Summer 2007, vol. 2.2

NEB expressions

a scientific update from New England Biolabs

Welcome to the summer edition of NEB Expressions. This issue highlights our growing line of DNA ladders and markers. It also addresses DNA methylation and its impact on restriction enzyme digests. The feature article highlights important research to overcome filarial diseases, a significant problem for many third world countries. Research on these infectious diseases has been a focus of NEB's parasitology group for over 20 years.

As always, we invite your feedback on our products, services and corporate philosophy.

inside:

NEW ENGLAND BioLabs® Inc.
the leader in enzyme technology

Combating Neglected Diseases

a genomic approach to identify potential drug targets

Sanjay Kumar, Jeremy Foster, Yinhua Zhang, Kshitiz Chaudhary, Jacopo Novelli, Barton Slatko and Clotilde Carlow, Division of Parasitology, New England Biolabs, Inc.

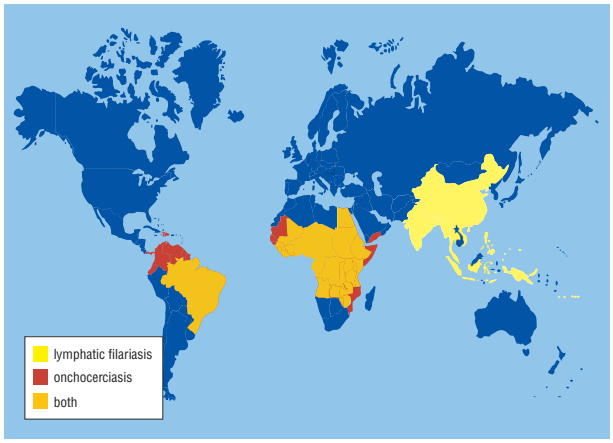


Figure 1: *Global distribution of lymphatic filariasis and onchocerciasis. (Adapted from WHO, http://who.int/tdr/)*

Lymphatic filariasis and onchocerciasis are tropical diseases caused by filarial parasites that are transmitted to humans by insects. Collectively, they afflict around 150 million people in over 80 countries (Figure 1) with more than 1.5 billion at risk of infection (1). In lymphatic filariasis, filarial nematodes such as *Wuchereria bancrofti* and *Brugia malayi* (Figure 2), take up residence in the lymphatic system where the thread-like adult worms live and reproduce for almost a decade, spawning millions of immature worms into the blood. The cycle continues when a female anopheline or culicine mosquito ingests the blood containing the worms. Clogged lymphatic ducts lead to severe swelling of limbs and genitalia, as well as damage to kidneys and the lymphatic system itself. In the later stages of infection, the disease is characterized by a disfiguring condition known as elephantiasis resulting in physical disability, severe social stigma and psychological distress (Figure 3). The World Health Organization estimates that lymphatic filariasis ranks third among the infectious diseases in terms of disability, after malaria and tuberculosis. A closely related filarial nematode, *Onchocerca volvulus*, the causative agent of onchocerciasis or River Blindness, is responsible for the second leading cause (after trachoma) of infectious blindness worldwide. *O. volvulus* adult worms are also long-lived, and are found in subcutaneous tissues.

(continued on page 2)

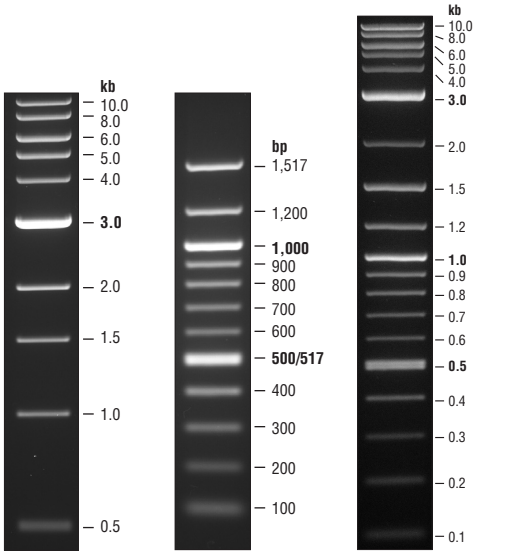
Quick-Load™ DNA Ladders

accurate band patterns with the convenience of tracking dye

Advantages

- Ready-to-load
- Size range from 0.1–10.0 kb
- Stable at room temperature
- Uniform band intensities
- Easy-to-identify reference bands
- Defined mass profile for sample quantification

For more information about DNA Ladders and Markers available at NEB, please turn to page 4.



