ver. 201912

# Solutions for Cancer Research

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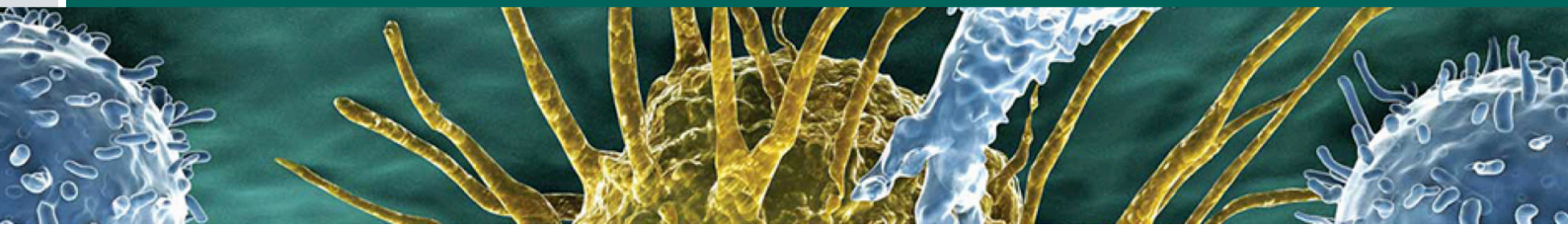
## Cancer 연구용 제품 가이드

- 암 바이오마커 (RNA, DNA, Exosome)
- 단일 암세포 분석 (CTC, Single cell)
- 면역항암제 (T cell, TCR, BCR)
- 암 후성유전학 (Epigenetics)
- HLA Typing (PCR, WGA, NGS)
- Gene editing (CRISPR)

TaKaRa

Clontech TaKaRa cellartis

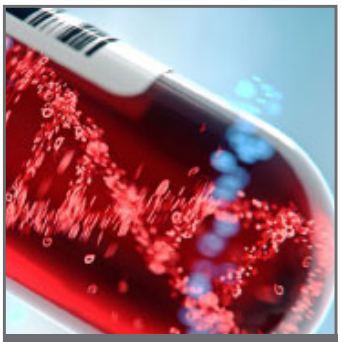


암 연구를 위한 제품 선택가이드

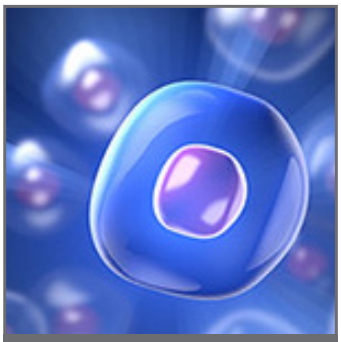
# Solutions for Cancer Research

암(癌, Cancer) 혹은 악성종양(惡性腫瘍, Malignant tumor, Malignant neoplasm)은 세포주기가 조절되지 않아 세포분열이 계속되는 질병으로, 폐암 · 위암 · 유방암 · 대장암 등이 있다. 암과의 싸움은 여전히 힘든 싸움으로 남아있지만, 암 연구 분야의 지속적인 발전은 큰 희망을 준다. 다카라바이오는 암 바이오마커 연구, 단일 암세포 분석, 암 후성유전인자 분석, HLA Typing, T-cell 치료 및 프로파일링, 항체치료, CRISPR/Cas9 유전자 편집 등의 암 연구를 위한 다양한 제품과 기술을 제공한다.

