

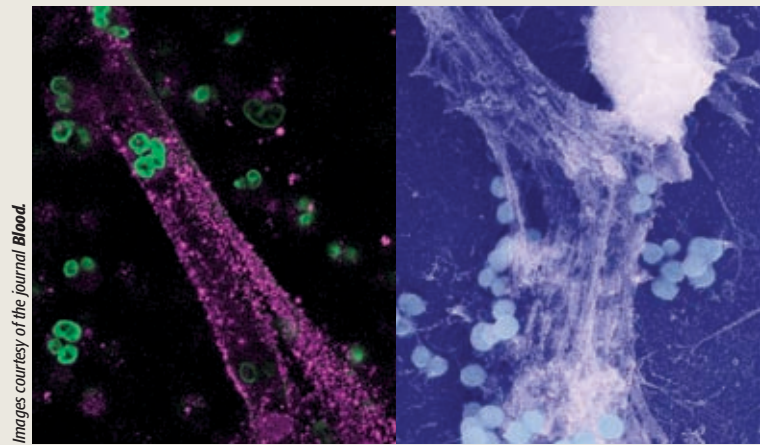
Working Without a NET Puts Newborns at Risk

When locked in mortal combat with infection, some mature white blood cells have a formidable weapon: a DNA net—neutrophil extracellular trap (NET)—that captures and kills bacteria invading the human body. But the white blood cells of newborn infants, born either at term or prematurely, lack the ability to form and cast this “death” NET, which may explain why millions of newborns worldwide are at greater risk for sepsis, a potentially deadly blood infection.

In the June 18 edition of the journal *Blood*, University of Utah researchers led by Christian C. Yost, M.D., pediatric intensive care physician and assistant professor of pediatrics, reported a study in which they analyzed neutrophils (white blood cells) in the umbilical cord blood of 16 premature infants. Yost found that, unlike mature neutrophils, those in the premature babies didn’t eject the DNA mixture as they prepared to die. Yost and Guy A. Zimmerman, M.D., professor of internal medicine and the study’s senior author, believe that may explain in part why newborns and preemies are more at risk for sepsis.

Zimmerman and Yost suspect the NET formation defect may stem from the deficiency of one or more key factors in regulatory mechanisms that govern the NET-generating process and that these factors have not had time to develop in the neutrophils of newborns, particularly premature infants.

“Neonatal neutrophil dysfunction—a term for these white blood cell



Images courtesy of the journal *Blood*.

Net 1: Strands of DNA (purple) from a mature neutrophil form a NET that contains nuclear material (green balls) to break down and destroy bacteria. **Net 2:** White strands of DNA form a NET to capture staph bacteria (blue balls) from a mature neutrophil (white ball at top of photo).

abnormalities—affects many infants, because there are so many premature births across the globe,” Yost said. “It’s a huge public health issue.”

Preterm births, typically defined as those occurring at 37 weeks or earlier, have increased 20 percent in the United States since 1990, according to a recent Institute of Medicine report. (bloodjournal.hematologylibrary.org/)

Autism Links In the April 27 online issue of the journal *Pediatrics*, U Department of Psychiatry researchers showed that women who give birth at 35 or older are 1.7 times more likely to have a child with an autism spectrum disorder (ASD), compared with women between the ages of 20-34. Children diagnosed with ASD also were nearly 1.8 times more likely to be the firstborn.

Although they didn’t identify a causal relationship between breech births and autism, researchers found that children diagnosed with the disorder were more than twice as likely to have been a breech presentation, meaning they were not born head first. Deborah A. Bilder, M.D., assistant professor of psychiatry, led the study of birth records of 8-year-old Utah children, which was conducted with the Utah Department of Health. (pediatrics.aappublications.org/)

PFDs in the Genes? Women who have pelvic floor disorders (PFDs) may be genetically predisposed to the problem. After analyzing the DNA of 70 women from 32 families with at least two cases of PFD, U of U School of Medicine researchers found significant evidence that genes in a region of the genome called chromosome 9q21 may be inherited together in women who have pelvic organ prolapse, a type of PFD in which the uterus, bladder or other pelvic organ drops down and protrudes abnormally.

