PROTOCOL

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ACCEL-NGS® ADAPTASE™ MODULE

for Single-Cell Methyl-Seq Library Preparation

Protocol for Cat. No. 33096

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Table of Contents

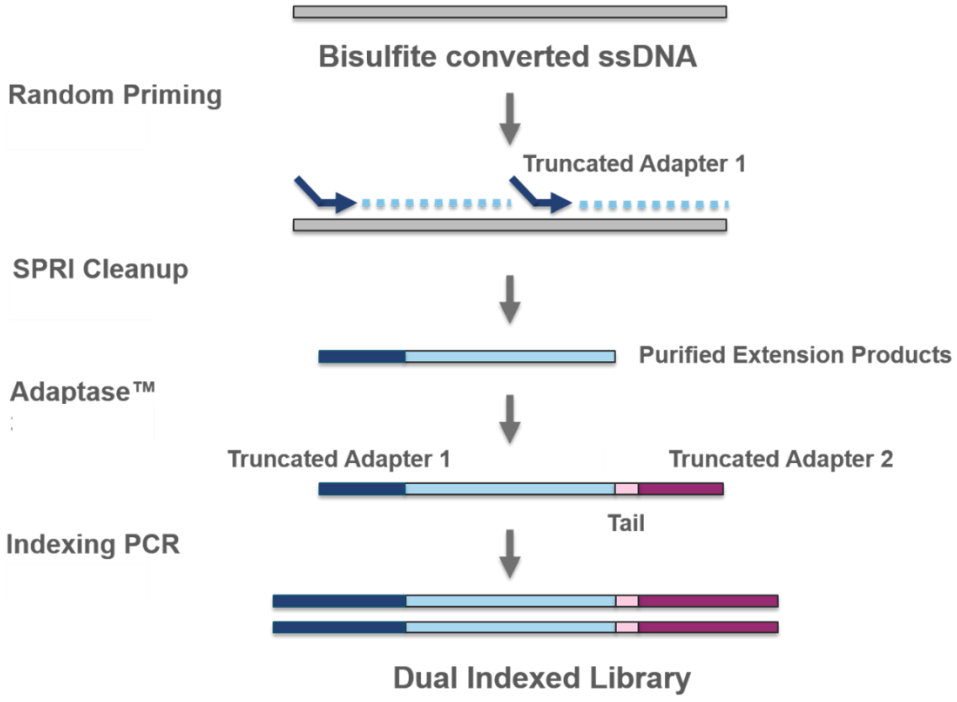
About This Guide

The Accel-NGS Adaptase Module can be used in conjunction with the Single-Cell Methyl-Seq Library Preparation Protocol included in the Appendix section of this manual. Further description of this protocol and its use with single nucleus methylcytosine sequencing (snmC-seq) can be found in the publication by Luo, et. al. "Single Cell Methylomes Identify Neuronal Subtypes and Regulatory Elements in Mammalian Cortex" *Science*, 2017. When performing the full single cell workflow, please use the instructions provided in the Appendix section of this protocol as it is the most up to date version for best performance.

For further information, please contact us at TechSupport@swiftbiosci.com.

The Adaptase Module adds a truncated P7 adapter sequence to the 3' end of single-stranded DNA (ssDNA) products resulting from random primed synthesis using bisulfite-converted DNA from single cells as substrate. Since the random primer incorporates a truncated P5 adapter to 5' ends, the subsequent Adaptase step completes truncated adapter attachment and is followed directly by PCR amplification with indexed primers to complete library construction.

Accel-NGS Adaptase Module Workflow for Single-Cell Methyl-Seq



- Following lysis and bisulfite conversion of single cells, random priming of bisulfite-converted DNA incorporates a truncated P5 adapter (Truncated Adapter 1) to 5' ends of synthesized fragments, and also effectively reduces fragment size to ~400 b for suitability with Illumina® sequencing. Optionally, indexed random primers can be used for downstream multiplexing capability.
- An enzymatic step using Exonuclease I and Shrimp Alkaline Phosphatase is then performed to digest unused random primer and inactivate dNTPS, followed by a SPRI™ bead-based purification step.
- Next, the highly efficient Adaptase step simultaneously tails and ligates the truncated P7 adapter (Truncated Adapter 2) to the 3' end of single-stranded products, which completes library construction.
- Library amplification is then performed using custom primers that incorporate dual indexing to enable 96-plex sequencing.