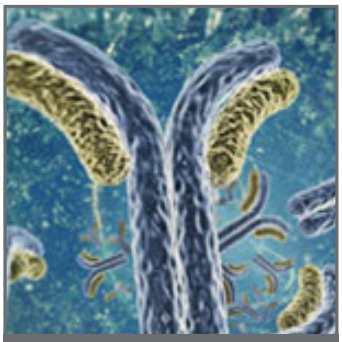
## 한눈에 보기 - Cancer 연구를 위한 제품가이드



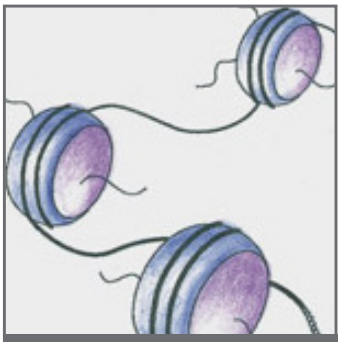




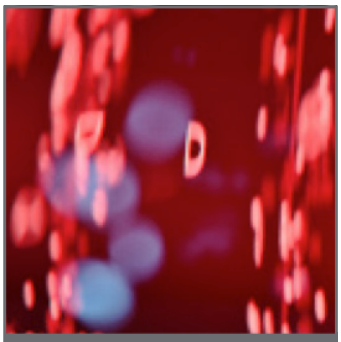




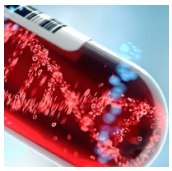












## 1. 암 바이오마커 (Cancer Biomarker Discovery)

Next Generation Sequencing (NGS) 기술의 발전에 따라 종양유전자 (oncogene), 종양억제유전자 (tumor suppressor gene)를 이용한 암 바이오마커 연구가 가속화되고 있다. 다카라바이오에서는 Liquid biopsy (Circulating tumor DNA (ctDNA), Cell-free RNA (cfRNA), Cell-free DNA (cfDNA), Urine 등), FFPE 샘플, Exosome 등에서 암 바이오마커 유전자를 검출 및 분석할 수 있는 제품을 제공한다.

### 1) Low input mRNA • DNA 염기서열 분석

- 소량의 RNA, DNA 샘플을 위한 NGS Library Preparation Kit
- FFPE RNA/DNA 및 Liquid biopsy 유래의 DNA, RNA 분석 가능 (ctDNA, cfRNA, cfDNA 외)

| 구분 | Code | 제품명 | 특징 |
|---|---|---|---|
| DNA-seq | R400679 | ThruPLEX® Plasma-Seq Kit | • Cell-free DNA 분석에 최적화<br>• Sample input: 1 ng  30 ng of cfDNA |
| | R400584 | ThruPLEX® Tag-seq 6S(12)Kit | • Low frequency variant 분석<br>• 16 million Unique Molecular Tags<br>• Sample input: 1 ng- 50 ng of cfDNA |
| | R400674 | ThruPLEX® DNA-seq Kit | • Low input DNA-seq library prep<br>• Sample input: 50 pg  50 ng of DNA |
| RNA-seq | 634411 | SMARTer® Stranded Total RNA-Seq Kit v2 - Pico Input Mammalian | • Cell-free mRNA, lncRNA 분석<br>• All-in-one kits for Illumina® NGS<br>• Sample input: 250 pg  10 ng total RNA |

### 2) Exosomal RNA 분석

- 고순도의 Exosome 분리를 위한 독자적인 Capturem™ membrane spin column
- Exosomal RNA 및 miRNA 분석을 위한 SMARTer® NGS 시리즈

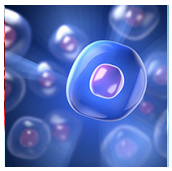
| 구분 | Code | 제품명 | 특징 |
|---|---|---|---|
| Exosome 분리 | 635723 | Capturem™ Exosome Isolation Kit (Cell Culture) | • 30분만에 Exosome 분리 (2 x $10^{11}$/column)<br>• No Precipitation, No Ultracentrifugation |
| | 635741 | Capturem™ Extracellular Vesicle Isolation Kit (Mini) | • Liquid biopsy (plasma, saliva, CSF)로부터 Extracellular vesicle (EV) 분리 |
| smRNA-seq | 635029 | SMARTer® smRNA-Seq Kit for Illumina® | • Small RNA/MicroRNA NGS library preparation<br>• All-in-one system for Illumina® NGS<br>• Sample input: 1 ng  2 µg of total RNA |
| RNA-seq | 634411 | SMARTer® Stranded Total RNA-Seq Kit v2 - Pico Input Mammalian | • Exosomal mRNA, lncRNA 분석<br>• All-in-one kits for Illumina® NGS<br>• Sample input: 250 pg  10 ng total RNA |

