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APOCOSIS

Associations for the Reciprocal and Mutual Sharing of Advantages and Disadvantages: Applicative Insights in Prevention or Cure of AIDS, Cancer and Leprous Diseases.

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Abstract

The merging of a new living system, healthy like a neurone or pathologic like a cancer clone, whatever its type of organisation, is always a transgression of older ones. It is achieved with the juxtapositions and encasements of previous systems. The new Wholeness is both more and less than the sum of its parts. It merges from the simultaneous metamorphoses of the partners that maintain their identity and their half-autonomy by the preservation of their individual and collective boundaries and their self-organisation (like the Eukaryotic cell, which merged from Monera [9]. The shuttle [8] of a step of organisation "*i*" to a higher adjacent one "*i+1*" is the result of the merging of a new spatial and temporal network, whatever its mode of integration, through the birth of an Association for the Reciprocal and Mutual Sharing of Advantages and of Disadvantages (ARMSADA), like a Lichen Organism. But, all the partners must loss simultaneously the capacity to destroy the others. Each advantage for a partner is always a disadvantage for all the others and reciprocally. No one partner is a winner, all are "winner and loser": ARMSADA is an association "for the best and the worst". The gain is only for the Wholeness! There is only one rule to survive: "to transform disadvantages into advantages" and "to prevent advantages from turning to disadvantages". When the ecoexotope (EXT) is changing, a disadvantage can turn to an advantage and conversely. To survive it is "to eat and not to be eaten". Preys or hosts and predators or parasites (like immune cells and HIV) struggle each other in a war without mercy. Each defensive innovation of a prey is followed by an aggressive one of its predators. "To attack" is never the best defence, but "to change" of trophic network. Only the metamorphosis of the endophysiotope (ENT) makes possible to self-control the dangers. In order that one survives, it is necessary that the others survive first, and reciprocally. During the genesis of a leguminous nodule, the host plant part metamorphoses into a tumour and the Bacteria metamorphose simultaneously into bacteroids. The fate of a cancer or HIV-infected cell, like that of a bacterium infected with a phage, is depending on the interactive percolation with its invading virus. That indeed explains the heterogeneity of a disease (cancer or AIDS), its evolutions and the diversity of the potential hosts: "the way is, both, the cause and the consequence of the history." As the previously proposed curative AIDS vaccine, to built with HIV engineered stem cells [10], the application of this systemic paradigm allows the design of new vaccines, like a curative cancer vaccine and a preventive leprous one.

Key words: cancer, curative vaccine, HIV, Mycobacterium, symbiosis (accepted 18 June 2008, revised 21 Sept. 2008, complementary data, figures and references available on Dec. 19th 2008 at: http://www.minilien.com/?oUtHBBpz46 for cancer, http://minilien.com/?USaw1HHJ4Z for AIDS, and http://minilien.com/?iUZIuv4lpL for leprosy).

