ADVANCED INSTRUMENTS

Solentim

White Paper

Clonality in stem cell derived therapies, a journey from process development to manufacturing

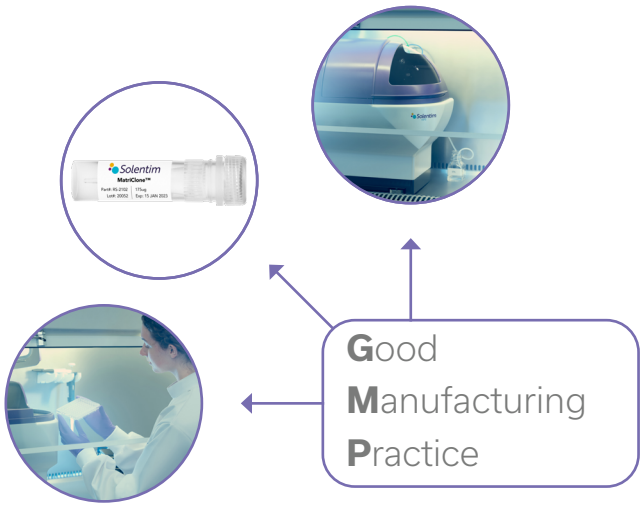

Figure 1. Integration of Solentim technologies into cGMP environment

Introduction

With a 30% growth rate and a projected $14 billion market by 2025, cell therapy, the use of cells as theactual therapy, is one of the most promising and increasingly valuable sectors in science. Using T cells, CAR-T cells and NK cells, often derived from hiPSC cells and using the latest in gene editing technologies, cell therapies represent possible treatments for a wide range of diseases including immune-oncology, neurodegenerative diseases, diabetes and heart failure.

Emergent companies in this space have an eye on the future production of clinical treatments. Whatever the timescale, the question of when and how to implement practices that will be scalable to cGMP (current Good Manufacturing Practice) often arise.

In December 2008, the European Commission enforced the "Regulation on Advanced Therapy Medicinal Products (ATMPs)" as the overarching legislation. The ATMP Regulation classifies gene-therapy, somaticcell- therapy and tissue-engineered products including stem-cell based products as pharmaceuticals when intended not for research but for human use. However, further scientific and technical developments continue to raise challenges for regulators, as GMP regulations have to be constantly adapted or even newly developed to meet the progress in this field and the clinical risk profile of these innovative products. Due to the early stage of a many cell therapies, the main focus of the regulators is currently on ensuring patient safety. Particularly in light of some of the extreme side effects and patient deaths seen with therapies such as CAR-T cells in the early stages of their development.

Upstream, there is a manufacturing bottleneck for researchers and biotech companies trying to produce new cell therapies and the cost of manufacturing is a barrier to progress. If the whole manufacturing process could be streamlined, the logistics improved and the supply chain simplified, with yields increased, that would significantly reduce the cost of goods and the complexity of getting the product to the patient, helping bring down the cost and meet the requirements of the regulators.

Adopting the GMP 'mindset' early on

Good Manufacturing Practice (GMP) applies as much to the clinical development setting as it does to manufacturing. Moreover, the GMP 'mind set', that of recognising and managing risk, has much to offer in the implementation of a research process with the ultimate aim of GMP being to protect the patient. From a clinic right down to a research bench, this mind set, talks to consistency of process, measurement and control of outcome and application of standards appropriate to their intended stage.

As companies scale up, expansion of existing methodologies minimises the cost and time invested in change. GMP is designed to understand and manage risk to ensure that the treatment is safe and meets quality standards. Transition from clinical to full scale manufacture is a critical step in the journey from cell therapy development to commercial manufacturing, and appropriate risk-based application of regulation is key to ensure safety and success at every stage of this process.

Single cell cloning in allogenic cell therapy

As the clinical future of cell therapy endeavours develop, so does the need to establish the regulatory framework and best practice in this area. Cell line development workflows using CHO cell types are well established in the production of monoclonal antibodies. In this area, there is a widely accepted regulatory expectation to use single cell cloning. By starting from a defined source cell variability, drift and ultimately product quality is best managed. Furthermore, enhancements to workflows, through maximal viability, seeding and out growth can be achieved.

Conventionally, instrumentation for single cell seeding and isolation has been designed with only the researcher in mind. Often encouraged to enable a wide range of use, such platforms are inherently difficult to validate and lack the original design approaches to make them scalable.

At Solentim, we recognize the current and future need of cell therapy customers for technologies that can be scaled towards a clinical GMP use. Systems for use today in research for effective workflows, but also designed to secure, reliable data to support the step to clinical manufacture.

Solentim products supporting the development of stem cell therapies

The VIPS instrument occupies a prominent position in therapeutic antibody and gene therapy cell line development workflows around the globe. Since its inception nearly 5 years ago, the combination of high efficiency, lower pressure seeding with in-built assurance by way of imaging the single cell in the dispensed droplet has enabled an efficient and assured front-end to workflows. In 2021, a new workflow was announced for iPSC clonality workflows utilising a novel 'imaging matrix' Laminin matrix called MatriClone. This matrix, based on Laminin-511 supports early clonal iPSC growth while maintaining pluripotency. Crucially, MatriClone is used as a soluble format and is added to the VIPS dispensing media so bypassing the need for time consuming and inconsistent plate pre-coating and imaging complications. Customers can continue to use their preferred media and ROCK inhibitors. Together, this provides a 19-25 day gene-editing of iPSCs workflow from nucleofection with gRNAs through to postsequencing expansion of top clones containing indels.

