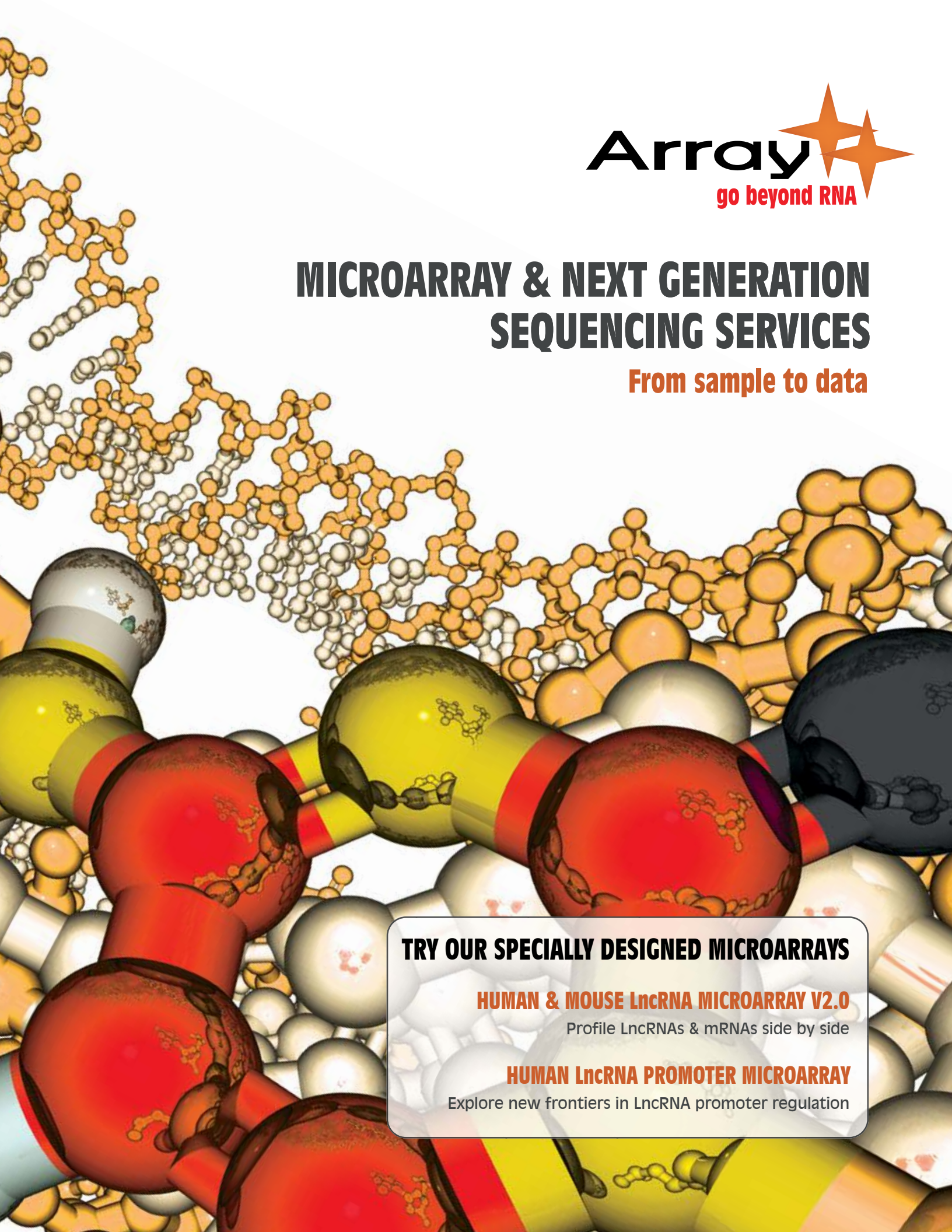

Arraystar
go beyond RNA

MICROARRAY & NEXT GENERATION SEQUENCING SERVICES

From sample to data

TRY OUR SPECIALLY DESIGNED MICROARRAYS

HUMAN & MOUSE LncRNA MICROARRAY V2.0
Profile LncRNAs & mRNAs side by side

HUMAN LncRNA PROMOTER MICROARRAY
Explore new frontiers in LncRNA promoter regulation

CONTENTS

LEAP FORWARD WITH OUR NEW MICROARRAY SERVICES

GO BEYOND RNA WITH ARRAYSTAR

Arraystar Inc. opened its doors in April 2009 and has quickly become the industry leader in LncRNA profiling technology. Our rapid growth and innovative product development has given us the ability to assist in advanced research projects and potentially aid in great scientific breakthroughs.

We offer a variety of integrated sample-to-data microarray and next generation sequencing services to meet all of your research needs. Our robust bioinformatics analysis comes standard with all of our services and greatly sets us apart of the rest of the pack. Just send us your samples and we'll do the rest!

Our ultimate goal is to help customers achieve their desired research aspirations. We strive to completely satisfy each and every customer and are continually building our business by "word of mouth." We make every effort possible to provide an easy and worry-free experience through superior customer service and stellar technical support before, during and well after your project is complete!

OUR CUSTOMERS

We have provided services to over 100 esteemed universities, hospitals, and research centers, such as:

- National Institutes of Health (NIH)
- Food & Drug Administration (FDA)
- Massachusetts Institute of Technology (MIT)
- Johns Hopkins University
- University of California San Diego
- Rockefeller University
- Columbia University
- University of Toronto
- M. D. Anderson Cancer Center
- Novartis Institutes for BioMedical Research
- GlaxoSmithKline
- Beth Israel Deaconess Medical Center

ARRAYSTAR LncRNA MICROARRAY V2.0

The Arraystar LncRNA Microarray V2.0 is engineered for the global profiling of LncRNAs and protein-coding transcripts in tandem. Each transcript is represented by a specific exon or splice junction probe that can identify individual transcripts—as well as many of their alternatively-spliced isoforms—reliably and accurately. Available for human and mouse, the Arraystar LncRNA Microarray V2.0 makes it possible to look beyond protein-coding genes and paint a more complete picture of RNA expression changes.

The Arraystar LncRNA Microarray V2.0 gives researchers the power to overcome many obstacles to the study of LncRNAs, including:

- There is no comprehensive public LncRNA database currently available;
- The expression level of LncRNAs is low—typically much lower than that of mRNAs—making LncRNAs difficult to detect;
- LncRNAs often overlap with, or are transcribed antisense to, protein coding genes, complicating the design of LncRNA-specific probes

HIGHLIGHTS

- Comprehensive and Reliable Array Content: LncRNA probes are designed using the most up-to-date and complete transcriptome databases in the world, including RefSeq, Ensembl, and others;
- The Most Thorough Coverage Available: Profiles LncRNAs and protein-coding transcripts side-by-side on the same chip;
- Specific Exon/Splice Junction Probes: Enables the identification of individual LncRNAs and protein-coding transcripts—as well as many of their alternatively-spliced isoforms—reliably and accurately;
- Efficient and Robust Labeling System: Makes possible the creation of Cy3- or Cy5-labeled antisense RNA with low input or degraded RNA samples;
- Systematic LncRNA Classification: Helps to identify the putative functional relationships between LncRNAs and their associated protein-coding genes

SPECIFICATIONS

	HUMAN	MOUSE
Probe Length	60 nt	60 nt
Probe Selection Region	Specific exon or splice junction probes along the entire length of the transcript	Specific exon or splice junction probes along the entire length of the transcript
Probe Specificity	Transcript-specific	Transcript-specific
LncRNAs	33,045	31,423
Protein Coding Transcripts (mRNAs)	30,215	25,376
LncRNA Sources	Databases: NCBI Refseq, UCSC Known Gene4 , Ensembl 37.59, H-invDB 7.0, RNAdb 2.0 and NRED; Literature: LincRNAs (Khalil, A.M., *et al*., 2009), lncRNAs with enhancer-like functions (Orom, U.A., *et al*.,2010), HOX Loci LncRNAs(Rinn, J.L., *et al*., 2007), and T-UCRs (Calin, G.A., *et al*.,2007).	Databases: NCBI Refseq, UCSC Known Gene 4, Ensembl 37.61, Fantom3, RNAdb 2.0 and NRED; Literature: LincRNAs (Khalil, A.M., *et al*.,2009), T-UCRs (Calin, G.A., *et al*.,2007), Evolutionarily constrained LncRNAs(Ponjavic, J., *et al*.,2009), Evolutionarily conserved LncRNAs (Willingham, A.T., *et al*., 2005)and UaRNAs (Mercer, T.R., *et al*.,2010)
mRNA Sources	NCBI Refseq	NCBI Refseq
Array Format	8 x 60K	8 x 60K

ARRAYSTAR HUMAN 2.1M LncRNA PROMOTER MICROARRAY

The Arraystar Human 2.1M Long non-coding RNA (LncRNA) Promoter Array is designed for the identification of epigenetic modifications and transcription Factor (TF) binding sites within LncRNA promoter regions. In addition, our LncRNA Promoter Array can survey other biologically significant genomic regions, including mRNA promoters, microRNA promoters, bivalent domains, CpG islands, and CpG island shores, at 100 bp spacing, for unbiased discovery of epigenetic modifications and TF binding sites. Further, probes for positive, negative and non-CpG control regions are included on the array to facilitate experimental performance assessment.

HIGHLIGHTS

The Arraystar Human LncRNA Promoter Array is the first commercially available microarray for profiling epigenetic modifications at the promoter regions of LncRNAs. It offers the most comprehensive and up-to-date LncRNA promoter compilation in a simple and convenient single-array format.

