EUROPEAN SOCIETY for VIROLOGY

Meeting on Early Events in Virus Infection

August 25 – 28, 2014, Congressi Stefano Frascini
Monte Verità, Ascona, Switzerland
Urs Greber and **Ari Helenius**, Organizers

Brissago Island

Gain of Function in Virology

Discussion with Simon Wain-Hobson and Giorgio Palù

Discussion leader: Bernhard Fleckenstein
Wednesday, August 27, 2014, 5.30 – 6.30 p.m.

Brief Informal Report

On behalf of the European Society for Virology, Secretary General Bernhard Fleckenstein expresses a warm welcome to the numerous participants, particularly Prof. Simon Wain-Hobson, Head of the Foundation for Vaccine Research, and Giorgio Palù, President of the European Society for Virology. In a short introductory statement, Fleckenstein reminds that, in late 2011, the groups of Ron Fouchier, Rotterdam, The Netherlands, and Yoshihiro Kawaoka, Universities of Wisconsin, USA, and Tokyo, Japan, reported on the work on the pathogenicity of H5N1 influenza viruses and transmissibility between ferrets. This work had stirred intensive discussion in the scientific community with regard to biosafety issues and biosecurity concerns, as selected virus variants could be misused in false hands. In September 2013, a Dutch district court enforced a government ruling which requested that an export licence is required for the international publication of gain of function (GOF) research. In October 2013, Giorgio Palù addressed a letter to José Manuel Barroso, President of the European Commission, criticizing the Dutch administrative measures. Palù inferred that GOF research should remain legitimate as to "predict / anticipate biological evolution and to provide us with critical information to specify preventive and therapeutic measures, e.g. the improved surveillance and proper evaluation of candidate vaccines and drugs." He proposes as the representative of a scientific organization "that Europe considers adopting a body similar to the US National Science Advisory Board for Biosecurity (NSABB) with the willingness to provide law officers with a proper scientific advice, making available the expertise of many European scientists."

In December 2013, Simon Wain-Hobson formulated an opposing letter to President Barroso, implying the proposition of (1.) a scientific briefing for the European Commission on so-called "gain of function research, more properly defined as research to increase the pathogenicity, transmissibility, or alter the host range of highly pathogenic microbes with pathogenic potential and (2.) consideration of a comprehensive risk-benefit assessment of this type of research." The letter of Simon Wain-Hobson was signed by numerous eminent scientists. On 16 December 2013, Sir John Skehel convened a meeting of the Royal Society in London, and the Royal Netherlands Academy of Arts and Sciences invited for a conference on GOF research on 25 June 2014 in Amsterdam. Giorgio Palù and Simon Wain-Hobson participated actively in both meetings. Though there were lively discussions, both events have shown that there are no insurmountable discordances between putative supporters and opponents of GOF research. However, it became clear that there must be differentiated between the substantial judgement of risk assessment and the formal discussion of future political structures in decision making and administrative regulations.

Giorgio Palù gives a 10-minute statement on the position of the European Society for Virology; it has been advocated in January 2014 in *Science* magazine (**343**, 368-369). It stems from the concern that international publication of scientific work in Europe may require export permits. It raised a number of serious issues, particularly the question who will decide what regulatory measures do apply and who will judge such criteria. The European scientific community is, according to Palù, overdue for discussion on how to regulate the dissemination of sensitive data in a way that does not compromise biosecurity, while maintaining the principle that acquiring important and meaningful knowledge cannot simply be stopped. The European Society for Virology believes that the European Commission should take steps to promote a common understanding of the current regulations by an exisiting working group or by a new advisory committee created to deal with dual-use research in a harmonized and balanced way throughout Europe. According to the Nuremberg Code, scientists have an obligation to do no harm. They should always take into consideration the reasonably foreseeable consequences of the own activities. The experiments should be such as to yield fruitful results for the good of society. But, Palù asks, who is going to decide? Dual use research of concern (DURC) reaches far beyond gain of function research on myxoviruses. Very different controversial scientific topics rise similar ethical questions, and there remains always the question of legitimizing regulatory decisions and administrative regulations. Gain of function dilemmas, Palù says, are not confined to virology; but the risks might be higher when the experiments are conducted on potentially pandemic pathogens. Though careful risk-benefit analyses

are undoubtedly required, it must become clear who is going to decide. Understanding how factors such as virulence, transmissibility, and viral fitness interconnect will, in Palù's view, require GOF experiments. Such approaches have frequently been fundamental pillars of scientific inquiry and are essential to the rigorous execution of scientific procedures. To this end, the European Society for Virology proposes, according to Palù, that quantitative risk-benefit analyses should be carried out by an *ad hoc*-independent board. A European Science Advisory Board for Biosecurity should be built up with the involvement of scientists, policy makers, biosecurity and biosafety experts, civil servants, and civil society.

