Is the new Wuhan Chinese coronavirus an avatar of a genetically engineered coronavirus to produce a curative AIDS vaccine? 1. Curative vaccines: what technology should be implemented?

Pierre BRICAGE
Health and Social Sciences, UPPA Université de Pau et des Pays de l'Adour,
Living Systems Evolution, UTLA Université du Temps Libre d'Aquitaine, Pau, France, Europe
pierre.bricage@univ-pau.fr
Association Française de **Science des Systèmes Cybernétiques, Cognitifs et Techniques**, Paris, France
http://afscet.asso.fr
http://www.afscet.asso.fr/pagesperso/Bricage.html

Abstract * Is the new Wuhan Chinese coronavirus an avatar of a genetically engineered coronavirus to produce a curative AIDS vaccine? Curative vaccines: what technology should be implemented?

Usually, common cold is not a danger, but a new strain of coronavirus is killing man species. Why? This virus could not have emerged spontaneously by natural mutations and wild strains recombinations, it is a genetic chimaera with artificial insertions of modified genes, an engineered genome of a coronavirus within a capsid of a Human Immunodeficiency Virus (HIV), which has been probably created to be a curative vaccine of AIDS.

Isn't it another more secured methodology to definitely cure sick people?

Keywords: 2019, AIDS, common cold, coronavirus, curative vaccine, genetic chimaera, genome engineering, Genetically Modified Organism GMO, host cell, Human Immunodeficiency Virus HIV, Wuhan

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Resumen ¿Es el nuevo coronavirus chino de Wuhan un avatar de un coronavirus modificado genéticamente para fabricar una vacuna curativa contra el SIDA? Vacunas curativas: ¿qué tecnología debe aplicarse?

El resfriado es una afección leve, sin embargo un nuevo coronavirus activa en el ser humano adulto mayor un gran catarro, que puede ser mortal. ¿Por qué? Este nuevo tronco viral está de entrada "humanizado" y el tratamiento de la enfermedad responde a los medicamentos anti-VIH. El virus está caracterizado por un genoma modificado que no puede proceder de mutaciones y de recombinaciónes genéticas aparecidas naturalmente. Es una quimera genética que combina estructuras (proteínas de envoltura) y propiedades funcionales (proteasa) a la vez de un coronavirus (el genoma) y el virus de Inmunodeficiencia Humana (la cápside). ¿Cómo este virus artificial concebido por ingeniería genética para ser una vacuna curativa del SIDA y sólo curar a los enfermos fue liberado en la naturaleza?

¿Puede ser considerada otra metodología para construir una vacuna curativa del VIH más controlable?

Palabras claves: *2019, célula huésped, coronavirus, ingeniería genética, Organismo Genéticamente Modificado, catarro, SIDA, vacunas curativas, Virus de Inmunodeficiencia Humana VIH, Wuhan.*

Résumé Le nouveau coronavirus chinois de Wuhan est-il un avatar d'un coronavirus génétiquement modifié pour fabriquer un vaccin curatif du SIDA ? Vaccins curatifs : quelle technologie mettre en œuvre ?

Le rhume est une affection bénigne pourtant un nouveau coronavirus déclenche, chez l'homme adulte âgé, un très très gros rhume qui peut être mortel. Pourquoi ? Cette nouvelle souche virale est d'emblée "humanisée" et le traitement de la maladie associée répond aux médicaments anti-VIH. Le virus est caractérisé par un génome modifié, qui ne peut pas provenir de mutations et de recombinaisons génétiques apparues naturellement. C'est une chimère génétique associant des structures (protéine d'enveloppe) et des propriétés fonctionnelles (protéase) à la fois d'un coronavirus (le génome) et du Virus de l'Immunodéficience Humaine (la capside). Comment ce virus artificiel conçu par génie génétique pour être un vaccin curatif du SIDA, et traiter uniquement les malades, a-t-il été "libéré" dans la nature ?

Une autre méthodologie de construction d'un vaccin curatif du VIH plus contrôlable est-elle envisageable ?

Mots clés : 2019, cellule hôte, chimère génétique, coronavirus, génie génétique, Organisme Génétiquement Modifié OGM, rhume, SIDA, vaccination curative, Virus de l'Immunodéficience Humaine VIH, Wuhan

Introduction

Human coronaviruses are usually considered harmless because they only cause common colds, non-serious diseases. But this is no longer the case with the two recent deadly epidemics of SARS and MERS, due to wild, non-human coronaviruses, whose genome had been able to acquire modifications, allowing them to cross the barrier of species and infect human respiratory cells.

I. A very, very bad, deadly cold.

Coronaviruses are transmitted by air, in close human contact, through inhalation of droplets emitted during sneezing or coughing, and through bodily contact with contaminated surfaces. In the open air and on dry surfaces, coronaviruses survive only for a few hours, but in aqueous environments they can survive for several days.

1. The provisional consensual history of the epidemic

On December 2019, the 30th, LI Wenliang, an ophthalmologist at the Central Hospital of Wuhan (Mainland China), announced to his Chinese colleagues the appearance of patients with a pneumonia resembling a resurgence of SARS (Severe Acute Respiratory Syndrome) which caused 349 deaths in China from 2002 to 2003. Some patients had already been affected since the 1st of December. There was no apparent epidemiological link between 13 of the 41 patients and those identified later, whose contamination was presumed to be from the Wuhan central market (Huang et al. 2020, Zhou et al. 2020).

On January 2020, the 4th, the pathogen was identified as neither influenza nor avian influenza, nor SARS or MERS (Middle East Respiratory Syndrome), but as a new viral strain that "included" both SARS and the common cold. On the 7th of January, the trail of SARS, - a lethal disease among people older than 60 years -, was ruled out with the identification of a new type of coronavirus, which was officially announced by the Chinese authorities on the 18th of January. The majority of the sick (residents of the Hubei Province, at Wuhan) has visited the city's main market.

The symptoms were those of an acute respiratory infection (fever, cough, very high not-common cold), which resulted in the death of fragile or elderly patients.

