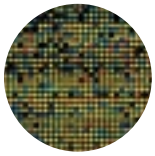
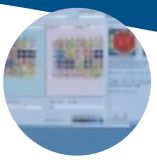

Advanced Solutions

FOR GENOMIC RESEARCH

ORDER ONLINE: **WWW.INCYTE.COM**

- **Take your research to the next level with our fully optimized BAC system**
- **Save time and money—let Incyte Genomics do the work**

NEW!

GEM™ MICROARRAY SERVICES

Detailed differential expression data from RNA samples you provide. Each GEM™ dual-channel microarray contains thousands of clones from sequence-verified Incyte Genomics libraries. Choose from human, mouse, or *Arabidopsis.*

(Clones also available.)

NEW!

GEMTOOLS™ DESKTOP SOFTWARE

Perform sophisticated expression analysis of GEM™ microarray data from your own computer.

CLONE RESOURCES

Clones and clone sets from proprietary and publicly available libraries (genomic and cDNA). Choose from human, mouse, rat, *Arabidopsis,* maize, soybean, and more.

(See our full library list on-line.)

ROBOTICS

With the largest commercial genomic automation facility in the country, we offer superior service and fast turnaround for all your picking, spotting, and re-racking needs.

PLASTICS

The highest-quality 384-well plates, 384- and 96-pin replicators, and culture trays specially designed for automated robotics systems.

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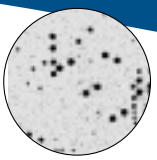

Advanced Solutions

NEW!

LIFEGRID™ ARRAYS AND REAGENT KIT

Complete kits for generating expression data in your own lab. Each high-density LifeGrid™ array contains thousands of clones from sequence-verified Incyte Genomics libraries. Choose from human, mouse, or *Arabidopsis.*

(Clones also available.)

GENE SCREENING

Identify target clones with our custom cDNA and genomic screening services (PCR or high-density nylon filter). Or use our genomic screening kits to identify target clones in your own lab (PCR pools or high-density nylon filters).

SEQUENCING AND ANALYSIS

Customized sequencing, bioinformatics, subcloning, and FISH analysis services.

MOUSE KNOCKOUTS

Full-service, custom-designed mouse knockout programs. We also offer gene expression and morphological analysis services, ES and MEF cells, and isolated RNA and DNA.

Find out more! And see our new, easier on-line ordering system at www.incyte.com. Or call toll-free in the United States 800.430.0030. International callers, dial +1 314.427.3222

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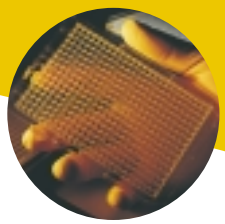

High-Quality Plastics

FOR AUTOMATED SYSTEMS

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Incyte Genomics understands that research relying on automated systems requires the highest-quality products. Our plastics have been specially designed for robotic picking, gridding, and arraying. With more gridding robots than any other commercial facility, we know the technology, functionality, and precision that you need in every component of your research. We've used that knowledge to improve existing designs for plastic disposable replicators, 384-well plates, and culture trays.

HIGH-THROUGHPUT PLASTIC PLATES, REPLICATORS, AND TRAYS

Volume discounts are available for all of our plastic products.
Please inquire for details.

384-WELL PLATES

Our 384-well plates have lids designed for automated stacking and round wells that reduce cross-contamination.

96-AND 384-PIN REPLICATORS

Our replicators virtually eliminate cross-contamination. They are ideal for manual and automated copying of 96- or 384-well plates, with accessories available to ensure accurate alignment for multiple plate copying.

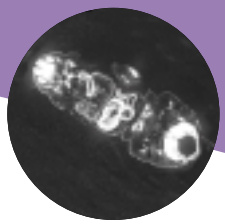
96-PIN LONG REPLICATORS

Our long-pin replicators are ideal for manual and automated copying of deep 96-well blocks.

CULTURE TRAYS

Our culture trays are designed with a low profile for high-speed, automated picking, and have square corners to allow for easier placement of membranes.

Service/Product	Catalog No.
384-Well Plates	ATD-3000
384-Pin Replicators	ATD-6000
96-Pin Standard Replicators	ATD-4000
96-Pin Long Replicators	ATD-5000
Culture Trays	ATD-7000



Localize Gene Expression

Custom ISH Service

IN SITU HYBRIDIZATION SERVICE

ORDER ONLINE: **WWW.INCYTE.COM**

- **Complete Custom *In Situ* Hybridization Services**
- **Expert Results, Publication Ready**

Incyte Genomics provides the highest-quality ISH service and interpretation of results. *In situ* hybridization is recognized as the premiere method to directly assay gene expression by localizing expression to specific tissues and cells. Our standard service analyzes gene expression at three stages of murine embryonic development.

OUR METHODS

You provide the plasmid containing your probe and we prepare the template and S^{35} label the probes. Our standard experiment consists of control, sense, and antisense probes hybridized against sagittal sections of day 9, day 12, and day 15 C57BL/6 embryos. Each time point and probe is run in duplicate for a total of 18 slides, 6-slides/time point.

You receive the sectioned, probed specimen, a written report describing the protocol used for each probe, and labeled photographs in hard copy and digital format.

Standard turnaround time is approximately 2 months. Our ISH service is fully customizable. We will work with you to design the most appropriate experiment to answer your gene expression questions. You may work from our tissue bank or submit your own sample for sectioning and analysis. Inquire for details.

Service	Catalog No.
Standard ISH -Sagittal sections -3 stages (d9, d12, d15) -6 slides/stage, multiple exposure times	# MK-3010
Custom Tissue Preparation	# MK-3020
Extensive Interpretation of ISH results -Full written report provided	# MK-3030
Extensive photographic documentation	# MK-3040
Custom ISH	# MK-3000

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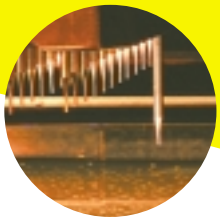
The World's Most Complete View of the Human Genome

RELATED SERVICES

We also offer Fluorene *In Situ* Hybridization services and GEM™ Gene Expression Microarrays. Inquire for details.



Plant BAC Libraries

ORDER ONLINE: **WWW.INCYTE.COM**

- **Use one of our quality plant libraries to facilitate your genomic research**
- **Libraries are available on high-density filters for in-house screening or purchase**

To create our high-quality plant libraries, we ligated large-size fractionated partial *Hin*d III fragments into the *Hin*d III site of the pBeloBACII vector, then subsequently electroporated the fragments into DH10B cells.

MAIZE LIBRARY
Source: Protoplasts
Strain: B73
Average Insert Size: 113 kb
Genomic Coverage: 12X
Number of Clones: 269,568
Creator: Incyte Genomics

CHLAMYDOMONAS LIBRARY
Source: Whole cell
Strain: CW92
Average Insert Size: 60 kb
Genomic Coverage: 10X
Number of Clones: 15,360
Creator: University of MN, St. Paul

ARABIDOPSIS LIBRARY – RELEASE I
Source: 4-6 week-old whole plant
Strain: Columbia
Average Insert Size: 187.5 kb
Genomic Coverage: 12.2X
Number of Clones: 6,528
Creator: California Institute of Technology

SOYBEAN LIBRARY
Source: 2-3 week-old seedlings from leaf materials
Strain: Williams 182
Average Insert Size: 114 kb
Genomic Coverage: 9X
Number of Clones: 92,160
Creator: Incyte Genomics

To find out more about these plant libraries, please contact Technical Support at **(800) 430-0030.**

(CONTINUED)

Plant BAC Libraries

NOW AVAILABLE

CUSTOM BAC LIBRARY CONSTRUCTION

Let Incyte Genomics construct your custom, large-insert libraries using the bacterial artificial chromosome (BAC) system.

Simply send us your plant, bacterial, or mammalian DNA source, and we'll provide you with a quality, high-molecular weight BAC library.

CUSTOMIZE YOUR RESEARCH

A custom BAC library allows you to take your research to the next level.

- Grid BAC clones on nylon arrays for screening by hybridization
- Grid BAC DNA on microarrays for comparative genome hybridization (CGH) and genome mismatch scanning (GMS) experiments
- Generate pools of DNA for PCR screening
- Sequence individual BAC clones to determine gene structure
- Use probes derived from BAC clones in FISH experiments
- Fingerprint an entire library for genome mapping
- End-sequence an entire library for genome projects

OTHER SERVICES

Using your custom BAC library, Incyte Genomics can provide the following services and products:

- Easy-To-Screen™ High-Density Filters
- Easy-To-Screen™ DNA Pools
- Custom screening projects
- Custom sequencing projects (whole inserts, BAC ends, etc.)
- Genome Mapping

Contact a Customer Service representative at www.incyte.com or at (800) 430-0030 to inquire about a custom BAC library.

Subcloning Services

LET OUR EXPERTS WORK FOR YOU

ORDER ONLINE: **WWW.INCYTE.COM**

REDUCE 100 KB GENOMIC INSERT TO A WORKABLE SIZE.

A simple, fast, and cost-effective way to reduce 100+ Kb BAC, PAC, and P1 positive clones into workable insert size clones.

Trained specialists who have years of experience in working with BAC, PAC, and P1 clones staff our world class cloning facility. We can quickly and efficiently isolate the clone you need to facilitate your research. Using Incyte Genomics' expertise will save you time, money, and resources, allowing you to focus your time and efforts on the part of the genome in which you are most keenly interested.

GENOMIC SUBCLONING

Our complete genomic subcloning service starts with a high-purity plasmid preparation of your clone. We work with your purified plasmid, or we will perform plasmid purification for your BAC, PAC, or P1 clones. We digest the sample individually with your choice of up to three of the following enzymes: *Bam*H I, *Eco*R I, *Hin*d III, *Kpn* I (Acc65i), *Pst* I, *Sac* I, *Xba* I,or *Xho* I. Once the digest is complete, we subclone the resulting fragments into the pZERO-2 vector from Invitrogen. The maximum insert size is up to 12 kb. The positive clone(s) will be identified using a probe which you provide, and then arrayed in a 96-well plate containing both positive and randomly selected subclones. At least one positive clone is guaranteed for this service. We will provide the 96-well plate to you for analysis. The entire process takes approximately 10 days.

SERVICE DESCRIPTION

BAC, PAC, or P1 DNA Preparation for Subcloning with PCR Confirmation

Incyte Genomics will provide you with a DNA prep of your clone. The prep and glycerol stock will be confirmed by PCR using the same primer pairs used in library screening.

BAC, PAC or P1 DNA Preparation for Subcloning with Hybridization Confirmation

We will provide you with a DNA prep of your clone. The prep and glycerol stock will be confirmed by hybridization using the same probe in library screening.

(CONTINUED)

Subcloning Services

SERVICE DESCRIPTION *(continued)*

Southern Analysis

We will provide you with southern analysis data on restriction fragment sizes of BAC, PAC, or P1 clones with eight different enzymes as follows: *Bam*H I, *Eco*R I, *Hin*d III, *Kpn* I (Acc65i), *Pst* I, *Sac* I, *Xba* I, and *Xho* I. The results from this service will help you choose the most appropriate size fragment for subcloning.

Nylon Filter of Subclones

We will provide you with an unprobed nylon filter that has been stamped with 96 BAC, PAC, or P1 subclones. The filter is denatured and cross-linked before being shipped.

Additional 96-Well Plate

We will provide you with 96 additional clones.

Service/Product	Catalog No.
HBAC, PAC, OR P1 DNA Preparation for Subcloning with PCR Confirmation	CL-0525
BAC, PAC, OR P1 DNA Preparation for Subcloning with Hybridization Confirmation	CL-0526
Southern Analysis	CL-0524
Nylon filter of Subclone	CL-0522
Additional 96-Well plate	CL-0523

RELATED SERVICES

We offer a full range of related services to further analyze your clones, including Genomic and cDNA sequencing, Genomic Mapping, Genomic and cDNA Screening, and Fluorescent *In Situ* Hybridization (FISH) Services. Custom services are always available in these and related areas.

