Exploration du virome humain : de la symbiose à la pathologie

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IHU Méditerranée Infection, Marseille

Séminaire Collège de France, le 17/01/2018

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1530

MÉDITERRANÉE INFECTION

Aix*Marseille université

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IRD Institut de recherche pour le développement

Inserm Institut national de la santé et de la recherche médicale

Picture from ScienceNews, 2013

What are viruses?

Simple definitions for real complexity…

Virus means “poison, venom” in Latin

Viruses are small (with exceptions), infectious, obligate intracellular parasites depending on host cells to replicate. Because they lack the resources for independent existence, they exist on the borderline of the definition of life.

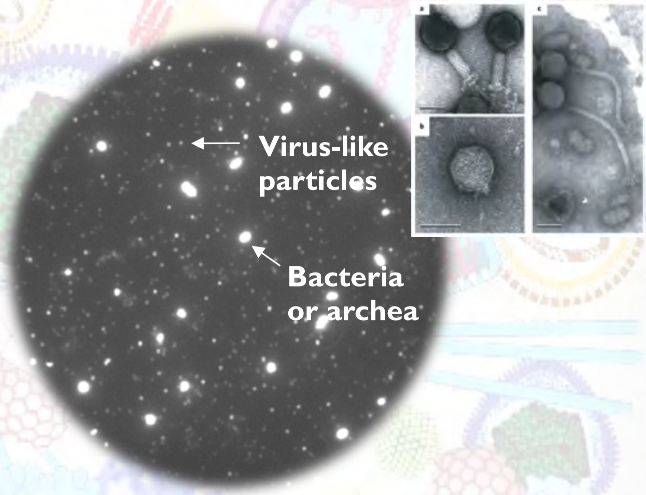
The virion (virus particle) consists of a nucleic acid genome surrounded by coat proteins (capsid) that may be enveloped in a host-derived lipid bilayer.

Viral genomes consist of either RNA or DNA. They may be single-, double, or partially double stranded. The genomes may be circular, linear, or segmented.

Why working on viruses?

- **Viruses are everywhere…**
  - ✓ Most abundant biological entity in aquatic and terrestrial environments (10^{31})
  - ✓ Infect organisms from the 3 domain of life (Eukaryotes, Bacteria, Archaea)

Abundances in 1 ml of seawater	
Virus/phages	**10^6-10^8**
Heterotrophic bacteria	1,000,000
Photosynthetic bacteria	100,000
Protozoa	4,000
Algae	3,000
Zooplankton	<<1



- **Viruses impact the ecosystem functions**

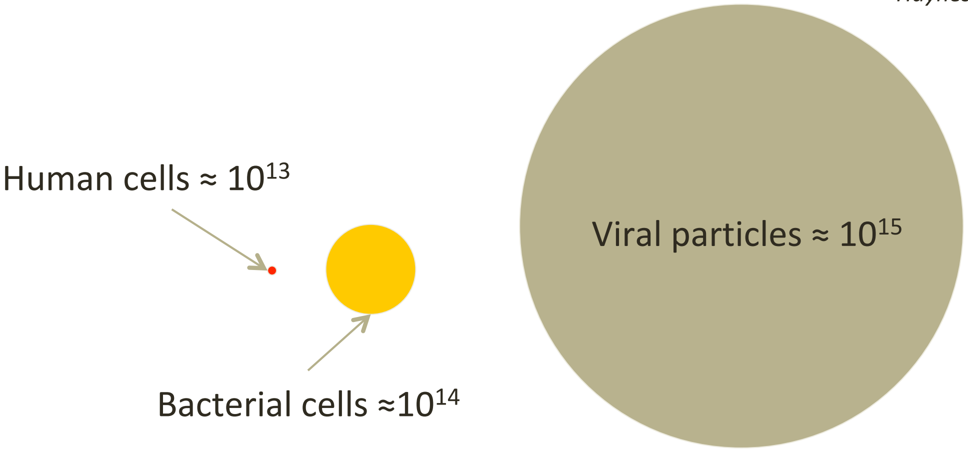
Through their lytic and lysogenic cycles, viruses play a fundamental role on microbial growth rates, nutrient cycling, genetic exchanges (and thus diversity, adaptation and evolution)

Suttle, Nature (2005)
Desnues et al., Nature (2008)

Viruses and humans

✓ It is estimated that there are 100 times more viruses in our body than human cells

Haynes & Rohwer (2010)



Human cells ≈ 10^{13}

Viral particles ≈ 10^{15}

Bacterial cells ≈10^{14}

✓ The number of free virions varies from 10^9 particles/g for body barriers (gut, oropharynx, skin) to 10^7 and 10^5 particles/ml for urine and blood, respectively

Haynes & Rohwer (2010)
Mokili, Curr. Op. Virol. (2012)

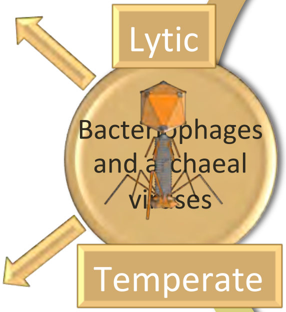
✓ Collectively, this viral flora is known as the **human virome**

The human virome is defined as the repertoire of all viruses that are found on the surface and inside our body

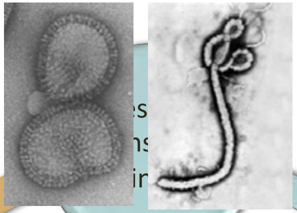
This includes viruses that cause acute, latent or chronic, symptomatic or asymptomatic infections

The human virome

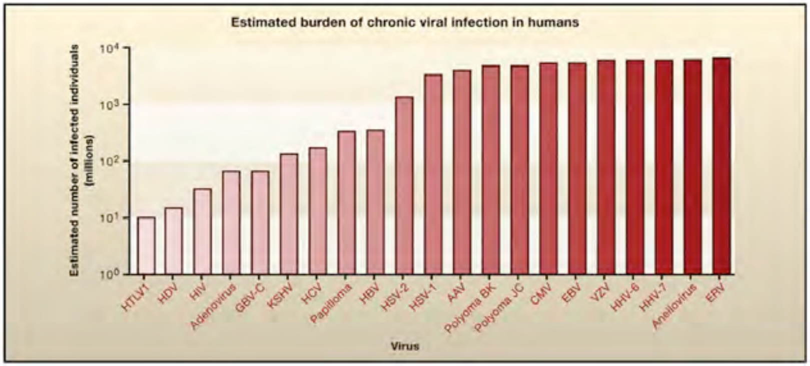
- ✓ Dysbiosis by predating on beneficial strain
- ✓ Maintain homeostasis by killing pathogens

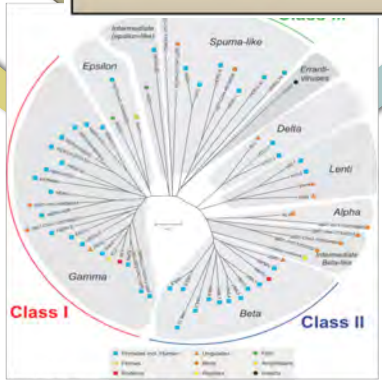


- ✓ Change the microbial host phenotype
- ✓ Increased pathogenicity, antibiotic resistance, and perhaps new metabolic capacity



Influenza and Ebola virions





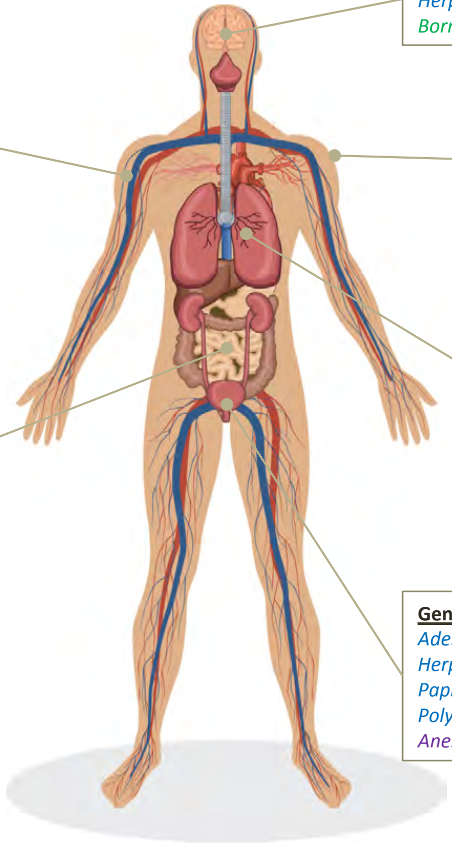
ative unrooted Pol neighbor joining (NJ) dendrogram

Each adult is chronically infected by 8-10 viruses

Virgin et al., Cell (2009)
Virgin, Cell (2014)

The human silent virome

The human body is a composite of highly heterogeneous ecosystems and viral communities differ in terms of abundance and composition within anatomical sites



Circulatory system

- *Adenoviridae*
- *Baculoviridae*
- *Herpesviridae*
- *Marseilleviridae*
- *Myoviridae*
- *Polyomaviridae*
- *Papillomaviridae*
- *Poxviridae*
- *Siphoviridae*
- *Anelloviridae*
- *Inoviridae*
- *Microviridae*
- *Parvoviridae*
- *Hepeviridae*
- *Flaviviridae*
- *Bunyaviridae*
- *Paramyxoviridae*
- *Retroviridae*

Digestive system

- *Herpesviridae*
- *Marseilleviridae*
- *Myoviridae*
- *Papillomaviridae*
- *Podoviridae*
- *Polyomaviridae*
- *Poxviridae*
- *Siphoviridae*
- *Anelloviridae*
- *Circoviridae*
- *Microviridae*
- *Picobirnaviridae*
- *Reoviridae*
- *Caliciviridae*
- *Astroviridae*
- *Virgaviridae*
- *Picornaviridae*

Viral Groups

- 🟦 - double stranded DNA viruses
- 🟪 - single stranded DNA viruses
- 🟨 - double stranded RNA viruses
- 🟥 - (+)single stranded RNA viruses
- 🟩 - (-) stranded RNA viruses
- 🟫 - Retroviruses

Nervous system

- *Herpesviridae*
- *Bornaviridae*

Integumentary system

- *Herpesviridae*
- *Myoviridae*
- *Papillomaviridae*
- *Podoviridae*
- *Polyomaviridae*
- *Siphoviridae*
- *Anelloviridae*
- *Circoviridae*
- *Inoviridae*
- *Microviridae*
- *Parvoviridae*

Respiratory system

- *Adenoviridae*
- *Iridoviridae*
- *Herpesviridae*
- *Mimiviridae*
- *Myoviridae*
- *Papillomaviridae*
- *Phycodnaviridae*
- *Podoviridae*
- *Poxviridae*
- *Siphoviridae*
- *Anelloviridae*
- *Parvoviridae*
- *Coronaviridae*
- *Picornaviridae*
- *Orthomyxoviridae*
- *Paramyxoviridae*

Genito/urinary system

- *Adenoviridae*
- *Herpesviridae*
- *Papillomaviridae*
- *Polyomaviridae*
- *Anelloviridae*

Popgeorgiev et al., Intervirology (2013)

How to study viruses?

Researches and progresses in virology are technollogically-driven

40’s: Electron microscopy

Visualization of viral particles.

Elucidation of ultrastructure and cellular/tissular localizations

50’s : cell culture

Isolation and production of virions. Study of the mechanisms of infection

Experimental models

80’s: Molecular biology

Rapid detection of novel viruses (or variants). Quantification of viral loads.

« Gold standard » in clinical diagnostic

How to study viruses?
Classical technics for virus discovery/ identification

Cellular

- Lack of standard protocol
- Some viruses are unable to propagate in cell culture conditions
- Viral derivation through repetitive cell infection

Serological

- Lack of standard protocol
- High antigenic diversity
- Low cross reactivity

Molecular

- Absence of conserved genes among all viruses
- New emerging or highly divergent viral genomes are not detected
- Detection limitations depending on the sample

Classical technics for virus identification

The metagenomic era

Viral metagenomics consist in the sequencing of all viral nucleic acids from a sample (culture independent) and in their analysis using bioinformatics

How to study viruses?

