Innovative Technology for Drug Target Discovery

GPScreen™: Genome-wide Drug Target Identification & Validation Services
**GPScreen™: Innovative Genome-wide Drug Target Screening Technology**

**GPScreen™ (Genome-wide S. pombe Screening)** is an innovative, high throughput drug target screening system using drug-induced haploinsufficiency (DIH) in the *S. pombe* genome-wide deletion mutant library (See page 4). Through the genome-wide screening on about 5,000 genes in the library at each gene level, **GPScreen™** provides the reliable drug targets, outperforming traditional drug target discovery technologies such as genome sequencing, SNP chip, microarray and protein chip which have limitations in presenting drug targets.

As of Jan 2017, 4,845 heterozygous deletion mutants are prepared and used for **GPScreen™** service, which is responsible for 98.6% genome coverage.

We also provide drug target validation service in human cells using Bioneer’s proprietary human siRNA library and **in vivo** delivery platform technology (SAMiRNA™) to verify the function of target genes identified from **GPScreen™**.

### Applications:
- Drug target identification
- Genome-wide drug target profiling for drug prioritization at an early stage of drug discovery
- Natural drug target discovery
- Mode of action study of small molecules
- Drug repositioning

### Features & Benefits:
- The most advanced genome-wide drug on/off-target identification technology
- Based on World’s-unique *S. pombe* genome-wide deletion library
- Drug target screening on about 5000 genes in *S. pombe* genome
- All classes of target ID is possible
- A state-of-art, high-throughput screening technology using qPCR with accuracy & reliability
Genome-wide Drug Target Screening using \textit{S. pombe} genome-wide deletion mutant library

\textit{S. pombe} genome-wide deletion mutant library was developed by Bioneer and KRIBB in Korea, in collaboration with Dr. Paul Nurse of Cancer Research Center in UK as reported in \textit{Nat. Biotech}, 28, 617–623 (2010). Fission yeast \textit{S. pombe} is the simplest cell division model organism. The library covering almost all genes/ORF (total of 4,914 different types) in \textit{S. pombe} genome was constructed by homologous recombination in which each ORF is replaced with a deletion cassette tagged with unique DNA sequence barcode (See the figure below). The library is available from Bioneer exclusively and can be used for genetic and chemical screening such as drug target identification, gene expression profiling and synthetic lethal profiling. \textit{S. pombe} has a higher homology with human genes than those of \textit{S. cerevisiae}; Moreover, it contains 3,500 homologs to human genes and 500 unique genes not in budding yeast, \textit{S. cerevisiae}.

Drug-induced Haploinsufficiency (DIH) is a phenomena in nature that reducing the copy number of a drug target gene from two copies to one often results in a strain that is sensitized to drugs that act on the product of the gene. DIH in yeast has now been considered as a valuable tool for drug target identification. Heterozygous diploid strain, which lack a copy of a gene, is significantly sensitive to drugs that act on the product of the gene while wild type strain is modestly affected by the drugs. Strains lacking one copy of the target gene grow significantly slow. By comparing the growth rate of clones, the drug targets are identified clearly. Using this principle, previous report has provided identifications of drug targets from budding yeast \textit{S. cerevisiae}.\textsuperscript{1}


\textit{S. pombe} genome-wide deletion mutant library (Nature Biotech., 2010)

A. Construction of \textit{S. pombe} deletion mutant.  B. Genetic status of \textit{S. pombe} heterozygous deletion mutant library.
Drug Target Validation in Human Cells using SAMiRNA™ & Human siRNA Library

SAMiRNA™ (Self-Assembled-Micelle-inhibitory-RNA) is a novel siRNA molecule conjugated with lipid and hydrophilic polymer, which spontaneously forms stable nanoparticles and optimized for systemic delivery without any other reagent and formulation process. With this feature, SAMiRNA™ nanoparticles incorporate siRNA, miRNA or even antisense oligonucleotide, with the ideal size for selective localization in either vascularized tumors via Enhanced Permeability and Retention (EPR) effects or for targeting tissues through the addition of ligand moieties on the surface of SAMiRNA™.

