Humans **I**n **V**ariety / **A**dapted **I**mmune **D**evelopmental **S**ymbiosis

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Abstract/ Summary

In this paper I will demonstrate a new prospective insight on the evolution of the Immune System of Humans. The Human Genome Project which discovered our genetic background by reducing the amount of protein coding genes to approximately 20.000 and augmented the RNA transcriptions, assumes vast proportions for future research which is centred on health and disease.

Thus the MHC-complex and the HLA-system give new insights on the co-evolution of the species particularly of mammals (and primates) with microbes. We have to take in account that evolution is an ongoing process which renders creatures susceptible to diseases in connection with environmental stimuli –specifically stress- leading to insights in the causes of many complex diseases like malaria, diabetes, lupus, multiple sclerosis, rheumatoid arthritis, many infections, influenza and cancer.

The HIV/AIDS- hypothesis will be dismantled specifically the sexual transmission of a virus. Instead an evolutionary adaption of ancient retrovirus established in the human genome renders viruses in a symbiotic interaction with the host genes of the immune system to participants in cell communication.

The ethics of the 21st century make us responsible for not prolonging a not wanted genocide by underestimating weaker voices in science. Instead we have to focus our scientific view on the latest research and apply the results for a life in dignity for all humans.

I. Introduction

As previously shown in my paper "Reconciliation between Pure Scientists and AIDS-Dissidents:
Could an ancient retrovirus, RNA-interference and stress be the answer to the divergent opinions ?" there is evidence , that HIV is an ancient retrovirus acting as a gene that can be influenced by environmental stress and small RNAs.
The Human Genome Project (HGP) gave us the information about less protein coding genes than we were aware before. Instead we are now eagerly discovering the Human Epigenome (HEP), looking for the methylated genes **[1,4]** and as to Jenuwein and Allis **[2]** histones of the DNA because of the big importance of gene expression in the different cells and tissues of our bodies**[3]**.
The Human Microbiome Project (HMiP) tries to specify the genes of the microbes living on and in our bodies **[5**]. We have 10fold more microbes than we have cells in one person and the genes of our symbioses, which contribute to our digestion, vitamin supplementation and gene activation are of high interest for research. The co-evolution of bacteria and their viruses gives new information about the acceleration of evolution **[6, 8]** and lateral (horizontal) gene transfer from microbes to their hosts **[7].** The Human Protein Project (HPP) and the Human Metabolom Project (HMP) will give additional information on the complexity of life and evolution.

II. The Diversity of Humans

"The genetic structure of the indigenous hunter-gatherer peoples of southern Africa, the oldest known lineage of modern human, is important for understanding human diversity "**[9].** These hunter-gatherers, known as Khoisan, San, or Bushmen, are genetically divergent from other humans. In term of nucleotide substitutions, the Bushmen seem to be, on average more different from each other than, for example, a European or an Asian. There is also a discontinuity between local hunter-gatherers and central Europe´s first farmers **[10].** By analyzing ancient DNA of neolithic hunter-gatherer and contemporary Scandinavians, Malstrom et al. revealed a lack of continuity **[11].** Humans underwent an adaption process which was influenced by geography **[12].** This resulted in differences including the immune system. People of African descent show reduced neutrophil count due to a regulatory variant **[13].** There is also an extensive genetic diversity in the HLA class II region of Africans from Gambia and Malawi. This diversity is twice as extensive as found in northern Europeans **[14].** In consequence we find differences in humoral responses between Ethiopian and Swedish persons who are claimed to be "infected" by HIV **[15].** Therefore it is necessary to investigate the nature and biological background of the immune system which is responsible for cell activation, receptor and antibody generation and the communication between all partners involved in the immune response.

