感冒与病毒

王奇慧

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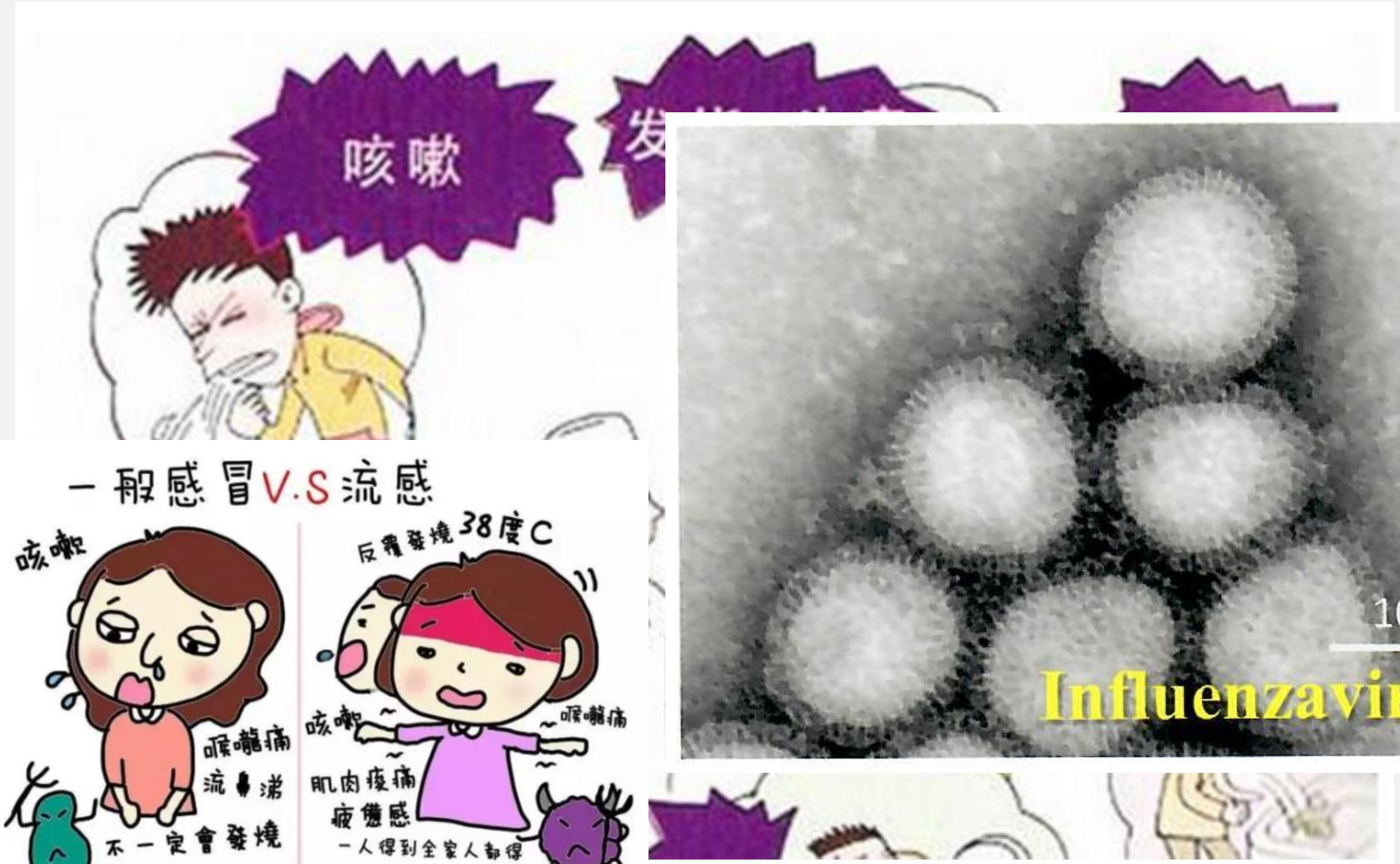
中国科学院微生物研究所
病原菌感染与宿主免疫研究组长
wangqihui@im.ac.cn

中国科学院微生物研究所位于鸟巢周围

中国科学院微生物研究所
Institute of Microbiology, Chinese Academy of Sciences

重感冒 ——流感病毒



http://www.sohu.com/a/115180099_103722

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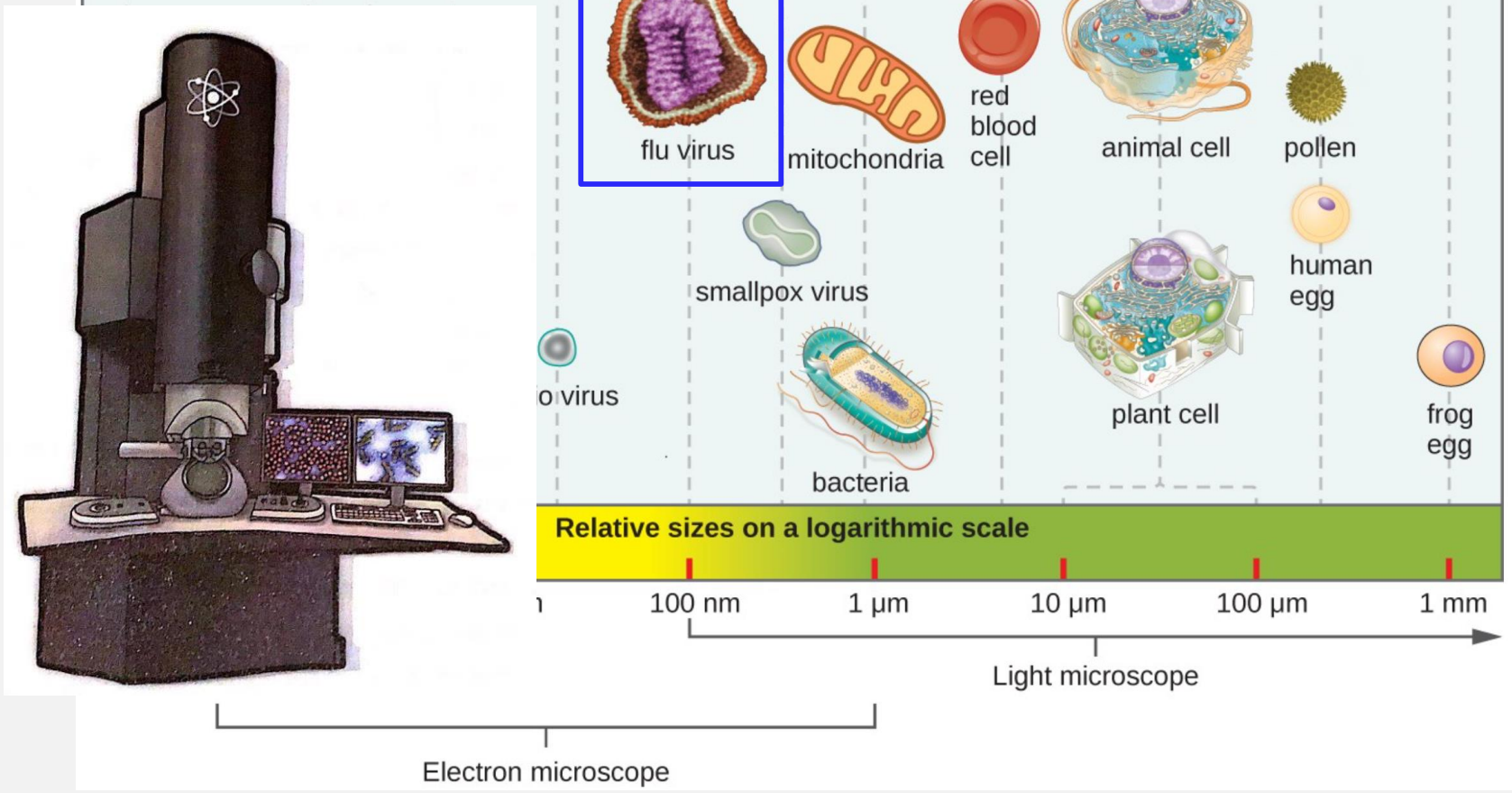
病毒的大小



