DECEMBER 10 - 12, 2014

SYMPOSIUM
HERRENHAUSEN PALACE, HANOVER, GERMANY

SUMMARY REPORT

DUAL USE RESEARCH ON MICROBES: Biosafety, Biosecurity, Responsibility

Organized by the Volkswagen Foundation in conjunction with the Max Planck Society

As soon as the scientist Möbius in Friedrich Dürrenmatt's satiric drama "Die Physiker" realized that his basic research might have an alternative use, he committed himself to an insane asylum – to protect the world from his knowledge. It is not a coincidence, that several speakers at the Volkswagen Foundation's conference "Dual Use Research on Microbes – Biosafety, Biosecurity, Responsibility" referred to this famous plot, in which Dürrenmatt's protagonist Möbius finally fails to keep his scientific ideas under cover. "Nothing that has been thought can ever be taken back," says **WILHELM KRULL** (Hanover), summing up the essence of the play in his opening speech. Therefore, humanity's only way to deal with new technological knowledge is to publicly discuss and regulate it. Whereas Dürrenmatt's drama featured advances in physics, the Volkswagen Foundation's conference focused on research on microbes, particularly gain of function (GOF) research on human pathogenic viruses like influenza, SARS and MERS.

Since 2011, GOF experiments making avian influenza viruses transmissible in mammals (and therefore also humans, probably) have triggered public debate. Initially, the question was, whether the results of such research could be published without breaching biosecurity regulations. Later, the discussion focused on whether microbes made through these experiments are a biosafety threat for humanity – so they shouldn't have been allowed in the first place. Virologist **RON FOUCHIER** (Rotterdam) himself kicked off the debate with a talk he gave at a conference in Malta in the autumn of 2011. There he presented the GOF experiments making the avian influenza virus variant H5N1 transmissible among ferrets. The purpose of the research was to find the genetic mutations, which enable H5N1 to become a potentially pandemic strain, so public health officials could detect and discern such strains in the wild. The hope is that identifying such a strain early would diminish the

risk of another influenza pandemic, which in 1918, for example, caused approximately 50 million deaths – "more than soldiers died in the Great War," **PETER PALESE** (New York City) said in a speech. He also cited the 300 million smallpox deaths in the first half of the 20th century to highlight the importance of GOF research on microbes. So far, the H5N1 virus is far from being comparably dangerous – it infected 667 humans and caused 393 deaths, according to **PALESE**. But **FOUCHIER's** and **YOSHIHIRO KAWAOKA's** (Madison) GOF experiments gave precise information explaining that just five mutations need to come together to make this virus a human health threat. "There is no other way to show this," **FOUCHIER** said at the Volkswagen Foundation's conference, which was held in Hanover. This information helped to convince politicians to maintain funding for influenza vaccine production and storage in places like Japan, **KAWAOKA** said in his speech. Meanwhile, the crucial mutations have actually been detected in wild birds, although within the genome of several different strains of influenza, not just one. "H7N9 is an intermediate between avian and human influenza viruses," he said. But the chances that they could recombine into one strain or that a strain could acquire these or comparable mutations through natural evolution are real, **FOUCHIER** says. "Flu does these experiments in nature all the time, even if we bury our heads in the sand." **FOUCHIER** said the current H10N7 influenza pandemic in seals in the North Sea, which has already killed 10 percent of the population, is comparable to the transmission experiments he did with H5N1 in ferrets in his BSL-3+-laboratory in Rotterdam.

Nevertheless, after Malta concerns were raised that the GOF H5N1 strains themselves were a threat to public health in two ways: First, because the knowledge of how to tweak an influenza virus into a potentially pandemic pathogen (PPP) could be used for bioterroristic or biological warfare purposes. Second, because the tweaked viruses could escape (or could be stolen) from the laboratory and could cause a pandemic. To judge arguments and give time for public debates, the scientific community issued a one-year moratorium, lasting until January 2013. Fifteen agents or toxins and seven classes of research of special concern were named and guidelines developed during the moratorium.

