Importance of vaccines and future perspectives

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The term vaccine is used to indicate compounds with different activities

1. Prevention of infectious diseases
2. Prevention of cancers due to infections
3. Immunotherapy of cancer
4. Immunotherapy of allergic disorders
5. Immunotherapy of autoimmune diseases

Prevention of infectious diseases

Exogenous microrganisms that penetrate into the body are challenged by a complex system of cells and molecules which operate synergically and constitute the

Immune System

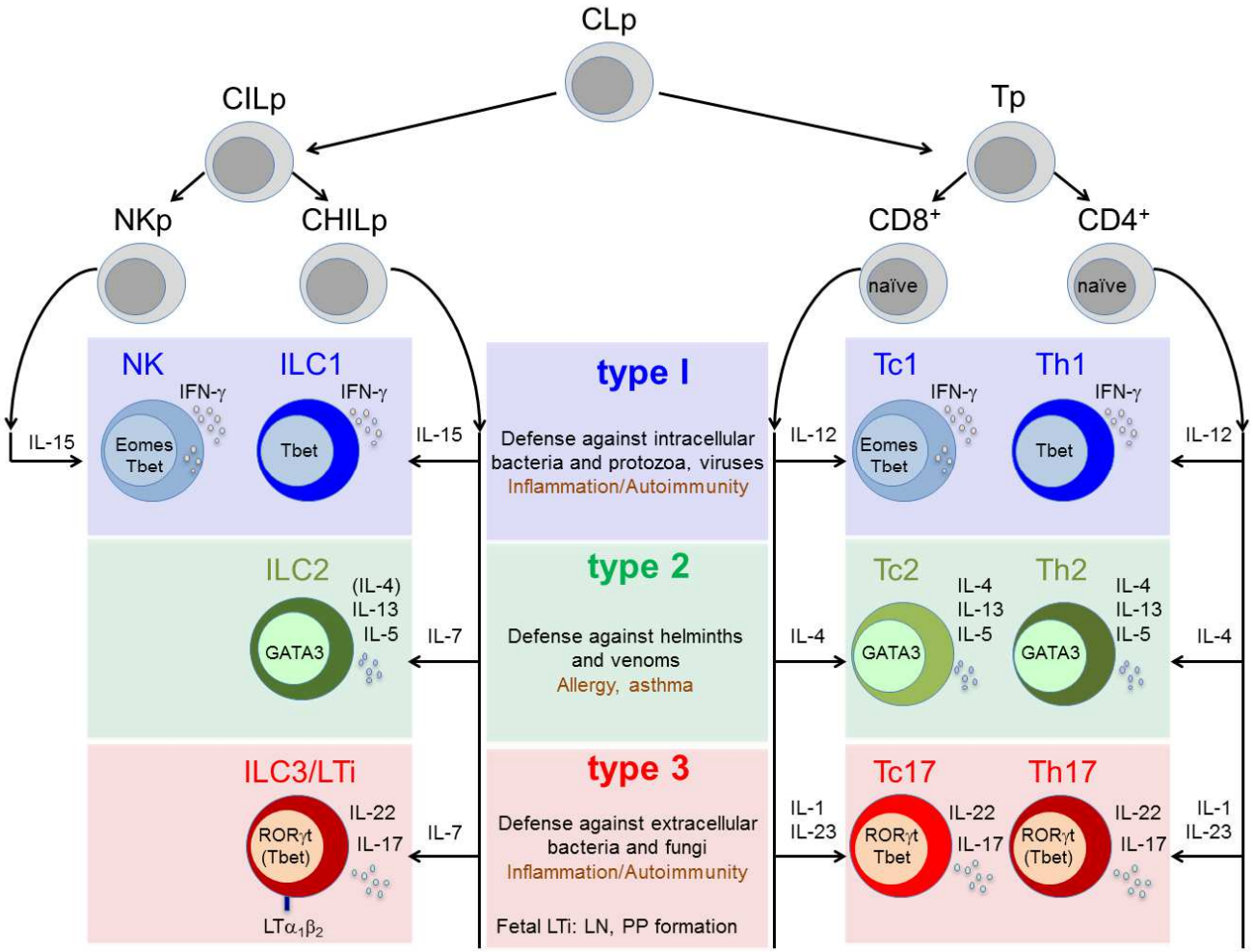
There are two main types of responses by the immune system

- **Natural or innate**
  (existing before the first infection)

- **Acquired or adaptive**
  (induced by the first infection)

The type of both innate and adaptive immune response is modulated according to the type of the infectious agent

The three major types of native and adaptive effector immunity



Annunziato F. et al., J. Allergy Clin Immunol. 135, 626-635, 2015

All three types of effector Th cells of the adaptive immunity (Th1, Th2, Th17) stimulate B lymphocytes to produce specific antibodies of the IgM, IgG and IgA classes (production of IgE antibodies being induced only by Th2 cells)