For more information regarding subcloning, please visit our web site at www.incyte.com, or contact one of our Customer Service representatives at 800-430-0030 or 314-427-3222, or via e-mail at help@incyte.com.

NEW!

Easy-to-Spot™ Drosophila ORF PCR Primer Set

NOW IT'S EASIER THAN EVER TO PRODUCE A DROSOPHILA MICROARRAY WITH OVER 14,000 GENE ELEMENTS

WWW.INCYTE.COM/BIOREAGENTS

Incyte's Easy-to-Spot Drosophila ORF PCR Primer Set offers you:

- **Pre-assembled PCR primer pairs to amplify unique ORF from over 14,000 Drosophila genes**
- **Primer design optimized for generating useful array elements**
- **Proven amplification success rate of greater than 90%**
- **Internal controls to monitor amplification and microarray fabrication processes**
- **PCR products evaluated in microarray experiments**

Incyte now provides access to PCR primers for open reading frames (ORF) representing the *Drosophila melanogaster* genome. Using genomic sequence information from the Berkeley Drosophila Genome Project (BDGP), Incyte selected 14,151 PCR primer pairs to amplify unique open reading frames from the Drosophila genome. The amplified DNA can be spotted for microarray fabrication.

GENE SPECIFIC PRIMER DESIGN

For primer design, Incyte targeted Drosophila genes defined in the GenBank release of March 24, 2000. We selected one exon from each gene and designed primers with the following parameters:

- No intronic sequence allowed
- 58 – 68°C melting temperature
- 100 – 600bp amplicons (40% between 450 – 600bp)
- No significant sequence identity among 11,525 of the genes (<70% identity over 100bp)

QUALITY CONTROL

Incyte tested the Drosophila primer pairs by amplifying genomic DNA. We carefully checked the resulting amplicons for multiple bands, incorrect fragment size, and low product yield (< 20ng/µl by Pico Green analysis). Primer pairs that failed these initial amplification specifications were redesigned and have also been incorporated into the set, resulting in a total success rate of greater than 90%. Primer purity and quality is further assured by random assessments using mass spectrophotometry.

INTERNAL CONTROLS

We have added 471 "barcode elements" to each Easy-to-Spot PCR Primer Set as internal plate controls. Every 96-well plate contains 3 of these "barcode elements" that can be used during the amplification process to monitor plate orientation and gel mobility. The controls also serve to verify position of each array element post-array fabrication and hybridization. The primer pair used to generate the barcode elements amplifies intronic sequence and will not compete for sample cDNA in a standard expression hybridization experiment.

(CONTINUED)

Easy-to-Spot™ Drosophila ORF PCR Primer Set

DELIVERABLES

The Drosophila Easy-to-Spot PCR Primer Set is provided in single reaction aliquots in 96-well plate format. Both primers from each pair are resuspended in HPLC water in one individual well. Each well contains 180pmol of the primer mix. The following information for each open reading frame is also supplied:

- Gene ID
- Gene name
- Exon size and sequence
- PCR fragment size
- Plate and well location
- Suggested amplification reaction conditions*
- Incyte's amplication reaction pass/fail data

* Incyte will provide the protocols used to achieve a 93% success rate with an average yield of 3µg. However, Incyte does not guarantee customers will have the same result. This is an amount generally sufficient to produce hundreds to thousands of microarrays (depending on instrumentation and protocols).

Easy-to-Spot Drosophila ORF PCR Primer Set (15,086 primer pairs)	Catalog No.	Price
1 reaction set	ETS-2001	$11,000
2 reaction set	ETS-2002	$21,500
3 reaction set	ETS-2003	$32,000
4 reaction set	ETS-2004	$42,500
5 reaction set	ETS-2005	$52,000
6 reaction set	ETS-2006	$60,000

Consult your Incyte Account Manager or distributor for a customized solution to meet your needs.

FIND OUT MORE!

To learn more about how your research can benefit from using our Easy-to-Spot Drosophila PCR Primer Set, call **1-800-430-0030** today.

INCYTE GENOMICS IS AN AUTHORIZED DISTRIBUTOR OF BERKELEY DROSOPHILA CLONES AND CLONE SETS.
WWW.INCYTE.COM/BIOREAGENTS

IF YOU ARE INTERESTED IN A DROSOPHILA MICROARRAY CHIP, PLEASE INQUIRE WITH INCYTE.

Incyte Custom Sequencing™

PUT THE WORLD'S LEADING SEQUENCING AND BIOINFORMATICS COMPANY TO WORK FOR YOU

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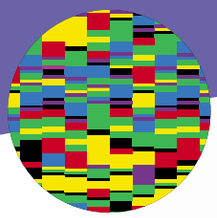
For Life.



Incyte Custom Sequencing

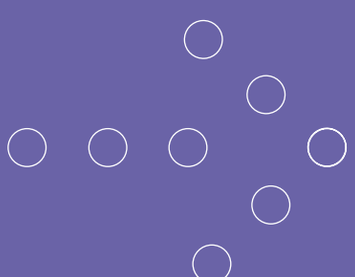
A COMPLETE GENOMIC SOLUTION FOR ALL OF YOUR RESEARCH NEEDS

As the pioneer of the genomics world, Incyte has set the industry standard for high-quality, high-throughput sequencing and bioinformatics. Incyte Custom Sequencing is a service that leverages several of Incyte's core competencies including library screening, library construction, sequencing and bioinformatics to generate valuable sequence and bioinformatics data for customers. By letting us provide you with the genomic services that you require, you will save time, resources and money, AND you will also have the ability to focus on your larger research objectives.

Incyte can start your project at a variety of different points. Whether your starting material is tissue, cells, RNA, DNA, clones, plaques, or ligation, Incyte can expedite the completion of your project and deliver high-quality data to you.

PROVEN ADVANTAGES

- **Intellectual Property** — Incyte performs the service, you own the data.
- **Expertise** — Incyte has sequenced tens of millions of samples of DNA, has extensive experience in library construction and offers world class bioinformatics.
- **High volume & fast turnaround** — Incyte's world class sequencing operation specializes in completing projects of 1,000 to 1,000,000 reads or more with unmatched turnaround time.
- **Project Management** — A project manager is assigned to each project to oversee all steps from sample receipt through final data delivery. Your project manager is available to answer any questions you may have about any aspect of your project.
- **Proven track record** — Incyte continues to work with the world's top pharmaceutical companies and has current sequencing contracts with academia, biotechnology, and pharmaceutical companies.
- **Demonstrated competency with a multitude of templates and organisms** — Incyte has the ability to work with cDNA and genomic templates. We have successfully sequenced many types of vertebrates, plants and micro-organisms.



PALO ALTO & FREMONT, CALIFORNIA
Incyte Genomics, Inc.
3160 Porter Drive
Palo Alto, California 94304
Telephone 650-855-0555
Toll Free Telephone 877-264-0858
Fax 650-855-0762

Incyte Genomics, Inc.
6519 Dumbarton Circle
Fremont, California 94555
Telephone 510-739-2100
Fax 510-739-2200

ST. LOUIS, MISSOURI
Incyte Genomics, Inc.
4678 World Parkway Circle
St.Louis, Missouri 63134
Telephone 314-427-3222
Toll Free Telephone 800-430-0030
Fax 314-427-3324

Incyte Genomics, Inc.
8620 Pennell Drive
St. Louis, Missouri 63114
Toll Free Telephone 800-430-0030
Fax 314-592-8200

CAMBRIDGE, UNITED KINGDOM
Incyte Genomics Ltd
Botanic House
100 Hills Road
Cambridge CB2 1FF
United Kingdom
Telephone +44 (0) 1223 454 900
Fax +44 (0) 1223 454 999

Incyte Genomics Ltd
214 Cambridge Science Park
Milton Road
Cambridge CB4 0WA
United Kingdom
Telephone +44 (0) 1223 424 877
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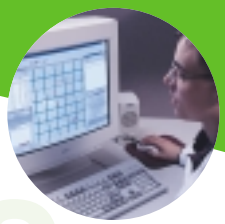


LifeGrid™ Arrays

HIGH-DENSITY ARRAYS AND REAGENT KIT

ORDER ONLINE: **WWW.INCYTE.COM**

- **Complete do-it-yourself expression kit, including arrays, labeling components, and hybridization solution**
- **A cost-effective alternative to most microarrays**
- **Approximately twice as many genes as competing products**
- **High sensitivity and reproducibility**

Get the most out of your gene expression experiments using the LifeGrid™ 1.0 array kit!

Incyte Genomics has combined its PCR-amplified DNA and filters with Ambion's labeling and hybridization reagents to create a unique, do-it-yourself screening kit. Now you can study gene expression in parallel for thousands of genes verified[1] by Incyte—all for less than the cost of most microarray systems.

ENDLESS POSSIBILITIES!

Using simple hybridization techniques, you can use ^{33}P-labeled probes prepared from your mRNA to identify expressed genes. By using multiple filters, you can hybridize probes from a time-course experiment, or from a set of normal and diseased samples to quickly identify differentially regulated genes for further study. Using Incyte Genomics' sequence and annotation data for these clones, you can decide which genes to follow for further study. Additionally, with thousands of data points resulting from each hybridization, LifeGrid™ arrays can be used to study known genes and pathways, identify novel targets, validate targets, and study the efficacy and toxicity of various compounds.

HUMAN LIFEGRID™ 1.0

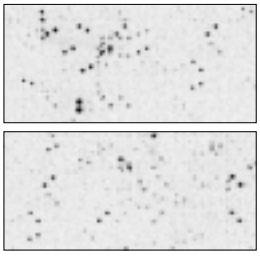
Our Human LifeGrid 1.0 kit consists of two identical 22 x 12 cm nylon filters, each spotted with more than 8,400[2] human PCR products, and all the reagents[3] needed to perform the experiment. These arrays are based on Incyte's cDNA clones representing unique human genes as defined in NCBI's UniGene database (http:www.ncbi.nlm-nih.gov/unigene).

GENE AND CLONE SELECTION

Clones used on LifeGrid™ arrays were mapped to the UniGene database via BLAST and additional alignment analysis of the sequences. Based on the results, the 5′-most representative clone was selected from Incyte's LifeSeq® reagent set.

(CONTINUED)

LifeGrid™ Arrays



Each array element is double-spotted to reduce false positives and increase result confidence.

ANALYSIS

After you've performed your gene expression experiment, Incyte Genomics can provide in-house analysis of your LifeGrid™ filters. Simply send us your data files from a Phosphorimager®, and we'll supply you with the following information:

- Element intensity
- Differential expression ratio
- Plate and well position
- Annotation
- A representative GenBank accession link (where applicable)
- Sequence
- Vector information

AVAILABLE SEQUENCE-VERIFIED CLONES

For additional *in vitro* research, each clone used on LifeGrid arrays is available from Incyte Genomics as a sequence-verified reagent. Clone sequence information is also available at www.incyte.com.

COMING SOON!

Mouse and Arabidopsis LifeGrid.™

For more information about LifeGrid™ 1.0, visit our web site at www.incyte.com/lifegrid, or contact one of our Customer Service representatives. Dial 800-430-0030 in the United States, or + 1 314-427-3222 international.

1. All clones come from sequence-verified libraries. During manufacturing, clones are rearranged and resequenced to reconfirm each clone's identity.
2. Number of elements may vary depending on amplification rates.
3. Customer must supply radiolabel.

