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Faculty of Medicine
The Chinese University of Hong Kong

ONCOLYTIC VIRUS THERAPY

Oncolytic Virus Therapy

A New Era of Cancer Treatment

Peter Luk

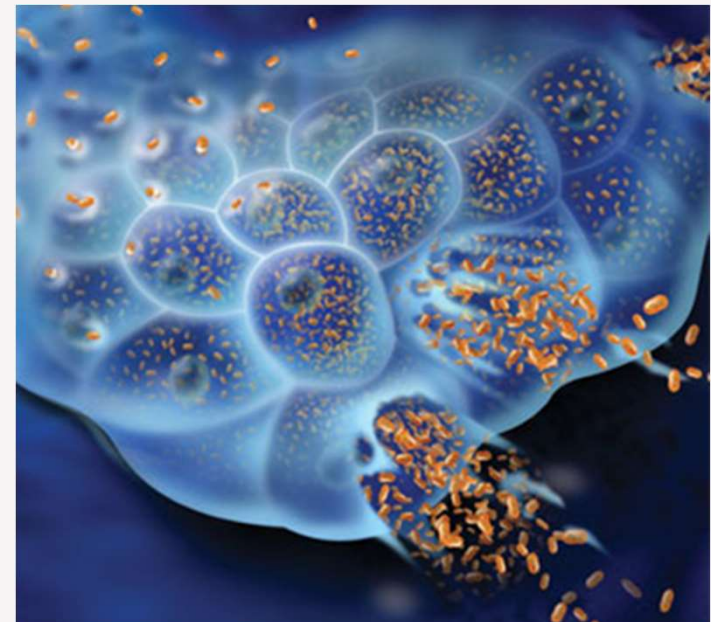
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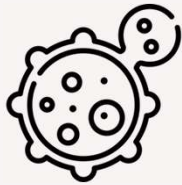
Date: 16 December 2021

Graduate research seminar

Supervisor: Professor Paul Chan



Today's Discussion



Cancer and Virus



Oncolytic Virus



OVs Undergoing
Clinical Trials

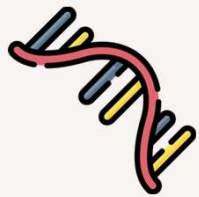


Future
Perspective

Presentation Outline

Virus and Human Cancer

~15% cancers are attributed to virus



Human T Lymphotropic Virus

Type 1

(HTLV-1)

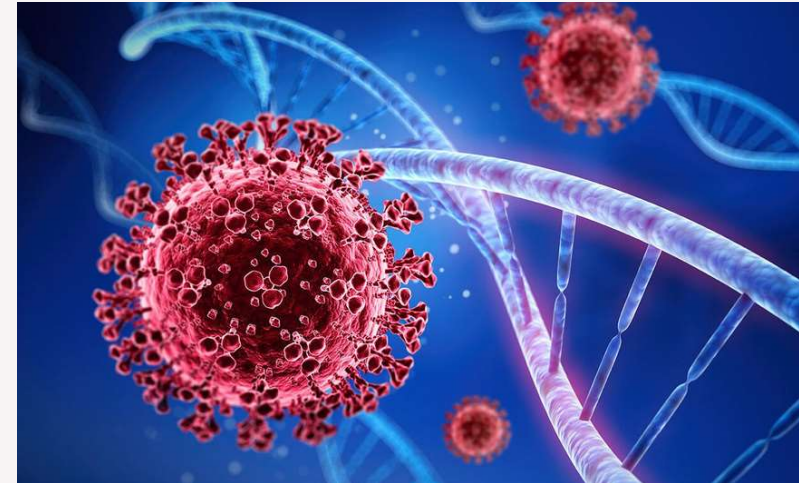
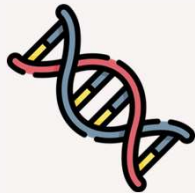
Hepatitis C Virus (HCV)

Epstein-Barr Virus (EBV)

Human Papillomavirus (HPV)

Hepatitis B Virus (HBV)

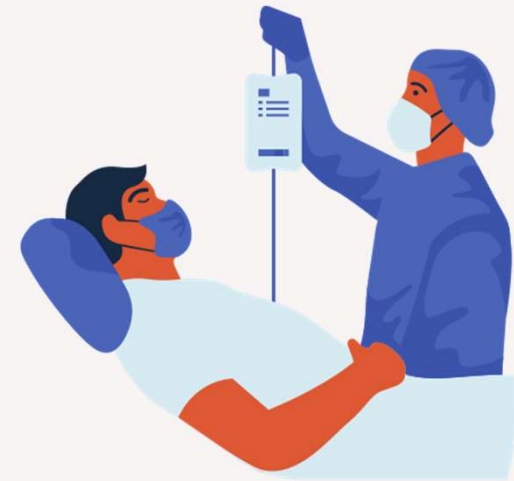
Human Herpesvirus-8 (HHV-8)



