TESTIMONIAL

Advancement through partnership

BD partnership with Cell and Gene Therapy Catapult and the PAT consortium

Reliance on drugs to cure illness has been a staple of healthcare for more than 100 years, but advances in cell and gene therapies mean that personalised cell or tissue based advanced therapy medicinal products (ATMPs) are becoming widely available to patients. Nonetheless, industries need to do more in terms of sharing information, improving processes, and reducing costs to drive further advancement.

Who are Cell and Gene Therapy (CGT) Catapult?

The CGT Catapult is an innovation and technology organisation. Established by Innovate UK, the CGT Catapult fosters collaborations between academia, industry, and healthcare providers to develop new technology and drive innovation. CGT Catapult experts cover all aspects of advanced therapies, from research and development to clinical adoption and every step in between. Their team of specialists work with collaborators to advance cell and gene therapies by making them safer, more effective, scalable and affordable.

The Process Analytical Technology (PAT) Consortium

The CGT Catapult brought together leading companies in a multi-partner, international consortium which assessed multiple novel process analytical technologies (PAT) to drive advancement of an optimal CAR-T cell bioprocess.

BD was delighted to be part of the PAT Consortium group and sees the partnership as a chance to work with cell therapy developers, ultimately helping make cell therapy products more affordable, accessible and commercialised quickly.

The consortium objectives:

• Apply advanced analytics to multiple replicates of an exemplar eight-day T cell bioprocess

• Gather extensive data to permit multiparametric analysis

• Build new network collaborations across the consortium

The goal: To reduce batch failures and manufacturing costs, allowing for accelerated progress towards cell and gene therapy commercialisation.

Why did CGT Catapult partner with BD?

CGT Catapult invited BD to be part of the PAT consortium to provide;

- Leading expertise in advanced multiparametric flow cytometry which is used to:
  - Assess and monitor product characterisation
  - Establish a target product profile (TPP) to define product identity, safety and potency
  - Ensure optimal processes are used to manufacture quality product
- Access to an extensive portfolio of reagents to support development of a novel 12 colour multi-parametric flow cytometry panel to provide in depth cell product characterisation
- Innovative quality instrumentation, proven in the field of cell therapy. The BD FACSLyric™ Flow Cytometer provided an efficient, automated and standardised solution with optimised workflows and standardised assay portability that helps to reduce variability, guarantee reliable performance and comparability of results.

Read on to discover what CGT Catapult had to say to some questions we asked them:

"How is the cell and gene therapy field evolving?"

"Why is it important to partner with companies like BD?"

"What are some of the key requirements of a flow cytometer in the cell therapy manufacturing environment?"

"Why is flow cytometry used in cell therapy?"

"What were some of the flow cytometry related challenges during the manufacturing QC of cell and gene therapy?"

Written Testimonial: CGT Catapult collaboration with Becton Dickinson on the PAT Consortium project

How is the cell and gene therapy field evolving?

The field has seen tremendous growth over the last ten years from a handful of clinical trials and companies to hundreds of therapies in development. As more advanced therapies are making their way into clinical trials on their way to the market the regulatory landscape has also evolved and demands **higher quality analytics**.

Why is it important to partner with companies like BD?

Although CGT Catapult has multiple centers and extensive in-house expertise, partnering with external partners allows both parties to access each other's knowledge base and c**ollaboratively drive forward** more than one party on their own. Moreover, collaborating with external partners gives us access to real-world problems and real-world solutions that our partners can provide.

About the PAT Consortium: Hadi Mirmalek-Sani, PAT Consortium Project Manager

Where did the idea for PAT Consortium come from?

We focus our innovation activities around a number of "Challenge Themes" as areas which present barriers and opportunities to advance cell and gene therapies – one such area is around process analytical technologies. The industry has a key opportunity at this stage to be able to bring greater understanding and control to the manufacturing of advanced therapy medicinal products, which is limited by biological variability during manufacture. Therefore, the application of new process analytical technologies have the potential to be very impactful.

What was the objective of the PAT Consortium?

