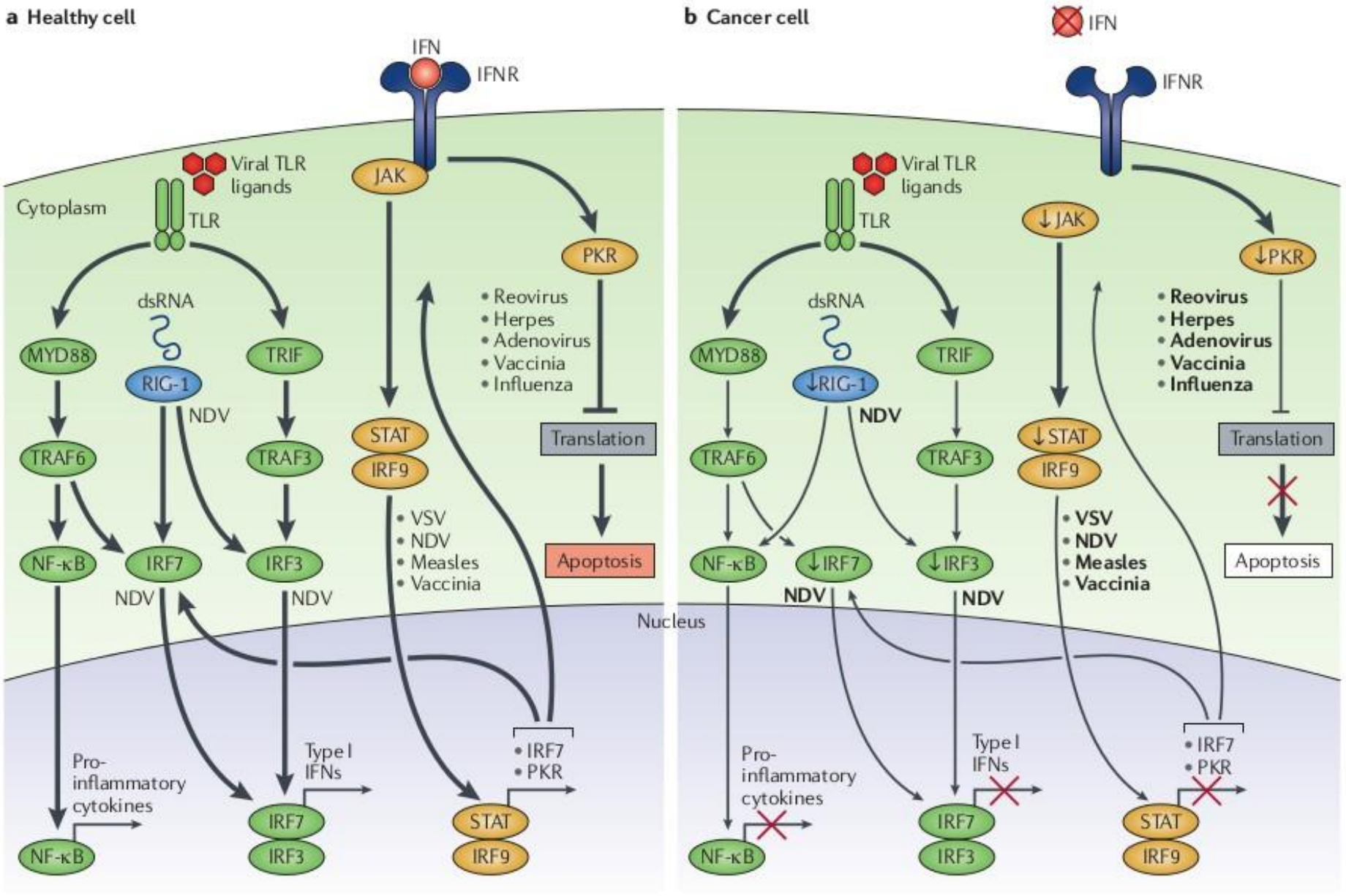
Онколитические вирусы. Доставка опухолеспецифичных антигенов антигенпрезентирующим клеткам

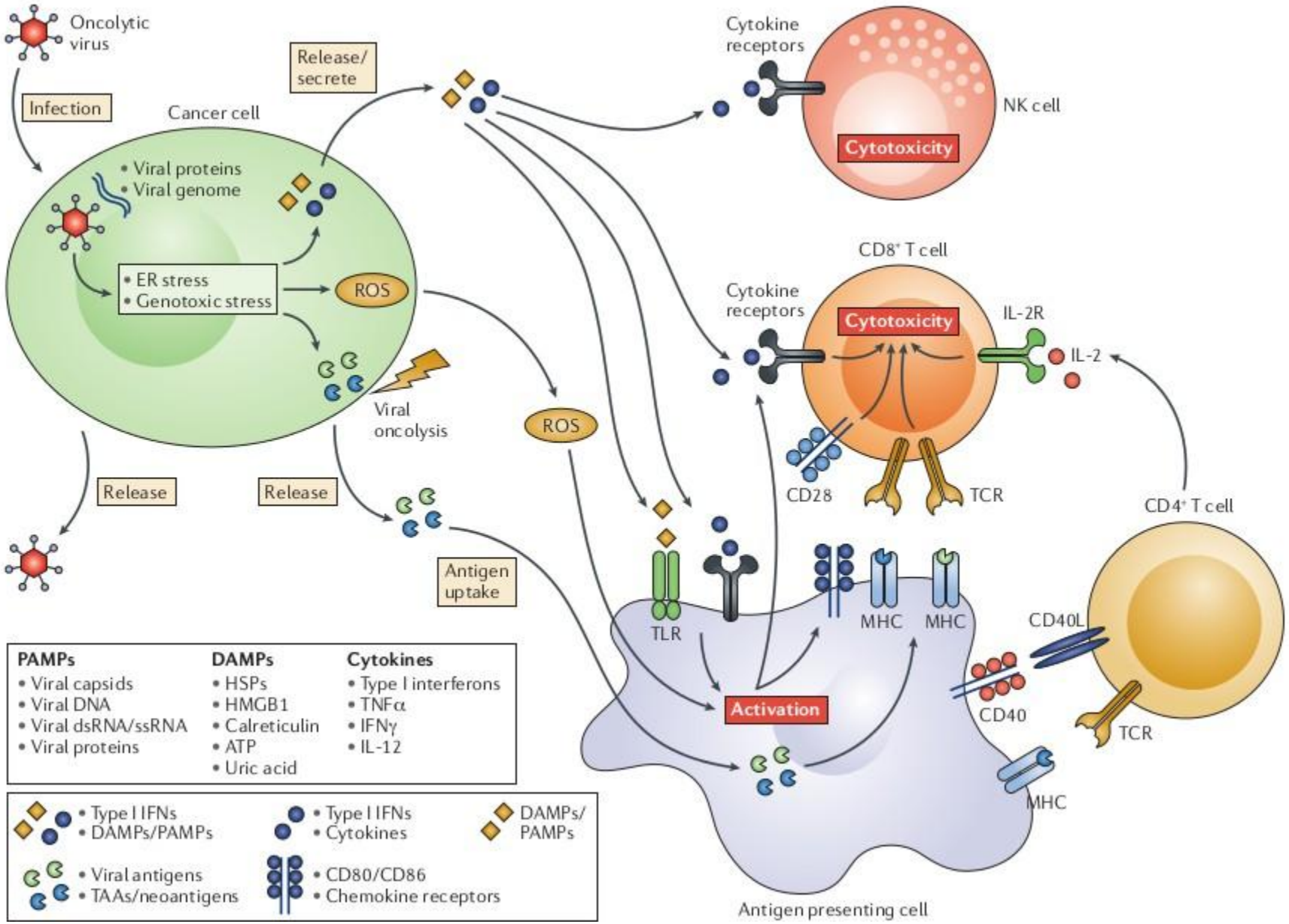
Лена Смертина
Фармация, 6 курс

План

- Иммунный ответ на вирусную инфекцию
- Компоненты противоопухолевого иммунитета
- Стратегии создания онколитических вирусов
- Immune checkpoints



https://doi.org/10.1038/nrd4663



https://doi.org/10.1038/nrd4663

Dendritic cells

Classical

CD8+ (lymphoid organs)

