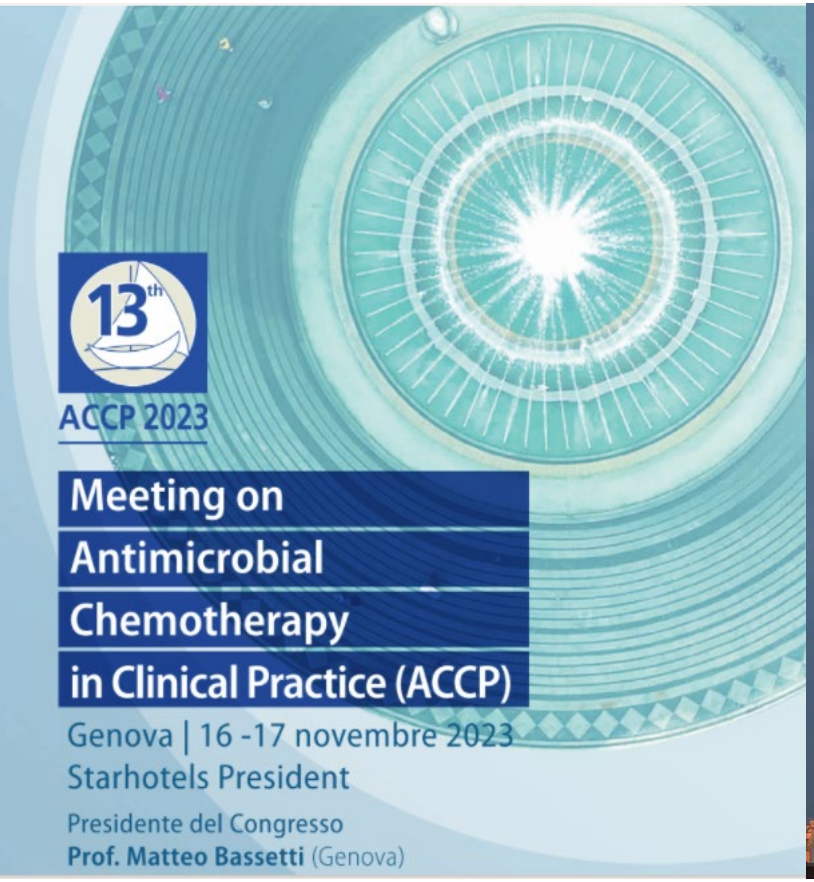
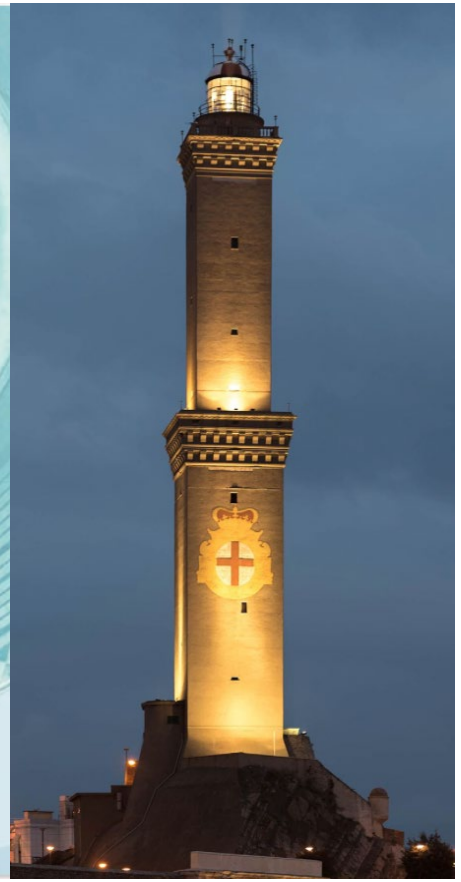
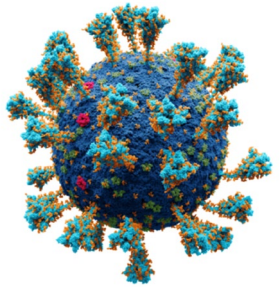
Storia della Virologia con uno sguardo alla pandemia da COVID-19





THERE IS ONE VIROLOGY AT THE SERVICE OF ONE HEALTH



A GLOBAL VISION FROM A VIROLOGIST'S PERSPECTIVE

Giorgio Palù, MD, FESCMID
Professor of Microbiology and Virology, Emeritus
Padua University, Italy
Professor of Neurosciences and of Science and Technology
Temple University, Philadelphia

AIFA AGENZIA ITALIANA DEL FARMACO

SIV ISV SOCIETA' ITALIANA DI VIROLOGIA ITALIAN SOCIETY FOR VIROLOGY

EUROPEAN SOCIETY for VIROLOGY

LA SCOPERTA DEL MONDO MICROBICO

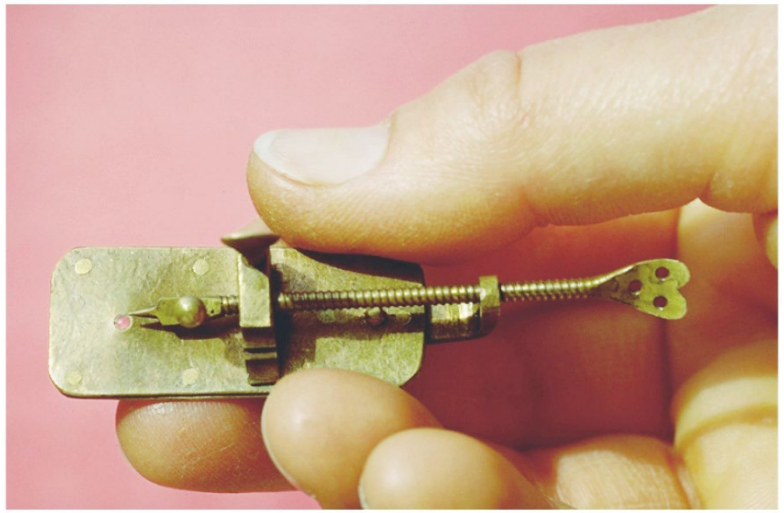
(i virus sono microbi non microrganismi)

Anton van Leeuwenhoek (1632-1723)

Era un commerciante di tessuti olandese con la passione delle lenti di ingrandimento

L'inizio delle sue osservazioni coincide con la fondazione della *Royal Society* il cui scopo era la diffusione e la pubblicazione dei lavori scientifici

Fu il primo a descrivere i batteri !

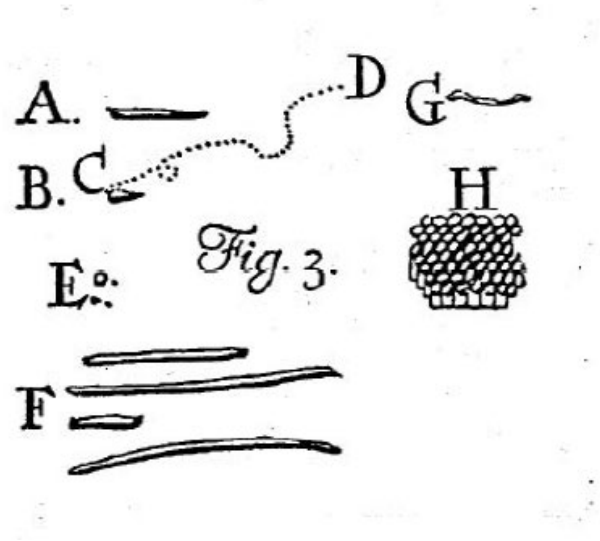


IL MICROSCOPIO
(il discrimine del visibile)

1. Lente tra due piastre metalliche
2. Messa a fuoco mediante viti
3. Osservazione con lo strumento vicino all'occhio
4. 50-300 ingrandimenti

Da una lettera di A. Van Leeuwenhoek

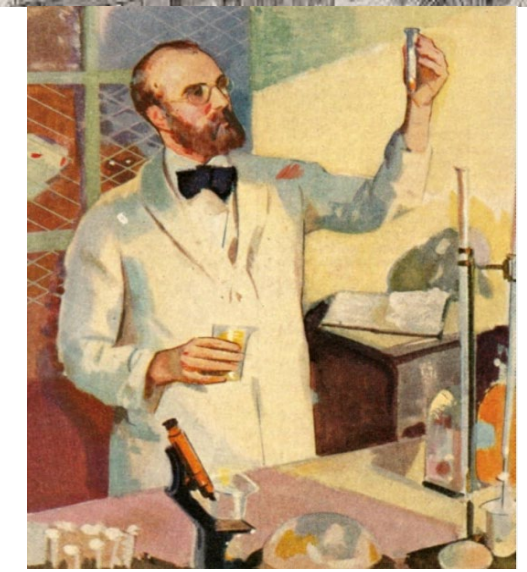
Philos. Trans. Royal Soc. London *vol. 14, 20 maggio 1684, n.159, pag.568-574*



Anton van Leeuwenhoek scopre gli ***animalcules*** **(1676)** e la loro incredibile abbondanza

<u>Le sue ricerche portarono un intero mondo invisibile alla consapevolezza degli scienziati dell'epoca</u>

I Principi e i Postulati delle Malattie Infettive



Louis Pasteur 1822

Robert Koch 1843

La Storia dei Premi Nobel Inizia con la Microbiologia
(ma segnerà anche la storia ed il successo della Virologia)

Emil Adolf von Behring

1901

Shibasaburo Kitasato

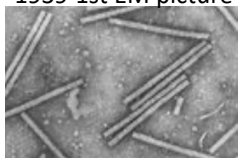
Virologia, Le Fasi:

- Eziologica
- Biologica
- Molecolare
- Strutturale
- Altri campi del sapere
- Presenti e futuri sviluppi

La Virologia prima del Microscopio Elettronico

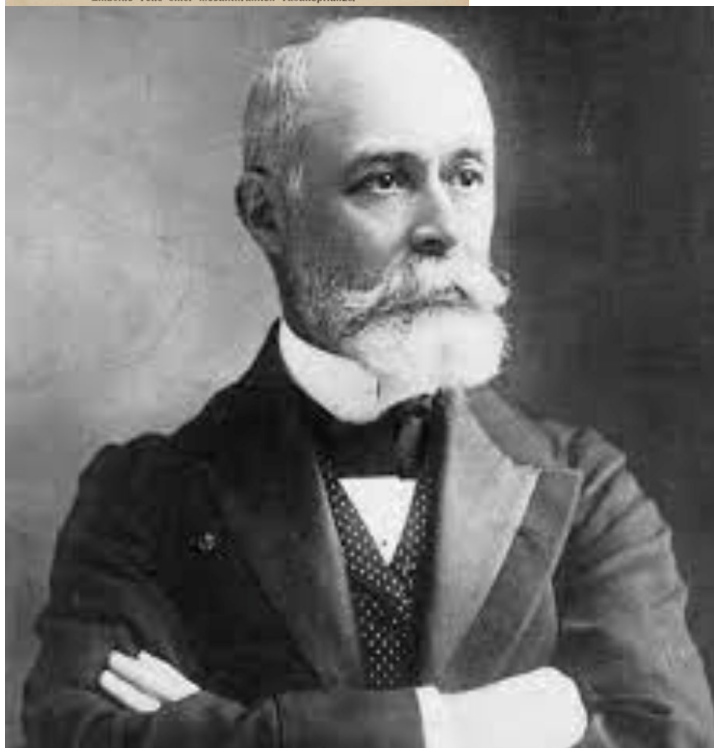
Osservazione, ultrafiltrazione e trasmissione dell'agente

1939 1st EM picture



WM Stanley 1935
crystals and isolation
TMV, Tobamovirus, Virgaviridae,
6,4 kb +RNA

Nomen Omen: Virus
Contagium vivum fluidum



Dmitry Ivanovsky 1892

Filtri Chamberland-Pasteur

«Tout virus est un microbe»
Louis Pasteur 1890

Martinus Beijerinck 1898

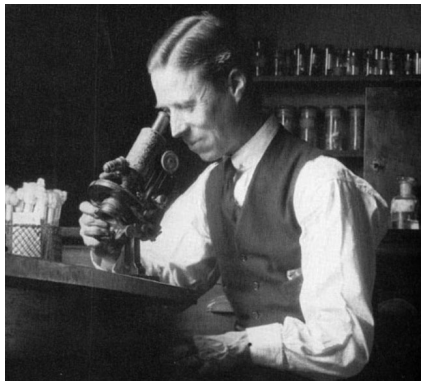
Virology at its Onset

(from plants to animals to the virome)

Friedrick Loeffler & Paul Frosch
1898 FMDV

Walter Reed 1900
Yellow fever

Vilhelm Ellerman & Oluf Bang
ALV 1908



Frederick Twort 1915

Felix d'Herelle 1917
The phage phenomenon

The Many Nobel Prizes to Virology Sign the Evolution of Life Sciences

-Cell Biology-

1954 Culture of poliovirus

John Enders

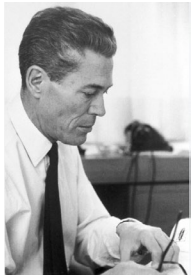
Frederick Robbins

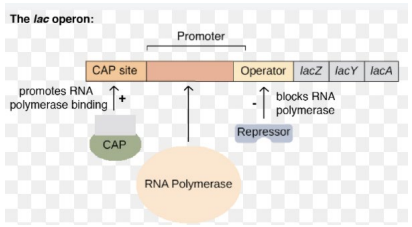
Thomas Weller

The Many Nobel Prizes to Virology Sign the Evolution of Life Sciences

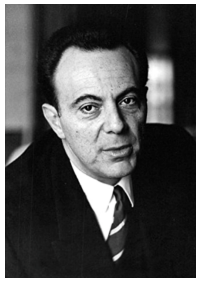
-Genetics, Cell & Molecular Biology-

1965 Gene control in bacteria and viruses

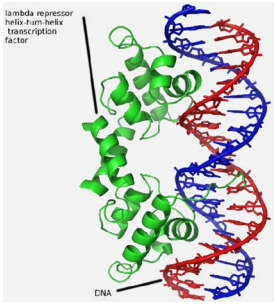


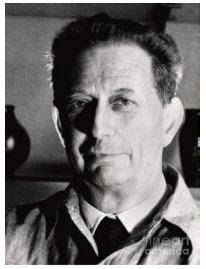


Jaques Monod



François Jacob

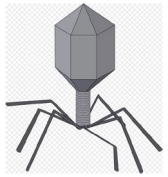




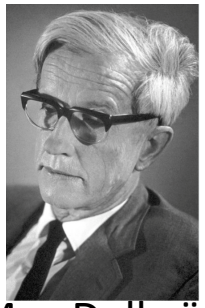
André Lwoff

1969 Gene structure and replication

Salvador Luria

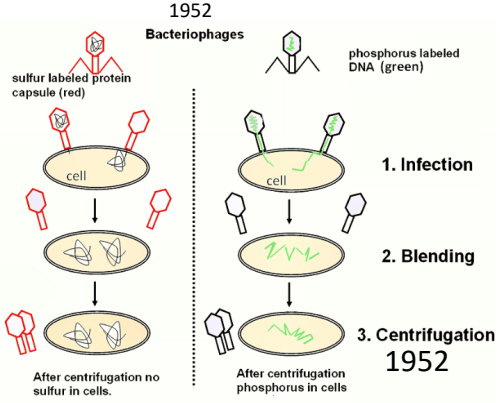


1943



Max Delbrück

1952

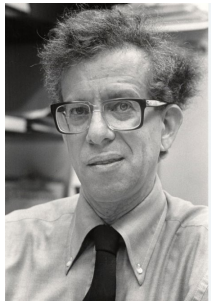


1952

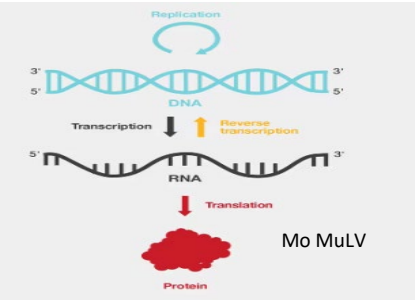
Alfred Hershey

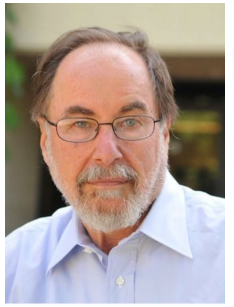
1975 Virus-cell interactions

Renato Dulbecco



Howard Temin



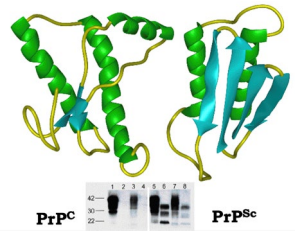


David Baltimore

The Many Nobel Prizes to Virology Sign the Evolution of Life Sciences

-New Viruses Discovery-

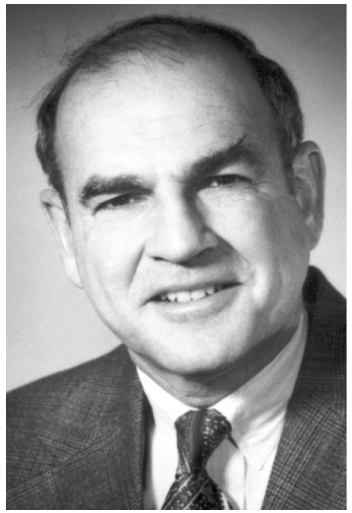
Conversion to scrapie



1951

Max Theiler YFV

1976



Baruch Blumberg & David Gajdusek
HBV & Kuru

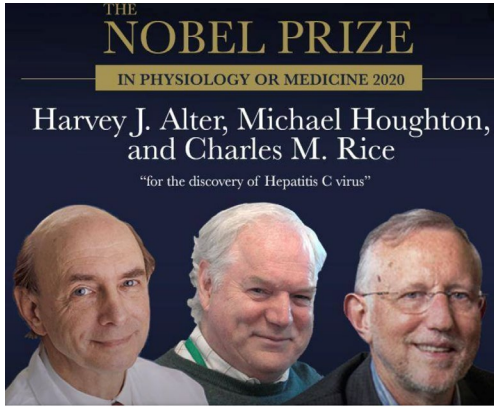
1997

Stanley Prusiner
Prions

2008

Luc Montagnier, Françoise Barré-Sinoussi, Harald zur Hausen
HIV - HPV

2020



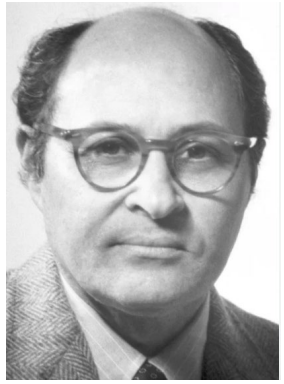
HCV

The Many Nobel Prizes to Virology Sign the Evolution of Life Sciences

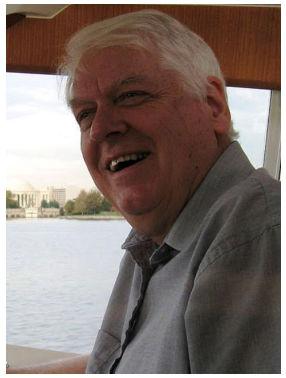
Cellular Immunology, Molecular Genetics & Genomics, Chemistry
Viruses as an indispensable tool

1978

Werner Arber



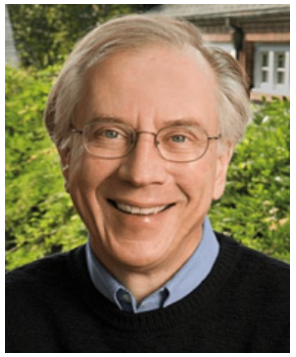
Daniel Nathans



Hamilton Smith

Restriction enzymes as a defence from viruses

1989



Sidney Altman & Thomas Cech
Catalytic RNA -Viroids-

1993

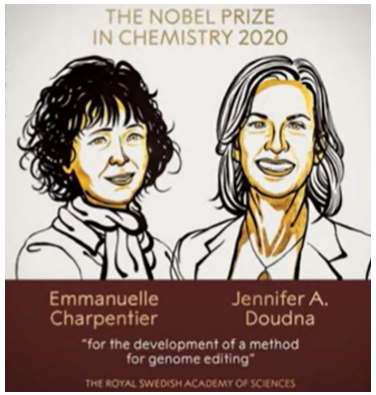
Richard Roberts & Philip Sharp
Introns (AdV)

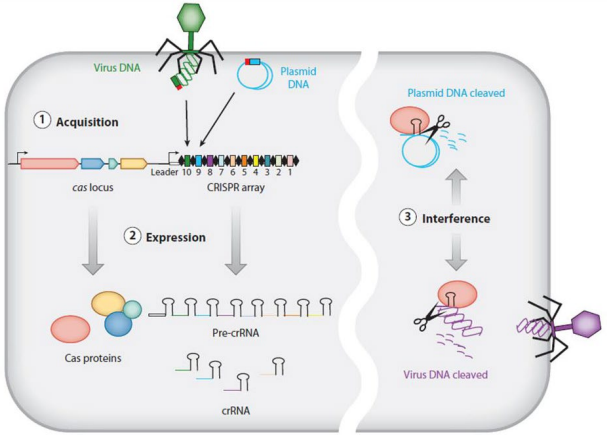
1996

Peter Doherty & Rolf Zinkernagel
Cellular immunity -LCMV-

(not to forget : Ehrlich& Mečnikov 1908; Bordet 1919)

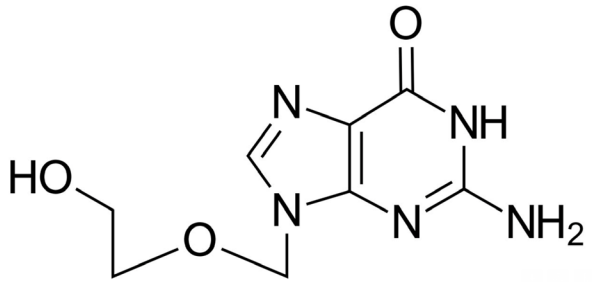
2020



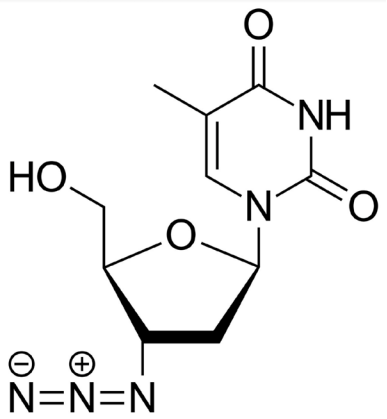


Emmanuelle Charpentier & Jennifer Doudna
Genome editing (innate immunity to phages)

Chemotherapy: Anti-Infectious ⇌ Anti-Cancer



Aciclovir



Azidothymidine

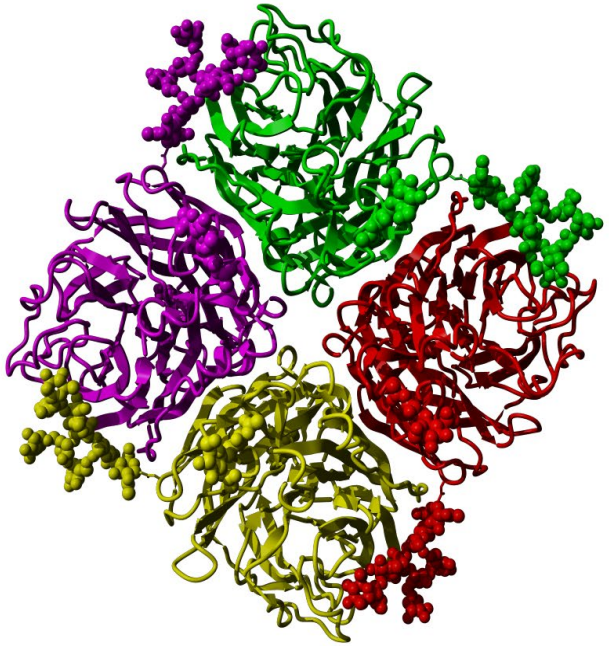
(not to forget: Domagk 1939; Chain,Fleming, Florey 1945; Waksman 1952; Bovet 1957)

1988

Gertrude Elion & George Hitchings, 1948 Burrough Wellcome and Whyte Black

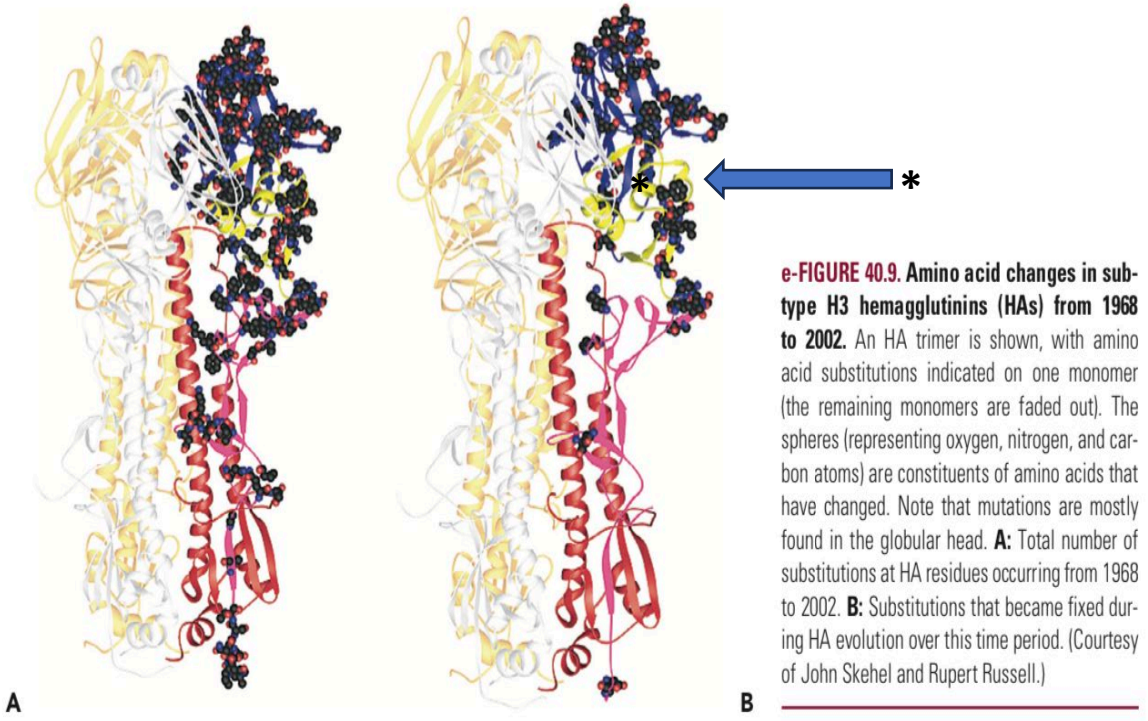
Structural Virology as the Key to Cell Physiology and Pathology (From André M Lwoff onwards)