Vaccines induce memory effector T cells before the first natural infection, thus preventing its possible consequent damages, that may occur despite the protection provided by the natural immunity

Since all three types of effector Th cells induce production of IgM, IgG, and IgA, all types of infectious agents having an extracellular phase can be challenged by specific protective antibodies

History

The first vaccine was developed to prevent smallpox infection

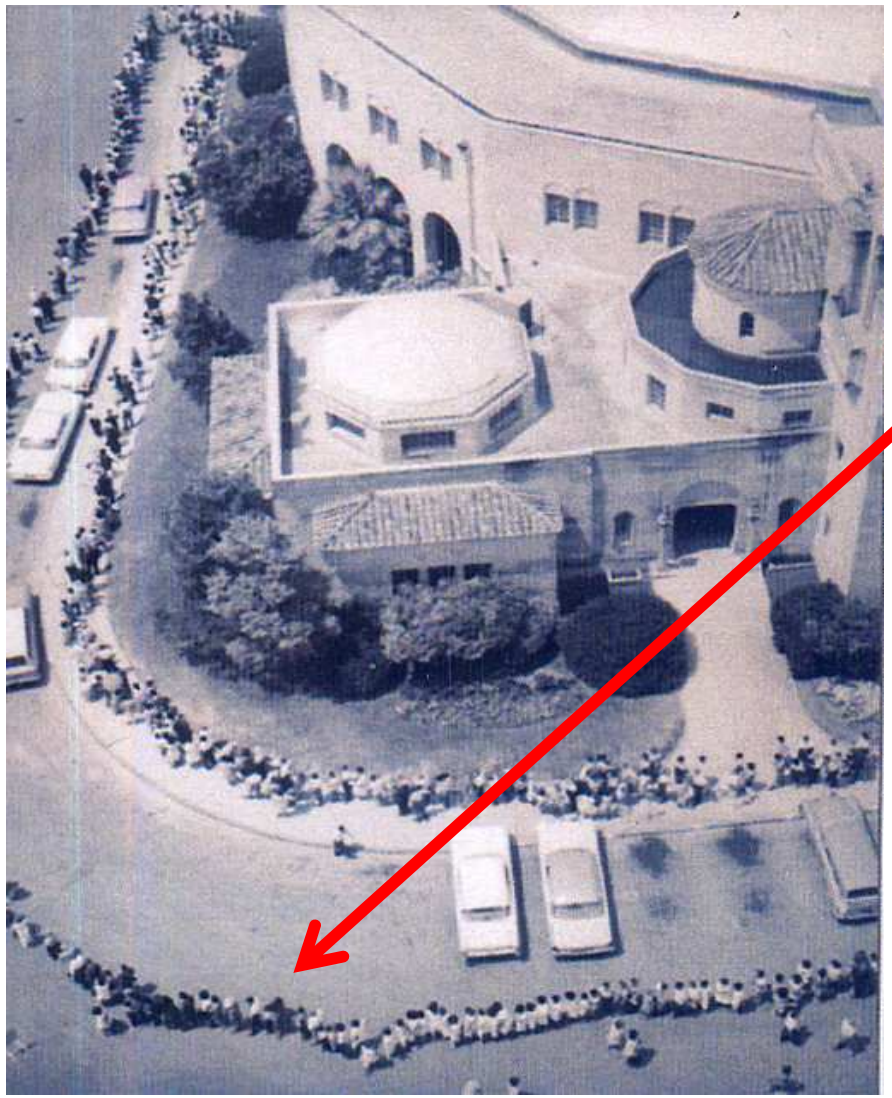
Smallpox viral infection was severe and diffuse worldwide for many centuries so that in India a smallpox goddess, Shitala Mala, was worshiped

On May 14, 1796 the Sodbery barber surgeon, Edward Jenner, injected in the arm of a child, James Phipps, the pus taken from the pustule of cow smallpox of the country woman Sara Nelmes and on July 1,1796 he inoculated in the same child the pus taken from a pustula of human smallpox whithout provoking any consequent disease

Edward Jenner did not have any awareness on the mechanisms responsible for his success, because the existence of the immune system was still unknown. Only 80 years later Louis Pasteur understood these mechanisms and allowed the development of "FIRST GENERATION" vaccines, based on the injection of whole, killed or live-attenuated, microrganisms which induced the development of memory effector T cells and then the production of protective antibodies

The last case of human smallpox was reported on 1977 and the WHO declared definitely extinct the smallpox virus infection on 1980

