資　料 1

新型インフルエンザウイルス出現のメカニズムと対策

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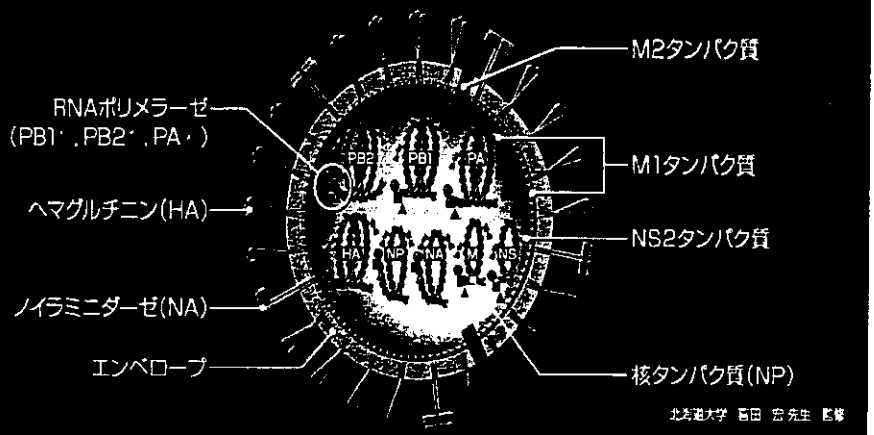
喜田　宏

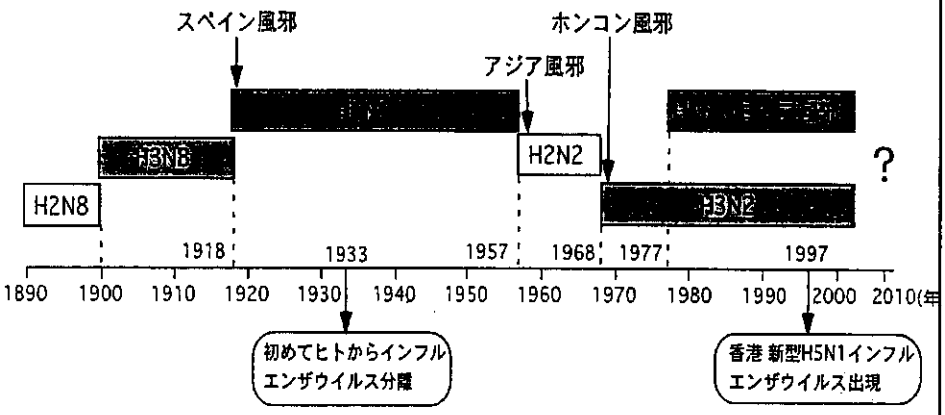
インフルエンザウイルスの構造模式図



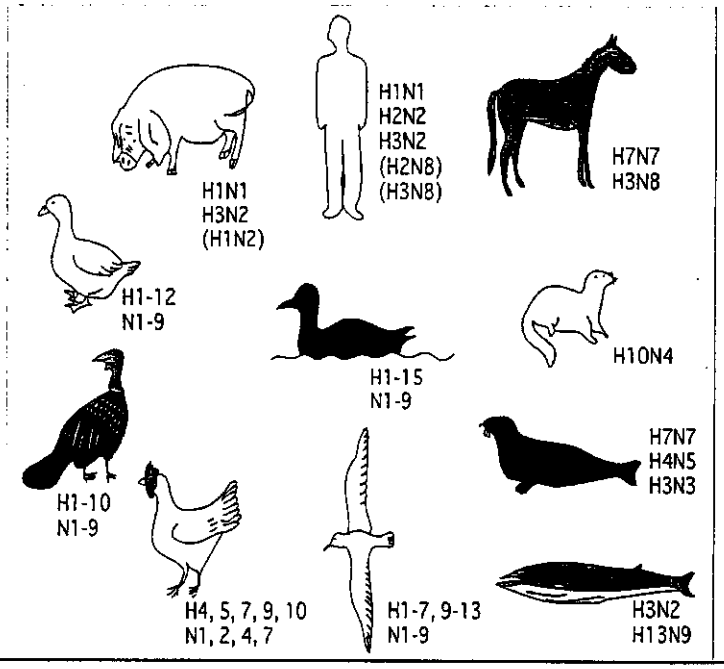
ヘマグルチニン(HA)の役割：気道上皮細胞表面のシアル酸レセプターに結合し、ウイルスの細胞内への侵入に与る。

ノイラミニダーゼ(NA)の役割：ウイルスが細胞内で複製して細胞質膜から発芽して成熟・遊離する時に、HAとNAに結合しているシアル酸糖鎖を切断し、感染細胞からウイルスを遊離させる。遊離した個々のウイルスは他の細胞に伝播して感染を拡大する。

