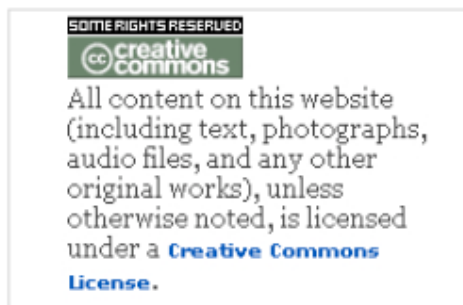


Systemic Complexity for human development in the 21<sup>st</sup> century  
**Systemic Complexity : new prospects to complex system theory**  
7<sup>th</sup> Congress of the UES **Systems Science European Union** Lisbon, Dec. 17-19, 2008



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**APOCOSIS**

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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.**

Pierre BRICAGE,

**Social and Health Sciences Engineering**

Faculté des Sciences & Techniques, Université de Pau & des Pays de l'Adour, 64000 Pau, France, Europe

[pierre.bricage@univ-pau.fr](mailto:pierre.bricage@univ-pau.fr)

Abstract

Cancer (malignant neoplasm) may affect people at all ages, even fetuses, and risk tends to increase with age. **A group of cells displays the traits of "uncontrolled growth and division beyond the normal limits", "invasion and destruction of adjacent tissues", and "spreading to other locations via lymph or blood".** These properties differentiate cancers from benign tumours, which are **self-limited and stay under control**.

**1. Cancer is the result of the failure of the capacity of to be hosted, of the endophysiotope of our cells, in response to the failure of the hosting capacity of their ecoexotope, the organism.**

There is only one rule of survival: **"to transform disadvantages into advantages" and "to prevent advantages turning to disadvantages"**. When the ecoexotope is changing, a disadvantage can turn to an advantage and conversely (Doberg & al. 1965). For stressed endangered cells, cancer is the way **not to die**.

**Cancer is a response for best survival of damaged cells ! How does that work ?**

The first cancerous agents that were found were viruses. Viruses appear to be the **second most important risk factor** for cancer development in humans, exceeded only by tobacco usage. The amount of cancers linked to AIDS or other viral sources is continuously increasing (Routes & al. 2000).

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 (Feng & al. 2008) : **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**

**2. Cancer is a disease of disfunctioning cellular genes due to unwanted viral gene expression.**

**How, when and why do these silenced killing dangers reborn ?**

**3. Cancer is induced by agents of cellular provirus lysis : radiations & chemicals altering DNA.**

The same ones are used in chemotherapy and radiotherapy. Some dose-dependence effects and threshold concentration dependencies may be impaired or reversed the activity of protective 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 does protect the virus of the killing by other cells. The result is the merging of a new **spatial and temporal network**, a new **mode of integration**, into a transformed **Association for the Mutual and Reciprocal Sharing of Advantages and of Disadvantages**, within the cell... an advantage for the "new" cell but a disadvantage for the organism inside which the new re-autonomy of the cancer cells disrupts the previous steady-state's controls.

**4. In order that one survives, it is necessary that the others survive first, and reciprocally.**

Like that of a bacterium infected with a phage, **the fate of a cancer cell is depending on the interactive percolation** with its invading virus (Bricage 2005B). 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."**

**5. The cancer is a disease of the breakage of the Association between the "parceners".**

Usually the breakage of the Association for the Reciprocal and Mutual Sharing of Advantages and DisAdvantages (ARMSADA) leads to apoptosis (Bricage 2005B), but sometimes to cancer (Ishikawa & al. 2008).



## La semi-autonomie du vivant, la stratégie du choc et le collège invisible : l'origine du cancer.

### Résumé

#### 1. Les cellules d'un organisme sont semi-autonomes.

Leur survie contribue à celle de l'organisme, qu'elles constituent et qui en retour les héberge.

L'endophysiotope de l'organisme est l'écoexotope de survie de l'endophysiotope des cellules.

Cette structure ergodique est apparue au cours de l'évolution du vivant par la mise en place d'associations à avantages et inconvénients réciproques et partagés entre partenaires (Bricage 2001).

La cellule eucaryote a ainsi émergé de la fusion, de monères et de virus, juxtaposés et emboîtés en un nouveau Tout (Bricage 2005B).

#### 2. Toute cellule contient dans son génome des génomes viraux juxtaposés et emboîtés.

Ces dangers contenus, intégrés, sont indispensables au bon fonctionnement cellulaire.

#### 3. À la suite d'une violence ces dangers contenus peuvent être libérés. (Bricage 2004)

Habituellement la cellule meurt par apoptose. Mais, qu'il soit physique, chimique, physiologique ou psychologique, le choc peut donner naissance à une cellule cancéreuse. Quand la capacité d'accueil de son écoexotop de survie ne peut plus assurer durablement sa survie, la seule issue de la cellule pour survivre est de changer la capacité d'être accueilli de son endophysiotop. Elle devient cancéreuse. Elle recupère une autonomie, de survie et de reproduction, incontrôlée et incontrôlable.

#### 4. Le cancer résulte d'un dysfonctionnement de l'expression d'un "collège invisible".

De nombreux acteurs de la cancérisation sont des virus. Or, les mêmes chocs qui sont responsables de la libération de virus endogènes sont utilisés pour tenter de détruire les cellules cancéreuses transformées par des gènes viraux exogènes, ... qui y ont déjà résisté, alors que les cellules normales y sont sensibles.

