Epigenetics from HIV to Immunization:

New Prospects on Health and Disease

IT IS EASIER TO BUILD STRONG CHILDREN THAN TO REPAIR BROKEN ADULTS...

-F. DOUGLASS-
„Nothing in Biology makes sense, except in the light of evolution“

This is from a 1973 essay by the evolutionary biologist and Russian Orthodox Christian Theodosius Dobzhansky, Criticising Young Earth creationism and espousing Evolutionary Creationism.

(American Biology Teacher, volume 35, 125 –129)
Overview

1. Genetics, HIV and the Immune System
2. Epigenetics
3. Microbes in Evolution
4. Immunization
5. What does it mean to be Human?
1. Genetics, HIV and the Immune System
2. Epigenetics
3. Microbes in Evolution
4. Immunization
5. What does it mean to be Human?
Genes for proteins
RNA molecules
???
Genomes: Coding, non coding, repetitive elements

PLANT and HUMAN: Both harbour about 25,000 genes

- S. CEREVISIAE: ~6,000 Gene
  - 16 Chromosomen
- S. POMBE: ~5,000 Gene
  - 3 Chromosomen
- ARABIDOPSIS: >25,000 Gene
  - 5 Chromosomen
- DROSOHILA: >14,000 Gene
  - 4 Chromosomen
- MAUS: >25,000 Gene
  - 20 Chromosomen
- MENSCH: >25,000 Gene
  - 23 Chromosomen


Christl Meyer, AIDS Research, Vienna/ Austria, 2018
Effect of the „kit“-gene

Figure 1-53 Human and mouse: similar genes and similar development. The human baby and the mouse shown here have similar white patches on their foreheads because both have mutations in the same gene (called kit), required for the development and maintenance of pigment cells. (From R.A. Fleischman, Proc. Natl. Acad. Sci. USA 88:10885–10889, 1991. © National Academy of Sciences.)
Example: Trisomie 21 (Down Synrom)
Genduplication as the driving force behind Evolution
“Any ape can reach for a banana, but only humans can reach for the stars.”

—V.S. Ramachandran
Over half of our DNA comes from retro-transposons, genetic elements that independently multiply and spread through the genome (de Koning et al., 2011).

On the move

The mechanisms by which a retrotransposon called LINE-1 duplicates itself and spreads through the human genome are becoming clearer. Martin. eLife 2018;7:e34901. DOI: https://doi.org/10.7554/eLife.34901

In mammals, a retrotransposon called LINE-1 is responsible for most of these multiplication events, either duplicating itself or lending its ‘photocopying’ machinery to other genetic elements.
Barbara Mc. Clintock (Nobel price for Physiology and Medicine 1983) Transposons „jumping genes“
Transposons are small pieces of DNA that get cut from one spot and spliced into an inappropriate spot—often right in the middle of a gene. The gene’s sequence is altered and it can no longer be used to produce the protein it codes for.

Transposons are jumping genes!
Humans and chimpanzees, which diverged from a common ancestor some 5 million years ago, differ in their genome sequences only in about 1 – 2 %.

Proviruses fixed in the germ line can provide us with a fossil record of viruses long extinct in the population.

In human DNA only 2- 3 % of the genome are coding. 97 % are noncoding (formerly called „junk DNA“). This DNA might be involved in gene regulation processes.

In humans, there are about 80.000 proviruses or their remnants, comprising about 6-8% of the genome, or about twice as many as genes.

John M. Coffin, Prof of Molecular Biology and Microbiology, Tufts University:

„There is more provirus in us than there is us in us“.
The Human Genome Project discovered our genetic background by reducing the amount of protein coding genes to approximately 20,000 and augmented the RNA transcriptions.


5. Bergmann JH, Spector DL. Long non-coding RNAs .....
Aleksandra E. Kornienko, Christoph P. Dotter, Philipp M. Guenzl, Heinz Gisslinger, Bettina Gisslinger, Ciara Cleary, Robert Kralovics, Florian M. Pauler and Denise P. Barlow

“Long non-coding RNAs display higher natural expression variation than protein-coding genes in healthy humans”

Human Genome

Nature 409, 860-921 (15 February 2001) / doi: 10.1038/35057062; Received 7 December 2000; Accepted 9 January 2001

Initial sequencing and analysis of the human genome

International Human Genome Sequencing Consortium Eric S. Lander...

