Cell Line Development

CellCelector Cell Line Development Instrument, Media, Reagents and Consumables

The Perfect Combination to meet Today's Cell Line Development Challenges

- Standardized Cell Line Development CellCelector instrument, featuring:
  - Enhanced productivity assessment
  - Reduced scanning times
  - Automated capillary calibration
  - Improved sensitivity
  - Maintenance-free picking
- EMA 410 Compliant Protein A beads and secondary antibody kit
- Next Generation Cell Line Development Nanowell plates
- Validated protocols to accelerate candidate clone identification
- Chemically defined, animal-free CHO media
- Proprietary CHO host cell line and optimized vector expression system

For further information, visit
www.sartorius.com/en/products/cell-selection-and-retrieval

CellCelector Cell Line Development

The new CellCelector Cell Line Development instrument, reagents and consumable portfolio has been specifically designed to address many common challenges within the cell line development process. From ensuring high clone outgrowth of difficult to culture cells, to quickly identifying top-performing candidate clones by optimizing the assessment of clone productivity, the new CellCelector Cell Line Development portfolio helps researchers accelerate identification of the ideal clone candidate at the earliest stage possible.

CellCelector CLD Platform

The CellCelector Cell Line Development instrument is a fully automated cell imaging and isolation instrument for the screening, detection and transfer of clones, specifically tailored towards the challenges encountered in daily cell line development workflows.

Combining the latest single cell isolation technology with a made to stock configuration to provide state-of-the-art monoclonality proof and viabilities in excess of 95%, the CellCelector Cell Line Development platform is available with optional five channel fluorescence to rapidly assess clone productivity at the earliest stages of the workflow.

Single cell picking arm with 80 µm glass capillary as standard

Nanowell plate source adapter

Single curved monitor analysis station

Heated deck tray to keep cells at a consistent 37°C

Flat | U-bottom destination adapter

4x and 10x objectives for rapid scanning and accurate picking

Optional fluorescence unit for accurate measurement of clone productivity

Figure 1. The new, made to stock CellCelector Cell Line Development instrument

CellCelector Cell Line Development New Features and Benefits

Imaging

Improved Sensitivity for Low Expression Target Molecules

- Many clones may only exhibit low levels of antibody production, resulting in low levels of fluorescence
- 2 new imaging modes have therefore been incorporated to provide greater resolution and sensitivity flexibility, resulting in a 16 times greater sensitivity option to enhance visualization of low expression target molecules (Fig. 2)

Improved Scanning Speed for Low Expression Target Molecules

- Reduced 24 well plate scanning time from 18 mins to 13 mins for clones with low expression, using the high sensitivity mode by reducing exposure time from the standard 127 ms to only 20 ms

Enhanced Fluorescent Imaging

- Implementation of a new shading correction algorithm to ensure homologous fluorescence imaging during clone productivity (Fig. 3)
- Improved visibility of picking area during picking

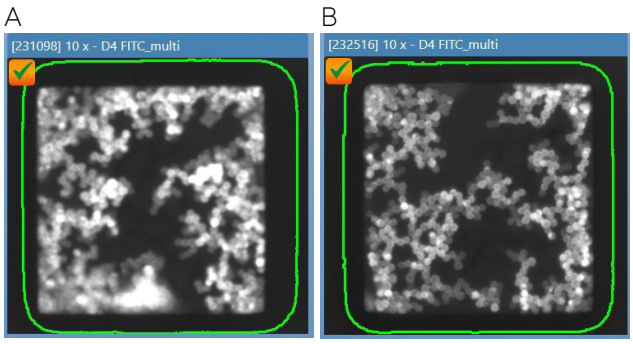


Figure 2. Greater fluorescence can be observed using the new sensitivity mode (A) vs. the standard imaging setting (B)

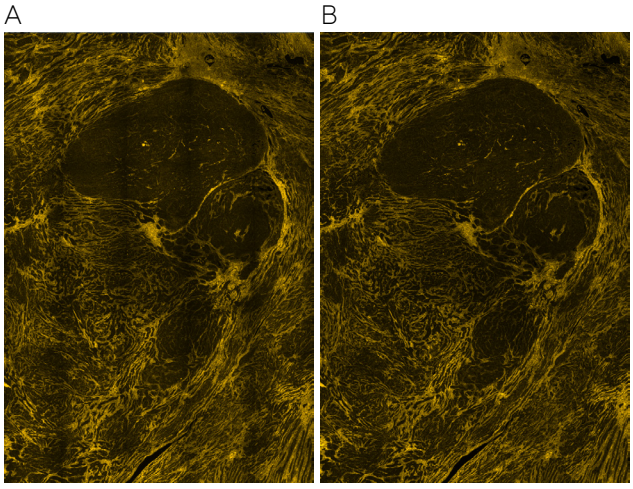


Figure 3. Enhanced fluorescent imaging in (A) previous generation CellCelector, and (B) new CellCelector CLD platform

