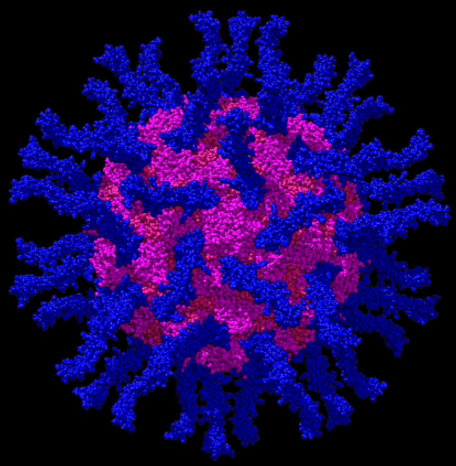


VIROLOGY LIVE

WITH VINCENT RACANIELLO

Therapeutic viruses

Session 25

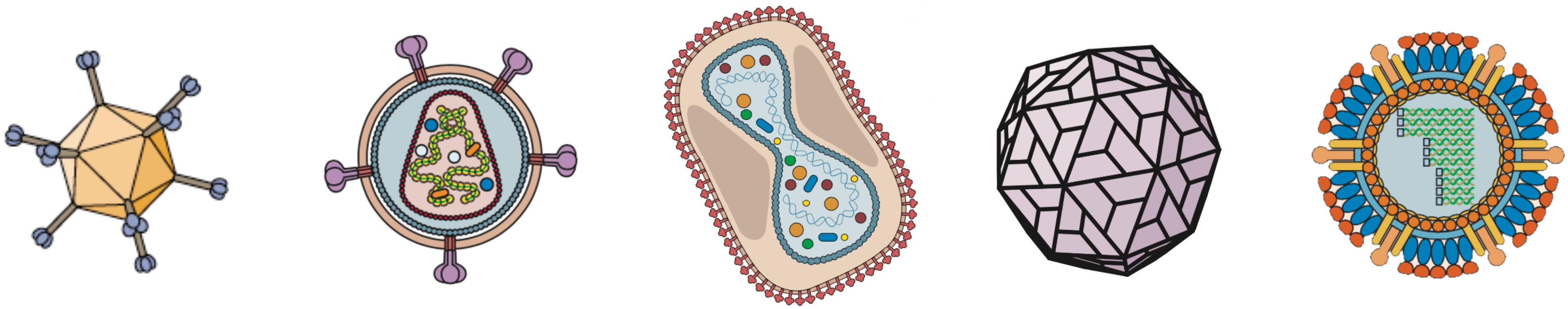
Virology Live

Fall 2021

“Trust science, not scientists”

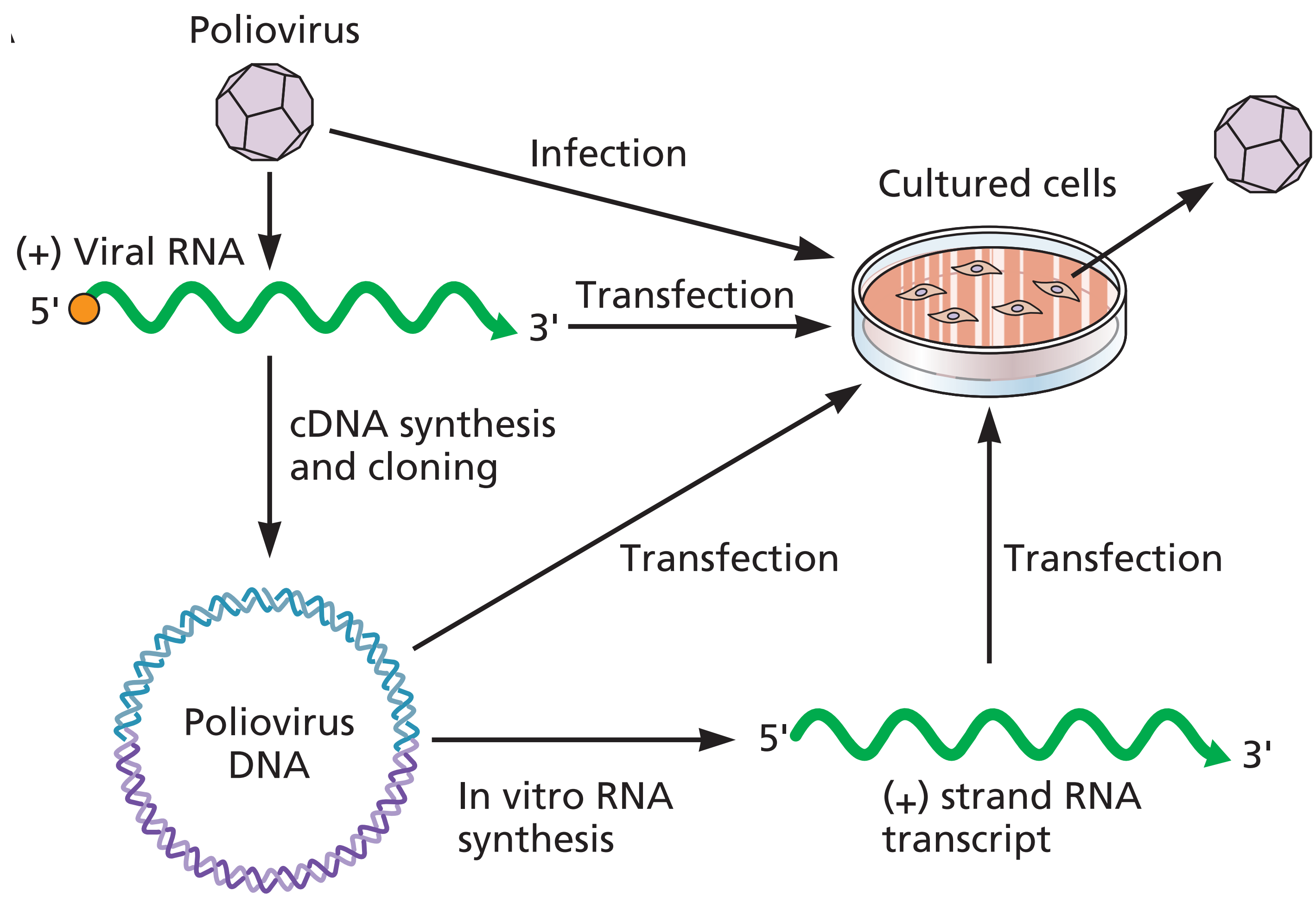
--Dickson Despommier

Therapeutic viruses



- Phage therapy for bacterial infections
- Gene therapy: deliver a gene to patients who lack the gene or carry defective versions
- To deliver antigens (viral vaccines)
- Viral oncotherapy

Infectious viral DNA: A key for vector development

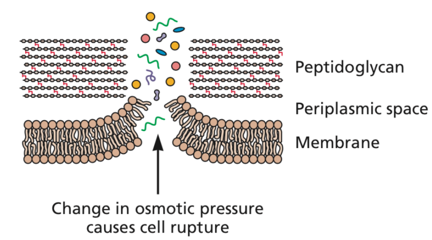


Phage therapy

- After discovering phages in 1915, d'Hérelle pursued their use to treat bacterial infections
- Co-founded Eliava Institute, 1923, active to this day
- Produced phages for antibacterial therapy during WWII
- Introduction of antimicrobial drugs in 1930s and later dampened enthusiasm for phage therapy
- Emergence of widespread resistance to antimicrobial drugs has revitalized interest in use of phages to treat bacterial infections

Principles of phage therapy

- Use of lytic bacteriophages to kill *specific* bacterial host (not beneficial flora)
- Pathogenic bacterium must be identified, and phage sensitivities determined before treatment



- Use of phage lysins for surface decontamination
- AgriPhage: approved by EPA 2005 to field treat bacterial tomato canker
- ListShield: Listeria phage approved by FDA for contamination of meat and poultry; first designation of GRAS

Phage therapy: clinical successes

CASE STUDY

Evolution, Medicine, and Public Health [2018] pp. 60–66
doi:10.1093/emph/eoy005

EVOLUTION, MEDICINE, & PUBLIC HEALTH

Phage treatment of an aortic graft infected with *Pseudomonas aeruginosa*

Benjamin K. Chan,[1] Paul E. Turner,[*,1,2] Samuel Kim,[3] Hamid R. Mojibian,[4]
John A. Elefteriades[5] and Deepak Narayan[3]

TWiEVO 44: The enemy of my enemy is my phage

BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-019-0437-z
nature medicine

Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*

Rebekah M. Dedrick[1,4], Carlos A. Guerrero-Bustamante[1,4], Rebecca A. Garlena[1], Daniel A. Russell[1], Katrina Ford[2], Kathryn Harris[2], Kimberly C. Gilmour[2], James Soothill[2], Deborah Jacobs-Sera[1], Robert T. Schooley[3], Graham F. Hatfull[1*] and Helen Spencer[2*]

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection

Robert T. Schooley,[a] Biswajit Biswas,[b,c] Jason J. Gill,[d,e] Adriana Hernandez-Morales,[f] Jacob Lancaster,[e] Lauren Lessor,[e] Jeremy J. Barr,[g,o] Sharon L. Reed,[a,h] Forest Rohwer,[g] Sean Benler,[g] Anca M. Segall,[g] Randy Taplitz,[a] Davey M. Smith,[a] Kim Kerr,[a] Monika Kumaraswamy,[a] Victor Nizet,[i,j] Leo Lin,[i] Melanie D. McCauley,[a] Steffanie A. Strathdee,[a] Constance A. Benson,[a] Robert K. Pope,[k] Brian M. Leroux,[k] Andrew C. Picel,[l] Alfred J. Mateczun,[b] Katherine E. Cilwa,[n] James M. Regeimbal,[b] Luis A. Estrella,[b] David M. Wolfe,[b] Matthew S. Henry,[b,c] Javier Quinones,[b,c] Scott Salka,[m] Kimberly A. Bishop-Lilly,[b,c] Ry Young,[e,f] Theron Hamilton[b]

TWiV 502: Texas road phage

But…

nature medicine

BRIEF COMMUNICATION

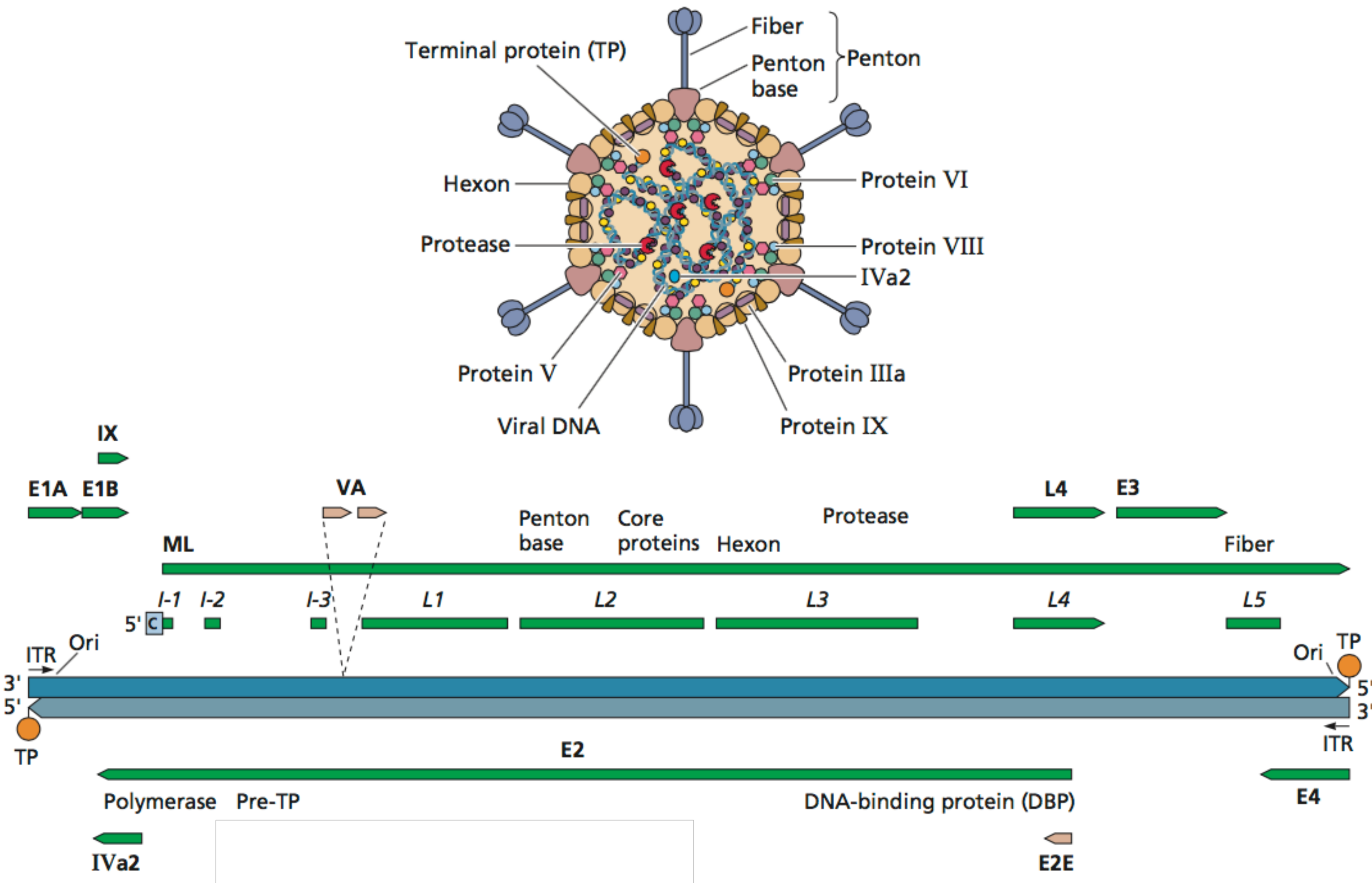
https://doi.org/10.1038/s41591-021-01403-9

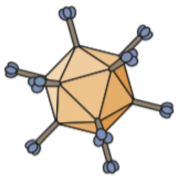
Check for updates

Potent antibody-mediated neutralization limits bacteriophage treatment of a pulmonary *Mycobacterium abscessus* infection

Rebekah M. Dedrick[1,6], Krista G. Freeman[1,6], Jan A. Nguyen[2,6], Asli Bahadirli-Talbott[2], Bailey E. Smith[1], Andrew E. Wu[2], Aaron S. Ong[2], Cheng Ting Lin[3], Lisa C. Ruppel[4], Nicole M. Parrish[5], Graham F. Hatfull[1] ✉ and Keira A. Cohen[2] ✉

Adenovirus vectors





Adenovirus vectors

- Efficiently infect post-mitotic cells
- Fast (48 h) onset of gene expression
- Episomal, minimal risk of insertion mutagenesis
- Up to 37 kb capacity
- Pure, concentrated preps routine
- >50 human serotypes, animal serotypes
- Drawback: immunity