Hemagglutinin bound to sialic acid
(Wilson, Skehel, Wiley 1981 Nature)



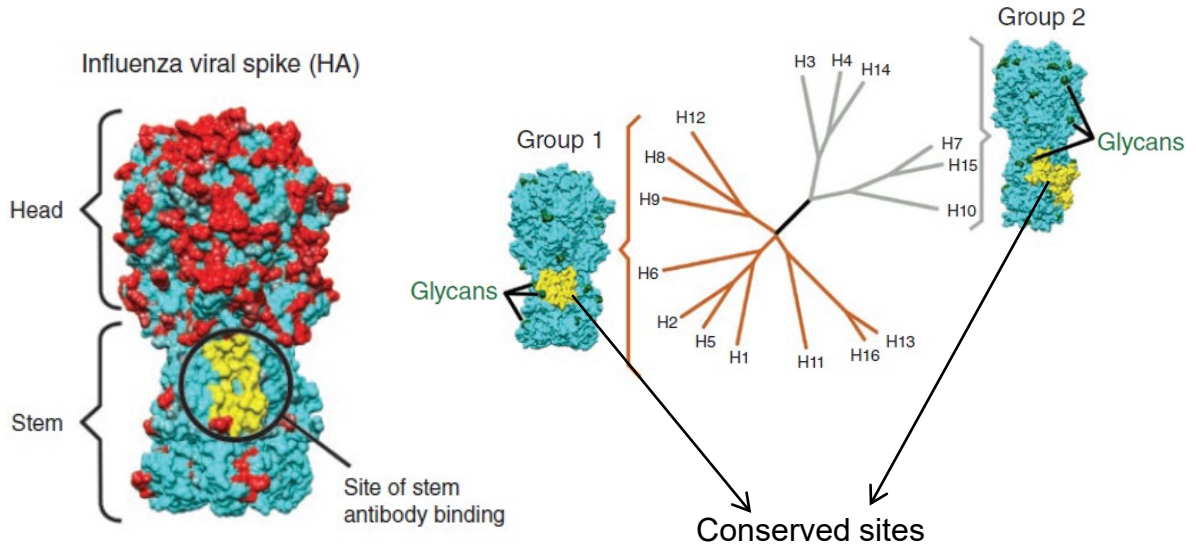
Neuraminidase of influenza virus
(Colman, Varghese, Laver 1983 Nature)

Structural Virology in the 80s: Peatty RNA Sequencing and Monoclonal Antibodies Selection (London, NIMR-MRC)

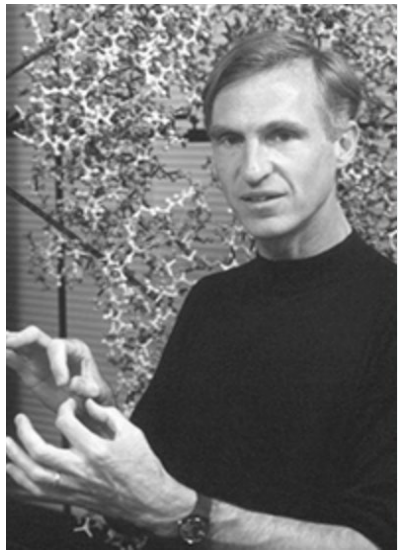


e-FIGURE 40.9. Amino acid changes in subtype H3 hemagglutinins (HAs) from 1968 to 2002. An HA trimer is shown, with amino acid substitutions indicated on one monomer (the remaining monomers are faded out). The spheres (representing oxygen, nitrogen, and carbon atoms) are constituents of amino acids that have changed. Note that mutations are mostly found in the globular head. **A:** Total number of substitutions at HA residues occurring from 1968 to 2002. **B:** Substitutions that became fixed during HA evolution over this time period. (Courtesy of John Skehel and Rupert Russell.)

*** Monoclonal variant aa 143**



Skehel JJ, Cell 2016



Don Wiley

Sir John J Skehel

Protein Structures are Druggable Targets

METRICS:

- One PhD student 4 years for 1 protein (not even sure it will be crystallized)
- Entire history of experimental biology (1958-2020) ~150,000 proteins.
- ***AlphaFold through genomes***
  - 6 months (Jun 2020- Dec 2020) all 20,000 human proteins.
  - 2021-2022 1 million proteins
  - 2023-2024 (predicted) 100 million proteins (all the known ones)

***Eric J. Topol, Demis Hassabis**. It's Not All Fun and Games: How DeepMind Unlocks Medicine'sSecrets - Medscape - Jun 15, 2022*

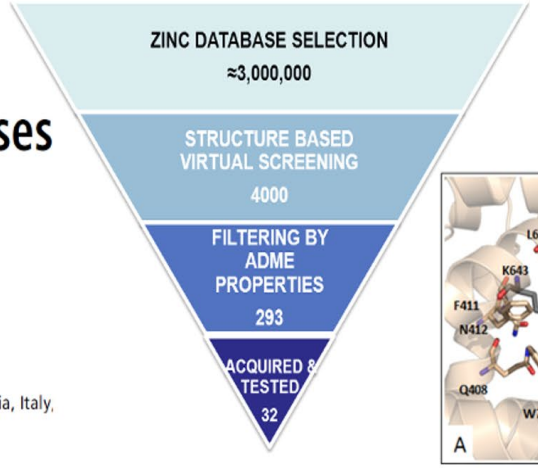
The revolution of AI

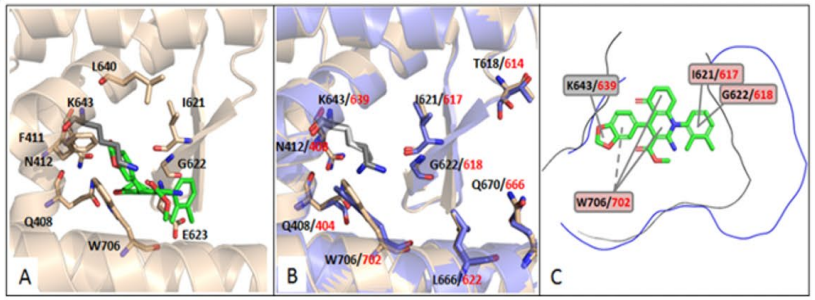
PNAS | April 17, 2012 | vol. 109 | no. 16 | 6247–6252

Small molecule inhibitors of influenza A and B viruses that act by disrupting subunit interactions of the viral polymerase

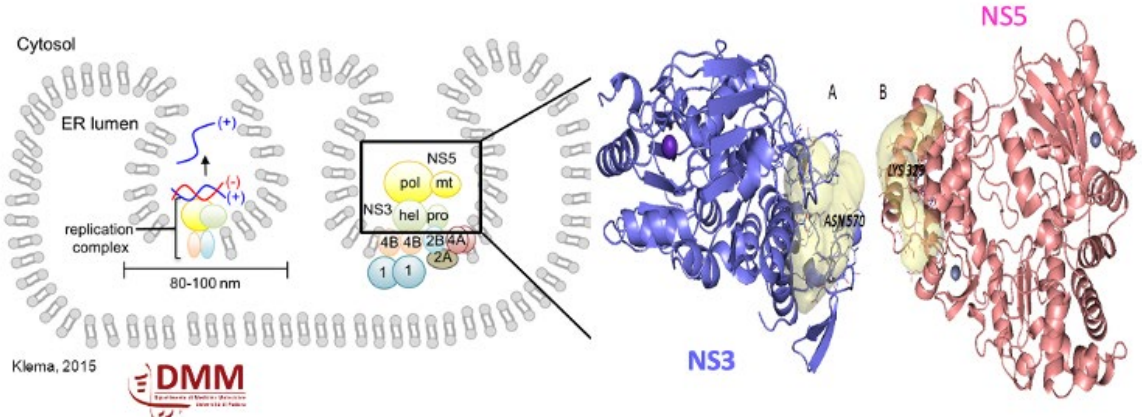
Giulia Muratore[a,1], Laura Goracci[b,1], Beatrice Mercorelli[a], Ágnes Foeglein[c,2], Paul Digard[c,3], Gabriele Cruciani[b,4], Giorgio Palù[a,4], and Arianna Loregian[a,4]

[a]Department of Molecular Medicine, University of Padua, 35121 Padua, Italy; [b]Department of Chemistry, University of Perugia, 60123 Perugia, Italy, and [c]Division of Virology, Department of Pathology, University of Cambridge, Cambridge CB2 1QP, United Kingdom

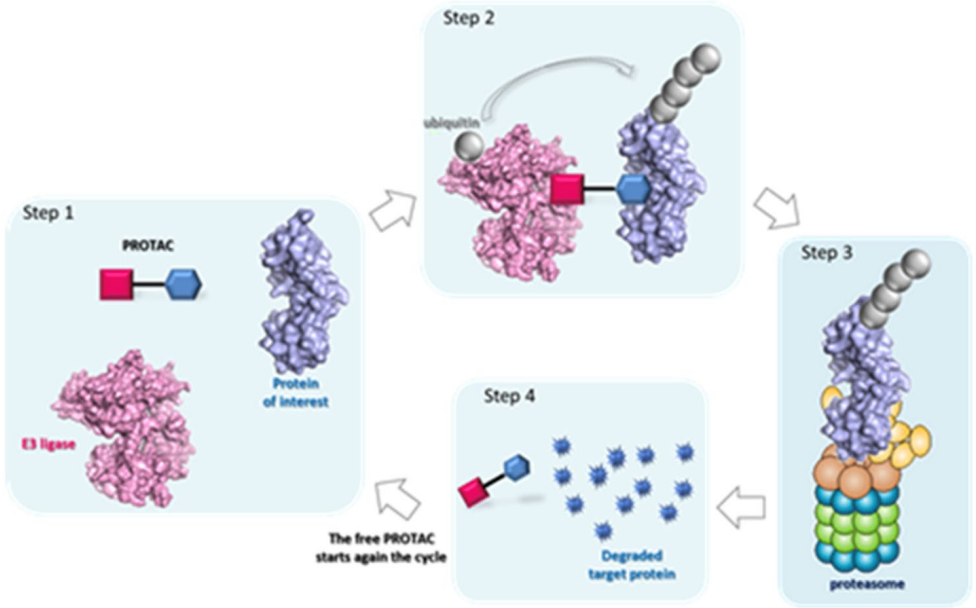




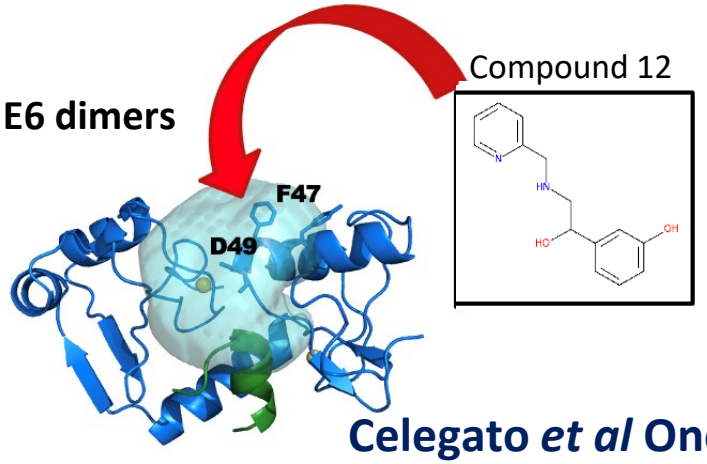
- **UNMET MEDICAL NEED:** lack of specific anti-DENV therapy



Small molecules disrupting PPI



E6 dimers



Compound 12

Candidate anti-HPV tumors compound

- Prevents p53 degradation
- Restore p53 levels
- Induces senescence

Celegato *et al* Oncogene, 2020

PROTAC approach for recycling inhibitors, De Santis *et al* EJMC 2021

The Tribute that Oncology Must Pay to Virology

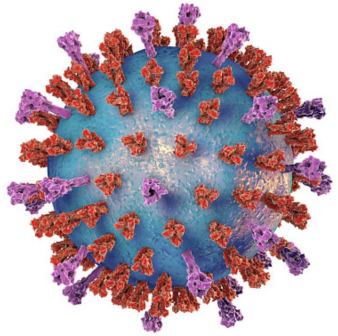
Peyton Rous 1911

1966

καρκίνος/*cancer*

De Naturalibus Facultatibus
(Galeno 129-216 dc)

1975



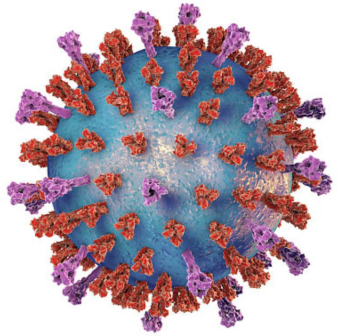
RSV

Renato Dulbecco

EBV

Not to forget the many disoveries of human and animal DNA tumor viruses

How did Viral Oncology then Develop?
The Lure of Virology



UNIVERSITA' DEGLI STUDI DI PADOVA

FACOLTÀ DI MEDICINA E CHIRURGIA

ISTITUTO DI MICROBIOLOGIA

Direttore: Prof. G. A. Meloni

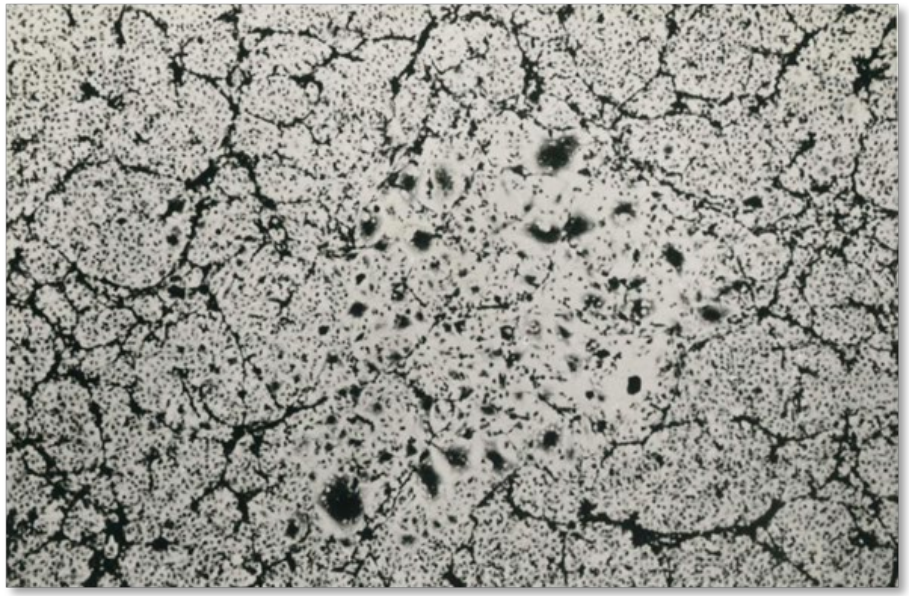
Tesi di Laurea

STUDIO DI ALCUNI ASPETTI DELL'ONCOGENESI VIRALE: TENTATIVI DI INDUZIONE DEL PROVIRUS DI GROSS CON DIVERSI AGENTI CHIMICI

Relatore:
Ch.mo Prof. G. A. Meloni

Laureando:
Giorgio Palù

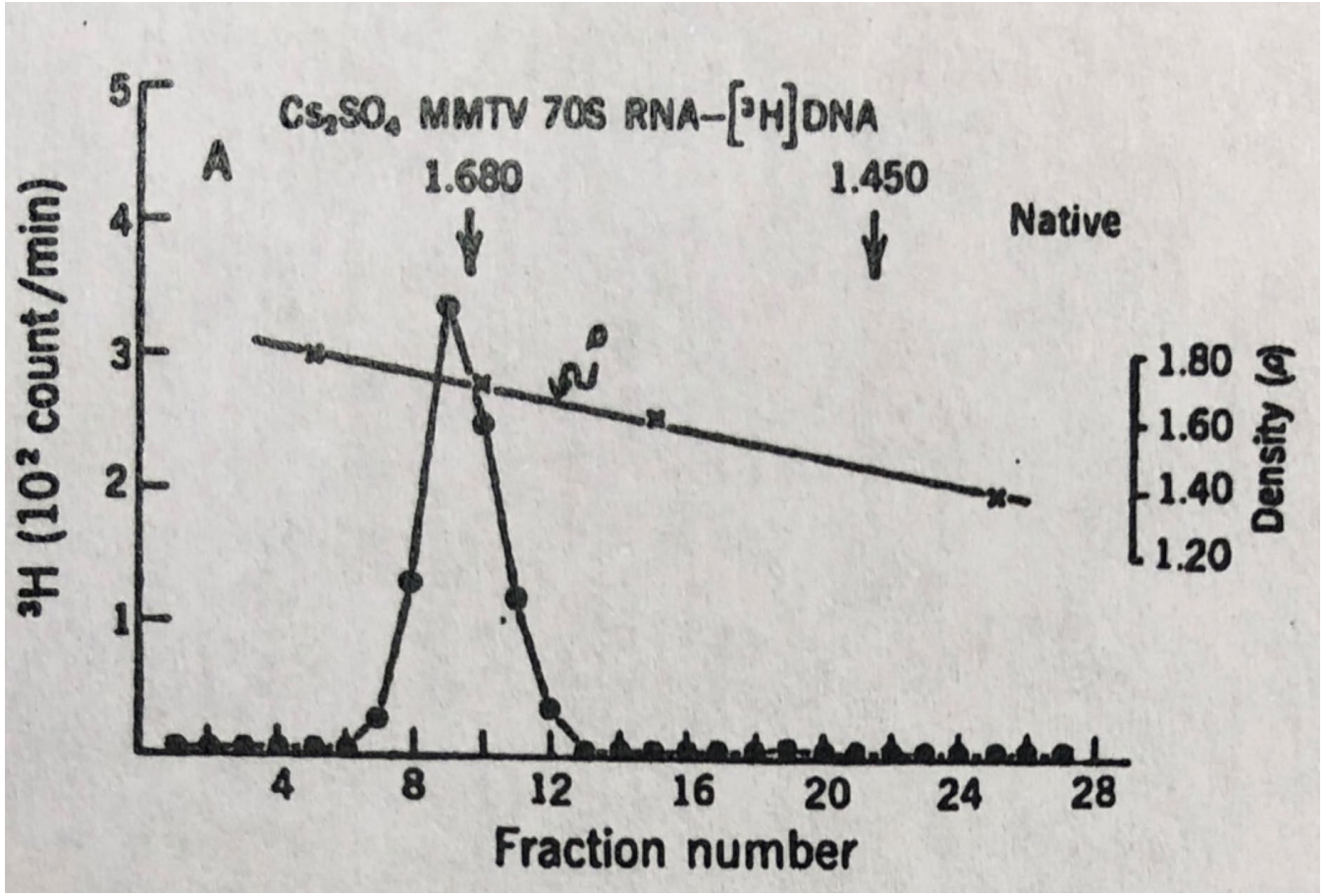
Anno Accademico 1972 - 73



Placca di MuLV; osservazione a 110x
Rarefazione del tappeto cellulare

ON THE CATCH FOR HUMAN TUMOUR VIRUSES

(Huebner, Todaro, Spiegelman……, Gallo)



Cesium sulphate gradient analysis of retroviral RNA-[3H]DNA complex
(J. Schlom & S. Spiegelman, Science 174, 840-843, 1971)

UNIVERSITA' DEGLI STUDI DI PAVIA

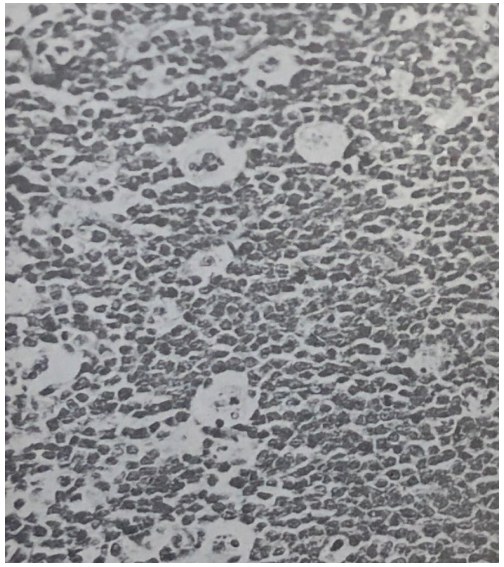
Facoltà di Medicina e Chirurgia
Scuola di Specializzazione in Oncologia
Direttore: Prof. Leonida Santamaria

Virus di Epstain Barr in linfomi Burkitt-like di soggetti caucasici

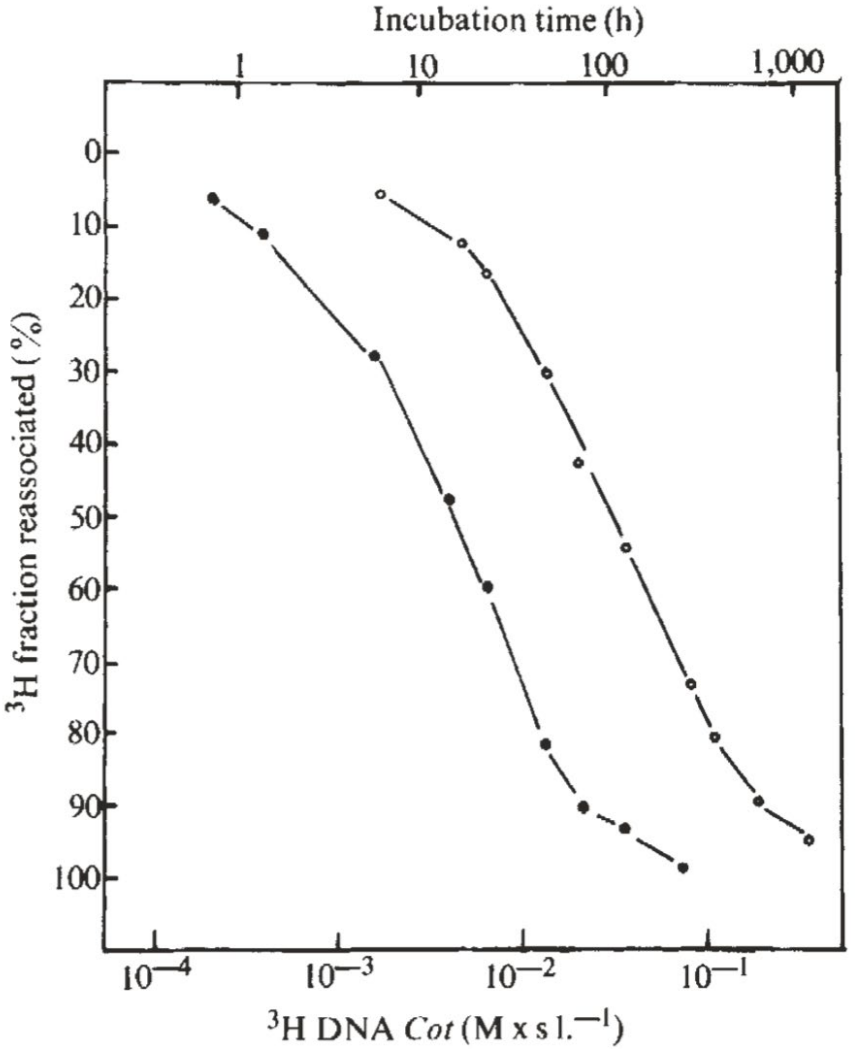
Relatore: Prof. L. Santamaria

Specializzando
Dott. Giorgio Palù

A.A. 1975-1976



Typical histology



DNA-DNA reassociation kinetics of a mixture of DNA from lymphoma biopsy and 3H-EBV DNA
(Europ J Cancer, 14, 15-22, 1978)

Factors that Led to the Consensus that Human Retroviruses Did not Exist

1. Failure to discover them after an extensive survey by many investigators in the 1950s, 1960s and 1970s

2. Ease of detection in animal models because of extensive viremia

3. Difficulties in growing primary human cells

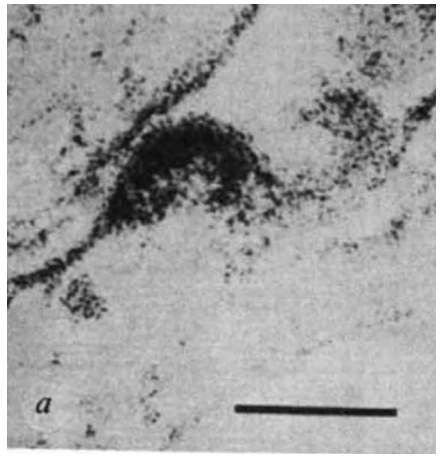
4. Results showing human sera with complement lysed animal viruses

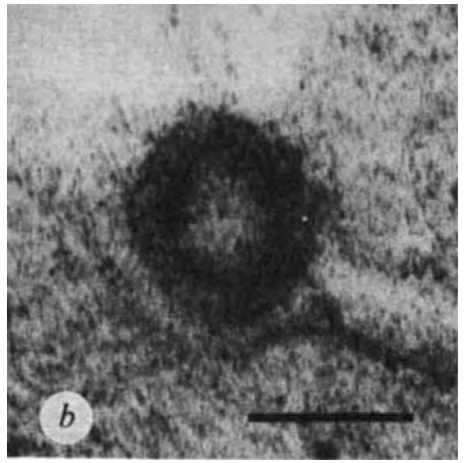
From Robert A Weiss, Retrovirology 2005, 2: 1-17

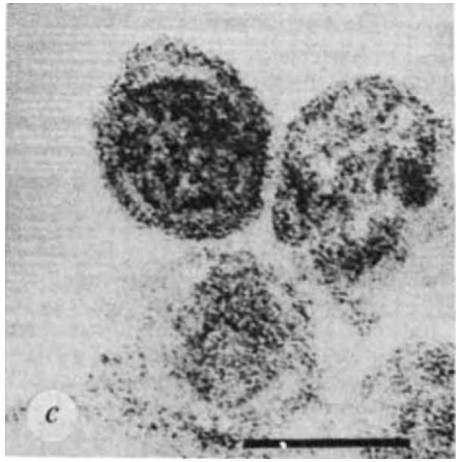
Isolation of a new type C retrovirus (HTLV) in primary uncultured cells of a patient with Sézary T-cell leukaemia

Bernard J. Poiesz, Francis W. Ruscetti, Marvin S. Reitz, V. S. Kalyanaraman & Robert C. Gallo

Laboratory of Tumor Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205, USA







IL-2 & classical Virology

Nature, 294, 268-271, 1981

The 1989 Nobel Prize in Physiology or Medicine
A Paradigm Change in Biology

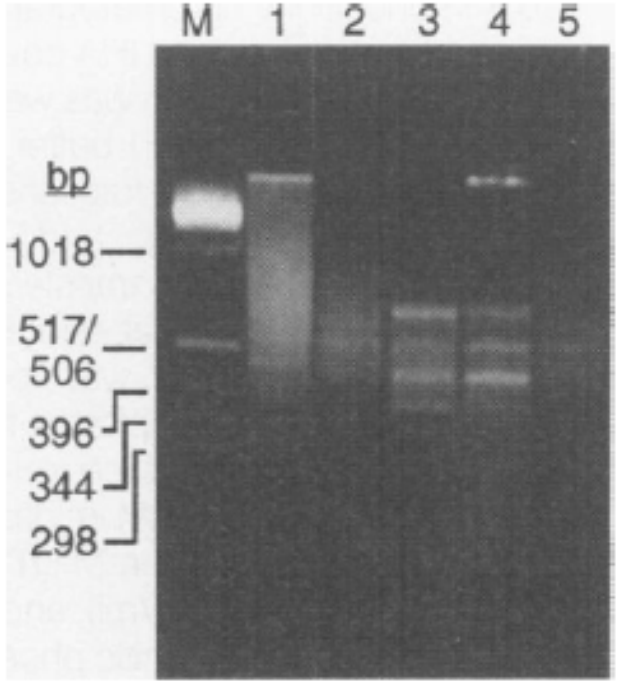
J. Michael Bishop & Harold E. Varmus

1989

"For their discovery of the cellular origin of retroviral oncogenes"

Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma by representational difference analysis

Fig. 1. Agarose gel electrophoresis of RDA products from AIDS-KS tissue and nondiseased tissue. RDA was performed on DNA extracted from KS skin tissue and unaffected normal skin tissue obtained at autopsy from a homosexual man with AIDS-KS (*8*). Lane 1 shows the initial PCR-amplified genomic representation of the AIDS-KS DNA after Bam HI digestion. Lanes 2 to 4 show that subsequent cycles of ligation, amplification, hybridization, and digestion of the RDA products resulted in amplification of discrete bands at 380, 450, 540, and 680 bp. RDA of the extracted AIDS-KS DNA performed against itself resulted in a single band at 540 bp (lane 5). Bands at 380 bp and 680 bp correspond to KS330Bam and KS631Bam, respectively, after removal of 28-bp priming sequences. Bands at 450 and 540 bp (KS390Bam and KS480Bam, respectively) hybridized nonspecifically to both KS and non-KS human DNA. Lane M is a molecular size marker.