Cancer Treatment

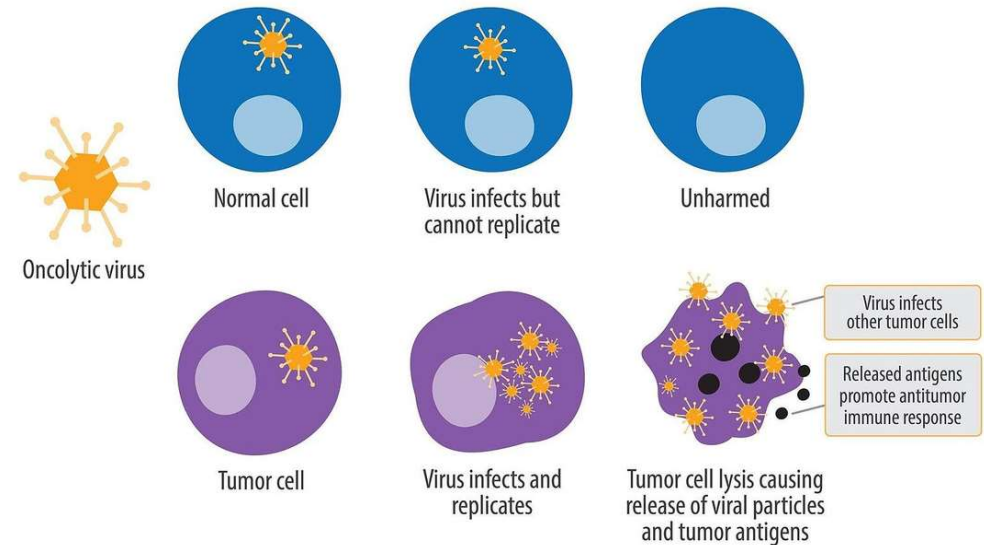
- Surgery
- Chemotherapy
- Radiation therapy
- Bone Marrow Transplant
- Hormone therapy
- Targeted Therapy
- Immunotherapy

