医 学 病 毒 学

周溪

1. 引言及课程简介
2. 肝炎病毒（丙型、甲型及戊型等）
3. 虫媒病毒（了解虫媒病毒的种类、感染及复制机制、与宿主相互作用等）
4. 肠道病毒（了解小 RNA 病毒的基本特征;重点掌握肠道病毒 71 型(EV71）的特征、感染及复制机制，以及致病机制）
5. 痘病毒与生物反恐（天花、牛痘病毒）
6. 抗病毒免疫（抗病毒天然免疫，获得性免疫，病毒逃避免疫监控的机制）

Chapter 1. Introduction to medical virology

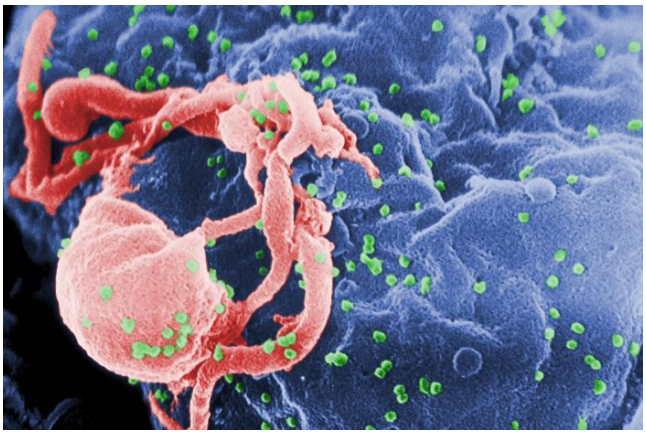
第一章 医学病毒学导论

The word "virus" appeared in 1599 and originally meant "venom".
Small size: 20-400 nm
Viruses are submicroscopic, obligate intracellular parasites.
Viral proteins and nucleic acids
Viruses themselves can not grow or undergo division
Viruses lack the genetic information that encodes apparatus necessary for the generation of metabolic energy or for protein synthesis
“病毒”一词在 1599 年出现，最初是指“毒液”。
体积小：20-400nm
病毒是亚显微镜，属于细胞内寄生虫。
病毒蛋白和核酸
病毒本身不能生长或分裂
病毒缺乏编码产生代谢能或蛋白质合成所必需的设备的遗传信息

Subviral particles
Infectious entities notably smaller and simpler than viruses
Viroids: naked circular RNA molecules infecting plants
Satellites: nucleic acid molecules with or without a capsid that require a helper virus for infection and reproduction
Prions: proteins that can exist in a pathological conformation that induces other prion molecules to assume that same conformation
亚病毒颗粒
传染性实体明显比病毒更小和更简单
病毒：感染植物的裸圆形 RNA 分子
卫星：具有或不具有需要辅助病毒感染和繁殖的衣壳的核酸分子
朊病毒：可以以诱导其他朊病毒分子呈现相同构象的病理构象存在的蛋白质

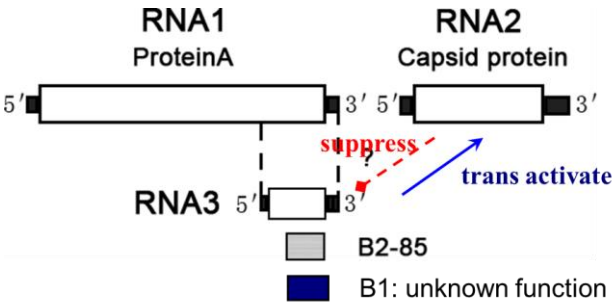
What does virology study:
Virology is the study of viruses and virus-like agents
Their structure, classification and evolution
Their ways to infect and exploit host cells for virus reproduction
Their interaction with host organism physiology and immunity
The diseases they cause
The techniques to isolate and culture them
Their use in research and therapy.
Virology is considered to be a subfield of microbiology or of medicine.
病毒学研究内容：

病毒学是病毒和病毒样物质的研究
他们的结构，分类和演变
他们的方式来感染和利用宿主细胞进行病毒繁殖
它们与宿主生物的生理和免疫的相互作用
他们造成的疾病
分离和培养它们的技术
它们用于研究和治疗。
病毒学被认为是微生物学或药物学的一个子领域。

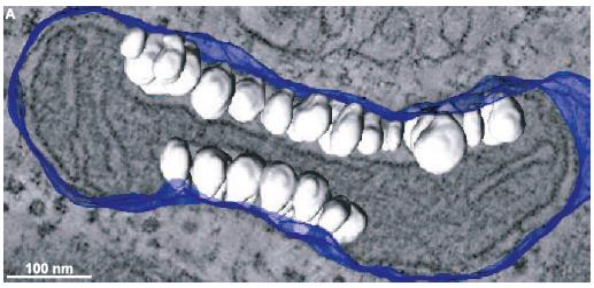


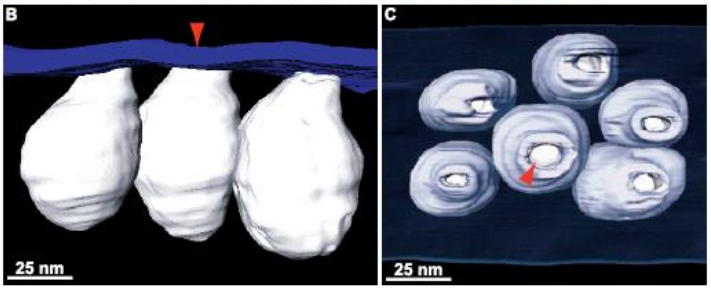
来自培养的淋巴细胞的 HIV-1 病毒体的扫描电子显微照片

Simplicity is beautiful
Example 1: Nodavirus genome and proteins
简单是美丽的
例 1：野田村病毒基因组和蛋白质

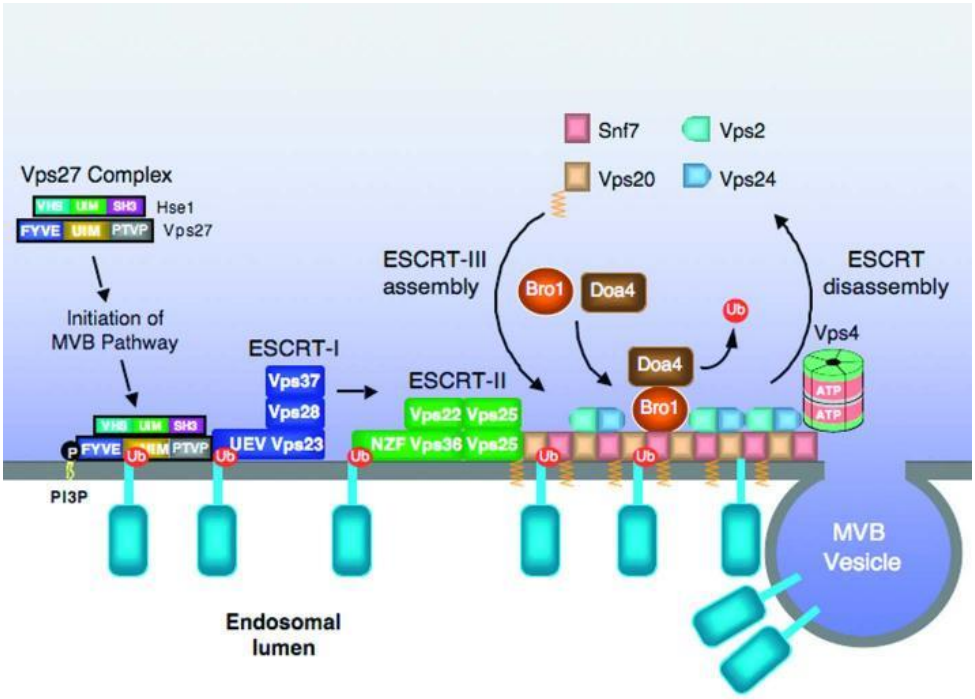


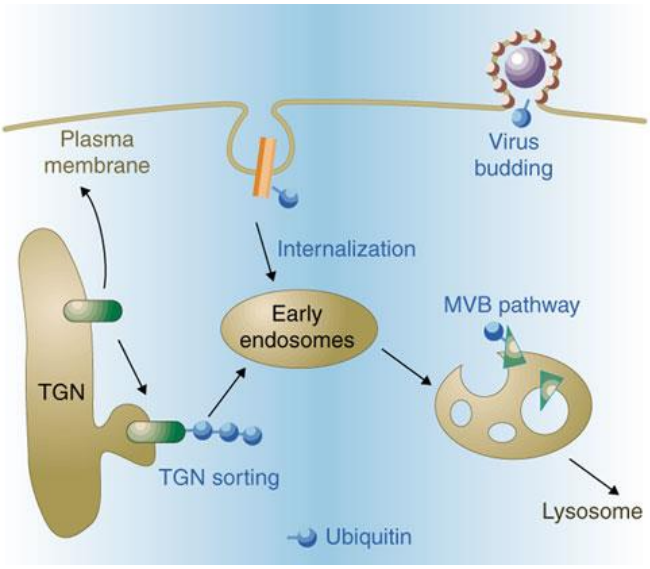
Example 2: 3D maps of nodavirus-modified mitochondria
例 2：野田村病毒修饰的线粒体的 3D 图





Example 3: Retrovirus budding by hijacking ESCRT machinery
例 3：劫持 ESCRT 机械的逆转录病毒出芽





Hosts of viruses
Human, Vertebrate animal, Inverbrate animal (insect), Plant, Fungi, Bacteria,
病毒的寄主
人类，脊椎动物，无脊椎动物（昆虫），植物，真菌，细菌，

What does medical virology study?

Viruses causing human diseases
Medical virology ≠ human virology
Antiviral therapies
Viral technologies that have medical implications
什么是医学病毒学研究？
引起人类疾病的病毒
医学病毒学≠人类病毒学
抗病毒治疗
具有医学意义的病毒技术

History

3700 BC, First written record of a virus infection (a priest with poliomyelitis), Memphis, ancient Egypt;
1196 BC, Pharaoh Ramses V, smallpox
1000 BC, Smallpox was described as a contagious diseases by Chinese practitioners;
A very early form of vaccination known as variolation was developed several thousand years ago in China.
In 1717, Lady Mary Wortley Montagu observed the practice in Istanbul and attempted to popularize it in Britain, but encountered considerable resistance.
In 1796 Edward Jenner developed a much safer method, using cowpox to successfully immunize a young boy against smallpox, and this practice was widely adopted.
Vaccinations against other viral diseases followed, including the successful rabies vaccination by Louis Pasteur in 1886. The nature of viruses however was not clear to these researchers.
In 1892, Russian scientist Dimitri Ivanovski showed "filterable agent" caused tobacco mosaic disease;
The existence of viruses that infect bacteria (bacteriophages) was first recognized by Frederick Twort in 1911, and, independently, by Felix d'Herelle in 1917.
1918 Spanish flu killed 3% to 6% of the entire global population (25 million death in its first 25 weeks, and 50—100 million in total); In late 1918, French scientists showed that a "filter-passing virus" could transmit the disease to people and animals;
In 1949 John F. Enders, Thomas Weller and Frederick Robbins reported growth of poliovirus in cultured human embryonal cells (They won Nobel Prize in 1954);
This work aided Jonas Salk in deriving a polio vaccine from deactivated polio viruses; this vaccine was shown to be effective in 1955. (Lasker Award in1956; founder of Salk Institute)
In 1963, the Hepatitis B virus was discovered by Baruch Blumberg (1976 Nobel Prize winner)
In 1965, Howard Temin described the first retrovirus (1975 Nobel Prize winner)
In 1975 the functioning of oncoviruses was clarified considerably
1976, the first recorded outbreak of Ebola hemorrhagic fever, a highly lethal virally transmitted disease.
In 1979, A worldwide vaccination campaign led by UN WHO resulted in the eradication of smallpo
In 1982, Stanley Prusiner discovered prions (1997 Nobel)
The first cases of AIDS were reported in 1981, and HIV, the retrovirus causing it, was identified in 1983 by Robert Gallo (Lasker) and Luc Montagnier (Nobel).
In 1987, Hepatitis C virus was identified
历史
公元前 3700 年，病毒感染（脊髓灰质炎牧师）的首个书面记录，孟菲斯，古埃及;
公元前 1196 年，法老拉姆西斯五世，天花
公元前 1000 年，天蝎被中国医生描述为传染病;
几千年前在中国开发了一种非常早期的接种疫苗，被称为变种。
在 1717 年，玛丽·沃特利·蒙塔古女士观察了伊斯坦布尔的做法，并试图在英国普及，但遇到了相当大的阻力。
爱德华·仁纳在 1796 年开发了一种更安全的方法，使用牛痘来成功地免疫一名年轻男孩对天花免疫，这种做法被广泛采用。

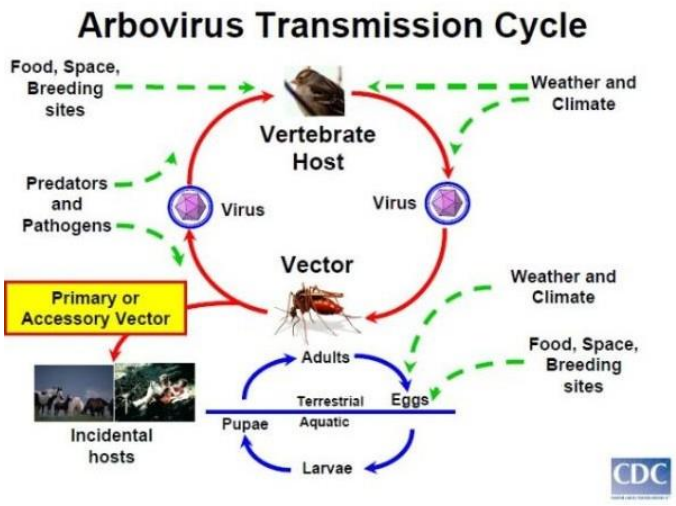
随后接种针对其他病毒性疾病的疫苗接种，包括路易斯·巴斯德于 1886 年成功的狂犬病疫苗接种。然而，这些研究人员尚不清楚病毒的性质。
1892 年，俄罗斯科学家 Dimitri Ivanovski 表示“过滤剂”引起烟草花叶病;
感染细菌（噬菌体）的病毒的存在于 1911 年被弗雷德里克·温特（Frederick Twort）首次承认，并于 1917 年由 Felix d'Herelle 独立承认。
1918 年，西班牙流感在全球人口中死亡 3％至 6％（前 25 周为 2500 万人死亡，总共为 5 亿至 1 亿人）;
1918 年末，法国科学家表示，“过滤通过病毒”可将疾病传播给人和动物;
1949 年，John F. Enders，Thomas Weller 和 Frederick Robbins 报道了培养的人类胚胎细胞中脊髓灰质炎病毒的生长（他们在 1954 年获得诺贝尔奖）;
这项工作帮助乔纳斯·萨尔克（Jonas Salk）从灭活的脊髓灰质炎病毒中获得脊髓灰质炎疫苗;这种疫苗在 1955 年被证明是有效的。（拉斯克奖在 1956 年; Salk 研究所的创始人）
1963 年，Baruch Blumberg 发现乙型肝炎病毒（1976 年诺贝尔奖得主）
1965 年，霍华德·蒂姆（Howard Temin）描述了第一个逆转录病毒（1975 诺贝尔奖获得者）
1975 年，明尼苏达病毒的功能得到了很大的澄清
1976 年，第一次记录爆发的埃博拉出血热，是致命的致病病毒传播疾病。
1979 年，联合国世卫组织领导的全球疫苗接种运动导致了根除小波动
1982 年，Stanley Prusiner 发现了朊病毒（1997 年诺贝尔奖）
1981 年报告了第一起艾滋病病例，由罗伯特·加洛（Lasker）和卢克·蒙塔尼（Luc Montagnier）（诺贝尔）于 1983 年确定了引起艾滋病毒的逆转录病毒。
1987 年确定了丙型肝炎病毒

Chapter 2 Flaviviruses —— The important arboviruses for global public health

第 2 章 虫媒病毒——对全球公共健康的重要虫媒病毒

Arbovirus - Arthropod-Borne virus
虫媒病毒

虫媒病毒传播循环



Flaviviridae (黄病毒科)
Flaviviridae family: enveloped, single-strand positive-sense RNA virus
黄病毒科：包膜单链阳性 RNA 病毒

Flaviviruses (黄病毒属) 53 种病毒
West Nile virus 西尼罗病毒
Yellow fever virus 黄热病病毒
Dengue virus 登革病毒
Japanese encephalitis virus 日本(乙型)脑炎病毒,
Tick-borne encephalitis virus 森林脑炎

Pestiviruses (瘟病毒属)
Bovine viral diarrhea virus 牛病毒性腹泻病毒
Classical swine fever virus 猪瘟病毒

Hepaciviruses (肝炎病毒属)
Hepatitis C virus 丙肝病毒

Genus Flavivirus (黄病毒属)
Type specie: yellow fever virus
"Yellow" in Latin is "flavus"
Yellow fever virus is the first filterable agent shown to cause human disease, the first virus shown to be arthopod-borne (1900), and the first virus isolated (1927).
In 53 species of flaviruses, 40 can cause human infection.
Flaviviruses are among the most important pathogens infecting humans and domestic animals
All are zoonotic viruses

黄病毒属
类型：黄热病毒
拉丁语中的“黄”是“flavus”
黄热病病毒是第一种可引起人类疾病的可过滤药物，第一种病毒显示为 arthopod-borne（1900），第一种病毒分离（1927）。
在 53 种黄素病毒中，40 种可引起人类感染。
黄病毒是感染人类和家畜的最重要的病原体之一
都是人畜共患病毒

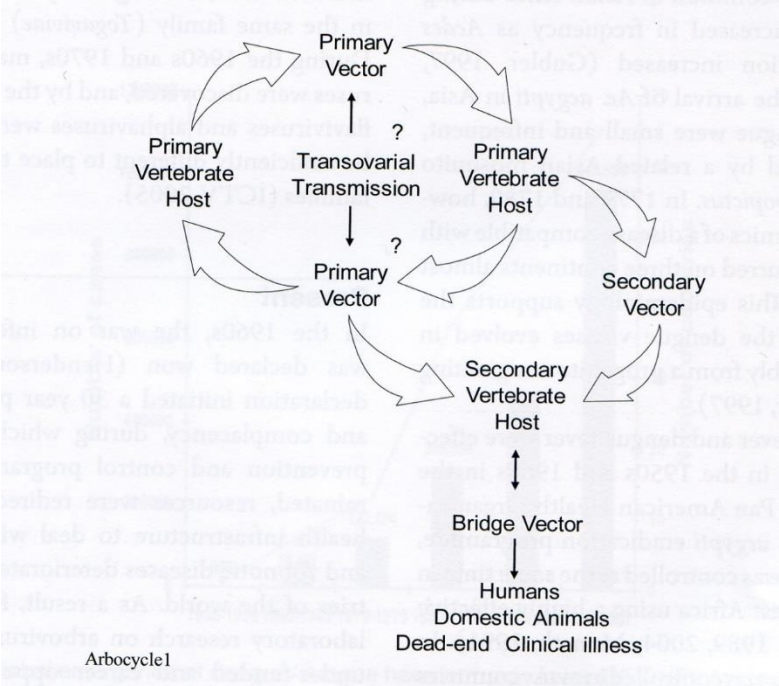
Mosquito as the vector for Flaviviruses
27 flaviviruses are determined to be mosquito-borne, including most important medically: Dengue virus (DEV), Japanese encephalitis virus (JEV), West Nile virus (WNV), Yellow fever virus (YFV) and etc.
蚊子作为黄病毒的载体
27 种黄病毒被确定为蚊子，包括最重要的医学上的：登革热病毒（DEV），日本脑炎病毒（JEV），西尼罗病毒（WNV），黄热病毒（YFV）等

Tick (蜱) as the vector for Flaviviruses
12 species of flaviviruses are determined to be tick-borne. Most of the tick-borne viruses that infect humans cause neurological disease, and some also cause haemorrhagic disease.
蜱作为黄病毒载体
确定 12 种黄病毒属于蜱传播型。 大多数感染人类的蜱传播的病毒会导致神经系统疾病，有些也会引起出血性疾病。

The diseases caused by mosquito-borne Flaviviruses
This group of viruses cause viscerotropic diseases in humans, have the ability to establish urban transmission cycles with domesticated Aedes species mosquitoes as the vectors.
Hosts: primates and mosquitoes
由蚊子传播的黄病毒引起的疾病
这组病毒在人类中引起内脏性疾病，具有建立城市传播周期的能力，以家养的伊蚊种蚊子为载体。
宿主：灵长类动物和蚊子

The diseases caused by mosquito-borne Flaviviruses
This group of viruses have birds as their principal vertebrate hosts, cause neurological diseases in humans, have bird-feeding *Culex* species mosquitoes as the principal vectors.
由蚊子传播的黄病毒引起的疾病
这组病毒有鸟类作为主要的脊椎动物宿主，在人类中引起神经系统疾病，以鸟类为主导的库蚊种蚊子为主要载体。
West Nile virus
Japanese encephalitis virus
Murray Valley encephalitis virus →encephalitis
St Louis encephalitis virus
西尼罗病毒
日本脑炎病毒
美利谷脑炎病毒 →脑炎
圣路易脑炎病毒

黄病毒传播周期



Past of Flaviviruses

Historically, flaviviruses have been major public problems for humans, particularly yellow fever virus and Dengue virus.

Both YFV and DENV were transmitted from Africa by Aedes aegypti.

Slave trade spreads Aedes aegypti together with DENV to Americas.

DENV was then transmittd to Asia-Pacific from Americas. And Aedes albopictus became vector.

During 1950s and 1960s, many public health programs successfully controlled yellow fever and dengue fever.

过去的黄病毒

历史上，黄病毒是人类的主要公共问题，特别是黄热病病毒和登革热病毒。

YFV 和 DENV 都是由非洲埃及伊蚊传播的。

奴隶贸易将埃及伊蚊与 DENV 一起传播到美洲。

然后，DENV 从美洲发送到亚太地区。 白纹伊蚊成为载体。

五十年代至六十年代，许多公共卫生项目成功控制了黄热病和登革热。

Present of Flaviviruses

In 1960s, declaration of "win" for the war on infectious diseases. "30 year period of apathy and complacency" - Dr. Pei-Yong Shi.

A major re-emergence of epidemic infectious diseases, particularly vector-borne flaviviruses.

Population growth in developing countries, environmental changes (global warming?), urbanization

Flaviviruses become a major public health challenge again.

Annually, tens of millions of cases and thousands of deaths.

现在的黄病毒

20 世纪 60 年代宣传传染病战争“胜利”。 “30 年冷漠与自满” - 裴永勇博士。

流行性传染病重大出现，特别是载体传播的黄病毒。

发展中国家人口增长，环境变化（全球变暖），城市化进程

黄病毒再次成为主要的公共卫生挑战。

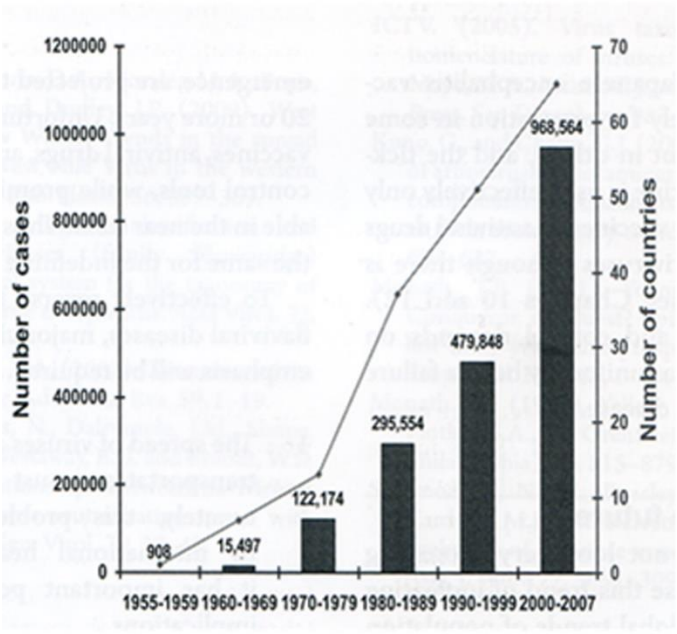
每年有数千万病例和数千人死亡。

Global emergence of dengue/dengue haeomorrhagic fever (DF/DHF)

Average annual number of DF/DHF cases reported to WHO

登革热/登革热出血热全球出现（DF / DHF）

向世卫组织报告的 DF / DHF 病例平均年数



Dengue virus in China

Most cases reported in Hainan, Guangdong and Guangxi.