Adenovirus vectors

- First generation vectors: E1, E3 deleted
- E1: encodes T antigens (Rb, p53)
- E3: not essential, immunomodulatory proteins

http://edoc.ub.uni-muenchen.de/13826/

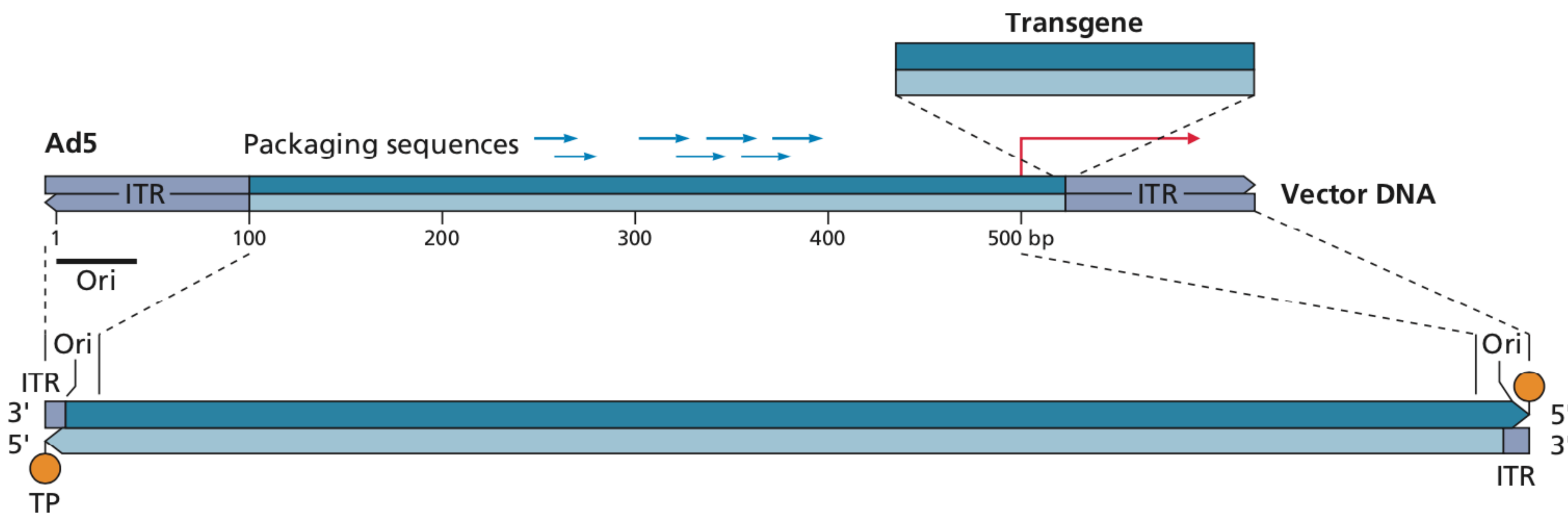
Adenovirus vectors

- Second generation vectors: E1, E3 deleted, plus deletions in E2 or E4
- More space for transgene

http://edoc.ub.uni-muenchen.de/13826/

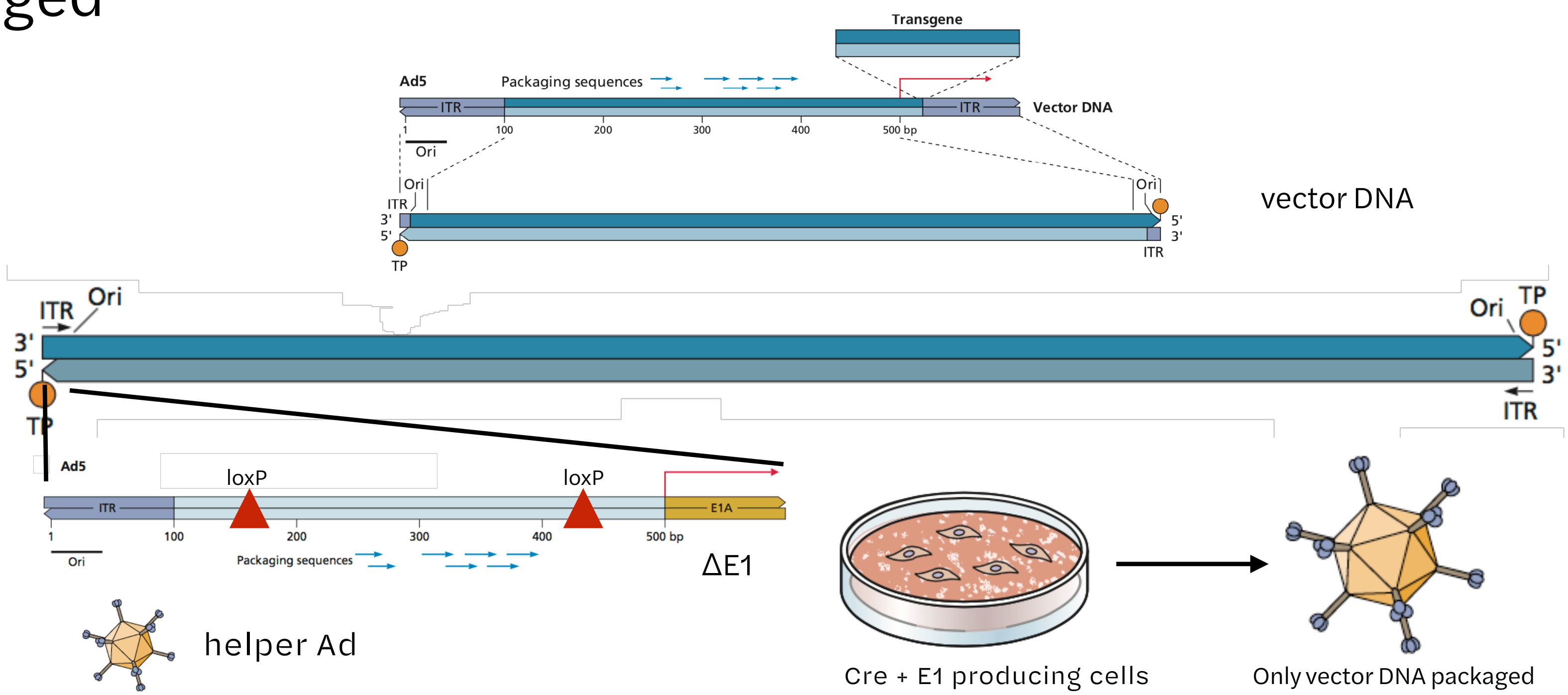
Adenovirus vectors

- Third generation 'gutless' vectors: all genes deleted, contain only two ITRs and *psi*
- Require helper virus, which is E1-deleted

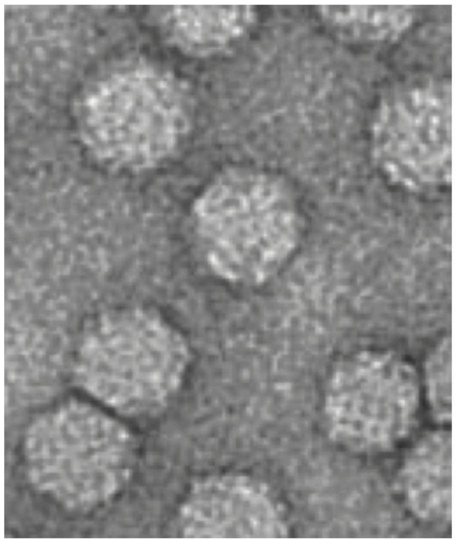


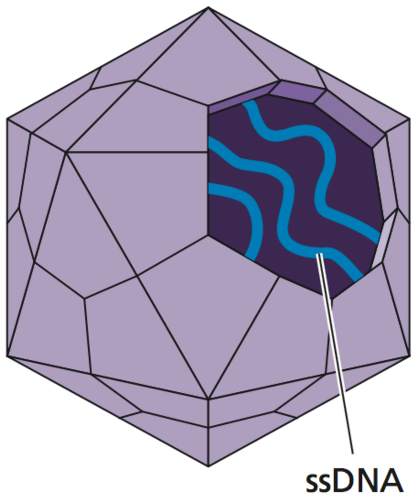
Adenovirus vectors

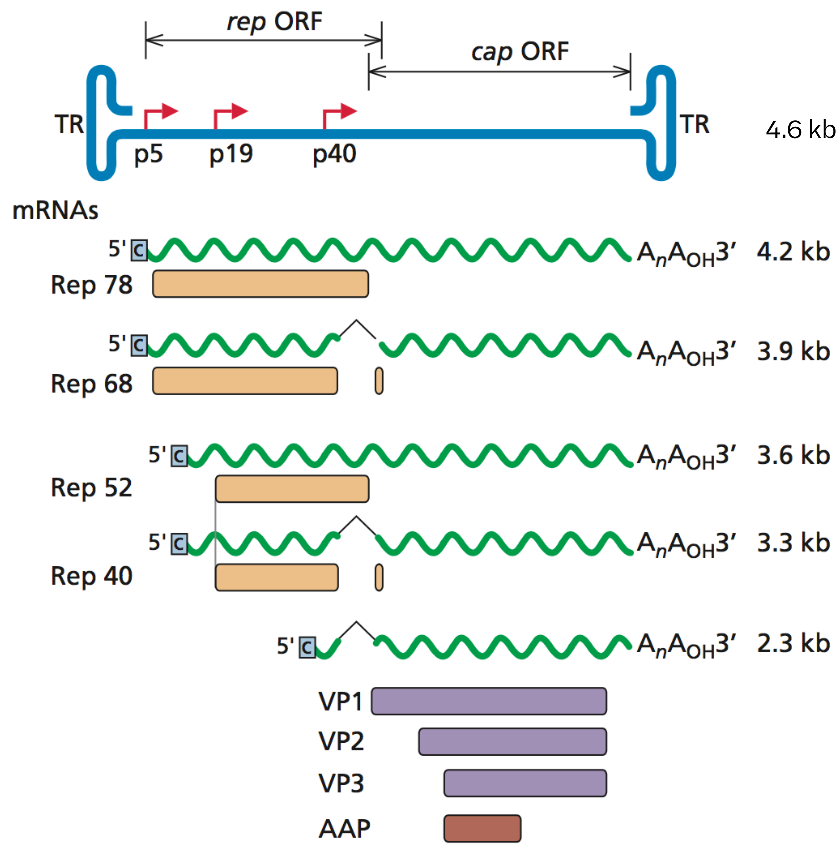
- Helper Ad has loxP flanking *psi*
- Propagation in Cre producing cells yields helper that cannot be packaged



