

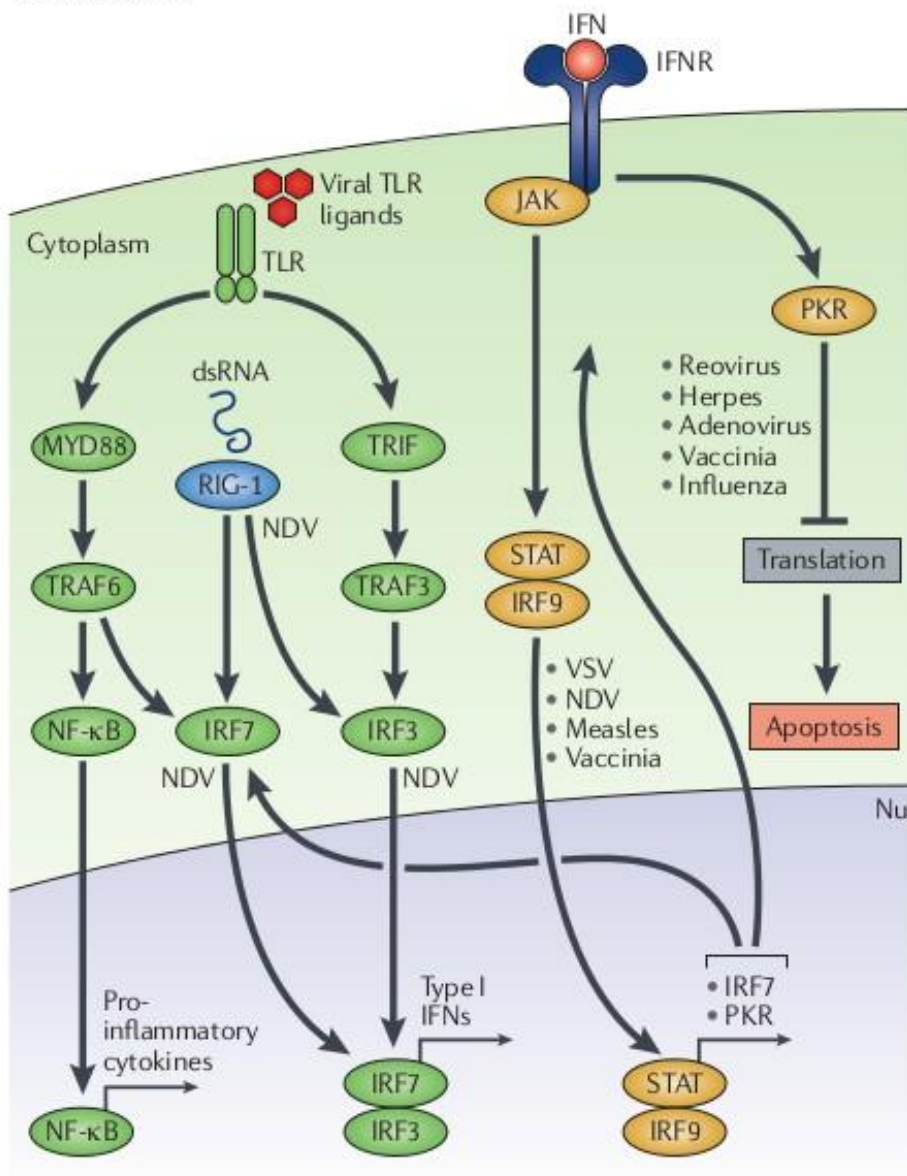
Онколитические вирусы.
Доставка
опухолеспецифичных антигенов
антигенпрезентирующим
клеткам

