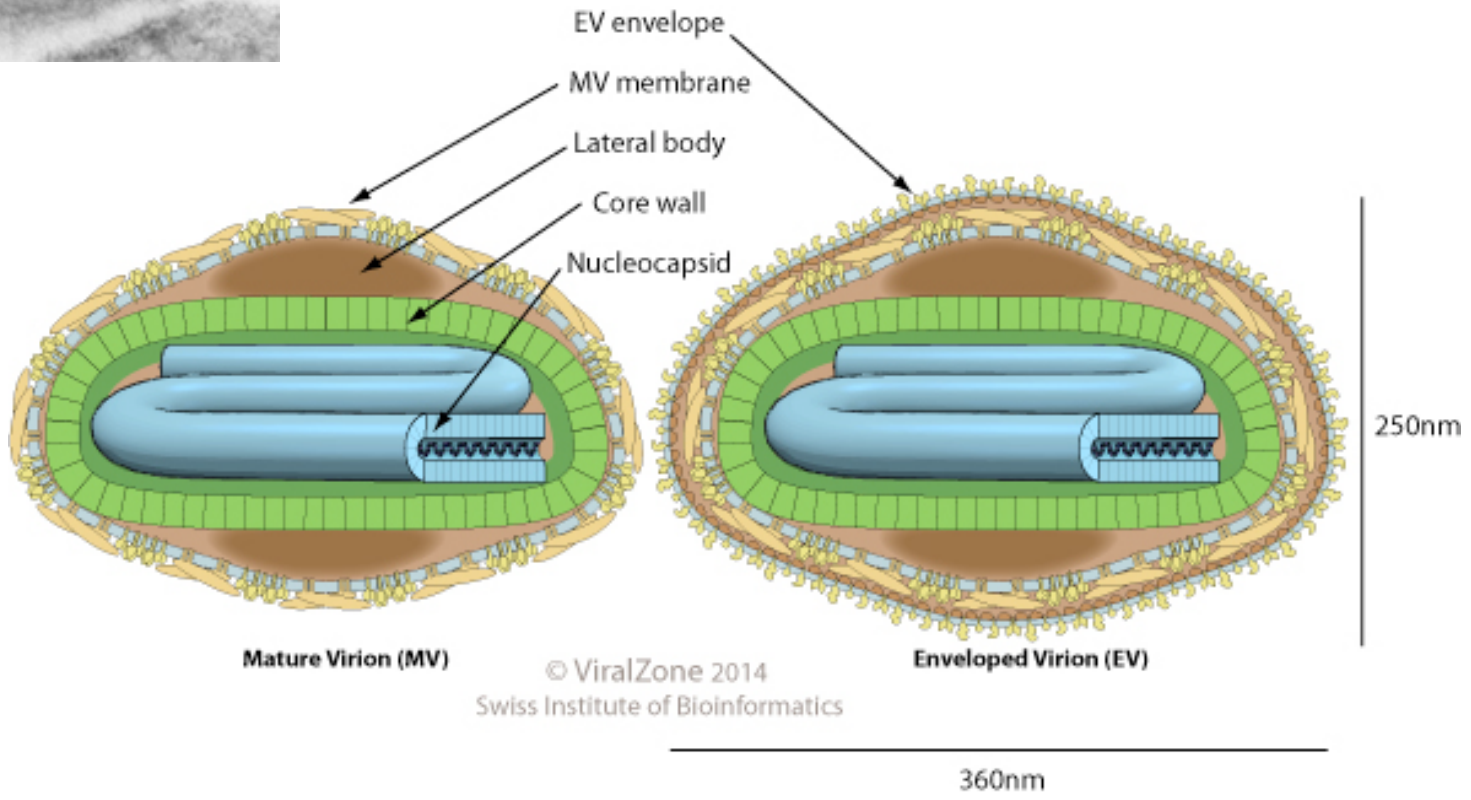


POXVIRUSES

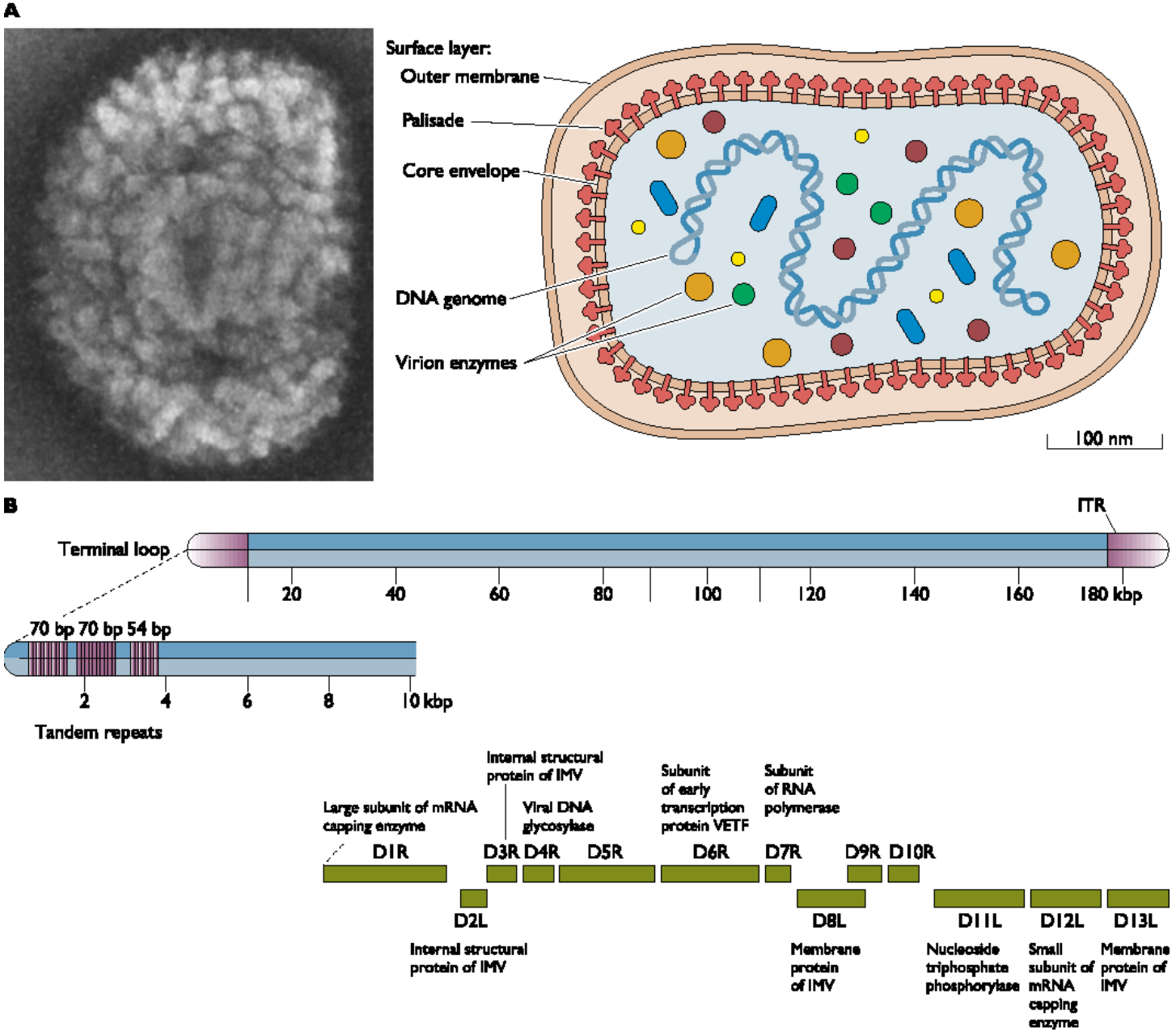


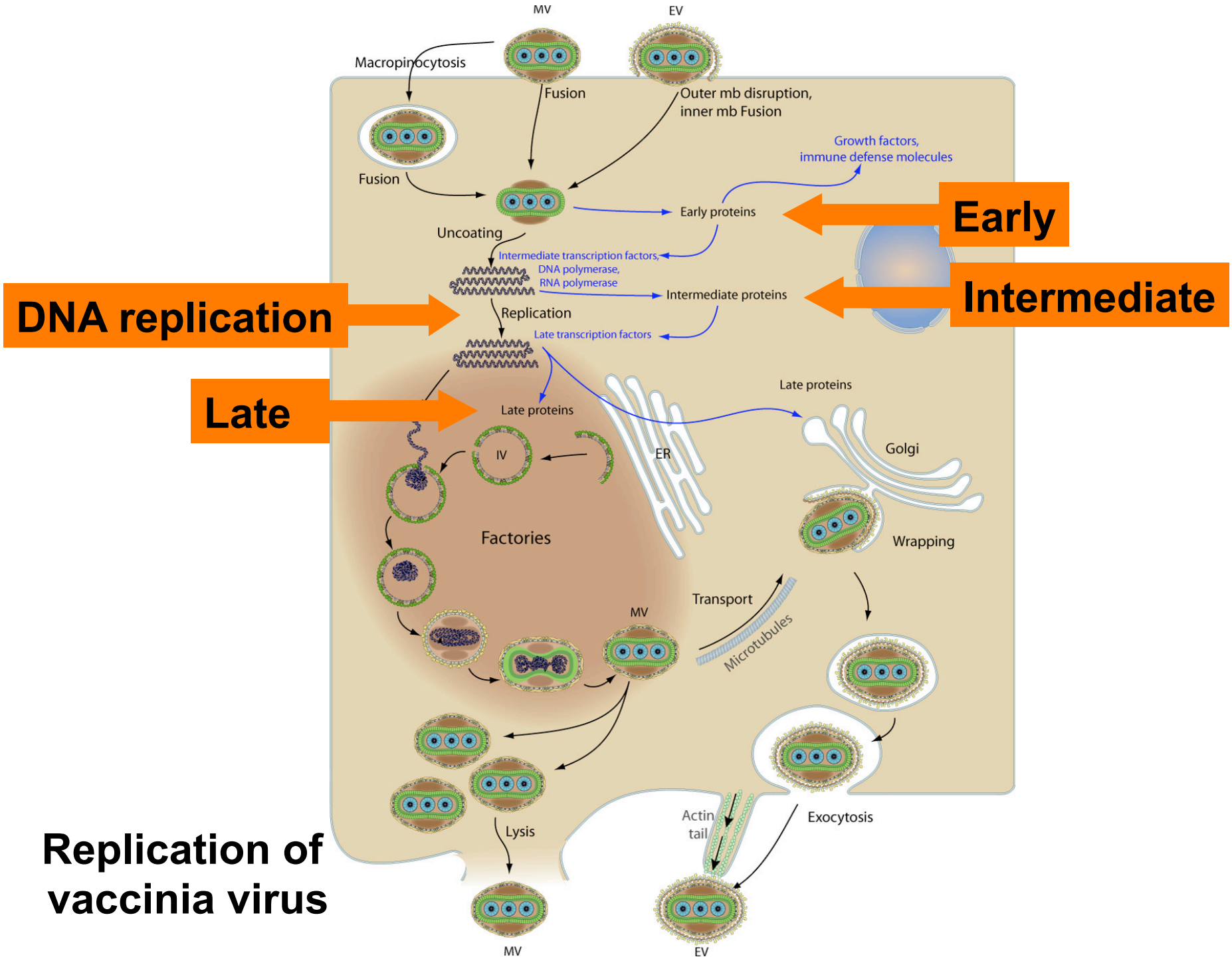
Poxviruses structure





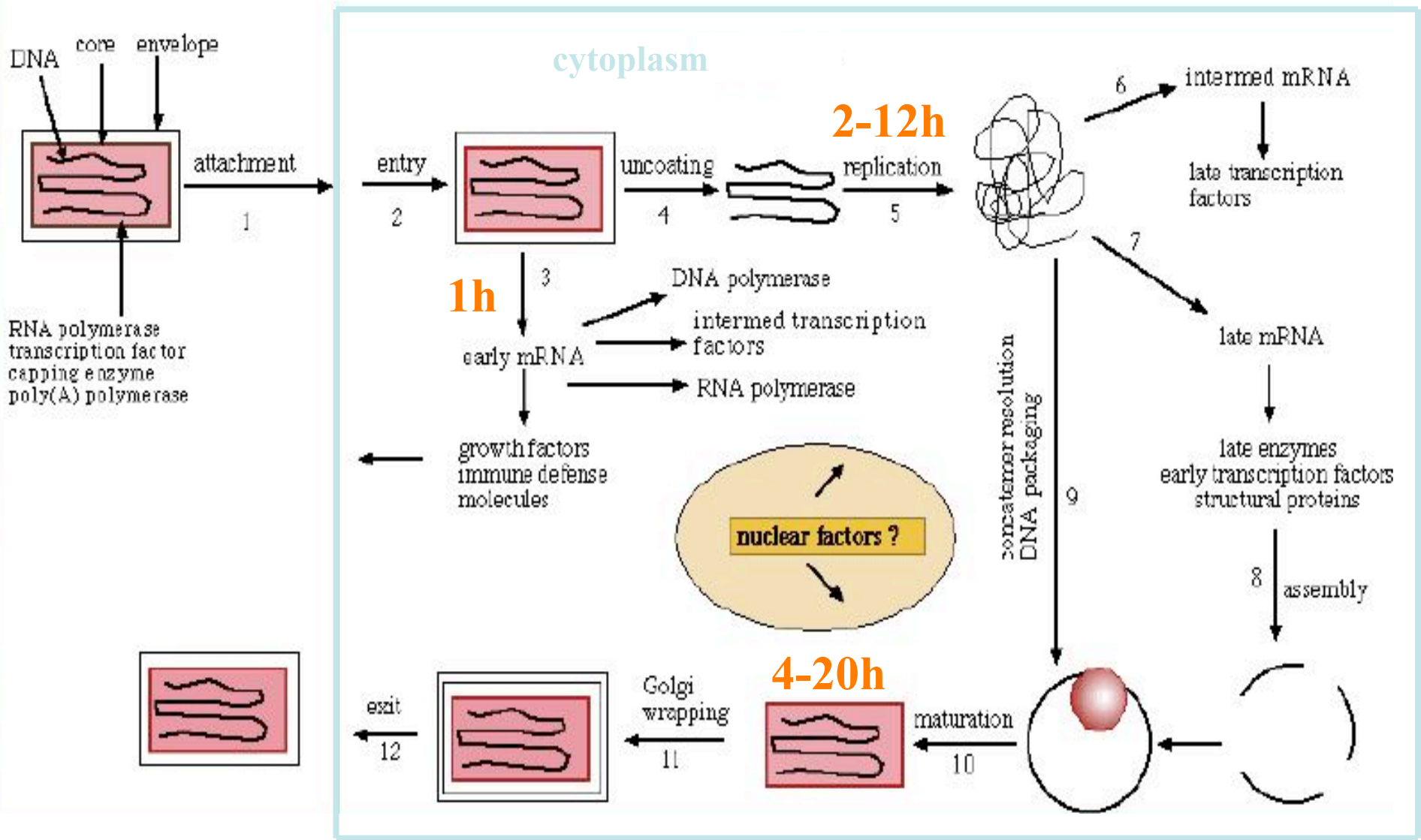
Structure and genome organization of the poxvirus **vaccinia** virus





Replication of vaccinia virus

Replication of vaccinia virus



Poxviruses:
The smallpox story

Smallpox first appeared in China and the Far East at least 2000 B.C.