...Here we report the results of a collaboration involving 20 groups from the United States, the United Kingdom, Japan, France, Germany and China to produce a draft sequence of the human genome.

...Hundreds of human genes appear likely to have resulted from horizontal transfer from bacteria at some point in the vertebrate lineage.

...Dozens of genes appear to have been derived from transposable elements.

...large recent segmental duplications... much more frequent in humans...
A major part of the immune system:

**MHC** - Major Histocompatibility – Complex and

**HLA** - Human Leucocyte Antigen – System give new insights on the co-evolution of the species, particularly of mammals (and primates) with microbes.
Introduction

DNA methylation is indispensable for vertebrate genome function. It is involved in diverse genomic processes such as gene regulation, chromosomal stability, and parental imprinting (Bird 2002), and interest in the function of DNA methylation is further heightened by the various human diseases associated with epigenetic dysfunction, a notable example being cancer (Laird 2003). However, the DNA methylation profile of the human genome is still largely a mystery.

The sequencing of the human genome (HGSC 2001) and creation of a whole-genome map of single nucleotide polymorphisms (SNPs) (Sachidanandam et al. 2001) laid the foundation for the Human Epigenome Project (HEP). For the HEP, we aim to analyse DNA methylation in the regulatory regions of all known genes in most major cell types and their disease variants, along with producing high-density snapshots of non-genic regions spread evenly across the human genome. Although genome-wide DNA methylation analyses have been performed previously (Costello et al. 2006; Strichman-Almashu et al. 2002), the HEP is the first systematic whole-genome study of DNA methylation at the sequence level.

As a prelude to the HEP, here we report the results of the HEP pilot study. DNA methylation profiling of the human major histocompatibility complex (MHC). The MHC, located on Chromosome 6 (6p21.3), is one of the most gene-dense regions in the human genome, containing genes with a high diversity of function, many of which are involved in the innate and adaptive immune systems. We chose to analyse the MHC for the pilot HEP study for three main reasons. (i) The MHC is associated with more diseases than any other region of the human genome, and therefore the generated data will be of interest to researchers with diverse biomedical interests. (ii) It is also the most polymorphic region in the genome, and therefore the data will allow study of the potential effects of the loss or gain of cytosine-guanine dinucleotide (CpG) methylation sites (due to SNPs) on gene expression and possibly other phenotypes. (iii) At the time when the HEP pilot study was initiated in 1999 (Beck et al. 1999), the MHC was one of the few regions within the human genome for which finished sequence and annotation were readily available (MHC Sequencing Consortium 1999).

Received June 6, 2004; Accepted September 25, 2004; Published November 25, 2004

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Abbreviations: CpG, cytosine-guanine dinucleotide; DNS, distributed annotation system; HEP, Human Epigenome Project; IG2, insulin-like growth factor 2; MHC, major histocompatibility complex; MALDI-MS, matrix-assisted laser desorption/ ionisation mass spectrometry; METHANE, Methylation Analysis Engine; MFP, methylation variable position; ROI, region of interest; SNP, single nucleotide polymorphism; TMT®, inversion-XI

Academic Editor: Peter B. Becker, University of Munich
HLA-sequences on Chromosome 6

Christl Meyer, AIDS Research, Vienna/Austria, 2018
HLA classes
Christl Meyer, AIDS Research, Vienna/Austria, 2018
HLA 6p21.3

"Virus" binding site

Christl Meyer, AIDS Research, Vienna/Austria, 2018
HIV Model

http://www.geocities.ws/chiakwongmin/HIV/HIV_photo-picture/
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Supplementary Table 1a: Full list of HLA allele-associated HIV polymorphisms in Nef

Brumme et al
Supplementary Table 1b: Full list of HLA allele-associated HIV polymorphisms in Protease, Reverse Transcriptase and VPR