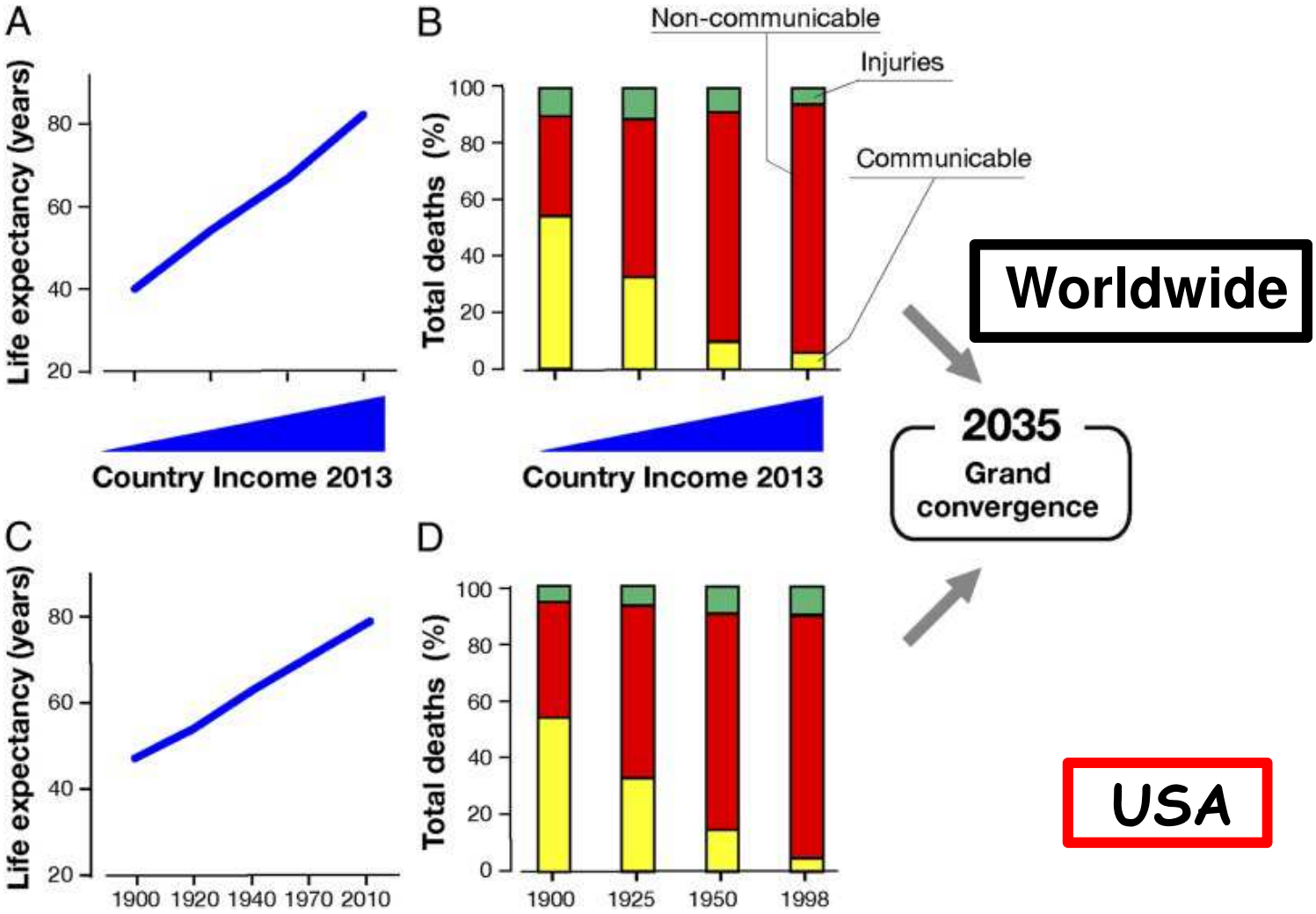
The "SECOND GENERATION" vaccines
(polio, measles, rubella, mumps, varicella)



Many people waiting on line to receive polio vaccination (Austin, Texas 1955)

Even poliomyelitis viral infection has been now virtually eradicated from all the world countries

Life expectancy and total deaths from communicable and uncommunicable diseases worldwide and in USA



Rappuoli R et al., PNAS 111:12288-12293, 2014

Two main obstacles to be overcome

- Emergency and diffusion of fashions and ideologies hostiles to vaccinations

- Traditional vaccines exhibit some limitations

The "decision-makers" in the choice of parents to avoid their sons vaccination

- Media trend to emphasize single rare cases of side effects of vaccination and scientific publications then foud to be wrong

  (Lancet paper reporting measles/parotitis/rubella vaccination as causative of autism and Crohn's disease, then found to be wrong and retired)

- Poor economic and/or educational parents conditions

- Inefficiency of healtcare professional

  -lack of information

  -ambivalence because of ideological reasons

  -fear to be blamed in the case of side effects

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Limitations of traditional vaccines