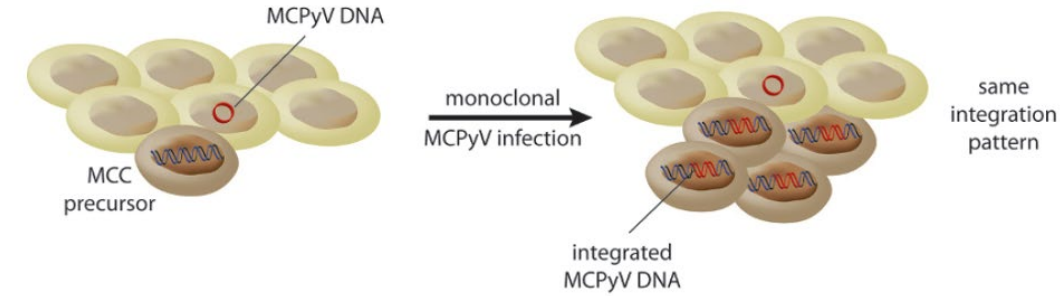


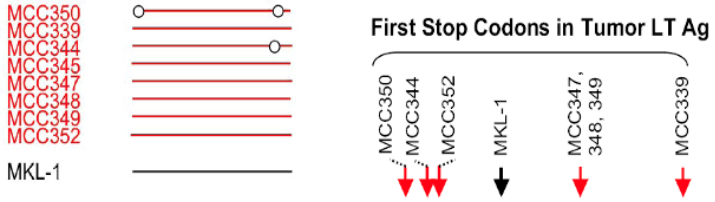
RDA technology

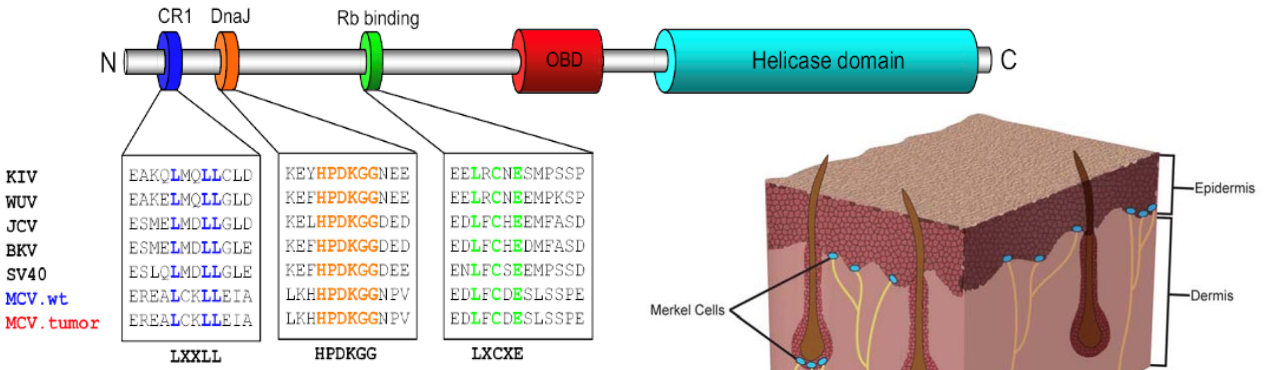
Chang et al. *Science* 1994

Discovery of new pathogens by using high-throughput sequencing technologies: MCPyV

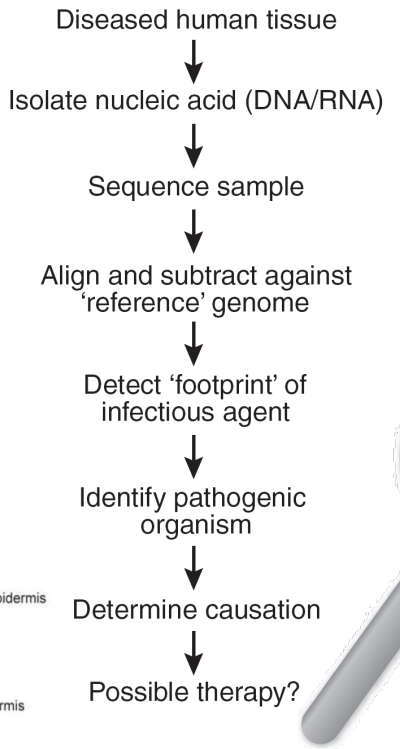
Tag mutations and integration into host cell genome

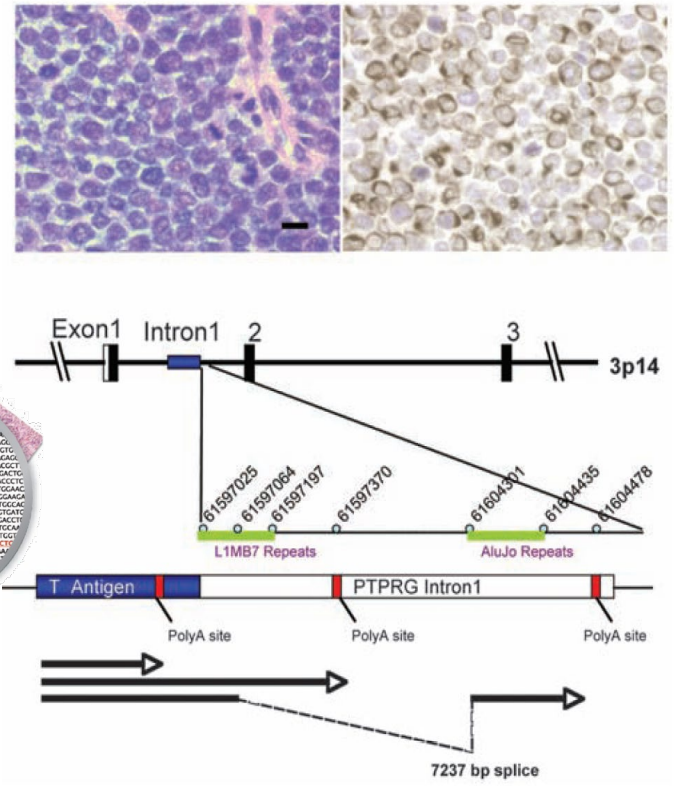






Genome sequencing

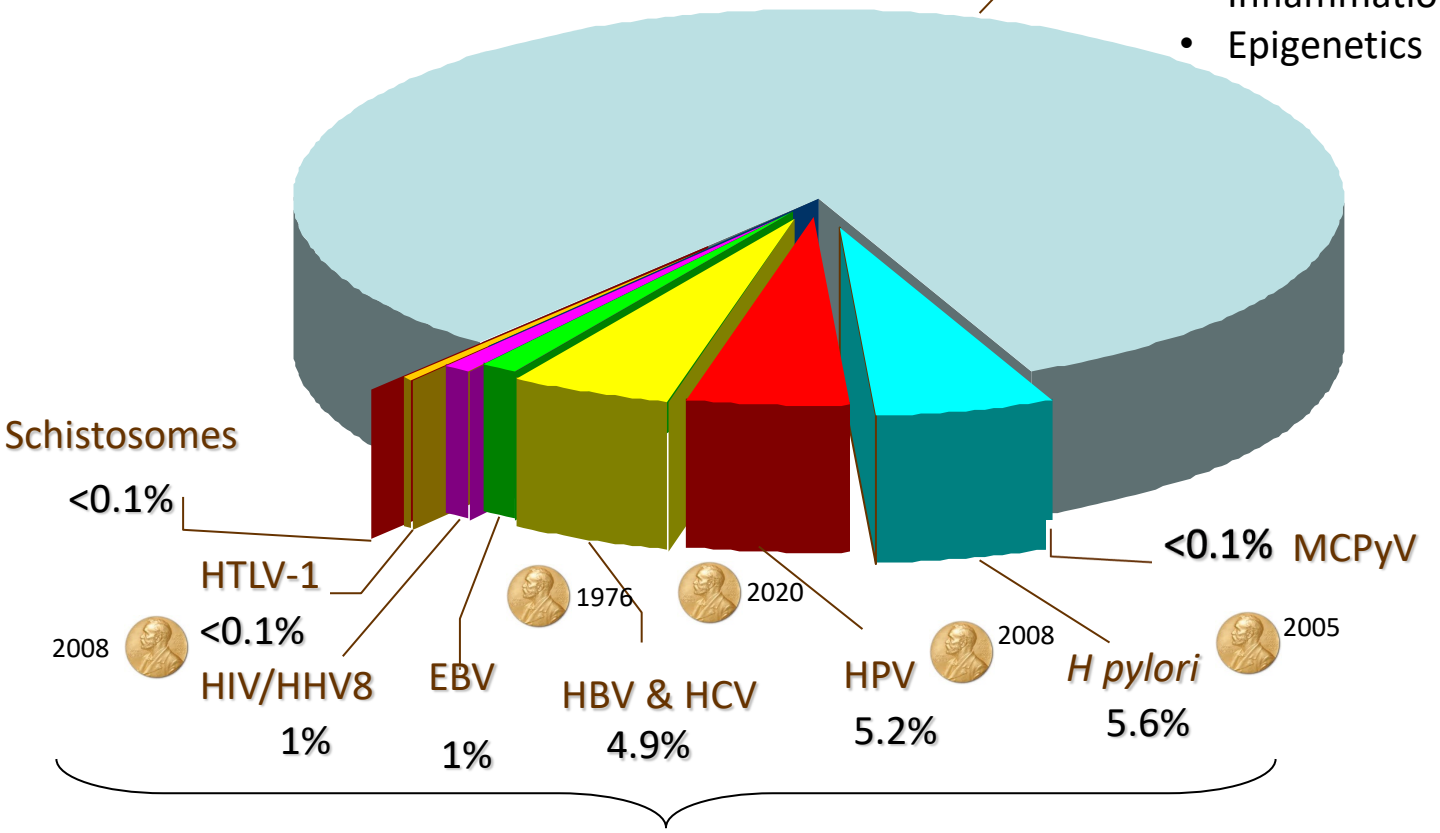


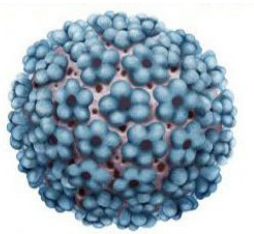


Shuda *et al.* Science 2008 ; Kassem *et al. Science 2008;* Feng et al. Science 2008

World Cancer Burden Caused by Infections

- Oncogenes
- Tumor supp. genes
- Mutator genes
- Inflammation
- Epigenetics

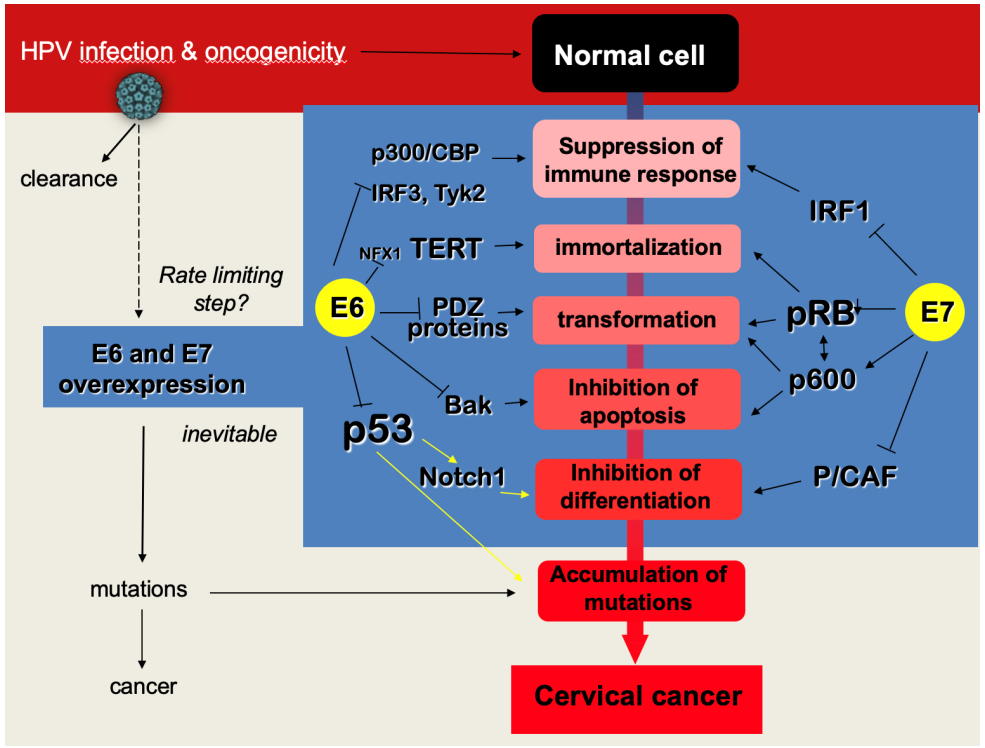




Total caused by infection = 18-20%

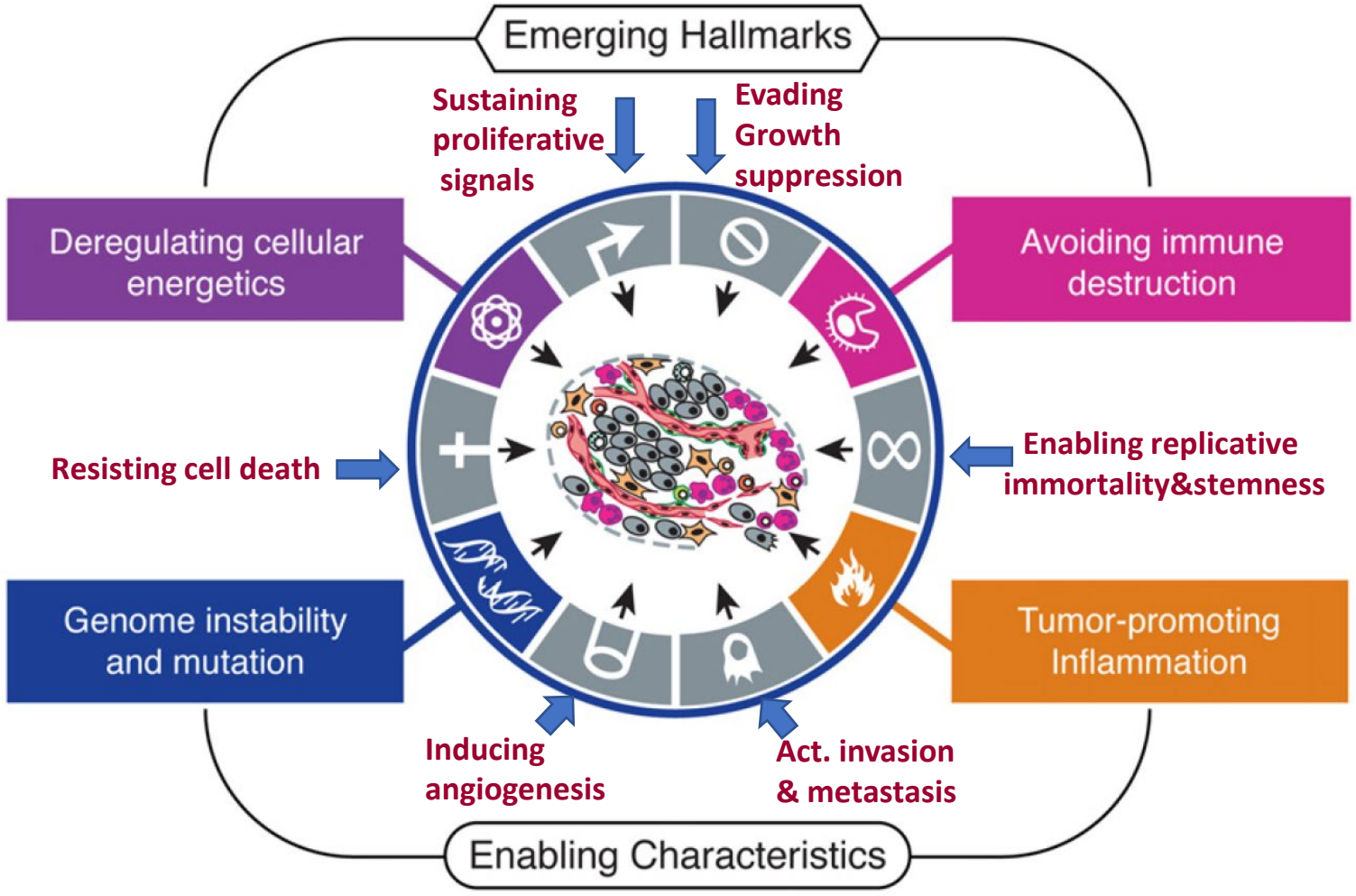
From CDC

HPV the Simplest Model that Recapitulates Oncogenesis



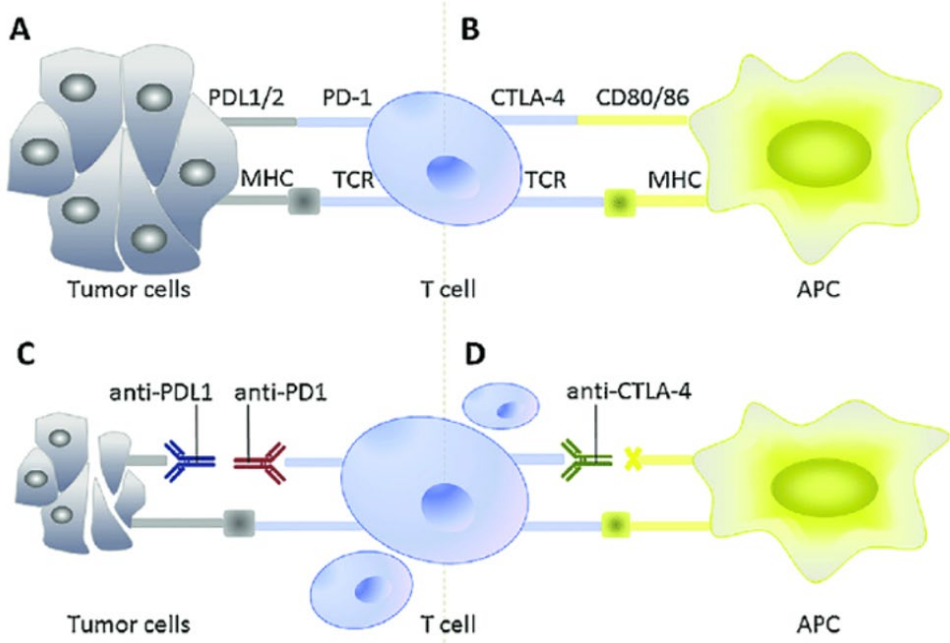
HPV epidemiology, animal models, human transmission experiments, classical virology, molecular dissection

Viral Oncology: Direct and Indirect Mechanisms

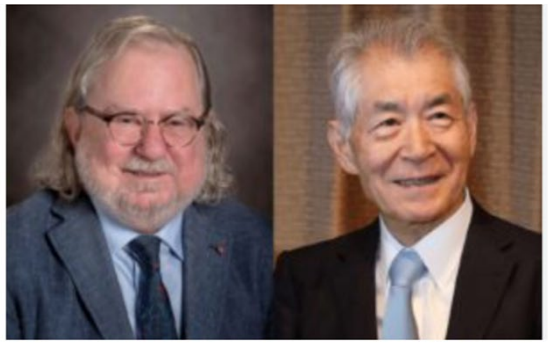


Hallmarks of Cancer: The Next Generation

Modified from Weinberg RA, Nat Rev Mol Cell Biol, 2019



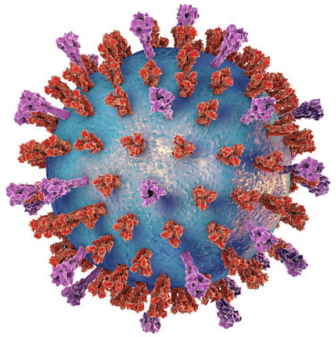
2018



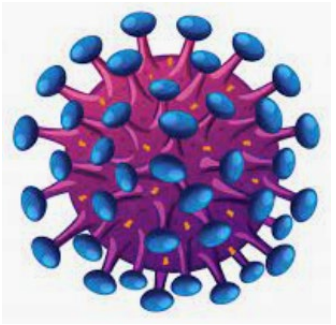
James P Allison Tasuku Honjo

(Georges Kohler, Cesar Milstein, Nielse Jerne 1984)

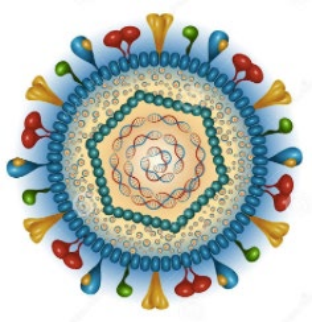
Viruses as a Tool for Therapy and Prevention



MoMuLV



HIV



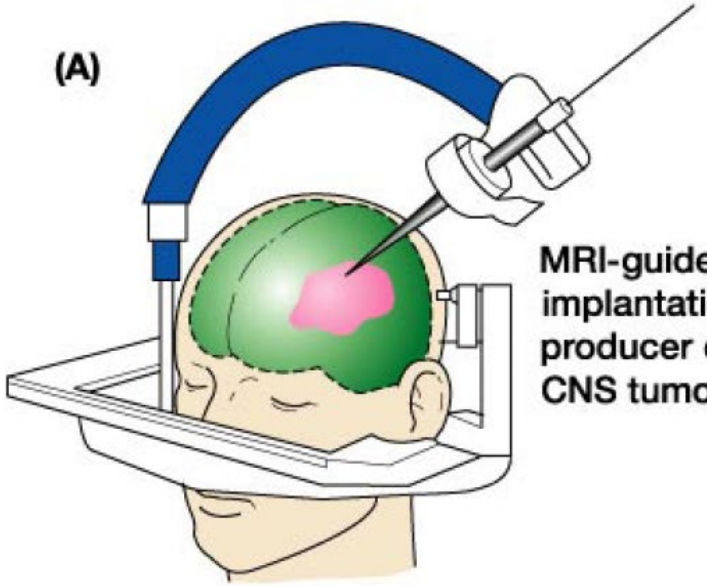
HSV

Bicistronic Moloney-based Retroviral Vector Expressing h*IL-2* and *HSV-TK* for Gene Therapy of Glioblastoma Multiforme

Colombo et al. Ster Func Neurosurg 1997
Pizzato et al. Gene Ther 1998
Palù et al. Gene Ther Mol Biol 1999
Palù et al. Gene Ther 1999
Barzon et al. JCE&M 2002
Barzon et al. Eur J Endocrinol 2003
Barzon et al. EOBT 2004
Barzon et al. Cancer Gene Ther 2005
Stefani et al. J Hepathol 2005
Colombo et al. Cancer Gene Ther 2005
Barzon et al. JCE&M 2005
Barzon et al. Cancer Gene Ther 2006

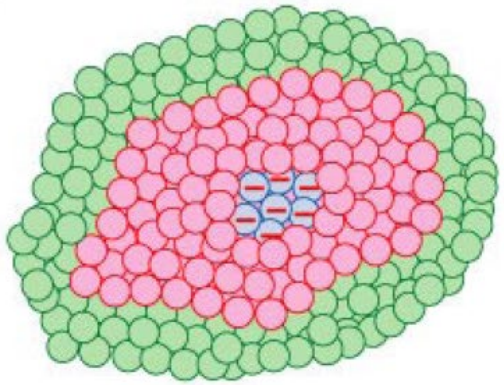
Gene Therapy for Glioblastoma Multiforme

(A)