The Pharaon Ramses V died of smallpox in 1157 B.C.

The disease reached Europe in 710 A.C. and was transferred to America by Hernando Cortez in 1520 - 3.5 million Aztecs died in the next 2 years.

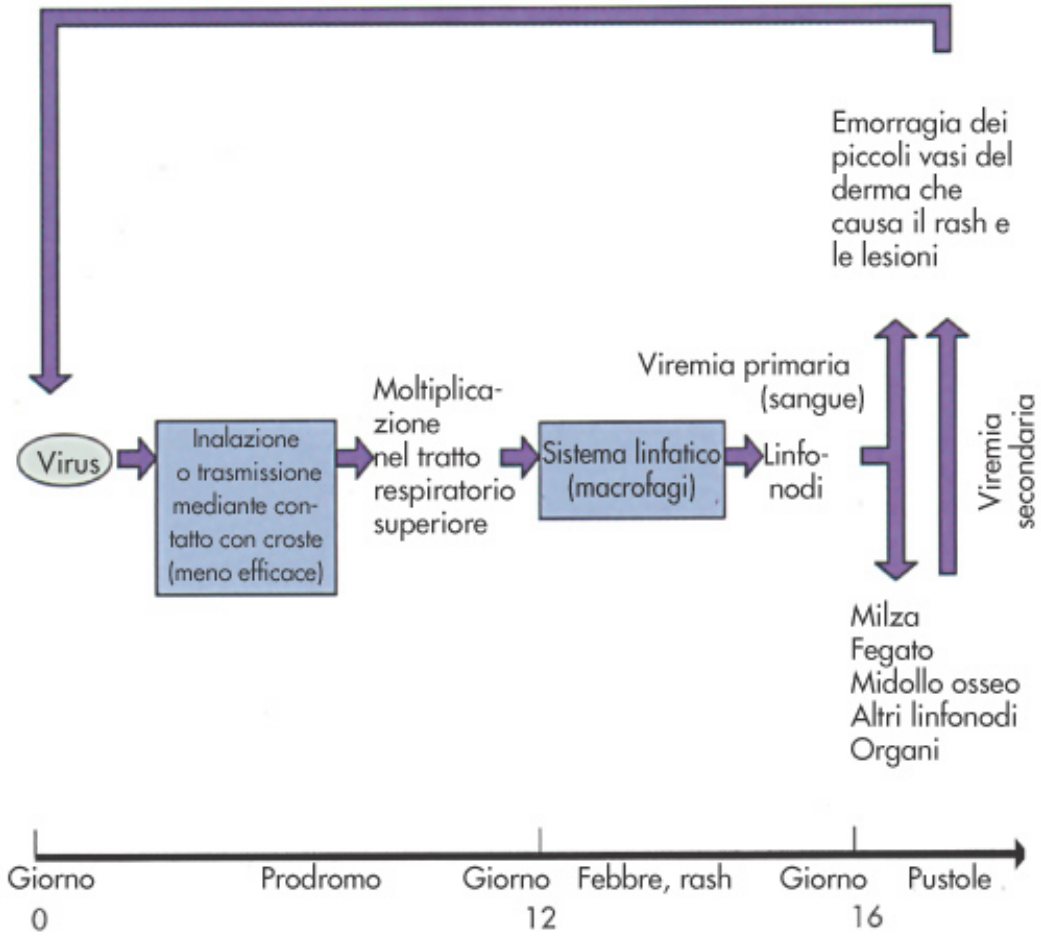
In the cities of 18th century Europe, smallpox reached plague proportions (7-12% of all deaths) and was a feared scourge - highly infectious.

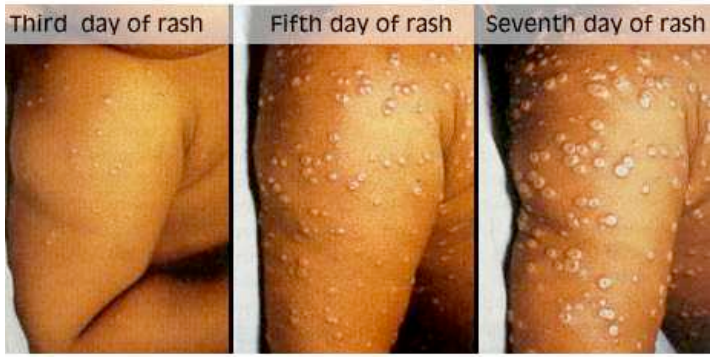
Five reigning European monarchs died from smallpox during the 18th century.

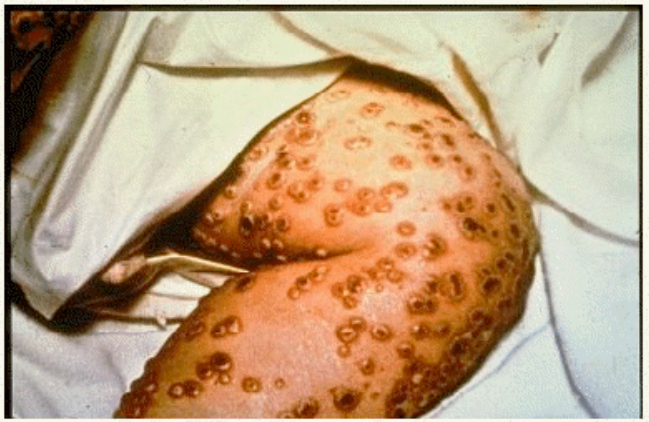
Smallpox has now been eradicated.

The last naturally occurring outbreak of smallpox was in Somalia on 26th October 1977.

Smallpoxvirus dissemination in the host







Patient's leg covered in smallpox

1978 - Smallpox eradication

INOCULATION

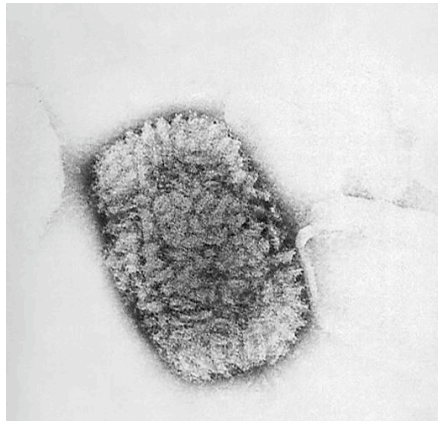
Those who are desirous to take the infection of the SMALL - POX, by inoculation, may find themselves accommodated for the purpose, by applying to.

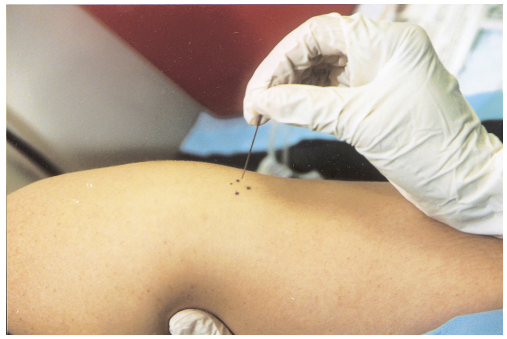
Stephen Samuel Hawley

Fiskdale, in Sturbridge.

February 7, 1801

N. B. A Pest-House will be opened, and accommodations provided by the first day of March next.





Virus	Disease
Variola virus	Smallpox
Vaccinia virus (smallpox vaccine)	Encephalitis and vaccinia necrosum (complications of vaccination)
Orf virus	Localized lesion
Cowpox virus	Localized lesion
Pseudocowpox virus	Milker's nodule
Monkeypox virus	Generalized disease
Bovine papular stomatitis virus	Localized lesion
Tanapox virus	Localized lesion
Yaba monkey tumor virus	Localized lesion
Molluscum contagiosum virus	Disseminated skin lesions

Epidemiology

Transmission
- Smallpox: respiratory droplets, contact with virus on fomites
- Other poxviruses: direct contact or fomites

At risk or risk factors
- Molluscum contagiosum: sexual contact, wrestling
- Zoonoses: animal handlers (contact with lesion)

Distribution of virus
- Ubiquitous
- No seasonal incidence
- Natural smallpox has been eradicated

Vaccines or antiviral drugs
- Live vaccine against smallpox (vaccinia virus)
- No antiviral drugs

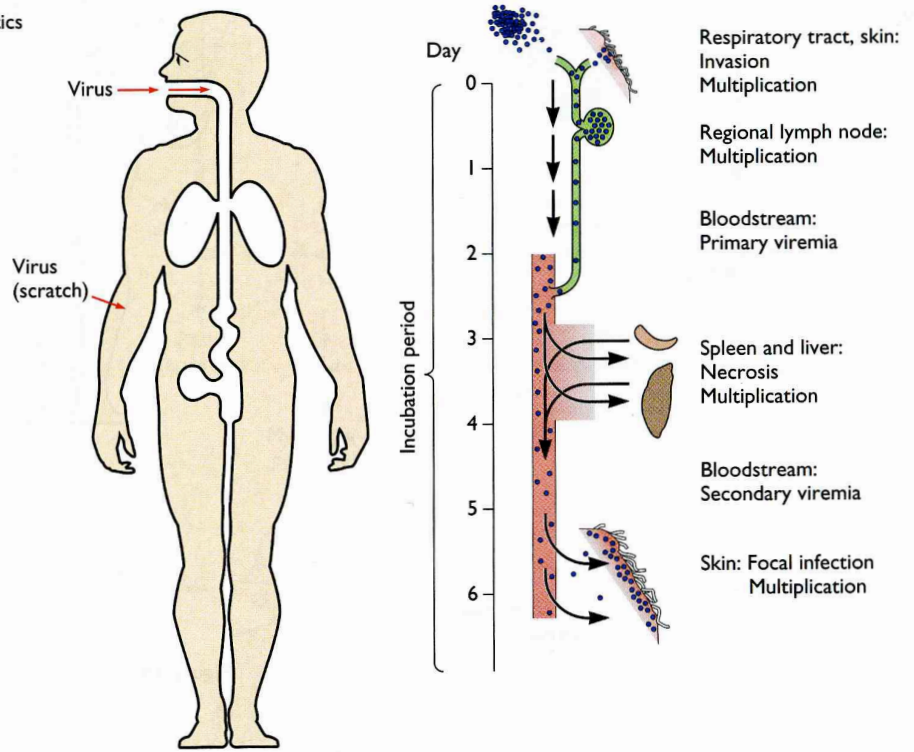
Disease mechanisms

Smallpox transmitted by respiratory tract secretions, spreads through lymphatics and blood

Molluscum contagiosum and zoonoses transmitted by contact

Sequential infection of multiple organs

Cell-mediated and humoral immunity important to resolve infection



Vaccinia Virus Vectors

- Vaccinia virus (Orthopoxvirus)
  - live vaccine
    - used for the eradication of smallpox
  - genome is ds DNA (187kb)
  - generally benign
  - broad host range

Vaccinia Virus

- Closely related to cowpox virus and variola (smallpox) virus.
- Replicate entirely within the cytoplasm.
- Virus particles are brick shaped, 300-400 nm in diameter with lipoprotein membranes that surround a complex core structure.
- The core contains a linear dsDNA genome and numerous virus-encoded enzymes that enable particles to synthesize translatable mRNA of early genes.
- The early genes are involved in stimulation of the growth of neighboring cells, defense against host immune responses, replication of the viral genome and transcription of the intermediate class of viral genes.

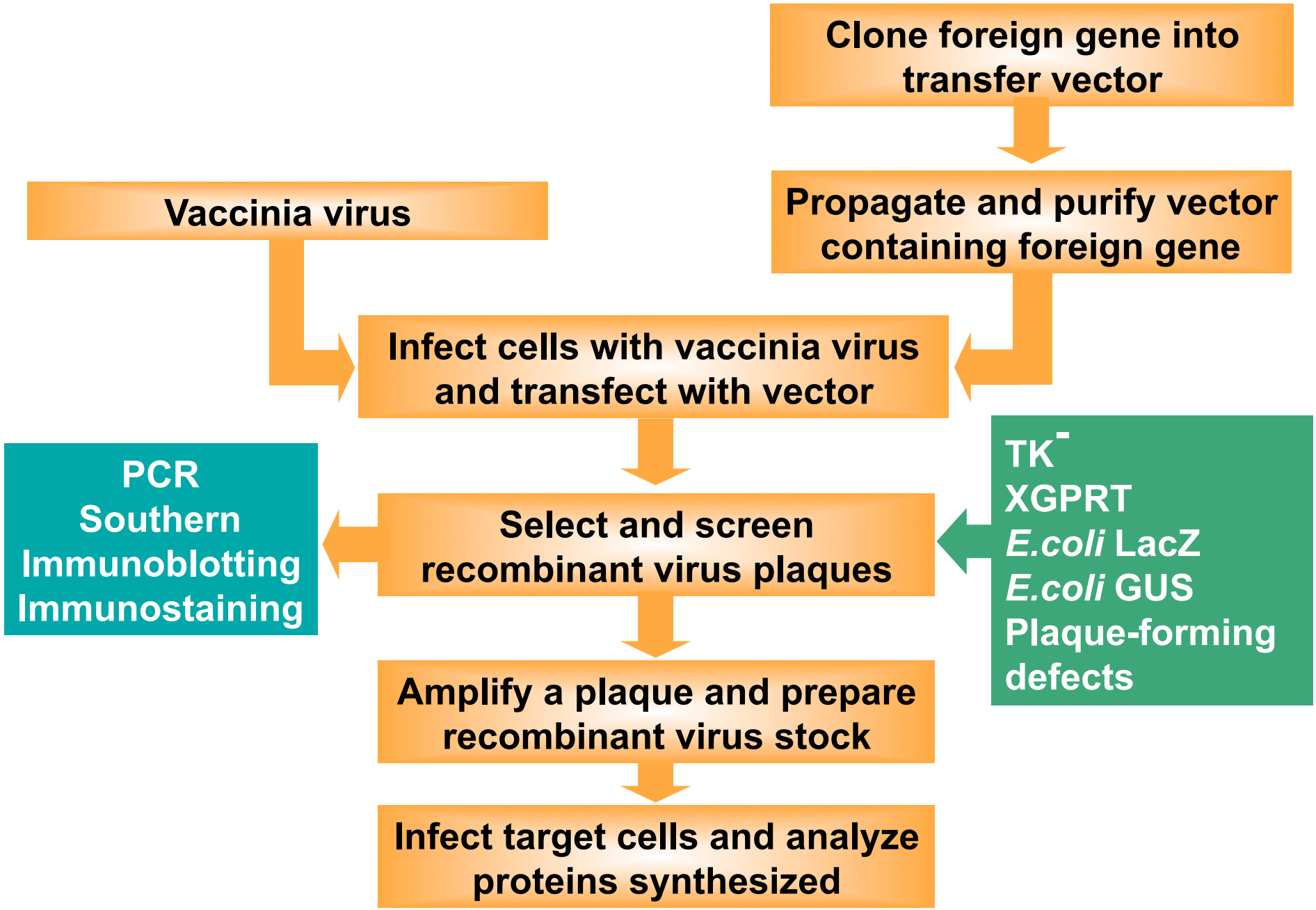
Favorable Features of Vaccinia Virus Vectors