1978, Foshan, Guangdong

1980, Hainan, then spread to Guangdong

2009, Yiwu, Zhejiang. > 200 cases

登革热病毒在中国

大多数病例报告在海南，广东，广西。

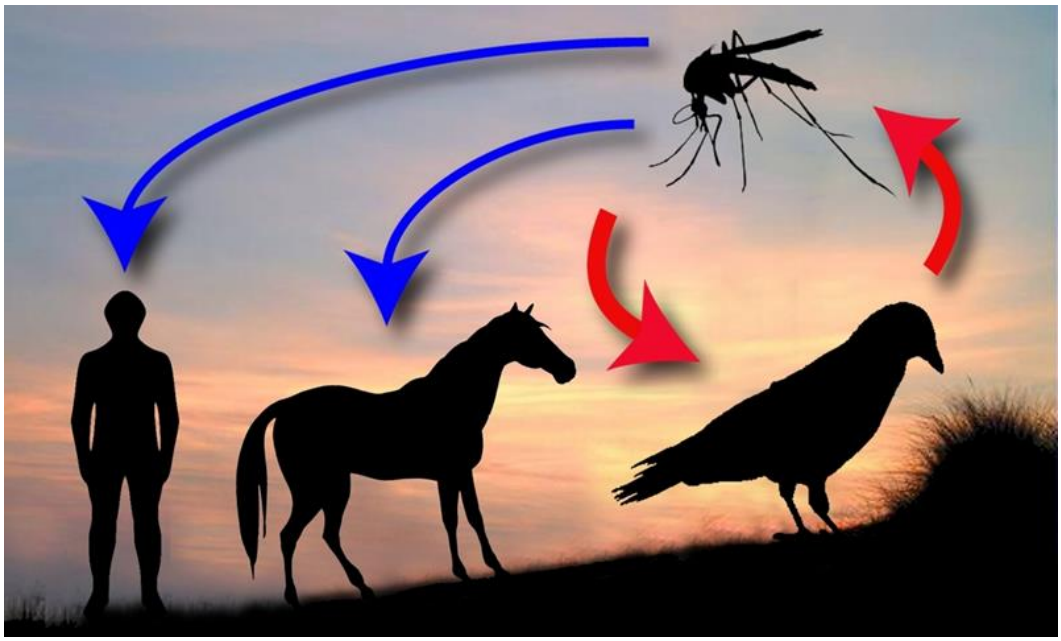
1978 年，广东佛山

1980 年，海南，然后传播到广东

2009 年，义乌，浙江。 > 200 例

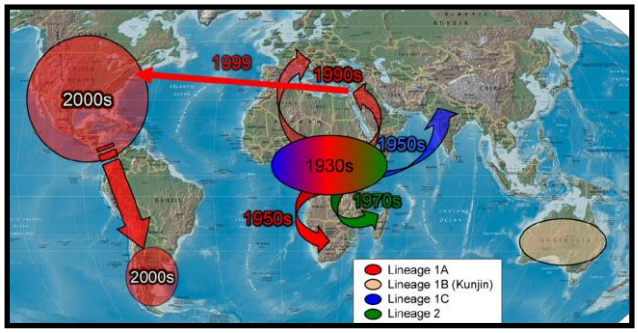
WNV transmission cycle

西尼罗病毒传播循环



Distribution of West Niles virus

No case report in China
Spread condition：mosquito、bird migration
Globalization and international travel
西尼罗病毒分布
中国无病例报道
传播条件：蚊子，鸟类迁徙
全球化与国际旅游



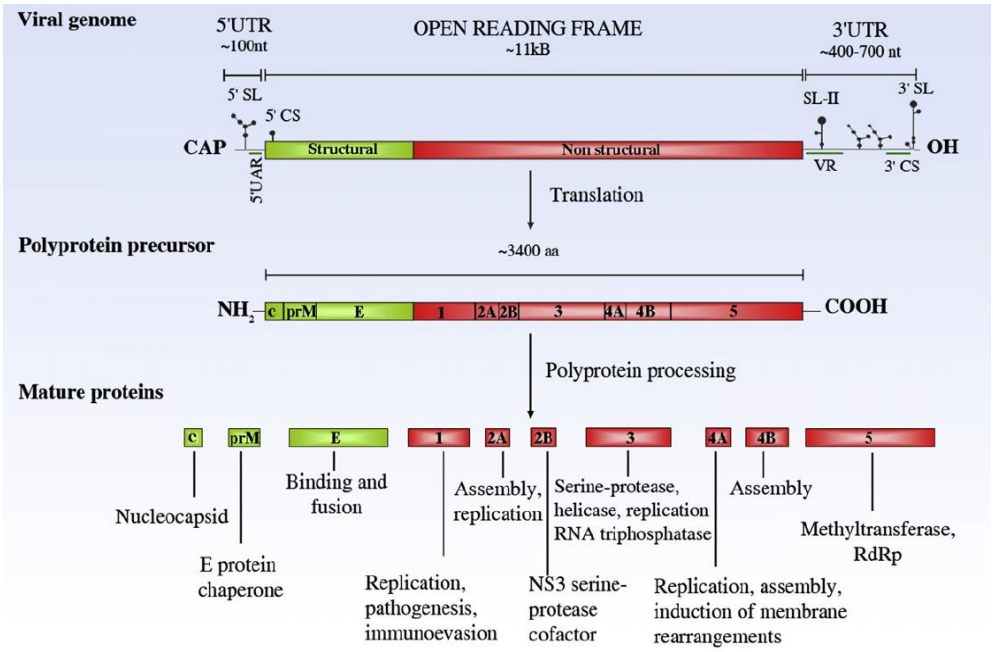
Milestone: In 1999, WNV jumped to North America
Rapid spread
Enhanced virulence (fatality rate: US 3-5%, Romania ~10%)
Lack of effective vaccine and anti-WNV drug
里程碑：1999 年，西尼罗病毒登陆北美
快速传播
增强毒力（死亡率：3-5%，罗马尼亚约 10%）
缺乏有效的疫苗和抗 WNV 药物

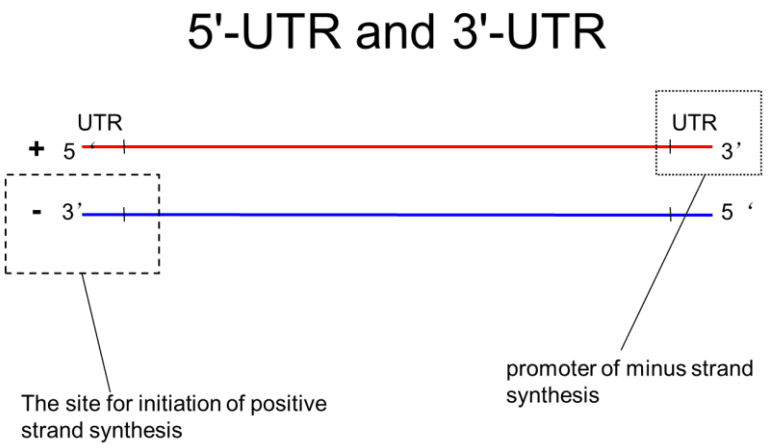
West Niles virus in Canada
2000, Canada–New York border
2002, Ontario and Quebec.
2003, Ontario, Quebec, Manitoba, Saskatchewan and Alberta.
2003-2007, WNV detected in birds in in Nova Scotia and New Brunswick.
西尼罗病毒在加拿大
2000 年，加拿大纽约边界
2002 年，安大略省和魁北克省。
2003 年，安大略省，魁北克省，马尼托巴省，萨斯喀彻温省和艾伯塔省。
2003-2007 年，新斯科舍省和新不伦瑞克省的鸟类检测到 WNV。

Challenges
Spread of flaviviruses and vectors thru modern global transportation must be prevented.
Lab-based detection system must be improved
Public health infrastructure in tropical developing countires must be developed
Progress in vaccine and anti-flaviviral drug development
Problems in vector control (insecticide resistance)
Global warming and tropical zone moves north.
Spread of flaviviruses, esp. West Niles virus, into non-tropical region (When spread into China?)
National security concerns
挑战
必须防止黄病毒和载体传播通过现代全球运输。
必须改进基于实验室的检测系统
必须发展热带发展中的公共卫生基础设施
疫苗和抗黄病毒药物开发进展

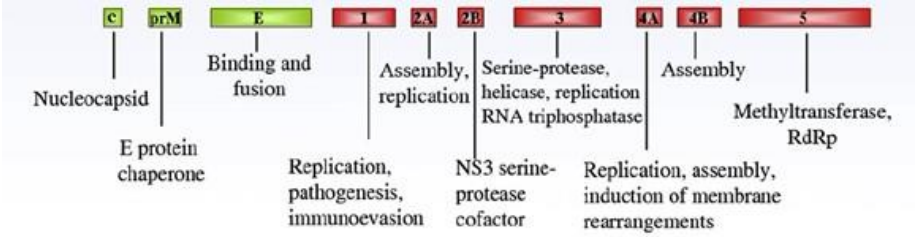
载体控制问题（杀虫剂抗性）
全球变暖和热带地区向北移动。
传播黄病毒，尤其是 西尼罗病毒，进入非热带地区（当传播到中国？）
国家安全关切

Flavivirus Genome Organization
黄病毒基因组成





引发正链合成的部位　负链合成启动子

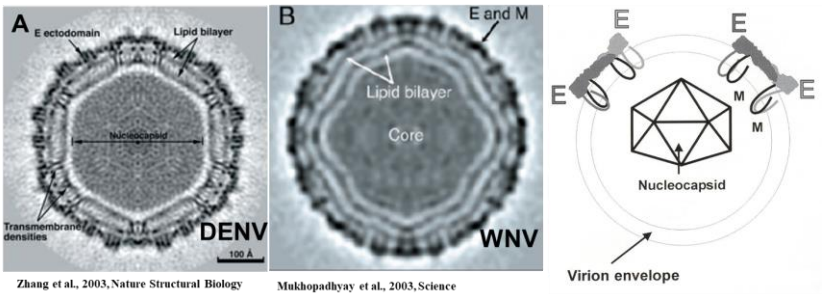


Structural Proteins:
C protein: form a ribonucleo-protein complex with packaged genomic RNA. 11 kDa
prM protein: generated in ER. PrM is cleaved by furin in Trans-Golgi (TGN) to form mature M protein.
E protein: envelop protein. The major component of flaviviral envelop. 3 domains, EDI, EDII and EDIII.
结构蛋白：

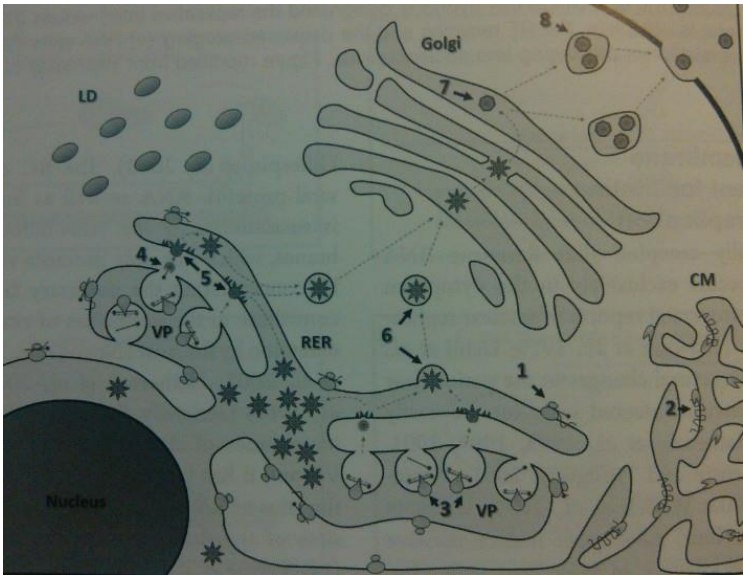
C 蛋白：与包装的基因组 RNA 形成核糖核蛋白复合物。 11 kDa
prM 蛋白：在 ER 中产生。 通过在高尔基体（TGN）中的弗林蛋白酶切割 PrM 以形成成熟的 M 蛋白。
E 蛋白：包膜蛋白。 黄病毒包膜的主要成分。 3 个领域，EDI，EDII 和 EDIII。

Nonstructural Proteins:
NS1 protein: contains ER transmembrane domain (possibly involves in viral RNA replication; anti-NS1 antibody's protective role.
NS2A: recruit viral RNA template to membrane-associated viral RNA replicase
NS2B: membrane-associated, partner protein of NS3, cofactor of protease (NS3)
NS3: serine protease, polyprotein processing. Possible helicase activity.
NS4A and NS4B: both membrane-associated.
NS5: RNA-dependent RNA polymerase (RdRp). Methyltransferase, involving in RNA cap formation
非结构蛋白：
NS1 蛋白：含有 ER 跨膜结构域（可能涉及病毒 RNA 复制;抗 NS1 抗体的保护作用。
NS2A：将病毒 RNA 模板招募到膜相关病毒 RNA 复制酶
NS2B：NS3 的膜相关的配子蛋白，蛋白酶（NS3）的辅因子
NS3：丝氨酸蛋白酶，多蛋白加工。可能的解旋酶活性。
NS4A 和 NS4B：均与膜相关。
NS5：RNA 依赖性 RNA 聚合酶（RdRp）。 甲基转移酶，涉及 RNA 帽形成

Viral Particle of Flaviviruses
An icosahedral nucleocapsid encloses the virion RNA
Spherical, 40-60 nm in diameter
Lipid envelope covered with surface projections, especially E, prM and M proteins
黄病毒病毒颗粒
二十面体核衣壳包围病毒粒子 RNA
球形，直径 40-60nm
脂质包膜覆盖着表面突起，特别是 E，prM 和 M 蛋白

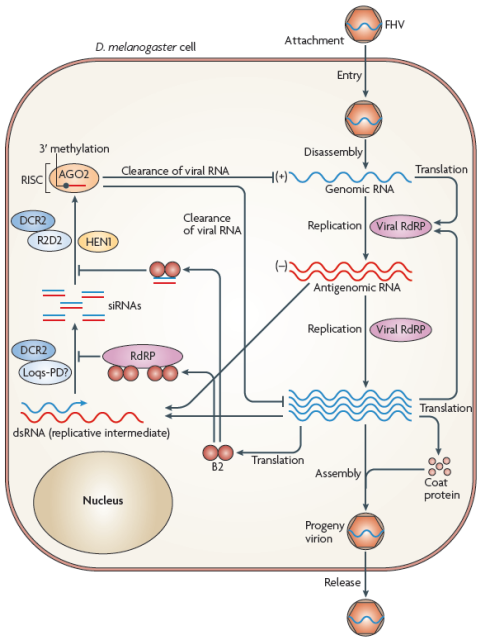


Zhang et al., 2003, Nature Structural Biology　　Mukhopadhyay et al., 2003, Science



(1) Genomic RNA is translated at the rough endoplasmic reticulum (RER) forming a polyprotein that crosses the RER membrane multiple times.
(2) The polyprotein is cleaved post-translationally by viral NS2B/3 protease and host cell signalase at either the RER or within virus-induced convoluted membranes (CM).
(3) The replication complex consisting of NS1, NS2A, NS4A, NS3 and NS5, sequestered within virus-induced vesicle packets (vP), generates and processes the RNA replicative form (via firstly minus-strand synthesis, then generation of positive strand progeny RNA).
(4) Progeny RNA exits the VP pore and is incorporated into the nucleocapsid by C protein.
(5) Nucleocapsids collect the envelope glycoproteins prM and E and form immature virions in the ER lumen.
(6) Immature virions are transported to the Golgi apparatus via individual vesicles.
(7) Virions traverse the Golgi apparatus allowing maturation of carbohydrate groups on envelope glycoproteins.
(8) Virions are transported in endosomes and via the trans-Golgi network, where acidification allows furin to cleave prM to M, thus forming mature particles. Mature virions then accumulate for secretion at the plasma membrane.
（1）基因组 RNA 在粗糙内质网（RER）上翻译，形成多次穿过 RER 膜的多蛋白质。
（2）通过病毒 NS2B / 3 蛋白酶和宿主细胞信号酶在 RER 或病毒诱导的卷积膜（CM）内翻译后多蛋白切割。
（3）由病毒诱导的囊泡包（vP）中隔离的由 NS1，NS2A，NS4A，NS3 和 NS5 组成的复制复合物产生并加工 RNA 复制形式（通过首次负链合成，然后产生阳性链后代 RNA）。
（4）后代 RNA 离开 VP 孔，并通过 C 蛋白掺入核衣壳中。
（5）核衣壳收集包膜糖蛋白 prM 和 E，并在 ER 腔中形成不成熟的病毒粒子。
（6）未成熟的病毒粒子通过个体囊泡运送到高尔基体。
（7）病毒穿过高尔基体，允许糖皮质糖蛋白上的碳水化合物成熟。
（8）病毒体在内体转运，通过反式高尔基体网络，其中酸化允许弗林蛋白酶将 prM 切割成 M，从而形成成熟的颗粒。然后成熟的病毒粒子积聚在质膜上分泌。

What are we doing now?
RNAi is a potent antiviral immune　in insects
PAMP: viral dsRNA
PRR:Dicer-2
我们现在在做什么？
RNAi 是昆虫中有效的抗病毒免疫
PAMP：病毒 dsRNA
PRR：切酶 – 2



RNAi-based host immunity and its viral suppressor

RNA interference (RNAi) is emerging as an important antiviral defense in a wide range of organisms from plants to animals;

For invertebrates like insects, the RNAi-mediated immunity is their primary and best studied antiviral immune response.

Viruses encode viral suppressors of RNA silencing (VSRs) to escape from the RNAi-mediated antiviral defense.

基于 RNAi 的宿主免疫及其病毒抑制因子

RNA 干扰（RNAi）正在成为从植物到动物的广泛生物体内的重要抗病毒防御技术;

对于像昆虫这样的无脊椎动物，RNAi 介导的免疫是其主要和最好研究的抗病毒免疫应答。

病毒编码 RNA 沉默（VSR）的病毒抑制因子从 RNAi 介导的抗病毒防御中逃脱。

Chapter 3 Picornaviruses

第三章 小 RNA 病毒

The family *Picornaviridae*

A picornavirus is a virus belonging to the family *Picornaviridae*.

Picornaviruses are non-enveloped, positive-stranded RNA viruses with an icosahedral capsid.

The name is derived from pico, meaning small, and RNA, referring to the ribonucleic acid genome, so "picornavirus" literally means small RNA virus.

In 1897, foot-and-mouth disease virus (FMDV), the first animal virus, was discovered. FMDV is the prototypic member of the Aphthovirus genus in the Picornaviridae family.

小 RNA 病毒家族

微小 RNA 病毒是属于小核糖核酸病毒科的病毒。

小核糖核酸病毒是具有二十面体衣壳的非包膜正链 RNA 病毒。

这个名称来源于 pico，意思是小的，RNA 是指核糖核酸基因组，所以“小核糖核酸病毒”字面上意指小 RNA 病毒。

1897 年，发现了口蹄疫病毒（FMDV），第一种动物病毒。 FMDV 是小 RNA 病毒科中 Aphthovirus 属的原型成员。

Genus of The family *Picornaviridae*

小 RNA 病毒的属

Aphthovirus 口蹄疫病毒
Avihepatovirus
Cardiovirus 心病毒属
Enterovirus
Erbovirus
Hepatovirus (HAV)
Kobuvirus
Parechovirus
Sapelovirus
Senecavirus
Teschovirus
Tremovirus

Structure

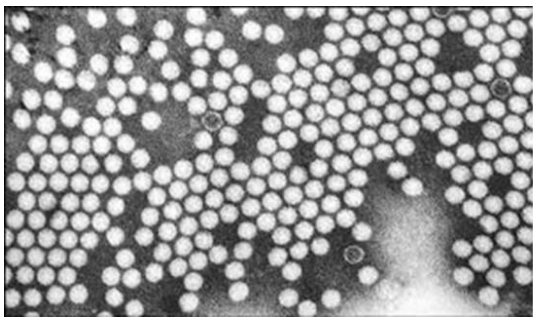
The capsid is an arrangement of 60 protomers in a tightly packed Icosahedral structure. Each protometer consists of 4 polypeptides known as VP (viral protein)1, 2, 3 and 4. VP2 and VP4 polypeptides originate from one protomer known as VP0 that is cleaved to give the different capsid components.

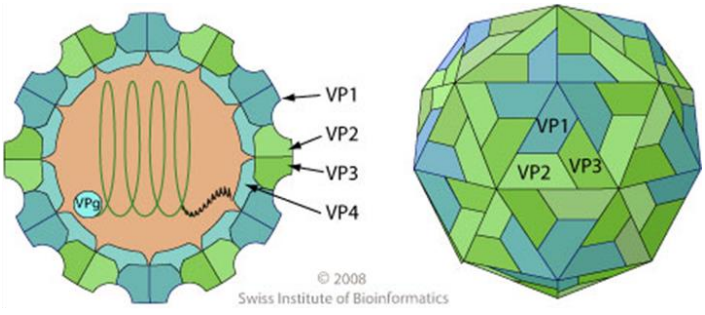
Depending on the type and degree of dehydration the viral particle is around 27-30 nm in diameter.

结构

衣壳是紧密包装的二十面体结构中的 60 个检测器的排列。每个细胞计数器由称为 VP（病毒蛋白）1,2,3 和 4 的 4 种多肽组成。来自称为 VP0 的一种原生质体的 VP2 和 VP4 多肽被切割以产生不同的衣壳组分。

取决于脱水的类型和程度，病毒颗粒的直径约为 27-30nm。



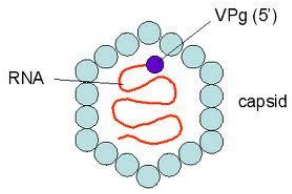


Genome

Picornaviruses contain a single stranded, positive sense RNA genome of between 7.2 and 9.0 kb in length.

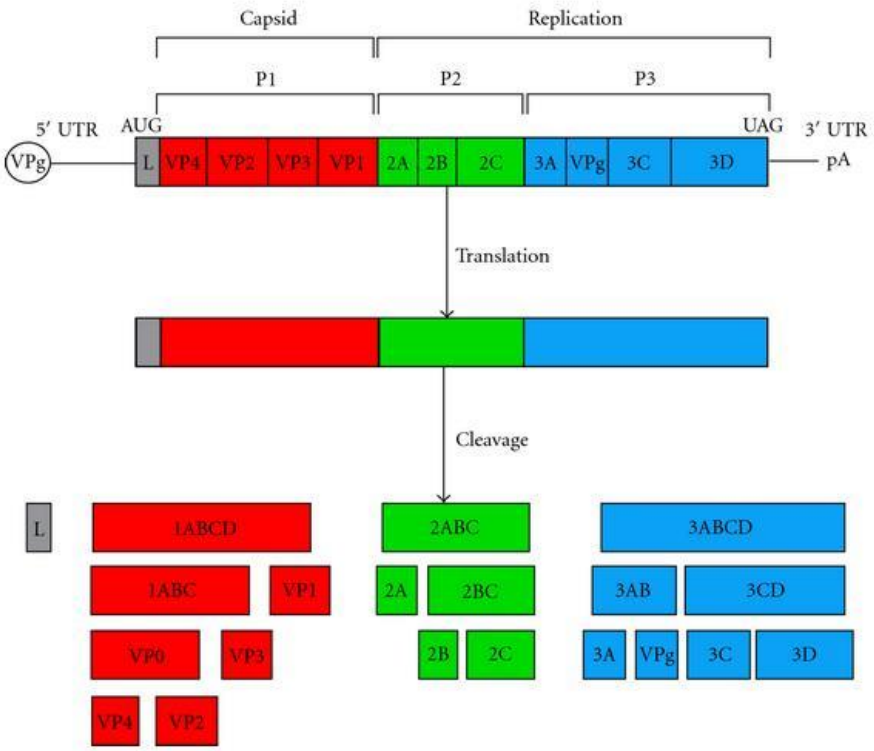
Like most positive sense RNA genomes, the genetic material alone is infectious; although substantially less virulent

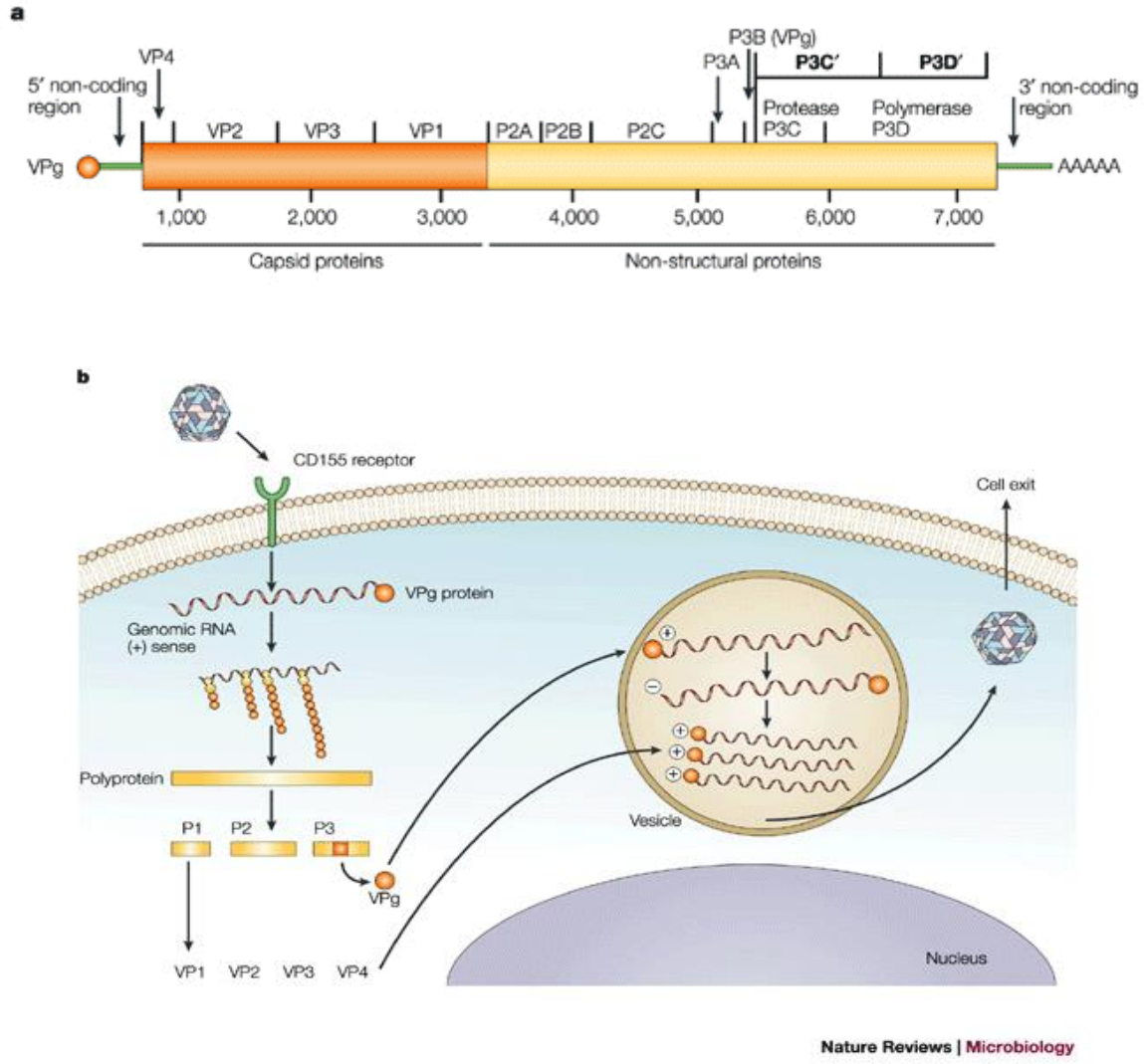
than if contained within the viral particle, the RNA can have increased infectivity when transfected into cells.
基因组
细小核糖核酸病毒包含长度为 7.2 至 9.0kb 之间的单链，正义 RNA 基因组。
像大多数正义 RNA 基因组一样，单独的遗传物质是感染性的; 尽管如果包含在病毒颗粒内的毒性大大降低，RNA 可以在细胞转染时具有增加的感染性。
The genome RNA is unusual. It do not have a 5' cap but a virally encoded protein known as VPg that is used as a primer for transcription by RNA polymerase. The genome has a poly(A) tail at the 3' end.
There is an UTR at both ends of the picornavirus genome. The 5' UTR is around 600-1200 nt in length and the 3' UTR is around 50-100 nt. It is thought that the 5' UTR is important in translation and the 3' in negative strand synthesis; however the 5' end may also have a role to play in virulence of the virus.



基因组 RNA 异常。 它不具有 5'帽，而是称为 VPg 的病毒编码的蛋白质，其用作 RNA 聚合酶转录的引物。 基因组在 3'末端有一个 poly（A）尾。
在小核糖核酸病毒基因组的两端有一个 UTR。 5'UTR 长度在 600-1200nt 左右，3'UTR 约在 50-100nt。 认为 5'UTR 在翻译中是重要的，在负链合成中是 3'重要的; 然而，5'末端也可能起到病毒毒力的作用。

The rest of the genome encodes structural proteins at the 5' end and non-structural proteins at the 3' end in a single polyprotein.
The polyprotein is organised as follows: L-1ABCD-2ABC-3ABCD with each letter representing a protein.
The 3B protein is the VPg protein. The 3D protein is the RNA polymerase.
基因组的其余部分编码 5'末端的结构蛋白，3'末端的非结构蛋白在单个多蛋白中编码。
多蛋白组织如下：L-1ABCD-2ABC-3ABCD，每个字母表示蛋白质。
3B 蛋白是 VPg 蛋白。 3D 蛋白是 RNA 聚合酶。





Enteroviruses

Enteroviruses are a genus of (+)ssRNA viruses associated with several human and mammalian diseases.

Serologic studies have distinguished 66 human enterovirus serotypes on the basis of antibody neutralization tests.

On the basis of their pathogenesis in humans and animals, the enteroviruses were originally classified into four groups, polioviruses, Coxsackie A viruses (CA), Coxsackie B viruses (CB), and echoviruses, but it was quickly realized that there were significant overlaps in the biological properties of viruses in the different groups.

