Medical Biotechnology 2023'

Biological therapies

Lecture 17-18th

Treatment of malignant tumors with oncolytic viruses

Oncogenic virus

A virus capable of inducing tumors. The RNA tumor viruses (family Retroviridae), which are well defined and rather homogeneous, or the DNA viruses, which contain a number of viruses capable of inducing tumors, including poxviruses, papillomaviruses, herpesviruses and polyomavirus.

Oncolytic virus

A type of virus that infects and lyses (breaks down) cancer cells but not normal cells. Oncolytic viruses can occur naturally or can be engineered by changing other viruses. Oncolytic virotherapy, a revolutionary tool for cancer treatment has shown promising results for the last two decades.

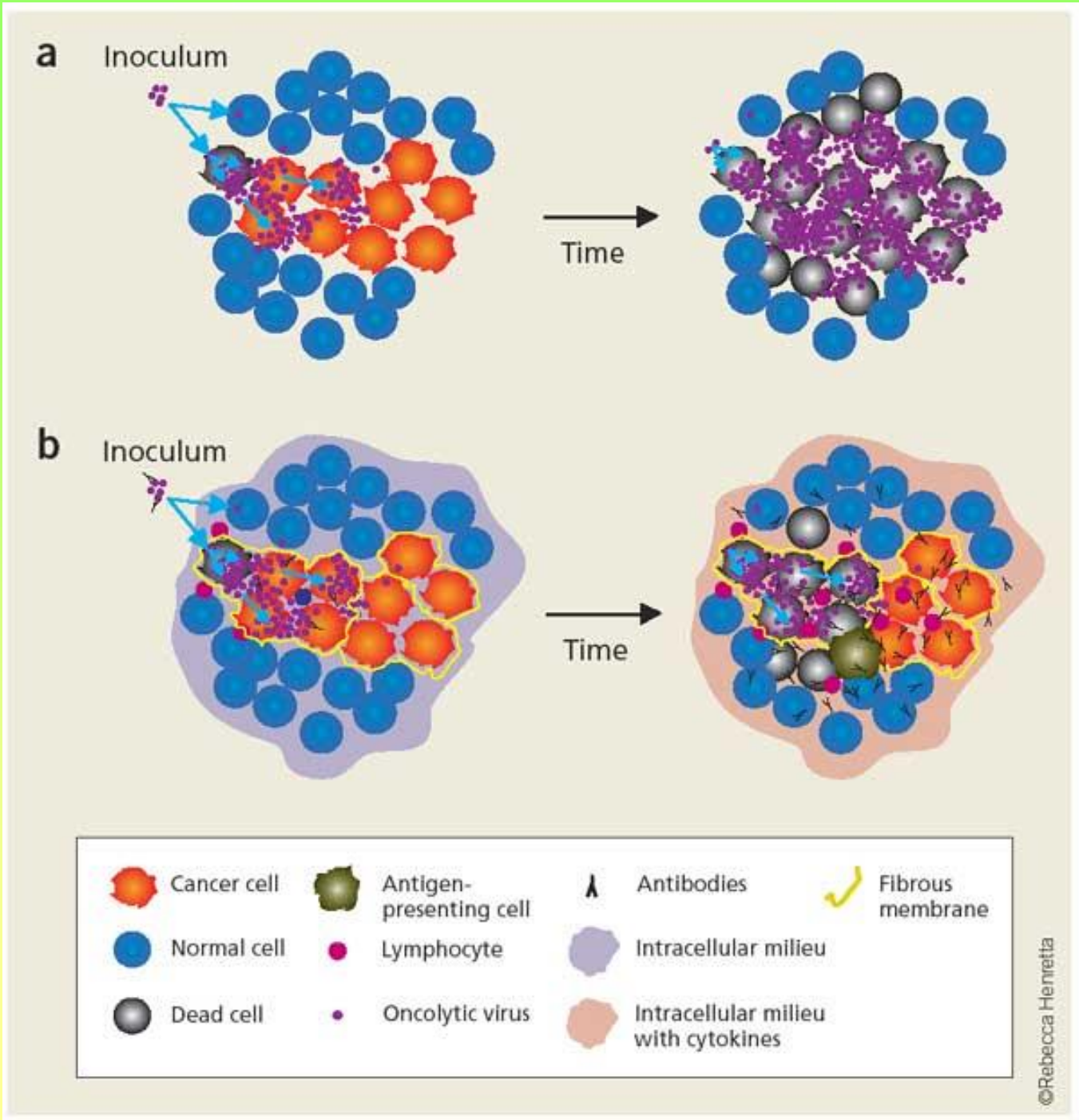
History of viral oncolysis

- In ***1904, George Dock*** reported a dramatic remission of chronic myeloid leukemia in a woman following a presumed infection by influenza virus.

- The first experimental demonstration of viral oncolysis is attributed to ***Levaditi*** and ***Nicolau***, who showed that vaccinia virus was able to inhibit tumors in both mice and rats. In the 1950s and 1960s, trials were conducted with multiple viruses that had been selected in tissue culture for their ability to replicate in tumor cells.