Лена Смертина
Фармация, 6 курс

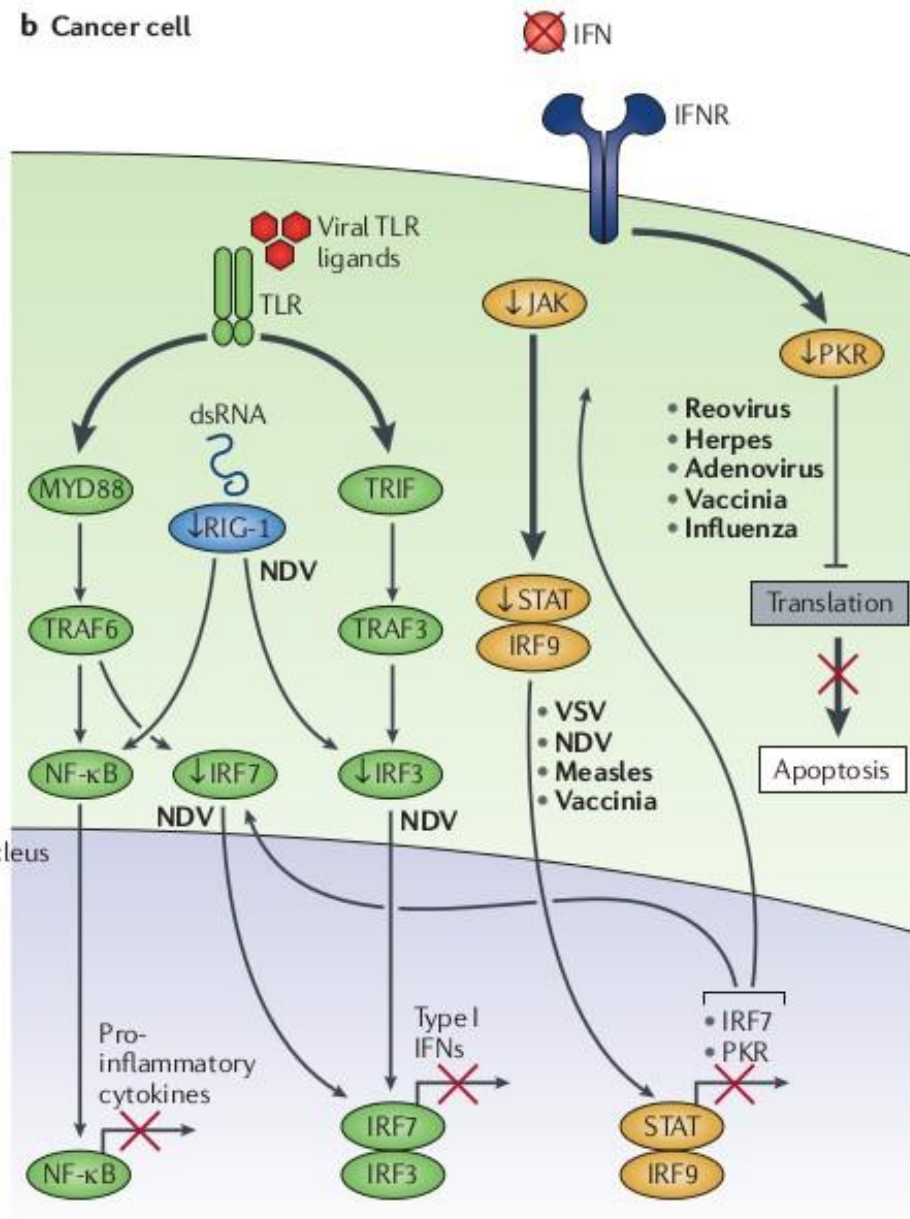
План

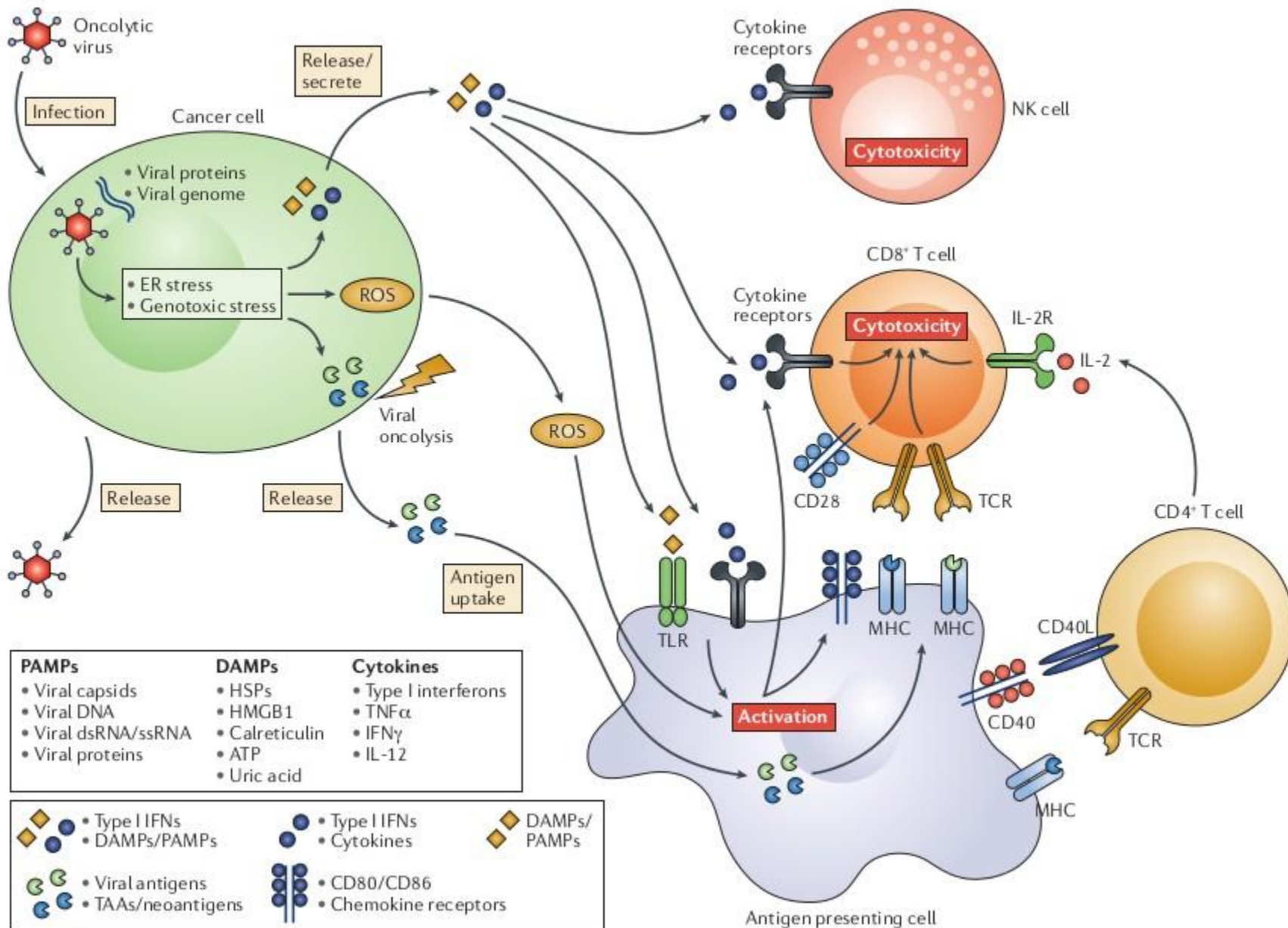
- Иммунный ответ на вирусную инфекцию
- Компоненты противоопухолевого иммунитета
- Стратегии создания онколитических вирусов
- Immune checkpoints

a Healthy cell

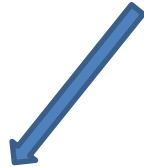


b Cancer cell





Dendritic cells

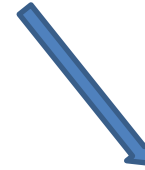


Classical

CD8+ (lymphoid organs)

CD103+ (intestinal mucosa)

CD11b+ (lymphoid organs)



Non-classical

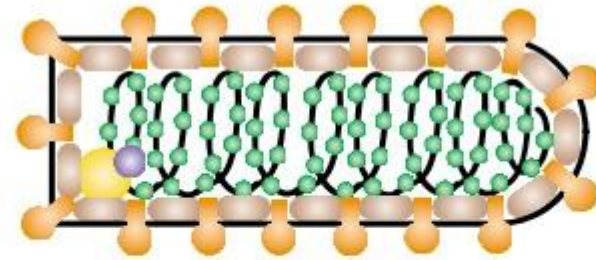
Langerhans cells

Monocyte-derived DC

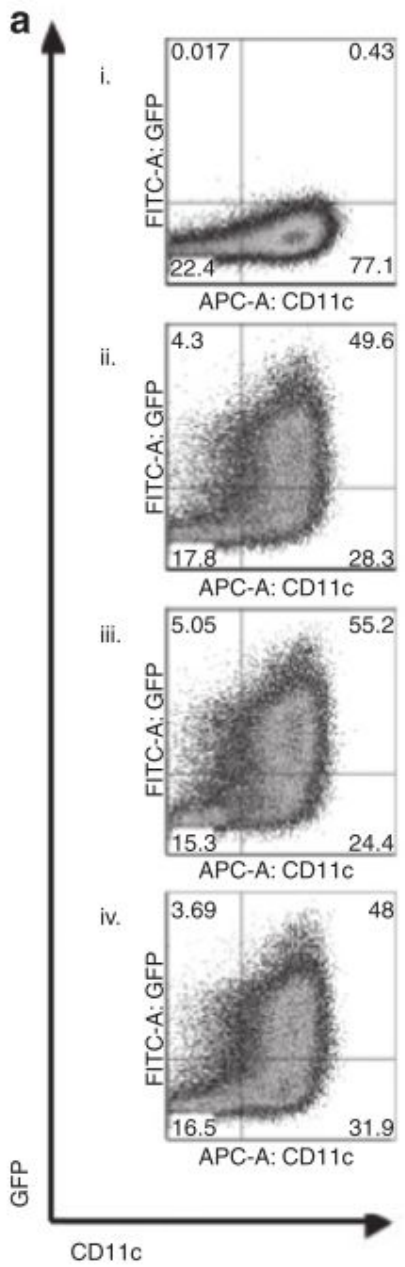
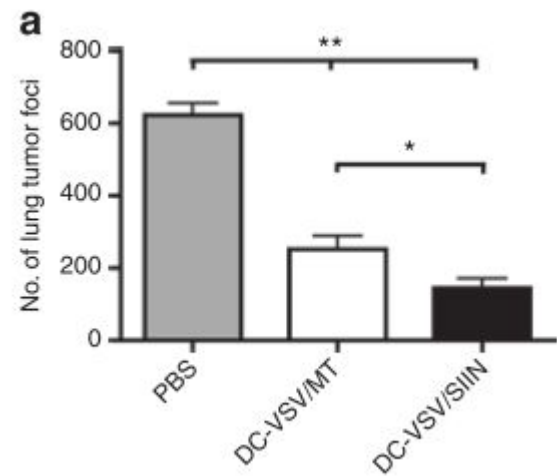
Plasmacytoid DC, CD1c+
(IRF7; IL-12, IL-6)

VSV (Vesicular Stomatitis Virus)

