

Viral and host factor relationships which determine host tropism

Quick review of the immune system

Contents

- Introduction of Immunology
- Innate/acquired immune systems and virus
- Structural virology
- Interferon defense system
- Inactivation of immune system
HIV-1/Ebola/Measles/Sandai/Rabies/
- Why vaccination so effective ?

Immunity

Immunitas (拉丁語) 免疫、免疫 — Immunity (英語)、免疫 (日本語)

~modern immunology~

You can be safe from infectious diseases once infected

You can avoid smallpox (天然痘) if you get cowpox (牛痘). Edward Jenner

Attenuated vaccine is useful. Luis Pasteur

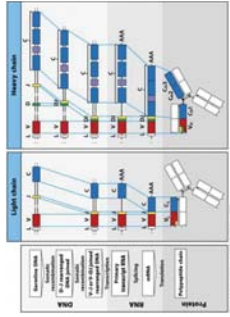


Edward Jenner (1788 – 1815)



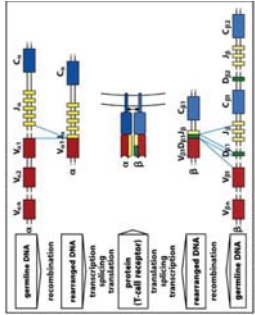
Louis Pasteur (1822-1895)

V-region genes are constructed from gene segments



Janevsky's Immunobiology

Rearrangement of TCR genes are similar to BCR



Janevsky's Immunobiology

Importance of peptide presentation

Cytotoxic T cells

細胞傷害性T細胞 (CTL)

T_H1 cell recognizes complex of invariant peptide with MHC class II and CD4 co-receptor

Helper T cell recognizes complex of invariant peptide with MHC class II and CD4 co-receptor

CD4 effector T (T_H1)

CD4 effector T, helper T (T_H1 or T_H2)

CD4 effector T, helper T (T_H1 or T_H2)

CD4 effector T, helper T (T_H1 or T_H2)

CD4 effector T, helper T (T_H1 or T_H2)

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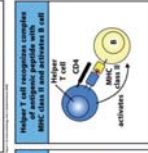
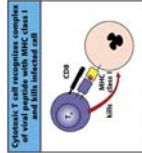
CD4 effector T, helper T (T_H1 or T_H2)

CD4 effector T, helper T (T_H1 or T_H2)

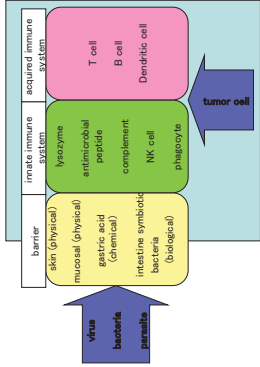
CD4 effector T, helper T (T_H1 or T_H2)

CD4 effector T, helper T (T_H1 or T_H2)

CD4 effector T, helper T (T_H1 or T_H2)



Human defense system (non-self and self)



Kajiwara's slide, edited

Immune regulation & antibody

Nobel Prize in Physiology or Medicine 1894

Establishment of Mechanism regarding Immune regulation

Principle for production of monoclonal antibody

Discovery of gene arrangement of antibody

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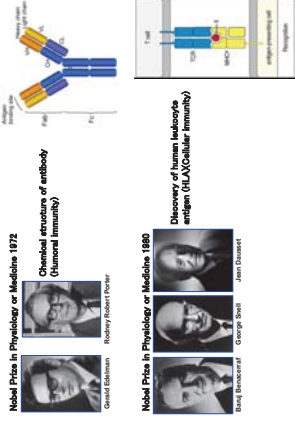
Discovery of gene arrangement of antibody

Discovery of gene arrangement of antibody

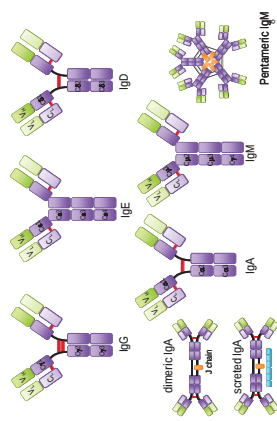
Discovery of gene arrangement of antibody