Adenovirus-associated virus vectors

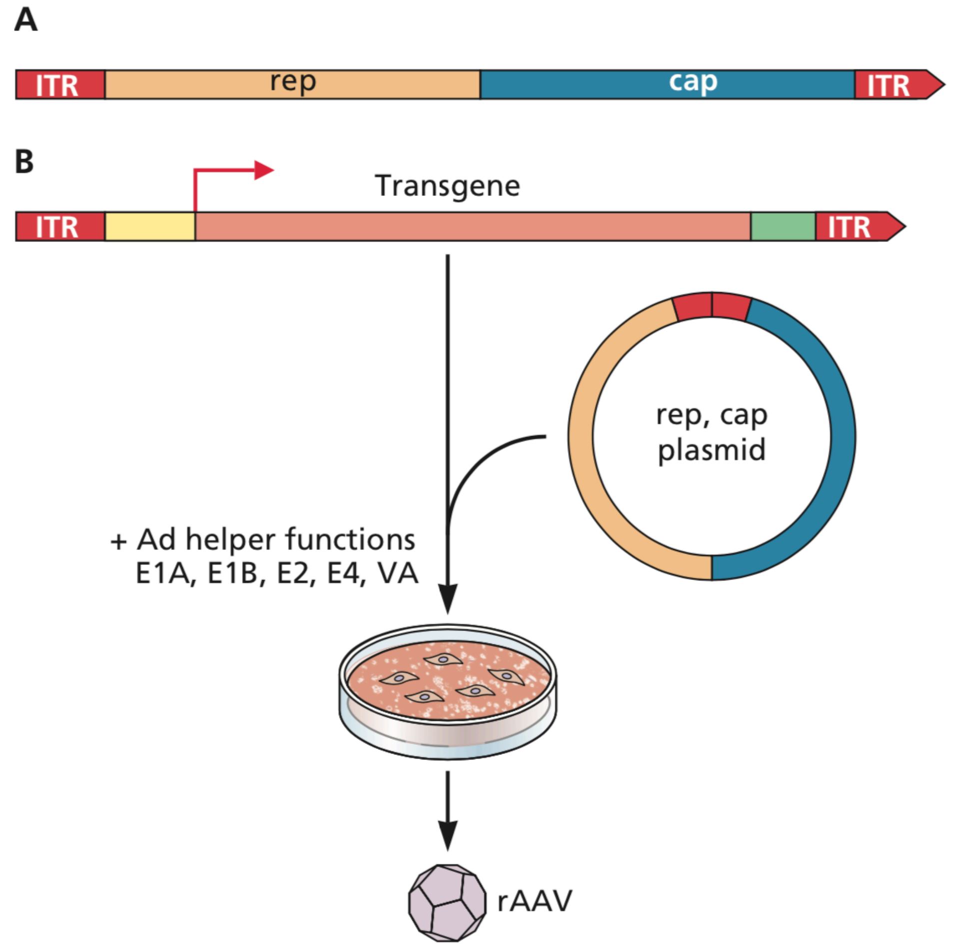


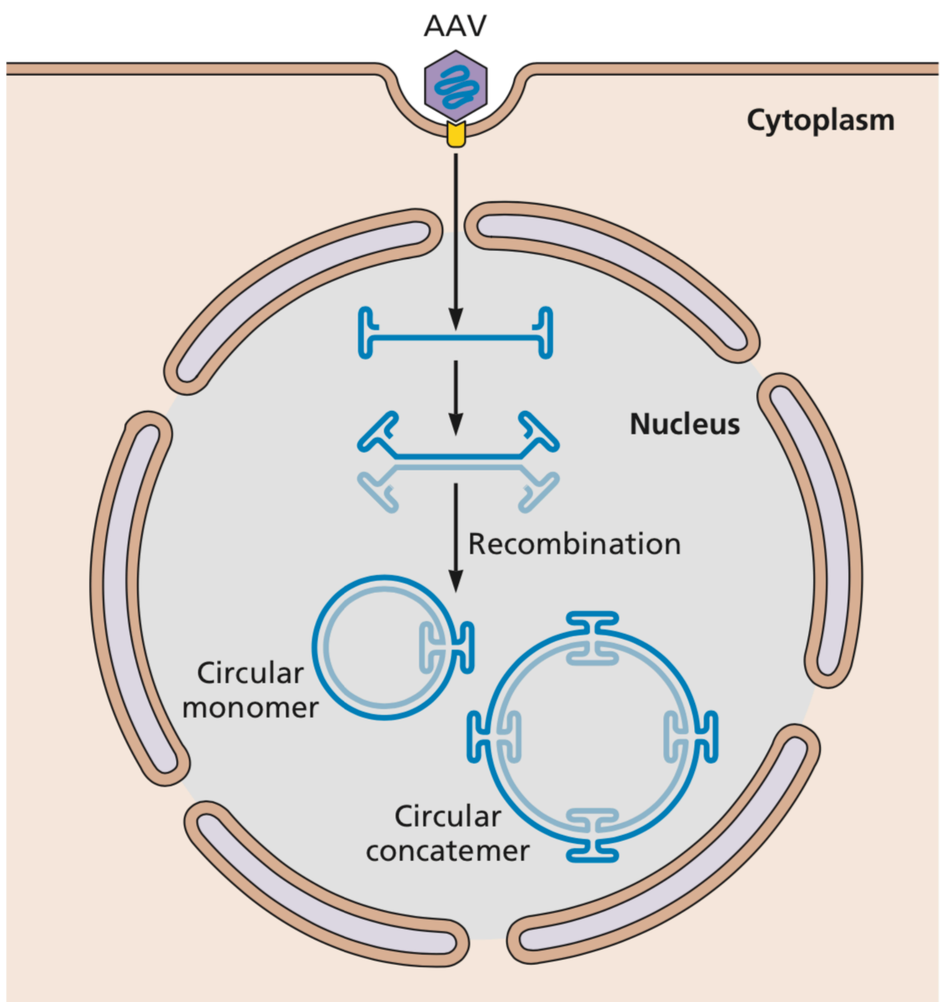




Adenovirus-associated virus vectors

- Long-term gene expression
- Multiple serotypes




AAV
Cytoplasm
Nucleus
Recombination
Circular
monomer
Circular
concatemer

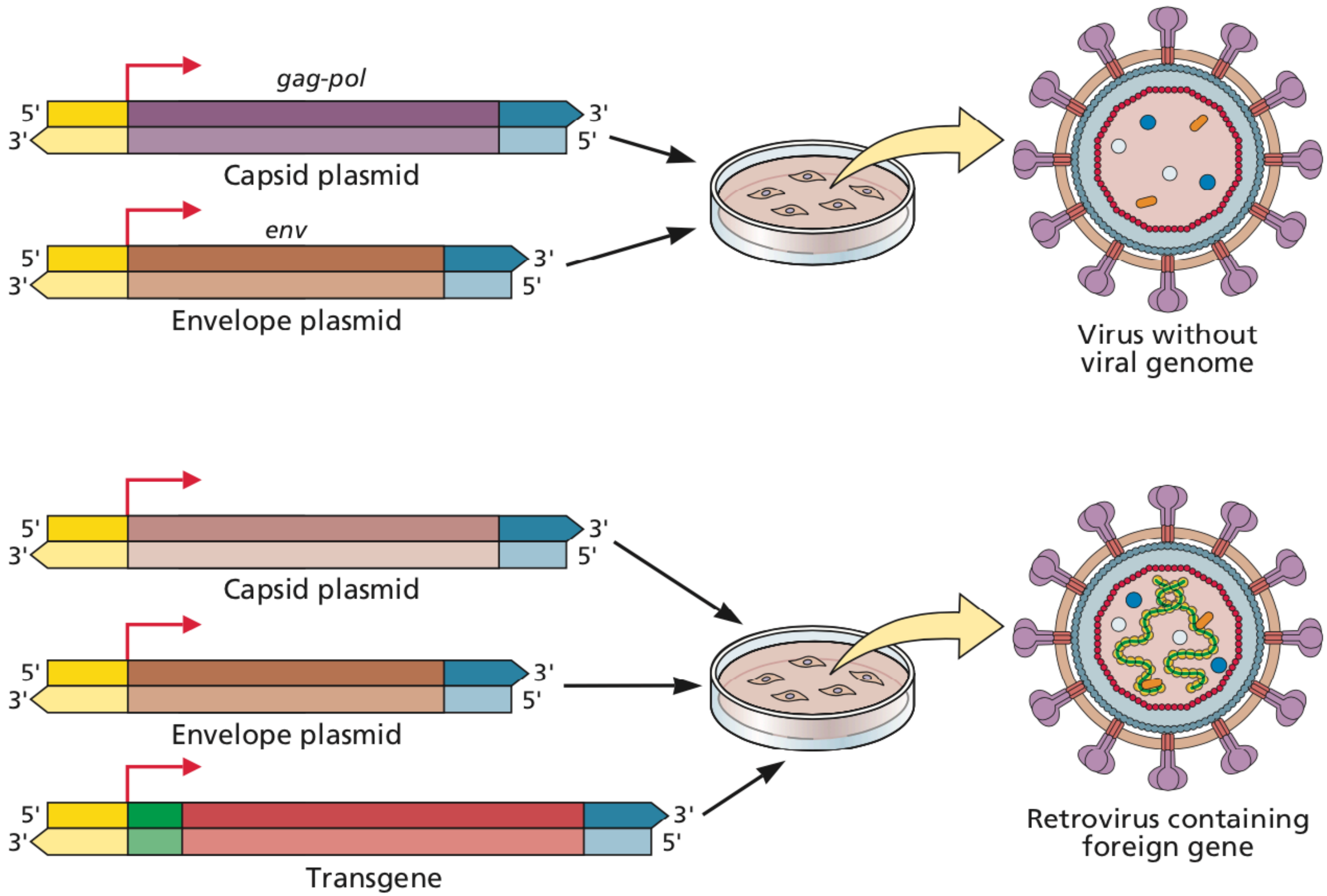
Go to:

b.socrative.com/login/student
room number: virus

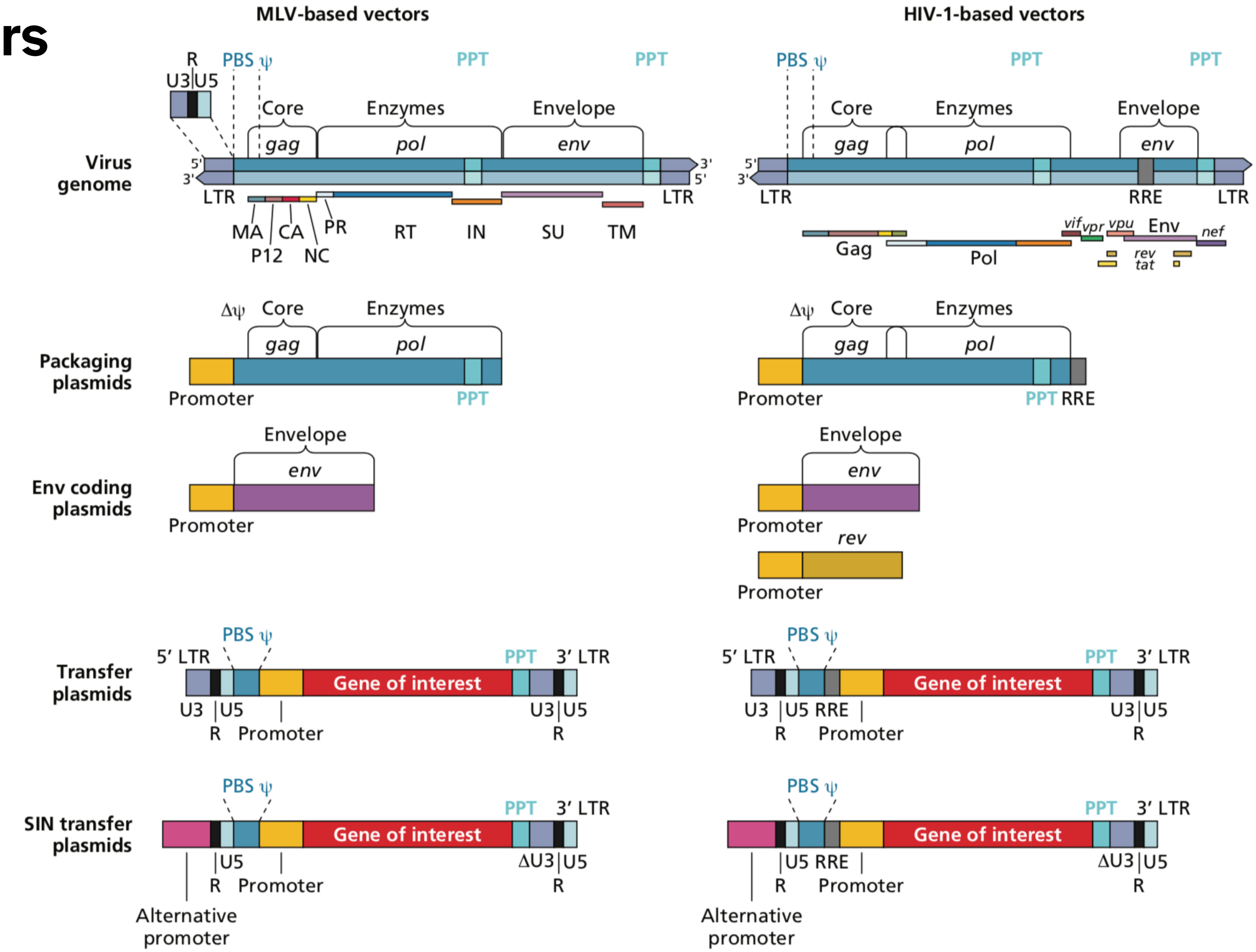
Which technology is indispensable for the production of therapeutic viruses?

A. X-ray crystallography
B. High-throughput genome sequencing
C. Synthesis of infectious DNA copies of viral genomes
D. Plaque assay
E. Immunofluorescence

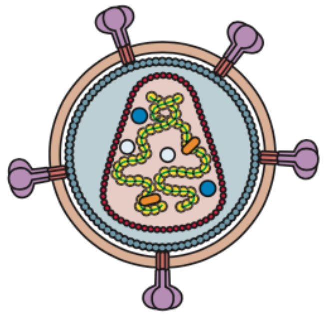
Retrovirus vectors



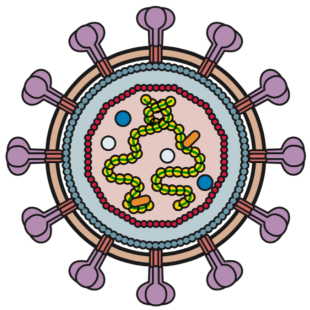
Retrovirus vectors



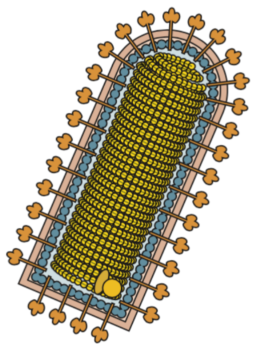
Retrovirus vectors



- Based on lentiviruses (HIV-1) or other retroviruses
- HIV can infect non-dividing cells

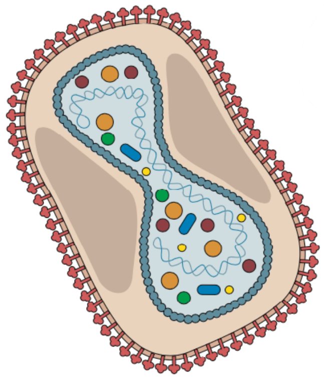


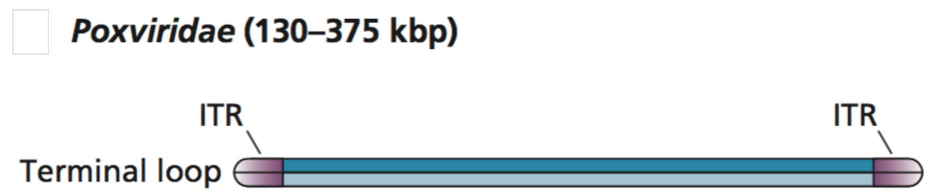
- Long-term expression (provirus)
- Up to ~8 kb transgene inserts
- Possibility for insertional mutagenesis (3'LTR inactivated or integration-deficient)



- Pseudotyping with VSV G

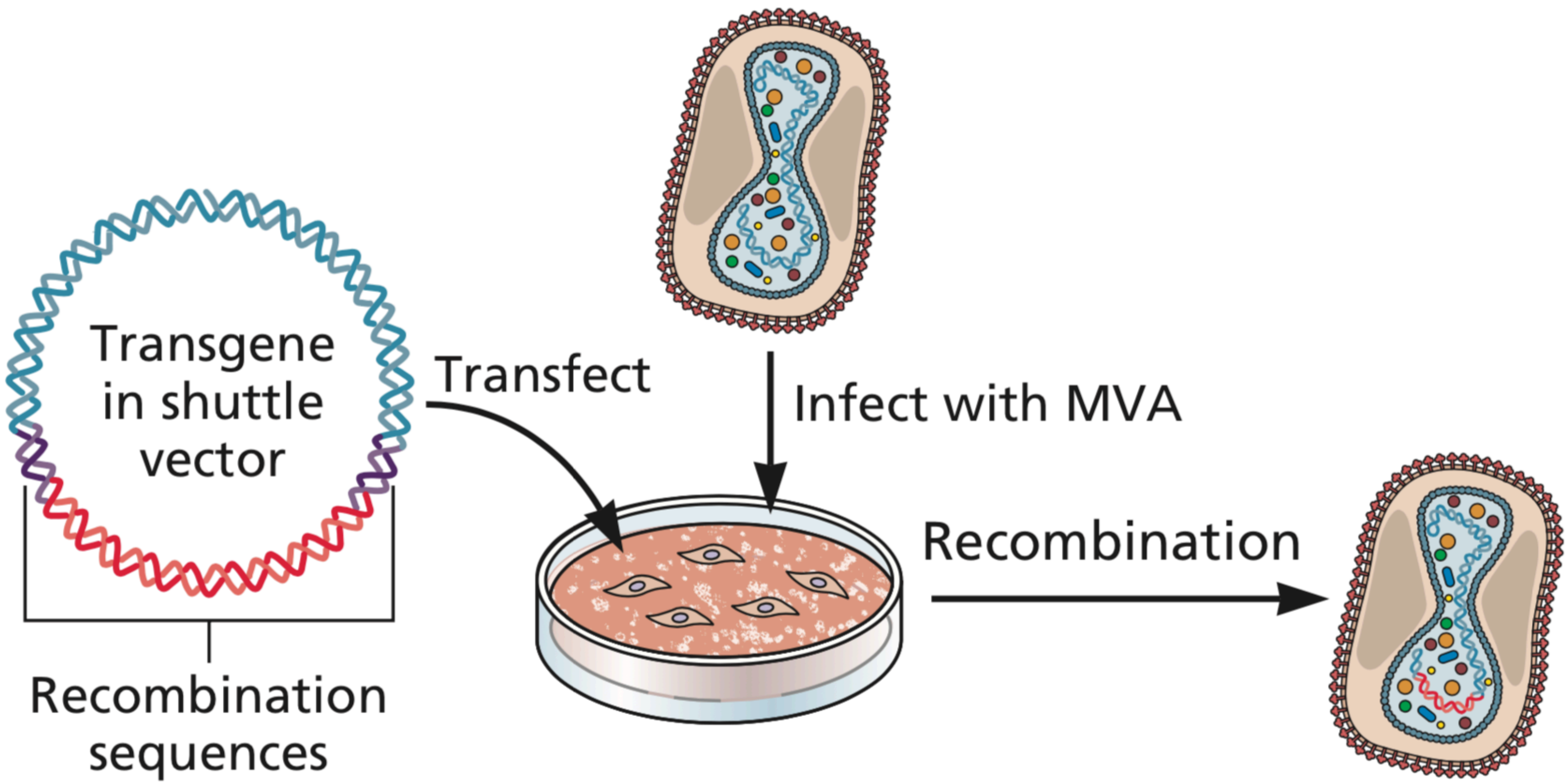
Poxvirus vectors



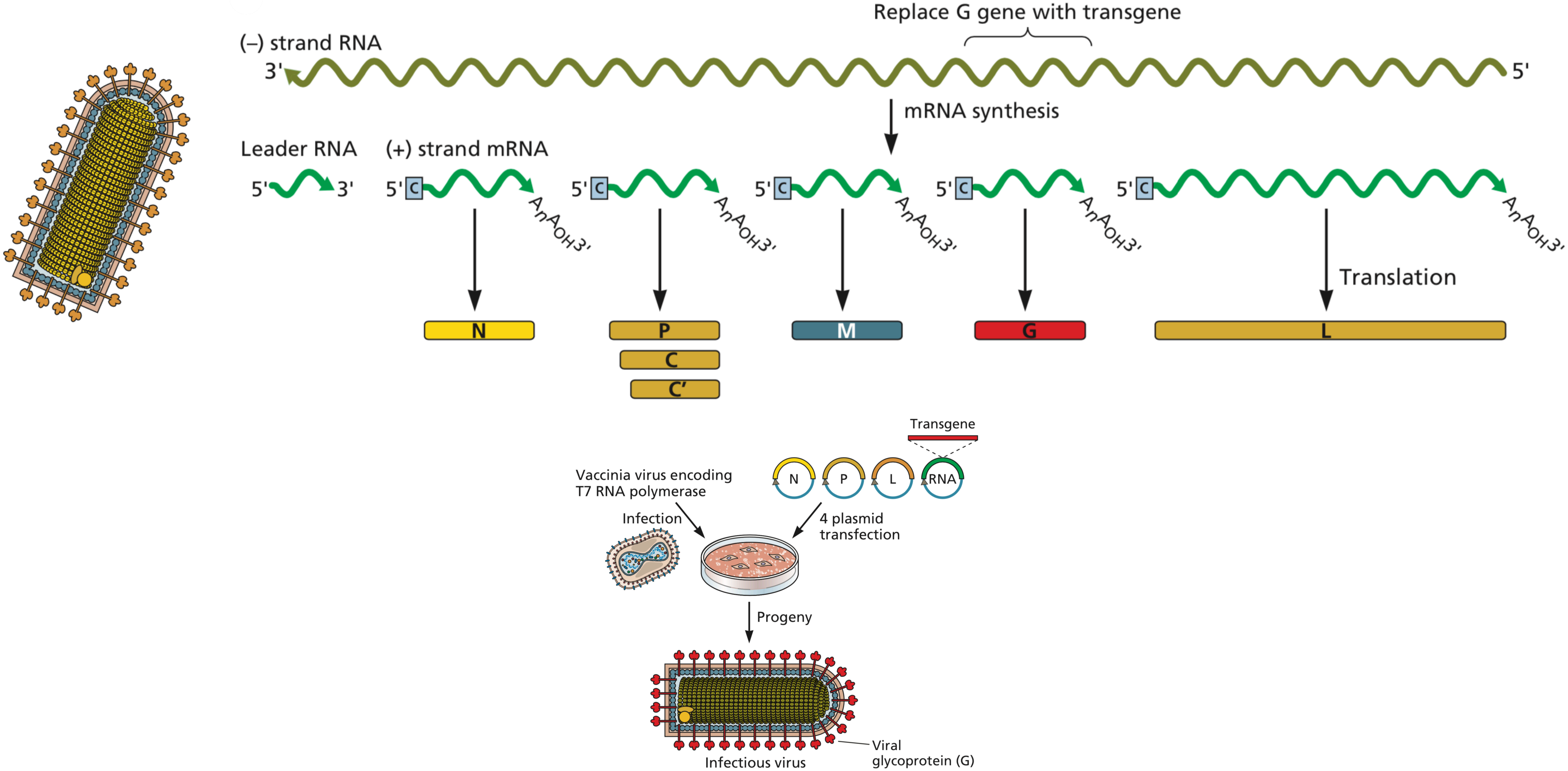


- Modified vaccinia virus Ankara, originally produced as alternative smallpox vaccine, part of US Strategic National Stockpile
- Replication-deficient vector: infectious in avian but not mammalian cells (passaged in chicken cells, assembly block)
- BSL-1
- Large capacity
- Also canary poxvirus