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40’s: Electron microscopy

Visualization of viral particles. Elucidation of ultrastructure and cellular/tissular localizations

50’s : cell culture

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« Gold standard » in clinical diagnostic

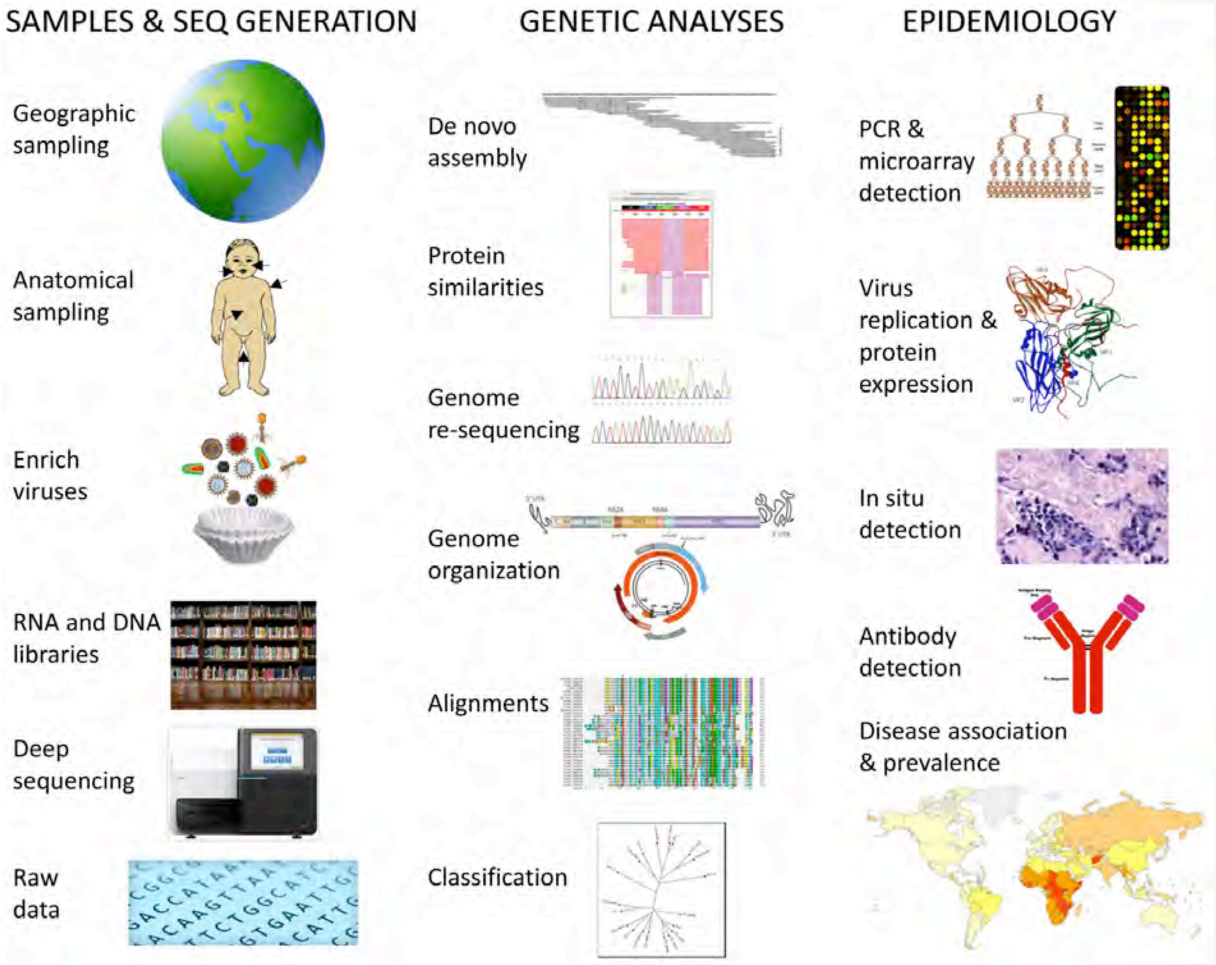
Mid-2000: NGS

Meta-analyses: study of viruses at the community scale (composition, structure, function diversity).

Viral discovery

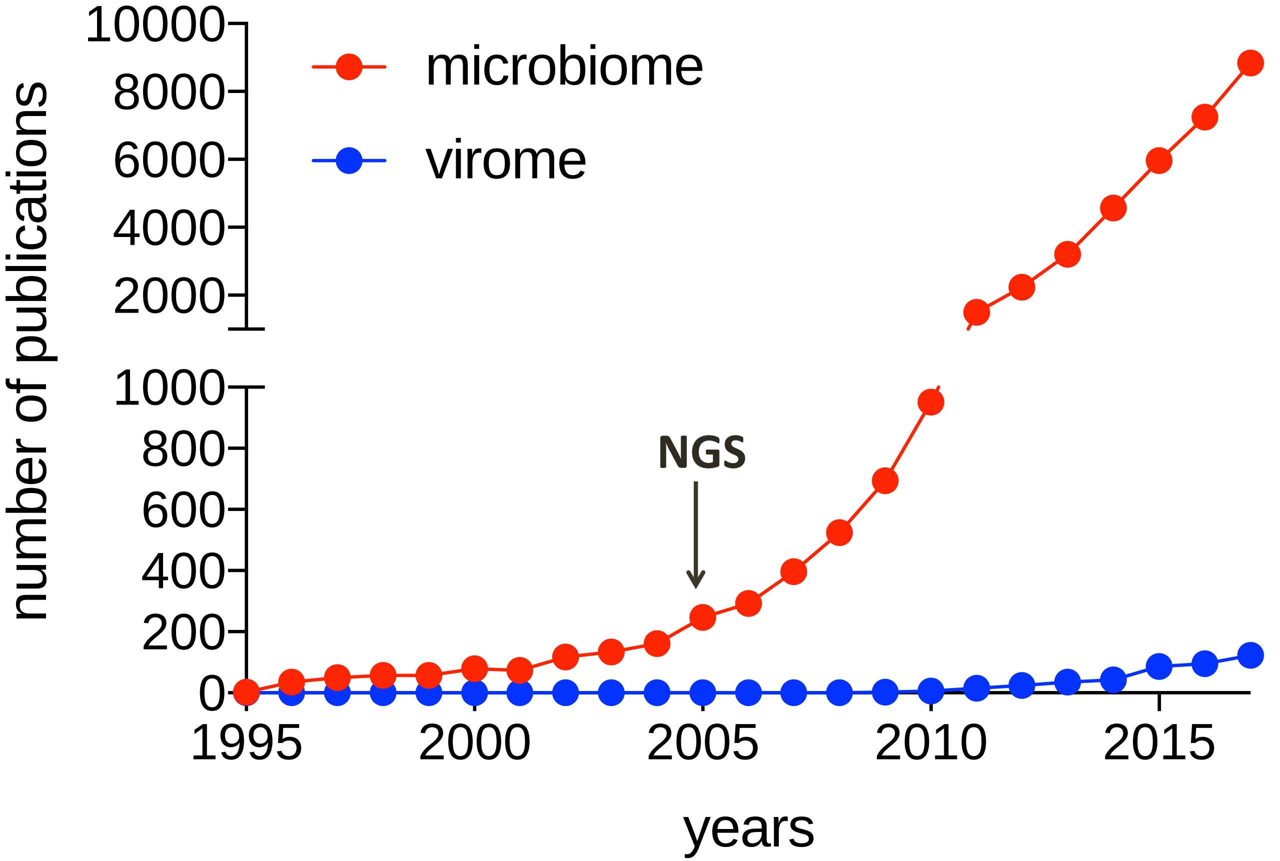
NGS=Next-Generation Sequencing

Schematic steps for determination of human virome and its impact on health

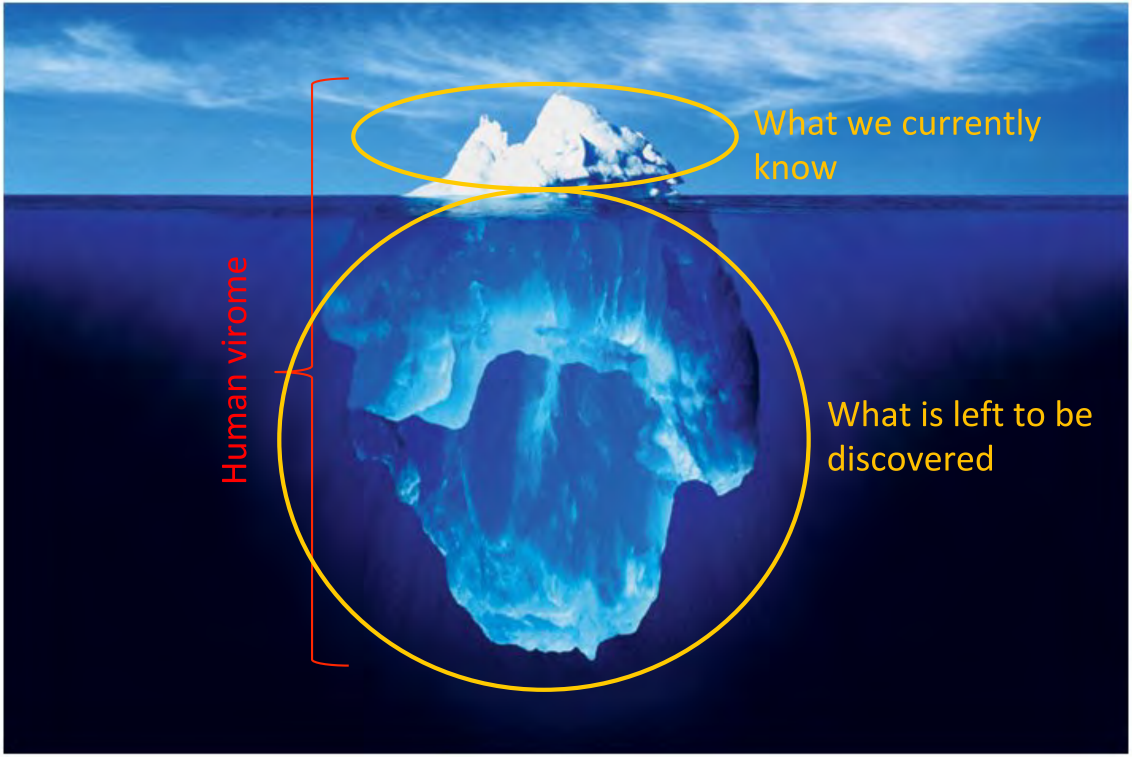


Delwart, PLoS Pathogens (2013)

The virome, a neglected part of the microbiome…



The human virome: the hidden face of the iceberg



An essential part of our own ecology remains *terra incognita*

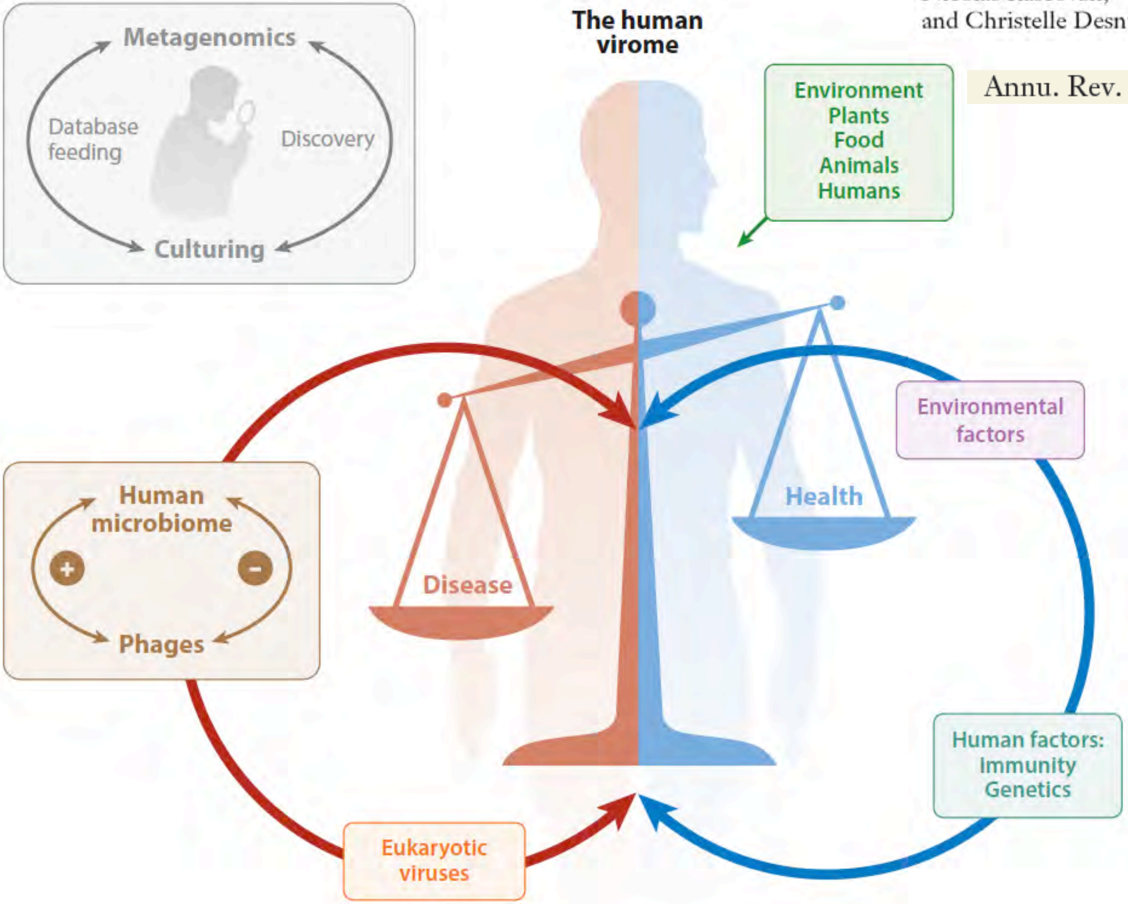
The human virome

Metagenomics and the Human Virome in Asymptomatic Individuals

Nicolás Rascovan,[1,2,*] Raja Duraisamy,[1,2,*] and Christelle Desnues[1,2]