III. The MHC/HLA-System and its Origin

Most interesting is the study from the Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 ISA, UK published in Nature/Vol 425/23 October 2003 "The DNA sequence and analysis of human chromosome 6" **[16, 30]** . This chromosome constitutes about 6% of the human genome and harbours 1,557 genes and 633 pseudo-genes. Within the essential immune loci of the major histocompatibility complex, HLA-B was found to be the most polymorphic gene. Among these are genes directly implicated in diseases like cancer and autoimmunity. Having a look at the supplementary tables, which give full lists of HLA allele-associated HIV polymorphisms in Protease, Reverse Transcriptase, VPR and Nef, they show that more than 240 gene variants of Nef are encoded by HLA. There are also tremendous variants for the other genes. The main effect of Nef is to block transport of MHC-I molecules to the cell surface, leading to accumulation in intracellular organelles **[23a].**

This study and the report from Brumme et al. "Evidence of Differential HLA Class I-Mediated Viral Evolution in Functional and Accessory/Regulatory Genes of HIV-1" [25] confirms the nature of HIV – showing that it is of endogenous origin – part of our genome and constituted by the high variability of the genes, which elucidates the variability of the HIV-variants and the immune escape. As Hedrick already stated in 1994 there is a high heterozygosity, reaching over 60% at some amino acid sites with primary function. In some populations there is an observed deficiency in homozygotes. There seems to be a balancing selection in the MHC region related to the function for protection against microbes. Probably there is a selection at the MHC involved in non-random mating and maternal-fetal interactions in pregnancy **[17]**.

The Mexican cohort **[27]** and the ANRS Genome Wide Association 01 Study **[28]** conclude that HLA/MHC controls HIV-reservoir and replication.

Gyllenstein et al. declared an allelic diversity that is generated by intraexon sequence exchange at the DRB1 locus of primates **[18].** In correspondence Doxiadis et al. state a phylogenetic evidence that supports the notion of the generation of new HLD- DRB genes as a dynamic and steadily ongoing process. This is due to the presence of indels (insertions/deletions), mainly mapping to intron. The research compared a large number of full-length sequences of rhesus macaques, chimpanzees and humans. As no evidence was found for convergent evolution, the combination of these observations indicates that ancient peptide binding motifs are frequently reshuffled among duplicated members of the HLA-DRB multigene family **[19].** Oosterhout stated in his review on population genomics and epidemiology the concern of transposons in the MHC of the vertebrate immune system. Transposons constitute a large proportion of the vertebrate genome, and on average more than 40% of the mammalian genome consists of these parasitic elements. TEs have a non-random distribution throughout the genome, and they show an increased density in the MHC in a wide range of vertebrates **[20].**

Genetic drift may play an important role in the population genetics.

John, Moore, James and Mallal from the Centre of Clinical Immunity and Biomedical Statistics, Royal Perth Hospital and Murdoch University, Western Australia published a paper "Characteristic **non-synonymous mutation** in HIV-reverse transcriptase sequence encoding an HLA-B7 restricted CTL epitope is associated with increased viral load". Characteristic mutations in HIV RT are evident at a population level. For-example, the presence of HLA-B7 in the Western Australian HIV Cohort Study is strongly associated with non-synonymous mutation at position 135 of HIV RT which is an anchor residue of a HLA B51 restricted CTL epitope. This mutation allows escape from the host CTL response. These results are important because of the occurrence on drug induced mutations **[21].**