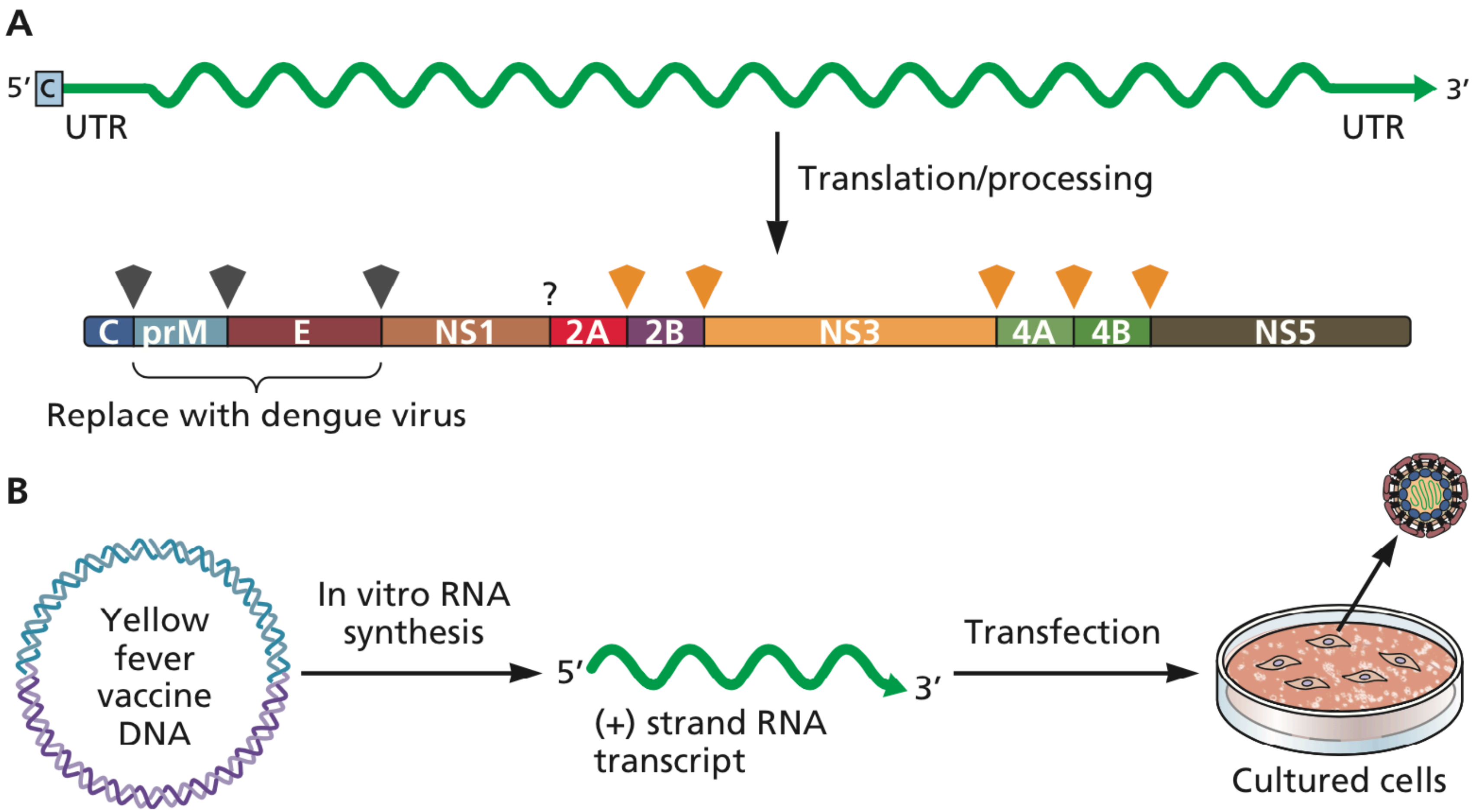
Modified vaccinia virus Ankara (MVA)



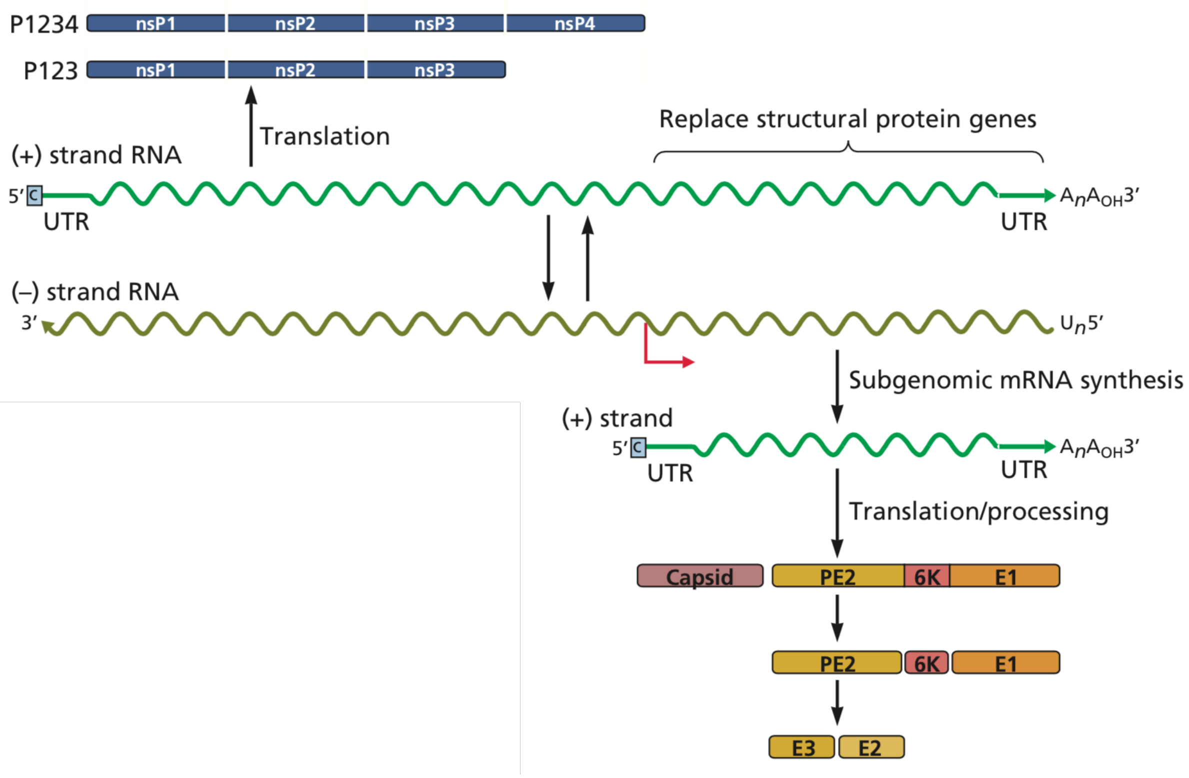
Vesicular stomatitis virus vector

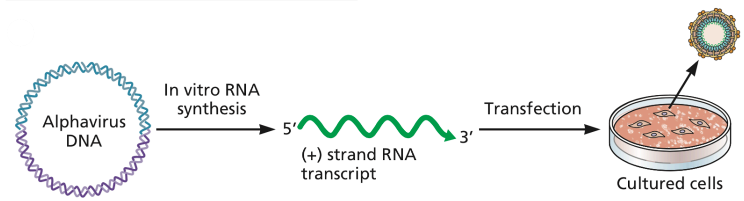


Flavivirus vectors

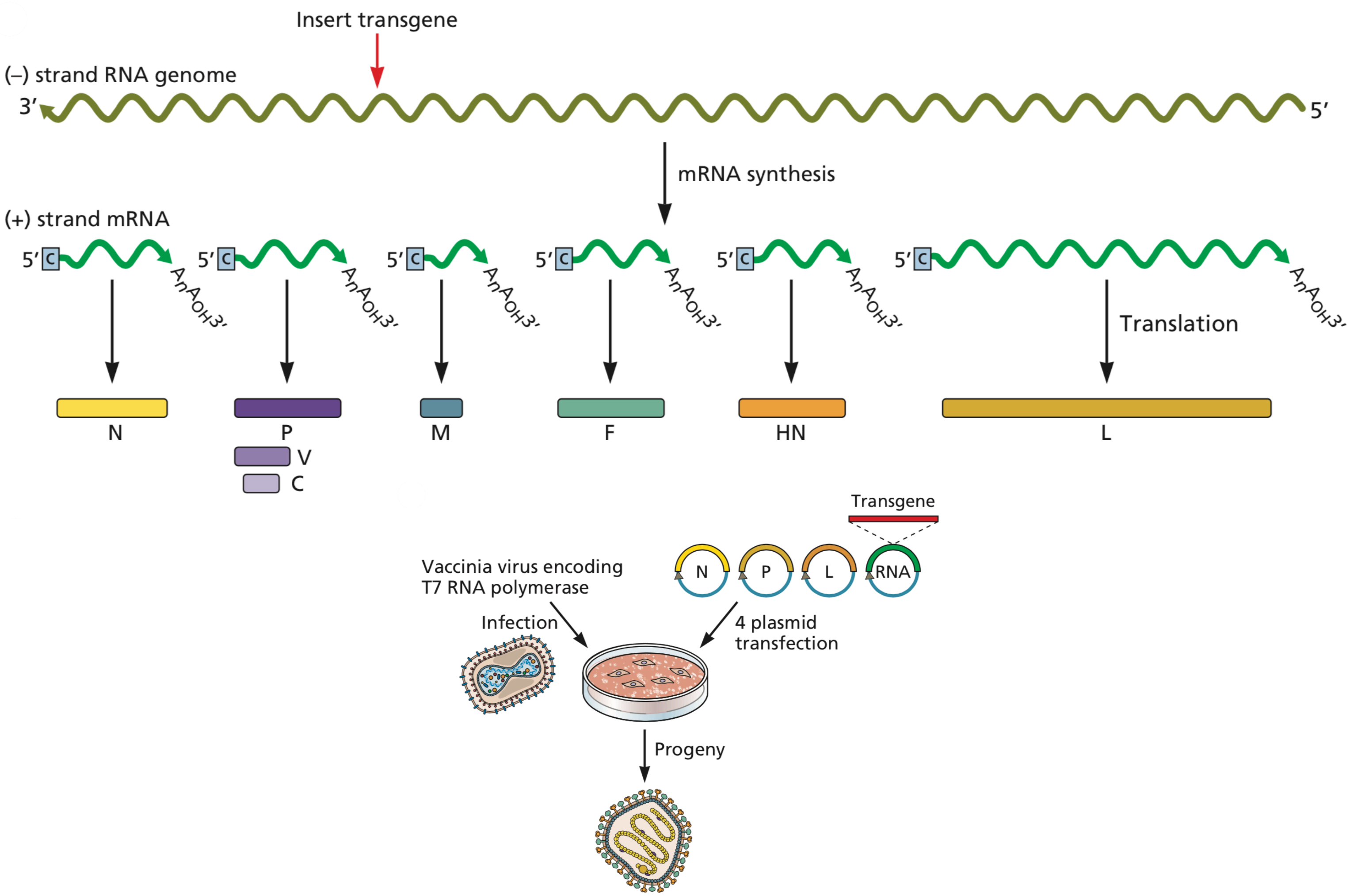


Alphavirus vectors





Newcastle disease virus vectors



Licensed vaccines that use viral vectors

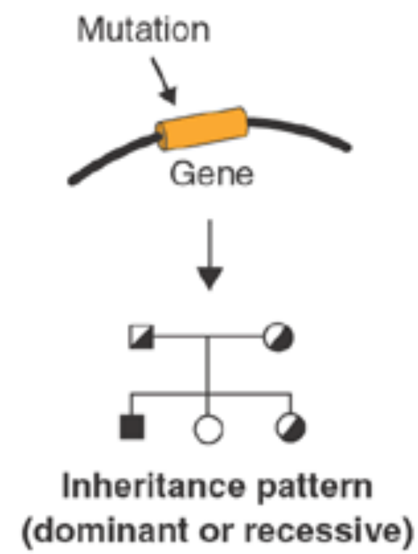
- Ervebo - glycoprotein coding region from *Zaire ebolavirus* in VSV vector
- Dengvaxia - prME coding region of 4 dengue virus serotypes in yellow fever vaccine vector
- Yellow fever vaccine vector: Japanese encephalitis virus (human), West Nile virus (horses)
- Newcastle disease virus vector: H5 avian influenza virus (chickens)
- Adenovirus 26 vector: Janssen COVID-19 vaccine (EUA)
- ChAdOx1 vector: AstraZeneca Vaxzevria (EUA in the EU)
- Sputnik: Ad5, Ad26 vectors (Gamaleya)

Some experimental human vaccines that use virus vectors

- Adenovirus type 5/HIV-1 *gag*, *pol*, *nef* genes
- Ad26.Zebov - Ebolavirus glycoprotein gene
- MVA - influenza H5 influenza virus
- MVA - HIV-1 env; canarypox RV144 AIDS trial
- MVA - MERS-CoV (camels)
- AAV - HSV, HPV, HIV-1, SARS-CoV
- VSV - MERS-CoV
- All platforms for SARS-CoV-2

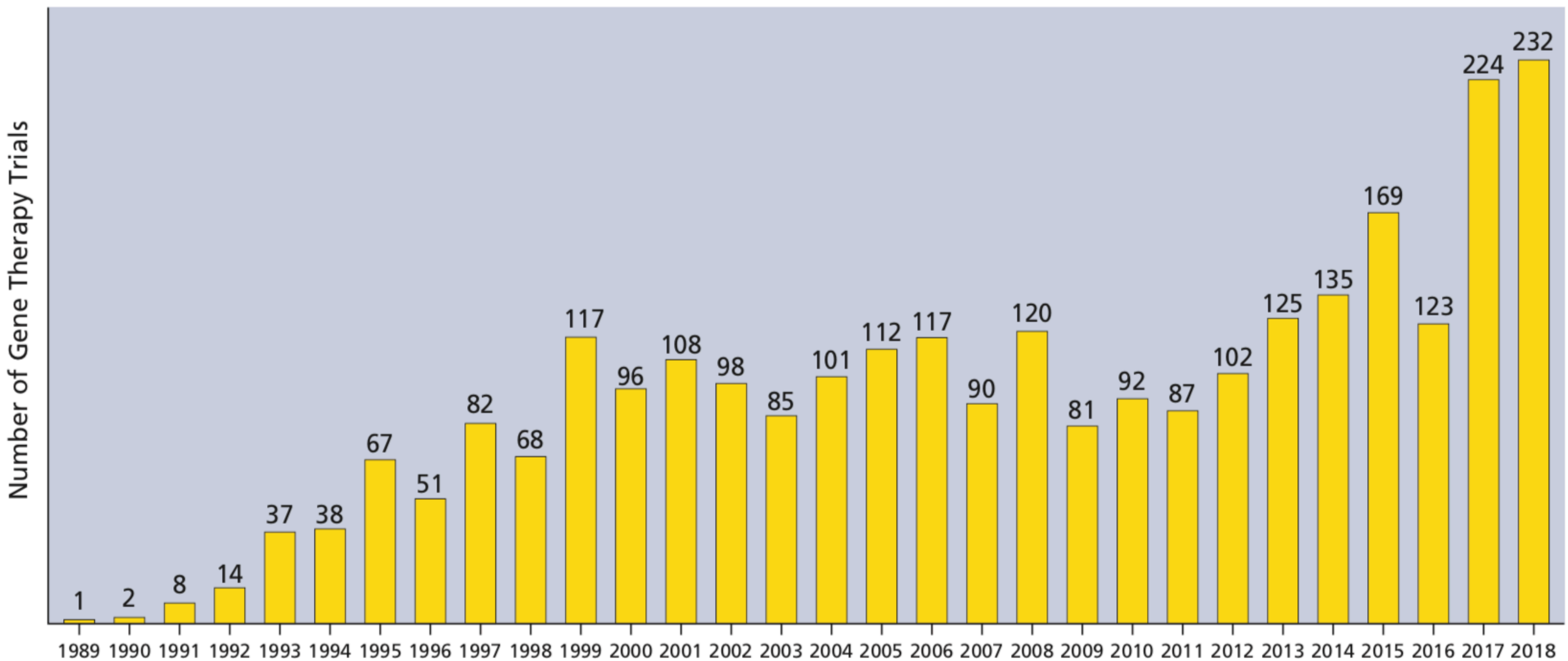
Gene therapy for monogenic diseases

- Caused by mutation in one gene
- >6,000, 1 out of 200 live births
- Amenable to viral gene therapy
- >1,800 clinical trials