Annu. Rev. Microbiol. 2016. 70:125–41

ANNUAL REVIEWS
CONNECT WITH OUR EXPERTS

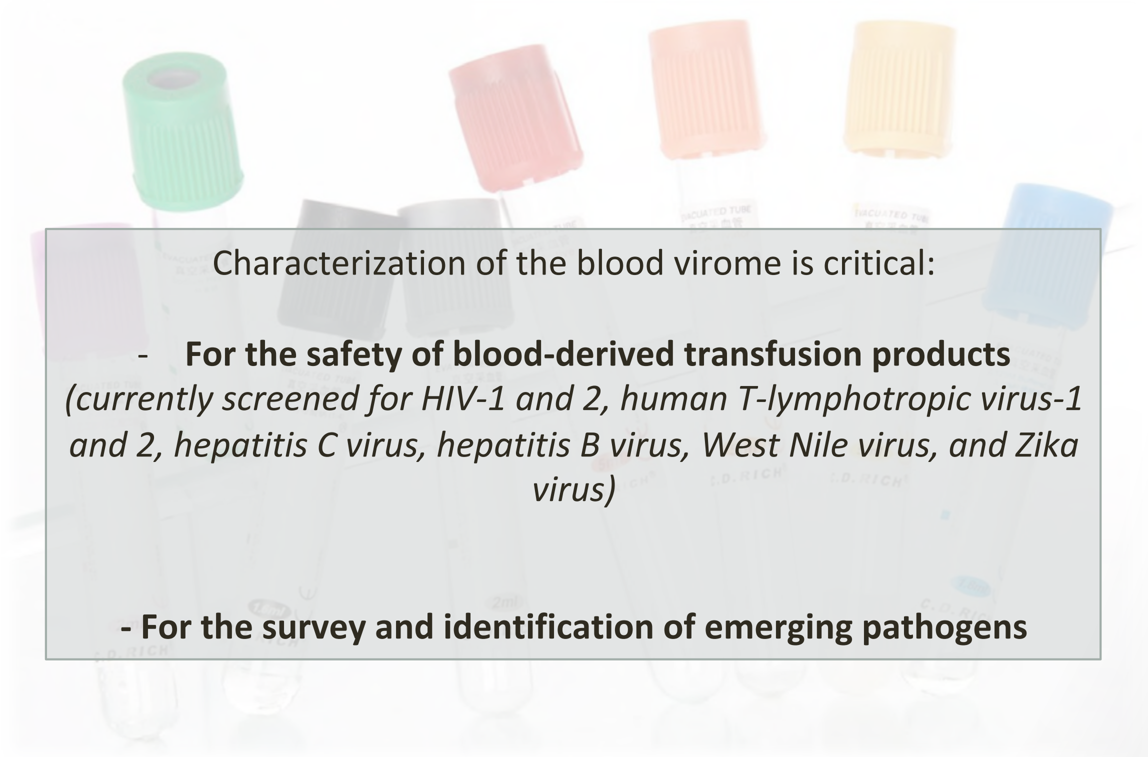


Virus-host interactions go beyond simple parasitism

Positive, neutral or negative interactions depend on the anatomical site, the immune/genetic status of the host and the presence of other viruses/microbes

Inside the human virome: the good, the bad and the neutral…

The example of the blood compartment



Characterization of the blood virome is critical:

- **For the safety of blood-derived transfusion products** *(currently screened for HIV-1 and 2, human T-lymphotropic virus-1 and 2, hepatitis C virus, hepatitis B virus, West Nile virus, and Zika virus)*

- For the survey and identification of emerging pathogens

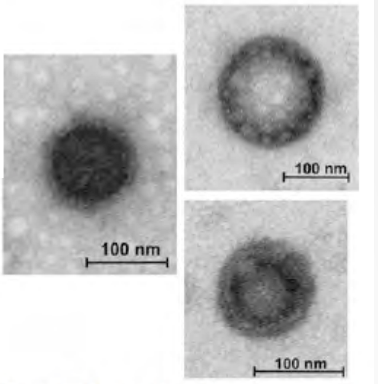
The blood virome

Method for discovering novel DNA viruses in blood using viral particle selection and shotgun sequencing

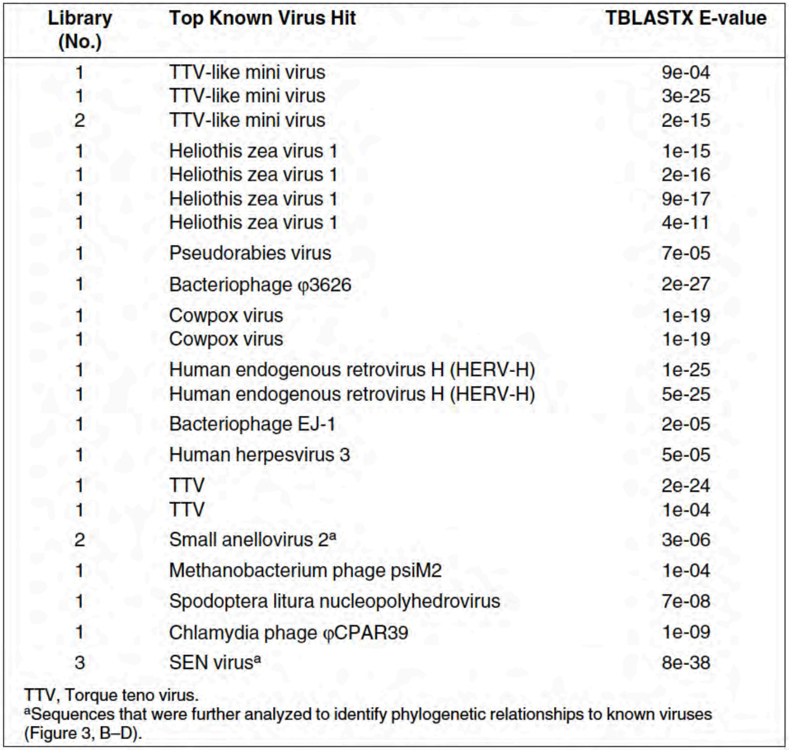
Vol. 39, No. 5 (2005)

Mya Breitbart and Forest Rohwer

BioTechniques
The International Journal of Life Science Methods



Asymptomatic blood donors



Library (No.)	Top Known Virus Hit	TBLASTX E-value
1	TTV-like mini virus	9e-04
1	TTV-like mini virus	3e-25
2	TTV-like mini virus	2e-15
1	Heliothis zea virus 1	1e-15
1	Heliothis zea virus 1	2e-16
1	Heliothis zea virus 1	9e-17
1	Heliothis zea virus 1	4e-11
1	Pseudorabies virus	7e-05
1	Bacteriophage φ3626	2e-27
1	Cowpox virus	1e-19
1	Cowpox virus	1e-19
1	Human endogenous retrovirus H (HERV-H)	1e-25
1	Human endogenous retrovirus H (HERV-H)	5e-25
1	Bacteriophage EJ-1	2e-05
1	Human herpesvirus 3	5e-05
1	TTV	2e-24
1	TTV	1e-04
2	Small anellovirus 2[a]	3e-06
1	Methanobacterium phage psiM2	1e-04
1	Spodoptera litura nucleopolyhedrovirus	7e-08
1	Chlamydia phage φCPAR39	1e-09
3	SEN virus[a]	8e-38

TTV, Torque teno virus.

[a] Sequences that were further analyzed to identify phylogenetic relationships to known viruses (Figure 3, B–D).

Shotgun libraries – sanger sequencing

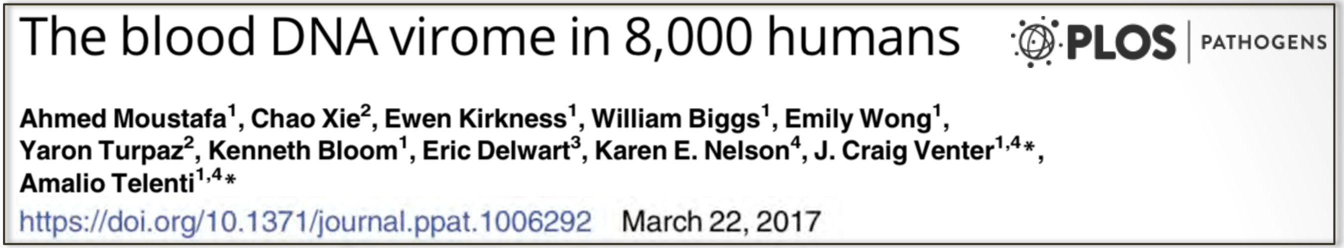
3 libraries (total of 50 blood samples)

22 sequences:

- Novel anelloviruses
- HHV3 (Varicella zoster virus)
- Other eukaryotic viruses
- bacteriophages

The blood virome

The blood virome



The blood DNA virome in 8,000 humans

PLOS | PATHOGENS

Ahmed Moustafa[1], Chao Xie[2], Ewen Kirkness[1], William Biggs[1], Emily Wong[1],
Yaron Turpaz[2], Kenneth Bloom[1], Eric Delwart[3], Karen E. Nelson[4], J. Craig Venter[1,4]*,
Amalio Telenti[1,4]*

https://doi.org/10.1371/journal.ppat.1006292 March 22, 2017

PNAS | October 18, 2016 | vol. 113 | no. 42 | 11901–11906

Deep sequencing of 10,000 human genomes

Amalio Telenti[a,b,1], Levi C. T. Pierce[a,c,1], William H. Biggs[a,1], Julia di Iulio[a,b], Emily H. M. Wong[a], Martin M. Fabani[a], Ewen F. Kirkness[a], Ahmed Moustafa[a], Naisha Shah[a], Chao Xie[d], Suzanne C. Brewerton[d], Nadeem Bulsara[a], Chad Garner[a], Gary Metzker[a], Efren Sandoval[a], Brad A. Perkins[a], Franz J. Och[a,c], Yaron Turpaz[a,d], and J. Craig Venter[a,b,2]

[a]Human Longevity Inc., San Diego, CA 92121; [b]J. Craig Venter Institute, La Jolla, CA 92037; [c]Human Longevity Inc., Mountain View, CA 94041; and [d]Human Longevity Singapore Pte. Ltd., Singapore 138542

1 petabyte (1 million gigabytes) of sequence data

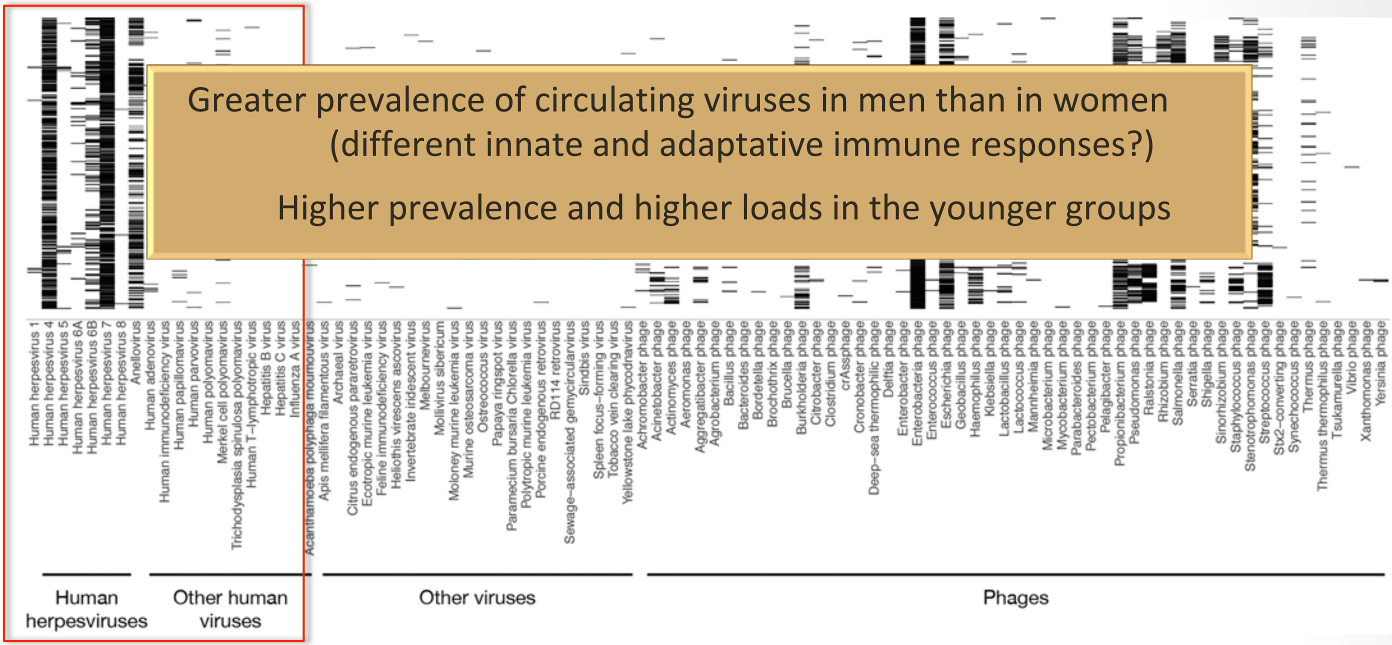
About 5% did not correspond to human DNA (0.01% of these were similar to viral sequences)

Sequences of 94 different DNA viruses were identified

19 were from known human viruses

The blood virome: persistent viruses

19 human viruses



Greater prevalence of circulating viruses in men than in women (different innate and adaptative immune responses?)

