Antiviral therapies and new vaccine types

Antivirals may have:

viral targets	(interfere with a particular phase of viral cycle)
host cell targets	(interfere with a cell component or process important for virus replication)

Ideal antiviral drugs

ARE: water soluble, stable in bloodstream, enter the cell easily, stable;

ARE NOT: toxic, mutagenic, carcinogenic, teratogenic, allergenic.

New antiviral therapies development rely on new tools (genomics, proteomics).

After drug discovery and preclinical testing (toxicity, efficacy, pharmacokinetics) on animals or *in vitro*, it is important to know the influence of a drug on a virus host.

Clinical testing phases:

0 – 10 people, pharmacokinetics (half-life, oral bioavailability), often skipped

I – 20-100 healthy volunteers, up to 1 year.

Is it safe for humans, what may be side effects (safety)?

II – couple of hundred of volunteers (100-300).

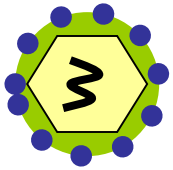
Is it effective and to what extent (efficacy, dose)?

III – comparison with the standard treatments, therapeutic effects (dose range)

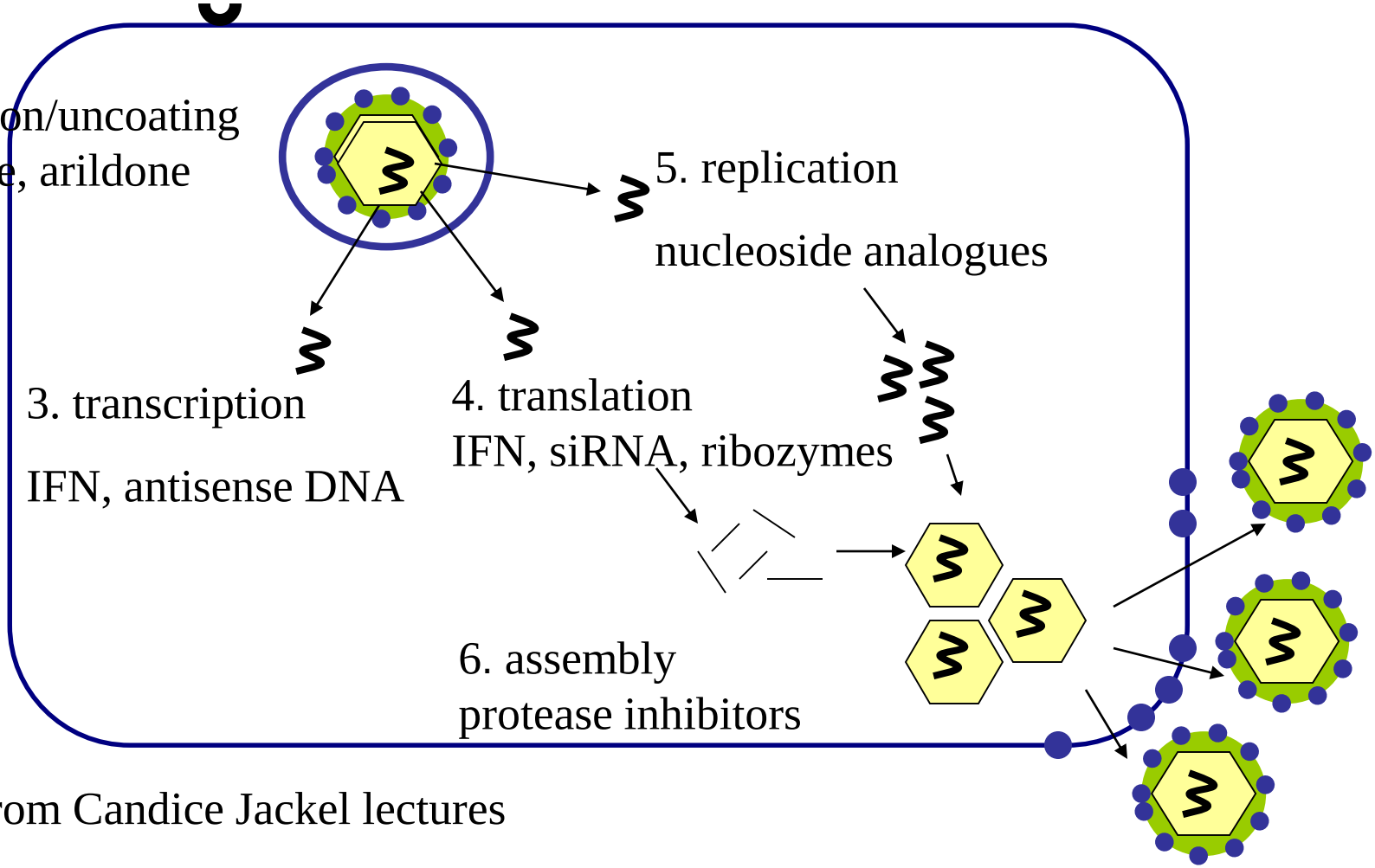
IV – whoever seeks the treatment, what are long-term effects?

Always consider the possibility of drug resistance development.

Terapies with viral targets

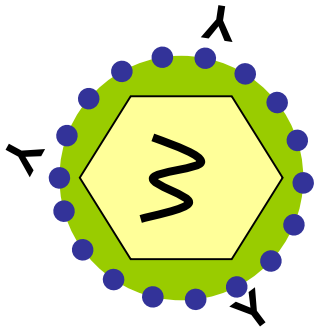


1. attachment (Abs, receptor antagonists)

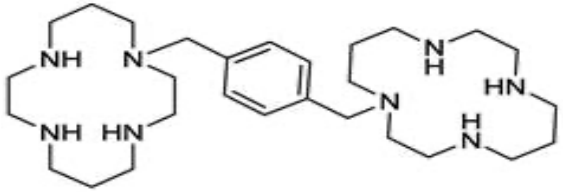


Adapted from Candice Jackel lectures

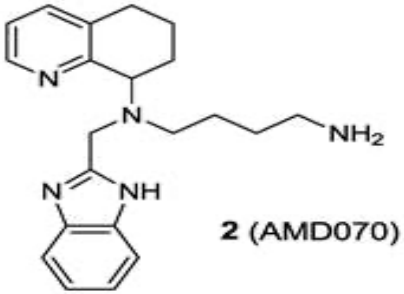
Attachment (adsorption) inhibitors



- Neutralizing antibodies
  - passive immunization
  - adoptive T-cell therapy (lymphocyte transfusion)
- Receptor antagonists
  - (glyco)peptides analogues of cell receptors
  - Inhibitors of chemokine receptors
- Others
  - galactomannan-sulphates (Dengue, YFV)



