Issue I 2019

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Enzymatic Methyl-seq: The Next Generation of Methylome Analysis

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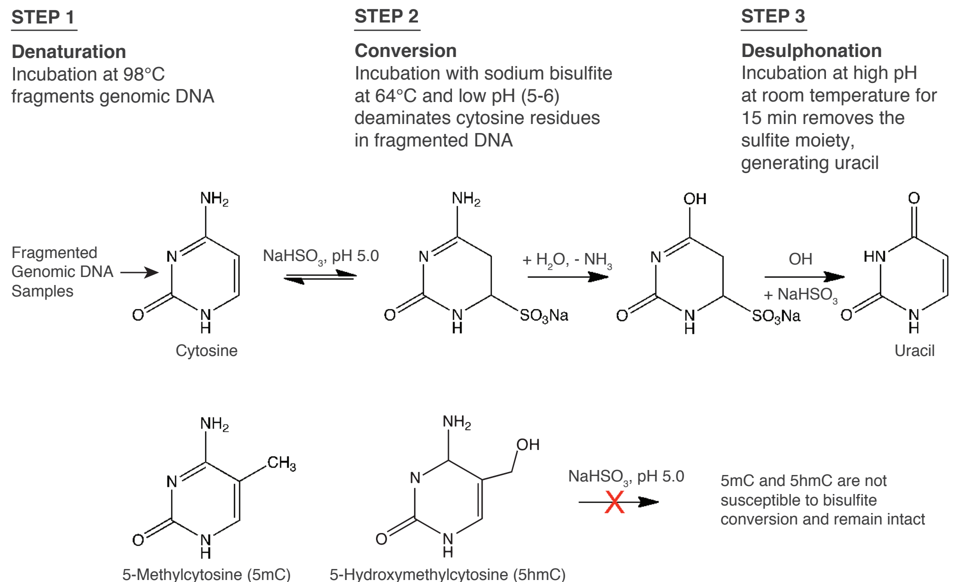
The identification of cytosine modifications within genomes, especially 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC), is important as they are known to have an impact on gene expression. Generally, low levels of methylation near transcription start sites are associated with higher transcription levels, while genes with regulatory regions containing high levels of cytosine modification are expressed at lower levels. The ability to analyze a complete methylome is important for studying diseases, including those associated with cancer, metabolic disorders and autoimmune diseases. Unfortunately, the current technologies for investigating 5mC and 5hmC are sub-optimal and do not permit a thorough evaluation of methylomes.

BISULFITE SEQUENCING

To date, the gold standard in methylome mapping has been bisulfite sequencing. In this method, DNA is chemically treated with sodium bisulfite, which results in the conversion of unmethylated cytosines to uracils, and the resulting uracils are ultimately sequenced as thymines (Figure 1). In contrast, the modified cytosines, 5mC and 5hmC, are resistant to bisulfite conversion, and are sequenced as cytosines (1). While the preparation of bisulfite libraries is relatively straightforward, the libraries have uneven genome coverage and therefore suffer from incomplete representation of cytosine methylation across genomes. This uneven coverage is the result of DNA damage and fragmentation, which is caused by the extreme temperatures and pH during bisulfite conversion. Sequenced bisulfite libraries typically have skewed GC bias plots, with a general under-representation of G- and C-containing dinucleotides and over-representation of AA-, AT- and TA-containing dinucleotides, as compared to a non-converted genome (2). Therefore, the damaged libraries do not adequately cover the genome, and can include many gaps with little or no coverage. Increasing the sequencing depth of these libraries can recover some missing information, but at steep sequencing costs. These bisulfite library limitations have driven the development of new approaches for studying methylomes.

FIGURE 1:
Bisulfite conversion overview

Sodium bisulfite treatment of DNA converts cytosine to 5,6-dihydrocytosine-6-sulphonate, which is converted to 5,6-dihydrouracil-6-sulphonate, and then desulphonated to uracil. In contrast 5mC and 5hmC are not susceptible to bisulfite treatment and remain intact.



ALTERNATIVE METHODS FOR DETECTING 5mC AND 5hmC

Additional approaches for investigating methylomes are available that either combine bisulfite conversion with another chemical modification or an enzymatic modification step, or that eliminate bisulfite conversion completely (Table 1).

5hmC can be detected using TET-assisted bisulfite sequencing (TAB-seq). Fragmented DNA is enzymatically modified using sequential T4 Phage ß-glucosyltransferase (T4-BGT) and then Ten-eleven translocation (TET) dioxygenase treatments before the addition of sodium

TABLE 1:
Summary of alternative methods of methylome analysis

SEQUENCING METHOD	CYTOSINE MODIFICATION	METHOD OF ANALYSIS	WEAKNESS
TET-assisted bisulfite sequencing (TAB-seq) (3)	5hmC	Enzymatic treatment with T4-BGT then TET followed by bisulfite treatment	DNA damage and sequencing bias
Oxidative bisulfite sequencing (oxBS) (4)	5mC	Treatment with an oxidation reagent, followed by bisulfite treatment	DNA damage and sequencing bias
APOBEC-coupled epigenetic sequencing (ACE-seq) (5)	5hmC	Enzymatic treatment with T4-BGT and APOBEC3A	APOBEC3A not commercially available
TET-assisted 5-methylcytosine sequencing (TAmC-seq) (6)	5mC	Enzymatic treatment, followed by enrichment for 5mC regions	Enriches for 5mC dense regions. Does not currently cover entire genome.

bisulfite (3). T4-BGT glucosylates 5hmC to form beta-glucosyl-5-hydroxymethylcytosine (5ghmC) and TET is then used to oxidize 5mC to 5caC (Figure 2). Only 5ghmC is protected from subsequent deamination by sodium bisulfite and this enables 5hmC to be distinguished from 5mC by sequencing.

