De Gentechvrije Burgers, 2de verbeterde aanvulling op en uitbreiding van onze zienswijze en bezwaar tegen de kenmerken GGO IM-MV 16-003, GGO IM-MV 16-004, GGO IM-MV 16-005, GGO IM-MV 16-006 en GGO IM-MV 16-007.

Staatssecretaris van IenM, Mevr. S.A.M. Dijksma

T.a.v. RIVM/VSP/Bureau GGO

Postbus 1

3720 BA Bilthoven

Lelystad, 29 november 2016.

Geachte mevrouw Dijksma,

Verbeterde 2de aanvulling (20-11-2016) op en uitbreiding van onze zienswijze, bezwaar en open brief van 31 oktober 2016, tegen de kenmerken GGO IM-MV 16-003, GGO IM-MV 16-004, GGO IM-MV 16-005, GGO IM-MV 16-006 en GGO IM-MV 16-007.

Wij maken via deze brief, nog enkele opmerkingen betreffende de ontwerpbeschikking vanwege de vergunningaanvraag van het Universitair Medisch Centrum Utrecht, te Utrecht, het Academisch Medisch Centrum, te Amsterdam, het Erasmus Medisch Centrum, te Rotterdam, het Prinses Máxima Centrum, te Utrecht en het Universitair Medisch Centrum Groningen, te Groningen, omdat wij het volgende lezen:

Nogmaals: antibioticaresistentiegenen, nieuwe ontwikkelingen, jonge kankerpatiënten als proefkonijn en meer.

Wij lezen;

4-02-2016: Nederlands Tijdschrift voor Geneeskunde: ***Op 18 november 2015 beschreven Chinese en Britse onderzoekers – voor het eerst – de overdraagbaarheid van resistentie voor het antibioticum colistine via een plasmide. 1. In bacterieland betekent dit dat de resistentie zich veel efficiënter zal verspreiden onder soortgelijke en andere bacteriesoorten.***
https://www.ntvg.nl/artikelen/antibioticaresistentie-gaat-het-nu-echt-mis
https://www.ncbi.nlm.nih.gov/pubmed/26603172?dopt=Abstract

Fragment COGEM over de opinie van de EFSA in 2007:

In 2004 heeft de EFSA een opinie uitgegeven over de toepassing van antibioticum- resistentiegenen in gg-gewassen (4). De EFSA heeft niet slechts geoordeeld over het gebruik van deze genen in gewassen voor veldproeven, maar ook voor teelt. Hierbij heeft zij ook de veevoederveiligheid en de voedselveiligheid in beschouwing genomen.

De EFSA neemt de stelling in dat genen die coderen voor resistentie tegen antibiotica welke gebruikt worden bij medische of veterinaire behandeling, speciale aandacht verdienen in de milieurisicoanalyse. Op basis van het belang van het antibioticum als therapie en het effect dat de resistentiegenen zullen hebben op het milieu en de gezondheid van mens en dier, heeft de EFSA antibioticumresistentiegenen ingedeeld in drie groepen:

In groep 1 bevinden zich resistentiegenen die reeds wijdverspreid zijn onder bodem- en darmbacterie¨n en die tevens resistentie veroorzaken tegen antibiotica welke van geen of weinig belang zijn als geneesmiddel. Een voorbeeld is het nptII gen.

Tot groep 2 behoren resistentiegenen die wijdverspreid zijn in micro-organismen in het milieu en die resistentie veroorzaken tegen antibiotica welke gebruikt worden als therapeuticum in bepaalde gebieden van de geneeskunde. Tot groep 2 behoort onder andere het aadA gen.

***Als laatste bestaat groep 3 uit antibioticumresistentiegenen die resistentie geven tegen antibiotica welke van zeer groot belang zijn in de geneeskunde. Onder deze groep vallen de genen nptIII en tetA** .*

De EFSA is van mening dat 1) de frequentie van genoverdracht van gg-planten naar bacterie¨n zeer laag is voor de drie genoemde groepen en dat 2) het is aangetoond - dan wel zeer waarschijnlijk is - dat een aanzienlijke 'pool' van resistentiegenen reeds aanwezig is in bacterie¨n in het milieu (4). Onder het milieu wordt in dit geval verstaan: bodem, planten, water, ***humane en dierlijke darm.*** *Voor resistentiegenen in groep 1 concludeert zij dat er geen beperkingen zijn ten aanzien van het gebruik in gg-gewassen. Over genen in groep 2 is de EFSA van mening dat deze aanwezig mogen zijn in gg-planten die gebruikt worden in veldproeven.* ***Daarentegen stelt de EFSA dat het gebruik van genen uit groep 3 in gg-planten niet toegestaan kunnen worden voor veldproeven of teelt vanwege het huidige klinische belang van de antibiotica waartegen ze resistentie veroorzaken.***

***CGM/070703-01** Advies gebruik van antibioticumresistentiegenen in gewassen voor veldproeven.*

Onze vraag: Is dit niet ook van toepassing op andere gentech toepassingen zoals deze medische gentechproef? *tetA* wordt in deze proef ook gebruikt!

Kite Pharma

(Is het bedrijf dat de therapie heeft ontwikkeld.)

About Kite Pharma

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged in the development of novel cancer immunotherapy products, with a primary focus on engineered autologous cell therapy (eACT™) designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA. For more information on Kite Pharma, please visit www.kitepharma.com. Sign up to follow @KitePharma on Twitter at www.twitter.com/kitepharma.

Forward-Looking Statements

This press release contains forward-looking statements for purposes of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. ***We may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things: the ability and timing of obtaining interim KTE-C19 data and submitting a BLA with the U.S. Food and Drug Administration for regulatory approval based on the ZUMA-1 study of KTE-C19. Various factors may cause differences between Kite's expectations and actual results as discussed in greater detail in Kite's filings with the Securities and Exchange Commission, including without limitation in its Form 10-Q for the quarter ended March 31, 2016. Any forward-looking statements that we make in this press release speak only as of the date of this press release.***

hm

De Gentechvrije Burgers, 2de verbeterde aanvulling op en uitbreiding van onze zienswijze en bezwaar tegen de kenmerken GGO IM-MV 16-003, GGO IM-MV 16-004, GGO IM-MV 16-005, GGO IM-MV 16-006 en GGO IM-MV 16-007.

We assume no obligation to update our forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.
http://ir.kitepharma.com/releasedetail.cfm?releaseid=978668

Dat is nogal wat! Het lijkt wel of men zeer onzeker is over het resultaat.

Kinderen vanaf 2 jaar mogelijk ook behandeld. (volgens gegevens producent).

Question 16
You need to confirm that the number of patients in the study (table 1 in A1.5) is increased to 230. Is it correctly stated that in your hospital only pediatric ALL patients will be treated?
Re Question 16: *It is correct that in the PMC* ***only children with ALL*** *will be included, and that the numbers may increase to 50 (originally planned 25), which makes the total number of patients included in all studies mentioned in table 1 230 instead of 250.* IM-MV 16-006_000 Rechtspersoon Prinses Máxima Centrum. (ALL= Acute lymphoblastic leukemia).

A Multi-Center Study Evaluating KTE-C19 in Pediatric and Adolescent Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ZUMA-4) site van clinicaltrials.gov
https://clinicaltrials.gov/show/NCT02625480

Is het wenselijk dat kinderen dezelfde gentechtherapeutica krijgen toegediend als volwassenen? En dat zij zo wie zo een gentechproefbehandeling krijgen? Het gaat in feite dus om twee of meer (ZUMA 1 t/m 7?) verschillende gentechtherapieën één of meer voor volwassenen vanaf 18 jaar en één voor kinderen vanaf 2 tot 21 jaar. De advertentietekst is dus onvolledig en misleidend.
Eerste resultaten: zie bijlage of http://ir.kitepharma.com/releasedetail.cfm?releaseid=990947

Dr. Mae Wan Ho waarschuwde reeds lang tegen gentech en droeg andere oplossingen aan.

Nu volgen in de bijlage enkele artikelen van Dr. Mae Wan Ho, die dit jaar helaas overleed, met onze grote dank voor alles wat zij voor de mensheid gedaan heeft.

Tekst overgenomen van:

http://www.i-sis.org.uk/Natural_Gene_Therapy_for_Precision_and_Safety.php

http://www.i-sis.org.uk/Why_GMOs_Can_Never_be_Safe.php

Zie de bijlagen.

Nogmaals: De Gentechvrije Burgers vinden dat deze gentech therapeuticum proeven absoluut geen doorgang mogen vinden. Het is gokken met genen.

Hoogachtend,

De Gentechvrije Burgers, 2de verbeterde aanvulling op en uitbreiding van onze zienswijze en bezwaar tegen de kenmerken GGO IM-MV 16-003, GGO IM-MV 16-004, GGO IM-MV 16-005, GGO IM-MV 16-006 en GGO IM-MV 16-007.

Miep Bos, woordvoerster van De Gentechvrije Burgers, Europees Consumentenplatform (The European GMO-free Citizens).

Donaustraat 170
8226 LC Lelystad
www.gentechvrij.nl

Deze verbetering van de 2de aanvulling op onze zienswijze/open brief van 31 oktober jl. is ook te vinden via **www.gentechvrij.nl/Bcel2.html**

Nagekomen: handtekening van de heer H. Poleij, penningmeester van Stichting Ekopark, Lelystad. De andere leden hebben al eerder getekend. Zie hieronder.

