The Knockout Mouse
And Other Adventures in Big Science
Among the myriad ways of measuring success of a research enterprise, two of the most widely accepted are ability to compete for funding and quality of publications. Recent rankings of each of these parameters place Baylor College of Medicine prominently among the best in the world.

**RESEARCH FUNDING**

Blue Ridge Institute for Medical Education Rankings of National Institutes of Health Funding Received by US Medical Schools

BCM ranked 17th in the country and #1 Texas.

BCM also had 10 departments ranked in the top 20 and five departments rank in the top 10.

- **1st** Molecular and Human Genetics
- **3rd** Molecular and Cellular Biology
- **4th** Pediatrics
- **9th** Physical Medicine & Rehabilitation
- **9th** Molecular Physiology & Biophysics

**TOP UNIVERSITIES**

The 2011 Performance Ranking of Scientific Papers for World Universities done by the National Taiwan University is based on statistics of scientific papers that reflect three major performance criteria—research productivity, research impact and research excellence.

**Clinical Medicine**

BCM ranks 40th in the world and 36th in the U.S.

**Life Sciences**

BCM ranks 28th in the world and 25th in the U.S.

In the Higher Education Evaluation and Accreditation Council of Taiwan (HEEACT) ranking of the world’s top 500 universities,

BCM ranks 63rd in the world and 41st in the U.S.

*In both the Performance and the HEEACT rankings, BCM is one of only a handful of health science universities included among a vast majority of full service universities.*
Welcome to BCM Quarterly.

The day to day pressures of surviving in academic medicine today—rising healthcare costs, limited research funding, shrinking reimbursements—can skew our outlook to the pessimistic. But, everyday at Baylor College of Medicine and academic medical centers around the country, we are making progress.

Some of this progress takes the form of multi-billion dollar initiatives such as the Human Genome Project or the Knockout Mouse Project featured on page 4. But smaller steps such as encouraging physicians to change behavior as in “Making Meaningful Use Meaningful” (page 8) can have significant impact. Our progress can also be observed in the decisions of individuals, such as two physician assistants who were inducted into the United States Navy at graduation (page 2), to put the needs of others first.

Staving off pessimism and keeping our perspective in the face of our current challenges makes it more important than ever that we take a few minutes from our hectic schedules to celebrate our progress. I invite you to take a break, peruse these pages and reflect for a moment on all ways healthcare providers and scientists are helping to enhance quality of life for people around the world.

Best regards.
Paul Klotman, MD
President and CEO, Baylor College of Medicine

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As a Ph.D. student in the laboratory of Dr. Huda Zoghbi (left), Dr. Rodney Samaco (right) studied Rett Syndrome, a neurological disorder that mainly affects young girls. Now, in his own laboratory, he will use funds from his NIH Director’s Early Career Award to study autism.

“For decades, we have seen patients with various genetic conditions including intellectual disability, autism, epilepsy, birth defects and many others, but often we have been unable to identify the abnormal gene. Now by sequencing the exome of these patients, we will have the potential to identify the abnormal gene in the majority of cases,” said Dr. Arthur Beaudet, the Henry and Emma Meyer Chair in Molecular Genetics at BCM.

Whole Exome Sequencing is the first test to be offered by the WGL, a joint project of the BCM Human Genome Sequencing Center, the BCM Department of Molecular and Human Genetics and the Medical Genetics Laboratories.
Baylor College of Medicine is the academic center around which the Texas Medical Center, the world’s largest health center, evolved.

Within the four schools that make up BCM, our faculty creates, implements and shares new knowledge, new systems and new technologies that improve the lives of our neighbors, our nation and our world.

**Baylor College of Medicine** – Consistently ranked as one of the leading research-intensive medical schools, BCM is the only private medical school in the Greater Southwest.

**The Graduate School of Biomedical Sciences at BCM** – BCM’s extensive research portfolio combined with faculty who are world-leaders in their field support 14 programs which are ranked among the top 10 percent of graduate programs in biological sciences.