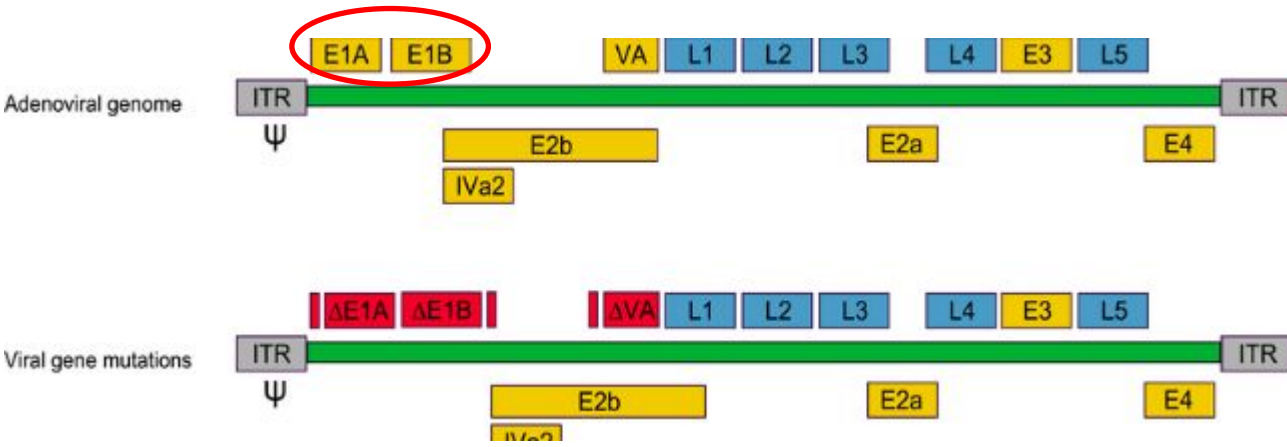
Family: *Rhabdoviridae*
Group: (-)ssRNA



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

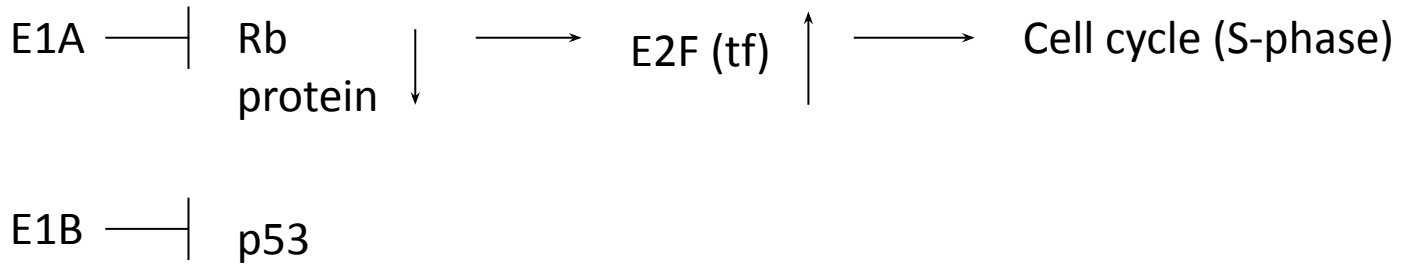


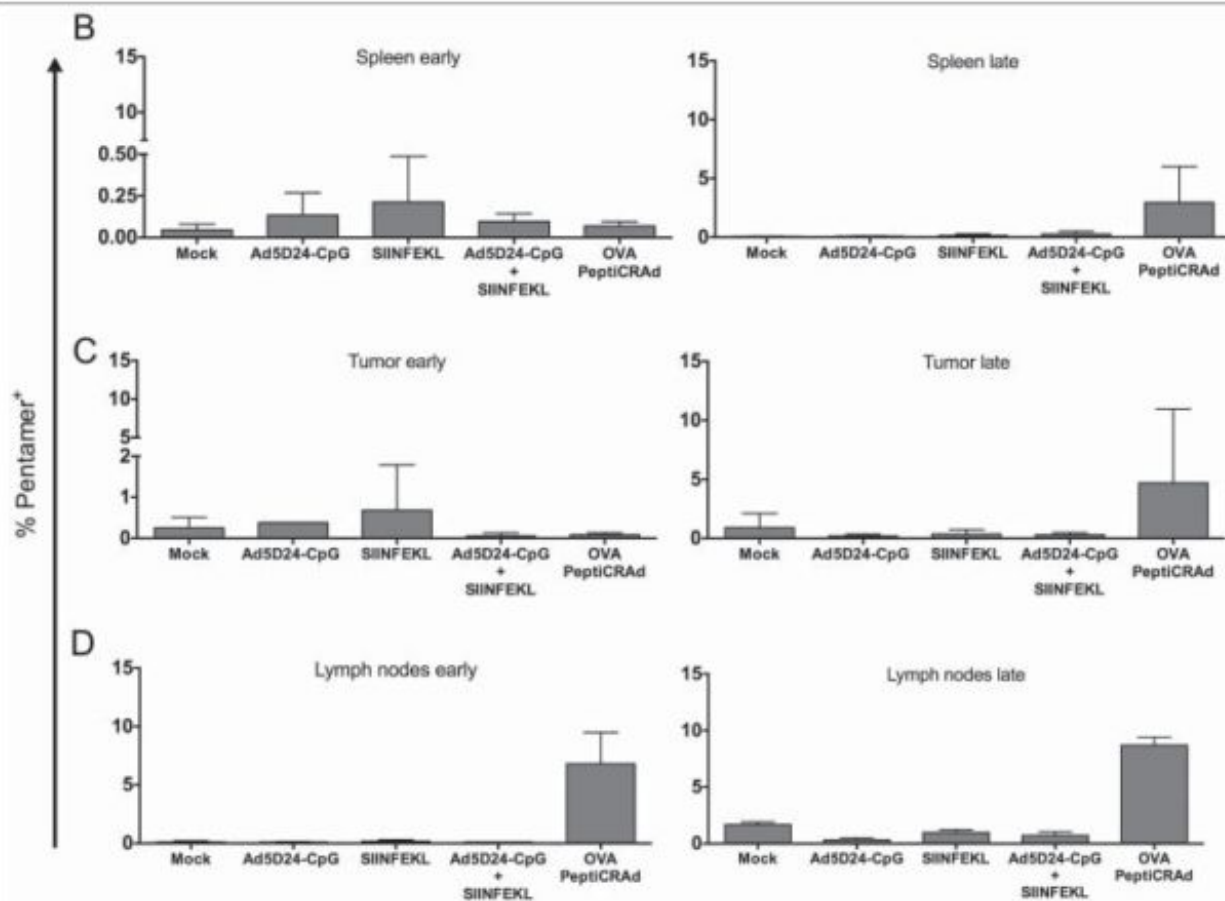
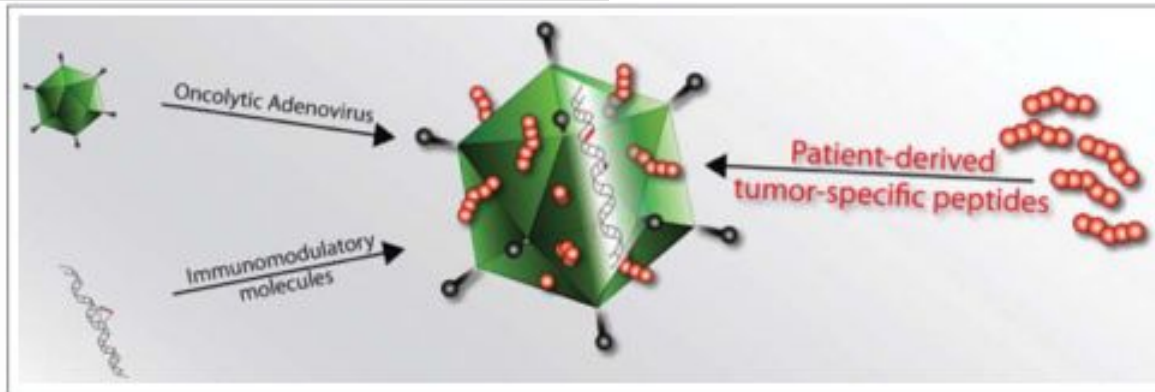
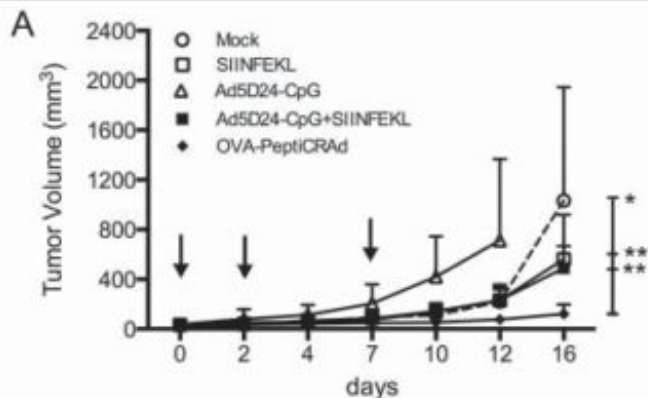
Adenoviruses



Family: *Adenoviridae*
Group: dsDNA

Cell receptors: CD46, CAR
(coxsackievirus adenovirus receptor)