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<td>B51</td>
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<td>B02</td>
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<td>B38</td>
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<td>B40</td>
<td>H</td>
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<td>B27</td>
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<td>R</td>
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<td>K</td>
<td>R</td>
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<td>R</td>
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<td>A</td>
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<td>A25</td>
<td>C</td>
<td>E</td>
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<td>VPR</td>
<td>55</td>
<td>A33</td>
<td>C</td>
<td>T</td>
</tr>
<tr>
<td>VPR</td>
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<td>A02</td>
<td>C</td>
<td>T</td>
</tr>
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<td>VPR</td>
<td>63</td>
<td>A26</td>
<td>C</td>
<td>T</td>
</tr>
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<td>B38</td>
<td>V</td>
<td>I</td>
</tr>
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<td>A29</td>
<td>T</td>
<td>T</td>
</tr>
<tr>
<td>VPR</td>
<td>84</td>
<td>B50</td>
<td>T</td>
<td>T</td>
</tr>
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<td>VPR</td>
<td>84</td>
<td>C16</td>
<td>C</td>
<td>T</td>
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<td>A31</td>
<td>C</td>
<td>Q</td>
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<td>C02</td>
<td>C</td>
<td>Q</td>
</tr>
<tr>
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<td>86</td>
<td>C06</td>
<td>C</td>
<td>P</td>
</tr>
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<td>VPR</td>
<td>88</td>
<td>C01</td>
<td>G</td>
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<tr>
<td>VPR</td>
<td>93</td>
<td>A25</td>
<td>S</td>
<td>S</td>
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</tbody>
</table>
Marked Epitope- and Allele-Specific Differences in Rates of Mutation in Human Immunodeficiency Type 1 (HIV-1) Gag, Pol, and Nef Cytotoxic T-Lymphocyte Epitopes in Acute/Early HIV-1 Infection

Zabrina L. Brumme et al. Partners AIDS Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

The so called mutation of the „HI-Virus“
“Life has a tendency to plurality, being colourfully, to independence, simply to freedom. The totalitarian system demands monolithical unity, uniqueness and discipline.” (Vaclav Havel, dissident and president – Charta 77 /Chech Republik)
What we realize

...and what is hidden.

Das, was wir sehen...

... und das, was verborgen ist.
HIV can not be the cause of AIDS – it is a genetic factor in evolution.

Figure 2. Schematic representation of the parallelism between human and nonhuman primate (NHP) models of HIV/SIV pathogenesis. EC, elite controllers; RP, rapid progressors; VNP, extreme viremic nonprogressors. (Adapted, with permission, from Guido Silvestri 2010.)

Cite this article as *Cold Spring Harb Perspect Med* 2012;2:a007203
The GAG "viral protease" is under positive selective pressure

Figure 3. Multilayer representation of HIV-1 clade B Gag. The various information layers align the sites under positive selective pressure (red), conservation scores (<90% conserved, black), the structured domains at the protein (dark blue), and viral RNA level (light blue) (Watts et al. 2009), the position of CTL (dark green), antibody (light green), and T helper epitopes (turquoise) compiled in the Los Alamos HIV database, and the Gag region overlapping with the viral protease (purple).

Cite this article as Cold Spring Harb Perspect Med 2012;2:a007203
„Dark matter“ of the genome may play a major biological role in cell development and metabolism including diseases like cancer.

Involved are many different Non coding RNA genes that have recently been detected.
Questions (concerning tests):

1. Is the test save and valid?

2. Does early detection prolong life-span?

3. Does early detection improve life-quality?
HIV-Test Insert:

Human Immunodeficiency Viruses (HIV-1/HIV-2): (Recombinant Antigens and Synthetic Peptides)

SENSITIVITY AND SPECIFICITY
At present there is no recognized standard for establishing the presence or absence of antibodies to HIV-1 and HIV-2 in human blood.
Specificity is based on testing of random blood donors and hospitalized patient populations (serum and plasma specimens).
**Western Blot Test**