- The methods of recombinant virus construction is relatively simple.
- The ability to infect a wide choice of cell types (most mammalian and avian cell lines).
- The transcription occurs in the cytoplasm and thus it does not require nuclear processing and RNA transport.
- The expression level is relatively high.
- Appropriate transport, secretion, processing and posttranslational modifications
- Retention of infectivity with cloning of large fragments of foreign DNA (> 20 kb)

Vaccinia Virus as a Viral Vector

- Large genome prevents direct cloning of antigen genes into Vaccinia genome
- Use homologous recombination to move foreign genes into Vaccinia genome
- Use of poxvirus promoters is essential because cellular and other viral promoters are not recognized by the vaccinia transcriptional apparatus

Flow Chart for Vaccinia Virus Expression System



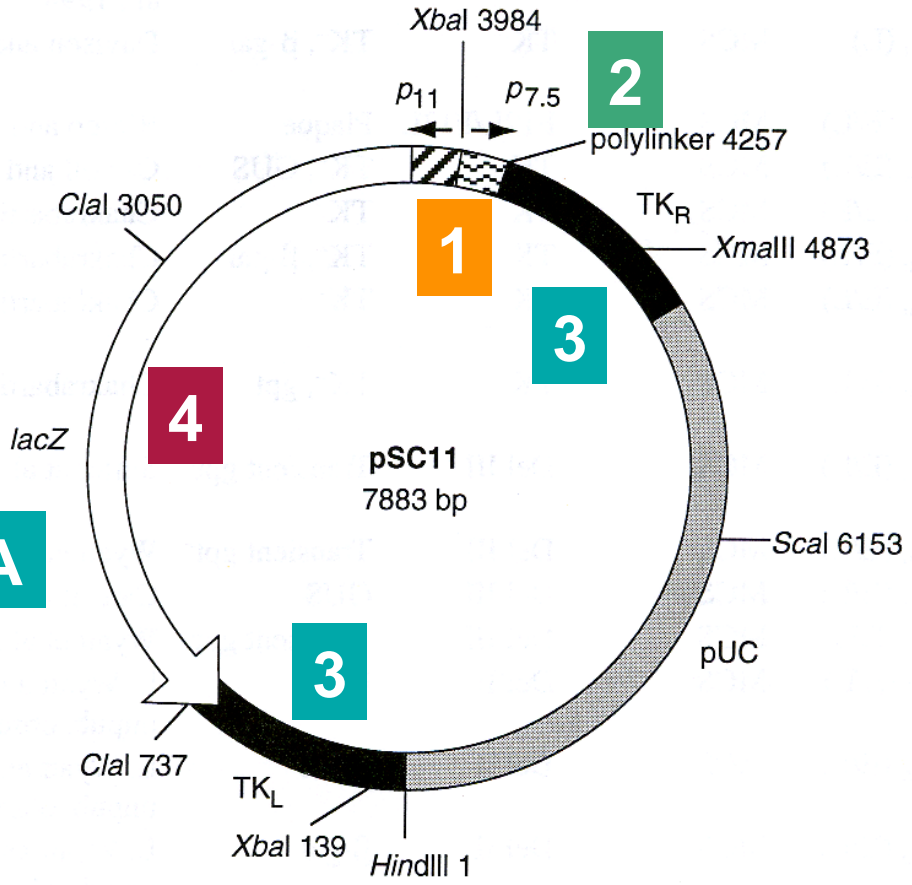
Vaccinia virus system: plasmid transfer vector pSC11

1.Vaccinia promoter(s)

2. MCS

3. Flanking Vaccinia DNA

4. Selection marker



polylinker:

pSC11 CCCGGG
└SmaI┘

STOP STOP STOP

pSC11ss GTCGACAGGCCTAATTAATTAA
└ SalI┘ └StuI ┘

pSC11 S-B-A-K-N G TCGACGTACA GATCTGTACGGGCC CGTACGGTAC CGTACGC GGCCGC
└SalI┘ └BglII┘ └ ApaI ┘ └ KpnI ┘ └ NotI ┘

Selection

TK-

Plaque

XGPRT

MVA

Vector[a]	Promoter[b]	Cloning sites[c]	Insertion sites[d]	Selection/ screening	Reference
pGS20	$p_{7.5}$ (E/L)	*Bam*HI; *Sma*I	TK	TK$^-$	Mackett et al., 1984
pSC11	$p_{7.5}$ (E/L)	*Sma*I; MCS	TK	TK$^-$, β-gal	Chakrabarti et al., 1985; Earl et al., 1990; Bacik et al., 1994
pMJ601, pMJ602	p_{syn} (L)	MCS	TK	TK$^-$, β-gal	Davison and Moss, 1990
pRB21	p_{syn} (E/L)	MCS	F12L/F13L	Plaque	Blasco and Moss, 1995
pMC02	p_{syn} (E/L)	MCS	TK	TK$^-$, GUS	Carroll and Moss, 1995
pSC59	p_{syn} (E/L)	MCS	TK	TK$^-$	Chakrabarti et al., 1997
pSC65	p_{syn} (E/L)	MCS	TK	TK$^-$, β-gal	Chakrabarti et al., 1997
pJS4	p_{syn} (E/L) ×2	MCS	TK	TK$^-$	Chakrabarti et al., 1997
pJS5	p_{syn} (E/L) ×2	MCS	TK	gpt	Chakrabarti et al., 1997
pG06	p_{syn} (E/L) ×2	MCS	Del III	Transient gpt[e]	Sutter et al., 1994
pLW-7	p_{syn} (E/L)	MCS	Del III	Transient gpt[e]	Wyatt et al., 1996
pMC03	p_{syn} (E/L)	MCS	Del III	GUS	Carroll and Moss, 1995
pLW-9	p_{H5} (E/L)	MCS	Del III	Transient gpt[e]	Wyatt et al., 1996
pLW-17	p_{H5} (E/L)	MCS	Del II	None	L. Wyatt and B. Moss, unpub. observ.
pLW-21	p_{syn} (E/L)	MCS	Del II	None	L. Wyatt and B. Moss, unpub. observ.
pLW-22	p_{syn} (E/L)	MCS	Del II	β-gal	L. Wyatt and B. Moss, unpub. observ.
pLW-24	$p_{7.5}$ (E/L)	MCS	Del II	None	L. Wyatt and B. Moss, unpub. observ.

[a] pRB21 was specifically designed for use with vaccinia virus vRB12, which has a deletion in the F13L gene. The plasmids pG06, pLW-7, pMC03, pLW-9, pLW-17, pLW-21, pLW-22, and pLW-24 were designed for MVA.

[b] Abbreviations: E, early; L, late; E/L, early and late. The designation "×2" refers to two oppositely oriented promoters that can be used for expression of two genes.

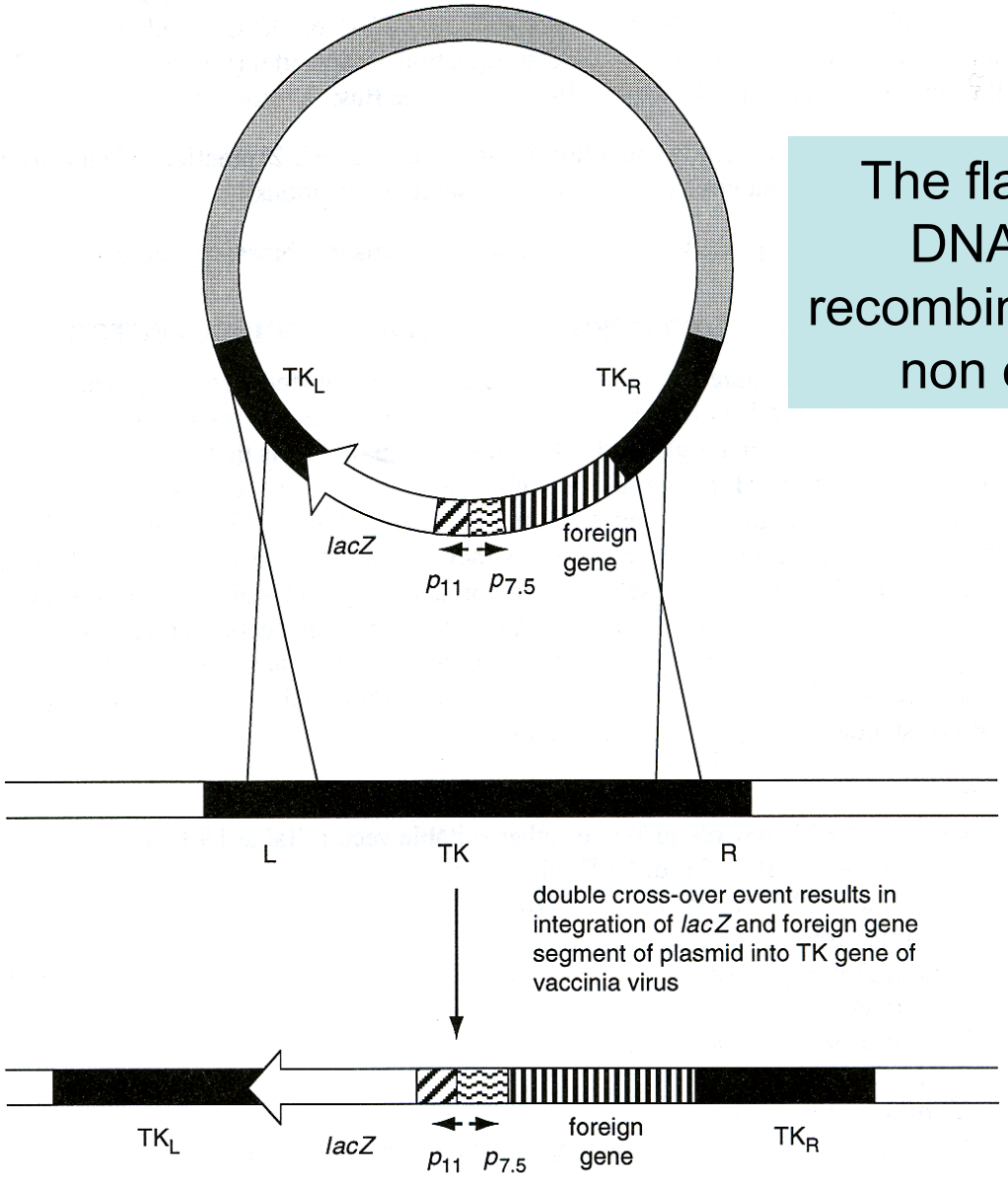
[c] *Sma*I digestion gives a blunt end for cloning any fragment that has been blunt-ended. MCS signifies multiple cloning sites.

[d] Abbreviations: TK, thymidine kinase locus; F12L/F13L, between F12L and F13L open reading frames; Del III, site of natural deletion in MVA.

[e] Transient selection in which XGPRT gene is deleted from recombinant vaccinia virus during recombination; see Background Information.

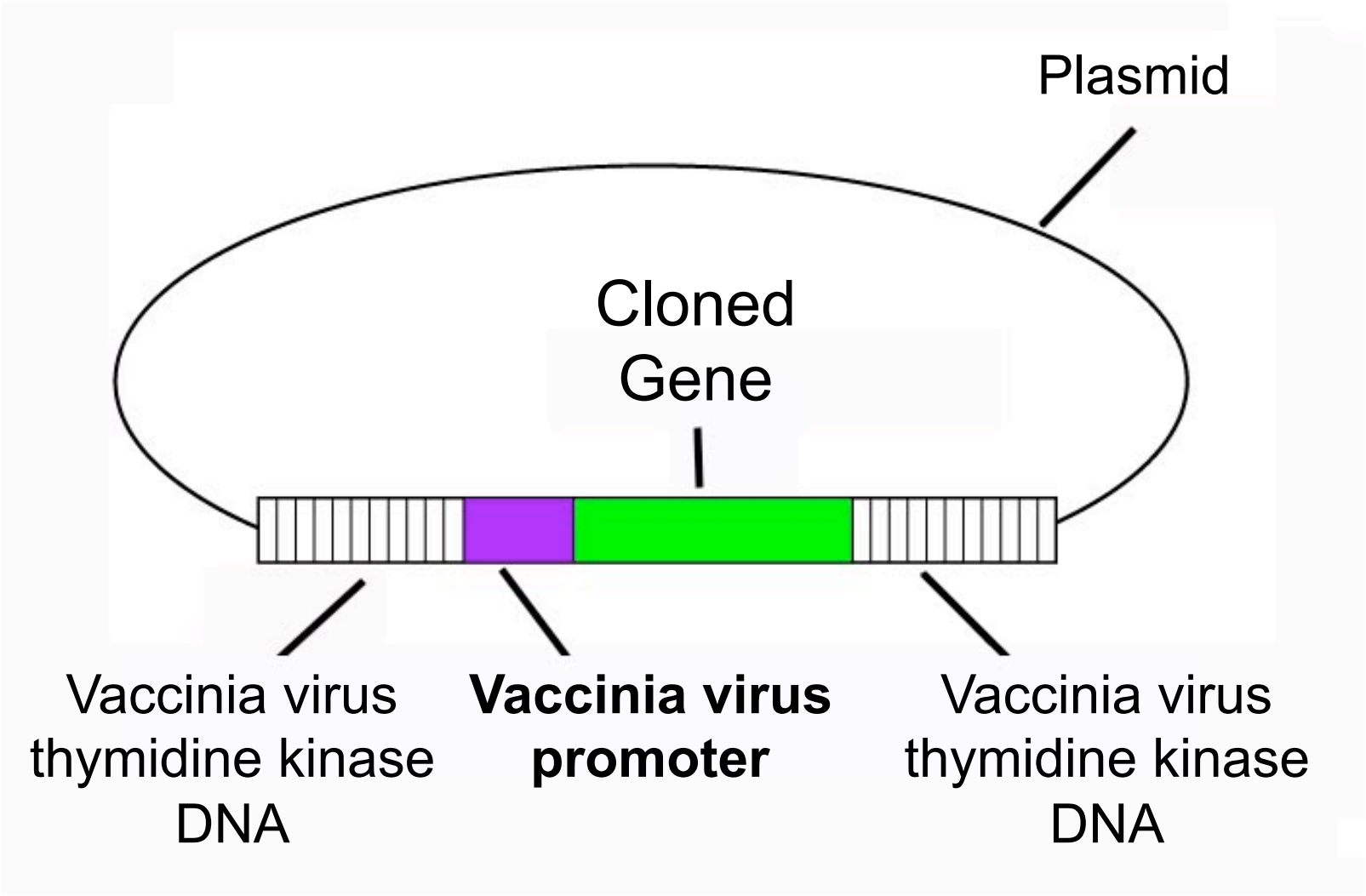
Vaccinia virus transfer vectors

Homologous recombination between a transfected plasmid and the vaccinia virus genome

