Live, Attenuated Vaccines

Live attenuated vaccines used in the UK schedule:

Rotavirus vaccine
MMR vaccine
Nasal flu vaccine
Shingles vaccine
Chickenpox vaccine (special groups only)
BCG vaccine against TB (special groups only)

Live travel vaccines used in the UK:

Yellow fever vaccine
Oral typhoid vaccine (not the injected vaccine)

Inactivated Vaccines

Immune responses

Live, attenuated vaccines stimulate protective immune responses when they replicate in the host.

The viral proteins produced within the host are released into the extracellular space surrounding the infected cells and are then acquired, internalized, and digested by scavenger cells, the antigen-presenting cells (APCs) that circulate throughout the body.

These APCs include macrophages, dendritic cells, and B cells, which The APCs recirculate and display fragments of the processed antigen on their cell surface, attached to MHC class II antigens. work together to expand immune response.

This complex of processed foreign antigen peptide and host MHC class II antigens form part of the specific signal with which APCs (along with the MHC peptide complex) triggers the activation of T-helper lymphocytes.

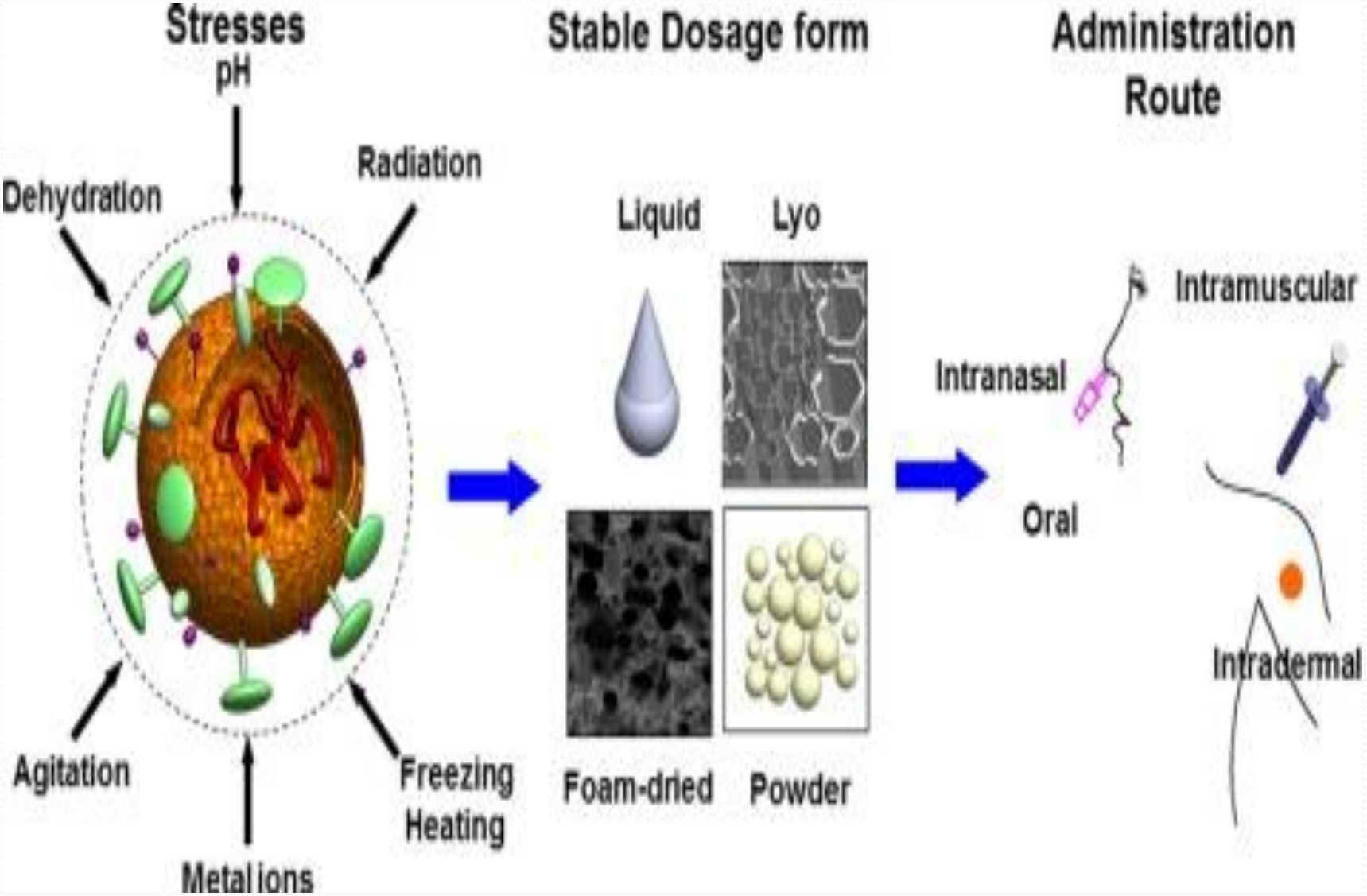
Immune responses

Activated T cells secrete molecules that act as powerful activators of immune cells.