Among the many host cell-derived proteins found in HIV-1, HLA-II appears to be selectively incorporated onto virions. **[21a].** The genetic diversity of the envelope glycoprotein from HIV-1 isolates from 8 countries in Africa is studied by Louwagie et al. The data confirm the existence of several genetic subtypes and broaden the genetic variability observed for envelope subtypes. The geographic spread of different subtypes was shown to be substantial **[21b].** "Rapid Evolution of Major Histocompatibility Complex Class I Genes in Primates Generates New Disease Alleles in Humans via Hitchhiking Diversity" The diversity created by single nucleotide variations (SNV) was not evenly distributed. It was rather concentrated within the gene-clusters HLA-A and HLA-B/C. These polymorphisms seem to be species specific. They might have been selected in adaption to the constantly evolving microbial antigenic repertoire **[26].** The Mexican cohort **[27]** and the ANRS Genome Wide Association 01 Study **[28]** find that HLA/MHC controls HIV-reservoir and replication.
Clerici and Shearer **[22]** present a model "The Th1-Th2 hypothesis of HIV infection: new insights" where they claim activation-induced, cytokine modulated, programmed cell death as a major factor in the pathogenesis of HIV infection in AIDS. Immunoregulatory cytokines are also produced by non T-cells, including monocytes/macrophages, natural killer cells and B-cells. So the authors prefer the terms type 1 and type 2 responses. They suggest an endogenous imbalance in the immunoregulatory cytokine network. HIV resistance in female sex-workers in Northern Thailand seems to be influenced by synergistic impact of HIV-specific cytotoxic T lymphocytes, HLA-A11, and chemokine –related factors **[23].**
Transcriptional analysis for host factors required by HIV-1 was performed by RNA interference. More than 250 HIV-dependency factors were identified. These proteins participate in cellular functions. Transcriptional analysis revealed that these genes were enriched for high expression in immune cells **[24].** In addition HIV incorporates HLA-DR which is a cell-surface protein in big quantities. Other proteins that have been found are HLA class I and various cell adhesion proteins as well as proteins from inside the cell like cyclophilin A, actin and ubiquitin **[29].** Thus HIV is not a virus.
Conclusion: HIV is an evolutionary adapted and partly active variable and heritable gene construct of our immune (MHC/HLA)-system.

IV. Sperm Proteins, Pregnancy and Protection of Health

The influence of human semen on immunity is of importance for estimating the impact on reactions concerning sexuality and child development. Jeremias et al. claim that human semen is both an inducer of an anti-inflammatory TH2 immune response and an inhibitor of TH1 cell mediated immunity. The induction of interleukin 10 and 70 kDa heat shock protein gene transcription and IFN-γ was examined **[31].** Virus-encoded (ORF) homologs of cellular interleukin-10 range in sizes for cellular Il-10 proteins **[32].** The result in both cases is a shift from T1 to T2 immune response which protects cells from immune attack an absolute necessary prevention for the fetus which could be otherwise attacked by maternal response to paternal antigens in the womb.There is a cross-reactivity of sperm and T-lymphozyte antigens that results in higher titers of antibodies in couples with antisperm immunity as compared with "normal" couples **[33].** A number of studies have suggested that an immune response to human leukocyte antigen HLA alloantigens may contribute to protection against HIV infection **[34].** Infectivity for HIV through heterosexual transmission is low, and sexual transmitted diseases (STDs) may be the most important cofactor for transmission **[35].**
Heterosexual and homosexual monogamous partners practising unprotected sex develop CD4+ and CD8+T cell proliferative responses to the partners´ unmatched cells and a minority may be tolerated. These together with other research results suggest that allogeneic immunity

may play a significant role in HIV **[36].** HIV-1 gp120 is an immunoglobulin superantigen which can bind to pre-immune serum Ig. The level of pre-immune anti-gp120 IgG is a polymorphic population trait, and low levels are a potentially specific and significant factor in homosexual transmission of HIV infection **[37].**
HIV-1 binds and enters normal sperm and can transfer HIV-1 like particles to normal human oocytes **[38].** Already in 1991 at the AIDS conference in June Calarco and Whitmer showed that HIV-1 expression can occur during early mammalian development **[39].**
Background maternal (rather than paternal) allergy confers stronger allergy risk for the offspring. Maternal responses to fetal antigens were related to fetal immune responses and subsequent allergy. The number of previous pregnancies was associated with stronger maternal responses to fetal alloantigens **[40].**
Conclusion: HIV is a natural product in sperms which has its origin in the HLA and protects the fetus from maternal rejection of paternal antigens by shifting T1 to T2. Heterosexual transmission of HIV is only suggested with additional pathogens in STDs. Homosexual transmission is due to rejection of alloantigens. Allogeneic immunity protects from infection but can be related to allergies also in the offspring.