https://courses.lumenlearning.com/

流感病毒的分类

流感病毒分为甲、乙、丙 三型

	甲型	乙型	丙型
致病性	强	强	一般
流行性	易引起大范围流行甚至世界性大流行	未引起过世界性大流行	很少造成流行

人类历史上流感病毒多次大流行

1918年 西班牙流感
10亿人感染
2-4千万 人死亡
H1N1

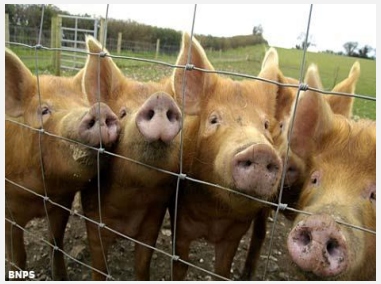
1957年 亚洲流感
1百万人死亡
H2N2

1968年 香港流感
1百万人死亡
H3N2

1997年 香港禽流感
直接由鸟类传染给人
H5N1

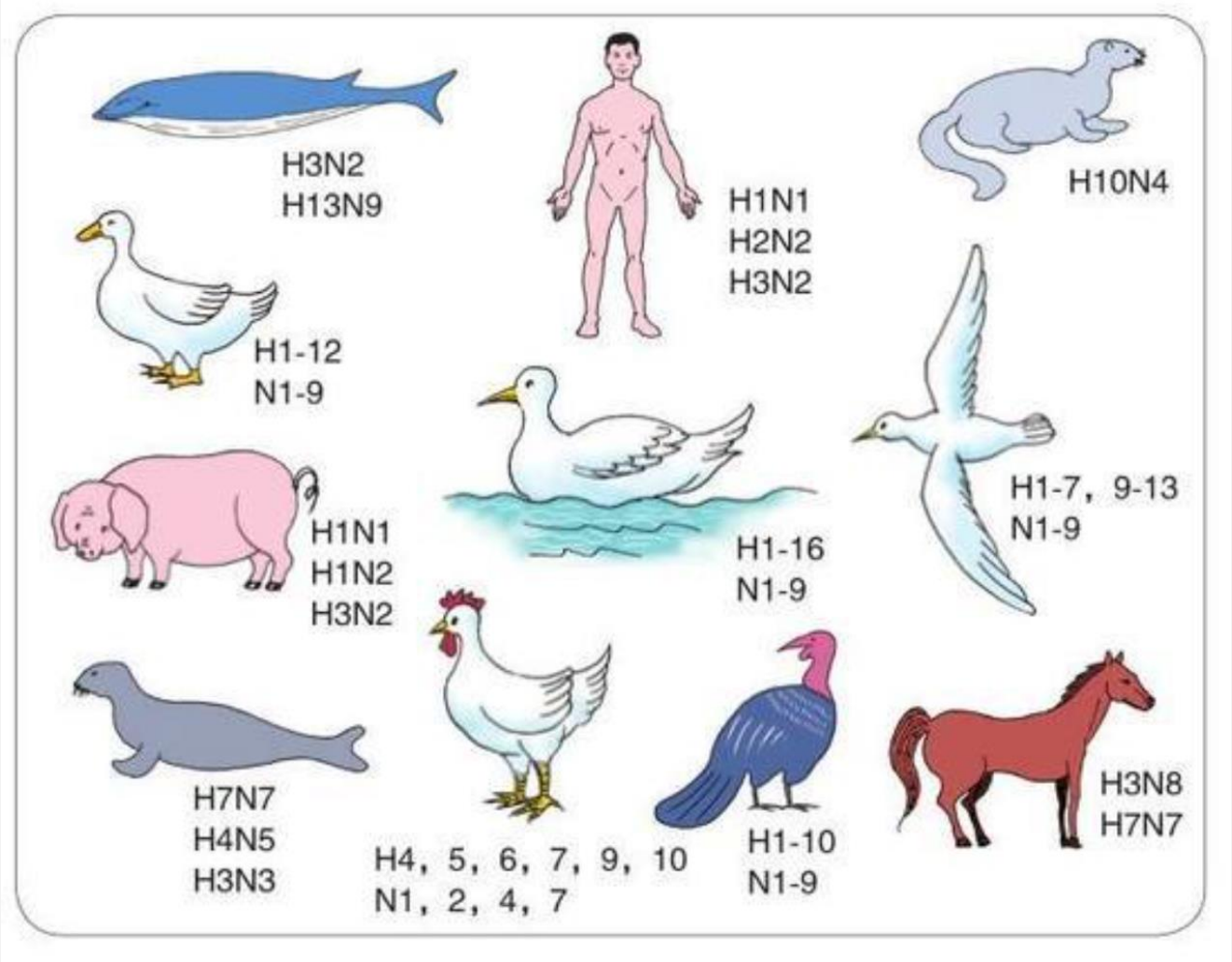
2003年
禽流感小范围传播
H5N1

2009 年墨西哥猪流感
H1N1

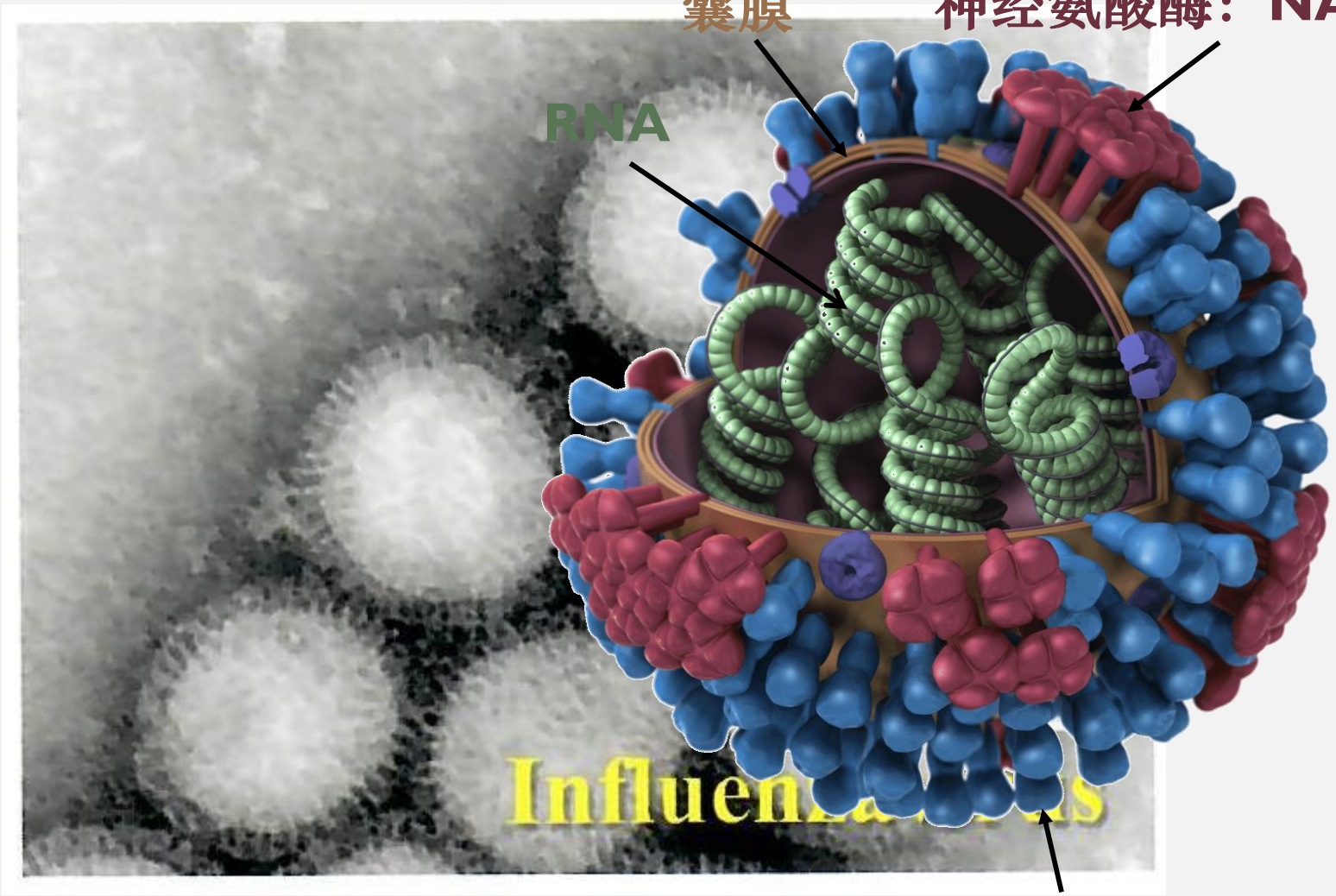


IAV HxNy感染的物种特异性

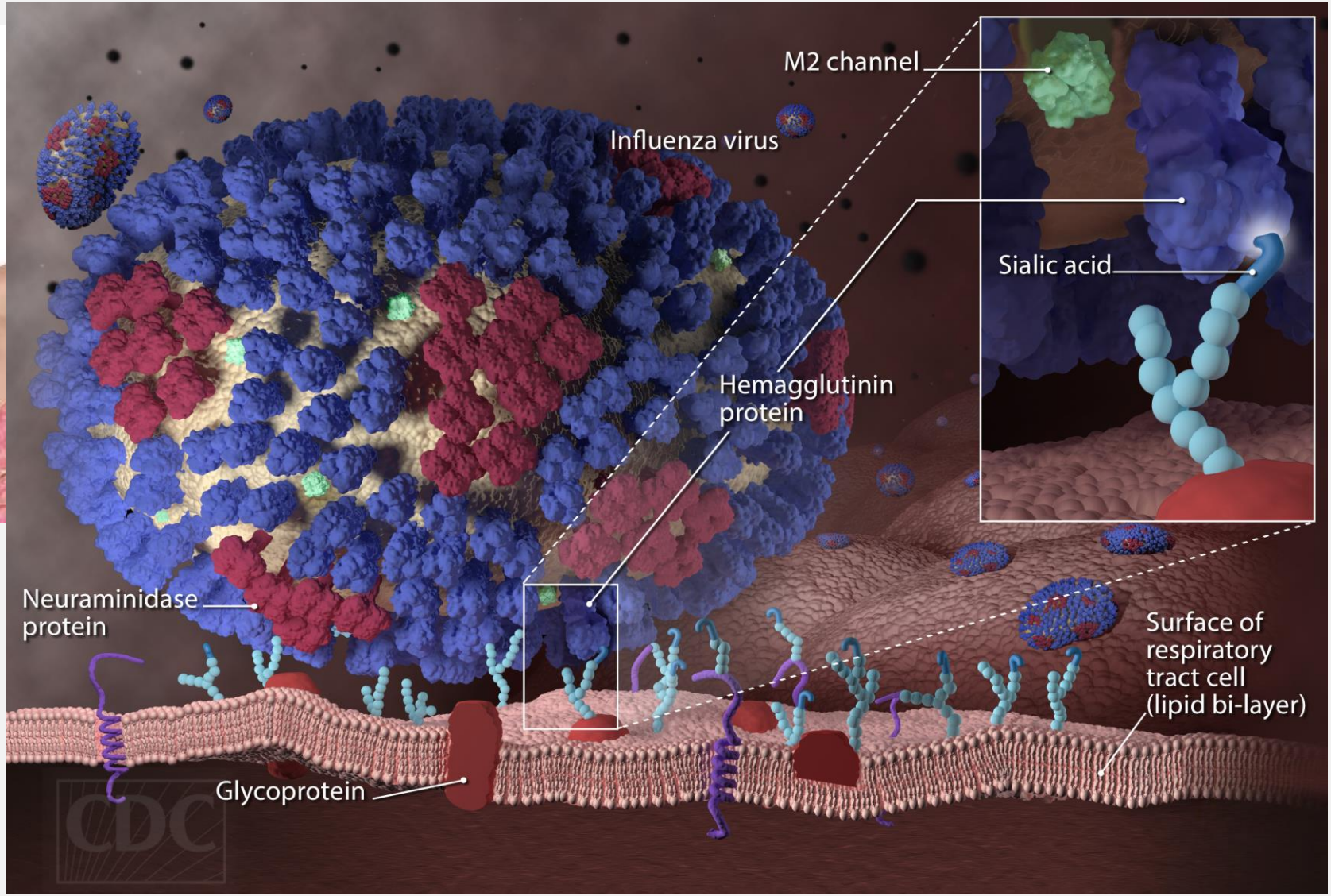
- ✓ HA: 1-16
- ✓ NA:1-9



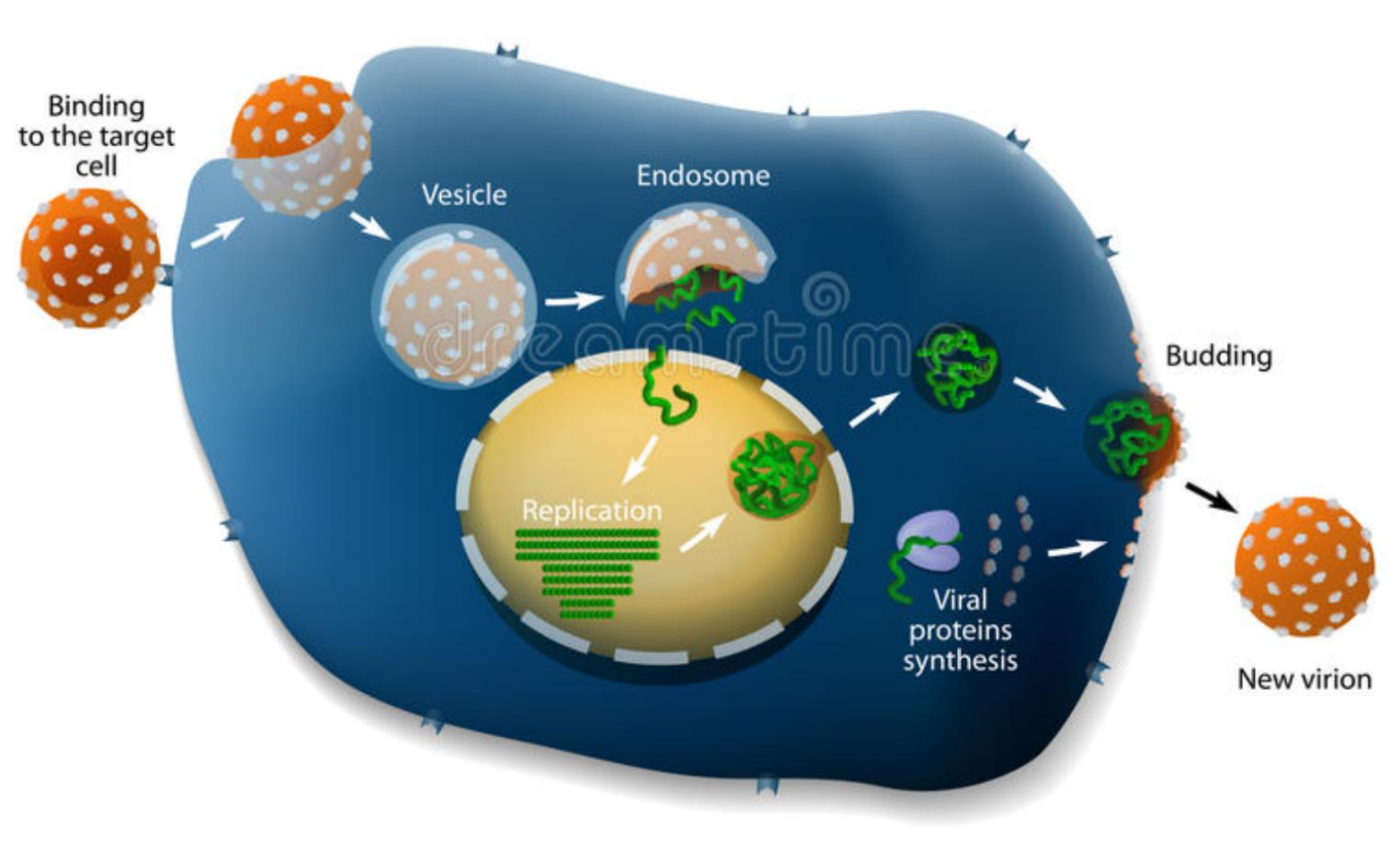
流感病毒的结构



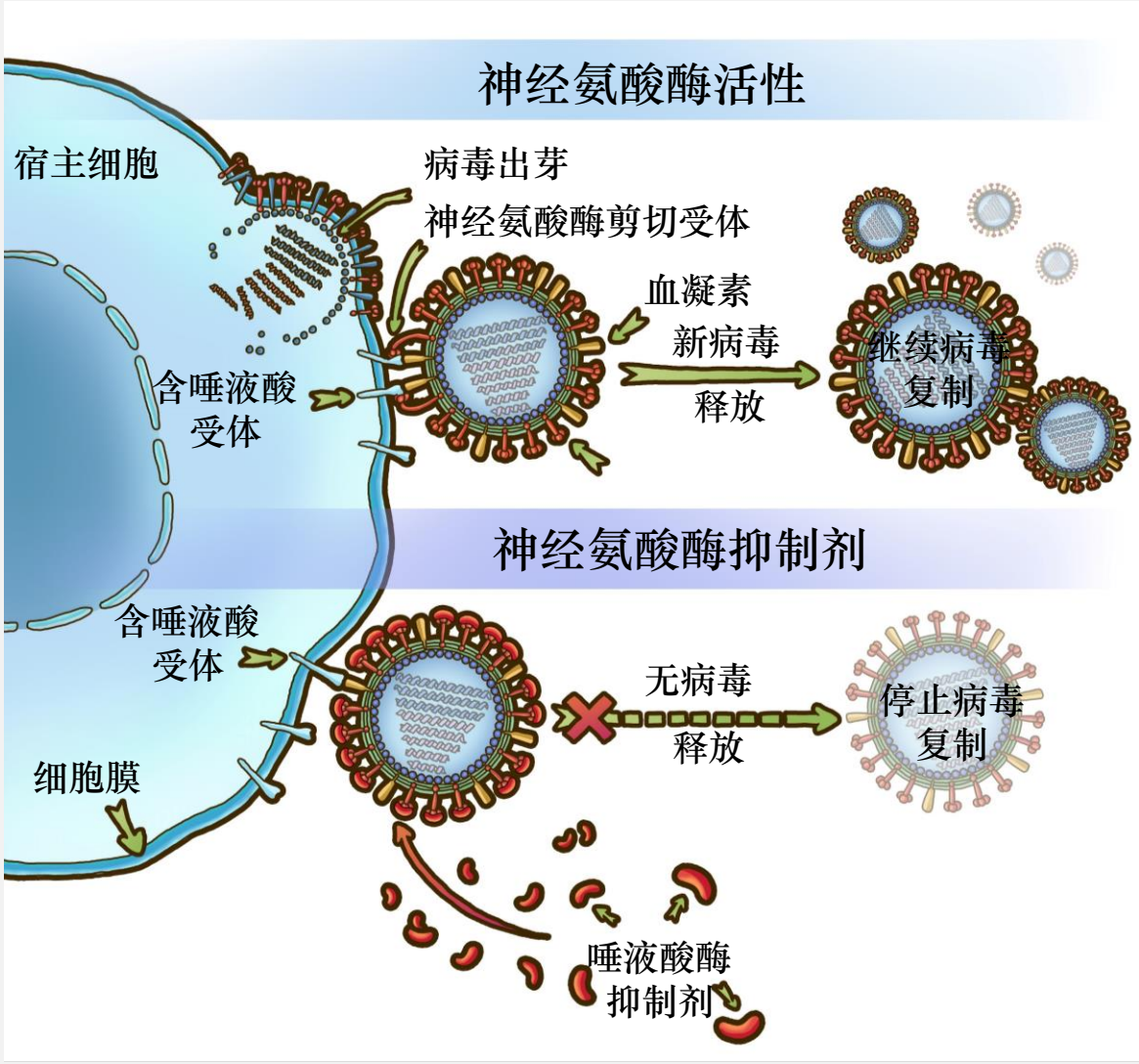
流感病毒的传播——侵入


M2 channel
Influenza virus
Sialic acid
Hemagglutinin protein
Neuraminidase protein
Surface of respiratory tract cell (lipid bi-layer)
Glycoprotein
CDC

流感病毒的传播——复制

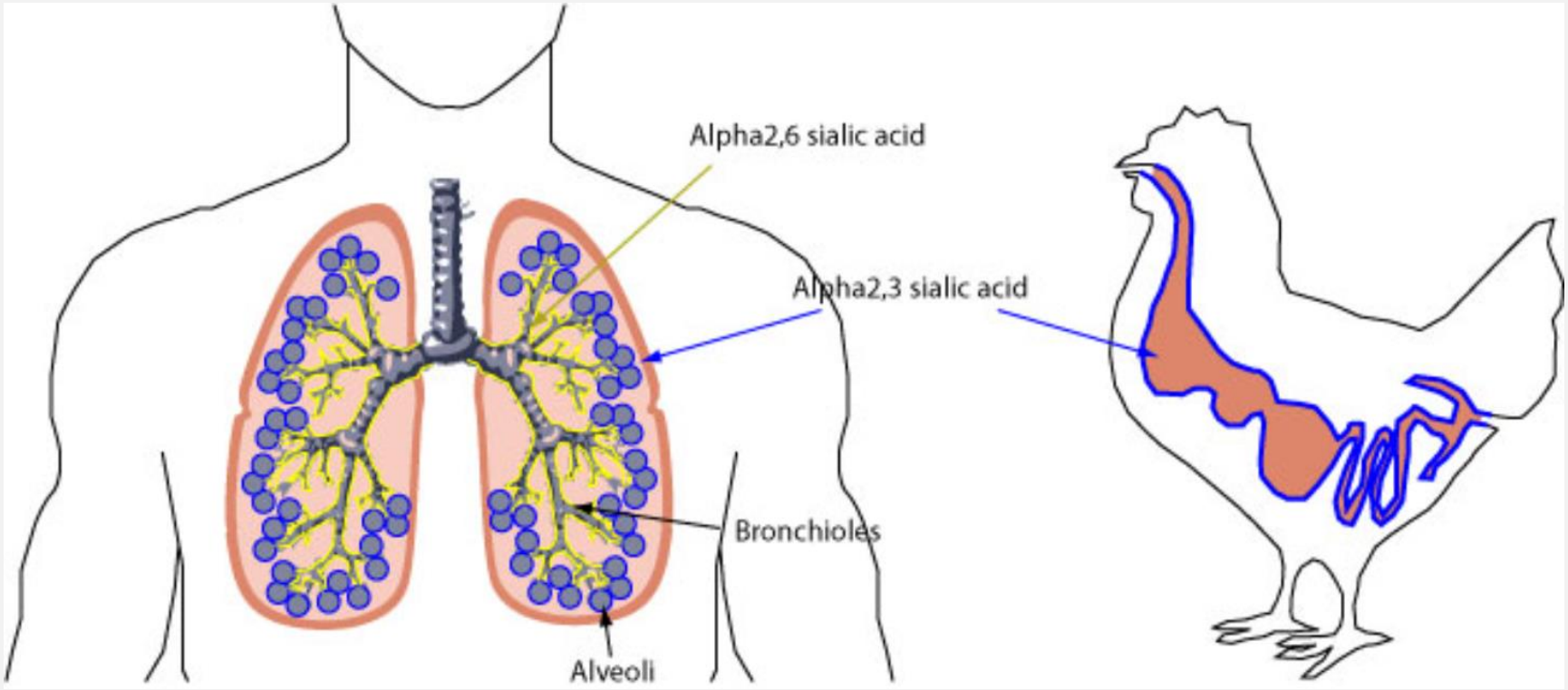

Binding
to the target
cell
Vesicle
Endosome
Replication
Budding
Viral
proteins
synthesis
New virion