On January the 20th, Thailand, South Korea and Japan reported cases of the same coronavirus in patients who had neither stayed in Wuhan nor visited people from Wuhan. The new coronavirus was recognized as readily transmissible from human to human. On the 23rd of January, the city of Wuhan (the seventh most populated city in China, with its twelve million inhabitants) was placed under quarantine. Wearing a respiratory mask was mandatory.

The viral incubation duration was under-estimated as being of 14 days.

Two other Chinese cities in the Hubei were also placed in confinement. In every major Chinese city (Beijing, Chengdu, Chongqing, Guangzhou, Hong Kong, Shanghai, …), all districts were gradually closed and it was forbidden to move from one district to another without a formal permission. On the 26th of January, multiple analyses showed that the Wuhan central market was not the only source of contamination. Many other contaminations unrelated to Wuhan were identified; the first was likely to have occurred early, in November 2019. Where? Why? How?

On January the 31st, the threshold of 10,000 contaminated persons was officially exceeded in China and a similar increase of cases of contamination was announced in 20 countries. The World Health Organization (WHO) declared an international public health emergency. After being himself contaminated on January the 10th, the first whistleblower, LI Wenliang, died on February the 7th. Nearly 30,000 patients were officially recognized in China.

The WHO announced a worldwide shortage of masks.

Since 2020 February the 4th, thousands of passengers cruising off Yokohama (Japan), among which 456 have been tested positive for the new coronavirus, have been quarantined. Concerned about the spread of the epidemic, Countries, like Canada, the United States and France, decided to repatriate their nationals. On February the 18th, the epidemic caused more than 73,000 patients, of whom 1,873 died. The United States, Australia, New Zealand and Papua New Guinea were closing their ports and airports to passengers from Asia. Mongolia, Nepal, Russia were closing their land borders with China. On February the 22nd, there were at least 2,345 deaths in mainland China, representing 3.1% of the identified symptomatic patient population.

On February the 28th, the WHO raised the level of pandemic risk to "very high" *due to the "difficulty in identifying cases because of non-specific symptoms and undetected transmission potential"*. However, "Past experience with coronaviruses and our current understanding of the virus do not indicate that common pets are spreading the disease or making people sick." said the Director of the WHO.

On the 29th of February, more than 85,900 cases of sick people and 2,941 deaths were officially recorded in 61 countries. On March 2020 the 1st, the American state of Washington, - where, in January, a man of about thirty years and returning from the city of Wuhan, had been tested positive for the virus, following the outbreak of the new coronavirus- , declared the state of emergency.

The local spread of the infectious disease from one person to another became evident.

Surely the virus was immediately "humanized".

2. The consensual, temporary characteristics of the new disease: the typical profile of patients.

All symptoms are similar to flu: fever, stiffness, generalized fatigue, shortness of breath, cough (Huang et al., 2002). Only biological tests allow a differential diagnosis. However, the 2 diseases do not affect the same groups of population. Males are more affected (51.4%) than females (48.6%) and they die more frequently: of the first 1,023 deaths, 63.8% were men and 36.2% were women. Young people are "spared": out of 44,672 confirmed cases, only 2% of patients are under 20 and 10% under 30. Among these 1,023 first deaths there is only 1 pubescent child. Seasonal influenza usually affects children and the elderly much more. Here too, age is a predisposition factor: 30% of the affected people aged between 60 and 80 die, but also 12.8% for those aged between 40 and 60. However, 80.9% of those affected have only a large cold, typical of a common human coronavirus, and they recover less or more quickly. The virus is much less aggressive than those of SARS (identified in China in 2002) and MERS (identified in Saudi Arabia in 2012). In 13.8% of cases the virus causes severe pneumonia with shortness of breath and "only" 4.7% of patients have severe respiratory failure with septic shock and multi-organic failure. As for the flu, being previously affected by another condition, such as diabetes, hypertension, cancer, chronic disease or immunodeficiency, is an aggravating factor, which multiplies by 2 to 3 the death risk of death. One important feature of the disease due to the new virus is the presence of a large amount of very sticky mucus in the small respiratory tract of patients, says ZHONG Nanshan, a famous Chinese specialist in respiratory diseases, at a press conference on the 27th of February. It's a very big cold,... a deadly one!

3. Paradoxical information resulting from the treatment of patients

Common signs of coronavirus infection are fever, cough, breathing difficulty, gastric symptoms and diarrhea. These symptoms can be treated, but there are none specific anti-viral drugs, preventive or curative vaccines. Severe cases can result in death by pulmonary embolism and/or renal failure, with or without heart and nervous damages as the alterations observed in AIDS.

As early as the 3rd of February 2020, the more severe cases in Wuhan were treated with combinations of drugs commonly used against flu (such as favipiravir, a guanine analogue, which is a RNA polymerase inhibitor of riboviruses) and AIDS (kaletra, acyclovir, ritonavir), or even with inhibitors of the HIV reversing transcriptase (remdesivir) - which is absent from coronaviruses -. Why such choices? The disease effectively responded to the treatment with these usual AIDS drugs and the Chinese hospital doctors have immediately used anti-AIDS drugs. Why? Therapeutic lucidity or social panic? Is it because the topology of the coronavirus protease has been modified to resemble that of HIV? Indeed the cleavage sites (amino acid sequences), and in particular those into the protein S, which are recognized by the coronavirus protease, are the same as those usually recognized by the HIV protease. However, the usual protease of HIV is an aspartic-protease whereas the usual protease of coronaviruses is a cysteine-protease.

Protease inhibitors used to treat AIDS (liponavir and rotinavir) have a three-dimensional symmetry optimized for the active site of aspartic-proteases, which is not at all that of cysteine-proteases. The catalytic pocket of the HIV protease is naturally absent from the catalytic site of coronavirus proteases. Why would these protease inhibitors (such as mozenavir) affect the chymotrypsin and papain activities of the new coronavirus? Softwares for representing the spatial three-dimensional structure of a protein (3D viewing) indicate that the protease of the new coronavirus is completely different from that of all other known coronaviruses.

