

Tracing Sarcoma to its Source

Using mice genetically engineered with cancer, U geneticists determined that synovial sarcoma develops in muscle cell precursors known as myoblasts. Their finding, published in the April issue of the journal *Cancer Cell*, may help in developing new treatments for this aggressive cancer.

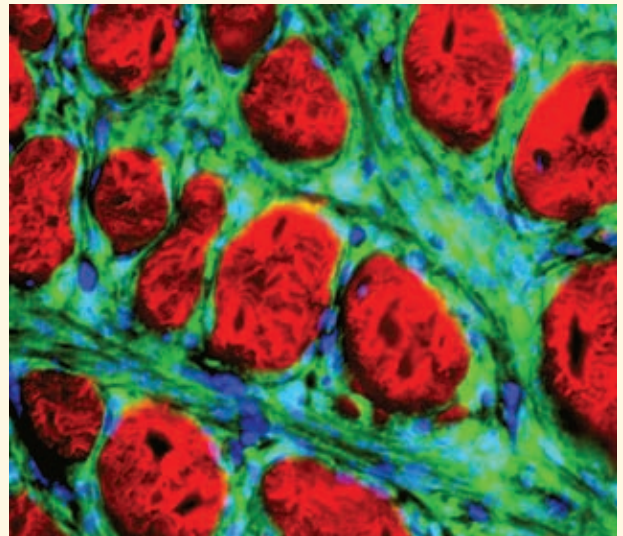
Teenagers and young adults account for most of the 900 cases of sarcoma diagnosed each year in the United States. Survival rates vary widely; as few as 25 percent of patients survive five years.

Myoblasts are the likely source of synovial sarcoma in humans, according to Mario R. Capecchi, Ph.D., distinguished professor of human genetics and biology, and co-chair of the Department of Human Genetics at the U School of Medicine who also is an investigator with the Howard Hughes Medical Institute.

To learn where the synovial sarcoma originates, Capecchi and his colleagues used mice in which they could activate the *SYT-SSX2* fusion gene in various muscle cells or their precursors. All synovial sarcomas contain an *SYT-SSX* fusion gene, which occurs when two chromosomes break and combine with another.

Although the fusion gene's precise role in causing synovial sarcoma is unknown, the researchers discovered that, when the gene was activated in myoblasts, the cells became cancerous 100 percent of the time. An unidentified factor in nearby joint cartilage also contributed to cancerous myoblasts.

The study's authors include: Malay Haldar, human genetics graduate student; Stephen L. Lessnick, M.D., assistant professor of pediatric hematology/oncology;



MALAY HALDAR, UNIVERSITY OF UTAH

University of Utah researchers have engineered a mouse model of synovial sarcoma, which should speed the search for new treatments for the human cancer. The model revealed that the cancer originates in muscle precursor cells called myoblasts. This photo shows a microscopic cross-section of part of a synovial sarcoma tumor. Cancerous cells that developed from myoblasts are shown in green and surround red muscle fibers. Cell nuclei are blue.

Jeffrey D. Hancock, M.D., fellow in pediatric hematology/oncology; and Cheryl M. Coffin, M.D., professor and chief of pediatric pathology. (www.cancerjournal.org)

Clues to Autism William M. McMahon, M.D., professor and chair of the Department of Psychiatry, helped to identify a gene that may predispose people to autism and confirmed that Utahns have an exceptionally high rate of the disorder.

In the Autism Genome Project (AGP), a worldwide consortium of researchers identified the *nerxin 1* gene, believed to be important for developing contact and communication between neurons. They also discovered that a previously unidentified region on chromosome 11 may contain another gene related to autism. Published online in the Feb. 19 edition of *Nature Genetics*, the project included Utah co-investigators McMahon and Hilary Coon, Ph.D., research professor of psychiatry.

In a study published in February by the U.S. Centers for Disease Control and Prevention, McMahon found that Utah had the third highest rate of autism—1 in 133 children—among 14 states examined. (<http://www.nature.com/search/executeSearch>)

Too Much of a Good Thing

Excessive levels of an antioxidant usually considered an important defense against heart disease—reduced glutathione—may harm the heart, causing reductive stress.

The finding, published in the Aug. 10 issue of *Cell*, also indicates that a new class of drugs can be developed to treat or even prevent heart disease caused by reductive stress, according to principal author Ivor J. Benjamin, M.D., Christi T. Smith Endowed Chair in Cardiology Research and division chief of cardiology at the U School of Medicine.

Co-authors from the U Division of Cardiology include: Namakkal S.

Rajasekaran, Ph.D., research associate; Andras Orosz, Ph.D., research instructor; Ryan P. Taylor, Ph.D., postdoctoral fellow; Xiu Q. Zhang, Ph.D., research associate; Tamara J. Stevenson, senior lab specialist; William H. Barry, M.D., professor; and Shannon J. Oldelberg, Ph.D., assistant professor. Others are from the University of Texas Southwestern Medical Center, Dallas, Harvard Medical School, and the Centre for Developmental Biology, Toulouse, France.