- Covers promoter regions for all annotated LncRNAs and protein-coding genes, as well as other features, such as CpG islands, CpG island shores, H3K4-K27 bivalent domains, potential microRNA promoters, and many others.
- Uses long (50 -75 mer) oligonucleotide probes, which deliver results with unparalleled sensitivity and specificity.
- Provides detailed annotation for each genomic feature, along with our comprehensive subgroup analysis, to satisfy all of your research needs.
- Generates an integrated regulation map of all LncRNAs and protein-coding genes, when combined with data from our Arraystar Human LncRNA Array V2.0 service.

SPECIFICATIONS

Total number of probes: 2.1M
Probe length: 50 -75 mer
Median Probe Spacing: 100 bp
High-throughput tiling regions:

TYPE	TILING REGIONS	NUMBER	BUILD	SOURCE
LncRNA	LncRNA promoter regions from 3.5 kb upstream of transcription start site (TSS) to 1.25 kb downstream of TSS	28,387	HG19	RefSeq, UCSC Knowngene, Ensembl 37.59, H-invDB 7.0, RNAdb 2.0, NRED
LincRNA	LincRNA promoter regions (3.5kb flanking regions at both sides of K4-K36 LincRNA locus)	3,280	HG19	Guttman, *et al*., 2009; Khalil, *et al*., 2009
UCR	Ultra conserved regions with 10 kb of flanking sequence	481	HG19	Bejerano, *et al*., 2004; Calin, *et al*., 2007
HOX clusters	HOXA, HOXB, HOXC and HOXD clusters with 30 kb of flanking sequence	4	HG19	Rinn, *et al*., 2007
mRNA	mRNA promoter regions from 3.5 kb upstream of TSS to 1.25 kb downstream of TSS	30,215	HG19	NCBI RefSeq
miRNA	Potential miRNA promoter regions (15 kb upstream to mature miRNA)	1,426	HG19	miRBase 17.0
Bivalent domains	K4-K27 bivalent domain regions	5,543	HG19	Bernstein, *et al*., 2006; Pan, *et al*., 2007; Zhao, *et al*., 2007
CpG islands	CpG island regions	27,000	HG19	UCSC
CpG island shores	2 kb regions flanking CpG islands	21,107	HG19	UCSC

LncRNA MICROARRAY SERVICE

LncRNA expression profiling utilizes microarrays to analyze transcriptome-wide LncRNA expression levels. Arraystar's LncRNA microarray services are available in human, mouse and rat, from sample preparation to in-depth data analysis. Our step-by-step quality controls are designed to ensure you get the most reliable results. Just send us your samples, and we'll do the rest!

RECENT PUBLICATIONS CITING OUR LncRNA MICROARRAY SERVICE

Yang, F., Zhang L, *et al*. (2011). Long non-coding RNA high expression in hepatocellular carcinoma facilitates tumor growth through enhancer of zeste homolog 2 in humans. *Hepatology* **54**, 1679-89.

Braconi, C., T. Kogure, *et al*. (2011). microRNA-29 can regulate expression of the long non-coding RNA gene MEG3 in hepatocellular cancer. *Oncogene* **30**, 1-7

ARRAYSTAR LncRNA MICROARRAY

Arraystar's scientists have developed robust LncRNA microarrays to evaluate the global expression of LncRNAs. In spring 2011, we launched Human LncRNA Microarray V2.0 and Mouse LncRNA Microarray V2.0. These newly-designed arrays have greatly improved probe specificity and more thorough coverage of LncRNAs compared with our ground-breaking V1.0 LncRNA microarrays.

MICROARRAY	SPECIES	FORMAT	DETECTED LncRNAS
Arraystar Human LncRNA microarray V2.0	Human	8 * 60K	LncRNAs (33,045)+coding genes (30,215)
Arraystar Mouse LncRNA microarray V2.0	Mouse	8 * 60K	LncRNAs (31,423)+coding genes (25,376)
Arraystar Rat LncRNA Array	Rat	4 * 44K	LncRNAs (~9,300)+coding genes (~15,200)

BIOINFORMATICS ANALYSIS

Arraystar's experienced scientists have a deep understanding of the LncRNA microarray platform and are experts in the analysis and interpretation of LncRNA profiling data, enabling us to employ the most powerful methods for normalization and data analysis, including subgroup classification. LncRNAs are classified according to the genomic position relationships between a particular LncRNA with its adjacent protein coding genes. These classes are 1) natural antisense; 2) intronic antisense; 3) bidirectional; 4) exon sense overlapping; 5) intron-sense overlapping; and 6) intergenic (Table 1). Further, we can perform additional LncRNA subgroup analyses such as HOX Loci LncRNA analysis, T-UCR analysis and enhancer-like LncRNA analysis, all of which help identify the putative functional relationships between LncRNAs and their associated protein-coding genes.

2 FOLD UP/DOWN-REGULATED LNCRNAS PASS T-TEST (GROUP 1 VS. GROUP 2)							
	P-VALUE, FOLD CHANGE AND REGULATION			ANNOTATION			
PROBE NAME	P-VALUE <0.05	FC ABSOLUTE >2	REGULA-TION	GENBANK ACCESSION	GENE SYMBOL	SOURCE	RELATIONSHIP
ASLNC01537	0.0012	4.1664	Up	NR_003716	HOTAIR	Refseq	Intergenic
ASLNC01507	0.0236	2.6177	Up	NR_023920	WT1AS	Refseq	Bidirectional
ASLNC02828	0.0001	2.5284	Down	HIV2506	_	RNAdb	Intronic anti-sense
ASLNC12685	0.0018	3.0126	Down	uc002zdu	LOC284837	UCSC_knowngene	Others

Table 1 - Differentially expressed LncRNA screening. *Differentially expressed LncRNAs (Fold change>2, p-value<0.05) in Group1 vs Group2. In column "Regulation", "Up" indicates up-regulated, "Down" indicates down-regulated.*

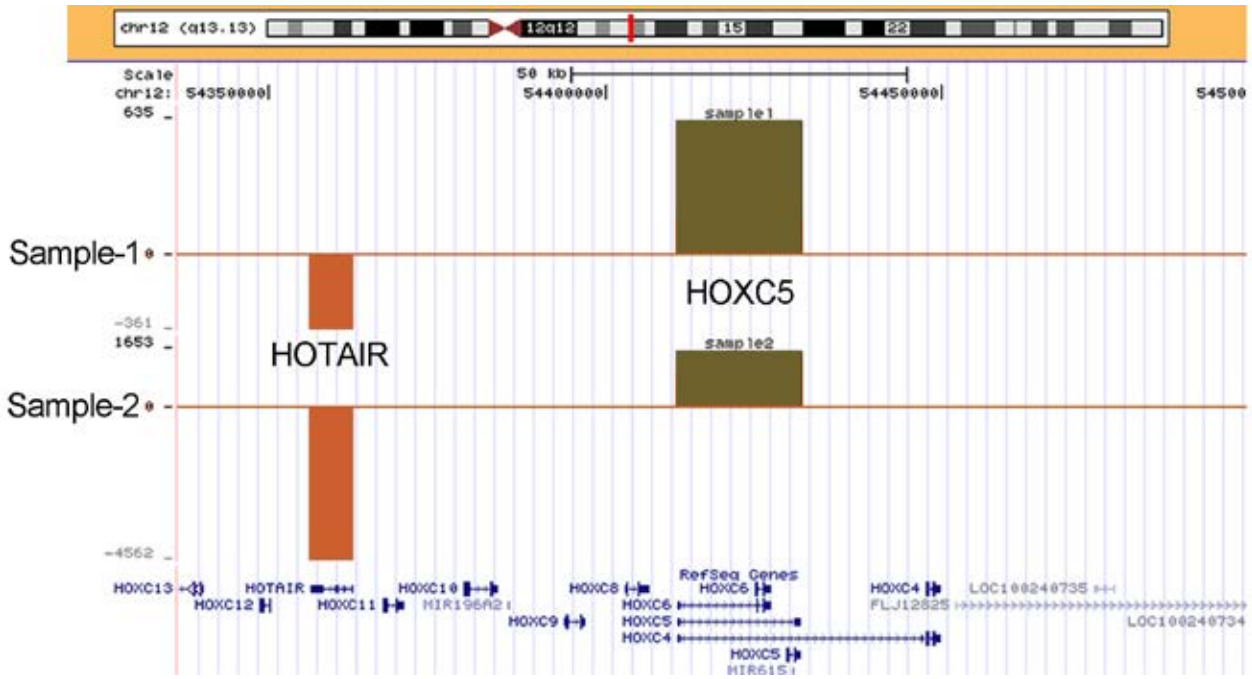

Figure1. Visualization of LncRNAs of interest. *LncRNA microarray results can be visualized in the UCSC Genome Browser. The figure indicates the magnitude and the direction of the changes in LncRNA expression, as well as the genomic position relationship between the lncRNAs and their adjacent protein coding gene.*

GENE EXPRESSION MICROARRAY SERVICE

Gene expression profiling utilizes microarrays to analyze genome-wide gene expression levels. Arraystar provides a full range of gene expression profiling services, from sample preparation to in-depth data analysis. Our step-by-step quality controls are designed to ensure you get the most reliable results. Just send us your samples, and we'll do the rest!