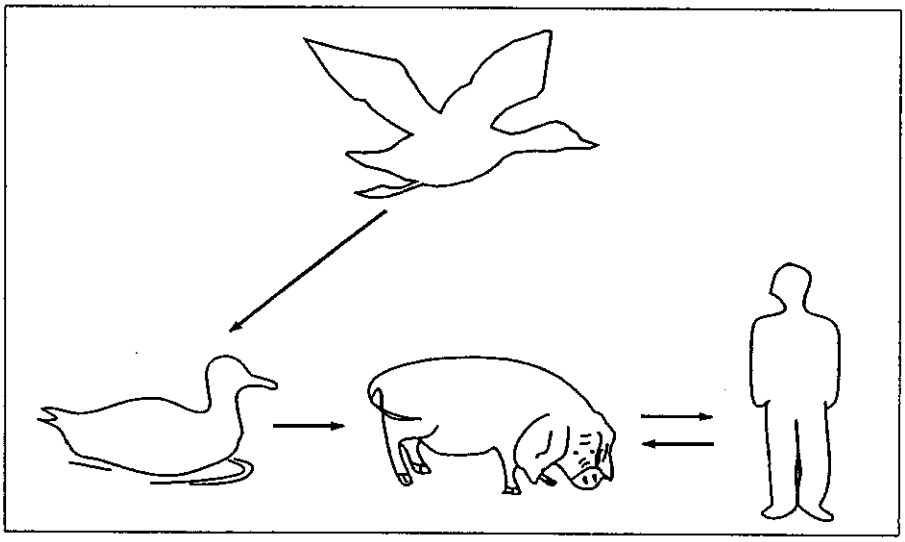
２０世紀に出現した新型インフルエンザウイルス

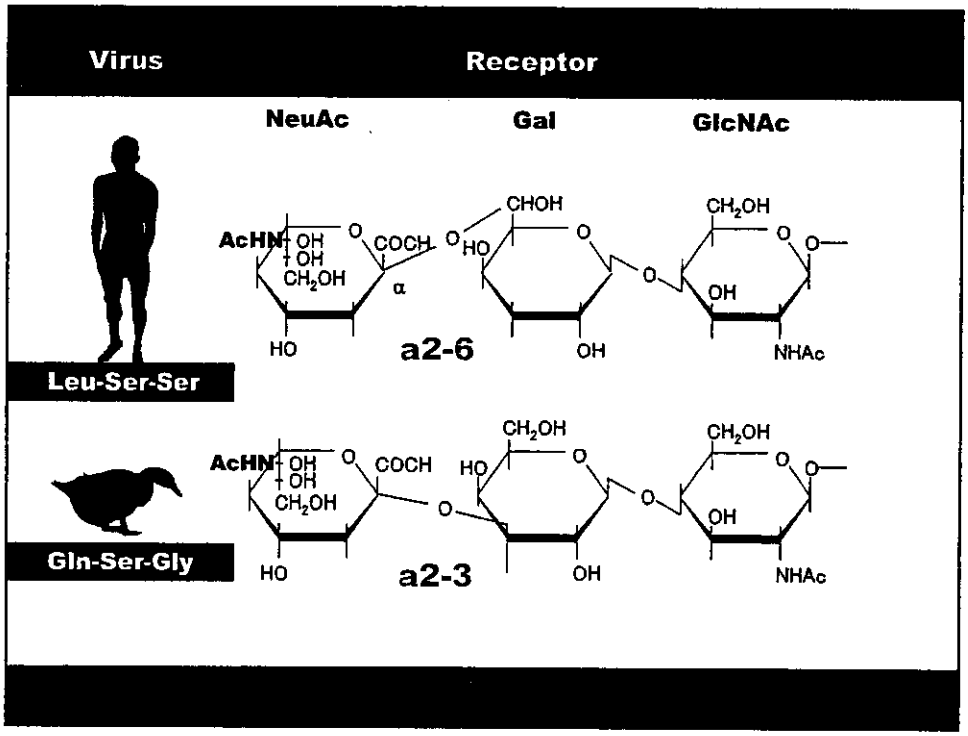


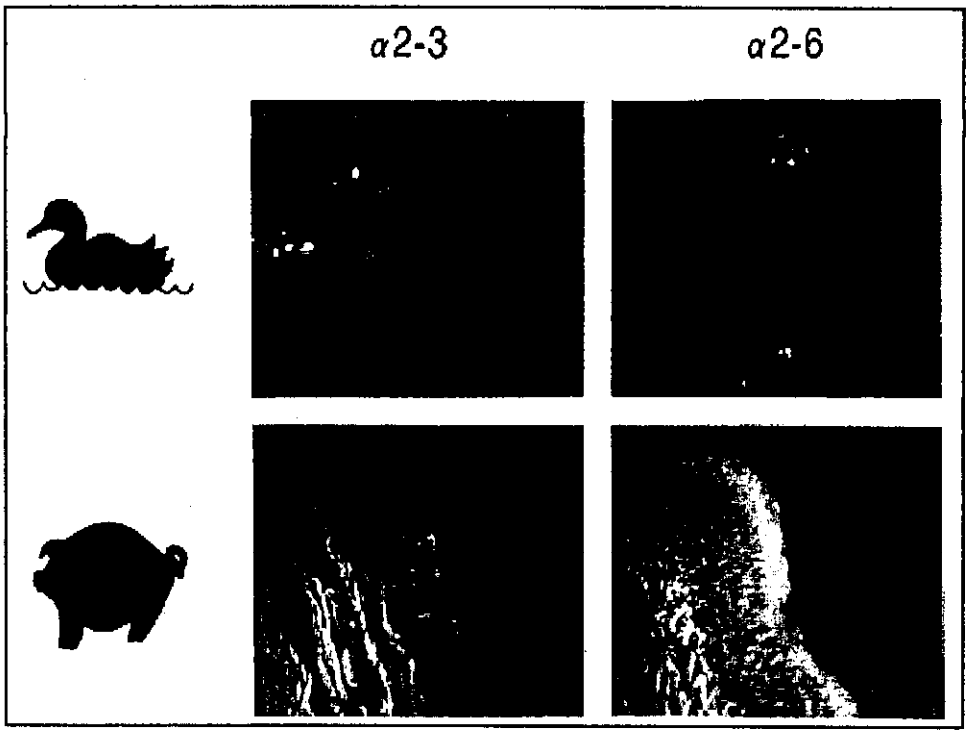