LifeGrid™ Bioreagents	Catalog No.
Human 1.0 High-Density Arrays and Reagent Kit	LG-1603
Human 1.0 High-Density Arrays - 2 filters	LG-1604
Human 1.0 High-Density Array - 1 filter	LG-1605
Reagent Kit	LG-1606
Clones	LG-1621
LifeGrid™ Services	**Catalog No.**
Filter Analysis - 2 filters	LG-1607
Filter Analysis - 1 filter	LG-1608

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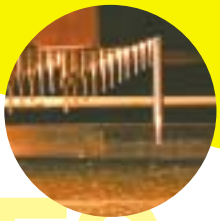
The World's Most Complete View of the Human Genome

Reagent Kit Manufactured for Incyte Genomics by Ambion® THE RNA COMPANY™



Robotic Services

ROBOTIC SERVICES

THE FASTEST, HIGHEST-QUALITY COLONY PICKING, SPOTTING, AND CLONE RE-RACKING SERVICES AVAILABLE.

ORDER ONLINE: **WWW.INCYTE.COM**

- **Rapid turnaround with accurate results**
- **Affordable services**
- **Customized to suit your needs**

With the largest number of gridding and picking robots in North America, Incyte Genomics provides the fastest, highest-quality robotic services available in the industry. Our automation expertise and high-speed robotic equipment allow us to tailor each project to your research needs. Our high-volume picking services provide fast results, while our spotting services allow you to custom design spotting patterns to suit your individual needs. High-throughput clone re-racking quickly provides you with your clone subsets, saving you time, money, and resources.

CUSTOM ROBOTIC COLONY PICKING SERVICES

Our high-speed robots array your genomic or cDNA library into 384-well plates at a rate of over 2,500 colonies per hour. We determine the titer of your genomic or cDNA library, and plate the appropriate number of clones onto agar. Scanned images of each clone are analyzed for size, roundness and color (blue/white, if appropriate). Colonies that meet the selection criteria are picked into individual wells of 384-well plates containing liquid freezing media. Arrayed libraries are stable at -80°C and will survive multiple freeze/thaw cycles. Incyte Genomics can also produce replica copies of the 384-well plates or corresponding 96-well plates. An average 50,000-clone library will be processed within 10-15 working days.

CUSTOM ROBOTIC SPOTTING SERVICES

When you need to screen your custom library in a matter of days, let Incyte Genomics help. Clones from your library are stamped onto positively charged nylon filters in a spotting format specifically designed for your project. We offer 22 cm x 22 cm nylon filters on which we can spot genomic or cDNA clones from either your custom library, an IMAGE Consortium library, or any Incyte Genomics library.

Each filter can contain up to 55,296 colonies, or 27,648 double-spotted clones. The average density chosen is 36,864 colonies, or 18,432 double-spotted clones per filter. Double spotting is imperative to allow for identification of true positive colonies, and for easy identification of clone addresses.

(CONTINUED)

Robotic Services

CUSTOM ROBOTIC SPOTTING SERVICES *(continued)*

The nylon filters are robotically spotted with bacterial clones, grown overnight, then lysed and all cellular material is removed. The filters are left with single-stranded DNA spotted at approximately 1 ng per colony. The filters are delivered fully processed and ready to be hybridized. Our filters can be hybridized up to 10 times.

We offer several spotting formats, and work with you to customize any spotting format you wish. We will customize and provide all the necessary literature to utilize your filters.

CUSTOM ROBOTIC CLONE RE-RACKING SERVICES

Using our high-speed robotic equipment, hundreds to thousands of individual clones can be quickly retrieved from any arrayed library to produce a customized clone set for your research needs. You provide a list of clone IDs or clone addresses of the target clones in a data table, spreadsheet, or Microsoft® Excel file, and we do the rest. We will retrieve target clones from one of our libraries, from the IMAGE Consortium cDNA collection, or from your custom library, and deposit them into new 96-well or 384-well plates containing liquid freezing media. This library subset is stable at -80°C and will survive multiple freeze/thaw cycles. Incyte Genomics will provide you with the 96-well or 384-well plates and an electronic file that links the original addresses/clone IDs of target clones to their new plate and well locations in the multi-well plates you receive. Incyte Genomics can also produce replica copies of the 96-well or 384-well plates.

For more information regarding Custom Robotic Services, please visit our web site at www.incyte.com, or contact one of our Customer Service representatives at (800) 430-0030 or (314) 427-3222, or via e-mail at service@stl.incyte.com.

Transgenic Technologies

CUSTOM MICE FOR CUSTOM SOLUTIONS

IncyteGenomics
For Life.

TRANSGENIC TECHNOLOGIES

Incyte Functional Genomics

CUSTOM MICE FOR CUSTOM SOLUTIONS

Incyte Genomics provides a systematic, scientifically driven approach to the development of animal models for the study and evaluation of gene function in the context of a complex mammalian system. We provide a full range of services from gene isolation and characterization to phenotype analysis. We have the ability to create complex animal models that answer complex questions about gene function in the context of a whole animal. We start by isolating and characterizing the gene of interest, then engineer a targeting vector specially designed for the target gene locus. Next, we isolate and characterize targeted ES cell clones that contain the designed knockout or knockin at the target locus, we produce chimeras, breed for germline transmission, and monitor for zygosity. Finally, we perform a standard panel of morphological and clinical analyses on the model. *In Situ* Hybridization and genome-wide expression profiling using the GEM™ microarray to round out the analysis of the model by examining changes in gene expression patterns.

PHASE 1-4

CUSTOMER PROVIDES:

cDNA

WE PERFORM THE FOLLOWING:

Gene Screening through Blastocyst Injection

- Isolation of Genomic Clone
- Generation of the Target Vector
- Isolation of homologously recombinant ES Clones
- Generation of Mouse Chimera

PHASE 3-4

CUSTOMER PROVIDES:

Targeting vector and screening probes

WE PERFORM THE FOLLOWING:

Electroporation through Blastocyst Injection

- Isolation of recombinant ES Clones
- Generation of Mouse Chimera

PHASE 5

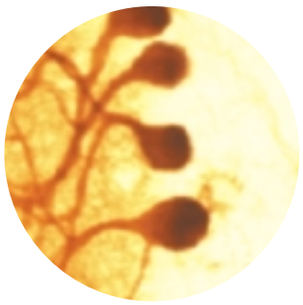
BREEDING

Breeding Chimeras and Genetic monitoring of offspring to identify mutant heterozygous and homozygous animals.

PHASE 6

PHENOTYPE ASSESSMENT

- **Morphology:** For overall health evaluation
- *In Situ* Hybridization to localize gene expression
- GEM™ for genome-wide expression profiling



INTEGRAL PROCESSES USED IN OUR MOUSE KNOCKOUT SERVICES

The following summarizes the integral processes we use to deliver the highest-quality custom murine models in order to decipher gene function in the context of a complex mammalian system.

PALO ALTO & FREMONT, CALIFORNIA
Incyte Genomics, Inc.
3160 Porter Drive
Palo Alto, California 94304
Telephone 650-855-0555
Toll Free Telephone 877-264-0858
Fax 650-855-0762

Incyte Genomics, Inc.
6519 Dumbarton Circle
Fremont, California 94555
Telephone 510-739-2100
Fax 510-739-2200

ST. LOUIS, MISSOURI
Incyte Genomics, Inc.
4678 World Parkway Circle
St.Louis, Missouri 63134
Telephone 314-427-3222
Toll Free Telephone 800-430-0030
Fax 314-427-3324

Incyte Genomics, Inc.
8620 Pennell Drive
St. Louis, Missouri 63114
Toll Free Telephone 800-430-0030
Fax 314-592-8200

CAMBRIDGE, UNITED KINGDOM
Incyte Genomics Ltd
Botanic House
100 Hills Road
Cambridge CB2 1FF
United Kingdom
Telephone +44 (0) 1223 454 900
Fax +44 (0) 1223 454 999

Incyte Genomics Ltd
214 Cambridge Science Park
Milton Road
Cambridge CB4 0WA
United Kingdom
Telephone +44 (0) 1223 424 877
Fax +44 (0) 1223 424 855

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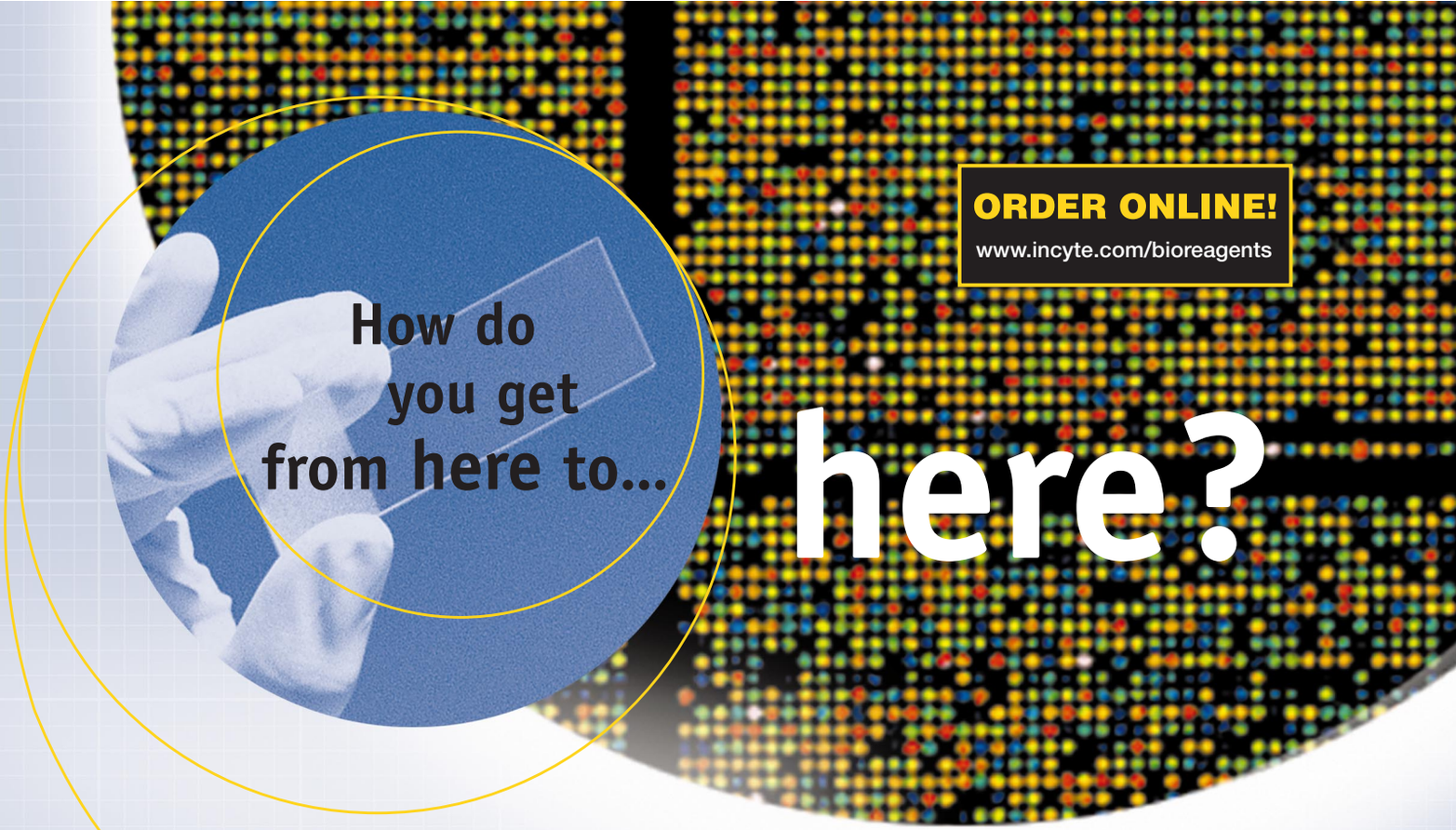
08001500 (225)



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New Easy-to-Spot™ DNA

PCR from cDNA clones for your Microarray Production

CUSTOM SEQUENCING
CLONE RESOURCES
GENE EXPRESSION
GENE SCREENING
MOUSE KNOCKOUTS
PLASTICS
ROBOTIC SERVICES

*Arabidopsis coming soon!

