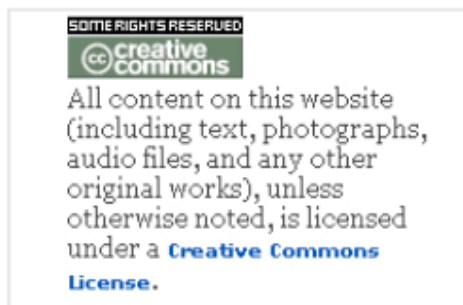


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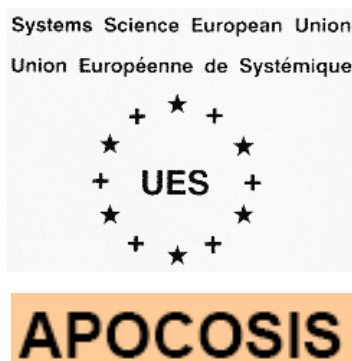
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# Cancer is a breaking of the cell's association for the reciprocal and mutual sharing of advantages and disadvantages through an aggression that results in a lack of non-autonomy

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## Abstract

Cancer may affect people at all ages, even foetuses. Risk tends to increase with age. A group of cells displays an “uncontrolled growth“, divides beyond the normal limits, invades and destructs adjacent tissues and spreads to other locations. These properties differentiate cancers from benign tumours, which self-limited “stay under control“. Cancer results from the breakage of the capacity of “to be hosted” of the endophysiotope (ENT) of cells, in response to the failure of the hosting capacity of their ecoexotope (EXT), the organism. There is only one rule of survival: “to transform disadvantages into advantages” and “to prevent advantages from turning to disadvantages“. When the EXT is changing, a disadvantage can turn to an advantage and conversely [24]. For stressed endangered cells, cancer is the way not to die. Cancer is a survival response of damaged cells! How is that process of retrogression working? Viruses were the first proved cancerous agents. Viruses are the second risk factor for cancer development in humans, exceeded only by tobacco usage. The amount of cancers linked to AIDS or any viruses is continuously increasing [51]. The genome of all organisms is inhabited by viral genomes. The presence of these “controlled risks“ is usually an advantage for the survival of both the inhabited cells and their inhabitant viruses [28]: the genetic material of a cancer virus is inserted into the host cell genome without any production of virus particles and with no cell death. Cancer is a disease of disfunctioning due to unwanted viral gene expression. How, when and why do these “silenced killing dangers“ reborn? Cancer is induced by agents of cellular provirus' lysis: radiations & chemicals altering DNA. The same that are used in chemotherapy and radiotherapy. Dose-dependence or threshold concentration effects may impaired or reversed the activity of preventive or curative agents. The stability of a cancerous cell is in the key fact that the virus does not kill the cell and reciprocally the cell prevents the virus to be killed by other cells. The result is the merging of a new spatiotemporal ENT network and a new mode of EXT integration into an Association for the Reciprocal and Mutual Sharing of Advantages and of Disadvantages (ARMSADA): an advantage for the “new” cell but a disadvantage for the organism inside which the re-autonomy of the cancer cells disrupts the previous steady-state's controls. In order that one survives, it is necessary that the others survive first, and reciprocally. The fate of a cancer cell, like the fate of a bacterium infected with a phage, is depending on the interactive “percolation“ with its invading virus [15]. That explains the heterogeneity of the disease, its evolutions and the diversity of the potential hosts: “the way is both the cause and the consequence of the history” [53]. Cancer is a disease of the breakage of the Association between the “parceners“. Usually that leads to apoptosis [15], but sometimes to cancer [35].