Oncolytic Virus therapy

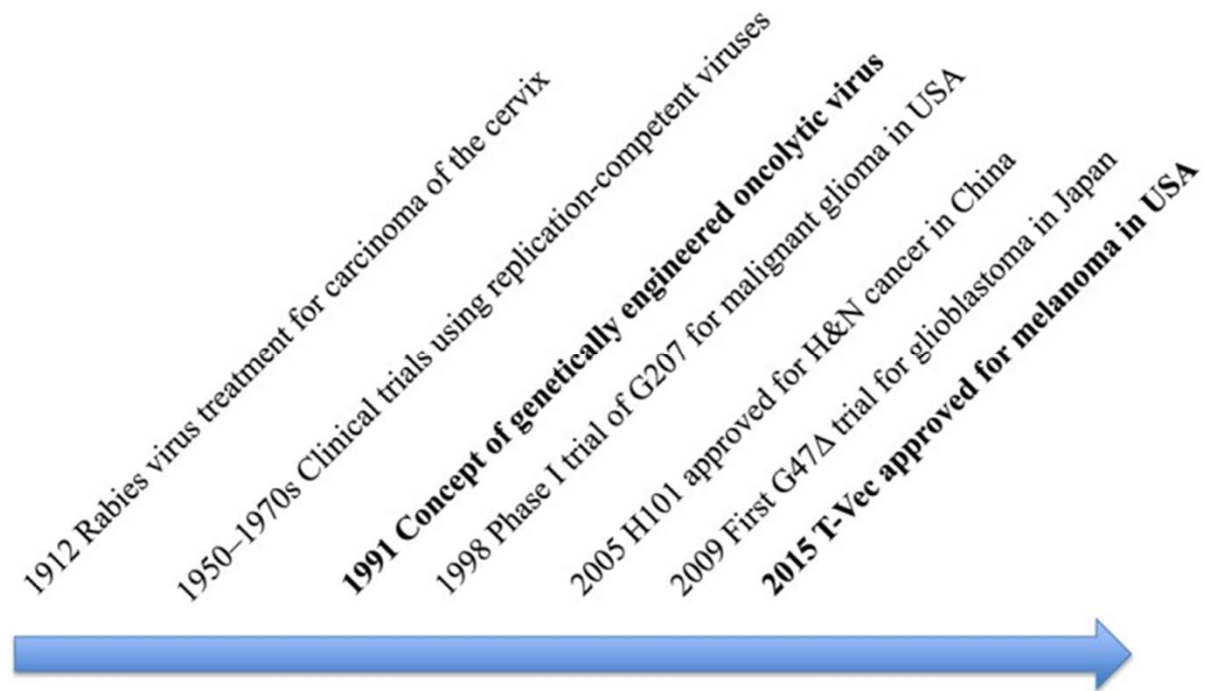


Oncolytic Virus (OVs) Therapy

- **Tumor Tropism:** selectively replicates in and kill cancer cells without harming the normal tissues
- **Stimulate the host-antitumor immune response**



Mary T, 2018





Natural

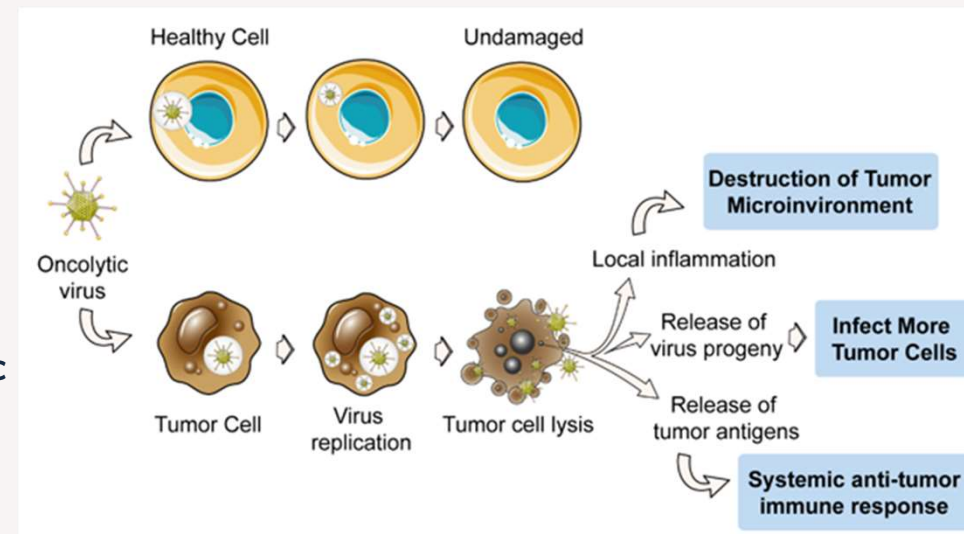
Naturally replicate in cancer cells
Nonpathogenic in humans

