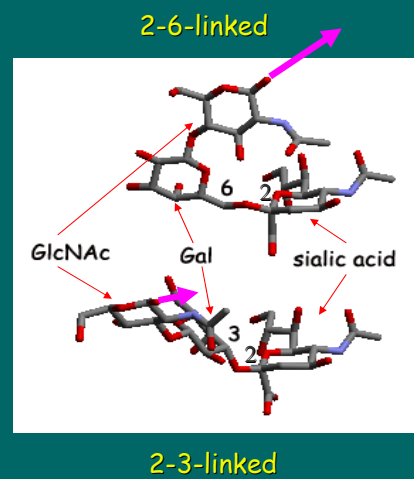
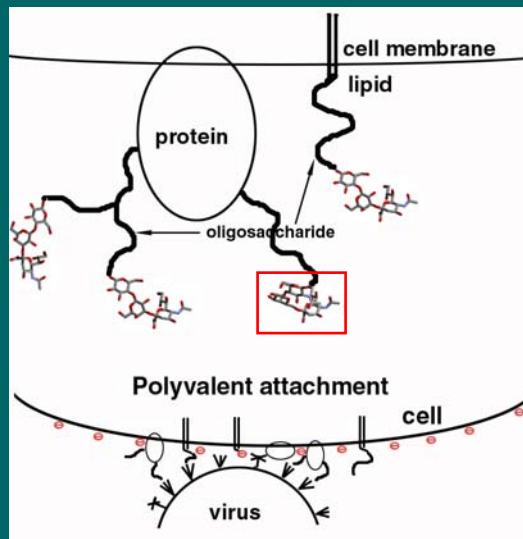


# Receptor specificity and host range

Mikhail Matrosovich

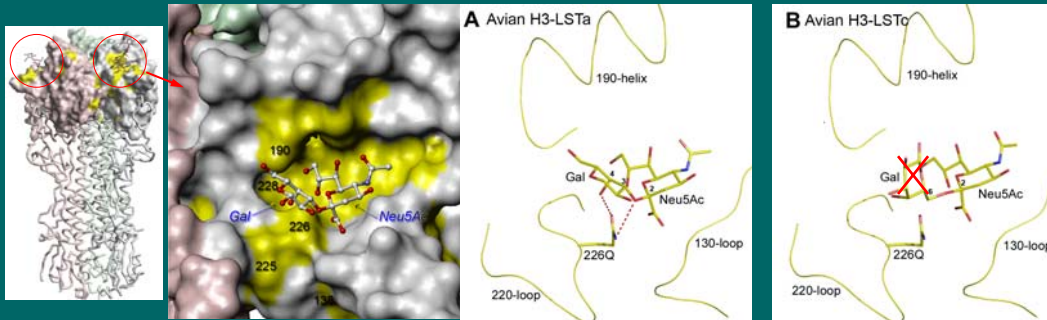
*Institute of Virology, Philipps University,  
Marburg, Germany*

## Cell-surface receptors of influenza viruses



## Receptor specificity of avian viruses

- Most viruses bind to 3-linked and do not bind to 6-linked Neu5Ac
- Expression of Neu5Ac2-3Gal in the duck intestine (*Ito et al., 1998*)
- Receptor-binding site (RBS) is highly conserved among HA subtypes



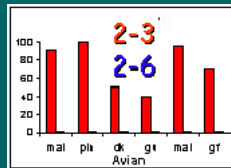
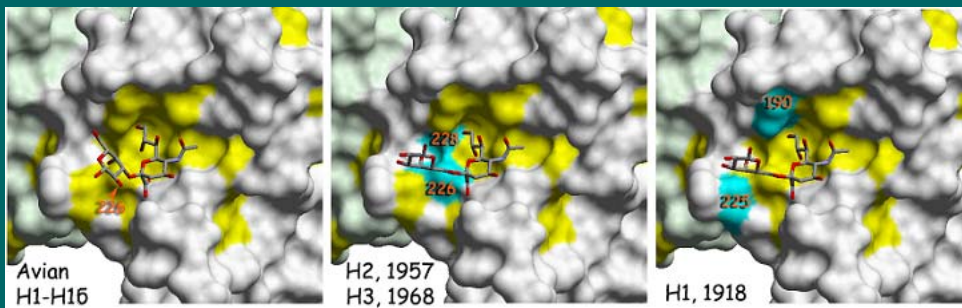
HA trimer

- Binding to both Neu5Ac and 3-linked Gal (Gln226) - Poor fit of 6-linked Gal  
 (*Ha et al., 2001,2003; Gamblin et al., 2004; Matrosovich et al., 1997,2000*)

