# Software to improve transfer and reproducibility of cell culture methods

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Cell culture is a vital component of laboratories throughout the scientific community, yet the absence of standardized protocols and documentation practice challenges laboratory efficiency and scientific reproducibility. We examined the effectiveness of a cloud-based software application, CultureTrax® as a tool for standardizing and transferring a complex cell culture protocol. The software workflow and template were used to electronically format a cardiomyocyte differentiation protocol and share a digitally executable copy with a different lab user. While the protocol was unfamiliar to the recipient, they executed the experiment by solely using CultureTrax and successfully derived cardiomyocytes from human induced pluripotent stem cells. This software tool significantly reduced the time and resources required to effectively transfer and implement a novel protocol.

Stem cell culture is a critical component of over 20,000 laboratories in both the private and public sectors [1]. The application of innovative cell culture technology, including sophisticated matrices, medium and environmental cues, has enabled scientists to more closely represent *in vivo* conditions and advance clinical therapies, yet the absence of standardized documentation and execution challenges laboratory efficiency and experimental reproducibility [2]. It is essential to adopt standards and tools that will enable the accurate transfer of science and promote reproducibility among lab members and between collaborating laboratories.

Stem cell-derived cell types are currently being utilized to understand development, optimize pharmaceutical screens, study various disease models and research regenerative therapies in clinical trials [2–4]. Unfortunately, it has proven challenging to reproduce stem cell culture and differentiation results, not only across laboratories but within the same laboratory [5]. Complex stem cell protocols often require multi-day hands-on manipulations and that various media formulations be applied to the cells in a specific sequence for optimal differentiation to the target cell lineage [6–8].

Commonly, labs adopt new culture protocols by having one member learn and execute a published protocol to understand and optimize the methods prior to training other colleagues. A majority of learners record materials, methods and observations in their paper lab notebooks as they decipher and execute the new protocol and then assemble these details into a separate protocol document for transfer to others. This type of approach can be effective but is highly variable and time-consuming as protocol format and content varies by author and often requires personal interactions to successfully transfer the knowledge. Additional challenges arise from inevitable laboratory turnover causing lost knowledge of minute details critical to the efficiency and reproducibility of scientific protocols [9]. Furthermore, traditional lab notebooks and static electronic documents do not facilitate daily scheduling and efficient recording of experimental details, nor do they easily permit mining or sharing of data and protocols with lab members and collaborators [10]. Table 1 shows that while some tools, like electronic lab notebooks (ELNs) or laboratory information management systems (LIMS), aim to solve these issues, they do not offer scientists an affordable off-the-shelf solution that specifically addresses complex stem cell protocols and vessel management.

CultureTrax® is a web-based software platform designed and built to accelerate scientific discovery and improve reproducibility of stem cell research. Its users can access an intuitive graphical interface via tablet or computer to effectively manage the daily tracking of multiple cell lines and intricate culture workflows within single and multi-well culture vessels. Built in a proprietary nonrelational database, CultureTrax accommodates all maintenance and differentiation methods for hPSCs and offers a

## METHOD SUMMARY

To improve reproducibility between researchers and increase laboratory efficiency, we developed and examined a cloud-based software application, CultureTrax®. Through direct access via a laboratory tablet, we performed a 14-day cardiomyocyte differentiation using a digital standard that was shared electronically. The software establishes a novel method of experimental transfer and execution by providing daily instructions and recipes for complex cell culture protocols.

**Table 1. Comparison of cell culture documentation tools.**

| | Structured for cell culture? | Flexible? | Efficient? | Affordable? | Easily shared? | Data mining? |
|---|---|---|---|---|---|---|
| Paper notebook | | ✓ | | ✓ | | |
| ELN | | ✓ | | ✓ | ✓ | ✓ |
| LIMS | ✓ | | ✓ | | ✓ | ✓ |
| CultureTrax® | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