Discovery of gene arrangement of antibody

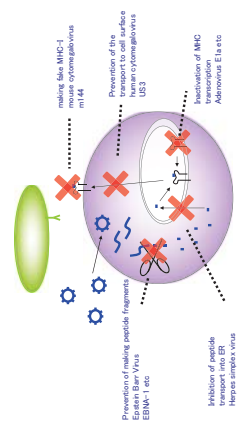
Discovery of the molecules of acquired immunology



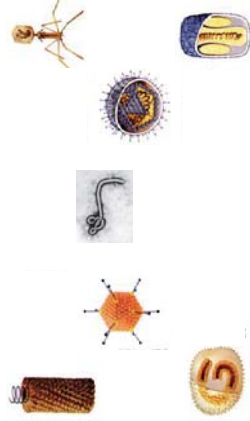
Structures of various antibodies



Various inhibition mechanisms of MHC-I by viruses



What's the name of these viruses?



Structural virology

Janevsky's Immunobiology

Janevsky's Immunobiology

What is virus?

A microorganism (the smallest) that can grow or reproduce only in a living cell. No metabolism systems of their own.
(自己増殖できない・代謝できない)

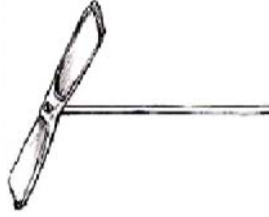
Viruses consist solely of a small segment of nucleic acid (DNA or RNA) encased in a simple protein shell. (タンパク質の殻とその内部に詰め込まれた核酸(DNA, RNA)のみからなる)

生物と定義されていない!

If the size of bacteria were a whale virus would be as small as dog or mouse



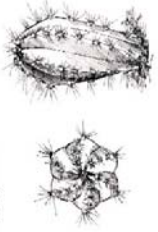
2 fold rotation symmetry



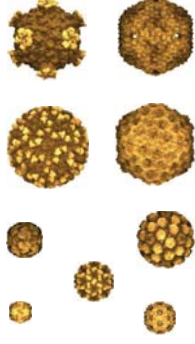
n-fold rotation symmetry

can be superimposed after $2\pi/n$ rotation

$n = 1, 2, 3, 4, 5, \dots$



Structure biology/virology?



Seeing is believing?

mirror symmetry



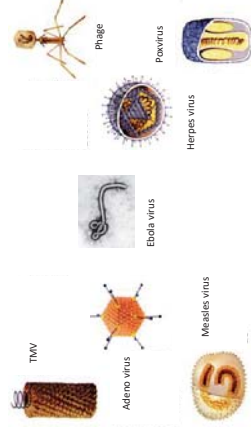
2 fold rotation symmetry



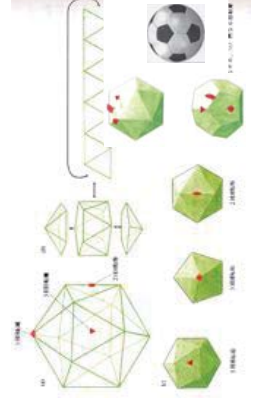
A little bit of Symmetry

- ◇ Rotation
- ◇ Translation
- ◇ Mirror
- ◇ Screw axis
- ◇ Inversion center/axis
- ◇ Glide plane

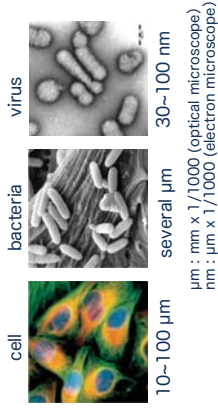
High symmetry



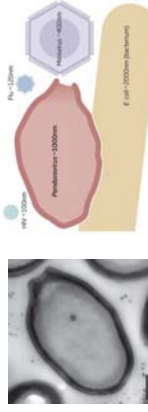
Icosahedral symmetry
(point group 532)



