Vaccines

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Statement of conflict

- None

Learning outcomes

- Know which categories of vaccines exist
- Know examples of vaccine delivery systems and adjuvants
- Know which factors contribute to the quality of a vaccine
- Know about trends with respect to vaccine delivery systems and alternatives for the needle

Vaccines

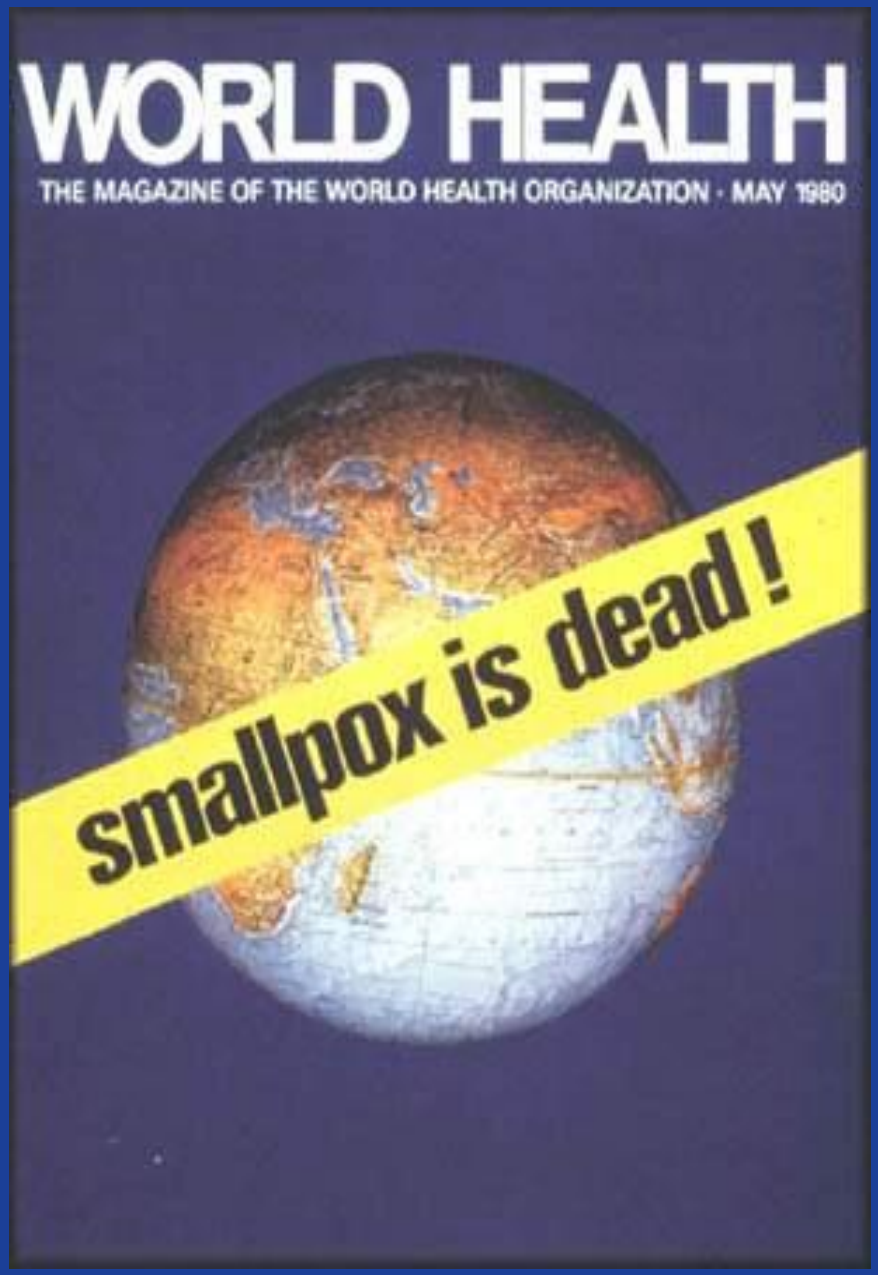
Vaccination

Cowpox virus
(Vaccinia)

Vacca = cow

1970s:

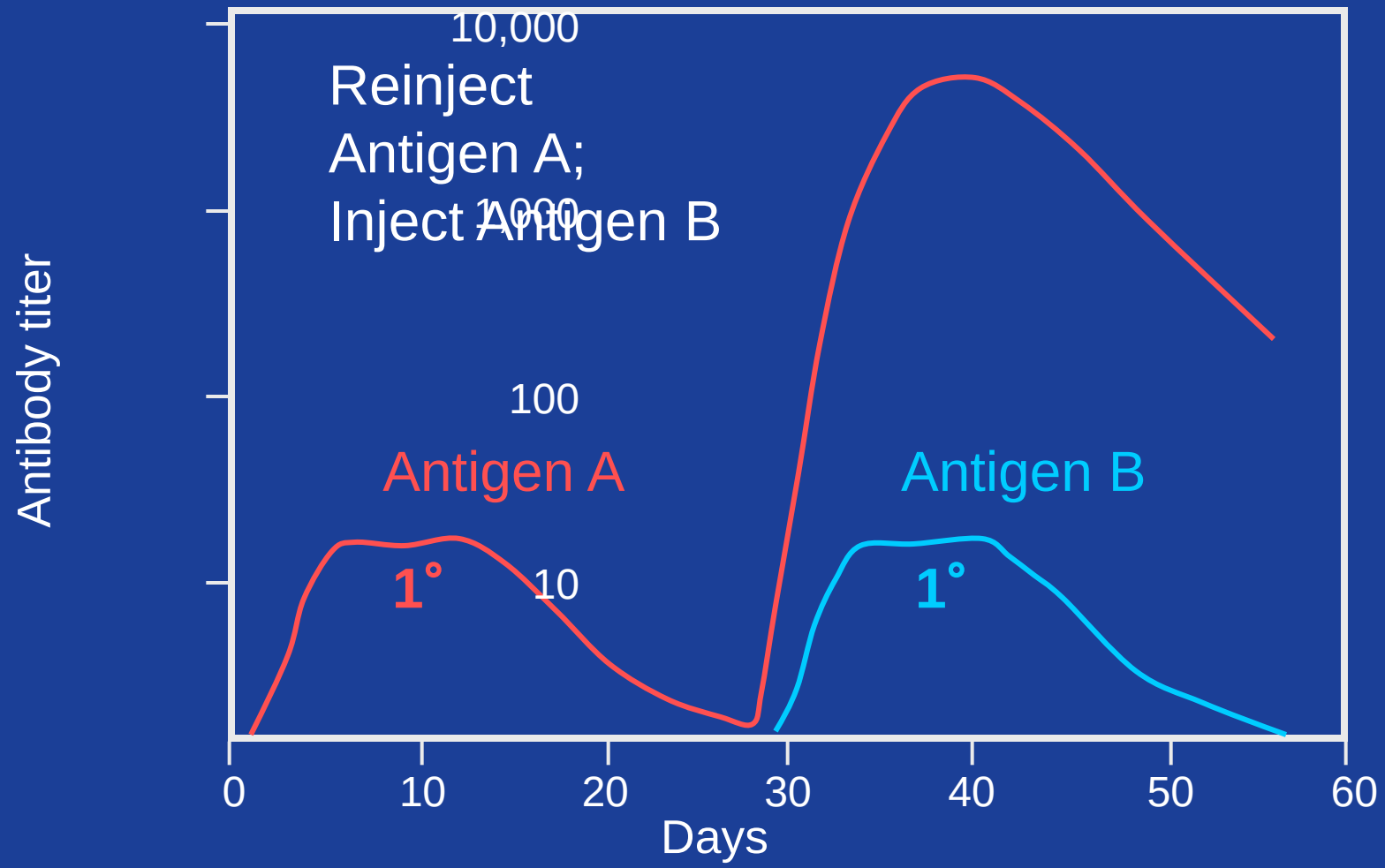
Global eradication of smallpox by vaccination



Vaccines can be helpful against

- Infectious diseases
  - Prions
  - Viruses
  - Bacteria
  - Fungi
  - Parasites
- Tumours
- Autoimmune diseases
- Addiction (eg nicotine)
- Allergy