Kit Contents

The Accel-NGS Adaptase Module contains enough reagents to prepare 96 reactions of single cell Methyl-Seq libraries (10% excess volume provided). Please be sure to read this protocol carefully before starting.

Reagents	Quantity (µl) 96 rxn	Storage (°C)
• Buffer G1	211	-20
• Reagent G2	211	-20
• Reagent G3	132	-20
• Enzyme G4	52	-20
• Enzyme G5	52	-20

Adaptase Controls	Quantity (µl) 96 rxn	Storage (°C)
1 (20 b)	15	-20
2 (50 b)	15	-20
3 (70 b)	15	-20

Reagents	Quantity (mL)	Storage (°C)
Low EDTA TE	20	Room Temp

Material and Equipment Not Included

General Materials

- Magnetic beads for clean-up steps, e.g., SPRIselect™ beads (Beckman Coulter, Cat. No. B23317/B23318/B23319)
- Magnetic rack for clean-up steps, e.g., Invitrogen DynaMag™ or Agencourt® SPRIPlate™, or similar magnetic rack compatible with 96-well plate magnetic bead clean-ups
- Centrifuge with 96-well plate compatibility
- Thermocycler with ramping temperature program capability
- Vortex
- Aerosol-resistant tips and P2 through P1000 range pipettes
- 200-proof/absolute ethanol (molecular biology-grade)
- Nuclease-free water (molecular biology-grade)
- Qubit® or other method for determining library concentration

Materials for Single-Cell

- FACS or other method for isolation and distribution of single cells
- EZ-96 DNA Methylation-Direct™ Kit [Zymo Research Cat. No. D5023 (Deep-Well Format)]
- MicroAmp® EnduraPlate™ Optical 96-well Clear GPLE Reaction Plate with Barcode (Thermo Fisher Cat. No. 4483348)
- MicroAmp Clear Adhesive Film (Thermo Fisher Cat. No. 4306311)
- Random Primer(s) with a P5 adapter 5’ tail sequence (see details in Appendix)
- Klenow Exo-DNA Polymerase (high concentration 50U/µl) supplied with Blue Buffer; Enzymatics Cat. No. P7010-HC-L)
- dNTPs
- Exonuclease I (20U/µl), (Enzymatics Cat. No. X8010F)
- Shrimp Alkaline Phosphatase (New England BioLabs Cat. No. M0371)

- Custom P5 Indexing PCR Primers (see details in Appendix)
- Custom P7 Indexing PCR Primers (see details in Appendix)
- KAPA HiFi HotStart ReadyMix (Kapa Cat. No. KK2602 / Roche Cat. No. 07958935001)
- Electrophoresis apparatus for agarose gels
- Qiagen® QIAquick® Gel Extraction Kit (Cat. No. 28704)

Notes on Starting Input Material

- Refer to the Single Cell Methyl-Seq Protocol in the Appendix section for instructions for use prior to and after performing the Adaptase step.
- When isolating and distributing single cells, use techniques that preserve cell integrity to maximize sample quality into the cell lysis and bisulfite conversion steps.
- Although bisulfite-converted DNA is single-stranded, perform the Denaturation Step prior to Adaptase due to secondary structure that may be present in the ssDNA.

Begin Your Accel-NGS Adaptase Module Protocol

For best results, please follow these suggestions:

- To maximize efficient use of enzyme reagents, remove enzyme tubes from -20 °C storage and place on ice, NOT in a cryocooler, for at least 10 minutes to allow reagents to reach 4 °C prior to pipetting. **Attempting to pipette enzymes at -20 °C may result in a shortage of enzyme reagents.**
- After thawing reagents, invert or briefly vortex (except enzymes) to mix them well. Briefly centrifuge to collect tube contents.
- Assemble a reagent master mix for the **Adaptase** step and scale volumes as appropriate, using 5% excess volume to compensate for pipetting loss.
- Always add enzymes last to master mixes, immediately before adding to samples.
- Before unsealing the MicroAmp seals on 96-well plates, briefly spin the plate to collect contents to prevent sample loss from adherence to the seal or cross-contamination. Use care to slowly remove the seal.
- Before starting, prepare a fresh 80% ethanol solution (0.8 mL molecular biology-grade 200-proof/absolute ethanol + 0.2 mL nuclease-free water per sample). Approximately 1 mL will be used per sample; formula is for proper volumetric addition and excess.
- Pre-program a thermocycler with the following programs to expedite the workflow:

Denaturation Thermocycler Program
95 °C hold incubate 3 min
Then immediately place samples on ice for 2 min

Adaptase Thermocycler Program
37 °C for 30 min.
95 °C for 2 min. for enzyme inactivation
4 °C hold

Denaturation

1. Use the **Denaturation Thermocycler Program** on the thermocycler and pause it at the first step to pre-heat to 95 °C until all samples are ready to be loaded.
2. Following elution from the post-random priming SPRI clean-up step, there will be a 10 µl eluate in each 0.2 ml PCR plate well.
3. Seal the plate and place in the thermocycler and run the Denaturation program. Place on ice **immediately** for 2 minutes. Proceed immediately to the **Adaptase** step.

Adaptase

1. Use the **Adaptase Thermocycler Program** on the thermocycler and pause it at the first step to pre-heat to 37 °C until all samples are mixed and loaded.
2. On ice, make the **Adaptase Reaction Mix** with the following amounts of each reagent in the specified order. Briefly spin the plate, unseal, add 10.5 µl mix to each well of the 96-well plate containing denatured sample. Total volume for each well will be 20.5 µl. Seal the plate.

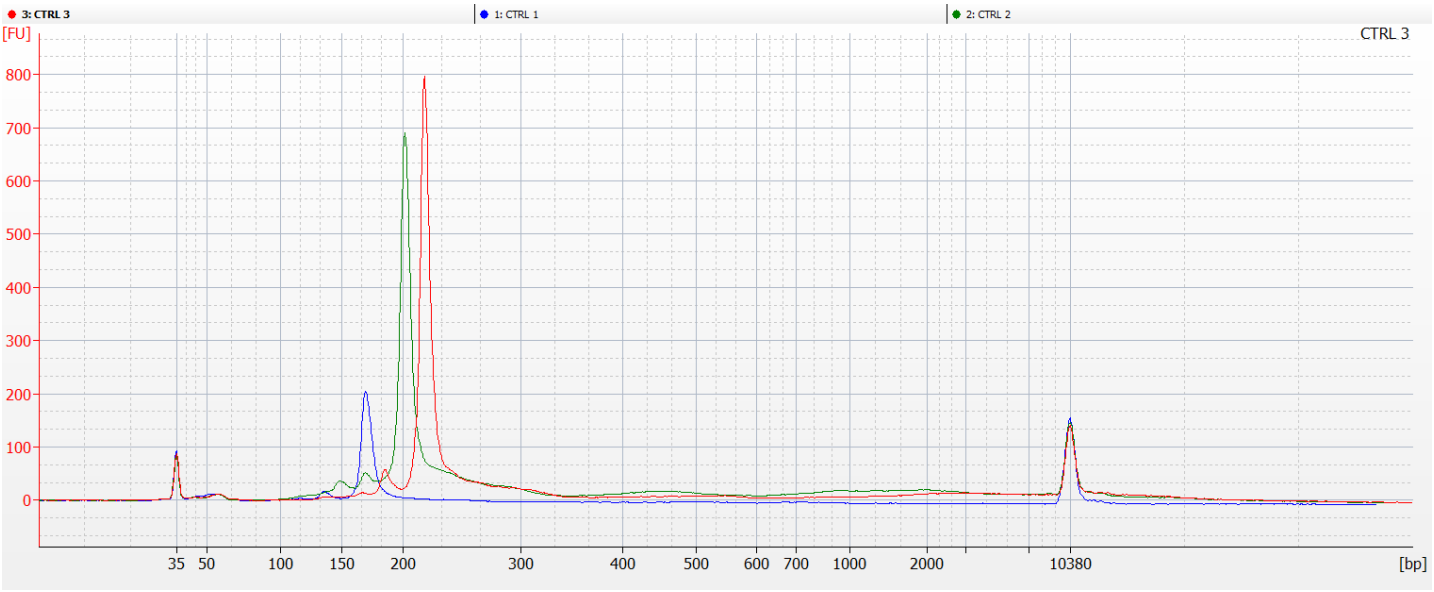
Assembly Order	ReagentS	Volume per Sample (µl)
Pre-assemble	Low EDTA TE	4.25
	• Buffer G1	2.0
	• Reagent G2	2.0
	• Reagent G3	1.25
Add just before use	• Enzyme G4	0.5
	• Enzyme G5	0.5