Survivre c'est transformer des inconvénients en avantages et éviter que des avantages deviennent des inconvénients.

#### 5. Pour que l'un survive, il faut d'abord que l'autre survive et réciproquement.

Au cours de l'évolution, seules se survivent les associations à avantages et inconvénients réciproques et partagés qui rendent les partenaires plus dépendants les uns des autres mais plus indépendants de leur écoexotop de survie (Bricage 2005A). Elles émergent par la perte simultanée par tous les partenaires de la capacité de détruire tous les autres.

À tous les niveaux d'organisation, le cancer résulte d'une déstructuration, spatiale ou temporelle, d'une Association à Avantages et Inconvénients Réciproques et Partagés, contrat synallagmatique, établi entre partenaires de niveaux d'organisation différents, pour le meilleur et pour le pire.

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Bricage P. (2001) Pour survivre et se survivre, la vie est d'abord un flux, ergodique, fractal et contingent, vers des macro-états organisés de micro-états, à la suite de brisures de symétrie. Atelier AFSCET "Systémique & Biologie", Paris. Institut International d'Administration Publique, 11 p. <http://www.afscet.asso.fr/ergodiqueW.pdf>

Bricage P. (2004) La Nature de la Violence dans la Nature. 9 p. Res-Systemica n° 4.

Bricage P. (2005A) La durabilité contractuelle du vivant. Anthropo-politique et gouvernement des systèmes complexes territoriaux, Presses de l'Université des Sciences Sociales de Toulouse, p. 111-117.

Bricage P. (2005B) The Cell originated through Successive Outbreaks of Networking and Homing into Associations for the Mutual and Reciprocal Sharing of Advantages and of Disadvantages, between the partners, with a benefit only for their wholeness. ICSS (Paris, France), 11 p. & 55 p. <http://minilien.com/?AhaGuV2gC> & <http://minilien.com/?MKDkk2v5My>

Doberg D.S. & al. (1985) Wounding and Its Role in RSV-Mediated Tumor Formation. Science 250: 676-678.

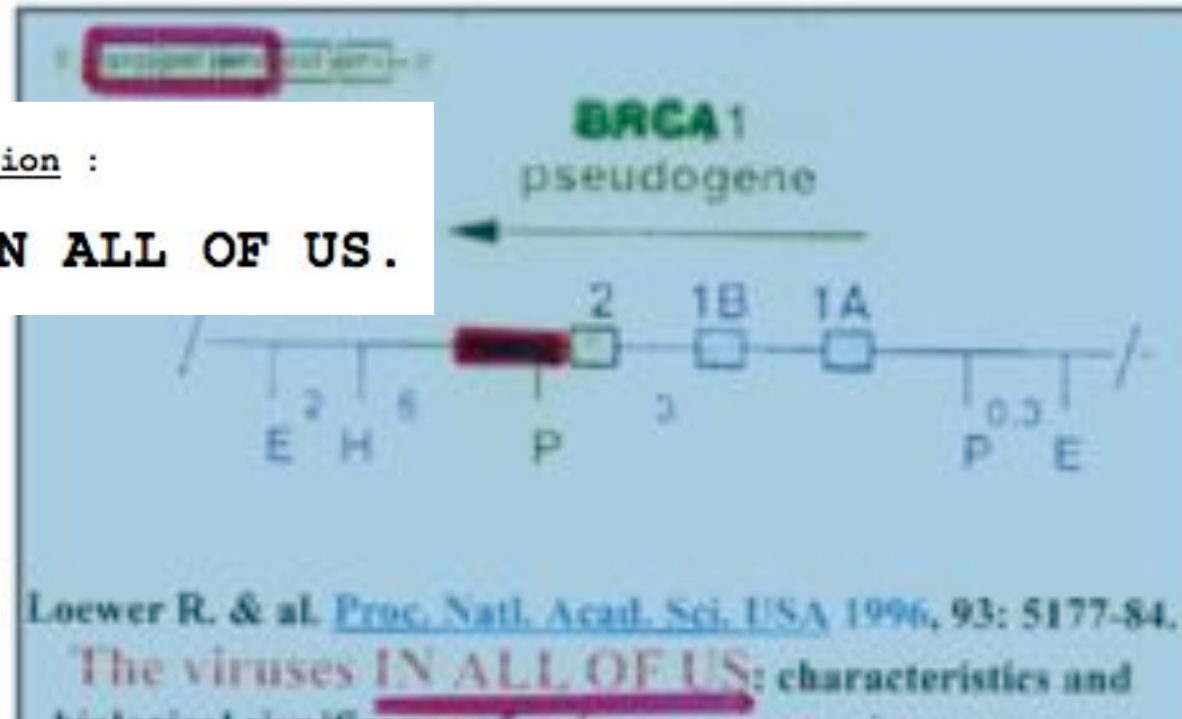
Feng H. & al. (2008) Clonal Integration of a Polyomavirus in Human Merkel Cell Carcinoma. Science 5666: 1096-1100.

Ishikawa K. & al. (2008) ROS-Generating Mitochondrial DNA Mutations Can Regulate Tumor Cell Metastasis. Science 5876: 661-664.

Routes J.M. & al. (2000) Dissimilar Immunogenicities of Human PapillomaVirus E7 and Adenovirus E1A Proteins Influence Primary Tumor Development. Virology 277: 48-57.

Discussion :

**VIRUSES ARE IN ALL OF US.**



We have in our genome  
a viral heritage, that is required for tissue specific differentiation.