Was the Wuhan coronavirus genetically transformed to look like the HIV?

The changes observed in its protein sequences (3 inserts coming from gp120 HIV and 1 insert from HIV gag) all increase the density of positive charges on the surface of these molecules. Such a non-random change involves the use of a protein engineering software tool to screen the genetic modifications prior to doing them. Genomic inserts 1 and 2 in glycoprotein S (each of 18 nucleotides, each coding for 6 amino acids) are completely identical to the corresponding HIV sequences. The genomic inserts 3 (36 nucleotides corresponding to 12 amino acids) and 4 (24 nucleotides corresponding to 8 amino acids) also closely resemble the corresponding HIV sequences.

These inserts, which can only come artificially from the corresponding sequences of the HIV genome, are all present at the active site of the S protein (which is a homo-tri-mere protein). The new protease of the new coronavirus also has a ternary symmetry, different from that of the usual coronavirus proteases. The structure of its active site is similar to that of the HIV protease and is accessible to the same substrates or inhibitors.

Then, the plasma of the healed persons was used by doctors to treat the sick ones. As the coronavirus carries antigenic proteins on its surface, spontaneously healed people probably secreted antibodies against the viral capsid (as in the case of MERS) and, in particular, against the modified protein S, which is biomimetic of the gp120 protein of HIV. Didn't these phenotypically resistant persons also become HIV-seropositive?

The traditional Chinese medicine has experienced a considerable repertoire of drugs, among which some are able to inhibit viruses infection. Knowing their mode of action would provide additional guidance not only in the struggle against the new virus but also in regard to its specific properties.

II. What are the functional characteristics of the new coronavirus?

Coronaviruses do circulate among animal reservoirs, such as bats (Hu et al., 2015), and can be transmitted to humans and their domestic animals (dromedaries, with MERS in 2012), wether directly (SARS) or indirectly (civet, for SARS in 2002, cat for feline enteric coronavirus and feline peritonitis), by air or in close contact (O'Connor et al., 2001).

1. The usual and *"common"* biological characteristics of common cold viruses

Adenoviruses - carcinogen viruses - have a DNA genome while a lot of both new emerging viruses - such as human immunodeficiency virus (HIV) or Ebola virus - and re-emerging ones - such as influenza viruses and coronaviruses - have an RNA genome; usually a single stranded one. That is also the case for other viruses such as the hepatitis C, West Nile fever, polio and measles viruses, which are very disabling, carcinogenic or deadly.

The capsid of these RNA viruses is always surrounded by a membrane envelope which is rich in lipids and glycoproteins: Envelope protein (E), Membrane protein (M), Spike protein (S), and, for some, Hemagglutinin Esterase (HE). These proteins are necessary for both the virus protection and entry into its host cell. The capsid ("protective box of the genome") contains proteins or/and enzymes necessary for the protection of the viral genome (Nucleocapsid N of coronaviruses) as well as its cytoplasmic replication (coronavirus) or its nuclear integration (retro-viruses such as HIV).

Rhinoviruses, para-influenza viruses and syncytial respiratory viruses are typically associated with common cold, which usually heals naturally within 7 to 14 days. As with the seasonal flu, past immune responses protect none at all against new emerging strains but only from old viral strains and eventually against very few new ones and only if there are common cross-linked antigenic interactions between the old and new invading strains.

Because of the constant emergence of new viral strains, you can get a cold again and again during all your life. But usually you don't die. Influenza (types A and B) and para-influenza, syncytium respiratory viruses, SARS or MERS coronaviruses as well as adenoviruses are associated with more or less severe pneumonia. As an intracellular parasite organism, all these viruses, like any other, act by hacking the cellular metabolism, which is diverted for the production of a viral offspring. The viral particles of a coronavirus have a diameter of about 100 nanometers. An infected cell, with an approximately 10 micrometers diameter, can thus release an harvest of thousands of viral particles.

The mutation rate of a single-stranded RNA virus often is very high - in the order of 1 per 1000 (a rate that is 10 to 100 times higher than that of the DNA viruses) -, so each released viral harvest always contains mutant viruses. The longer a virus circulates in a population, the more mutations it accumulates. However, the virus was "humanized" from the outset and the sequenced genomes are very homogeneous; they differ only by very few nucleotides (Ceraolo & Giorgi, 2020). The genome is stable. Why such a thing?

The first genome sequencing of a RNA virus (ribovirus), the MS2 bacteriophage virus, was done in 1976. Riboviruses have very high one-point mutation rates because their replication is error-sensitive and they do not have a specific RNA polymerase to detect and correct errors. The genomic organization of all coronaviruses (alpha-coronavirus, beta-coronavirus, gamma-coronavirus, delta-coronavirus) is the same. Most of the genome (2/3) consists of 2 coding sequences (the Open Reading Frames ORF1a and ORF1b) which encode the replication and transcription viral enzymes. The rest of the genome codes for the 4 structural proteins (E, M, N, S) and a varied set of proteins (called accessories, but that are essential for viral diversity and evolution) specific to each viral genus or species. The genome of only a few coronaviruses naturally encodes the Hemagglutinin Esterase.

The HE and S glycoproteins, which are usually arranged in di- and tri-meres respectively, have a very definite spatial structure, which includes potential glycosylation sites: 9 for HE and 21 to 35 for S.

2. Special features of the new coronavirus

The new virus is distant from bats coronaviruses and there is no evidence of an intermediate host between humans and bats, although the snake and pangolin have been proposed in that order. Only an inter-human transmission is well documented. On the 30th of January 2020, two complete sequences of the genome of the new coronavirus, taken from a couple of sick French people, were deposited on the platform of the Global Initiative on Sharing All Influenza Data (GISAID), which was originally developed for tracking the genetic evolution of influenza viruses (which is essential for the annual re-composition of influenza preventive vaccines), and where a coronavirus page has been created. About 20 sequences were already present and they are very close together. This lack of genetic diversity indicates that the new coronavirus did not need to mutate to adapt to and spread into the human species.