1. Cancers, AIDS or Leprosy are diseases of unwanted viral gene expression.

In cancers, cells display the traits of uncontrolled growth, invasion, destruction of tissues and spread to other locations, the same for the leprous diseases with the invading bacteria and for AIDS with the invading HIV. The first found cancerous agents were viruses [50]. The main ones associated with human cancers are Human PapillomaVirus, Hepatitis viruses, Epstein-Barr Virus, and Human T-Lymphotropic Virus. In acutely-transforming viruses, the viral genomes carry a gene that encodes for an overactive oncogene and the infected cell is transformed as soon as the gene is expressed [24]. In slowly-transforming viruses, the viral genome is inserted near a proto-oncogene in the host genome. Regulation elements (Figure 1) cause over-expression of that proto-oncogene, which induces uncontrolled cellular proliferation. Viral genome insertion is not specific and slowly-transforming cancer- or AIDS-viruses have a very long latency (Table 2). The genetic material of a cancer virus is inserted into the host cell genome without any production of virus particles and with no cell's death [19] but not the HIV's one which once (re-)produced kills the host cells. Repressors, inducible transcription factors, facilitate adaptation to deprivation by regulating the expression of genes (Figure 3) that control metabolism, cell proliferation, and apoptosis [47]. AIDS is a no-response of a prey to its invading killer predator but cancer is a micro-evolutionary response for best survival of a damaged cell [12]. The genome of every organism contains viral sequences. The bacterium *Yersinia pestis* contains in its genome, since thousands of years, a virus (a filamentous bacteriophage) conferring it its “virulence“ [52]. Moreover it has inherited a resistance to antibiotics which was acquired by viral transfer of genes of bacteria of food origin. The tuberculoid form of leprosy is associated with genes of predisposition [14]. Probably, any are of viral origin. A (patented) HIV-like retrovirus was evidenced in multiple sclerosis [45], a disease which looks like other diseases linked to HTLV1. Integrated into the genome, viruses induce changes that interact with the expression of non-coding genes [22]. This can change the fate of cells in all ways [11] (apoptosis, cancer retrogression, excision of virus-like sequences) and the fate of the organism. Endogenous retrotransposons may also evade through the capture of free capsids of other viruses [28]. But, phage resistance genes are present in many viruses that maintain their genome in the lysogen state in bacteria or cancer cells [44].

2. To survive it is “to eat” and “not to be eaten”.

A link has been evidenced between HIV infection and cancers or infectious diseases. The amount of cancers linked to AIDS is continuously increasing. HIV can directly infect and kill CD4+ T cells. The temporal variation of the number of activated lymphocytes, infected lymphocytes and free HIV particles obeys the law of predator-prey co-evolution [40]. The bone marrow stem cells and also the macrophages are infected. The low specificity of HIV's prey requirements is an advantage for the predator virus survival. AIDS is the result of the limiting “hosting capacity“ of the human ENT and of the unlimited “capacity to be hosted“ of the virus’ ENT. To survive it is not only “not to be killed”, it is “to turn disadvantages into advantages”, and “to avoid advantages to turn into disadvantages“ [7], in order to itself-survive (to reproduce). It is just what cancer or aids viruses and leprous bacteria are doing: obligate intracellular parasite they lack the necessary genes for independent survival,

Mycobacterium leprae was the first bacterium to be identified as causing disease in man : leprosy, a chronic infectious in which the bacterium is hosted by phagocytes, like HIV. The pleomorphic bacterium [6] is surrounded by a thick waxy coating (unique to mycobacteria) which renders it very difficult to destroy (it is an advantage for the bacillus) but it is the reason for its extremely slow replication rate, with the longest doubling time of all known bacteria (it is a disadvantage!). Leprosy and other mycobacterial diseases, as tuberculosis, result from modifications of the “hosting capacity“ of our EXT, unbearable by the limited “capacity of to be hosted“ of our ENT.