Enteroviruses isolated more recently are named with a system of consecutive numbers: EV68, EV69, EV70, and EV71, etc

肠道病毒

肠病毒是与几种人类和哺乳动物疾病相关的（+）ssRNA 病毒属。

血清学研究在抗体中和试验的基础上区分了 66 种人肠病毒血清型。

根据其在人和动物中的发病机制，肠道病毒最初分为四组，脊髓灰质炎病毒，柯萨奇 A 病毒（CA），柯萨奇 B 病毒（CB）和回波病毒，但很快就意识到有显着的重叠 不同组病毒的生物学特性。

最近隔离的肠道病毒以连续数字系统命名：EV68，EV69，EV70 和 EV71 等

Species

Bovine enterovirus
Human enterovirus A
Human enterovirus B
Human enterovirus C
Human enterovirus D
Human rhinovirus A
Human rhinovirus B
Human rhinovirus C
Porcine enterovirus B
Simian enterovirus A

种类

牛肠道病毒
人肠毒素 A
人肠道病毒 B
人肠道病毒 C
人肠道病毒 D
人鼻病毒 A
人类鼻病毒 B
人类鼻病毒 C
猪肠道病毒 B
猿猴肠病毒

Serotypes

- Coxsackievirus
  - serotypes CV-A2, CV-A3, CV-A4, CV-A5, CV-A6, CV-A7, CV-A8, CV-A10, CV-A12, CV-A14, & CV-A16 found under the species: Human enterovirus A.
  - serotypes CV-B1, CV-B2, CV-B3, CV-B4, CV-B5, CV-B6, CV-A9, & CV-A23 found under the species: Human enterovirus B.
  - serotypes CV-A1, CV-A11, CV-A13, CV-A17, CV-A19, CV-A20, CV-A21, CV-A22, & CV-A24 found under the species: Human enterovirus C.
- Echovirus
  - serotypes E-1, E-2, E-3, E-4, E-5, E-6, E-7, E-8, E-9, E-11, E-12, E-13, E-14, E-15, E-16, E-17, E-18, E-19, E20, E-21, E-24, E-25, E-26, E-27, E-29, E-30, E-31, E-32, & E-33 found under the species: Human enterovirus B.
- Enterovirus
  - serotypes EV-71, EV-76, EV-89, EV-90, EV-91, & EV-92 found under the species: Human enterovirus A.
  - serotypes EV-69, EV-73, EV-74, EV-75, EV-77, EV-78, EV-79, EV-80, EV-81, EV-82, EV-83, EV-84, EV-85, EV-86, EV-87, EV-88, EV-93, EV-97, EV-98, EV-100, EV-101, EV-106, & EV-107 found under the species: Human enterovirus B.
  - serotypes EV-95, EV-96, EV-99, EV-102, EV-104, EV-105, & EV-109 found under the species: Human enterovirus C.
  - serotypes EV-68, EV-70, & EV-94 found under the species: Human enterovirus D.
- Human rhinovirus
  - serotypes HRV-1, HRV-2, HRV-7, HRV-8, HRV-9, HRV-10, HRV-11, HRV-12, HRV-13, HRV-15, HRV-16, HRV-18, HRV-19, HRV-20, HRV-21, HRV-22, HRV-23, HRV-24, HRV-25, HRV-28, HRV-29, HRV-30, HRV-31, HRV-32, HRV-33, HRV-34, HRV-36, HRV-38, HRV-39, HRV-40, HRV-41, HRV-43, HRV-44, HRV-45, HRV-46, HRV-47, HRV-49, HRV-50, HRV-51, HRV-53, HRV-54, HRV-55, HRV-56, HRV-57, HRV-58, HRV-59, HRV-60, HRV-61, HRV-62, HRV-63, HRV-64, HRV-65, HRV-66, HRV-67, HRV-68, HRV-71, HRV-73, HRV-74, HRV-75, HRV-76, HRV-77, HRV-78, HRV-80, HRV-81, HRV-82, HRV-85, HRV-88, HRV-89, HRV-90, HRV-94, HRV-95, HRV-96, HRV-98, & HRV-100 found under the species: Human rhinovirus A.
  - serotypes HRV-3, HRV-4, HRV-5, HRV-6, HRV-14, HRV-17, HRV-26, HRV-27, HRV-35, HRV-37, HRV-42, HRV-48, HRV-52, HRV-69, HRV-70, HRV-72, HRV-79, HRV-83, HRV-84, HRV-86, HRV-91, HRV-92, HRV-93, HRV-97, & HRV-99 found under the species: Human rhinovirus B.
- Poliovirus
  - serotypes PV-1, PV-2, & PV-3 found under the species: Human enterovirus C.[6]

Coxsackie and echovirus

Coxsackie A viruses are mainly associated with human hand, foot and mouth disease. Coxsackie B viruses can cause mild signs and symptoms, similar to a "cold", but these viruses also can lead to more serious diseases, including myocarditis (inflammation of the heart 心肌炎); pericarditis (inflammation of the sac lining the heart 心包炎); meningitis (inflammation of the membranes that line the brain and spinal cord); and pancreatitis (inflammation of the pancreas 胰腺炎).

Echoviruses are a cause of many of the nonspecific viral infections. It is mainly found in the intestine, and can cause nervous disorders.

The usual symptoms of Coxsackie and echovirus are fever, mild rash, and mild upper respiratory tract (URT) illness.

柯萨奇和回声病毒

柯萨奇 A 病毒主要与人类手足口病有关。 柯萨奇 B 病毒可引起轻微的体征和症状，类似于“感冒”，但这些病毒也可能导致更严重的疾病，包括心肌炎； 心包炎；脑膜炎；和胰腺炎。

回波病毒是许多非特异性病毒感染的原因。 它主要发现于肠道，可引起神经障碍。

柯萨奇和回波病毒的常见症状是发烧，轻度皮疹和轻度上呼吸道（URT）疾病。

Rhinovirus 鼻病毒

There are three species of Rhinoviruses: Human Rhinovirus A, Human Rhinovirus B, and Human Rhinovirus C which contain over 100 serotypes.

Rhinoviruses are the most suspected causative agents of the common cold. This makes it difficult to develop a single vaccine against so many serotypes.

鼻病毒有三种：人鼻病毒 A，人鼻病毒 B 和人类鼻病毒 C，其含有超过 100 种血清型。

鼻病毒是感冒常见的致病因子。 这使得难以开发针对这么多血清型的单一疫苗。

Diseases caused by enterovirus

Poliomyelitis

Nonspecific febrile illness is the most common presentation of enterovirus infection. Other than fever, symptoms include muscle pain, sore throat, gastrointestinal distress, and headache. Abdominal discomfort may also be reported in some patients.

Enteroviruses are by far the most common causes of aseptic meningitis (无菌脑膜炎) in children. In the United States, enteroviruses are responsible for 阿 30,000 to 50,000 meningitis hospitalizations per year as a result of 30 million to 50 million infections.
Pleurodynia (胸膜痛) is characerized by severe paroxysmal pain in the chest and abdomen, along with fever, and sometimes nausea, headache, and emesis.
Pericarditis and/or myocarditis are typically caused by enteroviruses; symptoms consist of fever with dyspnea (呼吸困难) and chest pain. Arrhythmias (心律失常), heart failure, and myocardial infarction (心肌梗塞) have also been reported.
Acute hemorrhagic conjunctivitis (结膜炎) can be caused by enteroviruses.
Herpangina (疱疹性咽峡炎) is caused by Coxsackie A virus, and causes a vesicular rash in the oral cavity and on the pharynx, along with high fever, sore throat, malaise, and often dysphagia (咽下困难), loss of appetite, back pain, and headache. It is also self limiting, with symptoms typically ending in 3–4 days.
Hand, foot and mouth disease is a childhood illness most commonly caused by infection by Coxsackie A virus or EV71.
Encephalitis (脑炎) is rare manifestation of enterovirus infection; when it occurs, the most frequent enterovirus found to be causing the it is echovirus 9.
Bornholm disease (流行性胸膜痛) is enteroviral in origin.
A 2007 study suggested that acute respiratory or gastrointestinal infections associated with enterovirus may be a factor in chronic fatigue syndrome (慢性疲劳症候群)

- ✧ 肠道病毒引起的疾病
- ✧ 脊髓灰质炎
- ✧ 非特异性发热性疾病是肠道病毒感染的最常见表现。除了发烧，症状包括肌肉疼痛，喉咙痛，胃肠道痛苦和头痛。一些患者也可能报告腹部不适。
- ✧ 肠道病毒是儿童无菌性脑膜炎的最常见原因。在美国，由于 3000 万至 5000 万感染，肠病毒每年造成 30,000 至 5 万例脑膜炎住院。
- ✧ 胸膜炎由胸部和腹部严重阵发性疼痛伴有发热，伴有发热，有时恶心，头痛，呕吐。
- ✧ 心包炎和/或心肌炎通常由肠道病毒引起;症状包括发热与呼吸困难和胸痛。心律失常，心力衰竭和心肌梗死也有报道。
- ✧ 肠道病毒可引起急性出血性结膜炎。
- ✧ 疱疹病毒是由柯萨奇 A 病毒引起的，并引起口腔和咽部的泡状皮疹，伴有高烧，喉咙痛，不适，经常吞咽困难，食欲不振，背部疼痛和头痛。这也是自我限制，症状通常在 3-4 天结束。
- ✧ 手足口病是柯萨奇病毒或 EV71 感染最常见的儿童疾病。
- ✧ 脑炎是肠道病毒感染的罕见表现;发生这种情况时，发现最常见的肠道病毒是回波病毒 9。
- ✧ 博恩霍尔姆病是肠道病毒的起源。
- ✧ 2007 年的研究表明，与肠道病毒相关的急性呼吸道或胃肠道感染可能是慢性疲劳综合征的一个因素。

Poliovirus

The Profile of Poliovirus
The causative agent of poliomyelitis, a human Enterovirus
Member of the family of Picornaviridae
Composed of an RNA genome and a protein capsid.
The genome is a single-stranded positive-sense RNA genome that is about 7500 nt long.

脊髓灰质炎病毒

脊髓灰质炎病毒的简介
脊髓灰质炎的病原体，一种人肠道病毒
小核糖核酸病毒科家族成员
由 RNA 基因组和蛋白质衣壳组成。
基因组是约 7500 nt 长的单链正义 RNA 基因组。

The Profile of Poliovirus

Poliovirus was first isolated in 1909 by Karl Landsteiner and Erwin Popper.

In 1981, the poliovirus genome was published by two different teams of researchers— by Vincent Racaniello and David Baltimore at MIT and by Naomi Kitamura and Eckard Wimmer at the State University of New York, Stony Brook.

脊髓灰质炎病毒的简介

脊髓灰质炎病毒于 1909 年被 Karl Landsteiner 和 Erwin Popper 首次分离。

1981 年，脊髓灰质炎病毒基因组由麻省理工学院的 Vincent Racaniello 和 David Baltimore 由纽约州立大学石溪分校的 Naomi Kitamura 和 Eckard Wimmer 两个不同的研究小组出版。

The Structure of Poliovirus

30 nm in diameter.

Icosahedral symmetry.

Non-enveloped.

脊髓灰质炎病毒的结构

直径 30 nm。

二面体对称。

无包膜。

The Genome of Poliovirus

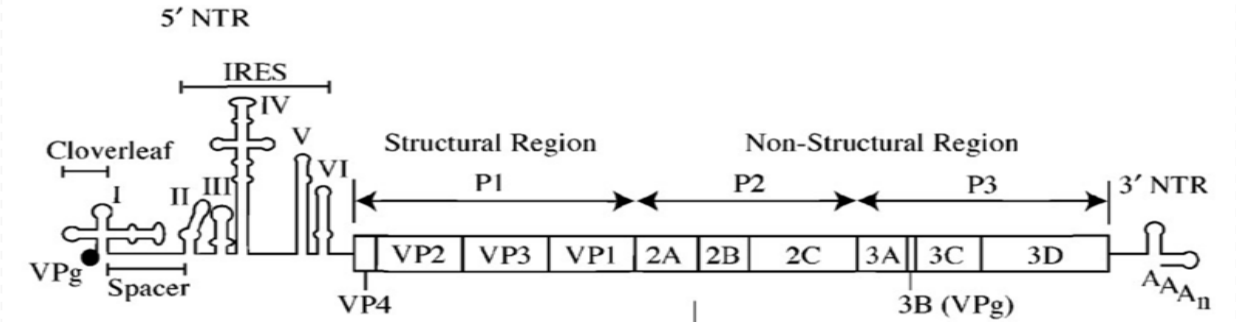
5'-NTR:

This region of the viral genome is called internal ribosome entry site (IRES) and it directs translation of the viral RNA.

脊髓灰质炎病毒基因组

5'-NTR：

病毒基因组的这个区域称为内部核糖体进入位点（IRES），它指导病毒 RNA 的翻译。



Poliovirus mRNA is translated as one long polypeptide.

This polypeptide is then autocleaved by internal proteases into approximately 10 individual viral proteins.

3Dpol

an RNA dependent RNA polymerase whose function is to copy and multiply the viral RNA genome.

2Apro and 3Cpro/3CDpro

proteases which cleave the viral polypeptide.

VPg (3B)

a small protein that binds viral RNA and is necessary for synthesis of viral positive and negative strand RNA.

2BC, 2B, 2C, 3AB, 3A, 3B

proteins which comprise the protein complex needed for virus replication.

VP0, VP1, VP2, VP3, VP4

proteins of the viral capsid.

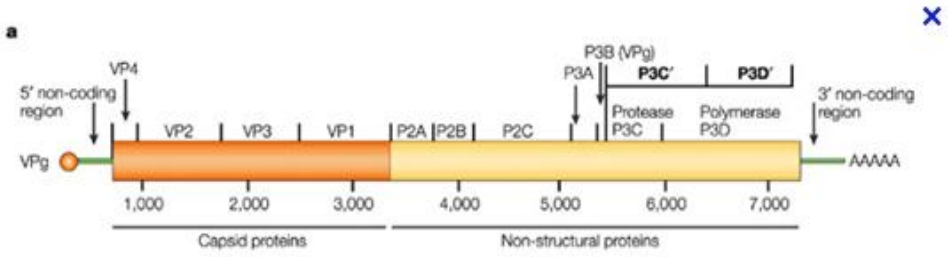
脊髓灰质炎病毒 mRNA 被翻译为一个长多肽。

然后，该多肽被内部蛋白酶自动切割成约 10 个单独的病毒蛋白。

3Dpol

RNA 的 RNA 聚合酶，其功能是复制和繁殖病毒 RNA 基因组。

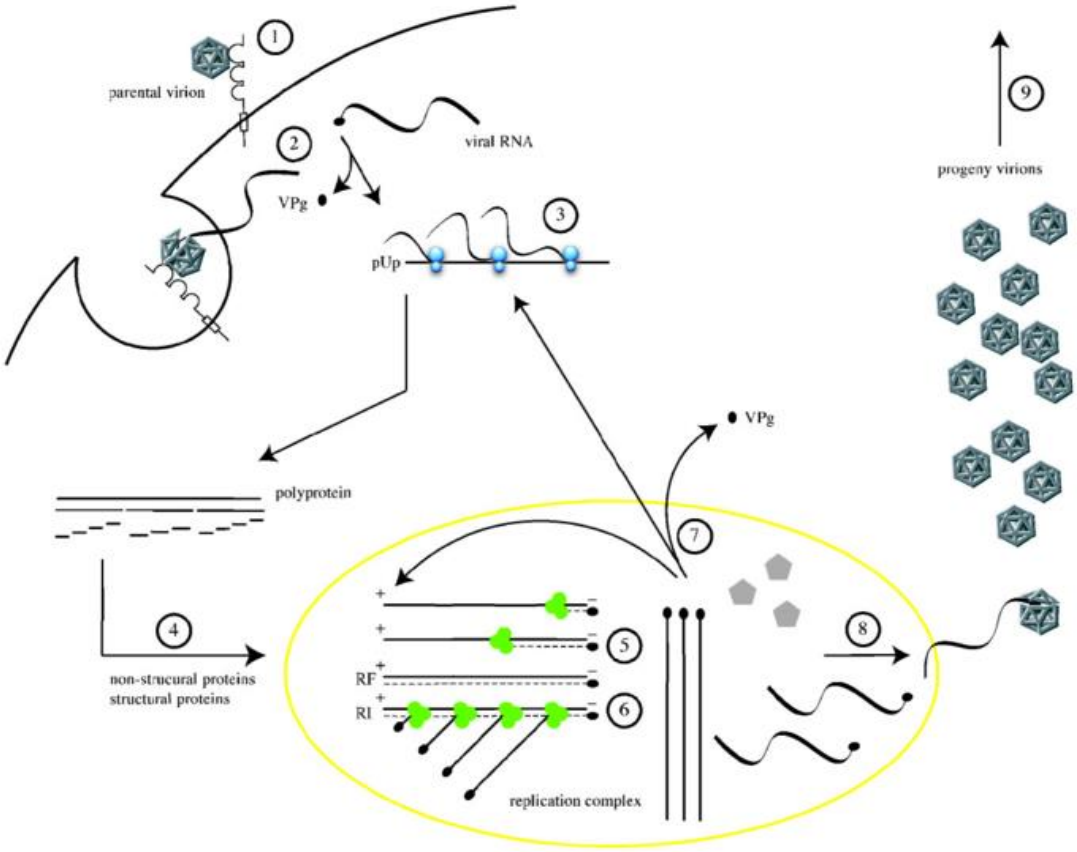
2Apro 和 3Cpro / 3CDpro
切割病毒多肽的蛋白酶。
VPg（3B）
结合病毒 RNA 的小蛋白质，并且是合成病毒阳性和负链 RNA 所必需的。
2BC，2B，2C，3AB，3A，3B
构成病毒复制所需的蛋白质复合物的蛋白质。
VP0，VP1，VP2，VP3，VP4
病毒衣壳的蛋白质。



The Life Cycle of Poliovirus

1) Initiated by binding to the cell surface receptor CD155.
2) The virion is taken up via endocytosis, and the viral RNA is released.
3) Translation of the viral RNA occurs by an IRES-mediated mechanism
4) The polyprotein is cleaved, yielding mature viral proteins
5) The positive-sense RNA serves as template for complementary negative-strand synthesis, producing double-stranded replicative form (RF) RNA
6) Many positive strand RNA copies are produced from the single negative strand
7) The newly synthesized positive-sense RNA molecules can serve as templates for translation of more viral proteins
8) or can be enclosed in a capsid which ultimately generates progeny virions. Lysis of the infected cell results in release of infectious progeny virions

1) 脊髓灰质炎病毒的生命周期
2) 通过结合细胞表面受体 CD155 引发。
3) 病毒粒子通过内吞作用被摄取，病毒 RNA 被释放。
4) 病毒 RNA 的翻译通过 IRES 介导的机制发生
5) 多蛋白被切割，产生成熟的病毒蛋白
6) 正义 RNA 用作互补负链合成的模板，产生双链复制形式（RF）RNA
7) 从单个负链产生许多正链 RNA 拷贝
8) 新合成的正义 RNA 分子可以作为更多病毒蛋白翻译的模板
9) 或可以封闭在最终产生后代病毒粒子的衣壳中。 感染细胞的裂解导致感染性后代病毒粒子的释放



Enterovirus 71

Enterovirus 71 (EV-71) is notable as one of the major causative agents for hand, foot and mouth disease (HFMD), and is sometimes associated with severe central nervous system diseases.

EV71 was first isolated and characterized from cases of neurological disease in California in 1969.

To date, little is known about the molecular mechanisms of host response to EV71 infection, but increases in the level of mRNAs encoding chemokines, proteins involved in protein degradation, complement proteins, and proapoptotis proteins have been implicated

肠病毒 71

肠病毒 71（EV-71）作为手足口病（HFMD）的主要病因之一，有时与严重的中枢神经系统疾病有关。

EV71 首先在 1969 年在加利福尼亚的神经疾病病例中分离和表征。

迄今为止，对于 EV71 感染的宿主反应的分子机制知之甚少，但是涉及编码趋化因子，参与蛋白质降解的蛋白质，补体蛋白质和促凋亡蛋白质的 mRNA 水平的增加已被牵连

Hand, foot and mouth disease

HFMD usually affects infants and children, and is quite common.

It is moderately contagious and is spread through direct contact with the mucus, saliva, or feces of an infected person.

It typically occurs in small epidemics in nursery schools or kindergartens, usually during the summer and autumn months. The usual incubation period is 3–7 days.

It is uncommon in adults, but those with immune deficiencies are very susceptible. HFMD is not to be confused with foot-and-mouth disease.

手足口病

HFMD 通常会影响婴幼儿，而且很常见。

它是中等传染性的，通过与感染者的粘液，唾液或粪便直接接触而传播。

它通常发生在幼儿园或幼儿园的小流行病，通常是在夏季和秋季的几个月。 通常的潜伏期是 3-7 天。

在成年人中不常见，但具有免疫缺陷的那些是非常敏感的。 HFMD 不要与口蹄疫混淆。

Outbreaks

1) In 1997, 31 children died in an outbreak in the Malaysian state of Sarawak.[4]
2) In 1998, there was an outbreak in Taiwan, affecting mainly children.There were 405 severe complications, and 78 children died. The total number of cases in that epidemic is estimated to have been 1.5 million.
3) In 2006, an outbreak in Kuching, Sarawak (according to the New Straits Times, March 14)
4) The largest outbreak of HFMD in India occurred in 2007 in the eastern part of the country in West Bengal. Authors found 38 cases of HFMD in and around Kolkata.
5) 2008, an outbreak in China, beginning in March in Fuyang, Anhui, led to 25,000 infections, and 42 deaths, by May 13. Similar outbreaks were reported in Singapore (more than 2,600 cases as of April 20, 2008), Vietnam (2,300 cases, 11 deaths), Mongolia (1,600 cases), and Brunei (1053 cases)
6) 2009, 17 children died in an outbreak during 03-04/2009 in China's eastern Shandong Province, and 18 children died in the neighboring Henan Province. Out of 115,000 reported cases in China from January to April, 773 were severe and 50 were fatal.
7) 2010, in China, an outbreak occurred in southern China's Guangxi Autonomous Region as well as Guangdong, Henan, Hebei and Shandong provinces. Until March 70, 756 children were infected and 40 died from the disease. By June, the peak season for the disease, 537 havedied
8) 2011, in Vietnam, the disease was reported to have claimed 98 lives, 75% of whom were children under 3 years old. Although there was no official declaration of an outbreak, over 42,000 cases have been reported. Over 10,000 new cases were recorded in the second half of August alone
9) WHO reporting between January to October of 2011 (1,340,259) states the number of cases in China has dropped by approx, 300,000 from 2010's (1,654, 866) cases. With new cases peaking in June. 437 deaths down from 2010 (537 deaths)
10) 2012, in Alabama, United States there is a reported outbreak of an unusual type of the disease. It is occuring in a season it is not usually seen and it is also infecting teenagers and adults. There are currently 14 laboratory confirmed cases by the CDC, with many other reported cases. Officials state there has never been an outbreak of hand, foot and mouth disease in the United States before. There has been some hospitalizations due to the disease but no reported deaths

1) 1997 年，马来西亚沙捞越州的爆发事件中有 31 人死亡[4]
2) 1998 年台湾发生疫情，主要影响儿童。共发生 405 例严重并发症，78 例死亡。该疫情的总数估计为 150 万。
3) 2006 年，沙捞越古晋（根据“三峡新时报”3 月 14 日）的爆发，
4) 印度最大的 HFMD 爆发发生在 2007 年在西孟加拉邦的东部地区。作者在加尔各答及其周围发现了 38 例 HFMD。
5) 2008 年 3 月，安徽阜阳 3 月份爆发的疫情在 5 月 13 日导致 25 000 例感染，42 例死亡。新加坡有类似的爆发事件（截至 2008 年 4 月 20 日为止，有 2600 多起），越南（2,300 人）案件 11 人，蒙古（1600 宗），文莱（1053 宗）
6) 2009 年 03 月 04 日，中国东部山东省发生 17 例儿童死亡，18 名儿童死于邻近河南省。 1 - 4 月中国 115000 例报告病例中，773 例严重，50 例死亡。
7) 2010 年，中国南方广西，广东，河南，河北，山东等省份发生疫情。直到 3 月 70 日，756 名儿童感染，40 人死于该病。到六月份，这个疾病的旺季，537 岁
8) 2011 年，在越南，据报疾病 98 人，其中 75％是 3 岁以下的儿童。虽然没有正式宣布爆发疫情，但已报告了超过 4.2 万例。八月下旬又录得超过一万个新病例
9) 世卫组织 2011 年 1 月至 10 月的报告（1,340,259）指出，中国的病例数从 2010 年（1,654,866 例）下降了约 30 万例。六月份新病例达到顶峰。 2010 年有 437 人死亡（537 人死亡）
10) 2012 年，在美国的阿拉巴马州，据报有一种不寻常类型的疾病爆发。它发生在一个季节，它通常不被看到，它也感染青少年和成年人。目前 CDC 有 14 个实验室确诊病例，还有其他许多报告的病例。官员说，美国以前从未发生过手足口病。由于这种疾病已经有一些住院治疗，但没有报告死亡

The order *Picornavirales*

Conserved RNA-dependent RNA polymerase

Genome has a protein attached to the 5' end

No overlapping open reading frames within the genome

All the RNAs are translated into a polyprotein before processing

小 RNA 病毒的顺序

保守的 RNA 依赖性 RNA 聚合酶

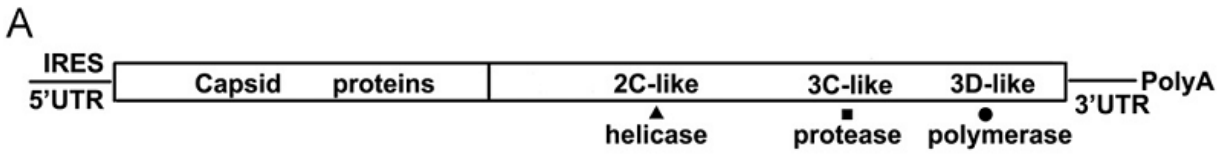
基因组具有附着在 5'末端的蛋白质

基因组内没有重叠的开放阅读框

所有 RNA 在加工前被翻译成多聚蛋白

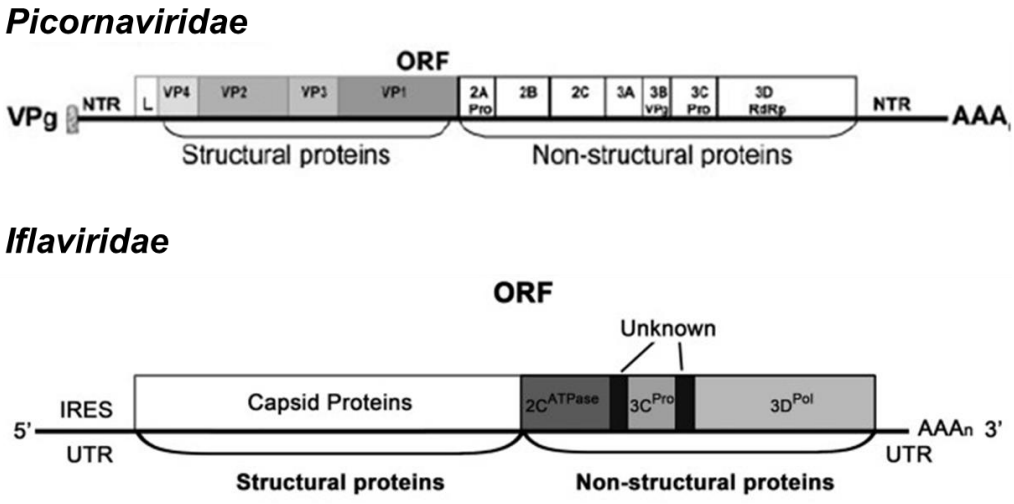
Families in *Picornavirales*

小 RNA 病毒家族



Genomes of the families *Picornaviridae* and *Iflaviridae*

微核心病毒科和箭虫科家族的基因组



Picornaviral Nonstructural Protein 2C

2C is well conserved among picornaviruses;

2C is involved in a variety of functions during the viral life cycle, including uncoating, host cell membrane rearrangements, RNA replication, and encapsidation;

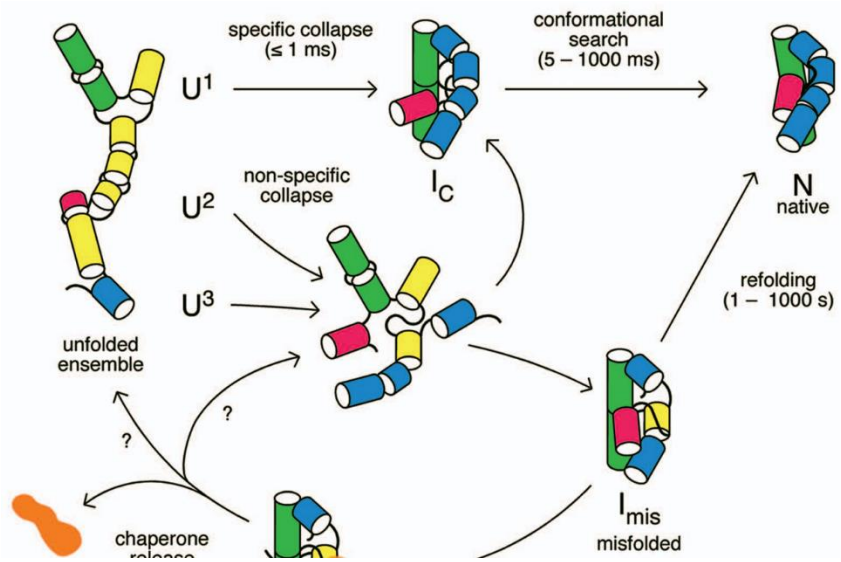
ATPase activity

Putative RNA helicase - conserved motifs typical of superfamily-3 (SF3) helicases

微小 RNA 病毒非结构蛋白 2C

2C 在小核糖核酸病毒中是保守的;
2C 在病毒生命周期中涉及各种功能，包括解开，宿主细胞膜重排，RNA 复制和壳化;
ATPase 活性
推定 RNA 解旋酶 - 超家族 3（SF3）解旋酶典型的保守基序

The tertiary structures of RNAs are important for their functions
RNA 的三级结构对其功能很重要
RNAs are easily trapped in misfolded conformation
RNA 容易陷入错误折叠的构象



RNA remodeling proteins
RNA remodeling proteins such as RNA helicases and RNA chaperones are required for correct folding of RNAs.
RNA 重塑蛋白
RNA 重组蛋白如 RNA 解旋酶和 RNA 伴侣是正确折叠 RNA 所必需的。

Helicases
解旋酶
6 Superfamilies: SF-1 to SF-6
6 超家族：SF-1 至 SF-6
Minimal functional unit is a monomer or a hexamer.
最小功能单元是单体或六聚体。
Directionality
方向性
ATP hydrolysis dependent
ATP 水解依赖
Helicases are involved in a variety of cellular processes
Helicases 参与各种细胞过程

RNA helicases vs. RNA chaperones
RNA 解旋酶与 RNA 分子伴侣

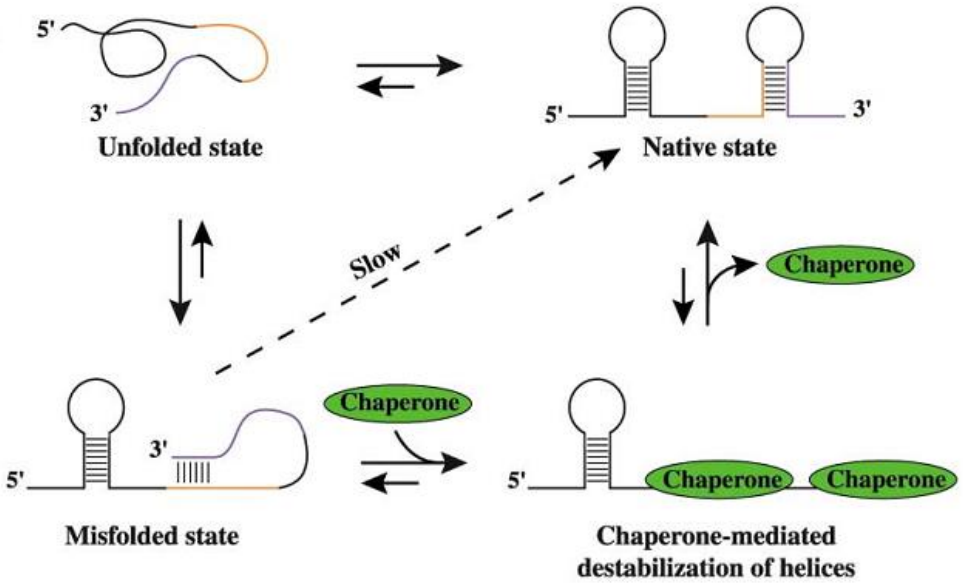
Box 1. General features of RNA remodeling proteins. NA is nucleic acid.