Higher prevalence and higher loads in the younger groups

Herpesviruses (0.1-20% of individuals)
Cytomegalovirus, Epstein-Barr virus, Herpes Simplex virus, and human herpesviruses 6, 7 and 8

Other human viruses (< 1%): papillomaviruses, parvoviruses, polyomavirus, adenovirus, human immunodeficiency virus and human T-lymphotropic virus

Several persistent viral infection

The blood virome: persistent viruses

Redefining Chronic Viral Infection

Herbert W. Virgin,[1,*] E. John Wherry,[2,*] and Rafi Ahmed[3,*]

Cell *138*, July 10, 2009 ©2009 Elsevier Inc.

Persistent viral infection is a process in dynamic and metastable equilibrium

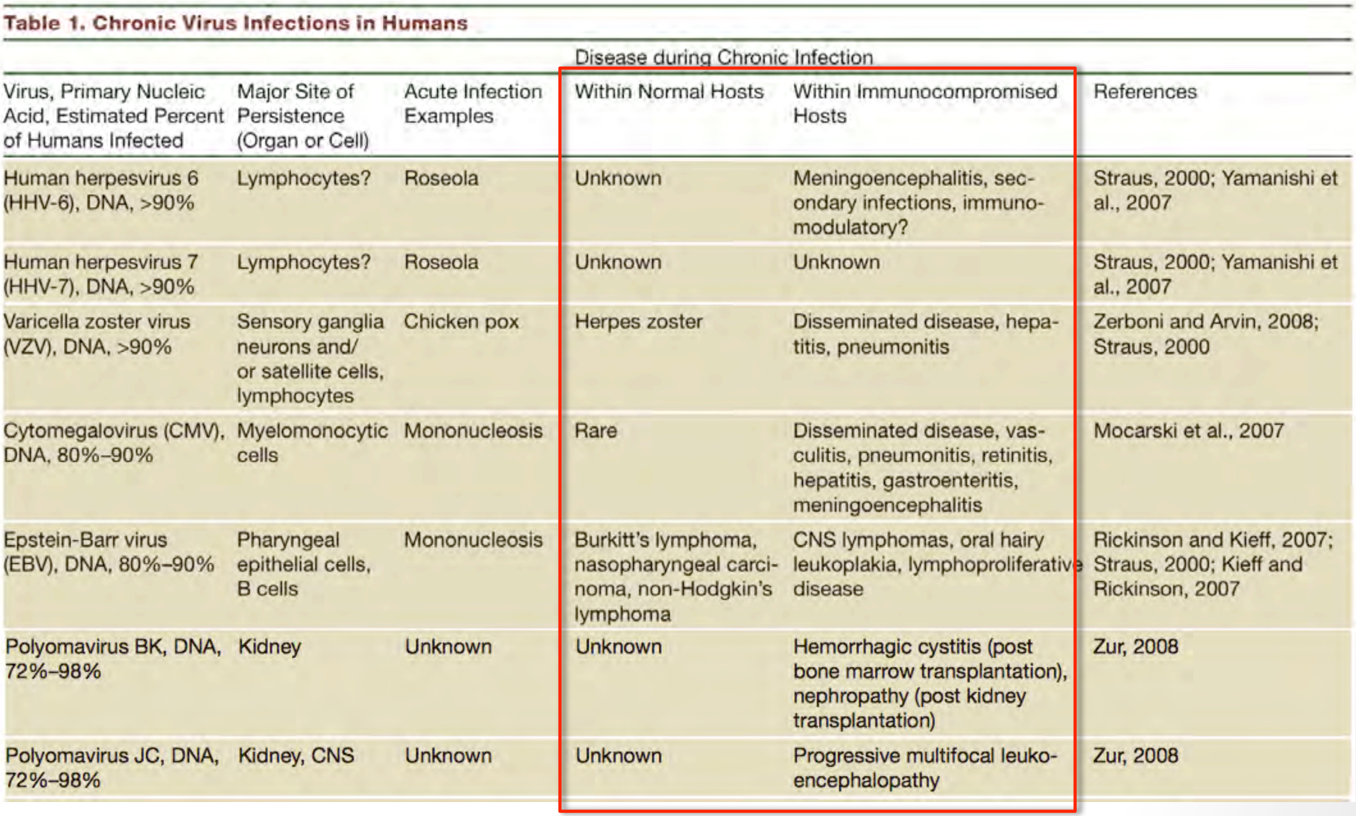


Table 1. Chronic Virus Infections in Humans

			Disease during Chronic Infection		
Virus, Primary Nucleic Acid, Estimated Percent of Humans Infected	Major Site of Persistence (Organ or Cell)	Acute Infection Examples	Within Normal Hosts	Within Immunocompromised Hosts	References
Human herpesvirus 6 (HHV-6), DNA, >90%	Lymphocytes?	Roseola	Unknown	Meningoencephalitis, secondary infections, immunomodulatory?	Straus, 2000; Yamanishi et al., 2007
Human herpesvirus 7 (HHV-7), DNA, >90%	Lymphocytes?	Roseola	Unknown	Unknown	Straus, 2000; Yamanishi et al., 2007
Varicella zoster virus (VZV), DNA, >90%	Sensory ganglia neurons and/or satellite cells, lymphocytes	Chicken pox	Herpes zoster	Disseminated disease, hepatitis, pneumonitis	Zerboni and Arvin, 2008; Straus, 2000
Cytomegalovirus (CMV), DNA, 80%–90%	Myelomonocytic cells	Mononucleosis	Rare	Disseminated disease, vasculitis, pneumonitis, retinitis, hepatitis, gastroenteritis, meningoencephalitis	Mocarski et al., 2007
Epstein-Barr virus (EBV), DNA, 80%–90%	Pharyngeal epithelial cells, B cells	Mononucleosis	Burkitt's lymphoma, nasopharyngeal carcinoma, non-Hodgkin's lymphoma	CNS lymphomas, oral hairy leukoplakia, lymphoproliferative disease	Rickinson and Kieff, 2007; Straus, 2000; Kieff and Rickinson, 2007
Polyomavirus BK, DNA, 72%–98%	Kidney	Unknown	Unknown	Hemorrhagic cystitis (post bone marrow transplantation), nephropathy (post kidney transplantation)	Zur, 2008
Polyomavirus JC, DNA, 72%–98%	Kidney, CNS	Unknown	Unknown	Progressive multifocal leukoencephalopathy	Zur, 2008

The benefice of persistent viral infections

The physiological role of most of these viruses in humans has yet to be defined

Promote human health

Indirectly

and/or

Directly

By eliminating other pathogens through cross-immunity

By viral interference

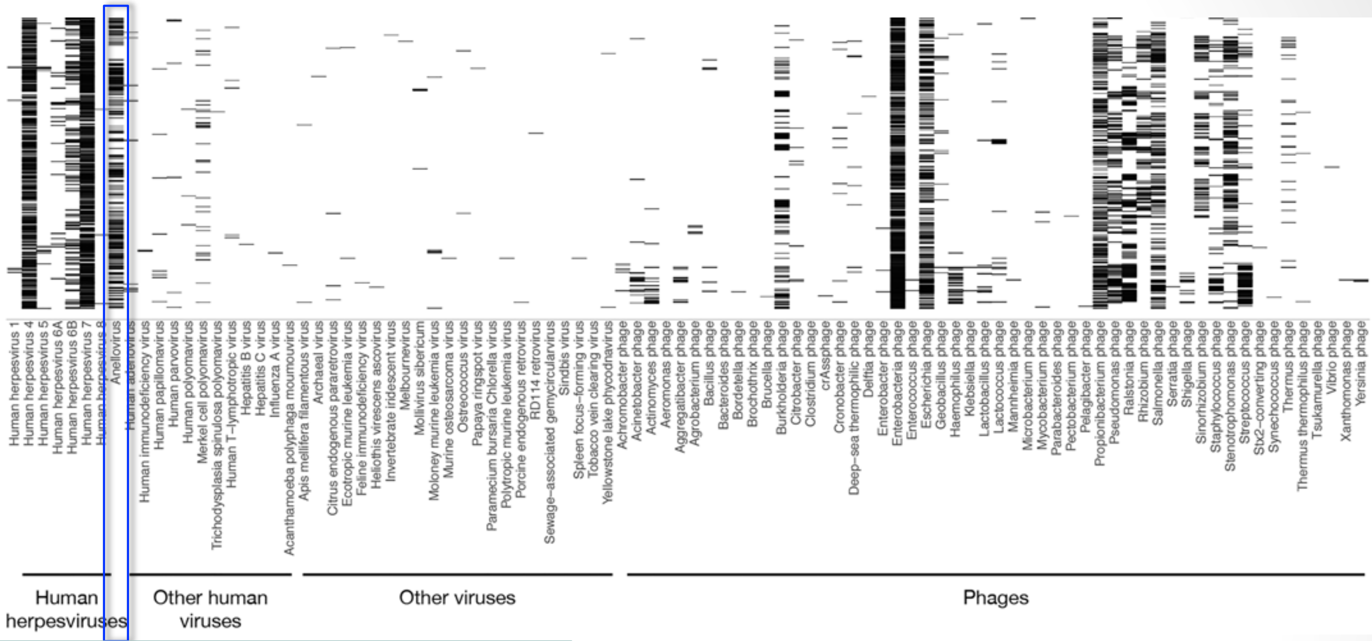
- Latent infection with murine gammaherpesvirus 68 (a model for EBV) or murine CMV (a model for human CMV) confers protection against *Listeria monocytogenes* and *Yersinia pestis* in mice

Barton et al., Nature (2007)

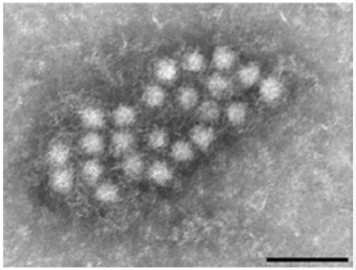
- Individuals with HIV, co-infected with Human Pegivirus (HPgV, also called GBV-C virus or hepatitis G virus) delay progression to AIDS

Xiang et al., NEJM (2001)

The blood virome: anelloviruses



Anelloviruses (9%) of the samples



Small ssDNA viruses from the *Anelloviridae* family
Three main viral groups:

- Torque Teno Virus (TTV, 1997)
- Torque Teno Mini Virus (TTMV, 2000)
- Torque Teno Midi Virus (TTMDV, 2007)

Anelloviruses cannot be cultivated and can be transmitted through transfusions

Bernardin et al., Transfusion (2010)

Anelloviruses

The blood virome: anelloviruses

- ❖ Prevalence in humans is very high (>50%), high level of genomic heterogeneity

- ❖ Their role in human physiology and disease is unclear: originally believed to be a new viral etiologic agent of hepatitis but now considered as non-pathogenic commensals

Spandole et al., Arch. Virol. (2015)

Anelloviruses as Biomarkers of immunocompetence?

- ❖ Increases in the anellovirus load in the blood associated with immunosuppression levels in transplant recipients and patients with HIV.