Arraystar's gene expression profiling service uses two of the most powerful platforms available: Agilent and Roche-NimbleGen. The availability of the array services from both platforms offers our customers a variety of choices in array content, density and analysis tools. The gene expression arrays that are most often selected by our customers include:

AGILENT WHOLE GENOME EXPRESSION ARRAYS

MICROARRAY	SPECIES	ARRAY FORMAT	PROBE LENGTH	DETECTED GENES	PROBES /TARGET GENE
Whole Human Genome Array	Human	4 * 44K	60-mer	41,000	1
Whole Mouse Genome Array	Mouse	4 * 44K	60-mer	41,000	1
Whole Rat Genome Array	Rat	4 * 44K	60-mer	41,000	1

ROCHE-NIMBLEGEN GENE EXPRESSION ARRAYS

MICROARRAY	SPECIES	ARRAY FORMAT	PROBE LENGTH	DETECTED GENES	PROBES /TARGET GENE
Homo Sapiens 12 * 135K Array	Human	12 * 135K	60-mer	44,049	3
Mus Musculus 12 * 135K v2 Array	Mouse	12 * 135K	60-mer	27,000	5
Rattus Norvegicus 12 * 135K Array	Rat	12 * 135K	60-mer	42,576	3

BIOINFORMATICS ANALYSIS

Arraystar has a strong bioinformatics team, who provide a thorough, comprehensive analysis of gene expression microarray data. In addition to providing you with differential expression data and statistical analysis, our bioinformatics experts generate highly effective visual tools that are useful in presentations and publications. These tools include box plots, scatter plots, volcano plots, heat maps and bar plots of significant GO terms (Figure 1).

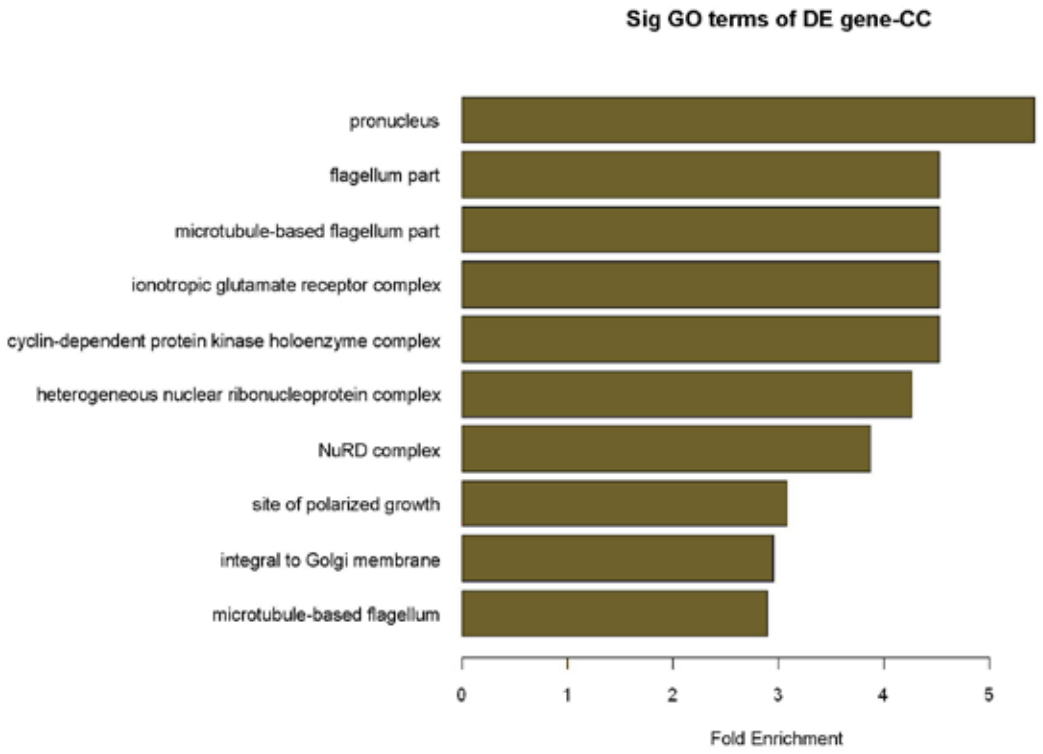

Figure 1. Gene Ontology (GO) Analysis. *Significant GO terms of differentially expressed genes. A bar plot of the 10 GO terms containing the largest fold enrichment of differentially expressed genes. The plot gives a more intuitive view of the significant GO terms.*

piRNA MICROARRAY SERVICE

piRNA expression profiling utilizes microarrays for genome-wide profiling of piRNA expression. Arraystar's piRNA expression profiling service is available for human, mouse and rat, from sample preparation to in-depth data analysis. Our step-by-step quality controls are designed to ensure you get the most reliable results. Just send us your samples, and we'll do the rest!

RECENT PUBLICATION CITING ARRAYSTAR'S piRNA MICROARRY SERVICE

Dharap, A., *et al*. (2011). Altered Expression of PIWI RNA in the Rat Brain After Transient Focal Ischemia. *Stroke* **42**, 1105-9.

ARRAYSTAR piRNA ARRAY

piRNA sequences for human, mouse, and rat are taken from the RefSeq database and mapped to the appropriate genome sequences (builds HG19, MM9 and RN4, respectively) using UCSC's Blat. Sophisticated strategies are employed in the selection of piRNAs and in the design of the corresponding 60-mer oligonucleotide probes.

MICROARRAY	SPECIES	DATABASE	FORMAT	DETECTED piRNAs
Arraystar Human piRNA Array	Human	HG19	4 * 44K	23,677
Arraystar Mouse piRNA Array	Mouse	MM9	4 * 44K	43,537
Arraystar Rat piRNA Array	Rat	RN4	4 * 44K	39,727

MeDIP/hMeDIP-CHIP SERVICES

Methylated/hydroxymethylated DNA immunoprecipitation microarray (MeDIP-chip/hMeDIP-chip) technology generates a detailed profile of genome-wide methylation and hydroxymethylation, respectively, providing insights into the mechanisms behind changes in gene expression in disease, during development, or under specific physiological conditions. Arraystar provides a full range of DNA methylation/hydroxymethylation profiling services, from sample preparation to in-depth data analysis. Our step-by-step quality controls are designed to ensure you get the most reliable results. Just send us your samples, and we'll do the rest!

INTRODUCTION TO 5-HYDROXYMETHYLCYTOSINE

DNA methylation is an important epigenetic modification that plays critical roles in cellular differentiation, development, and disease. In addition to 5-methylcytosine (5mC), substantial amounts of 5-hydroxymethylcytosine (5hmC), generated by the TET family of dioxygenases through oxidation of 5-methylcytosine (Ito, *et al*., 2010; Iyer, *et al*., 2009; Ko, *et al*., 2010; Kriaucionis and Heintz, 2009; Loenarz and Schofield, 2009; Tahiliani, *et al*., 2009), have been detected in diverse cell types and tissues in mammals (Ito, *et al*., 2010; Ko, *et al*., 2010; Kriaucionis and Heintz, 2009; Szwagierczak, *et al*., 2010; Tahiliani, *et al*., 2009).

Studies suggest that hydroxylation of 5mC influences DNA demethylation and gene regulation, possibly by inhibiting DNMT1 activity, causing a subsequent passive loss of methylation following DNA replication. An alternative model suggests that, 5hmC is converted to 5-carboxycytosine (5CaC) by Tet dioxygenase. Conversion of 5mC to 5hmC and 5CaC, followed by TDG mediated base excision of 5CaC, is a known pathway for active DNA demethylation (He, *et al*., 2011). In addition, hydroxylation of 5mC may promote transcriptional de-repression by dissociation of 5mC-binding proteins and/or recruitment of effector proteins. The high abundance of 5hmC in ES cells and in neuronal Purkinje cells, and 5hmC's contribution to DNA demethylation and gene regulation suggests, that this modification is important in stem cell biology and cancer (Delhommeau, *et al*., 2009; Ito, *et al*., 2010; Ko, *et al*., 2010; Koh, *et al*., 2011; Tahiliani, *et al*., 2009).

ARRAYSTAR LncRNA PROMOTER MICROARRAY is designed to investigate the epigenetic modifications and transcription factor binding sites within LncRNA promoter regions, and uncover other biologically significant genomic regions. These additional regions include, but are not limited to, mRNA promoters, miRNA promoters, H3K4-K27 bivalent domains, CpG islands and CpG island shores.

MICROARRAY	SPECIES	ARRAY FORMAT	COVERAGE
Arraystar Human 2.1M LncRNA Promoter Array	Human	1*2.1M	28,387 LncRNA promoters (-3.5kb ~ +1.25kb) 30,215 mRNA promoters (-3.5kb ~ +1.25kb) 1,426 miRNA promoters (-15kb ~ mature miRNA) 27,718 CpG islands, 21,107 CpG island shores, K4-K27 bivalent domain regions, UCR and HOX cluster regions

ARRAYSTAR microRNA GENOME DNA METHYLATION MICROARRAY is designed to profile miRNA-associated DNA methylation/hydroxymethylation patterns.

MICROARRAY	SPECIES	ARRAY FORMAT	COVERAGE
Arraystar microRNA Genome DNA Methylation Array	Human	3*720K	1,426 miRNA promoters (-40 kb ~ +15 kb of mature miRNA) 1,749 host gene promoters (-8 kb ~ 3 kb of TSS) 2,716 CpG islands nearby (-3 kb ~ + 3 kb of CpG island)

ROCHE-NIMBLEGEN CPG ISLAND AND PROMOTER MICROARRAYS can be used to analyze specific regulatory elements of the genome, such as gene promoters, microRNA promoters and CpG islands.