流感病毒如何感染人——释放

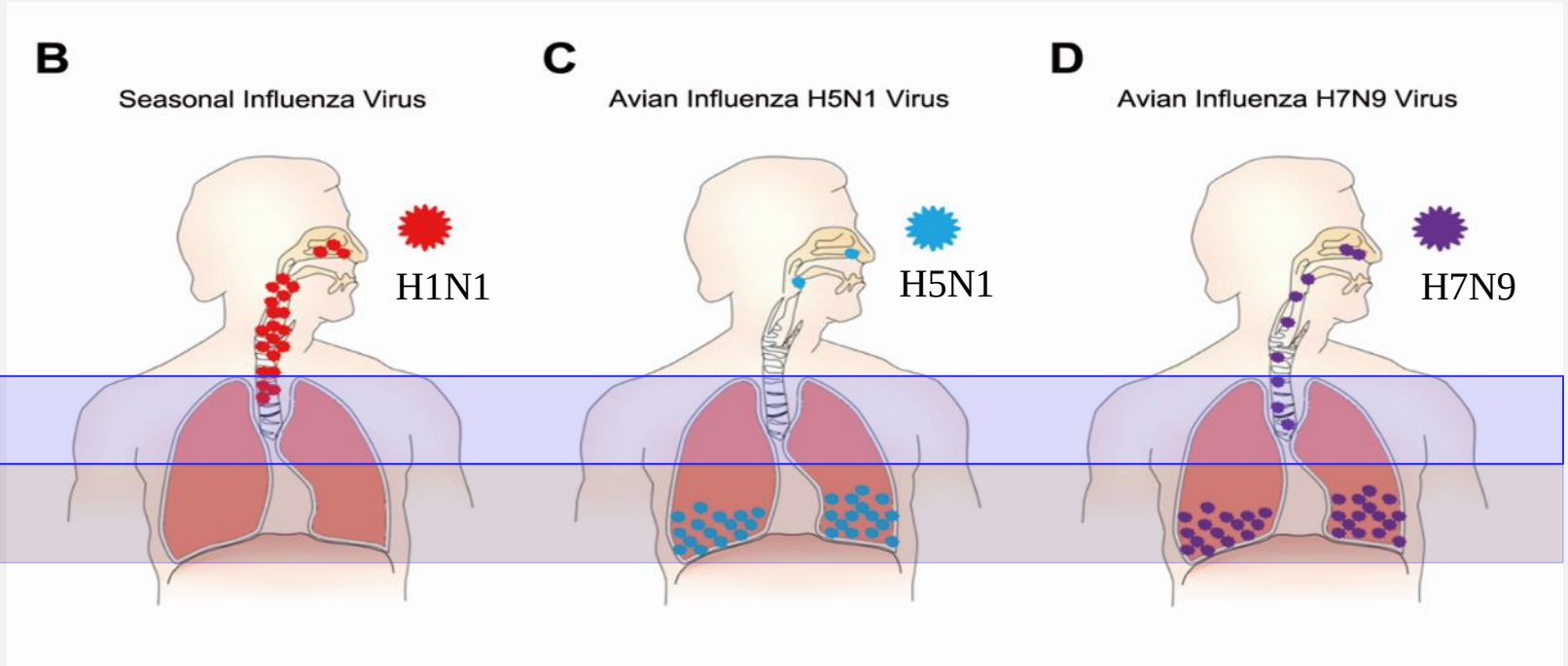


呼吸道受体特点

为什么流感病毒会有物种特异性？宿主、病毒



感染的物种特异性的原因
——病毒的特性



α2,6

H1N1

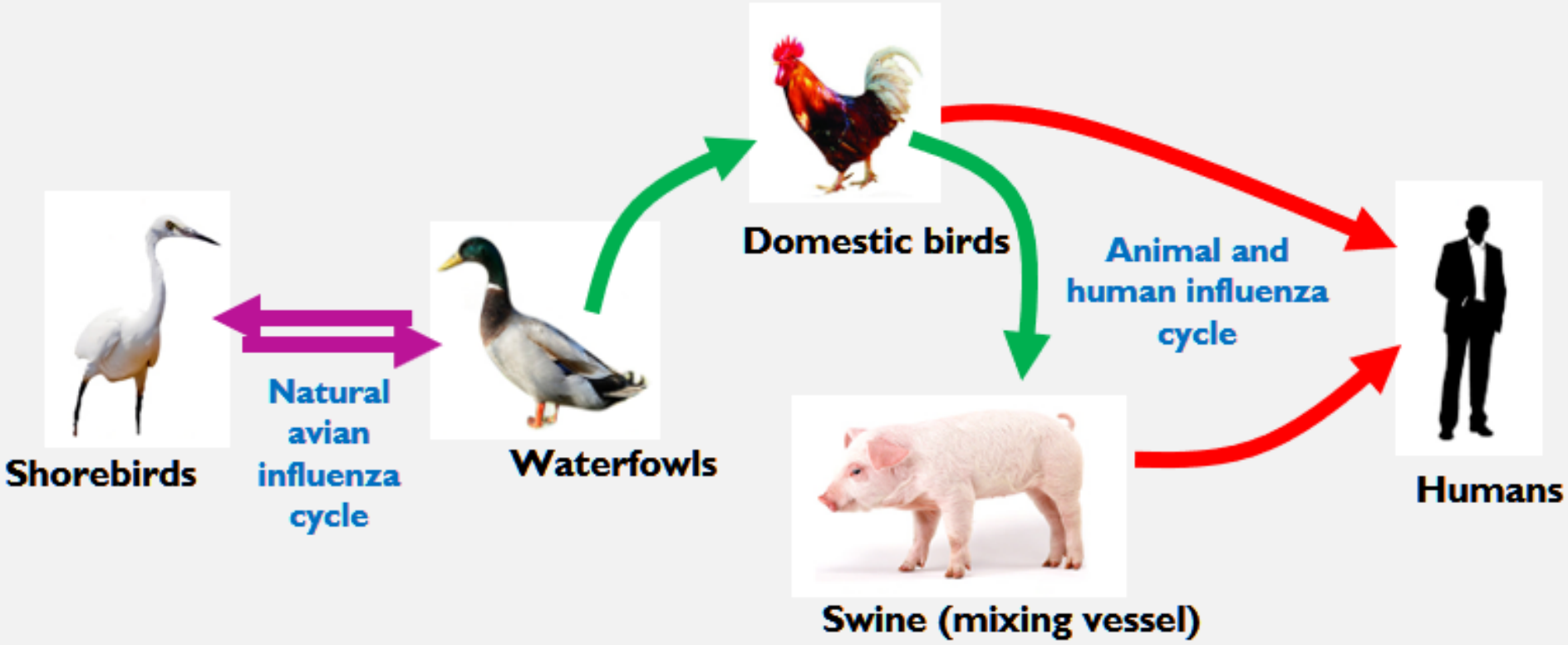
α2,3

H5N1

α2,3 & α2,6

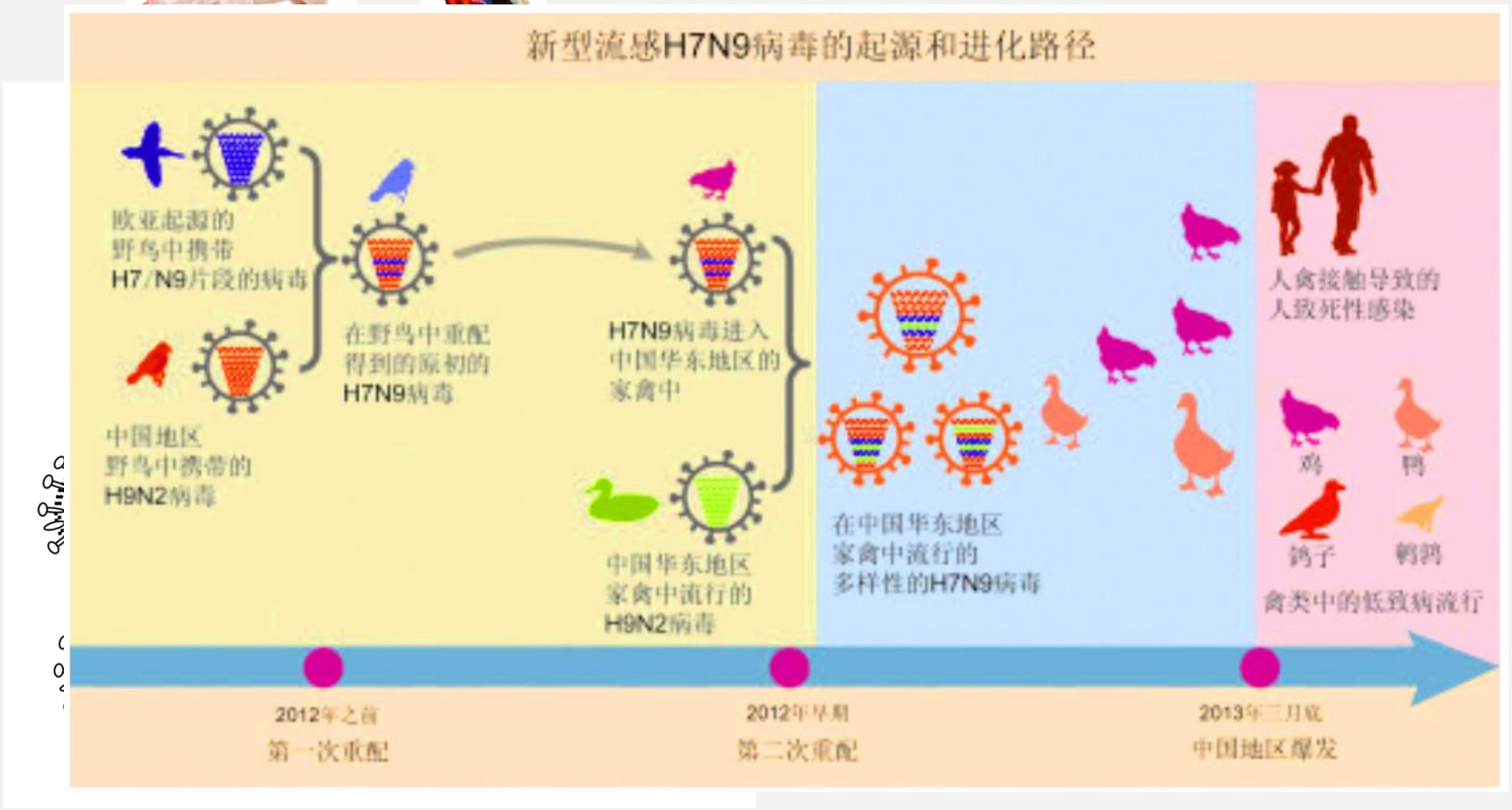
H7N9

自然界中的流感病毒



禽流感病毒天然跨种传播路径

流感病毒的混合器——鸡和猪



传染病流行的三个基本环节

传染源
（散播病原体的人或动物）

要控制！

易感人群
（对某种疾病缺乏免疫力者）

要保护！

控制传染源

卧床休息

接种
禽流感疫苗

扑杀病鸡

切断传播途径

佩戴口罩

开窗通风

保护易感人群

充足的睡眠

勤洗手

锻

戴口罩

流感病毒疫苗存在的问题

基因重排导致的病毒高度多变?

三价流感疫苗：H1N1, H3N2 and BV

四价流感疫苗：H1N1, H3N2 and BV and BY

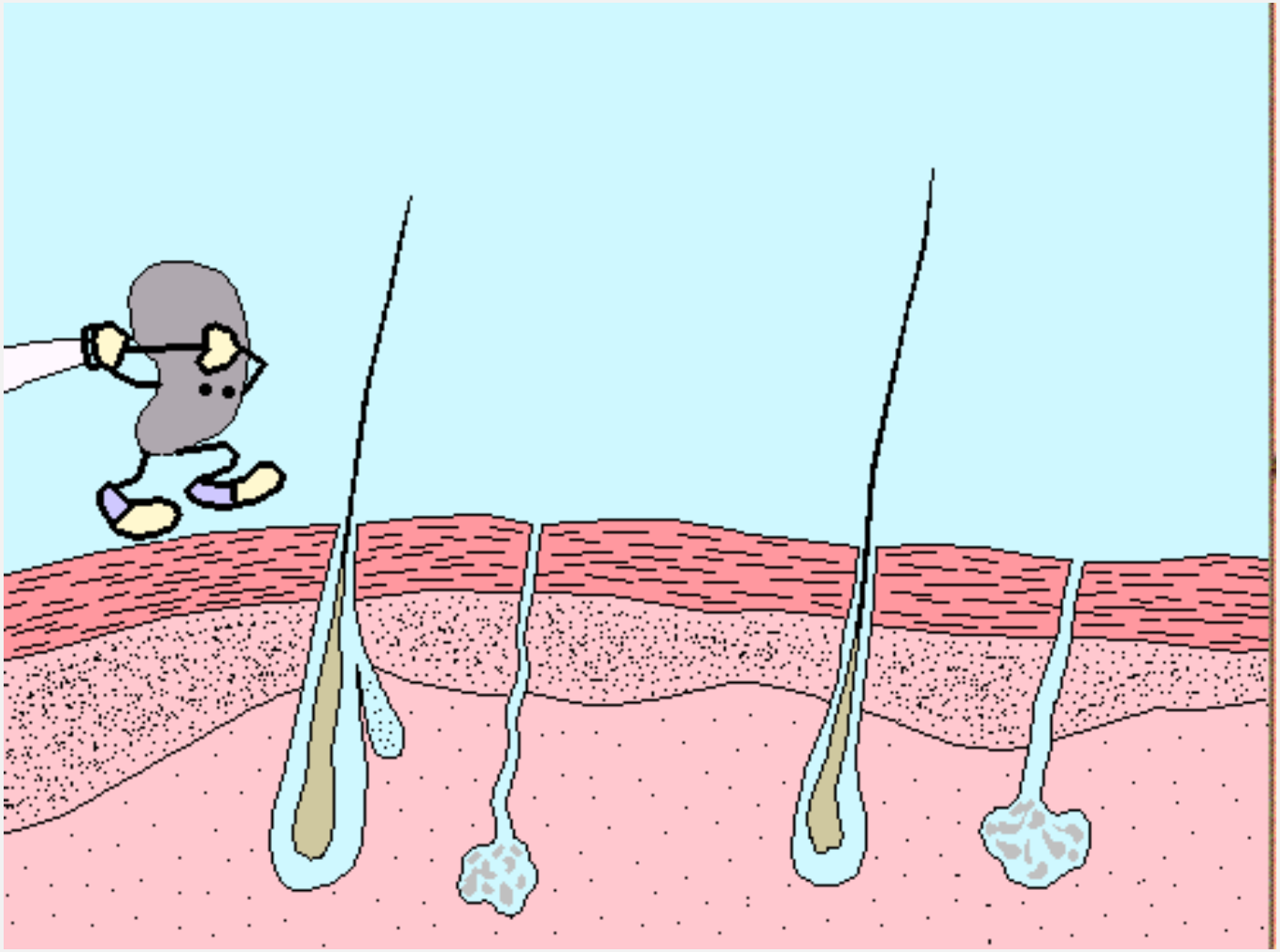
通用流感疫苗

病毒基因组的不稳定性?

