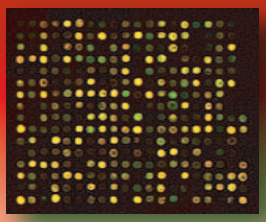
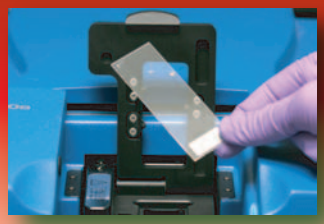


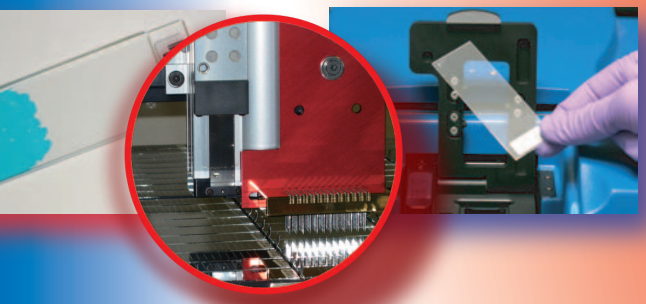


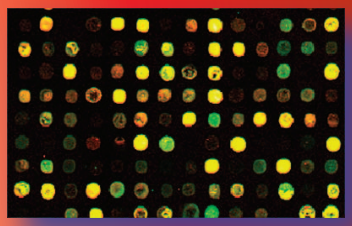
MICROARRAYS

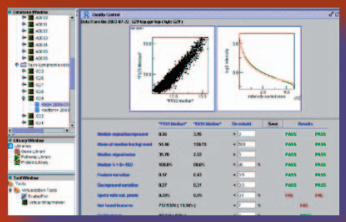
Center for Functional Genomics

Solving problems through Genomics research:
"A new dimension of discovery"

- **Centralized** facility to handle all aspects of microarray printing and processing
- **Optimize** all aspects of printing and processing of microarrays
- **Quality** control standard methods, experts
- **Creation** of validated database from standardized protocols and experimental designs
- **Collaborations** with scientists from numerous institutions with a wide variety of projects
- **Cooperation** between statisticians, informaticians, research scientists, and Center for Functional Genomics scientists







Biomarker discovery:

By screening thousands of genes in one experiment, microarrays are being used for the discovery of early biomarkers that indicate potential toxicity, increased risk for adverse effects, levels of efficacy, etc.. Such biomarkers will increase the pace at which new drugs are discovered, increase safety margins, and indicate exposures and potential safety risks of environmental and terrorism-agent exposures. Potentially low-cost tests can be designed from this biomarker discovery application.

Safety signatures:

Because microarrays make thousands of quantitative measurements on a sample, the pattern of the response is very complex and may provide a unique signature of safety or toxicity. Such patterns offer a potentially more powerful form of biomarker than traditional single-element biomarkers. Sophisticated pattern recognition software has been developed to discern and make these signatures useful.

Efficacy signatures:

Drugs with beneficial effects often target specific metabolic pathways to turn them on or off. Microarrays can be used to define an efficacy signature based on pathways and known drug targets that can result in high-throughput assays for screening new drugs.

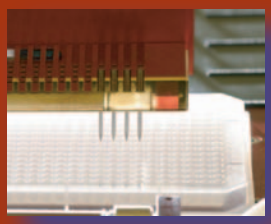
Microbe fingerprints:

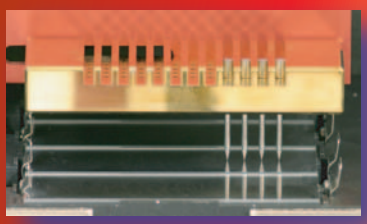
Rapid identification of unknown microbes is important in disease prevention and treatment, as well as in protection against bioterrorism weapons. Because thousands of probes can be placed on a microarray, detection systems can be designed for detection of such organisms in complex environmental samples.

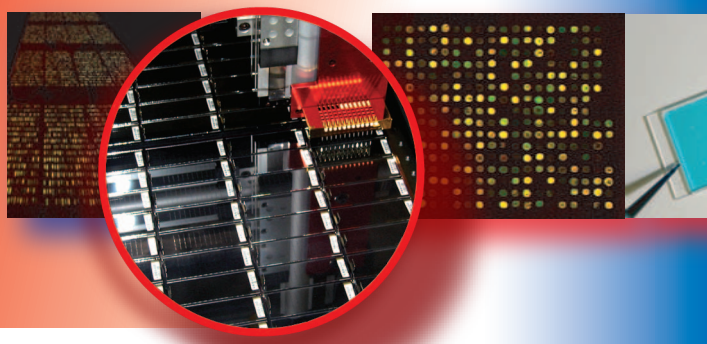
Individualized medicine:

Each person has a unique metabolic capability that results in individual-level responses to medicines. Thus, some people are more or less susceptible to the toxicity or efficacy of particular medicines. Microarrays can detect these unique gene expression patterns in individuals and will allow the safest and most effective medicine to be prescribed for a particular person. With this tool, life-saving drugs that may not be appropriate for everyone, because of adverse side effects, may be safely used on specific individuals.