MICROARRAY	SPECIES	ARRAY FORMAT	COVERAGE
HG19 RefSeq Promoter Array	Human	1 * 385K	18,028 promoters: - 2.2kb ~ +0.5kb
MM9 RefSeq Promoter Array	Mouse	1 * 385K	17,354 promoters: -2kb ~ +0.5kb
RN34 Promoter Array	Rat	1 * 385K	15,398 promoters: -2.25kb~+0.5kb
HG19 CpG Island Plus RefSeq Promoter Array	Human	3 * 720K	22,532 promoters: -2.4kb ~ +0.6kb (30,848 transcripts); 27,728 CpG islands
MM9 CpG Island Plus RefSeq Promoter Array	Mouse	3 * 720K	20,404promoters: -3kb ~ +0.8kb (22,881 transcripts); 15,980 CpG islands
RN34 CpG Island Plus RefSeq Promoter Array	Rat	3 * 720K	15,287 promoters: -3.9kb ~ +1kb (15,600 transcripts); 15,790 CpG islands
HG19 Deluxe Promoter v2 Array	Human	1 * 2.1M	26,210 promoters: -8kb ~ +3kb; 27,867 CpG islands; 730 miRNA promoters (-15kb to mature miRNA)
MM9 Deluxe Promoter v2 Array	Mouse	1 * 2.1M	24,507 promoters: -8kb ~ +3kb; 15,969 CpG islands; 599 miRNA promoters (-15kb to mature miRNA)

BIOINFORMATICS ANALYSIS

Promoter CpG content is an excellent predictor of transcriptional repression of a given gene. Arraystar's bioinformatics team is expert at analyzing MeDIP-chip data. Our unique MeDIP-chip analysis determines the CpG methylation states of mammalian gene promoters (Table 1). The degree of CpG methylation at promoters falls into three classes: High-CpG density promoters (HCP), low-CpG density promoters (LCP) and intermediate-CpG-density promoters (ICP), based on CpG ratio, GC content and length of the CpG-rich region.

Sample / Genename	Promoter_Classification	Deaded1	Deaded2	Deaded3	Deaded4	Deaded5	Deaded6	Deaded7	FE1	FE2	FE3	FE4	FE5	Good1	Good2	Good3	Good4	Good5	Good6	Good7	Siwo1	Siwo2	Siwo3	Siwo4	Siwo5	Siwo6	PositiveSampleCount	Chr	Strand	TransStart	TransEnd	Accession
A1BG	LCP					1	1	1					1						1	1			1				7	chr19	-	63556677	63549983	NM_130786
A1CF	ICP					1		1																	1		3	chr10	-	52315441	52236330	NM_138932
A2BP1	HCP									1	1	1										1					4	chr16	+	6009132	7703341	NM_001142333
A2BP1	ICP					1														1	1	1		1		1	6	chr16	+	7322751	7703341	NM_145892
A2M	LCP					1																					1	chr12	-	9159825	9111570	NM_000014
A2ML1	LCP																							1		1	2	chr12	+	8868416	8920644	NM_144670

Table 1. Results of a MeDIP-chip experiment that uncovered genes whose promoters contain methylated CpG islands. *Each gene is listed in the column at left. The promoter type (LCP, ICP, or HCP) is indicated in the column highlighted by the green box.*

DEP (Differential Enrichment Peak) Analysis

When comparing two samples/groups in a MeDIP-chip experiment, enrichment peaks may be insufficient to address slight differences between them. If at a given position enrichment peaks are identified for both samples, an underlying methylation difference could still be present. For the identification of these differentially enriched regions, Arraystar provides DEP analysis. The resulting data profiles from EP and DEP can be visualized using Roche-Nimblegen's SignalMap software (Figure 1).

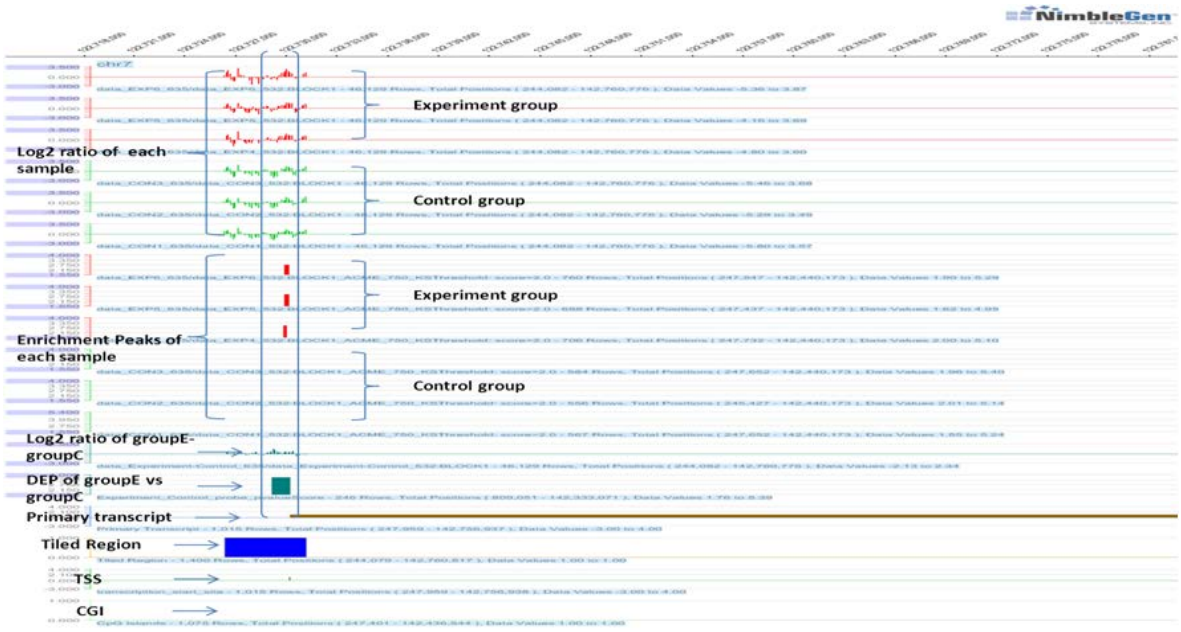

Figure 1. Visualization of the normalized log2-ratios, enrichment peaks (EP) and differential enrichment peaks (DEP) using Roche-Nimblegen's SignalMap software. *Red bars: Enrichment peaks in the Experimental group. Green bar: Differential enrichment peaks between the Experimental and Control groups.*

Identification of Differentially Methylated Regions (DMRS)

DMRs represent regions of the genome that display significant differences in DNA methylation levels among various cell and tissue types, diseases such as cancers, therapeutic treatments, etc. DMRs are associated with diverse regulatory roles and can serve as epigenetic biomarkers for diagnosis, prognosis and treatment options in clinical settings, as well as for drug design. Arraystar's Advanced Data Analysis takes advantage of the most sophisticated analytical methods available for using MeDIP data to identify DMRs. Some examples of DMR results from MeDIP are given in Tables 2.

dmr_information					dmr_attribution					gene_annotation					
dmrID	dmrChr	dmrleft	dmrright	dmrlength	groupA	groupB	dif	pvalue	dmrToTSS	GeneName	chrom	strand	accession	transStart	transEnd
dmr8	chr1	1275014	1275154	140	6.2528	10.1092	3.8564	0.0337	729	DVL1	chr1	-	NM_004421	1274355	1260520
dmr20	chr1	2927522	2927878	356	5.3408	2.6556	-2.6852	0.0255	-205	ACTRT2	chr1	+	NM_080431	2927905	2929327
dmr23	chr1	3596930	3597100	170	4.8440	7.9684	3.1244	0.0061	-80	TP73	chr1	+	NM_001126240	3597095	3640327
dmr29	chr1	9633814	9633964	150	3.4082	1.5927	-1.8155	0.0019	-487	PIK3CD	chr1	+	NM_005026	9634376	9711759
dmr35	chr1	12149254	12149702	448	3.4329	5.7914	2.3585	0.0079	-168	TNFRSF1B	chr1	+	NM_001066	12149646	12191864
dmr41	chr1	16552026	16552388	362	4.3157	1.7462	-2.5695	0.0193	672	FBXO42	chr1	-	NM_018994	16551535	16449145
dmr45	chr1	20179922	20180274	352	3.7627	1.3112	-2.4516	0.0109	579	PLA2G2A	chr1	-	NM_001161728	20179519	20174511
dmr46	chr1	21375798	21376068	270	2.5467	5.2073	2.6605	0.0020	6	EIF4G3	chr1	-	NM_003760	21375927	21005560
dmr47	chr1	21544564	21544720	156	6.5694	9.4194	2.8500	0.0395	21	ECE1	chr1	-	NM_001113348	21544621	21416326
dmr53	chr1	26070126	26070290	164	3.4868	1.6741	-1.8127	0.0292	-123	PAQR7	chr1	-	NM_178422	26070331	26060561
dmr63	chr1	27924694	27925034	340	2.0624	5.1219	3.0595	0.0001	-212	FAM76A	chr1	+	NM_001143915	27925076	27962008
dmr64	chr1	28717434	28717594	160	5.4619	9.8518	4.3899	0.0128	183	RCC1	chr1	+	NM_001269	28717331	28738194
dmr70	chr1	31942658	31942918	260	5.6157	3.1471	-2.4686	0.0017	433	COL16A1	chr1	-	NM_001856	31942355	31890434

Table 2. Differentially Methylated Regions in Promoters. *The columns in the "dmr_attribution" section (rust rectangle) display the differences in methylation status at a given locus between 2 different experimental conditions (represented by "Group A" and "Group B"). You can find detailed information about the DMRs in this table, including coordinates, length, methylation status and annotations of the related genes.*

ChIP-CHIP SERVICE

ChIP-chip combines Chromatin Immunoprecipitation (ChIP) with microarray technology to analyze how regulatory proteins interact with the genome, and provides insight into the mechanisms for histone modification and the regulation of transcription factors. We provide services for all the promoter arrays available from Roche-NimbleGen.