<table>
<thead>
<tr>
<th>HIV WESTERN BLOT STRIP</th>
<th>AFR</th>
<th>AUS</th>
<th>FDA</th>
<th>RCX</th>
<th>CDC 1</th>
<th>CDC 2</th>
<th>CON</th>
<th>GER</th>
<th>UK</th>
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<th>MAC</th>
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<tr>
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<td>ANY 2</td>
<td>ANY 1</td>
<td>ANY 1</td>
<td>ANY 1</td>
<td>p160/ p120 AND p41</td>
<td>p160/ p120 OR p41</td>
<td>p160/ p120 OR p41</td>
<td>ANY 1</td>
<td>ANY 1</td>
<td>ALL 3</td>
<td></td>
</tr>
<tr>
<td>POL</td>
<td>p32 AND</td>
<td>ANY 1</td>
<td>AND p32</td>
<td>ANY 1</td>
<td>AND OR p32</td>
<td>AND OR p32</td>
<td>ANY 1</td>
<td>AND OR</td>
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<tr>
<td>GAG</td>
<td>ANY 3 GAG OR POL</td>
<td>p24 AND</td>
<td>ANY 1</td>
<td>p24</td>
<td>p24</td>
<td>p24</td>
<td>ALL 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AFR = Africa; AUS = Australia; FDA = US Food and Drug Administration; RCX = US Red Cross; CDC = US Center for Disease Control; CON = US Consortium for Retrovirus Serology Standardization; GER = Germany; UK = United Kingdom; FRA = France; MACS = US Multicenter AIDS Cohort Study 1983-1992.

*Source: Val Turner, AIDS Research, Vienna/Austria, 2018*
What does this mean?

If you are tested HIV-positive in Germany or Africa, you can fly to Australia or France with your Western-blot test result and be claimed HIV-negative only because of the different standards that are applied.
False-positive human immunodeficiency virus type 1 western blot tests in noninfected blood donors.

Transfusion, 36: 45–52. doi: 10.1046/j.1537-2995.1996.36196190514.x

Low-risk blood donors (*PCR negative*) can have false-positive results on WB tests. Increased detection of env-only and p24/env-only WBs appears related to the enhanced sensitivity of newer enzyme immunoassays to gp41 and p24 antibodies.

Article first published online: 28 FEB 2003

Keith R. Sayre, MBA, Product Manager, AIDS/Hepatitis Business Unit, Ortho Diagnostic Systems, Inc., Raritan, NJ.
Roger Y. Dodd, PhD, Head, Transmissible Diseases Laboratory, American Red Cross, Rockville, MD.
Gary Tegtmeier, PhD, Director of Research, Community Blood Center of Greater Kansas City, Kansas City, MO.
Lynne Layug, MPH, MT(ASCP), Technical Officer, National Reference Laboratory for Infectious Disease, American Red Cross, Rockville, MD.
Steve S. Alexander, PhD, Principal Scientist, AIDS/Hepatitis Research and Development, Ortho Diagnostic Systems.

*6Michael P. Busch, Associate Professor in Residence, Department of Laboratory Medicine, University of California, San Francisco; and Vice President, Research and Scientific Services, Irwin Memorial Blood Centers, 270 Masonic Avenue, San Francisco, CA 94118-4496.
The diagnosis (prognosis) of a serious disease can lead to disease and death – even if the person was not sick before.

This is called the **NOCEBO-effect**!

The contrary – the **PLACEBO-effect** is scientifically better examined and proven.
"Combivir is classified by the FDA as a pregnancy category C drug. Pregnancy category C means that animal studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans"

http://www.aidsmeds.com/archive/Combivir_1083.shtml

“RPD [rapid disease progression] was three times more likely to occur in infants born to [AZT] treated mothers- compared with findings in untreated mothers.”