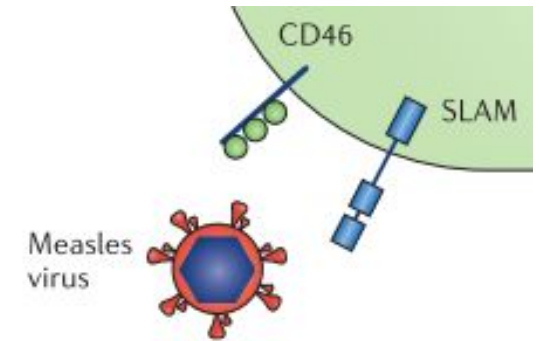
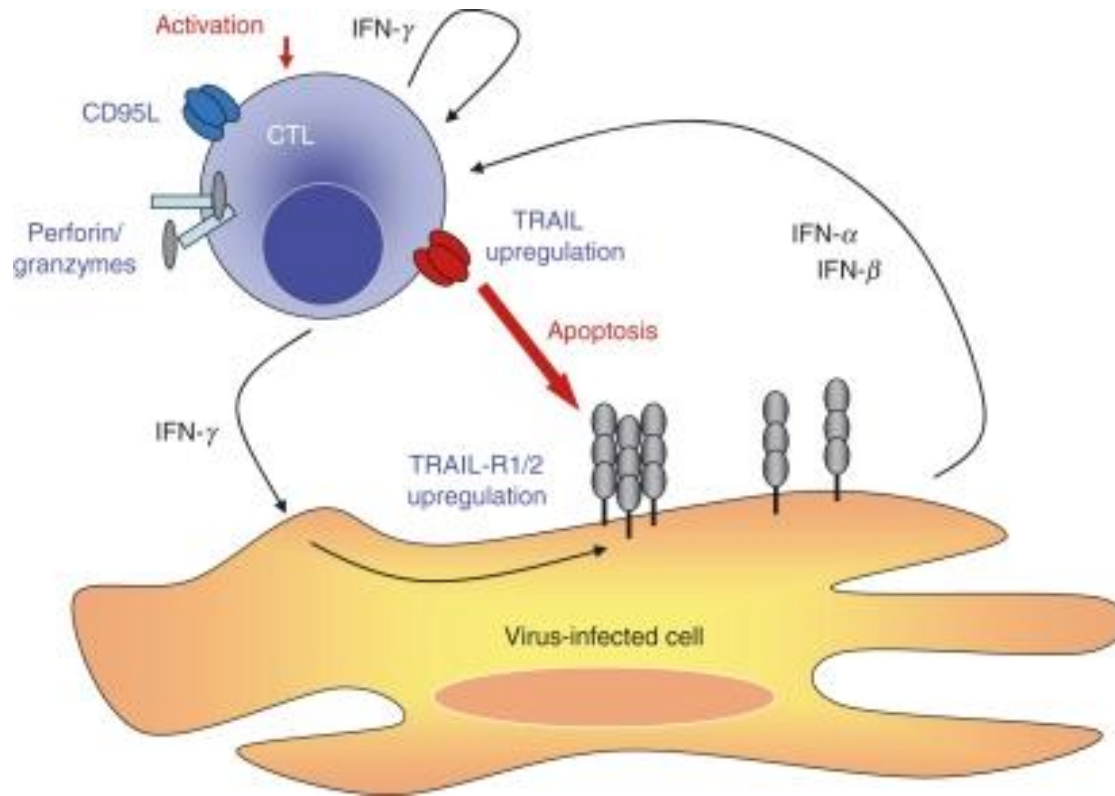




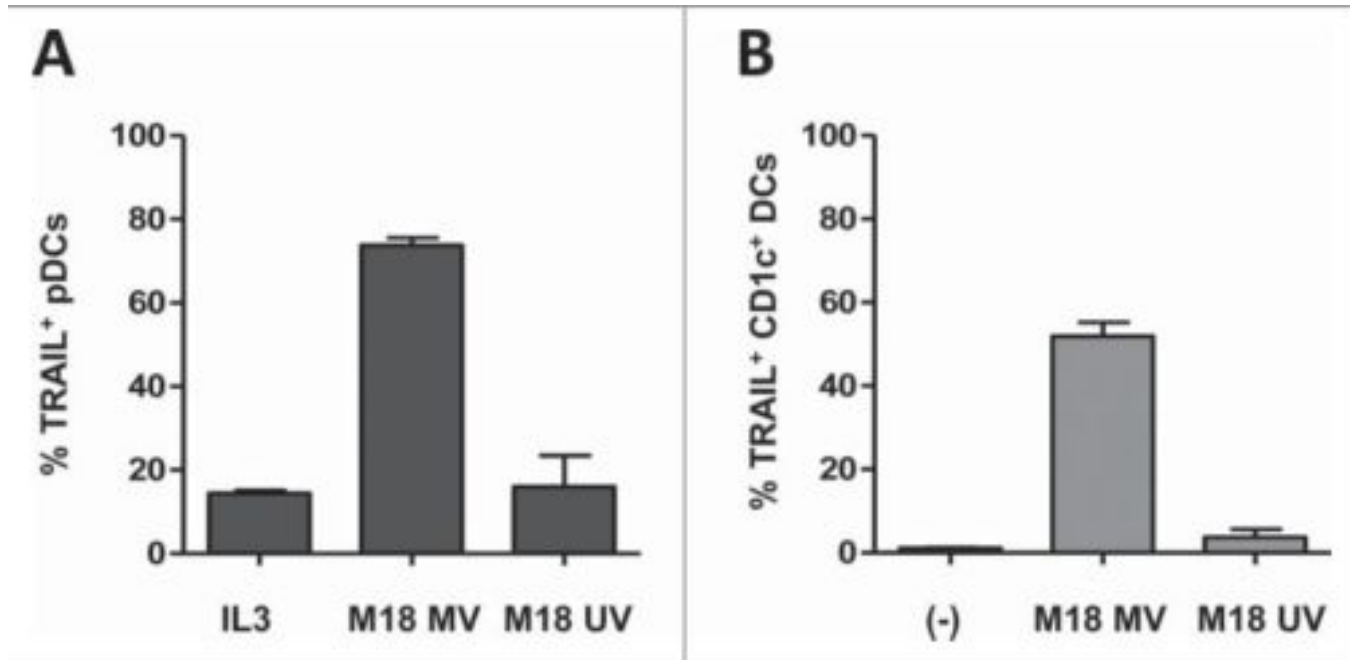
PeptiCRAd
(peptide-coated
conditionally
replicating
adenovirus)

Measles virus

Family: Paramyxoviridae
Group: (-)ssRNA



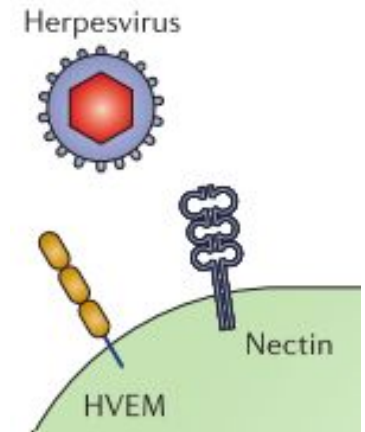
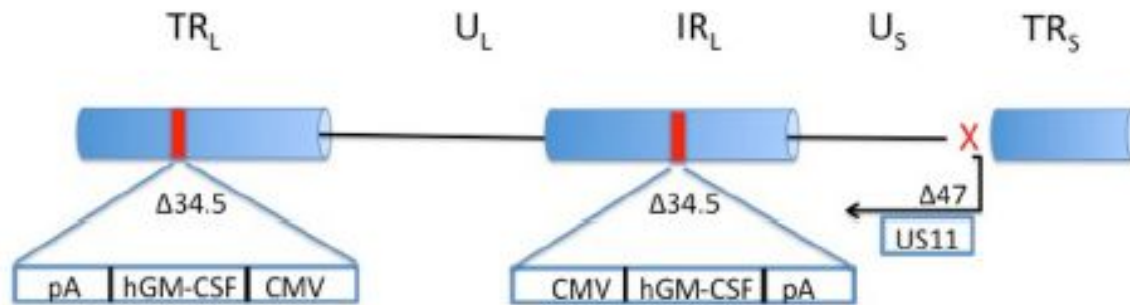
Flow cytometry assay



Herpes simplex virus

Family: Alphaherpesvirus
Group: dsDNA

T-VEC (Talimogen laherparepvec)