**School of Allied Health Sciences at BCM** – Drawing highly regarded applicants from throughout the region and the nation, the physician assistant and nurse anesthesia programs of BCM School of Allied Health Sciences consistently rank among the best in the country.

**National School of Tropical Medicine at BCM** – This newest academic component builds on the college’s over 100-year legacy of caring for our local and global community. It is the only school in the nation dedicated to patient care, research and education related to neglected tropical diseases, the most common infections of the world’s poorest people.

BCM physicians provide state-of-the-art care to patients from Houston and around the world at the Baylor College of Medicine Faculty Group Practice and our eight affiliated teaching hospitals.
SMART start for early success

Dr. Rodney Samaco credits the collaborative attitude of Baylor College of Medicine, with preparing him to receive a National Institutes of Health Director’s Early Independence Award, established to speed the careers of newly minted Ph.Ds. Samaco will use the $1.25 million five-year award in his study of the genetic and neurobiological basis of the social and behavioral dysfunction associated with autism spectrum disorders.

“Rodney is the kind of student who makes mentoring a most rewarding experience,” said Dr. Huda Zoghbi, director of the Jan and Dan Duncan Neurological Institute at Texas Children’s Hospital, Distinguished Service Professor of Molecular and Human Genetics at BCM and Samaco’s graduate mentor as well as a Howard Hughes Medical Institute investigator.

Samaco first came to BCM through the Summer Medical and Research Training (SMART) program, which provides college undergraduates experience working in biomedical research laboratories. “The opportunity I had there and the mentoring I received in the laboratory was important for my continued career in science,” he said.

“BCM faculty and leadership as well as local and national funding partners have provided support for the SMART program for 23 years because they realize how much developing scientists benefit from it,” said Dr. Gayle Slaughter, the program’s director.

The son of immigrants from the Philippines, Samaco also participated in the federally funded Initiative for Maximizing Student Diversity Activity program, which supports doctoral students from underrepresented minorities.

WHOLE EXOME SEQUENCING CLINICAL TEST NOW AVAILABLE

The last issue of BCM Quarterly reported on the use of whole genome sequencing to obtain a better diagnosis and adjust therapy for twins with a rare genetic abnormality. Now the Baylor College of Medicine Whole Genome Laboratory (WGL) is making sequencing available to patients around the world.

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SOCIAL DOC

A recent article in *American Medical News* analyzed use of social media by physicians. The article focused on the fact that many physicians are still struggling with if and how to utilize social media in their professional lives.

Dr. Bryan Vartabedian, assistant professor of pediatrics at BCM, is a pioneer in this realm. He was recently named one of 11 faces to follow in health care social media by *Fierce Health IT*.

The publication noted, “On any given day, his Twitter feed is flooded with advice-filled tweets, as well as re-tweets of advice and articles from fellow health professionals.” Vartabedian, who is a pediatric gastroenterologist at Texas Children’s Hospital, can be found on Twitter (@Doctor_V) and on his blog, www.33 Charts.com.

GRADUATING TO SERVE

Beyond the usual pomp and circumstance of graduation, this year’s commencement for the Baylor College of Medicine School of Allied Health Sciences included an additional ceremony—the induction of two physician assistant graduates into the United States Navy Medical Services Corps.

Amanda Harrelson, M.Sc., plans to serve for at least three years and then return to Houston. Harrelson, an accomplished cellist, performed with the Texas Medical Center Orchestra during her studies.

Amelia Ross, M.Sc., is stationed at the Brigade Medical Unit of the United States Naval Academy in Annapolis, Maryland, where she is one of the main health providers for the midshipmen of the Academy.

HEALTHCARE CAN LEARN FROM FINANCIAL MELTDOWN

Dr. Paul Klotman, president and CEO of Baylor College of Medicine, wrote an editorial calling on his peers to take a lesson from the current financial crisis and reform executive compensation in health care in a manner that promotes focus on health care’s primary mission; improving the health of patients and communities. An excerpt of the editorial as it appeared in the *Houston Chronicle* on December 23, 2011 is reproduced below.