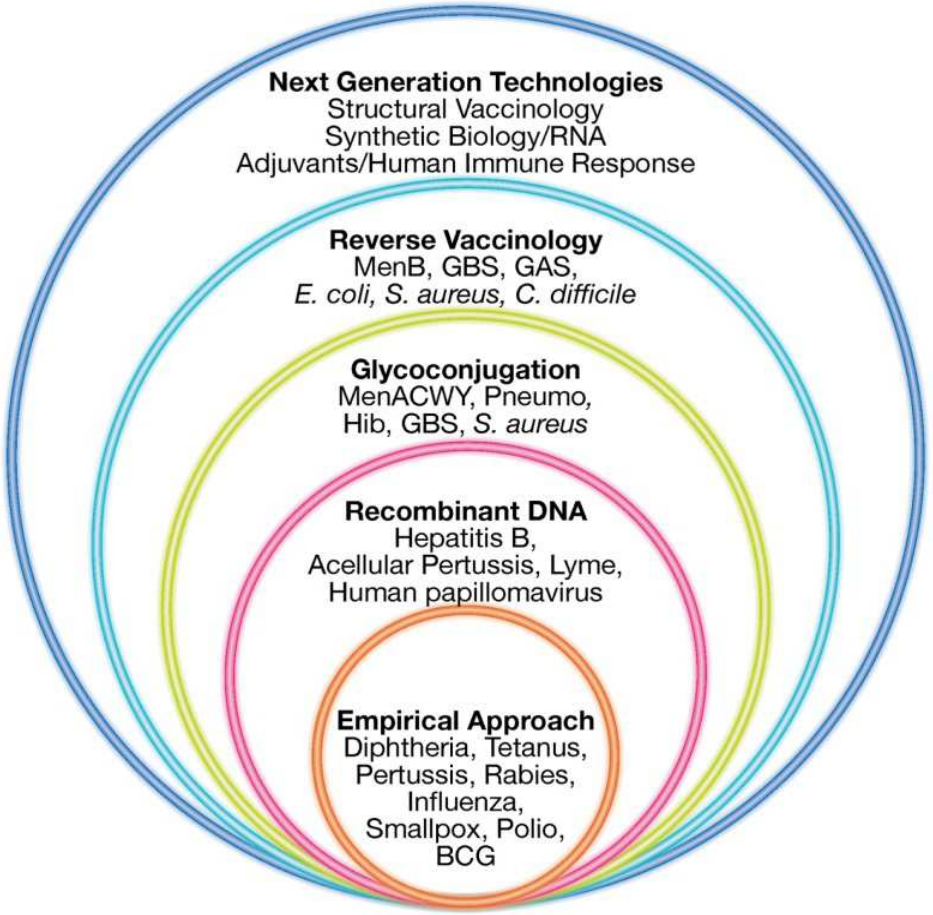
- Use not possible against microbes that do not grow *in vitro* (*Mycobacterium leper*, papilloma virus type 16 and 18)

- No protection against pathogens with antigenic hypervariability (HIV, HCV, serogroup B *Meningococcus*)

- No protection against pathogens with an intracellular phase, which cannot be controlled by antibodies, but only by T cells (malaria, tuberculosis)

- Very slow and time-consuming development, impairing a rapid response to the need of a new vaccine (influenza pandemia)