CD103+ (intestinal mucosa)

CD11b+ (lymphoid organs)

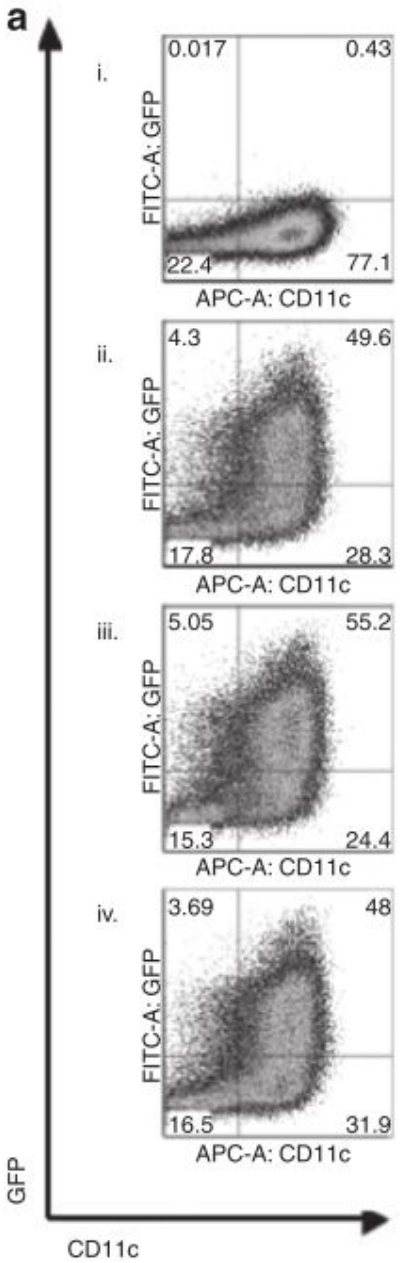
Non-classical

Langerhans cells

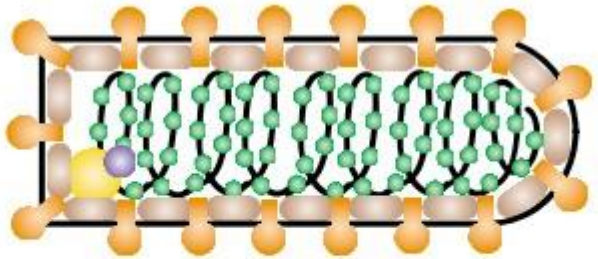
Monocyte-derived DC

<u>Plasmacytoid DC, CD1C+</u>
(IRF7; IL-12, IL-6)

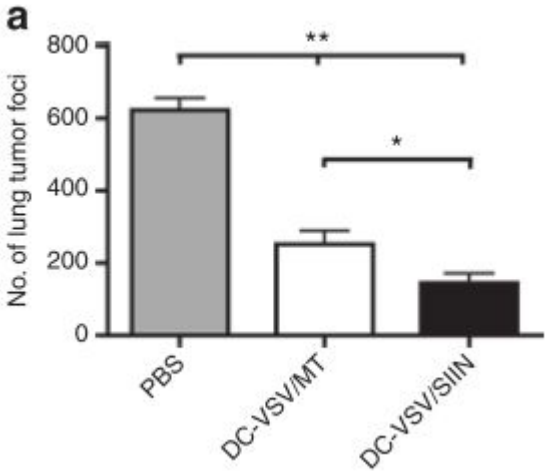
VSV (Vesicular Stomatitis Virus)



Family: *Rhabdoviridae*
Group: (-)ssRNA

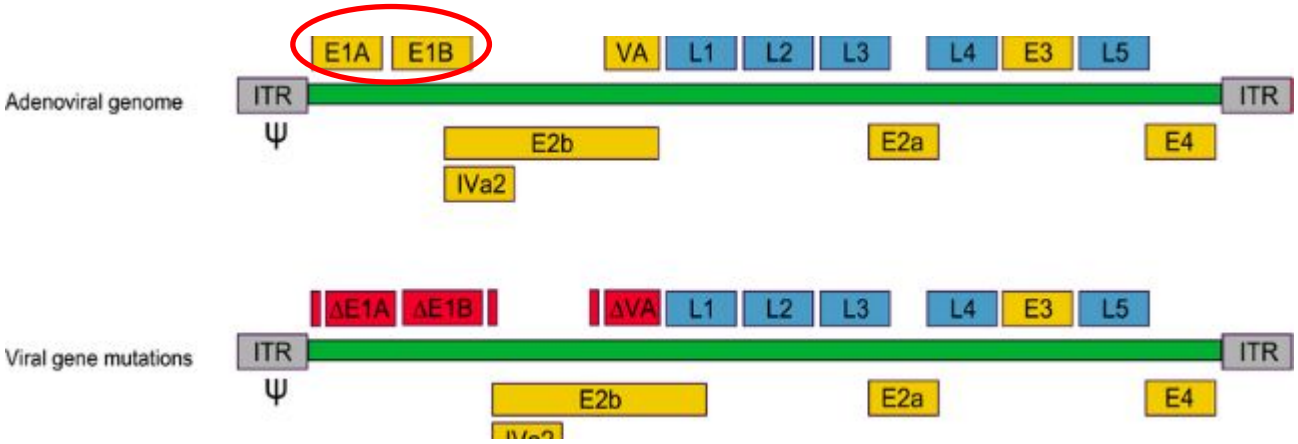


Inhibition of host transcription
Inhibition of nucleo-cytoplasmic transport
Cytotoxicity
Apoptosis
In vivo toxicity by blocking interferon expression
Attenuating mutation in VSV-AV1