1 kb DNA Ladder
0.8% TAE agarose gel

100 bp DNA Ladder
1.3% TAE agarose gel

2-Log DNA Ladder
1.0% TBE agarose gel

Combating Neglected Diseases

(continued from page 1)

Figure 2: *Parasitic nematode worm of the Superfamily filarioidea. Species responsible for lymphatic filariasis include Wuchereria bancrofti, Brugia malayi and Brugia timori. (Provided by WHO/TDR/Stammus)*

This species produces immature worms that migrate to the skin and eyes resulting in severe skin pathology and eye lesions. The vectors for *O. volvulus* are *Simulium* spp. blackflies that breed in fast flowing rivers.

Despite the severity of filarial disease and its impediment to progress in developing countries, research in this area is neglected and under-funded. There are no vaccines, while drug treatments such as ivermectin, albendazole, and diethylcarbamazine target the immature stages but not the long-lived adult worms. With the real threat of emerging drug resistance resulting from continued reliance on the limited arsenal of drugs that is available, a wider array of choices for drug targets will be invaluable in combating lymphatic filariasis and onchocerciasis.

For more than 20 years, New England Biolabs, Inc. has conducted basic research in molecular parasitology, and collaborated with the World Health Organization and researchers from other institutions and universities. Several laboratories at New England Biolabs are actively engaged in research aimed at identifying essential biological processes and molecules that can be used as targets in high throughput drug discovery pipelines. Much of that effort utilizes genomic sequence data as a core element.

Figure 3: *Infective larvae develop into adult worms (known as macrofilariae) in the afferent lymphatic vessels, causing severe distortion of the lymphatic system. Elephantiasis – painful, disfiguring swelling of the limbs – is a classic sign of late-stage disease. (Provided by WHO/TDR/Chandran)*

We and others have recently developed an *in silico* approach for discovering new filarial drug targets in which comparative sequence analysis and functional genomics data from the related model nematode *Caenorhabditis elegans* are combined into subtractive filters that can be used to identify potentially essential nematode genes and generate a pool of pre-validated candidate targets (2,3). Based on orthology assignments between *B. malayi* and *C. elegans*, the essentiality of the *B. malayi* genes can be inferred from the wealth of data from RNA interference (RNAi) experiments and other functional studies in *C. elegans*. RNAi, which serves as a technique to examine gene function, has been applied genome-wide in *C. elegans*, covering approximately 96% of its genes (reviewed in [4]). At present, there are over 60,000 records publicly available from WormBase (www.wormbase.org) reporting RNAi-generated phenotypes in *C. elegans*. Presumably, orthologs of these genes in *B. malayi* are also essential, as long as redundant pathways are not present.

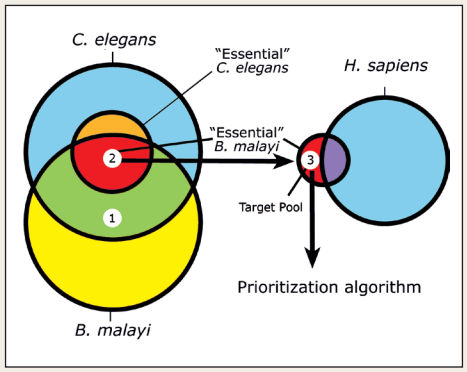


Figure 4: *Selection methodology. Venn diagrams representing the application of subtractive filters in silico to select "essential" B. malayi gene products (left), and subsequent refinement of targets (right). Overlapping areas (not to scale) represent orthologous sequences: (1) B. malayi-C. elegans orthologs; (2) ortholog pairs where the C. elegans ortholog is known to produce a deleterious phenotype when knocked down by RNAi; (3) "essential" B. malayi sequences after removal of human orthologs to produce the final target pool.*

Comparative sequence analysis can also be used to eliminate genes with possible mammalian orthologs. Combined with other measures of 'druggability', prioritization algorithms can be applied to the remaining set to produce a manageable list of targets for experimental validation (Figure 4).

In the absence of complete genomic sequence, the analysis so far has been limited to a collection of 400,000 nematode ESTs (2,3,5). Our next goal is to apply the same approach to the completed draft genomic sequence of *B. malayi*, which is expected to be released in the near future (6). A preliminary scan of the pre-release genome sequence data (www.tigr.org) using the method described predicts that a wide range of new potential drug targets will be uncovered. Nonetheless, even utilizing the current EST data set, the applicability of the bioinformatics approach was supported by the identification of known potential nematode drug targets such as chitin synthase (7,8,9), fatty acid desaturase (10) and cofactor independent phosphoglycerate mutase (iPGM) (11,12).

Phosphoglycerate mutase catalyzes the conversion of 2- and 3-phosphoglycerate in the glycolytic and gluconeogenic pathways. Normally, a highly conserved process such as glycolysis would not be considered a fruitful area for identifying selective drug targets. However, PGMs exist in two distinct forms: cofactor-dependent (dPGM) and cofactor-independent (iPGM). The two types possess different molecular weights, share no sequence similarity, have different tertiary structures and even use dissimilar catalytic mechanisms. iPGM serves as a potential filarial drug target because it is widely distributed in nematodes but completely absent from vertebrates; the latter exclusively utilize the dPGM form (12).