The primary objective was to apply real-time, at-line and off-line analytics to multiple replicates of an exemplar 8-day **T cell bioprocess** (as a proxy for CAR-T manufacturing) and gather as much data as possible to permit multiparametric analyses to the dataset. The secondary objective was to test this new PAT and build new network collaborations across the Consortium.

Why did the Consortium reach out to BD for participation?

Key to understanding the impact of novel PAT is knowing how the cells are changing during the bioprocess, meaning you need strong phenotypic data. **BD Biosciences have extensive expertise, abilities, and products in flow cytometry and analytics.**

The importance of flow cytometry in cell therapy: Giuseppa Piras, Senior Scientist

Why is flow cytometry used in cell therapy?

Cell therapy products need to meet quality and safety standards set by regulatory bodies prior to their use in patients. To this end, analytical characterisation during development and the manufacturing process assesses critical quality attributes through product specifications. **Multi-colour flow cytometry offers in-depth product characterisation** due to its ability to assess multiple markers simultaneously on each cell and thus support the development of **high-quality cell therapy products**.

What is flow cytometry used for at the Cell and Gene Therapy Catapult?

Given the need for robust and reproducible assays for Advanced Therapeutic Medicinal Products (ATMPs) and the direct impact on safety, CGT Catapult support the development, optimisation and qualification of flow cytometry panels that provide phenotypic information during the bioprocessing of cell products as well as assess viability, identity and purity of a cell product.

What was flow cytometry used for in the PAT consortium?

In the context of PAT consortium, flow cytometry was used as an analytical tool for bridging **CAR-T cell phenotyping** with in-process controls and final product specification.

What role does flow cytometry QC testing play in cell therapy manufacturing? Why is it important?

Since **flow cytometry plays a critical role in ATMP manufacturing**, the need for continual development of best practice, along with standardisation within the field is well recognised. Quality control testing provides documented verification that laboratory instruments are installed and operating according to the manufacturer's performance specifications, as well as meeting users' needs and expectations.

What were some of the flow cytometry related challenges during the manufacturing QC of cell and gene therapy?

The **major challenges for the manufacturing QC** of cell and gene medicinal products are related to the sources of variability in flow cytometry. These being: starting materials (i.e. donor variability, limiting amount of material to test), quality of reagents, equipment set up, sample preparation, and data analysis. The lack of standardisation is also due to lack of reference materials and relevant controls.

How did BD help address to those challenges?

BD has made significant contributions towards standardisation of process and data analysis through the use of ready-to-use reagents (i.e. ready-to-use multi colour panel), instrument QC with automated compensation and generation of worklists portable between instruments. Altogether these aspects will help to **reduce variability across manufacturing sites** and achieve robust quality assessment of cell products.

What are some of the key requirements of a flow cytometer in the cell therapy manufacturing QC environment?

Key requirements for a flow cytometer in the QC environment are standardisation of the data acquisition or analysis to be both instrument and operator independent. It should meet the minimal standards; for example, record generation, data access, and storage, for data integrity and auditing purposes, and it should come with calibration set up that includes automated compensation and algorithm-based analysis, that could guarantee reproducibility of batch QC analysis between instruments and manufacturing sites.

How did BD FACSLyric™ Flow Cytometer meet those requirements?

BD FACSLyric™ Flow Cytometer contributes to the standardisation of acquisition and analysis through the universal set-up platform, minimising the variability in data interpretation, and assay portability allows alignment across manufacturing sites, thus, making the tech transfer of analytical flow panels robust. In addition, it supports compliance with 21 CFR part 11 electronic data and signature regulations for data integrity and quality audits.

The benefits of working with BD and the use of the BD FACSLyric™ Flow Cytometer: Nicolyn Thompson, Scientist

Please can you tell me about what you use flow cytometry for and why it is important?

We frequently use flow cytometry for phenotyping of immune cells derived from freshly isolated leukopak or frozen cells.

What influenced your decision to use the BD FACSLyric™ Flow Cytometer in the PAT consortium and how do you think it could be useful for QC testing?

We have used the BD FACSLyric™ Flow Cytometer in the PAT consortium study as it allowed us to run and analyse multiple samples very rapidly. At present, we have not used the instrument for QC testing at CGT Catapult. However, the features of the instrument (generation of reports and ability to standardise assays across different laboratories) and its GMP compliant software capabilities will be an important aid in a QC environment.