Evolution of vaccine technologies
the "THIRD GENERATION" vaccines



Finco O. and Rappuoli R., Front. Immunol., 2014

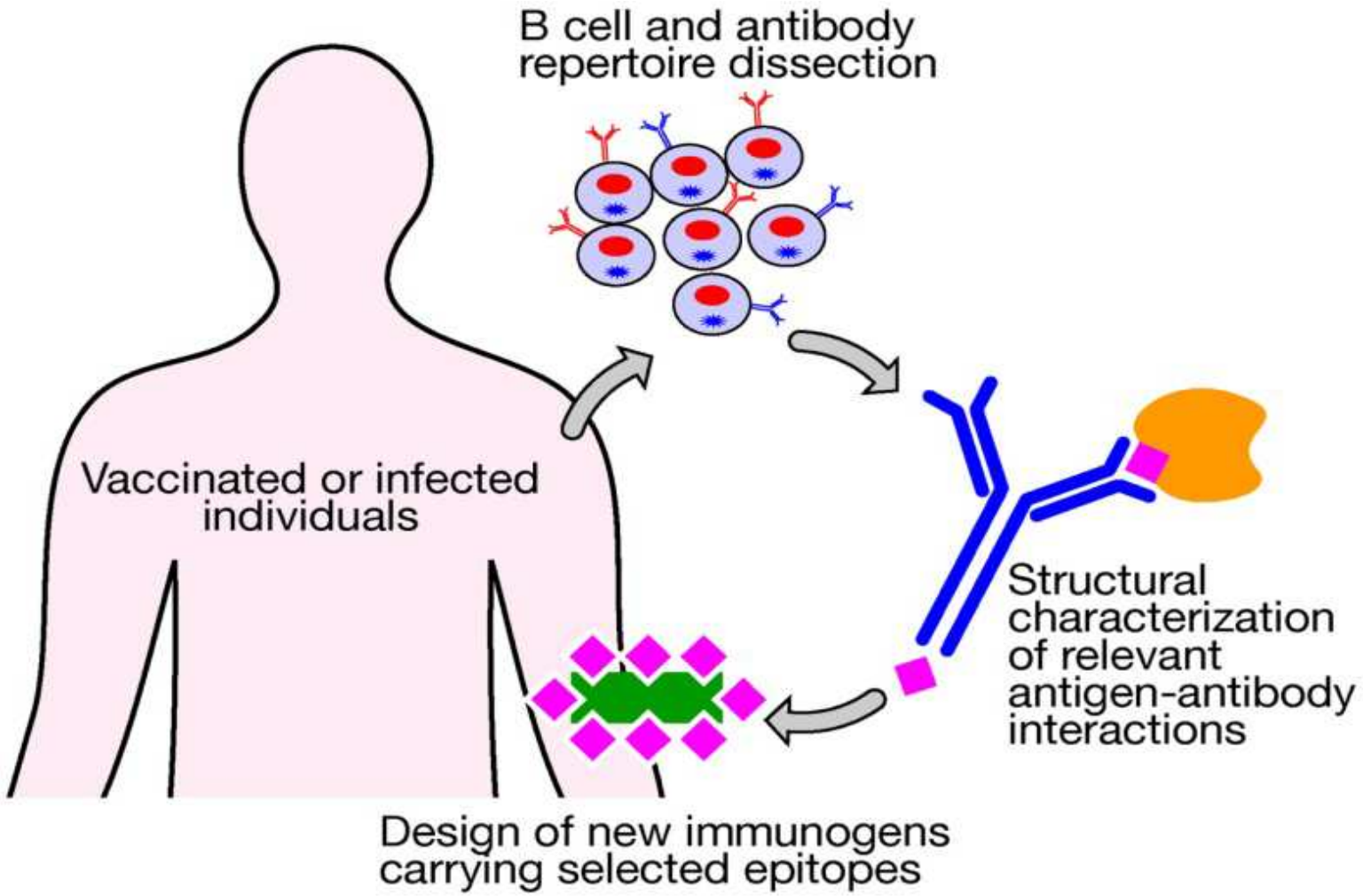
Reverse vaccinology

By sequencing the genome and by determining the whole antigenic repertoire of the infectious organism, several candidate protective targets can be identified and tested for their suitability as vaccine

The first universal vaccine developed by reverse vaccinology was against *Meningococcus* B (Bexsero)

Structural vaccinology

(structure-based antigen design)



Finco O. and Rappuoli R., Front. Immunol., 2014

Synthetic DNA and RNA vaccines

- Nucleic acid-based vaccines may overcome problems encountered when pathogens require a protective immunity mediated not only by antibodies, but also by T cells, including CD8+ cytotoxic T cells

- DNA vaccines are effective in animals, but the immune response they induce in humans is lower than that obtained with conventional vaccines and the risk potentially exists that the DNA plasmid can integrate into the host genoma

- RNA vaccines can avoid the risk of possible integration of DNA plasmid into the host genome and their efficacy and stability may be increased through the use of viral particle engineered to express a heterologous antigen in place of the viral structural genes

Nanocarrier-based vaccines

- Are based on the use of nanoparticles (NPs) (diameter <100 nanometers)

- They may be polymeric NPs, metallic NPs, magnetic NPs, dendrimers, etc. and protect the encapuslated antigen from the hostile *in vivo* environment

- They directly target the site in the body where disease or infection originated (not all body)

- They can be delivered even by oral or nasal route and can induce both humoral and cellular immune responses

An additional perspective problem that supports the importance of vaccination

- New and more powerful antibiotics are required to challenge several bacterial infections, but the contemporaneous development of antibiotic resistance will render unavoidably feckless any therapeuctic effect of these drugs

-The only solution will be the development of vaccines even against infectious agents that are presently manageable with antibiotic therapy

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Tumors due to chronic infections

Tumor	Causative infection
- Hepatocarcinoma	*-Hepatitis B and C virus*
- Cervix carcinoma	*-Papilloma virus*
- Stomach cancer	*-Helicobacter pylori*
- Burkitt lymphoma and nasopharingeal carcinoma	*-Epstein-Barr virus*

Hepatitis B virus (HBV) vaccination

- Universal vaccination of newborn, which started in Taiwan in 1984, decreased the prevalence of HBV infection from 9.8 to 0.3% in 2003

- The prevalence of HCC was also strongly reduced in Taiwan and in other oriental countries which introduced universal newborn vaccination (China, Thailand, Korea)

Human papilloma virus (HPV) vaccination

- The HPV vaccine is safe and effective, being highly protective against cervical cancer; however, its species-specificity limits protection to 70% of squamous cancers and it is therapeutically uneffective on already established cancers

- New generation vaccines exhibiting higher spectrum of activity, and even therapeutic effects, are required

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Two main approaches in cancer vaccination have been envisaged

- Prophylactic vaccines (to prevent cancer) are still at ideological level. Identifying specific gene mutations and blocking their downstream pathways with selected compounds seems to be a more promising strategy

- Therapeutic vaccines (to cure already established cancer): several clinical trials are in progress