https://doi.org/10.1016/j.molmed.2004.03.003

Adenoviruses

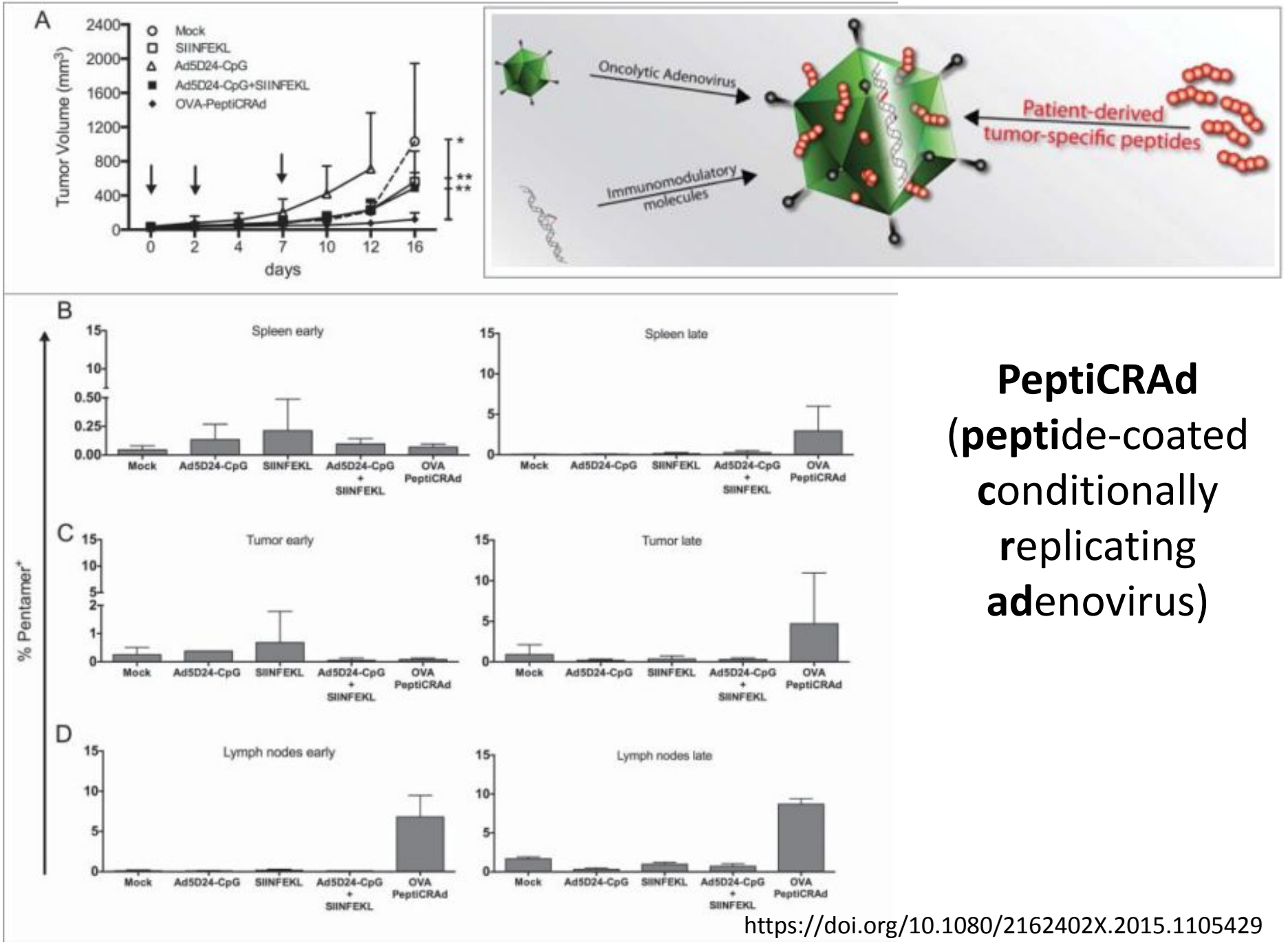


Family: *Adenoviridae*
Group: dsDNA

Cell receptors: CD46, CAR (coxsackievirus adenovirus receptor)

E1A ⊣ Rb protein ↓ → E2F (tf) ↑ → Cell cycle (S-phase)

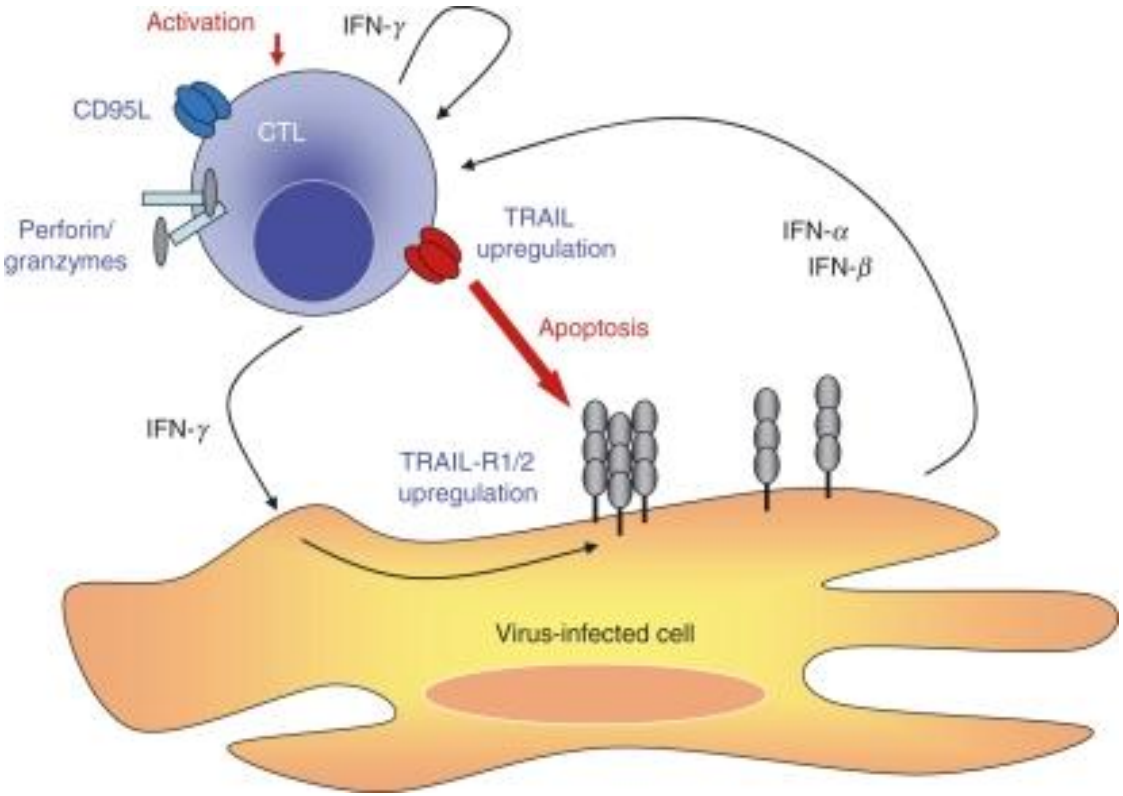
E1B ⊣ p53



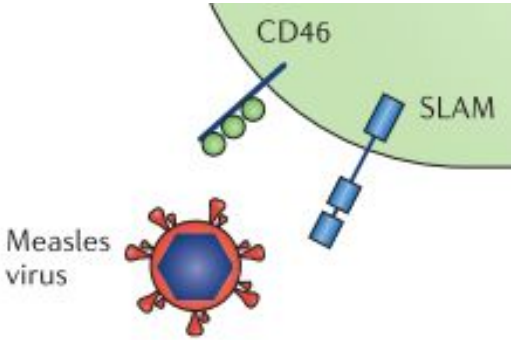
PeptiCRAd
(**pepti**de-coated
conditionally
replicating
adenovirus)