Collaborations have been initiated with many government and private institutions including: Other FDA Centers (CDER, CBER, CFSAN, CDRH), National Institute of Standards and Technology, National Institutes of Health, major microarray platform providers (Affymetrix, Agilent, Applied Biosystems, GE Healthcare, and Illumina), and RNA sample providers (Ambion and Stratagene).







Centralized one-stop microarray facility:

Full capabilities for production and processing of 2-color microarrays are available in one integrated unit. From RNA purification to final data analysis and interpretation, NCTR scientists have a complete solution to microarray experimental needs.

Experienced personnel:

The Center for Functional Genomics was established in 2001 and has a stable personnel base composed of 6 scientists, including three with Ph.D.s and two with M.S..s. Experienced in RNA purification, microarray fabrications, microarray hybridizations and data processing. The lead scientist has over 25 years of experience in developing and utilizing biotechnology.

Fully integrated large-scale gene expression analyses:

From small scale studies using low density custom-designed chips to large-scale studies requiring hundreds of high-density chips, the Center for Functional Genomics can fabricate chips and perform experiments and analysis to answer biological questions related to safety, efficacy, mechanisms, organism identification, and toxicity.

Dedicated Oracle database:

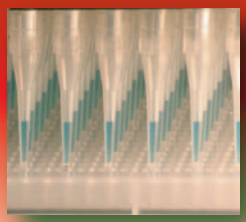
ArrayTrack is an integrated software system for managing, mining, and visualizing microarray gene expression data. It is a client-server system that uses an ORACLE server to store and integrate DNA microarray data and data from public resources about genes, proteins and pathways. The JAVA language was used to construct the entire user interface, query mechanism, data visualization and analysis tools.

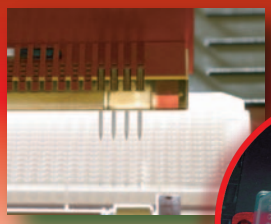
Custom fabrication of microarrays:

The Center possesses full capabilities to fabricate glass-slide based microarray chips containing hundreds to tens of thousands of gene elements. A contact-printing robotic arrayer is used to print a few arrays or many hundreds of high quality microarrays. Fabrication of microarrays with greater than 20,000 features can be produced.

Toxicogenomics:

Toxicogenomics is a new scientific sub-discipline that combines the emerging technologies of genomics, proteomics and bioinformatics to identify and characterize mechanisms of action of known and suspected toxicants. Microarrays have become an important part of this process and promise to revolutionize toxicology by providing more relevant information and requiring less cost than traditional animal-based toxicology studies.





Projects:

- Age-associated susceptibility
- Development and utility of a microarray chip specific for mitochondrial structure and function (MitoChip)
- Toxicogenomics of ochratoxin, valproic acid, PPAR-alpha agonists, herbal therapy products, AIDS therapy drugs, tattoo inks, tamoxifen, etc.
- Toxicogenomics of the altered genome: p53 status and hypomethylation, cancer susceptibility, understanding mutation assay, etc.
- Standardization of microarray technology
- Integration of metabolomic, proteomic, bioinformatics, and traditional toxicology endpoints with microarray information to create a Systems approach to understanding and interpreting health questions

LABORATORY & MICROARRAY FACILITIES

LABORATORY:

The Center for Functional Genomics contains 1150 square feet of laboratory space that consists of: 300 sq. ft. of limited-access clean-room for printing microarrays, 150 sq. ft. for processing microarrays following printing, 450 sq. ft. of ozone-controlled wet bench space to conduct microarray experiments, 250 sq. ft. of limited-access space for isolating RNA.

MAJOR EQUIPMENT

All major equipment necessary for microarray experiments is contained within the NCTR Center for Functional Genomics space as described above.

API ozone monitor
Amersham SlidePro automated hybridization instrument
Beckman Biomek FX liquid handling robot
Fast Prep Tissue Disrupter
GeneMachines OmniGrid 100 arrayer
NanoDrop scanning spectrophotometer
Stratagene Stratalinker for UV crosslinking
UV/VIS spectrophotometer
Agilent BioAnalyzer
Axon 4000B microarray scanner
BioRad iCycler for quantitative PCR
Freezers, -80 degree C (2); -20 degree C (2)
MilliQ water system
Savant Speed-Vac Concentrator
Thermocyclers
Uninterruptible power supply for arrayer and robot

EXPERIENCED RESEARCH STAFF

- Dedicated support staff with extensive experience in performance of microarray experiments
- Skilled researchers, each with 10 - 25 years experience in biological research, including; molecular biology, biochemistry, toxicology, reproductive biology, and microbial genetics

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