Immuntherapy with oncolytic viruses

- An ***oncolytic virus*** is a virus that preferentially infects and lyses cancer cells; these have obvious functions for cancer therapy, both by **direct destruction** of the tumor cells, and, if **modified,** as vectors enabling genes expressing anticancer proteins (E.g. p53) to be delivered specifically to the tumor site.
- Most current oncolytic viruses are engineered for tumour selectivity, though there are a few naturally occurring ones such as autonomous parvoviruses, Seneca Valley virus (SVV), myxoma virus, Reovirus (respiratory enteric orphan), and Newcastle disease virus (NDV).


a
Inoculum
Time
b
Inoculum
Time
Cancer cell
Antigen-presenting cell
Antibodies
Fibrous membrane
Normal cell
Lymphocyte
Intracellular milieu
Dead cell
Oncolytic virus
Intracellular milieu with cytokines
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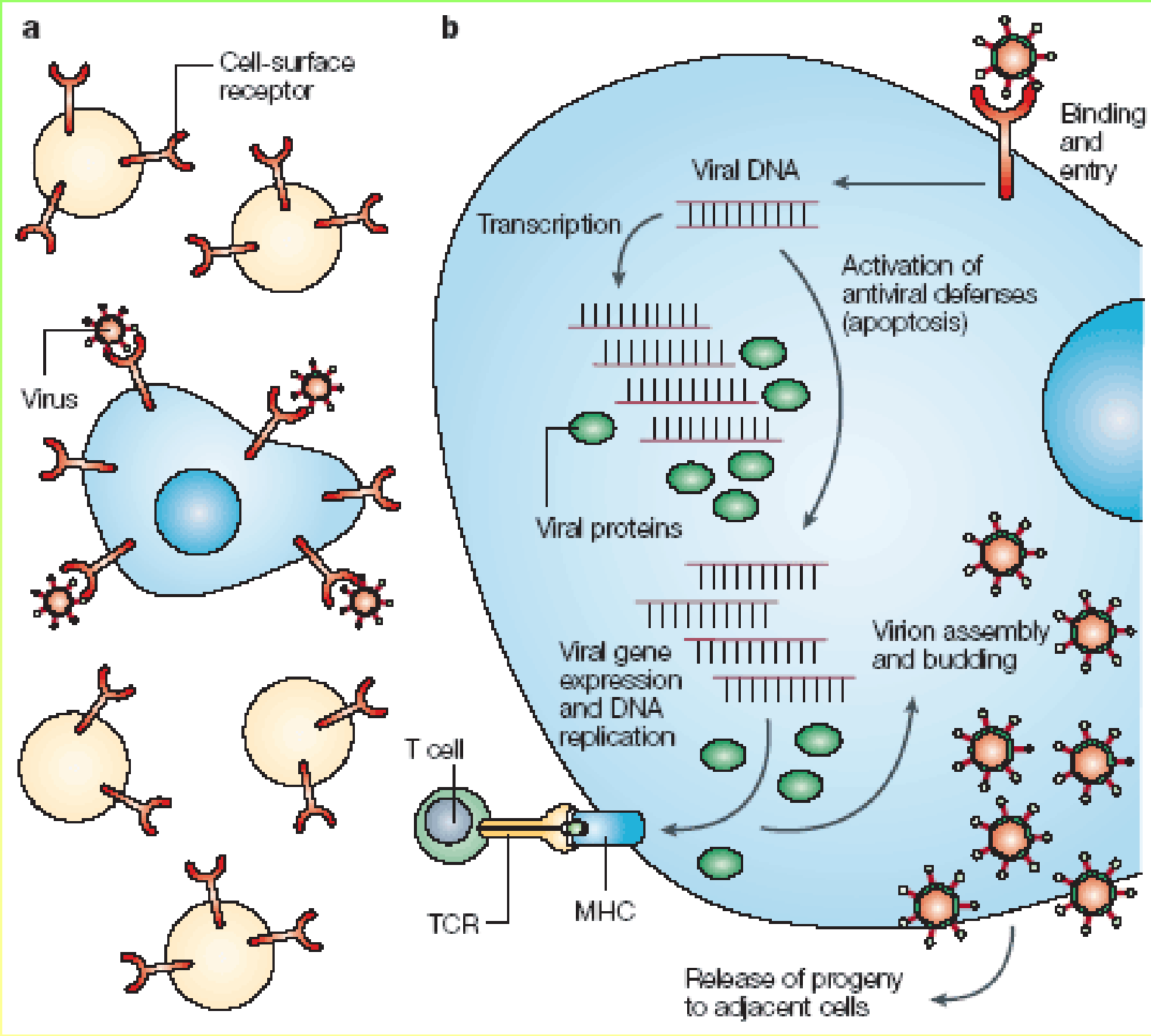
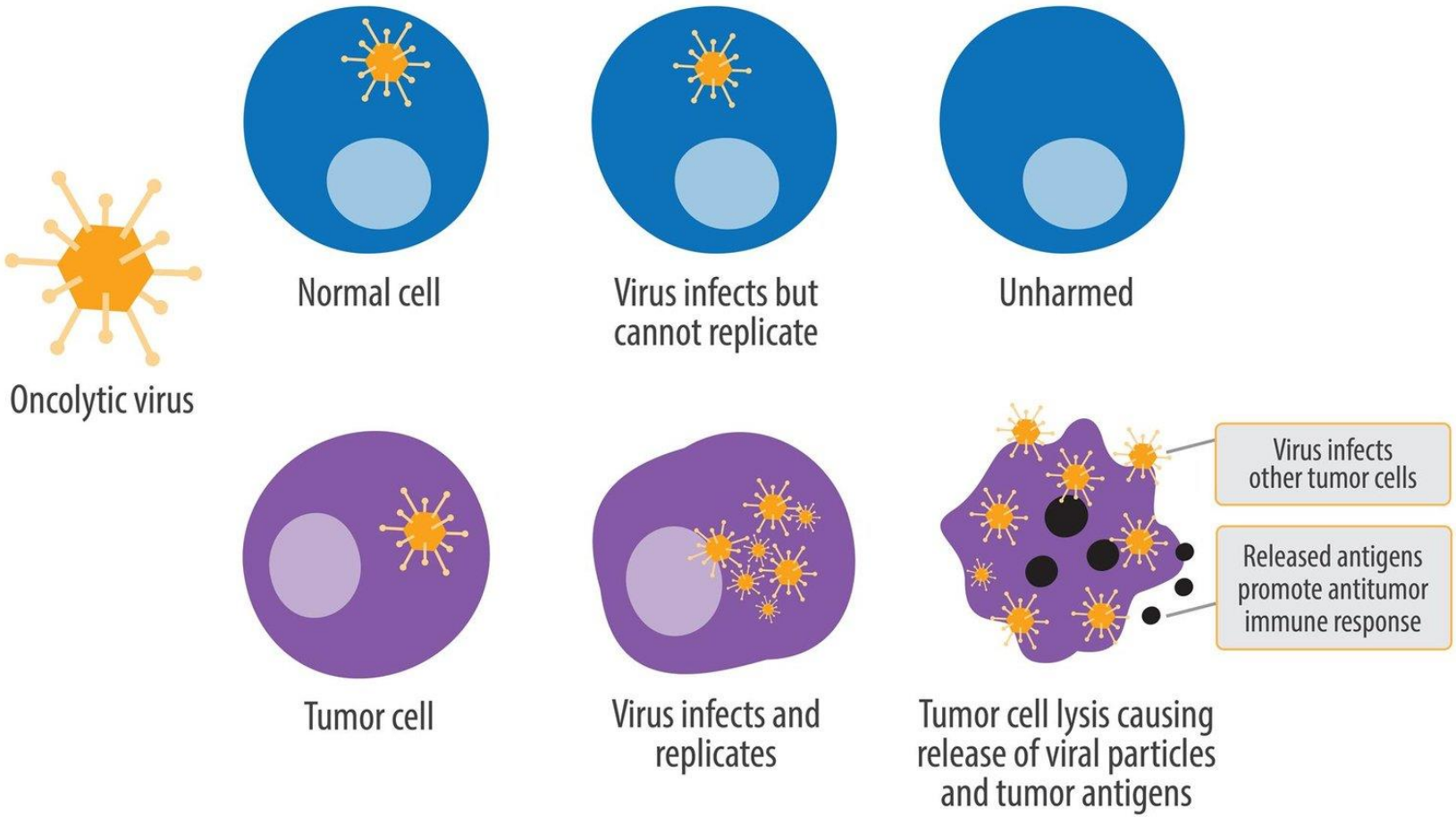
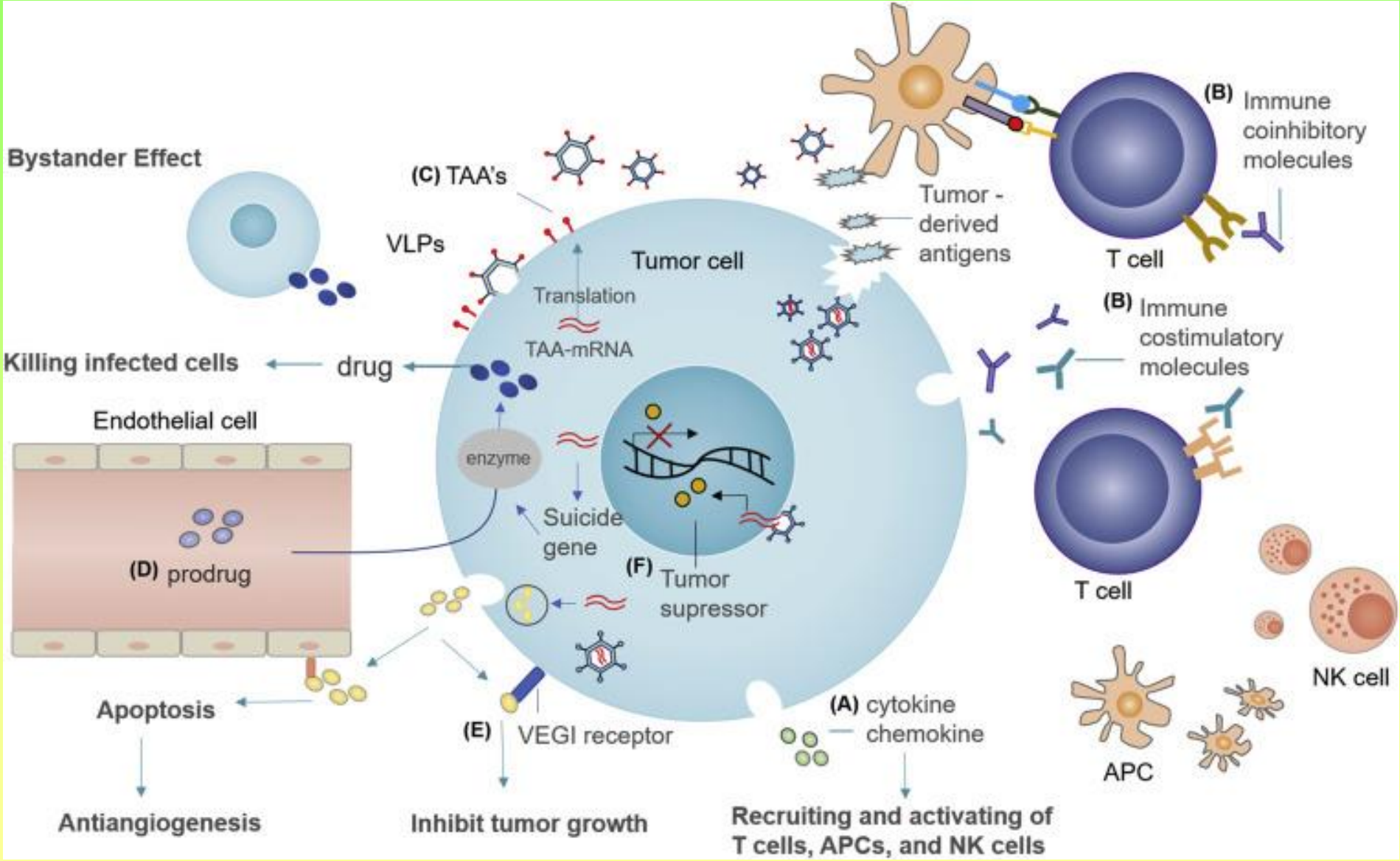