Giorgio Palù can report that President Barroso has answered to his letter, stating that he recognizes the need to develop outreach and guidance for the scientific community and wants to assure that these issues will be considered in the future, as Horizon 2020 plans to provide a practical guidance through dual use toolkits. Mr. Barroso agrees on the need to avoid negative consequences for individual European scientists and to avoid the risk that European research loses its competitive edge. Giorgio Palù concludes that medicine and biomedicine will always be founded on dual nature, Science and Humanism, which are reciprocal in essence.

Simon Wain-Hobson expresses in his 10-minutes statement the deep concern that GOF influenza research is frighteningly out of touch. Though natural selection over one centennium, only three pandemic hemagglutinin/ neuraminidase combinations in birds or mammals have led to pandemic influenza viruses. Other spillovers to humans have occurred, but all were dead end infections. Transmission experiments in ferrets, while weak at the core, remain risky, and there are even recent quantum jumps in GOF influenza risks. The purported benefits appear questionable to him and are not in a reasonable relationship to catastrophic risks. According to Wain-Hobson, scientists should recognize that individual good conscience does not justify ignoring the possible misuse of their scientific endeavour. He concludes that (1.) the risks of GOF research outweigh their purported benefits, (2.) this type of research should be frozen, (3.) an inventory is needed, (4.) national and international conferences are needed with all stakeholders to forge a consensus, and (5.) several risk and liability analyses are required.

The ensuing open discussion between the participants of the symposium essentially relates to the following considerations:

(1.) The discussion on the risks of GOF research should differentiate between biosafety and biosecurity issues. The aim of biosafety in virology relates to the avoidance of the inadvertent release of dangerous pathogens.

Biosecurity concerns the avoidance of deliberate release of pathogenic microorganisms, for instance to fulfill military or terroristic purposes. Most likely, persons aiming at the violation of biosecurity rules will not be amenable to the ethical discourse and will not be willing to obey legal regulations. Thus, there are arguments that the ethical discourse should focus more onto the biosafety issues.

(2.) It can be legitimate trying to suppress the publication of inappropriate research. Principal investigators have, in general, the right to impede publication by their dependent collaborators in the group. It is mentioned that the rights of Max Planck directors to disapprove the publication by their collaborators fall into the latter category and should not be precedent for the regulation of publications on DURC.

(3.) The spread of information can, at large, not be suppressed by administrative measures. The opinion has been put forward that the barring of publications by Dutch authorities cannot be a useful model for the future regulation of sensitive publications.

(4.) It is expressed that the judgement on biosafety situations must remain in the responsibility of scientists.

(5.) Executive boards and advisory committees should essentially consist of scientists, but they should also encompass members with a background in ethical sciences and representatives of the society at large. This is required to gain the trust of media and the public.

(6.) So far, there are no established structures that can give recommendations or formulate the necessary guidelines on biosafety issues at the European level.

(7.) ECDC, an institution associated with the European Commission, seems not yet prepared to provide the administrative basis to coordinate the political advice and to sustain the organization of an advisory body to cope with the biosafety issue related to virological GOF research.

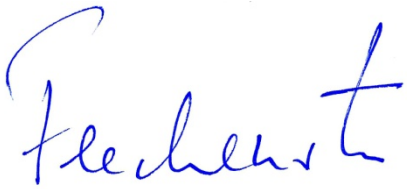
(8.) It is reported that administrative bodies in Germany have acted so far. The Central Committee for Biological Safety (ZKBS) has ruled that GOF myxovirus research will only be allowed under BSL4 conditions. The National Ethics Committee has recommended that a DURC committee should screen research proposals in the future. There seems to be consensus that parallel

structure can bear the danger of conflicts to the disadvantage of research. It should be secured that institutions such as ZKBS and DURC evaluation committees will interact. There should be no abundant regulation in a single country prior to general rules and decisions on unifying concepts in Europe.

(9.) It has been proposed that there should be a hierarchical structure in Europe. Accordingly, general rules should be formulated under the auspices of an advisory council at the European level; the administrative realization and legal execution should be done under the responsibility of the individual member states.

(10.) The Brissago meeting has given the impression that there are no irresponsible supporters or opponents of GOF research. None of the participants was advocating unreflected harmful practice in biomedical research. Nevertheless, there remained recognizably different views on how to judge the right balance between GOF research and necessary restrictions. Thus, it can be expected that the debate will continue in the future. Next events will be organized under the auspices of the European Association of Scientific Academies (EASAC) and the VW Foundation in a meeting that is scheduled for December 10 – 12, 2014, in Hanover, Germany.

Brissago, 27 August 2014



Bernhard Fleckenstein
- Secretary General of ESV -