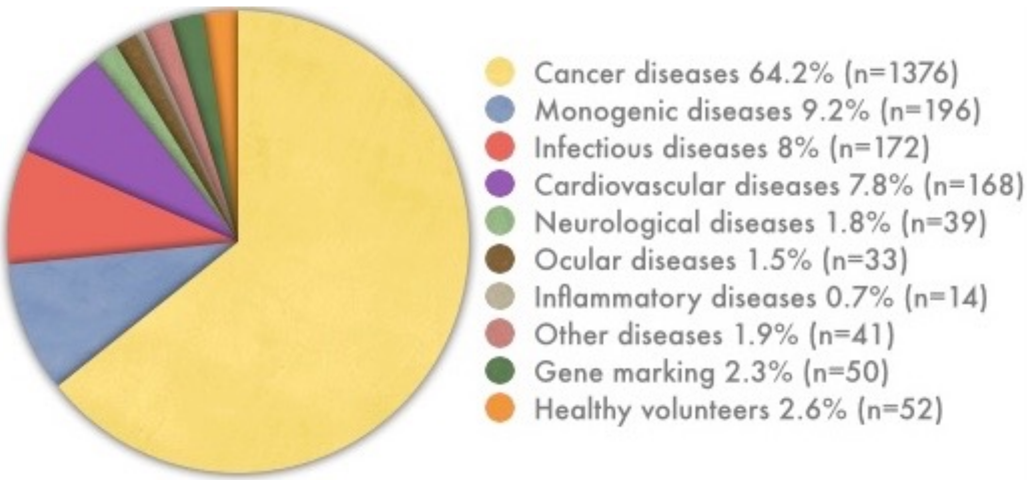


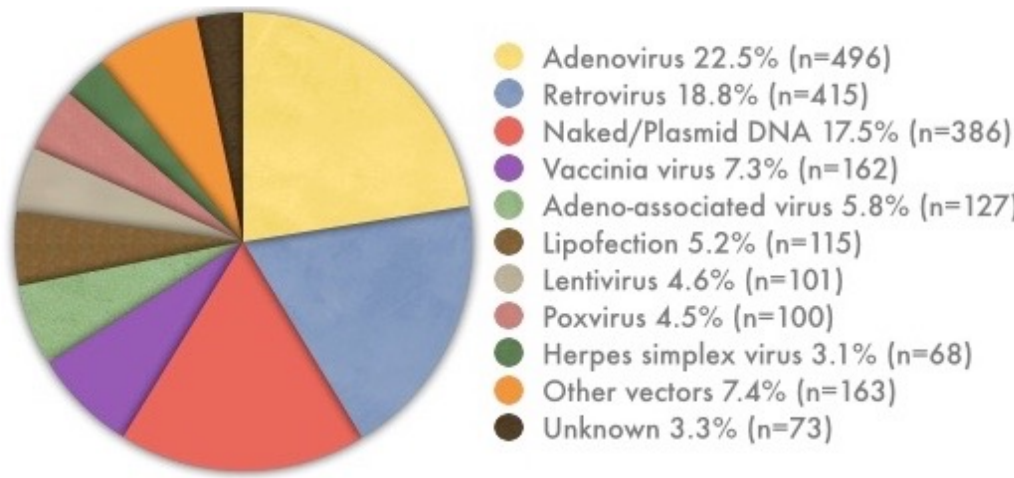
Disease	Defect	Incidence	Vector
Severe combined immunodeficiency	Adenosine deaminase (25%) Common cytokine receptor ɣ chain	<1 in 10^5 1 in 50-100,000	Retrovirus
Liproprotein lipase deficiency	Lipoprotein lipase	1-2 in 10^6	AAV
Hemophilia B	Factor IX defiency	1 in 30,000 males	AAV
Hemoglobinopathies and thalassemias	Defects in α- or β- globin gene	1 in 600 in specific ethnic groups	Lentivirus
α1-antitrypsin deficiency (emphysema, liver disease)	α1-antitrypsin not produced	1 in 3,500	AAV
Retinal degenerative disease, Leber's congenital amaurosis	Retinal pigment epithelium-specific 65 kDa protein	Inherited retinopathies (1 in 2000) $<10\%$ LCA (1 in 80,000)	AAV
X-linked adrenoleukodystrophy	ABCD1 transporter	1 in 20-50,000	Lentivirus
Wiskott-Aldrich syndrome (eczema-thrombocytopenia-immunodeficiency syndrome)	Was protein	1-10 in 10^6 males	Lentivirus

Clinical trials for gene therapy, 1989-2018

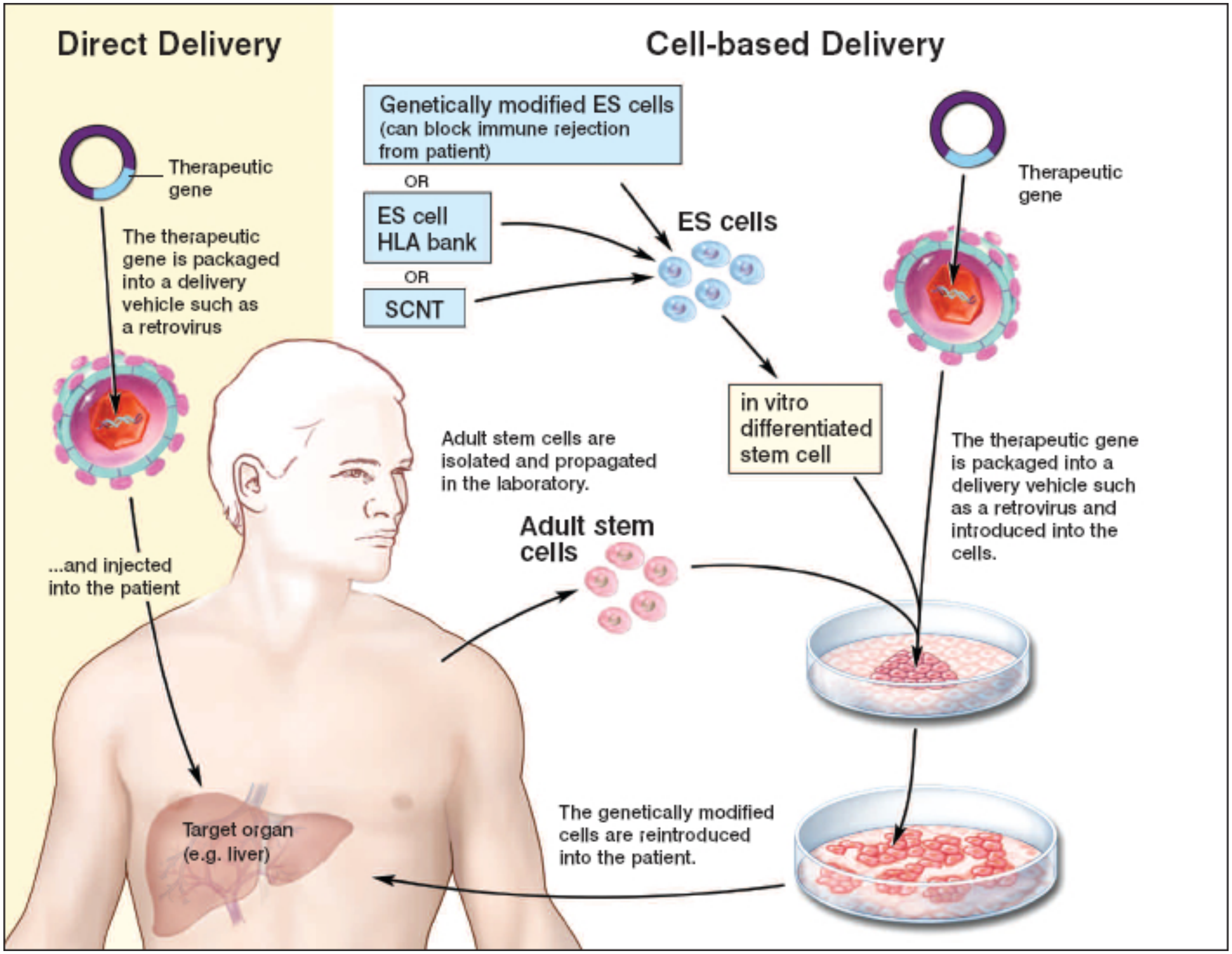


Indications addressed by gene therapy clinical trials



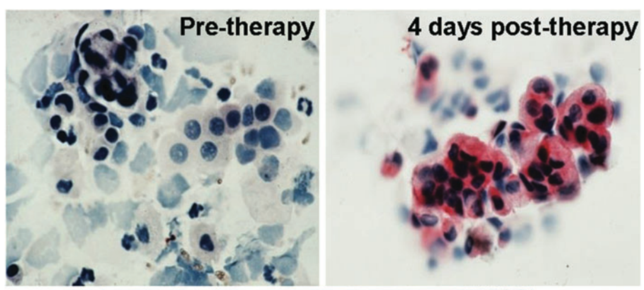


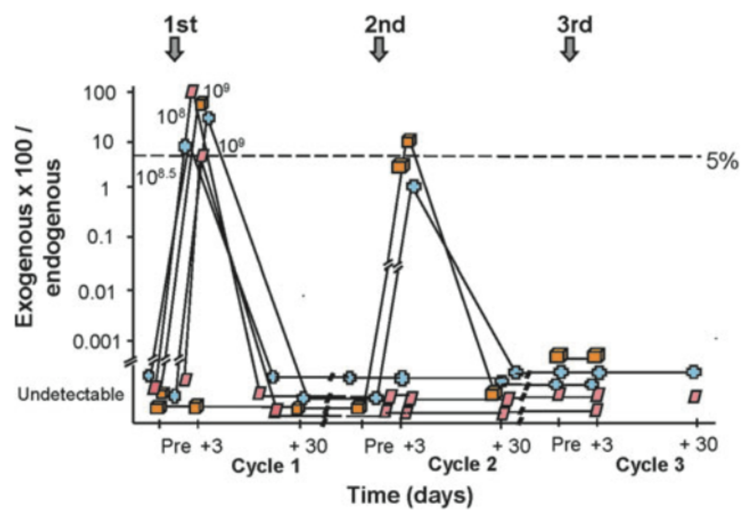
http://www.wiley.com/legacy/wileychi/genmed/clinical/


Direct Delivery
Cell-based Delivery
Therapeutic gene
The therapeutic gene is packaged into a delivery vehicle such as a retrovirus
...and injected into the patient
Target organ (e.g. liver)
Genetically modified ES cells (can block immune rejection from patient)
OR
ES cell HLA bank
OR
SCNT
ES cells
in vitro differentiated stem cell
Therapeutic gene
The therapeutic gene is packaged into a delivery vehicle such as a retrovirus and introduced into the cells.
Adult stem cells are isolated and propagated in the laboratory.
Adult stem cells
The genetically modified cells are reintroduced into the patient.

Early human viral gene therapy: 1993

- 23 year old male with cystic fibrosis, homozygous for ΔF508 mutation in *CFTR** gene
- 2×10^8 pfu $E1^-E3^-$ Ad with *CFTR* DNA administered to airway epithelium





*cystic fibrosis transmembrane conductance regulator

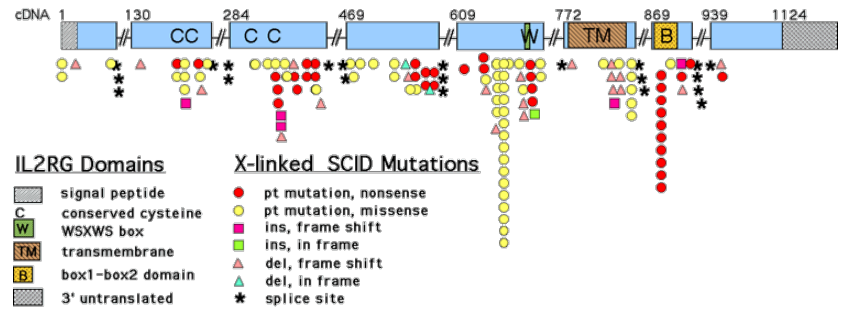
10.1089/hum.2013.2527

Setback: Jesse Gelsinger

- First person to die in a gene therapy clinical trial (1999)
- Ornithine transcarbamoylase deficiency - X linked disease that leads to accumulation of ammonia and glutamate in blood
- Patients with severe deficiencies have declining cognitive ability and premature death
- Given Ad vector with normal *OTC* gene at UPenn
- Died 4 days later: massive immune response, multiple organ failure
- Several rules of conduct broken

X-linked severe combined immune deficiency

- Immunodeficiency disorder, defect in T, B, NK cells



- Two trials, London and Paris, giving infants retrovirus with normal *IL2RG* gene (IL-2 receptor ɣ chain)

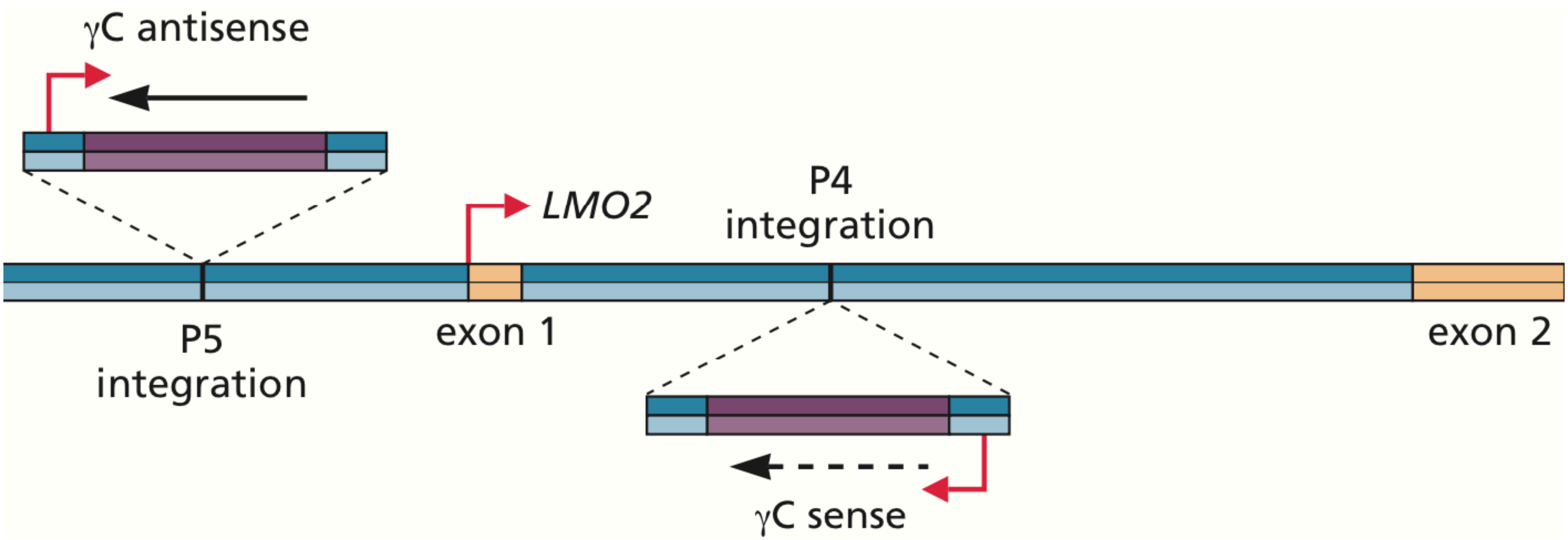
- CD34+ bone marrow hematopoietic precursor cells transduced with retrovirus vector, transplanted back into patients

- 4/9* infants in Paris, 1 in London developed T cell leukemia 3-6 years after treatment

