Cell Line Development

SERVICES

Selexis SURE Cell Line Development™

SELEXIS

Selexis SURE Cell Line Development™

Proprietary technology platform and comprehensive services for fast and reliable cell line development:

- From DNA to IND in 14 months
- Highly adaptable non-viral vectors with no carrying capacity limitation
- No gene amplification required
- Single site of integration into the host cell genome
- No endogenous gene disruption
- Novel high-throughput approach to address product-specific expression bottlenecks
- Validated track record in the expression of monoclonal antibodies, enzymes, Fc Fusions, GPCRs, ion channels…
- Full cell line data package including detailed vector information, host cell line pedigree, complete cell line documentation ready to use for IND filling
- Genome of the host CHO-M cell line fully sequenced enabling the precise mapping of the transgene integration site
- World class science, project management and highly efficient tech transfer to production facilities

HIGH PERFORMANCE

Single site integration in the host cell genome reduces the risk of endogenous gene disruption for unmatched stability and grams per liter productivities

RAPID DEVELOPMENT

High performance Selexis SUREclones™ in as little as 15 weeks

TRANSFER

Selexis SUREclones™ with Selexis SUREfeed™ strategy transferred to CMO

Based on the Selexis SURE*technology* Platform™ and our world-class expertise, Selexis SURE Cell Line Development™ Services significantly reduce the time, effort, and costs associated with generating high-performance mammalian cell lines for therapeutic protein production (i.e. monoclonal antibodies, growth factors, enzymes).

The development of high-yield production cell lines begins with the cloning of target genes into the SURE*tech* Vectors™ containing Selexis Genetic Elements™ (SGEs). In two rounds of transfection, these target gene-containing vectors are transfected into either the Selexis SURE CHO-M Cell Line™ or another fully documented cell line provided by the client using the SURE*fection*™ procedure. From the stable transfectant population clones are selected for high expression levels, activity and growth characteristics.

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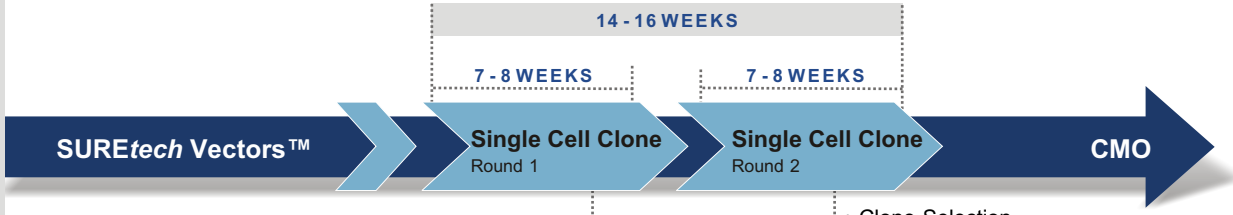
Manufacturing Cell Line in Less than 4 Months



High Performance and Stable Cell Lines

- Strong Expression Vectors
- Transposon Technology
- High Performance Host Cell
- Chemically Defined, Serum-free Medium
- Feed Strategy
- Experienced Tech Transfer

Candidate Clones

- Productivity assay
- Functional assay
- Manufacturing
- Preclinic/tox

- Clone Selection
- Expansion

Clonal Cell Lines

- Media/feed optimization
- cGMP manufacturing
- Clinical trial supply
- Market supply
- Research cell bank

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SURE Cell Lines At A Glance

SPEED
- 3 weeks for Selexis SURE*pools*™
- 15 weeks for Selexis SURE*clones*™

HIGH YIELD
- 1-5 g/L for MAbs
- Increase in recombinant protein expression levels by up to 20 fold

STABILITY
- Stable expression of recombinant proteins for more than 60 generations
- Single-site integration
- Not associated with chromosomal rearrangements or chromosomal breaks

FLEXIBLE
- Highly effective in a variety of cell lines
- 500 stable CHO cell pools for screening campaigns in 8 weeks

PROVEN
- More than 30 Selexis-generated cell lines are in clinical trials up Phase 3
- Technology has been and is currently being used by more than 70 companies worldwide

