2020 CAACB Workshop on
Adventitious Agent Control for Emerging Cell Lines and Cell Therapies

The Fall 2020 CAACB Workshop will be on Adventitious Agent Control for Emerging Cell Lines and Cell Therapies. Case studies and presentations will be presented around current approaches to managing the risk of adventitious agent contamination for both emerging cell lines and cell therapy products.

Tuesday, October 27, 2020
WebEx Webinar
10:30 AM – 1:30 PM [EDT]

10:30 – 10:50 AM	**Welcome, Introduction & Framing of Workshop** **Paul Barone** *Director, CAACB* **MIT Center for Biomedical Innovation**
10:50 AM – 12:55 PM	**SESSION 1: Adventitious Agent Control for Emerging Cell Lines** *Session Chair:* **Mike Wiebe**, **Quantum Consulting**
10:50 – 11:20 AM	**Anne Fournillier** *Global Head of Virology Technology Platform* **Sanofi Pasteur** **Viral Risk Assessment Methodology for Viral Vaccine Produced on Human MRC-5 Cells** Human MRC-5 cells are used at Sanofi Pasteur for the manufacturing of various vaccines. The strategy of control for specific viruses (bovine, porcine and human) needs to be defined via a risk assessment. The objective of the presentation is to present the methodology developed to carry out this risk assessment. The list of viruses identified at high risk to potentially contaminate the Working Cell Banks (WCBs) will be used to define the specific tests to implement on the new WCBs.

11:20 – 11:50 AM	**Donald Jarvis** *President; Professor of Molecular Biology* **GlycoBac | University of Wyoming** **Development of a Rhabdovirus Free Sf9 Cell Line** The baculovirus-insect cell system is a manufacturing platform that has been and is being used to produce several licensed products, including vaccines and an immunomodulator. In addition, many companies are developing this system for AAV vector manufacturing. Established cell lines derived from the caterpillar, Spodoptera frugiperda (Sf) are commonly used as the host component of this system. However, in 2014 it was discovered that all Sf cell lines tested are contaminated with a novel rhabdovirus, which is now known as Sf-rhabdovirus (Ma et al., J. Virol. 88:6576). To address this problem, GlycoBac created an Sf-rhabdovirus-negative (Sf-RVN) Sf cell line, which lacks this and other viral contaminants (Maghodia et al., Prot. Expr. Purif. 122:45). In this presentation, I will review the salient features of Sf-RVN cells and highlight their application as improved hosts for biologics manufacturing with the baculovirus-insect cell system. I also will discuss how Sf-RVN cells can be used to detect infectious Sf-rhabdoviral contaminants in insect cell lines, bioprocessing intermediates, and products manufactured with the baculovirus-insect cell system.
11:50 – 11:55 AM	**Stretch Break**
11:55 AM – 12:25 PM	**Patrice Riou** *Head of Global Analytical Experts, Analytical Sciences Research & Development* **Sanofi Pasteur** ***In vitro* Assay for Detection of Infectious Avian Retroviruses in Vaccines** In order to ensure the safety of vaccines produced on avian cells, rigorous testing for the absence of avian retroviruses must be performed. Current methods used to detect avian retroviruses often exhibit a high invalid-test/false-positive rate, rely on hard-to-secure reagents, and/or have readouts that are difficult to standardize. Herein, we describe the development and validation of two consistent and sensitive methods for the detection of avian retroviruses in vaccines: viral amplification on DF-1 cells followed by immunostaining for the detection of avian leukosis virus (ALV) and viral amplification on DF-1 cells followed by fluorescent product-enhanced reverse transcriptase (F-PERT) for the detection of all avian retroviruses. Both assays share an infectivity stage on DF-1 cells followed by a different endpoint readout depending on the retrovirus to be detected. A head-to-head comparison of the two endpoint methods showed that viral amplification on DF-1 cells followed by F-PERT is a suitable method to be used as a stand-alone test to ensure that vaccine preparations are free from infectious avian retroviruses.

