Automated Solutions for Hybridoma Antibody Development

Since the discovery of hybridoma technology by Köhler and Milstein in 1975, a large number of monoclonal antibodies have been generated by fusion of specific antibody expressing B cells with immortal nonproducing myeloma cells.

Your Guide to Workflow Intelligence

Review our solutions by Workstations  
Review our solutions by Workflow

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Beckman Coulter’s integrated workstations improve efficiency, consistency, and reliability of your antibody generation.

We understand that each lab is unique. Depending on your workflow and requirements, we can provide an integrated solution that combines liquid handling automation with laboratory equipment of your choice to meet your specific workflow needs.
Pre-Fusion

Example of a Workstation

1. Test Bleed
2. Isolate B Cells
3. Myeloma Cell Culture
4. Fusion & Hybridoma Selection
5. Hit Picking & Monoclonality
6. Clone Stability
7. Antibody Production
Example of a Workstation

- Biomek Automated Workstation
- Biomek Suite of Software
- Biomek Validated Disposable Tips
- Integrated Centrifuge
- Integrated Vi-CELL XR Cell Viability Analyzer
- Integrated Incubator
- Integrated Refillable Reservoir
- Robotic Shuttle
- Robotic Arm

Steps:

01 Test Bleed
02 Isolate B Cells
03 Myeloma Cell Culture
04 Fusion & Hybridoma Selection
05 Hit Picking & Monoclonality
06 Clone Stability
07 Antibody Production
Post-Fusion

Example of a Workstation
End-to-End

Example of a Workstation

Pre-Fusion

01 Test Bleed
02 Isolate B Cells
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Fusion

Post-Fusion

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07 Antibody Production
The hybridoma process is time-consuming and labor-intensive and requires following successive working phases and a number of complex steps to select the hybridoma clones of interest.

Learn about the Beckman Coulter solutions for automating the critical steps of hybridoma development that increase productivity and make it possible to produce specific monoclonal antibodies.
Successful hybridoma production starts with obtaining intact B cells. Test bleeds are performed to identify the animal generating antibodies of interest, followed by isolation of B cells from the spleen. The yield and purity of B cells are impacted by harvesting time after immunization and isolation methods. **OUR SOLUTIONS:**

**Biomek Automated Workstation**
- Separation of serum from whole blood
- Preparation of indirect ELISA plate by addition of known antigen and blocking agent, improving consistently and uniformity across all wells
- Analysis of Sera: Minimize human error for a multi-step process and improve reproducibility via controlled and consistent processing
- Preparation of density gradient for B cell separation and isolation of B cells from gradient post spin, reducing chance of shearing
- Gentle handling through controlled speed during washing step
- Tight control of media dispensing volumes

**Biomek Suite of Software**
- SAMI EX: controls plate movements with integrated devices for consistent processing
- SAMI PM: optimizes the utilization of integrated devices and schedules multi-week workflows
- DART: links sample identification and assay results throughout the process

**Integrated Vi-CELL XR Cell Viability Analyzer**
- Count and image cells
- Stain cells and measure viability

**Integrated Centrifuge**
- Separate serum from whole blood reliably and efficiently
- Spin gradient to isolate B cells

**Integrated Cell Sorter**
- Isolation of antigen-specific B cells

**Integrated Plate Washer**
- Rapid addition and removal of wash buffers for ELISA

**Integrated Incubator**
- Temporary storage of B cells

**Robotic Shuttle**
- Conveyor track eliminates human induced mishaps during transport

**Robotic Arm**
- Moves plates between Workstation, centrifuge and analyzers
Fusion efficiency for B cell hybridoma production depends on propagation of healthy myeloma cells, culture medium quality, timely addition of fusion media and selective media (HAT), incubation time, contamination control, and consistent processing. OUR SOLUTIONS:

**Biomek Automated Workstation**
- Cell plating, handling, and maintenance minimize human error, improving reproducibility
- Gentle handling through full pipetting template that includes pipetting speeds, positioning and movement
- Tight control of media dispensing volumes

**Robotic Arm**
- Moves plates between Workstation, centrifuge and analyzers

**Integrated Refillable Reservoir**
- In-line heating to achieve desired temperature for HAT medium

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**Integrated Vi-CELL XR Cell Viability Analyzer**
- Count and image cells
- Stain cells and measure viability

**Integrated Centrifuge**
- Pellet cells for PEG media removal

**Integrated Incubator**
- An incubator provides a consistent environment for the housing of growing cell cultures and for the temporary incubation of cells underdoing experimental assays.