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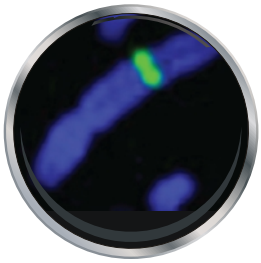
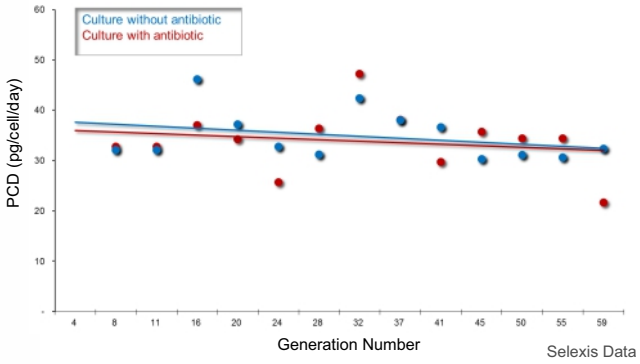
Selexis CHO-M Cell Line Stability



- ✓ Integration at single and unique site
- ✓ No chromosomal rearrangements/aberrations
- ✓ Very stable integration sites

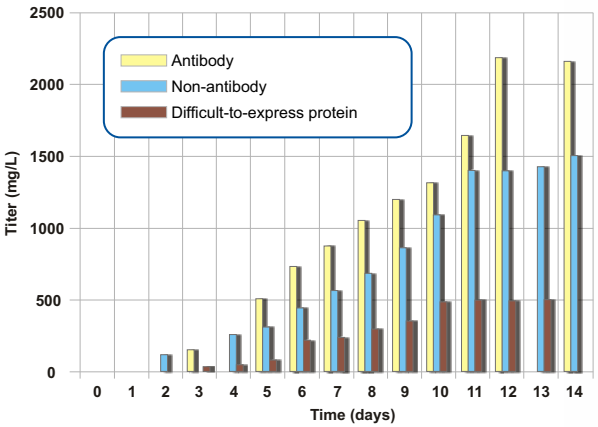
Stability of Selexis CHO-M Expressing IgG_1



Selexis Data

SELEXIS

Case Study: From DNA to IND in 14 Months



Varghese J, Alves W, Brill BJ, Wallace M, Calabrese D, Regamey A, Girod P. Rapid Development of High-Performance Stable Mammalian Cell Lines for Improved Clinical Development. *BioProcess J*, 2008; 7(4): 30-36.

MERRIMACK PHARMACEUTICALS

From DNA to IND in 14 months

- **ANTIBODY**
  >2 grams per liter
- **NON-ANTIBODY PROTEIN**
  >1 grams per liter
- **DIFFICULT-TO-EXPRESS PROTEIN**
  .5 grams per liter

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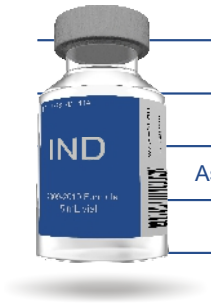
Client's Clinical Pipeline Using SURE*technology*™



	Phase 1	Phase 2	Phase 3	Market
THERAPEUTIC CANDIDATES				
Oncology	15	2		
Inflammation	8	1	1	
Blood disorders	3	1	1	
Asthma, allergies, respiratory	2			
Dermatology	1			

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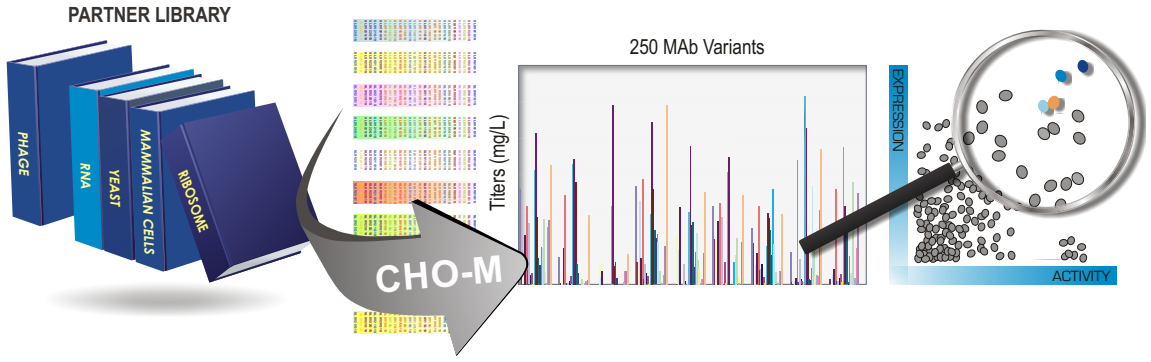
Lead Identification - Variant Screening