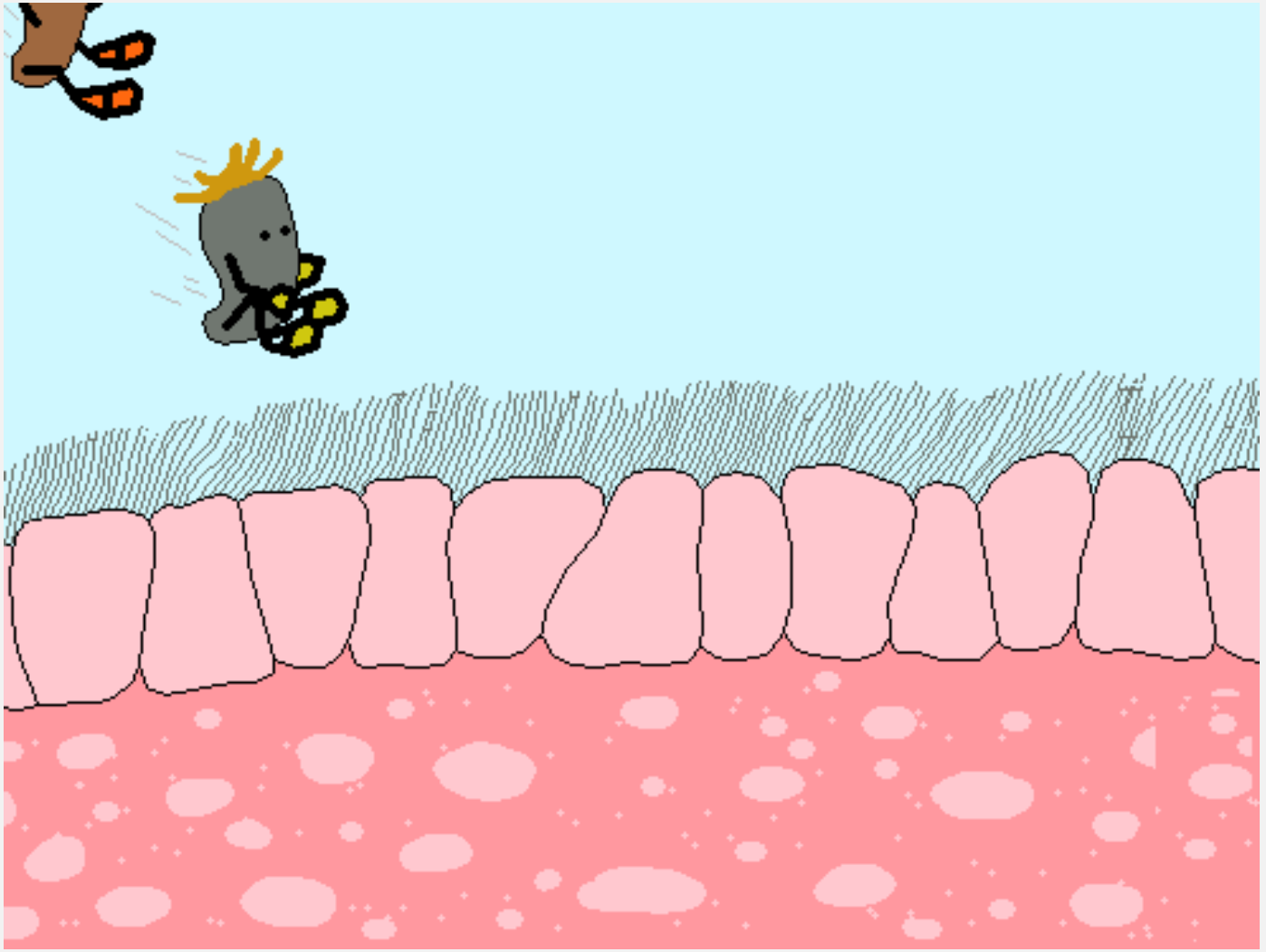
在每一个流感季节注射疫苗

人体的防御系统

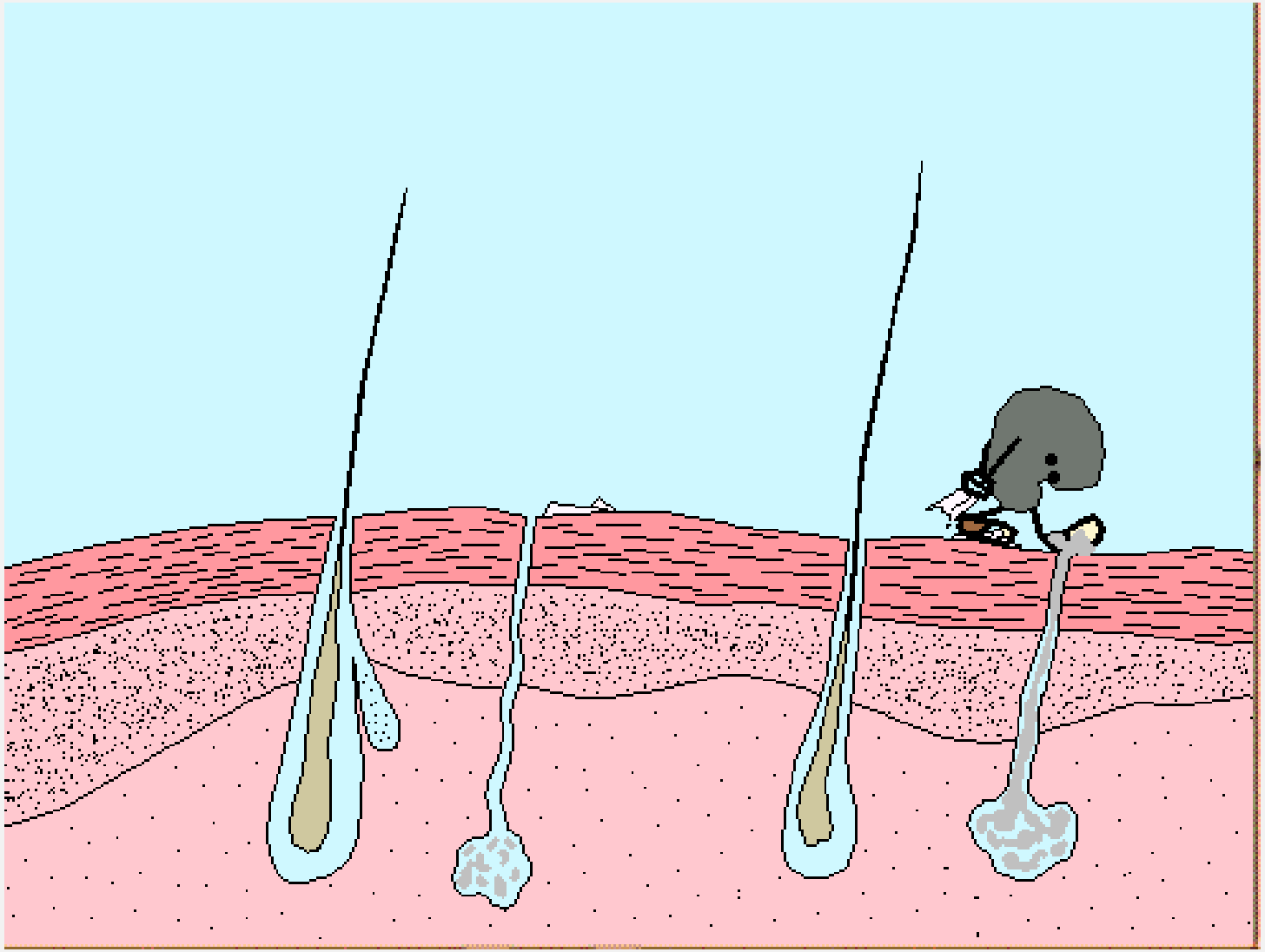
皮肤对病菌的阻挡作用



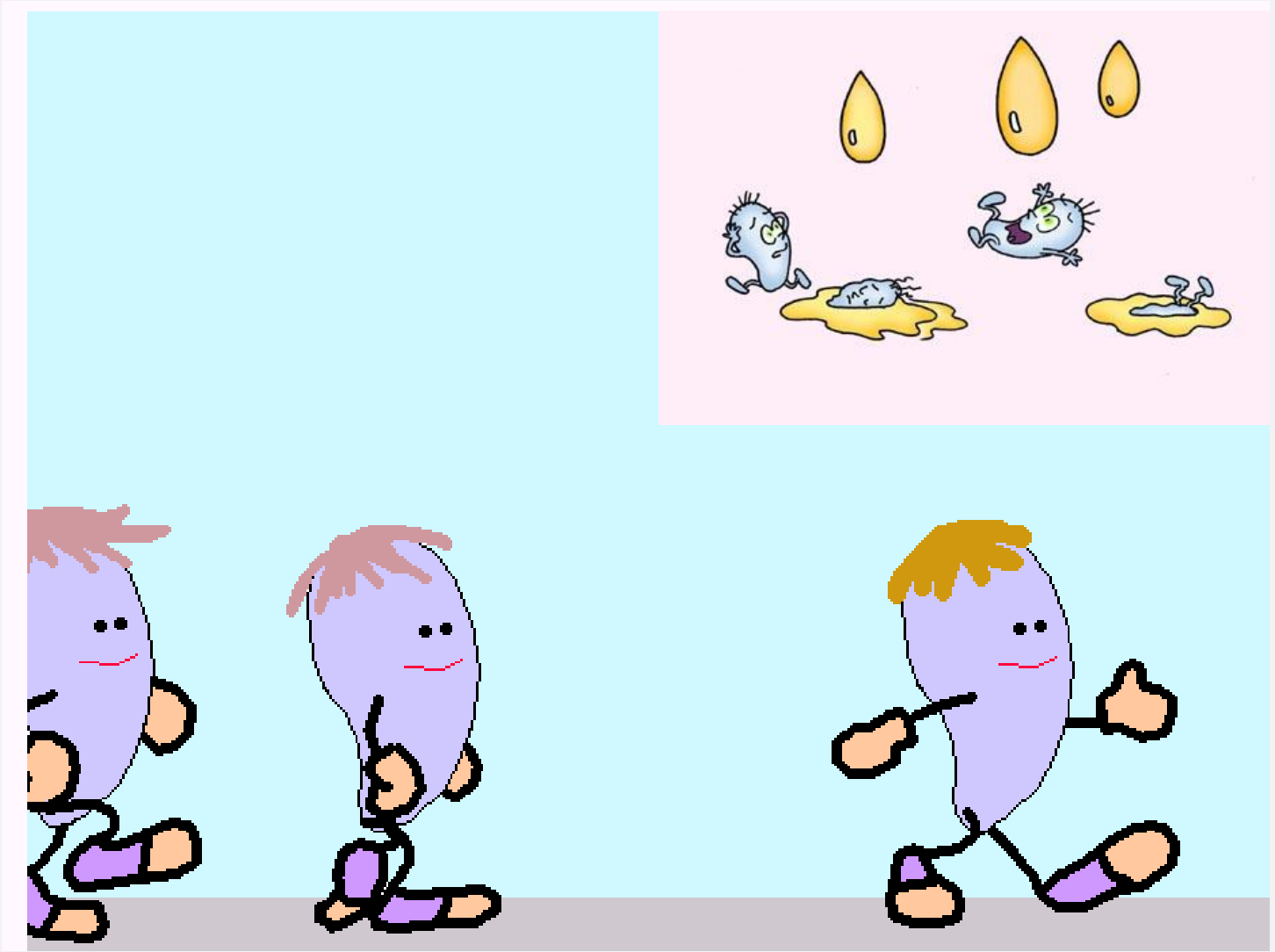
呼吸道黏膜上的纤毛清扫异物



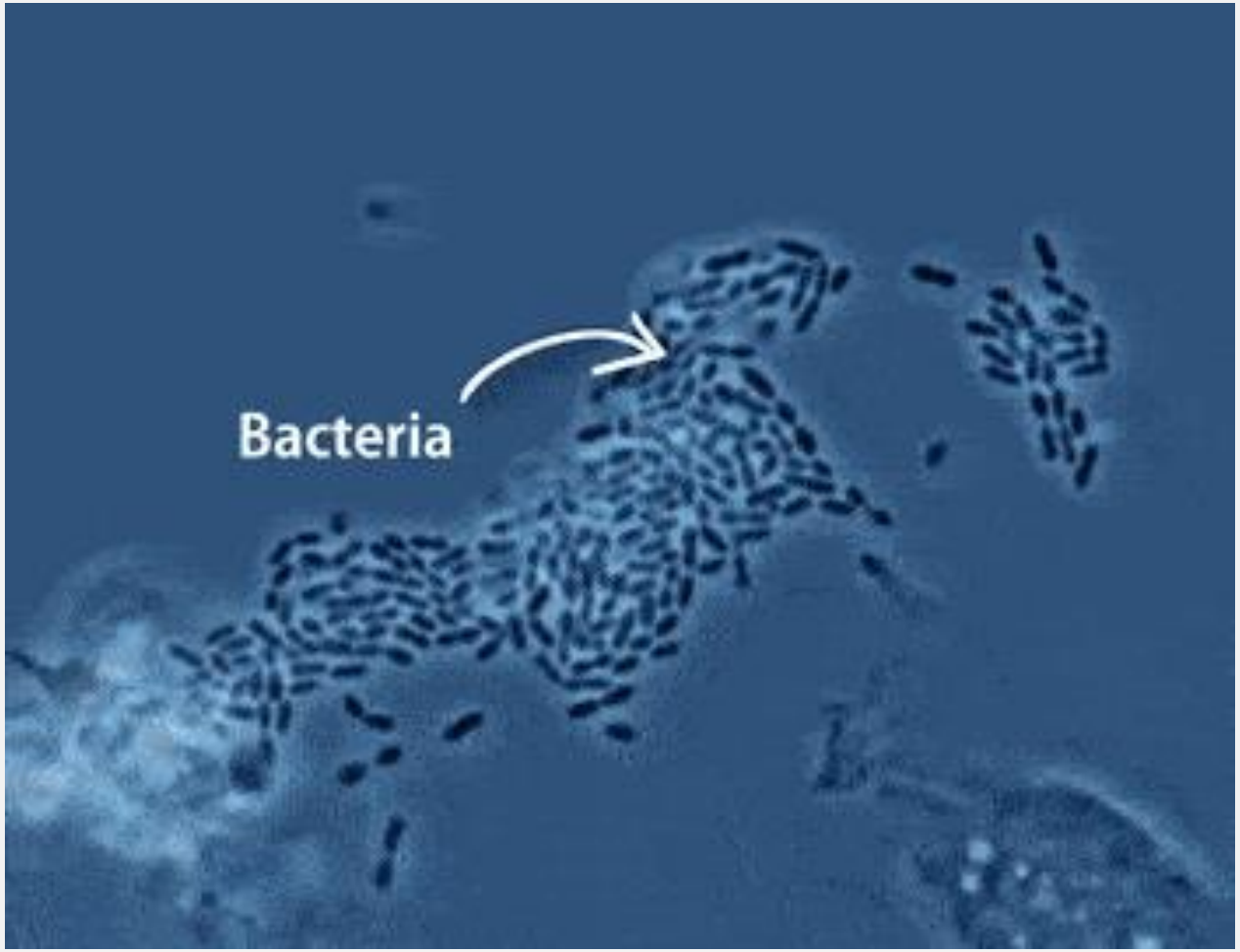
皮肤分泌物的杀菌作用



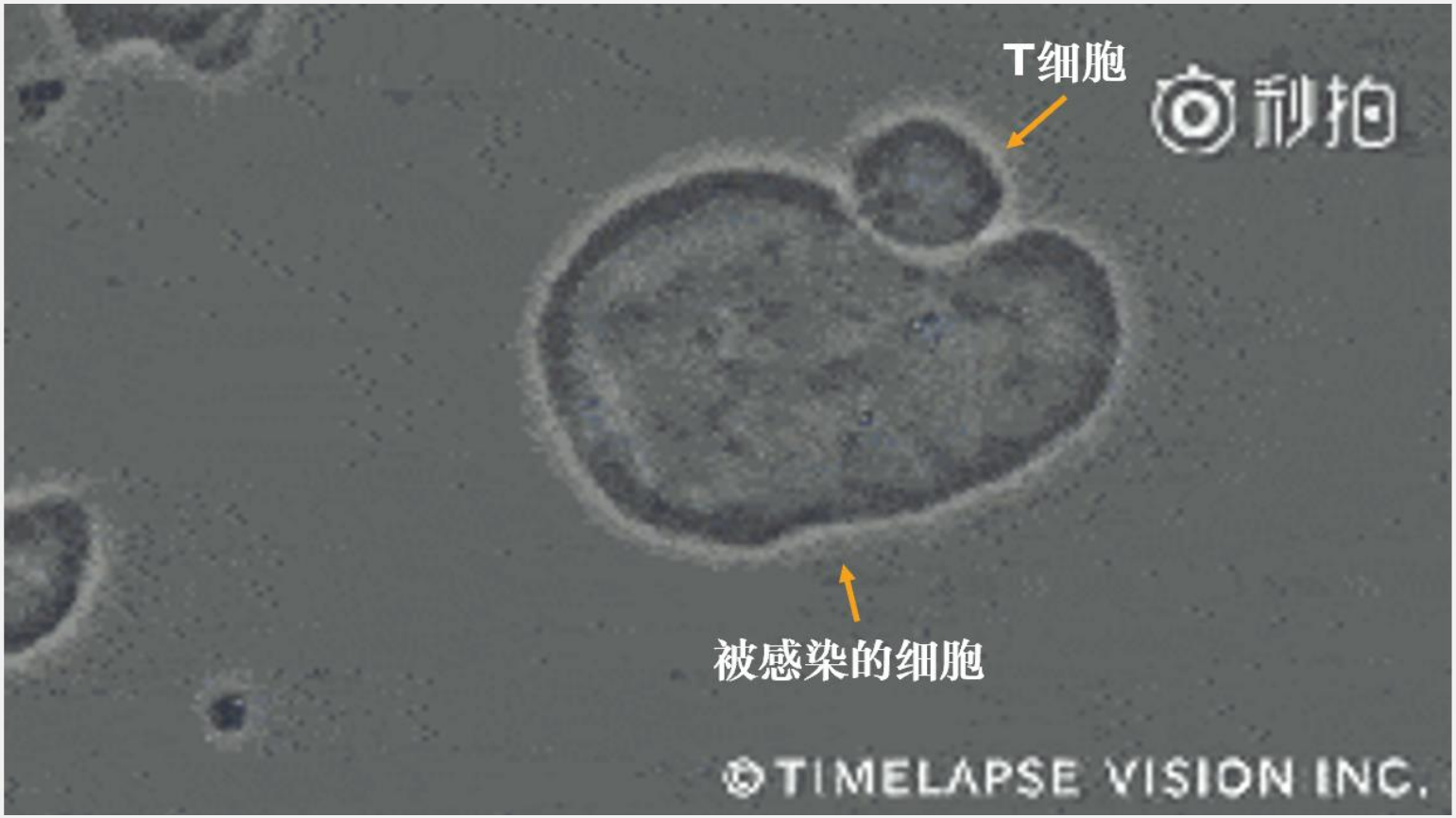
溶菌酶使细菌溶解



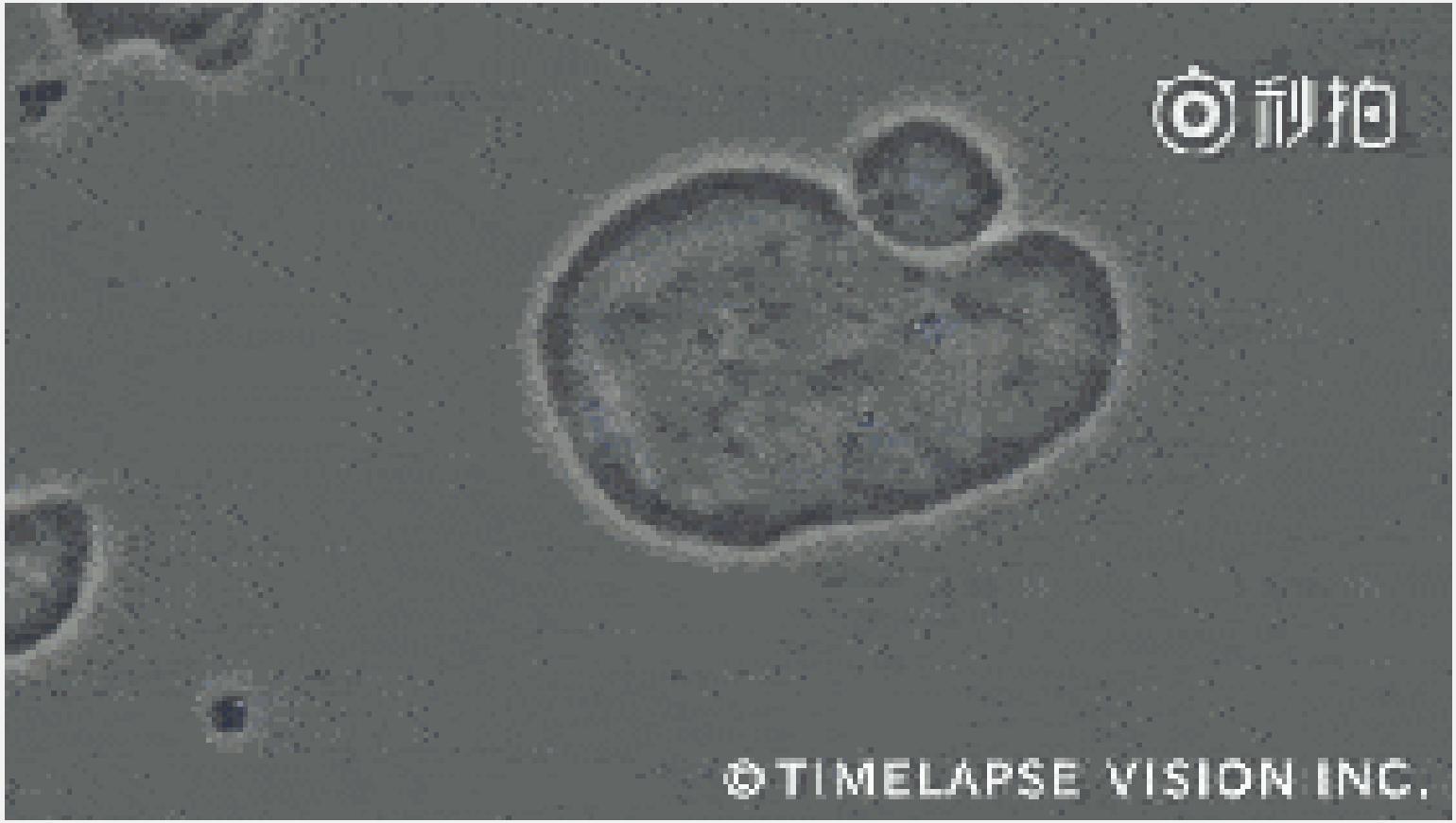
吞噬细胞吞噬病原体



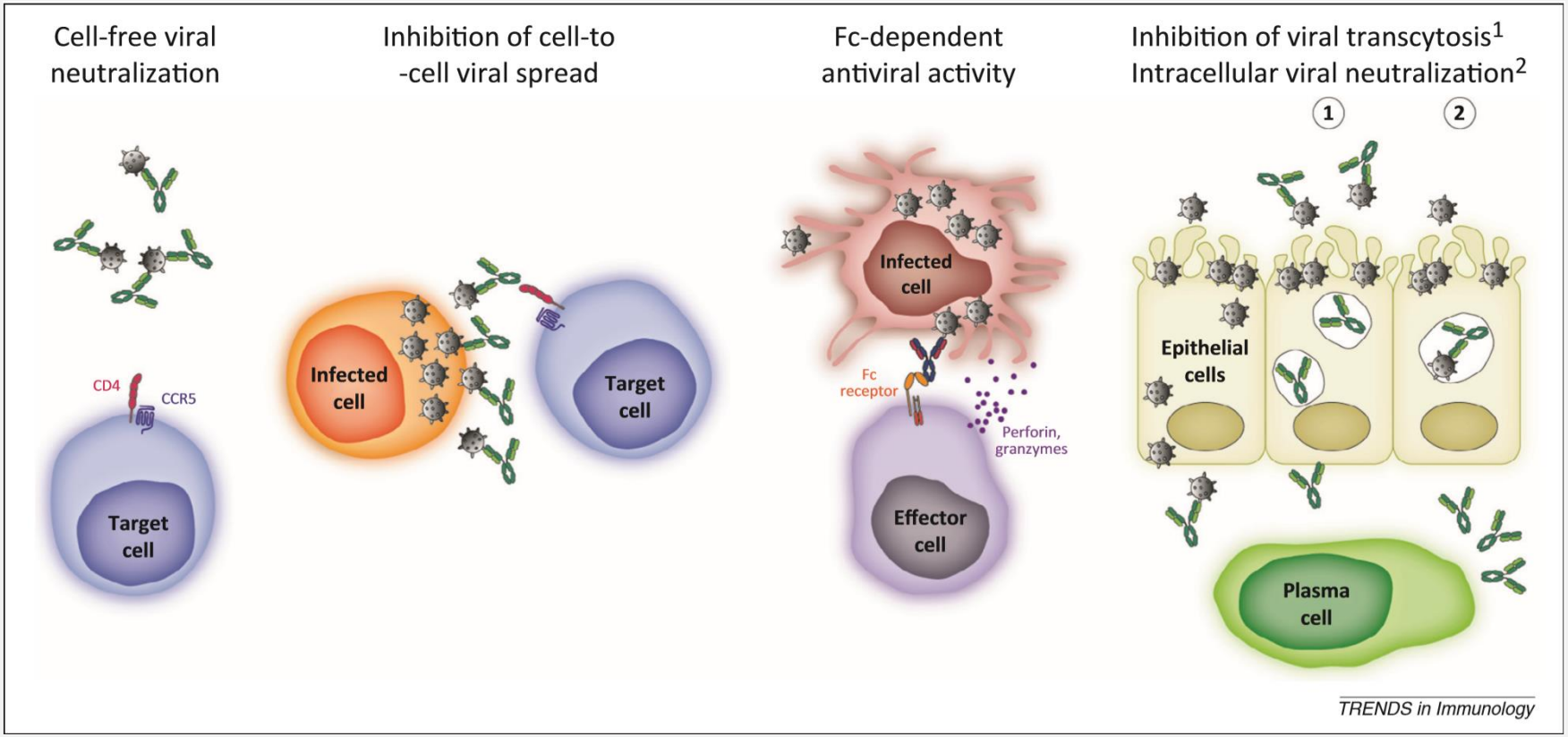
T细胞杀伤被感染的细胞



T细胞杀伤被感染的细胞



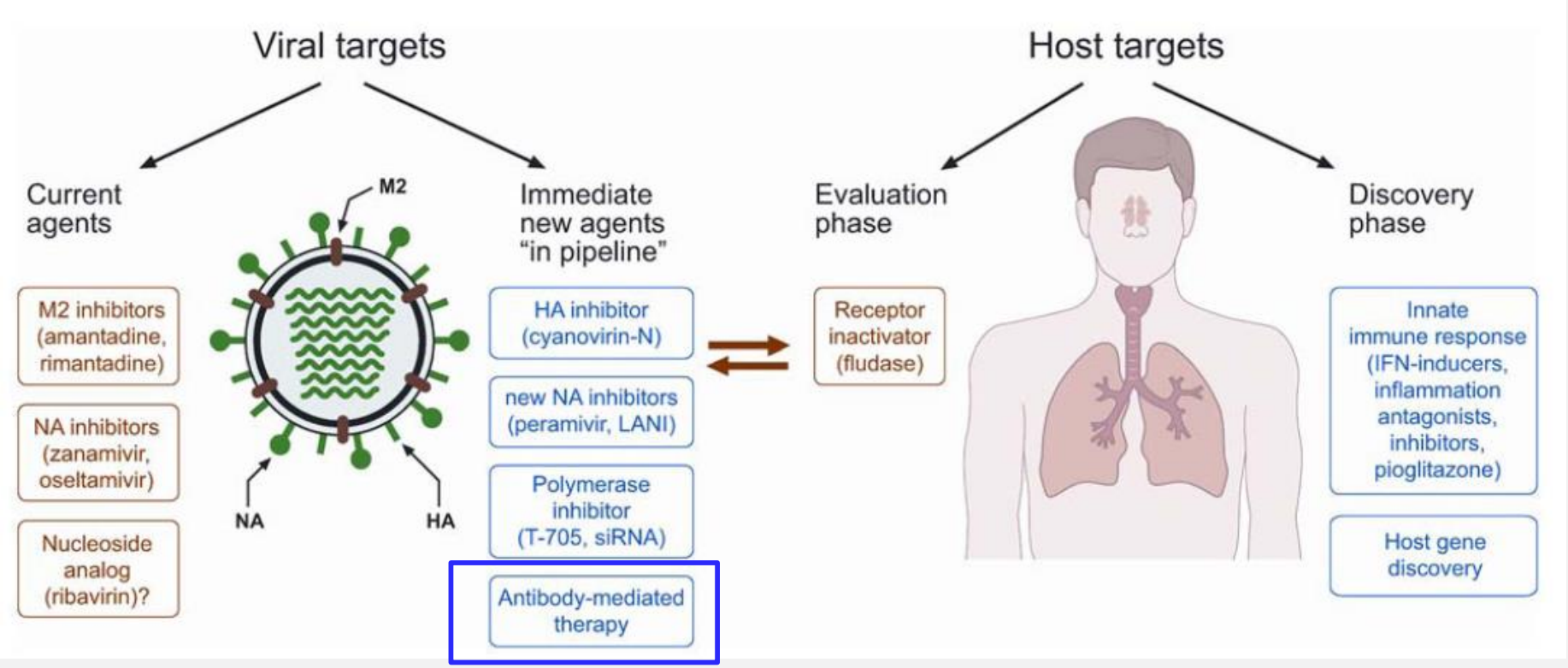
B细胞分泌的抗体



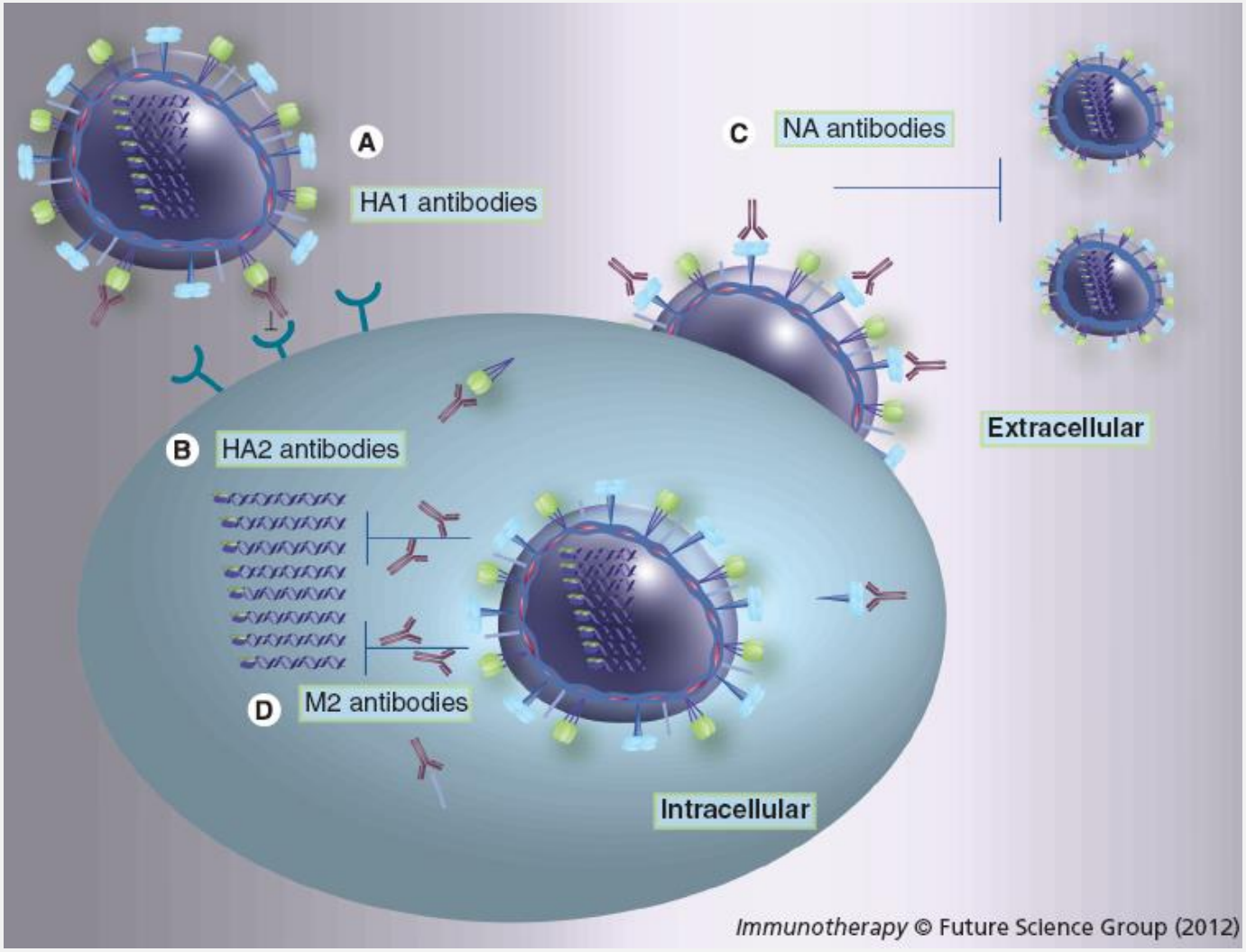
- ✓ 阻断游离的病毒感染
- ✓ 给病毒、被感染的细胞贴上标签

Mouquet, Trends in Immunology, 2014

治疗药物


Viral targets
Host targets
Current agents
Immediate new agents "in pipeline"
Evaluation phase
Discovery phase
M2
NA
HA
M2 inhibitors (amantadine, rimantadine)
NA inhibitors (zanamivir, oseltamivir)
Nucleoside analog (ribavirin)?
HA inhibitor (cyanovirin-N)
new NA inhibitors (peramivir, LANI)
Polymerase inhibitor (T-705, siRNA)
Antibody-mediated therapy
Receptor inactivator (fludase)
Innate immune response (IFN-inducers, inflammation antagonists, inhibitors, pioglitazone)
Host gene discovery