V. Auto-, Alloreactions and Diseases

Concerning to the afore mentioned HIV is a regulatory and even life promoting element of the immune system which has evolved in millions of years as a symbiotic partner that interacts in health and disease. Multiple interactions in cell communication are proofed concerning HIV specifically in GALT (gut associated lymphoid tissue) which makes sense for protecting the body from strange invaders. Mehandru et. al. from the Mount Sinai School of Medicine, and the Aaron Diamond AIDS Research Center emphasize that the gastrointestinal tract - associated lymphoid tissue constitutes the largest immune compartment in the body. More than 60% of the bodies total lymphocytes is estimated to be T-cell associated with the small intestinal epithelium **[45].** Dissemination of virus to GALT is mediated by an integrin and Gp 120 leading to the formation of virological synapses, which facilitate efficient cell-to-cell spreading of HIV-1 **[41].** Retroviral assembly is driven by Gag release which is promoted by clathrin adaptor complex AP-1 to intracellular sites of active budding – the machinery that forms intraluminal vesicles of the multivesicular body MVB. Protein sorting is critical for diverse cellular functions, like receptor down-regulation, degradation of membrane proteins and lysosome like organels, which includes attachment of ubiquitin to cargo proteins **[42**]. Teis et al. state that a certain complex (ESCRT) is required for cargo sequestration and vesicle formation during MVB sorting **[43].** In addition direct cell-cell communication mediated by plasma membrane-spanning gap junction (GJ) channels is vital to all aspects of cellular life. Cells internalize GJ in response to various stimuli. In this process clathrin, dynamin (GTPase) and other proteins are involved in internalizing double-membrane vesicles into cells **[44].** Exosomes correspond to the multivesicular body and are released upon exocytic fusion with the plasma membrane. They function in intercellular communication during the immune response. They might be involved in tissue developmental processes and seem to be of ancient origin **[46].** Stephen J. Gould has created the "Trojan exosome hypothesis" in which he and his colleagues propose that retroviruses exploit a cell-encoded pathway of intercellular vesicle traffic, exosome exchange and last but not least that alloimmunity is a central component of antiretroviral immunity **[47].** Antibodies against HLA neutralize HIV-1 in vitro. This was proved by alloimmune sera from polytransfused patients **[50].** An Article from Frank P. Ryan published in the Journal of The Royal Society of Medicine from 2004 talks about "mutualistic