a
Cell-surface receptor
Virus
b
Binding and entry
Viral DNA
Transcription
Activation of antiviral defenses (apoptosis)
Viral proteins
Viral gene expression and DNA replication
Virion assembly and budding
T cell
TCR
MHC
Release of progeny to adjacent cells

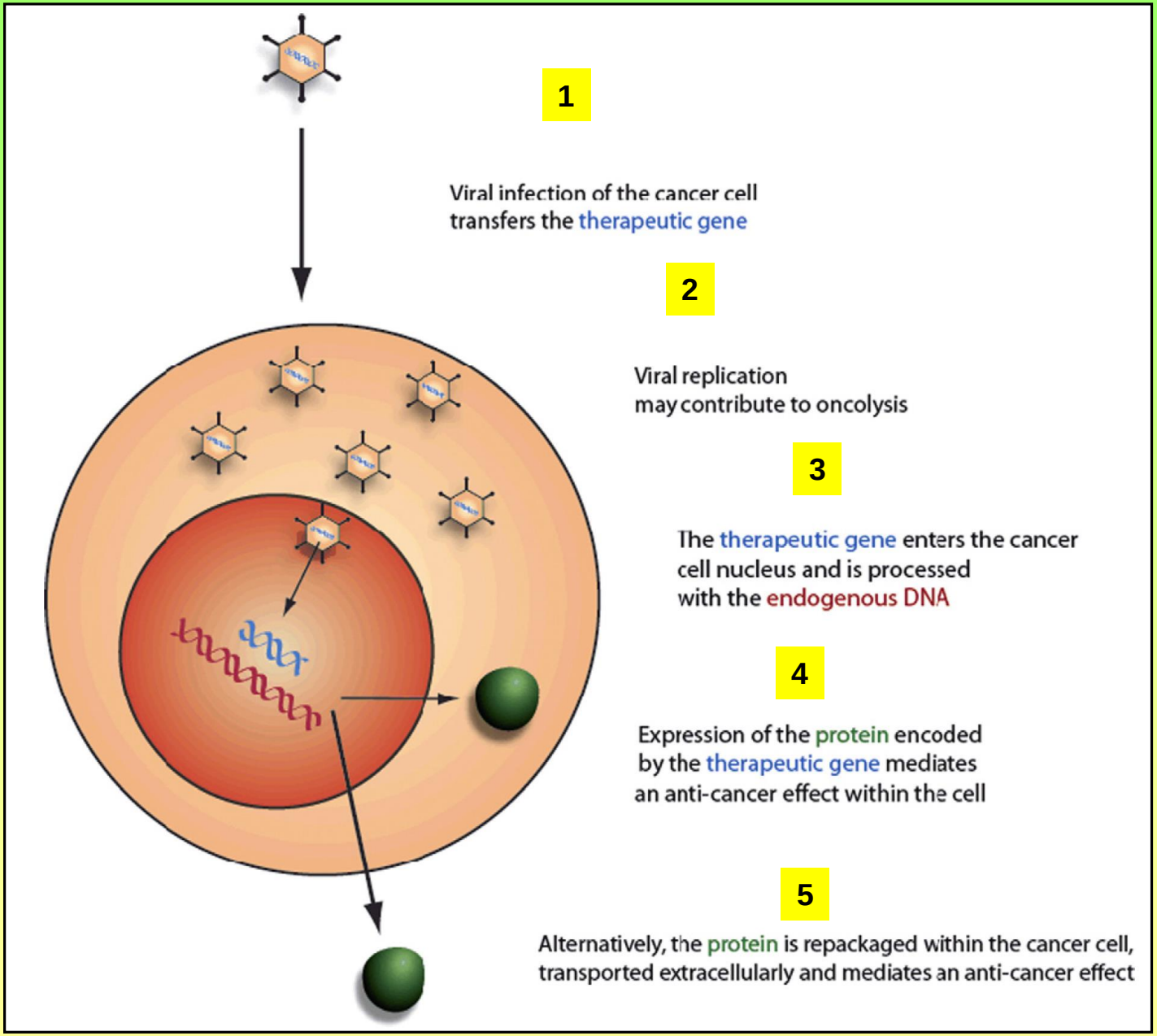
Antitumor Mechanisms of an Oncolytic Virus

