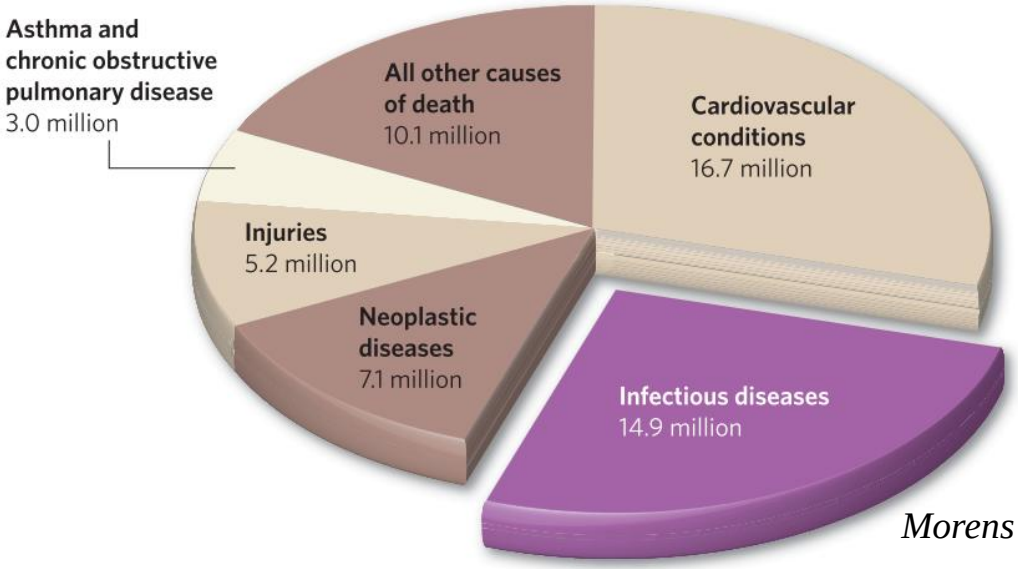
федеральное государственное бюджетное учреждение
«НАУЧНО-ИССЛЕДОВАТЕЛЬСКИЙ ИНСТИТУТ ГРИППА»
Министерства здравоохранения Российской Федерации

Современные подходы к разработке лекарственных препаратов широкого спектра действия для вновь возникающих вирусных инфекций

Директор,
заведующий отделом молекулярной биологии вирусов
ФГБУ «НИИ гриппа» Минздрава России,
к.б.н.
Васин Андрей Владимирович

12 марта 2017
Санкт-Петербург

Инфекционные заболевания являются одной из ведущих причин смертности населения

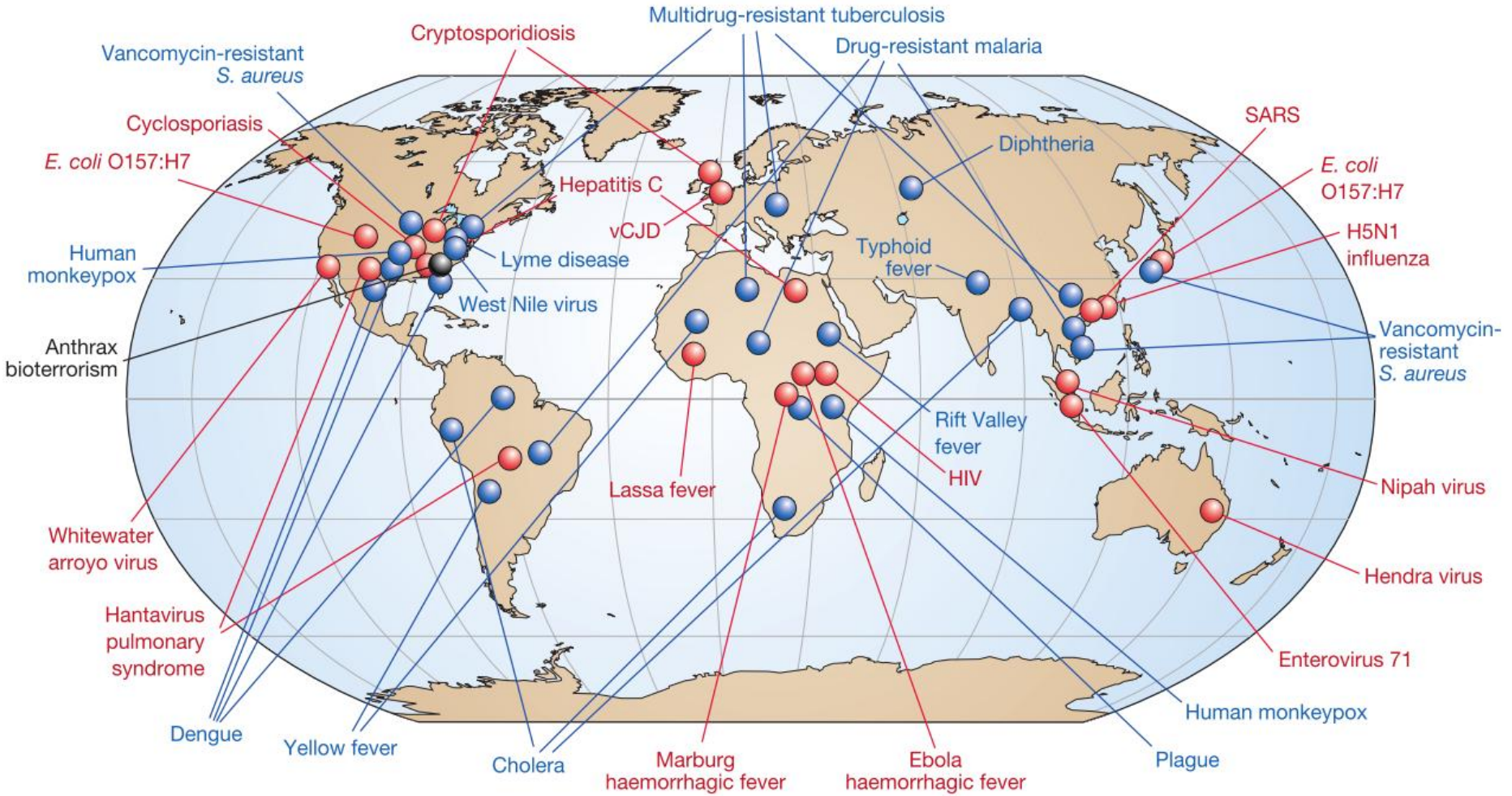


Infectious diseases	Annual deaths (millions)
Respiratory infections	3.96
HIV/AIDS	2.77
Diarrhoeal diseases	1.80
Tuberculosis	1.56
Vaccine-preventable childhood diseases	1.12
Malaria	1.27
STDs (other than HIV)	0.18
Meningitis	0.17
Hepatitis B and C	0.16
Tropical parasitic diseases	0.13
Dengue	0.02
Other infectious diseases	1.76

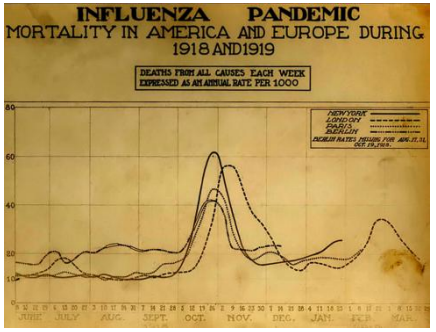
Morens et al., 2014

Вновь возникающие инфекционные заболевания (emerging infectious disease) – это заболевания, которые впервые появились в популяции и ранее в ней не встречались; либо ранее ограниченно присутствовали в популяции, но по какой-то причине получили широкое распространение (по числу случаев заболевания и/или географическому распространению).

Также к этой группе заболеваний относятся известные контролируемые инфекции, для которых появляются новые клинические формы, в том числе летальные



Morens et al., 2014




DEC. 14, 1918] A FILTRABLE VIRUS IN INFLUENZA. [THE BRITISH MEDICAL JOURNAL 645

A FILTRABLE VIRUS AS THE CAUSE OF THE EARLY STAGE OF THE PRESENT EPIDEMIC OF INFLUENZA.

(A PRELIMINARY NOTE.)

BY

MAJOR H. GRAEME GIBSON, R.A.M.C.,
MAJOR F. B. BOWMAN, C.A.M.C.,
AND
CAPTAIN J. I. CONNOR, A.A.M.C.

(*Interim Report to the Medical Research Committee.*)

A PRELIMINARY note by MM. Charles Nicolle and Charles Lebailly on investigations suggesting the etiological part played by a filtrable virus in influenza causes was communicated recently to the Académie des Sciences.[1] A similar claim for the importance of a filtrable organism in the production of common colds had previously been put forward by Major George B. Foster, Junr., Medical Corps, United States Army, in the *Journal of Infectious Diseases* of November, 1917 (Vol. xxi, No. 5, pp. 451–474).

These observations have raised the important question as to whether the micro organisms hitherto regarded as of etiological importance in influenza and certain other catarrhal conditions of the respiratory tract play a primary or a secondary part.

The following investigations, undertaken at the request of the Adviser in Pathology, British Expeditionary Force, France, appear, so far as they go, to confirm and amplify the work of MM. Nicolle and Lebailly, and it is thought desirable to publish a preliminary report without delay. Further experiments are in progress, and a detailed report will follow in due course.

Nicolle and Lebailly, in their communication to the Academy of Science, reported that the unfiltered bronchial secretion of patients suffering from "La Grippe" collected during the pyrexial period was virulent to Chinese bonnet and *Macacus cynomologus* monkeys when injected by the subconjunctival and nasal routes. They also reported that the inoculation of the filtered bronchial secretion caused the disease in two men inoculated by the subcutaneous route. In view of the serious nature of the present epidemic the repetition of the experiments on man with the filtered sputum was not thought to be warranted, and our experiments with both filtered and unfiltered secretions centrifuged, at about 1,500 to 2,000 revolutions per minute, for a minute and a half. The supernatant fluid was passed through a Chamberland L.1 *bis* candle, the filtrate being collected in a sterile vessel. Cultures were made in serum glucose broth and on human blood agar plates, in the preparation of which the blood had been citrated and heated to 55° C. for ten minutes before mixing with the agar. This medium had given us excellent growths of all the organisms met with in the epidemic. These cultures were found to remain quite sterile in respect of non-filtrable organisms.

That afternoon (November 9th) 0.25 c.cm. of the filtrate was inoculated under the conjunctiva of the left eye of monkey No. 1, and 0.75 c.cm. was instilled up its nostrils.

Subsequent History of Case (Monkey No. 1).

On the evening of November 15th the monkey appeared to be somewhat off colour, and on the morning of November 16th it was distinctly ill, moping, and at times resting its head on its arms. It would not take its food, had some suffusion of the conjunctivæ of both eyes, and its coat was "staring." On November 17th its coat was still "staring," but it was taking more interest in its surroundings and was eating its food again, and by November 18th, although its coat was still affected, it had apparently recovered.

Dates of Observation / Days of Disease — Nov. 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 / 1 2 3 4 5 6 7 8 9 10 11 12 — Temperature Rahr — 105° 104° 103° 102° 101°

CHART 1.—The days on which the monkey was ill are "shaded in" in the days of disease line. " = Inoculated.

The temperature chart, with records from the second day before inoculation up to the end of the experiment, is set forth in Chart 1. It will be observed that the temperature of this animal had fluctuated considerably while under observation previous to inoculation, a fact which makes it impossible to say how much the illness was associated with a true pyrexia. The incubation period in this case corresponded to that observed by Nicolle and Lebailly in their monkeys inoculated with unfiltered sputum.

The blood of the monkey was taken on the fifth day of his illness to determine its power of agglutinating Pfeiffer's bacillus. No agglutination was observed in dilutions of 1 in 2, 1 in 10, 1 in 45, 1 in 80, 1 in 100. The monkey was allowed to recover, and is being kept with a view to determining the possibility of reinfection.

