Successfully implementing NAMs: *practical applications in drug development and clinical practice*

3RCC

Schweizerische Eidgenossenschaft
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Eidgenössisches Departement des Innern EDI
Bundesamt für Lebensmittelsicherheit und Veterinärwesen BLV

December 13th, 2024
UniS, Room S003, University of Bern
9:00 – 17:30

Open registration
click **here** or
scan there:

Accreditation for 1 day of continuing education for animal experimentation and toxicology *(pending confirmation)*

08:30 - 09:00 **Registration**

09:00 - 09:15 **Introduction - can we measure replacement? Jenny Sandström**, Swiss 3RCC

09:15 - 09:45 **What is the regulatory status on NAMs? Tatjana Pecaric Petkovic**, Swissmedic

Session 1 Implementing NAMs in clinics: diagnostics and personalized medicine applications

09:45 - 10:05 **State-of-the-art on NAMs technology and innovations applied in the clinic Olivier Guenat**, University of Bern

10:05 - 10:25 **Coffee break**

10:25 - 11:15 **Case study I: Personalized drug combinations for cancer treatment in human organoids: clinically relevant approach Patrycja Nowak-Sliwinska**, University of Geneva, & **Jeremy Meyer**, HUG

11:15 - 12:05 **Case study II: Machine Learning-Driven, Label-Free Image Analysis Enhances Functional Assays for Predicting Treatment Responses for Cystic Fibrosis Patients using Patient-derived Organoids Sylke Höhnel-Ka**, Doppl, & **Georgia Mitropoulou**, CHUV

12:05 - 12:10 Take-home messages

12:10 - 13:00 **Lunch break**

Session 2 Implementing NAMs in drug discovery and development

13:00 - 13:20 **State-of-the-art on NAMs technology and innovations applied to drug discovery, with a focus on ADME-Tox Laura Suter-Dick**, School of Life Sciences, FHNW

13:20 - 13:50 **Regulatory acceptance during drug development – status Elisabeth Klenke**, Swissmedic

13:50 - 14:40 **Case study III: Switch from in vivo to in vitro potency assays for market batch release: analytical and regulatory challenges Francesco Nevelli** & **Morgane Rochemont**, Merck

14:40 - 15:30 **Case study IV: In vitro methods for tumorigenicity and teratogenicity evaluation of cell therapy products Silvana Libertini**, Novartis, & **Joana Ferreira**, AstraZeneca

15:30 - 15:50 **Coffee break**

15:50 - 16:40 **Case study V: The successful use of a 3D blood-brain barrier-glioblastoma model to optimize the starting dose for the first-in-human trial of a T-cell bispecific Elisabeth Husar** & **Alina Gavrilov**, Roche

16:40 - 16:45 Take-home messages

Session 3 Round table discussion

16:45 - 17:15 **Round table discussion**: *submit your questions via the poll by Dec 6th!*

17:15 - 17:20 **Closing remarks Aude Rapet**, Swiss 3RCC

17:20 - 19:00 **Networking Apéro**

What is the regulatory status on NAMs? Tatjana Pecaric Petkovic, Swissmedic

This session focuses on the role of Swissmedic in regulatory processes to ensure that only high quality, safe and effective therapeutic products are placed on the market. Attendees will gain insight into the basic differences between regulatory domains and get a clear understanding of how these frameworks shape regulatory decisions. The session will then transition to the regulatory integration of New Approach Methodologies (NAMs), defining their role and importance. Key topics will include the qualification, validation, and standardisation of NAMs, along with their context of use. Qualification requirements will be discussed in relation to their application, with more stringent standards for drug safety decisions and more flexible approaches for early-stage drug development.

State-of-the-art on NAMs technology and innovations applied in the clinic Olivier Guenat, University of Bern

This presentation will review significant achievements in the field of organoid and organ-on-chip technologies and their role in personalized medicine. We will start with the groundbreaking work of Hans Clevers' lab using intestinal organoids to make decisions in the treatment of cystic fibrosis and demonstrate their predictive ability. We will also present studies investigating how mechanical respiratory stimuli enhance lung defenses against COVID-19 and the use of vascularized models to determine the side effects of anti-fibrotic drug, Nintedanib, as observed in the clinic. Finally, we will address current challenges, particularly the heterogeneity of patient materials, which complicates reproducibility and points to areas where further innovation in non-animal methods (NAMs) is needed.

Case study I: Personalized drug combinations for cancer treatment in human organoids: clinically relevant approach Patrycja Nowak-Sliwinska, University of Geneva, & **Jeremy Meyer**, HUG

Patient-derived organoids hold significant potential for recapitulating certain architecture and function of the organs of origin. While this is a great step in the direction of 3R friendly science, the establishment and use of these new in vitro models remains challenging for certain tumor types. With our own focus on optimization of personalized therapies for treatment of colon carcinoma (CRC) patients. To address this issue, we elaborated a robust method for isolation and cultivation of patient-derived organoids (PDOs) isolated from CRC tumors and healthy colon tissue of the same patient. The whole process including of sensitivity test of various optimized multi-drug treatments is performed in a clinically-relevant timeframe.