Primary and secondary immune response – immunologic memory



Passive versus active vaccination

Passive

Administration of antibodies

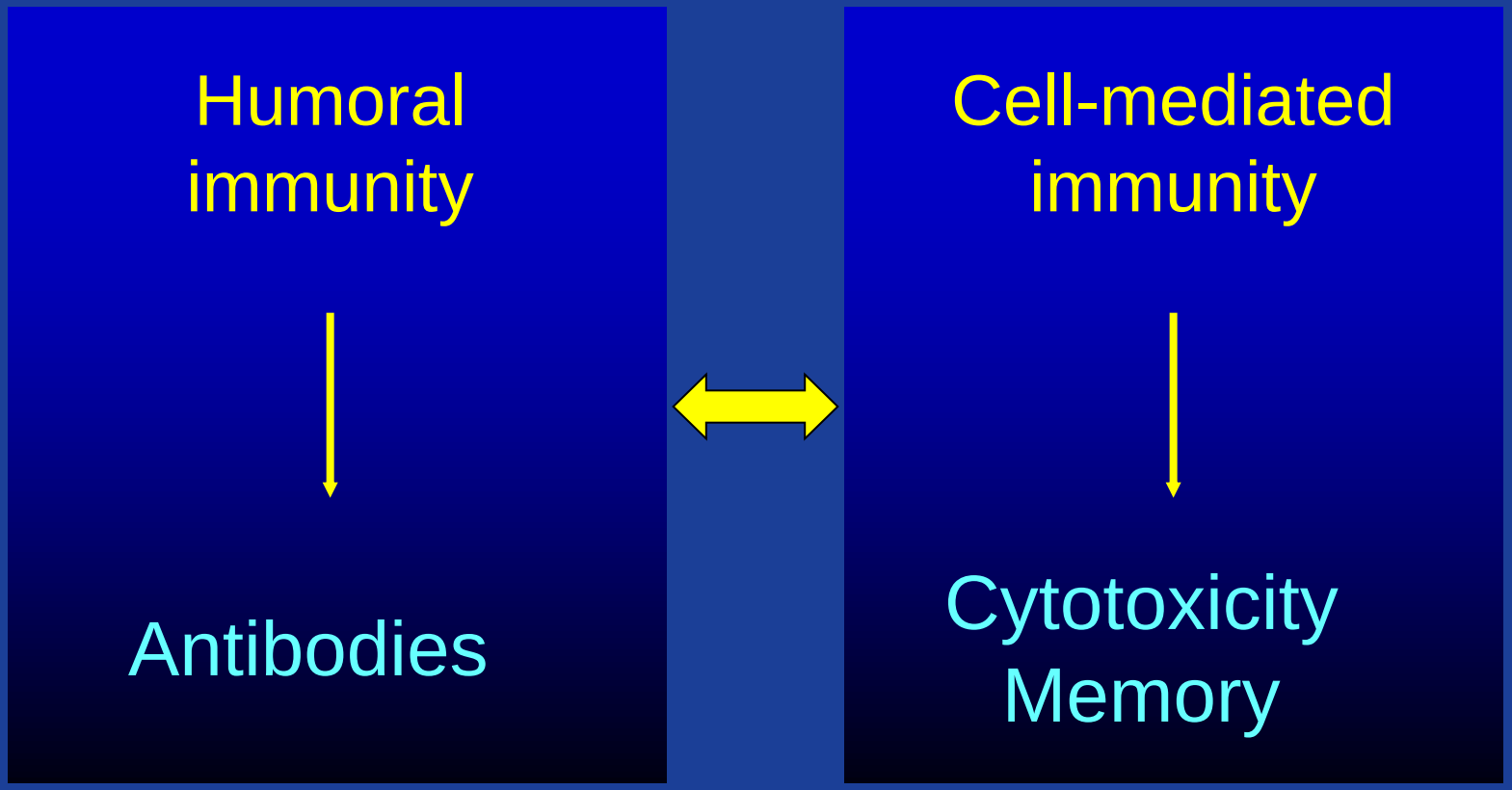
- Immediate effect
- Limited duration (serum half-life IgG ~ 3 weeks)

Active

Administration of antigens

- Takes weeks to become effective
- Potentially life-long protection

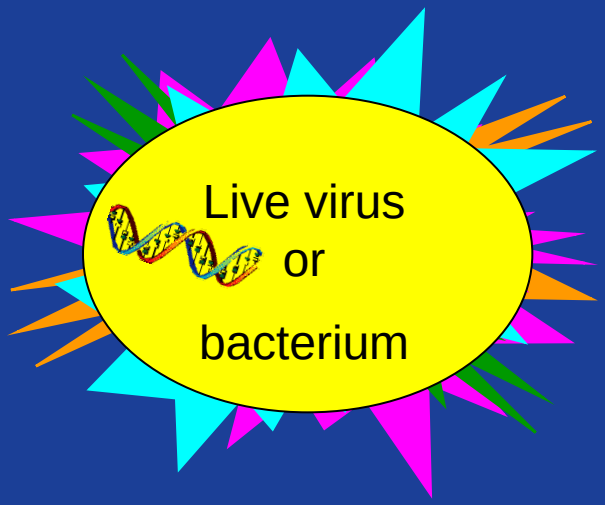
Humoural versus cellular immunity



What determines vaccine efficacy

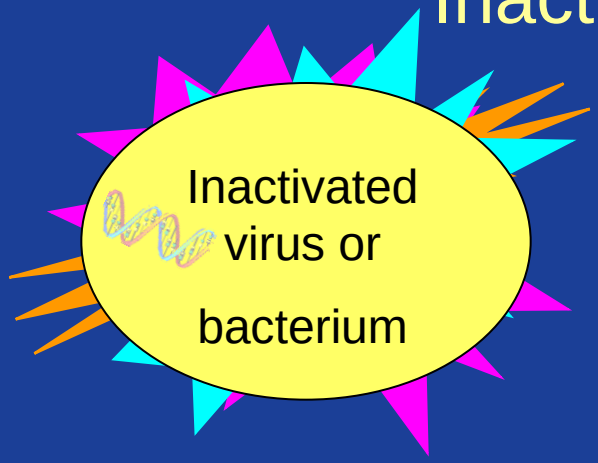
Pathogen	Host	Vaccine composition	Vaccination schedule
Port of entry	Species	Nature of antigenic component(s)	Administration route
Localization	Age	Antigen content	Number of doses
Antigenic var.	Genetic factors	Adjuvants	Immunisation intervals
Mutation freq.	Physical state	Delivery systems	
	Immune status	Combination with other vaccine components	Simultaneous administration of other vaccines (in one container)

Classical vaccine categories



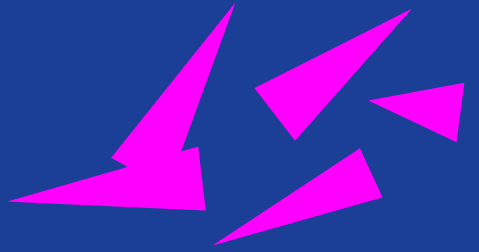
Live

Examples:
MMR
Oral polio
BCG



Inactivated

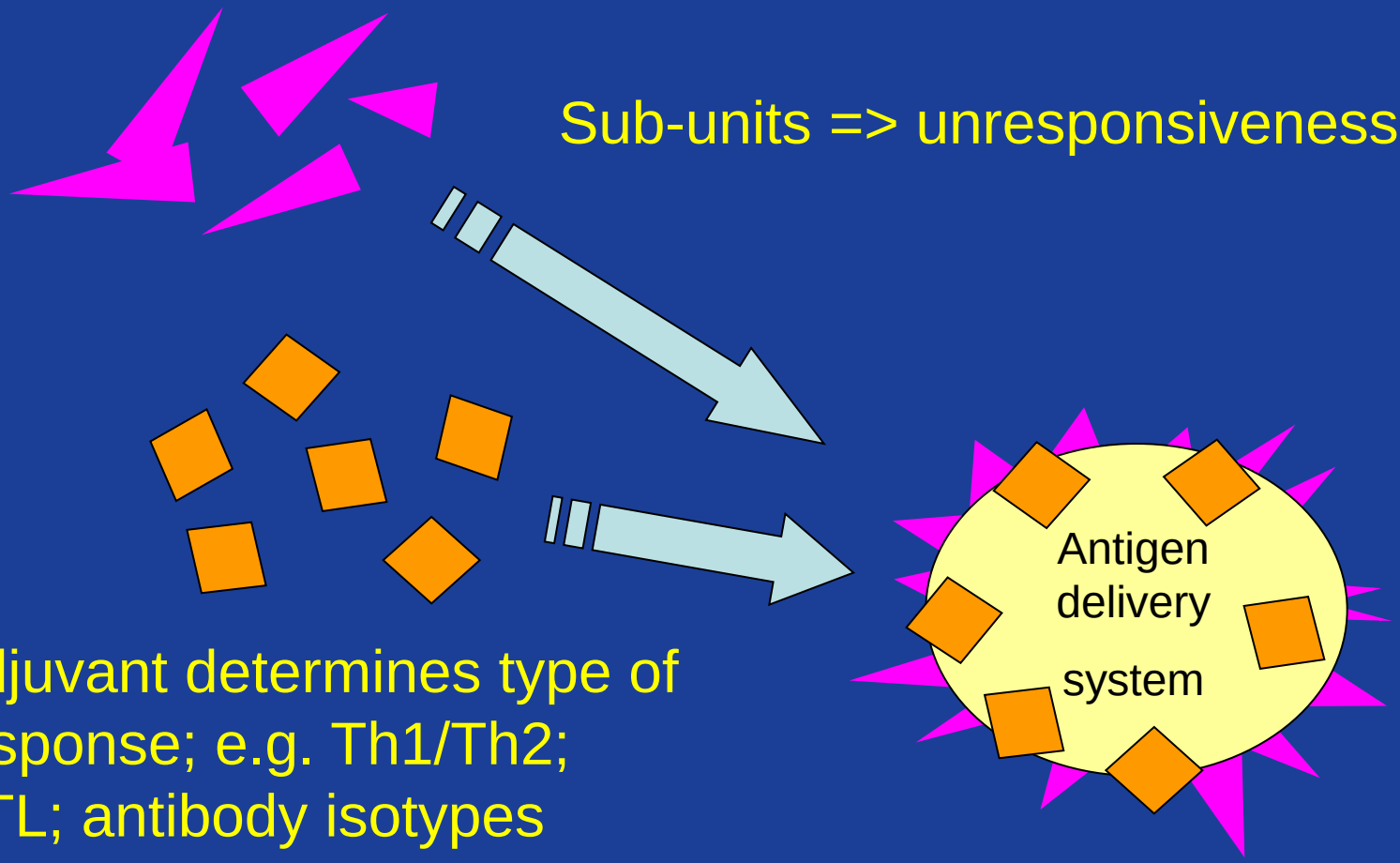
Examples:
Whole cell pertussis
Inactivated polio
Influenza