The gag, pol & env genes of retroviruses are inhabitants of pseudo-genes.  
And pseudo-genes are involved in **CANCER** expression.

Ting C.N. & al. Endogenous retroviral sequences  
are REQUIRED for tissue-specific expression  
of a human salivary amylase gene.  
Genes Dev. 1992, 6:1457-65.



Structure and phylogenetic analysis of  
 an endogenous retrovirus inserted into the  
 Human Growth Factor gene pleiotrophin.  
 Schaffke A.K. & A. Wellstein.  
 J. Virol. 1998, 72(7): 4065-4072.

Endogenous viral sequences and their potential contribution  
 to heritable virus resistance in plants.  
 Mene M.F. & al., The EMBO Journal 2002, 21(3): 461-469.

endogenous para-retroviruses  
 derived both from single-stranded  
 & double-stranded DNA viruses  
 with 91-98% homology  
 inserted into plant chromosomes  
 normally silent  
 providing viral immunity  
 no sign of infection  
 under a variety of growth conditions



no or few copies integrated      hundreds of integrated copies

RETROVIRUSES  
 are inserted into  
 RESTRICTED TIME- and TISSUE- DEPENDENT EXPRESSED GENES.

TRUE VIRAL GENOMES  
 are located into our chromosomes.

They are defective & non-infective: SILENCED,  
 having new promoters they are CONSTRAINED.  
 BUT they may be expressed in tumour cells.

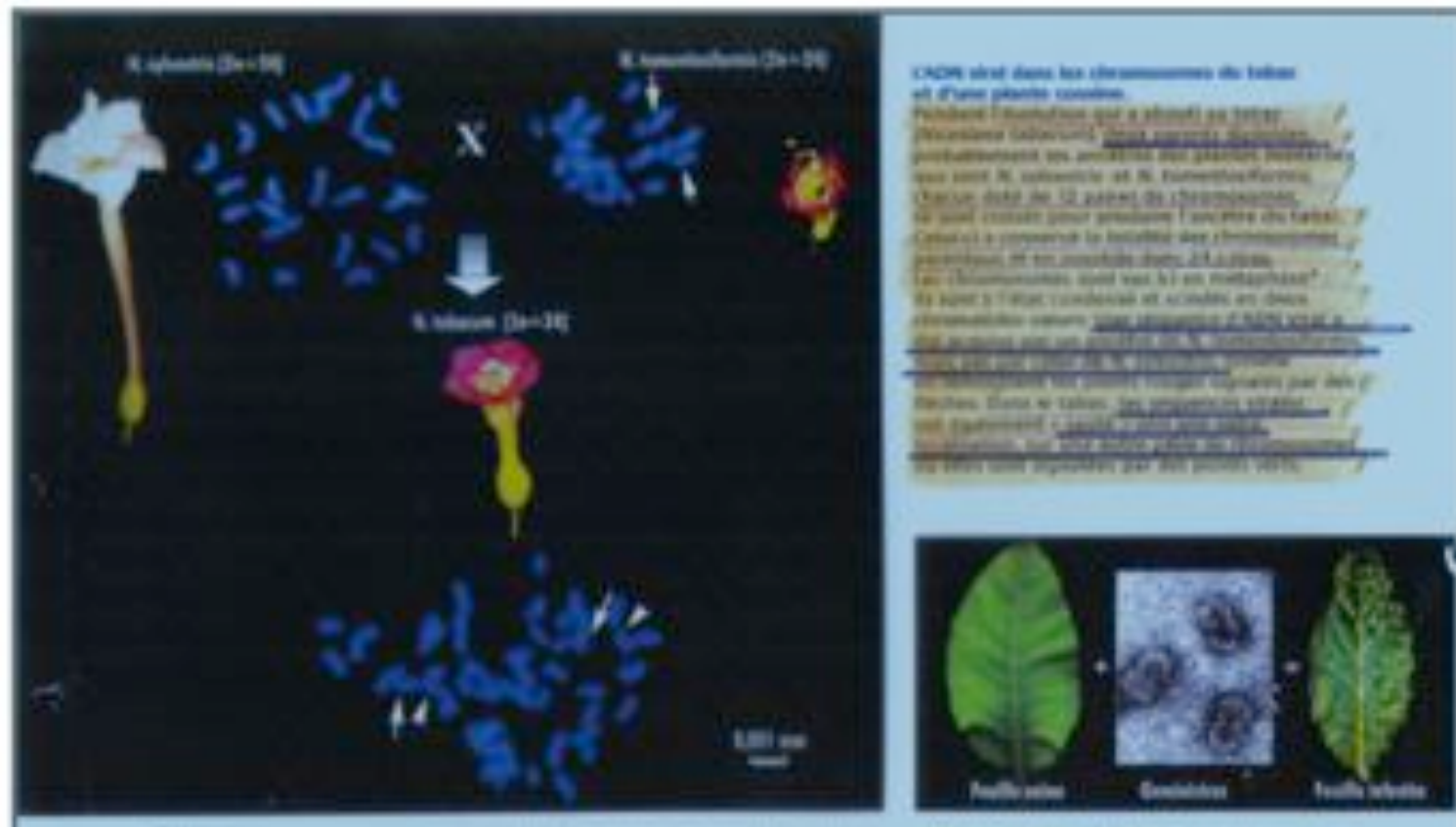
non-infective, replication defective retroviruses  
 with 85% homology to HERV-E  
 of ANCIENT origins, SILENCED  
 having generated NEW promoters!

