KONINKLIJKE NEDERLANDSE
AKADEMIE VAN WETENSCHAPPEN

# GAIN-OF-FUNCTION RESEARCH
# Report of a Debate between Prof. Giorgio Palù and Prof. Simon Wain-Hobson

*25 June 2014, Trippenhuis, Amsterdam*
*by Koos van der Bruggen*

# INTRODUCTION BY HANS CLEVERS, PRESIDENT OF KNAW

The potential risks of science suddenly became world news when Rotterdam-based virologist Ron Fouchier wanted to publish a paper on the mutations that make the H5N1 virus – better known as the bird flu virus – transmissible between mammals. A heated debate ensued focusing on the tricky balance between scientific freedom on the one hand and the interests of public health and security on the other.

For the Royal Netherlands Academy of Arts and Sciences the debate did not come as a complete surprise. The Academy had already pointed out the possibility of misuse to life science researchers in 2007 with its Code of Conduct for Biosecurity. This Code of Conduct has certainly contributed to awareness raising of scientists in The Netherlands. Moreover, the code has drawn attention internationally. It was presented at international conferences and courses and it has been or will be translated in several languages (English, Japanese, Indonesian, Ukrainian).

However, the debate that raged in scientific and political circles about the bird flu virus made clear that it was time to think seriously about the usefulness and necessity of additional policy measures. This led the Dutch State Secretary for Education, Culture and Science to ask the Academy to advise on dual-use research.

The Academy Board inaugurated August 2012 a Biosecurity Committee to prepare a new advisory report. This report built on the work of the Academy Biosecurity Working Group, which drafted the Code of Conduct in 2007. Chaired by Lous van Vloten-Doting, the Biosecurity Committee was assisted by a Focus Group representing science, industry and government.

One of the conclusions of this Biosecurity Committee in its report (December 2013) was that considering biosecurity aspects at an early stage of research may help avoid problems in the final stage of the project. It is also crucial for researchers to become aware of potential risks and remain so. This important topic should be considered at length, both in the laboratory and above all in university education programmes. The Committee proposed to create a modest institutional setting for dealing with these issues.

The debate on biosecurity is about scientific considerations, but not exclusively. It is also about two different perspectives: that of researchers in the life sciences and that of security specialists. He is convinced that the debate between professor Palù and prof. Wain-Hobson will illustrate this. On the one hand the debate will give the occasion to discuss about the scientific benefits and risks of gain-of-function research, and on the other hand the debate will deal with broader biosecurity issues.

It is his hope as president of the Academy that this debate will help to bridge the gap between science and society by creating room for interaction within the scientific world as well as between science and society.

# REMARKS BY THE CHAIRMAN, ANDRÉ KNOTTNERUS

This debate will concentrate on the benefits and risks of so called gain-of-function research. The H5N1 research projects conducted by the groups of the virologists Fouchier and Kawaoka have led to debate about this kind of research. In that context *gain-of-function* refers to research that increases the transmissibility, increases the pathogenicity, or alters the host range of H5N1 viruses. However, there are other definitions and interpretations of gain-of-function. One of the main purposes of this debate is to get to more clarity on this question of gain-of-function.

KNAW has invited two scientists who contributed to the debate on gain-of-function by writing a letter to the president of the EU-Commission, Mr Barroso. In his capacity as chairman of the European Society for Virology, professor Giorgio Palù, asked attention for the potential benefits of this kind of research. Professor Simon Wain-Hobson, chairman of the Foundation for Vaccine Research, responded with a letter- undersigned by 56 other scientists - that challenged the arguments in favour. In their opening statements both Dr Palù and Dr Wain Hobson will explain and elaborate their main arguments.
Following their presentations both speakers will – for the first time – have a debate with each other. Of course there will be attention for the more scientific aspects of gain-of-function research. However, the political and societal debate was not only – and probably not even in the first place – on science, but even more on the security aspects. One of the reasons for the debate is the risk of bioterrorism: the creation of a pandemic by terrorists having the knowledge and the biological agents. Since the attack with anthrax letters in the USA life scientists know – or should know – that this is a real issue of concern. How to deal with it, as science and as society?
This last question will certainly be one of the main issues in the broader debate with all of you as participants. It is not our intention to have a question and answer session, but we aim at a continuation and enrichment of the debate. Given the broad and diverse expertise that you represent I have all confidence that we will have a stimulating debate.
What do we want to achieve today? It is not to be expected that the debate will lead to consensus and to broadly shared conclusions. However, it will surely be possible to make an inventory of the main issues and arguments of the debate. It will also be possible to formulate some learning points. Finally we hope that some suggestions can be done. One of the planned activities is a conference organized by the Academy as follow-up to the 2013 advice report of KNAW on dual-use research.
During the debate we will follow the Chatham House rules: anyone who comes to the meeting is free to use information from the discussion, but is not allowed to reveal who made any comment. With their approval an exception is made for prof. Palù and prof. Wain-Hobson, as their positions are publicly known (e.g. because of their letters to Barroso).