https://doi.org/10.1080/2162402X.2015.1105429

Measles virus

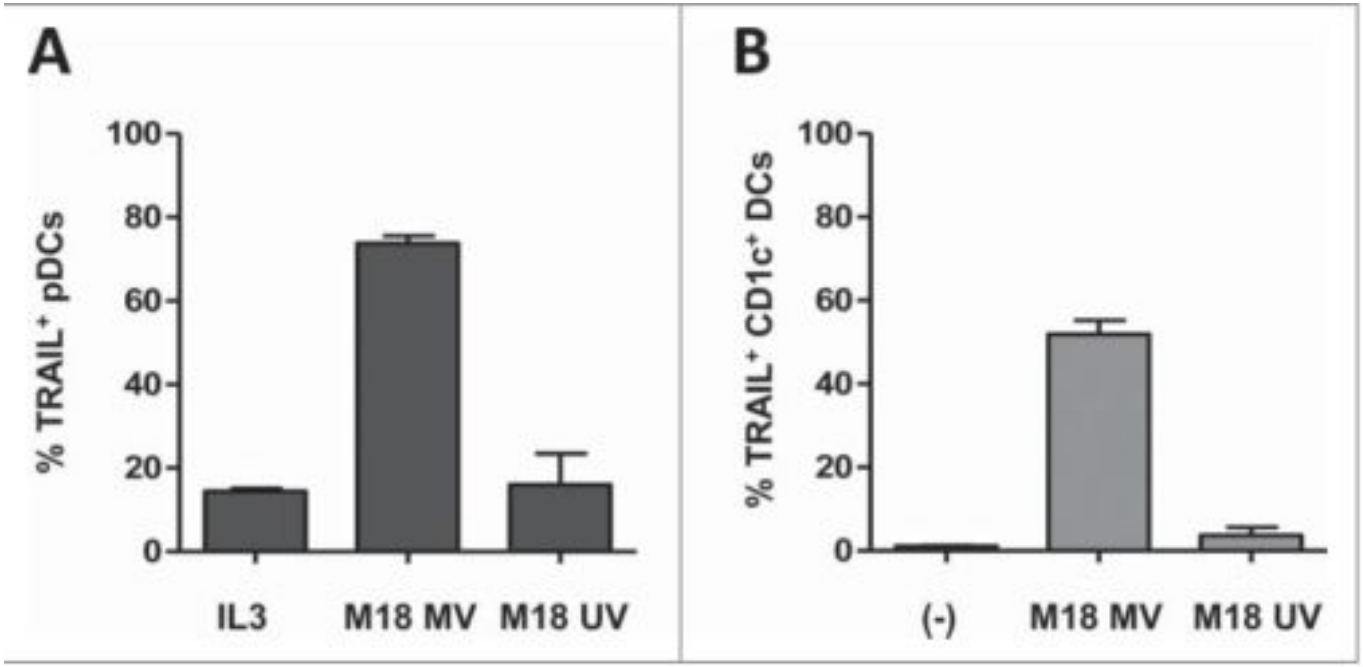


Family: Paramyxoviridae
Group: (-)ssRNA



https://doi.org/10.1080/2162402X.2016.1261240

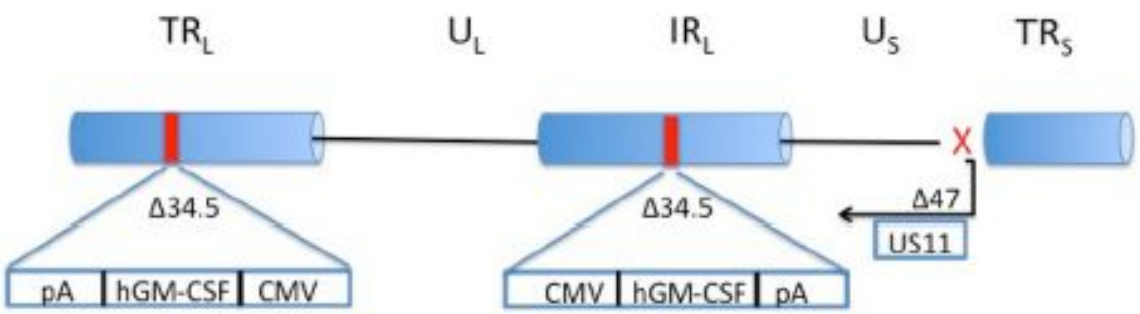
Flow cytometry assay



https://doi.org/10.1080/2162402X.2016.1261240

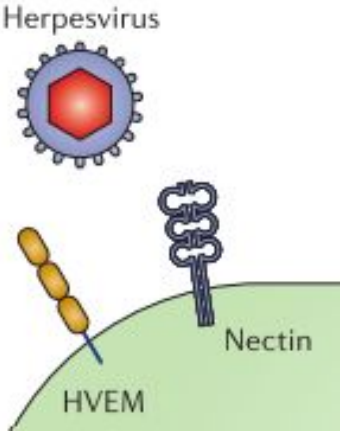
Herpes simplex virus

T-VEC (Talimogen laherparepvec)



Modifications	Rationale
Deletion of ICP34.5	Abolish Neurovirulence
Early Expression of US11	Cancer Cell Specific Replication
Deletion of ICP47	Permits Antigen Presentation
Insertion of hGM-CSF	Augments anti-tumor Immune response

Family: Alphaherpesvirus
Group: dsDNA



Herpes virus entry mediator

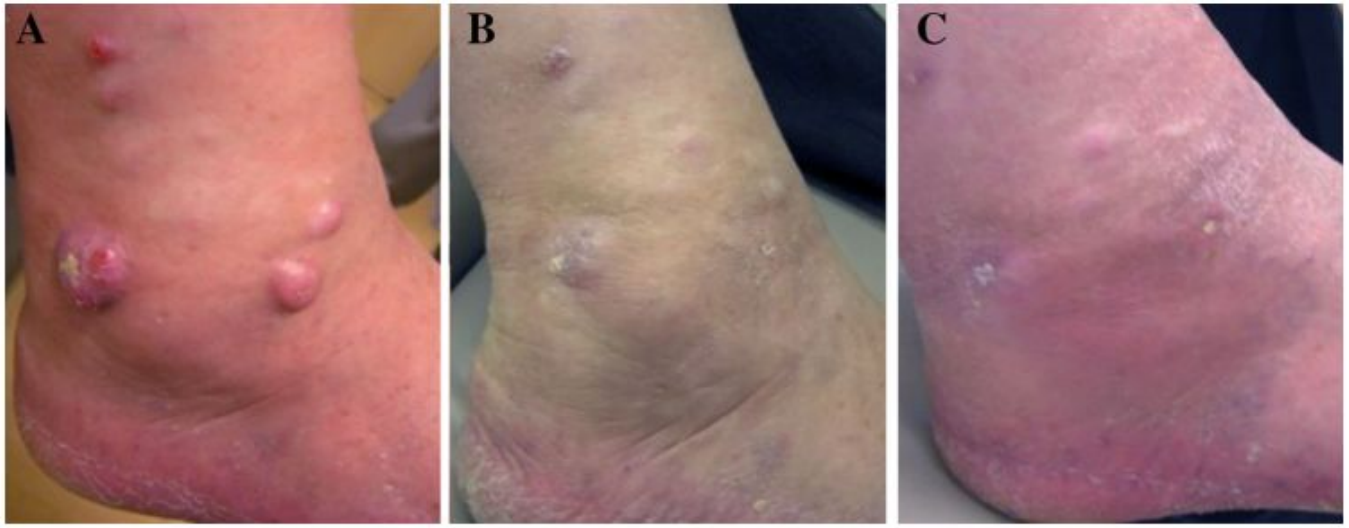
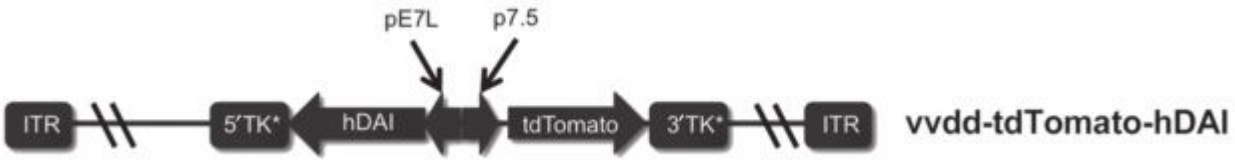


Fig. 2 Photograph of a melanoma patient (**a**) before; (**b**) 6 months after starting treatment with Talimogene laherparepvec (T-VEC); and (**c**) 9 months after starting treatment.

https://doi.org/10.1007/s40257-016-0238-9

Vaccinia virus

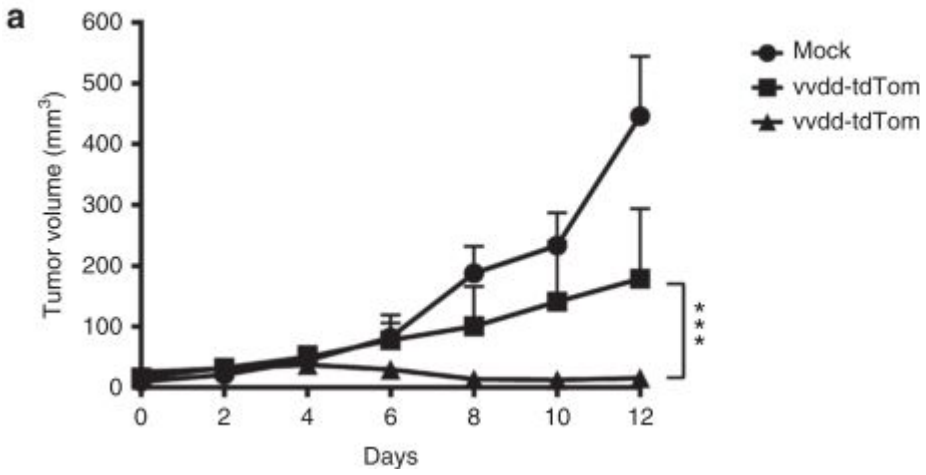
Family: poxvirus
Group: dsDNA (190 kb)