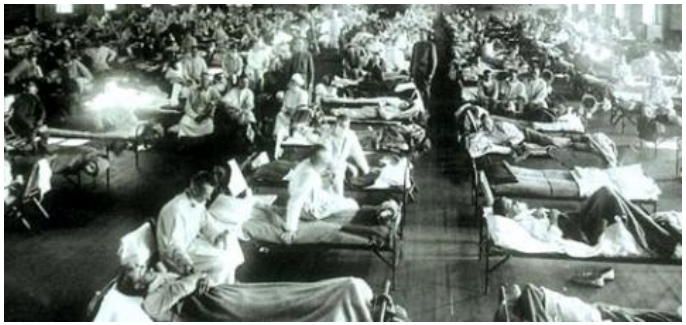
EXPERIMENT 2.—*Inoculation of Filtered Sputum taken from a Case of Influenza on the Third Day of the Disease.*

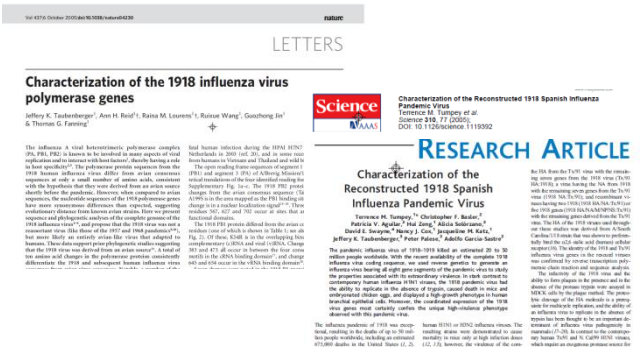
Source of Injective Material.—This experiment was carried out

SPANISH FLU 1918-1919

500 миллионов заболевших

20-40 миллионов смертельных случаев




nature

LETTERS

Characterization of the 1918 influenza virus polymerase genes

Jeffery K. Taubenberger[1], Ann H. Reid[1], Raina M. Lourens[1], Ruixue Wang[1], Guozhong Jin[1] & Thomas G. Fanning[1]

Science AAAS

Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus
Terrence M. Tumpey et al.
Science 310, 77 (2005);
DOI: 10.1126/science.1119392

RESEARCH ARTICLE

Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus

Terrence M. Tumpey,[1]* Christopher F. Basler,[2] Patricia V. Aguilar,[2] Hui Zeng,[2] Alicia Solórzano,[2] David E. Swayne,[3] Nancy J. Cox,[4] Jacqueline M. Katz,[4] Jeffery K. Taubenberger,[5] Peter Palese,[2] Adolfo García-Sastre[2]

Грипп

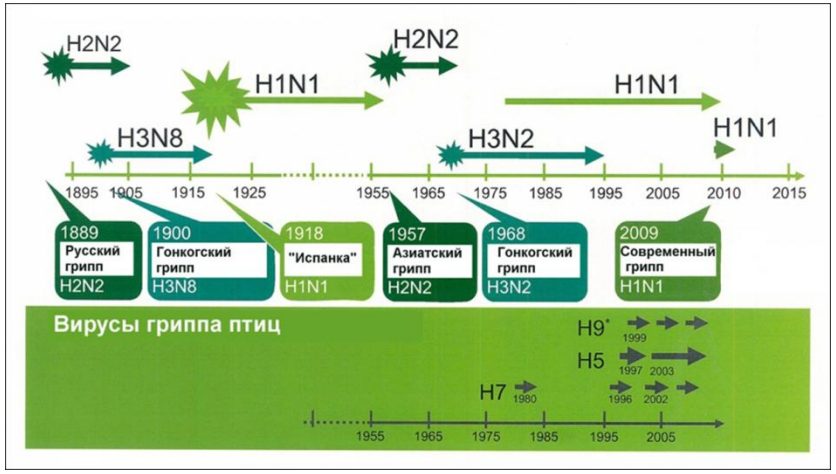
Вирусы гриппа ежегодно во время сезонных эпидемий инфицируют *не менее 15% населения* по всему миру.

Вирус гриппа характеризуется:

- беспрецедентной способностью к молниеносному глобальному распространению
- чрезвычайной вариабельностью генома
- тяжелым протеканием заболевания, сопровождающимся развитием различных осложнений

Заболеваемость гриппом и ОРВИ с 1986 по 1989 г. и с 1990 по 2008 г. (на 100 чел.)

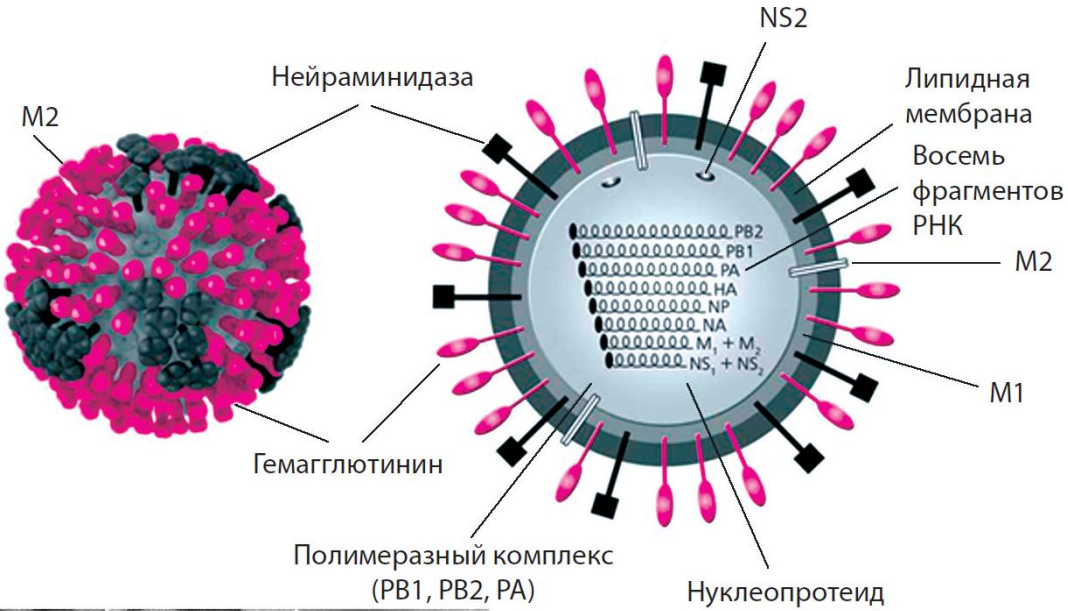
Период	Показатели	РФ	Москва	Санкт-Петербург	Города с населением	
					> 1 млн чел.	< 1 млн чел.
1986–1989 гг.	Среднегодовая заболеваемость	29,9	51,6	48,1	37,7	37,4
1990–2008 гг.	Кратность различий по сравнению с РФ	–	1,7	1,6	1,3	1,3
	Среднегодовая заболеваемость	21,3	29,3	24,0	26,4	24,6
	Кратность различий по сравнению с РФ	1,4	1,4	1,1	1,2	1,2
1969–1989 гг. и 1990–2008 гг.	Кратность снижения между периодами	–	1,8	2,0	1,4	1,5

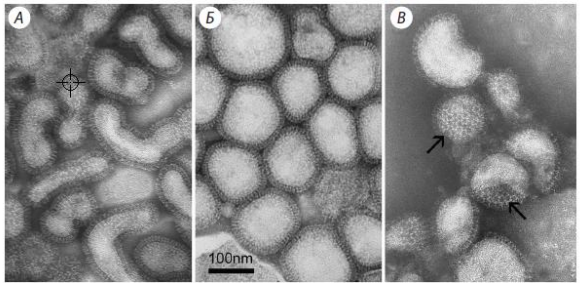


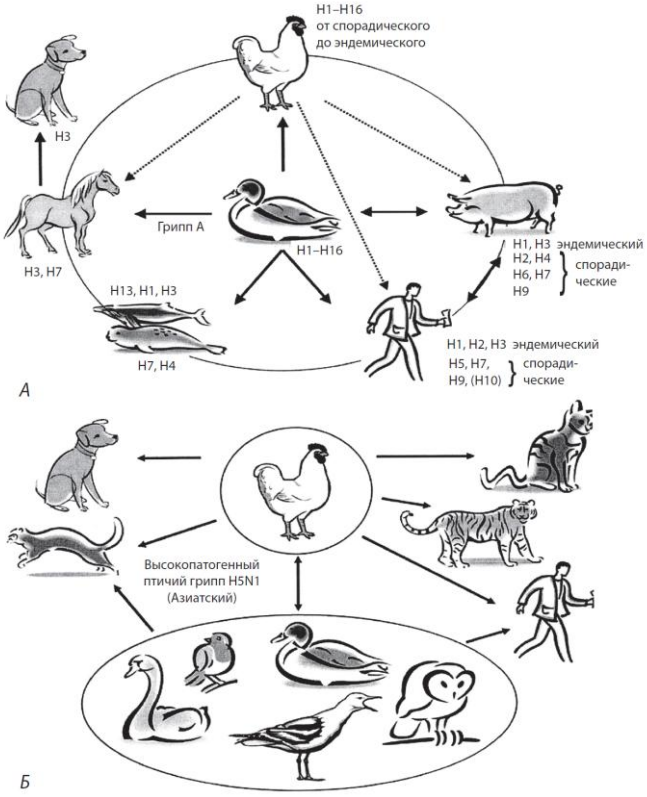
Эпидемии гриппа оказывают существенное влияние на мировую экономику. Ежегодно до *15 млрд долларов* тратится на лечения гриппа и вызванных им осложнений

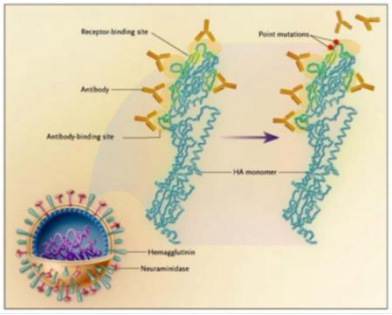
Глобальные экономические потери исчисляются *сотнями миллиардов долларов*

Структура вируса гриппа







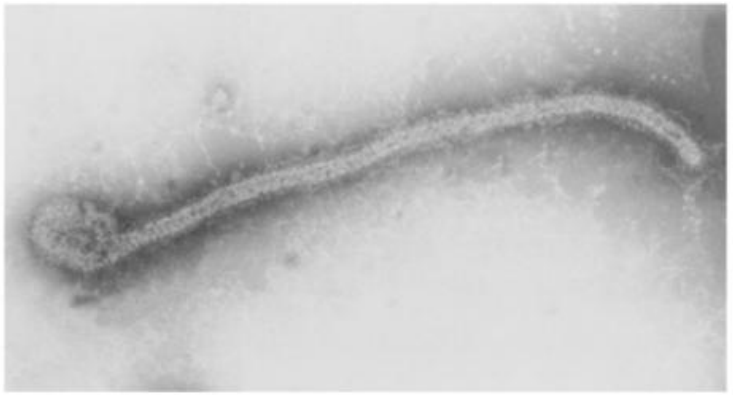


Вирусная РНК-полимераза при транскрипции и репликации допускает ошибки с частотой 1.5×10^{-5}. Возникающие мутации (например, в антигенных сайтах) позволяют избегать иммунного ответа (**антигенный дрейф**).

Реассортация геномных сегментов приводит к возникновению новых вариантов вируса (**антигенный сдвиг**).

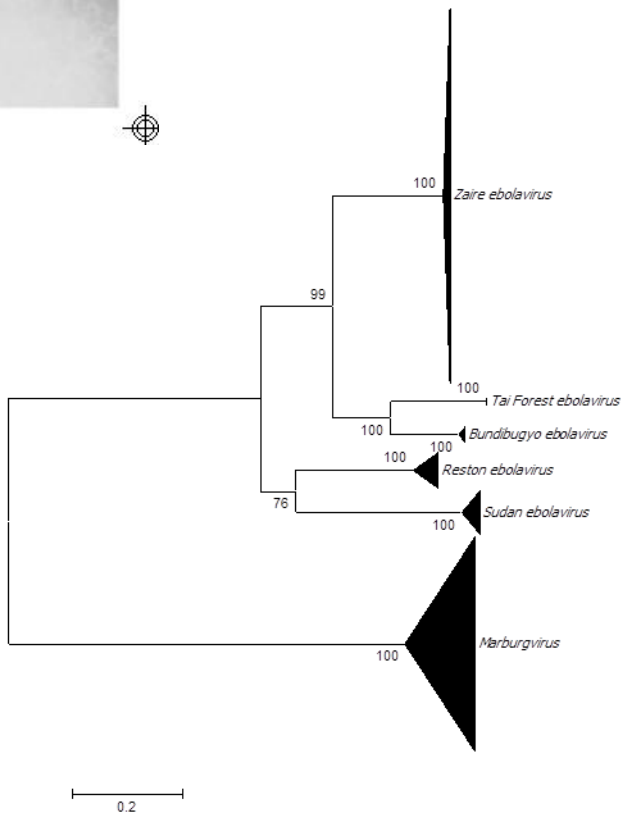
Длительное присутствие вирусов гриппа в популяции человека

Вирус геморрагической лихорадки Эбола (ГЛЭ)



D = 80 нм
L = 860-1200 нм
(до 14000 нм)

Отряд *Mononegavirales*
Семейство *Filoviridae*
Род *Ebolavirus*
Вид *Taı¨ Forest ebolavirus*
Вирус: вирус тайских лесов (Taı¨ Forest virus, TAFV)
Вид *Reston ebolavirus*
Вирус: вирус Рестон (Reston virus, RESTV)
Вид *Sudan ebolavirus*
Вирус: вирус Судан (Sudan virus, SUDV)
Вид *Zaire ebolavirus*
Вирус: вирус Эбола (Ebola virus, EBOV)
Вид *Bundibugyo ebolavirus*
Вирус: вирус Бундибугио (Bundibugyo virus, BDBV)
Род *Marburgvirus*
Вид *Marburg marburgvirus*
Вирус: вирус Марбург (Marburg virus, MARV)
Род *Cuevavirus*
Вид *Lloviu cuevavirus*
Вирус: вирус Лловиу (Lloviu cuevavirus, LLOV)