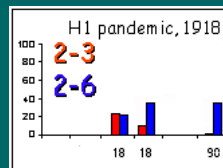
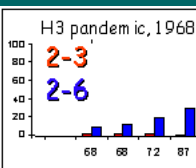
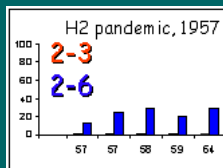


## The earliest pandemic strains from 1918, 1957, and 1968 carried mutations in the RBS and preferentially bound to 6-linked receptors

(*Connor et al., 1994; Matrosovich et al., 2000; Glaser et al., 2005*)



Avian viruses



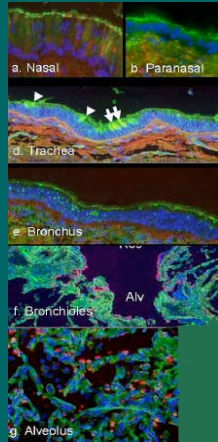
Pandemic viruses



# Receptors and viral tropism in human respiratory tract

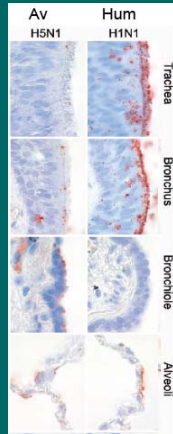
## Binding

Lectins 2-6 (green), 2-3 (red)



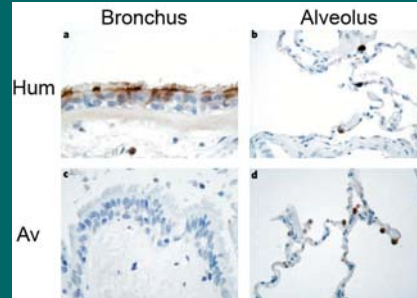
*Shinya et al., 2006*

Viruses

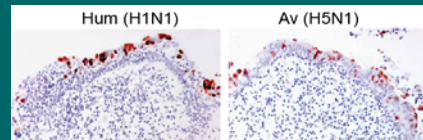


*van Riel et al., 2007*

## Infection ex vivo



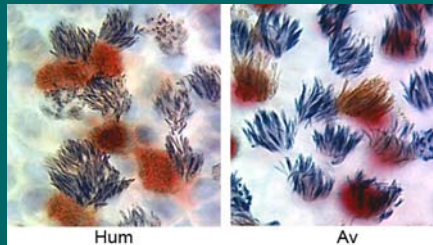
*Shinya et al., 2006*



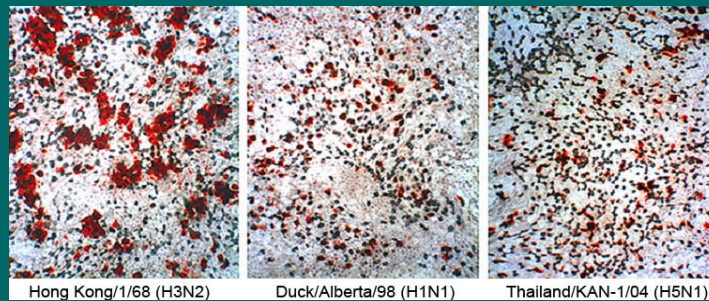
*Nicholls et al., 2007*

# Infection in differentiated airway epithelial cultures

8 h PI



24 h PI

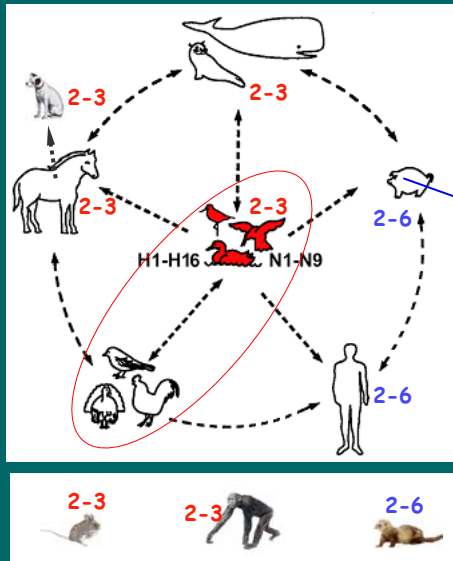


Hong Kong/1/68 (H3N2)

Duck/Alberta/98 (H1N1)

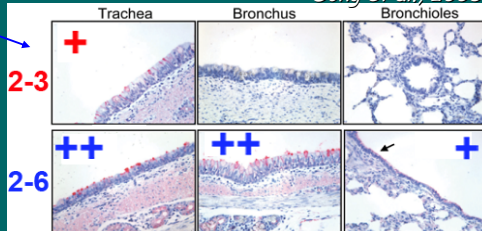
Thailand/KAN-1/04 (H5N1)

## Receptors in mammals



2-3: horse, sea mammals, dogs, cats; mice and monkeys. Receptors may not be identical to those in aquatic birds.

