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Aiding AIDS vaccine research

Professors Hagen von Briesen and **Andreas Meyerhans** have been central to the development and success to date of a new cryorepository with a novel cryotechnology platform in Germany that is improving the production, storage and distribution of samples for AIDS vaccine research

What is the Collaboration for AIDS Vaccine Discovery (CAVD)?

CAVD is an international network of scientists and experts dedicated to designing a variety of novel HIV vaccine candidates as well as advancing the most promising candidates to clinical trials. The CAVD fosters a spirit of open communication and sharing not only of data but also of methods, reagents, and specimens in a collegial network of research consortia and central service facilities. The CAVD was launched by the Bill & Melinda Gates Foundation in July 2006 and supports more than 500 investigators in 19 countries. This represents the largest private donation to AIDS vaccine research made so far.

Could you explain the role of the HIV Specimen Cryorepository (HSC)?

The HSC is hosted by the Fraunhofer Institute for Biomedical Engineering (IBMT) and therefore is related to Europe's largest research society for applied sciences. The goal of the HSC is to establish a state-of-the-art specimen repository, where samples and reagents relevant to HIV vaccine development are stored under controlled low-temperature conditions. Furthermore, we develop and provide high quality specimens, tools and procedures, having a direct benefit to the CAVD community.

Are you developing any novel cryoequipment or procedures at present?

Yes, the HSC in conjunction with Fraunhofer IBMT has developed a totally new cryotechnology platform that improves the freezing of samples and their quality. Smart cryotubes have been developed which carry an integrated memory chip that stores all identifiers, additional sample description, legal constraints, or the complete handling instructions. Thus, the sample information is always physically connected to the sample and cannot be lost. Even in the cryotank at a temperature of down to minus 180° C the sample with its memory chip is electronically connected with the outside world.

Furthermore, new cryoequipment has been developed in collaboration with companies: a hood for the storage tank and a workbench always guarantee handling and storage of samples at temperatures below minus 100° C. Thus, the samples do not warm up and the cooling chain is never interrupted. Ice formation in the tanks and on the samples is completely avoided. With such a biobank architecture, individual mistakes can be prevented.

Are you employing any methods or strategies that will enable you to focus more extensively on improving and distributing the new cryotechnology platform?

We are presenting our new technology to the research community at different conferences and congresses. The interest in the technology has been very high so we have just developed a white paper about biobanking which we will distribute to interested parties. Furthermore, the World Health Organization has proposed to update their guidelines regarding sample collection, handling and storage in cooperation with us. Our new technology will be incorporated into these guidelines as state-of-the-art.

Are there any achievements that you are particularly proud of?

Our technology has been commercialised and is produced by different companies which are operating globally. Our work within HSC has been the basis for these developments, which are unique and are based on patents of our Institute, the Fraunhofer IBMT. In cooperation with the companies, these devices have reached the market now. In this context, we were able to establish a regional cryorepository successfully at our primary site in South Africa. This lab handles and freezes its clinical samples according to our new standards, which is an important step to guarantee that the samples are processed at the highest standards directly at the place where they are taken. Thus, we have solved many problems which are influencing the specimen quality in any clinical trial.

In addition, we were able to produce large amounts of high quality HIV pseudoviruses and distributed them to laboratories all over the world. These biological reagents are now used in standardised assays to analyse the antibody response in individuals that were vaccinated with different candidate HIV vaccines. With this method it is possible to compare vaccine efficacies and hopefully identify the right mix that will be used in larger trials.

In a next step, the very demanding and challenging goal will be to automate the biobanking process and to develop fully automated cryobanks.

The cryo game

The **Fraunhofer Institute for Biomedical Engineering** hosts a new, state-of-the-art cryobank to store samples and reagents for HIV vaccine development, a facility that is crucial to a worldwide network of researchers

ALTHOUGH EXISTING HIV and AIDS treatment and prevention programmes are working, they often fail to reach the poorest and most disenfranchised individuals. A preventative HIV vaccine has the potential to control the global AIDS epidemic and avert the suffering of millions of people, but despite more than two decades of HIV vaccine research, the scientific challenges have so far blocked the development of such a vaccine. Over the past 20 years, the basis for numerous innovations in AIDS vaccination has been the findings of small teams of independent researchers. However, their efforts have thus far failed to produce an effective vaccine and a consensus has now emerged among researchers, advocates, and funders that large-scale projects featuring collaboration and concentration of efforts could accelerate the pace of HIV vaccine research.

In response, the Collaborative AIDS Vaccine Discovery (CAVD) consortium was launched in 2006 by the Bill & Melinda Gates Foundation. A worldwide network of researchers, the consortium's approach is based on the principle that HIV vaccine development will progress most rapidly and has the highest chance of success if individual initiatives are complemented by a collaborative effort. The CAVD provides funding for a range of innovative projects in the field of HIV vaccination, and the programme is designed to foster collaboration among researchers to speed up the communication of results and the sharing of ideas. In addition to focusing on fundamental HIV research, the projects funded by the CAVD have an emphasis on translational research, bridging the gap between basic discovery and product development, and the CAVD seeks a balance between productive competition and collaboration, with project teams using standardised tools and common preclinical and clinical platforms that permit the evaluation and sharing of results, while preserving the independent research crucial to innovation.