抗体药物


A
HA1 antibodies
C
NA antibodies
Extracellular
B
HA2 antibodies
D
M2 antibodies
Intracellular
Immunotherapy © Future Science Group (2012)

抗体药物——广谱的流感病毒抗体

Influenza	**MHAA4549A (earlier known as 39.29)**, Genentech, Inc.	**MHAA4549A** is a human immunoglobulin G1 (IgG1) mAb that binds to a highly conserved epitope on the stalk of Group 1 and Group 2 influenza A hemagglutinins and blocks the hemagglutinin-mediated membrane fusion in the endosome, neutralizing all known human influenza A strains. MHAA4549A was cloned from a single human plasmablast cell isolated from an influenza vaccinated donor MHAA4549A is in Phase 2 clinical trials (NCT02623322)	62
	VIS410, Visterra, Inc.	**VIS410** targets a conserved epitope in the stem of influenza A hemagglutinin (HA). It was engineered using structural information on antibody–antigen interfaces. VIS410 is in Phase 2 clinical trials (NCT02989194)	151
	CR6261, Crucell Holland BV and the National Institute of Allergy and Infectious Diseases (NIAID)	Isolated from a healthy, vaccinated individual using phage display selection on recombinant H5 HA, mAb **CR6261** targets a highly conserved helical region in the membrane-proximal stem of HA1/HA2 from 1918 H1N1 influenza and H5N1 influenza. It uses the Ig VH1–69 germline segment. CR6261 is in Phase 2 clinical trials (NCT02371668)	70
	CR8020, Crucell Holland BV and Retroscreen Virology Ltd.	**CR8020** is a broadly neutralizing influenza hemagglutinin stem-specific human mAb. CR8020 was isolated from a B cell of a donor vaccinated against influenza. A Phase 2 clinical trial was completed for CR8020 (NCT01938352)	74
	TCN-032, Theraclone Sciences	One of a panel of mAbs derived from memory B cells of healthy human subjects, **TCN-032** targets an epitope in the ectodomain of the influenza matrix 2 protein M2e. This epitope, first identified with the isolation of the panel of mAbs including **TCN-032**, is highly conserved in influenza A viruses. A Phase 2 clinical study was initiated for TCN-032 (NCT01719874)	76

Georgina et al., Vaccines, 2017

广谱抗体——我们的贡献

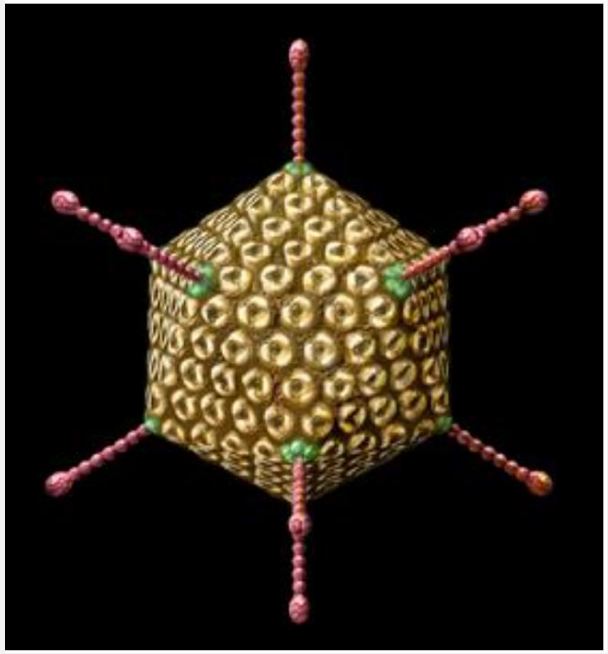
筛选的抗体与不同HA的结合情况
（微量中和IC_{50} (μg/mL)，-, 无中和活性; ND, 未检测）

	19	5	84λ	15	17	33	90λ
Group 1							
H1N1 (A/California/04/09)	1.907	17.93	—	—	—	—	—
H5N1 H5N1(/Anhui/1/2005)	2.126	—	—	—	—	—	—
H9N2 H9N2(A/duck/Nanjing/1/97)	1.658	—	—	—	—	—	—
Group 2							
H3N2 (A/Jiangxi/262/2005)	ND	ND	3.467	8.516	3.341	2.926	2.651
H3N2 (A/Switzerland/9715293/2013)	0.311	—	1.126	2.192	2.823	0.6423	0.8884
H7N9 (A/Anhui/1/2013)	3.513	2.793	4.592	—	—	—	—

Try to be the next !

腺病毒

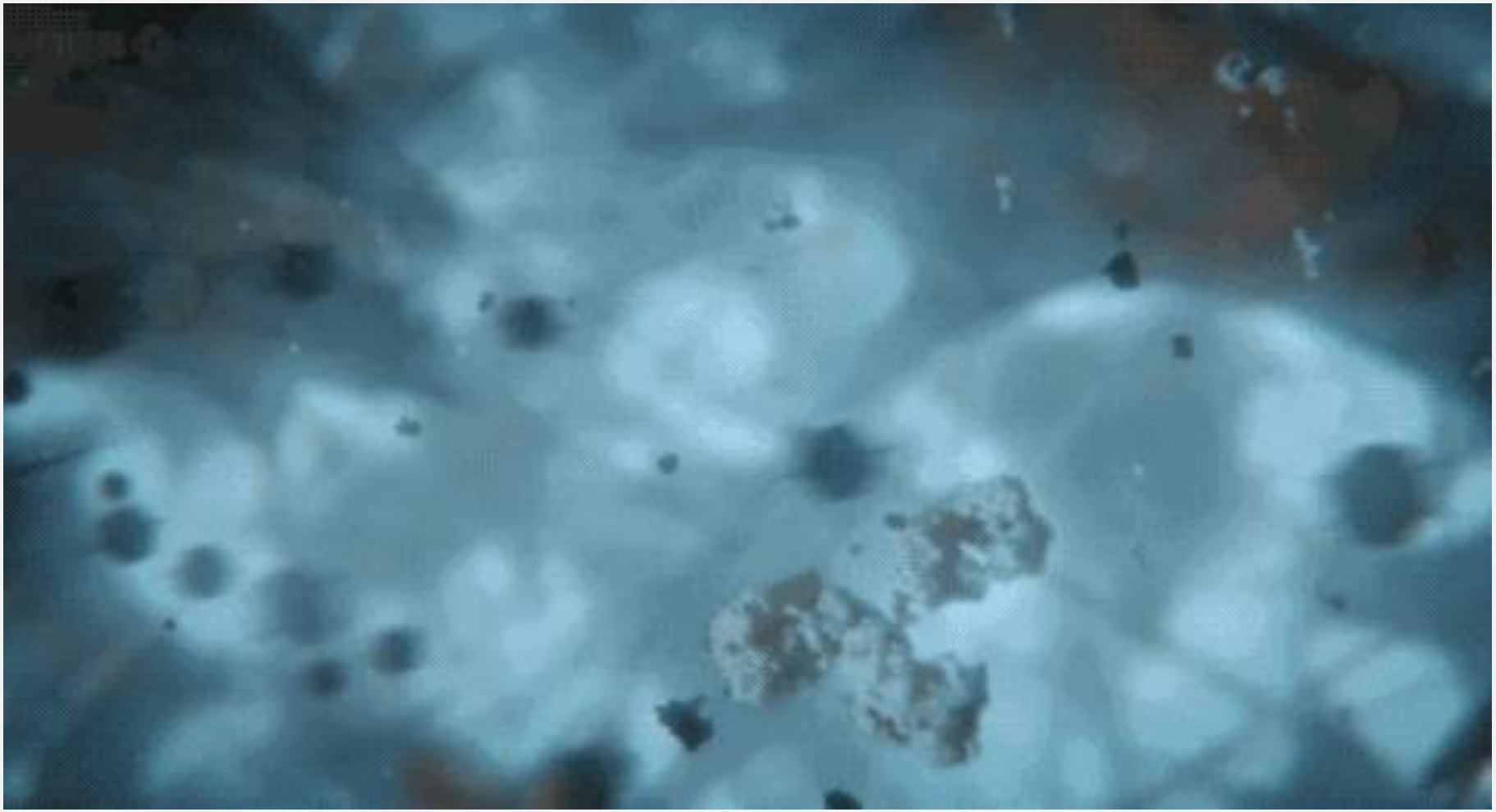
- ✓ 没有囊膜
- ✓ 病毒粒子直径70~90 nm
- ✓ 由240个六聚体和12个五聚体组成，其中五聚体位于顶角处，从每个顶角壳粒的基底伸出一根纤毛突起
- ✓ 现状双链DNA分子



