Immune prophylaxis and immune therapy

DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

LECTURE THESIS

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Key points

- Terms and definitions
- Vaccines
- Sera
- Immune therapy in immune mediated diseases (see lecture course):
  - Allergy
  - Autoimmunity
  - Immune deficiencies
  - Tumors
  - Transplantations
  - Infections

Immunization – terms and definitions

- **Immunization**:
  - a procedure designed to increase concentrations of antibodies and/or effector T-cells which are reactive against infection
- **Immunoprophylaxis**:
  - Immunization performed before exposure to an infectious agent
  - It is intended to prevent the infection
  - Usually the immunizing agent is a vaccine
- **Immunotherapy:**
  performed during an active infection
  it is intended to treat the infection
  Usually the immunizing agent is serum

Types of Immunization

- **Passive immunization**:
  - Protective Abs are introduced in the recipient to neutralize the infectious agent
  - No immunological memory; w/o T_h cells.

- **Active immunization**:
  - Induction of active adaptive immune response, with protection and memory.
  - Usually vaccines are introduced - stimulate host's immune system to produce specific antibodies or cellular immune responses or both which would protect against a disease.

How to induce passive and active immunization

Passive Immunization –

Natural - via placenta (IgG) or maternal milk

Artificial– via immune serum (human intervention)

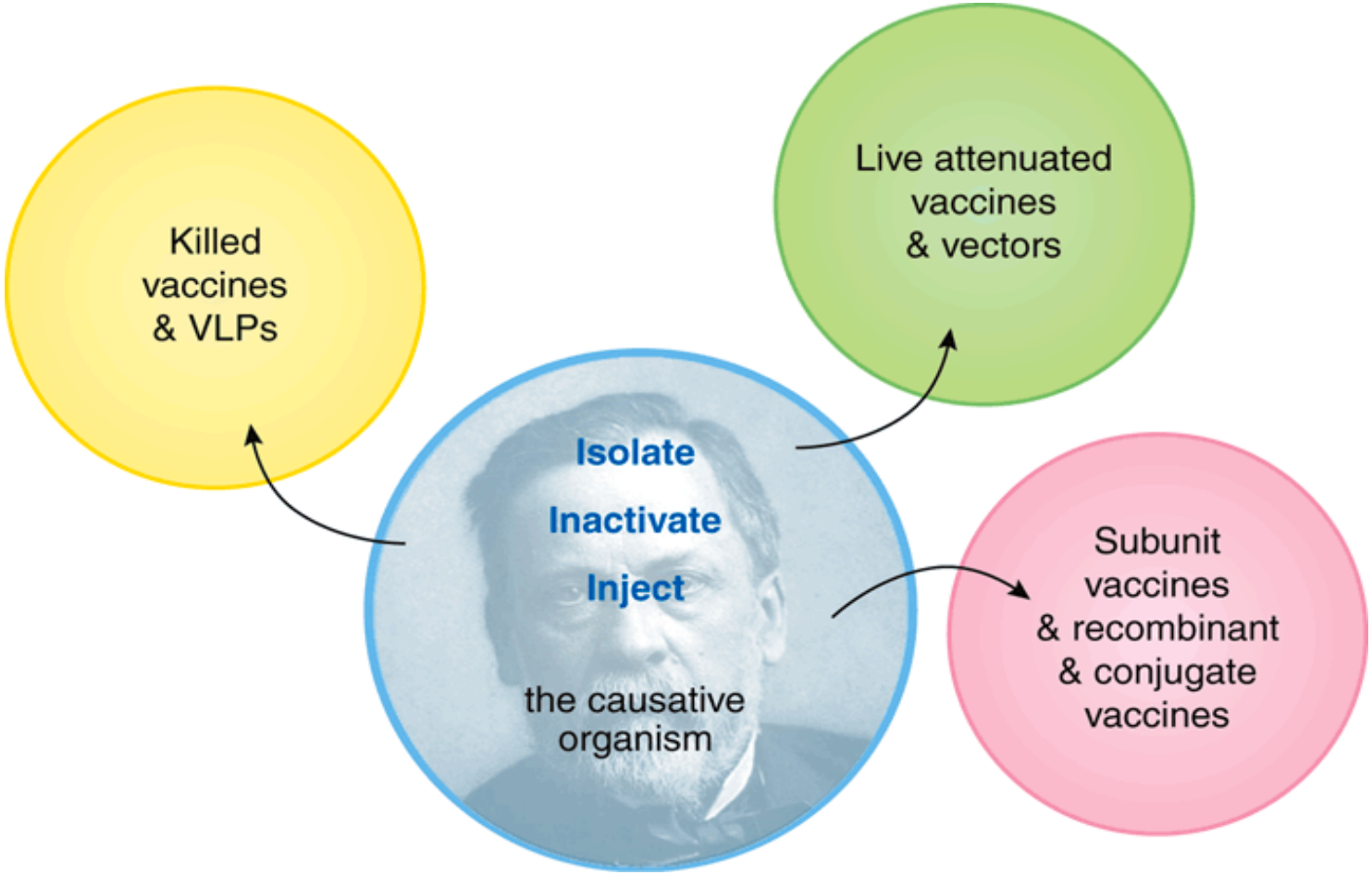
Active Immunization –

Natural infection - after cholera, grippe…

Artificial - through vaccines (microbial substances in non-infectious form; may contain bacteria or viruses)

- Performed either by i.m. or s.c. injection of killed or attenuated antigens (often with adjuvant) or by ingestion of attenuated live organisms.
- Antibodies and/or immune competent cells are generated

Types of Vaccines



Types of Vaccines

A. Inactivated (Killed by phenol) – cholera

B. Attenuated (Live, Non-infectious)

- example: BCG
- inactivated by heat, chemicals or genetic manipulation
- it stimulates both cell mediated and antibody mediated immune responses
- Risk - it could revert back to infectious agent

LIVE Vaccines are MORE EFFECTIVE THAN KILLED ONES

C. Toxoids

- inactivated toxins which are purified proteins
- stimulates the antibody mediated response only
- e.g. DT (diphtheria, tetanus toxoids)
- stimulate antibody mediated response only

Types of Vaccines

D. Component (subunit):

Contains purified components from bacteria and viruses instead of whole organism

Advantage: no pathogenic particles

Disadvantage: Is protein same as *in situ*? Cost!