In Germany, meanwhile, the National Ethics Council was asked by the Bundestag to develop guidance for governance of DURC, which was first presented in early May, 2014, and at this conference by **SILJA VÖNEKY** (Freiburg). A month later, in June 2014, the Deutsche Forschungsgemeinschaft, together with the National Academy of Sciences Leopoldina, published a brief set of principles for

scientists[1], and (independently) the Max Planck Society established its own rules already in 2010. Most importantly, opposed to such self-regulating guidelines developed by scientific institutions, the Ethics Council recommended developing a separate law and a DURC commission to decide about experiments of concern case by case.[2] These suggestions, especially the installation of a new commission, were controversely debated and not always well received from everyone in the scientific community.[3] At the conference, **VÖNEKY** addressed this criticism by stressing that laws (as opposed to scientific self-regulation) could transfer the personal responsibility and liability for a possibly negative research outcome from the scientist to the state. If scientists decide on their own to perform certain probably harmful experiments they might be liable for any damage done, if the experiment fails – in this case pathogenic pandemic microbes raging out of control. Such DURC projects seem to be quite rare. **CORNELIUS SCHMALTZ** (Brussels) said in his talk that just three GOF projects, which might be of concern, applied for Horizon 2020 funding by the European Union.

So, already on a national level, the conference in Hanover was going to be a meeting point for discussions about how to proceed with the various guidelines on the table. But then, the conference gained international awareness and importance, when the US government on October 17th, 2014, announced a halt in the funding of gain of function research related to influenza and coronaviruses SARS and MERS, which could make them more transmissible or pathogenic for mammals. At least 18 research projects were affected, including work that had been continued or restarted after the moratorium in the labs of **FOUCHIER** and **KAWAOKA.**

The reason for the governmentally forced pausing of DURC was a set of incidents in June, **HARVEY FINEBERG** (Washington, D.C.) explained in his speech. Although these were unrelated to gain of function research, they raised governmental and public concern about the degree of safety of procedures and practices in laboratories. In three unrelated incidents at the Centers for Disease Control and Prevention (CDC) employees were inadvertently exposed to incorrectly sterilized Anthrax bacteria; another lab sent a more dangerous virus than intended to a laboratory at the Department of Agriculture; and forgotten tubes with dangerous microbes were found in deep freezers, including smallpox, which should officially only exist in two BSL-4-containment labs in the USA and in Russia.

[1] „Wissenschaftsfreiheit und Wissenschaftsverantwortung“ http://www.leopoldina.org/de/publikationen/detailansicht/?publication%5Bpublication%5D=591&cHash=9d032389b60ee54fe8068cf06627c056

[2] „Biosicherheit – Freiheit und Verantwortung in der Wissenschaft“ http://www.ethikrat.org/dateien/pdf/stellungnahme-biosicherheit.pdf

[3] According to the Society for Virology, the establishment of an additional dual use commission is not appropriate.http://www.g-f-v.org/node/220

All these biosafety breaches raised the question about whether human pathogens – whether GOF or not – could be kept as securely as promised. “Now the NSABB [the National Science Advisory Board for Biosecurity] and the National Academy are asked to provide a reconsideration and direction for gain of function research sponsored by the US government,” **FINEBERG** said. Suddenly, the Hanover conference became the first time opportunity for scientists like **FOUCHIER** and **KAWAOKA** and opponents like **MARC LIPSITCH** (Cambridge) and **SIMON WAIN-HOBSON** (Paris) to actually come together and talk face to face (versus publishing contradictory papers and comments) about how GOF experiments of concern should be regulated.

The funding pause also changed the DURC debate fundamentally because it was a “very substantial change in with whom the responsibility rests,” **FINEBERG** stressed in his speech. “Now the responsibility has moved from science to the state.” That also means that such research should not be discussed solely in the scientific community but with a wider audience, including the public. **FINEBERG** explained that people judge differently when decisions about risks and benefits need to be made. “There are many different value systems people bring to this discussion,” **FINEBERG** said. So there will be different views, whether the risks coming with GOF research of concern are legitimate or not.

Unfortunately, there is no comprehensive risk assessment for GOF research, **MARC LIPSITCH** stressed in his speech. Using data of past biosafety breeches, he calculated that they happen with a relatively low chance of 0.01 to 0.1 percent per lab per year. But if it is a PPP that escapes from a lab, between 2 million and 1.4 billion people could be involved, he estimated. **FOUCHIER** as well as **PALESE** reject these estimations of case fatality rates and consider them to be “clearly wrong.” **LIPSITCH** admits that he might be wrong, but insists that such estimations need to be done and that it is not sufficient to simply reject others’ estimations without coming up with substitutes, because “the risk is clearly not zero.” He further stressed that it is not an offense against the freedom of research to consider not funding certain experiments or research projects. “Scientists and funding agencies continuously decide which experiments to fund out of many applications,” says **LIPSITCH.** They review all sorts of arguments why one research project should and another shouldn’t get a grant, “why not consider public health risks?”