Oxidative bisulfite sequencing (oxBS) provides another method to distinguish between 5mC and 5hmC (4). The oxidation reagent potassium perruthenate converts 5hmC to 5-formylcytosine (5fC) and subsequent sodium bisulfite treatment deaminates 5fC to uracil. 5mC remains unchanged and can therefore be identified using this method.

APOBEC-coupled epigenetic sequencing (ACE-seq) excludes bisulfite conversion altogether and relies on enzymatic conversion to detect 5hmC (5). With this method, T4-BGT glucosylates 5hmC to 5ghmC and protects it from deamination by Apolipoprotein B mRNA editing enzyme subunit 3A (APOBEC3A). Cytosine and 5mC are deaminated by APOBEC3A and sequenced as thymine.

Lastly, TET-assisted 5-methylcytosine sequencing (TAmC-seq) enriches for 5mC loci and utilizes two sequential enzymatic reactions followed by an affinity pull-down (6). Fragmented DNA is treated with T4-BGT which protects 5hmC by glucosylation. The enzyme mTET1 is then used to oxidize 5mC to 5hmC, and T4-BGT labels the newly formed 5hmC using a modified glucose moiety (6-N3-glucose). Click chemistry is used to introduce a biotin tag which enables enrichment of 5mC-containing DNA fragments for detection and genome wide profiling.

Libraries made from methods that combine enzymatic and sodium bisulfite identification of cytosine modifications all experience DNA damage and the inherent biases of bisulfite treatment. Furthermore, the described enzymatic methods have additional drawbacks. TAmC-seq is focused on loci and does not discriminate between methylated and unmethylated cytosines in the enriched DNA fragments. ACE-seq probes only 5hmC and requires APOBEC3A for deamination, which is not yet commercially available, making it more difficult to standardize library construction between labs.

ENZYMATIC METHYL-SEQ – A NEW APPROACH

The enzymatic methyl-seq workflow developed at NEB provides a much-needed alternative to bisulfite sequencing. This method relies on the ability of APOBEC to deaminate cytosines to uracils. Unfortunately, APOBEC also deaminates 5mC and 5hmC, making it impossible to differentiate between cytosine and its modified forms (7,8). In order to detect 5mC and 5hmC, this method also utilizes TET2 and an Oxidation Enhancer, which enzymatically modifies 5mC and 5hmC to forms that are not substrates for APOBEC. The TET2 enzyme converts 5mC to 5caC (Figure 2) and the Oxidation Enhancer converts 5hmC to 5ghmC (9,10,11). Ultimately, cytosines are sequenced as thymines and 5mC and 5hmC are sequenced as cytosines, thereby protecting the integrity of the original 5mC and 5hmC sequence information.

The NEBNext Enzymatic Methyl-seq Kit (EM-seq™) combines NEBNext® Ultra™ II reagents with these two enzymatic steps to construct Illumina® libraries that accurately represent 5mC and 5hmC within the genome. Converted libraries are amplified using NEBNext Q5U DNA polymerase (Figure 3). EM-seq libraries result in a more accurate representation of the methylome, with minimal DNA fragmentation or biases when compared to whole genome bisulfite sequencing (WGBS). The combination of the Ultra II reagents for library prep and the EM-seq conversion allows for lower input amounts compared to most WGBS workflows, with a range of inputs from 10 – 200 ng (for more details on

continued on page 4...

FIGURE 2: Enzymatic modification of cytosine

TET enzymes oxidize 5mC to 5hmC then 5fC and finally 5caC.

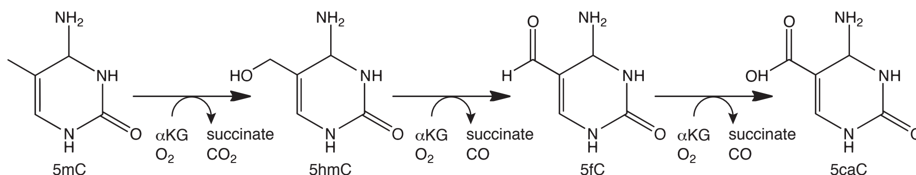
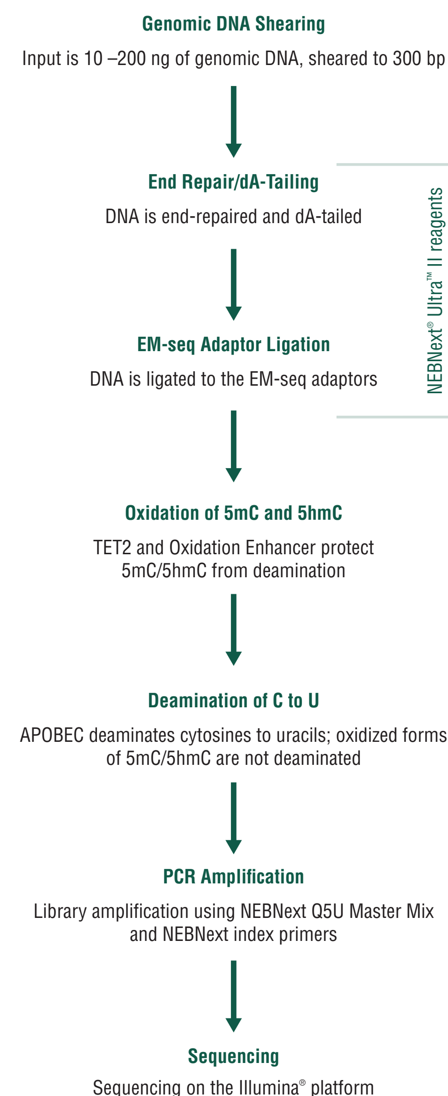


FIGURE 3: NEBNext EM-seq Kit Workflow

EM-seq utilizes two enzymatic steps to differentiate between modified and unmodified cytosines.



