EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

Exploratory Workshop Scheme

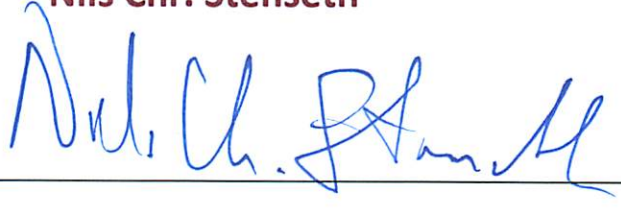
Standing Committee for Life, Earth and Environmental Sciences (LESC)

ESF Exploratory Workshop on

Plague and Natural Hosts- Evolutionary Interactions

Oslo, Norway, 8-10 October 2012

Convened by:
Nils Chr. Stenseth



SCIENTIFIC REPORT

1. Executive Summary

Workshop scientific objective

Researchers all over the world are working on increasing our understanding of pathogens, as these are an ever emerging threat to the stability of our economy and well being of individuals. Thanks to their efforts, there are constant advancements in many fields concerning dangerous pathogens, including, but not limited to functional genomics, pathology and eco-epidemiology. However, due to the separation of pathogen research into different fields, the continuity of our current knowledgebase of pathogens is poor: for instance, we may understand how a certain 'type' or strain of a pathogen affects a certain model host but we do not understand how a natural pathogen strain interacts with its natural host and hence within the environment. The goal of this workshop was to bring together a group of researchers who would not normally interact to discuss and design research projects, to better understand pathogens, in particular *Y. pestis* (plague). The better we understand pathogens such as plague (i.e. molecular interactions with its host, its pathology and eco-epidemiology) the better equipped we will be to minimize the risk to humans.

Workshop organization

The workshop '***Plague and natural hosts - Evolutionary Interactions***' was held at the Holmenfjord Hotell outside the capital of Norway, Oslo, from 8 to 10 October 2012. The workshop was convened by Prof. Dr. Nils Chr. Stenseth from CEES, at the University of Oslo, Norway. Over the course of these 3 days (2 half days and one full day), 17 participants from 10 countries came together at the hotel to discuss the subject of plague from the smallest to the largest biological scale.

The hotel itself is beautifully located, well furnished (including a spa), and overlooks the Oslo Fjord. For a good impression of the hotel and its surroundings, we recommend the website and the embedded movie at http://holmenfjordhotell.no/. The excellent restaurant offers a stunning view over the Oslo Fjord, and the dinners there contributed to the good atmosphere amongst the participants of the workshop, and allowed for convivial discussions and to become more acquainted with each other.

The organization and planning of the logistics were done by members of the Center for Ecological and Evolutionary Synthesis (the CEES) including the Administration (Dr. Gry Gundersen, Kari Rygg and Tore Wallem).

The 17 participants came from: Belgium (Anne Laudisot and Herwig Leirs), France (Elisabeth Carniel and Florent Sebbane), the Netherlands (Lisbeth Wilschut), Norway (Nils Christian Stenseth, Boris Valentijn Schmid, William Ryan Easterday, Kyrre Linné Kausrud and

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Hildegunn Viljugrein), Ireland (Mark Achtman), Finland (Timo Korhonen), Georgia (Lela Bakanidze and Giorgi Maghlakelidze), Azerbaijan (Shair Gurbanov), USA (James Bartholomew) and Estonia (Tanel Tenson). A few last-minute alterations in the participants created some logistical challenges, which were successfully met by the organizers. For the most part communication was not a problem, with Anne, Giorgi, Kyrre, and Lela translating the English to Russian for Shair Gurbanov.

Workshop agenda

The workshop was in total two working days spread over three and began in the early afternoon after lunch on Monday the 8th of October. Nils Chr. Stenseth gave a welcome speech as well as the ESF representative Tanel Tenson. From there talks, discussion followed for most of the first two days. We also discussed what were important topics to explore and how we should move forward.

Workshop scientific outcome

The main results from the meeting are that the different fields provided each other with the the state-of-the-art of current plague research to each other during two days of informal presentations, followed by a session in which was discussed what the current open-standing issues in plague research are. These outstanding issues were categorized into three groups, namely 1) the diversity observed in all aspects of *Y. pestis*; 2) the thresholds that determine plague outbreaks amongst its wildlife reservoir as well as within humans; and 3) the interactions of plague with its ecology, and the effect of those interactions on the evolution of plague.

We further determined the scientific and public relevance of *Y. Pestis*. In our opinion, these are 1) its ability to tie together multiple research fields, including those outside the natural sciences, such as history and archeology; 2) the possibility to study the disease in its natural environment, possible because the high impact of plague on its environment, which allows us to separate its effect from the inherently noise background of a natural setting, and 3) the opportunity to convey the way science works and progresses on a topic that continues to fascination the general population.