Sub-unit

Examples:
Diphtheria
Tetanus
Pneumococcal
Hepatitis

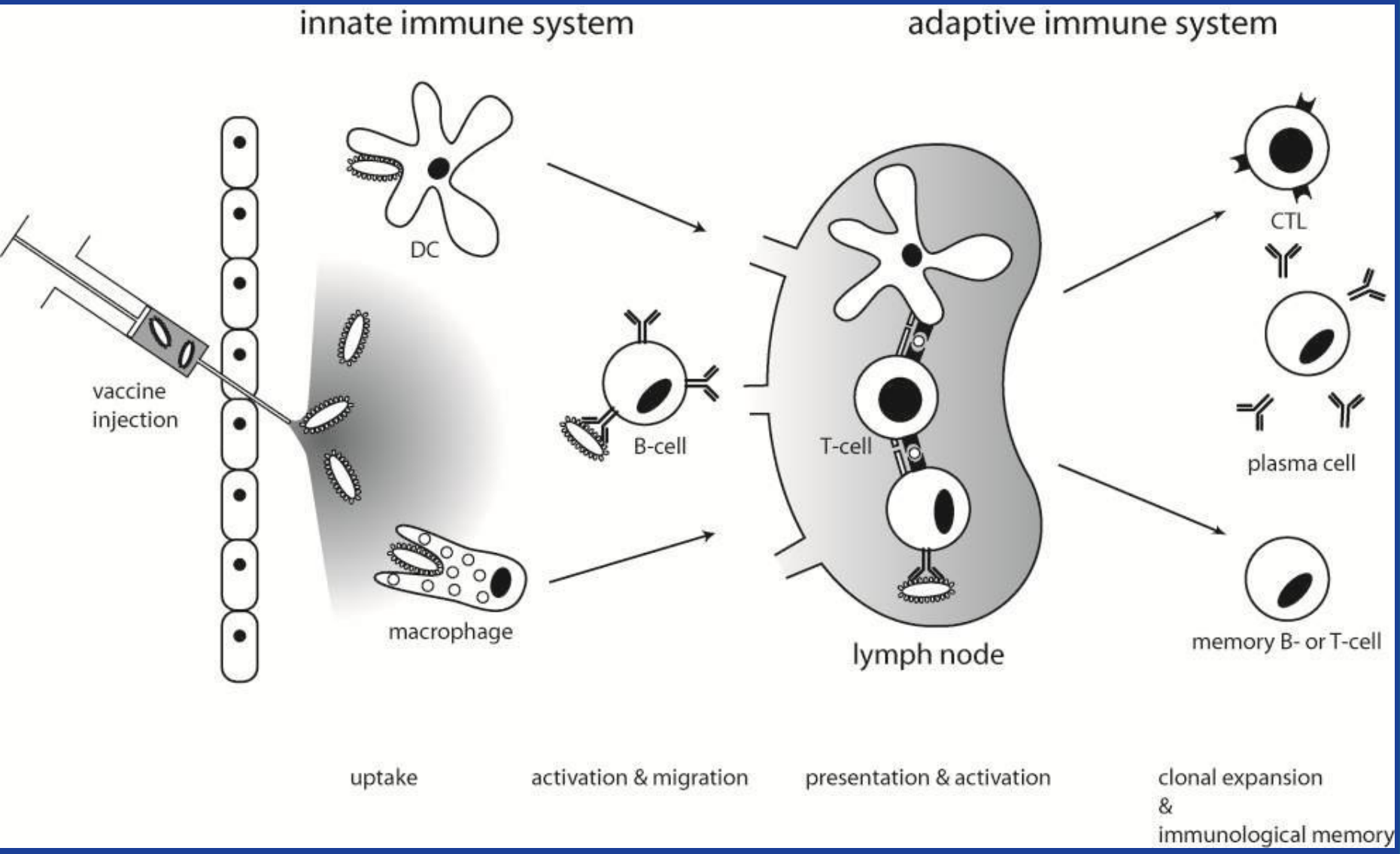
Sub-unit vaccines



Adjuvant determines type of response; e.g. Th1/Th2; CTL; antibody isotypes

Key components: antigen + delivery system + adjuvant

Antigen presentation



Antigen presentation forms

Adjuvant

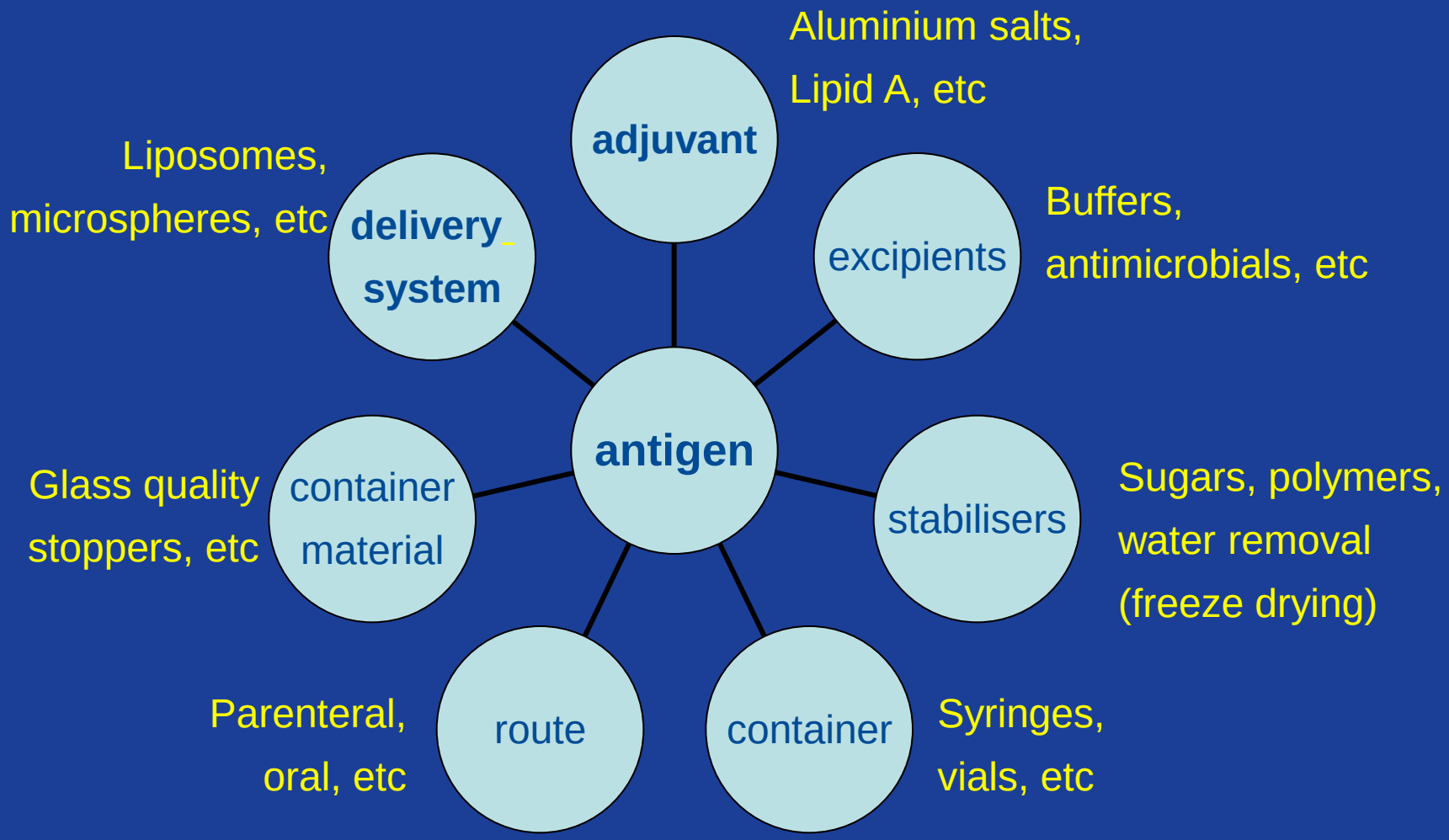
Any material that increases the immune response against an antigen (without being immunogenic by itself)

Delivery system

A device (colloidal particle) that allows multimeric presentation of antigens (may contain adjuvants)

NB: An adjuvant may act as a delivery system vice versa!