1 (Plerixafor, AMD3100)

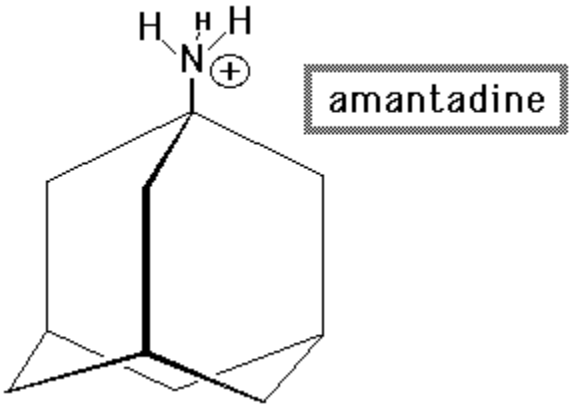


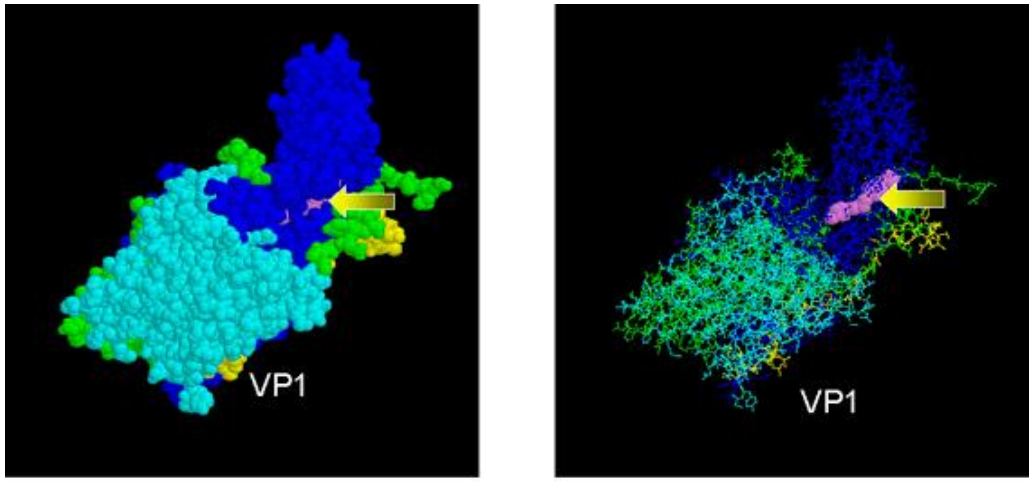
2 (AMD070)

AMD070, AMD3100 interfere with HIV adsorption and entrance into the CD4 cells– CXCR-4 is blocked. AMD070 in 2007 – phase III clinical trials, AMD3100 as Plerixafor approved by FDA in 2007.

Adsorption and uncoating inhibitors

- Successful if fusion and uncoating are pH-dependent
- Arildone, WIN
- Amantadine, Rimantadine?



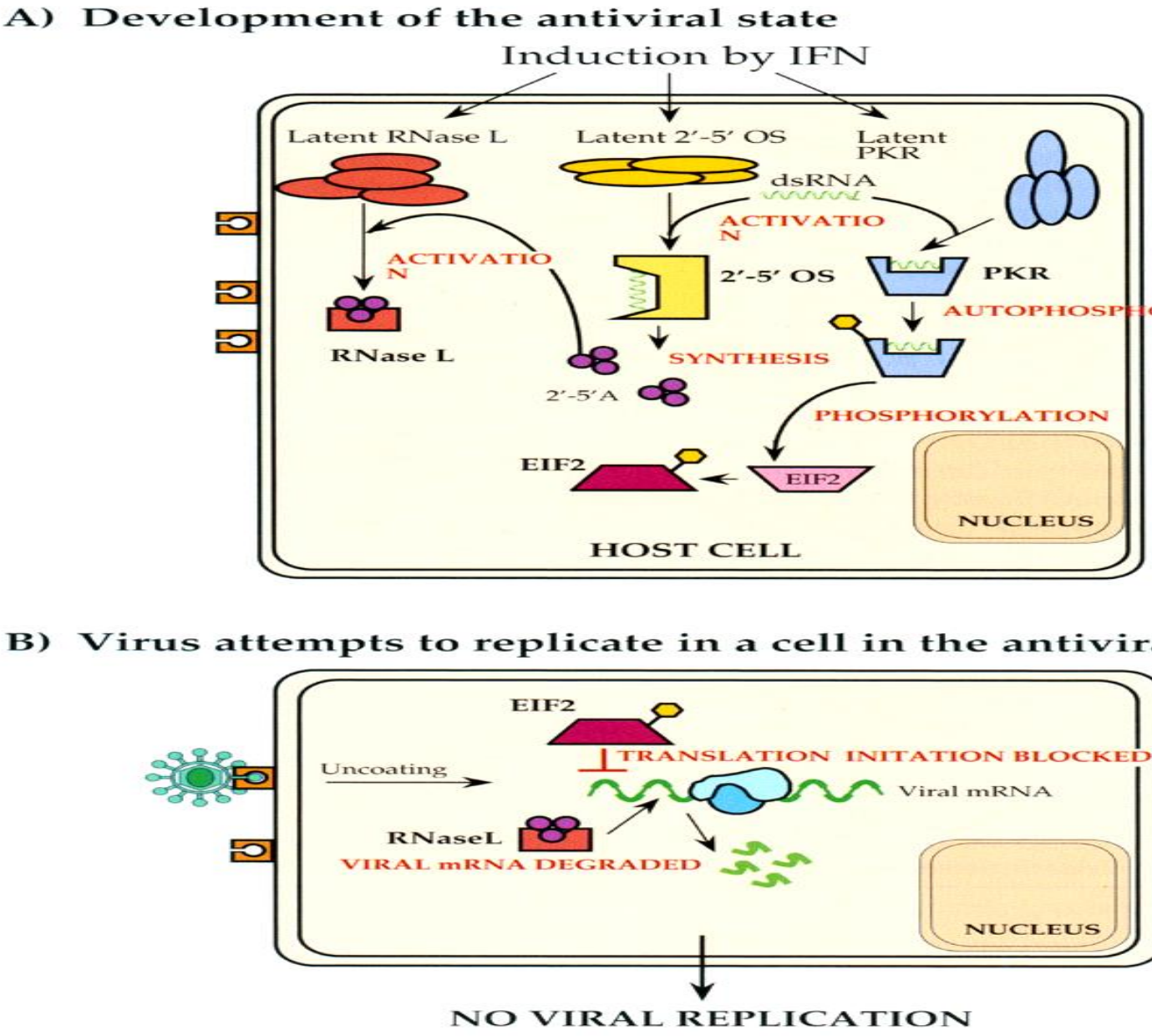


Human rhinovirus with WIN V1

WIN enters the VP1 canyon and blocks the ion transport (picornaviruses).