SIMON WAIN-HOBSON, in his speech, also questioned whether the value of GOF experiments really outweighs their risks. He made the point that the forced evolution of influenza viruses in the lab does

not reflect the viral evolution in the wild where other selective forces favor and work against certain viral mutations. He made a comparison with dog breeding: it is highly unlikely that any of the dog races that humans bred over the last centuries would have ever occurred in the wild simply from mutations in wolves' genomes. If this is true, and the mutations making influenza viruses more transmissible in ferrets in the lab are different from mutations in the wild, then GOF experiments might actually be misleading. Arguing against this, **FOUCHIER** and **KAWAOKA** pointed out that at least some of the mutations they found in GOF experiments can indeed be found in viral strains involved in human infections.

Instead of trying to find the mutations to make PPP through risky experiments, **ADEL MAHMOUD** (Princeton) favored a strategy to develop universal vaccines, like those being developed by **PETER PALESE's** lab. **MAHMOUD** argued that even if we knew in advance exactly which strain and which mutation would be the next pandemic threat, it would not necessarily help to develop an efficient vaccination. "We have no clue how [influenza] vaccines work," **MAHMOUD** said. Even now, when pharmaceutical companies develop the vaccine against seasonal flu, the influenza strain selected by the WHO as the one with the highest probability of causing the next season's flu is not necessarily the one used to make the vaccine. Some strains are just not growing efficiently in eggs, so that a different strain needs to be chosen – which then is less protective as a vaccine.

Estimating the risks does not only involve the experiments and the pathogenic agents, but also the laboratories where the research is done. **PAUL HUNTLY's** (Singapore) and **PETER CLEVESTIG's** (Stockholm) talk gave a deep, and to a degree disturbing, inside view of the state of art of biosafety management. **HARVEY FINEBERG** summed up what he learned in his speech in Washington, a week after the conference in Hanover: "Another very important insight that was developed at that meeting was the fact that when we talk about laboratory safety the traditional classifications of biohazard of BSL-2, -3, and -4 are not sufficiently informative or specific to give us the assurance that we would like about the security of any laboratory. A label like BSL-3 covers a wide variety of laboratory procedures and practices. We need to think about biosafety in terms of whole systems of construction, of operation, training, protocols, measuring and monitoring that create a degree of safety in the functioning of laboratories for a particular purpose." **HUNTLY** and **CLEVESTIG** made clear that even if national laws restrict certain experiments to BSL-3-labs, the procedures (and therefore safety and security) might differ significantly in different labs.

This leads to another of **FINEBERG's** key lessons from the Hanover meeting: "The topics that we are considering are global concerns, (...) and the possibilities of both the benefits and risks from the class of research of gain of function are not limited to any country." And not just the research and the ultimate risks and benefits are of global concern. The distribution of the knowledge is of course an international issue, too, added **VÉRONIQUE KIERMER.** She talked about the considerations at the journal "Nature", that go into the publication of DURC. She came to the conclusion that journal's editorial and review boards should not (and could not) be the only gatekeepers who decide which research results should be published, either fully or redacted, "because it is way too late in the process of research." Redaction is not the solution, she said, because redacting key data or methods disables subsequent research and peer review. Also, distributing the redacted information to a selected group of people on a need-to-know basis is practically unfeasible. It is also not clear who should be responsible for holding and securing these data, which criteria should be used to determine who is allowed to see the redacted information, and who should make these decisions. **KIERMER** instead called for international standards of biosafety and oversight as well as incentives for a robust laboratory culture of safety and transparency.