インフルエンザAウイルスの宿主動物とHAおよびNA抗原亜型の分布

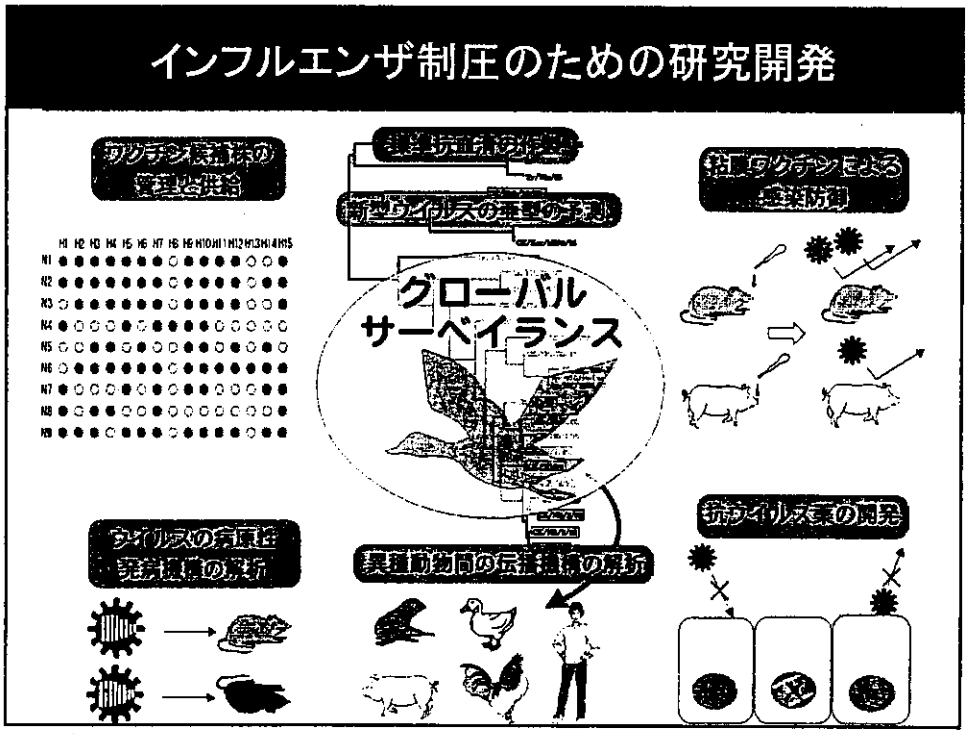


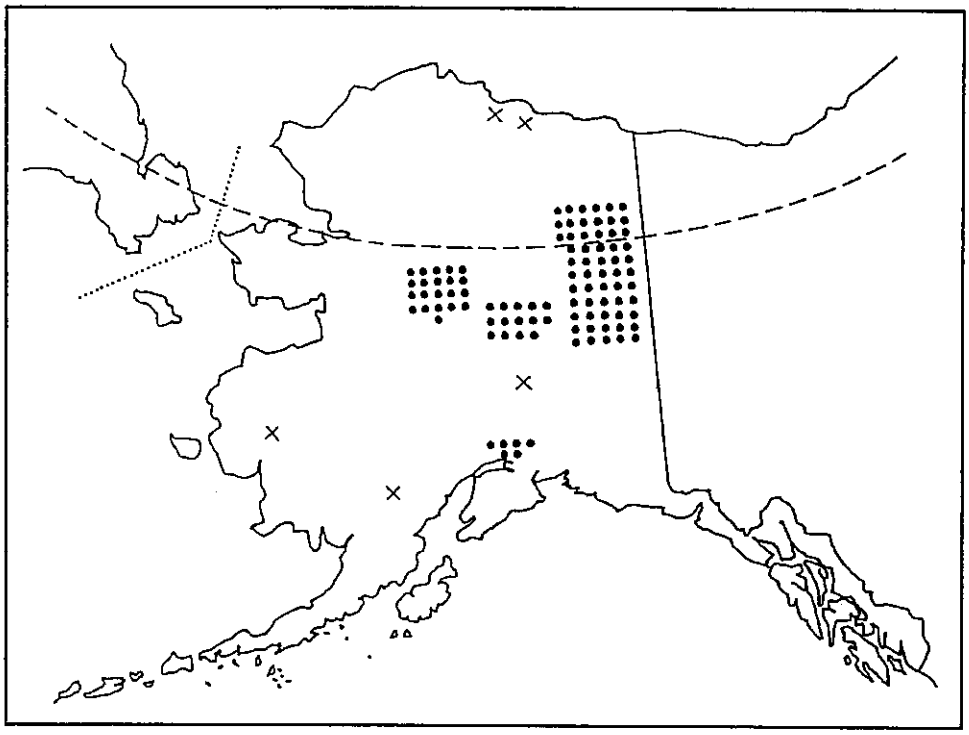
A/Hong Kong/68(H3N2)インフルエンザウイルスのHA遺伝子の導入経路