*Keywords: cancer, curative vaccine, hosted viruses, integrated constrained dangers, symbiosis*

Cancers are caused by abnormalities in the genome of transformed cells. That may be due to the effects of chemicals (as tobacco smoke), radiations, infectious agents, acquired through errors in DNA -replication, -repair or -methylation, even inherited (present in all cells from birth). The interactions between the genome and carcinogens explain why only some develop cancer after exposure [31]. A tumour is a new organ composed from

abnormally differentiated cells. But, only small populations of stem-like cells can form colonies in cell culture systems or engraft and recapitulate the entire diversity of the tumour phenotype when injected. Malignant tumours originate from the transformation of tissue stem cells by mutations that lead to the deregulation of the healthy mechanisms that control stem cell growth and proliferation [52]. Thus, like stem cells, cancer cells are resistant to apoptosis. Cancer cells display the same surface markers as their normal sister cells but exhibit uncontrolled proliferation, due to a reduced responsiveness to repressive [17] growth control. They are autonomous and controlled by pathways that are quiescent in normal non-autonomous adult cells [53].

## 1. Obligated hosting: the genome of organisms is inhabited by viral-like genes

Endogenous viruses are present in blood leukocytes from porcine breeds. Primers for gag-, env- and pol-related sequences of endogenous retroviruses, related to foamy retroviruses [36], are specific both for the porcine and Human RetroVirus-Like elements. The genome of tumours is inhabited by viral genes that escaped from the genome of other organisms [22] as the exogenous Jaagsiekte Sheep RetroVirus. The role of Human Endogenous RetroViruses (HERVs) in the induction of psoriasis has been suggested, based upon the observations of retrovirus-like particles in psoriasis from skin lesion plaques, urine and stimulated lymphocytes [4]. At least 8% of the human genome consists of retrovirus-related sequences: related to gammaretroviruses (such as Murine Leukaemia Virus), related to betaretroviruses (such as Mouse Mammary Tumour Virus), related to spumaretroviruses... Many genes that are nowadays necessary for the survival of the cell, like ARN coding genes [44], may have originate from ancient viral lytic genes from retroviruses. These endo-viruses, not only do not express virulence, but confer a resistance against similar related viruses [11] or other dangers [37]: among cells infected with a murine retrovirus, 20% are resistant to a toxin, a resistance frequency approximately 1,000 times higher than for uninfected cells [37]. The human genome, with only 1% of genes coding for proteins and 1% of "pseudogenes" (inactivated genes), is built with 40% of retrovirus-related transposons. Plenty of mariner transposons are hosted and some are active [50]. They are the relics of ancient infections of which the ancestors of our cells survived [26]. They have been "domesticated". Their presence which was previously a disadvantage is now an advantage for the survival. Proteins of the APOBEC family [27] prevents the viral expression through the additions in the viral genome of mutations that block viral reproduction, preventing the replication of the HIV. Many genes are controlled by viral promoters or activated by viral transcription factors. The same proteins are necessary both invading viruses repression, cancer cells survival or healthy cells functioning [20].

## 2. Disfunctioning risks: cancer is a disease of unwanted viral genes expression

Viruses were the first proved cancerous agents. Viruses are the second most important risk factor for cancer development in humans, exceeded only by tobacco usage. The International Centre for Cancer Research of the World Health Organisation was created in 1965 to study a viral induced cancer: the Burkitt Lymphoma, associated with the Epstein-Barr Virus. The main viruses associated with human cancers are Human PapillomaVirus (HPV), Hepatitis viruses B and C, Epstein-Barr Virus, and Human T-Lymphotropic Virus. In acutely-transforming viruses, the viral particles carry a gene that encodes for an overactive viral oncogene and the infected cell is transformed as soon as the gene is expressed [38]. The genome of slowly-transforming viruses is inserted near a proto-oncogene in the host genome. Transcription regulation actors cause over-expression of that oncogene, which in turn induces "de-controlled" cellular proliferation. Because viral genome insertion is not specific slowly-transforming viruses have very long tumour latency compared to acutely-transforming viruses. The genetic material of a cancer virus is inserted into the host cell genome without any production of virus particles and with no cell death