Analysis of potentially essential targets in *B. malayi* is not confined to the *B. malayi* genome. In fact *B. malayi*, *W. bancrofti* and *O. volvulus* each contain three genomes: their own chromosomal DNA, a mitochondrial genome and the genome of an intracellular obligate alpha-proteobacterial endosymbiont called *Wolbachia* (13). In 2005, the 1 Mb genome sequence of *Wolbachia*, the mutualistic endosymbiont that resides in the cells of *B. malayi*, was reported by NEB scientists (13), (Figure 5). The attractiveness of *Wolbachia* as an anti-filarial target is based on the obligate nature of the *Brugia-Wolbachia* interaction, and the demonstration that the antibiotic doxycycline severely affects development of worms in both laboratory animals and human trials (reviewed in [14]). Recently comparative genomic sequence information has been used to identify its metabolic pathways and predict potential drug targets. Based on the known pathways in *B. malayi*, the *Wolbachia* genome analysis suggested that the endosymbiont might supply its host with a number of important nutrients (13).

The genome sequence of nematodes and their endosymbionts represent a valuable resource in combating filarial diseases in the genomic era. The key to unlocking the identity of potential new drug targets is bioinformatic analysis. Validation requires a comprehensive study of the role of the target molecule in the worm and/or endosymbiont. Further development of the most promising targets will hopefully lead to the identification of new lead compounds.

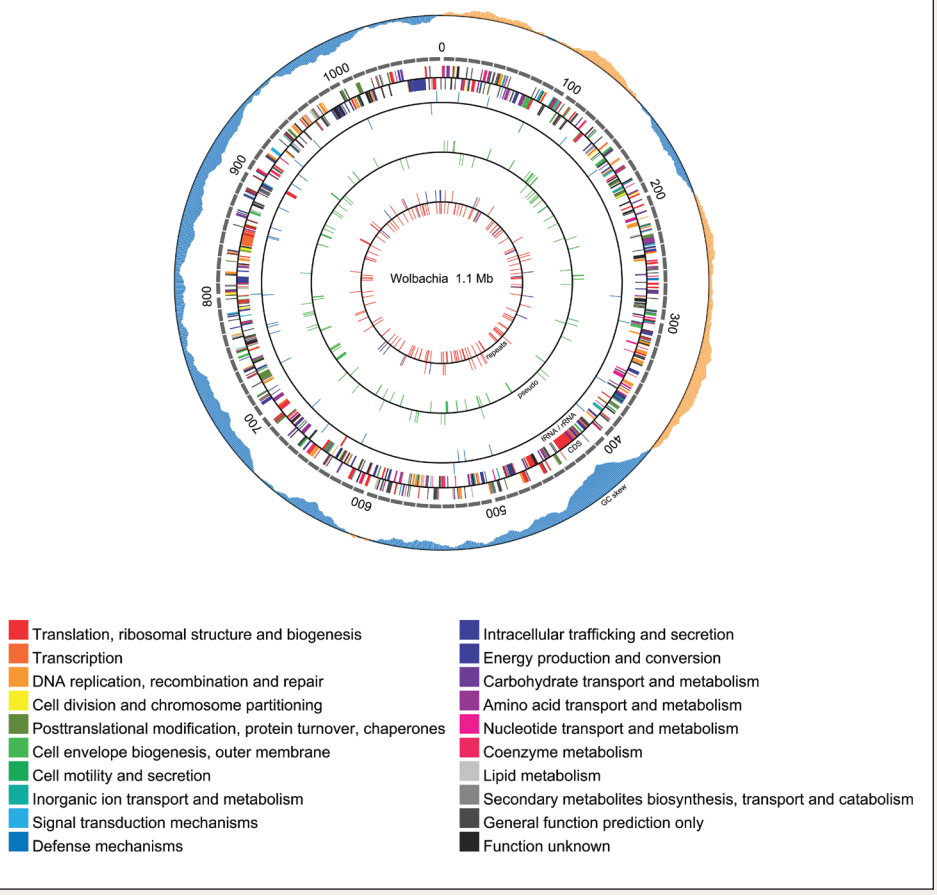


Figure 5: Genogram of the Wolbachia endosymbiont of B. malayi. *The scale indicates coordinates in kilobase pairs (kbp) with the putative origin of replication positioned at 0 kbp. The outermost ring indicates the GC-skew over all bases in the forward strand using a window size of 40 kbp and a step size of 1 kbp. Positive and negative skew are shaded gold and blue, respectively. Features are shown as paired rings separated by a circular baseline. In each pair, the outer and inner rings represent the forward and reverse DNA strands, respectively. Working inward from the scale, the features displayed are as follows: identified genes and their broad functional classification (multihued, as listed); tRNA (blue)/rRNA (red) genes; putative pseudogenes (green); repeated sequences (red) and transposon-related repeats (blue). See (13) for more details.*

The approach described for identifying new filarial drug targets is applicable to a wide variety of sequenced pathogens, ranging from microbial species to the metazoan parasite analyzed in our study. Given the rapid pace of technological advancements in high throughput genomics, scientists at NEB expect that the methodology will gain widespread applicability.