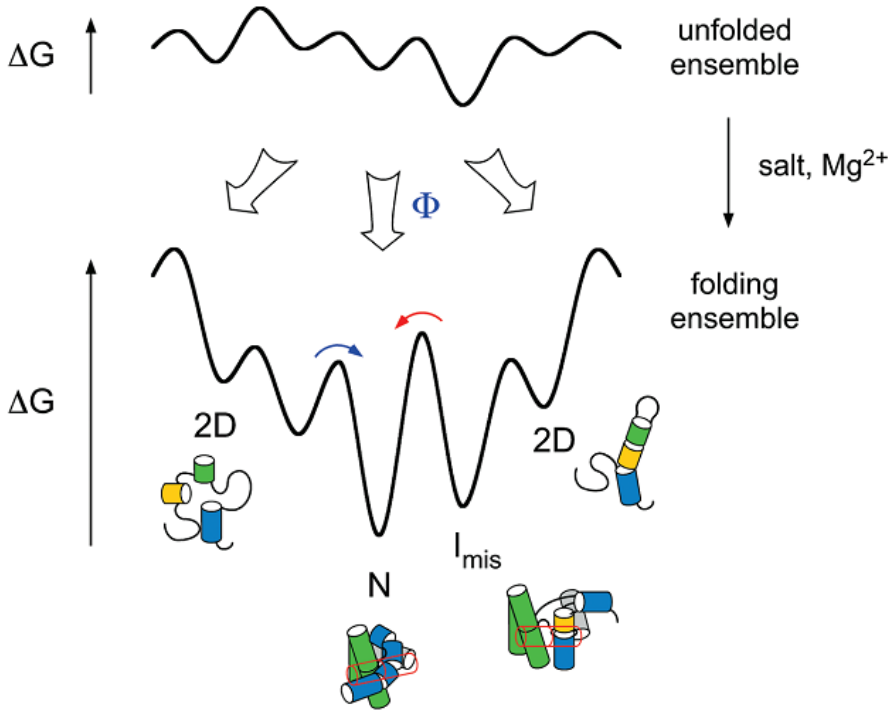
Helicases	Chaperones/Annealers
ATP-dependent	ATP-independent
Non-processive enzymes	Non-specific NA binding proteins

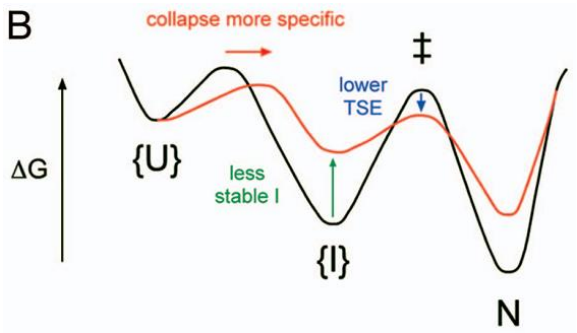
Shared Features/Properties
Rapid NA dissociation kinetics
Increase NA conformational dynamics
Positively charged domains

How RNA chaperone works?

RNA 伴侣如何工作？







Chapter4. Poxvirus and bioterrorism

第四章 痘病毒和生物恐怖

Poxviridae

Poxviruses (members of the family Poxviridae) are viruses that can, as a family, infect both vertebrate and invertebrate animals.

Orthopox (正痘病毒): smallpox virus (variola), vaccinia (cowpox) virus, monkeypox virus

Parapox: orf virus (羊痘病毒), pseudocowpox, bovine papular stomatitis virus;

Yatapox: tanapox virus, yaba monkey tumor virus;

Molluscipox: molluscum contagiosum virus (MCV) 接触传染性软疣病毒

痘病毒

痘病毒（痘病毒科的成员）是可以作为家庭感染脊椎动物和无脊椎动物的病毒。

直痘：天花病毒（天花），牛痘（牛痘）病毒，猴痘病毒

痘病毒：orf 病毒，假性痘病毒，牛丘疹性口炎病毒;

稻瘟病：金枪鱼病毒，亚巴猴肿瘤病毒;

软体动物：传染性软疣病毒（MCV）

Poxviruses are a genus of a single, linear, double-stranded segment of DNA viruses.

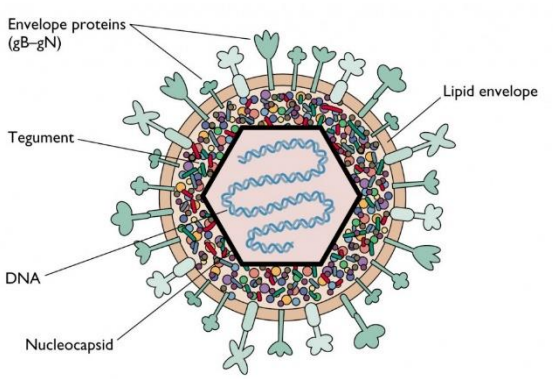
Poxviridae virions are generally enveloped (external enveloped virion- EEV),and shaped like a brick or as an oval form similar to a rounded brick.

The virion is exceptionally large, its size is around 200 nm

痘病毒是 DNA 病毒的单链，线性，双链片段。

痘病毒病毒颗粒通常是包封的（外包膜病毒粒子-EEV），并且形状像砖或椭圆形，类似于圆形砖。

病毒粒子特别大，其大小约为 200nm



Replication of Poxviruses

- ✧ Binding to a receptor on the host cell surface
- ✧ Uncoating with two steps:1.the outer membrane is removed as the particle enters the cell; 2. release the core into the cytoplasm.
- ✧ Non-structural protein are expressed for replication of the viral genome and the structural proteins are expressed to make the virus particle.
- ✧ The assembly of the virus particle occurs in the cytoskeleton of the cell.
- ✧ releasing the viruses
- ✧ The replication of poxvirus is unusual for a dsDNA virus because it occurs in the cytoplasm.
- ✧ Poxvirus encodes its own machinery for genome transcription, a DNA dependent RNA polymerase, while most dsDNA viruses require the host cell's proteins to perform transcription and those host proteins are found in the nucleus.

痘病毒复制

- ✧ 与宿主细胞表面的受体结合
- ✧ 用两个步骤开口：1.当颗粒进入细胞时，去除外膜; 2.释放核心进入细胞质。
- ✧ 非结构蛋白被表达用于病毒基因组的复制，结构蛋白被表达以产生病毒颗粒。
- ✧ 病毒颗粒的组装发生在细胞的细胞骨架中。
- ✧ 释放病毒
- ✧ 痘病毒的复制对于 dsDNA 病毒是不寻常的，因为它发生在细胞质中。

✧ 痘病毒编码其自身的基因组转录机制，一种 DNA 依赖性 RNA 聚合酶，而大多数 dsDNA 病毒需要宿主细胞的蛋白质进行转录，并且这些宿主蛋白在细胞核中发现。

Molluscum contagiosum virus (MCV) 接触传染性软疣病毒

MC is a viral infection of the skin or occasionally of the mucous membranes.

MCV has no animal reservoir, infecting only humans.

There are four types of MCV, MCV-1 to -4;

MCV-1 is the most prevalent and MCV-2 is seen usually in adults and often sexually transmitted.

This common viral disease has a higher incidence in children, sexually active adults, and those who are immunodeficient, and the infection is most common in children aged one to ten years old

- MC 是皮肤的病毒感染或偶尔的粘膜病毒感染。
- MCV 没有动物水库，仅感染人类。
- 有四种类型的 MCV，MCV-1 至-4;
- MCV-1 是最普遍的，并且通常在成年人中观察到 MCV-2，并且经常性传播。
- 这种常见的病毒性疾病在儿童，性活跃的成年人和免疫缺陷病人中的发病率较高，感染在 1 至 10 岁的儿童中最常见

Smallpox

Smallpox virus preferentially attacks skin cells, causing the characteristic pimples (called macules) associated with the disease.

Smallpox killed an estimated 400,000 Europeans per year during the closing years of the 18th century, and was responsible for an estimated 300–500 million deaths during the 20th century.

天花

天花病毒优先攻击皮肤细胞，导致与疾病相关的特征性丘疹（称为斑点）。

在十八世纪的最后几年，天花每年杀死了 40 万欧洲人，并在二十世纪造成约三亿五千万人的死亡。

Variola virus

Smallpox is caused by infection with variola virus.

Variola virus: belongs to the genus Orthopoxvirus, the family Poxviridae and subfamily chordopoxvirinae (脊椎动物痘病毒亚科).

Large brick-shaped virus, approximately 302 to 350 nanometers by 244 to 270 nm.

dsDNA, 186kbp, a hairpin loop at each end.

天花病毒

天花是由天花病毒感染引起的。

天花病毒：属于直链痘病毒属，痘病毒科和脊索动物痘病毒亚科家族。

大砖状病毒，大约 302 到 350 纳米，244 到 270 毫微米。

dsDNA，186kbp，每端发夹环。

spread of smallpox

Smallpox is highly contagious

1. Airborne:droplets expressed from the oral, nasal, or pharyngeal mucosa of an infected person
2. Directly contacting with infected bodily fluids or contaminated objects.
3. Rarely, smallpox has been spread by virus carried in the air in enclosed settings such as buildings, buses, and trains.

天花的传播

天花是高度传染性的

1.空气传播：由感染者的口腔，鼻腔或咽部粘膜表达的液滴

2.与受感染的体液或被污染的物体直接接触。

3.很少有天花板已经被空气传播，包括建筑物，公共汽车和火车等封闭环境。

Cowpox

Cowpox is a skin disease by a virus known as the Cowpox virus. The pox is related to the vaccinia virus and got its name from the distribution of the disease when dairymaids touched the udders of infected cows.

牛痘

牛皮痘是一种被称为牛痘病毒的病毒的皮肤病。 痘痘与痘苗病毒相关，并且当奶牛感染感染奶牛的乳房时，从疾病分布中得知它的名称。

Human cowpox virus

Human cowpox virus infections are commonly described in relation to contact with diseased domestic cats, sometimes directly from rats or domesticated house mice. Human infections usually remain localized and self-limiting but can become fatal in immunosuppressed patients.

人类牛皮癣病毒

人类牛痘病毒感染通常描述为与患病的家猫有联系，有时直接来自大鼠或家养小鼠。 人类感染通常保持局部和自限性，但在免疫抑制患者中可能变得致命。

Cowpox & Vaccine

The cowpox virus was used to perform the first successful vaccination against a disease, smallpox, which is caused by the related Variola virus.

Cowpox is similar to but much milder than smallpox. It resembles mild smallpox, and was the basis of the first smallpox vaccines. When the patient recovers from cowpox, the person is immune to smallpox.

牛皮癣疫苗

使用牛痘病毒进行针对由相关天花病毒引起的疾病，天花的首次成功接种疫苗。

天痘与天花相似但比天花温和。 它类似于轻微的天花，是第一批天花疫苗的基础。 当患者从牛痘中恢复时，该人可以免疫天花。

Vaccinia

Vaccinia virus is a large, complex, enveloped virus belonging to the poxvirus family. It has a linear, dsDNA genome approximately 190 kbp in length, and which encodes for approximately 250 genes.

牛痘

牛痘病毒是属于痘病毒家族的大型复杂的包膜病毒。 它具有长度为约 190kbp 的线性 dsDNA 基因，其编码约 250 个基因。

Vaccinia virus & Smallpox

A Vaccinia virus infection is very mild and is typically asymptomatic in healthy individuals, but it may cause a mild rash and fever. Immune responses generated from a Vaccinia virus infection protects the person against a lethal smallpox infection. For this reason, Vaccinia virus was, and is still being used as a live-virus vaccine against smallpox. Unlike vaccines that use weakened forms of the virus being vaccinated against, the Vaccinia virus vaccine cannot cause a smallpox infection because it does not contain the smallpox virus.

牛痘病毒和天花

痘苗病毒感染非常温和，在健康个体中通常无症状，但可能引起轻度皮疹和发烧。 从痘苗病毒感染产生的免疫应答保护人免受致命的天花感染。 因此，牛痘病毒仍然被用作针对天花的活病毒疫苗。 与使用被接种的病毒弱化形式的疫苗不同，痘苗病毒疫苗不会引起天花感染，因为它不含天花病毒。

Vaccinia virus & vaccine

Vaccinia virus is well-known for its role as a vaccine that eradicated the smallpox disease, making it the first human disease to be successfully eradicated by science.

牛痘病毒和疫苗

牛痘病毒作为一种根除天花病疫苗的作用而闻名，使其成为科学成功根除的第一种人类疾病。

According to the U.S. Centers for Disease Control and Prevention (CDC):

- ✧ A bioterrorism attack is the deliberate release of viruses, bacteria, toxins or other harmful agents used to cause illness or death in people, animals, or plants. These agents are typically found in nature, but it is possible that they could be mutated or altered to increase their ability to cause disease, make them resistant to current medicines, or to increase their ability to be spread into the environment. Biological agents can be spread through the air, water, or in food.
- ✧ Terrorists tend to use biological agents because they are extremely difficult to detect and do not cause illness for several hours to several days. Some bioterrorism agents, like the smallpox virus, can be spread from person to person and some, like anthrax, cannot
- ✧ Bioterrorism is an attractive weapon because biological agents are relatively easy and inexpensive to obtain, can be easily disseminated, and can cause widespread fear and panic beyond the actual physical damage they can cause.
- ✧ Military leaders, however, have learned that, as a military asset, bioterrorism has some important limitations; it is difficult to employ a bioweapon in a way that only the enemy is affected and not friendly forces.
- ✧ A biological weapon is useful to terrorists mainly as a method of creating mass panic and disruption to a state or a country. However, technologists such as Bill Joy have warned of the potential power which genetic engineering might place in the hands of future bio-terrorists.
- ✧ The use of agents that do not cause harm to humans but disrupt the economy have been discussed.[citation needed] A highly relevant pathogen in this context is the foot-and-mouth disease (FMD) virus, which is capable of causing widespread economic damage and public concern (as witnessed in the 2001 and 2007 FMD outbreaks in the UK), whilst having almost no capacity to infect humans.

根据美国疾病预防控制中心（CDC）：

- ✧ 生物恐怖袭击是故意释放用于在人，动物或植物中造成疾病或死亡的病毒，细菌，毒素或其他有害物质。这些药物通常在自然界中发现，但是它们可能被突变或改变以增加其引起疾病的能力，使其对当前药物有抵抗力或增加其传播到环境中的能力。生物制剂可以通过空气，水或食物传播。
- ✧ 恐怖分子倾向于使用生物制剂，因为它们难以发现并且不会在数小时至数天内引起疾病。一些生物恐怖主义者，如天花病毒，可以从一个人传播到一个人，一些，如炭疽，不能
- ✧ 生物恐怖主义是一种有吸引力的武器，因为生物制剂相对容易和便宜，可以很容易地传播，并可能引起广泛的恐惧和恐慌，超出它们可能导致的实际物理伤害。
- ✧ 不过军方领导了解到，作为军事财产，生物恐怖主义有一些重要的局限性;很难采用生物武器，只有敌人受到影响，而不是友军。
- ✧ 一种生物武器对恐怖主义分子有用，主要是作为对一个国家或一个国家造成大规模恐慌和破坏的一种手段。然而，Bill Joy 等技术人员已经警告说，遗传工程可能在未来的生物恐怖分子手中占有一席之地。
- ✧ 已经讨论了使用不会对人造成危害但破坏经济的药剂。在这方面，高度相关的病原体是口蹄疫（FMD）病毒，其能够引起广泛的经济损害和公众关注（如 2001 年和 2007 年在英国的口蹄疫暴发中所见到），而几乎没有感染人类的能力。

History

Use bubonic plague to infect enemy cities

At that time, Anton Dilger lived in Germany, but in 1915 he was sent to the United States carrying cultures of glanders, a virulent disease of horses and mules. Dilger set up a laboratory in his home in Chevy Chase, Maryland. He used stevedores working the docks in Baltimore to infect horses with glanders while they were waiting to be shipped to Britain. Dilger was under suspicion as being a German agent, but was never arrested. Dilger eventually fled to Madrid, Spain, where he died during the Influenza Pandemic of 1918.

In 1969, President Richard Nixon shut down all programs related to American offensive use of biological weapons.

Several cases of anthrax broke out in the United States in the 2001 anthrax attacks, caused deliberately. Letters laced with infectious anthrax were delivered to news media offices and the U.S Congress. The letters killed 5. Tests on the anthrax strain used in the attack pointed to a domestic source, possibly from the biological weapons program.
历史
使用瘟疫来感染敌方城市
那时候，安东·迪尔（Anton Dilger）住在德国，但是在 1915 年，他被送到美国，携带着腺体，马和骡子病毒的文化。 Dilger 在马里兰州 Chevy Chase 的家中设立了一个实验室。他在巴尔的摩的码头工作，在等待运往英国的时候，使用装卸工作人员来治疗带有腺体的马。 Dilger 被怀疑为德国人，但从未被捕。 Dilger 最终逃到了西班牙马德里，在那里他在 1918 年的流感大流行期间死亡。
1969 年，理查德·尼克松总统关闭与美国进攻生物武器有关的所有方案。
在 2001 年的炭疽病袭击中，有几例炭疽病爆发，故意造成。带有传染性炭疽病的信件已交付新闻媒体处和美国国会。信件死亡 5.袭击中使用的炭疽毒素的测试指向国内来源，可能来自生物武器计划。

Possible viruses may be used by bioterrorists
Smallpox
Ebola, Marburg
Influenza A
生物恐怖分子可能会使用可能的病毒
天花
埃博拉，马尔堡
甲型流感

Types of agents
Under current United States law, bio-agents which have been declared by the U.S. Department of Health and Human Services or the U.S. Department of Agriculture to have the "potential to pose a severe threat to public health and safety" are officially defined as "select agents".
The CDC categorizes these agents (A, B or C) and administers the Select Agent Program, which regulates the laboratories which may possess, use, or transfer select agents within the United States.
代理人的类型
根据目前的美国法律，由美国卫生和人类服务部或美国农业部宣布的具有“对公众健康和安全构成严重威胁的潜力”的生物制剂官方定义为“选择代理人”。
CDC 将这些代理人（A，B 或 C）归类，并管理选择代理程序，该程序管理可能拥有，使用或转移美国境内特定代理商的实验室。

Category A： These high-priority agents pose a risk to national security, can be easily transmitted and disseminated, result in high mortality, have potential major public health impact, may cause public panic, or require special action for public health preparedness.
Smallpox
Viral hemorrhagic fevers (Ebola, Marburg)
A 类
这些高优先权代理人对国家安全构成风险，易于传播和传播，造成高死亡率，潜在的重大公共卫生影响，可能引起公众恐慌，或要求公共卫生准备采取特别行动。
天花
病毒性出血热（埃博拉，马尔堡）

Category B： agents are moderately easy to disseminate and have low mortality rates. Viral encephalitis
Category C：agents are emerging pathogens that might be engineered for mass dissemination because of their availability, ease of production and dissemination, high mortality rate, or ability to cause a major health impact.
Nipah virus

Hantavirus
SARS
H1N1 a strain of influenza (flu)
HIV/AIDS
B 类药物适度传播，死亡率低。 病毒性脑炎
C 类药剂是可能由于其可用性，易于生产和传播，高死亡率或导致重大健康影响的能力而被设计用于大量传播的新出现的病原体。
尼帕病毒
汉坦病毒
SARS
甲型 H1N1 流感（流感）
艾滋病毒/艾滋病

Smallpox as a weapon

Today, very few people have immunity to smallpox, since the eradication of smallpox is shut down worldwide.
Smallpox in aerosol form is very stable
Borne by wind currents, it would be undetectable
If 50 people is infected, two weeks later, 500-1000 people will be infected
Physicians are not familar with smallpox, and may treat it as other illness
Lack of infrastructures to isolate infected people
天花作为武器
今天，很少有人对天花免疫，因为全球关闭天花。
气溶胶形式的天花素非常稳定
由风流传出，将无法检测
如果感染了 50 人，两周后，将有 500-1000 人感染
医生不熟悉天花，可以将其视为其他疾病
缺乏基础设施来隔离受感染的人

Chapter 5 Antiviral Drugs

第 5 章 抗病毒药物

Definition

Antiviral drugs are a class of medication used specifically for treating viral infections.

Like antibiotics for bacteria, specific antivirals are used for specific viruses.

Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development.

定义

抗病毒药物是专门用于治疗病毒感染的一类药物。

像细菌的抗生素一样，特定的抗病毒药物被用于特定的病毒。

与大多数抗生素不同，抗病毒药物不会破坏其目标病原体; 而是阻止他们的发展。

History

- ✧ Through the mid- to late-20th century, medical science and practice included an array of effective tools, ranging from antiseptics to vaccines and antibiotics, but no drugs to treat viral infections.
- ✧ While vaccines proved effective in preventing many viral diseases, they could not help once a viral infection set in. Prior to the development of antivirals, when someone contracted a virus, there was little that could be done other than treating the symptoms and waiting for the disease to run its course.
- ✧ Before 1975, specific and effective antiviral therapy was not thought possible because viruses are obligate intracellular parasites, relying on host cells to replicate.
- ✧ It was thought that any antiviral drug inhibiting viral replication would affect cellular metabolism, leading to cell injury or even death.
- ✧ The breakthrough occured when the structure of certain viral-encoded enzymes was shown to differ from the corresponding cellular enzymes.
- ✧ The first experimental antivirals were developed in the 1960s, mostly to deal with herpes viruses, and were found using traditional trial-and-error drug discovery methods. Researchers grew cultures of cells and infected them with the target virus. They then introduced into the cultures chemicals which they thought might inhibit viral activity, and observed whether the level of virus in the cultures rose or fell.
- ✧ This was a very time-consuming, hit-or-miss procedure, and in the absence of a good knowledge of how the target virus worked, it was not efficient in discovering effective antivirals which had few side effects. Only in the 1980s, when the full genetic sequences of viruses began to be unraveled, researchers began to learn how viruses worked in detail, and what chemicals were needed.
- ✧ As of 2011 dozens of antiviral treatments are available, and medical research is rapidly exploiting new knowledge and technology to develop more.

历史

- ✧ 到 20 世纪中期到 20 世纪末期，医学科学和实践包括一系列有效的工具，从防腐剂到疫苗和抗生素，但没有药物治疗病毒感染。
- ✧ 虽然疫苗被证明是有效预防许多病毒性疾病，但一旦发生病毒感染就无法帮助。在开发抗病毒药物之前，当有人感染病毒时，除了治疗症状和等待治疗之外，还有一点可以做疾病跑步。
- ✧ 1975 年以前，特异性和有效的抗病毒治疗是不可能的，因为病毒是依赖于宿主细胞复制的专性细胞内寄生虫。
- ✧ 据认为，任何抑制病毒复制的抗病毒药物都会影响细胞代谢，导致细胞损伤甚至死亡。
- ✧ 当某些病毒编码的酶的结构显示与相应的细胞酶不同时，发生突破。
- ✧ 第一个实验性抗病毒药物在 20 世纪 60 年代开发，主要用于治疗疱疹病毒，并使用传统的试错法药物发现方法。研究人员培养细胞培养并用目标病毒感染它们。然后他们将他们认为可能抑制病毒活性的化学物质引入培养物中，观察培养物中病毒水平是否上升或下降。

✧ 这是一个非常耗时的命中或错过的程序，由于缺乏对目标病毒如何运作的了解，发现有效的抗病毒药物几乎没有副作用，效率并不高。只有在 20 世纪 80 年代，当病毒的全部基因序列开始被解开时，研究人员才开始学习病毒的工作细节，以及需要哪些化学物质。
✧ 截至 2011 年，已有数十种抗病毒治疗方法，医学研究正在迅速开发新的知识和技术来开发更多。

Virus life cycle

✧ Viruses consist of a genome and sometimes a few enzymes stored in a capsule made of protein (called a capsid), and sometimes covered with a lipid layer (sometimes called an 'envelope').
✧ Viruses cannot reproduce on their own, and instead propagate by subjugating a host cell to produce copies of themselves, thus producing the next generation.
✧ Researchers working on such "rational drug design" strategies for developing antivirals have tried to attack viruses at every stage of their life cycles
✧ Viral life cycles vary in their precise details depending on the species of virus, but they all share a general pattern:
✧ Attachment to a host cell.
✧ Release of viral genes and possibly enzymes into the host cell.
✧ Replication of viral components using host-cell machinery.
✧ Assembly of viral components into complete viral particles.
✧ Release of viral particles to infect new host cells.

病毒生命周期

✧ 病毒由基因组组成，有时存在于由蛋白质制成的胶囊（称为衣壳）中，有时被脂质层（有时称为“包膜”）覆盖的酶。
✧ 病毒不能自己复制，而是通过征服宿主细胞来产生自己的副本来传播，从而产生下一代。
✧ 研究开发抗病毒药物的“合理药物设计”策略的研究人员试图在其生命周期的每个阶段攻击病毒
✧ 病毒生命周期的细节取决于病毒的种类，但都有一般的模式：
✧ 附着于宿主细胞。
✧ 将病毒基因和可能的酶释放到宿主细胞中。
✧ 使用宿主细胞机制复制病毒组分。
✧ 将病毒组分装配成完整的病毒颗粒。
✧ 释放感染新宿主细胞的病毒颗粒。

Limitations of vaccines

Vaccines are very effective on stable viruses, but are of limited use in treating a patient who has already been infected. They are also difficult to successfully deploy against rapidly mutating viruses, such as influenza (the vaccine for which is updated every year) and HIV.

Antiviral drugs are particularly useful in these cases.

疫苗的局限性

疫苗对稳定的病毒非常有效，但在治疗已经感染的患者方面的用途有限。

他们也很难成功部署快速突变病毒，如流行性感冒（每年更新的疫苗）和艾滋病毒。

在这些情况下，抗病毒药物特别有用。

Anti-viral targeting

✧ The general idea behind modern antiviral drug design is to identify viral proteins, or parts of proteins, that can be disabled.
✧ These "targets" should generally be as unlike any proteins or parts of proteins in humans as possible, to reduce the likelihood of side effects.
✧ The targets should also be common across many strains of a virus, or even among different species of virus in the same family, so a single drug will have broad effectiveness.
✧ For example, a researcher might target a critical enzyme synthesized by the virus, but not the patient, that is common across strains, and see what can be done to interfere with its operation.