A common cold is more or less disabling, but is never fatal. Seasonal influenza can be fatal, with a mortality rate of around 0.1% of those affected. The swine flu is much more fatal. SARS and the Spanish flu had a mortality rate of 10%, which is 100x more than that of the seasonal flu. The MERS is even more fatal, and the Ebola virus disease exceeded mortality rates of 50%. Estimates for the Wuhan coronavirus range from 1.5 to 3.5 infected persons per person infected, for the transmission rate, and from 0.1 to 5% for their mortality. Its contagiousness is of the same order as the usual one for common colds and seasonal flu.

The pathogen is neither the one of influenza or avian influenza, nor that of SARS (Severe Acute Respiratory Syndrome) or MERS (Middle East Respiratory Syndrome). It is a new strange strain, which is an intermediate between SARS and MERS strains, between influenza and rhinovirus, which seems to "include" SARS and the common cold. The sequencing of this (emerging?) coronavirus indicates that the catalytic sites of the 4 viral enzymes have a strong resemblance to those of the SARS and MERS viruses, which are often used in research laboratories.

The coronavirus genome encodes 4 enzymatic, non-structural proteins: a protease 3-chymotrypsin, a protease papain, an helicase and a dependent RNA-RNA polymerase. Are they, as *a priori* expected, similar to those encoded by the SARS and MERS virus genomes? Not at all!

With 4 'mutations' by inserting specific nucleotide sequences, the viral strain structural proteins does not resemble any other known genome sequences. 2 of these insert mutations are in ORF1a and 3 of these insert mutations are in ORF1ab. These mutations do completely change the amino acids of the corresponding proteins (Beal et al., 2020). The surface of the viral capsid protein thus possesses the equivalent of the HIV glycoprotein 120, allowing it - just as it allows the HIV capsid - to attach itself to CD4 and CCR5 membrane receptors in lymphocytes. Such insertions can only result from a genomic engineering operation directed and guided by a genetic engineering software tool and not at all from an accidental, gradual or cumulative process of natural selection in the wild.

3. Consensual false ways

In 2002, the SARS virus came from a species of bat virus; a bat species was the reservoir, and the virus was reportedly transmitted to humans by the civet (a small wild mammal sold on local markets) as the vector. Two mutations had allowed the civet SARS virus to be transmissible to humans, but it was not known how it had gone from the bat to the civet. Natural human coronaviruses are very close to those of domestic animals, such as cattle (O'Connor et al., 2001) or camelids and horses, while those of SARS and MERS were close to bat coronaviruses (Hu et al., 2015).

In 2017, 7% of 1,067 bats studied in China were virus carriers and 73 coronaviruses were identified. For more than 8 years, Chinese research teams have captured more than 10,000 individuals of various species of cave bats and analyzed their feces and blood. More than 500 new coronavirus species were identified, including about 50 SARS-related species. But just because a genetic resemblance does exist between two strains, this does not necessarily indicate the same provenance. Even if they contain rabies virus, Ebola virus and dozens of coronavirus species without being sick, and even if they are consumed by humans, why should bats necessarily be involved as reservoirs or vectors? The RNA genome of the new coronavirus is 89% similar to that of SARS-related coronaviruses found in bats of the species Rhinolophus sinicus and identified in 2005. The nucleotide sequence of the ORF1 subunit of the new virus is only 68% identical to that of the SARS virus, which does indicate a kinship, but not necessarily the same origin, or even a specific origin. Couldn't a 96% genetic background similarity be obtained from a laboratory strain which would originally be derived from a wild virus strain? Surely it could.

III. What is the most probable origin of the new coronavirus?

At a worldwide scale, within the 4 circulating human coronavirus strains, 2 are phylogenetically very close (229E and NL63), yet they inhabit very different *"ecological niches'* (Dijkman & van der Hoek, 2009). They use different input receptors to enter their specific host cells. Both are responsible for a heavy common cold in healthy adults, but one is associated with croup (diphtheria laryngitis) in children.

On the 19th of February 2020, a group of 27 leading scientists from 9 countries outside China condemned conspiracy rumors related to the release of this new coronavirus from the Wuhan Center for Disease Control and Prevention's (WCDCP) High Security Laboratory (a P4 laboratory, built the same as the one of Bio-Mérieux, in Lyon, France), where researchers are working on bat coronaviruses, and which is located only a few hundred meters from the Wuhan central market, the "initially assumed" location of the outbreak.

1. The real "non-consensual" tracks

The current coronavirus is phylogenetically very far from the civet's SARS virus. And all samples tested are very genetically homogeneous. Which is very surprising. Why?

The genome of the Wuhan coronavirus contains insertions similar to sequences of the HIV genome, i.e. 4 insertions into the sequence of the spicule glycoprotein S, which are not present in any other coronavirus. The corresponding amino acid residues are similar to those of the gp120 and gag protein sequences of HIV-1 (Pradhan et al., 2020). However, it is absolutely unlikely that a virus could naturally acquire these insertions wether that is by genetic mutation or recombination (Paraskevis et al., 2020). The inserts are discontinuous but not randomly inserted, the 4 inserts converge to constitute the site of binding of the virus to its receptor. These sequences represent less than 1% of the gene. They are not single mutations but "targeted" insertions.

The inserted sequences are present in all analyzed clinical isolates. The analysis using the Blastp software showed that all insertions aligned with the genome of the gp120 surface glycoprotein of the HIV shell and the HIV-1 gag complex. The HIV glycosamines (the gag complex) are involved in both binding the virus to the host cell membrane, packaging the virus and building viral particles. The gp120 protein provides the recognition of the host cell CD4 receptor, creating a high affinity binding site for a chemokine co-receptor. The S protein of the new coronavirus shares the closest ancestry with SARS GZ202, so their protein sequences were compared using Multialin software. This allowed to highlight insertions: GTNGTKR (IS1), HKNNKS, HKNKR (IS2), GDSSSG (IS3) and QTNSPRRA (IS4), which are not only absent from any S protein sequence of SARS but have also never been observed in any coronavirus. This is extremely astonishing; it is totally unlikely that a wild SARS virus could acquire, by spontaneous mutations or interspecific genetic recombinations, such "targeted" insertions in such a short time (since 2003 for SARS, 2013 for MERS), and especially not through a HIV recombination event (Olabode et al., 2019).