En dan dit: *The drugmaker recently pushed back the timeline for its plans to file an application for KTE-C19, its novel CAR-T cell therapy for diffuse large B-cell lymphoma, with the FDA in the beginning of 2017. The company had originally stated that it planned to file the drug with regulators before the end of the year. Knip*

En:

Lee Fraser, SVP, group director of science and medicine for pharmaceutical advertising agency Digitas Health LifeBrands, agrees with that approach. "We're not talking about medicine in the traditional sense," he said "Scalability is something they need to lock down. They need to ramp up in a cautious and appropriate way. To ensure the best commercial experience, they should start with those who know [the process] in a controlled way. It's an appropriately cautious way to introduce something new."

http://www.mmm-online.com/commercial/kite-pharma-to-keep-anticipated-car-t-launch-controlled-and-targeted-at-certain-hospitals/article/573174/

De Gentechvrije Burgers, zienswijze en bezwaar tegen de kenmerken GGO IM-MV 16-003, GGO IM-MV 16-004, GGO IM-MV 16-005, GGO IM-MV 16-006 en GGO IM-MV 16-007.

Lelystad, 31-10-2016.

Geachte staatssecretaris,

Wij maken bezwaar tegen de ontwerpbeschikking vanwege de vergunningaanvraag van het Universitair Medisch Centrum Utrecht, te Utrecht, het Academisch Medisch Centrum, te Amsterdam, het Erasmus Medisch Centrum, te Rotterdam, het Prinses Máxima Centrum, te Utrecht en het Universitair Medisch Centrum Groningen, te Groningen.

Vergunningaanvraag

Op 15 april 2016 heeft het Ministerie van Infrastructuur en Milieu (hierna: IenM) van het Universitair Medisch Centrum Utrecht, te Utrecht, het Academisch Medisch Centrum, te Amsterdam, het Erasmus Medisch Centrum, te Rotterdam, het Prinses Máxima Centrum, te Utrecht en het Universitair Medisch Centrum Groningen, te Groningen, vergunningaanvragen op grond van het Besluit genetisch gemodificeerde organismen milieubeheer 2013 (hierna: Besluit ggo) ontvangen voor introductie in het milieu van genetisch gemodificeerde organismen. De aanvragen zijn geregistreerd met de kenmerken GGO IM-MV 16-003, GGO IM-MV 16-004, GGO IM-MV 16-005, GGO IM-MV 16-006 en GGO IM-MV 16-007. De aanvragen betreffen klinische studies in patiënten met B-cel maligniteiten, waarbij autologe T-cellen van de patiënten ex vivo getransduceerd (genetische modificatie) worden met een retrovirale vector. Deze vector brengt een transmembrane, chimere anti-CD19 receptor tot expressie. De getransduceerde T-cellen worden weer teruggegeven aan de patiënten met als doel het opwekken van een afweerreactie tegen de B-cel maligniteiten. De werkzaamheden zijn voorgenomen plaats te vinden in de gemeenten Utrecht, Amsterdam, Rotterdam en Groningen. Kennisgevingstekst.

Wij dringen er bij u op aan geen toestemming te verlenen voor dit klinisch onderzoek met gentherapeutica, te veel is te onzeker. Want we lezen in de milieurisico analyse en enkele recente papers, die door de ziekenhuizen aan u zijn verstuurd over te veel bijwerkingen, zieken en een fatale afloop.

Wij ondersteunen de volgende stelling:
Richard Strohman is an eminent scientist and former Chair of the Department of Molecular and Cell Biology at Berkeley who stated the problem this way: ***When you insert a single gene into a plant or an animal, the technology will work you'll get the desired characteristic. But you will also have produced changes in the cell or the organism as a whole that are unpredictable. Genes exist in networks, interactive net- works which have a logic of their own and the fact that the industry folks don't deal with these networks is what makes their science incomplete and dangerous. We are in a crisis position where we know the weakness of the genetic concept, but we don't know how to incorporate it into a new, more complete understanding.*** *Bron:* [illegible]

Tevens ondersteunen wij de bezwaren van De Gentechvrije Burgers, (The European GMO-free Citizens) onafhankelijk Europees Consumentenplatform in te zien via www.gentechvrij.nl/Bcel2.html en verstuurd per post.

Naam	Straat	PC plaats	Datum	Handtekening
St Ekopark	Donaustr 152	8226 LC Lelystad	7-11-16	
M. Lieve secretaris				
T. Trump, voorzitter				
H Poley penningmeester	Houtsdrof 21	8219 PL Lelystad	25-11-16	

Bezwaar van De Gentechvrije Burgers tegen 5 ontwerpbeschikkingen. Vóór 6 december 2016, opsturen aan: Staatssecretaris van IenM, Mevr. S.A.M. Dijksma, T.a.v. RIVM/VSP Bureau GGO, Postbus 1, 3720 BA Bilthoven

Alle velden invullen, anders niet geldig.

Bijlagen.

Natural Gene Therapy for Precision and Safety

Spontaneous reversions of inherited disease mutations point the way to new approaches in gene therapy Dr. Mae-Wan Ho

Another example of natural *versus* artificial genetic modification

Natural gene therapy is the ability of cells in individuals with hereditary disease to back mutate the specific gene involved to regain lost function, thereby ameliorating the disease. This remarkable phenomenon is receiving increasing attention, thanks to cell sorting and DNA sequencing techniques that enable researchers to detect and analyse even rare populations of mutant cells. It looks like another example of the precise natural genetic modification that cells and organisms carry out on a routine basis in order to better survive.

In a recent review article, "The new genetics and natural *versus* artificial genetic modification" [1], I contrasted the precision of natural process with the crude, artificial counterpart that inevitably damages the genome and interferes with natural genetic modification, which incidentally also explains [2] Why GMOs Can Never be Safe (*SiS* 59). Among the most exquisite examples of natural genetic modification is the ability of cells and organisms to activate or mutate just the right genes in order to overcome an obstacle to growth [3] (Non-Random Directed Mutations Confirmed, *SiS* 60). In microorganisms, such non-random mutations are obviously adaptive; though not so in multicellular organisms in which cells acquiring a mutation to multiply may mean cancer. But there are situations where such apparently non-random mutations can benefit the organism as a whole, and natural gene therapy is one of them.

Somatic mosaics and spontaneous reversions of inherited disease mutations

It has long been assumed that except for lymphocytes in the blood, which undergo genetic rearrangements and hypermutations to generate antibodies and other proteins of the immune system, all cells in the body carry the same genome. And even lymphocytes with genetic rearrangements in the immunoglubulins should have the same gene sequences in the constant subunits of those proteins and in any other gene in the genome. However, researchers are discovering to their surprise that most individuals are genetically multiple personalities; they have populations of somatic cells with different genomes, a condition known as somatic mosaicism. Of particular interest are those resulting from reversion to normal of disease mutations inherited from their parents [4-6].

Mosaicisms resulting from reversion to normal of an inherited mutation were discovered because of milder than expected clinical course and/or the presence of both phenotypically normal and abnormal cells *in vivo* and in *vitro*.

4 7

To-date, diseases for which spontaneous reversions have been identified include tyrosinaemia type 1, X-linked severe combined immunodeficiency (X-SCID), autosomal adenine deaminase (ADA) SCID, Wiskoff-Aldrich syndrome, Bloom's syndrome, epidemolysis bullosa, Fanconi anaemia, X-linked ectodermal dysplasia and immunodeficiency, leucocyte adhesion deficiency type 1 [6], Duchenne muscular dystrophy [7], Charcot-Marie-Tooth disease type 1A [8], and Lesch Nyhan syndrome [9].

There are no systematic data on the prevalence of spontaneous reversions, but they may be more common and involve a wider range of inherited diseases than reported so far. Spontaneous revertant lymphocytes are found in 20 % of Bloom syndrome patients [4, 5], up to a level of 75 %. In hereditary tyrosinemia type (IHT1), a severe disease affecting primarily the liver, reversion was observed in 88 % of patients; with reverted surfaces of the liver ranging from 0.1 % to 85 % [10]. And more than 1/3 of patients with epidemolysis bullosa, a condition involving blistering of the skin, have revertant skin patches [11].

We shall look at some examples in more detail.

X-linked severe combined immunodeficiency (X-SCID)

The latest report of natural gene therapy occurred in a patient suffering from X-SCID caused by mutations in the gene *IL2RG* coding for the gamma immunoglobulin chain (gc) common to the receptors for several cytokines (signalling molecules secreted by cells of the immune system): interleukin (IL)- 2, IL-4, IL-7, IL-9, IL-15 and IL-21, which signal T (thymus) and NK (natural killer) cell to multiply. Mutations in the gene abolish the function of all of these receptors, resulting in the absence or diminished numbers of T and NK cells critical to the innate immune system; while B cells that secrete antibodies into the blood stream are normal. Consequently, afflicted individuals often have infections very early in life, and usually die two years after birth. X-linked diseases usually appear in males, who have only one X chromosome, while females with two X chromosomes are less likely to have the disease, but can be heterozygous carriers with one X chromosome bearing a normal 'wild type' allele (form of a gene), and the other the mutant allele.