- 27 trials with retroviral vectors halted

*treatment had worked

Inadvertent insertional activation of a cellular gene during gene transfer



The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Lentiviral Gene Therapy Combined with Low-Dose Busulfan in Infants with SCID-X1

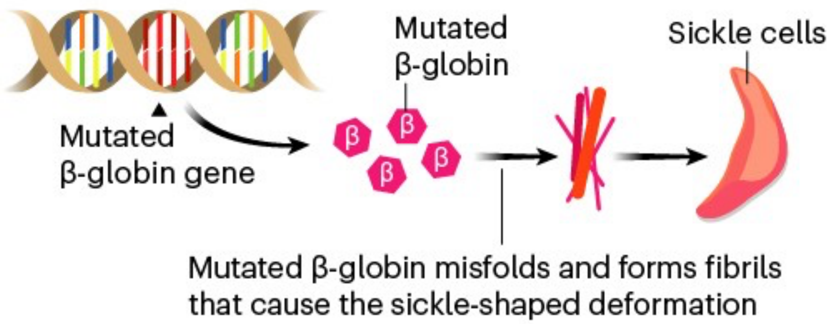
E. Mamcarz, S. Zhou, T. Lockey, H. Abdelsamed, S.J. Cross, G. Kang, Z. Ma, J. Condori, J. Dowdy, B. Triplett, C. Li, G. Maron, J.C. Aldave Becerra, J.A. Church, E. Dokmeci, J.T. Love, A.C. da Matta Ain, H. van der Watt, X. Tang, W. Janssen, B.Y. Ryu, S.S. De Ravin, M.J. Weiss, B. Youngblood, J.R. Long-Boyle, S. Gottschalk, M.M. Meagher, H.L. Malech, J.M. Puck, M.J. Cowan, and B.P. Sorrentino*

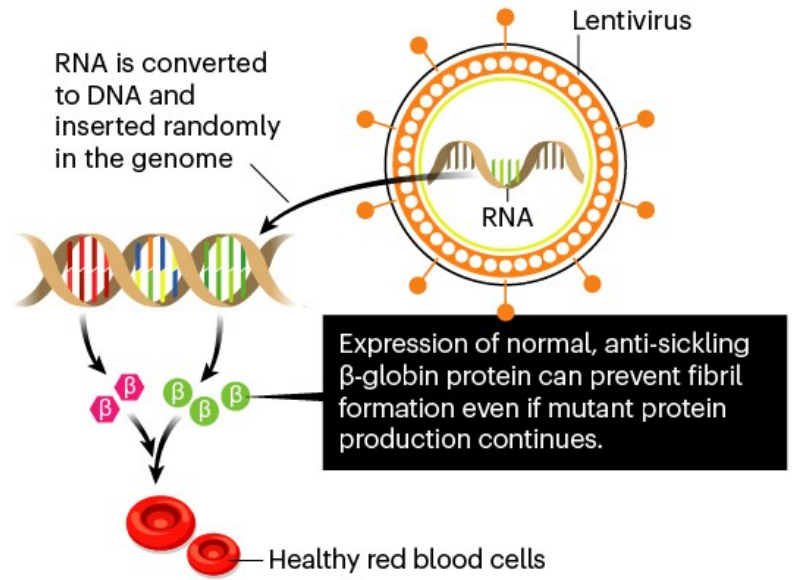
- Eight infants with SCID-X1 given bone marrow transplants with lentiviral *IL2RG* infected bone marrow stem cells

- After 18 months all had functional B and T cells

DOI: 10.1056/NEJMoa1815408

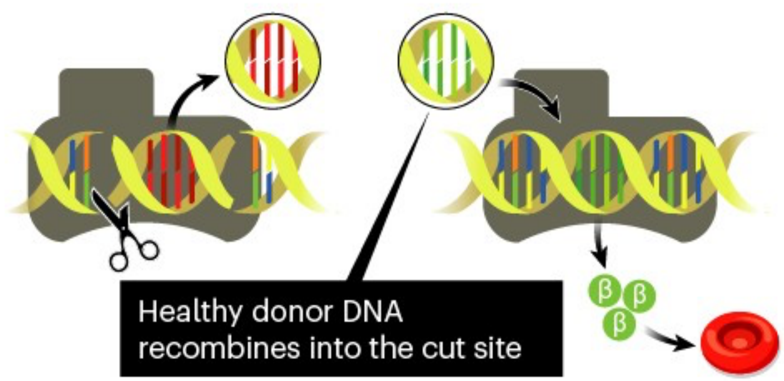
Sickle cell disease





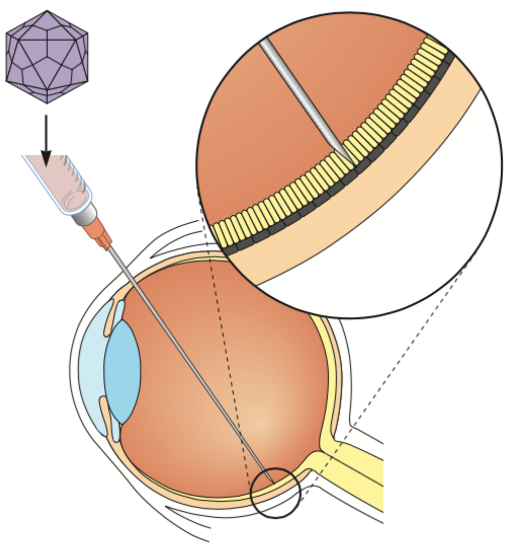
CRISPR/Cas9 mediated replacement

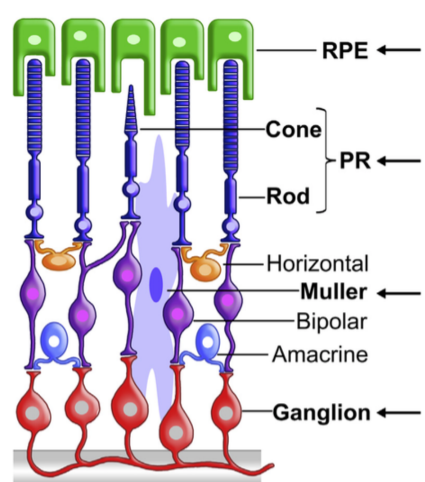
Delivered with viral vectors



Inherited retinopathies

- Common untreatable blinding conditions
- Monogenic, mutations in retinal photoreceptors and retinal pigment epithelium
- Many vectors tested in animal models, AAV most promising





AAV	LV	Ad
2/1[1,2] 2/4[2,3] 2/6[4] *2/7m8[5] **2/Tyr mutant[6,7]	HIV-1-VSVG[1,17,18,19] HIV-1-Mokola[1,18] HIV-1-RRV[21] HIV-1-GP64[22] FIV-VSVG[23] SIV-VSVG[25,26,27,43] EIAV-VSVG[30,31,32] BIV-VSVG[28,29]	5[33,34,35,42] 2[22,38] 5/F35++[22] 5ΔRGD[37,41] 6[22] Ch30[22] Ch63[22] 5/F17[37] 5/F35[39]
2/5[1,8,9,10] 2/7[8,10] 2/8[8,10,11,12,13,14] 2/9[8] *2/7m8[5] **2/Tyr mutant[6,7]	HIV-1-VSVG[1,19,20] HIV-1-GP64[22] FIV-VSVG[24] EIAV-VSVG[31,32]	5[22,33,37,42] 5/F35[39] 5ΔRGD[37,41] *5/F37[40]
*2/2[1,10,15] *2/6[15] **2/8[8,10,14] **2/9[8,10] *2/ShH10[16] *2/7m8[5] **2/Tyr mutant[6,7]	HIV-1-VSVG[21] FIV-VSVG[23,24] EIAV-VSVG[31]	**5[22,33,36] 5/F37[41] 5/F17[37] 5/F35[39]
**2/2[1,10,15] *2/6[15] **2/8[10,14] *2/7m8[5] **2/Tyr mutant[6,7]	FIV-VSVG[23] EIAV-VSVG[31]	*5[40] 5ΔRGD[37]

Progress in Retinal and Eye Research 43 (2014) 108e128

Leber congenital amaurosis

- Mutations in *RPE65* gene, encodes protein required for photoreceptor function
- Dog model: single subretinal injection of AAV vector with canine RPE65 gene restores visual function
- TWiV 350: Viral gene therapy with Katherine High http://www.microbe.tv/twiv/twiv-350/
- FDA approved December 2017

FDA News Release

FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

Luxturna is the first gene therapy approved in the U.S. to target a disease caused by mutations in a specific gene

Some viral gene therapy trial successes

- Severe combined immunodeficiency
- Adenosine deaminase
- Leber congenital amaurosis (Luxturna - FDA approved - $895,000 for two eyes)
- Hemophilia
- beta-Thalassemia
- Lipoprotein lipase (fat metabolism disorder)
- AveXis - AAV9 carrying spinal motor neuron 1 gene, for biallelic spinal muscular atrophy ($2.125 million, most expensive drug ever)

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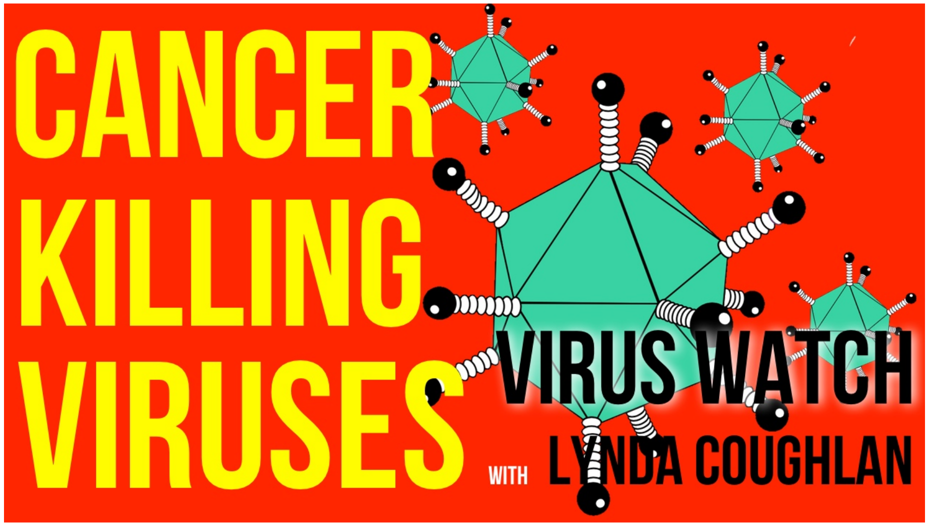
room number: virus

Which of these viral vectors are not likely to be compromised by immune memory in humans?

A. Newcastle disease virus
B. Vaccinia virus
C. Herpes simplex virus
D. Adenovirus

Viral oncotherapy

- Destroying tumors with viruses
- Some animal viruses selectively replicate in human tumors (myxoma, Seneca Valley virus)
- Modified viruses to target and kill tumors, often with immune enhancement



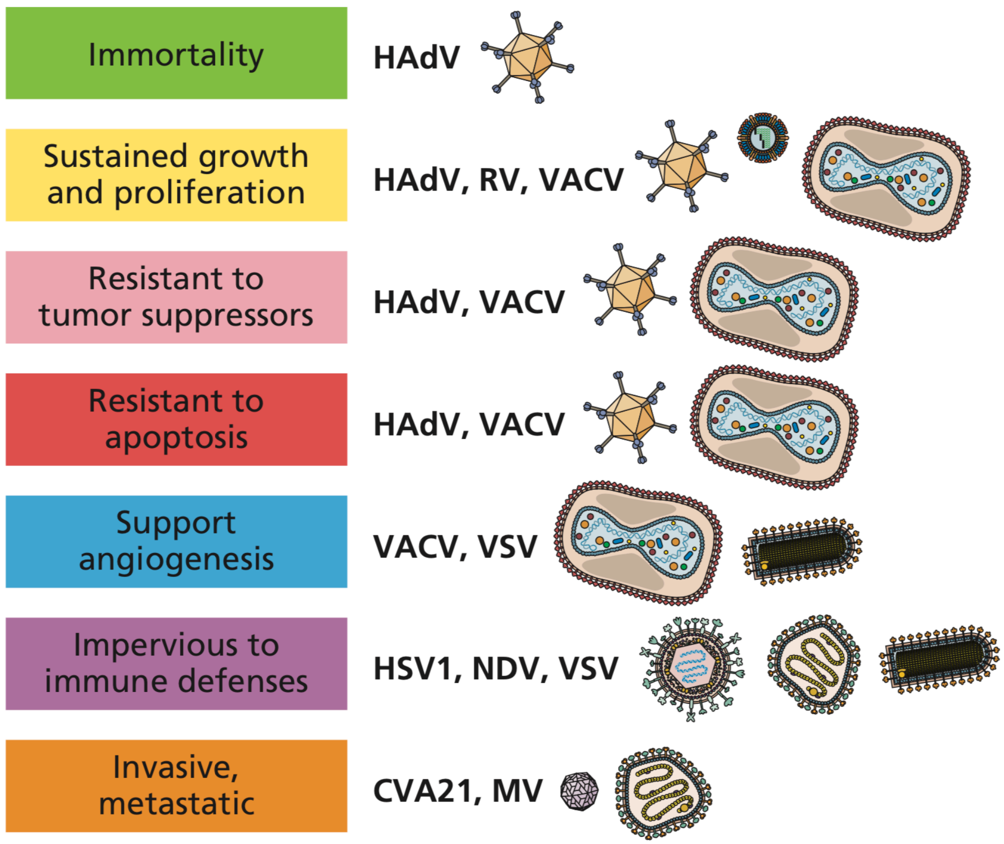
http://www.microbe.tv/viruswatch/cancer-killing-viruses/

Early studies of human viruses to treat cancers in humans before standardization of clinical trials

Year	Disease	Virus	No. of Patients	Outcomes
1949	Hodgkin's lymphoma	Hepatitis virus[a]	22	Hepatitis developed in 14; transient responses in 4; at least 1 treatment-related death
1952, 1954	Various advanced cancers	West Nile virus[b]	>100	>90% infected; transient responses in 10; mild to severe encephalitis in 10
1953	Acute leukemia	Epstein-Barr virus	5	3 infected and developed infectious mononucleosis; transient responses
1956	Cervical carcinoma	Human adenovirus	30	Transient tumor necrosis in 20

[a]Sera and/or tissue extracts from individuals with either infectious or serum hepatitis.
[b]An early isolate called Egypt 101 virus.

