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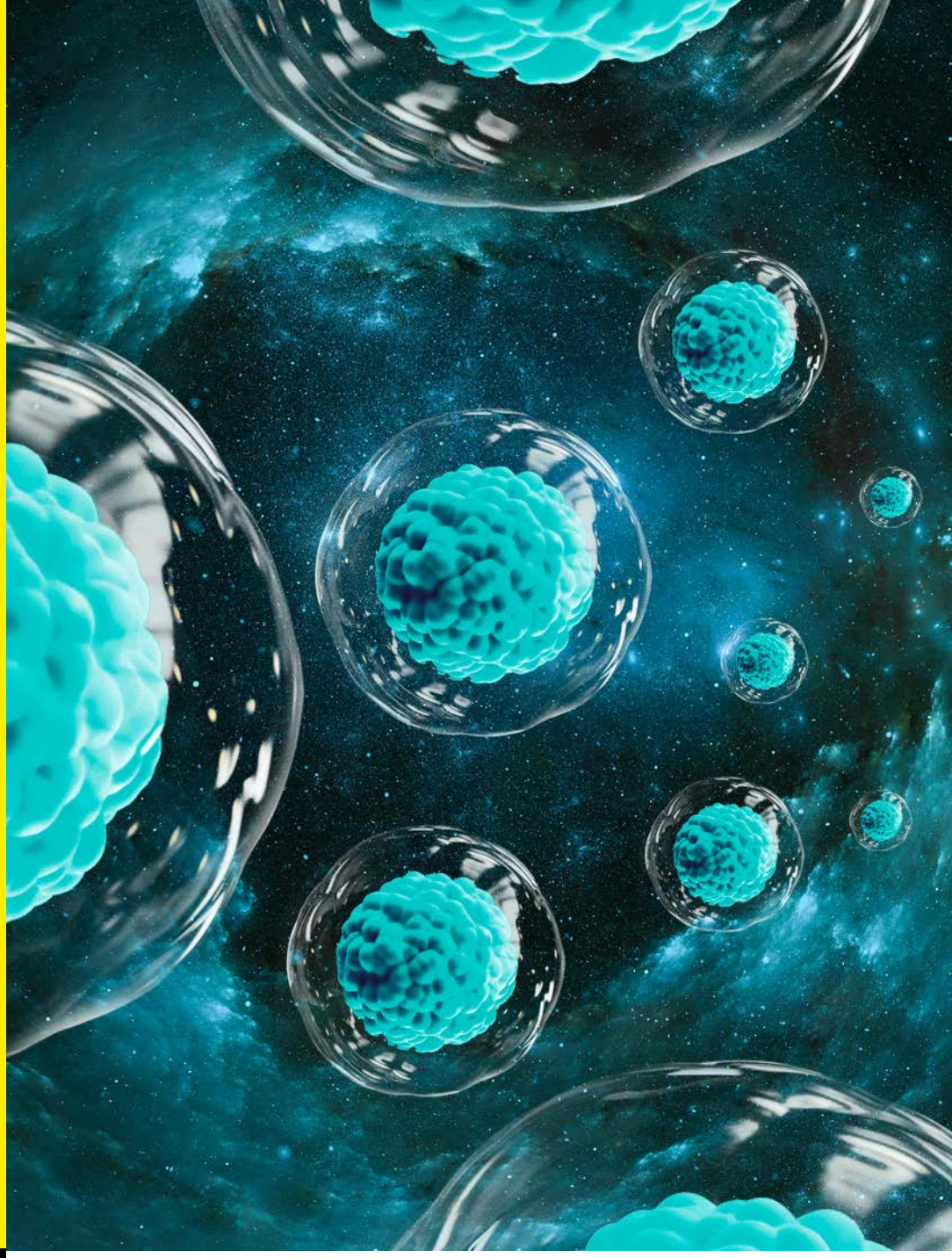
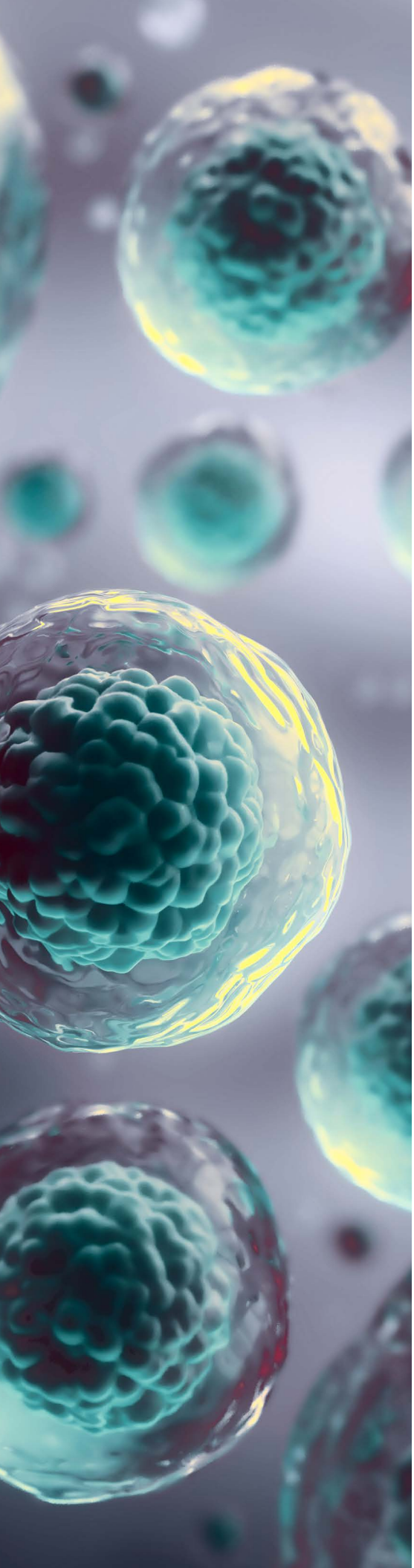