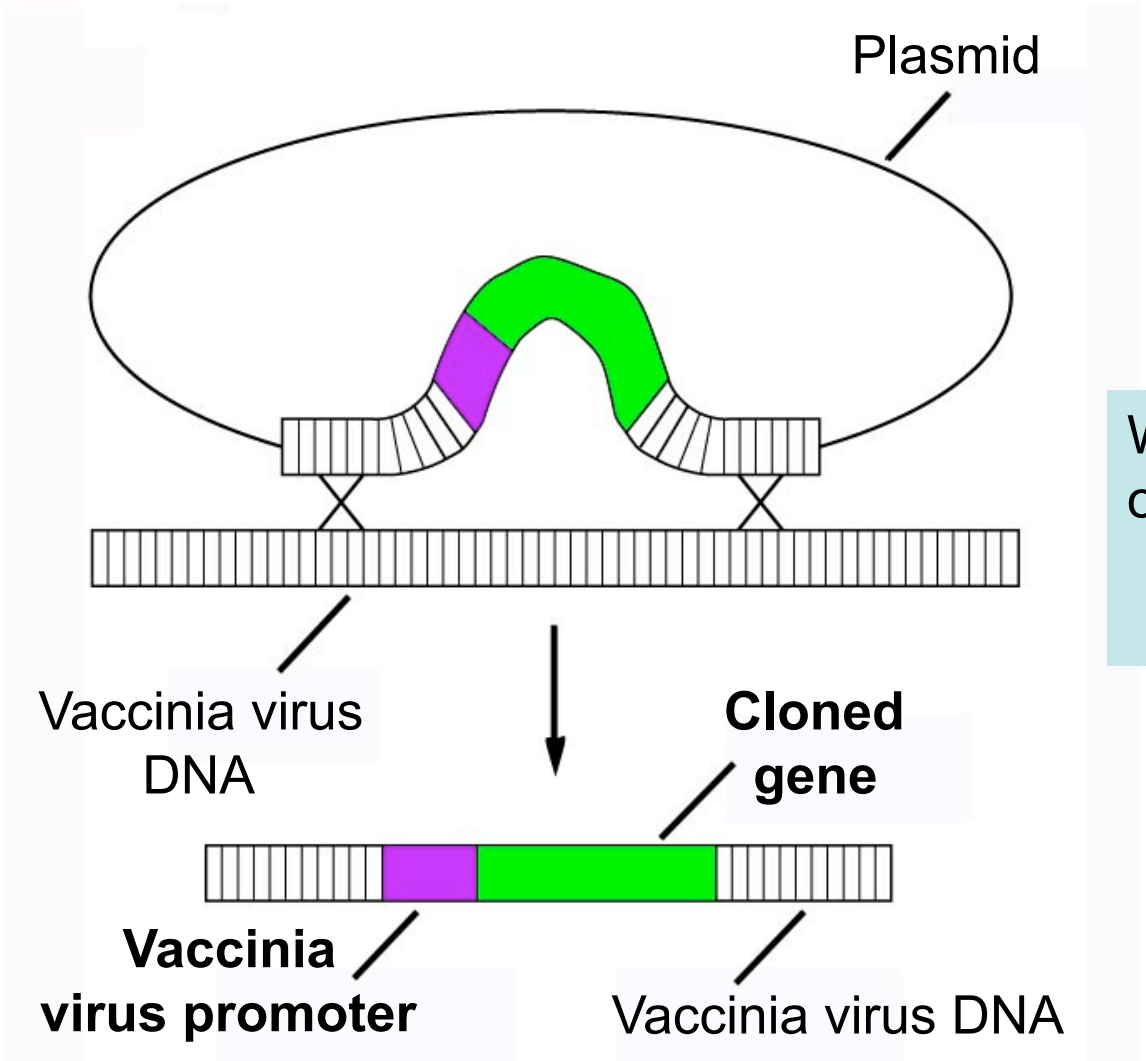


The flanking vaccinia virus DNA is chosen so that recombinantion will interrupt an non essential viral gene

Transfer vector for Homologous Recombination

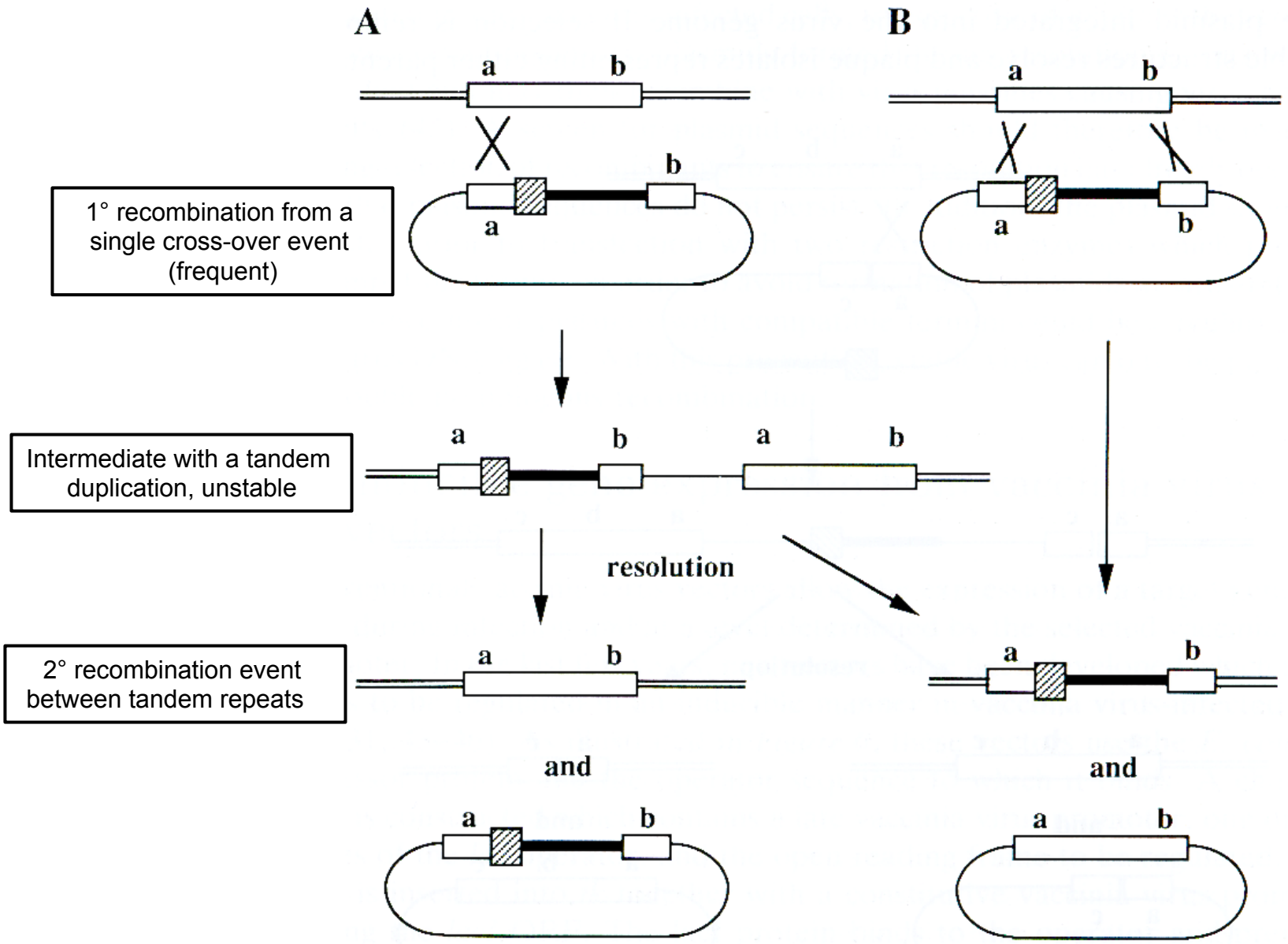


Homologous Recombination into the Vaccinia Genome

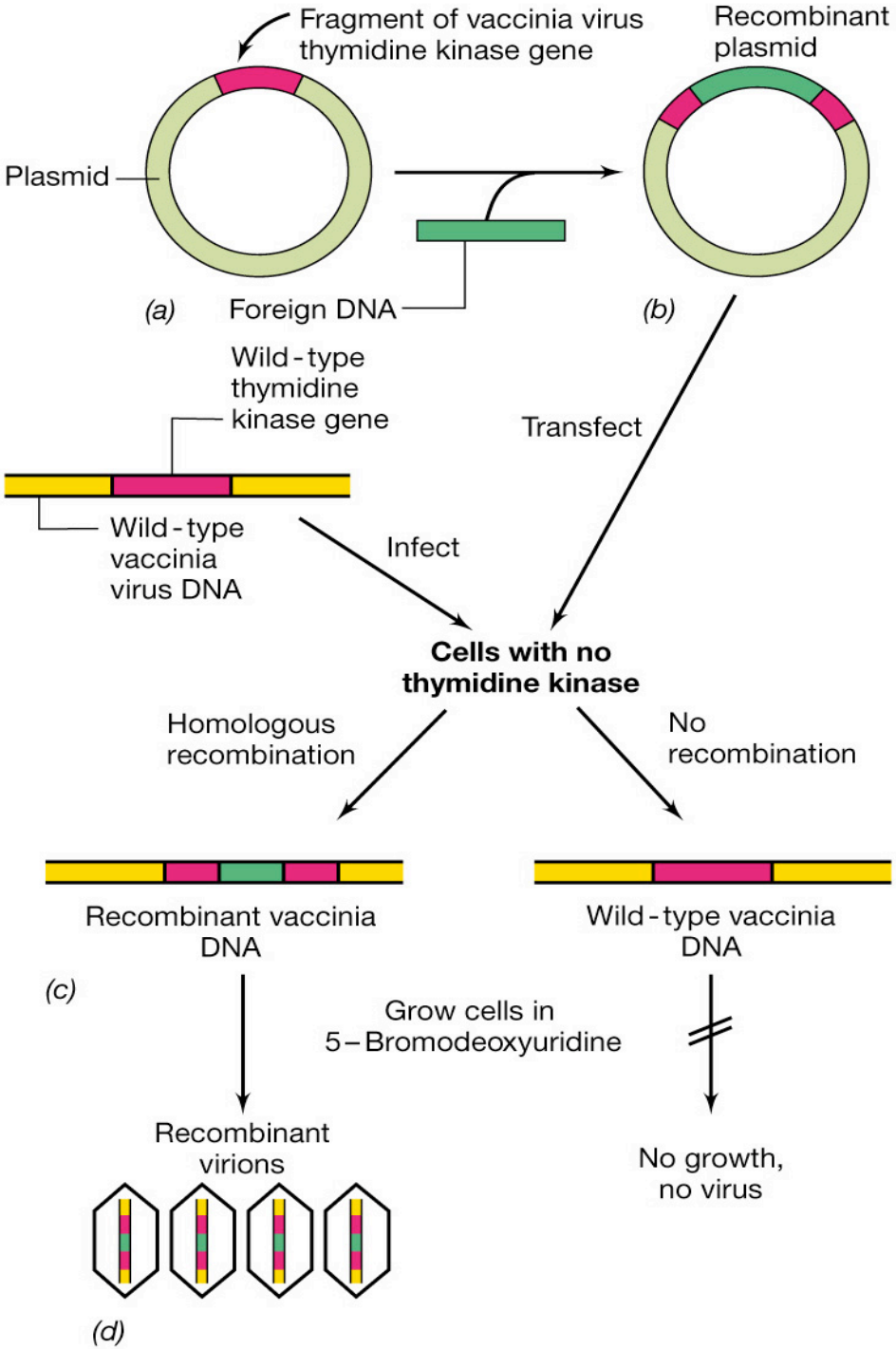


Without selection, the ratio of recombinant to parental vaccinia virus is usually **1:1000**

Formation of recombinants by single (A) or double (B) homologous recombinantion events



Selection of recombinant vaccinia virus by **5-bromodeoxyuridine**

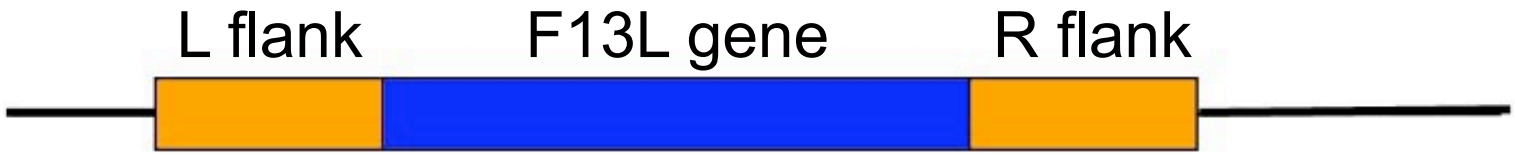


Development of Vaccinia Virus Vectors:
Selection of recombinants by complementation of plaque-forming defects

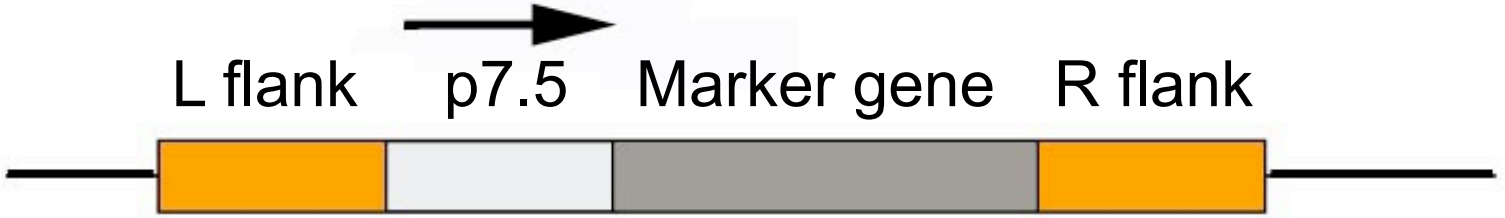
- The vaccinia gene F13L encodes VP37 that is specific of the outer envelope of EEV
- Initial experiments suggested that a F13L mutation (vRB12) prevented normal-size plaque formation on cells in culture (pin-point plaques)
- The strategy involves replacement by homologous recombination of F13L, with a selectable resistance marker