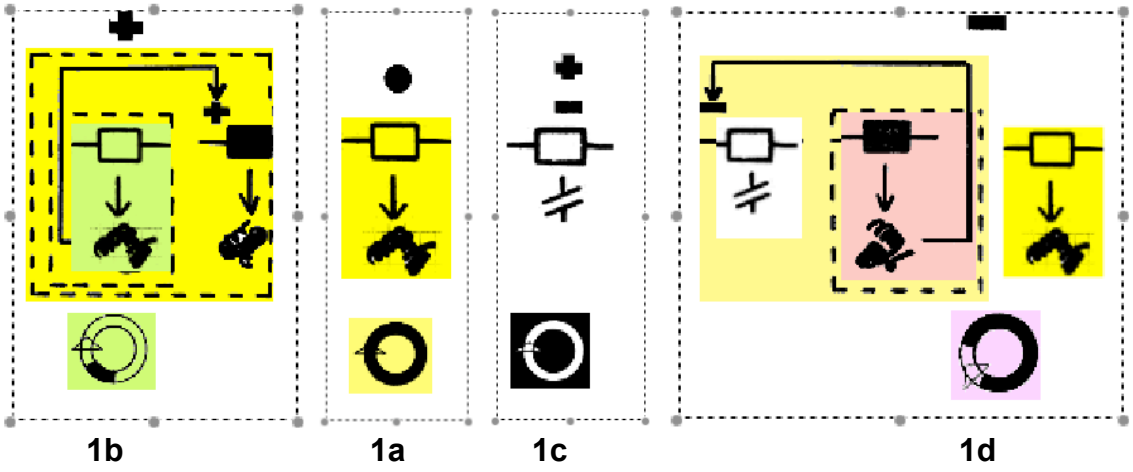

Figure 1: Dormant, constitutive, repressed and activated genes' expressions: the processes.

The interpretation of genome sequences and the exploration of their functions or the localization of their protein interactions is now possible in tissue culture [46]. During the cell cycle of survival (circle) there are 4 types of genes' expression: sometimes expressed genes depending on either their “activation” (**+** activated expressed genes) or “repression” (**-** inhibition breakage expressed genes), “never expressed” genes (no activation, no inhibition, “locked”, “dormant” $\underline{+}$), “ever expressed” genes (independent, “freed”, “constitutive” expression •). If a gene has to be expressed every time (circle in black), the cost of its regulation is null, the cost is only that of the expression of its encoded protein (in yellow): **1a**. But if a gene is under an activation control (**+**) the cost of its expression is the sum of the cost of the expression of its encoded protein (in yellow) plus that of the synthesis of the regulator protein (in green): **1b**. Thus the cost for an activation will be reduced if the gene will be expressed only over a short duration of the life cycle (the black part of the white circle). If a gene is never expressed (**1c**) there is no cost in protein synthesis, but their is a cost in the maintain of its corresponding gene sequence. However only 1 sequence needs to be maintained, like in constitutive expression (**1a**). But 2 genes must be maintained in the case of activated (**1b**) and repressed (**1d**) expressions. But why a dormant information would be conserved in the genome? In the case of a repressive control (**1d**) all over the cell cycle only 1 protein is expressed, either the repressor protein (in pink, during the black part of the cycle) because that of the controlled gene is not (in white) or the “de-controlled” protein, if inhibition breakage (in yellow, during the white part of the circle). Actually the situation of “up & down” regulation of gene expression [56] is far more complex (Figure 3) because the same regulator can have an inhibitory or a repressive action depending on the operon with which it binds [34, 35] and the regulon it is a part.

Disseminated infection caused by non-tuberculous-non-leprous Mycobacteria, which multiply in macrophages, is common in AIDS patients [1]. Paradoxically HIV also is a prey, eaten by the Langerhans cells [17] which derived from the same cell precursors that monocytes [46] that are eaten by HIV. To survive it is to eat and not to be eaten! However from a cell to an other, in different viral EXTs, the same viral ENT (Figure 3), the same expressed genes, give raise to different opposite responses [26]. Drug or virus resistances are often encoded by genes located within transposons or repeated

elements which regulation is depending on the same regulators that those of exogenous viruses [41], the same for prophage-like elements which are often present through repeated modules or/and lie within redundant repetitive elements.

Table 2: The costs for each type of genes' regulation: the regulation load.