Comparisons of Causes of Death and Mortality Rates Among HIV-Infected Persons: Analysis of the Pre-, Early, and Late HAART (Highly Active Antiretroviral Therapy) Eras

Crum, Nancy F MD, MPH‡; Riffenburgh, Robert H PhD‡; Wegner, Scott MD‡§; Agan, Brian K MD‡∥; Tasker, Sybil A MD‡¶; Spooner, Katherine M MD‡#; Armstrong, Adam W DO‡**; Fraser, Susan MD‡‡; Wallace, Mark R MD‡† on Behalf of the Triservice AIDS Clinical Consortium

JAIDS Journal of Acquired Immune Deficiency Syndromes:
February 1st, 2006 - Volume 41 - Issue 2 - p 194-200
doi: 10.1097/01.qai.0000179459.31562.16

Epidemiology and Social Science
Methods: Comparisons of death-related variables during the 3 eras were performed.
Results: The number of deaths declined over the study period, with 987 deaths in the pre-HAART era, 159 deaths in the early HAART era (1997-1999), and 78 deaths in the late HAART era (2000-2003) (P < 0.01). The annual death rate peaked in 1995 (10.3 per 100 patients) and then declined to <2 deaths per 100 persons in the late HAART era (P < 0.01). The proportion of deaths attributable to infection decreased, but infection remained the leading cause of death in our cohort, followed by cancer. Of those who died, there was an increasing proportion of non-HIV-related deaths (32% vs. 9%; P < 0.01), including cardiac disease (22% vs. 8%; P < 0.01) and trauma (8% vs. 2%; P = 0.01) in the post-HAART versus pre-HAART era. Despite the absence of intravenous drug use and the low prevalence of hepatitis C coinfection in our cohort, an increasing proportion of deaths in the HAART era were attributable to liver disease, although the numbers are small.
“Medical error—the third leading cause of death in the US”, British Medical Journal (3.5.2016).

Martin Makary from Johns Hopkins University School of Medicine in Baltimore.
Figure 1.1
The problem with perspective is that you need to know where you stand. (‘Ottawa shoes’ Patrick Brennan 1989. Reproduced with kind permission of the artist.)
In medical history decision making was paternalistic. Replaced by patient autonomy. This shift is exemplified in the legal requirement of *informed consent* to treatment. Shared decision making is now the ideal. But: The patient is the ultimative and authoritative decision maker, because he or she alone determines what will be done to his or her body and how this action will affect his or her life.
Chemical Substances (Medications) can lead to Mutations!

### Mutation frequency in ribavirin-treated poliovirus populations

<table>
<thead>
<tr>
<th>Population</th>
<th>G to A mutations</th>
<th>C to T mutations</th>
<th>Total mutation frequency&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal population</td>
<td>0.5</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>100 μM Ribavirin</td>
<td>—</td>
<td>1.3</td>
<td>2.5</td>
</tr>
<tr>
<td>400 μM Ribavirin</td>
<td>4.4</td>
<td>5.0</td>
<td>9.3</td>
</tr>
<tr>
<td>1000 μM Ribavirin</td>
<td>6.8</td>
<td>12.0</td>
<td>20.8</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mutations per 10,000 nt sequenced (reprinted with permission from Crotty et al., 2001)
HAART drives Evolution of HLA / HIV = Human genes!
Abacavir induces loading of novel self-peptides into HLA-B*57:01: an autoimmune model for HLA-associated drug hypersensitivity.


Source
Laboratory of Immunology, Division of Therapeutic Proteins, Office of Biotechnology Products, Center for Drug Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892, USA. Michael.norcross@fda.hhs.gov

CONCLUSION:
Our results support a model of drug-induced autoimmunity in which abacavir alters the quantity and quality of self-peptide loading into HLA-B57:01. Drug-induced loading of novel self-peptides into HLA, possibly by abacavir either altering the binding cleft or modifying the peptide-loading complex, generates an array of neo-antigen peptides that drive polyclonal T-cell autoimmune responses and multiorgan systemic toxicity.
Drug hypersensitivity reactions are an immune-mediated reaction to otherwise innocuous antigens derived from drugs. These reactions can affect many different organs, with the skin being the commonest. Skin involvement can range in severity with hypersensitivity syndrome (or DRESS) and the blistery reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis), also termed serious cutaneous adverse drug reactions, being the most severe and most feared. There is increasing evidence for the role of the immune system in the pathogenesis of these reactions, with drug-specific T cells having been identified in many patients.