Even if the genome of the new coronavirus is 96% identical to that of some bat coronavirus, or even if it were 99% identical to that of another animal, such as pangolin (the positive rate of beta-coronavirus presence is 70%), these coronavirus (from bat or pangolin) have no surface protein recognition of human receptors, and never got spicules of HIV type! How could the new coronavirus thus acquire the ability to infect a human host cell (Dijkman & van der Hoek, 2009)?

The new coronavirus and the HIV-1 are similar in size. Artificial, targeted changes in each other's genome will enable it to acquire this capacity. The new coronavirus has a coronavirus genome, modified by inserting HIV sequences, allowing it to be packaged in a HIV bio-mimetic capsid. Why would somebody build such a virus?

Since the SARS and MERS epidemics, advances in biotechnology have accelerated the study of coronaviruses for vaccine development. Weakened coronaviruses have been created as candidates for potential vaccines, both because of their assumed safety and their easy genetic manipulation. Why not use them to develop a curative or even a preventive vaccine against HIV infection and AIDS?

Nevertheless, in addition to the novel recognition properties (derived from the HIV genome part) of human CD4 and CCR5 receptors of lymphocytes, as a genetically modified organism the chimeric virus retains some physiological properties of common coronaviruses. The human Angiotensin Conversion Enzyme 2 (ACE2) thus remains a membrane cell receptor which is recognized by its surface glycoprotein (Du et al., 2009). This increases its range of human host cells, which may explain why the disease can suddenly worsen on the seventh day, when this date would usually correspond to the end of a common cold. That is, if it was a cold...

2. Why so many drastic emergency health and societal measures?

The contagious status of the new coronavirus disease appears to be low (1.4-2.5); lower than that of the influenza (2-3), SARS or AIDS (2-5) diseases, and close to the Ebola disease. His mortality seemed low; according to the WHO, the number of deaths reported in 1 month of epidemic was only 56 for the new coronavirus, against 64.5 and 68.6 for the previous SARS and MERS, 904 for the Ebola virus disease, 39,167 for the seasonal flu and 7,482 for measles. And rabies, if untreated by its curative vaccination specific procedure, is 100% fatal.

Despite its preventive vaccination, which is not compulsory though, the flu reaches about 4,000,000 people annually, among which 470,000 die. The high mortality of the Ebola virus helps to stop its spread easily by confinement. But how to stop the spread of an asymptomatic cold, a cold that can spread unnoticed? All our lives, we have colds whose severity depends on our individual sensitivity or resistance. This explains why, in the case of this "hybrid" virus, the duration of the incubation period is hyper-variable... from 2 days to 37 days, depending on the listed cases, and even sometimes without any apparent symptoms! Obviously, it also depends on every individual epidemiological past.

Because it was originally designed for curative AIDS vaccination, this modified virus has the infectivity properties of both a coronavirus and an inactivated HIV! The HIV contagiousness can be limited by preventive measures (condoms, drugs), but with the exception of the rabies virus, the direct and indirect mortality of HIV is the highest, comparable to that of the Ebola virus. Hence the establishment for caregivers of a level of health security comparable to that used to deal with the Ebola virus epidemic. All the more necessary since though it is easy to identify a patient infected with the Ebola virus, it may be impossible to identify an infected asymptomatic person, who is indeed a vector of the coronavirus!

How and why did this modified coronavirus escape from the research laboratory where it was created?

3. How was this virus, first "intelligently built", then "unintentionally released"?

Like any genome, viral or not, the genome of the new coronavirus contains "hot spots": hyper-variable areas where the probability of mutation or recombination is very high (Ceraolo & Giorgi, 2020). But these areas are located mainly in the specific viral protein sequences.

What about the main ORF sequences common to all coronaviruses when compared to HIV?

Since 2000, Canada and the United States have been undertaking research on coronaviruses that cause adverse conditions for intensive livestock (O'Connor et al., 2001), followed by pet research (Amar et al., 2012). Since 2013, collections of coronavirus strains have been established by the National Microbiology Laboratory of Canada (NMLC), a structure with the highest possible level of safety (P4), located in Winnipeg, Ontario. Experimental protocols (Canavagh, 2008) and genetic engineering tools (Masters & Rottier, 2005) for research on coronaviruses are very well documented and controlled (Enjuanes, 2005); it is perfectly possible to construct tailor-made synthetic coronaviruses through directed mutagenesis and excision and assembly of natural or artificial sequences ("plasmids" or "cassettes")! Software tools allow you to simulate the changes needed in a nucleotide sequence to obtain the amino acid changes which are needed to change the properties of a protein. Deep learning softwares work using freely available online databases of gene and protein sequences. The structure of S proteins can be genetically reconstructed (Du et al., 2009) and their biological activity tested *in vitro* (Narasaraju et al., 2010). For example, artificial proteins (or sVLP, synthetic Virus Like Particles) are built to make vaccines against avian coronaviruses (Lal, 2010). But nobody can know the biological reality of their effectiveness as long as they have not been used *in vivo*, which can give some surprises...

In July 2019, CBC News (the Canada's radio and television channel) referred to an eviction by the NMLC of foreign researchers whose access to the vaccine and antiviral therapies development section of the special pathogen program had been removed, following a very serious breach of contractual working conditions. The Public Health Agency of Canada (PHAC) had then initiated an administrative investigation into a breach of confidentiality and data protection. After a 3 months investigation on the smuggling of coronavirus strains, in October 2019, the PHAC described what it called "a policy breach and a breach of trust". The University of Manitoba reassigned the student researchers expelled from the program. This previously released by CBC news information was then, during the Wuhan epidemic, denied by CBC as news and referred to "fake news" on both Canadian and Chinese social networks, while evoking a conspiracy theory. We went from scientific reality to societal subjectivity and politics. Why?