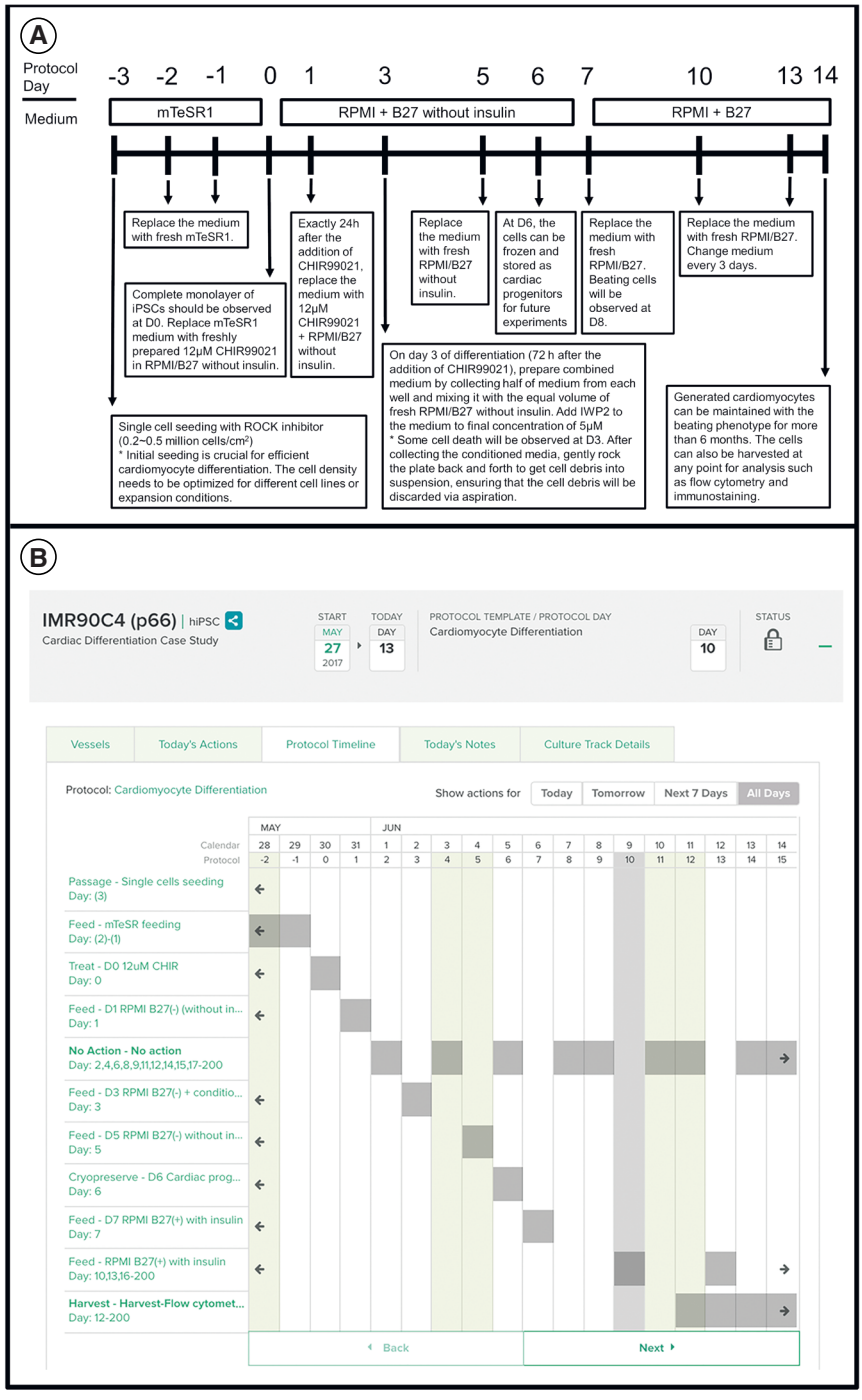


**Figure 1. A diagram of the cardiomyocyte differentiation (A) and the corresponding protocol timeline screenshot from CultureTrax® (B).** A standard 2D diagram **(A)** shows the principal culture actions required for each day of the differentiation, not including detailed methods or several procedures (single-cell seeding, cryopreservation and analysis). From CultureTrax **(B)**, a corresponding and interactive timeline of the source-generated protocol template is shown with culture actions listed for protocol days -3 through 15. The recipient used the timeline to visualize the start/finish date of the differentiation, verify the calendar date of required culture actions (x-axis), and link to the methods and materials shown in green (y-axis) to access detailed content for planning, preparation and execution.

standardized format for communicating and sharing complex stem cell protocols both electronically and via auto-generated reports (Supplementary Protocol). CultureTrax's highly semantic data structure allows automatic linking of experimental details such as cell line lineages, vessel and well identification, specific materials used, methods performed and analytical cell data generated. The software-as-a-service (SaaS) platform is currently in private beta with several leading research labs both in the US and UK (www.culturetrax.com).

In this study, we sought to understand the value of utilizing the CultureTrax software platform for training a scientist to successfully execute an unfamiliar protocol for induced pluripotent stem cell (iPSC)-derived cardiomyocyte differentiation [11]. We also sought to qualify the value of creating an electronic repository for culture data and resources (documents, lab materials, method details and timing) that was accessible from multiple devices and shareable between lab members.

Having prior experience with the method, a scientist (source) utilized CultureTrax to create a 'protocol template' from a previously published cardiomyocyte differentiation protocol [11]. A protocol template is a digitally formatted, standardized and executable protocol that a user creates with CultureTrax to be reused, edited and shared with others. To generate the protocol template, the source accessed the CultureTrax application from a laptop and followed the workflow to upload associated documents and materials, build complex recipes, and define the specific methods and timeline for required 'actions' (e.g., culture techniques such as single-cell seeding). The source used the CultureTrax platform to translate the daily requirements of the complex cardiomyocyte differentiation (Figure 1A) to a standardized protocol template, creating a day-by-day protocol timeline with direct links to their defined materials, recipes and actions required for successful differentiation (Figure 1B). The total time required for the source to establish the comprehensive protocol template was 6 h. With all of the populated materials, recipes and protocol templates being copy and editable, this upfront work significantly reduces the time commitment for future protocol template creation, editing or sharing while reducing the time required for maintaining a common

