MMHCC
the Mouse Models of Human Cancers Consortium

MMHCC Newsletter September 2008

MouseLine

Vitamin C Injections Slow Tumor Growth in Mice

Injecting high doses of vitamin C into mice with aggressive cancers slowed the growth of their tumors significantly without affecting normal tissues, researchers are reporting. While the potential anticancer effects of vitamin C (also known as ascorbate or ascorbic acid) have been studied for decades, the new findings provide "a firm basis" for advancing vitamin C as a pharmacologic agent for treating human cancer, they write in the August 5 Proceedings of the National Academy of Sciences.

To test vitamin C injections, Dr. Mark Levine of the National Institute of Diabetes and Digestive and Kidney Diseases and his colleagues delivered high doses of ascorbate into the veins or abdominal cavities of mice with aggressive forms of brain, ovarian, and pancreatic tumors. The injections reduced tumor growth by approximately half compared with xenografts in untreated mice.

The delivery method appears to be critical for efficacy. When vitamin C is taken orally, the body prevents blood levels of ascorbate from exceeding a narrow range. This may explain why two previous NCI-sponsored clinical trials found no survival benefit from vitamin C given orally. Although scientific interest in vitamin C for cancer diminished after the second study appeared in 1985, some complementary and alternative medicine practitioners have continued to administer high doses of ascorbate to cancer patients.

The new findings suggest that hydrogen peroxide formation, a result of the ascorbate treatment, is responsible for the anticancer activity. Thus, the study provides a much-needed biological rationale for testing the strategy in patients, notes an accompanying editorial.

The vitamin C treatments did not cure the mice, so the study authors suggested that high doses of intravenous ascorbate should be studied in combination with other cancer therapies in humans.

Source: http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_081908/page9#f

Publication:
Chen Q, Espey MG, Sun AY, Pooput C, Kirk KL, Krishna MC, Khosh DB, Drisko J, Levine M.
Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice.
Proc Natl Acad Sci U S A. 2008 Aug 12;105(32):11105-9
PMID: 18678913

MouseLine

Lapatinib Limits Growth of Breast Cancer Brain Metastases in Mice

Investigators from NCI's Laboratory of Molecular Pharmacology report that in a mouse model of breast cancer, the small-molecule inhibitor lapatinib (Tykerb) can cross the blood-brain barrier and prevent approximately 50 percent of large HER2-positive brain metastases. Their study appeared online July 29 in the Journal of the National Cancer Institute.

The drug trastuzumab (Herceptin) targets cancer cells that overexpress the protein HER2. These cells have shown a greater potential to spread (metastasize) to the brain, but trastuzumab, a large antibody molecule, cannot cross the blood-brain barrier to reach these metastatic cells.

Lapatinib, which is approved for the treatment of metastatic breast cancer, is a much smaller molecule that is capable of permeating the blood-brain barrier. Its effectiveness in clinical trials treating large secondary tumors in the brain has been limited, so the researchers wanted to see if it might be better at preventing the growth of these tumors when they are still small.

They injected mice with a breast-cancer cell line engineered to overexpress HER2. The mice received a low or a high dose of lapatinib, or a control solution, twice daily for 24 days. Those that received lapatinib in either dose developed half as many large metastases as those that received the control solution.

"What our model system shows is that lapatinib might prevent micrometastases from growing into life-threatening macrometastases," explained Dr. Patricia Steeg, senior author of the study. In the future, stated the authors, preventative therapy to suppress the growth of micrometastases could possibly be combined with standard treatments for large brain metastases, such as neurosurgery or radiation therapy.

Source: http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_080508/page3#b

Publication:
Gril B, Palmieri D, Bronder JL, Herring JM, Vega-Valle E, Feigenbaum L, Liewehr DJ, Steinberg SM, Merino MJ, Rubin SD, Steeg PS.
Effect of lapatinib on the outgrowth of metastatic breast cancer cells to the brain.
J Natl Cancer Inst. 2008 Aug 6;100(15):1092-103
PMID: 18664652

Meetings

September 21 – 25, 2008
CHI's-Multiplexed Genomics Tools: Targeting the Missing Links Between Health and Disease
Providence, Rhode Island
Meeting Information: http://www.healthtech.com/qpe/overview.aspx?c=570

September 21 – 27, 2008
7th Annual Workshop on the Pathology of Mouse Models for Human Disease
Ithaca, New York
Meeting Information: http://courses.jax.org/2008/path08.html

September 22 – 25, 2008
AACR-3rd Annual International Conference on Molecular Diagnostics in Cancer Therapeutic Development
Philadelphia, Pennsylvania
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/molecular-diagnostics-in-cancer-therapeutic-development.aspx