E. Recombinant:

Hepatitis B vaccine – purified viral coat protein

Streptococcus pneumoniae – capsular polysaccharide

Hemophilus influenzae (HiB) – capsular polysaccharide,

Nesseria meningiditis – capsular polysaccharide

stimulates the antibody mediated response only

Other vaccinations terms

- Booster Shots:
  - same vaccine given at a later date e.g. DT given every 10 years;
  - BCG - to refresh the memory cell population

- Adjuvant: chemicals in the vaccine solution that enhance the immune response
  - Alum – Ag
  - gives more time for memory cells to form

Common Vaccinations in Infants and Children

AGE	VACCINE
Birth- 2 months.	BCG and Hepatitis B (recombinant surface Ag)
2 months.	Diphtheria, tetanus, acellular pertussis (DTaP)
	Inactivated Polio virus (IPV)
	Haemophilus influenzae b (Hib-conjugate)
4 mos.	DTaP, IPV, Hib, PCV
6-18 mos.	Hep B, DTaP,Polio (IPV), Hib
12-15 mos.	DTaP, Hib
	Measles, mumps, rubella (MMR)
4-6 yrs	DTaP, IPV, MMR
11-12 yrs	DT

Combination vaccines

Examples:

influenza
trivalent OPV, inactivated IPV
DPT, DPT/Hib, etc.
MMR, MMRV
PnC/MnC

Advantages:

only one needle at a visit
may reduce number of visits
reduces costs of administration
geographic tailoring

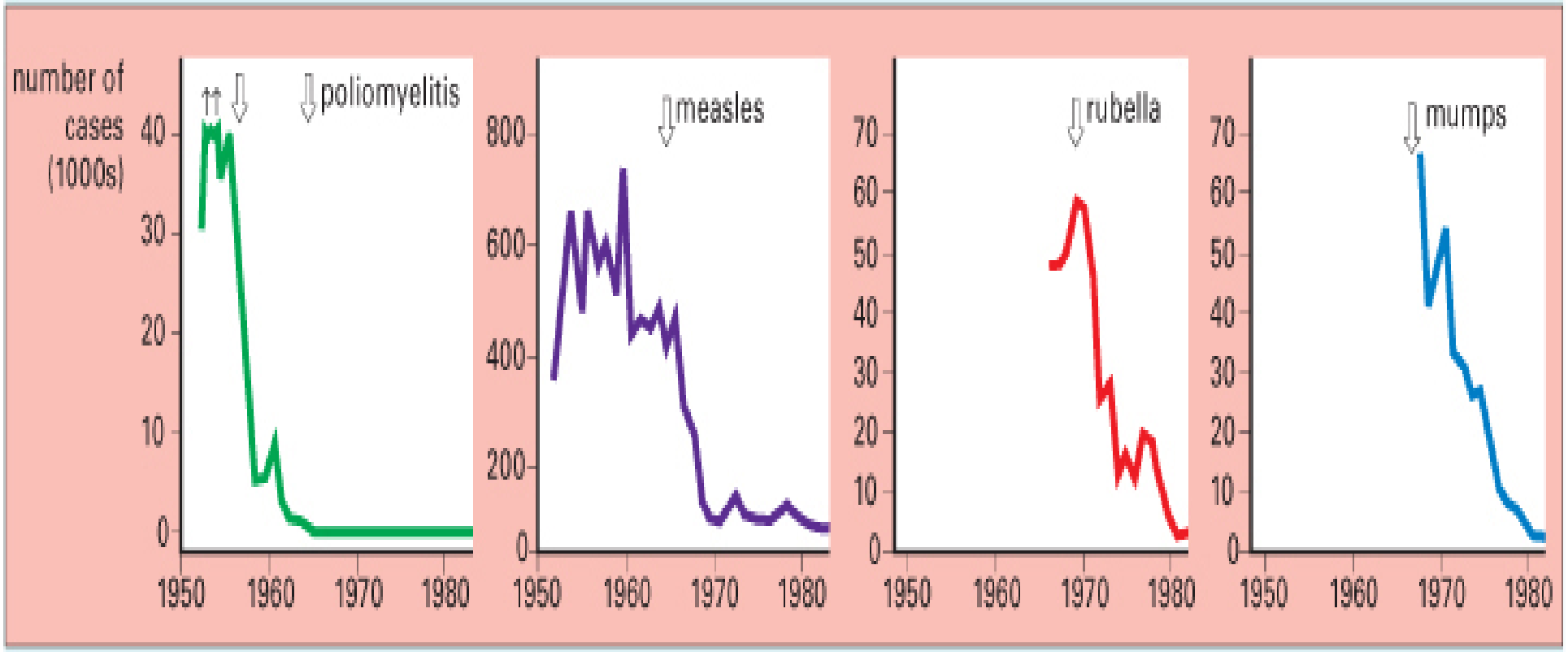
Disadvantages:

technically more difficult to produce
higher production costs
higher evaluation costs

Correlates ?

- Humoral component
  - Tetanus
  - Diphtheria
  - *H. influenzae*
  - *S. pneumoniae*
- Cellular components
  - BCG
  - Herpes type 1&2
  - Shingles (herpes zoster)
  - Influenza in elderly
  - Varicella (herpes zoster)
  - Measles

Effect of vaccination on the incidence of viral disease



Vaccines provide an antigenic stimulus that does not cause disease but can produce long lasting, protective immunity

CURRENT VACCINE PRACTICE

2–6 months	12–18 months	teenage	traveller	old age
polio diphtheria pertussis tetanus	measles mumps rubella	diphtheria tetanus BCG	hepatitis A and B yellow fever typhoid cholera	influenza pneumococcus

Immunotherapy – preformed Ab

Immune serum globulin – gamma-globulin that contains immunoglobulin extracted from the pooled blood of at least 1,000 human donors (usually more than 5-6 000)

- Treatment of choice for preventing measles, hepatitis A and replacing Ab in the immune deficient