MICROARRAY	SPECIES	ARRAY FORMAT	COVERAGE
HG19 RefSeq Promoter Array	Human	1 * 385K	18,028 promoters: - 2.2kb ~ +0.5kb
MM9 RefSeq Promoter Array	Mouse	1 * 385K	17,354 promoters: 2kb ~ +0.5kb
RN34 RefSeq Promoter Array	Rat	1 * 385K	15,398 promoters: -2.25kb~+0.5kb
HG19 RefSeq Promoter Array	Human	3 * 720K	22,542 promoters: -3.2kb ~ +0.8kb (30,893 transcripts)
MM9 RefSeq Promoter Array	Mouse	3 * 720K	20,404promoters: -3.2kb ~ +0.8kb (22,881transcripts)
RN34 RefSeq Promoter Array	Rat	3 * 720K	15,287 promoters: -4.28kb ~ +1.07kb (15,600 transcripts)
HG19 Deluxe Promoter v2 Array	Human	1 * 2.1M	26,210 promoters: -8kb ~ +3kb 730 miRNA promoters (-15kb to mature miRNA)
MM9 Deluxe Promoter v2 Array	Mouse	1 * 2.1M	24,507 promoters: -8kb ~ +3kb 599 miRNA promoters (-15kb to mature miRNA)

microRNA SEQUENCING SERVICE

Historically, the methods employed for characterizing microRNA (miRNA) have been computational prediction, qPCR, and microarray hybridization. These methods focus primarily on miRNA quantification and are limited to studying miRNA with previous sequence information or secondary stem loop structures. miRNA expression profiling has benefited greatly from recent advances in high-throughput sequencing technology. Direct sequencing offers the potential to detect variation in mature miRNA lengths, as well as enzymatic modifications of miRNAs such as RNA editing and 3' nucleotide additions. This provides a more complete view of the miRNA transcriptome. It also offers an opportunity to identify low-abundance miRNAs or those miRNAs exhibiting modest expression differences between samples, which may be functional, but cannot be detected by hybridization-based methods. Arraystar offers an integrated microRNA sequencing service from library construction to comprehensive data analysis. Our step-by-step quality controls are designed to ensure you get the most reliable results. Just send your samples to us, and we'll do the rest!

HIGHLIGHTS OF ARRAYSTAR'S microRNA SEQUENCING SERVICE

Superior Technology

- Highly accurate base-by-base sequencing eliminates the cross-hybridization that sometimes plagues microarrays
- The expression levels for any microRNA can be quantitatively evaluated by millions of short reads
- The count numbers of individual transcripts are used to measure the abundance of microRNA expression abundance

Comprehensive Coverage

- Compared with microarrays, sequencing does not depend on any prior sequence information, and provides information about all microRNAs within the sample, allowing for the potential discovery of novel microRNAs

Up-to-Date Annotation

- microRNA annotation always refers to the latest miRBase

High Specificity

- Single base resolution allows for the detection of all isomiR and miRNA* sequences
- Capable of discriminating mature microRNA from pre-microRNA

Unparalleled Reproducibility

- microRNA sequencing allows for the detection of low-abundance microRNAs and those with subtle variations, while exhibiting excellent reproducibility

Arraystar microRNA Sequencing Data Analysis

- We use the copy number of the most abundant isomiRs, all isomiRs or the miRBase sequences to quantify microRNA expression levels (Table 1), so that researchers can make the perfect choice to satisfy their individual research needs.

	TagCount_ Most_Abundant_ isomiRs		Fold Change	TagCount_ ALL_ IsomiRs		Fold Change	TagCount_ miRBase_seq		Fold Change
MATURE-ID	CON.	TEST	TEST VS. CON.	CON.	TEST	TEST VS. CON.	CON.	TEST	TEST VS. CON.
hsa-miR-1	11	685	0.0302158	47	1699	0.0333528	11	685	0.0302158
hsa-miR-2	208	10	10.9	257	10	13.35	208	10	10.9
hsa-miR-3	117	71	0.637795	260	123	0.492593	63	26	0.493151

Table 1. Differentially expressed microRNAs

MeDIP-SEQUENCING SERVICE

Whole genome DNA methylation profiling has benefited greatly from recent advances in high throughput DNA sequencing technology. MeDIP-sequencing (Methylated DNA immunoprecipitation in conjunction with high throughput sequencing) allows scientists to create high-resolution DNA methylation profiles on a genome-wide scale. Arraystar offers an integrated MeDIP-Sequencing service from library construction to comprehensive data analysis. Our step-by-step quality controls are designed to ensure you get the most reliable results. Just send us your samples, and we'll do the rest!

HIGHLIGHTS OF ARRAYSTAR'S MeDIP-SEQUENCING SERVICE

Optimized Library Preparation to Achieve High Sensitivity and Reliability

Our optimized library preparation makes it possible to analyze as little as 1 μg or less of starting genomic DNA. Strict quality assessment ensures the construction of high quality MeDIP-sequencing libraries.

Visualization of DNA Methylation Profiles

We provide DNA methylation profiles at 50 bp resolution, which can be visualized in the UCSC Genome Browser. Therefore, any regions of interest (ROIs), can be directly visualized, compared and analyzed (Figure 1, B and C).

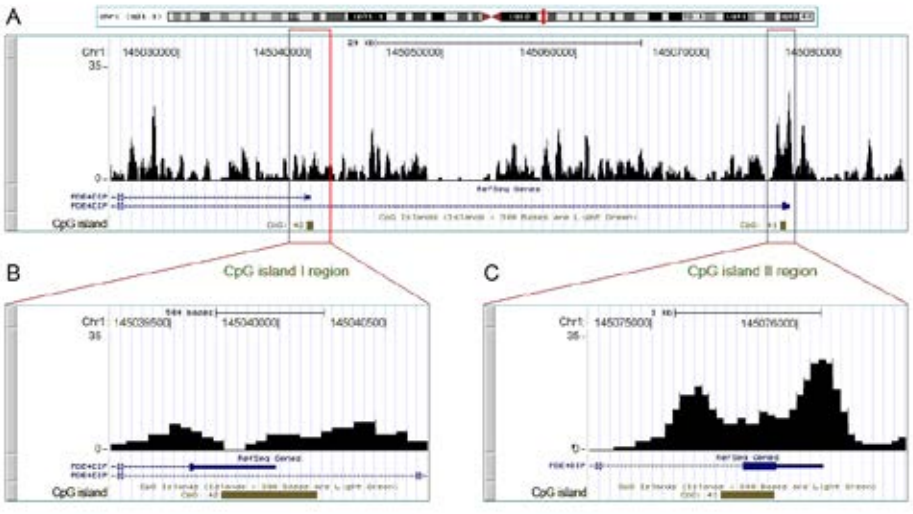

Figure 1. MeDIP-sequencing signals at the PDE4DIP locus. *A. MeDIP peaks at the PDE4DIP locus. B, C. DNA methylation peaks of two CpG islands in this region.*

Digital Quantification of DNA Methylation

To further quantify the DNA methylation level of a specific ROI, we use MeDIP-score (the number of extended reads per kb in the genome; Table 1)

CGI_NAME	CGI_LENGTH (BP)	RAW READ-COUNTS	NORMALIZED READ-COUNTS	MEDIP-SCORE (NORMALIZED READ-COUNTS/KB)	METHYLATION STATUS
chr5:158527374-158527983	609	5	5.733	9.41	Partially methylated
chrX:133680248-133680689	441	15	17.199	39.00	Methylated
chr3:49394855-49395942	1087	1	1.1466	1.05	Unmethylated

Table 1. Digital quantification of CpG island (CGI) methylation. *The methylation level of a specific CGI is represented by its MeDIP-score, which is calculated using the following formula: Normalized Read-counts/CGI_Length * 1000.*

Detailed analysis of the DNA methylation Profiles of Important Genomic Features

Arraystar provides not only whole genome DNA methylation profiles, but also the methylation profiles of specific regions, such as CpG islands (promoter, intragenic, downstream and intergenic CpG islands), promoters (HCP, ICP, LCP), CpG island shores, gene bodies, genomic repetitive regions, CTCFs and enhancers.

ChIP-SEQUENCING SERVICE

ChIP-sequencing (ChIP-Seq) combines chromatin immunoprecipitation (ChIP) with massively parallel DNA sequencing to identify and quantify in vivo protein-DNA interactions on a genome-wide scale. Sequencing ChIP-enriched DNA fragments enables scientists to analyze the interaction patterns of any protein of interest, such as transcription factors (TF), with DNA, or the patterns of any epigenetic chromatin modifications, across the entire genome, quickly and economically. Arraystar offers an integrated ChIP-Seq service from library construction to comprehensive data analysis. Our step-by step-quality controls are designed to ensure you get the most reliable results. Just send us your samples, and we'll do the rest!