3. Mix the reactions well by gently vortexing the plate, then quickly spin the plate to collect contents. Place plate in the thermocycler and run the program.
4. Proceed with the library amplification step (see Appendix).

Expected Results

Included with the kit are three Adaptase control substrates to validate performance of the reagents provided with the Adaptase Module. Each control is a ssDNA substrate that has a 5' truncated Illumina P5 adapter sequence and a 3' sequence that is 20 b (control 1), 50 b (control 2), or 70 b (control 3) in length.

The Adaptase controls are each at 3 µM concentration. For the experiment illustrated below, 1 µl of each control substrate was added to individual Adaptase reactions with 9 µl Low EDTA TE (do not combine substrates as they will concatamerize). The protocol was followed for Denaturation, Adaptase, and 6 cycles of PCR amplification using PCR conditions recommended in the Appendix Single Cell Protocol. A post-PCR bead clean-up using 40 µl beads (0.8X ratio) was eluted in 20 µl Low EDTA TE. Products were run on a High Sensitivity Bioanalyzer Chip, loading 1 µl per well. Peaks were visible at ~170 bp, 200 bp and 220 bp. Either a single or all three substrates can be used to validate Adaptase Module performance. The 20 b substrate produces a lower yield due to size selection constraint during the 0.8X SPRI clean-up.



Appendix

Section A: SPRIselect Clean-Up Protocol

Please use the following protocol for each SPRI clean-up step, substituting the correct **Sample Volume**, **SPRI Volume,** and **Elution Volume** as indicated for each clean-up step:

1. Invert or briefly vortex beads to homogenize the suspension before use.
2. Add the specified **SPRI bead volume** to each sample. Mix by pipetting up and down with a P200 tip until homogenous. Ensure no bead-sample suspension droplets are left on the sides of the wells of the plate.
3. Incubate the samples for 5 minutes at room temperature.
4. Place the sample plate on a 96-well side bar magnetic rack until the solution clears and a pellet is formed (about 2 minutes).
5. Remove and discard the supernatant without disturbing the pellet.
6. Add 180 µl of freshly prepared ethanol solution to the pellet while it is still on the magnet. Use care not to disturb the pellet. Incubate for 30 seconds, and then carefully remove the ethanol solution.
7. Repeat step 6 once for a second wash with the ethanol solution (and if using the 4-plex pooling method, perform a third ethanol wash).
8. Pulse-spin the sample plate in a centrifuge, and then place back onto the magnet and remove any residual ethanol solution from the bottom of each well.
9. Air-dry the pellet, watching the pellet to avoid cracking or over-drying.
10. Add the specified volume of Low EDTA TE to resuspend the pellet, mixing well by pipetting up and down until homogenous. If droplets of the resuspension are on the side of the tube, pulse-spin the plate to collect contents. After at least 2 minutes, place the tube on the magnet. Transfer the entire eluate of each well to a new PCR plate. Ensure that eluate does not contain magnetic beads (indicated by brown coloration in eluate).

Section B: Single Cell Methyl-Seq Library Prep Protocol with Adaptase Module

IMPORTANT!
Use barrier, low-bind tips for all steps with direct contacts to DNA. Use unfiltered tips for all ethanol washes.

1. Prior to library preparation, prepare Zymo lysis buffer containing proteinase K following the Zymo EZ96 direct kit manual. Preload 2 µl to each well of the 96-well plate that will be used for cell sorting. After sorting, heat the plate at 50 ºC for 20 min, following standard manual instructions. Elute the bisulfite converted DNA from the Zymo I-96 spin-plate with 12 µl EB, which will result in a 9 µl eluate for each single cell (3 µl dead volume).
2. To set up the Random Priming Step, briefly spin the plate, unseal, add P5L random primer to each well of the 96-well plate containing the single cell samples and seal the plate.