The therapeutic potential of SAMiRNA™ is highlighted by virtue of its negligible toxicity and superb in vivo serum stability as well as its long lasting target gene silencing efficacy proven in various cancer and lung fibrosis animal disease models. In addition, SAMiRNA™ has been shown to induce no innate immune response in human PBMC test and high dose-administrated rodent models. These data indicate SAMiRNA™’s exceptional therapeutic potential as an RNAi platform targeting for various diseases in vivo.

In vivo siRNA delivery challenges are overcome by SAMiRNA™ technology.

Bioneer’s AccuTarget™ Human Predesigned siRNA Library designed by Turbo si-Designer consists of 54,144 siRNAs for 18,048 human genes. Considering several important parameters including base composition, the number of repetitive bases in a row, thermodynamic instability, energy profiling and base preference, Turbo si-Designer identifies highly effective siRNA target sites with exceptional success rates. Bioneer’s AccuTarget™ Human Predesigned siRNAs demonstrate maximized knockdown efficiency for target genes and minimized off-target effect.

A. High efficiency of Bioneer’s AccuTarget™ Human Predesigned siRNA Libraries.  B. Structure of SAMiRNA™
Genome-wide Drug Target Identification & Profiling with **GPScreen™**

**Drug target identification with GPScreen™**

A. Chemical structure of cytochalasin A.

B. In the presence of cytochalasin A, a heterozygous deletion mutant of act1 shows decreased growth as a result of a decrease in functional Act1 protein. act1 was the only gene in the genome-wide screen to show this effect, demonstrating that act1 is a target of cytochalasin A. This result shows that **GPScreen™** can be used as a powerful tool for precise drug target identification of drug candidates.

**Drug target profiling for drug prioritization with GPScreen™**

A. Two known drugs with distinct in-vivo toxicity were treated to *S. pombe* genome-wide deletion mutant library pool at the GI50 concentration of each compound for 15 h, and their genome-wide drug target profiles were obtained by analyzing the barcode frequency of each mutant in comparison with that of DMSO control. B. Next, the promising targets (fitness value; > 4; plotted box area of A) of the two drugs were classified into gene functional groups in which non-toxic drug A showed a more selective target profile than that of toxic drug B, which is well correlated with their known in-vivo toxicity. These results suggest that **GPScreen™** can be used as a powerful tool for very effective drug toxicity evaluation at preclinical and early stages in drug R&D process.
Ordering Information

* Price and timeline can be varied according to the number of compounds. Please email us at gpscreen@bioneer.com for details.

1. Preliminary Activity Test in wild type *S. pombe*

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<thead>
<tr>
<th>Cat. no.</th>
<th>GPS-00</th>
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</thead>
<tbody>
<tr>
<td>Service</td>
<td>Determination of the growth-inhibitory activity (GI₅₀) of compounds using preliminary activity test in wild type <em>S. pombe</em></td>
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<td>Price</td>
<td>Inquire</td>
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2. Drug Target Identification & Profiling Service in *S. pombe*

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<th>Cat. no.</th>
<th>GPS-02-Genome-wide</th>
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<tbody>
<tr>
<td>Screening Size</td>
<td>Diploid mutant set (4,845 genes) (Essential; 1,277, Non-essential; 3,568) (98.6% genome coverage)</td>
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<tr>
<td>Application</td>
<td>Precise drug target identification &amp; Drug target profiling for drug prioritization</td>
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<td>Price</td>
<td>Inquire</td>
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3. Drug Target Validation in Human Cells

<table>
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<th>Cat. no.</th>
<th>GPS-03-Human cells</th>
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</thead>
<tbody>
<tr>
<td>Service</td>
<td>Drug target validation in human cells using Bioneer’s proprietary human siRNA library and in vivo delivery platform technology (SAMiRNA™) to verify the function of target genes identified from GPScreen™</td>
</tr>
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<td>Price</td>
<td>Inquire</td>
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