Transcription inhibitors

- Antisense DNA
  - Fomivirsen – first antisense drug approved, now withdrawn (not needed in HIV patients due to HAART)
    - antisense oligonucleotides (21-mer, phosphothioate – linkages resistant to nucleases)
    - complementary to IE2 gene of HHV-5 (hCMV)
    - approved in 1998.
- IFN
  - IFN-α
    - innate immunity, not specific, inhibits or abolishes transcription and translation in a cell
    - HCV - Sofosbuvir (Gilead Sciences, Foster City, California), combinations sofosbuvir, ribavirin and interferon cured 90% HCV genotype 1 patients (the most prevalent type) or sofosubivir & ribavirin - cured 78% patients with HCV-2 and HCV-3 genotypes (Nature News Blog, 23.4.2013).
  - artificial interferon inducers
    - Ampligen - immunomodulatory dsRNA, Rintatolimod



Two ways of reducing viral translation and replication:

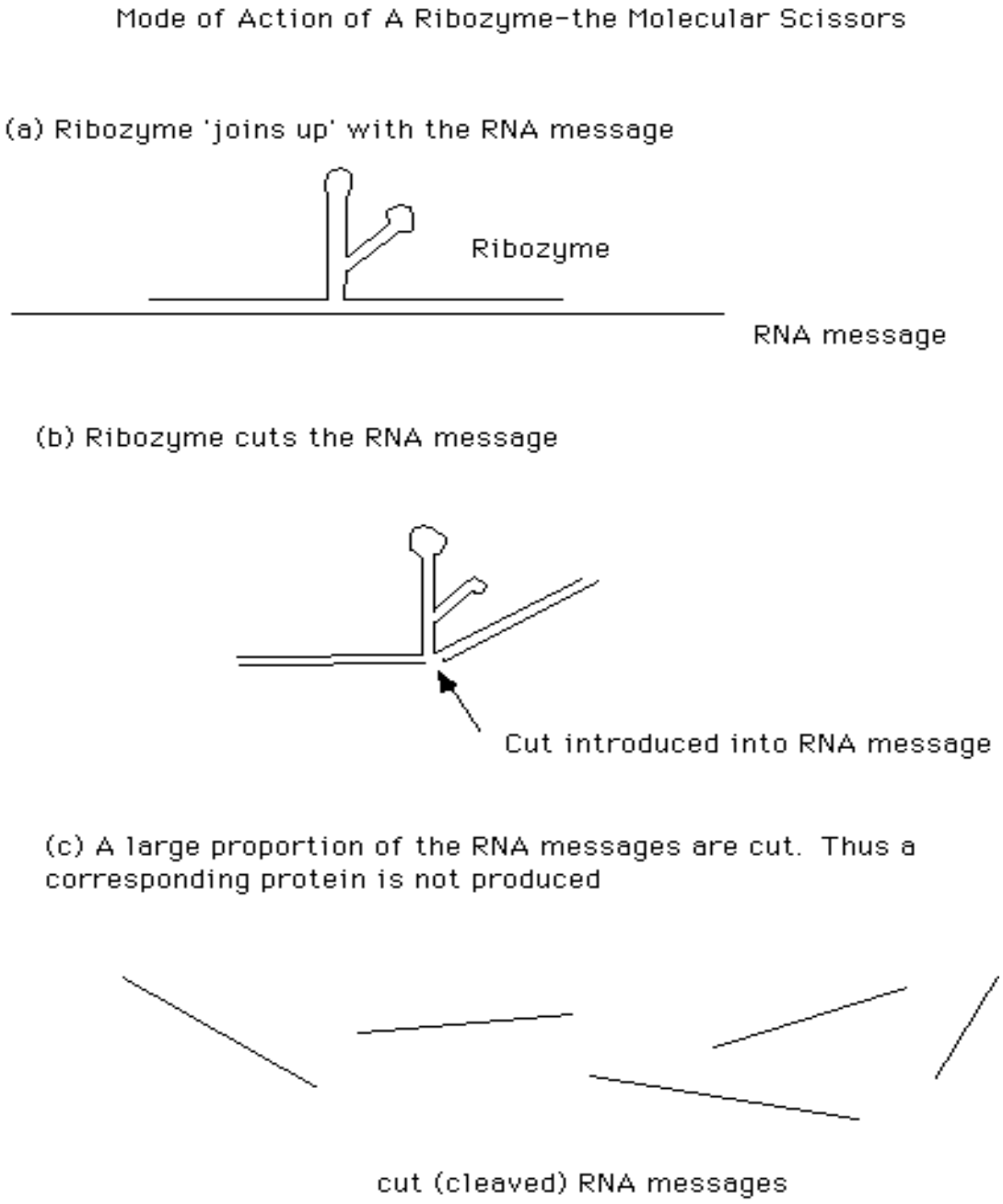
2’-5’oligo(A) synthetase (dsRNA-cofactor) and RNase L);

PKR (protein kinase activated by dsRNA, 68kDa)

Strauss&Strauss, 1st ed.

Translation inhibitors

- IFN
- siRNAs
- ribozymes
  - Specific targets
  - Heptazyme
    - HCV



Replication inhibitors

- Nucleoside analogues

  Acyclovir, purine analogue, anti-herpesvirus drug since 1983.