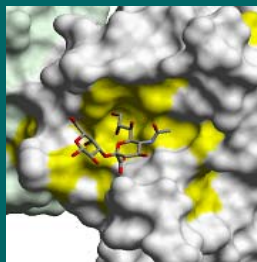
*Song et al., 2008*



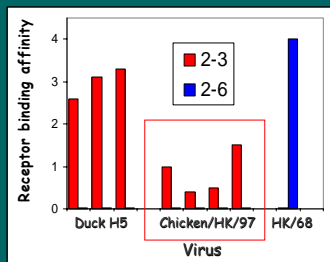
2-6: pigs; ferrets. Alteration of the receptor specificity of the avian virus in pigs may facilitate its transmission to humans (*Ito et al., 1998*)



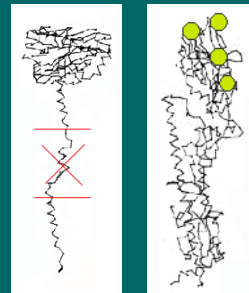
## H5N1 "bird flu" viruses in Hong Kong, 1997



No key changes in the RBS



Reduced affinity for 3-linked receptors



NA

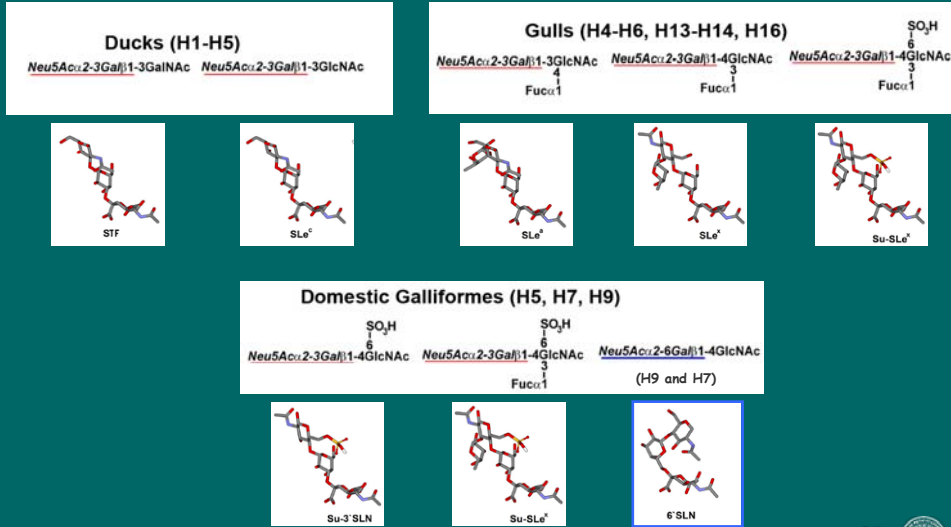
HA

Typical changes in H5 and H7 viruses from Galliformes



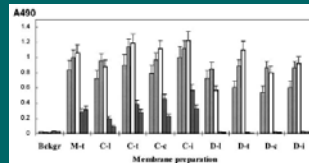
# Fine receptor specificity of avian viruses

(Gambaryan et al., 2002-2008)

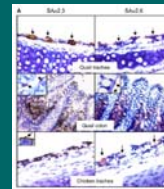


# Unlike ducks, chicken and quail express human-type receptors

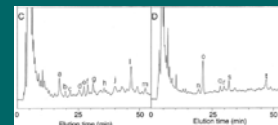
Arch Virol (2002) 147: 1197–1208  
**Differences between influenza virus receptors on target cells of duck and chicken**  
 A. Gambaryan<sup>1</sup>, R. Webster<sup>2</sup>, and M. Matrosovich<sup>1,2</sup>



Virology 346 (2006) 278 – 286  
**Quail carry sialic acid receptors compatible with binding of avian and human influenza viruses**  
 Hongquan Wan, Daniel R. Perez<sup>\*</sup>