A Modified Vaccinia Virus Genome

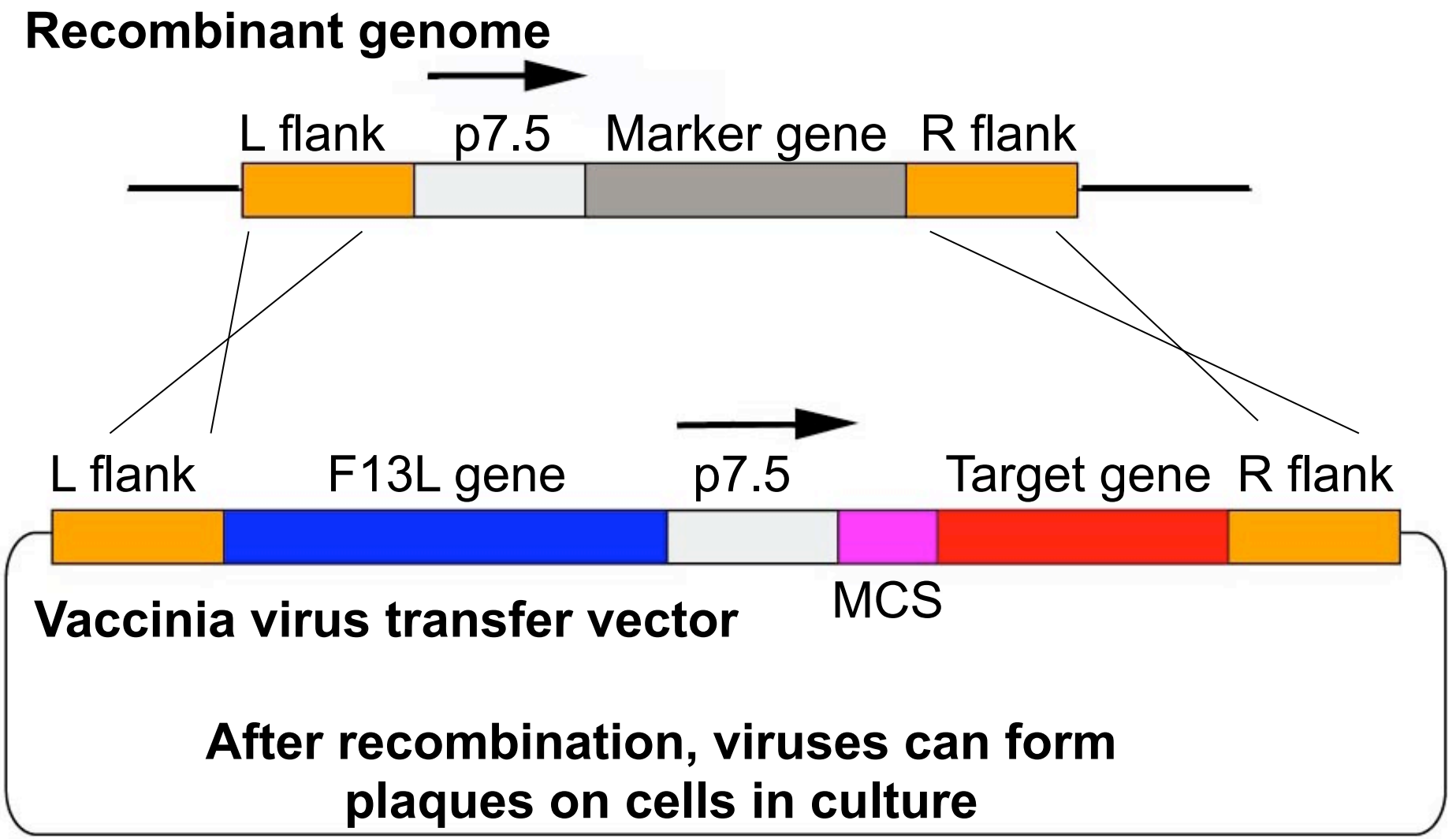
Wild-type genome



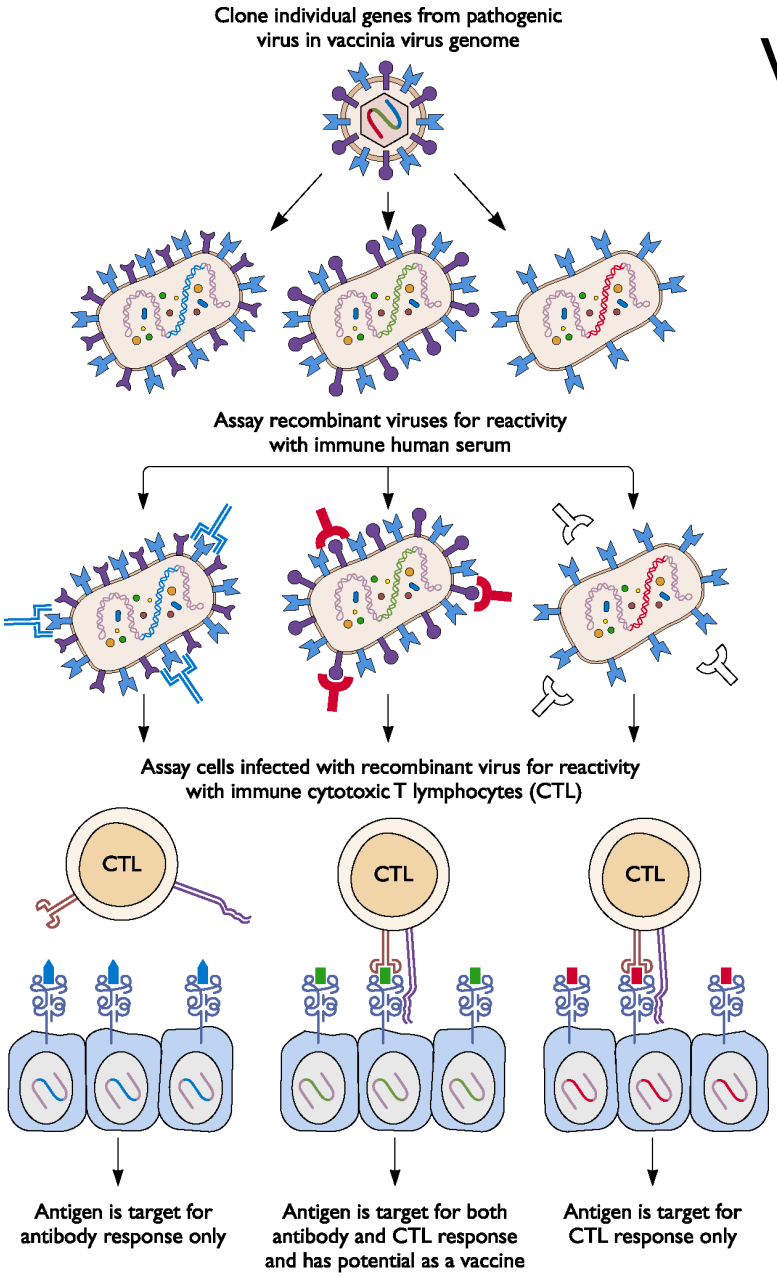
Recombinant genome



Homologous Recombination in Vaccinia



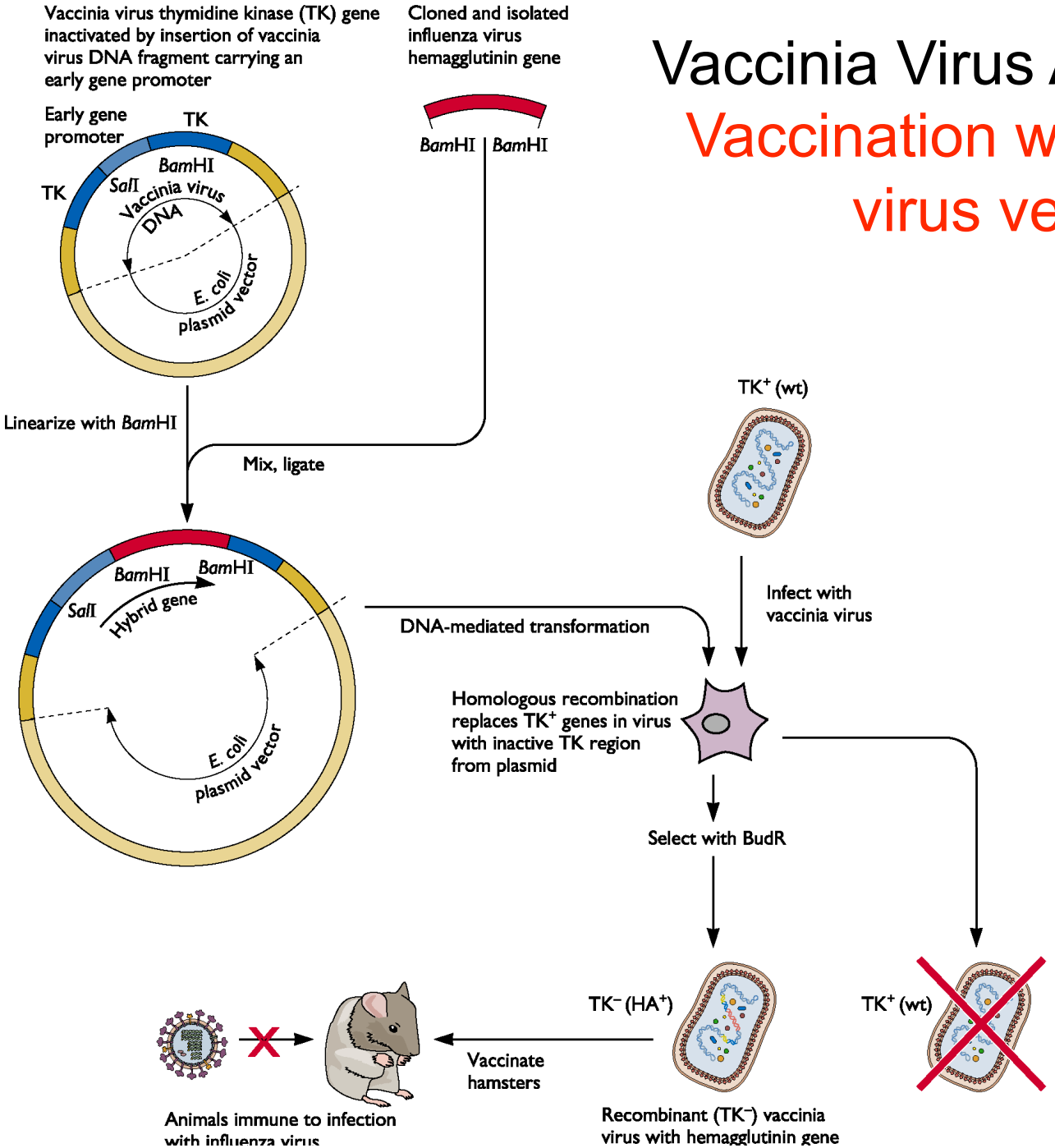
Vaccinia Virus Applications:
Epitopes identification



Vaccinia Virus Vectors as Vector Vaccines

- A live non-pathogenic virus can be used to immunize a host against a pathogen (e.g., pathogenic virus).
- The pathogen's proteins are delivered to the immune system in the context of the non-pathogenic infection promoted by the vector virus.
- This approach merges subunit vaccine and live attenuated virus technologies.
- This system provides all the "benefits" of a viral infection with respect to the immune response with none of the pathogenesis associated with the virulent virus.
- The vector initiates a local inflammatory response and the host mobilizes all the arms of its immune defense to this site, where the vaccine protein is presented and recognized and its memory is implanted in the immune system.

Vaccinia Virus Applications:
Vaccination with vaccinia virus vectors



Advantages of Vaccination with Vaccinia Virus Vectors

- Antigen is authentically expressed in mammalian cells
- Amount of antigen is amplified during replication of the live virus
- A single administration provides immunity
- Eliminates the need to purify the protein in the native state
- Protection afforded by immunization can be correlated with neutralizing Abs and CTLs
- The poxvirus life cycle allows for de novo synthesis of vaccine antigens in the cytosol and appears particularly suitable for efficient presentation via MHC-I molecules as a prerequisite for CD8 response

Vaccinia Virus Vaccine Disadvantages

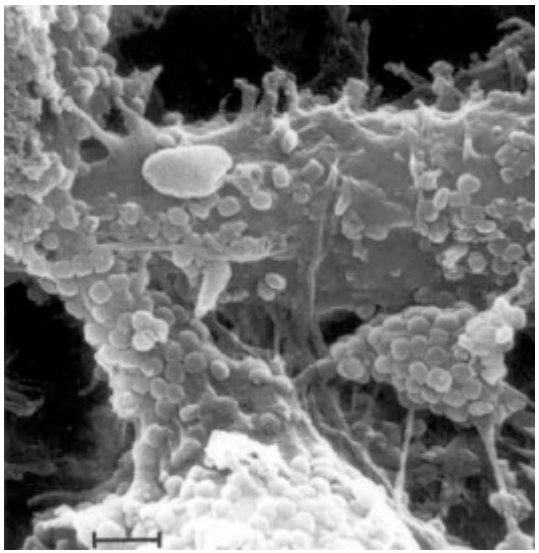
- The host is immunized against the viral vector as well the vaccine antigen (antivector immunity).
- Serious viral infection in immunocompromised individuals
  - AIDS and transplant patients, e.g.
- Low freq. of complications in humans
  - frequency of 3×10^{-6} (1 in 333,000)

Vaccination with Vaccinia Virus Vectors

Development of Modified Vaccinia Virus Ankara

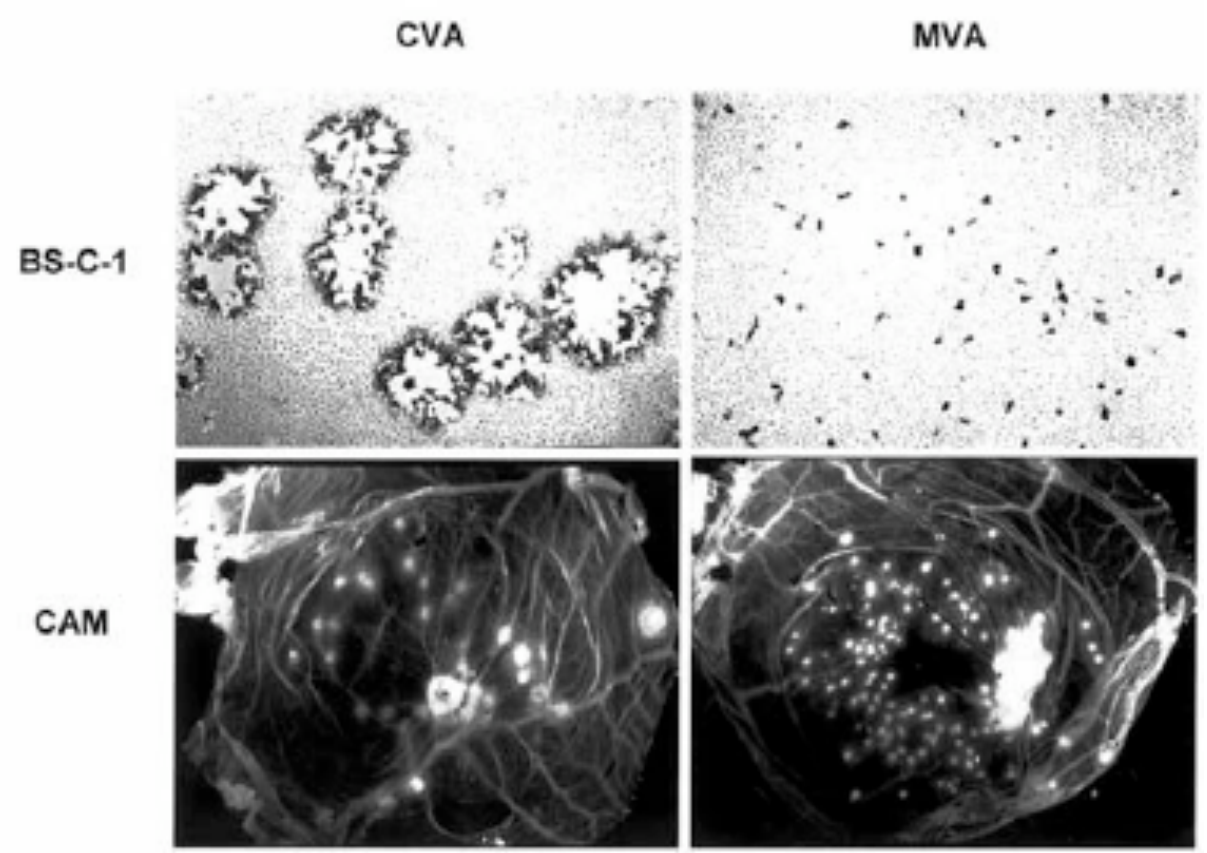
- This highly attenuated strain has been developed for use as safer vaccine during the last decades of smallpox eradication campaign.
- MVA contains multiple genomic deletions, which block replication at a late stage in most cell types with the sole exception of CEF and BHK21 cells.
- Thus, MVA is replication-defective in human cells.
- However, viral and recombinant protein expression occurs in all cell lines infectable by standard VV strain.