# PRESENTATION GIORGIO PALÙ

Professor Giorgio Palù presents himself as a representative of the University of Padova and as the president of the European Society for Virology (ESV) of which he introduces the main aims and the members of the board. One of the tasks of the ESV is to represent European virologists in the European policy centres and to promote the science and art of virology, especially among young investigators. From this background and in keeping with the functional organization of the host Institution, the Royal Netherlands Academy of Arts and Sciences (KNAW), he will frame his presentation in the context of the duality between arts *and* sciences. He agrees with the aims of the Foundation for Vaccine Research (FVR) – of which Simon Wain-Hobson is a representative – that promoting and funding vaccine research is very useful and necessary, although distinguishing between the ESV mission and that, yet commendable, of a Foundation.
Palù gives a short overview of the H5N1 debate: submissions by the groups of Fouchier and Kawaoka; discussion in the NSABB; publication in *Nature* and *Science*; Dutch court decision and the ongoing experiments with gain-of-function research, resulting in some recent new publications. Following a discussion on the subject at the European Congress of Virology held in Lyon, September 2013, ESV decided to write a letter to Mr. Barroso also on behalf of the European Society of Clinical Virology. The main points of this letter, that did not intend to dispute whether bad or good science have been conducted with GoF research on H5N1, were that: i) asking a court for an export permit is not the way to deal with dissemination of scientific data; ii) it is necessary to safeguard academic freedom and avoid discrimination of European research; iii) under the present EU regulation on dual use research of concern (DURC) (a legislation mainly covering a post-experimental phase) it is not clear who is going to decide on the feasibility of GoF experiments and legal harmonization in Europe is needed to avoid different interpretations by 28 different European countries. In his reaction Mr. Barroso showed understanding for the arguments in the ESV-letter. He wrote that dual use regulation is not intended to hamper research or trade and that the EU is now reviewing this regulation for export control. The international debate continued with a meeting at the Royal Society in London. Main conclusion of this meeting was that gain-of-function is not an appropriate description for this kind of research. Moreover this research is not limited to influenza, but it is also applied in other fields of microbiology. Another recommendation was that debate on this research should be started in the early phase of the project already, and it should be communicated to the public. In a letter to *Science* (January 2014) Palù repeated his view that export control and decisions of local courts should not be used for regulation of GoF research. There should come a harmonious regulation, shared by all relevant parties. Implementing such a regulation could be a task for an existing or possibly a new commission. GoF can then be treated as an example of dual use research of concern, as it is defined by the US National Scientific Advisory Board on Biosecurity (NSABB).

Dual use research is an ethical issue. Ethics itself can also be viewed as dual: doing good can lead to disastrous harm. This was already seen by ancient Greeks as Herodotos (500 BC). Moreover, ethics is relative to circumstances. In times of war it is justified to defend yourself according to the rules of the "jus in bello". Counter measures can be justified. The academic world is another example, as is shown by the history of the University of Padova. Its motto is *Universa Universis Patavina Libertas*, a plea for academic freedom. In fact the history of ethics reflects the history of Europe. It started with Socrates (αρετη, σοφια), then came Plato (άγαθόν εἶδος), Aristoteles (εύδαιμονία) and Saint Agostine (responsibility, charity). Famous are the writings of Kant and Illuminism: Humans are bound, from a knowledge of their duty as rational beings, to obey the categorical imperative to respect other rational beings. Utilitarianism (Mills) picked up the εύδαιμονία idea of Aristotle by pleading for maximizing happiness.

Bioethics was developed by an American oncologist. He was interested in the human being. Bioethics was directed at knowledge that was not available in medicine itself. It is about doing

harm and doing good: this means it is on risks and benefits. What is risk and what is benefit? We referred to this question in our letter to Mr Barroso in relation to the gain-of-function research projects. Benefits can be gained by developing new therapeutics, but benefits can also be related to knowledge per se. Man

has to pursue knowledge, as it is dicted in Dantes Divine Comedy. You cannot stop human knowledge. So far on philosophy. Present day science is a heritage of that philosophy. However, any knowledge brings about controversy.
This is also the case in virology. Every researcher knows the risks of contagion. But for preventing contagion you need to know. The risks of contagion have been known already for a long time in Italian cities as Venice, Genova and Padova. Prevention was so important in those days that there was an island for quarantine in the neighbourhood of Venice.

Today the debate is not limited to and did not start with the Gain-of-Function debate. There was a debate when recombinant DNA experiments started in the 1970s. People said: you cannot change nature (e.g. by making crops resistant against pathogens).The same debate took place on gene therapy in oncology. It is good that such debates take place, because we can learn from it, e.g. on the cloning experiments of Ian Wilmut with the cloning of Dolly and nowadays on synthetic biology. UN and UNESCO still have debates on cloning: Nobody is approving reproductive cloning, but therapeutic cloning is accepted by some countries. And now we also have the debate on gain-of-function, where the debate is on the pathogenicity of viruses.
Scientists do always have to consider the foreseeable consequences of their experiments for mankind and a risk-benefit evaluation relies primarily on their responsibility and on the respect of present regulation on biosafety and biosecurity. There have been – apart from H5N1 – more dual use experiments, e.g. with mouse pox, anthrax, *Clostridium botulinum* or with the "resurrection" of Spanish influenza. All these experiments could be misused. The military is doing such research to develop vaccines, to create Ebola virus chimeras, or to make a pathogen resistant. All these kinds of research evoke ethical questions. And it is true that these ethical questions do not always attract enough attention, certainly if human beings are not directly involved. However it is important always to take into consideration the declaration of Helsinki, the Hippocratic Oath and the medical principle of *primum non nocere* (first principle: do no harm).