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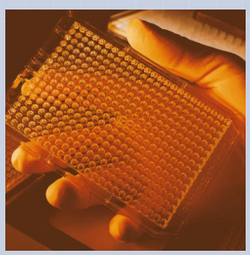
The World's Most Complete View of the Human Genome

Instead of spending time and money on instrumentation, reagents, and personnel, let Incyte Genomics provide you with DNA quickly and easily. Our Easy-to-Spot™ Human and Mouse DNA sets* offer:

- over 9,000 unique human genes and ~8,700 unique mouse genes corresponding to UniGene database and neatly assembled into convenient sets
- custom formatted sets of purified DNA ready to supply your microarray production operation
- an average length greater than 500 nucleotides
- DNA generated from a sequence-verified clone set

Find out more! **www.incyte.com/easytospot**



Resuspended in aqueous solution to suit your needs in your choice of 96- or 384-well format.

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customer request:
I need a novel gene—fast!
Incyte solution:
LifeSeq® GENE-BY-GENE
Instant access online to 60,000 unpublished human genes
Easy and free online access to the world's most powerful and comprehensive human sequence database with 60,000 unpublished genes from Incyte Genomics. Find your gene of interest and accelerate your research by purchasing the gene sequences and clones at a reasonable price.
• Get affordable access to the gene information you need
• Shorten your gene screening time
• Save months or even years of work
Visit www.incyte.com/genebygene
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LifeArray™ microarrays pack the winning punch with...

Unbeaten sensitivity

Unmatched reproducibility

Unrivaled gene content

Now every researcher can get the most sensitive, reproducible human, rat and mouse microarrays. Use them in your own lab or send us your samples for an unrivaled 5-15 day turnaround service.

www.incyte.com

Only LifeArray™ microarrays give you more than 50,000 gene transcripts not available in the public domain and the power to detect up to 1 part in 100,000 with a differential sensitivity of 1.7-fold at 99% confidence. No one else even comes close. Plus, cDNA clones matched to every element extend your research to the next round.

It's your experiment. Give yourself the upper hand.

> AVAILABLE NOW.

Visit incyte.com or call 1.800.430.0030 for a complete listing of LifeArray™ microarrays.

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LifeArray™ microarrays pack the winning punch with...

Unbeaten sensitivity

Unmatched reproducibility

Unrivaled gene content

Now every researcher can get the most sensitive, reproducible human, rat and mouse microarrays. Use them in your own lab or send us your samples for an unrivaled 5-15 day turnaround service. Only LifeArray™ microarrays give you more than 50,000 gene transcripts — 25,000 not available in the public domain — and the power to detect up to 1 part in 100,000 with a differential sensitivity of 1.7-fold at 99% confidence. No one else even comes close. Plus, cDNA clones matched to every element extend your research to the next round. It's your experiment. Give yourself the upper hand. Available now. Call or go online for a complete listing.

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LifeSeq® databases propel your quest for discovery with...

A stellar collection of rare and full-length gene transcripts

Out-of-this-world understanding of gene function

Mission-critical expertise, affordability and IP protection

> VISIT INCYTE.COM OR CALL 1.800.430.0030
to explore the galaxy's most pharmaceutically relevant genomic data.

With tens of thousands of full-length transcripts, the odds of target discovery and validation are better here than anywhere else. That's why more researchers are turning to LifeSeq® databases from Incyte. Only Incyte starts with actual gene transcripts anchored to the genome where each transcript is completed to full-length status using proprietary molecular biology and bioinformatics capabilities. Only Incyte integrates sequence data with expression, SNP and Proteome annotation for the best understanding of gene function. Only Incyte stocks tens of millions of cDNA clones to advance your research further. And only Incyte protects you with the world's largest, fastest growing gene patent estate. So before you boldly go where no one has gone before, consider taking along the one company that really understands "the business of genomics."

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LifeArray™ Drosophila Chip

EXPRESSION DATA FOR 93% OF THE DROSOPHILA GENOME IN A SINGLE FULL-SERVICE EXPERIMENT

VISIT **WWW.INCYTE.COM**

Incyte's state-of-the-art LifeArray™ chips service gives researchers a accurate, cost-effective way to perform detailed analysis of differential expression in normal and diseased or treated cells.

Incyte's LifeArray™ Drosophila gene expression microarray is the most comprehensive public domain fly microarray ever manufactured. The LifeArray™ Drosophila chip provides researchers with expression data for more than 14,000 ORFs, or 93% of the predicted genes of the Drosophila genome in a single full-service experiment

To minimize homology between microarray elements, ORFs are amplified using gene-specific primers. Primer design consists of two algorithm modules, fragment selection and primer selection. During fragment selection, all open reading frames (ORFs) are compared by BLAST analysis against the entire genome and to each other. Homologous and identical regions are excluded. Primer selection: primer pairs aree also compared by BLAST analysis against the Drosophila genome and are excluded if the last positions matched elsewhere in the genome. To control for false positives, ORFs are arrayed in duplicate on the LifeArray™ chip.

Every microarray is also arrayed with a control plate, which is used to assess changes in differential expression, generate a standard curve, monitor housekeeping genes, detect rRNA contamination, detect genomic DNA contamination, and inspect pen variability.

LifeArray™ Drosophila Chip	Metrics
Accuracy	Bias - 0.005
Limit of detectable expression	> 1.75-fold
Precision of expression (CV of expression response for any gene is 14%)	14%
Dynamic range	Total range of response 3 log 10s
Total non-redundant genes	14,153
Annotated quarterly against	GenBank

We take great care to assure the efficiency and accuracy of every step of our microarray manufacturing and hybridization, from incoming mRNA samples, to robust probe generation, to hybridization output and data summary. We screen two polyA RNA samples per microarray in a competitive hybridization.

NEW! LifeArray™

LIFE ARRAY™

THE MOST RELIABLE & COMPREHENSIVE GENE EXPRESSION CHIPS

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- **Chips with unmatched content at a price you can afford**
- **Flexible, easy-to-use turnkey system**
- **Verified clones and associated sequence data**
- **Unbeaten sensitivity & reproducibility**
- **Built with industry-leading bioinformatics expertise**

Give your research the upper hand with LifeArray™, the new easy-to-use gene expression chips from Incyte. LifeArray offers everything you need to perform reliable, reproducible expression experiments in your own lab — the most accurate chips with the most comprehensive content, reagent kits, protocols, software, and flexible hardware setups. *All at a price you can afford*. With only a few hours of training, any technician in your lab can reliably prepare and execute LifeArray experiments.

UNMATCHED GENE CONTENT

Only LifeArray delivers more than 100,000 gene transcripts — 40,000 not available in the public domain. And because we annotate LifeArray chips quarterly, you always have the most current information, even months after your experiment is done. *See our full list of LifeArray chips and content on the back of this sheet.*

ASSURED CLONE IDENTITY

To assure clone identity, our premier LifeArray chips are made using clone sets that are re-sequence-verified at multiple stages during production.

RESULTS YOU CAN TRUST

Our system-wide focus on quality control results in CVs of 12% at all levels of expression, and a limit on differential expression down to 1.75-fold at 99% confidence level. No other gene expression platform can boast that combination of sensitivity and reproducibility.

OPTIONS TO SUIT YOUR RESEARCH NEEDS

LifeArray™ — Everything you need for accurate, reproducible experiments in your own lab…LifeArray chips, reagent kits, protocols, hardware, and software.

Custom LifeArray™ — The same accurate, reproducible technology with content tailored to your specific area of interest. Select from Incyte genes, or provide your own.

LifeArray™ Service — Full service hybridizations of custom or premanufactured LifeArray™ chips, with results delivered in only 5-15 days.

SPECIAL OFFER!

Through May 31, 2001, you can get any 500 LifeArray™ chips — including a complete hardware and software system (an $85,000 value) and full set-up and training — for only $250,000. For more information, call +1.314.427.3222

LifeArray™

Choose LifeArray™ for your lab today.
The most comprehensive content and most accurate, reproducible experiments…*at a price you can afford*.

HUMAN (Fully Re-Verified)	Content	
Human Theme Series		
Human Drug Target	Non-redundant	8,669
(Incyte clones)	• Annotated	8,443
	• Incyte-unique	256
Human Foundation Series		
(Incyte clones)		
Human 1	Non-redundant	9,263
	• Annotated	4,414
	• Incyte-unique	4,849
Human 2	Non-redundant	9,435
	• Annotated	3,419
	• Incyte-unique	6,016
Human 3	Non-redundant	9,050
	• Annotated	3,277
	• Incyte-unique	5,773
Human 4	Non-redundant	9,263
	• Annotated	4,414
	• Incyte-unique	4,849
Human 5	Coming Soon!	
Human 6	Coming Soon!	
Human UniGene		
(Incyte clones mapped to UniGene)	Non-redundant	8,524
	• Annotated	8,393
	• Incyte-unique	131

RAT (Fully Re-Verified)	Content	
Rat Toxicology	Non-redundant	8,456
(Incyte clones)	• Annotated	6,043
	• Incyte-unique	2,413
Rat Foundation 1	Non-redundant	9,263
(Incyte clones)	• Annotated	4,414
	• Incyte-unique	4,849

MOUSE (Fully Re-Verified)	Content	
Mouse UniGene	Non-redundant	9,307
(Incyte-edited IMAGE clone)	• Annotated	9,307

OTHER (Initially Verified)	Content	
Rat CNS	Non-redundant	6,234
(Incyte clones)	• Annotated	4,553
	• Incyte-unique	1,681
Arabidopsis GenBank	Non-redundant	6,882
(Incyte & Ohio State clones)	• Annotated	6,882
Candida albicans	Non-redundant	6,554
(Incyte clones and ORFs)	• Annotated	3,776
	• Incyte-unique	2,778
Staph. aureus	Non-redundant	1,925
(ORFs)	• Annotated	1,774
	• Incyte-unique	151

WITH LIFEARRAY, YOU GET…

…the most comprehensive content and the most reliable, accurate technology. And now, to further your research without interruption, Incyte offers verified clones and associated sequence data for every human and animal model element represented on a LifeArray™ chip. Our new pricing structure makes it easier than ever before to get the most complete information about the genes you want to study.

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IncyteGenomics

MARCH 2001 (MBAKER)

Candidate Gene Discovery & Analysis

COMPREHENSIVE SNP DISCOVERY, GENOTYPING, AND ASSOCIATION DATA FOR KEY THERAPEUTIC AREAS

WWW.INCYTE.COM

Use data derived from Incyte's genetics programs and collaborations to:

- **Identify and characterize optimal therapeutic targets**
- **Gain a better understanding of the relationship between disease phenotypes and genetic variation**
- **Identify genetic markers of disease progression**

Only Incyte combines the best view of the human genome with disease-targeted genetic research. Our research programs and collaborations deliver important genetic data within key therapeutic areas and drug target classes to validate gene targets.

1. Identify Candidate Genes

Literature searches, conferences, and expert consultation

Biological data

Sequence searches
- In public domain databases
- In LifeSeq® Gold databases,
  - sequence similarity searches
  - co-expression analysis *in silico*

2. Prioritize Candidate Genes

Mapping information

Biochemical pathways

LifeExpress™ RNA & protein expression database
- Expression analysis
- Tissue distribution

Functional biology studies

Related disorders

Model organism studies

3. Discover, Validate, and Map Candidate Gene SNPs

***In silico* SNP discovery**
- Validated *in silico* SNPs from LifeSeq® Gold mapped to candidate genes
- SNPs from public domain databases mapped to candidate genes

Lab-based SNP discovery
- Comprehensive SNP screen using SSCP across Incyte's Human Diversity Panel
- Validated with double-stranded sequencing

Mutation screen
- Therapeutic area mutation screen against population with well-characterized clinical phenotype

4. Genotyping/Association Studies

Genotype candidate gene SNPs against clinical populations
- Case control
- Quantitative trait loci studies

5. Data Delivery

Annotated candidate genes

Sequence with polymorphic position and ethnic allele frequencies

Disease association study results

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11003000 (397)

Custom SNP Discovery Service

COMPREHENSIVE HIGH-THROUGHPUT SNP DISCOVERY

- You decide number and type of genes
- Proprietary fSSCP technology identifies >90% of polymorphisms
- Incyte Human Diversity Panel identifies allele frequencies in four major ethnic groups

IncyteGenomics
For Life.