Automated Cell Selection and Retrieval Opens a Universe of Possibilities

eBook



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Introduction

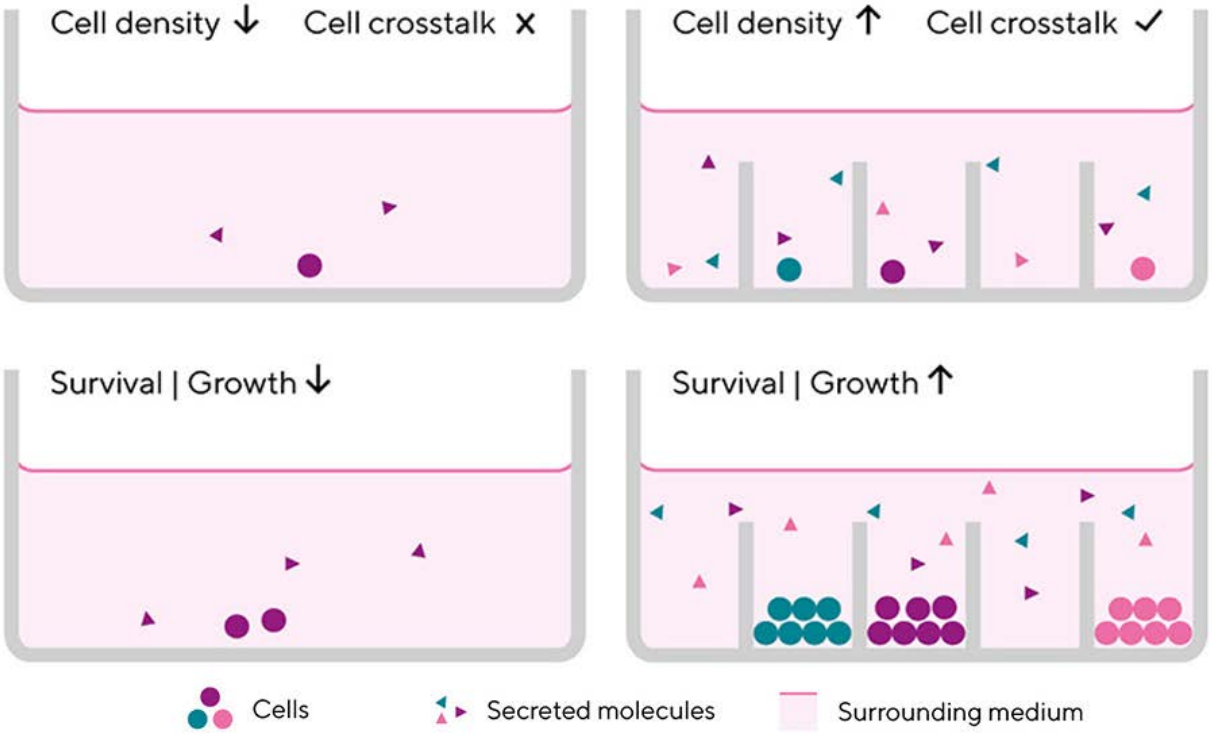
Single-cell isolation is critical to numerous research areas, including rare-cell analysis, biologics discovery, and stem cell studies. Yet, the process of identifying and isolating productive single cells continues to be a hurdle, due in part to resource-intensive, low-success techniques like limiting dilution.

Limiting dilution is a basic technique for generating a monoclonal cell line from a mixed cell population. It works based on the principal of Poisson distribution; essentially cells are serially diluted until there is a high probability of plating a volume that contains only one cell. Sometimes, multiple rounds are needed to isolate a single clone successfully.

It's well known that single cell cloning by limiting dilution is time consuming and difficult, but scientists choose it because it does not involve complicated lab equipment. Still, the process takes weeks to months and lots of manual steps without any guarantees. Limiting dilution is also stressful to cells because it deprives cells of crosstalk via growth-promoting factors in the media.

In industrial applications where speed and monoclonality matter, limiting dilution can be—limiting.

Automated robotic instruments are revolutionizing scientific research and bringing more productivity and throughput to routine workflows, thus accelerating important discoveries. This eBook highlights how automated, image-based systems, like CellCelector, are simplifying progress in a variety of research applications.



Unlike dilution techniques (left), CellCelector Nanowell Cell Culture Plates (right) allow growth-promoting cellular crosstalk in spite of the local separation. Read more about this technique on page 8.

Isolation of Rare Circulating Tumor Cells

Automated technologies for single-cell isolation can vastly simplify protocols and isolate individual CTCs or CTC clusters from enriched cell suspensions for molecular characterization at the single-cell level.

Understanding the heterogeneity in a cell population can reveal a wealth of insight into cell fate and function. In cancer, tumor heterogeneity plays a crucial role in both disease progression and resistance to therapies.

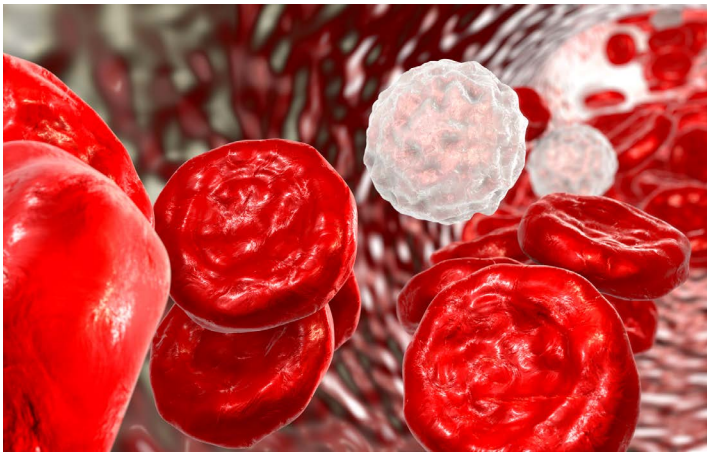
One of the main obstacles in the treatment of cancer is metastasis, which is how new tumors originating from the primary site get established at secondary sites. Advances in high-throughput genome sequencing, gene editing, advanced cell models and instrument technology are enabling scientists to dissect the underlying mechanisms that support metastasis, including circulating tumor cells (CTCs) and CTC clusters. Studying tumors at the single-cell level can help inform tailored therapeutic strategies that improve outcomes for patients.

The Role of CTCs in Cancer

CTCs are cells that break away from the primary tumor and enter the bloodstream. Once in the blood, CTCs can adapt to the microenvironment of additional sites, forming a new tumor. This process, called metastasis, is responsible for over 90% of cancer-related deaths and is an active area of research.

In order to colonize a secondary site, CTCs must first survive circulation in the blood, exit the circulatory system, and colonize a new site. This requires a host of advantageous mutations that allow CTCs to escape from immune surveillance in the blood and hijack other processes in their favor.

To understand the mechanisms behind metastasis, scientists isolate CTCs to study their functional, biochemical, and

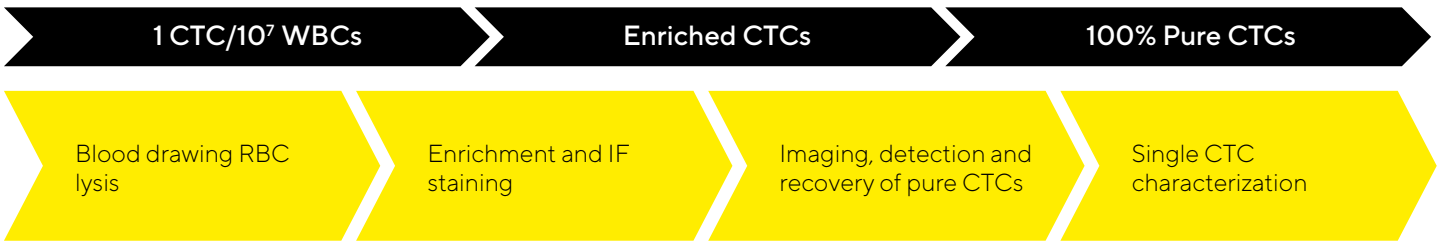


biophysical properties. This is the first step in developing new diagnostic tools and therapeutic strategies to block metastasis.

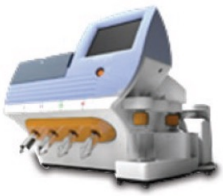
Finding the Needle in a Haystack

CTCs obtained through a simple blood draw can serve as a "liquid biopsy" to monitor tumor characteristics in real-time, including inter- and intra-tumor heterogeneity. Isolated cells are then used for DNA, RNA or proteome analysis. A liquid biopsy is a non-invasive approach that is complementary to a solid tumor biopsy in providing data to clinicians.