Genetically Modified

Engineer to direct target
unique cell surface or
Increase specificity

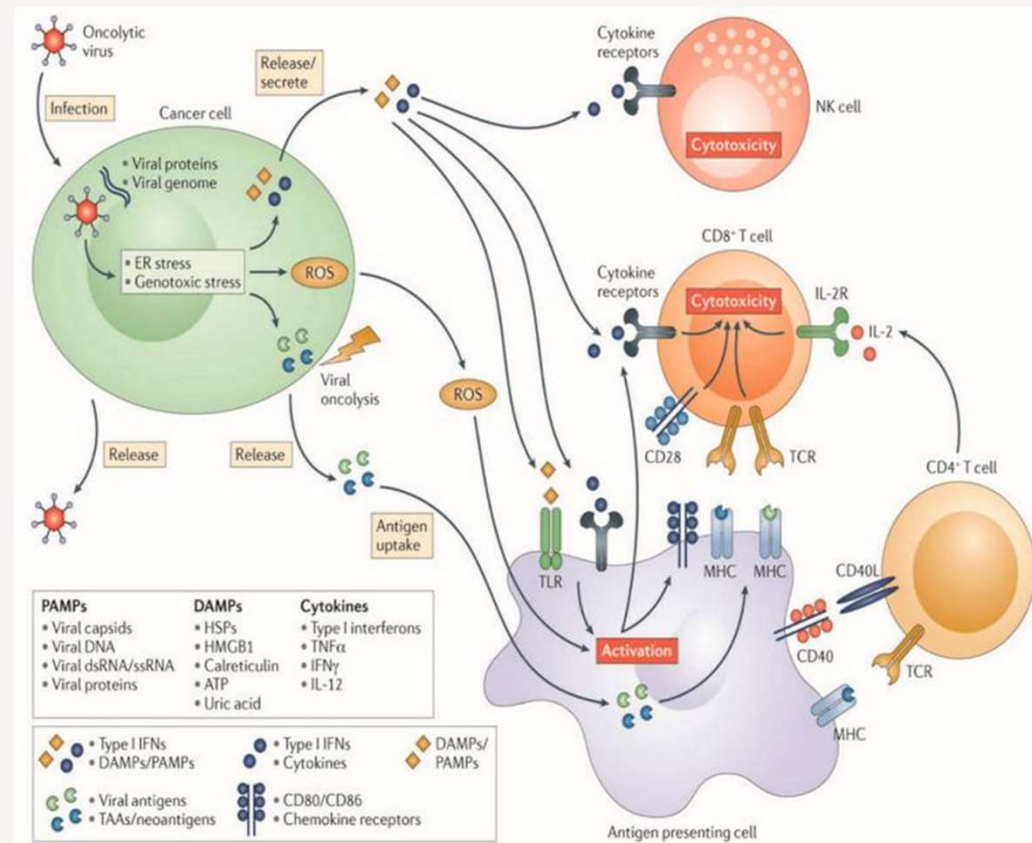
Mechanisms of OV's

- OV hijack tumor cell's protein synthesis,
- Promote viral products or infected tumor produce cytokines/ chemokines
- Release tumor-derived antigen after apoptosis
- Attract immune cells (cytotoxic T lymphocytes, natural killer cells, dendritic cells, phagocytic cells)
- Eliminate cancer cells



Systemic anti-tumor immunity



- Stress leads to ↑ROS, release IFNs
- Oncolytic cell death
- Release pathogen-associated molecular patterns (PAMPs), danger-associated molecular pattern signals (DAMPs)
- Activate antigen-specific CD4+ & CD8+ T cell response
- Expand into cytotoxic effector cells, traffic to tumor growth sites
- Promote an adaptive immune response to mediate tumor regression at distant tumor