Size of viruses

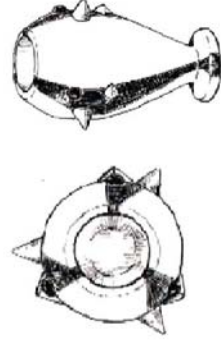


Largest ever - Pandoravirus -

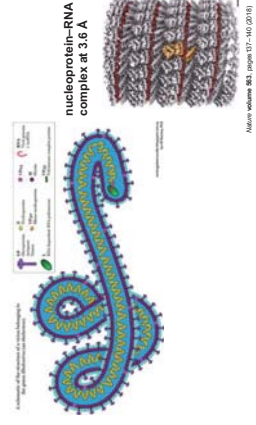
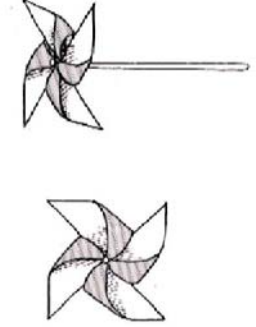


"The opening of the box will definitively break the foundations of what we thought viruses were," researcher Chantal Abergel, research director at the French National Center for Scientific Research in Marseilles, told Unesclence.
<https://www.livescience.com/83276-largest-viruses-seen-revealed-pandoravirus.html>
July 18, 2013 02:00pm ET

3 fold rotation symmetry



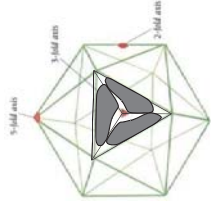
4 fold rotation symmetry



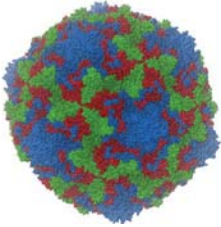
March volume 90, pages 37-40 (2011)

Icosahedral Symmetry

- 12 vertices
- 20 faces (equilateral triangles)
- 5-3-2 symmetry axes
- 60 identical* subunits in identical environments can form icosahedral shell
- asymmetric

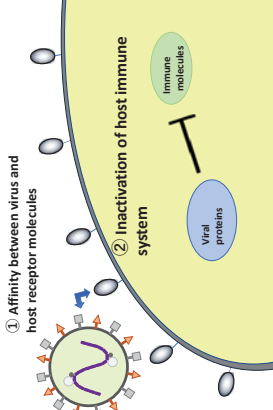


They have to make genome delivery system (protein shell). Using the same genome iteratively and producing many copies of protein enable virus to make a big particle carrier.

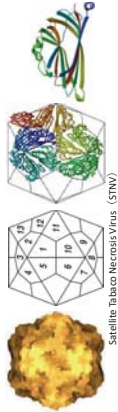


Significance of utilizing symmetry globular virus (icosahedral)

What determines virus-host specificity?



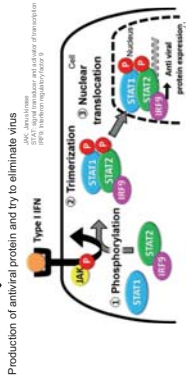
The smallest globular virus is composed of 60 subunits



- one subunit (195 residues) is used 60 times. The small number of DNA bases can convey much more nucleic acids (1120 bases)
- However, STNV cannot replicate by itself (Helper virus, TNV is necessary)

JAK-STAT system as innate immune system

- ♦ Viral recognition and exclusion system at the early stage of infection
- Detect viral entry and generate the type I interferon (IFN)
- Activation of the JAK-STAT pathway Type under the type I IFN receptor



