MMHCC
the Mouse Models
of Human Cancers Consortium

MMHCC Newsletter October 2008

MouseLine

Vaccine Prevents HER2 Tumors in Mice

Researchers at the Karmanos Cancer Institute in Michigan have tested a vaccine that they found to be 100 percent effective at preventing tumors in mice injected with breast cancer cells. The results of their study appeared September 15 in Cancer Research.

The researchers used breast cancer cells that mimic the HER2-positive tumors found in women, which account for 20 to 30 percent of breast cancer cases. Women with HER2-positive tumors can be treated with drugs that target the HER2 receptor, such as trastuzumab (Herceptin) and lapatinib, but in some women these drugs eventually stop working.

The researchers used a panel of four cell types that overexpress HER2 and represent the various prognoses for women with HER2-positive breast cancer: two types that were completely sensitive to targeted drugs, one with initial sensitivity to targeted drugs but eventual resistance, and one with complete resistance to HER2-targeted drugs.

Mice were vaccinated with bacterial DNA engineered to include the gene sequence for a large portion of the HER2 receptor. The researchers used "electrovaccination," where an electric pulse encourages cells to absorb DNA and produce the related protein for presentation to immune cells. After electrovaccination, the mice were injected with one of the four HER2 breast cancer lines. None of them developed tumors. However, control mice that had been electrovaccinated with a plasmid missing the HER2 DNA sequence developed tumors in every case. After 1 year of follow up, there were no adverse effects from vaccination.

In explaining the mechanisms of resistance to HER2-targeted drugs, the researchers noted that the various cell types they used in the study could co-exist in a single breast tumor, and that selective pressure after eliminating the drug-sensitive cells could cause increased growth of the drug-resistant cells. This would explain the relapse seen in some women.

Other tests in this study revealed aspects of how treatment-resistant cells in the mice were able to abandon HER2 and modify their cell-signaling strategy, employing an "escape mechanism" from HER2-targeted treatment.

"In patients whose tumors are refractory to drug and antibody therapy," the authors stated, "induction of comprehensive immunity by active vaccination will be critical to their long term protection."

Source: http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_092308/page3#b

Publication: Whittington PJ, Piechocki MP, Heng HH, Jacob JB, Jones RF, Back JB, Wei WZ.
DNA vaccination controls Her-2+ tumors that are refractory to targeted therapies.
Cancer Res. 2008 Sep 15; 68(18):7502-11.
PMID: 1879413

To unsubscribe from this newsletter please send an email to Dr. Betty Tarnowski tarnowsb@mail.nih.gov Send meeting announcements and other information you would like to have included in this newsletter to Ulli Wagner: ulrike@mail.nih.gov

MouseLine cont.

Most Cancer Clinical Trials Go Unpublished

Findings from fewer than one in five registered cancer clinical trials are published in peer-reviewed journals, according to a study that appeared September 15 in The Oncologist. This finding, the authors state, raises the concern of publication bias in cancer clinical trials.

Drs. Scott Ramsey and John Scoggins of the Fred Hutchinson Cancer Research Center and the University of Washington found that between 1999 and 2007, only 17.6 percent of cancer-related trials registered with ClinicalTrials.gov (the federal registry for clinical trials of interventions for serious or life-threatening conditions) went on to be published in widely accessible journals listed in the PubMed.gov online database. The researchers also found evidence of a selection bias on the part of investigators, who are less likely to publish results of a trial that did not meet its endpoints. Though more than 94 percent of the registered, industry-sponsored trials were never published, three-fourths of those in PubMed.gov reported positive results. By comparison, 59 percent of NCI-supported trials were published, half of which reported negative results.

In a related commentary, Dr. James H. Doroshow, director of NCI's Division of Cancer Treatment and Diagnosis, wrote that "the apparent lack of access to the final efficacy and toxicity data...poses multiple scientific and ethical questions." He described an NCI clinical trials database project expected to launch in 2009 that will address this problem by requiring administrative and outcome data for all intervention studies that receive NCI support.

The Oncologist is also considering creating a peer-reviewed, searchable venue for "well-executed trials that fail to meet positive endpoints," wrote Editor-in-Chief Dr. Bruce A. Chabner and Senior Editor Dr. Gregory A. Curt, for trials that are "'negative' in a sense, but valuable nonetheless."