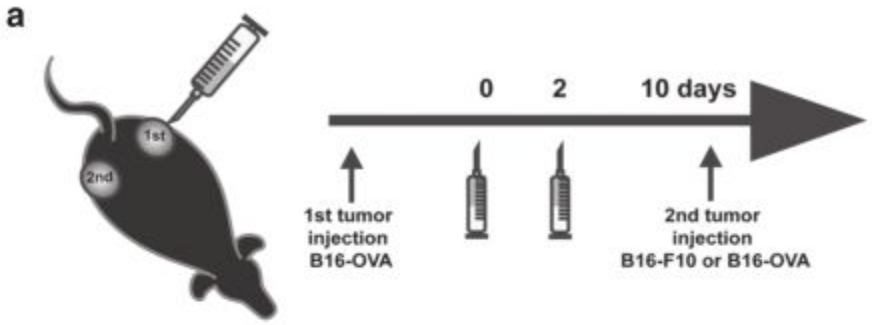


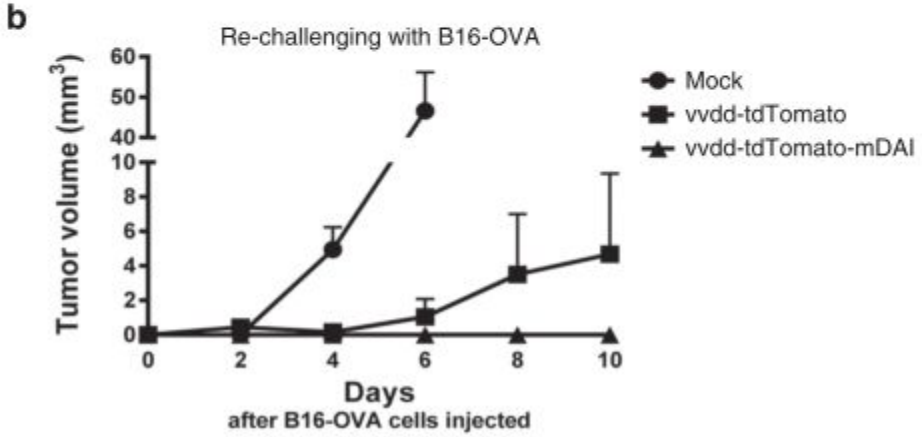
vvdd-tdTomato-hDAI

Intracellular pattern recognition receptor DNA-dependent activator of IFN-regulatory factors (**DAI**)

Deletions: thymidine kinase gene
vaccinia growth factor



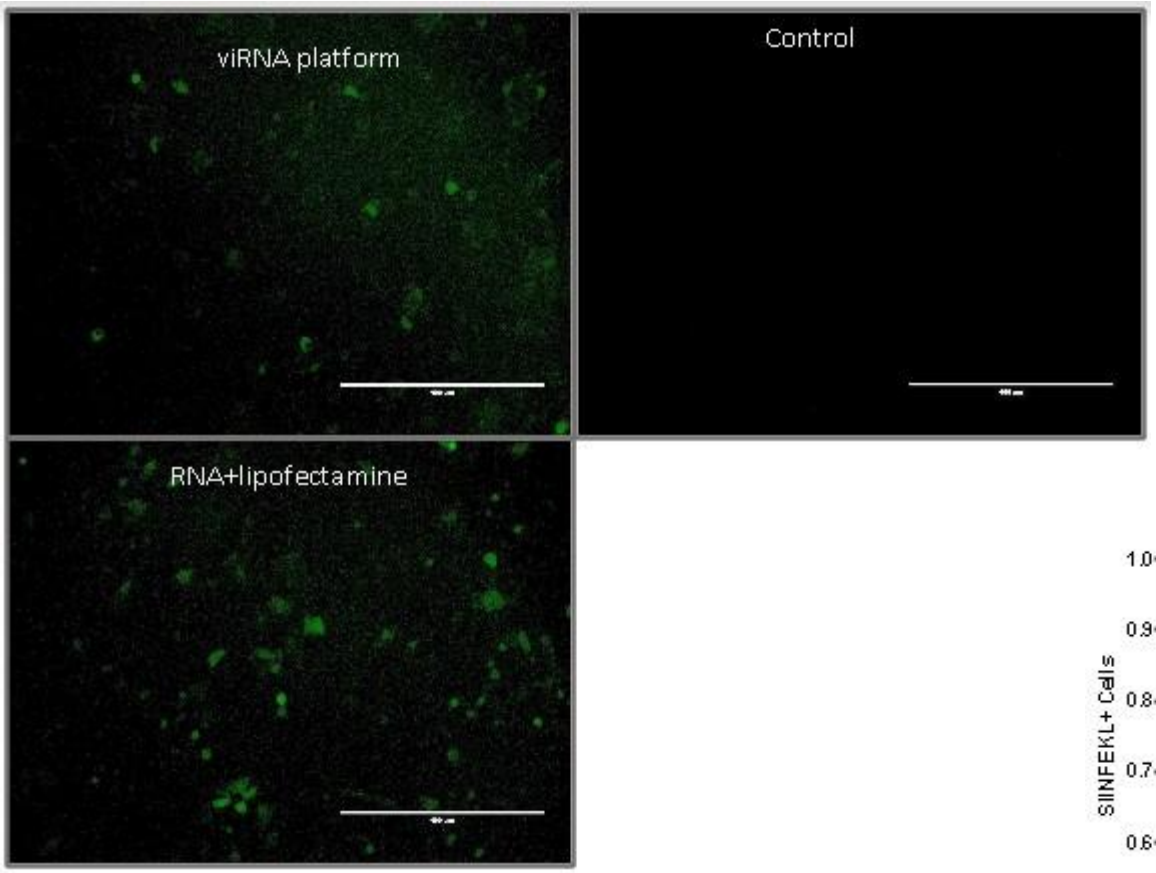




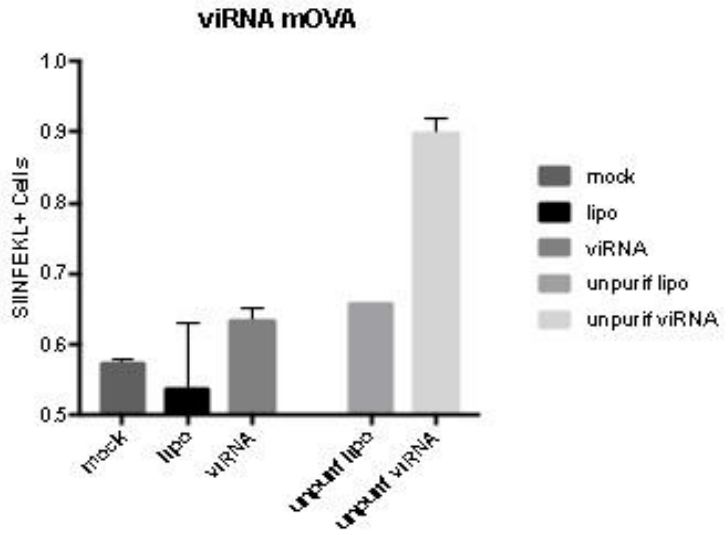
https://doi.org/10.1038/mto.2016.2

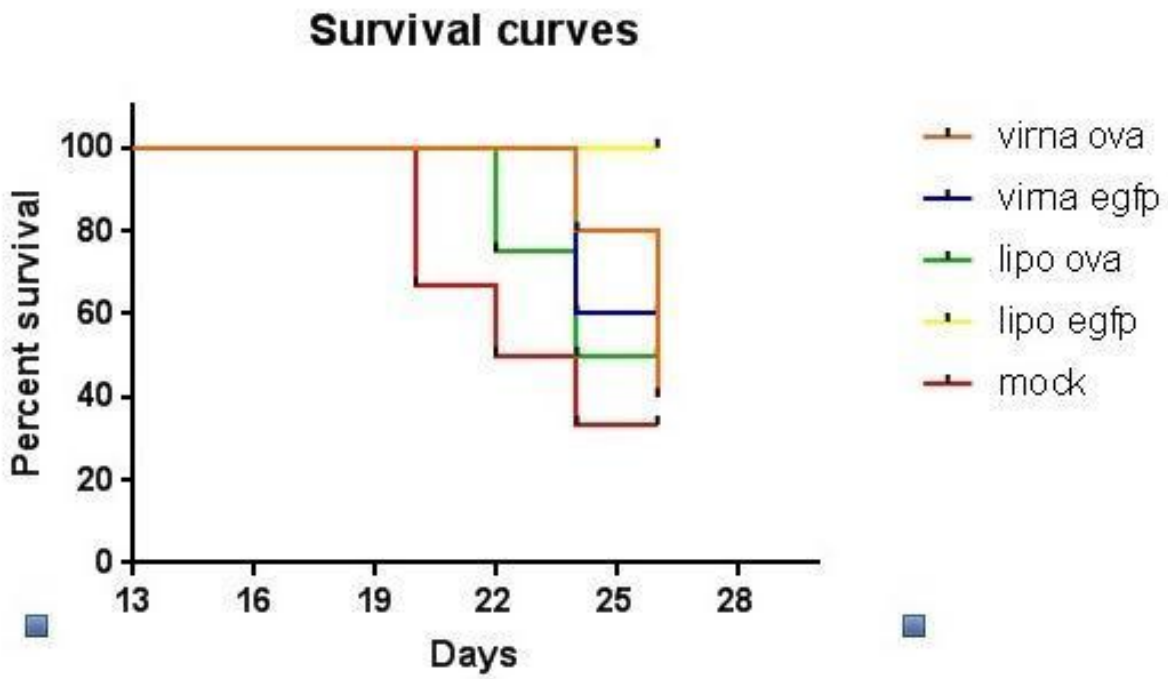
viRNA

Vaccinia virus + lipofectamine + mRNA (ovalbumin)