Picking

Automated Capillary Calibration During Picking

- Real-time vision based capillary adjustment to increase picking accuracy, efficiency and adjust for picking deviations during the cell line development workflow (Fig. 4)
- Simplified capillary exchange resulting in less manual interaction with the platform

Maintenance-Free Picking

- Optimised instrument fluidics facilitate maintenance-free picking and a significantly increased picking efficiency through a better capillary sealing
- More accurate volumetric aspiration using the glass capillaries

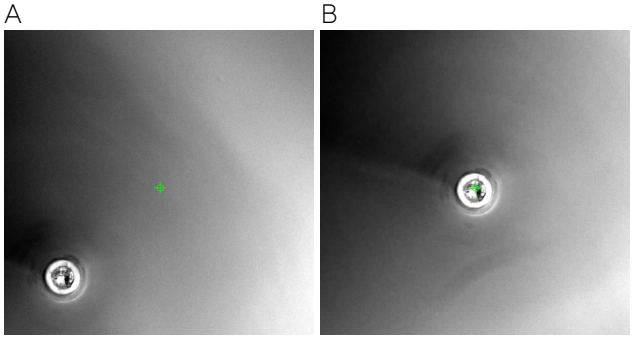


Figure 4. Automated vision based capillary adjustment, highlighting (A) capillary drift during an extended picking run, and (B) calibrated correction of the capillary position

CellCelector Cell Line Development Workflow

Key Advantages of the CellCelector within CLD

- Automated scanning and detection of monoclonal wells
- Rapid identification of top clones from hundreds of thousands of potential candidates
- High resolution, image-based documentation of monoclonal wells
- Up to 100% transfer efficiency and viability
- Simultaneous productivity assessment
- Automated documentation of transferred cells and clones

Cell seeding is performed in a similar manner to conventional cell culture plates and are randomly captured inside the Nanowells following a classic Poisson distribution. Automated scanning of the wells, followed by an automated identification of all Nanowells containing a single cell, provides a robust and documented image-based monoclonality proof (Fig. 5). A productivity assay can then be added to clones on Day 3, in order to identify high producing clones on Day 4. Results highlight an excellent correlation with subsequent titre results.

Figure 5. CellCelector Cell Line Development workflow

CellCelector Productivity Kit and Next Generation CLD Plates

CellCelector EMA 410 Compliant Productivity Kit

- Optimized EMA 410 Compliant protein A capture beads and secondary antibody to ensure consistency and adherence to regulatory standards
- Optimized workflows to ensure addition to already growing clones results in minimal cellular disturbance
- Specifically designed clone ranking protocols with high correlation to upstream titre measurements to ensure criterion-related validity

CellCelector Next Generation Nanowell Plates

- Up to 30% more Nanowells compared to a Standard Nanowell plate – the equivalent of 885 x 96 well plates
- Significantly greater outgrowth of difficult to culture CHO and HEK cells
- Less than 0.2% conflict wells – easily distinguishable from growing clones using the CellCelector Cell Line Development software
- Up to 15,000 "ready to pick", monoclonal validated, high producing clones after 4 days growth

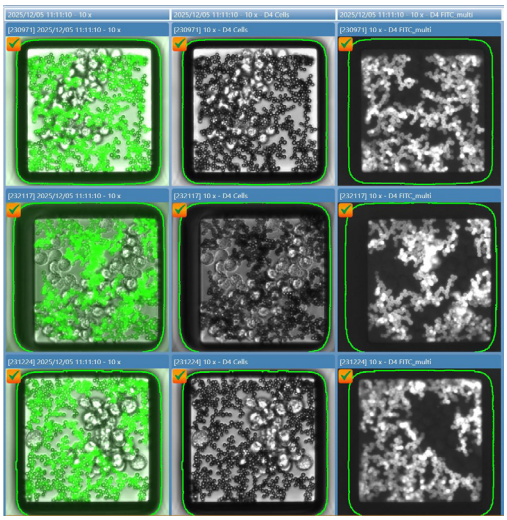


Figure 6. Day 4 CHO K1 productivity assay images, highlighting false colour images (left), brightfield (middle) and greyscale fluorescent signals (right)