References:

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3. Foster, J.M., et al. (2005) *Trends Parasitol.* 21, 101–104.
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14. Pfarr, K. and Hoerauf, A. (2006) *Mini-reviews in Medicinal Chemistry*, 6, 203–210.

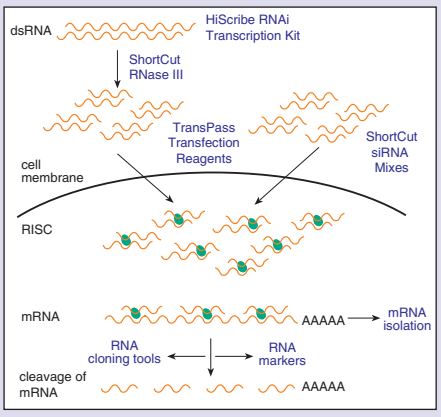
RNAi Overview

Over the last few years it has become apparent that small RNAs have a major role in the post-transcriptional regulation of gene expression in development, cancer biology, anti-viral defense and chromatin modification. The role of small RNAs is an active area of research that is aided by the technology of short interfering RNAs (siRNAs). siRNAs are used as reagents for selective gene knockdown.

NEB offers a range of products for RNA interference studies. This includes the ShortCut™ RNAi Kit for generating siRNA mixtures, the HiScribe™ RNAi Transcription Kit for dsRNA synthesis, high efficiency siRNA transfection reagents, and enzymatically generated potent siRNA mixes to examine areas such as kinase signaling, translational processing, apoptosis, transcription and chromatin regulation. ShortCut™ siRNA Mixes are validated silencing mixtures generated by NEB's proprietary ShortCut™ RNase II technology. Each mixture is a unique combination of many individual siRNAs that work collectively to knock down the target gene.

Advantages of ShortCut siRNA Mixes

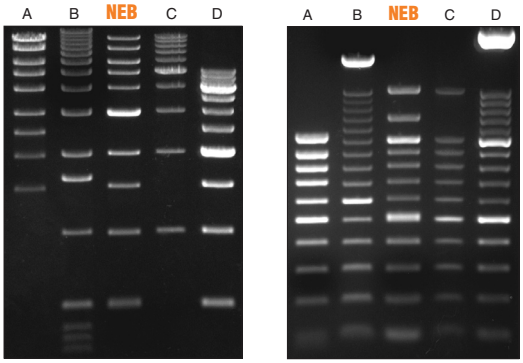
- Highly effective at low concentration (1–20 nM)
- Tested and validated with endogenous gene targets
- Supplied in solution, ready for transfection



Schematic of NEB's products for in vitro transcription and RNAi.

For more information on our growing line of RNA products, please visit www.neb.com or pages 176–191 of the NEB 2007•08 Catalog & Technical Reference.