symbiosis" and HERVs in our genomes that have lost the ability to survive independently, but their removal from our genome would also make us extinct" **[48].**
The American Society of Microbiology regards the subject of viral contribution to host evolution as so important that it has commissioned Luis Villareal to write a book to educate the next generation of scientists (Viruses and the evolution of life) **[49].** The envelope glycoprotein of HIV-1 gp120 has been identified as a member of the Immunglobulin superantigens (Ig-SAg) which bind selective to an unusually high proportion **of endogenous nonimmune Ig,** that are members of the VH3 Ig gene family **[51].** The importance for diseases might be that the up-regulation of expression of endogenous retroviral superantigens has substantial implications for understanding the pathology of virus infections i.e. Epstein-Barr virus **[52].** SAgs seem to be involved in allergy and autoimmune diseases **[53].** Thus they might be used as a therapeutic agent in the treatment of cancer. The light chain subunits of antibodies cloned from patients with systemic lupus erythematosus bind and hydrolize gp120 sAg **[55].** Already in 1990 research on other lupus patients stated about one third of them produced antibodies to the p24 gag protein of HIV-1 as demonstrated in Western blotting **[56].** In a study concerning HLA class I and II antigens in South African Blacks with Grave´s disease there was a significant increase in the frequency of HLA-DR3 in patients compared to control subjects, and a relationship in the DRI locus **[54].** Grave´s disease is due to autoimmunity. A study from multiple sclerosis patients provides "direct proof" that HTLV-I, which is similar to HIV, is involved in MS disease process **[57].** Approximately 25% of severe haemophilia A (HA) patients develop antibodies to factor VIII protein, which is due to impact of polymorphisms of the MHC complex class II and other factors like interleukin-10 **[58].** As antibodies to blood products were defined as HIV contaminated in previous studies **[59]** the reported data from 2009 may now be interpreted as gene expression of distinct SNPs. There is also a relation of HIV-1 acquisition to hormonal contraception and to herpes simplex virus type 2 among Kenyan women **[60].** The genetic predisposition to type 1 -diabetes is associated with genes of the HLA system, specifically with HLA-DR and –DQ **[61].** Research concerning transgenic mice resulted in activation of gene expression in HIV by Mycobacterium tuberculosis and suppression after antimycobacterial chemotherapy **[62].** This proves the bystander function of HIV in tuberculosis. As a result HIV is not the cause of the disease but tuberculosis is the disease and HIV is part of the communication system and part of an active immune system. Gene regulation is subject to hormone control specifically to corticosteroids in retroviral systems and to pregnancy in women **[63].** This might indicate stress and placental involvement of testing HIV positive. The HIV-1 VPR-protein might be protective against cancer by inducing apoptosis in tumour cells **[64].** Cell surface MHC class I-like proteins are up-regulated upon cell stress, including viral and bacterial infection and tumour transformation and are recognized by NKG2D a C-type lectin- activating receptor **[65].** Stress and depressive symptoms are associated with decrease of protective NK and CD8+ T lymphocytes in HIV-infected men **[66].** Individuals from Central Africa have a higher level of immune system activation compared with non-African populations that might be due to multiple and frequent exposures to viral, bacterial and parasitic antigens **[67].**
By comparing medical treatment for "HIV-infection" resistance to zidovudine was significantly higher in individuals with disease progression than in those from the control group **[68].** The variable region (V3) of the gp 120 surface envelope glycoprotein of HIV-1 is a highly variable disulfide-bonded structure which triggers cell infection and escape from antiviral drugs, specifically entry inhibitors and is a target for neutralizing antibodies **[69].**
After effective highly active antiretroviral therapy (HAART) people with HIV might experience an "immune restoration syndrome" which is established by lymphocyte recovery period and might be manifested by infectious agents such as cytomegalovirus or mycobacterium avium intracellulare or a sudden onset of sarcoidal granulomatous reactions. An uncontrolled Th1 response as a result of cytokine alterations via Il-2 is the causative

mechanism **[70]** as the authors of this study claim. In HIV Il-1 is increased which shifts the reactions to Th2 response. Reuse, Calao Kabeya et al. from Belgium propose a synergistic activation of HIV-1 expression by deacetylase inhibitors and prostratin as implications for treatment of latent infections. This might reduce the size of latent HIV-1 reservoirs in HAART-treated patients **[71].** A study from 2008 found an inactivation of HIV-1 by modification of nucleocapsid zinc fingers **[72].**
Conclusion: HIV is a symbiotic agent in GALT and other tissues, thus protective against microbes due to nutrition. Exosomes are produced and function in cell communication processes. Gp 120 is active as a superantigen that increases Th2 related antibody production in infections as a "booster" and might be due to allergy and autoimmunity. Stress is involved in gene expression. HIV is protective to cancer. Medications and HAART might have different (negative) impacts on the balance of the Th1 / Th2-system.