Properties of cancer cells that can facilitate reproduction of oncolytic viruses

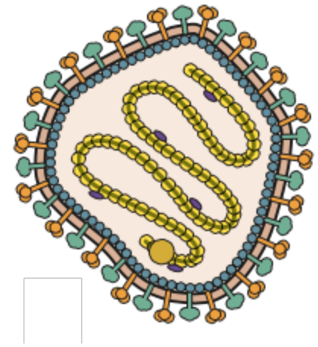


IFN defects are common in cancer cells

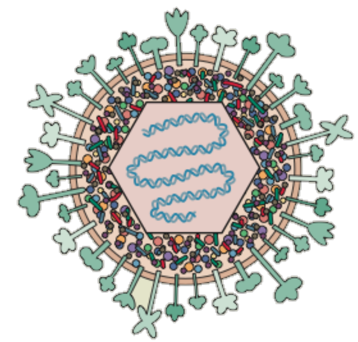
Mutations in viral genomes that impair countermeasures to the antiviral interferon defense[a]

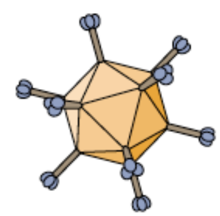
Virus	Gene mutated	Function eliminated
HAdV5	E1B 55 kDa (loss of expression)	Repression of ISG transcription
HSV-1	ICP345 (deletion)	Circumvention of effects of PKR activation
VACV (MVA)	B18 (deletion)	Sequestration of type 1 interferon
VSV	M (deletion, substitution at amino acid 51)	Repression of ISG expression

Tumor targeting

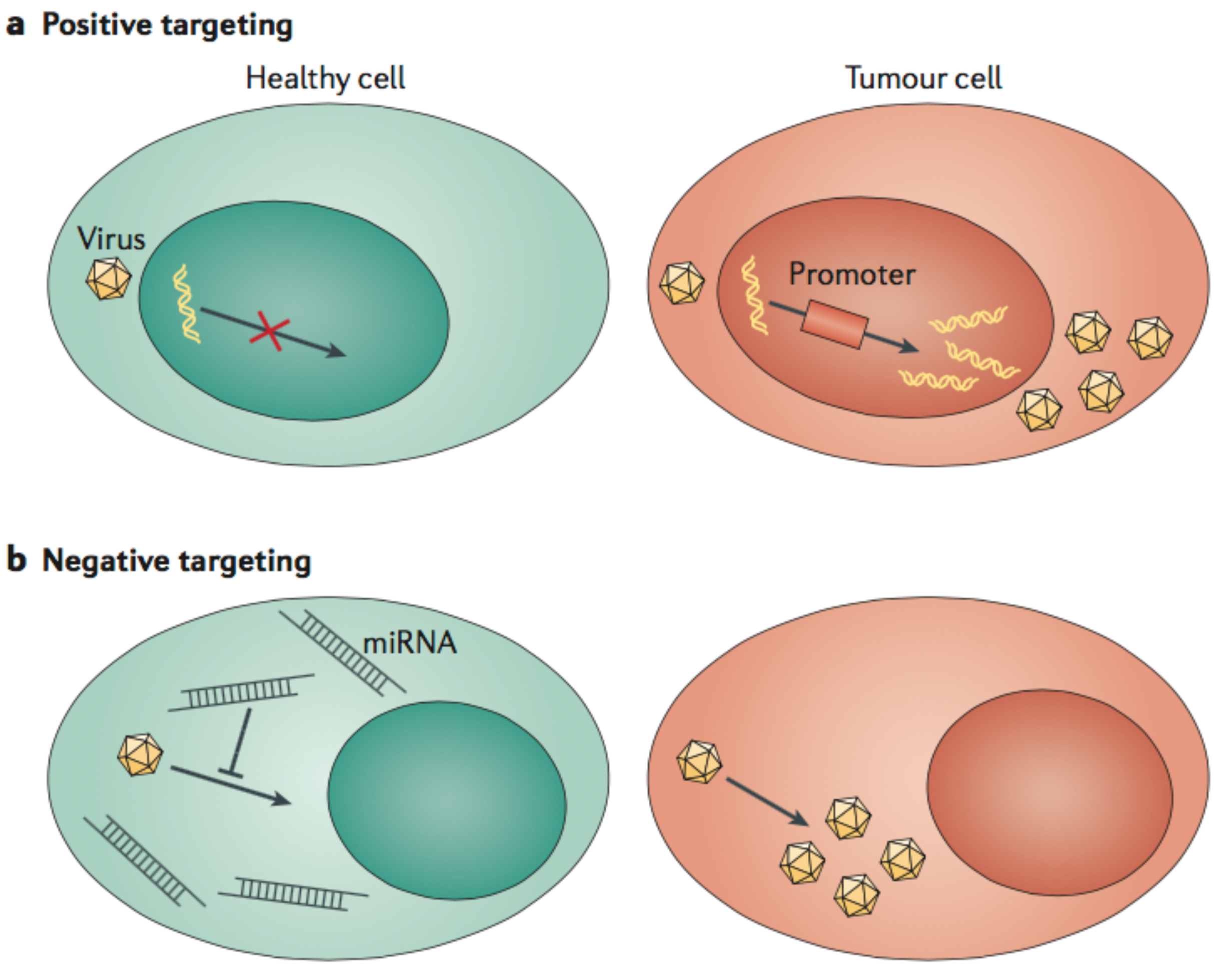


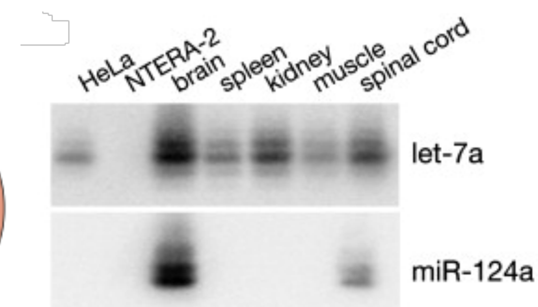
- Receptor targeting
  - Alter measles virus HA to target tumor markers (‘neoantigens’)
  - HSV glycoprotein D engineered to contain IL-13, or single chain antibodies against human epithelial growth factor receptor 2, on gliomas and breast tumors
  - Adenovirus: insertion of domains that recognize tumor Ag into fiber
  - Adaptors that bind fiber and retarget





Post-entry targeting

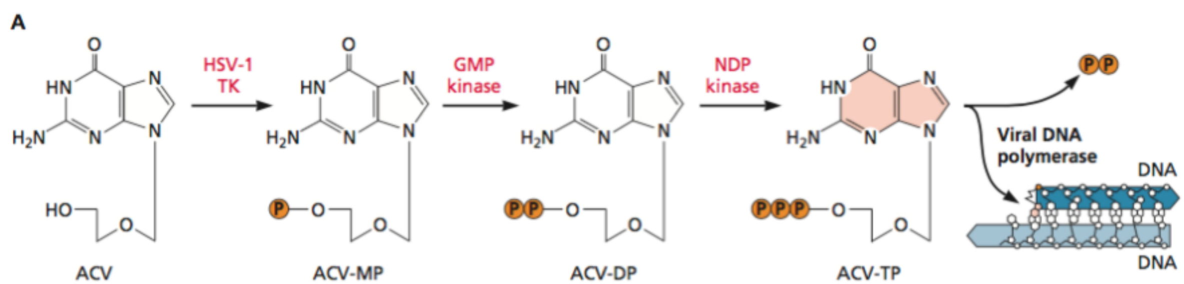


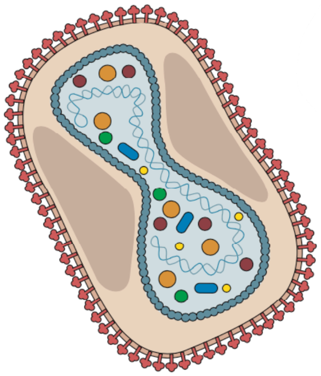


doi:10.1038/nrmicro3140

Arming viral vectors

- Enhance therapeutic efficacy of oncolytic virus: hard to infect 100% of cells
- Strategies that kill tumor cells surrounding those infected - bystander killing
- Prodrug convertases
- Ion transport protein
- Immunostimulatory factors

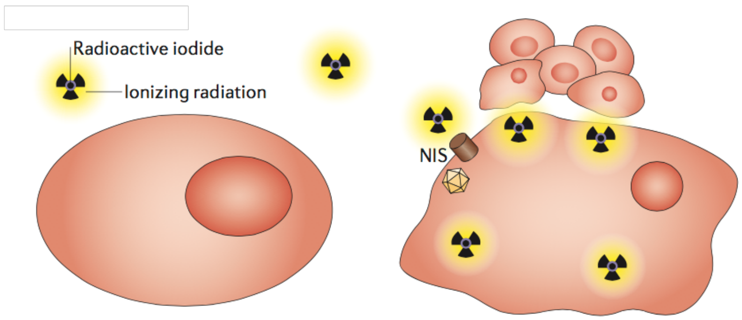




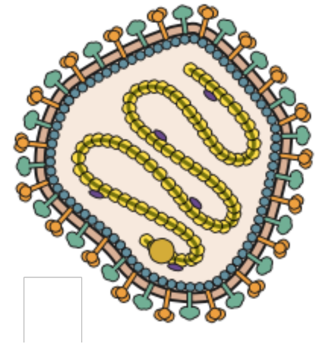
Myxoma virus

- Same virus introduced into Australia to kill European rabbits
- Does not replicate in any non-rabbit host
- Infects many types of human cancer cells
  - Failure of cells to induce anti-viral response
  - Activation of cell pathways related to transformation

Cancer	Animal model	Tumor establishment	MYXV Administration	Outcome
Acute myeloid leukemia	NSG	Human AML cells in bone marrow xenograft	*Ex vivo*	90% of mice free of human AML cells in BM
Multiple myeloma	NSG	Human MM cells in bone marrow xenograft	*Ex vivo*	100% of mice free of human MM cells in BM
Pancreatic cancer	NOD/SCID	Human pancreatic cancer cells in IP cavity	IP	Reduced tumor burden and prolonged survival
Pancreatic cancer	C57BL/6	Murine pancreatic cancer cells in IP cavity	IP	100% survival combined with gemcitabine
Glioma	CD-1 nude	Human gliomas in mouse brain	Intratumoral	92% of mice cleared of tumors and cured

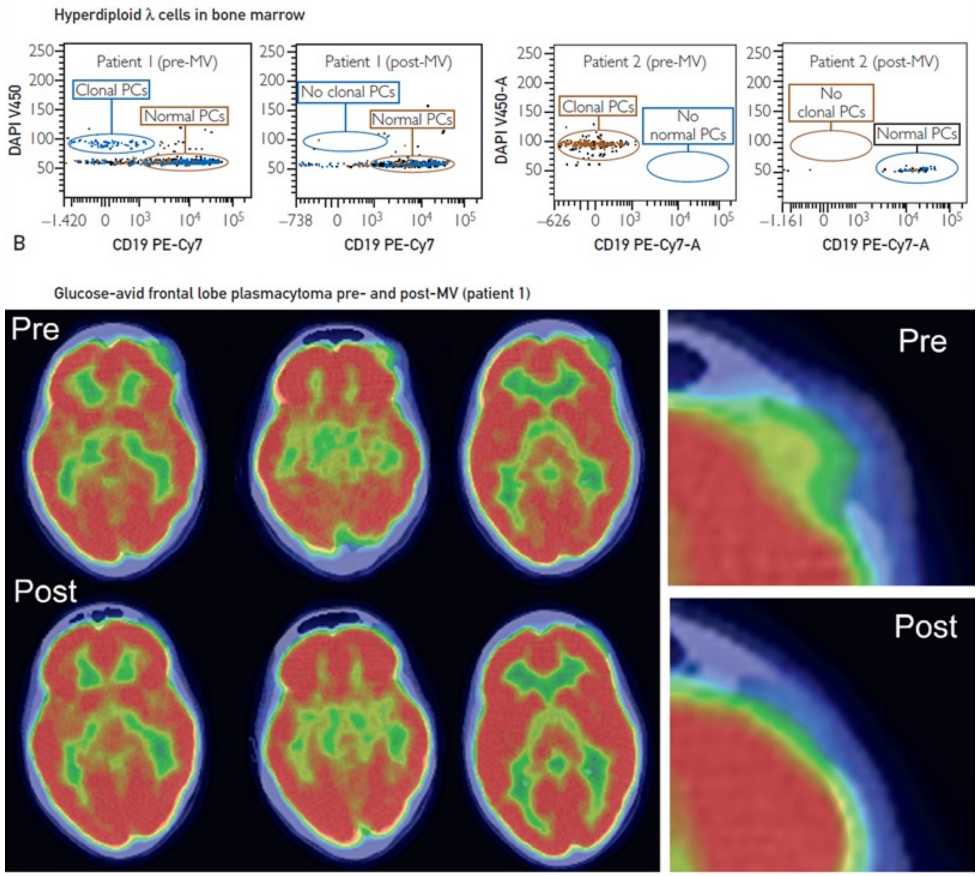


Measles virus



- Attenuated vaccine strain, preferentially replicates in tumors (cannot antagonize STAT1 and MDA5)
- Includes gene for human sodium-iodide symporter (NIS)
- During virotherapy, ɣ-emitting isotopes given allow visualization of virus replication in tumor
- Administration of β-emitting isotopes can induce radiation poisoning

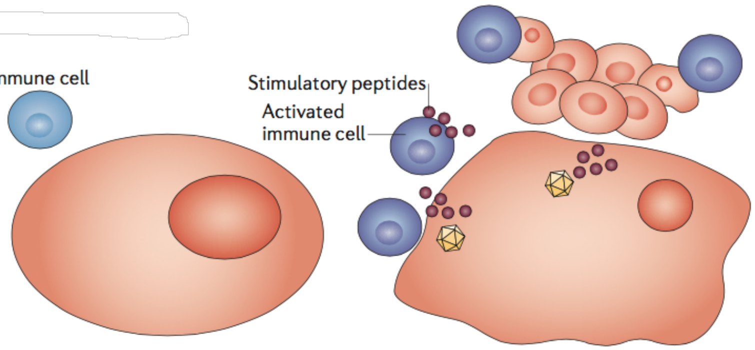
http://www.ncbi.nlm.nih.gov/pubmed/24292552



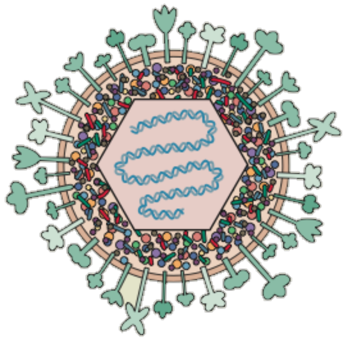
- Two patients with multiple myeloma given 10^{11} particles IV
- One of two had complete remission

http://www.ncbi.nlm.nih.gov/pubmed/24835528

Herpesvirus - Talimogene laherparepvec



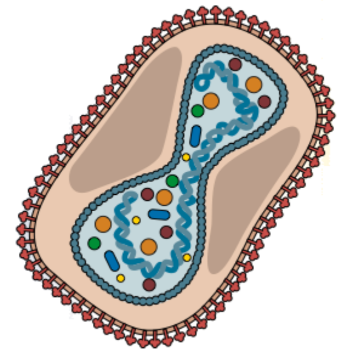
aka T-VEC



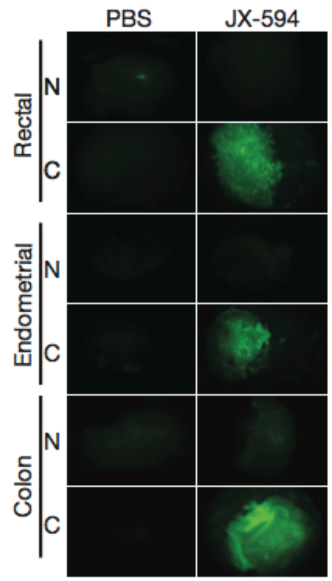
- Includes gene for GM-CSF: stimulate production of granulocytes and macrophages which stimulate adaptive immunity against tumor antigens
- Deletion of ICP34.5, US11 causes tumor-specific replication
- ICP47 deleted, no inhibition of antigen presentation
- Phase III completed for melanoma, intratumoral: 16% response vs 2% for GM-CSF alone
- FDA approved 2015: Imlygic (Amgen)

Vaccinia virus JX-594

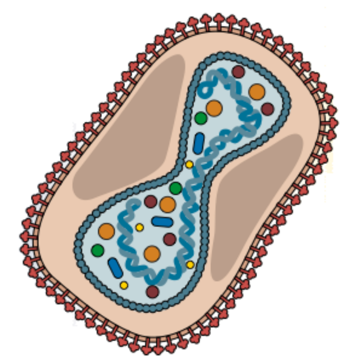
JENNEREX BIOTHERAPEUTICS



- Armed with GM-CSF
- Thymidine kinase gene deleted: elevated in tumors
- Tested for the ability to reach metastatic tumors after intravenous delivery (viremia)
- 23 patients with advanced, treatment-refractory solid tumors (lung, colorectal, melanoma, throid, pancreatic, gastric, ovarian, mesothelioma)



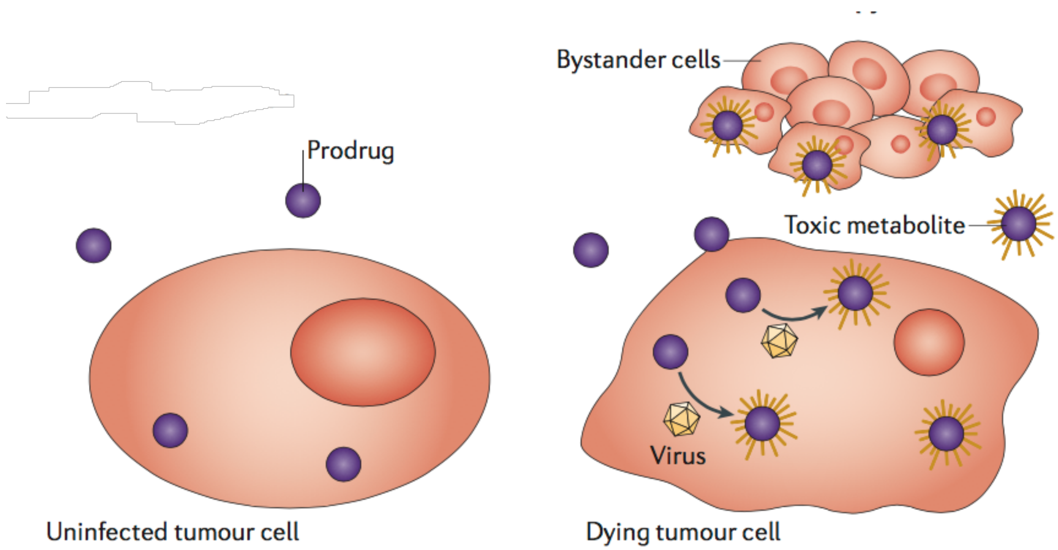
Vaccinia virus JX-594



- Virus replicated in tumors in nearly half of patients (β-gal)
- Anti-tumor activity demonstrated in half of patients
- Proof of concept