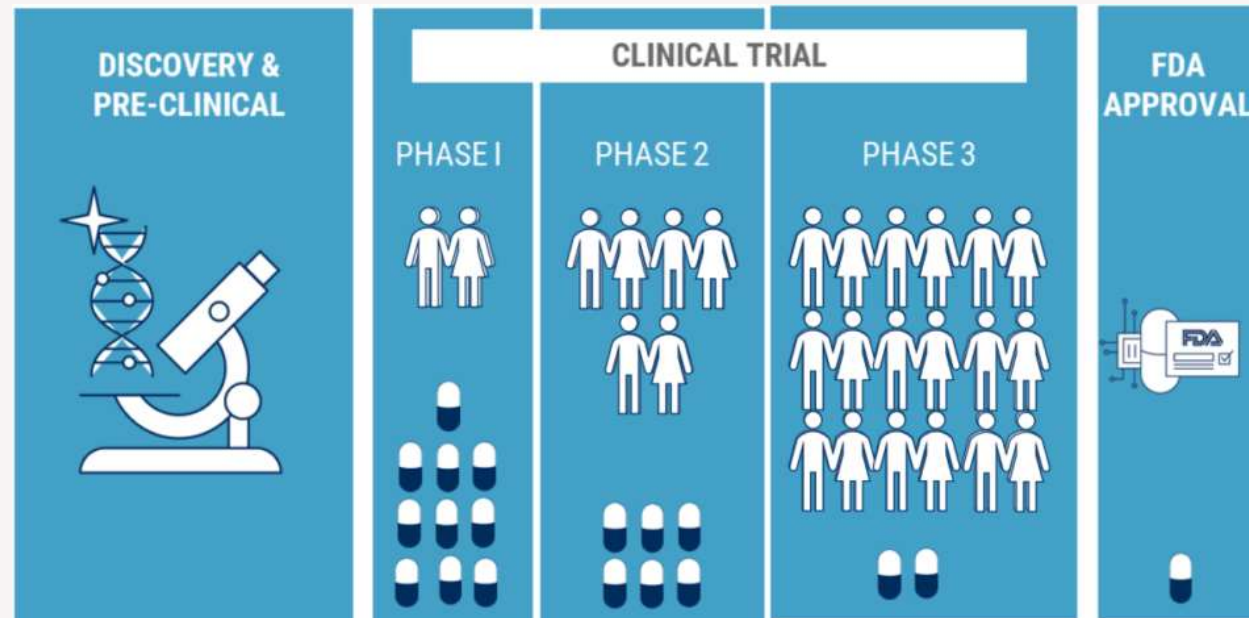


Nature Reviews | Drug Discovery

HL Kaufman *et al*, 2015

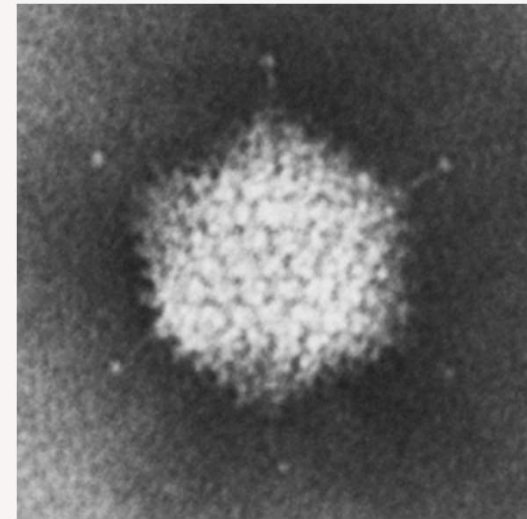
OVs Undergoing Clinical Trials

	
Adenoviruses	Paramyxoviruses
Herpesviruses	Enteroviruses
Poxviruses	Rhabdoviruses
Parvoviruses	Reoviruses



Adenovirus

- Non-enveloped, icosahedral, double-stranded DNA
- ~50 serotypes
- *Serotype 5
- Advantages:
 - High efficiency of gene transfer in dividing/ non-dividing cells
 - low risk of insertion mutagenesis
 - replication in an exponential manner
 - ~30 Clinical trials
 - H101

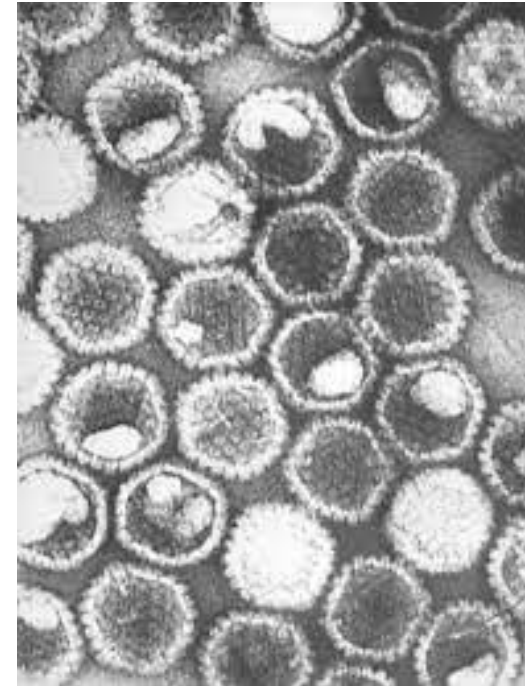


Oncorine (H101)

- Recombinant Adenovirus, serotype 5
- Approved by Chinese authorities for NPC in combination with chemotherapy in 2005
- Deletion in viral E1B-55k (p53 repressor)
- ~80% response rate > 40% with chemotherapy only
- Side effects: fever, local site pain, flu-like symptoms (all tolerated well)

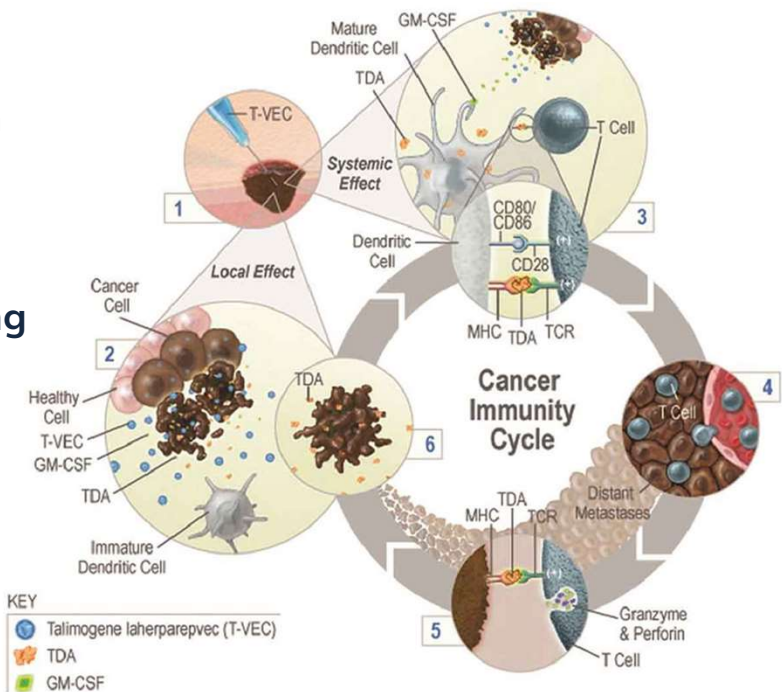
Herpesvirus

- Double-stranded DNA, icosahedral capsid
- >130 subtypes
- HSV-1/2, EBV, varicella-zoster virus
- *HSV-1
- Advantages:
- One of the best-known viruses, affecting ~70% of humans worldwide
- ~40 clinical trials
- T-Vec, Teserpaturev