A vaccine is more than an antigen



Examples of adjuvants

Adjuvant	Characteristics
Colloidal aluminium salts	Antigen adsorption crucial
Lipid A and derivatives	Fragment of bacterial endotoxin
Muramyl dipeptide (MDP)	Fragments of bacterial cell walls
Saponins	Plant triterpene glycosides
Cytokines	Interleukins, Interferon-γ
Cholera toxin, B subunit	Mucosal adjuvant
CpG	Bacterial DNA sequences
Many more…	Various sources and chemistries

Adjuvant mechanisms

Depot function

slow release of the antigen (from the site of injection)

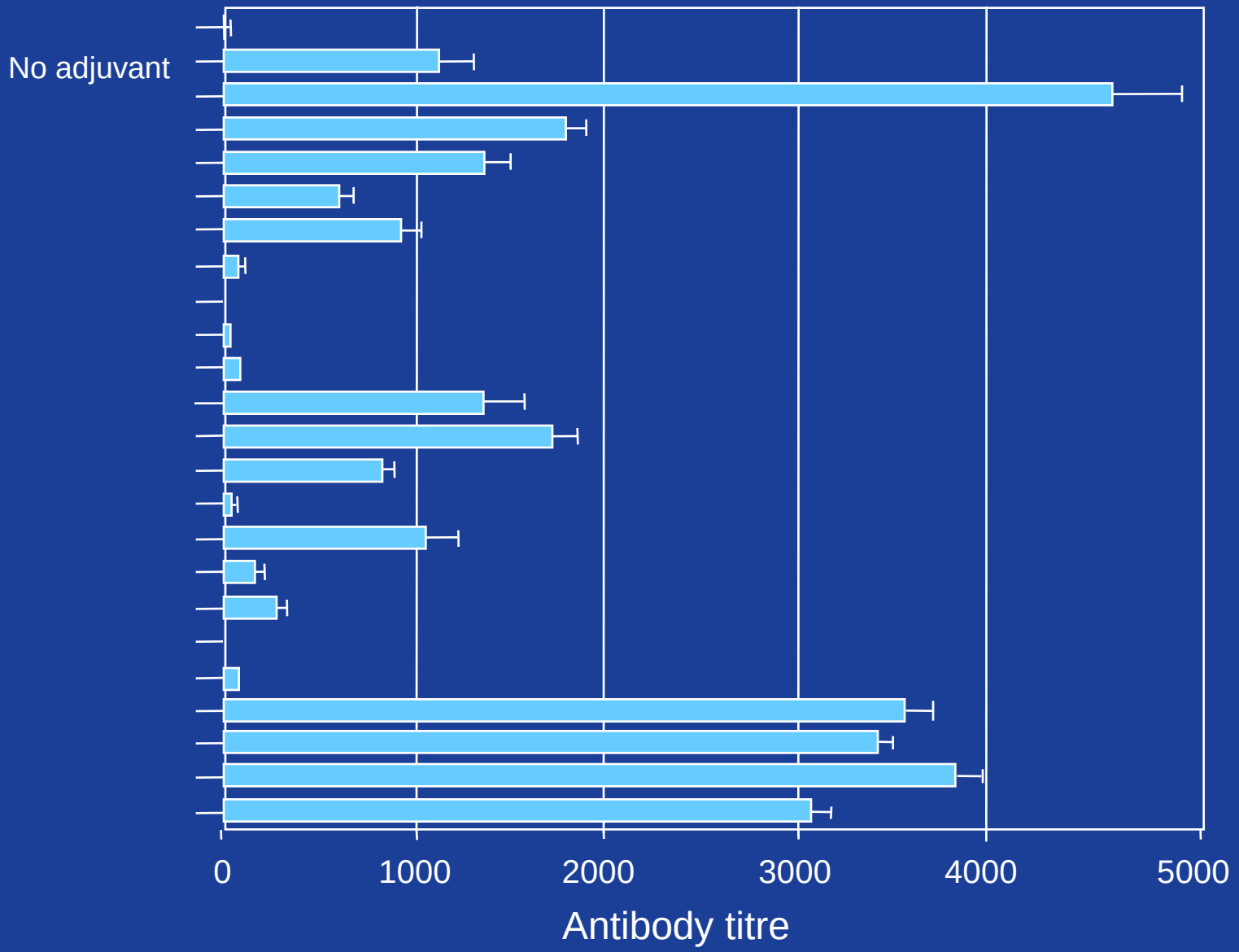
Attraction and stimulation of immunocompetent cells

(eg dendritic cells, lymphocytes) to the site of injection

Delivery

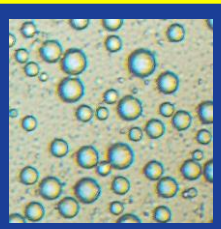
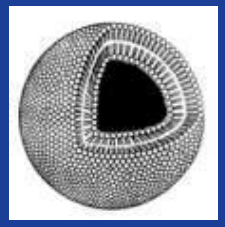
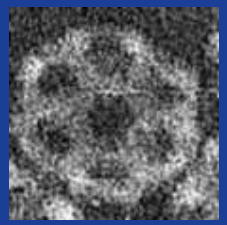
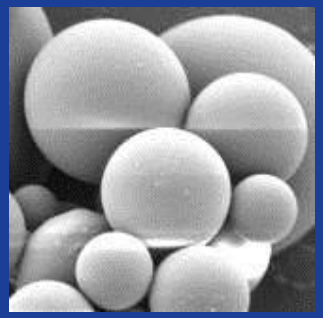
of the antigen to immunocompetent cells in lymph nodes

Serum antibody titres in mice immunized with 5 µg HIV-2 proteins and 24 different adjuvants