Also, as viral proteins are produced within the host cells, they are processed through proteasome degradation. Small parts of these processed intracellular proteins associate with cytosolic host cell MHC class I and display on the cell surface. These complexes together are recognized by a second class of T cells, killer or cytotoxic cells.

Characteristics of Live Attenuated Whole Organism Vaccines

- **ADVANTAGE**: processed by the immune system like the actual infection (MHC-II and MHC-I pathways)
- **ADVANTAGE**: elicit **sustained** immune responses similar to that of the actual infection
- **DISADVANTAGE**: not very stable – may require "cold chain"
- **DISADVANTAGE**: may revert to from a virulent form to virulence – particularly in the immune compromised


Stresses
pH
Dehydration
Radiation
Agitation
Freezing
Heating
Metal ions
Stable Dosage form
Liquid
Lyo
Foam-dried
Powder
Administration
Route
Intranasal
Intramuscular
Oral
Intradermal

Live attenuated vaccines

1. Wild viruses/bacteria attenuated by repeated passing in cell cultures /animal embryos (chick embryos)

↓ > 10 yrs (mutation & weakening)

2. Transformation of wild virus into vaccine virus

↓ Live attenuated vaccines

3. Injection of small dose of vaccine virus or bacteria

↓ Vaccination

4. Replication of vaccine virus or bacteria in the host

↓ Specific immune response

5. Induction of an immune response

↓

6. Protection against real infection

MMR vaccine

MMR vaccine can prevent **measles**, **mumps**, and **rubella.**

MEASLES (M) causes fever, cough, runny nose, and red, watery eyes, commonly followed by a rash that covers the whole body. It can lead to seizures (often associated with fever), ear infections, diarrhea, and pneumonia. Rarely, measles can cause brain damage or death.

MUMPS (M) causes fever, headache, muscle aches, tiredness, loss of appetite, and swollen and tender salivary glands under the ears. It can lead to deafness, swelling of the brain and/or spinal cord covering, painful swelling of the testicles or ovaries, and, very rarely, death.

RUBELLA (R) causes fever, sore throat, rash, headache, and eye irritation. It can cause arthritis in up to half of teenage and adult women. If a person gets rubella while they are pregnant, they could have a miscarriage or the baby could be born with serious birth defects.

Most people who are vaccinated with MMR will be protected for life.

MMR vaccine

Children need **2 doses of MMR vaccine**, usually:

First dose at age 12 through 15 months

Second dose at age 4 through 6 years

A third dose of MMR might be recommended for certain people in mumps outbreak situations.

MMR vaccine may be given at the same time as other vaccines. Children 12 months through 12 years of age might receive MMR vaccine together with varicella vaccine in a single shot, known as MMRV.

- MMR is a three part combine vaccination for measles, mumps and rubella.

Until 1971 the MMR was given as three separate vaccines. Before 1960 a vaccination for measles, mumps or rubella did not exist.

Currently 2010 manufactures are
- Merk as M-M-R II
- GlaxoKlienSmith as Priorix
- Serum Institute of India as Tresivac
- Sanofi Pasture as Trimovax

MMR contains 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus; 12,500 $TCID_{50}$ of mumps virus; and 1,000 $TCID_{50}$ of rubella virus. sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤ 0.3 mg), fetal bovine serum (< 1 ppm) 25 mcg of neomyci… (atenuvax,2010)

Image:

Disease immunized	Component vaccine	Virus strain	Propagation medium	Growth medium
Measles	Attenuvax	Enders' attenuated Edmonston strain[63]	chick embryo cell culture	Medium 199
Mumps	Mumpsvax[64]	Jeryl Lynn (B level) strain[65]		
Rubella	Meruvax II	Wistar RA 27/3 strain of live attenuated rubella virus	WI-38 human embryonic cell line	MEM (solution containing buffered salts, fetal bovine serum, human serum albumin and neomycin, etc.)