Reagent	Volume (µl)	Final Concentration
P5L random primer (5 µM)	1	250 nM

For downstream 4-Plex multiplexing, use random primers that incorporate AD002, AD006, AD008 and AD010. Alternatively, if not multiplexing, add a P5L non-indexed random primer.

3. Prepare the Random Priming Mastermix and keep on ice:

Reagent	Volume (µl)	Final Concentration
Blue Buffer (10×)	2	1x
Klenow exo- (50 U/µl)	1	50 U
dNTP (10 mM each)	1	0.5 mM each
H_2O	6	
Total Volume	**10**	

4. Denature the samples containing random primer in the 96-well plate using a thermocycler at 95 °C for 3 minutes. Immediately chill the plate on ice for 2 minutes.
5. Briefly spin the plate, unseal, add 10 µl of the Random Priming Mastermix to each well of the 96-well plate. Seal the plate. Mix the reactions well by gently vortexing the plate, then quickly spin the plate to collect contents.
6. Use a thermocycler to run the Random Priming Program

4 °C	5 min
0.1 °C/s to 25 °C	
25 °C	5 min
0.1 °C/s to 37 °C	
37 °C	60 min
4 °C	∞

7. Briefly spin the plate, unseal, add Exonuclease 1 and Shrimp Alkaline Phosphatase to each well of the 96-well plate. Seal the plate. Mix the reactions well by gently vortexing the plate, then quickly spin the plate to collect contents.

Reagent	Volume (µl)	Units
Exonuclease 1 (20 U/µl)	2	40 U
Shrimp Alkaline Phosphatase	1	1 U

8. Use a thermocycler to run the Enzymatic Digestion Program.

37 °C	30 min
4 °C	∞

9. Briefly spin the plate, unseal, add 0.8x SPRI beads – 18.4 µl to each well of the 96-well plate. Seal the plate. Mix the reactions well by gently vortexing the plate, then quickly spin the plate to collect contents.

IMPORTANT!
Avoid spinning the plate other than a pulse spin to collect contents. Centrifugation will cause beads to attach to the bottom of wells and make it more difficult to completely aspirate the solution/beads mix from wells.

10. If multiplexing using indexed random priming, combine the solution/beads mixture from four plates into one of the plates. Wash the beads with 200 µl 80% ethanol for three times, elute in 10 µl EB. If not multiplexing, wash beads with 200 µl 80% ethanol for two times and elute in 10 µl EB.
11. Prepare the Adaptase Mastermix and keep on ice.

Reagent	Volume (µl)
EB	4.25
Buffer G1	2.0
Reagent G2	2.0
Reagent G3	1.25
Enzyme G4	0.5
Enzyme G5	0.5

12. Seal the plate and denature the samples in the 96-well plate using a thermocycler Denaturation Program at 95 °C for 3 minutes. Immediately chill the tube on ice for 2 minutes.
13. Briefly spin the plate, unseal, add 10.5 µl of the Adaptase Mastermix into each well of the 96-well plate. Seal the plate. Mix the reactions well by gently vortexing the plate, then quickly spin the plate to collect contents.

14. Use a thermocycler Adaptase Program.

37 °C	30 min
95 °C	2 min

15. Briefly spin the plate, unseal, add PCR mixture below. Seal the plate. Mix the reactions well by gently vortexing the plate, then quickly spin the plate to collect contents.