Back to gain-of-function. In fact scientists do these experiments almost daily to probe the function of a gene. And of course scientists are aware of the risk of working with (new) pathogens. Risk management is necessary to deal with these risks. One of the issues in which Simon Wain-Hobson and I differ of opinion is the question if GOF research is necessary to unveil pathogenic mechanisms relevant to develop new therapeutics. Another question is how to prevent bioterrorism. Two approaches are reported in the scientific literature. One is by Miller and Palese. Their study shows that this research is useful and can be done in a way that bioterrorists cannot cause a pandemic on the basis of GOF research. The option again will be developed on who should regulate this kind of research and on whom should be addressed to. Five approaches can be discerned: complete autonomy, institutional control, an independent authority, a dual system with also governmental control or complete governmental control. This first option seems too rigorous, so a dual system seems most appropriated. On the EU level can be thought of an independent biosecurity review board. In the letter to Barroso the ESV did the suggestion to initiate an organisation like the NSABB in the United States. Such a construction would not hamper scientific research.
His conclusion is that the debate should go on, not only within science but also with other organisations and institutions such as primarily ECDC, Ethical boards, Biosafety and Biosecurity boards. This because it cannot be denied that science and politics have to deal with each other.

# PRESENTATION SIMON WAIN-HOBSON

His main thesis for this debate is as follows: gain-of-function avian influenza research is frighteningly out of touch. The flu that worries us is that among humans. Influenza viruses are characterized by two kinds of proteins called H (hemagglutinin) and N (neuraminidase) at the surface of the virus that allow it to get into and out of cells. Human pandemics have been provoked by H1N1 (Spanish flu 1918, 1977 and 2009), H2N2 (Asian flu, 1957) and H3N2 viruses (Hong Kong flu, 1968). By contrast the greatest reservoir of influenza viruses is among ducks, birds and chickens and they rarely cross over to humans. Occasionally an epidemic of avian flu spills over to humans and can give rise to hundreds of H7N9 infections in man in a matter of months. Fortunately, these viruses are almost never transmitted from human to human. This is the same as with the rabies virus. Such dead end infections are not new in virology. The question is could these viruses become transmittable between humans and if so how? In modern virological parlance, what mutations are necessary to convert such a virus into a highly transmissible virus between ferrets, the animal of choice in influenza biology. This is the basis of the H5N1 projects of Fouchier and Kawaoka. As is now well known, they succeeded in doing this for the H5N1 virus and it involved a handful of mutations.

It should be emphasized that the conditions in a laboratory differ enormously from those in nature. Influenza virus evolution takes years, while in a laboratory there is a massive acceleration thanks to the selection of mutants by the virologist. To illustrate this, suffice to say that for some reason nature has not yet succeeded in morphing any influenza virus into a major human pathogen other than H1N1, H2N2 and H3N2 in 100 years. Even the resurrection of the Spanish flu HIN1 virus did not help us to predict or prepare for the H1N1 flu pandemic of 2009.

This is one of the major scientific weaknesses in the so-called gain-of-function influenza research. We do not know if the experiments reflect what happens in nature. As an HIV expert he can say this because the lab is not a good template for what happens in the clinic. There are hundreds of possible trajectories and only a few can be tested in laboratory. One can never know which are the “right ones” – that can only be appreciated as being “right” once the pandemic has struck. As for obvious ethical reasons these experiments cannot be done in humans, an important objection to this work is that it is not falsifiable. This constitutes a real issue as science tries to solve problems, not to create them.

He gave two examples of quantum jumps in recent gain-of-function influenza research. An ostrich H7N1 virus was selected to become droplet transmissible between ferrets. It did not lose lethality - three out of five animals died (Sutton et al., J Virology 88, 6623 (2014)). A 60% lethality rate is much greater than the 2% that characterized Spanish flu. We must realize that until now no case of H7N1 in humans has been reported, so it is no threat to humans. The world is becoming a more dangerous place by making the virus aerosol transmittable. The second example is an unpublished experiment from Dr Kawaoka. He engineered the human 2009 pandemic H1N1 virus to escape neutralization by convalescent sera. By doing this the virus escaped vaccine coverage. It needs no explanation that if there ever were a lab accident the consequences could be enormous because this virus is unquestionably transmissible between humans.

The benefits of this kind of research: Scientists are used to work with the probability of benefits versus risks, just as they are used to handling dangerous agents. One of the arguments in favour of this gain-of-function research is developing vaccines and drugs. GOF research has nothing to offer for making vaccines. Development of vaccines is a very time-consuming and expensive effort. Moreover, each strain of influenza virus would need its own vaccine. And as mentioned above there is a great number of possible strains. And as it cannot be predicted which strain will cause an epidemic, this kind of research does not have much utility. Developing and stockpiling these vaccines would cost an enormous amount of money. As for drugs the choice is binary: we must hope that the next pandemic strain is sensitive to available drugs and use them accordingly. If the strain is resistant, it will take too long for the new drugs to be tested – by then the pandemic will be over.

Now the risks of gain-of-function research: There is always the risk of an accident. For a virus that the human system has never seen this could lead to millions of deaths. Wain-Hobson does not call this risk, but catastrophic risk. But there are also less catastrophic outcomes, e.g. the equivalent of a seasonal flu outbreak where mortality is less than a million. The economic burden of seasonal flu costs a lot of money (say $71-167 bn/year to US economy alone). What would be special in the event of release of a lab engineered virus is that it is genetically ‘barcoded’. It would be trivial to trace the origin. Massive liability

claims would be sought for the unwarranted deaths and economic damage. Liability experts (e.g. from RAND corporation) say that this really could lead to claims of 100 billion dollars and more, an amount that no insurance company would be willing, or able, to pay. Liability of this magnitude would jeopardize the existence of private universities and institutions such as the Institut Pasteur or even Harvard.