However, CTC isolation and subsequent characterization are technically challenging due to the low CTC cell numbers among an abundance of white and red blood cells (RBCs). For example, a one milliliter sample may contain as little as one CTC in a background of 10^7 white blood cells (WBCs). Leukocyte contamination interferes with downstream analysis of CTC-specific transcripts, and other markers, making enrichment a necessary step in single-CTC studies.



CellCelector



CTC Enrichment and Isolation

A typical CTC isolation and analysis workflow involves the following steps:

1- Blood draw and sample processing
2- CTC enrichment and staining
3- Imaging and isolation of pure CTCs
4- Single-CTC characterization

A wide range of analytical methods have been developed for CTC detection, enrichment, and isolation. These methods exploit CTC-specific properties such as surface marker expression or physical features (e.g. size, density, or deformability).

Following enrichment, CTCs are stained for immunofluorescence (IF) detection by microscopy and single-cell isolation. Having viable pure CTCs is critical to getting high-quality data in subsequent analyses.

Limitations in CTC Workflows

Cell culture protocols can influence the health, viability, and function of cells. Cell loss is common during CTC enrichment protocols that include many filtration steps to remove contaminating blood cells. Further, the added processing time can alter the expression profiles of CTCs due to environmental factors.

Another limitation of common CTC enrichment methods is that they all carry over some amount of contaminating background cells, which interfere with downstream studies. Automated technologies for single-cell isolation can vastly simplify protocols and isolate individual CTCs or CTC clusters from enriched cell suspensions for molecular characterization at the single-cell level.

Automated Rare-Cell Isolation

Automated systems for the identification and isolation of pure single cells offer many advantages over traditional methods for rare-cell isolation and retrieval. Platforms like the CellCelector can reliably deliver 100% pure single CTCs or CTC clusters from samples processed using any of the common enrichment techniques.

The CellCelector utilizes liquid buffered single-use glass capillaries that provide gentle aspiration with extremely high precision down to the nanoliter range. Each cell retrieval event is fully documented and traceable from the source to the destination, complete with images before and after picking.

Fast, Yet Gentle on Cells

Unlike manual or semi-automatic picking setups that rely on user skill, automated systems speed up the process, limiting manipulation of delicate cells. Vacuum-based or microdissection recovery systems, for example, cause stress to cells from shear stress or excessive heat, respectively.

The CellCelector system scans cells in brightfield, phase contrast or fluorescence channels to identify the cells of interest. Putative live CTCs are recovered into the destination vessel of choice for downstream analysis or recultivation. The cells spend no more than 10 seconds inside the capillary, allowing for a fast yet very gentle recovery process.

"Unlike manual or semi-automatic picking setups that rely on user skill, automated systems speed up the process, limiting manipulation of delicate cells."

A Flexible System for Single-CTC Research

Automated systems provide flexibility and speed for the isolation of pure CTCs for oncology applications. In one study, Yang et al. used the CellCelector system with the SIEVEWELL nanowell arrays for rare single-cell isolation to develop a blood-to-single CTC workflow, with high recovery for complex cell suspensions. When combined with specifically designed consumables, the CellCelector system provides a complete solution for detection and isolation of CTCs for downstream DNA, RNA, or proteome analysis.

Related Reading

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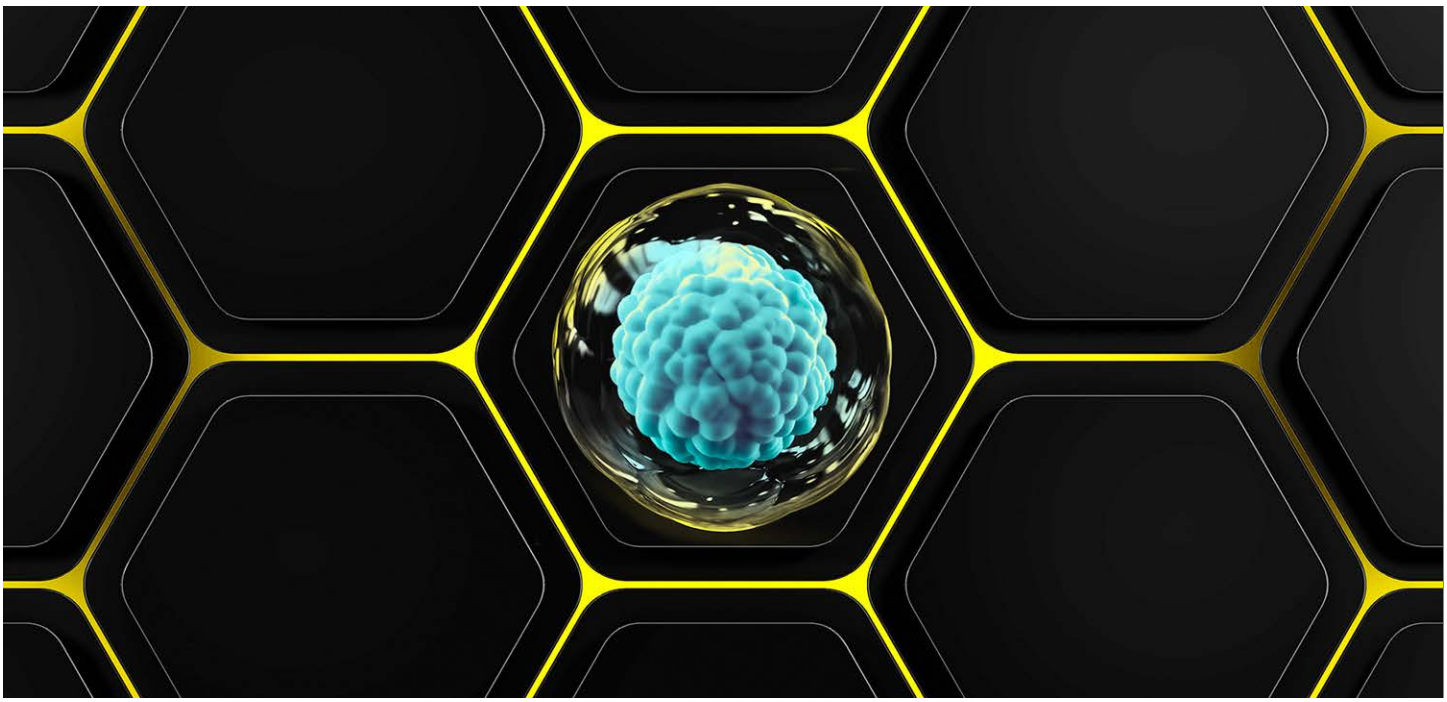


The CellCelector workflows allow handling of up to several hundred thousand blood cells per sample, without the need for sample volume reduction, and are compatible with a variety of upstream enrichment technologies, including positive immuno-magnetic enrichment, negative depletion of white blood cells based on CD45 surface markers, and label-free separation based on microfluidics or filters.

Cell-Line Development for Biologics Discovery

While fluorescence-activated cell sorting (FACS) and limiting dilution have traditionally been used for single-cell cloning, there is a growing shift towards automated, image-based solutions that simplify workflows, save costs, and support compliance requirements.

Genetic modification of mammalian cells has vast use in biopharmaceutical development. An important step early on is the isolation of clones with the desired mutation prior to downstream analysis. While fluorescence-activated cell sorting (FACS) and limiting dilution have traditionally been used for single-cell cloning, there is a growing shift towards automated, image-based solutions that simplify workflows, save costs, and support compliance requirements.