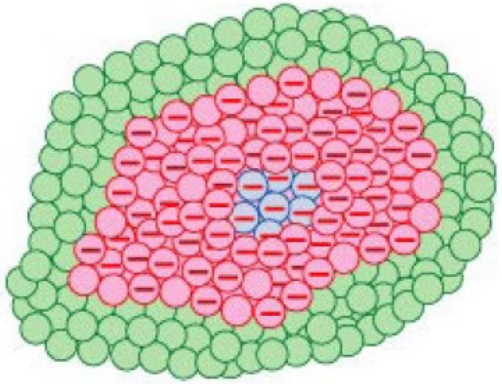
MRI-guided stereotactic implantation of vector producer cells (VPC) into CNS tumors *in situ*

(B)



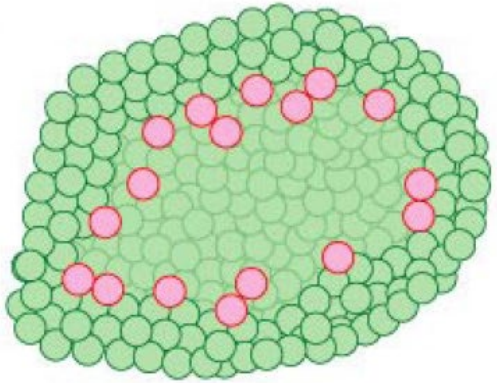
Vector producing cells inside the tumor

(C)



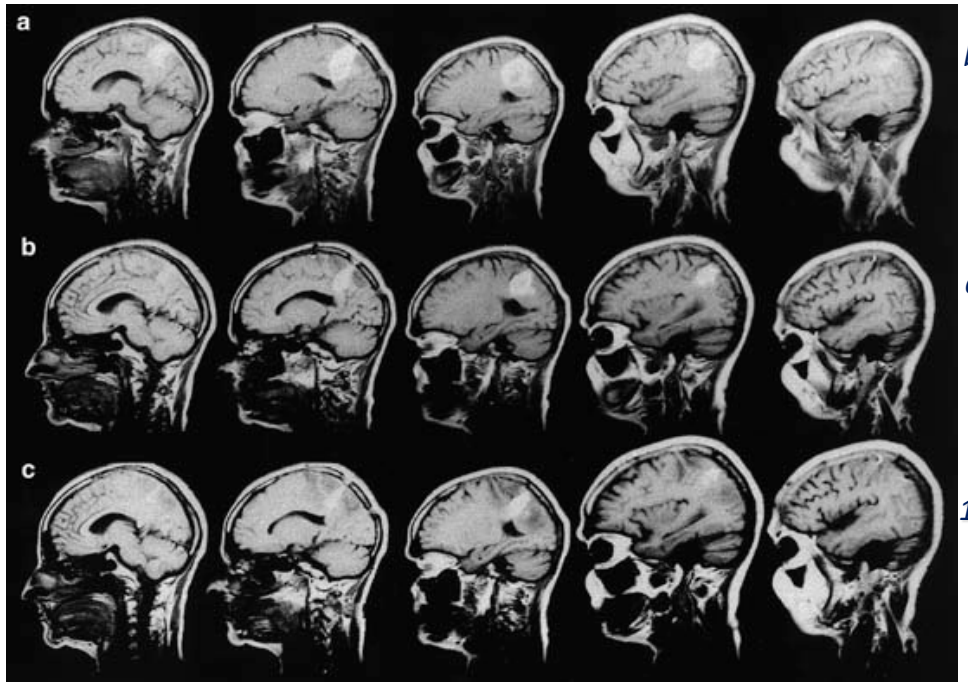
Retroviruses infect tumor cells but not normal cells

(D)



Gancyclovir kills the infected cells

Gene therapy in patients with recurrent GBM



before GT

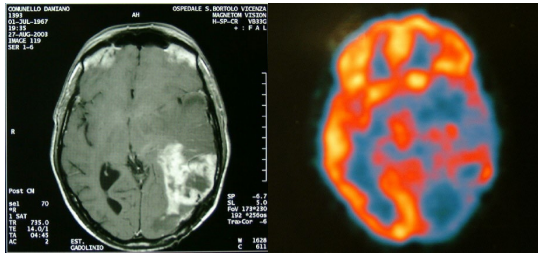
after GCV

1 month later

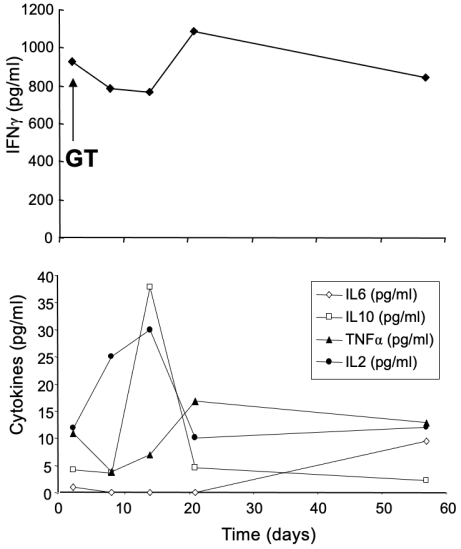
	Before tx	10 days post GT (before GCV)	46 days post GT (after GCV)
U/mL	0	8.5	2.8

Intracerebral IL-2 production, patient # 2

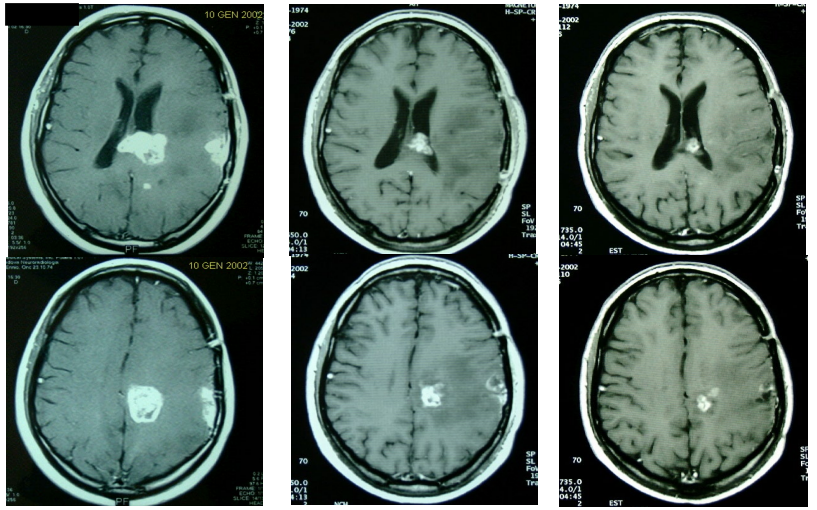
Palù G. et al. Gene Ther 1999



Patient # 12



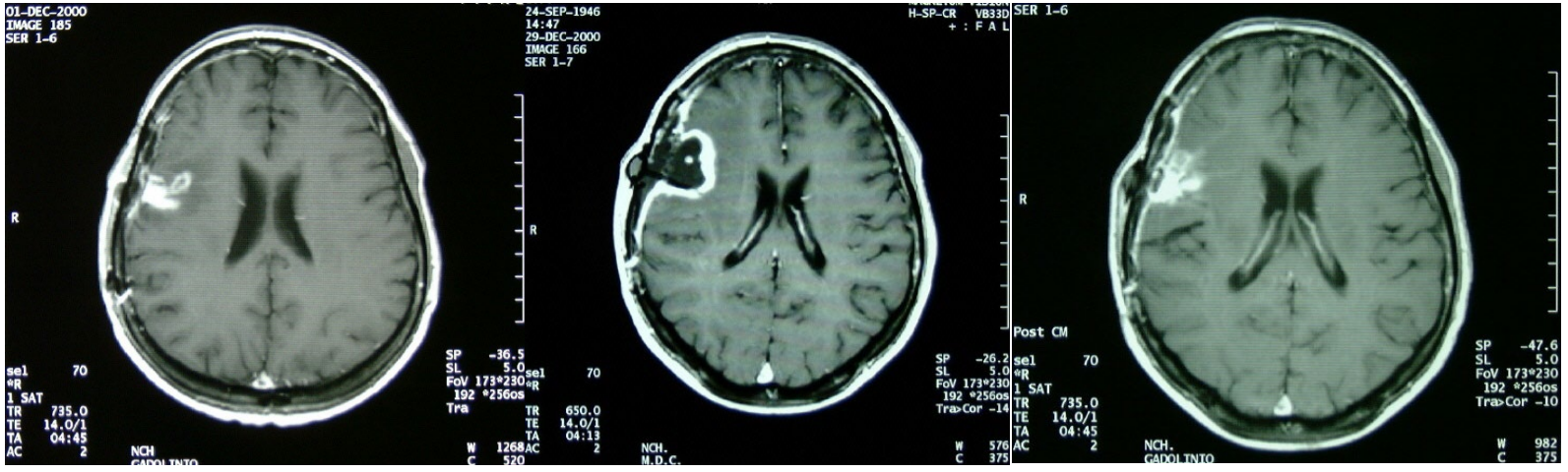
Palù G. Cancer Gene Ther 2005



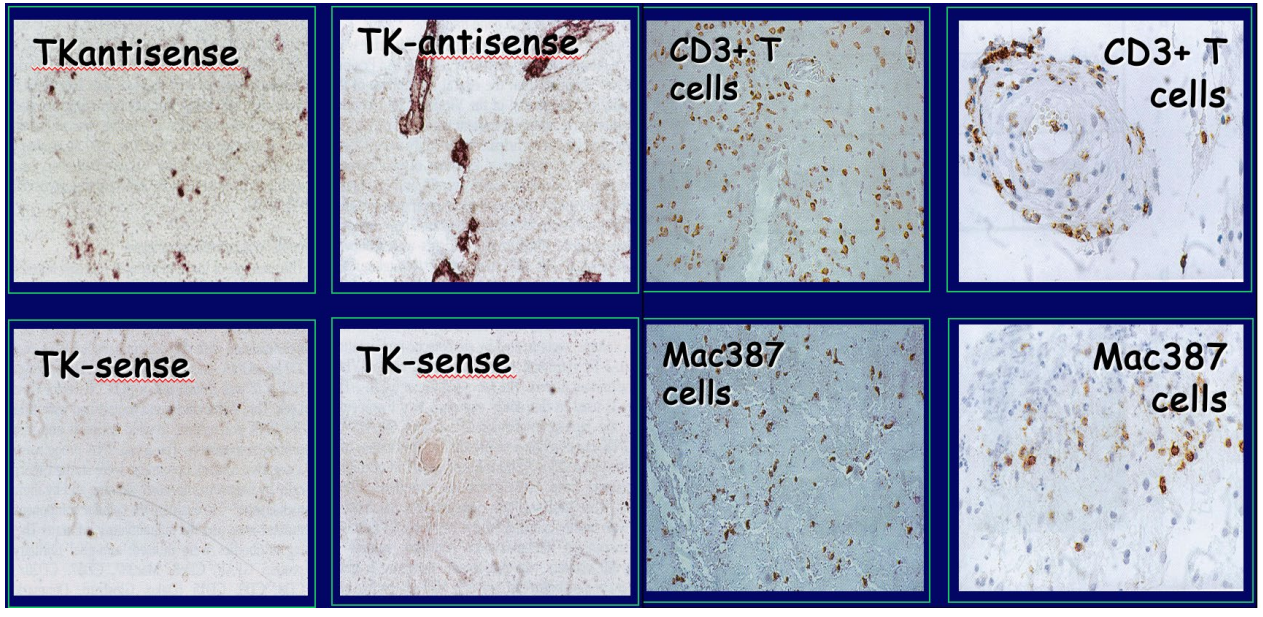
before GT *2 mo. after GT* *8 mo. after GT*

Gene Therapy of GBM

Patient # 6



relapse *after GCV* *Inflammation, 1 month after*



***In vivo* evidence of gene transfer**

Palù G. et al. Gene Ther 1999

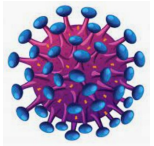
Gene Therapy (2005) 12, 299–310

www.nature.com/gt

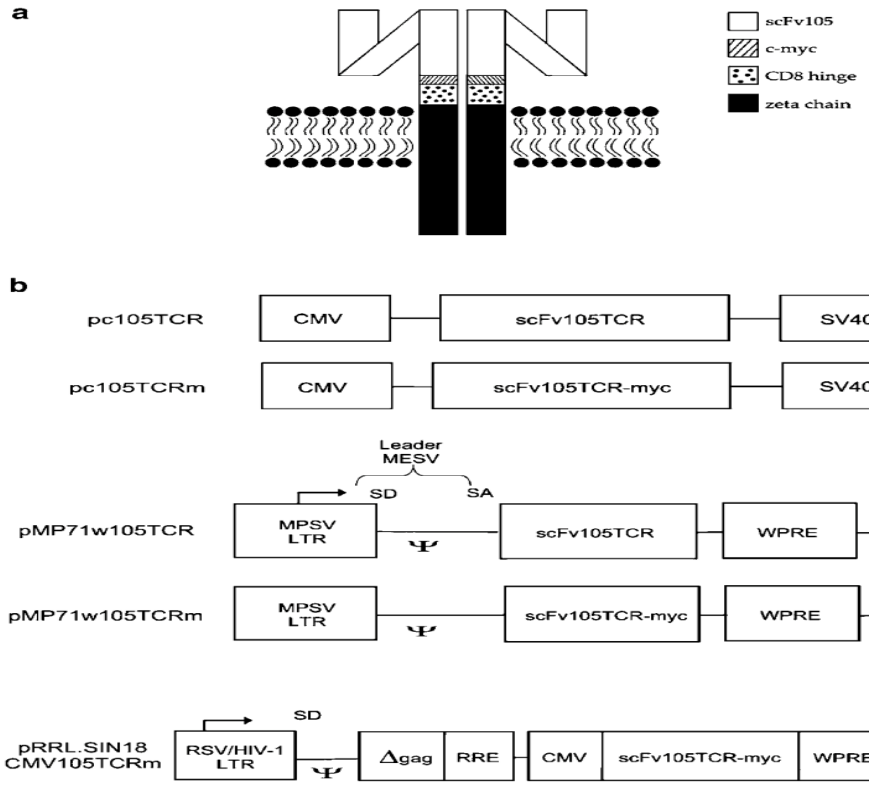
RESEARCH ARTICLE

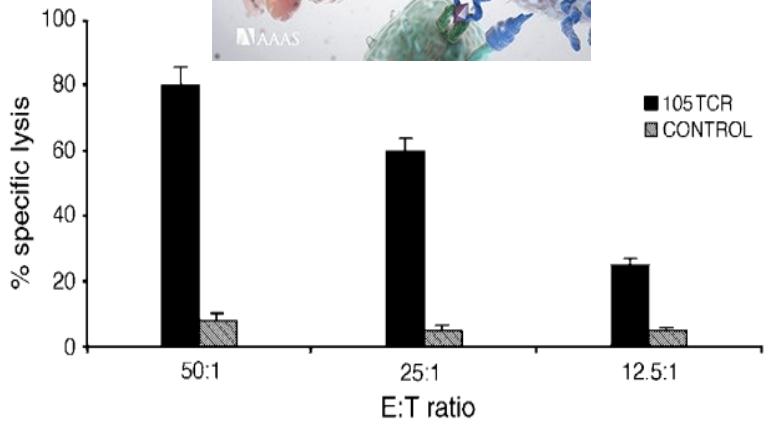
T-cell engineering by a chimeric T-cell receptor with antibody-type specificity for the HIV-1 gp120

S Masiero[1], C Del Vecchio[1], R Gavioli[2], G Mattiuzzo[1], MG Cusi[3], L Micheli[3], F Gennari[1], A Siccardi[4], WA Marasco[5], G Palù[1] and C Parolin[1]



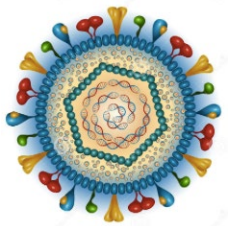
Ante-litteram CAR-T immunotherapy



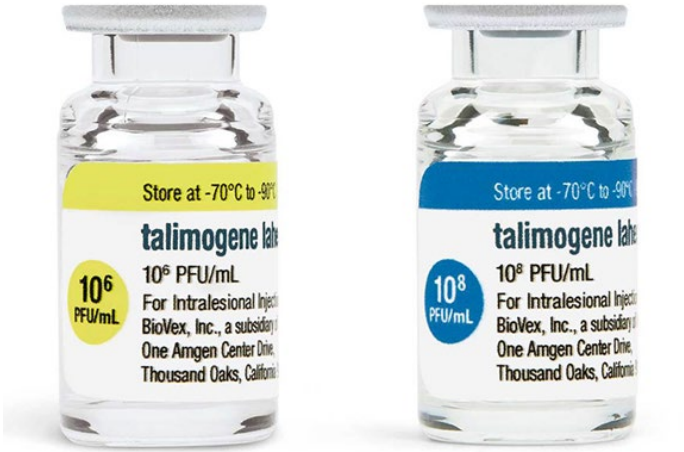


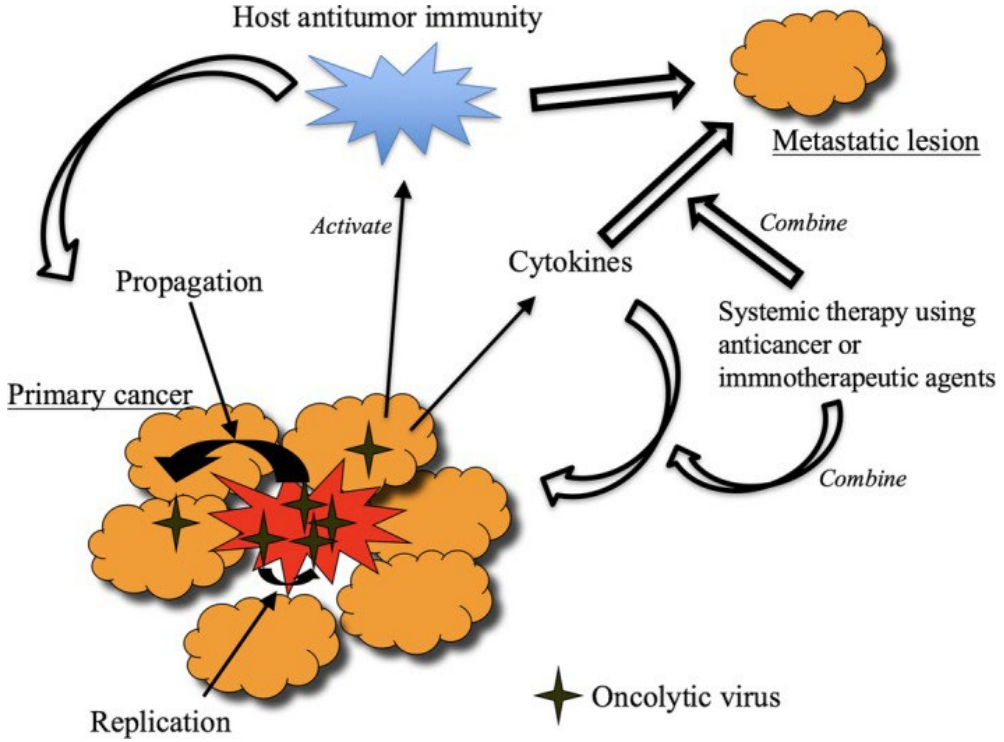
Oncolytic Virotherapy

- Viruses able to replicated in tumor cells but not in healthy cells.
- Replication of oncolytic viruses has 2 effects:
  - Kills tumor cells
  - Triggers an anti-tumoral immune responses.
- They can carry therapeutic genes in tumor cells.



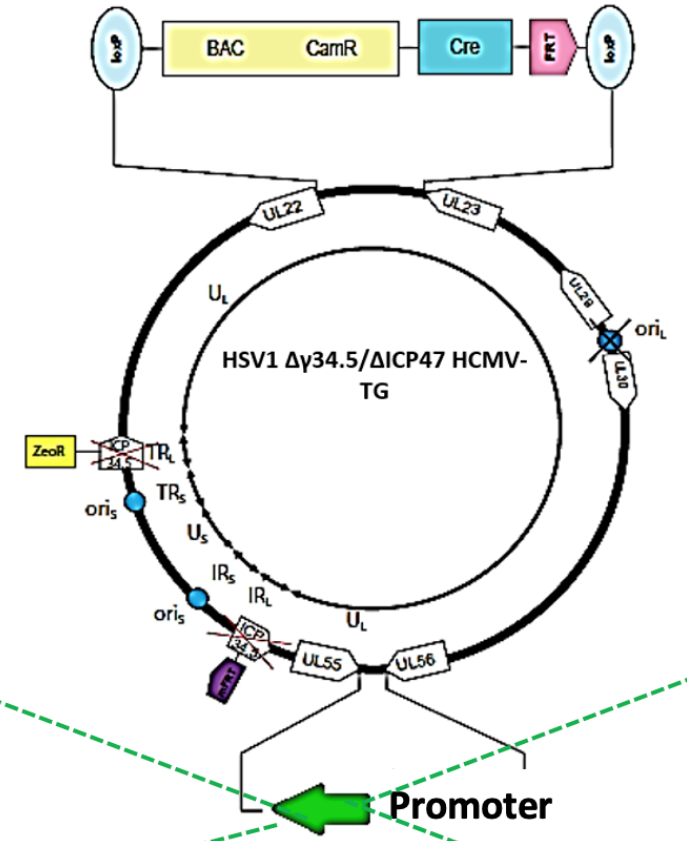
Oncolytic viruses are already in the clinic: talimogene laherparepvec (HSV-1) approved for metastatic melanoma(2016)





Fukuhara et al, *Cancer Science* (2016)

Arming oHSV-1 with Factors Acting on Anti-Cancer Immune Response



- **Soluble PD-1**: Inhibition of PDL-1 and PDL-2 (Xu et al. 2006)
- **Peptide binding to IL-4 Receptor α (p-IL4Rα)**: Inhibition of MDSCs functions (Roth et al.2012)
- **Single chain antibody Anti-CCR4**: depletes Treg lymphocytes (Chang et al. 2012)
- **Flt3 ligand** growth factor crucial for dentritic cells development
- **Human and mouse IL-12**: is one of the main mediators of Th1 response (Hess et al. 2001)

Reale A *et al* Pharmaceutics, 2021

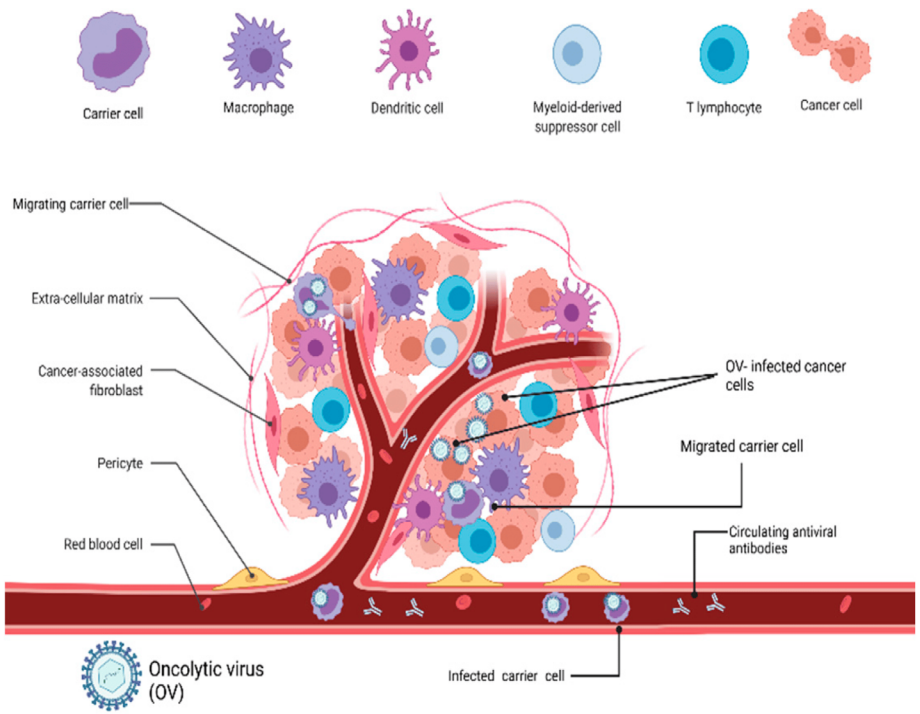
International Journal of
Molecular Sciences

MDPI

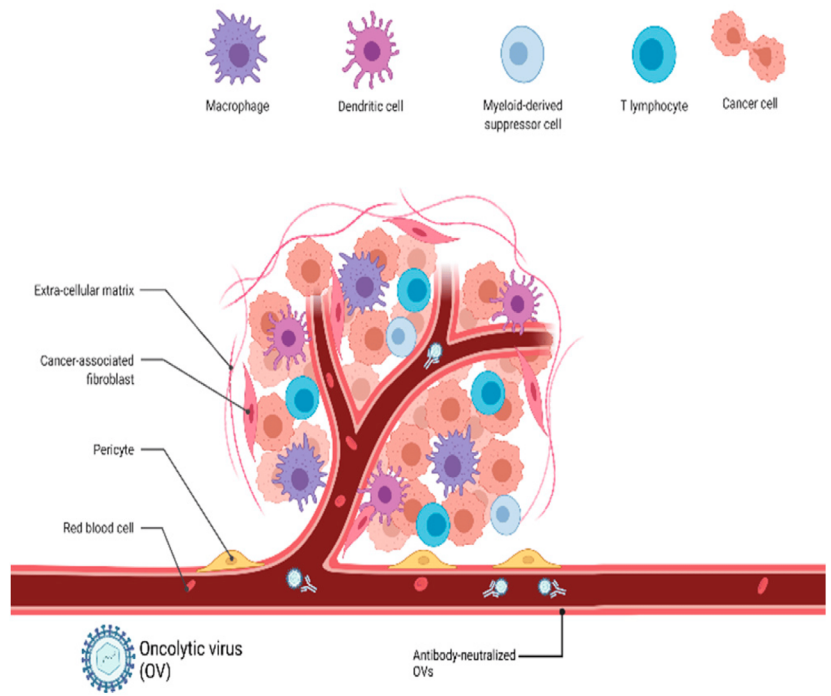
Article

Human Monocytes Are Suitable Carriers for the Delivery of Oncolytic Herpes Simplex Virus Type 1 In Vitro and in a Chicken Embryo Chorioallantoic Membrane Model of Cancer

Alberto Reale [1,*], Lea Krutzke [2], Massimiliano Cadamuro [1], Adriana Vitiello [1], Jens von Einem [3], Stefan Kochanek [2], Giorgio Palù [1], Cristina Parolin [1] and Arianna Calistri [1,*]