If we look into the genome of the new coronavirus, in the case of the gag, pol and env sequences - which are equivalent to those of HIV, and this for thousands of nucleotides -, 1/ on one hand, the most recent ancestor of the env sequence is older than the most recent ancestor of the gag and pol sequences, and, 2/ on the other hand, the evolution rate of the gag and pol sequences (their rate of effective change by nucleotide) is three times slower than that of the env sequence. Nevertheless, the gag sequences that encode for the poly-protein (p17, p24, p7, p6) and the pol sequences that encode for poly-protein (protease and RNA polymerase) are the most modified ones, unlike what is expected from a naturally occurring evolutive phenomenon.

And, as indicated above, the only changes observed in the env protein (gp120 like) cannot be of natural origin. The modification of the coronavirus protease is critical because it is the protein which, by its enzymatic activity, ensures the correct cutting of the gag, pol and env poly-proteins. For an exact cut, the amino acid sequences recognized by the enzyme must be consistent with the stereochemistry of the protease catalytic site. Any modification of the nucleotide sequence that affects the amino acid sequences of the peptides links, which must be precisely recognized for correct cutting, should therefore be "concerted" with appropriate modifications of the nucleotide sequence coding for the protease (Lal, 2010). A P4 laboratory gets all the biotechnological tools for such a kind of engineering process.

IV. What minimal risk engineering method for an individualized curative vaccine?

Does the new "HIV bio-mimetic" coronavirus have, like HIV, the same lympho-trophic and/or neuro-trophic properties, conferred by the modified gp120 like envelope protein? Could these emerging properties explain the rebound of the disease on the seventh day, the diversity of the symptoms and disease durations and the observed mortality?

Would a preventive or curative vaccine against the new coronavirus be easily produced? Since the Wuhan coronavirus was designed to be itself a vaccine virus - either preventive or curative - against AIDS, is it possible to build a vaccine against a vaccine? Is such a coronavirus-vaccine engineering method to be preferred and to pursue, because a common cold *a priori* is a disease that should only be benign?

1. The therapeutic utility of the HIV, virus of Acquired ImmunoDeficiency Syndrome (AIDS)

In 2012, a 7-year-old American girl with an acute lymphoblastic leukemia (the most common cancer among children) and 8 other patients were cured with a genetically modified HIV strain. Retroviruses are good vectors for genetic engineering because their RNA genome is easily modifiable and once in the host cell it is copied in the form of a DNA version that fits into the cell genome.

The HIV value resides in its ability to allow an effective transportation and insertion of a therapeutic gene. The usual vector is an artificially designed defective HIV; a vector-like viral shell but a non-infectious viral genome.

Fortunately the integrase enzyme that accompanies the retrovirus genome in the viral capsid is naturally absent from the new coronavirus genome.

2. The therapeutic use of stem cells.

Children born without immune defense ("bubble babies") can be cured thanks to a bone marrow stem cell transplant, with or without genetically modified cells. Usually very rare (1 case per 200,000 births, for the most common form), this severe combined immune deficit, is due to an anomaly of a membrane structure, which affects only boys. This curative therapy can only be an individually tailor-made one and it requires a long-term follow-up.

But, even with a very close compatible donor, this allo-graft of foreign stem cells, does present an almost inevitable risk of graft rejection (or of destruction of the grafted host). It is therefore very restrictive (with a life-long immuno-suppressing treatment) and risky (with cancers risk). Only self-transplants with your own stem cells do not present these dangers. Gene stem cell therapy was tried as early as 1999 - with self-transplantation eliminating the risk of rejection - but the risk of cancers, particularly leukemia, persists. These therapies are only possible in a confined clinical environment. An accompanying chemotherapy can be used to destroy old stem cells before the *in vivo* transplantation of *in vitro* modified stem cells.

3. The previously proposed curative vaccination methodology

In vitro cell cultures control and stem cell isolation technology both allow to envisage the design of a methodology for the development of a curative HIV vaccine - as the one previously proposed in September 2005, in Paris (Bricage 2005a) - which as cited, see below, combines an *in vitro* HIV-resistant stem cells selection device and a self-grafting of the resistant transformed stem cells (Bricage, 2005b):

« During evolution, not only the structure of the genome of a cell, but also the type of genes present in it, are co-selected, "built", by its past embedded viruses. At the same time as the cell metamorphoses (its proliferation is remotely controlled by the virus), the virus metamorphoses into an integrated "endovirus", through viral gene losses (of genes essential for free life, but not for endosyncenosis life) and genetic modifications (in relation to the new interactive virus-cell survival mode). For example, mosquito transposons are capsid-free viruses, which are amplified by retro-transcription from an RNA intermediate. These are either viruses that have become endogenous, internalized, without free phase, or RNAs of any origin, scattered, truncated, repeated, nested and juxtaposed, embedded potentially causing provirus. An RNA can cause a new gene to emerge or a gene reorganization. »

« Since many years, the technology of in vivo stem cell collection, their in vitro culture, and then their in situ re-implantation to the same individual are under control. Let us grow a large, renewed quantity of healthy mother cells of the lymphocyte line, taken from a HIV diseased individual (but below the threshold of contamination, ensuring the existence of viable intact, uninfected cells), in the presence of a limited and controlled amount of HIV virus. Sooner or later - but it is impossible to know when (after a week, a month, a year,...) - and differently from one individual to another - it depends on the genetically determined interactions between the individual's stem cells and the virus, in vitro -, the only surviving cells, selected in vitro, will be genetically modified stem cells that have integrated the virus in a stable endogenous form. Re-implanted in the same infected individual, they will give birth to a lineage resistant to lysis by the HIV. The process is applicable to any interactive cell/retrovirus pair. » (Bricage, 2005a)

« The principle is the same as the one in the rabies curative vaccination:
- only the infected individual is treated, his cloned stem cells are re-injected after verifying that they have not been transformed into cancer cells (Bricage, 2008),
- drugs, are used only as "in vivo retardants", to provide time to "speed up", in vitro, the virus. » (Bricage, 2005b).

