Escape of pathogens from the host immune response by mutations and mimicry.
Possible means to improve vaccine performance

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Contrasted effectiveness in vaccine

- Whereas vaccines against most RNA viruses (poliovirus, measles, Hepatitis A and B, smallpox, etc.), which are based on strains used for decades, show no loss of efficacy.

- To date, no effective vaccine has been developed against human *immunodeficiency virus* (HIV 1), *Herpes simplex virus* (HSV), *Hepatitis C virus* (HCV) or *Plasmodium falciparum* (malaria parasite) and development of an effective vaccine against *influenza A* is prevented by continual genetic variation of the virus strains.

Genetic variation alone does not explain resistance of certain pathogens to vaccination.

- High rate of genetic variation (mutations and recombinations) is generally suggested to account for the escape of certain pathogens from host immune response and to be the major obstacle to the development of effective vaccine (R. Sanjuan, *et al. J Virol* 2010).

- However, this commonly accepted assumption is at odds with the mutation rate data expressed either by the *number of modifications per nucleotide and per replication cycle* or the *number of modifications per genome and per replication cycle*.

- We suggest that this resistance would be due to the combination of *mutations of the pathogen genome* and of *mimicry of the host proteins by a large fraction of the pathogen epitopes.*

Mutation rates of pathogen organisms

- The high mutation rates of RNA viruses are due to deficiencies in the mechanisms of proofreading, leading to high error rate of both the RNA dependent polymerase of lytic viruses (riboviruses) and the reverse transcriptase of the retroviruses.

- RNA viruses have evolved so that their mutation rates when expressed *per genome and per replication cycle* have roughly similar values varying over approximately **0.8 for the riboviruses and 0.2 for retroviruses** (J. Drake *et al. Ann NY Acad Sci* 1999).

- In contrast the mutation rate among viral and cellular microbes with DNA chromosomes, similarly expressed *per genome and per replication cycle*, has been estimated with good accuracy to **0.0034** (J. Drake *et al. Ann NY Acad Sci* 1999). **This value is far lower than the mutation rate of RNA viruses and thus cannot account for an escape strategy**.

Mutation rates per base pair of some pathogens

Viruses	Mutation rates per base pair per replication ($\times 10^{-5}$)
Influenza A	0.71 – 7.3
Human immunodeficiency virus 1 (HIV 1)	0.073 – 4.9
Hepatitis C (HCV)	12
Herpes simplex (HSV)	0.0059
Plasmodium falciparum	< 0.00025
Polio	0.21 - 45
Measles	9
Hepatitis A	10 - 100

- It can be seen that fluA, HCV and HIV 1, for which vaccines are either non-existent or ineffective, are not distinguishable, on the basis of their mutation rates, from the other examples (polio, measles and hepatitis A), against which highly effective vaccines have been developed.

- The low mutation rate values of HSV, DNA based virus, and Plasmodium P. falciparum cannot explain the escape from human immune response and the difficulties encountered in the development of effective vaccine.

Host protein mimicry by some pathogen organisms

- In the case of pathogens against which no effective vaccines have been developed some proteins show sequence homologies with those of the host. This phenomenon, called molecular mimicry, allows these pathogens to evade host immune recognition by eluding it when the molecules of the immune system are mimicked or by making some of their proteins indistinguishable from those of the self.

- In addition, these pathogen antigens may induce autoantibodies and trigger autoimmune diseases that damage host tissues when genetic, hormonal or environmental factors are met.

Viral mimicry of host genes

- Extensive viral mimicry of 22 AIDS related autoantigens by HIV-1 proteins have been described (C. Carter *FEMS Immunol Med Microbiol* 2011) and exclusion of HIV epitopes shared with human proteins was recognized as a prerequisite for designing safer AIDS vaccines (A. Maksyutov *J Clin Virol* 2004)

- The N-terminal region of the HCV glycoprotein E2 is antigenically and structurally similar to human immunoglobulin (Ig) variable domains, the degree of similarity to Ig types being correlated with the virus immune escape and persistence in humans (Y. Hu, *Virology* 2005).