Risk factors such as childbirth, increased age, smoking, and obesity may contribute to

PFDs, but they do not fully explain the development of these disorders, according to Kristina Allen-Brady, Ph.D., research assistant professor of biomedical informatics and first author of the study, which appeared in the May 15 issue of the *American Journal of Human Genetics*. (cell.com/AJHG)

Brain Mapping in Double Time Research teams at the U of U and University of Colorado, Boulder, have made technical advances that will dramatically accelerate the process for high-speed “color” ultrastructure brain mapping.

The new automation tools, developed at Colorado’s Center for 3D Electron Microscopy, allow capture of 25,000 transmission electron microscope (TEM) images weekly. In parallel, the U of U Scientific Computing and Imaging Institute (SCI) developed software to automatically merge thousands of images into gigabyte-scale mosaics and align the mosaics into terabyte-scale volumes. Teams at the U Moran Eye Center developed TEM-compatible molecular probes and classification software to tag every cell with a molecular signature, creating “color” TEM imaging.

Robert Marc, Ph.D., director of research at the Moran center and U professor of ophthalmology and visual sciences, was senior author of the article published March 30 in *PLoS Biology*. (biology.plosjournals.org)

Preventing Strokes with Statins The same statin drugs that millions of people use to lower their cholesterol also might provide a safe and inexpensive treatment for a blood vessel disorder that can lead to fatal hemorrhagic strokes, seizures, paralysis or other problems.

If a clinical trial with people shows the same results as tests with mice, statins could be the first drug treatment for cerebral cavernous malformation (CCM), a disorder in which blood vessels become weak, dilated, and prone to leaking, according to U cardiologists Dean Y. Li, M.D., Ph.D., professor of internal medicine, and Kevin J. Whitehead, M.D., assistant professor of internal medicine, senior and first authors, respectively. Their study was published in the Jan. 18 issue of *Nature Medicine* online. (www.nature.com/nm/index.html)

Relative Risk of Colon Cancer Researchers at the University’s Huntsman Cancer Institute (HCI) discovered that siblings diagnosed with colon cancer share genetic similarities on a region of chromosome 7q31, suggesting a gene that causes familial colon cancer may reside in that chromosomal region. The study, published Nov. 1, 2008, in *Cancer Research*, also shows that siblings who share the genetic region tend to develop cancer 3.8 years sooner than siblings who do not.

Study leader Deborah Neklason, Ph.D., HCI investigator and U research assistant professor of oncological sciences, said the findings could lead to a better understanding of the cellular process that results in cancer, as well as bring more targeted research to eventually provide a screening test for genetic colon cancer. (cancerres.aacrjournals.org/content/vol68/issue21/)

Genetic “Hotspots” for Psoriasis

Using a new technique that allows a genomewide scan of millions of genetic mutations, researchers have identified four new genetic “hotspots” that affect the risk for psoriasis, the autoimmune disease that can affect the joints and cause red, scaly patches of skin in an estimated 7.5 million Americans. The study, which appeared in the Jan. 25 issue of *Nature Genetics*, also confirmed that two other DNA sites, discovered by U of U researchers and Celera Group, have a high association with psoriasis.

Gerald G. Krueger, M.D., U professor of dermatology and a Benning Presidential Endowed Chair holder, and Kristina C. Duffin, M.D., assistant professor of dermatology, led the Utah portion of the study. The researchers took advantage of a new technology called genomewide association studies (GWAS), which allowed them to comb more than 10 million genetic mutations in the human genome and identify those predicted to be associated with psoriasis. They identified 438,670 genetic mutations and then probed the DNA of 1,359 people with psoriasis and 1,400 without the disease to look for those mutations.

After identifying 18 DNA sites with the highest associations with psoriasis, the researchers expanded the study to include 5,048 people with psoriasis and 5,051 without the disease. They identified seven potential genetic hotspots for psoriasis. Three of the sites first had been identified in earlier studies by Krueger and other U of U and Celera Group researchers. The University of Michigan led the overall study, which included Washington University in St. Louis. (www.nature.com/ng/journal/v41/n1/index.html)



Psoriasis covers many areas of the body with red, scaly patches of skin such as on the shoulders, arms, legs, and chest of this girl, but also can cause joint inflammation. U of U researchers are part of a team that recently discovered four genetic “hotspots” that affect the risk for the autoimmune disease.