[28]. Repressors or inducible transcription factors facilitate adaptation to deprivation by regulating the expression of genes that control metabolism, angiogenesis, cell proliferation, and apoptosis [49]. Cancer is a micro-evolutionary response for best survival of a damaged cell that would have been killed or should die, but really does survive [40]. Normally DNA viruses (probability 0,999999) are not integrated in the cell genome and the viral infection results in the cell's death: lysis and burst of a new viral generation. Rarely (probability 0,0000009), in case of a mutant virus or an unusual phenotype of cell, the viral DNA is integrated into the cell DNA. Retroviruses integrate the cell DNA to subvert the cell genome to make a new generation of RNA viruses. Rarely, if a defective virus or an appropriate unusual genome change "as a Whole", there is no cell's death. The viral integration into the cell DNA promotes a dysregulation of the anti-oncogenic mechanisms of the growth control [19]. Retroviruses are cell transforming viruses. All transforming signal ways are present: amplification of the number of a gene, activation of a silent gene (or hyper-expression of its activity), repression of an active gene (or its hypo-expression), and normal expression but at the bad place and at the wrong time. "Viroid-like" microRNAs (miRNAs) play critical roles in development. Their dysregulated expression is evidenced in human malignancies. Recent evidences suggest that the processing of many primary miRNA transcripts is blocked post-transcriptionally in embryonic stem cells, carcinoma cells, and primary tumours [57]. A developmentally regulated RNA binding protein is a negative regulator [17] necessary and sufficient for the blocking of miRNA-mediated cleavages in embryonic stem cells and in cancer cells. With other factors it reprograms fibroblasts to pluripotent stem cells. The regulation of RNA processing may be critical in the de-differentiation that occurs in both reprogramming and oncogenesis. In cancer cells, promoting oncogenes are often activated, giving those transformed cells the new properties of hyperactive growth and division, protection against apoptosis, loss of respect for tissue boundaries and the ability to become established in diverse tissues. Tumour suppressor genes are often inactivated in cancer cells, resulting in the loss of normal functions, such as accurate DNA replication, control over the cell cycle, orientation and adhesion within tissues, and interaction with protective cells of the immune system. Cancers are induced by agents of cellular provirus lysis: the UV and ionizing radiations, the harmful chemicals that alter DNA. In addition to viruses, a link is noted between bacteria harboring viral-like genes in plasmids and cancers. Many bacteria are hosting genomes of viruses, which give them an increased, and inherited, survival aptitude. A vaccine, Gardasil, protects against 4 HPV types, that cause 70% of cervical cancers and 90% of genital warts.

### 3. Curative vaccination: a struggle against non-limited or "evaded" dangers

To survive it is "to eat and not to be eaten" [6]. Cancer is not an exception [39]. Preys or hosts and their predators or parasites (like cancer cells) struggle 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 ENT makes possible to contain the dangers [14]. When the EXT is changing, a disadvantage can turn to an advantage and conversely [8]. The "balance" advantages versus disadvantages is depending on the considered level of organisation (into the space and through the time). There is only one rule to survive: "to transform disadvantages into advantages" and "to prevent advantages from turning to disadvantages". At the  $i$  level of the cells, to eat itself (autophagy) is a strategy of survival for the organism (the  $i+1$  level) [47]. The cell's transformation is the result of a variety of metamorphoses depending on the place of integration of "the dangers" (the "unwanted" genes) and their moment of expression or not. The stability of the association is in the key fact that the virus does not kill the cell and reciprocally the cell does protect the virus of the killing by other cells. Infectious particles are not liberated following the fusion of some transformed cells with non-transformed permissive ones. The shuttle [10] 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 ARMSADA, like a Lichen Organism [5]. But, all the actors must lose simultaneously the capacity to destroy the other partners. Each advantage for a partner, both “hosting and hosted” (named “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 for the worst” [5, 7, 16]. The gain is only for the Whole! In order that one survives, it is necessary that the others survive first, and reciprocally. During the ontogeny of a leguminous nodule, the host plant part metamorphoses into a tumour and the Bacteria metamorphose simultaneously into bacteroids. The fate of a cancer cell, like the fate of a bacterium infected with a phage, is depending on the interactive “percolation” with its invading virus(es). That explains the heterogeneity of a disease (cancer or AIDS), its evolutions and the diversity of the potential hosts (and hostages): “the way is, both, the cause and the consequence of the history” [53]. The application of this systemic paradigm will allow to design a new type of curative cancer vaccine built with virus engineered cells, as the previously proposed curative AIDS vaccine, built with HIV engineered cells [15].

