Lesson 11

Final Project Startup
Final Project

- From sequence to model
  - HA or NA
- Biological question
  - Vaccine design
  - Drugs
  - Escape mutants
- Choose sides!
  - Virus versus human
- Poster
  - Presentation
Final Project Assessment

- Group poster presentations
  - All group members present the work and answer questions.

- Question for another group (buddy group)

- Individual oral exam starting from posters
  - May 22\textsuperscript{nd} and 29\textsuperscript{th}.
"Coming together is a beginning, keeping together is progress, working together is success".

Henry Ford
During the whole development of the space program, Larry had not contributed with anything whatsoever, and he knew that this was his absolutely last chance.

Stop! Stop! Don’t just push the button! Ehhh… Count down first! Yes! Countdown! That’s a good idea! Otherwise it will never make it to the Moon! Never!
Group Work & Rules

- Define your group
  - 2-4 members
- Establish a group name and a logo
- Discuss roles within your group based on the profiles of the individual members
- Agree on a written set of rules for:
  - Meetings
  - Conflict resolution
  - Decision making
  - Communication

Feed in potential conflicts
Feed in any good/bad group experiences
Handin of Project

- Deadline: Monday May 6\textsuperscript{th} at noon!

- For printing posters: Small fee (?)
  - Exact amount to be announced on CampusNet.
  - Or print it yourself…
Project Contents
From Sequence to Hypothesis

- Simple homology modelling
  - Modelling with a template

- Fold recognition and other sequence predictions
  - Working without a template

- Presenting the model

- Generating a hypothesis

- Produce testable conclusions
Homology Modelling

- HHpred or CPHmodels
  - Single or multi-template models
- Selecting a template
  - The three Rs
  - Template versus model properties/biology
  - Model validation
    - ProQ, Anolea etc.
Sequence Features

- The template-less regions
  - Secondary structure
    - PsiPred
  - Signal peptide
    - SignalP
  - Transmembrane helices
    - TMHMM, Phobius
  - Modification sites
    - NetNGlyc
  - Intrinsic protein disorder
    - DisEMBL, IUpred
Model Overview

- Generate complete model
  - Multimers and crystal symmetry

- Show general properties
  - Secondary structure
  - Active site/binding pocket
  - Indicate missing parts
  - Modifications
    - Glycosylation, cleavage etc.
Generating a Hypothesis

- Decide on project goal
  - Drug design, virus evolution, vaccine design etc.

- Graft ligands into/onto model from real structures

- Analyse interactions
  - Site chain mutagenesis/reorientation
  - Drug modifications
  - Electrostatics (surfaces)
  - Sequence/structure conservation (ProtSkin)

- Suggest changes & propose outcome

- Take suggestions to a biologist/chemist 😊
Project Topics

- HA or NA

- Your Favourite Protein
  - Special projects (typically related to master thesis or Ph.D. work)

- All projects need my approval!
Articles

- See HA & NA folder on CampusNet under Reading material.

- If you are having trouble getting a paper, let me know, and I will do my best to get it for you.
Bird Flu Is Still Here…
Urgent Warning On New Bird Flu H7N9: Could Pose Global Threat

As new death reports come in, a team of experts from China published a scary report yesterday in the New England Journal of Medicine (NEJM) suggesting that the new H7N9 avian flu virus is even more deadly than previously believed.

The conclusions: H7N9 causes unusually severe respiratory infection, sepsis and brain damage, and appears to be resistant to vaccination and treatment.

But here’s where it gets really worrisome. In a commentary on “global concerns” pertaining to H7N9, also in the NEJM, influenza experts Timothy Uyeki, MD and Nancy Cox discuss the potential of H7N9 to cause a pandemic (a fast-moving global epidemic) and warn that this possibility is real.

Given the severity and speed with which H7N9 is Infecting and killing people, Uyeki and Cox write, “It is possible that these severely ill patients represent the tip of the iceberg and that there are many more as-yet-undetected mild and asymptomatic infections.”

With today’s toll now at 11 deaths and 43 people infected, the threat is getting real.