Custom SNP Discovery

COMPREHENSIVE HIGH-THROUGHPUT SNP DISCOVERY SERVICE

Now you can get **detailed SNP data** from genes you specify using Incyte's high-throughput Custom SNP Discovery service. Each project includes:

- Gene-centric SNP discovery
- Sequence and genomic structure for each gene
- Polymorphism position
- Multi-ethnic allele frequency information
- Amino-acid change information

In addition to high-throughput systems and bioinformatics expertise, we support your projects with an integrated laboratory information management system that tracks projects from sample receipt through completion. We give you quarterly reports so you always know the status of your project.

Save valuable target discovery and planning time with custom SNP data:

- Select the most promising targets
- Stratify populations for more effective clinical trials
- Optimize target discovery and pre-clinical planning
- Identify genetic markers of disease progression

You also benefit from Incyte's full range of genomic resources, including:

- *Physical clones for every gene*
- *LifeExpress RNA & protein expression database*
- *LifeSeq® Gold & ZooSeq™ sequence databases*
- *Custom expression and sequencing services*

CREATORS OF
LifeSeq® Gold
The World's Most Complete View of the Human Genome

DETAILED SNP DATA

FROM GENES YOU SPECIFY

1. You specify genes to be analyzed

You define the number and type of genes to be analyzed. Our high-throughput systems and dedicated SNP discovery staff can analyze thousands of genes per year.

2. Gene Building and Primer Optimization

Incyte's bioinformatics group determines the full intron:exon structure of the genes using both publicly available and Incyte-proprietary information. Genes for which the full intron:exon structure is not available may be screened against our alternate cDNA panel.

Primer Design & Optimization

Construction of full gene, including intron:exon boundaries
Genomic structure enables the screening of entire ORFs including intron:exon boundaries.

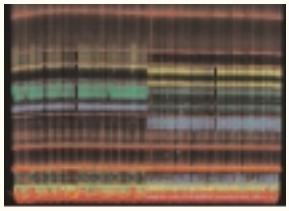
Construction of cDNA primer
Genes for which the full intron:exon structure is not available may be screened against our alternate cDNA panel.

Incyte can also perform bacterial artificial chromosome (BAC) mapping and sequencing of nominated genomic regions.

3. SNP Discovery by fSSCP

Our proprietary fSSCP technology identifies >90% of polymorphisms.

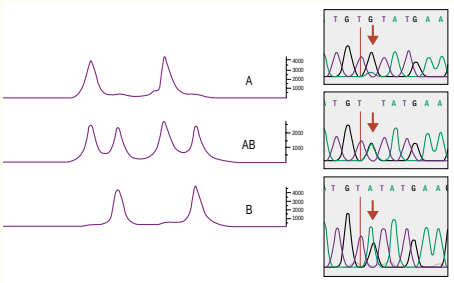
Genes are screened against Incyte's genomic DNA Human Diversity Panel, derived from consented individuals of known ethnicity. Our panel allows estimation of allele frequencies in four major ethnic groups.



SNP Discovery
Amplified primer products are run on SSCP gels by pooling DNA fragments, each labeled with a distinct dye, in a single gel.

4. SNP Confirmation

Sequence variations are confirmed using the recognized standard of double-stranded sequencing. Comparison of SSCP sequencing data enables allocation of sequence to allele pattern and the reliable estimation of population frequency for each SNP.



SNP Confirmation
Comparison of SSCP pattern type with sequencing data enables allocation of sequence to allele pattern. Population allele frequencies are generated from this data.

5. Data Delivery

Reliable, comprehensive SNP data is shipped to you quarterly and includes:

- Sequence and genomic structure for each gene
- Polymorphism position
- Multi-ethnic allele frequency information
- Amino-acid change information

> VISIT INCYTE.COM OR CALL 1.800.430.0030
to learn more about our Custom SNP Discovery Service

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4678 World Parkway Circle
St.Louis, Missouri 63134
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CAMBRIDGE, UNITED KINGDOM
Incyte Genomics Ltd
Botanic House
100 Hills Road
Cambridge CB2 1FF
United Kingdom
Telephone +44 (0) 1223 454 900
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214 Cambridge Science Park
Milton Road
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Genetics

GENE POLYMORPHISM AND DISEASE ASSOCIATION DATA SERVICES

- **Target discovery and characterization**
- **Candidate gene discovery**
- **Comprehensive SNP discovery and analysis** including allele frequencies
- **Therapeutic area studies**
- **Pharmacogenetics** polymorphisms in genes implicated in drug metabolism (ADME)

IncyteGenomics
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Genetics Programs & Services

VALUABLE DATA FROM OUR *IN SILICO* AND LAB-BASED TECHNOLOGIES

Only Incyte combines the best view of the human genome with disease-targeted genetic research.

Now you can get prioritized candidate gene lists, comprehensive SNP discovery and analyses, and statistically significant disease association data from Incyte.

Use data derived from Incyte's genetics programs and collaborations to:

- Identify and characterize optimal therapeutic targets
- Gain a better understanding of the relationship between disease phenotypes and genetic variation
- Enable faster clinical proof of principle
- Identify genetic markers of disease progression

CANDIDATE GENE IDENTIFICATION

To ensure the most complete identification of candidate genes, Incyte analyzes data from all available resources, including Incyte-proprietary sequence and expression databases, Incyte gene profiling programs, the public domain, scientific literature, conferences, and expert consultations.

COMPREHENSIVE SNP DISCOVERY

To help you select the most promising targets, we perform comprehensive SNP discovery across a prioritized candidate gene list. These SNPs are evaluated for disease and/or pharmacogenetic relevance in population studies.

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LifeSeq® Gold
The World's Most Complete View of the Human Genome

KEY RESEARCH AREAS

Our research programs and collaborations deliver important genetic data within key therapeutic areas and drug target classes.

Therapeutic Areas

- Cardiovascular disease
- Diabetes (Type 2)
- Inflammation & immune response
- Neurobiology (Alzheimer's disease)
- Obesity
- Osteoarthritis
- Osteoporosis

Drug Target Classes

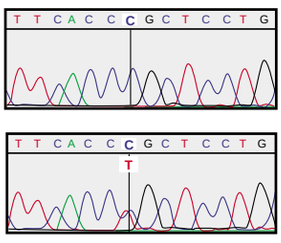
- G-protein-coupled receptors
- Ion channels
- Known drug targets
- Nuclear receptor super family

PHARMACOGENETICS (ADME)

Incyte identifies and characterizes genes involved in individual variations in drug absorption, dispersion, metabolism, and excretion (ADME). Use data resulting from our pharmacogenetics research for predictive toxicity and to design therapeutics tailored to individual genotypes.

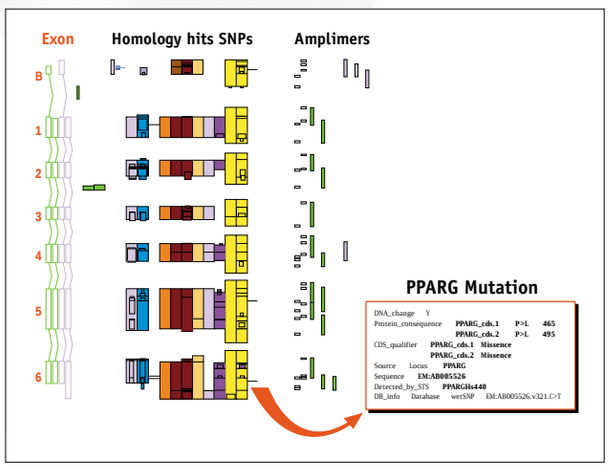
You also benefit from Incyte's full range of genomic resources, including:

- *Physical clones for every gene*
- *LifeExpress RNA & protein expression database*
- *LifeSeq® Gold & ZooSeq™ sequence databases*
- *Custom expression and sequencing services*



PROOF OF PRINCIPLE / TYPE 2 DIABETES

Incyte's proven genetics approach resulted in the identification of the role of PPARγ (peroxisome proliferator-activated receptor gamma) in physiological indicators associated with Type 2 Diabetes. The data viewed here was recently reported in *Nature* (402, 880-883 [1999]).



GRAPHIC DISPLAY FROM OUR CANDIDATE GENE DATABASE

Through our candidate gene database, you can access related information about genes of interest. The database includes links to OMIM™, lists of key papers, and other substantiating evidence for a gene's potential role in a particular therapeutic area.

WE ALSO OFFER:

CUSTOM SNP DISCOVERY SERVICE

Now you can get detailed SNP data from genes you specify using Incyte's high-throughput SNP discovery service.

IN SILICO SNP DATA

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CAMBRIDGE, UNITED KINGDOM
Incyte Genomics Ltd
Botanic House
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United Kingdom
Telephone +44 (0) 1223 454 900
Fax +44 (0) 1223 454 999

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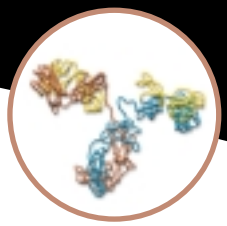


Activation of T Cells

ANTI-CD3- AND ANTI-CD28-TREATED JURKAT

CHRISTOPHER HOPKINS, PH.D., DAVID PETERSON, PHILLIP HAWKINS, BENJAMIN COCKS, PH.D.
INCYTE GENOMICS LIFE SCIENCES RESEARCH DIVISION

CANDIDATE GENE IDENTIFICATION

This paper demonstrates candidate gene identi-fication using select immunology and inflammation experiments performed at Incyte Genomics.

- **T Cell Line Jurkat, Anti-CD3, Time Course**
- **T Cell Line Jurkat, Anti-CD3+Anti-CD28, Time Course**

Incyte identifies genes potentially involved in t-cell activation, timing of expression events, and potential involvement of genes in the antigenic vs. costimulatory signals.

Data from these experiments are available in Incyte's LifeExpress™ database.

EXPERIMENT OVERVIEW

The first critical step in an adaptive immune response is the activation of T lymphocytes, which results in the proliferation and differentiation of antigen-specific effector T cells. Activation is initiated by a complex cell surface interaction between antigen-presenting cells (APC) and the T cells (Crabtree and Clipstone 1994; Grakoui et al. 1999).

Optimal activation is achieved through two distinct signals:

- The signal delivered through the bound T-cell-receptor-CD3 complex
- A co-stimulatory signal delivered through the binding of T-cell-CD28 molecules to the same antigen-presenting cell

These signaling events originate on the surface of the T cell and are transmitted through the cytosol, ultimately resulting in transcriptional changes in the nucleus that lead to cell proliferation (Figure 1). The signals sent by the CD3 and CD28 molecules on the T-cell surface are normally stimulated by the aggregation of these molecules in the cell surface membrane during interactions with the APC.

In this experiment, the T-cell-activation signaling process is simulated by inducing aggregation of the CD3 and CD28 complexes with mouse anti-human CD3 and mouse anti-human CD28 antibodies, respectively. Treatment of the cells with divalent antibodies creates a cross-linking effect that causes aggregation of these complexes within the cell membrane, initiating the signaling process. The purpose of this experiment is therefore to mimic the signaling processes that occur after aggregation of CD3 and CD28 molecules within the cell membrane. The cell line used in the experiment is Jurkat, a commonly used and accepted model for immunological studies that proliferates in culture without stimulation.

EXPERIMENT DESIGN

Cell treatments

Jurkat cells were stimulated in vitro with mouse anti-human CD3 (soluble, 1 µg/ml) and mouse anti-human CD28 (soluble, 1 µg/ml), at intervals of 0.5, 1, 2, 4, and 8 hours. Jurkat cells were maintained in culture in IMDM + 10 % FCS at 37° C in 5% CO_2 atmosphere. These treated cells were compared to untreated Jurkat cells kept in culture in the absence of stimuli.