### 3.1. Curation using another free danger to destroy a hosted pre-existing one

#### 3.1.1. Curation through working back cell to non-autonomy to restore apoptosis

The injection of a viral vector is used to restore a damaged or absent gene. Adult human fibroblasts can be reprogrammed to a pluripotent state after the viral integration of transcription factors. However, questions remained. Are specific genomic integration sites needed? How tumorigenicity might be reduced [3]? Stem and cancer cells are characterized by low levels of miRNAs, a phenomenon linked to pluripotency and oncogenesis. Precursors are detectable but processing to the miRNA mature form is inhibited [57]. The restoration of RhoB expression, through recombinant adenovirus transduction with a single dose of the reporter gene vector virus, leads to ovarian tumour regression with the activation of the intrinsic apoptotic cascade. But, at the cell body, an incoming virus stimulates its own uptake [21] by mimicking the uptake of apoptotic cell corpses [45]. But the requirements for reprogramming different somatic cell types to a pluripotent state are not equivalent, it is probably the same for the “de-retrogression”: the reverting of cancer cells to “constrained” non-autonomous ones [3].

#### 3.1.2. Curation by tumour cell assassination through an exogenous viral lysis

A tumour killing virus may be loaded into a cell type that houses to tumours [32]. Parvoviruses can stop the tumour progress in man, because, even if they infect all the cells, they multiply only in the cancer cells which they destroy [54]. Half of cancer cells have mutations in the p53 gene that controls cell's division and death. The tumour suppressor activity of the p53 protein is explained by its ability to induce apoptosis. In response to cellular stresses, p53 interacts with the pro-apoptotic mitochondrial membrane protein Bak, which is the first step of the induction of apoptosis [33]. And, to replicate in cells, the viruses prevent apoptosis. But a genetically-engineered harmless human adenovirus can replicate in and kills only p53 deficient mutant cells [48].

#### 3.1.3. Curation of an endo-provirus, or -pseudo-virus, with an antagonistic one.

In somatic cells [30] of plants, fungi and worms, RNA interference functions to silence endogenous repeated and parasitic DNA, including transposons. Silencing [55] of oncogenes, or other genes contributing to tumour malignancy or progression, has been done by RNA interference in mice using viral plasmid vector. Gene transfer into chicken embryos is currently achieved with retrovirus vectors [34]. A retrovirus vector carrying human ProMyelocytic Leukemia (PML) cDNA was successfully constructed and expressed

in bladder cancer cells. Transfection of PML DNA with retrovirus vector inhibits growth of human bladder cancer cells [41] .

### 3.2. Curation by the death of the sick cells after they returned to non-autonomy

The interaction between a virus and its host cell, like that between a predator and its prey, is an arms race, with each new viral attack parried by the host and each new defence of the host one-upped by the "to be hosted" virus: a rapid end-less escalation of virus/host arms race. The merging of a new living system is always achieved by the juxtapositions and encasements of previous systems [9]. The new Whole merges from the simultaneous metamorphoses of the partners that maintain their identity and half-autonomy by the preservation of the self-organisation of their individual and collective boundaries, like the eukaryotic cell merged from Monera [14]. The cancer is a disease of the breakage of the ARMSADA between the parcerers. Usually the breakage leads to apoptosis, but sometimes to cancer: mutations in mitochondrial DNA can spur metastasis and mtDNA in tumour cells tends to be riddled with mutations far more than in normal tissues [35]. On the short duration, the cell lysis (probability 0,9999) is an advantage for the virus and a disadvantage not only for the permissive cells but and the whole organism. However virus coded proteins are usually expressed on the surface of the host cell, making the cell a target for destruction by the immune system. At the long duration, the hosting (inhabited) cells are killed by the hosted (inhabitant) virus, it is a disadvantage for the virus, and an advantage for the organism as a Whole, because it is now "vaccinated" against the virus and its other relatives. But if the cells' deaths result in the organism's death without its reproduction, it is a disadvantage for the both species: the virus and the organism. At the short duration, the cancerous state, the transformation without lysis of non-permissive cells (probability 0,0001), is an advantage both for the virus and the cell. Thus it is "naturally" selected. Why? Because the autonomous transformed cancer cells have lost the contact inhibition of growth and gained the immortality: not only they are not killed but also they survive and multiply indefinitely and the whole ENT of the organism is their permissive EXT. Simultaneously the virus survives indefinitely within the ENT of the cell, which is its permissive EXT. No killed cells of the tumour can elicit immune protection against live cells of an other tumour. But at the long duration, even if it is a disadvantage for the organism, it is an advantage for the system, if the organism ("the prey") has given birth a new generation of preys for "the predator" (the virus). There is only one rule of survival: "to transform disadvantages into advantages" and "to prevent advantages turning to disadvantages".