- ✧ Once targets are identified, candidate drugs can be selected, either from drugs already known to have appropriate effects, or by actually designing the candidate at the molecular level with a computer-aided design program.
- ✧ The target proteins can be manufactured in the lab for testing with candidate treatments by inserting the gene that synthesizes the target protein into bacteria or other kinds of cells. The cells are then cultured for mass production of the protein, which can then be exposed to various treatment candidates and evaluated with "rapid screening" technologies.

靶向抗病毒

- ✧ 现代抗病毒药物设计背后的一般思想是鉴定可以被禁用的病毒蛋白质或蛋白质部分。
- ✧ 这些“目标”通常应与人类中任何蛋白质或蛋白质的部分不同，以减少副作用的可能性。
- ✧ 目标也应该在许多病毒株中甚至在同一家族中的不同病毒种类中是常见的，因此单一药物将具有广泛的有效性。
- ✧ 例如，研究人员可能针对由病毒合成的关键酶，而不是病毒，这是常见的跨毒株，并看看可以做什么干扰其操作。
- ✧ 一旦确定了目标，可以选择候选药物，从已知已知具有适当作用的药物中选择，或者通过计算机辅助设计程序实际设计分子水平的候选物。
- ✧ 目标蛋白质可以在实验室中制造，通过将合成目标蛋白质的基因插入细菌或其他种类的细胞中进行候选处理。然后将细胞培养以大量生产蛋白质，然后将其暴露于各种治疗候选物并用“快速筛选”技术进行评估。

Before cell entry

One anti-viral strategy is to interfere with the ability of a virus to infiltrate a target cell.

The virus must go through a sequence of steps to do this, beginning with binding to a specific "receptor" molecule on the surface of the host cell and ending with the virus "uncoating" inside the cell and releasing its contents.

Viruses that have a lipid envelope must also fuse their envelope with the target cell, or with a vesicle that transports them into the cell, before they can uncoat.

Using agents which mimic the virus-associated protein (VAP), natural ligands of the receptor or anti-receptor antibodies

细胞进入前

一种抗病毒策略是干扰病毒渗透靶细胞的能力。

病毒必须经过一系列步骤才能做到这一点，从与宿主细胞表面上的特定“受体”分子的结合开始，并以细胞内的“解开”病毒结束并释放其内容。

具有脂质包膜的病毒也必须将它们的包膜与靶细胞融合，或者在将它们运送到细胞内的囊泡之前将其熔化。

使用模拟病毒相关蛋白（VAP），受体天然配体或抗受体抗体的试剂

Entry inhibitor

A very early stage of viral infection is viral entry, when the virus attaches to and enters the host cell.

A number of "entry-inhibiting" or "entry-blocking" drugs are being developed to fight HIV.

HIV most heavily targets the immune system's white blood cells known as "helper T cells", and identifies these target cells through T-cell surface receptors designated "CD4" and "CCR5".

Attempts to interfere with the binding of HIV with the CD4 receptor have failed to stop HIV from infecting helper T cells, but research continues on trying to interfere with the binding of HIV to the CCR5 receptor in hopes that it will be more effective.

进入抑制剂

当病毒附着到宿主细胞时，病毒感染的非常早期阶段是病毒进入。

目前正在开发一些“入门禁”或“入境阻止”药物来对付艾滋病毒。

艾滋病毒最重要的目标是称为“辅助性 T 细胞”的免疫系统的白细胞，并通过称为“CD4”和“CCR5”的 T 细胞表面受体鉴定这些靶细胞。

干扰艾滋病毒与 CD4 受体结合的尝试未能阻止艾滋病毒感染辅助性 T 细胞，但研究继续试图干扰艾滋病毒与 CCR5 受体的结合，希望更有效。

Uncoating inhibitor

Inhibitors of uncoating have also been investigated.

Amantadine and rimantadine, have been introduced to combat influenza. These agents act on penetration/uncoating. Pleconaril works against rhinoviruses, which cause the common cold, by blocking a pocket on the surface of the virus that controls the uncoating process. This pocket is similar in most strains of rhinoviruses and enteroviruses, which can cause diarrhea, meningitis, conjunctivitis, and encephalitis.

脱壳抑制剂

还研究了涂层抑制剂。

金刚酸和金刚乙胺已被引入抗击流感。 这些药剂可用于穿透/涂抹。

Pleconaril 通过阻止病毒表面上的口袋来控制脱皮过程，抵抗鼻病毒，导致感冒。 这种口袋在大多数鼻病毒和肠道病毒菌株中是相似的，可引起腹泻，脑膜炎，结膜炎和脑炎。

During viral synthesis	病毒合成期间
Reverse transcription	逆转录
Integrase	整合
Transcription	转录
Translation / antisense	翻译/反义词
Translation / ribozymes	翻译/核酶
Protease inhibitors	蛋白酶抑制剂

Reverse transcription

- ✧ One way of doing this is to develop nucleotide or nucleoside analogues that look like the building blocks of RNA or DNA, but deactivate the enzymes that synthesize the RNA or DNA once the analogue is incorporated. This approach is more commonly associated with the inhibition of reverse transcriptase (RNA to DNA) than with "normal" transcriptase (DNA to RNA).
- ✧ The first successful antiviral, acyclovir, is a nucleoside analogue, and is effective against herpesvirus infections. The first antiviral drug to be approved for treating HIV, zidovudine (AZT), is also a nucleoside analogue.
- ✧ An improved knowledge of the action of reverse transcriptase has led to better nucleoside analogues to treat HIV infections. One of these drugs, lamivudine, has been approved to treat hepatitis B, which uses reverse transcriptase as part of its replication process. Researchers have gone further and developed inhibitors that do not look like nucleosides, but can still block reverse transcriptase.
- ✧ Another target being considered for HIV antivirals include RNase H - which is a component of reverse transcriptase that splits the synthesized DNA from the original viral RNA.

逆转录

- ✧ 这样做的一个方法是开发看起来像 RNA 或 DNA 的结构单元的核苷酸或核苷类似物，但一旦掺入了类似物，就会使合成 RNA 或 DNA 的酶失活。这种方法通常与逆转录酶（RNA 到 DNA）的抑制相比，与“正常”转录酶（DNA 到 RNA）的抑制相关。
- ✧ 第一个成功的抗病毒药物阿昔洛韦是一种核苷类似物，对疱疹病毒感染有效。被批准用于治疗 HIV 的第一种抗病毒药物齐多夫定（AZO）也是核苷类似物。
- ✧ 改进的逆转录酶作用的知识已经导致更好的核苷类似物来治疗 HIV 感染。其中一种药物拉米夫定已被批准用于治疗乙型肝炎，其使用逆转录酶作为其复制过程的一部分。研究人员已经进一步发展出不像核苷的抑制剂，但仍然可以阻断逆转录酶。
- ✧ 被认为是 HIV 抗病毒药物的另一个目标包括 RNase H，RNase H 是从原始病毒 RNA 分裂合成的 DNA 的逆转录酶的一个组成部分。

Transcription

Once a virus genome becomes operational in a host cell, it then generates messenger RNA (mRNA) molecules that direct the synthesis of viral proteins.
Production of mRNA is initiated by proteins known as transcription factors.
Several antivirals are now being designed to block attachment of transcription factors to viral DNA.
转录
一旦病毒基因组在宿主细胞中变得可操作，则其产生引导病毒蛋白质合成的信使 RNA（mRNA）分子。
mRNA 的产生由称为转录因子的蛋白质引发。
现在正在设计几种抗病毒药物来阻断转录因子与病毒 DNA 的连接。

Translation / antisense

- ✧ Genomics has not only helped find targets for many antivirals, it has provided the basis for an entirely new type of drug, based on "antisense" molecules. These are segments of DNA or RNA that are designed as complementary molecule to critical sections of viral genomes, and the binding of these antisense segments to these target sections blocks the operation of those genomes.
- ✧ A phosphorothioate antisense drug named fomivirsen has been introduced, used to treat opportunistic eye infections in AIDS patients caused by cytomegalovirus, and other antisense antivirals are in development.
- ✧ An antisense structural type that has proven especially valuable in research is morpholino antisense.
- ✧ Morpholino oligos have been used to experimentally suppress many viral types: caliciviruses, flaviviruses (WNV, dengue, HCV), coronaviruses.

翻译/反义

- ✧ 基因组学不仅有助于发现许多抗病毒药物的靶点，而且还为基于“反义”分子的全新药物提供了基础。这些是被设计为与病毒基因组的关键部分的互补分子的 DNA 或 RNA 片段，并且这些反义片段与这些靶标部分的结合阻止了这些基因组的操作。
- ✧ 已经引入了名为 fomivirsen 的硫代磷酸酯反义药物，用于治疗由巨细胞病毒引起的 AIDS 患者的机会性眼部感染，其他反义抗病毒药物正在开发中。
- ✧ 已被证明在研究中特别有价值的反义结构类型是吗啉反义。
- ✧ 已经使用 Morpholino 寡核苷酸来实验地抑制许多病毒类型：杯状病毒，黄病毒（WNV，登革热，HCV），冠状病毒。

Translation / ribozymes

Yet another antiviral technique inspired by genomics is a set of drugs based on ribozymes, which are enzymes that will cut apart viral RNA or DNA at selected sites. In their natural course, ribozymes are used as part of the viral manufacturing sequence, but these synthetic ribozymes are designed to cut RNA and DNA at sites that will disable them.
A ribozyme antiviral to deal with hepatitis C has been suggested, and ribozyme antivirals are being developed to deal with HIV. An interesting variation of this idea is the use of genetically modified cells that can produce custom-tailored ribozymes. This is part of a broader effort to create genetically modified cells that can be injected into a host to attack pathogens by generating specialized proteins that block viral replication at various phases of the viral life cycle.
翻译/核酶
基因组学启发的另一种抗病毒技术是一套基于核酶的药物，它们是在选定部位切断病毒 RNA 或 DNA 的酶。 在其自然过程中，核酶被用作病毒制造顺序的一部分，但是这些合成核酶被设计为在将会禁用它们的位点上切割 RNA 和 DNA。
已经提出了用于治疗丙型肝炎的核酶抗病毒药物，正在开发用于治疗 HIV 的核酶抗病毒药物。 这个想法的一个有趣的变化是使用可以生产定制的核酶的转基因细胞。 这是创建转基因细胞的一个更广泛的努力的一部分，可以通过产生在病毒生命周期的各个阶段产生阻断病毒复制的专门蛋白质来注入宿主来攻击病原体。

Protease inhibitors

- ✧ Some viruses include an enzyme known as a protease that cuts viral protein chains apart so they can be assembled into their final configuration.
- ✧ HIV includes a protease, and so considerable research has been performed to find "protease inhibitors" to attack HIV at that phase of its life cycle.
- ✧ Protease inhibitors became available in the 1990s and have proven effective, though they can have unusual side effects, for example causing fat to build up in unusual places.
- ✧ Improved protease inhibitors are now in development.
- ✧ Protease inhibitors have also been seen in nature. A protease inhibitor was isolated from the Shiitake mushroom (Lentinus edodes). The presence of this may explain the Shiitake mushrooms noted antiviral activity in vitro.

蛋白酶抑制剂

- ✧ 一些病毒包括一种称为蛋白酶的酶，可以将病毒蛋白链分开，从而将其组装成其最终构型。
- ✧ 艾滋病毒包括蛋白酶，因此已经进行了大量的研究，以在其生命周期的这个阶段发现“蛋白酶抑制剂”来攻击 HIV。
- ✧ 蛋白酶抑制剂在 20 世纪 90 年代成为可用，已被证明是有效的，尽管它们可能具有不寻常的副作用，例如引起脂肪在不寻常的地方产生。
- ✧ 改进的蛋白酶抑制剂正在开发中。
- ✧ 蛋白酶抑制剂在自然界中也被看到。 从香菇（Lentinus edodes）中分离出蛋白酶抑制剂。 这种情况可能解释了香菇在体外注意到抗病毒活性。

Release Phase

The final stage in the life cycle of a virus is the release of completed viruses from the host cell, and this step has also been targeted by antiviral drug developers.

Two drugs named zanamivir (Relenza) and oseltamivir (Tamiflu) that have been recently introduced to treat influenza prevent the release of viral particles by blocking a molecule named neuraminidase that is found on the surface of flu viruses, and also seems to be constant across a wide range of flu strains.

发作阶段

病毒生命周期的最后阶段是从宿主细胞中释放已完成的病毒，此步骤也是抗病毒药物开发者的目标。

最近引入治疗流感的两种名为扎那米韦（Relenza）和奥司他韦（Tamiflu）的药物通过阻断在流感病毒表面发现的名为神经氨酸酶的分子来预防病毒颗粒的释放，并且似乎在 广泛的流感病毒株。

Immune system stimulation

- ✧ A second category of tactics for fighting viruses involves encouraging the body's immune system to attack them, rather than attacking them directly. Some antivirals of this sort do not focus on a specific pathogen, instead stimulating the immune system to attack a range of pathogens.
- ✧ One of the best-known of this class of drugs are interferons, which inhibit viral synthesis in infected cells. One form of human interferon named "interferon alpha" is well-established as part of the standard treatment for hepatitis B and C, and other interferons are also being investigated as treatments for various diseases.
- ✧ A more specific approach is to synthesize antibodies, protein molecules that can bind to a pathogen and mark it for attack by other elements of the immune system. Once researchers identify a particular target on the pathogen, they can synthesize quantities of identical "monoclonal" antibodies to link up that target. A monoclonal drug is now being sold to help fight respiratory syncytial virus in babies, and antibodies purified from infected individuals are also used as a treatment for hepatitis B.

免疫系统刺激

- ✧ 打击病毒的第二类战术涉及到鼓励身体的免疫系统进行攻击，而不是直接攻击他们。一些这样的抗病毒药物不会专注于特定的病原体，而是刺激免疫系统攻击一系列病原体。
- ✧ 最着名的这类药物之一是干扰素，其抑制感染细胞中的病毒合成。名为“干扰素α”的人类干扰素的一种形式已经成为乙型和丙型肝炎的标准治疗的一部分，其他干扰素也被作为各种疾病的治疗进行研究。
- ✧ 更具体的方法是合成抗体，可以结合病原体的蛋白质分子，并将其标记为免疫系统的其他元件的攻击。一旦研究人员识别病原体上的特定靶点，他们就可以合成大量相同的“单克隆”抗体来连接该靶标。目

前正在出售一种单克隆药物，以帮助对抗婴儿中的呼吸道合胞病毒，而从感染个体中纯化的抗体也用作乙型肝炎的治疗。

Sofosbuvir (brand name Sovaldi)
SOVALDI is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor;
Use together with ribavarin;
No inteferon needed.
It was discovered at Pharmasset and developed by Gilead Sciences.
Sofosbuvir（品牌名：Sovaldi）
SOVALDI 是丙型肝炎病毒（HCV）核苷酸类似物 NS5B 聚合酶抑制剂;
与利巴韦林一起使用
不需要干扰素
在 Pharmasset 发现并由吉利德科学研发。

Simeprevir (brand name Olysio)
Protease inhibitor
The third protease inhibitor drug for the treatment of Hep C.
The other 2: boceprevir (brand name Victrelis, made by Merck) and telaprevir (brand name Incivek, made by Vertex)
Must be used with interferon
辛普雷维（品牌 Olysio）
蛋白酶抑制剂
用于治疗 Hep C 的第三种蛋白酶抑制剂药物
另外 2：boceprevir（品牌名称 Victrelis，由 Merck 制造）和 telaprevir（品牌 Incivek，由 Vertex 制造）
必须与干扰素一起使用

Chapter 6. Important negative-stranded RNA viruses

第六章 重要的负链 RNA 病毒

Group V—negative-sense ssRNA viruses [edit]

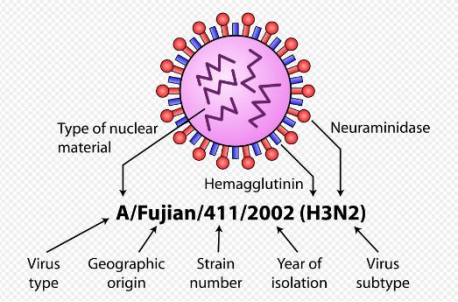
There is one order and eight families recognised in this group. There are also a number of unassigned speci

- Order *Mononegavirales*
  - Family Bornaviridae—Borna disease virus
  - Family Filoviridae—includes Ebola virus, Marburg virus
  - Family Paramyxoviridae—includes Measles virus, Mumps virus, Nipah virus, Hendra virus, RSV and NDV
  - Family Rhabdoviridae—includes Rabies virus
  - Family Nyamiviridae—includes Nyavirus
- Unassigned families:
  - Family Arenaviridae—includes Lassa virus
  - Family Bunyaviridae—includes Hantavirus, Crimean-Congo hemorrhagic fever
  - Family Ophioviridae
  - Family Orthomyxoviridae—includes Influenza viruses
- Unassigned genera:
  - Genus *Deltavirus*—includes Hepatitis D virus
  - Genus *Dichorhavirus*
  - Genus *Emaravirus*
  - Genus *Nyavirus*[22]—includes Nyamanini and Midway viruses
  - Genus *Tenuivirus*
  - Genus *Varicosavirus*
- Unassigned species:
  - Taastrup virus
  - Sclerotinia sclerotiorum negative-stranded RNA virus 1

Orthomyxoviridae and Influenza virus
正粘病毒科和流感病毒

Orthomyxovirus Genera, Species, and Serotypes

Genus	Species (* indicates type species)	Serotypes or Subtypes	Hosts
Influenza virus A	*Influenza A virus**	H1N1, H1N2, H2N2, H3N1, H3N2, H3N8, H5N1, H5N2, H5N3, H5N8, H5N9, H7N1, H7N2, H7N3, H7N4, H7N7, H7N9, H9N2, H10N7	Human, pig, bird, horse
Influenza virus B	*Influenza B virus**	Victoria, Yamagata[5]	Human, seal
Influenza virus C	*Influenza C virus**		Human, pig, dog
Isavirus	*Infectious salmon anemia virus**		Atlantic salmon
Thogotovirus	*Thogotovirus**		Tick, mosquito, mammal (including human)
	Dhori virus	Batken virus, Bourbon virus, Jos virus	
Quaranjavirus [6]	*Quaranfil virus*,* *Johnston Atoll virus*		



Structure

✧ Virion: Roughly spherical (80-120 nm in diameter), sometimes filamentous;

✧ Hemagglutinin (HA or H) 血球凝集素：a protein that mediates binding of the virion to target cells and entry of the viral genome into the target cell；

✧ Neuraminidase (NA or N) 神经氨酸苷酶：NA is involved in the release of progeny virions from infected cells;

✧ HA:NA = ~4–5:1

✧ 18 subtypes of HA and 9 subtypes of NA

结构

✧ Virion：粗球形（直径 80-120 纳米），有时丝状;

✧ 血凝素（HA 或 H）血球凝集素：介导病毒粒子与靶细胞的结合和病毒基因组进入靶细胞的蛋白质;

✧ 神经氨酸酶（NA 或 N）神经氨酸苷酶：NA 参与从感染细胞释放后代病毒粒子;

✧ HA：NA=~4-5:1

✧ HA 的 18 个亚型和 NA 的 9 个亚型

✧ **Genome**

✧ The entire IAV genome is 13,588 bases long and is contained on eight RNA segments that code for 11 proteins.

✧ Segment 1 encodes RNA polymerase subunit (PB2).

✧ Segment 2 encodes RNA polymerase subunit (PB1) and the PB1-F2 protein, which induces cell death, by using different reading frames from the same RNA segment.

✧ Segment 3 encodes RNA polymerase subunit (PA); an alternate form of this polymerase can sometimes be made with a change to the reading frame (PA-X).

✧ Segment 4 encodes for HA (hemagglutinin). About 500 molecules of hemagglutinin are needed to make one virion. HA determines the extent and severity of a viral infection in a host organism.

✧ Segment 5 encodes NP, which is a nucleoprotein.

✧ Segment 6 encodes NA (neuraminidase). About 100 molecules of neuraminidase are needed to make one virion.

✧ Segment 7 encodes two matrix proteins (M1 and M2) by using different reading frames from the same RNA segment. About 3000 matrix protein molecules are needed to make one virion.

✧ Segment 8 encodes two distinct non-structural proteins (NS1 and NEP) by using different reading frames from the same RNA segment.

基因组

✧ 整个 IAV 基因组为 13,588 个碱基长，并且包含在编码 11 个蛋白质的 8 个 RNA 区段上。

✧ 片段 1 编码 RNA 聚合酶亚基（PB2）。

✧ 片段 2 通过使用来自相同 RNA 片段的不同阅读框编码 RNA 聚合酶亚基（PB1）和 PB1-F2 蛋白，其诱导细胞死亡。

✧ 片段 3 编码 RNA 聚合酶亚基（PA）；有时候可以通过改变阅读框（PA-X）来进行该聚合酶的替代形式。

✧ 片段 4 编码 HA（血凝素）。 需要约 500 分子的血凝素来制造一个病毒体。 HA 确定宿主生物体中病毒感染的程度和严重程度。

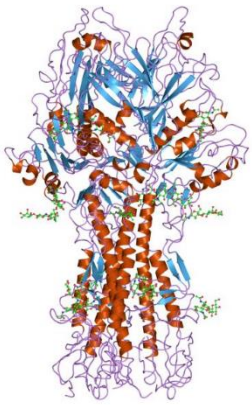
✧ 片段 5 编码 NP，其是核蛋白。

✧ 区段 6 编码 NA（神经氨酸酶）。 需要约 100 个分子的神经氨酸酶来制备一个病毒体。

✧ 片段 7 通过使用来自相同 RNA 片段的不同阅读框编码两种基质蛋白（M1 和 M2）。 需要约 3000 个基质蛋白分子来制备一个病毒体。

✧ 片段 8 通过使用来自相同 RNA 片段的不同阅读框编码两种不同的非结构蛋白（NS1 和 NEP）。

Hemagglutinin



✧ A glycoprotein found on the surface of influenza viruses;

✧ It allows the recognition of target vertebrate cells, accomplished through the binding to these cells' sialic acid-containing receptors;

✧ Once bound it facilitates the entry of the viral genome into the target cells by causing the fusion of host endosomal membrane with the viral membrane.

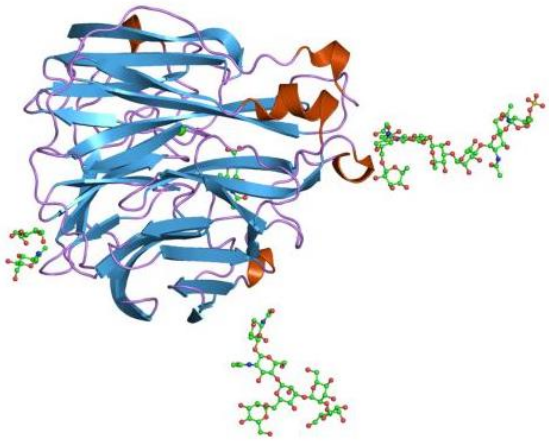
血凝素

✧ 在流感病毒表面发现的糖蛋白;

✧ 它允许通过与这些细胞含唾液酸的受体的结合来实现目标脊椎动物细胞的识别;

✧ 一旦结合，通过引起宿主内体膜与病毒膜的融合便于病毒基因组进入靶细胞。

Neuraminidase



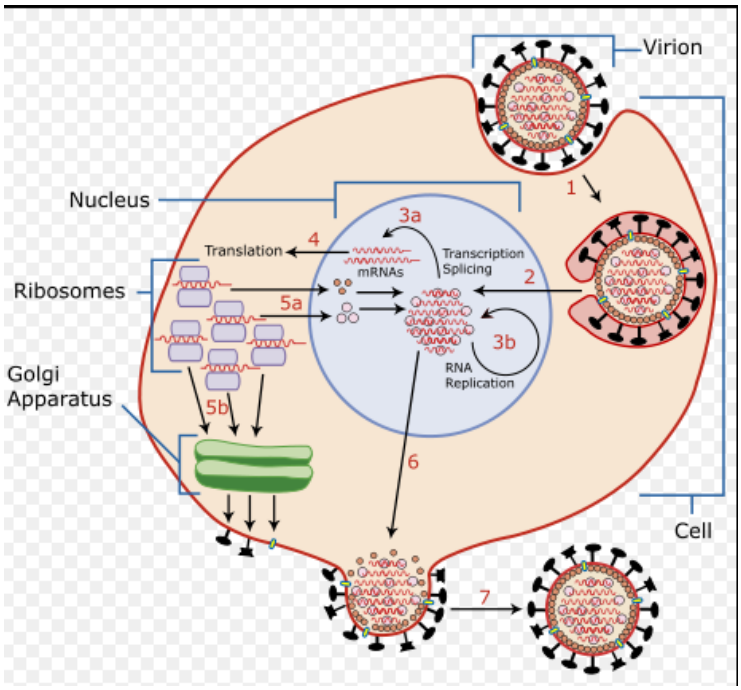
- ✧ When influenza virus replicates, it attaches to the interior cell surface using HA, and its presence inhibits release of the particle after budding;
- ✧ Viral neuraminidase cleaves terminal neuraminic acid residues from glycan structures on the surface of the infected cell.
- ✧ This promotes the release of progeny viruses and the spread of the virus from the host cell to uninfected surrounding cells.
- ✧ Neuraminidase also cleaves sialic acid residues from viral proteins, preventing aggregation of viruses.

神经氨酸酶

- ✧ 当流感病毒复制时，它使用 HA 附着在内部细胞表面，并且其存在抑制芽出现后颗粒的释放;
- ✧ 病毒性神经氨酸酶从感染细胞表面的聚糖结构切割末端神经氨酸残基。
- ✧ 这促进后代病毒的释放和病毒从宿主细胞扩散到未感染的周围细胞。
- ✧ 神经氨酸酶还可以从病毒蛋白中切割唾液酸残基，防止病毒聚集。

Replication cycle

复制循环



Key points of IAV replication

- ✧ *Orthomyxoviridae* viruses are one of two RNA viruses that replicate in the nucleus (the other being retrovirus).
- ✧ RNA Polymerase PA cleaves off the cellular mRNA near the 5' end and uses this capped fragment as a primer for transcribing the rest of the viral RNA genome in viral mRNA.
- ✧ Since RNA proofreading enzymes are absent, the RdRP makes a single nt error roughly every 10,000 nts. Nearly every newly influenza virus will contain a mutation.
- ✧ The separation of the genome into eight separate segments of vRNA allows mixing (reassortment) of the genes if more than one variety of influenza virus has infected the same cell.

IAV 复制要点

- ✧ 正粘病毒科病毒是在核中复制的两种 RNA 病毒之一（另一种是逆转录病毒）。
- ✧ RNA 聚合酶 PA 在 5'端附近切除细胞 mRNA，并使用此封端片段作为引物，用于转录病毒 RNA 中其余

的病毒 RNA 基因组。

- ✧ 由于 RNA 校对酶不存在，RdRP 大约每 10,000 nts 发生单个 nt 错误。 几乎每一种新流感病毒都会含有突变。
- ✧ 如果多于一种的流感病毒感染了相同的细胞，则将基因组分离成 vRNA 的八个单独片段，允许混合（重配）基因。

Vaccination and treatment

- ✧ Vaccines are composed of either inactivated or live attenuated virions of the H1N1 and H3N2 human IAVs, as well as those of influenza B viruses.
- ✧ Because the antigenicities of the wild viruses evolve, vaccines are reformulated annually by updating the seed strains.
- ✧ However, when the antigenicities of the seed strains and wild viruses do not match, vaccines fail to protect the vaccinees.
- ✧ Even when they do match, escape mutants are often generated.
- ✧ Drugs available for the treatment of influenza include Amantadine and Rimantadine, which inhibit the uncoating of virions by interfering with M2, and Oseltamivir (marketed under the brand name Tamiflu), Zanamivir, and Peramivir, which inhibit the release of virions from infected cells by interfering with NA.
- ✧ However, escape mutants are often generated for the former drug and less frequently for the latter drug.