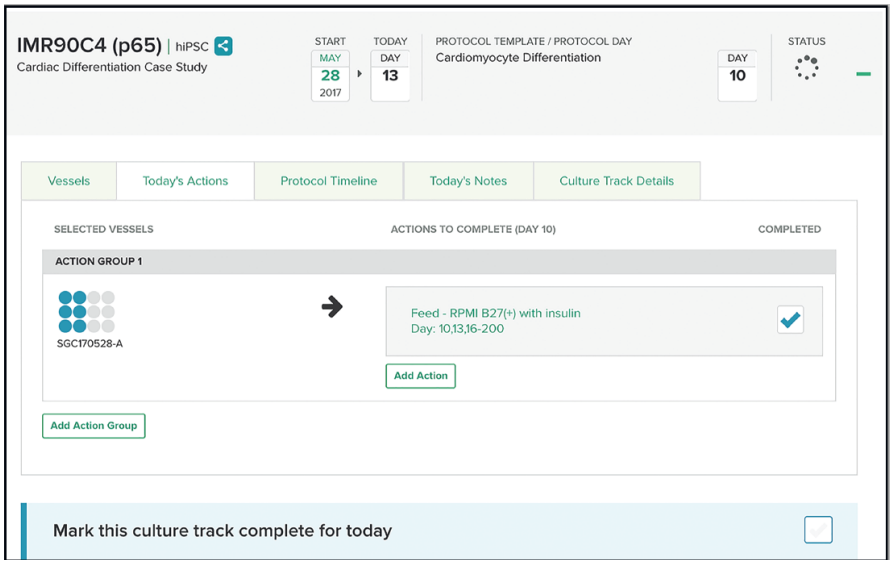


**Figure 2. A daily culture track screenshot from CultureTrax®.** The recipient's culture track is shown with one iPSC line (IMR90-4) at passage 65 cultured in six wells of a 12-well vessel on protocol day 10 of the source's cardiomyocyte differentiation protocol template. The software kept track of differentiation progress and presented daily reminders for required culture actions according to the protocol template and day (i.e., Day 10 = Feed with RPMI B27 (+) with insulin).

repository for laboratory resources from an estimated 4 h/week to 1 h/week.

A scientist (recipient), who was unfamiliar with the method, accessed the software from an iPad tablet directly mounted to a biosafety cabinet and began the cell differentiation by entering a 'culture track' into the platform. A culture track is one cell line and passage number being cultured within a group of vessels that is organized by the same protocol template. The recipient selected the source's protocol template from the shared library to execute the culture track and added cell line and passage information as well as starting vessels for the experiment. During the 2-week cell differentiation, the CultureTrax platform automatically provided daily prompts to the recipient with required material recipes to prepare, actions to take and corresponding method details to execute for the culture track (Figure 2). The recipient followed the protocol template provided by the source with no additional support or training from others (representing an estimated 8-h reduction in new protocol training time) and independently used the CultureTrax application to reference linked resources, record observations, and attach images and flow cytometry data.

By solely using the CultureTrax platform to follow the shared protocol template, the recipient differentiated cardiomyocytes from human iPSCs (IMR90-4) and observed contracting cells (~65 contractions/min) at day 14 (Supplementary Video 1) of the differentiation. Greater than 85% of cells expressed cardiac troponin T, a cardiomyocyte-specific marker [12,13], by flow cytometry (Supplementary Figure 1). The recipient was successful on the first trial utilizing CultureTrax, a major hurdle when incorporating novel protocols to the laboratory. The recipient's results were similar to previous published studies and those ongoing in the laboratory [7,11]. In addition to cardiomyocyte differentiation, we have used CultureTrax to successfully implement the differentiation of brain microvascular endothelial cells, neurons, endothelial cells and epithelial progenitor cells all from iPSCs.

As cell culture continues to advance with progress in various technologies and increasing protocol complexity, ensuring

reproducibility and troubleshooting of day-to-day operations and data will be a more significant task for cell culture management. In this case study, the recipient of the shared protocol template was able to successfully differentiate cardiomyocytes from iPSCs without costly mistakes or further instruction from the source, ultimately increasing the lab's efficiency and productivity and drastically reducing training time to a matter of hours compared with days. Protocol format and attention to detail can vary amongst individuals and, along with normal lab turnover, contribute to the loss of reproducibility and effectiveness of some protocols. Often, protocols are spread between several sources and are highly variable in format/layout so that new recipients cannot easily extrapolate a 'daily' action list. A cell culture platform that is user-friendly and enables the creation and sharing of standardized protocol templates, directly links to daily culture techniques and recipe procedures, and allows for notes, documents, images and data to be directly imported to the culture record is a valuable tool that can help eliminate these issues. The CultureTrax software we examined significantly decreases the time constraints of managing complex stem cell research, improves organization and access to laboratory resources and can help ensure future lab members and collaborators are able to effectively transfer and reproduce the original work.

## Author contributions

SGC, GJ, SPP and TS conceived and designed the experiments. SGC and GJ performed the experiments. SGC analyzed the data. SGC, GJ and TS wrote and corrected the manuscript. SGC, SPP and TS supervised the study.

## Open access



## Competing & financial interests disclosure

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## Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/full/10.2144/btn-2018-0062

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