Arming with prodrug convertases

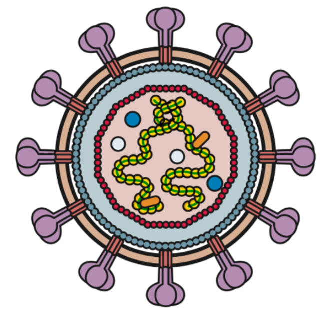
- Thymidine kinase converts ganciclovir to ganciclovir triphosphate
- Cytosine deaminase converts 5-fluorocytosine to 5-fluorouracil
- These nucleoside analogues stop DNA replication of tumor cells



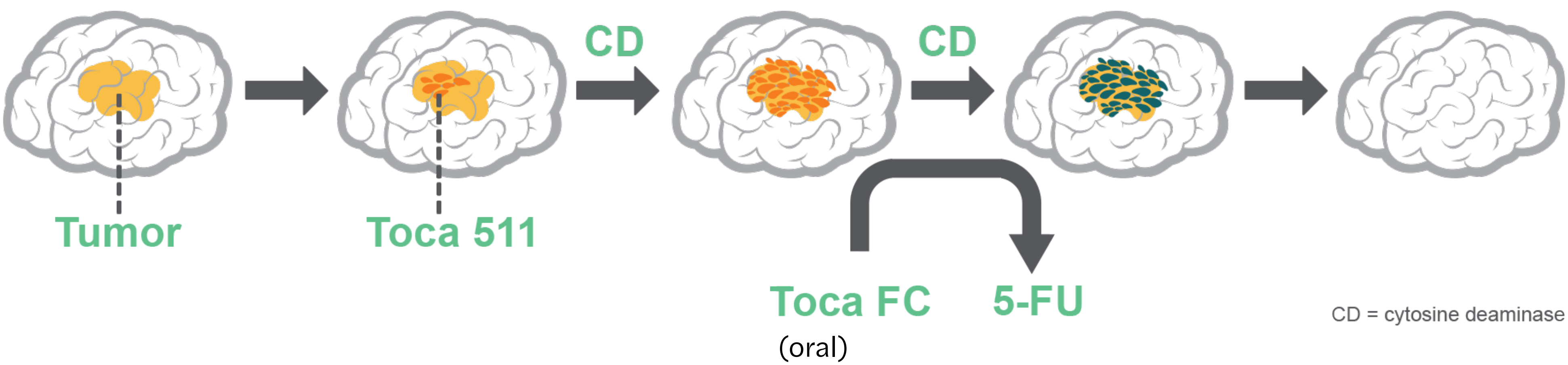
http://www.ncbi.nlm.nih.gov/pubmed/24292552

Toca 511

Tocagen
Touching Your Life

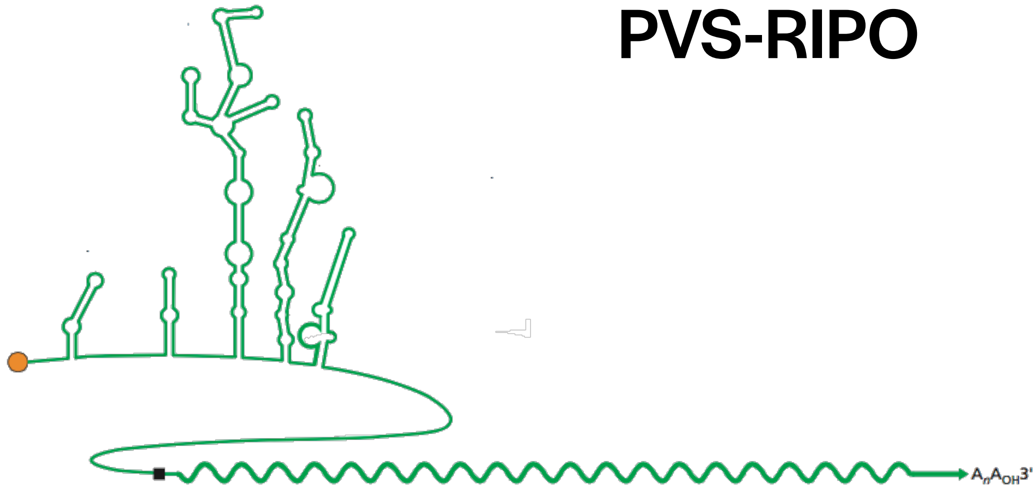


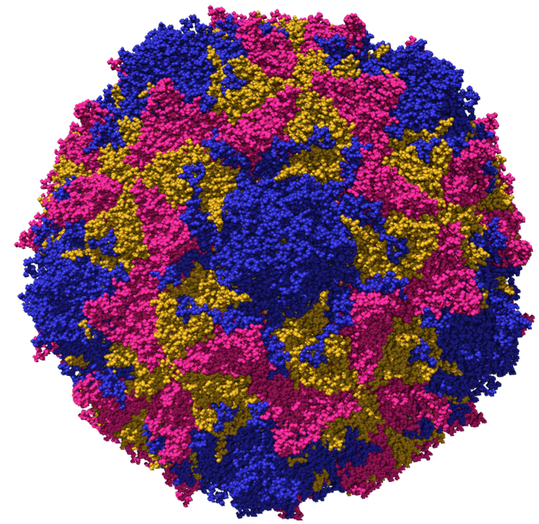
- Amphotropic murine leukemia retrovirus armed with cytosine deaminase
- Given intratumoral or intravenous with 5-fluorocytosine
- Phase I and II for glioma



tocagen.com

PVS-RIPO

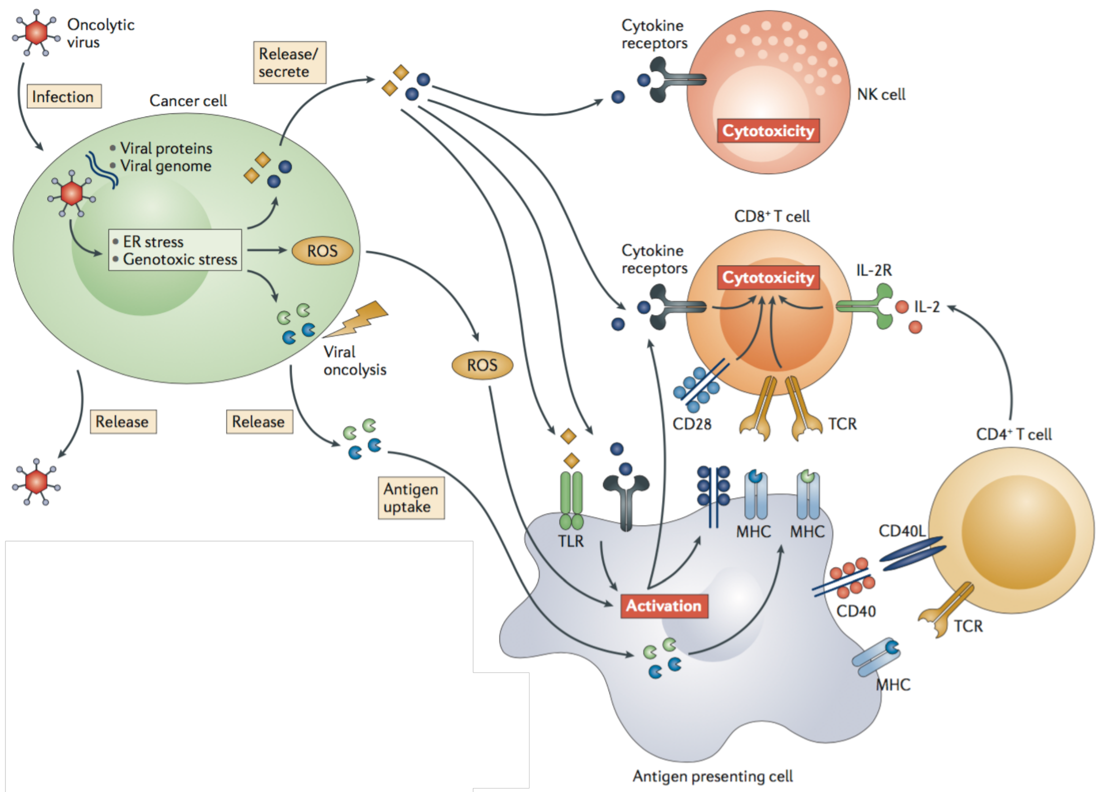




- Poliovirus Sabin with IRES from rhinovirus 2: attenuating
- Tumor cells up-regulate poliovirus receptor
- Intratumoral, Phase II for glioma in 61 patients
- Median survival 12.5 months vs 11.3 months in historical controls

N Engl J Med 2018; 379:150-161

Therapeutic efficacy is a combination of lysis of cancer cell by virus and indirect activation of anti-tumor immune responses



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room number: virus

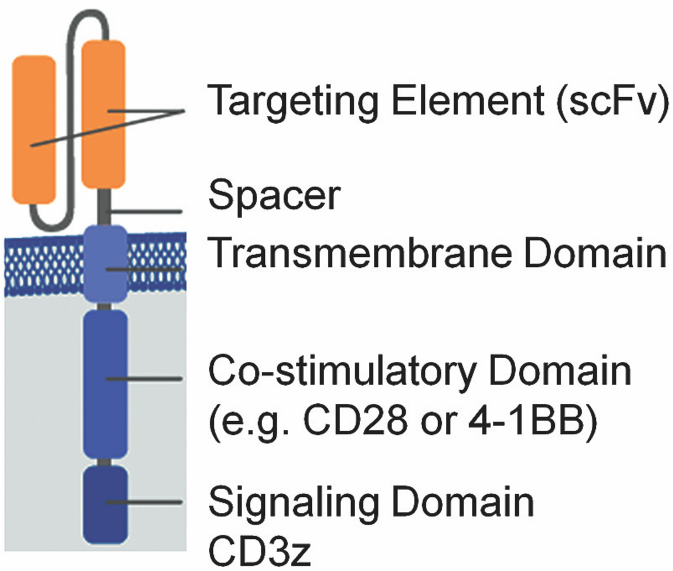
Which of the following statements about oncolytic viruses is incorrect?

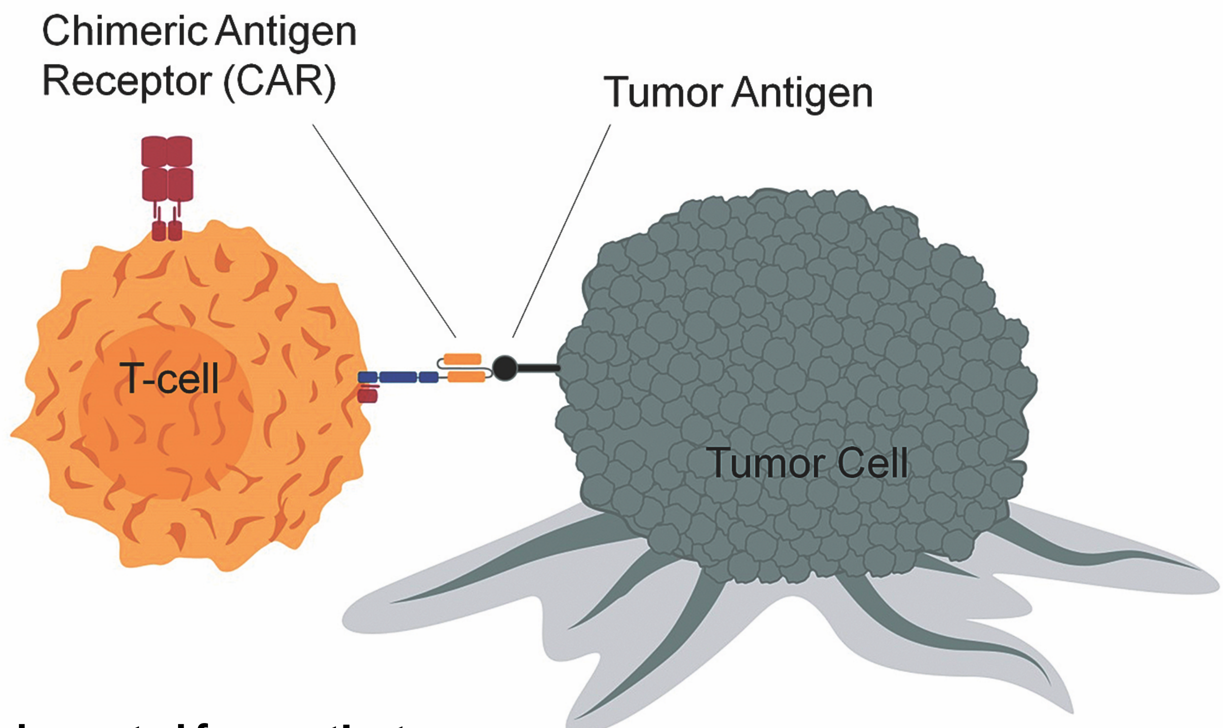
A. Infection by oncolytic viruses leads to destruction of tumor cells only at the site of virus inoculation
B. Some viruses of nonhuman animals can reproduce selectively in human tumor cells
C. Viruses with both DNA and RNA genomes can be developed as oncolytic agents
D. Various mutations in viral genomes that confer tumor-selective reproduction eliminate or impair viral gene products that counter host interferon defense

Cancer Immunotherapy: CAR-T cells

FDA approved 2017

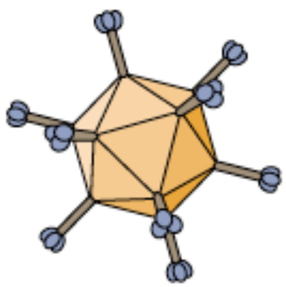
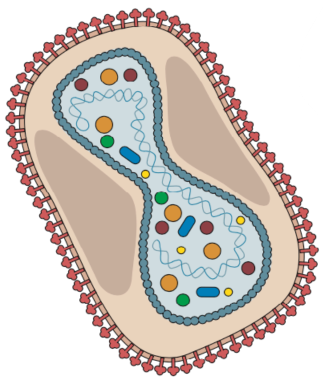
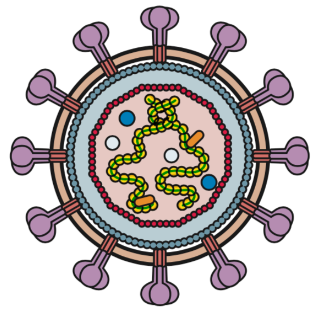
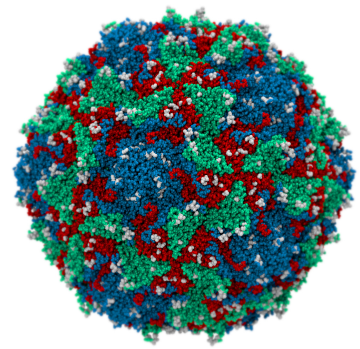
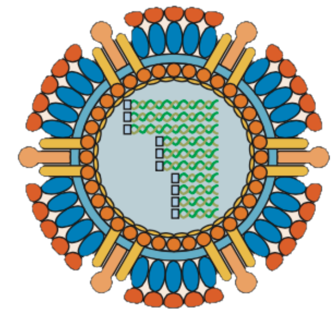
CAR: Modular Design





- **T cells harvested from patient**
- **Deliver CAR gene via lentivirus vector**

The importance of basic research

- Therapeutic viruses have been made possible because of fundamental advances in virology, recombinant DNA, immunology, and clinical science
- There must be a balance between translational research and basic research

Thank you

Don't forget what you have learned here!

Come back for Viruses Live in Fall 2022

Be curious!

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