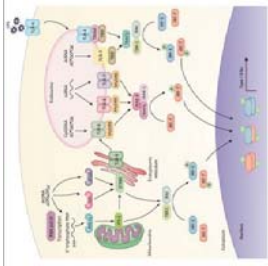
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IFN-β	U01490	Interferon beta	[1]
IFN-γ	U01491	Interferon gamma	[1]
IFN-λ	U01492	Interferon lambda	[1]
IFN-δ	U01493	Interferon delta	[1]
IFN-ε	U01494	Interferon epsilon	[1]
IFN-ζ	U01495	Interferon zeta	[1]
IFN-η	U01496	Interferon eta	[1]
IFN-θ	U01497	Interferon theta	[1]
IFN-ι	U01498	Interferon iota	[1]
IFN-κ	U01499	Interferon kappa	[1]
IFN-λ1	U01500	Interferon lambda 1	[1]
IFN-λ2	U01501	Interferon lambda 2	[1]
IFN-λ3	U01502	Interferon lambda 3	[1]
IFN-λ4	U01503	Interferon lambda 4	[1]
IFN-λ5	U01504	Interferon lambda 5	[1]
IFN-λ6	U01505	Interferon lambda 6	[1]
IFN-λ7	U01506	Interferon lambda 7	[1]
IFN-λ8	U01507	Interferon lambda 8	[1]
IFN-λ9	U01508	Interferon lambda 9	[1]
IFN-λ10	U01509	Interferon lambda 10	[1]
IFN-λ11	U01510	Interferon lambda 11	[1]
IFN-λ12	U01511	Interferon lambda 12	[1]
IFN-λ13	U01512	Interferon lambda 13	[1]
IFN-λ14	U01513	Interferon lambda 14	[1]
IFN-λ15	U01514	Interferon lambda 15	[1]
IFN-λ16	U01515	Interferon lambda 16	[1]
IFN-λ17	U01516	Interferon lambda 17	[1]
IFN-λ18	U01517	Interferon lambda 18	[1]
IFN-λ19	U01518	Interferon lambda 19	[1]
IFN-λ20	U01519	Interferon lambda 20	[1]
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IFN-λ27	U01526	Interferon lambda 27	[1]
IFN-λ28	U01527	Interferon lambda 28	[1]
IFN-λ29	U01528	Interferon lambda 29	[1]
IFN-λ30	U01529	Interferon lambda 30	[1]
IFN-λ31	U01530	Interferon lambda 31	[1]
IFN-λ32	U01531	Interferon lambda 32	[1]
IFN-λ33	U01532	Interferon lambda 33	[1]
IFN-λ34	U01533	Interferon lambda 34	[1]
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IFN-λ36	U01535	Interferon lambda 36	[1]
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IFN-λ63	U01562	Interferon lambda 63	[1]
IFN-λ64	U01563	Interferon lambda 64	[1]
IFN-λ65	U01564	Interferon lambda 65	[1]
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IFN-λ68	U01567	Interferon lambda 68	[1]
IFN-λ69	U01568	Interferon lambda 69	[1]
IFN-λ70	U01569	Interferon lambda 70	[1]
IFN-λ71	U01570	Interferon lambda 71	[1]
IFN-λ72	U01571	Interferon lambda 72	[1]
IFN-λ73	U01572	Interferon lambda 73	[1]
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IFN-λ98	U01597	Interferon lambda 98	[1]
IFN-λ99	U01598	Interferon lambda 99	[1]
IFN-λ100	U01599	Interferon lambda 100	[1]

HIV-1

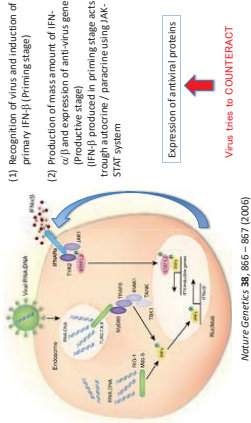
Antiviral interferon-stimulated genes

Gene Name	Accession Number	Function	Reference
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IFIT4	U01502	Interferon-induced protein 4	[1]
IFIT5	U01503	Interferon-induced protein 5	[1]
IFIT6	U01504	Interferon-induced protein 6	[1]
IFIT7	U01505	Interferon-induced protein 7	[1]
IFIT8	U01506	Interferon-induced protein 8	[1]
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IFIT10	U01508	Interferon-induced protein 10	[1]
IFIT11	U01509	Interferon-induced protein 11	[1]
IFIT12	U01510	Interferon-induced protein 12	[1]
IFIT13	U01511	Interferon-induced protein 13	[1]
IFIT14	U01512	Interferon-induced protein 14	[1]
IFIT15	U01513	Interferon-induced protein 15	[1]
IFIT16	U01514	Interferon-induced protein 16	[1]
IFIT17	U01515	Interferon-induced protein 17	[1]
IFIT18	U01516	Interferon-induced protein 18	[1]
IFIT19	U01517	Interferon-induced protein 19	[1]
IFIT20	U01518	Interferon-induced protein 20	[1]
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IFIT79	U01577	Interferon-induced protein 79	[1]
IFIT80	U01578	Interferon-induced protein 80	[1]
IFIT81	U01579	Interferon-induced protein 81	[1]
IFIT82	U01580	Interferon-induced protein 82	[1]
IFIT83	U01581	Interferon-induced protein 83	[1]
IFIT84	U01582	Interferon-induced protein 84	[1]
IFIT85	U01583	Interferon-induced protein 85	[1]
IFIT86	U01584	Interferon-induced protein 86	[1]
IFIT87	U01585	Interferon-induced protein 87	[1]
IFIT88	U01586	Interferon-induced protein 88	[1]
IFIT89	U01587	Interferon-induced protein 89	[1]
IFIT90	U01588	Interferon-induced protein 90	[1]
IFIT91	U01589	Interferon-induced protein 91	[1]
IFIT92	U01590	Interferon-induced protein 92	[1]
IFIT93	U01591	Interferon-induced protein 93	[1]
IFIT94	U01592	Interferon-induced protein 94	[1]
IFIT95	U01593	Interferon-induced protein 95	[1]
IFIT96	U01594	Interferon-induced protein 96	[1]
IFIT97	U01595	Interferon-induced protein 97	[1]
IFIT98	U01596	Interferon-induced protein 98	[1]
IFIT99	U01597	Interferon-induced protein 99	[1]
IFIT100	U01598	Interferon-induced protein 100	[1]