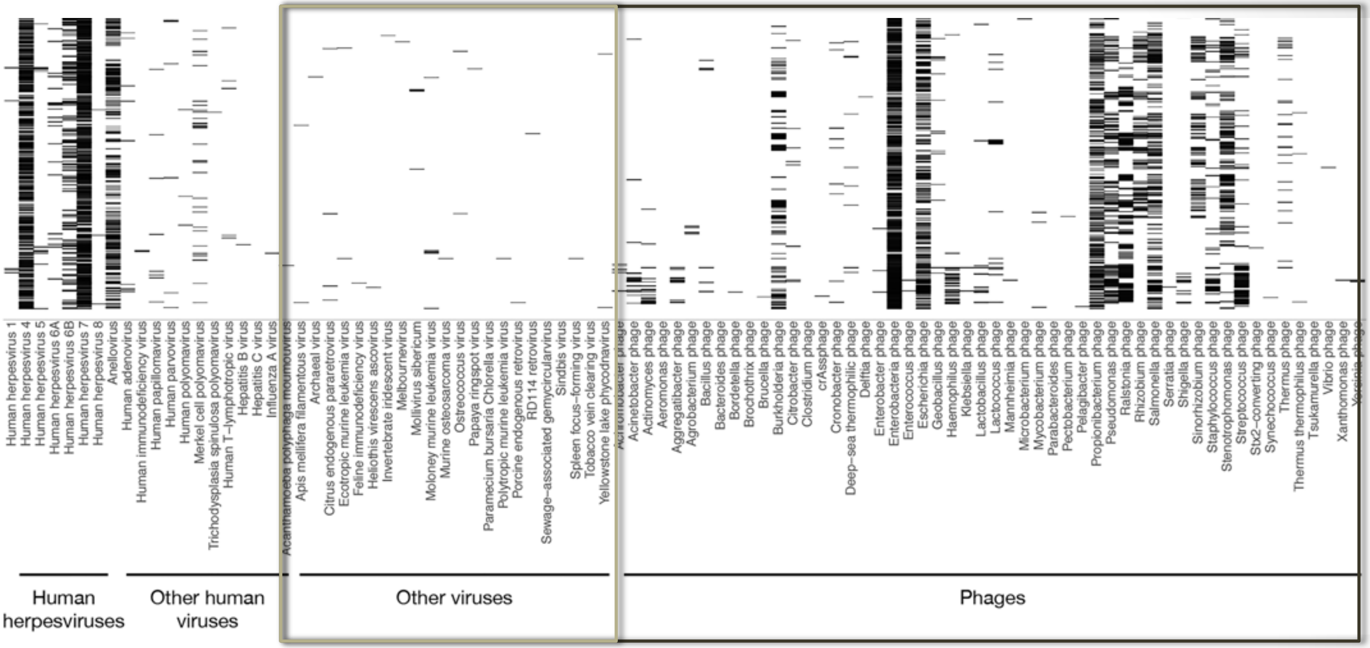
De Vlaminck et al., Cell (2013)
Li et al., J. Virol. (2013)
Young et al., Am. J. Transplant. (2015)

- ❖ In the gut, sequences related to anelloviruses peaked in the first years of life then their abundance progressively decreased → correlated with the interval between maternal IgG protection and complete development of the infant's immune system?

Lim et al., Nat. Med. (2015)

- ❖ Predictors of adverse outcomes after transplantation *Blatter et al., Pedriat. Transpl. (2017)*

The blood virome: giant viruses



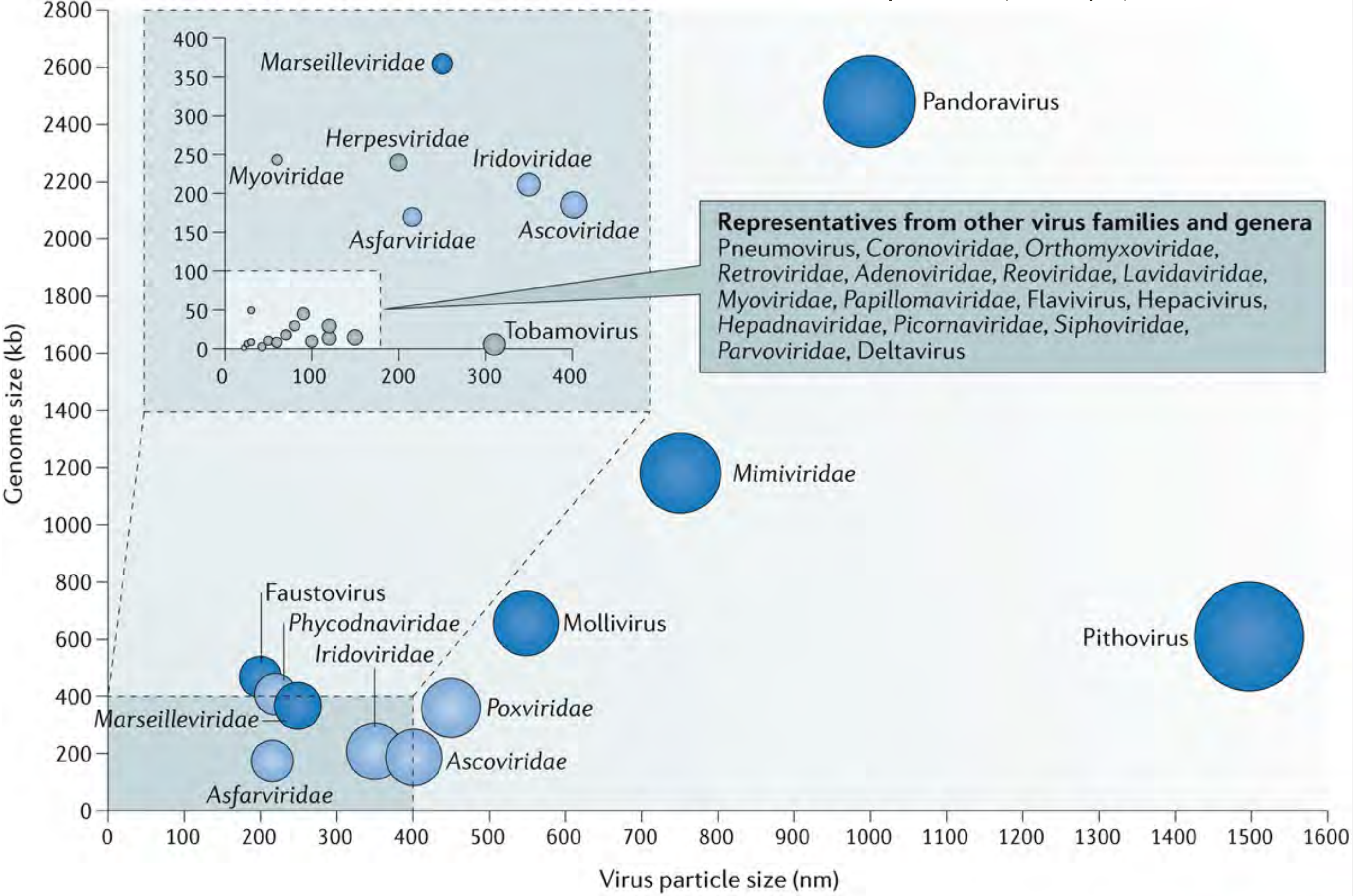
Extensive contamination of commercial reagents and from the environment

Sequences related to giant viruses belonging to 4 genera:

- *Mollivirus (8 individuals)*
- *Chlorovirus (3 individuals)*
- *Marseillevirus(2 individuals)*
- *Mimivirus (1 individual)*

What are giant viruses?

- Viruses with bacterial like sizes
- The biggest viral genomes ever sequenced (2.5 Mpb)



Colson et al. Nat Rev Microbiol (2017)

Nature Reviews | Microbiology

The blood virome: giant viruses

Marseillevirus-Like Virus Recovered From Blood Donated by Asymptomatic Humans

Nikolay Popgeorgiev,[1] Mickaël Boyer,[1,a] Laura Fancello,[1] Sonia Monteil,[1] Catherine Robert,[1] Romain Rivet,[1] Claude Nappez,[1] Said Azza,[1] Jacques Chiaroni,[2] Didier Raoult,[1] and Christelle Desnues[1]

The Journal of
Infectious Diseases

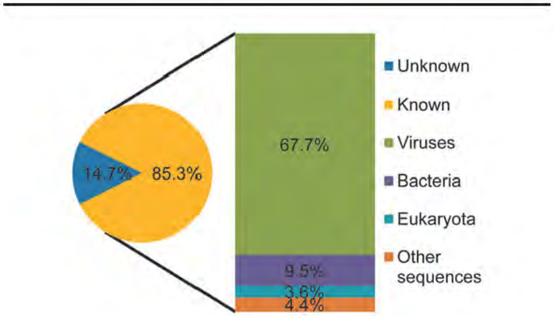


Figure 1. Classification of the human blood virome metadata. Taxonomic distribution of metagenomic reads are based on the GenBank taxonomic classification of the best BLASTn hit (E value, $<10^{-5}$).

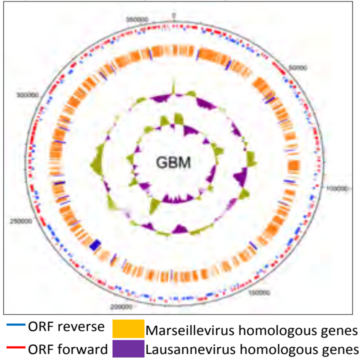
Blood donors (n=10) virome

2.5% of the viral sequences were related to a new virus (called Giant Blood Marseillevirus, GBM) closed to Marseillevirus

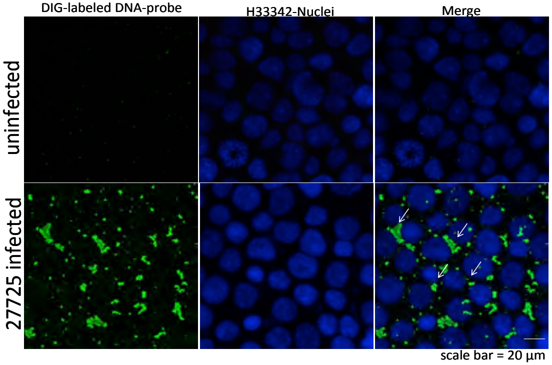
For 1 donor, we detected in the blood:

- Viral DNA (NGS & PCR)
- Viral proteins (2D Western Blot)
- Viral particles (MET)
- Anti-Marseillevirus IgG (ELISA)

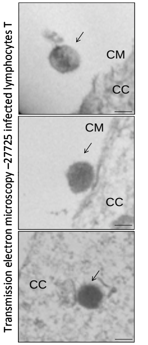
Giant blood Marseille-like virus (GBM) chromosome predicted using SOLiD™ genomic data



Fluorescence *in situ* hybridization - 27725 infected human lymphocytes T cells



scale bar = 20 µm



CC: Cell cytosol; CM: Cell Membrane; scale bar = 100 nm

GBM is able to infect human T-lymphocytes

The blood virome: giant viruses

Marseillevirus prevalence in multitransfused patients suggests blood transmission

Nikolay Popgeorgiev[a], Philippe Colson[a], Isabelle Thuret[b], Jacques Chiarioni[c], Pierre Gallian[d], Didier Raoult[a], Christelle Desnues[a,*]

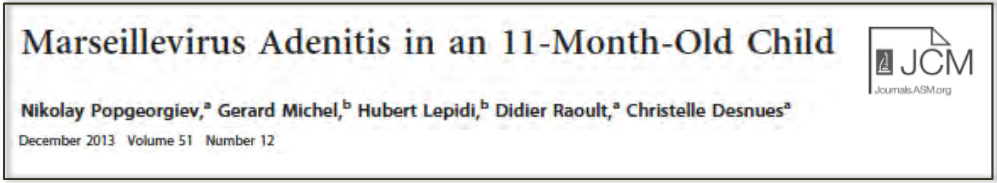
Journal of Clinical Virology 58 (2013) 722–725

- Detection of anti-Marseillevirus IgG (ELISA) and viral DNA (PCR) on 196 individuals
- 174 blood donors and 22 thalassemia patients (frequent transfusion acceptors)

	Blood donors	Thalassemia patients	p-value*
Sample number	174	22	
Male/Female (Male %)	91/83 (52.3%)	12/10 (54.5%)	
Median age (range)	46 (21-70)	23.5 (8-49)	
IgG positive			
Number	22/174 (12.6%)	5/22 (22.7%)	0,165
Male/Female (Male %)	10/12 (45.5%)	3/2 (60%)	
Median age (range)	47.5 (22-70)	30 (17-49)	<0,0001
PCR positive			
Number	7/174 (4%)	2/22 (9.1%)	0,267
Male/Female (Male %)	3/4 (42.9%)	1/1 (50%)	
Median age (range)	37 (21-61)	31 (21-41)	
IgG positive/ PCR positive			
Number	4/174 (2.3%)	1/22 (4.5%)	0,452
Male/Female (Male %)	2/2 (50%)	1 (0%)	
Median age (range)	31 (22-53)	41	

⇨ GBM prevalence (serological and molecular) in thalassemia patients compared to the general population suggest blood transmission

The blood virome: giant viruses

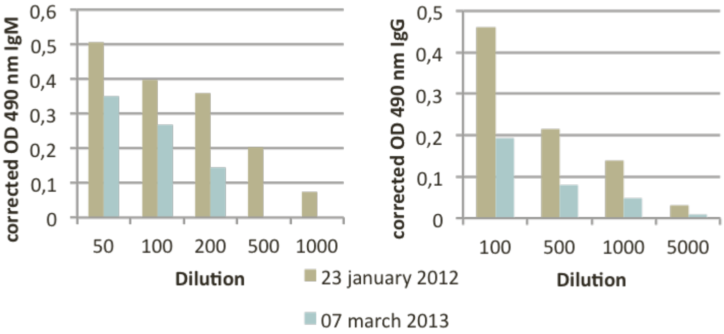


Marseillevirus Adenitis in an 11-Month-Old Child

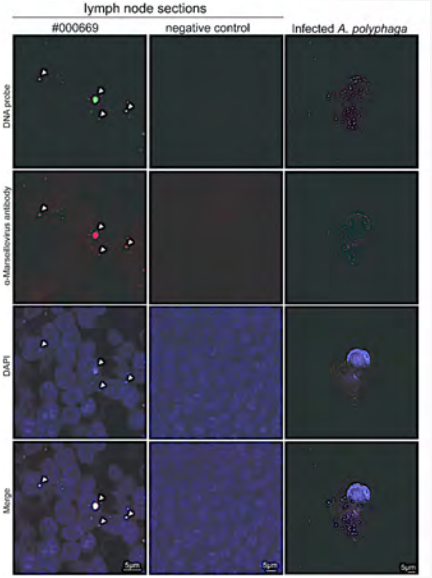
Nikolay Popgeorgiev,[a] Gerard Michel,[b] Hubert Lepidi,[b] Didier Raoult,[a] Christelle Desnues[a]