RNA Preparation

Jurkat cells were lysed in Trizol® and total RNA fraction was recovered according to the manufacturer protocols. Poly-A mRNA was purified using the standard oligo-dT selection method. Cy3 and Cy5 probes were prepared according to the standard protocol developed by Incyte.

Hybridizations

Comparative hybridizations were performed at each time point against an untreated control, assaying each time-point sample in duplicate on three different GEM™ gene expression microarray designs: the UniGEM™ V microarray, LifeGEM™ 1 microarray, and LifeGEM™ 2 microarray, which represent approximately 15,800 gene clusters in total. Differential expression ratios were then analyzed using Incyte's LifeExpress™ RNA software.

RESULTS

Query criteria

We selected for analysis only those microarray elements in the anti-CD3+ anti-CD28 treatment that passed Incyte's quality control criteria, gave differential expression ratios of greater than 2.1-fold difference in at least one time point, and showed a coefficient of variation of less than 50%.

Clustering

Across the three GEM microarray types, 82 elements met these criteria. The patterns of expression ratios over time for each of these 82 elements were clustered using a K-means algorithm in LifeExpress RNA software (six bins, Euclidean distance, non-standardized). This clustering method yielded five clusters that each exhibited a distinct expression pattern during the eight hours of the experiment: "Early"-induced, "Early-High"-induced, "Mid-1"-induced, "Mid-2"-induced, and "Late"-induced. These five clusters, comprised of 49 unique genes represented by 62 elements, with 10 genes represented by more than one element, were selected for further analysis (Table 1, Figure 2).

Anti-CD3 vs. Anti-CD3+Anti-CD28 Treatment

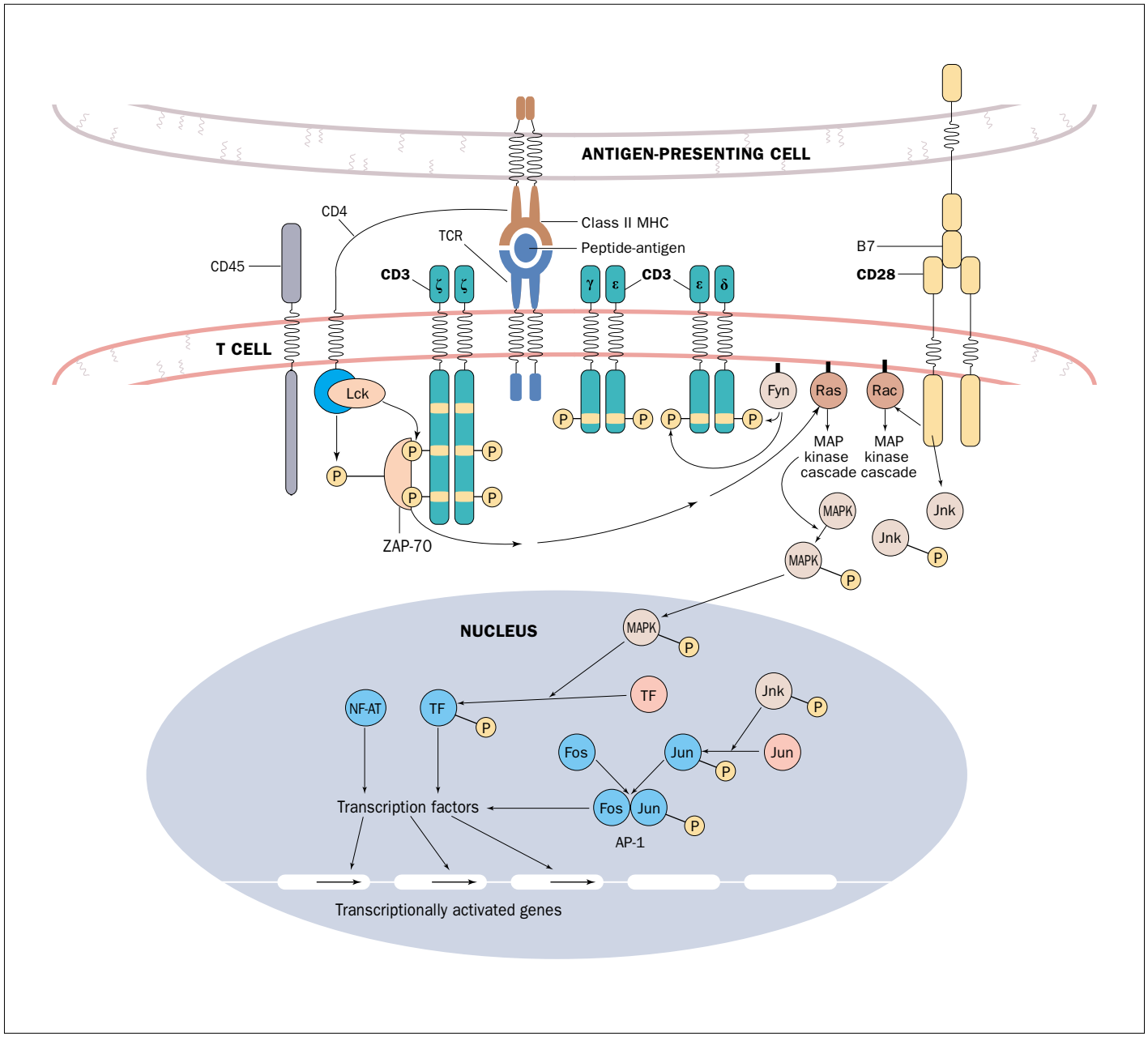
The differential expression ratios of the selected elements from the anti-CD3+ anti-CD28 treatment were compared to the ratios found in the anti-CD3 experiment (Figure 3). Several elements were found to have different expression when comparing the two treatments. The 0.5 and 1 hour time points showed the greatest difference between treatments while very little difference was observed at either 4 or 8 hours. As expected, none of the genes was differentially expressed (>2-fold change) in either treatment at 0 hours.

DISCUSSION

Microarray hybridizations enable the researcher to examine the expression levels of large numbers of genes simultaneously. In the context of a treatment time-course experiment, in which each time-point sample is compared to a t=0 control, temporal patterns of expression can also be identified.

Figure 1.

Schematic representation of T-cell interaction with antigen-presenting cell (APC).

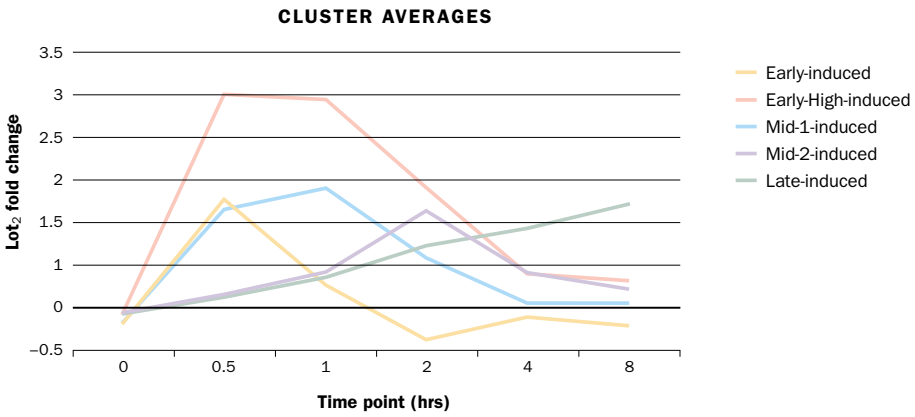


Cluster	Hit description	Function
Early	Human fos proto-oncogene (c-fos)	Member of AP-1 leucine zipper transcription factor
	Human Hsp27 ERE-TATA-binding protein	Estrogen receptor element-TATA DNA binding protein
	Human jun dimerization protein gene	Member of AP-1 leucine zipper transcription factor
Early-High	Human early-growth response 2 protein (hEGR2)	Zinc finger transcription factor associated with growth and differentiation
	Human early-growth response protein similar to EGR-1	Zinc finger transcription factor associated with growth and differentiation
	Human protein tyrosine phosphatase (PAC-1)	Mitogen-induced nuclear protein tyrosine phosphatase
	Human TR3 orphan receptor	Member of steroid-binding receptor family
Mid-1	EGR3=EGR3 protein	Human early-growth factor related to Egr-1 and EGR2
	Human CD69 gene	Early-induced cell surface glycoprotein during lymphoid activation
	Human c-jun proto oncogene (JUN)	Member of AP-1 leucine zipper transcription factor
	Human early-growth response 2 protein (hEGR2)	Zinc finger transcription factor associated with growth and differentiation
	Human G0S3 mRNA, complete cds.	Homolog of murine fos; putative G0/G1 switch regulatory gene
	Human mRNA for GRS protein	Member of Bcl-2 gene family; regulatory protein
	Human mRNA for TR3beta, complete cds.	Isoform of human TR3
	Human myeloid cell differentiation protein	Gene associated with myeloid leakemia cell differentiation to monocyte/macrophage
	Human pilot mRNA	T-cell-activation-associated transcript. Homology to leucine zipper region of EGR
	MAD3	Induced following adherance of moncytes; Ankyrin repeat and phosphorylation site
Mid-2	AHNAK nucleoprotein	Large protein gene; typically repressed in neuroblastoma and tumor-derived cell lines
	EGR alpha=early-growth response gene	Zinc finger transcription factor associated with growth and differentiation
	Human 3-hydroxy-3-methylglutaryl CoA reductase	Membrane-bound glycoprotein
	Human cell line KG1 transcriptional regulator	p54 regulatory protein
	Human clone pSK1 interferon gamma receptor	Human interferon gamma receptor
	Human clones 23667 and 23775 zinc finger	Zinc finger containing protein
	Human CpG island DNA genomic Mse1 fragment	Unknown
	Human CpG island DNA genomic Mse1 fragment	Unknown
	Human MADER mRNA	Nuclear protein associated with mitogen-stimulated lymphocytes
	Human MAP kinase 3c gene, complete cds.	Mitogen-activated protein kinase
	Human mRNA for inwardly rectifing potassium	Potassium channel belonging to Kir4 family
	Human mRNA for myoblast cell surface antigen	Cell surface antigen
	Human mRNA for slow skeletal troponin C	Skeletal muscle troponin
	Human p97 mRNA, complete cds.	Translational regulator; surpresses cap dependent and independent translation
	Human PRDII-BF1 gene for a DNA-binding protein	Zinc finger DNA-binding protein; binds positive regulatory domain of IFN-beta promoter
	Human splicing factor SRp55-1 (SRp-55)	mRNA splicing factor; associated with alternative splicing of CD44 & CD45 during T-cell activation
	Human transcription factor IL-4 Stat mRNA	Member of signal transducer and activators of transcription DNA-binding protein
	Human, gene for membrane cofactor protein	Membrane glycoprotein; member of the regulators of complement activation genes
	protein-tyrosine phosphatase	Protein tyrosine phosphatase
	PTB-associated splicing factor	Polypyrimidine tract-binding protein associated with pre-mRNA splicing
Late	c6.1A...TCR C alpha	Gene associated with prolymphomic leukemia
	Human ARSE gene, complete cds.	Associated with chrondodysplasia phenotype
	Human CpG island DNA genomic Mse1 fragment	Unknown
	Human Hanukah factor serine protease	T-cell-specific serine protease
	Human heat-shock protein, E. coli DnaJ	Homolog of bacterial heat-shock protein
	Human heat-shock protein HSP70B' gene	Heat-shock protein similar to HSP70
	Human Hsc 70 pseudogene	Heat-shock protein pseudogene
	Human mRNA for BiP protein	Immunoglobulin heavy chain-binding protein member of heat-shock protein 70 family
	Human mRNA for lipophilin A	Human homolog of rat prostatein, protein secreted from prostate
	Human Src-like adapter protein mRNA	Interacts with Eck receptor tyrosine kinase
	Human tra1 mRNA	Homolog of murine tumor rejection antigen gp96
	Human tyrosine phosphatase mRNA	Protein tyrosine phosphatase

Table 1.

