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Universal LIMS based platform for the automated processing of cell-based assays

Abstract: Nowadays, cell-based assays are an elementary tool for diagnostics, animal-free substance testing and basic research. Depending on the application, the spectrum ranges from simple static cell cultures in microtiter plates to dynamic co-cultures in complex micro physiological systems (organ-on-a-chip). Depending on the complexity of the assay, numerous working steps have to be performed and the data from different analysis systems have to be processed, combined and documented. A universal platform has been developed for the automated handling of cell-based assays, which combines a laboratory information management system (LIMS) with a laboratory execution system (LES), a universal laboratory automation platform and established laboratory equipment. The LIMS handles the administration of all laboratory-relevant information, the planning, control and monitoring of laboratory processes, as well as the direct and qualified processing of raw data. Using a kidney-on-a-chip system as an example, the realization of complex cell-based assays for the animal-free characterization of the toxicity of different antibiotics will be demonstrated. In the kidney-on-a-chip system the artificial proximal tubular barrier was formed by seeding human immortalized proximal tubule cells (RPTEC) and human blood outgrowth endothelial cells (BOEC) on ThinCert™ membranes. Transepithelial electrical resistance (TEER) was measured daily to evaluate the barrier function of the cellular layers. Fluid handling and TEER measurements were performed using a laboratory automation platform that communicates directly with the LIMS. The LES supports laboratory assistants in executing the manual handling steps of the experiments.

Keywords: LIMS, LES, SiLA, cell based assay, lab automation

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1 The challenge to automate cell-based assays

Cell-based assays are nowadays widely used in drug discovery [1], personalized medicine [2,3] and basic research. This is due to the fact that cell sources like immortalized cell lines and iPS derived cells [4] offer a new range of possibilities regarding the assay sensitivity and reproducibility. Moreover these cell sources could be harvested and cultivated donor specific, what offers a wide range of patient specific assays. Thus a lot of clinical researchers are going to develop cell based assays to predict drug specific interactions *in vitro*. In many therapeutic schemes interactions of drugs with kidney specific cells of the tubular and/or glomerular compartment as well as the disruption of the kidney barriers formed by those cells are of major interest [5]. During the past decade a lot of handling steps of these assays like media exchange and online monitoring via imaging have been automated using laboratory automation platforms [6,7]. Nevertheless all these assays contain a multitude of steps, including initial cell seeding, supplementation and measurements, which are executed manually. This could lead to a multitude of problems, if data integrity during all the steps across the assay process is not adequate. Therefore laboratory informatics is needed to translate information technology into science by managing electronic records to optimize laboratory operations. Multiple systems may fulfil these requirements, including laboratory information management systems (LIMS) and scientific data management systems (SDMS) [8]. Based on a nephrotoxicity assay, we will show how the LIMS integration of manual and automated workflows and complex datasets of different sources will solve those issues.

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2 Nephrotoxicity assay

Testing nephrotoxicity *in vitro* means to investigate malfunctions of the glomerular or tubular barrier using cell culture models of those. Therefore the cellular assay is based on ThinCert™ inserts containing barrier models. Because the majority of molecular transporters, that play an important role in secretion and reabsorption of drugs, are located in the proximal tubule, most toxic effects arise in that part of the kidney [9]. According to that, toxicity testing is based on an *in vitro* model of the proximal tubule. The whole assay consists of 3 processes with several sub processes and steps and is shown in figure 1. It always starts with the formation of the tubular barrier. This process contains several manual sub processes like cell seeding, cell maintenance and quality

Figure 1: Nephrotoxicity assay at a glance. The standard assay consists of 3 steps: Barrier formation, Toxicity assay and End point analysis. All Steps are divided into sub processes that are done manually (indicated by human icon) or by laboratory automation system (gear icon).

assurance, that are divided into working steps, for instance media exchange. The total time to form the barrier is about 4 to 7 days. When the barrier is formed and characterized – to ensure quality aspects – the toxicity assay is going to start. Taking clinically relevant malfunctions during medication into account, several parameters including cell viability, barrier integrity and metabolic analysis have to be investigated. To emulate *in vivo* like physiological conditions, regarding pressure and shear stress, the ThinCert™ inserts are integrated into a micro physiological systems (MPS) called ZEBRA-Chip [10]. Like during barrier formation, manual steps including assembly and loading of solutions are performed. Nevertheless the execution of several working step during cell maintenance and quality assurance is done by a laboratory automation platform and the MPS control unit. This means that, in opposite to the barrier formation, sub processes like media exchange and TEER measurement are run automatically. The last Process of the assay is the endpoint analysis. Caused by exposure times of staining's this process takes 1-3 days and is performed manually. In general the whole assay consist of 10 sub processes which are done by laboratory assistants and 3 sub processes that are performed by laboratory robots or the MPS control unit. The most crucial sub process in laboratory automation is the TEER measurement because it is performed manually and automatic within the same assay. Hence TEER measurement is used to show how the automation and integration into a Laboratory execution system (LES) is done.