**Robotic Shuttle**
- Conveyor track eliminates human induced mishaps during transport
- Speed and acceleration can be controlled to prevent splashing in larger-well plates

**Biomek Validated Disposable Tips**
- Certified endotoxin-free and trace metal-free to eliminate contamination
- Volume capacity: 30µl to 1070µl
- Available wide bore to prevent cell shearing
- Sterile filtered to prevent contamination

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**Fusion Process**

1. **Pre-Fusion**
   - Test Bleed
2. **Fusion**
   - Isolate B Cells
   - Myeloma Cell Culture
   - Fusion & Hybridoma Selection
3. **Post-Fusion**
   - Hit Picking & Monoclonality
   - Clone Stability
   - Antibody Production
Post Fusion: Hit Picking & Monoclonality

Accurate picking of high producing hybridoma cells and verification of monoclonality are necessary to ensure the antibodies of interest are derived from a specific clonal population. **OUR SOLUTIONS:**

**Biomek Automated Workstation**
- High capacity multi-channel head for processing high number of plates
- Data driven pipetting enables hit-picking
- Cell plating, handling and maintenance of the plates to and from the analyzers and incubator minimize human error, improving reproducibility and enabling continuous processing

**Integrated Imager such as CloneSelect™**
- Verify monoclonality
- Optimize and monitor clonal outgrowth

**Robotic Arm**
- Moves plates between Workstation and analyzers

**Biomek Suite of Software**
- SAMI EX: controls plate movements with integrated devices for consistent processing
- SAMI PM: optimizes the utilization of integrated devices and schedules multi-week workflows
- DART: links sample identification and assay results throughout the process

**Integrated Titer Analyzer such as Octet® Systems**
- Measure antigen specific binding and titer

**Integrated Incubator**
- Provides a consistent environment for the housing of growing cell cultures and for the temporary incubation of cells underdoing experimental assays.

**Biomek Validated Disposable Tips**
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Clone Stability

Select stable clones by performing multiple rounds of serial dilution to identify the most stable and highest-producing single cell clone. This step is labor intensive and requires weeks to complete. **OUR SOLUTIONS:**

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- Data driven pipetting enables hit-picking
- Cell plating, handling and maintenance of the plates to and from the analyzers and incubator minimize human error, improving reproducibility and enabling continuous processing

**Integrated Refillable Reservoir**
- In-line heating to achieve desired temperature of cell culture medium

**Integrated Incubator**
- An incubator provides a consistent environment for the housing of growing cell cultures and for the temporary incubation of cells underdoing experimental assays.

**Integrated Imager such as Cloneselect Systems**
- Verify monoclonality
- Optimize and monitor clonal outgrowth

**Biomek Suite of Software**
- SAMI EX: controls plate movements with integrated devices for consistent processing
- SAMI PM: optimizes the utilization of integrated devices and schedules multi-week workflows
- DART: links sample identification and assay results throughout the process

**Robotic Arm**
- Moves plates between Workstation, centrifuge and analyzers

**Integrated Titer Analyzer such as Octet® Systems**
- Measure desired protein concentration

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Expand and cryopreserve selected clones to start the screening process. Certifying clone productivity and quality is fundamental to generating high-yield quality antibodies. Maintaining cell culture health and stable production are common pitfalls during this step. **OUR SOLUTIONS:**