MMR Vaccine Side Effects Per the Center for Disease Control

- **Mild problems**
  - Fever
  - Mild rash
  - Swelling of glands in the cheeks or neck
- **Moderate Problems**
  - Seizure (Jerking or Staring) caused by fever
  - Temporary pain and stiffness in the joints
  - Temporary low platelet count, which can cause a bleeding disorder
- **Severe Problems (Very Rare)**
  - Serious allergic reaction
  - Deafness
  - Long-term seizures, coma, or lowered consciousness
  - Permanent brain damage

BCG VACCINE

BCG VACCINE for percutaneous use is an attenuated, live culture preparation of the Bacillus of Calmette and Guerin (BCG) strain of Mycobacterium bovis. The TICE® strain used in this BCG VACCINE preparation was developed at the University of Illinois from a strain originated at the Pasteur Institute.

The medium in which the TICE® BCG organism is grown for preparation of the **freeze-dried** cake is composed of the following ingredients: **glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, and iron ammonium citrate.**

The final preparation prior to freeze drying also contains lactose.

The freeze-dried BCG preparation is delivered in vials, each containing 1 to 8 x 10 8 colony forming units (CFU) of BCG which is equivalent to approximately 50 mg (wet weight), as lyophilized (freeze-dried) powder

Other brands of BCG vaccine used in other countries may contain different ingredients.

Method of administration

BCG vaccination is recommended for infants and children with negative tuberculin skin tests

The tuberculin skin test (also called the Mantoux test) may be given before you are offered the BCG vaccine.

If a hard red lump develop at the test site, this is a positive result. It means that the immune system already recognise TB, because of exposure to the disease in the past. In this case the BCG vaccine should not be given because you already have some immunity to TB, and the vaccine may cause unpleasant side effects. If you have no reaction to the skin test, this is a negative result, and you can safely have the BCG vaccine.

BCG is given as a single intradermal injection at the insertion of the deltoid. If BCG is accidentally given subcutaneously, then a local abscess may form (a "BCG-oma") that can sometimes ulcerate, and may require treatment with antibiotics immediately

The vaccination usually leaves a small scar.

The BCG vaccine effective duration has been determined to be 15 years.

BCG VACCINE

Storage: The intact vials of BCG VACCINE should be stored **refrigerated at 2-8°C** (36-46°F).

This agent contains live bacteria and **should be protected from direct sunlight**.

The product should **not be used after the expiration date** printed on the label. and has a shelf life of 24 months.

The vaccine is **administered percutaneously** utilizing a sterile, single-use multiple puncture device of a plastic holder for a thin, wafer-like stainless steel plate from which 36 points protrude (Figure 1).

After the vaccine is prepared, the skin site is cleansed with an alcohol or acetone sponge and allowed to dry thoroughly.

Indications and Contraindications

INDICATIONS AND USAGE BCG VACCINE (TICE® strain)

is indicated for the prevention of tuberculosis in persons not previously infected with M. tuberculosis who are at high risk for exposure. As with any vaccine, immunization with BCG VACCINE may not protect 100% of susceptible individuals.

CONTRAINDICATIONS BCG VACCINE

should not be given to persons (a) whose immunologic responses are impaired because of HIV infections, congenital immunodeficiency such as chronic granulomatous disease or interferon gamma receptor deficiency, leukemia, lymphoma, or generalized malignancy or

(b) whose immunologic responses have been suppressed by steroids, alkylating agents, antimetabolites, or radiation.

BCG VACCINE should not be administered to HIV-infected or immunocompromised infants, children, or adults. Prior to administration, the possibility of allergic reactions should be assessed. Allergy to any component of BCG VACCINE or an anaphylactic or allergic reaction to a previous dose of BCG VACCINE are contraindications for vaccination.

side effect

Very common side effect (affecting 9 out of 10 people):

Hardness at the injection site, followed by a raised blister.

Uncommon side effects (affecting up to 1 in 100 people at each dose):

Headache and a raised temperature (fever)

An ulcer which develops from the blister at the injection site, two to six weeks after injection. This may be painful and take several weeks or months to heal fully.