### 3.3. Application: curation with a strategy of *ex vivo* curative self-vaccination

In its principle, the strategy is similar to my previously proposed one to fight against HIV [15]: - first, as soon as possible, taking up, but only from a sick patient, both healthy and cancerous cells, and putting them in culture *in vitro* [23], - then selection, through their survival, of the only phenotypically healthy cells having integrated, "strongly" into their genome, a "harmless" transducing retrovirus (killing only the cancerous cells), - and finally, *in vivo* re-implantation of these modified cells, both with the harmless virus. But it is different in its purpose: the goal is to reveal the dangers which are expressed but non-recognized, so they can be recognized and destroyed [19]. Some viruses cause cancers, the others do not because their presence is recognized and they are destroyed [51]: the viral genome allows to express proteins associated with the tumour, and the antigenic presentation of these proteins activates the immune system [1]. Why have the meristematic cells, of the apexes of stems and roots of vegetables, an indefinite growth? Why do they resist to the infections by exogenous viruses? Because, as any animal stem cell, they have the characteristics of unlimited growth... of a cancer cell [56]! Why? Because they contain constrained integrated endoviruses (like in banana or tobacco species genomes). Their

properties of tumourisation (if dangers “evade”) and/or of regeneration (if the dangers, like HERVs, remain still constrained) are linked. During the floral differentiation (acquisition of the capacity of reproduction for the organism) the meristematic cells lose their inner capacity of growth (vegetative multiplication). They lose the eternity! What is a disadvantage for their ENT but an advantage for the preservation of the alive species of which their organism (their EXT) is a part. This breakage is checked and oriented by genes of the cancer [2]. The FVE protein, in flowering plants, participates in a protein complex repressing the transcription of a gene (FLC, encoding a MADS-box) that inhibits flowering, through a histone de-acetylation mechanism, which imposes the FVE protein to interact with a retinoblastoma cancer protein [2]. The product of the breast cancer susceptibility gene BRCA1 regulates transcription factors activated during CB1R-stimulated neurone outgrowth which is inhibited by its depletion [18].

A danger can be "controlled" by an other danger! "2 are better than 1" [29]. Two dangers together can be an advantage (ago-antagonism) [46]! A danger can become indispensable to the future survival: the sheep organism needs a retrovirus to reproduce [25]. During the metamorphosis of the insects, during the nodulation of the legumes, the “domesticated cancerisation” of the stem cells (of the imaginal disks or the roots) allows the merging of new structures. Processes of engineering cells with engineered viruses [43] are currently used for gene therapy [59]: in order to realize a vaccination treatment for malignant human gliomas with genetically modified tumour cells, retrovirus-mediated cytokine-gene transduction has been “domesticated” [58]. A “good” virus is not a dead one! But a "very alive" one, and which ENT is "definitely integrated" [42] into the ENT of a cell, like the non-autonomous mitochondrial genome is integrated into that of the nucleus, like, during the genesis of the cell's ancestor, a virus has been integrated giving rise to the centrosome [14]. The domestication of “inside & outside” viruses is the next stage of the symbiotic integration of *Homo species* into its EXT: the ENT of the earth biosphere. “For the best and for the worst” [17], the new Wholeness will be both more and less than the sum of its parts.

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