Stieneker et al. *Vaccine* 1995;13:45–53

Examples of delivery systems

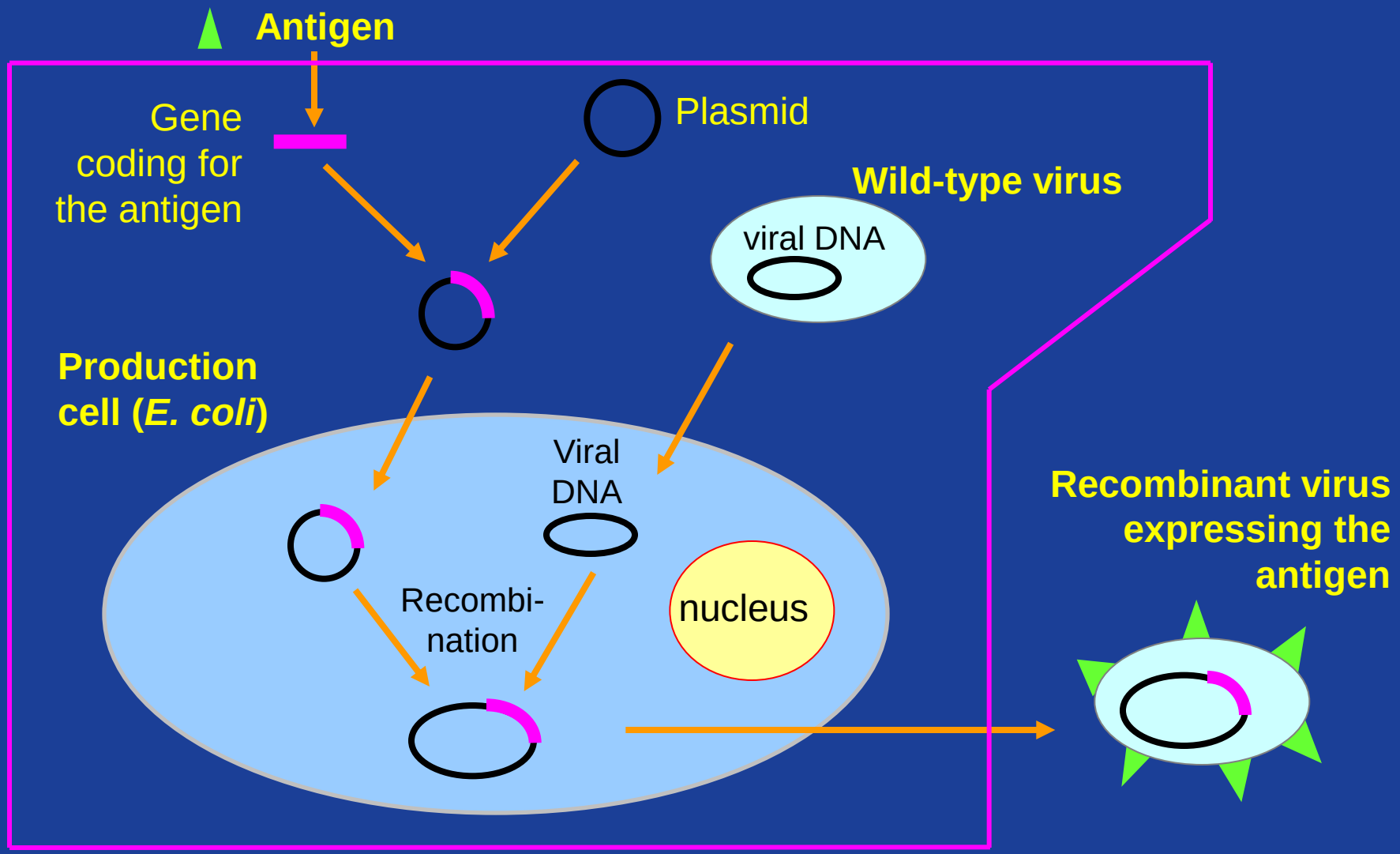
Delivery system		Characteristics
Emulsions		w/o or o/w (**μm** range)
Liposomes		Phospholipid membrane vesicles (**0.05–1 μm**)
ISCOMs		Micellar lipid-saponin complexes (ca. **0.05 μm**)
Microparticles		Biodegradable polymeric spheres, eg PLGA (**1–1000 μm**)

Trends in vaccine development

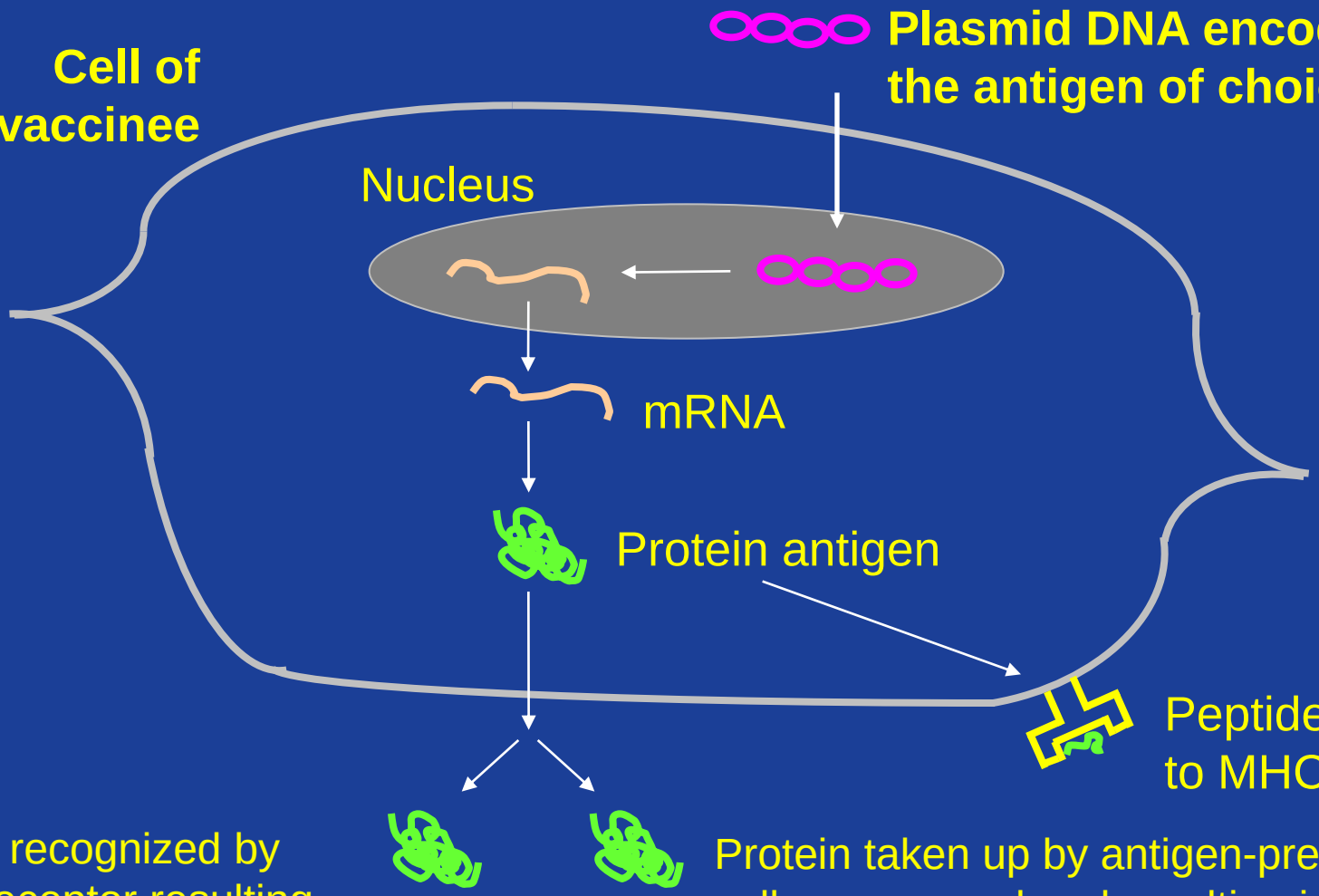
- Recombinant DNA technology
  - First recombinant vaccine in 1985 (Hep B)
  - Live vectors/in clinical trials
  - DNA vaccines/in clinical trials

- Alternatives for the needle
  - Combination vaccines
  - Single-shot vaccines
  - Mucosal (oral, nasal, pulmonary) vaccines
  - Epidermal vaccines
  - Needle-free injection devices

Live vectors as delivery system
eg *recombinant vaccinia virus*



DNA vaccination – principle



Alternatives for the needle

Why alternatives?

- Simpler
- Safer
- Patient compliance

Which alternatives?

- Mucosal (oral, nasal, pulmonary)
- (Epi)dermal
- Needle-free injection devices

Combination vaccines – hurdles

- Pharmaceutical incompatibility
- Immunological incompatibility
  - Matching of immunization schedules
  - Combination of vaccine components may mutually influence their efficacy

Live mucosal vaccines

Classical oral vaccines: adenovirus, cholera, polio, typhoid

Influenza Virus Vaccine Live, Intranasal

fluMist®

2006-2007 Formula

FOR NASAL ADMINISTRATION ONLY

Rx only

DESCRIPTION

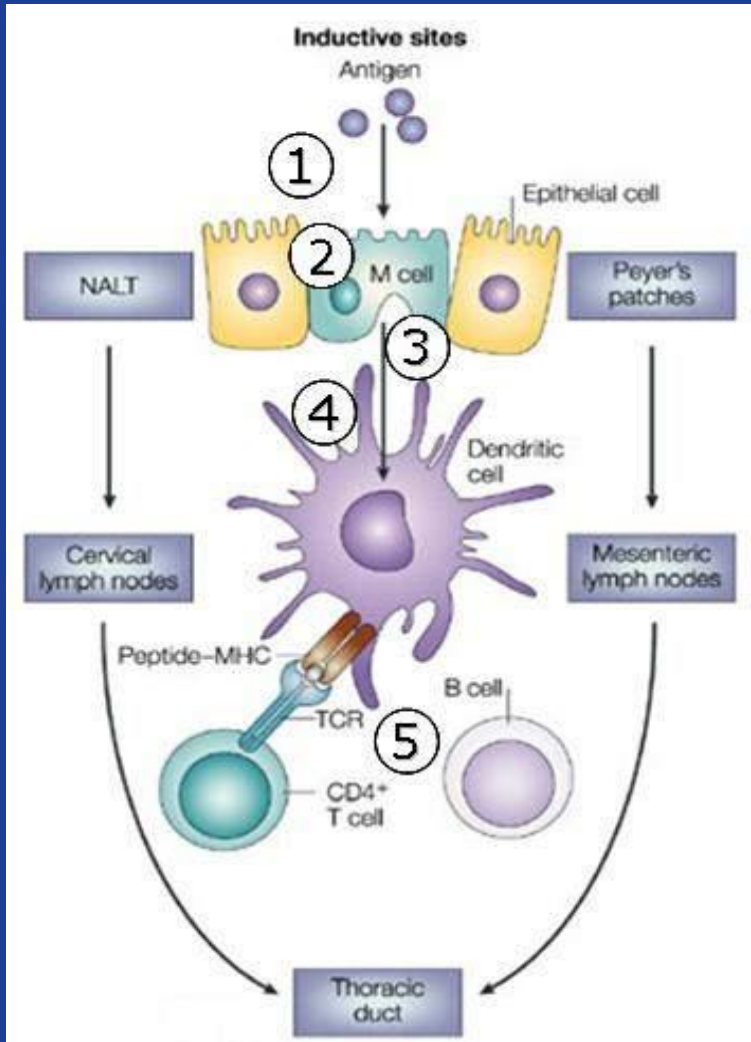
Influenza Virus Vaccine Live, Intranasal (FluMist®) is a live trivalent nasally administered vaccine intended for active immunization for the prevention of influenza.