NEBNext EM-seq, see page 6).

EM-SEQ PERFORMANCE

Intact DNA

Several pieces of data suggest that the process of generating EM-seq libraries does not damage DNA in the same way as bisulfite sequencing. EM-seq libraries give higher PCR yields despite using fewer PCR cycles for all DNA input amounts (see page 6), indicating that less DNA is lost during enzymatic treatment and library preparation, as compared to WGBS. Reduced PCR cycles, in turn, translates into more complex libraries and fewer PCR duplicates during sequencing (data not shown). EM-seq libraries also have larger insert sizes than WGBS (Figure 4), which further supports the fact that DNA remains intact.

EM-seq Libraries Have Reduced Bias

The preservation of DNA integrity is also demonstrated by the GC bias graphs (Figure 5), and the dinucleotide coverage distribution graph (Figure 6). Both of these figures indicate that reduced bias is associated with the EM-seq libraries. The EM-seq libraries have a flat GC bias distribution (Figure 5) with even coverage at both GC and AT rich regions, and do not display a preference for any dinucleotide combination (Figure 6). This is in stark contrast to WGBS, which shows a skewed GC bias profile along with the previously mentioned dinucleotide biases. Reduced library bias improves the mapping and therefore coverage of CpGs.

CpG Detection

Human DNA is methylated almost exclusively in CpG contexts. EM-seq global CpG methylation levels for human NA12878 DNA are consistent with WGBS libraries (Figure 7A), indicating that EM-seq libraries accurately detect methylation. The more striking difference between EM-seq and WGBS libraries becomes apparent when the focus is shifted to CpG coverage. EM-seq libraries detect more CpGs to a higher depth of coverage than WGBS libraries (Figure 7B). The ability to detect more CpGs at a greater depth also increases confidence in the data and leads to more accurately defining methylation within a region of interest. This in turn aids in detecting methylation changes in diseased states such as cancer. In addition, increased CpG coverage has an economic impact – with more CpGs detected using the same number of reads compared to WGBS, EM-seq represents significant cost-savings.

Potential Applications

In addition to making Illumina libraries, there are other potential applications for the EM-seq technology. Many of these applications already exist, but can now be improved upon because of the intact nature of enzymatically-converted DNA and the accuracy of CpG detection. Lower input DNA is also a driving factor for some of these applications. Converted DNA can be detected on arrays, and can be used for target enrichment, reduced representation-type libraries or amplicon detection. Different types of DNA inputs, such as

FIGURE 4:
NEBNext Enzymatic Methyl-seq (EM-seq) libraries have larger inserts

EM-seq library insert sizes are larger than whole genome bisulfite sequencing (WGBS) libraries. Library insert sizes were determined using Picard 2.18.14. The larger insert size indicates that EM-seq does not damage DNA as bisulfite treatment does.

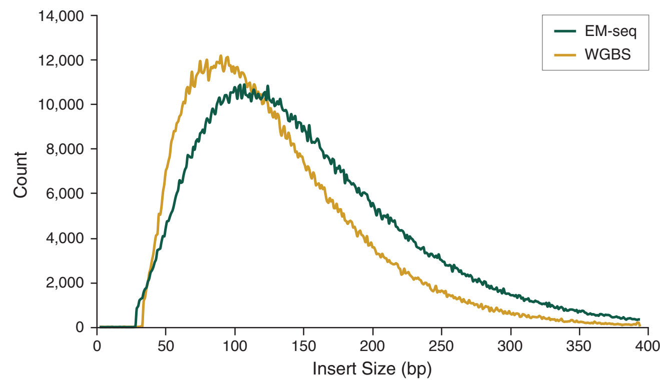


FIGURE 5:
EM-seq has superior uniformity of GC coverage

GC coverage was analyzed using Picard 2.18.14 and the distribution of normalized coverage across different GC contents of the genome (0-100%) was plotted. EM-seq libraries have significantly more uniform GC coverage, and lack the AT over-representation and GC under-representation typical of WGBS libraries.

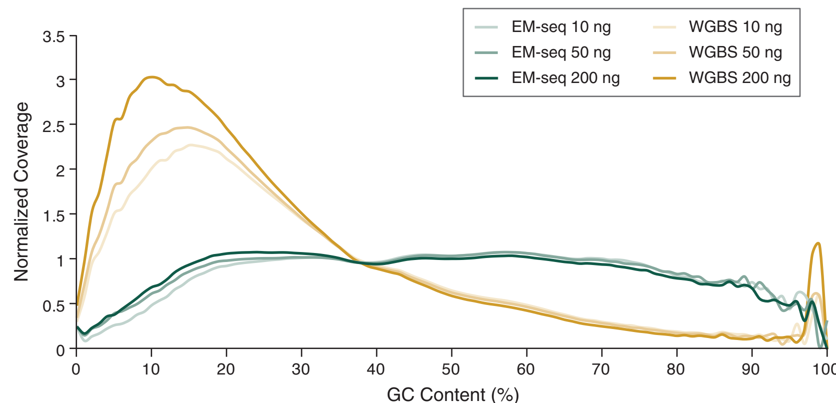
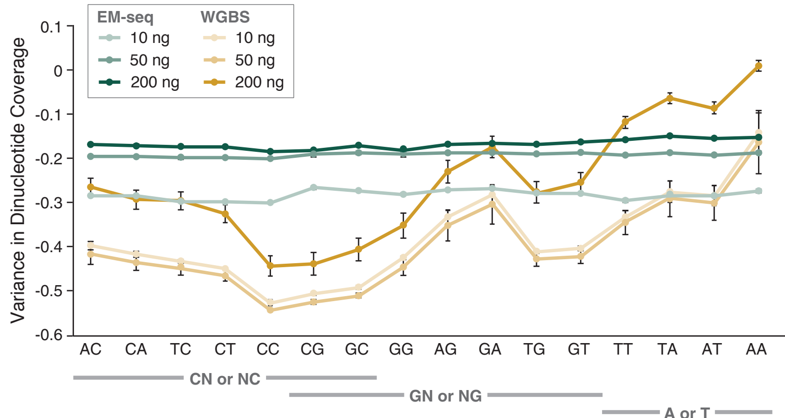