战争总是在不经意间开始

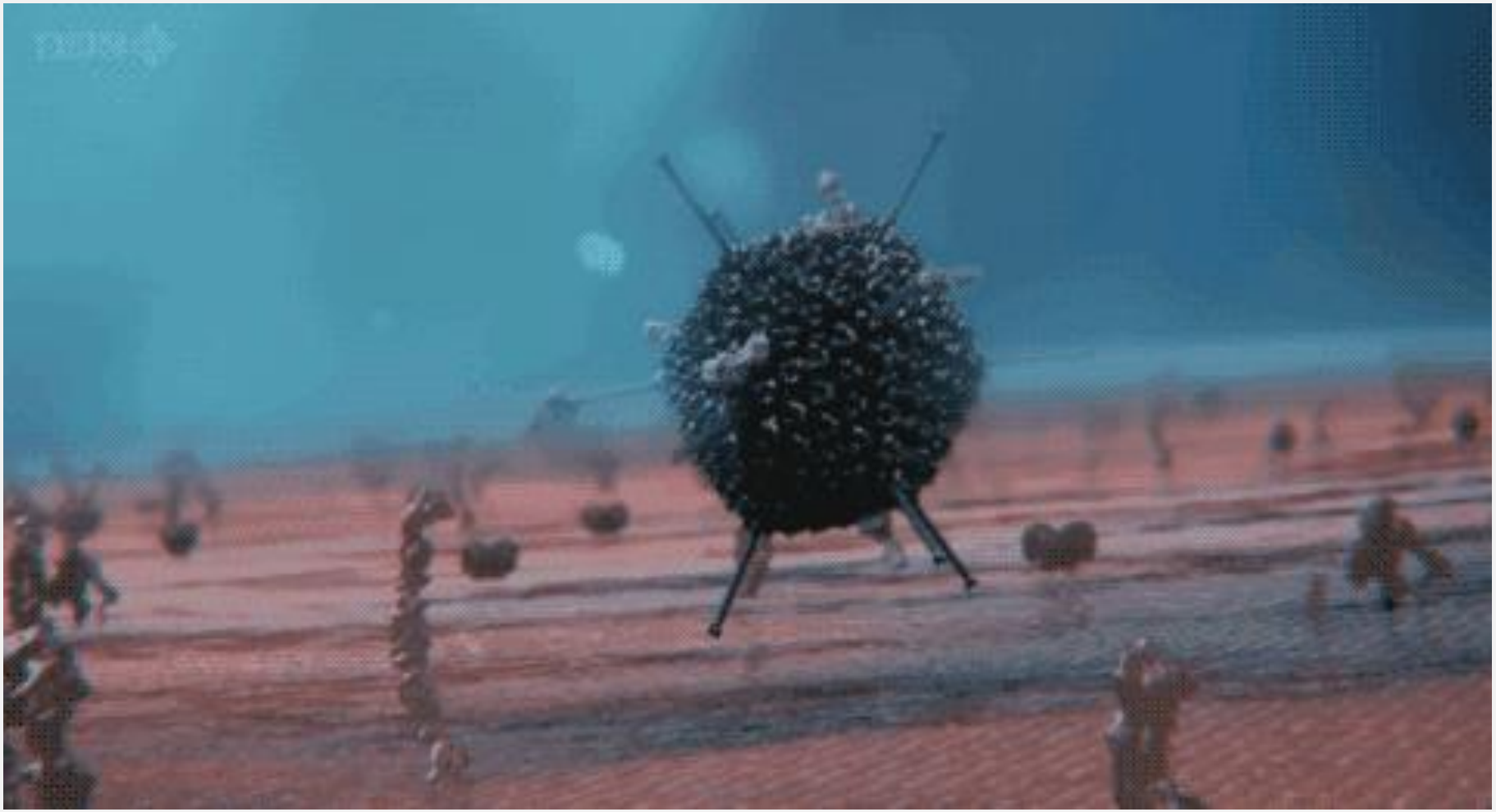
常在河边走，哪有不湿鞋的

病毒敢死队的目标是细胞核，人体也不是吃素的

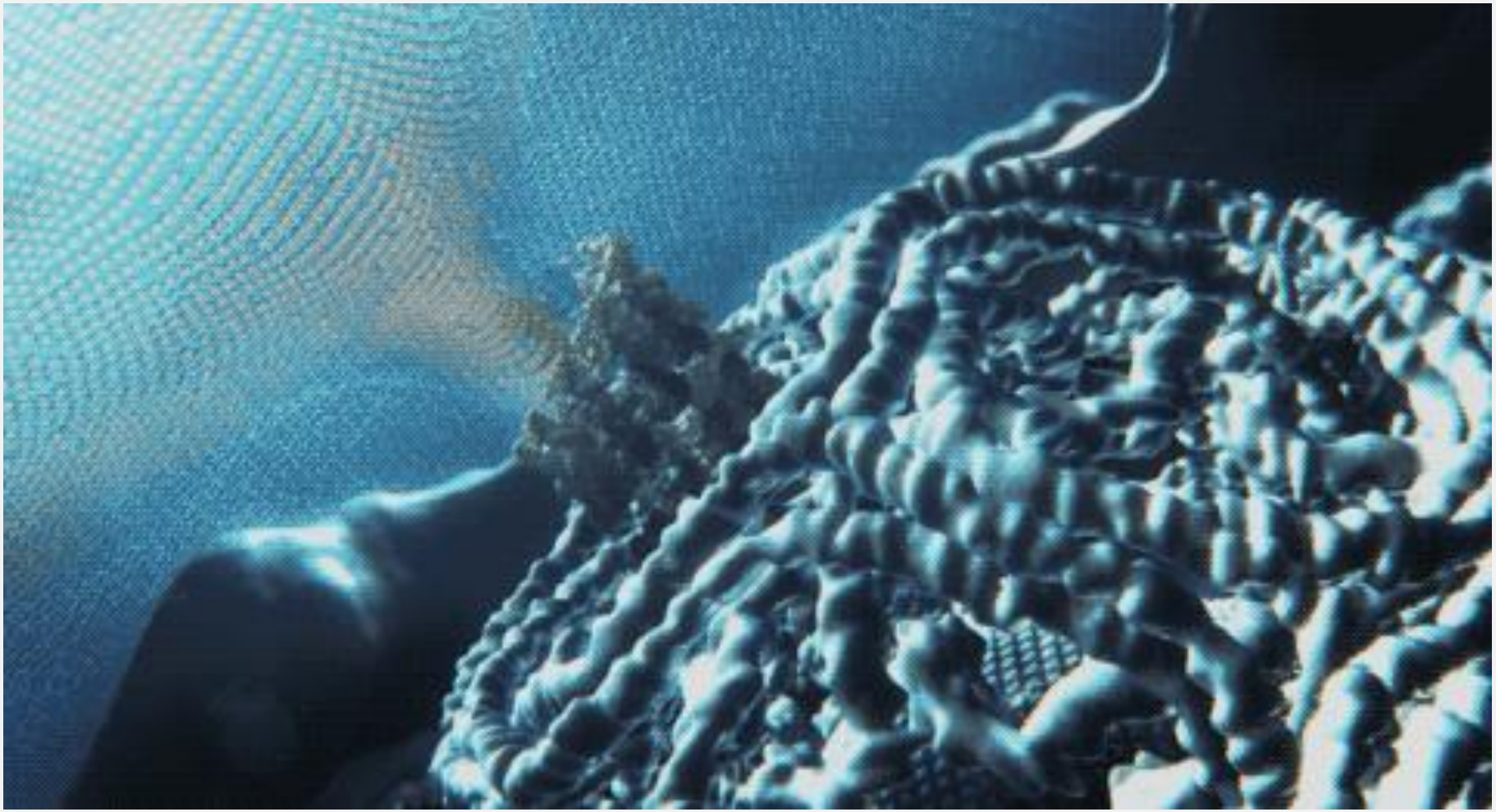


抗体和白细胞联手组成了人体免疫系统的第一道防线

进入细胞的通行证——受体，必杀技之一



武功再高也怕菜刀，技术再强也怕群殴



内吞体——一部分病毒在此粉身碎骨

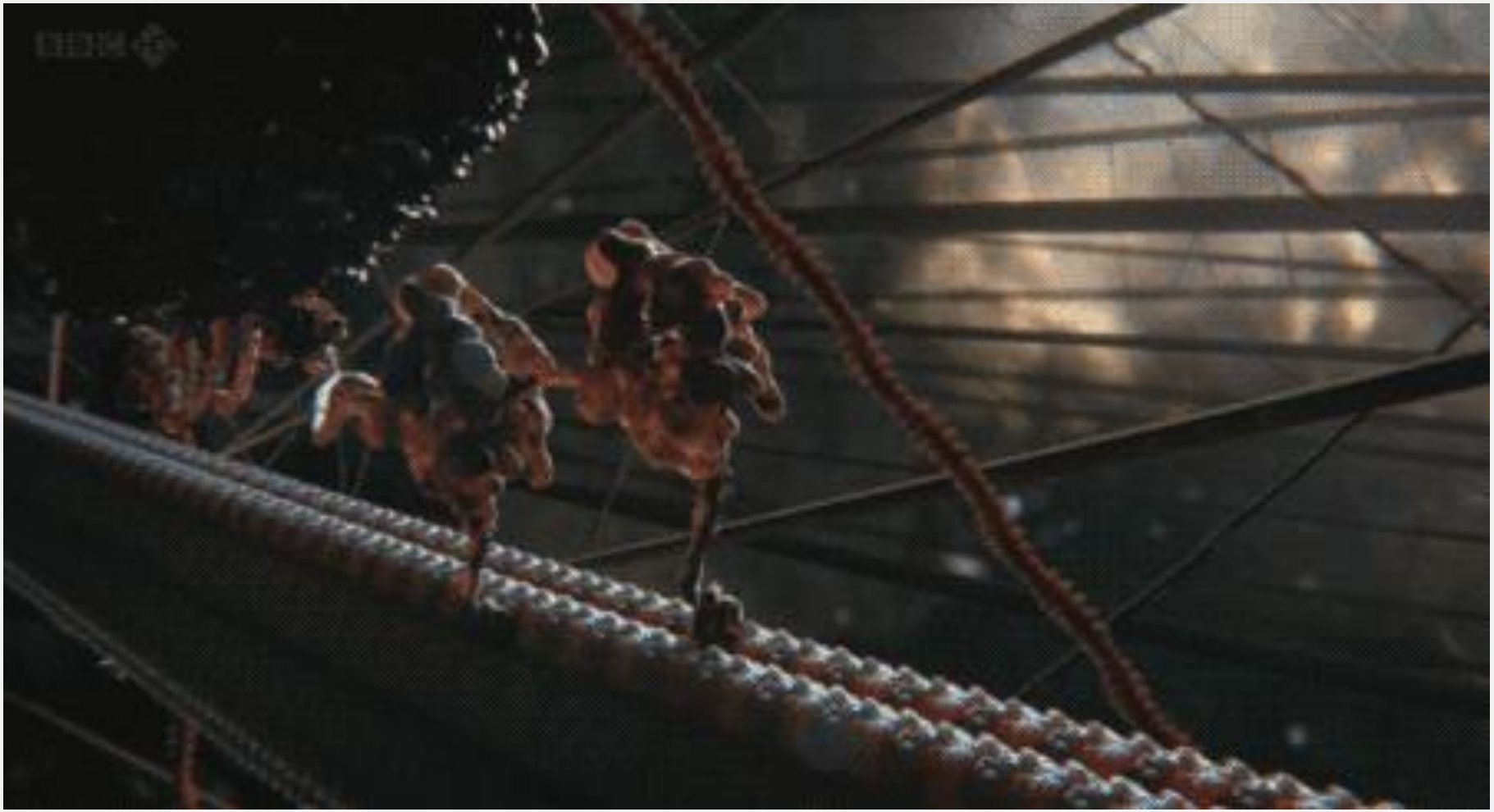
病毒的必杀技之二

病毒充满套路

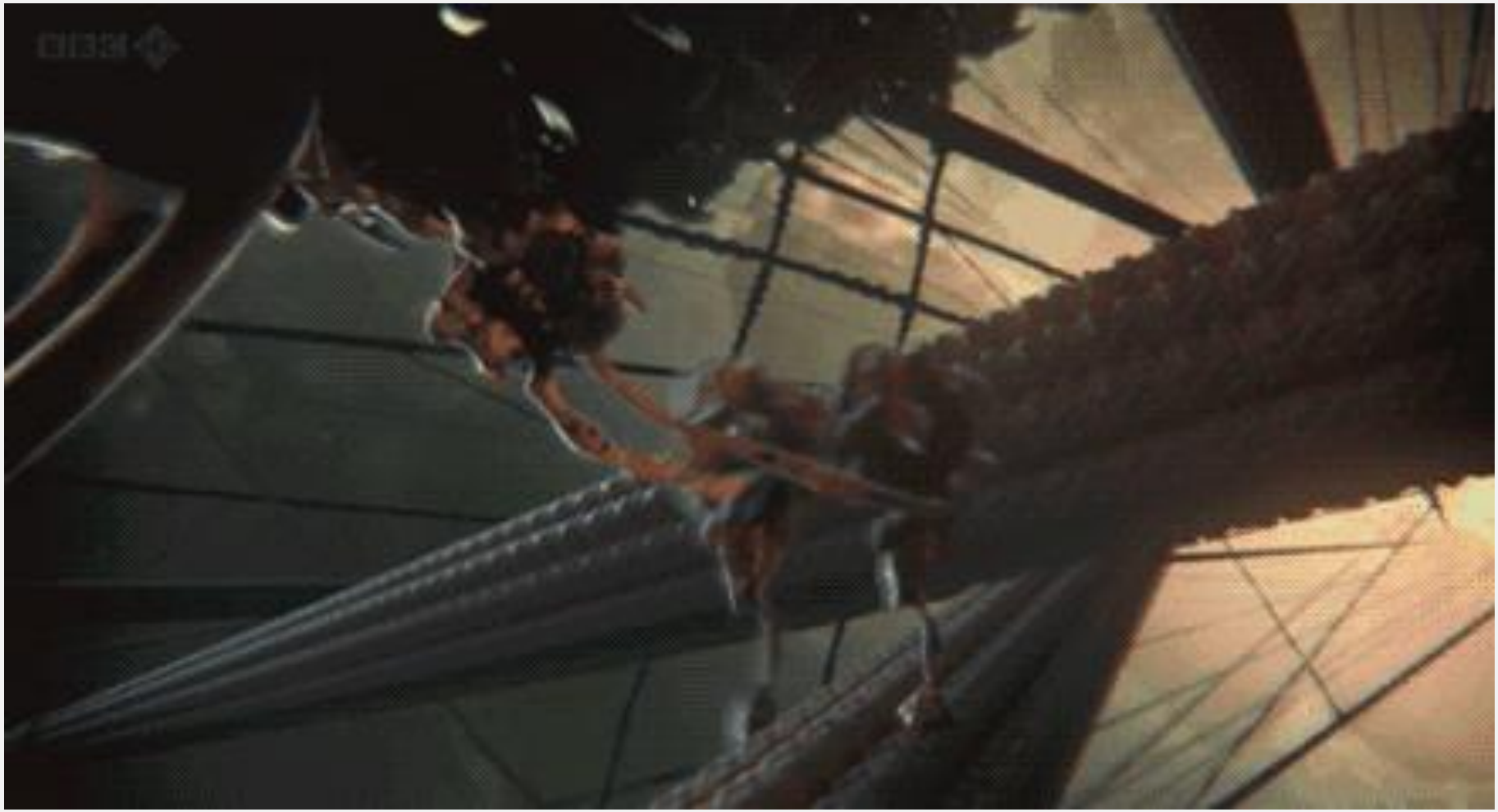
一部分病毒重获自由，吸附马达蛋白

“绑架”马达蛋白，向目的地进发

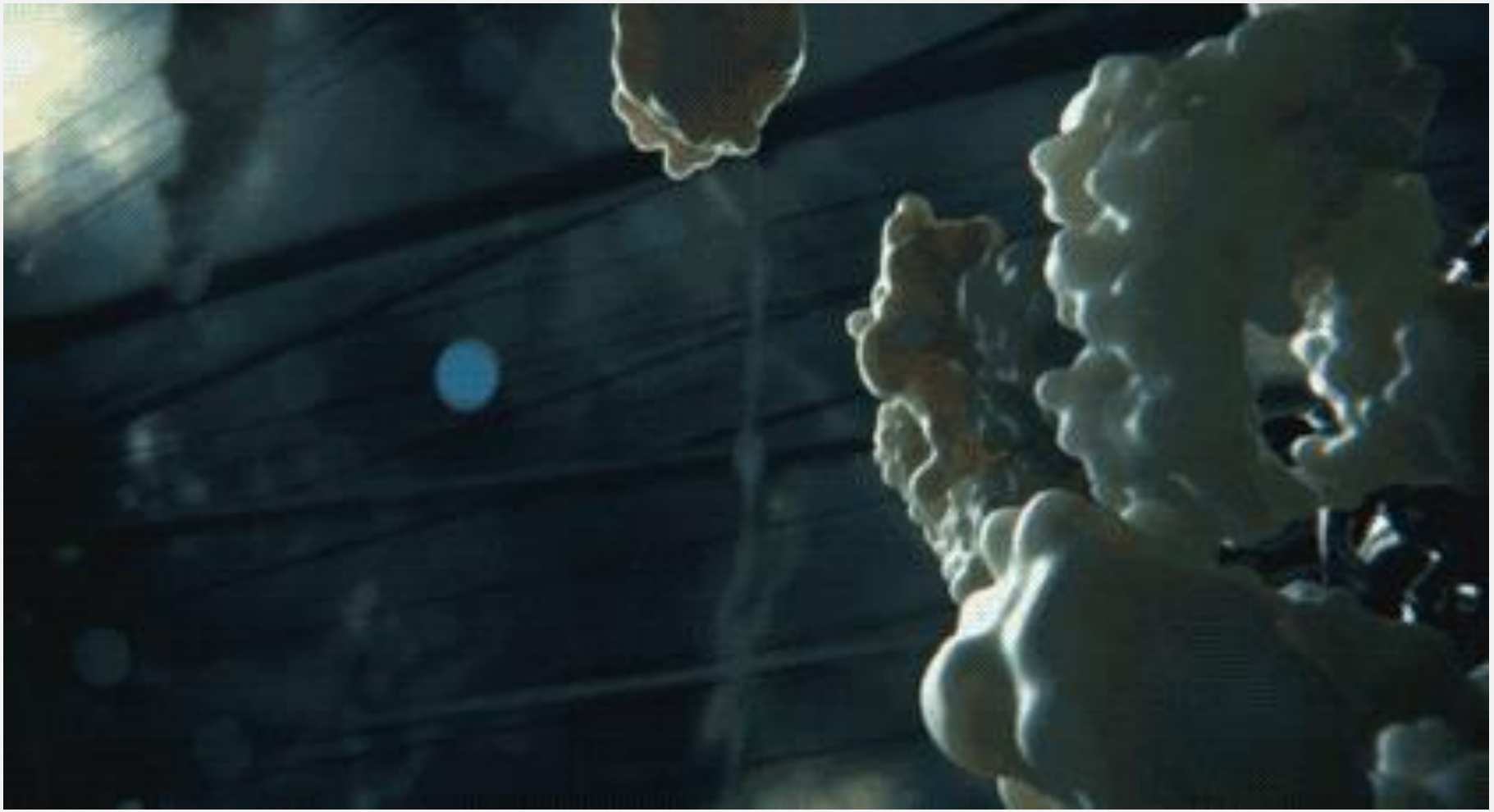
“绑架”马达蛋白，向目的地进发



撞了南墙也不回头的马达蛋白