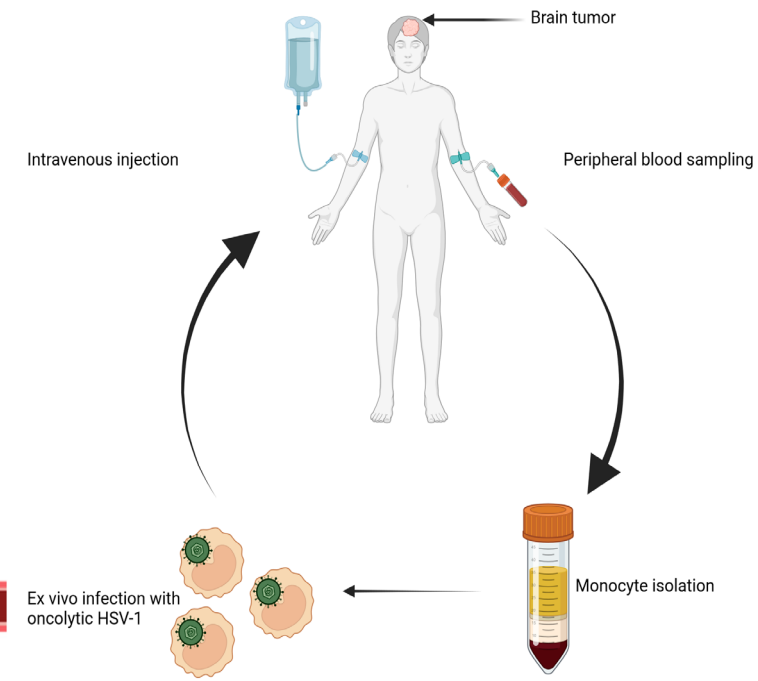


(a)

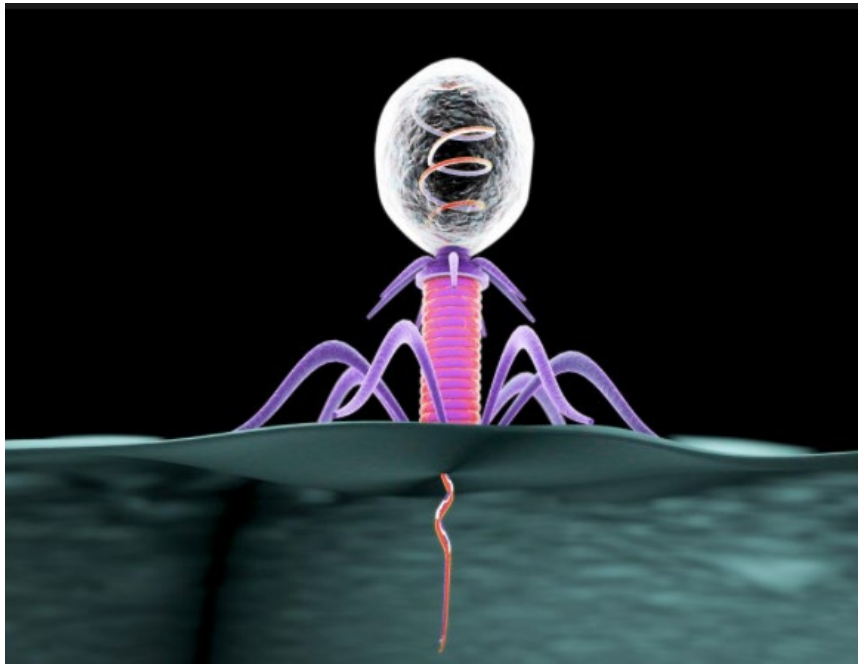


(b)

***In vivo* strategy**



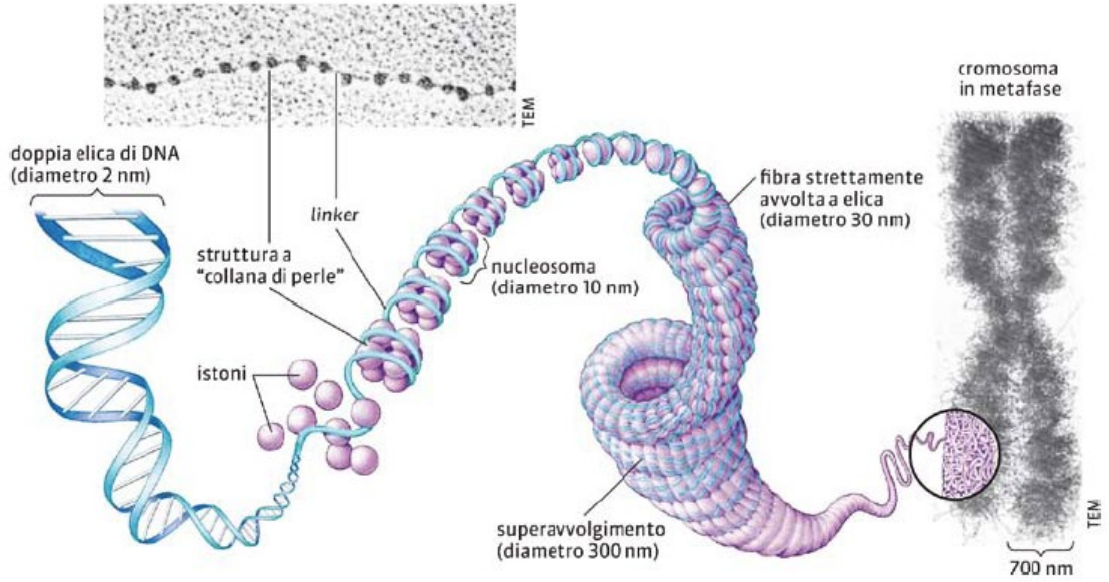
A Resurgence of Bacteriophages

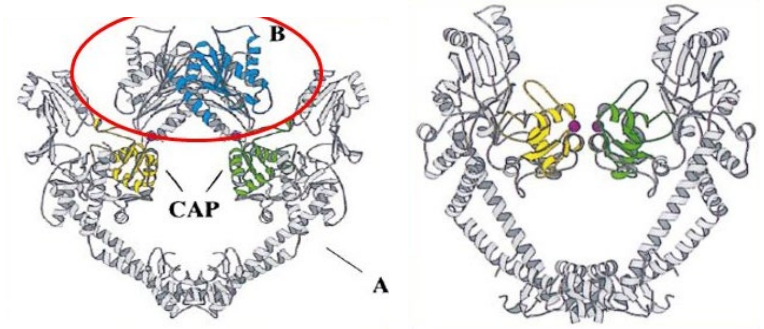


Is Parkinson linked to phages?

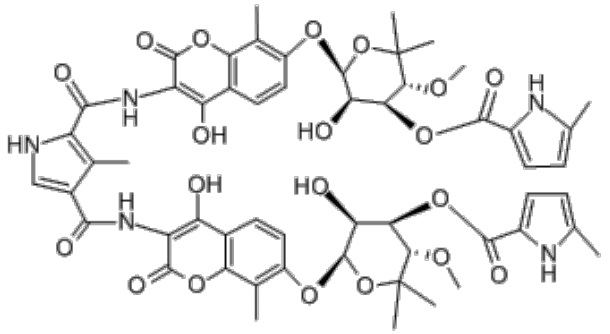
New antibiotics for AMR

From Bacteria to Viruses and Eukaryote Genomes



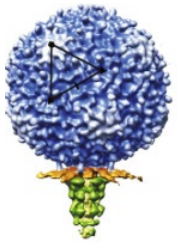


DNA-gyrase



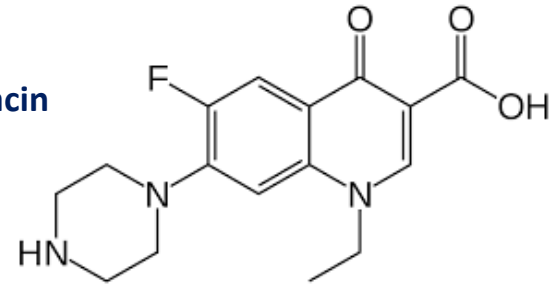
Coumermycin A1

Prof. Gian Carlo Schito



N4

Norfloxacin

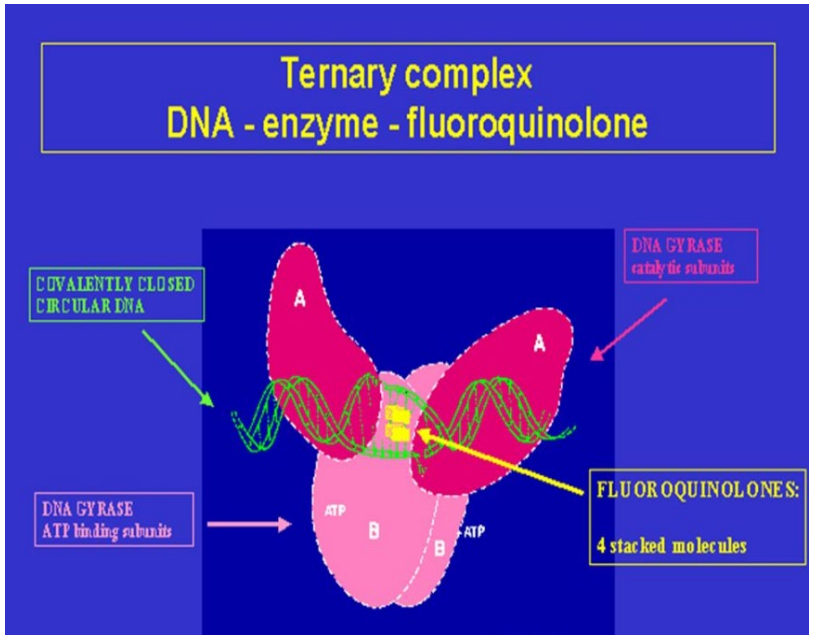


A Cation Critical Function and a Mechanism Solved

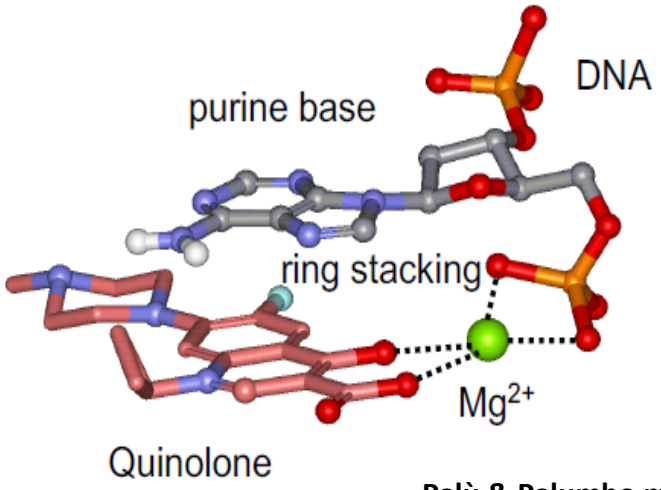
Quinolone binding to DNA is mediated by magnesium ions. Palù G, Valisena S, Ciarrocchi G, Gatto B, Palumbo M. **Proc Natl Acad Sci U S A.** 1992 Oct 15;89(20):9671-5.

On the mechanism of action of quinolone drugs. Palumbo M, Gatto B, Zagotto G, Palù G. **Trends Microbiol.** 1993 Sep;1(6):232-5.

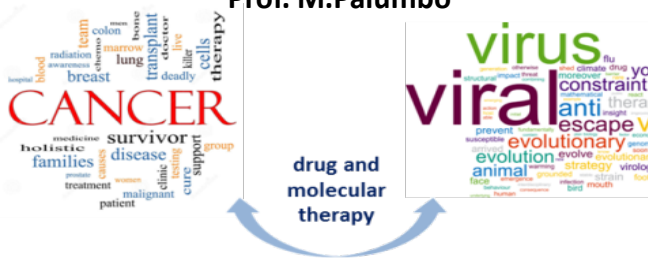
Prof. M.Palumbo



Shen model 1989-1993



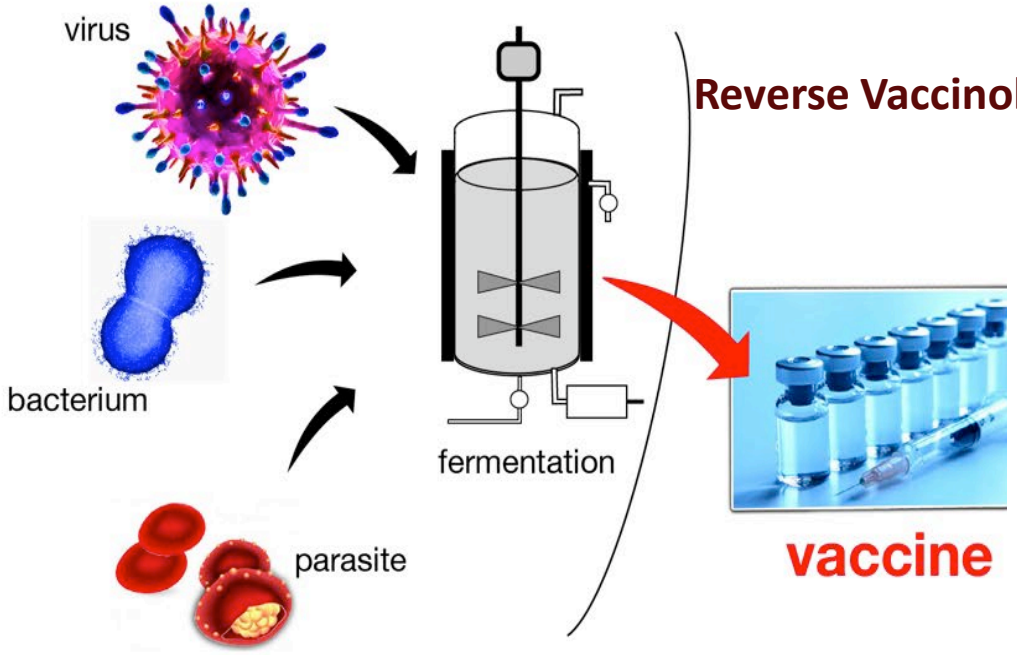
Palù & Palumbo model



Da Jenner a Pasteur a Hilleman

Isolare
Inattivare
Iniettare il microrganismo causa di malattia

CLASSICAL VACCINOLOGY
growing pathogens



Reverse Vaccinology 2.0:


Gaston Ramon 1920

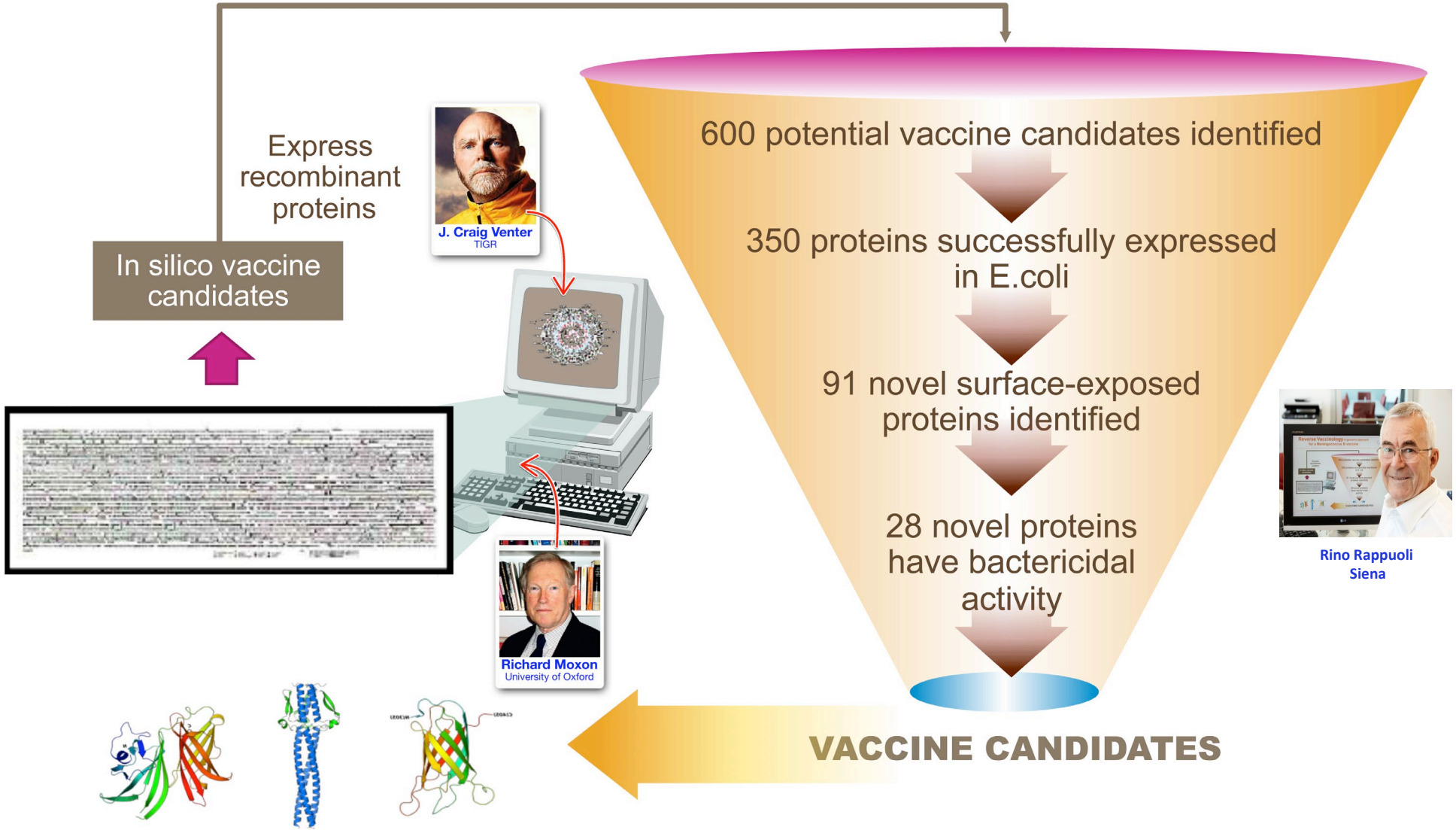

Jonas Edward Salk 1955


Albert Sabin 1963


Maurice Hilleman 1970

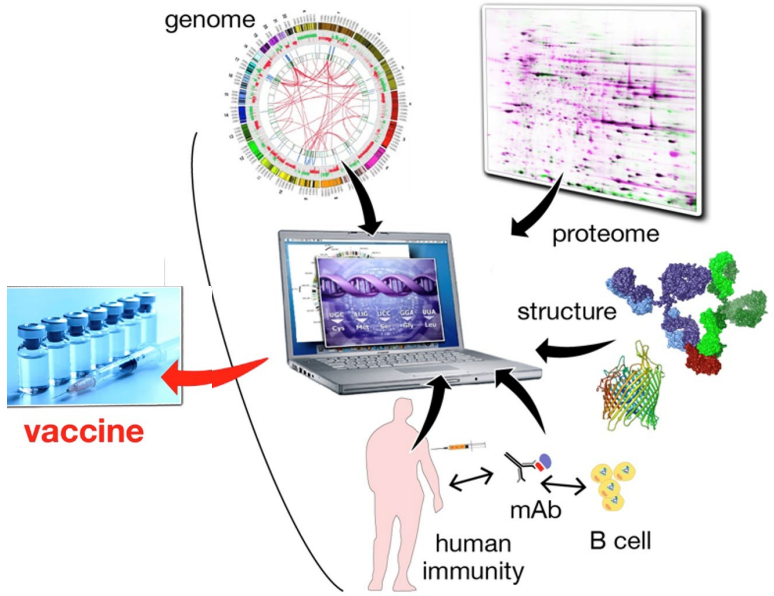
…la vaccinologia diventa scienza

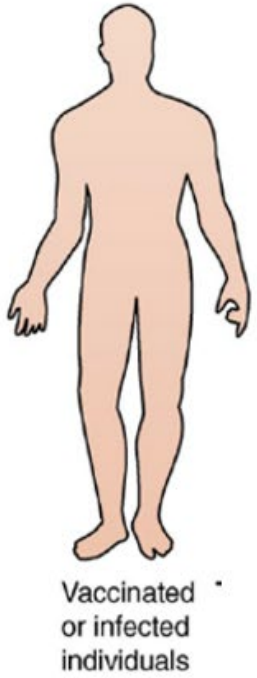
Reverse Vaccinology 1.0:
Approccio genomico per un vaccino contro il Meningococco B

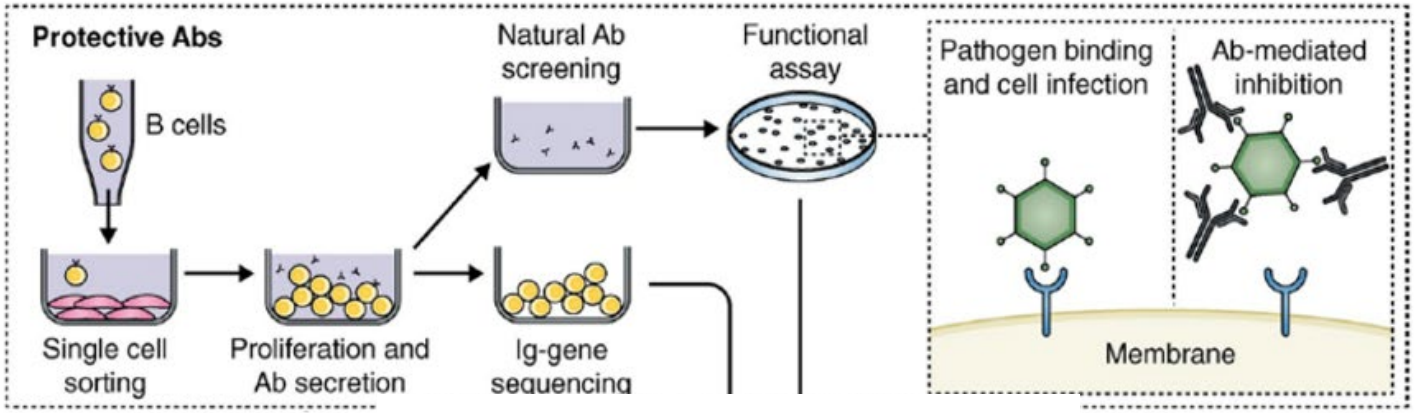


Reverse Vaccinology 2.0:

L'Immunologia e la struttura degli antigeni insegnano a disegnare il vaccino





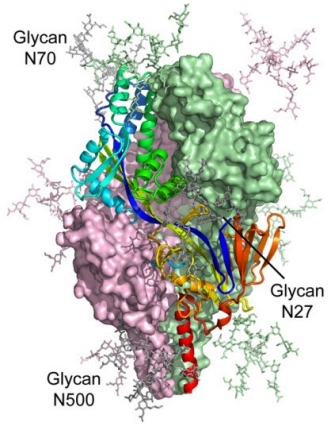


Vaccines
discovery of protective antigens
antigen structure
structure-based design

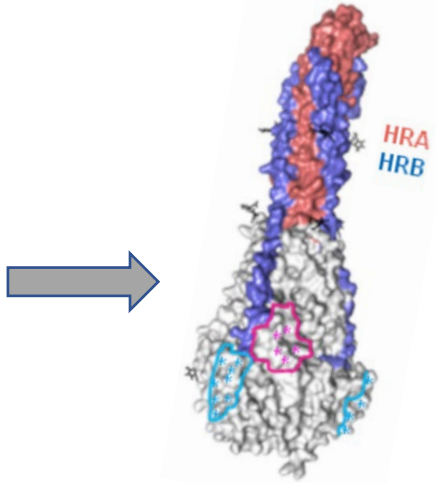
Monoclonal Antibodies
for prevention and therapy

Rappuoli R *et al JEM, 2016*

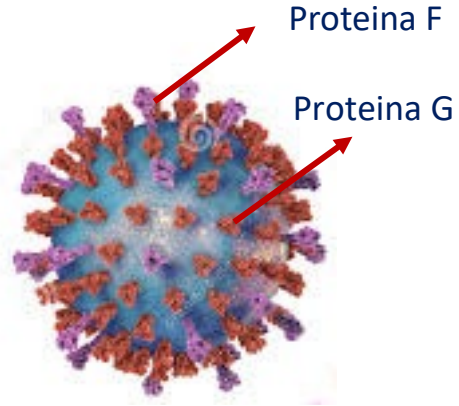
Reverse Vaccinology 2.0:
Structural Vaccinology, l'esempio di RSV