Choose DNA Ladders from NEB for quality, consistency and value

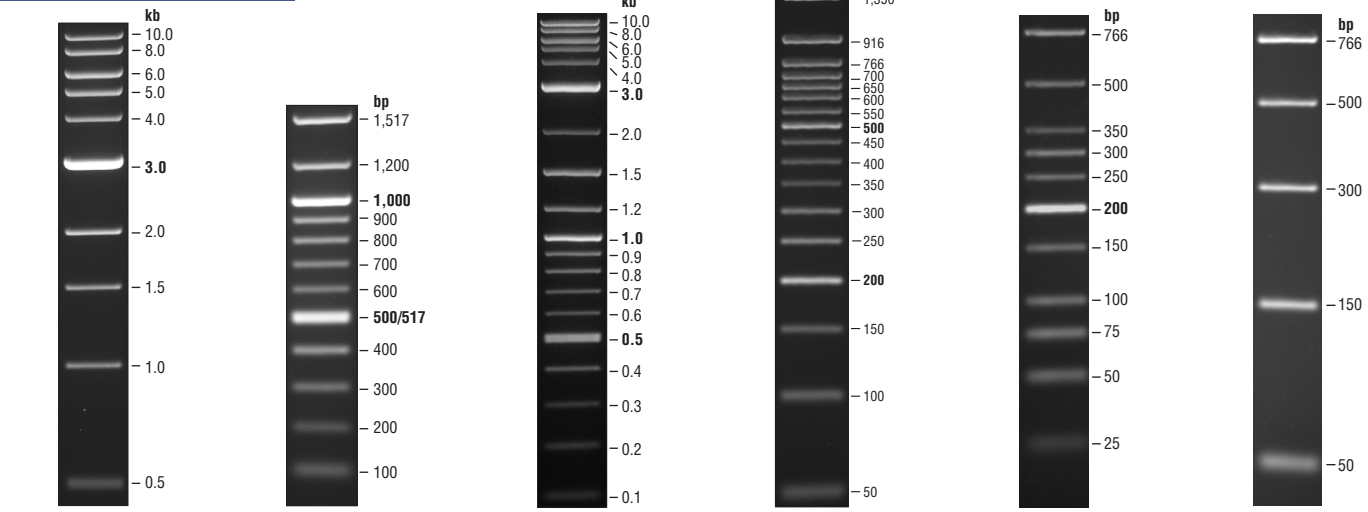


Comparison of the NEB 1 kb (left) and 100 bp (right) DNA Ladders to other commercially available DNA Ladders from suppliers A, B, C and D. Note: A 500 bp DNA Ladder from supplier D is used in the 1 kb DNA Ladder comparison.

- Stable at room temperature
- Sharp uniform bands
- Easy-to-identify reference bands
- Can be used for sample quantitation
- No extra backbone DNA present
- Quick-Load™ ladders contain bromophenol blue for tracking
- TriDye™ ladders contain three dyes to monitor migration

New! For your convenience, supplemental loading dye is now supplied with all DNA Ladders and Markers.

DNA Ladders



1 kb DNA Ladder
0.8% TAE agarose gel.
NEB #N3232

100 bp DNA Ladder
1.3% TAE agarose gel.
NEB #N3231

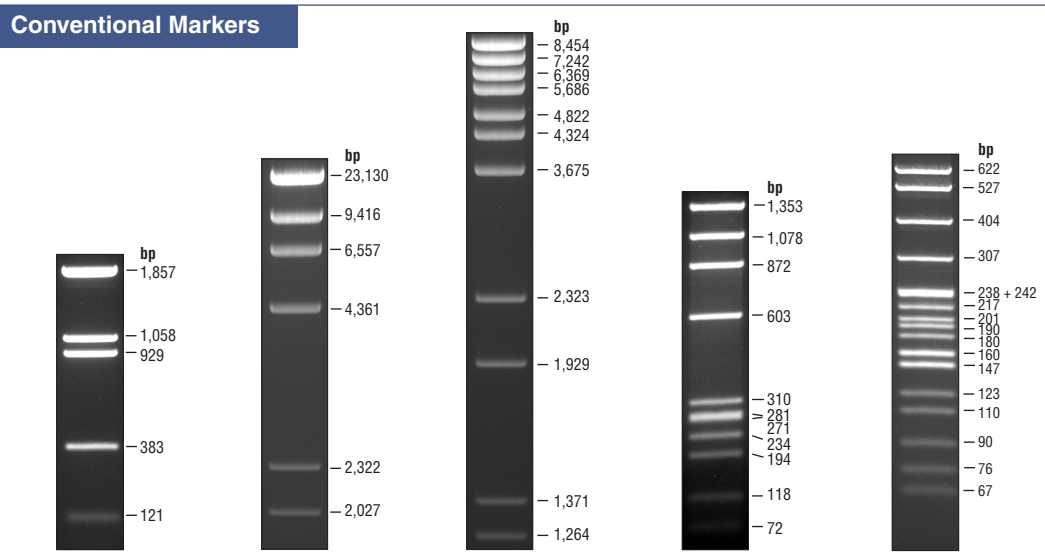
2-Log DNA Ladder
1.0% TBE agarose gel.
NEB #N3200