THE HIV SPECIMEN CRYOREPOSITORY

One of the CAVD's research teams is establishing a state-of-the-art specimen repository, the HIV Specimen Cryorepository (HSC), where samples and reagents relevant for HIV vaccine development can be stored under the highest quality conditions and may be shared among laboratories in the CAVD community. The HSC is hosted at the Fraunhofer Institute for Biomedical Engineering in Germany, and is led by Professor Hagen von Briesen, working closely with Professor Andreas Meyerhans at the Universitat Pompeu Fabra in Barcelona on the production of biologicals. Several other distinguished institutions in Europe and the U.S. are also involved in the HSC project, including the World Health Organization in Geneva, the National Institute for Biological Standards and Control in London, the San Raffaele Scientific Institute in Milan, the University of Lund and the University of Saarland.

Von Briesen and Meyerhans' individual areas of expertise match perfectly and synergistically: Meyerhans is a virologist and von Briesen has a background in applied virology, HIV clinical studies, sample collection and handling, as well as virus isolation and characterisation. In the HSC project, both scientists are trying to harmonise and optimise the freezing procedures of immune cells with new cryotechnologies, as well as providing standardised biologicals (namely pseudoviruses and HIV clones) which are produced centrally at the HSC laboratory

HIV vaccine development has the highest chance of success if individual initiatives are complemented by a collaborative effort

and used by the entire CAVD community. The generated specimens stored at HSC include: clinical samples and virus strains from the field; reagents developed by vaccine discovery centres such as hybridomas, clones and peptides; and bioreagents such as HIV pseudovirus stocks. As well as the establishment of a large-scale, centralised cryostorage facility, von Briesen's team have also been working on the development of new processes, cryoequipment and bioreagents. The project has created a novel cryobanking concept that provides the technological and biophysical prerequisites for secure and expandable cryobiotechnology to support the CAVD.

NEW HARMONISATION

In the initial phase of the project, the HSC team developed a novel cryotechnology platform to improve the storage and handling of samples. This included the development of smart cryosubstrates, with the addition of an integrated memory chip attached to the cryotubes that can store all identifiers, sample descriptions, legal constraints, and the complete set of parameters for operating the laboratory workflow. The HSC has partnered with the company PermaCryo Technology to produce the substrates industrially, and they are now commercially available globally. Likewise, the Fraunhofer Institute for Biomedical Engineering has been collaborating with the company ASKION to develop new cryoequipment: biobank architecture which will improve the storage and handling of samples that is also now on the commercial market. In 2010, the HSC developed two chemically fully defined, endotoxin-free and xeno- and protein free cryomedia, which they have proved to be statistically equal or better than cell cryopreservation with FBS-based cryomedia. Likewise, the PBMC cryopreservation results not only in high cell recovery and viability values, but also in the maintenance of T-cell functionality.

Another focus of the HSC has been the manual and automated production of bioreagents in a production facility that was established in close collaboration with Meyerhans. A novel, automated system for the preparation of HIV pseudoviruses is now operating successfully and in addition, the production of biomaterials has been extended to infectious molecular clones (IMCs). Up to now, more than 75 different HIV pseudoviruses and 20 IMCs amounting to 80,000 ml in total have been produced and distributed globally to CAVD partners under standardised, optimised and validated conditions. Meyerhans explains this harmonised approach has two important advantages: "The new technology helps to improve the sample quality. This is of high importance as biological assays can only be conducted if the samples are in prime condition. Bad quality samples cannot be used for research anymore. On the other hand, results can only be compared if every lab works according to the same protocols and under the same conditions. Thus, joint research is not possible without harmonisation". Despite the advantages, the harmonisation process has been the main challenge of the HSC project, since it can be very difficult to change the existing, entrenched operating procedures of research institutes.

IMPROVING WORLD HEALTH

More than 1,900 types of samples are now stored in the cryobank, and these specimens can be ordered via the project's online inventory. With more than 40 material shipments each year, the HSC service function is widely used by the CAVD and operates as a link between the different research groups: "With our newly developed technology and cryoprocedures, we are supporting the vaccine developers," von Briesen enthuses.

The next phase of the HSC project will focus on employing, improving and distributing the new cryotechnology platform, developing new cryomedia and establishing new cooperations in the field of research and development as well as technology transfer. All these new developments and service functions of HSC should help to advance novel vaccine candidates into clinical testing. In addition, the cryorepository provides training and capacity building for regional centres and technology transfer to the CAVD consortia. Von Briesen believes that the work within the CAVD is vitally important for world health: "It goes beyond basic research questions and has a large translational component that may help to improve healthcare at a global level. It feels good to be part of a global enterprise trying to combat HIV and AIDS".

INTELLIGENCE

THE COLLABORATION FOR AIDS VACCINE DISCOVERY

OBJECTIVES

The goal is to establish a state-of-the-art specimen repository, the HIV Specimen Cryorepository (HSC).

KEY COLLABORATORS

Dr Ulrich Fruth, World Health Organization, Switzerland • **Dr Marianne Jannson**, Lund University, Sweden • **Professor Dr Wolfgang Preiser**, Stellenbosch University, South Africa • **Dr Meghna Ramaswamy**, National Institute for Biological Standard and Control (NIBSC), UK • **Dr Gabriella Scarlatti**, DIBIT - San Raffaele Scientific Institute, Italy • **Professor Dr Heiko Zimmermann**, University of Saarlandes (UdS), Germany

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HAGEN VON BRIESEN is Associate Professor at the IBMT and Principle Investigator of the Global HIV Vaccine Research Cryorepository. von Briesen co-founded a start-up company (Analysis GmbH) for virus validation and safety studies.

ANDREAS MEYERHANS is ICREA Research Professor at the University Pompeu Fabra. He has won the 'Langener Wissenschaftspreis' prize for excellent scientific work in the field of viral pathogenesis and holds several patents.