The patient, a boy, was diagnosed at 6 years of age with normal lymphocyte counts, but suffered from recurrent pneumonia and mollusca contagiosa (viral infection affecting the skin) [12]. As proliferative response of T cells and NK cells to the gc interleukins was poor, the researchers analysed the gene *IL2RG*. This turned up two forms of the gene, one mutant and the other normal, despite the fact that there was only one X chromosome. The normal version predominated in both naïve and mature $CD8^+$ T cells, which increased over time. A fraction of gd^+T cells (subpopulation of T cells abundant in gut mucosa) and differentiated effector memory T cells carried the reversion, while NK or B cells repeatedly tested negative. The patient has steadily improved over the past 7 years since diagnosis, only suffering once from an atypical pneumonia caused by *Mycoplasma pneumonia*; and after several years, his molluscum contagiosum started to disappear spontaneously as well.

The mutation inherited by the boy occurred in the extracellular part of the protein which sits in the cell membrane, resulting in the replacement of tyrosine 219 with asparagine. The reversion was a back mutation that restored tyrosine. Neither the mutation nor the reversion had been reported previously.

Other reversions of X-linked SCID mutations have been reported earlier. A patient with low to normal numbers of T cells and normal expression of gc chain in his T cells was diagnosed at one year of age [13]. At 6 month of age, the patient was treated for a large abscess containing bacilli Calmette-Guerin, probably resulting from a vaccination with bacilli Calmette-Guerin two weeks after birth. The abscess was successfully treated by a regimen of three antituberculosis drugs. Over the following two years, the patient had no further infections complications. He had been living at home for 12 months in good health, and continued to receive antibiotic prophylaxis as well as monthly infusions of immune globulins.

Direct genomic sequence analysis of the patient's B-cell lines detected a single point mutation in the *gc* gene with a base change from T to C at position 343 in exon 3, corresponding to amino acid 115, replacing the normal cysteine codon with one coding for arginine. DNA analysis revealed that the patient's mother was heterozygous for this mutation, so his normal T cells could have been derived from the mother. But T cell karyotyping ruled out this possibility. Like the more recent case of spontaneous reversion, neither NK cells nor B cells tested normal. So the reversion must have occurred after the T cell lineage separated from the B and NK progenitor cells in the bone marrow.

Both research teams favour an explanation for a reversion event conferring a distinct selective advantage *in vivo*. However, as the response of T cells to gc interleukins was poor, it is not clear what the selective advantage could be.

Adenosine deaminase deficiency severe immunodeficiency syndrome (ADA-SCID)

ADA-SCID is an autosomal recessive disorder, i.e., one depending on genes encoded on chromosomes other than the sex determining chromosomes, and two mutant copies are needed for the disease to appear. It is characterized by multiple viral, fungal and bacterial infections early in life and marked failure to thrive; and in the absence of therapy, death before age one. Two unrelated patients with ADA-SCID were presented early in life with apparently life-threatening disease [4]. But instead of dying as expected during infancy or early childhood, they had improved over time, and were alive 12 and 18 years later respectively. The older received no bone marrow transplant because a matched sibling donor was lacking, he received partial exchange transfusions intermittently, but had not had any therapy for several years. The younger had a sibling who died of the disease before 2 years of age. He had not received any therapy for religious reasons. In both patients, somatic mosaicism was identified as the probable basis for the unusually mild clinical course.

In the older child, a missense mutation was identified in a B-lymphoid cell line and in fibroblasts, but the mutation in the second allele could not be identified. Fourteen years later, however, fresh B lymphoid cell line was obtained from the patient. This enabled the researchers to identify the second, splice-site mutation that resulted in an unstable mRNA. But in the B cell line established 14 years later, the splice site mutation was gone, and 50 % of expressed ADA mRNA was normal while 50 % carried the previously described missense mutation.

In the second unrelated younger patient, blood samples were obtained from both the parents as well as the patient. In the patient the maternally transmitted missense mutation was found in 13/15 B cell lines and in only 17% of single alleles cloned from blood DNA. The maternal

missense mutation was only 11 bp upstream of the splice site mutation from the father. Although the results suggested site specific reversion, they could not rule out intragenic recombination (exchange of parts in the same gene) or gene conversion of a short tract, where one allele acts as template for converting the other. The patient had greater residual immune function and lower concentrations of toxic metabolites compared with the other family members carrying the same inherited mutations. He also had substantial ADA activity and enzyme protein in both T and B cell lines and was relatively healthy. Enzyme replacement, while further lowering toxic metabolites was accompanied by diminution in the number of revertant cells, which should be a strong counter-indication for the treatment.

Reversions have been reported in three additional ADA-SCID patients. Two compound heterozygous patients exhibited site specific single nucleotide reversions. Again recombination between the two alleles (intragenic recombination) or gene conversion cannot be ruled out.

More recently, an ADA-SCID patient with a single allele reversion of a mutation in T cells was given enzyme placement therapy; this led to the disappearance of the revertent T cells after three months, development of a germinal cell tumour, and death at the age of 67 months from sepsis [14]. The boy was diagnosed at age of 1 month. By 23 months, he suffered several moderate to severe infections and failure to thrive. But he showed increased lymphocyte counts that were mostly T cells though still below normal for age. In contrast, B cell counts had remained unchanged while NK cell counts improved slightly. By age 50 months, the patient already exhibited normal numbers of total lymphocytes but suffered multiple infections and chronic lung damage despite the continued use of prophylactic antibiotics and intravenous immunoglobuliins. He was placed on enzyme replacement therapy with PEG-ADA (polyethylene-glycol modified bovine ADA).

This highlights the lack of understanding on the physiology of spontaneous reversions, and the treatment appropriate for such cases. All the signs are that spontaneous reversions can ameliorate severe disease symptoms and may even restore health. So it is important to understand the precise mechanisms that bring about such spontaneous reversions, and the environmental interventions most appropriate for promoting what amounts to natural gene therapy.

Frequent mutation reversions in hereditary tyrosinemia type 1 (HT1)

Spontaneous reversions are not restricted to mutations affecting haemopoietic cells. HT1 is a severe liver disease affecting also the kidneys and nervous system, caused by a deficiency of fumarylacetoacetate hydrolase (FAH), the last enzyme in the catabolic pathway of tyrosine. HT1 is clinically heterogeneous, with no correlation between genotype and phenotype. There are two main forms. The acute form is characterized by liver failure in the first months of life and death within the first year if untreated. The chronic form is milder with chronic liver disease, renal tubular dysfunction and hypophosphatemia with rickets. Chronic patients are at high risks of developing hepatocellular carcinoma later in life. Both forms often present with extensive liver injury and regeneration of liver cells. Initially, the primary effective therapy was liver transplant, but since 1992, drug therapy with 2-(2-nitro-4-trifluoro-methylbenzoyl)-1, 3-cyclohexane-dione (NTBC) has been used to reduce the accumulation of toxic metabolites and ameliorate the several clinical symptoms. There are 41 known mutations in

the FAH gene but no clear relationship exists between a particular mutation and clinical manifestation. Different mutations have been found to revert to normal in patients.

In a study carried out on the livers of 26 French Canadian HT1 patients who underwent liver transplant, spontaneous reversion was found in 88 % of the patients with reverted surfaces ranging from 0.1 % to 85 % [9]. The most common mutation in the sample was found in all but two of the patients, and in homozygous form in 21 of them. Three other rare mutations were identified. The reverted cells were found as nodules of regeneration, and they have feature of normal liver cells. Reversion was correlated with amelioration of disease. The surface of reversion was 1.6 % of the liver in the group of acute patients who had severe hepatic crises. In contrast, the average surface of reversion was 36 % in the chronic group who did not have hepatic crises, with 1 exception. In the subacute group, the average surface of reversion was 2.8 % in patients with symptoms similar to those of the acute group, whereas a higher surface of reversion (22 %) was found in those showing more chronic symptoms.

One patient with no hepatic or neurological crises was in good health, and had discontinued her restrictive diet without any reported deterioration. Transplant was done at age 10 years and 9 months solely to avoid eventual development of hepatocellular carcinoma. Her liver had an almost normal appearance with little fibrosis and a surface of reversion of 85%, the highest observed.

The unusually high reversion rates found in this condition has been attributed to the mutagenicity of the accumulating metabolite fumarylacetoacetate, and the selective advantage of normal cells. However, there was no report that mutations in other genes had increased, or that normal cells can invariably outcompete mutant cells. Mostly, normal and mutant cells tended to co-exist.

Duchenne muscular dystrophy (DMD)

DMD is a recessive X-linked form of muscular dystrophy which results in muscle degeneration and eventual death. It is caused by a mutation in the very large dystrophin gene coding for an important component within muscle tissue that provides structural stability to the dystroglycan complex of the cell membrane [15]. Dystrophin positive fibres have been found in as many as 40 % of DMD patients [7]. Such dystrophin positive fibres also occur in cardiac muscle and in skeletal muscle of the mouse disease model. A study carried out in the 1990s investigated the prevalence of dystrophin-positive fibres in muscles of MDM patients by direct counting on immunostained sections in biopsy specimens from 85 patients. Dystrophin positive fibres were found in 22 specimens (26 %) at frequencies ranging from 0.01 to 6.81 %. Frequencies over 1 % were found only in patients older than 6 years. Of the 42 DMD cases screened by cDNA probes, 32 had an intragenic deletion, and dystrophin-positive myofibres were found in 14 (33 %) of them. In 9 patients, the deletions involved 1 to 3 exons and in only 1 patient 9 exons. All deletions were located between exons 44 and 53.

The prevalence of dystrophin-positive fibres by counting the total number of observed positive clusters was 3.7×10^{-3} (which estimates the reversion rate per progenitor cell).