2. Scientific Content of the event

SUMMARY OF THE SCIENTIFIC PRESENTATIONS

Note that many of the presentations involved work that is work in progress, and has not been published yet, and thus can only be described in general terms in this public document.

Talk Jim: description of the current state of the welcome trust work in Georgia, Tblisi, and current efforts of improving its scientific level both through collaborations and

bringing in people with knowledge of the field to Tblisi.

Discussion: focused on how to achieve this. Shair takes the opportunity to highlight the possiblity of also doing similar research in Azerbaijan

Talk Mark: briefs the group on the genetic variation of plague. discussed plague in terms of its latest phylogeography, based on (unpublished) current and aDNA samples

Discussion: (classified), as well as a discussion about the confidence of the dating of ancestral nodes in plague's phylogenetic tree.

Talk Elisabeth: discussed recently published work on tracking infections of plague through mouse bodies, the detailed observations on the immunological response raised by the body against plague infections, and the gaps in the knowledge that her group is currently trying to fill in.

Discussion: discussion focused on the disease dynamics of plague, on an epi-ecological level, given how the disease spreads through a body.

Talk Florent: updated us on the functional evolution of *Y. pestis*, based on the evolution the related bacterium of virulence of *Y. pseudotuberculosis* in fleas. He discussed bacterial load in fleas. Focused on what is yet unknown.

Discussion: focused on how little is known about actual causes of death in case of sepsis, and other forms of plague. We also discussed medieval human plague pathology.

Talk Nils: Summarized the work of CEES on the role of climate, and ecology on plague dynamics and transmission

Discussion: focused on some of the work presentedin, in particular the effect of rodent population fluctuations on plague spread.

Day 2.

Talk Herwig: presents work on cellular automata disease models of the Prebalkhash desert, and their implication on plague persistence mechanisms.

Discussion: Whether infected gerbils still play a role in the transmission of plague, or that they are burrow-bound.

Talk Liesbeth: showcased the success rate of analysing rodent burrows densities in Kazakhstan, based on sattelite data.

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Discussion: feasability of more informative surveillance of the current condition of plague systems from space.

Talk Boris: introduced the group to his analysis on medieval plague outbreaks, and the consequences his results have for plague routes of transmission.

Discussion: results were discussed in the light of the latests knowledge of plague's phylogeography. Mark raises the point of (un-)reliability of historical plague records.

Talk Anne: presented her experimental work on alternative routes of plague persistence / transmission through soil fauna.

Discussion: discussion focused on mechanisms of plague persistence, including the recent cases in Algeria.

Day 3.

Talk Timo: discussed the protein 3d structure basis of variations in plague virulence, based on the variation in 3d structure of the virulence factors, and explained the molecular pathways through which virulence factors were working with the host system.

Discussion: results were discussed in the light of plague evolution.

3. Assessment of the results, contribution to the future direction of the field, outcome

Results in terms of workshop objective, and what was learned:

The aim of the workshop was to bring scientists of diverse expertise together that do not typically work together. The subject of the workshop was plague, and the aspects that were discussed ranged from the sub-organismal to large and long time scale processes. The presence of this broad range of expertise was a very interesting experience for the participants, as many were exposed to research topics that do not constitute their regular scientific focus. Moreover, the presentations frequently presented as-of-yet unpublished research, in effect providing every attendant of the workshop with an update on the state-of-the-art of other fields that related to plague research. Details (as far as possible) of this are listed in the short descriptions of the talks and the discussions following the talks. Everyone was able to teach the others about their field of expertise relating to the plague pathogen, and many found the meeting extremely

useful to develop new contacts, as well as discuss in detail with those with very similar research topics. In this regard, the workshop is likely to have been very useful as it appeared to have increased the interdisciplinary coordination of research on plague. Most attendees were interested in pursuing joint funding projects within this type of framework. It became our joint focus as a group to discuss and sketch out how collaboration would be possible.

New research objectives formulated:

Host mechanism for Plague immunity: In some mouse strains innate immunity to *Yersinia pestis* infections is high compared to other mice strains. Their immunity seems to stem from up-regulation of certain pathways in primary phagocytic cells (macrophages and neutrophils). This may be the same or a similar pathway that *Rhombomys opimus* (great gerbil) uses to manage *Y. pestis* infections. We think this would be interesting to do more research on these mechanisms in natural hosts to discover how immunity works as well as how immunity changes over the lifetime of individuals.