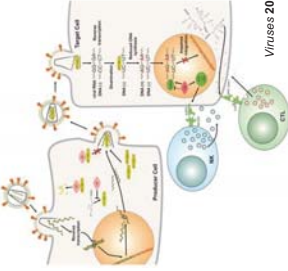
Interferon (type I) production



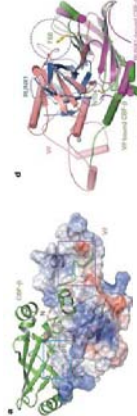
Viral infection and IFN system



Impact of the cellular restriction factor APOBEC3



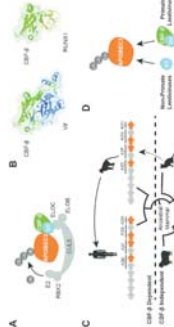
Vif and RUNX1 overlap when interacting with CBF-β



The essential nature of the primate lentiviral Vif/CBF-β interaction is highlighted by the extensive interface evident in a recent crystal structure (4800 Å³) [17]. CBF-β functions canonically as a cofactor to the RUNX family of transcription factor proteins to regulate the expression of a battery of genes involved in hematopoietic and bone cell development

Nature volume 505, pages 229–233 (09 January 2014)

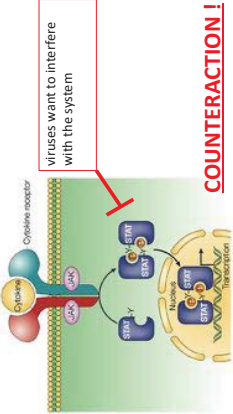
Deactivation of APOBEC3 by HIV-1



HIV-1 Vif forms an APOBEC3 ubiquitin ligase complex by hijacking the transcriptional cofactor CBF-β to form a scaffold for the recruitment of a cullin-RING ligase complex consisting of CUL5, ELOB, ELOC, and RBX2

PLoS Pathogens 12(12):e1005958

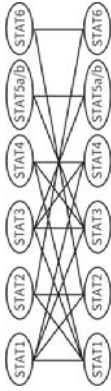
Inactivation of the JAK/STAT pathway



Nature Reviews Immunology 3, 900-911

STAT family

Formation of both homo/hetero dimer makes it possible to convey more than 50 cytokine stimulation signals



COUNTERACTION!

STAT family

7 family of STATs (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STAT6). Most of them can form a homodimer. The following table is for hetero dimer.

Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic
STAT1 (P50AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT2 (B57AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT3 (I70AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT4 (I48AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT5A (I94AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT5B (I97AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT6 (B47AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%

Greg M. et al., JAK-STAT2.1, e23060 (2013)

Similarity of STAT molecules

Identify (B-E)	Identify (B-E)	Identify (B-E)	Identify (B-E)	Identify (B-E)	Identify (B-E)	Identify (B-E)	Identify (B-E)	Identify (B-E)	Identify (B-E)
STAT1 (P50AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT2 (B57AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT3 (I70AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT4 (I48AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT5A (I94AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT5B (I97AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%
STAT6 (B47AA)	52.6%	50.5%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%	45.8%

Similarity (B-E)

数字の小さい方のSTATを基に(ラメーターを調出)
(右上半分—Identity, 左下半分—Similarity)