Source: http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_092308/page3#b

Publications:

Practicing on the Tip of an Information Iceberg? Evidence of Underpublication of Registered Clinical Trials in Oncology
Scott Ramsey, John Scoggins
The Oncologist 2008; 13: 925-929

Publishing Cancer Clinical Trial Results: A Scientific and Ethical Imperative
James H. Doroshow
The Oncologist 2008; 13: 930-932

Meetings

July 14 - 16, 2008
AACR-The Latest Advances in Breast Cancer Research
Hyogo, Japan
Meeting Information:
http://www.jca.gr.jp/jasjc2/index.html

October 23 – 24, 2008
CHI's-Adaptive Clinical Trial Designs: Improving the Efficiency of Drug Development
Washington, D.C.
Meeting: http://www.healthtech.com/adt/overview.aspx?c=663

October 27 – 28, 2008
AACR-Centennial Conference: The Future of Cancer Research: Science and Patient Impact
Buffalo, New York
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/centennial-symposium-the-future-of-cancer-research.aspx

October 27 – 29, 2008
International Society for Transgenic Technologies (ISTT) Meeting
7th Annual Meeting of the Complex Trait Consortium
Toronto, Ontario, CANADA
Meeting Information: http://www.mshri.on.ca/nagy/tt2008/

October 30 – November 1, 2008
61st Annual Symposium on Cancer Research
Systems Biology of Cancer
Houston, Texas
Meeting Information: http://www.mdanderson.org/conferences

November 3 – 6, 2008
AACR-3rd Joint American-Israeli Conference on Cancer
Jerusalem, Israel
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/translational-cancer-medicine---israel.aspx

November 4 – 8, 2008
Chemotherapy Foundation Symposium XXVI: Innovative Cancer Therapy for Tomorrow
New Perspectives in Oncology Practice
New York, New York
Meeting Information: http://www.chemotherapyfoundationsymposium.org/

Meetings cont.

November 11 - 14, 2008
AACR-Targeting the P13-Kinase Pathway in Cancer Prevention
Cambridge, Massachusetts
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/special-conferences/targeting-the-pi3-kinase-pathway-in-cancer.aspx

November 16 - 19, 2008
AACR–7th International Conference on Frontiers in Cancer Prevention Research
Washington, D.C.
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/frontiers-in-cancer-prevention-research.aspx

Notices and Funding Opportunities

Reminder Concerning Grantee Compliance with Public Access Policy and Related NIH Monitoring Activities
NOT-OD-08-119
National Institutes of Health
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-119.html

SCAW IACUC-Advanced Workshop on October 8, 2008 in Las Vegas, NV
NOT-OD-08-120
National Institutes of Health
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-120.html

Non-Competing Grant Awards under the Current Continuing Resolution
NOT-OD-09-002
National Institutes of Health
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-002.html

Repository News

Discontinuation of Strain
The NCI MMHCC Repository has discontinued distribution of mouse strain 01XE3, FVB/N-Tg(MMTV-PyVT)634Mul as this model is available through the Jackson Laboratory
http://jaxmice.jax.org/strain/002374.html

caBIG™ Tools

caBIG™ Life Sciences Distribution
The caBIG™ tools inventory includes over 40 software tools, database technologies, and Web-based applications in the areas of: clinical trials management, biospecimens, imaging, genome annotation, proteomics, microarrays, pathways, data analysis and statistical tools, data sharing, infrastructure, vocabularies, and translational research. They are based on open-source software and free.
The most recent releases are **suites of interoperable tools for** clinical trials management and **life sciences.**

The tools brought together in the **caBIG™ Life Sciences Distribution** facilitate the discovery of the next generation of cancer diagnostics and therapeutics to realize the vision of Molecular, or Personalized, Medicine. These tools support a variety of capabilities from tracking and managing biospecimens, to analyzing and integrating microarray data. Together, they enable cancer researchers to more easily integrate, analyze, and share data from many different sources

Life Sciences Distribution capabilities and tools include:

- caArray
- Cancer Genome-Wide Association Studies (caGWAS)
- caTissue Core
- National Cancer Imaging Archive (NCIA)
- geWorkbench (coming soon)
- Clinical Trials Object Data System (CTODS)
- caGrid

For more information see attached brochure.

National Cancer Institute

Getting Connected with caBIG™

LIFE SCIENCES DISTRIBUTION

The tools brought together in the Life Sciences Distribution facilitate the discovery of the next generation of cancer diagnostics and therapeutics to realize the vision of Molecular, or Personalized Medicine. They support a variety of capabilities from tracking and managing biospecimens, to analyzing and integrating microarray data. Together, they enable cancer researchers to more easily integrate, analyze and share data from many different sources.

