**Protocols of CH-seq**

For CH-RNA-seq, frozen cells of each tissue need to thawed at 37℃ and centrifuged at 500g for 5min first. Then fresh fixed or thawed frozen cells were resuspended with 100ul inPBS, 400ul TritonX-100 in inPBS (10ul 10% TritonX-100 in 390ul inPBS) was added. The mixture was incubated on ice for 3min for permeabilization. Next, cells were pelleted and resuspended with 500ul DEPC treated Water, 3ml 0.1N HCl was added slowly. After incubating for 5min on ice, 3.5ml TritonX-100 in Tris-HCl (35ul 10% TritonX-100 in 3.5ml 1M Tris-HCl pH8.0) was added to quench the permeabilization. Cell were then washed once with 1ml inPBS and filtered with 40μm strainer. Cell density was determined using a blood cell counting chamber. For reverse transcription, cell numbers for each tissue were estimated and corresponding volume of cells in inPBS was split into four 96-well plates. For each well, 6.5ul cells (from 5000 to 20000) were mixed with 0.5ul 10mM dNTP (Thermo Fisher Scientific) and 0.5ul 100μM RT barcode primer (see in Table S1), the mixture was incubated at 65℃ for 5min and immediately placed on ice. 2ul 5X RT buffer (31mM Tris-HCl pH8.0,37.5mM NaCl,3.1mM MgCl2,10mM DTT), 0.5ul Maxima H Minus RTase (Thermo Fisher Scientific) and 0.1ul Murine RNase inhibitor were premixed, and 2.5ul RT mixture was added to each well. Reverse transcription was carried out by incubating the plates at gradient temperature:3 cycle (8℃ for 12s, 15℃ for 45s, 20℃ for 45s, 30℃ for 30s, 42℃ for 2 min, and 55℃ for 3 min) and 55℃ for 60min.After reverse transcription, plates were placed on ice for 1min to stop reaction. All the reagents were pooled together into a 15ml centrifuge tube and then centrifuged at 500g for 5min. Pellet was washed with inPBS twice and resuspended with hybridization buffer (50mM Tris-HCl,10mM MgCl2,10mM DTT,0.1% TrinX-100,10% PEG8000 (Sigma-ALDRICH),1% Murine RNase inhibitor). Hybridization buffer within cells were split into eight 96-well plates (3ul for each well) and 2ul 25μM pre-annealing hybridization primers (50μM HY head oligo,50μM barcoded HY primer oligo, mixed equally and incubated at 95℃ for 2min, then slowly cooled to 25℃ with a temperature ramp of −0.1℃ /s) were added to each well. Plates were incubated at 37℃ for 90 min and 0.5ul 100μM block tail primer oligo was added to block any redundant hybridization primers. After blocking for 30min at 37℃, all reagents were pooled into a 15ml centrifuge tube and then centrifuged at 500g for 5min. Pellet was washed with inPBS twice and resuspended with 40ul inPBS. Then 60ul PNK mix (10ul 10X PNK buffer (NEB), 20ul T4 Polynucleotide Kinase (NEB), 10ul 10mM ATP(NEB), 20ul DEPC treated water) was added. The PNK reaction was carried out at 37℃ for 30min. Then 1ml ice-cold inPBS was added to stop the reaction. Cells were then filtered using a 40μm strainer. The reagent was centrifuged at 500g for 5min, after discarding the supernatants. The pellet was again resuspended with inPBS, and the density of cells was estimated. After splitting into one or more 96-well plates. There were 5000~8000 cells per well. The volume was adjusted to 8ul. Second strand synthesis mix (1.33ul 10X buffer, 0.66ul second strand synthesis enzyme mix) was added into each well and the plates were incubated at 16℃ for 3 hours (stop point at 4℃). Then,10ul cell lysis buffer (20 mM Tris pH 8.0, 400 mM NaCl, 100 mM EDTA, 4.4% SDS (Sangon Biotech)) and 2ul proteinase K (Sangon Biotech) were added to the wells. Cell lysis was performed at 55℃ for 60min. Then 1ul PMSF (1mM) was added to quench the lysis reaction. The plates were incubated at 37℃ for 10min.For each well, the mixture was then purified using 1.5X VAHTS DNA Clean Beads (Vazyme Biotech). Then 10ul product in DEPC treated water was transferred into new 96-well plates. For each plate, we randomly chose 10 wells to quantified the dsDNA concentration using Equalbit3.0. TruePrep DNA Library Prep Kit V2 (Vazyme Biotech) was used for libraries construction. The libraries were finally mixed and the concentration of dsDNA was quantified.