**Abstract**

**HLA genes as genomic biomarkers of predisposition.** The 'revolution' started with abacavir where the predisposition to hypersensitivity was linked to HLA-B*57:01, which was confirmed in a clinical trial, and where its implementation has shown to reduce the incidence of hypersensitivity in a cost-effective manner. Since then, associations have also been shown for allopurinol (HLA-B*58:01)- and carbamazepine (HLA-B*1502 and HLA-A*3101)-induced serious cutaneous adverse drug reactions. The latter is interesting since the association with HLA-B*1502 is present in certain South-Eastern Asian populations, and the predisposition is phenotype specific (only for SJS/TEN). The utility of this biomarker has been shown in a prospective cohort study performed in Taiwan. By contrast, the association with HLA-A*3101 is seen in more diverse ethnic groups, and predisposes to mild as well more severe cutaneous reactions associated with carbamazepine. It is important to note that strong HLA associations have also been shown with a number of drugs that cause liver injury including flucloxacillin, lumiracoxib, lapatinib and ximelagatran, indicating that the immune system is also important in the pathogenesis of other forms of drug-induced organ toxicity. Copyright © 2012 S. Karger AG, Basel.
Paracelsus:

Everything is dependent on the concentration
Stress

Body

Soul

Mind

Immune balance

T1

cancer

cell proliferation, lack of apoptosis

T2

antibody production, T-cell decline

"AIDS"
A symbiotic interaction that originates from the genes of the immune system leads to communication particles (exo- and endosomes) that act differently within the immune system.
The whole cell-communication in and between cells of an organism depends on the activity of molecules like RNAs, Proteins, Exo- and Endosomes, Informosomes and Clathrines, to mention just some of them.


**HIV Type 1 Can Act as an APC upon Acquisition from the Host Cell of Peptide-Loaded HLA-DR and CD86 Molecules**

Jocelyn Roy, Genevièvre Martin, Jean-François Giguère, Dave Belanger, Myriam Petit and Michel J. Tremblay
The Human Microbiome Project (HMiP) tries to specify the genes of the microbes living on and in our bodies.

We have 10-fold more microbes than we have cells in a human being.
Evolution is accelerated by (ancient) lateral (horizontal) gene transfer from microbes to their hosts.
Humans underwent an evolutionary adaption process which was influenced by geography. This resulted in differences including the immune system. People of African descent show reduced neutrophil count due to a regulatory variant.

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.

In consequence we find differences in humoral responses between Ethiopian and Swedish persons who are claimed to be “infected” by HIV.
Doxiadis et al. state a phylogenetic evidence that supports the notion of the generation of new HLA-DRB genes as a dynamic and steadily ongoing process. This is due to the presence of indels (insertions/deletions), mainly mapping to intron.
THE HIV GENOME

„...analysis of the proteins of the virus demands mass production and purification...
I repeat, we did not purify.“

LUC Montagnier, Pasteur Institute, July 18th 1997

From: Eleni PapadopulosEleopulos Biophysicist, Department of Medical Physics, Royal Perth Hospital, Perth, Western Australia
Phylogenetic tree of „HIV“

One spike is made of three gp120+gp41 subunits
Conclusion:

HIV means evolutionary adapted genetic variation instead of virus mutation!
„Open Reading Frames“ Leading to variations

HIV-model
Initial sequencing and analysis of the human genome

International Human Genome Sequencing Consortium Eric S. Lander...

...Here we report the results of a collaboration involving 20 groups from the United States, the United Kingdom, Japan, France, Germany and China to produce a draft sequence of the human genome.

...Hundreds of human genes appear likely to have resulted from horizontal transfer from bacteria at some point in the vertebrate lineage.

...Dozens of genes appear to have been derived from transposable elements.

...large recent segmental duplications...much more frequent in humans...
"HIV" is found most near genes and CG sequences / bacterial origin;

Population genomics of intrapatient HIV-1 evolution
Zanini et al. eLife 2015;4:e11282. DOI: 10.7554/eLife.11282

MHC of the vertebrate immune system:

• Non-random distribution
• Increased gene density in the MHC/HLA

Crisp, A et al.  
Expression of multiple horizontally acquired genes is a hallmark of both vertebrate and invertebrate genomes. Genome Biology; 12 March 2015
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.
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.

Why?

This protects the male genes in the fetus.
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.