T-VEC (Imlygic™)

- Local immunotherapy, kills melanoma cells in skin and lymph nodes
- Genetically modified herpes virus
- Deletion in γ 34.5 and α 47 genes
- human granulocyte-macrophage colony-stimulating factor (GM-CSF) inserted in γ 34.5 loci
- γ 34.5: negate the host cell's shut-off of proteins synthesis upon viral infection, inactivation render virus unable to replicate in normal cells and still replicate in cancer cells
- α 47: antagonize host cell's transporter associated with antigen presentation, deletion downregulates MHC class I expression
- GM-CSF: enhance antitumor immunity induction



KJ Harrington *et al*, 2015

Clinical Outcome of T-Vec

- Clinical trial shows the drug is well-tolerated by patients
- OpTiM study (Phase 3 trial)
- Common adverse events (AEs): fatigue, chills and pyrexia; only grade 3/4 AE: cellulitis
- No fatal treatment-related AE
- In 2015, FDA approved as the first OV therapy for patients with advanced melanoma



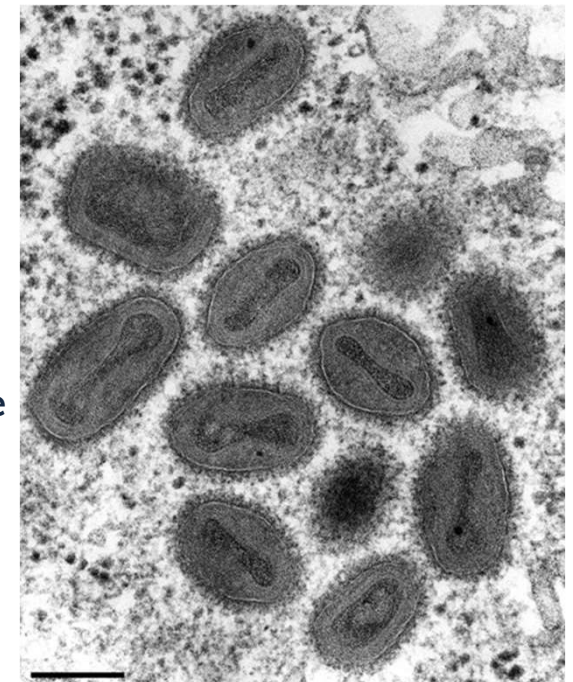
Teserpaturev (G47Δ)

- Triple-mutated, third-generation oncolytic herpes simplex virus
- Insert *E.Coli* LacZ gene to inactivate ICP6 gene
- ICP6 encodes a large subunit of ribonucleotide reductase (RR), essential for viral DNA synthesis
- ICP6 inactivation, HSV-1 can only replicate in proliferating cells with high levels of host RR
- In 2016, granted a “Sakigake” breakthrough therapy in Japan, for patients with malignant glioma