RECENT PUBLICATION CITING OUR ChIP-SEQUENCING SERVICE

Jiang, H., *et al*. (2011). Role for Dpy-30 in ES Cell-Fate Specification by Regulation of H3K4 Methylation within Bivalent Domains. *Cell*, **144**, 513-525.

HIGHLIGHTS OF ARRAYSTAR ChIP-SEQUENCING SERVICE

- Genome-wide peak or binding site detection with around 10 million uniquely aligned reads
- Annotation and distribution of protein binding sites in relation to gene annotation (Figure 1)
- Putative TF target detection and functional analysis
- Motif analysis of TF binding sites
- High-resolution visualization of binding profiles within regions of interest (Figure 2)

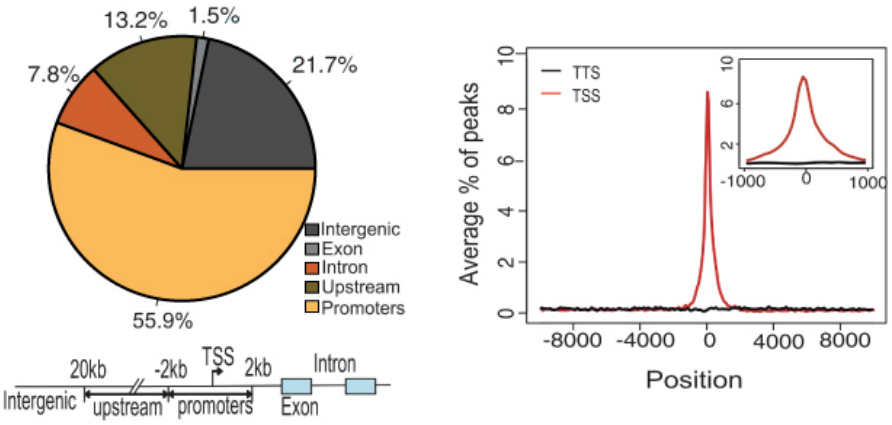

Figure 1. ChIP-peak distribution across five different genomic regions. *Left: Core promoters are defined as occurring within -2kb to +2kb from the transcription start site (TSS). Upstream regions lie within -2 to -20 kb from the TSS, whereas intergenic regions are those not defined as either promoter, upstream, intron or exon. Right: Distribution of TF binding sites occurring within -10kb to +10 kb from the TSS. Inset: Higher resolution of the same peak profile with 1kb of chromosomal DNA flanking either side of the TSS.*

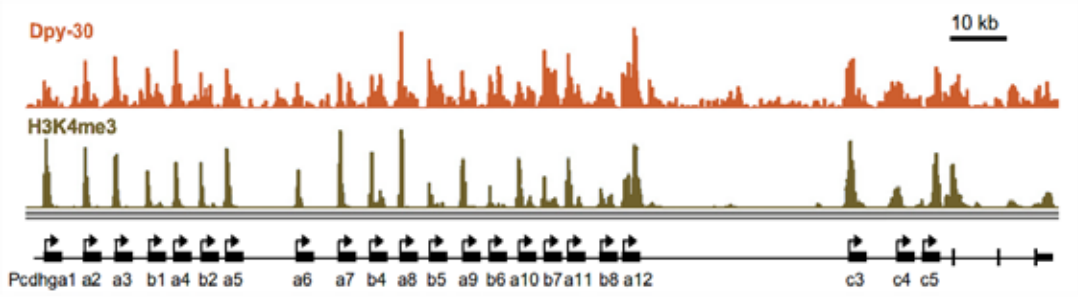

Figure 2. ChIP-Seq signals of Dpy-30 and H3K4me3 visualized together in the UCSC Genome Browser. *Representation of gene loci includes the Pcdhg gene cluster. The visualization of ChIP-Seq binding clearly shows strong genome-wide overlap in both peak distribution and relative heights. (Jiang, H., et al., Cell, 2011. 144,513. Dpy-30 library construction, sequencing and basic data analysis was performed at Arraystar Inc.)*

RNA SEQUENCING SERVICE WITH LncRNA ANALYSIS

RNA sequencing profiles the entire population of both coding and non-coding RNA in any eukaryotic species, and enables mapping and digital quantification of all transcripts, including those that are expressed at extremely low levels. Arraystar offers an integrated RNA Sequencing service, from sequencing library preparation to comprehensive data analysis. Aside from determining differential expression levels among samples, our service also detects alternative splice sites, for both coding as well as long non-coding RNAs, using our proprietary LncRNA database. Our step-by-step quality controls are designed to ensure you get the most reliable results. Just send us your samples, and we'll do the rest!

HIGHLIGHTS OF ARRAYSTAR'S RNA SEQUENCING SERVICE

Complete LncRNA Database
Our unique, proprietary LncRNA database integrates all annotated LncRNAs culled from reliable public data sources, such as NCBI RefSeq, UCSC, RNAdb2.0, H-inviDB5.0 and Fantom3.0, as well as influential LncRNA publications.

Universal Discovery
We use strand-specific library construction to enable the detection of all transcripts without bias.

Digital Readout
Sequencing determines the actual number of each transcript in the library population, and eliminates background noise.

Splicing Event Detection
Researchers can use sequencing data to identify splicing events and discover novel isoforms using junction reads in the library.

Tunable Coverage
Digital sequencing is convenient for researchers to tune coverage depth with specific designs and discover rare transcripts with low reads

High-Quality Results
The high sensitivity and accuracy of digital sequencing allows for the precise, reliable quantification of differential expression between samples.

LncRNA: EXPRESSION AND REGULATION

INTRODUCTION

Long non-coding RNAs (LncRNAs) are evolutionarily conserved, eukaryotic transcripts greater than 200 nucleotides in length that do not generally code for proteins. Increasing evidence suggests that LncRNAs are important regulators of a surprisingly wide variety of biological functions (Mercer, T.R., *et al*.,2009), including epigenetic silencing, transcriptional regulation, RNA processing, and RNA modification[1]. In addition, LncRNAs have been associated with human diseases such as cancers, Alzheimer's disease, and heart disease[2]. Having a better understanding of the functional roles of LncRNAs offers tremendous potential to advance our understanding of cell regulatory and disease mechanisms.

WHAT ARE LONG NON-CODING RNAS?

Abundance and distribution of LncRNA

Most of a typical eukaryotic genome is transcribed into LncRNAs. LncRNA expression is tightly regulated during both the transcriptional and RNA processing stages. LncRNA expression usually occurs at low levels and is often regulated in a tissue-specific manner, or by certain physiological conditions. LncRNAs can also be differentially localized to particular subcellular compartments. Taken together, the expression characteristics of LncRNAs makes it challenging to delineate the mechanisms underlying their transcription and regulation, and to determine their potential functional roles in the biology of an organism[3].

Genomic Organization

It is evident that the vast majority of non-coding RNAs overlap with, or are transcribed antisense to, protein-coding genes. LncRNA genes are also expressed in either intergenic or intronic regions of the genome. The genomic organization of LncRNAs relative to that of protein-coding genes can be grouped into five major classes (Figure 1).

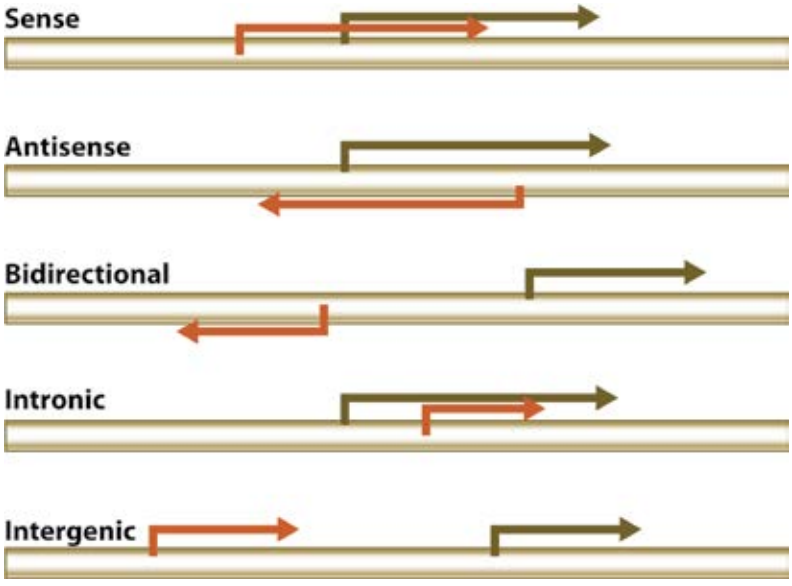

Figure 1. Genomic relationships between LncRNAs and protein coding genes.

Evolution and Conservation

In contrast to microRNAs, LncRNAs generally lack strong evolutionary conservation. Many well-described LncRNAs, such as AIR and Xist, are poorly conserved. LncRNA sequences may be more plastic than protein coding genes and thus can evolve rapidly. However, LncRNA promoter sequences are often very well conserved[4]. More recently, it has been reported that some large intergenic non-coding RNAs (lincRNAs) are evolutionarily conserved [5].