50 bp DNA Ladder
1.8% TBE agarose gel.
NEB #N3236

Low Molecular Weight DNA Ladder
1.8% TBE agarose gel.
NEB #N3233

PCR Marker
1.8% TBE agarose gel.
NEB #N3234

Conventional Markers



pBR322 DNA–BstNI Digest
1.4% agarose gel.
NEB #N3031

Lambda DNA–HindIII Digest
1.0% agarose gel.
NEB #N3012

Lambda DNA–BstEII Digest
1.0% agarose gel.
NEB #N3014

ϕX174 DNA–HaeIII Digest
1.7% agarose gel.
NEB #N3026

pBR322 DNA – MspI Digest
1.8% agarose gel.
NEB #N3032

DNA Ladders/Markers Selection Chart

DNA Ladder/Marker	Catalog #	Range	Supplied with loading dye	Quantitation	Size (µg) S	Size (µg) L	# of gel lanes S	# of gel lanes L
Ladders								
1 kb DNA Ladder	N3232S/L	0.5–10.0 kb	✓	✓	100	500	200	1000
TriDye	N3272S	0.5–10.0 kb	N/A	✓	62.5	N/A	125	N/A
Quick-Load	N0468S	0.5–10.0 kb	N/A	✓	62.5	N/A	125	N/A
100 bp DNA Ladder	N3231S/L	100–1,517 bp	✓	✓	50	250	100	500
TriDye	N3271S	100–1,517 bp	N/A	✓	62.5	N/A	125	N/A
Quick-Load	N0467S	100–1,517 bp	N/A	✓	62.5	N/A	125	N/A
2-Log DNA Ladder	N3200S/L	0.1–10.0 kb	✓	✓	100	500	100	500
TriDye	N3270S	0.1–10.0 kb	N/A	✓	125	N/A	125	N/A
Quick-Load	N0469S	0.1–10.0 kb	N/A	✓	125	N/A	125	N/A
Biotinylated	N7554S	0.1–10.0 kb	N/A	✓	25	N/A	25	N/A
50 bp DNA Ladder	N3236S/L	50–1,350 bp	✓	✓	100	500	100	500
Low MW DNA Ladder	N3233S/L	25–766 bp	✓	✓	50	250	100	500
PCR Marker	N3234S/L	50–766 bp	✓	✓	30	150	100	500
Conventional Markers								
pBR322 DNA-BstNI Digest	N3031S/L	121–1,857 bp	✓	✓	50	250	50	250
Lambda DNA-HindIII Digest	N3012S/L	2,027–23,130 bp	✓	✓	150	750	150	750
Lambda DNA-BstEII Digest	N3014S/L	702–8,454 bp	✓	✓	150	750	150	750
ØX174 DNA-HaeIII Digest	N3026S/L	72–1,353 bp	✓	✓	50	250	50	250
pBR322 DNA-MspI Digest	N3032S/L	67–622 bp	✓	✓	50	250	50	250
Lambda DNA-Mono Cut Mix*	N3019S/L	1,503–48,502 bp	✓	✓	50	250	100	500
PFG Markers**								
MidRange I PFG Marker	N3551S	15–300 kb	N/A	–	–	N/A	50	N/A
MidRange II PFG Marker	N3552S	24–300 kb	N/A	–	–	N/A	50	N/A
Yeast Chromosome PFG Marker	N0345S	225–1,900 kb	N/A	–	–	N/A	50	N/A
Lambda Ladder PFG Marker	N0340S	50–1,000 kb	N/A	–	–	N/A	50	N/A
Low Range PFG Marker	N0350S	0.1–200 kb	N/A	–	–	N/A	50	N/A

**Best separated by Pulse Field Gel Electrophoresis.*

***To learn more about markers for pulsed-field gel electrophoresis, please visit www.neb.com.*

N/A – Not applicable

New Magnetic mRNA Isolation Kit

isolate intact poly(A)$^+$ RNA from cells and tissue

The Magnetic mRNA Isolation Kit is designed to isolate intact poly(A)$^+$ RNA from crude cell lysates or tissue without requiring phenol or other chaotropic reagents. The technology is based on the coupling of oligo d(T)$_{25}$ to 1µm paramagnetic beads which are then used as the solid support for the direct binding of poly(A)$^+$ RNA. The procedure permits the manual processing of multiple samples and can be adapted for automated high-throughput applications. Additionally, magnetic separation technology permits elution of intact mRNA in small volumes eliminating the need for precipitation.

Advantages

- Ideal for high throughput applications
- Complete isolation in less than one hour
- No need for phenol or other organic solvents
- No need to precipitate poly(A)$^+$ transcripts in eluent

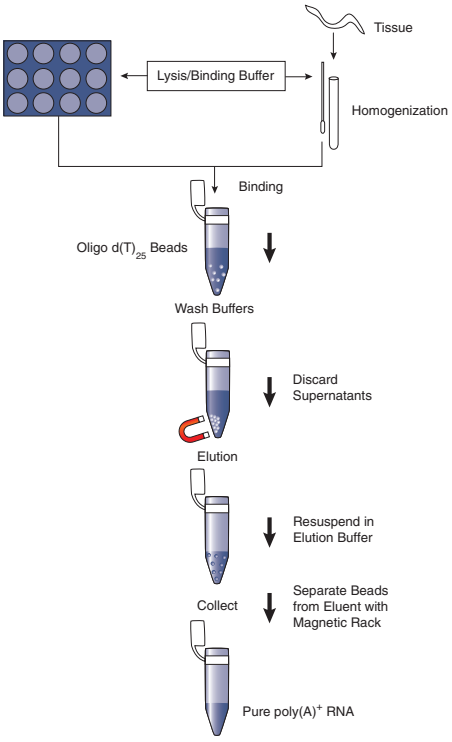
#S1550S 25 isolations

Special Offer

For a limited time, purchase the Magnetic mRNA Isolation Kit and receive a free 6-tube Magnetic Separation Rack.