Hospitals and health care institutions—particularly those that are not-for-profit—exist to provide quality health care that improves not only the health of their patients but also that of the community. Cost-effectiveness, evidence-based medicine and quality go hand-in-hand with that mission.

Health care CEOs must lead their institutions in creating value in medicine—the quality, safety and cost-effectiveness that benefit not only the health care system and payers, but also patients. Accomplishing these goals can be painful, but in the end, they will make their institutions stronger, the health care system viable and—most important—patients safer and healthier.

CEOs must take that bold step in tying pay increases and bonuses to measurable factors that best benefit the community in which such health care entities exist—quality of care, safety, improved outcomes and cost-effectiveness. Health care organizations should set a transparent set of goals each year. Annual reporting to the community on success toward these goals should then form the basis for executive compensation.

The health care institutions that survive in these difficult economic times ...will be those that provide the community with the highest quality health care it needs in a cost-effective manner.
“Dr. Andreas Tolias was recently honored by the NIH with a $2.5 million Pioneer Award. Rather than supporting a specific idea, this award is given to scientists who show exceptional creativity in proposing bold and highly innovative research approaches to major challenges in biomedical and behavioral research. Congratulations to Dr. Tolias and all his colleagues who have recently been honored for their achievements.”

Dr. Paul Klotman, president and CEO

**ACCOLADES**

Dr. Dolores Lamb, Lester and Sue Smith Chair in Basic Urologic Research and director of the new Center for Reproductive Medicine at BCM, assumed the presidency of the American Society for Reproductive Medicine. She is the first basic scientist to head the society.

Dr. George Bisset, Ill, professor of radiology at BCM, was named president of the Radiological Society of North America.

Dr. Robert Roush, associate professor of medicine – geriatrics at BCM, was elected president of the National Association for Geriatric Education and the National Association of Geriatric Education Centers.

Dr. Jose Suarez, professor of neurology at BCM, has been elected first president of the Neurocritical Care Research Network.

Dr. Bobby Kapur, assistant professor of medicine – emergency medicine and director of the Center for Globalization at BCM, has been awarded the Order of the International Federation for Emergency Medicine in recognition of his contributions to the development of emergency medicine.

In recognition of her clinical care and advocacy for veteran patients, Dr. Kimberly Arlinghaus, associate professor of psychiatry and behavioral sciences at BCM, received the Humility Award at the annual Sierra Tucson “Gratitude for Giving” celebration.

The American Society of Nephrology (ASN) is launching the William E. Mitch, III, MD, FASN, International Scholars Program. Mitch, professor of medicine – nephrology at BCM, is a former ASN president and recipient of the society’s John P. Peters Award.

Dr. Sally Ann Holmes, associate professor of physical medicine and rehabilitation at BCM, and executive of the Spinal Cord Injury Care Line at the Michael E. DeBakey Veterans Affairs Medical Center, received the Operation American Heroes Foundation Founder’s Award.

Dr. George Hutton, associate professor of neurology and medical director of the Maxine Mesinger Multiple Sclerosis Comprehensive Clinical Care Center at BCM, was inducted into the National MS Society’s 2011 Volunteer Hall of Fame for Health Professionals.

Dr. David Buck, professor of family and community medicine at BCM and president and founder of Healthcare for the Homeless-Houston, has received the St. Luke’s Episcopal Health Charities 2011 Community Health Leadership Award.

Dr. Malcolm Brenner, professor of medicine – hematology and medical oncology and director of the Center for Cell and Gene Therapy at BCM, Texas Children’s Hospital and The Methodist Hospital, received the 2011 American Society of Hematology Mentor Award.

Dr. Mary Brandt, professor of pediatrics and associate dean of student affairs at BCM, has been named the new chair of the Section on Surgery for the American Academy of Pediatrics.