ENDOGENOUS viral sequences are responsible from VIRAL RESISTANCES in plants.  
 DNA VIRUSES with more than 90% homology with free ones are inserted into plant chromosomes.  
 They provide, through their silenced survival and coordinated reproduction WITHIN the cell  
 and WITH the cell, an immunity against the same viruses relatives.

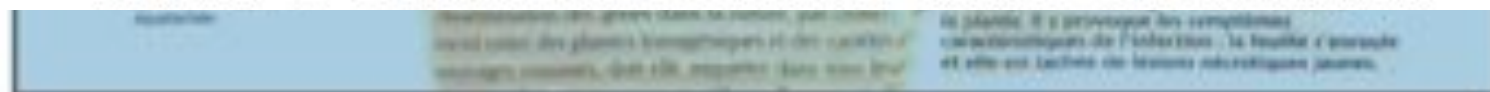
These integrated, silenced but present and still alive, ancient free viruses  
 remain active and may be de-constrained, through inter-species hybridization for example.

in the human genome  
 at least 10,000 copies of viruses of other ones

de-constrained through hybridization  
 or in vitro propagation



The tobacco plant's genome is containing **VIRUSES INHERITED** from the genome of one ancestor species. This DNA has both **jumped from a locus to an other with its multiplication** into the genome. It gives to the plant host an immunity against the same viruses.





Phylogenetic tree of mycobacteria, based on 15S rDNA sequences

Fast growing mycobacteria

Slow growing mycobacteria

Genome rearrangement by replication-directed translocation

Shawlett K.M., Toller & Richard J. COHEN  
Department of Molecular and Medical Genetics, University of Toronto, Toronto, Canada

Micrograph showing several orange, spherical structures, likely Mycobacterium leprae, against a light background.

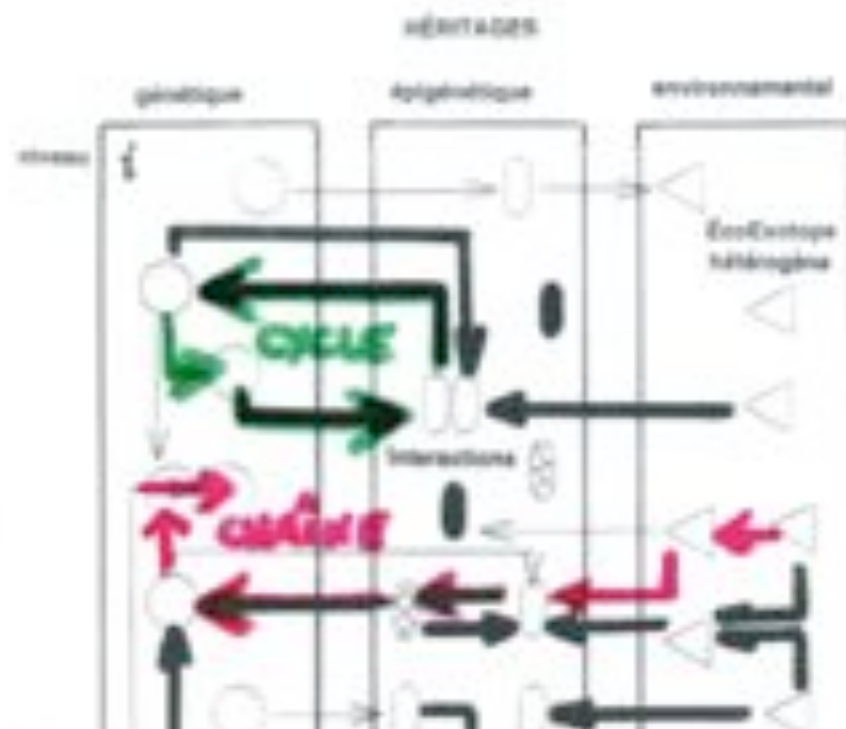
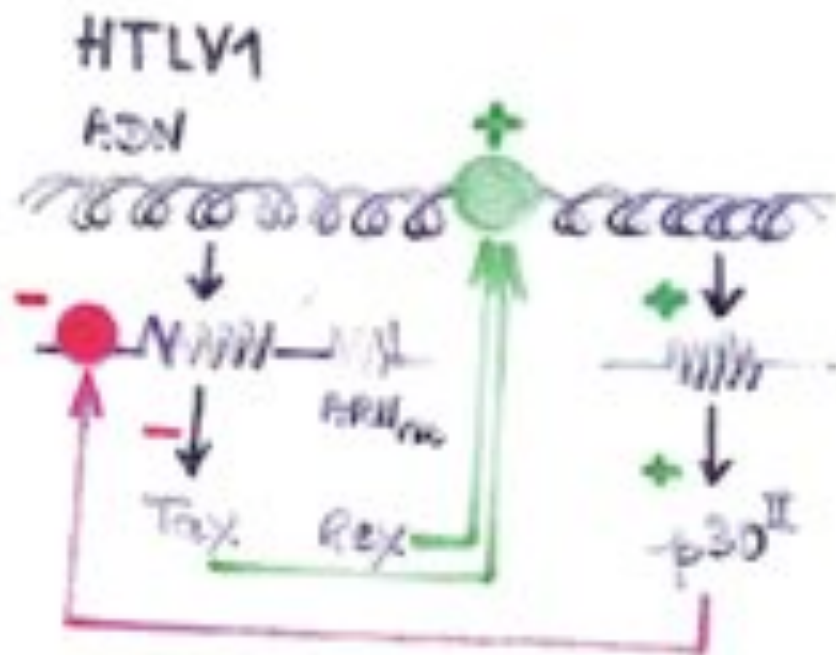
**hidden guests**