December 2013 Volume 51 Number 12

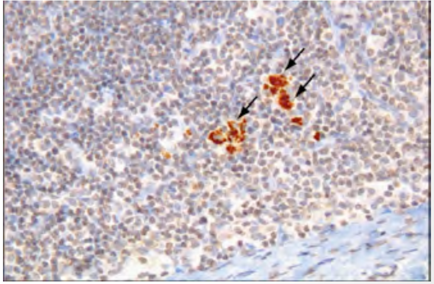
- High titers of anti-Marseillevirus IgG and IgM in Jan-2012
- GBM PCR positive (Jan-2012)



- Eleven months old child hospitalized in Marseille in 2012
- Adenopathy with unknown etiology
- Medical record of exacerbated reaction to BCG vaccination
- All 16S PCRs were negative, cultures were negative
- HIV, EBV and CMV PCRs and serologies were negative



Anti-Marseillevirus immunohistochemistry



- In March 2013, GBM PCR was negative
- IgM titers have decreased , IgG titers are stable

THE LANCET Infectious Diseases

Marseillevirus in lymphoma: a giant in the lymph node

Sarah Aherfi, Philippe Colson, Gilles Audoly, Claude Nappez, Luc Xerri, Audrey Valensi, Matthieu Million, Hubert Lepidi, Regis Costello, Didier Raoult

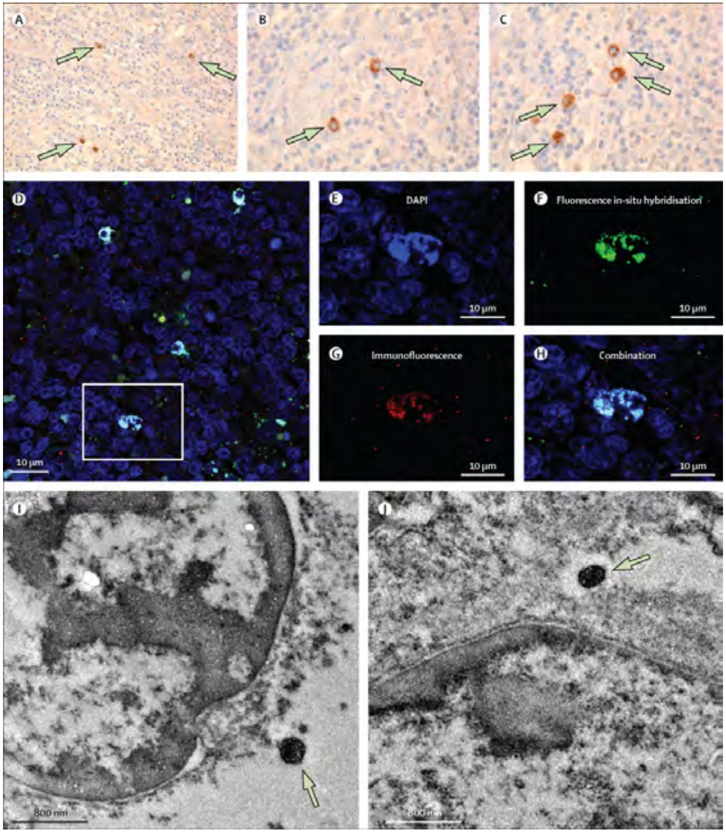
www.thelancet.com/infection **Vol 16 October 2016**

Case:

- 30-year-old woman living in Marseille
- Admitted to the hospital in May, 2014, for a dry cough and with a 1-year history of lymphadenopathies.
- Clinical examination revealed bilateral axillar and left subclavicular lymphadenitis.
- PET and CT scanning revealed several hypermetabolic lymphadenopathies (cervical, supraclavicular, axillar, mediastinal, latero-aortic, coeliac, and in the internal mammary)
- Serological tests were negative for hepatitis B virus, hepatitis C virus, HIV, and cytomegalovirus, and indicated previous infection and immunity against Epstein-Barr virus.
- Pathological examination of a left axillar lymph node biopsy sample showed evidence of many Reed-Sternberg and Hodgkin cells surrounded by an inflammatory granuloma composed of lymphoid elements, macrophages, and eosinophils.

Classic nodal Hodgkin's lymphomas with mixed cellularity (WHO classification type 3)

The lymph node was Marseillevirus PCR positive (sequencing 100% identical to the marseillevirus)

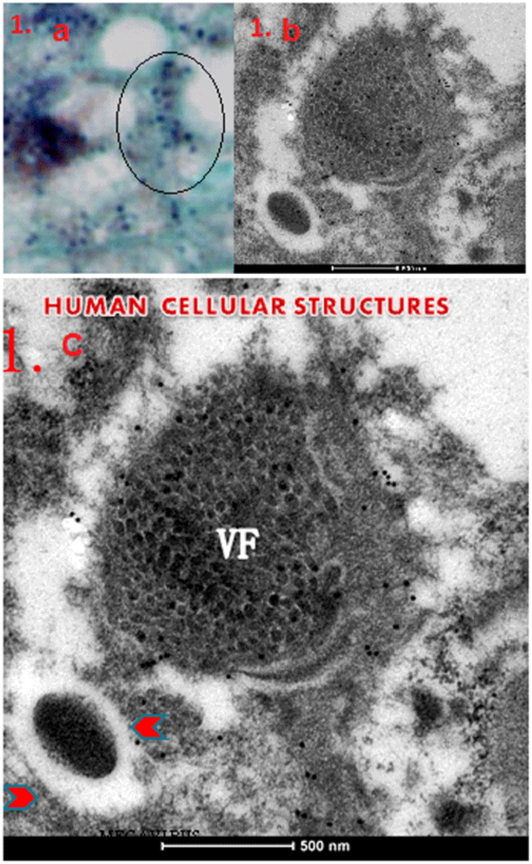


- Immunohistochemical detection of marseillevirus in the patient lymph node by use of a mouse polyclonal anti-marseillevirus antibody with haemalum counterstaining. Arrows show the intracellular location of the virus in the macrophage cytoplasm
- thin section of the lymph node can be shown by FISH (DNA probe 152F1-153R2, in green) and immunofluorescence (anti-marseillevirus antibody, in red); nucleic acid was stained with DAPI.
- Electron microscopy images of the embedded lymph node show giant virion-resembling structures.

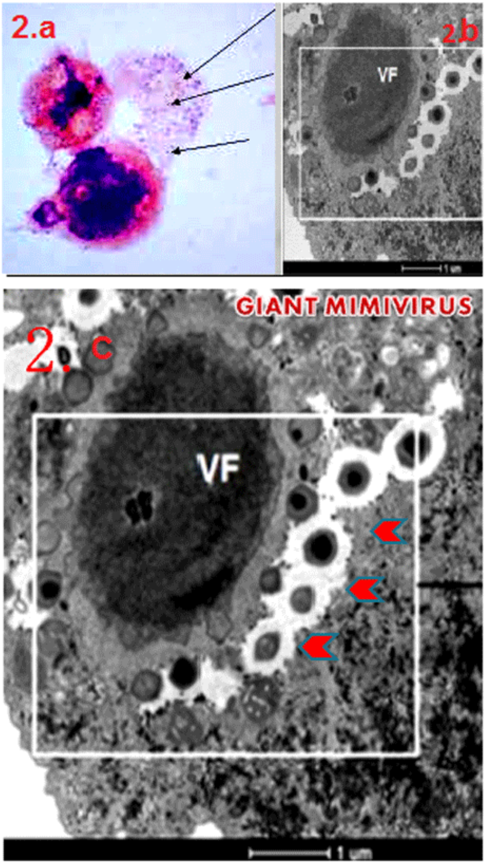
From July 2014, the patient underwent a standard chemotherapy regimen for Hodgkin's lymphomas. Complete remission was achieved.

Giant viruses in human, contaminant? role?

1. HUMAN TISSUES

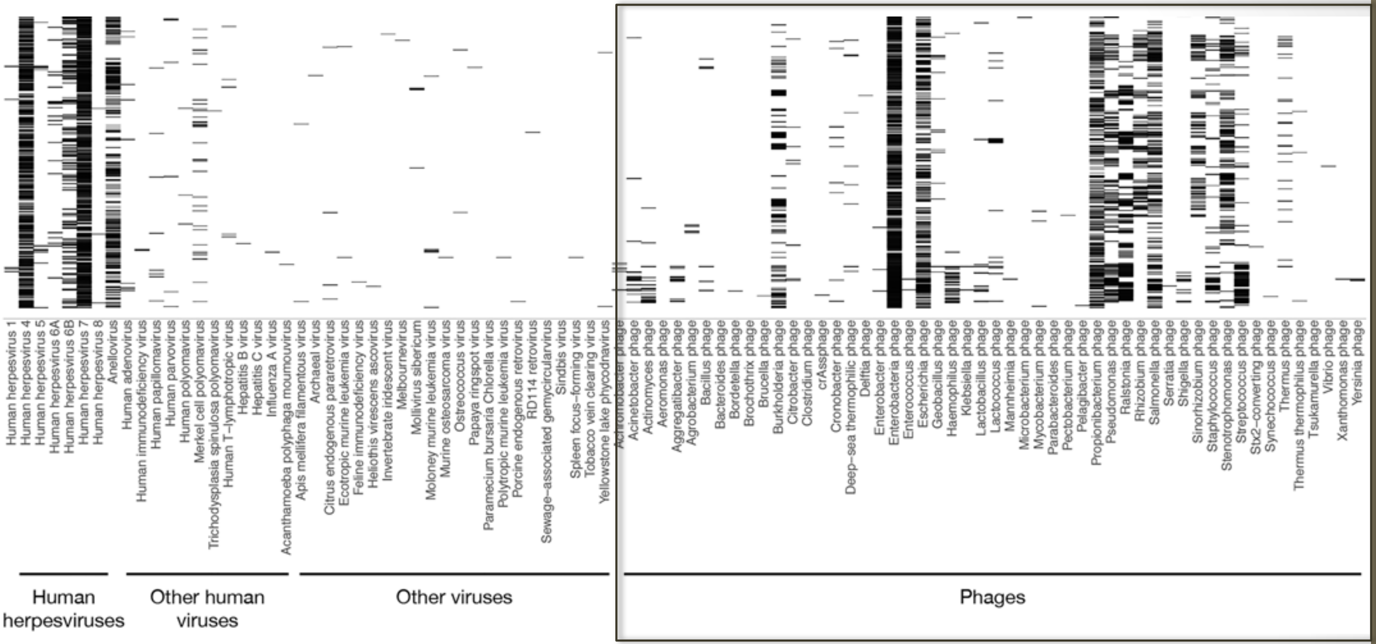


2. AMOEBAS



Lusi et al., F1000Research (2017)

The blood virome: the phages



Sequences belonging to 52 different phages

Enterobacteria, Burkholderia, Escherichia, Ralstonia, Stenotrophomonas, Ralstonia, Pseudomonas phages were highly prevalent and detected in 2-11% of the individuals

Bacteriophages, contaminant or real?

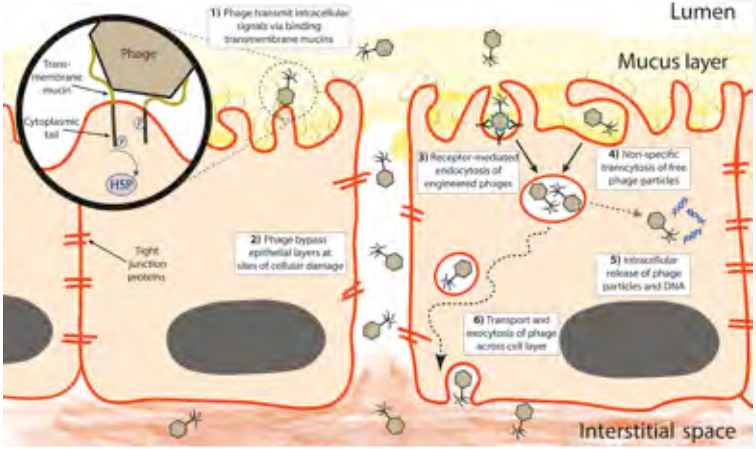
Phage sequences are **always** detected in viral metagenomic data from human blood

The gut is the largest reservoir of phages in human. Phages are significantly enriched at the mucosal surface.