FIGURE 6:
Dinucleotide coverage distribution

Dinucleotide coverage distribution for EM-seq and WGBS libraries showing the variance in coverage for dinucleotides in the reads when compared to unconverted Ultra II library dinucleotide distribution. EM-seq libraries show even coverage across all dinucleotide combinations compared to WGBS. C-containing dinucleotides are underrepresented in WGBS libraries and A/T containing dinucleotides are overrepresented.



low input cell free DNA (cfDNA) or damaged FFPE DNA, can also be used.

CONCLUSION

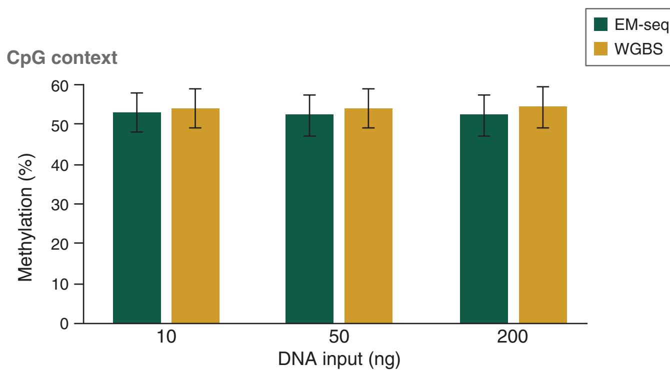
Bisulfite sequencing, while commonly used, is sub-optimal in detecting 5mC and 5hmC – large amounts of DNA are needed, DNA can be damaged, and sequences are biased towards AT-rich regions. Other methods that couple chemical or enzymatic treatment with bisulfite sequencing also share similar limitations. EM-seq provides the first commercially-available, non-bisulfite method that comprehensively addresses the limitations of bisulfite sequencing and represents a new opportunity for more complete methylome analysis. EM-seq libraries are not damaged and have longer inserts, higher PCR yields with fewer PCR cycles, and lack biases associated with GC content. More CpGs are identified with greater coverage depth using EM-seq, as compared to WGBS. These advantages all contribute to EM-seq having more usable sequencing data when comparing the same number of reads for EM-seq and WGBS, which ultimately reduces sequencing costs. EM-seq is the only commercially-available alternative to bisulfite sequencing that provides an effective method for accurate and comprehensive detection of 5mC and 5hmC across the genome, and offers a new, more accurate alternative for studying disease states.

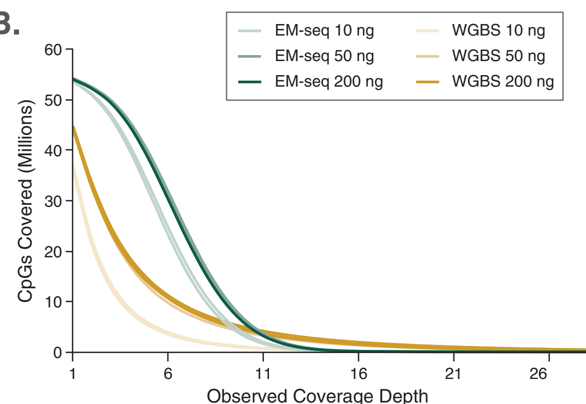
FIGURE 7:
EM-seq identifies detect more CpGs to a higher depth of coverage than WGBS

10, 50 and 200 ng Human NA12878 genomic DNA was sheared to 300 bp using the Covaris S2 instrument and used as input into EM-seq and WGBS protocols. For WGBS, NEBNext Ultra II DNA was used for library construction, followed by the Zymo Research EZ DNA Methylation-Gold Kit for bisulfite conversion. Libraries were sequenced on an Illumina NovaSeq® 6000 (2 x 100 bases). 324 million paired end reads were aligned to hg38 using bwa-meth 0.2.2.

A: Methyl Dackel was used to determine methylation levels, which were found to be similar between EM-seq and WGBS.

B: Coverage of CpGs with EM-seq and WGBS libraries was analyzed, and each top and bottom strand CpGs were counted independently, yielding a maximum of 56 million possible CpG sites. EM-seq identifies more CpGs at lower depth of sequencing.





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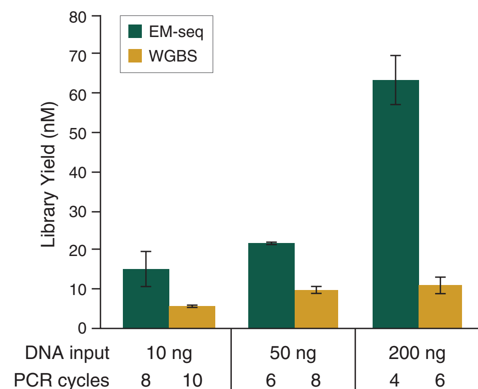
Heads up!