Rising Demand for Biologics

Biopharmaceutical products, or biologics, include proteins (e.g. hormones, vaccines, antibodies), engineered cells and viruses that are used to prevent or treat a range of diseases. This is an active area of research, driven by breakthroughs like CAR-T cell immunotherapies and inhibitory mAbs that target immune checkpoint proteins, like programmed cell death protein 1 (PD-1). Therapeutic monoclonal antibodies (mAbs) continue to rise in popularity with over 100 approved for clinical use.

Unlike conventional small molecule drugs that are chemically synthesized, biologics are made by living organisms or cells. Hybridomas, human embryonic kidney (HEK) cells and Chinese hamster ovarian (CHO) cells are commonly used mammalian cell lines for producing mAbs and other therapeutic recombinant protein products.

Cell-Line Development

Hybridoma technology is one of the predominant methods of developing mAbs. In this method, primary B cells are isolated from animals immunized with the antigen of interest. Since B cells are short-lived and difficult to culture, they are fused with myeloma cells to create immortalized hybridomas as the antibody-secreting source. One of the critical needs in the industry is access to cost-effective, high-throughput tools for streamlining hybridoma development, which is both time-consuming and expensive.

Once a highly specific antibody is identified, it is produced in large quantities for further characterization. Cell-line development is the process of establishing a robust and stable cell culture system for biologics production. This process begins by transfecting the host cell with an expression vector carrying the gene of interest. Cell lines used for the development and commercial production of biotherapeutics face additional scrutiny to ensure stability, monoclonality, and product quality.

Traditional Methods of Single-Cell Cloning

Traditional methods of single-cell isolation and cloning are limiting dilution, single-cell sorting by FACS, and single-cell printing. While widely used, these methods have important drawbacks when it comes to outgrowth rates and time-to-result.

Limiting dilution is a basic technique for generating a monoclonal cell line from a mixed cell population. It works based on the principal of Poisson distribution; cells are serially diluted until there is a high probability of plating a volume that contains only one cell. Sometimes, multiple rounds are needed to ensure monoclonal status. This

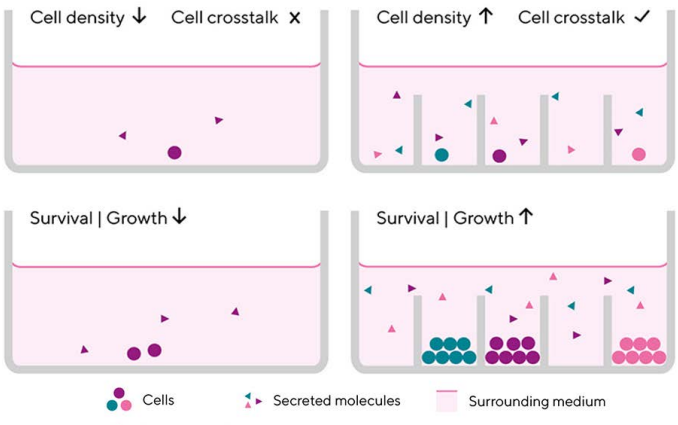
process requires weeks to months and many manual steps. Dilution is also stressful to cells as it deprives them of crosstalk via growth-promoting factors in the media. FACS and single-cell printing expose cells to physical stress, compromising cell health and viability. The process can also activate cell stress pathways, which can alter cell behavior and function.

High-Throughput Nanowell-Based Cloning

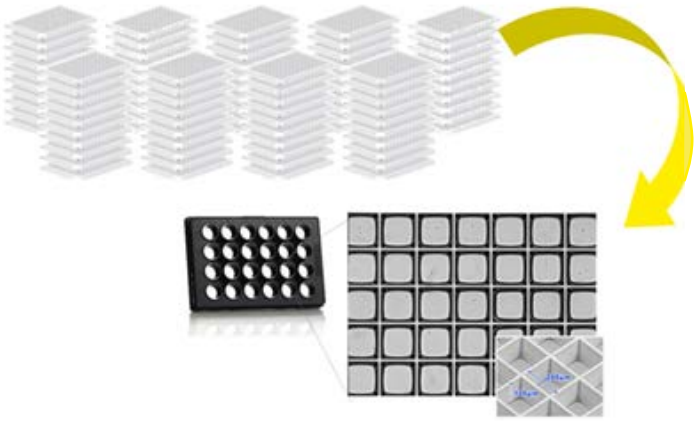
A new method called high-throughput nanowell-based image-verified cloning (HT-NIC) speeds up the cell-line development process by producing colonies that are 100% verified monoclonal, with significantly better outgrowth rates. This technique combines the CellCelector system with unique nanowell plates to identify monoclonal high-producer clones.

The key to the throughput advantage with HT-NIC is the nanowell plates. Nanowell plates are 6- or 24-well cell culture plates that have thousands of tiny (e.g. 200 µm) nanowells at the bottom of each well. Nanowells can effectively isolate single cells within a much smaller area. For example, a single well from a 24-well nanowell plate can yield up to 500 target clones. By comparison, getting this many clones using the limiting dilution method requires more than two dozen 96-well plates.

The CellCelector system allows for rapid and precise selection of high-producer hybridoma and CHO cells in antibody discovery workflows. In one study, Matochko et al. used the platform to isolate individual antigen-specific primary B cells from XenoMouse® models immunized with a recombinant therapeutic protein, EGFR. The unique nanowell technology allowed for the identification of antigen-positive hits in one day.



Unlike dilution techniques (left), the HT-NIC method (right) allows growth-promoting cellular crosstalk.



Verified Monoclonality with Automated Imaging

Monoclonality of the producer cell is critical to manufacturing a safe and reliable biologic. In traditional workflows, monoclonal status is assessed either manually or retroactively after outgrowth. The HT-NIC method automatically verifies monoclonality.

Following the initial seeding, each cell receives a unique ID and is tracked through growth, assessment, and colony picking. After several days of growth, nanowell plates are automatically scanned (e.g. for expression of fluorescent markers) and ranked for viability and monoclonal status. Clones verified as monoclonal and healthy are automatically picked and transferred to multi-well plates for further expansion. Importantly, this process supports compliance with full documentation, including images acquired both before and after colony selection.

Healthier Cells with Stronger Outgrowth

Cultured cells are more likely to thrive together where they have access to natural growth factors shared through the media. In contrast to traditional cell culture plates, the HT-NIC method supports cell health and outgrowth rates due to the unique architecture of its nanowell plates.

Although single cells are physically isolated within tiny nanowells, they can maintain chemical crosstalk through shared media inside the well. Using nanowell plates improves cell health and increases the likelihood of success with difficult-to-grow cell types, while maintaining the monoclonality of all single cells.

"High-throughput nanowell-based image-verified cloning (HT-NIC) can speeds up the cell-line development process by producing colonies that are 100% verified monoclonal, with significantly better outgrowth rates."

Accelerated Antibody Discovery and Production

The therapeutic mAb market is expected to continue growing at a steady rate. Meeting this demand requires adoption of technologies that streamline processes. Automated methods, like HT-NIC, relieve common bottlenecks in cell-line development to deliver productive, verified monoclonal colonies in less than a week, helping companies meet competitive time-to-market goals.