疫苗接种和治疗

- ✧ 疫苗由 H1N1 和 H3N2 人 IAV 的灭活或活的减毒病毒粒子以及乙型流感病毒的病毒组成。
- ✧ 由于野生病毒的抗原性发生变化，每年通过更新种子株来重新配制疫苗。
- ✧ 然而，当种子菌株和野生病毒的抗原性不匹配时，疫苗不能保护接种者。
- ✧ 即使他们匹配，逃避突变也经常产生。
- ✧ 可用于治疗流行性感冒的药物包括金刚烷胺和金刚乙胺，其通过干扰 M2 抑制病毒体的释放，以及通过干扰来抑制病毒粒子从感染细胞释放的奥司他韦（以品牌名称 Tamiflu 销售），扎那米韦和帕拉米韦 与 NA。
- ✧ 然而，逃避突变体往往是针对前一种药物而产生的，而后者则较少发生。

1918 flu pandemic

1918/01-1920/12

- ✧ Resulted in 50-100 million deaths (3 to 5% the world‘s population), and life expectancy dropped by about 12 years;
- ✧ Most influenza outbreaks disproportionately kill juvenile, elderly, or already weakened patients; in contrast, the 1918 pandemic predominantly killed previously healthy young adults;
- ✧ Modern research, using virus taken from the bodies of frozen victims, has concluded that the virus kills through a cytokine storm (overreaction of the body's immune system). The strong immune reactions of young adults ravaged the body, whereas the weaker immune systems of children and middle-aged adults resulted in fewer deaths among those groups.
- ✧ The global mortality rate from the 1918/1919 pandemic is not known, but an estimated 10% to 20% of those who were infected died.
- ✧ This flu killed more in 24 wks than AIDS has killed in 24 yrs, more in a yr than the Black Death killed in a century.
- ✧ The disease killed in every corner of the globe. 17M died in India, 390,000 died in Japan; In the Dutch East Indies (now Indonesia), 1.5M have died among 30M inhabitants. In Tahiti 13% of the population died during only a month. Similarly, in Samoa 22% of the population of 38,000 died within two months.
- ✧ U.S. 500,000 to 675,000 died. Canada 50,000. Brazil 300,000 (including its president). UK 250,000, France 400,000.

1918 年流感大流行

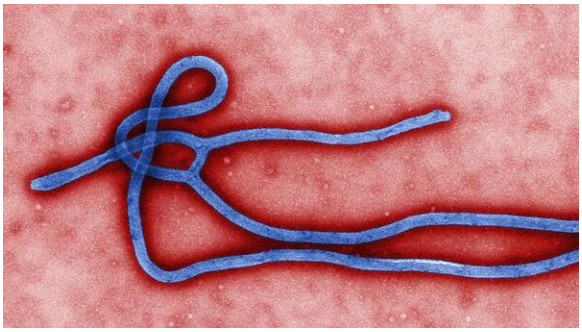
1918 / 01-1920 / 12

✧ 造成 5-100 万人死亡（世界人口 3%至 5%），预期寿命下降约 12 年;
✧ 大多数流感疫情不成比例地杀死少年，老年人或已经衰弱的患者;相比之下，1918 年大流行病主要杀死了以前健康的年轻人;
✧ 现代研究使用从冷冻受害者身体获取的病毒，得出结论，病毒会通过细胞因子风暴（身体的免疫系统过度反应）而死亡。年轻成年人强烈的免疫反应摧毁了身体，而儿童和中年成年人的免疫系统较弱，导致这些群体的死亡人数减少。
✧ 1918/1919 年大流行的全球死亡率尚不清楚，但估计有 10%至 20%的感染者死亡。
✧ 这种流感在 24 周内比艾滋病在 24 年内死亡更多，比一个世纪中杀死的黑人死亡人数更多。
✧ 这种疾病在全球各个角落都死亡。印度 1700 万人死于日本;在荷兰东印度群岛（现印度尼西亚），有 3000 万人死于 150 万人。在大溪地，只有一个月，13%的人死亡。同样的，在萨摩亚，二十八点二十三万人口在两个月内死亡。
✧ 美国 50 万至 675,000 人死亡。加拿大 50,000。巴西 30 万（包括其总统）。英国 25 万，法国 40 万。

Filoviridae and Ebola virus
丝状病毒科和埃博拉病毒

Family *Filoviridae*: genera, species, and viruses

Genus name	Species name	Virus name (abbreviation)
Cuevavirus	*Lloviu cuevavirus**	Lloviu virus (LLOV)
Ebolavirus	*Bundibugyo ebolavirus*	Bundibugyo virus (BDBV; previously BEBOV)
	Reston ebolavirus	Reston virus (RESTV; previously REBOV)
	Sudan ebolavirus	Sudan virus (SUDV; previously SEBOV)
	Taï Forest ebolavirus	Taï Forest virus (TAFV; previously CIEBOV)
	*Zaire ebolavirus**	Ebola virus (EBOV; previously ZEBOV)
Marburgvirus	*Marburg marburgvirus**	Marburg virus (MARV)
		Ravn virus (RAVV)



Ebola virus (EBOV)
✧ Ebola virus is the single member of the species Zaire ebolavirus, which is the type species for the genus Ebolavirus, family Filoviridae, order Mononegavirales.
✧ The EBOV genome is a single-stranded RNA ~19,000 nts.
✧ EBOV's mortality rate up to 83-90%
✧ EBOV is also listed as a select agent, WHO Risk Group 4 Pathogen (requiring BSL4-equivalent containment), a U.S. NIAID Category A Priority Pathogen, U.S. CDC Category A Bioterrorism Agent.

埃博拉病毒（EBOV）
✧ 埃博拉病毒是扎伊尔埃博拉病毒的单一成员，它是埃博拉病毒属，斐洛伊病毒属（Filoviridae），单宁属（Mononegavirales）的种类。
✧ EBOV 基因组是单链 RNA~19,000nt。
✧ EBOV 的死亡率高达 83-90%
✧ EBOV 也被列为世卫组织风险组 4 病原体（需要 BSL4 等效遏制），美国 NIAID A 类优先病原体，美国 CDC A 类生物恐怖剂。

Structure
✧ Virion: cylindrical/tubular. Generally ~80 nm in diameter, with variable length, typically 800 nm, but sometimes up to 1000 nm.
✧ Viral glycoprotein (GP) projecting as 7-10 nm spikes from its lipid bilayer surface.
✧ VP40 and VP24 are located between the envelope and the nucleocapsid, in the matrix space.
✧ At the center of the virion structure is the nucleocapsid, which is composed of a series of viral proteins attached to an 18–19 kb linear (-)RNA w/o 3′-polyA or 5′-capping;
✧ The RNA is helically wound and complexed with the NP, VP35, VP30, and L proteins.

结构
✧ Virion：圆柱形/管状。 通常~80nm 直径，具有可变长度，通常为 800nm，但有时高达 1000nm。

✧ 从其脂质双层表面突出为 7-10nm 尖峰的病毒糖蛋白（GP）。
✧ VP40 和 VP24 位于信封和核壳之间，位于矩阵空间中。
✧ 在病毒粒子结构的中心是核衣壳，其由连接到 18-19kb 线性（ - ）RNA w / o 3'-聚 A 或 5'-封端的一系列病毒蛋白质组成;
✧ RNA 与 NP，VP35，VP30 和 L 蛋白螺旋缠绕并复合。

Genome

✧ Each virion contains a 18,959-18,961 nt linear (-)-ssRNA.
✧ The 3′ terminus is not polyadenylated and the 5′ end is not capped.
✧ This viral genome codes for 7 structural proteins and one non-structural protein.

✧ Sections of the NP, VP35 and the L genes from filoviruses have been identified as endogenous in the genomes of several groups of small mammals.
✧ Its 3'-end 472 nt and 5'-end 731 nt are sufficient for replication of a viral "minigenome", though not sufficient for infection.
✧ The mutation rates in filoviral genomes have been estimated to be 0.46-8.21×10−4 nt substitutions/site/year, i.e. ~ ¼ of IAV's mutation rate.

基因组

✧ 每个病毒粒子含有 18,959-18,961 个线性（ - ） - ssRNA。
✧ 3'末端不是聚腺苷酸化的，5'末端不被封端。
✧ 该病毒基因组编码 7 个结构蛋白和一个非结构蛋白。

✧ 已经在几组小型哺乳动物的基因组中鉴定了来自叶病毒的 NP，VP35 和 L 基因的部分内源。
✧ 其 3'末端 472 nt 和 5'末端 731 nt 足以复制病毒"小基因组"，尽管不足以感染。
✧ 野生病毒基因组的突变率估计为 0.46-8.21×10-4 nt 取代/位点/年，即 IAV 突变率的 1/4。

Replication

✧ The virus begins its attack by attaching to host receptors through the glycoprotein (GP) surface and is endocytosed into the host cell.
✧ To penetrate the cell, the viral membrane fuses with vesicle membrane, and the nucleocapsid is released into the cytoplasm.
✧ Encapsidated, negative-sense genomic ssRNA is used as a template for the synthesis (3'-5') of polyadenylated mRNAs and, using the host cell machinery for translation.
✧ These viral proteins are processed: a glycoprotein precursor (GP0) is cleaved to GP1 and GP2, which are then heavily glycosylated.
✧ These two molecules assemble, first into heterodimers, and then into trimers to give the surface peplomers.
✧ As viral protein levels rise, a switch occurs from translation to replication. Using the (-)ssRNA as a template, a complementary +ssRNA is synthesized; this is then used as a template for the synthesis of new genomic (-)ssRNA, which is rapidly encapsidated.
✧ The newly formed nucleocapsids and envelope proteins associate at the host cell's plasma membrane; budding occurs, destroying the cell.

复制

✧ 该病毒通过通过糖蛋白（GP）表面附着于宿主受体而开始其攻击，并被内吞到宿主细胞中。
✧ 为了穿透细胞，病毒膜与囊泡膜融合，并且核衣壳被释放到细胞质中。
✧ 封闭的负义基因组 ssRNA 用作多聚腺苷酸化 mRNA 的合成（3'-5'）的模板，并使用宿主细胞机制进行

翻译。

- ✧ 处理这些病毒蛋白质：糖蛋白前体（GP0）被切割成 GP1 和 GP2，然后被严重糖基化。
- ✧ 这两个分子首先聚合成异二聚体，然后聚合成三聚体以给予表面的多肽。
- ✧ 随着病毒蛋白水平的升高，从转换到复制就发生了转换。使用（-）ssRNA 作为模板，合成补体+ ssRNA; 然后将其用作合成新的基因组（-）ssRNA 的模板，其被快速包封。
- ✧ 新形成的核衣壳和包膜蛋白在宿主细胞的质膜上缔合;发芽，破坏细胞。

Ebola virus disease (EVD)

- ✧ The first outbreak occurred on 26 August 1976 in Yambuku.
- ✧ The first recorded case was Mabalo Lokela, a 44-year-old schoolteacher. The symptoms resembled malaria, and subsequent patients received quinine. Transmission has been attributed to reuse of unsterilized needles and close personal contact, body fluids and places where the person has touched.
- ✧ Since the first recorded clinical description of the disease during 1976 in Zaire, the recent Ebola outbreak that started in March 2014, in addition, has reached epidemic proportions and has killed more than 8000 people as of January 2015.
- ✧ This outbreak has been centered in West Africa, an area that had not previously been affected by the disease. The toll has been particularly grave in three countries: Guinea, Liberia, and Sierra Leone. A few cases have also been reported in countries outside of West Africa, all related to international travelers who were exposed in the most affected regions and later showed symptoms of Ebola fever after reaching their destinations.

埃博拉病毒病（EVD）

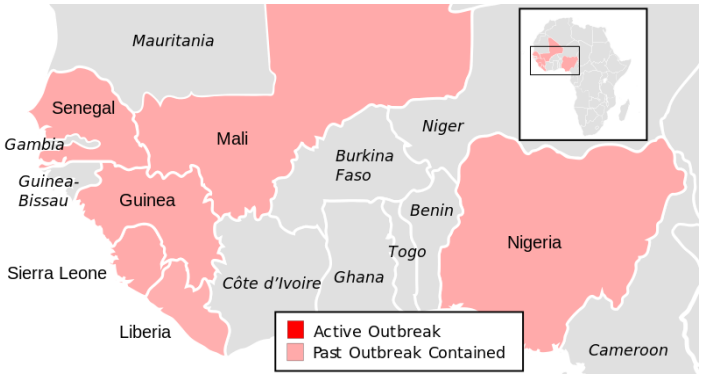
- ✧ 第一次爆发发生在 1976 年 8 月 26 日在 Yambuku。
- ✧ 第一起案件是一名 44 岁的学校教师 Mabalo Lokela。症状类似于疟疾，随后的患者接受了奎宁。传播被归因于重新使用未灭菌的针头和密切的个人接触，体液和人们所触及的地方。
- ✧ 自 1976 年扎伊尔首次记录该疾病的临床描述以来，自 2014 年 3 月开始的埃博拉疫情爆发事件此外已经达到了疫情，到 2015 年 1 月已经死亡 8000 多人。
- ✧ 这一疫情一直集中在西非，这个地区以前没有受到这种疾病的影响。在三个国家，几内亚，利比里亚和塞拉利昂的收费特别严重。在西非以外的国家也有报道了一些案例，这些案件都与在受影响最严重地区暴露的国际旅客有关，后来在到达目的地后出现埃博拉热症状。

West African Ebola virus epidemic

- ✧ The most widespread epidemic of Ebola virus disease in history began in 2013 and continued for over two years, resulting in significant loss of life and social disruption, mainly in three West African countries: Guinea, Liberia, and Sierra Leone.
- ✧ As of 8 May 2016, WHO and respective governments have reported a total of 28,657 suspected cases and 11,325 deaths, though the WHO believes that this substantially understates the magnitude of the outbreak.

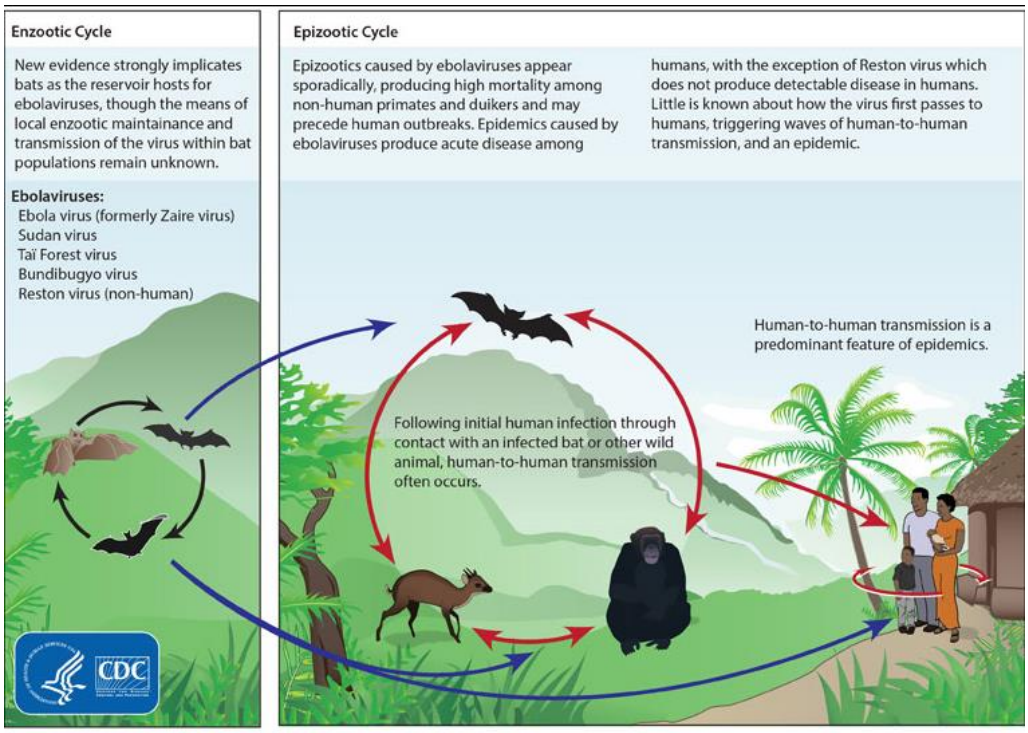
西非埃博拉病毒流行病

- ✧ 历史上最广泛的埃博拉病毒病流行病始于 2013 年，持续了两年多，主要在三个西非国家：几内亚，利比里亚和塞拉利昂造成重大的生命和社会破坏。
- ✧ 截至 2016 年 5 月 8 日，世卫组织和各自的政府共报告了 28,657 例疑似病例和 11,325 例死亡病例，尽管世卫组织认为这大大低估了疫情的严重程度。



Transmission

传播



Treatment

- ✧ No proven Ebola virus-specific treatment exists, however measures can be taken to improve a patient's chances of survival.
- ✧ Ebola symptoms may begin as early as two days or as long as 21 days after one is exposed to the virus. They usually begin with a sudden influenza-like stage characterized by feeling tired, fever, and pain in the muscles and joints. Later symptoms may include headache, nausea, and abdominal pain. This is often followed by severe vomiting and diarrhoea.
- ✧ In past outbreaks it has been noted that some patients may experience the loss of blood through bleeding internally and/or externally, however data published in October 2014 showed that bleeding had been a rare symptom in this outbreak.
- ✧ Another study published in 2014 suggested that a person's genetic makeup may play a major role in determining how an infected person's body reacts to the disease, with some infected people experiencing mild or no symptoms while some progress to a very severe stage that includes massive bleeding.
- ✧ According to WHO, the main reason that most patients in American and European hospitals survived was due to the use of IV fluids along with constant measuring of blood chemistry.

治疗

- ✧ 没有证明埃博拉病毒特异性治疗存在，但是可以采取措施来改善患者的生存机会。
- ✧ 一天暴露于病毒后，埃博拉症状可能早于两天或长达 21 天。他们通常以突然的流感样状态开始，其特征在于感觉到肌肉和关节的疲劳，发烧和疼痛。稍后的症状可能包括头痛，恶心和腹痛。这往往是严重的呕吐和腹泻。
- ✧ 在过去的爆发中，已经注意到，一些患者可能会通过内部和/或外部的出血来体验血液的流失，但是在 2014 年 10 月发布的数据显示，出血在这次爆发中是罕见的症状。
- ✧ 2014 年发表的另一项研究表明，一个人的遗传构成可能在确定感染者的身体对疾病的反应方面可能发挥重要作用，一些感染者经历轻度或无症状，而某些进展到非常严重的阶段，包括大量出血。
- ✧ 据世卫组织统计，美国和欧洲医院大多数患者存活的主要原因是由于使用 IV 液体以及不断测量血液化学成分。

Rhabdoviridae family and Rabies virus

- ✧ The genome encodes 5 proteins: nucleoprotein (N), phosphoprotein (P), matrix (M), glycoprotein (G) and polymerase (L).
- ✧ All rhabdoviruses have two major structural components: a helical ribonucleoprotein core (RNP) and a surrounding envelope
- ✧ The rabies virus has a bullet like shape with a length of about 180 nm and a cross-sectional diameter of about 75 nm.
- ✧ One end is rounded or conical and the other end is planar or concave. The lipoprotein envelope carries knob-like spikes composed of Glycoprotein G. Spikes do not cover the planar end of the virion.
- ✧ Beneath the envelope is the membrane or matrix (M) protein. The core of the virion consists of helically arranged ribonucleoprotein.

狂犬病病毒科和狂犬病病毒

- ✧ 基因组编码 5 种蛋白质：核蛋白（N），磷蛋白（P），基质（M），糖蛋白（G）和聚合酶（L）。
- ✧ 所有的弹状病毒都有两个主要的结构组分：螺旋核糖核蛋白核心（RNP）和周围的信封
- ✧ 狂犬病毒具有长度约为 180nm，截面直径为约 75nm 的子弹形状。
- ✧ 一端为圆形或圆锥形，另一端为平面或凹形。 脂蛋白包膜带有由糖蛋白 G 组成的细胞样的尖峰，尖峰不覆盖病毒粒子的平面末端。
- ✧ 信封下面是膜或基质（M）蛋白质。 病毒粒子的核心由螺旋排列的核糖核蛋白组成。

Chapter 7 - Viral Oncology

第七章 病毒性肿瘤学

Cancer

- ✧ Known medically as a malignant neoplasm;
- ✧ A broad group of various diseases, all involving unregulated cell growth.
- ✧ In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body.
- ✧ The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream.
- ✧ Not all tumors are cancerous. Benign tumors do not grow uncontrollably, do not invade neighboring tissues, and do not spread throughout the body.

癌症

- ✧ 医学上称为恶性肿瘤;
- ✧ 广泛的各种疾病，都涉及不受管制的细胞生长。
- ✧ 在癌症中，细胞不可控地分裂和生长，形成恶性肿瘤，并侵入身体的附近部位。
- ✧ 癌症也可能通过淋巴系统或血液流向身体的更远的部位。
- ✧ 不是所有的肿瘤都是癌性的。 良性肿瘤不能不受控制地生长，不会侵入邻近的组织，并且不会遍及全身。

- ✧ Determining what causes cancer is complex.
- ✧ Many things are known to increase the risk of cancer, including tobacco use, certain infections, radiation, lack of physical activity, poor diet and obesity, and environmental pollutants. These can directly damage genes or combine with existing genetic faults within cells to cause the disease.
- ✧ Approximately five to ten percent of cancers are entirely hereditary.
- ✧ Cancer can be detected in a number of ways, including the presence of certain signs and symptoms, screening tests, or medical imaging.
- ✧ Once a possible cancer is detected it is diagnosed by microscopic examination of a tissue sample.
- ✧ 确定什么导致癌症是复杂的。
- ✧ 众所周知，许多事情会增加癌症的风险，包括烟草使用，某些感染，辐射，身体活动不足，饮食和肥胖以及环境污染物等。 这些可以直接损害基因或与细胞内的现有遗传缺陷相结合，引起疾病。
- ✧ 大约百分之五至百分之十的癌症完全是遗传性的。
- ✧ 可以以多种方式检测癌症，包括某些体征和症状的存在，筛查测试或医学成像。
- ✧ 一旦检测到可能的癌症，就通过对组织样本的显微镜检查进行诊断。

- ✧ Cancer is usually treated with chemotherapy, radiation therapy and surgery.
- ✧ The chances of surviving the disease vary greatly by the type and location of the cancer and the extent of disease at the start of treatment.
- ✧ While cancer can affect people of all ages, and a few types of cancer are more common in children, the risk of developing cancer generally increases with age.
- ✧ In 2007, cancer caused about 13% of all human deaths worldwide (7.9 million).
- ✧ Rates are rising as more people live to an old age and as mass lifestyle changes occur in the developing world
- ✧ 癌症通常用化疗，放射治疗和手术治疗。
- ✧ 疾病存活的机会随着癌症的类型和位置以及治疗开始时的疾病程度而有很大差异。
- ✧ 虽然癌症可以影响所有年龄段的人，而且几种类型的癌症在儿童中更常见，但是发展癌症的风险通常随年龄增长而增加。
- ✧ 2007 年，全球人类死亡人数（790 万）占癌症的 13％。
- ✧ 随着越来越多的人过着生活，随着群众生活方式的变化发生在发展中国家，房价也在上涨

Signs and symptoms - Local Effects

- ✧ Local symptoms may occur due to the mass of the tumor or its ulceration.
- ✧ For example, mass effects from lung cancer can cause blockage of the bronchus resulting in cough or pneumonia,
- ✧ Esophageal cancer can cause narrowing of the esophagus making it difficult or painful to swallow,
- ✧ Colorectal cancer may lead to narrowing or blockages in the bowel resulting in changes in bowel habits.
- ✧ Masses of breast or testicles may be easily felt.
- ✧ Ulceration can cause bleeding which, if it occurs in the lung, will lead to coughing up blood, in the bowels to anemia or rectal bleeding, in the bladder to blood in the urine, and in the uterus to vaginal bleeding.
- ✧ Although localized pain may occurs in advanced cancer, the initial swelling is usually painless. Some cancers can cause build up of fluid within the chest or abdomen.

体征和症状 - 局部效应

- ✧ 局部症状可能由于肿瘤的肿块或其溃疡而发生。
- ✧ 例如，肺癌的质量效应会引起支气管阻塞，导致咳嗽或肺炎，
- ✧ 食道癌可引起食道狭窄，使其吞咽困难或痛苦，
- ✧ 结肠直肠癌可能导致肠道变窄或阻塞，导致排便习惯的变化。
- ✧ 可能容易感觉到乳房或睾丸的质量。
- ✧ 溃疡可引起出血，如果发生在肺部，会导致咳嗽血液，肠道中出现贫血或直肠出血，膀胱内血液中的尿液，以及子宫阴道出血。
- ✧ 虽然局部疼痛可能发生在晚期癌症中，但初始肿胀通常是无痛的。 一些癌症可引起胸部或腹部液体积聚。

Systemic symptoms

- ✧ General symptoms occur due to distant effects of the cancer that are not related to direct or metastatic spread. These may include: unintentional weight loss, fever, being excessively tired, and changes to the skin.
- ✧ Leukemias, and cancers of the liver or kidney can cause a persistent fever of unknown origin.
- ✧ Specific constellations of systemic symptoms, termed paraneoplastic phenomena, may occur with some cancers. Examples include the appearance of myasthenia gravis 重症肌无力 in thymoma 胸腺瘤 and clubbing 杵状膨大 in lung cancer.

全身症状

- ✧ 由于与直接或转移性扩散无关的癌症的远距离影响，发生一般症状。 这些可能包括：无意的减肥，发烧，过度疲劳和皮肤变化。
- ✧ 白血病和肝脏或肾脏的癌症可引起不明原因的持续发热。
- ✧ 全身症状的特定星座，称为副肿瘤现象，可能与某些癌症有关。 例子包括胸腺瘤和棍棒痰状膨大在肺癌中的肌无力重症肌无力的出现。

Metastasis

Symptoms of metastasis are due to the spread of cancer to other locations in the body.

They can include enlarged lymph nodes (which can be felt or sometimes seen under the skin and are typically hard), hepatomegaly (enlarged liver) or splenomegaly (enlarged spleen) which can be felt in the abdomen, pain or fracture of affected bones, and neurological symptoms.

转移

转移的症状是由于癌症扩散到身体其他部位。

它们可以包括可以在受影响的骨骼的腹部，疼痛或骨折中感觉到的扩大的淋巴结（其可以被感觉或有时在皮肤下看到并且通常是硬的），肝肿大（肝脏增大）或脾肿大（脾脏增大），以及 神经症状。

Causes – Heredity

- ✧ The vast majority of cancers are non-hereditary ("sporadic cancers").
- ✧ Hereditary cancers are primarily caused by an inherited genetic defect.

- ✧ Less than 0.3% of the population are carriers of a genetic mutation which has a large effect on cancer risk and these cause less than 3–10% of all cancer.
- ✧ Some of these syndromes include: certain inherited mutations in the genes BRCA1 and BRCA2 with a more than 75% risk of breast cancer and ovarian cancer,
- ✧ Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) which is present in about 3% of people with colorectal cancer.

原因 - 遗传
绝大多数癌症是非遗传性的（“零星癌症”）。
遗传性癌症主要由遗传性遗传缺陷引起。
少于 0.3％的人口是遗传突变的携带者，对癌症风险影响很大，而这些因素导致的癌症少于 3-10％。
这些综合征中的一些包括：BRCA1 和 BRCA2 基因中某些遗传突变具有超过 75％的乳腺癌和卵巢癌风险，
遗传性非息肉性结肠直肠癌（HNPCC 或 Lynch 综合征），其存在于约 3％的结肠直肠癌患者中。

Chemicals

- ✧ Cancer pathogenesis is traceable back to DNA mutations that impact cell growth and metastasis.
- ✧ Substances that cause DNA mutations are known as mutagens, and mutagens that cause cancers are known as carcinogens.
- ✧ Particular substances have been linked to specific types of cancer. Tobacco smoking is associated with many forms of cancer, and causes 90% of lung cancer.
- ✧ Many mutagens are also carcinogens, but some carcinogens are not mutagens.
- ✧ Alcohol is an example of a chemical carcinogen that is not a mutagen.
- ✧ In Western Europe 10% of cancers in males and 3% of cancers in females are attributed to alcohol.

化学制品
癌症发病机制可追溯到影响细胞生长和转移的 DNA 突变。
导致 DNA 突变的物质被称为诱变剂，引起癌症的诱变剂被称为致癌物质。
特定物质与特定类型的癌症有关。 吸烟与许多形式的癌症有关，导致 90％的肺癌。
许多诱变剂也是致癌物质，但一些致癌物质不是诱变剂。
酒精是不是诱变剂的化学致癌物质的例子。
在西欧 10％的男性癌症和 3％的女性癌症归因于酒精。

Tobacco

- ✧ Decades of research has demonstrated the link between tobacco use and cancer in the lung, larynx, head, neck, stomach, bladder, kidney, esophagus and pancreas.
- ✧ Tobacco smoke contains over fifty known carcinogens, including nitrosamines 亚硝胺 and polycyclic aromatic hydrocarbons 多环芳烃.
- ✧ Tobacco is responsible for about one in three of all cancer deaths in the developed world, and about one in five worldwide.
- ✧ Lung cancer death rates in the United States have mirrored smoking patterns

烟草
数十年的研究已经证明了烟草使用与肺，喉，头，颈，胃，膀胱，肾，食道和胰腺癌的关系。
烟草烟含有超过五十种已知的致癌物质，包括亚硝胺和多环芳烃。
烟草在发达国家的大约有三分之一的癌症死亡事件中占有一席之地，全球约有五分之一。
美国的肺癌死亡率反映了吸烟模式

Diet and exercise

- ✧ Diet, physical inactivity, and obesity are related to approximately 30–35% of cancer deaths.
- ✧ In USA, excess body weight is associated with the development of many types of cancer and is a factor in 14–20% of all cancer deaths.