•Non-nucleoside inhibitors of polymerase

  Nevirapine, Delaviradine (NNRTI)

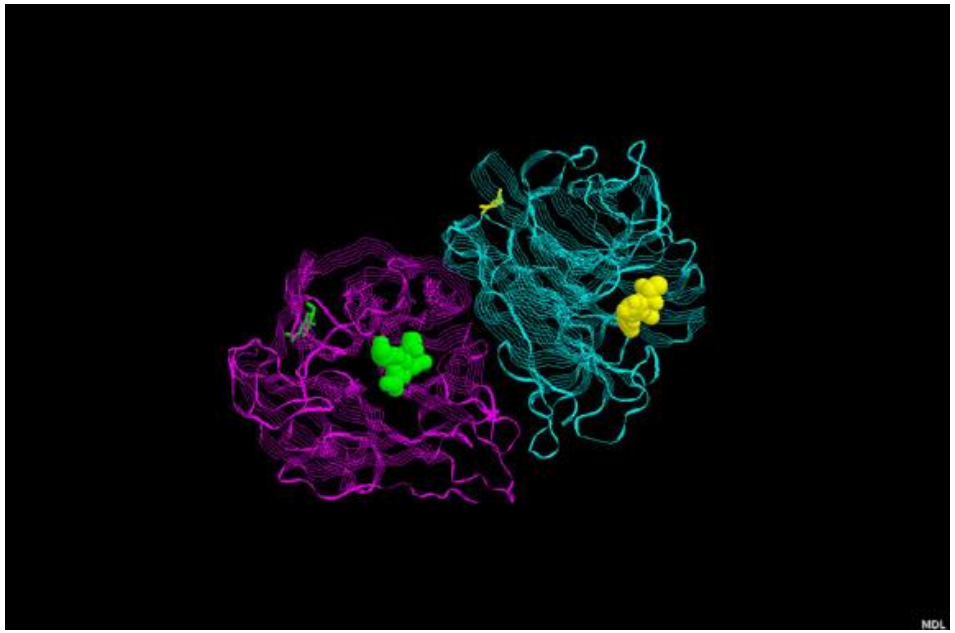
  Foscarnet (phosphonoformic acid, PFA, anti-HHV-5 drug)

Nevirapine

Virion assembly inhibitors

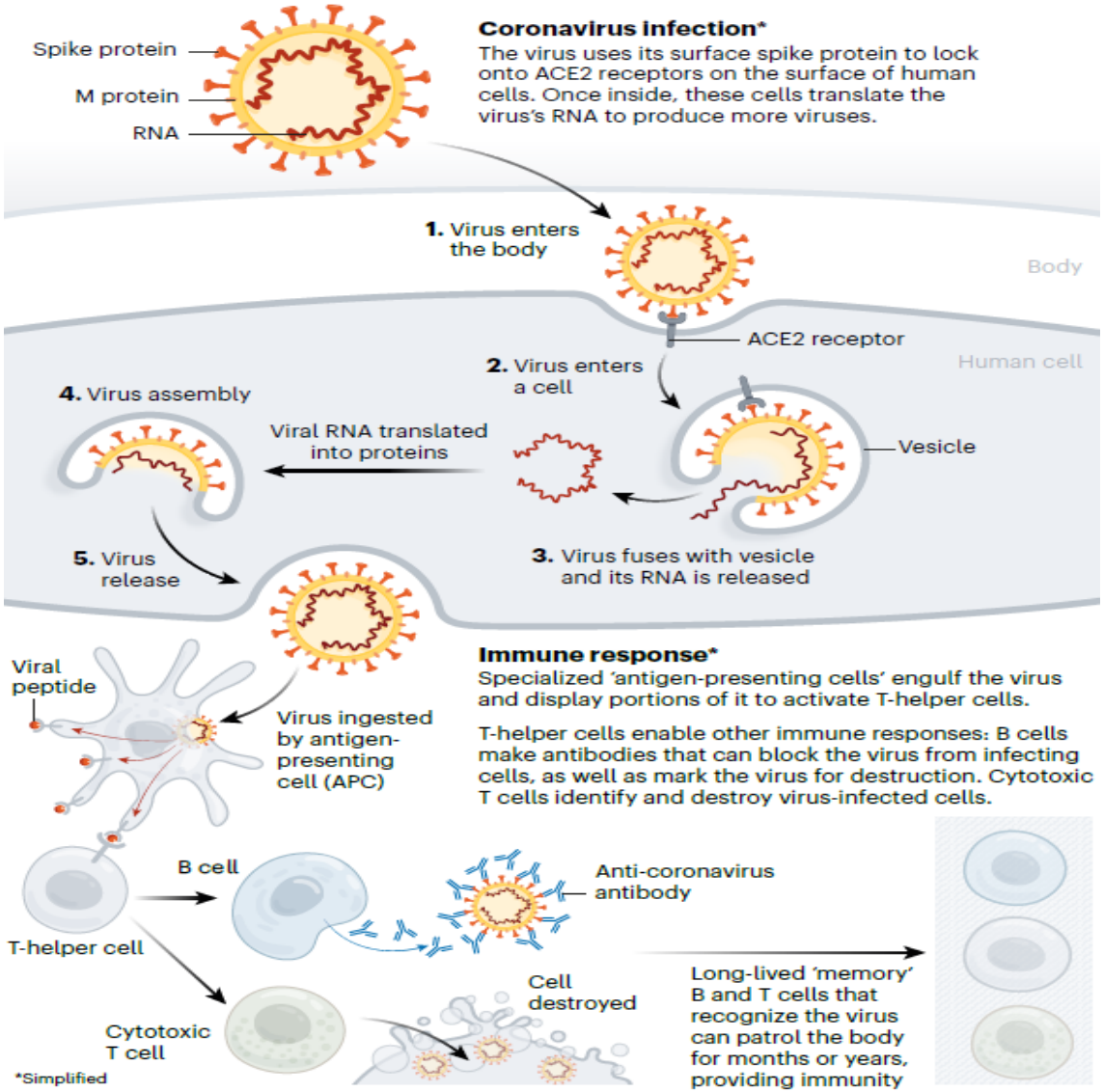
- Protease inhibitors

- Neuraminidase inhibitors Oseltamivir (Tamiflu)
- Zanamivir (Relenza)
- Designed drugs
- NA is a 3D key to anti-influenza drug design.



Antiviral adaptive immunity – basis for vaccine development

The body's adaptive immune system can learn to recognize new, invading pathogens, such as the coronavirus SARS-CoV-2.