<table>
<thead>
<tr>
<th>Biomek Automated Workstation</th>
<th>Integrated Vi-CELL XR Cell Viability Analyzer</th>
<th>Integrated Capper/Decapper</th>
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</thead>
<tbody>
<tr>
<td>- Cell plating, handling, maintenance and freezing minimize human error, improving reproducibility and enabling continuous processing</td>
<td>- Count and image cells</td>
<td>- Cap tubes to optimal torque</td>
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<tr>
<td><strong>Biomek Suite of Software</strong></td>
<td>- Stain cells and measure viability</td>
<td>- Reliably increase throughput</td>
</tr>
<tr>
<td>- SAMI EX: controls plate movements with integrated devices for consistent processing</td>
<td><strong>Integrated Centrifuge</strong></td>
<td><strong>Integrated Incubator</strong></td>
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<td>- SAMI PM: optimizes the utilization of integrated devices and schedules multi-week workflows</td>
<td>- Remove culture media to prep for freezing step</td>
<td>- An incubator provides a consistent environment for the housing of growing cell cultures and for the temporary incubation of cells underdoing experimental assays.</td>
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<td>- DART: links sample identification and assay results throughout the process</td>
<td><strong>Integrated Refillable Reservoir</strong></td>
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<tr>
<td><strong>Integrated Freezer</strong></td>
<td>- In-line heating to achieve desired temperature of cell culture medium</td>
<td>- Certified endotoxin-free and trace metal-free to eliminate contamination</td>
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<td>- Cryopreservation of hybridoma cells</td>
<td><strong>Pre-Fusion</strong></td>
<td>- Volume capacity: 30µl to 1070µl</td>
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<td><strong>Fusion</strong></td>
<td><strong>Post-Fusion</strong></td>
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Biomek Automated Workstation

Improve procedural ELISA, achieve single cell suspension reliably, simplify and improve transfection process, improve single cell reliability, and adapt to basic cell culture workflows.

- Extend production scale and centralize operations
- Leverage dual-arm pipetting
- Increase flexibility with reagent and media mixing, and cell passaging and plating
- Improve efficiency by directly integrating required components
- Simplify serial dilutions with built-in spanning transfer system
- Improve analysis efficiency with sample and data tracking*
- Take control of multi-day planning*
- Monitor progress with platform status light
- Remote system monitoring using on-deck cameras

*Possible through optional software packages DART and SAMI.
Integrated Incubator

An incubator provides a consistent environment for the housing of growing cell cultures and for the temporary incubation of cells undergoiing experimental assays.

- Temperature can range from 4°C to 70°C, with a relative high humidity (RH) of up to 98% stable CO₂ conditions, and shaking
  - Mammalian cell conditions: 37°C, 95% RH, and 5% CO₂
- A Biomek integration with an incubator reduces recovery loss and assay variance
  - Increase throughput
  - Streamline long-term cell culture processes
  - Eliminate manual, repeated accessing of cells
Integrated Octet® Systems

Comprehensively characterize and optimize for cell clone lead(s), then, accurately measure target protein kinetics and concentration.

- Label-free biophysical characterization for various stages of cell line development
  - Screen during clone selection to quickly rank by titer or off-rates
  - Reduce sample prep time by assaying proteins directly in crude mixtures
  - Measure specific binding interactions - determine affinity constants, epitope binning
- Complete solution for label-free protein kinetics and quantitation
  - Ligand capture surfaces include antibodies, recombinant proteins, DNA, RNA, and virus-like particles
  - ELISA replacement offering increased productivity and accuracy, with off-the-shelf kits for Host Cell Protein and Residual Protein A impurity detection
Robotic Arm

Offers dependable precision and flexibility that not only increases useable workspace, but reliably operates around the clock to eliminate human variability.

- Multiple axis points can reach peripheral equipment
- Walk away capability increases personnel productivity
- Accelerates time to results
- Enhance data reproducibility
- Improve laboratory ergonomics
- Integrates with Biomek workstations
Biomek Validated Disposable Tips

• Validated and approved for use on Biomek systems
• Color-coded racks already in Biomek software for ease of use
• Range of volume capacities from 30µl to 1070µl
• Wide selection including:
  - Wide bore to prevent cell shearing
  - Filtered to prevent contamination
  - Conductive to enable liquid level sensing (span-8 pod)
• Biomek pipette tips from Beckman Coulter are certified to be:
  - Endotoxin-free
  - Trace metal-free
  - Sterile
  - Sterile filtered
  - RNase- and DNase-free

Bio-certification “free of” claims are defined as the lower limit of detection based on the sensitivity of the test method or instrumentation used.
Integrated Capper/Decapper

Hands-free automated capping and decapping technology ensures sample protection, wholeness, and quality.