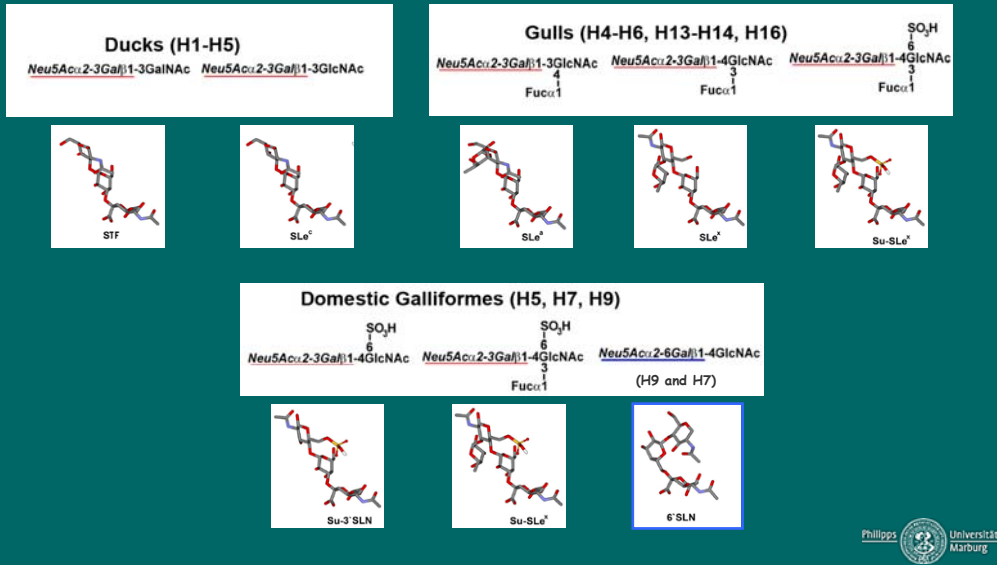


Glycobiology vol. 17 no. 7 pp. 713–724, 2007  
**The quail and chicken intestine have sialyl-galactose sugar chains responsible for the binding of influenza A viruses to human type receptors**  
 Chao-Tan Guo<sup>1,2,3</sup>, Noriko Takahashi<sup>1,4,5</sup>, Hirokazu Yagi<sup>1,6</sup>, Koichi Kamada<sup>1,7</sup>, Tadatsubu Takahashi<sup>1,8</sup>, Shuang-Qin Yi, Yong Chen<sup>1</sup>, Toshihiro Ito<sup>9</sup>, Koichi Otsuki<sup>10</sup>, Hiroshi Kida<sup>11</sup>, Yoshihiro Kawano<sup>11,13</sup>, Kazuya I-P Jwa Hidar<sup>1,2</sup>, Daisei Miyamoto<sup>1,2</sup>, Takashi Suzuki<sup>1,2</sup>, and Yasuo Suzuki<sup>1,2,4</sup>



# Fine receptor specificity of avian viruses

(Gambaryan et al., 2002-2008)

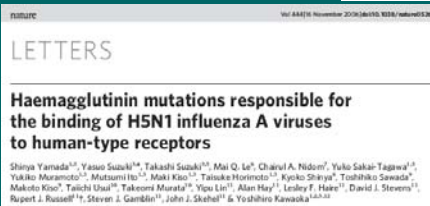


# "Humanizing" mutations in the RBS of human H5N1 isolates

- S227N (2003)

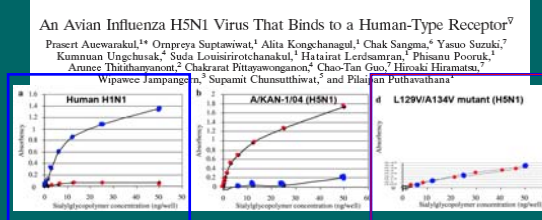


- N186K + Q196R,  
- Q192R + S227N



- L133V + A138V

An Avian Influenza H5N1 Virus That Binds to a Human-Type Receptor<sup>7</sup>



## Summary 1

- Receptor specificity of influenza viruses correlates with expression of receptor moieties on target cells.
- Human respiratory epithelium contains avian-type receptors and can be infected with avian viruses. However, paucity of avian-type receptors in upper airway may limit human-to-human transmission.
- Presence of avian-type receptors in the human bronchioles and alveoli might contribute to high pathogenicity of avian viruses.

## Summary 2

- Receptor specificity of influenza viruses is not limited to recognition of 2-3 and 2-6 linkages. Viruses of different avian species differ in their fine receptor specificity. Viruses of some birds could have enhanced propensity for interspecies transmission to other birds and to mammals.
- Human-type receptors (Neu5Ac2-6Gal) are present on epithelial cells of galliformes; evolution of viruses in these species may increase binding to receptors in humans.