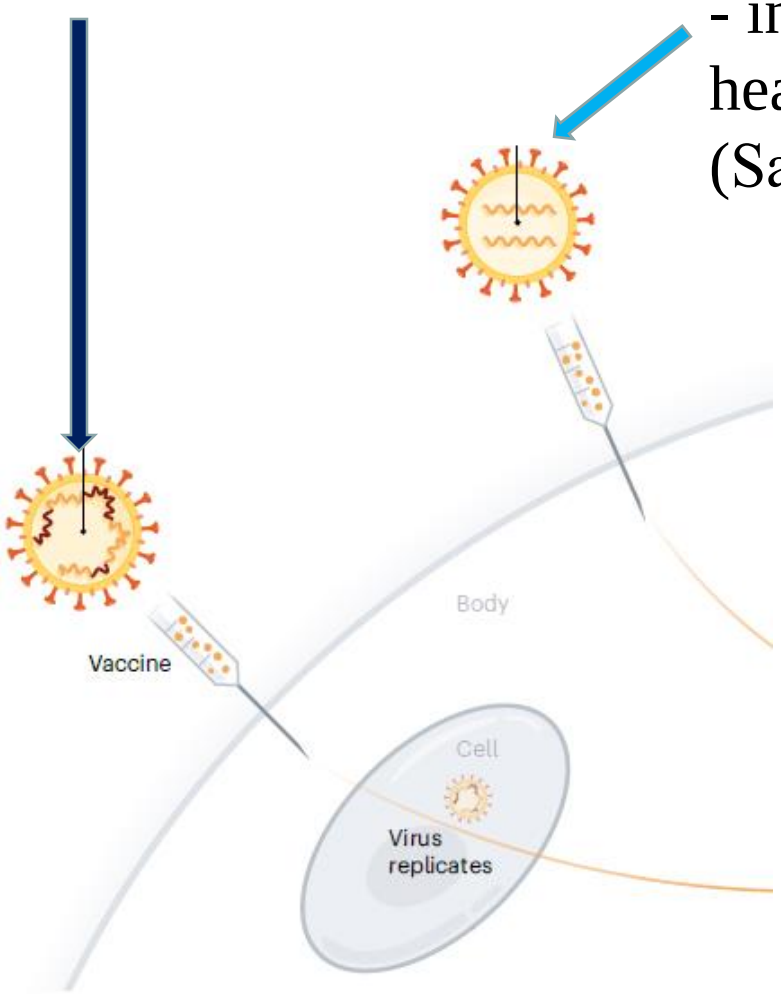


- **Types of vaccines:**

1. Complete viral particles

- attenuated, „live”) vaccines
(Sabin’s - OPV, small pox, measles, mumps…)

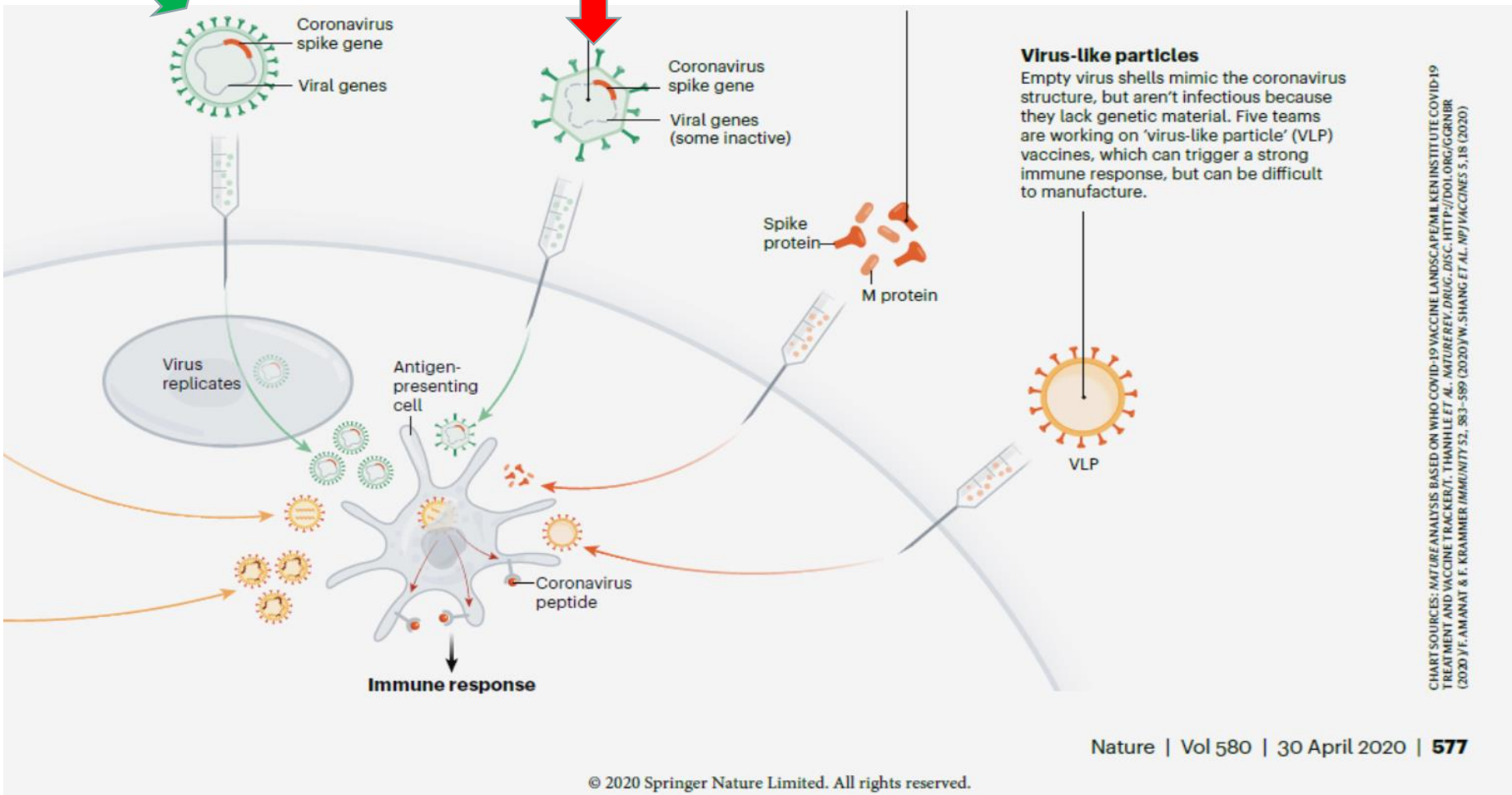
- inactivated viruses - irradiation, heath, chemicals (formaldehyde)
(Salk’s - IPV, hepatitis A, B, …)