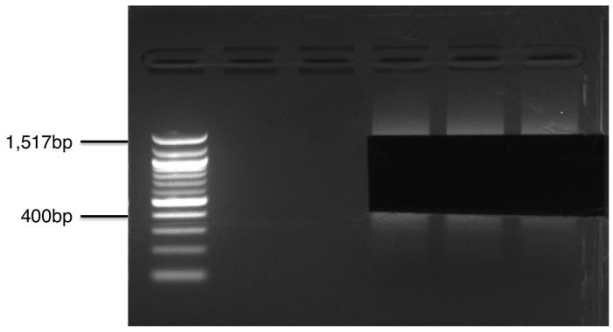
Reagent	Volume (µl)	Final Concentration
Custom P5L index primer (100 µM)	0.3	600 nM
Custom P7L index primer (10 µM)	5.0	1 µM
KAPA HiFi HotStart ReadyMix	25.0	1x

16. Use a thermocycler Indexing PCR Program.

95 °C	2 min
98 °C	30 sec
98 °C	15 sec
64 °C	30 sec
72 °C	2 min
Go to step 3 for 16 times (repeat steps 3-5 for total of 17 cycles*)	
72 °C	5 min
4 °C	∞

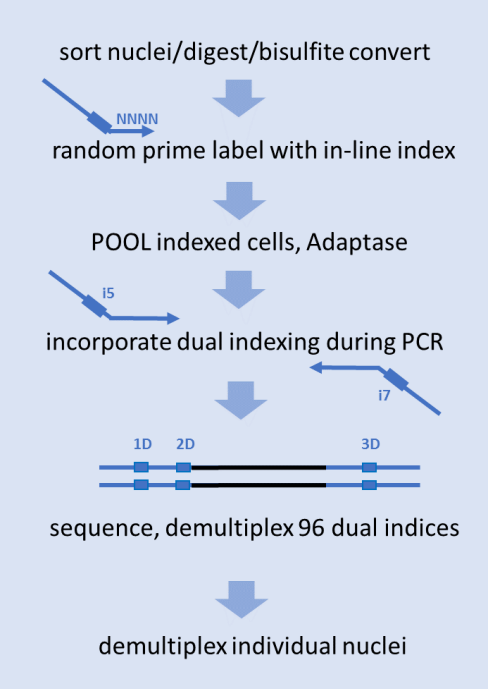
* If multiplexing using indexed random priming (4 cell library), a total of 17 cycles should be performed. If not multiplexing (single cell library), a total of 19 cycles should be performed.

17. Briefly spin the plate, unseal, purify the amplified libraries with two rounds of 0.8x SPRI beads — 40.6 µl for the first round with the 50.8 µl sample. The elution from the first round can be any volume between 10-50 µl of Low EDTA TE. For the second round, use a corresponding 0.8x SPRI bead volume. For each round of SPRI purification, wash with 80% ethanol twice.
18. Combine the libraries into a pool and load onto a 2% agarose gel for size selection to further remove adapter dimers. Cut between 400 bp and 1.5 kb and purify the library using Qiagen QIAquick Gel Extraction Kit. Next, the library concentration in the eluate can be quantified for pooling and loading either by fluorometric reading or qPCR.



Section C: Oligonucleotide Sequences

Please order the following oligonucleotides from Integrated DNA Technologies (idtdna.com), making sure to specify 'hand-mixing' option for the random primers to ensure the highest quality synthesis regarding N base composition. If performing cell multiplexing during the Adaptase and PCR steps, libraries will contain three dimensional indices: a random priming in-line index, and standard Illumina TruSeq HT i5 and i7 indices (see figure below). If not multiplexing cells at 4-plex, remove the 6 base in-line index sequence just 5' to the N sequence and order a single random primer only. Random primers should be HPLC purified.



P5L Indexed Random Primers

P5L_AD002	/5SpC3/TTCCCTACACGACGCTCTTCCGATCTCGATGT(N1:25252525)(N1)(N1) (N1)(N1)(N1) (N1)(N1)(N1)
P5L_AD006	/5SpC3/TTCCCTACACGACGCTCTTCCGATCTGCCAAT(N1:25252525)(N1)(N1) (N1)(N1)(N1) (N1)(N1)(N1)
P5L_AD008	/5SpC3/TTCCCTACACGACGCTCTTCCGATCTACTTGA(N1:25252525)(N1)(N1) (N1)(N1)(N1) (N1)(N1)(N1)
P5L_AD010	/5SpC3/TTCCCTACACGACGCTCTTCCGATCTTAGCTT(N1:25252525)(N1)(N1) (N1)(N1)(N1) (N1)(N1)(N1)

Library Amplification Primers

The P5L and P7L primers are a custom length to accommodate the shorter adapter tails on the random primers. Do not use standard P5 and P7 indexing primers supplied with Swift Indexing Kits. The indexing primers can be ordered as desalted. The indexes that are incorporated by these primers are present in the [i5] and [i7] positions and are used for multiplexed sequencing. If also using the in-line indexes, each library will then need to be further demultiplexed into 4 cell-specific libraries. No custom indexing file is necessary when sequencing these libraries. The indices used are the standard Illumina TruSeq HT indices.