Molecular Archaeology: In terms of current research and the focus of future research we find molecular archaeology (e.g. aDNA analysis) to be very exciting and useful for several reasons. The first is molecular clocks. The development of molecular clocks can be done using a nucleotide substitution rate which can be calculated in laboratory using sequencing and culture. Whether or not this rate matches the actual in the species is generally unknown because we cannot go back in time and sample the organism. The combination of molecular archaeology and the historical magnitude (numbers of individuals killed) of *Y. pestis* outbreaks in Europe through the Black Death and subsequent waves of the disease allows for the preservation of enough genetic material to partially sequence plague genomes. To date it has been possible to find signatures of *Y. pestis* throughout Europe. In depth sequencing projects will help reconstruct the spread of *Y. pestis* throughout this time period as well as allow a bioinformatics approach to looking at possible mechanical differences which may show a critical point in the evolution of virulence in *Y. pestis* that facilitated its spread through Europe.

Eco-epidemiological disease dynamics: the implications of the future results learned from the above topics may not only be limited to a change in virulence but also affect plague's pathology and other disease characteristics. This in turn can lead to changes in larger scale processes: eco-epidemiology and co-evolutionary dynamics. Co-evolutionary dynamics is interesting as it seems these processes from periods of equilibrium between immunity and virulence where there is little Darwinian evolution happening. Yet a change in one of these variable (i.e. changes the relative difference between the two variables) can through evolutionary dynamics change such an equilibrium from being stable to being unstable. This leaves two possible outcomes: a new equilibrium that is eventually reached by the pathogen, or extinction of one of the species (both if the host goes extinct).

Concrete plans and actions:

We are discussing outlining and applying for an ERC Synergy grant in the near future. We are well positioned for such a grant as the research being done by our consortium forms cross-disciplinary research team. In short, we as a group from very diverse backgrounds were able to come together and begin developing ideas for projects which are interconnected and complementary to one another while covering a large range of disciplines and scales. As a result of this workshop we are setting up collaborations and projects. We are also discussing writing larger grants to tackle a large amount of the questions above.

The following are a series of topics we think should be addressed in order to develop a better understanding of *Yersinia pestis* (and which can be applied to other pathogens):

Category 1: the diversity of *Y. pestis* (genotypically/phenotypically/ecologically)

Category 2: Threshold Epidemiology

Category 3: Ecology and Evolution

These questions have been worked out in more detail and have been distributed to the workshop participants.
Different expertises brought together that range from the molecular radiography to extra-terrestrial remote-sensing.

- Obtaining new refined data (both in the field, from satellite imaging, and laboratory)
- The answers will follow from an integration from molecular biology to community ecology
- Use *omics (genomics, transcriptomics, soil metagenomics) to effectively glue together the different fields.

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FINAL PROGRAMME

Monday, 8 October 2012

Morning	*Arrival*
11:30	*Lunch at the Hotel*
13.30-14.00	**Welcome by Convenor** **Nils Chr. Stenseth** (CEES, Oslo, Norway)
14.00-14.20	**Presentation of the European Science Foundation (ESF)** **Tanel Tenson,** Standing Committee for Life, Earth and Environmental Sciences (LESC)
Afternoon session	
14.20-14.40	**Jim Bartholomew- Opportunities for pathogen research in Tbilisi**
14.40-15.10	**Mark Achtman- Molecular evolution of *Yersinia pestis***
15.10-15.50	**Elisabeth Carniel- Pathology of *Yersinia pestis***
15.50-16.20	**Florent Sebbane- Functional evolution of *Yersinia pestis***
16.20-17.50	**Nils Chr. Stenseth- Dynamics of plague outbreaks**
17.50-18.30	**Discussion of workshop theme- Ryan Easterday**
19.00	*Dinner*

Tuesday, 9 October 2012

Morning session:	
09.00-12.30	Additional Talks were given by Herwig Leirs, Lisbeth Wilschut, Boris Schmid and Anne Laudisot
12.30-14.00	*Lunch*
14.00-16.30	**Afternoon Session:**
14.00-17.00	**Open discussion forum / data sharing**
19.00	*Dinner*

Wednesday, 10 October 2012

08.30-9.30	*Breakfast*
09.30-12.00	**Morning Session:**
09.30-10.00	**Timo Kohonen**- Y. pestis gene regulation and virulence pathways
10.00-11.00	**Concluding discussion of possible funding, summarizing meeting**
11.00-12.30	**discussion on follow-up activities/networking/collaboration**
12.30	*Lunch*
	End of Workshop and departure

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Final List of Participants

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Statistical information on participants

Country representation

Name of country (10 total)	*number of participants (17 total)*
Azerbaijan	1
Belgium	2
Estonia	1
Finland	1
France	2
Georgia	2
Ireland	1
Netherlands	1
Norway	5
USA	1

Gender representation

Male	Female
12	5