Thus HIV positivity means an allergic reaction!
Multiple interactions in cell communication are proved concerning HIV, specifically in GALT (gut associated lymphoid tissue) which makes sense for protecting the body from strange invaders from nutrition!
retrotransposon-mediated diversity.


Figure 1: HIV-Human protein interaction network.

**19 HIV proteins that interact with 1452 human proteins through 3959 interactions.**

Blue nodes are human proteins and red nodes are HIV proteins.
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“ can be protective to cancer.

Medications and HAART might have different (negative) impacts on the balance of the Th1 / Th2- system.
The whole cell-communication in and between cells of an organism depends on the activity of molecules like **RNAs, Proteins, Exo- and Endosomes, Informosomes and Clathrines**, to mention just some of them.


**HIV Type 1 Can Act as an APC upon Acquisition from the Host Cell of Peptide-Loaded HLA-DR and CD86 Molecules**

Jocelyn Roy, Geneviève Martin, Jean-François Giguère, Dave Belanger, Myriam Pétrin, and Michel J. Tremblay

Christl Meyer, AIDS Research, Vienna/Austria, 2018
The RNA-family

Gene family hierarchy map

- Non-coding RNAs
  - MicroRNAs
  - Transfer RNAs
  - Long non-coding RNAs (lncRNAs)
  - Small nucleolar RNAs
  - Ribosomal RNAs
  - Small nuclear RNAs
  - rRNAs, 7SL, cytoplasmic
  - piwi-interacting RNA clusters
  - Viral RNAs
  - RNAs, re-association Y

- Nuclear-encoded mitochondrial transfer RNAs
  - Cytoplasmic transfer RNAs
  - Mitochondrially encoded tRNAs

- 5S ribosomal RNAs
  - Ribosomal 45S RNA clusters
  - 45S pre-ribosomal RNAs
  - 40S ribosomal RNAs
  - 5.8S ribosomal RNAs
  - 18S ribosomal RNAs

- Ribosomal 45S rRNA genes outside of clusters

Christl Meyer, AIDS Research, Vienna/
Austria, 2018
African Americans are the racial/ethnic group most affected by HIV.

African Americans accounted for an estimated 44% of all new HIV infections among adults and adolescents (aged 13 years or older) in 2010, despite representing only 12% to 14% of the US population.


http://www.cdc.gov/hiv/topics/surveillance/resources/reports/index.htm#supplemental.

Subpopulations representing 2% or less of the overall US epidemic are not reflected in this chart. Abbreviations: MSM, men who have sex with men; IDU, injection drug user.
NIH Research Money Budgeted per Death

- Cardiovascular (CVD = Heart and Stroke)
- Hepatitis C
- Hepatitis B
- Diabetes
- Prostate
- Alzheimer's
- Parkinson's
- COPD (Chronic Obstructive Pulmonary Disease)

HIV/AIDS
"Combivir is classified by the FDA as a pregnancy category C drug. Pregnancy category C means that animal studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans"

http://www.aidsmeds.com/archive/Combivir_1083.shtml

“RPD [rapid disease progression] was three times more likely to occur in infants born to [AZT] treated mothers- compared with findings in untreated mothers.”

The nervous and the immune system share a lot of biochemical molecules, i.e.

Hormons (Cortisol)
Transmitter (Gamma-Amino-Butyrat)
**Interleukine Il 2, Il 10...**

**Both systems are involved in learning processes!**
The Immune-System comprises high variability and fluctuation through Transposable Elements.

It has to distinguish between **SELF** and **NON-SELF**!

Learning means to add **NEW** informations to knowledge!

Christl Meyer, AIDS Research, Vienna/Austria, 2018
Anergy is the missing reaction to an antigen by shutting down the immune reaction. Anergy is a mechanism by which the immune system prevents T-cells from attacking the body's own tissues. Anergy is a permanent characteristic. Under normal conditions it is not reactivated. Some systems are activated despite anergy by Interleukin-2.