Dr. Meng Wang, assistant professor with the Huffington Center on Aging at BCM, is one of the recipients of the 2011 Ellison Medical Foundation New Scholar Award in Aging.

Dr. Thuy Phung, assistant professor of pathology at BCM, has been awarded the Research Scholar Grant from the American Cancer Society.

Dr. Steven Carpenter, associate professor of radiology at BCM, was recognized with an Educator of the Year Award by the Association of Residents in Radiation Oncology in partnership with the American Society for Radiation Oncology.

Dr. Amy McGuire, associate professor in the Center for Ethics and Health Policy at BCM, was appointed to the National Advisory Council for Human Genome Research.

Karlie Jones, a graduate student in molecular physiology and biophysics at BCM, was awarded the best poster presentation award for cell and animal models session at this year’s International Myotonic Dystrophy Consortium.

Dr. Kalpesh Thakkar, assistant professor of pediatrics – gastroenterology, hepatology and nutrition at BCM, was included in the 2011 Becker’s ASC Review list, “125 leading Gastroenterologists in America.”

Dr. Joseph S. Coselli, professor and chief of the division of cardiothoracic surgery at BCM, and Dr. Scott LeMaire, professor and director of research in the division of cardiothoracic surgery, were awarded the 2011 St. Luke’s Episcopal Hospital Distinguished Scientist Award.

Dr. Alvaro Munoz, instructor of urology at BCM, won second place in the Beaumont Health System’s Jack Lapides Essay Contest on Urodynamic and Neurourology Research.
Becoming a leading center for development and phenotyping of knockout mice required years of investment in talent and infrastructure. Some of the leaders of this effort at BCM are pictured here.

Top left: Dr. Franco DeMayo, co-principle investigator for BCM’s role in the Knockout Mouse Project and director of the Genetically Engineered Mouse Core.

Top right: Dr. Corey Reynolds, manager of the Mouse Phenotyping Core

Bottom left: Dr. Cecilia Ljungberg, director of the RNA In Situ Hybridization Core

Bottom right: Dr. Isabel Lorenzo, supervisor of the Mouse Embryonic Stem Cell Core
The most well known example of this approach, frequently referred to as big science, was the Human Genome Project. In 2003, two consortiums, one of which included Baylor College of Medicine as a prominent member, announced completion of the entire sequence of the human genome.

When Dr. Richard Gibbs, director of the BCM Human Genome Sequencing Center (HGSC), was recently elected to membership in the Institute of Medicine, he viewed his election as a validation of this approach to science. For most of his career, he experienced the bias of many in the scientific community against research that is not hypothesis-driven. His election validated the big-science approach that creates a treasure trove of data for scientists to mine for the bits of precious information that explain the normal human condition and disease states.

Gibbs, who in 2011 was one of the top 10 U.S. principal investigators in funding received from the National Institutes of Health (NIH), has been a leader in establishing the infrastructure that made BCM one of the nation's primary participants in the Human Genome Project and, more recently, helped the HGSC secure a four-year, $85.2 million renewal award from the National Human Genome Research Institute (NHGRI) to advance the study of genomics and its use in the diagnosis and treatment of disease.

“NHGRI relies on the large-scale centers to be its sequencing production and intellectual powerhouses,” said Dr. Adam Felsenfeld, program director for NHGRI's Genome Sequencing Program in the Division of Extramural Research. This sentiment is indicative of the value NIH places on institutions that have invested in building infrastructure to support big science.
Genome sequencing is not the only area of big science for which BCM has developed the infrastructure to lead.

In 2003, Dr. Monica Justice, professor of molecular and human genetics at BCM and colleagues wrote in *Nature*, “Now that the mouse and human genome sequences are complete, biologists need systematic approaches to determine the function of each gene.” In other words, it is one thing to know what the genes are, but we also need to know what they do and how they do it.