2. Vector vaccines

– recombinant viruses in vectors - replicable (Ebola vaccine - in attenuated measles virus)

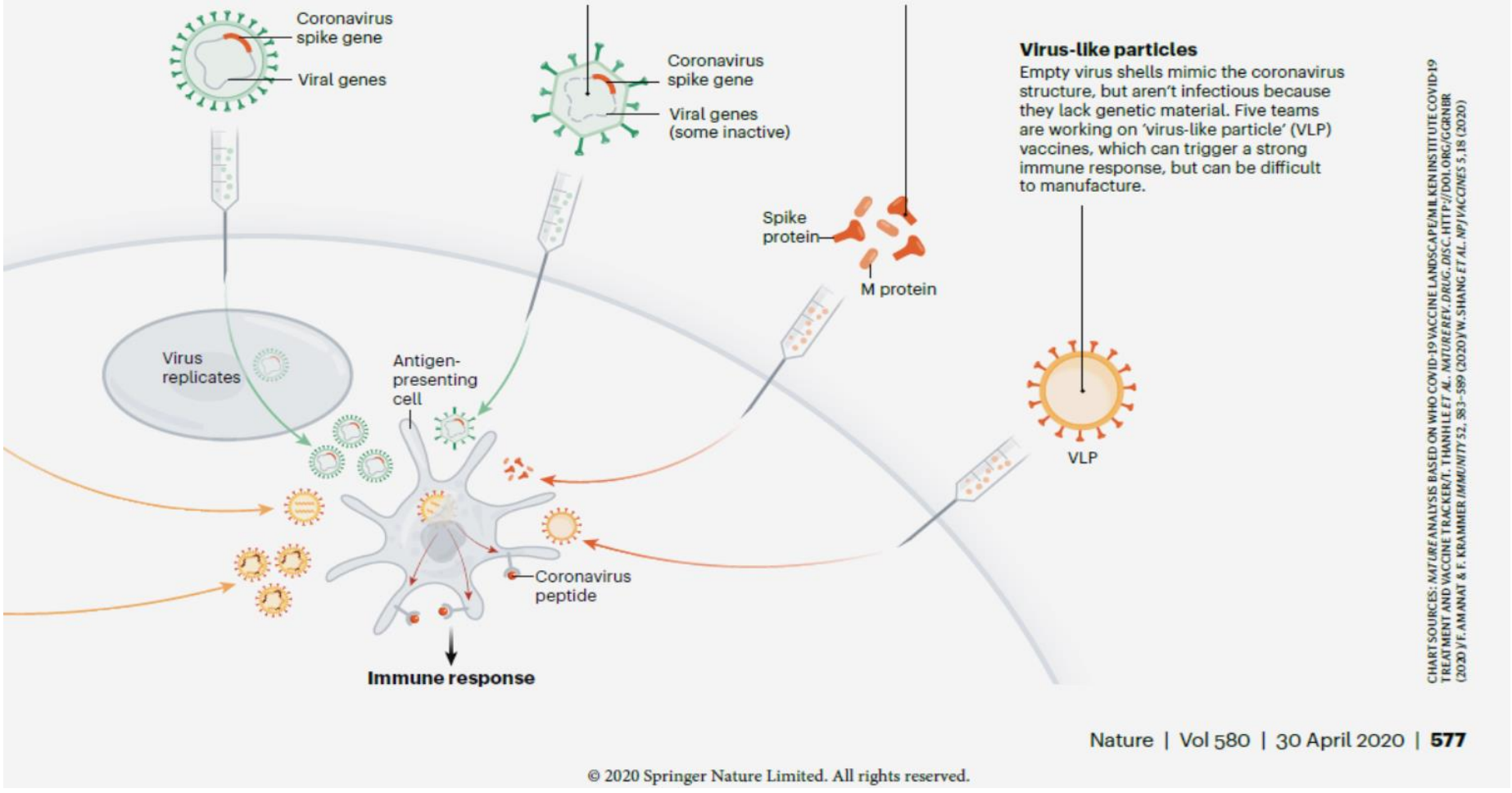
or not replicable (adenovirus vectors in humans).