Cellular Localization

The tissue-specific expression patterns of many LncRNAs seen in development, and the distinct subcellular localization of LncRNAs, strongly suggest that their expression is under precise control. Although some LncRNAs have been reported to be transcribed by RNA polymerase III, the majority are transcribed by RNA polymerase II. In contrast to most mRNAs, which ultimately localize to the cytoplasm after processing, most LncRNAs remain in the nucleus[6]. Some LncRNAs are, however, exported to the cytoplasm[7]. The biological significance of cytoplasm-localized LncRNAs is currently not well-understood.

Regulation of LncRNA Expression

Recently, increased attention has been focused on the transcriptional regulation of the LncRNA genes themselves. LncRNAs are transcribed by RNA polymerase II, and most of them have the hallmarks typical of Pol II-transcribed gene products: 7-methylguanosine capping and polyadenylation. Many LncRNAs are expressed in tissue- and/or developmental specific patterns, suggesting that transcription of LncRNA genes must be under tight control [8]. As is typical for RNA polymerase II-transcribed protein-coding genes, LncRNA gene expression can be regulated by several different mechanisms (Figure 2).

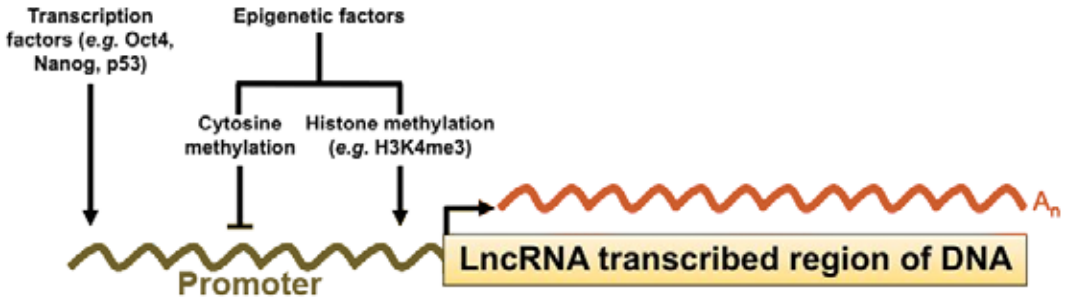

Figure 2. LncRNA expression can be regulated by transcription and epigenetic factors. *Green coiled line represents an LncRNA promoter. Rust coiled line represents an RNA polymerase II-transcribed, polyadenylated LncRNA (although not all LncRNA transcripts are polyadenylated). Bent arrow indicates direction of transcription. LncRNA transcription has been shown to be positively regulated by several well-characterized transcription factors (such as Oct4, Nanog, and p53). Epigenetic factors can have opposing effects on lncRNA transcription. Cytosine methylation (such as at CpG islands) can repress LncRNA expression, whereas methylation of lysine residues on histones (such as trimethylation of lysine 4 on histone H3) can activate LncRNA transcription.*

WHY DO WE STUDY LncRNAs?

Recent findings suggesting that LncRNAs function in various aspects of cell biology have increased awareness for their potential to contribute to disease. Many association studies have identified LncRNAs that are aberrantly expressed in several diseases, especially cancer.

Linking LncRNA and Cancer

The overexpression of some LncRNAs has also been found to be a good marker for several human tumors. Colon carcinoma cells show significantly higher levels of OCC-1 gene transcripts[9]. In prostatic tumors, two LncRNA genes, PCA3 and PCGEM1, are significantly overexpressed compared with normal tissue[10]. The expression of the LncRNA MALAT1 correlates with tumor development, progression and survival in lung, liver and breast cancer[11]. More recently, the highly conserved mouse ortholog of MALAT1 was found to be highly expressed in hepatocellular carcinoma[12]. The expression of another LncRNA, HOTAIR, is increased in primary breast tumors and metastasis, and HOTAIR expression levels in primary tumors is a powerful predictor of eventual metastasis and death. Moreover, enforced expression of HOTAIR in epithelial cancer cells induced genome-wide re-targeting of PRC2 to an occupancy pattern[13].

LncRNA and Other Diseases

In addition to cancer, LncRNAs also exhibit aberrant expression in other diseases, such as heart disease, psoriasis, and Alzheimer's disease. Recently, it has been demonstrated that overexpression of an LncRNA, PRINS, is associated with psoriasis susceptibility[14]. An antisense LncRNA, BACEAS, which regulates the expression of the sense BACE1 gene, a crucial enzyme in Alzheimer's disease etiology, is overexpressed in several regions of the brain in individuals with Alzheimer's disease (Figure 3). Since alteration of BACE1AS expression may also mediate epigenetic changes, which modulate gene expression and contribute to disease etiology, this LncRNA could serve as an attractive drug target candidate for Alzheimer's disease[15].

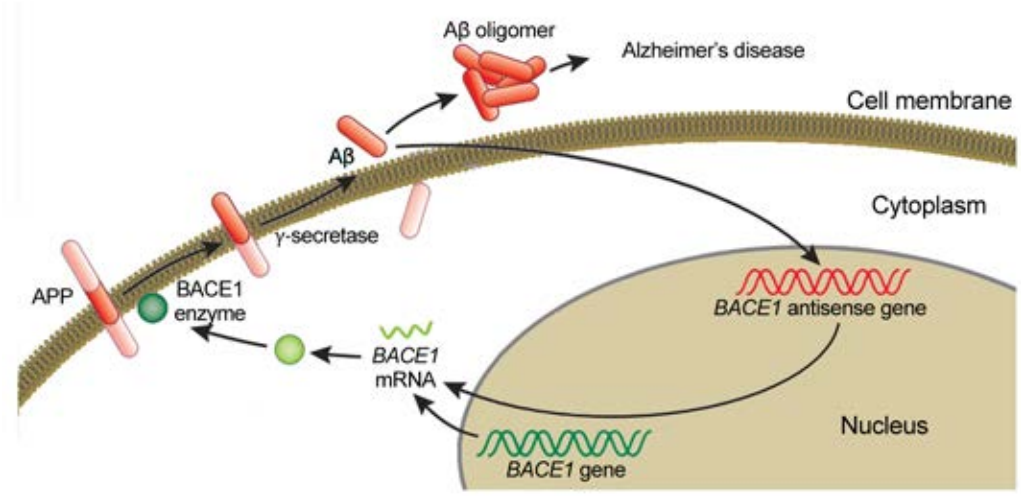

Figure 3. BACEAS promotes Alzheimer's disease progression.

HOW DO WE STUDY LncRNAs?

Arraystar offers two ground-breaking services that have made us the industry leader in LncRNA research: The Arraystar LncRNA Expression and Promoter microarray services.

Our LncRNA arrays let you profile the expression of both LncRNAs and mRNAs together on a single chip. Not only will you uncover the differentially expressed LncRNAs and mRNAs, but also the physical, and potentially the functional, relationships between them. Our LncRNA promoter array is the first commercially available microarray that allows you to profile protein binding or methylation sites at gene promoters for both LncRNAs and mRNAs. Using our LncRNA expression and promoter arrays in tandem will help you find the important mechanisms influencing these expression level changes.

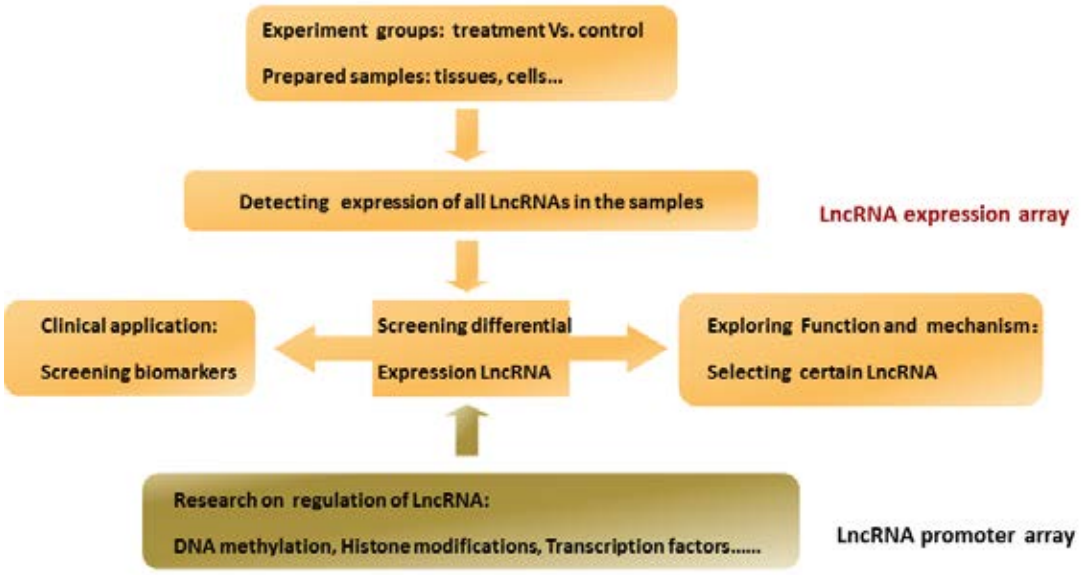

Figure 4. Strategies for studying LncRNAs.

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THE BIOGENESIS AND FUNCTION OF piRNAs

INTRODUCTION

Piwi-interacting RNAs (piRNAs) are a class of small, germline-specific, non-coding RNAs that interact with the Piwi (P-element Induced Wimpy Testis) subfamily of proteins. The Piwi subfamily consists of Piwi, Aubergine and AGO3 in flies, MILI, MIWI and MIWI2 in mice, and HILI, HIWI1, HIWI2 and HIWI3 in humans [1]. Although the biogenesis and function of piRNAs are not well understood, it is likely that piRNAs play a key role in germ line development.