« That is a gene therapy of HIV by HIV (and not by another vector)... which allows to bypass the possible epidemiological differences related to sex and to avoid the risks of intergenerational genetic restoration, linked to cytoplasmic heredity... We can hope for a clonal advantage in favor of the modified stem cells... The technology is certainly expensive... but probably less than the current everlasting chemical treatment, with very heavy side effects, which results only in delaying the death of the individual, and selects viral variants resistant to drugs and even more virulent! One can hope to "technologically" create one of the "natural" phenotypes of AIDS resistance. »

« And it's safe for other people, wether sick or healthy! »

The allo-transplant of stem cells from AIDS-resistant donors was carried out successfully; it allowed the recipients to recover from AIDS in 2008 and 2011. And very recently in 2019.

Conclusion

Without mentioning the chronic AIDS pandemic, or the epidemic episodes of SARS or MERS, since 2009, there have been 5 major health crises: - the swine flu in 2009, in the United States and in Europe, with the H1N1 pandemic, - the re-emergence of poliomyelitis, in Central Asia, in the Middle East and in Central Africa, in 2014, - the Ebola virus outbreaks in West Africa, in 2014 and 2019, and - the Zika virus epidemic in South America, in 2016. And today, in the midst of this new coronavirus epidemic, during seasonal flu, mainland China is also hit by the avian flu virus.

These global and systemic crises are increasingly closer and closer, and more diverse and intense!

With this new coronavirus epidemic, the manufacturing activity has collapsed to its lowest level in China history. The same goes for service activities and education, which are based on human interactions. Most of the Chinese people stayed, forced at home in February 2020, for fear of contracting this new coronavirus. All the countries have been experiencing a collapse in demand in sectors involving gatherings of people, such as transport, hotels, restaurants and tourism. *"When China catches a cold, the whole world coughs! "*

In November 2019, a deadly marine mammal virus, the Phocine Disempter Virus (PDV), which until then was present only in the Arctic Atlantic Ocean, actually spread to the Pacific Ocean (Vanwormer et al., 2019). As a result of global warming, ice melted and ways opened between the Atlantic and Pacific oceans, thus allowing contact between infected animals (in Atlantic Ocean) and healthy animals (in Pacific Ocean). This virus attacks sea otters, seals and sea lions, causing breathing difficulties typical of colds, with fever, nasal discharge and eyesight. Disoriented, every sick animal is unable to dive, hunt and thus feed. And to survive that is first to eat!

Will the new coronavirus naturally adapt to cats and dogs (Amer et al., 2012)?

Many species of wild birds host both influenza viruses and common cold coronaviruses. Could these viruses recombine among themselves and adapt to humans? This is how new human influenza viruses are born, by genetic recombination, during avian cell (avian flu), porcine (swine flu) or human co-infections (human pandemic flu) and by "jumping" then from one species to another.

Without even mentioning the already emerging viral diseases (due to Ebola virus, West Nile virus, Zika virus) or re-emerging ones (dengue, yellow fever) - which have family ties - and chronic ones (AIDS), it is to be feared that diseases of viral origin - either from new coronavirus and rhinoviruses, or from older viral diseases, such as measles (WHO, 1998) - will become more common (Fontanet et al., 2020). In Canada, Chile, Netherlands and France, a contagious cancer of viral origin (Bricage, 2008a) is invading different species of domestic and wild mussels.

Confinement is very unpopular for those, sick or not, who experience it and are stigmatized, while it is very popular for others who feel reassured. But that is only an emergency, temporary solution. It is somehow locking the epidemic in a place of sacrifice, which would allow everyone outside that place to be protected, or rather to believe that they can be protected. In the absence of a specific drug (chloroquine, a preventive treatment drug for malaria, has been used to treat this new disease) or effective, inexpensive and not-disabling medications, the only solution is vaccination, when it is available : 1/ either a preventive vaccination (as for yellow fever, or zika?), possibly generalizable, compulsory or not, for "routine" diseases, 2/ or a curative vaccination, on a case-by-case basis, with the incurred risks explained, recognized and accepted, and only for sick subjects (AIDS or cancers) (Bricage, 2005b, 2008b). Here the difficulty is that individuals who use social networks to inform themselves are more subject to "fake news" than others and thus more exposed to misinformation, and not just about vaccines! In the current state of the new coronavirus topic, politics has replaced scientific reality and now true news are claimed to be fake ones. Sooner or later, on the internet, distinguishing reality from fiction becomes very difficult, which does not contribute to the discussion of what is true or not!

This is urgent and worrisome because HIV is sexually transmitted and there is a risk that a "hybridized" virus with HIV may also be sexually transmitted. With the continuous increase of human populations, the risks of the emergence of new diseases, or of the re-emergence of old, poorly controlled diseases (measles, rubella), are increasing according to power laws (Yoshikura, 2014), and events that we thought as rare are becoming frequent. This is a characteristic marker of systemic crises. New societal paradigms are needed (Bricage, 2008d, 2010).

In July 2019, human embryos were genetically engineered to provide them with an hereditary genetic resistance to HIV infection. Are new synthetic viruses responsible for incurable diseases, or diseases protectors, integrated into the genome, likely to threaten or facilitate the survival of the human species in the coming years? It is quite possible. This raises ethical and legal questions about security and control, as well as about the transparency of the researches carried out in this area and in any other kind of high-risk area.