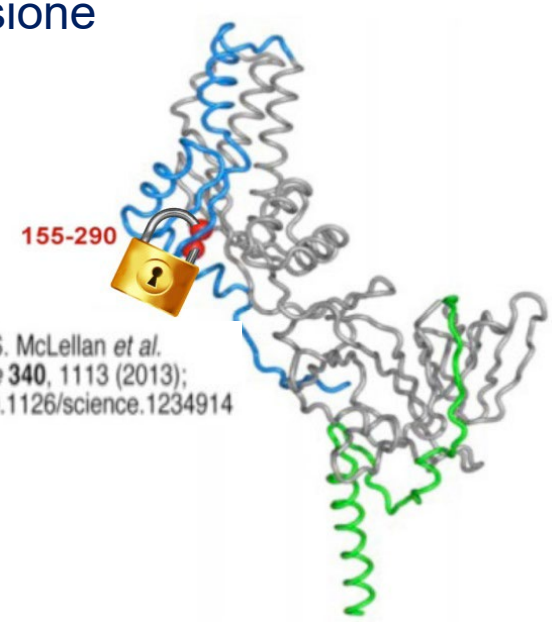


Pre-fusione

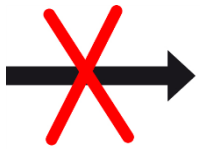


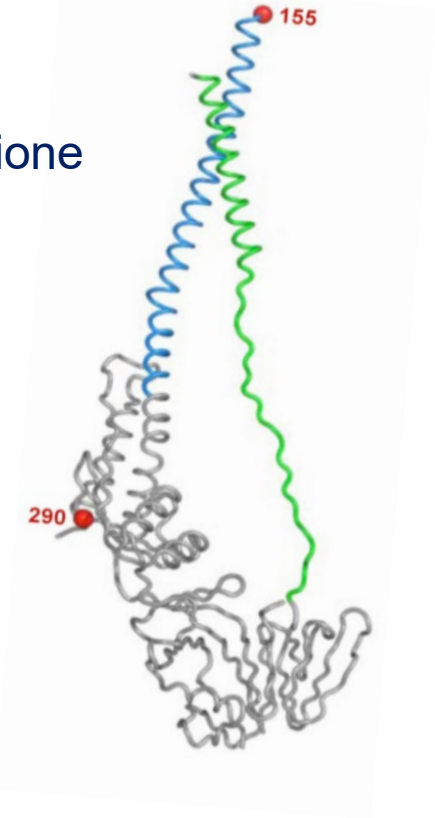
Post-fusione



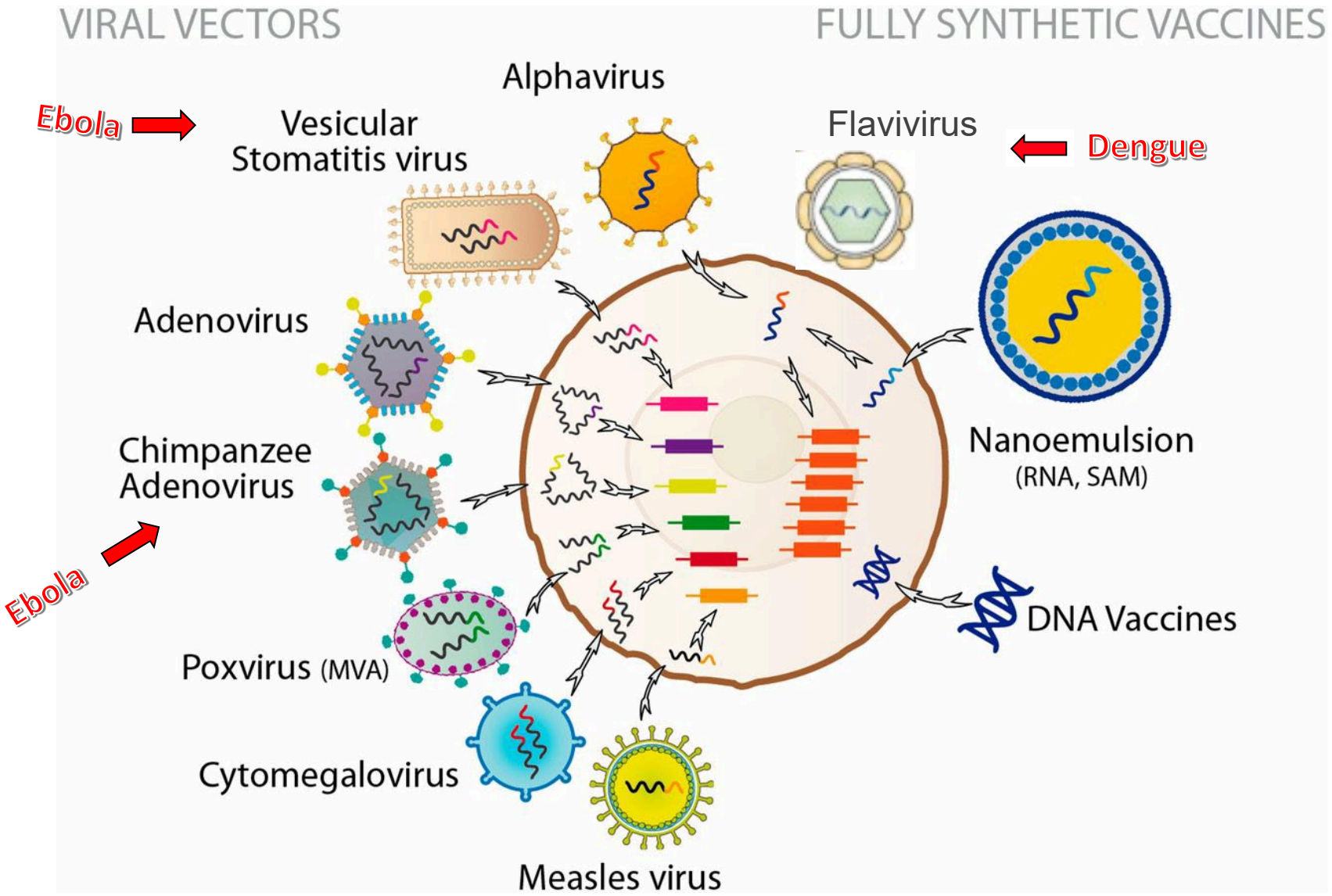


Science
Jason S. McLellan *et al.*
Science **340**, 1113 (2013);
DOI: 10.1126/science.1234914



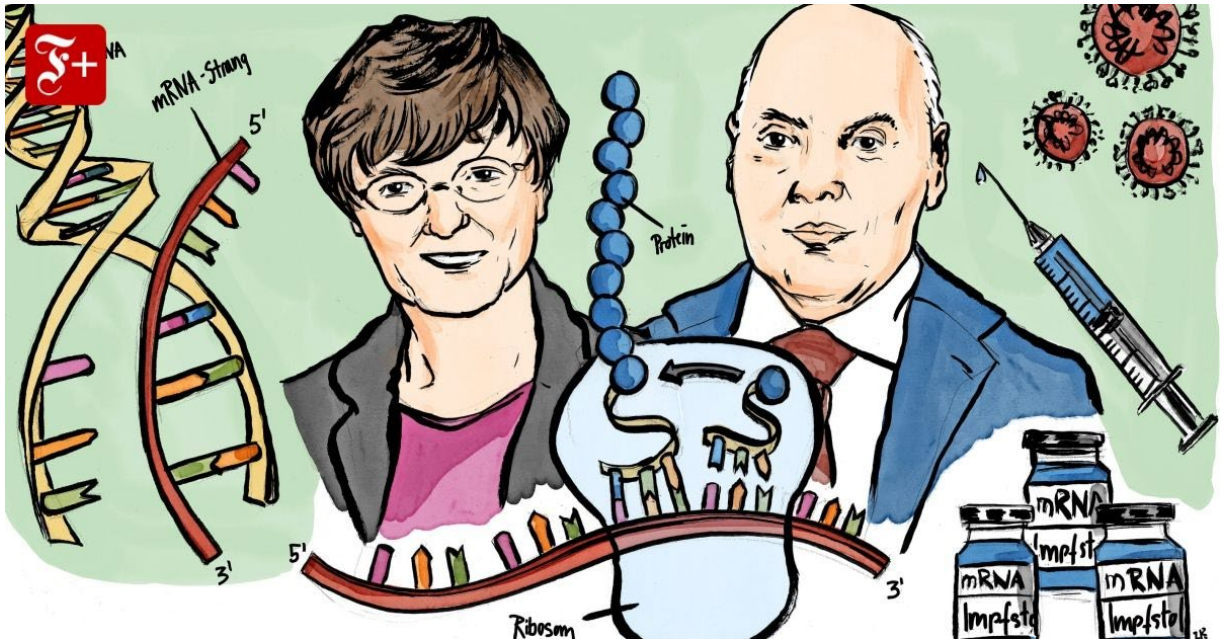


VACCINE PLATFORMS

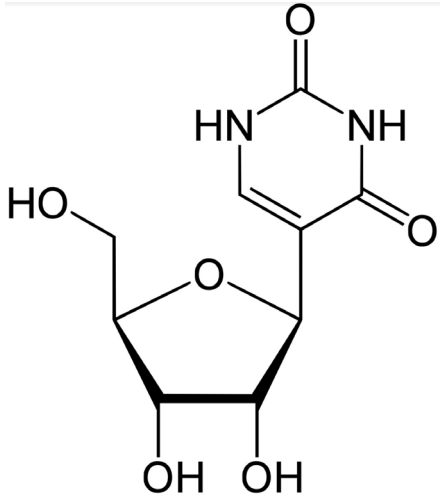


The Long Story of mRNA Vaccines: from Uridine to Pseudouridine

8th Innovation shoulf always rely upon previous knowledge



In 2005, the pair reported that rearranging the chemical bonds on one of mRNA's nucleotides, uridine, to create an analogue called pseudouridine, seemed to stop the body identifying the mRNA as a foe.



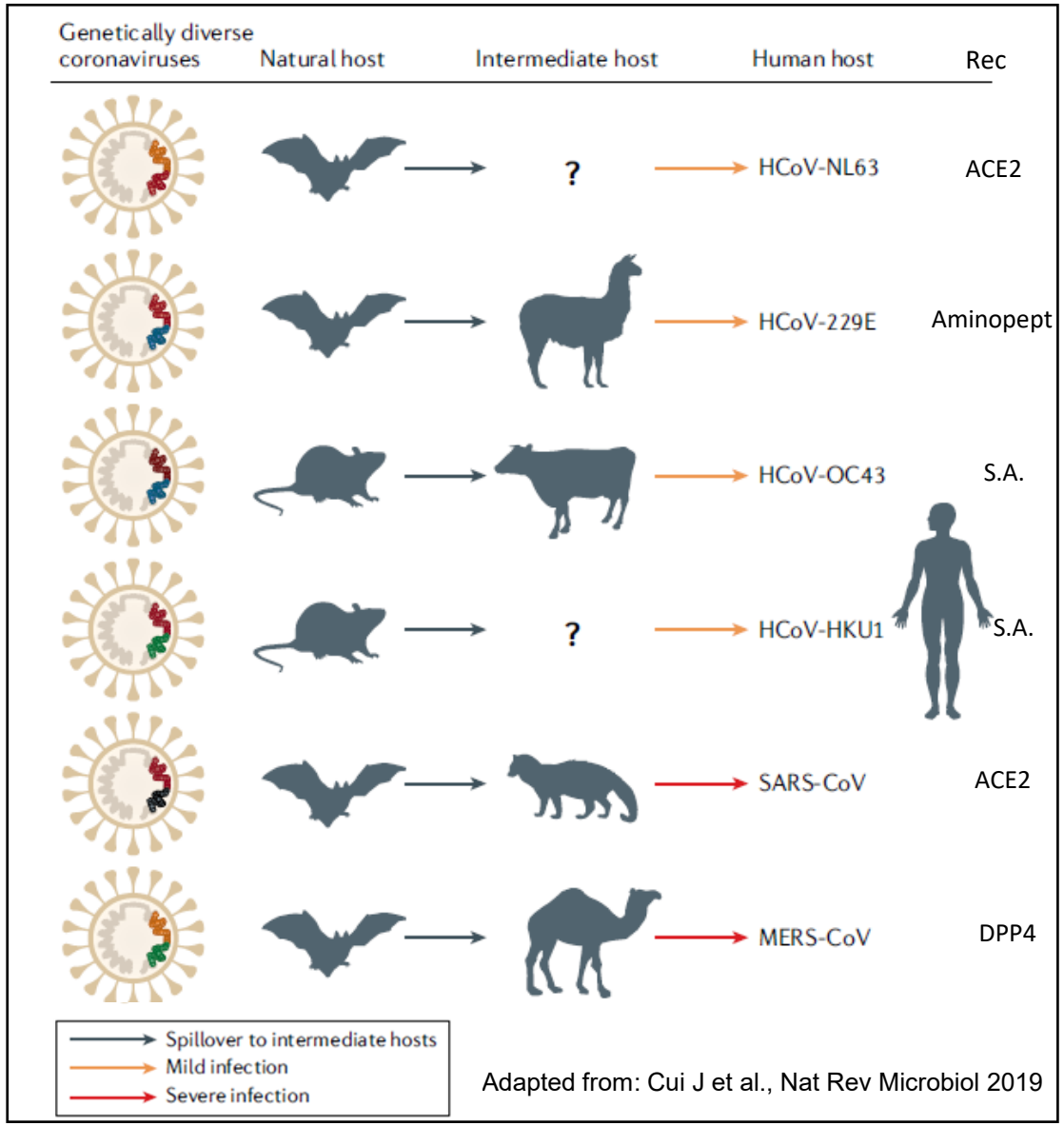
2022 Breakthrough Prize in Life Sciences awarded to mRNA pioneers Drew Weissman and Katalin Karikó

Moderna was founded in 2010 by D Rossi, TA Springer, KR Chien, RS Langer & N Afeyan

2023

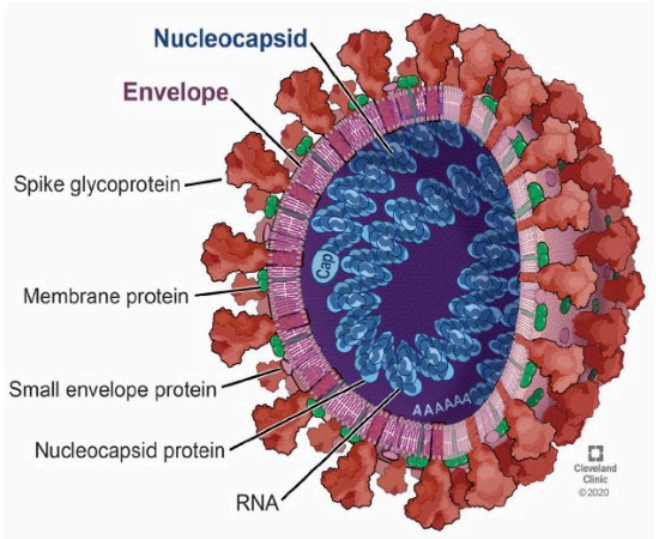
Lessons from COVID-19: Origin of Human Coronaviruses

(up to December 19)



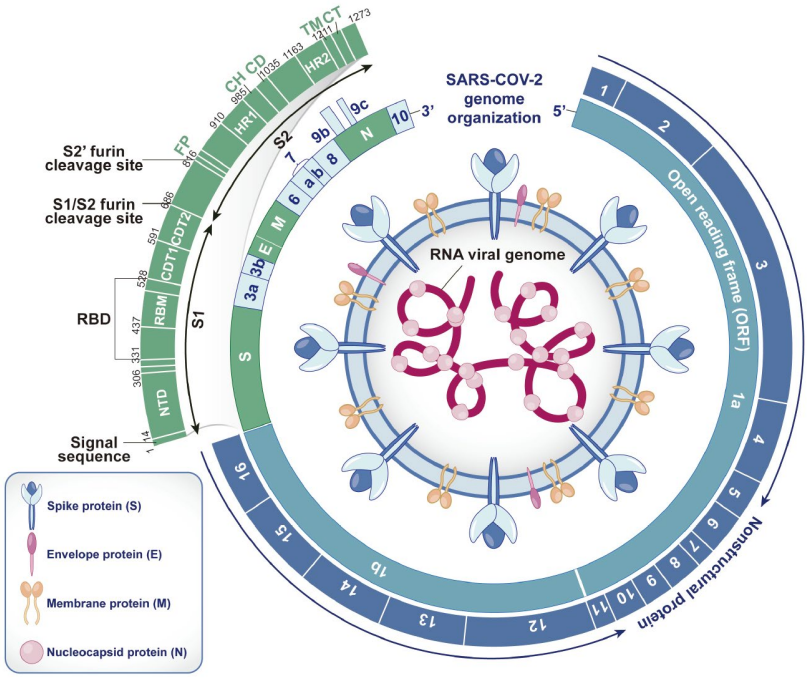
Adapted from: Cui J et al., Nat Rev Microbiol 2019

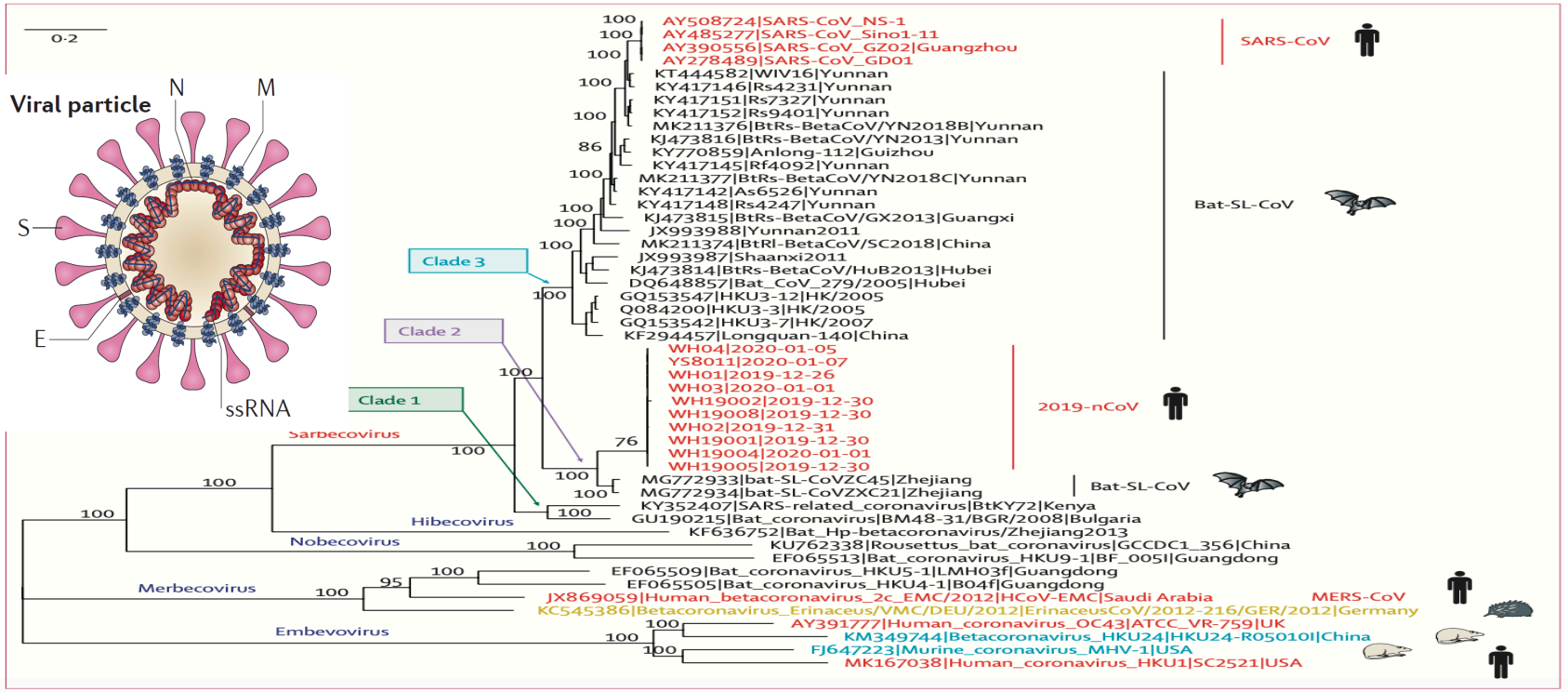
Infections are Zoonotic in Nature

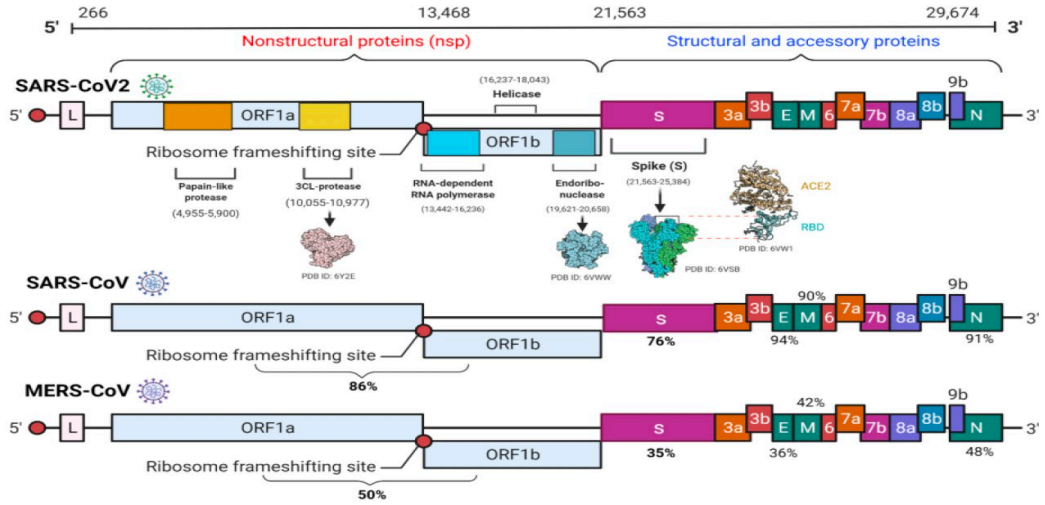


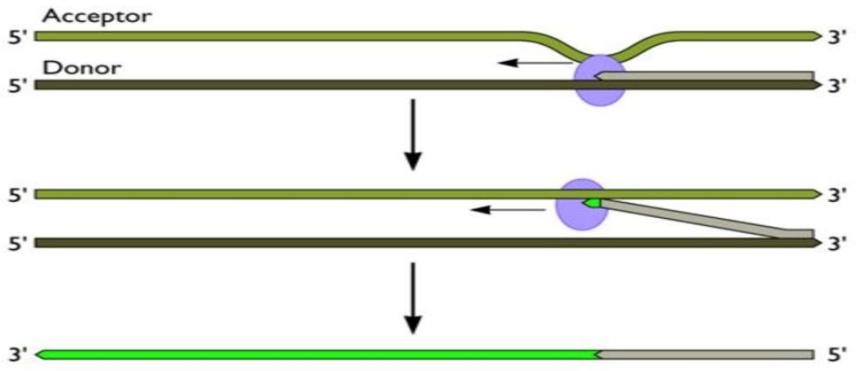
Salata C & Palù G. Path and Dis 2020

The Virologist's Role: Origin and Nature of the Phenomenon







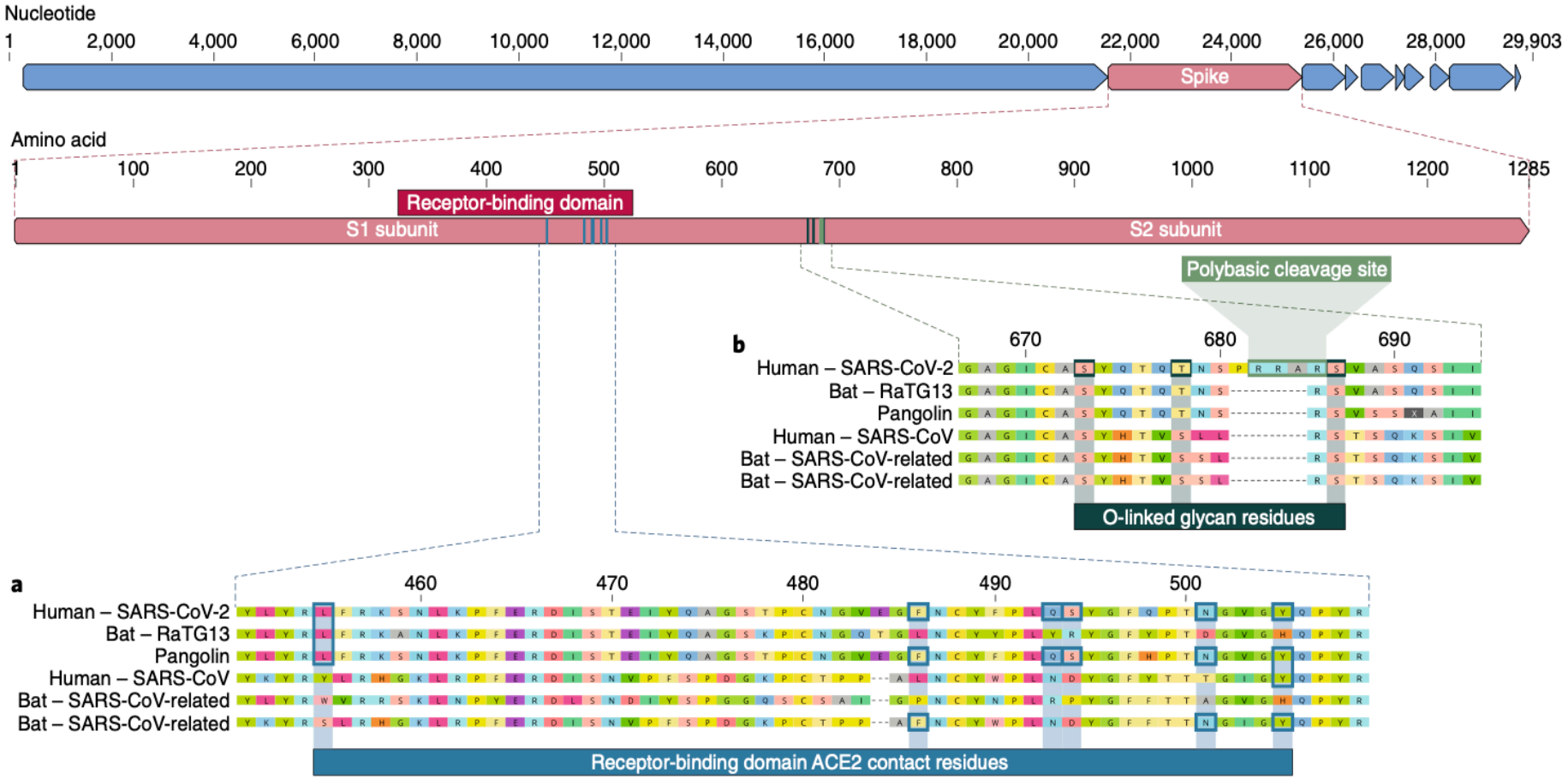


Recombination

Dec 2019 A new Coronavirus in Whuan

Features of the Spike Protein in SARS-CoV-2

First Paper Questioning its Origin



K.G.Andersen et al, NatureMed, April 2020

More about SARS-CoV-2 Origin

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac

Non-uniform aspects of SARS-CoV-2 intraspecies evolution reopen questions on its origin, Hassan SS *et al* 2021

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

journal homepage: www.elsevier.com/locate/yabbi

The importance of accessory protein variants in the pathogenicity of SARS-CoV-2, Seyran M *et al.* Arch Biochem Biophys 2022

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Periodically aperiodic pattern of SARS-CoV-2 mutations underpins the uncertainty of its origin and evolution Hassan SS *et al* 2022

Contents lists available at ScienceDirect

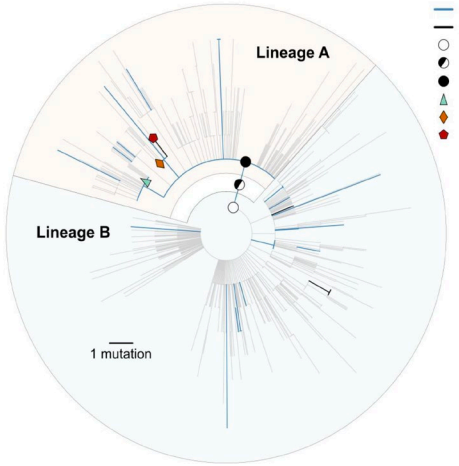
International Journal of Biological Macromolecules

