

Monoclonal Antibody Contract Manufacturing

Overview

Meridian Life Science[®], Inc. (MLS) is an industry leader in the commercial production of critical raw materials for diagnostic manufacturers. Core capabilities include both *in vitro* and *in vivo* methodologies. MLS has the resources to manufacture and purify monoclonal antibodies using a wide array of protein purification methods at quantities ranging from research (mg) to commercial (g) scale. All manufacturing is performed according to cGMP guidelines, with corresponding documentation and quality reviews.

Pilot to Commercialization Capabilities

1. **Pilot Studies:** MLS offers fixed-fee pilots based on final cell culture volume (1L, 5L, 10L, or 20L) or number of mice (minimum 20 mice) and is independent of antibody yield and purity.
2. **Cell Culture Optimization:** Extensive cell line optimization services, including conversion to serum free media, cell culture conditions (cell density, temperature, supplements, etc.), and antibody harvest methods.
3. **Cell Banking:** MLS offers cell banking services for your critical cell lines including generation and characterization of the bank, cryopreservation, and dual site storage.
4. **Downstream Process Development:** Extensive capabilities in filtration, centrifugation, and all forms of column chromatography from Protein A or G to SEC, HIC, and IEC.
5. **Validation Lots:** MLS understands the regulatory requirement to validate three successive production lots for critical biological reagents used in commercial products.
6. **Analytical Methods:** Vast experience in biochemical or molecular characterization (SDS-PAGE, Western, Silver, ELISA, HPLC, Protein concentration (BCA, UV-vis), cell viability/density).
7. **Commercial Production:** MLS has been manufacturing critical biological reagents for the diagnostics and biopharmaceutical industry for 25+ years with the quality systems and inventory management required to provide consistent supply.

Why Partner with MLS?

- ▶ Unparalleled experience and proven track record (25+ yrs)
- ▶ Core expertise in cell culture, ascites, protein production and purification
- ▶ Flexibility in scale and production systems
- ▶ Complete R&D and Process Development service
- ▶ Dedicated project management
- ▶ All manufacturing conducted under Quality Systems: ISO 9001:2008, QSR, and 21 CFR 820, 210, and 211
- ▶ Complete confidentiality