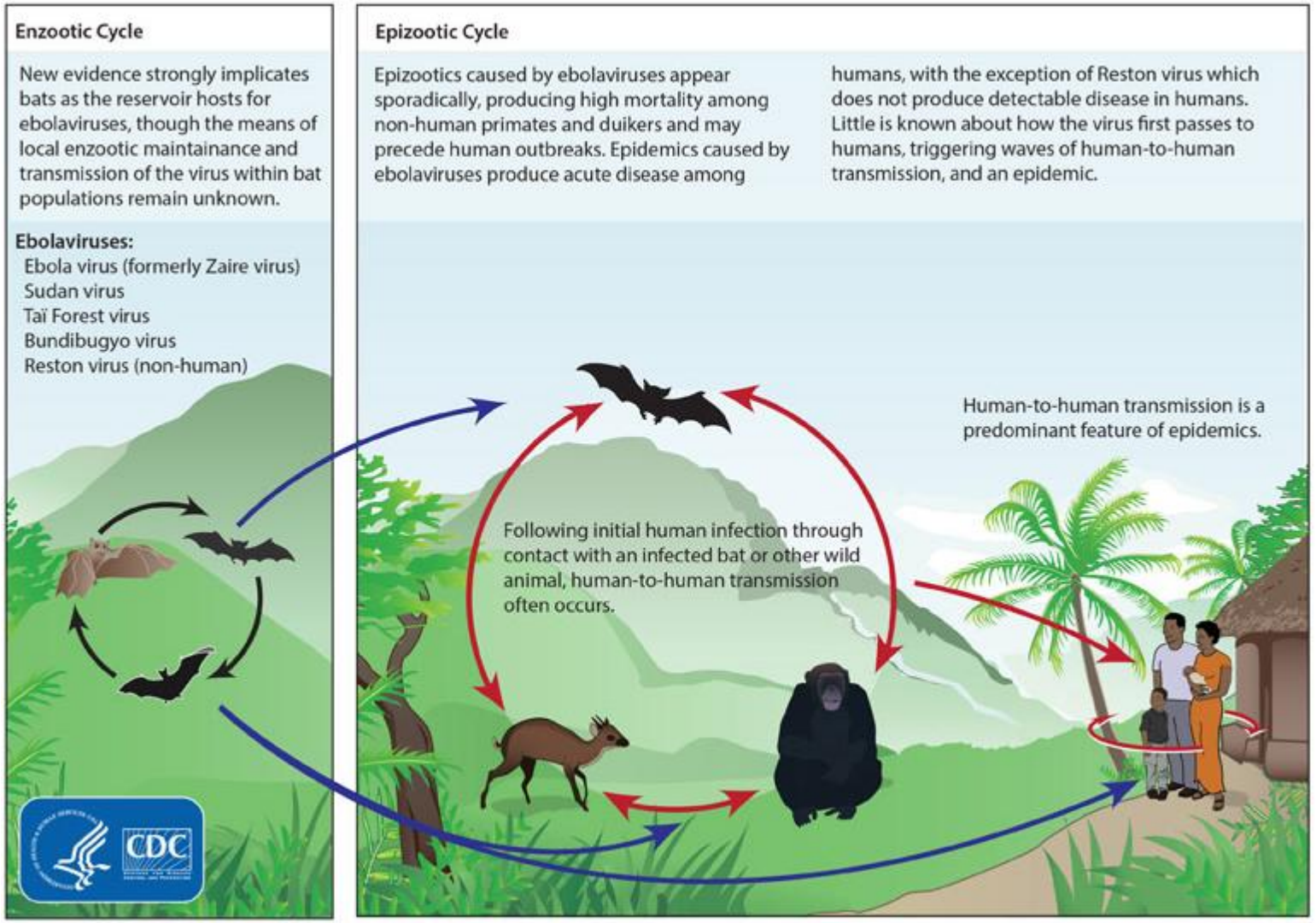


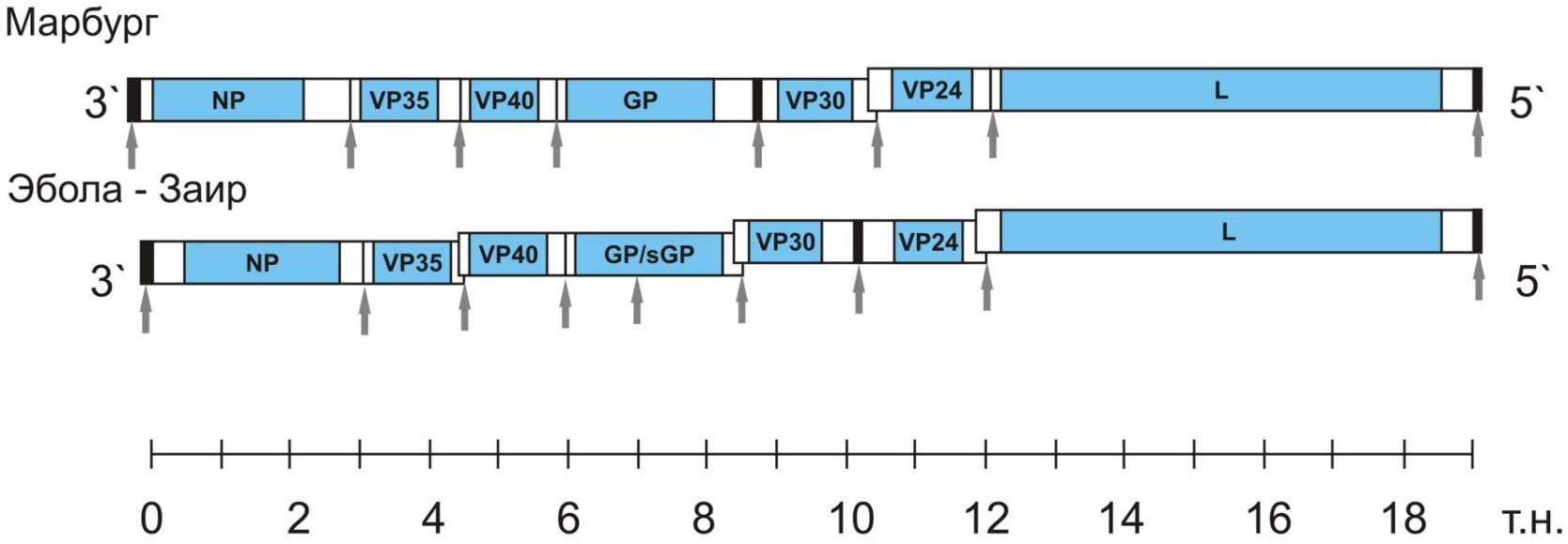
BSL-4

Эпидемические вспышки геморрагических лихорадок, вызванных филовирусами

Filovirus (species)	Year	Outbreak location	Place of origin	Human cases (% mortality)
LVMARV	1967	Marburg/Frankfurt, Germany; Belgrade, Serbia	Uganda	32 (23)
	1975	Johannesburg, South Africa	Zimbabwe	3 (33)
	1980	Nzoia and Nairobi, Kenya	Western Kenya	2 (50)
	1987	Kisumu, Kenya	Western Kenya	1 (100)
	1998–2000	Durba/Watsa, DRC	DRC	154 (83)
	2004–2005	Uíge, Angola	Angola	252 (90)
	2007	Uganda (western)	Uganda	4 (25)
	2008	The Netherlands	Uganda	1 (100)
	2008	United States	Uganda	1 (0)
ZEBOV[a]	1976	Yambuku, DRC	DRC	318 (88)
	1977	Tandala, DRC	DRC	1 (100)
	1994	Ogooué-Invindo province, Gabon	Gabon	52 (60)
	1995	Kikwit, DRC	DRC	315 (79)
	1996	Mayibout, Gabon	Gabon	37 (57)
	1996	Booue, Gabon and Johannesburg, South Africa	Gabon	60 (75)[b]
	2001–2002	Ogooué-Invindo province, Gabon; Cuvette region, RC	Gabon?	124 (79)
	2002–2003	Cuvette region, RC; Ogooué-Invindo province, Gabon	RC?	143 (90)
	2003	Mboma and Mbandza, RC	RC	35 (83)
	2005	Etoumbi and Mbomo in Cuvette region, RC	RC	12 (75)
	2007	Kasai Occidental province, DRC	DRC	264 (71)
	2008–2009	Kasai Occidental province, DRC	DRC	32 (47)
SEBOV	1976	Nzara, Maridi, Tembura, Juba, Sudan	Southern Sudan	284 (53)
	1979	Nzara, Yambio, Sudan	Southern Sudan	34 (65)
	2000–2001	Gulu District, Mbarrara, and Masindi, Uganda	Uganda	425 (53)
	2004	Yambio County, Sudan	Southern Sudan	17 (41)
	2011	Uganda (central)	Uganda	1 (100)
BEBOV	2007	Bundibugyo district, Uganda	Uganda	149 (25)[c]
ICEBOV (CIEBOV)	1994	Tai Forest, Ivory Coast, and Basel, Switzerland	Ivory Coast	1 (0)
	1995	Liberia	Liberia?	1 (0)
REBOV	1989	Reston, Virginia (also Pennsylvania and Texas)	Philippines[d]	4 (0)
	1992	Siena, Italy	Philippines	0 (0)
	1996	Alice, Texas	Philippines	0 (0)
	2008	Philippines	Philippines	0 (0)

Ebola virus transmission from fruit bats to humans. The virus is transmitted by contact with contaminated body fluids. Source: Centre for Disease Control, USA





Однонитевая (-)-РНК длиной 19 000 н:

3`-лидер – *NP – VP35 – VP40 – GP – VP30 – VP24 – L* – 5`-трейлер

(50-70 н.) (25-677 н.)

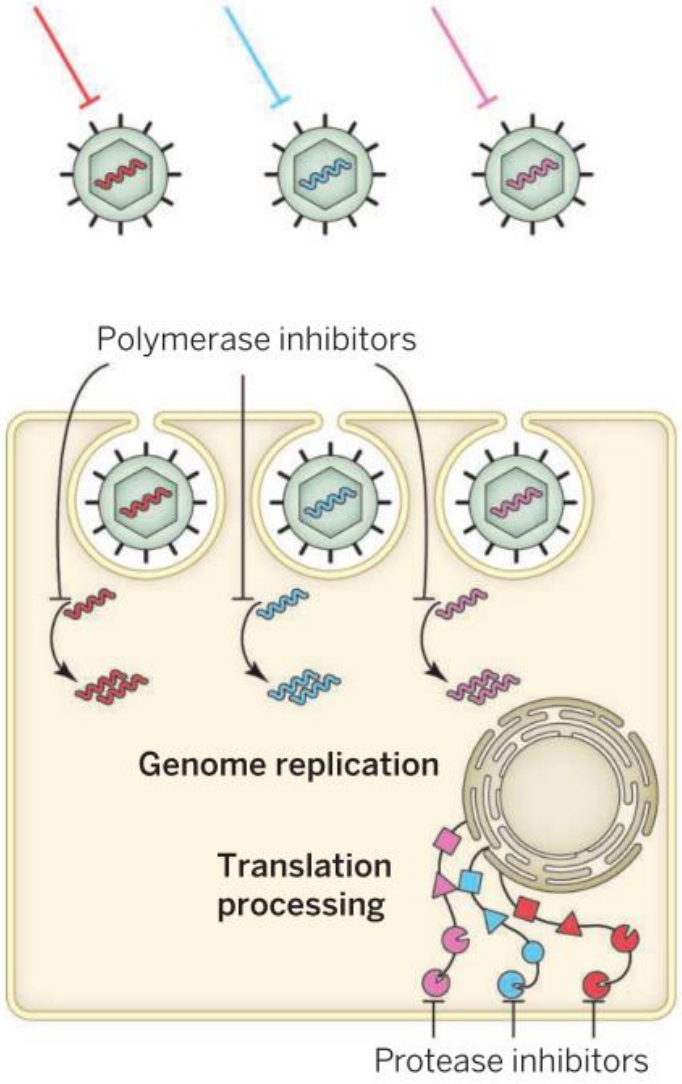
NP – нуклеопротеин
VP – белок вириона
GP – гликопротеин
L – полимераза

Гены разделены короткими межгенными областями, однако некоторые гены перекрываются