**endogenous risks**

Tracing leprosy: an Erb-a remedy?  
LA BOSTON, 05/18/03  
The leprosy pathogen Mycobacterium leprae attacks Schwann cells in the peripheral nervous system, causing them to degenerate. Recent work by Taperoff et al. shows that a direct mechanism of demyelination induced by M. leprae depends on the binding of the 6S...  
Trends in pharmacological sciences, 2002 23(4)

Susceptibility to leprosy is associated with HPAK2 and HPAK3  
BT Ma, A Kishik, VT Nguyen, MO Moroni, C DeFueron, HT Vu, CP Gu, TH Nguyen, HD Nguyen, BK Phan...  
Leprosy is caused by Mycobacterium leprae and affects about 700,000 individuals each year. It has long been thought that leprosy has a strong genetic component, and recently we mapped a leprosy susceptibility locus to chromosome 2 (region 220-228 Mb)...  
PLoS 2004 1(4) 12 "Chromosome 6q25 is linked to susceptibility to leprosy in a Vietnamese population"  
Nature Genetics, vol.33, march 2003

*Mycobacterium leprae* is also containing **HIDDEN ENDOGENOUS RISKS** that are responsible of the rearrangement of its genome and that also allow its survival through the control of the type of relationship between the bacterium and its host.



The RELATIONSHIP between genes and their regulated expression, in HTLV1, are the result of interactions between the ENDOphysiotope and the ecoEXOtope of the virus.

DATA are available on line at: <http://www.afscet.asso.fr/heritage.pdf>

DATA are available on line at: <http://www.afscet.asso.fr/resSystemica/Crete02/bricage.pdf>

<http://www.afscet.asso.fr/heritage.pdf>



héritage = potentiel reçu

temporel

i+1

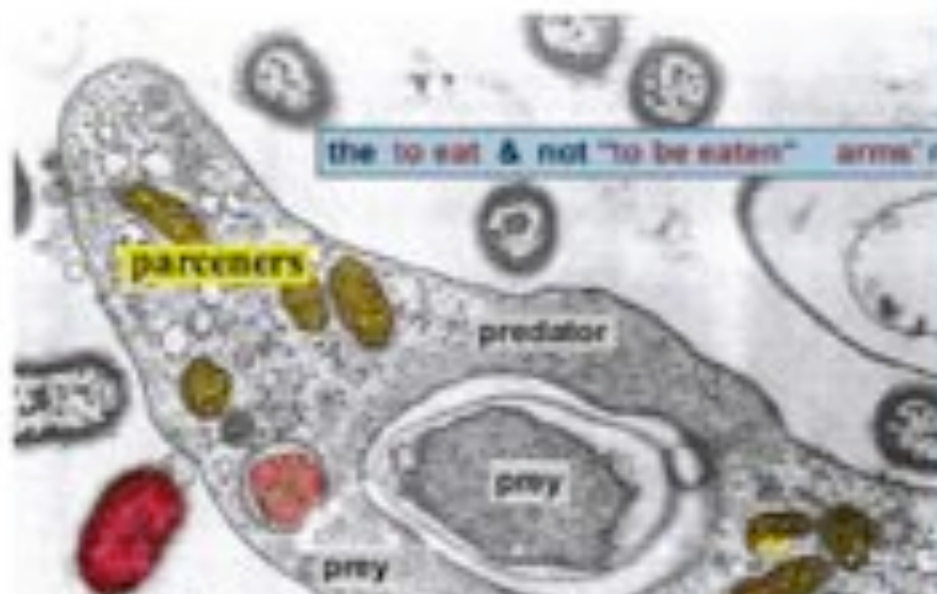
amortisseur de violences

non modifiable

non réductible

interactions directes



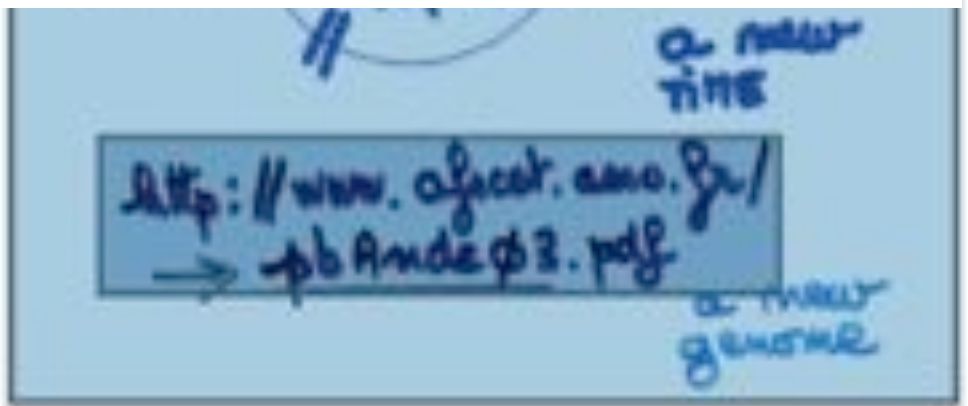


There is **NO DIFFERENCE** between an amoeba and its preys and a bacterio**PHAGE** and its preys. **The INTEGRATION** Of the phage into the genome of the bacterium gives rise to **A NEW WHOLE** in which the virus survives INTO A NEW SPACE and INTO A NEW TIME.