(<http://www.cell.com/content/article/abstract?uid=PIIS0092867407008495>)

Solution for Stress Incontinence New research should help women who suffer from stress urinary incontinence decide which of two types of surgery will work best for them.

Up to 50 percent of American women are affected by stress urinary incontinence, although only about 15 percent require treatment.

Peggy Norton, M.D., U professor of obstetrics and gynecology, and chief, Division of Urogynecology, is a co-author of the national study, published in the May 24 issue of *The New England Journal of Medicine*, which reported that women were more satisfied with surgery involving an insertion of a sling, made of their own tissue, than with the Burch procedure, which involves suturing underlying ligaments. However, the sling procedure can lead to negative side effects, including urinary tract infections and difficulty urinating. (<http://content.nejm.org/cgi/content/short/356/21/2143>)

Pain Relief under a Shell Researchers discovered that venomous molecules found in the predatory marine cone snail have therapeutic potential and could lead to new pain-relief drugs. The snails produce a range of more than 50,000 disulfide-rich neurotoxins called conotoxins. Published in the April issue of *Chemistry & Biology*, the study revealed that peptide-polymer hybrids (polytides) of conotoxin significantly improved analgesic properties in animal models.

Authors from the U of U include: Grzegorz Bulaj, Ph.D., assistant professor of medicinal chemistry, College of Pharmacy; Doju Yoshikami, Ph.D., professor of biology; and Baldomero M. Olivera, Ph.D., distinguished professor of biology, HCl investigator, and Howard Hughes Medical Institute professor. (<http://www.chembiol.com/content/article/abstract>)

Blood Logic Heart attack, cancer, and organ transplant patients could benefit from a recent discovery about clot retraction. U researchers found that the drug rapamycin, used in patient treatments, also blocks clot remodeling in blood vessels.

The study's lead author, Andrew S. Weyrich, Ph.D., associate professor of internal medicine and an investigator in the U Program in Human Molecular Biology and Genetics (HMBG), and senior author, Guy A. Zimmerman, M.D., professor of internal medicine and HMBG director, published their findings in the March 1 issue of *Blood*.

HMBG co-authors from the Eccles Institute of Human Genetics include: Hansjorg Schwertz, postdoctoral fellow; Neal D. Tolley, research associate; Jason Foulks, postdoctoral fellow; and the late Melvin M. Denis, M.D., Ph.D. From the School of Medicine are: Elliott Spencer, postdoctoral fellow; Larry W. Kraiss, M.D., professor of vascular surgery; Kurt H. Albertine, Ph.D., professor of pediatrics; and Thomas M. McIntyre, Ph.D., former professor of internal medicine and pathology. (<http://bloodjournal.hematologylibrary.org/cgi/content/abstract/bloodjournal;109/5/1975>)

Muscling out Steroids for Infant Bronchiolitis

Using steroid medication to treat bronchiolitis in infants does not prevent hospitalization or improve their respiratory symptoms, according to a study published in the July 26 issue of *The New England Journal of Medicine*.

Howard M. Corneli, M.D., U of U professor of pediatrics, was principal investigator for the study, which the U and Primary Children's Medical Center led for the Pediatric Emergency Care Applied Research Network (PECARN) to resolve controversy from previous research.

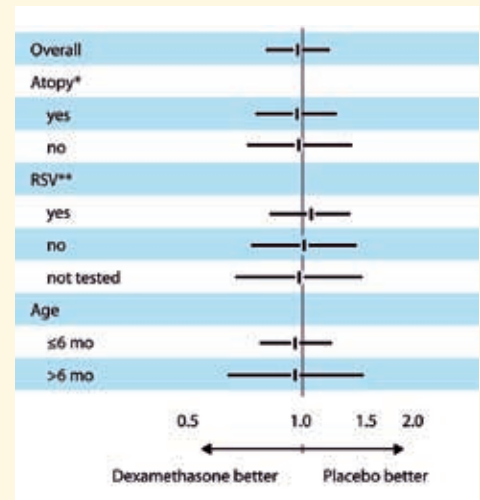
Emergency departments at 20 hospitals across the country participated in the study conducted between November and April, when bronchiolitis is prevalent. A common viral lower respiratory infection in infants, bronchiolitis is the leading cause of hospitalization for U.S. infants and accounts for more than 100,000 admissions each year. Associated hospital charges exceed \$700 million annually.

The study compared hospitalization rates for 600 children, between the ages of two and 12 months, with moderate to severe bronchiolitis who visited emergency rooms. Patients were treated with dexamethasone, a glucocorticoid form of steroid medication, or a placebo. They were evaluated after one hour and, again, after four hours. Results showed an identical hospital admission rate at nearly 40 percent. But the placebo group did as well as the group treated with active medication.

The best solution to the problem of bronchiolitis, according to Corneli, might be to find a vaccine for Respiratory Syncytial Virus (RSV), the most common cause of bronchiolitis, accounting for 50-80 percent of all cases.