All caBIG™ Life Sciences Distribution components can be plugged into the national caGrid backbone that connects caBIG™ informatics resources across research organizations.

The individual tools included in this bundle are free and available for immediate download and use in organizations, and the bundling of these related and synchronous tools will facilitate even easier and more streamlined adoption in institutions.

This document provides an overview of the Life Sciences Distribution. It describes what the bundle is designed to do, its features and benefits, and the requirements for implementing the tools.

Capabilities and tools included in this bundle

- Biobanking management system [caTissue Core]
- Virtual clinical data repository [Clinical Trials Object Data System (CTODS)]
- Genome-wide data management system [Cancer Genome-Wide Association Studies (caGWAS)]
- *In vivo* image repository [National Cancer Imaging Archive (NCIA)]
- Microarray data management system [caArray]
- Microarray gene expression and sequence data management [geWorkbench]
- caBIG™-compatible systems architecture [caGrid]

The Life Sciences Distribution is part of the National Cancer Institute's overarching goal to connect the people, institutions, and data in the cancer community through caBIG™. This collection of tools and capabilities is one of three "bundles" that have been designed to help support and streamline clinical trials, imaging, tissue banking, and integrative cancer research, and to provide the materials needed to join the secure caBIG™ data-sharing framework.

Visit https://caBIG.nci.nih.gov/inventory for more detailed information and access to caBIG™ resources.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Getting Connected with caBIG™

LIFE SCIENCES DISTRIBUTION

Tools	Description	Benefits
caArray	caArray is a microarray data management system that guides the annotation and supports the exchange of array data.	• Provides both web browser-based and programmatic access to microarray data • Facilitates integration of array data with diverse data types including clinical, imaging, tissue, and other functional genomics data through harmonization with relevant caBIG™ models • Connects to analytical tools like geWorkbench
Cancer Genome-Wide Association Studies (caGWAS)	Cancer Genome-Wide Association Studies (caGWAS) allows researchers to integrate, query, report, and analyze a variety of data types from multiple sources including microarray, genomic, immuno-histochemistry, imaging, and clinical data through a single application.	• Facilitates rapid sharing of information • Accelerates the process of analyzing results from various biomedical studies • Allows researchers and bioinformaticians to access and analyze clinical and experimental data across multiple clinical studies
caTissue Core	caTissue is a biobanking management tool to collect, manage, process, annotate, request, and distribute biospecimens and associated information.	• Provides browser-based and programmatic access to biospecimen data • Provides a means for collecting, processing, storing, and distributing specimens for correlative science cancer research • Manages tissue, fluid, cell, and molecular biospecimen information • Allows users to find and request specimens needed for use in molecular correlative studies
geWorkbench	geWorkbench is a desktop bioinformatics platform that offers a comprehensive and extensible collection of tools for the management, analysis, visualization, and annotation of microarray-based gene expression and sequence data.	• Desktop application with a powerful graphical interface • Enables integrated analysis of genomic data (gene expression, sequence, pathway, structure) • Brings together analysis and visualization tools for gene expression, sequences, pathways, and other biomedical data • Provides seamless access to databases, computational services, and biological annotation sources • Enables sophisticated analysis of genomic data through the integration of visualization tools, external databases, and computational services
National Cancer Imaging Archive (NCIA)	NCIA is a searchable repository of *in vivo* cancer images, such as CT, MRI, and Digital X-rays. NCIA also contains annotation files (PDF, image markup) and annotation data provided by a curator. Cancer images are integrated with clinical and genomic data.	• Enables development of imaging resources that will lead to improved clinical decision support • Provides an accessible repository for images along with key annotations • Accelerates diagnostic imaging decision-making and quantitative imaging assessment of drug response • Serves as a platform for image data management and integration with other research data types
Data Repository	**Description**	**Benefits**
Clinical Trials Object Data System (CTODS)	CTODS is a database and software system for storing and sharing clinical trials data in both identifiable and de-identified form.	• Enables a cancer research organization to utilize data from any in-house caBIG™-compatible Clinical Trials Data Management System (CDMS) or data source for non-clinical research. • Enables a cancer research organization to share or access de-identified clinical trials data (data that have all patient identification information removed) over the national caGrid
Infrastructure	**Description**	**Benefits**
caGrid	caGrid is a service-oriented architecture and federation that connects caBIG™-compatible systems together regardless of where they are installed.	• Query across data resources installed in different locations • Automatically integrate comparable data from different sources • Create workflow pipelines for data retrieval and analysis using resources across the grid