Mature piRNAs are short, single-stranded RNA molecules approximately 26-32 nucleotides in length. Mouse testis contains more than 50,000 distinct piRNA molecules [2], about 1-2 orders of magnitude more than the number of known miRNAs. Individual piRNAs are poorly conserved throughout evolution, and are strikingly different from microRNAs in their length, expression patterns, and genomic organization.

BIOGENESIS OF piRNAs

Unlike siRNAs and miRNAs, piRNAs are not generated from dsRNA precursors. Rather, piRNAs are likely produced from a primary transcript that traverses an entire piRNA cluster and subsequently processed into mature piRNAs. The mechanism of this process is not well understood. However, evidence from flies demonstrates that the first 10 nucleotides of piRNAs bound to Aub or Piwi, which typically begin with uridine, are often complementary to the first 10 nucleotides of piRNAs bound to Ago3, and usually contain an adenosine at position 10. These observations led to the proposal of the "ping-pong" model, in which new piRNAs are generated by amplification mediated by this complementarity [3].

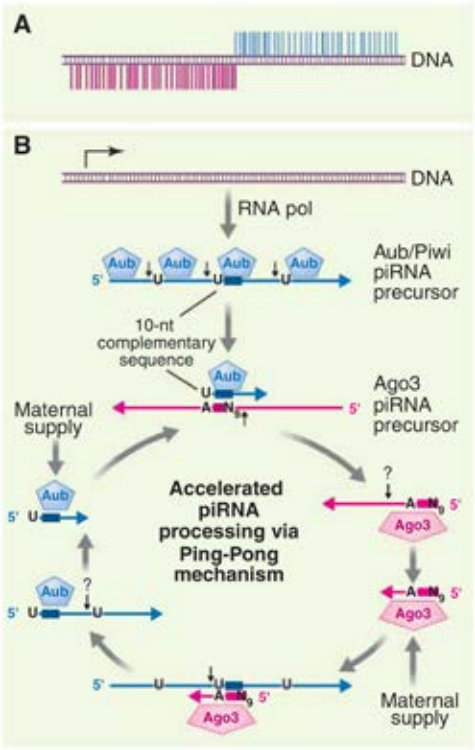

Figure 1. The "ping-pong" model for piRNA biogenesis. *Complementarity between piRNA sequences causes amplification of new piRNA molecules [3].*

FUNCTION OF piRNAs

Mammalian piRNAs can be divided into two classes, pre-pachytene and pachytene, depending on the stage of meiosis in which they are expressed during spermatogenesis [2]. piRNAs may have distinct functions according to their sequence features [1].

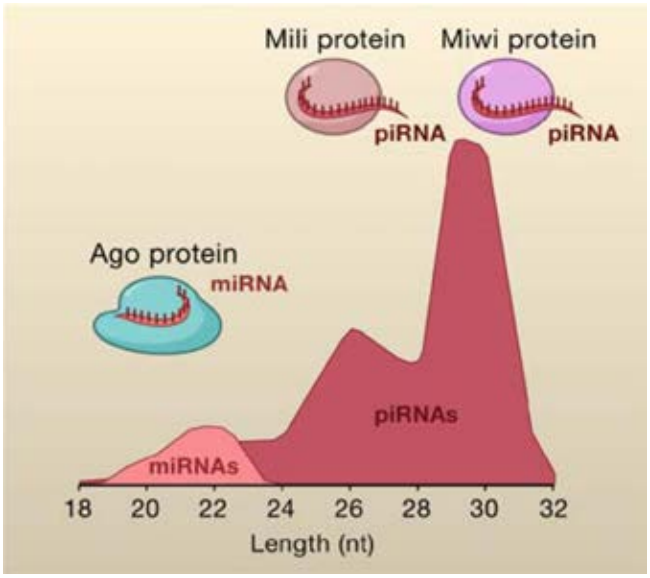

Figure 2. piRNAs in mouse, associated with Piwi proteins such as Mili and Miwi, can be divided into two classes with divergent functions[4].

Numerous lines of evidence indicate that piRNAs have indispensable roles in spermatogenesis.

- Involvement in spermatocyte development: Complete loss of Miwi and Mili causes meiotic arrest during spermatogenesis, leading to seminiferous tubules devoid of sperm.
- Regulation of translation: Miwi and piRNAs associate with the cap binding complex and modulate mRNA stability during the production of proteins required for spermatogenesis [5].
- Preservation of genomic integrity: Mili-and Miwi-2 null mice have increased activity of retro-transposons, suggesting that piRNAs protect the germline genome from deleterious transposon insertions [6].

PERSPECTIVE

Although piRNAs have been discovered in multiple species in recent years, we still do not know how a new piRNA response is initiated, and the exact function of piRNAs in development remains elusive. There are many open questions in the piRNA field ripe for further study. Due to the large number of piRNAs, characterization of individual piRNAs is more challenging than that of single miRNAs. However, the refinement of microarray and high-throughput sequencing techniques will enable researchers to learn much more about the biological roles of individual piRNAs in the near future.

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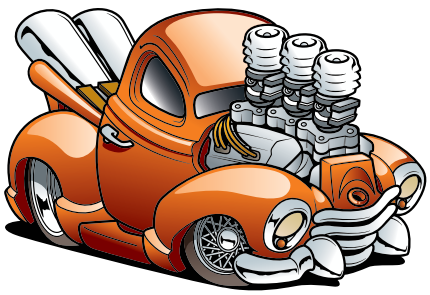

RECENT PUBLICATIONS CITING ARRAYSTAR'S SERVICES

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Stroke **42**, 1105-1109

Braconi, C., *et al.*,
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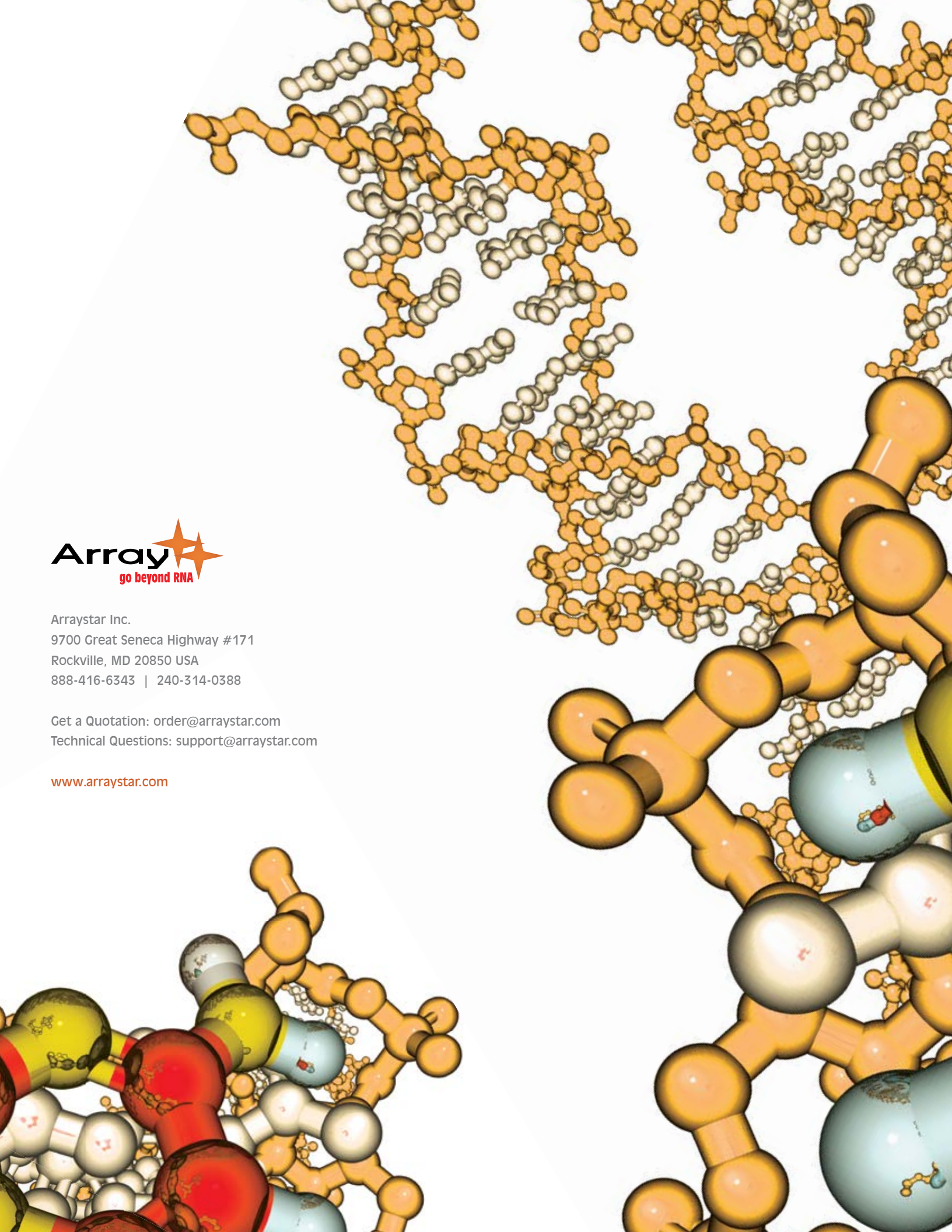
4750-4756



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