12:25 – 12:55 PM	**Olivier Vandeputte** *Senior Manager, GSK Vaccines* **GlaxoSmithKline** **Application of Next Generation Sequencing to a Candidate Vaccine-Producing Cell Line for Adventitious Virus Detection** A new cell line has been adapted for growth in suspension using animal-free synthetic medium. The use of fetal bovine serum during the early steps of development before GMP stages was identified as a potential viral safety risk. A risk assessment was performed and the occurrence of unknown or discrete replicative viruses had to be addressed. To mitigate this risk, two master cell banks were tested using New Generation Sequencing (NGS), in addition to compendial assays conducted according to the standard testing plan. Nucleic acids were extracted and used for NGS. Sequencing reads were first checked for quality and then mapped to the host genome. The remaining unmapped reads were mapped to a proprietary database composed of viral genome sequences. All libraries produced high quality reads and less than 0.3% of them mapped to a virus genome. All the control spikes were detected and many reads mapped to known contaminants or plasmids. None of the reads were indicative of a contamination of the cell banks by an adventitious agent. NGS was added to the general testing plan for the release of cell banks and proved helpful in mitigating the risks associated to the use of animal derived raw material.
12:55 – 1:25 PM	**Panel Discussion** Panel Moderator: **Jean-Pol Cassart** *Director Viral Safety, Global Quality Control* **GlaxoSmithKline** Panelists: **Anne Fournillier** *Global Head of Virology Platform, Manufacturing Technology Department* **Sanofi Pasteur** **Donald Jarvis** *President; Professor of Molecular Biology* **GlycoBac | University of Wyoming** **Patrice Riou** *Head of Global Analytical Experts, Analytical Sciences Research & Development* **Sanofi Pasteur** **Olivier Vandeputte** *Senior Manager, GSK Vaccines* **GlaxoSmithKline**
1:25 – 1:30 PM	**Adjourn** **Paul Barone** *Director, CAACB* **MIT Center for Biomedical Innovation**

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Wednesday, October 28, 2020

WebEx Webinar
10:30 AM – 1:05 PM [EDT]

10:30 – 10:35 AM	**Welcome Day 2** **Paul Barone** *Director, CAACB* **MIT Center for Biomedical Innovation**
10:35 AM – 12:55 PM	**SESSION 2: Adventitious Agent Control for Cell Therapies** *Session Chair:* **Jacqueline Wolfrum**, **MIT Center for Biomedical Innovation**
10:35 – 11:05 AM	**Houman Dehghani** *Senior Director, Process and Product Development* **Allogene Therapeutics** **Foundations of Viral Safety for Allogeneic Cell Therapies** The fundamental principles of viral safety that have been developed and used in biologics manufacturing for decades remain applicable to advanced medicinal products such as cell and gene therapies. Allogeneic CART cell therapies start with healthy donor PBMC and aim to deliver many doses from a single product batch that would serve multiple patients. Production of allogeneic CART cell therapies begins with PPBMCs derived healthy donors. Selection of healthy donors is defined by 21 CFR and other applicable guidelines. Considerations have to be given to exposure of the general population to different disease agents, endemic viruses, and emerging viruses as well as other disease agents. This necessitates a dynamic and advanced approach that combines the established principles of viral safety with advanced technologies to detect infectious agents. This presentation will describe these approaches as well as provide case studies for consideration.

11:05 – 11:35 AM	**Sebastian Teitz** *Scientific Coordinator, Cologne Technical Center, Asahi Kasei Bioprocess* **Asahi Kasei** **The Role of Virus Filtration in Pathogen Safety of Cell Therapy Products** Development and manufacturing of cell and gene therapy (CGT) products provides many new challenges for the assurance of pathogen safety. With unique raw materials and testing schemes, CGT products can have a substantially higher risk of virus contamination compared to traditional recombinant products, yet the viral clearance provided by their downstream purification steps can be significantly lower. One of the most effective and robust unit operations for removal of viral contaminants is virus filtration. However, the largely size-based mechanism also makes virus filtration difficult to implement in many CGT manufacturing processes. Here we discuss strategies to utilize the well-established performance of virus filters to increase pathogen safety for cell-therapy products. Effective viral clearance during cell-therapies production can incorporate virus filtration especially as an upstream barrier, as a result from the nature of the product. Overall, the unique and novel nature of risks associated with new therapeutic modalities call for implementation of robust protection strategies to ensure patient safety and supply security.
11:35 – 11:40 AM	**Stretch Break**
11:40 AM – 12:00 PM	**Thomas R. Kreil** *Vice President, Global Pathogen Safety* **Takeda** **Emerging Cell Lines, Emerging Cell Therapies & Options / Need for Adventitious Agent Control** Changes of biomanufacturing cell lines over time have resulted in quite different virus challenges that may potentially be encountered, and have thus also required adaptation of control strategies. The advent of cell therapy, a new treatment modality based on administration of cells to patients, will even more profoundly change possible virus challenges as well as the means available to manage the risk. Past issues and options to implement virus risk management interventions will be discussed.
12:00 – 12:30 PM	**Kasey Kime** *Senior Manager, Regulatory Affairs, Clinical and Compliance* **Thermo Fisher** **Biological Raw Material Considerations for Use in Cell and Gene Therapy Manufacturing** This presentation will provide an overview of the biological safety considerations from both a supplier and user perspective for raw/ancillary materials used for the further manufacturing of Cell and Gene Therapies. An overview of the common regulatory guidelines related to cell and gene therapy raw materials will be discussed in addition to practical tips for performing biological raw material risk assessment covering sourcing aspects, biosafety, and traceability documentation expectations.