CrownBio
CONNECTING SCIENCE TO PATIENTS




Bystander Effect
(C) TAA's
VLPs
Tumor cell
Translation
TAA-mRNA
drug
Killing infected cells
Endothelial cell
enzyme
Suicide gene
(D) prodrug
(F) Tumor supressor
Apoptosis
(E) VEGI receptor
Antiangiogenesis
Inhibit tumor growth
(A) cytokine chemokine
Recruiting and activating of T cells, APCs, and NK cells
Tumor - derived antigens
(B) Immune coinhibitory molecules
T cell
(B) Immune costimulatory molecules
T cell
NK cell
APC

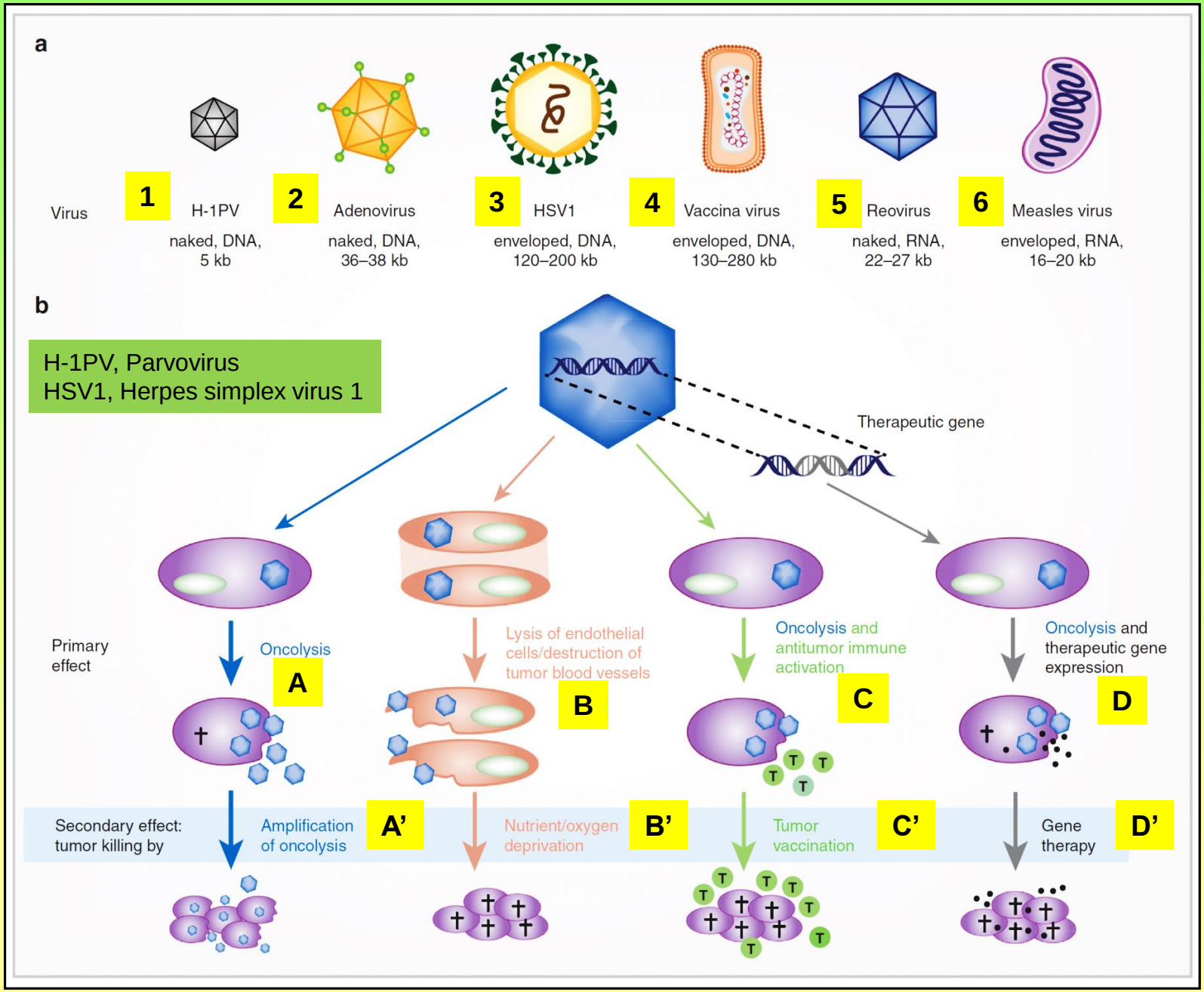
Combined viral gene therapy and oncolysis



In addition to viral oncolysis, viral vectors of gene therapy are capable of introducing a gene whose protein product mediates a cytotoxic effect.

Bourke MG et al, Cancer Treatment Rev, 2011

Oncolytic viruses and their modes of action



Ungerechts G, Mol Therapy — Methods & Clin Dev, 2016

Optimizing oncolytic viruses (1)

What are the features that are required for oncolytic viruses to be used effectively to treat cancer?

- Not a human pathogen, but infects human cells. This will minimize the chance that pre-existing immunity against the vector will hinder its therapeutic utility.
- Limited side-effects or toxicity to normal tissues.
- Recombinant technology is available. This technology will facilitate the introduction of transgenes that can be used to monitor viral spread, and to arm vectors with therapeutic or suicide genes.