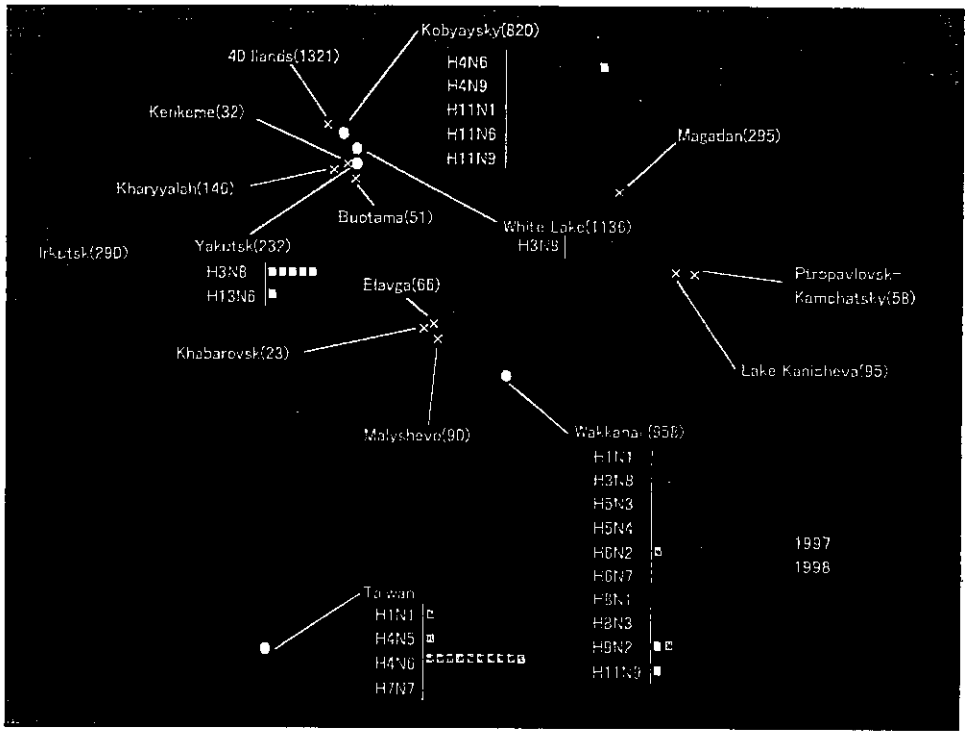


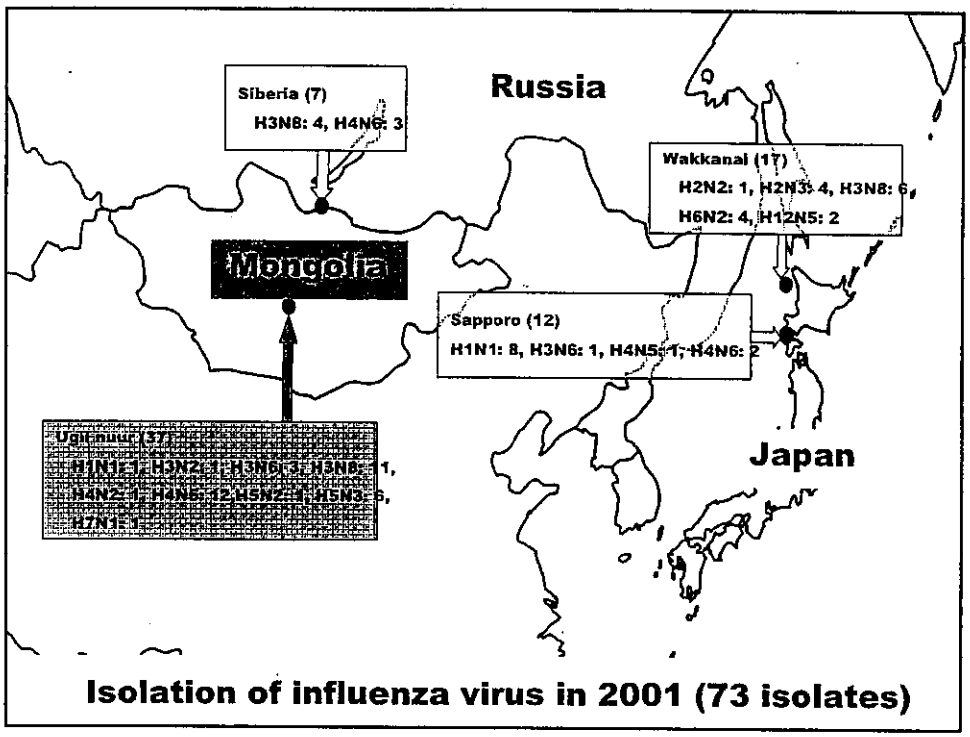



α2-3
α2-6

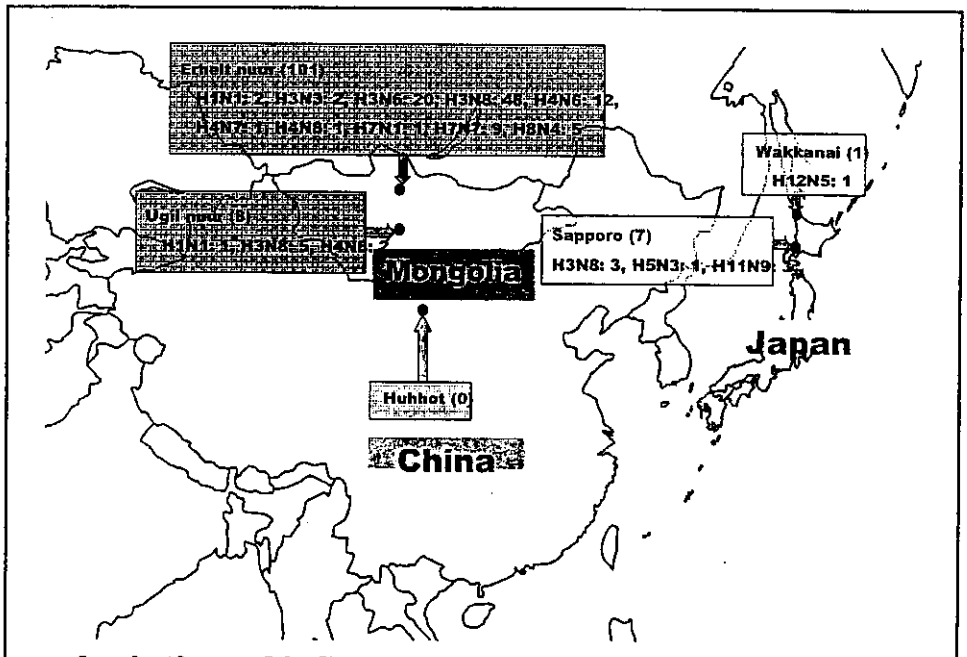

インフルエンザ制圧のための研究開発
ワクチン候補株の
管理と供給
新型ウイルスの出現の予測
グローバル
サーベイランス
粘膜ワクチンによる
感染防御
ウイルスの病原性
発育機構の解析
異種動物間の伝播機構の解析
抗ウイルス薬の開発




Kobyaysky(820)
H4N6
H4N9
H11N1
H11N6
H11N9
40 Islands(1321)
Kenkeme(32)
Magadan(295)
Kharyyalah(140)
Buotama(51)
White Lake(1136)
H3N8
Irkutsk(290)
Yakutsk(232)
H3N8
H13N6
Etavga(66)
Petropavlovsk-
Kamchatsky(58)
Khabarovsk(23)
Lake Kanicheva(95)
Malyshevo(90)
Wakkanai (958)
H1N1
H3N8
H5N3
H5N4
H6N2
H6N7
H8N4
H8N3
H9N2
H11N9
1997
1996
Taiwan
H1N1
H4N5
H4N6
H7N7



Isolation of influenza virus in 2001 (73 isolates)



Isolation of influenza virus in 2002 (117 isolates)

Background

- H1 to H15 and N1 to N9 subtypes of influenza A viruses are in ducks.
- 1957 H2N2 and 1968 H3N2 viruses are reassortants between avian viruses of Eurasian lineage and the preceding human strains, and even 1918 H1N1 Spanish influenza virus is probably a reassortant generated in pig between avian virus of North American lineage and human strain.
- The avian virus genes from the Eurasian gene pool are in southern China.
- Pigs are susceptible to each of the HA subtypes avian influenza viruses and generate reassortants.