Swelling of lymph nodes in the armpit larger than 1 cm across

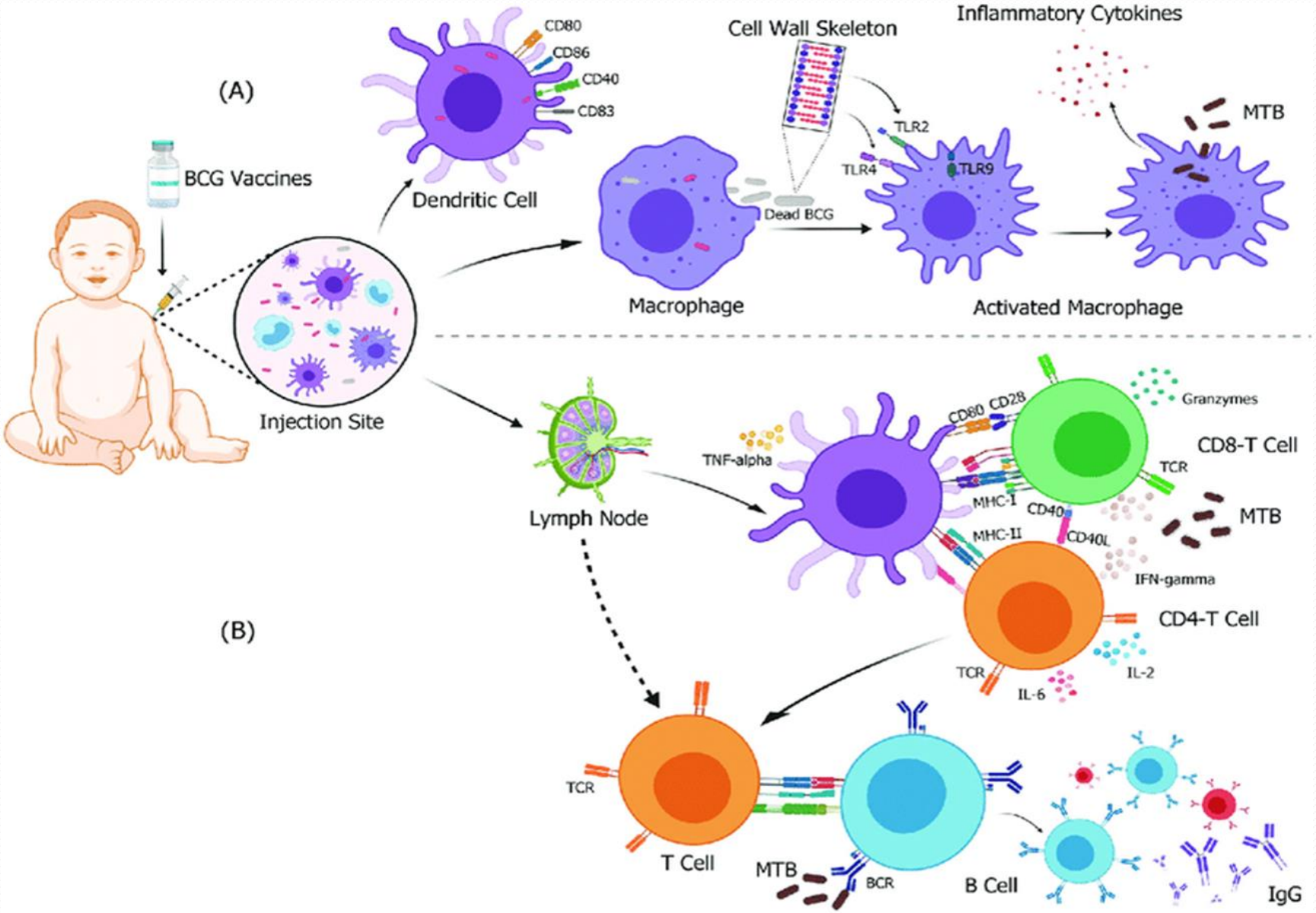
An enlarged lymph node that becomes infected (lymphadenitis)

Rare side effects (affecting up to 1 in 1000 people at each dose):

More severe skin reactions. These usually heal within a few weeks.

Bone inflammation (osteitis or osteomyelitis)