That was the same with the bacteria that NOW are the mitochondria into the amoeba.

The prophage is **not a PROphage** but a gene **parcener** into the bacterial genome, like the mitochondria are organelle parceners **constitutive of** the cell's amoeba.

DATA are available on line at: <http://www.afscet.asso.fr/pbAnde03.pdf>





During its **LIFE CYCLE**,

a cell, usually, is **FIRST** a stem cell S, that **multiplies** giving rise to a clone of cells C, that differentiate D, and finally die.

Only any cells of the germinal lineage eventually survive from a generation to the following one.

**BUT** during the way of its life, the cell may be infected by a virus V, virus which, usually, lyses the hosting cell L.

**BUT**, through apoptosis A, the suicide of the cell kills the virus.

**BUT**, if the cell does not suicide itself, a tumour cell T may merge.

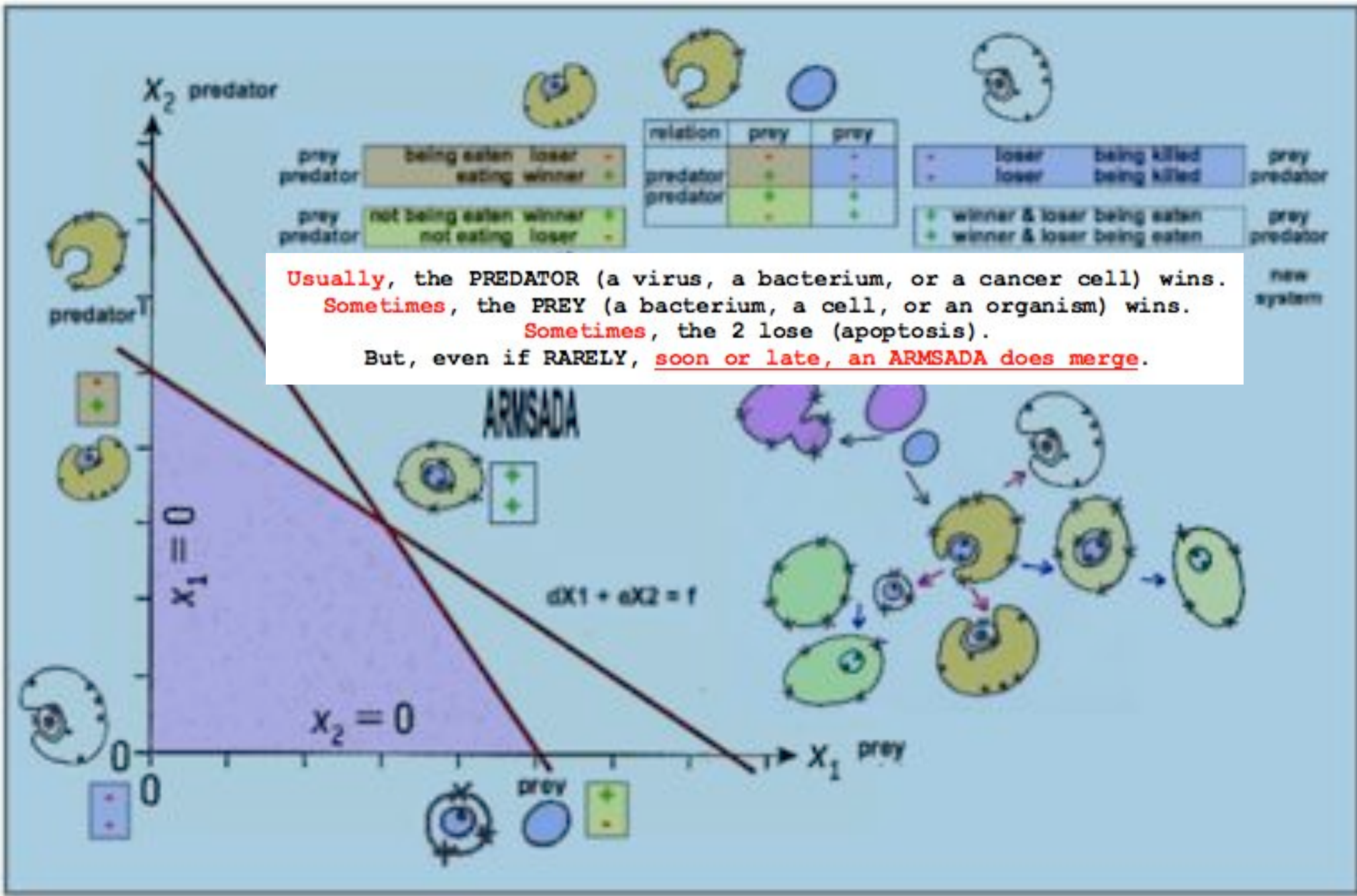
DATA are available on line at: <http://www.afscet.asso.fr/resSystemica/Paris05/bricage.pdf>



A tumour cell may also merge from a **STRESSED CELL**.

I have assumed that there is "a special type of interactions" O, in which **no virus is produced, no cancer cell is merging, BUT A NEW PHENOTYPE** of cell E, **AN EMERGENT WHOLENESS** in which the cell is both **RESISTANT TO VIRUS AND CANCER**.





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.