12:30 – 1:00 PM	**Panel Discussion** Panel Moderator: **Houman Dehghani** *Senior Director, Process and Product Development* **Allogene Therapeutics** Panelists: **Kasey Kime** *Senior Manager, Regulatory Affairs, Clinical and Compliance* **Thermo Fisher** **Thomas R. Kreil** *Vice President, Global Pathogen Safety* **Takeda** **Sebastian Teitz** *Scientific Coordinator, Cologne Technical Center, Asahi Kasei Bioprocess* **Asahi Kasei**
1:00 – 1:05 PM	**Adjourn** **Paul Barone** *Director, CAACB* **MIT Center for Biomedical Innovation**

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Thursday, October 29, 2020

WebEx Webinar
10:30 AM – 1:30 PM [EDT]

10:30 – 10:35 AM	**Welcome Day 3** **Paul Barone** *Director, CAACB* **MIT Center for Biomedical Innovation**
10:35 AM – 12:50 PM	**SESSION 3: Rapid Testing Methods for Products With a Short Shelf Life** *Session Chair:* **James Leung**, **MIT Center for Biomedical Innovation**
10:35 – 11:05 AM	**Maria Bednar** *Scientist II AT Virology* **Biogen** **Potential of Next-Generation Sequencing Method for Adventitious Virus Detection in Cell Banking** Viral safety is essential testing for biological products, *in vivo*, *in vitro*, and PCR are currently used for adventitious virus detection. These assays can take a significant amount of time, result in unexpected outcomes, be labor intensive, require the use of many animals, and are limited in the amount of data that can be collected. Next-generation sequencing (NGS) can be used to increase viral safety by producing more in-depth data, speed up testing timelines, and eliminate the need for animal testing. Biogen has been working to develop an assay for the use of NGS for adventitious virus testing. An NGS workflow has several steps that require optimization to find the optimal overall protocol. Starting with the extraction protocol, all the way through to bioinformatic analysis of generated sequences. Here we will present the overall push for replacing current testing methods with NGS, and also some data and considerations for doing so.

11:05 – 11:35 AM	**John Duguid** *Senior Director, Research & Development* **Vericel** **Rapid Sterility and Mycoplasma Tests for Cell and Gene Therapy** Rapid detection of contaminants is essential for cell and gene therapy products with short shelf lives. Integrating quality into the process through lot segregation, raw material qualification, environmental control, personnel training, and detailed procedures is critical because final test results for conventional microbiological tests may not be available prior to product release or patient administration. Developing, validating, and implementing rapid microbiological methods enables real-time release of these products, however. Applying a risk-based approach during development mitigates most issues prior to validation and facilitates successful implementation. Proactively removing these obstacles provides convincing evidence that the advantages of rapid methods outweigh the limitations, garnering support from regulators for implementation as routine product release tests. Including rapid methods in official compendia should accelerate industry adoption as tests using advanced technologies become mainstream.
11:35 – 11:40 AM	**Stretch Break**
11:40 AM – 12:10 PM	**Wayne Miller** *North America Sales Manager, Sales Specialists/Tech Service* **Sartorius Stedim** **Rapid Sterility Testing of ATMP's-Validation of a qPCR Method** With the advent of novel treatments utilizing ATMP's, routine sterility testing is challenging as the shelf life of the treatment tends to be very short. In many cases, the treatment is given prior to having the standard QC release testing complete. This presentation will cover the validation of a qPCR based rapid sterility test validation for ATMP's.
12:10 – 12:45 PM	**Chakameh Azimpour and Ren-Yo Forng** *Senior Scientist, BioSafety Development Manager* | *Scientific Director, Process Development* **Amgen** **Rapid Sterility and Mycoplasma Detection Method for Biologics and Short Shelf-life Cell Therapy Products** Regulatory agencies recommend microbial testing, including sterility and mycoplasma testing, on the product at the manufacturing stage when the test is most likely to detect contamination. Due to the limited expiry of many cell-therapy products, it is not feasible to perform the compendial testing that often take weeks to complete. Here we review the regulatory guidance for microbial testing on cell-therapy product with short shelf-life. Feasibility study of a rapid mycoplasma testing on CHO-based in-process samples is being used as proof of concept for application of such rapid testing for control of cell therapy production. Additionally, feasibility study of a rapid sterility test technology using a test article representative of drug products demonstrated that a valid sterility test outcome can be obtained between 10 hours and 9 days depending on the type of test microorganism included in the study.

12:45 – 1:15 PM	**Panel Discussion** Panel Moderator: **Stacy L. Springs** *Senior Director of Programs; Executive Director, Biomanufacturing@MIT-CBI* **MIT Center for Biomedical Innovation** Panelists: **Maria Bednar** *Scientist II AT Virology* **Biogen** **John Duguid** *Senior Director, Research & Development* **Vericel** **Ren-Yo Forng** *Scientific Director, Process Development* **Amgen** **Wayne Miller** *North America Sales Manager, Sales Specialists/Tech Service* **Sartorius Stedim**
1:15 – 1:30 PM	**Closing Remarks** **Stacy L. Springs** *Senior Director of Programs; Executive Director, Biomanufacturing@MIT-CBI* **MIT Center for Biomedical Innovation**