Differential expressed genes.

A



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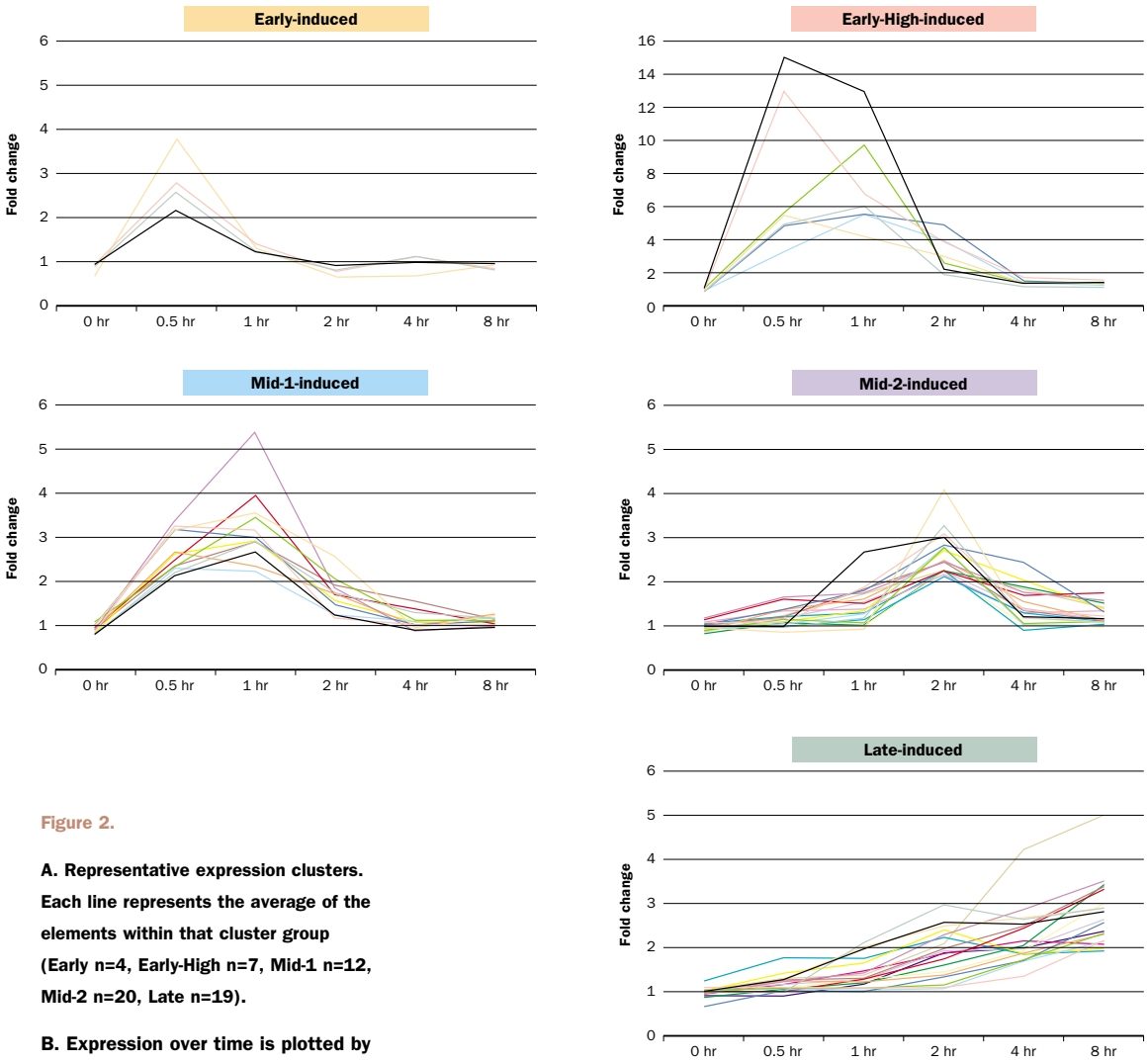


Figure 2.

A. Representative expression clusters. Each line represents the average of the elements within that cluster group (Early n=4, Early-High n=7, Mid-1 n=12, Mid-2 n=20, Late n=19).

B. Expression over time is plotted by cluster group for each gene determined to be differentially expressed.

Using this analysis, genes with similar expression patterns can be clustered together. Genes with similar expression behavior may either have similar functions or be involved in similar processes. Furthermore, knowing the temporal pattern of expression of genes relative to each other gives researchers insight into how gene products may regulate other genes, and into the pathways that develop from the complex interaction of many genes. For example, genes encoding DNA-binding proteins and transcription factors are often expressed very early in response to a treatment. Genes that are regulated, either induced or repressed, by these early factors respond shortly after the expression of their corresponding regulators.

In this experiment, treatment of Jurkat cells with mouse anti-human CD3 and anti-human CD28 was intended to simulate the signaling that leads to T-cell activation. Analysis of the transcript levels at 0.5, 1, 2, 4, and 8 hours yielded five distinct expression patterns, identified by K-means clustering with LifeExpress RNA software.

The timing of expression gives insight into the sequence of events during the activation process. For example, it might be postulated that genes within the Mid-2 or Late clusters, whose peak expression occurs at 2 and 8 hours respectively, might be induced by regulatory genes whose peak expression occurs earlier — such as those genes in the Early (0.5 hour) or Early-High (0.5–1 hour) clusters. In fact, many of the genes showing early induction are DNA-binding proteins and transcription factors known to be involved in cell proliferation and/or T-cell activation. Among the earliest and most highly induced transcripts were early-growth response (EGR) genes 1, 2, and 3. The EGR proteins are thought to have pleiotropic effects including involvement in the transition of cells out of the G_0 phase of the cell cycle.

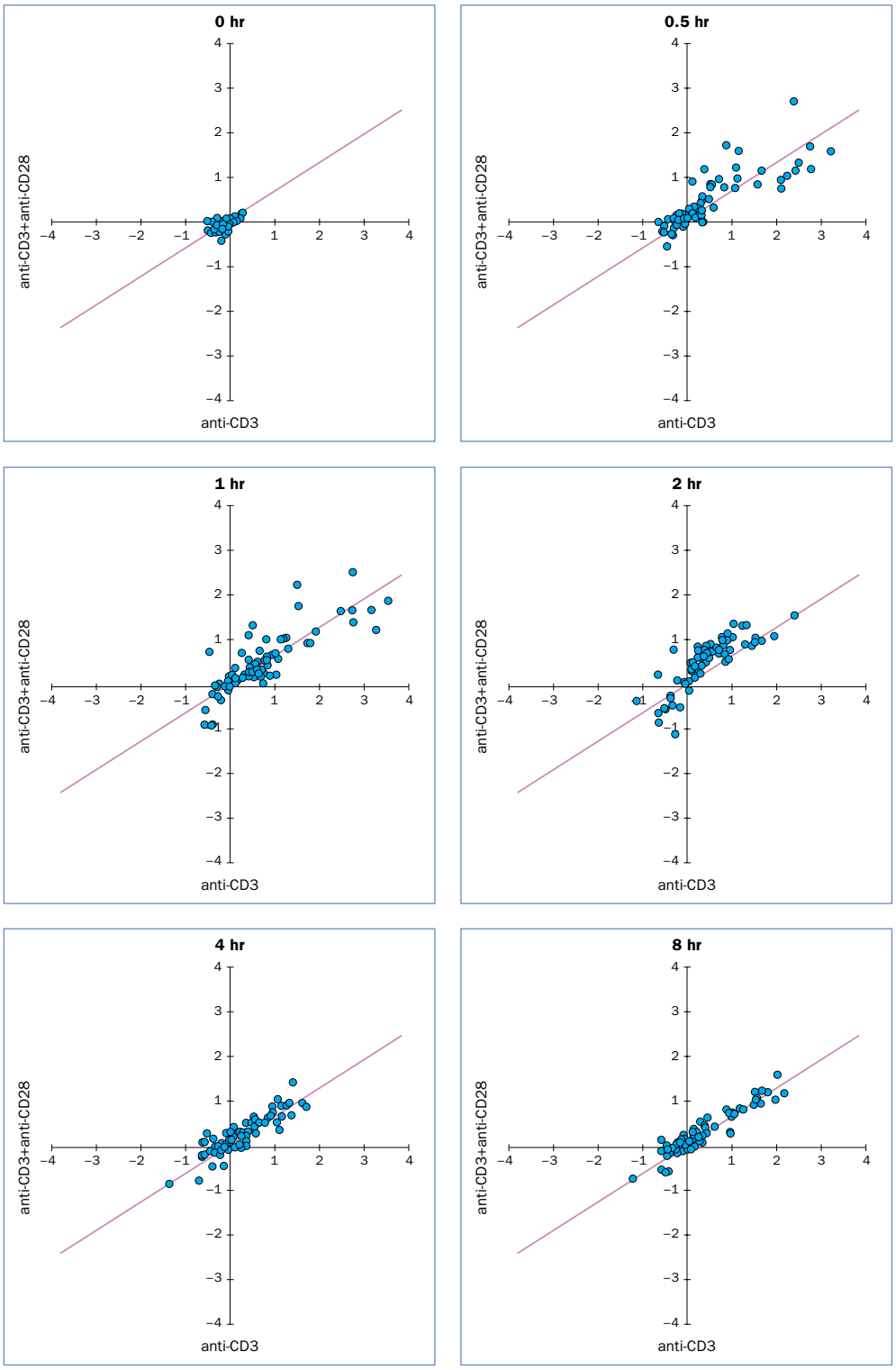
We would expect that many of the early-induced genes would be transcription factors or DNA-binding proteins. In this survey of three GEM microarray designs, 18 of the 49 differentially expressed genes (37%) were classified as transcription factors. Many of these contain zinc finger motifs associated with dimerization. The AP-1 genes are well-characterized members of this family. Many immune-responsive genes are known to be activated by the cooperative activity of NFAT (nuclear factor of activated T cells) and AP-1 (Crabtree and Clipstone 1994). AP-1 is a heterodimer composed of the leucine zipper containing proteins Fos and Jun. In this study, two of the Early genes (c-fos and jun) and two of the Mid-1 genes (c-jun and GOS3) are members of AP-1 component homologs (Table 1). It is not surprising that these genes would be induced early during the activation process and may induce some of the later T-cell-activation-specific transcripts. For example, IL-4 Stat, an immunomodulatory cytokine known to be secreted by activated T cells, which reaches a 3-fold increase at the 2-hour time point, may be regulated by one of these earlier AP-1 genes.

Many phosphatase and kinase activities are associated with the signaling cascade necessary for T-cell activation. Within the Early-High cluster of genes, we find PAC-1, a protein tyrosine phosphatase originally cloned from T cells and known to be induced by mitogens. Two other protein tyrosine phosphatases occur in the Mid-2 and Late clusters (Table 1). MAP 3c, a kinase known to be involved in growth and differentiation, clustered with the Mid-2 genes.

Most of the genes we identified as differentially expressed in this experiment were of known function. For many, we are not surprised by their potential involvement in T-cell activation (e.g. EGRs, tyrosine

Figure 3.

Anti-CD3 vs. anti-CD3+anti-CD28 treatment. The ratios of expression of the genes identified to be differentially expressed in the anti-CD3+anti-CD28 treatment are plotted against the ratios of their expression in the anti-CD3-only treatment on a Log_2 scale.


0 hr
0.5 hr
1 hr
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anti-CD3+anti-CD28
anti-CD3
−4
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−2
−1
1
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4

kinases, jun/fos). The data resulting from this experiment confirms their involvement in T-cell activation and at the same time sheds light on the timing of their expression relative to each other.