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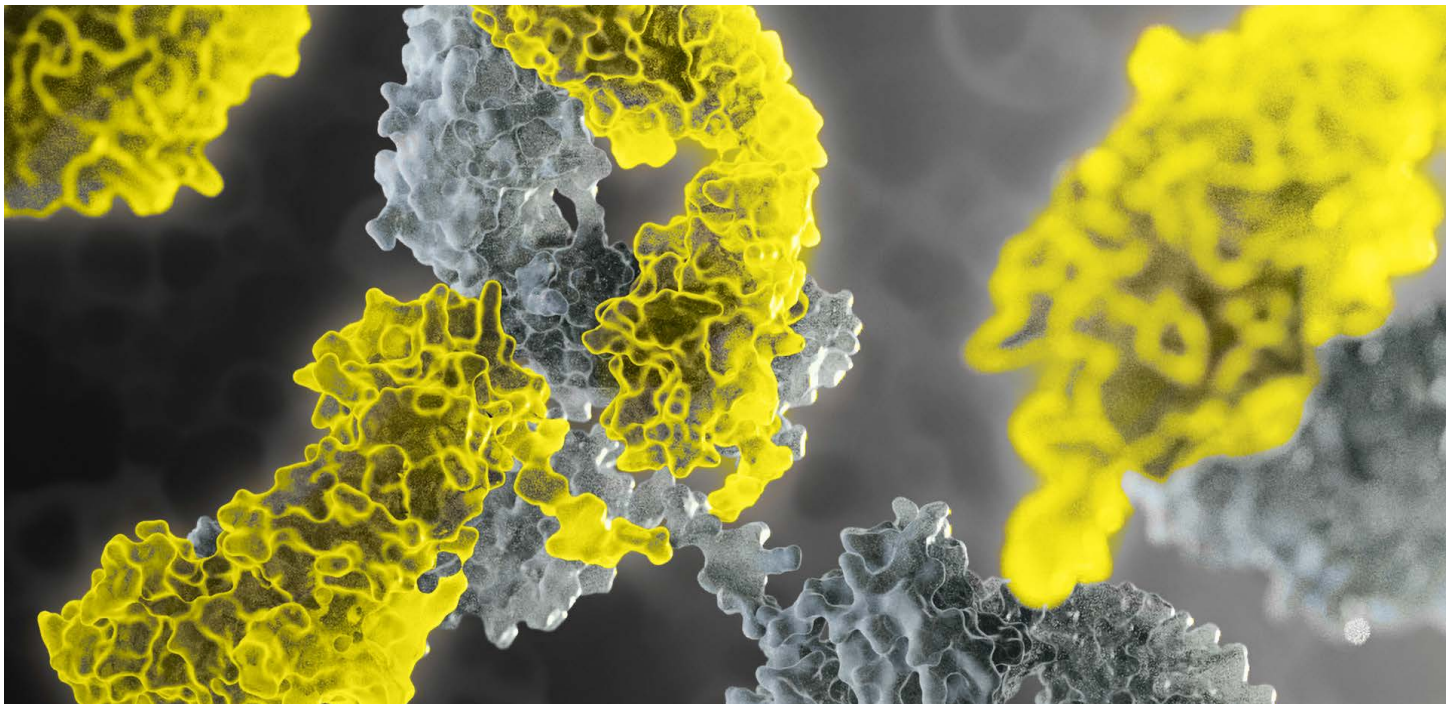


A fundamental step in the development of new cell lines for antibody production is the identification of single cell-derived clones that produce high and consistent levels of the target protein. Compared to the time-consuming and labor-intensive steps of conventional techniques, productivity screening with the CellCelector can be performed in a more efficient way.

Precise Transfer of Stem Cell Clones and Colonies

Image-based automated technologies for cell detection, isolation and retrieval minimize workflow steps and help to maintain the viability and delicate programming of stem cells.

Stem cells are valuable to a wide range of biomedical and pharmaceutical research applications due to their high self-renewal and differentiation potential. In medicine, stem cell transplantation is used to treat blood disorders, such as leukemia and lymphoma. Stem cell differentiation can also be used to regenerate specialized cells of the heart or nervous system as treatment in cardiovascular disease and neurodegenerative diseases, respectively.

Working with human stem cells is not easy as they are high-maintenance, expensive and require constant monitoring during development. Scientists use specialized laboratory techniques for clonal passaging of stem cells, stem cell colonies as well as isolating specific parts of a stem cell colony. Advanced systems for cell analysis are then used to characterize pluripotency and viability in downstream steps.

Induced Pluripotent Stem Cells (iPSCs)

The most commonly used type of stem cells in clinical research are pluripotent stem cells, which can differentiate into any cell type. These include embryonic stem cells that are derived from the inner mast of a human embryo, or induced pluripotent stem cells (iPSCs), which are derived from adult cells that have been genetically reprogrammed to behave like embryonic stem cells.

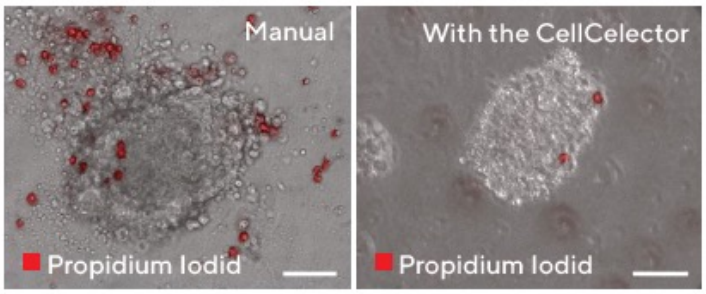
The popularity of iPSCs is due to the variety of cell types that can be differentiated from them and their capacity for infinite expansion. This flexibility provides many opportunities for the development of specific, physiologically relevant cell and tissue models (in 2D and 3D) for pharmacological testing, cancer research, organoid modelling and neurodevelopmental biology, reducing the need for animal models. In addition, iPSCs are increasingly used in translational applications, such as autologous cell therapies.

Challenges in Stem Cell Line Development

Stem cells are cultured in the lab using specialized “recipes” that vary depending on the application. In iPSC development, somatic cells are reprogramed in culture using pluripotency-inducing cofactors, such as Oct3/4, KLF4, Sox2 and c-Myc1. Routine analysis is part of generating a stem cell line and is used to verify the expression of specific genes, ensure clonality, check growth rate and viability, and perform genomic analysis. Performing these characterizations depends on the precise detection and retrieval of stem cells throughout development.

The isolation and transfer of stem cell colonies is often a stressful procedure resulting in significant cell death. Using trypsin or similar enzymatic digestion methods to facilitate the release of adherent stem cells from the culture plate can have distinct effects on the cell phenotype, especially freshly-reprogrammed stem cells, and could result in unintentional differentiation. Furthermore, it can lead to the cross-contamination of different colonies, compromising clonality.

Manual scraping with pipette tips or cell scrapers as means of transfer is laborious and time consuming. Therefore, it is crucial to implement a gentle-mechanical transfer method with high specificity to maximize both the viability as well as the clonality of picked stem cell colonies, while maintaining their pluripotent characteristics.



Clusters of hESC after automated picking using the CellCelector (right) or manual picking with a pipette tip as a control (left). The propidium iodide staining shows dead human embryonic stem cells (red). Images were kindly provided by Oliver Brüstle and Simone Haupt, Life and Brain GmbH, Bonn, Germany.