Previously, concerns about H7N9 centered primarily around whether the virus was capable of human-to-human transmission. Because cases were limited to one area of China and because this type of avian flu appeared to be transmitted solely from bird to human, experts were telling us not to worry, that it should be possible to contain.

However, as early as last week, the CDC warned about the possibility of the virus continuing to mutate in ways that could make it more and more dangerous.
What the Researchers Found

In an analysis of the virological data and circumstances surrounding the first three fatalities, a large team of Chinese researchers found that the patients became ill quickly, developed very severe pneumonia and upper respiratory distress, and their condition deteriorated very quickly with sepsis and failure of multiple organs. Particularly worrying is that two of the three developed encephalopathy, or infection of the membrane surrounding the brain.

Some of the background information in the report also offers reason for concern. Yes, all three of the victims had previously existing health conditions; one had COPD, and two had hepatitis B. One was obese. But while one patient was 87, the other two were only 27 and 35. And while two of the three had had contact with poultry in the weeks before falling ill (one was a butcher, the other had been in a poultry shop), one had no record of contact with birds.
Why Experts Are So Worried

The NEJM report contained extensive data and analysis of the genetic sequence of H7N9 and the history of development of H7 viruses. Here are just a few of the conclusions that might make your hair stand on end:

1. **Infected chickens and other birds don’t show symptoms.** The H7N9 virus will infect chickens with asymptomatic illness, so that it spreads widely through poultry flocks without farmers’ knowledge. Quote: “H7N9 viruses are a low-pathogenic avian influenza A virus and that infection of wild birds and domestic poultry would therefore result in asymptomatic or mild avian disease, potentially leading to a “silent” widespread epizootic in China and neighboring countries.”

2. **The H7N9 spreads more easily to people than similar viruses.** Quote: “The gene sequences also indicate that these viruses may be better adapted than other avian influenza viruses to infecting mammals.”

3. **Vaccines developed for other H7 viruses aren’t effective.** Clinical trials so far have shown that vaccines developed against other H7 strains of influenza are showing extremely limited response against H7N9.
4. Existing flu tests in the U.S. won’t detect the H7N9 virus. Quote: “Since available diagnostic assays used in clinical care (e.g., rapid influenza diagnostic tests) may lack sensitivity to identify H7N9 virus and since existing molecular assays will identify H7N9 virus as a nonsubtypeable influenza A virus, critical public health issue is the rapid development, validation, and deployment of molecular diagnostic assays that can specifically detect H7N9 viral RNA.”

Reassuringly, the researchers go on to say that such a test has already been developed in China and is hopefully on the way here.

5. No Vaccine for months. While news reports have optimistically touted efforts to create a vaccine against H7N9, Cox and Uyeki warn that this will take many months to do. Chinese officials announced yesterday they expect to have a vaccine ready in 7 months.

This story is moving so fast that there’s too much to cover in one report. More to come. Please add your comments; would particularly welcome insights from virologists, immunologists and public health experts. And follow me on Twitter, @MelanieHaiken and subscribe to my posts on Facebook.
And We Might Need New Drugs…

CDC Statement on Oseltamivir (Tamiflu®) Resistance and Antiviral Recommendations

For Immediate Release: January 9, 2009
Contact: CDC Division of Media Relations (media), Phone: (404) 639-3286

On December 19, 2008, CDC issued interim guidance for health care professionals (http://www.cdc.gov/flu/professionals/antivirals/summary.htm) on the use of influenza antiviral medications (http://www.cdc.gov/flu/protect/antiviral/index.htm) this flu season. The guidance was issued in response to early data from a limited number of states indicating that a high proportion of influenza A (H1N1) viruses are resistant to the influenza antiviral medication oseltamivir (Tamiflu®). Worldwide, the proportion of H1N1 viruses that are resistant to oseltamivir has been increasing so this development is not surprising.
Influenza Virus Basics

- Neuraminidase
- Hemagglutinin
- RNA
- M₂ protein (only on type A)
The Two Mechanisms whereby Pandemic Influenza Originates.