Some scientists argue that there is not much guidance on these biosafety issues. Of course there is the Fink report of 2004 (NRC - National Research Council (2004), *Biotechnology Research in an Age of Terrorism*. Washington DC: National Academies of Science). And there is the InterAcademy Panel 2007 Statement on Biosecurity. This statement has been signed by 76 Academies of Sciences, such as KNAW, Royal Society, Leopoldina and the US NAS. Basically this statement says that scientists have an obligation to do no harm (the Hippocratic oath). It also says that individual good conscience of scientists does not imply that one can ignore the possibility of misuse. However, many scientists do so. Scientists are responsible for the knowledge they produce and publish. The statement also refers to the necessity of oversight over the research. This certainly is relevant for funders but also journal editors should adhere to these principles in making their decisions on the publication of dual use research. Amazingly hardly anyone knows about this document. It is good to have such a statement, but it is important that people know about it! So, maybe there is not so much a lack of guidance, but a lack of good communication of that guidance. For the moment scientists effectively transfer their biosafety and biosecurity problems to journal editors who have to handle them at "5 minutes before midnight".

From his point of view we should freeze on gain-of-function research, because not doing so means waiting for an accident. With this breathing space virologists can look for more coordination and cooperation in taking safety and security measures, because they are very divergent now. Very important – and Giorgio Palù and Simon Wain-Hobson agree on this – is having more debates with more stakeholders getting in; lawyers, defence experts, insurance companies, etc. We need more risk – benefit analysis, although with the disagreement among virologists, it seems hard to get an agreement on the benefits. For the moment learned societies, governments and funders do little to advance this field. They fund and support this research without taking care of risk or liability.

Wain-Hobson finishes with this statement: On 22 March 2012, Russian president-elect Vladimir Poutin promised to develop new weapons based on advanced technologies, including genetics (Raymond Zilinskas, The Soviet biological warfare program and its uncertain legacy, Microbe v9, p151, 2014). Although the Soviet Union was one of the initiators and first signatories and depository state of the Biological and Toxin Weapons Convention, there are clear signals that they went on with research and development of biological weapons until 1990. It has never been verified, because that was not possible for political reasons. So, how do we understand this recent statement from Poutin? Bluff or a serious warning?

Virology is hopelessly misguided in pursuing gain-of-function research. It will not lead help us predict or prevent influenza. Although virology has made great advances, it is a dream that is still years away. Indeed flu viruses may always be one step ahead of us precisely because they evolve to escape immunity to them. As long as that is the case debate is needed, among virologists, but also with experts from other fields.

# DEBATE BETWEEN PALÙ AND WAIN-HOBSON

**Chair**
The discussion will first be directed at the more scientific issues and after that on more general and policy-related subjects. A first question for Professor Palù: what are the most important statements in the presentation of Wain-Hobson with which you agree and with which you disagree?

**Palù**
I am well aware that there are many unpredictable aspects in influenza research. You cannot predict which virus strain will occur or prevail. However, it is somehow possible to anticipate on the likelihood of future developments. That is why governments, scientists and pharmaceutical industry are preparing vaccines for likely outbreaks as in the case of H5N1 and other subtypes or variants of influenza virus. This kind of research is done in laboratories of BSL-3 level or higher. And still accidents can happen as is shown by the very recent events with anthrax research in the CDC laboratories. But this does not change my opinion that research aimed to understand mechanisms of pathogenicity is very important as it is to understand what mutations make a virus more or less stable.
I think that Wain-Hobson and I agree in a broad outline, e.g. on the importance of ethical, scientific and social debate on this kind of research. I agree that stakeholders in this research have to be aware of the risks (also the financial risks).
The main point of disagreement is that you cannot stop science and scientific curiosity. Of course you have to be aware of the risks, but there is no reason to stop a rational endeavor in science. In gene therapy we had comparable discussions after an accident in the 1990's (and in therapeutic human cloning as well). Stopping science – as Wain-Hobson is proposing regarding Gain-of-function research – is not a solution.

**Wain-Hobson**
Let us compare with chemistry. In chemistry research to make a poison gas as sarin more soluble and thus better applicable is forbidden. This is regulated by the Organization for the Prohibition of Chemical Weapons (OPCW). So it is not evident that every scientific project has to be done. In daily practice we as scientists reject or refuse scientific proposals or clinical trials because of uncertainty or doubt about the risks. There are projects or experiments that are in conflict with the Hippocratic Oath. Scientists should do no harm. Thus the idea that everything is possible, is wrong. Moreover decisions have to be taken on financial grounds: money is not unlimited. And in that case interesting but socially less relevant projects tend to loose out against scientifically less interesting but more promising projects.

**Palù**
This indeed is not a new thing, because these decision mechanisms have existed already for a long time. In the case of gain-of-function research Barroso replied to us by saying that he understood our problem. He agreed that you cannot solve it just by an export permit. And he did not want to interfere in academic freedom. However, you have to reduce the chance on risky accidents.

**Chair**
There are many examples of dual use research that are done on almost a day to day basis without any discussion at all. How to discern this research from types of dual use research that are to be regulated?

**Wain-Hobson**
As a virologist I cannot judge all other kinds of research. For an opinion on influenza research I trust experts as John Skehel from the Royal Society. In 2012 we organized a debate at the RS, with Fouchier and Kawaoka as participants. This meeting allowed me to discover a whole new area of science politics and science administration. Still we need a lot more discussion on this area. Until now there has not been enough debate. Until now the European Society for Virology (ESV) did not initiate any debate. For the American Society on Microbiology (ASM) it is the same. People are uncomfortable with this issue.