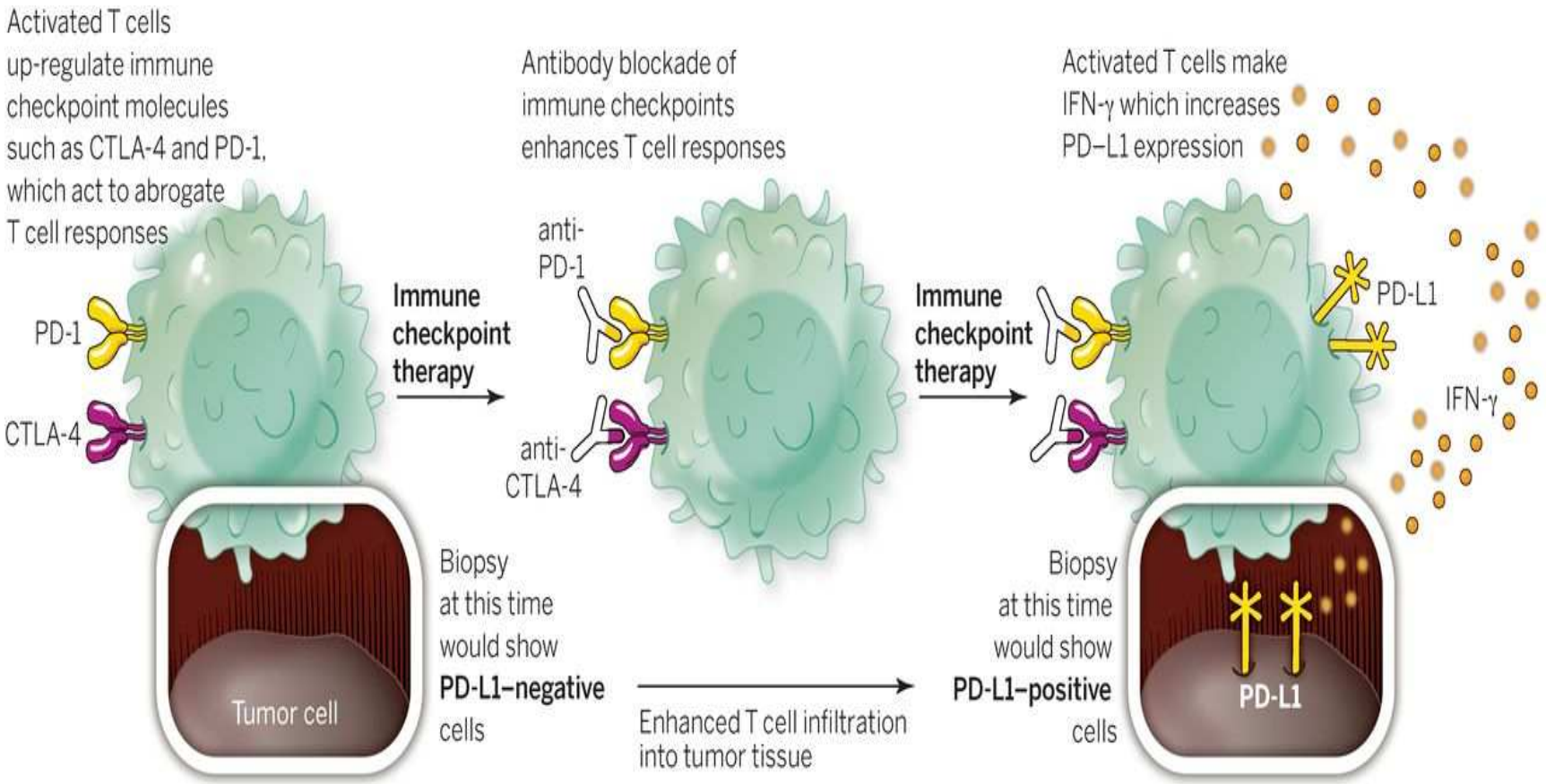
Therapeutic vaccines for cancer

- Aimed to potentiate the tumor-associated antigen (TAA)-specific T cell response (mainly due to cytotoxic CD8+ T cells)

- Many attempts have been based on DC targeting with TAA

- The most modern approaches
    - Nanovaccines
    - Gene-modified DCs

The immune checkpoint therapy
(releasing the impaired T-cell response)



PD-1 interferes with TCR signaling; CTLA-4 interferes with T-cell co-stimulation

Sharma P, Allison JP, Science 348:56-61, 2015

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Basic differences of immunotherapy in allergic and autoimmune diseases

- The purpose of immunotherapy in allergic and autoimmune diseases is to dampen the immune response against allergens or autoantigens, respectively

- This does not need stimulation or potentiation of adaptive immune responses, but rather the opposite, i.e. the induction of stable antigen-specific inducible T regulatory (iTreg) cells ("immune tolerance")