麻疹ウイルス Measles Virus (MV)

Infection : airborne, droplet, and contact

Symptoms include fever, cough, runny nose, red eyes and a generalized, maculopapular erythematous rash.
serious complications such as pneumonia, bronchitis, otitis media, acute brain inflammation

spread by coughing and sneezing via close personal contact or direct contact with secretions

Vaccination is significantly effective (representative of the success)

Even though the presence of the effective vaccine, a major cause of childhood morbidity and mortality world wide, (50 people death / hour)

refer : Meas. sec. WHO

SEC-MALS

SEC-MALS: Size Exclusion Chromatography combined with Multi-Angle Light Scattering

◆ Absolute molecular weight in

solid solution (with water)

right axis: observed mass (colored line)

left axis: calculated mass (colored line)

start

start

start

start

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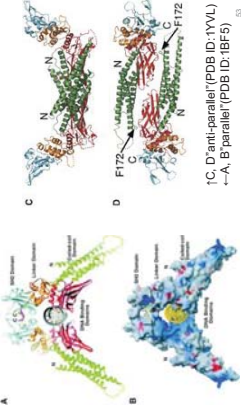
start

start

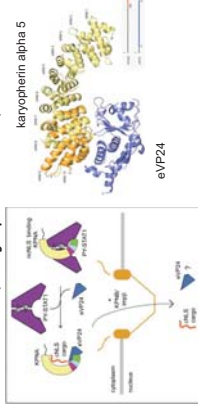
start

start

STAT1: Localization Linked to Tyrosine Phosphorylation and DNA Binding



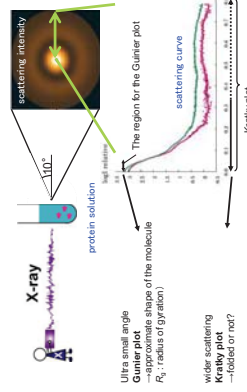
Ebolavirus VP24 antagonizes interferon signaling by binding host importin (karyopherin α5)



Cell Host Microbe. 2014 Aug 13;16(2):187-200

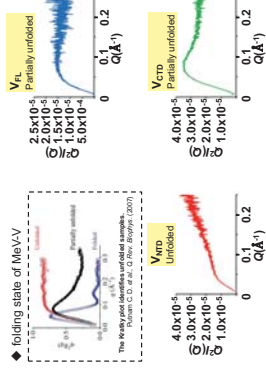
SEC-SAXS

SEC-SAXS: Size Exclusion Chromatography coupled with Small Angle X-ray Scattering



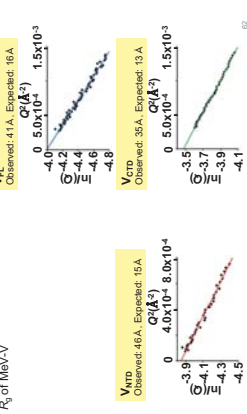
SEC-SAXS Kratky plot

SEC-SAXS: Size Exclusion Chromatography coupled with Small Angle X-ray Scattering



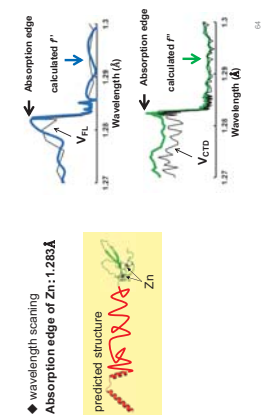
SEC-SAXS Guinier plot

SEC-SAXS: Size Exclusion Chromatography coupled with Small Angle X-ray Scattering



V_{FL} V_{CTD} element analysis (XAFS)

XAFS: X-ray Absorption Fine Structure

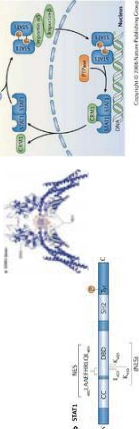


STAT1: Export from the nucleus

After STAT1 finishes 'transcriptional work' followed by IFN stimulation, it disappears from nucleus within a couple of hours. It is not degraded, but exported from nucleolus.

While STAT1 is bound to DNA, NES is masked thus can stay in nucleus.