→ Avian viruses of any subtype can contribute genes for reassortants.

→ None of the 15 HA and 9 NA subtypes can be ruled out as potential candidates for future pandemics.

The aims of the project

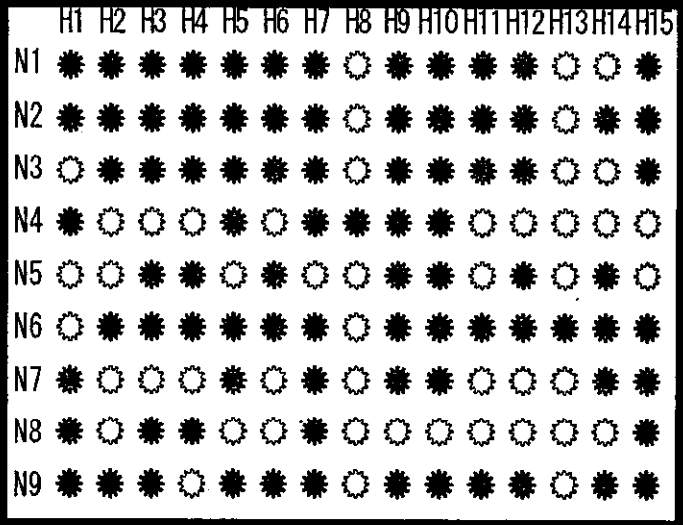
- To share viruses, reagents, methodologies for rapid characterization of isolates, and genetic information obtained at regular intervals.
- To provide virus strains for vaccine preparation and diagnostic purposes.
- To attempt to define the gene sequences permitting interspecies transmission of avian influenza viruses to mammals.
- To develop new technologies for rapid diagnosis based on microarray technologies, antigen detection method using immuno-PCR, and/or nanotechnology.

Present status of the library of vaccine strain candidates

Influenza viruses of 49 combinations of HA and NA subtypes have been isolated from fecal samples of ducks in Alaska, Siberia, Mongolia, Taiwan, China, and Japan

So far, more than 37 other combinations have been generated by genetic reassortment in the laboratory. Thus, avian influenza viruses of 86 combinations of HA and NA subtypes have been stocked as vaccine strain candidates. Their pathogenicity, antigenicity, genetic information and yield in chicken embryo have been analyzed

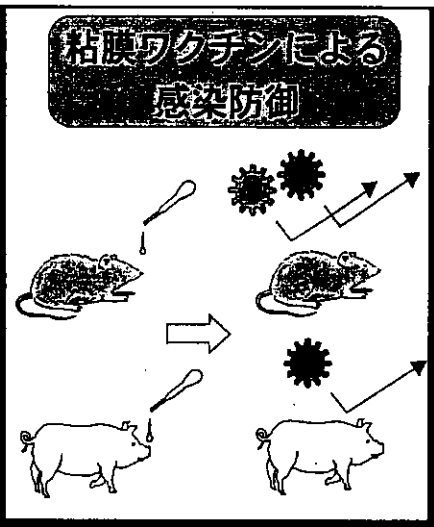
All of the 135 combinations will become available soon



Influenza A viruses of 86 combinations of HA and NA subtypes

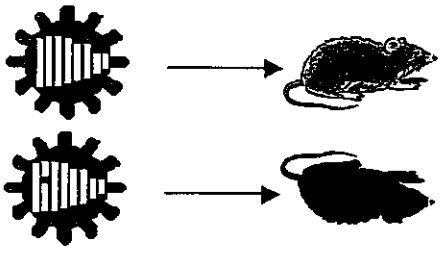
Field isolates of 50 combinations of HA and NA subtypes are shown in black. 36 combinations shown in red are reassortants generated in the laboratory. Thus, avian influenza viruses of 86 combinations of HA and NA subtypes have been stocked as vaccine strain candidates.