Selexis SURE*variant* Screening™

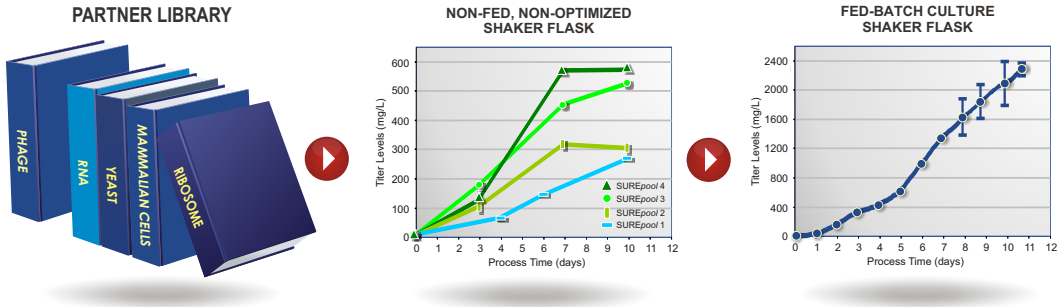
Pick the Best Candidate for Improved Clinical Success



Partner Library → 250 Variants → Pool Screening → Leads Identified

Cells used for drug development are critically important in almost every aspect of biologics drug discovery, development and manufacturing. The Selexis SURE*technology* Platform™, which is well-established as a fast and cost effective approach for generating manufacturing cell lines, has been adapted to speed identification and development of novel biotherapeutics. Selexis' SURE*variant* Screening™ accelerates and improves outcomes from partners' library selection campaigns by reducing the time and costs associated with identifying lead candidates.

Using the SURE*variant* Screening™ platform, Selexis can generate panels of up to 500 CHO-M cell pools (SURE*pools*™), each expressing different protein variants. Typical expression levels in the supernatants (SURE*natants*™) for MAbs vary between 50-500 mg/L. Containing the recombinant proteins expressed with mammalian post-translational modifications, the SURE*natants*™ can be readily assessed for activity. The Selexis SURE*pools*™ expressing lead candidates may be banked (stored) and reused for further assays. The Selexis SURE*pools*™ expressing the top clinical candidates can be transferred to the Selexis' SURE Cell line Development Platform™ to generate high-producing clonal cell lines ready for cGMP manufacturing, ensuring a match between preclinical and clinical material, most notably with glycan composition. From SURE*variant* Screening™ to the clonal cell line, this complex process may be completed in as short as 15 weeks. **Further, Selexis SURE*variant* Screening™ can reduce your development costs by over $500,000 per clinical candidate!**



SUREvariant SCREENING
Up to 500 variants screened for **ACTIVITY** and **EXPRESSION** at the same time

SUREpools
Typical MAb expression levels up to 500 mg/L
5 weeks from transfection

SUREclones
Typical fed-batch expression levels > 2 grams of protein
5 weeks post screening

Selexis Lead Identification Strategy:

1. Weeds out candidates that cannot be easily expressed in mammalian cells
2. Allows promising candidates (highly active) which would be lost (not highly expressed) to cross the threshold of expression and be detected
3. Determines the values of mammalian protein modifications early
4. Ensures a steady supply of preclinical material
5. Significantly minimizes development time and costs by eliminating the need for repeated transient transfections
6. Reduces manufacturing issues through early selection of candidates that are readily expressed
7. Eliminates unforeseen complications that can occur on transfer from HEK293 expression to CHO expression
8. Promotes faster, more informed decision-making