Herpes virus entry mediator

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

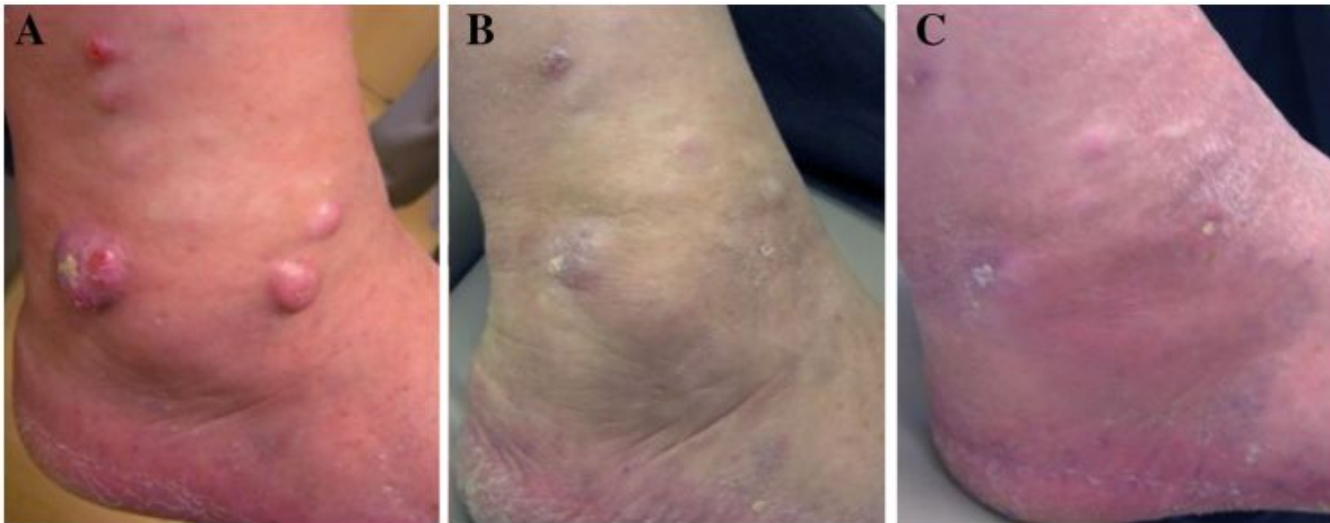


Fig. 2 Photograph of a melanoma patient (a) before; (b) 6 months after starting treatment with Talimogene laherparepvec (T-VEC); and (c) 9 months after starting treatment.

Vaccinia virus

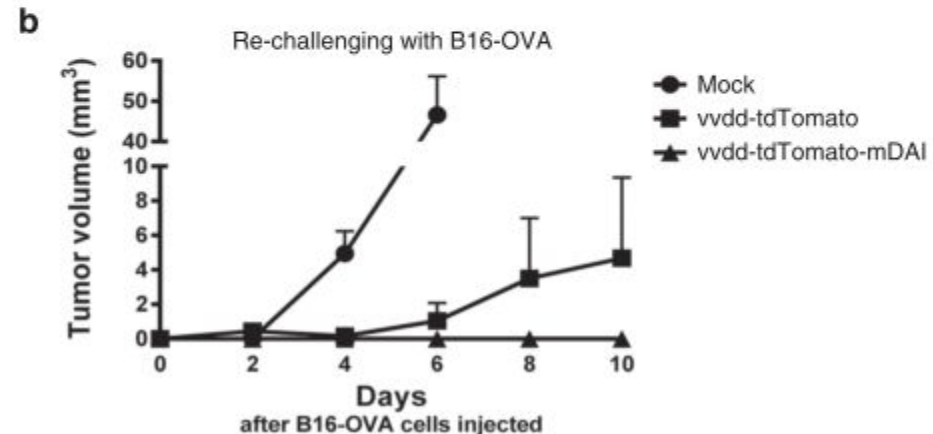
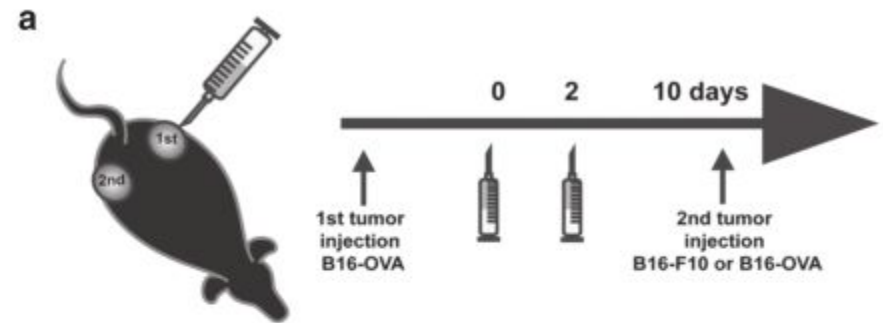
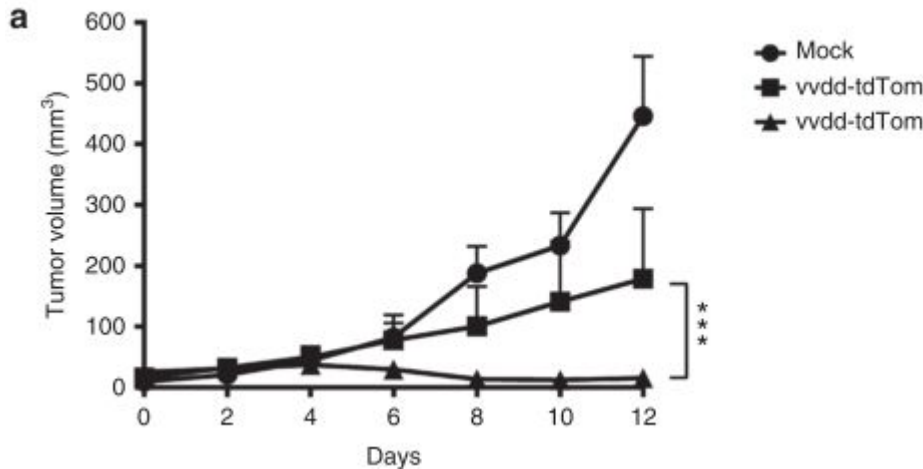
Family: poxvirus

Group: dsDNA (190 kb)



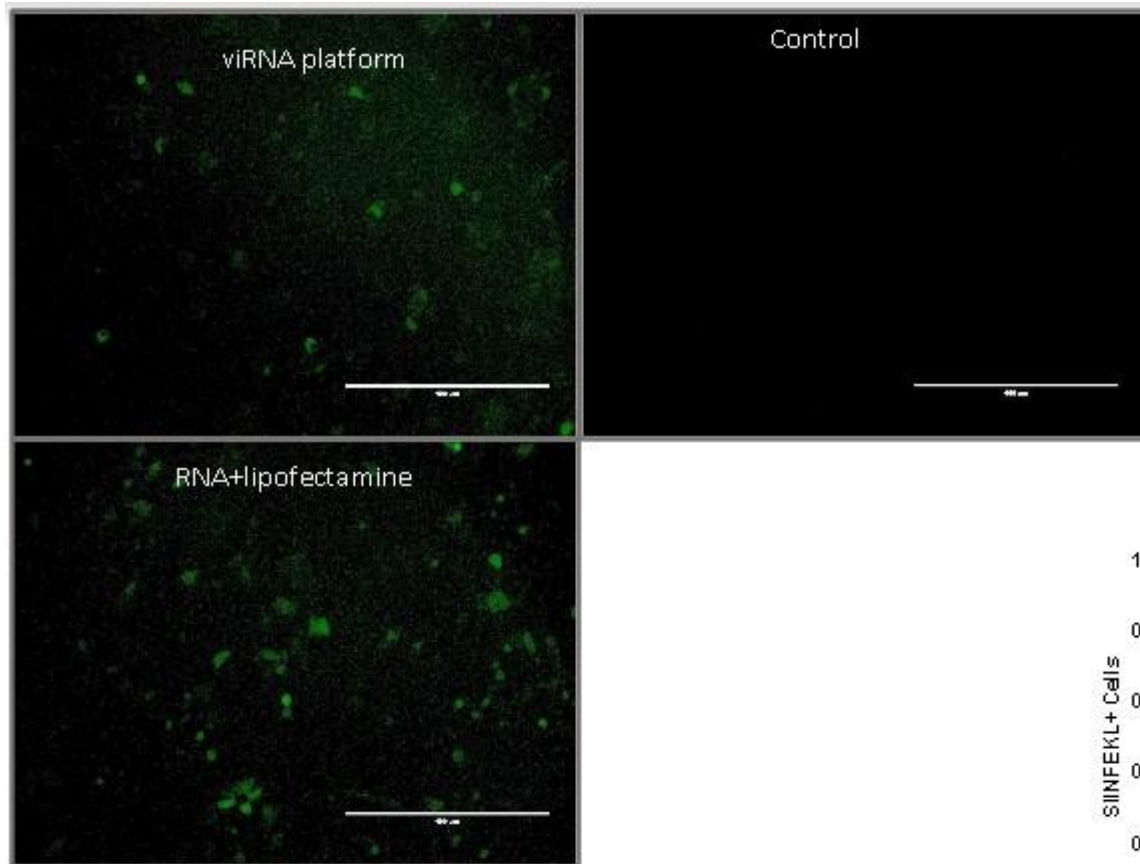
Intracellular pattern recognition receptor DNA-dependent activator of IFN-regulatory factors (**DAI**)