- ✧ Physical inactivity is believed to contribute to cancer risk not only through its effect on body weight but also through negative effects on immune system and endocrine system.
- ✧ Diets that are low in vegetables, fruits and whole grains, and high in processed or red meats are linked with a number of cancers.
- ✧ This may partly explain differences in cancer incidence in different countries for example gastric cancer is more common in Japan with its high salt diet and colon cancer is more common in the United States.
- ✧ Immigrants develop the risk of their new country, often within one generation, suggesting a substantial link between diet and cancer.

饮食和运动

- ✧ 饮食，身体不活动和肥胖与大约 30-35％的癌症死亡有关。
- ✧ 在美国，多余的体重与多种癌症的发展有关，是所有癌症死亡的 14-20％的一个因素。
- ✧ 认为身体不活动不仅通过其对体重的影响而且对免疫系统和内分泌系统的负面影响也对癌症的风险有贡献。
- ✧ 蔬菜，水果和全谷物低，加工或红肉高的饮食与许多癌症有关。
- ✧ 这可能部分解释了不同国家癌症发病率的差异，例如胃癌在日本较为常见，其高盐饮食和结肠癌在美国更常见。
- ✧ 移民发展新一代的风险，通常在一代之内，表明饮食与癌症之间存在实质联系。

Radiation

Up to 10% of invasive cancers are related to radiation exposure;

Medical use of ionizing radiation is a growing source of radiation-induced cancers;

Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies;

radio frequency radiation from mobile phones, electric power transmission, and other similar sources have been described as a possible carcinogen by the World Health Organization

辐射

多达 10％的侵入性癌症与放射线相关;

电离辐射的医疗使用是辐射诱发的癌症的日益增长的来源;

长时间暴露在紫外线下可能导致黑色素瘤和其他皮肤恶性肿瘤;

来自手机，电力传输和其他类似来源的射频辐射被世界卫生组织描述为可能的致癌物

Physical agents

Some substances cause cancer primarily through their physical, rather than chemical, effects on cells.

A prominent example of this is prolonged exposure to asbestos, naturally occurring mineral fibers which are a major cause of mesothelioma 间皮瘤, a type of lung cancer.

Nonfibrous particulate materials that cause cancer include powdered metallic cobalt and nickel, and crystalline silica.

Usually, physical carcinogens must get inside the body (such as through inhaling tiny pieces) and require years of exposure to develop cancer

物理因素

一些物质主要通过对细胞的物理而不是化学作用而导致癌症。

一个突出的例子是长期接触石棉，天然存在的矿物纤维，这是间皮瘤的主要原因，一种肺癌。

导致癌症的非纤维颗粒材料包括粉末状金属钴和镍，以及结晶二氧化硅。

通常，物理致癌物必须进入体内（如通过吸入小块），需要多年的暴露才能发展成癌症

Hormones

- ✧ Some hormones play a role in the development of cancer by promoting cell proliferation.Hormones are important agents in sex-related cancers such as cancer of the breast, endometrium 子宫内膜, prostate, ovary, and testis, and also of thyroid cancer and bone cancer.
- ✧ An individual's hormone levels are mostly determined genetically, so this may at least partly explains the presence of some cancers that run in families that do not seem to have any cancer-causing genes.

✧ For example, the daughters of women who have breast cancer have significantly higher levels of estrogen and progesterone than the daughters of women without breast cancer. These higher hormone levels may explain why these women have higher risk of breast cancer, even in the absence of a breast-cancer gene.

激素

✧ 一些激素通过促进细胞增殖在癌症的发展中发挥作用。激素是性相关癌症的重要因素，如乳腺癌，子宫内膜，前列腺，卵巢和睾丸，以及甲状腺癌和骨骼 癌症。

✧ 个体的激素水平主要是基因决定的，所以这可能至少部分地解释了在似乎没有任何致癌基因的家庭中存在的一些癌症的存在。

✧ 例如，与没有乳腺癌的妇女的女儿相比，具有乳腺癌的女性的雌激素和孕激素水平明显高于女性。 这些更高的激素水平可能解释了为什么这些女性乳腺癌的风险较高，即使没有乳腺癌基因。

Infection

✧ Worldwide approximately 18% of cancer deaths are related to infectious diseases.

✧ This proportion varies in different regions of the world from a high of 25% in Africa to less than 10% in the developed world.

✧ Viruses are the usual infectious agents that cause cancer but bacteria and parasites may also have an effect.

✧ A virus that can cause cancer is called an oncovirus.

✧ These include human papillomavirus (cervical carcinoma), Epstein-Barr virus (B-cell lymphoproliferative disease and nasopharyngeal carcinoma), Kaposi's sarcoma herpesvirus (Kaposi's Sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma), and Human T-cell leukemia virus-1 (T-cell leukemias).

✧ Bacterial infection may also increase the risk of cancer, as seen in Helicobacter pylori-induced gastric carcinoma.

✧ Parasitic infections strongly associated with cancer.

感染

✧ 全球约有 18%的癌症死亡与传染病有关。

✧ 世界不同地区的这一比例在非洲高达 25%，发达国家低于 10%。

✧ 病毒是导致癌症的常见感染因子，但细菌和寄生虫也可能产生影响。

✧ 可引起癌症的病毒称为癌症病毒。

✧ 这些包括人乳头状瘤病毒（宫颈癌），爱泼斯坦 - 巴尔病毒（B 细胞淋巴增殖性疾病和鼻咽癌），卡波西肉瘤疱疹病毒（卡波西肉瘤和原发性渗液淋巴瘤），乙型肝炎和丙型肝炎病毒（肝细胞癌）和人类 T 细胞白血病病毒-1（T 细胞白血病）。

✧ 细菌感染也可能增加癌症的风险，如幽门螺杆菌诱导的胃癌所见。

✧ 寄生虫感染与癌症密切相关。

Hallmarks of Cancer 癌症的标志

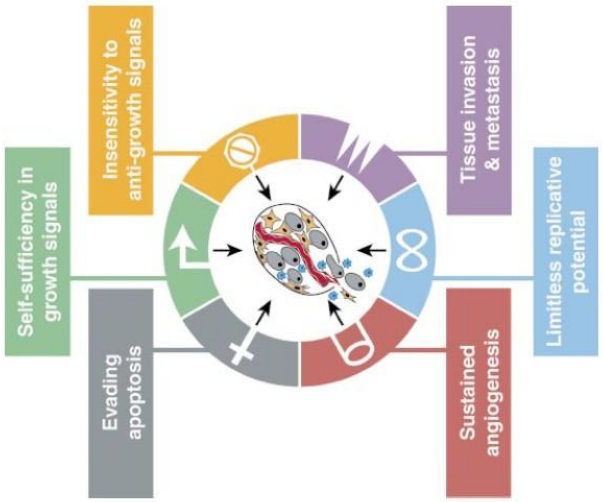


Figure 1. Acquired Capabilities of Cancer
We suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies.

Self-sufficiency in growth signals

- ✧ Normal cells require external growth signals (growth factors) to grow and divide. These signals are transmitted through receptors that pass through the cell membrane. When the growth signals are absent, they stop growing.
- ✧ Cancer cells can grow and divide without external growth signals. Some cancer cells can generate their own growth signals. For example, glioblastomas can produce their own platelet-derived growth factor (PDGF), and sarcomas can produce their own tumor growth factor α (TGF-α).
- ✧ Receptors themselves can be overexpressed. For example, the epidermal growth factor receptor (EGF-R/erbB) is overexpressed in stomach, brain and breast cancers, while the HER2/neu receptor is overexpressed in stomach and breast cancer. Or, mutated receptors can send signals without any growth factors at all.

自给自足的增长信号（什么鬼）

- ✧ 正常细胞需要外部生长信号（生长因子）生长和分裂。 这些信号通过穿过细胞膜的受体传播。 当增长信号不存在时，它们停止增长。
- ✧ 癌细胞可以生长和分裂而没有外部生长信号。 一些癌细胞可以产生自己的生长信号。 例如，胶质母细胞瘤可以产生自己的血小板衍生生长因子（PDGF），肉瘤可以产生自己的肿瘤生长因子 α（TGF-α）。
- ✧ 受体本身可以过度表达。 例如，表皮生长因子受体（EGF-R / erbB）在胃，脑和乳腺癌中过表达，而 HER2 / neu 受体在胃和乳腺癌中过度表达。 或者，突变的受体可以发送没有任何生长因子的信号。

Insensitivity to anti-growth signals

Cancer cells are generally resistant to growth-preventing signals from their neighbours.

The growth of normal cells is kept under control by growth inhibitors in the surrounding environment, in the extracellular matrix and on the surfaces of neighboring cells. These inhibitors act on the cell cycle clock, by interrupting cell division (mitosis) in the interphase

对抗生长信号的不敏感

癌细胞通常抵抗来自其邻居的生长阻止信号。

正常细胞的生长由周围环境，细胞外基质和相邻细胞表面的生长抑制剂保持控制。 这些抑制剂通过中断细胞分裂（有丝分裂）作用于细胞周期时钟

Evading apoptosis

Apoptosis is a form of programmed cell death (cell suicide), the mechanism by which cells are programmed to die in the event they become damaged. Cancer cells characteristically are able to bypass this mechanism.

Apoptosis can be triggered by an overexpressed oncogene, and this may be the primary means by which such mutant cells are continually removed. Conversely, cancer cells must overcome apoptosis to progress.

逃避细胞凋亡

细胞凋亡是程序性细胞死亡（细胞自杀）的一种形式，细胞凋亡机制被细胞编程死亡。 癌细胞特征性地能够绕过这种机制。

细胞凋亡可以由过表达的癌基因触发，这可能是继续去除这些突变细胞的主要手段。 相反，癌细胞必须克服凋亡进展。

Limitless reproductive potential

- ✧ Non-cancer cells die after a certain number of divisions. Cancer cells escape this limit and are apparently capable of indefinite growth and division (immortality). But those immortal cells have damaged chromosomes, which can become cancerous.
- ✧ Mammalian cells have an intrinsic program, the Hayflick limit, that limits their multiplication to about 60-70 doublings, at which point they reach a stage of senescence.
- ✧ The counting device for cell doublings is the telomere, which loses DNA at the tips of every chromosome during each cell cycle. Many cancers involve the upregulation of telomerase, the enzyme that maintains telomeres.

无限生殖潜力

✧ 非癌细胞在一定数量的分裂后死亡。 癌细胞逃避这个极限，显然能够无限增长和分裂（不朽）。 但是那些不死的细胞已经损害了染色体，这可能变得癌变。
✧ 哺乳动物细胞具有内在的程序，即 Hayflick 限制，限制了它们的增殖至约 60-70 倍，此时它们达到衰老阶段。
✧ 用于细胞倍增的计数装置是端粒，其在每个细胞周期期间在每个染色体的末端丢失 DNA。 许多癌症涉及端粒酶的上调，端粒酶是维持端粒的酶。

Sustained angiogenesis

Angiogenesis is the process by which new blood vessels are formed. Cancer cells appear to be able to kickstart this process, ensuring that such cells receive a continual supply of oxygen and other nutrients.

Cancer cells initially lack angiogenic ability, limiting their ability to expand. In order to progress, they must develop a blood supply

持续血管生成

血管生成是形成新血管的过程。 癌细胞似乎能够启动这一过程，确保这样的细胞能够持续供应氧气和其他营养物质。

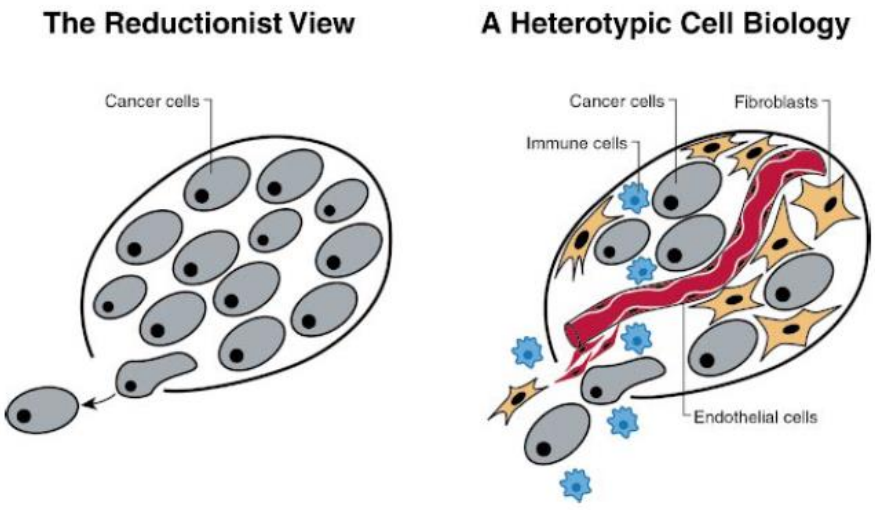
癌细胞最初缺乏血管生成能力，限制了其扩张能力。 为了进步，他们必须发展血液供应

Tissue invasion and metastasis

Cancer cells can break away from their site or organ of origin to invade surrounding tissue and spread (metastasize) to distant body parts.

组织侵袭转移

癌细胞可以从其部位或器官移开，侵入周围组织并传播（转移）到远处的身体部位。



Updates - 2010

✧ In his 2010 NCRI conference talk, Hanahan proposed four new hallmarks:
✧ Deregulated metabolism: most cancer cells use abnormal metabolic pathways to generate energy, a fact appreciated since the early twentieth century, but only now gaining renewed research interest.
✧ Evading the immune system: cancer cells appear to be invisible to the body's immune system.
✧ Unstable DNA: cancer cells generally have severe chromosomal abnormalities, which worsen as the disease progresses.
✧ Inflammation: recent discoveries have highlighted the role of local chronic inflammation in inducing many types of cancer.

更新 - 2010

✧ 在他的 2010 年 NCRI 大会上，哈南提出了四个新的标志：

✧ 放松的新陈代谢：大多数癌细胞使用异常的代谢途径产生能量，这是自二十世纪初以来受到赞赏的一个事实，但是现在才获得了更新的研究兴趣。
✧ 避免免疫系统：癌细胞似乎对身体的免疫系统是不可见的。
✧ 不稳定的 DNA：癌细胞通常具有严重的染色体异常，随着疾病的进展而恶化。
✧ 炎症：最近的发现突出了局部慢性炎症诱导许多类型癌症的作用。

Oncovirus 肿瘤病毒

Viral Oncogenesis

Cancer is a genetic disease

Oncogenesis comprises the processes of multi-step mutations, resulting in uncontrolled cell growth, increasing disorganization of cells and ultimately cancer.

Epigenetic factors also play important roles

Target of tumor viruses (oncoviruses): tumor suppressor genes and oncogenes

病毒性肿瘤发生

癌症是遗传性疾病

肿瘤发生包括多步突变的过程，导致不受控制的细胞生长，增加细胞的组织和最终的癌症。

表观遗传因素也起重要作用

肿瘤病毒（甲基病毒）靶标：肿瘤抑制基因和致癌基因

Oncovirus

An oncovirus is a virus that can cause cancer.

This term originated from studies of acutely-transforming retroviruses in the 1950–60s, often called oncornaviruses to denote their RNA virus origin.

It now refers to any virus with a DNA or RNA genome causing cancer and is synonymous with "tumor virus" or "cancer virus".

The vast majority of human and animal viruses do not cause cancer, probably because of long-standing coevolution between the virus and its host.

肿瘤病毒

甲状腺病毒是可以引起癌症的病毒。

该术语起源于 1950 - 60 年代急性转化逆转录病毒的研究，通常称为鹦鹉螺细菌表示其 RNA 病毒来源。

现在指任何具有引起癌症的 DNA 或 RNA 基因的病毒，与“肿瘤病毒”或“癌症病毒”同义。

大多数人类和动物病毒不会导致癌症，这可能是因为病毒与其宿主之间长期存在的共同作用。

Oncovirus-induced cancer

✧ Worldwide, the WHO International Agency for Research on Cancer estimated that in 2002 17.8% of human cancers were caused by infection
✧ 11.9% being caused by one of seven different viruses.
✧ The importance of this is that these cancers might be easily prevented through vaccination (e.g., papillomavirus vaccines), diagnosed with simple blood tests, and treated with less-toxic antiviral compounds.
✧ Generally, tumor viruses cause little or no disease after infection in their hosts, or cause non-neoplastic diseases such as acute hepatitis for hepatitis B virus or mononucleosis 单核血球增多症 for Epstein-Barr virus.
✧ A minority of persons (or animals) will go on to develop cancers after infection. This has complicated determining whether or not a given virus causes cancer.

肿瘤病毒诱导的癌症

✧ 世界卫生组织国际癌症研究机构估计，2002 年，17.8％的人类癌症是由感染引起的
✧ 11.9％是由七种不同病毒之一引起的。
✧ 这样做的重要性在于，可以通过接种疫苗（例如乳头瘤病毒疫苗）容易地预防这些癌症，诊断为简单的血液检测，并用较低毒性的抗病毒化合物治疗。

✧ 一般来说，肿瘤病毒在其宿主感染后几乎或几乎不发生疾病，或引起非肿瘤性疾病，如乙型肝炎病毒的急性肝炎或单核细胞增多症，用于爱泼斯坦 - 巴尔病毒的单核血球增多症。
✧ 少数人（或动物）会在感染后继续发展为癌症。 这确定给定的病毒是否导致癌症是复杂的。

Different forms of oncoviruses

Tumor viruses come in a variety of forms:

- Viruses with a DNA genome, such as adenovirus
- Viruses with an RNA genome, like the Hepatitis C virus (HCV)
- Retroviruses having both DNA and RNA genomes: Human T-lymphotropic virus (HTLV) and hepatitis B virus (HBV), which normally replicates as a mixed double and single-stranded DNA virus but also has a retroviral replication component.

不同形式的瘤胃病毒

肿瘤病毒有多种形式：

- 具有 DNA 基因组的病毒，如腺病毒
- 具有 RNA 基因组的病毒，如丙型肝炎病毒（HCV）
- 具有 DNA 和 RNA 基因组的逆转录病毒：人类 T 淋巴细胞病毒（HTLV）和乙型肝炎病毒（HBV），其通常复制为混合的双链和单链 DNA 病毒，但也具有逆转录病毒复制组分。

✧ In many cases, tumor viruses do not cause cancer in their native hosts but only in dead-end species.
✧ For example, adenoviruses do not cause cancer in humans but are instead responsible for colds, conjunctivitis 结膜炎 and other acute illnesses. They only become tumorigenic when infected into certain rodent species, such as Syrian hamsters.
✧ Some viruses are tumorigenic when they infect a cell and persist as circular episomes or plasmids, replicating separately from host cell DNA (Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus).
✧ Other viruses are only carcinogenic when they integrate into the host cell genome as part of a biological accident, such as polyomaviruses and papillomaviruses.
✧ 在许多情况下，肿瘤病毒不会在其本地的宿主中引起癌症，而只会在死亡物种中引起癌症。
✧ 例如，腺病毒不会在人体中引起癌症，而是对感冒，结膜炎和其他急性疾病负责。 当它们感染到某些啮齿动物物种时，如叙利亚仓鼠，它们才变得致瘤。
✧ 当病毒感染细胞时，一些病毒是致病性的，并且作为循环细胞或质粒持续存在，与宿主细胞 DNA（爱泼斯坦 - 巴尔病毒和卡波西氏肉瘤相关的疱疹病毒）分开复制。
✧ 当它们作为生物学事故的一部分整合到宿主细胞基因组中时，其他病毒只是致癌的，如多瘤病毒和乳头状瘤病毒。

Viral Oncogenesis of Retroviruses

Transducing and non-transducing oncoviruses

Transducing: cause cancer early (in days in chicken) and 100% efficiency

Non-transducing: cause cancer within weeks or months. Non-transducing oncovirus cannot transform culture cells

The 3rd group: months to years development of cancer

转导和非转导癌基因

转导：早期（以鸡为天）引起癌症，效率达 100％

非转导：在数周或数月内引起癌症。 非转录因子病毒不能转化培养细胞

第三组：几个月到几年发展癌症

Transducing oncovirus and v-oncogenes

Transducing oncoviruses contain transduced cellular genes which becomes oncogenes and would cause cancer very rapidly;

Non-transducing oncovirus does not contain v-oncogenes

V-oncogenes' counterpart in cells are called c-oncogenes or proto-oncogenes

Non-transducing oncovirus can initiate integration of the provirus adjacent to a c-oncogene to cause tumor
转染癌基因病毒和致癌基因
转录瘤衣包含转导的细胞基因，其成为癌基因并将非常迅速地导致癌症;
非转录癌基因病毒不含有致癌基因
V-致癌基因在细胞中的对应物称为癌基因或原癌基因
非转导性甲状腺炎病毒可以启动与癌基因相邻的原病毒的整合以引起肿瘤

Oncogenes

Oncogenes encode components of celllar signal transduction
Their activation leads to a constitutive growth signal
In 1980s, virologists found tumor suppressor genes which can be inhibited by viral proteins
Viral oncology studies significantly controbuted for the understanding of basic mechanisms of oncogenesis
癌基因
致癌基因编码细胞信号转导的成分
它们的激活导致组成型生长信号
20 世纪 80 年代，病毒学家发现可以被病毒蛋白抑制的肿瘤抑制基因
对于肿瘤发生的基本机制的理解，病毒学肿瘤学研究有显着的争议

Mechanisms of viral oncogenesis

- ✧ A direct oncogenic viral mechanism involves either insertion of additional viral oncogenic genes into the host cell or to enhance already existing oncogenic genes (proto-oncogenes) in the genome.
- ✧ Indirect viral oncogenicity involves chronic nonspecific inflammation occurring over decades of infection, as is the case for HCV-induced liver cancer.
- ✧ These two mechanisms differ in their biology and epidemiology: direct tumor viruses must have at least one virus copy in every tumor cell expressing at least one protein or RNA that is causing the cell to become cancerous.
- ✧ Because foreign virus antigens are expressed in these tumors, persons who are immunosuppressed such as AIDS or transplant patients are at higher risk for these types of cancers.
- ✧ Chronic indirect tumor viruses, on the other hand, can be lost (at least theoretically) from a mature tumor that has accumulated sufficient mutations and growth conditions (hyperplasia) from the chronic inflammation of viral infection.
- ✧ In this latter case, it is controversial but at least theoretically possible that an indirect tumor virus could undergo "hit-and-run" and so the virus would be lost from the clinically diagnosed tumor.

病毒性肿瘤发生机制

- ✧ 直接致癌病毒机制涉及将另外的病毒致癌基因插入宿主细胞或增强基因组中已经存在的致癌基因（原癌基因）。
- ✧ 间接病毒致癌性涉及几十年的感染发生的慢性非特异性炎症，如 HCV 诱导的肝癌的情况。
- ✧ 这两种机制的生物学和流行病学不同：直接肿瘤病毒必须在每个肿瘤细胞中至少有一个病毒拷贝，表达至少一种导致细胞变成癌变的蛋白质或 RNA。
- ✧ 由于外来病毒抗原在这些肿瘤中表达，免疫抑制的患者如 AIDS 或移植患者对这些类型的癌症的风险较高。
- ✧ 另一方面，慢性间接肿瘤病毒可以从已经从病毒感染的慢性炎症累积足够的突变和生长条件（增生）的成熟肿瘤中丢失（至少在理论上）。
- ✧ 在后一种情况下，这是有争议的，但至少在理论上可能的是，间接肿瘤病毒可能经历“命中和运行”，因此病毒将从临床诊断的肿瘤中丢失。

Timeline of Discovery

- ➢ 1908: Oluf Bang and Vilhelm Ellerman, U of Copenhagen, first demonstrated that avian leukosis virus could be transmitted after cell-free filtration to new chickens, causing leukemia.

- 1910: Peyton Rous at Rockefeller extended Bang and Ellerman's experiments to show filtrable cell-free transmission of a solid tumor sarcoma to chickens.
- 1933: Richard Edwin Shope discovered cottontail rabbit papillomavirus or Shope papillomavirus, the first mammalian tumor virus.
- 1936: Mouse mammary tumor virus shown by John J. Bittner to be an "extrachromosomal factor" (i.e., virus) transmitted among laboratory strains of mice by breast feeding.[6] This was an extension of work on murine breast cancer caused by a transmissible agent as early as 1915, by A.F. Lathrop and L. Loeb.
- 1954: Ludwik Gross, working at the Bronx VA medical center isolated murine polyomavirus causing a variety of salivary gland and other tumors in specific strains of newborn mice. This was not widely appreciated until the results were confirmed by scientists at NIH reproducing the experiments under the same conditions.
- 1961: Simian Vacuolating virus 40 (SV40) discovered by Eddy at NIH, and Hillman and Sweet at Merck laboratory. Several years later it was shown to cause cancer in Syrian hamsters, raising alarm that persists today. Scientific consensus now strongly agrees that this is not likely to cause human cancer although the controversy still persists.

发现时间表

- 1908 年：Oluf 邦和韦勒廉·埃勒曼，哥本哈根的 U，首先证明了禽白血病病毒可能无细胞过滤到新的鸡后进行传输，从而导致白血病。
- 1910 年：洛克菲勒的佩顿·鲁斯（Bang Pereton Rous）延长了 Bang 和 Ellerman 的实验，显示了实体肿瘤肉瘤对鸡的可过滤的无细胞传播。
- 1933 年：理查德·埃德温·肖佩（Richard Edwin Shope）发现了棉尾巴兔乳头瘤病毒或 Shope 乳头瘤病毒，第一种哺乳动物肿瘤病毒。
- 1936：由约翰·J·比特纳示出小鼠乳腺肿瘤病毒是一个“染色体外因子”（即，病毒）的母乳喂养的小鼠的实验室菌株中发送[6]这是早在 1915 年由 A.F.Lathrop 和 L.Leeb 提出的由传染性药物引起的鼠乳腺癌的工作的延伸。
- 1954 年：Ludwik Gross 在布朗克斯 VA 医学中心工作，分离出在特定新生小鼠中引起各种唾液腺和其他肿瘤的鼠多瘤病毒。直到 NIH 的科学家证实结果在相同条件下再现实验之前，这一点尚未得到广泛的认可。
- 1961 年：Eddy 在 NIH 发现的 Simian Vacuolating 病毒 40（SV40），以及默克实验室的 Hillman 和 Sweet。几年后，它被证明在叙利亚仓鼠中引起癌症，引起了今天持续的恐慌。现在的科学共识强烈地认为，这不可能引起人类癌症，尽管争议仍然存在。

Human Oncoviruses

- 1964: Anthony Epstein, Bert Achong and Yvonne Barr identify the first human cancer virus from Burkitt lymphoma cells. A herpesvirus, this virus is formally known as human herpesvirus 4 but more commonly called Epstein-Barr Virus or EBV.
- mid-1960s: Baruch Blumberg first physically isolated and characterized Hepatitis B while at NIH and later Fox Chase Laboratory, receiving the 1976 Nobel Prize in Medicine or Physiology. Although this agent was the clear cause of hepatitis and might contribute to liver cancer hepatocellular carcinoma, this link was not firmly established until epidemiologic studies were performed in the 1980s by R. Palmer Beasley and others.
- 1980: Human T-lymphotropic virus 1 (HTLV I), the first human retrovirus was discovered by Bernard Poiesz and Robert Gallo at NIH and Mistuaki Yoshida and coworkers in Japan.
- 1984–86: Harald zur Hausen, together with Lutz Gissman, discovered first HPV16 and then HPV18 responsible for approximately 70% of cervical cancers. For discovery that human papillomaviruses (HPV) cause human cancer, zur Hausen won a 2008 Nobel Prize.
- 1987: HCV was discovered by panning a cDNA library made from diseased tissues for foreign antigens recognized with patient sera. This work was performed by Michael Houghton at Chiron, a biotechnology company, and D.W. Bradley at CDC. HCV was subsequently shown to be a major contributor to liver cancer (hepatocellular carcinoma) worldwide.