References
Selected publications citing the use of ThruPLEX-Plasma Seq Kit for non-invasive monitoring of tumor chemo-resistance

1. Mayrhofer, M. *et al.* Cell-free DNA profiling of metastatic prostate cancer reveals microsatellite instability, structural rearrangements and clonal hematopoiesis. *Genome Med.* 10, 8598 (2018).
2. Mouliere, F. *et al.* Detection of cellfree DNA fragmentation and copy number alterations in cerebrospinal fluid from glioma patients. *EMBO.* 12, e9323 (2018).
3. Murtaza, M. *et al.* Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. *Nature* 497, 108112 (2013).
4. Patel, K. M. *et al.* Association of plasma and urinary mutant DNA with clinical outcomes in muscle invasive bladder cancer. *Sci. Rep.* 7, 5554 (2017).
5. Xia, Y. *et al.* Copy number variations in urine cell free DNA as biomarkers in advanced prostate cancer. *Oncotarget* 7, 3581835831 (2016).

References
Selected publications citing the use of SMARTer smRNA-Seq Kit for noninvasive miRNA profiling in prostate cancer diagnosis

1. Guelfi, G. *et al.* Next generation sequencing of urine exfoliated cells: an approach of prostate cancer microRNAs research. *Sci. Rep.* 8, 7111 (2018).



## 2. 단일 암세포 분석 (Single Cancer Cell Analysis)

종양세포에서 나타나는 복잡성 (Complexity)과 이질성 (Heterogeneity)은 종양세포 (cancer cell), 지속성 암세포 (Cancer persister cells), 순환종양세포 (Circulating Tumor Cell; CTC)를 단일세포 수준에서 해석함으로써 분석 가능하다. 그러나 단일세포를 연구하려면 아주 민감하고 재현성 높은 분석 방법이 필요하며, 다카라바이오에서는 독자적인 SMARTer® 기술을 이용하여 단일세포 수준의 염기서열 분석을 위한 제품을 제공한다.

### 1) Single-cell Genome Sequencing

| 구분 | Code | 제품명 | 특징 |
|---|---|---|---|
| WGA | R300718 | PicoPLEX® Single Cell WGA Kit v3 | • Whole Genome Amplification (WGA)<br>• Single cell CNV 분석의 Gold standard<br>• High fidelity 효소 사용으로 SNV 검출 가능<br>• Sample input : 1  10 cells |
| DNA-seq | R300669 | PicoPLEX® Gold Single Cell DNA-Seq Kit | • Single cell DNA-Seq library preparation<br>• Cancer Single cell_CNV, SNV 동시 분석 가능<br>• Sample input: 1  5 cells |

### 2) Single-cell Transcriptome Sequencing

- SMART-Seq® Technology : Single cell RNA-seq 분석의 기준
- Single cell full-length cDNA 합성과 증폭

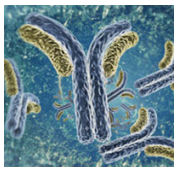
| Code | 제품명 | 특징 |
|---|---|---|
| 634470 | SMART-Seq® Single Cell Kit | • Single cell로부터 고품질의 full-length cDNA 합성<br>• RNA 함량이 낮은 세포 (e.g. PBMC)의 단일세포 분석<br>• Sample input : Single cell, 2 pg of RNA |
| 634888 | SMART-Seq® v4 Ultra® Low Input RNA Kit for Sequencing | • Whole Transcriptome Amplification (WTA)<br>• Sample input: 10 pg - 10 ng total RNA, 1 - 1,000 cells |
| 634437 | SMART-Seq® HT Kit | • High-throughput Single cell NGS library prep<br>• Sample input: 10 pg - 10 ng total RNA, 1 - 100 cells |
| 634442 | SMART-Seq® Stranded Kit | • Single cell Strand-specific RNA-Seq<br>• Sample input: 10 pg - 10 ng total RNA, 1 - 1,000 cells |
| 635040 | SMART-Seq® v4 3' DE Kit | • Single cell differential expression (DE) 적용<br>• 3'-end transcript analysis<br>• Sample input: 10 pg - 10 ng Total RNA, 1 - 100 cells |
| 635025 | SMART-Seq® v4 Ultra® Low Input RNA Kit for the Fluidigm® C1™ System | • Fluidigm C1™을 이용한 Auto preparation kit<br>• Sample input: Single cell only |