There's a new alternative to bisulfite sequencing – Introducing NEBNext® Enzymatic Methyl-seq (EM-seq™)

While whole genome bisulfite sequencing (WGBS) has been the gold standard for methylome analysis, it also damages DNA, resulting in fragmentation, loss and bias. In contrast, EM-seq enzymatic conversion minimizes damage to DNA and, in combination with the supplied NEBNext Ultra™ II Illumina® library preparation reagents, produces high quality libraries that enable superior detection of 5mC and 5hmC from fewer sequencing reads.

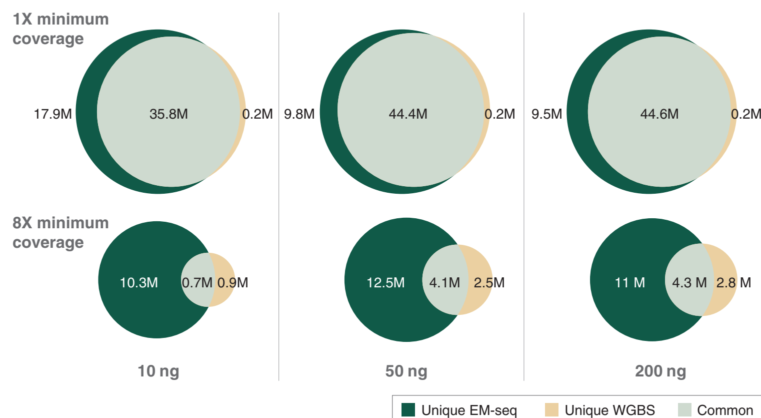
EM-seq produces higher yields than WGBS using fewer PCR cycles

10, 50 and 200 ng Human NA12878 genomic DNA was sheared to 300 bp using the Covaris® S2 instrument and used as input into EM-seq and WGBS protocols. For WGBS, NEBNext Ultra II DNA was used for library construction, followed by the Zymo Research EZ DNA Methylation-Gold™ Kit for bisulfite conversion. For all input amounts, EM-seq library yields were higher, and fewer PCR cycles were required, suggesting greater DNA loss in the WGBS protocol. Error bars indicate standard deviation.



EM-seq identifies more CpGs than WGBS, at lower sequencing coverage depth

Coverage of CpGs with EM-seq and WGBS libraries was analyzed using 324 million paired end reads. The number of unique and common CpGs identified by EM-seq and WGBS at 1x and 8x minimum coverage for each input amount are shown. EM-seq covers at least 20% more CpGs than WGBS at 1x minimum coverage threshold. The difference in CpG coverage increases to two-fold at 8x minimum coverage threshold.



Advantages

- Superior sensitivity of detection of 5mC and 5hmC
- Achieve greater mapping efficiency
- Generate more uniform GC coverage
- Detect more CpGs with fewer sequence reads
- Experience uniform dinucleotide distribution
- Obtain larger library insert sizes
- Take advantage of high-efficiency library preparation with NEBNext Ultra II reagents
- Conversion module also available separately

Visit **www.NEBNext.com** to learn more and request a sample.

ORDERING INFORMATION

PRODUCT	NEB #	SIZE
NEBNext Enzymatic Methyl-seq Kit	E7120S/L	24/96 rxns
NEBNext Enzymatic Methyl-seq Conversion Module	E7125S/L	24/96 rxns
NEBNext Q5U™ Master Mix	M0597S/L	50/250 rxns
NEBNext Multiplex Oligos for Enzymatic Methyl-seq (Unique Dual Index Primer Pairs)	E7140S/L	24/96 rxns

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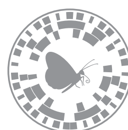

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Monarch® Genomic DNA Purification Kit

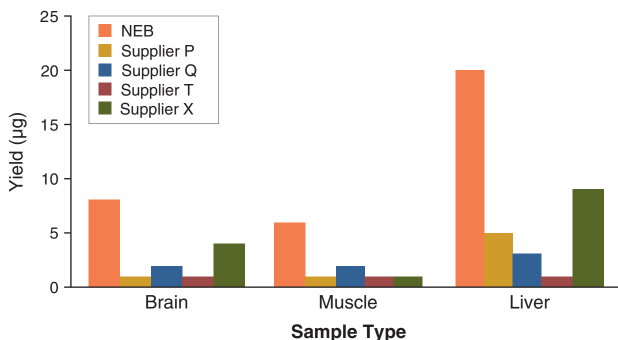
The Monarch Genomic DNA Purification Kit is a comprehensive solution for cell lysis, RNA removal, and purification of intact genomic DNA (gDNA) from a wide variety of biological samples, including cultured cells, blood and mammalian tissues. Additionally, bacteria and yeast can be processed with extra steps to enhance lysis in these tough-to-lyse samples. Protocols are also included to enable purification from clinically-relevant samples, such as saliva and cheek swabs, as well as rapid cleanup of previously extracted gDNA. Purified gDNA has high quality metrics, minimal residual RNA, and is suitable for downstream applications, such as endpoint PCR, qPCR and library prep for next generation sequencing (NGS).