Modified vaccinia virus Ankara (MVA)

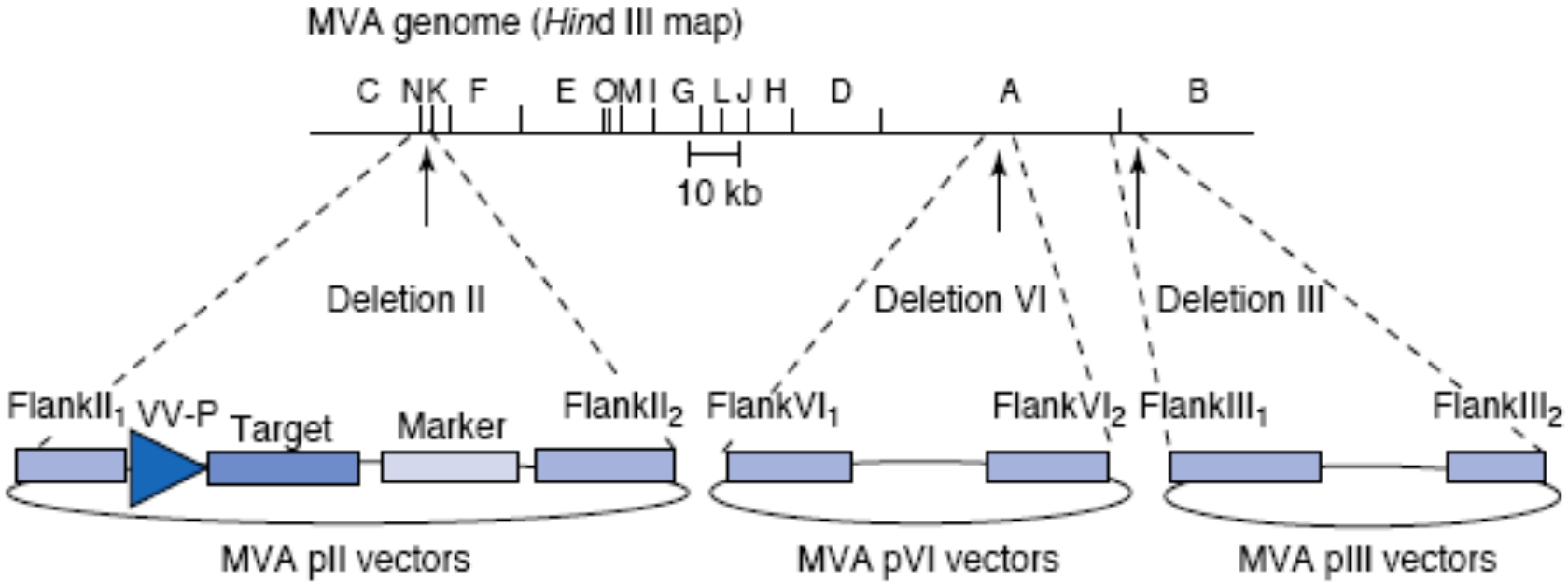


MVA-infected CEF

After 516 CEF passage, MVA was unable to productively grow in cell cultures of human origin and it was found to be avirulent in various lab animals

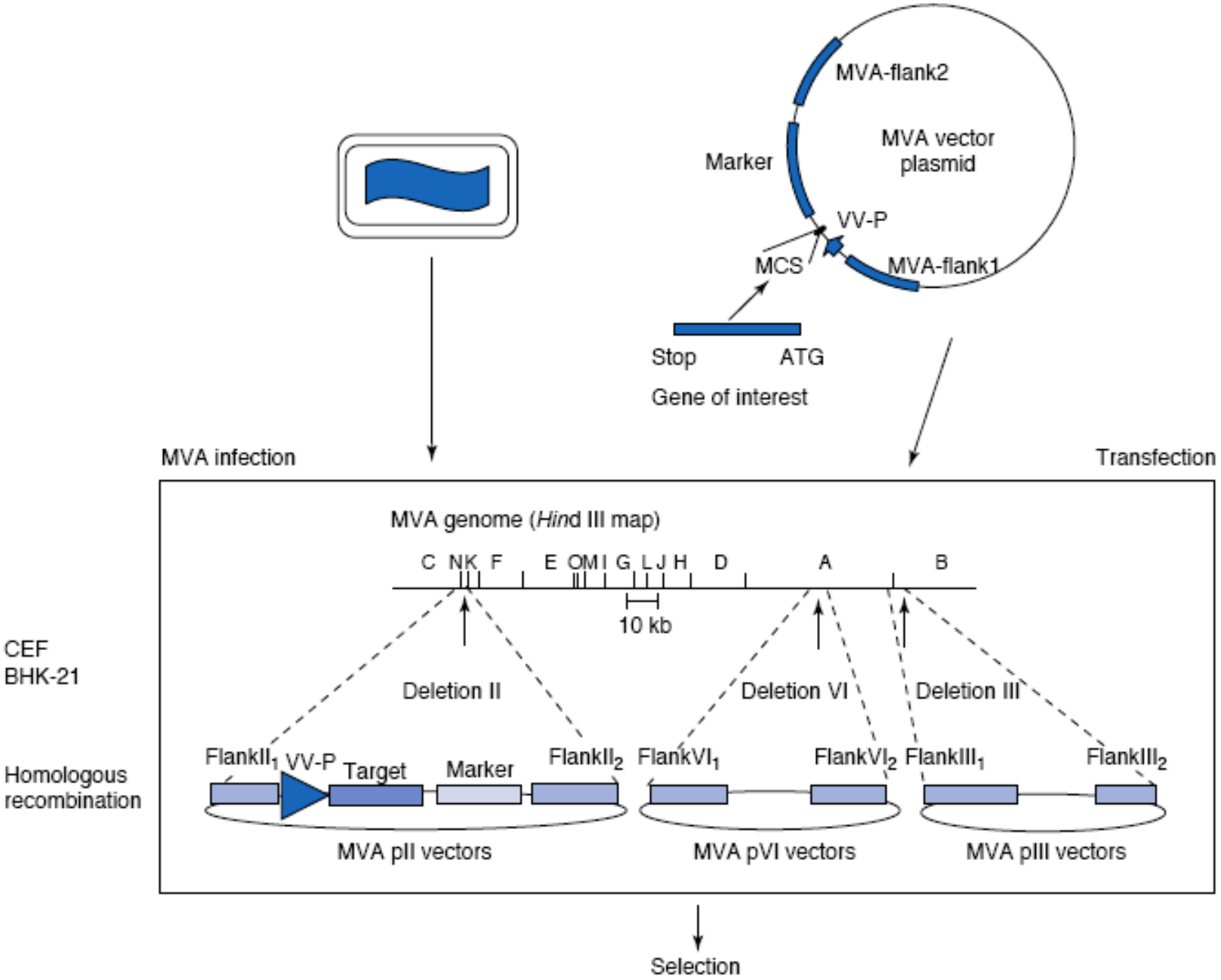


Modified vaccinia virus Ankara (MVA) genome



During attenuation MVA genome had suffered large deletions totalling a loss of about 15% of genetic information

The generation of recombinant MVA

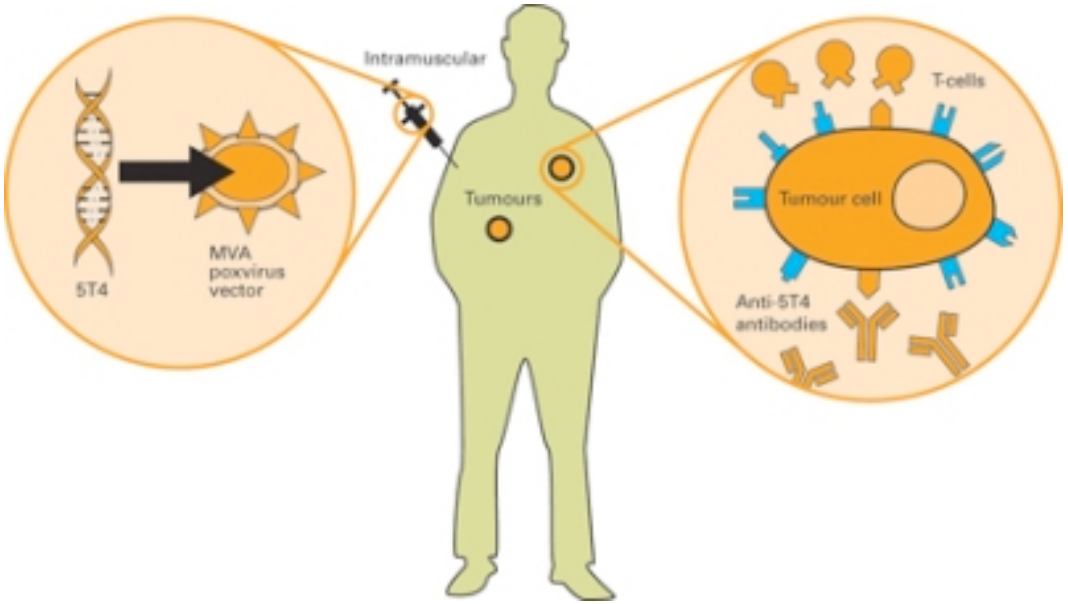


Advantages of Vaccination with MVA

Recombinant MVA is a prime candidate poxvirus vector for a generation of new vaccines against infections and tumors, suitable for prophylactic and therapeutic immunization of humans

- High-level biological safety (BSL1)
- Ability to activate appropriate innate immune mediators upon vaccination
- Capacity to deliver substantial amounts of heterologous antigens even in nonpermissive cells
- In animal models, MVA vaccines have been found immunogenic and protective against various infectious agents (HIV, influenza, PIV, measle, RSV, SARS)

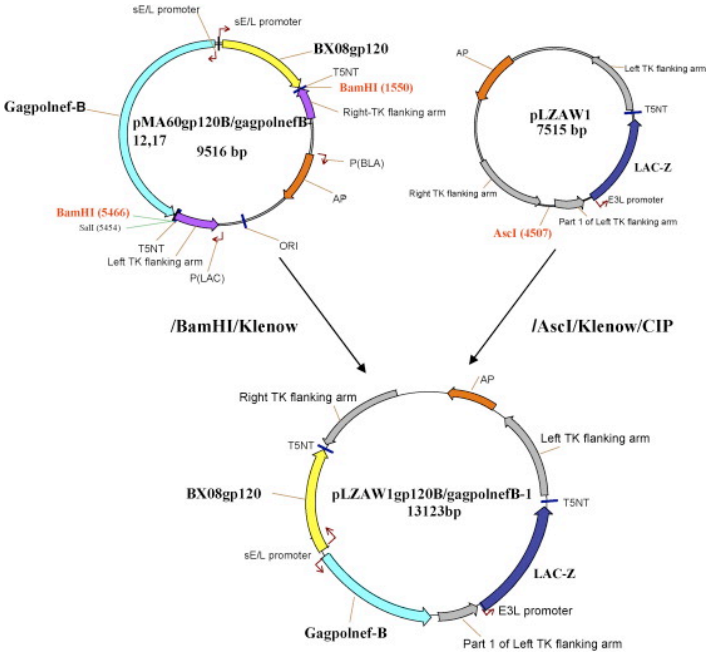
Recombinant MVA as vector vaccines



First clinical evaluation of recombinant MVA vaccines.

Target disease	Antigen	Clinical trial
AIDS	HIV-1 Nef	Phase I/II, immunotherapy
AIDS	HIVA multiantigen	Phase I, prophylaxis
Cervical cancer	HPV E2	Phase I/II, immunotherapy
Breast cancer	MUC1	Phase I, immunotherapy
Melanoma	Tyrosinase	Phase I/II
Malaria	*P. falciparum* ME-Trap	Phase I, prophylaxis
Malaria	*P. falciparum* ME-Trap	Phase I, prophylaxis

Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 2863–2885
Vaccine
www.elsevier.com/locate/vaccine



Head-to-head comparison on the immunogenicity of two HIV/AIDS vaccine candidates based on the attenuated poxvirus strains MVA and NYVAC co-expressing in a single locus the HIV-1_{BX08} gp120 and HIV-1_{IIIB} Gag-Pol-Nef proteins of clade B

Carmen Elena Gómez [a], Jose Luis Nájera [a], Eva Pérez Jiménez [a], Victoria Jiménez [a], Ralf Wagner [b], Marcus Graf [c], Marie-Joelle Frachette [d], Peter Liljeström [e], Giuseppe Pantaleo [f], Mariano Esteban [a,*]

Abstract

In this investigation we have generated and defined the immunogenicity of two novel HIV/AIDS vaccine candidates based on the highly attenuated vaccinia virus strains, MVA and NYVAC, efficiently expressing in the same locus (TK) and under the same viral promoter the codon optimized HIV-1 genes encoding gp120 and Gag-Pol-Nef antigens of clade B (referred as MVA-B and NYVAC-B). In infected human HeLa cells, gp120 is released from cells and GPN is produced as a polyprotein; NYVAC-B induces severe apoptosis but not MVA-B. The two poxvirus vectors showed genetic stability of the inserts. In BALB/c and in transgenic HHD mice for human HLA-A2 class I, both vectors are efficient immunogens and induced broad cellular immune responses against peptides represented in the four HIV-1 antigens. Some differences were observed in the magnitude and breadth of the immune response in the mouse models. In DNA prime/poxvirus boost protocols, the strongest immune response, as measured by fresh IFN-γ and IL-2 ELISPOT, was obtained in BALB/c mice boosted with NYVAC-B, while in HHD mice there were no differences between the poxvirus vectors. When the prime/boost was performed with homologous or with combination of poxvirus vectors, the protocols MVA-B/MVA-B and NYVAC-B/NYVAC-B, or the combination NYVAC-B/MVA-B gave the most consistent broader immune response in both mouse models, although the magnitude of the overall response was higher for the DNA-B/poxvirus-B regime. All of the immunization protocols induced some humoral response against the gp160 protein from HIV-1 clone LAV. Our findings indicate that MVA-B and NYVAC-B meet the criteria to be potentially useful vaccine candidates against HIV/AIDS.