References
Selected publications citing the use of PicoPLEX technology for high performance CNV analysis and the genomic profiling of single cells from FFPE tumor tissues and circulating tumor cells, and G&T-seq

1. Lieselot D. *et al.* (2017). Performance of four modern whole genome amplification methods for copy number variant detection in single cells. *Scientific Reports* 7: 3422
2. Babayan A. *et al.* (2017). Comparative study of whole genome amplification and next generation sequencing performance of single cancer cells. *Oncotarget* 8: 56066-56080
3. Williamson S.C. *et al.* (2016). Vasculogenic mimicry in small cell lung cancer. *Nature Communications* 7: 13322
4. Morrow C. J. *et al.* (2016). Tumourigenic non-small-cell lung cancer mesenchymal circulating tumour cells: a clinical case study. Annals of Oncology 27 (6): 11551160
5. Premasekharan G. *et al.* (2016). An improved CTC isolation scheme for pairing with downstream genomics: Demonstrating clinical utility in metastatic prostate, lung and pancreatic cancer. *Cancer Letters* 380 (1): 144 152
6. Cayrefourcq L. *et al.* (2015). Establishment and Characterization of a Cell Line from Human Circulating Colon Cancer Cells. *Cancer Research* 75 (5): 892-901
7. Macaulay I.C. *et al.* (2015). G&T-seq: parallel sequencing of single-cell genomes and transcriptomes. *Nature Methods* 12: 519522

References
Selected publications citing the use of SMART-Seq solutions for single-cell RNA-seq in various different cancer applications

1. Chung W. *et al.* (2017). Single-cell RNA-seq enables comprehensive tumour and immune cell profiling in primary breast cancer. *Nature Communications* 8: 15081
2. Zheng H. *et al.* (2018). Single-cell analysis reveals cancer stem cell heterogeneity in hepatocellular carcinoma. *Hepatology* doi: 10.1002/hep.29778. [Epub ahead of print]
3. Kim K.T. *et al.* (2015). Single-cell mRNA sequencing identifies subclonal heterogeneity in anti-cancer drug responses of lung adenocarcinoma cells. *Genome Biology* 16: 127
4. Han K.Y. *et al.* (2018). SIDR: simultaneous isolation and parallel sequencing of genomic DNA and total RNA from single cells. *Genome Research* 28: 7587
5. Chiu H.S. *et al.* (2018). Pan-Cancer Analysis of lncRNA Regulation Supports Their Targeting of Cancer Genes in Each Tumor Context. *Cell Reports* 23(1): 297312



## 3. 면역항암제 (Cancer Immunotherapy)

수술, 화학요법, 방사선요법과 같은 전통적인 암 치료는 암 말기 환자에게 매우 제한된 효능만을 보여주었을 뿐만 아니라, 화학요법과 방사선요법은 간혹 상당히 심각한 부작용을 일으킨다. 따라서 보다 혁신적이고 효과적인 암 치료를 위해 면역항암제가 개발되고 있으며, 이는 높은 특수성과 안전성, 낮은 부작용과 같은 장점을 가진다. 다카라 바이오에서는 면역항암제 개발을 위한 다양한 연구 툴을 제공하고 있다.