Parato KA et al, Nature Rev Cancer, 2005

Optimizing oncolytic viruses (2)

- Viral life cycle should include rapid replication, cytolysis and spread. This will facilitate amplification of each viral therapeutic dose, allowing the virus to spread more rapidly than the vector-specific immune response. This will also maximize the efficacy of each therapeutic application - a virus capable of cell–cell transmission would have the added benefit of spreading with minimal systemic exposure and restricted or delayed immune involvement. This will allow the virus to rapidly kill the tumor cell in which it replicates, rather than establishing a chronic infection, to minimize cell destruction.
- Can be given systemically.

Parato KA et al, Nature Rev Cancer, 2005

Optimizing oncolytic viruses (3)

- Is a potent adjuvant, enabling the virus to also act as an anticancer vaccine. This serves not only to eradicate the tumor, but also to establish anti-tumor immunity and to contain metastases.
- Does not recombine with the host cell genome, or even enter the nucleus. This will minimize the risk of virus-host genetic recombination events.
- Selective replication in tumor cells to limit the infection of normal cells, based on genetic defects of tumor cells, overexpression of cell-surface proteins or receptors that also bind viral particles, or factors in the tumor microenvironment that facilitate viral replication and spread.

Parato KA et al, Nature Rev Cancer, 2005

- The first and most potent virus to be used in oncolytic virotherapy is *human adenovirus*.
- Recently, ongoing extensive research has suggested that other viruses like *herpes simplex virus (HSV)* and *measles virus* can also be considered as potential candidates in cancer therapy.
- An HSV-based oncolytic virus, *T-VEC*, has completed phase III clinical trial and has been FDA approved for use in biological cancer therapy.
- Moreover, the vaccine strain of the measles virus has shown impressive results in pre-clinical and clinical trials.

HSV-based oncolytic viruses

- Seven HSV-based oncolytic viruses among which *T-VEC* has been approved in US and EU.
- T-VEC was generated by deleting the ICP34.5 and ICP47 genes, and inserting two copies of human (GM-CSF) gene in place of ICP34.5.
- Deletion of ICP34.5 in T-VEC ensures abortive infection in normal cells thereby enabling its replication to be cancer cell-specific.
- Deleting ICP47 decreases the immune destruction and enhancing the cell surface expression of MHC I in cancer cells with increase the tumor specific antigen presentation.