Advantages

- Use with a wide variety of sample types
- Generate higher yields, especially with tough samples (e.g., brain and muscle)
- Isolate longer DNA (peak size > 50 kb), which is ideal for long-read sequencing platforms
- Effectively remove RNA (< 1% residual RNA)
- Includes RNase A
- Save time with fast protocols, efficient lysis steps and minimal hands on time

The Monarch Genomic DNA Purification Kit provides excellent yields for difficult tissue types

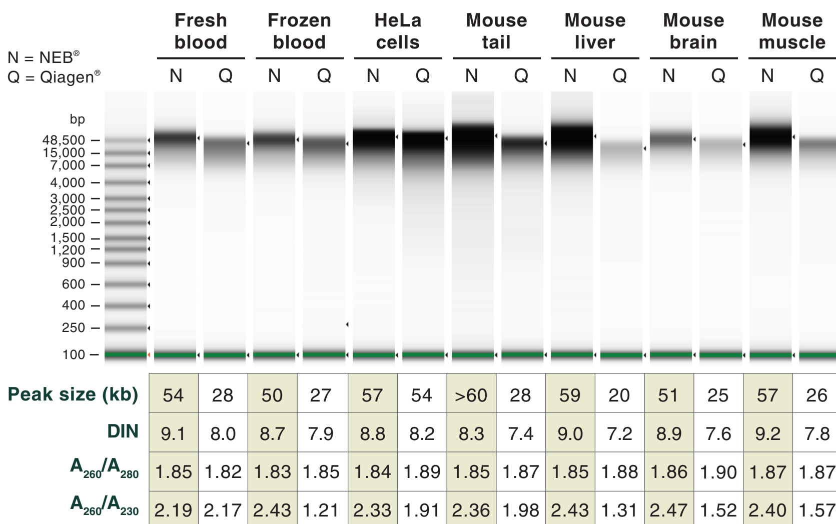
Duplicate 10 mg samples of RNAlater®-stabilized rat tissue were cut to small pieces and subsequently lysed and purified according to the protocols provided for each kit. Optional RNase A steps were included. Elution was carried out with 100 µl elution buffer provided in the respective kits. Yields displayed are averages of the duplicate samples, and represent the genomic DNA yield after correcting for the RNA content as determined by LC-MS. Results indicate that the Monarch Genomic DNA Purification Kit provides excellent yields for a wide range of tissues, which can be problematic for other commercial kits.



Migrate to Monarch

The Monarch Genomic DNA Purification Kit provides excellent yields of higher quality, higher molecular weight DNA than the Qiagen® DNeasy® Blood & Tissue Kit

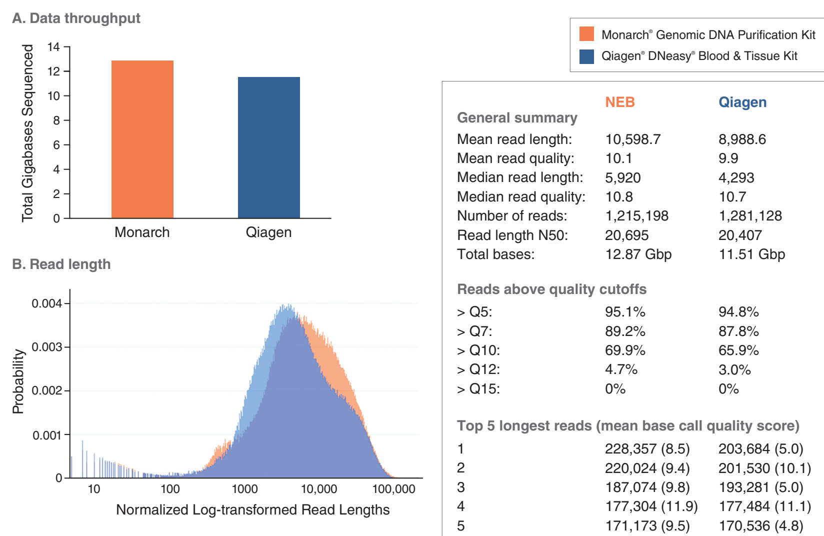
Agilent Technologies® 4200 TapeStation® Genomic DNA ScreenTape was used for analysis of blood, cultured cell, and tissue samples purified using the relevant protocols of the Monarch Genomic DNA Purification Kit and the Qiagen DNeasy Blood & Tissue Kit. gDNA was eluted in 100 µl and 1/100 of the eluates (~1 µl) was loaded on a Genomic DNA ScreenTape. Starting materials used: 100 µl fresh human whole blood, 100 µl frozen pig blood, 1x10⁶ HeLa cells and 10 mg frozen tissue powder. Monarch-purified gDNA samples typically show peak sizes 50 – 70 kb and DINs of ~9. DNeasy-purified gDNA peak sizes are typically <30 kb with DINs ~7-8. DNeasy kits produce lower yields and low A260/230 ratios for liver, brain, muscle and frozen blood.



	Fresh blood N	Fresh blood Q	Frozen blood N	Frozen blood Q	HeLa cells N	HeLa cells Q	Mouse tail N	Mouse tail Q	Mouse liver N	Mouse liver Q	Mouse brain N	Mouse brain Q	Mouse muscle N	Mouse muscle Q
Peak size (kb)	54	28	50	27	57	54	>60	28	59	20	51	25	57	26
DIN	9.1	8.0	8.7	7.9	8.8	8.2	8.3	7.4	9.0	7.2	8.9	7.6	9.2	7.8
A_{260}/A_{280}	1.85	1.82	1.83	1.85	1.84	1.89	1.85	1.87	1.85	1.88	1.86	1.90	1.87	1.87
A_{260}/A_{230}	2.19	2.17	2.43	1.21	2.33	1.91	2.36	1.98	2.43	1.31	2.47	1.52	2.40	1.57

The Monarch Genomic DNA Purification Kit generates high quality DNA for nanopore sequencing

HeLa cell genomic DNA was extracted using either the Monarch Genomic DNA Purification Kit or the Qiagen DNeasy Blood & Tissue Kit. One microgram of purified DNA was used to prepare Oxford Nanopore Technology (ONT) sequencing libraries following the ONT 1D Ligation Sequencing Kit (SQK-LSK109) protocol without DNA fragmentation. Libraries were loaded on a GridION (Flow cell R9.4.1) and the data was collected for 48 hrs. Libraries produced using the Monarch gDNA exceeded the Qiagen libraries on common sequencing metrics including: A. total sequencing data collected, B. read length. Data was generated using NanoComp (Bioinformatics, Volume 34, Issue 15, 1 August 2018, Pages 2666–2669).