caBIG™
cancer Biomedical Informatics Grid ™

Features

caArray

- Web-based forms for researcher submission and annotation of data consistent with MIAME guidelines
- Bulk data import of MAGE-TAB files
- Group-based permission scheme including settings for publishing data to the public domain
- Search and navigate features to readily discover and extract data of interest
- Submission and retrieval of Affymetrix, GenePix, and Illumina native expression array files
- Submission and retrieval of Affymetrix and Illumina native SNP array files

caGWAS

- Standardized model to represent SNP genotype data, SNP association findings, population frequency data, and clinical phenotype
- Support for search and retrieval of genome-wide association findings in the context of genes or chromosomal regions of interest
- Allows users to load GWAS studies and provides powerful search capabilities for small datasets or bulk downloads of large genotype files
- Allows for genome-wide SNP association studies
- Provides touch points to clinical and specimen annotations through the caBIG™-compatible interface

caTissue Core

- Web-based application for entering or searching for biospecimens
- Tracking of multiple specimens from the same participant
- Tracking of refined materials (RNA, DNA, Protein) that are used for molecular analysis
- Role-based permission scheme for repository personnel and researchers
- Tracking of quality assurance, distribution, derivation, and aliquotting of biospecimens
- Flexible storage container structure

geWorkbench

- Analysis and visualization tools for microarray-based gene expression profiling data from a variety of systems including Affymetrix MAS5/GCOS, Matrix format (geWorkbench), RMAExpress, and GenePix
- Analysis and visualization tools for gene and protein sequence data (FASTA); plug-in components including filter and normalize, promoter analysis, regulatory networks, differential expression, enrichment analysis, annotation, sequence analysis, and pattern discovery
- Support for pathways (BioCarta), gene ontologies, networks, and patterns based on regular expressions
- Integrated access to many external data sources and computational services (e.g., GoldenPath at Santa Cruz, NCBI BLAST, BioCarta diagrams through caBIO)
- Front-end to caArray and access-provider to caGrid-enabled computational resources
- Additional viewers including molecular structure and raw expression

NCIA

- Searchable repository of *in vivo* cancer images
- Access to image archives and imaging resources
- Facilitates development and validation of analytical software tools that support lesion detection and classification software, accelerate diagnostic imaging decisions, and quantify imaging assessment of drug response

Features

CTODS

- Based on open standards and standards-based tools designed to enable cancer research community to share, interpret, and integrate de-identified information
- Consistent with the Biomedical Research Integrated Domain Group (BRIDG) model that underpins data interchange standards and technology solutions, which enable harmonization between the biomedical/clinical research and healthcare arena

Features

caGrid

- Nationally-deployed, standards compliant, data and analysis grid that any caBIG™-compatible system can plug into or draw from
- Businesss Process Execution Language (BPEL) workflow engine for data analysis pipeline construction and execution
- Federated, cross-domain data mining and integration
- Standardized programming interfaces for application developers

BUNDLE REQUIREMENTS

The caBIG™ Life Sciences Distribution is multi-platform, and it will run on any appropriately powered and configured systems capable of running the underlying software infrastructure. Windows, Linux, and MacOSX operating systems are all supported. Check the caBIG™ tools Web page (https://cabig.nci.nih.gov/tools) for the most up-to-date information on the system requirements outlined below.

SUPPORTING SOFTWARE

- Apache Ant
- Apache Axis
- Java Development Kit (JDK)
- JBoss Application Server
- MySQL Database
- Hibernate
- Common Security Module: CSM
- Globus, part of caGrid installation
- Other software: MIRC T29-a and Cedara I-Response Workstation (IRW) (for NCIA), Castor (for CTOM)

RESOURCES

Specific tool information: https://cabig.nci.nih.gov/tools

caGrid information: https://cabig.nci.nih.gov/workspaces/Architecture/caGrid

Overview of caBIG™: http://cabig.cancer.gov

Detailed information about caBIG™, including training compatibility, etc: https://cabig.nci.nih.gov

For general information about "Getting Connected with caBIG™": https://cabig.nci.nih.gov/getting_connected

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