**Palù**
Let me remind you of another meeting at the Royal Society (December 2013). There was agreement on the importance of gain-of-function research, as a scientific approach daily used in biomedical laboratories (like loss of function), and on the fact that GOF is not an appropriate definition of those activities dealing with the manipulation of pathogenic microorganisms with pandemic potential.

**Wain-Hobson**
But this was a meeting of 12 people. They cannot decide what is happening in China or India. We need a bigger debate, especially on the issue of academic freedom. One of the aspects is the question who is paying for the research. At Pasteur Institute we are partly paid by philanthropists, who donate their money often for specific purposes, often fighting certain diseases. We have been rather successful in the past, but we cannot do everything. Donations and grant proposals lead to utilitarian considerations. Only by doing so we all agree that there is no such thing as absolute academic freedom. Still we have a remarkable freedom, but we cannot have 100% freedom. There is a very small number of experiments that cannot or should not be done.

**Palù**
Today with developments in synthetic biology you can modify life and change the coding sequence of DNA. It has to be recognized that gain-of-function is an important methodology for practice. You have to make clear in publications that gain (or loss) of function helps to dissect the function of a gene. Present day science cannot do without! In the end in both letters (ESV and FVR) it is asked for the same thing: to have an institutional observatory to judge on some particular important experiments in this field. And let us not forget that the research projects of Kawaoka and Fouchier have been approved by recognized institutions as NIH.

**Wain-Hobson**
That may be the case, but fact is that there is a lack of oversight. In this respect I must react to the reference to synthetic biology. This could lead to the development of organisms that do not exist on the planet. This is a consequence of freedom of scientific enquiry. And many people say bravo. Scientists are doing some 'wacky stuff". However the drive of most synthetic biologists is to make new (synthetic) drugs against e.g. malaria. It is very complex research, done for 50-60% in bacteria and then finished in chemical laboratories. But what they are not doing is trying to make a bug more pathogenic. They would be horrified by such an idea. And we are now debating increasing pathogenicity of known microbes!

**Chair**
Both of you plead for more risk-benefit analysis. This implies that you accept that there is no zero risk. How to deal with this?

**Palù**
A zero risk does not exist, but you have to approach it as close as possible. In preparing a research project you have to take responsible measures to reach a maximal reduction of the risk. However, my experience is that even governments are not always conscious of the possible risks.
There are some ways to deal with risks. Recently an article on botulinum was – for reasons of biosecurity - published without all technical details that would make it possible to reproduce the experiment. I do not think that is a good solution if you want to go for science.

**Wain-Hobson**
Indeed, this is an interesting example that also was relevant in the debate on the papers of Fouchier and Kawaoka. In this respect I ask attention for another possible risk. My personal experience is that papers that are submitted to scientific journals can be hacked even before they are published, so even with publication of redacted manuscripts it is possible to get the full version. Biologists are computer naïve!

**Chair**
In the letter of ESV an advisory committee is proposed which is comparable with the U.S NSABB. You also plead for "workable common policies" for scientific research and publication. In the letter of the FVR is pleaded for a comprehensive risk benefits analysis and for a good scientific briefing of the European Commission. In my view the proposals in both letters are not so much different and I wonder if they could

be combined. Both proposals deal with the responsibility – and self-regulation - of the scientific community. But there are situations where self-regulation does not work and then you need some form of governmental policy.

**Wain-Hobson**
Palù and I agree on the importance of such debates with all involved parties (e.g. also lawyers). I repeat that until now there has not been enough discussion about this issue. Many organizations and learned societies did not (yet) participate. Moreover there is a great division of opinions, greater than I ever saw before on scientific issues. Because of that I am happy with a meeting next December in Hannover, organized by the Volkswagen Stiftung, where all relevant parties have been invited. But in the U.S. it has not yet been possible to organize an open discussion. From my point of view this KNAW-debate is really unique. We must hope that these debates will lead to a sort of consensus without a “pax Giorgio” or “pax Simon” as outcome.

**Palù**
Indeed, this is also the view of ESV. Europe has a tradition of centuries of war. Now we have one currency. So we should also be able to discuss in all openness on these scientific issues.

**Chair**
With this common conclusion we finish this part of the debate.

# EXCHANGE OF VIEWS

**International state of affairs regarding biosecurity**

**United Kingdom**
In the UK the Royal Society has organized a couple of meetings on gain-of-function research. In 2012 there was a large meeting in presence of Fouchier and Kawaoka as well as of people from NSABB. Both presented and justified their positions. It was a well-received meeting. Especially the possibility of experimenters and regulators to meet each other was appreciated. This had not happened before. The meeting did regulators realize that they had to do their work conscientiously, based on real knowledge, not on authority. At the second event (December 2013) there were only 10 people. Five were more or less in favor and five more or less against gain-of-function research. There were two main outcomes: one was that there should be more open discussion throughout Europe on gain-of-function research. The European academies – assembled in EASAC – took this up and started an initiative involving the member academies. What did not succeed was to get away from the concept of gain-of-function. Gain-of-function is the read-out for all experiments in genetic modification. The debate should not be on that, but on potentially dangerous experiments which do not only have to be related to genetic modification. We still not have as catching a title as gain-of –function. Introducing the concept of dual use research seemed to lead to introducing a different group of people (security experts) that were not present at the meeting.
In the UK there have not been introduced changes in the regulatory procedures for research as a consequence of the gain-of-function debate, which got a lot of attention in the UK. These regulations are mainly based on the procedures for genetic modification research. It is obvious that everyone in this process has to accept responsibility: the individual scientist, the ethics committees, the funders, the publishers, the referees etc. If everybody takes his responsibility properly, then there is no need for more regulation in the UK, where regulations are already more strictly than in the US. This certainly is the case for avian regulations, because of the environment.