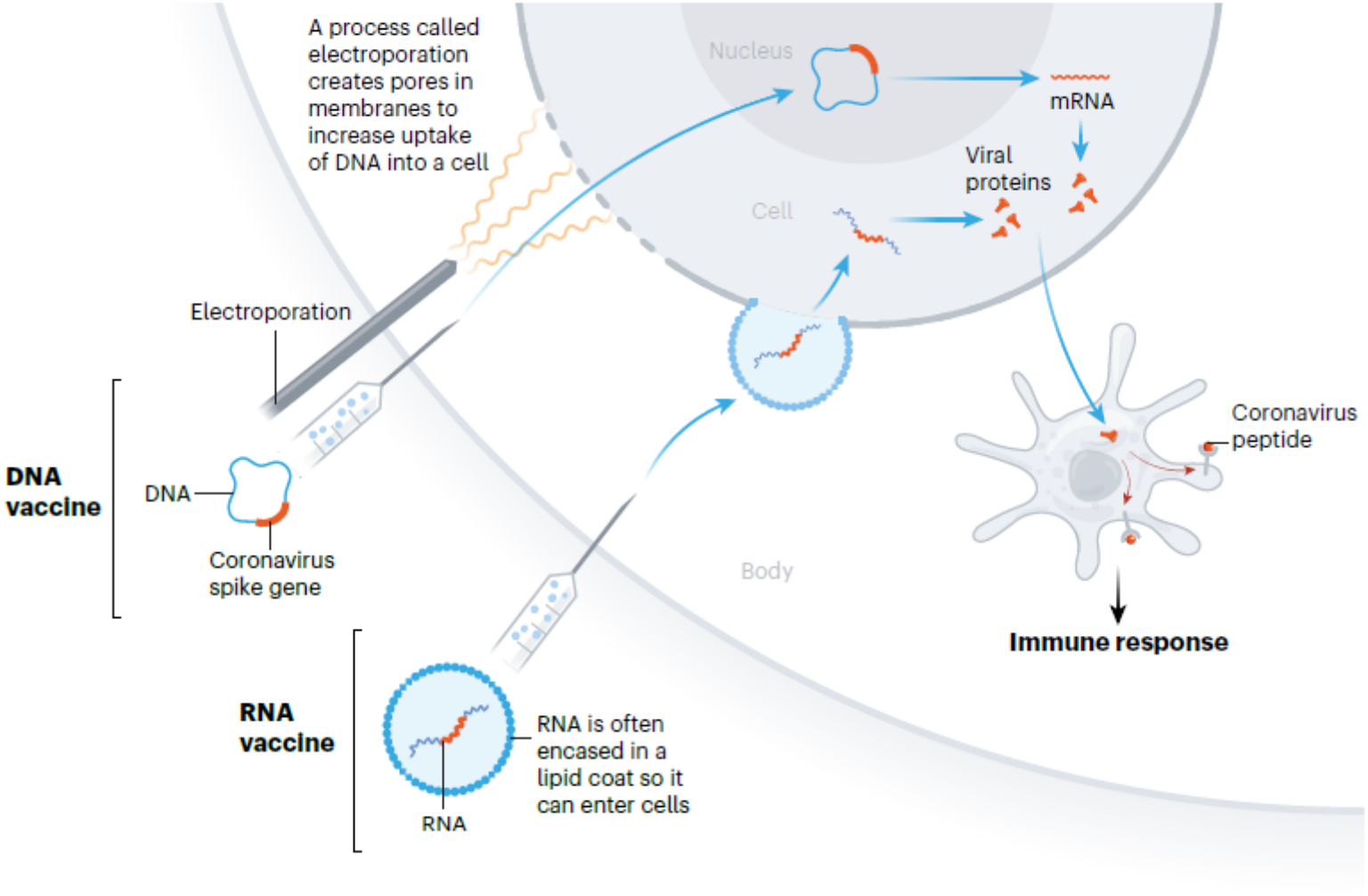
3. Virus proteins as vaccines – protein subunits (S, M) envelope proteins or glycoproteins (purufied or recombinant)

4. VLPs (HPV vaccine).

Protein vaccines are stable, easy storage and transport, not virulent, good as polyvaccines but higher doses are effective, costly manufacturing, quick immune response is not induced (IFN), antibody production is induced late.



5. DNA and RNA vaccines – safe (no infectious material… S-protein gene), good humoral and cell immunity induced.
First approved RNA vaccine for humans for SARS-CoV-2 2020/21.



DNA vaccines

(Nat. Rev. Genet., 9: 776-788, 2008.

1990s - DNA (plasmid) injected subcutaneously (cutaneous, intramuscular exposure) can elicit humoral and cellular immunity, (inducing especially cytotoxic T lymphocytes, CTLs).

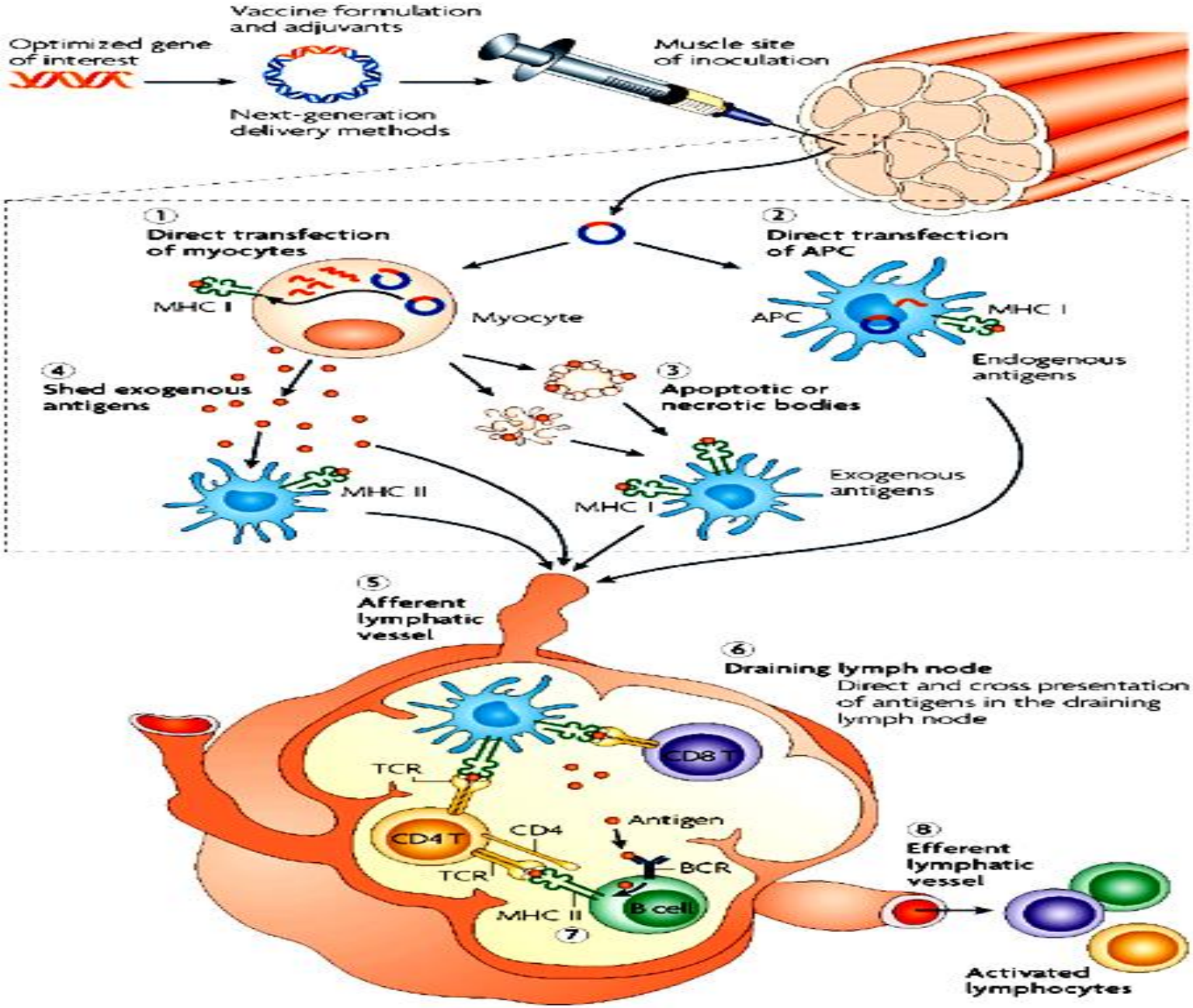
In veterinary medicine 4 DNA vaccines approved for:

canine melanoma, 2007, USA,

growth hormone releasing hormone (swine and food animals), 2007, Australia,

West Nile virus (horses), 2005, USA,

Infectious hematopoietic necrosis virus (salmon), 2005, Canada.