Deletions: thymidine kinase gene
vaccinia growth factor

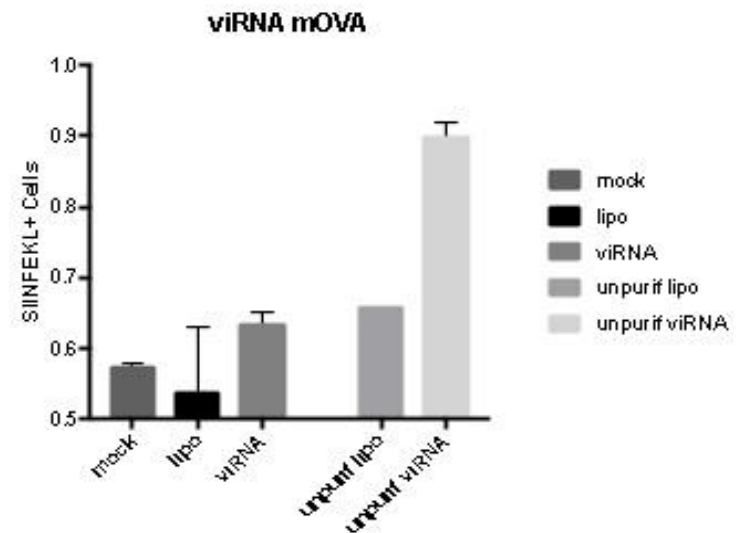


viRNA

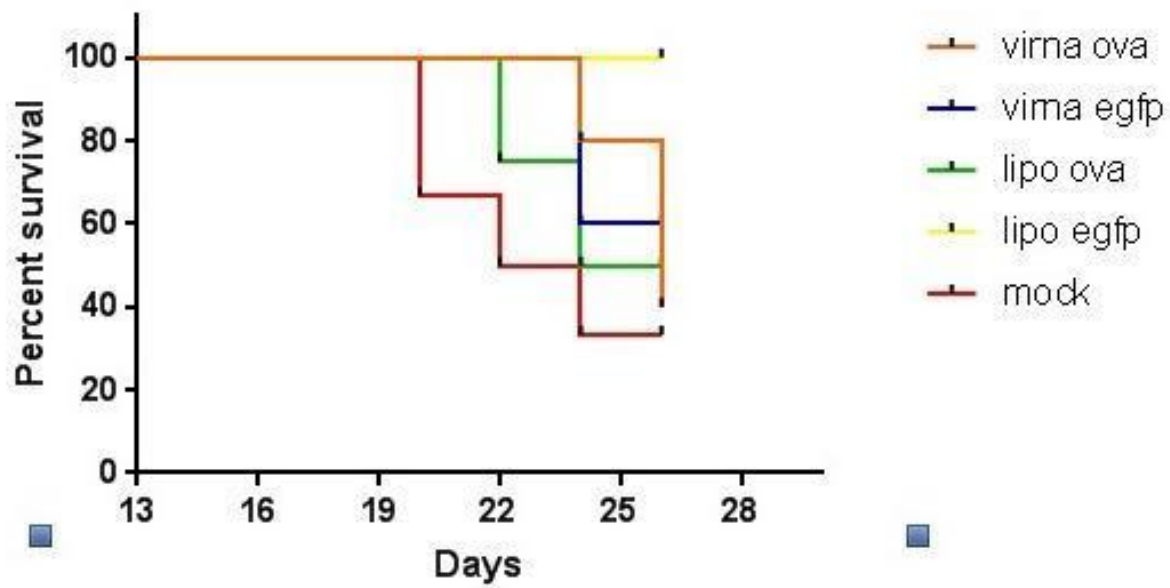
Vaccinia virus + lipofectamine + mRNA (ovalbumin)



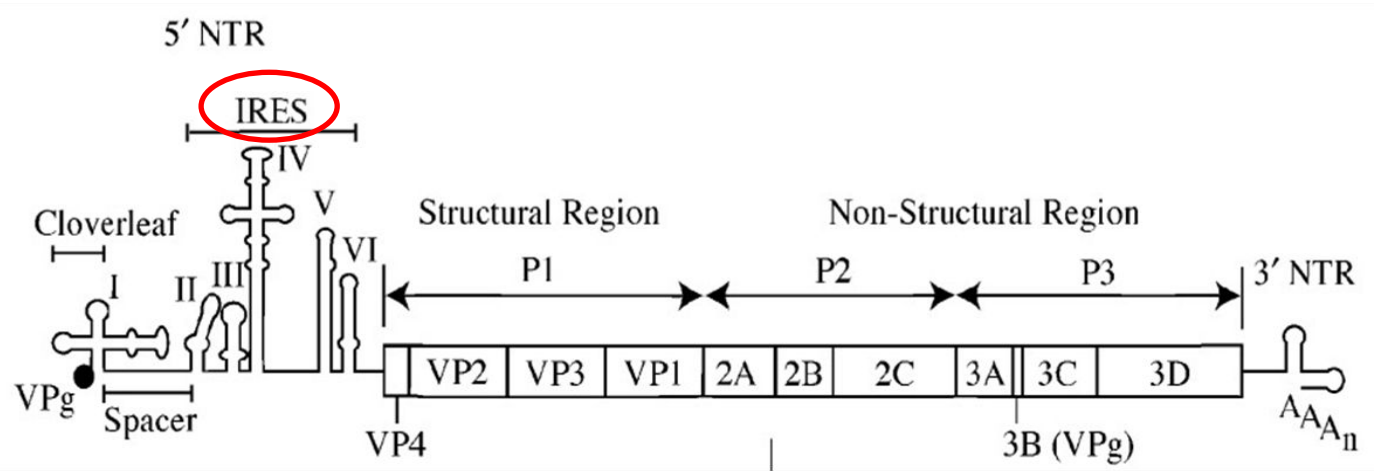
Naïve splenocytes
Flow cytometry assay



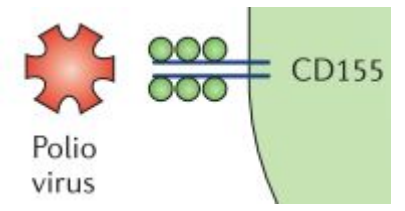
Survival curves



Poliovirus

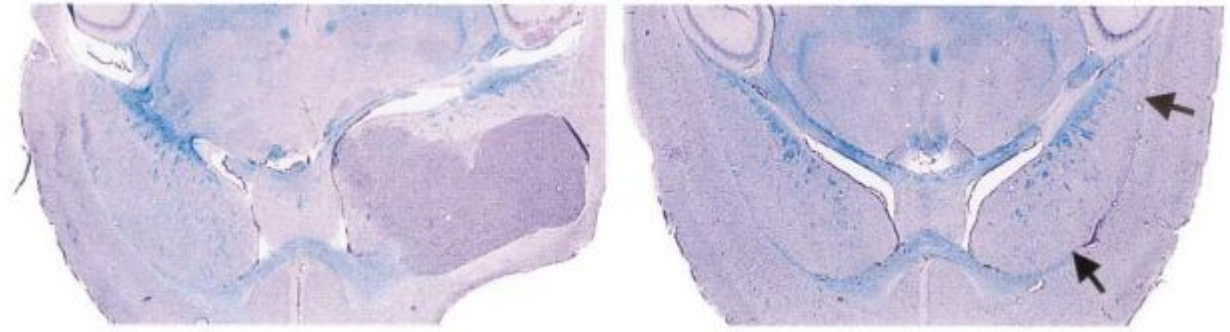


Family: Picornaviridae
Group: ssRNA



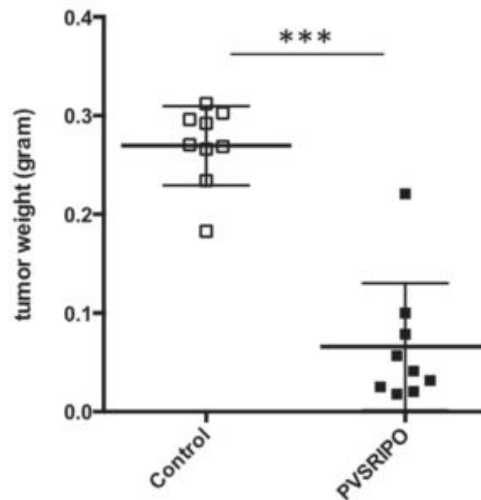
↑ CD155 in glioma cells

Exchange of the poliovirus internal ribosomal entry site with its counterpart from human Rhinovirus type 2 resulted in attenuation of neurovirulence in primates