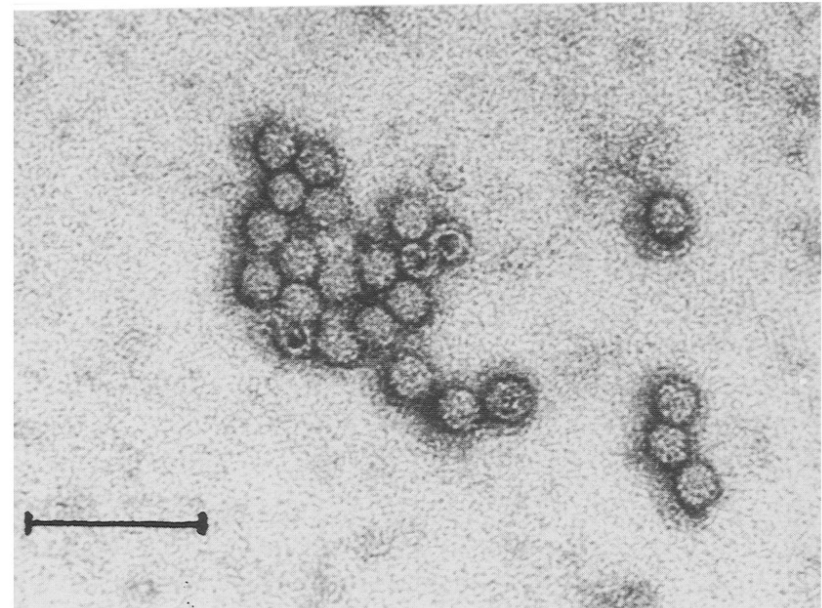
Poxvirus

- Generally enveloped, brick/oval shape
- Large size genome, single, linear, double-stranded DNA
- >80 species, 22 genera
- *vaccinia virus
- Smallpox
- Advantages:
- Rapid replication and infection cycle vaccinia viruses cause cell lysis within 12-48h
- Pexa-Vec (JX-594), genetically engineered vaccinia virus
- mutation in TK gene, conferring cancer cell-selective replication and insertion of human GM-CSF
- Adv: Intravenous stability for delivery, strong cytotoxicity, safe
- Clinical trials in combination with ipilimumab, durvalumab, nivolumab



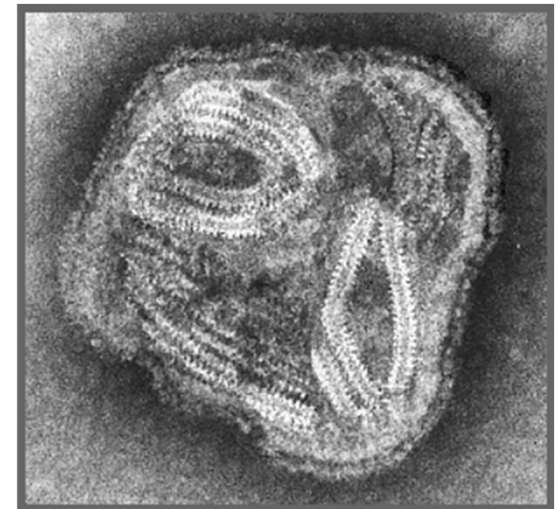
Parvovirus

- Non-enveloped, linear, single-stranded DNA
- Small size virion (23-28nm)
- *Rat H-1 parvovirus (H-1PV strain)
- Advantage:
- Remarkable oncoselectivity
- lack of pathogenicity in human
- small



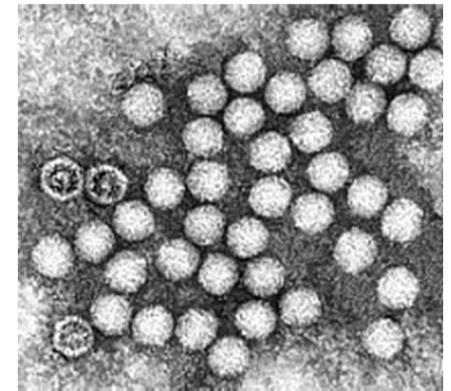
Paramyxovirus

- Large, enveloped, negative-sense RNA virus
- Wide range of distinct clinical illness in human
- Measles, mumps, parainfluenza virus
- *Avian-specific Newcastle disease virus (NDV), Sendai virus
- Advantages:
 1. NDV oncolysate vaccine
 2. Autologous tumor cell vaccine
 3. Oncolytic NDV alone/ combine with durvalumab



Enterovirus (Picornaviridae)

- Small, positive-sense, single-stranded RNA virus
- >90 subtypes
- *Coxsackievirus, Enteric Cytopathogenic Human Orphan (ECHO) serotype 1, 7 and 12
- Oncolytic potential discovered in 1950s by Dr. Voroshilova
- Massive screening for children's faecal samples during polio eradication campaign
- Identified enterovirus and their oncolytic properties
- Rigvir