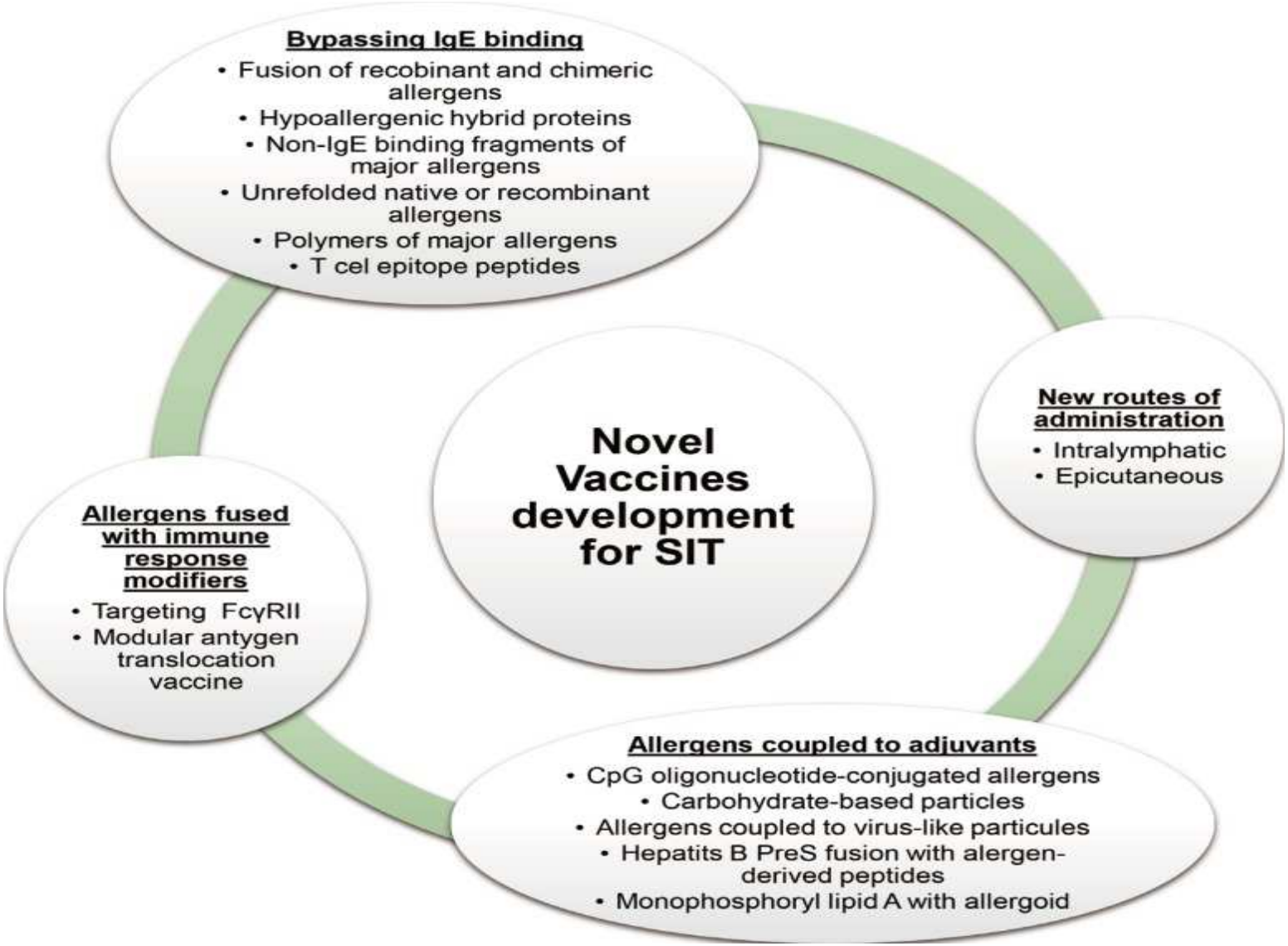
Present status of specific immunotherapy (SIT) in allergy

- SIT is currently the only available causal treatment for some (even if not all) IgE-mediated allergic diseases

- Subcutaneous SIT (SC-SIT) with whole allergenic extracts has been proven to be effective, but it can expose patients to the risk of serious adverse events