### 1) T Cell Therapy를 위한 RetroNectin®

- T cell에 효율적인 TCR/CAR 유전자 도입을 위한 Transduction enhancer
- T cell 확대배양의 효율을 증진시키는 Co-stimulator로써 적용
- 유전자치료 임상 실험 목적으로 전 세계 44개 기관에서 68개 이상의 프로토콜에 적용

| Code | 제품명 | 특징 |
|---|---|---|
| T202 | RetroNectin® GMP grade (Recombinant Human Fibronectin Fragment CH-296) | • Retrovirus, Lentivirus transduction enhancer<br>• Polybrene, Protamine 대비 낮은 독성<br>• Enhanced T-cell expansion |
| WK552S | LymphoONE™ T-Cell Expansion Xeno-Free Medium, 1L Bottle | • Serum-Free, Xeno-Free T-cell 배양 배지<br>• T-cell의 높은 증식율 유지 |
| T210 | Anti-CD3 mAb GMP grade | • GMP grade의 Anti-CD3 Monoclonal Antibody<br>• T-cell activation을 위한 stimulator |

### 2) TCR, BCR Profiling 분석을 위한 SMARTer® Immune Profiling Kits

- 5' RACE (Rapid Amplification cDNA Ends)와 NGS 기술의 조합으로 보다 간편하고 강력한 Profiling
- TCRα, TCRβ chain 또는 BCR Heavy chain (H), Kappa chain (κ), Lamda chain (λ) 개별 또는 동시 분석

| 구분 | Code | 제품명 | 특징 |
|---|---|---|---|
| TCR | 635014 | SMARTer® Human TCR a/b Profiling Kit | • Human Bulk TCR 분석<br>• Sample input:<br>10 ng - 3 µg Human blood RNA,<br>50 - 10,000 lymphocytes |
| | 634431 | SMARTer® Human scTCR a/b Profiling Kit | • Human single cell TCR 분석 |
| | 634402 | SMARTer® Mouse TCR a/b Profiling Kit | • Mouse Bulk TCR 분석<br>• Sample input:<br>10 ng - 500 ng total RNA<br>또는 1,000 - 10,000개의 purified T-cell |
| | 640182 | ICELL8® Human TCR a/b Profiling Reagent Kit | • ICELL8® cx Single-Cell System로 분리한 Single cell로부터 TCR Profiling |
| BCR | 634466 | SMARTer® Human BCR IgG IgM H/K/L Profiling Kit | • Human Bulk BCR 분석<br>• UMI based correction 적용으로 정확한 분석<br>• Sample input:<br>10 ng - 1 µg of PBMC RNA<br>또는 1 - 100 ng of B cell RNA |
| | 634422 | SMARTer® Mouse BCR IgG H/K/L Profiling Kit | • Mouse Bulk BCR 분석<br>• Sample input: 10 ng - 3 µg total RNA |

## 3) Antibody Therapeutics

- Monoclonal antibody, Antibody drug conjugates (ADC) 항체의약품, 치료제 연구
- Construct 제작부터 정제, 분석을 위한 제품

| 구분 | Code | 제품명 | 특징 |
|---|---|---|---|
| Expression construct 제작 | 639648 | In-Fusion® HD Cloning Kit | • Antibody expression construct 제작을 위한 High-throughput cloning<br>• Fast (15 min), Efficient (>95%), Seamless |
| His-tag 단백질 정제 | 635710 | Capturem™ His-Tagged Purification Miniprep Kit | • His-tagged 단백질 정제<br>• 실온에서 5 ~ 15분이면 고순도 단백질 정제 |
| Biotin-tag 단백질 정제 | 635733 | Capturem™ Streptavidin Miniprep Columns | • Biotinylated 단백질 정제 |
| 항체 정제 IP | 635717 | Capturem™ Protein A Miniprep | • Protein A를 이용한 고순도 항체 정제 |
| | 635725 | Capturem™ Protein G Miniprep | • Protein G를 이용한 고순도 항체 정제 |
| | 635721 | Capturem™ IP & Co-IP Kit | • Protein A를 이용하여 IP & Co-IP를 15분만에 |
| MS 분석 샘플 전처리 | 635740 | Capturem™ Trypsin Miniprep Kit (Mass Spectrometry Grade) | • 단 4분, Trypsin digestion<br>• Autolysis 최소화 |
| | 635728 | Capturem™ Pepsin | • 단 3분, Pepsin digestion |