Of perhaps greater interest to some researchers are the genes of unknown function or of functions previously not associated with T-cell activation. We found three sequences similar to DNA identified from cloned CpG island sequences that were clustered within either the Mid-2- or Late-induced transcripts. These are attractive candidates for further study of their potential involvement in activation. In addition, we observed that a clone with similarity to an unknown zinc finger containing protein was also expressed 4-fold higher at the 4-hour time point.

When comparing how genes that have been identified to be associated with the anti-CD3+anti-CD28 treatment behave when given only the anti-CD3 treatment, we find that several of them are differentially modulated by the two treatments (Figure 3). By examining which genes are associated with which treatments, the researcher gains insight into their involvement in the two different signals.

Results presented here represent part of Incyte's larger ongoing research programs in the study of autoimmune diseases, transplantation, and inflammation. Incyte is also conducting research incorporating appropriate model systems and clinical materials in a number of other key therapeutic areas.

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Grakoui A, Bromley SK, Sumen C, Davis MM, Shaw AS, Allen PM, and Dustin ML 1999. *Science* 285:221–227. The immunological synapse: a molecular machine controlling T-cell activation.

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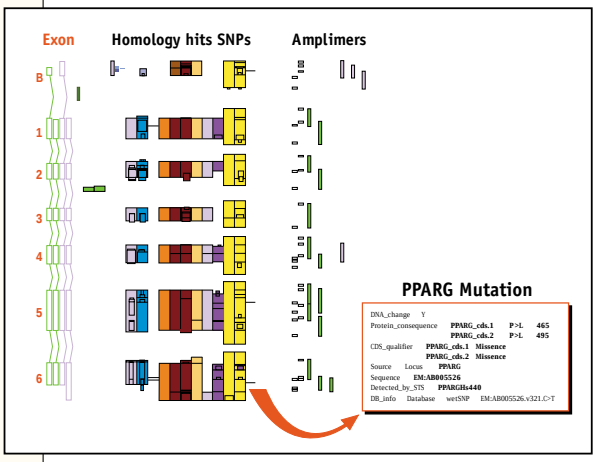

PROOF OF PRINCIPLE

(Published in the Journal *Nature*)

Incyte's proven genetics research approach resulted in the identification of the role of PPARγ (peroxisome proliferator-activated receptor gamma) in physiological indicators associated with Type 2 Diabetes. The data viewed here was recently reported in *Nature* [402, 880-883 (1999)].

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Incyte Genomics, Inc.
3160 Porter Drive
Palo Alto, California 94304
Telephone 650-855-0555
Toll Free Telephone 877-264-0858
Fax 650-855-0762

Incyte Genomics, Inc.
6519 Dumbarton Circle
Fremont, California 94555
Telephone 510-739-2100
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ST. LOUIS, MISSOURI
Incyte Genomics, Inc.
4678 World Parkway Circle
St.Louis, Missouri 63134
Telephone 314-427-3222
Toll Free Telephone 800-430-0030
Fax 314-427-3324

Incyte Genomics, Inc.
8620 Pennell Drive
St. Louis, Missouri 63114
Toll Free Telephone 800-430-0030
Fax 314-592-8200

CAMBRIDGE, UNITED KINGDOM
Incyte Genomics Ltd
Botanic House
100 Hills Road
Cambridge CB2 1FF
United Kingdom
Telephone +44 (0) 1223 454 900
Fax +44 (0) 1223 454 999

Incyte Genomics Ltd
214 Cambridge Science Park
Milton Road
Cambridge CB4 0WA
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Genomics Knowledge Platform

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Platform	CPU	Speed (MHz)	RAM	Web Browser
Windows 95/98	Pentium	166	32 MB	Communicator 4.7 (Java) or IE 4.01 SP2 (Java)
Windows NT	Pentium	166	64 MB	Communicator 4.7 (Java) or IE 4.01 SP2 (Java)
Mac OS 7.6.1 or above	PowerPC 604	180	32 MB	Communicator 4.5 (HTML) or IE 4.5 (Java)
UNIX Workstation (SUN, SGI)	N/A	150	64 MB	Communicator 4.5 (HTML) or IE 4.5 (Java)

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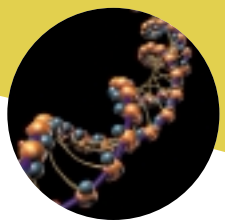

LifeSeq® Gold

THE MOST COMPREHENSIVE TRANSCRIBED GENE VIEW OF THE HUMAN GENOME

WWW.INCYTE.COM

Ways to Access Lifeseq® Gold:

- ***LifeSeq Gold installed*** **— Available for Installation on your research site's intranet network, for complete access behind your own fire wall.**
- ***LifeSeq Gold online*** **— Secure, easy, and convenient Internet access to an Incyte-hosted site providing the most current version of LifeSeq Gold.**
- ***LifeSeq Gene-By-Gene™*** **— Affordable, pay-per-view method of accessing your gene of interest.**
- ***LifeSeq Subscriber Sponsored Access Program*** **— Obtain access through collaborations with participating pharmaceutical partners.**

LifeSeq® Gold, the world's most extensive source of human gene information, is now available online. Give your scientists all the genomic data and associated clone reagents they need to identify new disease-associated genes, novel drug targets, and potential diagnostic or therapeutic proteins. Soon, every human gene and protein will be represented as a full-length sequence in this state-of-the-art human gene-centric, relational database.

Discover LifeSeq® Gold

- **120,000 GENE TRANSCRIPTS WITH MORE THAN 60,000 GENE TRANSCRIPTS NOT AVAILABLE ANYWHERE ELSE** — LifeSeq® Gold contains more than 6.3 million sequences, 4.9 million of which are Incyte proprietary, from over 1,200 different tissue libraries, representing more than 90% of the human genes. In addition, it contains public domain genomic data that has been curated and aligned with Incyte's gene transcript data using our proprietary processes.
- **DIRECTED PROGRAM TOWARED GENE CLOSURE** — Using a coordinated battery of techniques, we are rapidly approaching full-length gene sequence closure for a large portion of the human gene set. High-throughput directed shotgun sequencing of 5'-complete cDNA clones is one key component of this program.
- **MORE THAN 30,000 5'-COMPLETE OR FULL-LENGTH GENE SEQUENCES** Thousands more are added with each release.
- **ACCESS TO INCYTE'S INTELLECTUAL PROPERTY** — LifeSeq® Gold partners have immediate access to the largest commercialized IP portfolio. Incyte has pioneered the non-exclusive licensing model for gene-related patents focusing on pharmaceutically relevant genes. Incyte has filed patent applications covering portions of more than 50,000, including 7,000 that are full length.
- **WORLD-CLASS BIOINFORMATICS** — Incyte's computing facilities process high-quality data using rigorous analytic and annotation methods. LifeSeq® Gold's powerful yet sensitive assembly engine organizes data into distinct genes and their splice variants, providing a gene-centric view of the human genome.

(CONTINUED)

LifeSeq® Gold

- **OVER 215,000 SEQUENCE-VERIFIED REAGENTS** — LifeSeq® Gold partners have access to more than 215,000 sequence-verified clone reagents archived in our LifeSeq® GeneAlbum™ reagent set. Reagents are flagged in the LifeSeq® Gold database to accelerate research projects linked to these genes. For wide-scale *in vitro* research, more than 50,000 of these sequence-verified reagents are arrayed on our high-density GEM™ microarrays.
- **STANDARD AND ADVANCED ANALYSIS TOOLS** — In addition to a full range of standard built-in analysis tools, LifeSeq® Gold contains Incyte's own curated protein function hierarchy, plus electronic Northerns coupled with detailed tissue donor information to help you understand the role of particular genes in disease. The versatile Gene Query and Library Comparison Query functions in LifeSeq® Gold supply a wide variety of methods for identifying and comparing detailed gene information.

With LifeSeq® Gold, you get access to the world's leading human gene information database and reagent set. Find out more about LifeSeq® Gold and how you can use it to accelerate your discovery projects.

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LifeSeq® Gold Update

HUMAN GENE SEQUENCE DATABASE

Incyte's LifeSeq® Gold database—the most powerful human gene information-based tool—provides the most precise and comprehensive view of human genes available. Incyte's unique approach of first sequencing ESTs and then mapping them to genomic sequences provides the best view of the human genome for drug and diagnostic discovery. LifeSeq Gold includes more than 4.9 million proprietary and more than 1.4 million carefully edited and quality checked public domain sequences processed using Incyte's state-of-the-art bioanalysis. LifeSeq Gold contains all of Incyte's proprietary human sequence and expression data, plus our proprietary full-length gene information, sequence information for all GeneAlbum™ reagents, and public-domain data that Incyte has carefully edited and checked for quality.

EST Data

As of the September 2000 release, LifeSeq Gold contains more than 6.4 million sequences, of which more than 76% are proprietary to Incyte.

Sequences	
Incyte-Proprietary Sequences	4,965,394
Incyte-Edited Public Sequences[1]	1,424,363
Available in sequence database FASTA file only	
Incyte-Proprietary Sequences	68,143
Incyte-Edited Public Sequences	0
Total Sequences	**6,457,900**

[1]For a full breakdown of the number and sources of Incyte-edited sequences from publicly available databases, see the Release Notes in each LifeSeq® Gold data release.

Full-Length Sequences	
Hand-Edited Full-Length Sequences	13,992

Gene Bins	
Annotated Non-Singleton Bins	55,534
Unique Non-Singleton Bins	147,944
Total Non-Singletons	***203,478***
Annotated Singleton Bins	55,079
Unique Singleton Bins	259,813
Total Singletons	***314,892***
Total Gene Bins	**518,370**

Libraries	
Incyte	998
Public	294
Available in sequence database FASTA file only	
Incyte	25
Public	0
Total Libraries	**1,317**

Please email questions, comments, and suggestions about LifeSeq Gold to Curtis Adams, Ph.D., cadams@incyte.com.

Genomic Data

Incyte began releasing genomic data with LifeSeq Gold in November 1999. Genomic data includes both finished and unfinished human genomic sequences from the public domain. The Genomic Viewer provides a graphical display of annotated genomic sequences with aligned gene transcript sequences.

Genomic Statistics	
Total base pairs processed	3,245,326,241
Singleton gene bins represented by aligned templates	178,849
Non-singleton gene bins represented by aligned templates	151,415

Clone Reagents

Reagents are available for nearly every sequence represented in LifeSeq Gold. Verified reagents are available as listed below.

Verified Clone Reagents	
Completely Sequenced Full-Length Reagents	3,311
Sequence-Verified Clone Reagents	215,301
Genes with GeneAlbum™ Verified Reagents	85,380
Non-Singleton Genes	83,316
Singleton Genes	2064

IncyteGenomics

LifeSeq® Public

ORDER ONLINE: **WWW.INCYTE.COM**

The easiest access and more tools than ever to help you understand and develop solutions to your research needs... at no cost to you!

LifeSeq® Public provides the best view of the human genes found in the public domain. Incyte Genomics, the proven expert in compiling proprietary data for large commercial companies, is now offering free access to sequence data from the public domain, plus a portion of the sequences from Incyte's proprietary LifeSeq® Gold sequence database.

Once you find your gene of interest using LifeSeq® Public, Incyte also provides direct access to all the sequence-verified reagents you will need during your research, saving you weeks or even months in the lab.

Check out LifeSeq® Public to discover what it has to offer:

- It's FREE
- Assembled public domain data plus a portion of Incyte proprietary sequences
- Access to Incyte proprietary cDNA clones and public IMAGE clones
- Leading edge bioinformatics that are used in our flagship database LifeSeq® Gold
- Sequences obtained from human tissue sources and human cell lines rather than gene prediction algorithms
- Annotation, Predicted Protein Function, and possible Splice Variants for each Assembled Sequence
- Novel intuitive user interface that allows straightforward access to our sequences
- Private research bench in which you can store your research information

Register for LifeSeq® Public and view a detailed tutorial at www.incyte.com.

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