Selexis SURE Cell Line Development™

**Manufacturing Cell Line in Less than 4 Months**

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 filing
- 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

Based on the Selexis SUREtechnology 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 SUREtech 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 SUREfection™ procedure. From the stable transfecant population clones are selected for high expression levels, activity and growth characteristics.

**Selexis SURE Cell Line Development™**

**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 SUREclones™ in as little as 15 weeks

**TRANSFER**
- SUREclones™ with SUREfeed™ strategy transferred to CMO

Selexis - A Serial Innovation Company
**Selexis CHO-M Cell Line Stability**

**SURE Cell Lines At A Glance**

**SPEED**
- 3 weeks for Selexis SUREpools™
- 15 weeks for Selexis SUREclones™

**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

**Case Study: From DNA to IND in 14 Months**

**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

**Client’s Clinical Pipeline Using SUREtechnology™**

<table>
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<th>THERAPEUTIC CANDIDATES</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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</tbody>
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**Selexis Data**

SUREclones
Leads Identified
8
Pool Screening
7
5

5. Significantly minimizes development time and costs by eliminating the need for repeated transient transfections

7. Eliminates unforeseen complications that can occur on transfer from HEK293 expression to CHO expression

8. Promotes faster, more informed decision-making

Cells used for drug development are critically important in almost every aspect of biologics drug discovery, development and manufacturing. The Selexis SUREtechnology 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' SUREvariant Screening™ accelerates and improves outcomes from partners' library selection campaigns by reducing the time and costs associated with identifying lead candidates.

Using the SUREvariant Screening™ platform, Selexis can generate panels of up to 500 CHO-M cell pools (SUREpools™), each expressing different protein variants. Typical expression levels in the supernatants (SUREnats™) for MAbs vary between 50-500 mg/L. Containing the recombinant proteins expressed with mammalian post-translational modifications, the SUREnats™ can be readily assessed for activity. The Selexis SUREpools™ expressing lead candidates may be banked (stored) and reused for further assays. The Selexis SUREpools™ 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 SUREvariant Screening™ to the clonal cell line, this complex process may be completed in as short as 15 weeks. Further, Selexis SUREvariant Screening™ can reduce your development costs by over $500,000 per clinical candidate!
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-Mplus™ 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-Mplus™ 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.
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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SURE CHOomics™ SNAPSHOT

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

PUTTING CHOomics™ 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-Mp/us™ Library generation

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

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Case Study: Novel Therapeutic Minibody

Expression of an exciting new therapeutic minibody was hitting a production bottleneck. The minibody gene was readily transcribed using the Selexis SUREtechnology 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 CHOomics™, Selexis was able to determine the exact DNA sequence of the molecular chaperone and knock it down using the SUREtechnology™ 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 auxiliary secretory proteins, Selexis was able to boost minibody production 6X, allowing the development program to get back on track.

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