October 6 - 7, 2008
Aging and Cancer: Two Sides of the Same Coin?
An American Federation for Aging Research Conference in cooperation with the American Association for Cancer Research
New York, New York
Meeting Information: http://www.afar.org/cancerconf.html

October 8, 2008
CHI's-Accelerating Proof of Concept: Better Early Decision-Making for More Effective Drug Development
Boston, Massachusetts
Meeting Information: http://www.healthtech.com/pfc/overview.aspx?c=669

October 20 – 21, 2008
CHI's-Discovery on Target RNAi for Screening
Boston, Massachusetts
Meeting Information: http://www.healthtech.com/dot/rnaid/rnaid.aspx?&c=494

October 21 – 24, 2008
EORTC-NCI–AACR Symposium on Molecular Targets and Cancer Therapeutics
Geneva, Switzerland
Meeting Information: http://www.ecco-org.eu/Conferences-and-Events/EORTC-NCI-AACR-2008/page.aspx/268

Notices and Funding Opportunities

Integration of Mouse Models into Human Cancer Research (U01)
RFA-CA-08-018
National Cancer Institute
Application Receipt Date(s): November 14, 2008
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-018.html

Limited Competition for the Biomedical Informatics Research Network Community Service Award (U24)
RFA-RR-08-008
National Center for Research Resources
http://grants.nih.gov/grants/guide/rfa-files/RFA-RR-08-008.html

Quantitative Imaging for Evaluation of Responses to Cancer Therapies (U01)
PAR-08-225
National Cancer Institute
http://grants.nih.gov/grants/guide/pa-files/PAR-08-225.html

Etiology, Prevention, and Treatment of Hepatocellular Carcinoma (R01, R21, P01)
PA-08-243, PA-08-244, PAR-08-245
National Cancer Institute
National Institute on Alcohol Abuse and Alcoholism
National Institute of Diabetes and Digestive and Kidney Diseases
http://grants.nih.gov/grants/guide/pa-files/PA-08-243.html
http://grants.nih.gov/grants/guide/pa-files/PA-08-244.html
http://grants.nih.gov/grants/guide/pa-files/PAR-08-245.html

September IACUC 101 & 201 PLUS Workshops in San Francisco, California
NOT-OD-08-103
National Institutes of Health
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-103.html

Collaborative Studies on Systems Biology of Complex Phenotypes (R01)
RFA-GM-09-007
National Institute of General Medical Sciences
http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-09-007.html

Metals in Medicine (R01)
PA-08-251
National Institute of General Medical Sciences
National Cancer Institute
National Institute of Environmental Health Sciences
Office of Dietary Supplements
http://grants.nih.gov/grants/guide/pa-files/PA-08-251.html

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caBIG™ Tools

Cancer Genome-Wide Association Scan (caGWAS)

Cancer Genome-Wide Association Studies (caGWAS) allows researchers to integrate, query, report, and analyze significant associations between genetic variations and disease, drug response or other clinical outcomes. New breakthroughs in SNP array technologies make it possible to genotype hundreds of thousands of single nucleotide polymorphisms (SNPs) simultaneously, enabling whole genome association studies. Within the Clinical Genomic Object Model (CGOM), the caIntegrator team created a domain model for Whole Genome Association Study Analysis. CGOM-caGWAS is a semantically annotated domain model that captures associations between Study, Study Participant, Disease, SNP Association Analysis, SNP Population Frequency and SNP annotations.

Following the principals of caBIG, caGWAS APIs and web portal provide:

- A semantically annotated domain model, database schema with sample data, seasoned middleware, APIs, and web portal for GWAS data;
- platform and disease agnostic CGOM-caGWAS model and associated APIs;
- the opportunity for developers to customize the look and feel of their GWAS portal;
- a foundation of open source technologies;
- a well-tested and performance-enhanced platform, as the same software is being used to house the CGEMS data portal at https://caintegator.nci.nih.gov/cgems;
- accelerated analysis of results from various biomedical studies; and
- a single application through which researchers and bioinformaticians can access and analyze clinical and experimental data from a variety of data types, as caGWAS objects are part of the CGOM, which includes microarray, genomic, immunohistochemistry, imaging, and clinical data.

Intended Audiences: Translational Research
Tool Maturity Assessment: Stable Release (Adoption in Progress)
Installation Level: Intermediate - technical assistance may be required, download may require supporting infrastructure or software

For more information visit: https://cabig.nci.nih.gov/tools/caGWAS

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