Each 0.5 mL dose is formulated to contain $10^{6.5-7.5}$ $TCID_{50}$ (median tissue culture infectious dose) of live attenuated influenza virus reassortants of the strains recommended by the U.S. Public Health Service (USPHS) for the 2006-2007 season: A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 [1]. These strains are (a) *cold-adapted (ca)* (i.e., they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type viruses); (b) *temperature-sensitive (ts)* (i.e., they are restricted in replication at 37°C (Type B strains) or 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently); and (c) *attenuated (att)* so as not to produce classic influenza-like illness in the ferret model of human influenza infection. The cumulative effect of the antigenic properties and the *ca, ts,* and *att* phenotype is that the attenuated vaccine viruses replicate in the nasopharynx to induce protective immunity.

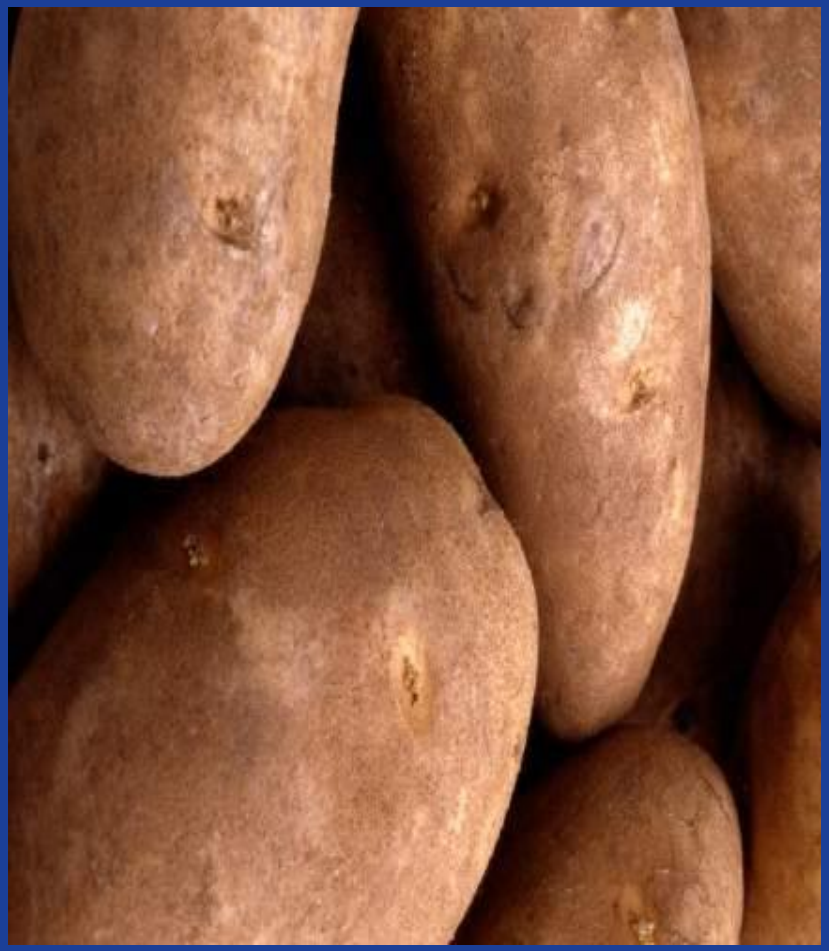
Delivery issues in mucosal immunization

Crucial steps

1. Residence time
2. M-cell uptake (particles!)
3. Transport to dendritic cells
4. Dendritic cell uptake
5. Dendritic cell maturation, control of T-cell response

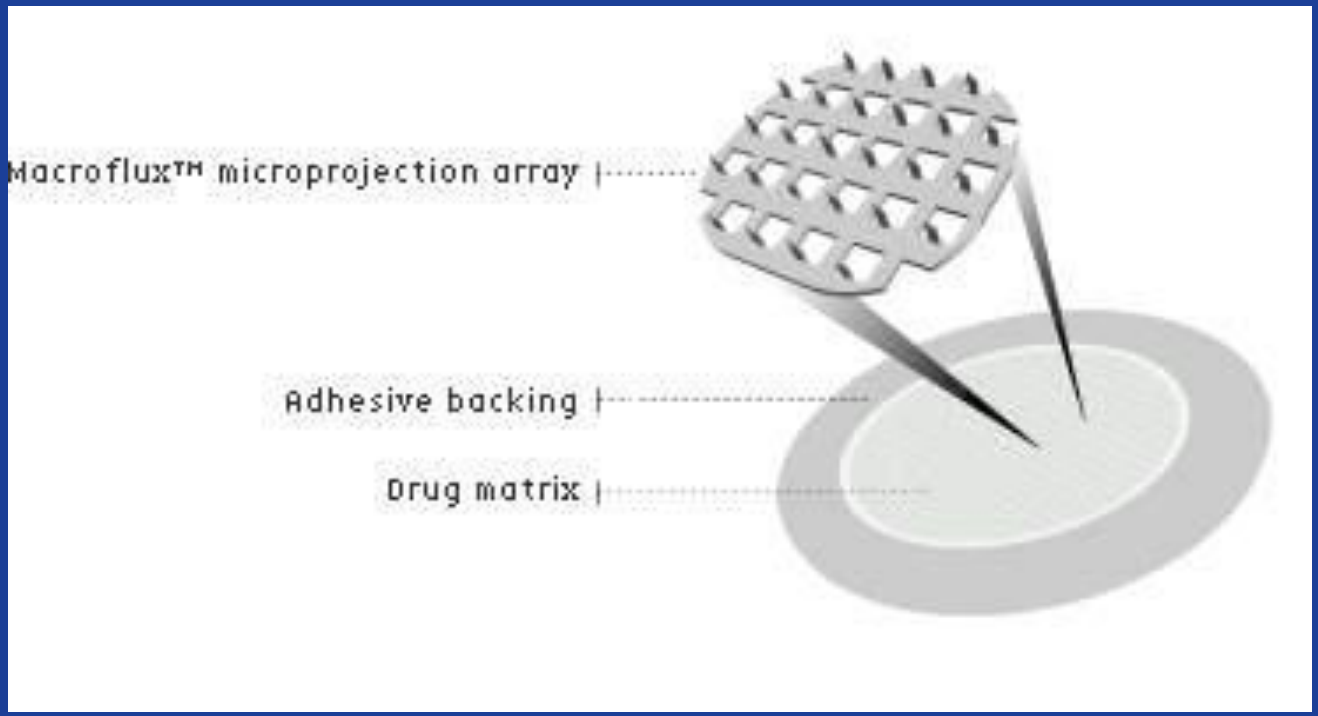


Edible vaccines



Vaccination via the skin

Patches with microneedle arrays



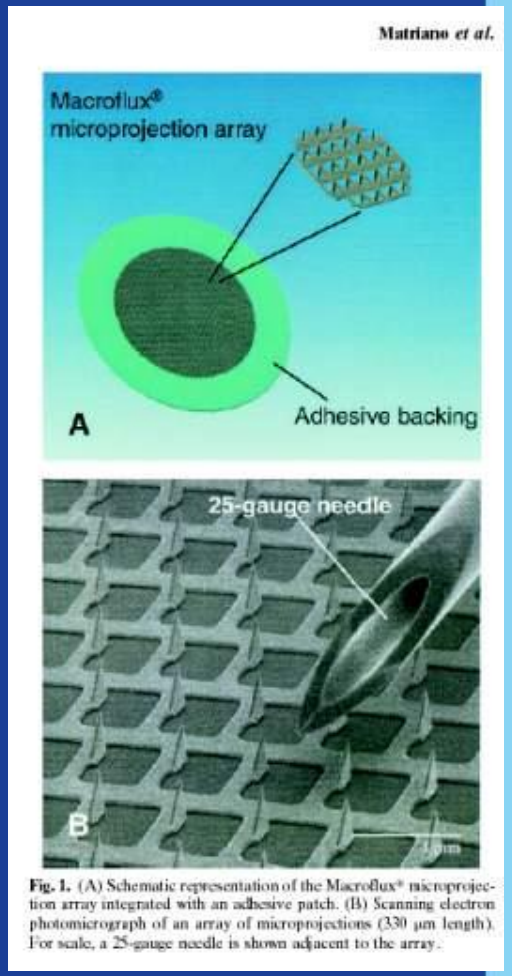


Fig. 1. (A) Schematic representation of the Macroflux® microprojection array integrated with an adhesive patch. (B) Scanning electron photomicrograph of an array of microprojections (330 μm length). For scale, a 25-gauge needle is shown adjacent to the array.