Magnetic mRNA Isolation Kit with 6-tube Magnetic Rack

#E1550S 25 isolations



Facilitate the isolation of poly(A)$^+$ RNA using the Magnetic mRNA Isolation Kit.

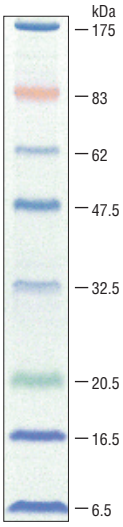
New ColorPlus Prestained Protein Marker, Broad Range

convenient and versatile

The ColorPlus Prestained Protein Marker contains 8 bands in range of 6.5–175 kDa, with two colored bands for easy identification.

Advantages

- Easy-to-identify reference bands
- Convenient band spacing
- Uniform band intensities



ColorPlus Prestained Protein Marker, Broad Range, 10–20% SDS PAGE

ColorPlus Prestained Protein Marker, Broad Range

#P7709S 175 mini-gel lanes
#P7709L 875 mini-gel lanes
#P7709V 83 mini-gel lanes

> New to NEB Expressions

NEB FAQ Spotlight

At New England Biolabs, Inc., we take a personalized approach to technical support. The same scientists (product managers) who purify and quality-control our products answer their technical questions. Our research staff is also available as a technical resource, and have expertise in DNA sequencing, methylation, cloning, over-expression, fermentation, protein purification, RNAi and epigenetics.

NEB Expressions will regularly highlight pertinent FAQs received by our scientists that may help you in designing your experiments and analyzing your data.

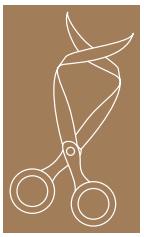
Q Is there a restriction enzyme that does not cut human genomic DNA? This would be helpful in isolating synthetic DNA fragments from human DNA.

A There are no GATC methylated sites in human DNA, therefore DpnI, which recognizes only Gm6ATC DNA, would not digest human genomic DNA. If the foreign DNA fragment were synthesized in a methylated form, it would be cut by DpnI and could therefore be differentiated from the human DNA.

Our bioinformatics department has a useful link to tables with relevant cut site frequency data. Site frequencies for all prototype enzymes are listed chromosome by chromosome. This table can be accessed at the following website:

http://tools.neb.com/~posfai/HUMAN/human_chr.counts.1.html

To access NEB Technical Support please contact your distributor.



DNA Methylation and Restriction Digests

avoiding difficulties associated with digesting methylated DNA

Two common types of methylation that can block cutting at a restriction site are Dam and Dcm methylation. Both arise from replicating DNA in a strain of *E. coli* that has functional Dam and Dcm methylation systems.

Sites that are Blocked by dam/dcm Methylation

Restriction by some enzymes can be inhibited due to methylation caused by the common *E. coli* methyltransferases. Dam methyltransferase causes methylation of the adenine in the sequence GATC while Dcm methyltransferase causes methylation of the first cytosine in the sequence CC(A/T)GG. Any restriction enzyme whose site contains either of these sequences may be affected by the relevant methylation. For example, the site for AlwI (GGATC4/5) contains the recognition site for Dam methyltransferase, GATC. If the DNA was produced in a methylating *E. coli* strain, the adenine would be methylated and cleavage by AlwI would be blocked. This can be avoided by cloning the DNA into a *dam*⁻ strain such as GM2613 or our *dam*⁻/*dcm*⁻ Competent *E. coli* (NEB #C2925). These strains do not have a functional Dam methyltransferase.

dam/dcm Overlapping Sites

Restriction sites can also be blocked if an overlapping site is present. In this case, part of the dam or dcm sequence is generated by the restriction enzyme sequence followed by the flanking sequence. For example, the site for ClaI (AT/CGAT) contains GAT. If it is followed by a C, the A can be methylated, and cleavage will be blocked. On the other hand BamHI is not Dam/Dcm sensitive; the BamHI site contains GATC but cleavage by this enzyme is not blocked even when the A is methylated. The same principles apply for dcm methylation but the enzyme sites affected would contain the sequence CC(A/T)GG.

For more information regarding methylation sensitivity please refer to pages 314–316 of the 2007•08 NEB Catalog & Technical Reference, or www.neb.com.