3 LIMS and LES an introduction

A laboratory information management system (LIMS) is a software module for research laboratories to acquire, analyze, store, and monitor laboratory data. The LIMS improves work processes by increasing productivity, traceability, sample turnaround time and data security in life sciences [11,12]. As requirements of laboratories change, the demand for advanced data management solutions is growing. Thereby resulting in modern, flexible laboratory information systems, integrating SDMS (scientific data management systems), LES, and other informatics solutions into the LIMS [11]. The LIMS is the backbone of a laboratory, supporting the whole operation. Therefore, it provides all information from a single source and eliminates communication gaps between laboratory assistants (LAs), scientists and other stakeholders, while also complying with the regulatory requirements in life sciences. Other benefits include efficient laboratory

workflows, simple retrieval of laboratory data, accelerated validation process and data quality assurance.

Besides the LIMS, LES aid in the execution of laboratory workflows, including material and product release, as well as quality testing. For laboratory professionals, LES replaces paper with electronic processes and automates the interaction with methods, instruments, and supplies in routine laboratory procedures. By automated execution, protocols are completed efficiently and in a compliant and controlled fashion. In life sciences, LES is ideally suited to support key procedures in quality control and laboratory testing. Thus, method execution, calibration of instruments, data acquisition from instruments, data exchange and storage, as well as data review and processing are executed via LES.

3.1 Automation platform

The developed LES is based on the platform of Abetter LIMS (qualitytype GmbH, Dresden, Germany). A two-level portal robotics platform (PRP) (GeSiM mbH, Großberkmannsdorf, Germany) was used for laboratory automation, regarding the handling of liquids, imaging and the measurement of TEER [6]. Therefore microtiter plates and kidney-on-a-chip systems are placed on a temperature controlled holder plate, which is located between the two bridges. A versatile tool handler is mounted to the upper bridge. It can be equipped with various fluid handling systems, sensors (TEER-Electrode) and tools. Another tool handler is mounted to the lower bridge. Each well or kidney-on-a-chip system can be maintained separately with different cell culture media as well as monitored by fluorescence imaging and TEER-measurement.

3.2 LIMS integration via LES

To make use of the beneficial effects that are described above for automation of data handling and processing of the nephrotoxicity assay, a universal LIMS platform has been developed. It combines a LIMS with a LES for the automated handling of cell-based assays, and additionally integrating a universal laboratory automation platform and established laboratory equipment. Figure 2 shows the management of all laboratory-relevant information within the described assay monitored by the LIMS, such as the planning, control and monitoring of laboratory processes, as well as the direct and qualified processing of raw data. Thus, it induces the work steps according to the assays protocol via the LES to the LA or via portal robotic control (PRC) to the PRP. The LES guides the LA through the manual work steps of the

Figure 2: LES pathways and communication between LIMS and LES. The laboratory assistant (LA) is interacting with the LIMS via LES (left column). Automated processes are controlled by the portal robotics control (PRC) (right column).

experiments by using an interactive graphical user interface. The data gained during the experiment, as well as the documentation, recorded by checkboxes in between work steps by the LES, are returned to the LIMS.

3.3 SiLA - Standardization in Lab Automation

Conforming with the data management procedures shown in Figure 2, a powerful, but universal data management standard is needed to face the obstacles during integration and implementation of laboratory informatics solutions [12]. Associations such as SiLA (Standardization in Lab Automation) and the International Consortium for Innovation and Quality in Pharmaceutical Development are making significant attempts to introduce new interfaces and data management standards to facilitate system integration [13]. At the moment, the lack of integration standards is the major challenge to a greater application of laboratory informatics in many laboratories. With no unified strategy, laboratories largely continue to follow conventional procedures, regardless of efficiency, connectivity and interoperability between systems. SiLA standards will enable a modular and versatile system approach to solve this issue. In line with these efforts, the TEER Measurement System was integrated as shown in Figure 3.

For manual handling of TEER measurement the LA is guided by the LES. The TEER measurement Device (EVOM) was connected to a BeagleBone black (BBB) that converts analog to digital signals and acts as a data converter to the SiLA Standard. Afterwards data are transferred to the LIMS. Automated processes by the PRP were controlled by a SiLA ready computer that acts as PRC and integrates a LabJack A/D converter for transformation of analog Signals.

Figure 3: Dataflow during TEER measurement. The manually recorded data (left column) are converted by a BeagleBone black (BBB) that acts as SiLA-Box. Data of automated processes (right column) are converted to SiLA by portal robotics control (PRC).

4 Conclusion

This work shows how a combination of LIMS and LES can be used to integrate various manual and automated laboratory processes of cell based assays within one informatics solution. Standard analog laboratory devices, like the TEER system used here, can be integrated easily in such systems by using embedded computers or hardware that can already function as a SiLA converter. The combination of laboratory informatics, devices and universal gateways therefore helps to improve quality of acquired data and reduces sample turnaround time.

Author Statement

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