**CANCER  
Curative Vaccine**

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

**HIV induced AIDS  
Curative Vaccine**



If you will search **on line** with the **KEY WORDS**:  
"stem cell", "curative vaccine" & HIV (in English), or  
"cellule souche", "vaccin curatif" & VIH (en français), you will find  
only 2 references in 2005, and 8 references in 2008,  
BUT all derived from the 2 in French.

the original source :

<http://www.mindien.com/?UJHBBaek4> (file: UESLisboaPBcancerRef.pdf)

the title title : *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. Complementary Data, Figures & References.*

the author/author : Pierre BRICAGE

the pages/pagination : 26 p.

the year/année : 2008

& the book's publication : 7<sup>th</sup> Systems Science European Union Congress Proceedings, Lisbon, Autonomy and Systemic Workshop, Lisboa, Portugal.

the original source : <http://www.mindien.com/?UJHBBaek4> (file: UESLisboaPBHivAidsRef.pdf)

the title title : *Associations for the Reciprocal and Mutual Sharing of Advantages and Disadvantages: Applicative Insights in Prevention or Cure of (HIV Induced) AIDS. Complementary Data, Figures & References.*

the author/author : Pierre BRICAGE

the pages/pagination : 21 p.

the year/année : 2008

& the book's publication : 7<sup>th</sup> Systems Science European Union Congress Proceedings, communication # 8, Lisboa, Portugal.

the original source : <http://www.mindien.com/?UJHBBaek4> (file: UESLisboaPBleproseRef.pdf)

the title title : *Associations for the Reciprocal and Mutual Sharing of Advantages and Disadvantages: Applicative Insights in Prevention or Cure of AIDS, Cancer and Leprous Diseases. Complementary Data, Figures & References. Leprosy, tuberculosis & Mycobacteria.*

the author/author : Pierre BRICAGE

the pages/pagination : 12 p.

the year/année : 2008

& the book's publication : 7<sup>th</sup> Systems Science European Union Congress Proceedings, communication # 8, Lisboa, Portugal.

[ymkxsis1d4.pdf](#)  
of Sharing of Advantages  
ferences. ARMEADA "From  
hole".

Congress Proceedings

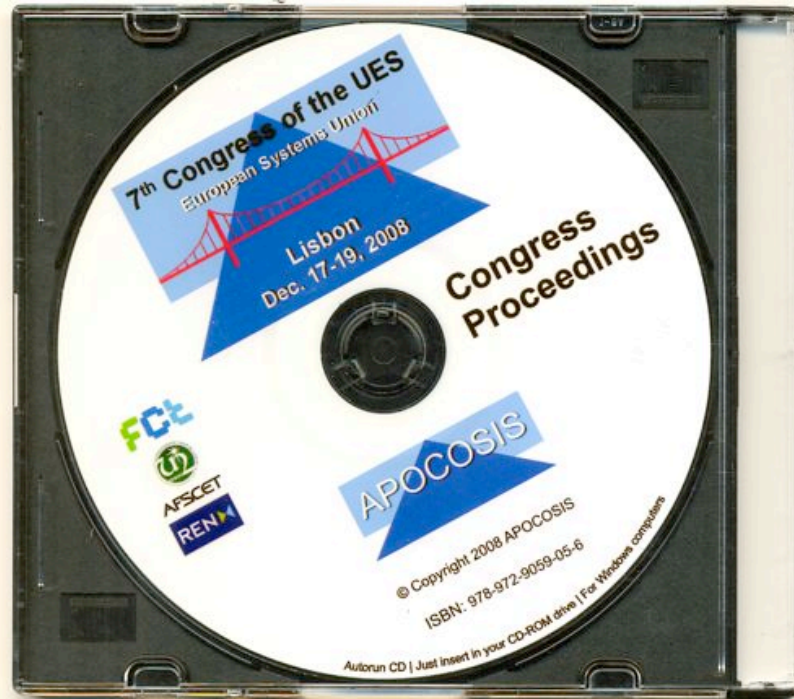
communication # 8, Lisboa, Portugal.



Résultats 1 - 7 sur 7 pour "stem cell" HIV 2005 "curative vaccine".

Résultats 1 - 2 sur 2 pages en français pour "cellules souches" VIH 2005 "vaccin curatif".

Résultats 1 - 8 sur 8 pour "stem cells" HIV 2008 "curative vaccine".



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à disposition de vaccin curatif (vaccin Pasteur), le patient .... remédiées par des transfusions de cellules souches auto- ...

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hes" VIH 2005 "vaccin curatif" - ne correspondent à aucun document.

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Résultats 1 - 3 sur 3 pages en français pour "cellules souches" VIH 2007 "vaccin curatif".

Résultats 1 - 5 sur 5 pour "stem cells" HIV 2006 "curative vaccine".