Problems: puberty and infectious tissues (lung cells with virus-infection).
ALLOANTIGENs

An **allergic reaction** against variants of molecules (glyco-proteins, nucleic acids) of the same species might occur if the variants of contact (blood-components, leucocytes, sperms) activate the immune-system. Those people might also test „HIV-positive“
The Nobel Prize in Physiology or Medicine 2011

Bruce A. Beutler and Jules A. Hoffmann: Discoveries concerning the Activation of **Innate Immunity**

**DendriticCells**

Steinman: Discovery of the Dendritic Cell and its Role in **Adaptive Immunity**: Mediating the Communication between innate and adaptive immunity.

Toll-like receptor ligands will directly alter the functions of regulatory T cells

Toll-like receptor ligands will directly alter the functions of regulatory T cells
HIV- antibodies are
• Autoantibodies as we all produce them.
• Allergy-antibodies, which are induced by molecular similarity.
• A hint for an active or
• Imbalanced immune-system (stress).
• Increased after some vaccinations.

HIV – „Viruses“ are
• Particels of cell-communication (Endo- and Exosomes).

Christl Meyer, AIDS Research, Vienna/Austria, 2018
The Rest belongs to other diseases or wrong diagnosis!

Like hunger, malaria, tuberculosis, lung- and gut-infections, drugs.
AIDS is gene expression and / or self-organized mutation (genome extension) and therefore EVOLUTION under elevated stress.

The aim is the survival under unfavorable environmental conditions. Medications themselves bring on these situations by which the cell responds with mutations.
1. Genetics, HIV and the Immune System
2. Epigenetics
3. Microbes in Evolution
4. Immunization
5. What does it mean to be Human?
Epigenetics

Stimuli from the environment change gene expression. This effect can be transmitted through generations.

Christl Meyer, AIDS Research, Vienna/ Austria, 2018
Psychoneuroimmunology (PNI) is an interdisciplinary field of research, which deals with the interaction of the nerve system, the hormone system and the immune system. The scientific basis is that messenger molecules (like hormones and other substances) of the nervous system influence the immune system and vice versa.
Pregnancy and the future of the next generations:

Mother - 1st generation
Fetus - 2nd generation
Reproductive cells - 3rd generation

Christl Meyer, AIDS Research, Vienna/Austria, 2018
Organic Food during Mother's Pregnancy Reduces Risk of Male Birth Defects

*Expecting mothers eating mostly organic produce reduce risk of urogenital anomalies in male offspring*  
*Dr Eva Sirinathsinghji*

Pesticides are the other obvious candidate for the observed disparity in disease rates between those eating organic versus conventional foods. Several classes of pesticide have been shown to have endocrine disrupting effects including glyphosate, 2,4-D, atrazine, endosulfan, linurin, vinclozolin and dichlorodiphenyldichloroethylene (DDE).
Syncytin-mediated cell–cell fusion

Syncytin and placenta development

Dupressoir A et al. PNAS 2005;102:725-730
Syncytin, which is expressed by endogenous retroviruses of the pregnant women, leads to cell fusion by building up the placenta in normal development.

Humans have 400% more of retroviral genes than of human genes

Dupressoir A et al. PNAS 2005;102:725-730

Christl Meyer, AIDS Research, Vienna/ Austria, 2018
Why it is so important that mothers breastfeed their babies:

• The antibodies of the mother protect the child from infections.
• The emotional relationship and the primal sense of trust are strengthened.
EVOLUTION and MUTATION

Lack of genetic diversity
Extinction of the Population

DNA mutations
On
Off

Evolutionary death
(no adaptability)
Immediate death
(genetic breakdown)

Mutation rate

Population fitness

Easy life
Hard life

„gene chaos“

Extinction of the Individual

Christl Meyer, AIDS Research, Vienna/Austria, 2018
Result:
The more of Stress
The more of Mutations.
Prenatal stress alters the brain transcriptome in male newborn offspring.


http://www.plosone.org/article/info:doi/10.1371/journal.pone.0056967
Normal cellular *homeostasis* is a *delicate balance* between the rate and magnitude of *oxidant formation* and the *rate of oxidant elimination*.

Oxidative stress can, therefore, be defined as the *pathogenic* outcome of the overproduction of oxidants that overwhelsms the cellular antioxidant capacity.