Other study sites were located in Pennsylvania, California, Michigan, Ohio, Missouri, New York, Washington, D.C., Massachusetts, Maryland, and New Jersey.

(<http://content.nejm.org/content/vol357/issue4/index.shtml>)



Estimated risk ratios for hospital admission among infant bronchiolitis patients treated with dexamethasone are compared to those for patients who received placebos. Horizontal lines represent 95 percent confidence intervals. Risk ratios less than 1 favor dexamethasone; a value of 1.0 indicates equivalence between the two groups. Specific subgroups also were evaluated. These included patients with a past medical history of eczema or family history of asthma (*), and those who tested positive for respiratory syncytial virus (**).

Resist Exercise? Eccentric exercise resistance training has been proven to prevent thigh-muscle atrophy, a common ailment following anterior ligament reconstruction surgery.

In a study published in the March issue of *Journal of Bone and Joint Surgery*, researchers used MRI images to measure the differences between patients using eccentric therapy versus standard rehabilitation. Muscle size and strength improved more than twofold in the eccentric group.

Faculty from the College of Health's Division of Physical Therapy involved in the study included: Leland E. Dibble, Ph.D., P.T., associate professor; J. Parry Gerber, Ph.D., P.T., former graduate student; Paul C. LaStayo, Ph.D., P.T., associate professor; and Robin L. Marcus, Ph.D., P.T., associate professor. Faculty from the medical school's Department of Orthopaedic Surgery included: Robert T. Burks, M.D., professor, and Patrick E. Greis, M.D., associate professor. (www.ejbs.org/cgi/content/abstract/89/3/559)

Ditto on Results A study published in the Feb. 15 issue of *The New England Journal of Medicine* does not support treating children with acute Kawasaki disease with a single-pulsed dose of intravenous methylprednisolone in addition to the conventional intravenous immune globulin therapy.

Typically, intravenous immune globulin and aspirin reduce the risk of coronary-artery abnormalities and systemic inflammation. Some children still develop abnormalities, however. Previous studies have suggested that primary corticosteroid therapy might be beneficial. In the study, co-authored by L. LuAnn Minich, M.D., U professor of pediatric cardiology, results showed that both the placebo and treated groups had similar results for the number of days spent in the hospital, days with fever, rates of re-treatment with intravenous immune globulin, and numbers of adverse events. (<http://content.nejm.org/cgi/content/abstract/356/7/663>)

Wear It Well A skin patch for hormone replacement therapy may be safer than pills, according to a study published in the February issue of *Circulation*.

That's good news for women who want to use estrogen for menopause symptom relief—and valuable information for women who have a history of blood clots, according to study co-author Eliot A. Brinton, M.D., research associate professor of cardiovascular genetics in the School of Medicine.

The study, which included women between ages 42-58, found that oral estrogen increases the risk of venous blood clots in postmenopausal women. Patients taking oral estrogen had a 4.2 times higher risk compared to women not taking estrogen replacement, while those using the patch had 0.9 times the risk. (<http://circ.ahajournals.org/cgi/content/abstract/115/7/840>)

Sharing Pathways A new treatment for psoriasis that involves targeting key inflammatory mediators (IL-12 and IL-23) is highly effective, according to a recent study.

The results shed light on other immune-mediated diseases that share the same signaling pathways, specifically inflammatory bowel disease (IBD). A previous study suggests that therapeutics that target the IL-12 and IL-23 signaling pathway appear to treat both psoriasis and IBD.

Gerald Krueger, M.D., professor of dermatology, co-authored the study published in the Feb. 8 issue of *The New England Journal of Medicine*. (<http://content.nejm.org/cgi/content/abstract/356/6/580>)

A Father's Burden While it has long been known that having more children can be detrimental to a mother's health, a new study shows that fathers pay a price, too.

In one of the largest studies ever to examine mortality and reproduction, co-author Ken R. Smith, Ph.D., Huntsman Cancer Institute investigator and U professor of family and consumer studies, found that for each additional child a man had after his first, his mortality rate went up by 12 percent in the five years after his final child was born. For mothers, the mortality rate rose 21 percent for each additional child.

The study was published in the Dec. 27, 2006, issue of the *Proceedings of the National Academy of Sciences*. (<http://www.pnas.org/cgi/content/abstract/104/2/553>)

Deterring Diabetes By blocking production of a fat molecule that plays an important role in insulin resistance, U researchers improved insulin sensitivity in obese rats, ultimately preventing the development of type 2 diabetes.

Some 21 million Americans have either type 1 or type 2 diabetes. The results of the study, published in the March 6 issue of *Cell Metabolism*, could be instrumental in developing drugs to treat or prevent in humans type 2 diabetes, a disease directly linked with obesity. "Insulin-sensitizers are some of the most commonly prescribed drugs on the market," said doctoral student William L. Holland, who co-authored the study with Scott A. Summers, Ph.D., associate professor of internal medicine. (<http://www.cellmetabolism.org>)