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Selected publications citing RetroNectin GMP grade reagent use in TCR/CAR therapies
1. Kochenderfer, J. N., *et al.* (2012) B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigenreceptortransduced T cells. *Blood* 119 (12):27092720
2. Robbins, P. F., *et al.* (2011) Tumor Regression in Patients with Metastatic Synovial Cell Sarcoma and Melanoma Using Genetically Engineered Lymphocytes Reactive With NY-ESO-1. *J. Clin. Oncol.* 29 (7):917924
3. Zhang, L., *et al.* (2013) Evaluation of γ-retroviral vectors that mediate the inducible expression of IL-12 for clinical application. *J. Immunother.* 35(5):430439
4. Brentjens, R., *et al.* (2013) CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia. *Science Translational Medicine* 5 (177):177ra38
5. Ramos C. A. *et al.* (2017). Clinical and Immunological Responses after CD30-Specific Chimeric Antigen Receptor-Redirected Lymphocytes. *The Journal of Clinical Investigation* 127 (9): 346271
6. Tang X.Y. *et al.* (2016). Third-Generation CD28/4-1BB Chimeric Antigen Receptor T Cells for Chemotherapy Relapsed or Refractory Acute Lymphoblastic Leukaemia: A NonRandomised, Open-Label Phase I Trial Protocol. *BMJ Open* 6 (12)
7. Ali S.A. *et al.* (2016). T Cells Expressing an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor Cause Remissions of Multiple Myeloma. *Blood* 128 (13): 16881700
8. Stroncek D.F. *et al.* (2016). Myeloid Cells in Peripheral Blood Mononuclear Cell Concentrates Inhibit the Expansion of Chimeric Antigen Receptor T Cells. *Cytotherapy* 18 (7): 893901
9. Tomuleasa C. *et al.* (2018). Chimeric Antigen Receptor T-Cells for the Treatment of B-Cell Acute Lymphoblastic Leukemia. *Frontiers in Immunology*: 19 February

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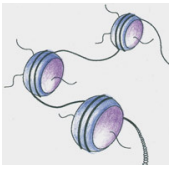
Selected publications citing the use of In-Fusion HD Cloning for HTP antibody cloning
1. Spidel J.L. *et al.* (2016). Rapid high-throughput cloning and stable expression of antibodies in HEK293 cells. *Journal of Immunological Methods* 439: 50–58
2. Chen C.G. *et al.* (2014). One-step zero-background IgG reformatting of phage-displayed antibody fragments enabling rapid and high-throughput lead identification. *Nucleic Acids Research* 42 (4): e26
3. Meng W *et al.* (2015). Efficient generation of monoclonal antibodies from single rhesus macaque antibody secreting cells. *mAbs* 7 (4): 707–718



## 4. 암 후성유전학 (Cancer Epigenomics)

암 후성유전학 연구에서는 암 특이적 DNA-binding proteins, 히스톤 변형 (histone-modification), DNA 메틸화 (DNA methylation) 등을 분석한다. Chromatin Immunoprecipitation Sequencing (ChIP-seq) 및 최신 기술인 Cut&Run-seq은 NGS를 이용하는 후성유전학 연구 방법으로, 분석을 위해 회수되는 DNA의 양이 매우 적어 극소량의 DNA 분석을 위한 특수한 제품이 필요하다.

| Code | 제품명 | 특징 |
|---|---|---|
| R400674 | ThruPLEX® DNA-seq Kit | • ChIP-seq, Cut&Run-seq Library Preparation<br>• 3 Steps in one tube 프로토콜 (hands-on 15분)<br>• Sample input: 50 pg 50 ng of ChIP DNA |

References
Selected publications citing the use of ThruPLEX technology for whole genome sequencing, targeted sequencing, CNV analysis and ChIP-seq studies in various types of cancers
1. McNair C. *et al.* (2018). Differential impact of RB status on E2F1 reprogramming in human cancer. *Journal of Clinical Investigation* 128(1): 341358
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3. Cato L. *et al.* (2017). Development of Bag-1L as a therapeutic target in androgen receptordependent prostate cancer. *eLife* 6: e27159
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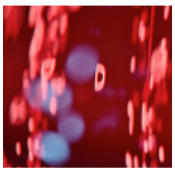

## 5. HLA Typing

Human Leukocyte Antigen (HLA)는 매우 다형성이 높은 영역 (highly polymorphic region)으로, 면역 조절에 관련된 여러 개의 유전자로 구성되어있다. HLA Typing 기법은 암 발병기전과 관련된 반복적인 돌연변이 (target recurrent mutation)와 핫스팟 (hotspot site)을 연구하는 아주 중요한 분석 방법이다. HLA Typing을 위한 NGS는 복잡한 DNA 주형을 광범위하게 분석하기 위하여 높은 특이성과 정확성을 요구한다. 다카라바이오는 Targeted sequencing을 위한 high-fidelity polymerase와 NGS Library preparation kit를 제공한다.