VI. Evolution Never Ends

Human endogenous retroviruses (HERVs) have been estimated to be part of the genome and are replication incompetent. HERV-W encodes a highly fusogenic membrane glycoprotein within functional retrovirus genes which has been proposed to play a role in normal placental development not only in humans but also in simian and pig cells. The HERV-W entered the genome of primates approximately 25 million years ago. They are replication defective because of mutations within functional retrovirus genes. The existence of individual open reading frames corresponding to gag, pol and env have been shown to encode proteins in some cases. HERVs could be potentially assembled into infectious virions through transcomplementation with virion proteins encoded by different HERVs **[73].**
This research from 2000, published in the Journal of Virology 2001, by Dong Sung An et al. from UCLA AIDS Institute, Los Angeles, California was done before the Human Genome Project was published and the tremendous occurrence of HERVs were detected in the Human genome specifically in the MHC/HLA. The authors also claim that a functional envelope glycoprotein would confer the ability to be transmitted vertically and / or horizontally. Kumar et al from All India Institute of Medical Sciences, New Delhi, India revealed a two fold higher expression of CXCR4 mRNA in early as compared to term human placenta. Chemokines and their receptors may play a crucial role in angiogenesis and proliferation in cell function. The receptor expression may be developmentally regulated and its role in the early stages of pregnancy is implicated when embryogenesis and organogenesis takes place **[74].** They suggest that CXCR4 may not have a direct role in HIV infection, as only 1-2% of the placental transmission of HIV takes place in the early placenta. Allogeneic stimulation in early pregnancy improves pre- and postnatal ontogenesis by activation of the female immune system and enhancement of rise of plasma progesterone. The dissimilarity of mother and foetus induces stress resistance in the progeny of BALB/cLac mice **[75].** This evolutionary development acts also as a mechanism for creating phenotypic diversity **[77].** In seropositive children a well known cross-reactivity between HLA-DR and gp 120 is marked **[76], [78].**
Conclusion: These research results indicate an evolutionary effect of HERVs and cell receptors and other proteins of the immune system and an allogeneic stimulation in pregnancy which is protective for life.

VII. About Testing, Responsibility and Ethics

What is the conclusion from the scientific research all together?

1. HIV does not exist. It is gene expression from the HLA-system for generating immune molecules in and between cells or a laboratory gene construct in experimental design.
2. People have differences in their MHC/HLA genes and their products thus South Africans test naturally most often HIV positive, which is of evolutionary purpose.
3. To test HIV positive does not mean to be infected with a virus.
4. A positive test result in mother and child is a normal biological process, as the mother fights the allograft (fetus) and the child gets the antibodies. Pregnancy is not a disease!
5. White blood cells have a genetic marker on the cell membrane which can stimulate allergic reactions through transfusion of blood products and by sexual contact with body fluids. Homosexuals and drug users have problems with alloreactions (allergy) and stress but not with an exogenous virus! Other sexual transmitted diseases might be a problem, thus condoms are effective.
6. The HLA (HIV)-genes are protective in other diseases (some cancers).
7. We have to discuss the terms “Virus” , “Exosomes” , “Endosomes” and “Genes” as evolution applies horizontal gene transfer and communication particles in normal biological processes like pregnancy and T1/T2-balance and in diseases **[79] [80].**
8. Stress might lead to dysbalance of the immune system and thus to disease.
9. Evolution is still going on. Thus we will find new “HIV-mutants” (transposition). The diversity of the MHC/HLA-system is granting co-evolution with microbes and is due to symbiogenesis.
10. We have to stop testing because the tests are not scientifically proofed and give false results. Testing for HIV is absolutely unethical!
11. Testing leads to fear and stress (nocebo effect) and might induce disease.
12. Treating with antiretrovirals might be harmful and even kill people. Drugs induce mutations and lead to disease. There is no specific disease that could be called AIDS. AIDS does not exist without testing. We have to be responsible for the living conditions of people, like food, vitamins, selen and minerals as well as pure drinking water, drug prevention and (oxidative) stress reduction.

- ***We are responsible for what we do and what we neglect.***
- ***Later generations will judge on our behaviour in science and ethics.***
- ***We have to stop this wrong assessment immediately!***

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