Viral mimicry of host genes

- Molecular mimicry between cytoplasmic dynein and influenza A virus was reported by T. Yamada *et al*. (*Acta Neuropathol* 1996).
- Human autoantibodies from patients with systemic rheumatic disease was described by H. Guldner *et al.* (*J Exp Med* 1990) to recognize epitopes shared by influenza B virus and by p68 associated with small nuclear ribonucleoprotein.
- Autoimmune responses resulting from molecular mimicry between parasite protein sequences and human proteins has been reviewed by A. Vogel *et al.* (*Clin Liver Dis* 2002).
- Molecular mimicry between host proteins and HSV encoded proteins such as chemokine receptors or the human IL-6 have been reviewed by PM Murphy (*Infect Agents Dis* 1994) and MJ Boulanger *et al.* (*J Mol Biol* 2004) respectively.

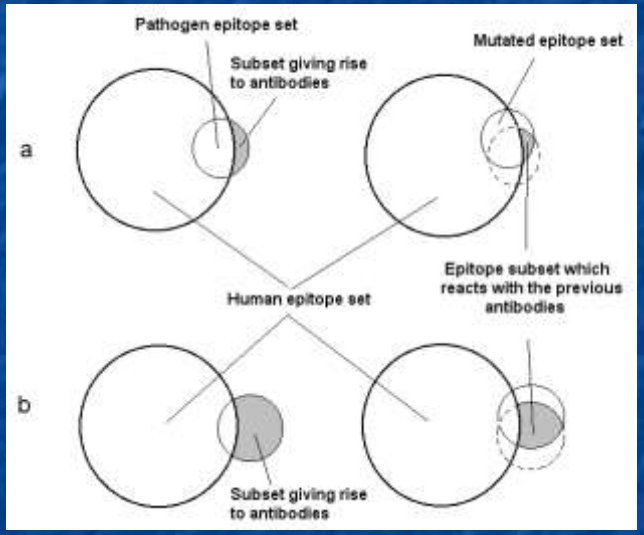
Viral mimicry of host genes to escape host immune response

- Interestingly, this strategy of host immune response escape using mimicry of host cell protein by viral encoded proteins is rarely reported regarding RNA viruses which respond to vaccine so there is no data concerning mumps or rabies viruses.
  - *No evidence has been found that measles, mumps and rubella vaccination during adolescence might trigger autoimmunity (*B. Lindberg *Pediatrics* 1999*).*
  - *Noticeably host protein mimicry by pathogen is less frequently reported when there is an effective vaccine against it, than when there is not.*

- By restricting the number of foreign epitopes, **molecular mimicry combined with the mutation of the genome are certainly a more efficient mechanism to escape the immune response than mutability alone.** It is probably the major obstacle to the development of some vaccines.

Influence of mutations on the efficiency of the immune response

- Fig. 1 depicts the set of antigen epitopes of the host and the pathogen as the points of the area of circles. The immune system reacts against the pathogen epitopes which are foreign to the host (not included into the host epitope set).



(a) The pathogen shares most of its epitopes (small circle) with the host (large circle). Few antibodies would be produced and a small fraction of them would remain active against the mutated pathogen (in gray).
Some mutations may then shift the virus epitope set and a fraction of antibodies produced by previous infections or vaccination may be inactive against the mutated epitopes.
In these conditions, the combined effects of host epitope mimicry and mutations would impede the development of an effective vaccine.

(b) When the number of pathogen epitopes foreign to the host is high, multiple antibodies would be produced and a sufficient part of them would react with the mutated pathogen (in gray).In case of moderate level of mimicry, the number of mutations being the same, the effect of mutation rate would be reduced. ***This is probably the case for the pathogen against which effective vaccines have been developed, or after the treatment we propose.***

Proposition to improve immune response.

- Aim:
  - Increase the number of pathogen epitopes foreign to the host, in order to enhance the immune response.
- Method:
  - Suppression, in the thymus, of the epitopes in common between the self and the pathogen by intrathymic injection of antibodies against the pathogen (G. Berger *Med Hypotheses* 2002).
  - These polyclonal antibodies could be obtained by vaccination of an animal species and purified by affinity chromatography, with the microorganism proteins bound to the matrix of the column.