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Slides of the corresponding academic seminar (**biodiversité et évolution du vivant**) and some complementary data (UTLA ÉDUCATION EN LIBRE ACCÈS), are available, in French or in English, at
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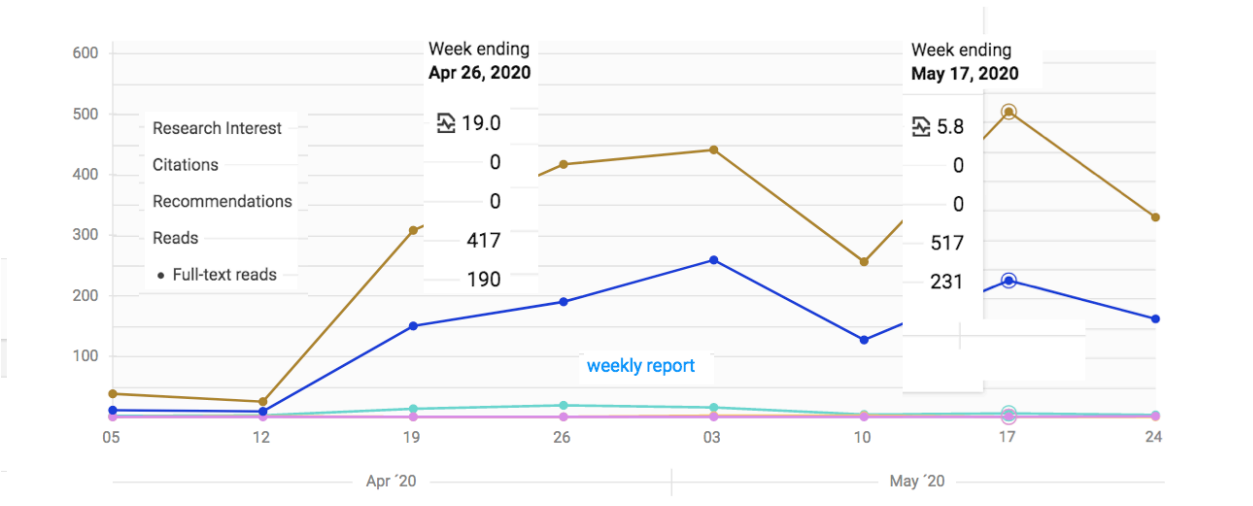

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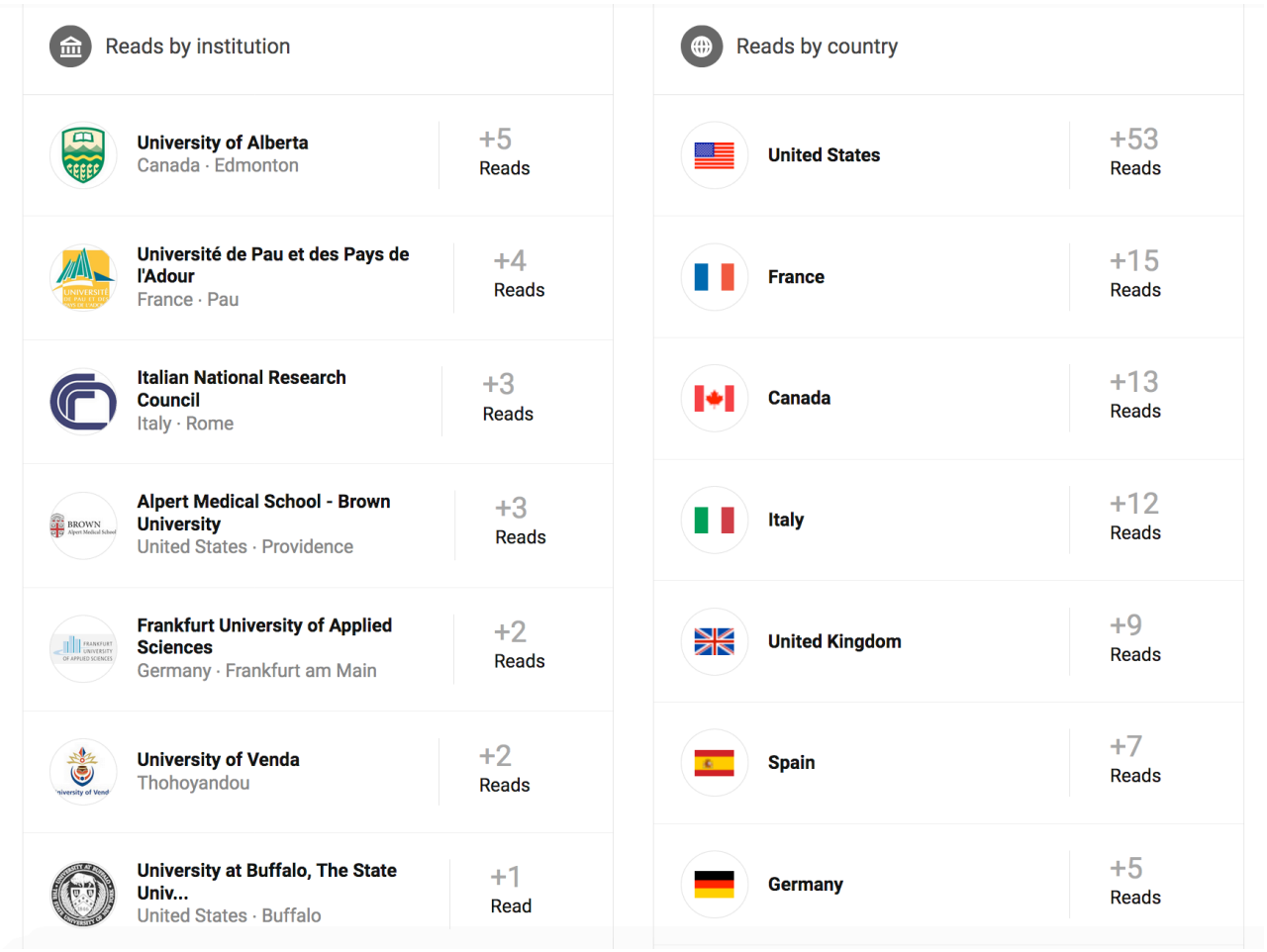

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