Automated Retrieval of Stem Cells

Image-based automated techniques for cell detection, isolation and retrieval minimize workflow steps and help to maintain the viability and delicate programming of stem cells. One example of such a system is the CellCelector system. It has specifically designed picking modules for adherent cells and cell colonies that are extremely gentle, while also highly specific, making the system ideally suited for automated clonal passaging of stem cells, stem cell colonies as well as isolating specific parts of a stem cell colony.

For picking of adherent colonies, the CellCelector combines a very gentle, crosswise scrape movement with a simultaneous aspiration of the colony. This gently loosens the colony from the base of the culture plate or feeder cell layer, while preserving survival, proliferation, and morphology when compared to manual selection. Automated platforms can significantly simplify workflows in common stem cell experiments, such as clonal isolation, doublet splitting and colony forming cell assay.

Clonal Stem Cell Picking

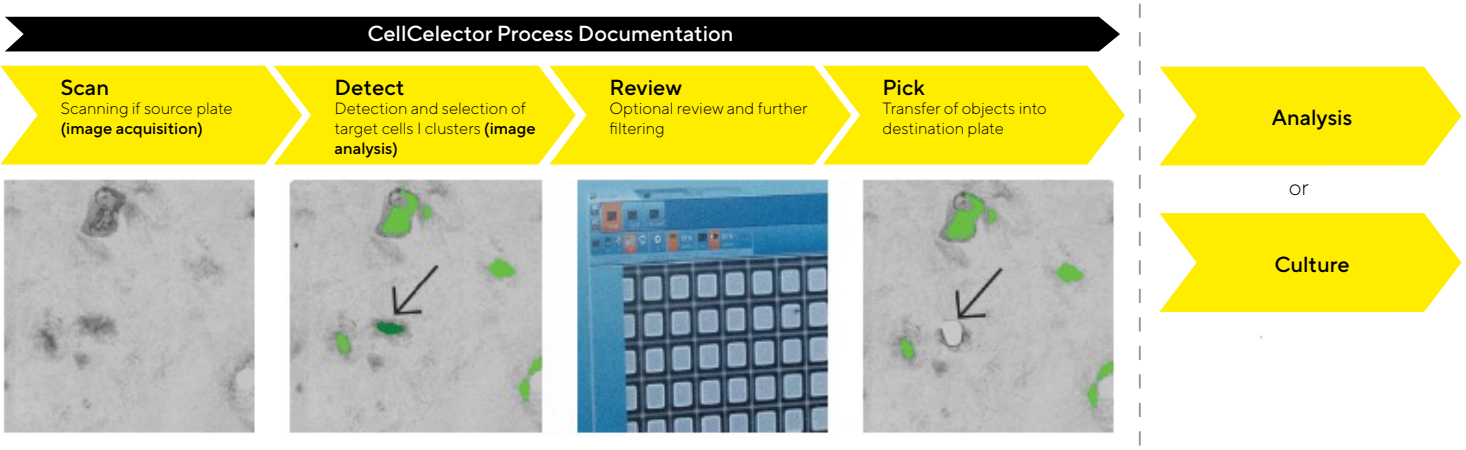
iPSCs are widely used in stem cell research, not only for the development of cellular disease models and as test systems for new drugs, but also for the development of new regenerative cell therapies. Like all cell-line development protocols, iPSCs that are subject to gene editing must be isolated from a heterogenous cell population. To get a clonal cell population, single cells are grown into clones and then individual clones are isolated.

Automated solutions that can identify the desired stem cell colonies or clones and isolate them without any cross-contamination from neighboring clones are of high value. Furthermore, the process must be as gentle as possible in order to avoid cell loss or unintentional cell differentiation. An image-based system can automatically identify and isolate viable, newly-derived iPSC colonies, while retaining pluripotency.

Hematopoietic Stem Cell Colonies

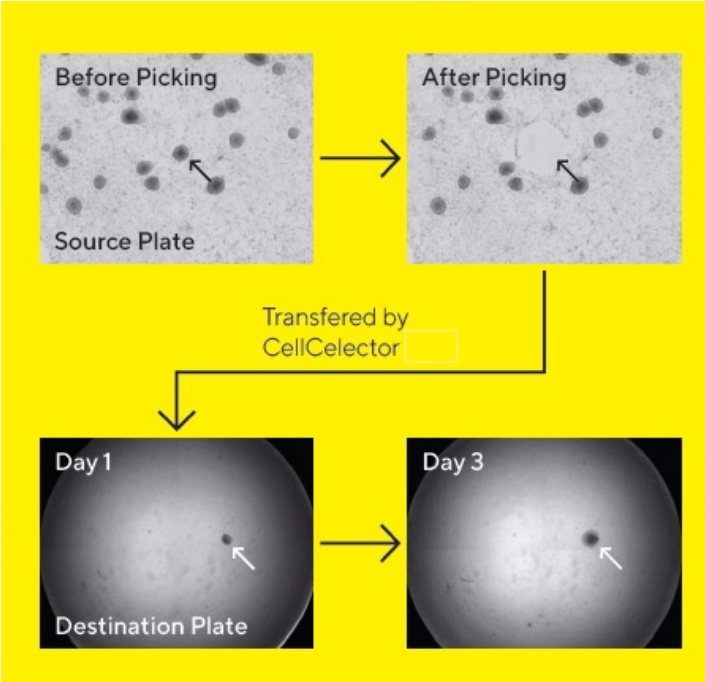
Hematopoietic stem and progenitor cells (HSPCs) are responsible for the maintenance of the hematopoietic system by giving rise to myeloid and lymphoid lineages. HSPCs derived from bone marrow, cord blood or peripheral blood are studied to understand hematopoiesis and leukemogenesis.

A widely used in vitro assay for the study of HSPCs is the colony forming cell (CFC) assay, which is a measure of how well progenitor cells can differentiate in semi-solid media. Stem cell colonies are imaged, detected, and picked from semi-solid media to study enumeration of myeloid versus erythroid colonies, differentiation state, gene expression profiles or gene mutations.

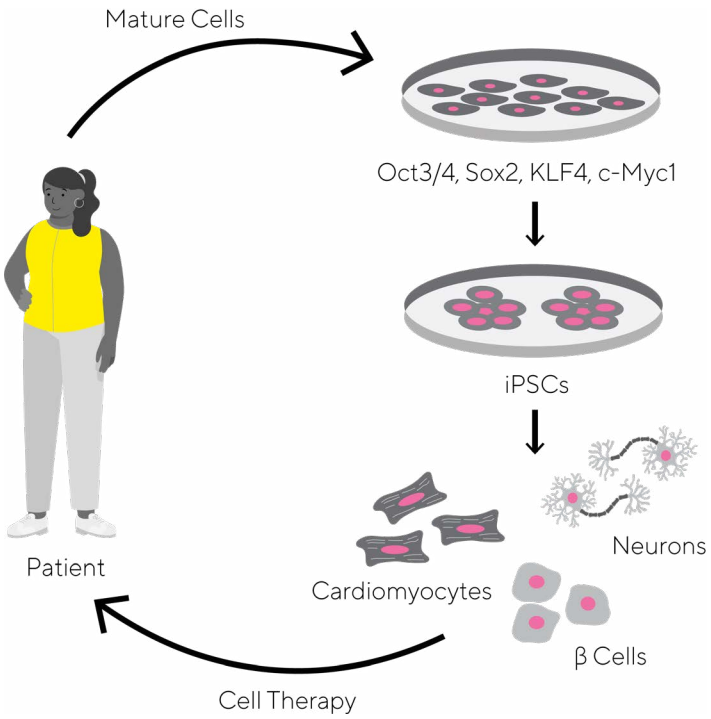


"Automated solutions that can identify the desired stem cell colonies or clones and isolate them without any cross-contamination from neighboring clones are of high value."