Current FDA-approved antivirals and their targets

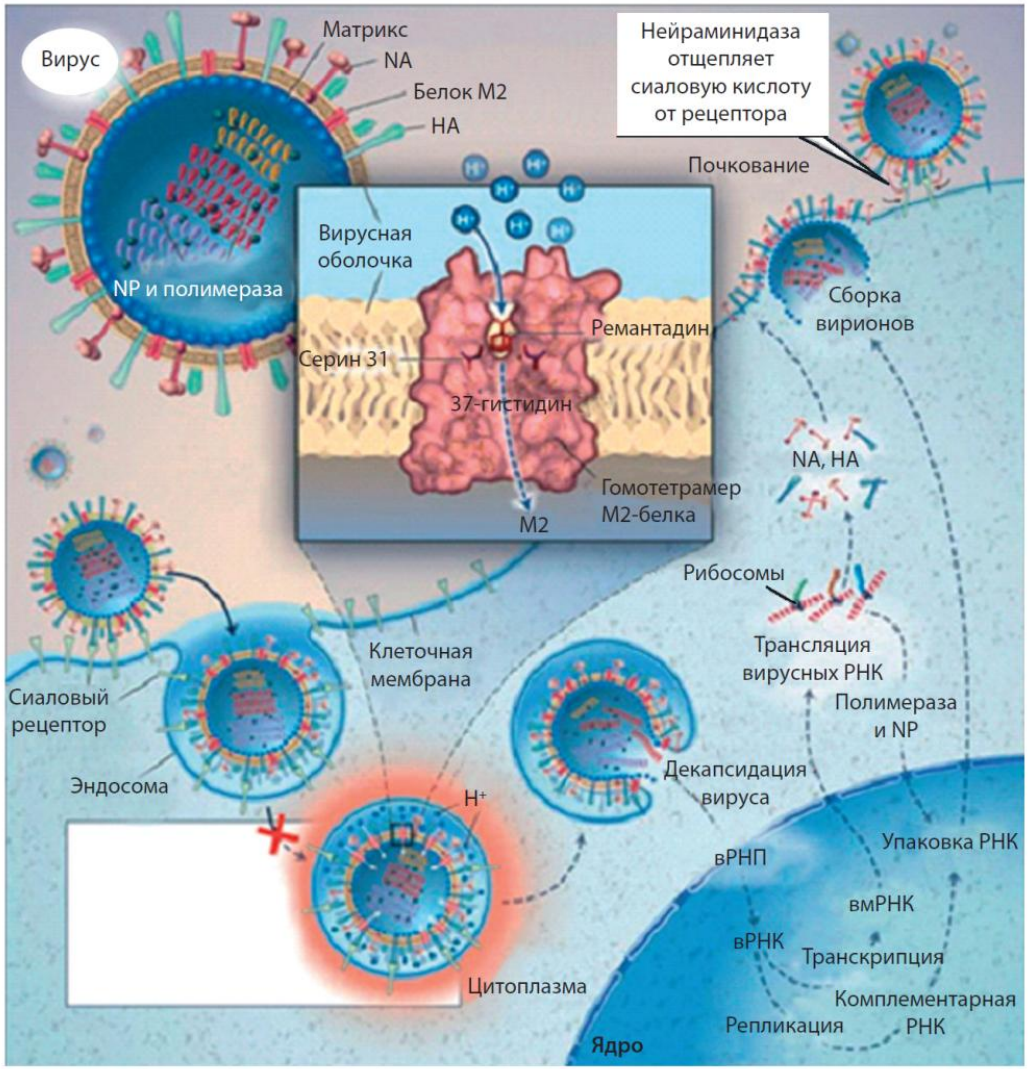
DrugBank ID	Name	Type	Year of first approval as an antiviral	Virus	Target(s)
DB00249	Idoxuridine	Small molecule	1963	HSV	DNA, viral thymidine kinase
DB00915	Amantadine	Small molecule	1966	Influenza virus	Viral matrix protein M2
DB00987	Cytarabine	Small molecule	1969	Herpesviruses	Human cytidine deaminase, human cytochrome P450 3A4, human deoxycytidine kinase, human 5'-nucleotidase, human deoxycytidylate deaminase
DB00194	Vidarabine	Small molecule	1976	HSV, VZV	Viral DNA polymerase, viral thymidine kinase, DNA
DB00811	Ribavirin	Small molecule	1980	HCV, RSV	Human inosine-5'-monophosphate dehydrogenase 1, human adenosine kinase, human cytosolic purine 5'-nucleotidase
DB00787	Aciclovir	Small molecule	1982	HSV1, HSV2, VZV	Viral DNA polymerase, viral thymidine kinase
DB00495	Zidovudine	Small molecule	1987	HIV	Viral reverse transcriptase
DB01004	Ganciclovir	Small molecule	1989	CMV	Viral DNA polymerase, viral thymidine kinase, DNA
-	Tromantadine	Small molecule	Later than 1990	HSV	Human glycoproteins
-	Interferons	Proteins	1990s	Hepatitis, etc.	Human IFNARs
DB00900	Didanosine	Small molecule	1991	HIV	Viral reverse transcriptase
DB00529	Foscarnet	Small molecule	1991	CMV, HSV	Viral DNA polymerase
DB00943	Zalcitabine	Small molecule	1992	HIV	Viral reverse transcriptase
DB00426	Famciclovir	Small molecule	1994	HSV, VZV	Viral DNA polymerase
DB00478	Rimantadine	Small molecule	1994	Influenza virus	Viral matrix protein M2
DB00649	Stavudine	Small molecule	1994	HIV	Viral reverse transcriptase
DB00709	Lamivudine	Small molecule	1995	HIV, HBV	Viral reverse transcriptase
DB00432	Trifluridine	Small molecule	1995	HSV	Viral thymidylate kinase
DB00577	Valaciclovir	Small molecule	1995	HSV, VZV, CMV	Viral DNA polymerase, viral thymidine kinase
DB00369	Cidofovir	Small molecule	1996	CMV	Viral DNA polymerase
DB00224	Indinavir	Small molecule	1996	HIV	Viral protease
DB00238	Nevirapine	Small molecule	1996	HIV	Viral reverse transcriptase
DB00299	Penciclovir	Small molecule	1996	HSV	Viral DNA polymerase, viral thymidine kinase
DB00503	Ritonavir	Small molecule	1996	HIV	Viral protease
DB01232	Saquinavir	Small molecule	1996	HIV	Viral protease
DB00705	Delavirdine	Small molecule	1997	HIV	Viral reverse transcriptase
DB00220	Nelfinavir	Small molecule	1997	HIV	Viral protease
DB01048	Abacavir	Small molecule	1998	HIV	Viral reverse transcriptase
DB00625	Efavirenz	Small molecule	1998	HIV	Viral reverse transcriptase
-	Fomivirsen	Oligonucleotide	1998	CMV	Viral mRNA
DB00110	Palivizumab	Humanized monoclonal antibody	1998	RSV	Viral fusion glycoprotein F0
DB00701	Amprenavir	Small molecule	1999	HIV	Viral protease
DB00198	Oseltamivir	Small molecule	1999	Influenza virus	Viral neuraminidase
DB00558	Zanamivir	Small molecule	1999	Influenza virus	Viral neuraminidase
DB00632	Docosanol	Small molecule	2000	HSV	Viral envelope glycoprotein
DB01601	Lopinavir	Small molecules	2000	HIV	Viral protease
DB00022	Peginterferon alfa-2b	Protein	2001	HCV	Human IFNARs
DB00300	Tenofovir	Small molecule	2001	HIV, HBV	Viral DNA
DB01610	Valganciclovir	Small molecule	2001	CMV	DNA
DB00718	Adefovir Dipivoxil	Small molecule	2002	HBV	Viral DNA polymerase
DB00008	Peginterferon alfa-2a	Protein	2002	Hepatitis	Human IFNARs
DB01072	Atazanavir	Small molecule	2003	HIV	Viral protease
DB00879	Emtricitabine	Small molecule	2003	HIV	Viral reverse transcriptase
DB00109	Enfuvirtide	Protein	2003	HIV	Viral envelope glycoprotein
DB01319	Fosamprenavir	Small molecule	2003	HIV	Viral protease
DB00442	Entecavir	Small molecule	2005	HBV	DNA
DB00932	Tipranavir	Small molecule	2005	HIV	Viral protease
DB01264	Darunavir	Small molecule	2006	HIV	Viral protease
DB01265	Telbivudine	Small molecule	2006	HBV	Viral DNA polymerase, DNA
DB04835	Maraviroc	Small molecule	2007	HIV	Human CCR5
DB06817	Raltegravir	Small molecule	2007	HIV	Viral integrase
DB06414	Etravirine	Small molecule	2008	HIV	Viral reverse transcriptase
DB08873	Boceprevir	Small molecule	2011	HCV	Viral NS3 protein
DB08864	Rilpivirine	Small molecule	2011	HIV	Viral reverse transcriptase
DB05521	Telaprevir	Small molecule	2011	HCV	Virus NS3-4A protease

“One drug, one bug”



Marston et al., 2014

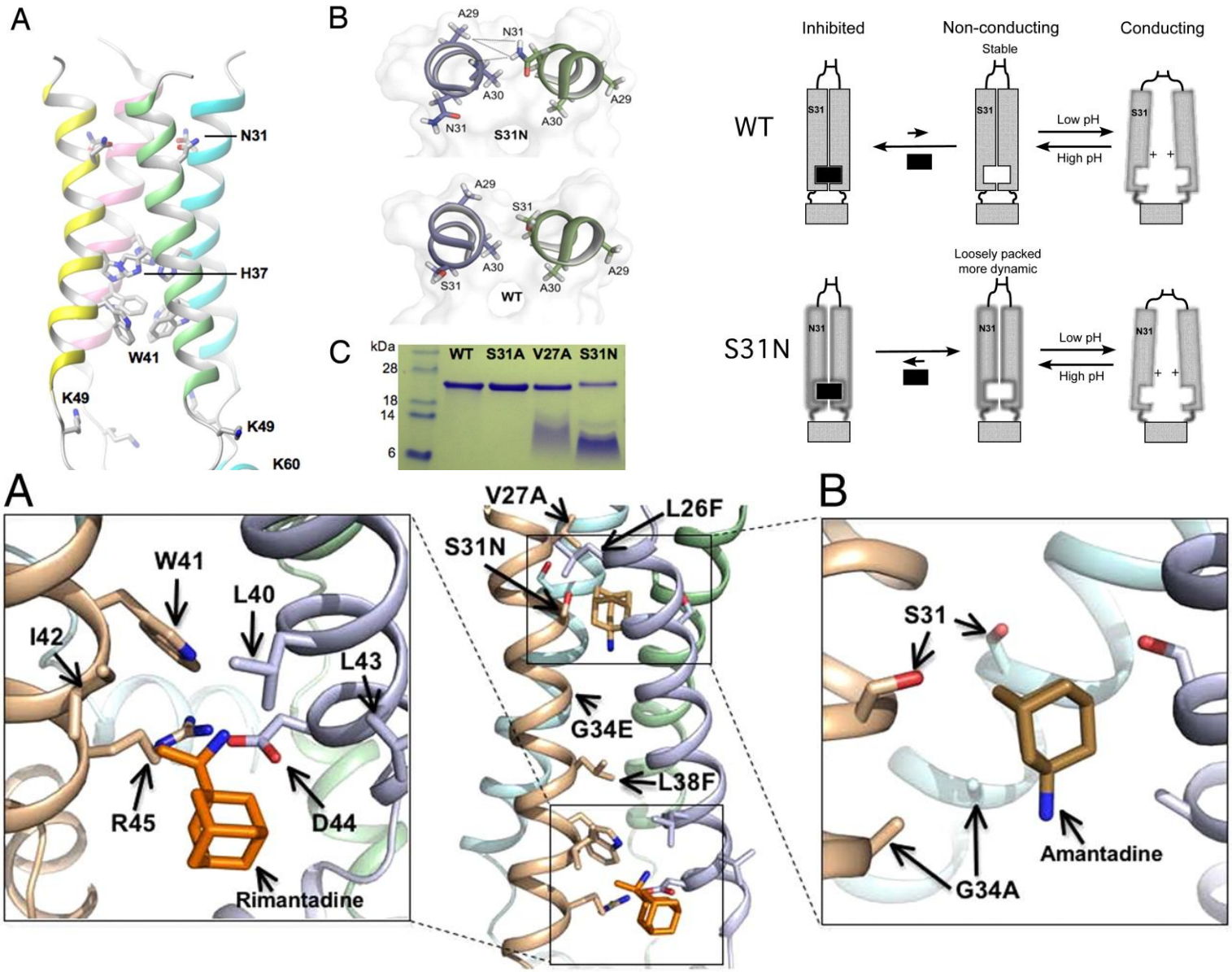
Препараты для лечения гриппа



Действующее вещество	Наименование препарата
Ингибиторы M2	
Амантадин	Симметрел
Ремантадин	Флумадин
Ингибиторы NA	
Озелтамивир	Тамифлю
Занамивир	Реленза
Перамивир	
Комбинированные	
Умифеновир	Арбидол

Формирование и быстрое распространение в человеческой популяции вирусов гриппа, устойчивых к действию имеющихся противовирусных препаратов

Proposed adamantane binding sites of the M2 channel.