The predominate method for determining the function of a gene in a mammal is to create a knockout mouse—a mouse in which a gene has been disrupted or deactivated by a variety of means. Historically, a researcher interested in a specific gene for a specific condition would develop a mouse with that gene knocked out. “This method required many laboratories to dedicate resources and develop expertise in creating knockout mice,” said Justice. “Once all the effort was done to create the mouse, the researcher would generally limit investigation to the trait or traits in which he or she was interested.” For example, a cardiac researcher might look at heart function, but completely overlook any impact the loss of the genes had on the kidney.

“I originally came to Baylor to work with (Dr.) Allan Bradley (who now leads the Mouse Genomics Team at the Wellcome Trust Sanger Institute in the United Kingdom) because the two of us realized our combined skill sets would allow us to address questions about functions of genes in certain sections of the mouse genome,” said Justice. She and Bradley were not focused on a particular trait or disease. Rather they wanted to understand the impact of the loss of a gene in various areas of the body.

Justice, Bradley and colleagues developed many of the tests necessary to study the phenotype—the observable characteristics—of knockout mice. “Many of the tests we use on mice are similar to those you would receive from a physician, but we had to develop the tools and techniques to do these on a much smaller organism,” said Justice. As they began looking at all the changes in phenotype that resulted from knocking out single genes, “We discovered we knew very little about the mammalian genome,” recalls Justice. “We found that 95 percent of the genes we were investigating had functions that no one knew anything about. It really shocked people that we know so little.”

In the fall of 2003, mouse geneticists met to discuss the future of their field. The result was an international effort with the audacious goal of creating knockout mice strains for all 21,000 protein-coding genes in the mouse genome.

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Dr. Monica Justice
The NIH launched a trans-institutional initiative known as the Knockout Mouse Project (KOMP), which collaborated with the International Knockout Mouse Phenotyping Consortium and other international groups. The phase one goal of creating knockout mouse embryonic stem cell lines for the 21,000 genes is expected to be attained this year.

Over the past decade, Justice and her BCM colleagues have developed a vast array of shared resources for development and phenotyping of knockout mice. These include a Mouse Embryonic Stem Cell Core, Genetically Engineered Mouse Core, Behavior Core, Mouse Phenotyping Core, and Pathology Laboratory.

“Because BCM has invested so heavily in mouse genetics, we were ready to move and move quickly when the NIH announced it was initiating phase two of KOMP,” said Justice.

The goal of KOMP2 over the course of five years is to transform the knockout mouse embryonic stem (ES) cells created in KOMP1 into adult mice for 2,500 knockout mouse strains and conduct extensive phenotype studies on each strain. The researchers will evaluate knockout mice’s behavior, neurophysiology, vision, sleep and hearing, as well as aspects of metabolic, cardiovascular and immune function. “No other mouse project has involved such extensive analysis,” said Justice.

With KOMP2’s aggressive timeline, researchers applying for funding had to be ready to hit the ground running. In just two months, Justice worked with her colleagues throughout BCM as well as collaborators at the Sanger Institute to pull together a grant that led to BCM being named the lead institution for a $34 million award to phenotype 833 knockout mice over the next five years. The remainder of the 2,500 will be completed by groups led by the University of California at Davis and Jackson Laboratories.

“My own background as well as the skill and expertise of the colleagues with whom I am fortunate to work at BCM contributed significantly to our ability to successfully compete for such a large and prestigious award,” said Justice. “But, carrying out a project of this magnitude would not be feasible without significant institutional support. The administration’s backing has been crucial to our success.”

In the final months of 2011, BCM’s willingness to invest for success helped secure millions of dollars in grant funding. For information on some of these grants, see page 11.
Enacted as part of the American Recovery and Reinvestment Act of 2009, the Health Information Technology for Economic and Clinical Health Act, or HITECH Act, supports the adoption of electronic health records. This act rolls out a multistage incentive plan, commonly referred to as meaningful use, over several years to encourage all healthcare providers to use electronic health records in ways expected to enhance quality of care, increase efficiency of care delivery and reduce medical errors.