MVA-B Vaccine

The results of a phase I clinical trial

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Safety and immunogenicity of a modified pox vector-based HIV/AIDS vaccine candidate expressing Env, Gag, Pol and Nef proteins of HIV-1 subtype B (MVA-B) in healthy HIV-1-uninfected volunteers: A phase I clinical trial (RISVAC02)

Felipe García[a,*,1], Juan Carlos López Bernaldo de Quirós[b,1], Carmen E. Gómez[c,1], Beatriz Perdiguero[c,1], Jose L. Nájera[c,1], Victoria Jiménez[c,1], Juan García-Arriaza[c,1], Alberto C. Guardo[a,1], Iñaki Pérez[a,1], Vicens Díaz-Brito[a,1], Matilde Sánchez Conde[b,1], Nuria González[d,1], Amparo Alvarez[d,1], José Alcamí[d,1], José Luis Jiménez[b,1], Judit Pich[a,1], Joan Albert Arnaiz[a,1], María J. Maleno[a,1], Agathe León[a,1], María Angeles Muñoz-Fernández[b,1], Peter Liljeström[e,1], Jonathan Weber[f,1], Giuseppe Pantaleo[g,1], José M. Gatell[a,1], Montserrat Plana[a,1,2], Mariano Esteban[c,1,2]

Background: To investigate the safety and immunogenicity of a modified vaccinia virus Ankara vector expressing HIV-1 antigens from clade B (MVA-B), a phase-I, doubled-blind placebo-controlled trial was performed.

Methods: 30 HIV-uninfected volunteers at low risk of HIV-1 infection were randomly allocated to receive 3 intramuscular injections (1×10^8 pfu/dose) of MVA-B ($n = 24$) or placebo ($n = 6$) at weeks 0, 4 and 16. All volunteers were followed 48 weeks. Primary end-points were adverse events and immunogenicity.

Results: A total of 169 adverse events were reported, 164 of grade 1–2, and 5 of grade 3 (none related to vaccination). Overall 75% of the volunteers showed positive ELISPOT responses at any time point. The magnitude (median) of the total responses induced was 288 SFC/10^6 PBMC at week 18. Antibody responses against Env were observed in 95% and 72% of vaccinees at week 18 and 48, respectively. HIV-1 neutralizing antibodies were detected in 33% of volunteers.

Conclusions: MVA-B was safe, well tolerated and elicited strong and durable T-cell and antibody responses in 75% and 95% of volunteers, respectively. These data support further exploration of MVA-B as an HIV-1 vaccine candidate.

Clinical Trials.gov identifier: NCT00679497.

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0022-538X/11/$12.00 doi:10.1128/JVI.05165-11

The HIV/AIDS Vaccine Candidate MVA-B Administered as a Single Immunogen in Humans Triggers Robust, Polyfunctional, and Selective Effector Memory T Cell Responses to HIV-1 Antigens▽‡

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Attenuated poxvirus vectors expressing human immunodeficiency virus type 1 (HIV-1) antigens are considered promising HIV/AIDS vaccine candidates. Here, we describe the nature of T cell immune responses induced in healthy volunteers participating in a phase I clinical trial in Spain after intramuscular administration of three doses of the recombinant MVA-B-expressing monomeric gp120 and the fused Gag-Pol-Nef (GPN) polyprotein of clade B. The majority (92.3%) of the volunteers immunized had a positive specific T cell response at any time postvaccination as detected by gamma interferon (IFN-γ) intracellular cytokine staining (ICS) assay. The $CD4^+$ T cell responses were predominantly Env directed, whereas the $CD8^+$ T cell responses were similarly distributed against Env, Gag, and GPN. The proportion of responders after two doses of MVA-B was similar to that obtained after the third dose of MVA-B vaccination, and the responses were sustained (84.6% at week 48). Vaccine-induced $CD8^+$ T cells to HIV-1 antigens after 1 year were polyfunctional and distributed mainly within the effector memory (TEM) and terminally differentiated effector memory (TEMRA) T cell populations. Antivector T cell responses were mostly induced by $CD8^+$ T cells, highly polyfunctional, and of TEMRA phenotype. These findings demonstrate that the poxvirus MVA-B vaccine candidate given alone is highly immunogenic, inducing broad, polyfunctional, and long-lasting CD4 and CD8 T cell responses to HIV-1 antigens, with preference for TEM. Thus, on the basis of the immune profile of MVA-B in humans, this immunogen can be considered a promising HIV/AIDS vaccine candidate.

Rabies: an example of a vaccinia virus-based vaccine to prevent an infectious disesae

Virus	Disease
Lyssavirus	
• **Rabies virus**	Rabies
• Related viruses of rodents and bats	Rarely cause rabies-like encephalitis
Vesiculovirus	
• Vesicular stomatitis virus	Flu-like illness

Epidemiology

Transmission
- Reservoir: wild animals
- Vectors: wild animals, unvaccinated dogs and cats
- Bite of rabid animal (virus in saliva), aerosols (in caves harboring rabid bats)

Distribution of virus
- Ubiquitous, except certain islands
- No seasonal incidence

At risk or risk factors
- Animal handlers, veterinarians
- Those in countries with no pet vaccinations or quarantine

Vaccines or antiviral drugs
- Vaccines for pets and wild animals
- Inactivated virus vaccine for at-risk personnel, postexposure prophylaxis
- No antiviral drugs

Disease mechanisms

Replicates in muscle at bite site

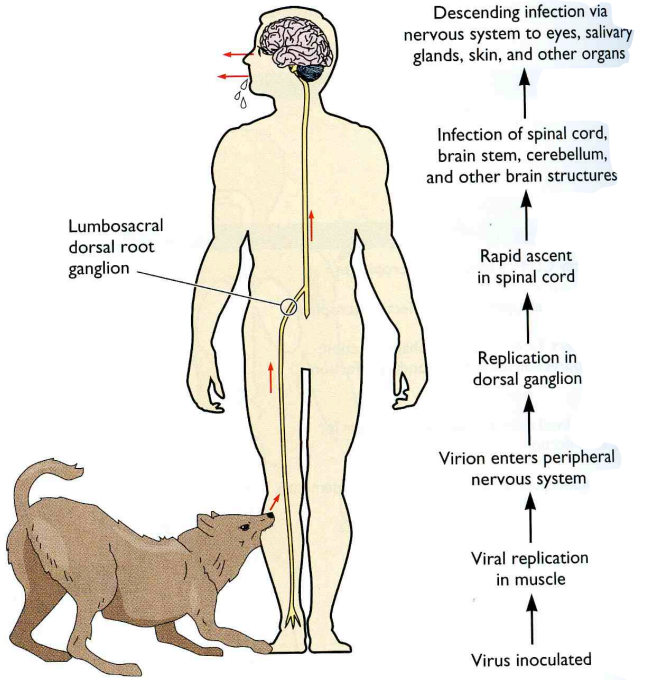
Incubation period of weeks to months, depending on inoculum and distance of bite from central nervous system

Infects peripheral nerves and travels to brain

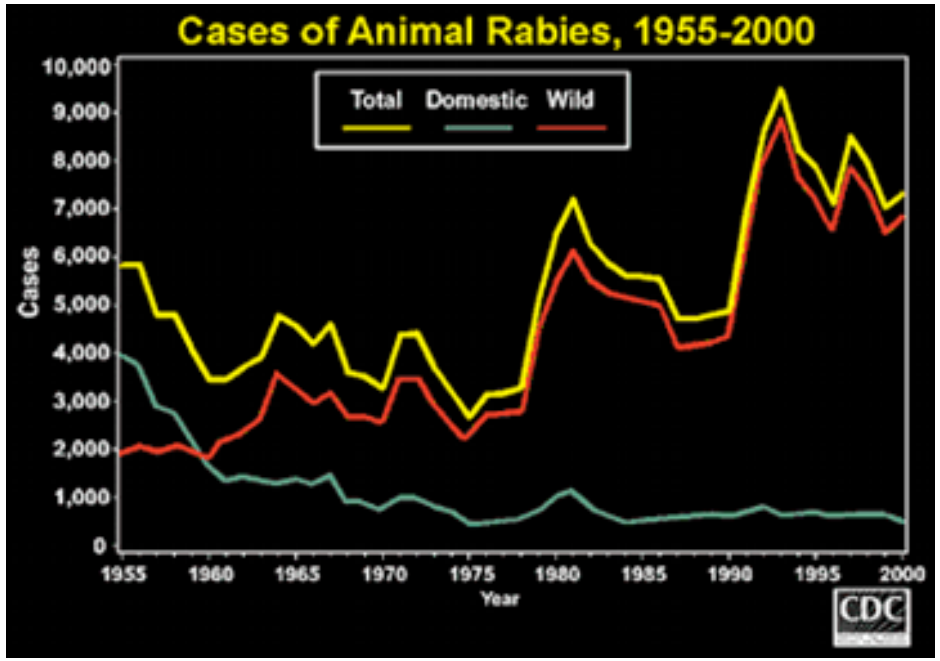
Replication in brain causes hydrophobia, seizures, hallucinations, paralysis, coma, and death

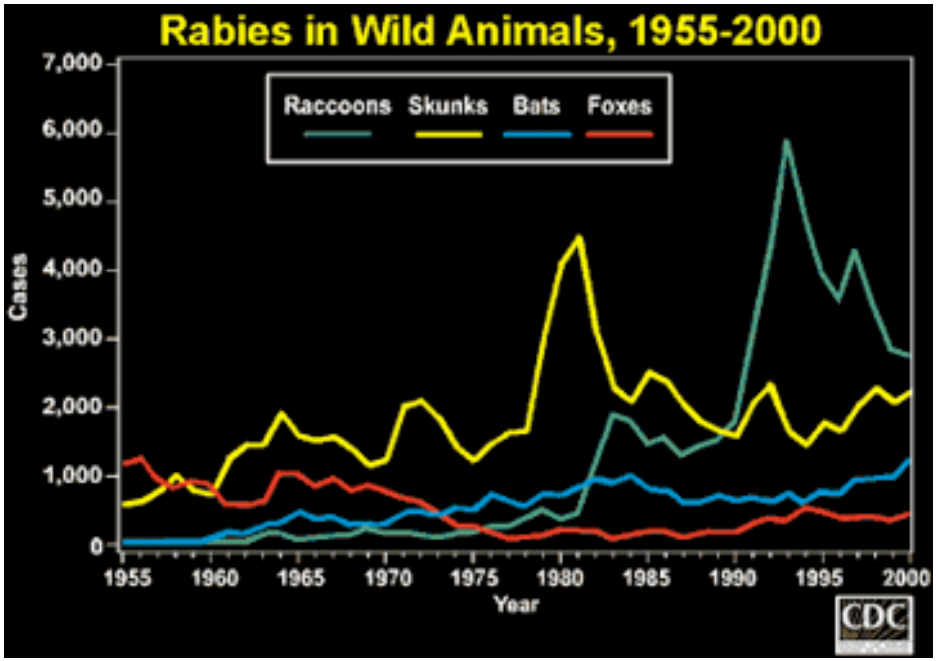
Spreads to salivary glands, from which it is transmitted

Postexposure immunization can prevent disease due to long incubation period



Rabies’ incidence in USA 1955-2000





Suggested reading: Nature, 354, 520- 522, 1991

Large-scale eradication of rabies using recombinant vaccinia–rabies vaccine

B. Brochier*, M. P. Kieny†, F. Costy‡, P. Coppens*, B. Bauduin*, J. P. Lecocq†, B. Languet§, G. Chappuis§, P. Desmettre§, K. Afiademanyo||, R. Libois|| & P.-P. Pastoret*

FIG. 2 Geographic distribution of 79 foxes (78 healthy, 1 rabid) shot or found dead in the area vaccinated three times (collection period: October 15, 1990 to April 30, 1991). ●, Animals tetracycline-positive; ○, animals tetracycline-negative; ♀, rabid tetracycline-negative fox.