Transfer of murine embryonic stem cell colony cultivated on feeder cells into a 96-well destination plate using the CellCelector. The isolated colony was re-detected on days 1 and 3 by the CellCelector.



Extracting viable cells from semi-solid media, such as Matrigel, is difficult. The medium is hard to manipulate, often requiring additional steps to dissolve the matrix components, which can affect the health and differentiation status of stem cells. Automated cell retrieval platforms like the CellCelector that can accurately isolate colonies from a variety of media can streamline routine assays in gene therapy and regenerative medicine.



Hematopoietic Daughter Cell Splitting

In lineage studies of hematopoietic stem cells (HSCs), one way to understand cell fate decisions is to study the "daughter" cells originating from one "mother" HSC on the single-cell level. This involves isolating single daughter cells in a process that is called "doublets splitting", followed by molecular and functional assays like single-cell sequencing or transplantation assays.

Dilution- and FACS-based methods for isolating daughter HSC cells are not ideal as they are time-consuming and may influence the cell's programming. Additionally, daughter cells are very low in number, making them hard to capture using traditional approaches. The CellCelector's interactive picking mode allows easy and precise splitting of doublets, with real-time visualization. Additionally, the process is fully documented, allowing complete traceability.

Transforming Stem Cell Research

Automated solutions for cell isolation support stem cell research with fast, yet gentle picking of single stem cells, stem cell colonies or partial colonies. Compared to manual methodologies, automation provides higher viability and outgrowth rates, without influencing the cell's molecular programming.

- **Clonal Stem Cell Picking**
  Perform clonal passaging of stem cells and stem cell colonies or isolate specific parts of a stem cell colony.

- **Hematopoietic Stem Cell Colonies (HPSCs)**
  Automated counting and picking of individual HPSC colonies to access myeloid vs. erythroid colonies, differentiation state, gene expression profiles or gene mutations.

- **HSC Daughter Cell Splitting**
  Gently isolate daughter cells in full view and with complete traceability of each cell to minimize risk of damage.

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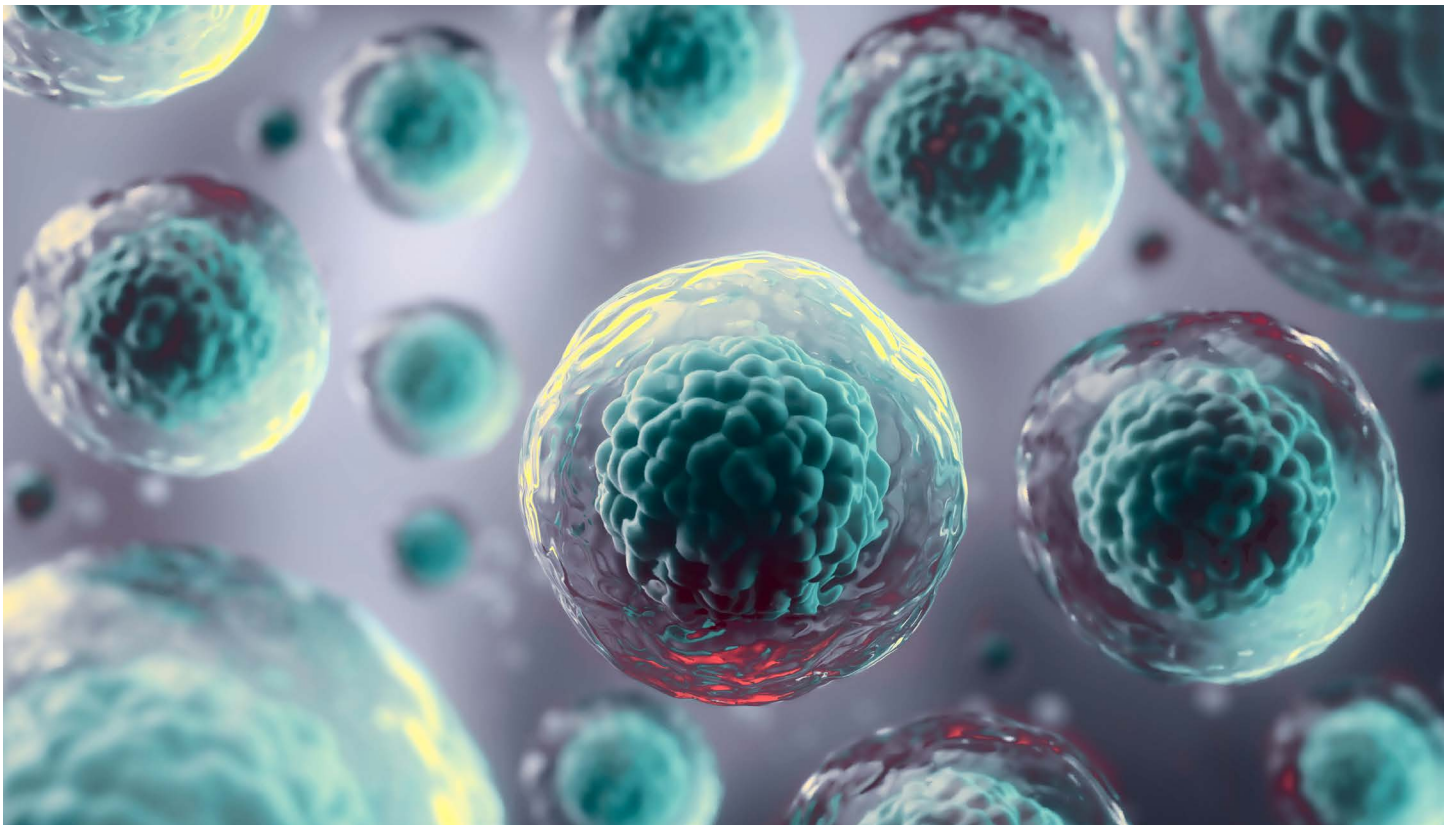

CellCelector Flex allows for automated, gentle and precise retrieval of stem cells, stem cell colonies or colony fractions for all stem cell applications. The whole workflow is fully automated and documented by providing live imaging during picking, cell tracking data from source to destination plate, and high-quality images before and after picking.

Hear from an Expert: Dr. Andris Abramenkovs, Sartorius AG Product Manager Talks CellCelector

Dr. Andris Abramenkovs
Product Manager, Sartorius

Dr. Andris Abramenkovs is currently a Product Manager with Sartorius AG, having been with the company since June 2019. This comes after earning a PhD in Medical Sciences from Uppsala University in Sweden, where he researched DNA damage, repair, and treatment options. He aspires to continuously develop his skills and expertise in both research and development and scientific projects through problem solving, laboratory experiments, and scientific communication. Dr. Abramenkovs spoke with Labroots about the CellCelector technology in this exclusive interview.

Q: What is CellCelector?