P5L_D501	AATGATACGGCGACCACCGAGATCTACACTATAGCCTACACTCTTTCCCTACACGACGCTCT
P5L_D502	AATGATACGGCGACCACCGAGATCTACACATAGAGGCACACTCTTTCCCTACACGACGCTCT
P5L_D503	AATGATACGGCGACCACCGAGATCTACACCCTATCCTACACTCTTTCCCTACACGACGCTCT
P5L_D504	AATGATACGGCGACCACCGAGATCTACACGGCTCTGAACACTCTTTCCCTACACGACGCTCT
P5L_D505	AATGATACGGCGACCACCGAGATCTACACAGGCGAAGACACTCTTTCCCTACACGACGCTCT
P5L_D506	AATGATACGGCGACCACCGAGATCTACACTAATCTTAACACTCTTTCCCTACACGACGCTCT

P5L_D507	AATGATACGGCGACCACCGAGATCTACACCAGGACGTACACTCTTTCCCTACACGACGCTCT
P5L_D508	AATGATACGGCGACCACCGAGATCTACACGTACTGACACACTCTTTCCCTACACGACGCTCT

P7L_D701	CAAGCAGAAGACGGCATACGAGATCGAGTAATGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D702	CAAGCAGAAGACGGCATACGAGATTCTCCGGAGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D703	CAAGCAGAAGACGGCATACGAGATAATGAGCGGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D704	CAAGCAGAAGACGGCATACGAGATGGAATCTCGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D705	CAAGCAGAAGACGGCATACGAGATTTCTGAATGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D706	CAAGCAGAAGACGGCATACGAGATACGAATTCGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D707	CAAGCAGAAGACGGCATACGAGATAGCTTCAGGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D708	CAAGCAGAAGACGGCATACGAGATGCGCATTAGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D709	CAAGCAGAAGACGGCATACGAGATCATAGCCGGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D710	CAAGCAGAAGACGGCATACGAGATTTCGCGGAGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D711	CAAGCAGAAGACGGCATACGAGATGCGCGAGAGTGACTGGAGTTCAGACGTGTGCTCTT
P7L_D712	CAAGCAGAAGACGGCATACGAGATCTATCGCTGTGACTGGAGTTCAGACGTGTGCTCTT

Section D: Data Analysis and Informatics Considerations

The Accel-NGS Adaptase Module adds a low complexity synthetic tail with an average length of 10 bases to the 3' end of each fragment during the addition of the adapter molecule. The random priming step also introduces 9N bases at the beginning of Read 1 and additionally a 6 base in-line index if performing multiplexed cell processing. Since both the beginning of read 1 and read 2 introduce synthetic sequences that may contain artificial Cytosine residues, it is important to trim the synthetic sequences prior to data analysls. Also, some aligners will produce a compromised mapping rate if synthetic sequence is present. Therefore, please trim 10 bases from the beginning of Read 1 and Read 2 if performing single cell processing, and trim 16 bases from the beginning of Read 1 and Read 2 if performing multiplexed cell processing using the 6 base in-line indexing.

Further description of data analysis with single nucleus methylcytosine sequencing (snmC-seq) can be found in the publication by Luo, et. al. "Single Cell Methylomes Identify Neuronal Subtypes and Regulatory Elements in Mammalian Cortex" *Science*, 2017.

Additionally, if using the 4 in-line indices for cell multiplexing during the workflow, be aware that the sequence complexity at the start of Read 1 will be compromised and may impact data quality. Therefore, a high complexity spike-in such as PhiX may be recommended depending on the Illumina sequencing platform utilized.

If you experience problems with your library prep, please contact us at TechSupport@swiftbiosci.com.

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