### 1) Targeted sequencing을 위한 High-fidelity PCR Polymerase

- Targeted Sequencing (NGS, Sanger)을 위한 Target amplification에 최적
- 매우 높은 정확도로 GC 함량이 높은 long fragment target 증폭 (>30 kb)

| Code | 제품명 | 특징 |
|---|---|---|
| R050A | PrimeSTAR® GXL DNA Polymerase | • GC-rich, long fragment target 증폭에 최적<br>• 3' → 5' exonuclease 활성으로 에러율 최소화 |
| R051A | PrimeSTAR® GXL Premix | • Premix type의 PrimeSTAR® GXL DNA Polymerase |

### 2) HLA Typing을 위한 Whole Genome Amplification (WGA)

| Code | 제품명 | 특징 |
|---|---|---|
| R300718 | PicoPLEX® Single Cell WGA Kit v3 | • NGS, Sanger, Array를 이용한 HLA typing을 위한 WGA<br>• SNV, CNV의 민감도 있는 검출<br>• Sample input : 1 10 cells |
| R300669 | PicoPLEX® Gold Single Cell DNA-Seq Kit | • NGS Library Preparation for HLA Typing<br>• Sample input: 1 - 5 cells |

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Selected publications citing the use of SMARTer PicoPLEX technology for HLA Typing
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## 6. Gene Editing for Cancer Therapy & Drug Discovery

암 연구에서 유전자 편집 기술은 종양유전자의 메커니즘 분석, 항암제 개발의 대상 유전자 동정, 세포 기반 치료의 암세포 식별 등 다양하게 적용 가능하다. 다카라바이오에서는 다양한 유전자 편집 기술을 위한 Guide-it™ 시리즈를 제공하고 있다.

| 구분 | Code | 제품명 | 특징 |
|---|---|---|---|
| Drug target 분석 | 632646 | Guide-it™ CRISPR Genome-Wide sgRNA Library System | • Brunello library 기반의 76,000개의 sgRNA library<br>• 4 sgRNAs per gene, 19,114 genes targeted |
| sgRNA 합성 | 632636 | Guide-it™ Complete sgRNA Screening System | • *In vitro* transcription 방법의 sgRNA 합성<br>• 12 µg 이상의 고품질 sgRNA 제작 가능<br>• sgRNA candidates 효율 검증을 위한 스크리닝 |
| 삽입 유전자의 ssDNA template | 632644 | Guide-it™ Long ssDNA Production System | • 목적 유전자 삽입을 위한 ssDNA HDR Donor Template 제작<br>• Long ssDNA template 합성 가능 (~ 5 kb) |
| WT Cas9 | 632641 | Guide-it™ Recombinant Cas9 (Electroporation-Ready) | • Wild type spCas9<br>• Low glycerol 농도로 낮은 세포 독성<br>• 높은 편집 효율 |
| K/O 확인 | 631448 | Guide-it™ Mutation Detection Kit | • T7E1, CEL1 Assay보다 명확한 Knock-out 검출 |
| 유전자 삽입 변이 검출 | 632659 | Guide-it™ Knockin Screening Kit | • SNP, 삽입된 유전자 도입 검출 |

References
Selected publications citing the use of various Guide-it CRISPR/Cas9 kits for different cancer applications
1. Lao Y.H. *et al.* (2018). HPV Oncogene Manipulation Using Nonvirally Delivered CRISPR/Cas9 or Natronobacterium gregoryi Argonaute. *Advanced Science*: 1700540
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