“People may argue about specifics such as whether we are measuring the right parameters or have we set appropriate

Making Meaningful Use Meaningful

One would have to be living in isolation on a remote island to miss the daily reports, laments and outcries about defects in the U.S. healthcare system and government attempts at reform. That aside, said Dr. Jeffrey Steinbauer, chief medical information officer, Faculty Group Practice, at least one government initiative “got it right.”
targets, but this act has been more effective in encouraging rapid adoption of technology than anything I have seen in my 20 years focused on healthcare IT,” said Steinbauer.

Each stage of meaningful use defines specific indicators or tasks within the electronic medical record that healthcare professionals must complete with a specified percentage of patients. For example, one of the indicators in stage one is printing an after visit summary and giving it to 50 percent of patients seen. Physicians who satisfy the requirements in each phase receive a financial incentive.

In order to qualify for the first financial incentive, physicians had to be compliant with all indicators in stage one during any 90-day period in 2011. Thanks to early planning, close cooperation between information technology and clinical leadership, extensive engagement of physicians and staff, and strategic communications, 84 percent of the physicians practicing within the Baylor Clinic qualified for this incentive. In addition, continued advanced planning with an eye towards phases two and three of meaningful use are helping to ensure that these physicians will meet standards for future incentives as well.

In early 2011, when many institutions across the country were just beginning to focus on meaningful use, Steinbauer and Jenifer Jarriel, former chief information officer at BCM, were invited to speak at a large healthcare IT conference. The room was packed for their presentation entitled “Orchestrating a Response to Meaningful Use” by Making “MUSIC” (Meaningful Use Supporting Innovative Care). Over the course of the year, as more and more BCM physicians met the meaningful use criteria, both Steinbauer and Jarriel were regularly fielding calls from colleagues across the country seeking guidance on how to copy Baylor’s success at their own institutions.

“While the financial rewards are good incentives,” said Steinbauer, “I believe the real impetus behind the success of meaningful use is that it is the right thing to do. The overwhelming majority of physicians want to do what is right for their patients. Congress gave us the resources to create the tools and processes to help physicians increase their usage of electronic medical records. When the need for change is presented clearly with good data and resources are available, knowing they are taking steps to improve care is all the incentive most physicians need.”

QUALITY ENHANCER OR PANDORA’S BOX?

While encouraging physicians to use electronic medical records is widely viewed as a quality enhancing mechanism, debate still rages as to what types of access patients should have.

The U.S. Department of Health and Human Services jointly with other government agencies proposed a rule allowing patients to access test results directly from the laboratory by request. A report by researchers at Baylor College of Medicine and the Michael E. DeBakey Veteran’s Affairs Medical Center in the *Journal of the American Medical Association* advocated for more research to prevent unwanted consequences from this seemingly positive action.

“We need to be balanced and think of both intended and unintended consequences that might result,” said Dr. Hardeep Singh, assistant professor of medicine-health services at BCM. “At this time, we do not have all the answers about what the best practices might be. The scientific knowledge needed to develop these best practices is still evolving.”
**MICROBIOME PROFILE KIDS WITH ABDOMINAL PAIN**

Every child suffers from a “belly ache” now and then. However, a significant number of them have much more—a deep and visceral pain that returns again and again. The first major report from the Texas Children’s Microbiome Center and Baylor College of Medicine’s Alkek Center for Metagenomics and Microbiome Research may provide insights on the cause of this pain.

The microbiome refers to the billions of bacteria, viruses and fungi that inhabit the human body. In a report published in the journal *Gastroenterology*, Dr. James Versalovic, professor of pathology & immunology at BCM and director of the Texas Children’s Microbiome Center, and colleagues identified specific bacterial signatures in children with recurrent abdominal pain and irritable bowel syndrome.