Predicting A-fib Treatment Outcomes Using a technique called delayed-enhancement magnetic resonance imaging (DE-MRI), School of Medicine researchers found they may be able to predict whether radio frequency (RF) ablation will effectively treat atrial fibrillation (AF), a heart rhythm disorder that causes rapid and/or irregular heartbeats and scarring or fibrosis in the left atrium.

The researchers used DE-MRI to create 3-D images of the left atrium before RF ablation. Patients were assessed six months after the procedure, and only 14 percent classified as having minimal scarring had suffered a recurrence of AF, while 75 percent of the patients with extensive scarring had a recurrence.

Nassir F. Marrouche, M.D., assistant professor of internal medicine and director of the Atrial Fibrillation Program, was senior author of the study, published in the April 7 issue of the journal *Circulation*. (circ.ahajournals.org/content/vol119/issue13/)

Familial Component to Brain Cancer A study using the Utah Population Database at the U of U has shown that a family history of brain cancer increases one’s chances of succumbing to the disease by up to fourfold. Researchers Lisa A. Cannon-Albright, Ph.D., professor of biomedical informatics, and Deborah Blumenthal, M.D., co-director of Tel-Aviv University’s Neuro-oncology Services and former U faculty member, researched the medical records of some 1,500 Utahns who had genealogical records for at least three and as far back as 10 generations.

Even if brain cancer has appeared in one’s family, the chances of descendants and relatives getting it are still relatively low. Less than 5 percent of the approximately 17,000 primary brain tumors annually identified in Americans are hereditary. The study appeared Sept. 23, 2008, in the journal *Neurology*. (neurology.org/content/vol71/issue13/)

Molecular Explanation for Iron Overload Researchers led by Jerry Kaplan, Ph.D., U professor of pathology and assistant vice president for health sciences research, identified a molecular explanation for the dominant inheritance pattern of hepcidin-resistant hemochromatosis, an iron overload disease in which the body builds up too much iron.

The body’s iron balance is maintained when a liver-produced hormone called hepcidin binds with ferroportin, a protein that transports iron from inside of cells. When hepcidin binds with ferroportin, it results in the addition of a phosphate group to ferroportin, a process called phosphorylation. In a study in the Feb. 16-20 *Proceedings of the National Academy of Sciences* online, Kaplan showed that, for phosphorylation to take place, an enzyme called Jak2 must bind with ferroportin.

In hepcidin-resistant hemochromatosis, mutations in ferroportin result in an inability to respond to adequate levels of hepcidin. The disease is dominantly inherited, meaning if either parent carries the gene, their offspring have a 50-50 chance of getting it. (pnas.org/content/by/year/2009)

Genetic Link to Social Behavior A study led by Brain Institute researcher and USTAR professor of pediatrics Julie R. Korenberg, M.D., Ph.D., has traced the role of a gene in the social

behavior of children with a rare genetic disorder known as Williams syndrome.

Published in the Feb. 9 online issue of the *American Journal of Medical Genetics*, the study shows that a gene called *GTF2I* plays a role in the extremely outgoing and social behavior of children with Williams syndrome. Korenberg also showed that another gene, *GTF2IRD1*, contributes to visual-spatial performance in children with the disorder (see pg. 22). (3.interscience.wiley.com/journal/99018624/home)

On-and-Off Switch for Cancer

When combined, two previously unknown enzymes appear to control an “on-and-off switch” for critical genes that could trigger cancer or other diseases and birth defects. Genetically manipulating the enzymes could lead to therapies that slow or prevent the onset of tumors.

David A. Jones, Ph.D., professor of oncological sciences and senior director of translational research at HCl, and Bradley R. Cairns, Ph.D., professor of oncological sciences, HCl investigator, and Howard Hughes Medical Institute investigator, identified a previously unknown enzyme process that controls the levels of DNA methylation on genes.

Methylation is a cellular process required for healthy cell growth and development. In cancerous and diseased cells, methylation can go awry, shutting off genes that should be turned on and vice versa. Defects in DNA methylation are strongly associated with the early development of cancer and other diseases. Jones and Cairns’ study was published in the Dec. 26, 2008, issue of *Cell*. (cell.com/archive?year=2008)

—Compiled by Phil Sahn