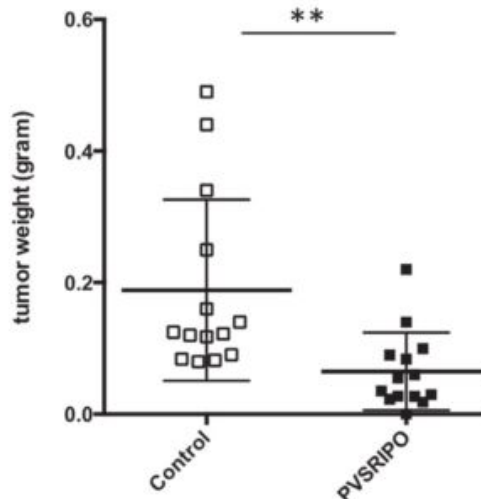
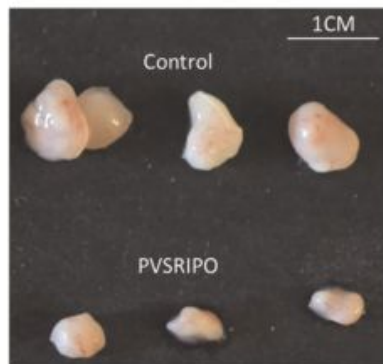
PVSRIPO in human breast and prostate cancer xenograft models

A.



SUM 149 breast cancer cell line

B.



DU145 prostate cancer cell line

Cowpea mosaic virus

Family: Secoviridae
Group: (+)ssRNA

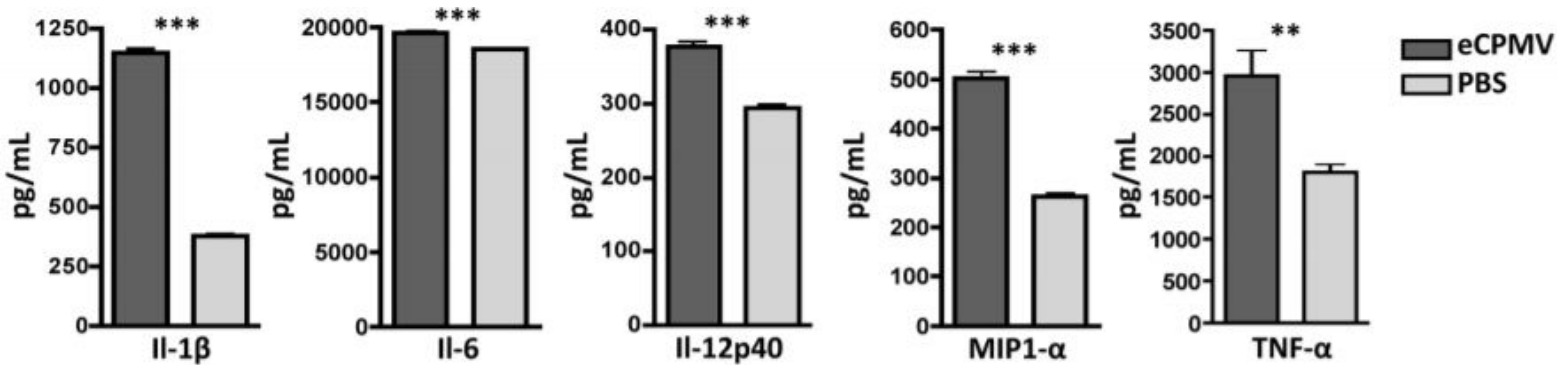
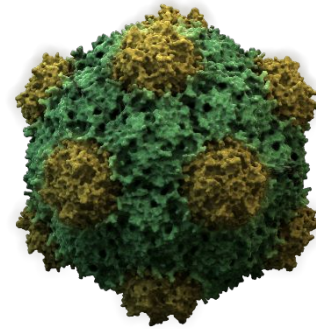
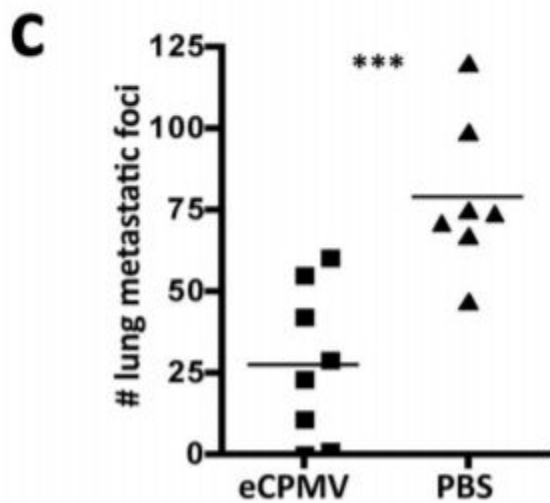
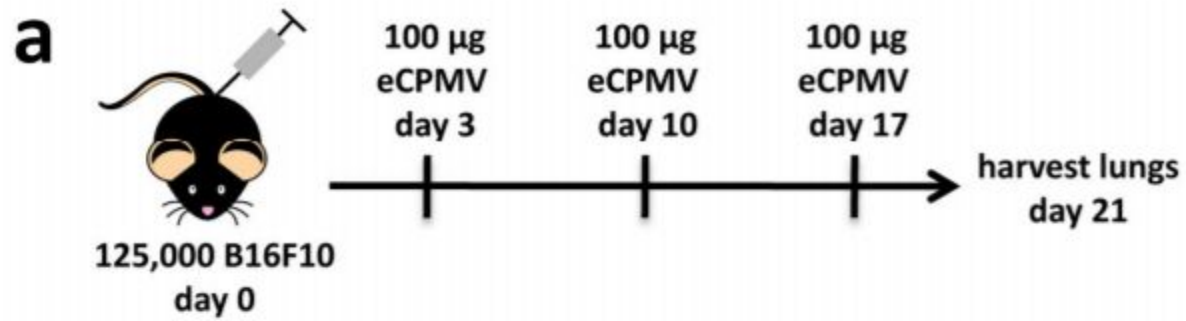
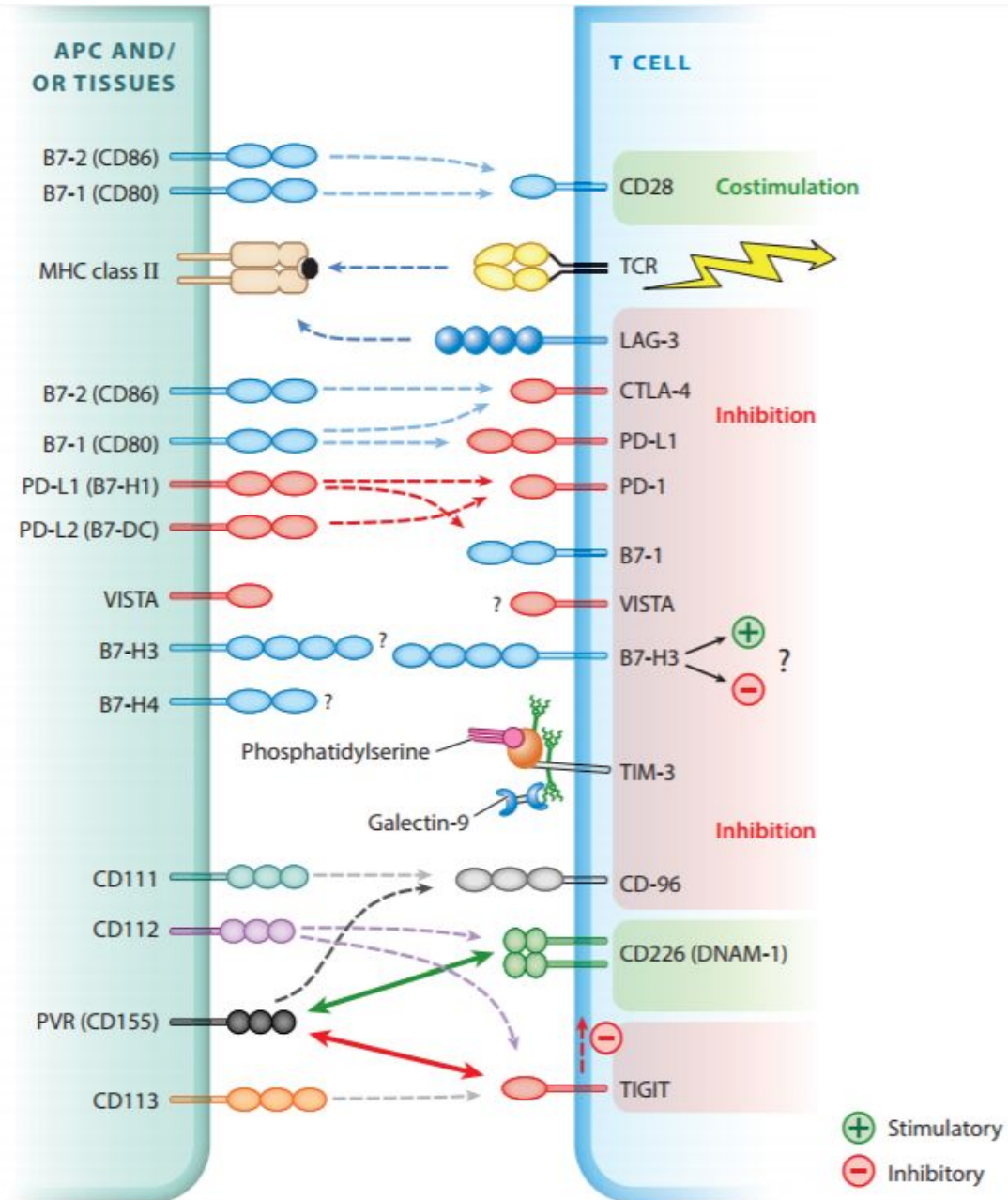