“When we characterized the bacteria in the intestines of children with irritable bowel syndrome, we found it was different from what we found in healthy children,” said Dr. Robert Shulman, professor of pediatrics – gastroenterology at BCM and the Texas Children’s Hospital Foundation Chair in Pediatric Gastroenterology. “We also found that the severity of their pain and how frequently it occurred was associated with certain types of bacteria.”

“The next step is to see if there is causation and whether we can use this information to devise new treatments,” said Versalovic, who is the Milton J. Finegold Professor of Pathology & Immunology at BCM.

**POTASSIUM CHANNEL LINKED TO HYPERTENSION**

Potassium channels are tiny pores that allow only potassium to flow into and out of a cell while excluding all other ions.

The gene K2P6.1 or TWIK-2 is one of a family of potassium channel genes. Its role in the vasculature was recently discovered by Dr. Robert Bryan, professor of anesthesiology at Baylor College of Medicine and colleagues. A report on their work was published in the journal *Hypertension*.

Bryan and colleagues developed a mouse that lacked this particular gene. “All of these mice were hypertensive,” said Dr. Eric Lloyd, instructor of anesthesiology at BCM. “And they were hypertensive at a very young age. This is the first time that loss of a potassium channel caused this severity of hypertension in a young mouse without an external influence.”

**MEMORY PILL: SCIENCE FICTION**

Lack of a molecule known as PKR confers neural super powers on mice, according to a recent study reported in *Cell* by Dr. Mauro Costa-Mattioli, assistant professor of neuroscience at Baylor College of Medicine and colleagues.

“We found that when we genetically inhibit PKR, we increased the excitability of brain cells and enhanced learning and memory, in a variety of behavioral tests,” Costa-Mattioli said. For instance, when the authors assessed spatial memory (the memory for people, places and events), they found that normal mice had to repeat a task multiple times over many days in order to remember it. By contrast, mice lacking PKR learned the task after only one training session.

Another key finding was the fact that PKR inhibitor—a small molecule that blocks PKR activity—could enhance memory in mice that were not genetically altered and thus acts as a “memory-enhancing drug.”
“How are our brains wired?” said Dr. Hugo Bellen, professor of molecular and human genetics at Baylor College of Medicine. “If you wire a brain, you have to connect billions of neurons. How do you achieve the necessary specificity? Many different mechanisms are involved and much is achieved during the development of the organism.”

In a report in the journal *Neuron*, Bellen and colleagues identified a novel gene called rich (ric1 homologue) that acts to ensure that the specificity of certain neurons for their target is established properly. When the rich protein is mutated, the researchers believe that it can no longer activate another protein called Rab6, which is important in the formation of synapses.

“This is a novel mechanism by which you can regulate in an unanticipated fashion how a specific neuron connects to another neuron,” said Bellen, who holds the March of Dimes Chair in Developmental Biology and is a Howard Hughes Medical Institute investigator.

Many cancers are driven by the overexpression of oncogenes. These oncogenes promote processes that allow cells to grow unchecked. On the other hand, these oncogenes create additional stresses that must be subverted for the cancer cell to survive. One classical example of an oncogene that creates such a delicate balance is c-myc, which is activated in 20-40 percent of all cancers.

Researchers at Baylor College of Medicine and colleagues developed ways to exploit the dependence of cancers on oncogenes to kill the cells without harming normal tissues. A report on their work appeared in the journal *Science*.

Dr. Thomas Westbrook, assistant professor of molecular and human genetics at BCM, and colleagues discovered that when they inhibited a gene called SUMO-activating enzyme (SAE) in mice with a myc-driven breast cancer, the tumors stopped growing and many of them melted away. “If you inhibit it in normal cells, nothing happens,” said Westbrook. Thus turning off SAE may be a great way to kill cancers without many of the side effects of traditional chemotherapies.
**CELL THERAPY SAFETY SWITCH**

Stem cell transplantation that includes specially modified immune system T-cells enhances the chance of recovery from diseases such as leukemia or lymphoma because each T-cell acts as a serial killer, spreading death among the many cancer cells.

