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Development of robust vaccine and antiviral drug against fictively mutated influenza virus H1N1

Project Description

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The actual new influenza (swine influenza) virus H1N1

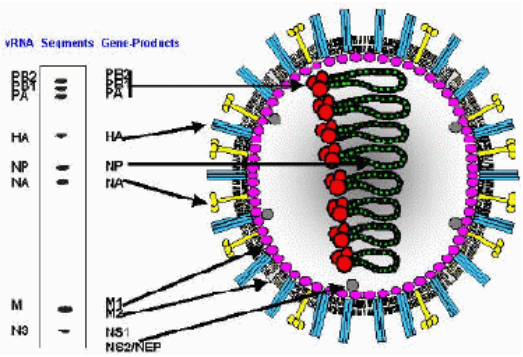

Fig.1: The influenza-A virion. HA (Haemaglutinin) und NA (Neuraminidase) are the characterizing proteins of a influenza A type virus. H1N1 has a HA protein of the type 1 and a NA Protein also of the type 1.

Contstraints for a pandemia in human civilization

For a pandemia under humans the following things must be given:

- Most humans don't have an immunity against this virus,
- The virus can replicate itsself effectively in human body
- A fast expansion of the virus in human population by human-to-human propagation

For the actual H1N1 virus these constraints are given, but actually the disease pattern is not to harmful. But if the virus mutates the disease pattern could evolve much more serious. For example the pandemia of the Spanish influenza after the world war I killed about 20 Mio. People. It was also a H1N1 influenza virus.

Disease pattern of fictively mutated H1N1 mutated virus

If the virus mutates so that it includes sequences like H1N1 viruses of former serious pandemia outbreaks, the disease pattern would propably much more serious. It must be undergone a literature research and analysis which patterns are actual not in the new H1N1 but were in former H1N1 serious outbreaks and were known to be responsible for specific disease pattern.

Project definition

To be ready for an potential outbreak, there must be developed two things:

- An antiviral drug for persons, which have been infected with this virus. This could also be antibodies produced by animals which have been infected intentionally by such fictively mutated virus
- A vaccine for people who still didn't have been infected in the time

So the project includes the following working packages

1. Identification of harmful mutations
2. Design and Production of a robust vaccine against a fictive mutated H1N1
3. Design and production of a robust antiviral drug against this fictive mutated H1N1

Identification of harmful mutations

Shall be done by literature recherche.

Design and Production of a robust vaccine against a fictive mutated H1N1

It must be designed a H1N1 where the harmful sequence parts are disactivated, but recognized by the immune system, such that the immune system recognizes it and produces antibodies. Because it a to high risk to use the whole designed virus which could get out of control only specific protein parts shall be reproduced by plasmid vectors in E.coli and purificated afterwards. These purificated proteins shall be the vaccination agents.

Steps:

1. Insertion of a harmful sequence part into the actual H1N1 virus by insertion/deletion technique

2. Propagation of the designed virus.

3. Disactivating the harmful sequence by point mutation.

4. Propagation of the designed virus from 3.

5. Testing chain: A. Feed several animals the virus from 2. Where the insertion has been successful, the animals are expected to become very ill or die. B. Take this virus and undergo treatment of 3 and propagate the virus C. Feed several animals with the virus of 4. Some animals now don't get ill, but produce antibodies against the virus of 2. D. This is tested by giving them the virus of 2.

6. From the result virus there are cut out RNA sequences of proteins and put into plasmids (as cDNA), and then propagated and expressed (to proteins) in E.coli.

7. The viral proteins are purificated.

8. The purificated proteins are tested as vaccination in the test chain (see 5. (instead of whole virus now the purificated proteins are used for vaccination))

Used methods: Recombination of viral RNA, cell based/egg based viral propagation, animal experiment (vaccination), protein purification

Design and production of a robust antiviral drug against this fictive mutated H1N1

1. Identification of harmful active sites at proteins of the fictive virus (with the harmful not inactivated sequence parts)
2. Design of a drug for one of the active sites, wich blockes the whole virus from docking to a cell: identifying candidates by docking of by homology modeling predicted drug (similar to Tamiflu and others) into the active site. The 3 D structure of the active site is also computed by homology modeling.

Used methods: Computational Biology (Homology Modeling, Docking with a IGEEH developed Lagrangian Multiplier Algorithm)), Rational Drug Design