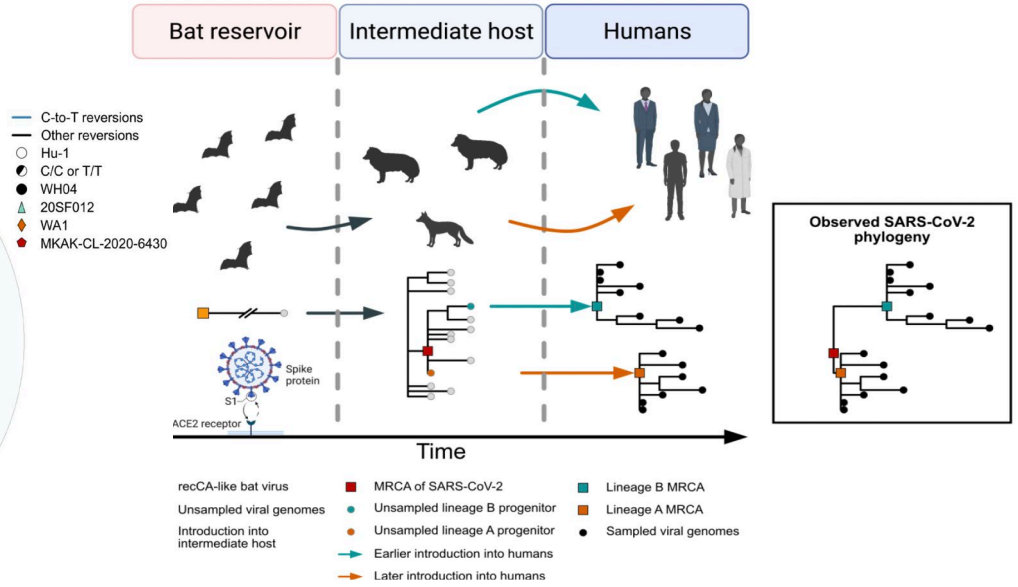
journal homepage: www.elsevier.com/locate/ijbiomac

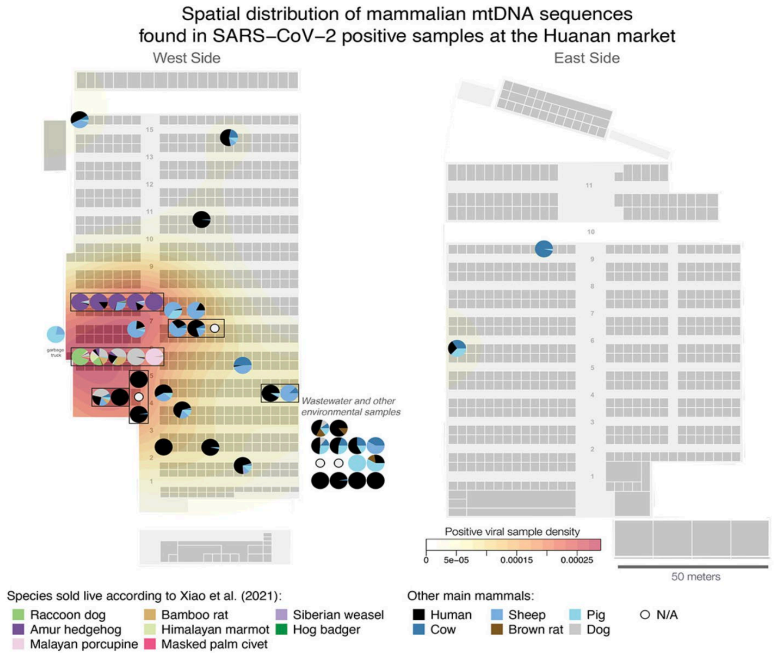
Implications derived from S-protein variants of SARS-CoV-2 from six continents, Hassan SS *et al,* 2022

Urgent need for phylogeny studies in Southeast Asia for coronaviruses M. Seyran *et al*, Biomolecules 2021

ANOTHER INTERMEDIATE HOST? (Science or fiction? -media scoop-)







Science

RESEARCH ARTICLES

Cite as: M. Worobey *et al.*, *Science* 10.1126/science.abp8715 (2022).

The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic

Michael Worobey[1]*, Joshua I. Levy[2], Lorena Malpica Serrano[1], Alexander Crits-Christoph[3], Jonathan E. Pekar[4,5], Stephen A. Goldstein[6], Angela L. Rasmussen[7,8], Moritz U. G. Kraemer[9], Chris Newman[10], Marion P. G. Koopmans[11,12], Marc A. Suchard[13,14,15], Joel O. Wertheim[16], Philippe Lemey[17,18], David L. Robertson[19], Robert F. Garry[18,20,21], Edward C. Holmes[22], Andrew Rambaut[23], Kristian G. Andersen[2,24]*

Science

RESEARCH ARTICLES

Cite as: J. E. Pekar *et al.*, *Science* 10.1126/science.abp8337 (2022).

The molecular epidemiology of multiple zoonotic origins of SARS-CoV-2

Jonathan E. Pekar[1,2]*, Andrew Magee[3], Edyth Parker[4], Niema Moshiri[5], Katherine Izhikevich[5,6], Jennifer L. Havens[1], Karthik Gangavarapu[5], Lorena Mariana Malpica Serrano[7], Alexander Crits-Christoph[8], Nathaniel L. Matteson[4], Mark Zeller[4], Joshua I. Levy[4], Jade C. Wang[9], Scott Hughes[9], Jungmin Lee[10], Heedo Park[10,11], Man-Seong Park[10,11], Katherine Ching Zi Yan[12], Raymond Tzer Pin Lin[12], Mohd Noor Mat Isa[13], Yusuf Muhammad Noor[13], Tetyana I. Vasylyeva[14], Robert F. Garry[15,16,17], Edward C. Holmes[18], Andrew Rambaut[19], Marc A. Suchard[3,20,21]*, Kristian G. Andersen[4,22]*, Michael Worobey[7]*, Joel O. Wertheim[14]*

nature

https://doi.org/10.1038/s41586-023-06043-2

Accelerated Article Preview

Surveillance of SARS-CoV-2 at the Huanan Seafood Market

Received: 17 February 2022

Accepted: 3 April 2023

Accelerated Article Preview

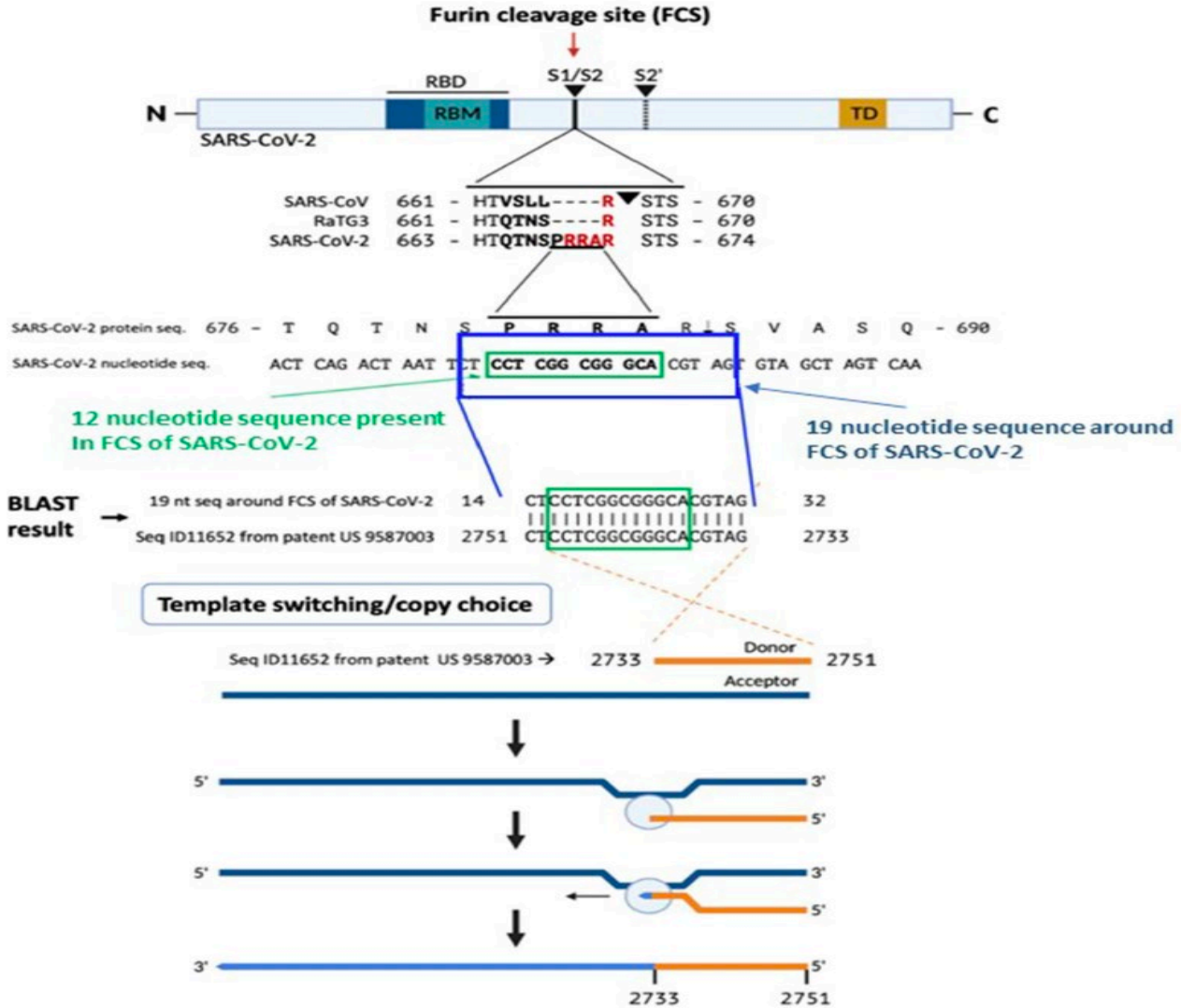
William J. Liu, Peipei Liu, Wenwen Lei, Zhiyuan Jia, Xiaozhou He, Weifeng Shi, Yun Tan, Shumei Zou, Gary Wong, Ji Wang, Feng Wang, Gang Wang, Kun Qin, Rongbao Gao, Jie Zhang, Min Li, Wenling Xiao, Yuanyuan Guo, Ziqian Xu, Yingze Zhao, Jingdong Song, Jing Zhang, Wei Zhen, Wenting Zhou, Beiwei Ye, Juan Song, Mengjie Yang, Weimin Zhou, Yuting Dai, Gang Lu, Yuhai Bi, Wenjie Tan, Jun Han, George F. Gao & Guizhen Wu

MSH3 Homology and Potential Recombination Link to SARS-CoV-2 Furin Cleavage Site

frontiers in Virology

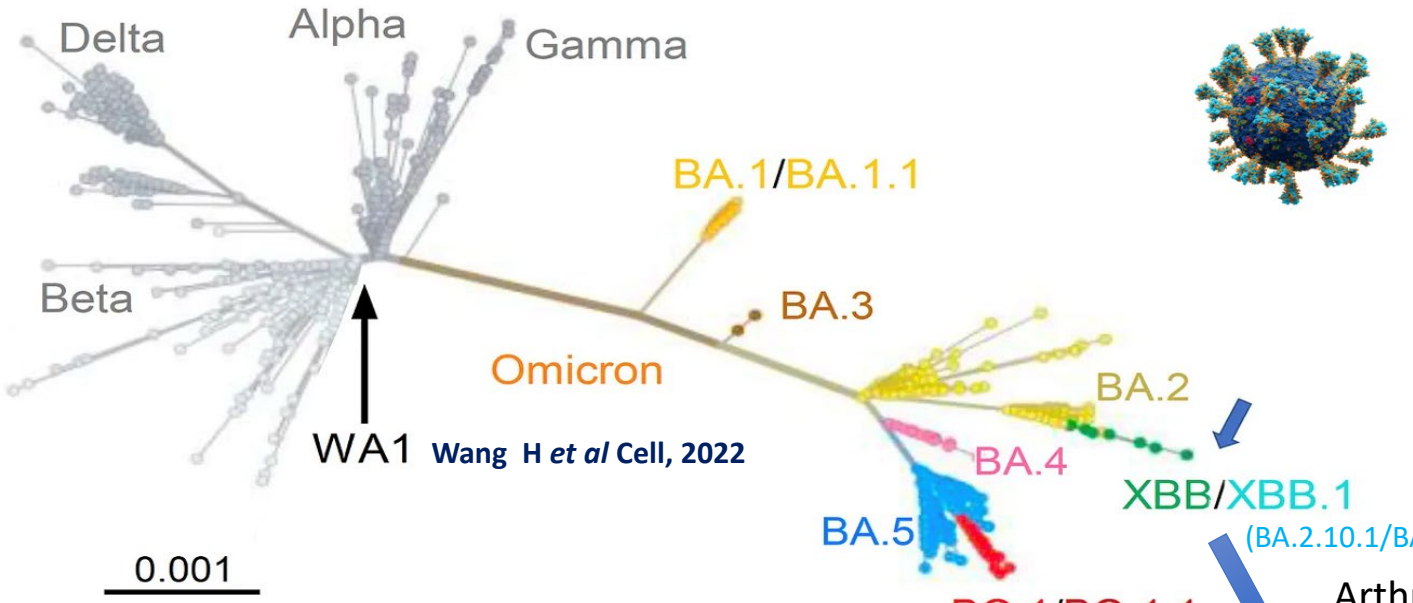
PERSPECTIVE
published: 21 February 2022
doi: 10.3389/fviro.2022.834808

Balamurali K. Ambati[1], Akhil Varshney[2], Kenneth Lundstrom[3], Giorgio Palú[4], Bruce D. Uhal[5], Vladimir N. Uversky[6] and Adam M. Brufsky[7]*



THE CONTINUING VIRUS EVOLUTION

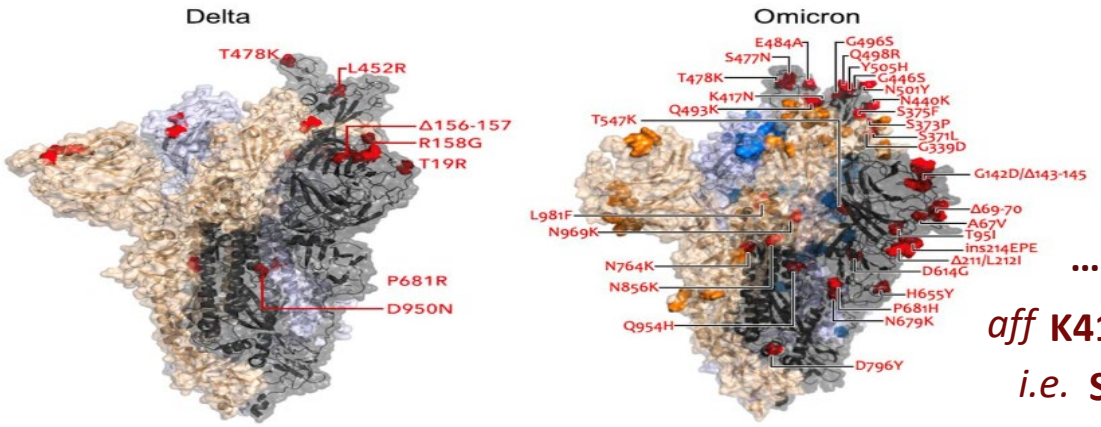
A case of convergent, homoplasic mutations



Wang H *et al* Cell, 2022

Arthur
Cerberus
Kraken
Eris/EG.5
Pirola BA.2.86…..
2023…..

….up to an endemic virus



Mutations of different variants of the SARS-CoV-2 spike protein. There's a lot.

Telenti A *et al* Sc Transl Med, 2022

aff **K417N, N501Y, Q493R, Y505H**

i.e. **S477N, T478K, E484A**

f.c.s. **H655Y, N679K,P681H**

v.l. **R203K/G204R N protein**

12 mutated aa residues in S and 8 residues in >60% of available sequences

48 mutated aa residues in S and 34 residues in >60% of available sequences

ELSEVIER

COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

journal homepage: www.elsevier.com/locate/csbj

Communications

On the intrinsic nature of viral pathogenesis: The assumption of a Darwinian paradigm to describe COVID-19 pandemic

Pier Francesco Roggero [a,1], Arianna Calistri [a,1], Giorgio Palù [a,b,*]

[a] Department of Molecular Medicine, University of Padua, via A. Gabelli 63, 35121 Padua, Italy
[b] Italian Medicines Agency, Via del Tritone 181, 00187 Rome, Italy

$$k \approx R0xL \qquad Lc = [Lx(1 - \frac{\%A}{100})]$$

Calculated k for SARS-CoV-2 variants. R0 and L values were retrieved from the John Hopkins Coronavirus Resource Center, accessed in July 2022 [18]. A% stands for percentage of asymptomatic patients.

SARS-COV-2	R0	L%	A%	k
B1.1.7 (Alfa)	4	2	27	5.84
B.1.351 (Beta)	4.5	1.8	27	5.91
P.1 (Gamma)	5	1.6	30	5.60
B.1.617 (Delta)	7	1.1	30	5.39
B.1.1.529 (Omicron)	14	0.6	40	5.04

Calculated k for 2014 Ebola virus parameters. Values adopted for k calculation are reported in [20].

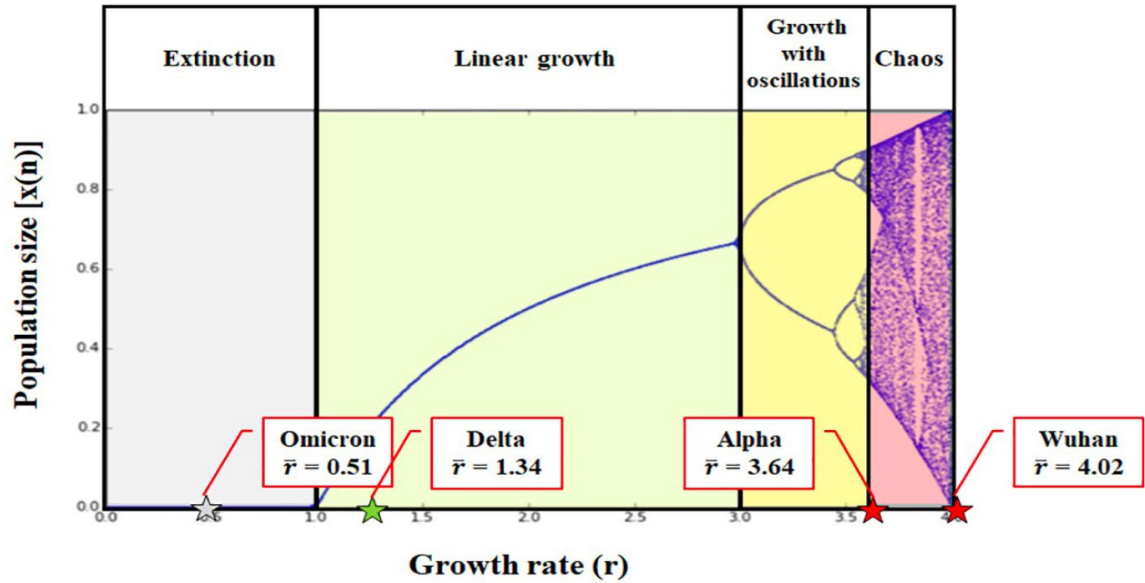
Ebola virus	R0	L%	k
Guinea	1.51	74	111
Sierra Leone	2.53	48	120
Liberia	1.59	71	112

PLOS ONE

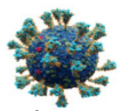
RESEARCH ARTICLE

The chaos law is a principal driver of natural selection: A proposition on the evolution of recently emerged coronaviruses

Pier Francesco Roggero[1☯], Arianna Calistri[1☯], Giorgio Palù[1,2]*



Logistic map (chaos theory)



$$x(n+1) = r * x(n) * [1 - x(n)]$$

where x is the size of a population and r is the growth rate

r < 1.0: the population size is attracted to 0 (extinction)

1.0 < r < 3: the population size is attracted to stable and exact values

3 < r < 3.57: the population size oscillates between a discrete and precise 2^n number of values (with n ≥ 1 and integer)

***r* ≈ 3.56995:** starts chaos

3.57<r<4: population is growing in a chaotic way

r > 4: almost all the initial conditions will eventually leave the interval [0,1] and diverge.

Applied to

emerging viruses

$$r = \frac{\ln 2 \times 365}{T}$$

$$A = P(1+x)^n$$

$$\bar{r} = \frac{\sum_{i=1}^{n} w_i r_i}{\sum_{i=1}^{n} w_i}$$

Chance vs Chaos in Virus Evolution

Where

T = doubling time (days)

Daily interest rate

Weighted arithmetic mean

Table 1. Parameters for SARS-CoV-2.

START	END	T	SARS-CoV-2 variant	P	*d*	*d* (%)	*r*	$\bar{r}$	*r*/*d*(%)
22 JAN 2020	25 JUN 2020			10					
26 JUN 2020	07 AUG 2020	63	**Wuhan**	20	0.0111	1.11%	4.02	**4.02**	3.62
08 AUG 2020	15 OCT 2020	69	**Alpha**	40	0.0101	1.01%	3.67		3.63
16 OCT 2020	24 DEC 2020	70	**Alpha**	80	0.0099	0.99%	3.61	**3.64**	3.65
25 DEC 2020	10 MAY 2021	137	**Delta**	160	0.0051	0.51%	1.85		3.62
11 MAY 2021	05 JAN 2022	240	**Delta**	320	0.0029	0.29%	1.05	**1.34**	3.64
06 JAN 2022	09 NOV 2022	308	**Omicron**	640	0.0022	0.22%	0.82		3.65
10 NOV 2022	06 JUL 2023	239[a]	**Omicron**	691	0.00032	0.032%	0.117	**0.51**	3.66

Table 2. Parameters for SARS-CoV-1.

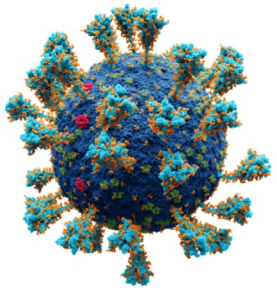
START	END	T	P	*d*	*d*(%)	*r*	$\bar{r}$	*r*/*d*(%)
16 NOV 2002	01 MAR 2003		1000					
02 MAR 2003	05 APR 2003	34	2000	0.0206	2.06	7.44		3.61
06 APR 2003	25 APR 2003	19	4000	0.0372	3.72	13.32		3.58
26 APR 2003	20 MAY 2003	24	8000	0.0293	2.93	10.54		3.6
21 MAY 2003	19 MAY 2004	364[a]	8500	0.00017	0.017	0.06	**1.77**	3.53

Table 3. Parameters for MERS-CoV.

START	END	*t*	P	*d*	*d* (%)	*r*	$\bar{r}$	*r*/*d*(%)
01 JUN 2012	31 DEC 2012	213	14					
01 JAN 2013	31 DEC 2013	365	114	0.0057	0.57	2.10		3.68
01 JAN 2014	31 DEC 2014	365	495	0.004	0.4	1.47		3.67
01 JAN 2015	31 DEC 2015	365	987	0.0019	0.19	0.69		3.63
01 JAN 2016	31 DEC 2016	365	1236	0.0006	0.06	0.22		3.75
01 JAN 2017	31 DEC 2017	365	1486	0.0005	0.05	0.18		3.68
01 JAN 2018	31 DEC 2018	365	1633	0.0003	0.03	0.09		3.14
01 JAN 2019	31 DEC 2019	365	1845	0.0003	0.03	0.12		4.07
01 JAN 2020	01 MAY 2023	1216	2604	0.0028	0.028	0.10	0.39	3.69

Table 4. Parameters for Ebola virus.

START	END	T	P	*d*	*d* (%)	*r*	$\bar{r}$	*r*/*d*(%)
01 DEC 2013	14 JUL 2014		1000					
15 JUL 2014	09 AUG 2014	25	2000	0.0281	2.81	10.12		3.60
10 AUG 2014	31 AUG 2014	21	4000	0.0336	3.36	12.05		3.59
01 SEP 2014	05 OCT 2014	34	8000	0.206	2.06	7.44		3.61
06 OCT 2014	22 OCT 2014	16	16000	0.0443	4.43	15.81		3.57
23 OCT 2014	13 APR 2016	538[a]	28700	0.00109	0.11	0.40	1.94	3.64



Among the Many Other Open Issues….