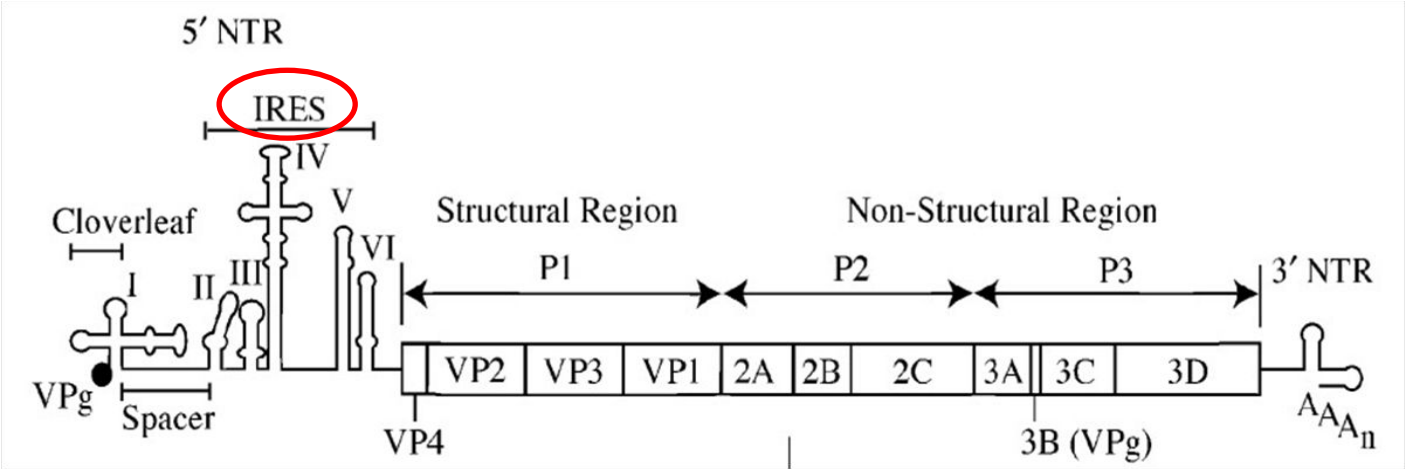


Naïve splenocytes
Flow cytometry assay

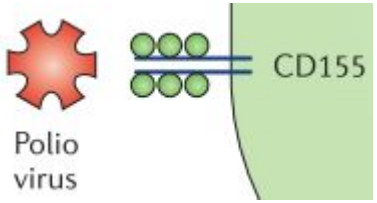



Survival curves
Percent survival
100
80
60
40
20
0
13
16
19
22
25
28
Days
virna ova
virna egfp
lipo ova
lipo egfp
mock

Poliovirus

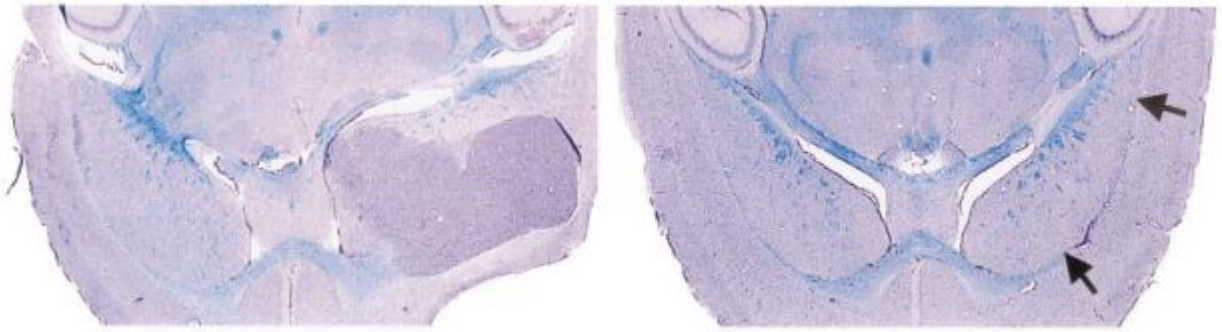


Family: Picornaviridae
Group: ssRNA



CD155 in glioma cells

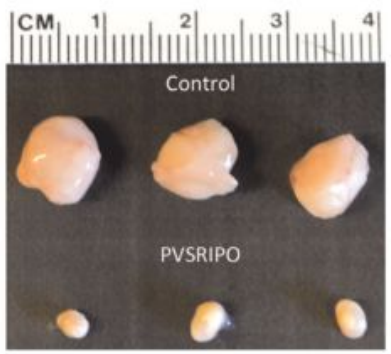
Exchange of the poliovirus **i**nternal **r**ibosomal **e**ntry **s**ite with its counterpart from human Rhinovirus type 2 resulted in attenuation of neurovirulence in primates

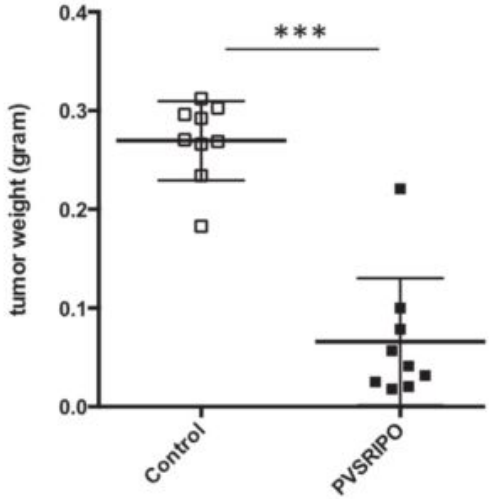


https://doi.org/10.18632/oncotarget.12975

PVSRIPO in human breast and prostate cancer xenograft models

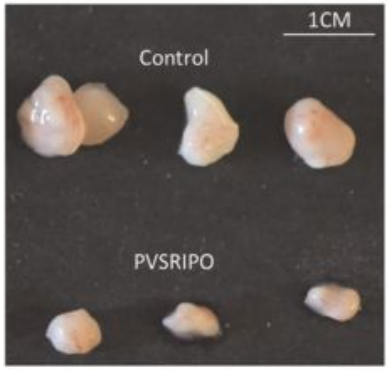
A.

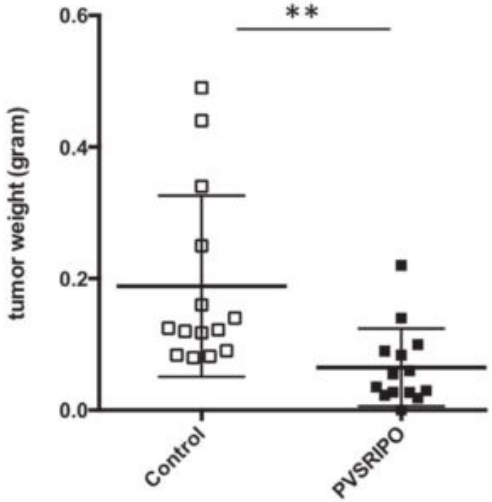




SUM 149 breast cancer cell line

B.