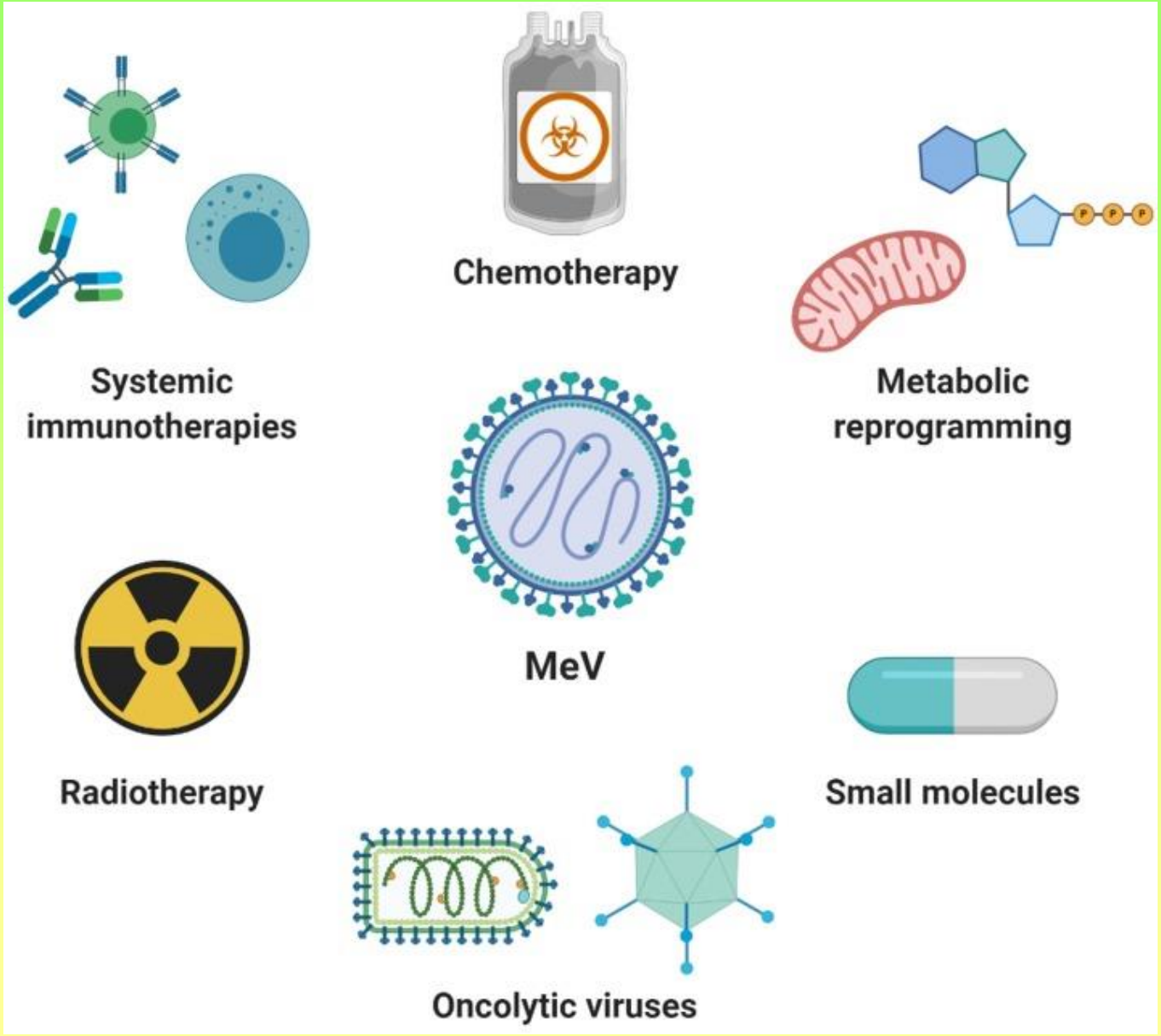
Adenovirus-based oncolytic viruses

- Recombinant oncolytic adenovirus to be used in combination with chemotherapy for the treatment of nasopharyngeal carcinoma in late 2005.
- Deletion of 24 bps in the E1A region and the engineering of the RGD-4C motif into the HI-loop enhances the replication and infectivity of the adenovirus in cancer cells and reduces the sequestration of adenovirus by normal cells.
- Adenovirus-based oncolytic viruses have exploited the p53 inactivation in most cancer cells.

Measles-based oncolytic viruses

- Safe live-attenuated MV vaccine is very promising as the risk of reverting back of the non-segmented genome into the pathological form is very unlikely.
- MV vaccine used in intratumoral treatment.
- Attenuated, replication-competent vaccine strains of MeV exhibit a natural oncotropism and have thus been explored as novel anti-tumor therapeutics.