- Sublingual SIT (SL-SIT) is safer, but probably less effective, than SC-SIT

Novel vaccine developments for AIT



Jutel et al., Allergy Asthma Immunol Res. 8: 191-197, 2016

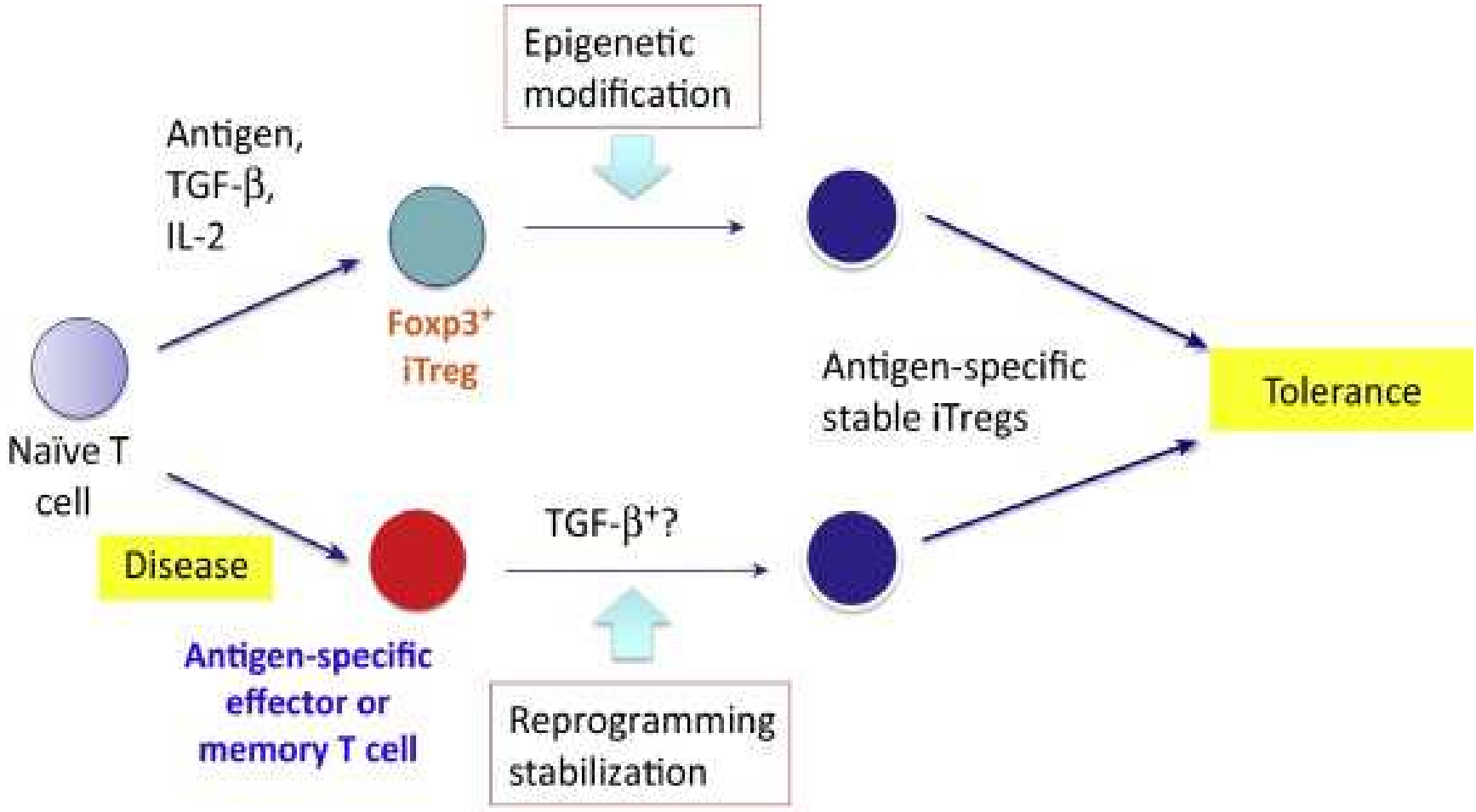
Problems dealing with autoantigen-specific immunotherapy in autoimmunity

- The nature of determinant autoantigen and/or its peptide epitope is often unclear and can vary among patients

- While Th2 cells are clearly responsible for allergic disorders, whether Th1, Th17, or both cell types are involved in the genesis of autoimmune diseases, is still unclear

- Antigen-specific iTregs cells are unstable

Two possible ways to generate stable Ag-specific inducible Treg cells



Kanamori M et al., Trends Immunol 11:803-811, 2016

Concluding remarks (I)

- Classic vaccines against infectious microrganisms have contributed to the radication of severe infections, such as smallpox and polyomyelitis, and are dramatically increasing life expectancy and decreasing total deaths from communicable diseases throughout all the world

- Classic vaccines can also protect against cancers due to chronic infections (such as papilloma and HBV)

- Evolution of vaccine technologies is already in progress (reversal and structural vaccinology, DNA and RNA vaccines, nano-vaccines) and will allow further improvement in the efficacy and quality of vaccination

Concluding remarks (II)

- The term vaccines is commonly used also to indicate treatment modalities of established diseases not due to infections, such as the majority of cancers, allergy and autoimmunity

- Several trials are in progress to treat cancer with TAA, mainly based on TAA DC targeting. However, clinical results obtained by using "immune checkpoint" therapies (i.e. releasing the impaired immune response) seem to be more promising

- The purpose of immunotherapy in allergic and autoimmune diseases is different because directed to dampen the immune response

-Allergen-specific immunotherapy is currently the only available causal treatment for some (even if not all) IgE-mediated allergic diseases

-Treatment of autoimmune diseases with autoantigen vaccinations is presently more hope than reality