Whereas most conference attendees seemed to agree that the discussion – ultimately started over biosecurity concerns about **FOUCHIER's** and **KAWAOKA's** GOF work in 2011 – now focuses almost exclusively on biosafety concerns of GOF experiments, **RAYMOND ZILINSKAS** (Monterey) reminded the audience that there is still a biosecurity risk involved in the free publication of science on PPP. **ZILINSKAS** reported about the GOF-like experiments in the former Soviet Union from 1972 to 1992. In several labs like "Vektor" in Novosibirsk, up to 60,000 people were involved in research programs like "Ferment" or "Faktor" on Ebola and Marburg viruses and bacteria like Anthrax and the Plague. The goal was to add new features to the microbes, making them more pathogenic and transmissible. The "Chimera"-project, for example, introduced Ebola virus genes into the Vaccinia genome. According to **ZILINKSAS,** the Russian President Boris Yeltsin declared that "the Soviet Union violated the Biological and Toxin Weapons Treaty." But his order to shut down the program succeeded only partly. President Putin publicly disagreed with Yeltsin's judgment and said that "the Soviet Union conducted only defensive research," **ZILINKSAS** quoted him and added: "We do not know what happens there now, and should be really concerned." In a "directive on weapons" of Putin from 2012, task 4 names "the development of weapons based on new physical principles: radiation, geophysical, wave, psychophysical, genetics, psychophysical, etc."

In such a situation, where so many different perspectives and possible outcomes need to be considered, the public expectations towards scientists are even higher than ever before, said **VOLKER STOLLORZ** (Cologne): “What is needed is humility and accepting the dense and piled world we live in. Therefore, the modern scientist cannot be a priest. What the modern scientist may have left as a basis of authority is a kind of independence and a notion of scientific integrity.”

But even this authority is endangered, **STOLLORZ** warns, because the public knows that with the ever increasing experimental power and the growing diversity of scientific disciplines nobody can claim to grasp precisely what may happen. “Researchers who want to perform experiments creating man-made, new, more virulent, and transmissible microbial life forms not existing in nature have to first and foremost acknowledge the existence of the society they experiment in,” **STOLLORZ** said. Societies need time to understand and digest the new science, because the regulation has to adapt constantly to the new realities made possible by scientists. **STOLLORZ** compares this with immigration: “We are immigration societies for scientific knowledge, so we need many vigilant immigration officers at the borders between science and society.”

What exactly the process should be like is still an open question. “How could we actually make progress?” **FINEBERG** asked, pointing out, that DURC and GOF and PPP had been debated for several years. “I can tell you that some of the scientists feel like they are treading water, like in the movie Groundhog Day, every day they have to wake up and read live and rehearse and revisit the same arguments and discussion and debates, sometimes with the same people and sometimes with a slightly widened audience.” **FINEBERG’s** hope is to move beyond a wordy debate, “that can only take us so far.”

Shortly after the conference, things indeed made progress: Just a week after the conference in Hanover and a day after a hearing in Washington, the US government granted exceptions to the financing pause to seven DURC-related research projects, five working with MERS, and two with influenza viruses – although there is still not a solution in sight as to how and by whom DURC should be governed, neither in the USA nor in Europe. The exemptions were possible just because the projects were judged “urgently necessary to protect the public health” – a wording that was included in the original announcement of the financing halt. The fact that the government made these decisions without public input probably doesn’t raise public’s trust in the existing decision process.

In the end, as was pointed out by **MARK YARBOROUGH** (Sacramento) in his concluding speech, there is more to consider for the scientific community than just a certain set of experiments or the degree of freedom of research. The public's trust in science is also at stake. **MICHAEL SPECTER** (New York City), from his experience as a journalist, did not quite agree with Yarborough's estimation of how much trust the public still has in judgments by scientists. But it seemed to be a consensus upon the podium that there might be further loss of trust, if the public would understand that scientists prefer to make decisions about potentially risky projects without substantial involvement of public or governmental institutions. Without doubt, the Volkswagen Foundation's DURC conference with speakers and attendees from all parts of society and the world, was a trust building event and hopefully also one that will lead to the establishment of global regulatory structures that will help humankind to deal with DURC – so that no scientist would ever feel the urge to fake mental illness as Dürrenmatt's Möbius did.

Sascha Karberg

MORE INFORMATION

FOR PICTURES AND AUDIOS:

http://www.volkswagenstiftung.de/dualuseresearch

CONTACT

VolkswagenStiftung
Dr. Henrike Hartmann (Funding Team Persons and Structures)
Kastanienallee 35
30519 Hannover
Tel: 0049 (0)511 83 81 - 376
hartmann@volkswagenstiftung.de