Any protein (like an enzyme or a regulator) has a limited time of action, depending on its concentration and its half-life. There is always a concentration threshold below which the inhibitor or the activator is not active. Thus (Figure 1), in the case of an activated expression (-**1b**- **activation**), the activation starts after a latent phase (lag duration) which is the sum of the latent period of the synthesis of the activator plus that of the synthesis of the regulated protein. Reversely, when the activation stops (**de-activation)** the lag duration is the sum of the duration of the latent period of the disappearance of the activator plus the disappearance of the regulated protein (**1+1**). In the case of a repressed expression (-**1d**- **repression**), the repression starts after a lag (depending from dose-dependence threshold effects) which is thus equal either to the latent period of the synthesis of the regulator or that of the disappearance of the regulated protein (**1 or 1**). When the repression stops (**de-repression** = inhibition breakage) the latent period is also only the longest duration of either the latent period of the disappearance of the activator or that of the disappearance of the regulated protein. Thus, from an economic point of view, a repressed control must be twice favoured, because its cost (in duration, in information and in use of this information) is lower than that of an activated control. With fewer modules expressed in the same time (only 1 protein is active at a time: **1 or 1**), it is more reactive (repression needs the synthesis of only 1 regulator protein), it is far more speedy than activation (which needs 2 proteins: the regulator plus the controlled protein) and thus it is more robust. The natural selection does indeed, soon or late [11], facilitate the repressive controls (with only 1 protein expressed, even during all the cycle, versus 2 proteins expressed even during a short part of the cycle).

types of control	gene sequences	protein synthesis	lag duration
never expressed	1	0	infinite
ever expressed	1	1	0
repression	1 + 1	1 or 1	at de-repression: repressor clearing + protein synthesis at repression: protein clearing or repression threshold
activation	1 +1	1 + 1	at activation: activator synthesis + protein synthesis at de-activation: activator clearing + protein clearing

3. Cancer, AIDS and leprosy diseases are the results of no-controlled dangers.

M. leprae, HIV or viral oncogenes are strictly intracellular, so drugs must penetrate into the infected cells, but they also penetrate into the healthy ones, which are damaged [25]. What is the real effectiveness of drugs? How to evaluate it [51]? The undesirable by-side effects are numerous. And anti-cancer, anti-leprous or anti-HIV drugs may be agents of cellular provirus lysis. It was thought that by treating also against the HPVs the transmission of HIV could decrease, because a synergy exists between the 2 viruses. Nothing at all! The treatment does not reduce the risk of contamination [57]. Let us not forget that “the Whole is both the more and the less that the sum of its parts“. In human monocytes, *M. tuberculosis* increases the production of HIV [53]. The whole-genome comparison of “virulent” (pathogen) and avirulent bacteria reveals a dis-structure of their genomes [29]. The alteration of the regulons [36] awakes dangers [48] that evade (Figure 3)! Like cancers, leprosy is a disease of cell survival's disfunctioning and of unwanted immunology expression. *M. leprae* invade the cell hyaloplasm like did the ancestor of the present mitochondria [3], but now the cellular ENT is no more a free EXT for ENTs of other similar invading Bacteria. Despite their ability to infect and persist in the macrophages of the host, despite their apparent sequestration, mycobacteria reside in vacuoles that remain accessible. But bacterial wall fragments are actively released: a dynamic war between

the bacterial and cell compartments is maintained [4]. The drug resistance is gained through a defensive retrogression [42] as in cancer [34]: when the EXT of survival turns to stressing conditions, some mutations (disadvantages for the ENT's survival) turn to advantages. The expression of viral genes depends on a continuous proteins synthesis [37]. “To stop it” stops the cell's viral lysis or cancerisation. But, drug or virus resistance/susceptibility may be controlled with only 1 protein [54], and the action of that “keystone actor” [11] is being lagged into the space or through the time [13].