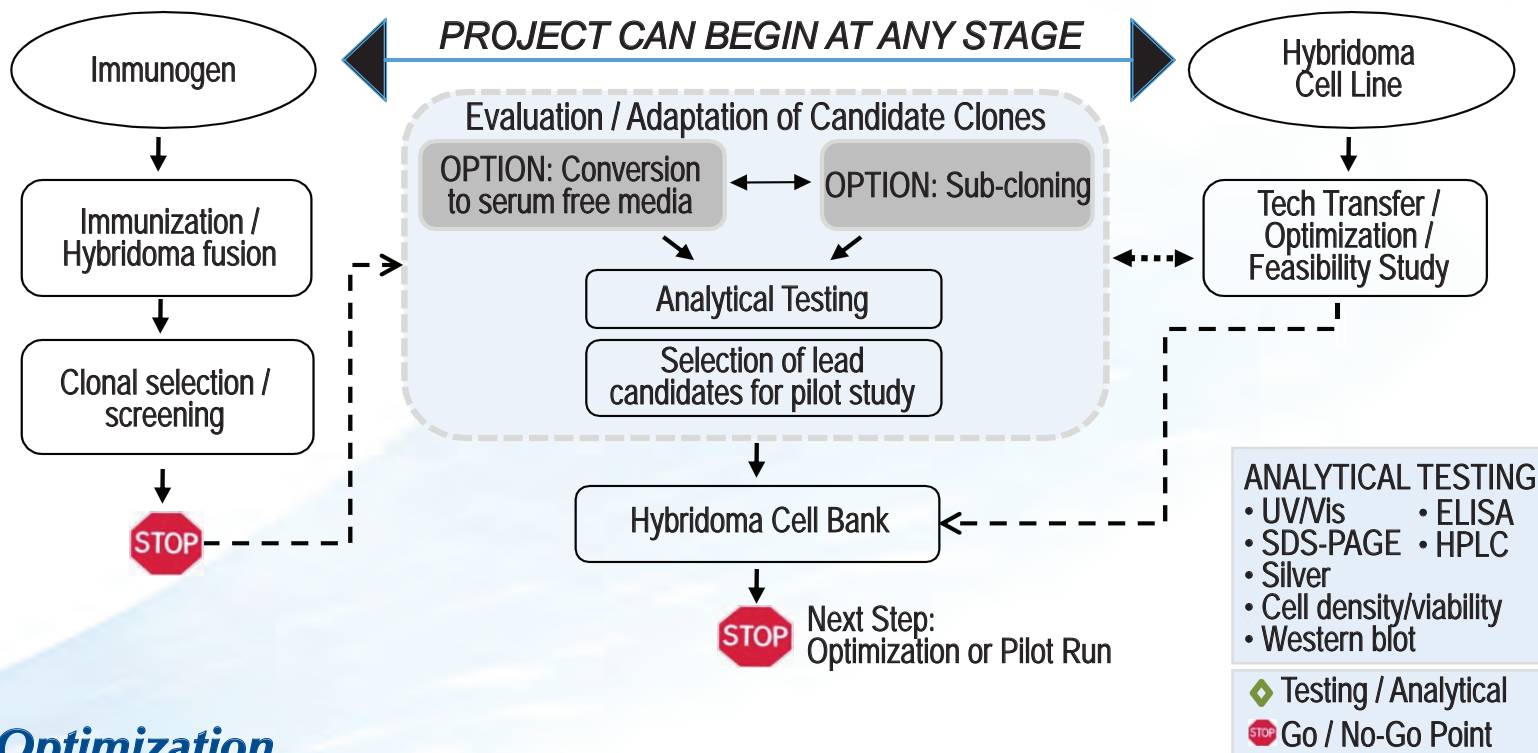
We understand that the variable nature of most biological processes often requires ongoing R&D support. MLS has been and will continue to be a proactive partner to our clients working to ensure that projects receive the technical expertise required for successful execution.

For More Information on Contract Manufacturing and Custom R&D Development:
Contact a MLS Representative at contract-mfg@meridianlifescience.com.

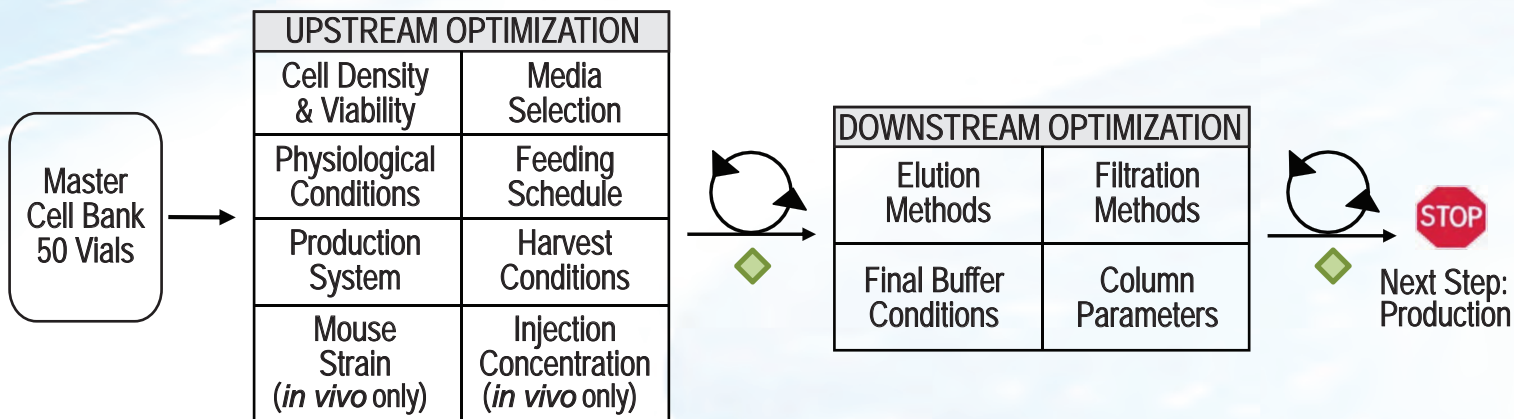
Custom *In Vitro* or *In Vivo* Monoclonal Development and Manufacturing