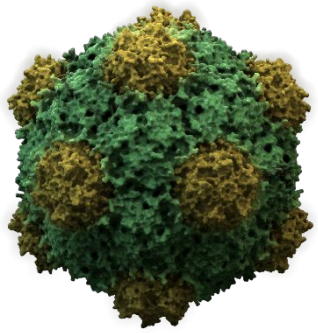


DU145 prostate cancer cell line

https://doi.org/10.18632/oncotarget.12975

Cowpea mosaic virus

Family: Secoviridae
Group: (+)ssRNA



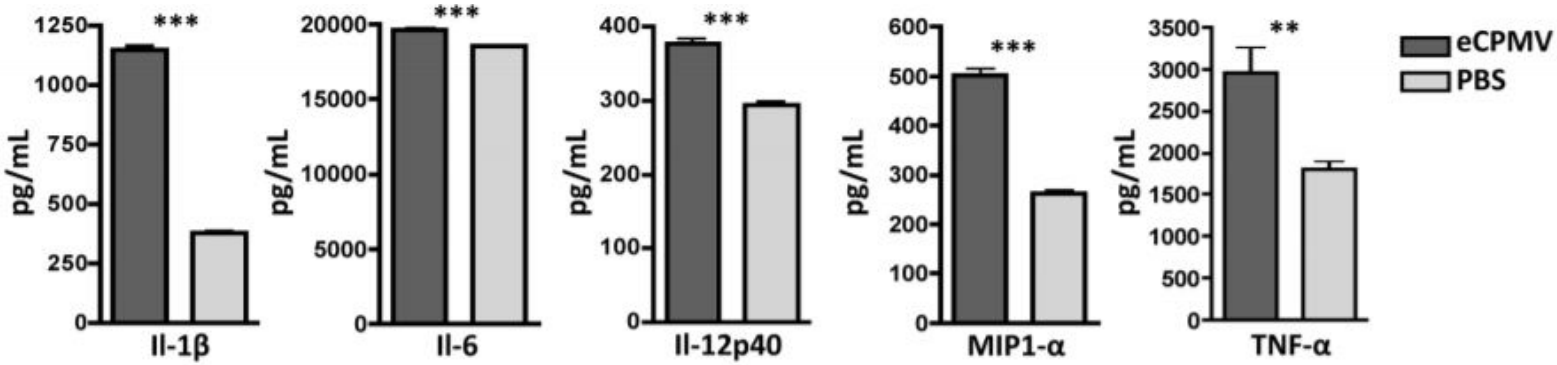
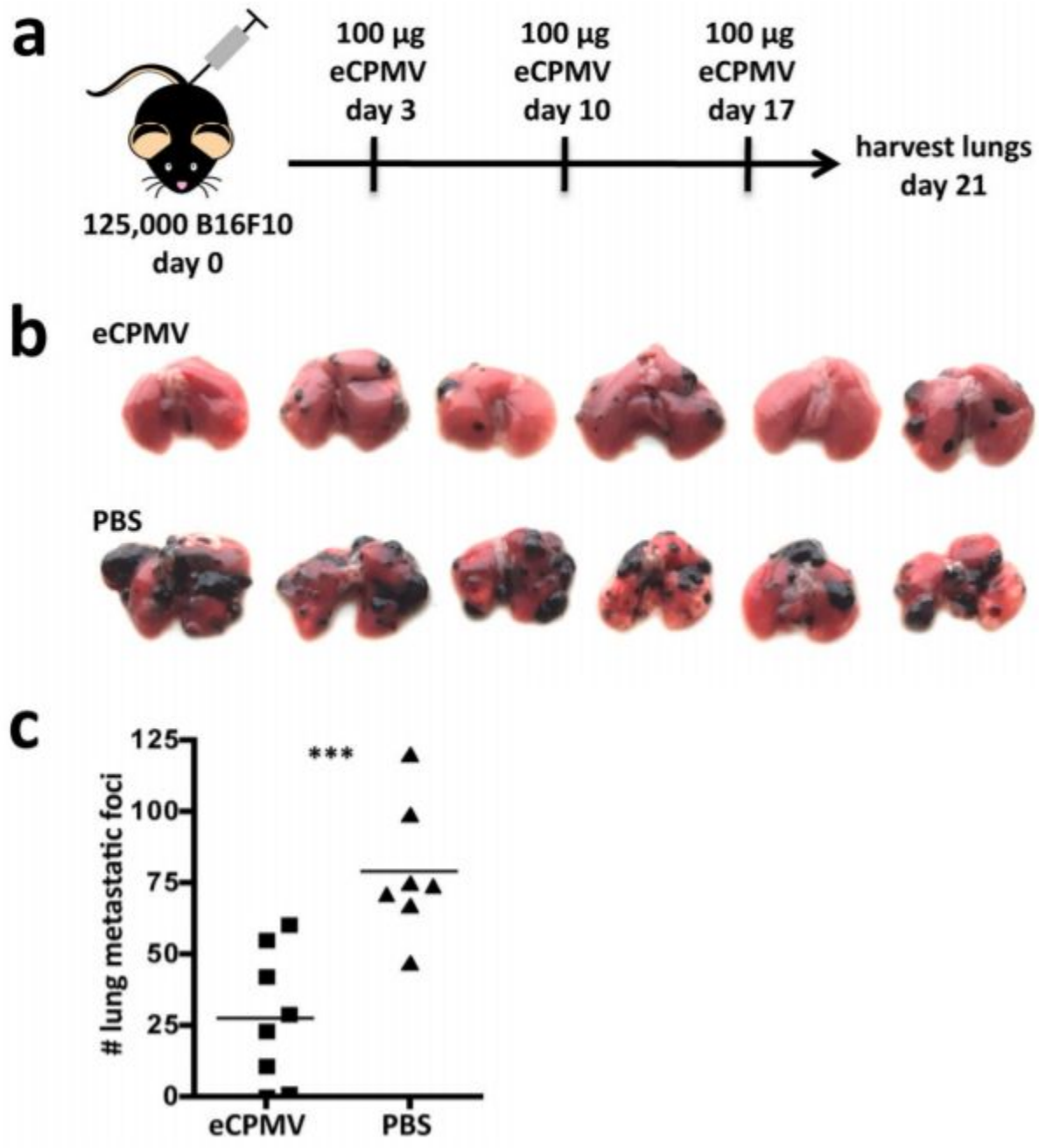
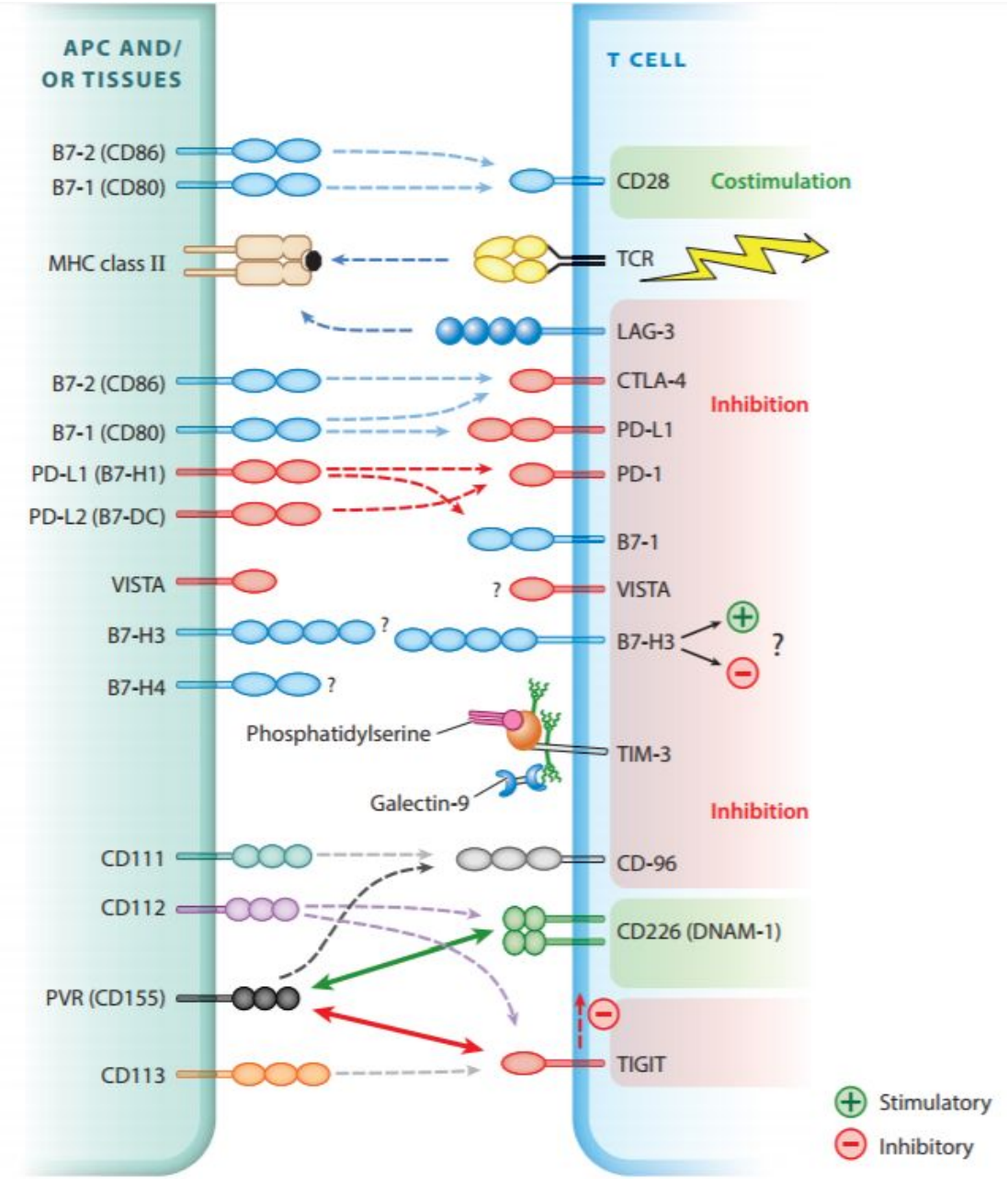