Another way to estimate the rate of reversion is from the observation that one third of all possible deletions may restore the correct reading frame, the reversion rate in these patients would be one-third of the actual rate at which deletions are produced, which is about 1 %.

Leukocyte adhesion deficiency type 1 (LAD-1)

LAD-1 is an autosomal recessive immunodeficiency caused by mutations in the b2-integrin CD18, leading to the inability of white blood cells, particularly neutrophils to adhere to the endothelium and migrate to sites of infection. Three LAD-1 patients with markedly reduced Cd18 expression in neutrophils each had a small population of lymphocytes, predominantly T cells, with normal C18 expression, and a memory/effector phenotype [6]. Microsatellite (short repeated sequences used as genetic fingerprinting) analyses proved that these originated from the patient. Sequencing showed that in each patient, one of the CD18 alleles had undergone further mutation. All three survived to adulthood without bone marrow transplants, and in all three, reversions were heterozygous.

Patient 1 was homozygous for a missense mutation of A to C at nucleotide 392, and all DNA clones derived from his CD18- lymphocytes carried the mutation. In contrast, 4/10 of CD18+ clones showed A to T mutation at nt 392, which replaced serine (codon TCT) with phenylalanine (codon TTT). The remaining 6 of 10 CD18+ clones had reversed the original missense mutation from C back to A at nt 392 for the amino acid tyrosine. Patient 2 was homozygous for the missense G to A mutation at nt 850, which was found in all DNA clones from her $CD18^-$ cells. Her $CD18^+$ T cells showed 3 different sequences. Five of 10 clones carried the original G to A mutation in the codon *G*GC (glycine) to *A*GC (serine), 3 of 10 clones had G to C missense mutation at nt850 leading to arginine. Two of the 1o clones had a second site mutation C to G at nt 852 in addition to the original mutation G to A at nt 850, also leading to arginine at amino acid position 284, but using two different codons. Thus, in both patients, reversion was not to the wild type but to a third amino acid that restored function.

Patient 3 was a compound heterozygote. His mutation at A to G at nt 1052 was not detected in either parent, indicating it was a de novo mutation. He also carried a splice mutation caused by a 12-bp addition to the transcript, resulting in an in-frame addition of 4 amino acids (PSSQ, proline-serine-serine-glutamine) between proline 247 and glutamic acid 248 (247 _ PSSQ). This splice mutation arose by C to A substitution in the 3' end of intron 6, generating an aberrant splice acceptor site. Only the splice mutant had undergone reversion to wild type.

In all patients, the reverted CD18 molecules supported the proliferation response of cells to stimulation by the superantigen and IL-2 better than the mutant molecule. (Superantigens are a class of antigens causing non-specific activation of T-cells, resulting in polyclonal T cell activation and massive cytokine release.) Reversion events were not identified in progenitor cells, neutrophils or monocytes, indicating that the events did not take place at a pluripotent stem cell level, but occurred in lineage committed progenitors

Patient 1 was a white male diagnosed at 1o weeks after birth and had no matched related donors. He had sepsis at 10 months of age, followed by other problems including chronic infections, recurrent ulcers, inflammatory bowel disease recurrent, nonhealling groin and

perianal ulcers requiring multiple skin grafts. Matched unrelated bone marrow transplant at age 21 years was complicated by severe graft-versus-host disease and death.

Patient 2 was a white female with omphalitis (infection of umbilical cord stump) at 10 days after birth, and diagnosed for LAD-1 at 6 years of age. After a succession of infections and inflammatory conditions followed by extensive gingivitis (gum disease) which was resolved by the removal of all permanent teeth, her gingivitis resolved at 22 years. At 28 years old, she was doing very well.

Patient 3 was a white male presented at 10 years of age with poor wound healing after tracheostromy for complicated infection of the voice box and windpipe. At 18, he developed crohn's disease and recurrent poorly healing ulcers on the legs and thighs and severe gum disease. At 28, he had emergency surgery that resulted in removal of part of his large intestine. At 35 he started on the drug infliximab for colitis, to which he has responded well.

Bloom syndrome (BS)

BS is an autosomal recessive disorder characterized by instability of DNA. About one fifth of patients have mosaicism in lymphoid cells with a small percentage of cells exhibiting low sister chromatid exchange. (Sister chromatid exchange is a sign of DNA instability in BS.) Virtually all such individuals with mosaicism in the rate of sister chromatid exchange have been heterozygous for two different mutations, and the mosacism can be shown to result from intragenic recombination [4]. However 2/7 of the reversion patients were homozygous for the mutations, and could not have revertant cells by intragenic recombination. One patient was homozygous for the mutation 1544insA (insertion of base A at position 1544) and the other for the mutation 2702GtoA. The revertant cells were heterozygous for each of the mutations that had reverted back to the wild type, indicating that true back mutations can also occur [6].

Reversion of somatic cells in patients with inherited disorders was first detected in Bloom syndrome patients in 1977. Although the authors considered selection of the revertant phenotype as an explanation, they admitted that the role of selection in phenotype reversion in humans has been difficult to assess.

Wiskott-Aldrich syndrome (WAS)

WAS is a rare X-linked disorder characterized by thrombocytopenia (decrease in blood platelets), eczema, and immunodeficiency. It is caused by mutations in the WAS protein gene *WASP*. A research team identified 3 members of a single family who were WAS revertants. The first patient had a spontaneous reversion of a 6bp insertion and was described previously (see [4]). The team analysed samples from 3 additional WAS patients from the same kindred and found 2 of them also had revertant cells [16]. Molecular analysis confirmed that the same true back mutation had occurred in two of the three additional patients. One of them had died at age 33 of renal failure, the other age 16 is in good health and on prophylactic antibiotic treatment. No WASP expressing cells was detected in the youngest patient (1 year of age). It is not known if reversion is age related.

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As in the previous patient, WASP expressing cells were only detectable among T lymphocytes, but not in B cells or NK cells, suggesting that the reversion event occurred in a T-cell progenitor. Evidence for a selective advantage of WASP expressing cells is that in both patients, the percentage of WASP expressing cells was markedly higher among T memory cells than in naïve T lymphocytes.

Fanconi anaemia (FA)

FA is an autosomal recessive condition characterized by congenital abnormalities, progressive bone marrow failure, fragile chromosomes and susceptibility to cancer. There are at least 11 groups and 8 FA genes identified: *FANCA*, *FANCC*, *FANCD1/BRCA2*, *FANCD2*, *FANCE*, *FANCF*, *FANCG/XRCC9*, and *FANCL/PHF9*. The genes are involved in an integrated cell response to DNA damage during the stationary phase, especially from DNA interstrand crosslinks. A key step in the response is the addition of one ubiquitin molecule to the FANCD2 protein. There is very high clinical variability among FA patients, only partially attributed to different genotypes. Revertant cells may also account for the clinical variability. However, neither the frequency nor the consequence of different reversions is known. The large number of genes and possible mutations make molecular analysis difficult. Diagnosis of FA is based on the chromosome breakage and cell cycle tests, which depend on the hypersensitivity of FA cells to DNA cross-linking agents [17 and reference therein].

A study carried out in 53 FA patients in France [17] characterized by FANCD2 and chromosome breakage tests detected ubiquitinated FANCD2 (reversion) in peripheral blood lymphocytes in 8 (15%) of the patients. FA reversion was further confirmed in these patients by comparing primary fibroblasts with peripheral blood lymphocytes. Reversion was associated with higher blood counts and clinical stability or improvement.

Epidermolysis bullosa (EB)

EB is a recessive autosomal disorder typically caused by mutations in the type XVII collagen gene *COL17A1*. A special form of EB, dystrophic EB involves recessive autosomal mutations in the type VII collagen gene *COL7A1*. A 21 year old man carrying homozygous nonsense mutation in the gene had an unaffected skin patch on his neck where blisters never occurred. The patch stained normally for collagen VII immunologically, whereas the protein was strongly reduced in affected skin. In the unaffected skin, the somatic nucleotide substitution G to T at nt6510 reverted the nonsense codon to tyrosine, thereby restoring functional protein production [18]. Reversion mosaicism is considered rare in dystrophic EB. But it might be more common than previously thought. The patient was the third identified by the authors in a short period of time, and the mechanism of reversion differed from those previously reported. The first dystrophic EB reversion mosaicism identified was due to intragenic recombination, and the second due to nucleotide deletion. The authors stated: "This is important because the natural gene therapy phenomenon may provide opportunities for revertant cell therapy."

More than 1/3 of patients with the typical EB involving mutations in *COL17A1* display revertant skin patches; correction mechanisms are highly diverse, and include back mutations, additional nucleotide changes, insertions or deletions and gene conversions, sometimes within

the same patient. Reversion mosaicism has been described also for patients with EB simplex due to mutations in the keratin gene *KRT14*.

Epidermal stem cells populate only small skin areas, so it seems likely that the correction mutation arose in earlier stages of embryonic epidermal stem cell development.

The authors highlighted promising therapeutic opportunities, such as revertant cell therapy, i.e., grafting ex vivo–grown reverted keratinocytes onto affected skin. Already, keratinocytes and fibroblasts can be reprogrammed into induced pluripotent stem cells (iPSCs) and subsequently differentiated into keratinocytes, providing an unlimited source of autologous keratinocytes (see [19] The Promise of Induced Pluripotent Stem Cells, *SiS* 51), although such transplants with iPSCs are not without risks, and the preferred option is to encourage the patient's own stem cells to replace lost cells in situ and in vivo.