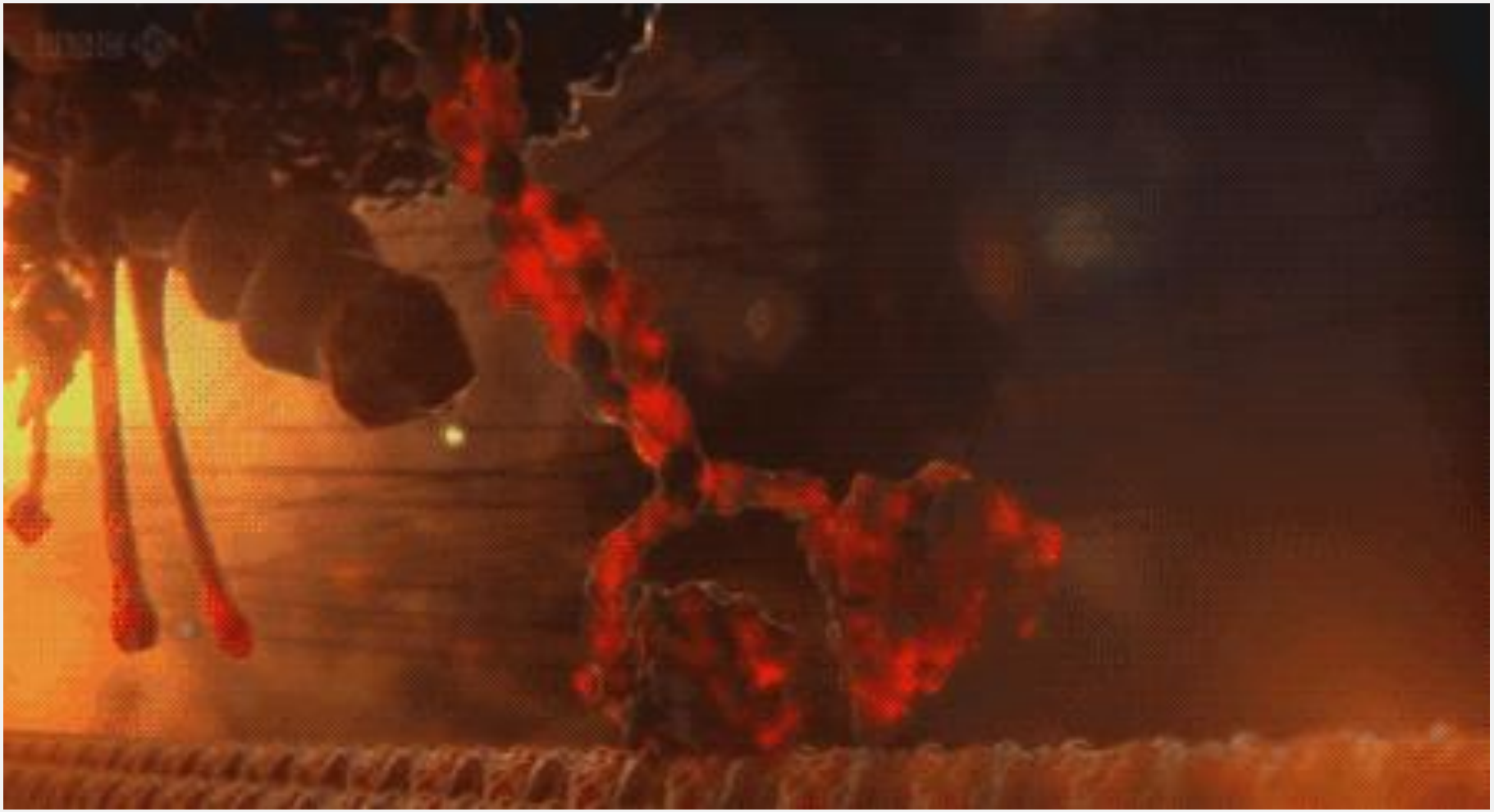
抗体送来了“鸡毛信”，蛋白酶们出动



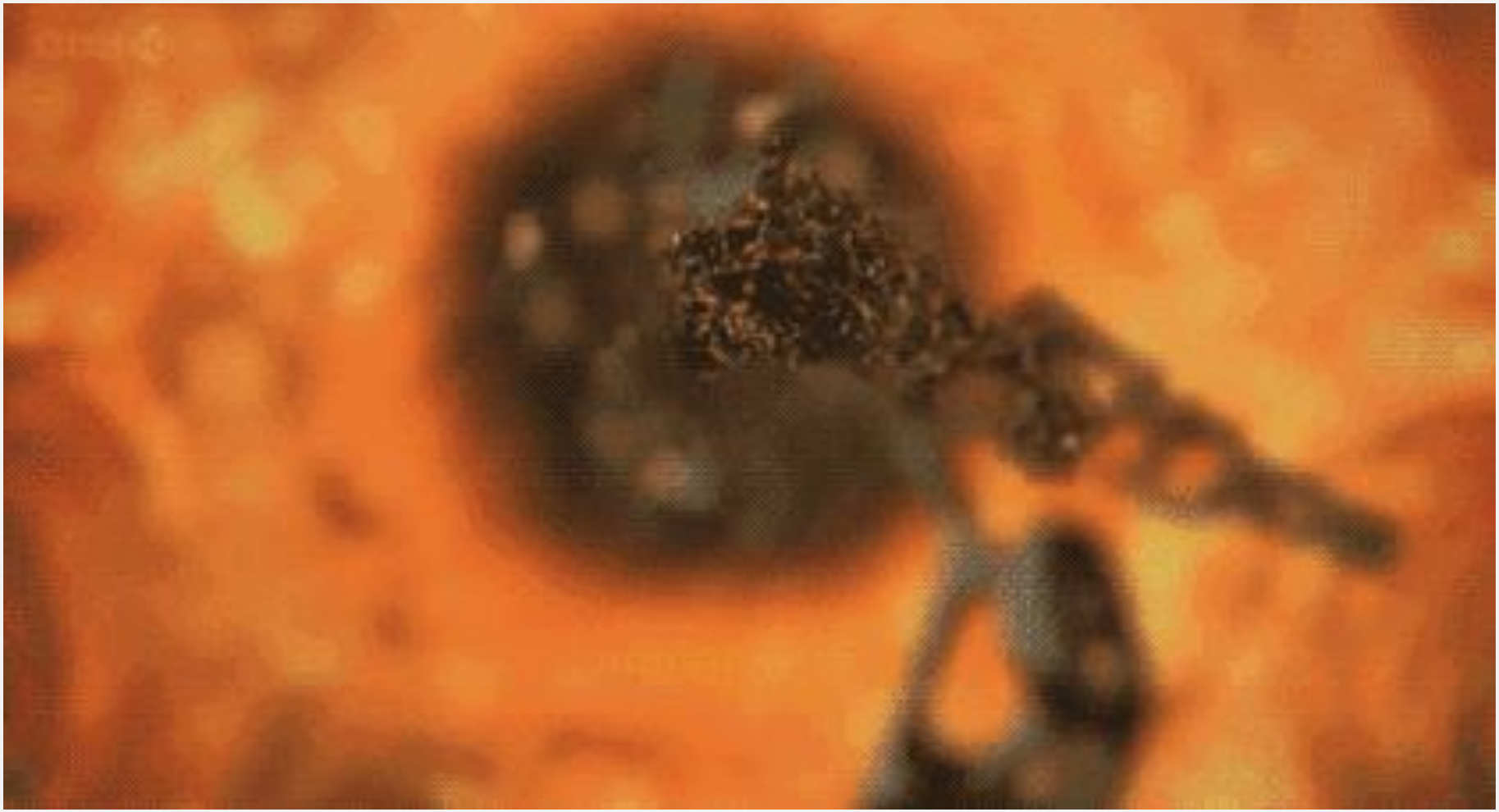
蛋白酶大显身手

今天运气有点“背”，一个病毒到达细胞核膜

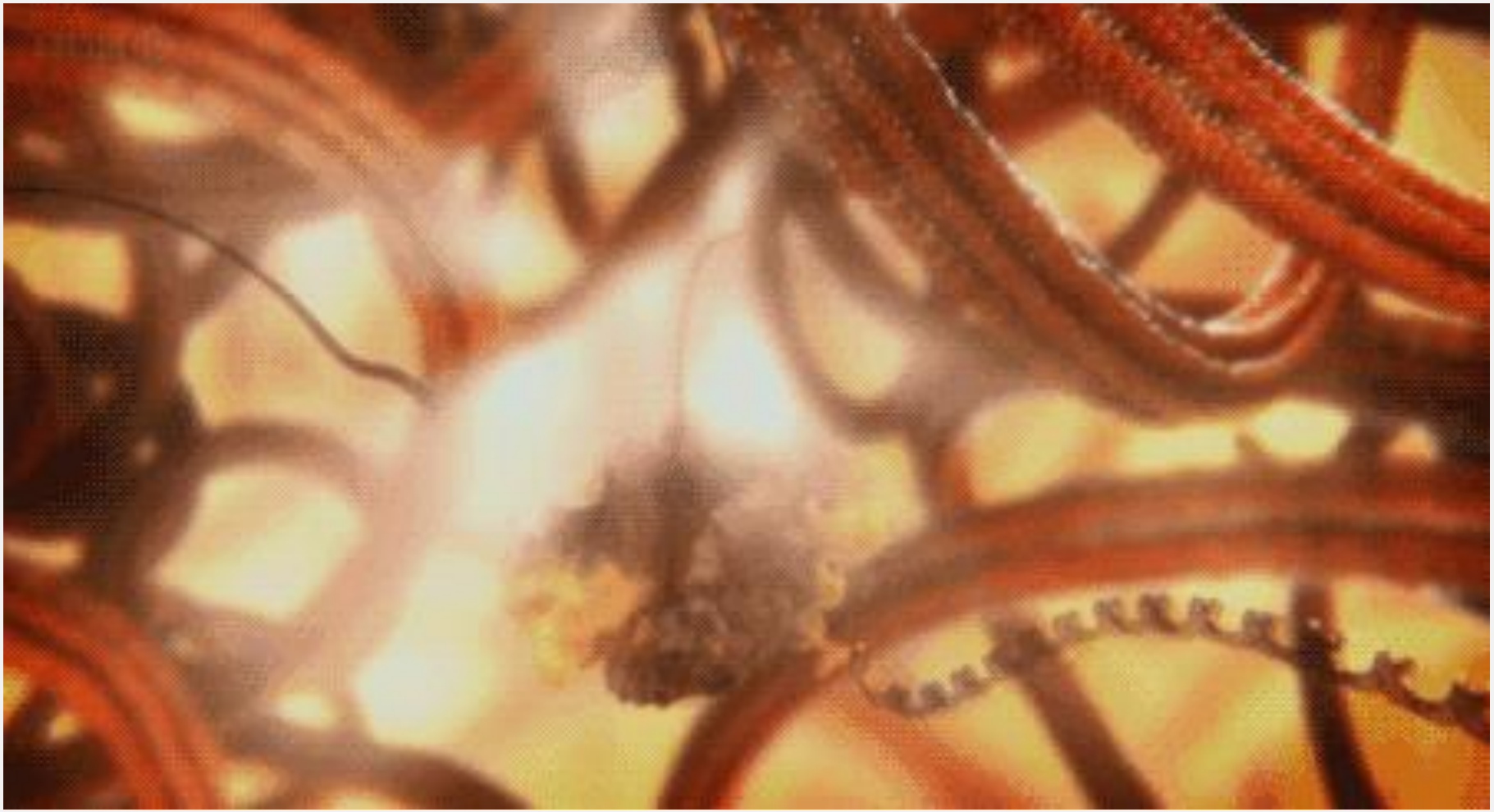
马达蛋白助力，撕碎病毒外壳



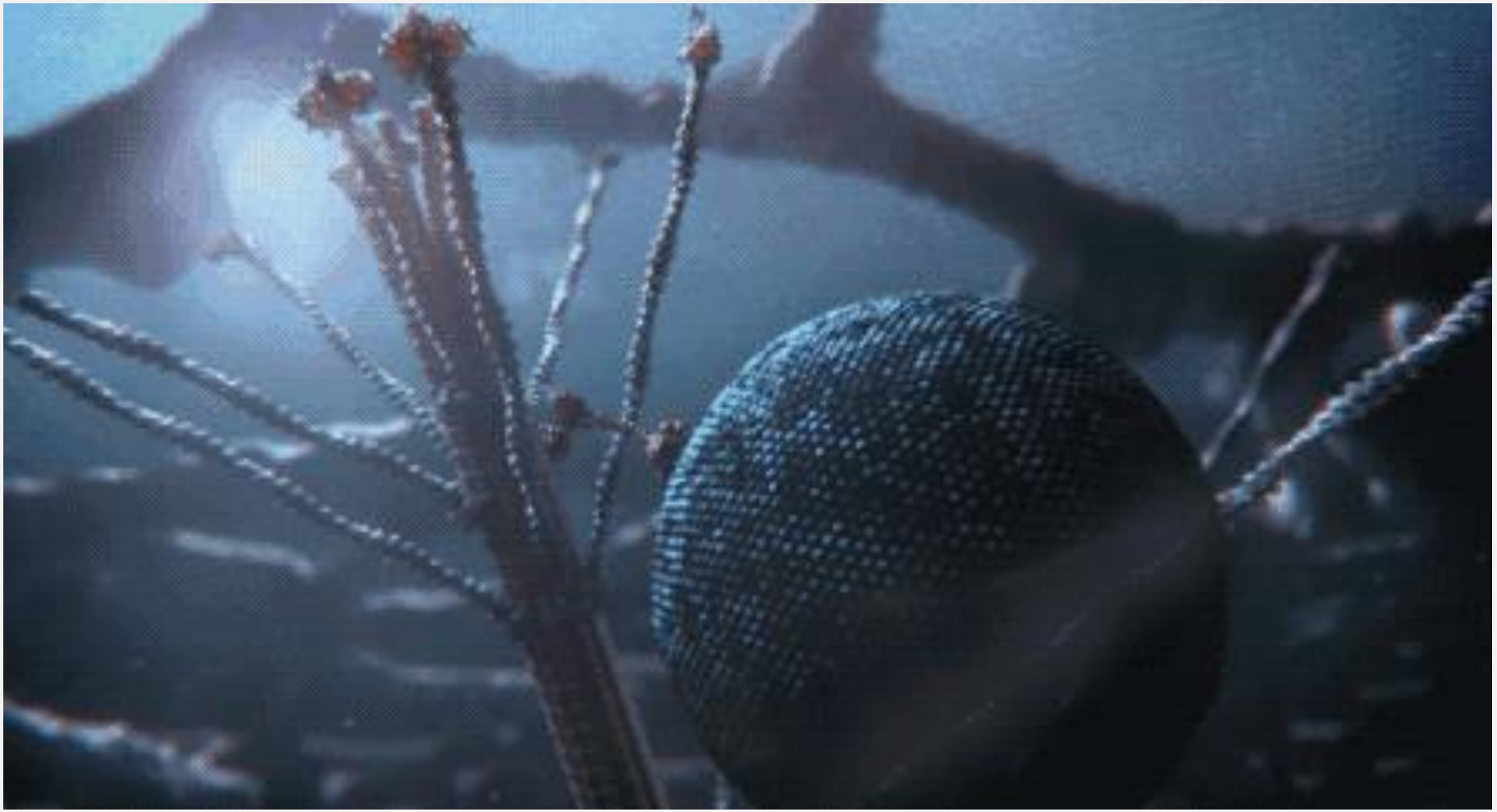
剧情大反转，病毒DNA成功进入细胞核，病毒的必杀技之三



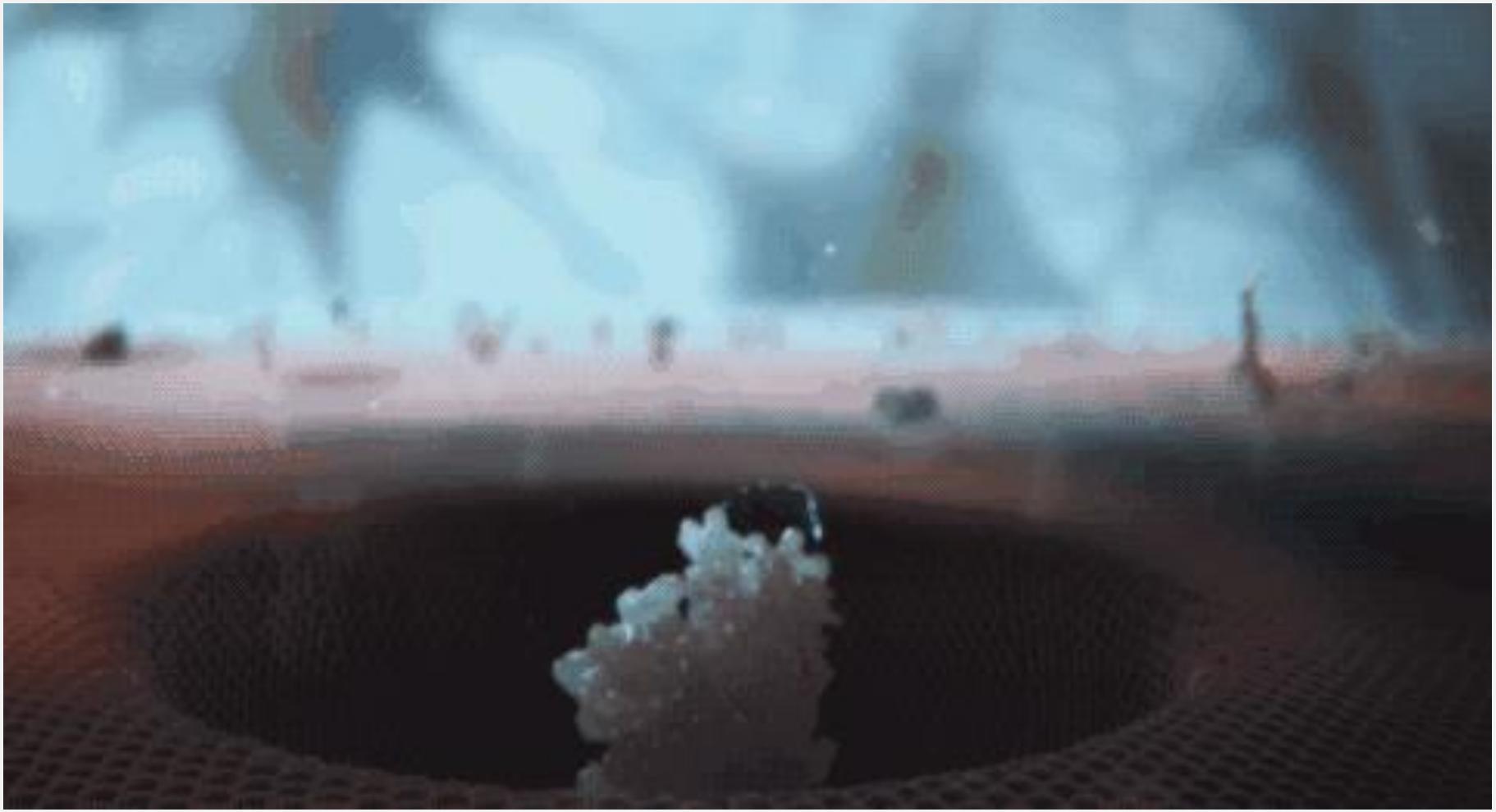
病毒DNA“鸠占鹊巢”



细胞在死前的挣扎，释放“信号肽”



“信号弹”

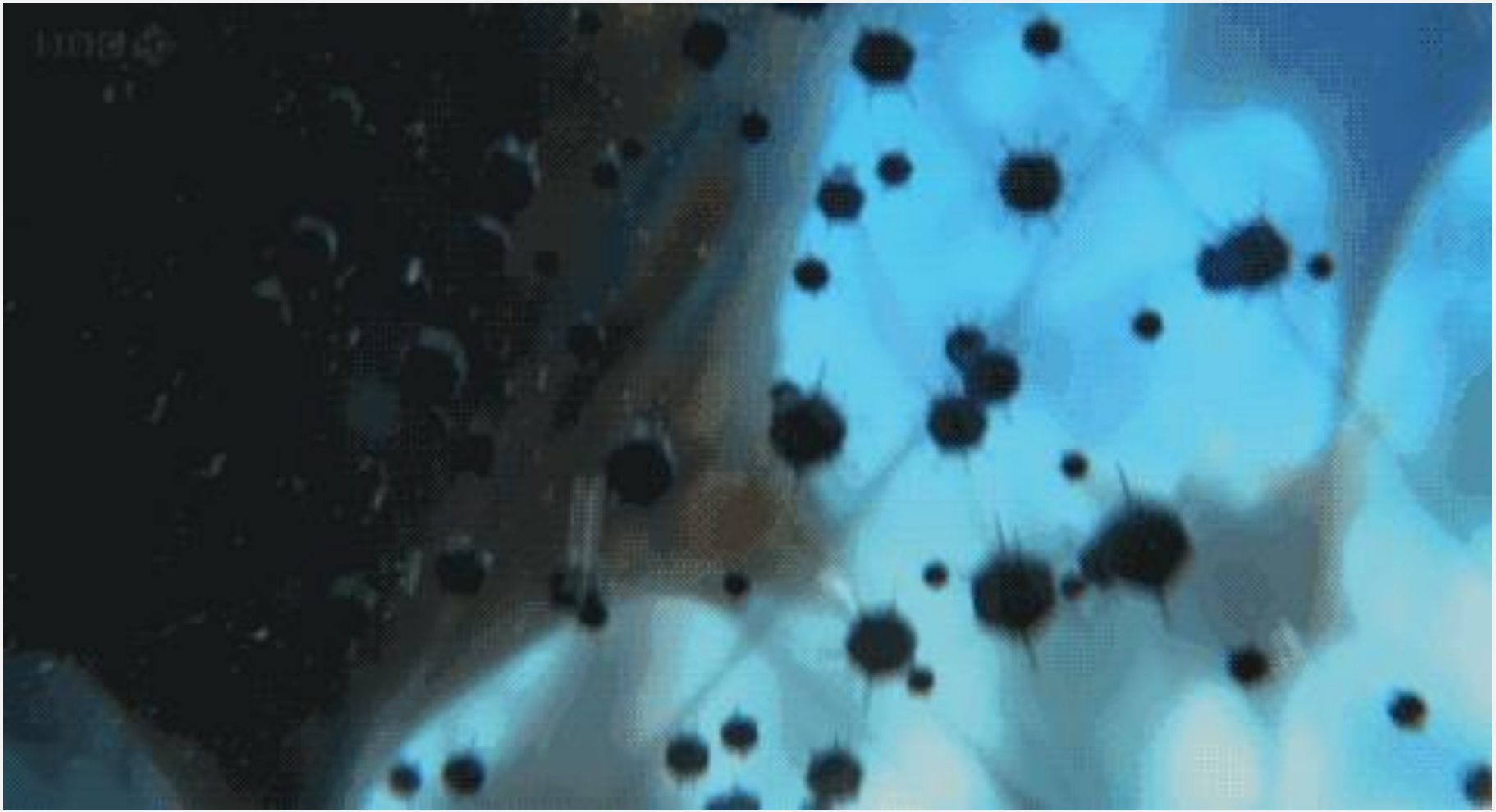


病毒DNA牢牢控制细胞工厂

病毒大军以成型

病毒号令生产蛋白炸弹，破坏细胞的“钢筋混凝土”