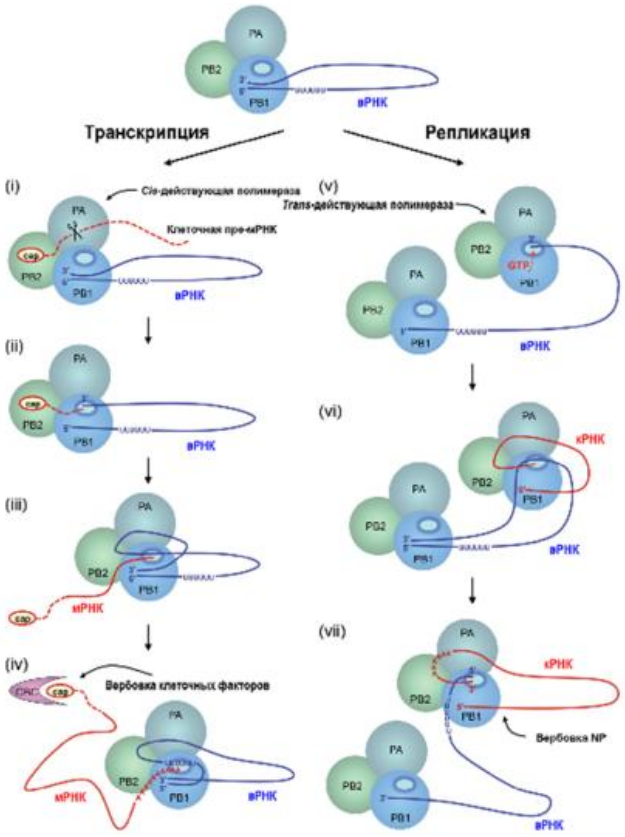


Rafal M. Pielak et al. PNAS 2009;106:7379-7384

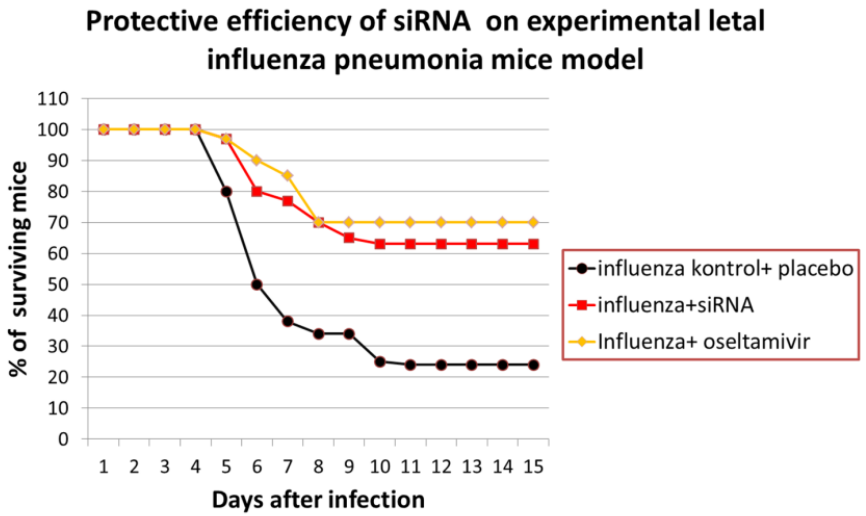
PNAS

Направленная разработка лекарственных препаратов на основе пептидов и малых РНК

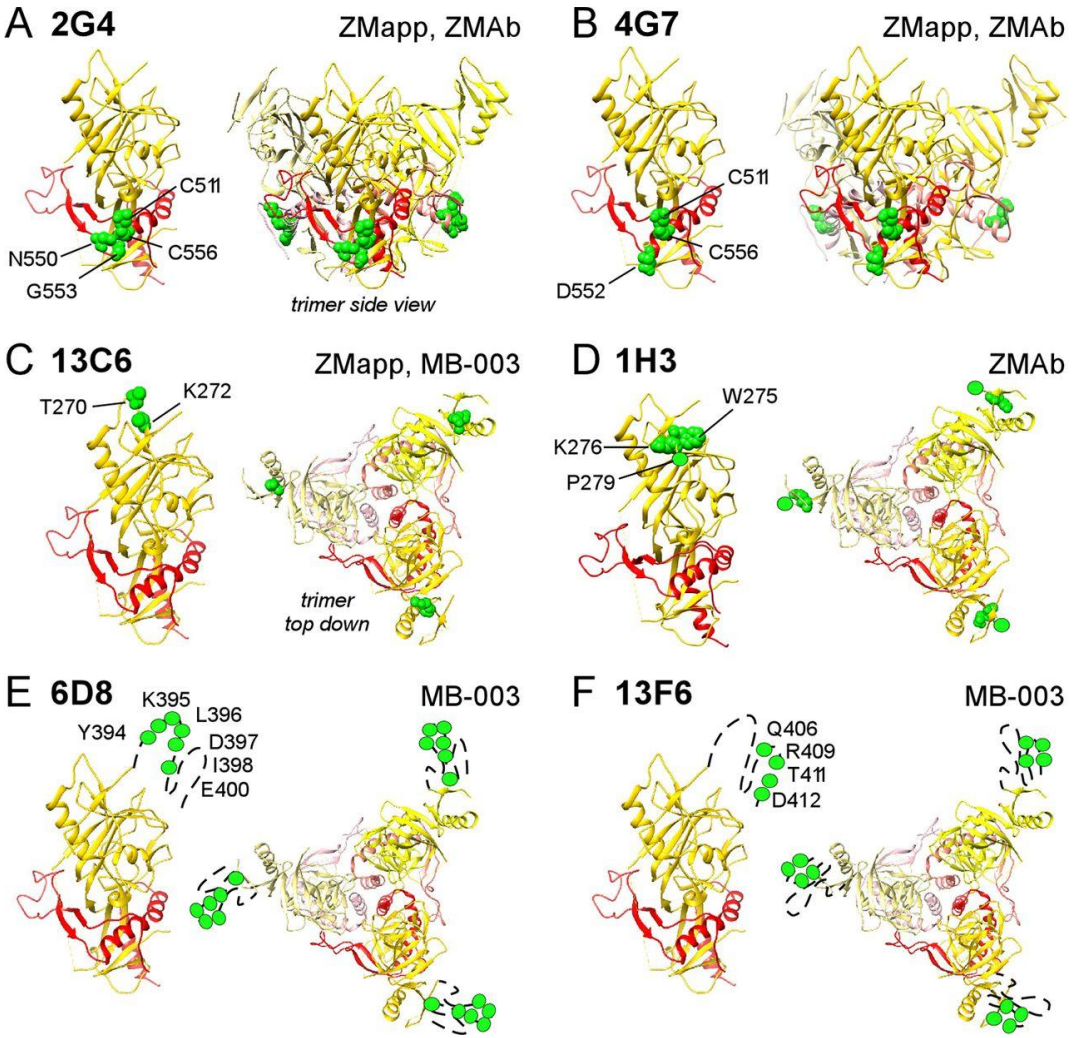
РНК-зависимая РНК-полимераза вируса гриппа А



I	PA-44-1	UGCUUCAAUCCGAUGAUUGdTdT
	PA-44-2	CAAUCAUCGGAUUGAAGCAdTdT
II	PA-1630-1	UGAGCCACACAAAUGGGAA
	PA-1630-2	UCCCAUUUGUGUGGCUCGU
III	PA-2069-1	GCAAUUGAGGAGUGCCUGAdTdT
	PA-2069-2	UCAGGCACUCCUCAAUUGCdTdT
IV	PA-2100-1	GAGGAGUGCCUGAUUAAUGA
	PA-2100-2	AUUAAUCAGGCACUCCUCga
V	PA-2110-1	UGAUCCCUGGGUUUUGCUUdTdT
	PA-2110-2	AAGCAAAACCCAGGGAUCAdTdT
Uni	Uni-R-1	CCUUGUUUCUACUGAUCACGCGU
	Uni-R-2	CGCGUGAUCAGCAAAAGCAGG



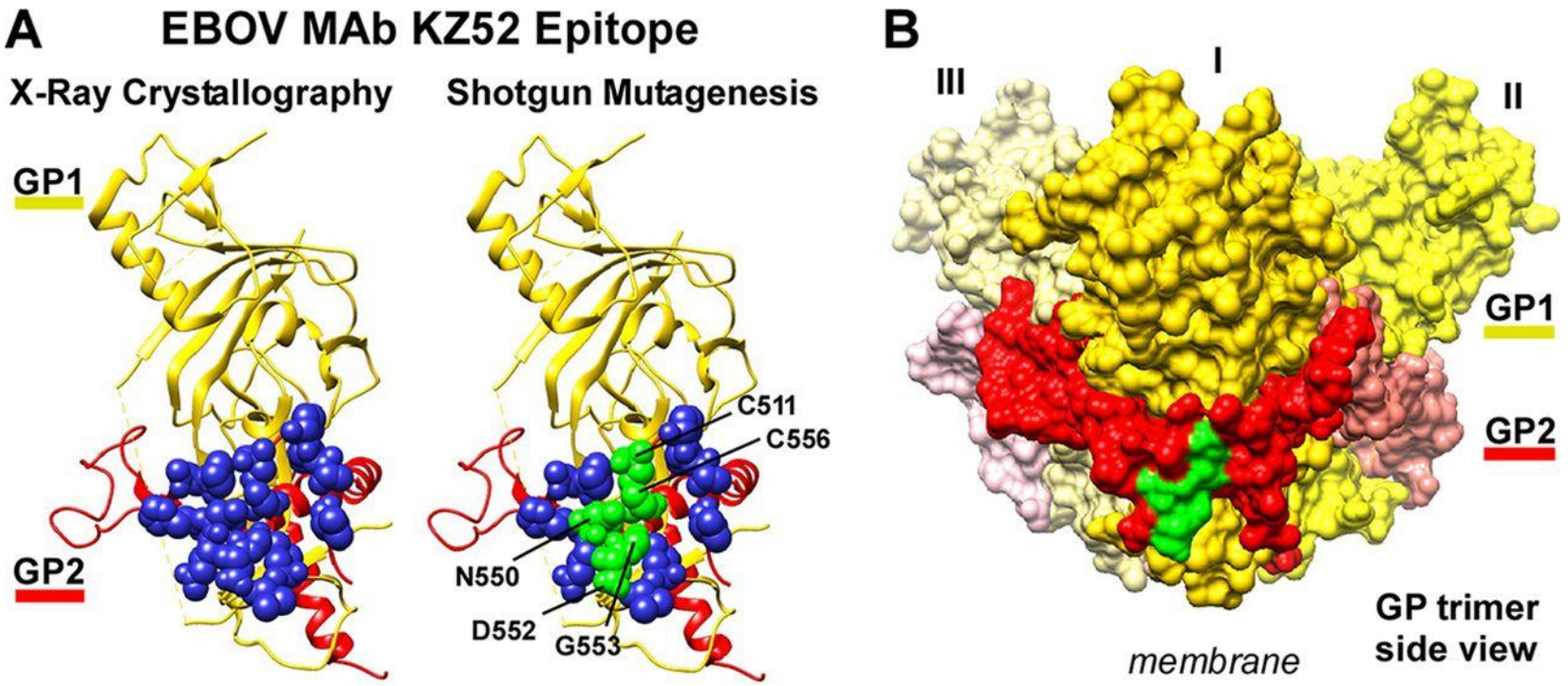
Epitope mapping of EBOV cocktail MAbs.



Edgar Davidson et al. J. Virol. 2015;89:10982-10992

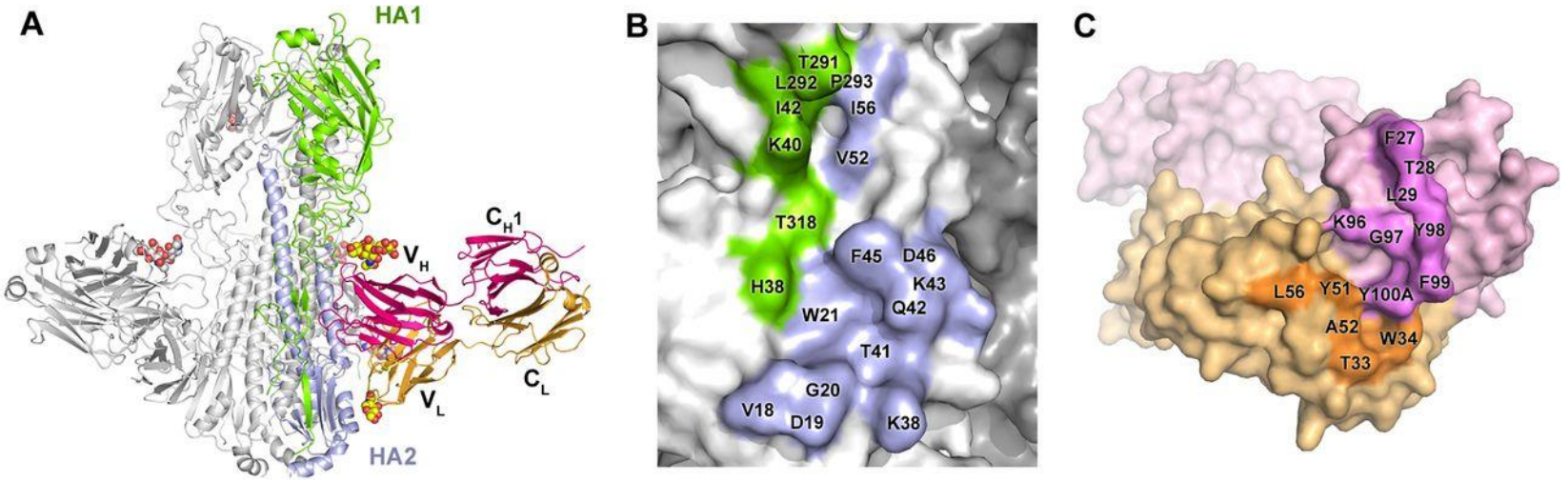
Journal of Virology

Mapping of MAb KZ52 identifies the energetically critical epitope residues of the interaction.



Edgar Davidson et al. J. Virol. 2015;89:10982-10992

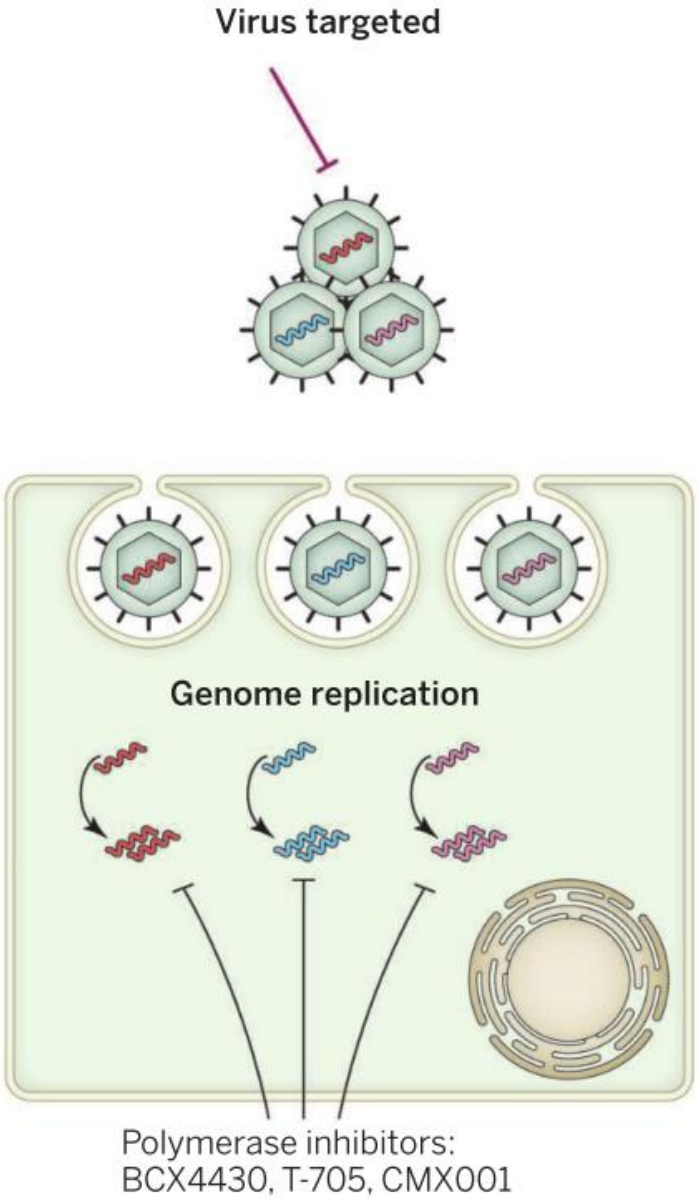
C179 binds an epitope in the HA stem.