Matriano et al. (2002) Pharm. Res. 19: 63-70

Vaccination via the skin

DNA vaccines: tattoo you!

nature REVIEWS IMMUNOLOGY

Nature Reviews Immunology **5**, 587 (August 2005) | doi:10.1038/nri1672

Vaccines: Tattoos that your mother will like

Elaine Bell

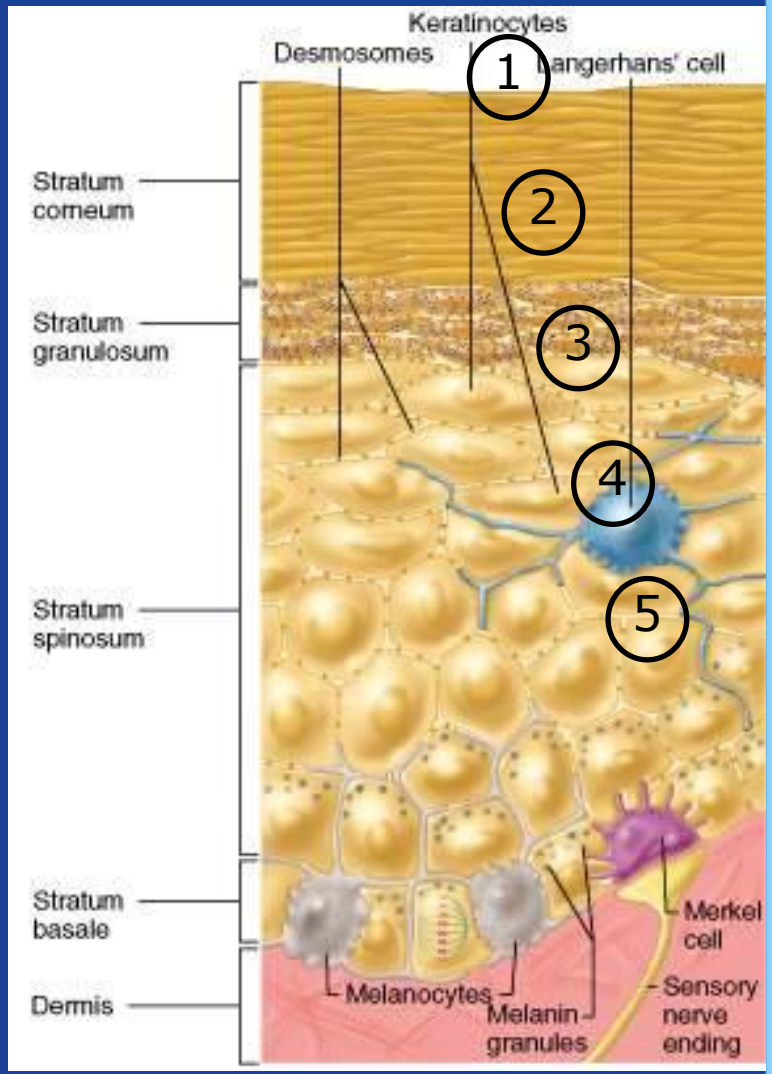
Immune responses that are elicited following the administration of DNA vaccines tend to develop rather slowly, and to achieve these responses, the vaccines need to be administered at several time points. Now, Adriaan Bins and colleagues report a new vaccination strategy that results in potent antibody and T-cell responses within 12 days.

It is thought that the slow development of immune responses after DNA vaccination is a consequence of only a small number of cells being transfected and of these cells only expressing a small amount of antigen, although there is little direct evidence for this. So,

Delivery issues in epidermal immunization

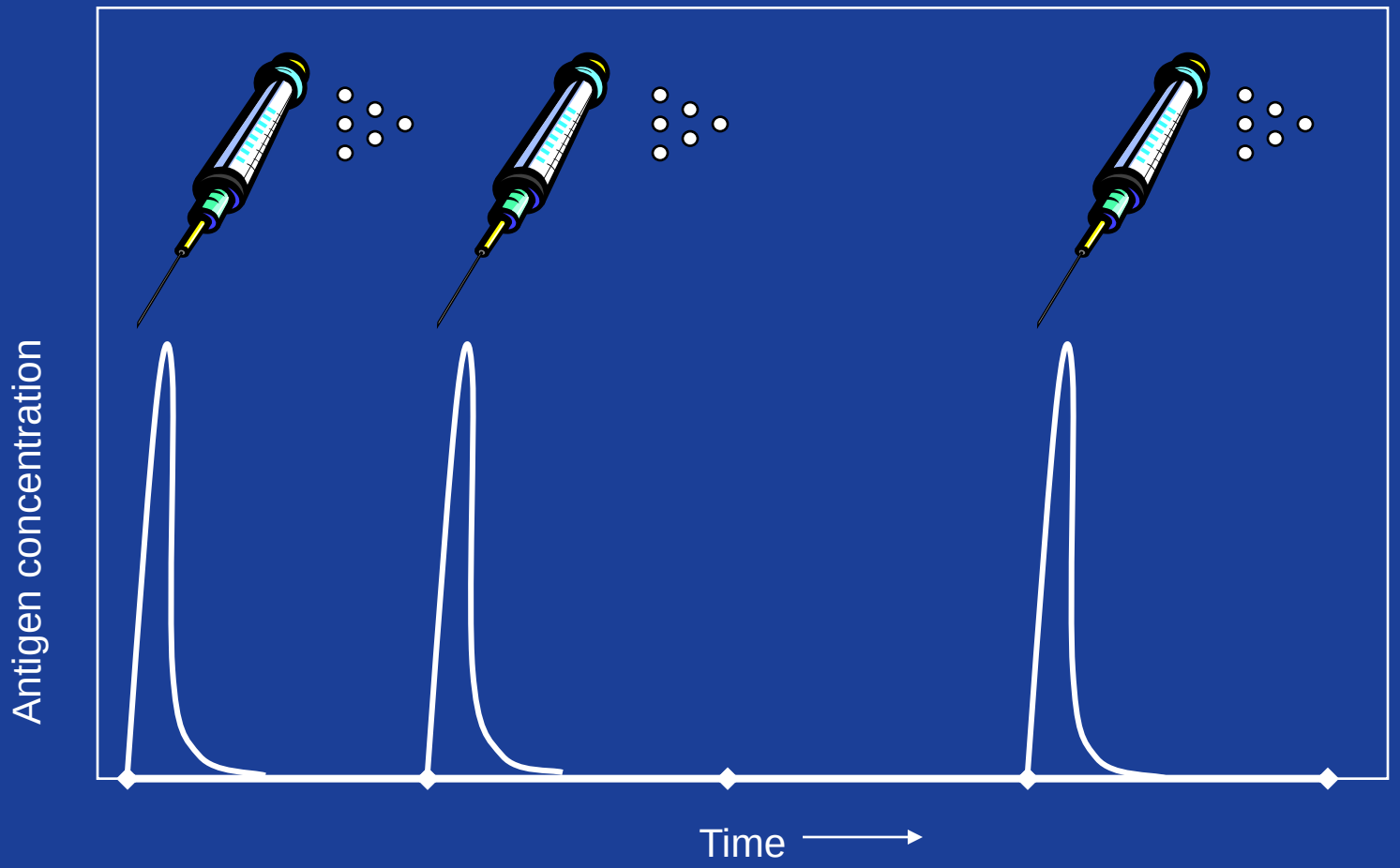
Crucial steps

1. Reduction of barrier function
2. Transport across the stratum corneum
3. Transport to Langerhans cells
4. Dendritic cell uptake
5. Dendritic cell maturation, control of T-cell response