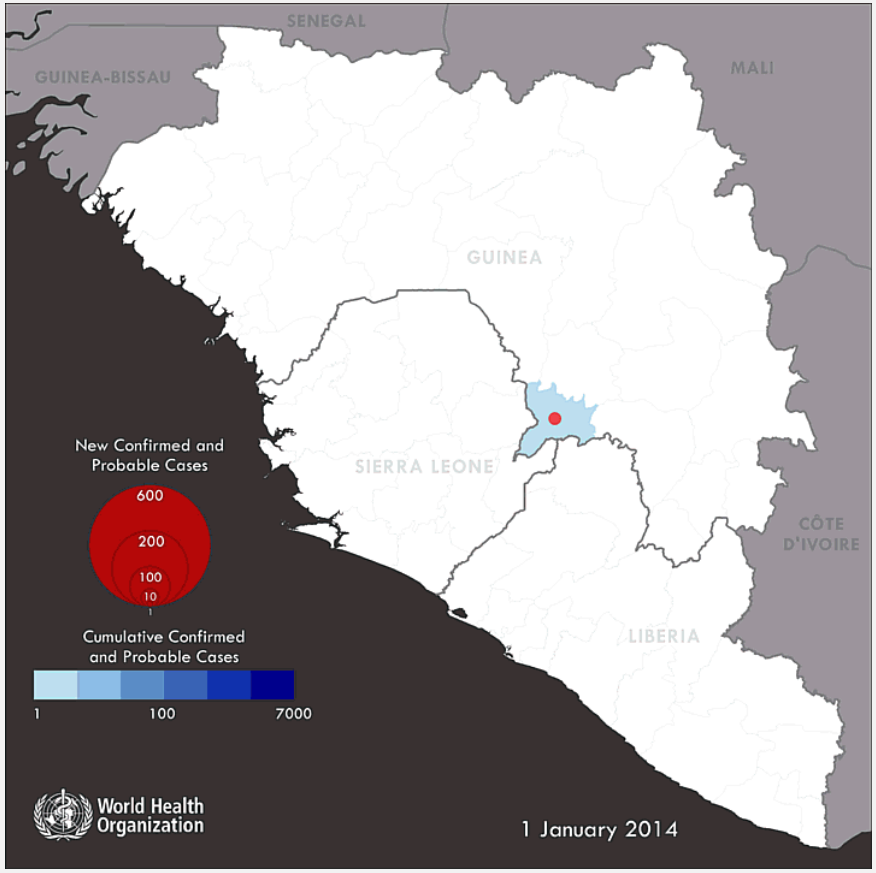
剧情再次反转，信号弹传递信息，抗体重整装备

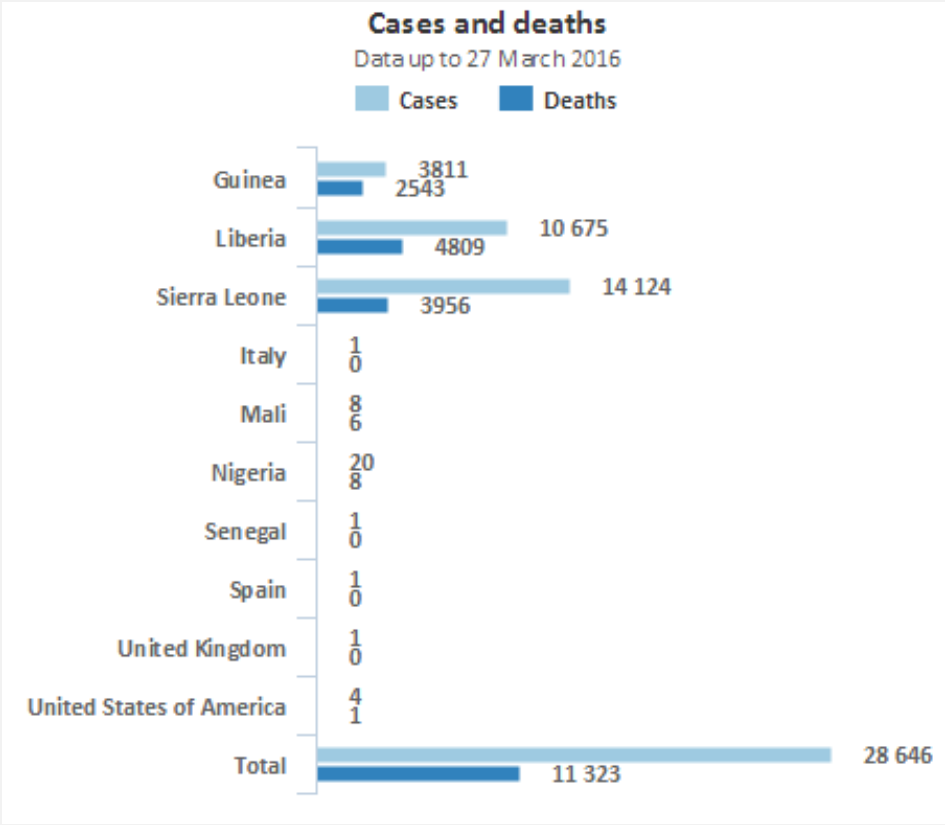


巨型白细胞奔赴战场，战场周围健康的细胞启动自毁

鼻腔充血、鼻塞——48小时

2014年西非暴发埃博拉疫情

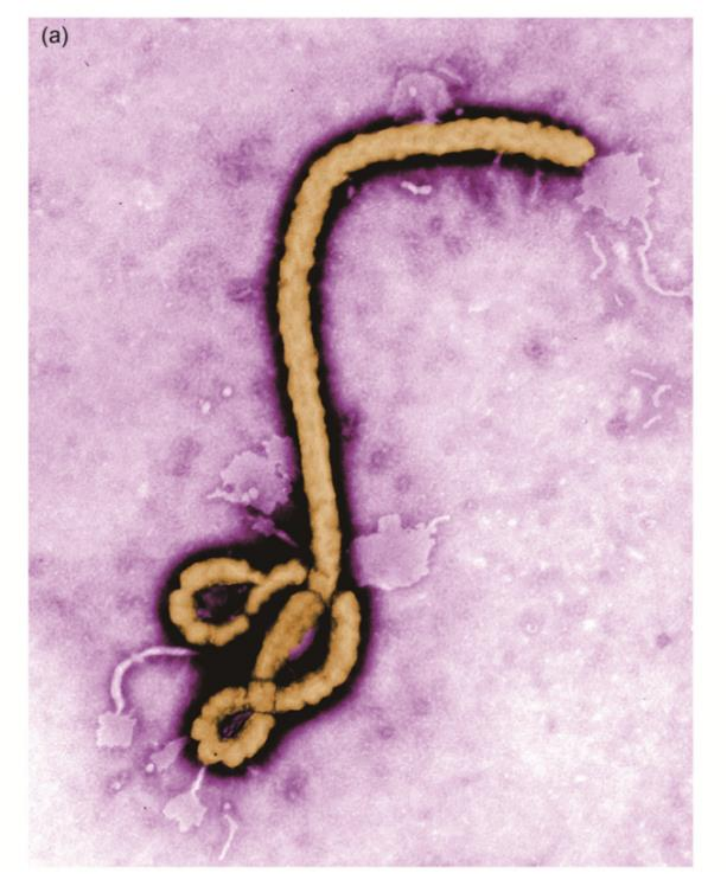


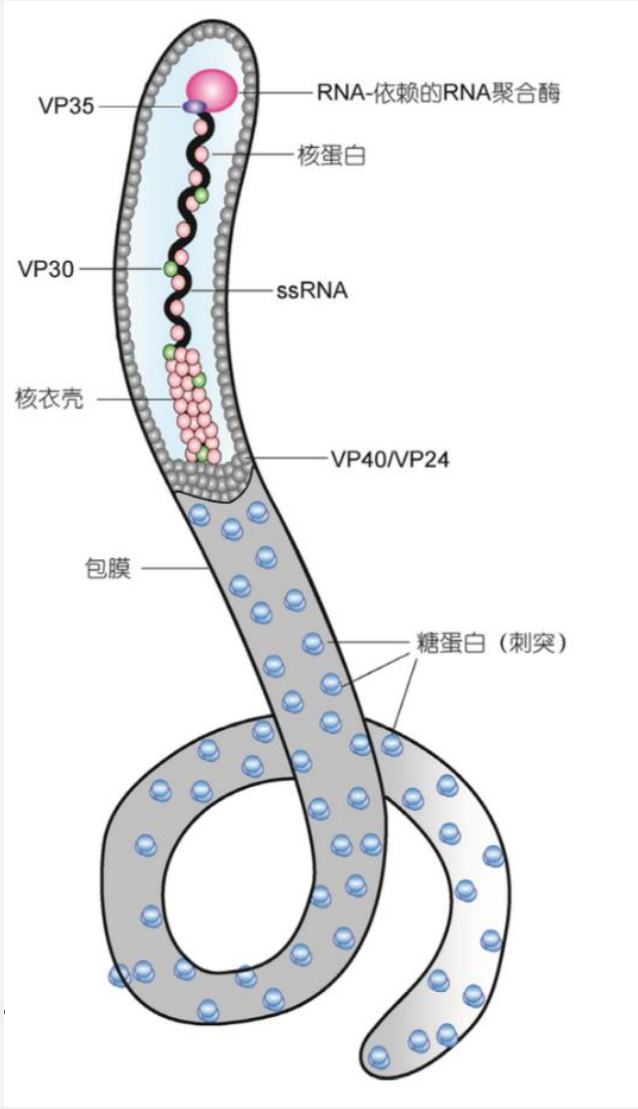


我国代表队赶赴西非

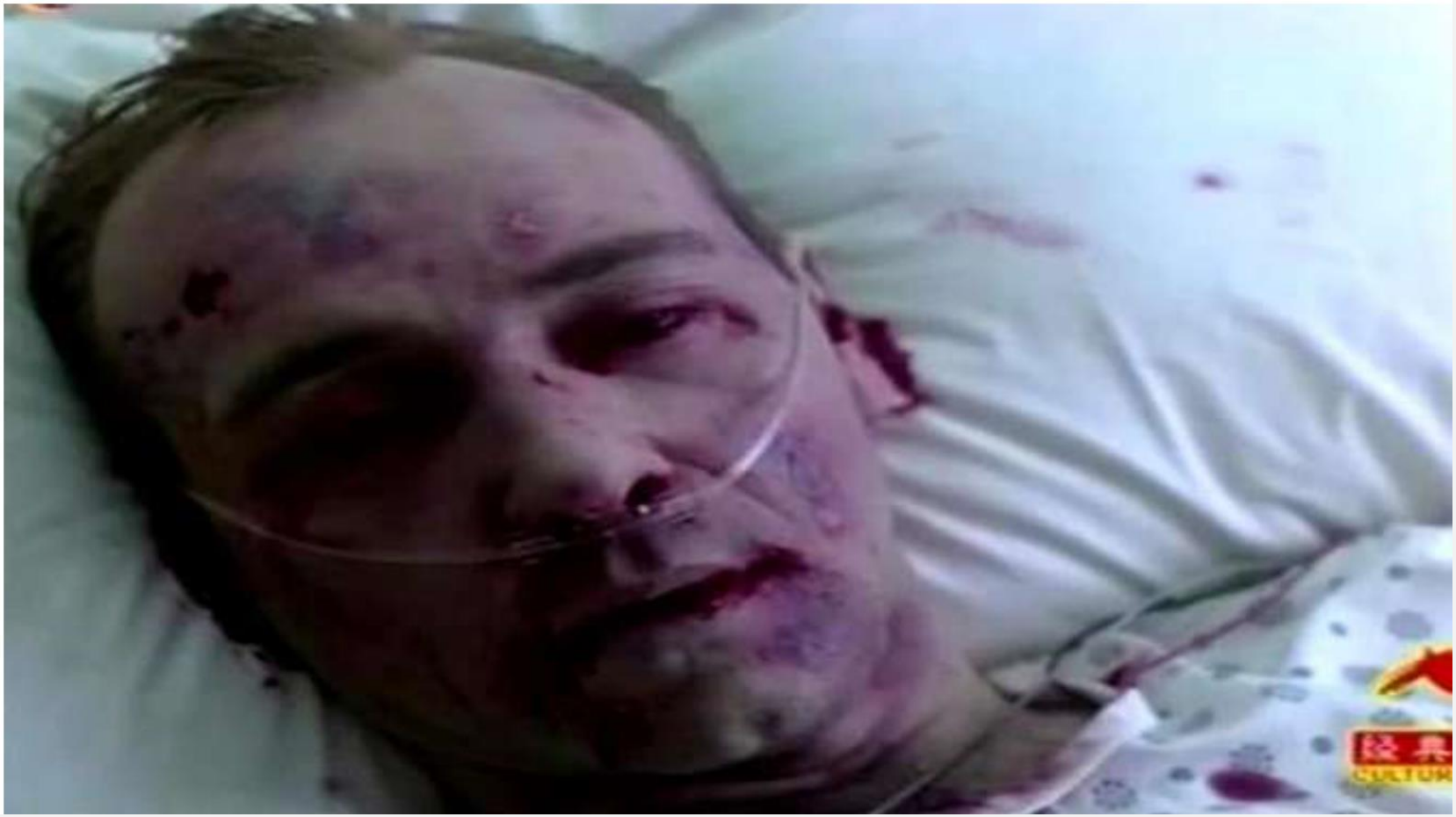
解放军援非医疗队赴塞移动实验室检测队启程

埃博拉病毒

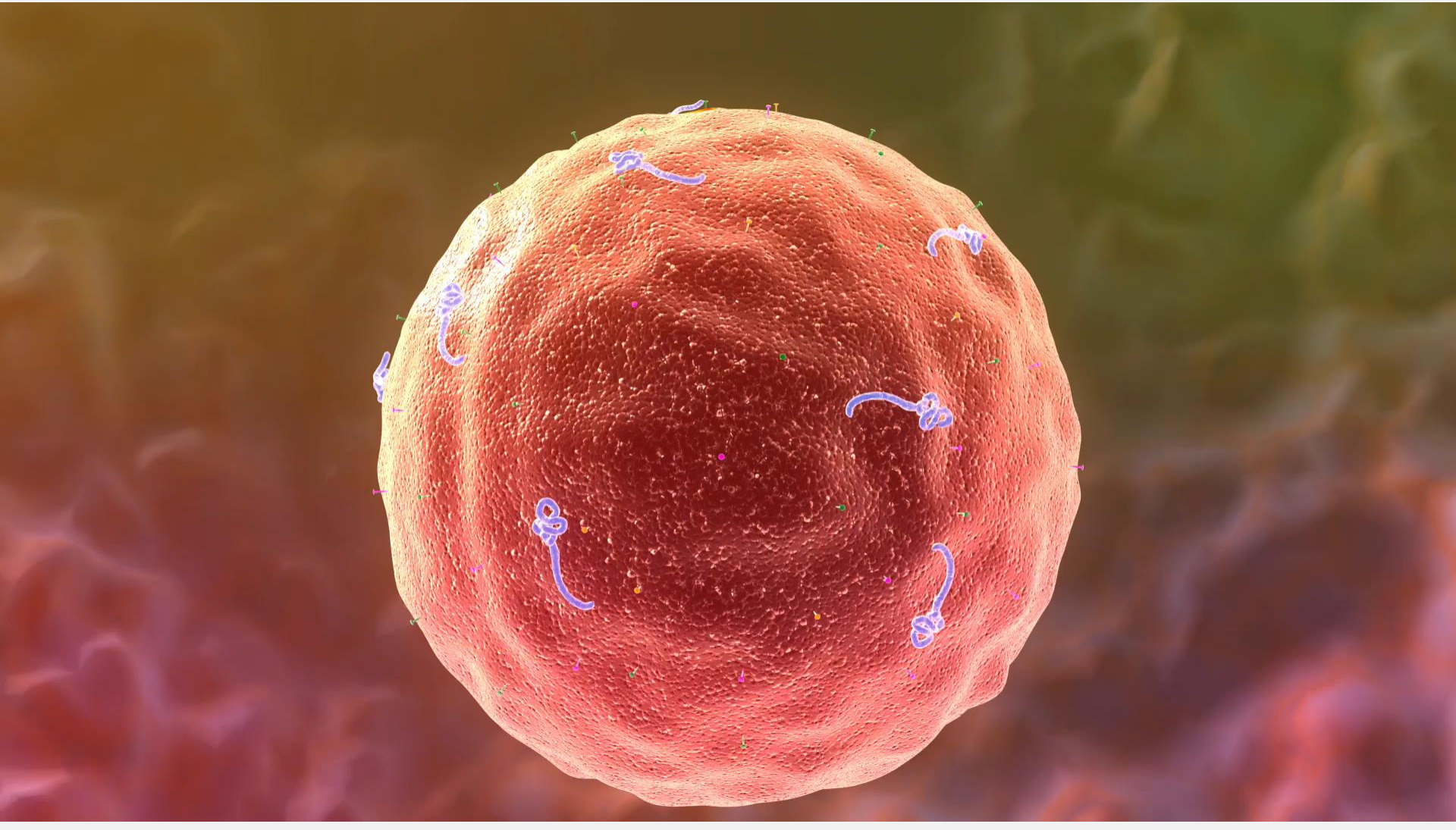


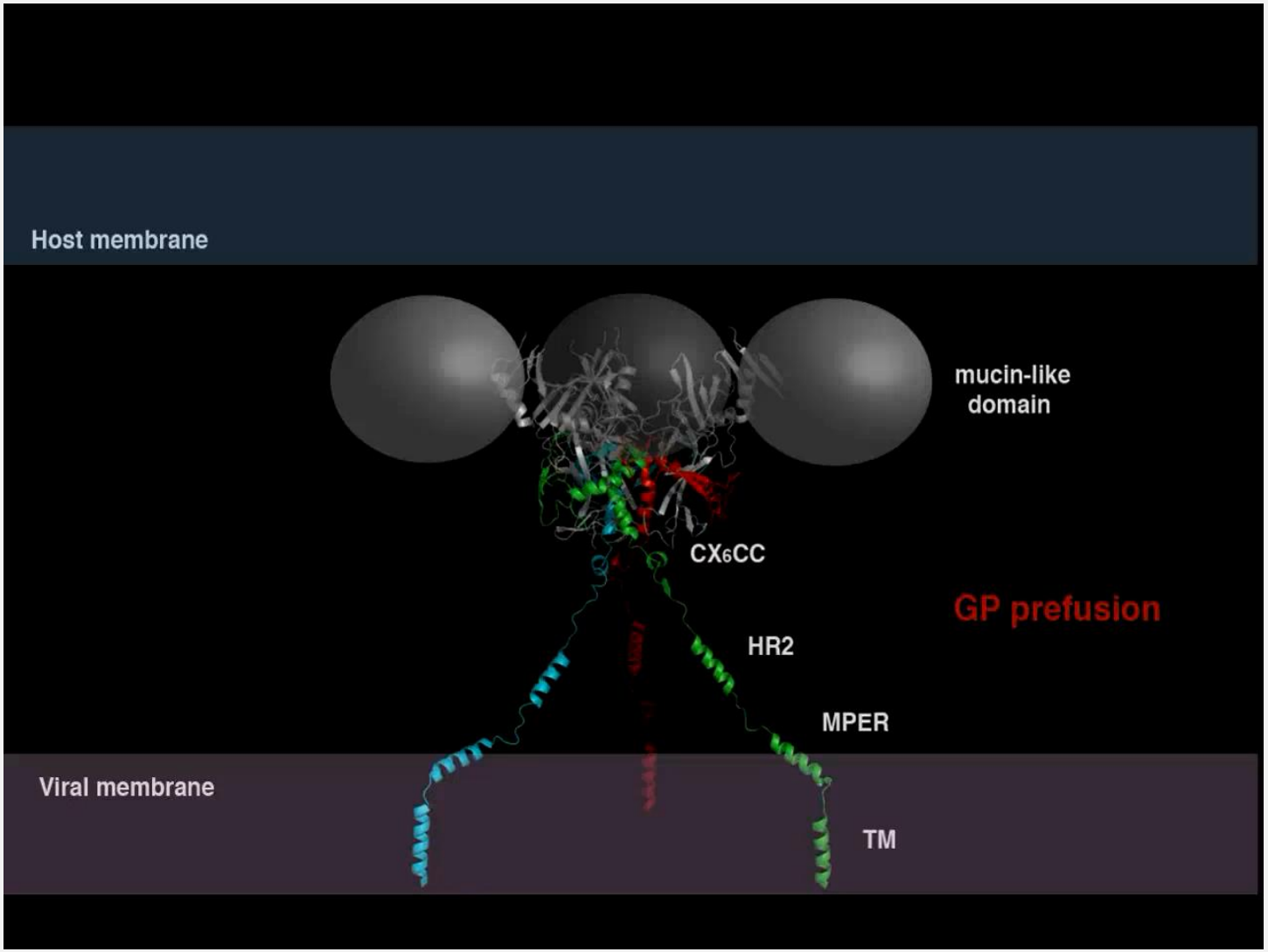


埃博拉出血热症状——七窍流血

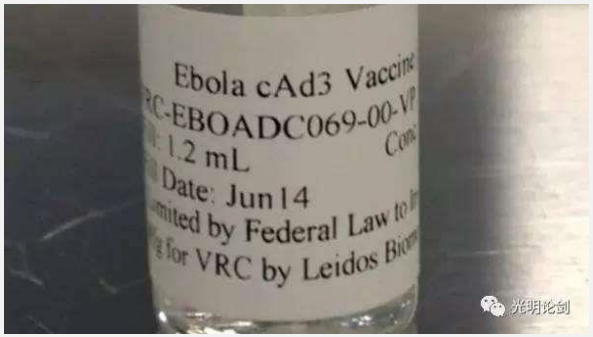


埃博拉病毒如何感染细胞




Host membrane
mucin-like domain
CX6CC
GP prefusion
HR2
MPER
Viral membrane
TM

埃博拉疫苗—中国人女科学家的贡献

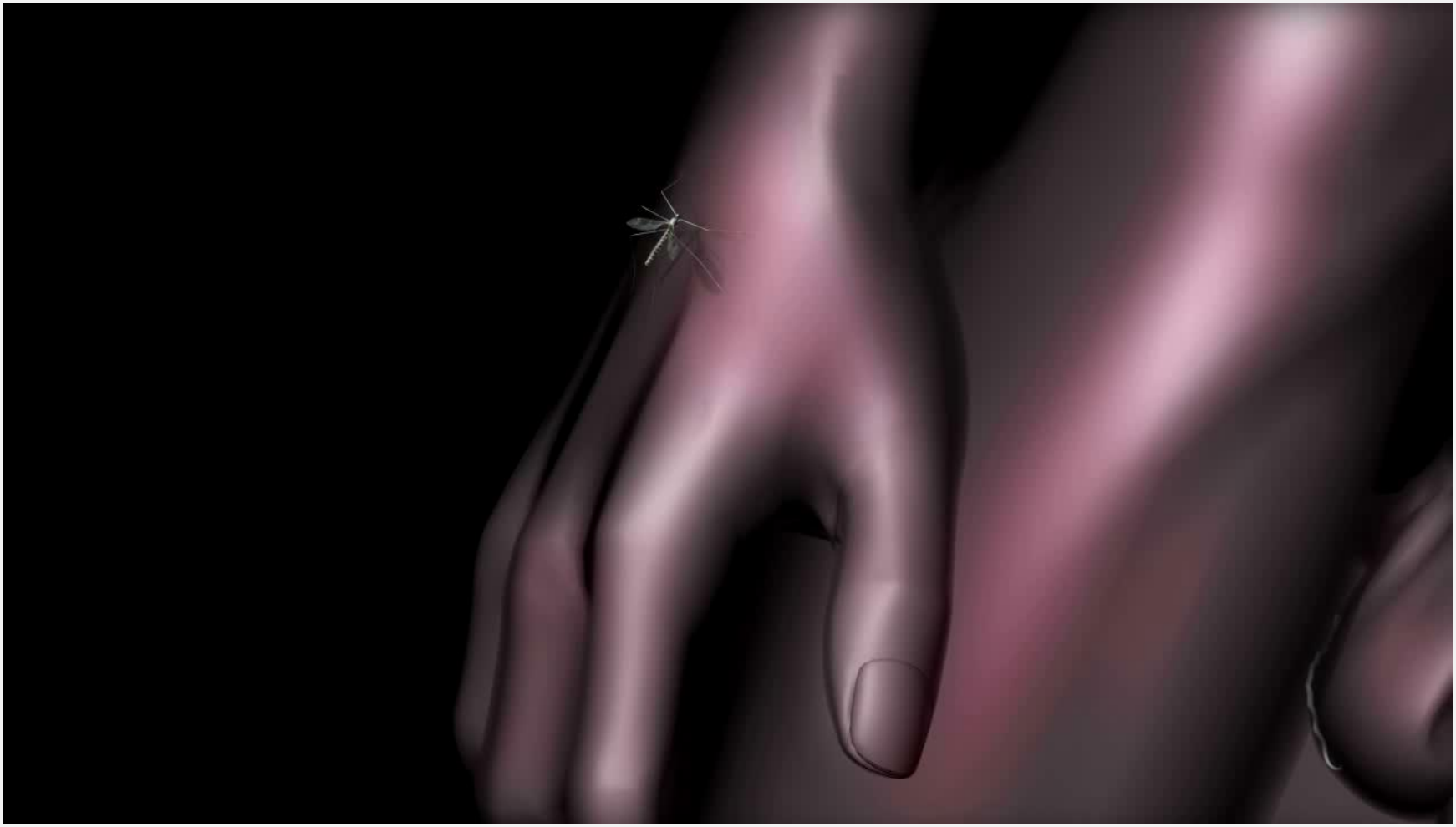


她带领团队研制出列入我军战略储备的第一个基因工程疫苗，她带队研制的埃博拉疫苗使我国完全自主研发的疫苗第一次走出国门。

军事医学科学院某研究所所长陈薇——

习主席祝愿她在医学尖端领域取得更大成绩

从人体内分离治疗寨卡病毒感染的抗体



To be continued…..