4. Failure of all the present therapies & spread of drug-resistant clones.

M. leprae was sensitive to dapsone, but resistance against this antibiotic has developed over time [6]. Therapy with dapsone alone is now strongly contraindicated. A multi-drug treatment is now recommended, with dapsone, rifampicin and clofazimine. As a food source, antibiotics would seem to be a poor choice for bacteria. However, readily cultured bacteria from the soil can consume antibiotics as sole carbon sources. These bacteria are from several genera, some of which are closely allied to human and livestock pathogens, and are also generally extremely resistant to many antibiotics. Consumption is not restricted to antibiotics derived from natural products but also includes synthetic ones, as well as new-generation molecules, such as levofloxacin. This heretofore unrecognized source of antibiotic-metabolizing bacteria represents a potential pool of antibiotic resistance genes for pathogenic bacteria [16]. « *Survivre, c’est “transformer des inconvénients en avantages“ ET “éviter que des avantages deviennent des inconvénients“, pour SE survivre* » [8]. With the escalation of world travel, the risk of transmission, with contact with long-term carrier organisms, inhabitants of the respiratory, intestinal or genital tracts of human, is highest with the increasing number of human populations [31]. Furthermore, Bacteria and viruses constantly undergo mutations and may also acquire genes from other viruses. Such genetic modifications may afford pathogenic bacteria survival advantages and increased virulence properties, which may lead to the emergence of multi-drug-resistant clones. All occurs as if leprosy were a disease of immune-deficiency like AIDS. The lymphocytes T which control the immune response, amplifying it or limiting it, would exert a suppressive action on defenses against *M. leprae* [35]. But, as for HIV, cells tanks exist (the fat cells in the case of *M. tuberculosis*) which protect the germ “in dormancy” from the action of antibiotics. But we can detect genes of controlling dangers [15].

5. The biological “struggle“ against released, de-controlled or not-constrained dangers passes through the “domestication“ of other free dangers.

Even if we can do it for many viruses [23], a vaccine designed to prevention is an “*illusion*“ for AIDS! The double inoculation, at the same time, of attenuated tuberculous bacilli (BCG) and of leprous bacilli restores a immunity with respect to *M. leprae* [43]. But, even in Europe, leprosy or tuberculosis, like AIDS, are still present. They “do not kill, but condemn” Advances in HIV research have not made a vaccine designed to prevent AIDS available. But viruses are an alternative of antibiotics [39].