Dr. Abramenkovs: The CellCelector is a unique platform in the single-cell retrieval space. It combines a powerful high-content imaging system with a fully automated cell-picking robot. Its patented picking technology gives extremely fast scanning and picking speeds, while still being gentle on cells. What sets CellCelector apart from other technologies is the flexibility. It can detect, select and isolate single cells and single-cell clusters, spheroids, organoids, tissue fragments, adherent colonies from both liquid and semi-solid media.

Q: What are the scientists who use CellCelector saying about it?

Dr. Abramenkovs: What surprises most scientists about CellCelector technology is how quickly and easily it moves around cells, while preserving cell viability during the picking process. This gentle picking process gives one of the highest outgrowth rates in the industry, while also minimizing impact on biological systems. The flexibility to harvest cells in different setups in one system also stands out to users.

Q: What are the unique needs in antibody discovery workflows?

Dr. Abramenkovs: Monoclonal antibodies have wide clinical applications in oncology, immunology, hematology, and even infectious disease and migraines. All biologics are produced by cells. Selecting high-producing clones for the target antibody is one of the most critical and time-consuming early steps in the antibody discovery process. This is where the CellCelector is an indispensable tool.

Q: How does CellCelector streamline cell-line development?

Dr. Abramenkovs: The goal of cell-line development is to get productive clones with proof of monoclonality, and the CellCelector provides that with speed and ease. After transduction, we can plate cells directly onto the Nanowell plates, which are designed to physically isolate individual cells without diluting out growth-promoting factors in the media. The CellCelector software allows you to identify and monitor the growth of monoclonal cells over several days and isolate the best growing clones. You can also assess the productivity of each clone, rank them and transfer for further expansion or characterization.

Q: Why do scientists study rare cells and how are they isolated?

Dr. Abramenkovs: Rare cell populations can be extremely important for diagnostic purposes as well as in research. For example, circulating tumor cells are found in low abundance in cancer patients and by studying them we can identify

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Dr. Andris Abramenkovs
Product Manager, Sartorius

novel lifesaving treatments. Compared to general cell isolation, identifying rare cells usually requires more complex phenotypic analysis, which the CellCelector can easily support. The fast acquisition times allow for quick screens of large numbers of cells to identify rare cells. After isolation, the cells can be deposited on a cooled deck to preserve DNA and RNA integrity for sequencing.

Q: How does the CellCelector facilitate stem cell research?

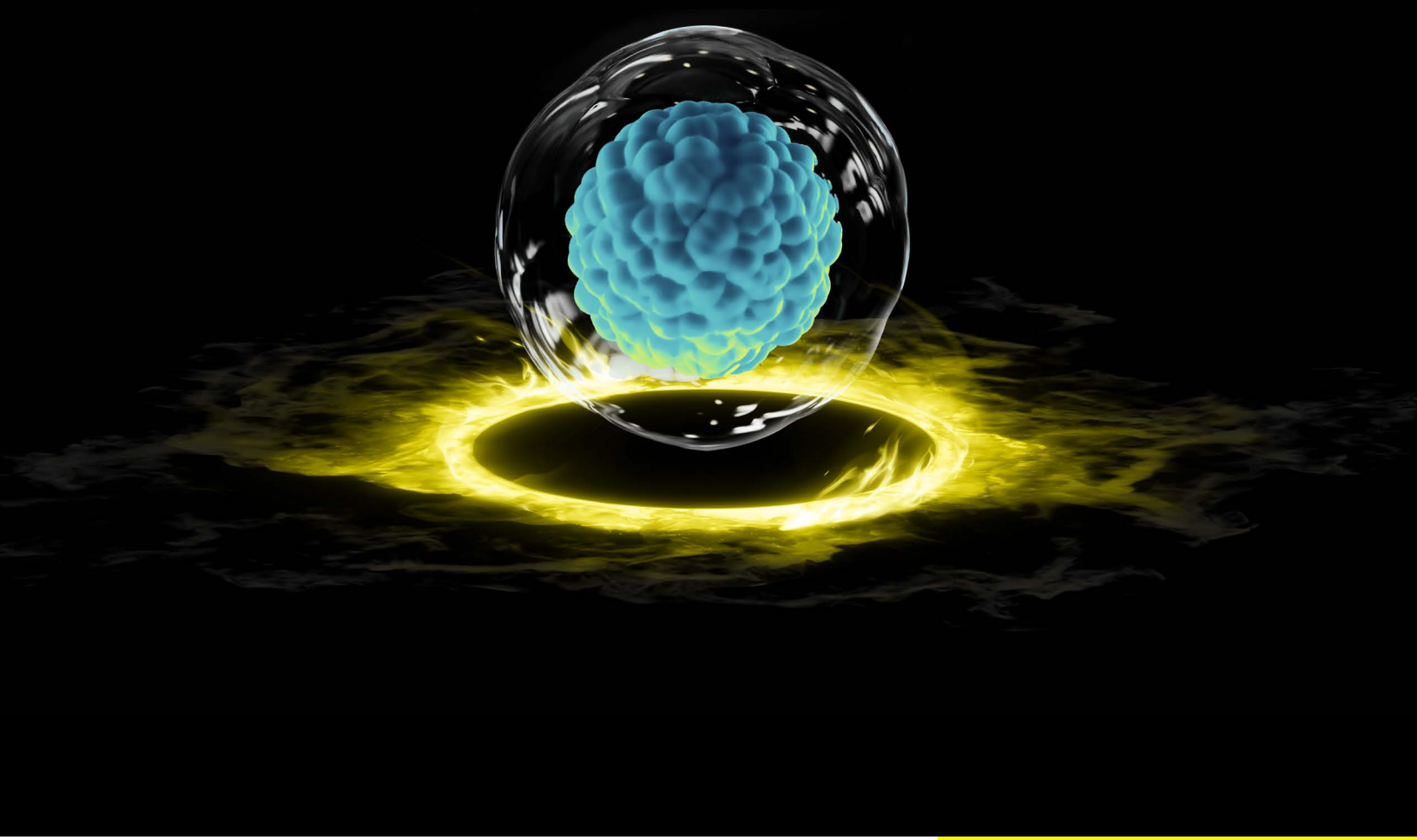
Dr. Abramenkovs: Transferring stem cell colonies is often a stressful process that results in many dead cells. Using enzymatic digestion methods can help, but it can have distinct effects on the cell phenotype, especially freshly reprogrammed stem cells, and could result in unintentional differentiation. With CellCelector you can detach stem cell colonies gently and without compromising their properties and viability. Our technology also supports growing stem cell colonies on feeder cells, which is a key requirement for many stem cell cultures.

Q: What do you see as the future of this technology?

Dr. Abramenkovs: This technology will become increasingly more important as we move towards biologics as pharmaceuticals. Automated picking of the best-producing clones while preserving viability will significantly accelerate development of new therapeutic strategies and the high viability to generate new disease models or cell-based treatments. In cancer research, CellCelector is already making an impact by simplifying the process of isolating and characterizing circulating tumor cells, and I can see it playing an even more prominent role in the future.

CellCelector Flex:
Patented picking technology provides extremely quick scanning and picking speeds, leading to fast cell retrieval. Gentle cellular transfer results in high cell integrity and outgrowth rates. Picking/transfer efficiencies of up to 100% can be achieved for some applications, such as single cell cloning.

One Tool To Retrieve Them All.



Empower your research with the leading cell and colony screening and isolation system

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