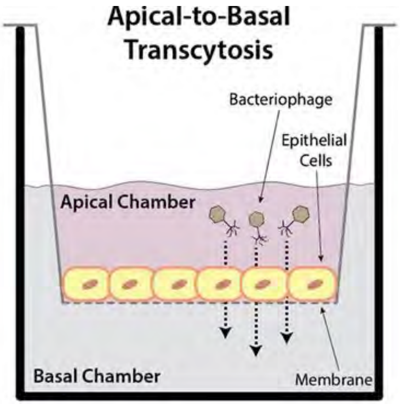
Barr et al., PNAS (2013)

Route of entry from the gut to the lymph, blood and organs:

- Leaky gut (cellular damaged)
- Trojan-horse mecanism
- Receptor-mediated endocytosis (phage display)
- Non-specific cellular uptake



Barr et al., Immunological reviews (2017)



Apical-to-basal transcytosis observed with every phage type investigated across diverse cell lines

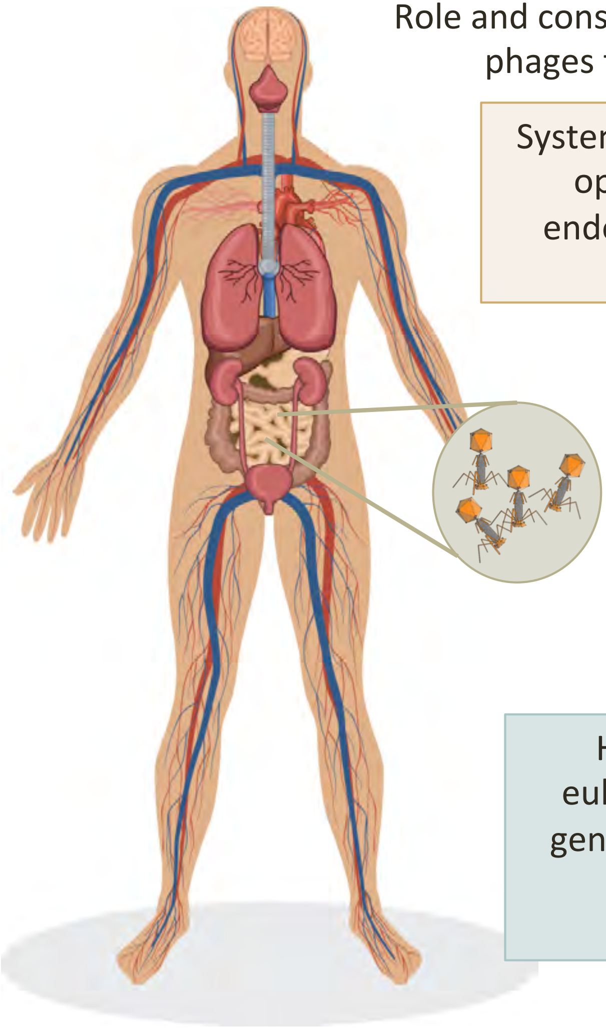
0.1% of total bacteriophages transcytosed over a 2-h period

31 billion of phage transcytotic events per day

Nguyen et al. mBio (2017)

Role of phages in the human blood?

Role and consequences of this continuous low-level stream of phages from gut to the blood, lymph, and organs?



System-wide antimicrobial against the intrusion of any opportunistic gut microbe The potential role of endogenous bacteriophages in controlling invading pathogens.

Nguyen et al. mBio (2017)
Górski et al., Cell Mol Life Sci. (2005)

Long-term immunologic tolerance through interactions with regulatory T cell populations and downregulation of specific and nonspecific immune reactions

Górski et al., Future Medicine (2017)

Horizontal gene transfer between phages and eukaryotes, transcription and translation of phage genetic material within epithelial cells and the body

↓

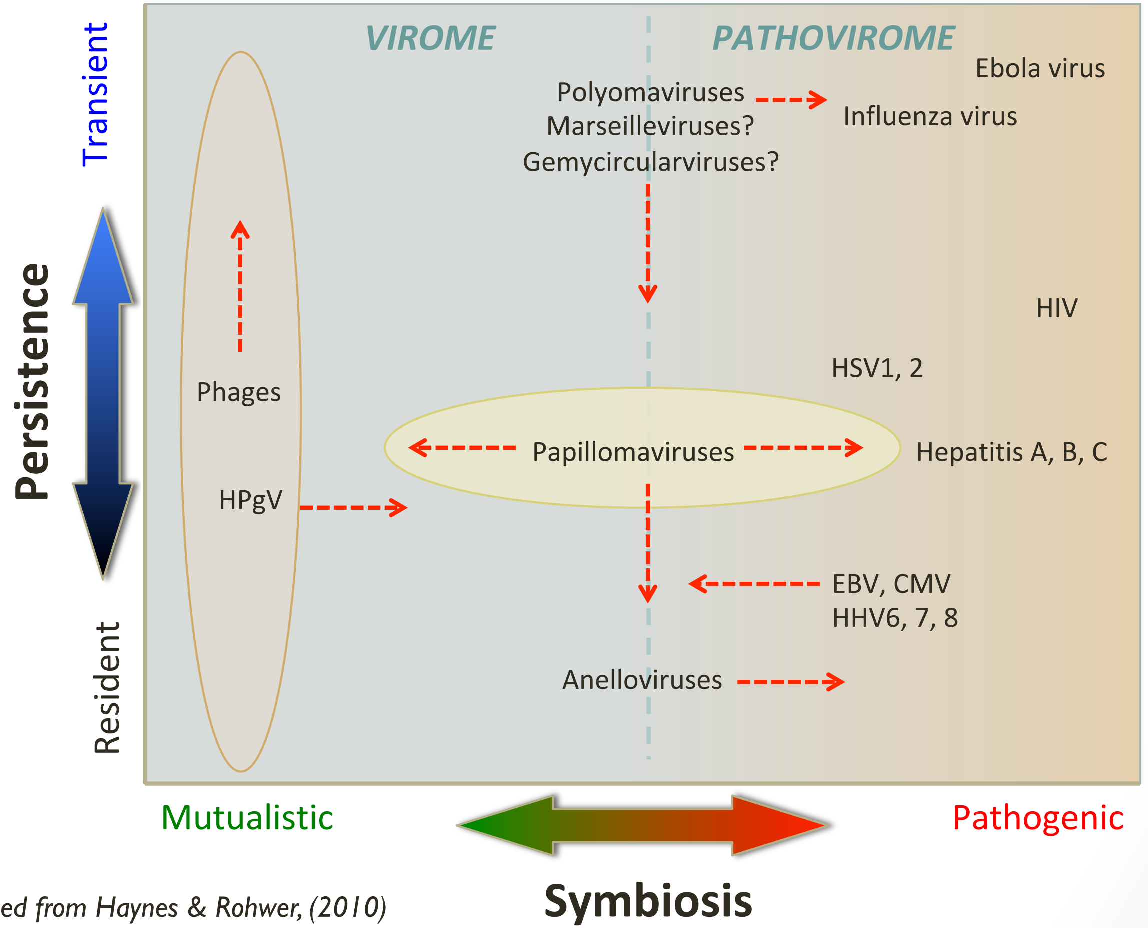
Our third genome

Barr et al., Immunological Rev. (2017)

The blood virome: the phages

The blood virome: from symbiosis to pathology

A yet largely incomplete picture of human blood-associated viruses…



Transient

Persistence

Resident

VIROME

PATHOVIROME

Ebola virus

Polyomaviruses

Influenza virus

Marseilleviruses?

Gemycircularviruses?

HIV

HSV1, 2

Phages

Papillomaviruses

Hepatitis A, B, C

HPgV

EBV, CMV

HHV6, 7, 8

Anelloviruses

Mutualistic

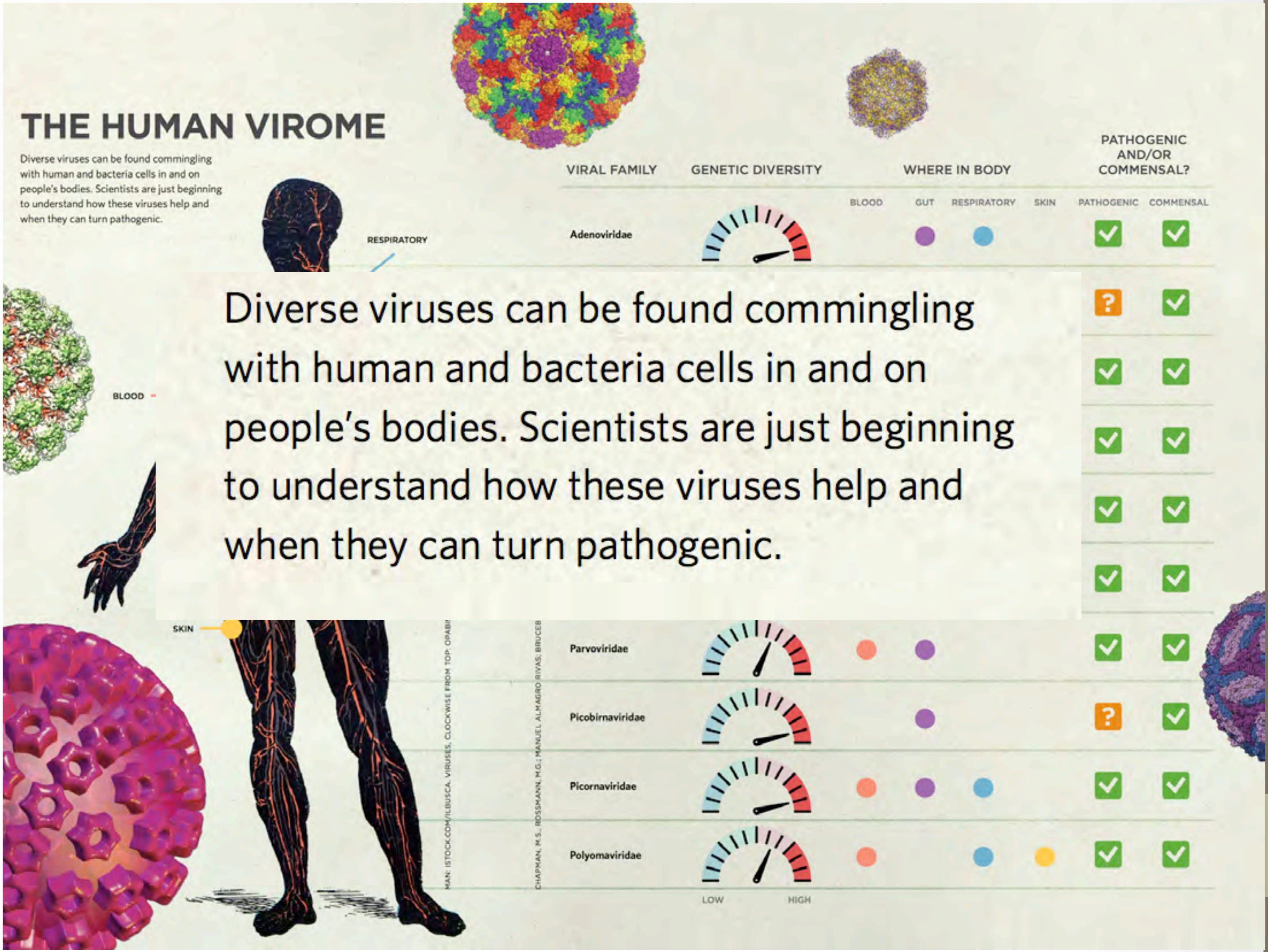
Pathogenic

Symbiosis

Adapted from Haynes & Rohwer, (2010)

The blood virome

Introduction to the human virome



THE HUMAN VIROME

Diverse viruses can be found commingling with human and bacteria cells in and on people's bodies. Scientists are just beginning to understand how these viruses help and when they can turn pathogenic.

VIRAL FAMILY	WHERE IN BODY: BLOOD	GUT	RESPIRATORY	SKIN	PATHOGENIC AND/OR COMMENSAL?: PATHOGENIC	COMMENSAL
Adenoviridae		●	●		✓	✓
					?	✓
					✓	✓
					✓	✓
					✓	✓
					✓	✓
Parvoviridae	●	●			✓	✓
Picobirnaviridae		●			?	✓
Picornaviridae	●	●	●		✓	✓
Polyomaviridae	●		●	●	✓	✓

Diverse viruses can be found commingling with human and bacteria cells in and on people's bodies. Scientists are just beginning to understand how these viruses help and when they can turn pathogenic.