Cyrille Dreyfus et al. J. Virol. 2013;87:7149-7154

Journal of Virology

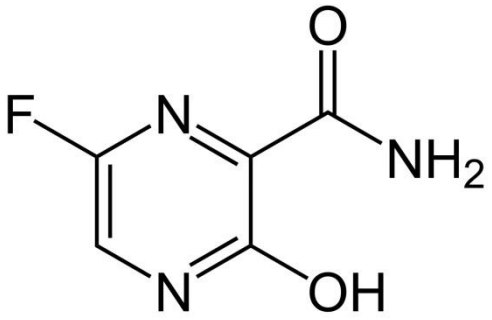
“One drug, multiple bugs”

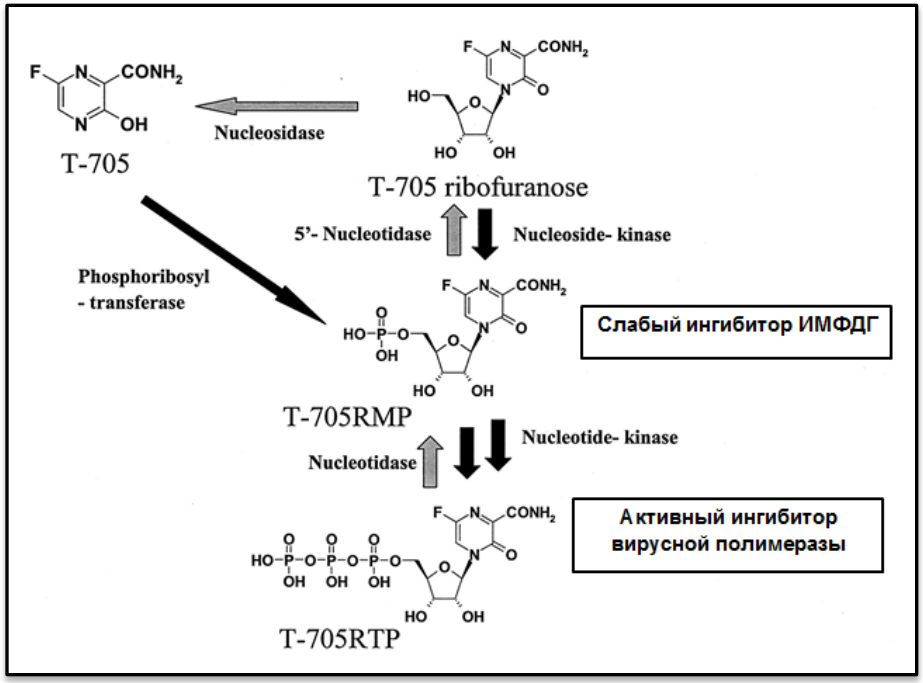


Marston et al., 2014

Фавипиравир

T-705 (5-фтор-2-оксо-1H-пиразин-3-карбоксамид) – это препарат из группы пиразинокабоксамидов, являющийся ингибитором полимеразы вируса гриппа





Структура T-705 и пути внутриклеточного превращения в трифосфат – субстрат вирусной полимеразы

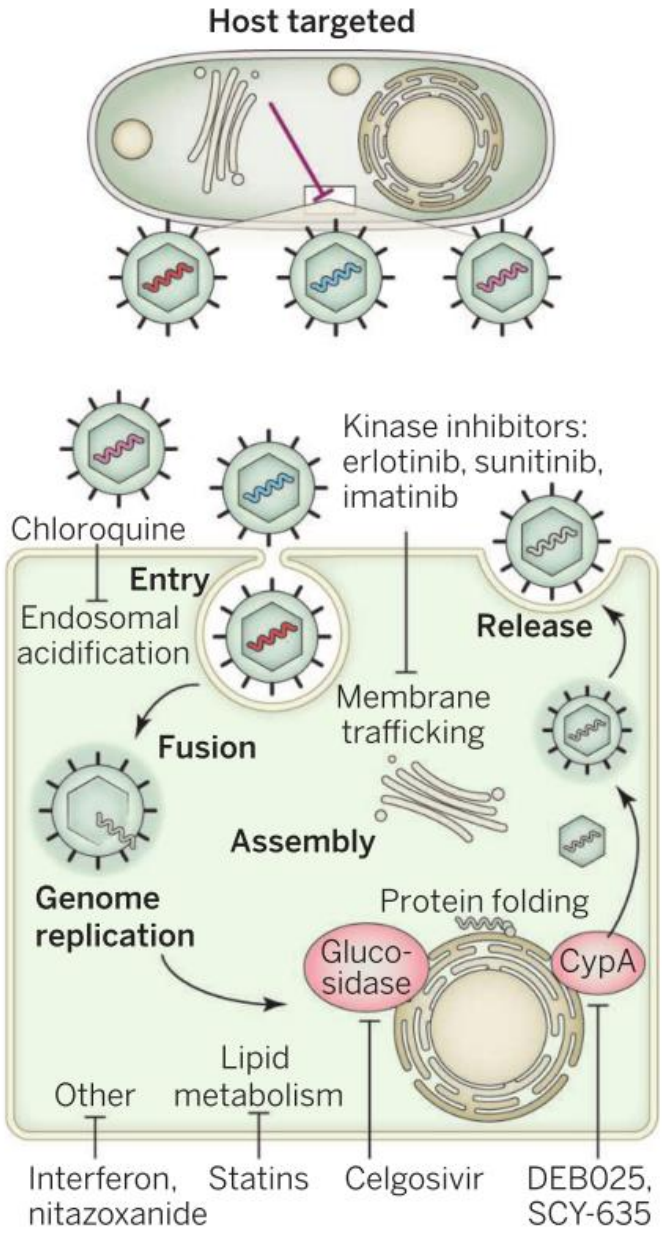
Концепция вироклетки («virocell»)

«*The virocell (or ribovirocell), being a cellular organism, corresponds to the 'living form' of the virus, whereas virions are in fact the equivalent of seeds or spores for multicellular organisms*»

(Patrick Forterre. 2012. The Virocell Concept. eLS).

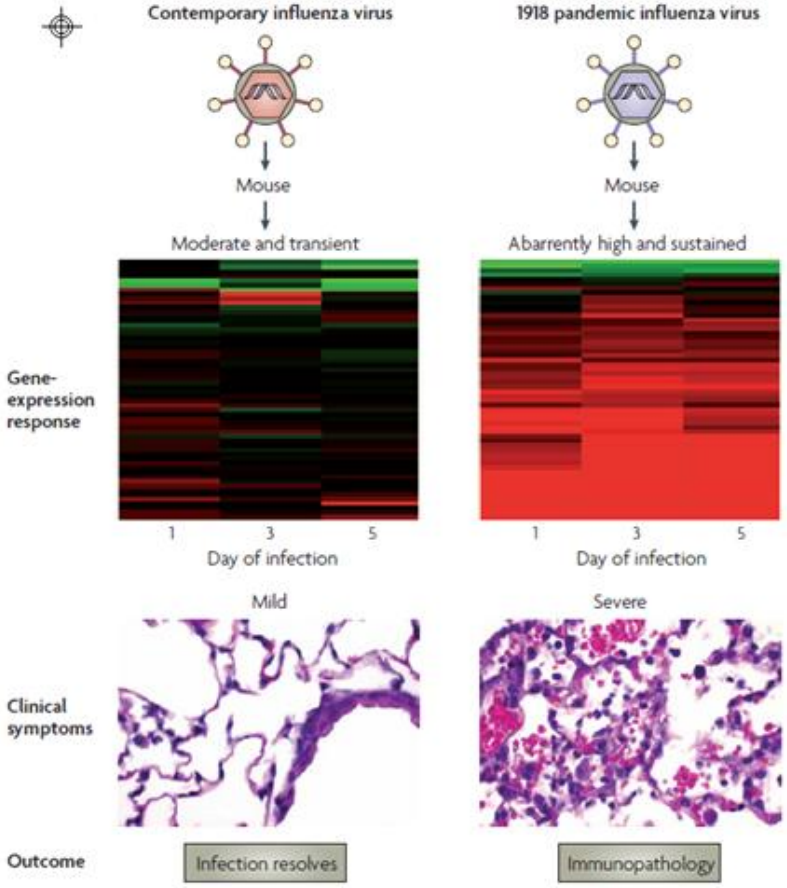
Концепция вироклетки направлена на унификацию клеточного и вирусного миров в единую сеть, основанную на клеточной теории жизни.

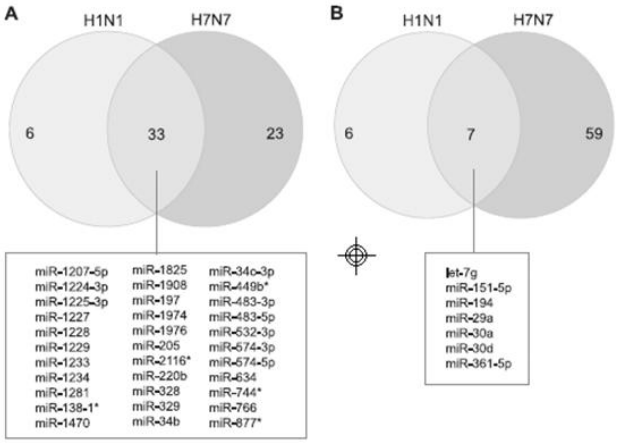
«*The virocell concept tells us that viruses are too important for life evolution and cell biology to be only interesting for virologists*»

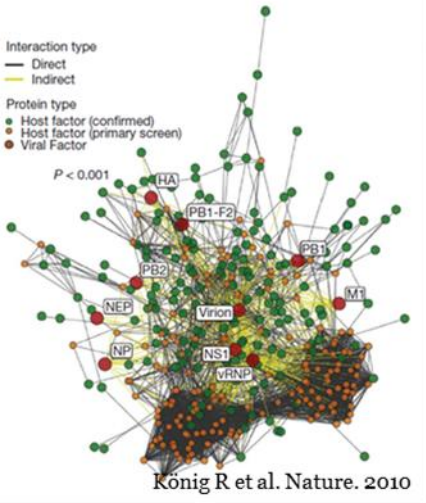


Marston et al., 2014

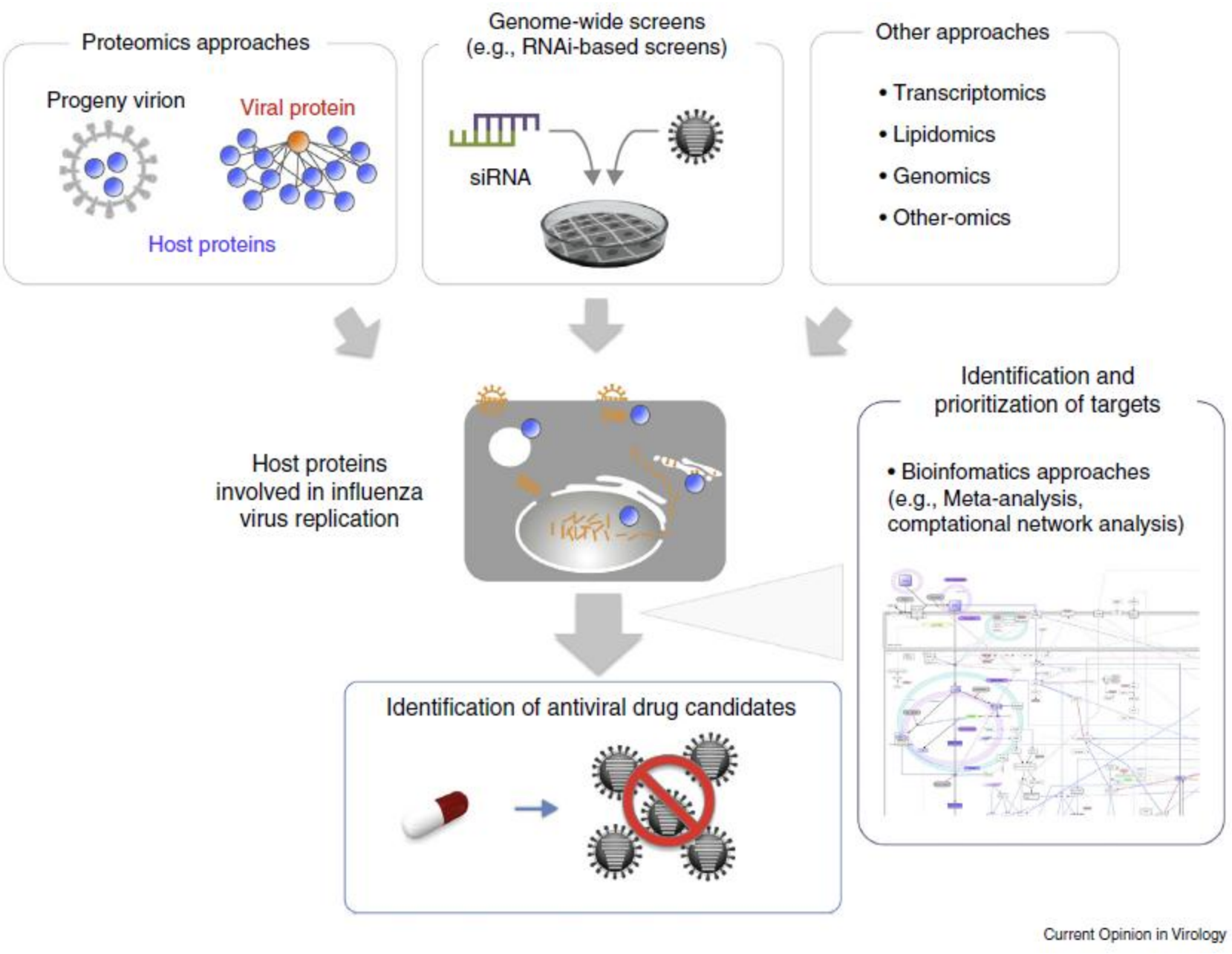
Методы высокопроизводительного анализа (microarray, NGS, масс-спектрометрия, siРНК-скрининг ..)