What were some of the flow cytometry related challenges during the manufacturing QC of cell and gene therapy?

The general challenge facing the industry is the need for standardisation, repeatability, reduction in costs and in the time it takes to set up a panel and analyse the data.

How did BD help address to those challenges?

The BD FACSLyric™ Flow Cytometer has the features of reduced requirement for setting up compensation (required to be run every 60 days). **The worklist and assays can be imported across different BD FACSLyric™ Flow Cytometers**, thus maintaining standardisation. User-defined assays can be created in advance, and a worklist can be run, and data analysis automatically generated into a report.

What are some of the key requirements of a flow cytometer in the cell therapy manufacturing QC environment?

Standardisation of instrument settings, automation of data analysis. User-friendly software both for analysis and operating the instrument, assay portability, reduction in costs and the time it takes to run an assay and data analysis.

How did BD FACSLyric™ Flow Cytometer meet those requirements?

Upon creating a multi-tube user-defined assay and running the samples in a worklist, all gating were standardised across experimental runs. There is also a built-in capability to automatically check and correct laser alignment. Upon performing a daily performance QC and Assay and Tube settings QC, there is no requirement to perform the daily "standard" compensation. The BD FACSuite™ Software also allowed easy analysis of the data at a workstation outside of the lab. It also has f**eatures that support 21 CFR Part 11 compliance and support a workflow with audit trail and e-signature.**

How has the BD FACSLyric™ Flow Cytometer helped your lab and the user's day to day?

We typically run a large panel (12 colours). For our requirement, the instrument has a blue, red and violet laser configuration. Upon running BD® CS&T beads, the built-in capability **automatically checks and corrects laser alignmen**t, allowing for optimal optical alignment at all times. It has a user-friendly software, and data and reports are easily generated upon running an assay as a worklist.

How have you found the reliability, reproducibility, and uptime?

We have used the instrument regularly during multiple experimental runs over the past 12 months and have found no technical issue in terms of reliability and reproducibility. Daily setup and performance checks using BD® CS&T beads automatically adjust instrument parameters ensuring reproducible and accurate day to day results. The highest % difference measured between assigned and actual target value is < 0.4%. **PMT voltages are automatically updated** to maintain target MFI values and **spillover values are automatically updated** as part of daily QC. Compensation is required every 60 days only.

How has the technical support from your BD engineer team been?

Technical support has been very helpful. The BD engineer team were always available to answer any query and provide support.

How did you find the training and support that the team have been given?

Our experienced team found the training very informative and helpful. There were always occasions where the BD applications support team was readily available to assist with technical and routine queries. This included the provision of training on how to use the instrument, panel development, setting up an assay, exporting data and general maintenance of the instrument.

How has BD and the BD FACSLyric ™ Flow Cytometer helped in the PAT consortium?

It has helped us to generate phenotypic data that was provided to the consortium members, during the assessment of their respective technologies. The phenotypic data generated can assist in the building of quality by design methodologies for CAR-T cell bioprocessing.

I know you haven't had the chance to use it yet but how do you envisage assay portability will help you and your collaborators?

It will potentially reduce Technical Transfer time between sites, help to maintain standardisation of flow cytometry analysis, data analysis and results generation.

Do you run samples manually or on the BD FACS™ Universal Loader and if you did use the automated sample loader, please describe how this helps to improve efficiency and lab throughput/scaling capacity?

We primarily use the universal loader. It greatly reduces the hands-on time of individually loading FACS tubes onto the SIT.

How do you plan to use the BD FACSLyric™ outside of the work you have done in the PAT consortium?

We will continue to apply the BD FACSLyric™ to generate robust phenotyping data of cell populations within our bioprocess development labs.

BD FACSuite™ software is only supporting some features relative to 21 CFR part 11.
User-defined assays are not claimed as IVD products, for more information, please refer to more information here.

CE BD FACSLyric™ Flow Cytometer with the BD FACSuite™ Clinical and BD FACSuite™ Application are in vitro diagnostic medical devices bearing a CE mark.

BD Flow Cytometers are Class 1 Laser Products.

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