**Germany**
There are two root problems that have to be discussed. There is a need for education on dual use and biosecurity issues. The second issue is oversight. The Biological Weapons Convention has taken initiatives on these two issues. In spite of that there has been little progress. There is hope that recent developments, such as the recommendations in the report Improving Biosecurity of KNAW will help to improve the situation in Germany. In Germany the government (Ministries of Health and of Science and Education) asked the Ethics council to address the issue of biosecurity and freedom and responsibility of research. Also was asked if Germany does have enough regulations to protect its citizens from dangerous situations that may arise from the life sciences. A working group Biosecurity of the Ethics Council has been working on the report for 1.5 years. The report was published last May. It is a comprehensive and in-depth report. In the recommendations the Ethics Council tries to get a good balance between giving the individual scientist enough responsibility and developing new regulations to make sure that scientists would give enough attention to the risks of so called dual use research of concern (DURC). What came out in the first recommendation was the need for more education for life scientists. The second recommendation was for a code of conduct (like The Netherlands). Furthermore there were recommendations for some more regulation, such as the installation of a national DURC committee. Such a committee can give a recommendation (not an obligation) on possible dual use research. This could be tested in an experimental period of four years to see if the recommendations are followed. If not so, other regulation can come in place. One of the issues that needs attention – as was given in this debate – is that not any gain-of-function research should be evaluated, but that the concern should be only with possible dangerous developments.
In addition: in Germany are three institutions that are connected with biosecurity. One, there is the German Ethics Council. There is also a Central Committee for Biological Safety that has advised that gain-of-function research should fall under BSL-4 conditions. And there is the German Society for Virology. This society has warned for a possible duplication between a new DURC committee and the Central Committee for Biological safety. This could lead to divergent recommendations. Therefore the virologists plead for close collaboration between both committees, where one concentrates on biosafety and the other on biosecurity.

A second addition: the Volkswagen Stiftung will organise a conference on gain-of-function research on 10-12 December in Hannover. It will be an open discussion with scientists, policy makers, security experts etc.

**The Netherlands**
The activities of the KNAW started in 2006 when a Biosecurity Working Group was installed that was asked to develop a code of conduct for biosecurity. The small working group was advised by a broad advisory committee consisting of stakeholders from different backgrounds (science, laboratory practice, ministries, industry). They contributed to a practice oriented and relevant code of conduct. Such a code is important for awareness raising.
However, the H5N1 debate proved that sometimes more is needed than a code of conduct. When you are doing experiments with a possible dual use risk, it is difficult for individual researchers or institutes – even if they are aware of biosecurity aspects – to assess the amount of risk. Most of them are no experts in security issues. Because of that it is important to involve security and intelligence experts. The difficulty to assess the exact risk makes it also difficult to define strict regulations. The second KNAW biosecurity committee came up with maybe a typical Dutch proposal: talking with each other. There should be an institution where scientists can get help if they have the impression that their research project could have a problematic dual use aspect. Therefore the KNAW-committee proposed to install a small standing committee on biosecurity. This committee can ad hoc be expanded with experts on specific relevant fields. The main task of this committee is helping scientists to find out if there are biosecurity risks in their proposals. The committee could give advice, e.g. that there is no dual use problem, or that some modifications should be desirable and sometimes the advice could be to not to proceed with the project, e.g. if misuse of a project would upset society. This advice should be brought to an institution that can bear responsibility. In the view of the KNAW this should be the Health Council in The Netherlands. KNAW has the conviction that the advice of the Committee will be taken seriously, because it can prevent that the researchers in a later stage of the project get confronted with the export control regime, that still is in place. Until this moment (25 June) the government has not yet taken a decision on this KNAW advice.

**European Commission**
In the Directorate General of the European Commission several projects are supported in the field of influenza research. These include some of the gain-of-function projects that are debated here today. The DG research is closely involved in the review process of the export control regulation of 2009. Regarding the export control regulation there will be attention for the question if new legal measures are required. In this review the social and economic risks and benefits will be evaluated.
There is also attention for the question how to deal with these issues in the new EU-framework program. This may lead to some recommendations and guidelines for this kind of research. After the internal debate stakeholders and experts will be involved in this discussion. In this process there is also attention for existing guidelines and best practices in the member states.

**European Center for Disease Prevention and Control (ECDC)**
ECDC is an EU Agency that works in close collaboration with DG SANCO (Directorate for Health and Consumer Protection) and other relevant bodies of the EC (including DG RTD and DG TRADE). According to the Article 3 of the Founding Regulation, ECDC's mission is to identify, assess and communicate current and emerging threats to human health posed by infectious diseases. In order to achieve this mission, ECDC works in partnership with national health protection bodies across Europe to strengthen and develop continent-wide disease surveillance and early warning systems. By working with experts throughout Europe, ECDC pools Europe's health knowledge to develop authoritative scientific opinions about the risks posed by current and emerging infectious diseases. With regards to the dual-use issues in research topic – it is a complex topic that influences the work of ECDC in the microbiological and preparedness activities in many ways. For example, when the information of the H5N1 project of Fouchier became known in 2011, ECDC performed a risk assessment from a public health and including a biosafety perspective. However, there are many priorities within ECDC. Following this, ECDC has kept on monitoring developments and the recent letters to Barosso prompted Director Dr Marc Sprenger to set up an *ad hoc* team of