Integration and Optimization of Customer Process (R&D to Commercial Scale)

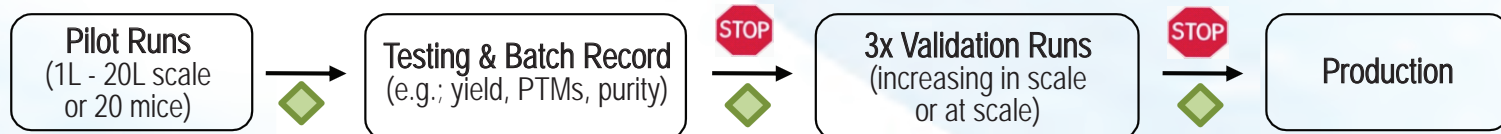
Development, Clonal Selection, and Adaptation



Optimization



Manufacturing



MLS Regulatory and Quality Systems

- ISO 9001:2008 certified
- EC 1774/2002 approved
- Regulatory Affairs and Quality Assurance/Quality Control:
 - √ Provide necessary support for R&D to cGMP production
 - √ Support tech transfer, batch records and release, and Certificates of Analysis

Development and Clonal Selection

Development Services:

- Immunization and hybridoma fusion services offered through partnership with trusted lab
- Multiple mouse strains: BALB/c or strain of choice
- Clonal selection and screening
- Cell line sub-cloning to ensure homogenous population
- Master and Working cell bank production and maintenance
- Specificity analysis by ELISA: methods can be developed or tech transferred
- Additional analytical testing available (SDS-PAGE, HPLC, mycoplasma, sterility, etc.)
- Customizable program

Pilot, Validation, and Routine Manufacturing

Custom Services:

- Flexible scheduling
- Dedicated project manager
- Fixed-fee pilot projects: 1L, 5L, 10L, 20L
- Quotes on a per mg or gram basis can be provided for validation runs and routine production (once yield is confirmed by pilot study)

Overview of In Vivo Services

Cell Line Service:

- IgM Cell line production and purification
- Mycoplasma Testing
- Viability Monitoring
- Multi site Master or Working Cell Bank

Cell Line Rescue:

- Old or low yielding cell lines
- Yield optimization improvements
- Previously unsuccessful cultured cell lines

Adaptation and Optimization

Upstream Optimization:

- Conversion from ascites to cell culture
- Adaptation to growth in serum-free media
- Scale-up conditions
- Matrix analysis studies – compare effect of variables on yield:
 - Production system
 - Media selection
 - Seeding cell density
 - Fed-batch method vs. terminal harvests
 - Physiological conditions (e.g., dissolved O₂)

Culture Systems:

- CL-1000 flasks
- Tissue culture flasks
- Cell Factories
- Roller bottles - smooth or ridged
- Spinner flask
- Wave Bioreactor®

Ascites Service:

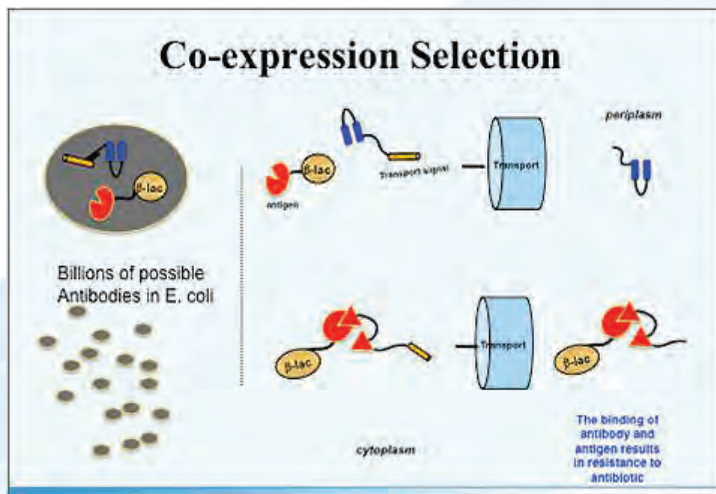
- Large facility with 55,000 mice capacity
- Pilot program – 20 mice minimum
- Large scale production of up to 5,000 mice per lot
- Lot-to-Lot Consistency
- Fixed pricing after pilot run
- Competitive Bulk Pricing
- Flexibility in Custom Options
- Fast turnaround time