粘膜ワクチンによる感染防御



- 不活化インフルエンザウイルス全粒子をマウスおよびブタの鼻腔内に与えると、呼吸器粘膜局所の分泌型 IgA抗体ばかりでなく、血中の IgG 抗体の産生をも誘導する。
- 抗原性が異なる強毒株の攻撃に対する感染防御免疫をも賦与する。
- 抗原提示メカニズムが明らかになった今、HAワクチンは優れているといえるか？
- 注射によるワクチン接種は安全か？

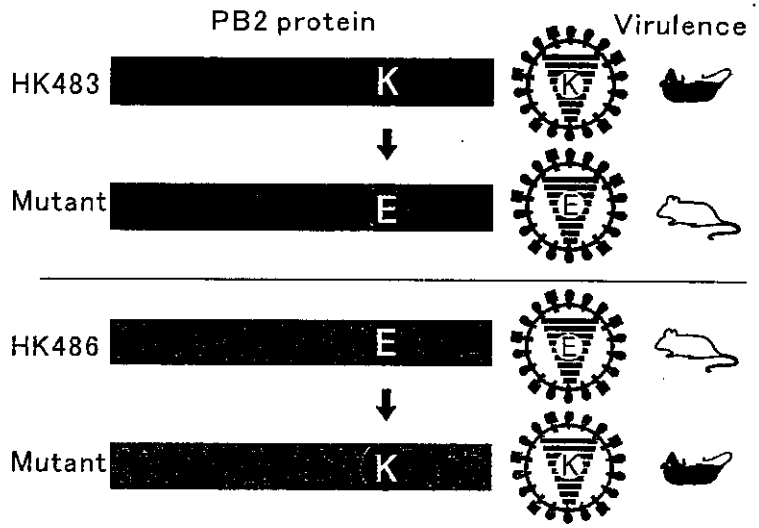
ウイルスの病原性発病機構の解析



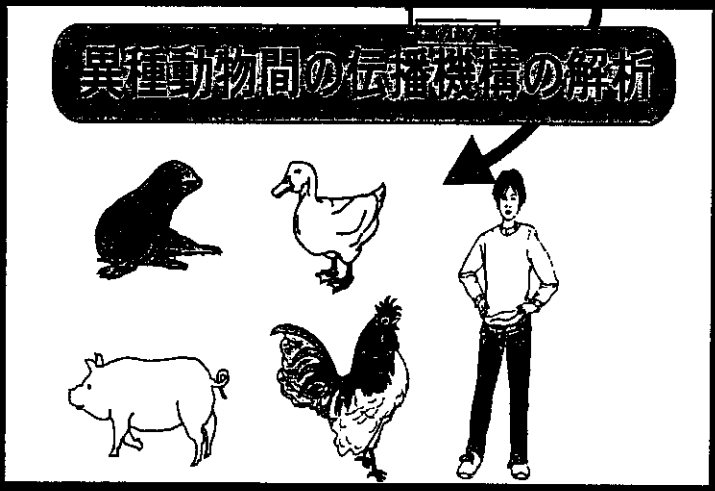
香港H5N1インフルエンザウイルスの病原性に
PB2 蛋白分子の627番アミノ酸が関与

香港H5N1インフルエンザウイルスの病原性

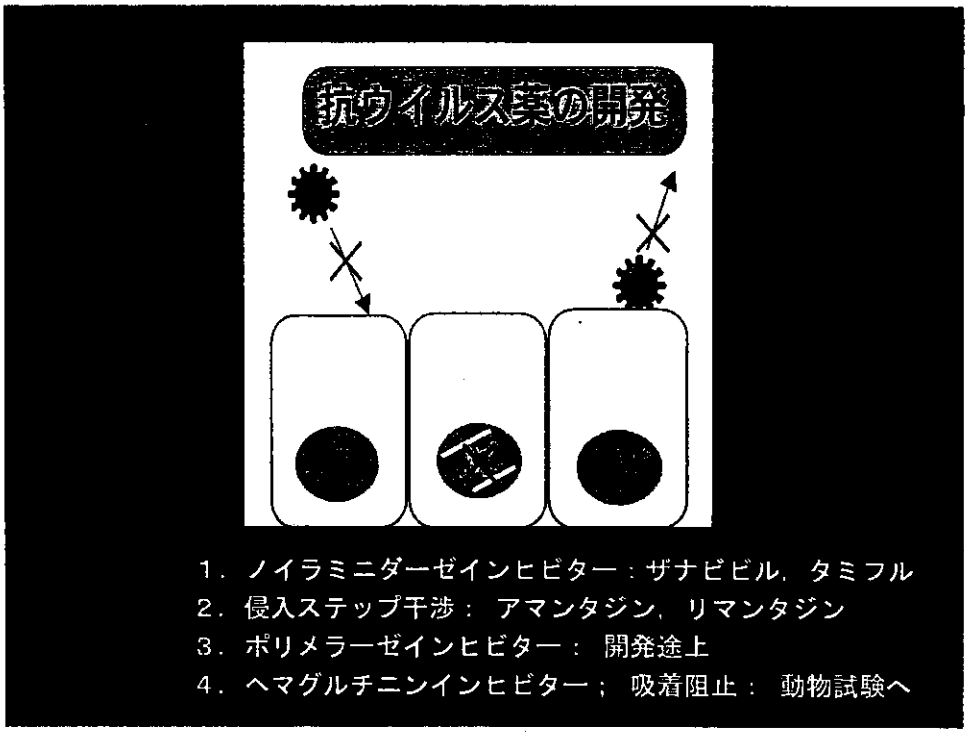
河岡義裕 (東京大学医科学研究所)



Hatta M, Gao P, Halfmann P, Kawaoka Y. **Science** 298:1840-1842, 2001.