Figure 1. eCPMV nanoparticles are inherently immuonogenic

a, Bone marrow-derived dendritic cells (BMDCs) exposed to eCPMV produce elevated levels of pro-inflammatory cytokines *in vitro*.

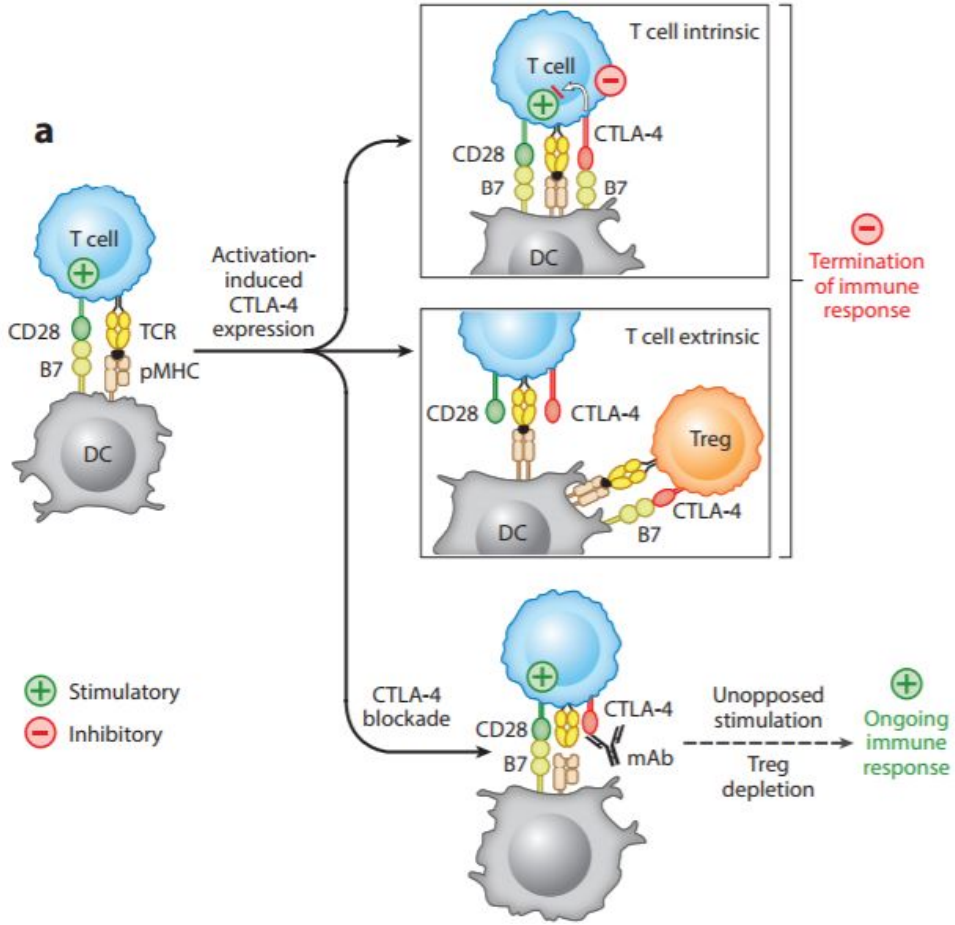

a
100 µg
eCPMV
day 3
100 µg
eCPMV
day 10
100 µg
eCPMV
day 17
harvest lungs
day 21
125,000 B16F10
day 0
b
eCPMV
PBS
c
lung metastatic foci
125
100
75
50
25
0
***
eCPMV
PBS

Co-inhibitory pathways



Cytotoxic T-lymphocyte antigen 4 (CTLA-4)

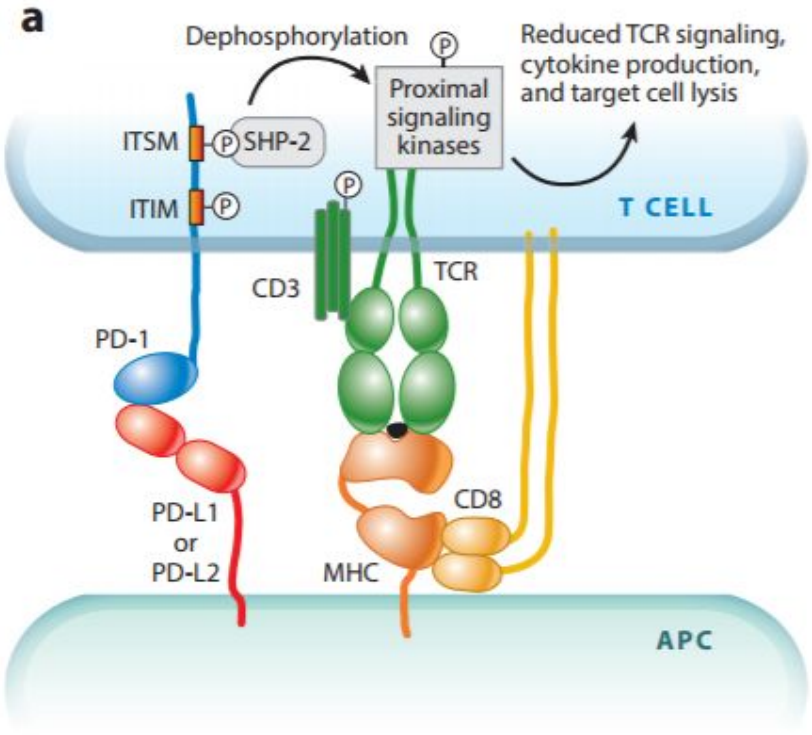
- Homolog of CD28 (binds CD80 and CD86)
- Multiorgan inflammation develops in CTLA-4 knockout mice



Ipilimumab
Tremelimumab

Programmed death 1 (PD-1)

- The level of PD-1 is high when T-cells are repetitively stimulated
- Expressed on NKs, B-cells, Tregs, macrophages
- Has 2 ligands: PDL-1 and PDL-2 (on APCs, tumor cells)



Nivolumab
Pembrolimumab

10.1146/annurev-immunol-032414-112049