A team at University of Groningen in the Netherlands and Free University Brussesls in Belgium had carried out a trial on a patient with typical EB [20]. The patient's own revertant cells taken from skin biopsies were expanded in culture into sheets for transplant to replace diseased skin. The team also devised a new technique using adhesive tape to remove the diseased epidermis over an area for receiving the transplant, which is simple, effective, and almost painless. The transplant was very successful, and the acceptor site healed without scarring. Unfortunately, the replacement skin had too few revertant cells to prevent blistering.

It is likely that appropriate culture conditions are needed to promote the growth of revertant cells, again highlighting the need for investigations into the environmental/ physiological factors that may encourage progenitor or stem cells to revert to normal function and to multiply.

Directed mutation a good working hypothesis

This review makes no claim to being exhaustive. Nevertheless it already indicates that many individuals with inherited single gene disorders (20 to 30 % or more) regain the lost gene function in a variable proportion of their somatic cells, which is correlated with amelioration of clinical symptoms and/or an improvement in health. The mechanisms for such reversions are genetically diverse, ranging from true back mutation to the wild type involving single nucleotide substitution, deletion, or insertion, or deletion of multiple nucleotides, to intragenic recombination, gene conversion, and compensatory mutation in the same gene.

Many researchers have commented that the phenomenon amounts to natural gene therapy; though the common assumption that reversion events are purely random appeared to have discouraged any further investigations into possible environmental and physiological factors involved.

The phenomenon is most reminiscent of directed mutations that have now been confirmed in bacteria [3]. Some researchers have pointed to common mechanisms for directed mutations that might apply to *E. coli*, yeast and human cells alike. For example, the secondary stem-loop structure of single stranded DNA exposed during transcription leaves unpaired G and C bases in loops intrinsically mutable, and these are where mutation hotspots tend to be located [20]. However, we still need a mechanism to direct mutagenesis to just the right genes.

There is evidence suggesting that molecules intercommunicate by electromagnetic signals and molecules that interact attract one another by resonating to the same frequencies (see [21] The Real Bioinformatics Revolution, *SiS* 33). That may be how cells know which genes to turn on, and how sequential enzymes in metabolic pathways get organized into multi-enzyme complexes within the cytoplasm (see Chapter 18 of [22] Living Rainbow H_20, ISIS publication). In the same way, the accumulation of specific metabolites or 'signaling' molecules may emit signals to direct the transcription and mutation of specific genes expressing the appropriate enzyme or target protein involved in the biological function blocked by the inherited germline mutation. The end result is back mutation to the wild type or the recovery of a functional protein by another mutational/recombination event. Directed mutation is a reasonable working hypothesis for further investigations on the frequent reversion of inherited disorders. The immediate prediction of directed mutation is that the rate of mutation in other (functionally irrelevant) genes are not increased, which can be readily confirmed or falsified. Another prediction is that there should be specific electromagnetic frequencies, most likely at subtle or subliminal levels (see [23] The Principle of Minimal Stimulus in the Dynamics of the Living Organism, SiS 60) that might enhance the rates of reversion events. Directed mutation is part and parcel of the new genetics and natural genetic modification that we have come to expect [1], which demands a complete overhaul of reductionist biology and medicine still largely based on the old Mendelian genetics.

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Why GMOs Can Never be Safe

The new genetics tells us that organisms need to engage in natural genetic modification in order to survive; artificial genetic modification interferes fundamentally with the natural process, and it is well-nigh impossible to avoid doing so Dr. Mae-Wan Ho

This report is based on invited lectures delivered in ***GMOs and Food Safety International Forum 2013****, 9-10 July 2013, Yunnan University of Finance Economics, Kunming, Yunnan; and 13 July 2013, Gloria Plaza Hotel Beijing, China.*

Power point presentation available for download here

From ivory tower academic to science activist

I was an ivory-tower academic who had rejected mechanistic biology from the start, and kept changing fields in search of the meaning of life, until just over 20 years ago, when some of the world's top physicists and chemists inspired me (see [1] Quantum Jazz Biology, interview) to invent a new quantum physics of the organism [2] The Rainbow and the Worm, The Physics of Organisms. Soon after that, I met remarkable people like Vandana Shiva and Chee Yokeling of the Third World Network, who taught me just how important science is in shaping people's lives and how crucial to get the science right. To me, science is the most intimate knowledge of nature that is beautiful beyond compare; it is also reliable knowledge that enables us to live sustainably with nature, and I have dedicated my life since to defending and promoting that science.

The greatest danger of GM

One main theme of my book [3] Genetic Engineering Dream or Nightmare, *the Brave New World of Bad Science and Big Business* - first published by Vandana in 1997 and by Third World Network in 1998 ahead of the commercial publications and translations – is to elaborate what I consider to be the greatest danger of genetic modification: its being misguided by the ideology of genetic determinism.

The rationale and impetus for genetic engineering and genetic modification is the 'central dogma' of molecular biology that assumes DNA (deoxyribose nucleic acid) carries all the instructions for making an organism. Individual 'genetic messages' in DNA faithfully copied into RNA (ribosenucleic acid), is then translated into a protein via a genetic code; the protein determining a particular trait, such as herbicide tolerance, or insect resistance; one gene, one character. If it were really as simple as that, genetic modification would work perfectly. Unfortunately this simplistic picture is an illusion.

Instead of linear causal chains leading from DNA to RNA to protein and downstream biological functions, complex feed-forward and feed-back cycles interconnect organism and environment at all levels to mark and change RNA and DNA down the generations (Figure 1). Molecular geneticists have coined the term 'fluid genome' by 1980. The fluid genome belongs in the organic quantum paradigm of interconnectedness, as Vandana says. Organisms

work by *intercommunication* at every level, and not by *control*. Control belongs in the static mechanistic paradigm of the central dogma.

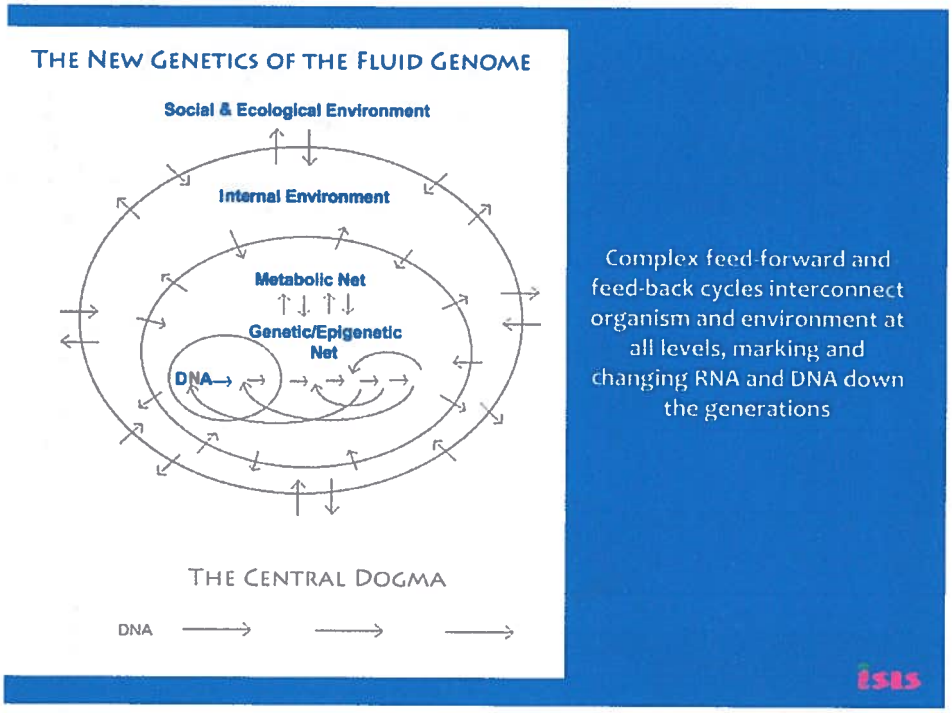

Figure 1 The new genetics of the fluid genome versus the central dogma

In order to survive, the organism needs to engage in natural genetic modification in real time, an exquisitely precise molecular dance of life in which RNA and DNA respond to, and participate fully in 'downstream' biological functions. That is why organisms and ecosystems are particularly vulnerable to the crude, artificial GM RNA and DNA created by human genetic engineers. It is also why genetic modification can probably never be safe.

More importantly, the human organism shapes its own development and evolutionary future; that is why we must take responsible action to ban all environmental releases of GMOs *now*. Not only have GM crops failed to deliver on the many false promises, they are unsafe for health and the environment [4] (Ban GMOs Now, I-SIS publication), and obstructing the shift to sustainable non-GM agriculture that's productive, resilient and health-promoting (see [5] Food Futures Now *Organic *Sustainable *Fossil Fuel Free , I-SIS/TWN publication), and precisely what we need in times of climate change.

Big difference between natural and artificial genetic modification

A GMO (genetically modified organism) is simply an organism with synthetic genetic material inserted into its genome. It is made in the laboratory with sterile techniques, which also means without sex. The genome is all the genetic material of an organism (apart from those in mitochondria and chloroplasts), a copy of which is in practically every cell; and in cells with a nucleus, the genome is enclosed within the nucleus, organised into chromosomes. Each chromosome unwinds into long threads of chromatin, consisting of proteins coating the double helix DNA. Strip off the proteins, and the DNA can be chopped

and changed and recombined in test tubes, copied, amplified, and transferred into any organism, and that is what artificial genetic engineering and genetic modification involves (Figure 2).