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## CANCER CURATIVE VACCINE

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1. texte écrit CANCER & autonomie <http://www.afscet.asso.fr/resSystemica/Lisboa08/bricage1.pdf>

2. texte écrit AIDS & CANCER curative vaccines <http://www.afscet.asso.fr/resSystemica/Lisboa08/bricage2.pdf>

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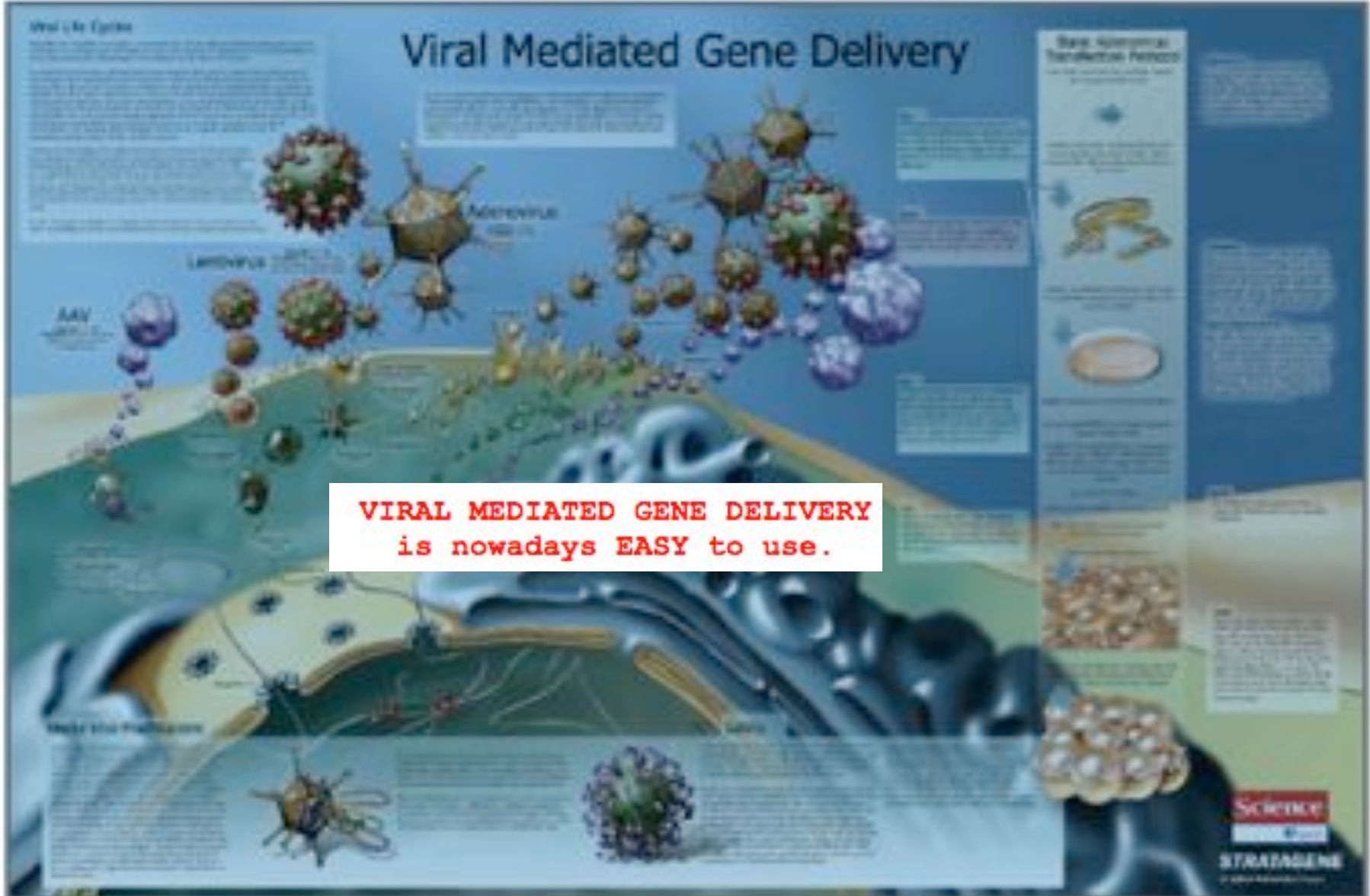
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# Viral Mediated Gene Delivery



**AAV Life Cycle**  
Adeno-associated virus (AAV) is a non-replicating virus that has become a popular vector for gene delivery. It is small, stable, and can cross the blood-brain barrier. AAVs are naturally associated with Adenovirus and Herpesvirus. The AAV life cycle involves attachment to a cell, penetration into the cytoplasm, and transport to the nucleus where the viral genome is integrated into the host genome.

**Adenovirus**  
Adenovirus is a double-stranded DNA virus that is highly stable and can infect a wide range of cells. It is commonly used for gene delivery because it can enter cells through endocytosis and deliver its genome to the nucleus. However, it can also cause immune responses and has a limited capacity for packaging foreign DNA.

**Gene, Nonviral Transfection Methods**  
Nonviral methods for gene delivery include electroporation, liposomes, and microinjection. These methods are generally safer than viral methods but often have lower efficiency and may require the use of toxic reagents. Electroporation uses electrical pulses to create temporary pores in the cell membrane, allowing DNA to enter. Liposomes are lipid-based vesicles that fuse with the cell membrane to deliver DNA. Microinjection involves directly injecting DNA into the cell.

**VIRAL MEDIATED GENE DELIVERY is nowadays EASY to use.**

**AAV Gene Transduction**

AAV gene transduction is a highly efficient method for delivering genes to target cells. It is particularly useful for gene therapy because AAVs can infect non-dividing cells and integrate their genomes into the host genome. This allows for long-term expression of the delivered gene. AAVs are also used in research to study gene function and to create transgenic animal models.

**Adenovirus Gene Delivery**

Adenovirus gene delivery is a widely used method for transient gene expression. It is highly efficient and can infect a wide range of cell types. However, it is limited by its immunogenicity and its inability to integrate into the host genome. Adenovirus vectors are often used for short-term gene expression in cell culture and in animal models.

**Science**  
STRATAGENE