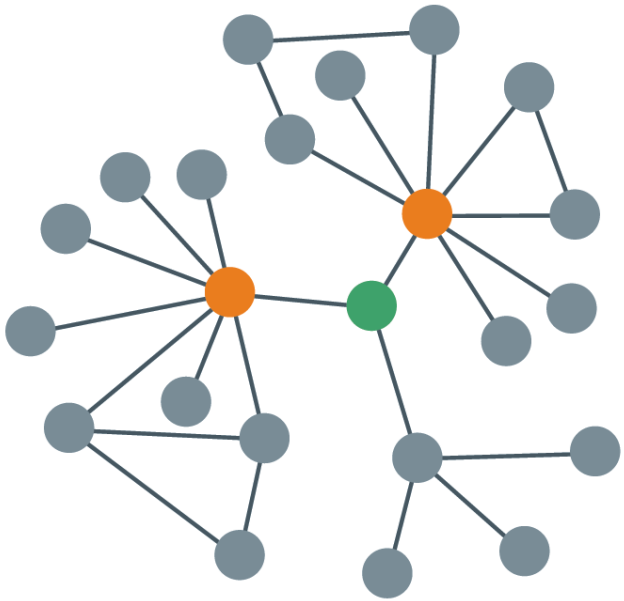




König R et al. Nature. 2010


Proteomics approaches
Progeny virion
Viral protein
Host proteins
Genome-wide screens
(e.g., RNAi-based screens)
siRNA
Other approaches
• Transcriptomics
• Lipidomics
• Genomics
• Other-omics
Host proteins
involved in influenza
virus replication
Identification and
prioritization of targets
• Bioinfomatics approaches
(e.g., Meta-analysis,
comptational network analysis)
Identification of antiviral drug candidates
Current Opinion in Virology

Анализ методами системной вирусологии

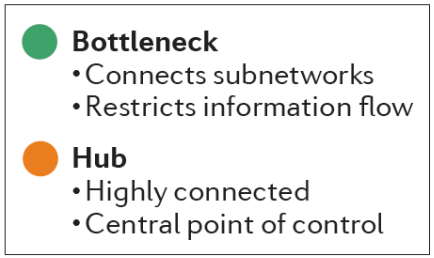


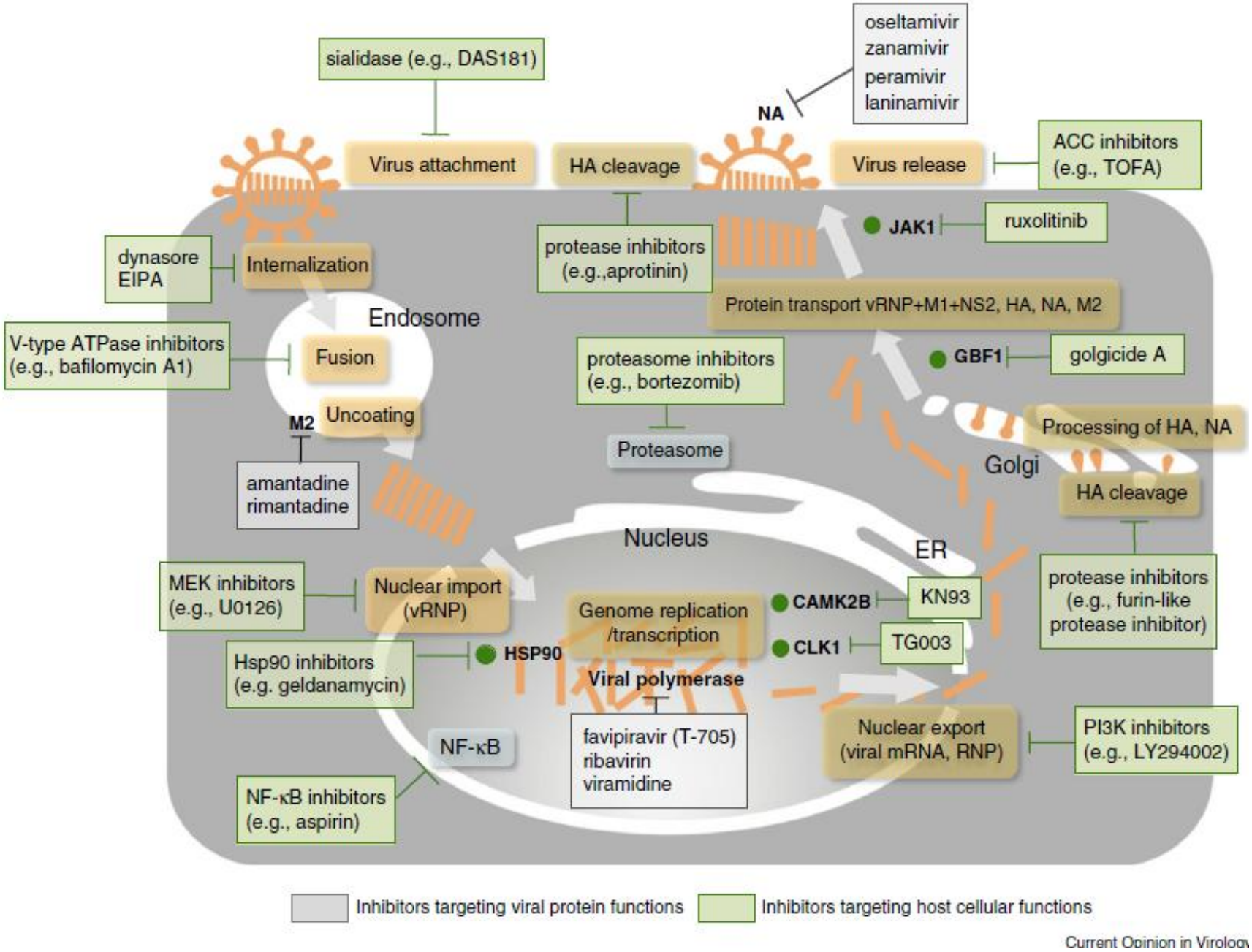
Модель взаимодействий между вирусом и организмом хозяина

Изучение, осмысление и предсказание молекулярных механизмов протекания инфекции

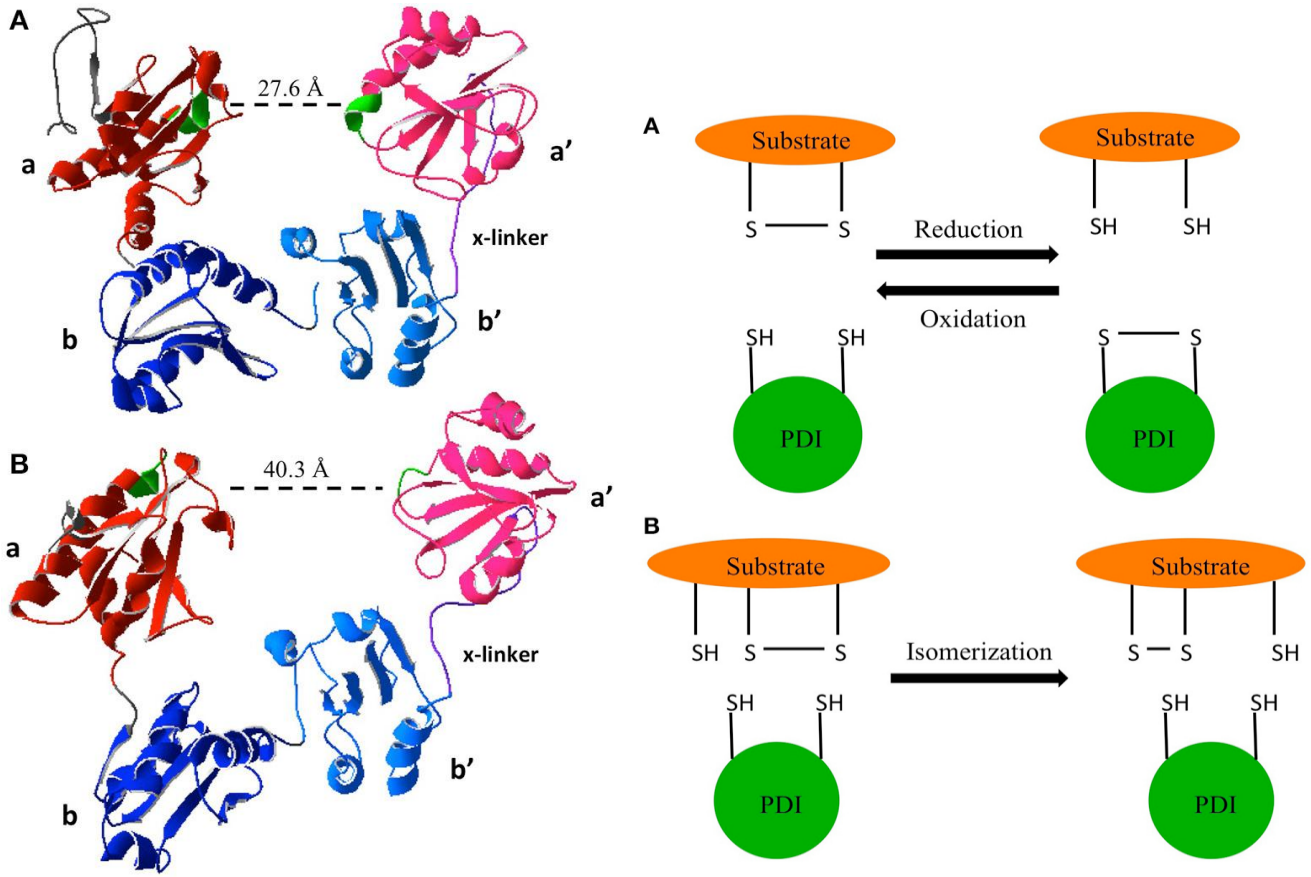
Определение ключевых регуляторов инфекции (индивидуальные гены, клеточные взаимодействия, метаболические пути и. т.п.)

Мишени для разработки новых противовирусных средств, диагностические маркеры, оценка эффективности вакцин

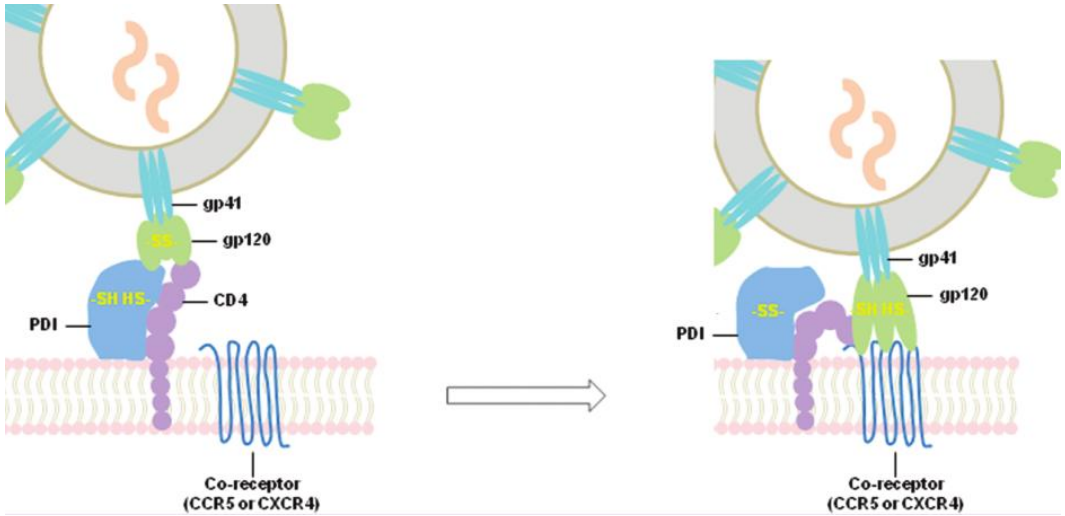



sialidase (e.g., DAS181)
oseltamivir
zanamivir
peramivir
laninamivir
NA
Virus attachment
HA cleavage
Virus release
ACC inhibitors
(e.g., TOFA)
dynasore
EIPA
Internalization
protease inhibitors
(e.g.,aprotinin)
JAK1
ruxolitinib
Protein transport vRNP+M1+NS2, HA, NA, M2
Endosome
V-type ATPase inhibitors
(e.g., bafilomycin A1)
Fusion
proteasome inhibitors
(e.g., bortezomib)
GBF1
golgicide A
M2
Uncoating
Proteasome
Processing of HA, NA
Golgi
amantadine
rimantadine
HA cleavage
Nucleus
ER
MEK inhibitors
(e.g., U0126)
Nuclear import
(vRNP)
Genome replication
/transcription
CAMK2B
KN93
protease inhibitors
(e.g., furin-like
protease inhibitor)
CLK1
TG003
Hsp90 inhibitors
(e.g. geldanamycin)
HSP90
Viral polymerase
NF-κB
favipiravir (T-705)
ribavirin
viramidine
Nuclear export
(viral mRNA, RNP)
PI3K inhibitors
(e.g., LY294002)
NF-κB inhibitors
(e.g., aspirin)
Inhibitors targeting viral protein functions
Inhibitors targeting host cellular functions
Current Opinion in Virology

Протеиндисульфидизомераза (PDI) – клеточный фермент, катализирующий образование нативных дисульфидных связей в синтезируемых пептидах, а также являющийся молекулярным шапероном, участвующим в процессе фолдинга белковых цепей.