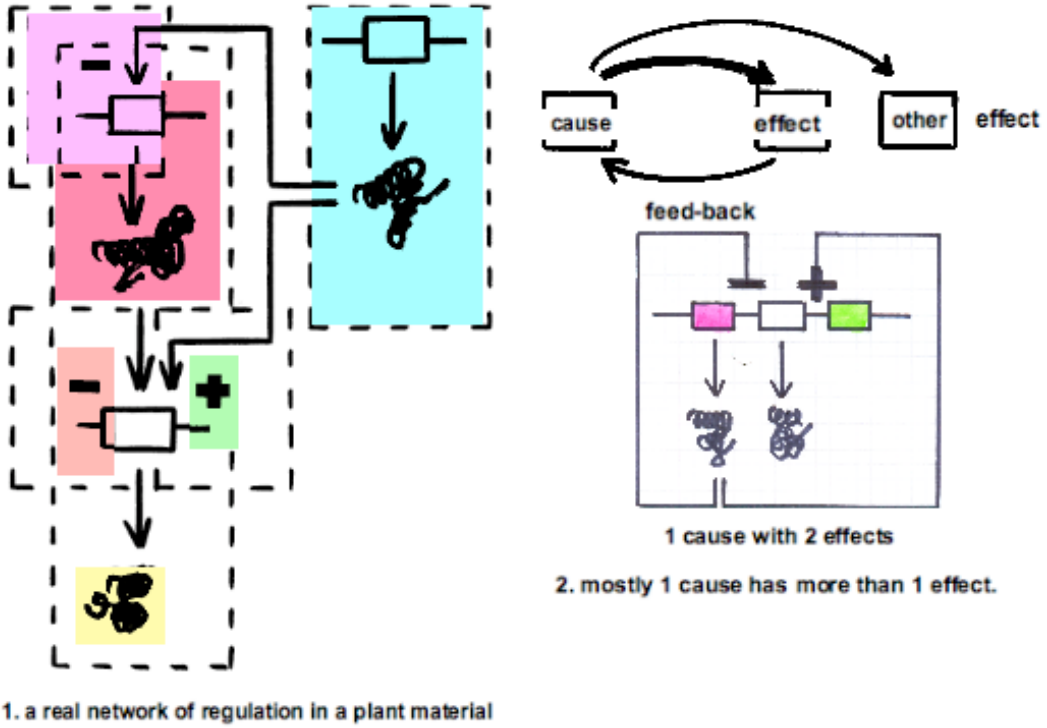

Figure 3. Evaluation of the risk of disfunctioning of a system and of the cost of the prevention of this risk: costs, disadvantages or risks versus gains, advantages or robustness. **1.** A real network of regulation in a plant material. Why are there 2 juxtaposed systems of inhibition (**-** in pink & salmon)? Why the same system (in blue) has 2 opposite (antagonistic) effects (**+** in green & **-** in pink)? **2.** Mostly 1 cause has more than 1 effect. Why? When there are 2 effects (pleiotropy) for 1 cause (1 cost), the modularity of the system is lowered and the cost of its maintenance decreases: it is an advantage. But the risk of its alteration increases (because "1 cause makes to effects"): it is an inconvenient, a disadvantage. Any abnormality of the target (or of the effect) is a risk, but the existence of 2 targets lowers the risk (it is an advantage), and different ways of retro-control (separate feed-backs or additive ones) are allowed, new ways may appear (**3.2.**): it is an "evolutionary" advantage (*exaptation*). When the cause is endogenous (from the ENT), any abnormality of the coding gene or of its product(s) may be a risk. In the case of a dormant gene (Figure **1c**) the only risk is activation. When it is an exogenous cause (from the EXT), the cost of maintenance is lowered (advantage) but both activation and repression are possible risks (it is a disadvantage). There is no advantage(s) without disadvantage(s): to survive it is "to avoid advantages from turning to disadvantages" and simultaneously "to turn disadvantages into advantages". In the case of **repression** (Figure **1d**) during the repression phase the risk is similar to the sum of that of a constitutive expression (expressed regulator) plus that of a dormant one (no-expressed protein), conversely during the de-repression phase the risk is that of the dormant no-expression (no-expressed regulator) plus that of constitutive expression (expressed protein). In the case of activation (Figure **1a**) during the activation phase the risk is the sum of 2 risks of the constitutive type (which is the greatest risk), during the de-activation phase the risk is the sum of those of 2 dormant states (like in provirus dormancy!). The risk is continuous. A repressive system is less risky, easier to maintain and more robust, than an activator one, thus the juxtaposition and encasement of repressive regulatory systems (**3.1.**) has been selected through the merging of ARMSADAs... which has favoured recurrently the merging of ARMSADAs of ARMSADAs "in the risky ways of life survival, the way is constructed during the way". For a review about the paradigm of ARMSADA [9, 10, 11] look at: http://minilien.com/?IlzFET9WhX. Activator systems are convenient only to initiate or modulate inhibitory ones. During development, the way from a step to an other one (metamorphosis) is initiated by activator systems, or in a better way through inhibition breakage. The maintenance of a step of development (growth) is insured by inhibitory ones which blocks the other steps' expressions, and modulated by the interactions between activator and inhibitor ones. The lowest cost to contain a danger it to make it

dormant (Figure **1c**). A lot of cancers merges from abnormal activation of a dormant gene: “hip-hop” from a dormant state to a constitutive one. But this risk usually is very rare. And, a dormant viral gene, if “domesticated” may be used, if re-activated at the right time and into the good place, to selectively lyse a cancer cell. In the case of a constitutive expression (Figure **1a**) the risk of abnormality is everlasting. The “to be constrained” danger has to be very big to run such a risk. The best way of survival is the hosting of dangers which are repressed by their own regulatory system (like bacteriophages which are integrated into bacteria): the hosting of dangers which are limited in their expression to proteins that confer an immunity of their hosting cell. All that explains the evidence of a HIV curative vaccine [11]. Usually a repressor protein is constitutively expressed for over-infection exclusion [44]. But viral antigen proteins can induced misguided activation of antiviral pathways [58]. The same repressor/activator protein inhibits/permits the translation of different regulatory antagonistic protein effectors. The same protein, depending on its length, may be an activator or a repressor [55].