- ✧ 1994: Patrick S. Moore and Yuan Chang (a husband and wife team then at Columbia University) working together with Frank Lee and Ethel Cesarman isolated Kaposi sarcoma-associated herpesvirus (KSHV or HHV8). This search was prompted from work by V. Beral, T. Peterman and H. Jaffe who showed from accumulating evidence from the epidemic of Kaposi sarcoma associated with AIDS, that this cancer must have another infectious cause besides HIV itself. This agent was predicted to be a new virus. Subsequent studies revealed that KSHV is indeed the "KS agent" and is responsible for the epidemiologic patterns of KS and related cancers.
- ✧ 2008: Chang and Moore, now at the University of Pittsburgh Cancer Institute, developed a new method to identify cancer viruses based on computer subtraction of human sequences from a tumor transcriptome, called digital transcriptome subtraction (DTS).

人类病毒

- ✧ 1964 年：Anthony Epstein，Bert Achong 和 Yvonne Barr 从伯基特淋巴瘤细胞中鉴定出首例人类癌症病毒。疱疹病毒，这种病毒正式称为人类疱疹病毒 4，但更常见的叫做爱泼斯坦 - 巴尔病毒或 EBV。
- ✧ 20 世纪 60 年代中期：Baruch Blumberg 首先在美国国立卫生研究院和随后的福克斯大通实验室身体分离和鉴定乙型肝炎，获得 1976 年诺贝尔医学或生理学奖。虽然这种药物是肝炎的明显原因，并且可能有助于肝癌肝细胞癌，但是由 R. Palmer Beasley 等人于 1980 年代进行流行病学研究之前，这一联系并没有牢固地建立起来。
- ✧ 1980 年：人类 T 淋巴细胞病毒 1（HTLV I），第一人类逆转录病毒是由 NIH 的吉他和罗伯特·加洛以及日本的同事发现的。
- ✧ 1984-86：Harald zur Hausen 与 Lutz Gissman 一起，发现了 HPV16，然后 HPV18 负责大约 70％的宫颈癌。为了发现人类乳头瘤病毒（HPV）引起人类癌症，祖尔·豪森获得了 2008 年诺贝尔奖。
- ✧ 1987 年：通过淘汰由患病血清识别的外来抗原的患病组织的 cDNA 文库而发现 HCV。这项工作是由生物技术公司 Chiron 的 Michael Houghton 和 D.W.布拉德利在 CDC。 HCV 随后显示是全世界肝癌（肝细胞癌）的主要贡献者。
- ✧ 1994 年：Patrick S. Moore 和 Yuan Chang（哥伦比亚大学的丈夫和妻子团队）与 Frank Lee 和 Ethel Cesarman 一起分离了 Kaposi 肉瘤相关的疱疹病毒（KSHV 或 HHV8）。这项检索是由 V.Beral，T. Peterman 和 H. Jaffe 的工作提出的，他们从艾滋病相关的卡波西肉瘤流行病的累积证据中得出结论，除了艾滋病毒本身之外，这种癌症还必须有另一种传染病。该药物预计是一种新的病毒。随后的研究显示，KSHV 确实是“KS 代理”，并且负责 KS 和相关癌症的流行病学模式。
- ✧ 2008 年：现在匹兹堡大学癌症研究所的 Chang 和 Moore 开发了一种基于计算机从肿瘤转录组（称为数字转录组减法（DTS））转录组的人类序列中减去癌症病毒的方法。

DNA oncoviruses

- ✧ Human papilloma virus (HPV), a DNA virus, causes transformation in cells through interfering with tumor suppressor proteins such as p53. Interfering with the action of p53 allows a cell infected with the virus to move into a different stage of the cell cycle, enabling the virus genome to be replicated. Forcing the cell into the S phase of the cell cycle could cause the cell to become transformed. Some types of HPV increase the risk of, e.g., cervical cancer.
- ✧ Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8) is associated with Kaposi’s sarcoma, a type of skin cancer.
- ✧ Epstein-Barr virus (EBV or HHV-4) is associated with four types of cancers
- ✧ Merkel cell polyomavirus – a polyoma virus – is associated with the development of Merkel cell carcinoma
- ✧ Human cytomegalovirus (CMV or HHV-5) is associated with mucoepidermoid carcinoma 粘液表皮样癌 and possibly other malignancies.

DNA 甲基病毒

- ✧ 人乳头状瘤病毒（HPV）是一种 DNA 病毒，通过干扰肿瘤抑制蛋白如 p53，导致细胞转化。 干扰 p53 的作用可使感染病毒的细胞进入细胞周期的不同阶段，从而能够复制病毒基因组。 将细胞强制进入细胞周期的 S 期可导致细胞转化。 某些类型的 HPV 会增加例如宫颈癌的风险。
- ✧ 卡波西肉瘤相关疱疹病毒（KSHV 或 HHV-8）与卡波西肉瘤相关，皮肤癌是一种皮肤癌。
- ✧ 爱泼斯坦 - 巴尔病毒（EBV 或 HHV-4）与四种类型的癌症有关

✧ Merkel 细胞多瘤病毒 - 多瘤病毒与 Merkel 细胞癌的发展有关
✧ 人巨细胞病毒（CMV 或 HHV-5）与粘液表皮样癌粘液表皮样癌和可能的其他恶性肿瘤有关。

Chapter 8 - Human papillomavirus (HPV)

第八章人乳头瘤病毒（HPV）

HPV genotypes

HPV is a small, nonenvelope, double - stranded DNA virus of the Papillomaviridae family.

Different HPVs are defined by their genotypes, with more than 100 described to date.

HPV genotypes are clustered into genera based on genetic relatedness.

Within each genus, HPVs are categorized into species based on distinct genotypes;

Members of a species have similar biological properties or phenotypes.

Differences of 10% or more in the viral capsid gene (L1) are noted as different HPV types, differences of 2% – 10% as subtypes, and differences of less than 2% are variants

HPV 基因型

HPV 是 Papillomaviridae 家族的一种小的，非信号的双链 DNA 病毒。

不同的 HPV 是由它们的基因型定义的，迄今为止描述了超过 100 种。

基于遗传相关性将 HPV 基因型聚类成属。

在每个属中，HPV 被分为基于不同基因型的物种;

一个物种的成员具有相似的生物学特性或表型。

病毒衣壳基因（L1）中 10％以上的差异被鉴定为不同的 HPV 类型，2％-10％的差异作为亚型，差异小于 2％是变体

Alpha and Beta genera α 和 β 属

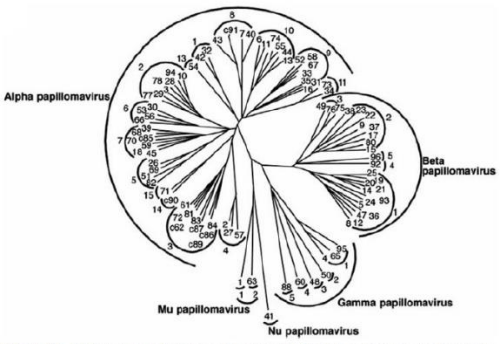


Figure 1.1. HPV cladogram. HPV types are categorized based on their genetic similarities. The genus alpha papillomaviruses primarily infect mucosal epithelium, and the genus beta papillomaviruses primarily infect the skin (figure from Doorbar, 2006).

Signs and symptoms 体征和症状

Disease	HPV type
Common warts	2, 7
Plantar warts	1, 2, 4, 63
Flat warts	3, 10, 8
Anogenital warts	6, 11, 42, 44 and others[11]
Anal lesions	6, 16, 18, 31, 53, 58 reference
Genital cancers	• Highest risk:[11] 16, 18, 31, 45 • Other high-risk:[11][12] 33, 35, 39, 51, 52, 56, 58, 59 • Probably high-risk:[12] 26, 53, 66, 68, 73, 82
Epidermodysplasia verruciformis	more than 15 types
Focal epithelial hyperplasia (oral)	13, 32
Oral papillomas	6, 7, 11, 16, 32
Oropharyngeal cancer	16
Laryngeal papillomatosis	6,11

Key Points

✧ Some types of sexually transmitted human papillomaviruses (HPVs) can cause genital warts. Other types, called high-risk or oncogenic HPVs, can cause cancer.

✧ High-risk HPVs cause virtually all cervical cancers. They also cause most anal cancers and some vaginal, vulvar, penile, and oropharyngeal （口咽） cancers.

✧ Most infections with high-risk HPVs do not cause cancer. Many HPV infections go away on their own within 1 to 2 years. However, infections that last for many years increase a person’s risk of developing cancer.

关键点

✧ 某些类型的性传播的人乳头状瘤病毒（HPV）可能会导致生殖器疣。 其他类型，称为高风险或致癌性 HPV，可引起癌症。

✧ 高危 HPV 会导致几乎所有的宫颈癌。 它们还引起大多数肛门癌和一些阴道，外阴，阴茎和口咽癌（口咽癌）。

✧ 大多数高风险 HPV 感染者不会导致癌症。 许多 HPV 感染在 1 至 2 年内自行消失。 然而，持续多年的感染会增加患者发生癌症的风险。

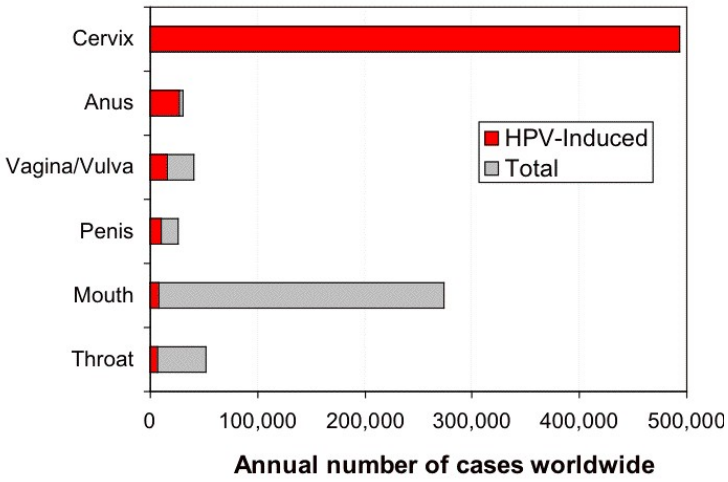
Association between HPV infection and cancer

- ✧ High-risk HPV infection accounts for approximately 5% of all cancers worldwide.
- ✧ However, most high-risk HPV infections occur without any symptoms, go away within 1 to 2 years, and do not cause cancer. These transient infections may cause cytologic abnormalities, or abnormal cell changes, that go away on their own.
- ✧ Some HPV infections, however, can persist for many years. Persistent infections with high-risk HPV types can lead to more serious cytologic abnormalities or lesions that, if untreated, may progress to cancer.

HPV 感染与癌症之间的关联

- ✧ 全球高危 HPV 感染占全部癌症的约 5%。
- ✧ 然而，大多数高风险的 HPV 感染发生没有任何症状，在 1 至 2 年内消失，不会导致癌症。 这些短暂的感染可能会导致细胞学异常或异常的细胞变化。
- ✧ 然而，一些 HPV 感染可以持续多年。 持续感染高危 HPV 类型可导致更严重的细胞学异常或病变，如果未经治疗，可能会进展为癌症。

HPV-induced cancers HPV 诱导的癌症

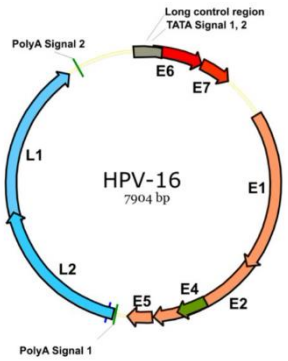


Transmission

- ✧ Since cervical and female genital infection by specific HPV types is highly associated with cervical cancer, those types of HPV infection have received most of the attention from scientific studies.
- ✧ HPV infections in that area are transmitted primarily via sexual activity.
- ✧ At least 40 identified HPV types infect the genital tract. If a college woman has at least one different partner per year for four years, the probability that she will leave college with an HPV infection is greater than 85% (USA data).

传播

- ✧ 由于特定 HPV 类型的宫颈和女性生殖器感染与子宫颈癌高度相关，因此 HPV 感染的这些类型受到科学研究的广泛关注。
- ✧ 该地区的 HPV 感染主要通过性活动传播。
- ✧ 至少有 40 个确定的 HPV 类型感染生殖道。 如果一名大学女性每年至少有一名不同的伴侣持续四年，她将因 HPV 感染而离开大学的可能性大于 85%（美国数据）。



Genome organization of HPV Type 16, one of the subtypes known to cause cervical cancer. E1-E7 early genes, L1-L2 late genes: capsid

HPV16 型 HPV 基因组组织是已知导致子宫颈癌的亚型之一。 E1-E7 早期基因，L1-L2 晚期基因：衣壳

HPV infection

HPV infection is limited to the basal cells of stratified epithelium, the only tissue in which they replicate.

The virus cannot bind to live tissue; instead, it infects epithelial tissues through micro-abrasions or other epithelial trauma that exposes segments of the basement membrane.

The infectious process is slow, taking 12–24 hours for initiation of transcription. It is believed that involved antibodies play a major neutralizing role while the virions still reside on the basement membrane and cell surfaces.

HPV 感染

HPV 感染仅限于分层上皮的基底细胞，即它们复制的唯一组织。

病毒不能结合活组织; 相反，它通过暴露基底膜段的微擦伤或其他上皮创伤来感染上皮组织。

感染过程缓慢，开始转录需要 12-24 小时。 相信所涉及的抗体在病毒颗粒仍然存在于基底膜和细胞表面上时起着主要的中和作用。

HPV life cycle

- ✧ The HPV life cycle strictly follows the differentiation program of the host keratinocyte 角化细胞.
- ✧ It is thought that the HPV virion infects epithelial tissues through micro-abrasions, whereby the virion associates with putative receptors such as alpha integrins and laminins, leading to entry of the virions into basal epithelial cells through clathrin-mediated endocytosis and/or caveolin-mediated endocytosis depending on the type of HPV.
- ✧ At this point, the viral genome is transported to the nucleus by unknown mechanisms and establishes itself at a copy number between 10-200 viral genomes per cell.
- ✧ A sophisticated transcriptional cascade then occurs as the host keratinocyte begins to divide and become increasingly differentiated in the upper layers of the epithelium.
- ✧ HPV 生命周期
- ✧ HPV 生命周期严格遵循宿主角质形成细胞的分化程序。
- ✧ 据认为，HPV 病毒粒子通过微擦伤感染上皮组织，由此病毒体与推定的受体如 α 整联蛋白和层粘连蛋白结合，导致通过网格蛋白介导的胞吞作用和/或小窝蛋白介导的病毒粒子进入基底上皮细胞 内吞作用取决于 HPV 的类型。
- ✧ 在这一点上，病毒基因组通过未知机制转运到细胞核，并以每个细胞 10-200 个病毒基因组之间的拷贝数确定自身。
- ✧ 然后随着宿主角质形成细胞在上皮的上层开始分裂并变得越来越分化，就会发生复杂的转录级联。

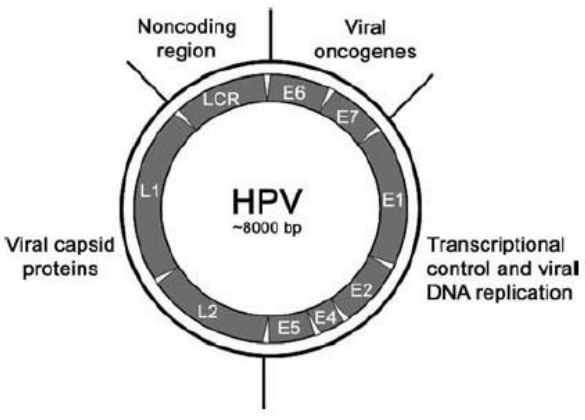
Early and Late Genes 早期和晚期基因

E6/E7 proteins

- ✧ E6 and E7 are the HPV proteins associated with cancer.
- ✧ The HPV genome is composed of six early (E1, E2, E4, E5, E6, and E7) genes, two late (L1 and L2) genes, and a non-coding long control region (LCR).
- ✧ After the host cell is infected E1 and E2 are expressed first.
- ✧ High E2 levels repress expression of the E6 and E7 proteins.
- ✧ When the host and HPV genomes integrate, E2 function is disrupted, preventing repression of E6/E7.

E6 / E7 蛋白

- ✧ E6 和 E7 是与癌症相关的 HPV 蛋白。
- ✧ HPV 基因组由六个早期（E1，E2，E4，E5，E6 和 E7）基因，两个晚期（L1 和 L2）基因和非编码长控制区（LCR）组成。
- ✧ 宿主细胞感染后，首先表达 E1 和 E2。
- ✧ 高 E2 水平抑制 E6 和 E7 蛋白的表达。
- ✧ 当宿主和 HPV 基因组整合时，E2 功能被破坏，阻止了 E6 / E7 的镇压。



Roles of E6/E7 in cancer

✧ E6/E7 proteins inactivate two tumor suppressor proteins, p53 (inactivated by E6) and pRb (inactivated by E7).

✧ The viral oncogenes E6 and E7 are thought to modify the cell cycle so as to retain the differentiating host keratinocyte in a state that is favourable to the amplification of viral genome replication and consequent late gene expression.

✧ E6 in association with host E6-associated protein, which has ubiquitin ligase activity, acts to ubiquitinate p53, leading to its proteosomal degradation.

✧ E7 (in oncogenic HPVs) acts as the primary transforming protein. E7 competes for retinoblastoma protein (pRb) binding, freeing the transcription factor E2F to transactivate its targets, thus pushing the cell cycle forward.

E6 / E7 在癌症中的作用

✧ E6 / E7 蛋白使两种肿瘤抑制蛋白，P53（E6 失活）和 pRb（E7 失活）失活。

✧ 认为病毒致癌基因 E6 和 E7 可以修饰细胞周期，以保持差异化宿主角质形成细胞处于有利于扩增病毒基因组复制和后期基因表达的状态。

✧ 与具有泛素连接酶活性的宿主 E6 相关蛋白相关的 E6 作用于泛素化 p53，导致其蛋白质体降解。

✧ E7（致癌性 HPV）作为初级转化蛋白。 E7 竞争视网膜母细胞瘤蛋白（pRb）结合，释放转录因子 E2F 以转录其靶标，从而推动细胞周期向前发展。

E2 and E1

✧ E2 protein has several critical roles in HPV genome expression and replication.

✧ E2 is expressed early in the viral life cycle and is found in basal and suprabasal layers of stratified squamous epithelium infected by HPV. E2 binds as a dimer to DNA and recognizes a motif in the noncoding region of HPV genome 5′ of the early promoter.

✧ E2 recruits the HPV viral helicase E1 to the viral origin and increases the DNA-binding affinity to the noncoding region;

✧ Both E1 and E2 together utilize cellular machinery for DNA replication and transcription.

✧ Although E2 is a transcriptional activator at low concentrations, high levels of E2 repress expression of E6 and E7 from the late promoter.

✧ Finally, E2 also functions to segregate the HPV genome as cells divide by tethering the genome to cellular chromosomes during mitosis.

✧ E2 蛋白在 HPV 基因组表达和复制中具有几个关键作用。

✧ E2 在病毒生命周期早期表达，并发现在 HPV 感染的分层鳞状上皮的基底层和 supababasal 层。 E2 作为二聚体结合到 DNA 上并识别早期启动子的 HPV 基因组 5'的非编码区的基序。

✧ E2 将 HPV 病毒解旋酶 E1 募集到病毒来源，并增加与非编码区的 DNA 结合亲和力;

✧ E1 和 E2 一起利用细胞机制进行 DNA 复制和转录。

✧ 尽管 E2 是低浓度的转录激活因子，但高水平的 E2 抑制来自晚期启动子的 E6 和 E7 的表达。

✧ 最后，E2 也用于分离 HPV 基因组，因为细胞在有丝分裂期间将基因组系到细胞染色体上分裂。

E4

The E4 protein is found in the suprabasal and granular layers of stratified squamous (鳞状) epithelium.

Without a functional E4 protein, HPV episomal DNA cannot amplify from their initial 50 – 100 copies per cell to the several thousands normally seen

E4 蛋白存在于分层鳞状上皮细胞的上层和颗粒层中。

没有功能性 E4 蛋白，HPV 附加型 DNA 不能从每个细胞的初始 50-100 拷贝扩增到几千个正常的

E5

✧ E5 protein has effects on both cellular transformation and viral genome amplification.

✧ Although HPV E5 has little effect on monolayer undifferentiated keratinocytes in vitro, E5 does increase the number of suprabasal cells dividing in organotypic cultures grown to mimic stratified squamous epithelium.

✧ Additionally, in differentiated keratinocytes, E5 induces HPV genome amplification. HPV16 E5 can cause epithelial hyperplasia, abnormal cellular differentiation, and skin tumors when expressed in mice.
✧ This effect occurs through the epidermal growth factor receptor,although this may not be consistent across all HPV types
✧ E5 蛋白对细胞转化和病毒基因组扩增均有影响。
✧ 虽然 HPV E5 在体外对单层未分化的角质形成细胞几乎没有影响，但是 E5 确实增加了在生长到模拟分层鳞状上皮的器官型培养物中分裂的上基质细胞的数量。
✧ 另外，在分化的角化细胞中，E5 诱导 HPV 基因组扩增。 当在小鼠中表达时，HPV16 E5 可引起上皮增生，异常细胞分化和皮肤肿瘤。
✧ 这种作用通过表皮生长因子受体发生，尽管在所有 HPV 类型中这可能不一致

L1 and L2

✧ The viral coat proteins L1 and L2 are expressed from the late promoter after a change in splicing patterns and a transition to the late polyadenylation site.
✧ Three hundred sixty L1 proteins organize into 72 capsomers, with one L2 protein associated with each pentavalent capsomer.
✧ The capsomers self-assemble without HPV DNA in vitro as virus-like particles (VLPs) and in the cellular nucleus in vivo to encapsulate the HPV genome into infectious virus particles.
✧ 病毒外壳蛋白 L1 和 L2 在剪接模式发生变化并转变为晚期多聚腺苷酸化位点后从后期启动子表达。
✧ 三百六十个 L1 蛋白组织成 72 个帽形体，一个 L2 蛋白与每个五价胶囊蛋白相关。
✧ 在体外将瓶颈自身组装成病毒样颗粒（VLP），并在体内的细胞核中将 HPV 基因组装入感染性病毒颗粒中。

How are HPV infections detected?

✧ HPV infections can be detected by testing a sample of cells to see if they contain viral DNA or RNA.
✧ The most common test detects DNA from several high-risk HPV types, but it cannot identify the type(s) that are present.
✧ Another test is specific for DNA from HPV types 16 and 18, the two types that cause most HPV-associated cancers.
✧ A third test can detect DNA from several high-risk HPV types and can indicate whether HPV-16 or HPV-18 is present.
✧ A fourth test detects RNA from the most common high-risk HPV types. These tests can detect HPV infections before cell abnormalities are evident.

如何检测 HPV 感染？

✧ 可以通过测试细胞样品来检测 HPV 感染，以观察其是否含有病毒 DNA 或 RNA。
✧ 最常见的检测方法是检测几种高危 HPV 类型的 DNA，但不能识别存在的类型。
✧ HPV16 型和 18 型 HPV 的另一项测试是两种导致大多数 HPV 相关癌症的 DNA。
✧ 第三个测试可以检测几种高危 HPV 类型的 DNA，并且可以表明是否存在 HPV-16 或 HPV-18。
✧ 第四个测试检测来自最常见的高危 HPV 类型的 RNA。 这些测试可以在细胞异常明显之前检测 HPV 感染。

What are treatment options for HPV-infected individuals?

✧ There is currently no medical treatment for HPV infections. However, the genital warts and precancerous lesions resulting from HPV infections can be treated.
✧ Methods commonly used to treat precancerous cervical lesions include cryosurgery, LEEP, surgical conization, and laser vaporization conization.
✧ HPV-infected individuals who develop cancer generally receive the same treatment as patients whose tumors do not harbor HPV infections, according to the type and stage of their tumors.

✧ However, people who are diagnosed with HPV-positive oropharyngeal cancer may be treated differently than people with oropharyngeal cancers that are HPV-negative.

HPV 感染个体的治疗方案是什么？

✧ 目前没有 HPV 感染的治疗。 然而，可以治疗由 HPV 感染引起的生殖器疣和癌前病变。

✧ 通常用于治疗癌前期宫颈病变的方法包括冷冻手术，LEEP，手术锥形化和激光蒸发锥化。

✧ 根据其肿瘤的类型和阶段，发展为癌症的 HPV 感染个体通常接受与肿瘤不携带 HPV 感染的患者相同的治疗。

✧ 然而，诊断为 HPV 阳性口咽癌的人可能与 HPV 阴性的口咽癌患者不同。

HPV vaccines

- HPV vaccine prevents infection with certain species of human papillomavirus associated with the development of cervical cancer, genital warts, and some less common cancers.
- Two HPV vaccines are currently on the market: Gardasil and Cervarix.
- Both vaccines protect against the two HPV types (HPV-16 and HPV-18) that cause 70% of cervical cancers, 80% of anal cancers, 60% of vaginal cancers, and 40% of vulvar cancers.
- These HPV types also cause most HPV induced oral cancers, and some other rare genital cancers. Gardasil also protects against the two HPV types (HPV-6 and HPV-11) that cause 90% of genital warts.
- The vaccines provide little benefit to women having already been infected with HPV types 16 and 18, which includes most sexually active females. For this reason, the vaccine is recommended primarily for those women not yet having been exposed to HPV during sex. The WHO position paper on HPV vaccination clearly outlines appropriate, cost-effective strategies for using HPV vaccine in public sector programs.
- Both vaccines are delivered in three shots over six months. In most countries, they are approved only for female use, but are approved for male use in countries like USA and UK. The vaccine does not have any therapeutic effect on existing HPV infections or cervical lesions.
- In 2010, 49% of teenage girls in the US got the HPV vaccine.
- Women should continue to seek cervical screening, such as Pap smear testing, even after receiving the vaccine. Cervical cancer screening recommendations have not changed for females who receive HPV vaccine. Without continued screening, the number of cervical cancers preventable by vaccination alone is less than the number of cervical cancers prevented by regular screening alone.
- Both men and women are carriers of HPV. The Gardasil vaccine also protects men against anal cancers and warts and genital warts.
- No efficacy trials for children under 15 have been performed. Duration of vaccine efficacy is not yet answered by rigorous methodologic trials. Cervarix efficacy is proven for 7.4 years with published data through 6.4 years while Gardasil efficacy is proven for 5 years. Age of vaccination is less important than the duration of efficacy.

HPV 疫苗

- HPV 疫苗可预防某些与宫颈癌，生殖器疣和一些较不常见的癌症发展相关的人乳头状瘤病毒感染。
- 目前市场上有两种 HPV 疫苗：Gardasil 和 Cervarix。
- 两种疫苗可以防止导致 70％的宫颈癌，80％的肛门癌，60％的阴道癌和 40％的外阴癌的两种 HPV 类型（HPV-16 和 HPV-18）。
- 这些 HPV 类型也引起大多数 HPV 诱导的口腔癌和一些其他罕见的生殖器癌。 Gardasil 还可以防止导致 90％生殖器疣的两种 HPV 类型（HPV-6 和 HPV-11）。
- 疫苗对已经感染了 16 型和 18 型 HPV 的女性几乎没有好处，其中包括大多数性活跃女性。因此，该疫苗主要用于那些在性别期间尚未接触 HPV 的妇女。世卫组织关于 HPV 疫苗接种的立场文件清楚地概述了在公共部门计划中使用 HPV 疫苗的适当的，具有成本效益的策略。
- 两种疫苗都在六个月内三次投放。在大多数国家，它们仅被批准为女性使用，但在美国和英国等国家被批准用于男性使用。疫苗对现有的 HPV 感染或宫颈病变没有任何治疗作用。
- 2010 年，美国有 49％的女孩患有 HPV 疫苗。

- 妇女应继续寻求宫颈筛查，如巴氏涂片检查，即使接受疫苗后。宫颈癌筛查建议对于接受 HPV 疫苗的女性没有改变。没有继续筛查，仅通过接种可预防的子宫颈癌的数量就少于通过常规筛查而预防的宫颈癌的数量。
- 男性和女性都是 HPV 的携带者。 Gardasil 疫苗还保护男性免受肛门癌和疣和生殖器疣的侵害。
- 没有对 15 岁以下的儿童进行功效试验。疫苗疗效的持续时间尚未通过严格的方法学试验来回答。Cervarix 的疗效证明为 7.4 年，公布的数据为 6.4 年，而 Gardasil 疗效证明为 5 年。接种时间不如疗效持续时间重要。

By15 生技 1 杨家益
虽然这课没了署名并没有什么卵用