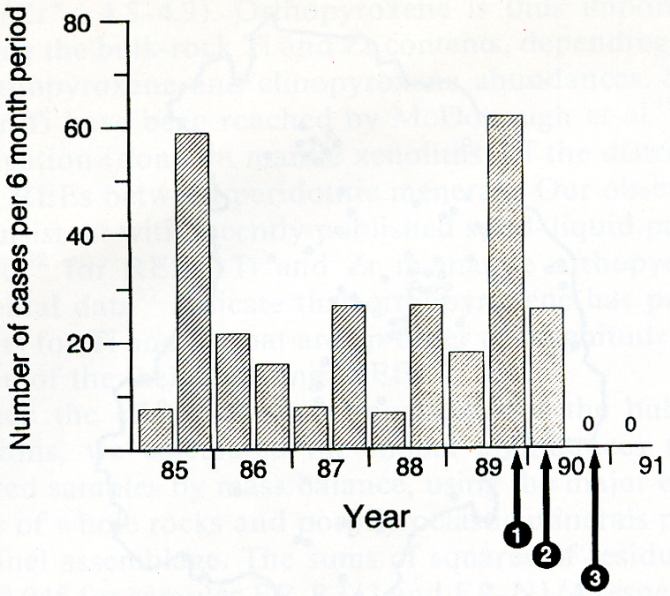
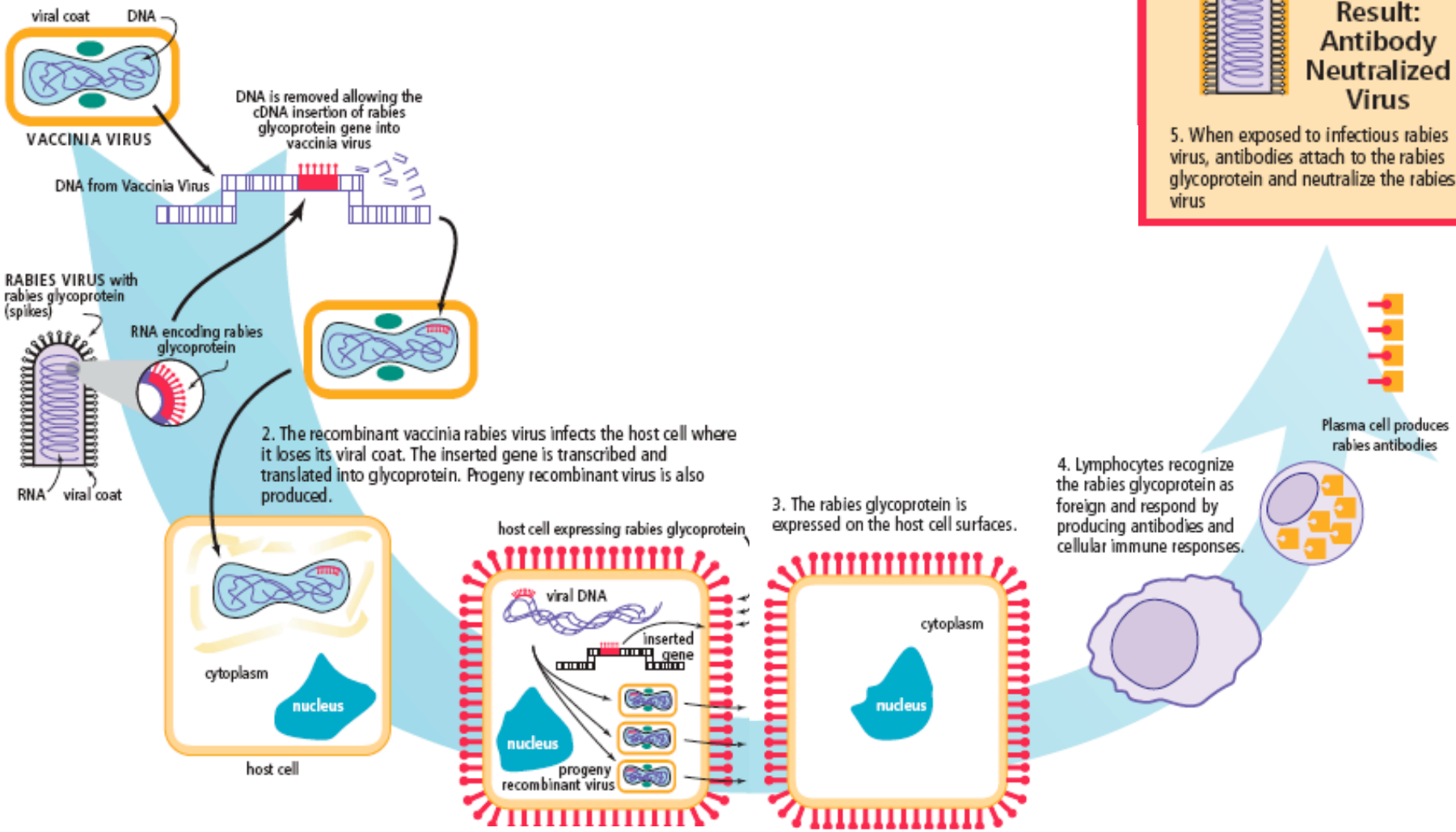
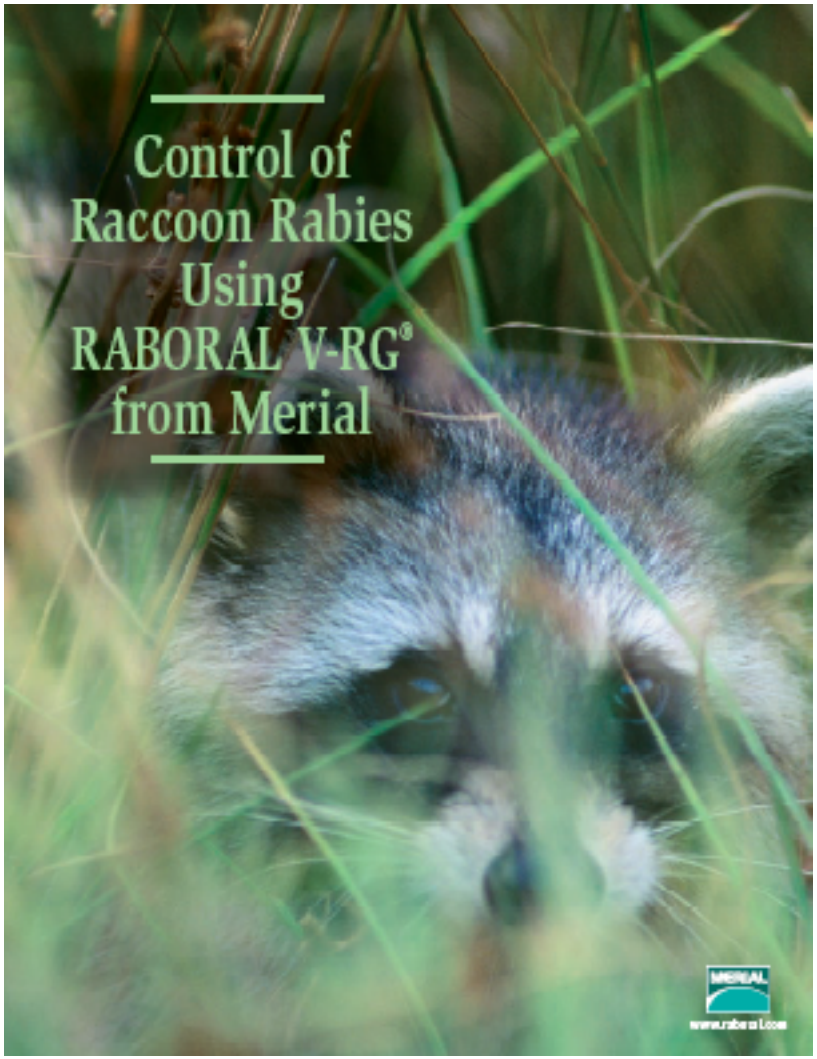


FIG. 3 Seven-year evolution of the incidence of rabies in domestic livestock. Histogram boxes plot the half-yearly (Jan–Jun and Jul–Dec) numbers of cases of rabies notified in sheep and cattle in the target area before and following vaccination. The arrows indicate the rough timing of the three large-scale campaigns of vaccine-bait dispersal.

Raboral V-RG®

Oral Rabies Vaccine For Wildlife





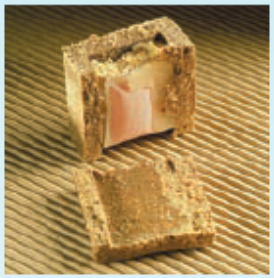
Raboral V-RG®

Oral Rabies Vaccine For Wildlife

RABORAL V-RG Baits

There are two bait formats used to deliver the vaccine.

RABORAL V-RG consists of a fish-meal polymer bait that is hollowed out through the center. This not only provides a strong attractant to raccoons, but also is strong enough to withstand being dropped from airplanes.



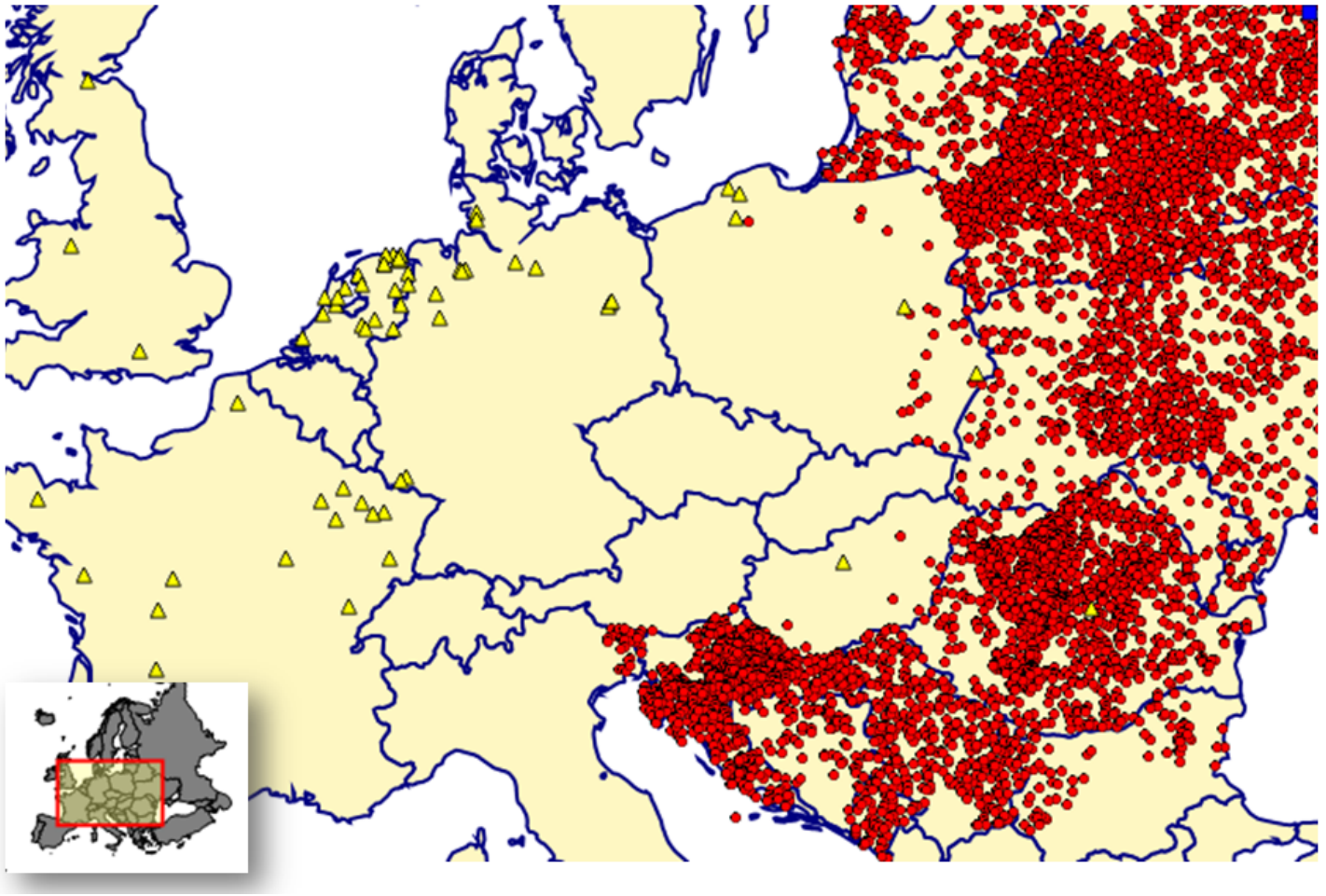
A sachet containing rabies vaccine is inserted into the baits and sealed in with wax (bait shown cut open above). When the raccoon bites into the bait, the sachet is ruptured allowing the vaccine to flow into the raccoon's mouth and throat.

The RABORAL V-RG coated sachet contains rabies vaccine and is coated in wax and fishmeal crumbles. When the raccoon bites into the sachet, it is ruptured allowing the vaccine to flow into the raccoon's mouth and throat.

Rabies in Italy

Ministero della Salute

2008-2010



La rabbia silvestre in Italia

Ministero della Salute

- **Nell'ottobre del 2008 la rabbia è ricomparsa in Italia; il primo focolaio è apparso nel territorio del Comune di Resia (UD), a seguito dell'evolversi dell'epidemia che interessa i paesi dell'est limitrofi (Slovenia e Croazia).**
- **Nel corso del 2009 e inizio 2010 l'epidemia si è diffusa in direzione Sud- Ovest, comprendendo il Friuli Venezia Giulia, il Veneto in particolare la provincia di Belluno, fino ai casi più recenti riscontrati nella provincia di autonoma di Trento.**
- **La prevalenza dei casi ha interessato gli animali selvatici, per lo più le volpi, che rappresentano il principale serbatoio della malattia, ed alcuni caprioli e tassi. Sono stati riscontrati positivi anche animali domestici tra cui cani, gatti un cavallo ed un asino.**
- **Nell'Ordinanza Ministeriale del 26 novembre 2009, sono stati disposti i seguenti provvedimenti: obbligo di vaccinazione antirabbica dei cani e altri animali da compagnia sensibili al seguito di persone che si recano nelle zone interessate, obbligo di vaccinazione dei cani di proprietà e degli animali domestici sensibili condotti al pascolo nelle zone interessate, campagne di vaccinazione orale delle volpi mediante vaccino addizionato a specifiche esche distribuite sul territorio interessato dalla malattia e in un'ampia zona di protezione circostante.**
- **Dal dicembre 2009 è stato attivato un piano di vaccinazione orale delle volpi nei confronti della rabbia che ha interessato le Regioni del nord-est italiano. Nel 2010 sono state completate quattro campagne di vaccinazione, effettuate con mezzi aerei, su un'area di oltre 30.000 kmq.**
- **Grazie a questi interventi sanitari la malattia è ritenuta sotto controllo e al momento si assiste ad una riduzione dei casi accertati: infatti si è passati dalle 49 positività al virus registrate nelle volpi nel mese di gennaio 2010, ai 9 casi del giugno 2010.**

Ministero della Salute

Comunicato stampa n. 38

Data comunicato: **26 febbraio 2013**

Italia di nuovo Paese indenne da rabbia

L'Italia ha riacquisito lo status di Paese indenne da rabbia. Lo status di Paese indenne da rabbia, come stabilito dalle procedure dalla Organizzazione Mondiale della salute animale (OIE), può essere riacquisito, trascorsi due anni dall'accertamento dell'ultimo caso di malattia che in Italia risale al 14 febbraio del 2011. Il risultato è stato conseguito a seguito dell'applicazione delle misure previste dalle Ordinanze che il Ministero della Salute ha emanato nel novembre 2009 e nel febbraio del 2012 la cui applicazione è stata curata dalla Direzione generale della sanità animale

Un esteso piano di vaccinazione orale antirabbico nelle volpi e l'obbligo di vaccinazione dei cani presenti nelle zone a rischio e degli animali condotti al pascolo in diversi parti dei territori del Nord Est d'Italia, effettuati col sostegno finanziario dall'Unione Europea, sono stati efficacemente attuati nei territori interessati con la collaborazione del centro nazionale di referenza presso l'Istituto Zooprofilattico di Padova e dai veterinari sia pubblici che privati.

Nonostante la favorevole situazione epidemiologica l'Italia manterrà un piano di vaccinazione nelle volpi nella Regione Friuli Venezia Giulia, lungo il confine italo-sloveno, in considerazione del permanere della situazione di rischio nell'area balcanica.