- Lasts 2-3 months

Immunotherapy – preformed Ab

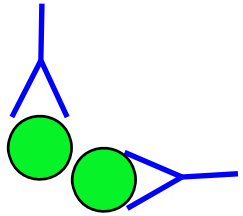
Specific immune globulin- prepared from convalescent patients in a hyperimmune state

- Contains high titer of specific Ab
- Used in pertussis, tetanus, chickenpox, hepatitis B
- Sera produced in horses are available for diphtheria, botulism, spider and snake bites
- Act immediately and can protect patients for whom no other useful medication exists

Effectors functions of antibodies

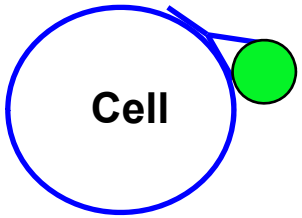
Neutralization

reduce the pathogen load



Inhibit bacterial toxins

prevent contacts with host cell



Complement mediated lyses

inhibits the pathogen penetration of the host cell

↳Complement binding ➔pathogen destruction

Antianthracis gamma-globulin

- **Preparation contains antitoxins.**
- **It is gamma-globulin fraction of serum of the hyper-immunized animals.**

Immunity after introduction?

Passive

Humoral

Antibacterial

Specific

Antidiphtherial antitoxic serum

- preparation - by hyperimmunization of a diphtherial toxoid.
- Effective mean of specific therapy of diphtheria.
- Complications after introduction of heterogenic serum - may induce anaphylactic shock and serum illness.

Immunity after introduction?

Passive

Humoral

Antibacterial

Specific

Sources of Passive Immunity

- Blood or blood products
- Homologous pooled human antibody (immune globulin)
- Homologous human hyperimmune globulin
- Heterologous hyperimmune serum (antitoxin)

Classification of the serum preparations

- **homogeneous serum**: obtained from blood donor volunteers, that have been immunized.

- **heterogeneous serum**: obtained from blood of animals hyperimmunized.

Hypersensitivity reactions by injection of the heterogeneous serum

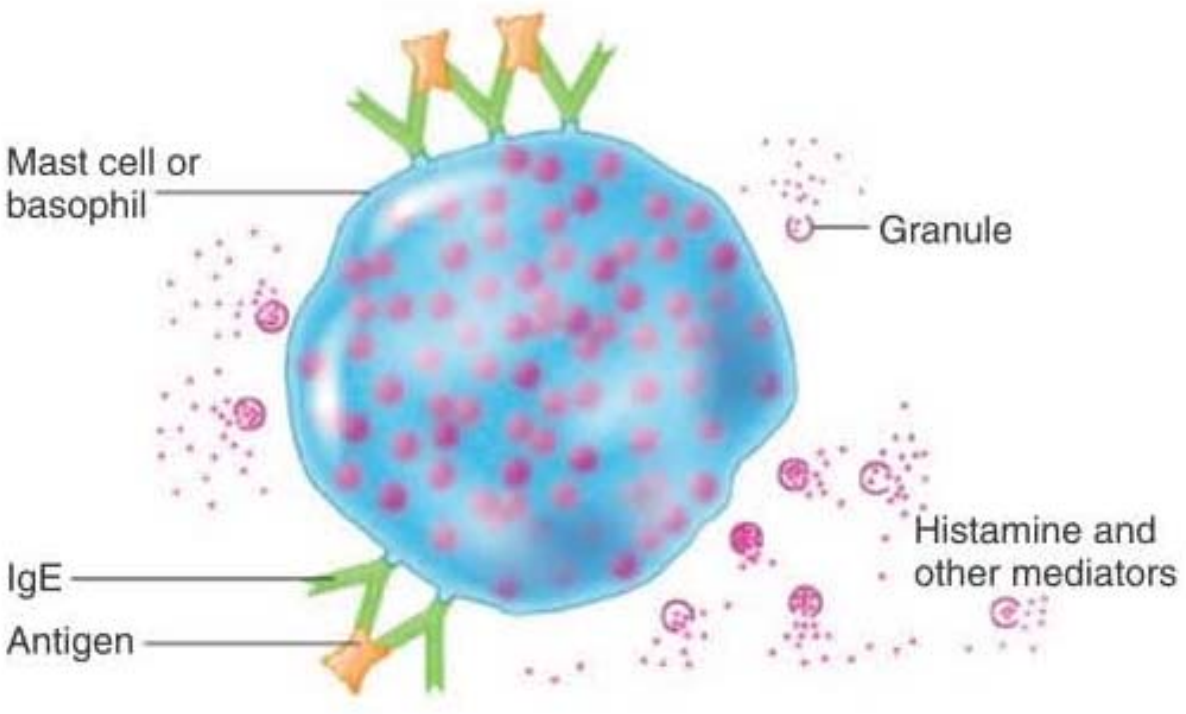
Anaphylactic shock

- within 2 to 30 minutes after a person sensitized to an antigen.
- Anaphylactic responses can be:
  - systemic reactions (produce shock and breathing difficulties and are sometimes fatal), or
  - localized reactions (include common allergic conditions - hay fever, asthma, and hives - slightly raised, often itchy and reddened areas of the skin).

Serum Sickness

A systemic form of hypersensitivity of immediate reaction. It appears 7 to 12 days following single injection of high concentration of foreign serum

The mechanism of anaphylaxis



- IgE antibodies, produced in response to an antigen (heterogenic antibody), coat mast cells and basophils.

- When an antigen bridges the gap between two adjacent antibody molecules of the same specificity, the cell under goes degranulation and releases histamine and other mediators.

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Avoid allergens

Doctor prescribed medications

Allergy shots
(immunotherapy)

Continue allergy
education

A.D.A.M.