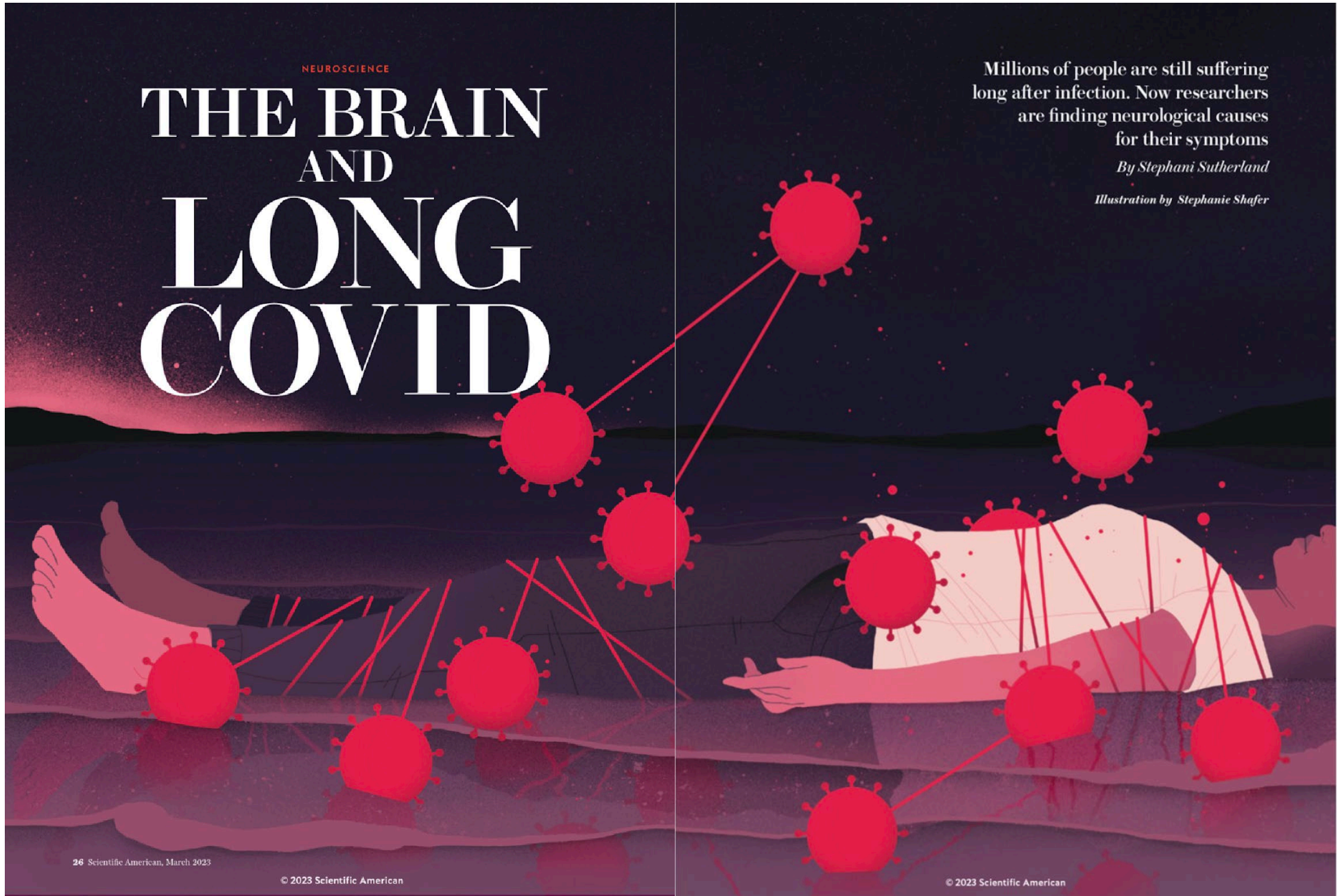
NEUROSCIENCE

THE BRAIN AND LONG COVID

Millions of people are still suffering long after infection. Now researchers are finding neurological causes for their symptoms

By Stephani Sutherland

Illustration by Stephanie Shafer

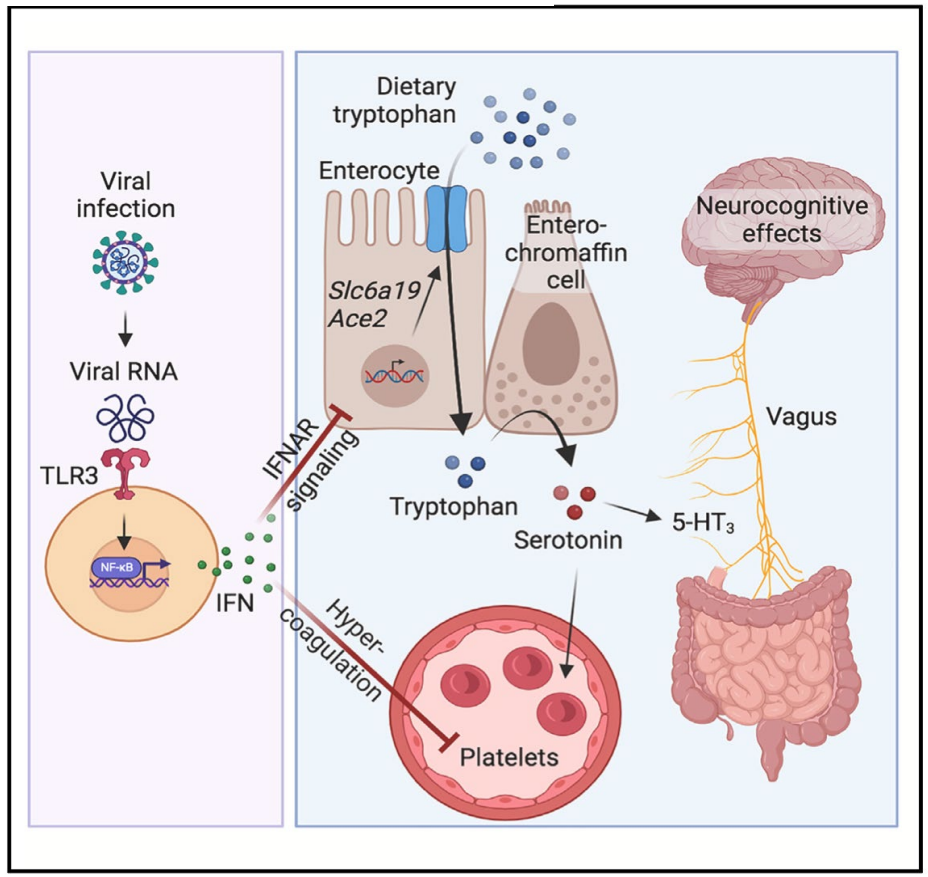


Cell

Serotonin reduction in post-acute sequelae of viral infection

Highlights

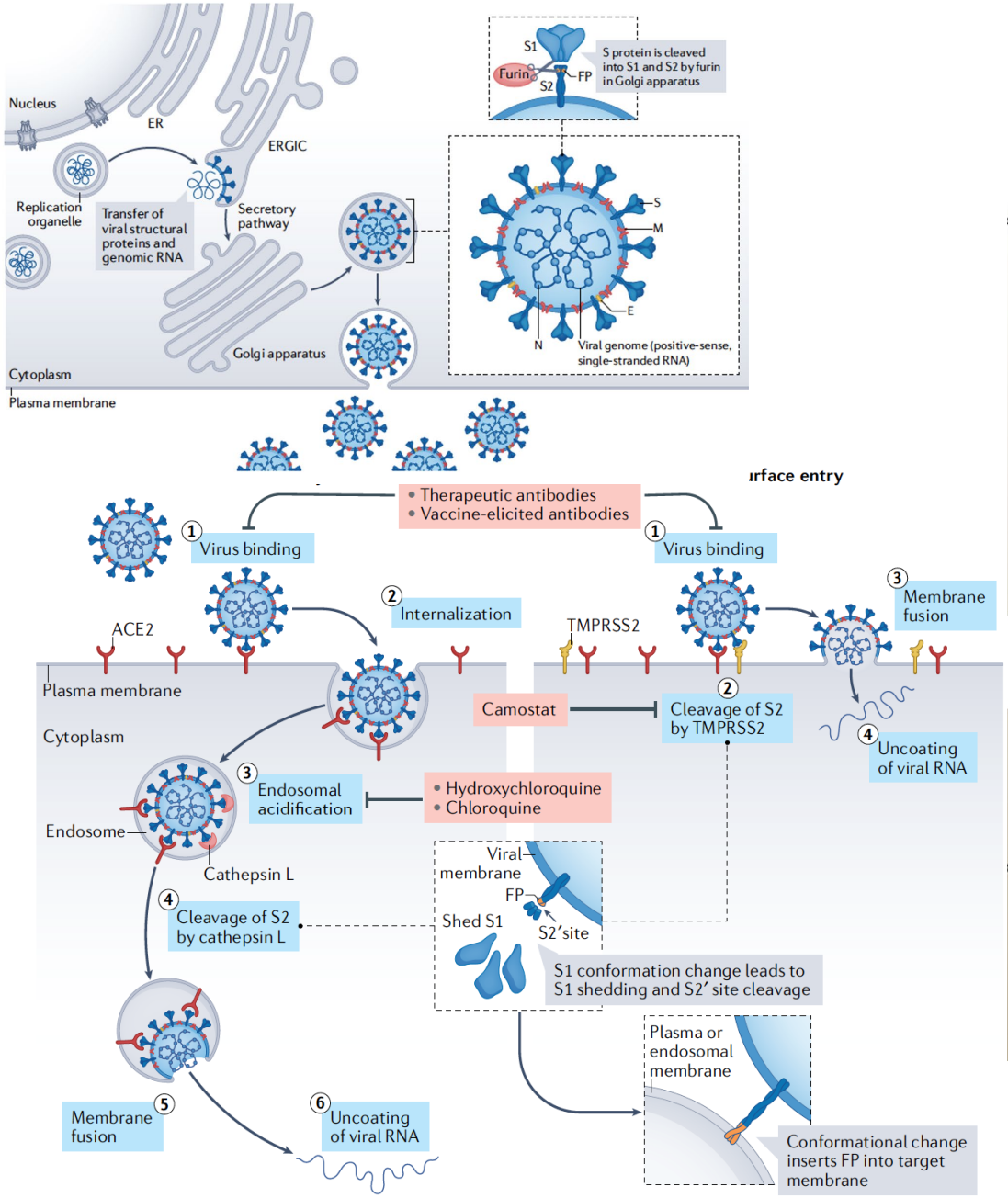
- Long COVID is associated with reduced circulating serotonin levels
- Serotonin depletion is driven by viral RNA-induced type I interferons (IFNs)
- IFNs reduce serotonin through diminished tryptophan uptake and hypercoagulability
- Peripheral serotonin deficiency impairs cognition via reduced vagal signaling

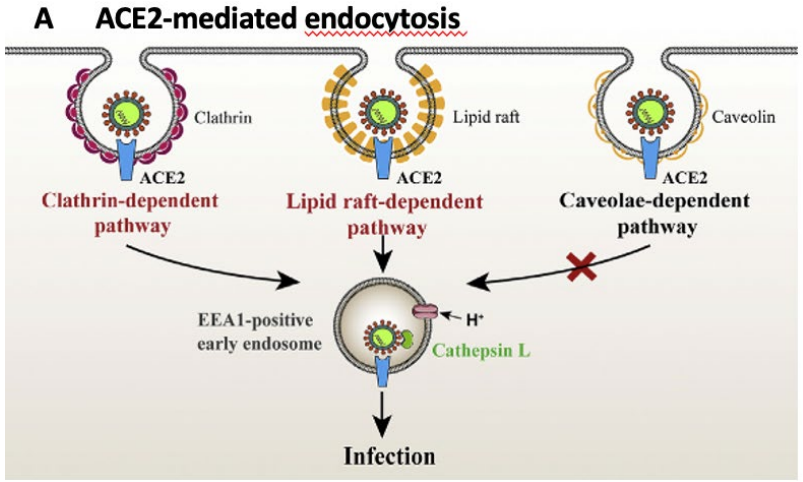


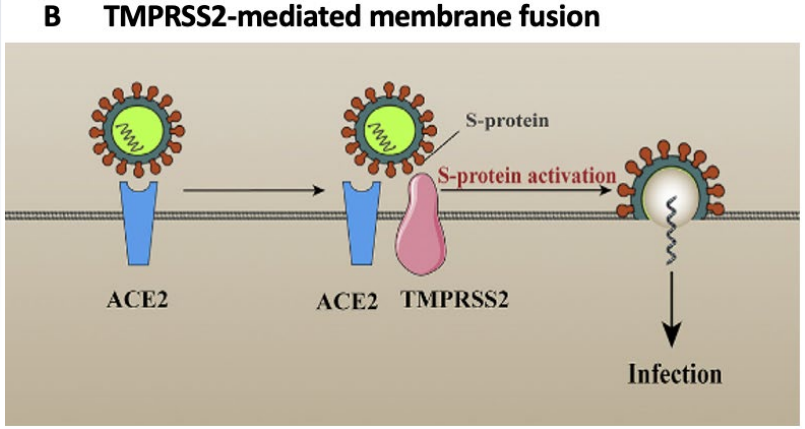
Wong et al., 2023, Cell *186*, 1–17
October 26, 2023
https://doi.org/10.1016/j.cell.2023.09.013

CellPress

Entry, a Biological Issue: Fusion vs RME





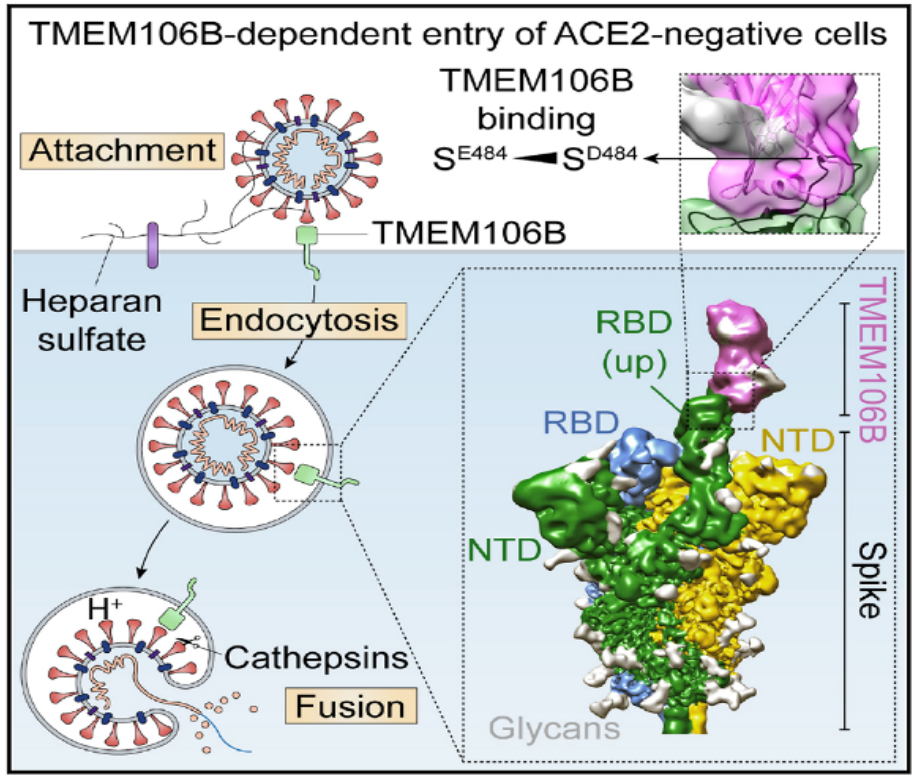


The Role of Other Receptors/Coreceptors:

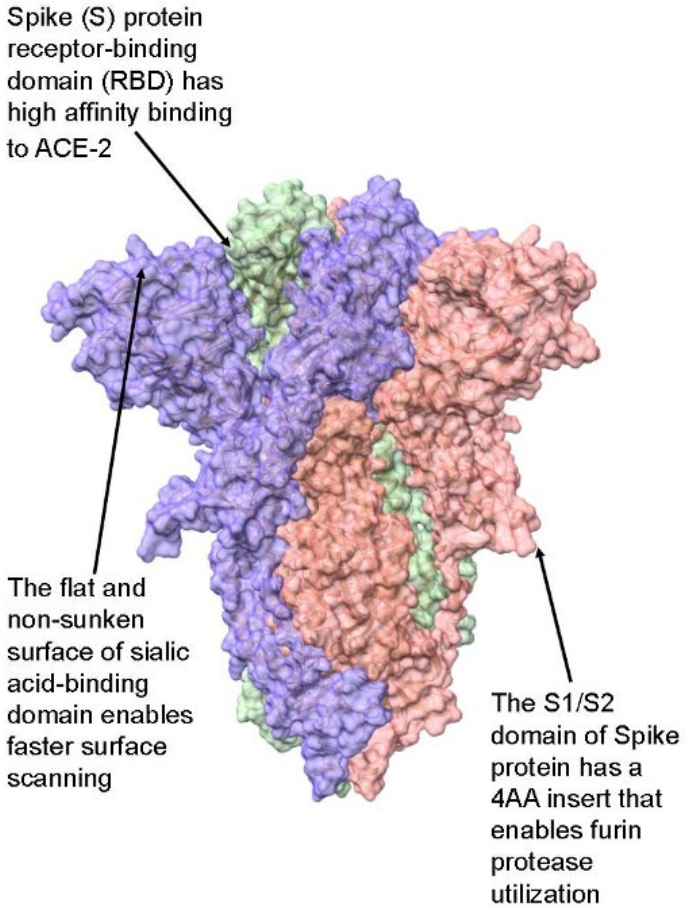
AXL, ASGR1/KREMEN, TfR, Integrin, TMEM, FITIM, HSPG, SA, CD147, NRP1, CTL…..

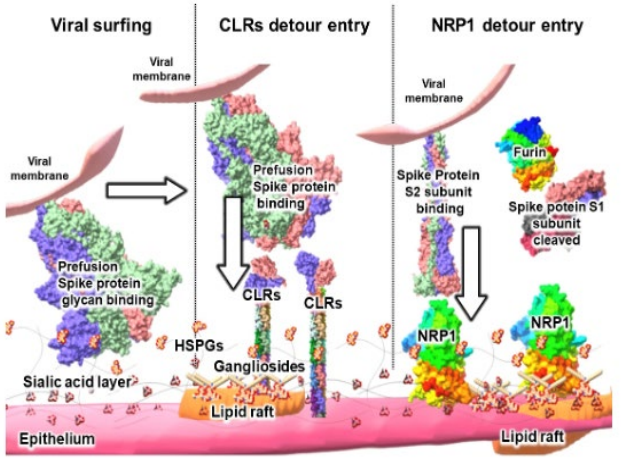
Cell

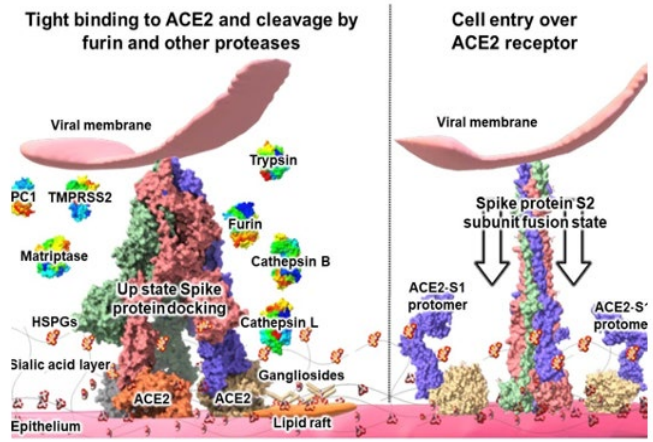
TMEM106B is a receptor mediating ACE2-independent SARS-CoV-2 cell entry



Baggen et al., 2023, Cell *186*, 3427–3442
August 3, 2023 © 2023 The Author(s). Published by Elsevier Inc.
https://doi.org/10.1016/j.cell.2023.06.005



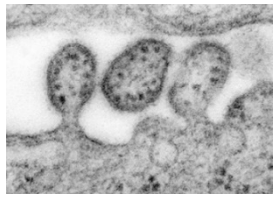


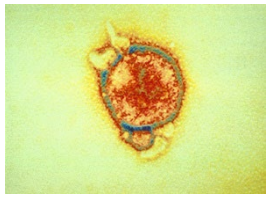


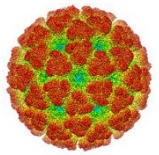
Seyran M et al. J Med Virol. 2020; Proteomics, 2020;

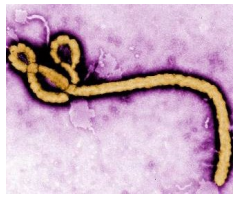
SS Hassan et al. Environ. Res. 2022;The FEBS Journal, 2020

Emerging and re-emerging deadly viral infections during the last decades


Lassa

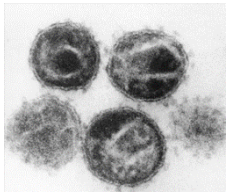

Nipah/Hendra

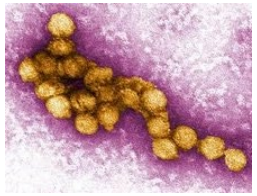

CHIKV

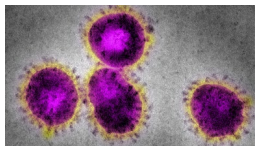

Ebola


MPV

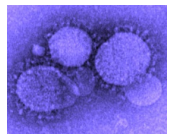
Menangle
Bunya
Arena
New p.flu

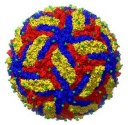

HIV

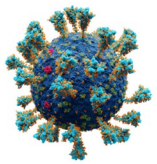

WNV


SARS


H1N1sw


MERS


ZIKV


SARS-Cov-2

Next viral threat?

1980 1990 2000 2010 2020

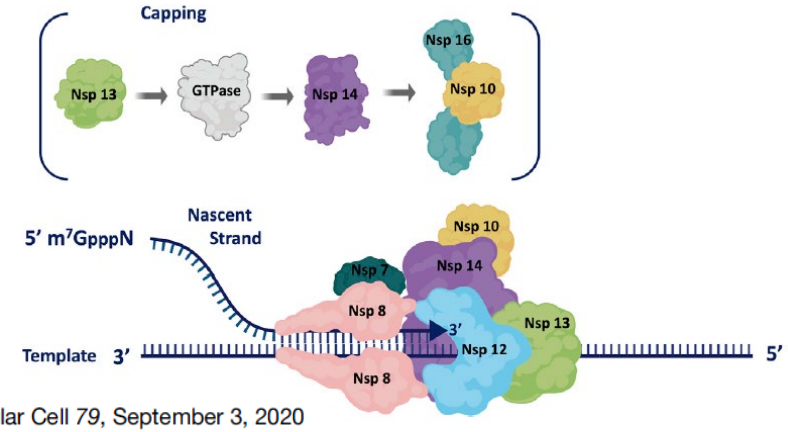
direct and indirect costs of zoonotic diseases estimated to exceed US$ 220 bllion in the last decade alone

https://wwwnc.cdc.gov – http://documents.worldbank.org

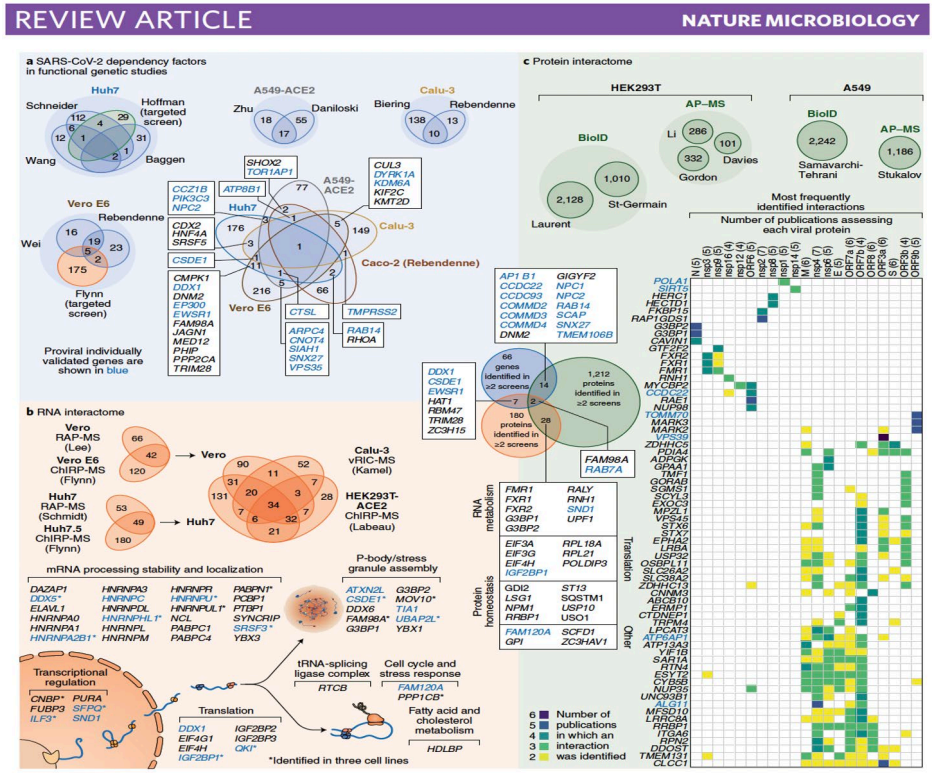
SIV ISV
SOCIETA' ITALIANA DI VIROLOGIA
ITALIAN SOCIETY FOR VIROLOGY

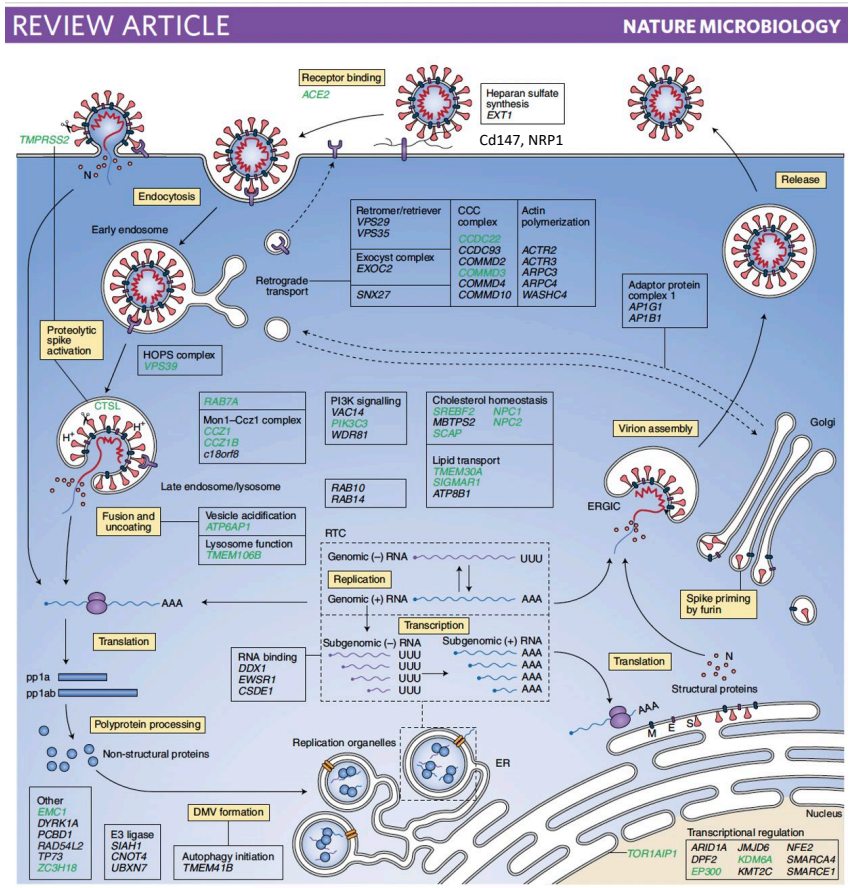
One Virology One Health

CLINICAL IMPLICATIONS OF BASIC VIROLOGY



Molecular Cell 79, September 3, 2020





AIFA AGENZIA ITALIANA DEL FARMACO

Grazie