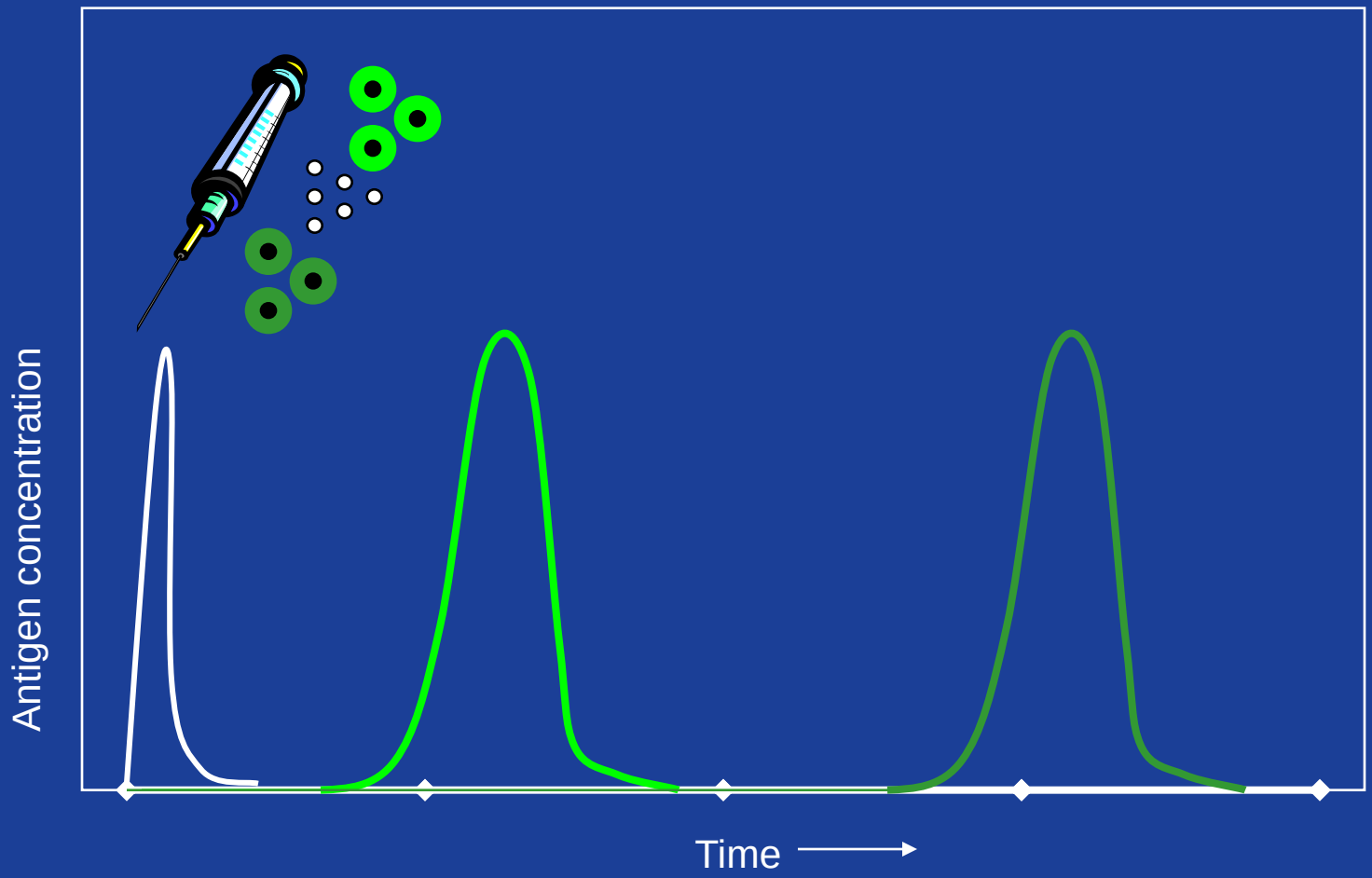
The concept of pulsed release (1)

Multiple injections



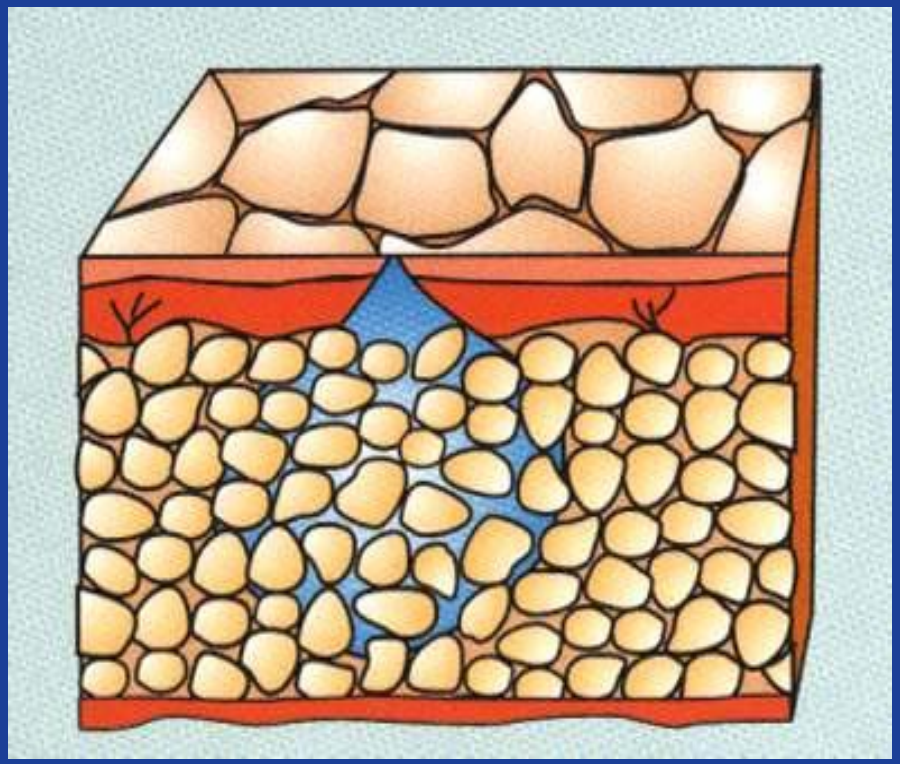
The concept of pulsed release (2)

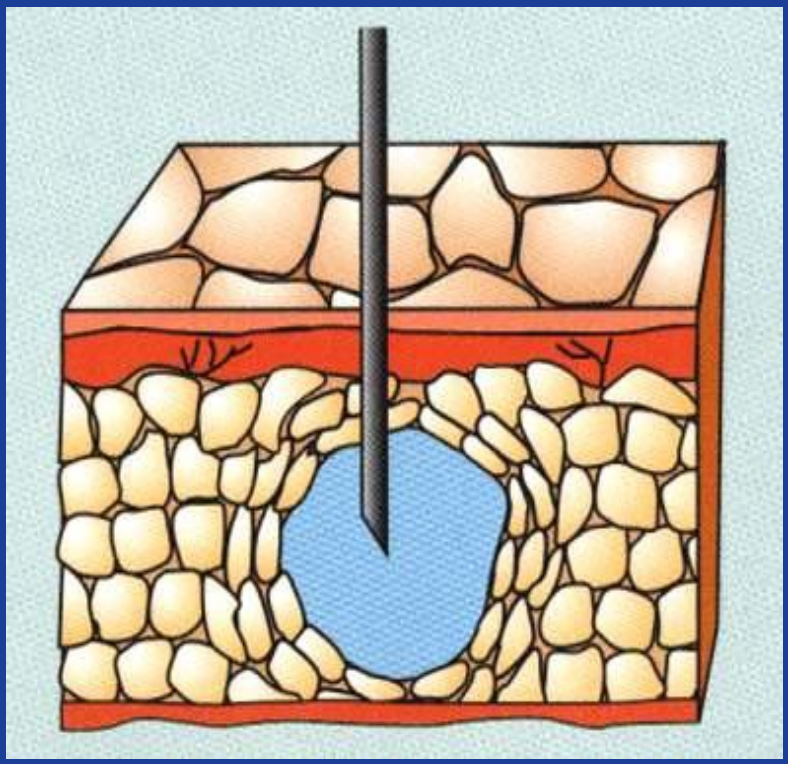
Combining a priming dose with controlled release microspheres



Needle-free injection devices

Jet injectors versus needles





Summary

- Formulation largely determines vaccination efficacy
  - Adjuvants
  - Delivery systems
- Approaches to reduce number of injections:
  - Combination vaccines
  - Mucosal (oral, nasal, pulmonary) delivery
  - Epidermal immunisation
  - Needle-free injection

Conclusions

- Vaccine categories: live, inactivated, sub-unit; rDNA techniques are gaining ground
- Especially sub-unit vaccines require delivery systems (particles) and adjuvants (various compounds)
- A vaccine is more than an antigen
- Currently several alternatives for the needle are being investigated