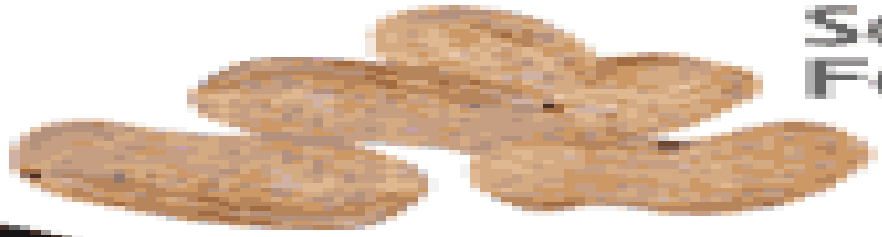
Controlling Allergies

Try to avoid the most common allergens

Dust Mites

Pollen

Some Foods



Pet Dander

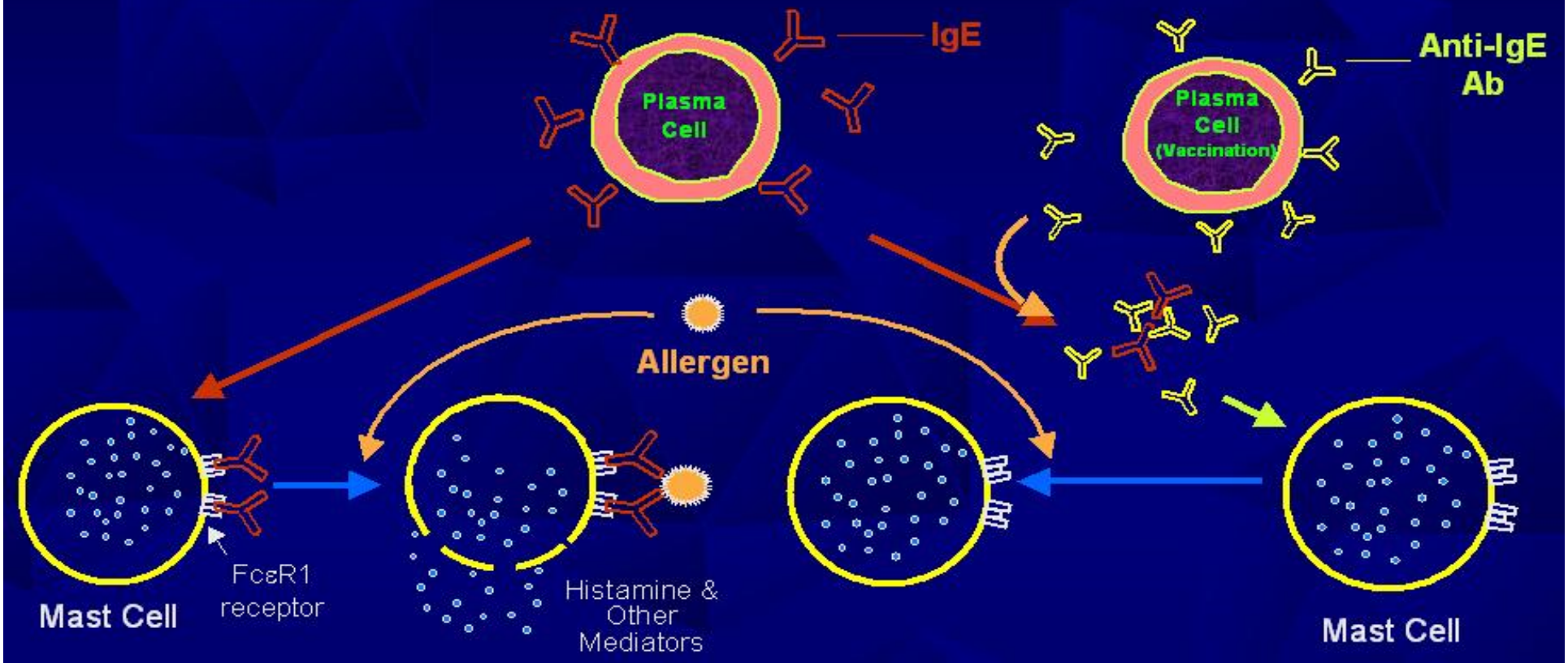
Principal Treatment of TYPE I ALLERGY

1. NON-SPECIFIC PHARMACOLOGICAL THERAPY
   - ANTI-HISTAMINE DRUGS
   - DECONGESTIVE DRUGS
   - GLUCOCORTICOIDS

IMMUNE THERAPY IN TYPE I

2. IMMUNE THERAPY
   - SPECIFIC:
     - ALLERGEN-SPECIFIC
     - HYPOSENSIBILITY
     - ALLERGOID TREATMENT
   - NON-SPECIFIC
     - MO ABS AGAINST IGE (ANTI-IGE ABS) - ANTI-IDIOTYPIC THERAPY
     - INHIBITION OF IL-4 AND IL-5

UBITh® IgE Immunotherapeutic: mechanism



Type I hypersensitivity reaction

No allergy reaction

UBI

Principles of complex treatment of PID

1. Bone-marrow transplantation – limited !

Stem cell transplantation – perspective !

2. Gene therapy – in well established and known gene defects, limited experience!

3. Replacement therapy – Ig IV (in HI-ID); C1-INH in HAE

4. Adequate antimicrobial therapy – essential role !
- treatment of acute infections
- long-time antibacterial, anti-viral and anti-fungal prophylaxis

5. Live vaccines are contradictory!

6. Immunomodulators

Pharmacological immunomodulators

- **Isoprinosine** – antiviral (HSV) and immunostimulatory effect (activates T Ly, NK, B ly, MF)

Biological immune modulators

- **IV and SC Ig**

Anti-oxidative substances

- **Vit. E, C, A**
- **Samento, Detox, Oxybor**
- **Picnogenol, Co-enzyme Q**
- **Mg, Se**

Treatment of AID

1- Metabolic control:

Graves' disease: antithyroid drugs, surgical, radiation

Hashimoto's thyroiditis: Thyroxin.

Pernicious anemia: vitamin B12.