Figure 1. eCPMV nanoparticles are inherently immunogenic

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

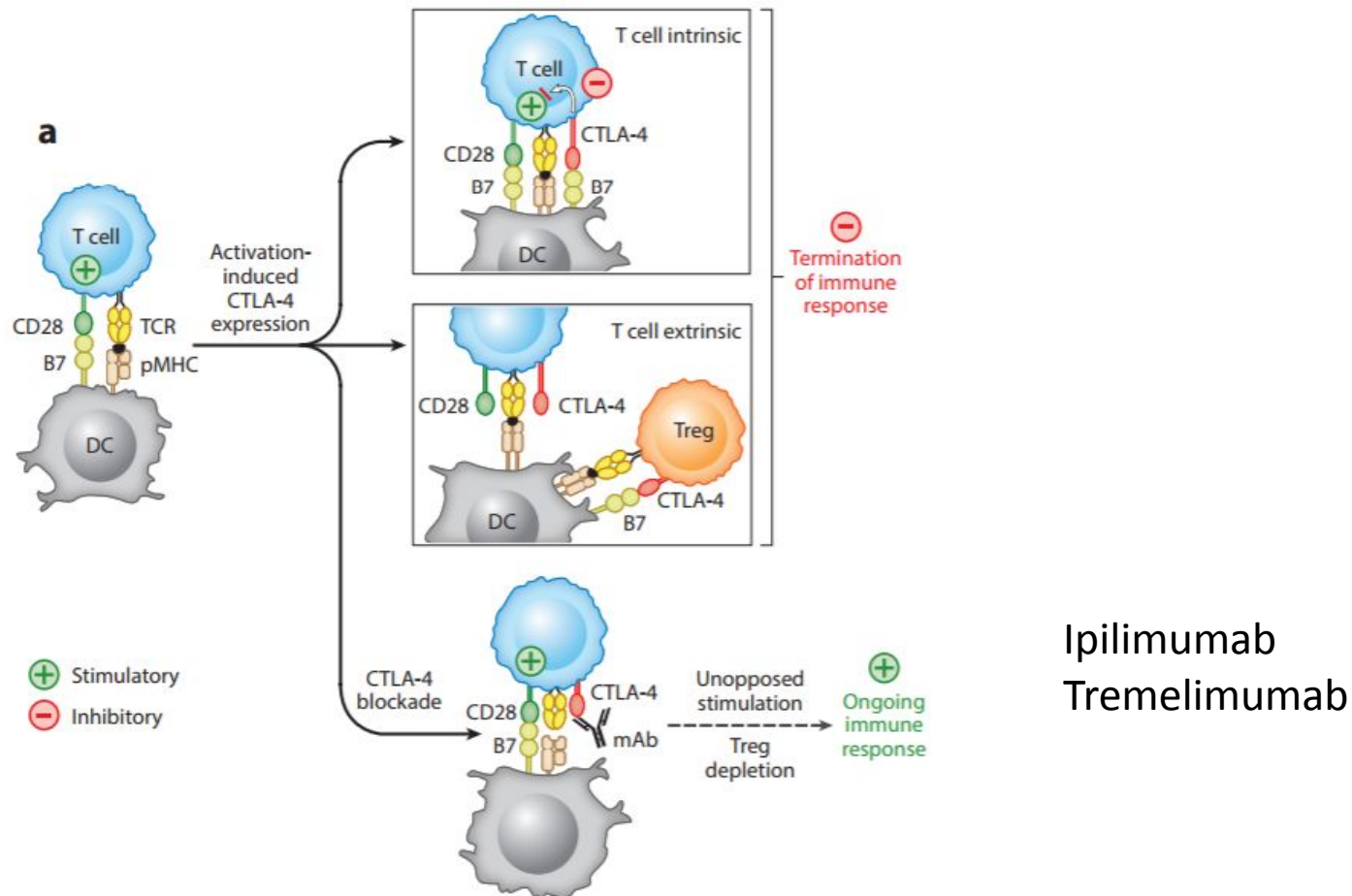


Co-inhibitory pathways



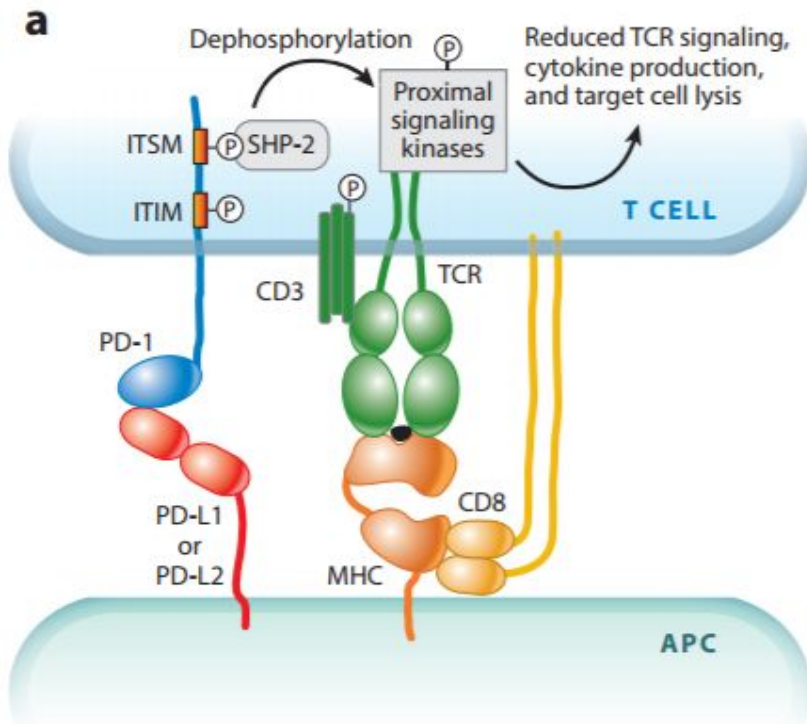
Cytotoxic T-lymphocyte antigen 4 (CTLA-4)

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



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