Wave Bioreactor is a registered trademark of GE Healthcare Bioscience BioProcess Corp.

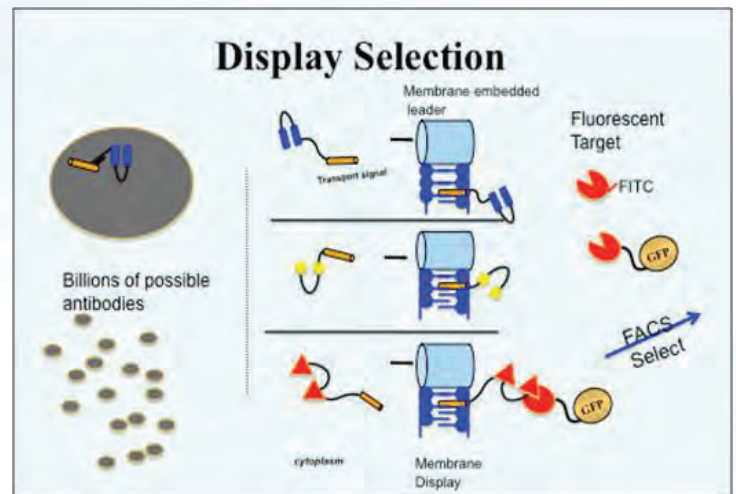
Meridian Life Science – Vybion Partnership ProCode™ Technology for Antibody Development

Meridian Life Science, Inc. (MLS) and Vybion have entered into an exclusive agreement to offer a stand-alone technology platform for the development of antibodies that can be engineered into a flexible range of formats. ProCode has demonstrated the ability to select binders from libraries and affinity mature these binders.

ProCode works in two formats allowing for Co-expression Selection of scFv and target as well as a familiar Display Selection format to accommodate a range of targets. Library construction strategies utilized ProCode's solubility optimized human scFvs (HuSelect) that comprise multiple frameworks and randomized and multiple length CDR inserts. The ProCode technology permits engineering of selected MAb, develop cell lines and optimize culture through process development.



HuSelect scFv libraries with novel modified leaders are expressed on the inner *E. coli* membrane. Fluorescent antigen target binds, and is selected, for example, by FACS after the cell wall is permeabilized.



HuSelect scFv libraries with novel leaders are co-expressed with target antigen fused to antibiotic resistance gene. Only soluble scFvs that bind to target confer antibiotic resistance following transport. Antibiotic pressure selects, in multiple rounds, for higher affinity.

ProCode Advantages:

- ▶ Rapid affinity maturation to low pM
- ▶ **Complete panels** of high affinity binders in a few weeks. More effective functional screening.
- ▶ Stand-alone technology
- ▶ Better stability, lower aggregation
- ▶ Effective in oxidizing and reducing environments
- ▶ Reduced time to market

ProCode Technology Features:

- ▶ Novel transport 'self edits' for folded proteins only
- ▶ Solubility optimized scFv libraries
- ▶ Multiple libraries each with unique frameworks and synthetic randomized CDRs
- ▶ Two selection modes can accommodate a range of targets or specific target epitopes
- ▶ Target binding epitope mapping by display of overlapping target sequences



For Information on How the ProCode Technology Can Help Your Antibody Development;

Please Contact Dr. Victor Van Cleave • Vice President of R&D and Contract Manufacturing • Meridian Life Science, Inc. • victor.vancleave@meridianlifescience.com