However, the T-cells present a special risk. Sometimes the transplanted T-cells attack the patient’s healthy tissues causing graft versus host disease, which is disabling and often fatal. A new system that activates when the cells go out of control and terminates them almost immediately serves as a safety switch, said researchers from the Center for Cell and Gene Therapy at Baylor College of Medicine, Texas Children’s Hospital and The Methodist Hospital in a report in a recent issue of the *New England Journal of Medicine*.

To make the safety switch, the researchers introduced into the T-cells a gene called iCasp9. When the patient receives a specific drug, it joins together two single molecules of iCasp9 and makes it active—rapidly triggering the death of the cell.

Within 30 minutes of administration of the drug, 90 percent of the T-cells died. The T-cells continued to decrease in number over the next 24 hours and graft versus host disease went away completely. The small number of T-cells that remained was able to expand and fight infections, but did not cause further graft versus host disease.

**LOSS OF ENZYME STYMIES DIFFERENTIATION OF BLOOD-FORMING CELLS**

In the bone marrow, blood-forming (hematopoietic) stem cells become one of the myriad kinds of blood cells in the body or they can self-renew, maintaining that pool.

However, the lack or mutation of a gene for an enzyme called Dnmt3a results in an abundance of stem cells and a lack of blood cells, said a consortium of researchers led by Dr. Margaret Goodell, professor of pediatric—hematology and director of the Stem Cells and Regenerative Medicine Center at Baylor College of Medicine in a report in the journal *Nature Genetics*.

When a stem cell gets a signal telling it to differentiate, it needs certain genes to remain in the stem cell state. Before it can differentiate, Dnmt3a must target those genes and add a methyl group to them. If the cell lacks functional Dnmt3a, the cell will have a harder time overcoming the barriers to differentiation.

**ARGinine PARADOX UNRAVELED**

“Arginine is the single amino acid in the body that makes nitric oxide,” said Dr. Brendan Lee, professor of molecular and human genetics at Baylor College of Medicine and a Howard Hughes Medical Institute investigator. Even though there may be sufficient arginine in the cell to produce enough nitric oxide for the cell’s needs, giving more arginine results in the production of more nitric oxide. That is the arginine paradox. In a recent report published in *Nature Medicine*, Lee and colleague propose a solution to the arginine paradox.

The answer rests with argininosuccinate lyase (ASL). Lee began studying this enzyme after caring for a three-year-old patient 13 years ago whose lack of ASL resulted in very high blood pressure. His studies in mice demonstrated this enzyme has two separate functions. “The first is to make arginine and the second is to hold together a complex of proteins that transfers arginine inside the cell,” said Lee. These findings open a door into ways to explore the effect of nitric oxide on a host of disorders including that suffered by Lee’s former patient.

**NOROVIRUS VACCINE FEASIBLE**

An experimental norovirus vaccine provided significant protection against both viral infection and its associated gastrointestinal illness, said a consortium of researchers led by Baylor College of Medicine in a report in the *New England Journal of Medicine*.

Norovirus illness is one of the most common causes of acute stomach and intestinal illness. “This study shows it is feasible to make a vaccine that will protect against norovirus infection and the illness it causes,” said Dr. Robert Atmar, professor of medicine – infectious diseases at BCM. This represents the first clinical demonstration of vaccine protection against norovirus.

Funds for this publication were provided by the BCM President’s Circle.
THE SAN ANTONIO BREAST CANCER SYMPOSIUM IS THE LARGEST BREAST CANCER MEETING IN THE WORLD.

In December of 2011, more than 7,000 breast cancer clinicians, researchers and advocates from over 100 countries met at this Baylor College of Medicine co-hosted meeting to discuss groundbreaking research in basic science, prevention and new treatments.

SAVE THE DATE
THE 35TH ANNUAL SABCS

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