Case study II: Machine Learning-Driven, Label-Free Image Analysis Enhances Functional Assays for Predicting Treatment Responses for Cystic Fibrosis Patients using Patient-derived Organoids Sylke Höhnel-Ka, Doppl, & **Georgia Mitropoulou**, CHUV

The talk will cover a clinical study using rectal biopsies from healthy individuals and cystic fibrosis (CF) patients to grow organoid cultures to predict patient treatment responses. Using a microcavity array approach and forskolin-induced swelling assays, we measured CFTR function and response to currently approved CF treatments. Digital holographic microscopy (DHM) enabled precise quantification of fluid dynamics within the organoids, tracking parameters such as fluid uptake and swelling rates. These results were compared with clinical data, including sweat chloride levels and forced expiratory volume (FEV), from CF patients before and after one year of treatment. A positive correlation was shown between organoid function recovery and FEV, while a negative correlation was shown with sweat chloride levels. The study suggests that in vitro organoid analysis can predict patients' clinical responses, indicating the potential for personalized CF therapies.

Regulatory acceptance during drug development – status Elisabeth Klenke, Swissmedic

This session will explore the current regulatory acceptance of New Approach Methodologies (NAMs), examining what regulators can accept today in the context of efficacy and safety from a legal point of view. We will discuss case studies to illustrate how NAMs are being implemented to support replacement, refinement and reduction of animal testing. The session will also cover the relevant guidelines from key regulatory bodies, such as the International Council for Harmonisation (ICH) and the Organisation for Economic Co-operation and Development (OECD), and their role in promoting the use of NAMs. Finally, we will look at ongoing harmonisation efforts and collaborations between regulators, aimed at increasing the global acceptance and integration of NAMs.

Case study III: Switch from in vivo to in vitro potency assays for market batch release: analytical and regulatory challenges Francesco Nevelli & **Morgane Rochemont**, Merck

Since early 90's, Fertility Hormones have been routinely tested with in-vivo potency assay for market batch release. Relating to Follicle Stimulating Hormone, the Steelman–Pohley in-vivo bioassay is the only currently used method since it is published in the pharmacopoeias. An alternative in-vitro method was developed in Merck laboratories, a deep experimental phase was carried out to investigate the method performances and to demonstrate that the in-vitro assay was suitable to replace the in-vivo assay in quality control testing. An extended structure-activity relationship (SAR) study was performed to evaluate the capability of the two assays in discriminating chemical structural modification that could occur to the hormone molecule. The final goal was to support the regulatory acceptance for the replacement of the in-vivo bioassay by the in vitro test. The new assay is now approved in many countries, and international roll-out is still ongoing. Perspective on regulatory challenges will be shared in the session. This is a fundamental milestone showing how Merck businesses and researchers are committed to the 3R principles, reducing animal use, improving the time-to-release and drug availability to our patients keeping the highest quality control on their products.

Case study IV: In vitro methods for tumorigenicity and teratogenicity evaluation of cell therapy products Silvana Libertini, Novartis, & **Joana Ferreira**, AstraZeneca

Tumorigenicity and teratogenicity are two key safety concerns linked to cell therapy-based products, especially those derived from stem cells. However, evaluation of these risks is particularly challenging due to the lack of relevant and/or sufficiently sensitive in vivo models. Here, we describe the Highly Efficient Culture (HEC) assay and its use to monitor potential teratogenicity of human pluripotent stem cells (hPSC) derived product. In this example, the teratogenicity may arise from residual hPSC still present in the final product. We also describe an in vitro package, including a soft-agar colony forming assay (SACF) and a growth in low attachment (GILA) assay, offered as an alternative to in vivo long-term study for evaluation of tumorigenic risk of locally administered genetically modified stem cells.

Case study V: The successful use of a 3D blood-brain barrier-glioblastoma model to optimize the starting dose for the first-in-human trial of a T-cell bispecific Elisabeth Husar & **Alina Gavrilov**, Roche

The selection of an optimal first-in-human (FIH) dose that is not too low (subtherapeutic) or too high (unsafe) presents a challenge with CD3 bispecific constructs. For molecules with immune agonistic properties, the starting dose should be based on the minimal anticipated biological effect level (MABEL). In most cases, the MABEL is based on the most sensitive readout in a relevant 2D in vitro system. However, this approach often results in a very low starting dose, leading to too many dose escalation steps to reach a therapeutic dose for cancer patients. The blood-brain barrier (BBB) complicates treatment of glioblastoma further by hindering drug delivery to the tumor. On the other hand, tumors can compromise the integrity of the BBB, resulting in a highly heterogeneous vasculature with non-uniform permeability. To account for these special circumstances we developed a 3D blood-brain barrier glioblastoma model to optimize the FIH dose and predict the therapeutic dose. Our translational strategy was discussed with the FDA and the Danish Health Authority and received regulatory approval in Europe, USA, Canada and Australia.