For CH-ATAC-seq, 96-384 uniquely indexed Tn5 transposase were assembled prior to tagmentation. For each well, the Tn5 primers (25pM Tn5 primer A oligo, 50pM Tn5 ME oligo, as well as 25pM the barcoded Tn5 primer B oligo, see in Table S1) were mixed, then the plate was incubated at 95℃ for 2min and slowly cooled to 10℃ with a temperature ramp of −0.1℃/s. Tn5 transposase (Vazyme Biotech) was diluted and mixed with annealed Tn5 primers, and the mixture was then incubated at 30℃ for 60min,which leads to a final indexed Tn5concentration of 40ng/ul. Frozen nuclei in freezing buffer were thawed at 37℃ and centrifuged at 500g for 5min. Thawed frozen nuclei or fresh fixed nuclei were resuspended with 1ml RSBT and filtered with a 40um cell strainer to remove any clumps during [cryopreservi](https://dict.youdao.com/w/cryopreserved/#keyfrom=E2Ctranslation)ng. Nuclei was centrifuged at 500g for 5min and resuspended in tagmentation buffer (10mM Tris-HCl pH7.5, 5mM MgCl2, 10% DMF (Sigma-ALDRICH), 1%BSA, 0.1% Tween-20, 0.01% digitonin and 0.4X PBS). For each tissue, nuclei density was determined using a blood cell counting chamber. Nuclei were then split into 96-well plates. For each well, 23.5ul nuclei (10000-15000 nuclei) was mixed with 1.5ul indexed Tn5. Then the tagmentation was carried out at 55℃ for 30min, and 25ul 2X stop buffer (40mM EDTA,1mM Spermidine) was separately added into 96 wells. The plate was incubated at 37℃ for 15min to completely stop tagmentation. All the reagent was pooled together into a 15ml centrifuge tube and then centrifuged at 500g for 5min. The pellet was washed twice with RSBT before split into new 96-well plates. The hybridization, blocking and PNK reaction were carried out as described in CH-RNA-seq. After PNK reaction, 1ml ice-cold RSBT was added in pooled reagent were then filtered using a 40μm cell strainer. The medium was centrifuged at 500g for 5min. After discarding the supernatants, the pellet was again resuspended with RSBT. The density of nuclei was estimated and nuclei were split into new 96-well plates (5000-8000 nuclei per well). The volume of each well was adjusted to 8ul. Then 2ul gap-fill mix (1ul 10X Ampligase DNA ligase buffer, 0.3ul Ampligase DNA ligase (Lucigen), 0.5ul 10mM dNTP, 0.2ul T4 DNA polymerse (NEB)) was then added into each well. The plates were incubated at 37℃ for 60 min. Then 2ul nuclei lysis buffer (1ul 10mM Tris-HCl pH8.0,0.5ul proteinase K,0.5ul 1%SDS) was added to release the fragments in nuclei by incubating at 55℃ for 60 min. For each well, the mixture was then purified using 1.5X VAHTS DNA Clean Beads. Then 10ul product in DEPC treated water was then transferred into a new 96-well plate. For each well, 14ul PCR mix (12ul 2X KAPA HiFi HotStart ReadyMix (Kapa Biosystems), 1ul 10mM P5 primer,1ul 10mM indexed P7 primer) were added to the plates. The PCR program was as follows: 72°C for 5 min;98°C for 3 min; 12 cycles of 98°C 10 s, 65°C 15 s, and 72°C 1 min;72°C 5 min and 4°C hold. After pooling PCR products, 1.0X VAHTS DNA Clean Beads were used to purify the DNA library, the concentration of dsDNA was quantified.

**MGI library preparation and sequencing**

The purified linear DNA library was circularized into single strand DNA (ssDNA) library using VAHTS® Circularization Kit for MGI (Vazyme). Then ssDNA library was amplified using DNBSEQ DNB preparation kit (MGI). Amplified DNA nanoball (DNB) was sequenced with custom primers (Table S1) on MGI DNBSQ-T7 with dark reaction model (CH-RNA-seq: 51 cycles of read1 with dark reaction from 11-33,100 cycles of read2; CH-ATAC-seq: 100 cycles of read1 with dark reaction from 11-33,44-62, 100 cycles of read2).