Nature Reviews | Genetics

They may protect against:

viral,

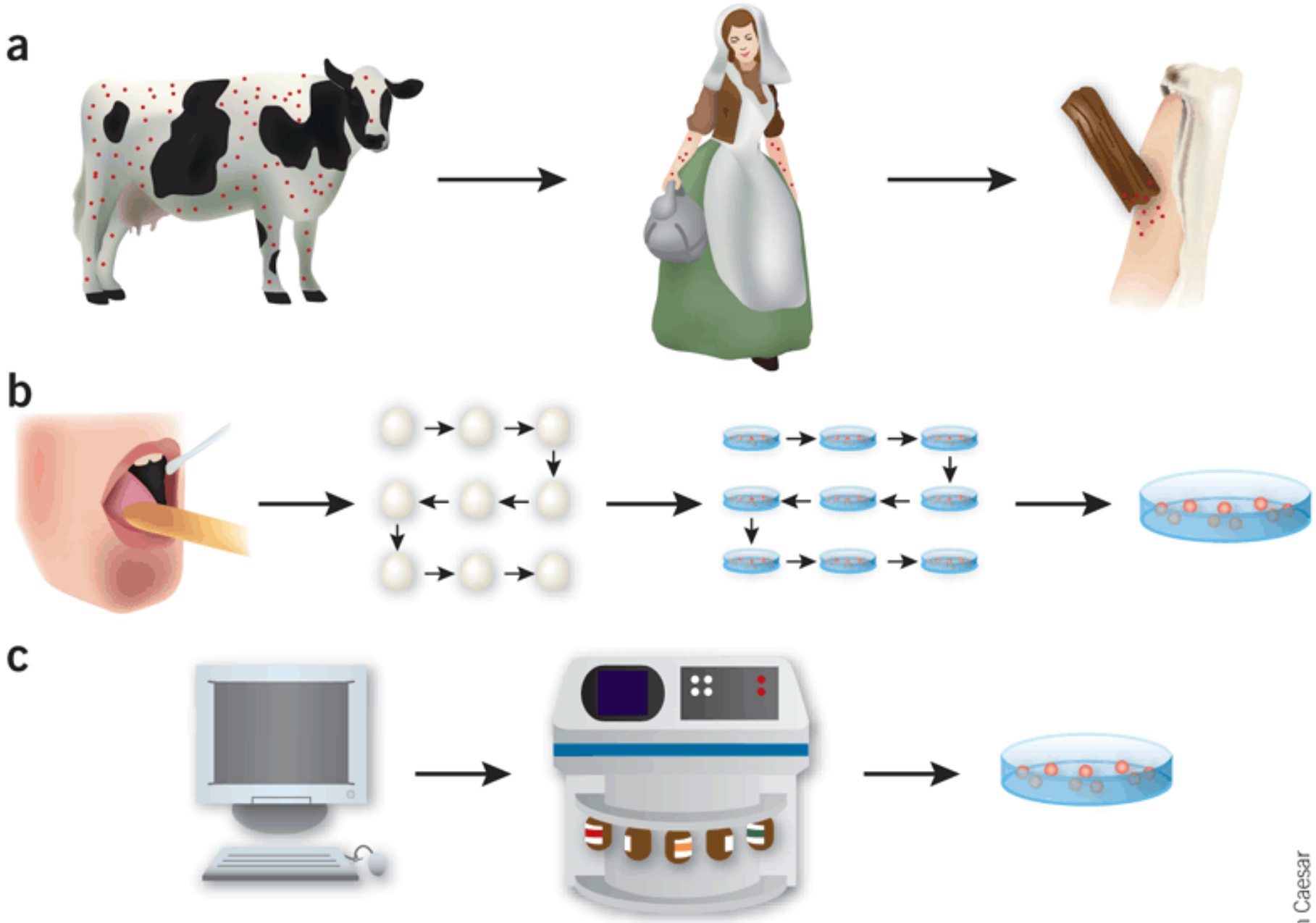
bacterial,

parasitic infections,

cancer, ischemia, allergies, autoimmune diseases – depending on the antigen type inserted into a plasmid.

Safe! No downsides of attenuated live or inactivated virus vaccines but have some others (Table in the paper).

They can be used for pre-vaccination (classical vaccines are applied afterwards).



Nat. Biotech. 26(9): 1000-1001, 2008.

New viral vaccines

New vaccine types developed from information on:

protein subunits (data from structural studies invaluable)

nucleic acid sequence databases (for DNA and recombinant vaccines)

cell-signaling microarrays (the choice of the most suitable adjuvant).

Live attenuated viruses are the most efficient vaccines –

single dose, long-lasting protection, cost-effective (high virus titer, minimal manipulation), no adjuvant needed.

Attenuation in biological systems (passaging), one virion replication (b), or from a related virus (a) are obsolete methods.

Attenuation through manipulation of *codon pair bias*.

Science 320: 1784-1787, 2008.

Poliovirus, preferentially uses some codons for translation (and anticodon pairs on tRNA).

Poliovirus capsid protein P1 codon manipulation can reduce virus translation and replication efficiency.

SAVE approach (synthetic attenuated virus engineering):

Synonymous mutations are introduced into DNA, (preferential viral codons are changed), that gene is recombined with wild-type genome segments to generate attenuated viruses (reduction in translation, replication, selection for attenuated neurotropism).

Many antiviral drugs and therapies are currently in different phases of testing (TGEV- swine transmissible gastroenteritis virus plant vaccine, measles H in a mouse model).

Generation of resistant virus strains is possible.

Combined therapy is often necessary:

Highly active anti-retroviral therapies (HAART)

zidovudine (AZT) , lamivudine (3TC) and protease inhibitor (Indinavir).

Genomics, proteomics, other new methodologies will stimulate new antiviral therapy and drugs discovery…