5.1. Curation of the viral infection through an other viral infection.

The defense against provirus excision (AIDS), virus expression (cancer), or bacterial invasion (leprosy or tuberculosis) is in an infection with an other virus that restores the apoptosis through the reversion of cancer-cells to “normality” [12] or kills the infected cells before the first hosted virus reproduced (cancer or HIV sick cell assassination through an other sooner viral lysis). More than 50 species of Mycobacteria have all more than 10 plasmids (that easily transfer drug resistance) but also phages that killed them all “specifically“ [21]. All were detected in AIDS patients! Mycobacteriophages share a common regulatory system with the phage repressor binding to multiple operator and stop-operator sites located throughout the phage genome [27]. Guided/misguided “domesticated” viral lysis can lead either to the lysis of tumours (or bacteria) or to growth of cancer [58].

5.2. Towards an *ex vivo* self-curative vaccination [11].

The goal is to make tip over the prey-predator system towards an associative mutualistic “*synallagmatique*” one. For that it is necessary to cross through a critical auto-organised state, by juxtaposition and encasement (Figure 1). Such a rare event can lead to a disaster [2]. But, *in vitro* it is without danger for the organism. All the technologies: - the predictive tests (of cancer, AIDS, or leprosy or tuberculosis), - the *in vivo* gene therapy with the controlled administration of vector viruses (with gene in their transformed genome, or antigen expressed in their capsid), - the ex *vivo* gene transformation of tumour cells or immune cells (Genetic Modified Cells) are patented since more 10 years. And one can even now carry out the reprogramming of original cells by retroviruses [30] to select *in vitro* an integrated framework of compatible genes for a healthy cell's state [10, 11, 12].

5.3. The only curative solution to cancer and AIDS [11] is the integration of the related viruses into the Association for the Mutual Sharing of Advantages and DisAdvantages [9], which is “constitutive” of our cells [10], to revert the sick cells to healthy phenotypes.

A good virus is not a dead one, but a quite alive one, whose ENT is integrated into that of the cell, just as the mitochondrial genome is integrated into that of the cell nucleus (Figure 1), like the sheep organism needs a retrovirus to reproduce “itself” [18]. Like did the “natural selection” for the other “constrained” dangers that are

lodged [20] in all genomes. Thus the cost of breaking “selected” gene associations is a slippage of an advantage to a dis-advantage [33]. The “domestication” of viruses by the man species has reached a technological level to do it with a good efficiency [5] because, due to the robustness of the gene regulation processes [36], ARMSADAs are favoured by the natural selection both *in vivo* and *in vitro*. Hundred of Mycobacteriophages [21] and cancer-cell phages or virus-infected cells phages do exist, we need to seek them [45].

Thus the only alternative to the drug treatments that generate resistances is the use of “domesticated” viruses, e.g. “harmless to our cells”, but “ready to reach and destroy” bacteria or viruses lodged within these cells. This solution is not only curative for AIDS [11], cancer cells [12] or leprous cells, but also preventive for cancer cells, and the same viruses which can *in vivo* eat bacteria (or cells) can eat them also *ex vivo* (in corpses, waters or soils). Only are alive, organisms that are infected by viruses [49]. And only the homing into ARMSADAs “naturally” protects against viruses attacks [38].

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Look at http://en.wikipedia.org/wiki/Cancer & http://en.wikipedia.org/wiki/Leprosy, for a review of the susceptibilities to the diseases, and at http://en.wikipedia.org/wiki/Infection, http://en.wikipedia.org/wiki/Mycobacterium_leprae & http://en.wikipedia.org/wiki/Virus for a review of the properties of the pathogens (with the key words : HIV, AIDS, cancer, leprosy).