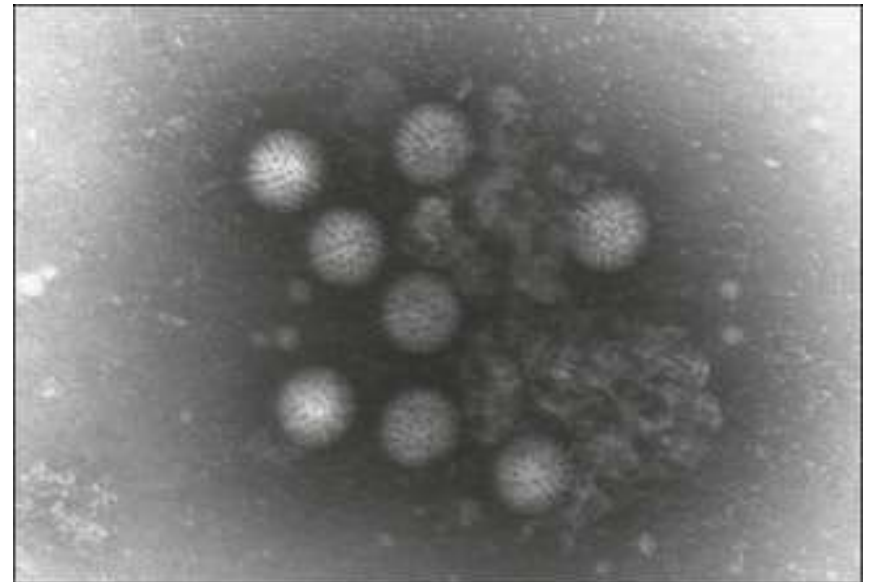
Rhabdovirus

- Enveloped, single negative-sense, single-stranded RNA virus
- *Vesicular stomatitis virus (VSV) and Maraba virus
- Advantage:
- Low pathogenicity
- Fast, cytoplasmic replication
- Used extensively to develop vaccines against infections (Ebola, Marburg, Zika, SARS)
- ~10 Clinical trials



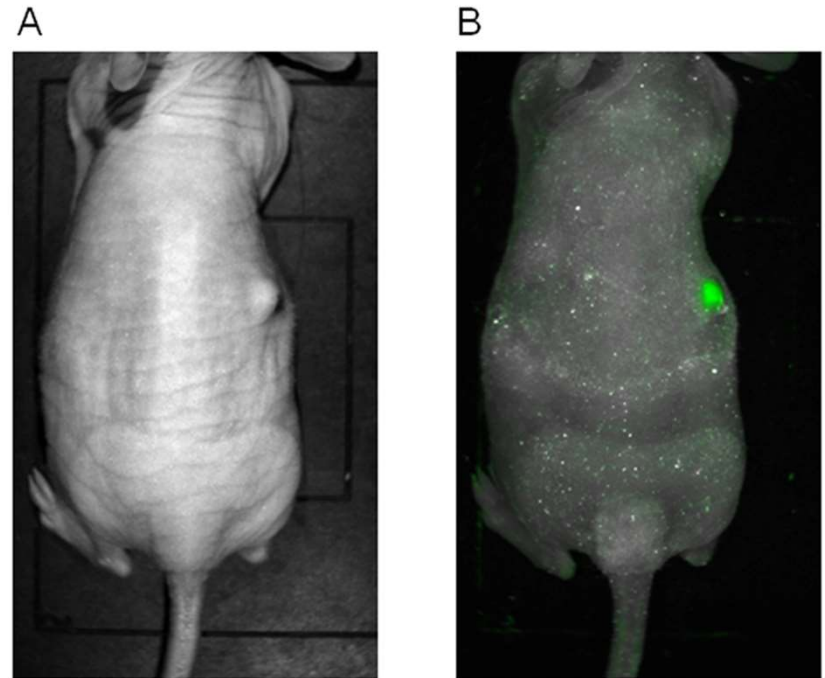
Reovirus

- Non-enveloped, double-stranded RNA viruses
- **R**espiratory **E**nteric **O**rphan virus
- Infections in plants, fish, birds, animals and humans
- Rotaviruses & orthoreovirus cause intestinal and respiratory infections in human
- Exploit altered signaling pathways (Ras) in cancer cells
- ~40 Clinical trials
- Pelareorep (Reolysin), unmodified isolated of reovirus



Other Implications

- Arm OVs with reporter genes for cancer imaging
- Used for detect tumor origin, patient-specific treatment selection, target delivery, presence of metastases
- Fluorescence imaging, use GFP to detect tumor behavior (amplification, invasion, metastasis)
- Modify chicken vaccine strain, NDV/B1 >NDV(F3aa)-GFP



Pindong Li *et al*, 2012

Limitations of OV's

- **Virus carrying the parental wild-type virus can be a disadvantage**
 - HSV-1 spread from cell-cell and does not cause viremia, T-Vec/G47 Δ is best administrated intralesionally, may not be suitable for intravenous delivery
- **Efficacy, OV diminished by circulating antibodies**
 - For reovirus, neutralizing anti-reovirus antibody titers reached max. by day 7. Systemic treatment should be administered in rapid, repeated within the first week



Future Perspectives

- Understand the oncolytic mechanisms
- Establish appropriate clinical trial design, dosing regimens, pharmacodynamics assays
- Overcome problem of pre-existing viral immunity to improve efficacy
- Focus on genetically modified OVs
- Biosafety
- \$\$



Reference

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Thank you!