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Secretion Bottlenecks

Selexis SURE CHO-M*plus*™ Libraries

TECHNOLOGY

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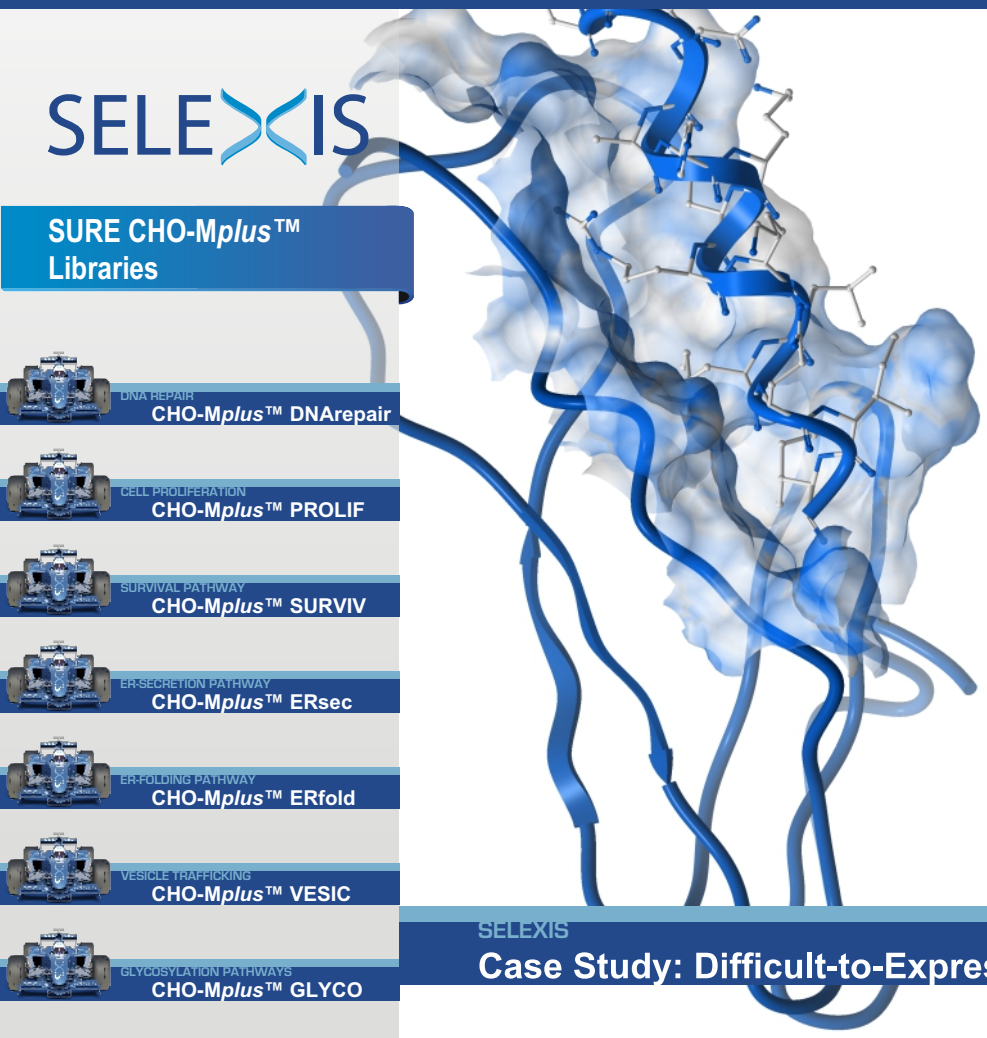
SURE CHO-M*plus*™ Libraries

- DNA REPAIR — CHO-M*plus*™ DNArepair
- CELL PROLIFERATION — CHO-M*plus*™ PROLIF
- SURVIVAL PATHWAY — CHO-M*plus*™ SURVIV
- ER-SECRETION PATHWAY — CHO-M*plus*™ ERsec
- ER-FOLDING PATHWAY — CHO-M*plus*™ ERfold
- VESICLE TRAFFICKING — CHO-M*plus*™ VESIC
- GLYCOSYLATION PATHWAYS — CHO-M*plus*™ GLYCO



With certain recombinant proteins, optimal expression cannot be achieved by elevated transcription alone. Low productivity can be the result of a myriad of issues including faulty cleavage and protein precipitation, improper folding, metabolic overload, or backlog in protein translocation or vesicle trafficking. Within each of the Company's SURE CHO-M*plus*™ Libraries, between 8-12 secretory components have been modified to address specific secretion bottlenecks, such as aberrant glycosylation or improper protein folding. The SURE CHO-M*plus*™ Libraries have been shown to significantly improve production levels of a broad range of proteins including difficult-to-express monoclonal antibodies, enzymes, structural proteins and fusion proteins such as Fc-fusions and minibodies.