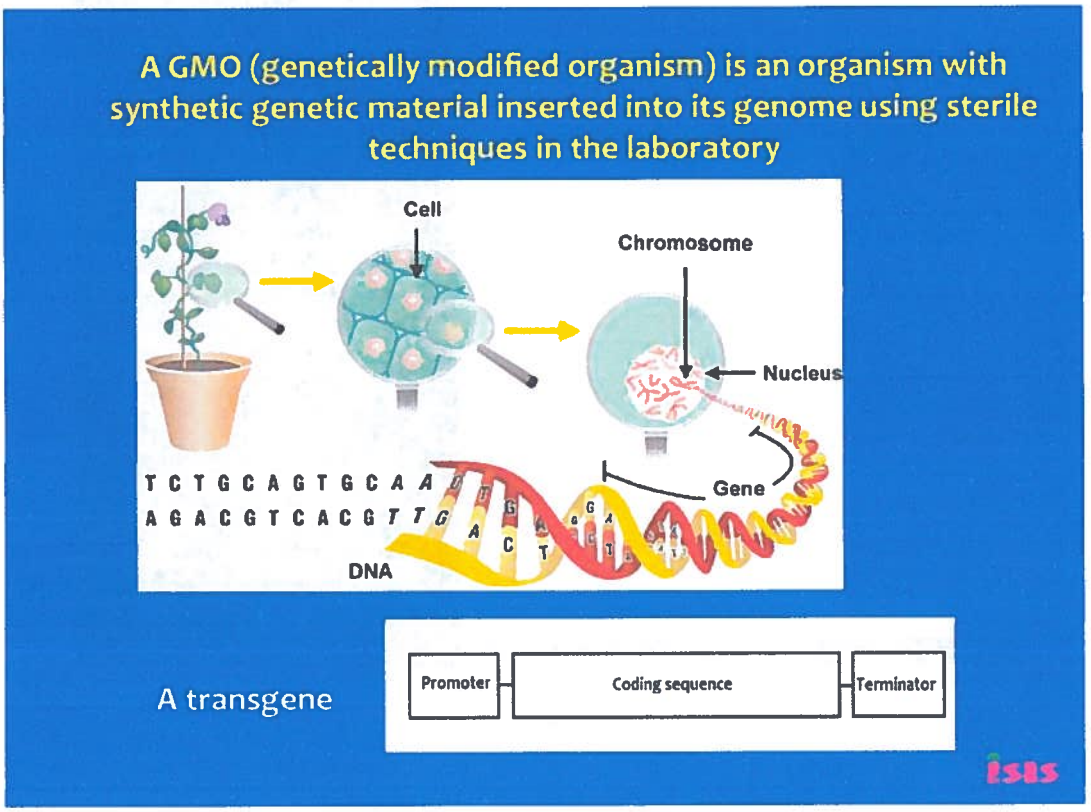

Figure 2 What is involved in making a GMO (see text)

A transgene (Fig. 2) is a unit of the synthetic genetic material transferred into cells to make a GMO that expresses the required protein. It consists of a signal for starting the transcription, the *promoter*, the *coding sequence* determining the amino acid sequence of the protein and the signal for ending, the *terminator*. The three parts of the transgene are typically from different sources and variously modified with synthetic sequences that bear no relationship to any natural DNA; and this applies to each of the parts as well. More than one transgenes are usually included in a GM construct, most often, an antibiotic resistance gene to help select for cells that have taken up the GM construct.

There are big differences between natural genetic modification done by organisms themselves and the artificial genetic modification done by 'genetic engineers' in the lab (Table 1). Natural genetic modification is precise and predictable. It happens in the right place, at the right time without damaging the genome, and as appropriate to the organisms as a whole in relation to its environment. In contrast, artificial genetic modification is crude, imprecise, unpredictable and uncontrollable. The artificially created GM constructs have to be smuggled in by (disarmed) pathogenic bacteria and viruses that infect the cells, or otherwise forced into the cells by gene guns or electric shocks. The artificial constructs get scrambled in the process and could land anywhere in the genome, scrambling and damaging the genome in the process.

Aggressive promoters are used essentially to force foreign genes to be expressed out of context.

Table 1 Contrasting natural and artificial genetic modification

Natural genetic modification	Artificial genetic modification
Precisely negotiated by the organism as a whole	Crude, imprecise, unpredictable uncontrollable
Takes place at the right place & time without damaging the genome	Forced into cells with no control over where & in what forms the artificial constructs land with much collateral damage to the genome
Appropriate to the organism as a whole in relation to its environment	Aggressive promoters force foreign genes to be expressed out of context

There is, therefore, nothing natural about artificial genetic modification done in the lab.

- It lacks the precision and finesse of the natural process
- It is greatly enhanced gene transfer without sex, also called horizontal gene transfer
- GM constructs are designed to cross species barriers and to jump into genomes with aggressive promoters to force expression of transgenes out of context
- It enables genes to be transferred between species that would never have exchanged genes otherwise
- GM constructs tend to be unstable – with weak joints from being cobbled together from different sources as well as well-known break points associated with promoters and terminators - and hence, more prone to further horizontal gene transfer after it has integrated into the genome

Consequently, all the signs are that genetic modification is inherently hazardous.

GM inherently hazardous

Reliable evidence obtained by scientist independent of the biotech industry fully corroborates real life experiences of farmers in the field from different parts of the world (hitherto dismissed by the scientific establishment as "anecdotal evidence"): GM feed and other exposures to GMOs invariably cause harm, regardless of the species of animal, the GM crop, or the genes and constructs involved. A full list is presented in our report [4], and it includes the most horrendous cases of excess deaths, birth defects, infertility, tumours and cancers (some of which will be presented by other scientists at this conference). The inevitable conclusion one comes to is that genetic modification is inherently hazardous, on account of the new genetics of the fluid and responsive genome. I list the categories of hazards in Table 2.

Table 2 Hazards of GMOs

1. Uncontrollable, unpredictable impacts on safety due to the genetic modification process*
Scrambling the host genome*
Widespread mutations*
Inactivating genes*
Activating genes*
Creating new transcripts (RNAs) including those with regulatory functions*
Creating new proteins
Creating new metabolites or increasing metabolite to toxic levels*
Activating dormant viruses*
Creating new viruses by recombination of viral genes in GM insert with those in the host genome*

2. Toxicity of transgene protein(s) introduced (intentionally or otherwise)
Transgene protein toxic*
Transgene protein allergenic or immunogenic*
Trangenic protein becoming allergenic or immunogenic due to processing*
Unintended protein created by sequence inserted may be toxic or immunogenic

3. Effects due to the GM insert and its instability*
Genetic rearrangement with further unpredictable effects*
Horizontal gene transfer and recombination*
Spreading antibiotic and drug resistance*
Creating new viruses and bacteria that cause diseases
Creating mutations in genomes of cells to which the GM insert integrate including those associated with cancer*

4. Toxicity of herbicides used with herbicide tolerant GM crops*

*Documented in scientific literature

Although the weight of evidence against the safety of GMOs is overwhelming, we are still largely in the dark as to the precise nature of the hazard(s) associated with different GMOs. Toxicity has been found for transgene products such as the Bt proteins from different strains of the soil bacteria *Bacillus thuringiensis* expressed in many GM crops, while the multiple toxicities, endocrine disrupting propensity and carcinogenicity of glyphosate herbicides, heavily used with glyphosate tolerant GM crops, are no longer in doubt as reviewed in detail in our report [4]. There remains a range of hazards not so easily identified without dedicated research, even though evidence exists for most, if not all of them in the scientific literature. These are due to the unpredictability and uncontrollable nature of the genetic modification process itself (Table 2, category 1), which can activate or inactivate genes, scramble genomes, create new proteins, new nucleic acids, new metabolites, and others due to the transgenic DNA and its instability (Table 2 category 3), of horizontal gene transfer - the direct transfer of DNA into the genomes of cells - from the GMO to all other species that come into contact with the GMO.

Transgene instability & the illegality of GMOs

Since the 1990s, some of us have raised the possibility of unintended secondary horizontal gene transfer from GMOs released into the environment with detailed reviews and reports,

many of which were sent to our regulators (see [4] for references). At first the regulators and GM proponents denied that horizontal gene transfer could happen at all, or the probability is so tiny as to be practically zero. Later, when it became clear from molecular genetic analyses that rampant horizontal gene transfer has taken place in the course of evolution and in recent times, they said horizontal gene transfer is a natural process and therefore no need to worry; anti-GM is just anti-science.

Horizontal gene transfer is indeed a natural process, normally under the control of the organism itself, which is why GM DNA is such a threat. On account of its increase propensity for horizontal gene transfer, GM DNA can take over the natural process to gain access to the organisms' genome regardless of whether it is appropriate or not.

The increased propensity of GM DNA for horizontal gene transfer translates into the instability of transgenic lines. Transgenes not only get silenced (no longer expressed) in successive generations, but can also become rearranged or lost. Transgene instability is an open secret buried under the permissive regulatory carpet. Independent scientists in Europe first discover that all commercially approved and hence risk assessed and molecularly characterized GM inserts were different from what was reported by the companies. Since then, at least one of them, MON 810, was found to have rearranged again, and now there is a substantial literature on transgene instability (see [4]). This is not at all surprising, given that GM DNA is unstable, and the foreign DNA does not really fit in with the whole organism, which is why transgenes tend to be silenced or lost.