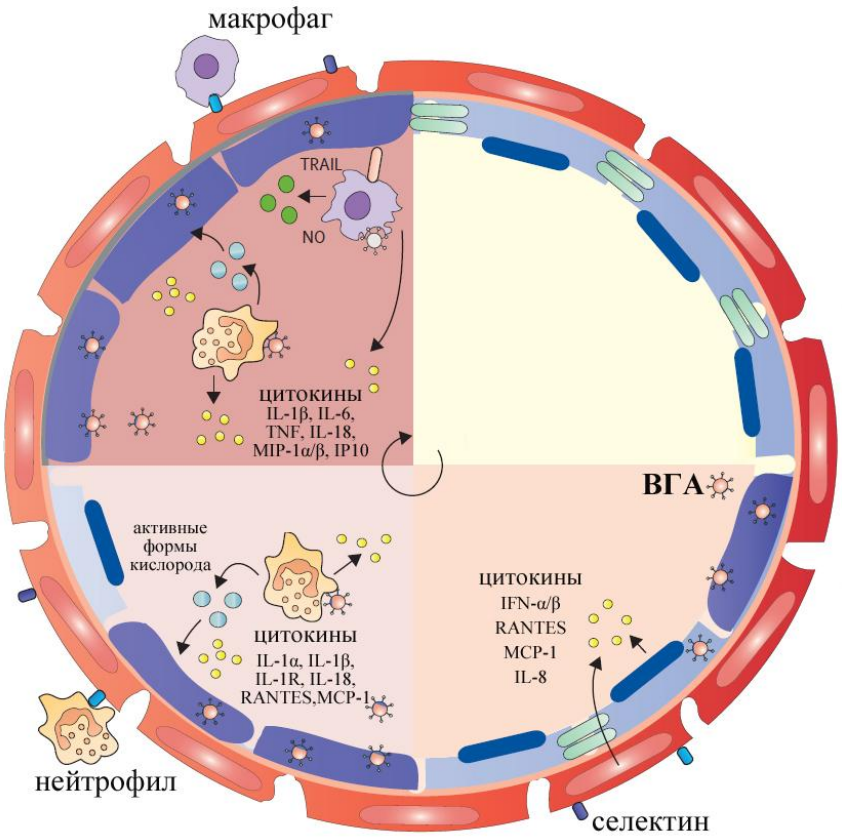
Восстановительная активность поверхностной PDI важна для при вхождении ВИЧ-1 в клетку

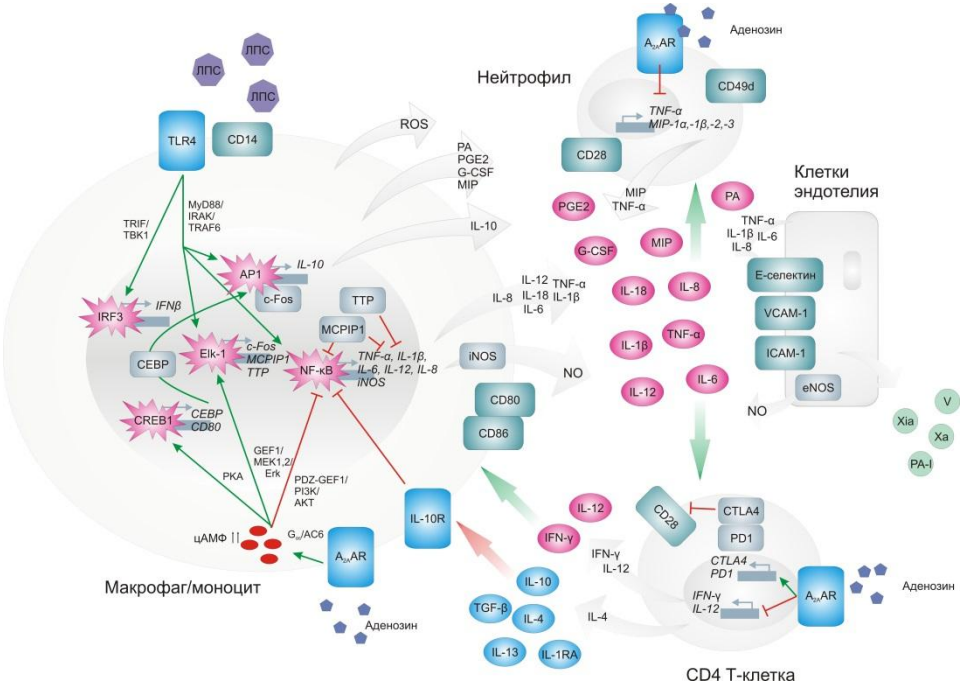


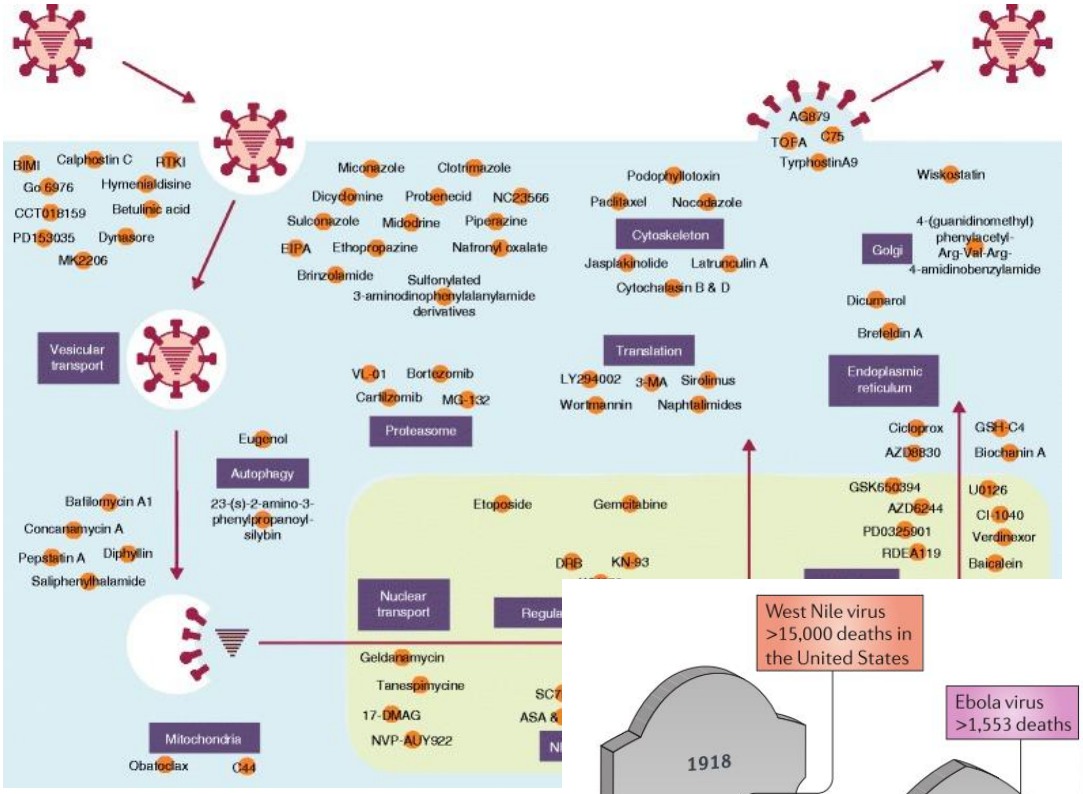
PDI кластеризуется в области CD4, первичного рецептора ВИЧ-1, который имеет разные сайты связывания с PDI и gp120. gp120 ВИЧ-1 связывается с CD4, после чего происходит катализируемое PDI восстановление по крайней мере двух из девяти дисульфидных связей gp120. Восстановление стабилизирующих структуру дисульфидных связей gp120 приводит к крупным конформационным изменениям, способствующим взаимодействию gp120 с корецепторами CCR5 и CXCR4.

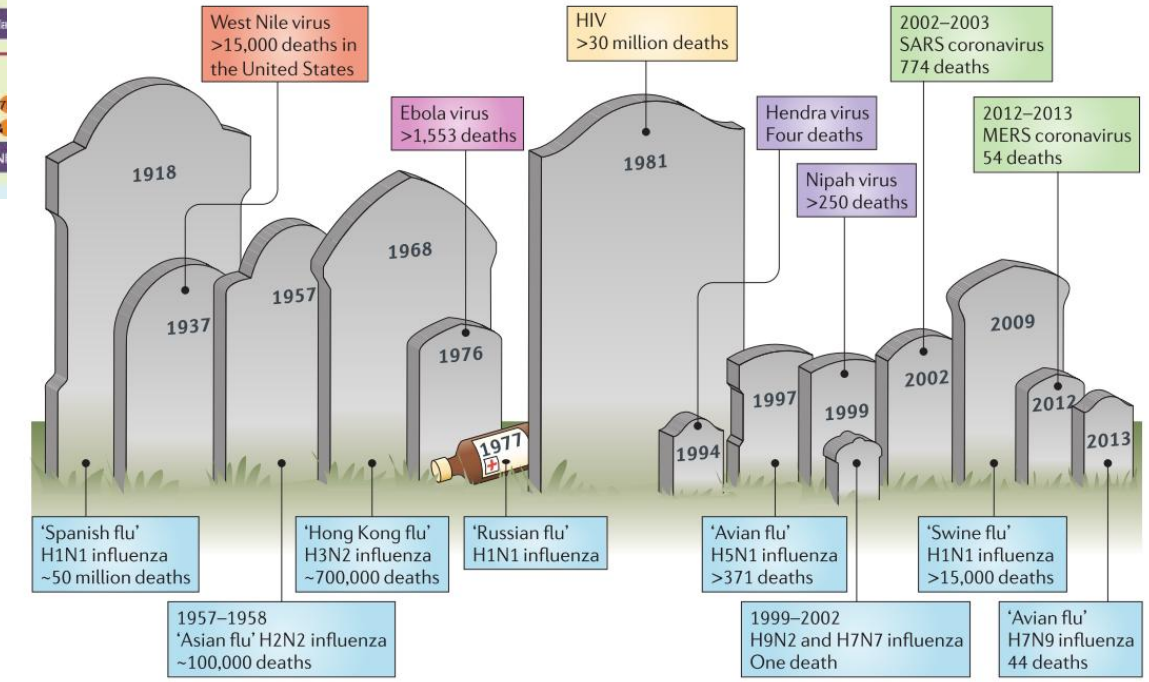
Khan et al., 2011

Вирус-индуцированный дисбаланс иммунного ответа






AG879
TQFA
C75
TyrphostinA9
BIMI
Calphostin C
RTKI
Go 6976
Hymenialdisine
CCT018159
Betulinic acid
PD153035
Dynasore
MK2206
Miconazole
Clotrimazole
Dicyclomine
Probenecid
NC23566
Sulconazole
Midodrine
Piperazine
EIPA
Ethopropazine
Natronyl oxalate
Brinzolamide
Sulfonylated 3-aminodinophenylalanylamide derivatives
Podophyllotoxin
Paclitaxel
Nocodazole
Cytoskeleton
Jasplakinolide
Latrunculin A
Cytochalasin B & D
Wiskostatin
Golgi
4-(guanidinomethyl) phenylacetyl-Arg-Val-Arg-4-amidinobenzylamide
Dicumarol
Brefeldin A
Endoplasmic reticulum
Vesicular transport
Translation
LY294002
3-MA
Sirolimus
Wortmannin
Naphtalimides
VL-01
Bortezomib
Carfilzomib
MG-132
Proteasome
Eugenol
Autophagy
23-(s)-2-amino-3-phenylpropanoyl-silybin
Ciclopirox
AZD8830
GSK650394
AZD6244
PD0325901
RDEA119
GSK-3-C4
Biochanin A
U0126
CI-1040
Verdinexor
Baicalein
Bafilomycin A1
Concanamycin A
Pepstatin A
Diphyllin
Saliphenylhalamide
Etoposide
Gemcitabine
DRB
KN-93
Nuclear transport
Geldanamycin
Tanespimycine
17-DMAG
NVP-AUY922
Mitochondria
Obatoclax
C44


West Nile virus
>15,000 deaths in the United States
HIV
>30 million deaths
2002–2003
SARS coronavirus
774 deaths
Ebola virus
>1,553 deaths
Hendra virus
Four deaths
2012–2013
MERS coronavirus
54 deaths
Nipah virus
>250 deaths
1918
1937
1957
1968
1976
1977
1981
1994
1997
1999
2002
2009
2012
2013
'Spanish flu'
H1N1 influenza
~50 million deaths
'Hong Kong flu'
H3N2 influenza
~700,000 deaths
'Russian flu'
H1N1 influenza
'Avian flu'
H5N1 influenza
>371 deaths
'Swine flu'
H1N1 influenza
>15,000 deaths
1957–1958
'Asian flu' H2N2 influenza
~100,000 deaths
1999–2002
H9N2 and H7N7 influenza
One death
'Avian flu'
H7N9 influenza
44 deaths