1. レセプター特異性
2. ウイルス蛋白のpH抵抗性

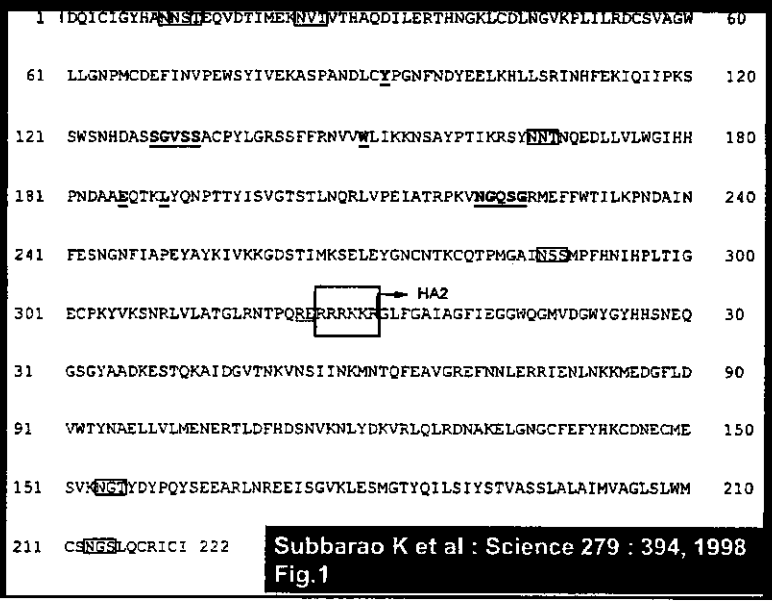

抗ウイルス薬の開発
1．ノイラミニダーゼインヒビター：ザナビビル，タミフル
2．侵入ステップ干渉： アマンタジン，リマンタジン
3．ポリメラーゼインヒビター： 開発途上
4．ヘマグルチニンインヒビター； 吸着阻止： 動物試験へ

Amino acid sequences at the cleavage sites of influenza A virus HAs

Subtype sequences	Strains	Amino acid ↓
H1	Dk/Alberta/35/76(H1N1)[b]	IQSR GLF
H2	Mal/MT/Y61(H2N2)[b]	IESR GLF
H3	Dk/Menphis/928/74(H3N8)[b]	KQTR GLF
H4	Dk/Czechoslovakia/56(H4N6)[b]	KASR GLF
H5	Ck/Scotland/59(H5N1)[b]	**RKKR GLF**
H5	Ty/MN/3/92(H5N2)[a]	RETR GLF
H6	Shw/Australia/1/72(H6N5)[b]	IETR GLF
H7	FPV/Rostock/34(H7N1)[b]	**KKRKKR GLF**
H7	Mal/Alberta/195/89(H7N3)[a]	KKTR GLF
H8	Ty/Ontario/6118/68(H8N4)[b]	VEPR GLF
H9	Ty/Wisconsin/66(H9N2)[b]	RSSR GLF
H10	Ck/Germany/N/49(H10N7)[b]	VQGR GLF
H11	Dk/England/56(H11N6)[b]	IASR GLF
H12	Dk/Alberta/60/76(H12N5)[b]	VQDR GLF
H13	Gl/Maryland/704/77(H13N6)[b]	ISNR GLF
H14	Mal/Gurjev/263/82(H14N5)[b]	KQAK GLF
H15	Shw/Australia/2576/79(H15N9)[b]	IRTR GLF

Senne et al, 1996[a], Kovacova et al, 2002[b]

Amino acid sequence of the H5 HA of A/Hong Kong/156/97(H5N1)



Subbarao K et al : Science 279 : 394, 1998
Fig.1

Pathogenicity of influenza virus

1. Cleavability of the HA protein into HA1 and HA2 is crucial and consecutive alignment of basic amino acids (R and K) at the cleavage site relates to the pathogenicity for chicken.

   Cleavage activation of the HA by ubiquitous protease

   → penetration by fusion into host cell

   → extensive replication → systemic infection

2. Amino acid constitution of PB2 protein and NA protein are also related with pathogenicity of the virus for mammals.