Key Points to Consider:

- Mammalian genomic DNA is not Dcm or Dam methylated. Inhibition of enzyme activity by Dcm and Dam methylation is not an issue when digesting mammalian DNA.
- Mammalian and plant DNA that has been cloned into a methylating *E. coli* strain will be Dam/Dcm methylated. Most commonly used laboratory *E. coli* strains methylate DNA.
- Mammalian and plant genomic DNA are CpG methylated. Some enzymes are inhibited by CpG methylation. More information on CpG methylation can be found on pages 314–316 of the NEB 2007•08 Catalog.
- Most bacterial DNA (including *E. coli* DNA) is not CpG methylated. Inhibition of enzyme activity by CpG methylation is not an issue for most DNA prepared from common *E. coli* strains.
- DNA amplified by PCR does not contain any methylated bases.
- Some enzyme recognition sequences have overlapping methylation sites. These sites are formed partially by the recognition sequence of an enzyme and partially by flanking DNA.
- To avoid Dam/Dcm methylation when subcloning in bacteria, choose NEB's *dam*⁻/*dcm*⁻ Competent *E. coli* for propagation.

dam⁻/*dcm*⁻ Competent *E. coli*

Methyltransferase Deficient Cloning Strain

Dam⁻/*dcm*⁻ chemically competent *E. coli* cells are suitable for growth of plasmids free of dam and dcm methylation.

Transformation Efficiency: > 2 x 10^6 cfu/ug

Advantages

- Allows for growth of plasmids free of Dam and Dcm methylation
- Activity of nonspecific endonuclease I (EndAI) eliminated for highest quality plasmid preparations
- Free of animal products
- T1 phage resistant *(FhuA2)*
- Available in single-use transformation tubes (50 µl each) or in larger volume (6 tubes of 200 µl)

dam⁻/*dcm*⁻ Competent *E. coli*

C2925H	20 tubes x 0.05 ml
C2925I	6 tubes x 0.2 ml

Dam/Dcm Sensitive Restriction Enzymes available from NEB

The following enzymes are blocked or impaired by dam or dcm methylation when using DNA isolated from a methylating *E. coli* strain. In order to achieve cleavage with these enzymes, the DNA should be passed through a *dam*⁻/*dcm*⁻ strain.

Acc65I	BslI	HphI	PspGI
AlwI	BsmFI	Hpy188I	PspOMI
AlwNI	BspDI	Hpy188III	Sau96I
ApaI	BspEI	MboI	ScrFI
AvaII	BspHI	MboII	SexAI
BanI	BssKI	MscI	SfiI
BcgI	BstXI	NlaIV	SfoI
BclI	ClaI	NruI	StuI
BsaI	DpnII	PflMI	StyD41
BsaBI	EaeI	PhoI	TaqI
BsaHI	EcoO109I	PpuMI	XbaI

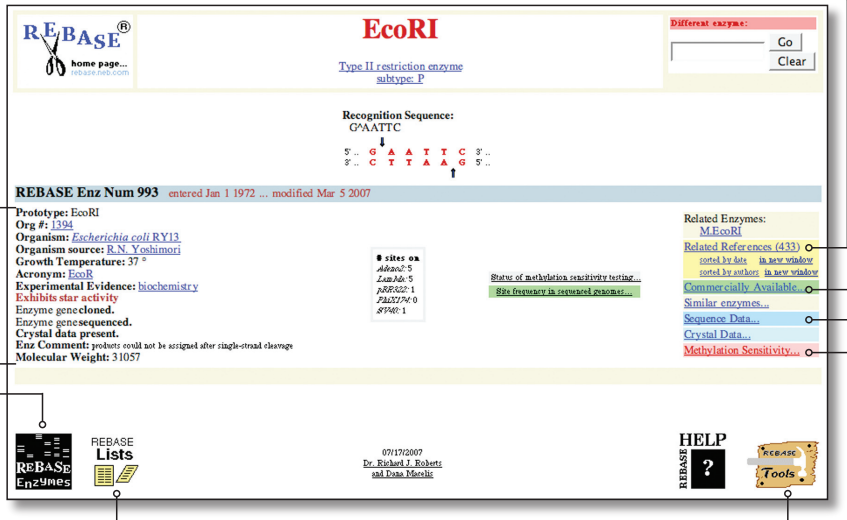
The 2007•08 Activity Chart for Restriction Enzymes is now available

Please contact your distributor if you have not received a copy.

REBASE – The Restriction Enzyme Database

REBASE (The Restriction Enzyme Database) is a complete listing of all known restriction endonucleases. This comprehensive site contains data such as recognition sequences, cleavage sites, methylation sensitivity, isoschizomers and commercial availability of enzymes.

rebase.neb.com/rebase/



Summary of enzyme source, status and properties

Click here for a complete list of enzymes in the database including recognition sequences, isoschizomers and commercial suppliers

Lists all references containing this enzyme, with links to reference details

Lists available suppliers

Includes labeled map view, links to sequence databases, gene information and ability to download DNA and protein sequence files

Contains detailed methylation sensitivity testing data

Click here for specialized information (star activity, methylation, cleavage type, etc.), REBASE genomes and sequence collections

Click here for access to available tools (theoretical digests, BLAST, NEBcutter, REBpredictor)

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