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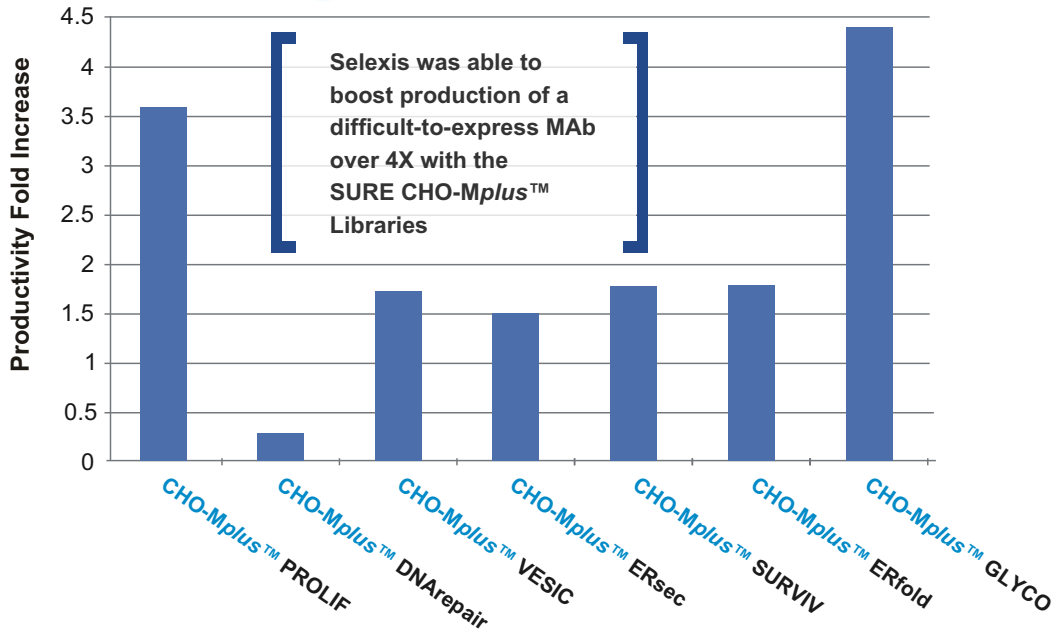
Case Study: Difficult-to-Express MAb



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Designer Cell Lines / Detailed Regulatory Packages

Selexis SURE CHO*omics*™

TECHNOLOGY

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SURE CHO*omics*™ SNAPSHOT

IDENTIFIED

- 16,289 mRNA sequences and transcript levels
- 5,748 “silent” genes
- Under-expressed and mutant molecular chaperones

PUTTING CHO*omics*™ TO USE

- Detailed regulatory packages
- Mapping recombinant gene integration sites
- Designer cell lines
- Knocking -in or -out components that improve productivity for particular proteins
- CHO-M*plus*™ Library generation

The Large Scale Study of the Selexis SURE CHO-M Genome & Transcriptome:

23 Gb of the CHO-M genome sequenced and assembled

98% of coding DNA sequence is common to both CHO-M and CHO-K1

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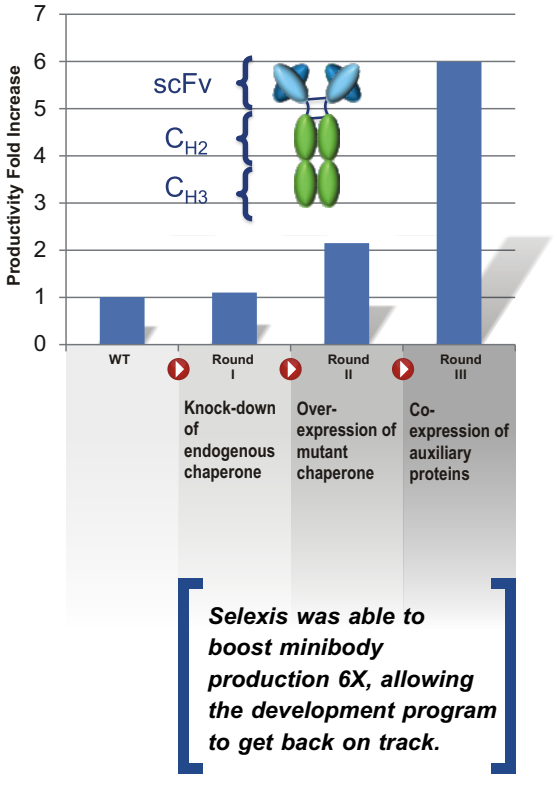
Case Study: Novel Therapeutic Minibody



Selexis was able to boost minibody production 6X, allowing the development program to get back on track.

Expression of an exciting new therapeutic minibody was hitting a production bottleneck. The minibody gene was readily transcribed using the Selexis SURE*technology* Platform™, however, the high levels of transcription did not translate into high productivity levels. Detailed evaluation of the cell line determined that one of the molecular chaperones was binding the minibody too tightly, trapping it within the ER. Using the data from SURE CHO*omics*™, Selexis was able to determine the exact DNA sequence of the molecular chaperone and knock it down using the SURE*technology*™ Platform. Selexis then over-expressed a mutant form of the chaperone with reduced binding for the minibody, which allowed for transport through the secretory pathway. Finally, by overexpressing key auxillary secretory proteins, Selexis was able to boost minibody production 6X, allowing the development program to get back on track.

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