IDDM: insulin

2- Antiinfalamtory and cytotoxic drugs:

Nonsteroidal antiinflamatory (NSAID)

Corticosteroids

Cytotoxic drugs: Cyclophosphamide, Azothioprine, Cyclosporin

3- Thymectmy: Myasthenia gravis

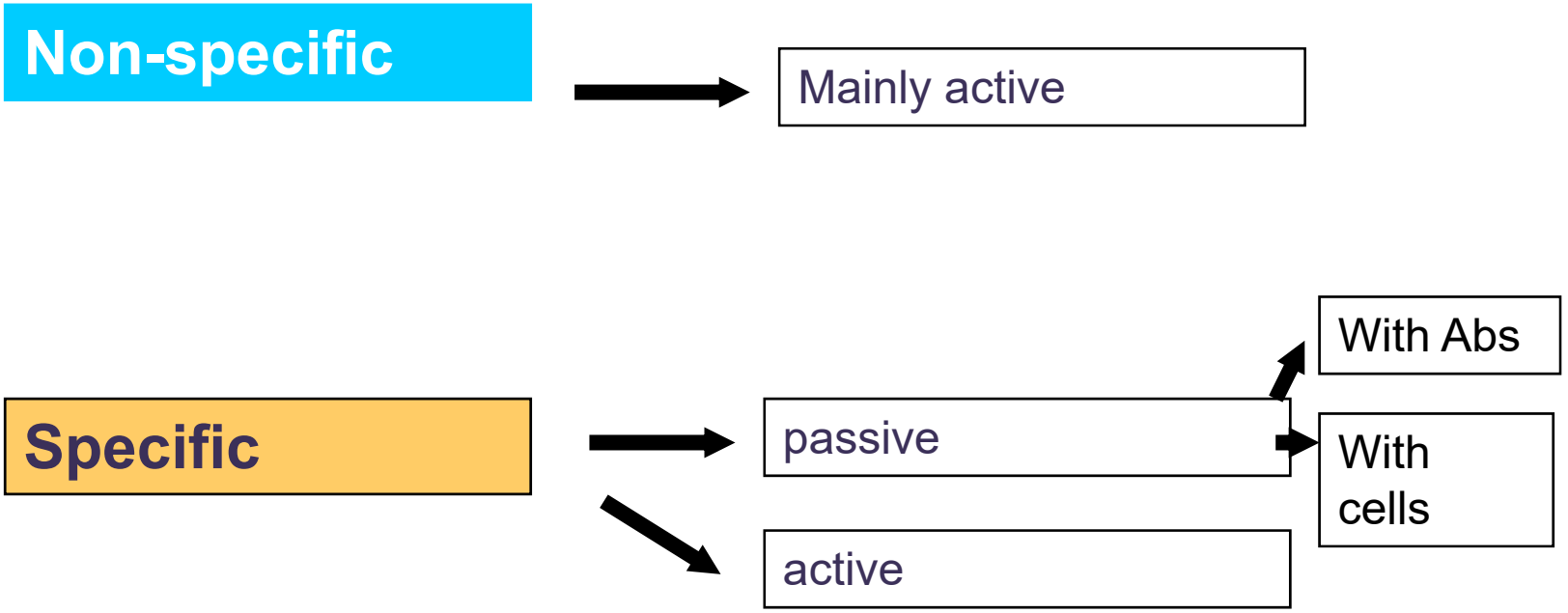
4- Plasmapheresis or Plasma exchange: GBS, SLE, Goodpasture's

5- Spleenectomy: Hemolytic anemia, ITP

6- Intravenous Gammaglobulin therapy: in GBS, Dermatomyositis

7- Cytokines and inhibitors: anti-TNF in RA, anti-idiotype Abs, anti-IL2 receptor antibodies, anti-CD4 antibodies, anti-TCR antibodies

Strategy in Tu immunotherapy



Active non-specific anti-Tu immunotherapy

- **BCG vaccine; Corynebacterium parvum vaccines (mel mal, Ca ovarii…)**
- **CK: *IFN–α*, *IFN-γ* (leukoses); *IL-2* (mel mal, Ca renis); *TNF-α***
- **Synthetic immunomodulators**

  Levamisol **(Ca colonis)**

  Bestatin

Specific anti-Tu immunotherapy

1. Passive – with Abs

- Anti-idiotypic (B cell lymphomas)
- Mo Ab
  - *mouse*
  - *humanized* (Ca gl. mammae)
  - *biospecific*

Mechanisms:

- *immunotoxins* (oncohaematology)
- ADCC

anti-CTLA-4 and PD-1* Mo Abs

Specific anti-Tu immunotherapy

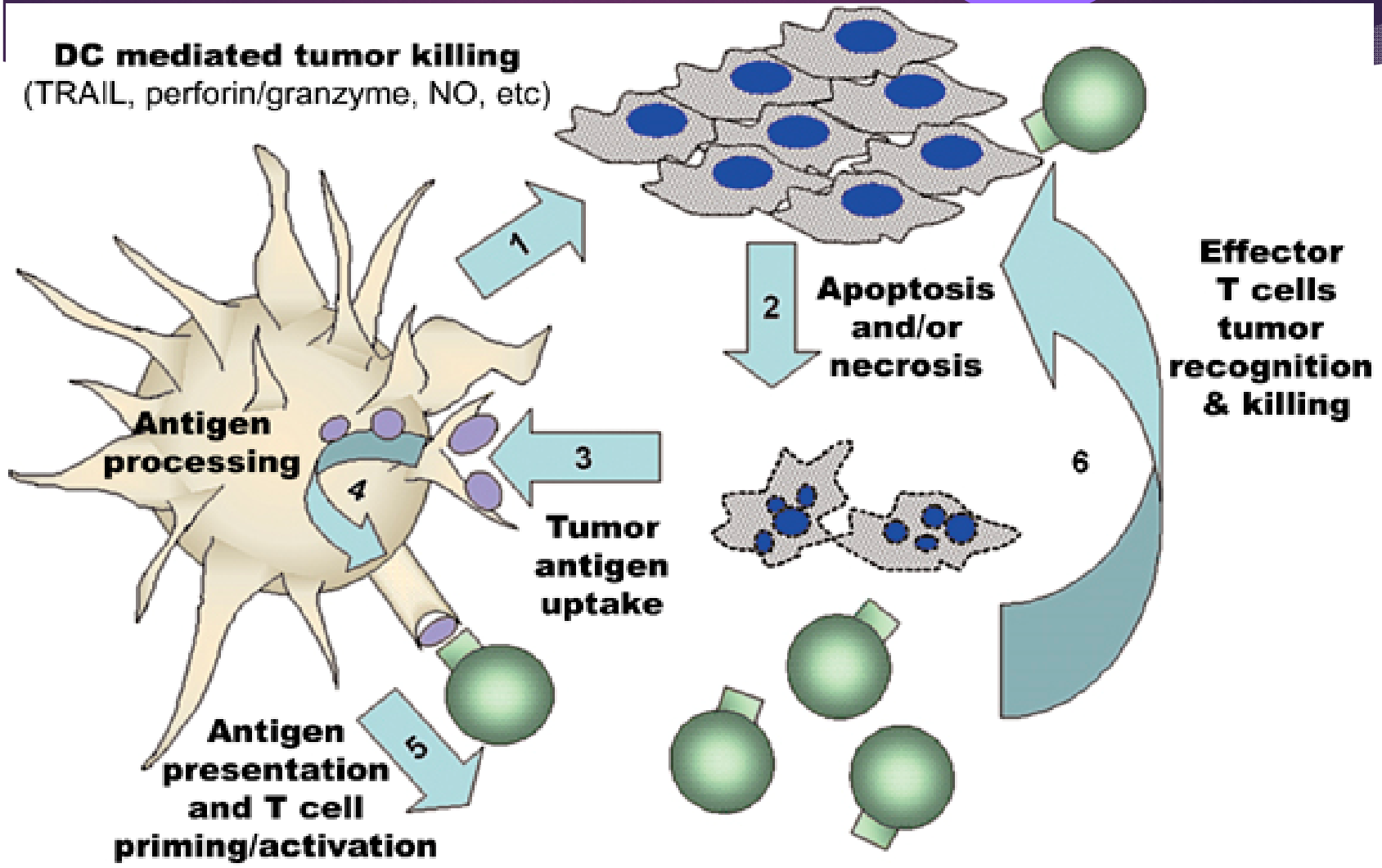
2. Cellular adoptive

- LAK (+IL-2). Ca pulmonis
- TIL (mel mal)

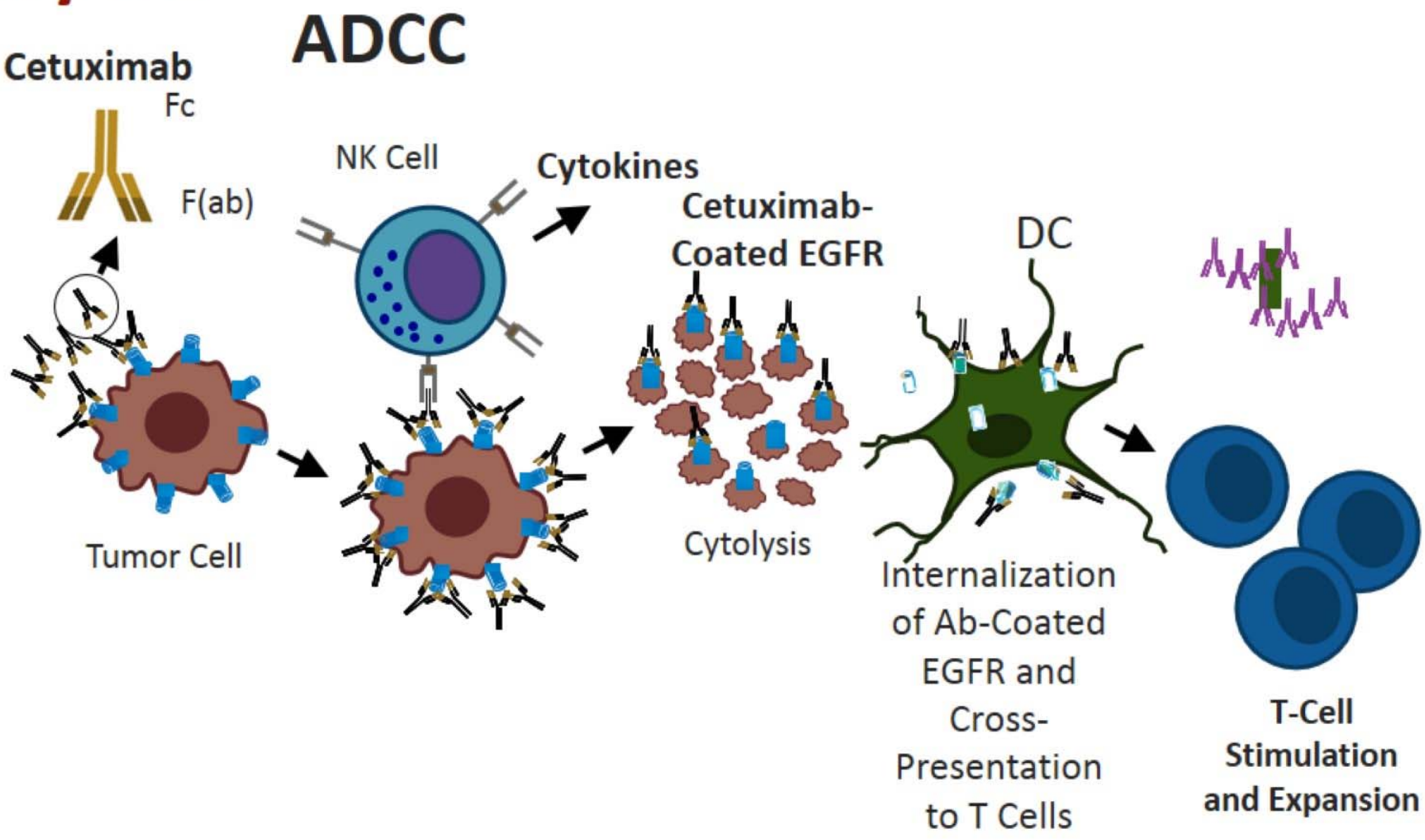
3. Active (vaccination)

- Anti-Vi vaccines - anti- HBV (Ca hepatis), antiEBV, anti-HTLV
- recombinant (DNA) vaccines. Th1 IR.
- DC (APC). In leukaemias
- Peptide vaccines - Ca gl. mammae, Ca colonis….