interdisciplinary experts *(led by Dr Amanda Ozin – Microbiology Coordination Section)* to develop an ECDC opinion about the need to better engage with the public health sector on this topic (see Frontiers Special Issue on Dual Use topic). Moreover, the ECDC has supported the continuing multi-disciplinary/perspective dialogue in a "dual-use" debate with the wide-range of public health professionals that will attend the "European Conference on Applied Infectious Disease Epidemiology (ESCAIDE)" on November 6th, 2014 in Stockholm, Sweden. Furthermore ECDC liaises closely with the European Biosafety Association (EBSA) and they will plan as well to take the discussion further with the biosafety professional community in the EU at their annual conference in April 2015, in Vienna.
The dual issue will never go away, but creating a culture of "safety and responsibility" is a reasonable way forward and can be seen as being as important as being in compliance with the various EU and Member State laws (e.g. workers protection, export control, GMO, etc…). There are a number of initiatives that could be supported by ECDC and their networks in the public health field to reach this goal, but the EU Member States would have to want to support this as one of the many priorities in public health and communicate this through the appropriate channels. ECDC as an advising body on risks can play a role in advising on these debates and in relevant scientific advice and preparedness activities.

**European Academies Scientific Advisory Council (EASAC)**
EASAC is advising the European Union and has in the recent past paid attention to a number of comparable issues in the life sciences. EASAC decided to take up the debate that had come up around gain-of-function research. EASAC does so by sharing the different perspectives with the involved academies. There will be attention for good practices in this field. EASAC is talking with European institutions to find out what can help them in this debate. There is a personal link between EASAC and the (global) Inter Academy Panel, so that the debate in that institution also can be promoted.

## Responsibility and awareness of scientists

From the point of view of researchers there is the question why they should go to committees such as proposed by KNAW. From the Dutch perspective the reason for asking the committee is having more certainty than e.g. lists can give about the possible dual use character of the proposal. And by having that certainty there can be a better anticipation on the possible hindrances (such as the need of an export licence). In the German proposal the first step is going to a local biosecurity officer. The next step is the proposed national committee.

One of the signalized problems is the lack of specific biosecurity knowledge of many local committees that judge research proposals. This could have as a consequence that such committees never will signalize examples of dual use research, although that could be expected given the kind of research that is being done. All the more reason for a national advisory committee that has the possibility to ask ad hoc experts.

It is a point of discussion if scientists are really unaware of the risks or underestimating risks. This is the view of security experts and one of the consequences could be that life scientists should get education in security issues. However, most researchers who are doing gain-of-function research are aware of biosecurity risks, dual use etc. Young researchers are educated in this field. The picture that gain-of-function researchers are wild cowboys is wrong. Proposals are reviewed, all kinds of permission are needed. In this research it is realized that gain-of-function in one respect (as transmittability) will influence other functions (such as pathogenicity).

A reference is made to the rules at the Max Planck Institutes. There the director of an Institute has the right to block the publication of a manuscript if he/she thinks that this publication can damage the reputation of the Institute. This could be the case with dual use publications. This procedure shows that there are some rules already so that we are not in a total vacuum.

Different dualities can be discerned in this debate. One duality is that between biosafety and biosecurity. In languages as German and Dutch there is no difference between the words for safety and for security. Maybe that is even better, because it makes researchers aware of the whole range of possible problems. This is also expressed in the word biorisk.

The other duality is between risks and benefits. One of the essential questions in this debate should be how the public health benefits of gain-of-function research can be weighed against the risks. There is no place where that weighing can be done. The big problem is that scientists do

not agree on this. The problem with gain-of-function is the split up of the scientific (or virological) community (although it concentrates around some very specific experiments). Despite these problems a solution has to be found, if only because the public does not like and not accept a situation of permanent uncertainty. To reach this, leadership is needed.

# CONCLUDING REMARKS

First it is emphasized that all researchers (for or against gain-of function) are devoted and driven people trying to solve important problems. It is important to stress the need for an open discussion on these kinds of issues, not only within science, but also between science and the public. This is necessary for the public trust in science.
In this debate it became clear that the individual responsibility of scientists will not cease to be an important aspect for dealing with gain-of-function research. This responsibility can be strengthened by ethical review boards and codes of conduct. However as standards need to be defined and since self-regulation may sometimes fail, regulation will always be necessary. Even if there is regulation, things will never be regulated for 100%. It is good to be careful with new regulation. Look first what already exists and how that can be adapted to this new kind of research. It is also good to realize that different regulations can serve the same principles. Given the different approaches in various EU-member states it is interesting to see if and how a European regulation can develop. The export regulation of the EU is an example. It is positive that this regulation is now evaluated to see if it needs to be adapted. In the same line we appreciate that EASAC is dealing with this issue from the perspective of the academic world.

And of course it is hoped that this debate has contributed to the further development of solving the important problems of biosecurity and dual use research.

# ABOUT THE SPEAKERS

**Hans Clevers**
The geneticist and physician Hans Clevers has been the President of the Royal Netherlands Academy of Arts and Sciences (KNAW) since 1 June 2012. He has also been professor of molecular genetics at Utrecht University Medical Centre (UMC-U) since 2002. From 2002 to 2012, he was the director of the Hubrecht Institute, one of the sixteen KNAW institutes. Hans Clevers is seen as an enthusiastic, engaged, and inspiring researcher who is one of the world leaders in his field. His research deals with the intestine, in both its healthy and diseased state.
Prof. Clevers has received countless research prizes in recent years, including the Spinoza Prize (2001), the Louis-Jeantet Prize (2004), the Josephine Nefkens Prize for Cancer Research, the Meyenburg Prize (both in 2008), the Kolff Prize, the Ernst Jung Medical Award, and the Léopold Griffuel Prize (all in 2011). In 2012, he was awarded the Léopold Griffuel Prize, the William Beaumont Prize, and the prestigious international Heineken Prize for Medicine. He was also made a *Chevalier of the French Legion d'Honneur* and a Knight of the Order of Orange-Nassau. In 2013 he was awarded one of the 'Breakthrough Prices in Life Sciences'. In 2014 the Massachusetts General Hospital Award in Cancer Research has been given to Hans Clevers.