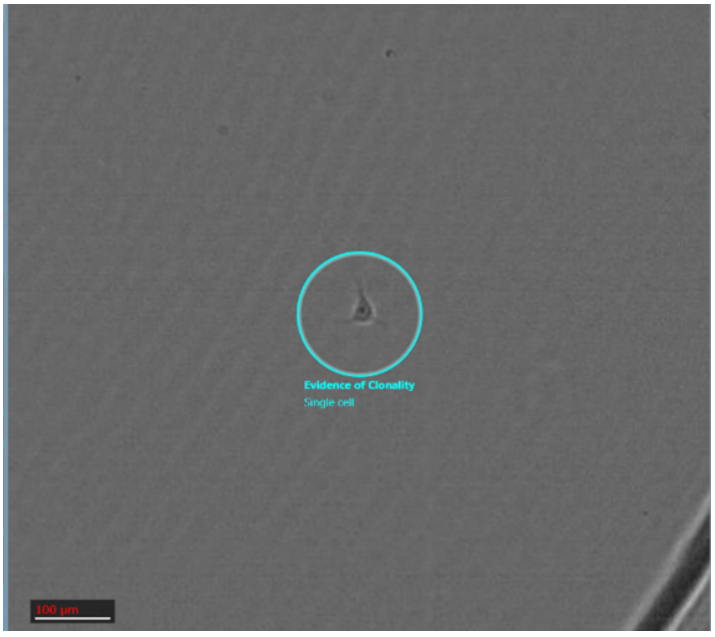

Figure 2. Example iPSC cell seeded and imaged in VIPS accelerated clonality workflow for iPSC cells. Download the application note here

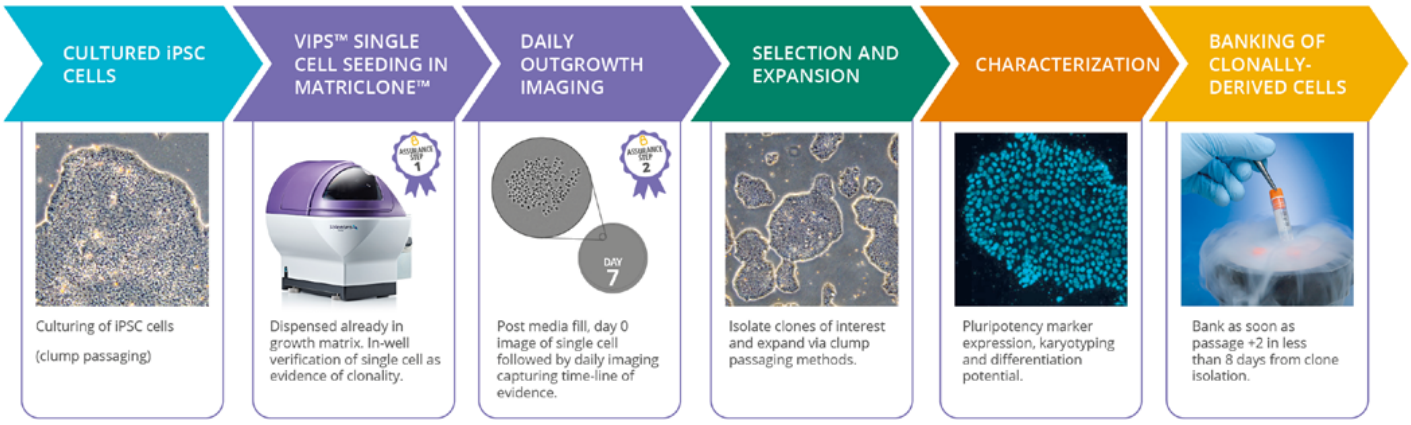

Figure 3. New workflow from Solentim utilises the high efficiency seeder VIPS™ and the imaging ready MatriClone™. The workflow takes only 30 days and results in a Clonality Report for use as part of an IND.

Commentary from Simon Hoffman, cGMP Consultant

" Without sufficient GMP expertise, companies either implement too much or too little GMP relative to the scale of their organisation and its specific needs, resulting either in unnecessary costs or insufficient quality management. A company running clinical studies will need cGMP that is proportional to those studies but not to commercial manufacture. Within the context of cell therapy, whatever the stage it is at, a quality vendor should be able to proactively work with customers in the areas of full risk analysis before installation, assessing all cGMP risks and business risks. Steps should be taken to ensure that instruments and reagents integrate with business and cGMP requirements, offering supplier assurance including quality agreements, audit hosting/certification, risk management itself, validation and qualification. The supplier should also provide a full list of SOPs (Standard Operating Procedures) for biology and use of the instrument.

I have been party to the implementation of the Solentim single cell seeder into customer stem cell labs, meeting their GMP standards. Furthermore, with their technology, the process is inherently robust, making the ability to standardize the process, help establish and meet the future regulatory expectations for clonality and make the number of gene editing projects more achievable and far more scalable. It will allow for groups to more easily perform clinical gene editing and cloning of iPSCs across a broader range of cell therapies."

Solentim is committed to supporting our customers compliance to the recognised world-class, global standards of cGMP with the implementation of GAMP-5, FDA 21 CFR Part 11 and Eudralex Volume 4 requirements.

All of Solentim's products can be fully installed, qualified/validated, in line with customer global regulatory requirements, e.g. FDA, EMA, MHRA and other relevant guidance including ISO and GAMP*. The Clonality Report documenting the history of the clone from the colony all the way back to the single cell is also a vital component of any future IND submission.

** cGMP-grade MatriClone for manufacturing is available from Solentim. Dispensing consumables are supplied sterile and can be assigned to individual projects inviting solutions in the areas of cellular reprogramming, gene-editing and allogenic production.*

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