The implications of transgene instability are far reaching. ***Transgene instability makes a mockery of the risk assessment process, because any change in transgene expression, or worse, rearrangement or movement of the transgenic DNA insert(s) would create another transgenic plant different from the one that was characterized and risk assessed. And it matters little how thoroughly the original characterization and risk assessment may have been done. The legislature should take note: unstable transgenic lines are illegal. Not only should they not be still growing commercially, they are also strictly ineligible for patent protection***.

Horizontal gene transfer from GMOs does happen and often

There is now no doubt that horizontal gene transfer from GMOs does happen. For the first time, a proper study was carried out in 2012 by scientists in China, who found ampicillin resistance bacteria in all 6 of China's major rivers [6]. Sequencing confirmed that the gene is a synthetic version derived from the laboratory, and different from the wild type. It is the same as the version present in numerous GM crops released in China commercially or in field trials (see [7] GM Antibiotic Resistance in China's Rivers, SiS 57). The researchers suggested that horizontal gene transfer of genetically engineered plasmids may underlie the rise in antibiotic resistance in animals as well as humans.

In the only authenticated feeding trial of GM food on human volunteers carried out by scientists in the UK, the complete transgene DNA of Roundup Ready soybean was recovered from the colostomy bag in 6 out of 7 subjects after a single meal, at levels up to 3.7 % of intake. In 3 subjects, about 1 to 3 per million bacteria cultured from the contents of the colostomy bag were positive for the GM soybean transgene, showing that *horizontal transfer*

of GM DNA had occurred; but no bacteria were found to have taken up the vastly more abundant non-transgenic soybean DNA. This is direct evidence that GM DNA has a much greater propensity for horizontal gene transfer, as I have maintained from the start [3].

It is now clear that ***horizontal transfer of GM DNA does happen, and very often***. Evidence dating from the early 1990s indicates that ingested DNA in food and feed can indeed survive the digestive tract, and pass through the intestinal wall to enter the bloodstream. The digestive tract is a hotspot for horizontal gene transfer to and between bacteria and other microorganisms.

Recent evidence obtained with direct detection methods indicates that horizontal transfer of GM DNA is routinely underestimated, largely because the overwhelming majority of bacteria in the environment and particularly in the gut cannot be cultured. GM DNA transfers at high frequencies to bacteria and fungi on the surfaces of leaves and stems, helped by the plant wound hormones; and the soil around the plant roots (rhizosphere) is also a hotspot for horizontal gene transfer. Higher organisms including human beings are even more susceptible to horizontal gene transfer than bacteria, because unlike bacteria, which require sequence homology (similarity) for incorporation into the genome, higher organisms do not.

To make things worse, DNA and RNA are now known to be actively secreted by living cells in a nucleic acid intercommunication system; the nucleic acids are taken up by target cells to modify gene expression and may be integrated into the cell's genome. The profile of the circulating nucleic acids changes according to states of health and disease. Cancer cells use the system to spread cancer around the body. This nucleic acid intercom leaves the body very vulnerable to GM DNA and RNA, because they can take over the system for horizontal gene transfer into cells of all tissues including germ cells.

One type of nucleic acids, the microRNAs (miRNAs), are specifically involved in gene silencing via a vastly complex and flexible process that changes according to the environmental context. Consequently, GMOs based on miRNAs have many potentially adverse off-target effects, which are radically unpredictable and uncontrollable [8] RNA Interference "Complex and Flexible" & Beyond Control, *SiS* 59).

Dangers of GM DNA and its horizontal transfer

What are the dangers of GM DNA from horizontal gene transfer? Horizontal transfer of DNA into the genome of cells *per se* is harmful, but there are extra dangers from the genes or genetic signals in the GM DNA, and also from the vector used in delivering the transgene(s).

· GM DNA jumping into genomes cause 'insertion mutagenesis' that can lead to cancer, or activate dormant viruses that cause diseases

· GM DNA often contains antibiotic resistance genes that can spread to pathogenic bacteria and make infections untreatable

· Horizontal transfer and recombination of GM DNA is a main route for creating new viruses & bacteria that cause diseases

· The CaMV 35S promoter, widely used in GM DNA for crops on the mistaken assumption that it works only in plants, actually works in practically all living species including bacteria and human cells; recent research also suggests it may enhance the multiplication of disease-associated viruses including HIV (human immunodeficiency virus). In addition, the promoter overlaps with a virus gene (gene VI) that inhibits gene-silencing, a crucial host defence against viral infections

· The *Agrobacterium* vector, most widely used for creating GM plants is found to transfer genes also to fungi and human cells, and to share genetic signals for gene transfer with common bacteria in the environment. In addition, the *Agrobacterium* bacteria and its gene transfer vector tend to remain in the GM crops created, constituting a ready route for horizontal gene transfer to all organisms that come into contact with the GMO or the soil on which GM crops are grown. In 2008, *Agrobacterium* was linked to the outbreak of Morgellons disease. The Centers for Disease Control in the US launched an investigation but failed to investigate the link to *Agrobacterium*.

The full story of what I have tried to convey is in the final chapter of our report [4] with more than 140 references for that chapter alone. I hope this convinces you to avoid GMOs as far as possible; and especially don't let your children eat GM food. We must ban further environmental releases while we recall and destroy existing ones. We can't wait for our central governments, or the European Union, or the United Nations to do that. Ban them from your home, your local community, your fields, your village, your town, your city, your province. The governments will follow your lead.

It is often said that GMOs once released is uncontrollable. But nothing is really controllable in the new fluid-genome organic paradigm. Fortunately, organisms are resilient, and able to heal themselves, and ecosystems are like organisms [2]; once we stop releasing GMOs and stop insulting them with other practices of industrial monoculture, ecosystems can recover and regain their health and productivity under sustainable agro-ecological farming [5]. That's all the more reason for us to stop GMOs *now*; before it is really too late.

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Got something to say about this page? Comment

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Douglas Hinds Comment left 22nd July 2013 15:03:29
Excellent. Meshes perfectly with what I have been attempting to convey through occasional short comments in diverse forums. Two points you may want to consider emphasizing further: The role of gametes in Eukaryotes vs. incompletely cobbled packages of patented but never actually tested synthetic gene packages in GMO commercial products sloppily integrated in evolutionarily tested whole genomes through the use of pathogens and (obviously) pathogenic processes. Felicidades y muchos saludos. (I'll try to get this translated into Spanish, for you). Douglas Hinds Center for Community and Rural Development Alliance for Environmental and Social Responsibility in Development Mexico Mexico

Mae-Wan Ho Comment left 22nd July 2013 15:03:46
Thank you Douglas. Can you please expand on the role of gametes in Eukaryotes vs synthetic gene packages? Are you referring to what they are trying to do in synthetic biology? That's a whole grade up from the usual genetic modification, and rightly, we should be extra worried about the whole exercise. They treat organisms as lego pieces, and said so in public.

Paul Vonharnish Comment left 22nd July 2013 17:05:06
Dear Dr. Mae-Wan Ho: Thank you for your contributions to this critical issue. I have read several of your articles, and am wondering if you have seen the correlations between these unexpected DNA sequence breaks and the role of electromagnetic induction on cellular biology? Electromagnetic induction from household wiring, cellular tower systems, radio and television broadcast, and wi-fi mesh networks, cause single and double strand breaks in DNA. This is a short presentation from Dr. Martin Blank, but there are thousands of peer-reviewed studies in agreement.
http://www.youtube.com/watch?v=a6wLFeIrCtU&feature=player_embedded#at=268 Also see the 2012 BioInitiative Report on the EM radiation issue.
http://www.bioinitiative.org/report/wp-content/uploads/pdfs/BioInitiativeReport2012.pdf

Mae-Wan Ho Comment left 22nd July 2013 18:06:14
Paul, thank you for your comment. Yes indeed, organisms depend on electric and electromagnetic fields for intercommunication, they are precise and ultraweak, which is why external em fields can interfere, and very badly. My book the Rainbow Worm deals a lot with the sensitivity of organisms to ultraweak fields, basically because they are quantum coherent. I have written a lot on the subject, among the latest, Mobile phones damage the brain, and Life is Water Electric. Please find them on ISIS site using the Google search engine.

David Llewellyn Foster Comment left 28th July 2013 21:09:16
Dr Ho, thank you for this article that I propose to absorb very fully. I've been following your work now for sixteen years. I'd like to recommend a series of short amateur videos about soil biologist Dr Thierry Vrain who used to work for Ag Canada and is now an organic smallholder in Surrey BC. He is an outspoken, extremely experienced critic of GM, having worked in the field and his views are of significant value in my opinion
http://www.tonu.org/2013/05/27/thierry-vrain-part-six /

Dee Comment left 1st February 2015 09:09:14
Fantastic article. I have no knowledge of this area. Now I understand clearly what the dangers are. Do you do public speaking engagements through international media? I am convinced that much of the current conflict in the Ukraine is down to corporate interests in GMO being thwarted by the failed EU deal that led to the Maidan coup. EU farmers and consumers are hostile to this 'science' and Monsanto is widely distrusted. But they are already in the Ukraine and on double want to expand. I am also convincing that Russia is distinctly alarmed at the possibility of cross.border contamination. Thank you again for a brilliant article.