In 1918, an H1N1 virus closely related to avian viruses adapted to replicate efficiently in humans. In 1957 and in 1968, reassortment events led to new viruses that resulted in pandemic influenza. The 1957 influenza virus (Asian influenza, an H2N2 virus) acquired three genetic segments from an avian species (a hemagglutinin, a neuraminidase, and a polymerase gene, PB1), and the 1968 influenza virus (Hong Kong influenza, an H3N2 virus) acquired two genetic segments from an avian species (hemagglutinin and PB1). Future pandemic strains could arise through either mechanism.
# Influenza Virus Variants

<table>
<thead>
<tr>
<th>Year and Country</th>
<th>Virus</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995, United Kingdom</td>
<td>H7N7</td>
<td>A/Eng/268/95</td>
</tr>
<tr>
<td>1997, Hong Kong</td>
<td>H5N1</td>
<td>A/HK/156/97</td>
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<tr>
<td></td>
<td></td>
<td>A/HK/148/97</td>
</tr>
<tr>
<td>1999, Hong Kong</td>
<td>H9N2</td>
<td>A/HK/1073/99</td>
</tr>
<tr>
<td>2003, Hong Kong</td>
<td>H5N1</td>
<td>A/HK/213/03</td>
</tr>
<tr>
<td>2003, the Netherlands</td>
<td>H7N7</td>
<td>A/Neth/33/03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/Neth/219/03</td>
</tr>
<tr>
<td>2003, Hong Kong</td>
<td>H9N2</td>
<td>A/HK/2018/03</td>
</tr>
<tr>
<td>2004, Vietnam</td>
<td>H5N1</td>
<td>A/VN/1203/04</td>
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<td></td>
<td></td>
<td>A/VN/1194/04</td>
</tr>
<tr>
<td>2004, Thailand</td>
<td>H5N1</td>
<td>A/Thai/16/04</td>
</tr>
<tr>
<td>2004, Canada</td>
<td>H7N3</td>
<td>NA</td>
</tr>
<tr>
<td>2004, Egypt</td>
<td>H10N7</td>
<td>NA</td>
</tr>
</tbody>
</table>

* H5 and H9 viruses have generally been associated with respiratory disease, whereas H7 has generally been associated with conjunctivitis. NA denotes not available.
The Poster

- A0 (1189mm x 841 mm)
- 1/3 for figures
- 1000 words max.
  - Keep the introduction short
  - IMRAD
- Printing
Poster Session

- Meet at **8.00 AM** in room 062

- Presentation
  - 15-20 minutes per group including questions/discussion.

- Buddy group questions
  - *Each group member* should formulate *one key question* to ask the buddy group at the poster session.

- Buddy groups will be announced on CampusNet one week before the poster session.
Oral Exam

- **The exam:**
  - Brief project presentation (3-4 minutes; from A4 print of poster).
  - Discussion of various aspects of your project. Questions can fall within any topic covered by the course curriculum.

- **NOTE:** *The total examination time including your presentation and grading is 20 minutes.*

- **Rules of thumb:**
  - Answer questions as **briefly** and concisely as you can.
  - Ask to **have questions repeated** or rephrased if you don't understand them.
  - In case you don't know the answer, **ask for another question.**

  - Do **not** expect to be corrected during the exam if you give wrong answers – it is better for our evaluation of you to ask another question.
Deliverables

- Project synopsis
  - Project title + 100 word (max.) summary
  - Mail to me: blicher@cbs.dtu.dk
  - Deadline: April 29th (next Monday)

- Poster
  - Deadline: May 6th (Monday) @ noon.

- Buddy group questions
  - Deadline: May 8th (at the poster session)
Important Dates

- Project synopsis
- Poster deadline:  
  – Monday April 6th at noon!
- Exam dates:  
  – May 22nd + 29th
- Course evaluation on CampusNet  
  – May 1st to May 8th
Exam Date Preferences

- If you have special preferences/needs regarding the exam date...

- May 22\textsuperscript{nd} + 29\textsuperscript{th}
  - 8.00 AM to 5.00 PM, location TBD.

- ... send me a mail (blicher@cbs.dtu.dk) with your preferred date and reason.