**André Knottnerus**
André Knottnerus was appointed chairman of the Scientific Council for Government Policy in May 2010. Before he has been the president of the Health Council of the Netherlands for nine years. He was responsible for numerous advisory reports to the government, among which reports on bioterrorism and on pandemic development (including the 2009 flu pandemic).
He began his career as a GP in Amsterdam, where he was also attached to VU University Amsterdam. He studied epidemiology at Maastricht University, obtaining his PhD degree with a thesis on the evaluation of diagnostic tests. Since 1988 he is professor of General Practice and has published a great deal on primary care, public health and quality of care. More than 65 young scientists have obtained their doctorates under his supervision. He has received various awards for this scientific and executive work.
In the early nineties he was dean of the Medical Faculty in Maastricht, and from 1994 to 2002 he was founding director of the Netherlands School of Primary Care Research. He is editor-in-chief of the Journal of Clinical Epidemiology, and member of the Royal Netherlands Academy of Sciences (KNAW). From 2009 to 2012 he was chair of the Medical Section of the Academy.

**Giorgio Palù**
Giorgio Palù is working in the fields of Molecular, Applied (Biotechnology) and Clinical Virology and Microbiology. He is involved in development of molecular and cellular therapies and design of viral and non-viral vectors for gene transfer, somatic gene therapy and vaccinology for neoplastic, infectious and genetic diseases. He is an author of over 400 publications in international journals of biomedicine and a keynote lecturer at many International Congresses, as well as for Research and Educational Institutions. He is in the Editorial boards of some influential journals in his working field. He has been the Head of the Unit of Clinical Microbiology and Virology, Padova University Hospital/Veneto Region since 1996. He combines this function with a number of other tasks and activities for this university and for national and regional healthcare. Palù received several awards, such as the L. Pauling Award for Molecular Medicine (1997) and the International Prize in Medicine Bruno da Longobucco (2005). He has been the president of the European Society for Virology since 2013. Outside his work he is a writer, tennis player and cyclist.

**Simon Wain-Hobson**
Simon Wain-Hobson comes from a family of artists and went into science in part to do something different! He obtained his DPhil in biophysics from the University of Oxford. During a post-doc at the Weizmann Institute in Israel he met his French wife and moved to Paris where he switched to human virology, working notably on the AIDS virus HIV, from the earliest hour. Being the first to publish its genetic map his group went on to show that it evolved from a chimpanzee virus. They highlighted with exquisite precision the phenomenal genetic variation and rapid evolution of HIV. After more than 25 years work with the AIDS virus his group found a remarkable connection that allowed them to move into cancer

research - cancer genomes harbor tens of thousands of mutations. The Pasteur group showed that humans encode a DNA mutator enzyme, APOBEC3A, which can mutate chromosomal DNA. It is now accepted that this enzyme is a human mutagen on a par with ultraviolet light and cigarette smoke. He is Professor at the Institut Pasteur and has published more than 200 papers. A member of the European Molecular Biology Organization, Academia Europaea, he is Director of the French papillomavirus reference laboratory. He won the André Lwoff prize in 1996 and Athena prize from the French Academy of Sciences in 2007 and is Officier de la Légion d'Honneur. He is presently Board Chair of the Foundation for Vaccine Research in Washington DC. He collects 18C English drinking glasses and publishes on the subject.

# LIST OF PARTICIPANTS

**Chairman and speakers**
Hans Clevers (president KNAW, word of welcome)
André Knottnerus (chairman)
Giorgio Palù (debater, European Society for Virology)
Simon Wain-Hobson (debater, Foundation for Vaccine research)

**Participants**
Ayse Aidin (Ministry of Foreign Affairs)
Linda van den Berg (Netherlands Biosecurity Office)
Tom van den Berk (Netherlands Center for Counter Terrorism)
Maaike van den Biggelaar (Ministry of Health, Welfare and Sport)
Annemarie Bouma (Ministry of Economic Affairs)
Gert Demmink (Eagle Compliance Company, dual use counsellor)
Robin Fears (European Academies Science Advisory Council, EASAC)
Mariet Feltkamp (Leiden University Medical Center, virologist)
Bernard Fleckenstein (secretary-general ESV)
Henrike Hartmann (VolkswagenStiftung)
Sander Herfst (Erasmus Medical Center, virologist)
Evelien Kampert (National Institute for Public Health and the Environment)
Kathryn Nixdorff (Univ. Darmstadt, adviser German Ethikrat)
Amanda Ozin (European Centre for Disease Prevention and Control, ECDC)
Irene Plank (European Commission, DG Research & Innovation)
Peter Rottier (president section virology of Dutch Society for Microbiology)
Mirjam Schaap (Netherlands Biosecurity Office)
John Skehel (Royal Society)
Dirk Stemerding (Rathenau Institute for technology assessment)
Birgit Toebes (Groningen University, International Law)
Lous van Vloten – Doting (president Advisory Committee Biosecurity KNAW)
Gijsbert van Willigen (Dutch Biological Safety Officers Platform)

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