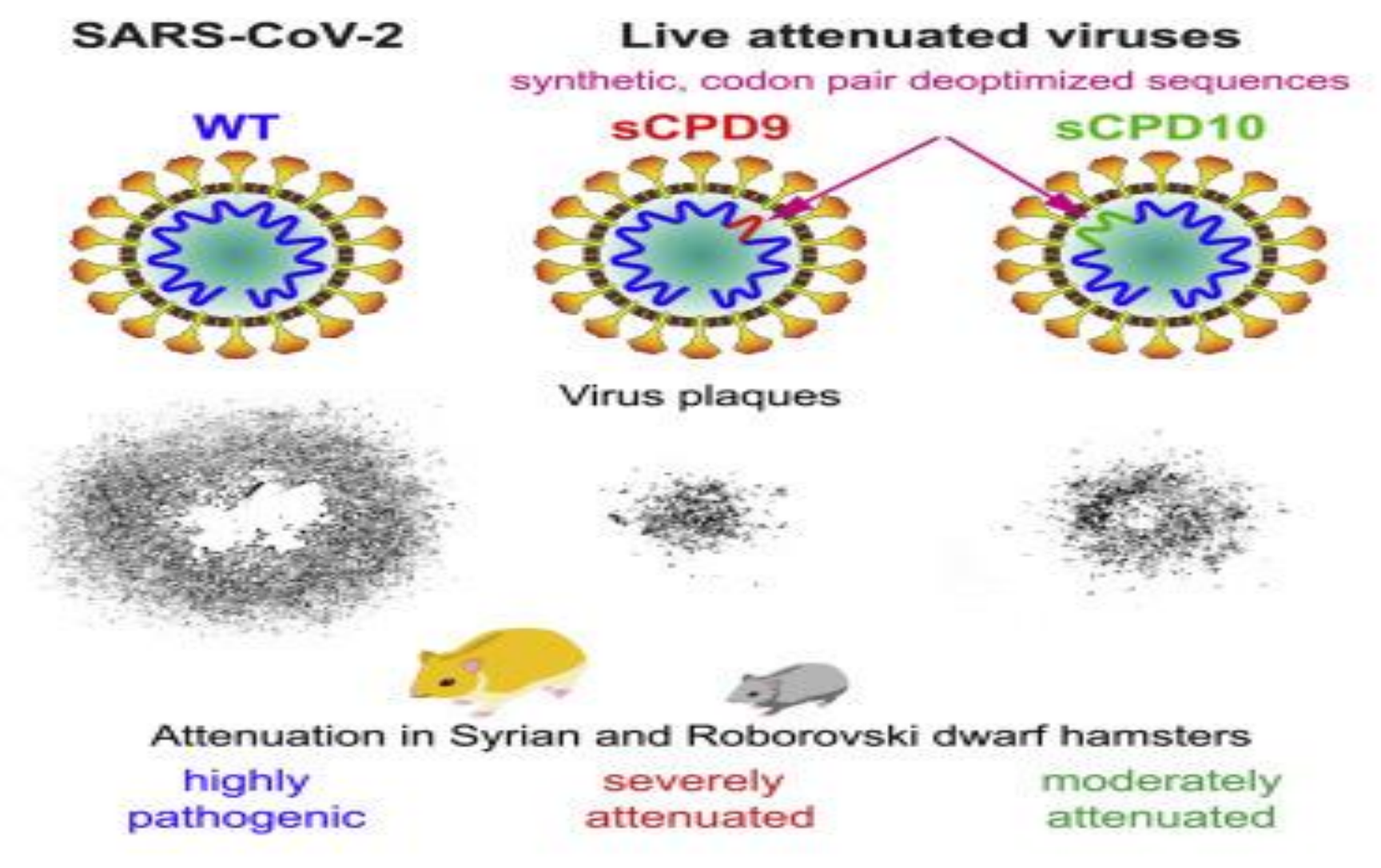
An abscess at the injection site.


(A)
BCG Vaccines
Injection Site
Dendritic Cell
CD80
CD86
CD40
CD83
Macrophage
Cell Wall Skeleton
Dead BCG
TLR2
TLR4
TLR9
Inflammatory Cytokines
MTB
Activated Macrophage
(B)
Lymph Node
TNF-alpha
CD80 CD28
Granzymes
CD8-T Cell
TCR
MHC-I
CD40
MTB
MHC-II
CD40L
IFN-gamma
CD4-T Cell
TCR
IL-2
IL-6
TCR
T Cell
MTB
BCR
B Cell
IgG

Development of safe and highly protective live-attenuated SARS-CoV-2

Trimpert et al.(2021) construct safe and efficacious live attenuated SARS-CoV-2vaccine candidates by recoding theSARS-CoV-2 genome. The lead vaccine candidate, sCPD9, is a pathogenic in Syrian and Roborovski dwarf hamsters. A single intranasal droplet vaccination withsCPD9 induces strong neutralizing antibody responses and protects hamsters from disease caused by SARS-CoV-2.

Trimpert et al., 2021, Cell Reports 36, 109493August 3, 2021 2021 The Authors.https://doi.org/10.1016/j.celrep.2021.109493 ll


SARS-CoV-2
Live attenuated viruses
synthetic, codon pair deoptimized sequences
WT
sCPD9
sCPD10
Virus plaques
Attenuation in Syrian and Roborovski dwarf hamsters
highly pathogenic
severely attenuated
moderately attenuated


Thank you