DC participation against Tu

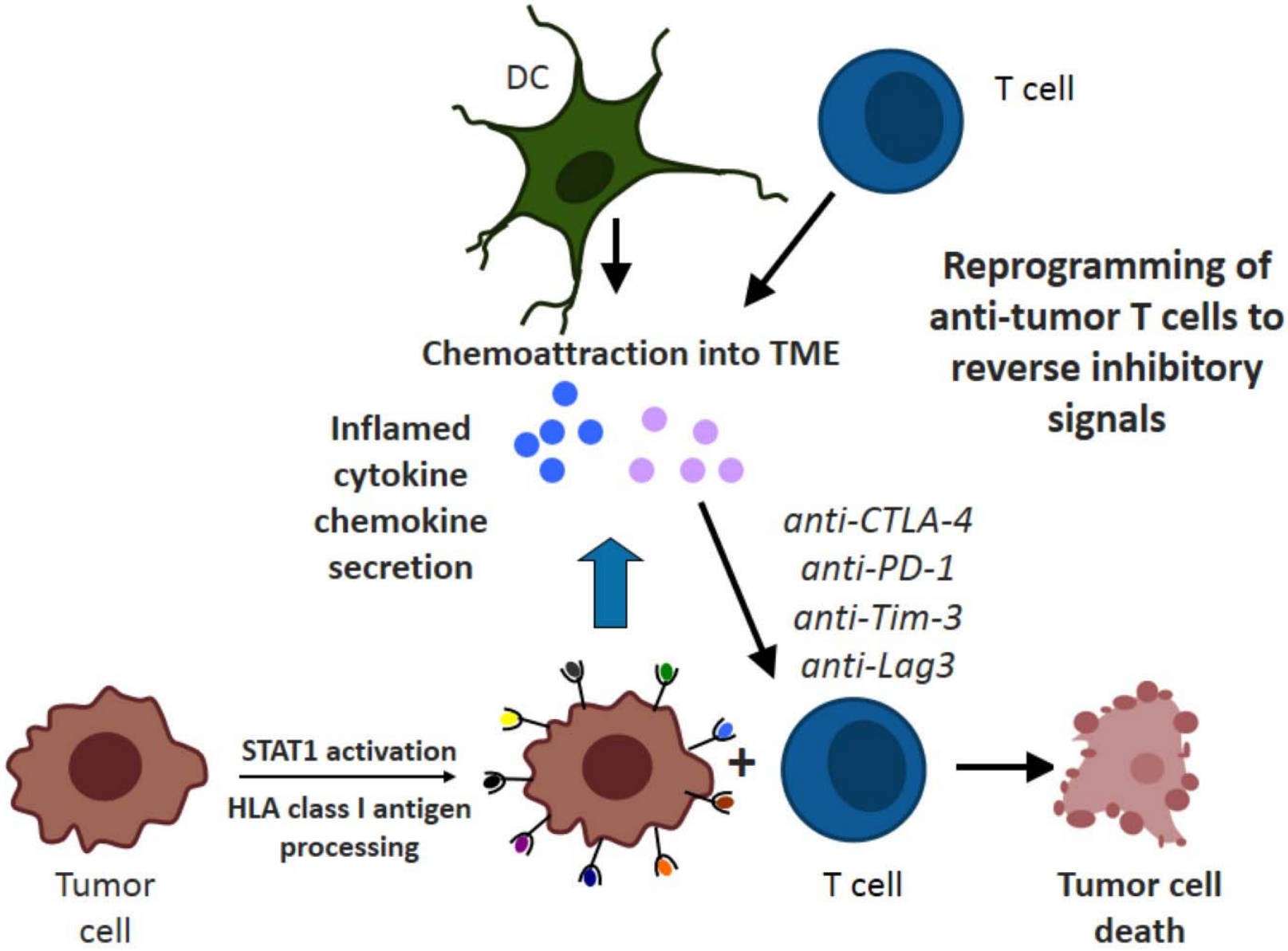


Cross-Presentation of Tumor Antigens by DC

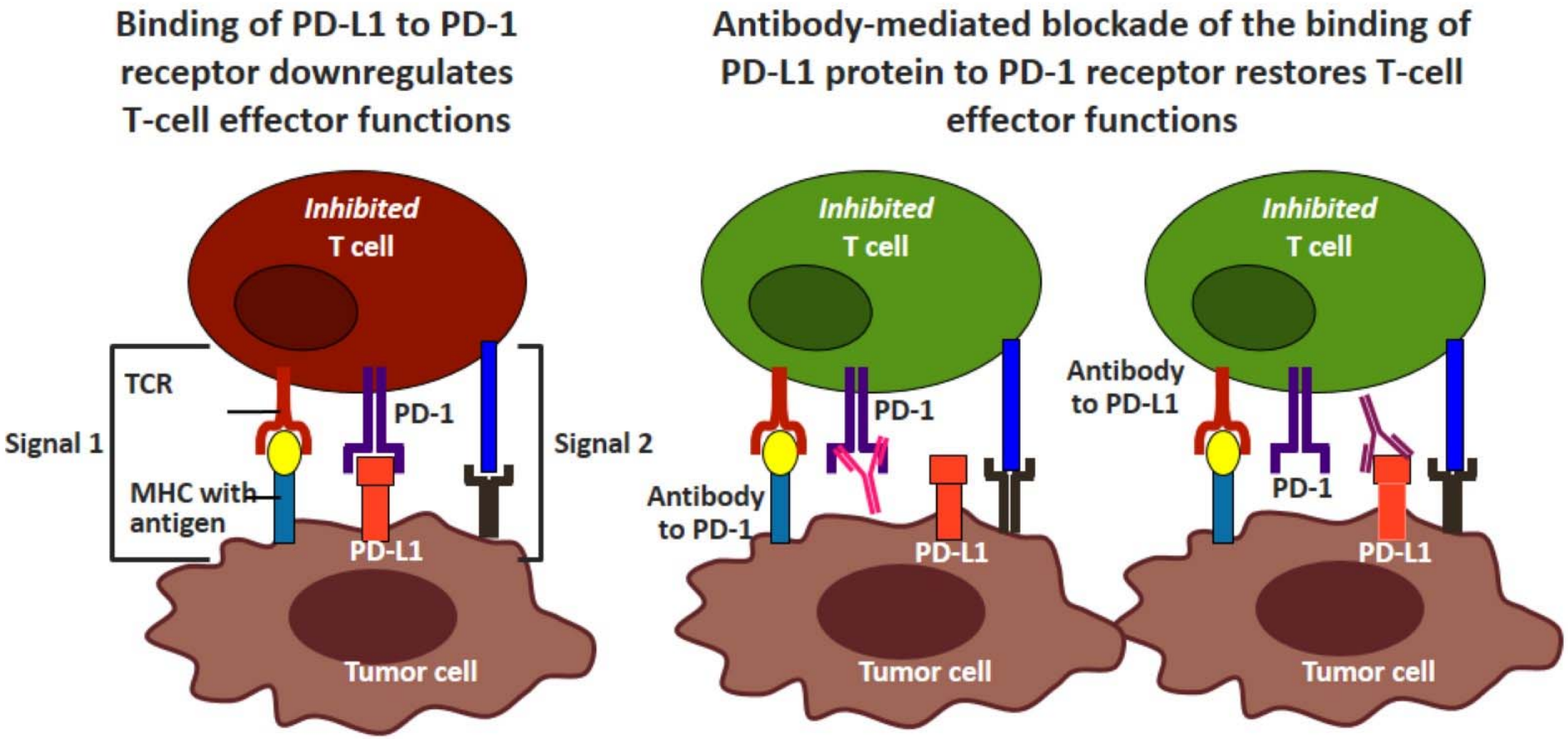


Ferris RL. *J Clin Oncol*. 2010;28:4390-4399.

Targeting the Tumor Microenvironment

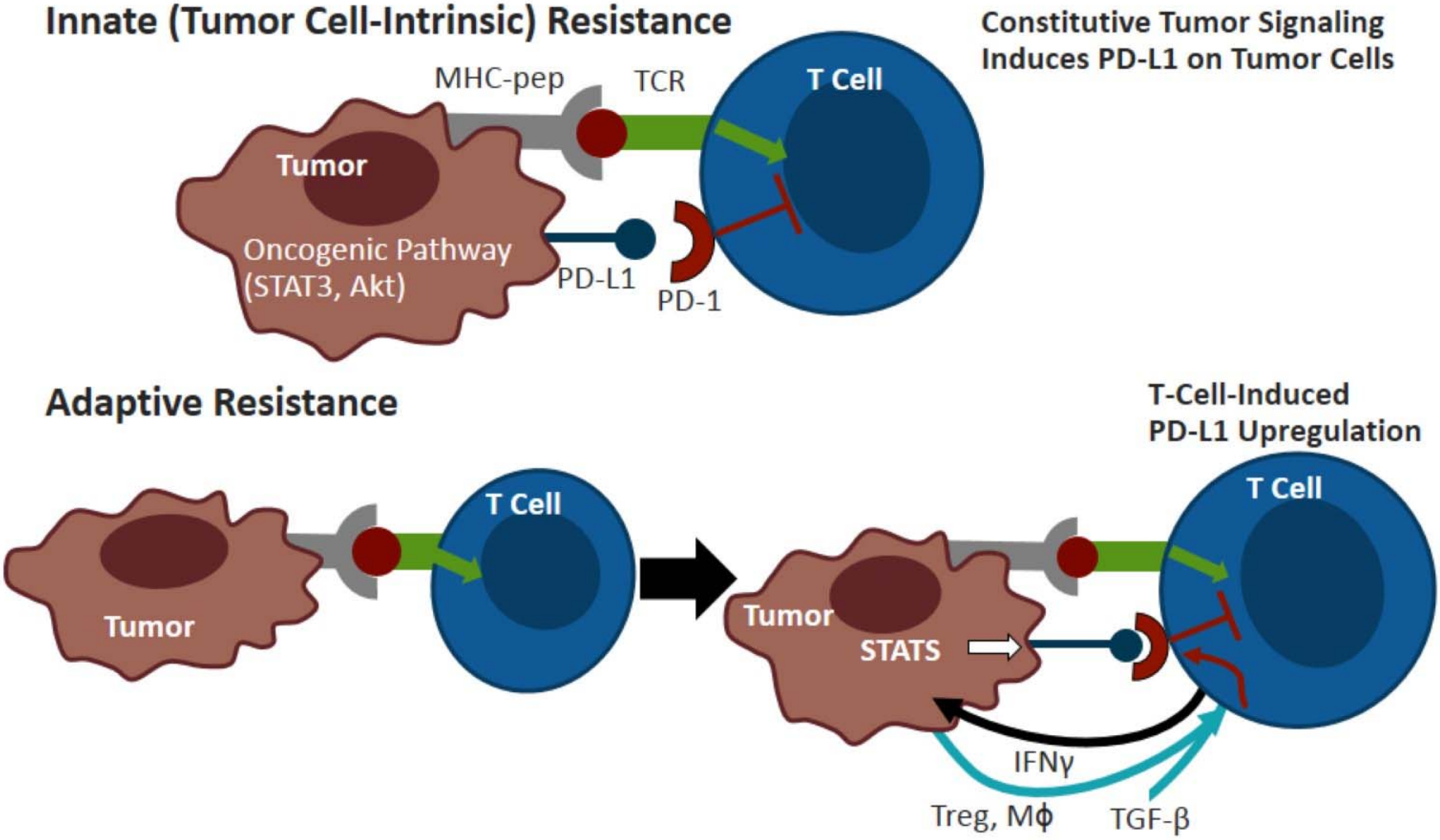


PD-1/PD-L1 in the Immune Response



Sznol M, Chen L. *Clin Cancer Res.* 2013;19:1021-1034.

Mechanisms for the Upregulation of PD-L1 in Tumors



Oncolytic Virus Strategies

- Inside a healthy cell, the virus is unable to replicate, leaving the cell unharmed
  - Talimogene laherparepvec: proposed mechanism of action for systemic immunologic effect
- Inside a cancer cell, the virus replicates and secretes GM-CSF until the cell lyses, releasing more viruses, GM-CSF, and antigens
- GM-CSF attracts DCs to the site, which process and present the antigens to T cells. The T cells are now "programmed" to identify and destroy cancer cells throughout the body

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THANK YOU FOR YOUR ATTENTION