Delwart, The Scientist (2016)

Future of human viromics

METHODOLOGICAL CHALLENGES

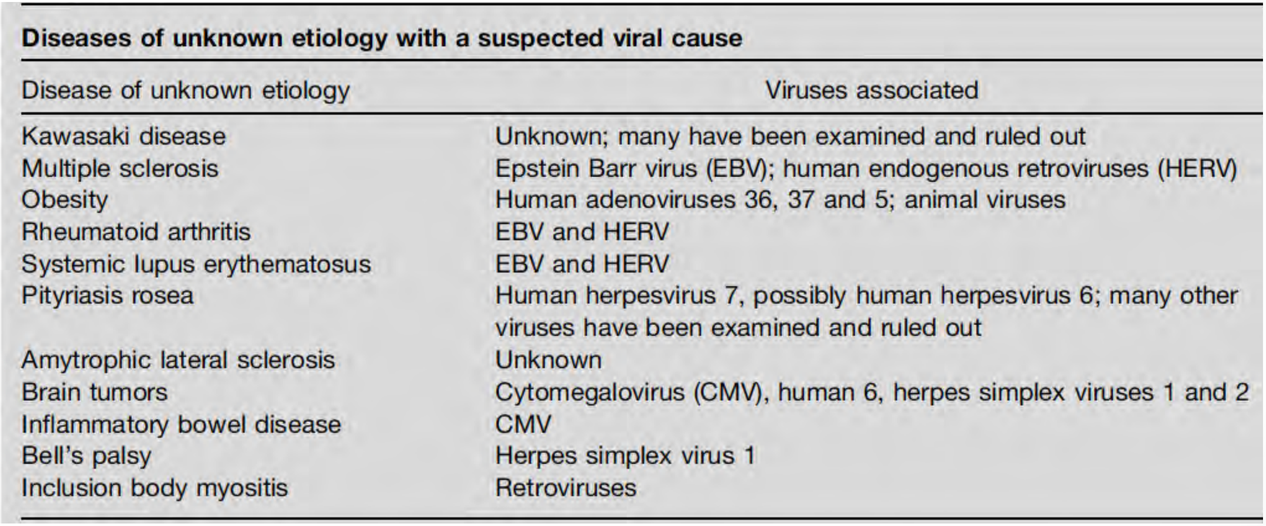
- ✓ Genome partitioning: enrich the viral fraction or remove host DNA contaminations
- ✓ Development of protocols targeting RNA viruses
- ✓ Development of bioinformatics to deal with unknown sequences (viral dark matter)
- ✓ Improved sequencing technologies (reads length and fidelity) and computational platforms

→ Single molecule nanopore technology (minION)

Cheap, single molecule DNA sequencing in a device no larger than a USB key
Real-time sequencing, DNA is not damaged
30 % error rate

Future of human viromics

- ✓ Pursue efforts on pathologies with unknown etiology, validation of the Koch's postulate

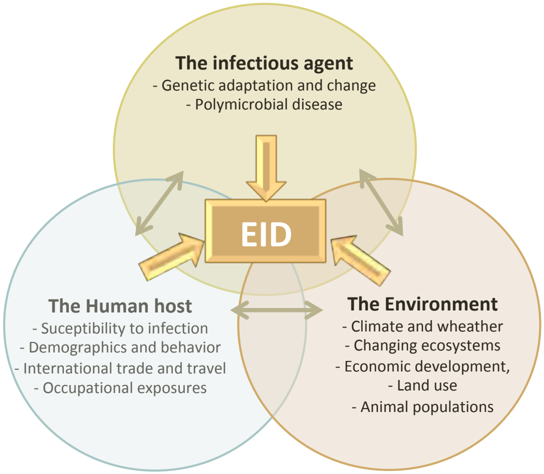


Diseases of unknown etiology with a suspected viral cause

Disease of unknown etiology	Viruses associated
Kawasaki disease	Unknown; many have been examined and ruled out
Multiple sclerosis	Epstein Barr virus (EBV); human endogenous retroviruses (HERV)
Obesity	Human adenoviruses 36, 37 and 5; animal viruses
Rheumatoid arthritis	EBV and HERV
Systemic lupus erythematosus	EBV and HERV
Pityriasis rosea	Human herpesvirus 7, possibly human herpesvirus 6; many other viruses have been examined and ruled out
Amytrophic lateral sclerosis	Unknown
Brain tumors	Cytomegalovirus (CMV), human 6, herpes simplex viruses 1 and 2
Inflammatory bowel disease	CMV
Bell's palsy	Herpes simplex virus 1
Inclusion body myositis	Retroviruses

Wylie et al. Curr. Op. Microb, (2013)

Emerging infectious diseases (EID)



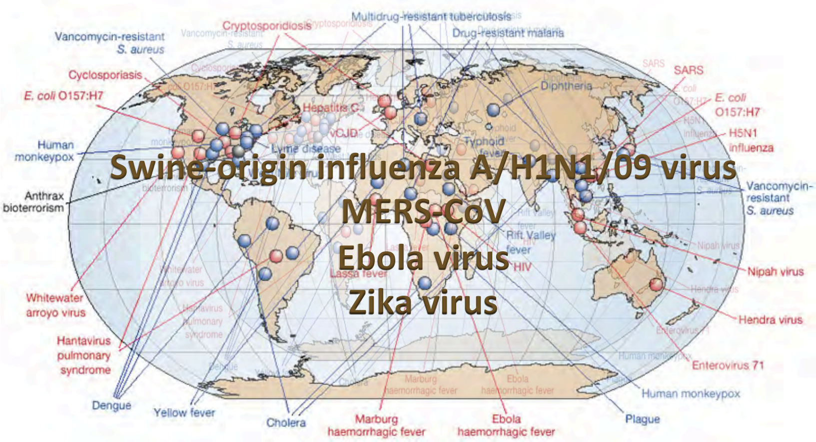
The infectious agent
- Genetic adaptation and change
- Polymicrobial disease

EID

The Human host
- Suceptibility to infection
- Demographics and behavior
- International trade and travel
- Occupational exposures

The Environment
- Climate and wheather
- Changing ecosystems
- Economic development,
- Land use
- Animal populations

Factors of emergence
(Morens et al., 2008, Lancet Infect Dis)

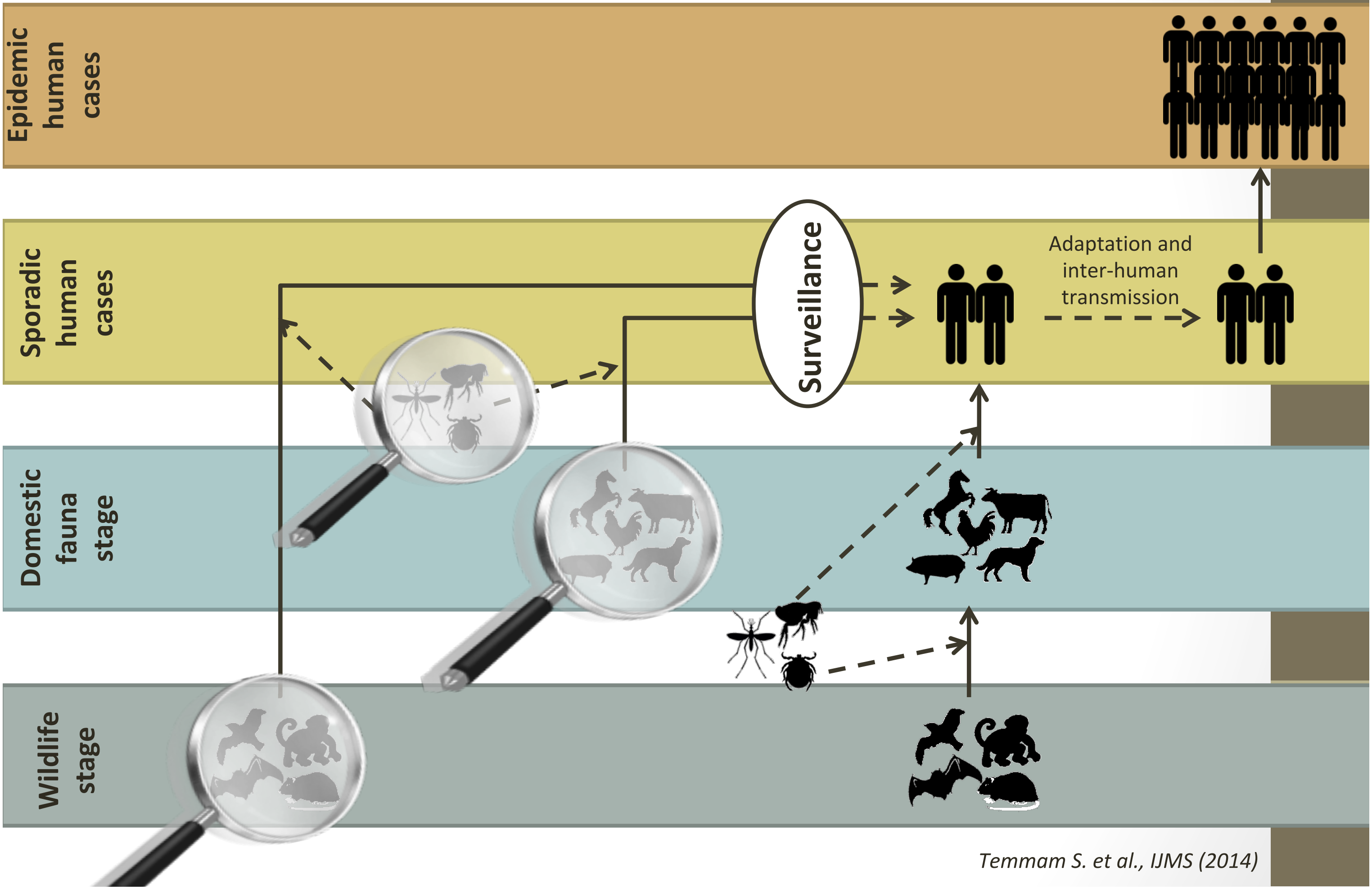


Swine-origin influenza A/H1N1/09 virus
MERS-CoV
Ebola virus
Zika virus

Zoonosis is a source of up to 75% of emerging infectious diseases in humans
Vaccine development takes time and require a huge amount of resources

Assess the danger posed by viruses that thrive in animals and could cross to human

Zoonotic viruses and human health



Temmam S. et al., IJMS (2014)

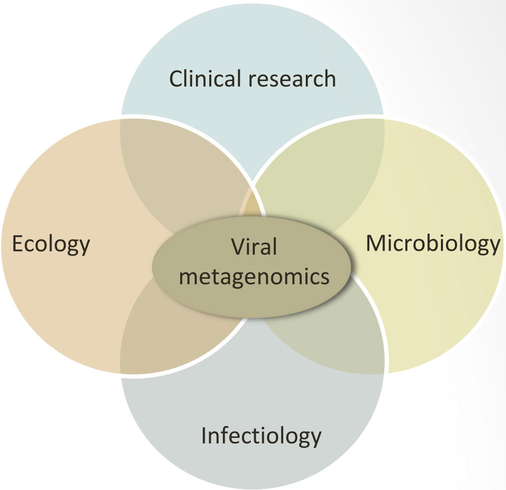
The ecology of human health and disease

Olaf Hajek, New York times, July 2012

Future perspectives

Our research axes

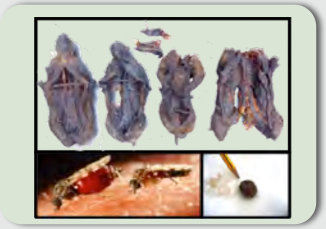
We investigate the composition, the diversity, the dynamic and the evolution of human, animal and environmental viromes



Human virome and pathogen discovery

1. Pathogen discovery
3. Role of viruses in dysbiosis
4. Get the best from our virome

Emerging viruses vectors and reservoirs



Inventory of viruses in vectors and reservoirs to prevent and detect emerging zoonoses

Environmental viromes

Viral communities in extreme and human-impacted environments

Paleoecology of health (human and animals)

Diversity and evolution of viral and microbial communities from the past

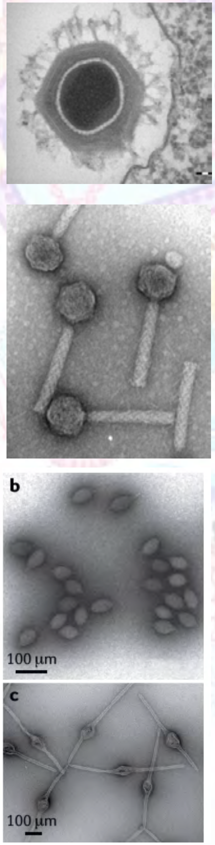
www.pathovirome.wordpress.com

The Pathovirome team

nature REVIEWS MICROBIOLOGY

Consider something viral in your research

- **Viruses offer opportunities for new discoveries.** *Viruses really are the ‘dark matter’ of the biological universe and a rich source for discovery.*
- **Viruses can be markers of changes in the biology of ecosystems.** *The signal from the virome will be the earliest, strongest and easiest to observe.*
- **Biology and evolution makes less sense without viruses.** *Viruses move genes between genomes; they are one of the selective forces — if not the primary force — acting on individual cells.*



Rohwer & Youle, Nat. Rev. Microbiol (2011)

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