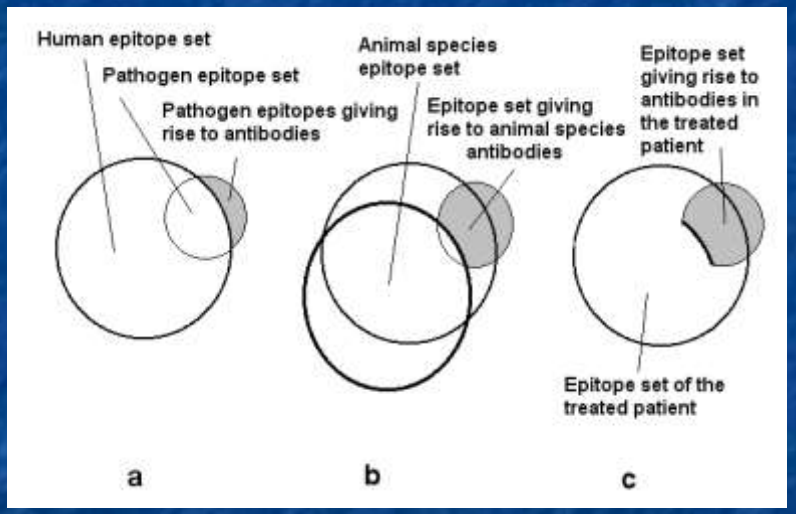
Proposition to improve immune response.

- Implementation:

  - The choice of the animal species for the antibody production is particularly important. It must be immunologically distant from humans in order to induce different antibodies against the pathogen but not too much to avoid important immune response against them.

- Fig.2:

  The epitope sets are represented by the points of the area of circles.



(a) The pathogen shares most of its epitopes (small circle) with the host (large circle). Only the small subset outside the human epitope set would give rise to antibodies (in gray).

(b) The animal species epitope set (thick lined circle) is different from the human epitope set and more pathogen epitopes would elicit antibodies (in gray).

They are purified by affinity chromatography and injected into the thymus of the patient.

(c) The negative selection of the CD4+ and CD8+ lymphocytes specific of the blocked epitopes would be prevented and a greater number of pathogen epitopes would be recognized as foreign and would induce an immune response (in gray).

Proposition to improve immune response.

- Implementation:
  - The injection of antibodies ought to be performed into the medullary portion of the thymus, where negative selection takes place, while positive selection is controlled in the cortex (J. Sprent *Fundamental immunology,* 3rd ed., 1993). This operation is certainly difficult, but, even if the fixation of antibodies on epitopes of the self is randomly distributed between the compartments, some thymocytes may undergo positive selection by contact with cortical cells not altered by the antibodies. Then, by moving to the next medulla which has received antibodies, they could escape to the negative selection and appear as CD4+ and CD8+ mature cells.

Discussion

- Experimental intrathymic injections of antigens of all kinds (MHC I or MHC II peptides, cell extracts, bone marrow, splenocytes, islet cells) have been shown to prevent graft rejection, by a mechanism involving the clonal deletion of certain allo and xenoreactive T cells in the thymus (W. Hancock *Am J Pathol* 1994, M. Shimizu *Hokkaido Igaku Zasshi* 1979, J. Goss *Transplantation* 1993, N. Chowdhury *J Surg Res*1995).Intrathymic administration of antibodies has already been reported (T. Ermak *Immunobiology* 1990).

- Although the thymus is involuted in adults and abnormal in certain diseases such as AIDS (R. Elie *N Engl J Med* 1983). Recent data suggests, the adult thymus can still contribute to cell reconstitution [(D. Douek and R. Koup *Vaccine* 2000).

Discussion

- Besides adverse immunological response to allo and xenoproteins (such as urticaria), repeated injections of antibodies may induce the formation of antiidiotypic antibodies that could displace the injected xenoantibodies from their complexes with the self epitopes in the thymus. However, in the case of dangerous infections and in the absence of an effective vaccine, these drawbacks would be negligible.

- On the other hand, blocking with antibodies the epitopes, in the thymus, common to the self and to the pathogen, could modify the production of the autoantibodies responsible of the autoimmune diseases. This issue requires further study.

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More about Gérard Berger (1938-2017)

www.gerardberger.fr

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