Dephosphorylation of STAT1—Loss of DNA binding affinity—Exposure of NES
→ Cargo of Exportin (ex. Crm1)

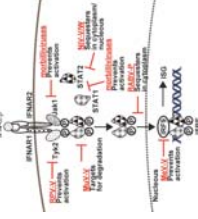


COUNTERACTION!

Accessory proteins PIVM/C can act as an inhibitor of the IFN pathway

✓ STAT

✓ can bind to Tyk2, Jak1, IRF9 ?



Work as an important factor to determine viral host tropism

Measles virus entry

Entry of Measles Virus

Paramyxoviridae Morbillivirus

negative strand RNA

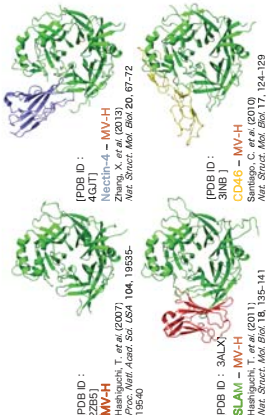
Two glyco proteins located at envelope membrane are important

Receptor binding (hemagglutinin) H protein)

Fusion (F) protein

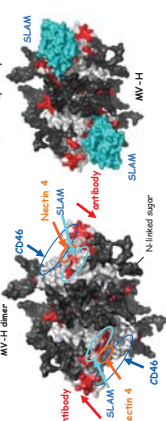


Crystal structures of MVH-receptor complex



Why is vaccination so effective (MV)?

relationship between glycosylation and antibody/receptor binding sites



- ✓ Extensive masking by sugars limits the availability of potential epitopes on the surface of MVH for antibody recognition
- ✓ Accessible regions include the highly conserved SLAM-binding site, which is crucial for MV entry
- ✓ Ensure the production of effective neutralizing antibodies during vaccination

A member of the family Paramyxoviridae

- measles virus
- canine distemper virus
- mumps virus
- peste-des-pestis-ruminants virus (羊痘ウイルス)
- phocine distemper virus (アザラシジステンバウイルス)

Hemagglutinin(H)

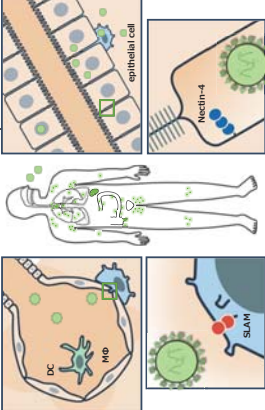


Fusion Protein (F)

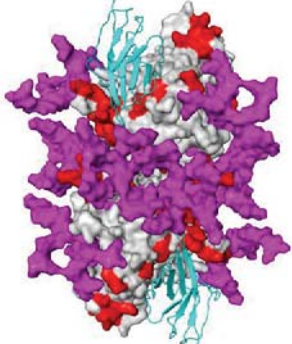
Enveloped virus with a nonsegmented, negative-strand RNA genome

Vaccination has been successful

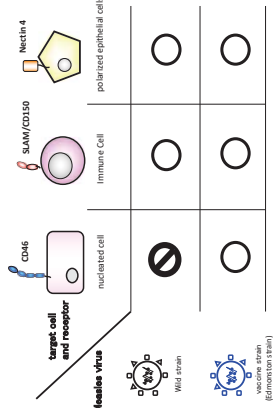
Infection route and receptors



RED; epitope regions of neutralizing antibodies

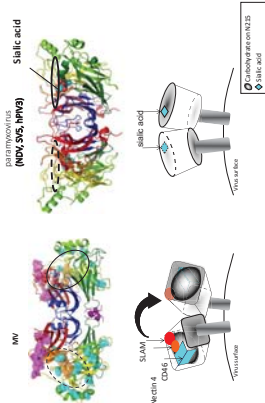


All receptors for Measles virus

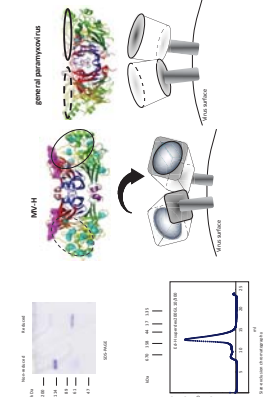


Yong Y et al. Curr Top Microbiol Immunol 2008

Dimerization manner is unique



Dimerization manner is unique



Why is the vaccination so effective (MV and CDV)?