General summary	NEB	Qiagen
Mean read length:	10,598.7	8,988.6
Mean read quality:	10.1	9.9
Median read length:	5,920	4,293
Median read quality:	10.8	10.7
Number of reads:	1,215,198	1,281,128
Read length N50:	20,695	20,407
Total bases:	12.87 Gbp	11.51 Gbp
Reads above quality cutoffs		
> Q5:	95.1%	94.8%
> Q7:	89.2%	87.8%
> Q10:	69.9%	65.9%
> Q12:	4.7%	3.0%
> Q15:	0%	0%
Top 5 longest reads (mean base call quality score)		
1	228,357 (8.5)	203,684 (5.0)
2	220,024 (9.4)	201,530 (10.1)
3	187,074 (9.8)	193,281 (5.0)
4	177,304 (11.9)	177,484 (11.1)
5	171,173 (9.5)	170,536 (4.8)

ORDERING INFORMATION

PRODUCT	NEB #	SIZE
Monarch Genomic DNA Purification Kit	T3010S/L	50/150 preps
COLUMNS AVAILABLE SEPARATELY		
Monarch gDNA Purification Columns	T3017L	100 columns and 200 tubes
Monarch Collection Tubes II	T2018L	100 tubes
BUFFERS AND REAGENTS AVAILABLE SEPARATELY		
Monarch gDNA Tissue Lysis Buffer	T3011L	34 ml
Monarch gDNA Cell Lysis Buffer	T3012L	20 ml
Monarch gDNA Blood Lysis Buffer	T3013L	20 ml
Monarch gDNA Binding Buffer	T3014L	65 ml
Monarch gDNA Wash Buffer	T3015L	60 ml
Monarch gDNA Elution Buffer	T3016L	34 ml
Monarch RNase A	T3018L	1 ml
Proteinase K, Molecular Biology	P8107S	2 ml

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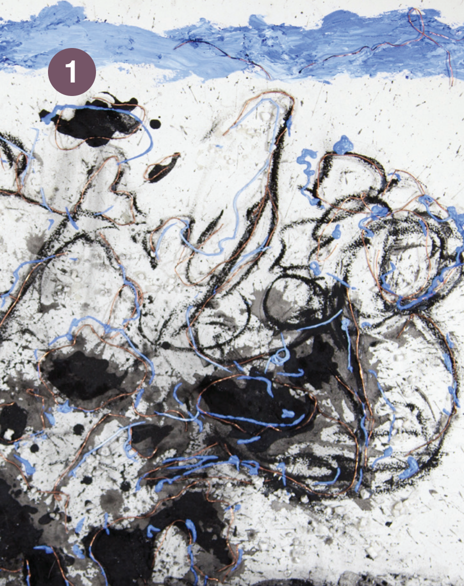

1. CoCuCaC – elements of the periodic table that begin with C were used to sketch a figurine
2. Fe-F – iron, fluoride and magnets are used to capture magnetic fields
3. Gunpowder Revolver – the artistic properties of gunpowder elements

ArCHEMY at the interface between art and science

Dan Jay,
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Dan Jay is a Professor of Developmental, Molecular and Chemical Biology and the Dean of the Sackler Graduate School of Biomedical Sciences at Tufts University School of Medicine. He is also an Adjunct Professor of Drawing and Painting at the School of Museum of Fine Arts. Dan has worked in both artistic and scientific fields for 30 years and seeks to inspire young minds where art and science meet. His career was markedly influenced by how light interacts with dyes and pigments, and he invented Chromophore-Assisted Light Inactivation of protein function, a technology that uses light targeted by dyes to generate loss of function in living cells to address their roles in cellular processes.

There has not always been a gap between art and science. In the last century, growth of knowledge made specialization necessary and even desirable to focus and conform to one's field to the detriment of acquiring knowledge of other disciplines. As fields differentiated, there came to be a lack of a common language and disdain for amateurism. As a result, the fields of art and science became overly specialized and do not speak to the vast majority of society.

However, there is rich ore to be mined at the interface between fields, and while art and science have differences that challenge their interaction, there are also commonalities. Both fields require creativity, are highly experimental and aim to reveal truth and understanding. We think of scientists as highly logical and rigorous, presenting to the public in research articles that emphasize the progression from a current gap in knowledge to a testable hypothesis that is supported or refuted by controlled experiments. But actually, science also occurs by creative flights of fancy and fortuitous accidents that are then rigorously tested and codified into a research paper as if everything had happened by a logical progression. In contrast, art is presented as the product of creative strokes of genius appearing magically and mysteriously from some sacred muse. In reality, much of an artist's work is experimentation and troubleshooting, with a logical progression of decisions leading to the finished artwork. So, artists and scientists have more in common than public perception would suggest and moreover, perhaps have something to contribute to each other's work.

Today, there is a growing interest in cross-disciplinary work, and a desire for reunification of knowledge or at least an appreciation that disciplines can inform each other in novel ways. The emergence of STEAM (Science, Technology Engineering, Art and Math) education is an indication that this idea has traction.

There is a long history of science influencing art such as metallurgy, whereby the smelting of bronze or gold was employed for use in sculpture, or in the 19th century when the chemical synthesis of new pigments contributed a bright new palette emblematic of the impressionist school.