- Cap tubes to optimal torque
- Reliably increase throughput
- Improve laboratory ergonomics
- Benchtop or integrated use
- Internal controls prevent contamination and debris introduction
Integrated SpectraMax® i3x Multi-Mode Microplate Reader

From imaging of cell confluence and viability under different treatment conditions to quantitation of nucleic acids and protein to western blot analysis, a wealth of new knowledge is captured using a single instrument.

- Base model includes absorbance, fluorescence, and luminescence read modes for 6- to 384-well microplates
- User-exchangeable detection modules expand the system’s detection capabilities
- Engineered for performance with Spectral Fusion™ illumination for increased sensitivity across the entire excitation range
- Cooled photomultiplier tube (PMT) for improved detection in low light.
- The SpectraMax Injector Cartridge with SmartInject™ Technology allows for flash based applications, including dual luciferase and ATP assays.
- The SpectraMax MiniMax 300 Imaging Cytometer option allows for live cell imaging and StainFree™ analysis
Integrated CloneSelect™ Imager

Rapidly and objectively monitor cell growth, verify cell line monoclonality, and normalize measurements specific to cell productivity.

- Ultra-fast benchtop imaging system for:
  - Confluence measurement
  - Growth curve generation
  - Cell number estimation
  - Monoclonality verification
- Colony forming assays
- Cytotoxicity assays
- Cell migration assays

- Consistent results in less time
- Saves all images and generated data
- Integrates with Biomek workstation
Integrated Vi-CELL XR Cell Viability Analyzer

Eliminate human error and user bias when counting cells and determining viability.

- Automated solution for Trypan Blue viability assays
- Analyze mammalian, insect, and yeast cell types (2–70 microns)
- Clumpy samples can be differentiated in number and viability
- Quickly and reliably assess cell shape, size, growth rate, and doubling time
- Enhance statistical reliability
- Convenient reagent kit, concentration control, and sample cups
- Viable cells are outlined in green and nonviable in red:
Suite of SW

Every time your sample moves, data moves. Biomek suite of software provides the most flexibility for modification, multi-day planning and data quality. Automatic data tracking and storage saves time and eliminate manual data handling errors. Few highlights include:

**DART: Data Acquisition and Reporting Tool**
- Gather data and synthesis runtime information.
- Generate data reports via MS Excel table and pivot views, and SQL views.
- Integrate with your Laboratory Information Management System for automatic data transfer.

**SAMI EX**
- Create schedules with the benefits of an optimized, predictable static schedule.
- Save process time and control method variation with interleaving sub-processes.
- Use live data to drive methods/processes.

**SAMI Process Management**
- Use this calendar organizational tool to add, monitor, and plan for multiple methods and other events.
- Schedule and run multiple processes simultaneously.
- Integrate long-running processes into a centralized, visual workflow management tool.

**Biomek Method Launcher**
- Select, set up, run, and track methods in a few simple mouse clicks.
Beckman's Integrated Solutions team have integrated 300+ third-party devices from 60+ manufacturers to meet your diverse and ever-evolving automation needs. Examples of analyzers integrated:

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<th>Purpose</th>
<th>Manufacturer</th>
<th>Model</th>
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<td>Molecular Devices</td>
<td>SpectraMax L</td>
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<td>Thermo Fisher Scientific</td>
<td>Luminoskan Ascent</td>
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<td>Microplate Cytometry</td>
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<td>Celligo S Cell Imaging Cytometer</td>
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<td>Tecan</td>
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<td>Infinite M200, M200 PRO, M1000 PRO</td>
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The Tube Barcode Scanner is under development, not available for sale yet.