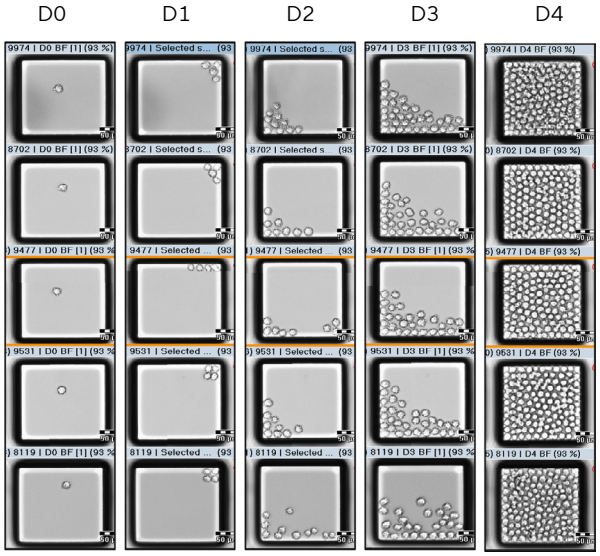
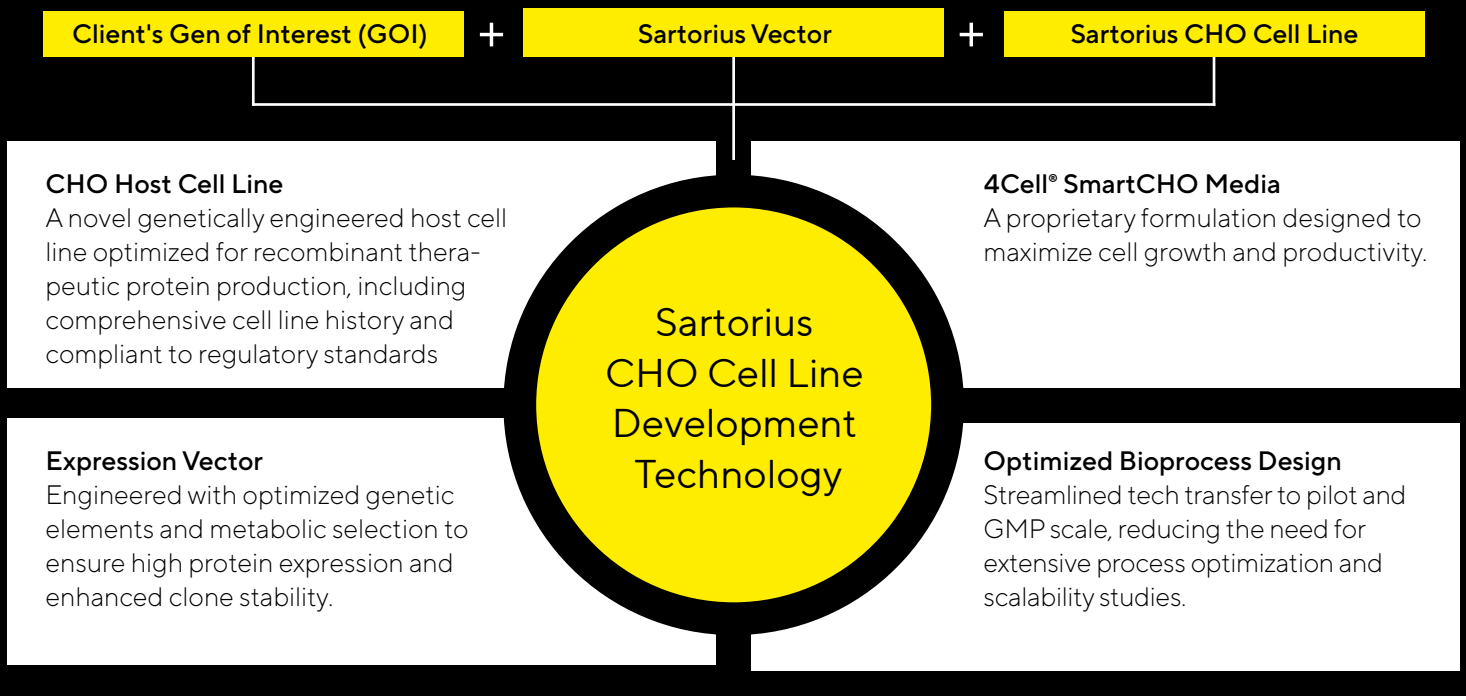


Figure 7. Significant clone growth after 4 days using the Next Generation Nanowell plates



Cell Lines and Vectors

Sartorius' CHO Cell Line Development portfolio provides drug developers and CDMOs with a high-yielding, stable CHO cell line for the production of recombinant therapeutic proteins. The technology entails an expression vector system extensively developed to work synergistically with our novel, genetically engineered host cell line to provide exceptionally high titers and productivities, even prior to process optimization.