Paul Vonharnish Comment left 22nd September 2016 14:02:07
Hello: Your comment regarding the introduction of Agrobacterium to human disease is quite correct. The comments below are given by Alan B. MacDonald MD in his Fiberopathy Lecture of March 30 2014. Morgellon disease is only one of many genetically induced disease states in the human genome... > Published on Apr 6, 2014 ["Fiber accumulation diseases disturb healthy human tissue structure. Asbestos diseases result from entry of mineral geological fibers of various forms of Asbestos. These are EXTRINSIC FiberOpathies, meaning that the fibers are produced outside of the human body. Many examples of Extrinsic Fiber accumulation diseases exist. Disease producing Fiber accumulations may be the result of the body producing Mis-folded proteins and Pathological biochemical's resulting in INTRINSIC Fiberopathies. Amyloid diseases and Mad Cow Diseases are examples of diseases in which the Pathological fibers are manufactured within the living human body. Self Aggregation and Self Polymerization are hallmarks of INTRINSIC Fiberopathies in the human host. Correct identification of the true origin and chemical structure of Pathological fibers is essential in the understanding of FiberOpathities. This Presentation will review the State of the art in Fiber Analysis, and known mechanisms of disease in both Extrinsic and Intrinsic FiberOpathies. A Fiber accumulation diseases of Plants, namely GALL disease will then be surveyed. The Principle of Self Assembly or Self polymerization, as discussed for Amyloids, will be extended to the formation of Cellulose fibers in plant diseases. Finally, a discussion of the mysterious Fiber accumulations in human skin, namely Morgellons Diseases will be integrated with concepts in FiberOpathy Diseases in animals and plants. The concept of Morgellons diseases as an In Situ Cellulosic cutaneous Human FiberoOpathy will be introduced, based on Insect transmitted Agrobacterium infections to the human host by Tick vectors."] http://www.youtube.com/watch?v=47ByuAvmSC8

En

.....Personalized medicine in cancer therapy may well be extremely time-consuming and costly, if not downright misdirected. Cancer cells under attack in one pathway can switch to another pathway, or else develop drug resistance that enable them to survive and multiply, as bitter experience in cancer therapy has revealed [7] . 7. Garraway LA and Jänne PA.

Circumventing cancer drug resistance in the era of personalized medicine. Cancer Discovery 2012, published online 28 February 2012; doi: 10.1158/2159-8290.CD-12-0012

There is evidence in support of the view that cells become cancerous as the result of epigenetic 'adaptive' mutations in response to chronic stress or environmental stimuli that promote cell proliferation ([8] Cancer an Epigenetic Disease, SiS 54).

Tot slot: **Dr. Michael Godfrey**

Comment left 2nd April 2012 20:08:21

The continued search for the patentable "quick fix" and the implied cause being the patient's so-called genetic defects will continue to fail as the accumulating evidence confirms that at least 90% of cancers have environmental causes. As one example - high levels of (dental)transitional metals and xenoestrogens (parabens)have both been found in breast cancers. http://www.i-sis.org.uk/Personalized_Medicine_for_Cancer_Fact_or_Fiction.php

Kite Pharma Announces Positive Topline KTE-C19 Data from ZUMA-1 Pivotal Trial in Patients with Aggressive Non-Hodgkin Lymphoma (NHL)

Study Met Primary Endpoint of Objective Response Rate (p < 0.0001) at Interim Analysis

First Multicenter Pivotal Trial of CAR-T Therapy to Report Positive Outcome

Company Plans to Present Additional Data at Upcoming Scientific Meeting

SANTA MONICA, Calif.--(BUSINESS WIRE)-- Kite Pharma, Inc., (Nasdaq:KITE) today announced positive topline results from a pre-planned interim analysis of ZUMA-1 for its lead product candidate, KTE-C19, in patients with chemorefractory diffuse large B-cell lymphoma (DLBCL). KTE-C19 met the primary endpoint of objective response rate (ORR), p < 0.0001, with ORR of 76 percent, including 47 percent complete remissions (CR).

ZUMA-1 enrolled patients with chemorefractory aggressive NHL into two cohorts. Cohort 1 included patients with DLBCL, and Cohort 2 enrolled patients with transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL). Kite's intent is to seek regulatory approval of KTE-C19 in DLBCL, TFL and PMBCL based upon the combined data of both cohorts.

The interim analysis of ZUMA-1 evaluated the ORR in the first 51 patients in Cohort 1 with at least three months of follow-up. This analysis also included an additional 11 patients in Cohort 2. The table below summarizes the response rates from this interim analysis together with the previously reported results from the Phase 1 portion of ZUMA-1 (Neelapu ASCO 2016).

	ZUMA-1 Phase 1		ZUMA-1 Phase 2					
	DLBCL (n=7)		DLBCL (n=51)		TFL/PMBCL (n=11)		Combined (n=62)	
	ORR (%)	CR (%)	ORR (%)	CR (%)	ORR (%)	CR (%)	ORR (%)	CR (%)
ORR	71	57	76	47	91	73	79	52
Month 3	43	43	39	33	64	64	44	39
Months 6 and 9	43	43	Data Pending					

Across the combined 62 patients, the most common grade 3 or higher adverse events included neutropenia (66 percent), anemia (40 percent), febrile neutropenia (29 percent), thrombocytopenia (29 percent), and encephalopathy (26 percent). Grade 3 or higher cytokine release syndrome (CRS) and neurological toxicity was observed in 18 percent and 34 percent of patients, respectively. Two patients died from KTE-C19 related adverse events (hemophagocytic lymphohistiocytosis and cardiac arrest in the setting of CRS).

The Phase 2 interim outcomes in ZUMA-1 are largely consistent with results from the Phase 1 portion of the study and the National Cancer Institute (NCI) study based on the same CAR construct, a low-dose cyclophosphamide-fludarabine conditioning regimen, and Kite's proprietary manufacturing process (Kochenderfer ASCO 2016).

"ZUMA-1 enrolled patients with chemorefractory aggressive NHL, a disease that is very difficult to treat. The combined CR rate of 39 percent at three months is very exciting as it represents nearly a five-fold increase from the CR rate of 8 percent seen in the SCHOLAR-1 study in a similar patient population," said Jeff Wiezorek, M.D., Senior Vice President of Clinical Development. "ZUMA-1 is the largest CAR-T study reported in NHL. We were able to manufacture KTE-C19 for 99 percent of patients enrolled in the study, and successfully handle the study logistics and adverse event management at over 20 sites, most of which had no prior experience in CAR-T therapy."

Additional data from this interim analysis will be submitted for presentation at an upcoming scientific meeting. The primary analysis of 101 patients with chemorefractory aggressive NHL (DLBCL, TFL and PMBCL) will include approximately six months of follow-up and is expected in the first quarter of 2017.

"We are grateful to the study participants and investigators who have made this important research possible. What started at the NCI over a decade ago with the pioneering work of Steven A. Rosenberg, M.D., Ph.D., has evolved into a technology that has the potential to fundamentally change the outlook of patients with cancer. For patients with aggressive NHL, every day matters and a new treatment option like KTE-C19 is desperately needed," said Arie Belldegrun, M.D., FACS, Chairman, President and Chief Executive Officer of Kite. "I am proud of what we have achieved to date and excited to apply our advanced learnings from ZUMA-1 to our ongoing clinical development programs to bring continued innovation to patients and the scientific community at large."

ZUMA-1 is supported in part by funding from The Leukemia & Lymphoma Society (LLS) Therapy Acceleration Program®.

Conference Call and Webcast Details

Kite will host a live conference call and webcast today at 4:30PM Eastern Time (1:30PM Pacific Time) to discuss the results of this interim analysis. To

access the live conference call by telephone, please dial (877) 301-8565 (U.S.) or (678) 562-4240 (International). The conference ID number for the live call is 88811489. The webcast will be made available on the Company's website at www.kitepharma.com under the Investors tab in the Events and Presentations section. Following the live audio webcast, a replay will be available on the Company's website for approximately 30 days.

About KTE-C19

Kite Pharma's lead product candidate, KTE-C19, is an investigational therapy in which a patient's T-cells are engineered to express a chimeric antigen receptor (CAR) to target the antigen CD19, a protein expressed on the cell surface of B-cell lymphomas and leukemias, and redirect the T-cells to kill cancer cells. KTE-C19 has been granted Breakthrough Therapy Designation status for DLBCL, TFL, and PMBCL by the U.S. Food and Drug Administration and Priority Medicines (PRIME) regulatory support for DLBCL in the EU.

About Kite Pharma

Kite Pharma, Inc., is a clinical-stage biopharmaceutical company engaged in the development of novel cancer immunotherapy products, with a primary focus on engineered autologous cell therapy (eACT™) designed to restore the immune system's ability to recognize and eradicate tumors. Kite is based in Santa Monica, CA. For more information on Kite Pharma, please visit www.kitepharma.com. Sign up to follow @KitePharma on Twitter at www.twitter.com/kitepharma.

Cautionary Note on Forward-Looking Statements

This press release contains forward-looking statements for purposes of the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Forward-looking statements include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things: expectations regarding the clinical effectiveness and safety of KTE-C19 and timing of the primary analysis of ZUMA-1. Various factors may cause differences between Kite's expectations and actual results as discussed in greater detail in Kite's filings with the Securities and Exchange Commission, including without limitation in its Form 10-Q for the quarter ended June 30, 2016. Any forward-looking statements that we make in this press release speak only as of the date of this press release. We assume no obligation to update our forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

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