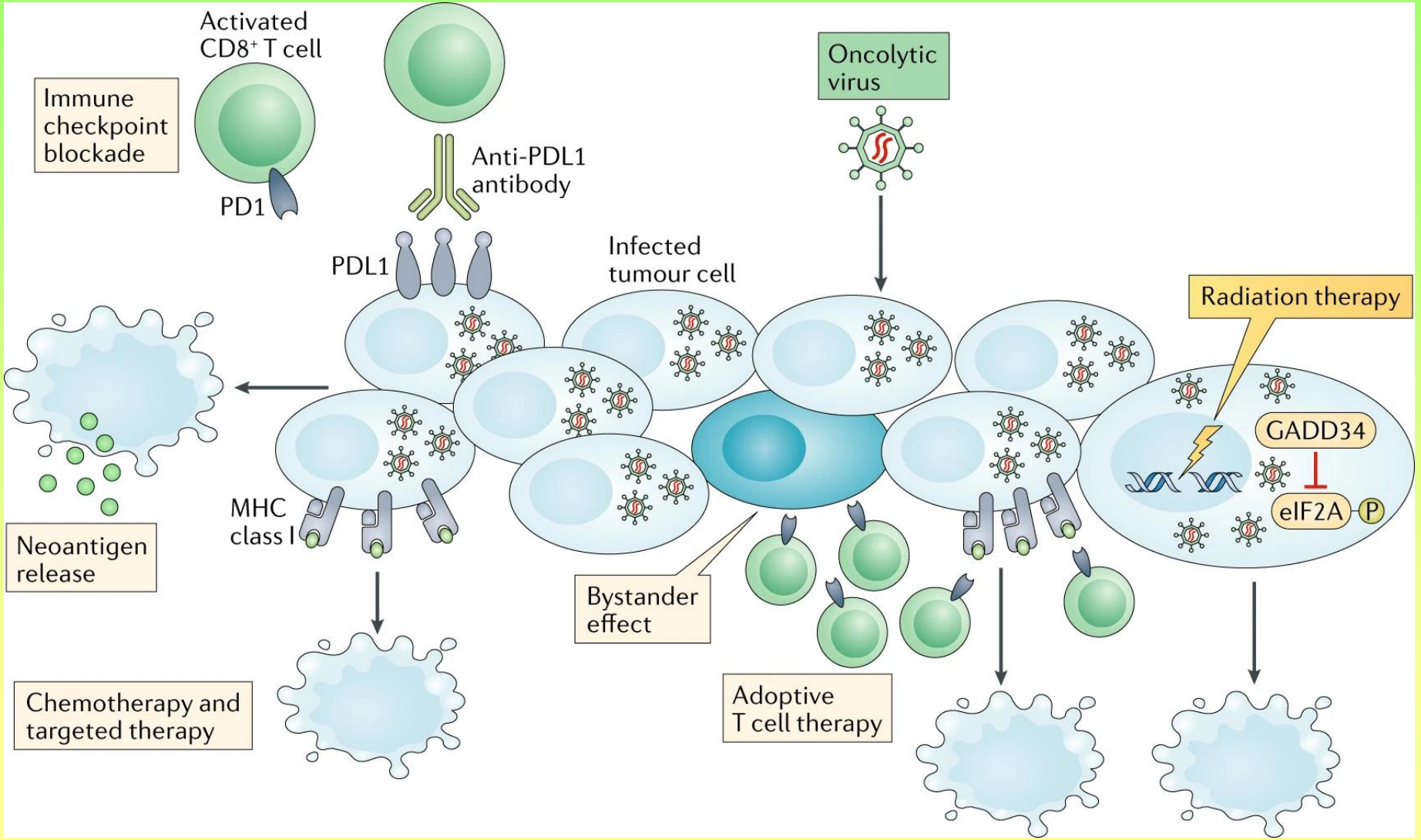
Combinatorial oncotherapy includes MeV



Future perspectives

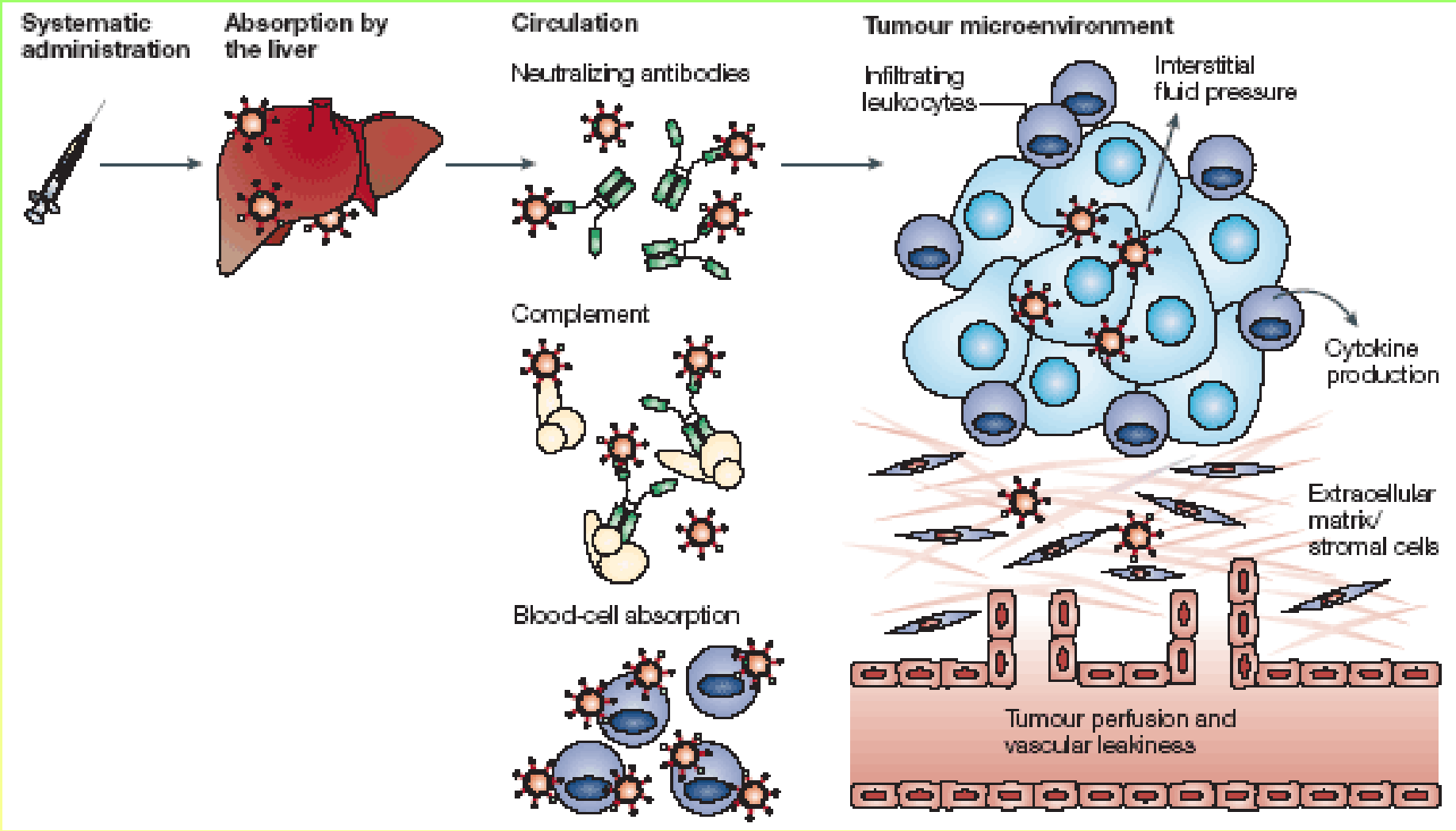
- Several viruses including vaccinia virus, reovirus, parvovirus, picornavirus have been assessed as potential candidates for oncolytic virotherapy.
- In most cases, systemic administration does not work well due to preexisting immunity.
- Some of the novel approaches involve the use of nanoparticles, complex viral particle ligands, and immuno-modulatory agents.
- Delivery of the virus into the tumor via nanoparticles uses a technologically complex image-guided delivery system.

Oncolytic viruses as the foundation of combination therapy in cancer



Limitations of oncolytic virus therapies

- Viral agents administered intarvenously can be particularly effective against metastatic cancers, which are especially difficult to treat conventionally.
- However, blood-borne viruses can be deactivated by neutralizing antibodies and cleared from the blood stream quickly e.g. by Kupfer cells in the liver, which are responsible for adenovirus clearance.


Systematic administration
Absorption by the liver
Circulation
Neutralizing antibodies
Complement
Blood-cell absorption
Tumour microenvironment
Infiltrating leukocytes
Interstitial fluid pressure
Cytokine production
Extracellular matrix/ stromal cells
Tumour perfusion and vascular leakiness

General conclusions

- Presently, many oncolytic viruses are undergoing clinical trials for applications in single therapy or combination therapy, and most of them are safe and show almost no dose-limiting toxicities.
- Therefore, the use of oncolytic viruses in cancer biotherapy has the potential to be an ideal and painless therapeutic option for the cancer patients in future if the above-mentioned challenges are appropriately dealt with.