Proprietary Genetically Engineered Host Cell Line

- CHO DG44 (DHFR-deficient)
- Fully documented and tested to meet cGMP regulatory standards
- Suspension growth in chemically-defined medium
- Fast growing with short doubling times of 15-16 hours
- Long-term stability over 70+ generations
- Growth >25 million cells/ml in fed-batch and >100 million cells/ml in perfusion

Optimized Vector Expression System

- Metabolic DHFR selection system
- Low DHFR levels: stringent selection
- No Methotrexate, no amplification, no antibiotics
- Scaffold/Matrix Attached Regions: enhanced and stable expression
- Signal peptides: enhanced secretion
- 5' and 3' Untranslated Regions: stabilize mRNA, enhanced expression
- Optimized for single and multi-gene products
- Freedom-to-operate (No IP restrictions)

CellCelector CHO Media Formulations

Sartorius' CHO media portfolio was developed for the cultivation of Chinese Hamster Ovary (CHO) and other mammalian cell lines. CHO cells can be used for both stable and transient expression of recombinant proteins. Our CHO media portfolio includes several media formulations and companion feeds suitable for the most common CHO cell lines, in batch, fed batch and perfusion cultures.

An important consequence of the diversity within CHO cells is that each variant — and even each subclone — has distinct metabolic requirements, demanding different media | feed compositions to maximize performance. Choosing the right media and feed is the foundation of effective protein production. The decision tree outlines how to enhance the success of CHO media screening by utilising two pre-selected combinations of media and feeds (Figure 8).

Data supporting the decision tree are available in a separate application note. Furthermore, the white paper ‚CHO Media Screening Success Using Benchmarking Studies' presents various case studies on optimising different media and feed combinations for CHO cell cultures to enhance recombinant protein production in the biopharmaceutical industry.

CellCelector CHO Media Recommendations

Process	Batch | Fed-batch				Perfusion
Expression system	Transient	Stable			
Cell line		CHO DG44	CHO-K1 & CHO-S	CHO-GS	CHO-DG44
First choice medium	4Cell® CHO TF Medium	4Cell® SmartCHO PM	4Cell® CHO Medium TCX6D	4Cell® CHO-GS Medium TCX10D	4Cell® SmartCHO PM
Second choice medium		4Cell® CHOlean Medium			
High titer feed	4Cell® SmartCHO Feeds FMA | FMB				

Figure 8: A Pre-Selection of 4Cell® CHO Media and Feeds to Guide the Initial Media Selection Process

Ordering Information

CellCelector Reagents and Consumables

Product	Description	Format	Order Number
CellCelector CLD Instrument	Optimized configuration for cell line development workflows and processes	MTS	CC1315
CellCelector CLD Fluorescence Unit	Five channel fluorescence CLD unit comprising of DAPI | FITC | TRITC | Cy5 | Cy7	MTO	CC1316

CellCelector Reagents and Consumables

Product	Description	Format	Order Number
CellCelector CLD Productivity Reagent Kit	EMA 410 Compliant Protein A Beads and Secondary Antibody	MTS	CC1317
CLD Nanowell Plate for CHO and HEK cells	24 microwell, 85k Nanowell Ultra-Low Attachment Coated Plate	MTS	CC0094
CLD Nanowell Plate for IPSCs	24 microwell, 85k Nanowell Plasma Treated Plate	MTS	CC0095

Chemically Defined, Animal-Free CHO Media Portfolio

Medium	Description	Format	Order Number
4Cell® CHO TF Medium	Ideal medium for transient CHO cells.	Liquid | 1 L | bottle	886-0001
4Cell® SmartCHO Production Medium (PM)	Used for effective cultivation of any CHO cell lines - high yields of the active protein	Liquid | 2 × 1 L | bottles	CFP3FB2107
4Cell® CHO Medium TCX6D	Basal medium supplemented with a growth factor	Liquid | 1 L | bottle	1070-0001
4Cell® CHO-GS Medium TCX10D	For long-term high-performance growth of CHO-GS cells	Liquid | 1 L | bottle	1150-0001
4Cell® CHOlean Medium	Robust growth medium for multiple applications	Liquid | 1 L | bottle	1140-0001
4Cell® SmartCHO Feed Medium A (FMA)	4Cell® SmartCHO FMA and 4Cell® SmartCHO FMB are the ideal companion feeds and help drive high titers when used together	Liquid | 2 × 1 L | bottles	CFP3FB3108
4Cell® SmartCHO Feed Medium B (FMB)		Liquid | 2 × 125 mL | bottles	CFP3FB4109

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