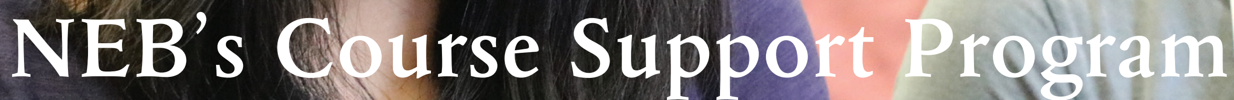
It is also true that art informs science; for example, MIT has faculty experts in Origami, the Japanese art of paper folding, in part because it tells us about topology and folding in constrained systems such as protein folding. Additionally, the neuroanatomical drawings of Ramon y Cajal led to mechanistic hypotheses regarding different subsets of neurons to visualize circuitry.

ArCHEMY (www.archemy.com) is the idea of alchemy with art, or using chemicals and chemical reactions to make new marks on paper. For example, combining liquid nitrogen with art media freezes the media in a way that encapsulates it with the liquid nitrogen, which become explosive pellets when rapidly warmed to room temperature.

In a tribute to the periodic table, elements that begin with the same letter were used to create art. For example, CoCuCaC (Figure 1) is a piece where liquid nitrogen was combined with charcoal powder, water and glue, to build a splattered base, upon which a sketch of a figurine was made using charcoal powder, cobalt blue paint, copper wire and white chalk (calcium carbonate). Another example is the use of Fe and F (Figure 2) – iron and fluoride as rusted steel wool and fluorinated toothpaste, whereby iron filings and rust are used to capture the fields of magnets that were placed under the work.

The Gunpowder (Figure 3) series uses the components of gunpowder as an allegory for gun violence and social injustice. Gunpowder consists of carbon, sulfur and potassium nitrate, which separately are black, yellow and white pigments – when mixed they are explosive, when separated they can be used to create art. Workshops with school children provide an opportunity for them to use these media to express their concerns about these timely issues.

This generation is poised to take advantage of the benefits proffered by the internet and the growing interest in STEAM initiatives. The increasing dissatisfaction for traditional barriers between fields may resonate with the young and help them to find their voice in the richness between fields. What new beauty might flow? What insight might come when art informs science, or vice versa? What extraordinary work might flow from this?



NEB's Course Support Program

Penny Devoe is an Associate Director in the Marketing Department at NEB. In this article, Penny shares insight on NEB's efforts to support educational outreach through our course support program.

Q: What is NEB's philosophy on supporting science education in the life sciences?

A: NEB has a strong commitment to support education of the life sciences. We are dedicated to inspiring young scientists and improving the quality of science education for students by providing reagents, educational materials and employee knowledge and time. In fact, many of our employees are involved in educational outreach and will present at local schools or volunteer to participate in local science fairs.

Q: What support does NEB offer to teaching labs?

In addition to the educational content available on neb.com, NEB offers a list of our most popular products for free to support teaching labs in the US. In fact, we donate many NEB products to high schools, colleges and teaching programs throughout the country.

Q: How long has NEB been offering free reagents to teaching labs?

NEB has been providing free reagents to institutions for over 30 years. Advancing science has always been a priority at NEB, and what better way to achieve this than supporting schools who are training our young scientists. We support hundreds of schools every year through this program.

Q: Can you share some examples of groups that have taken advantage of this program?

NEB provides reagents for the Molecular Biology Summer Workshop that we host at Smith College every summer. This is a two-week course where non-scientists can gain a wide array of molecular biology experience. We have also supported the Gloucester Marine Genomics Institute, and BioTeach, a life sciences education program offered through the Massachusetts Biotechnology Education. Other programs include iGEM - Internationally Genetically Engineered Machines competition, BioBuilder, HHMI, and the Amgen® Biotech Experience – a science education program to help teachers bring biotech to the classroom.

Q: How can an educator apply for course support?

Anyone who is interested can visit our Course Support and Reagent Donation page (www.neb.com/reagentdonation) to learn more. There, you can submit an inquiry for information, and we will quickly get back to you with more details. It is important that all the information needed is provided – we have detailed instructions available on our website for a successful submission.

Q: Can an educator from outside of the US participate?

An international educator can contact their local subsidiary or distributor, which again, can be accessed from the Course Support page.

Q: What else does NEB do to promote life science education?

In addition to course support throughout the world, NEB employees also volunteer their time to offer Science Days for both local teachers and students. Please visit our webpage **www.neb.com/promoting-science-education** for additional information on other programs and initiatives that NEB is involved with in promoting the life sciences.

Learn more about NEB's course support program in our latest NEB TV episode.

Visit **www.neb.com/NEBTV**

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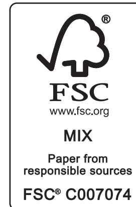

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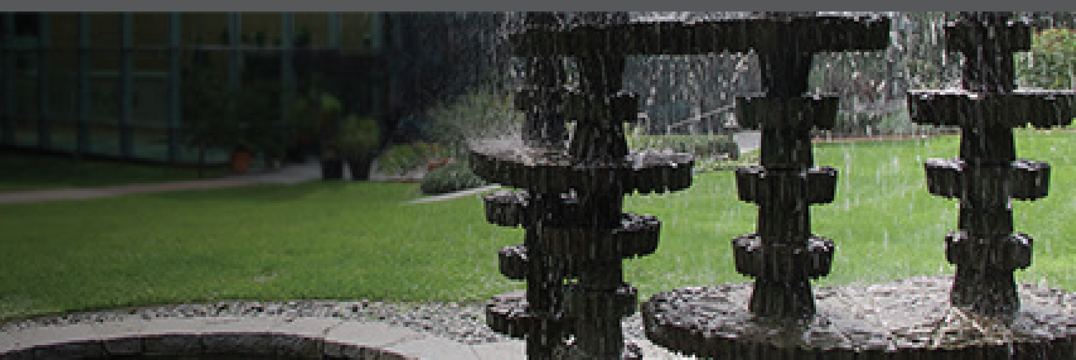

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